

Gary M. Coppola
Herbert F. Schuster

**α -Hydroxy Acids
in Enantioselective Syntheses**



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Gary M. Coppola
Herbert F. Schuster

α -Hydroxy Acids in Enantioselective Syntheses



Gary M. Coppola
Dr. Herbert F. Schuster
Department of Metabolic Diseases
Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NY 07936-1080
USA

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Cover picture: The molecule depicted on the cover is (+)-milbemycin β_3 along with its electrostatic isopotential surface. Milbemycin was chosen because the spiroketal portion of the structure was synthesized from both malic and tartaric acids.

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To
my wife, Maro,
and my children,
Stefan and Kristiana

H.F.S.

To
my parents,
Richard and Josephine Coppola,
my wife, Joanne,
and my children,
Matthew and Laura

G.M.C.

Preface

With the mechanical separation of the optical isomers of sodium ammonium tartrate, Louis Pasteur, in 1848, realized that two molecules behaving differently toward polarized light, despite the appearance of identical chemical properties, must be different. Chirality was born. Nature produces enantiomerically and diastereomerically pure molecules with a wide range of chiral carbon centers. Enzymes, possessing inherent chirality as a consequence of the unique situation that all amino acids in living organisms are left-handed, provide rigid templates that accommodate only specific spatial arrangements of atoms. Chemists, eager to imitate nature, have developed very ingenious approaches that are capable of exploiting both steric and electronic factors to produce chiral carbon centers with high optical purity.

The modern synthetic chemist has available a collection of asymmetric molecules from nature's chiral pool that can be selectively transformed to incorporate their chiral centers into a target molecule with excellent optical integrity. One important class of compounds from the chiral pool is the amino acids, which are readily available in both *S* and *R* forms. The diversity of functional groups present in the various amino acids allows for a range of synthetic transformations leading to target molecules in which the initial amino acid chiral center either remains intact or directs the formation of new chiral centers. Our book *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids*, John Wiley & Sons, 1987, focused on the synthetic utility of amino acids geared toward the synthesis of biologically active molecules as well as natural products. The book was well received by the chemical community and indicated to us the importance of keeping scientists aware of the availability and utility of abundant chiral starting materials. With the pharmaceutical industry rapidly moving away from the development of racemic drugs, it is becoming important to research and developmental chemists to have access to synthetic routes that efficiently lead to each enantiomeric form of a new drug in order to minimize potential adverse side effects from the undesired antipode.

This prompted us to write a book focusing on the naturally occurring α -hydroxy acids, which may be considered relatives of the amino acids since these α -hydroxy acids can be obtained from amino acids in optically pure form. We have chosen to discuss the chemistry of lactic, mandelic, malic, and tartaric acids, focusing on chemistry that incorporates the chiral center of these acids into the final spatial arrangement of atoms. We also discuss how these chiral centers can direct the creation of new chiral centers. Most of our chemical discussion is concerned with the more abundant natural antipode of each of these acids. It should be kept in mind that, unless otherwise noted, all the reactions employed in the transformation of the natural antipode into a target molecule apply identically to the unnatural antipode. In fact, it is the beauty of these chiral starting materials that identical chemical reactions can be used to prepare all possible antipodes of a target molecule with excellent optical integrity.

Our goal is to provide chemists a concise and practical source of information regarding asymmetric synthesis of a variety of compounds ranging from relatively simple molecules with only one asymmetric center to exceedingly complex ones having numerous chiral centers. Our schemes show the absolute stereochemistry of all the chiral carbon centers, and provide detailed summaries of the reaction conditions employed. Wherever possible, we have included both chemical and optical yields, as well as some indication of diastereomeric purity. Our discussions focus on the important facts a chemist might need in order to undertake a

synthetic challenge that utilizes a particular hydroxy acid. Tables of physical data for key α -hydroxy acid derivatives are provided at the end of each of the chapters. Also, in the accompanying appendices at the end of the book we include several tables of reaction conditions used for the protection, deprotection, and manipulation of functional groups so one can quickly view a menu of reagents and conditions for a particular chemical transformation.

It is our sincere hope that this book will provide you, the synthetic chemist, with new opportunities for achieving your synthetic goals. For those students who are reading this book in order to enhance your synthetic repertoire, we hope you will enjoy the chemistry and not be intimidated by the sight of complex molecules. However, it is perhaps this sense of awe evoked by the many beautiful molecules given to us by nature's laboratories that continues to challenge chemists to recreate them for themselves.

East Hanover, New Jersey
January 1997

Gary M. Coppola
Herbert F. Schuster

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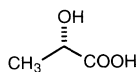
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1 Lactic Acid



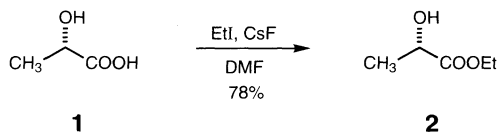
(S)-2-Hydroxypropanoic Acid (Lactic Acid)

Lactic acid occurs naturally in sour milk and in minor amounts in the muscle of animals, including humans. Commercially, lactic acid is produced by the fermentation of carbohydrates.

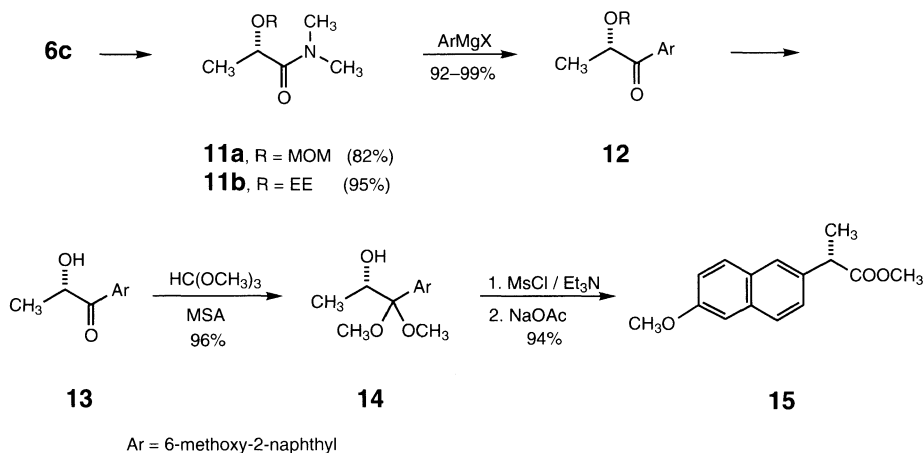
This chapter is organized according to the nature and complexity of lactic acid itself and its derivatives. We begin by discussing the chemistry surrounding lactic acid and its esters. Then lactic acids with the hydroxyl function protected by a variety of removable groups are presented sequentially. A table of physical data associated with all the common protected lactic acid derivatives, discussed throughout this part of the book is presented at the end of the chapter.

1.1 Reaction at the Ester Site

L-(+)-Lactic acid (**1**), the naturally occurring form, is commercially available from a large number of suppliers, and is inexpensive. At this writing, the price of 1 kg is less than \$60. Although **1** may be esterified with an alkyl iodide in the presence of CsF [1], carrying out this process is unnecessary since many lactic acid esters are commercially available, and some are even less expensive than the parent acid. For example, 500 g of ethyl (S)-(–)-lactate (**2**) can be purchased for less than \$14.



Analogous to amino acids, α -hydroxy acids form cyclic anhydrides when treated with phosgene. However, a much more efficient reagent for this transformation with lactic acid is trichloromethyl chloroformate. By this method, L-lactic acid O-carboxyanhydride (**3**) is prepared as a crystalline solid in 46% yield [2]. Although **3** has found application in polymer chemistry, its use in asymmetric synthesis has been limited. Reaction of **3** with 4-bromobenzaldehyde methylthio(thiocarbonyl)hydrazone in the presence of TFA gives a mixture of **4** (25%) and **5** (56%), which is separable by column chromatography [3].

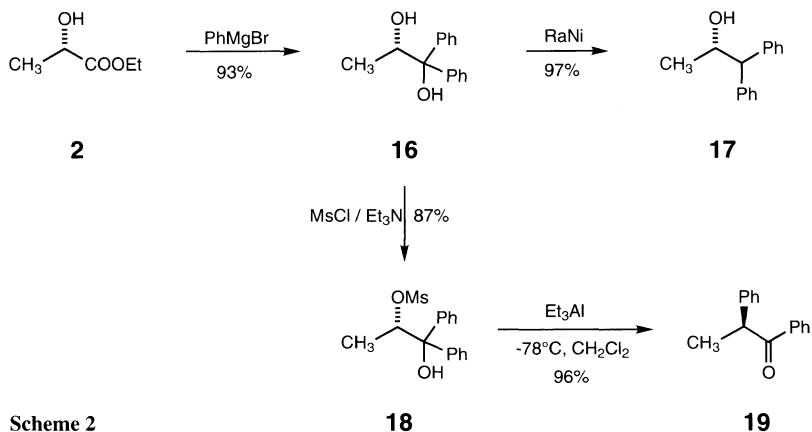


Scheme 1

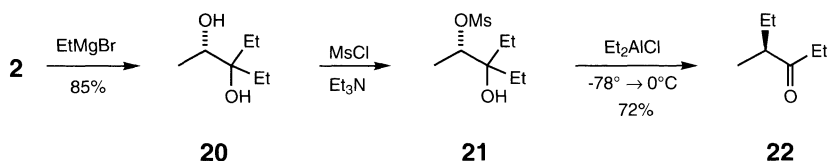
mesylation and hydrolytic rearrangement gives the target molecule **15** with an optical purity $>98\%$.

The ester function of ethyl lactate is susceptible to attack by Grignard reagents. Reaction of **2** with 3 equivalents of phenylmagnesium bromide gives diol **16** in high yield. Hydrogenolysis of **16** with Raney nickel furnishes 1,1-diphenyl-2-propanol (**17**) in nearly quantitative yield [8] (Scheme 2).

Diol **16**, when mesylated and then treated with triethylaluminum, undergoes a pinacol-type rearrangement to afford optically pure (*S*)-1,2-diphenyl-1-propanone (**19**) in 96% yield. Migration of the phenyl group is stereospecific, with complete inversion of the preexisting chiral center [9]. Likewise, ethylmagnesium bromide (3.5 equivalents) adds to **2** at room temperature to give diol **20**. Mesylation followed by stereospecific 1,2-alkyl migration promoted by diethylaluminum chloride furnishes (*S*)-4-methyl-3-hexanone (**22**), an enantiomer of an ant alarm pheromone [10]. The corresponding (*R*)-enantiomer is accessible from (*R*)-methyl lactate.



Scheme 2



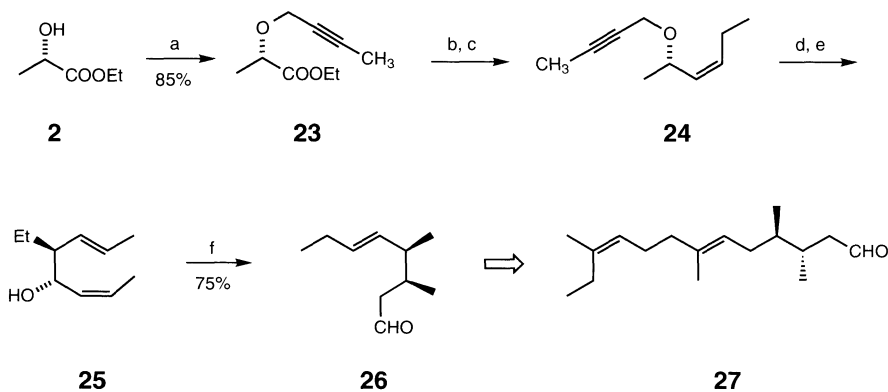
Another natural product, (+)-faranal (**27**), a trail pheromone of the Pharaoh's ant, has also been synthesized starting with **2** (see Scheme 3) [11]. The crucial transformation in the sequence is a [2,3] Wittig rearrangement of **24** which, after *cis*-hydrogenation, gives diene **25** in >96% *ee*. This intermediate, when treated with potassium hydride, undergoes an anionic oxy-Cope rearrangement to afford the *erythro* aldehyde **26** in 91% *ee*.

The chiral methyl substituent of a 2-methyl-1-oxacephalosporin can be supplied by ethyl lactate according to the route outlined in Scheme 4 [12,13]. The common intermediate **30**, can lead to either the 3-substituted 2-methyl-1-oxacephem (**33**) or the 2-methyl-3-nor-1-oxacephem (**34**).

(*S*)-(-)-Methyloxirane (**40**) is available in multigram quantities from L-ethyl lactate by initial reduction of the ester to (*S*)-(+)-propane-1,2-diol (**36**). Conversion of the primary alcohol to a suitable leaving group provides intermediates **38** or **39**, which afford the epoxide (96% *ee*) upon treatment with base [14,15] (Scheme 5). Oxirane **40** is also accessible from O-EE-protected ethyl lactate (see Section 1.4.4). (*R*)-(+)-methyloxirane can be similarly synthesized from L-ethyl lactate *via* its O-tosyl (Section 1.2.2.1) or O-mesyl derivative (Section 1.2.2.2).

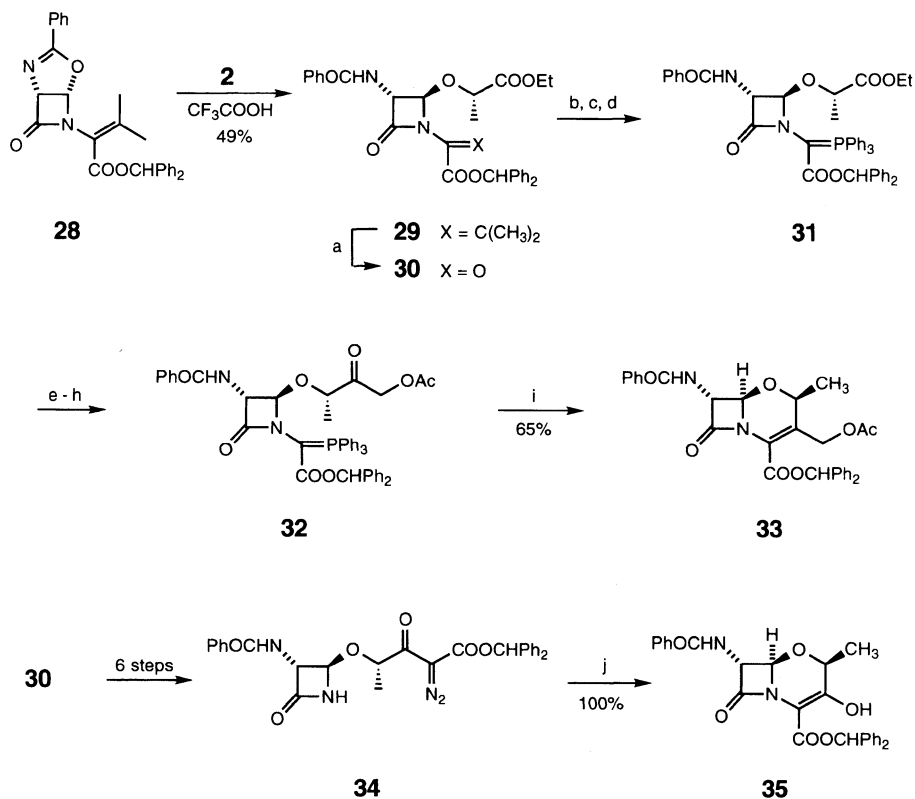
Organometallics open epoxide **40** regioselectively and stereospecifically to give chiral alcohols. This strategy has been utilized to supply key stereogenic centers in the lichen macrolide (+)-aspicilin (**44**) (Scheme 6) and in brefeldin A (**50**) (Scheme 7). The synthesis of **44** is accomplished in 15 steps and 13% overall yield [16], where the lengthy alkyl portion of the molecule containing stereo center C-17 is supplied by lactic acid and the triol segment is derived from D-mannose.

Likewise, the first step in the synthesis of **50** is a regioselective ring opening of epoxide **40** with organolithium compound **45**. By a series of manipulations, sulfone **47c** is produced in 50% overall yield with 97% *ee* [17]. Ring opening of lactone **48** with the lithiated sulfone **47c**

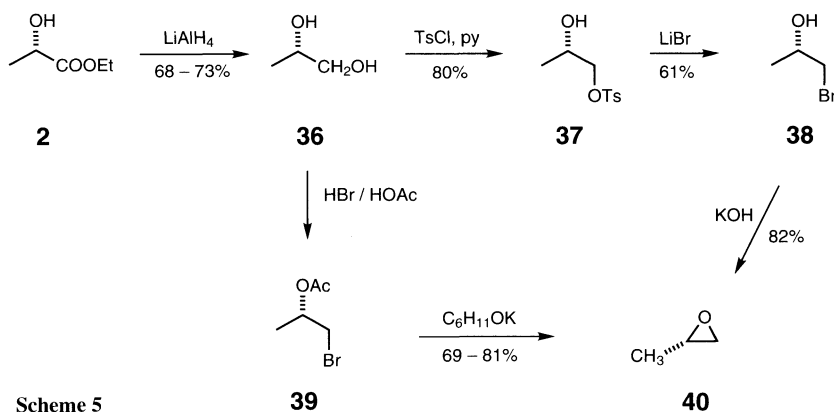


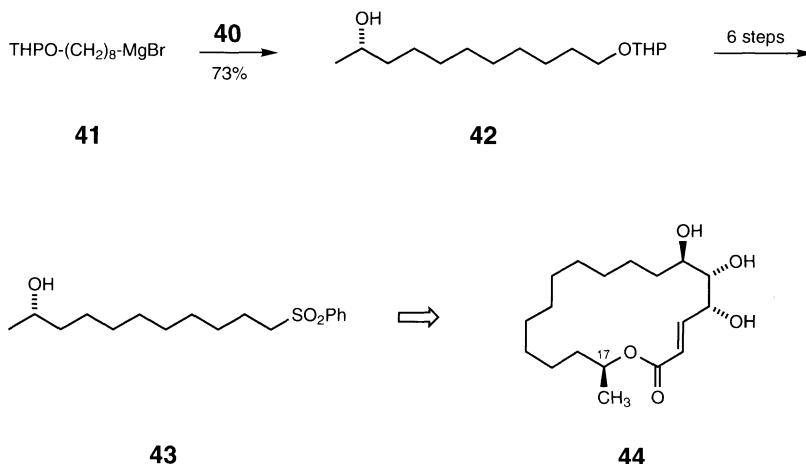
Scheme 3

conditions: (a) $\text{CH}_3\text{C}\equiv\text{CCH}_2\text{OC}(=\text{NH})\text{CCl}_3$, H^+ ; (b) DIBAL (82%); (c) *n*-PrPPh₃Br, *n*-BuLi, -78 °C (98%); (d) *n*-BuLi, -78 °C (75%); (e) H_2 (95%); (f) KH, 18-crown-6

**Scheme 4**

conditions: (a) O₃, CH₂Cl₂, -60 °C, 30 min.; (b) Zn, HOAc, CH₂Cl₂, -10 °C, 30 min.; (c) SOCl₂, pyridine, 0 °C, 30 min., (98%); (d) Ph₃P, CHCl₃, (45%); (e) NaOH, acetone; (f) ClCOEt, N-methylmorpholine; (g) CH₂N₂; (h) NaOAc, (87%); (i) toluene, hydroquinone, reflux; (j) rhodium(II) acetate, EtOAc, 60 °C

**Scheme 5**



Scheme 6

gives **49** (after selective benzylation). Ten additional steps are required to complete the synthesis of brefeldin A.

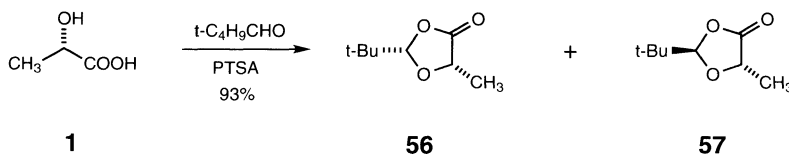
The volatile component of the mandibular secretion of *Andrena haemorrhoa F.* contains 2,7-dimethyl-1,6-dioxaspiro[4.6]undecane. All four thermodynamically stable stereoisomers of the spiro acetal pheromone have been prepared using the two enantiomers of ethyl lactate (which supplies the 2-methyl substituent *via* butyrolactone **51**) and the two enantiomers of 3-hydroxybutanoate (which supplies the 7-methyl *via* iodide **52**). Scheme 8 shows the synthesis of the (2*S*, 5*S*, 7*R*)-isomer **55**. The overall yield in the sequence is 9%, and the purity of the final product is 97% [18].

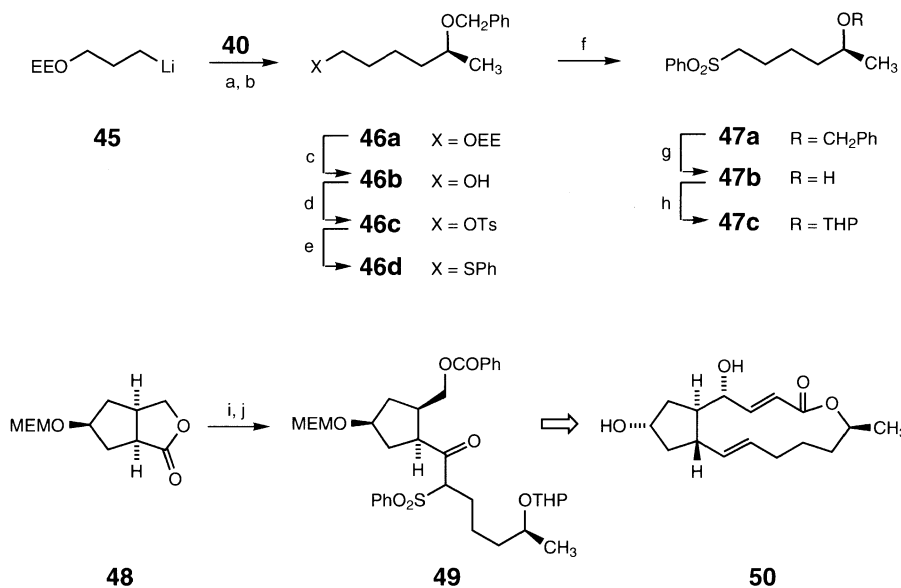
1.1.1 α -Alkylation of Lactic Acid

Alkylation of lactates is not possible directly, since any enolate formation would destroy the chirality at the asymmetric center. This can be circumvented without use of a chiral auxiliary by employing the “self-reproduction of chirality” approach of Seebach, which incorporates lactic acid into a dioxolane ring and takes advantage of the bulky R group at the newly formed stereo center at C-2 to direct alkylation to the C-5 carbon.

The 1,3-dioxolanone is formed by treating **1** with pivaldehyde under acidic catalysis. This produces a 4 : 1 mixture of **56** and **57**. Pure **56** (96% *ds*) is obtained by two recrystallizations of the mixture from ether/pentane at -78°C [20,21].

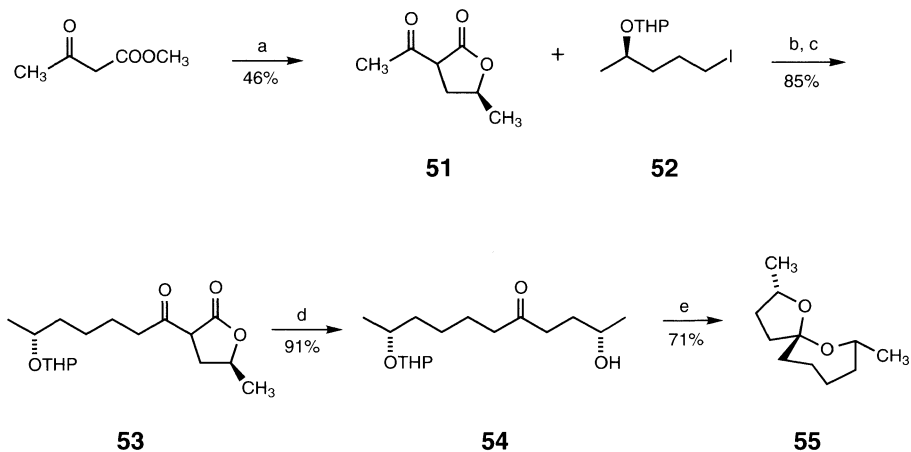
Deprotonation of **56** is accomplished with LDA, and alkylation with a primary alkyl, allyl, or benzyl bromide or iodide introduces a second substituent at C-5 (**58**) with diastereo-





Scheme 7

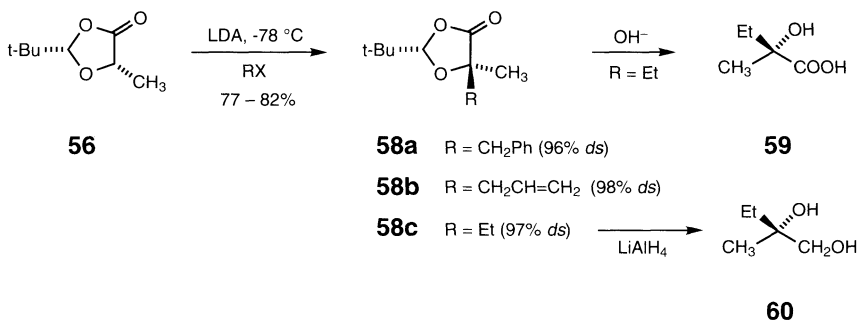
conditions: (a) THF, -30 °C; (b) PhCH₂Br; (c) H⁺, H₂O; (d) TsCl, pyridine; (e) PhSLi, THF, 25 °C; (f) MCPBA, CHCl₃, -10 °C; (g) H₂, Pd/C, MeOH; (h) DHP, H⁺; (i) **47c**, LiHMDS, -78 ° \rightarrow -20 °C; (j) PhCOCl, HOAc



Scheme 8

conditions: (a) **40**, NaOCH₃, 2 weeks [19]; (b) NaH, THF, phosphoric hexamethyltriamide; (c) *n*-BuLi; (d) KOH, H₂O; (e) PTSA, MgSO₄

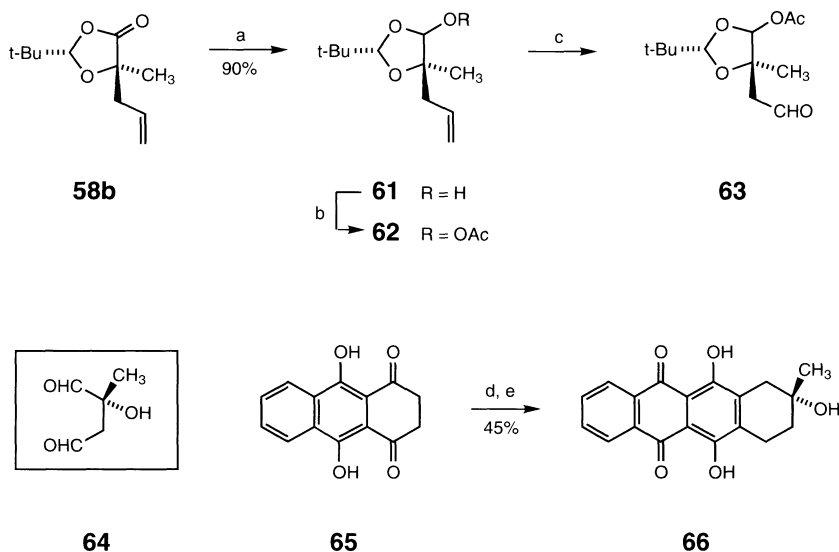
selectivity exceeding 95%. Alkaline hydrolysis regenerates the α -alkyllactic acid **59**, whereas reductive conditions produce (*R*)-(+)-2-methyl-1,3-butanediol (**60**) from **58c**.



The enolate of **56** is highly nucleophilic and shows little basicity. Aldehydes as well as acetone, cyclopentanone, and acetophenone react readily to generate adducts in high yield.

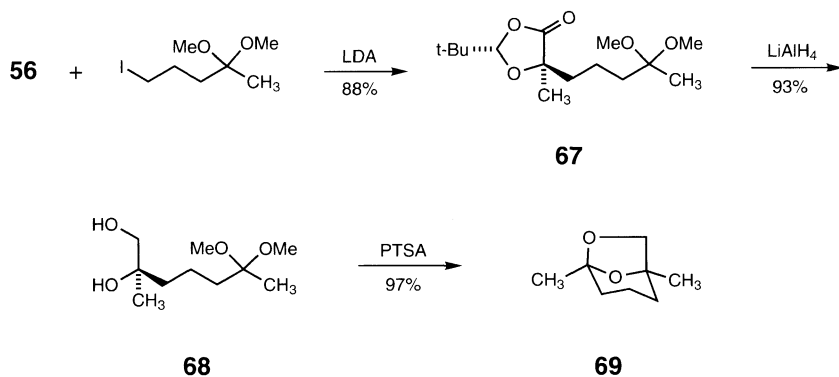
Dioxolanone **58c**, when reduced to lactol **61**, is a masked 1,4-dialdehyde (**64**) equivalent. The aldehyde, which is “freed” by ozonolysis and acidic hydrolysis, undergoes a Marschalk reaction with leucoquinizarine (**65**) to give rhodomycinone **66** in 45% yield [22] (Scheme 9).

Both enantiomers of frontaline, an aggregation pheromone of the Western pine beetle, have been synthesized using chiral dioxolanones derived from (*S*)- or (*R*)-lactic acid [23]. Alkylation of **56** with the dimethyl acetal of 5-iodo-2-pentanone affords trisubstituted dioxolanone **67** in high yield. Reductive cleavage of the hetero ring followed by acid-catalyzed *trans*-acetalization leads to (*R*)-(+)-frontalin (**69**) in 73% overall yield from (*S*)-(+)-lactic acid



Scheme 9

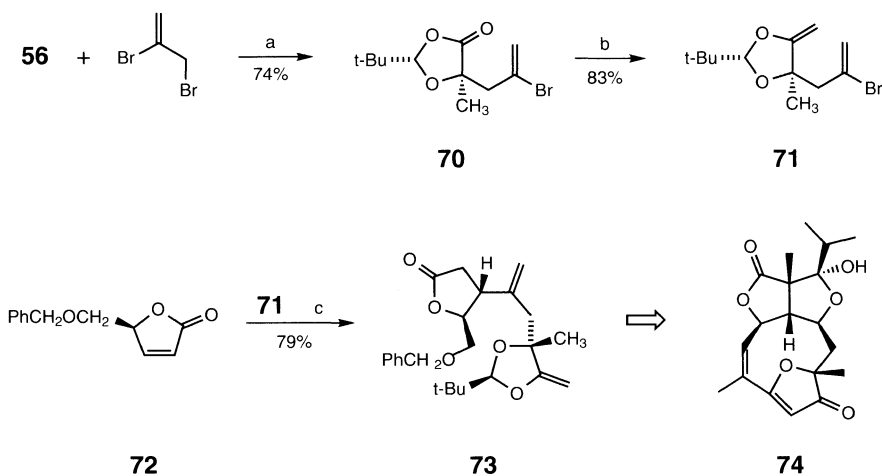
conditions: (a) DIBAL, THF, -78 °C; (b) Ac₂O, pyridine (96%); (c) O₃, MeOH, -78 °C, 20 min; (d) 1N HCl, 30 min; (e) **63**, 1N NaOH



Scheme 10

(Scheme 10). An analogous synthesis starting from (*R*)-(-)-lactic acid produces (*S*)-(-)-frontalin.

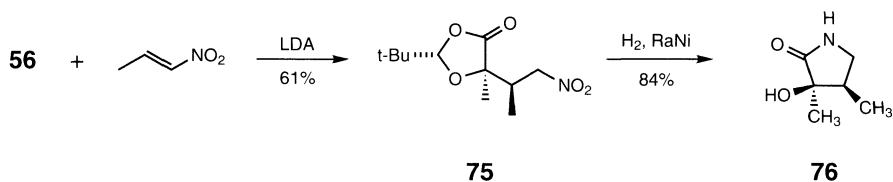
(+)-Eremantholide A (**74**), a member of the furanoheliangolides, has been synthesized in 21 steps starting from **56** [24]. The early part of the synthesis is outlined in Scheme 11. Alkylation of **56** with 2,3-dibromopropene affords the (2*S*, 4*R*)-dioxolanone **70** (> 98% *de*) and reaction with Tebbe reagent produces **71**. The bromide is converted to a mixed cuprate, and the organometallic is added in a 1,4-fashion to butenolide **72**, which is derived from D-mannitol.



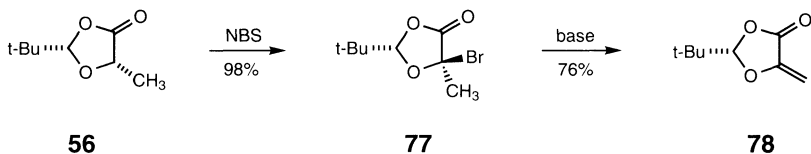
Scheme 11

conditions: (a) LDA, -78 °C; (b) $\text{Cp}_2\text{TiCl}_2\text{-Al}(\text{CH}_3)_3$; (c) *t*-BuLi, ether, then cuprous *n*-pentane

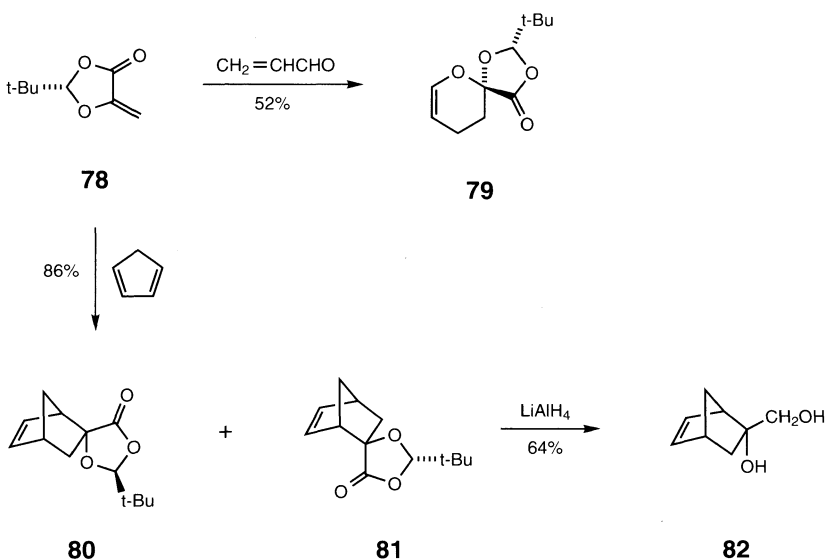
Michael addition of the enolate of **56** to (*E*)-1-nitropropene gives adduct **75** with a diastereoselectivity of 93%. Catalytic hydrogenation of the nitro group over Raney nickel at 25 atm produces lactam **76** as a result of elimination of pivaldehyde [25].



Bromination of **56** with NBS in refluxing CCl_4 gives **77** (96% *ds*) as a single isomer in near-quantitative yield [26]. Dehydrohalogenation with either DBU [27] or triethylamine results in the formation of **78** in good yield.



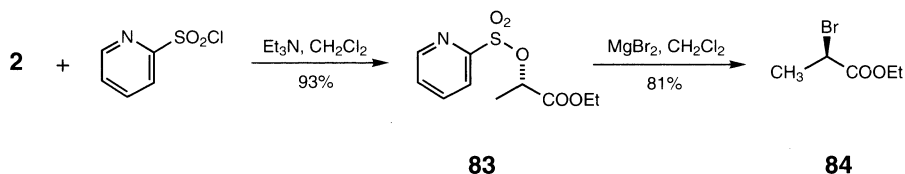
Compound **78** behaves as an excellent dienophile in the Diels–Alder reaction (Scheme 12). Reaction of **78** with acrolein at $70\text{ }^\circ\text{C}$ for 4 days produces the hetero adduct **79** in 52% yield [28]. Treatment with cyclopentadiene at room temperature for 3 days leads to a 96 : 4 mixture of *exo*-**80** and *endo*-**81**, with an *ee* of 90% for **80**. Considering that the optical purity of **78** is 96%, this translates into a selectivity 95% for the Diels–Alder reaction. Treatment of the mixture with LiAlH_4 produces a 96.5 : 3.5 mixture of *exo/endo*-hydroxymethylnorbornene which, after recrystallization, furnishes pure (1*R*, 2*R*)-2-hydroxybicyclo[2.2.1]hept-5-ene-2-methanol (**82**). The use of Lewis acid catalysis [$\text{TiCl}_2(\text{O-}i\text{-iso-Pr})_2$] and low temperature ($-20\text{ }^\circ\text{C}$) in the cycloaddition reaction increases the *endo/exo* selectivity, but also decreases both the π -face selectivity and the yield.



Scheme 12

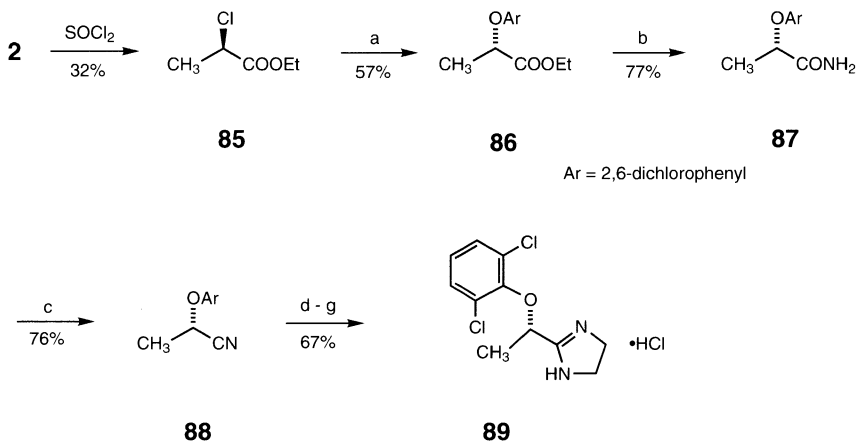
1.2 Inversion Reactions

The stereo center of lactic acid and its derivatives can be inverted with a variety of reagents and nucleophiles with minimal loss of optical integrity. The hydroxyl group of ethyl L-(–)-lactate (**2**) can be converted to a 2-pyridylsulfonate (**83**) upon treatment with 2-pyridinesulfonyl chloride. Displacement of the sulfonate with magnesium bromide occurs within 10 min at 0 °C to furnish ethyl (*R*)-2-bromopropionate (**84**) [29]. Reaction of the 2-pyridylsulfonate group occurs much more rapidly than that of the corresponding arylsulfonate due to the proximity of the nitrogen atom to the reacting site. This allows coordination of the magnesium bromide with the nitrogen lone pair, thereby placing the nucleophile in a favorable location near the reactive carbon.



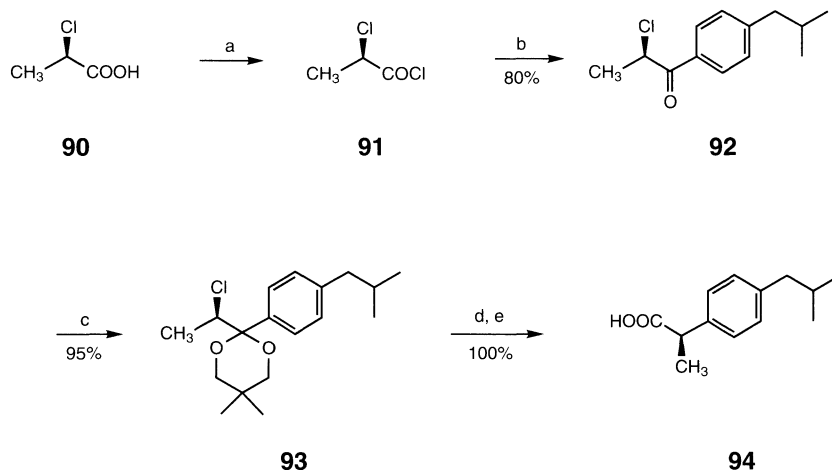
Ethyl lactate can also be converted to (*R*)-(+)-ethyl 2-chloropropionate (**85**) by treating it neat with thionyl chloride and a catalytic amount of DMF. By a series of manipulations, shown in Scheme 13, **85** is converted in 7 steps to (–)-Lofexidine (**89**) [30], a stereoselective α_2 -adrenoceptor agonist used in the treatment of hypertension. This synthesis takes advantage of two consecutive inversion reactions (**2** \rightarrow **85** \rightarrow **86**) to produce the desired stereochemistry in the final product.

Optically pure (*R*)-2-chloropropionic acid (**90**) is available by diazotization of L-alanine in 6N HCl [31]. Using the corresponding acid chloride **91** as an acylating agent, Friedel–Crafts reaction with isobutylbenzene produces aryl ketone **92** with an enantiomeric purity of 85%.



Scheme 13

conditions: (a) potassium 2,6-dichlorophenolate, 2-butanone; (b) NH_3 , EtOH; (c) TiCl_4 , N-methylmorpholine, CHCl_3 ; (d) HCl, EtOH; (e) EtOH, 20 min; (f) ethylenediamine; (g) HCl

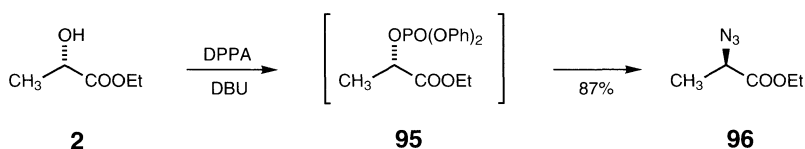


Scheme 14

conditions: (a) $(\text{COCl})_2$; (b) isobutylbenzene, AlCl_3 ; (c) 2,2-dimethyl-1,3-propanediol, PTSA; (d) ZnCl_2 , toluene; (e) 37% HCl

Repeated crystallization from methanol raises the optical purity to 98%. Rearrangement of acetal **93** with zinc chloride followed by ester hydrolysis furnishes (*R*)-ibuprofen (**94**) (82% optical purity) [32] (Scheme 14).

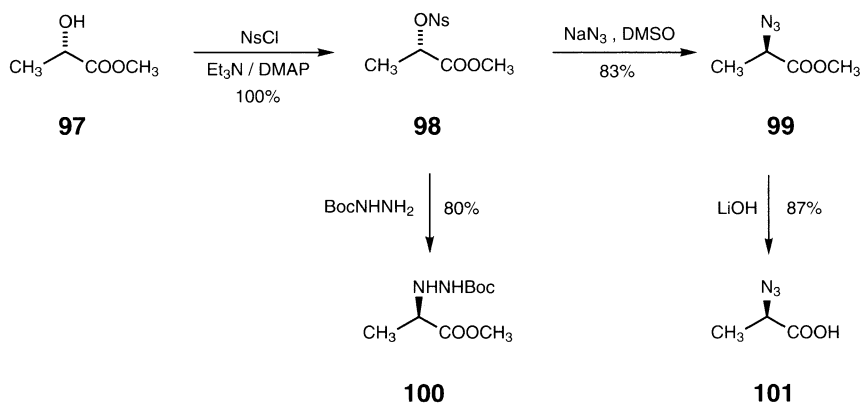
The scarcity of unnatural D-amino acids makes these compounds attractive synthetic targets, especially when one considers the disparity of price relative to their naturally occurring partners. If the hydroxyl group of an L-lactate could be displaced by a nitrogen nucleophile with inversion of configuration, this would allow easy access to D-alanine derivatives. Such a transformation can be realized by the reaction of **2** with diphenyl phosphorylazide and DBU to produce the (*R*)-azidoester **96** (98% *ee*) [33]. The initial step of the reaction is the formation of phosphonate **95**. The resulting liberated azide then completely displaces the phosphonate group, with nearly total inversion of the stereo center.



2-Nosyloxyesters undergo substitution reactions with inversion of configuration (Scheme 15). The corresponding nosyl lactate **98** is prepared in quantitative yield from **97** upon treatment with 4-nitrobenzenesulfonyl chloride in the presence of triethylamine and DMAP [34]. Reaction of **98** with sodium azide in DMSO (55 °C) gives the (*R*)-azidoester **99**. Hydrolysis of the ester with lithium hydroxide in aqueous THF furnishes the azido acid **101** (92% *ee*). Reduction of the azide group is easily accomplished either under catalytic conditions or with triphenylphosphine and water.

Alternatively, displacement of the nosyloxy group of **98** with *tert*-butylcarbazate provides access to Boc-protected 2-hydrazinyl ester **100** [35]. The reaction conditions, which require

refluxing for 5 days in acetonitrile, lead to some erosion of chirality, giving a product with only 72% *ee*. The use of a triflate instead of the nosyloxy substituent allows the reaction to proceed at lower temperature and over a shorter time, affording **100** with an enantiomeric excess surpassing 95% (see Section 1.2.2.3).



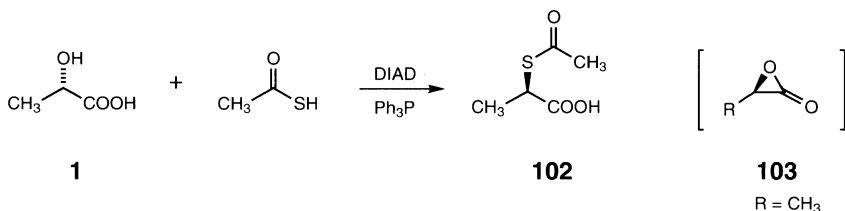
Scheme 15

1.2.1 Mitsunobu Reaction

Many strategies in organic synthesis involve inversion of a stereo center in order to reach the target molecule. In the era of modern chemistry, the most widely used reaction when alcohols are involved is the Mitsunobu reaction. In general, the hydroxyl function is activated with dialkyl azodicarboxylate/ Ph_3P reagent, after which reaction with a nucleophile occurs *via* an $\text{S}_{\text{N}}2$ mechanism with inversion of configuration.

1.2.1.1 Sulfur Nucleophiles

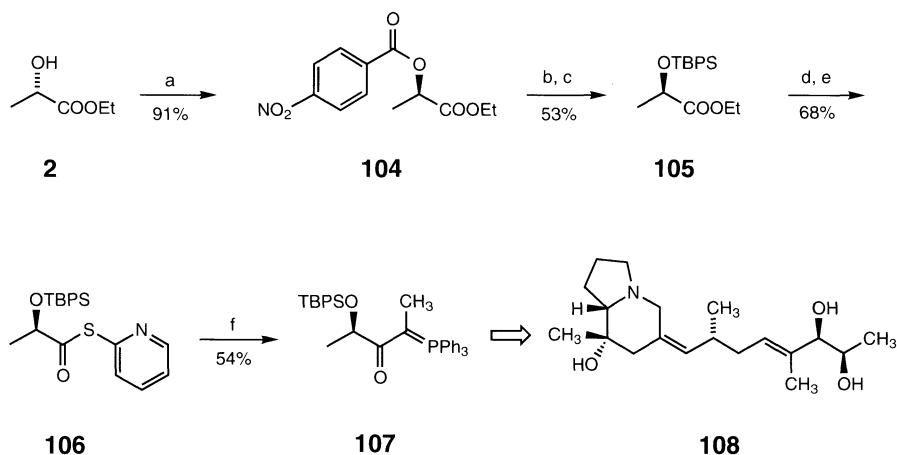
(*R*)-2-(Acetylthio)propionic acid (**102**) is obtained in 40% yield when a mixture of (*S*)-lactic acid and thioacetic acid is added to the preformed DIAD/ Ph_3P adduct in THF at 0 °C [36]. Unfortunately, the optical purity of the product is only 71%. The loss of optical integrity may be attributed to competitive formation of α -lactone **103** as a result of intramolecular $\text{S}_{\text{N}}2$ attack of the carboxyl on the activated hydroxyl. A second $\text{S}_{\text{N}}2$ reaction of thioacetic acid



with **103** results in a second inversion and formation of (*S*)-2-(acetylthio)propionic acid. Interestingly, in the case of mandelic acid, the reaction proceeds with 92.5% retention of configuration, which implies that the α -lactone route *via* **103** (R=Ph) may predominate.

1.2.1.2 Oxygen Nucleophiles

Inversion of the hydroxyl center with oxygen nucleophiles allows one to gain access to (*R*)-lactic acid derivatives. This strategy has been used to establish the correct stereochemistry in the alkylidene side chain of pumiliotoxin B (**108**) [37], a cardiac agent isolated from the Panamanian poison frog (Scheme 16). In the key reaction, conversion of **2** to (*R*)-*p*-nitrobenzoyl ester **104** proceeds in high yield and with essentially complete inversion of configuration.

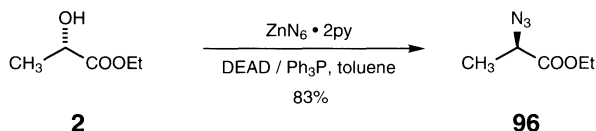


Scheme 16

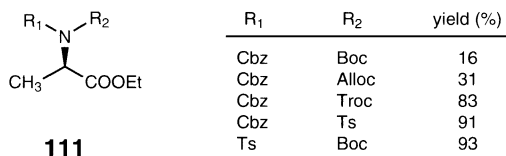
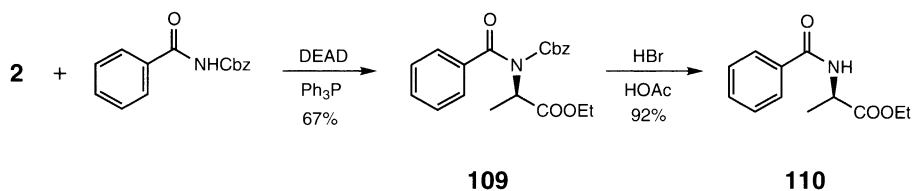
conditions: (a) DEAD, Ph_3P , 4-nitrobenzoic acid; (b) K_2CO_3 , EtOH, 15 min, rt; (c) *t*-butyldiphenylsilyl chloride, imidazole; (d) KOH, MeOH; (e) 2-pyridinethiol, DCC, rt, 9 h; (f) *s*-BuLi, ethyl triphenylphosphonium bromide

1.2.1.3 Nitrogen Nucleophiles

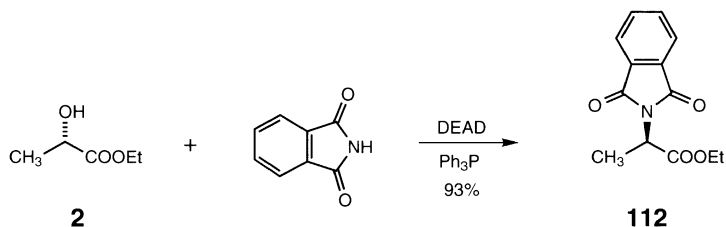
Zinc azide bis-pyridine complex (the more stable form of zinc azide) behaves as an excellent nucleophile in the Mitsunobu reaction and furnishes (*R*)-azidoester **96** in high yield with complete inversion at C-2 [38].



The reaction of ethyl L-lactate with *N*-benzyloxycarbonylbenzamide under Mitsunobu conditions produces **109** stereospecifically. Removal of the Cbz protecting group under acidic conditions gives (*R*)-(-)-*N*-benzoylalanine ethyl ester (**110**) [39]. A host of differentially *N,N*-diprotected (*R*)-alanines (**111**) can be prepared analogously by reaction of **2** with an imidodicarbonate or tosylcarbamate [40]. The enantiomeric excess in Mitsunobu products **111** exceed 95%.



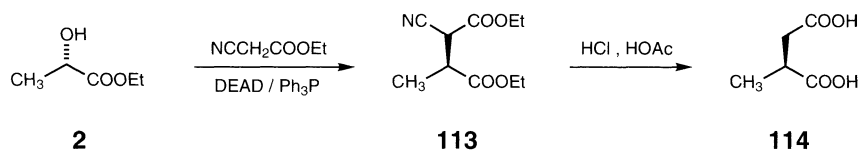
Lastly, phthaloyl-protected (*R*)-alanine **112** is formed in high yield by reaction of **2** with phthalimide [40]. Recently, polystyrene-supported methyl azodicarboxylate has been used as a replacement for the soluble dialkyl azodicarboxylates in the Mitsunobu reaction [41]. Yields generally are not as high as in the classical reaction (e.g., **2** → **112**, 45% yield), but, purification can be expedited simply by filtration of the nonexplosive resin.



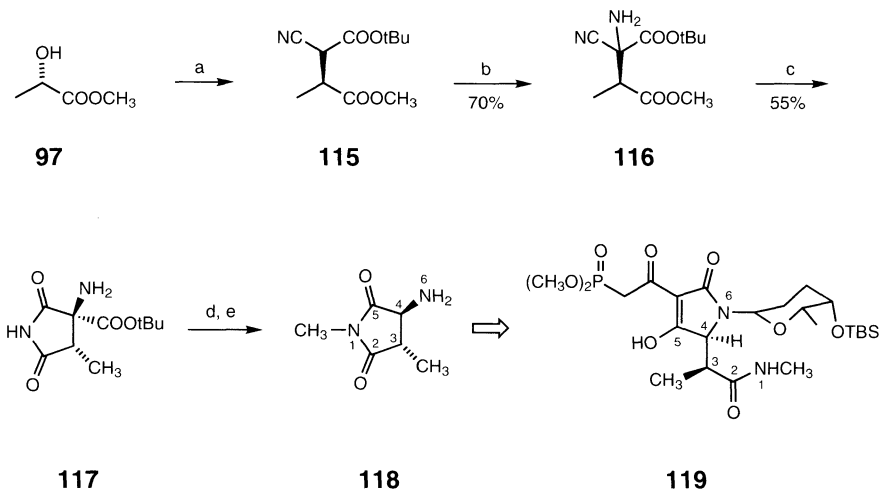
1.2.1.4 Carbon Nucleophiles

Active methylene groups undergo Mitsunobu reactions with alcohols. Thus, when ethyl cyanoacetate is reacted with ethyl L-lactate, diethyl 2-cyano-3-methylsuccinate (**113**) is formed in 61% yield [42]. Acidic hydrolysis furnishes (*S*)-(-)-methylsuccinic acid (**114**) in 29% yield with an optical purity of 99% [43].

A close analog, **115**, is critical in establishing the stereochemistry of the tetramic acid subunit (**119**) of streptolydigin [44]. Amination of **115** followed by nitrile hydration of **116**



under phase-transfer conditions produces optically pure imide **117**. N-Methylation and subsequent decarboxylation affords the aminoimide **118** as a 2:1 mixture of *trans* and *cis* (epimeric at C-4) isomers. This center is completely epimerized to the *trans* stereochemistry later in the synthesis.



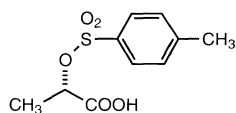
Scheme 17

conditions: (a) $\text{NCCH}_2\text{COOtBu}$, DEAD / Ph_3P ; (b) $\text{Ph}_2\text{P}(\text{O})\text{ONH}_2$, CH_3ONa , CH_3OH ; (c) H_2O_2 , NaOH , Bu_4NHSO_4 ; (d) CH_2N_2 (90%); (e) 1. CF_3COOH , 2. Al_2O_3 (87%)

1.2.2 O-Sulfonyl Lactates

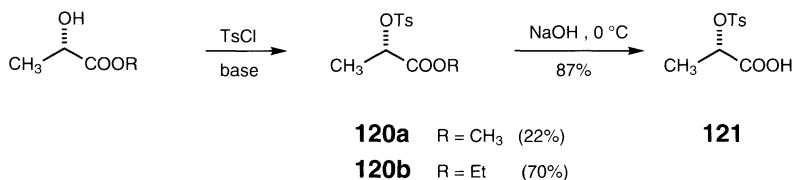
A more classical approach to inverting a hydroxyl-bearing stereo center involves converting it to a suitable leaving group (e.g., tosyl, mesyl, or triflate) so that it reacts with a nucleophile according to an $\text{S}_{\text{N}}2$ mechanism.

1.2.2.1 O-(*p*-Toluenesulfonyl) L-Lactic Acid Derivatives

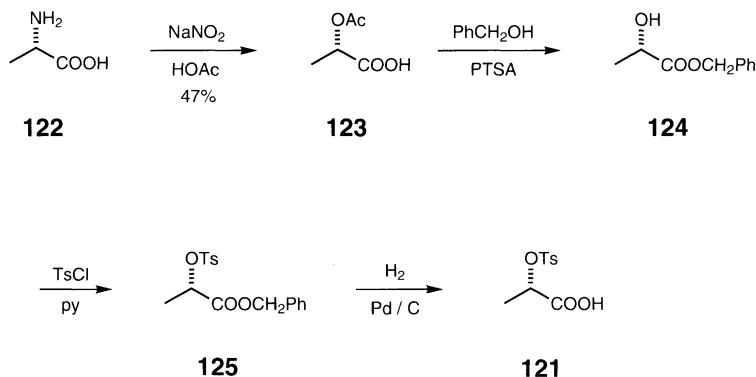


(*S*)-2-[[[4-Methylphenyl]sulfonyl]oxy]propanoic Acid

Tosyl lactates **120** are readily prepared by treating the corresponding L-lactic acid ester with *p*-toluenesulfonyl chloride in the presence of either pyridine [45] or triethylamine [30]. Ethyl ester **120b** has been prepared on a multi-kilogram scale in nearly 97% yield [46]. Careful hydrolysis of the ester furnishes (*S*)-(–)-2-tosyloxypionic acid **121**.



A more circuitous route to **121** utilizes L-alanine (**122**) as the chiral source [47] (Scheme 18). In the first step, nitrous acid deamination of **122** in acetic acid produces (*S*)-(–)-acetoxypionic acid (**123**) with greater than 96% retention of configuration [48]. The acid **121** is obtained in 55% overall yield from **123**.



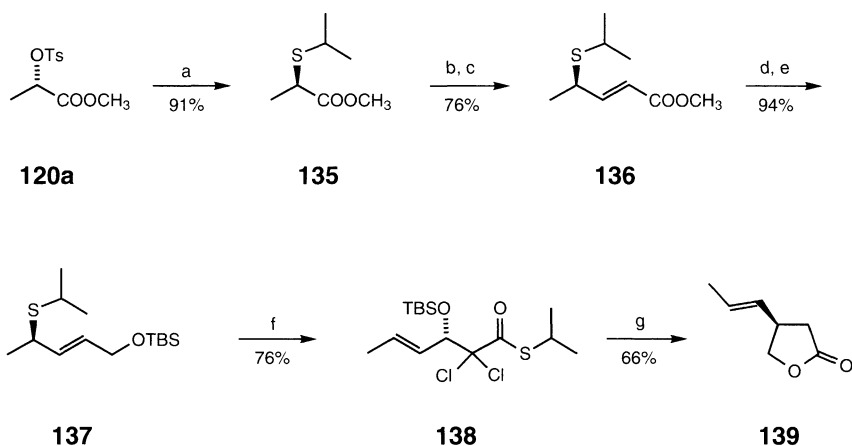
Scheme 18

Acid **121** can be converted to acid chloride **126** with either thionyl chloride [46] or oxalyl chloride [49]. Friedel–Crafts acylation on *m*-difluorobenzene with **126** gives the (*R*)-chloro-ketone **127** (97% *ee*) in 80% overall yield from **121**. Epoxidation of **127** affords **128** with >95% diastereoselectivity. Reaction of the epoxide with triazole furnishes *trans*-epoxide (2*S*, 3*S*)-**129**, an isomer of an important intermediate for the preparation of a class of triazole antifungal agents (Scheme 19).

Lithium di-*n*-butylcuprate reacts with **121** to produce (*S*)-(+)–2-methylhexanoic acid (**130**) with 98% inversion of the stereo center. Similarly, lithium diphenylcuprate gives (*S*)-(+)–2-phenylpropionic acid (**131**) with 95% inversion. Yields for this process are generally low, however [47].

Reduction of tosyl lactate **120b** with sodium borodeuteride at 100 °C (48 h) in the absence of any solvent furnishes deuteriopropionate **132** [50].

Displacement of the tosyl function of **120a** with potassium thiolacetate in boiling acetone produces (*R*)-2-acetylthiopropionic acid methyl ester (**133**) with an optical purity of 92% [45]. Alternately, **133** may be obtained with higher optical purity from an identical reaction with

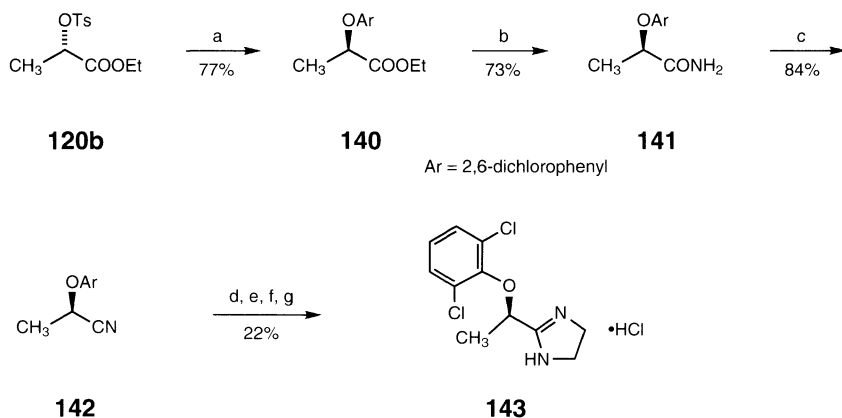


Scheme 20

conditions: (a) *i*-PrSH, CH₃CN; (b) DIBAL, CH₂Cl₂, -78 °C, 90 min; (c) Ph₃PCHCOOCH₃, -78 ° → rt; (d) DIBAL, 0 °C, 50 min; (e) TBS-Cl, imidazole, DMF, 16 h; (f) Zn / Cu, ether, reflux 3-4 h, Cl₃CCOCl; (g) Zn, HOAc, 100 °C, 2-3 h

84%. An intermolecular Claisen rearrangement of **137** gives **138** with a chirality transfer of at least 98%. Attempted dehalogenation of **138** affords butyrolactone **139**.

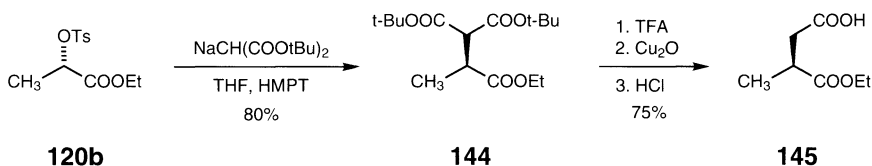
(+)-Lofexidine (**143**), a weakly active α_2 -adrenoceptor agonist, has been synthesized in 8 steps starting from ethyl L-lactate according to the route shown in Scheme 21 [30]. The key reaction in the synthesis is that of tosylate **120b** with 2,6-dichlorophenol. The transformation occurs with nearly complete inversion of configuration. The cardiovascular activity of **143** is approximately one-tenth that of the corresponding (–)-enantiomer **89**.



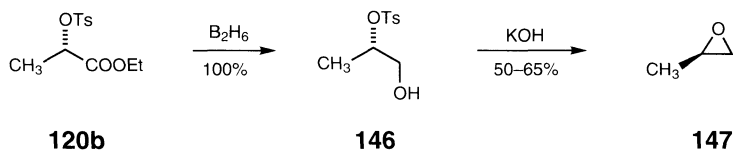
Scheme 21

conditions: (a) potassium 2,6-dichlorophenolate, 2-butanone; (b) NH₄OH, EtOH; (c) TiCl₄, N-methylmorpholine, CHCl₃; (d) HCl (gas), EtOH; (e) EtOH, 20 min; (f) ethylenediamine; (g) HCl

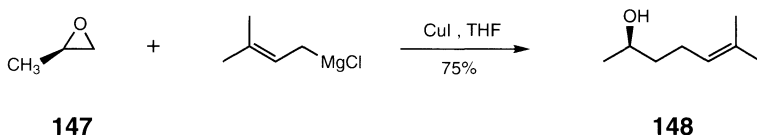
The asymmetric center of **120b** can be inverted with carbon nucleophiles, as demonstrated by the synthesis of 1-ethyl (*S*)-(-)-2-methylsuccinate (**145**) [52]. The reaction of **120b** with sodium di-*tert*-butylmalonate gives triester **144** with total inversion of configuration. Hydrolysis and decarboxylation furnishes the monoacid **145** (99% *ee*) in 54% overall yield from ethyl L-lactate.



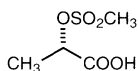
(*R*)-(+)-Methyloxirane, a useful chiral intermediate, has been employed in the synthesis of a variety of natural products. It is readily prepared in multi-gram quantities from ethyl L-lactate *via* tosylate **120b** [53,54]. Reduction of the ester proceeds quantitatively with diborane over a period of 5 days to afford (*S*)-(+)-propane-1,2-diol 2-tosylate (**146**). Cyclization with KOH gives epoxide **147** with 97% inversion of configuration.



Reaction of **147** with the mixed cuprate of 3-methyl-2-butene gives, in one step, (*R*)-(-)-sulcatol (**148**) the enantiomer of an aggregation pheromone of a wood-boring ambrosia beetle [53]. Oxirane **147** has also been instrumental in the synthesis of (2*S*, 5*R*)-2-methyl-5-hexanolide (**151**), one of the antipodes of the sex pheromone of the carpenter bee [54] (Scheme 22) and the macrolide fungal metabolite (*R*)-recifeiolide (**155**) [55] (Scheme 23).

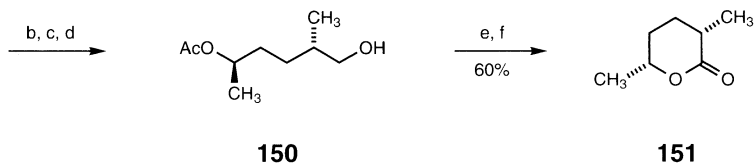
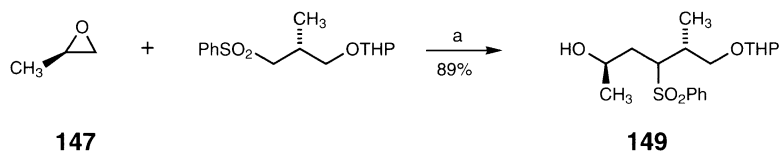
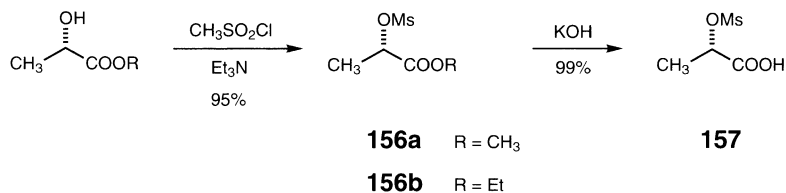


1.2.2.2 O-(Methanesulfonyl) L-Lactic Acid Derivatives

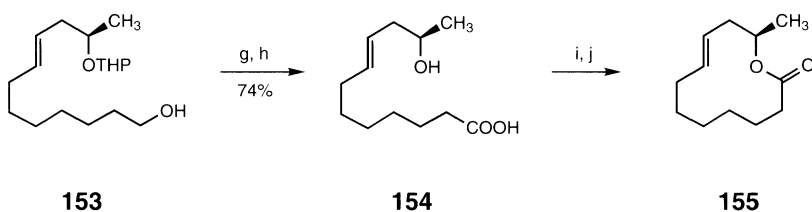
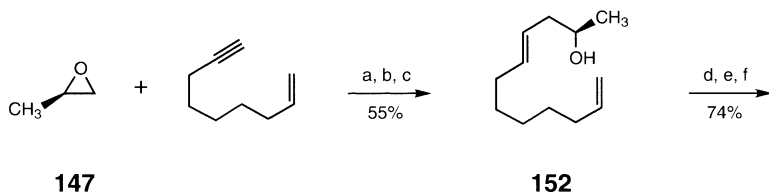


(*S*)-2-[[[(Methyl)sulfonyl]oxy]propanoic Acid

Mesy lactates **156** are readily prepared by treating the corresponding L-lactic acid esters with methanesulfonyl chloride in the presence of triethylamine [56,57]. Hydrolysis of the carboxylate ester furnishes (*S*)-(-)-2-mesyloxypropionic acid (**157**) [46,58].

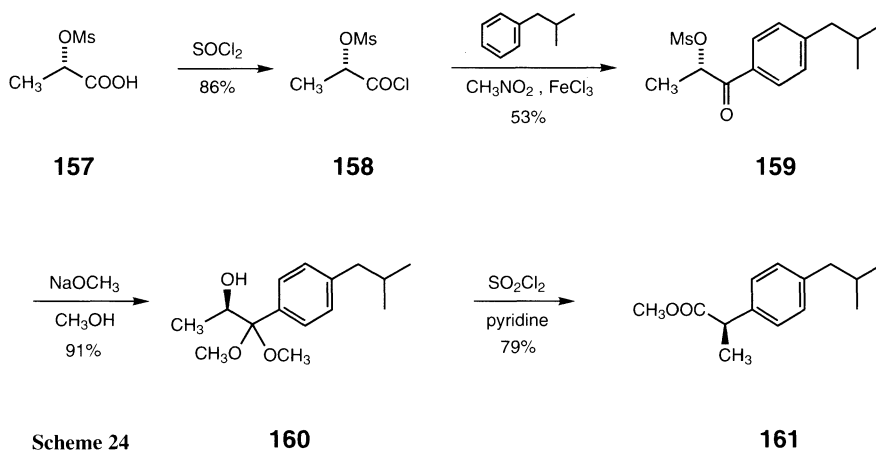
**Scheme 22**

conditions: (a) *n*-BuLi, -78 °C → rt; (b) Na / Hg, EtOH (91%); (c) Ac₂O, DMAP (73%); (d) PTSA, MeOH (82%); (e) Jones oxidation; (f) K₂CO₃, MeOH, then 1N HCl

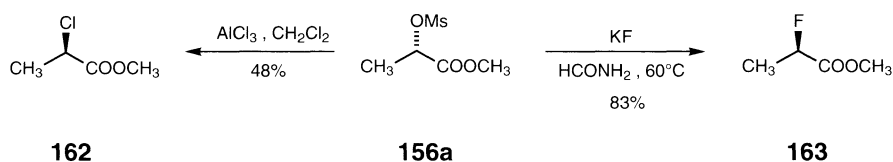
**Scheme 23**

conditions: (a) DIBAL, 0 °C, 30 min; (b) *n*-BuLi, rt, 30 min; (c) **147**, rt, 24 h; (d) DHP; (e) bis(1,2-dimethylpropyl)borane; (f) H₂O₂, NaOH; (g) NCS-Me₂S, Et₃N; (h) Ag₂O; (i) (2-py-S)₂, Ph₃P; (j) AgBF₄

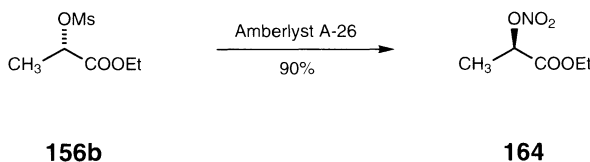
Compound **157** has been used in a short synthesis of (*R*)-ibuprofen methyl ester (**161**) [58] (Scheme 24). Acetalization of optically pure aryl ketone **159** under basic conditions produces hydroxy acetal **160** (74% *ee*), where the configuration at the asymmetric carbon is inverted. Treatment of **160** with sulfuryl chloride in pyridine at $-50\text{ }^{\circ}\text{C}$ causes facile 1,2-aryl migration and affords the target molecule **161** stereospecifically.



(*R*)-2-Halopropionic acid derivatives are readily accessible from lactic acid *via* its mesylate. Thus, treatment of **156a** with AlCl_3 affords methyl (*R*)-2-chloropropionate (**162**) with 88% *ee* [59]. Reaction of **156a** with KF in formamide produces methyl (*R*)-2-fluoropropionate (**163**) (96% *ee*). The use of formamide as solvent not only increases the reaction rate but also favors $\text{S}_{\text{N}}2$ reaction due to its high polarizability. The $t_{1/2}$ is approximately 30 min, and reaction is complete in 3 h [57]. (*R*)-2-Fluoropropionic acid is prepared from **163** by transesterification with formic acid. Amberlyst A-26 (F^-) can be used as an alternate fluoride source in the conversion of mesyl lactates to chiral α -fluoroesters. This polymer-supported reagent produces clean $\text{S}_{\text{N}}2$ reactions [60].

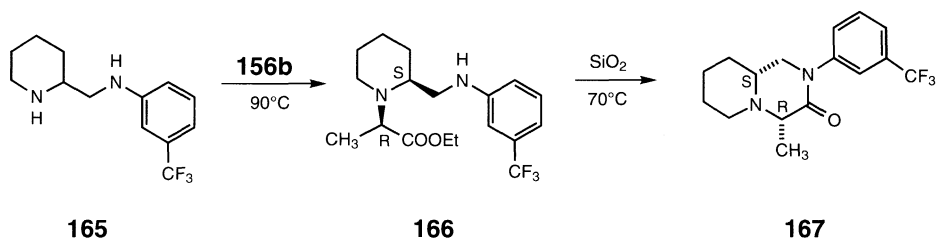


(*R*)-Nitroester **164** is produced in high yield by displacement of the mesylate **156b** with the nitrate form of the ion-exchange resin Amberlyst A-26 [61]. The resin is prepared by washing the chloride form with aqueous potassium nitrate solution. The enantiomeric excess of the

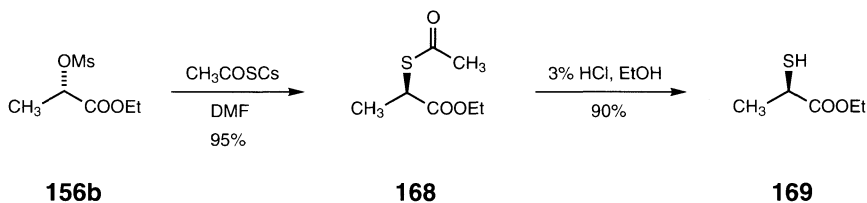


product **164** is 78%. The partial racemization can be explained by S_N2 displacement of the nitroester group by nitrate anion, which is in excess during the reaction.

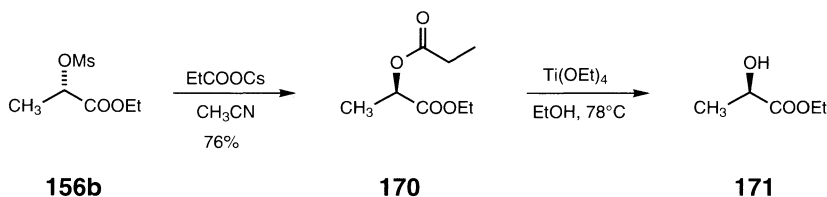
2-Aryloctahydro-2*H*-pyrido[1,2-*a*]pyrazine, a class of psychotropic drugs, can be synthesized in optically active form using **156b** as the chiral source [62]. Heating a mixture of **156b** with **165** for 16 h produces a 1:1 mixture of (*R*, *S*)-**166** and its *R,R*-isomer. Silica gel chromatography causes the *R*, *S*-isomer to cyclize to the desired product **167**. On a large scale, cyclization can be induced by treating the mixture with 10 weights of silica gel prior to chromatography. The optical antipode of **167**, where the 4-methyl group has the *S*-configuration, can be prepared using ethyl (*R*)-2-bromopropionate (**84**) in place of **156b**.



The cesium salt of thioacetic acid undergoes clean S_N2 substitution with **156b** to afford (*R*)-2-acetylthiopropionic acid ethyl ester (**168**) in nearly quantitative yield and with 100% *ee* [63]. Acid hydrolysis furnishes ethyl (*R*)-2-mercaptopropionate (**169**) (92% *ee*).

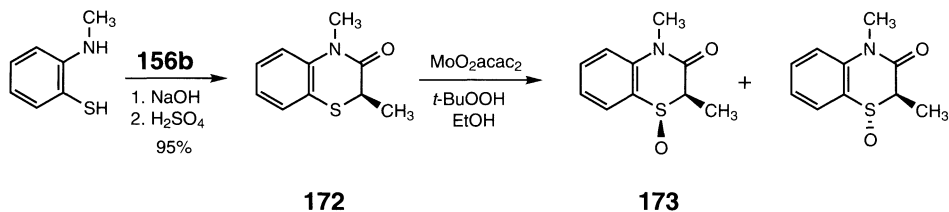


The properties of cesium salts can be taken advantage of to convert (*S*)-ethyl lactate to its *R*-enantiomer without racemization [63]. Treatment of mesylate **156b** with cesium propionate gives (*R*)-(acyloxy)propionate (**170**) in good yield [72]. Titanium-mediated transesterification of the (*S*)-enantiomer of **170** under essentially neutral conditions has been reported to give ethyl L-lactate (60% yield) with no racemization [64]. Application of this methodology to (*R*)-**170** should give ethyl D-lactate (**171**).

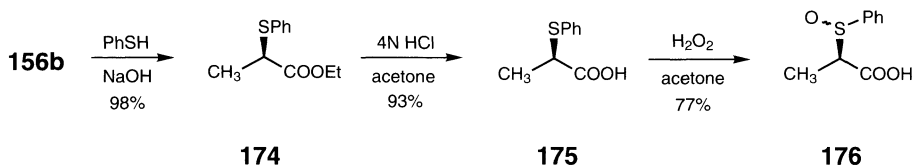


Reaction of *o*-methylaminothiophenol with **156b** in the presence of base at 0 °C for 1.5 h and then at room temperature for 2 days furnishes benzothiazinone **172** in nearly quantitative

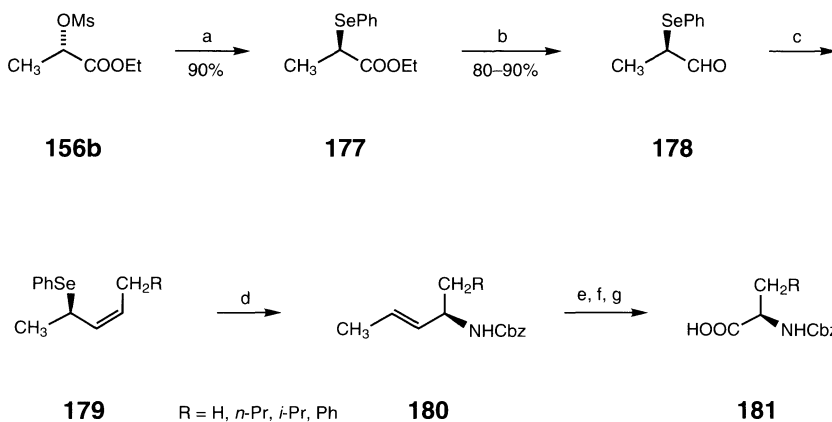
yield. Oxidation of the sulfur produces a mixture of diastereomeric sulfoxides, *cis*-**173** isolated in 36% yield, and the corresponding *trans*-isomer isolated in 6% yield [65].



Analogously, treatment of **156b** with thiophenol affords ethyl (*R*)-2-(phenylthio)propionate (**174**). Acidic hydrolysis gives (*R*)-2-(phenylthio)propionic acid (**175**). In this case, oxidation of the sulfur produces a near statistical mixture of diastereomeric sulfoxides **176**, which can be separated by fractional crystallization.



If selenophenol is used in place of thiophenol, ethyl (*R*)-2-(phenylseleno)propionate (**177**) is formed also in high yield. Partial reduction of the ester to aldehyde affords (*R*)-2-(phenylseleno)propanal (**178**) with 90–98% *ee*. This intermediate has been used for the synthesis of a variety of Cbz-protected D-amino acids [66] (Scheme 25).

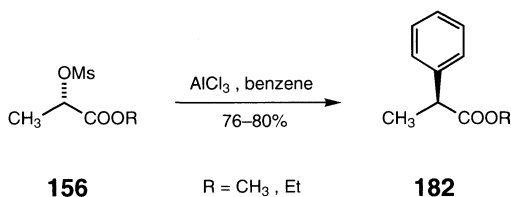


Scheme 25

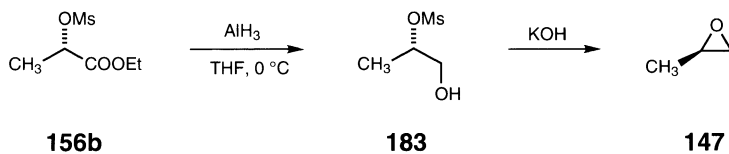
conditions: (a) PhSeNa, EtOH, H₂O; (b) DIBAL, CH₂Cl₂ / hexane (3:1), -78 °C; (c) RCH₂CH=PPh₃, toluene, -78 °C; (d) NCS, Cbz-NH₂, pyridine, MeOH, 0 °C; (e) O₃, CH₂Cl₂, -78 °C; (f) Me₂S; (g) CrO₃, H₂SO₄

(*Z*)-Allylic selenides **179** are formed in 58–69% yield under Wittig conditions using salt-free alkylidene triphenylphosphorane. *N*-Chlorosuccinimide/carbamate-promoted [2,3]-sigmatropic rearrangement affords allylic amines **180** in 45–64% yield. The olefin is transformed to an acid by conversion to an aldehyde followed by Jones oxidation. The resulting *D*-amino acids **181** are produced in 58–72% yield with enantiomeric excess values of 78–84%.

Friedel–Crafts alkylation of benzene with mesyl lactates under nonracemizing reaction conditions affords methyl or ethyl (*S*)-2-phenylpropionate (**182**) in high chemical yield and 97% optical yield [67,68]. The excellent stereoselectivity results from the ability of the Lewis acid to form a complex with **156** prior to the back-side attack of benzene with net inversion of configuration. Analogous reaction with isobutylbenzene produces a mixture of regioisomeric products from which (*S*)-ibuprofen is isolated.



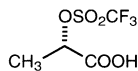
In an improved preparation of (*R*)-(+)-methyloxirane (**147**), the ester group of **156b** is reduced with AlH_3 within 30 minutes to give (*S*)-2-(mesyloxy)-1-propanol (**183**). Cyclization with potassium hydroxide furnishes the desired epoxide in 72% overall yield from **156b** and 71% overall yield from ethyl *L*-lactate [69].



7-Ethyl-2-methyl-1,6-dioxaspiro[4.5]decane is a pheromone produced by two varieties of bees, *Parvespula vulgaris* L. and *Andrena haemorrhoa* F. The *2R, 5R, 7R*-isomer (**188**) has been synthesized using **147**, ultimately derived from ethyl *L*-lactate, to supply the chiral stereocenter at C-2 (Scheme 26) [19]. The second chiral intermediate **185** is derived from (*S*)-(–)-malic acid.

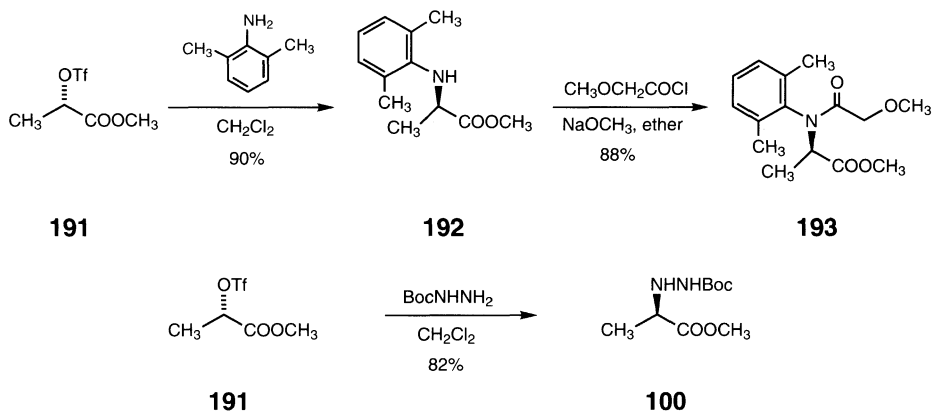
The overall yield in the sequence is 42.6% starting from **184**, and the optical purity of the final product is 96%. The remaining three possible stereoisomers of **188** have been prepared using (*S*)-methyloxirane, also available from ethyl *L*-lactate (see Section 1.4.4), and the enantiomer of **185**, available from (*S*)-malic acid.

1.2.2.3 O-(Trifluoromethanesulfonyl) L-Lactic Acid Derivatives



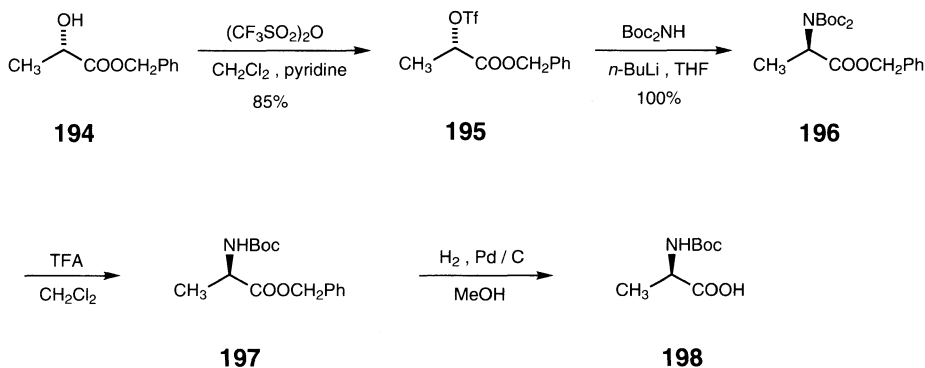
(*S*)-2-[[Trifluoromethyl)sulfonyl]oxy]propanoic Acid

The enhanced leaving ability of the triflate group allows $\text{S}_{\text{N}}2$ substitution reactions to occur at lower temperatures and over shorter periods of time relative to other leaving groups. When



The benign reaction conditions used in the $\text{S}_{\text{N}}2$ reaction of triflates allows one to gain access to synthetically useful quantities of (*R*)-*N*-Boc alanine (**198**) [40] (Scheme 27). In the inversion step, the reaction of **195** with di-*tert*-butylimidodicarbonate must be performed at -28°C in order to prevent racemization. Even at this temperature reaction is complete within two hours to give **196** with greater than 96% *ee*. In comparison, Mitsunobu reaction between various lactates and Boc_2NH gives negligible amounts of inversion products.

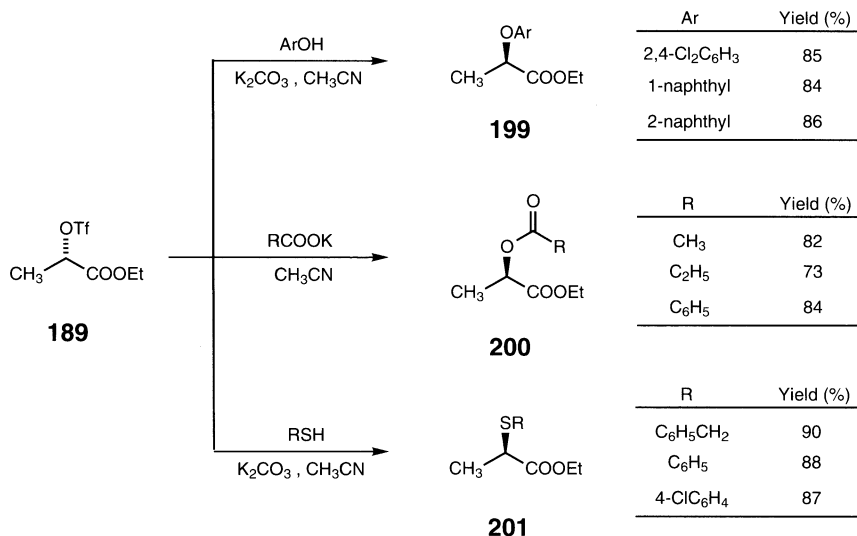
One Boc group is removed with trifluoroacetic acid, after which the benzyl ester is hydrogenolyzed to the desired acid **198** in 83% overall yield from **195**. This process is amenable to ^{15}N -labelling.



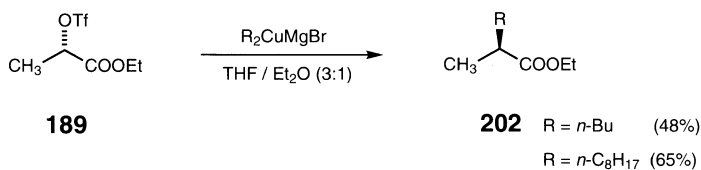
Scheme 27

Other nucleophiles react with equal facility with **189** [72] (Scheme 28). Phenols furnish (*R*)-2-aryloxypropanoates (**199**) in high yield. Even protected sugar derivatives displace the triflate group to afford muramic acid analogs [73]. Potassium salts of alkyl or aryl carboxylic acids produce (*R*)-lactates (**200**) and mercaptans give (*R*)-thiolactates (**201**) [72].

Magnesiocuprates react with lactate derivative **189** to give the corresponding (*S*)-2-methylalkanoic acids (**202**) in moderate yield, however, optical yields are quite impressive, with enantiomeric excesses ranging from 95 to 99% [74]. This is superior to reactions with corresponding tosylates or mesylates where highly competitive reduction or elimination processes predominate.



Scheme 28



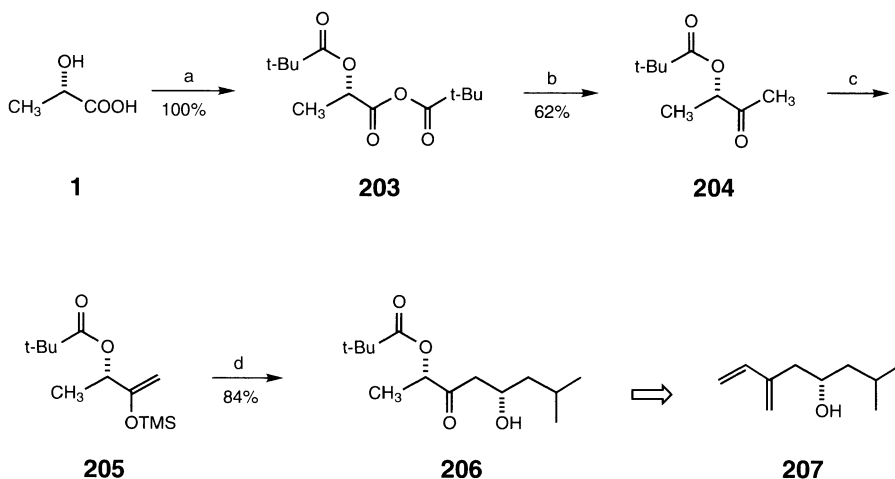
1.3 O-Acyl Lactates

The presence of an acyl group on the oxygen of lactic acid derivatives allows chemical manipulations to be performed that would otherwise not be feasible with the corresponding unsubstituted analogs. In addition, the functional groups may be used as synthetic “handles” for further transformations. O-Acetyl lactates are covered as a separate topic in Section 1.4.1.

An example of this strategic approach is a six step synthesis of (*S*)-(-)-ipenol (**207**), a constituent of the sex pheromone of the bark beetle, which is outlined in Scheme 29 [75]. L-Lactic acid is activated through formation of mixed anhydride **203**, and subsequent addition of methylmagnesium bromide furnishes methyl ketone **204**. Aldol condensation of enol silyl ether **205** with isovaleraldehyde gives the adduct **206** (89% *ds*).

The synthesis is completed by Wittig olefination followed by hexakis(*tert*-butylisoni-trile)molybdenum-catalyzed elimination of the pivalate to give **207** in 21% overall yield for the six step sequence. The strategy in this synthesis takes advantage of the chirality of the lactic acid to control stereochemistry in the aldol condensation, and it also furnishes the “handle” to introduce the final unsaturation.

Acylation of (*S*)-ethyl lactate **2** with 2-bromopropionyl bromide gives acylated derivative **208**. Intramolecular Grignard reaction produces (*S*)-2,4-dimethyltetronic acid (**209**). Through

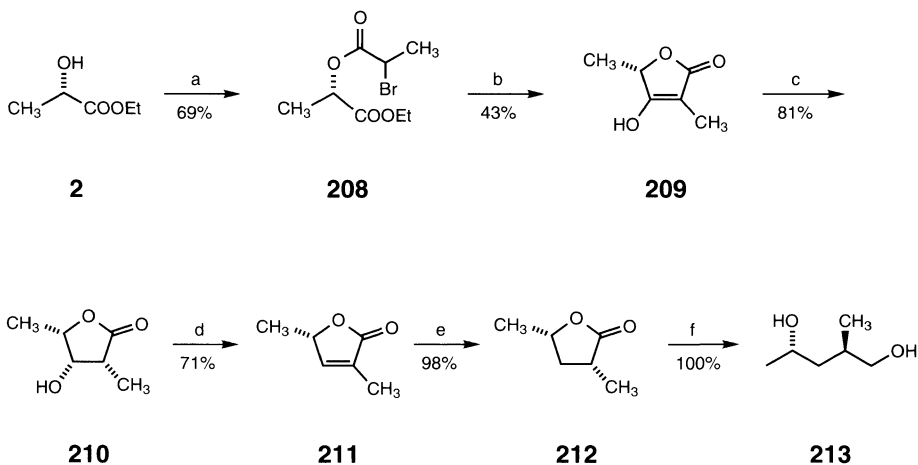


Scheme 29

conditions: (a) $t\text{-C}_4\text{H}_9\text{COCl}$, 2-picoline (2 eq), DMAP (10 mol%), ether, 0 °C; (b) CH_3MgBr , THF, -78 °C; (c) TMS-Tf, Et_3N , benzene; (d) isovaleraldehyde, TiCl_4

a series of reductions and dehydration, (2*R*, 4*S*)-1,4-dihydroxy-2-methylpentane (**213**), the C-5 to C-9 fragment of the polypropionate unit of geodiamolide and jaspamide, is formed [76] (Scheme 30).

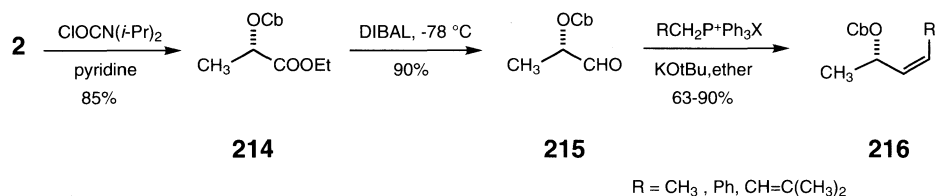
α -Lithiated derivatives of **216**, which are configurationally stable at -70 °C, are useful in asymmetric homoaldol reactions. These carbamates are readily accessible by acylation of **2** with *N,N*-diisopropylcarbamoyl chloride, conversion of the ester to aldehyde **215**, and Wittig olefination [77]. Alkenyl carbamates **216** are produced without racemization in high yield, and



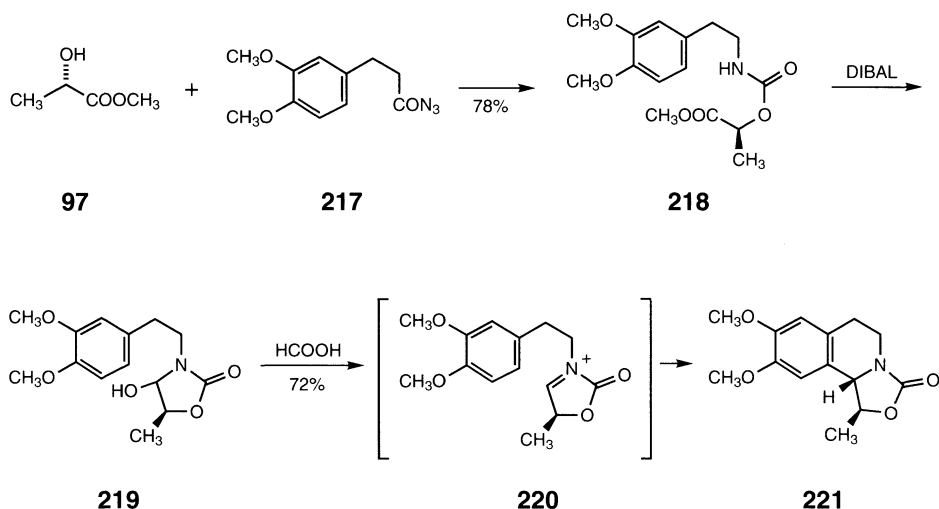
Scheme 30

conditions: (a) 2-bromopropionyl bromide; (b) Mg, THF, reflux 48 h; (c) H_2 , RaNi , 1300 psi, H_2O , 70 °C; (d) TsCl , Et_3N , DMAP; (e) H_2 , Pd / C, 45 psi, 1 h; (f) LiAlH_4 , ether, -78 °C \rightarrow rt

with *Z/E* ratios ranging from 89 : 11 to 47 : 53. The *E*-isomer can be enriched by treatment with 2.5 mol% of iodine. Pure isomers are readily isolated by chromatographic separation.



Chiral 1,2,3,4-tetrahydroisoquinolines are accessible from *O*-carbamyl lactates via *N*-oxaacyliminium cyclization (Scheme 31). The precursor for the generation of the chiral *N*-oxaacyliminium ion **220** is prepared by reaction of (*S*)-methyl lactate (**97**) with azide **217** followed by partial reduction of **218** with diisobutylaluminum hydride. Cyclization of **219** with formic acid at room temperature for 14 h gives the oxazolo[4,3-*a*]isoquinoline (**221**) without racemization [78]. Reductive cleavage of the oxazoline ring with lithium aluminum hydride furnishes the corresponding 1-hydroxyalkyl-1,2,3,4-tetrahydroisoquinoline in 98% yield.



Scheme 31

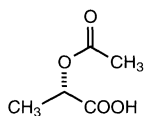
1.4 O-Protected Lactic Acid Derivatives

Protected lactates are extremely versatile intermediates in asymmetric synthesis. The wide variety of available protecting groups allows a host of deprotective reaction conditions to be used in a later stage of a synthesis. These can be acidic, basic, or neutral. Table 1.1 lists the protective groups mentioned in this section and some standard methods for their removal.

Table 1.1. Conditions for removal of protecting groups

Group	Conditions	Reference
OAc	1N NaOH, dioxane	48
	NaOEt, EtOH	84
	LiOH (1 eq.), THF, MeOH, H ₂ O	91
CH ₂ Ph	H ₂ , 5% Pd/C, MeOH	98, 175
	H ₂ , 10% Pd/, THF	150
	H ₂ , Pd(OH) ₂ , THF	159
	HCOONH ₄ , 10% Pd/C, acetone	218
BOM	H ₂ , Pd(OH) ₂	102
	H ₂ , 10% Pd/, MeOH	104
	Na/NH ₃ , -78 °C	105
	Li/NH ₃ , THF, aniline	186
	PhSH, BF ₃ ·Et ₂ O, CH ₂ Cl ₂	111
EE	PPTS, EtOH or MeOH	7, 112
	1M HCl, dioxane	114
	HCl (conc.), THF	108
	96% H ₂ SO ₄ , MeOH	107
	HOAc-H ₂ O-THF (3 : 1 : 1)	192
	Amberlyst-15, THF-H ₂ O	253
	catechol boron bromide, CH ₂ Cl ₂	118
MEM	1M HCl, 60 °C	7
	HCl (conc.), MeOH, 15 min	121
	PhSH, BF ₃ ·Et ₂ O, CH ₂ Cl ₂	200
MOM	PTSA, MeOH	207
	3M HCl, CH ₃ CN	127
	1N HCl, MeOH	204
	HOAc-THF-H ₂ O (3 : 1 : 1)	132
	CF ₃ COOH	135
	HF, CH ₃ CN	144, 167, 216
	Bu ₄ NF ⁻ , THF, 0 °	130
TBPS	CF ₃ COOH	135
	Bu ₄ NF ⁻ , THF, rt	136, 138
THP	12N HCl, MeOH	141
	0.1N H ₂ SO ₄ , acetone	186
	PPTS, MeOH	230
	PTSA, MeOH	255

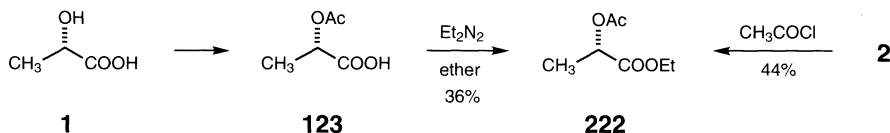
1.4.1 Acetyl



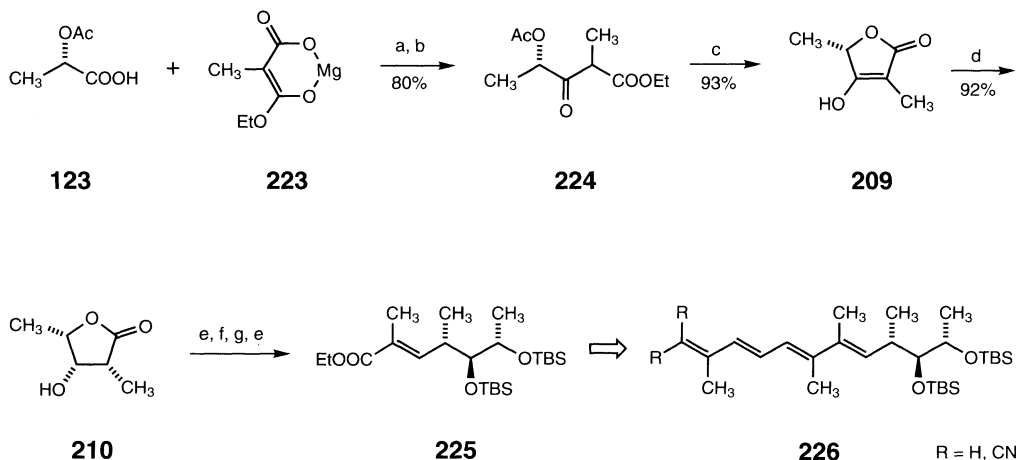
(S)-2-(Acetyloxy)propanoic Acid

L-2-Acetoxypropionic acid (**123**) is readily prepared by the acylation of L-lactic acid with either acetic acid/sulfuric acid in benzene (50% yield) [79] or with an excess of acetyl chloride (80% yield) [80]. One is not limited exclusively to the use of lactic acid as the starting material. Diazotization of L-alanine in acetic acid furnishes **123** in 47% yield with at least 96% retention of configuration [48].

Esterification of **123** with diazoethane furnishes ethyl (*S*)-2-acetoxypropionate (**222**). Alternatively, direct treatment of ethyl L-lactate (**2**) with acetyl chloride in benzene gives **222** in slightly higher yield [81].



Acid **123** has been used in the synthesis of the antipodal C1–C12 tetraene fragment **226** of calyculins isolated from a marine sponge [82] (Scheme 32). The synthesis begins by activating the carboxyl group of **123** with CDI and then coupling with the magnesium enolate of ethyl hydrogen malonate (**223**) to give β -ketoester **224**. Exposure to acid gives butenolide **209**. After catalytic hydrogenation to **210**, hydroxyl protection, partial reduction to lactol, and

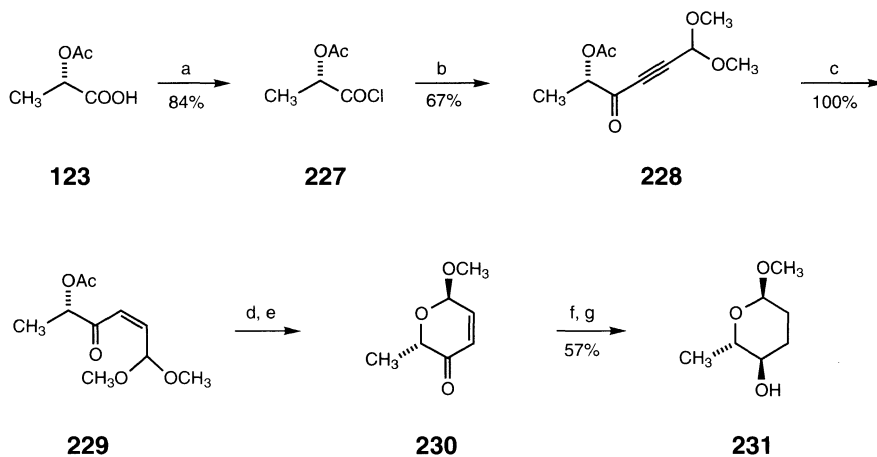


Scheme 32

conditions: (a) CDI, rt, 1 h; (b) THF / ether, rt, 62 h; (c) aq. HCl, MeOH, rt, 21h; (d) H₂, 5% Rh / Al₂O₃; (e) TBS-Cl, imidazole, DMF; (f) DIBAL, toluene, -78 °C, 15 min; (g) EtOOC(CH₃)=PPh₃, benzene, 100 °C

Wittig reaction affords intermediate **225**, which is elaborated to tetraene **226** in 7 steps. The natural stereochemistry can be obtained by beginning the synthesis with D-lactic acid.

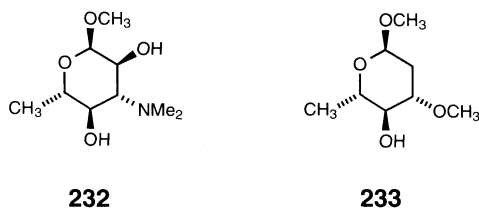
Treatment of **123** with thionyl chloride furnishes acid chloride **227** in high yield. By the route outlined in Scheme 33, a variety of 6-deoxy-L-hexoses can be prepared from common intermediate **230** [48]. This intermediate is obtained as an anomeric mixture (2 : 1 α/β), where the desired α -anomer is separated by column chromatography and recrystallization. Reduction of the olefin and ketone gives optically pure methyl α -L-amicetoside (**231**).



Scheme 33

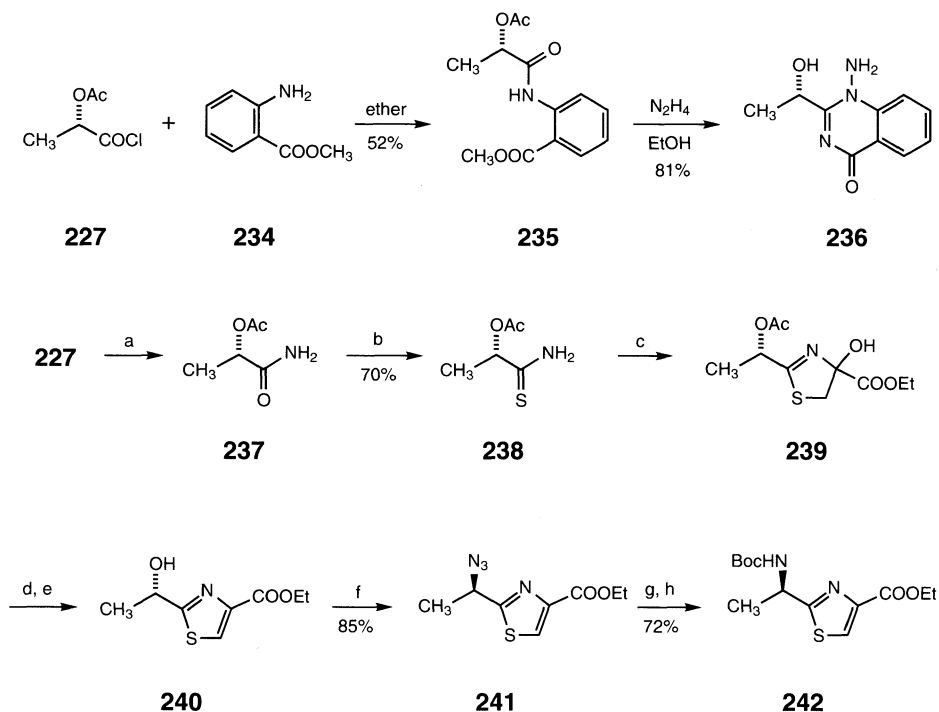
conditions: (a) SOCl₂; (b) propionaldehyde dimethyl acetal, EtMgBr, CuCl, THF; (c) H₂, Pd / BaSO₄, quinoline, EtOAc; (d) 1N NaOH, dioxane; (e) H₃PO₄, CCl₄; (f) H₂, 10% Pd / C, MeOH, 1 atm; (g) LiAlH₄, ether

Compound **230** can also be converted to the monosaccharides methyl α -L-mycaminoside (**232**) in three steps and methyl α -L-oleandroside (**233**) in four steps.



Acylation of methyl anthranilate (**234**) with **227** followed by cyclization with hydrazine gives *N*-aminoquinazolone **236**, which is closely related to the natural product chrysogine (des-amino **236**) [83].

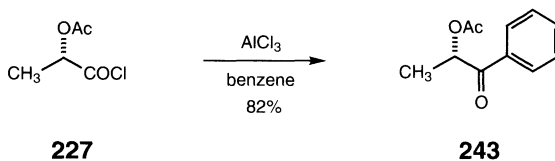
Optically active 2-(1-aminoalkyl)-thiazole-4-carboxylate (**242**), a precursor for the syntheses of dolastatin 3 isomers, is readily prepared from **227** according to the series of reactions outlined in Scheme 34 [84]. In the pivotal reaction, **238** \rightarrow **239**, it is crucial to use ethyloxirane as an additive in order to trap the liberated hydrobromic acid and thereby stop the reaction at the intermediate **239**. Dehydration with triflic anhydride forms optically pure thiazole **240**. Without ethyloxirane, thiazole **240** is produced directly from **238** with 40–60% *ee*.



Scheme 34

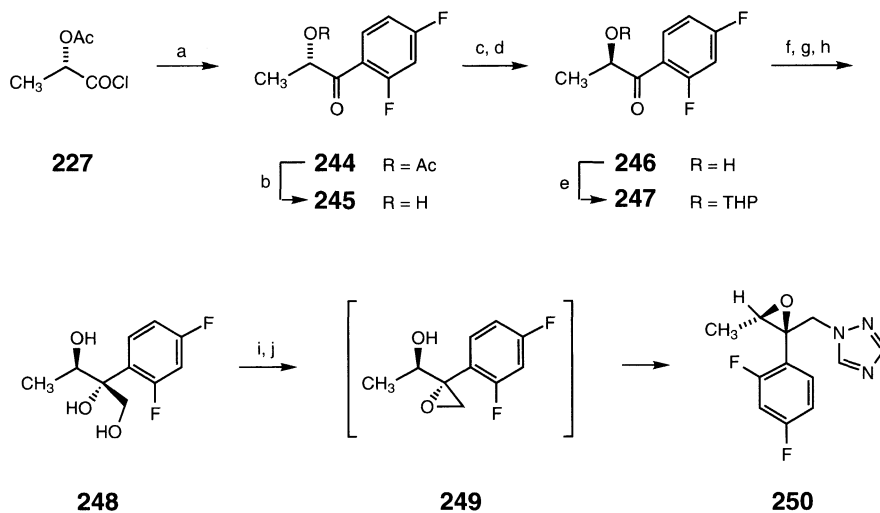
conditions: (a) NH_3 ; (b) Lawessons reagent, dioxane; (c) ethyl bromopyruvate, ethyloxirane, EtOH; (d) $(CF_3CO)_2O$, 0 °C (73%); (e) NaOEt, EtOH (92%); (f) DEAD, Ph_3P , HN_3 , toluene; (g) H_2 , Pd / C, EtOH; (h) Boc $_2O$, dioxane

Friedel–Crafts acylation of benzene with **227** affords **243** with an estimated *ee* of 88% [85].

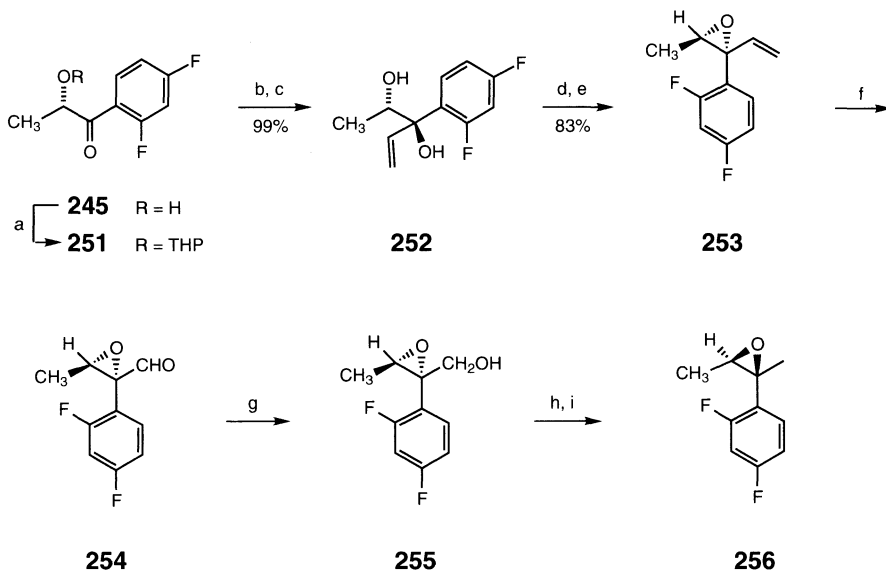


Analogous reaction of **227** with *m*-difluorobenzene gives a 1 : 1 mixture of **244** and **245** which, upon treatment with acid, gives pure **245** in 67% yield (> 99.5% *ee*) [86]. Inversion of the hydroxyl is accomplished by conversion to the tosylate followed by slow addition of lithium hydroxide at -15 °C. This gives (*R*)-**246** (94.5% *ee*), which has been carried on to triazolylmethyloxirane (2*S*, 3*S*)-**250**, an intermediate in the preparation of triazole antifungal agents (Scheme 35). If **245** is not inverted but carried through the same synthetic sequence *via* (*S*)-**251** (see Scheme 36), the enantiomeric epoxide (2*S*, 3*R*)-**256** is produced. The 2*S*, 3*S*-isomer **129** is discussed in Section 1.2.2.1.

Another approach to (2*S*, 3*R*)-**256** uses intermediate **245** and a Grignard reaction to introduce the necessary elements [87] (Scheme 36).

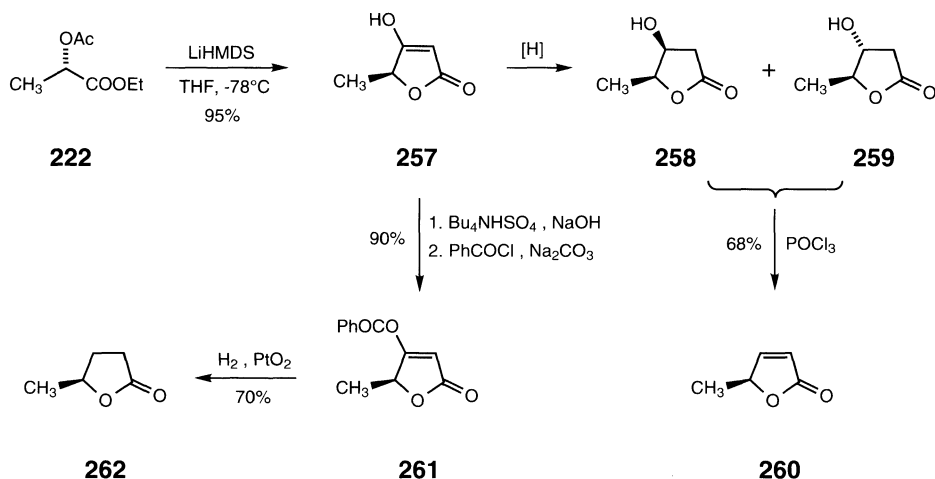
**Scheme 35**

conditions: (a) *m*-difluorobenzene, AlCl_3 ; (b) H_2SO_4 , MeOH; (c) *p*-toluenesulfonic anhydride, pyridine -10°C (76%); (d) LiOH, DMF, -15°C (73% yield, 94.5% ee); (e) DHP, PPTS, CH_2Cl_2 ; (f) (dimethylisopropoxysilyl)methylmagnesium chloride, ether; (g) NaHCO_3 , H_2O_2 , THF / MeOH; (h) PTSA, MeOH; (i) MsCl, pyridine (96%); (j) triazole, NaH, DMF

**Scheme 36**

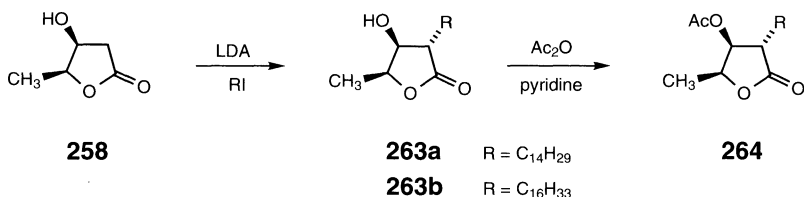
conditions: (a) DHP, PPTS, CH_2Cl_2 ; (b) vinylmagnesium bromide, THF; (c) H^+ ; (d) MsCl, pyridine; (e) NaH, DMF; (f) OsO_4 , NaIO_4 , MeOH- H_2O ; (g) NaBH_4 , MeOH (70% from **253**); (h) MsCl, Et_3N , CH_2Cl_2 ; (i) triazole, NaH, DMF

Various 2-furanone chiral building blocks are readily accessible from *O*-acetyl lactate derivative **222** according to the series of reactions outlined in Scheme 37. Deprotonation of **222** with 2–4 equivalents of LiHMDS gives (*S*)- γ -methyltetronic acid (**257**) in nearly quantitative yield [88]. Reduction of **257** with ammonia–borane affords a 25 : 75 mixture of **258** and **259**, whereas catalytic hydrogenation over rhodium/carbon produces an 85 : 15 mixture of **258** and **259** [89]. Dehydration of the mixture with phosphorus oxychloride furnishes the 5*S*-butenolide **260** [(+)-angelica lactone]. Dihydrofuranone **262** is made by benzoylation of the tetrabutylammonium salt of **257** followed by catalytic hydrogenation.

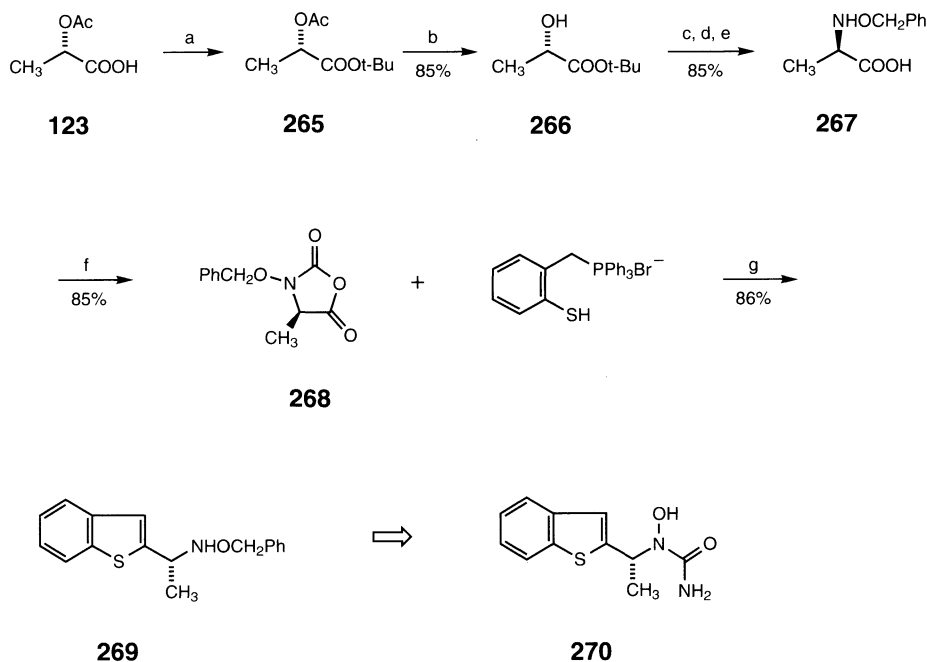


Scheme 37

The **258/259** mixture obtained by catalytic hydrogenation can be easily separated by column chromatography to afford pure **258** in 76% yield [90]. Alkylation of **258** with tetradecyl iodide or hexadecyl iodide gives the (3*S*, 4*S*, 5*S*)-dihydrofuranones **263** in 53% yield. Acetylation gives derivatives **264**, which are enantiomeric to lipid metabolites produced by the Gorgonian coral *Plexaura flava*.



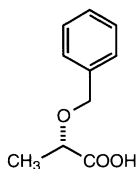
Zileuton, a potent and selective inhibitor of 5-lipoxygenase, can be prepared in optically active form on a laboratory scale using lactic acid as the chiral source [91] (Scheme 38). The key intermediate, *N*-carboxyanhydride **268** is formed in 6 steps from **123**, and has an optical purity greater than 98%.



Scheme 38

conditions: (a) 60% HClO₄, *t*-BuOAc; (b) LiOH, THF, MeOH, H₂O; (c) Tf₂O, 2,6-lutidine, CH₂Cl₂, 0 °C; (d) PhCH₂ONH₂, CH₂Cl₂; (e) CF₃COOH, CH₂Cl₂; (f) COCl₂, toluene, THF, 45 °C; (g) NaH, THF, DMF

1.4.2 Benzyl

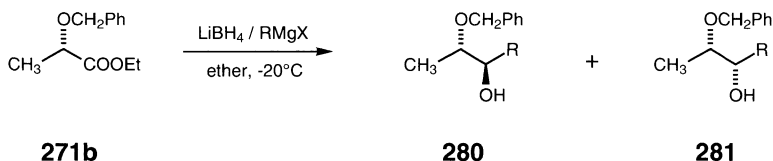


(S)-2-(Phenylmethoxy)propanoic Acid

Benzylation of lactic acid esters can be accomplished by two methods. Treatment of methyl or ethyl L-lactate with benzyl bromide and silver oxide provides the corresponding (S)-2-benzylxypropionates **271** with high optical purity [92,93]. Use of standard basic conditions (NaH, DMF) results in considerable racemization (50–75% *ee*).

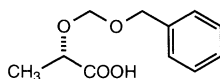
Alternately, ethyl L-lactate can be benzylated without racemization using benzyl trichloroacetimidate [94,95]; however, this reagent is rather expensive.

(S)-2-Benzylxypropanoic acid (**274**) is accessible in two steps *via* asymmetric alkylation of glycolic acid derivative **272**. Methylation of **272** proceeds in high yield to give **273** with 97% *de*. Other alkylating agents such as benzyl bromide, 1-iodobutane, 1-iodooctane, or isopropyl



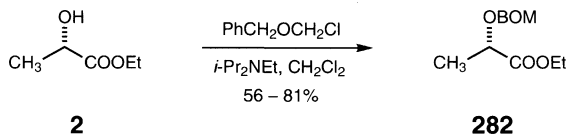
R	Yield (%)	ratio 280:281
CH ₃	87	6 : 1
Et	74	6 : 1
<i>i</i> -Pr	71	5.1 : 1

1.4.3 Benzyloxymethyl (BOM)

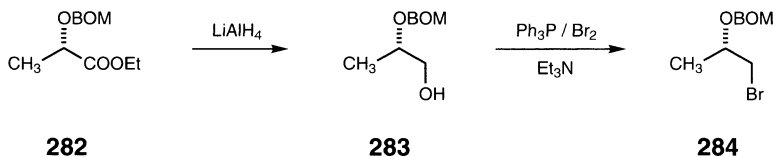


(*S*)-2-[(Phenylmethoxy)methoxy]propanoic Acid

Protection of ethyl L-lactate with a BOM group is readily accomplished with chloromethyl benzyl ether in the presence of Hunig's base [100,101].



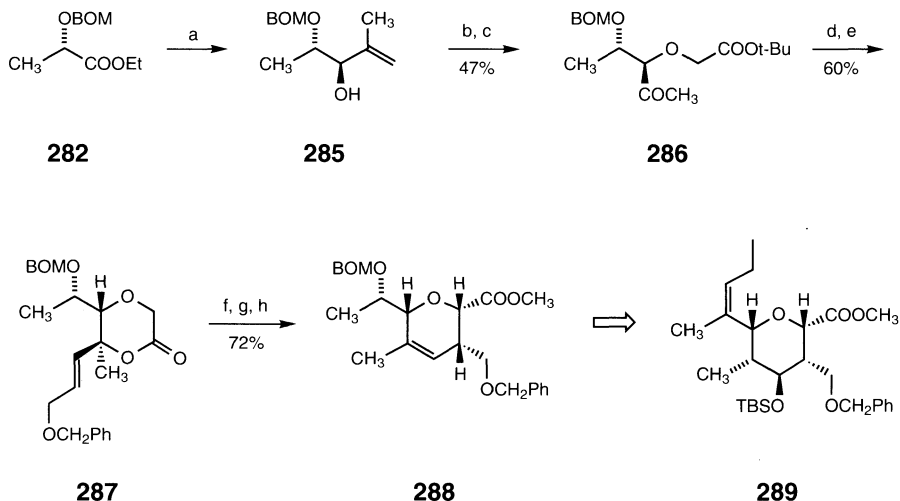
Reduction of the ester with lithium aluminum hydride furnishes alcohol **283**, which can easily be converted to bromide **284**. The overall yield from **2** → **284** is 66%. Removal of the protecting group is accomplished by hydrogenolysis ($\text{H}_2/\text{Pd}(\text{OH})_2$) [102].



Construction of the C-7 to C-13 subunit of erythronolide A and B aglycones proceeds through the highly functionalized tetrahydropyran **289**. The genesis of the stereochemistry associated with **289** is lactic acid. The *anti*-allylic alcohol **285** is formed from **282** in a single reaction using a mixture of 2-propenylmagnesium bromide and lithium borohydride [99]. Under the reaction conditions the lithium borohydride does not compete with the Grignard reagent for the ester, but after addition of the Grignard reagent to the ester the intermediate ketone is reduced preferentially by lithium borohydride rather than reacting further with

excess Grignard reagent. The high *anti*:*syn* selectivity (30:1 for **285**) can be explained by chelation-controlled addition of hydride to the intermediate ketone carbonyl.

In a second chelation-controlled addition, **286** is converted to **287** by addition of Grignard reagent to the acetyl carbonyl (80:1 diastereoselectivity) followed by lactonization. Dioxanone–dihydropyran Claisen rearrangement (**287** → **288**) establishes the desired carbon skeleton. It is ironic that the original (*S*)-lactate stereocenter, which was responsible for all the stereochemistry, is ultimately destroyed in **289**. An additional 11 steps is required to reach the target C-7 to C-13 fragment [103].



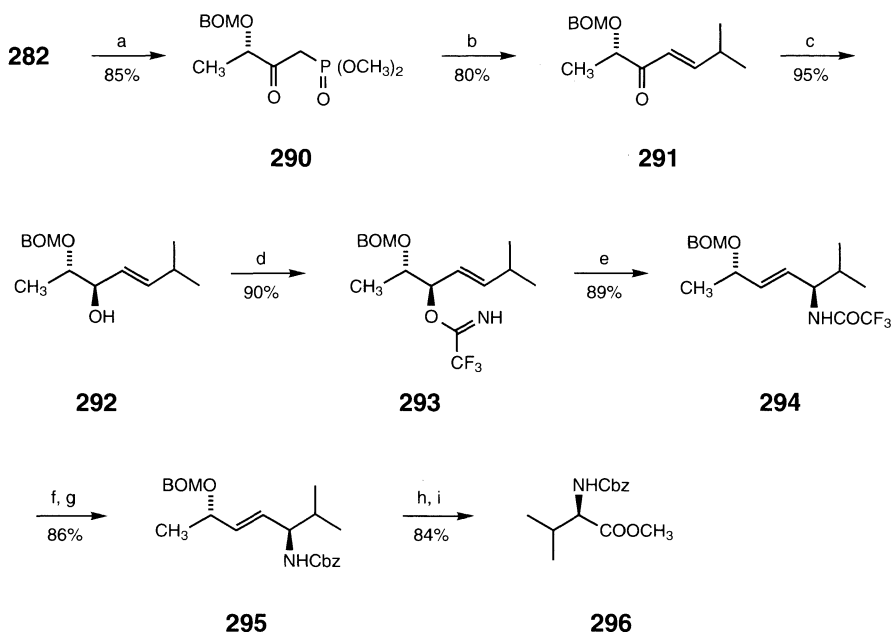
Scheme 39

conditions: (a) LiBH_4 , $\text{CH}_2=\text{C}(\text{CH}_3)\text{MgBr}$, THF, 0°C ; (b) $\text{BrCH}_2\text{COOt-Bu}$, benzene, 50% aq. NaOH, Bu_4NHSO_4 , 10°C ; (c) O_3 , CH_2Cl_2 , -78°C then Me_2S ; (d) (*E*)- $\text{PhCH}_2\text{OCH}_2\text{CH}=\text{CHMgBr}$, ether, -78°C ; (e) CF_3COOH , benzene; (f) LDA, THF, -78°C , TMS-Cl; (g) toluene, 110°C then 5% aq. HCl, CH_2Cl_2 ; (h) CH_2N_2 , ether, MeOH, -5°C

The synthesis of Cbz-protected D-valine methyl ester (**296**) (Scheme 40) begins with addition of an organometallic reagent to the ester function of **282**. The resulting phosphonate **290** undergoes a Wittig reaction with isobutyraldehyde to afford **291**. Chelation-controlled reduction of the ketone with zinc borohydride furnishes the *anti*-alcohol **292** (98% *de*). A [3,3] rearrangement of trifluoroacetimidate **293** produces allylic amine **294**. Elaboration of the olefin to an ester furnishes the D-valine derivative **296** with 85% *ee* [101].

A thiazole heterocycle is an effective synthetic equivalent of an aldehyde. Thus, it has been used in a concise synthesis of protected L-(–)-rhodnose (**302**), a subunit of the antibiotic streptolydigin (Scheme 41). Addition of 2-lithiothiazole to the ester group of **282** affords acylthiazole derivative **297**. Reduction of **297** to **298** with L-Selectride proceeds with high *syn* selectivity (93% *ds*) according to the non-chelation Felkin–Anh model for diastereoselection. Conversion of the thiazole to aldehyde (**299**) followed by introduction of another thiazole unit, this time through a Wittig reaction, furnishes **300**. Release of the aldehyde and removal of the BOM group gives the desired 4-OTBS-protected rhodnose **302** as a mixture of anomers [104].

In an effort to establish the configuration of the allylic diol functionality of pumiliotoxin B, Overman [105] synthesized *syn* and *anti*-diols **305** and **306** using lactic acid to set the

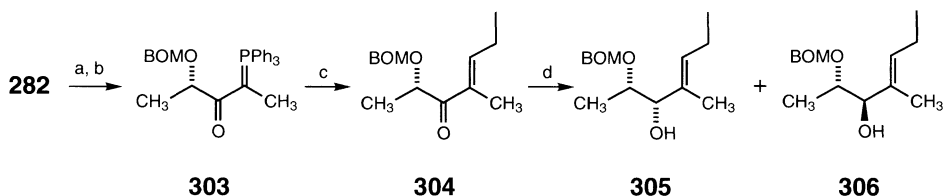


Scheme 40

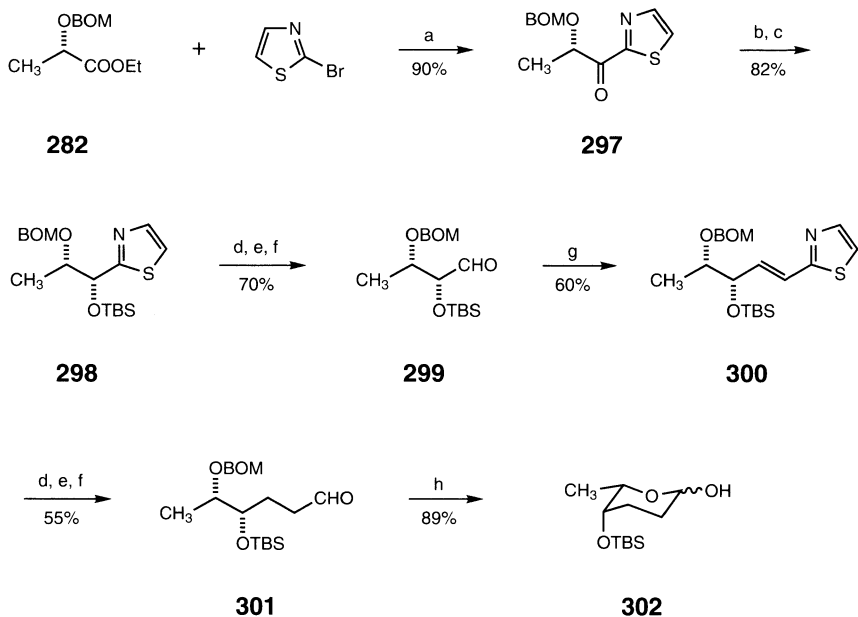
conditions: (a) $(\text{MeO})_2\text{P}(\text{O})\text{Me}$, *n*-BuLi; (b) *i*-PrCHO, LiCl, DBU, CH_3CN ; (c) $\text{Zn}(\text{BH}_4)_2$, ether, $-35\text{ }^\circ\text{C}$; (d) *n*-BuLi, CF_3CN ; (e) xylene, reflux; (f) $\text{Ba}(\text{OH})_2$, MeOH; (g) Cbz-Cl, KHCO_3 ; (h) O_3 , Me_2S ; (i) Br_2 , MeOH, H_2O

stereochemistry. Reduction of enone **304** with diisobutylaluminum hydride produces a 3 : 2 mixture of **305** and **306**, which can be separated by HPLC. Removal of the BOM group with Na/NH_3 at $-78\text{ }^\circ\text{C}$ gives the respective diols in quantitative yield. High *anti* selectivity (2 : 98) is obtained if the reduction is performed under chelation control with lithium aluminum hydride in ether ($-10\text{ }^\circ\text{C}$). If *tert*-butyldimethylsilyl is used as the protecting group instead of BOM, chelation is prevented, thus giving high *syn* selectivity (95 : 5) with lithium aluminum hydride.

Diol **307**, prepared from **282** in a sequence similar to the one described above, forms acetone **308** when treated with acetone under acidic conditions. Exposure of **308** to SnCl_4 produces highly functionalized tetrahydrofuran **309** via a pinacol-type rearrangement with complete preservation of enantiomeric purity [106].

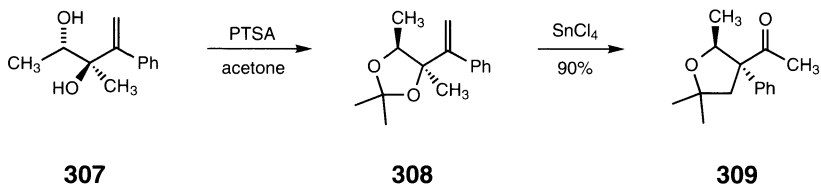


conditions: (a) 5% KOH, MeOH, 2-pyridinethiol, DCC; (b) $\text{CH}_3\text{CH}=\text{PPh}_3$, THF; (c) $\text{CH}_3\text{CH}_2\text{CHO}$, $50\text{ }^\circ\text{C}$; (d) diisobutylaluminum hydride

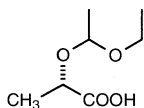


Scheme 41

conditions: (a) *n*-BuLi, ether, -78 °C; (b) L-Selectride, THF, -78 °C; (c) TBS-Cl, imidazole, DMF; (d) CH₃I, CH₃CN; (e) NaBH₄, MeOH, -10 °C; (f) HgCl₂, CH₃CN – H₂O; (g) thiazole–CH₂P⁺Ph₃Cl⁻, KOt-Bu, THF; (h) H₂, 10% Pd / C, MeOH

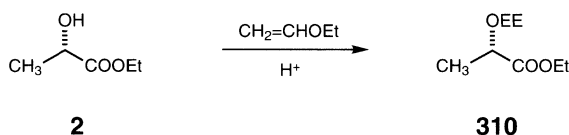


1.4.4 Ethoxyethyl (EE)

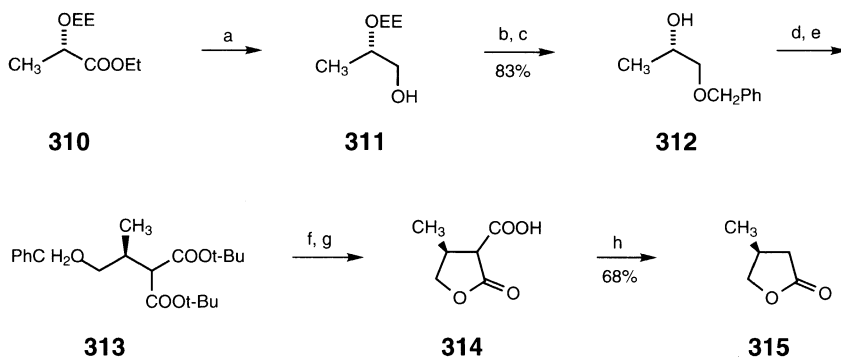


(S)-2-(1-Ethoxyethoxy)propanoic Acid

The 1-ethoxyethoxy protecting group is attached to ethyl L-lactate by treating **2** with ethyl vinyl ether in the presence of either 36% HCl [107] or trifluoroacetic acid [108].



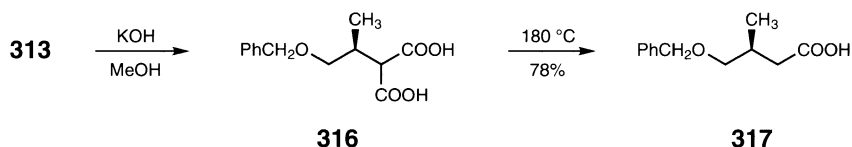
Compound **310** has been used in a stereoselective synthesis of (*S*)-4,5-dihydro-4-methyl-2(3*H*)furanone (**315**) (Scheme 42), an important chiral building block. After reduction of the ester, protection of the primary alcohol, removal of the EE group, and tosylation of the secondary alcohol, reaction with di-*tert*-butyl malonate gives **313** with 97% inversion of configuration [107]. Hydrolysis, debenzoylation, lactonization, and decarboxylation furnishes the product **315** (93% *ee*).



Scheme 42

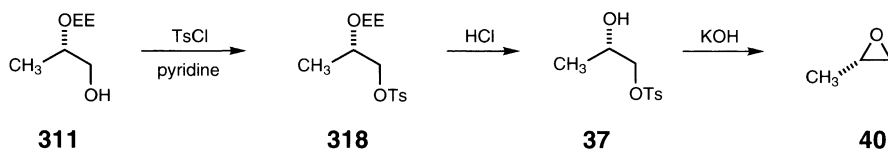
conditions: (a) LiAlH_4 , ether, rt (82% from **2**); (b) NaH, ether, PhCH_2Cl ; (c) 96% H_2SO_4 , MeOH; (d) TsCl, pyridine, 0 °C (89%); (e) $\text{CH}_2(\text{COOtBu})_2$, KOtBu, DMF, rt; (f) KOH (2.2 equiv), H_2O ; (g) H_2 , Raney Ni, 130 °C, 130 bar; (h) 180 °C

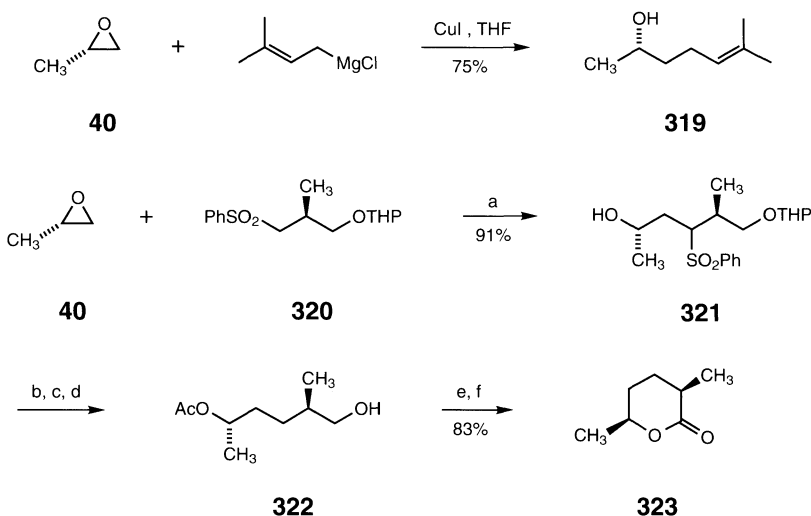
If malonate **313** is hydrolyzed and decarboxylated without removing the protecting group, (*S*)-4-benzyloxy-3-methylbutanoic acid (**317**) is produced in 30% overall yield from ethyl L-lactate (**2**).



One of the earlier syntheses of (*S*)-(–)-methyloxirane (**40**) utilizes the EE protecting group as an integral part of the process [108]. The 5-step sequence, starting from ethyl L-lactate, proceeds in 46% overall yield and gives **40** with high optical purity.

Oxirane **40** has been used in the synthesis of a variety of natural products, such as (*S*)-(+) -sulcatol (**319**), the aggregation pheromone of a wood-boring ambrosia beetle [53], and (2*R*,





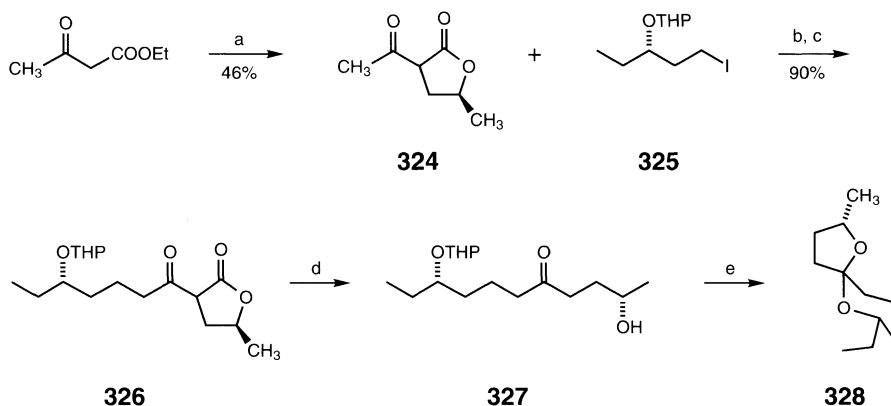
Scheme 43

conditions: (a) *n*-BuLi, -78 °C → rt; (b) Na / Hg, EtOH (99%); (c) Ac₂O, DMAP (91%); (d) PTSA, MeOH (91%); (e) Jones CrO₃; (f) K₂CO₃, MeOH, 1N HCl

5*S*)-2-methyl-5-hexanolide (**323**) (99.8% *ee*), the sex pheromone of the carpenter bee. The synthesis of **323** is accomplished in 63% overall yield from **320** [54] (Scheme 43).

One of the four stable stereoisomers of 7-ethyl-2-methyl-1,6-dioxaspiro[4.5]decane, a bee pheromone, has been synthesized using **40** according to the route shown in Scheme 44. The 2*S*, 5*S*, 7*S*-isomer **328**, derived from both ethyl L-lactate and malic acid (precursor for **325**), is produced in good yield with an optical purity of 96% [19].

Throughout this chapter we have shown that organometallic reagents add to the ester group of a protected lactate to give chiral α-hydroxyketones. It is sometimes more convenient to use

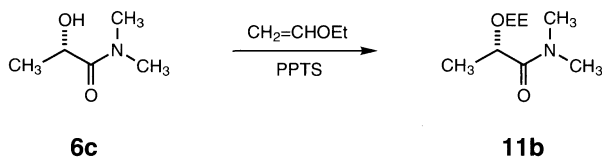


Scheme 44

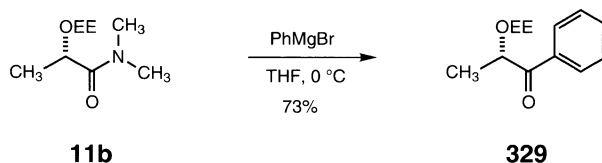
conditions: (a) **40**, NaOCH₃, 2 weeks; (b) NaH, THF / HMPA; (c) *n*-BuLi; (d) KOH, H₂O; (e) 2N HCl, 0–5 °C

an amide functionality rather than an ester, since the corresponding reactions can be carried out at higher temperatures.

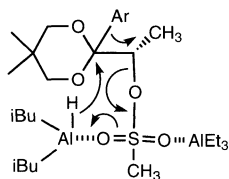
EE-Protected lactamide **11b** is readily prepared by treating *N,N*-dimethyl lactamide (**6c**) with ethyl vinyl ether in the presence of an acid catalyst [109,110].



The reaction of **11b** with phenylmagnesium bromide at 0 °C is complete within 30 minutes to give the phenylpropanone derivative **329** [85].



This concept has been used in an interesting synthesis of optically active (*R*)-(-)- α -curcumene (**334**) [110] (Scheme 45). The crucial step in the synthesis, the reductive-rearrangement of **331** to **332**, proceeds in nearly quantitative yield and with complete stereospecificity (> 99% *ee*). The rearrangement, whose mechanism is shown below, is quite general, and it occurs with a variety of aryl or alkenyl groups.

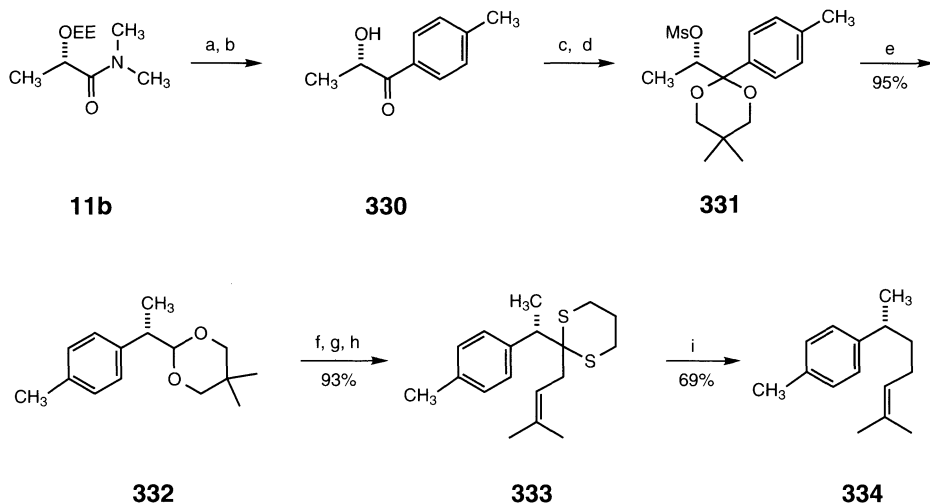


Alkyl Grignard reagents as well as organolithium reagents add to **11b** with equal facility. The utility of this process is exemplified in the total synthesis of protomycinolide IV (**335**), a biogenetic precursor of macrolide antibiotics of the mycinamicin family [111].

The framework of the macrolide can be assembled from the two segments **342** and **348**, each of which is derived from ethyl *L*-lactate *via* lactamide **11b** (Schemes 46 and 47).

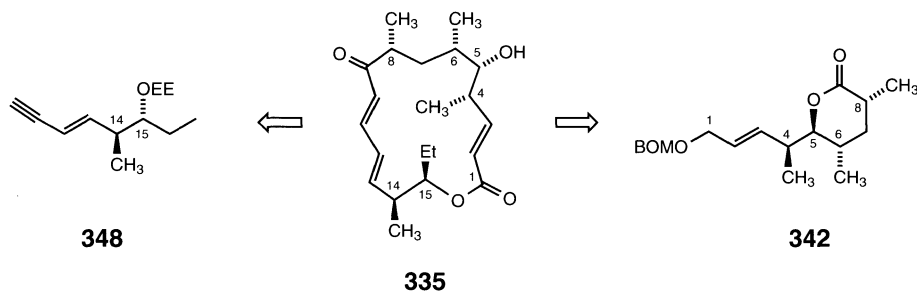
The salient feature of the synthesis is the organoaluminum-promoted stereospecific pinacol-type 1,2-rearrangement common to both segments. The **338** → **339** rearrangement (Scheme 46) proceeds with preservation of alkene geometry, and is completely enantiospecific. The other 1,2-rearrangement, **345** → **346** (Scheme 47), also proceeds with no *E/Z* isomerization of the olefin and with complete enantiospecificity.

The usefulness of the organoaluminum-mediated pinacol-type rearrangement is demonstrated in the synthesis of (+)-eldanolide (**354**), a wing-gland pheromone of the African sugar-cane borer [112] (Scheme 48). The key reaction, the rearrangement of **350** → **351**,



Scheme 45

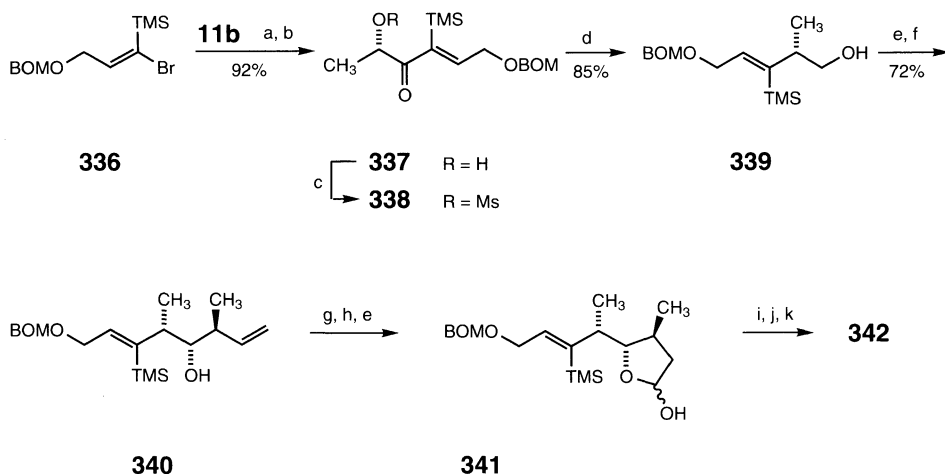
conditions: (a) 4-methylphenylmagnesium bromide; (b) PPTS, EtOH; (c) 2,2-dimethyl-1,3-propanediol, TMS-Cl, MeOH; (d) MsCl, pyridine; (e) DIBAL, Et₃Al, toluene, -42 ° → -20 °C; (f) HS(CH₂)₃SH, BF₃·Et₂O, CH₂Cl₂; (g) *n*-BuLi; (h) (CH₃)₂C=CHCH₂Br; (i) CuCl₂, ZnCl₂, LiAlH₄



proceeds stereospecifically. The introduction of the second asymmetric center is accomplished by reduction of the ketone with Super-Hydride, which furnishes exclusively the *anti*-diol **352** with >98% *ee*. This high stereoselectivity can be explained by the Felkin–Anh model for diastereoselection.

The asymmetric pinacol-type rearrangement can also be taken advantage of to synthesize simple chiral α -methyl ketones of type **357** or **359** (Scheme 49). The common starting material **355**, which is prepared by Grignard addition to **11b**, reacts with either Grignard reagents or alkenyl lithium derivatives to give the corresponding tertiary alcohols. Triethylaluminum-promoted rearrangement of the mesylates **356** or **358** gives either **357** (75–96% yield) [9] or **359** (64–93% yield) [113], with enantiomeric excesses usually >99%.

By adjusting the oxidation state of the carbon adjacent to the asymmetric center prior to rearrangement one can gain access to chiral α -methyl esters **363** [114] (Scheme 50). The rearrangement substrate **362** is prepared by addition of 1-hexynyllithium to **11b** followed by either catalytic hydrogenation to give *Z*-**361** ($R^2=C_4H_9$, $R^1=H$) or dissolving metal reduction, which gives the *E*-isomer ($R^1=C_4H_9$, $R^2=H$). 1,2-Rearrangement of mesylate **362** with cal-

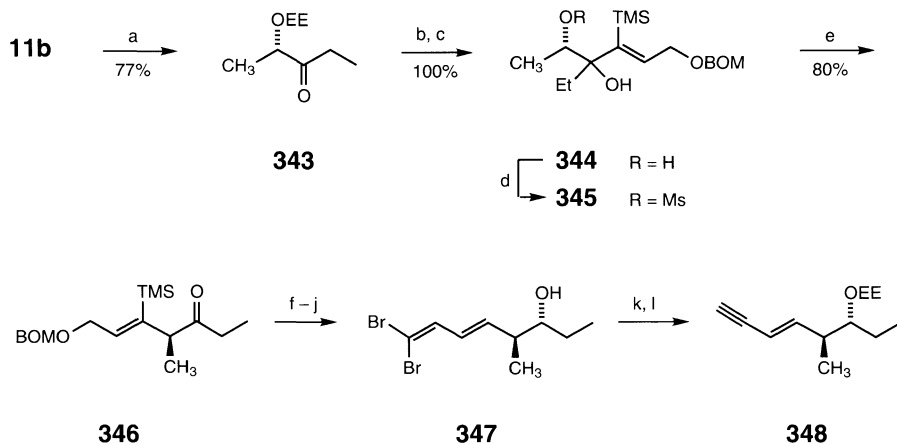


Scheme 46

conditions: (a) *n*-BuLi, -100 °C; (b) H₂SO₄, dioxane; (c) MsCl, Et₃N, CH₂Cl₂; (d) DIBAL, Et₃Al, CH₂Cl₂, -78 °C → -20 °C; (e) Swern oxidation; (f) CH₃CH=CHCH₂Br, CrCl₂, THF; (g) DHP, PPTS (94%); (h) (c-C₆H₁₁)₂BH, THF, then H₂O₂ (97%); (i) KH, Mikolajczyk reagent (76%); (j) HgCl₂, CH₃CN - THF (92%); (k) LDA, CH₃I, THF - HMPA, -78 °C (88%)

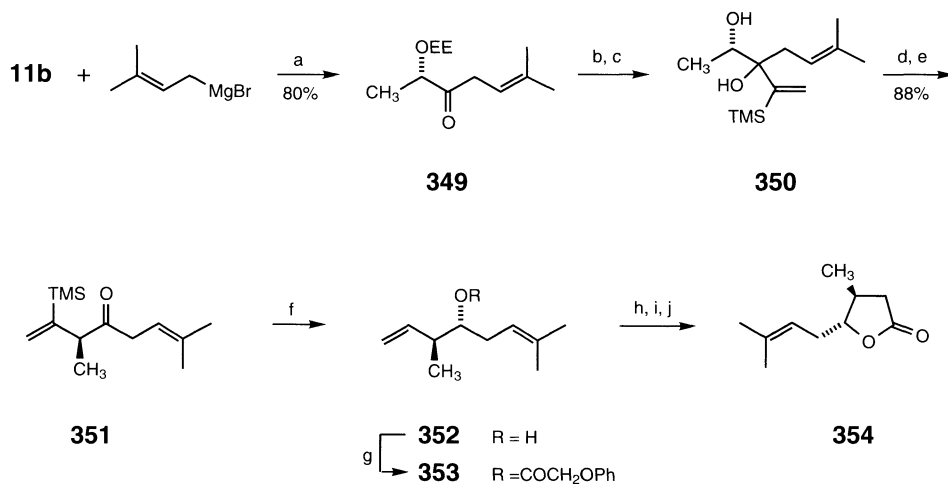
cium carbonate occurs with complete retention of the olefin geometry and produces esters **363**, which are optically pure.

More complex lithium acetylides such as **364** can be added to **11b** to give, for example, chiral α -hydroxyketone **365** (after deprotection). This particular intermediate has been carried



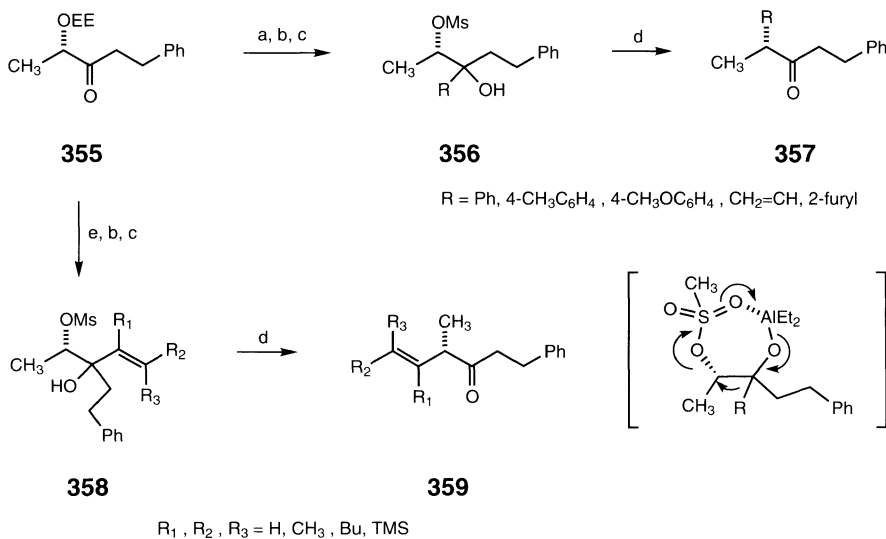
Scheme 47

conditions: (a) EtMgBr, THF, 0 °C; (b) **336**, *n*-BuLi, -10 °C; (c) PPTS, MeOH; (d) MsCl, Et₃N, CH₂Cl₂; (e) Et₃Al, CH₂Cl₂, -78 °C; (f) L-Selectride, THF, -78 °C (95%); (g) NaH, HMPA, PhOCH₂COCl, pyridine (100%); (h) PhSH, BF₃•Et₂O, CH₂Cl₂ (95%); (i) Swern oxidation; (j) CBr₄, PPh₃, Zn, CH₂Cl₂; (k) CH₂=CHOEt, PPTS, CH₂Cl₂ (100%); (l) LDA, THF 0 °C (81%)



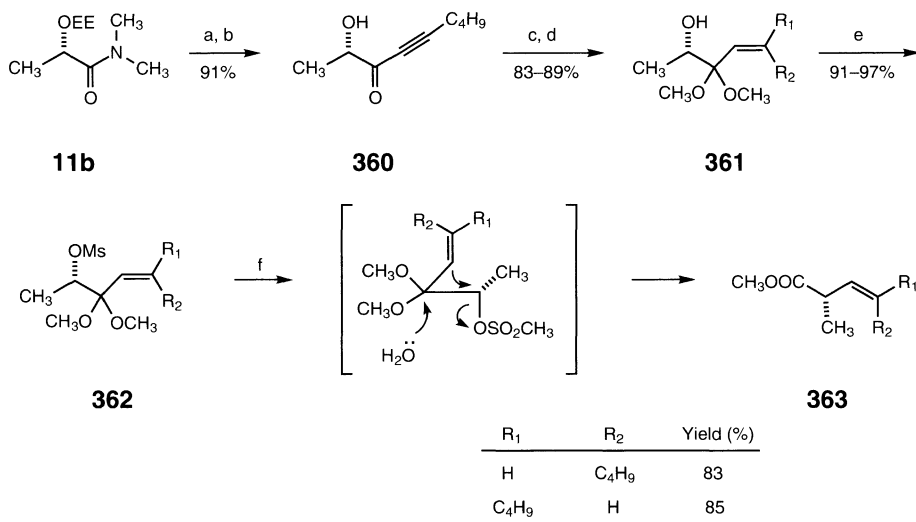
Scheme 48

conditions: (a) THF, 0 °C; (b) CH₂=C(TMS)Li, CeCl₃, -78 °C (91%); (c) PPTS, MeOH (91%); (d) MsCl, Et₃N, CH₂Cl₂; (e) Me₃Al, CH₂Cl₂, -78 °C; (f) Super-Hydride, THF, -78 °C, then H₂O₂ (95%); (g) PhOCH₂COCl, pyridine, CH₂Cl₂ (91%); (h) (c-C₆H₁₁)₂BH, THF, 0 °C, then H₂O₂; (i) CrO₃, pyridine; (j) LiOH, EtOH - H₂O



Scheme 49

conditions: (a) RMgX or RLi; (b) PPTS, EtOH; (c) MsCl, Et₃N, CH₂Cl₂; (d) Et₃Al, CH₂Cl₂, -78 °C; (e) R₂(R₃)C=C(R₁)Li or MgBr

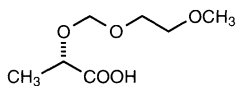


Scheme 50

conditions: (a) 1-hexynyllithium; (b) 1M HCl, dioxane; (c) HC(OCH₃)₃, CH₃SO₃H, MeOH, 0 °C; (d) H₂, Pd-Pb or Na / NH₃, EtOH, THF, -78 °C; (e) MsCl, pyridine; (f) CaCO₃, MeOH – H₂O (7:3), 90 °C, 2–3 hr

on to (+)-davanone (**371**), an essential oil of *Aldemisia pallens* [115] (Scheme 51). Once again, the important transformation in the synthesis is a reductive 1,2-rearrangement (**366** to **367**). Epoxidation followed by hydrogenolysis and benzylation introduces the second asymmetric center in compound **368**. Iodocyclization leads to the heterocyclic backbone of the natural product.

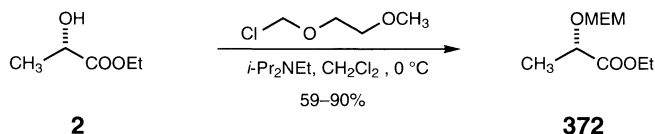
1.4.5 (Methoxyethoxy)methyl (MEM)

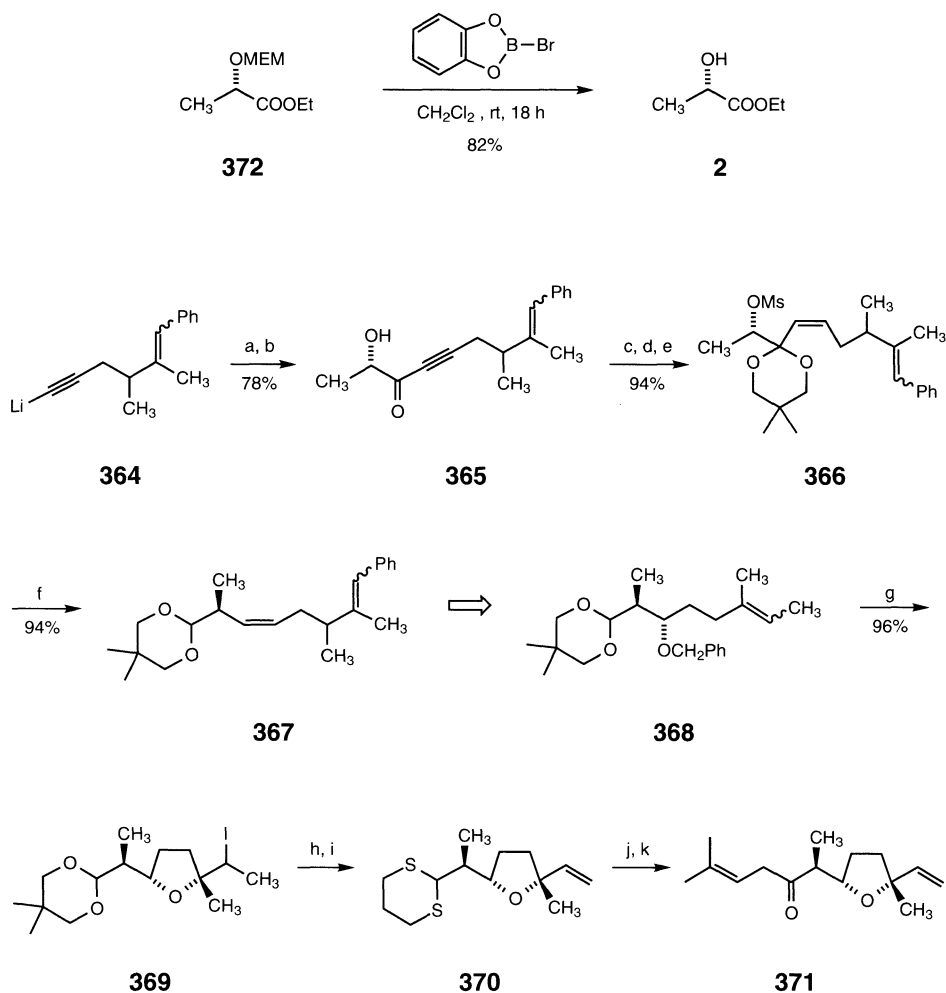


(S)-2-[(2-Methoxyethoxy)methoxy]propanoic Acid

Protection of ethyl L-lactate with a MEM group is easily accomplished by alkylation with (2-methoxyethoxy)methyl chloride in the presence of Hunig's base (**2** → **372**) [100,116,117].

The protecting group can be removed under mild conditions by treating **372** with one equivalent of catechol boron bromide [118]. This reagent is also effective for cleaving other protecting groups, such as *tert*-butyl, allyl, benzyl or MOM ethers, as well as N-Cbz and N-Boc functionalities.

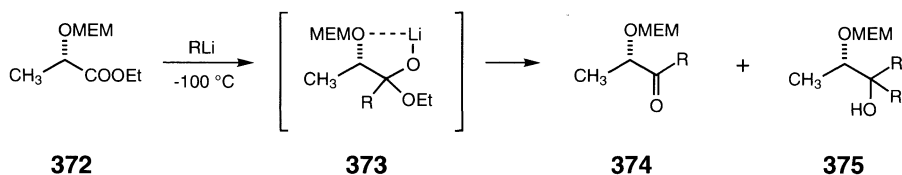


**Scheme 51**

conditions: (a) **11b**; (b) H_3O^+ ; (c) $\text{HOCH}_2\text{C}(\text{CH}_3)_2\text{CH}_2\text{OH}$, TMS-Cl; (d) H_2 , Pd - Pb, quinoline; (e) MsCl, pyridine; (f) DIBAL, Et_3Al , toluene, -42°C ; (g) I_2 , CaCO_3 , CH_2Cl_2 , 0°C ; (h) KO t -Bu, DMF (94%); (i) $\text{HS}(\text{CH}_2)_3\text{SH}$, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (84%); (j) n -BuLi, $\text{BrCH}_2\text{CH}=\text{C}(\text{CH}_3)_2$ (41%); (k) NCS, AgNO_3 , CH_3CN , H_2O (72%)

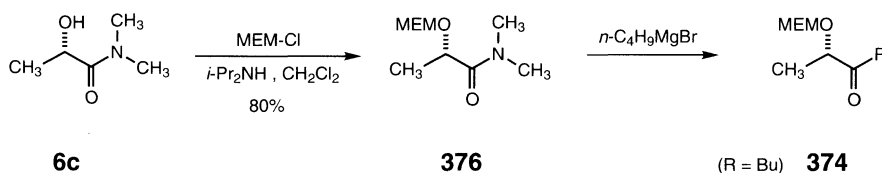
The chelative ability of the oxygen atoms in the MEM group results in an ideal environment for the addition of organolithium reagents to the ester group of **372**. If the reaction is performed at -100°C in ether/pentane (1:1) for a maximum of 10 min, protected α -hydroxyketones **374** are produced, with only minor amounts of alcohol **375** appearing [5]. At temperatures below -80°C the intermediate **373** is sufficiently stable to prevent *in situ* formation of **374**, which upon further addition of RLi is responsible for production of the undesired alcohol **375**.

The identical reaction based on a MOM-protected lactate, which contains one less oxygen, produces a 3:1 mixture of α -hydroxyketone/alcohol with only 56–58% *ee*.



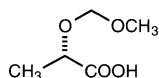
R	374 (%)	375 (%)	% ee
CH ₃	70	3	>95
<i>n</i> -C ₄ H ₉	75	8	>98

A superior method for effecting the transformation is to use lactamide **376** instead of ester **372**. In this case the reaction is performed in THF/ether (7:3) at 5 °C and within 10 min product **374** is formed in 80% yield with an enantiomeric excess of >99%.



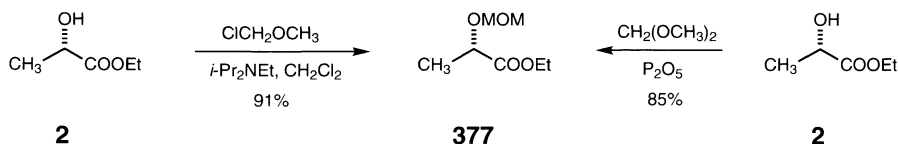
The bulk of the chemistry associated with MEM lactates has been accomplished with MEM lactaldehyde, and is discussed in Section 1.5.4.

1.4.6 Methoxymethyl (MOM)

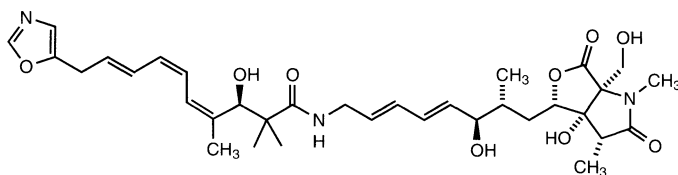


(*S*)-2-(Methoxymethoxy)propanoic Acid

Protection of ethyl L-lactate with a MOM group (**377**) can be effected in high yield with either chloromethyl methyl ether in the presence of Hunig's base [100,119] or with dimethoxymethane and phosphorus pentoxide [120].

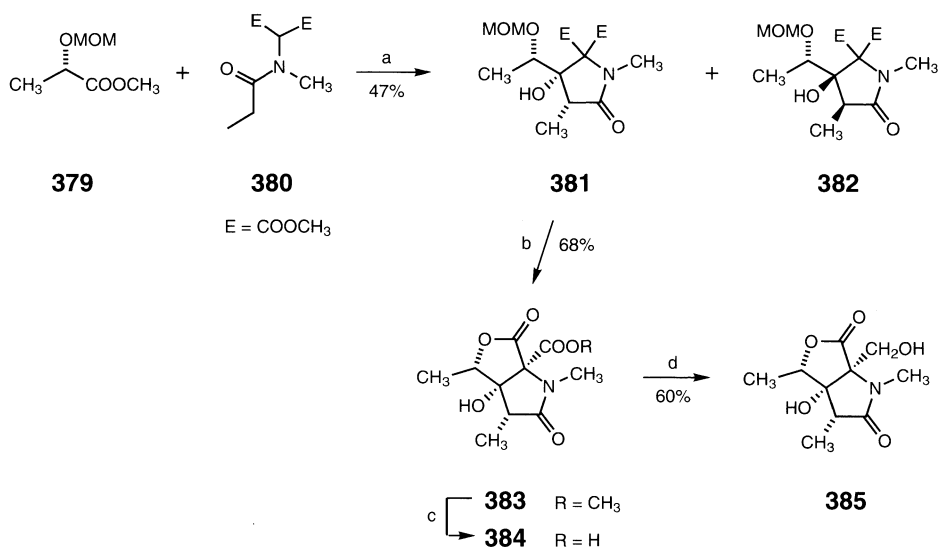


The chiral bicyclic lactam-lactone fragment of the antibiotic neoxazolomycin (**378**) has been synthesized using the MOM-protected methyl L-lactate analog **379** as the source of chirality [121] (Scheme 52).



378

Inverse addition of the dianion generated from **380** to lactate **379** results in a 2 : 1 mixture of diastereomers **381** and **382**. After separation of the mixture by column chromatography, the major diastereomer **381** is lactonized by acidic removal of the MOM group.



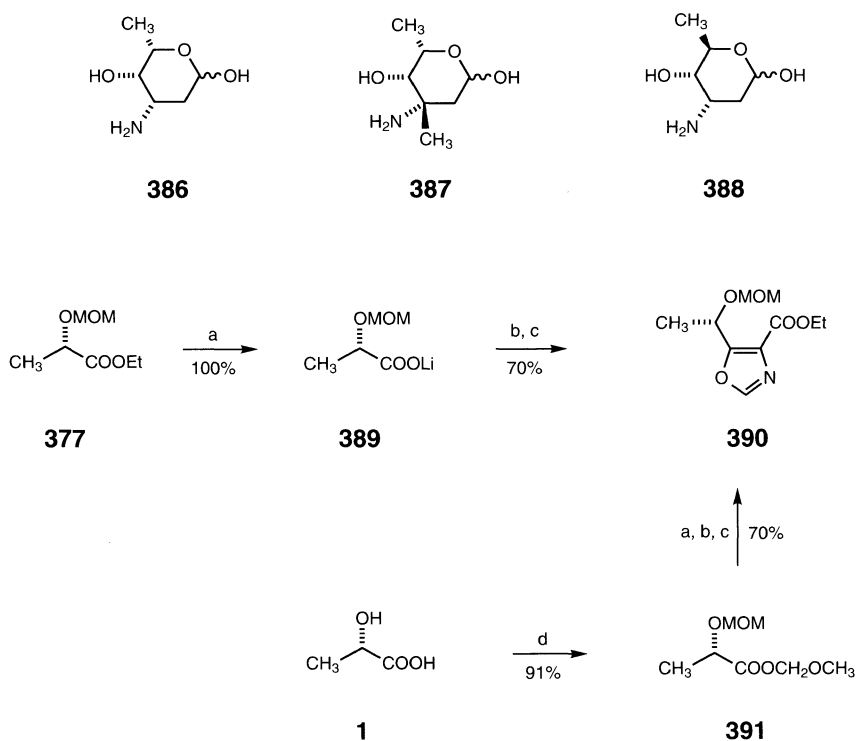
Scheme 52

conditions: (a) *s*-BuLi, THF, -78 °C; (b) MeOH, conc. HCl; (c) LiOH, THF, H₂O; (d) DMF, (COCl)₂, CH₃CN – THF, 0 °C, then NaBH₄, DMF

A related family of 3-amino-2,3,6-trideoxyhexoses, L-daunosamine (**386**), the carbohydrate component of anticancer anthracycline antibiotics, L-vancosamine (**387**), the carbohydrate component of the antibiotics vancomycin and sporaviridin, and D-ritosamine (**388**), the enantiomer of the carbohydrate component of the antibiotic ristomycin, has been prepared from [119].

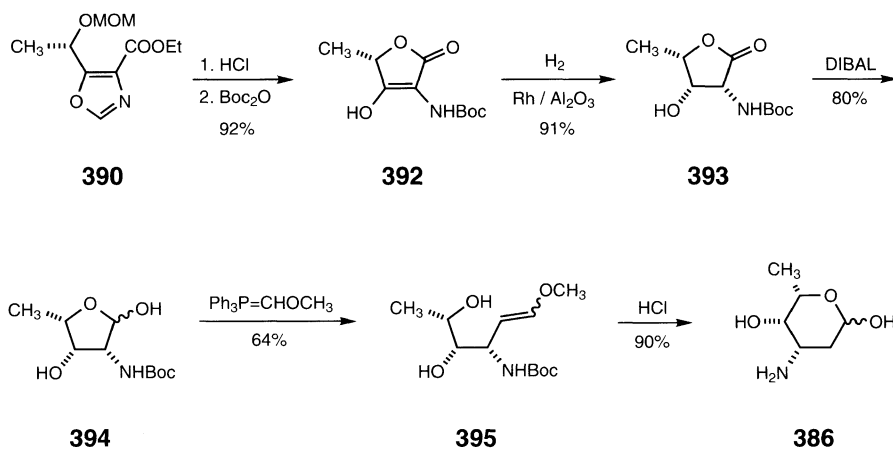
The synthesis of all three sugars proceeds through a common intermediate, *L*-lyxo-1,4-lactone (**393**). Lactates **377** or **391** are converted to the lithio derivative **389** by alkaline hydrolysis with lithium hydroxide. The carboxylate is then activated with DPPA and reacted with the sodium salt of ethyl isocyanoacetate to give oxazole **390** (Scheme 53).

The oxazole ring is readily cleaved with 10% HCl, which also removes the MOM group, and quantitatively gives 3-amino-5-methyltetronic acid. Hydrogenation of the Boc-protected



Scheme 53

conditions: (a) LiOH, THF, H₂O; (b) DPPA, DMF; (c) CNCH₂COOEt, NaH; (d) ClCH₂OCH₃, *i*-Pr₂NEt, CH₂Cl₂

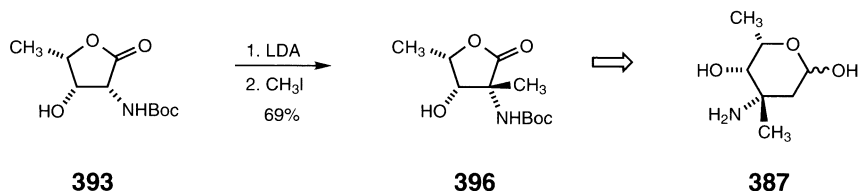


Scheme 54

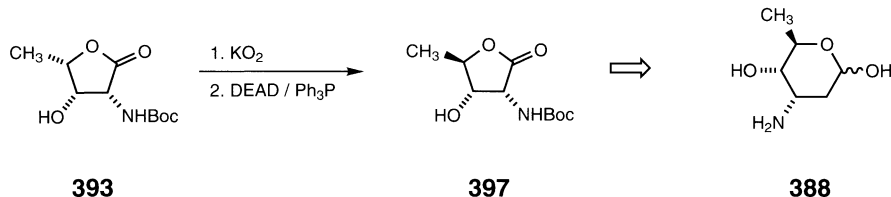
derivative **392** over 5% rhodium–alumina at 120 atm affords the crucial lactone **393** as the sole product. The overall yield of **393** from ethyl L-lactate (**2**) is 52%.

Conversion of **393** to L-daunosamine (**386**) is accomplished by reduction of the lactone to lactol **394** followed by a Wittig reaction and acid hydrolysis with 20% HCl–THF (1 : 1.7) [122] (Scheme 54).

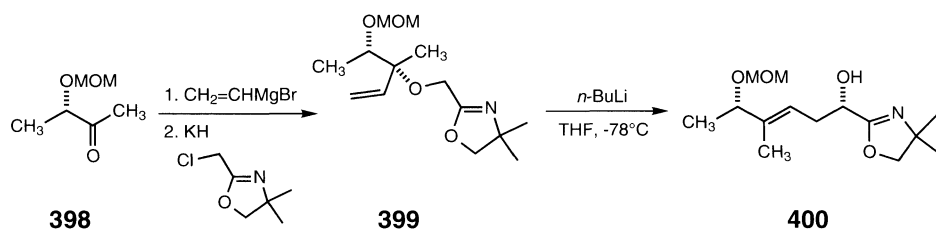
In the synthesis of L-vancosamine (**387**) the required methyl substituent is introduced by alkylation of the enolate of **393** with methyl iodide. The methylation occurs from the less hindered side of the molecule to furnish **396** as a 96 : 4 mixture of β and α -methyl isomers [123]. The remainder of the synthesis parallels that of L-daunosamine: lactol formation (73% yield), Wittig reaction (56% yield), and acid hydrolysis (46% HF–methanol, 33% yield).



In the synthesis of D-ristosamine (**388**), all that is required is inversion of the 5-methyl group of lactone **393**. This is readily accomplished by opening the lactone ring with potassium superoxide, acidification to pH 4, and a Mitsunobu reaction. Once again, reduction of the lactone to lactol (71% yield) followed by Wittig reaction and acid hydrolysis (HCl, methanol) affords the desired sugar **388**, isolated as the diacetate in 23% yield [124].



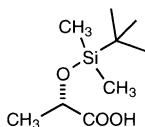
Methyl ketone **398**, which is available from **379** according to procedures previously discussed, has been used as a chiral precursor for rearrangement studies. The requisite substrate **399** is prepared by addition of vinylmagnesium bromide to **398**, which produces a tertiary alcohol with > 95% optical purity. Deprotonation of oxazoline ether **399** with *n*-butyllithium results in a [2,3] Wittig rearrangement and furnishes **400** as the sole product [125]. This remote transfer of chirality is of potential use in constructing fragments associated with a variety of macrolides.



1.4.7 Silyl Groups

Although trimethylsilyl lactic acid derivatives are known, they are not sufficiently stable to many reaction conditions to be synthetically useful.

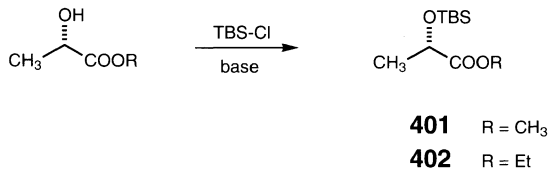
1.4.7.1 *tert*-Butyldimethylsilyl (TBS)



(*S*)-2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]propanoic Acid

A more stable, and consequently more synthetically useful protecting group, is the *tert*-butyldimethylsilyl (TBS) functionality. Ethyl or methyl lactate is easily protected with this group by treatment with *tert*-butyldimethylsilyl chloride in the presence of a suitable base. The use of imidazole in DMF furnishes **401** or **402** in 90–99% yield [126,127,128,130], whereas triethylamine/DMAP in tetrahydrofuran affords **401** in 90% yield [129].

Vinylation of **401** is accomplished by initial saponification with lithium hydroxide to yield the lithium salt **403**, followed by addition of one equivalent of vinyl lithium to give **404**. After



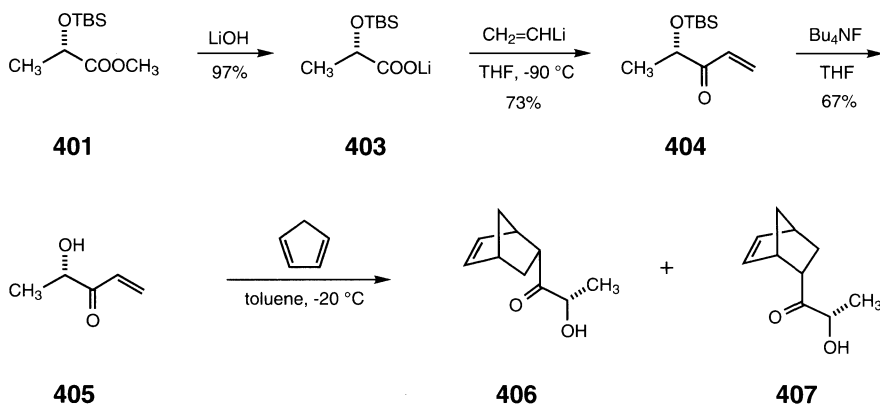
deprotection, the optical purity of the enone **405** was determined to be >99% *ee* [130]. The use of **405** as a dienophile in the Diels–Alder reaction is demonstrated by reaction with cyclopentadiene at 20 °C, which produces a 4 : 1 mixture of *endo* cycloadducts **406** and **407**.

Compound **412**, a potentially useful chiral synthon for the synthesis of alkaloids, is prepared from silyl-protected lactate **402** as shown in Scheme 56 [127]. Diels–Alder reaction between Danishefsky's diene and the acyl amine generated from acetoxymethyl lactamide **409** under thermal conditions, produces a mixture of the desired piperidone **410** (10% yield) and partial condensation product **411** (30% yield).

Selective reduction of the 4-keto group of either **410** or **411** gives an intermediate alcohol which, upon silyl deprotection, cyclizes to the bicyclic system **412** by an S_N2' mechanism. The product is obtained as a mixture of epimers at the C-2 carbon, but these are readily separated by column chromatography.

Chirality transfer *via* an ene reaction is a useful method for preparing enantiomerically pure substances. This strategy is elegantly demonstrated by the use of lactic acid as the chiral source for adducts **415**, which are obtained with high optical purity [128] (Scheme 57).

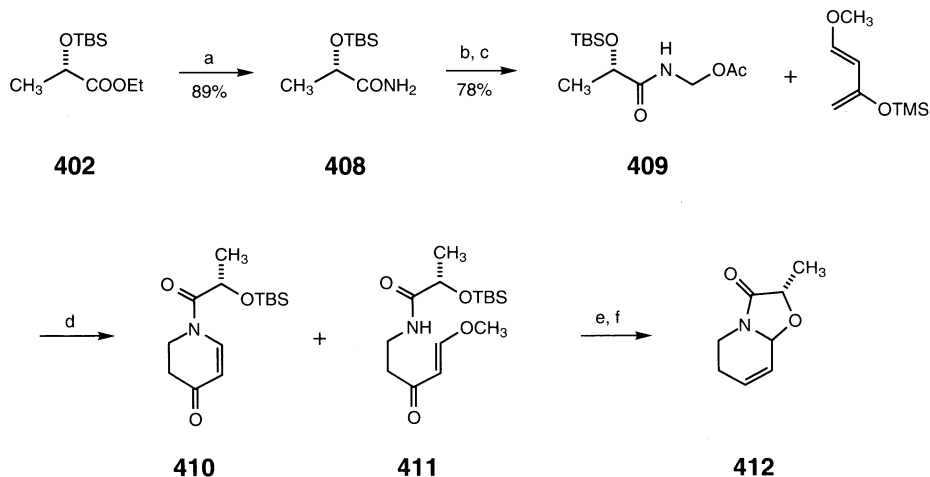
The necessary 2-(ethylthio)allyl silyl ether **414** is prepared in good yield from **402** by conversion to thioester **413** followed by treatment with Tebbe reagent. Reaction of **414** with a variety of aldehydes in the presence of Me₂AlCl produces adducts **415** in high yield. To



Scheme 55

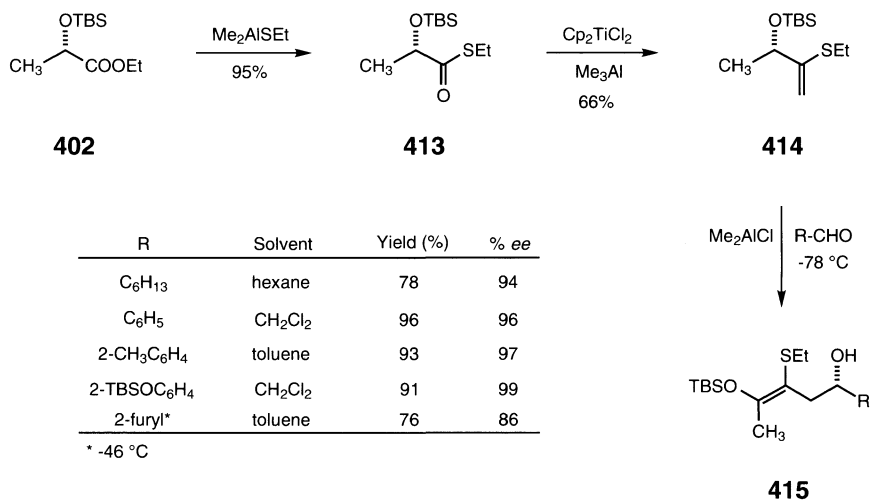
obtain high *ee* values, the use of non-polar solvents is important. The adduct derived from 2-OTBS benzaldehyde (entry 4) is a useful precursor for the synthesis of optically active anthracyclines.

Stereoselective addition of carbon nucleophiles to α -hydroxyketones is an excellent method for the preparation of *syn* or *anti*-diols. The nature of both the organometallic reagent and the hydroxyl protecting group influences which isomer is formed. Protecting groups capable of chelation with the metal form *anti*-diols (see Section 1.4.3). The TBS group, which is incapable of chelation, is the protecting group of choice when *syn*-diols are desired. This concept is demonstrated in the synthesis of (2*R*, 3*S*)-(-)-trachelanthic acid (**418**), the necic acid of the antitumor agent indicine *N*-oxide [131] (Scheme 58).



Scheme 56

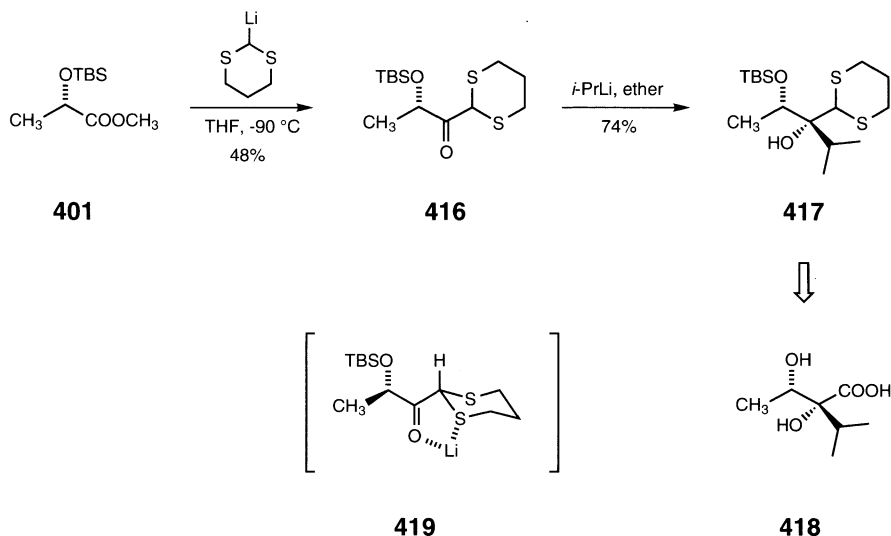
conditions: (a) NH_3 (gas), MeOH, 4 days; (b) $(\text{CH}_2\text{O})_n$, Cs_2CO_3 , rt; (c) Ac_2O , pyridine; (d) *o*-dichlorobenzene, 180°C ; (e) NaBH_4 , CeCl_3 , MeOH; (f) 3M HCl, CH_3CN



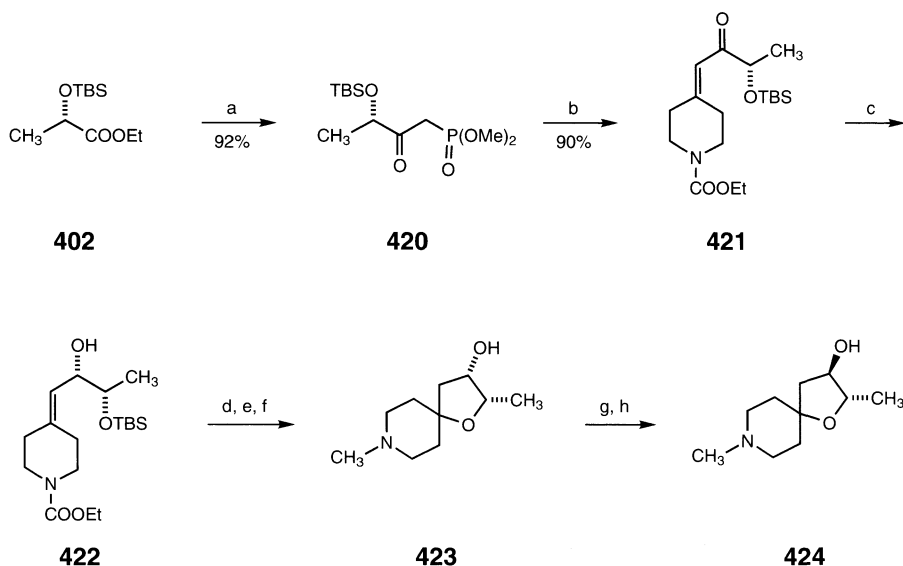
Scheme 57

Addition of isopropyllithium to propanone **416**, which is derived from **401** by reaction with 2-lithio-1,3-dithiane, gives *syn*-diol **417** (*syn* : *anti* = 97 : 3). The high stereoselectivity can be explained by invoking the Felkin–Anh model where, in the five-membered chelated intermediate **419**, the ether oxygen and the noncoordinated sulfur are designated as the “large” groups. Addition of the nucleophile occurs from the less hindered axial side of the dithiane to give the *syn*-product.

The remainder of the synthesis is essentially functional group manipulation, where protecting groups are changed and the dithiane is hydrolyzed to an aldehyde, which is then



Scheme 58



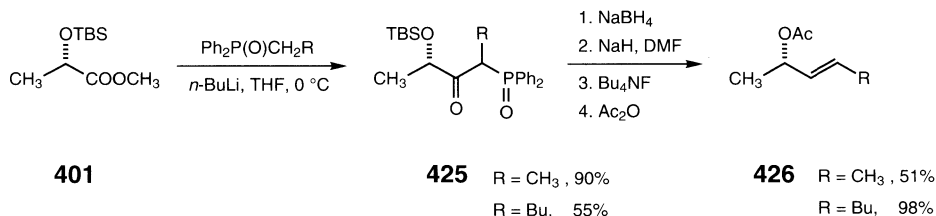
Scheme 59

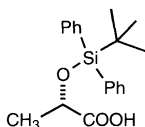
conditions: (a) $(\text{MeO})_2\text{P}(\text{O})\text{CH}_3$, $n\text{-BuLi}$, THF, -70°C ; (b) *N*-carbethoxy-4-piperidone, $n\text{-BuLi}$;
 (c) *L*-Selectride, THF, -70°C ; (d) HOAc, THF, H_2O ; (e) $\text{Hg}(\text{OAc})_2$, CH_3CN ;
 (f) AlH_3 , ether, 0°C ; (g) PhCOOH , DEAD, Ph_3P ; (h) DIBAL, CH_2Cl_2 , 0°C

oxidized to an acid with pyridinium dichromate. No racemization is observed during the entire process starting from methyl *L*-lactate.

Wittig reagent **420**, available from **402** by addition of lithium methylphosphonate to the ester group, is a versatile intermediate in the synthesis of optically active muscarine analogs [132] (Scheme 59). Wadsworth–Emmons reaction of β -ketophosphonate **420** with *N*-carbethoxy-4-piperidone affords adduct **421** with an optical purity $>98\%$. Ketone reduction and subsequent removal of the silyl protecting group, followed by mercury-assisted cyclization and ester reduction, furnishes epimuscarine analog **423**. The natural configuration (**424**) is obtained by inversion of the hydroxyl under Mitsunobu conditions.

Chiral allylic acetates **426** can be prepared using a similar β -ketophosphonate (**425**), also derived from lactic acid. The desired **425** is formed *via* reaction of lithiated diphenylphosphonate with **401**. Reduction of the ketone gives an intermediate alcohol which, upon treatment with base, forms the (*E*)-Wittig olefin. Removal of the silyl protecting group followed by acetylation gives the product **426** ($>98\%$ *ee*) [133].

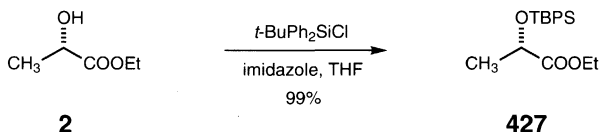


1.4.7.2 *tert*-Butyldiphenylsilyl (TBPS)

(S)-2-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]propanoic Acid

The enhanced stability of the TBPS group relative to the TMS or TBS groups, in addition to its steric bulk, makes this protecting group extremely versatile to the organic chemist.

Ethyl L-lactate can be protected with a TBPS group by reaction with *tert*-butyldiphenylsilyl chloride and imidazole in either tetrahydrofuran [134] or DMF [135]. Alternatively, using DBU as the base in methylene chloride furnishes **427** in 100% yield [140].



The combination of lactic acid and tartaric acid has been used in the synthesis of (+)-polyoxamic acid (**435**), the unusual amino acid component of polyoxin B (Scheme 60). The lactic acid component, ylide **429**, is available from **427** by hydrolysis, conversion to thioester **428**, and reaction with excess methylenetriphenylphosphorane. Wittig olefination with L-tartrate-derived aldehyde **430** gives the (*E*)-enone **431**. Reduction to *syn*-alcohol followed by treatment with trifluoroacetonitrile affords **432**.

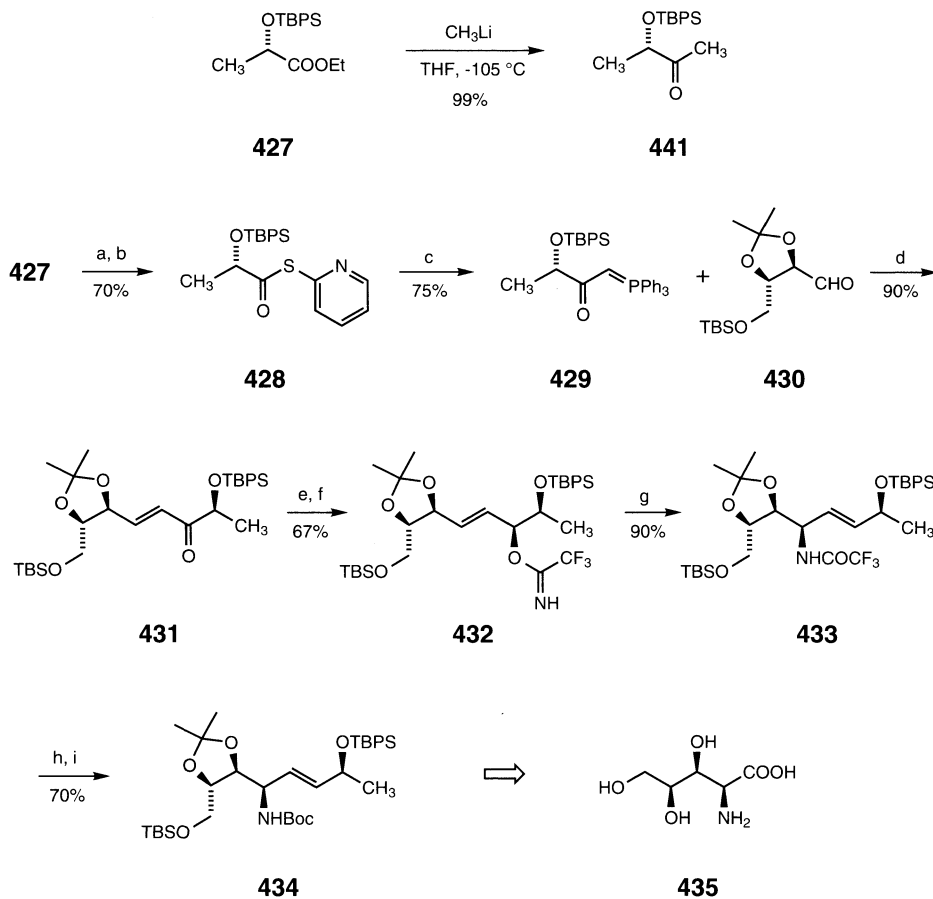
In the key reaction, a [3,3] rearrangement of trifluoroacetimidate **432** provides allylic amine **433** as a single diastereomer. After protecting-group adjustment, ozonolysis of the olefin, and oxidation of the aldehyde to acid, hydrolysis of all the protecting groups under acidic conditions furnishes the desired product [135]. The sole function of the lactic acid, whose carbon skeleton is removed by the ozonolysis, is to ensure the appropriate stereochemistry of the amino group.

The preparation of protected 4-deoxy-L-threose **440** can be realized by addition of a formyl anion equivalent to the ester group of **427** followed by stereoselective reduction. The reagent of choice is lithiated bis-*p*-tolylthiomethane, which gives ketone **436** in high yield (at a reaction temperature of $-78\text{ }^{\circ}\text{C}$) without formation of any tertiary alcohol. Compare this to lithiated 1,3-dithiane, which must be added at $-90\text{ }^{\circ}\text{C}$ or below (see compound **416**).

Reduction of the ketone can be accomplished with a variety of hydride reagents, but diisobutylaluminum hydride ($-78\text{ }^{\circ}\text{C}$ in toluene) provides the best results, with a *syn* : *anti* ratio of 85 : 15 [136,137]. If the *anti*-isomer (**438**) is desired, the protecting group should be removed prior to reduction. In this case sodium borohydride in methanol ($-50\text{ }^{\circ}\text{C}$) provides a 25 : 75 mixture of *syn* (**437**) and *anti*-diols.

Removal of the protecting group with fluoride provides diol **439**. At the diol stage, the *syn* : *anti* mixture can be easily separated by chromatography. Acetonide formation followed by mercury-assisted hydrolysis of the dithioacetal group furnishes the desired threose **440**.

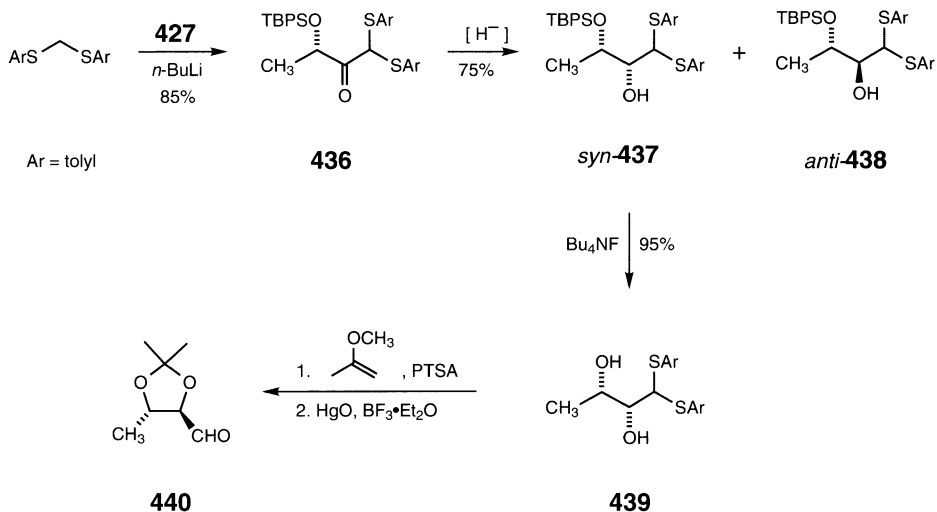
Simple lithium alkyls such as methylolithium add quantitatively to **427**, to give in this case (*S*)-3-[[(*tert*-butyldiphenylsilyl)oxy]-2-butanone (**441**), while completely retaining enantiomeric integrity at the chiral center [134,138].

**Scheme 60**

conditions: (a) KOH, MeOH; (b) 2-mercaptopyridine, DCC; (c) $\text{Ph}_3\text{P}=\text{CH}_2$, THF; (d) benzene, Δ ;
 (e) L-Selectride, $-78\text{ }^\circ\text{C}$; (f) *n*-BuLi, CF_3CN , $-78\text{ }^\circ\text{C}$; (g) xylene, Δ , 20 h; (h) NaBH_4 , EtOH;
 (i) Boc_2O

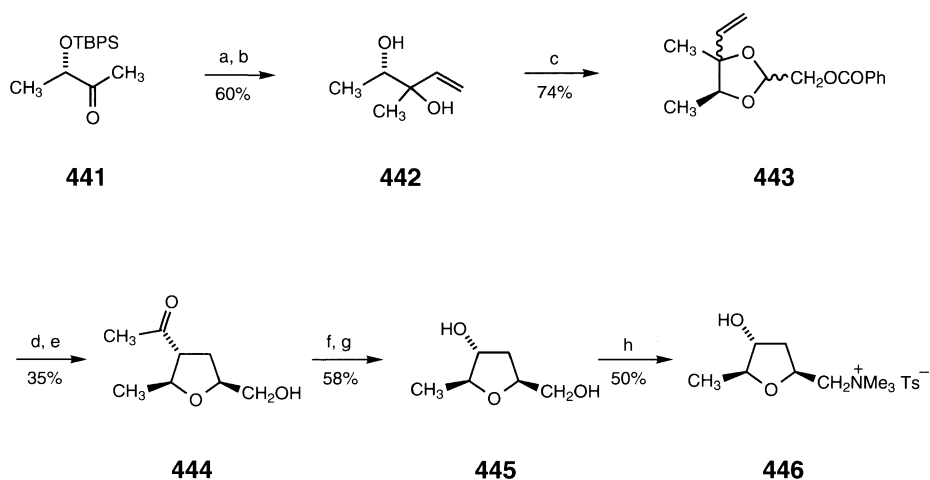
Derivative **441** is an extremely useful intermediate for the construction of highly functionalized chiral tetrahydrofurans *via* Lewis acid-promoted rearrangement of allylic acetals. This is elegantly demonstrated by the synthesis of optically pure (+)-muscarine tosylate (**446**) [138] (Scheme 62).

Addition of vinyl lithium to **441** gives **442** as a mixture of *syn* and *anti* diols. The beauty of this synthesis is that both the *syn* and the *anti*-diol stereoisomers rearrange to the same tetrahydrofuran product. Thus, acetal **443** undergoes a Prins pinacol rearrangement to tetrahydrofuran **444** upon treatment with SnCl_4 in nitromethane. The transformation proceeds with complete preservation of enantiomeric purity. Baeyer–Villiger reaction stereospecifically introduces the 3-hydroxy substituent, and conversion to the quaternary ammonium salt completes the target molecule **446**.



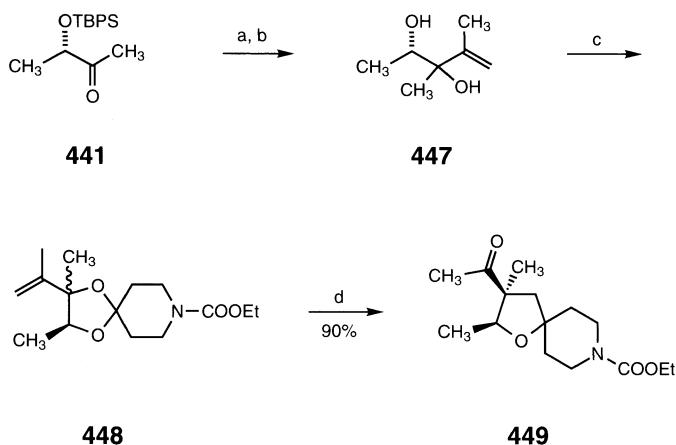
Scheme 61

More complex systems such as **449**, which is structurally related to a class of powerful muscarinic agonists, are easily constructed using this methodology as well [139] (Scheme 63). The conversion **441** \rightarrow **448** proceeds in 59% overall yield, and gives **448** as a 6 : 1 mixture of isomers. SnCl_4 -promoted rearrangement produces the highly functionalized tetrahydrofuran **449** with $>96\%$ *ee*.

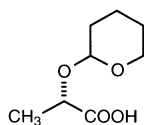


Scheme 62

conditions: (a) $\text{CH}_2=\text{CHLi}$, THF, -78°C ; (b) Bu_4NF , THF; (c) $\text{PhCOOCH}_2\text{CHO}$, PTSA, CH_2Cl_2 ; (d) SnCl_4 , CH_3NO_2 ; (e) KOH , MeOH ; (f) 3,5-dinitroperoxybenzoic acid, CH_2Cl_2 ; (g) NaOCH_3 ; (h) Me_3N , TsCl

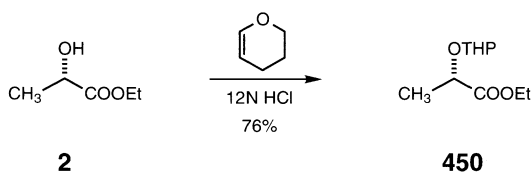
**Scheme 63**

conditions: (a) $\text{CH}_2=\text{CHLi}$, THF, -70°C ; (b) Bu_4NF ; (c) N-carbethoxy-4-piperidone, PTSA; (d) SnCl_4 , CH_3NO_2

1.4.8 Tetrahydropyran (THP)

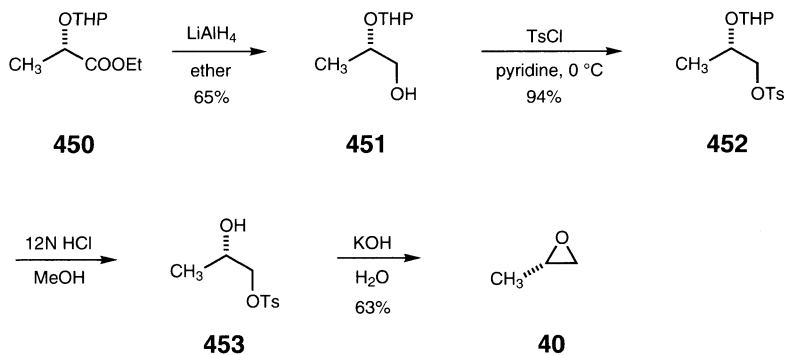
(*S*)-2-[(Tetrahydropyran-2-yl)oxy]propanoic Acid

Using standard conditions for THP-protection, ethyl L-lactate is converted to the tetrahydro-2-pyranyloxy derivative **450** by reaction with dihydropyran in the presence of acid catalyst [141,142].



Reduction of the ester followed by tosylation furnishes the useful differentially protected propanol derivative **452** [141,142]. Removal of the THP group and subsequent cyclization gives (*S*)-(-)-methyloxirane (**40**) [141] (Scheme 64), the versatility of which has been discussed in sections 1.1 and 1.4.4.

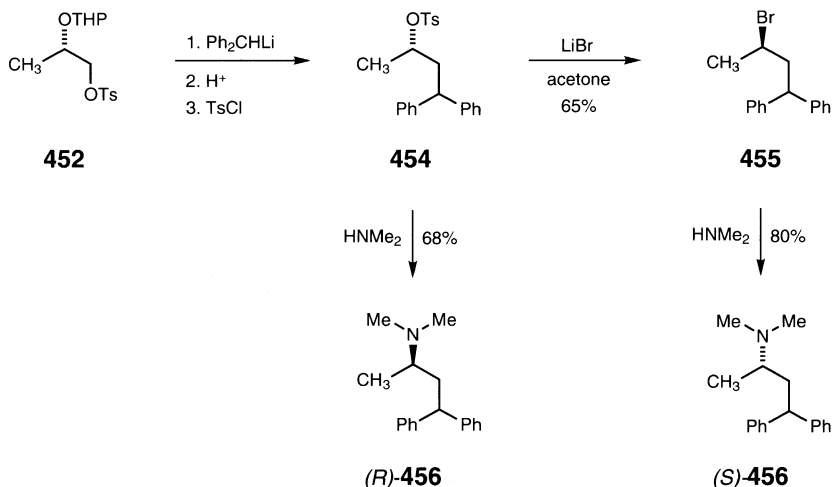
Intermediate **452** has also been used for the synthesis of both enantiomers of recipavrin (**456**), a spasmolytic agent that exerts musculotropic and anticholinergic action [143] (Scheme 65). Displacement of the tosyl function of **452** with diphenylmethyl lithium followed by replacement of the THP protecting group with a tosyl group gives **454**. An $\text{S}_{\text{N}}2$ reaction of



Scheme 64

454 with dimethylamine furnishes (*R*)-recipavrin with nearly complete inversion of the asymmetric center (96% *ee*). (*S*)-Recipavrin is prepared from **454** by two consecutive inversion reactions, where the tosylate is first converted to bromide **455** and the bromide ion is displaced with dimethylamine (84% *ee*).

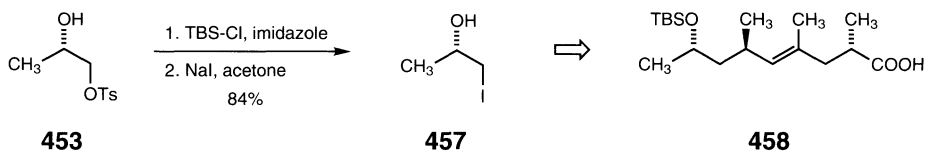
Treatment of **456** with bromoethane gives the corresponding enantiomeric quaternary ammonium salt, emepromium bromide, which is an anticholinergic agent with effects similar to atropine.



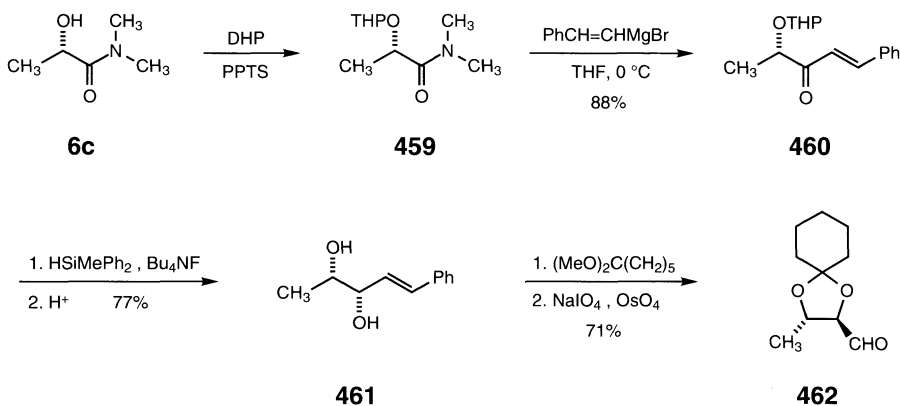
Scheme 65

The related intermediate **453** has also been used to supply the chiral hydroxyl center of the hydroxynonenoic acid **458** [144]. This acid fragment is common to jaspamide and geodiamolide A, both of which are cyclodepsipeptides isolated from lower marine organisms (sponges).

THP-Protected lactamide **459** has been used to synthesize (*2R, 3S*)-2,3-(cyclohexylidenedioxy)butanal (**462**), a key intermediate for the synthesis of L-daunosamine, the amino sugar component of natural anthracycline antibiotics [85] (Scheme 66). The crucial reaction in the sequence is the *syn*-selective hydrosilane/fluoride reduction of ketone **460**, which

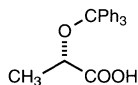


produces the desired diol **461** as an 87 : 13 mixture of *syn* and *anti* isomers. Ketalization of the diol followed by oxidative cleavage of the olefin furnishes the target molecule **462**. This compound is very similar to the one designated **440** (see Section 1.4.7.2).



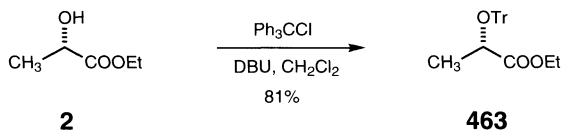
Scheme 66

1.4.9 Triphenylmethyl (Trityl)



(S)-2-(Triphenylmethoxy)propanoic Acid

An efficient method for tritylation of ethyl L-lactate is the treatment of **2** with triphenylmethyl chloride and DBU in methylene chloride [140]. This procedure is general for tritylation of secondary alcohols, that under standard conditions react slowly or not at all.



The chemistry associated with trityl-protected lactic acid derivatives is associated mainly with the corresponding lactaldehyde, and is discussed in Section 1.5.8.

1.5 O-Protected Lactaldehydes

α -Alkoxy aldehydes are extremely versatile intermediates in organic synthesis. Chiral α -alkoxy aldehydes enjoy the added benefit of being a potential source of one or more asymmetric centers introduced in a single reaction. In exploiting the rich chemistry of aldehydes one can choose from a veritable menu of synthetic transformations of which the aldehyde group is capable of undergoing.

A significant portion of this section is dedicated to the addition of organometallic reagents to the aldehyde portion of the molecule as a way of producing diols. Since the two π -faces of the chiral aldehyde carbonyl are diastereotopic, addition of carbon nucleophiles can lead to varying ratios of diastereomers. The outcome of addition is governed by the nature of the reagent and the type of protecting group on the α -hydroxyl moiety.

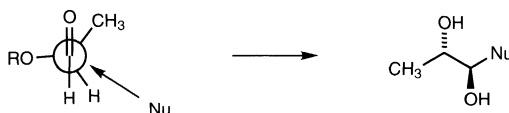
The diastereoselectivity of the resulting diol can be predicted on the basis of two distinct models. The generalized version of the Felkin model [145], shown in the Newman projection below, assumes that the α -chiral aldehyde adopts a conformation that places the largest group (L), in this case an OR group, perpendicular to the plane of the carbonyl. The approach of the attacking nucleophile also occurs perpendicular to the carbonyl, from the side opposite the large group. Anh [146] refined the model such that the approaching nucleophile attacks more nearly on a Burgie–Dunitz trajectory.



Felkin–Anh Model

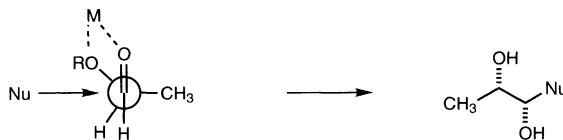
Applying the general model to lactaldehydes, the alkoxy group is assumed to be the “large” group. Consequently, attack of the nucleophile from the less hindered side results in the predominant formation of an *anti*-diol.

If the organometallic reagent is capable of chelation, the second model becomes operative. This model, sometimes called Cram’s cyclic model [147] involves the assistance of a che-



Felkin–Anh Model

anti



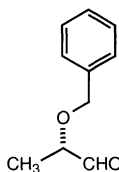
Cram's Cyclic Model

syn

lating metal to form a rigid cyclic transition state. In this case, attack of the nucleophile from the less hindered side results in the predominant formation of a *syn*-diol.

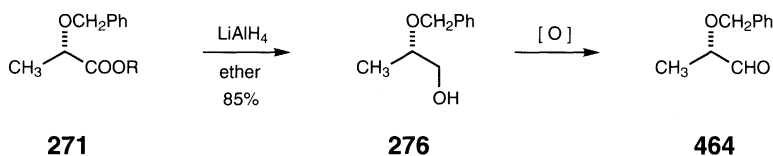
Therefore, by judicious choice of a protecting group and an organometallic reagent one can design a synthesis to produce the desired relative and absolute stereochemistry of the diol functionality. In general, protecting groups such as TBS or TBPS, which are incapable of chelation, afford *anti*-diols, whereas groups with one or more oxygen atoms, such as BOM, MEM, or MOM, are capable of chelation and give *syn*-diols.

1.5.1 Benzyl



(*S*)-2-(Phenylmethoxy)propanal

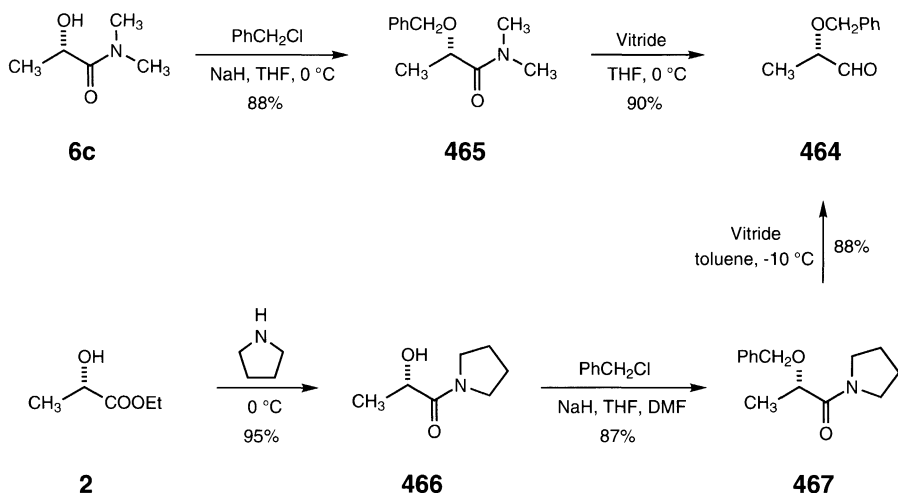
Benzyl-protected (*S*)-lactaldehyde (**464**) can be prepared from either the methyl or ethyl lactate derivative **271** by reduction of the ester with lithium aluminum hydride followed by oxidation of **276** under Swern conditions (83% yield) [92,148] or with PCC in methylene chloride [149]. Aldehyde **464** can also be obtained directly from **271** by partial reduction with diisobutylaluminum hydride at $-78\text{ }^{\circ}\text{C}$ [117,150].



The potential drawback to this preparation is the method for making **271**. Standard conditions for alkylation of lactates using benzyl bromide and sodium hydride in DMF proceed in low yield and with some degree of racemization. Other alkylating reagents such as benzyl trichloroacetimidate, which does not lead to racemization, are rather expensive (see Section 1.4.2).

A more cost-effective and reliable route to **464** uses lactamides **465** or **467** as the precursor [95,117] (Scheme 67). These are readily available from lactamides **6c** and **466** by standard inexpensive benzylation conditions (benzyl chloride, sodium hydride) or phase-transfer conditions (benzyl chloride, sodium hydroxide, tetrabutylammonium chloride, 92% yield). These alkylations, which have also been performed with *p*-chlorobenzyl chloride and *p*-methoxybenzyl chloride, proceed with no racemization. Reduction of lactamides **465** or **467** with sodium bis(2-methoxyethoxy)aluminum hydride (Vitride) furnishes (*S*)-2-benzyl-oxypropanal (**464**) in high yield. The aldehyde itself is not very stable, and has a propensity to hydrate, so it should be used immediately after preparation.

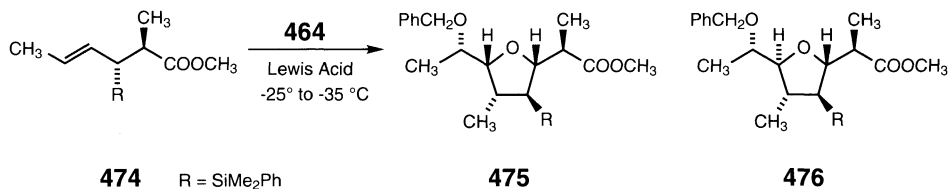
Reaction of lactaldehydes with organometallic reagents produces chiral diols. Consider for example the tin tetrachloride-mediated addition of allyltrimethylsilane to **464** (Scheme 68). Under these chelation- controlled conditions, a 92.3 : 7.7 mixture of *syn* (**468**) and *anti* (**469**)



Scheme 67

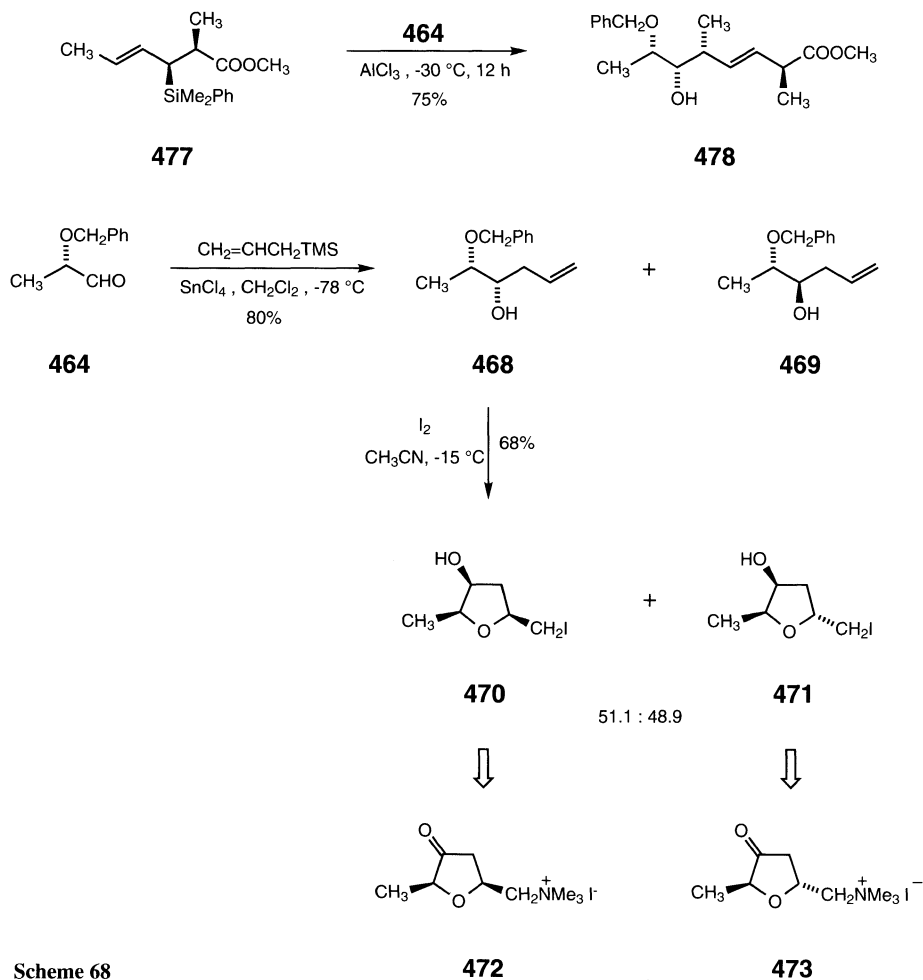
diols is produced *via* Cram's cyclic transition state. After separation by flash chromatography, diastereomer **468** is cyclized to a near statistical mixture of **470** and **471** by treatment with iodine. Again, these isomers are separable by column chromatography. Compound **470** has been converted to (+)-muscarone (**472**) (>98% *ee*), whereas **471** leads to (-)-allo-muscarone (**473**), also with >98% *ee* [151]. The enantiomers of these compounds have been synthesized as well starting from (*R*)-lactate.

An interesting extension of this methodology using chiral crotyl silane **474** produces tetrahydrofurans directly as a result of 1,2-silicon migration and heterocyclization [152]. Under boron trifluoride etherate catalysis (non-chelation controlled conditions), *cis*-2,5-disubstituted tetrahydrofuran (**475**) is produced in 50% yield, whereas tin tetrachloride (chelation control) gives the *trans*-2,5-disubstituted tetrahydrofuran (**476**) in 75% yield. Stereoselectivities in both cases exceed 40 : 1.

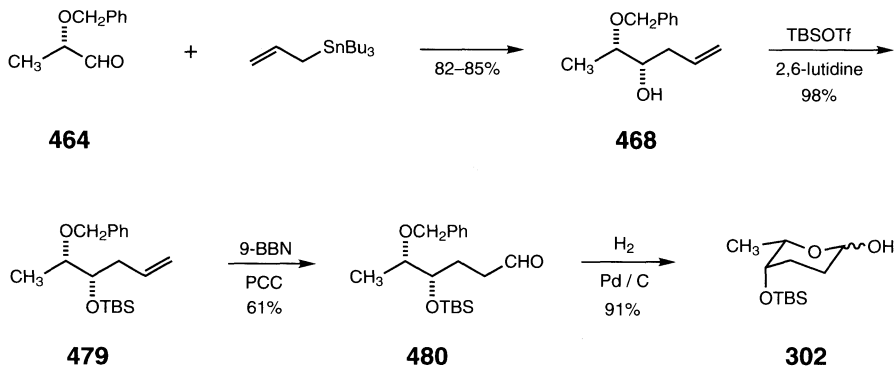


When the enantiomeric crotyl silane **477** is added to **464** with aluminum chloride catalysis, virtually no tetrahydrofuran products are produced. Instead, octenoic acid derivative **478** (with the *syn*-diol configuration) is formed as a single diastereomer.

Allylstannanes undergo similar reaction with α -alkoxy aldehydes under Lewis acid catalysis. The treatment of **464** with allyl tri-*n*-butylstannane in the presence of either MgBr₂·Et₂O [150] or lithium perchlorate-diethyl ether [153] furnishes protected *syn*-diol **468** with a diastereoselectivity of at least 25 : 1. This intermediate has been carried on to TBS-protected L-(-)-rhodnose (**302**) in an overall yield of 46% starting from *O*-benzyl ethyl lactate **271b** [150] (Scheme 69).

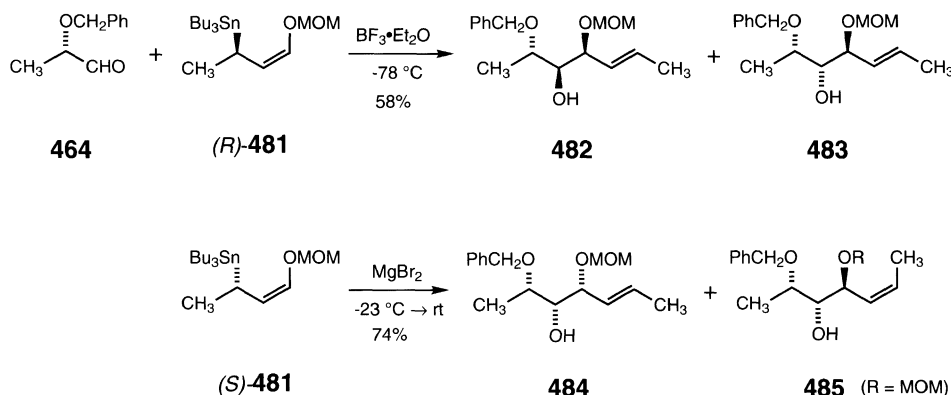


Scheme 68



Scheme 69

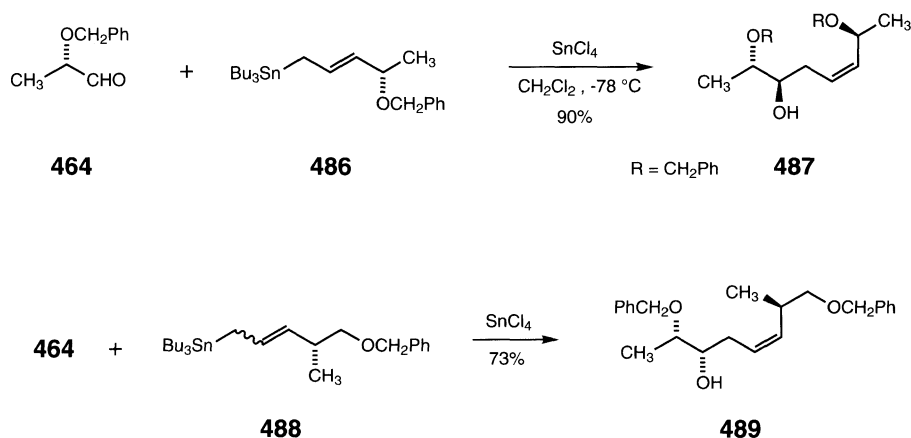
Using γ -alkoxyallylstannanes, one can gain access to a variety of stereochemically unique triols that may be of use in carbohydrate synthesis. Reaction of **464** with chiral stannane (*R*)-**481** gives a 92 : 8 mixture of homoallylic alcohols **482** and **483**. A similar reaction of **464** with the enantiomeric (*S*)-**481** under chelation-controlled conditions produces a 93 : 7 mixture of **484** and **485** [154] (Scheme 70).



Scheme 70

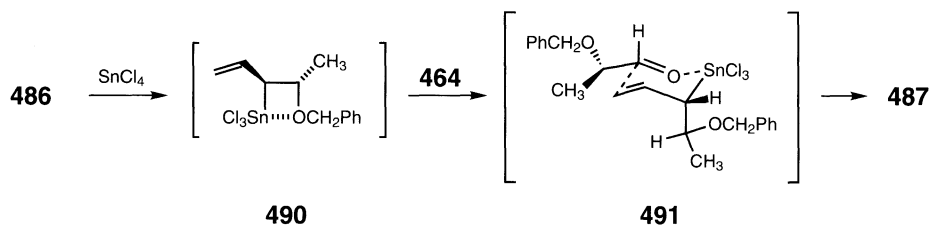
δ -Alkoxyallylstannanes show excellent 1,5-asymmetric induction upon reaction with aldehydes. Consequently, reaction of stannanes **486** or **488** with **464** gives diols **487** or **489** with > 95% diastereoselectivity [155,156] (Scheme 71). In the case of **487**, the stereochemical outcome of the reaction is sensitive to the chirality of the aldehyde. Upon reaction of (*S*)-**464** with (*S*)-**486**, a “matched pair”, one sees excellent stereoselection (> 95%), whereas with the enantiomeric (*R*)-**464** and (*S*)-**486**, a “mismatched pair”, the stereoselectivity falls to 70 : 30.

Mechanistically, the first step in the reaction is a transmetallation of allylstannane **486** with SnCl_4 to give an intermediate allyltin trichloride **490**. Reaction with aldehyde **464** proceeds



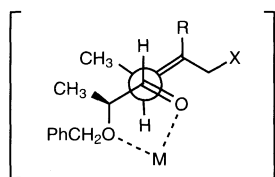
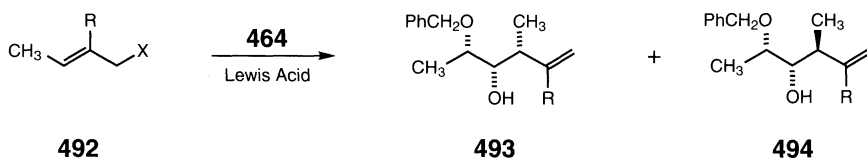
Scheme 71

through a chair-like transition state (**491**), in which the group α to the tin adopts an axial position in order to relieve steric interactions with the chlorine atoms on tin. Since the alkyl group of the aldehyde prefers to be in an equatorial position, the (*S*)-enantiomer **464** allows **490** to approach the *re* face of the aldehyde in accordance with the Felkin–Anh model, thus the “matched pair”. With the enantiomeric (*R*)-**464**, where the hydrogen and the methyl group of the aldehyde in transition state **491** are switched, the methyl group blocks the *re* face (“mismatched pair”), allowing alternative processes to compete and thus reducing stereoselectivity.



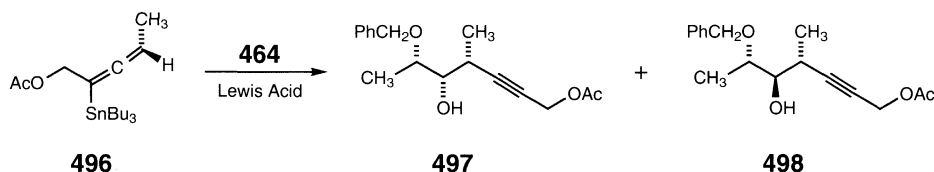
An unusual case of diastereoselectivity occurs in condensation reactions using β -methyl crotyl silanes or stannanes. In the absence of a β -substituent, reaction of **492** with **464** under chelation-controlled conditions gives the expected all-*syn* homoallylic alcohol **493** (R=H) as the predominant isomer. However, when a β -methyl group is introduced into **492**, the stereochemical outcome of the reaction changes to favor the *anti*-isomer **494** [157].

Mechanistically, when R=H, the usual *syn* selectivity is observed due to the preference of the reactants to adopt an antiperiplanar transition state, which places the aldehyde carbonyl and olefin opposite each other. When the β -methyl substituent is added, the transition state prefers the synclinal conformation (**495**) therefore leading to the formation of **494**.

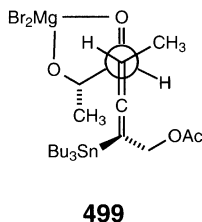
**495**

X	R	Lewis Acid	Yield (%)	493 : 494
SnBu ₃	H	MgBr ₂	80	90 : 10
SnBu ₃	CH ₃	MgBr ₂	85	24 : 76
TMS	CH ₃	MgBr ₂	80	11 : 89
TMS	CH ₃	SnCl ₄	90	3 : 97

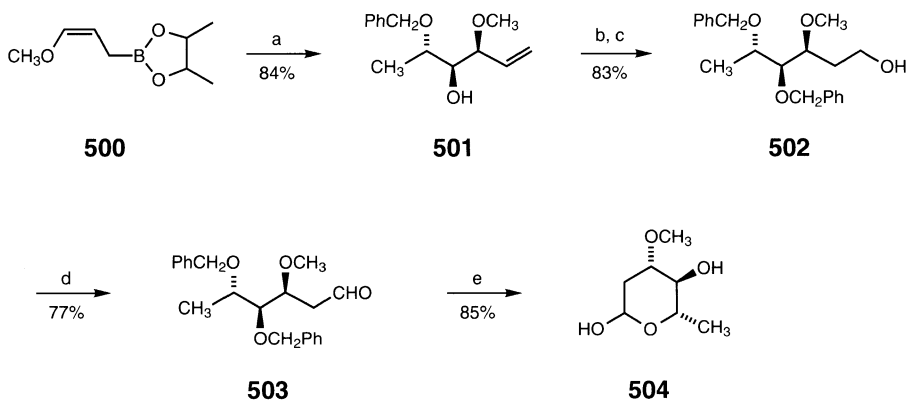
The use of allenylstannanes in this type of reaction furnishes homopropargylic alcohols. Reaction of **464** with (*S*)-**496** under Lewis acid catalysis affords **497** with excellent diastereoselectivity [158]. Boron trifluoride etherate-promoted addition produces a 68 : 32 mixture of *syn*- and *anti*-alcohols **497** and **498** (95% yield), while MgBr₂·Et₂O-promoted addition produces **497** with virtual exclusion of the *anti*-isomer (> 99 : 1).



The enhanced *syn* stereoselectivity again can be explained by chelation of magnesium to the aldehyde, leading to an antiperiplanar transition state **499** in which steric interactions are minimal.



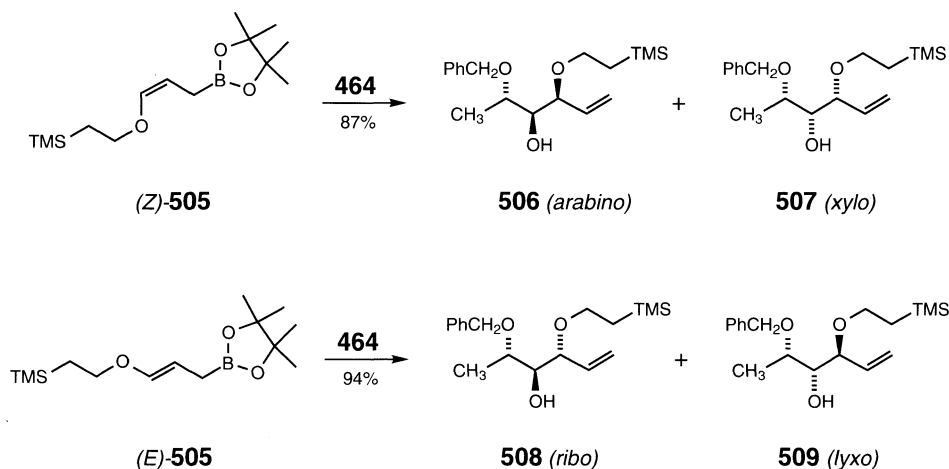
The three contiguous stereochemical centers of oleandrose (**504**), an important carbohydrate present in the avermectins, can be readily assembled in one step by the addition of a γ -methoxyallyl boronate (**500**) to **464** [159] (Scheme 72). This key reaction gives triol derivative **501** along with two minor isomers in a ratio of 8.7 : 1.2 : 1. Separation of these isomers is possible at the alcohol stage (**502**). Oxidation of the alcohol **502** to aldehyde **503** followed by hydrogenolysis of the benzyl groups gives **504** with 90% *ee*.



Scheme 72

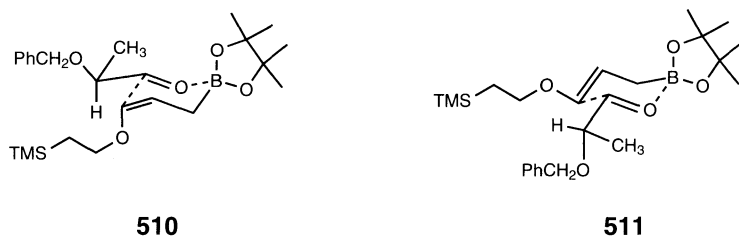
conditions: (a) **464**, THF; (b) KH, PhCH₂Cl, THF, 0 °C; (c) 9-BBN, THF, then H₂O₂; (d) PCC, NaOAc, Celite, CH₂Cl₂; (e) H₂, Pd(OH)₂, THF

In an analogous study of this type of reaction, both (*Z*) and (*E*)- γ -alkoxyallylboronates (**505**) react with **464** to give triol derivatives [160]. The (*Z*)-**505** boronate produces an 82 : 18 mixture of **506** and **507**, whereas the (*E*)-**505** boronate shows reversed selectivity, affording a 40 : 60 mixture of **508** and **509** (Scheme 73).



Scheme 73

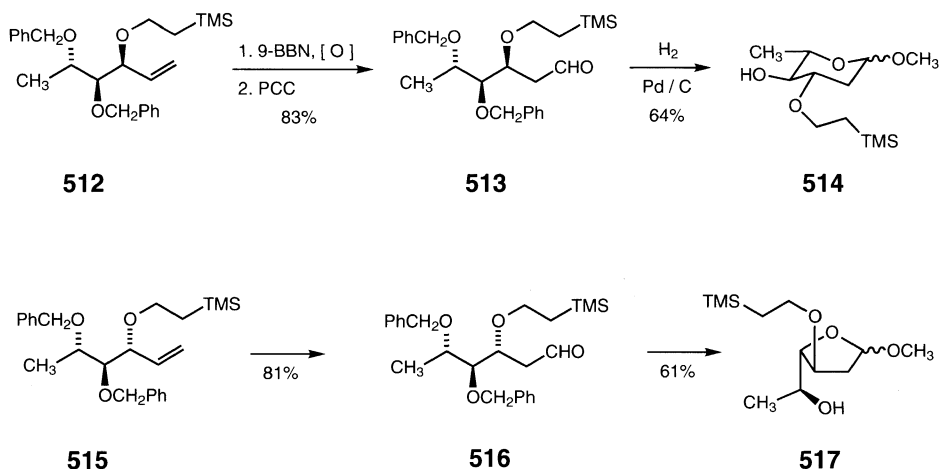
This can be rationalized by the reactants positioning themselves in a Cornforth-type transition state instead of a Felkin–Anh transition state. The preferred alignment of (Z)-505 and 464 can be represented by transition state **510**, whereas (E)-505 and 464 can be represented by **511**.



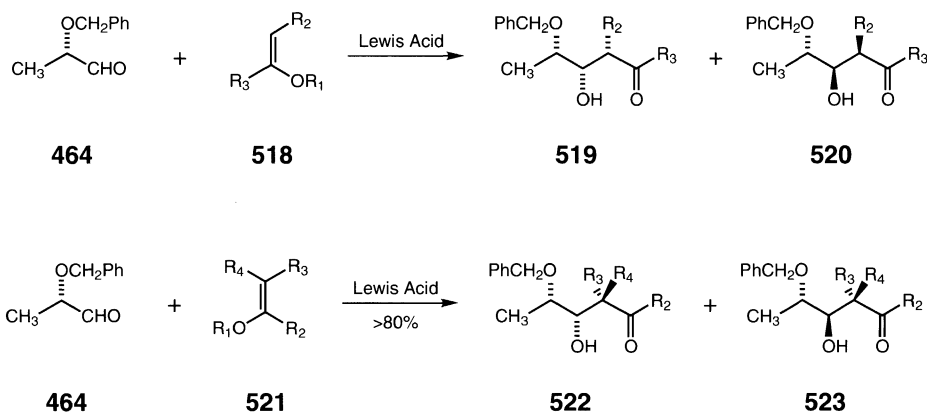
Compounds **506–509** are useful intermediates for the preparation of glycosides and furanosides. Benzylation of the mixture of homoallylic alcohols **506** and **507** gives a mixture of dibenzylated derivatives from which the major diastereomer **512** (Scheme 74) can be isolated by HPLC. Conversion of the olefin to an aldehyde followed by hydrogenolysis of the benzyl groups furnishes glycoside **514** (*arabino* configuration) directly as a 72:28 α/β -anomeric mixture. Similar treatment of the **508/509** mixture affords dibenzyl derivative **515**, from which an analogous set of reactions results in the formation of the methyl furanoside **517** as a 1:1 anomeric mixture.

The use of enol ethers **518** as the nucleophile in Lewis acid-mediated additions to (*S*)-2-benzyloxypropanal (**464**) leads to chiral β,γ -dihydroxy ketones **519** and **520**. The stereoselectivity of addition can be modulated by the nature of the Lewis acid. Non-chelating Lewis acids produce *anti*-isomer **520**, whereas under chelation control the *syn* isomer **519** is formed (Table 1.2).

Increasing the oxidation state from enol ether to ketene acetal allows one to gain access to *syn*- β,γ -dihydroxy esters (**522**) when the aldol addition is carried out under chelation control (Table 1.3). An excellent replacement for the standard Lewis acids in this type of reaction is $\text{Eu}(\text{fod})_3$ [92].



Scheme 74

Table 1.2. Aldol addition of enol ethers to **464**

R ¹	R ²	R ³	Lewis acid	Yield (%)	519 : 520	Reference
TMS	H	<i>tert</i> -Bu	BF ₃	85	10 : 90	161
TMS	H	<i>tert</i> -Bu	TiCl ₄	81	95 : 5	162
TMS	H	<i>tert</i> -Bu	SnCl ₄	86	> 99 : 1	163
TMS	H	Ph	SnCl ₄	68	> 99 : 1	163
TMS	CH ₃	Ph	TiCl ₄	—	97 : 3	161, 163, 164
TMS	CH ₃	Ph	F ⁻	—	18 : 82	161
CH ₃	SCH ₃ [a]	CH ₃	MgBr ₂	70	99 : 1	165, 166

[a] A mixture of (*E*) and (*Z*)-enol ether **518** was used, therefore the stereocenter at R² is also a mixture

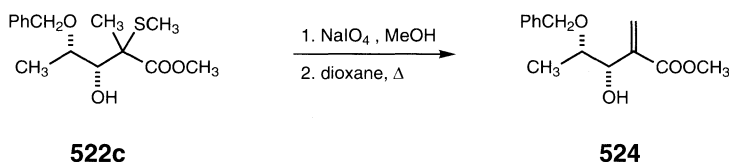
Table 1.3. Aldol addition of ketene acetals to **464**

R ¹	R ²	R ³	R ⁴	Lewis acid	522 : 523	Reference
TBS	OCH ₃	H	H [a]	LiClO ₄	92 : 8	167
TMS	OCH ₃	CH ₃	CH ₃	SnCl ₄	> 97 : 3	162
TMS	OCH ₃	CH ₃	SCH ₃ [b]	MgBr ₂	18 : 1	168
TMS	O <i>tert</i> -Bu	H	SCH ₃ [b]	MgBr ₂	25 : 1	165
TBS	S <i>tert</i> - Bu	H	CH ₃	SnCl ₄	97 : 3	169

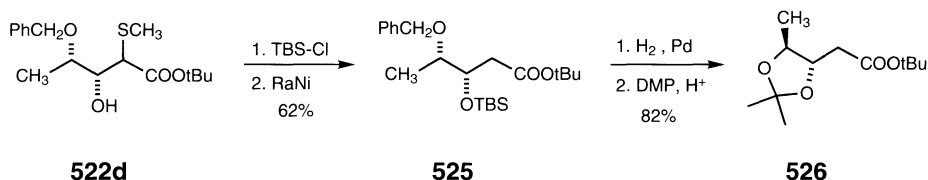
[a] Alcohol obtained after removal of the TBS group with HF

[b] A mixture of (*E*) and (*Z*) ketene acetal **521** was used, therefore the stereocenter at R³, R⁴ is also a mixture

The methylthio group of derivatives **522c** and **522d** can be used as a synthetic “handle” for further chemical transformations. Oxidation of the sulfur of **522c** followed by thermal elimination results in the formation of α,β -unsaturated ester **524** in 50–65% overall yield from **464** [168].



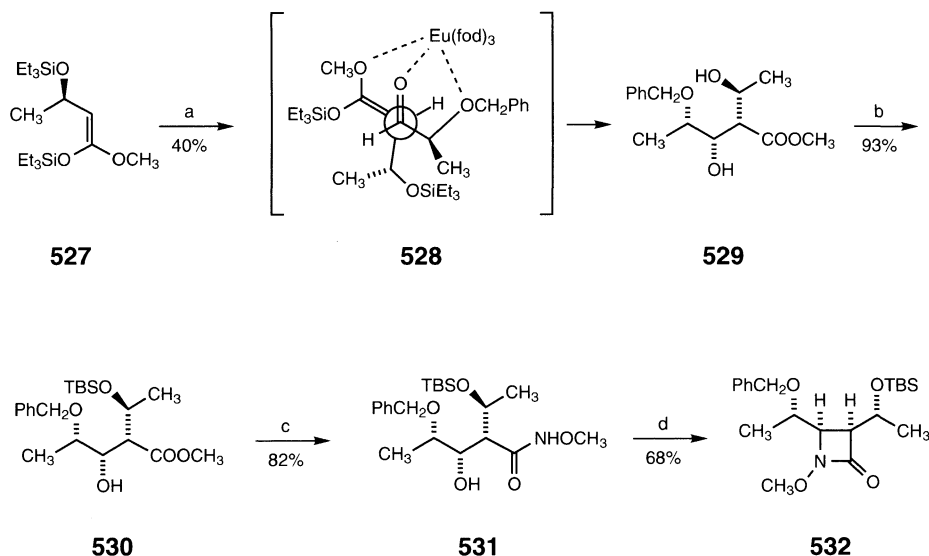
Desulfurization of **522d** with Raney nickel followed by debenzoylation and acetone formation gives **526** [165] in good yield. Both **525** and **526** are useful building blocks for the construction of macrolides and ionophores.



More complex ketene silyl acetals such as **527** (Scheme 75) undergo aldol condensation with **464** catalyzed by lanthanide(III) reagents to give a *syn*-adduct (e.g., **529**) with high diastereoselectivity [170]. The use of Eu(*fod*)₃ as the catalyst produces **529** (*syn* : *anti* ratio = 96 : 4) in 40% yield, whereas with Pr(*fod*)₃ the yield is slightly higher (52%) and the diastereoselectivity is slightly lower (*syn* : *anti* ratio = 95 : 5). It is interesting to note that trimethylsilylcyanide adds to **464** under europium(III) catalysis to afford a *syn*-cyanohydrin, but the diastereoselectivity is not as high as that observed with enol ethers or ketene acetals (*syn* : *anti* ratio = 71 : 29) [171].

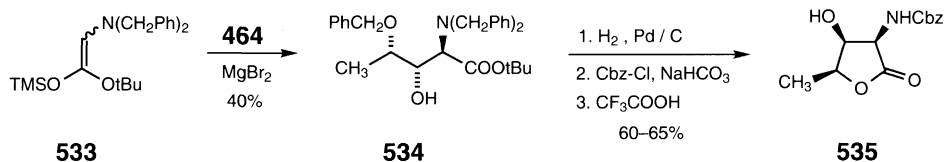
By the series of reactions outlined in Scheme 75, **529** is converted to β -lactam **532**, a useful intermediate for carbapenem syntheses.

Dibenzylamino silyl ketene acetal **533** reacts with **464** in an aldol fashion under standard Lewis acid catalysis to furnish the *syn*-adduct **534** with nearly complete stereocontrol



Scheme 75

conditions: (a) **464**, $\text{Eu}(\text{fod})_3$, CH_2Cl_2 , -40°C ; (b) TBS-Cl, imidazole, DMF; (c) CH_3ONH_2 (6 eq), Me_3Al (6 eq), toluene; (d) Ph_3P , DMAD, THF

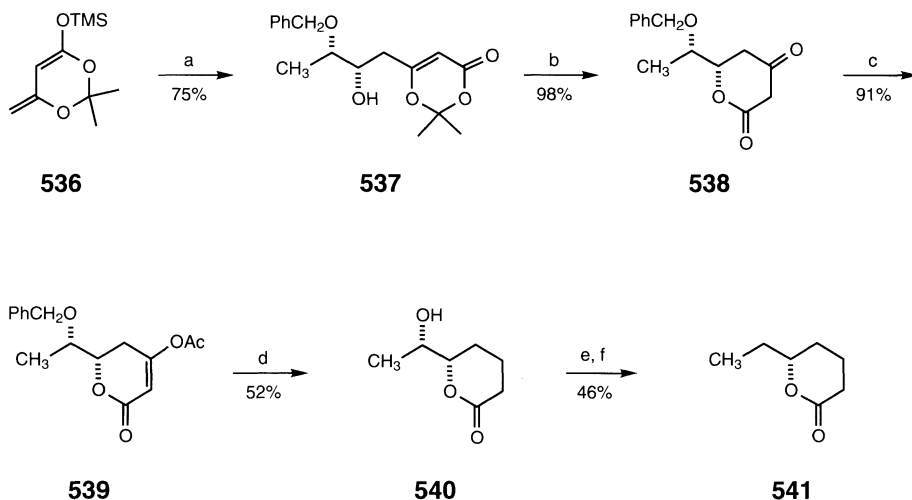


(*syn*:*anti* ratio = 98.6:1.4). With minor chemical manipulations, **534** can easily be transformed into lactone **535**, which is a known intermediate in the synthesis of L-daunosamine and L-vancosamine [172].

Cyclic ketene silyl acetal **536** has been used in a synthesis of the chiral δ -lactone **541** (Scheme 76). The chelation-controlled aldol reaction of **536** with **464** gives *syn*-adduct **537** as the sole product [173].

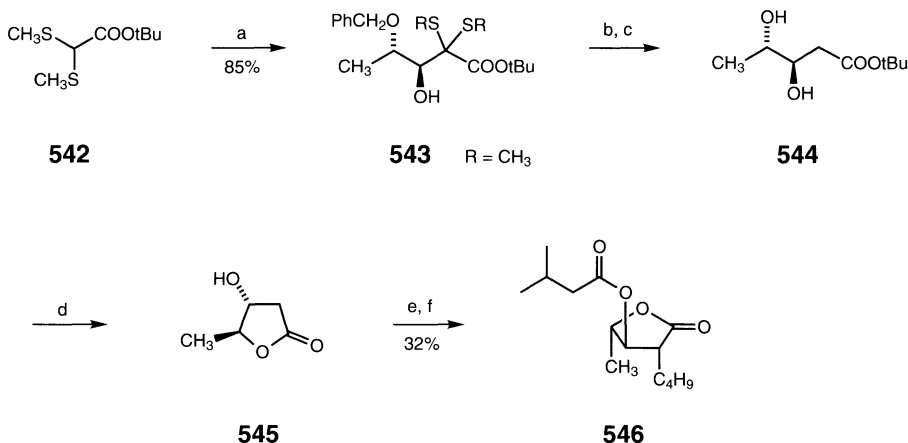
Ester enolates add to **464** producing adducts with varying diastereoselectivities depending on the nature of the ester. In the synthesis of (+)-blastmycinone (**546**), aldol reaction of lithiated **542** with **464** gives adduct **543** with high *anti*-selectivity (> 35:1) [166]. Desulfurization, debenzoylation, and acid-catalyzed lactonization gives optically pure lactone **545** in 62% overall yield from **543**. Stereospecific alkylation of the lactone with butyl iodide followed by acylation affords the desired product (Scheme 77).

In the synthesis of the branched sugar cladinoside (**552**) the aldol reaction of lithiated **547** with **464** does not proceed with high diastereoselectivity, although a respectable 70:23 ratio of *anti*-isomers **548** and **549** is obtained. The remainder of the mixture is the *syn*-3,4-isomer. The hydroxyl is then protected with a BOM group and the ester is reduced. At this stage the isomers are chromatographically separated, and the major isomer **550** is obtained in 54% yield



Scheme 76

conditions: (a) **464**, TiCl_4 , CH_2Cl_2 , -78°C ; (b) K_2CO_3 , MeOH ; (c) CH_3COCl , pyridine, CH_2Cl_2 ; (d) H_2 , Pd/C , HCl ; (e) thiocarbonyl diimidazole, CH_2Cl_2 ; (f) Bu_3SnH , AIBN

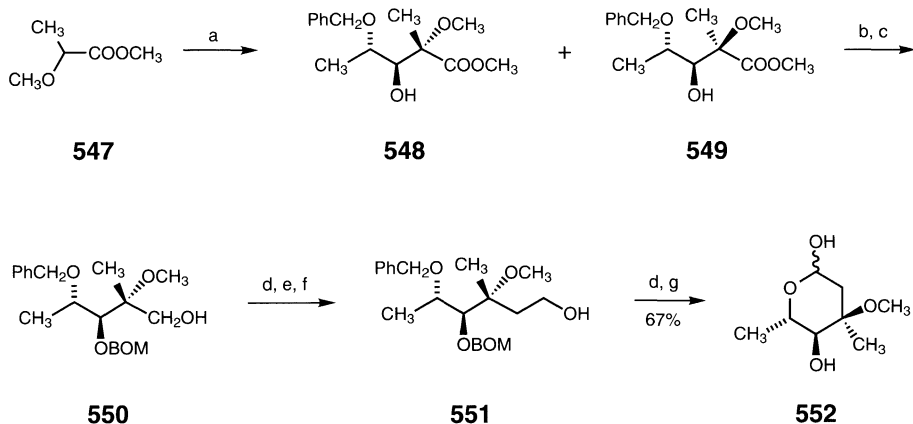


Scheme 77

conditions: (a) LDA , THF , -78°C , **464**; (b) H_2 , RaNi , EtOH ; (c) H_2 , Pd/C , EtOH ; (d) CF_3COOH , toluene; (e) $n\text{-BuLi}$, THF/HMPA , $n\text{-butyl iodide}$; (f) isovaleryl chloride, DMAP

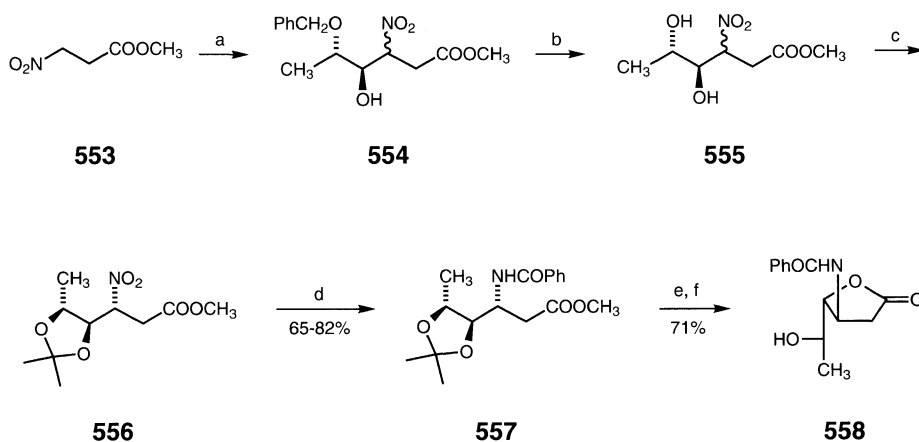
based on aldehyde **464** [174]. Chain extension, oxidation of the alcohol to an aldehyde, and simultaneous removal of both protecting groups leads to **552** as a mixture of anomers (Scheme 78).

An interesting variation on the theme is a nitroaldol reaction of methyl 3-nitropropionate (**553**) with **464**. The reaction is catalyzed by neutral alumina and gives **554** as a mixture of isomers [175] (Scheme 79). Debenzoylation and ketalization gives rise to the L-ribo acetone **556** as the major product (43% overall yield from **464**), and this is then converted in three



Scheme 78

conditions: (a) LDA, THF, $-78\text{ }^{\circ}\text{C}$, **464**; (b) BOM-Cl, $i\text{-Pr}_2\text{NEt}$; (c) LiAlH_4 ; (d) Swern oxidation (95%);
 (e) $\text{Ph}_3\text{P}=\text{CH}_2$, THF (96%); (f) 9-BBN, H_2O_2 , OH^- (84%); (g) H_2 , Pd / C, EtOAc, HClO_4

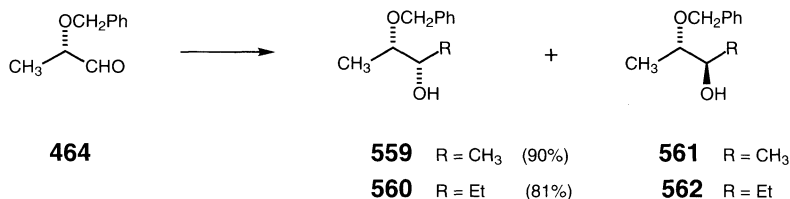


Scheme 79

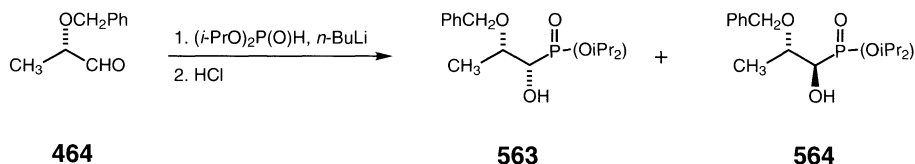
conditions: (a) **464**, neutral alumina; (b) 5% Pd / C, MeOH, H^+ ; (c) DMP, CSA, acetone;
 (d) H_2 , RaNi , $\text{O}(\text{COPh})_2$, MeOH; (e) $\text{CF}_3\text{COOH} - \text{H}_2\text{O}$ (9:1), $0\text{ }^{\circ}\text{C}$; (f) HCl, CH_2Cl_2

steps to the aminodeoxy sugar **558**. A parallel series of reactions starting from (*R*)-2-benzyloxypropanal furnishes the corresponding enantiomer. These sugars are synthetic precursors to L-ristosamine, L-acosamine, and L-daunosamine.

Addition of simple alkyl groups to aldehyde **464** furnishes partially protected alkane diols **559** or **560** as the major product. The methyl analog is prepared using the reagent CH_3TiCl_3 (CH_2Cl_2 , $-78\text{ }^{\circ}\text{C}$) which produces a 92:8 mixture of the *syn*-**559** and *anti*-**561** isomers [164]. The corresponding ethyl analog is available by reaction with tetraethyllead in the presence of titanium tetrachloride [176]. 1,2-Asymmetric induction is extremely high, as evident by the formation of a 98:2 mixture of **560** and **562**.



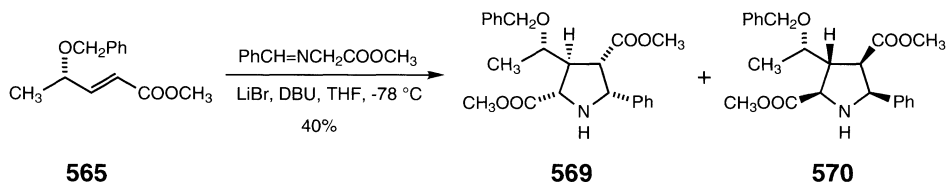
The synthesis of α,β -dihydroxyphosphonic acids is easily accomplished by the addition of lithiated diisopropyl phosphite to **464**. Unfortunately, under these conditions there is no asymmetric induction, and a 1 : 1 mixture of **563** and **564** is produced, but the two are separable by flash chromatography [177]. The highest ratio of diastereomers (1 : 3) is obtained using diisopropyl trimethyl phosphite. Treatment of either **563** or **564** with trimethyl-silyl-bromide followed by hydrogenolysis of the benzyl protecting group furnishes the corresponding free dihydroxyphosphonic acid.



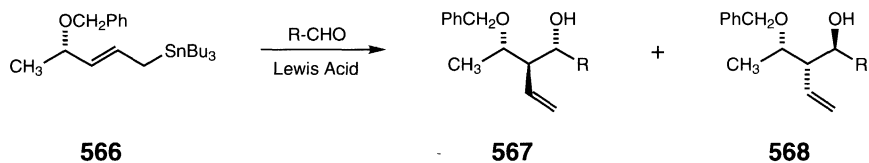
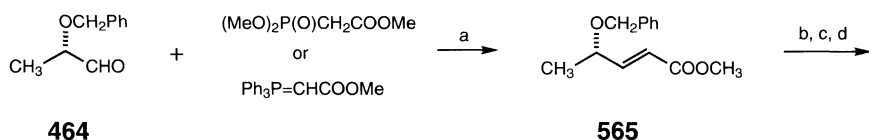
The aldehyde group of (*S*)-2-benzyloxypropanal not only undergoes aldol reactions but also more classical transformations to furnish a wide variety of synthetically useful intermediates.

The preparation of α,β -unsaturated ester **565** is easily accomplished by treatment of **464** with either trimethyl phosphonoacetate under Horner–Emmons conditions [178] or with the corresponding phosphorane under Wittig conditions [179]. Reduction of the ester to alcohol, conversion to chloride, and displacement with tributyltin lithium gives the allylstannane **566**. Reaction of this stannane with aldehydes under Lewis acid catalysis furnishes 2-vinyl-1,3-diol derivatives **567** or **568**, the stereochemistry of which depends on the nature of the Lewis acid [179]. The best examples are shown in Scheme 80.

Cycloaddition of **565** with azomethine ylide, generated from aryl glycine imine, furnishes tetrasubstituted pyrrolidines **569** and **570** in a ratio of 78 : 22 [178]. The diastereomeric ratio can be increased to 96 : 4 by using debenzylated **565**, which is available from the corresponding TBS-protected lactaldehyde.



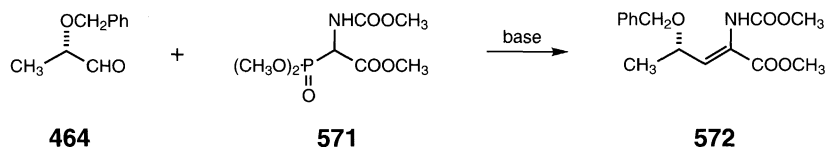
Wadsworth–Horner–Emmons olefination of aldehyde **464** with glycine phosphonate **571** affords dehydroamino acid **572**. The stereochemical outcome of the reaction hinges on the base used for deprotonation. A lithium base such as LDA gives a 1.5 : 1 mixture of (*Z*)-**572** and the corresponding *E* isomer (88% yield), whereas a potassium base (potassium *tert*-butoxide) produces only the *Z*-isomer, in 77% yield [180].



R	Lewis Acid	Yield (%)	567 : 568
	MgBr ₂ • Et ₂ O	45	29 : 71
	MgBr ₂ • Et ₂ O	35	5 : 95
	MgBr ₂ • Et ₂ O	40	>95 : 5
	BF ₃ • Et ₂ O	61	>95 : 5

Scheme 80

conditions: (a) NaH, THF, -30 °C (for phosphonate); (b) DIBAL; (c) MsCl, LiCl, Et₃N, DMF; (d) Bu₃SnLi, THF – hexane

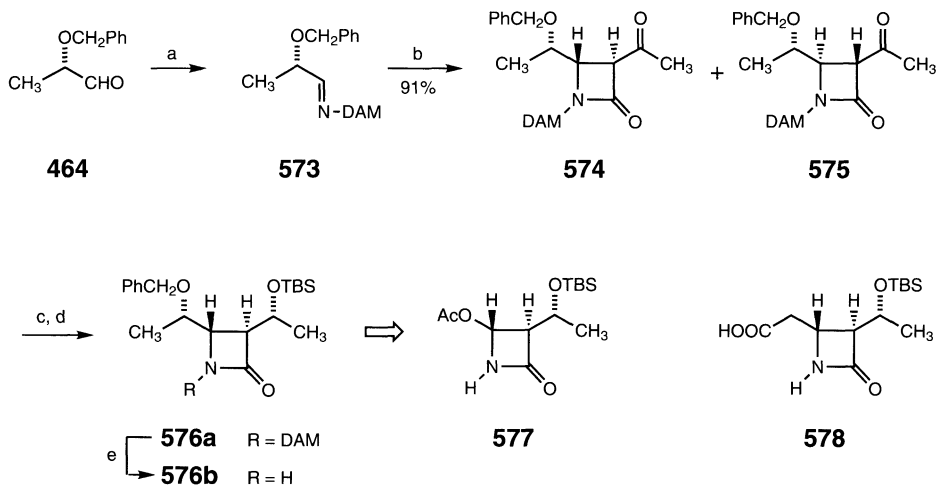


[2+2]-Cycloaddition of chiral imines with diketene allows one to gain access to chiral β -lactams. An interesting example of this is the reaction of lactate-derived imine **573** with diketene, which produces a 7.3 : 1 mixture of **574** and **575** [117]. Chromatographic separation of the major isomer furnishes **574** with an enantiomeric excess of 96%.

Reduction of the acetyl group followed by protection gives **576a**. If K-Selectride is used as the reducing agent, the secondary alcohol is formed as a 12 : 1 mixture of epimers. The minor epimer can be converted to the desired product by Mitsunobu inversion [117]. Removal of the DAM group under oxidative conditions can be effected with CAN, which furnishes **576b** in high yield. If the reduction is performed with triethylsilane–TFA–anisole in the presence BF₃•Et₂O, simultaneous hydrosilation and removal of the DAM group occurs to give **576b** (64% yield) directly as a 17 : 1 mixture of epimers [181]. The presence of BF₃•Et₂O in this

reaction is essential to increase the reaction rate, which in turn inhibits the formation of decomposition products.

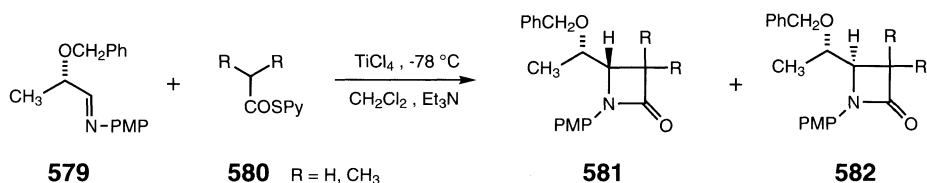
Derivative **576** has been carried on to **577**, an important carbapenem intermediate [94], and **578**, a key intermediate in the synthesis of thienamycin [117,182].



Scheme 81

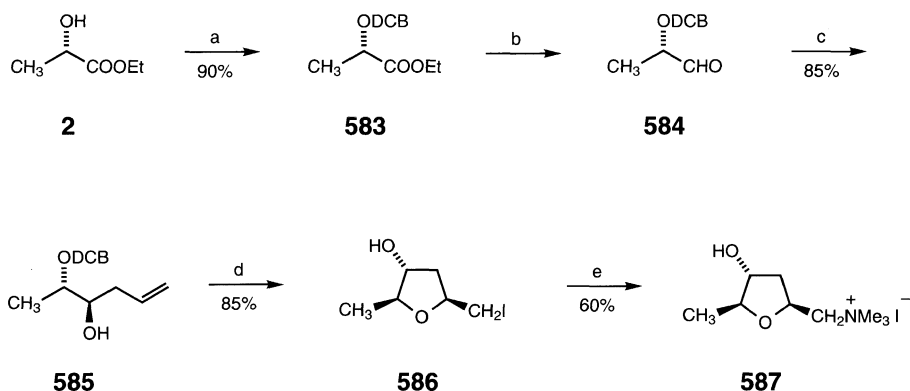
conditions: (a) DAM-NH₂, MgSO₄, toluene; (b) diketene, imidazole, CH₂Cl₂, -35 °C; (c) K-Selectride, THF, 0 °C (92%); (d) TBS-Cl, imidazole, DMF (97%); (e) CAN, CH₃CN – H₂O, -10 °C (93%)

Alternatively, *p*-methoxyphenylimine **579** has been used in a one-pot synthesis of β -lactams [183]. Reaction of **579** with the titanium enolate of a pyridyl thioester **580** produces the β -lactam nucleus. If R=H, a 65 : 35 mixture of **581** and **582** is obtained in 54% yield, but if R=CH₃ the diastereomeric ratio increases to 98 : 2 (80% yield). If **581** (R=H) is the desired product, an analogous reaction with the corresponding O-TBS-protected imine gives **581** with a stereoselectivity > 98 : 2.



(+)-Muscarine (**587**), an alkaloid isolated from the red fly agaric mushroom *Amanita muscaria*, is a powerful acetyl choline agonist and it, or its analogs, may have implications for the treatment of Alzheimer's disease. Although several syntheses have been reported, the shortest and most efficient to date is the five step approach shown in Scheme 82 [184].

Two interesting features of the synthesis worthy of some discussion are the addition of an organometallic reagent to aldehyde **584** and the choice of the protecting group. The zinc-mediated allylation of **584** produces a chromatographically separable 71 : 29 mixture of *anti* diastereomer **585** and the corresponding *syn* diastereomer (not shown). This stereoselectivity

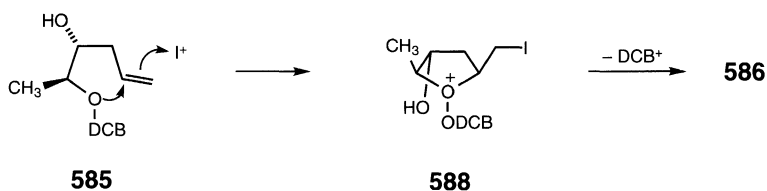


Scheme 82

conditions: (a) 2,6-dichlorobenzyl bromide, silver oxide, ether; (b) DIBAL, ether, $-78\text{ }^{\circ}\text{C}$; (c) allyl bromide, Zn, H_2O , NH_4Cl ; (d) I_2 , CH_3CN , $0\text{ }^{\circ}\text{C}$; (e) Me_3N , EtOH

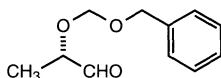
is the reverse of what one would expect from the predicted chelation-controlled model, but in this instance the solvent plays an important role in diastereoselection. Since the reaction is carried out in water, the aqueous medium disrupts chelation, thereby causing the process to occur through a Felkin–Anh transition state, which favors formation of the *anti* isomer. If the allylation is conducted with allylmagnesium bromide in an organic solvent, the *syn* isomer predominates, as predicted from the Cram model.

The 2,6-dichlorobenzyl (DCB) protecting group, due to its inherent delicate balance of steric and electronic characteristics, plays a key role in the iodocyclization of **585** \rightarrow **586**. Its slightly larger steric profile forces the 2- and 5-substituents of oxonium ion **588** into a *cis* orientation in order to alleviate potential 1,2- or 1,5-interactions. In addition, the DCB group is electronically balanced in such a way that dealkylation of the oxonium ion is slow enough to allow equilibration to the thermodynamically favored intermediate **588**. These two factors result in the stereospecific formation of **586**.



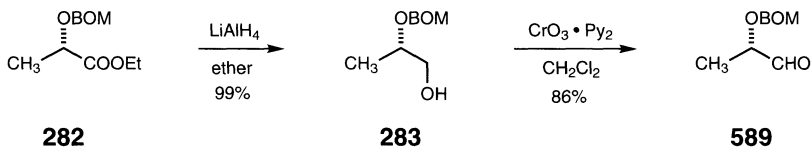
It is interesting to note that intermediate **585** has also been synthesized in six steps from D-threonine [185].

1.5.2 Benzyloxymethyl (BOM)

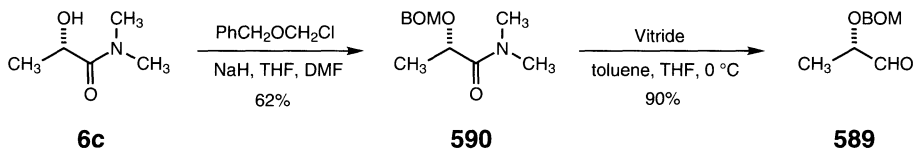


(S)-2-[(Phenylmethoxy)methoxy]propanal

BOM-protected lactaldehyde is available from lactate **282** via a two-step sequence involving reduction of the ester to alcohol **283** followed by Collins oxidation [100,186], or directly by partial reduction of the ester with diisobutylaluminum hydride in hexane at $-90\text{ }^{\circ}\text{C}$ (80% yield) [100].

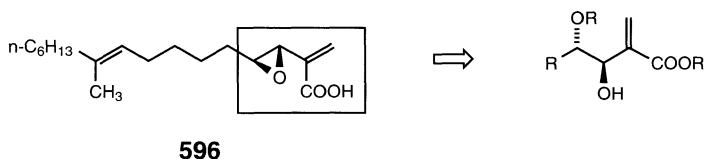


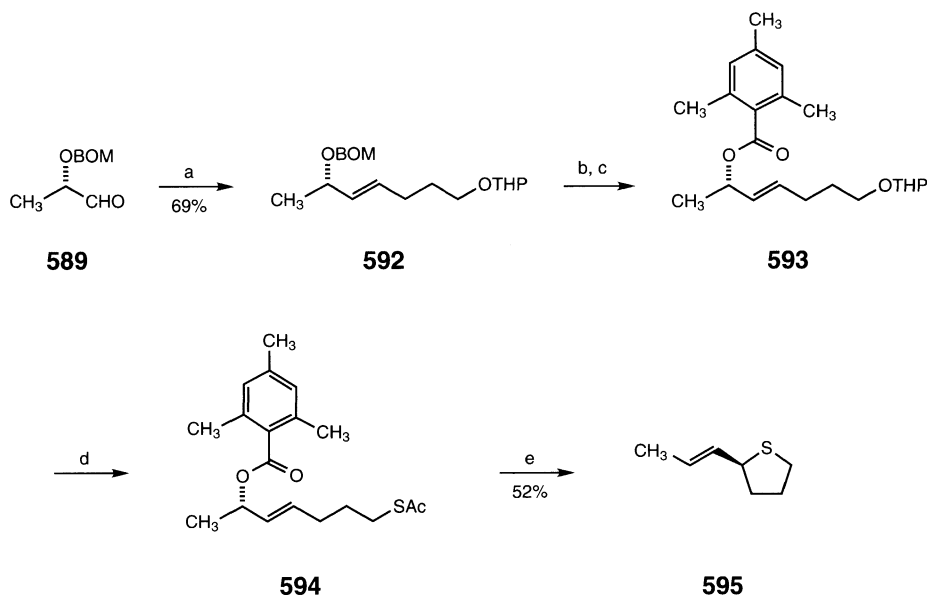
Alternatively, aldehyde **589** can be obtained from lactamide **6c** by alkylation with benzyloxymethyl chloride, which gives **590** with absolutely no racemization, followed by reduction of the amide with Vitride [95].



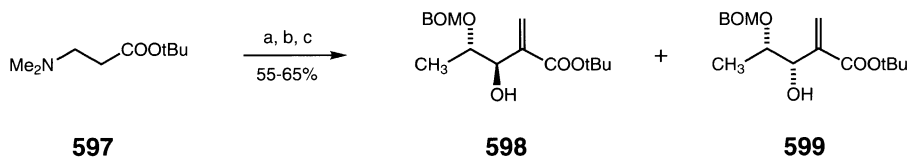
An interesting synthesis of thiophene **595** makes use of **589** in construction of the intermediate **594**. Wittig reaction of **589** with phosphorane **591** affords differentially protected diol **592**. Selective removal of the BOM group gives the secondary alcohol (76% optically pure), which upon mesitylation gives **593**. Removal of the THP group and conversion of the alcohol to an *S*-acetyl function gives **594**. Treatment of this compound with lithium methoxide produces an intermediate thiolate anion that cyclizes to thiophene **595** via an intramolecular $\text{S}_{\text{N}}2$ reaction. Addition of the thiolate ion occurs *anti* to the departing mesitoate, and results in formation of a 93 : 7 mixture of *E/Z*-isomers [186].

α -Methylene- β -hydroxy- γ -alkoxy esters are useful synthons for the synthesis of long-chain antibiotics such as thermozymocidin and conocandin (**596**). Conceptually, compounds of this type should be available through an aldol-type reaction between an aldehyde and an acrylate α -anion equivalent.



**Scheme 83**

conditions: (a) THPO(CH₂)₃CH=PPh₃ (**591**); (b) Li-NH₃, THF, aniline; (c) MeLi, mesitoyl chloride; (d) 0.1N H₂SO₄, acetone; (e) LiOCH₃ (10 eq), THF



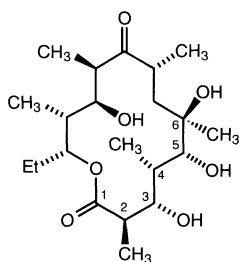
conditions: (a) LDA, THF, -78 °C, then **589**; (b) CH₃I, MeOH, -15 °C; (c) DBU, acetone

In practice, sequential treatment of chiral aldehyde **589** with the lithium enolate of β -(dimethylamino)propionate (**597**) followed by methyl iodide and then DBU, leads to esters **598** and **599** directly (*anti* : *syn* ratio = 80 : 20) [100,187]. The predominance of the *anti* diastereomer (**598**) is predicted by the Felkin model. The *tert*-butyl ester of **597** appears to be important, because analogous reaction with the corresponding methyl ester results in decreased diastereoselectivity (*anti* : *syn* ratio = 65 : 35).

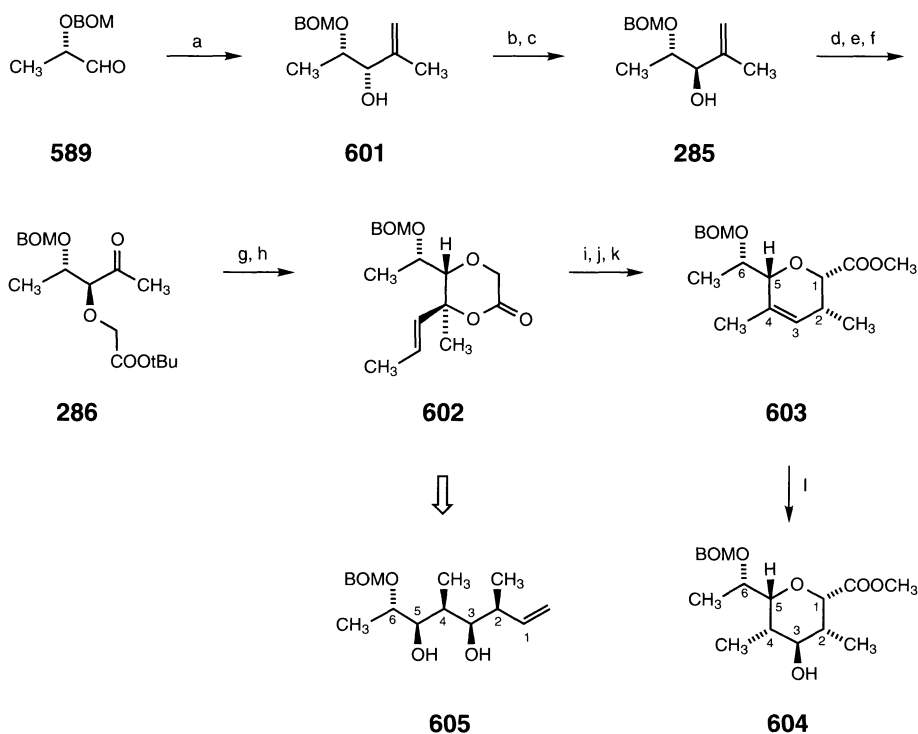
An important intermediate in the construction of the C-1 to C-6 ring fragment (**605**; see Scheme 84) of erythronolide B aglycone (**600**) is the highly functionalized tetrahydropyran **604**. Amazingly, all the stereochemistry associated with this molecule can be traced back to the simple lactaldehyde derivative **589**.

Chelation-controlled addition of 2-propenylmagnesium bromide to **589** affords a 4 : 1 mixture of allylic alcohols **601** and **285**. Since the stereochemistry of the major *syn* isomer **601** does not possess the correct configuration for the C-5 carbon of the fragment, it is converted to the desired *anti* isomer **285** by oxidation to an intermediate enone followed by reduction of the carbonyl with zinc borohydride (20 : 1 *ds*).

In a second chelation-controlled addition, **286** is converted to **602** by the addition of *trans*-propenylmagnesium bromide to the acetyl carbonyl, followed by lactonization. Dioxanone-

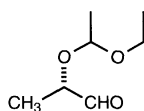
**600**

dihydropyran Claisen rearrangement (**602** → **603**) establishes the desired carbon skeleton. Oxidative hydroboration of the olefin introduces the final stereocenter at C-3 as a single isomer. Functional-group manipulation and reductive fragmentation of the tetrahydropyran C–O bond gives the target fragment **605** [188]. The entire thirteen-step sequence starting from ethyl lactate **282** proceeds in 11% overall yield, with 20 : 1 diastereoselectivity for each of the newly formed stereocenters from C-2 to C-5.

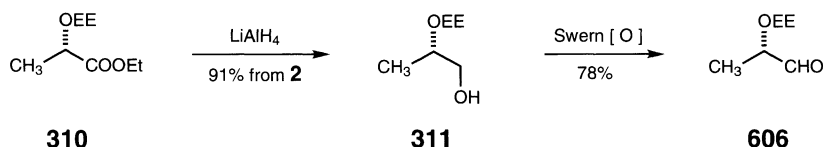
**Scheme 84**

conditions: (a) CH₂=C(CH₃)MgBr, THF, -78° → 25 °C; (b) Swern oxidation; (c) Zn(BH₄)₂, ether, -78 °C; (d) NaH, BrCH₂COOH; (e) *t*-BuOH, CH₂Cl₂, DCC, DMAP; (f) O₃, CH₂Cl₂ – MeOH (1:1), -78 °C, then Me₂S; (g) *trans*-CH₃CH=CHMgBr; (h) CF₃COOH; (i) LDA (2 eq), TMSCl, Et₃N; (j) toluene, 110 °C; (k) CH₂N₂, ether; (l) B₂H₆, then NaOH, H₂O₂

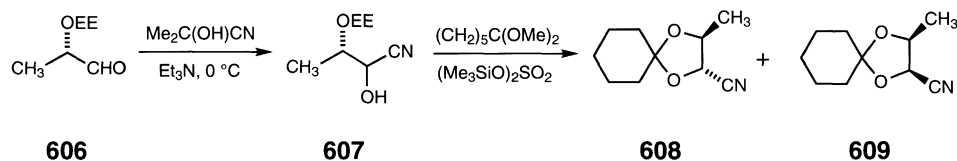
1.5.3 Ethoxyethyl (EE)

*(S)*-2-(1-Ethoxyethoxy)propanal

EE-protected lactaldehyde **606** is readily available from lactate **310** in two steps by reduction of the ester with lithium aluminum hydride to give *(S)*-2-ethoxyethyl-1,2-propanediol (**311**) followed by Swern oxidation to the aldehyde [189].

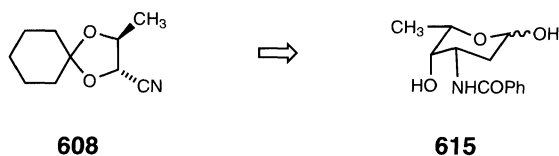


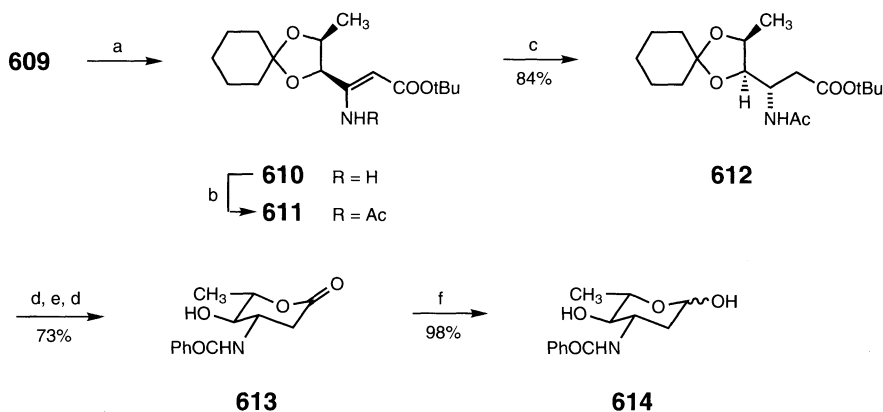
Addition of acetone cyanohydrin to **606** in the presence of a catalytic amount of triethylamine affords cyanohydrin **607** as a mixture of isomers. Ketalization with cyclohexanone dimethyl acetal gives a near statistical mixture (45 : 55) of (2*S*, 3*S*)-**608** and (2*R*, 3*S*)-**609**, which is separable by column chromatography (96% overall yield). Each isomer, with an optical purity greater than 95%, is a versatile intermediate, and they have been used in the synthesis of amino sugars *N*-benzoyl-L-acosamine (**614**) [189] (Scheme 85) and *N*-benzoyl-L-daunosamine (**615**) [190].



In the synthesis of L-acosamine, condensation of the predominant isomer **609** with the magnesium enolate of *tert*-butyl acetate gives **610** in 54% yield. Acetylation to **611** (77% yield) and subsequent catalytic hydrogenation in an autoclave (70 Kg/cm²) furnishes **612** as a single isomer. Acid hydrolysis of the ketal, benzoylation under Schotten–Baumann conditions, and lactonization affords **613**. Reduction of the lactone to a lactol with diisobutylaluminum hydride gives *N*-benzoyl-L-acosamine (**614**) as an anomeric mixture.

An identical series of reactions using the minor isomer **608** furnishes *N*-benzoyl-L-daunosamine (**615**) in comparable yield.





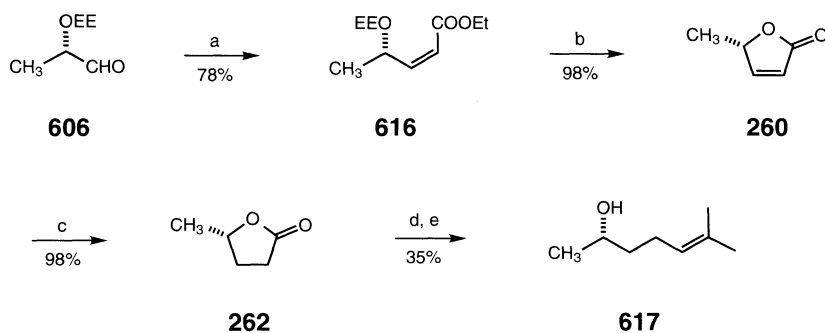
Scheme 85

conditions: (a) $\text{CH}_2=\text{C}(\text{OtBu})\text{OMgX}$, ether, $0\text{ }^\circ\text{C}$; (b) Ac_2O , pyridine; (c) H_2 , Rh / C, THF, $55\text{ }^\circ\text{C}$; (d) 2N HCl; (e) PhCOCl , aq. NaHCO_3 – acetone (5:2); (f) DIBAL, THF, $-60\text{ }^\circ\text{C}$

Chiral butenolides are versatile intermediates in asymmetric synthesis. In particular, (*S*)-(+)- β -angelica lactone (**260**) is extremely useful for the synthesis of γ -valerolactone natural products. It can be prepared in a straightforward manner by Wittig olefination of **606** with (ethoxycarbonylmethylene)triphenylphosphorane, which gives pentenoate **616** as an 82 : 18 mixture of *Z* and *E* isomers. After separation of the isomers by column chromatography, the desired (*Z*)-**616** is simultaneously deprotected and lactonized by treatment with a catalytic amount of sulfuric acid to furnish **260** in nearly quantitative yield [191].

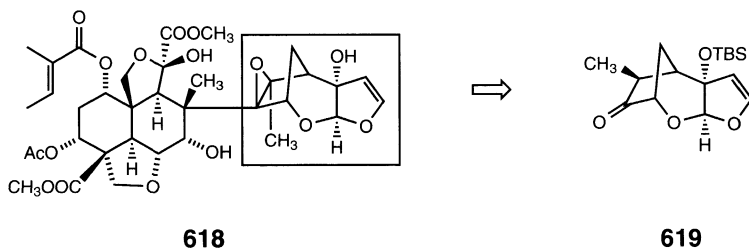
Lactone **260** can be transformed into the aggregation pheromone (*S*)-(+)-sulcatol (**617**) in three steps by catalytic hydrogenation of the olefin, partial reduction of the lactone to a lactol, and Wittig olefination with isopropylidetriphenylphosphorane (Scheme 86).

Azadirachtin (**618**), a terpenoid with strong antifeedant activity, possesses a unique bicyclic acetal subunit. Retrosynthetic analysis indicates that the intermediate **619** would be a suitable candidate for use in a convergent synthesis of the natural product.



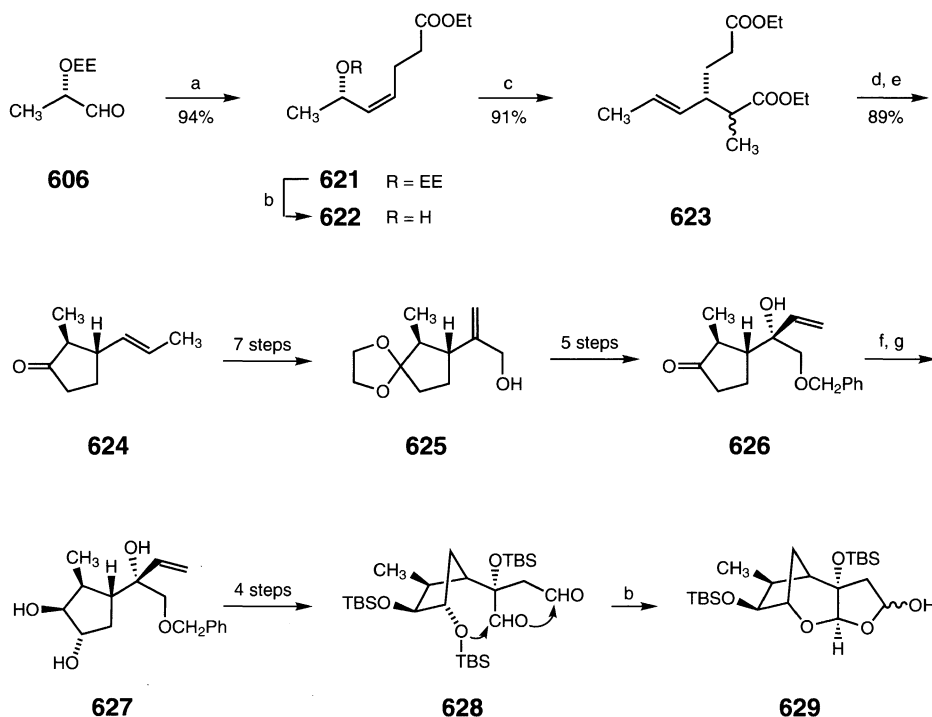
Scheme 86

conditions: (a) $\text{Ph}_3\text{P}=\text{CHCOOEt}$, MeOH; (b) 30% H_2SO_4 , MeOH; (c) H_2 , Rh / Al_2O_3 , EtOAc; (d) DIBAL, THF, $-78\text{ }^\circ\text{C}$; (e) $\text{Ph}_3\text{P}=\text{C}(\text{CH}_3)_2$, THF



The synthetic route to **619** is a rather lengthy 27-step sequence outlined in Scheme 87 [192]. The first key reaction is a Wittig olefination of **606** with phosphorane **620** to give **621** with >98% *Z*-selectivity. Subsequent Claisen rearrangement of the free alcohol **622** provides **623** with >98% stereoselectivity. Dieckmann condensation followed by decarboxylation gives the thermodynamically more stable *trans*-cyclopentanone **624** (*trans*:*cis* ratio = 7:1).

The next key series of reactions results in the transformation of **625** to **626**. The first step is a Sharpless epoxidation of the allylic alcohol. This is followed by a regiospecific oxirane ring opening with potassium benzyloxide to introduce the required oxygen that will eventually



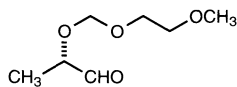
Scheme 87

conditions: (a) $\text{Ph}_3\text{P}=\text{CH}(\text{CH}_2)_2\text{COOEt}$ (**620**), THF, -78°C ; (b) $\text{HOAc} - \text{H}_2\text{O} - \text{THF}$ (3:1:1) (100%); (c) $\text{EtC}(\text{OEt})_3$, propionic acid, xylene, 140°C ; (d) KH , THF; (e) NaCl , H_2O , DMSO , 130°C ; (f) LDA , THF, -78°C , then MoOPH , -30°C (40%); (g) $\text{Me}_4\text{NBH}(\text{OAc})_3$, HOAc , CH_3CN (83%)

become an aldehyde later in the synthesis. Dehydration of the intermediate primary alcohol and hydrolysis of the acetal then gives **626**.

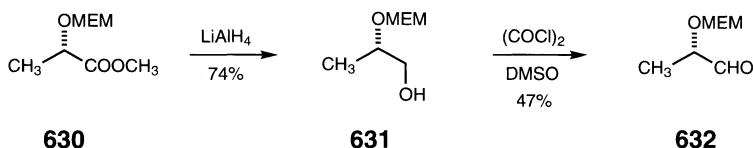
The last key reaction is the conversion of **628** to **629**. Selective desilylation under acidic conditions results in the spontaneous formation of the desired ring skeleton as a 3 : 1 diastereomeric mixture at the hemiacetal carbon. This is of little consequence, since the chiral center in question is destroyed when converted to the enol ether.

1.5.4 (Methoxyethoxy)methyl (MEM)



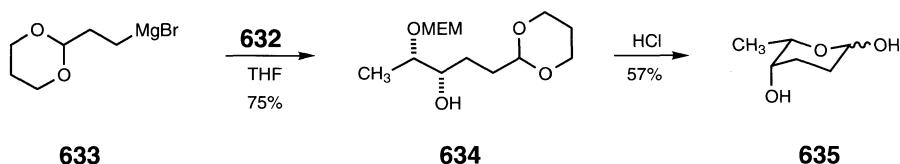
(*S*)-2-[(2-Methoxyethoxy)methoxy]propanal

MEM-Protected lactaldehyde **632** is prepared by the reduction of methyl lactate **630** with lithium aluminum hydride followed by oxidation of the resulting propanol **631** under Swern conditions [148]. A more straightforward approach is direct reduction of MEM ethyl lactate **372** with diisobutylaluminum hydride. When the reaction is performed at $-78\text{ }^{\circ}\text{C}$ or below, aldehyde **632** is obtained in 78–92% yield [100,116,117,129].



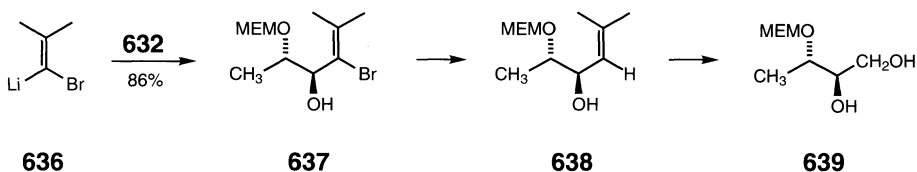
A short synthesis of L-(–)-rhodinosose (**635**), the trideoxyhexose subunit of the antibiotic streptolydigin, takes advantage of the propensity of Grignard reagents to add to lactaldehydes under chelation control (Cram's cyclic model) to produce *syn*-diols.

The key reaction, addition of Grignard reagent **633** to aldehyde **632**, proceeds at $-100\text{ }^{\circ}\text{C}$ to give adduct **634** with 95 : 5 *syn* diastereoselectivity [116]. The overall yield of the four-step sequence starting from ethyl L-lactate (**2** → **632** → **634** → **635**) is 31%.



Addition of vinyl lithium reagent **636** to **632** occurs largely from the *re* side (Felkin–Anh selectivity) to give the *anti* diastereomer **637** (85% *de*) [193]. Lithium–bromine exchange at $-78\text{ }^{\circ}\text{C}$ followed by protonation affords **638** in 89% yield with complete retention of olefin geometry. Ozonolysis of **638** followed by lithium aluminum hydride reduction of the intermediate aldehyde furnishes protected triol **639** in 78% yield.

When chiral organometallic reagents are added to chiral lactaldehydes, the outcome of the addition depends upon the synergistic effect between the two reaction partners. In one



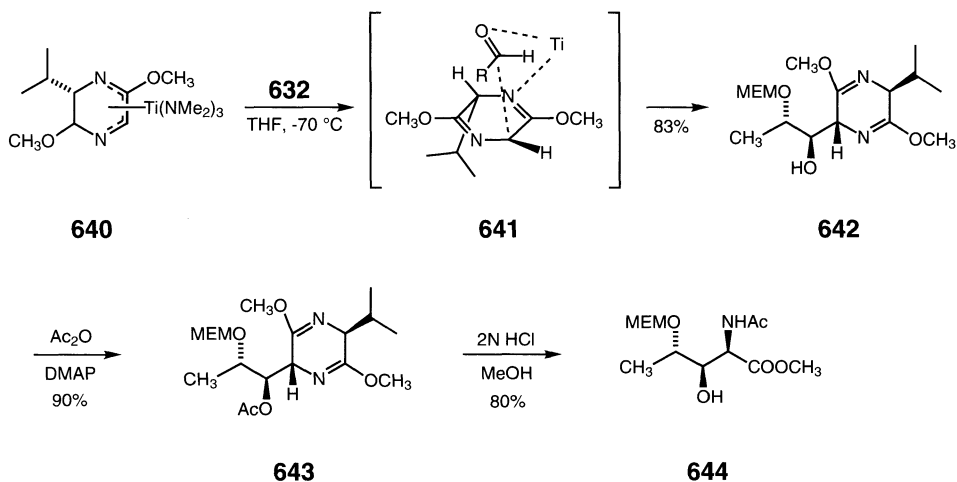
combination, the diastereofacial selectivity of both partners will be supportive (“matched pair”), generally accompanied by high diastereoselectivity. On the other hand, when the diastereofacial selectivity of the partners is in opposition (“mismatched pair”), diastereoselectivity is reduced.

A pertinent example of “matched pairing” is the reaction of (*S*)-lactaldehyde **632** with a titanium derivative (**640**) of the bislactim ether of cyclo-(L-Val-Gly) [194]. In the transition state (**641**), the disposition of the chiral center (R group) of the aldehyde is favorable with respect to the heterocycle, whereas in a “mismatched pair” the R group and the H would be reversed, and the interaction would be unfavorable. Consequently, carbonyl attack follows the Felkin model and gives the *anti* isomer **642** with an *anti*:*syn* ratio of 98.8:1.2.

The bislactim heterocycle behaves like a masked amino acid moiety and, after *O*-acylation, acidic hydrolysis furnishes the *N*-acyl amino acid ester **644** as a single diastereomer (Scheme 88). The acetyl group migrates from oxygen to nitrogen on distillation of the product.

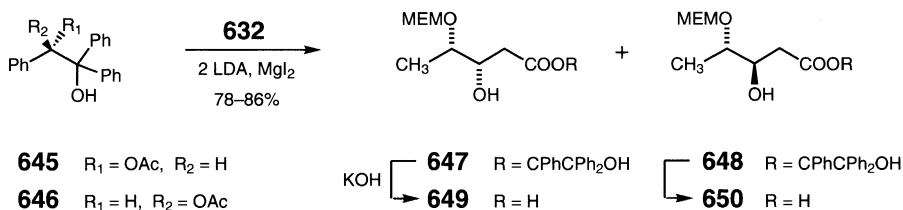
Addition to **632** of chiral enolates generated from mandelic acid-derived (*S*) or (*R*)-2-hydroxy-1,2,2-triphenylethyl acetate (HYTRA) produces *syn* or *anti*-dihydroxypentanoates of the type **647** or **648** [195]. In order to achieve the highest diastereoselectivity, the lithium enolates are transmetalated to magnesium in conjunction with carrying out the reaction at -125 to -135 °C in THF/2-methylbutane cosolvent.

The use of (*S*)-HYTRA (**645**) produces the mixture of **647** and **648** in an 87:13 ratio, whereas (*R*)-HYTRA (**646**) reverses the selectivity to favor the *anti* isomer **648** (*syn*:*anti* ratio = 8:92). At first glance, predominant formation of the *anti* isomer appears to violate the Cram cyclic model for chelation controlled conditions. However, the stereochemical outcome of this reaction is determined by reagent control rather than substrate control, which means that the diastereoselectivity is governed by the chirality of the HYTRA rather than **632**.

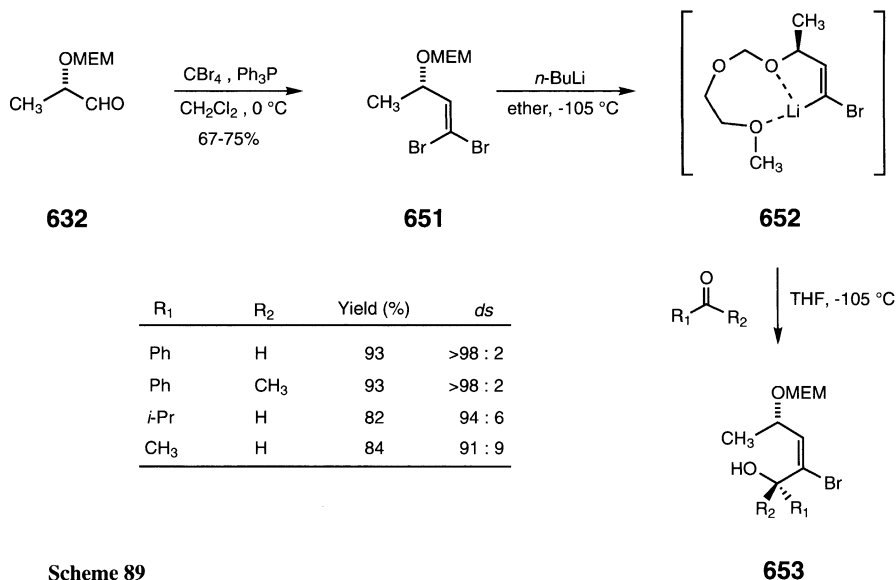


Scheme 88

Recrystallization of adducts **647** or **648** raises the diastereomeric purity to >98%. The free acid **649** or **650** is available from the adduct in nearly quantitative yield by base hydrolysis. This not only releases the desired acid, but also regenerates the chiral auxiliary, which may be recovered and recycled.



A unique chiral vinylolithium reagent (**652**) has been developed to make use of the MEM-protected lactaldehyde **632** as the source of asymmetry [196,197]. The organometallic precursor, dibromoalkene **651**, is prepared by treatment of **632** with carbon tetrabromide/triphenylphosphine reagent (Scheme 89).

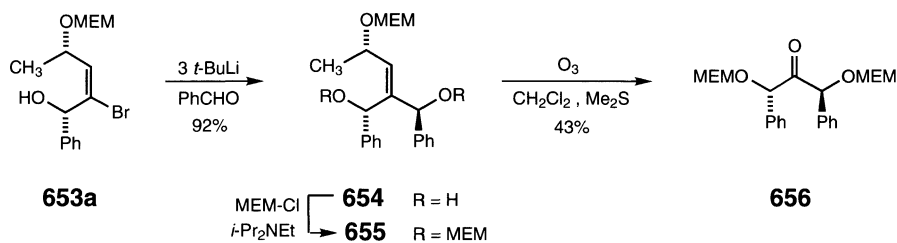


Scheme 89

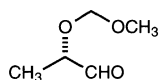
The organometallic is generated by lithium–bromine exchange using *n*-butyllithium in ether, which produces exclusively the thermodynamically favored (*Z*)-vinylolithium reagent **652** (our terminology in this instance reflects the configuration relative to lithium, not bromine). Subsequent addition of carbonyl compounds to this reagent affords adducts **653** with high diastereoselectivity. In order to achieve these high selectivities, ether/THF cosolvent must be used; however, this solvent mixture is deleterious to the exclusive formation of the (*Z*)-lithium reagent **652**. To circumvent the problem, lithium–halogen exchange is accomplished in ether, and THF is subsequently added prior to reaction with the carbonyl compound. The anion has also been quenched with carbon dioxide to give the (*Z*)-carboxylic acid derivative, with 99 : 1 regioselectivity. A second lithium–bromine exchange on **653** followed by protonation affords the corresponding (*Z*)-alkene (H in place of Br) in 90% yield.

It is interesting to note that the MEM group is critical for achieving high stereo- and enantioselectivities in the conversion of **651** to **653**. When analogous reactions are performed with the dibromoalkene protected with an ethoxymethyl group, which differs from the MEM group only by the terminal oxygen atom, both selectivities are diminished. The ratio of (*Z*)- and (*E*)-vinyllithium reagent drops to 87:13, while the stereoselectivity of carbonyl addition (e.g., to benzaldehyde) is reduced to 6.25:1 for the *Z*-adducts. The extra oxygen atom is obviously important for dual chelation of the lithium in **652**, which may in turn also position the methylene bridge in a favorable location with respect to the asymmetric center.

Enantiomerically pure C_2 -symmetric ketone **656** is available from carbinol **653a** by lithium–bromine exchange, addition of benzaldehyde, and ozonolysis [198]. In the first step, diol **654** is formed as a 75:25 mixture of diastereomers at the newly formed asymmetric center. The minor diastereomer is removed by column chromatography after ozonolysis.

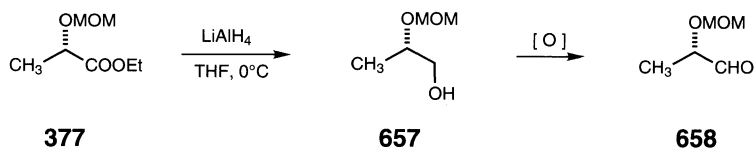


1.5.5 Methoxymethyl (MOM)



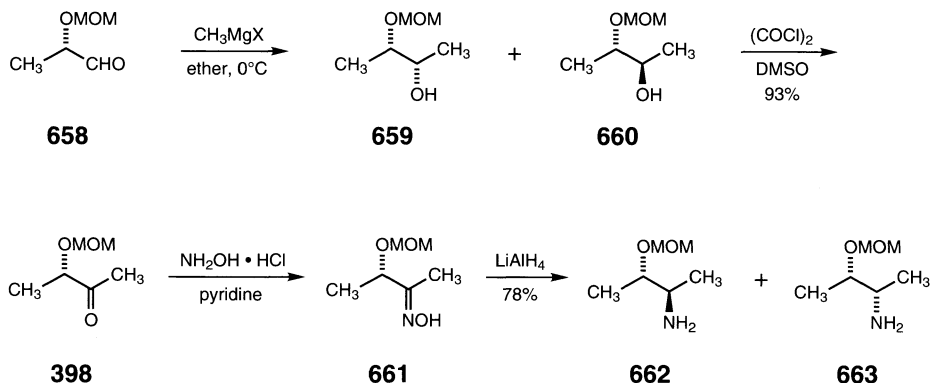
(*S*)-2-(Methoxymethoxy)propanal

The preparation of MOM-protected lactaldehyde **658** parallels that of the MEM derivative. It can be obtained in a two-step sequence in which lactate **377** is initially reduced to the propanol **657** and then oxidized to the aldehyde under Swern conditions [199] or with Collins reagent [100]. Overall yields starting from ethyl L-lactate (**2**) average about 50%. Alternatively, ester **377** can be reduced directly to aldehyde **658** (52% yield) with diisobutylaluminum hydride at -78°C [120,200].



Grignard reagents add to **658** in a fashion similar to that previously described for lactaldehydes to give predominantly *syn* alcohols as a result of chelation-controlled addition to the aldehyde. Consequently, when methyl Grignard is added to **658**, a 75:25 mixture of alcohols **659** and **660** is formed [199] (Scheme 90).

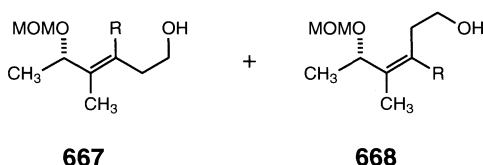
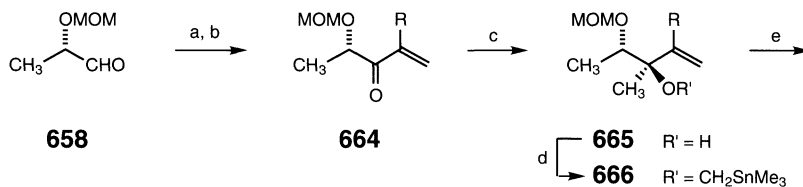
Oxidation of the mixture under Swern conditions produces ketone **398**, which upon treatment with hydroxylamine furnishes oxime **661**. Metal hydride reduction of **661** with either lithium aluminum hydride or AlH_3 results in the predominant formation of the *anti* amine **662** (*anti*:*syn* ratio = 70:30).



Scheme 90

A strategically similar approach has been used for the synthesis of tetrasubstituted acyclic olefins [201] (Scheme 91). The initial addition of a Grignard reagent to **658** followed by Swern oxidation of the intermediate mixture of alcohols affords enone **664**. Chelation-controlled addition of methyl Grignard to **664** gives the *anti* tertiary alcohol **665** as a single diastereomer.

After alkylation of the alcohol with iodomethyltrimethyltin (to give **666**), transmetalation to the lithium derivative, and [2,3] Wittig rearrangement of the resulting α -lithio ether, a mixture of *trans*-**667** and *cis*-**668** olefins is produced. In all cases the *trans* olefin predominates.



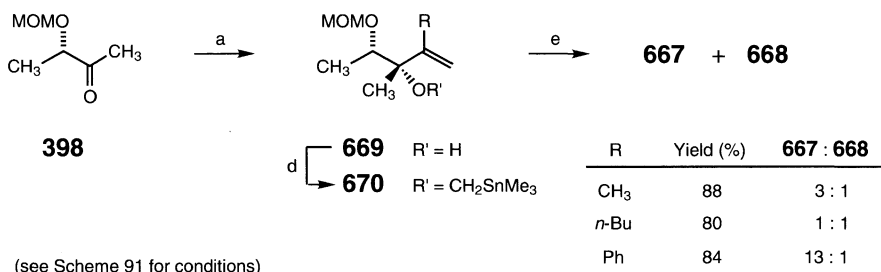
R	Yield (%)	667 : 668
CH ₃	84	10 : 1
<i>n</i> -Bu	80	3 : 1
Ph	83	4 : 1

characterized as benzoate derivative

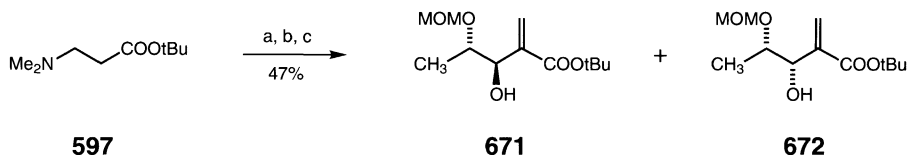
Scheme 91

conditions: (a) $\text{CH}_2=\text{C}(\text{R})\text{MgBr}$, THF, -78°C ; (b) $(\text{COCl})_2$, DMSO; (c) CH_3MgBr , THF, -78°C ; (d) KH, $\text{Me}_3\text{SnCH}_2\text{I}$, DME; (e) CH_3Li , THF, -78°C

When the [2,3] Wittig rearrangement is performed on the diastereomeric *syn* ether **670**, similar *trans* selectivity is observed in the formation of olefins **667** and **668**, although the magnitude of the effect is generally not as great as in the *anti* case. One exception is the phenyl derivative **667c**, in which the *anti*:*syn* ratio is increased to 13 : 1.

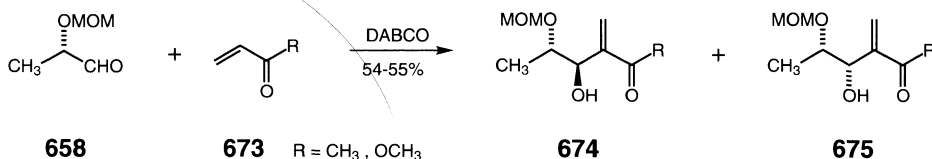


Addition of the lithium enolate of β -(dimethylamino)propionate (**597**), an acrylate α -anion equivalent, to **658** leads ultimately to the formation of α -methylene- β -hydroxy- γ -alkoxy esters **671** and **672** in a ratio of 83 : 17 [100]. The predominant formation of the *anti* isomer **671** is a direct result of Felkin-type addition. Ester **671** is a potentially useful synthon for the synthesis of long-chain antibiotics such as conocandin (**596**).

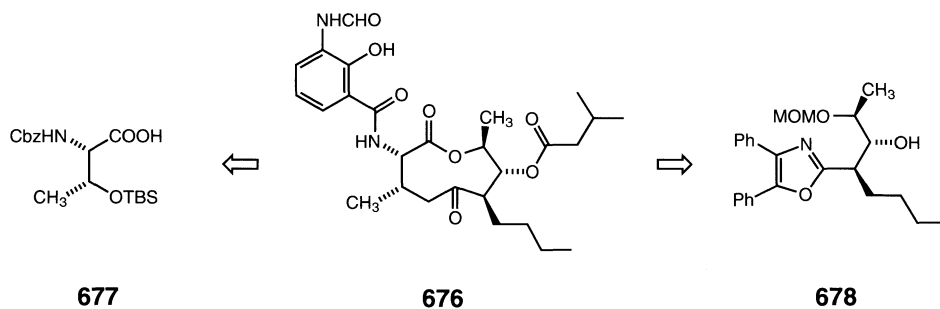


conditions: (a) LDA, THF, -78 °C, then **658**; (b) CH₃I, MeOH, -15 °C; (c) DBU, acetone

Similar types of compounds (**674**) are available through a direct reaction of **658** with the vinylcarbonyl compounds **673** in the presence of a catalytic amount of DABCO (10 mol%) [202]. For both derivatives, the *anti* isomer (**674**) predominates to approximately the same extent (70 : 30). In the case of enone **673** (R=CH₃), using 1-azabicyclo[2.2.2]octan-3-ol instead of DABCO as the catalyst increases the yield of the reaction from 54% to 80%. If the *syn* configuration is desired, it is available from the reaction of lactaldehyde **464** with ketene acetals under chelation-controlled conditions (see compound **524**, Section 1.5.1).

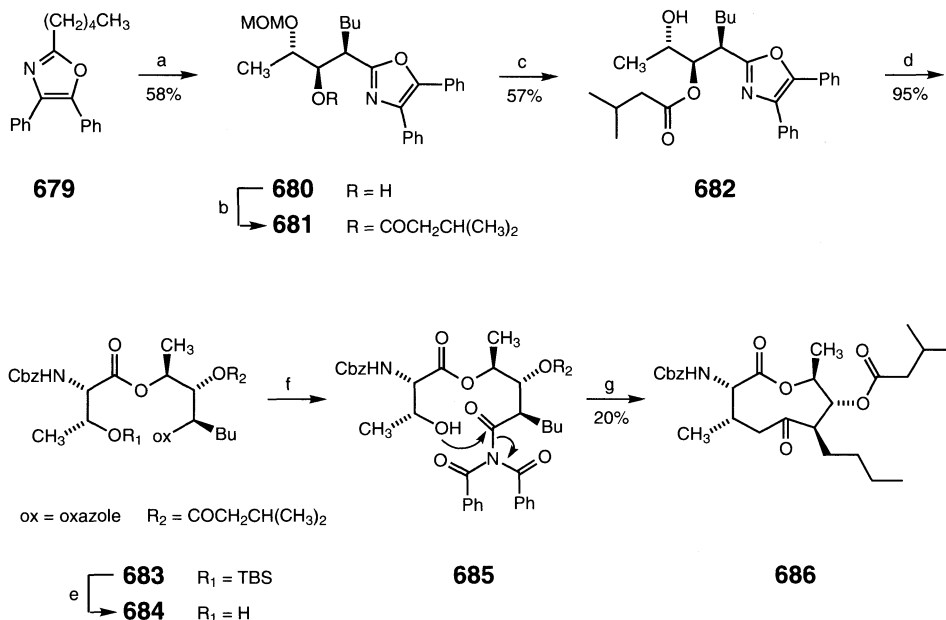


The synthesis of antimycin A₃ (**676**), a potent antifungal agent, makes use of lactaldehyde **658** to establish the stereochemistry of the three contiguous asymmetric centers in the “eastern” half of the dilactone skeleton *via* intermediate **678**. Strategically, the 4,5-diphenyl-oxazole heterocycle is used as a template for protection of the latent activated carboxylate group, which is unmasked by photooxygenation [120,200]. The chiral “western” half of the dilactone framework is derived from the differentially protected L-threonine derivative **677**.



The synthesis of the antimycin A₃ nucleus (**686**) is outlined in Scheme 92. In the first step, an aldol-type reaction of metallated **679** with lactaldehyde **658** produces **680** as a 4 : 3 : 2 : 1 mixture of the four possible diastereomers at the two newly formed asymmetric carbons. The major diastereomer **680** corresponds to the natural configuration of **676**. Although the desired diastereomer can be separated at this stage by repeated chromatography, it is more practical to perform the separation on the acylated derivative **681**.

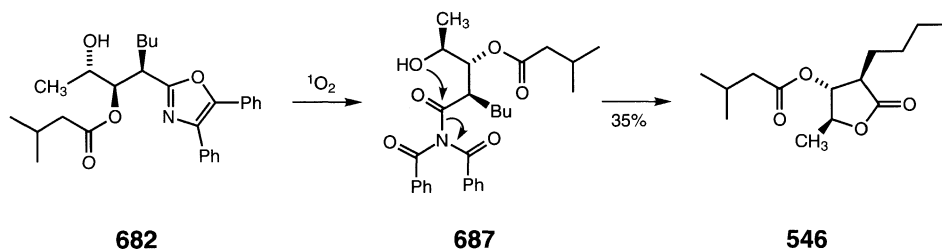
After removing the MOM group, esterification with threonine derivative **677**, and deprotection of the the TBS group, dye-sensitized photooxygenation of **684** cleanly affords triamide **685**. Without isolation, **685** is lactonized to the antimycin A₃ dilactone **686** in xylene in the presence of a catalytic amount of PPTS.



Scheme 92

conditions: (a) *n*-BuLi, THF, -78 °C, then **658**; (b) (CH₃)₂CHCH₂COCl, pyridine (74%); (c) BF₃ · Et₂O, PhSH, CH₂Cl₂; (d) **677**, DCC, DMAP, CH₂Cl₂; (e) Bu₄NF, THF, 0 °C (64%); (f) ¹O₂, CH₂Cl₂, Sensitox, 25 °C; (g) PPTS, xylene

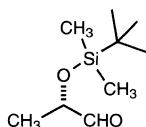
If the photooxygenation reaction is performed on intermediate **682**, (+)-blastmycinone (**546**), is produced directly without isolation of the triamide **687**.



1.5.6 Silyl-Protected Lactaldehydes

Silyl protecting groups impart a combination of unique steric and electronic properties on lactaldehyde that affects its overall reactivity. Of particular importance is the reaction of *O*-silyl lactaldehydes with organometallic reagents to furnish diols (after deprotection). The steric demands imposed by the silyl group (especially the massive bulk of the TBPS group) in conjunction with the reluctance of the silyloxy group to chelate almost assures the predominant formation of *anti* diols *via* a Felkin–Anh transition state. Therefore, when *anti* selectivity is desired, the silyl function is the protecting group of choice.

1.5.6.1 *tert*-Butyldimethylsilyl (TBS)

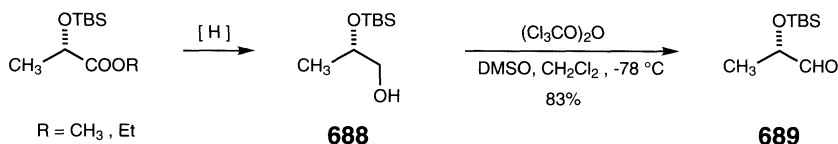


(*S*)-2-[[[1,1-Dimethylethyl]dimethylsilyl]oxy]propanal

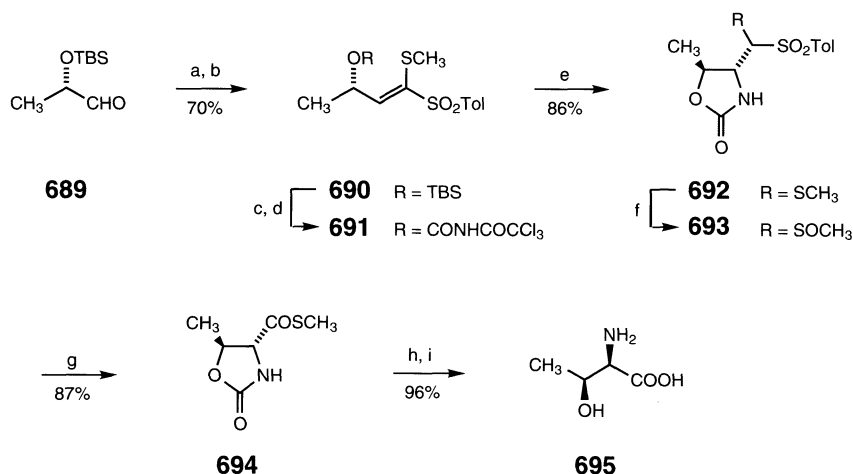
TBS-protected lactaldehyde **689** is readily prepared with high enantiomeric purity by a mild oxidation of the propanol **688** under Swern-type conditions using bis(trichloromethyl)carbonate (triphosgene)–DMSO [203]. Triphosgene is a white crystalline solid that is easily handled, and it is a safe alternative for such other DMSO activators as phosgene or diphosgene dimer.

Alternatively, **689** is available from lactate esters **401** or **402** by partial reduction with diisobutylaluminum hydride at $-78\text{ }^{\circ}\text{C}$ [117,129,148]. Yields for this process typically range from 76–100%.

Lactaldehyde **689** has been used as the chiral source in an interesting synthesis of unnatural D-threonine (**695**) [204] (Scheme 93). The first of the two most important reactions in the sequence is the conversion of **691** to **692**. The transformation proceeds by partial methanolysis of the trichloroacetyl group followed by intramolecular conjugate addition, which forms the oxazolidinone ring in **692** stereospecifically at C-4 and C-5. The second critical reaction is a Pummerer rearrangement of **693** to **694**, which introduces the requisite carboxyl function (as



a methyl thioester) with retention of configuration. The thioester group is then hydrolyzed under weakly basic conditions and the oxazolidinone ring cleaved under strongly acidic conditions to furnish D-threonine (**695**) in 45% overall yield starting from **689**.



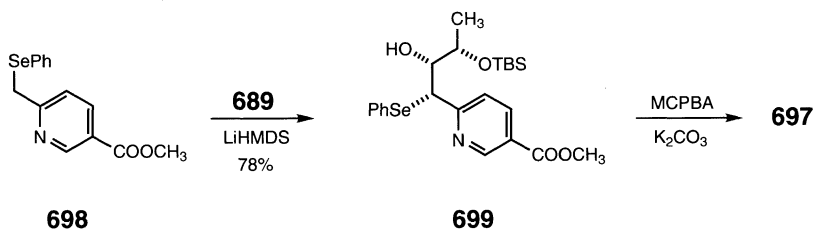
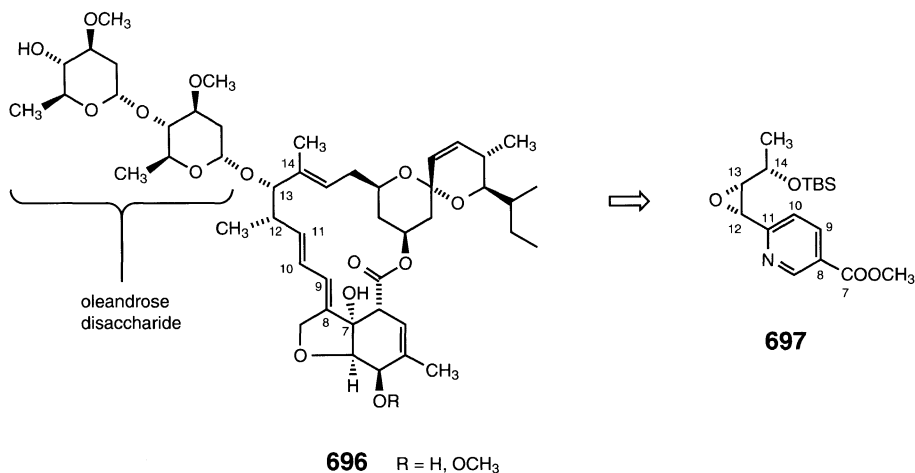
Scheme 93

conditions: (a) CH₃SCH₂SO₂Tol, *n*-BuLi, THF, -78 °C; (b) MsCl, pyridine; (c) 1N HCl, MeOH; (d) Cl₃CCONCO, CH₂Cl₂, 0 °C; (e) K₂CO₃, MeOH – CH₂Cl₂ (3:5); (f) MCPBA, CH₂Cl₂, 0 °C (90%); (g) (CF₃CO)₂O, pyridine, CH₂Cl₂, -15 °C; (h) K₂CO₃, H₂O – dioxane (1:1); (i) 6N HCl, 110 °C

The avermectins (**696**) represent an important class of macrolides used in the control of parasitic disease. Two skeletal fragments have been synthesized using TBS-lactaldehyde **689** as the source of chirality.

The first, synthon **697**, establishes the stereochemistry at C-12 and C-13 of the macrolide nucleus (after introduction of the methyl group at C-12). As an added bonus, the pyridine ring behaves as a masked form of the desired diene. Its synthesis is readily accomplished by a Darzens-type condensation of selenomethyl pyridine **698** with **689**. The resulting adduct **699** is formed as an 84 : 16 mixture of diastereomers. Oxidation of the selenium followed by intramolecular displacement of the phenylselenone by the hydroxyl group affords **697** in 45% overall yield [205].

The synthesis of the second fragment, the oleandrose disaccharide appendage, is outlined in Scheme 94 [206,207]. The sequence begins with the addition of vinylmagnesium bromide to **689**, which produces a 5 : 1 mixture of diastereomeric alcohols **700**. Without separation, these are quantitatively converted to the cyclic sulfite **701** upon deprotection and treatment of the resulting diols with thionyl chloride. Reaction of **701** with diiron pentacarbonyl under ultrasonic conditions produces a mixture of diastereomeric iron complexes which, when carbonylated at 230 atm, gives β,γ -unsaturated lactone **702**.



Epoxidation of the olefin leads to a mixture of unstable epoxides which, when ring opened with 2% triethylamine in pyridine, gives allylic alcohols **703** and **704** in 49 and 26% yields respectively. Compound **704**, called osmundalactone, is the aglycone of a naturally occurring glycoside isolated from the Vermont royal fern.

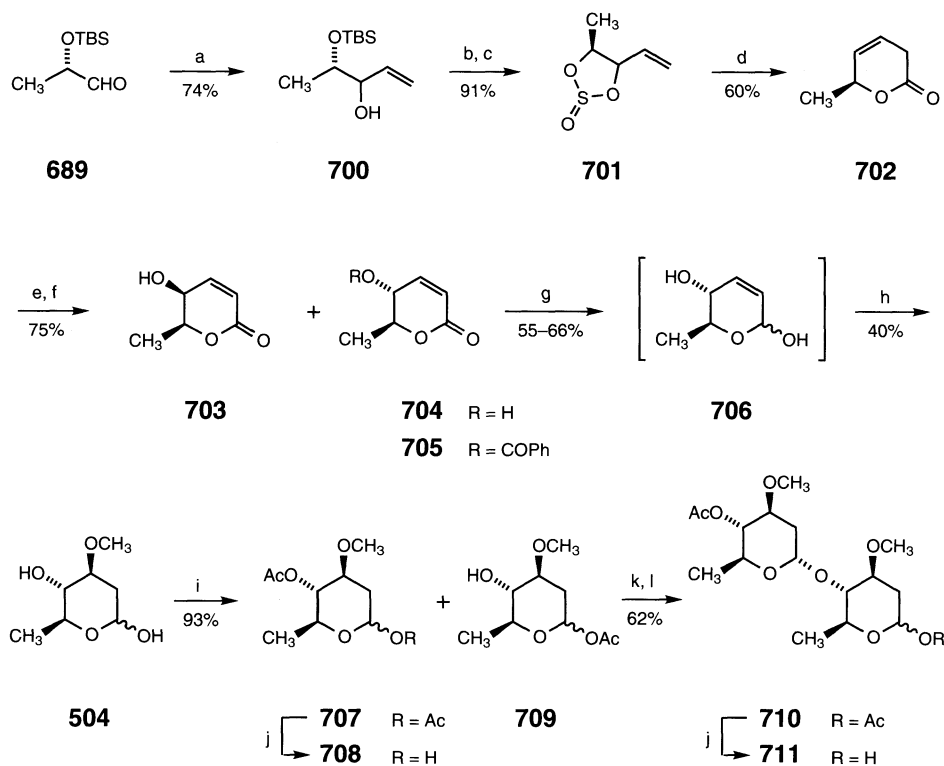
Since the natural configuration corresponds to the minor isomer **704**, the hydroxyl group of the major isomer **703** can be inverted under Mitsunobu conditions (PhCOOH, Ph₃P, DEAD) to give benzoate **705**. Either **704** or **705** can be reduced to lactol **706** with diisobutylaluminum hydride at -78°C . Immediate treatment of **706** with DBU in methanol affords oleandrose (**504**) along with a minor amount of the isomeric cymarose (epimeric at OCH₃, 15% yield).

Acetylation of **504** produces a 1 : 1 mixture of diacetate **707** and monoacetate **709**. After removal of the anomeric acetate of **707**, compounds **708** and **709** are coupled to give the oleandrose disaccharide **710**.

Derivatives of three related amino sugars, daunosamine (**386**), the carbohydrate component of adriamycin and daunorubicin, acosamine, a C-4 epimer of daunosamine, and ristosamine, the carbohydrate component of ristomycin, have been prepared from lactaldehyde **689**. All three syntheses begin with the same first step, the addition of methyl propiolate to **689**.

In the synthesis of *N*-benzoyl-L-daunosamine (**615**) (Scheme 95), addition proceeds according to the Felkin model to give a 5 : 1 mixture of the *anti*-**712** and *syn*-**713** isomers. Since the minor product **713** possesses the desired stereochemistry, the mixture is oxidized to ketone **714** and the carbonyl is then reduced with L-Selectride to regenerate the *syn* isomer **713** (*syn* : *anti* ratio > 12 : 1).

The critical step in the synthesis is the conversion of **716** to **717**, which proceeds by an intramolecular conjugate addition of the carbamoyl group to the (*Z*)- α,β -unsaturated ester. Cyclization occurs with complete 1,3-*anti* selectivity (> 100 : 1) [208]. It should be noted that



Scheme 94

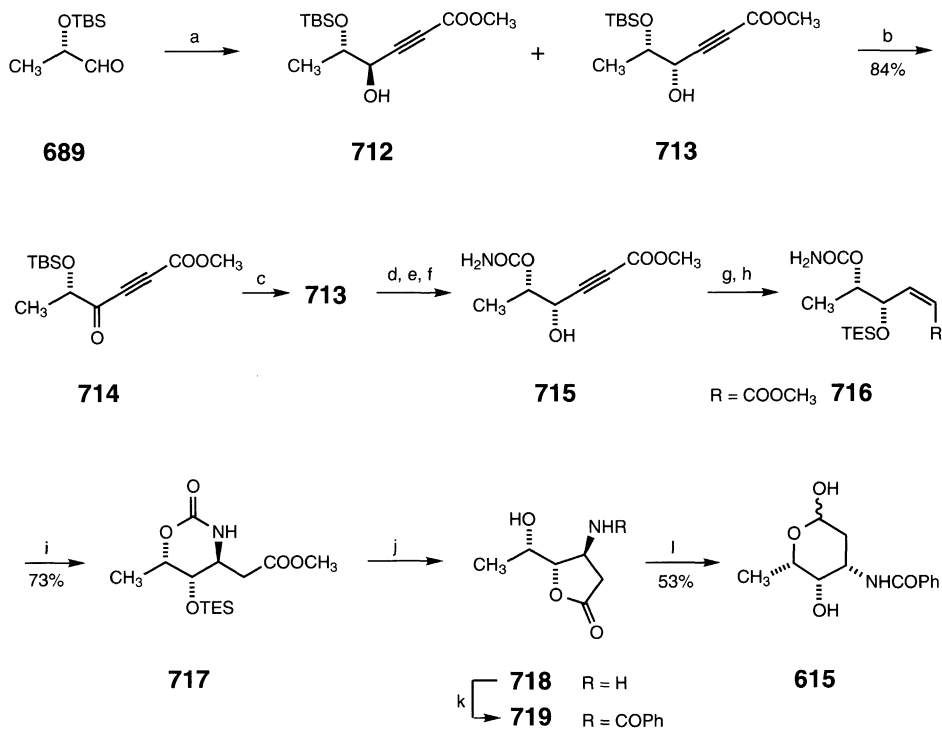
conditions: (a) $\text{CH}_2=\text{CHMgBr}$, THF; (b) PTSA, MeOH; (c) SOCl_2 , CCl_4 ; (d) $\text{Fe}(\text{CO})_9$, benzene, ultrasound, then CO (230 atm); (e) dimethyldioxirane, ether, 0°C ; (f) Et_3N , pyridine; (g) DIBAL, -78°C ; (h) DBU, MeOH; (i) HOAc, CDI, CH_2Cl_2 ; (j) LiBHET_3 , THF, -78°C (95%); (k) CDI, CH_2Cl_2 ; (l) AgClO_4

the contaminating *anti* isomer in the formation of **713** is removed later in the synthesis by recrystallization of **716**.

In the synthesis of *N*-acetyl L-acosamine (**726**) (Scheme 96), the desired stereochemistry is present in the predominating *anti* isomer **712**, so it is necessary that the mixture be purified by column chromatography at this stage [209]. Once again, preferential intramolecular conjugate addition of the allylic carbamate of **722** in the critical reaction affords oxazolidinone **723** with 40 : 1 *syn* selectivity. Alkaline hydrolysis followed by lactonization gives a 3 : 1 mixture of δ -lactone **724** and γ -lactone **725**. Treatment of the mixture with DIBAL and subsequent hydrolysis of the remaining O-acetyl group furnishes the desired product **726**.

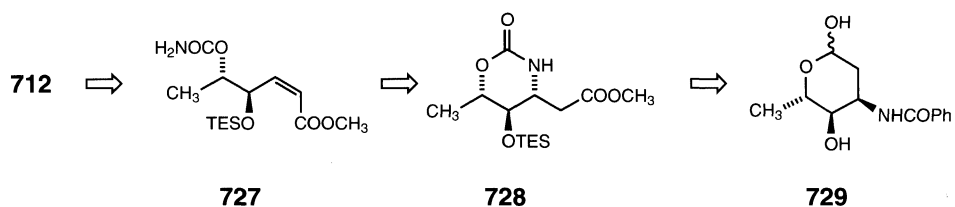
The synthesis of *N*-benzoyl L-ristosamine (**729**) parallels that of **615** (Scheme 95) on the basis of *anti*-**712** instead of *syn*-**713** [209].

Conjugated polyene fragments occur in a wide variety of naturally occurring organic compounds, such as macrolides, carotenoids, and leukotrienes. The synthesis of *all-trans* triene **734** is readily accomplished by low-valent titanium-induced reductive elimination of 1,6-dibenzoate-2,4-diene **733** [210] (Scheme 97). The requisite *cis*, *cis*-diene geometry is obtained by a stereospecific reduction of diyne **731** with activated zinc-copper couple.



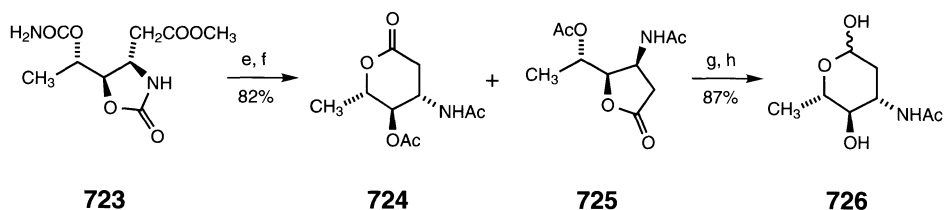
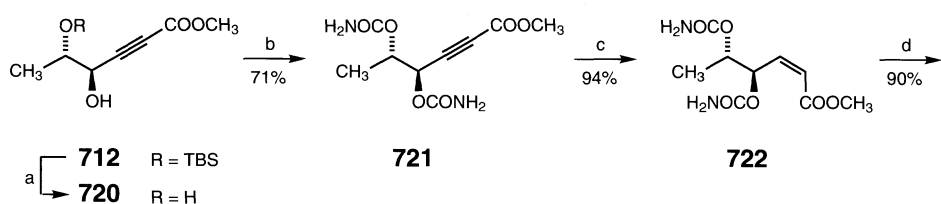
Scheme 95

conditions: (a) methyl propiolate, LDA, THF, -78 °C; (b) Jones reagent, acetone; (c) L-Selectride, THF, -78 °C; (d) DHP, H⁺ (84%); (e) Bu₄NF (74%); (f) ClSO₂NCO, -78 °C, then H₂O, 60 °C (55%); (g) Et₃SiCl, imidazole, DMF (89%); (h) H₂, Lindlar catalyst, toluene (71%); (i) KO^t-Bu, THF, 0 °C; (j) NaOH; (k) PhCOCl, NaHCO₃; (l) DIBAL, THF, -78 °C



The asymmetric aldol reaction of chiral aldehydes with ketene silyl acetals provides immediate access to β,γ -dihydroxy acid derivatives. The reaction can be promoted with a variety of catalysts, the nature of which may determine the stereochemical outcome of the condensation.

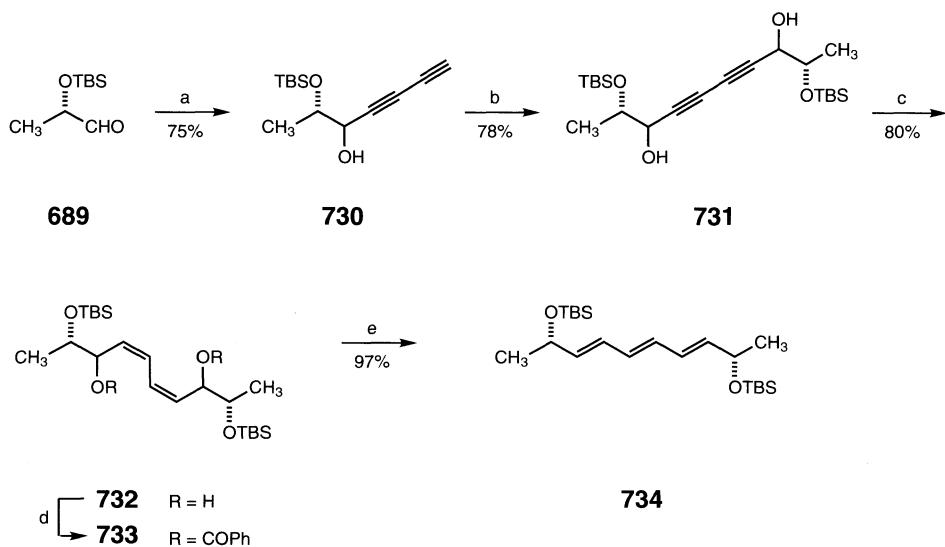
The use of europium(III) catalyst (5 mol%) in the aldol reaction of **689** with **735** causes the aldehyde to bind with the catalyst in a monodentate fashion, thus allowing the reactants to adopt an antiperiplanar transition state (**736**) that results in the formation of *anti* diol **737** (94% *ds*) [211].



Scheme 96

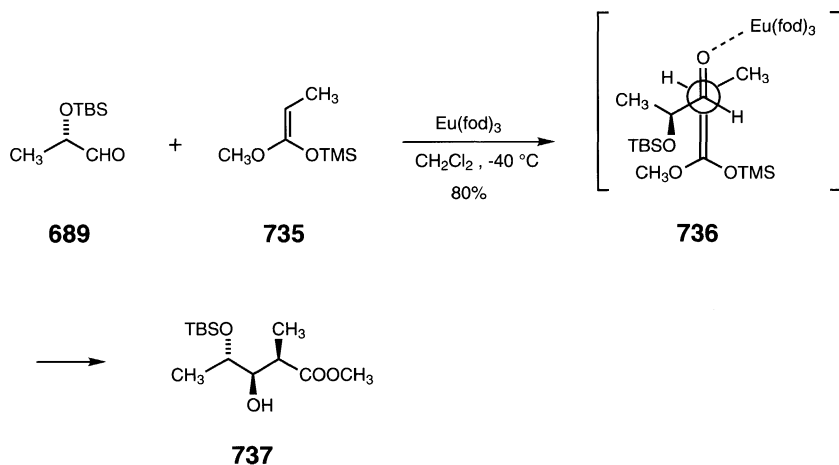
conditions: (a) THF – H₂O – HOAc (1:1:1) (88%); (b) ClSO₂NCO, CH₂Cl₂, -20 °C, then H₂O, 60 °C;
 (c) H₂, Lindlar catalyst, MeOH; (d) KO^tBu, THF, 0 °C; (e) 1N NaOH, 60 °C; (f) Ac₂O;
 (g) DIBAL, THF, -78 °C; (h) 1N NaOH

If a chiral catalyst is used to promote the aldol reaction, the determination of stereoselectivity is shifted from substrate control to catalyst control (see Scheme 98). Consequently, when either (*S*)-2-*tert*-butyldimethylsilyloxypropanal (**689**) or its enantiomer (*R*)-2-*tert*-butyldimethylsilyloxypropanal (**741**) is reacted with **738** in the presence of tin(II) triflate and



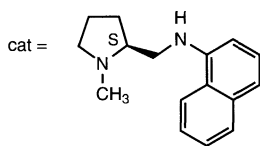
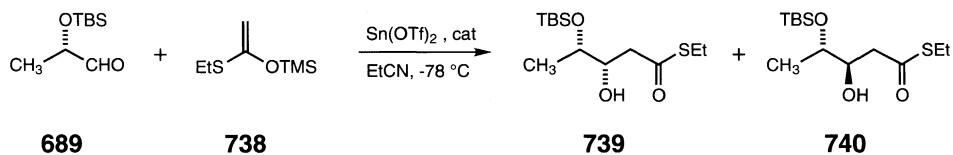
Scheme 97

conditions: (a) $\text{C}\equiv\text{C-C}\equiv\text{C-MgBr}$, 0 °C; (b) EtMgBr, **689**, -78 °C; (c) Zn / Cu, MeOH – H₂O;
 (d) PhCOCl, pyridine (71%); (e) TiCl₃, LiAlH₄, THF, 65–70 °C

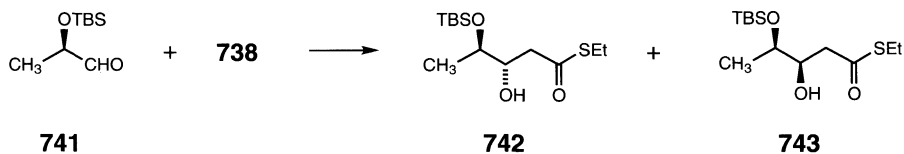


(*S*)-proline-derived diamine **744** (20 mol%), the result is diastereomers **739** or **742**, in which the newly formed asymmetric center has the *S* configuration [212]. When the enantiomeric (*R*)-proline-derived diamine catalyst is used the diastereoselectivity is reversed, thus providing **740** or **743** as the major stereoisomer, where the newly formed asymmetric center has the *R* configuration.

A similar result is obtained in the homoaldol reaction of enantiomeric TBS-lactaldehydes with the titanated (*E*)-2-alkenyl carbamate **745** [213]. Reaction of **689** with **745** furnishes **747** with 96 : 4 diastereoselectivity. Likewise, the corresponding reaction of **741** with **745** provides **748** with 70 : 30 diastereoselectivity. As in the previous case, the newly formed

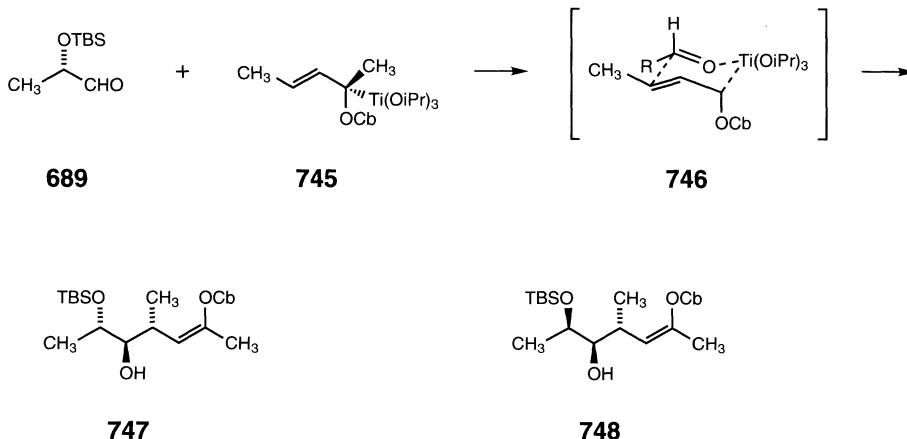


Cat.	Yield (%)	739:740	742:743
S	91	96 : 4	96 : 4
R	85	6 : 94	4 : 96

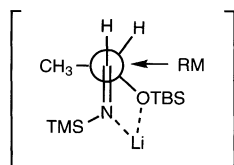
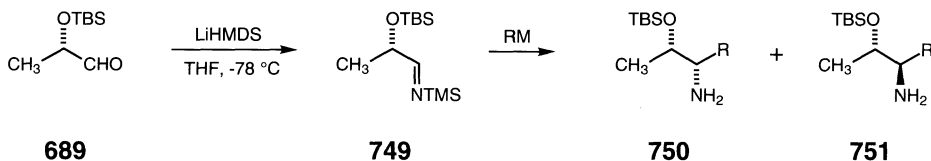


Scheme 98

asymmetric centers have the same configuration regardless of the inherent diastereofacial preference of the lactaldehyde. In the transition state (**746**), the titanium-bearing stereogenic center determines which face of the olefin will be attacked.

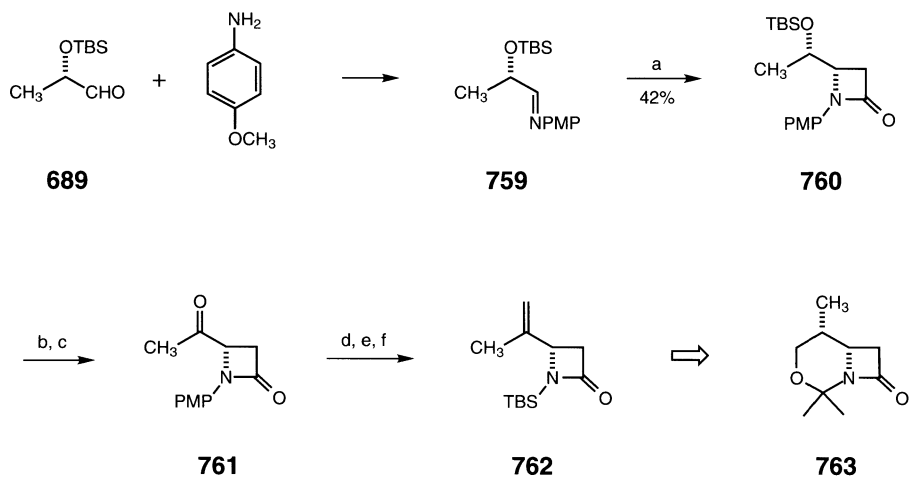


Addition of organometallic reagents to imines derived from lactaldehydes results in the diastereoselective formation of amino alcohols. The required imine (**749**) is generated *in situ* by the addition of lithium hexamethyldisilazide to **689** at low temperature. Addition of lithium alkyls or Grignard reagents to the azomethine carbon preferentially forms the *syn* diastereomer **750**, presumably through the chelated transition state **752** [214]. One anomaly is presented by the case of allylmagnesium chloride, which gives almost exclusively the *anti* isomer **751**. To date it is not understood why this dramatic reversal of stereochemistry occurs.



RM	Yield (%)	750:751
<i>n</i> -BuLi	46	98 : 2
<i>s</i> -BuLi	39	57 : 43
C ₆ H ₁₁ CH ₂ Li	70	80 : 20
PhCH ₂ MgBr	50	100 : 0
CH ₂ =CHMgCl	66	4 : 96

Silylimine **749** has also been used as a chiral template in the synthesis of the carbapenem (+)-PS-5 (**758**), an antibiotic isolated from the fermentation broth of soil microorganisms [215,216] (Scheme 99). The crucial ring-forming step (**749** \rightarrow **753**) is accomplished by reaction of **749** with the lithium enolate of *tert*-butyl butanoate. The resulting β -lactam is

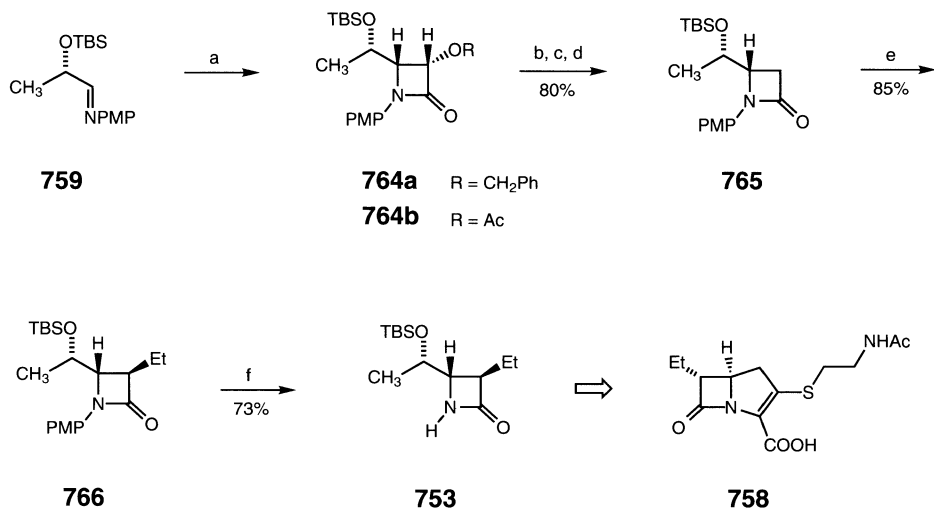


Scheme 100

conditions: (a) CH_3COSPy , TiCl_4 , Et_3N , CH_2Cl_2 , -78°C ; (b) HF , CH_3CN ; (c) H_2CrO_4 , THF , 40°C ; (d) Ph_3PCH_3 , $n\text{-BuLi}$, THF , -40°C ; (e) CAN , CH_3CN , -20°C ; (f) TBS-Cl , Et_3N , CH_2Cl_2

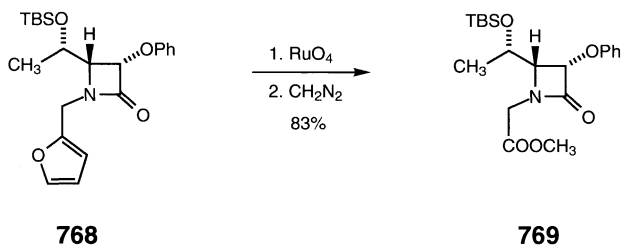
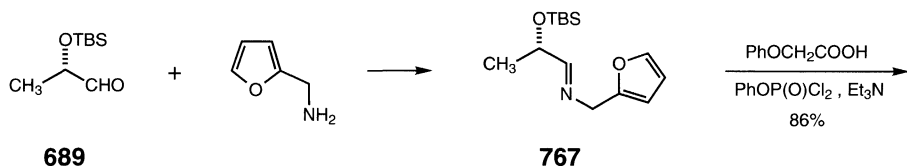
mediated oxidation of the furan heterocycle followed by esterification with diazomethane gives ester **769** [219].

3-Amino-substituted β -lactams are accessible by reaction of furfurylimine **767** with the Dane salt **770** in the presence of phenyl dichlorophosphate. The resulting *cis*- β -lactam **771** is formed with a diastereomeric excess of 91%. Compound **772** is converted to methyl ketone



Scheme 101

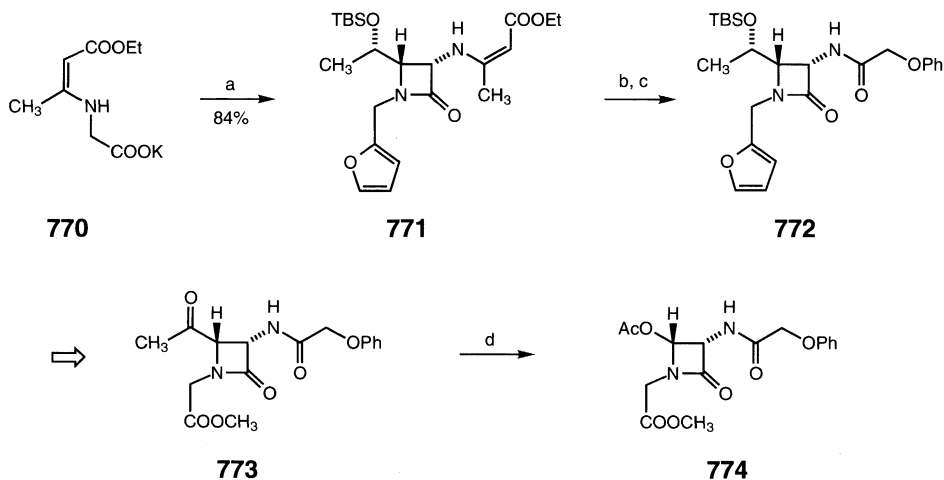
conditions: (a) ROCH_2COCl , Et_3N , CH_2Cl_2 , -78°C ; (b) HCO_2NH_4 , 10% Pd/C , acetone (90%); (c) CS_2 , NaH , DMF , then CH_3 ; (d) Bu_3SnH , AIBN , toluene; (e) LDA , THF , -78°C , then EtI (4 eq), $-78^\circ\text{C} \rightarrow \text{rt}$; (f) CAN , $\text{CH}_3\text{CN} - \text{H}_2\text{O}$, 0°C



Scheme 102

derivative **773** by oxidation of the furan, esterification, fluoride-induced desilylation, and oxidation, all of which have been previously discussed. Baeyer–Villiger reaction then produces the interestingly substituted *cis*-acetoxy- β -lactam **774** (Scheme 103).

Higher diastereoselectivities in the β -lactam-forming steps can be achieved by using the more bulky TBPS protecting group instead of a TBS group on imine **767**. Thus, reaction of the TBPS-protected imine with phenoxyacetic acid gives **768** (TBPS) with greater than 95% *de*. Similarly, reaction with Dane salt gives **771** (TBPS) as a single diastereomer.

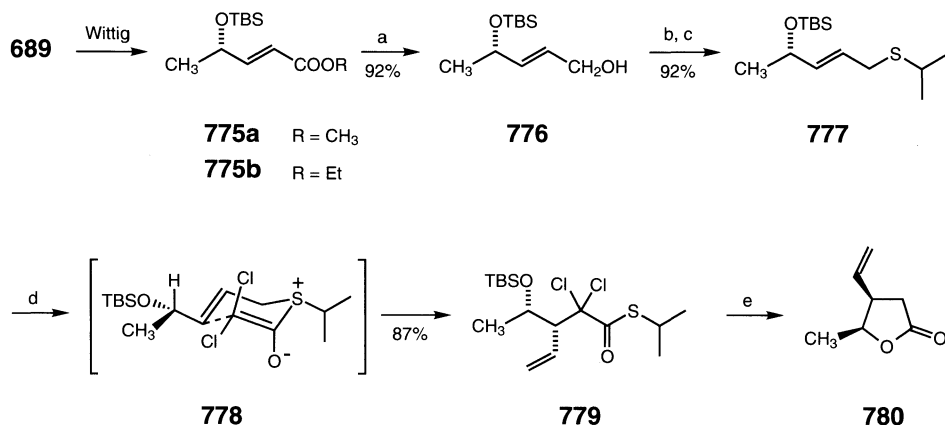


Scheme 103

conditions: (a) **767**, $\text{PhOP(O)Cl}_2 \cdot \text{Et}_3\text{N}$; (b) HCl , MeOH ; (c) $\text{PhOCH}_2\text{COCl}$, Et_3N , DMAP; (d) MCPBA

Wittig reactions play an important role in expanding the synthetic utility of lactaldehydes. Aldehyde **689** can be converted to the useful intermediate α,β -unsaturated ester **775a** by reaction with $\text{Ph}_3\text{P}=\text{CHCOOCH}_3$ (51% yield) [220]. A 7.3 : 1 mixture of *E* and *Z* isomers is formed under these conditions, which can be separated by chromatography.

With ethyl ester **775b**, the *E/Z* ratio can be increased to 14 : 1 by using triethyl phosphonoacetate under Horner–Emmons conditions [221]. The chemical yield of the reaction also increases to 80%.



Scheme 104

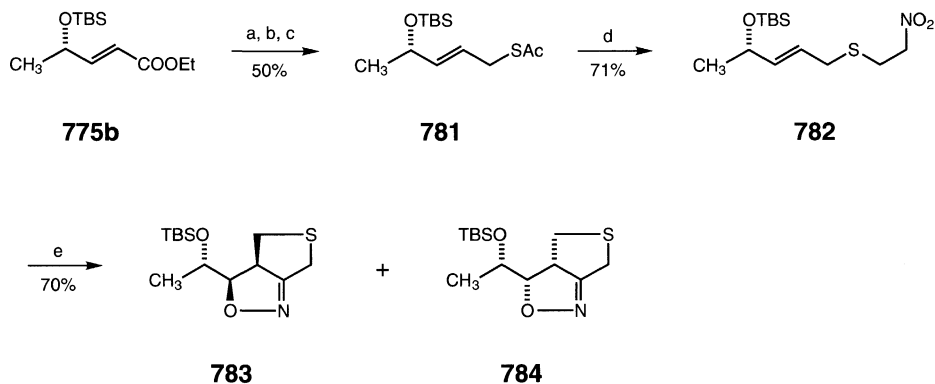
conditions: (a) DIBAL, THF, 0 °C; (b) CH_3COSH , Ph_3P , DEAD, THF, 0 °C; (c) NaOEt, EtOH, then *i*-PrBr, 20 °C; (d) Cl_3CCOCl , Zn / Cu, ether, 40 °C; (e) HOAc, Zn, 110 °C

Ester **775a** has been used as an intermediate in synthesizing substrates that produce 1,2-asymmetric induction in the ketene Claisen rearrangement of allylic sulfides [220] (Scheme 104). Reduction of **775a** with diisobutylaluminum hydride gives allylic alcohol **776** (> 94% *de*). Conversion to thioether **777** is accomplished with thioacetic acid under Mitsunobu conditions; this is followed by saponification of the resulting *S*-acetyl intermediate and alkylation with isopropyl bromide.

Treatment of allyl sulfide **777** with dichloroacetone, generated *in situ* by reductive elimination of chlorine from trichloroacetyl chloride, results in an intramolecular ketene Claisen rearrangement giving **779** with high 1,2-*syn* selectivity (94% *de*). Reductive dechlorination and subsequent lactonization affords chiral butyrolactone **780**, with an optical purity that exceeds 95%.

By a similar series of transformations, ethyl ester **775b** has been converted to nitroethyl allylic sulfide **782**. This has been used as a substrate for an intramolecular nitrile oxide cycloaddition, which furnishes a 64 : 36 mixture of the diastereomers *anti*-**783** and *syn*-**784** [221] (Scheme 105).

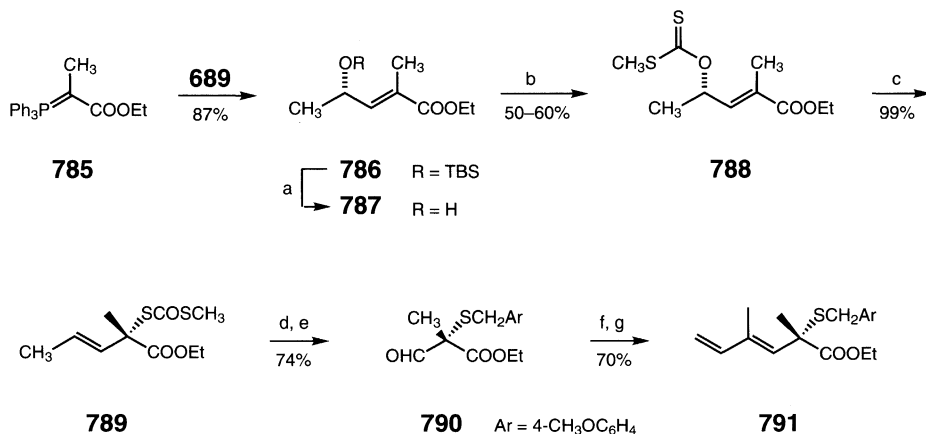
The synthesis of (*5S*)-thiolactomycin (**792**), an enantiomer of an antibacterial agent, makes use of a Wittig olefination early in the sequence as a way of preparing α,β -unsaturated ester **786** (Scheme 106). The key step in the synthesis is an allyl xanthate–dithiocarbonate rearrangement of **788** to **789**. This process occurs upon distillation of **788** at 145 °C (0.4 mm Hg) and gives the desired product **789** in nearly quantitative yield. Chirality transfer is equally efficient, with an enantiomeric excess of at least 98% [222].

**Scheme 105**

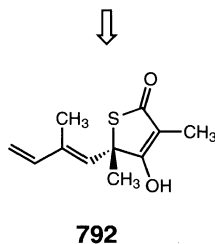
conditions: (a) DIBAL, CH_2Cl_2 , -78°C ; (b) $\text{CH}_3\text{SO}_2\text{Cl}$, Et_3N , CH_2Cl_2 ; (c) CH_3COSH , Et_3N , CH_3CN ;
(d) EtONa , EtOH , $\text{AcOCH}_2\text{CH}_2\text{NO}_2$; (e) 4- $\text{ClC}_6\text{H}_4\text{NCS}$, Et_3N , benzene

The diene function is introduced by reaction of **790** with the lithium salt of 2-triethylsilylpropanal *N-tert*-butylimine, which after hydrolysis produces an intermediate α,β -unsaturated aldehyde. Subsequent Wittig condensation with triphenylphosphonium methylide then affords the diene **791**. The final conversion to **792** requires six additional steps [223].

A Wittig reaction of **689** with $\text{Ph}_3\text{P}=\text{CHCH}_2\text{CH}_2\text{OLi}$ initiates the synthetic sequence leading to (–)-tabtoxinine β -lactam (**806**), a potent irreversible inhibitor of glutamine synthetase [224] (Scheme 107). The resultant homoallylic alcohol **793** is formed as a 20:1

**Scheme 106**

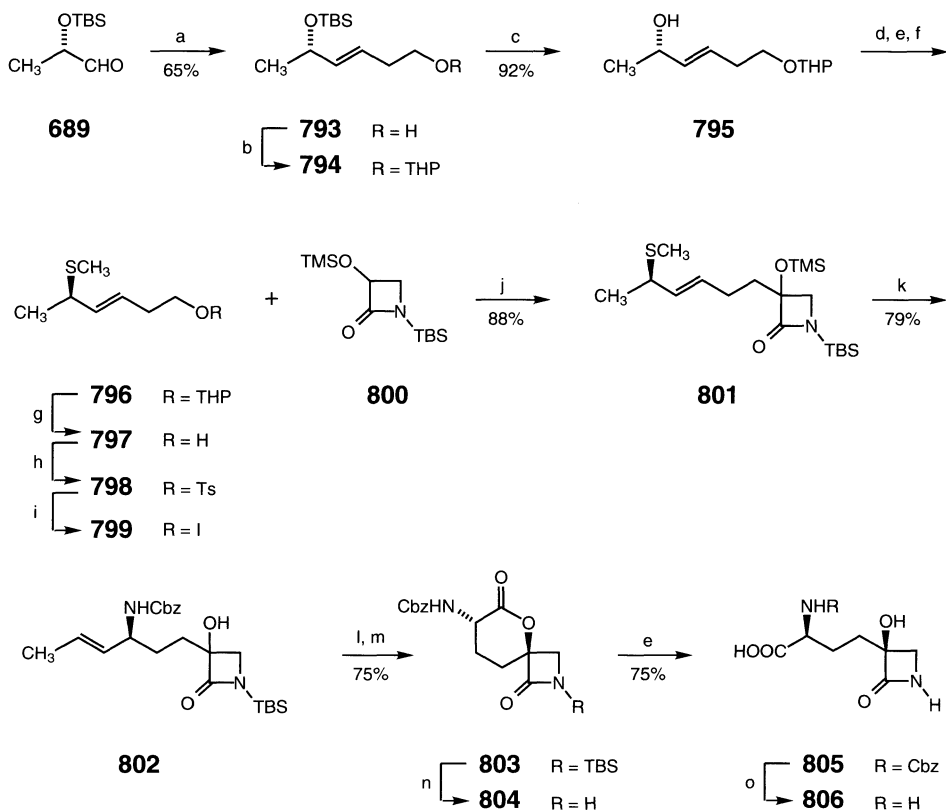
conditions: (a) Bu_4NF , T HF (84%); (b) NaH , CS_2 , CH_3 ; (c) 145°C ;
(d) KOH , 4-methoxybenzyl chloride; (e) O_3 , Me_2S ;
(f) $\text{CH}_3(\text{SiEt}_3)\text{CH}=\text{NtBu}$, LDA; (g) $\text{CH}_2=\text{PPh}_3$



mixture of *E* and *Z* isomers. Three key features of this synthesis are (1) the development of **799** as a new synthetic equivalent for an α -amino acid cation ($\text{HOOCCH}(\text{NH}_2)\text{CH}_2\text{CH}_2^+$); (2) stereoselective [2,3]-sigmatropic sulfilimine rearrangement of methyl sulfide **801** to protected amine **802**; and (3) selective lactone ring opening of spiro lactam **804** to the Cbz-protected product **805**.

The desired stereochemistry for the amino acid cation synthon is achieved by inversion of the stereocenter of **795** with thioacetic acid under Mitsunobu conditions to give **796**. Functional group manipulation then gives the target iodide **799**. The optical purity of alcohol **797** is $>95\%$ *ee*.

Alkylation of the lithium enolate of **800** with **799** gives **801** as an inseparable 1 : 1 mixture of *C*-3 diastereomers. [2,3]-Sigmatropic rearrangement of **801** occurs upon treatment with MSH followed by triethyl phosphite. Protection of the newly formed amine is accomplished *in situ* with benzyl chloroformate in the presence of sodium bicarbonate. The rearrangement occurs with 85% chirality transfer and concomitant loss of the TMS protecting group.

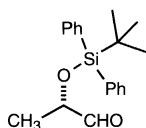


Scheme 107

conditions: (a) $\text{Ph}_3\text{P}=\text{CHCH}_2\text{CH}_2\text{OLi}$; (b) DHP, PPTS, CH_2Cl_2 ; (c) Bu_4NF , THF; (d) CH_3COSH , DIAD, Ph_3P , CH_2Cl_2 ; (e) NaOH; (f) CH_3I , 0°C ; (g) HCl, MeOH (54% from **795**); (h) TsCl, pyridine, 4°C (64%); (i) NaI, DME, 85°C ; (j) LDA, THF, $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$; (k) MSH, $\text{P}(\text{OEt})_3$, NaHCO_3 , then Cbz-Cl; (l) O_3 , -78°C , Me_2S ; (m) PCC, CH_2Cl_2 ; (n) Bu_4NF , HOAc, THF (84%); (o) H_2 , 10% Pd / C (100%)

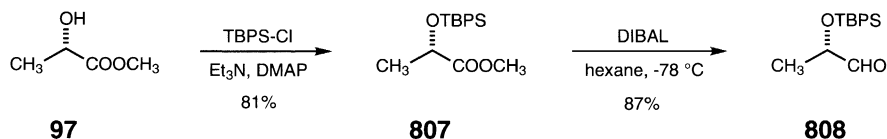
Ozonolysis of **802** followed by PCC oxidation of the resultant mixture of lactols furnishes a 1 : 1 mixture of spiro lactams. The desired diastereomer **803** is readily separated by fractional crystallization. Careful hydrolysis of the lactone with 1N NaOH in THF–H₂O (3 : 1) gives the Cbz-protected tabtoxinine β -lactam **805** in good yield.

1.5.6.2 *tert*-Butyldiphenylsilyl (TBPS)



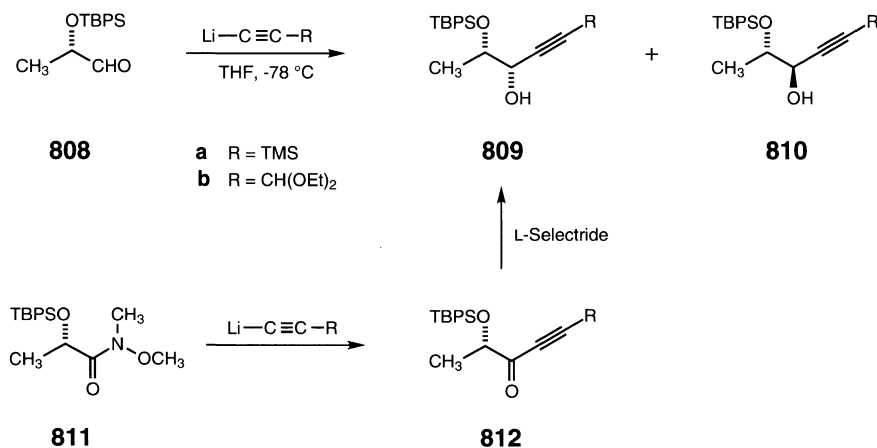
(*S*)-2-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]propanal

Lactaldehyde derivative **808** can be prepared in high yield by direct reduction of methyl ester **807** with diisobutylaluminum hydride at low temperature [129].



Acetylenic diols, potential building blocks for the synthesis of L-hexoses and L-pentoses, are available with either *syn* or *anti* configuration using TBPS-protected L-lactic acid derivatives as the chiral source (Scheme 108).

The *anti* stereochemistry is obtained, as predicted by the Felkin model, by addition of lithioacetylene derivatives to siloxyaldehyde **808**. Trimethylsilylacetylene produces a 17 : 83 mixture of **809a** and **810a**, and 3,3-diethoxypropyne gives a 23 : 77 mixture of **809b** and **810b**.



Scheme 108

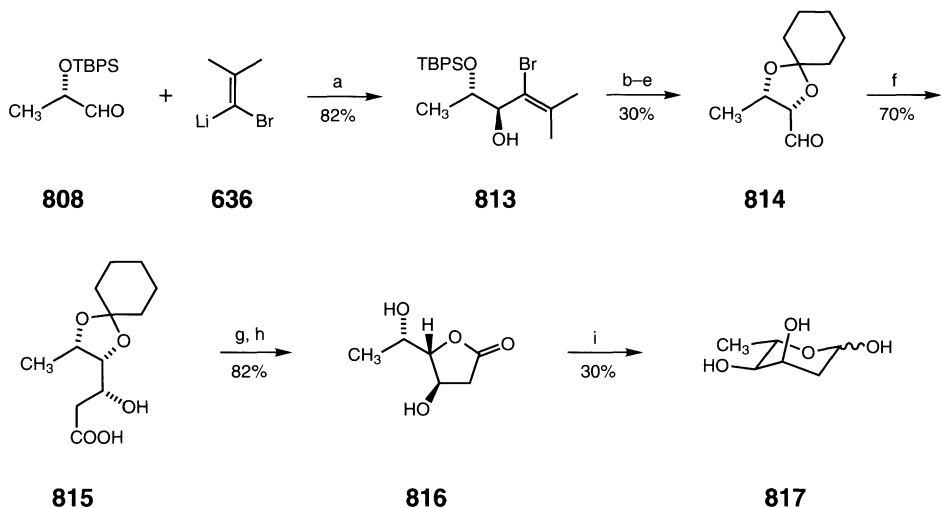
In both cases the TBPS group is removed with fluoride to afford the corresponding diols, R=TMS (90% overall yield) and R=CH(OEt)₂ (70% overall yield) [225].

syn Stereochemistry is obtained by reduction of ketone **812** with L-Selectride, a reaction which also proceeds through a Felkin-type transition state. When R=TMS, a 93 : 7 mixture of **809a** and **810a** is produced, and when R=CH(OEt)₂, a 95 : 5 mixture of **809b** and **810b**.

The requisite ketones **812** are prepared by reaction of the lithioacetylene reagent with *N*-methoxy-*N*-methylamide (**811**). Reactions with this functional group are known to proceed without racemization. Thus, **812a** is obtained in 46% yield, and **812b** in 93% yield.

The high *anti* selectivity exhibited by the addition of organolithium reagents to **808** is exploited as a way of supplying two chiral centers for L-digitoxose (2,6-dideoxy-*ribo*-hexose) (**817**), an antibiotic sugar component [226] (Scheme 109).

Addition of lithio alkene **636**, a formaldehyde-anion equivalent (⁻CHO), to **808** at low temperature gives adduct **813** with a diastereomeric excess of 92%. Lithium-bromine exchange, desilylation, ketalization, and ozonolysis furnishes aldehyde **814** (>98% *de*). The last stereocenter is introduced by aldol condensation with R-HYTRA, thus giving **815** as a 91 : 9 mixture of isomers. Lactonization to **816** followed by reduction with disiamylborane gives **817**, which is separated from the accompanying minor isomer by column chromatography.

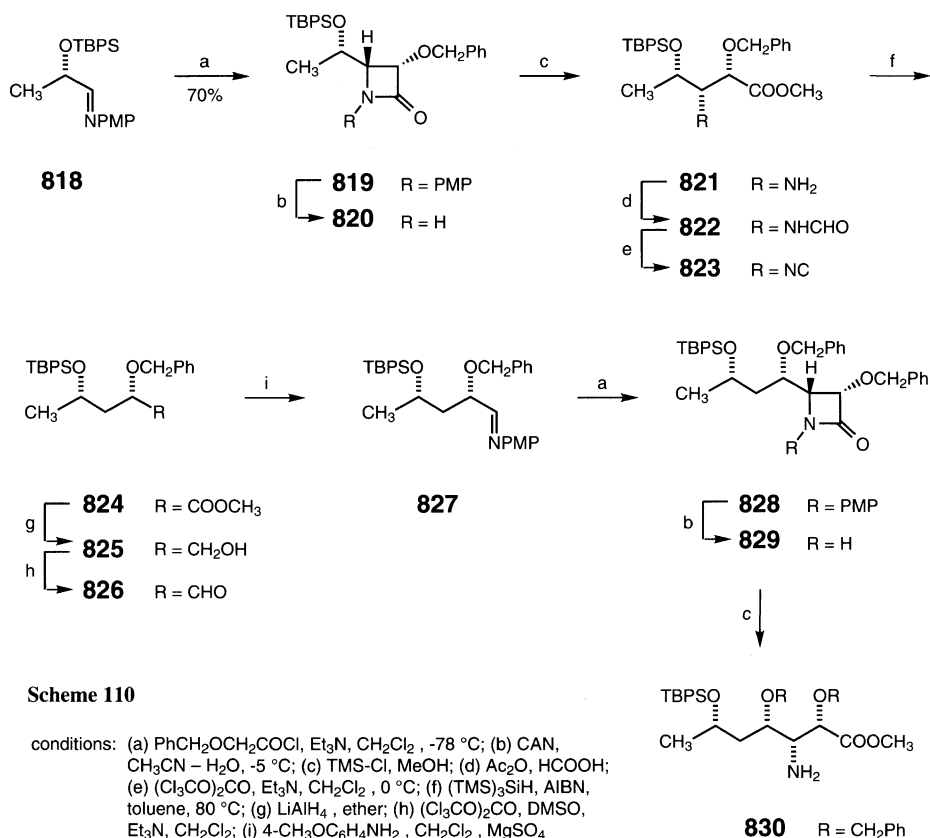


Scheme 109

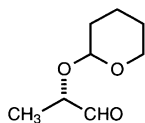
conditions: (a) *t*-BuLi, THF, -105 °C; (b) *t*-BuLi, THF, then H₃O⁺; (c) Bu₄NF; (d) cyclohexanone, HC(OEt)₃, PTSA; (e) O₃, CH₂Cl₂, -78 °C, Me₂S; (f) R-HYTRA, LDA, -78 °C; (g) KOH, MeOH; (h) CF₃COOH, H₂O; (i) Si₂H, THF

An interesting approach to chiral 2-amino-1,3-diols makes use of an asymmetric Staudinger reaction that incorporates the required functional groups into a β -lactam nucleus. The condensation of imine **818** with benzyloxyketene produces β -lactam **819** with 95% diastereoselectivity [218]. After dearylation with ceric ammonium nitrate the amino polyol is released as an isoserine derivative (**821**) by cleavage of the β -lactam with chlorotrimethylsilane in methanol [227] (Scheme 110). The amino group can be removed by conversion to isocyanide **823** followed by reduction with tris(trimethylsilyl)silane in the presence of AIBN, which furnishes *erythro* α,β -dialkoxy ester **824** without racemization.

This process is iterative. Ester **824** can be converted to imine **827** by reduction of the ester function to an alcohol, oxidation to an aldehyde, and Schiff-base formation with 4-methoxy-aniline. The [2 + 2] cycloaddition reaction of **827** with benzyloxyketene gives β -lactam **828** in 75% yield as a single diastereomer. Subsequent dearylation affords **829** (50% yield), which upon treatment with chlorotrimethylsilane in methanol furnishes **830** in quantitative yield as a single diastereomer.

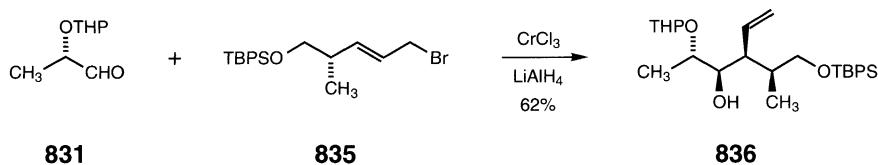


1.5.7 Tetrahydropyran (THP)



(*S*)-2-[(Tetrahydropyran-2-yl)oxy]propanal

THP-protected lactaldehyde (**831**) can be prepared by two routes. The first is a two-step procedure in which the ester group of **450** is reduced to an alcohol (**451**) and then oxidized to

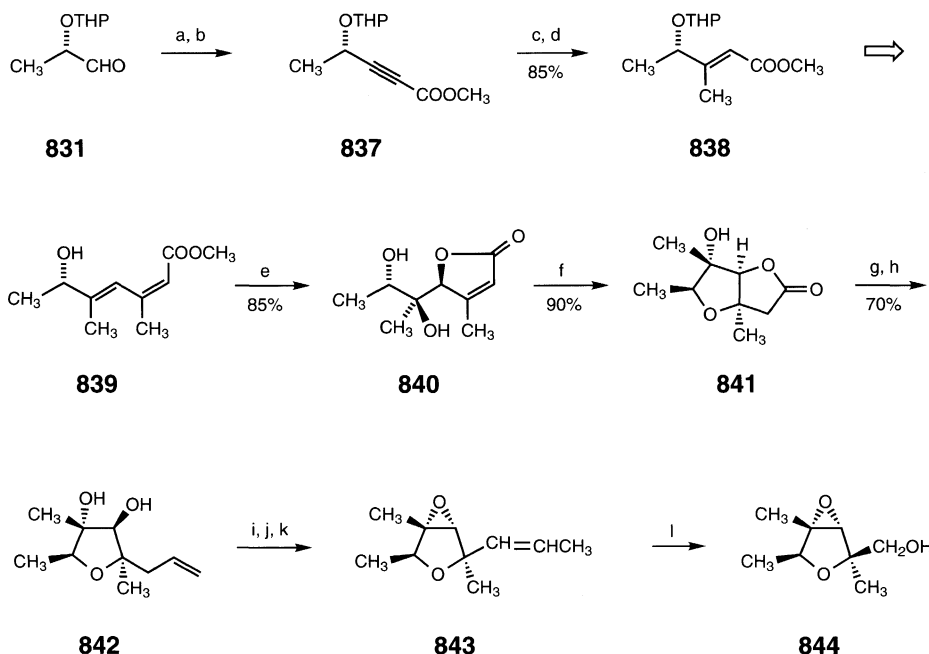


with methyl chloroformate to furnish acetylenic ester **837**. After conversion to *E*-ester **838**, conjugate dimethylcuprate addition affords *E,Z*-diene **839**.

Stereospecific osmylation produces lactone **840** as a single diastereomer. This, upon treatment with sodium bicarbonate, gives bicyclic lactone **841** in high yield. Reduction of lactone **841** to a lactol followed by Wittig olefination affords allyltetrahydrofuran **842**. Palladium(II) isomerization of the olefin, epoxidation, ozonolysis, and reduction gives the target compound **844** with 95% optical purity.

As demonstrated with other lactaldehydes in this chapter, the Wittig reaction plays an important role in the conversion of lactaldehyde **831** to synthetically useful intermediates as well as to natural products.

Horner–Emmons olefination of **831** provides α,β -unsaturated ester **845** with high *E* selectivity. Bases most commonly used to effect the transformation are sodium hydride (for $\text{R}=\text{CH}_3$) [231] and potassium *tert*-butoxide (for $\text{R}=\text{Et}$) [232]. Ester **845b** is also accessible

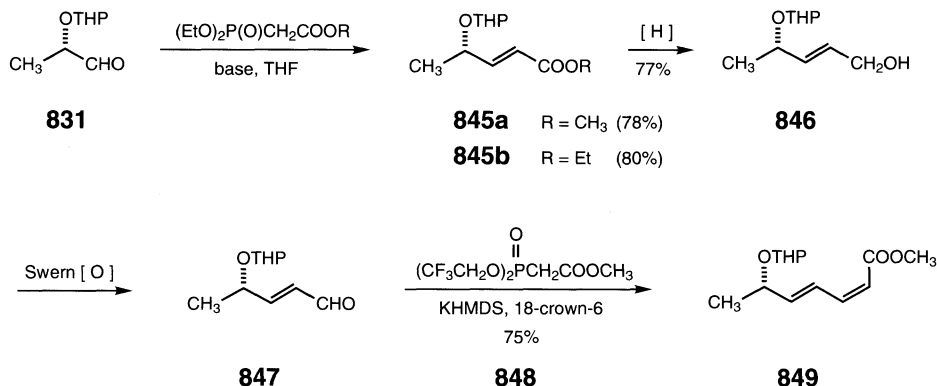


Scheme 112

conditions: (a) BrCCl_3 , HMPT, -23°C ; (b) 2 eq *n*-BuLi, ClCOOCH_3 , -78°C ; (c) PhSnA, MeOH; (d) MeMgBr, CuI, THF, -78°C ; (e) OsO_4 , NMO, THF – H_2O , 0°C ; (f) NaHCO_3 , MeOH; (g) DIBAL, CH_2Cl_2 , -78°C ; (h) $\text{Ph}_3\text{P}=\text{CH}_2$, THF; (i) $\text{PdCl}_2(\text{PhCN})_2$, benzene; (j) MsCl, pyridine, CH_2Cl_2 ; (k) NaOCH_3 , MeOH; (l) O_3 , CH_2Cl_2 – MeOH, -78°C , NaBH_4

from **831** via a Wittig reaction with carboethoxymethylenetriphenylphosphorane, however the product is a mixture of *E* and *Z* isomers [233].

The ester function of **845b** is readily reduced to allylic alcohol **846** with either diisobutylaluminum hydride in toluene at $-78\text{ }^{\circ}\text{C}$ [231] or aluminum hydride in ether at $-60\text{ }^{\circ}\text{C}$ [234]. Swern oxidation gives α,β -unsaturated aldehyde **847**.



Scheme 113

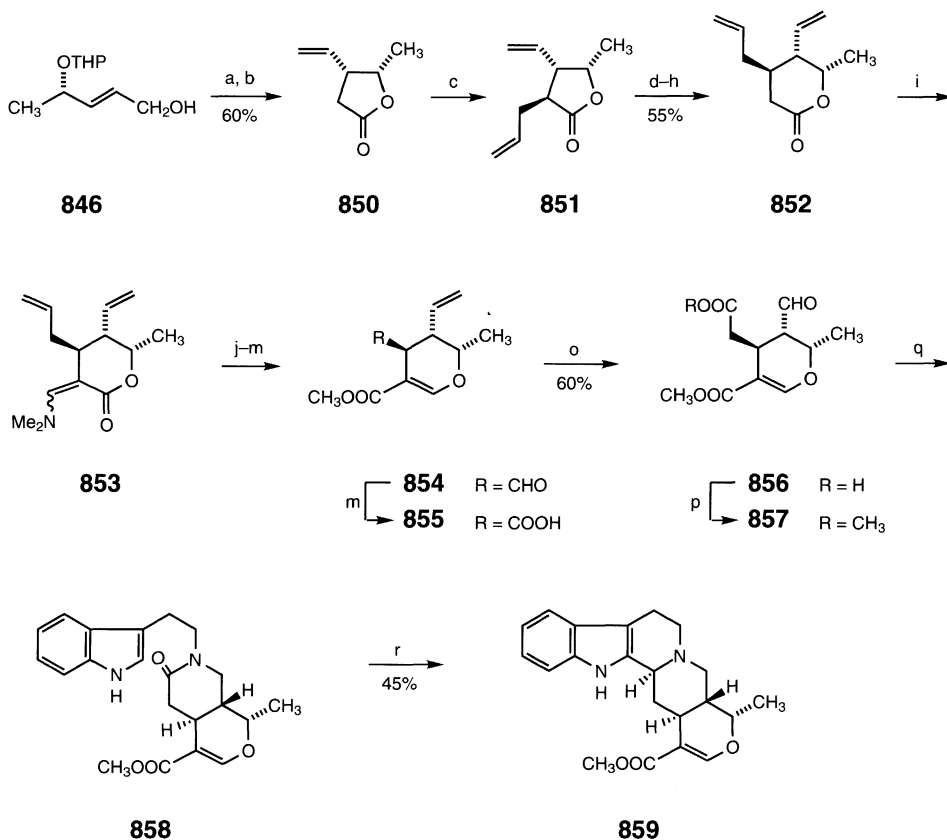
The Horner–Emmons reaction can be tuned to favor the formation of *Z*-olefin by using bis(2,2,2-trifluoroethyl)carboxymethyl phosphonate (**848**), a reagent developed by Clark Still. Consequently, olefination of **847** with **848** gives *E,Z*-diene ester **849** with 15:1 selectivity [232] (Scheme 113).

Allylic alcohol **846** has been employed in the synthesis of several natural products, as illustrated in Scheme 114 for the preparation of (–)-elenolic acid (**856**), a secoiridoid monoterpene isolated from the olive *Olea europea*. The initial reaction is an orthoester Claisen rearrangement of **846** using triethyl orthoacetate, followed by lactonization with pyridinium *p*-toluenesulfonate. The resulting lactone is obtained as a 3:1 mixture of *cis*-**850** and its *trans* isomer. After stereospecific alkylation of **850** with allyl bromide, the conversion of **851** to **852**, which is essentially an expansion of the lactone by insertion of a methylene unit, requires five steps to accomplish. The remainder of the synthesis is uneventful, and furnishes pure **856** [234].

The ester of **856**, (–)-methyl elenolate (**857**), upon reductive amination with tryptamine followed by Bischler–Napieralski cyclization, furnishes (–)-ajmalicine (**859**).

Allylic alcohol **846** is instrumental in controlling the stereochemistry in the synthesis of (+)-roccellaric acid (**864**) [231] (Scheme 115). The key step is an Ireland–Claisen rearrangement of propionate **861**, which produces **862** as a mixture of isomers (epimeric at the methyl group). The minor diastereomer is removed at the lactone stage (**863**). Debenzylation and oxidation of the alcohol to an acid furnishes the natural product.

The synthesis of (2*S*, 6*R*, 8*S*)-2,8-dimethyl-1,7-dioxaspiro[5,5]undecane (**868**), one of the spiroacetal components of the pheromone isolated from the olive fruit fly, hinges on a dialkylation of tolylmethyl isocyanide with bromide **866**. The bromide is obtained from **845b** by sequential reduction of the olefin and ester followed by conversion of the resulting alcohol to bromide. Acidic hydrolysis of dialkylated product **867** provides the pheromone **868** directly [233].

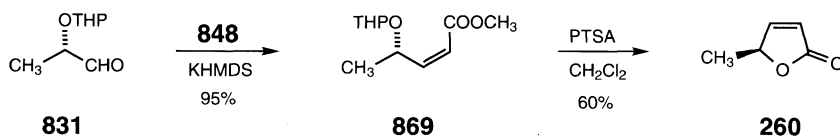


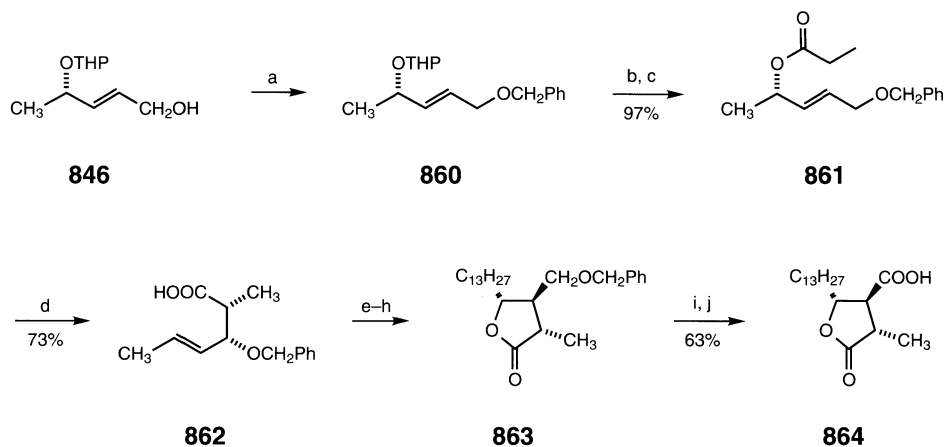
Scheme 114

conditions: (a) CH₃C(OEt)₃, *t*-BuCOOH, 140 °C; (b) PPTS, EtOH; (c) allyl bromide, LDA, THF, -78 °C; (d) DIBAL, CH₂Cl₂, -78 °C; (e) α -methoxymethylenetriphenylphosphorane, glyme; (f) TBS-Cl, imidazole, DMF; (g) PCC, CH₂Cl₂; (h) PTSA, MeOH; (i) N,N-dimethylformamide dimethyl acetal, 170 °C; (j) 1N HCl, ether; (k) 5% H₂SO₄, MeOH; (l) OsO₄, pyridine, 0 °C, then 2% NaHSO₃; (m) Pb(OAc)₄, THF, 0 °C; (n) Jones oxidation; (o) OsO₄, NaIO₄, THF – H₂O, 0 °C; (p) CH₂N₂; (q) tryptamine perchlorate, NaBH₃CN, MeOH; (r) POCl₃, benzene

A short synthesis of (+)-angelica lactone (**260**) takes advantage of Horner–Emmons olefination of **831** with the Still reagent (**848**; Scheme 113) to give (*Z*)- α,β -unsaturated ester **869** in high yield and geometric purity. Removal of the THP group under mild acidic conditions furnishes the (5*S*)-butenolide **260** [133].

Jaspamide (**870**) and the geodiamolides (**871**) are naturally occurring marine cyclodepsi-peptides isolated from sponges. A feature common to both systems is the non-peptide C-1 to



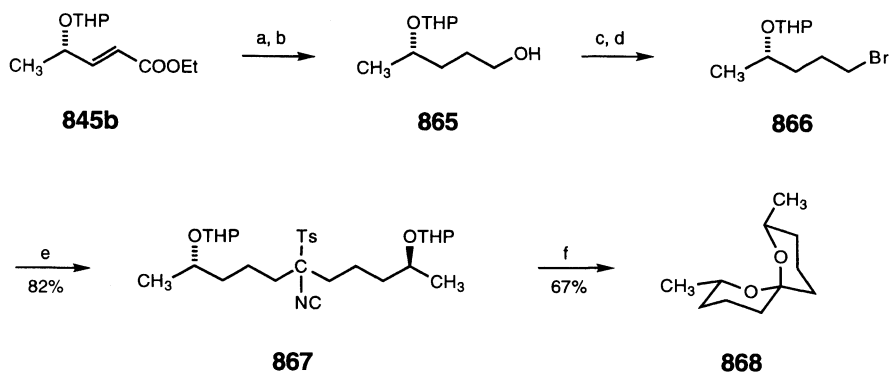
**Scheme 115**

conditions: (a) PhCH_2Cl , NaH, DMF, 40 °C; (b) PTSA, MeOH; (c) propionic anhydride, DMAP, pyridine; (d) LDA, TMS-Cl, -78 °C \rightarrow 22 °C; (e) O_3 , MeOH, -78 °C; (f) $\text{C}_{12}\text{H}_{25}\text{CH}=\text{PPh}_3$, THF, -78 °C; (g) I_2 , KI, THF - H_2O , K_2CO_3 ; (h) Bu_3SnH , AIBN, toluene; (i) H_2 , Pd / C, MeOH; (j) PDC, DMF

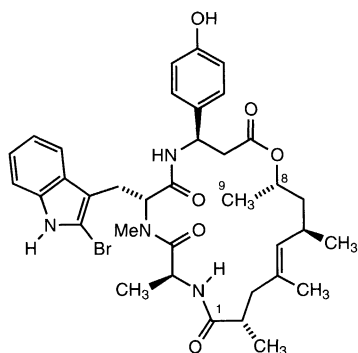
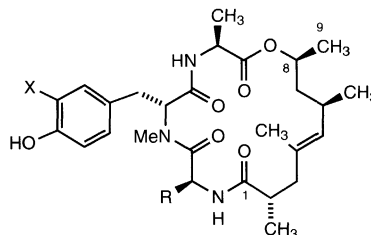
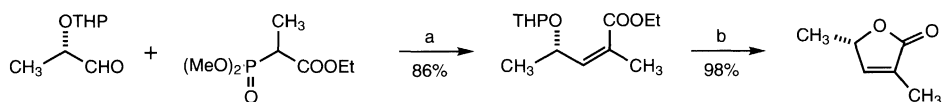
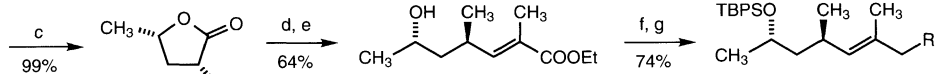
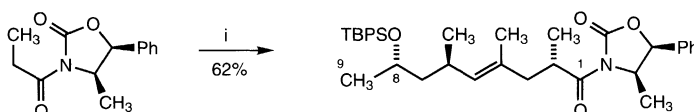
C-9 fragment. Its synthesis in protected form (**878**) has been accomplished as shown in Scheme 117 [235].

Stereoselective Horner–Emmons reaction of **831** with **872** gives (*Z*)- α,β -unsaturated ester **873** with a selectivity of $>20:1$. Removal of the THP group under acidic conditions affords butenolide **211**, and subsequent catalytic hydrogenation gives the *cis*-dimethylbutyrolactone **212** as the only diastereomer. Reduction of lactone to lactol followed by Wittig homologation results in the formation of the (*E*)- α,β -unsaturated ester **874** with 94:6 regioselectivity. Asymmetric alkylation of **877** with bromide **876** using Evans methodology introduces the final stereocenter of **878** at C-2 with an enantioselectivity of 98:2.

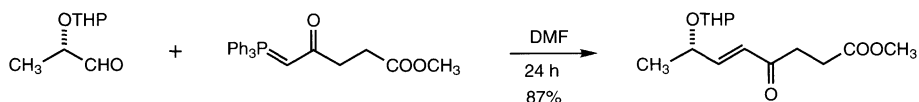
Homologation of **831** to δ -ene- γ -keto ester **880** is accomplished by Wittig olefination with levulinate ylide **879**. The product **880** is obtained with 95% *E* geometry [236].

**Scheme 116**

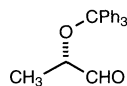
conditions: (a) H_2 , Rh / Al_2O_3 ; (b) LiAlH_4 , ether; (c) MsCl, Et_3N ; (d) LiBr, THF; (e) TosCH_2NC , 40% NaOH / H_2O - CH_2Cl_2 (1:2), Bu_4NBr ; (f) 2N H_2SO_4 , MeOH - H_2O (4:1)

**870****871** R = H, CH₃
X = Cl, Br, I**831****872****873****211****212****874****875** R = OH
876 R = Br**877****878****Scheme 117**

conditions: (a) KHMDS, 18-crown-6; (b) 30% H₂SO₄, MeOH; (c) H₂, Rh / Al₂O₃, EtOAc; (d) DIBAL, THF, -78 °C; (e) **875**, benzene; (f) TBPS-Cl, imidazole, DMF; (g) DIBAL, toluene; (h) PBr₃, pyridine, ether (88%); (i) LDA, **876**, -78 °C

**831****879****880**

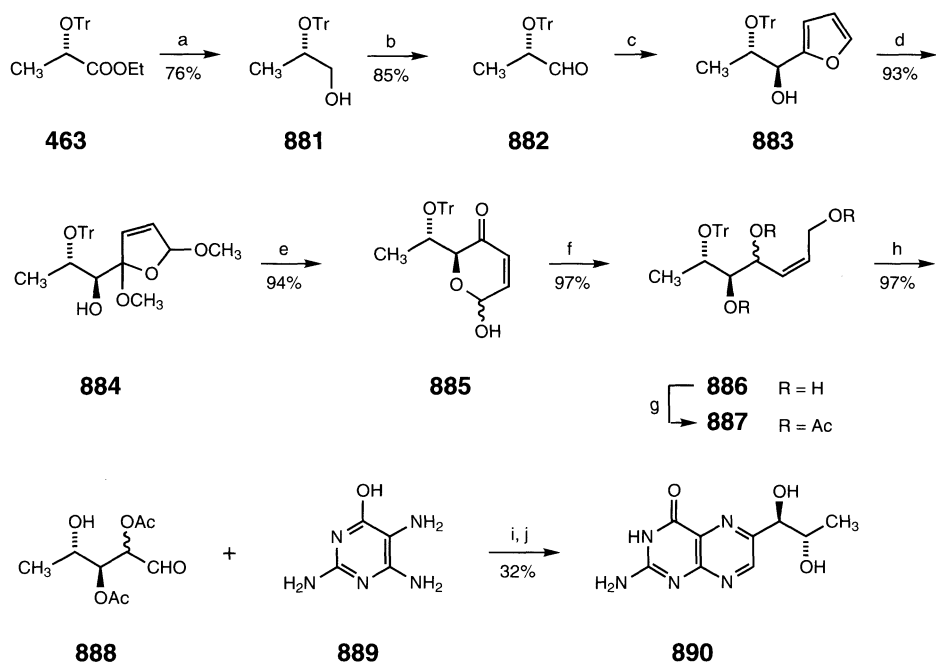
1.5.8 Triphenylmethyl (Trityl)



(S)-2-(Triphenylmethoxy)propanal

(-)-Biopterin (**890**), a pterin isolated from human urine, is an important precursor of tetrahydrobiopterin, which is useful in the treatment of Parkinson's disease. The *anti*-diol arrangement in the side chain is accessible *via* organometallic addition to a lactaldehyde (Scheme 118).

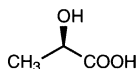
In this case the trityl-protected lactaldehyde **882** is prepared from trityl lactate **463** by reduction of the ester with lithium aluminum hydride followed by oxidation under Swern conditions. An aldol-type addition of titanated furan produces a 6 : 1 mixture of *anti* and *syn* adducts from which the pure *anti* diastereomer **883** is isolated by column chromatography (55% yield, >95% *de*). Treatment of **883** with bromine in methanol followed by acidic hydrolysis gives the ulose **885**. A 1,4-reduction to **886**, acetylation to **887**, and ozonolysis affords the unstable aldehyde **888**, which is immediately coupled with 2,5,6-triamino-4-pyrimidinol (**889**) to afford **890** [237].



Scheme 118

conditions: (a) LiAlH_4 , ether, 0°C ; (b) Swern oxidation, -60°C ; (c) furan, *n*-BuLi, -50° to -62°C , then $\text{Ti}(\text{O}i\text{-Pr})_3\text{Cl}$; (d) NaHCO_3 , MeOH, then Br_2 ; (e) PTSA, THF, H_2O (10:1); (f) $\text{CeCl}_3 \cdot 7 \text{H}_2\text{O}$, NaBH_4 , MeOH; (g) Ac_2O , pyridine (80%); (h) O_3 , CH_2Cl_2 , -60°C , then Me_2S ; (i) PhNHNH_2 , $\text{Na}_2\text{S}_2\text{O}_4$, I_2 ; (j) NH_4OH

1.6 D-Lactic Acid Derivatives

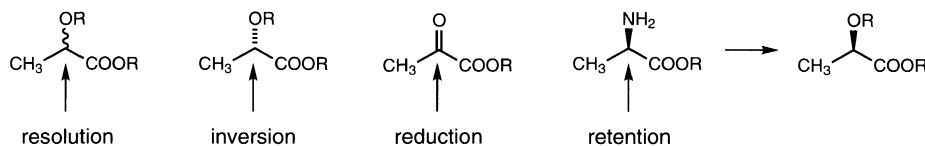


(R)-2-Hydroxypropanoic Acid

The purpose of this section is not to reiterate the chemistry of L-lactic acid and apply it to the corresponding D-lactic acid, but rather to focus on the uses of D-lactic acid derivatives for the syntheses of potentially useful chemical intermediates, biologically active compounds, and natural products.

Unnatural D-lactic acid is not as readily accessible as the natural form, so the cost of its derivatives is substantially higher than in the case of L-lactic acid. In fact, as of this writing, and on a per-gram basis, D-lactic acid is approximately 173 times as expensive as L-lactic acid. If D-lactic acid or one of its derivatives is to be used as a starting point for a designed synthesis, gram quantities are usually required in order to ensure reasonable amounts of final product. Due to the potential expense, it may be more advantageous to undertake the preparation of D-lactic acid or one of its simple derivatives instead of attempting to purchase the compounds.

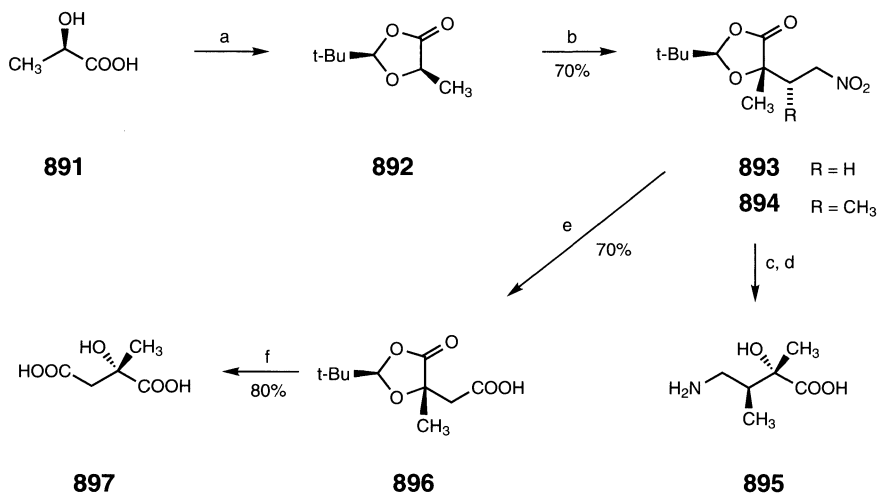
Fortunately, a host of methods is available for achieving this goal. They include: resolution of a D,L-mixture [238]; inversion of L-lactic acid derivatives (see Sections 1.2.1.2 and 1.2.2.2); asymmetric reduction of pyruvates catalytically [239], enzymatically [240], or with chiral boranes [241]; and diazotization of D-alanine derivatives, which proceeds with net retention of configuration [242,243]. In addition, D-lactic acid can be obtained by the fermentation of glucose with *Lactobacillus leichmannii* in the presence of calcium carbonate [244].



D-Lactic acid (**891**), when incorporated into a dioxolane ring (**892**), can be α -alkylated effectively and with high diastereoselectivity due to the directing effect of the bulky *tert*-butyl group. The lithium enolate of **892** adds to nitroolefins in a 1,4-fashion to produce Michael adducts **893** and **894** with diastereoselectivities of >98% and 93% respectively [25]. Reduction of the nitro group of **894** followed by acidic hydrolysis of the dioxolanone ring furnishes amino hydroxy acid **895** as its hydrochloride salt. A Nef-type reaction on **893** affords carboxylic acid **896**, and acid hydrolysis cleaves the dioxolanone ring to give (+)-(*S*)-citramalic acid (**897**) (Scheme 119).

The angiotensin-converting enzyme (ACE) inhibitor imidapril (**905**) is a potent and long-lasting antihypertensive agent. The key dipeptide fragment is formed stereospecifically late in the synthesis after coupling D-lactate-derived acid chloride **900** with L-asparagine-derived 2-oxoimidazolidine **901** [245,246] (Scheme 120).

The synthesis of naturally occurring *N*-acetylneuraminic acid (**912**) utilizes the chirality of D-lactate (**898**) to set the stereochemistry of hetero Diels–Alder adduct **910** [247] (Scheme 121). The dienophile, (*S*)-seleno aldehyde **908**, is prepared by inversion of mesylate **906** followed by controlled reduction of the ester with diisobutylaluminum hydride at low tem-

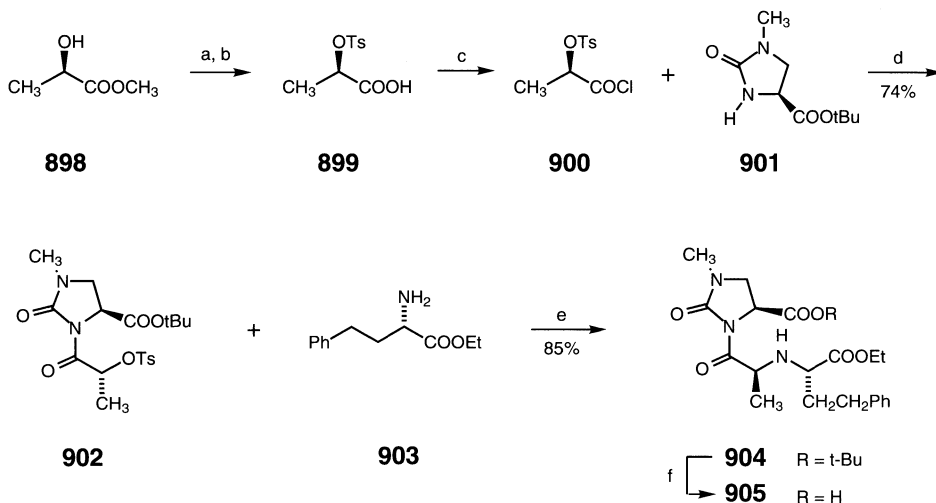


Scheme 119

conditions: (a) *t*-C₄H₉CHO, PTSA; (b) LDA, RCH=CHNO₂, -100 °C; (c) H₂, Pd / C, 1N HCl (95%); (d) 2N HCl, 70 °C (39%); (e) NaNO₂, C₄H₉ONO, DMSO; (f) 2N HCl, 80 °C

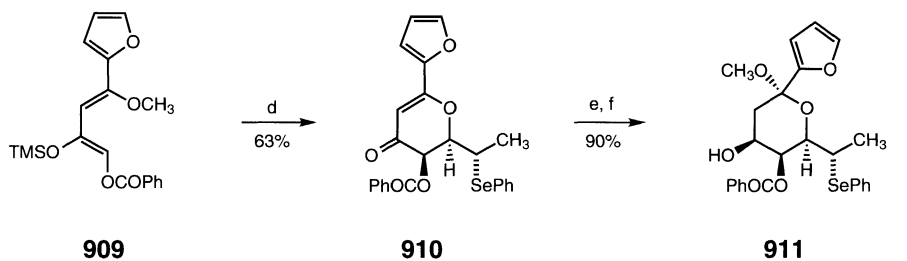
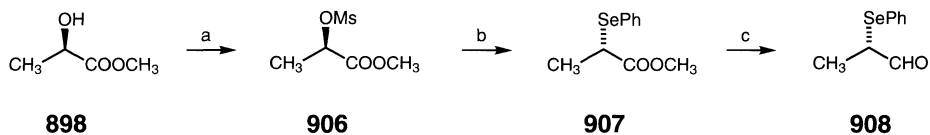
perature. The aldehyde is prone to racemization, and is generated *in situ* prior to reaction with **909**.

The hetero Diels–Alder reaction (**909** → **910**) produces a 5 : 1 mixture of diastereomers from which *cis*-**910** is isolated by flash chromatography (95% optically pure). Reduction of the ketone carbonyl followed by methanolysis furnishes the axial glycoside **911**. The furan heterocycle behaves as a masked carboxylic acid function that can be liberated by oxidation with ruthenium tetroxide. The conversion of **911** to **912** requires 13 steps.

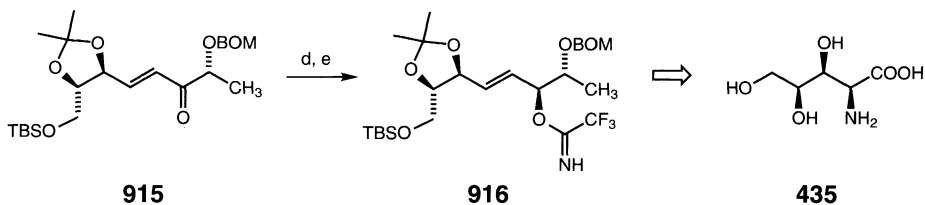
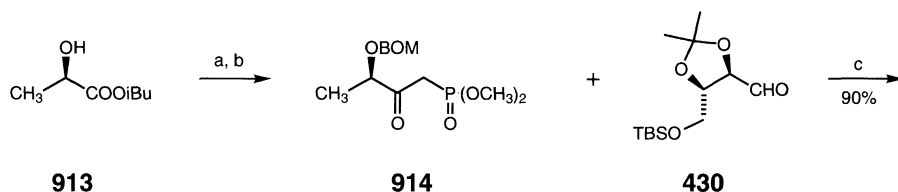
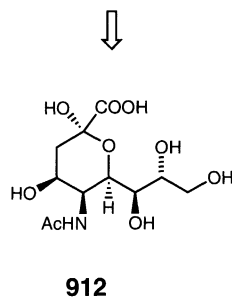


Scheme 120

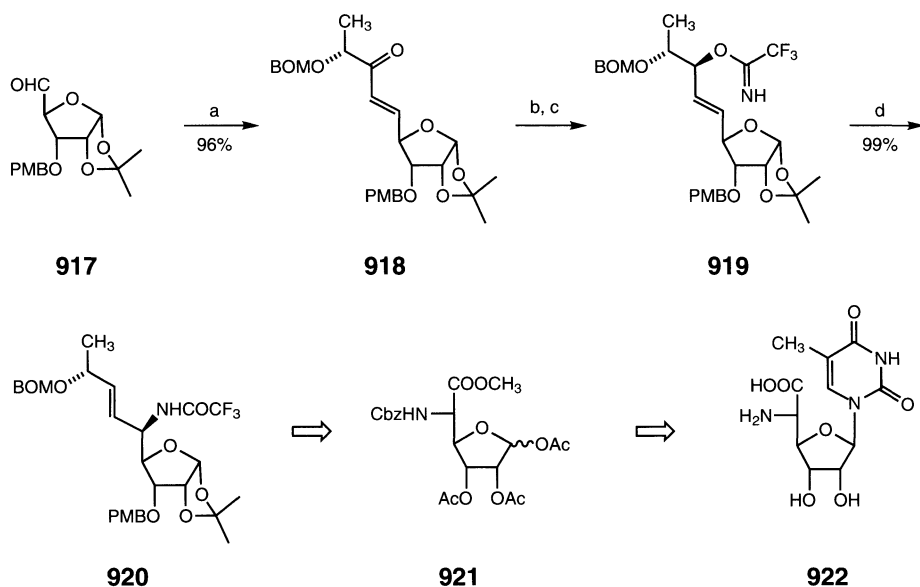
conditions: (a) TsCl, Et₃N, CH₂Cl₂ (66%); (b) 10% NaOH (93%); (c) SOCl₂, CHCl₃; (d) KO^t-Bu, THF, -50 °C; (e) Et₃N, DMSO, 80 °C; (f) 15% HCl, dioxane (90%)

**Scheme 121**

conditions: (a) MsCl; (b) PhSeNa; (c) DIBAL, CH₂Cl₂ / hexane, -78 °C;
 (d) **908**, BF₃ • Et₂O, -78 °C; (e) NaBH₄, CeCl₃,
 CH₂Cl₂, -78 °C; (f) CSA, MeOH, HC(OCH₃)₃, benzene

**Scheme 122**

conditions: (a) BOM-Cl, *i*-Pr₂NEt (44%); (b) (CH₃O)₂P(O)CH₃, *n*-BuLi (90%); (c) LiCl, DBU, CH₃CN;
 (d) Zn(BH₄)₂, ether; (e) *n*-BuLi, CF₃CN



Scheme 123

conditions: (a) LiCl, DBU, CH₃CN; (b) Zn(BH₄)₂, ether, -40 °C (98%); (c) *n*-BuLi, CF₃CN (93%); (d) xylene (reflux)

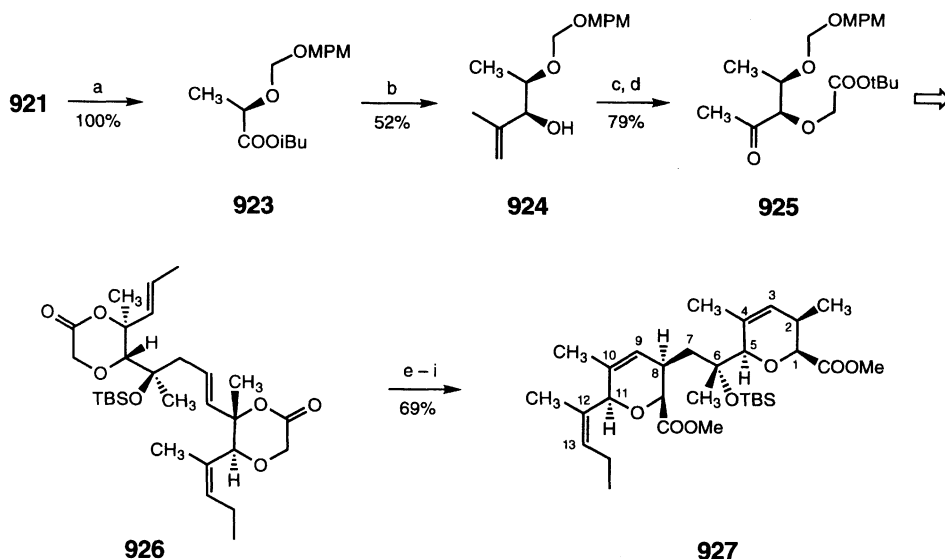
The synthesis of (+)-polyoxamic acid (**435**), the unusual amino acid component of polyoxin B, incorporates backbone assembly *via* a Horner–Emmons olefination of L-tartrate-derived aldehyde **430** with (*R*)-lactate-derived β-ketophosphonate **914** [101] (Scheme 122). The key introduction of the chiral amine stereocenter is accomplished by a trifluoroacetimidate rearrangement, outlined in Scheme 60 (Section 1.4.7.2).

Applying this methodology to more complicated systems allows one to gain access to more unusual amino acids, such as thymine polyoxin C (**922**) [101] (Scheme 123). The critical reduction of the keto group of **918** is accomplished with zinc borohydride, and it leads to the intermediate alcohol with >96% *de*. The alcohol, on reaction with trifluoroacetonitrile, affords acetimidate **919**, which upon heating undergoes a clean [3,3] rearrangement to give the trifluoroacetamide **920** in nearly quantitative yield. The olefin is converted to a carboxylate by ozonolysis and oxidation.

In an amazing transformation, optically pure erythronolide template **927** is generated from **926** by a double dioxanone–dihydropyran [3,3] sigmatropic rearrangement [248] (Scheme 124). The template contains the fundamental 13-carbon framework of erythronolide A or B (**600**) with seven of its asymmetric centers established. The synthesis of **927** requires 18 steps to complete, and the genesis of all the stereochemistry can be traced to isobutyl D-lactate (**913**). It is speculated that the remaining six stereocenters of erythronolide B can be introduced by hydroboration of the three olefinic segments of the bis(dihydropyran) **926**.

1.6.1 D-Lactaldehydes

(*R*)-2-Benzoyloxylactaldehyde (**929**) is readily prepared by benzylation of a D-lactic acid ester with benzyl bromide in the presence of freshly prepared silver oxide [249,250] followed



Scheme 124

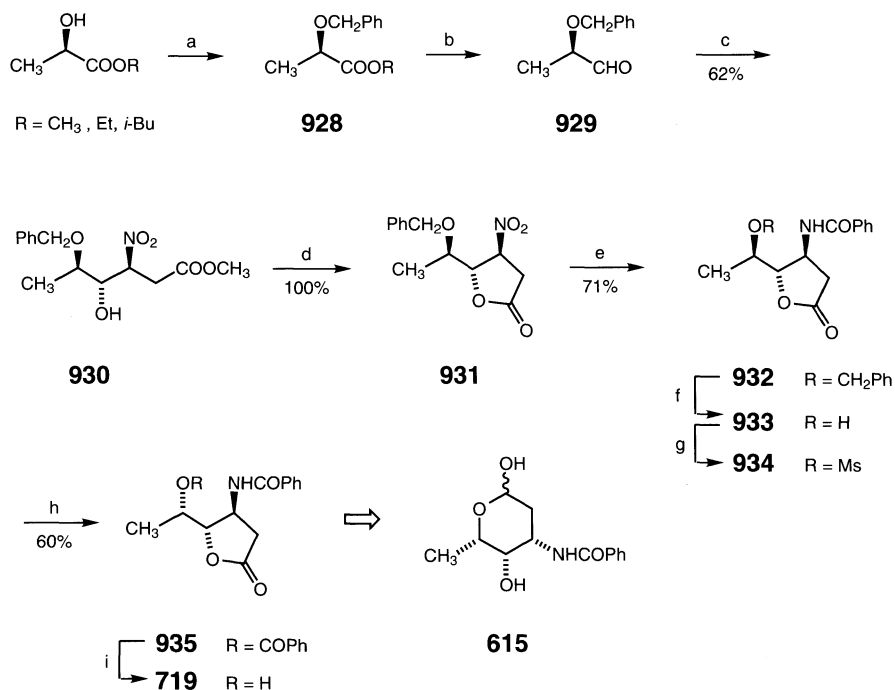
conditions: (a) MPMOCH_2Cl , $\text{t-Pr}_2\text{NEt}$, CH_2Cl_2 ; (b) LiBH_4 , $\text{CH}_2=\text{C}(\text{CH}_3)\text{MgBr}$, THF, -10°C ;
 (c) $\text{BrCH}_2\text{COOt-Bu}$, 50% NaOH, Bu_4NHSO_4 ; (d) O_3 , CH_2Cl_2 / MeOH (1:1), -78°C ;
 (e) LiHMDS , THF, -78°C ; (f) TMS-Cl , Et_3N ; (g) toluene, 110°C ; (h) 2% HCl, ether;
 (i) CH_2N_2 , ether, 0°C

by partial reduction of the ester function with diisobutylaluminum hydride at -78°C [175,249,250].

Lactaldehyde **929** has been used in a synthesis of *N*-benzoyl L-daunosamine (**615**), a derivative of the carbohydrate component of adriamycin [175] (Scheme 125). Two important reactions in the synthetic pathway are the conversions **929** \rightarrow **930** and **933** \rightarrow **935**. The nitroaldol reaction of **929** with methyl 3-nitropropionate leads to a mixture of three isomeric adducts from which the major diastereomer **930** is separated by crystallization and chromatography. After lactonization and functional group adjustment, the hydroxyl stereocenter of the D-ribo lactone **933** must be inverted to match the correct configuration of the target sugar. This is accomplished by conversion to the mesylate **934** and subsequent treatment with sodium benzoate. The resulting *L-lyxo* lactone **935** is then carried on to **615** as shown in Scheme 95 (Section 1.5.6.1).

Aplysiatoxin (**939**), a potent marine toxin isolated from the sea hare *Stylocheilus longicauda* and the blue-green algae *Lyngbya majuscula*, contains an interesting macrolactone that incorporates a rigid spiroketal moiety. The C-27 to C-31 chiral segment of the macrolactone is readily synthesized as the differentially protected acid **938** starting from **929**, as shown in Scheme 126 [249]. The stereochemistry of the diol is established by tin-mediated addition of allyltrimethylsilane to **929**. The resultant homoallylic alcohol **936** is formed as a 95:5 mixture of diastereomers, readily separable by chromatography. The free hydroxyl is protected with an *o*-nitrobenzyl group (**937**), which is easily removed photochemically. Permanganate oxidation of the olefin furnishes the desired acid **938**.

Allylboronate **940**, a chiral allylic alcohol α -carbanion equivalent, reacts with aldehyde **929** as a "matched pair" giving adduct **941** as an 89:11 mixture of diastereomers. A similar



Scheme 125

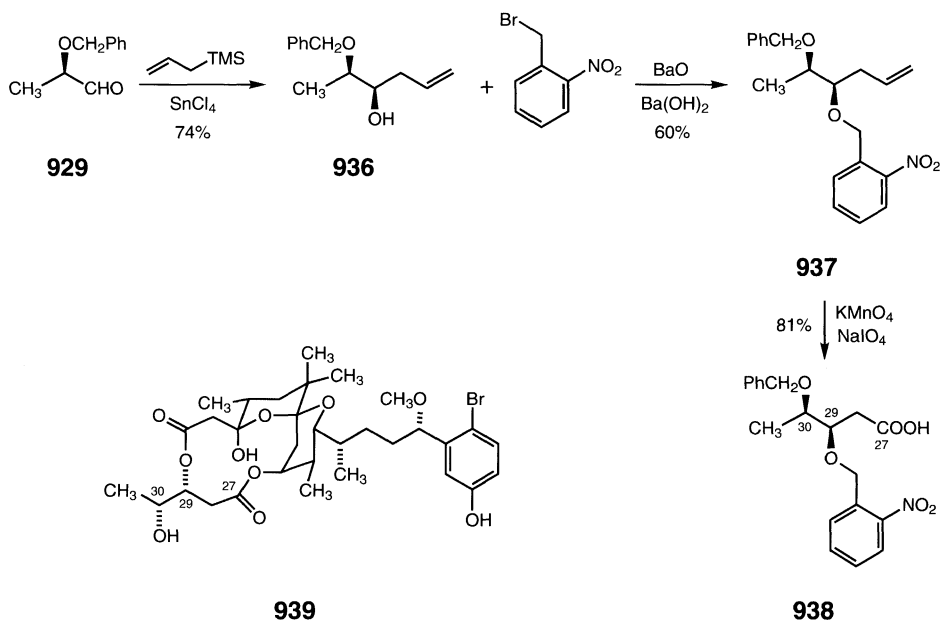
conditions: (a) Ag_2O , PhCH_2Br ; (b) DIBAL, hexane / ether (3:1), -78°C ; (c) $\text{CH}_3\text{OOCCH}_2\text{CH}_2\text{NO}_2$, Al_2O_3 ; (d) HCl , CH_2Cl_2 ; (e) H_2 , RaNi , MeOH , $(\text{PhOC})_2\text{O}$; (f) H_2 , 5% Pd/C , MeOH , H^+ (100%); (g) MsCl , pyridine (91%); (h) PhCOONa , DMF ; (i) NaOCH_3 (cat), MeOH (79%)

reaction of (*R,R*)-**940** and **929**, a “mismatched pair,” produces **943** as an 84 : 16 mixture [251] (Scheme 127).

The carbon skeleton of the *D-galacto*-3,6-dideoxy-3-*C*-methylhexose **948**, an important intermediate in the synthesis of rifamycin S, is readily assembled by a homoaldol reaction of **929** with titanated (*E*)-2-butenyl *N,N*-diisopropylcarbamate [250]. The adduct is obtained as a nearly statistical mixture of diastereomers from which the desired optically pure (> 95% *ee*) **944** is isolated by column chromatography (Scheme 128).

Epoxidation of the olefin occurs with high diastereofacial selectivity to give carbamoyloxirane **945**. This epoxide is not extremely stable, and is treated directly with methanesulfonic acid to afford the β -*D-talo*-furanoside **946**. The stereocenter at C-2 must be inverted to match the configuration of the natural product. This is accomplished by triflate formation followed by an $\text{S}_{\text{N}}2$ reaction with cesium acetate. Hydrolysis of the OAc group furnishes the desired β -*D-galacto*-furanoside (**947**). *O*-Methylation, benzyl group hydrogenolysis, acidic hydrolysis, and dithioacetal formation completes the synthesis of **948** in 11 steps and 5.7% overall yield from **929** [252].

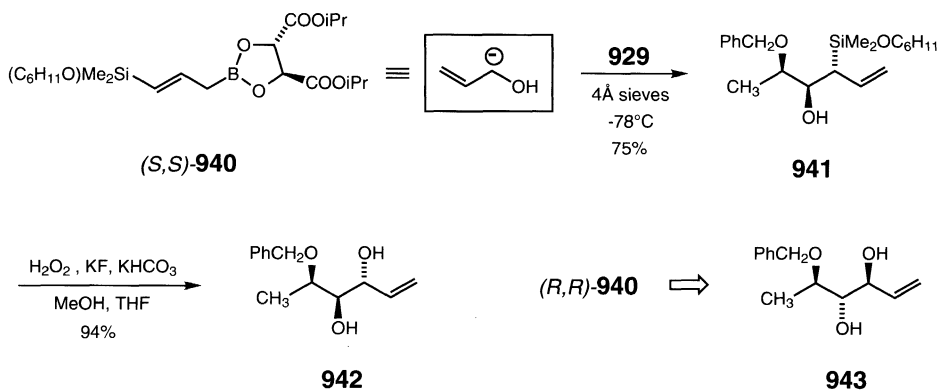
Chiral 3,5,6-trihydroxyheptanoic acids are potentially useful intermediates for the synthesis of natural products. The backbone can be constructed by a titanium-mediated aldol reaction of silyl enol ether **536** with **929**. The *syn* adduct **949** is formed exclusively, as predicted by the chelation-controlled Cram cyclic model.



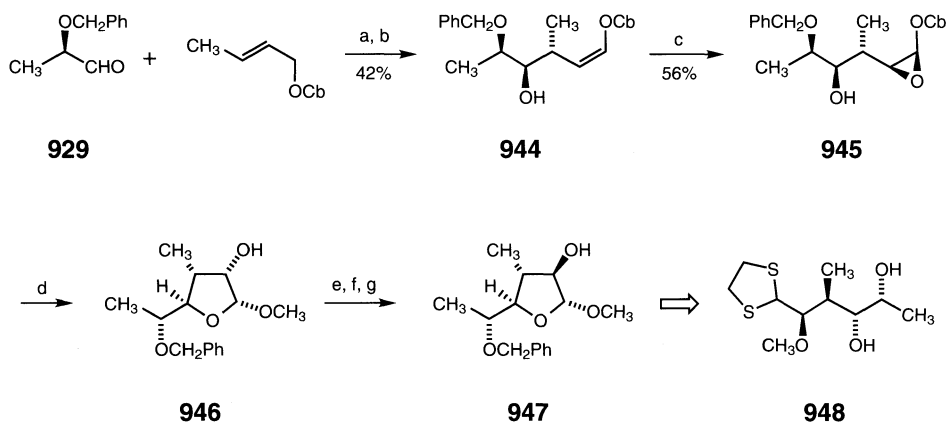
Scheme 126

After TBS protection, methanolysis of the dioxolenone liberates the heptanoic acid ester **950**. Stereocontrolled reduction of the β -keto function furnishes either *syn* or *anti* diols depending on the hydride reagent employed. Diethylmethoxyborane–sodium borohydride gives *syn*-diol **952** as a single isomer in 86% yield, whereas tetramethylammonium triacetoxyborohydride produces a mixture of *anti* and *syn*-diols **953** and **952** (ratio *anti* : *syn* = 10 : 1) in 85% yield [173] (Scheme 129).

EE-Protected D-lactaldehyde **954** is an efficient chiral source for the asymmetric center of (+)-diploidalide A (**960**), a metabolite isolated from the culture filtrate of the plant pathogenic fungus *Diplodia pinea* [253] (Scheme 130). The carbon skeleton is assembled through two olefination reactions, the first a Wittig reaction of **954** with phosphorane **955** to give the *Z*



Scheme 127

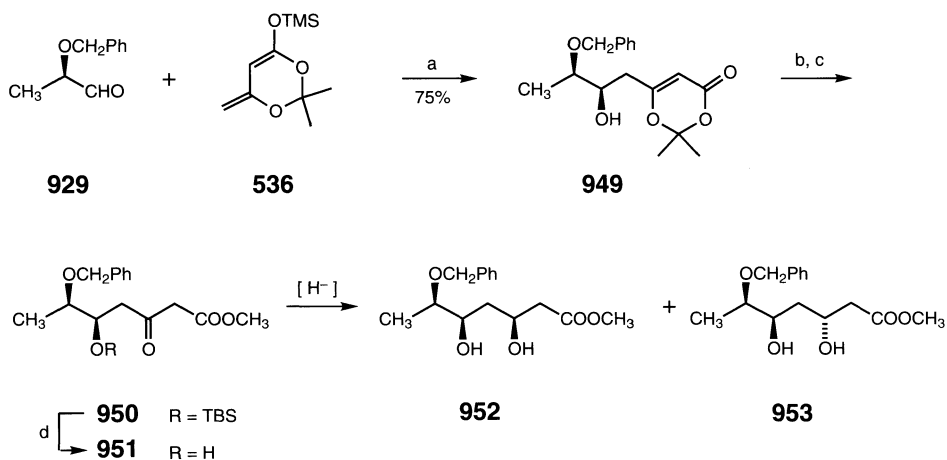


Scheme 128

conditions: (a) *n*-BuLi, hexane, TMEDA, ether, -78 °C; (b) Ti(O*i*-Pr)₄; (c) *t*-BuOOH, CH₂Cl₂, ClCH₂CH₂Cl, VO(acac)₂; (d) CH₃SO₃H, MeOH, -78 °C; (e) (CF₃SO₂)₂O, pyridine (84%); (f) CsOAc, DMSO, 50–55 °C (76%); (g) KOH, MeOH (90%)

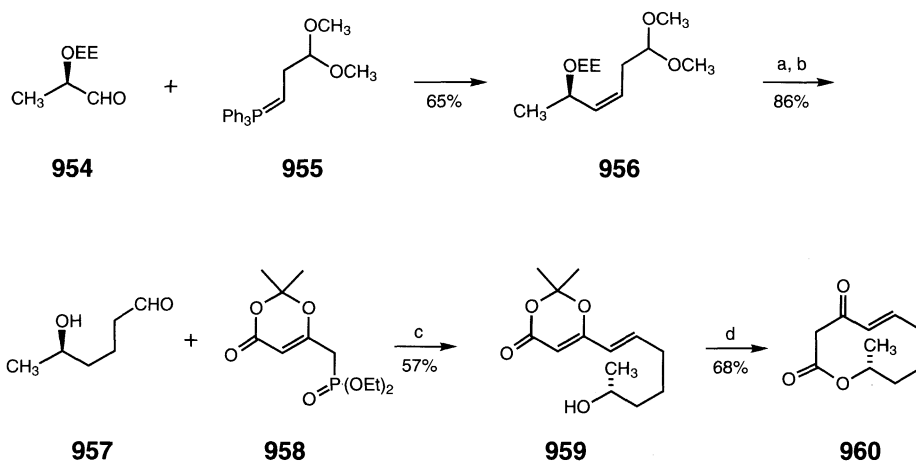
olefin **956**, and the second a Horner–Emmons-type reaction of aldehyde **957** with phosphonate **958** to give the *E* olefin **959**. Thermolysis of **959** under high-dilution conditions affords the desired lactone **960** with minimal polymeric byproducts.

TBS-Protected D-lactaldehyde **961** is used as the chiral source for the synthesis of β -lactam **969**, a key intermediate in the synthesis of the antibiotic monobactam Aztreonam [254] (Scheme 131). The crucial step in the synthesis, the reaction of *N*-trimethylsilylimine **962** with the lithium enolate of STABASE (**963**), affords *trans*- β -lactam **964** with 98% diastereoselectivity. Desilylation, Jones oxidation, and Baeyer–Villiger oxidation provides acetoxy β -lactam **968**, which in itself is a useful intermediate for the preparation of β -lactam anti-



Scheme 129

conditions: (a) TiCl₄, CH₂Cl₂, -78 °C; (b) TBS-Cl, imidazole, DMF (98%); (c) CH₃OH, toluene (91%); (d) Bu₄NF, THF (73%)

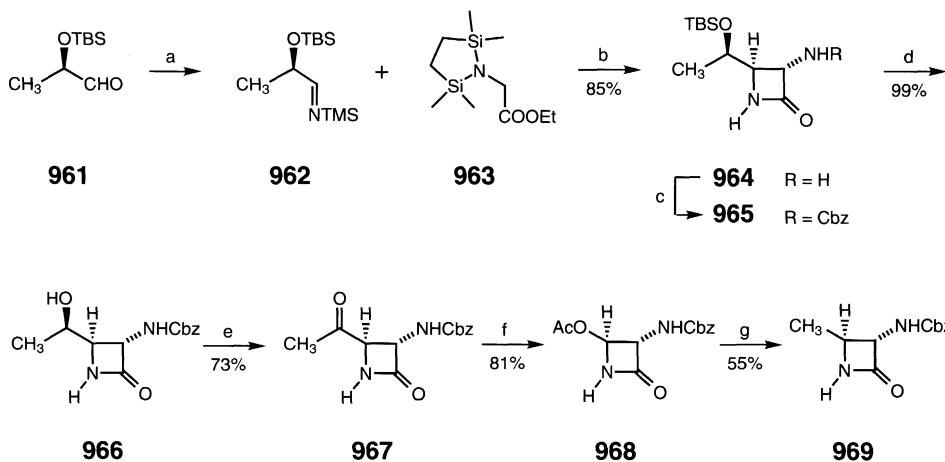


Scheme 130

conditions: (a) H_2 , PtO_2 , EtOAc; (b) Amberlyst-15, THF – H_2O (98:2); (c) KOtBu, THF, $-78^\circ \rightarrow 25^\circ C$;
 (d) toluene (10^{-4} M), reflux

biotics. Displacement of the acetoxy group with methyl cuprate furnishes **969**, which can be carried on to Aztreonam.

Four of the eight possible stereoisomers of blastmycinolactol (**975**, **978**, **983**, and **986**) have been synthesized from one common intermediate derived from THP-protected lactaldehyde **970** [255] (Schemes 132 and 133). Blastmycinolactol is an immediate precursor to blastmycinone, a degradation product of antimycin A_3 (**676**).



Scheme 131

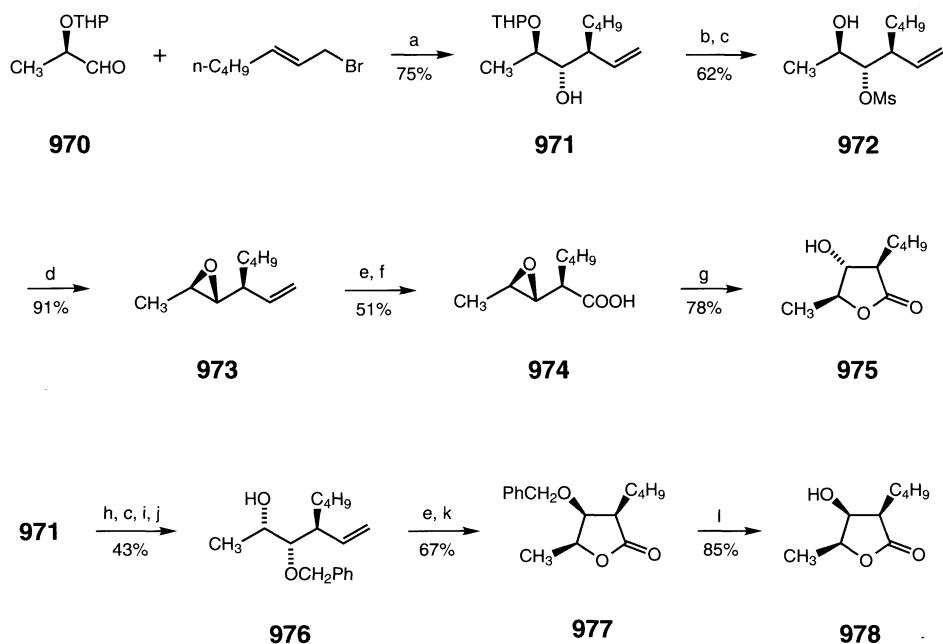
conditions: (a) LiHMDS, THF, $-40^\circ C$; (b) LDA, THF, $-78^\circ C$; (c) Cbz-Cl, $NaHCO_3$; (d) HF, CH_3CN ;
 (e) Jones reagent; (f) MCPBA, $CHCl_3$; (g) CuCN, CH_3Li , THF

The key transformation, a Hiyama reaction of 1-bromo-2-(*E*)-heptene with **970**, produces the Felkin–Anh product **971** with >99 : 1 diastereoselectivity. The key to accessibility to the four stereoisomers of blastmycinolactol is the differentiated 2- and 3-hydroxyl groups in **971**.

Protection of the 3-OH with a benzyl group, then removal of the THP group followed by a Mitsunobu reaction affords **976**, in which the hydroxyl stereocenter at C-2 is inverted. Conversion of the olefin to an aldehyde results in lactol formation, and subsequent oxidation furnishes lactone **977**. Removal of the benzyl protecting group by hydrogenolysis gives diastereomer **978**.

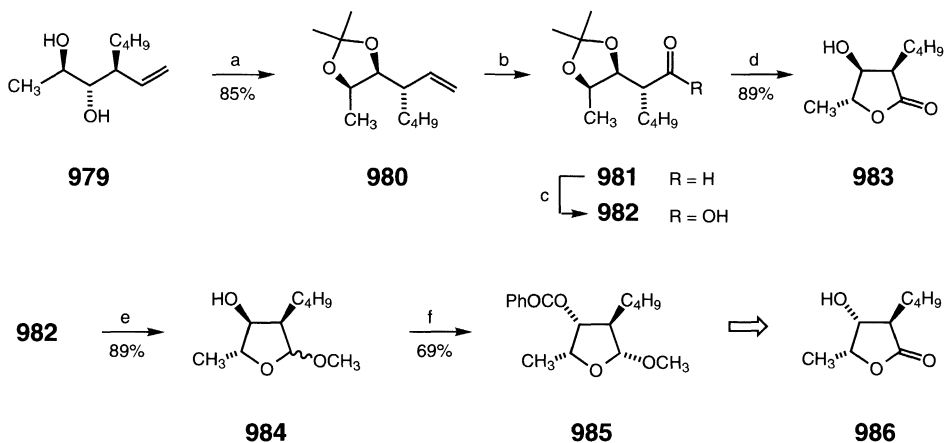
Conversion of **971** to epoxide **973** via mesylate **972** results in inversion of the configuration at C-3 due to an S_N2 reaction. Transformation of the olefin to an acid followed by lactonization results in a second inversion, this time at C-2, producing diastereomer **975**. If no inversion reactions are performed, the third diastereomer **983** can be obtained from diol **979** as shown in Scheme 133.

Synthesis of the final diastereomer **986** requires a single inversion at C-3. Attempted Mitsunobu reaction of **971** fails due to steric hinderance. This can be circumvented by converting aldehyde **981** to furanoside **984**. Although **984** is formed as a 2 : 1 mixture of α and β -anomers, the desired β -anomer is isolable by column chromatography. The α -anomer can be equilibrated to a mixture of α and β -anomers by treatment with PTSA and the mixture recycled. Only the β -anomer undergoes Mitsunobu reaction to give **985**. The α -anomer produces only a mixture of elimination products.



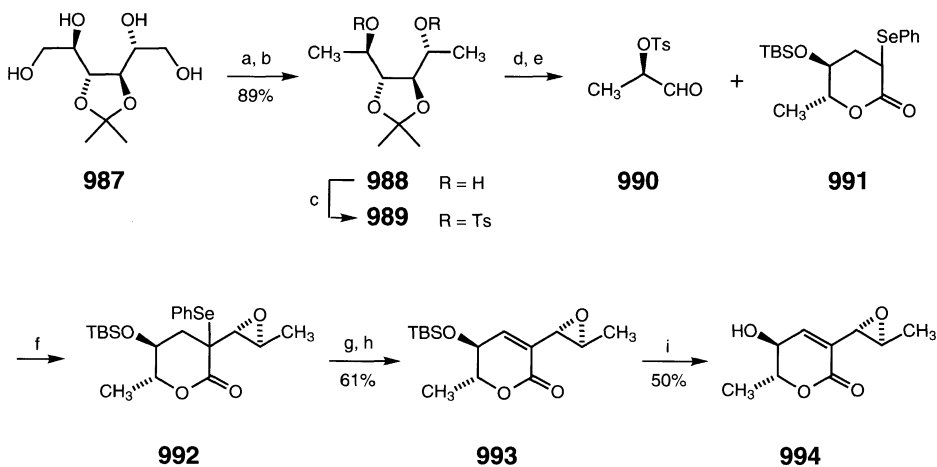
Scheme 132

conditions: (a) CrCl₃, LiAlH₄, THF, 0 °C; (b) MsCl, Et₃N, CHCl₃; (c) PTSA, MeOH; (d) NaOCH₃, MeOH, CHCl₃; (e) O₃, MeOH, -78 °C, then PPh₃; (f) NaIO₄, RuO₂ (cat), CH₃CN, CCl₄, H₂O₂; (g) 2N H₂SO₄, THF; (h) PhCH₂Cl, NaH, DMSO, THF; (i) DEAD, Ph₃P, PhCOOH; (j) KOH, MeOH; (k) PCC, CH₂Cl₂; (l) H₂, 10% Pd / C, MeOH, HCl



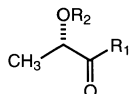
Scheme 133

conditions: (a) 2,2-dimethoxypropane, PTSA, MeOH; (b) O_3 , MeOH, $-78^\circ C$, then Ph_3P (85%); (c) $NaIO_4$, RuO_2 (cat), CH_3CN , CCl_4 , H_2O (60%); (d) 2N H_2SO_4 , THF; (e) PTSA, MeOH; (f) DEAD, Ph_3P , $PhCOOH$, THF



Scheme 134

conditions: (a) $TsCl$, pyridine; (b) $LiAlH_4$; (c) $TsCl$, Et_3N (93%); (d) CF_3COOH , H_2O (82%); (e) $NaIO_4$ (86%); (f) $LiHMDS$, $-78^\circ C$; (g) H_2O_2 ; (h) $NaHCO_3$, H_2O ; (i) Bu_4NF , $PhCOOH$

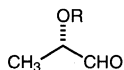
Table 1.4. Physical properties of lactic acid derivatives

R ¹	R ²	[α] _D (°)	Solvent (<i>c</i>)	<i>mp</i> , °C or <i>bp</i> , °C (mm Hg)	Reference
OH	Ac	-47.3	CHCl ₃ (6.8)	101–104 (3)	48
		-52.8	neat	135–140 (16)	80
		-49.3	CHCl ₃ (7.3)	115–117 (2)	79
OH	Ms	-53.3	CHCl ₃ (1)	70–73	46
		-53.9	CHCl ₃ (1)	69	58
OH	SO ₂ Ph	-34.9	CHCl ₃ (1)		46
OH	Ts	-36.7	CHCl ₃ (1)	108–110	46
		-43.4	CHCl ₃ (5.3)	110–111	47
		-86	EtOH (0.96)	53–55	96, 97
OCH ₃	H	-8.4	neat	50 (19)	93
OCH ₃	Ms	-56.4	CHCl ₃ (1)	80–82 (0.5)	59, 68
OCH ₃	Ns	-9.9	CHCl ₃ (1.4)	52–3	34
OCH ₃	Ts	-61.1	neat	182–183 (1)	68
		-32.6	CHCl ₃ (2.9)	120–122 (10 ⁻³)	45
		-78.4	neat	98.5–100 (1.5)	93
OCH ₃	CH ₂ Ph	-78.4	neat	98.5–100 (1.5)	93
OCH ₃	TBS	-31.7	95% EtOH (0.66)	95 (30)	129
		-26.9	CCl ₄ (1.89)	20 (15)	130
OCH ₃	TBPS	-51.8	95% EtOH (0.78)		129
OEt	H	-11.9	neat	59–60 (20)	50
		-11.0	neat		30
OEt	Ac	-44.7	neat	45–48 (8)	79
		-49.0	CHCl ₃ (1.0)	88 (32)	81
		-52.9	CHCl ₃ (4.32)	75–76 (0.03)	69
OEt	Ms	-63.06	neat		56
		-52.3	CHCl ₃ (1.0)	106 (2.5)	58
		-54.6	CHCl ₃ (4.36)		65
		-36.7	CHCl ₃ (1.0)	141 (0.75)	46
		-31.4	CHCl ₃ (1.5)		29
OEt	SO ₂ Ph	-36.7	CHCl ₃ (1.0)	141 (0.75)	46
OEt	2-SO ₂ Py	-31.4	CHCl ₃ (1.5)		29
OEt	Ts	-51.0	neat	146–147 (1)	30
		-35.5	CHCl ₃ (1.0)	33–34	46
		-34.77	CHCl ₃ (1.0)	33–33.5	50
		-66.3	neat	140–143 (14)	98
OEt	CH ₂ Ph	-66.3	neat	140–143 (14)	98
OEt	BOM	-43.5	95% EtOH (1.7)		100
OEt	EE	-68.7	CHCl ₃ (5.0)	80 (20)	108
OEt	MEM	-64.0	CHCl ₃ (1.0)	120–122 (20)	100
		-66.7	CHCl ₃ (1.17)	84 (1)	117
		-42.5	EtOH (1.0)	75–76.5 (5)	116
OEt	MOM	-84.0	CHCl ₃ (1.6)	179–181 (750)	100
		-79.3	MeOH (1.0)	57 (6)	119
		-88.1	CHCl ₃ (2.85)	39 (0.35)	120

Table 1.4. (continued)

R ¹	R ²	[α] _D (°)	Solvent (c)	mp, °C or bp, °C (mm Hg)	Reference
OEt	TBS	-28.9	CHCl ₃ (1.26)	40 (0.2)	126
		-21.4	MeOH (1.0)		127
OEt	TBPS	-45.1	MeOH (1.0)		134
		-41.1	CHCl ₃ (2.0)		136
OEt	THP			66-68 (0.25)	141
OEt	Tr	-32.4	CHCl ₃ (1.44)		237
OEt	CONiPr ₂	+25.4	neat	91 (0.05)	77
O <i>tert</i> -Bu	H	-4.96	CHCl ₃ (2.54)		91
O <i>tert</i> -Bu	Ac	-53.0	CHCl ₃ (3.34)		91
OCH ₂ Ph	Ts	-28.6	CHCl ₃ (5.05)		47
OCH ₂ Ph	Tf	-37.8	CHCl ₃ (1.81)		40
OMOM	MOM	-77.7	MeOH (1.0)		119
Cl	Ts	+8.6	CCl ₄ (1.0)	40.5-42.5	46
NH ₂	Ac	-10.4	CHCl ₃ (1.94)	59-60	84
NH ₂	TBS	-13.2	MeOH (1.0)		127
N(CH ₃) ₂	H	-8.1	neat		6
		+0.85	MeOH (1.01)	71-74 (0.7)	7
N(CH ₃) ₂	BOM	-64.4	CHCl ₃ (2.62)		95
N(CH ₃) ₂	MOM	-95.3	MeOH (1.03)	102-103 (15)	7
		-49.2	CHCl ₃ (4.78)	108 (1)	117
		-66.9	CHCl ₃ (1.72)	42-42.5	117

Table 1.5. Physical properties of protected lactaldehydes



R	[α] _D (°)	Solvent (c)	mp, °C or bp, °C (mm Hg)	Reference
CH ₂ Ph	-52.2	CHCl ₃ (6.5)		92
	-66.8	neat		117
BOM	-13.4	CHCl ₃ (1.6)	100 (1)	95, 100
EE	-56.9	CHCl ₃ (6.31)	53-54 (17)	189
MEM	-12.1	CHCl ₃ (1.0)		100
	-29.3	EtOH (1.0)	53-54 (0.6)	116
MOM	-28.8	95% EtOH (1.0)	95 (15)	129
	-12.6	CHCl ₃ (1.6)	90 (23)	100
TBS	-11.8	CHCl ₃ (1.54)	94-95 (10)	203
	-6.13	95% EtOH (1.0)	79 (28)	129
	-12.0	CHCl ₃ (1.5)		208
TBPS	-10.2	95% EtOH (1.2)	108-110 (0.05)	129
THP			110 (20)	117
Tr	-14.4	CHCl ₃ (1.14)	102-103	237

Conversion of the blastmycinolactol diastereomers to the corresponding blastmycinones should be achievable by acylation of the free hydroxy group with isovaleryl chloride, as shown in Scheme 77 (Section 1.5.1).

(*R*)-2-Tosyloxypropanal (**990**) is available from 3,4-*O*-isopropylidene-D-mannitol (**987**) by conversion of the two terminal hydroxyl groups to methyl groups, tosylation of the free secondary hydroxyl groups, and oxidative diol cleavage [256]. The aldehyde is rather labile, and tends to hydrate on standing in air.

In the synthesis of aspyrone (**994**), an antibiotic isolated from the culture broth of *Aspergillus* species, lactaldehyde **990** supplies the asymmetric centers of the epoxide in the side chain (Scheme 134). The molecule is assembled convergently by addition of the lithium enolate of D-rhamnose-derived α -phenylseleno- δ -lactone **991** to aldehyde **990**. After an initial aldol-type reaction, the intermediate alkoxide displaces tosylate to provide epoxide **992** with >99.8% stereoselectivity. Peroxide-induced elimination of phenylselenide furnishes TBS-protected aspyrone **993** in 61% overall yield from **990**.

References

1. T. Sato, J. Otera, and H. Nozaki, *J. Org. Chem.* **57**, 2166 (1992).
2. K. Toyooka, Y. Takeuchi, and S. Kubota, *Heterocycles* **29**, 975 (1989).
3. K. Toyooka, Y. Takeuchi, H. Ohto, M. Shibuya, and S. Kubota, *Chem. Pharm. Bull.* **39**, 777 (1991).
4. G. R. Wolf, J. G. Miller, and A. R. Day, *J. Am. Chem. Soc.* **78**, 4372 (1956).
5. M. Larcheveque and Y. Petit, *Synthesis*, 60 (1986).
6. D. Seebach, H. Kalinowski, B. Bastani, G. Crass, H. Daum, H. Dorr, N. P. DuPreez, V. Ehrig, W. Langer, C. Nussler, H. Oei, and M. Schmidt, *Helv. Chim. Acta* **60**, 301 (1977).
7. Y. Honda, A. Ori, and G. Tsuchihashi, *Bull. Chem. Soc. Jap.* **60**, 1027 (1987).
8. J. P. Vigneron, M. Dhaenens, and A. Horeau, *Tetrahedron* **33**, 507 (1977).
9. K. Suzuki, E. Katayama, and G. Tsuchihashi, *Tetrahedron Lett.* **24**, 4997 (1983).
10. G. Tsuchihashi, K. Tomooka, and K. Suzuki, *Tetrahedron Lett.* **25**, 4253 (1984).
11. S. Wei, K. Tomooka, and T. Nakai, *J. Org. Chem.* **56**, 5973 (1991).
12. T. Okonogi, S. Shibahara, Y. Murai, S. Inouye, and S. Kondo, *Heterocycles* **31**, 791 (1990).
13. T. Okonogi, S. Shibahara, Y. Murai, S. Inouye, and S. Kondo, *Heterocycles* **31**, 797 (1990).
14. J. Gombos, E. Haslinger, and U. Schmidt, *Chem. Ber.* **109**, 2645 (1976).
15. M. K. Ellis and B. T. Golding, *Organic Syntheses, Coll. Vol. VII*, John Wiley and Sons, New York, 1990, p. 356.
16. G. Quinkert, E. Fernholz, P. Eckes, D. Neumann, and G. Durner, *Helv. Chim. Acta* **72**, 1753 (1989).
17. H. Gais and T. Lied, *Angew. Chem., Int. Ed. Engl.* **23**, 145 (1984).
18. K. Mori, H. Soga, and M. Ikunaka, *Liebigs Ann. Chem.*, 2194 (1985).
19. K. Mori and M. Ikunaka, *Tetrahedron* **40**, 3471 (1984).
20. D. Seebach and R. Naef, *Helv. Chim. Acta* **64**, 2704 (1981).
21. D. Seebach, R. Naef, and G. Calderari, *Tetrahedron* **40**, 1313 (1984).
22. K. Krohn and U. Muller, *Tetrahedron* **42**, 6635 (1986).
23. R. Naef and D. Seebach, *Liebigs Ann. Chem.*, 1930 (1983).
24. R. K. Boeckman, Jr., S. Kyoon, and D. K. Heckendorn, *J. Am. Chem. Soc.* **113**, 9682 (1991).
25. G. Calderari and D. Seebach, *Helv. Chim. Acta* **68**, 1592 (1985).
26. J. Mattay, J. Mertes, and G. Maas, *Chem. Ber.* **122**, 327 (1989).
27. W. R. Roush and B. B. Brown, *J. Org. Chem.* **57**, 3380 (1992).
28. J. Mattay, G. Kneer, and J. Mertes, *Synlett.*, 145 (1990).
29. S. Hanessian, M. Kagotani, and K. Komaglou, *Heterocycles* **28**, 1115 (1989).
30. J. Biedermann, A. Leon-Lomeli, H. O. Borbe, and G. Prop, *J. Med. Chem.* **29**, 1183 (1986).
31. S. J. Fu, S. M. Birnbaum, and J. P. Greenstein, *J. Am. Chem. Soc.* **76**, 6054 (1954).
32. O. Piccolo, F. Spreafico, G. Visentin, and E. Valoti, *J. Org. Chem.* **52**, 10 (1987).
33. A. S. Thompson, G. R. Humphrey, A. M. DeMarco, D. J. Mathre, and E. J. J. Grabowski, *J. Org. Chem.* **58**, 5886 (1993).
34. R. V. Hoffman and H. Kim, *Tetrahedron* **48**, 3007 (1992).

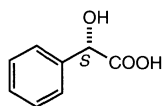
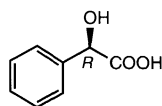
35. R. V. Hoffman and H. Kim, *Tetrahedron Lett.* **31**, 2953 (1990).
36. B. Strijtveen and R. M. Kellogg, *Recl. Trav. Chim. Pays-Bas* **106**, 539 (1987).
37. L. E. Overman, K. L. Bell, and F. Ito, *J. Am. Chem. Soc.* **106**, 4192 (1984).
38. M. C. Viaud and P. Rollin, *Synthesis*, 130 (1990).
39. H. Morimoto, T. Furukawa, K. Miyazima, and O. Mitsunobu, *Chem. Lett.*, 821 (1973).
40. F. Degerbeck, B. Fransson, L. Grehn, and U. Ragnarsson, *J. Chem. Soc., Perkin I Trans.*, 245 (1992).
41. L. D. Arnold, H. I. Assil, and J. C. Vederas, *J. Am. Chem. Soc.* **111**, 3973 (1989).
42. T. Kurihara, M. Sugizaki, I. Kime, M. Wada, and O. Mitsunobu, *Bull. Chem. Soc. Jap.* **54**, 2107 (1981).
43. O. Mitsunobu, *Synthesis*, 1 (1981).
44. R. H. Schlessinger, and D. D. Graves, *Tetrahedron Lett.* **28**, 4385 (1987).
45. L. N. Owen and M. B. Rahman, *J. Chem. Soc. (C)*, 2432 (1971).
46. M. Imfeld, M. Suchy, P. Vogt, T. Lukac, M. Schlageter, and E. Widmer, *Helv. Chim. Acta* **65**, 1233 (1982).
47. S. Terashima, C. C. Tseng, and K. Koga, *Chem. Pharm. Bull.* **27**, 747 (1979).
48. M. Ohzeki, T. Mizoguchi, K. Koga, and S. Yamada, *Chem. Pharm. Bull.* **25**, 2676 (1977).
49. T. Konosu, Y. Tajima, T. Miyaoka, and S. Oida, *Tetrahedron Lett.* **32**, 7545 (1991).
50. S. Brandange and L. Morch, *Acta Chem. Scand.* **B33**, 776 (1979).
51. R. Oehrlein, R. Jeschke, B. Ernst, and D. Bellus, *Tetrahedron Lett.* **30**, 3517 (1989).
52. M. Larcheveque and Y. Petit, *Synthesis*, 162 (1991).
53. B. D. Johnston and K. N. Slessor, *Can. J. Chem.* **57**, 233 (1979).
54. K. Mori and S. Senda, *Tetrahedron* **41**, 541 (1985).
55. K. Utimoto, K. Uchida, M. Yamaya, and H. Nozaki, *Tetrahedron Lett.*, 3641 (1977).
56. C. Albano and S. Wold, *Acta Chem. Scand.* **B35**, 357 (1981).
57. E. Fritz-Langhals and G. Schutz, *Tetrahedron Lett.* **34**, 293 (1993).
58. T. Yamachi, K. Hattori, K. Nakao, and K. Tamaki, *Bull. Chem. Soc. Jap.* **60**, 4015 (1987).
59. U. Azzena, G. Delogu, G. Melloni, and O. Piccolo, *Tetrahedron Lett.* **30**, 4555 (1989).
60. S. Colonna, A. Re, G. Gelbard, and E. Cesarotti, *J. Chem. Soc., Perkin I Trans.*, 2248 (1979).
61. G. Cainelli, F. Manescalchi, G. Martelli, M. Panunzio, L. Plessi, *Tetrahedron Lett.* **26**, 3369 (1985).
62. L. Baiocchi and G. Picconi, *Tetrahedron Asymm.* **2**, 231 (1991).
63. B. Strijtveen and R. M. Kellogg, *J. Org. Chem.* **51**, 3664 (1986).
64. D. Seebach, E. Hungerbuhler, R. Naef, P. Schnurrenberger, B. Weidmann, and M. Zuger, *Synthesis*, 138 (1982).
65. R. Breitschuh and D. Seebach, *Synthesis*, 1170 (1992).
66. J. N. Fitzner, R. G. Shea, J. E. Fankhauser, and P. B. Hopkins, *J. Org. Chem.* **50**, 417 (1985).
67. O. Piccolo, F. Spreafico, G. Visentin, and E. Valoti, *J. Org. Chem.* **50**, 3945 (1985).
68. O. Piccolo, U. Azzena, G. Melloni, G. Delogu, and E. Valoti, *J. Org. Chem.* **56**, 183 (1991).
69. L. R. Hillis and R. C. Ronald, *J. Org. Chem.* **46**, 3348 (1981).
70. F. Effenberger, U. Burkard, and J. Willfahrt, *Liebigs Ann. Chem.*, 314 (1986).
71. F. Effenberger, U. Burkard, and J. Willfahrt, *Angew. Chem., Int. Ed. Engl.* **22**, 65 (1983).
72. U. Burkard and F. Effenberger, *Chem. Ber.* **119**, 1594 (1986).
73. W. Kinzy and R. R. Schmidt, *Liebigs Ann. Chem.*, 407 (1987).
74. Y. Petit, C. Sanner, and M. Larcheveque, *Tetrahedron Lett.* **31**, 2149 (1990).
75. B. M. Trost and M. S. Rodriguez, *Tetrahedron Lett.* **33**, 4675 (1992).
76. J. Chiarello and M. M. Joulie, *Syn. Commun.* **19**, 3379 (1989).
77. J. Schwark and D. Hoppe, *Synthesis*, 291 (1990).
78. S. Kano, Y. Yuasa, and S. Shibuya, *Heterocycles* **23**, 395 (1985).
79. S. G. Cohen, J. Crossley, E. Khedouri, R. Zand, and L. H. Klee, *J. Am. Chem. Soc.* **85**, 1685 (1963).
80. G. Bianchi, F. Achilli, and A. Gamba, *J. Chem. Soc., Perkin I Trans.*, 417 (1988).
81. B. A. Jones, J. S. Bradshaw, and R. M. Izatt, *J. Heterocyclic Chem.* **19**, 551 (1982).
82. J. Matsubara, K. Nakao, Y. Hamada, and T. Shioiri, *Tetrahedron Lett.* **33**, 4187 (1992).
83. R. S. Atkinson, B. J. Kelly, and J. Williams, *Tetrahedron* **48**, 7713 (1992).
84. U. Schmidt, P. Gleich, H. Griesser, and R. Utz, *Synthesis*, 992 (1986).
85. M. Fujita and T. Hiyama, *J. Org. Chem.* **53**, 5405 (1988).
86. T. Konosu, T. Miyaoka, Y. Tajima, and S. Oida, *Chem. Pharm. Bull.* **39**, 2241 (1991).
87. T. Konosu, T. Miyaoka, Y. Tajima, and S. Oida, *Chem. Pharm. Bull.* **40**, 562 (1992).
88. S. Brandange, L. Flodman, and A. Norberg, *J. Org. Chem.* **49**, 927 (1984).
89. S. Brandange, K. Jansbo, and T. Minassie, *Acta Chem. Scand.* **B41**, 736 (1987).
90. R. M. Ortuno, J. Bigorra, and J. Font, *Tetrahedron* **44**, 5139 (1988).
91. C. Hsiao, and T. Kolasa, *Tetrahedron Lett.* **33**, 2629 (1992).
92. K. Takai and C. H. Heathcock, *J. Org. Chem.* **50**, 3247 (1985).

93. K. Mislow, R. E. O'Brien, and H. Schaefer, *J. Am. Chem. Soc.* **84**, 1940 (1962).
94. Y. Ito, T. Kawabata, and S. Terashima, *Tetrahedron Lett.* **27**, 5751 (1986).
95. Y. Kobayashi, M. Takase, Y. Ito, and S. Terashima, *Bull. Chem. Soc. Jap.* **62**, 3038 (1989).
96. M. Enomoto, Y. Ito, T. Katsuki, and M. Yamaguchi, *Tetrahedron Lett.* **26**, 1343 (1985).
97. K. Steiner, U. Graf, and E. Hardegger, *Helv. Chim. Acta* **54**, 845 (1971).
98. D. P. G. Hamon, R. A. Massy-Westropp, and T. Pipithakul, *Aust. J. Chem.* **27**, 2199 (1974).
99. S. D. Burke, D. N. Deaton, R. J. Olsen, D. M. Armistead, and B. E. Blough, *Tetrahedron Lett.* **28**, 3905 (1987).
100. L. Banfi, A. Bernardi, L. Colombo, C. Gennari, and C. Scolastico, *J. Org. Chem.* **49**, 3784 (1984).
101. A. Chen, I. Savage, E. J. Thomas, and P. D. Wilson, *Tetrahedron Lett.* **34**, 6769 (1993).
102. J. M. Chong and K. K. Sokoll, *Tetrahedron Lett.* **33**, 879 (1992).
103. S. D. Burke, F. J. Schoenen, and M. S. Nair, *Tetrahedron Lett.* **28**, 4143 (1987).
104. A. Dondoni, G. Fantin, M. Fogagnolo, and P. Pedrini, *Tetrahedron* **45**, 5141 (1989).
105. L. E. Overman and R. J. McCready, *Tetrahedron Lett.* **23**, 2355 (1982).
106. M. H. Hopkins and L. E. Overman, *J. Am. Chem. Soc.* **109**, 4748 (1987).
107. U. Berens and H. Scharf, *Synthesis*, 832 (1991).
108. B. Seuring and D. Seebach, *Helv. Chim. Acta* **60**, 1175 (1977).
109. H. Ohta, M. Ikemoto, H. II, Y. Okamoto, and G. Tsuchihashi, *Chem. Lett.*, 1169 (1986).
110. Y. Honda, M. Sakai, and G. Tsuchihashi, *Chem. Lett.*, 1153 (1985).
111. K. Suzuki, K. Tomooka, E. Katayama, T. Matsumoto, and G. Tsuchihashi, *J. Am. Chem. Soc.* **108**, 5221 (1986).
112. K. Suzuki, T. Ohkuma, and G. Tsuchihashi, *Tetrahedron Lett.* **26**, 861 (1985).
113. K. Suzuki, E. Katayama, and G. Tsuchihashi, *Tetrahedron Lett.* **25**, 1817 (1984).
114. Y. Honda, A. Ori, and G. Tsuchihashi, *Chem. Lett.*, 13 (1986).
115. Y. Honda, A. Ori, and G. Tsuchihashi, *Chem. Lett.*, 1259 (1987).
116. T. R. Kelly and P. N. Kaul, *J. Org. Chem.* **48**, 2775 (1983).
117. Y. Ito, Y. Kobayashi, T. Kawabata, M. Takase, and S. Terashima, *Tetrahedron* **45**, 5767 (1989).
118. R. K. Boeckman, Jr. and J. C. Potenza, *Tetrahedron Lett.* **26**, 1411 (1985).
119. Y. Hamada, A. Kawai, T. Matsui, O. Hara, and T. Shioiri, *Tetrahedron* **46**, 4823 (1990).
120. H. H. Wasserman and R. J. Gambale, *J. Am. Chem. Soc.* **107**, 1423 (1985).
121. A. S. Kende and R. J. DeVita, *Tetrahedron Lett.* **29**, 2521 (1988).
122. Y. Hamada, A. Kawai, and T. Shioiri, *Tetrahedron Lett.* **25**, 5409 (1984).
123. Y. Hamada, A. Kawai, and T. Shioiri, *Tetrahedron Lett.* **25**, 5413 (1984).
124. Y. Hamada, A. Kawai, and T. Shioiri, *Chem. Pharm. Bull.* **33**, 5601 (1985).
125. M. D. Wittman and J. Kallmerten, *J. Org. Chem.* **53**, 4631 (1988).
126. W. Li, W. R. Ewing, B. D. Harris, and M. M. Joullie, *J. Am. Chem. Soc.* **112**, 7659 (1990).
127. A. Diez, H. Pe-Quiang, D. S. Grierson, H. Husson, and M. Rubiralta, *Heterocycles* **31**, 485 (1990).
128. K. Tanino, H. Shoda, T. Nakamura, and I. Kuwajima, *Tetrahedron Lett.* **33**, 1337 (1992).
129. S. K. Massad, L. D. Hawkins, and D. C. Baker, *J. Org. Chem.* **48**, 5180 (1983).
130. B. Stammen, U. Berlage, R. Kindermann, M. Kaiser, B. Gunther, W. S. Sheldrick, P. Welzel, and W. R. Roth, *J. Org. Chem.* **57**, 6566 (1992).
131. T. Sato, R. Kato, K. Gokyu, and T. Fujisawa, *Tetrahedron Lett.* **29**, 3955 (1988).
132. G. Shapiro, D. Buechler, and S. Hennet, *Tetrahedron Lett.* **31**, 5733 (1990).
133. M. Beckmann, H. Hildebrandt, and E. Winterfeldt, *Tetrahedron Asymm.* **1**, 335 (1990).
134. L. E. Overman and G. M. Rishton, *Org. Syn.* **71**, 56 (1992).
135. I. Savage and E. J. Thomas, *J. Chem. Soc., Chem. Commun.*, 717 (1989).
136. G. Guanti, L. Banfi, A. Guaragna, and E. Narisano, *J. Chem. Soc., Perkin I Trans.*, 2369 (1988).
137. G. Guanti, L. Banfi, and E. Narisano, *J. Chem. Soc., Chem. Commun.*, 136 (1986).
138. M. H. Hopkins, L. E. Overman, and G. M. Rishton, *J. Am. Chem. Soc.* **113**, 5354 (1991).
139. L. E. Overman and G. M. Rishton, *Org. Syn.* **71**, 63 (1992).
140. S. Colin-Messenger, J. Girard, and J. Rossi, *Tetrahedron Lett.* **33**, 2689 (1992).
141. R. G. Ghirardelli, *J. Am. Chem. Soc.* **95**, 4987 (1973).
142. J. M. G. Cowie and H. W. Hunter, *Makromol. Chem.* **191**, 1393 (1990).
143. A. J. Aasen and L. Schjelderup, *Acta Chem. Scand.* **B42**, 206 (1988).
144. U. Schmidt, W. Siegel, and K. Munding, *Tetrahedron Lett.* **29**, 1269 (1988).
145. M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2199 (1968).
146. N. T. Anh, *Top. Curr. Chem.* **88**, 145 (1980).
147. D. J. Cram and D. R. Wilson, *J. Am. Chem. Soc.* **85**, 1245 (1963).
148. S. Desert and P. Metzner, *Tetrahedron* **47**, 10327 (1992).
149. I. Hasan and Y. Kishi, *Tetrahedron Lett.* **21**, 4229 (1980).
150. R. H. Schlessinger and D. D. Graves, *Tetrahedron Lett.* **28**, 4381 (1987).

151. M. DeAmici, C. Dallanocce, C. De Micheli, E. Grana, A. Barbieri, H. Ladinsky, G. Battista Schiavi, and F. Zonta, *J. Med. Chem.* **35**, 1915 (1992).
152. J. S. Panek and R. Beresis, *J. Org. Chem.* **58**, 809 (1993).
153. K. J. Henry, Jr., P. A. Grieco, and C. T. Jagoe, *Tetrahedron Lett.* **33**, 1817 (1992).
154. J. A. Marshall and G. P. Luke, *J. Org. Chem.* **56**, 483 (1991).
155. A. H. McNeill and E. J. Thomas, *Tetrahedron Lett.* **33**, 1369 (1992).
156. J. S. Carey and E. J. Thomas, *Synlett.*, 585 (1992).
157. K. Mikami, K. Kawamoto, T. Loh, and T. Nakai, *J. Chem. Soc., Chem. Commun.*, 1161 (1990).
158. J. A. Marshall and X. Wang, *J. Org. Chem.* **57**, 1242 (1992).
159. P. G. M. Wuts and S. S. Bigelow, *J. Org. Chem.* **48**, 3489 (1983).
160. R. W. Hoffmann, R. Metternich, and J. W. Lanz, *Liebigs Ann. Chem.*, 881 (1987).
161. M. T. Reetz and K. Kessler, *J. Chem. Soc., Chem. Commun.*, 1079 (1984).
162. M. T. Reetz, K. Kessler, and A. Jung, *Tetrahedron Lett.* **25**, 729 (1984).
163. C. H. Heathcock, S. K. Davidsen, K. T. Hug, and L. A. Flippin, *J. Org. Chem.* **51**, 3027 (1986).
164. M. T. Reetz, K. Kessler, S. Schmidtberger, B. Wenderoth, and R. Steinbach, *Angew. Chem., Int. Ed. Engl.* **22**, 989 (1983).
165. J. Uenishi, H. Tomozane, and M. Yamato, *Tetrahedron Lett.* **26**, 3467 (1985).
166. J. Uenishi, H. Tomozane, and M. Yamato, *J. Chem. Soc., Chem. Commun.*, 717 (1985).
167. M. T. Reetz and D. N. A. Fox, *Tetrahedron Lett.* **34**, 1119 (1993).
168. A. Bernardi, S. Cardani, C. Gennari, G. Poli, and C. Scolastico, *Tetrahedron Lett.* **26**, 6509 (1985).
169. C. Gennari, A. Bernardi, G. Poli, and C. Scolastico, *Tetrahedron Lett.* **26**, 2373 (1985).
170. J. Gu, M. Terada, K. Mikami, and T. Nakai, *Tetrahedron Lett.* **33**, 1465 (1992).
171. J. Gu, M. Okamoto, M. Terada, K. Mikami, and T. Nakai, *Chem. Lett.*, 1169 (1992).
172. L. Banfi, S. Cardani, D. Potenza, and C. Scolastico, *Tetrahedron* **43**, 2317 (1987).
173. M. Sato, Y. Sugita, Y. Abiko, and C. Kaneko, *Tetrahedron Asymm.* **3**, 1157 (1992).
174. C. H. Heathcock and S. H. Montgomery, *Tetrahedron Lett.* **26**, 1001 (1985).
175. S. Hanessian and J. Kloss, *Tetrahedron Lett.* **26**, 1261 (1985).
176. Y. Yamamoto and J. Yamada, *J. Am. Chem. Soc.* **109**, 4395 (1987).
177. F. Hammerschmidt, *Liebigs Ann. Chem.*, 469 (1991).
178. R. Annunziata, M. Cinquini, F. Cozzi, L. Raimondi, and T. Pilati, *Tetrahedron Asymm.* **2**, 1329 (1991).
179. B. W. Gung and A. J. Peat, *Syn. Commun.* **21**, 1797 (1991).
180. R. S. Coleman and A. J. Carpenter, *J. Org. Chem.* **58**, 4452 (1993).
181. Y. Kobayashi, Y. Ito, and S. Terashima, *Bull. Chem. Soc. Jap.* **62**, 3041 (1989).
182. Y. Ito and S. Terashima, *Chem. Lett.*, 445 (1987).
183. R. Annunziata, M. Cinquini, F. Cozzi, and P. G. Cozzi, *J. Org. Chem.* **57**, 4155 (1992).
184. T. H. Chan and C. J. Li, *Can. J. Chem.* **70**, 2726 (1992).
185. R. Amouroux, B. Gerin, and M. Chastrette, *Tetrahedron* **41**, 5321 (1985).
186. G. Stork and A. F. Krefit, III, *J. Am. Chem. Soc.* **99**, 3851 (1977).
187. L. Banfi, L. Colombo, C. Gennari, and C. Scolastico, *J. Chem. Soc., Chem. Commun.*, 1112 (1983).
188. S. D. Burke, F. J. Schoenen, and C. W. Murtiashaw, *Tetrahedron Lett.* **27**, 449 (1986).
189. T. Hiyama, K. Nishide, and K. Kobayashi, *Tetrahedron Lett.* **25**, 569 (1984).
190. T. Hiyama, K. Nishide, and K. Kobayashi, *Chem. Lett.*, 361 (1984).
191. S. Kang, D. Lee, and S. Kim, *Org. Prep. Procedure Int.* **22**, 651 (1990).
192. Y. Nishikimi, T. Imori, M. Sodeoka, and M. Shibasaki, *J. Org. Chem.* **54**, 3354 (1989).
193. M. Braun and H. Mahler, *Angew. Chem., Int. Ed. Engl.* **28**, 896 (1989).
194. M. Grauert and U. Schollkopf, *Liebigs Ann. Chem.*, 1817 (1985).
195. U. Mahler, R. M. Devant, and M. Braun, *Chem. Ber.* **121**, 2035 (1988).
196. H. Mahler and M. Braun, *Tetrahedron Lett.* **28**, 5145 (1987).
197. H. Mahler and M. Braun, *Chem. Ber.* **124**, 1379 (1991).
198. M. Braun and J. Moritz, *Chem. Ber.* **122**, 1215 (1989).
199. H. Iida, N. Yamazaki, and C. Kibayashi, *J. Chem. Soc., Chem. Commun.*, 746 (1987).
200. H. H. Wasserman and R. J. Gambale, *Tetrahedron* **48**, 7059 (1992).
201. X. Tong and J. Kallmerten, *Synlett.*, 845 (1992).
202. S. E. Drewes, T. Manickum, and G. H. P. Roos, *Syn. Commun.* **18**, 1065 (1988).
203. C. Palomo, F. P. Cossi, J. M. Ontoria, and J. M. Odriozola, *J. Org. Chem.* **56**, 5948 (1991).
204. M. Hirama, H. Hioki, and S. Ito, *Tetrahedron Lett.* **29**, 3125 (1988).
205. C. Andre-Barres, Y. Langlois, and M. Gomez-Pacios, *Tetrahedron Asymm.* **1**, 571 (1990).
206. M. J. Ford, J. G. Knight, S. V. Ley, and S. Vile, *Synlett.*, 331 (1990).
207. S. V. Ley, A. Armstrong, D. Diez-Martin, M. J. Ford, P. Grice, J. G. Knight, H. C. Kolb, A. Madin, C. A. Marby, S. Mukherjee, A. N. Shaw, A. M. Z. Slawin, S. Vile, A. D. White, D. J. Williams, and M. Woods, *J. Chem. Soc., Perkin I Trans.*, 667 (1991).

208. M. Hirama, I. Nishizaki, T. Shigemoto, and S. Ito, *J. Chem. Soc., Chem. Commun.*, 393 (1986).
209. M. Hirama, T. Shigemoto, and S. Ito, *J. Org. Chem.* **52**, 3342 (1987).
210. G. Solladie, G. B. Stone, and A. Rubio, *Tetrahedron Lett.* **34**, 1803 (1993).
211. M. Terada, J. Gu, D. C. Deka, K. Mikami, and T. Nakai, *Chem. Lett.*, 29 (1992).
212. S. Kobayashi, A. Ohtsubo, and T. Mukaiyama, *Chem. Lett.*, 831 (1991).
213. O. Zschage, J. Schwark, T. Kramer, and D. Hoppe, *Tetrahedron* **48**, 8377 (1992).
214. G. Cainelli, D. Giacomini, E. Mezzina, M. Panunzio, and P. Zarrantonello, *Tetrahedron Lett.* **32**, 2967 (1991).
215. G. Cainelli and M. Panunzio, *J. Am. Chem. Soc.* **110**, 6879 (1988).
216. P. Andreoli, G. Cainelli, M. Panunzio, E. Bandini, G. Martelli, and G. Spunta, *J. Org. Chem.* **56**, 5984 (1991).
217. R. Annunziata, M. Cinquini, F. Cozzi, and P. G. Cozzi, *Tetrahedron Lett.* **33**, 1113 (1992).
218. C. Palomo, F. P. Cossio, J. M. Ontoria, and J. M. Odriozola, *Tetrahedron Lett.* **32**, 3105 (1991).
219. A. D. Brown and E. W. Colvin, *Tetrahedron Lett.* **32**, 5187 (1991).
220. U. Nubbemeyer, R. Ohrlein, J. Gonda, B. Ernst, and D. Bellus, *Angew. Chem., Int. Ed. Engl.* **30**, 1465 (1991).
221. R. Annunziata, M. Cinquini, F. Cozzi, G. Dondio, and L. Raimondi, *Tetrahedron* **43**, 2369 (1987).
222. M. S. Chambers, E. J. Thomas, and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1228 (1987).
223. M. S. Chambers and E. J. Thomas, *J. Chem. Soc., Chem. Commun.*, 23 (1989).
224. R. E. Dolle, C. Li, R. Novelli, L. I. Kruse, and D. Eggleston, *J. Org. Chem.* **57**, 128 (1992).
225. G. Guanti, L. Banfi, and E. Narisano, *Gazz. Chim. Ital.* **117**, 681 (1987).
226. M. Braun and J. Moritz, *Synlett.*, 750 (1991).
227. C. Palomo, J. M. Aizpurua, R. Urchegui, and J. Garcia, *J. Org. Chem.* **58**, 1646 (1993).
228. J. K. Cha and R. J. Cooke, *Tetrahedron Lett.* **28**, 5473 (1987).
229. S. Brandage and B. Lindqvist, *Acta Chem. Scand.* **B39**, 589 (1985).
230. J. Mulzer, L. Kattner, A. R. Strecker, C. Schroder, J. Buschmann, C. Lehmann, and P. Luger, *J. Am. Chem. Soc.* **113**, 4218 (1991).
231. J. Mulzer, N. Salimi, and H. Hartl, *Tetrahedron Asymm.* **4**, 457 (1993).
232. G. Okay, *Syn. Commun.* **19**, 2125 (1989).
233. J. S. Yadav and V. R. Gadgil, *Tetrahedron Lett.* **31**, 6217 (1990).
234. S. Hatakeyama, K. Saijo, and S. Takano, *Tetrahedron Lett.* **26**, 865 (1985).
235. S. Kang and D. Lee, *Synlett.*, 175 (1991).
236. R. C. Ronald and C. J. Wheeler, *J. Org. Chem.* **48**, 138 (1983).
237. K. Mori and H. Kikuchi, *Liebigs Ann. Chem.*, 963 (1989).
238. H. Borsook, H. M. Huffman, and Y. Liu, *J. Biol. Chem.* **102**, 449 (1933).
239. R. L. Augustine, S. K. Tanielyan, and L. K. Doyle, *Tetrahedron Asymm.* **4**, 1803 (1993).
240. H. Simon, J. Bader, H. Gunther, S. Neumann, and J. Thanos, *Angew. Chem., Int. Ed. Engl.* **24**, 539 (1985).
241. H. C. Brown, P. V. Ramachandran, S. A. Weissman, and S. Swaminathan, *J. Org. Chem.* **55**, 6328 (1990).
242. T. Kolasa and M. J. Miller, *J. Org. Chem.* **52**, 4978 (1987).
243. N. Bischofberger, H. Waldmann, T. Saito, E. S. Simon, W. Lees, M. D. Bednarski, and G. M. Whitesides, *J. Org. Chem.* **53**, 3457 (1988).
244. M. Brin, *Biochem. Preparations* **3**, 61 (1953); *Chem. Abstr.* **48**:2167h (1954).
245. H. Kubota, K. Nunami, M. Yamagishi, S. Nishimoto, and K. Hayashi, *Chem. Pharm. Bull.* **39**, 1374 (1991).
246. H. Kubota, K. Nunami, K. Hayashi, Y. Hashimoto, N. Ogiku, Y. Matsuoka, and R. Ishida, *Chem. Pharm. Bull.* **40**, 1619 (1992).
247. S. J. Danishefsky, M. P. DeNinno, and S. Chen, *J. Am. Chem. Soc.* **110**, 3929 (1988).
248. S. D. Burke, K. C. Lee, and D. Santafianos, *Tetrahedron Lett.* **32**, 3957 (1991).
249. R. E. Ireland, S. Thaisrivongs, and P. H. Dussault, *J. Am. Chem. Soc.* **110**, 5768 (1988).
250. D. Hoppe, G. Tarara, and M. Wilckens, *Synthesis*, 83 (1989).
251. W. R. Rousch and P. T. Grover, *Tetrahedron* **48**, 1981 (1992).
252. G. Tarara and D. Hoppe, *Synthesis*, 89 (1989).
253. R. K. Boeckman, Jr., and J. R. Pruitt, *J. Am. Chem. Soc.* **111**, 8286 (1989).
254. P. Andreoli, L. Billi, G. Cainelli, M. Panunzio, E. Bandini, G. Martelli, and G. Spunta, *Tetrahedron* **47**, 9061 (1991).
255. J. Mulzer, T. Schulze, A. Strecker, and W. Denzer, *J. Org. Chem.* **53**, 4098 (1988).
256. T. Sugiyama, T. Murayama, and K. Yamashita, *Tetrahedron Lett.* **31**, 7343 (1990).

2 Mandelic Acid

**1****2**

(*S*)-Mandelic (**1**) and (*R*)-mandelic acid (**2**) are the more familiar names for the chiral antipodes of α -hydroxybenzeneacetic acid, also known as phenylglycolic acid or amygdalic acid. As orthorhombic plates from water, pure mandelic acid melts at 119 °C and has a $K_a = 4.3 \times 10^{-4}$ M. Mandelic acid is moderately soluble in water (1 g to 6.3 mL water) and very soluble in ether and isopropanol. Therapeutically, mandelic acid is most commonly used as a urinary antiseptic [1].

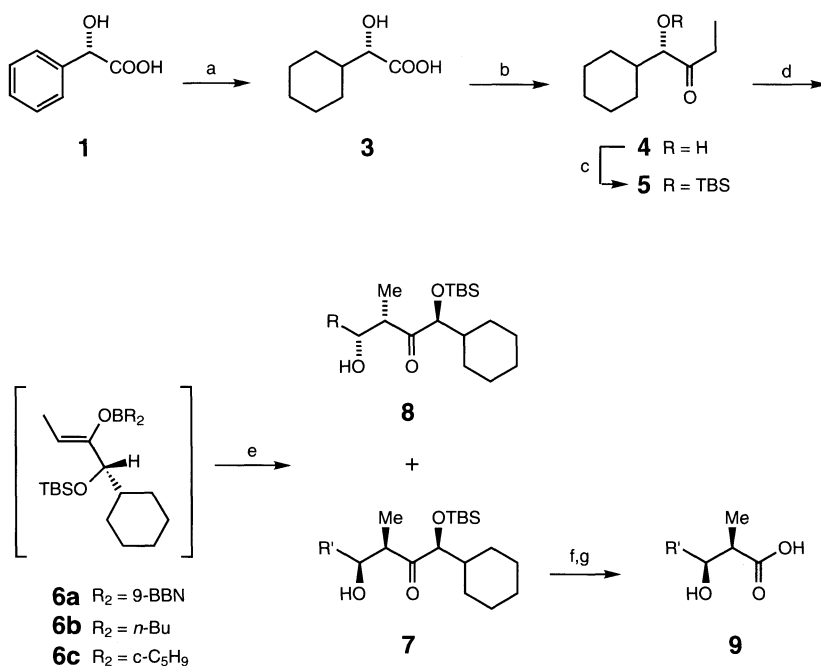
Mandelic acid and its derivatives are utilized as convenient precursors for the introduction of a chiral center, and they possess the extra advantage of bearing a useful functional group. Many mandelic acid derivatives also act as chiral auxiliaries for the induction of a chiral center in stereoselective transformations. Numerous natural products, such as macrolides and ionophore antibiotics, possess a carbon framework that may be viewed synthetically as arising from a sequence of highly stereo- and enantioselective aldol condensations. Boron enolates, chiral auxiliaries derived from mandelic acids **1** or **2**, provide remarkably high aldol stereoselectivity.

Catalytic hydrogenation of **1** in the presence of rhodium on aluminum oxide proceeds smoothly to afford (*S*)-hexahydromandelic acid (**3**) [2]. Subsequent treatment of **3** with ethyllithium provides in 75% yield the ketone **4**, which is O-silylated to afford **5**. Generated *in situ* with the appropriate dialkylboron triflate and **5**, the boron enolates **6a–c** react with a variety of aldehydes to provide exclusively a mixture of *syn*-aldol products **7** and **8** in 70–80% yields, often with excellent stereoselectivities.

This result suggests an exclusive *Z*(O)-enolate geometry for these boron enolates. Moreover, the ratio of **7** to **8** becomes impressively high with increasing size of the boron ligands. Desilylation and sodium metaperiodate oxidation of **7** yields the *syn* β -hydroxy- α -methylcarboxylic acids **9**, which are fundamental structural units found in numerous natural products of propionate origin. It is recommended by the authors that **6a** be used for aldehydes with an α -substituent and that **6c** be used for aldehydes carrying no α -substituent (Scheme 1) [3].

6-Deoxyerythronolide B (**18**; Scheme 2), a monocyclic 14-membered lactone containing 10 asymmetric centers, is produced by blocked mutants of *Streptomyces erthreus*, and is a common biosynthetic precursor leading to all the erythromycins. A convergent total synthesis of **18** requires the appropriate chiral left- and right-hand fragments, which provides an excellent opportunity for these chiral boron enolates to demonstrate their versatility.

Preparation of the left-hand fragment, which incorporates the C-11 to C-13 portion of **18**, utilizes the aldol reaction of *R*-boron enolate **10** with propionaldehyde to provide the α -hydroxy acid **11** in 85% yield and 100:1 stereoselectivity. Subsequent diazomethane esterification, O-silylations, DIBAL reduction, and Collins oxidation affords the optically pure aldehyde **12** in an overall yield of 75%.

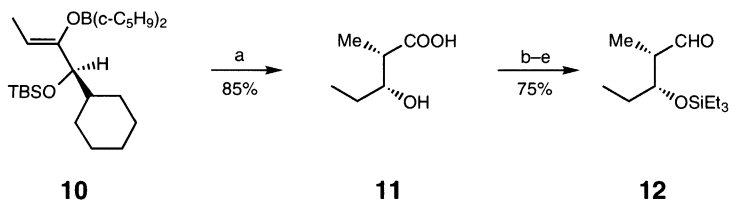


Aldehyde	Boron enolate	ratio7:8
C ₆ H ₅ CHO	6a	14:1
	6b	40:1
	6c	75:1
CH ₃ CH ₂ CHO	6a	17:1
	6b	50:1
	6c	>100:1
<i>i</i> -PrCHO	6a	>100:1
	6b	>100:1
	6c	no reaction

Scheme 1

conditions: (a) Rh/Al₂O₃; (b) 3.5 equiv. EtLi, ether, -78 to 0 °C (75%); (c) TBSCl, DMAP, DCM; (d) R₂BOTf, *i*-Pr₂NEt, DCM, -78 °C; (e) R'CHO, DCM, 0 °C; (f) conc. HF-MeCN (1:20 v/v), rt, 3.5 h; (g) NaIO₄, MeOH, H₂O

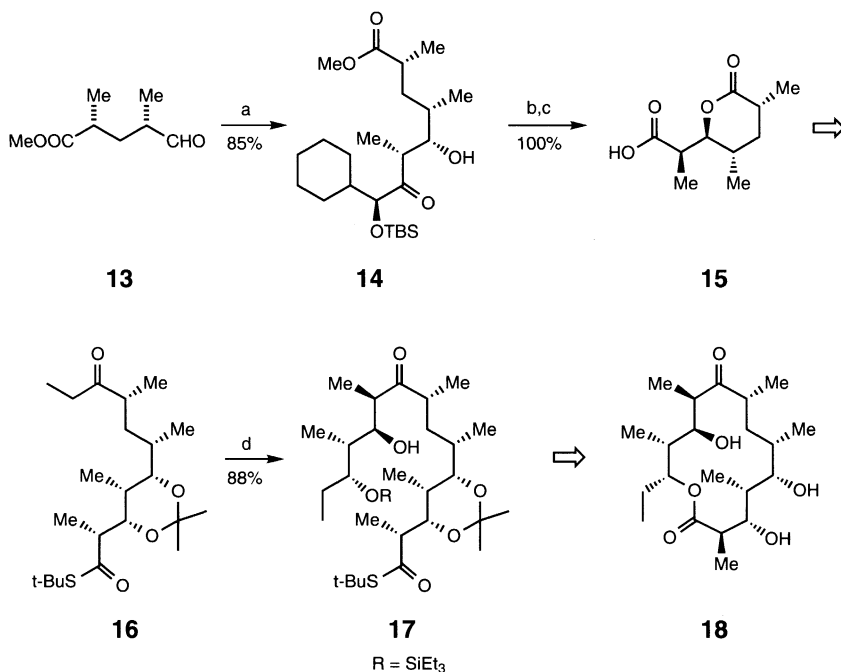
The construction of the right-hand fragment **16** utilizes the aldol reaction of **6a** with (–)-aldehyde **13** to afford in 85% yield and 40 : 1 stereoselectivity the aldol product **14**. This is quantitatively converted in multigram quantities to the optically pure Prelog–Djerassi lactic acid (**15**). A second boron-enolate aldol reaction is conducted with **6a** and **15**, and, following appropriate functional group transformations, **16** is obtained. Coupling of **12** and **16** with lithium bis(trimethylsilyl)amide at -78 °C affords in 88% yield the desired *seco*-acid **17**, in which the observed stereoselectivity is 17 : 1. It is presumed that this selectivity is due



conditions: (a) $\text{CH}_3\text{CH}_2\text{CHO}$, -78°C , DCM; (b) CH_2N_2 ; (c) Et_3SiCl , DMAP, DCM;
(d) DIBAL, hexane-ether; (e) CrO_3 -pyridine, DCM

to the expected coordination of lithium cation with the ethereal oxygen attached to the β -carbon of aldehyde **12**, in accordance with the Cram cyclic model. Low selectivity (1.8–1.5 : 1) is observed utilizing a boron-enolate mediated aldol condensation. Finally, a sequence of transformations converts **17** to **18** (Scheme 2) [4].

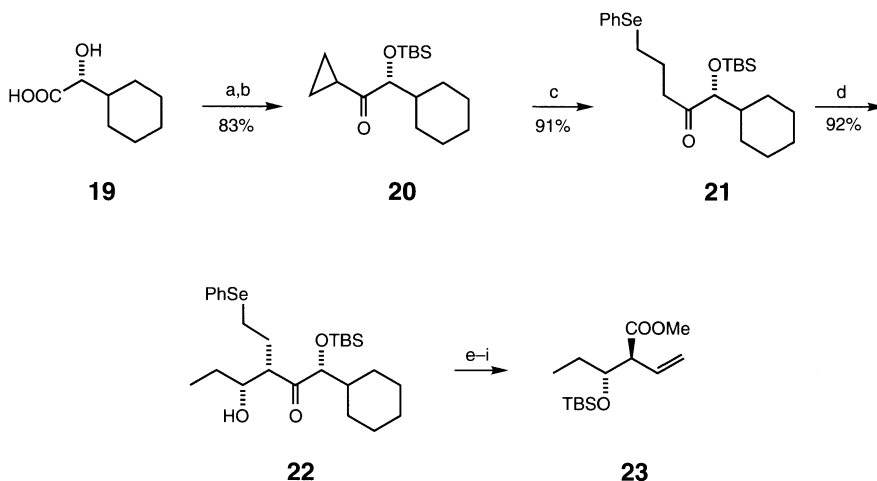
The aldol methodology described is useful for the preparation of diastereomerically pure *syn* aldol products. Preparation of the corresponding *anti*-3-hydroxy-2-methylcarbonyl aldol products can be achieved utilizing a *syn*-intermediate that possesses two different functional groups, an olefin and an ester, both of which can be appropriately modified to achieve the



Scheme 2

conditions: (a) **6a**, hexane, 0°C , 1.5 h; (b) conc. HF–MeCN (1:20 v/v), rt, 3.5 h;
(c) NaIO_4 , MeOH– H_2O ; (d) LiHMDS, -78°C , **12**

desired *anti*-stereochemistry. Thus, treatment of *R*-hexahydromandelic acid (**19**) with 3.5 equivalents of cyclopropyllithium in ether, followed by silyl protection, affords **20** in 83% overall yield. The cyclopropane ring is opened with lithium benzeneselenoate in the presence of 12-crown-4 at 70 °C in benzene to provide **21** in 91% yield. The dicyclopentylboron enolate of **21**, prepared *in situ*, is subsequently reacted with propanal to give the expected 2,3-*syn* aldol product **22** in 97% yield with 100:1 diastereoselectivity. This is converted in five steps to the key intermediate **23** (Scheme 3). Notice that **23** possesses *syn* stereochemistry with respect to the 3-hydroxyl and olefin groups, but *anti* stereochemistry relative to the 3-hydroxyl and ester groups [5].

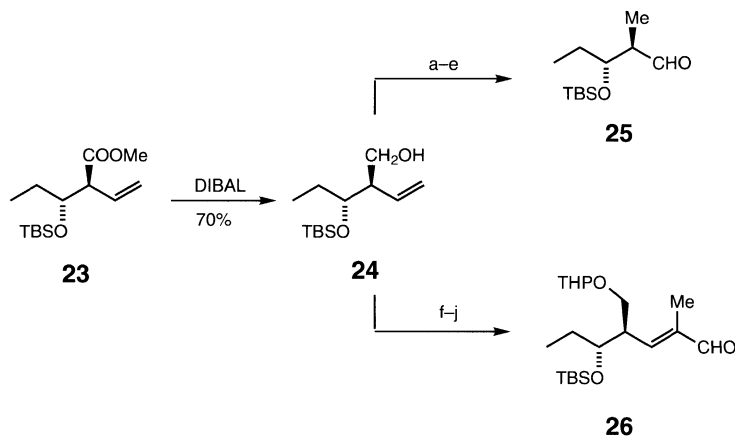


Scheme 3

conditions: (a) $c\text{-C}_3\text{H}_7\text{Li}$, Et_2O , -78° to 0°C , 2h; (b) TBSCl , imidazole, DMAP, THF, 70°C , 12 h; (c) PhSeCl , 12-crown-4, C_6H_6 , reflux, 18 h; (d) $(c\text{-C}_5\text{H}_9)_2\text{BOTf}$, $i\text{-Pr}_2\text{NEt}$, DCM, -78°C then EtCHO , 0°C ; (e) $\text{HF}\text{-MeCN}$ (1:20 v/v); (f) O_3 , DCM, -78°C then pyridine, 50°C (86% 2 steps); (g) NaIO_4 , $\text{MeOH}\text{-H}_2\text{O}$; (h) CH_2N_2 , Et_2O ; (i) TBSOTf , 2,6-lutidine, DCM

Reduction of the ester function in **23** with DIBAL leads to the primary alcohol **24**, which is tosylated, converted to the iodide, reduced to a methyl group, and oxidized with PCC to *R*-aldehyde **25**. Alternatively the hydroxyl group in **24** can be protected as a THP ether, the olefin ozonolyzed to an aldehyde that undergoes a Wittig olefination followed by a DIBAL reduction, and finally a Collins oxidation to provide α,β -unsaturated aldehyde **26** containing the critical *anti*-stereochemistry (Scheme 4) [5].

Tylonolide hemiacetal (**33**), the aglycone of the antibiotic tylosin, possesses an *anti* 14-hydroxymethyl-15-acyloxy stereochemistry conveniently contained in **26**, which may be viewed as the “western” half of **33**. In order to prepare the “eastern” half of **33**, an aldol reaction leading to the desired *syn* stereochemistry at C-3 and C-4 is exploited. The reaction of achiral aldehyde **27** with the *S*-boron enolate **28** proceeds with the expected diastereofacial selectivity to provide, in a combined yield of 80% after O-silylation, a separable mixture of **29** (derived from the *R*-enantiomer of **27**) and **30** (from the *S*-enantiomer of **27**). Subsequent functional group transformation of **30** ultimately leads to the α -(TMS)methylketone **31**. The anion of **31**, generated with lithium hexamethylsilazide in THF at -78°C , undergoes a Peterson condensation with **26** to afford in 60% yield the *seco*-acid **32**. Treatment of **32** with 70% acetic acid at 85°C for one hour affords **33** in 60% yield. The attractive feature of this



Scheme 4

conditions: (a) TsCl, pyridine, 0 °C, 4 h; (b) NaI, acetone, reflux 8 h; (c) NaBH₃CN, HMPA, 70 °C, 8 h; (d) O₃, MeOH, -78 °C then NaBH₄; (e) PCC, DCM, rt, 1 h; (f) DHP, PPTS, DCM, rt, 4 h; (g) O₃, MeOH/DCM, -78 °C then DMS to rt; (h) Ph₃P=CMeCOOEt, 100 °C, 12 h; (i) DIBAL, toluene, 0 °C, 30 min; (j) C₅H₅NHCrO₃Cl(DCM), rt, 1 h

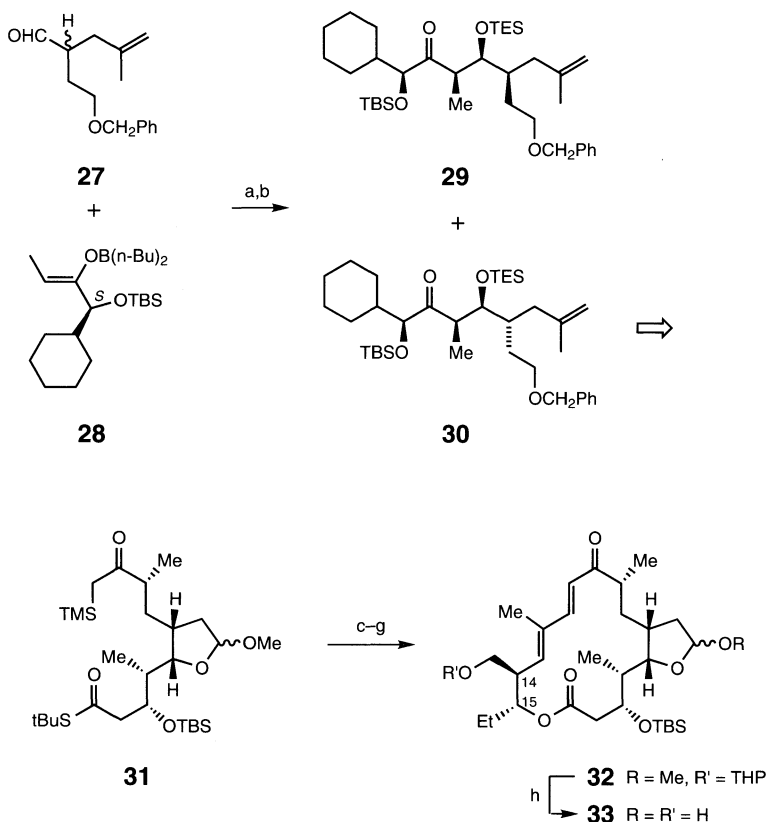
synthesis is its application of boron-enolate aldol methodology to the synthesis of the chiral fragments with extremely high *syn* or *anti* diastereoselectivity (Scheme 5) [6].

It is clear that the presence of the benzeneselenoethyl moiety in **21** or **22** is not required as a latent double bond in subsequent transformations. It would thus be synthetically more attractive to be able to prepare the unsaturated ketones directly. Reaction of *S*-hexahydromandelic acid (**3**) with either (*E*)- or (*Z*)-propenyllithium followed by hydroxy silylation opens the way to both **34** and **35**. Boron enolates of either **34** or **35**, prepared *in situ*, undergo reaction with aldehydes to afford aldol products, albeit with low selectivity when R=TBS. Interestingly, the *E*-isomer **34** provides mainly the 2,3-*anti* products **36** (1 : 3.5 *syn* : *anti*), while the *Z*-isomer **35** affords mainly the *syn* products **37** (3 : 1 to 10 : 1 *syn* : *anti*). However, the corresponding O-triethylsilyl-protected boron enolates of **34** or **35** undergo smooth aldol reaction with aldehydes to yield the 2,3-*syn* products **37** with high diastereoselectivity (> 100:1) (Scheme 6) [7].

These boron enolates can be considered as chiral nucleophiles wherein chirality observed in the products of the aldol reactions arises from the chiral auxiliary mandelic acid. An alternative approach to the diastereo- and enantioselective carbon-carbon bond forming reaction is to react an achiral anion precursor with an electrophilic equivalent containing a chiral auxiliary derived from mandelic acid.

The condensation [8] of either (*S*)-**1** or (*R*)-**2** with aromatic aldehydes or acetophenone provides, after recrystallization, *cis*-1,3-dioxolan-4-ones (*2S,5S*)-**38** or (*2R,5R*)-**39** with 99% optical purity (Scheme 7). Alkyl adducts usually require chromatographic separation of the *cis*, *trans* isomers, and in some cases the mixture may be difficult or impossible to separate.

In the presence of boron trifluoride etherate, **39** (R=H and Ar=C₆H₅) reacts smoothly with silyl enol ethers (the achiral anion source) at low temperatures (-80 to -30 °C) to provide a chromatographically separable mixture of diastereomeric acids from which either **40** or **41** can be obtained in good yield. Oxidative decarboxylation of the chiral auxiliary with freshly crystallized lead tetraacetate occurs without racemization of the newly formed chiral center to provide either **42** or **43** with 98% *ee*. Noteworthy is the fact that if pure *cis* isomers are used, such as **39**, they undergo facile isomerization to a 65 : 35 *cis* : *trans* mixture at the low reaction



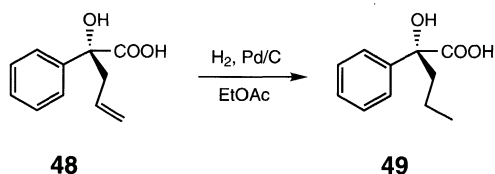
Scheme 5

conditions: (a) DCM, rt, 17 h; (b) Et_3SiOTf , 2,6-lutidine, DCM; (c) *n*-BuLi, $(\text{Me}_3\text{Si})_2\text{NH}$, -78°C , THF, then **26**; (d) TFAA-Hg, Na_2HPO_4 , DCM; (e) HF-pyridine, THF, rt, 40 h (83% 4 steps); (f) $(\text{PhO})_2\text{POCl}$, Et_3N , THF; (g) DMAP, C_6H_6 , 80°C 18 h (32% 2 steps); (h) 70% AcOH (100%)

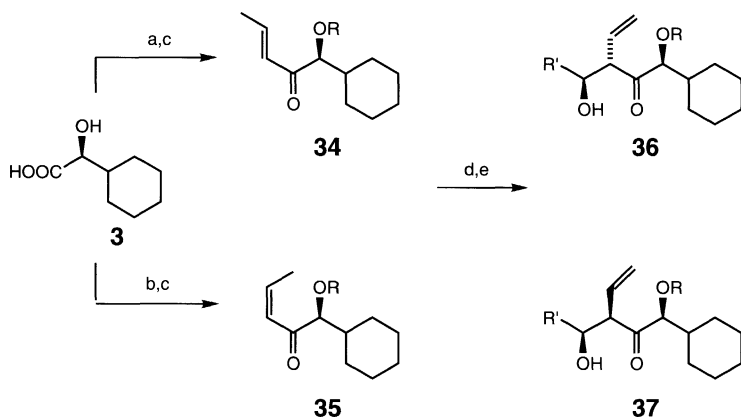
temperatures, and the product obtained appears to be independent of the starting geometry of the dioxolones. These stereochemical results are consistent with nucleophilic attack from the less hindered oxonium ion, predominantly *trans* to the phenyl substituents (Scheme 8) [9].

The reaction of (*S*)-**1** with isobutyraldehyde in benzene provides a 92 : 8 mixture of *cis*-**44** and *trans*-**45**, whereas the same reaction with pivaldehyde affords only *cis*-**46** in 74% yield. The reaction of (*S*)-**1** with pivaldehyde dimethyl acetal in the presence of pyridinium *p*-toluenesulfonate in a refluxing mixture of cyclohexane-ethyl acetate provides a 97 : 3 *cis* : *trans* mixture of **46**, but in only 25% yield [10]. Treatment of **46** with LDA at -70°C followed by alkylation with methyl iodide proceeds in 94% yield to provide a 93 : 7 mixture of *cis*, *trans* isomers. Potassium hydroxide hydrolysis affords (*S*)-(+)-atrolactic acid (**47**) possessing 85% *ee* (Scheme 9).

Interestingly, (*S*)-(+)- α -allylmandelic acid (**48**), prepared similarly, can be recrystallized and then hydrogenated to optically pure (*S*)-(+)- α -propylmandelic acid (**49**), a compound produced in only 76% *ee* by the direct alkylation procedure [11].

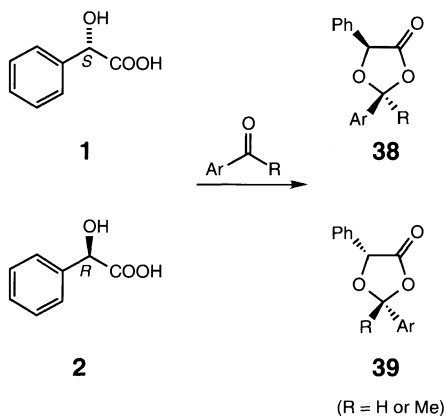


A milder preparation of these 1,3-dioxolanones is illustrated in Scheme 10, this time utilizing **2**. Rhodium triflate, $[\text{Rh}(\text{CH}_3\text{CN})_3(\text{triphos})]^{3+}(\text{CF}_3\text{SO}_3^{1-})_3$, catalyzed acetalization of pivaldehyde with **2** followed by a single crystallization from ether/pentane furnishes pure *cis* **50** in high yield (80–90%). Diastereoselective alkylation of the lithium enolate of **50** with

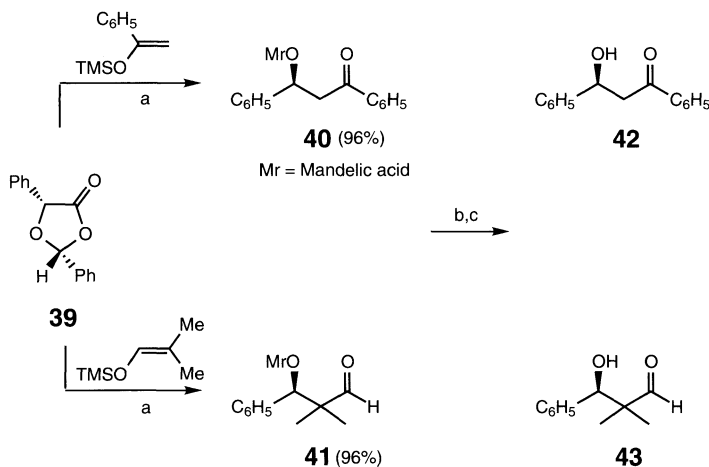


Scheme 6

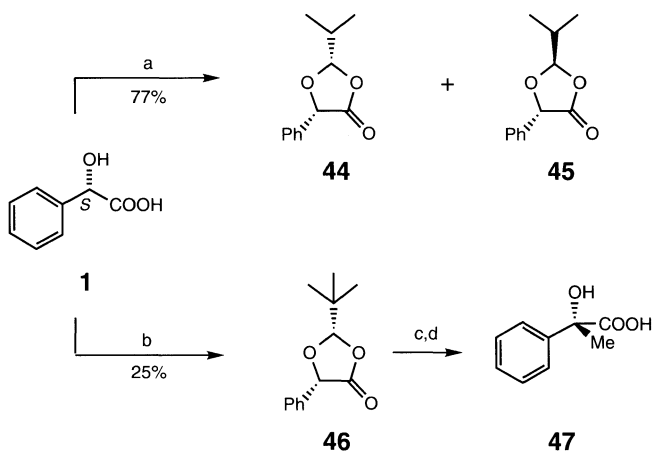
conditions: (a) 3.5 equiv. (*E*)-MeCH=CHLi, Et₂O, –78 °C to rt; (b) 1.9 equiv. *n*-BuLi, 1.6 equiv. (*Z*)-MeCH=CHLi, Et₂O, –78 °C to rt; (c) either TBSOTf, 2,6-di-*t*-butyl-4-methylpyridine, DCM, 0 °C or Et₃SiCl, *i*-Pr₂NEt, DMF rt; (d) *i*-Pr₂NEt, (c-C₅H₉)₂BOTf, –78 °C; (e) R'CHO, DCM, 0 °C to rt



Scheme 7

**Scheme 8**

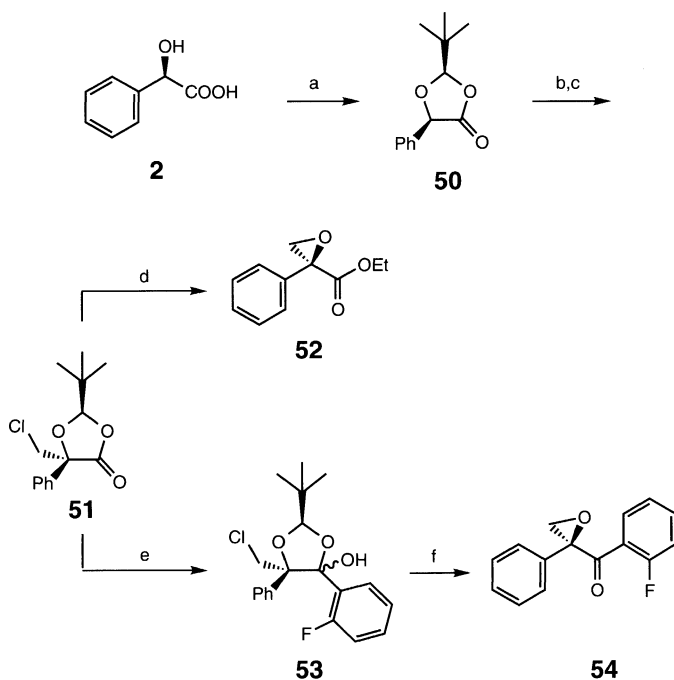
conditions: (a) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, DCM, -80°C ; (b) $\text{Pd}(\text{OAc})_4$, $\text{EtOAc-Et}_2\text{O}$ (1:4); (c) HCl, THF

**Scheme 9**

conditions: (a) isobutyraldehyde, TsOH, C_6H_6 , 80°C ; (b) pivaldehyde, TsOH, C_6H_6 , 80°C ; (c) LDA, THF-HMPA, -78°C , MeI (94%); (d) KOH, $\text{MeOH-H}_2\text{O}$

chloriodomethane affords **51** in 70% yield with 90% *ds*. Treatment of **51** with 2-fluorophenyllithium at -70°C followed by acetic acid quench provides a mixture of hemiacetals **53** which, after treatment with sodium ethoxide and crystallization of the crude product, leads in 60% yield to the α,β -epoxyketone **54** possessing 99% *ee*. Interestingly, treatment of **51** with sodium ethoxide furnishes ethyl α -phenylglycidate **52** in 85% yield with 94% *ee* [12].

As a result of their potent pharmacological activity, 4-aryl-1,2,3,4-tetrahydroisoquinolines have attracted numerous synthetic efforts. Treatment of (*S*)-**1** with acetone under acid catalysis generates (*S*)-(+)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-one (**55**) in 80% yield. Reaction of **55** with methylamine followed by lithium aluminum hydride reduction of the resultant amide provides (*S*)-(+)-*N*-methylamino-1-phenylethanol [(*S*)-(+)-halostachine] (**56**). *N*-



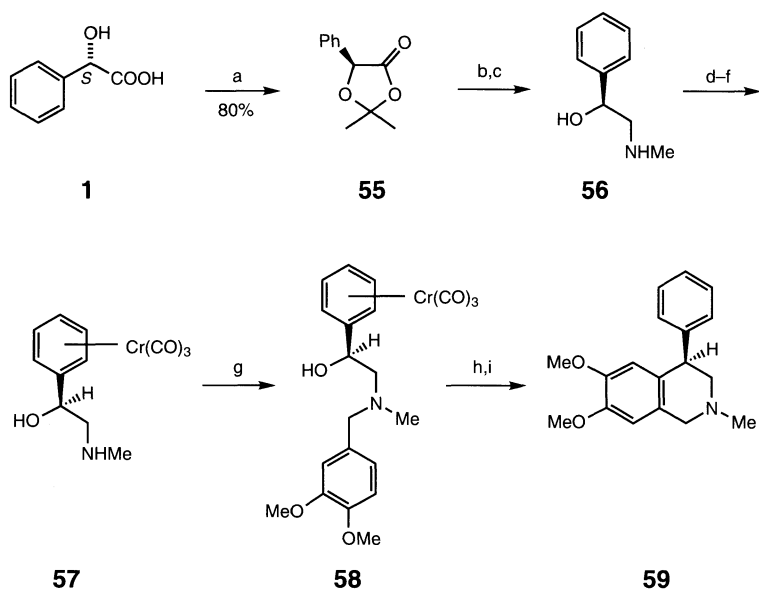
Scheme 10

conditions: (a) $[\text{Rh}(\text{MeCN})_3(\text{triphos})]^{+3} \cdot 3(\text{Tf})^{-1}$, pivaldehyde, isopropyl orthoformate, C_6H_6 , 25°C (80-90%); (b) LDA, THF, -70°C ; (c) ClCH_2I , -70°C to rt (70%); (d) NaOEt, EtOH, 0°C (85%); (e) 1-bromo-2-fluorobenzene, *n*-BuLi, THF, -70°C then AcOH at -70°C ; (f) NaOEt, EtOH then crystallize from *i*- $\text{C}_3\text{H}_7\text{OH}$ (60%)

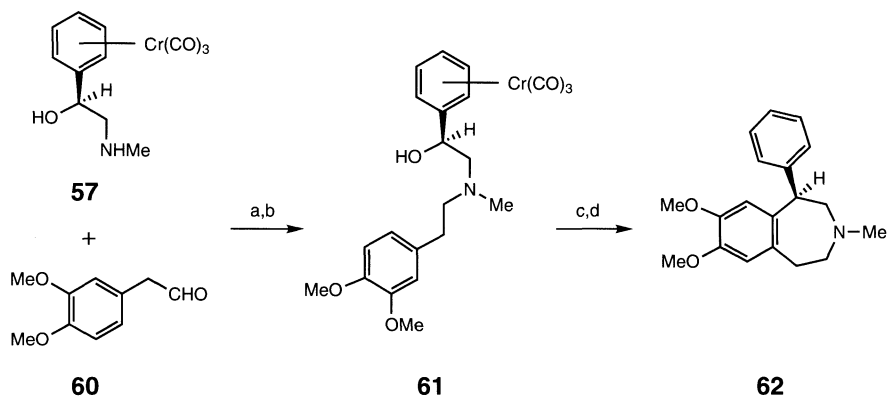
Boc protection of the amine, complexation with hexacarbonylchromium, and then amine deprotection with neat formic acid provides (*R*)-(+)-halostachine(tricarbonyl)chromium(0) (**57**). Treatment of **57** with 3,4-dimethoxybenzyl bromide in dichloromethane affords in 36% yield (*R*)-(+)-tricarbonyl $\{\eta^6$ -2-[3,4-dimethoxybenzyl(methyl)amino]-1-phenylethanol}-chromium(0) (**58**), which undergoes a highly selective acid-promoted cyclization that proceeds with retention of configuration to yield, after decomplexation, optically pure (*R*)-(+)-6,7-dimethoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**59**) in moderate yield (Scheme 11) [13].

Condensation of **57** with homoveratraldehyde (**60**) in the presence of molecular sieves, followed by sodium borohydride reduction, affords the chromium tricarbonyl complex **61** in moderate overall yield. The acid-promoted cyclization of **61** proceeds with retention of configuration to afford, after air decomplexation, optically pure (*R*)-(+)-1-phenyl-3-methyl-1,2,4,5-tetrahydrobenz[*d*]azepine (**62**) (Scheme 12) [14]. The 1,2,4,5-tetrahydro-3*H*-benz[*d*]azepine skeleton is found in nature, and alkaloids possessing this skeleton are referred to as "benzazepine alkaloids". Moreover, the dopaminergic activity possessed by this class of compounds resides mostly in the (*R*)-enantiomer [15,16].

The anions of such cesium salts as cesium thioacetate or cesium benzoate often undergo extremely clean $\text{S}_{\text{N}}2$ substitution reactions. Optically active thiols, especially those sensitive to racemization, can be prepared using cesium thiocarboxylates as nucleophiles. The reaction of ethyl (*R*)-*O*-mesylmandelate (**64**), readily prepared from the commercially available

**Scheme 11**

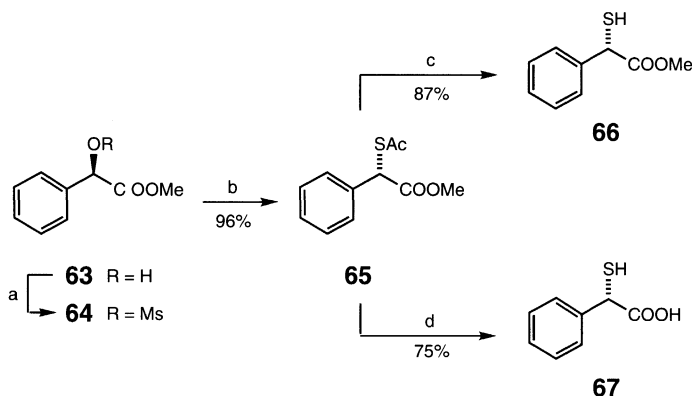
conditions: (a) acetone, H_2SO_4 ; (b) MeNH_2 , EtOH (97%); (c) LiAlH_4 , THF (92%); (d) Boc_2O , Et_3N , DCM (89%); (e) $\text{Cr}(\text{CO})_6$, Bu_2O , THF (63%); (f) HCOOH , 20 °C, 5 h (95%); (g) $3,4\text{-(MeO)}_2\text{C}_6\text{H}_3\text{CH}_2\text{Br}$, DCM (36%); (h) $\text{HBF}_4\cdot\text{OMe}_2$, DCM (67%); (i) air (98%)

**Scheme 12**

conditions: (a) TsOH , DCM (86%); (b) NaBH_4 , MeOH (62%); (c) $\text{HBF}_4\cdot\text{OMe}_2$, DCM (76%); (d) air, sunlight, Et_2O (99%)

mandelic ester **63**, with cesium thioacetate (prepared *in situ* from cesium carbonate due to the hygroscopic nature of the salt) in absolute ethanol provides a 96% yield of completely inverted ethyl (*S*)-2-acetylthio-2-phenylacetate (**65**) with 98% *ee*. The same reaction carried out in DMF leads to completely racemized product. Subsequent hydrolysis of **65** with 3%

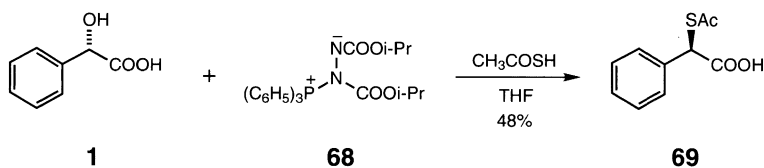
HCl–methanol produces the transesterified methyl (*S*)-2-mercapto-2-phenylacetate (**66**) in 87% isolated yield with 93% *ee*. Acid hydrolysis of **65** with concentrated hydrochloric acid at ambient temperature under stirring for four days gives (*S*)-2-mercapto-2-phenylacetic acid [(*S*)-thiomandelic acid] (**67**) in 75% yield and 85% *ee* (Scheme 13) [17].



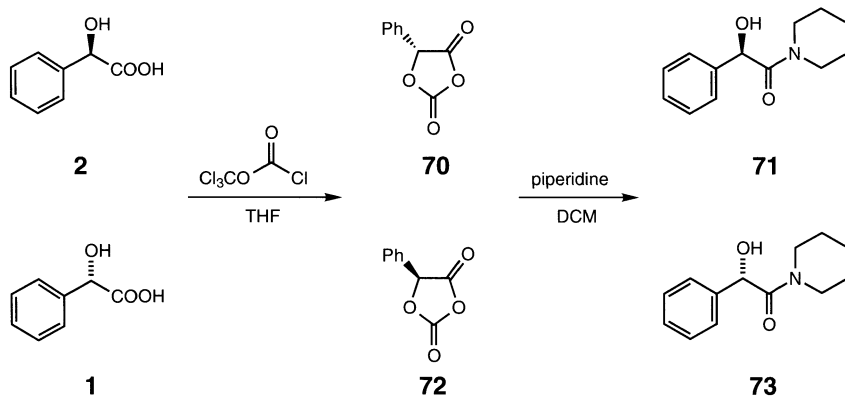
Scheme 13

conditions: (a) MsCl, Et₃N; (b) Cs₂CO₃, CH₃COSH, EtOH; (c) 3% HCl, MeOH; (d) HCl (conc.), rt, 4 d

A modified Mitsunobu procedure in which **63** is first treated with the preformed complex **68** (prepared by reaction of triphenylphosphine and diisopropyl azodicarboxylate) and then cesium thioacetate leads to significant racemization [17]. However, if the free acid is reacted instead with an appropriate thioacid (rather than the ester and a cesium salt), optical yields improve significantly. Thus, thioacetylation of (*S*)-**1** can be accomplished by treating it with **68** followed by the addition of thioacetic acid in THF to provide in 48% yield (*S*)-2-(acetylthio)-2-phenylacetic acid (**69**) with 84% *ee* after recrystallization. The low yield is due in part to the unavoidable formation to the extent of at least 50% of a viscous, polymeric material. The reaction is complete in minutes, however, and proceeds with retention of configuration. Presumably this is a result of a double inversion mechanism that passes through an α -lactone. Interestingly, the corresponding reaction with lactic acid does occur with inversion [18].



(*R*)-5-Phenyl-1,3-dioxolan-2,4-dione [D-mandelic acid *O*-carboxyanhydride] (**70**) is an important mandelylation agent for the preparation of cephalosporin antibiotics that display enhanced activity [19–22]. A novel and facile synthesis of **70** involves the reaction of (*R*)-**2** with trichloromethyl chloroformate in THF, which produces a 72% yield of optically active **70**. Utilization of (*S*)-**1** affords in 75% yield (*S*)-5-phenyl-1,3-dioxolan-2,4-dione (**72**). Stir-

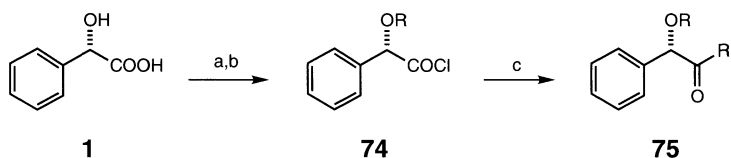


Scheme 14

ring either **70** or **72** with piperidine in dichloromethane at 0 °C for 10 min results in an 84% yield of optically pure amide **71** or a 72% yield of optically pure **73** (Scheme 14) [23].

Chiral α -hydroxyketones and their derivatives are valuable key intermediates used mainly as chiral synthons or stereodirecting groups for the enantioselective synthesis of naturally occurring products or biologically active compounds. While acylation of an organometallic reagent with an α -hydroxyacid derivative appears to be a simple and direct route, this approach usually affords poor yields of the desired products. The reaction of a soft organozinc reagent with α -acetoxypropionyl chloride fails to provide any α -hydroxyketone whatsoever [24].

Organomanganese compounds are highly chemoselective reagents that react selectively with a carboxylic acid chloride bearing either an ester or keto functionality in the terminal position [25,26]. (*S*)-**1** is easily converted in good yield to the α -acetoxy-carboxylic acid chloride **74**. Subsequent acylation of an organomanganese reagent takes place under mild conditions to provide in high yield the expected ketone **75**. In fact, the optical purity of the final product depends only on the optical purity of **74**, since no isomerization is observed in the organomanganese reaction (Scheme 15) [27].

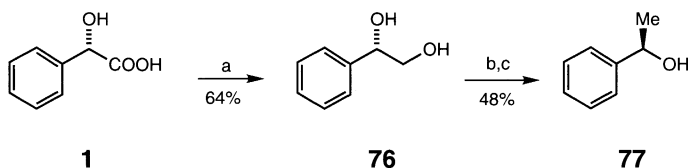


R	R'	Yield (%)	% ee
Me	<i>n</i> -C ₆ H ₁₃	85	94
<i>t</i> -Bu	<i>n</i> -C ₈ H ₁₇	71	91
Ph	<i>n</i> -C ₈ H ₁₇	80	98.8

Scheme 15

conditions: (a) RCOCl, 2 equiv. AcCl, 20 °C, 2 h ; (b) (COCl)₂, DMF, DCM, 20 °C, 2 h ; (c) R'MnCl, THF, -10 °C, 3 h

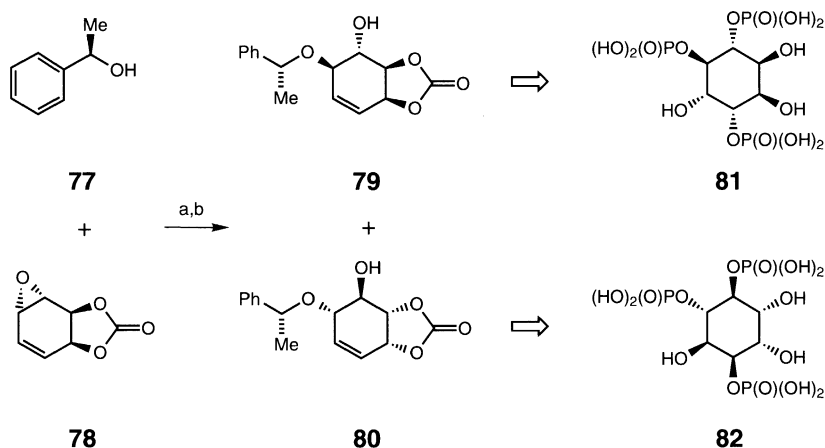
Mandelic acid derivatives are useful resolving agents. While (*R*)-(+)-phenethyl alcohol (**77**) is commercially available, it is relatively expensive. As shown in Scheme 16, (*S*)-**1** can be converted readily into multigram quantities of **77**. Reduction of **1** with borane–dimethyl sulfide provides the diol **76**, which is selectively tosylated at the primary hydroxy position and then detosylated with lithium aluminum hydride to provide **77** in 48% overall isolated yield (Scheme 16). The low yield is a result of the problematic tosylation step, in which ditosylation is unavoidable.



Scheme 16

conditions: (a) BH₃·DMS, THF; (b) TsCl, pyridine, 0 °C; (c) LiAlH₄, Et₂O/THF, 22 h

The reaction of **77** with racemic epoxide **78** in the presence of a catalytic amount of HBF₄·OEt₂ in dichloromethane produces a 1:1 mixture of diastereomeric alcohols (67% yield) that upon separation affords **79** and **80**. Further modification of **79** provides D-(–)-*myo*-inositol 1,4,5-trisphosphate (**81**) (D-(–)-IP3), while **80** affords L-(+)-*myo*-inositol 1,4,5-trisphosphate (**82**) (L-(+)-IP3) (Scheme 17) [28].

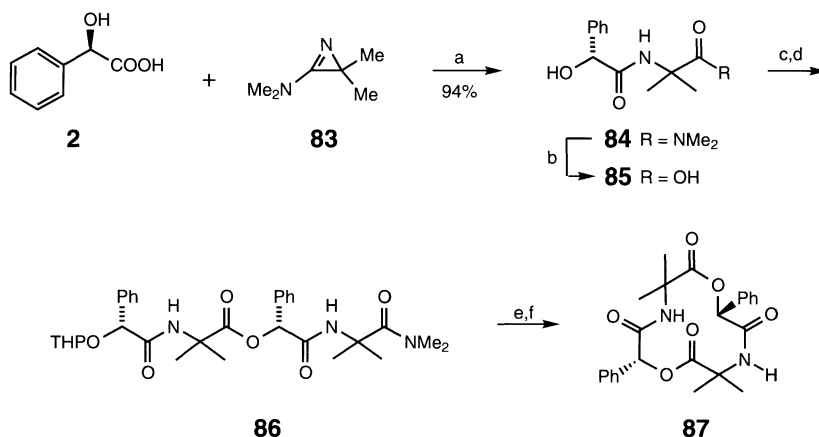


Scheme 17

conditions: (a) HBF₄·Et₂O, DCM (67%); (b) HPLC with a 1" Dynamax 83, 123-6 column, 6% isopropano–petrol, 15 mL/min

The reaction of **2** with 3-(dimethylamino)-2,2-dimethyl-2*H*-azirine (**83**) affords in 94% yield the diamide (*R*)-(–)-2-(2-hydroxy-2-phenylacetamido)-*N,N*-2-trimethylpropionamide (**84**). Selective acidic hydrolysis of **84** with gaseous hydrogen chloride in acetonitrile–water provides the acid **85**. The hydroxyl group is protected as a THP ether and the compound is converted to the depsipeptide **86** in good yield. Cyclization of **86** occurs with gaseous hydrogen chloride in toluene at 100 °C to furnish in 88% yield cyclo[*R*]-Mns-Aib-(*R*)-

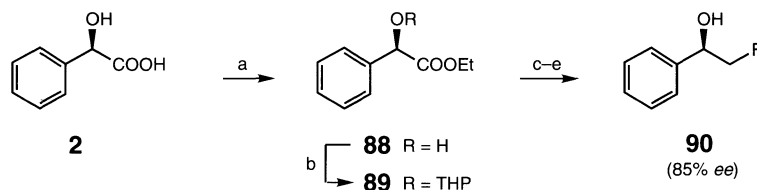
Mns-Aib] or (*R,R*)-(-)-3,3,9,9-tetramethyl-6,12-diphenyl-1,7-dioxo-4,10-diazacyclododecan-2,5,8,11-tetrone (**87**) (Scheme 18) [29].



Scheme 18

conditions: (a) MeCN, rt; (b) HCl(g), MeCN:H₂O (4:1), 60–70° C (96%);
 (c) DHP, MeCN, HCl (85%); (d) CDI, **84**, THF, Na-imidazole (83%);
 (e) 2 N HCl, MeCN (51%); (f) HCl(g), toluene, 100 °C (88%)

While both the ethyl and methyl esters of *R* and *S* mandelic acids are commercially available, these can also be easily prepared in high yield. Fischer esterification of **2** affords in 91% yield the ethyl ester **88**, which is then protected as the THP ether **89**. Lithium aluminum hydride reduction, conversion to the tosylate, and nucleophilic substitution with cesium fluoride affords **90** characterized by 85% *ee* (Scheme 19) [30].

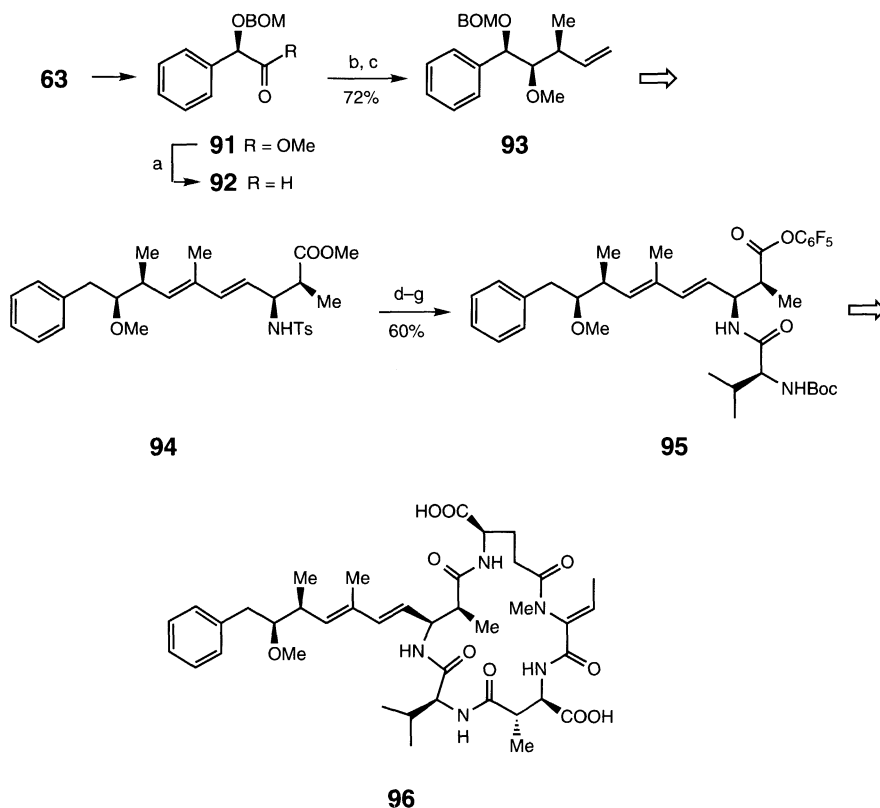


Scheme 19

conditions: (a) EtOH, TsOH, C₆H₆ (91%); (b) DHP, TsOH, DCM (74%);
 (c) LiAlH₄, Et₂O (65%); (d) TsCl, Et₃N, DCM (91%);
 (e) CsF, triethylene glycol, 110 °C (24%)

Motuporin (**96**), isolated from crude extracts of the marine sponge *Theonella swinhoei* Gray, is a cyclic pentapeptide that is an extremely potent protein phosphatase-1 inhibitor. The convergent total synthesis of **96** shown in Scheme 20 utilizes the (*R*)-stereocenter in **91** to introduce the chirality required in the diene fragment of **96**. Methyl (*R*)-*O*-benzyloxymethylmandelate (**91**), prepared by treating **63** with benzyloxymethyl chloride, is converted to the corresponding aldehyde **92** with DIBAL. The aldehyde then undergoes a Lewis acid-promoted crotylstannane addition to afford an 8 : 1 *syn* : *anti* diastereomeric mixture of pro-

ducts resulting from a chelation-controlled transition state. O-alkylation with methyl iodide and isolation of the major diastereomer provides **93** in an overall yield of 72%. Having served its purpose of creating two new chiral centers, the *R*-hydroxy group originally present in **91** is reductively cleaved to leave a harmless benzylic position. Through a series of further conversions, including a modified Julia olefination, **93** is transformed into the amino acid (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-decadienoic acid (**94**). Subsequent ester hydrolysis, amine deprotection, coupling with Boc-*L*-valine pentafluorophenyl ester, and Adda pentafluorophenyl ester formation, results in the activated ester **95**. This is then utilized in convergent completion of the synthesis of motuporin (**96**) (Scheme 20) [31].

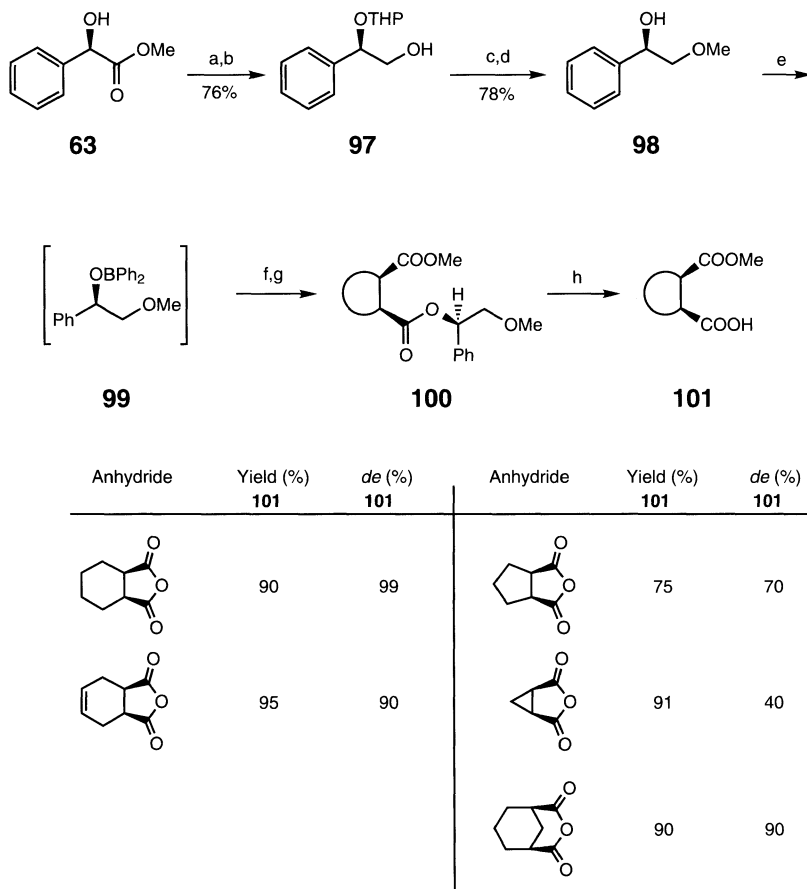


Scheme 20

conditions: (a) DIBAL, $-78\text{ }^{\circ}\text{C}$; (b) $n\text{-Bu}_3\text{SnCH}_2\text{CH}=\text{CHCH}_3$, $\text{MgBr}_2\cdot\text{Et}_2\text{O}$ (74% 2 steps); (c) NaH, MeI (98%); (d) LiOH; (e) Na-Naphthalene, THF, $-78\text{ }^{\circ}\text{C}$; (f) Boc-*L*-valine- OC_6F_5 ; (g) $\text{C}_6\text{F}_5\text{OH}$, DCC, (60% 4 steps)

The ability to differentiate between two enantiotopic carbonyl groups in a symmetrical dicarboxylic anhydride in order to generate a chiral product is extremely useful, since the resulting product can be subsequently converted into either enantiomeric species by selective transformations of the chemically distinguishable functional groups. (*R*)-2-Methoxy-1-phenylethanol (**98**), prepared from **63** by a four-step sequence, reacts in the presence of a

catalytic amount of diphenylboryl triflate to give the diphenylboric ester **99**. This species stereoselectively esterifies cyclic *meso* dicarboxylic anhydrides to produce the 1*S*, 2*R* products **100**. The highest yields are achieved using toluene at 0 °C together with two equivalents of the chiral source. Presumably the oxygen atom of the methoxy group coordinates to boron to form a rigid five-membered ring structure that leads to preferential attack at the pro-*S* carbonyl group. Catalytic hydrogenation [32] of diester **100** provides the chiral half-ester **101** (Scheme 21) [33].

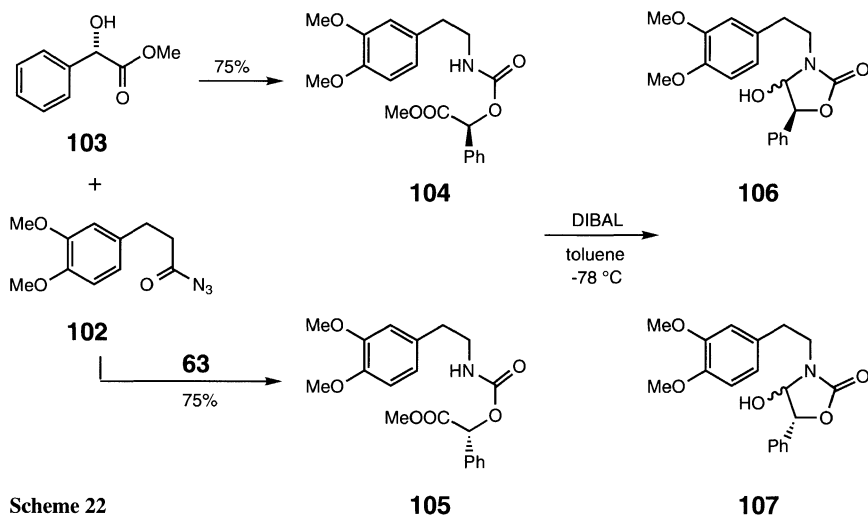


Scheme 21

conditions: (a) DHP, TsOH; (b) LiAlH₄; (c) NaH, MeI; (d) MeOH, TsOH; (e) *n*-BuLi, toluene, Ph₂BCl, 0 °C; (f) dicarboxylic anhydride, AgOTf, Ph₂BCl, toluene, 0 °C; (g) CH₂N₂; (h) H₂, Pd/C, MeOH

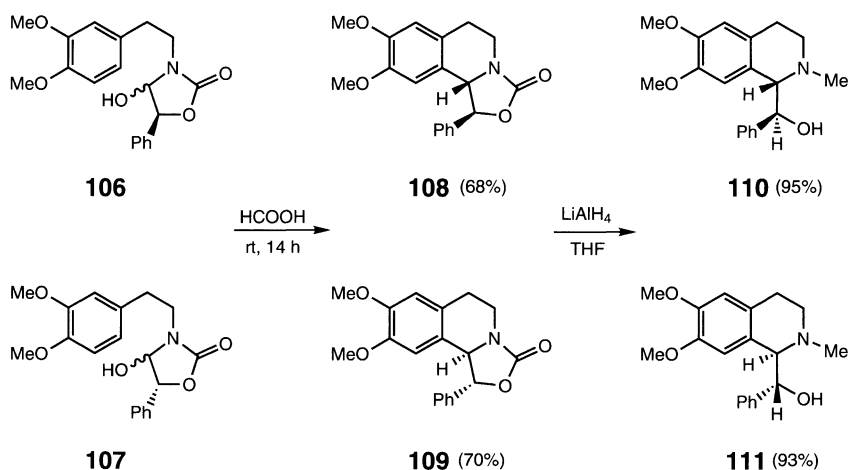
The π -cyclization of *N*-acyliminium ions onto aromatic rings is a useful method for the preparation of isoquinolines fused with heterocycles. Heating azide **102** with one of the compounds methyl (*S*)-mandelate (**103**) or methyl (*R*)-mandelate (**63**) in toluene provides the carbamates **104** and **105** respectively. DIBAL reduction of **104** or **105** with DIBAL in toluene

at $-78\text{ }^{\circ}\text{C}$ produces an aldehyde that undergoes ring closure to one of the cyclic carbamates **106** or **107** (Scheme 22).



Scheme 22

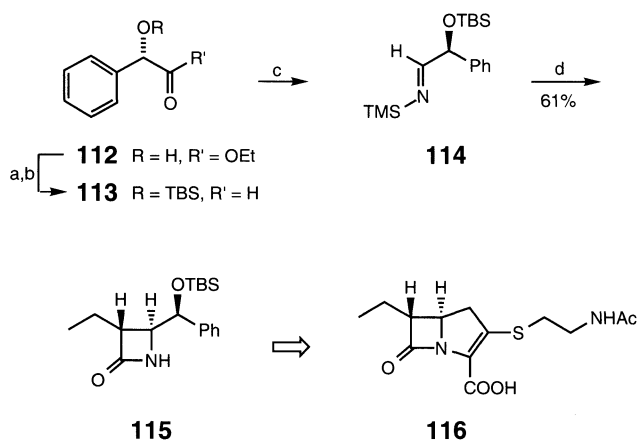
Treatment of **106** or **107** with formic acid at room temperature leads to the corresponding 1-substituted oxazolo[4,3-*a*]isoquinoline **108** or **109**, where the absolute configuration of the α -substituent of the intermediate iminium carbon does not suffer racemization during the cyclization. Reduction of the isoquinoline with lithium aluminum hydride yields the appropriate 1-(α -hydroxy- α -phenyl)-1,2,3,4-tetrahydroisoquinoline (**110** or **111**) (Scheme 23) [34].



Scheme 23

Absolute stereochemistry is a central problem in the synthesis of such biologically significant natural products as β -lactams. The cycloaddition of an enantiomerically pure α -hydroxy-*N*-(trimethylsilyl)imine **114**, prepared from the mandelic aldehyde **113**, constitutes a useful approach to the complete enantio- and diastereoselective synthesis of optically pure azetidinones.

Protection of the hydroxy group in **112** as a TBS ether, DIBAL reduction at $-78\text{ }^\circ\text{C}$ to furnish the aldehyde **113**, and treatment with lithium hexamethyldisilazide at $-78\text{ }^\circ\text{C}$ generates (*S*)-2-[(*tert*-butyldimethylsilyloxy)-2-phenyl-*N*-(trimethylsilyl)ethanimine (**114**) *in situ*. When **14** is treated with one equivalent of lithium *tert*-butylbutanoate, the ensuing cycloaddition reaction provides the β -lactam **115** as a single isomer in 84% yield. The observed outstanding 1,2-like induction presumably arises from a coplanarity between the oxygen and nitrogen atoms of the imine due to the chelation of lithium cations present in solution. The enolate then attacks from the less hindered face of the diastereotopic plane of the imine group. Oxidative cleavage of the protected hydroxybenzyl side chain, introduction of the necessary appendages in the 4 position of the azetidinone ring, and assembly of the bicyclic ring system affords the natural *trans*-carbapenem (+)-PS-5 (**116**) (Scheme 24) [35].

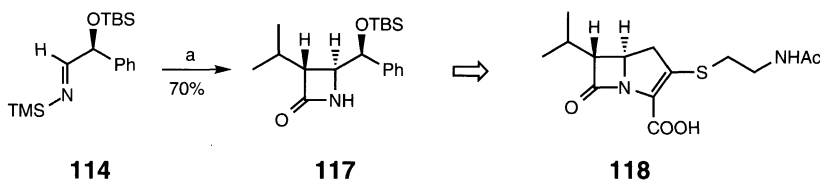


Scheme 24

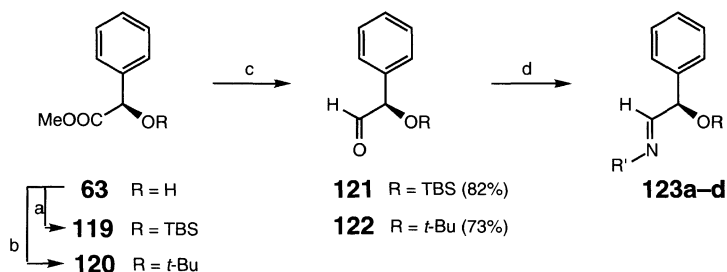
conditions: (a) TBSCl, imidazole, DMF (94%); (b) DIBAL, hexane, $-78\text{ }^\circ\text{C}$ (88%); (c) LiHMDS, THF, $-78\text{ }^\circ\text{C}$; (d) *tert*-butyl butanoate, LDA, THF, $-78\text{ }^\circ\text{C}$

The reaction of **114** with lithium *tert*-butylisovalerate produces the azetidinone **117** in 70% yield with total diastereoselectivity. A sequence of transformations similar to that described above transforms **117** into the natural *trans*-carbapenem (+)-PS-6 (**118**) (Scheme 25) [35].

Optically active 3-amino-2-hydroxycarboxylic acid derivatives are often key components of medicinally important compounds. The synthesis of isopropyl (2*R*,3*S*)-3-amino-4-cyclohexyl-2-hydroxybutyrate (**126**) (Scheme 28) takes advantage of a [2+2]-cycloaddition reaction of the chiral imines **123**, prepared from **63**, to assemble the important diastereomeric azetidinone **124** as the crucial precursor for completion of this novel synthesis. Protection of the hydroxy group of **63** as either the TBS ether **119** or the *tert*-butyl ether **120**, followed by a DIBAL reduction at $-78\text{ }^\circ\text{C}$, produces smoothly one of the aldehydes **121** or **122**. Condensation of these aldehydes with either di-*p*-anisylmethylamine or benzylamine in the presence of anhydrous magnesium sulfate affords the four possible chiral imines **123a-d** (Scheme 26).

**Scheme 25**

conditions: (a) *tert*-butyl isovalerate, LDA, THF, $-78\text{ }^{\circ}\text{C}$



123	R	R'	Yield (%)
a	TBS	DAM	100
b	TBS	PhCH ₂	100
c	<i>t</i> -Bu	DAM	100
d	<i>t</i> -Bu	PhCH ₂	98

Scheme 26

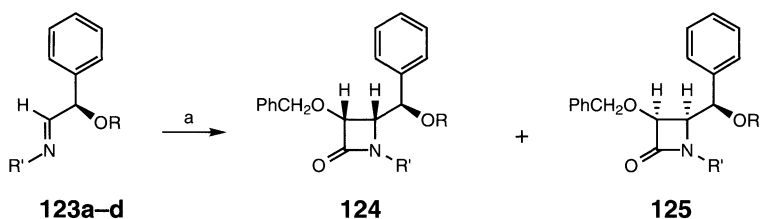
conditions: (a) TBSCl, imidazole, DMF, rt (98%); (b) Me₂C=CH₂, H₂SO₄, DCM, rt, 2 d (83%); (c) DIBAL, Et₂O-hexane, $-78\text{ }^{\circ}\text{C}$; (d) DAMNH₂ or PhCH₂NH₂, anhydrous MgSO₄, toluene, 0 $^{\circ}\text{C}$ 50 or 60 min

The imines undergo [2+2]-cycloaddition with benzyloxyketene, generated *in situ*, to furnish separable mixtures of 3,4-*cis*-2-azetidinones **124** and **125**. The best chemical yield (88%) and diastereoselectivity (15 : 1) is realized for the reactions employing **123a** and **123d** as chiral imines (Scheme 27).

The major diastereomer **124a** is converted in four steps to optically pure **126** (Scheme 28). The DAM protecting group is easily cleaved under mild hydrolytic conditions [36].

A similar sequence of reactions utilizing **103** as the starting mandelic acid derivative provides as the major azetidinone **127**, which is elaborated through a four-step sequence to (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutyric acid (**128**) (Scheme 29) [36].

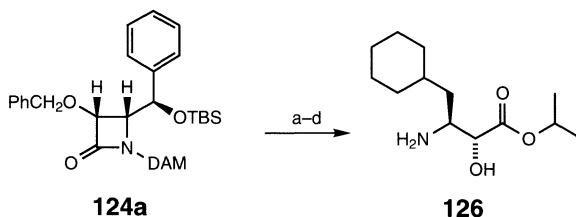
The stereocontrolled synthesis of 1,2-aminols is of interest due to the utility of these substances as efficient synthons for a variety of natural products. A highly stereoselective addition of lithium alkyls or Grignard reagents to the O-protected α -hydroxy-*N*-trimethylsilylimines generated *in situ* constitutes the path for the preparation of these 1,2-aminols. Thus, the addition-elimination reaction of lithium hexamethylsilylamide with aldehyde **129**, easily obtained in two steps from **103**, leads to the α -OTBS-*N*-TMS-imine **130** (Scheme 30).



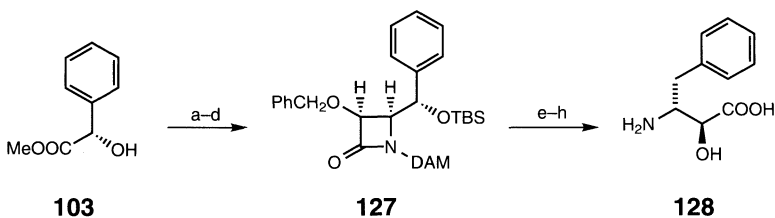
123	Yield (%)	124:125
a	88	10:1
b	59	12:1
c	77	9:1
d	62	15:1

Scheme 27

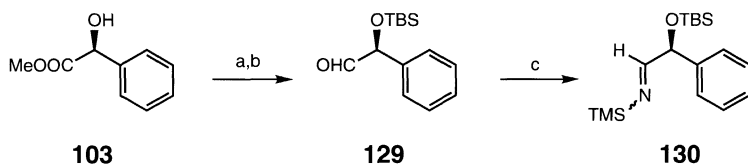
conditions: (a) PhCH₂OCH₂COCl, Et₃N, DCM, rt

**Scheme 28**

conditions: (a) HCl, *i*-PrOH, rt, 18 h, then 60 °C, 3 h (84%);
 (b) Cl₃COCOCl, pyridine, DCM, 0 °C, 10 min (90%);
 (c) H₂, Pd/C, EtOAc, rt, 18 h (94%); (d) H₂, 5% Rh/Al₂O₃, AcOH (97%)

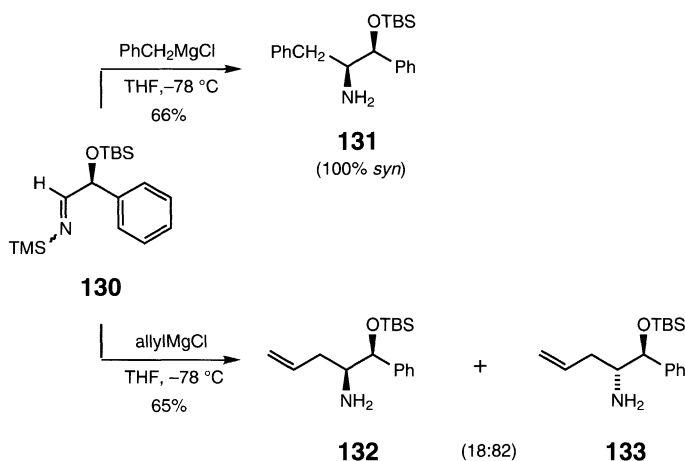
**Scheme 29**

conditions: (a) TBSCl, imidazole, DMF (93%); (b) DIBAL, Et₂O-hexane, -78 °C (80%);
 (c) DAMNH₂, anhydrous MgSO₄, toluene, 0 °C (100%); (d) PhCH₂OCOCl, Et₃N, DCM (90%, 8:1); (e) HCl, *i*-PrOH, rt, 18 h then 60 °C, 3 h (70%);
 (f) Cl₃COCOCl, pyridine, DCM, 0 °C, 10 min (93%); (g) H₂, Pd/C, EtOAc, rt, 18 h (92%); (h) 6 M HCl, 100 °C, 4 h then ion exchange resin (AG-50XW2, acid-form) (85%)

**Scheme 30**

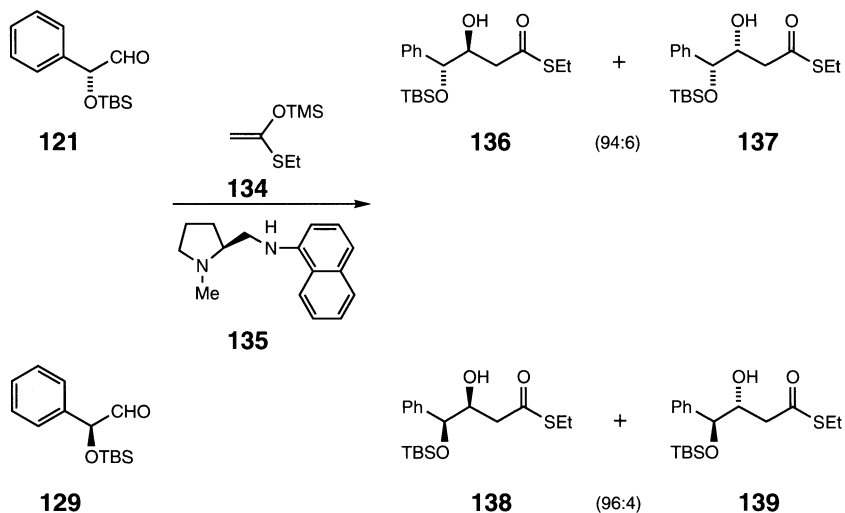
Conditions: (a) TBSCl, imidazole, DMF, rt; (b) DIBAL, hexane, $-78\text{ }^{\circ}\text{C}$; (c) LiHMDS, $-78\text{ }^{\circ}\text{C}$

The addition of benzylmagnesium chloride to **130** at $-78\text{ }^{\circ}\text{C}$ is strongly influenced by chelation of the α -hydroxy center with the magnesium cation; diastereofacial selectivity consistent with the Cram cyclic model therefore results in a 66% yield of the *syn* isomer **131** only. Interestingly, and for reasons not quite clear, the addition of allylmagnesium chloride proceeds with high diastereoselectivity to provide the *anti* isomer **133** as the major diastereomer (Scheme 31) [37].

**Scheme 31**

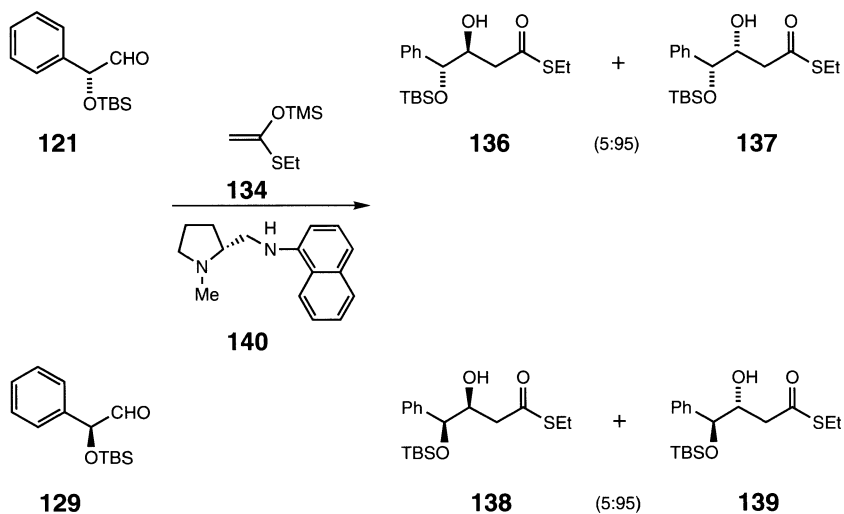
The aldol condensation is a powerful tool for the stereoselective synthesis of acyclic molecules with contiguous chiral centers. The catalytic asymmetric aldol reaction of (*R*)-2-*tert*-butyldimethylsilyloxy-2-phenylacetaldehyde (**121**) with the achiral silyl enol ether 1-ethylthio-1-trimethylsilyloxyethene (**134**) in the presence of tin(II) trifluoride and the chiral promotor (*S*)-1-methyl-2-[(*N*-naphthylamino)methyl]pyrrolidine (**135**) in propionitrile at $-78\text{ }^{\circ}\text{C}$ proceeds smoothly to give a 94 : 6 mixture of diastereomeric aldol adducts **136** and **137** in 85% yield (Scheme 32). When performed on (*S*)-**129** this same reaction affords in 85% yield a 96 : 4 mixture of diastereomers **138** and **139**. It is noteworthy that the newly created chiral centers in both of the major diastereomers **136** and **138** has the *S* configuration, suggesting that the stereochemistry of the aldol reaction is controlled by the chiral promotor and not the chiral aldehydes.

Utilization of the chiral promotor (*R*)-1-2-[(*N*-naphthylamino)methyl]pyrrolidine (**140**) in this aldol reaction reverses the diastereoselectivity, so that all four possible optically active



Scheme 32

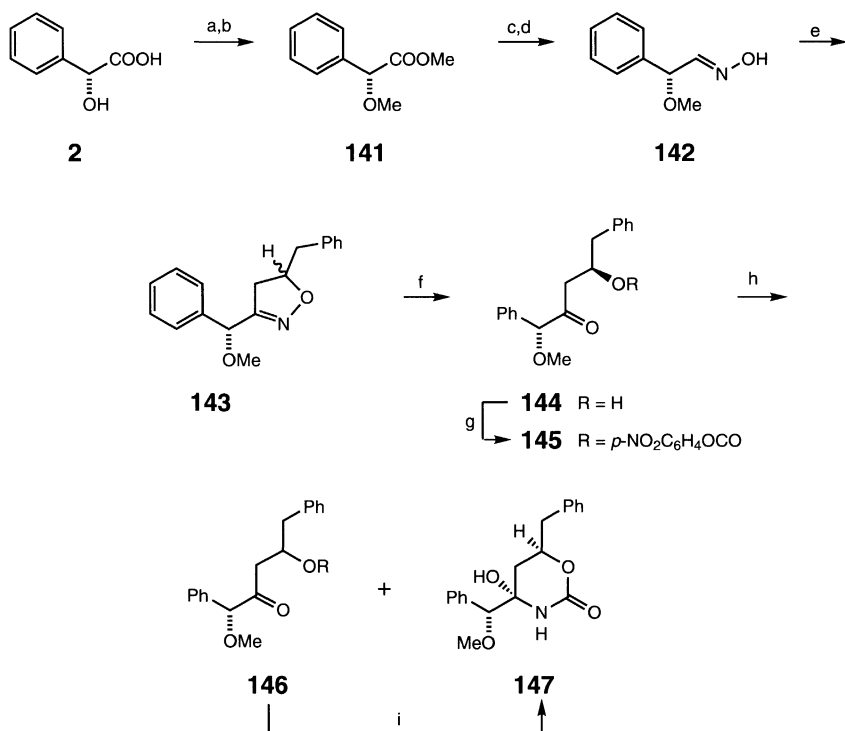
diastereomers can be easily prepared by suitable combination of a chiral aldehyde and a catalyst (Scheme 33) [38].



Scheme 33

The ability of the intramolecular nitrile oxide–olefin [3 + 2] cycloaddition reaction to furnish isoxazolines suitable for further elaboration is illustrated in Scheme 34 utilizing (*R*)-mandelic acid (**2**). Chiral oxime **142**, prepared in four steps from **2**, is oxidized to a nitrile

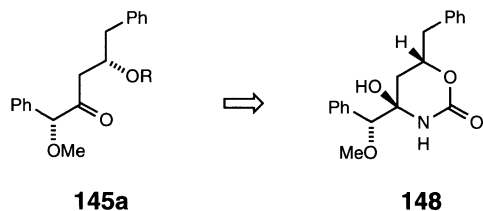
oxide with Chlorox, and in the presence of allylbenzene and triethylamine it undergoes a [3 + 2] cycloaddition reaction to afford a mixture of diastereomeric isoxazolines **143**. Hydrolytic reduction of this mixture leads to the β -hydroxyketone **144**. This is converted to ortho ester **145**, chromatographically separated to provide the desired diastereomer, and converted to a mixture of the cyclic hydroxycarbamate **147** along with 15% of the uncyclized isomer **146**, which can be transformed into **147** with either DBU in THF or 1N HCl in acetonitrile. This cyclic hydroxycarbamate functionality is found in the antitumor agent maytansine [39].



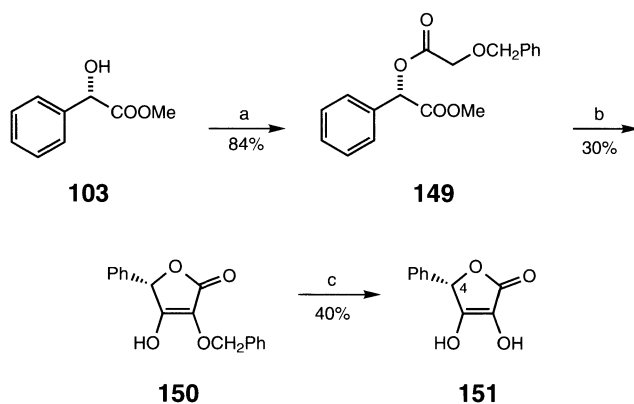
Scheme 34

conditions: (a) H₂SO₄, MeOH, reflux, 2.5 h; (b) MeI, Ag₂O, DMF, rt, 24 h; (c) DIBAL, -78 °C, DCM; (d) NH₂OH, EtOH, rt, 1.5 h; (e) allylbenzene, Chlorox, Et₃N, DCM, rt, 1 h (70%); (f) H₂, Raney Ni, MeOH-H₂O, AcOH, rt; (g) *p*-NO₂C₆H₄OCOCl, pyridine, DCM, 0 °C, 30 min; (h) NH₃, MeOH-DCM, -78 ° to -20 °C, 1 h; (i) DBU in THF or 1N HCl in MeCN

The epimeric **145a** is similarly transformed into the cyclic hydroxycarbamate **148** [39].



Synthesis of optically active 4-aryl-2-hydroxytetronic acids, possible antilipidemic and antiaggregatory agents, is complicated by the stereochemical lability of the C-4 stereogenic center toward racemization. However, an intramolecular Claisen condensation using a non-nucleophilic, sterically hindered base can be successfully used to prepare some of these interesting compounds. Methyl (*S*)-(+)-mandelate (**103**), protected as the (phenylmethoxy)-acetyl derivative **149**, undergoes a kinetic-controlled intramolecular Claisen reaction with lithium dicyclohexylamide (prepared *in situ*) at $-100\text{ }^{\circ}\text{C}$ to provide in 30% yield (*S*)-(+)-4-hydroxy-5-phenyl-3-(phenylmethoxy)-2(*5H*)-furanone (**150**) with 98% *ee*. Other non-nucleophilic bases, such as LiHMDS, LDA, *tert*-butyllithium, or LiICA, either provide products in low chemical yields and with extremely poor enantioselectivities, or else do not lead to any of the desired product at all. Subsequent debenzoylation of **150** under hydrogen-transfer conditions affords enantiomerically pure (*S*)-(+)-3,4-dihydroxy-5-phenyl-2(*5H*)-furanone (**151**) in 40% yield (Scheme 35) [40].

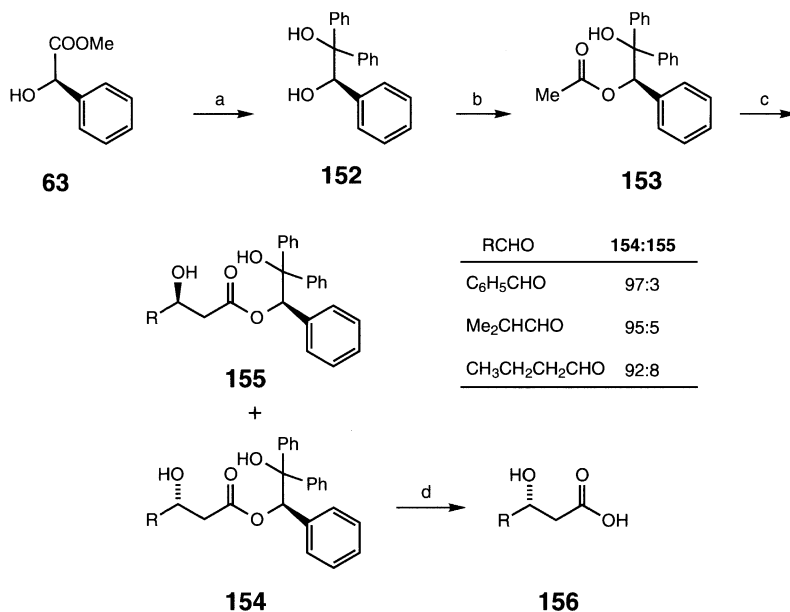


Scheme 35

conditions: (a) $\text{PhCH}_2\text{OCH}_2\text{COCl}$, pyridine, DCM, $0\text{ }^{\circ}\text{C}$, 1 h; (b) $(\text{C}_6\text{H}_{11})_2\text{NH}$, *n*-BuLi, $-100\text{ }^{\circ}\text{C}$, THF; (c) 10% Pd/C, cyclohexene, EtOH, reflux, 1 h

Mandelic acid-derived chiral (α -substituted) acetate enolate addition to aldehydes leading to chiral β -hydroxycarboxylic acids illustrates the versatility of the readily available ester **63**. The addition of phenylmagnesium bromide to methyl (*R*)-mandelate (**63**) gives the (*R*)-diol **152**, which is acetylated to (*R*)-2-acetoxy-1,1,2-triphenylethanol (**153**) [(*R*)-HYTRA]. Deprotonation with LDA at $-78\text{ }^{\circ}\text{C}$ provides an enolate that is then transmetalated with magnesium bromide and further cooled to $-115\text{ }^{\circ}\text{C}$ before reaction with an aldehyde to produce **154** as the major diastereomer with a yield of 84–95%. Heating **154** in aqueous methanol containing potassium hydroxide provides the optically active β -hydroxyacid **156** (Scheme 36) [41–44].

The synthetic applicability of readily accessible **153** is illustrated by the convenient preparation of L-digitoxose (**160**), which is an interesting sugar component of several antibiotics possessing antitumor activity. (*S*)-Ethyl lactate (**157**) is converted through a sequence of chemical transformations to the chiral aldehyde **158** possessing 98% *de*. When **158** undergoes an aldol reaction with doubly deprotonated **153**, the carboxylic acid **159** is obtained as the major diastereomer in a 91:9 ratio after alkaline hydrolysis of the crude aldol adducts. Treatment of this mixture with trifluoroacetic acid cleaves the acetal moiety and generates a mixture of lactones. Reduction of the lactone mixture with disiamylborane followed by

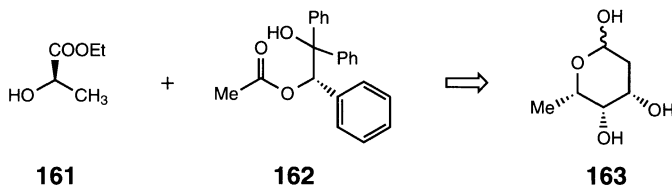


Scheme 36

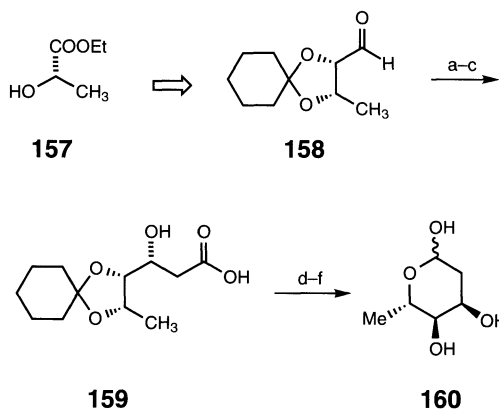
conditions: (a) PhMgBr, Et₂O, <10 °C, 2-3 h, then reflux 3 h and rt 18 h; (b) acetyl chloride, pyridine, DCM, 0 °C, 4 h; (c) LDA, -78 °C, THF, cool to -128 °C, then aldehyde; (d) KOH, H₂O, MeOH, reflux

hydrolysis and chromatographic separation provides β -L-digitoxose (**160**) possessing 98% *ee* as determined on the basis of optical rotation (Scheme 37) [45].

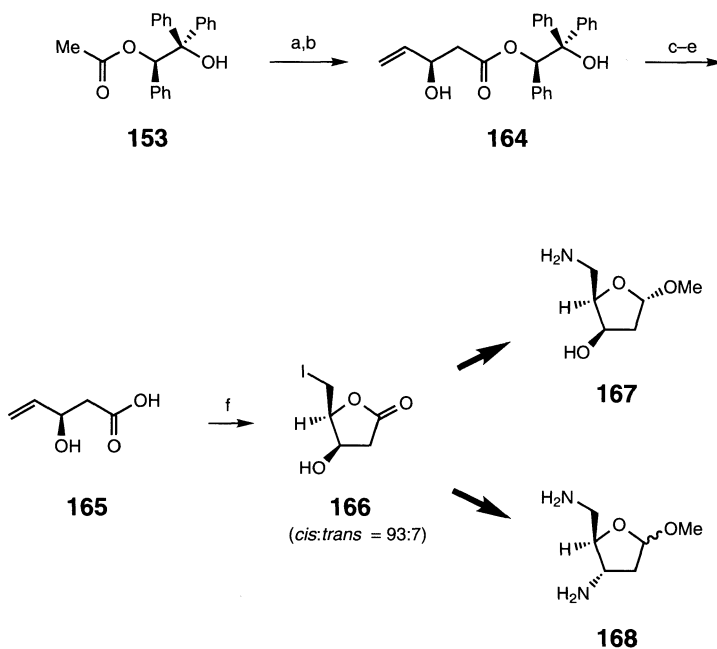
The ready accessibility of both (*R*)-ethyl lactate (**161**) and *S*-HYTRA (**162**) facilitates an identical synthesis of D-digitoxose (**163**) [45].



Aminodeoxy sugars are biochemically interesting due to their efficiency as enzyme inhibitors as well as their potential anti-HIV activity. Double deprotonation of **153** and subsequent treatment with acrolein affords **164** as the major diastereomer (92 : 8). Alkaline hydrolysis of this crude mixture provides (*R*)-3-hydroxy-4-pentenoic acid (**165**) with 83.5% *ee*. This is easily enhanced by resolution via the (*S*)-1-phenethylammonium salt, so that **165** can in fact be obtained with 99% *ee*. Iodolactonization of **165** generates the second stereogenic center and provides the furanone skeleton **166**, isolated with 97.8% *de*. Depending on the sequence of transformations chosen, **166** can be converted either to methyl (3*R*,4*R*)-5-amino-2,5-

**Scheme 37**

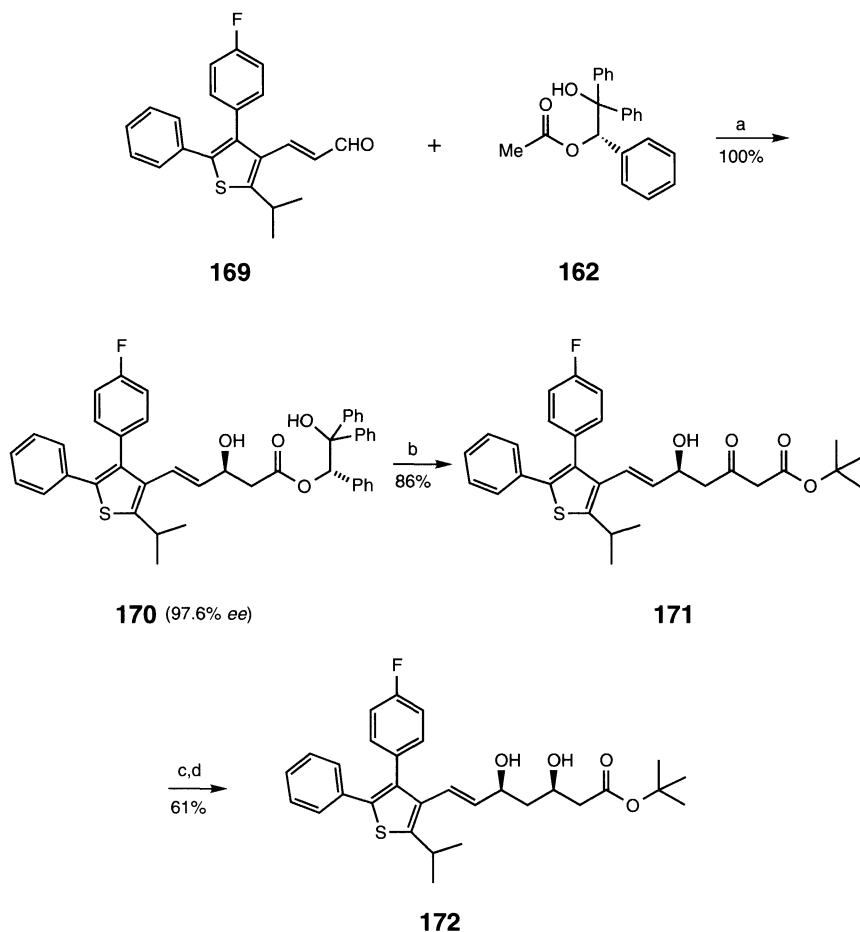
conditions: (a) **153**, LDA, $-78\text{ }^{\circ}\text{C}$ to $0\text{ }^{\circ}\text{C}$, THF, 1 h;
 (b) **158**, THF, $-78\text{ }^{\circ}\text{C}$; (c) KOH, MeOH, $25\text{ }^{\circ}\text{C}$, 18 h;
 (d) CF_3COOH , H_2O , $20\text{ }^{\circ}\text{C}$, 1.5 h; (e) $\text{Si}_2\text{BH}-\text{THF}$,
 $25\text{ }^{\circ}\text{C}$, 18 h, then H_2O , $70\text{ }^{\circ}\text{C}$, 1 h; (f) chromatography

**Scheme 38**

conditions: (a) 2 LDA, THF, $-78\text{ }^{\circ}\text{C}$; (b) $-125\text{ }^{\circ}\text{C}$, acrolein; (c) KOH, MeOH, H_2O (60%);
 (d) (S)-(-)-1-phenethylamine, Et_2O (81%); (e) NaOH (aq) then HCl (42% from **153**);
 (f) NaHCO_3 , Et_2O , I_2 in THF, $0\text{ }^{\circ}\text{C}$, no light (87%)

dideoxy- α -pentofuranoside (**167**) or to methyl (3*S*,4*R*)-3,5-diamino-2,3,5-trideoxy- α , β -pentofuranoside (**168**) (Scheme 38) [46].

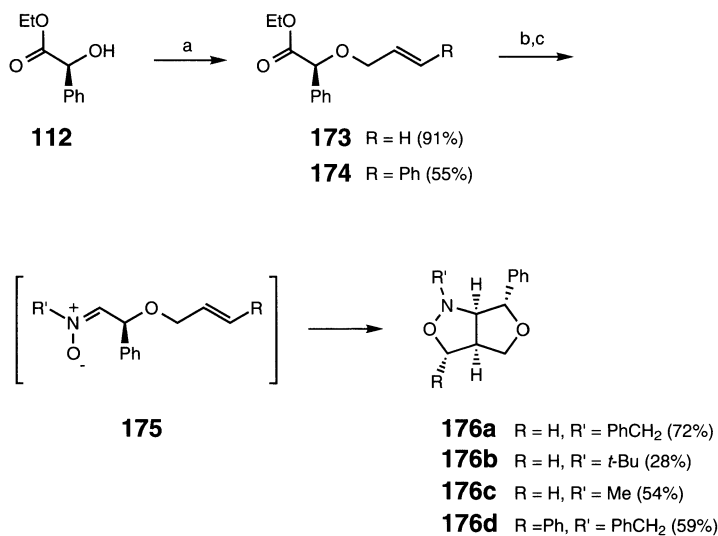
The major rate-limiting enzyme in cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl Coenzyme A reductase (HMG-CoA reductase), has been a therapeutic target for many research groups. A synthesis of the functionalized thiophene **172**, prepared for its biological activity, illustrates the utility of **162** for the introduction of one of the hydroxy chiral centers present in the molecule. This chiral center is then exploited for the introduction of the second chiral hydroxy center. Treatment of aldehyde **169** with the double anion of **162** at $-95\text{ }^\circ\text{C}$ in THF affords as the major product **170** (98.8 : 1.2). Treatment of the adduct with excess *tert*-butylacetate enolate at $-78\text{ }^\circ\text{C}$ followed by acidic work-up furnishes the β -hydroxyketone **171** in 86% isolated yield. Chelation-controlled reduction of the ketone, accomplished by initial complexation of the ketone and the hydroxy group with triethylborane followed by sodium borohydride addition, provides the desired dihydroxyester **172** (Scheme 39) [47].



Scheme 39

conditions: (a) LDA, THF, $-95\text{ }^\circ\text{C}$; (b) *tert*-butyl acetate, LDA, $-78\text{ }^\circ\text{C}$ to $-25\text{ }^\circ\text{C}$;
(c) Et_3B , THF–MeOH (4:1); (d) NaBH_4 , THF–MeOH (4:1)

Recently, an intramolecular 1,3-dipolar cycloaddition of transient enantiomerically pure oxa-alkenyl nitrones illustrated a synthesis of enantiomerically pure 3,7-dioxa-2-azabicyclo[3.3.0]octanes. Treatment of (*S*)-**112** with allyl bromide or cinnamyl chloride in diethyl ether in the presence of silver(I) oxide affords the alkylated esters **173** and **174**, respectively. No racemization occurs in this process, as determined by proton nmr. Reduction of the esters with DIBAL at $-72\text{ }^{\circ}\text{C}$ provides the corresponding aldehydes, which are immediately reacted with *N*-alkylhydroxylamines in order to minimize racemization. The resulting nitrones **175** cannot be isolated, but undergo spontaneous intramolecular 1,3-dipolar cycloaddition to the enantiomerically pure 3,7-dioxa-2-azabicyclo[3.3.0]octanes **176a-d** (Scheme 40) [48].



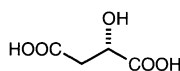
Scheme 40

conditions: (a) allyl bromide or cinnamyl chloride, Et₂O, Ag(I)O, rt;
 (b) DIBAL, hexane, $-72\text{ }^{\circ}\text{C}$; (c) R'-NHOH, Et₂O
 or DCM, 0–5 $^{\circ}\text{C}$ 2h, then rt 1–3 d

References

1. The Merck Index, 11th Ed., pg 898 (1989).
2. T. Hirano, S. Inoue and T. Tsuruta, *Makromol. Chem.* **177**, 3237 (1976).
3. S. Masamune, W. Choy, F. A. J. Kerdesky and B. Imperiali, *J. Am. Chem. Soc.* **103**, 1566 (1981).
4. Masamune, M. Hirama, S. Mori, Sk. A. Ali and D. S. Garvey, *J. Am. Chem. Soc.* **103**, 1568 (1981).
5. S. Masamune, T. Kaiho and D. S. Garvey, *J. Am. Chem. Soc.* **104**, 5521 (1982).
6. S. Masamune, J. W. Ellingboe and W. Choy, *J. Am. Chem. Soc.* **104**, 5526 (1982).
7. D. Boschelli, J. W. Ellingboe and S. Masamune, *Tetrahedron Lett.* **32**, 3395 (1984).
8. M. Farines and J. Soulier, *Bull. Chem. Soc. Fr.*, 332 (1970).
9. S. H. Mashraqui and R. M. Kellogg, *J. Org. Chem.* **49**, 2513 (1984).
10. N. Chapel, A. Greiner and J.-Y. Ortholand, *Tetrahedron Lett.* **32**, 1441 (1991).
11. G. Frater, U. Muller and W. Gunther, *Tetrahedron Lett.* **22**, 4221 (1981).
12. T. Fruh and G. M. Ramos Tombo, *Synlett.*, 727 (1994).
13. S. J. Coote, S. G. Davies, D. Middlemiss and A. Naylor, *J. Chem. Soc., Perkin Trans. I*, 2223 (1989).
14. S. J. Coote, S. G. Davies, D. Middlemiss and A. Naylor, *Tetrahedron Lett.* **30**, 3581 (1989).
15. C. Kaiser, P.A. Dandridge, E. Garvey, R. A. Hahn, H. M. Sarau, P. E. Setler, L. S. Bass and J. Clardy, *J. Med. Chem.* **25**, 697 (1982).
16. J. Weinstock, H. Oh, C. W. DeBrosse, D. S. Eggeston, M. Wise, K. E. Flaim, G. W. Gessner, J. L. Sawyer and C. Kaiser, *J. Med. Chem.* **30**, 1303 (1970).
17. B. Strijtveen and R. M. Kellogg, *J. Org. Chem.* **51**, 3664 (1986).
18. B. Strijtveen and R. M. Kellogg, *Recl. Trav. Chim. Pays-Bas* **106**, 539 (1987).
19. C. L. Branch and M. J. Pearson, *J. Chem. Soc., Perkin Trans. I*, 2268 (1979).
20. M. Narisada, T. Yoshida, H. Onoue, M. Ohtani, T. Okada, T. Tsuji, I. Kikkawa, N. Haga, H. Satoh, H. Itani and W. Nagata, *J. Med. Chem.* **22**, 757 (1979).
21. R. A. Firestone, J. L. Fahey, N. S. Maciejewicz, G. S. Patel and B. G. Christensen, *J. Med. Chem.* **20**, 551 (1977).
22. T. Aoki, T. Konoike, H. Itani, T. Tsuji, M. Yoshioka and W. Nagata, *Tetrahedron* **39**, 2515 (1983).
23. K. Toyooka, Y. Takeuchi and S. Kubota, *Heterocycles* **29**, 975 (1989).
24. E. E. Blaise and A. Haller, *C. R. Acad. Sci. Paris*, 596 (1912).
25. G. Cahiez and B. Laboue, *Tetrahedron Lett.* **30**, 7369 (1989).
26. G. Cahiez and B. Laboue, *Tetrahedron Lett.* **33**, 4439 (1992).
27. G. Cahiez and E. Metais, *Tetrahedron Lett.* **36**, 6449 (1995).
28. S. V. Ley, M. Parra, A. J. Redgrave and F. Sternfeld, *Tetrahedron* **46**, 4995 (1990).
29. D. Obrecht and H. Heimgartner, *Helv. Chim. Acta* **73**, 221 (1990).
30. T. Kitazume, M. Asai, J. T. Lin and T. Yamazaki, *J. Fluorine Chem.* **35**, 477 (1986).
31. R. J. Valentekocich and S. L. Schreiber, *J. Am. Chem. Soc.* **117**, 9069 (1995).
32. M. M. Vavon and P. Peignier, *Bull. Soc. Chim. Fr.* **45**, 293 (1929).
33. M. Oshima and T. Mukaiyama, *Chem. Lett.*, 377 (1987).
34. S. Kano, Y. Yuasa and S. Shibuya, *Heterocycles* **23**, 395 (1985).
35. P. Andreoli, G. Cainelli, M. Panunzio, E. Bandini, G. Martelli and G. Spunta, *J. Org. Chem.* **56**, 5984 (1991).
36. Y. Kobayashi, Y. Takemoto, Y. Ito and S. Tershima, *Tetrahedron Lett.* **31**, 3031 (1990).
37. G. Cainelli, D. Giacomini, E. Mezzina, M. Panunzio and P. Zarrantonello, *Tetrahedron Lett.* **32**, 2967 (1991).
38. S. Kobayashi, A. Ohtsubo and T. Mukaiyama, *Chem. Lett.*, 831 (1991).
39. P. N. Confalone and S. S. Ko, *Tetrahedron Lett.* **25**, 947 (1984).
40. D. T. Witiak and A. K. Tehim, *J. Org. Chem.* **55**, 1112 (1990).
41. M. Braun, S. Graf and S. Herzog, *Org. Syn.* **72**, 32 (1993).
42. M. Braun and S. Graf, *Org. Syn.* **72**, 38 (1993).
43. M. Braun and R. Devant, *Tetrahedron Lett.* **25**, 5031 (1984).
44. R. Devant, U. Mahler and M. Braun, *Chem. Ber.* **121**, 397 (1988).
45. M. Braun and J. Moritz, *Synlett.*, 750 (1991).
46. S. Graf and M. Braun, *Liebigs Ann. Chem.*, 1091 (1993).
47. R. E. Damon, G. M. Coppola, H. Yu, R. G. Engstrom and T. J. Scallen, presented at the 206th ACS National Meeting, Chicago, Il., Aug. 22-27 (1993).
48. H. G. Aurich and F. Bieseimer, *Synthesis*, 1171 (1995).

3 Malic Acid

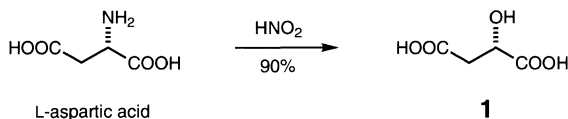


(*S*)-Hydroxybutanedioic Acid

The L-(–)-form of malic acid occurs naturally in apples and other fruits hence its German name *Apfelsäure* (“apple acid”). It is an extremely versatile 4-carbon building block possessing an additional carboxyl group at the 4-position that serves as a useful “handle” easily manipulated to provide a variety of synthetically useful functionalities.

Although L-malic acid (**1**) can be isolated from a variety of fruits, it is manufactured industrially by the fermentation of fumaric acid with immobilized fumarase as the biocatalyst [1]. This process is capable of producing up to 30 tons of the acid per month. L-Malic acid is commercially available from many suppliers, and is relatively inexpensive. The current price is approximately \$208/Kg.

The cost of L-malic acid can be dramatically reduced by preparing it from L-aspartic acid, the current price of which is only \$53.70 for 2 Kg. This process requires only a single step, in which the amino group of aspartic acid is converted to the desired hydroxyl function under nitrous acid deamination conditions [2]. The configuration of the chiral center is retained, affording **1** with 97% *ee*.



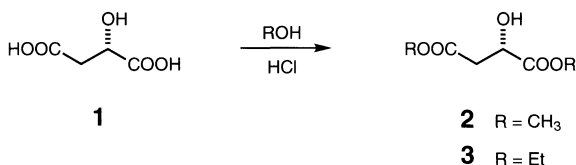
The present chapter concludes with a table of physical data associated with the common derivatives of malic acid discussed throughout this part of the book.

3.1 The Basics

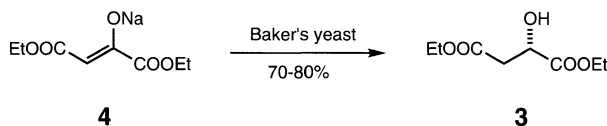
Malic acid, although useful itself in many synthetic applications, achieves its true potential as a versatile chiral synthon when converted to one of its simple analogs. Rudimentary manipulations of **1** allow rapid access to esters, amides, and various O-protected derivatives. Each of these is widely used as a starting point in the tactical synthesis of medicinal agents, natural products, and agrochemicals as discussed in the remainder of this chapter.

3.1.1 Malic Acid Diesters and Amides

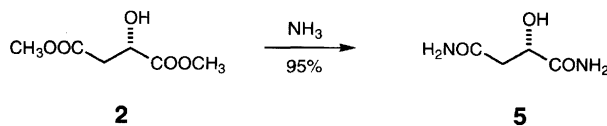
(*S*)-Malate esters, some of which are commercially available, do not have as wide a supply base as malic acid itself. Moreover, the esters are significantly more expensive than native malic acid. Dimethyl (*S*)-malate (**2**), the most common ester, costs more than 18 times as much as **1**. Diethyl (*S*)-malate (**3**), the next most commonly used ester, is not even available commercially. Malate esters are easily prepared from (*S*)-malic acid under a variety of conditions, so it is often more advantageous to prepare these relatively expensive and rare analogs rather than purchase them. The requisite conversion to **2** or **3** is accomplished by treatment of **1** with an appropriate alcohol in the presence of either HCl gas [3,4,5] or concentrated HCl [6,7] to give the ester in 70–90% yield. Alternatively, **2** can be prepared from **1** by treatment with methanol in the presence of thionyl chloride [8] (98% yield), or with diazomethane in ether [9] (95% yield).



Another interesting approach to the less readily accessible diethyl (*S*)-malate (**3**) is enantioselective bioreduction of sodium diethyl oxalacetate (**4**) with baker's yeast (*Saccharomyces cerevisiae*). Under fermenting conditions, **3** is produced in high yield with >98% *ee* [10].



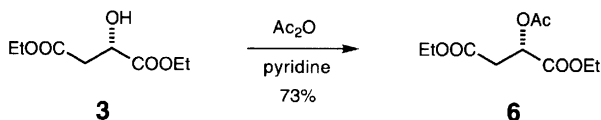
Dimethyl (*S*)-malate (**2**), when exposed to ammonia, forms (*S*)-(-)-hydroxysuccinamide [(*S*)-malamide] (**5**) in nearly quantitative yield [11].



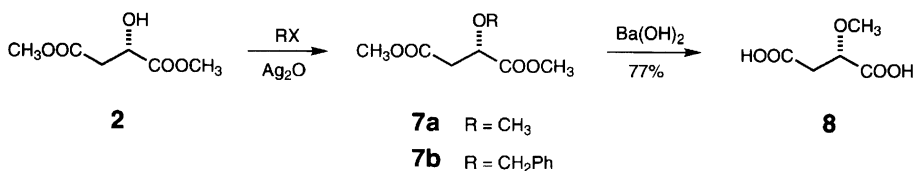
3.1.2 O-Protected Malates

In the course of planning a synthesis it may not appear feasible to start with a malic acid derivative possessing a free hydroxyl functionality. This group might not be compatible with certain reaction conditions, or with other functional groups that might arise as the synthesis proceeds. In these instances it is desirable to functionalize the hydroxyl moiety with a group that is both complementary to the intended synthesis and easily removed under the mildest possible conditions. Many of the standard OH protecting groups are suitable for this purpose.

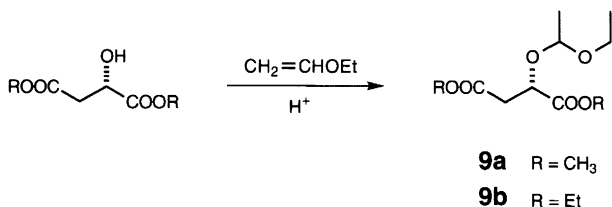
Diethyl (*S*)-malate (**3**) is readily acetylated with acetic anhydride in pyridine to give diethyl (*S*)-acetoxy succinate (**6**) in good yield [7].



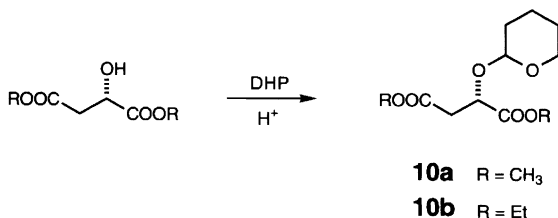
Alkylation of dimethyl (*S*)-malate (**2**) at oxygen can be accomplished with an alkyl halide in the presence of silver oxide. The methoxy derivative **7a** forms in 74% yield [3], while the benzyloxy analog **7b** is produced in 84% yield [12]. Alternatively, **7b** can be prepared by treating **2** with *O*-benzyl trichloroacetimidate in the presence of trifluoroacetic acid (68% yield) [13]. Upon treatment of malate ester **7a** with barium hydroxide, (*S*)-methoxysuccinic acid (**8**) is obtained in high yield [3].



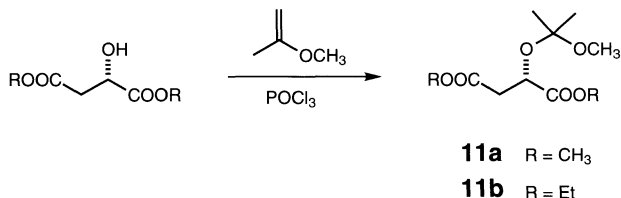
The 1-ethoxyethyl (EE) protecting group can be introduced by reaction of the appropriate malate ester with ethyl vinyl ether in the presence of an acidic catalyst, such as pyridinium *p*-toluenesulfonate [14] or trifluoroacetic acid [15,16]. In either case, the (*S*)-malate ester EE ether **9** is isolated in quantitative yield.



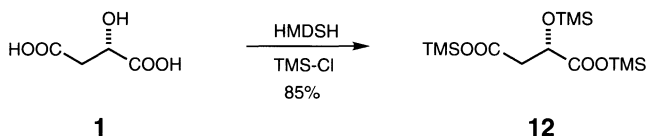
A protecting group structurally related to the EE group is the tetrahydropyranyl (THP) functionality, in which the framework of the EE fragment has been incorporated into a 6-membered ring. Malate esters are easily protected with a THP group by treatment with dihydropyran in the presence of an acid catalyst such as *p*-toluenesulfonic acid [17,18], pyridinium *p*-toluenesulfonate [6], or concentrated HCl [19]. Yields are routinely high with THP (*S*)-malates **10** being isolated in nearly 100% yield.



A third member of the family of acid-removable protecting groups is the 2-methoxy-2-methylpropyl functionality. This is introduced by treating the appropriate malate ester with 2-methoxypropene in the presence of a catalytic amount of phosphorus oxychloride [6,20]. The labile ketals **11** are formed in nearly quantitative yield, and are generally used immediately without purification.

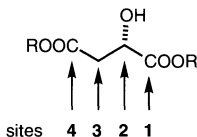


The fully silylated malate ester **12** is prepared from (*S*)-malic acid by treatment with a slight excess of hexamethyldisilazane containing one equivalent of trimethylsilyl chloride [21].



3.2 Site-Selective Reactions of Malic Acid Derivatives

In order truly to unleash the synthetic potential of malic acid it is imperative that one be able to perform discrete operations at each of the four carbon centers of the molecule. Since malic acid by nature contains two nearly identical carboxylic acid groups, it is important to establish a way to differentiate between the two if one wishes to selectively manipulate either one.



The chemistry discussed in this section illustrates various techniques used to manipulate each of the four carbon sites of malic acid derivatives, leading ultimately to useful chiral intermediates, biologically active compounds, or interesting natural products.

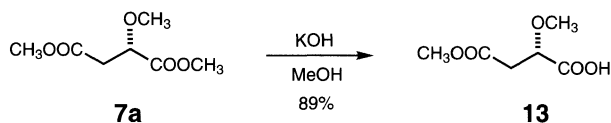
3.2.1 C-1 Selective Reactions

This section focuses on the chemistry associated with the carboxyl group in the 1-position of malic acid derivatives. Manipulations such as selective hydrolysis, reduction, or cyclization

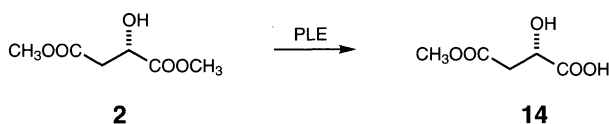
reactions are discussed, along with subsequent transformations leading to other interesting molecules. Chemistry at the 1-carboxylate position that results in second-generation malic acid derivatives used to direct reactions to alternate sites is presented in the form of examples in the corresponding sections of the chapter.

3.2.1.1 Hydrolysis and Related Reactions

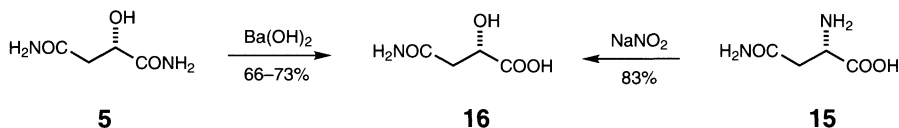
Ester hydrolysis is one of the most rudimentary manipulations in organic chemistry. The 1-ester function in a malate can be selectively hydrolyzed to an acid by treatment with one equivalent of potassium hydroxide. In this way **7a** is converted to **13** in high yield [3].



Hydrolysis can also be accomplished under enzymatic conditions. Dimethyl (*S*)-malate (**2**), when incubated with pig liver esterase (400 units per 43 mmol of substrate), is hydrolyzed regioselectively to the optically pure acid **14** [22].



(*S*)-Malamide (**5**) is also hydrolyzed selectively to *L*- β -malamidic acid (**16**) using barium hydroxide as the base [11]. A more straightforward synthesis of **16** can be accomplished in one step by nitrous acid deamination of the inexpensive *L*-asparagine (**15**) [23,24].



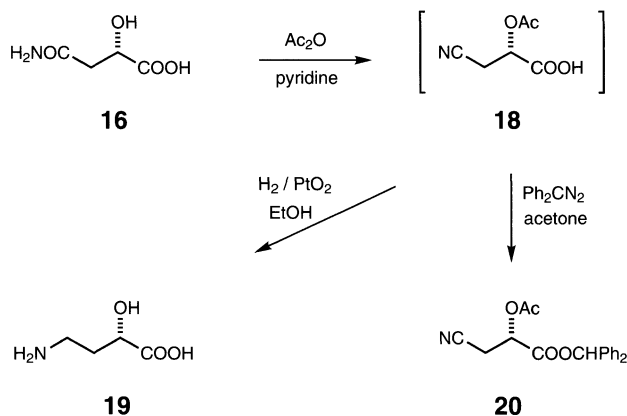
L- β -Malamidic acid (**16**) is the penultimate intermediate in the synthesis of (*S*)-isoserine (**17**), an amino acid component of several biologically active peptides. Treatment of **16** with sodium hypochlorite in alkaline solution produces **17** (28% yield) *via* a Hofmann rearrangement [23].



Significantly higher yields can be realized by converting **16** to its *O*-acetyl derivative (acetic anhydride, pyridine, acetonitrile) followed by treatment with bis[trifluoro-acetoxy]-phenyliodine. The resulting *O*-acetyl (*S*)-isoserine is then hydrolyzed to **17** with concentrated

hydrochloric acid (82% yield) [25]. The purpose of O-acylation of **16** is to prevent oxidation of the α -hydroxy group.

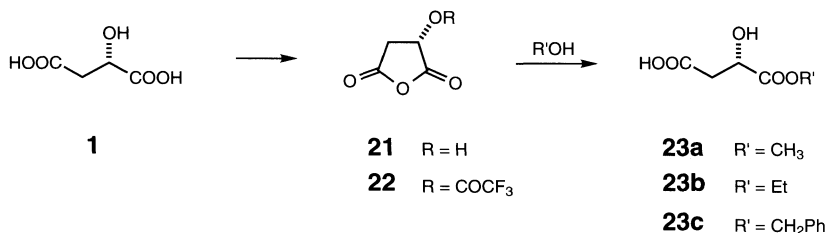
The amide group of **16** can be converted to a nitrile with acetic anhydride in pyridine at room temperature to give the relatively unstable acid **18**. Immediate hydrogenation of the nitrile with platinum oxide furnishes (*S*)-4-amino-2-hydroxybutyric acid (**19**) in 30% overall yield (Scheme 1). Conversion of **18** to the stable benzhydryl ester **20** is accomplished by treatment with diazodiphenylmethane (84% yield) [26].



Scheme 1

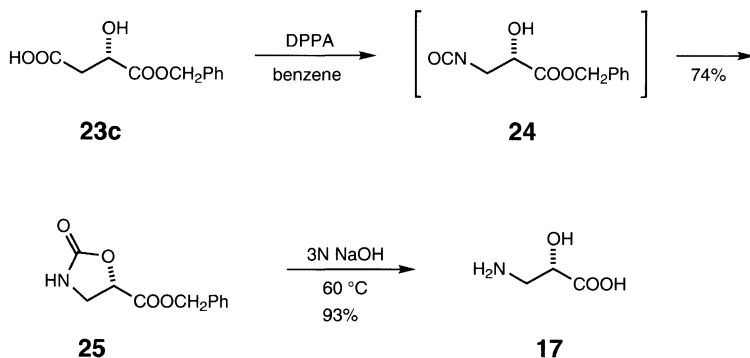
As we have just seen, hydrolysis of malic acid derivatives at the 1-position is relatively straightforward. But what if a chemist desires a malic acid half ester in which only the 4-carboxyl exists as a free acid? Derivatives of this type are also accessible from *L*-malic acid through C-1 site-selective reactions.

Applying the same strategy but varying the approach, one can take advantage of the electrophilicity of the 1-carboxyl carbonyl. This is exemplified by formation of a cyclic anhydride (**21**, **22**), which provides additional activation at the desired site of attack. Nucleophilic addition of an alcohol to the C-1 carbonyl opens the anhydride to give the monoester **23**.



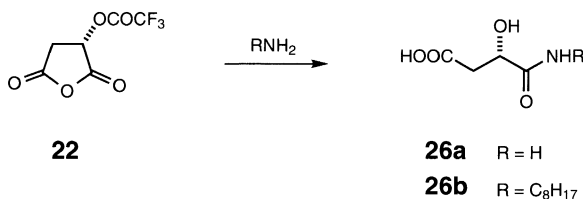
In practice, treatment of (*S*)-malic acid with DCC causes formation of the anhydride **21**. Subsequent reaction with the appropriate alcohol affords esters **23** in approximate 64% yield. A superior approach generates the anhydride **22** with trifluoroacetic anhydride. Subsequent quenching with an alcohol furnishes the desired ester **23** in essentially quantitative yield [27].

Ester **23c** has been used in a short synthesis of (*S*)-isoserine (**17**) (Scheme 2) [28]. Treatment of **23c** with diphenylphosphoryl azide gives an intermediate isocyanate **24** via a Curtius rearrangement. Spontaneous cyclization results in the formation of cyclic carbamate **25** in 74% yield. Alkaline hydrolysis affords **17** in high yield without any racemization.



Scheme 2

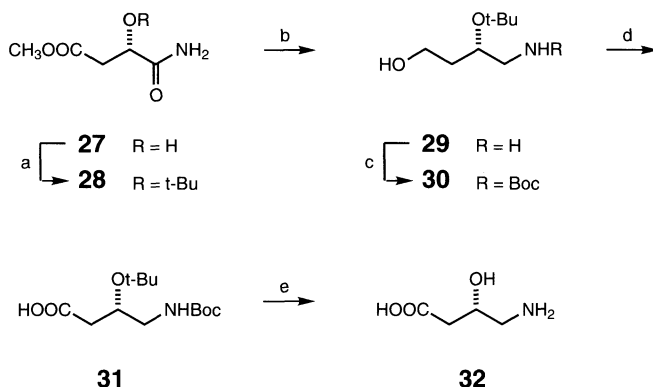
Anhydride **22** can also be opened with amines to furnish amides **26** in good yield (73–80%) [29,30].



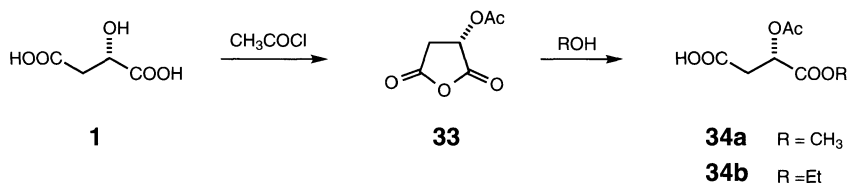
Amide **26a** can be converted directly to methyl ester **27** upon treatment with 3% methanol–HCl. This ester is used as a starting point for the synthesis of γ -amino- β -hydroxybutyric acid (**32**), a GABA derivative of great biological and synthetic importance (Scheme 3) [30].

Exhaustive reduction of both the C-1 and C-4 functionalities of *tert*-butyl-protected derivative **28** with lithium aluminum hydride furnishes amino alcohol **29**. Oxygen protection is required in order to avoid potential racemization during the reduction step. Standard OH protecting groups such as THP, Boc, or TBPS are not effective under the particular reducing and oxidizing conditions used in this synthesis. Protection of the amine with a Boc group proceeds in high yield to give **30**. Oxidation of the alcohol to carboxylic acid **31** is accomplished with zinc permanganate, after which simultaneous removal of both protecting groups under acidic conditions affords enantiomerically pure **32** in nearly quantitative yield.

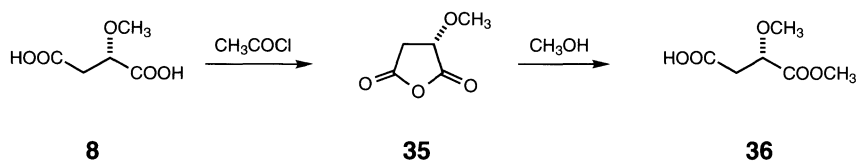
Malic acid 1-esters bearing a protecting group on the hydroxyl function are readily accessible via the anhydride route just discussed. If anhydride formation is carried out using either acetic anhydride in the presence of a catalytic amount of concentrated sulfuric acid [31] or simply with acetyl chloride as the solvent [32–36], (*2S*)-acetoxy succinic anhydride (**33**) is produced in 90–95% yield. Treatment of the anhydride with an alcohol at 50 °C for one hour affords the corresponding (*S*)-2-acetoxy-3-carboxypropionate **34** (R=CH₃, 73–100% yield [2,36]; R=Et, 80–95% yield [33,34]).

**Scheme 3**

conditions: (a) isobutylene, H_2SO_4 (70%); (b) LiAlH_4 ; (c) Boc_2O , dioxane, rt (90%);
(d) zinc permanganate, acetone (55%); (e) 4N HCl -dioxane (95%)

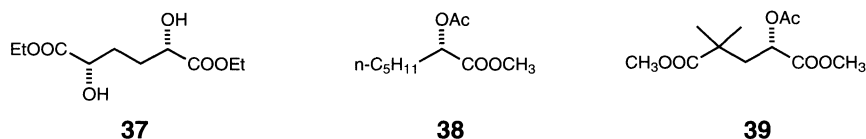


In like manner, treatment of (*S*)-methoxysuccinic acid (**8**) with acetyl chloride followed by methanol gives methyl (*S*)-2-methoxy-3-carboxypropionate (**36**) [3].



Esters **34** have been used as substrates in Kolbe electrolysis reactions. Anodic oxidative coupling of the sodium salt of **34b** gives (2*S*,5*S*)-diethyl 2,5-dihydroxyadipate (**37**) in 54% yield with >95% *ee* [37]. Electrolysis of **34a** in the presence of pentanoic acid with a stabilized current (60 V, 1.5–2 A) over a period of 50 h produces methyl (*S*)-2-acetoxyheptanoate (**38**) in 48% yield [36]. Electrolysis of **34a** with an excess of methyl dimethylmalonate in methanol containing sodium methoxide affords the (*S*)-acetoxydiester **39** [38].

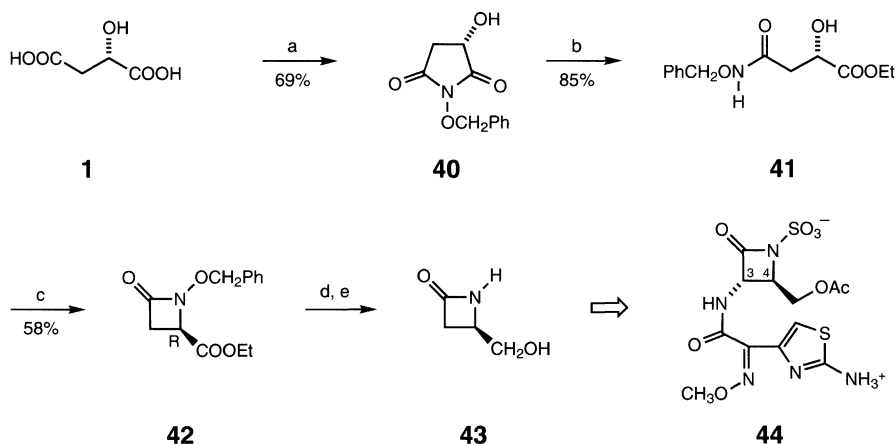
Additional reactions of esters **34** that selectively utilize the C-4 carboxyl group in further transformations are discussed in Section 3.2.4.



3-Acylamino-2-oxo-1-sulfoazetidines, several of which have been isolated from certain strains of bacteria, have attracted considerable attention due to their potent antibacterial properties. Azetidinone **44**, with a 3*S* configuration similar to that in penicillin, possesses considerable activity against Gram-negative organisms.

The azetidinone core is synthesized from L-malic acid according to the route outlined in Scheme 4 [39]. The initial two steps are a variation on the theme of ring opening of malic anhydrides with alcohols. In this case, succinimide **40** is used in place of the anhydride. Regiospecific ring opening of **40** with lithium ethoxide occurs at C-1 to produce hydroxamate **41** in high yield. Cyclization under Mitsunobu conditions affords β -lactam **42** with inversion of configuration at the C-4 carbon.

Nitrogen is introduced into the 3-position of the azetidinone ring as an azido group by reaction of TBS-protected **43** with 2,4,6-triisopropylbenzenesulfonyl azide. The reaction is stereospecific, yielding the desired *trans* 3*S*,4*R* relationship.



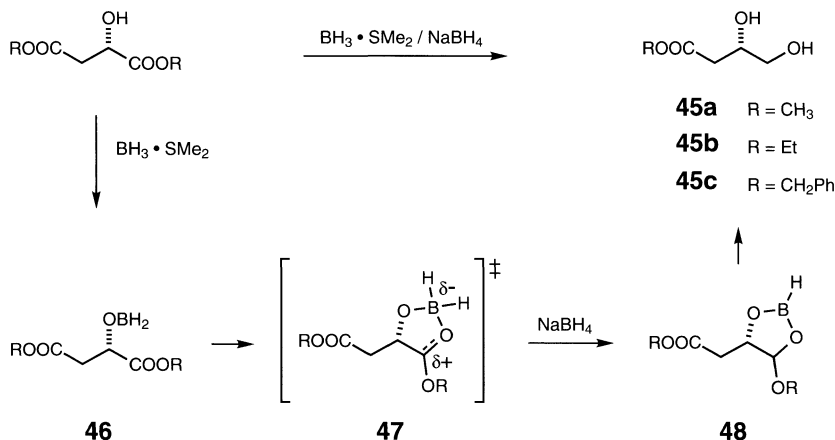
Scheme 4

conditions: (a) $\text{PhCH}_2\text{ONH}_2$, xylene, reflux 6 h; (b) LiOEt , THF, $-78^\circ\text{C} \rightarrow \text{rt}$; (c) DEAD, Ph_3P , THF; (d) H_2 (1 atm), 10% Pd/C, MeOH (55%); (e) NaBH_4 , MeOH (81%)

3.2.1.2 Reduction

Malate esters are easily reduced in a highly selective fashion using either diborane [40,41] or borane–methyl sulfide complex [42–45] in the presence of a catalytic amount of sodium borohydride (5 mol%) to give diol esters **45**. Yields of **45a** and **45b** generally range from 80–97%, while **45c** is formed in 60% yield [46]. Dimethyl (*S*)-malate is reduced with 99 : 1 selectivity as regards C-1 to C-4 ester reduction, while diethyl (*S*)-malate shows even greater selectivity (200 : 1).

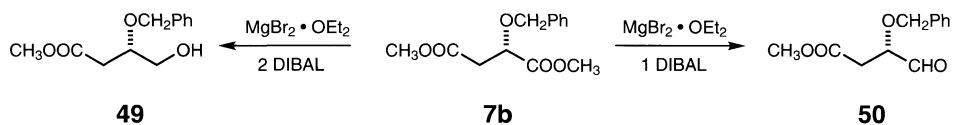
Mechanistic studies [47] have shown that neither diborane nor the BMS complex is the reducing agent. These only serve to form the initial oxyborane-type intermediate **46**. Only after the sodium borohydride is added does reduction take place. In a simplified version of the mechanism (Scheme 5), reduction proceeds under kinetically controlled conditions almost exclusively through transition state **47**, which ultimately leads to **45**.



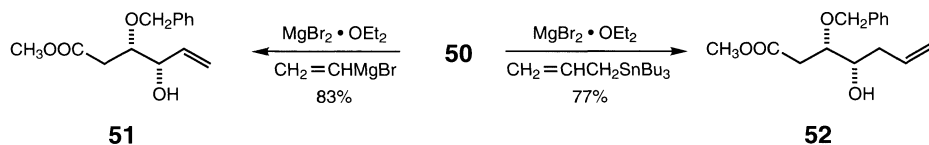
Scheme 5

Although this procedure is highly efficient, it is not applicable to malate derivatives in which the hydroxyl function carries a protecting group. No regioselectivity is observed under these circumstances. The problem can be circumvented by selective activation of the C-1 ester *via* bidentate complexation of the C-1 carbonyl and the protected hydroxyl with magnesium, which leads to 5-membered ring chelation rather than the 6-membered chelate.

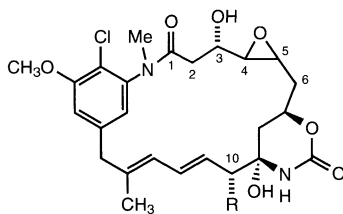
Conversion of **7b** to the mono protected diol **49** is achieved in high yield by pre-complexation with magnesium bromide etherate in methylene chloride at 0 °C followed by addition of 2 equivalents of diisobutylaluminum hydride at -40 °C [13]. As an added bonus, aldehyde **50** is also accessible by the same route with a minor variation in reaction conditions. After complexation of **7b** with magnesium bromide etherate, the reduction is carried out by adding one equivalent of diisobutylaluminum hydride at -95 °C to give **50** in 78% yield.



Aldehyde **50** is an excellent chiral intermediate in reactions with organometallics. Addition at -78 °C of vinylmagnesium bromide to **50**, that has been precomplexed with magnesium bromide etherate, affords the chelation-controlled product **51** with remarkably high diastereofacial selectivity (155 : 1). It is imperative that methylene chloride be used as the solvent in order to achieve this level of selectivity. In fact, if commercial vinylmagnesium bromide in THF is to be employed, the THF must be removed and replaced with methylene chloride [13] or else selectivity drops to 40 : 1. An analogous reaction of **50** with allyl tri-*n*-butylstannane at -23 °C furnishes chelation-controlled product **52** with 49 : 1 stereoselectivity.

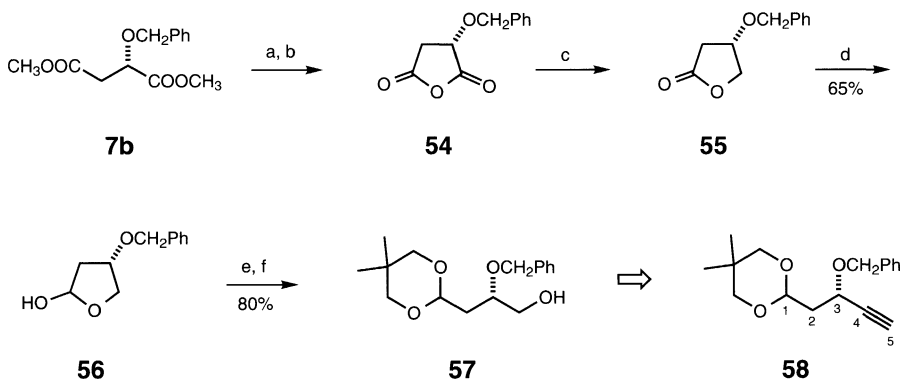


The naturally occurring maytansinoid macrocycles have been intensively investigated because of their interesting antitumor properties. The C1–C5 fragment of bis-*nor*-4,6-maytansinoid **53** is readily assembled starting from benzyl-protected dimethyl (*S*)-malate (**7b**), as shown in Scheme 6 [12].



53 R = H, OCH₃

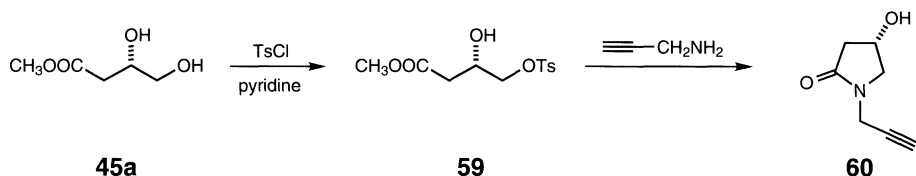
C-1 Selective reduction of malates is not restricted exclusively to the diesters, but succeeds with anhydrides as well. Selective reduction of anhydride **54** at the C-1 site with sodium borohydride affords lactone **55** in 61% overall yield from **7b**. A second reduction of the lactone carbonyl with diisobutylaluminum hydride furnishes lactol **56**, which is then converted to acetal **57** with 2,2-dimethylpropane-1,3-diol. Introduction of the required acetylene group requires an additional 5 steps.



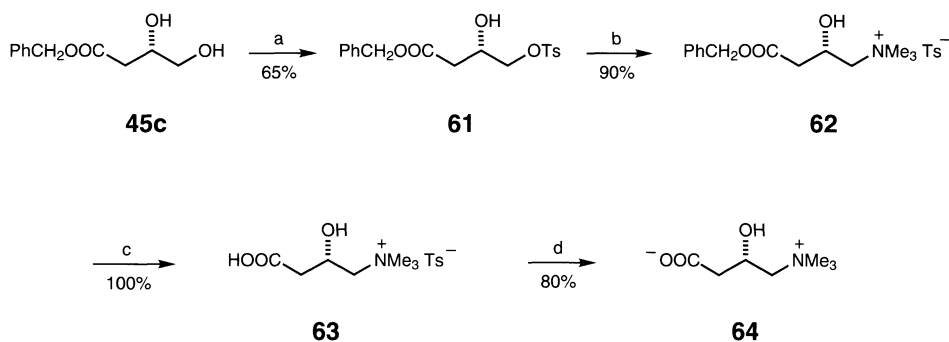
Scheme 6

conditions: (a) OH⁻; (b) CH₃COCl, reflux; (c) NaBH₄, THF; (d) DIBAL, -40 °C; (e) 2,2-dimethylpropane-1,3-diol, PTSA; (f) H⁺

The primary alcohol of diol ester **45a** is susceptible to selective activation that allows reactions to take place at the C-4 carbon. Tosylation of **45a** under standard conditions produces the crystalline 4-tosyloxy alcohol **59**. Displacement of the tosyl group with propargylamine followed by concomitant cyclization gives the propargylic pyrrolidinone **60** in 25% overall yield from L-malic acid (**1**) (the esterification and reduction steps are not shown). This pyrrolidinone is used as an intermediate in the synthesis of enantiomerically pure hydroxylated oxotremorine derivatives [40].



Tosylation of benzyl ester **45c** affords the 4-tosyloxy alcohol **61**. Displacement of the tosylate group with trimethylamine followed by hydrogenolysis of the benzyl ester furnishes (*S*)-carnitine (**64**) [46]. Attempted synthesis of **64** *via* the methyl ester **45a** fails at the hydrolysis step (leading to **63**), which proves to be sluggish. The enantiomeric (*R*)-carnitine can be synthesized by an identical sequence of reactions starting from (*R*)-malic acid (Scheme 7).

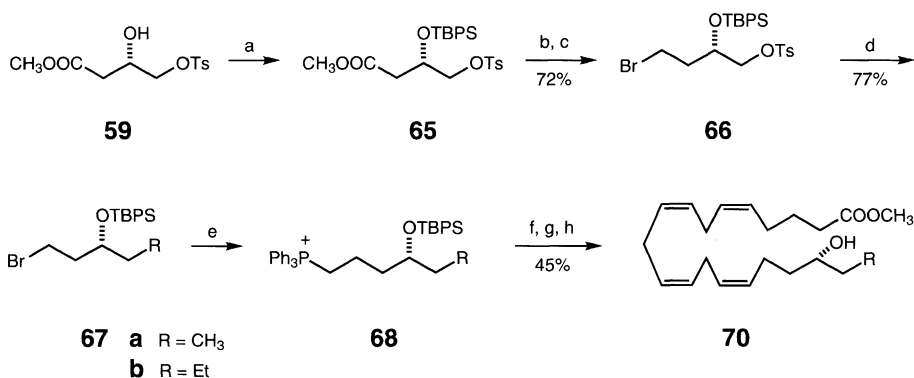


Scheme 7

conditions: (a) TsCl, pyridine; (b) NMe₃, toluene; (c) H₂, 10% Pd/C, MeOH; (d) ion exchange

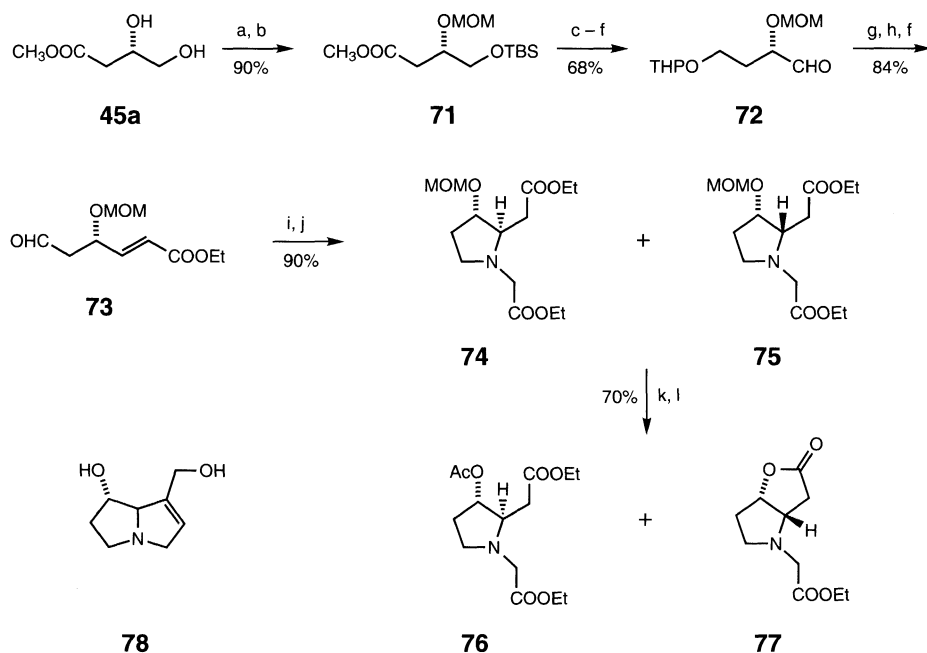
Further protection of the secondary alcohol function of tosylate **59** is accomplished by silylation with TBPS-Cl. This intermediate has been used in the enantiospecific synthesis of the 18- and 17-hydroxyeicosatetraenoic acids **70**, which are cytochrome P450 arachidonate metabolites isolated from a variety of mammalian tissues (Scheme 8) [45]. Manipulation of both ends of **65**, which involves displacement of the tosylate with an organic cuprate and conversion of the ester group to a phosphonium salt, leads to the crucial intermediate **68**. Generation of the ylide (step f) followed by Wittig reaction with aldehyde **69** furnishes the desired (*R*)-hydroxyeicosatetraenoates **70**. Mitsunobu inversion of the hydroxyl group (PhCOOH, DEAD, Ph₃P then NaOMe, MeOH) leads to the corresponding (*S*)-hydroxyeicosatetraenoates in good yield.

Selective silylation of the primary hydroxyl group of **45a** followed by MOM protection of the remaining secondary alcohol furnishes differentially protected diol ester **71** in high yield [48]. As shown in Scheme 9, **71** is readily converted to the (2*R*,3*S*)-pyrrolidine **76**, which is a potentially useful precursor for the synthesis of optically active necine bases such as (+)-heliotridine (**78**). Functional group manipulation of **71** leads to protected aldehyde **73**, which undergoes a tandem reductive alkylation with glycine ethyl ester and intramolecular Michael addition to furnish a 3 : 2 diastereomeric mixture of **74** and **75**. The mixture is easily separated after deprotection of the MOM group and subsequent acetylation. Under these conditions pyrrolidine **74** simply becomes O-acetylated to give optically pure **76**, whereas **75** cyclizes to

**Scheme 8**

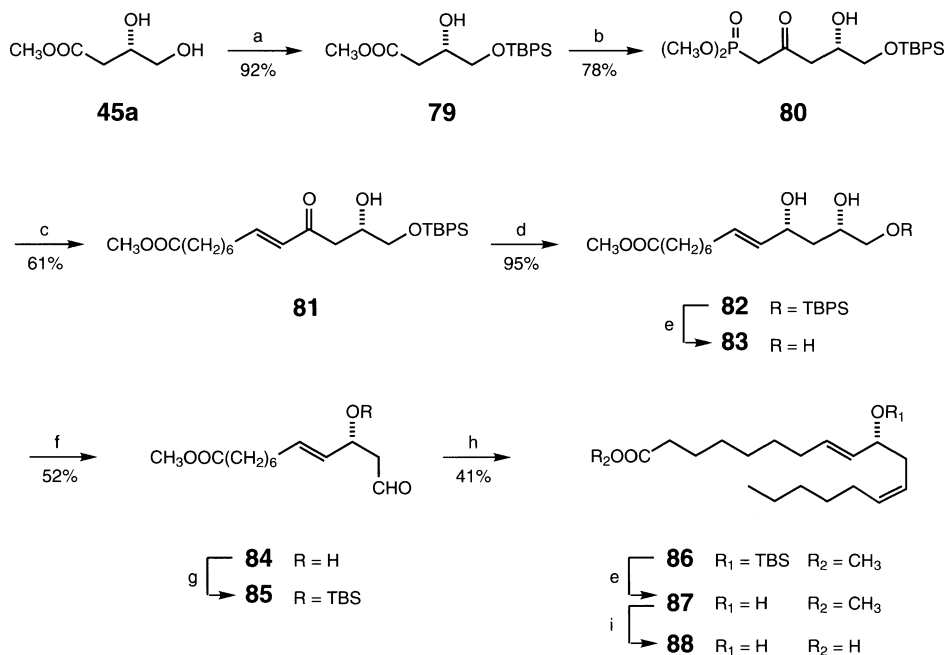
conditions: (a) TBPS-Cl, Et₃N, THF (1:3), AgNO₃ (1.5 eq); (b) DIBAL, CH₂Cl₂, -78 °C; (c) CBr₄, Ph₃P, CH₂Cl₂, 0 °C; (d) R₂CuLi (3 eq), ether, 0 °C; (e) Ph₃PCH₂Li, THF, -78 °C → -30 °C; (f) NaHMDS, THF, -40 °C; (g) CH₃OOC(CH₂)₃CH=CHCH₂CH=CHCH₂CH=CHCH₂CHO (**69**), -78 °C → 0 °C; (h) Bu₄NF, THF

form the Geissman–Weiss-type lactone **77** due to the *cis* relationship between the ester and the hydroxyl group.

**Scheme 9**

conditions: (a) TBS-Cl, DMAP, Et₃N, CH₂Cl₂, 0 °C; (b) MOM-Cl, *i*-Pr₂NEt, CH₂Cl₂, 0 °C → rt; (c) LiAlH₄, THF, -40 °C; (d) DHP, PPTS, CH₂Cl₂; (e) Bu₄NF, THF; (f) Swern [O]; (g) (*i*-PrO)₂P(O)CH₂COEt, NaH, THF, 0 °C; (h) PPTS, EtOH, 50 °C; (i) EtOOCCH₂NH₂⁺HCl, MeOH, 0 °C; (j) NaBH₃CN, MeOH, 0 °C; (k) HCl, THF, EtOH; (l) Ac₂O, DMAP, CH₂Cl₂

A synthesis of the naturally occurring fungitoxic C-18 hydroxy fatty acid **88**, isolated from the stromata of *Epichloe typhina*, begins with diol **45a** whereby the chiral hydroxyl group is used to induce asymmetry at the lone chiral center of the target molecule (Scheme 10) [49]. After silylation of the primary hydroxy group of **45a** with a TBPS group, compound **79** is converted with the lithium salt of dimethyl methylphosphonate to the β -ketophosphonate **80**. This is subjected to a Horner–Emmons reaction with methyl 8-oxooctanoate to give enone **81** as a single product. Stereoselective reduction of the enone carbonyl with zinc borohydride affords *syn* diol **82** as a result of 1,3-asymmetric induction (70% *de*). Oxidative cleavage of triol **83** produces β -hydroxy aldehyde **84**, thus destroying the original asymmetric center furnished by the malic acid. A Wittig olefination completes the carbon skeleton of the target molecule (*Z*:*E* ratio = 95 : 5). Desilylation followed by enzymatic hydrolysis of **87** with pig liver esterase gives the desired product **88** with 70% *ee*.



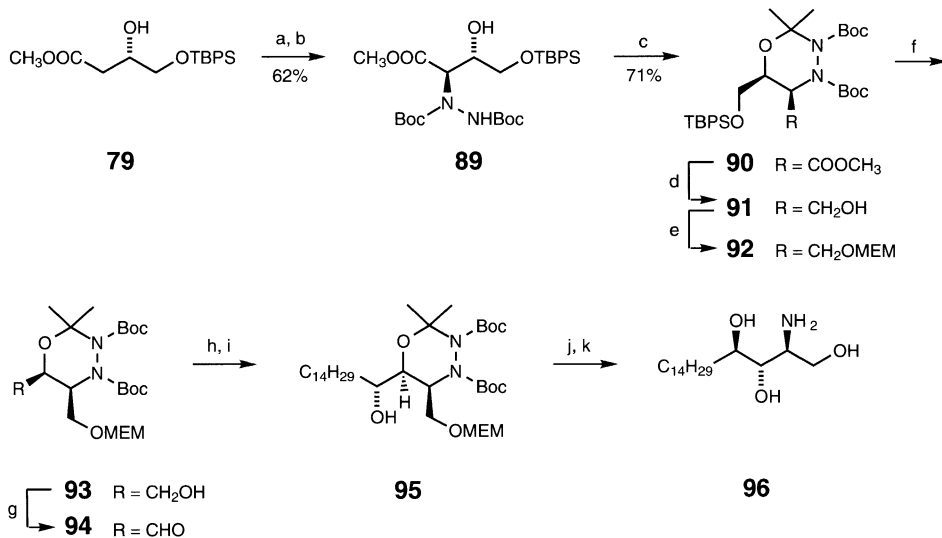
Scheme 10

conditions: (a) TBPS-Cl, HMPA, pyridine, CH_2Cl_2 , 0 °C; (b) $(\text{CH}_3\text{O})_2\text{P}(\text{O})\text{CH}_3$, *n*-BuLi, THF, -78 °C; (c) $\text{CH}_3\text{OOC}(\text{CH}_2)_6\text{CHO}$, LiCl, *i*-Pr₂NEt; (d) $\text{Zn}(\text{BH}_4)_2$, ether, -20 °C; (e) Bu₄NF, THF (89%); (f) NaIO₄, H₂O/acetone; (g) TBS-Cl, poly(4-vinylpyridine), HMPA; (h) $\text{Ph}_3\text{P}=(\text{CH}_2)_4\text{CH}_3$, ether, -78 °C; (i) PLE, 0.1M phosphate buffer (80%)

In an interesting application of enolate chemistry associated with silyl derivative **79**, electrophilic amination allows convenient access to the synthetic equivalent of 2-deoxy-2-aminotetroses. This methodology has been applied to the stereoselective synthesis of *D-ribo*-C₁₈-phytosphingosine (**96**) (Scheme 11) [41].

Reaction of the enolate of **79** with di-*tert*-butylazodicarboxylate results in the formation of a 2 : 1 mixture of *anti* isomer **89** and the *syn* isomer (not shown). The two isomers are easily

separated and then converted to the *N,O*-isopropylidene acetal **90**. Standard functional group manipulation converts the methyl ester to a protected alcohol (**92**), and the silyl-protected alcohol to an aldehyde (**94**). Addition of tetradecylmagnesium bromide to **94** produces a 65:35 mixture of the desired *anti* isomer (**95**) together with the *syn* isomer (not shown). Diastereoselectivity is enhanced by using lithium tetradecyne in the presence of HMPA (*anti* : *syn* = 85 : 15). Catalytic hydrogenation of the acetylenic triple bond furnishes **95** in 80–90% yield. The final product is released from the heterocyclic system by simultaneous acidic hydrolysis of the acetal, MEM, and Boc groups to give an intermediate hydrazino derivative whose N–N bond is then cleaved by catalytic hydrogenolysis. Compound **96** is finally isolated as its tetraacetyl derivative by exhaustive acetylation with acetic anhydride in pyridine.

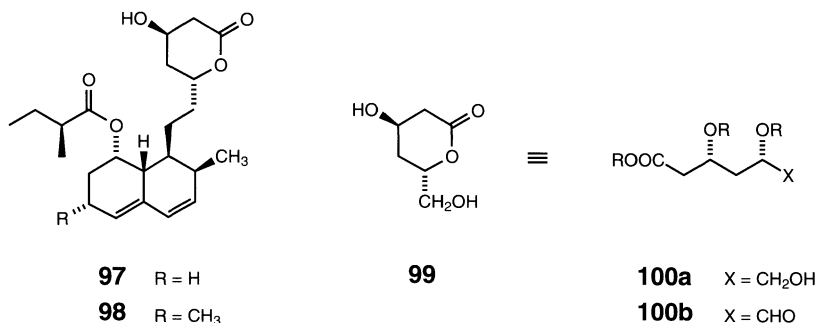


Scheme 11

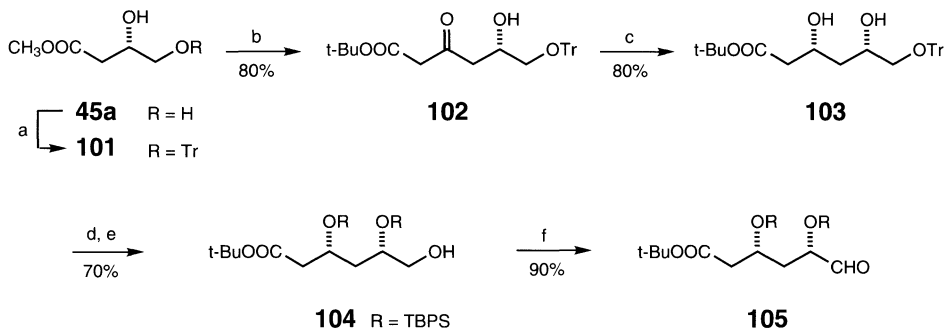
conditions: (a) LDA, THF; (b) BocN=NBoc; (c) $\text{CH}_2=\text{C}(\text{OCH}_3)\text{CH}_3$, PTSA; (d) CaCl_2 , NaBH_4 , THF, EtOH (90%); (e) MEM-Cl, Et_3N , CH_3CN (91%); (f) Bu_4NF , THF (91%); (g) Swern [O]; (h) $n\text{-C}_{12}\text{H}_{25}\text{C}\equiv\text{C-Li}$, THF, HMPA (71%); (i) H_2 , 10% Pd/C, EtOH (80–90%); (j) HOAc, 1N HCl (2:1), 70 °C; (k) H_2 , PtO_2 , EtOH/ H_2O

The fungal metabolites compactin (**97**) and mevinoлин (**98**) are potent inhibitors of cholesterol biosynthesis that target the rate-limiting enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (HMG–CoA reductase). Compounds of this type comprise a class called “statins”, of which **98**, called Lovastatin, was the first to reach the market as a cholesterol-lowering agent in man.

Intense research has been carried out by a large number of groups to modify and simplify the lower hydrophobic portion of the molecule, which contains six asymmetric centers. Many of these groups have adopted similar synthetic strategies, which disconnect the lactone fragment **99** from the lower half by breaking the ethylene bridge C–C bond. Typically, the *syn*-dihydroxy ester **100**, a ring-opened version of the lactone, serves as a useful synthetic equivalent for **99** itself. Strategically, alcohol **100a** can be used in coupling reactions with suitably functionalized lower-half synthons, or aldehyde **100b** can enter into a Wittig-type reaction to join the two partners.



Intermediates of type **100** are readily synthesized from (*S*)-malic acid via diol ester **45a** (Scheme 12) [50]. Tritylation of the primary alcohol gives mono protected diol **101**. Reaction of **101** with an excess of *tert*-butyl lithioacetate furnishes the hydroxy β -ketoester **102**. The key reaction, a *syn*-selective reduction of the β -hydroxy ketone moiety using diethylmethoxyborane–sodium borohydride gives *syn*-3,5-dihydroxy ester **103** with >99% *de*. Silylation of both hydroxy groups followed by detritylation furnishes **104**, equivalent to **100a**, the alcohol version of **100**. Oxidation of the primary alcohol with PCC affords **105**, analogous to aldehyde version of **100b**.



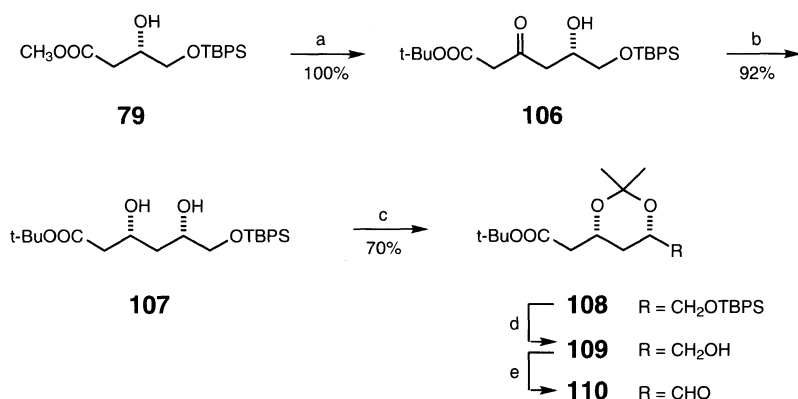
Scheme 12

conditions: (a) trityl chloride, pyridine, CH₂Cl₂, 0° → 25 °C (85%); (b) LiCH₂COO^tBu (4.4 eq), THF, –78° → 0 °C; (c) Et₂BOCH₃, NaBH₄, THF–MeOH, –78 °C; (d) TBPS–Cl, imidazole, DMF, 70 °C, 18 h; (e) CF₃COOH, CH₂Cl₂; (f) PCC, 4Å molecular sieves, CH₂Cl₂

A minor variation in the preparation of synthon **100** is illustrated in Scheme 13 [51]. In this instance the *syn*-selective reduction **106** → **107** proceeds with 90% *de*, and the resulting diol is protected as an acetonide (**108**).

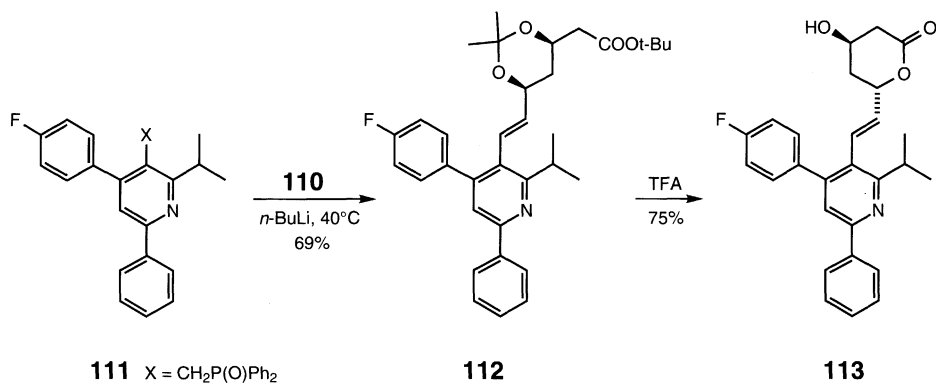
Intermediate aldehyde **110** has been used to synthesize HR 780 (**113**), a fully synthetic HMG–CoA reductase inhibitor that exhibits higher potency and longer half-life than mevinnolin (**98**) [51]. A Horner olefination of phosphane oxide **111** with **110** gives adduct **112** with an *E/Z* ratio of 98 : 2. Deprotection of **112** with trifluoroacetic acid and concomitant lactonization forms the desired molecule in good yield.

An example in which an HMG–CoA reductase inhibitor is convergently synthesized by a coupling methodology is illustrated in Scheme 14. The target molecule **117**, an alkylated phenol, surpasses the activity of mevinnolin (**98**) both *in vitro* and *in vivo* [52]. The critical



Scheme 13

conditions: (a) LiCH₂COOt-Bu (3.5 eq), THF, -70 °C; (b) Et₃B, THF-MeOH, NaBH₄, -70 °C; (c) Me₂C(OMe)₂, PTSA, acetone; (d) Bu₄NF, THF (80%); (e) Swern [O] (97%)

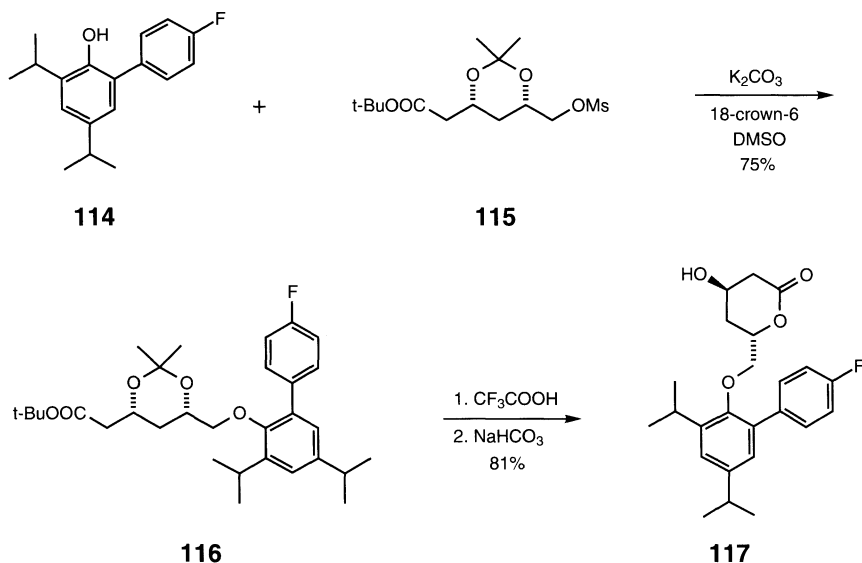


coupling step is accomplished by displacement of the mesylate **115**, generated from acetonide **109**, with phenol **114**. Mesylate **115** is readily prepared from **109** by treatment with methanesulfonyl chloride and pyridine in methylene chloride (90% yield). Other leaving groups such as tosylate or iodide were investigated but found to produce products of reduced stereochemical integrity and purity. Removal of the acetonide protecting group and lactonization furnishes optically pure lactone **117** in good overall yield.

As can be seen from the two previous examples as well as many others cited in the literature [53], the complex stereochemistry of the decalin portion of compactin or mevillin is not required for biological activity, and in many instances, replacement with “flat” fragments results in enhanced activity relative to the natural products.

Although synthons **100** are extremely useful for construction of lactones associated with HMG-CoA reductase inhibitors, they are not limited exclusively to that role. Simple methylation α to the ester group generates useful building blocks for the synthesis of such polyfunctionalized natural products as scytophycin C or roxaticin. The requisite hydroxy β - ketoester **120** is prepared from **45a** as shown in Scheme 15 [54].

Diastereoselective reduction of the keto function can be tailored to produce either 3,5-*syn* (**121**) or *anti* (**122**) dihydroxy esters simply by choosing the appropriate reducing agent.



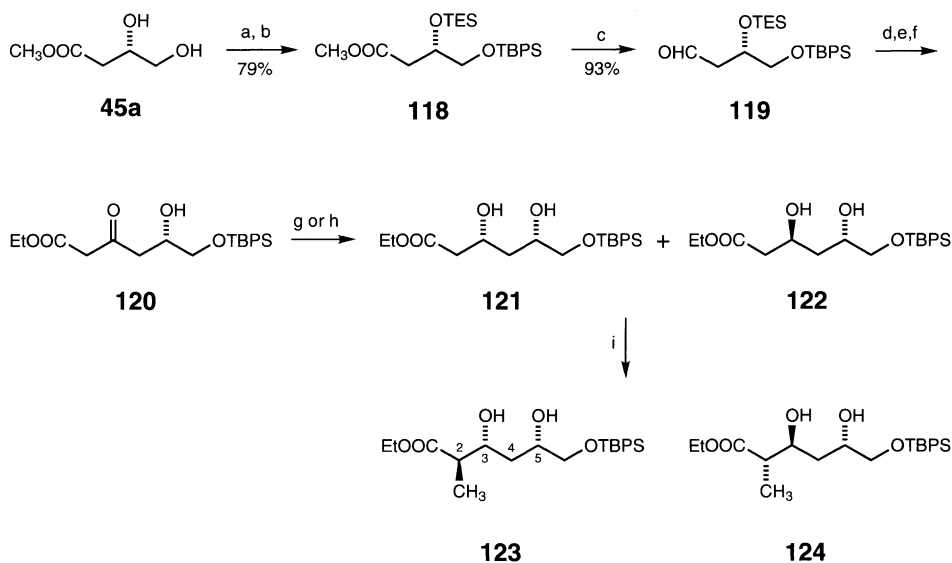
Scheme 14

Diethylmethoxyborane–sodium borohydride gives the *syn* product **121** in 96% yield and 30 : 1 diastereoselectivity, whereas tetramethylammonium triacetoxyborohydride furnishes the *anti* product **122** in 90% yield and 1 : 12 diastereoselectivity. Methylation of the trianion of either **121** or **122** using 5 equivalents of LDA and 10 equivalents of methyl iodide gives 2,3-*anti* **123** (63% yield, 6 : 1 diastereoselectivity) or 2,3-*anti* **124** (61% yield, 13 : 1 diastereoselectivity) respectively.

The stereoselectivity of the methylation reactions can be reversed, thus producing a 2,3-*syn* relationship, by first lactonizing the 3,5- dihydroxy esters **121** or **122** and then performing the alkylation on the lactones (Scheme 16). Methylation of **125** gives **126** (33 : 1 diastereoselectivity), while methylation of **128** affords **129** (1 : 18 diastereoselectivity). In either case the stereochemistry of the newly introduced methyl group is governed primarily by the C-3 hydroxyl group and not the C-5 substituent. Acetonide formation then furnishes the appropriate protected synthons **127** and **130**, which are complementary to **123** and **124**.

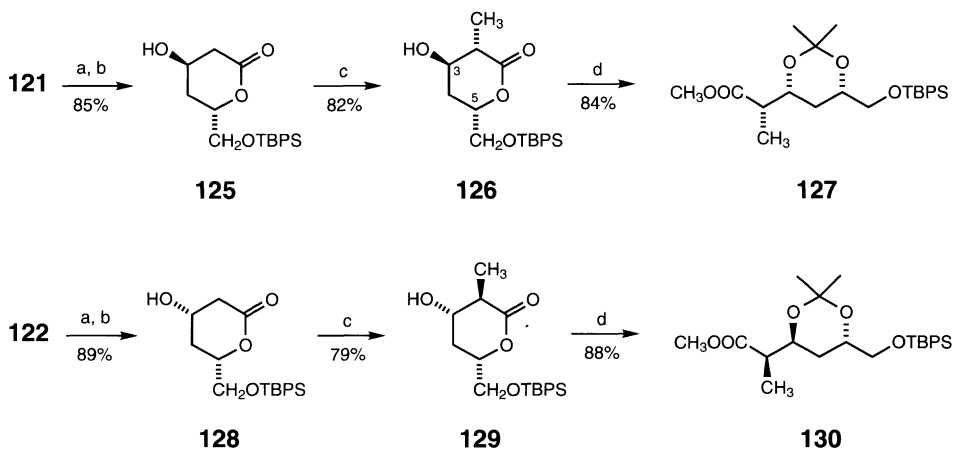
A 13-step synthesis of benzoylpedarin (**140**), a key building block for the construction of pederin, has been reported starting with (*S*)-malic acid *via* diol ester **45a**, as shown in Scheme 17 [43]. In the initial O-methylation step, **45a** \rightarrow **131**, alkylation must be accomplished under mild conditions (diazomethane–silica gel) in order to obtain high yield. Under standard basic conditions the product **131** tends to undergo elimination.

The two key steps in the synthesis entail introducing two new stereocenters (**132** \rightarrow **136** and **137** \rightarrow **138**) by an aldol-type reaction using allylboronates **133** and **134** as aldehyde enolate equivalents. In the first condensation, the newly formed hydroxyl stereocenter of **136** is produced with 87% diastereoselectivity. This high selectivity can be rationalized by assuming that the reactant adopts a chair transition state (**135**) with an equatorial arrangement of the aldehyde residue. The second aldol reaction (**137** \rightarrow **138**) proceeds with 80% diastereoselectivity due to the “mismatched pair” of reactants. Nevertheless, this selectivity is quite respectable.



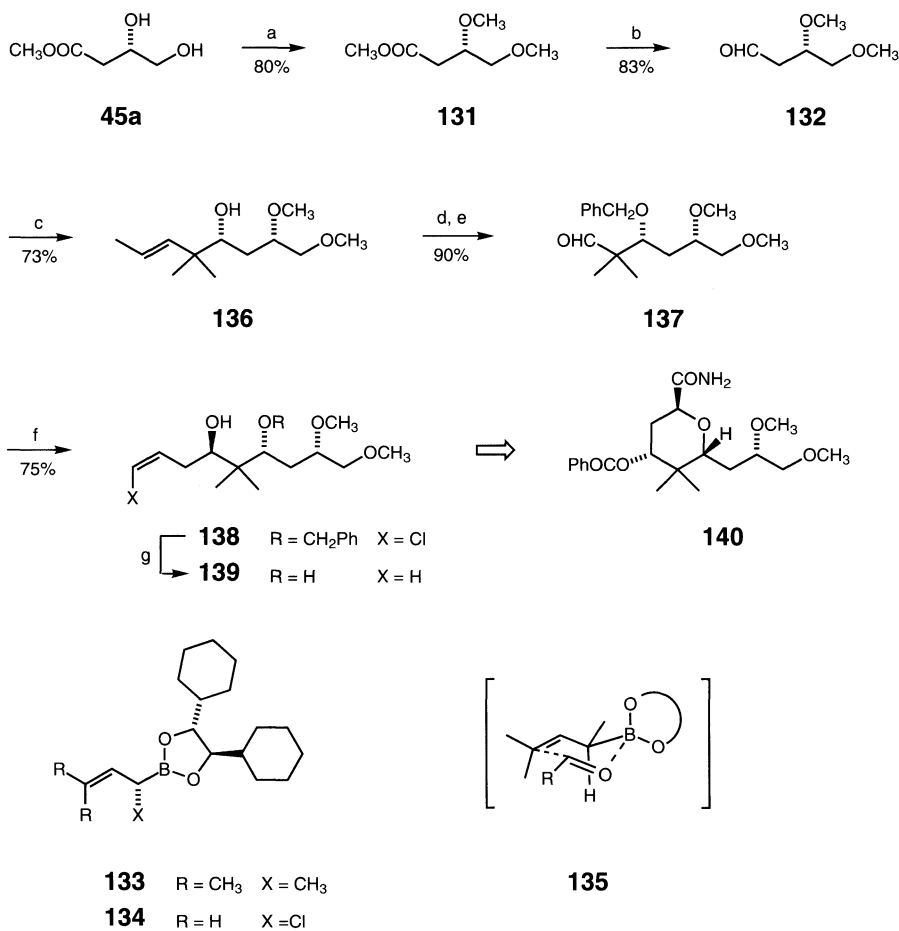
Scheme 15

conditions: (a) TBPS-Cl, imidazole, DMF, 0 °C; (b) Et_3SiCl , 0 °C; (c) DIBAL, ether, -78 °C; (d) CH_3COOEt , LDA, THF, -78 °C (92%); (e) PDC, 4Å molecular sieves, CH_2Cl_2 (81%); (f) HOAc, H_2O , THF (96%); (g) Et_2BOCH_3 , NaBH_4 , THF, -78 °C; (h) $\text{Me}_4\text{NBH}(\text{OAc})_3$, HOAc, CH_3CN , 0 °C; (i) LDA, THF-HMPA, CH_3I , -78 °C



Scheme 16

conditions: (a) LiOH, THF, H_2O , 0 °C; (b) 4Å molecular sieves, benzene, reflux; (c) LDA (3 eq), THF-HMPA (5 eq), -40 °C then CH_3I (10 eq), -78 °C; (d) DMP, MSA, MeOH, CH_2Cl_2



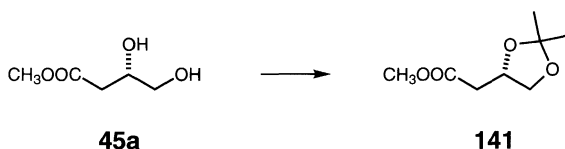
Scheme 17

conditions: (a) CH₂N₂, silica gel, ether; (b) DIBAL, toluene, -78 °C; (c) **133**, petroleum ether, 40–60 °C, 4 kbar; (d) NaH, PhCH₂Br, DMF; (e) O₃, CH₂Cl₂, -78 °C; (f) **134**, THF, -78 °C; (g) Li, NH₃, THF, -78 °C

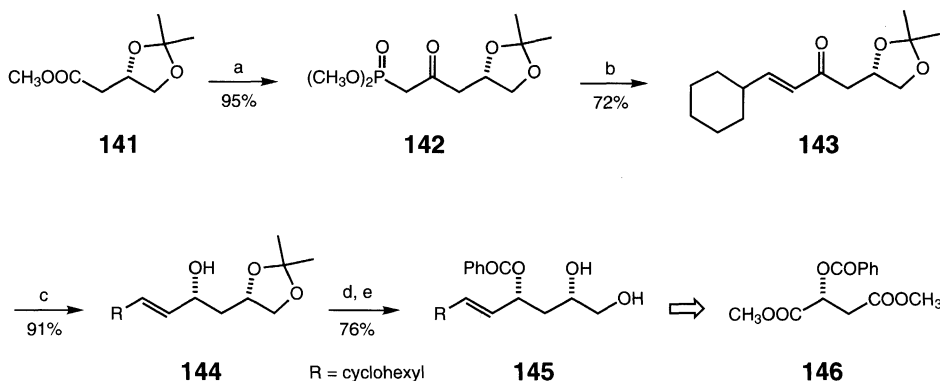
Substitution of both the two hydroxyl groups in diol ester **45a** simplifies manipulation of the remainder of the molecule. As just shown, the dimethoxy analog **131** proved extremely useful for the purpose it was designed for, but methoxy groups generally are not suitable for hydroxyl protection if they ultimately must be removed.

Incorporation of both the hydroxyls of **45a** into an acetonide nicely protects both functionalities, and the protection is easily removed under mild acidic conditions. This strategy is accomplished by treating **45a** with acetone and PTSA (73% yield) [22], 2,2-dimethoxypropane and PPTS (93% yield) [55], or 2-methoxypropene and PPTS (70–82% yield) [44] to give the desired acetonide **141**.

In a rather lengthy transformation of (*S*)-malic acid, acetonide **141** is converted to β -ketophosphonate **142** by reaction with the lithium salt of dimethyl methylphosphonate (Scheme 18) [49]. A Horner–Emmons reaction with cyclohexancarboxaldehyde produces



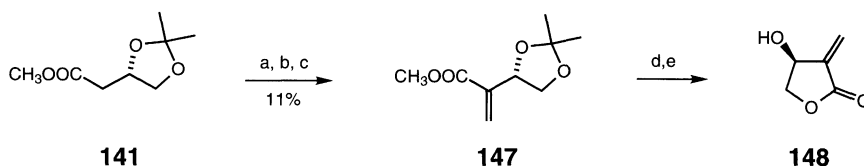
enone **143** as a single product. Diastereoselective reduction of the enone is best carried out with zinc borohydride, which gives predominantly the 1,3-*syn* product **144** in a 90 : 10 ratio. Benzoylation of the alcohol followed by deacetalization furnishes diol **145**. Conversion of the diol to an ester (NaIO₄; Jones oxidation; CH₂N₂) gives dimethyl (*R*)-*O*-benzoylmalate (**146**).



Scheme 18

conditions: (a) LiCH₂P(O)(OCH₃)₂, THF, -78 °C; (b) C₆H₁₁CHO, LiCl, *i*-Pr₂NEt; (c) Zn(BH₄)₂, ether, -20 °C; (d) PhCOCl, pyridine, CH₂Cl₂; (e) PTSA, MeOH

Acetonide **141** has also been used in a short synthesis of (-)-tulipalin B (**148**), a naturally occurring lactone with cutaneous allergenic activity (Scheme 19) [22]. Methylenation of **141** is accomplished by treatment of the enolate anion with Eschenmoser salt, followed by permethylation and elimination of the resulting trimethylammonium salt. Unfortunately, the yield is rather low, but unreacted **141** can be recovered in 80% yield. Saponification of the ester and subsequent acid-catalyzed deprotection with concomitant lactonization furnishes **148**.

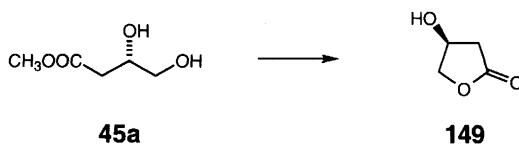


Scheme 19

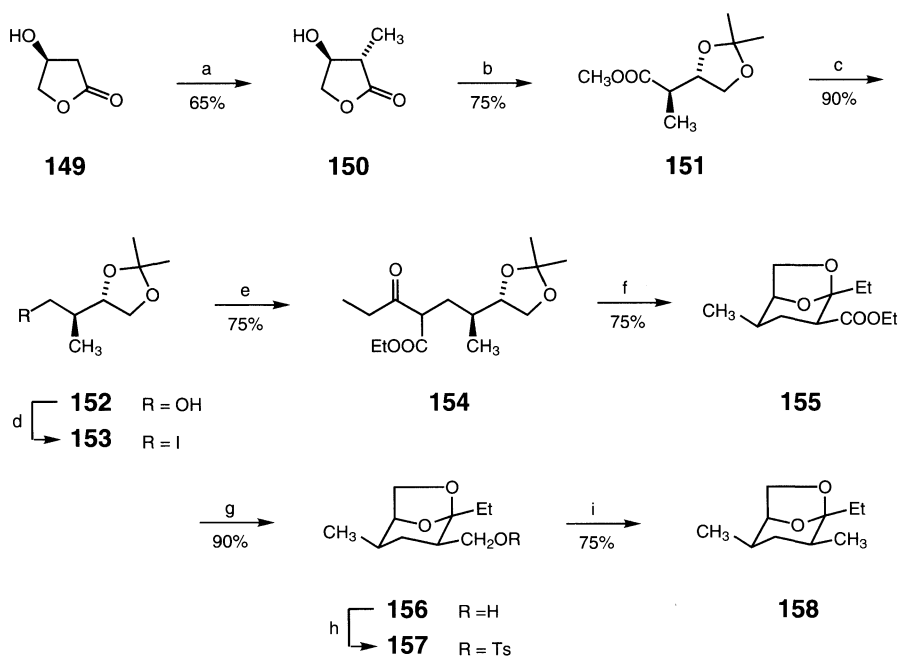
conditions: (a) LDA, CH₂=N⁺Me₂⁻; (b) CH₃I; (c) DBU, acetone; (d) Ba(OH)₂; (e) 1N HCl

Please refer to Section 3.3.1.1.1 for further uses of acetonide **141**.

(*S*)-3-Hydroxy-4-butanolide (**149**) is a useful precursor for the synthesis of natural products. It can be conveniently prepared by lactonization of diol ester **45a** using trifluoroacetic acid (90% yield) [42] or sodium borohydride (83% yield) [2].



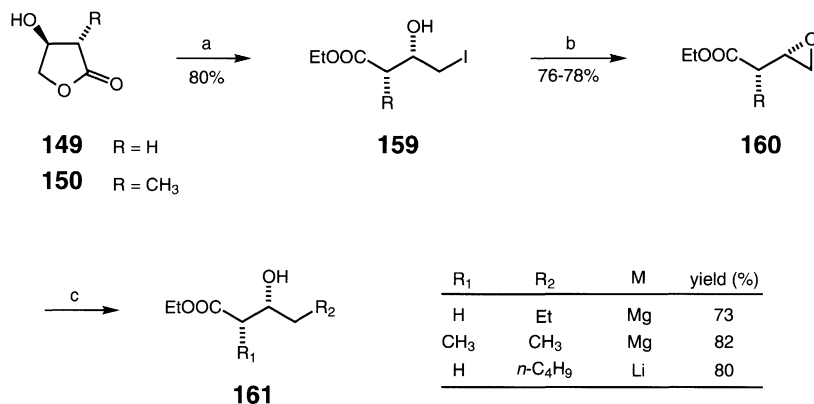
(-)- α -Multistriatin (**158**), one of the essential components of the aggregation pheromone of the European elm bark beetle *Scolytus multistriatus*, is synthesized in optically pure form starting from lactone **149** (Scheme 20) [56]. Alkylation of **149** at -95°C furnishes the *trans* lactone **150** with a *trans*:*cis* ratio of 98:2. After opening the lactone under acidic conditions and protecting the diol as an acetonide, intermediate **151** is converted in 3 steps to iodide **153**. Alkylation of ethyl propionylacetate with **153** under phase-transfer conditions gives the β -ketoester **154**, which contains all the necessary carbons for the skeleton of the target molecule. Cyclization under acidic conditions produces a 75:25 mixture of diastereomers from which the major equatorial ester **155** is isolated by chromatography. A 3-step transformation of the ester to a methyl group completes the synthesis of the natural product.



Scheme 20

conditions: (a) 2 LDA, CH_3I , THF, -95°C ; (b) DMP, PTSA, MeOH, acetone; (c) LiAlH_4 , ether (99%); (d) TsCl, pyridine, 0°C then NaI, acetone (98%); (e) ethyl propionylacetate, NaOH, $\text{Bu}_4\text{N}^+\text{HSO}_4^-$; (f) 3N HCl, CH_3CN , 50°C ; (g) LiAlH_4 , ether, 10°C ; (h) TsCl, pyridine, DMAP, CH_2Cl_2 (85%); (i) NaBH_4 , DMSO, 50°C

In the presence of ethanol, butanolides **149** or **150** undergo mild cleavage with trimethylsilyl iodide to form the iodohydrin **159** in good yield. Cyclization of **159** to epoxide **160** under basic conditions (e.g., sodium carbonate) leads to isomerization within 5 min, but use of silver oxide affords **160** with no racemization. Opening the epoxide with cuprates furnishes β -hydroxyesters **161** with >99% *ee* (Scheme 21) [57]. The scope of this reaction can be extended to include cuprates derived from substituted vinyl halides.



Scheme 21

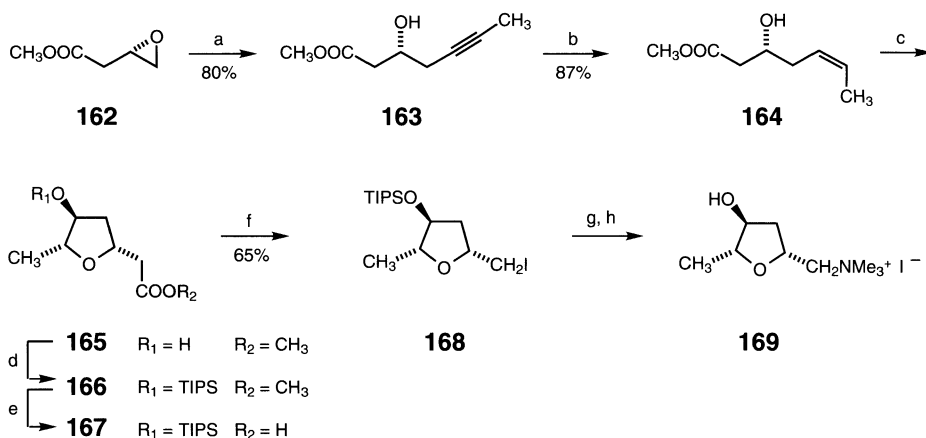
conditions: (a) TMSI, EtOH, CH₂Cl₂; (b) Ag₂O, glyme, reflux; (c) (R₂)₂CuM, THF

(+)-Muscarine, a metabolite from the Fly Agaric mushroom *Amanita muscaria*, has attracted much interest because of its potent acetylcholine agonist properties. A synthesis of its enantiomer, (–)-muscarine iodide (**169**), is outlined in Scheme 22 [58]. The synthesis begins with epoxide methyl ester **162**, which is prepared analogously to the ethyl ester **160** (Scheme 21). The key steps in the synthesis are cyclization to the hydroxy tetrahydrofuran **165**, which produces a 94 : 6 epimeric mixture at C-4 (separable by chromatography), and the Barton–Hunsdiecker degradation of **167** to the crucial iodide **168**. If the synthesis were conducted with (*R*)-malic acid instead of (*S*)-malic acid it should be possible to prepare the naturally occurring (+)-muscarine by this route.

3.2.1.3 Cyclization

The close proximity of the hydroxyl group and the 1-carboxyl function in malic acid provides a “handle” for differentiation between the two carboxylic acid functions. The tendency toward 5-membered ring formation rather than 6-membered rings permits this differentiation to be realized in cyclization reactions. This Section is devoted to cyclizations incorporating either the oxygen or the carbon atom of the 1-carboxyl group.

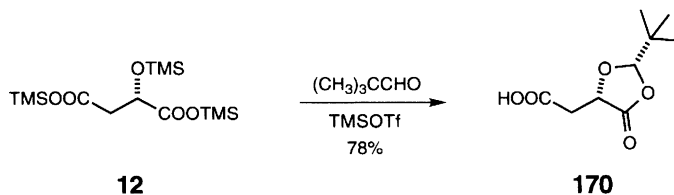
(*S*)-Malic acid (**1**) reacts with aldehydes or ketones under acidic catalysis to form dioxolanones. Of particular interest is the reaction of **1** with pivaldehyde in the presence of PTSA and sulfuric acid, which produces *cis*-dioxolanone **170** in 67% yield [59]. The choice of solvent is crucial to ensuring high *cis*-stereoselectivity. If the reaction is carried out in benzene, a 3 : 2 equilibrium mixture of *cis* and *trans* isomers is obtained. Under heterogeneous conditions in pentane the ratio of *cis* to *trans* isomers increases dramatically: to 50 : 1 (> 98% *ds*).



Scheme 22

conditions: (a) propyne, *n*-BuLi, THF, -78°C , $\text{BF}_3\cdot\text{OEt}_2$; (b) H_2 , 5% Pd/BaSO₄, quinoline, EtOAc; (c) I_2 (3 eq), NaHCO₃ (3 eq), CH₃CN; (d) TIPS triflate, *i*-Pr₂NEt, CH₂Cl₂, 0°C (95%); (e) KOH, MeOH, H₂O (98%); (f) (COCl)₂, benzene, DMF, pyridine, then N-hydroxypyridine-2-thione then CH₃; (g) Bu₄NF, THF; (h) Me₃N, EtOH

Even greater diastereoselectivity is achieved by performing the cyclization with silylated malate **12** at -25°C in the presence of 9 mol% trimethyl trifluoromethanesulfonate. Dioxolanone **170** is obtained with a *cis*:*trans* ratio 100:1 [21]. The stereoselectivity in this reaction is highly temperature dependent. Raising the reaction temperature to 0°C drastically reduces the *cis*:*trans* ratio (to 4:1).

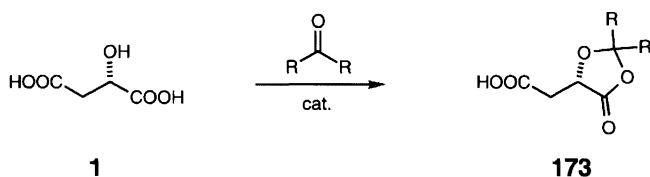
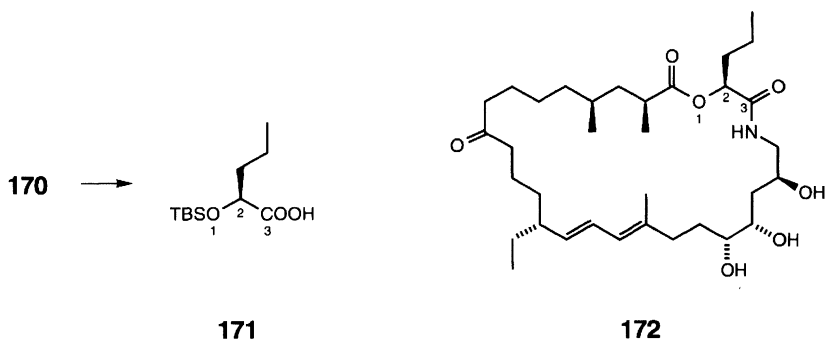


A Kolbe cross-coupling electrolysis reaction of **170** with propionic acid (MeOH, Et₃N, 35°C) furnishes methyl (*S*)-2-hydroxypentanoate which, after protection (TBS-Cl, imidazole, DMF) and saponification (KOH, EtOH), gives the TBS-protected α -hydroxy acid **171** in 58% overall yield [60]. This hydroxy acid supplies the O-1 to C-3 fragment in the convergent synthesis of the antibiotic myxovirescine (**172**).

Although useful in generating chiral fragments, dioxolanone **170** is primarily used for C-2 site-selective reactions on the malic acid framework. These are discussed further in Section 3.2.2.2.

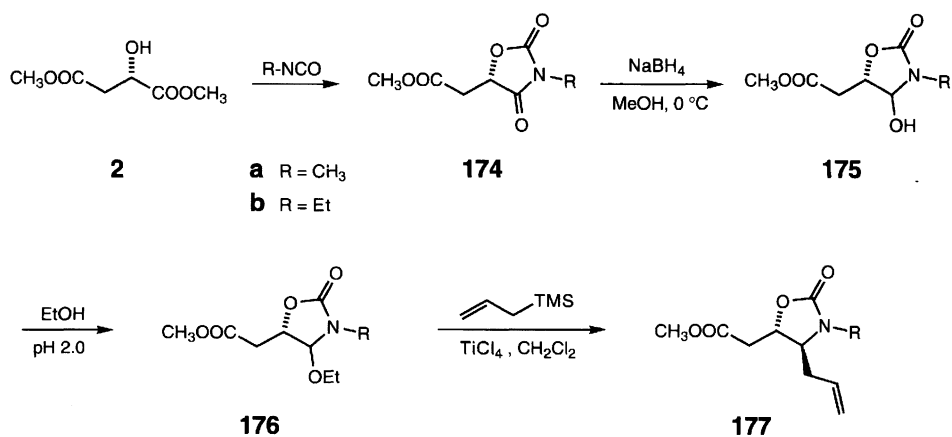
Formaldehyde, 2,2-dimethoxypropane, or cyclohexanone reacts with (*S*)-malic acid under acidic catalysis to form dioxolanones of type **173**. These are primarily used for C-4 site-selective reactions on the malic acid framework, and are discussed in Section 3.2.4.

Cyclization of dimethyl (*S*)-malate (**2**) with methyl or ethyl isocyanate affords oxazolidin-2,4-diones (**174**) in 60 or 62% yield, respectively. This heterocyclic system provides the basic



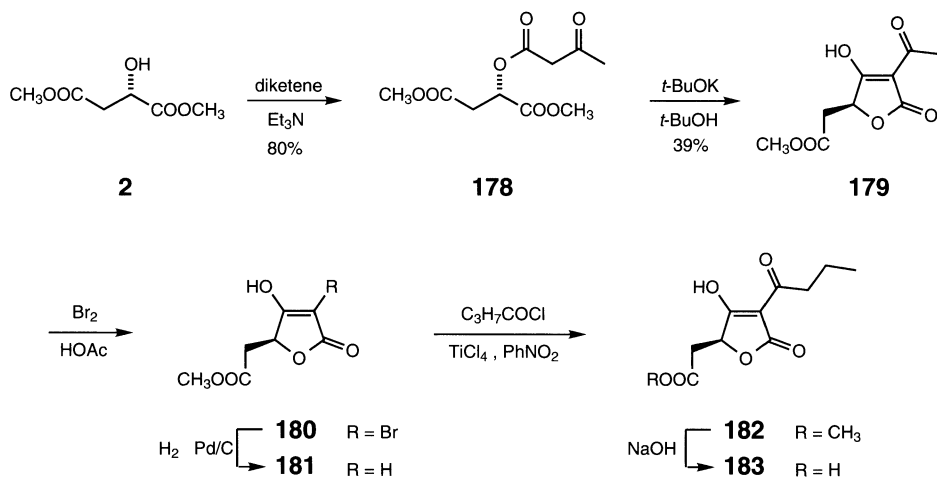
173	R	Cat.	Yield (%)	Ref.
a	H	PTSA	—	61
b	CH ₃	PTSA	75–85	62
c	(CH ₂) ₅	BF ₃ ·OEt ₂	95	63

framework, incorporating a masked vicinal amino alcohol moiety, that serves as a potential statine precursor (e.g., **177**) (Scheme 23) [64]. Selective reduction of the C-4 carbonyl furnishes the corresponding 4-hydroxy derivatives **175**, which, when treated with ethanol at pH 2.0 at 0 °C, give the 4-ethoxyoxazolidin-2-ones **176a** (50% yield) and **176b** (48% yield). Alkylation of **176** with allyltrimethylsilane in the presence of titanium tetrachloride proceeds through an intermediate iminium salt to provide **177a** (73% yield) and **177b** (75% yield).



Scheme 23

The second mode of cyclization of malates involves reaction with the C-1 carbonyl carbon. An elegant example is the synthesis of the naturally occurring tetrone acid (*S*)-carlosic acid (**183**) (Scheme 24) [4,65]. The cyclization substrate, acetoacetate derivative **178**, is prepared in high yield from the reaction of dimethyl (*S*)-malate (**2**) with diketene. Treatment of the thermolabile **178** with potassium *tert*-butoxide effects the desired cyclization to the 3-acyltetrone acid **179** in 39% yield. The acetyl group is removed by bromination (to give **180**) followed by catalytic hydrogenolysis (to **181**). Reacylation of the 3-position with butyryl chloride followed by mild saponification of the ester group furnishes the natural product. With the exception of the cyclization step (**178** → **179**), the rest of the synthetic yields fall within the range 70–80%.



Scheme 24

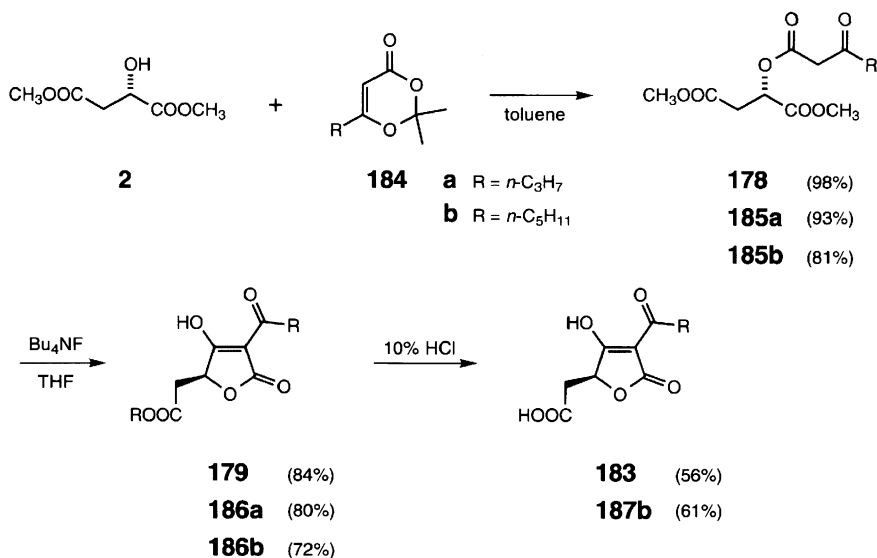
A more direct route to (*S*)-carlosic acid (**183**) and a closely related analog, (*S*)-viridicatic acid (**187b**), avoids the 3-step deacylation–reacylation sequence **178** → **182**. The requisite acyl group is introduced directly in the first step by reaction of **2** with the appropriately substituted 1,3-dioxin-4-one **184** in refluxing toluene. Cyclization with tetrabutylammonium fluoride affords the 3-acyltetrone acid **179** or **186** in good yield. Hydrolysis of the ester under acidic conditions affords the product **183** or **187b** with complete preservation of configuration at the original malic acid chiral center [66].

3.2.2 C-2 Selective Reactions

This Section focuses on the chemistry associated with the hydroxyl-bearing carbon of malic acid.

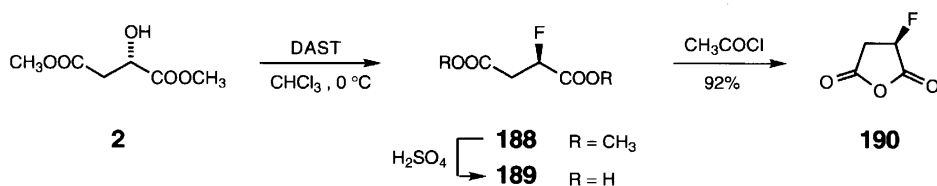
3.2.2.1 Inversion Reactions

Treatment of dimethyl (*S*)-malate (**2**) with DAST results in displacement of the hydroxyl group by fluorine [67]. The reaction proceeds stereospecifically with inversion of config-

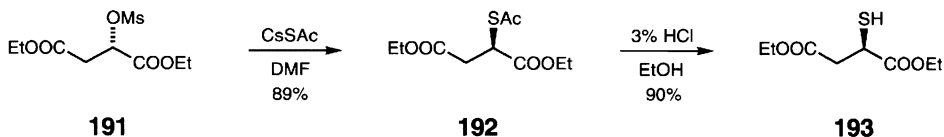


Scheme 25

uration to give dimethyl (*R*)-2-fluorosuccinate (**188**) in 85% yield, along with 6% dimethyl fumarate (as a result of dehydration). Hydrolysis of the esters with 5% sulfuric acid furnishes the crystalline (*R*)-2-fluorosuccinic acid (**189**) (71% yield), which can be converted to anhydride **190** upon refluxing with acetyl chloride.



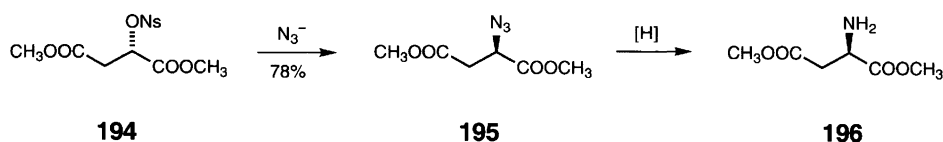
Mesylate **191**, prepared from **3** (MsCl, Et₃N, ether, -20 °C), undergoes clean S_N2 displacement with cesium thioacetate to give (*R*)-2-(acetylthio)succinate (**192**) with 100% *ee* [68]. The cesium salt of thioacetic acid is readily prepared by treatment with cesium carbonate in methanol.



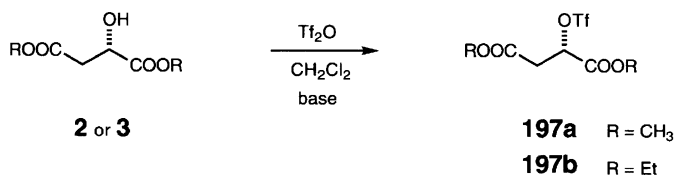
Deacylation of **192** under acidic conditions affords diethyl (*R*)-2-mercaptosuccinate (**193**) with 93% *ee*, which indicates that a minor amount of racemization occurs at this step.

Attempts to hydrolyze the esters to free acids (6N HCl, dioxane) results in considerable racemization, furnishing (*R*)-2-mercaptosuccinic acid (81% yield) with only 61% *ee*.

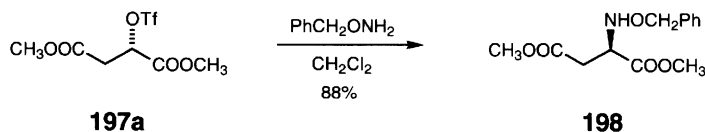
2-Nosyloxy malate **194**, prepared from **2** in 80% yield (NsCl, Et₃N, DMAP, CH₂Cl₂, 0 °C), undergoes clean inversion when treated with 1,1,3,3-tetramethylguanidinium azide to give dimethyl (*R*)-2-azidosuccinate (**195**) with > 95% *ee* [69]. Mild reduction of the azide group with triphenylphosphine affords dimethyl (*R*)-aspartate (**196**) with no observable racemization.



The highly reactive trifluoromethylsulfonyloxy (triflate) group is introduced into malate esters by treatment of **2** or **3** with trifluoromethanesulfonic anhydride at -78 °C in the presence of 2,6-lutidine [70,71,72], or at 0 °C in the presence of pyridine [73]. Yields are generally high, often exceeding 90%. Triflates **197** can be generated in situ, and need not be isolated.



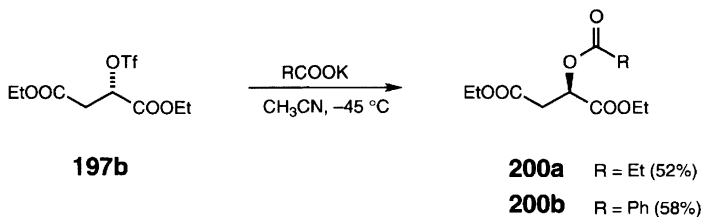
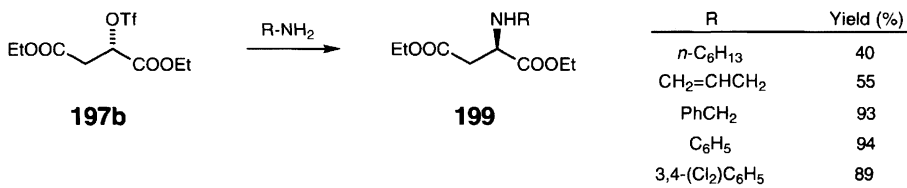
Displacement of the triflate group of **197a** with *O*-benzylhydroxylamine is complete within 25 min at room temperature to give the (*R*)-*N*-benzyloxyaspartic acid derivative **198** with 95% optical purity [70]. Hydrogenolysis of the benzyloxy group (H₂, Pd/C, MeOH, 1 atm) affords **196**.



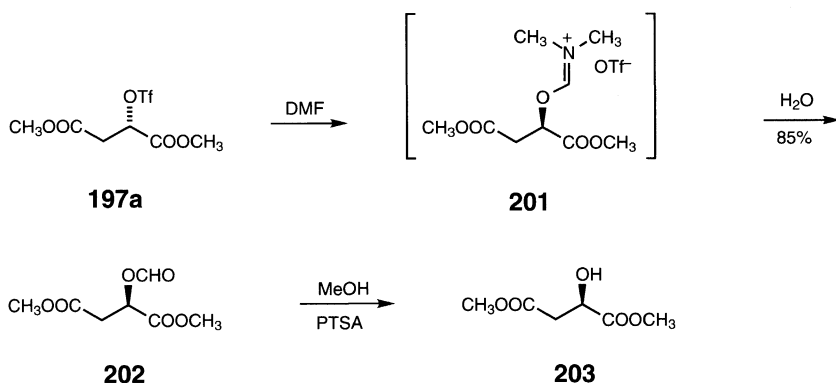
N-Substituted (*R*)-aspartates **199** are obtained from triflate **197b** upon reaction with amines [73]. Basic amines react readily at -70 °C, whereas the less basic anilines require a temperature of 0 °C to ensure complete reaction. The advantage of using the triflate leaving group over other groups such as mesylate, tosylate, or halogen is that its increased reactivity decreases the extent of racemization and elimination encountered as a consequence of the more drastic reaction conditions required to displace the latter groups.

Displacement on the triflate **197** with oxygen nucleophiles allows immediate access to (*R*)-malic acid derivatives. Potassium propionate or potassium benzoate cleanly inverts the stereocenter of **197b** to give *O*-acyl (*R*)-malates **200** in moderate yield [74].

An interesting and efficient method of converting dimethyl (*S*)-malate (**2**) to dimethyl (*R*)-malate (**203**) uses dimethylformamide as the nucleophile in an S_N2 reaction with triflate **197a** [71]. The displacement is rapid, and is complete within 15 min at room temperature. The intermediate formate **202** can either be isolated and purified prior to conversion to **203**, or

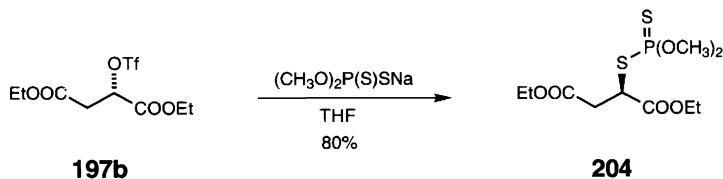


alcoholized directly (Scheme 26). Using pure **202** in the methanolysis step results in the formation of **203** in 65% yield with 100% optical purity. When the formate is not isolated, the chemical yield increases to 93%, but the optical purity drops slightly to 98%.



Scheme 26

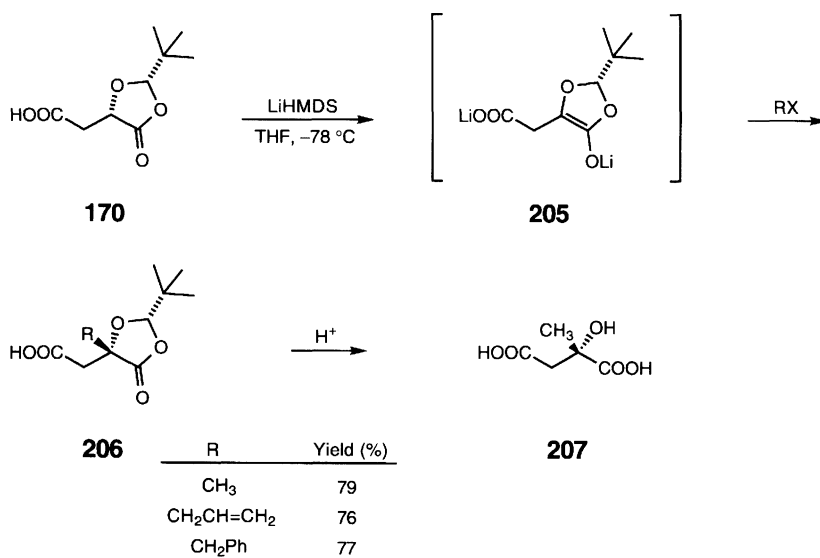
Malathion, one of the most effective and widely used organophosphate insecticides, is relatively non-toxic to mammals due to rapid degradation by carboxyesterases in the liver. Its (*R*)-(+)-enantiomer (**204**) can be readily synthesized from L-malic acid *via* its triflate **197b** [5,72]. The carbon–sulfur bond is formed in a single inversion reaction using freshly prepared sodium *O,O*-dimethylphosphorodithioate as the nucleophile. The three-step process starting from L-malic acid (**1** \rightarrow **3** \rightarrow **197b** \rightarrow **204**) proceeds in 67% overall yield. The enantiomeric (*S*)-(–)-malathion is prepared analogously starting from D-malic acid.



3.2.2.2 Alkylation

The introduction of alkyl groups into the malic acid framework further expands its synthetic utility as an important and inexpensive source of chirality for the construction of asymmetric molecules. Consequently, methods for alkylating the C-2 or C-3 carbons of malic acid both chemoselectively and diastereoselectively are highly desirable.

As in the case of lactic acid, incorporation of the 1-carboxyl and 2-hydroxyl groups into a dioxolanone ring increases the susceptibility of the hydroxyl-bearing carbon to substitution reactions. With malic acid, dioxolanone **170** can be readily alkylated in a highly stereoselective fashion to furnish alkylated dioxolanones **206** with diastereoselectivity surpassing 95% (Scheme 27) [59].



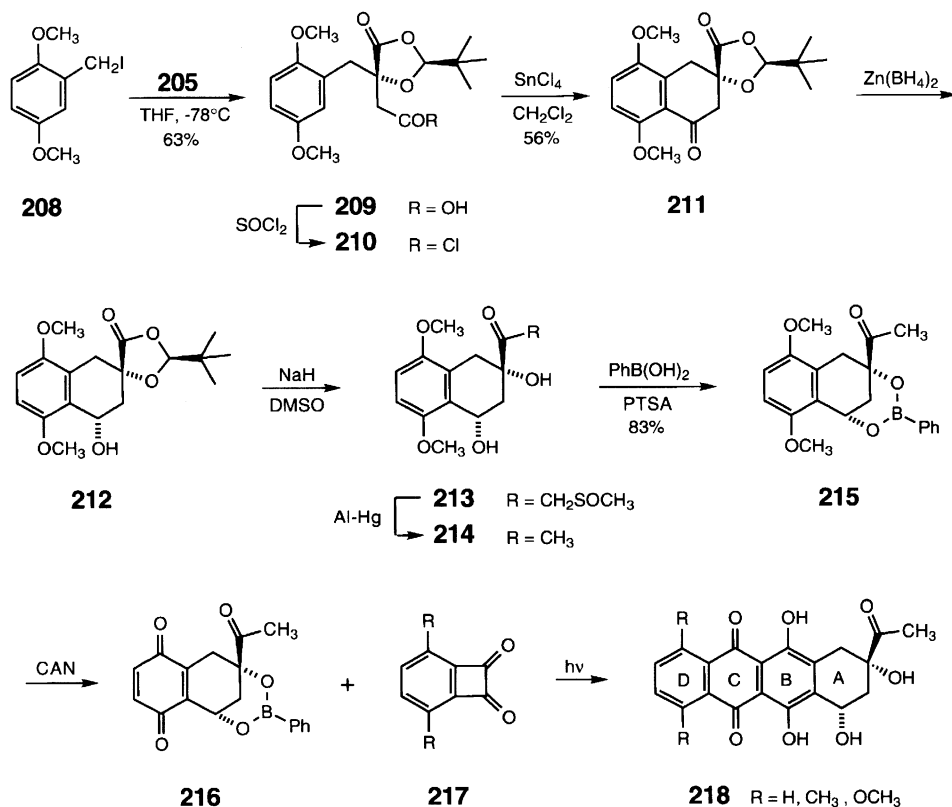
Scheme 27

In the enolate-forming step, the chiral center inherent to the malic acid is destroyed (**205**), but in the alkylation step the bulky *tert*-butyl group directs the approach of the incoming electrophile to the opposite face of the enolate, thereby furnishing alkylated derivatives **206** with the same hydroxyl configuration as in the starting malic acid. This process is called “self-reproduction of chirality”. Acidic hydrolysis of **206** (R=CH₃) furnishes (*S*)-(+)-citramalic acid (**207**). For further uses of citramalic acid see Section 3.5.

This alkylation methodology has been employed in the synthesis of enantiomerically pure daunomycinone derivatives (Scheme 28). The AB building block **215** is constructed by alkylation of **170** with 2,5-dimethoxybenzyl iodide (**208**) to give **209** followed by cyclization of **210** to the tetralone **211** [75]. Selective reduction of the ketone with zinc borohydride gives a mixture of alcohols, 45% of the α -OH (**212**) and 36% of the corresponding β -OH.

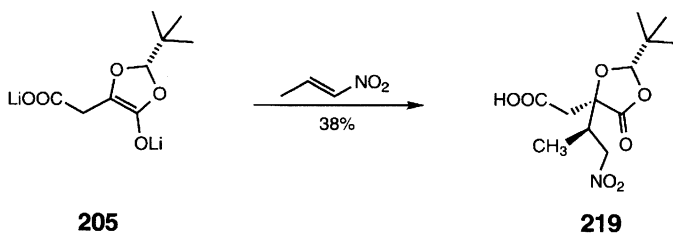
Opening of the dioxolanone ring with dimsyl anion affords β -ketosulfoxide **213**, which is subsequently converted to acetyl derivative **214** by extrusion of sulfur with aluminum amalgam in 90% overall yield. The cyclic boronate **215**, with the desired stereochemical configuration at both hydroxyl groups, is formed by treatment of **214** with phenylboronic acid.

Oxidation of **215** with CAN produces naphthoquinone **216** which, in a single cycloaddition step with bisketenes generated photochemically from 1,2- benzocyclobutanediones **217**, gives daunomycinone derivatives **218** [76].



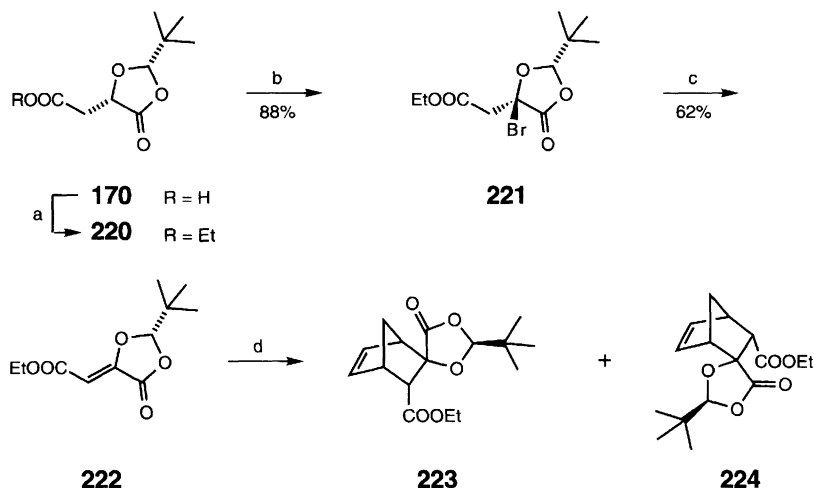
Scheme 28

Enolate **205** also adds to (*E*)-1-nitropropene in a Michael fashion to give adduct **219** with 85% *ds* [77].



Bromination of the ester **220** (derived from **170**) results in formation of bromodioxolanone **221** with 61–85% *ds*. Dehydrobromination leads to the olefin **222** with >96% *ee* (Scheme 29). In a Diels-Alder reaction of **222** with cyclopentadiene, only two of the four possible

diastereomers are formed, in a ratio that depends on the reaction temperature. In each case, diastereomer **223** predominates, but as the temperature increases the ratio of **223**:**224** decreases [78].



Temp.	Time	223 : 224	Yield (%)
rt	19 days	95:5	76
100 °C	12 h	91:9	73.6
140 °C	4 h	82:18	88

Scheme 29

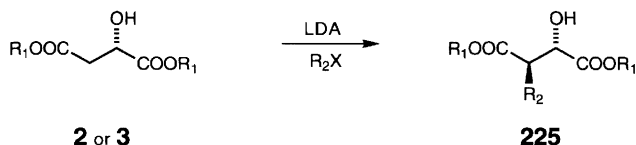
conditions: (a) EtBr, Et₃N, toluene, 100 °C (85%); (b) NBS, AIBN, CCl₄, 80 °C; (c) Et₃N, CCl₄; (d) cyclopentadiene

3.2.3 C-3 Selective Reactions

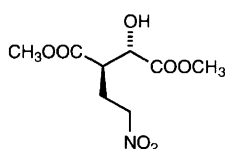
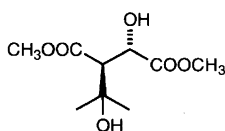
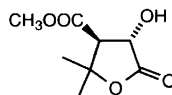
Substitution at the C-3 carbon of malic acid primarily involves alkylation reactions. In contrast to alkylations at the C-2 carbon (Section 3.2.2.2), which require prior manipulation of the 1-carboxyl and hydroxyl groups, alkylation at the C-3 carbon can be performed directly on malic acid esters.

Doubly deprotonated dimethyl or diethyl (*S*)-malate is readily generated at -78 °C with 2.2 equivalents of LDA. Subsequent addition of an alkyl halide produces *anti* 3-alkyl malates (**225**) with diastereoselectivities in excess of 90%. Better results are obtained using LiHMDS as the base [82]. The 3-benzyl derivative **225c** can be isolated in 70% yield with >35:1 diastereoselectivity.

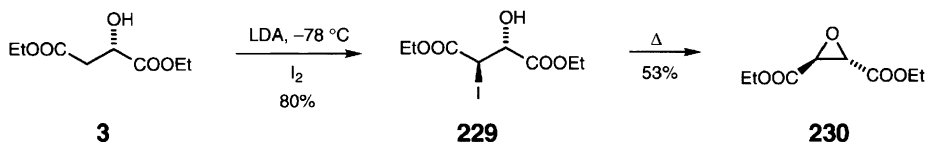
Addition of nitroethylene to the alkoxyenolate generated from **2** affords Michael adduct **226** in 31% yield with a diastereomeric ratio of 85:15 [83]. Likewise, addition of acetone to the same enolate leads to **227** as a 3:1 mixture of *anti* and *syn* isomers. Upon distillation the product lactonizes to afford the butyrolactone derivative **228** in 55% yield [79].



225	R ₁	R ₂	Yield (%)	ds (%)	Ref.
a	CH ₃	CH ₃	65	91	79
b	Et	CH ₃	88	91	79, 80
c	Et	CH ₂ Ph	48	91	79
d	CH ₃	CH ₂ CH=CH ₂	—	94	86
e	Et	CH ₂ CH=CH ₂	70	92	79, 81

**226****227****228**

Quenching the alkoxyenolate derived from **3** with iodine gives an intermediate iodide **229** with 2 : 1 *anti* : *syn* selectivity. Upon warming, iodine is displaced intramolecularly by the hydroxy group, thus forming epoxide **230** in satisfactory yield [79].

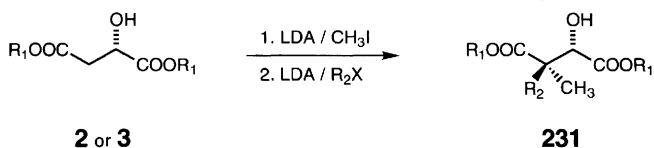


3,3-Dialkylmalates (**231**) are readily obtained from **2** or **3** by sequential deprotonation and alkylation. The high diastereoselectivity of the second alkylation step is a result of preferential attack of the electrophile from the *re*-face of the enolate.

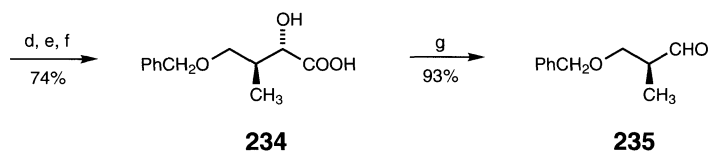
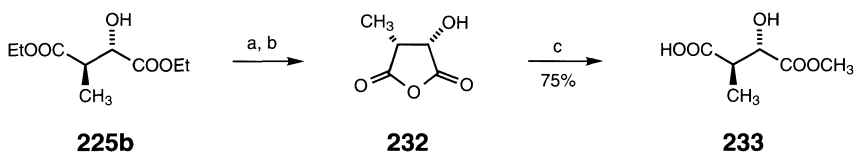
Using chemical manipulations previously described in this chapter, 3-alkylated malates can be transformed into a variety of useful intermediates or final products.

Hydrolysis of both ester groups of **225b** followed by cyclization furnishes anhydride **232**. Selective ring opening with methanol gives the monoester **233**. Reduction of the carboxylic acid, benzoylation of the resulting alcohol, and saponification affords α -hydroxy acid **234**. Electrochemical oxidative decarboxylation furnishes enantiomerically pure aldehyde **235**. This process can also be used for preparing 3,3-dialkyl malates **231** [84].

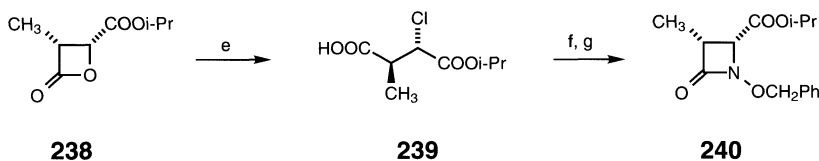
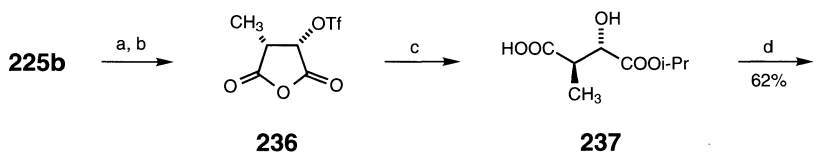
A similar strategy permits a variety of chiral succinic acid fragments to be generated, which can be further converted to β -lactam intermediates, useful for natural product synthesis (Scheme 31). The *cis*- β -lactone **238** is formed as a result of inversion of the hydroxyl-bearing carbon under Mitsunobu conditions. Opening of the lactone with lithium chloride (with inversion of configuration) gives optically pure *anti* chloride **239**. Subsequent hydroxamate formation with *O*-benzylhydroxylamine and cyclization furnishes the *cis*- β -lactam **240** [85].



231	R ₁	R ₂	Yield (%)	ds (%)	Ref.
a	CH ₃	CH ₃	94	—	79, 80
b	CH ₃	Et	36	90	80
c	CH ₃	CH ₂ CH=CH ₂	74	95	81
d	Et	Et	—	93	84
e	Et	CH ₂ Ph	—	95	84
f	Et	CH ₂ CH=CH ₂	—	96	84

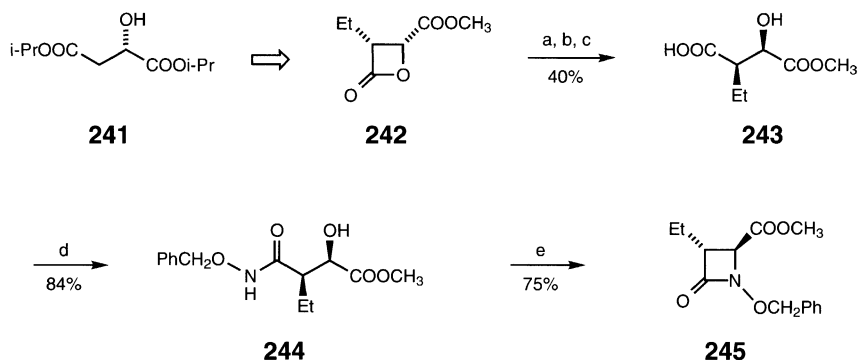
**Scheme 30**

conditions: (a) KOH, MeOH–H₂O (8:2); (b) CH₃COCl; (c) CH₃OH; (d) B₂H₆, THF (85%); (e) benzyl trichloroacetimidate; (f) KOH, MeOH–H₂O (4:1); (g) -2e (i = 180mA/cm²), MeOH

**Scheme 31**

conditions: (a) KOH, dioxane–H₂O; (b) TFAA; (c) *i*-C₃H₇OH; (d) DEAD, Ph₃P; (e) LiCl; (f) WSC, H₂NOCH₂Ph (70%); (g) NaH, DMF–CH₂Cl₂ (3:5) (98%)

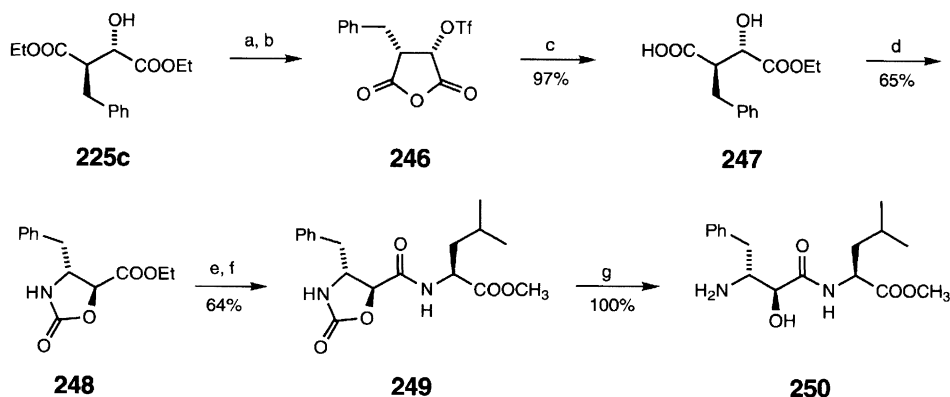
To obtain the corresponding *trans*- β -lactam **245** a similar sequence of reactions starting from diisopropyl (*S*)-malate (**241**) is used to form the *cis*- β -lactone **242** (see Schemes 31 and 32). Complete hydrolysis of **242** followed by anhydride formation and methanolysis occurs with retention of configuration to give the monoacid **243**. Hydroxamate formation and Mitsunobu lactamization (with inversion) affords the *trans*- β -lactam **245** [27]. A parallel series of reactions has also been carried out starting with diisopropyl (*R*)-malate.



Scheme 32

conditions: (a) KOH, H₂O; (b) TFAA; (c) CH₃OH; (d) WSC, H₂NOCH₂Ph; (e) DEAD, Ph₃P

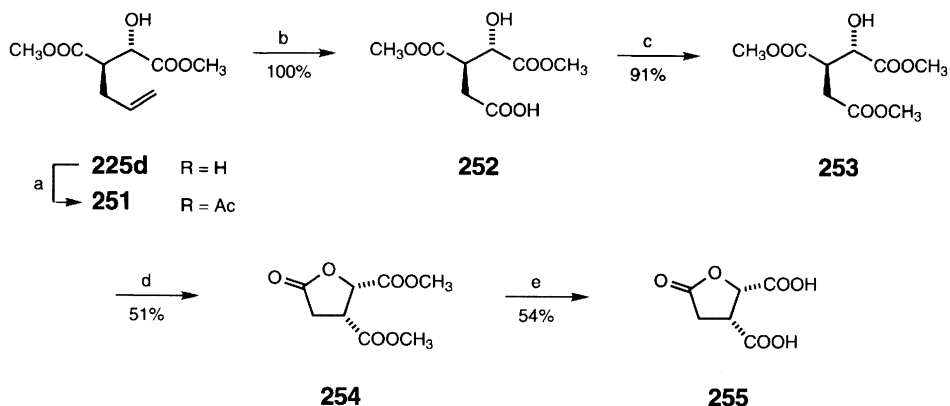
The 3-benzylmalate **225c** is converted to monoester **247** via anhydride **246**. Curtius rearrangement of the carboxylic acid group produces an intermediate isocyanate that is trapped internally by the hydroxyl group to give oxazolidinone **248** (Scheme 33). Saponification of the methyl ester, coupling with leucine methyl ester, and hydrolysis of the oxazolidinone ring furnishes (–)-bestatin (**250**), a potent inhibitor of leucine aminopeptidase as well as an antitumor and antimicrobial agent [82]. Oxazolidinone **248** can also be saponified (under the conditions of step g) to give (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutyric acid (AHPBA) in quantitative yield.



Scheme 33

conditions: (a) 1N NaOH, dioxane (100%); (b) TFAA, 0 °C; (c) EtOH; (d) DPPA, Et₃N, toluene, 90 °C; (e) LiOH, THF, H₂O; (f) Leu-OCH₃, NMM, EDAC, HOBT, DMF; (g) 1N NaOH, EtOH

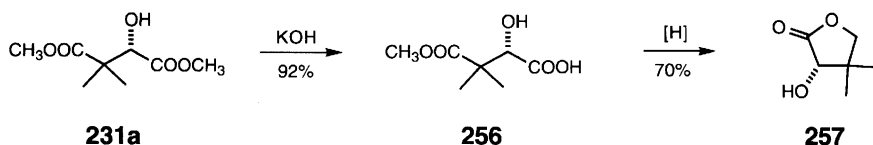
The synthesis of (+)-isocitric acid lactone (**255**) is accomplished in 5 steps starting from the (2*S*,3*R*)-allyl malate **225d**, as shown in Scheme 34 [86]. The key step in the sequence is oxidation of the allyl function with periodate and then permanganate to a carboxylate (**251** → **252**), which occurs in quantitative yield. Once the carbon framework is in place, all that remains is an acid-catalyzed lactonization to **254** and hydrolysis to the desired product.



Scheme 34

conditions: (a) Ac_2O , DMAP (98%); (b) NaIO_4 , H_2O , K_2CO_3 , KMnO_4 ; (c) MeOH, CH_3COCl , 60 °C; (d) PTSA, α -dichlorobenzene, 120 °C; (e) 1N HCl

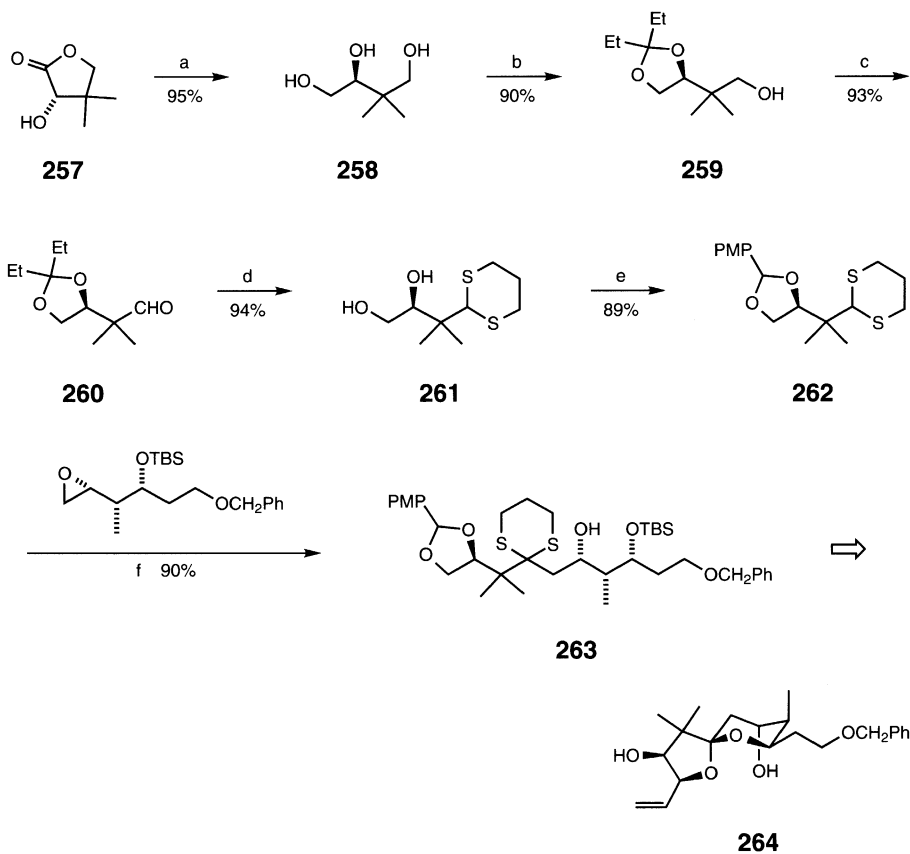
Pantolactone, an important intermediate for the synthesis of pantothenic acid (a constituent of Coenzyme A), is commercially available in only one optically active form. The (*R*)-(–)-enantiomer currently sells for slightly less than \$1.00 per gram. The (*S*)-(+)–Pantolactone (**257**) must be synthesized, and it is readily accessible from L-malic acid *via* the 3,3-dimethyl analog **231a** [80]. Selective hydrolysis of the 1-ester furnishes the monoacid **256**. Reduction of the 4-ester with L-Selectride followed by lactonization then gives **257** in 40% overall yield starting from dimethyl (*S*)-malate (**2** → **231a** → **256** → **257**).



Malic acid-derived (*S*)-pantolactone (**257**) has been used as a starting point for the stereoselective construction of the C-14 to C-25 spiroketal subunit of calyculin (Scheme 35) [87].

3.2.4 C-4 Selective Reactions

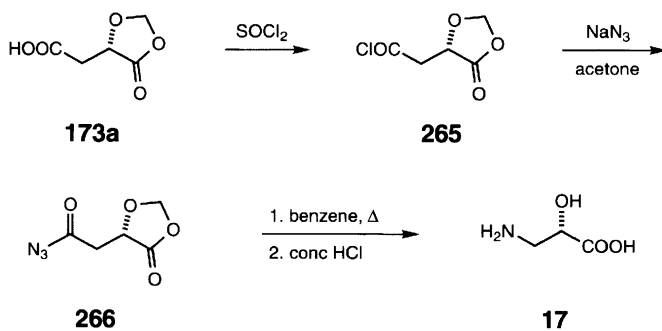
Reactions at the C-4 carboxyl group of malic acid usually require some sort of prior manipulation at the other end of the molecule to facilitate the desired transformation. For example, tying up both the 1-carboxyl and 2-hydroxyl groups into a dioxolanone ring (**173a**) makes it possible for the remaining 4-carboxylic acid to be converted easily to an acid chloride (**265**) under standard conditions. Treatment of **265** with sodium azide followed by a



Scheme 35

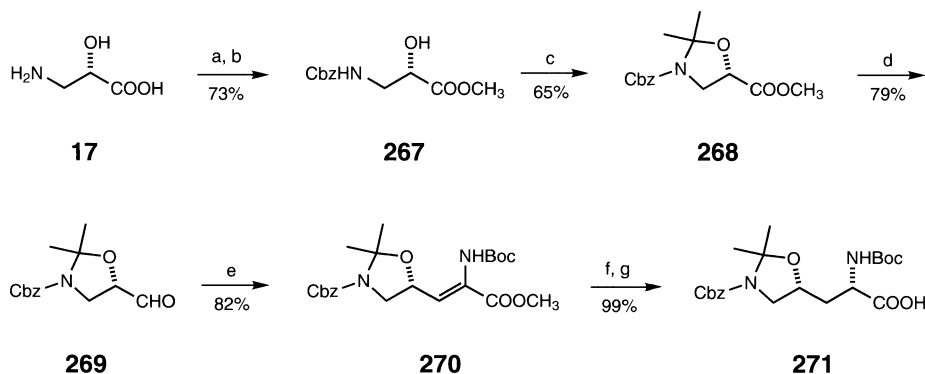
conditions: (a) LiAlH_4 ; (b) 3-pentanone, PTSA, THF; (c) DMSO, $(\text{COCl})_2$, Et_3N , CH_2Cl_2 , $-78\text{ }^\circ\text{C}$; (d) $\text{HS}(\text{CH}_2)_3\text{SH}$, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , $0\text{ }^\circ\text{C}$; (e) 4-methoxybenzaldehyde dimethylacetal, PTSA, DMF; (f) *n*-BuLi, TMEDA

Curtius rearrangement in boiling benzene generates an intermediate oxazolidinone that is hydrolyzed under acidic conditions to give multigram quantities of (*S*)-isoserine (**17**) in 46% overall yield from (*S*)-malic acid (**1**) (Scheme 36) [61].



Scheme 36

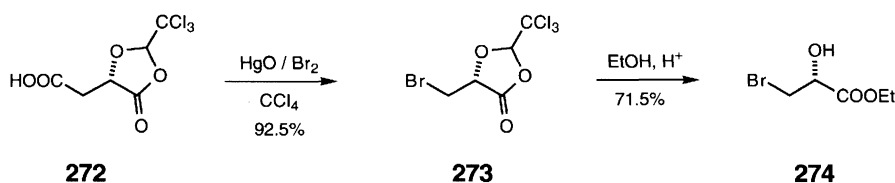
(*S*)-Isoserine can, in turn, be converted to the protected (2*S*,4*R*)-4-hydroxyornithine derivative **271**, as shown in Scheme 37 [88]. The reduction **268** → **269** is accompanied by partial racemization (25%), but the diastereomers can be separated at the stage of compound **271**. The oxazolidine ring of **271** is easily cleaved by aqueous acetic acid at room temperature.



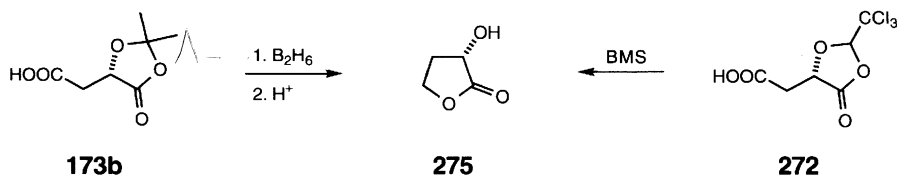
Scheme 37

conditions: (a) Cbz-Cl, dioxane, 1N NaOH; (b) CH_2N_2 , MeOH, ether, 0 °C; (c) DMP, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, acetone; (d) DIBAL, toluene, -78 °C; (e) $(\text{MeO})_2\text{P}(\text{O})(\text{NHBOc})\text{CHCOOCH}_3$, KO^tBu , CH_2Cl_2 , -70° → rt; (f) H_2 , (*R,R*)-[Rh(1.5-COD)(DIPAMP)] BF_4^- , MeOH; (g) 1N LiOH, THF

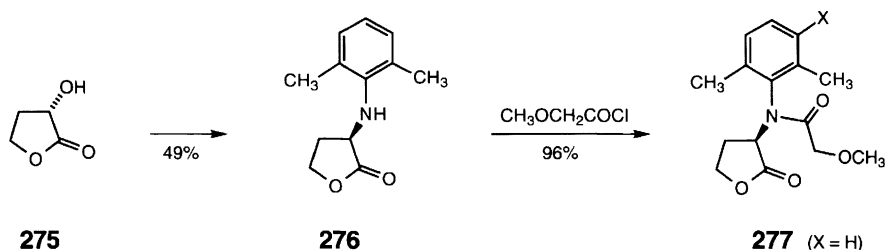
Reaction of (*S*)-malic acid, protected as a chloral acetal (**272**), with red mercuric oxide followed by careful portionwise addition of bromine during irradiation with a 100 W lamp produces bromomethyldioxolanone **273** in high yield. Removal of the protecting group with ethanol and Dowex 50 W (a strongly acidic ion exchange resin) gives bromohydroxy ester **274** [106].



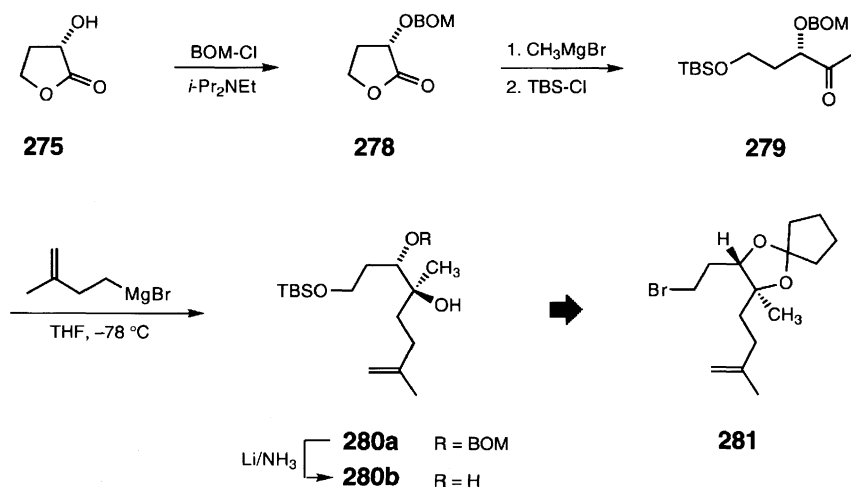
Reduction of the carboxylic acid group of dioxolanone **173b** [40,62] or **272** [89] furnishes (3*S*)-hydroxybutyrolactone (**275**). The yield in the step **272** → **275** varies considerably (20–55%), whereas the conversion of **173b** → **275** proceeds consistently in high yield.



Butyrolactone **275** has been used in the enantioselective synthesis of a precursor (**277**, X=H) of CGA8000 (clozylacon) (**277**, X=Cl), an agrochemical fungicide especially suited for soil application against oomycetes [89]. The hydroxyl group of **275** is activated as a triflate (TFAA, pyridine, CCl_4), and subsequent $\text{S}_{\text{N}}2$ reaction with 2,6-dimethylaniline in the presence of potassium carbonate produces the (3*R*)-anilinobutyrolactone **276** with 94.7% *ee*. Acylation with methoxyacetyl chloride gives **277** in nearly quantitative yield, although slight racemization occurs affording a product with 88.6% *ee*.



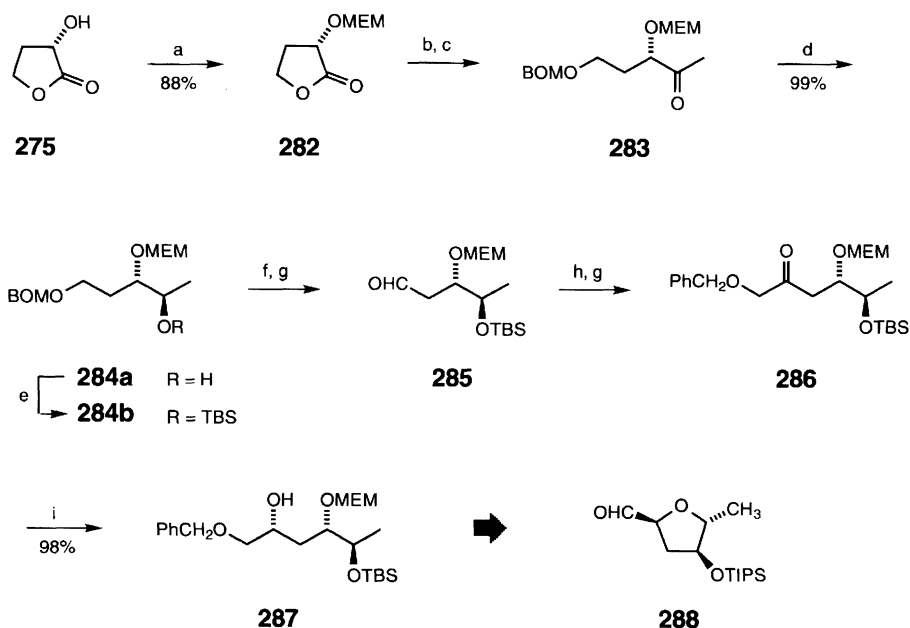
The central fragment (**281**) of monensin is prepared from **275** as outlined in Scheme 38 [62]. The key step in the sequence is addition of 3-methyl-3-butenylmagnesium bromide to **279**. Since **279** contains the necessary features for chelation-controlled addition of the Grignard reagent to the carbonyl group, product **280a** is formed with high diastereoselectivity (50 : 1).



Scheme 38

MEM-Protected butyrolactone **282** is instrumental in the stereoselective synthesis of the C-12 to C-17 fragment of the antibiotic aplasmomycin (Scheme 39) [90]. The key steps are those that result in the formation of new asymmetric centers. Reduction of **283** with zinc borohydride gives the *anti*-alcohol **284a** with 15 : 1 diastereoselectivity as the result of chelation-controlled addition of hydride to the carbonyl group. The isomers are separable at the stage of intermediate **285**. A second hydride reduction of **286** at -78°C affords the *syn*-alcohol **287**

with 5:1 diastereoselectivity. The degree of 1,3-asymmetric induction can be increased to 10:1 by performing the reaction at $-123\text{ }^{\circ}\text{C}$.

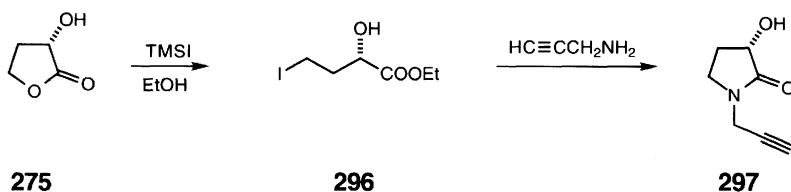


Scheme 39

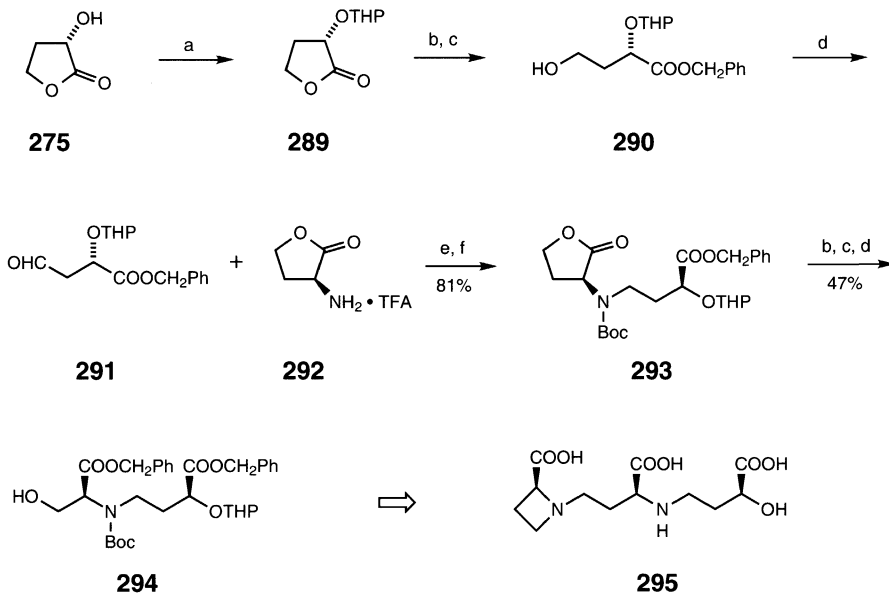
conditions: (a) MEM-Cl, $i\text{-Pr}_2\text{NEt}$; (b) CH_3Li , THF, $-78\text{ }^{\circ}\text{C}$ (98%); (c) BOM-Cl, $i\text{-Pr}_2\text{NEt}$ (89%); (d) $\text{Zn}(\text{BH}_4)_2$, ether, $-78\text{ }^{\circ}\text{C}$; (e) TBS-Cl, imidazole, DMF; (f) Li/NH_3 , $-78\text{ }^{\circ}\text{C}$ (97%); (g) $\text{CrO}_3 \cdot 2\text{py}$, CH_2Cl_2 (84%); (h) $\text{PhCH}_2\text{OCH}_2\text{Li}$, THF, $-78\text{ }^{\circ}\text{C}$ (72%); (i) $\text{LiAlH}(\text{O}-t\text{-Bu})_3$, ether, $-123\text{ }^{\circ}\text{C}$

THP-Protected butyrolactone **289** is one of the chiral fragments used in the total synthesis of 2'-deoxymugineic acid (**295**), a metal chelator excreted from wheat root (Scheme 40) [91]. The sequence **275** \rightarrow **291** proceeds with an overall yield of 55%.

Concomitant ring opening of lactone **275** and esterification of the resulting α -hydroxy acid with trimethylsilyl iodide in ethanol produces iodoester **296**. Subsequent treatment with propargylamine affords pyrrolidinone **297** in 45% overall yield from (*S*)-malic acid. The product is used as an intermediate for the preparation of hydroxyl-containing oxotremorine analogs potentially useful for the treatment of senile dementia [40].



In the synthesis of (–)-tetrahydrolipstatin (**308**) (Scheme 41), a β -lactone antibiotic and pancreatic lipase inhibitor, the intermediate alcohol **298** is not allowed to lactonize, but is



Scheme 40

conditions: (a) DHP, PTSA, CH_2Cl_2 , 0°C ; (b) 2.5% KOH; (c) PhCH_2Br , 18-crown-6; (d) PCC, CH_2Cl_2 ; (e) NaBH_3CN ; (f) Boc_2O , Et_3N

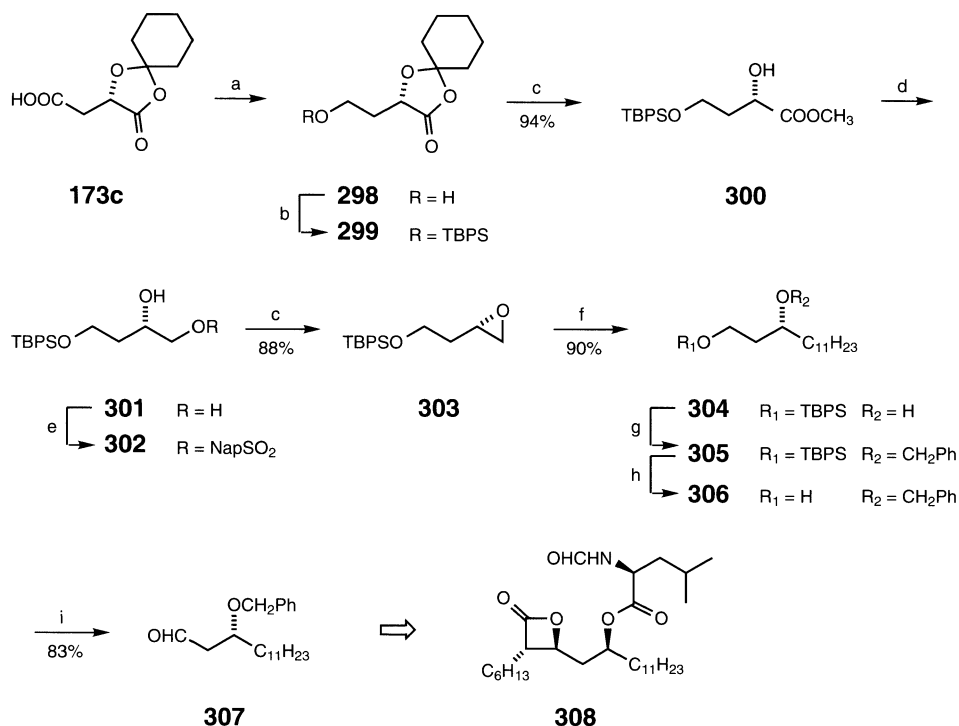
instead immediately silylated to give TBPS-protected dioxolanone **299**. Opening the dioxolanone ring with methanol catalyzed by sodium methoxide affords α -hydroxy ester **300**. Reduction of the ester, selective reaction of the primary OH with 2-naphthalenesulfonyl chloride, and base-catalyzed cyclization gives epoxide **303**. Opening the oxirane ring with *n*-decyllithium furnishes the (3*R*)-1,3-dihydroxytetradecane **304**, which is then manipulated in such a way as to prepare the key aldehyde **307**.

The synthesis is completed by titanium-mediated addition of (*E*)-1-(trimethylsilyl)-2-nonene to the aldehyde, conversion of the resulting terminal vinyl group to an acid, β -lactonization, debenzoylation, and Mitsunobu reaction with (*S*)-*N*-formylleucine, thus producing the target molecule **308**. The last step proceeds with inversion of configuration [63].

The interesting TBS-protected acid chloride **310**, available from monoester **23a** by dual silylation of the hydroxyl and ester groups followed by treatment with oxalyl chloride, is an important intermediate in the synthesis of a key fragment (**312**) of rhisobactin (**314**), a microbial siderophore (Scheme 42) [92]. Completion of the synthesis of **314** is accomplished by reductive amination of **312** with *D*-alanine-derived aldehyde **313** followed by hydrolysis of the methyl esters and hydrogenolysis of the Cbz protecting group.

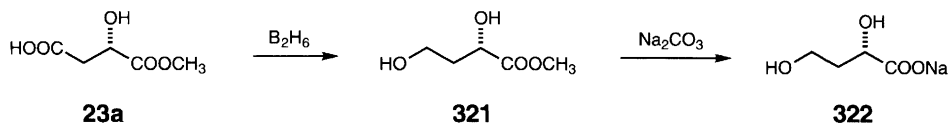
The silyl ester group of **309** can be selectively hydrolyzed under mild conditions to afford TBS-protected monoester **315**. Functional group manipulation leads to allylic sulfide **318** which, when allowed to react with dichloroketene, undergoes a ketene Claisen rearrangement yielding **319** with >90% *de*. Removal of the silyl protecting groups results in lactonization to give **320** (Scheme 43) [93].

Selective reduction of the carboxylic acid group of **23a** produces a mixture of diol **321** and lactone **275**. Hydrolysis of the mixture with aqueous sodium bicarbonate affords pure salt **322** [94].



Scheme 41

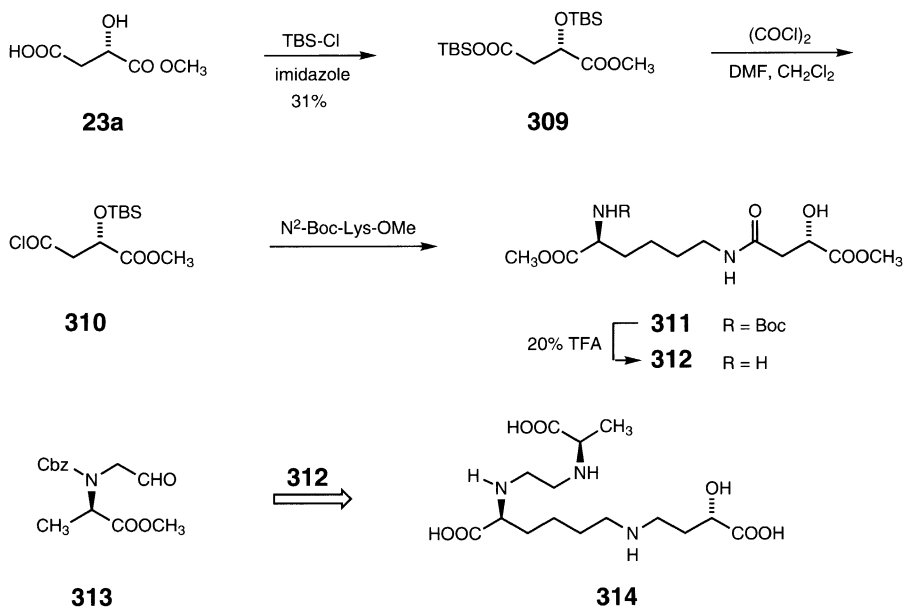
conditions: (a) BMS, B(OCH₃)₃ (100%); (b) TBPS-Cl, imidazole, DMF (85%); (c) CH₃OH, NaOCH₃; (d) BMS, NaBH₄ (100%); (e) 2-naphthalenesulfonyl chloride, pyridine, DMAP (86%); (f) *n*-C₁₀H₂₁Li, BF₃·Et₂O; (g) benzyl trichloroacetimidate, CF₃COOH (86%); (h) 48% HF-CH₃CN/CH₂Cl₂ (5:95) (99%); (i) PDC, CH₂Cl₂



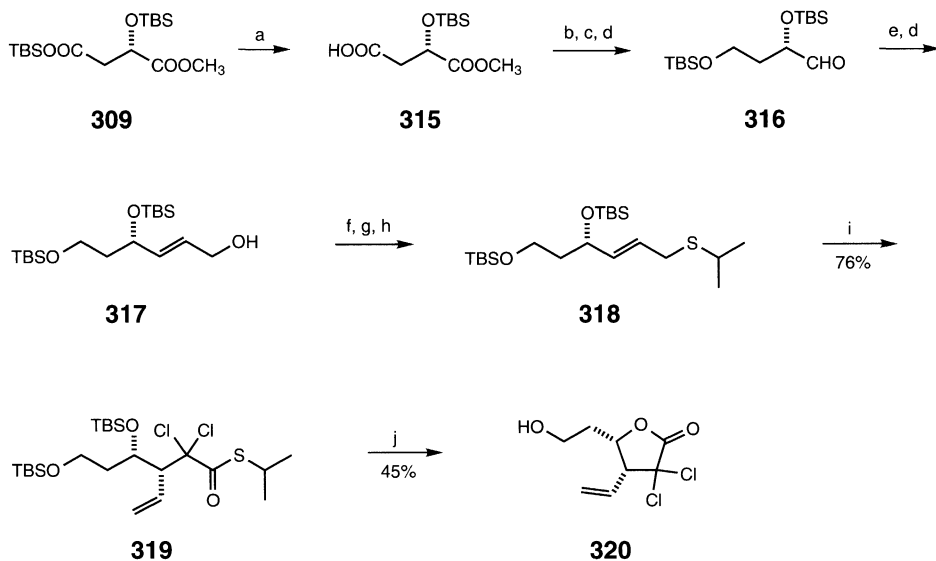
1 α ,25-Dihydroxy-24(*R*)-fluorocholecalciferol (**326**), a fluorinated derivative of the physiologically active vitamin D₃ metabolite, exhibits longer half-life and increased anti-rachitogenic activity than its desfluoro counterpart due to fluorine occupying one of the principal sites of the calcitriol catabolism.

The side chain is constructed from (*S*)-malic acid *via* the acetoxyester **34b** (Scheme 44) [35]. Reduction of the carboxylic acid with diborane or BMS [33] affords hydroxy ester **323** in essentially quantitative yield. Hydrolysis followed by acidification gives the lactone **275** in moderate yield. Fluorination with DAST proceeds with inversion of configuration, producing the fluoro lactone **324** with >98% *ee*. Treatment of this lactone with an excess of methyl-lithium under carefully controlled conditions furnishes the desired fluoro diol **325**.

Scheme 45 shows an interesting series of transformations beginning with ester **323** that leads ultimately to α,β -unsaturated ester **334**. The important step in the sequence is conversion of Grignard reagent **333** to a cuprate, followed by a stereoselective Michael addition to methyl

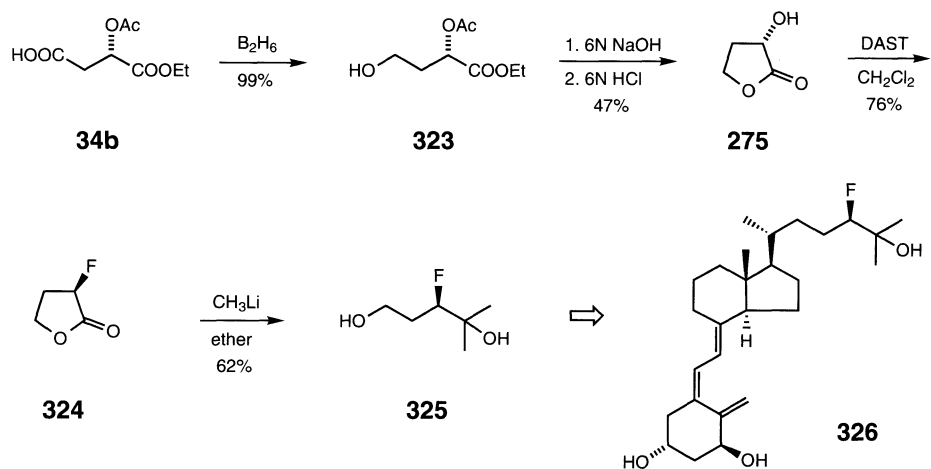


Scheme 42



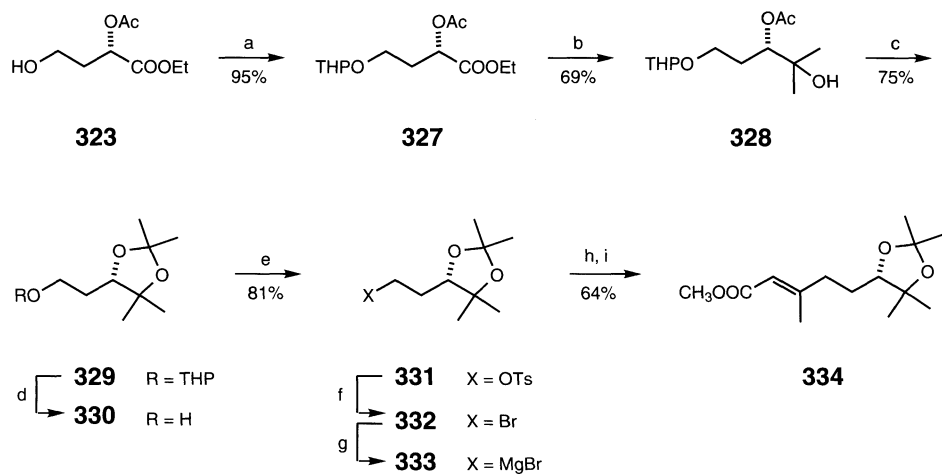
Scheme 43

conditions: (a) K_2CO_3 , $\text{MeOH-H}_2\text{O}$ (7.3:1), rt, 1hr; (b) BMS; (c) TBS-Cl, imidazole, DMF; (d) DIBAL, THF, $-78\text{ }^\circ\text{C}$; (e) $\text{Ph}_3\text{P=CHCOOCH}_3$; (f) AcSH, Ph_3P , DEAD, THF, $0\text{ }^\circ\text{C}$ (95%); (g) NaOEt, EtOH; (h) $i\text{-C}_3\text{H}_7\text{Br}$ (92%); (i) CH_3COCl , Zn-Cu, ether; (j) 48% HF, CH_3CN



Scheme 44

tetrolate. The product **334** is formed with 94–96% (*E*)-geometry [34]. This intermediate was designed to supply the two symmetrical terminal fragments for the polyene lycopene epoxides and glycols, however those products were in fact obtained as a complex mixture of isomers.

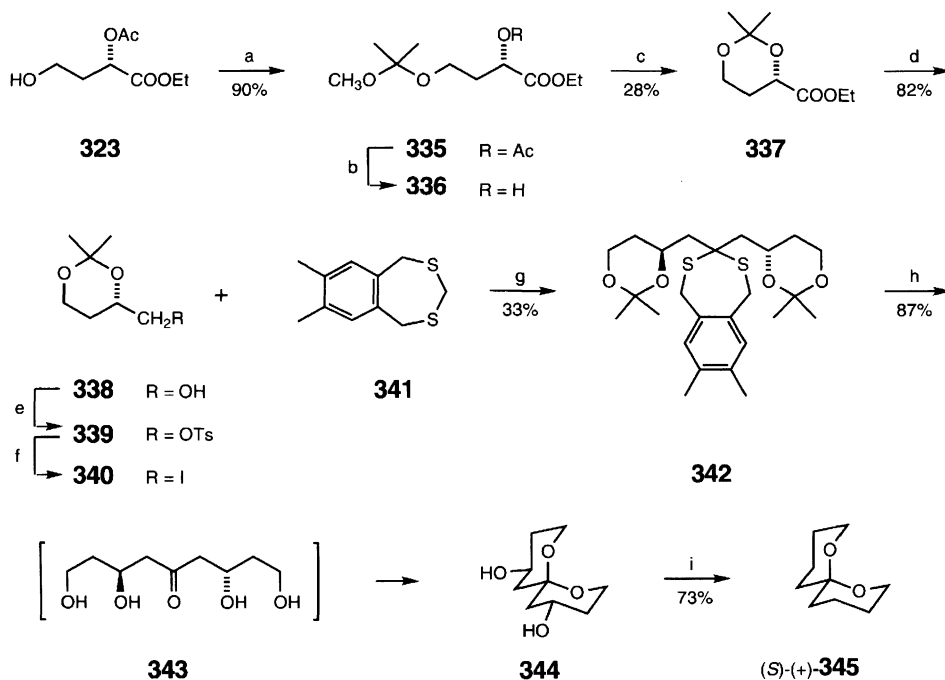


Scheme 45

conditions: (a) DHP, PPTS; (b) CH_3Li ; (c) DMP, PTSA; (d) PPTS, EtOH (88%); (e) TsCl, pyridine; (f) LiBr (95%); (g) Mg; (h) CuI, pyrrolidine; (i) methyl tetrolate

1,7-Dioxaspiro[5.5]undecane is the major component of the sex pheromone of the olive fruit fly. The synthesis of its (*S*)-enantiomer (*S*)-**345** is outlined in Scheme 46 [95,96]. The synthesis begins with (*S*)-malic acid and proceeds through intermediate **323**, which is sub-

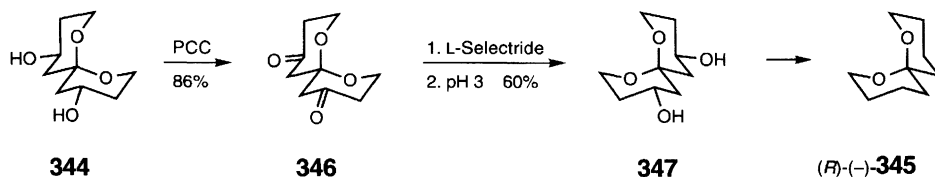
sequently protected with 2-methoxypropene. Removal of the acetyl group followed by Lewis acid isomerization furnishes ester **337**. Bis alkylation of 7,8-dimethyl-1,5-dihydro-2,4-benzodithiepin (**341**) with iodide **340** in a stepwise fashion gives **342**. Copper-mediated hydrolysis of the dithiepin heterocycle produces an intermediate tetrahydroxy ketone **343** that spontaneously forms the spiroacetal **344** as a single crystalline product in 28.7% yield from **340**. The hydroxyl groups are readily removed by an Ireland deoxygenation procedure, thus giving the (*S*)-pheromone **345**. The entire sequence from malic acid requires 13 steps, and proceeds with an overall yield of 6.1%.



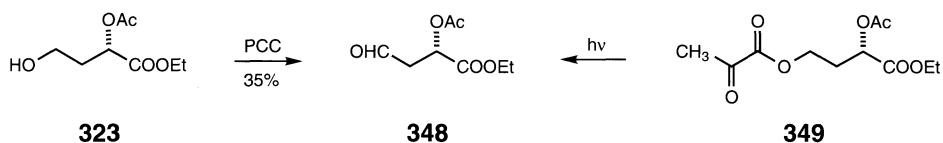
Scheme 46

conditions: (a) 2-methoxypropene, PPTS; (b) NaOEt, EtOH (94%); (c) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, ether; (d) LiAlH_4 , ether; (e) TsCl, pyridine (93%); (f) NaHCO_3 , NaI (92%); (g) *n*-BuLi, THF, -35°C ; (h) $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, CuO, acetone– H_2O (99:1); (i) *n*-BuLi, $(\text{Me}_2\text{N})_2\text{P}(\text{O})\text{Cl}$ then Li/EtNH₂, *t*-BuOH–THF

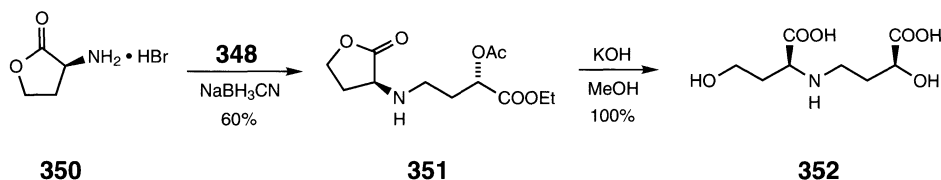
The corresponding (*R*)-enantiomer can be obtained from **344** by oxidation of the hydroxyl groups to diketone **346**. Selective reduction of the carbonyls followed by acidic workup furnishes the thermodynamically stable diol **347** with 100% *de*. Ireland deoxygenation gives the (*R*)-pheromone (*R*)-**345** in 51% yield. Thus, both enantiomers of 1,7-dioxaspiro[5.5]undecane are available from one chiral source, (*S*)-malic acid.



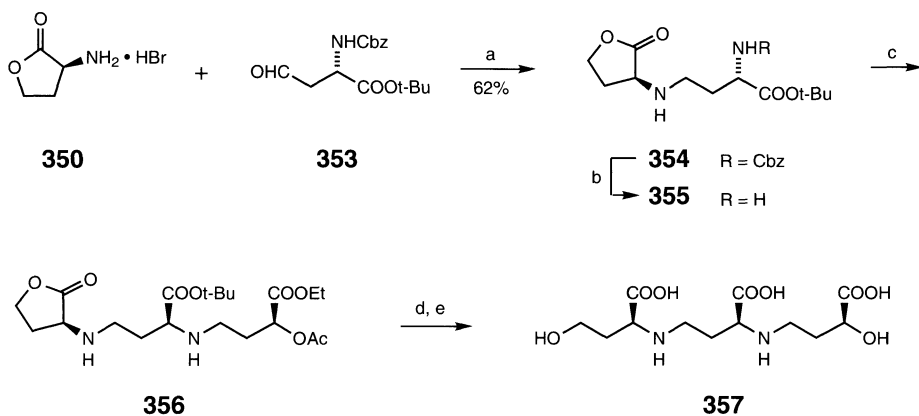
(*S*)-Malic β -semialdehyde derivative **348** is directly accessible from **323** by PCC oxidation [97] or by conversion of **323** to pyruvyl ester **349** followed by photoreduction [98]. The latter route proceeds in slightly higher yield (51% overall yield from **34b** \rightarrow **323** \rightarrow **349** \rightarrow **348**), but requires one more step than the PCC route.



Aldehyde **348** has been used in the synthesis of a series of iron-chelating agents. Avenic acid B (**352**), a minor component in the root extracts of *Avena sativa*, is easily synthesized in two steps by reductive amination of **348** with L-homoserine lactone hydrobromide (**350**) under controlled pH (6–7) followed by alkaline hydrolysis [97].



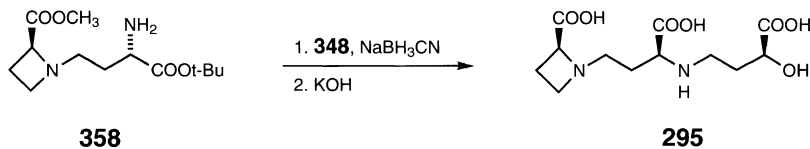
Avenic acid A (**357**), the major component in the root extracts of *Avena sativa*, is synthesized by the similar route shown in Scheme 47 [98]. The central amino acid fragment is introduced by reductive amination of L-aspartic β -semialdehyde (**353**) with L-homoserine lactone hydrobromide (**350**). After removal of the Cbz protecting group under hydrogenolytic conditions, reductive amination of the malic β -semialdehyde **348** with **355** gives the lactone diester **356** in 50% yield.



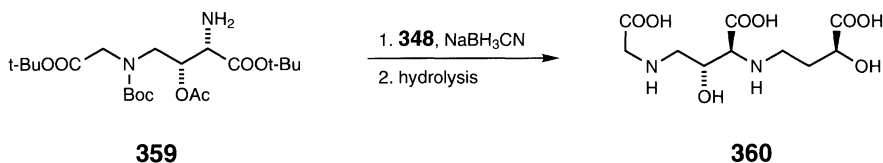
Scheme 47

conditions: (a) NaBH_3CN , pH 6.0; (b) H_2 , Pd/C; (c) **348**, NaBH_3CN , pH 6.0; (d) CF_3COOH ; (e) 1% KOH

2'-Deoxymugineic acid (**295**), a third constituent of *Avena sativa*, is prepared by reductive amination of **348** with amine diester **358** (58% yield). Compound **358** is in turn prepared by reductive amination of **353** with L-azetidine-2-carboxylic acid.



2'-*epi*-Distichonic acid A (**360**) is readily synthesized by reductive amination of **348** with L-methionine-derived amino diester **359** followed by sequential hydrolysis with 1N HCl and then 1% KOH [33]. The coupling step proceeds in 58% yield.

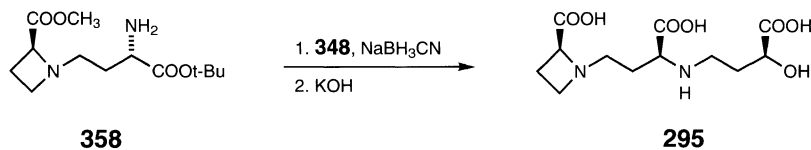


3.3 Reactions at Both Carboxylate Sites

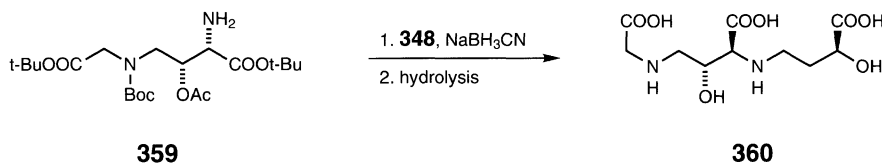
In Section 3.2 we explored reactions directed to certain specific sites of the malic acid framework. In this section, reactions that include both of the carboxylic acid or ester groups of malates will be discussed. Actually throughout the chapter we have touched on reactions that fit into this category. Simple hydrolysis of malate esters to the respective malic acids, or conversion of malic acids to their anhydrides (e.g. **21**, **33**, **232**), exemplifies these rudimentary transformations. Although presented in earlier sections, such reactions were in fact intended to introduce chemistry associated with a specific functional group of malic acid. Here we concentrate on more substantial transformations, ones that lead to extremely useful enantiomerically pure intermediates.

In the synthesis of prostaglandins, the Corey lactone intermediate **368** is instrumental in establishing the stereochemistry in the carbocyclic core. Its synthesis from (*S*)-malic acid is outlined in Scheme 48 [99,100]. (*S*)-(-)-2-Acetoxy succinyl chloride (**361**) is prepared in one pot from **1** by sequential treatment with acetyl chloride (which generates anhydride **33**) followed by 1,1-dichloromethyl methyl ether in the presence of a catalytic amount of zinc chloride. Reaction of **361** with five equivalents of the dianion of methyl hydrogen malonate furnishes (*S*)-4-acetoxy-3,6-dioxosuberate (**362**) as an unstable oil that undergoes slow elimination of acetic acid on standing. Immediate cyclization using basic magnesium carbonate under controlled pH (6.0–6.5) gives **363** in 50% overall yield from **361**. Catalytic reduction of the double bond produces the *trans*-cyclopentanone derivative **364**. It is likely that the hydrogenation occurs in the expected *cis* fashion, but because of facile keto–enol tautomerism of the resulting β -keto ester the thermodynamically more stable *trans* product **364** is isolated. Reduction of the ketone with sodium borohydride at the optimum pH of 5.25 affords alcohol **365**. Removal of the acetyl group with either potassium carbonate or sodium

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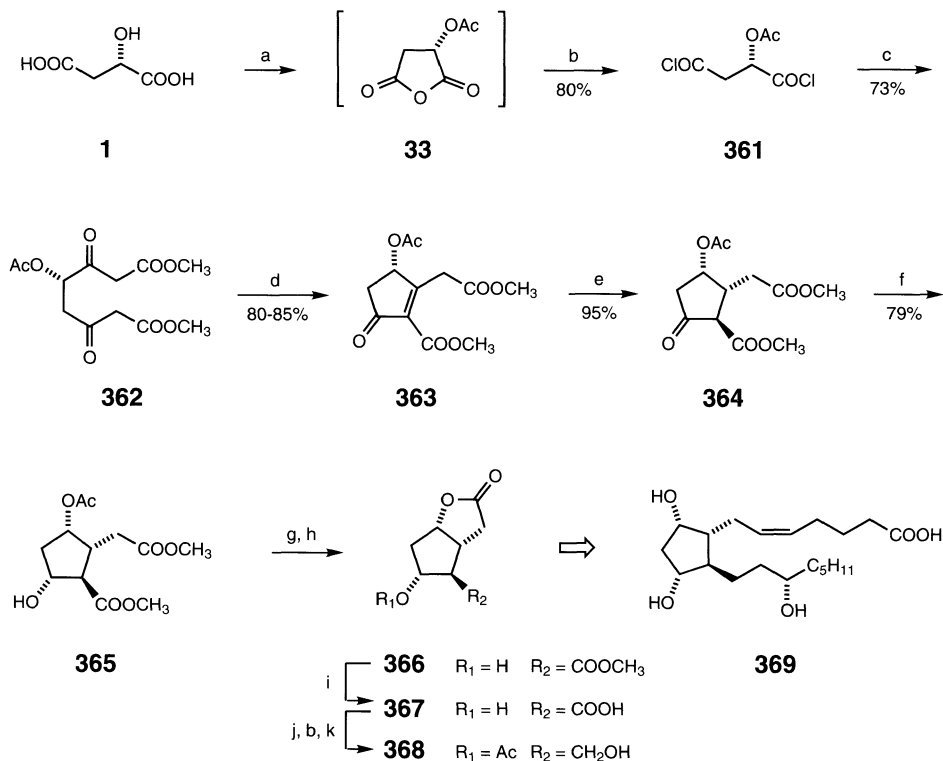


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methoxide results in spontaneous cyclization, which gives the lactone **366** in 34% overall yield from **362**. A series of straightforward reactions affords the Corey lactone **368**, which was then elaborated to (+)-PGF_{2α} (**369**) by known methods.



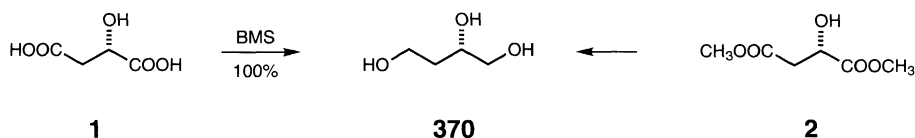
Scheme 48

conditions: (a) CH₃COCl; (b) Cl₂CHOCH₃, ZnCl₂; (c) KOOCCH₂COOCH₃, *i*-PrMgBr, THF, 0 °C; (d) MgCO₃, Mg(OH)₂·*n*H₂O, ether-H₂O; (e) H₂ (1 atm), 5% Pd/BaSO₄, benzene; (f) NaBH₄, pH 5.25; (g) K₂CO₃, MeOH; (h) citric acid; (i) KOH, MeOH; (j) CH₃COCl; (k) NaBH₄, -30 °C

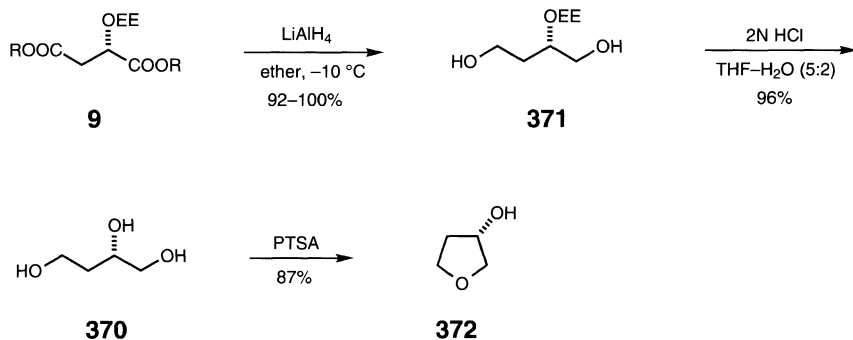
3.3.1 Reduction

Exhaustive reduction of malic acid or its esters furnishes (*S*)-(-)-1,2,4-butanetriol (**370**). Direct treatment of **1** with BMS and trimethylborate at 0 °C gives **370** in quantitative yield [101]. Reduction of dimethyl (*S*)-malate (**2**) with either sodium borohydride at room temperature [102] or lithium aluminum hydride at 65 °C [8] affords **370** in 96% and 100% yield, respectively.

Triol **370** can also be prepared by reduction of EE-protected dimethyl malate **9a** [14,15] or diethyl malate **9b** [16] to give (*S*)-2-(1-ethoxyethoxy)-1,4-butanediol (**371**) in high yield. Deprotection under acidic conditions then furnishes **370** (Scheme 49). Cyclization of **370** (obtained by this route) under acidic conditions results in the formation of (*S*)-(+)-3-



hydroxytetrahydrofuran (**372**) with $>99\%$ *ee* [103]. A similar reaction using **370** obtained by the direct reduction of **2** with lithium aluminum hydride affords **372** with 94% *ee*. The lower optical purity is attributed to partial racemization during reduction of the unprotected dimethyl (*S*)-malate (**2**).



Scheme 49

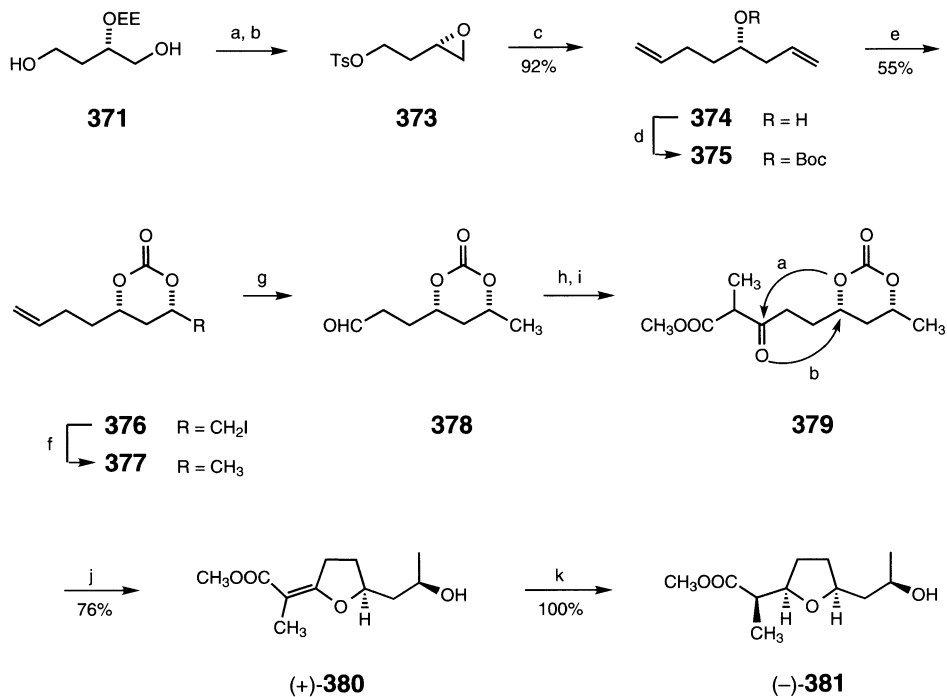
Nonactin (**384**), a member of a family of antibiotics isolated from a variety of *Streptomyces* cultures, has been synthesized in a rather amazing fashion generating 16 asymmetric centers in which (*S*)-malic acid is the only source of chirality [14]. The two crucial skeletal subunits, (–)-methyl 8-*epi*-nonactate (**381**) and (+)-methyl nonactate (**383**), are prepared from the common intermediate **379** (Schemes 50 and 51).

Protected diol **371** is first converted to its bis-tosylate. Removal of the EE protecting group and potassium carbonate-induced cyclization leads then to epoxide **373** in 76% overall yield from **2** ($2 \rightarrow 9a \rightarrow 371 \rightarrow 373$). Opening the oxirane ring with a divinylcuprate reagent affords the chiral octadienol **374**. Iodocyclization of cyclic carbonate **375** produces a 6.5 : 1 mixture of *cis* and *trans* iodocarbonates from which the desired *cis* isomer (**376**) is isolated by chromatography. Hydride removal of the halogen, ozonolysis of the olefin, addition of methyl propionate enolate to the aldehyde, and oxidation of the resulting alcohol furnishes the desired intermediate **379**.

At this point, the beauty of the synthesis emerges. Methanolysis of the carbonate protecting group and oxalic acid-catalyzed cyclodehydration of the resulting hydroxy ketone (path a, as shown in Scheme 50) provides **380**. Catalytic reduction introduces the remaining two chiral centers to give **381** as the major product (88 : 9 : 3).

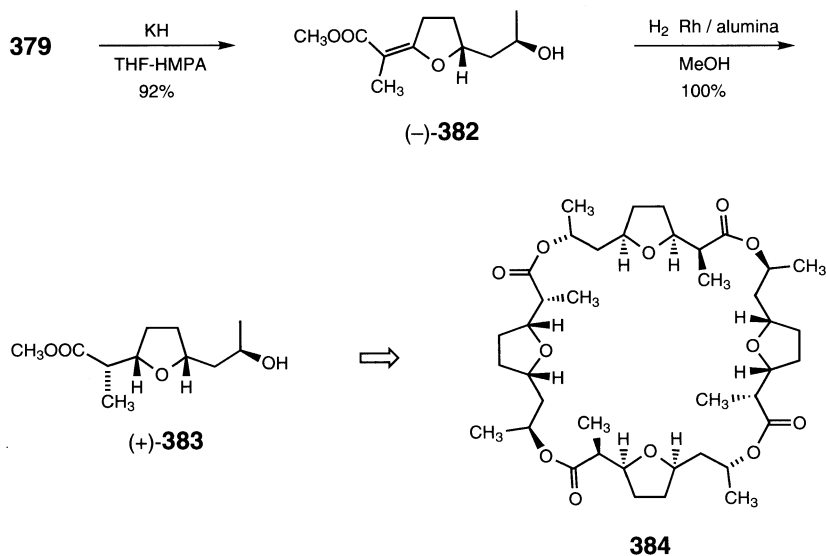
Treatment of the carbonate **379** with potassium hydride induces cyclization of the resulting β -keto enolate with the oxygen at C-6 (path b, Scheme 50), thus forming the diastereomeric product **382** as a result of inversion of configuration during the cyclization. Catalytic reduction provides the remaining stereocenters, and gives **383** as the major product (88 : 9 : 3).

Nonactin is assembled by coupling the subunits **381** and **383** with inversion of configuration at the hydroxyl center of **381**. After ester cleavage, the resulting dimeric acid is simultaneously dimerized and cyclized to provide the natural product **384**.



Scheme 50

conditions: (a) TsCl, pyridine (92%); (b) PPTS, MeOH then K₂CO₃; (c) CH₂=CHLi, CuCN, THF; (d) 2-(((*t*-butoxycarbonyl)oxy)imino)-2-phenylacetonitrile, THF (98%); (e) I₂, CH₃CN, -20 °C; (f) Bu₃SnH, THF, 40 °C (98%); (g) O₃, MeOH, -78 °C; (h) CH₃CH=C(OTMS)OCH₃, TiCl₄, CH₂Cl₂, -78 °C (85%); (i) Jones [O] (91%); (j) K₂CO₃, MeOH then oxalic acid; (k) H₂ (60 psi), 5% Rh/alumina, MeOH

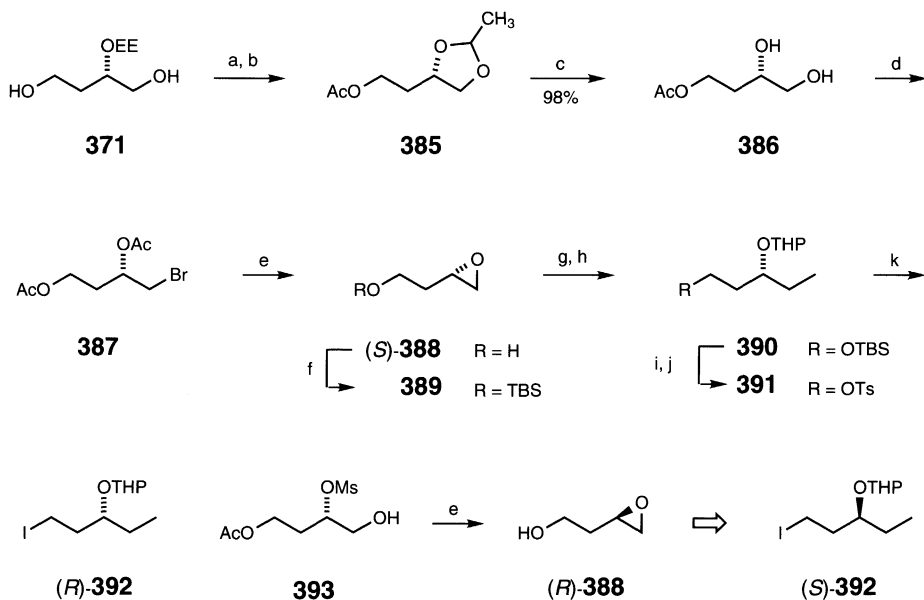


Scheme 51

7-Ethyl-2-methyl-1,6-dioxaspiro[4.5]decane is a constituent of the antiaggregative pheromone produced by several varieties of bees. All of the four thermodynamically stable stereoisomers of this spiroacetal have been synthesized using (*S*)-malic acid and (*S*)-lactic acid as the sources of chirality [15].

The two critical enantiomeric pieces (*R*)-**392** and (*S*)-**392**, both derived from malic acid, are synthesized *via* the EE-protected diol **371** as shown in Scheme 52. Treatment of **371** with boron trifluoride etherate results in the formation of acetal **385**. Hydrolysis of the acetal furnishes **386** in 98.4% overall yield from **2**. Conversion of the terminal hydroxy to a bromide followed by base-catalyzed cyclization (with retention of configuration) gives the (*S*)-epoxide **388**. Regioselective opening of the oxirane with methyl cuprate and protection of the newly formed secondary alcohol with a THP group affords **390**. Conversion of the TBS-protected hydroxyl to an iodide *via* tosylate **391** furnishes one of the desired fragments, (*R*)-**392** with >99% *ee*. The sequence starting from (*S*)-malic acid requires 14 steps, and proceeds in 13.2% overall yield.

The enantiomeric fragment (*S*)-**392** is available from **386** by mesylation (**393**) followed by base-catalyzed cyclization (with inversion of configuration) to the (*R*)-epoxide **388**. A similar series of reactions transforms (*R*)-**388** to the iodide (*S*)-**392** with 100% *ee*.

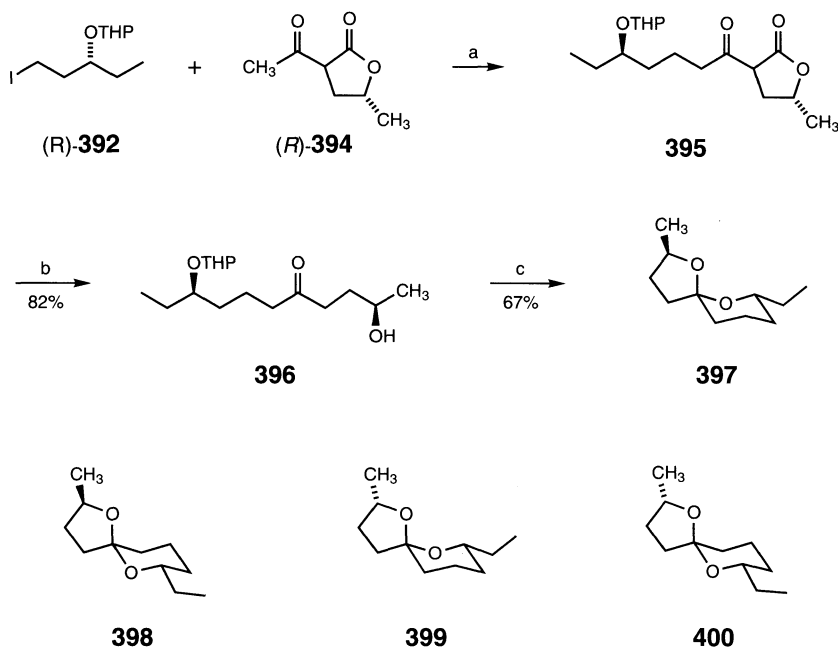


Scheme 52

conditions: (a) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, ether; (b) Ac_2O , DMAP, pyridine, CH_2Cl_2 ; (c) HOAc, H_2O , reflux; (d) HBr, HOAc; (e) K_2CO_3 , MeOH, THF; (f) TBS-Cl, Et_3N , DMAP, CH_2Cl_2 ; (g) CH_3MgBr , CuBr, THF, -40°C ; (h) DHP, hexane, Amberlyst-15; (i) Bu_4NF , THF; (j) TsCl, pyridine, CH_2Cl_2 , -10°C ; (k) NaI, acetone

Scheme 53 illustrates the final construction of the spiroacetal. Alkylation of the dianion of the lactic acid-derived acetyl butyrolactone (*R*)-**394** with iodide (*R*)-**392** furnishes **395**. Hydrolysis of **395** with concomitant decarboxylation furnishes **396** which, upon removal of the THP protecting group under acidic conditions, forms the (*2R,5R,7R*)-diastereomer **397** in 42.6% overall yield from (*R*)-**392**.

The remaining three diastereomers are synthesized analogously. Thus, (*S*)-**392** and (*R*)-**394** produces (*2R,5S,7S*)-**398**, (*R*)-**392** and (*S*)-**394** produces (*2S,5R,7R*)-**399** and (*S*)-**392** and (*S*)-**394** produces (*2S,5S,7S*)-**400**, each with 96% optical purity.



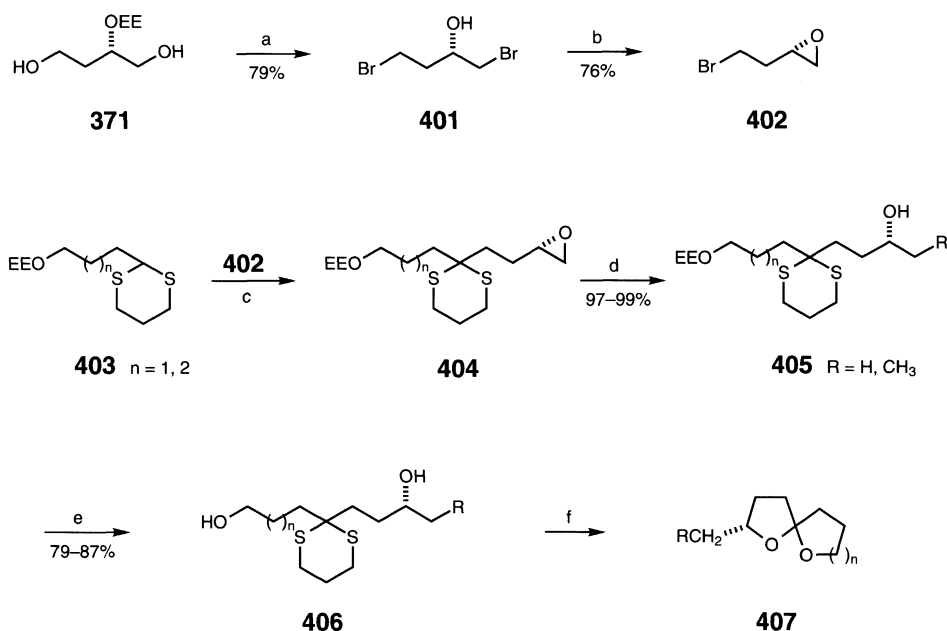
Scheme 53

Conditions: (a) NaH, THF then *n*-BuLi, $-15\text{ }^{\circ}\text{C}$; (b) KOH, H_2O , MeOH; (c) 2N HCl, $0\text{--}5\text{ }^{\circ}\text{C}$

Other spiroacetal natural products have been prepared using malic acid-derived epoxides as the chiral source (Scheme 54). Chalcogran (**407**, $\text{R}=\text{CH}_3$, $n=1$) is the principal component of the aggregation pheromone of the beetle *Pityogenes chalcographus* (L.), a pest of Norway spruce. Spiroacetal **407** ($\text{R}=\text{H}$, $n=2$) is a minor volatile component found in the common wasp, *Paravespula vulgaris*.

The bromo epoxide **402** used in these syntheses is prepared from **371** by initial conversion to (*S*)-1,4-dibromo-2-butanol (**401**) [16] followed by cyclization with potassium hydroxide [18]. Alkylation of 1,3-dithiane first with EE-protected ω -chloroalcohols to give **403** and then with the (*S*)-epoxide **402** affords **404**. Opening the oxirane with either Super-Hydride or methyl cuprate creates the requisite carbon skeletons **405** with the appropriate functionality patterns. Removal of the EE protecting group and mercury-mediated hydrolysis of the thioacetal directly furnishes the spiroacetals **407** as a 3 : 2 mixture of diastereomers [16].

A somewhat similar strategy is used for the synthesis of the antibiotic vermiculin (Scheme 55) [104,105]. Alkylation of 1,3-dithiane with **402** affords monoalkylated derivative **408** in high yield. Opening the oxirane with lithio 2-methyl-1,3-dithiane produces **409**, which is then formylated, protected, and subjected to a Wittig-type reaction to give an α,β -unsaturated ester. Hydrolysis of the ester and removal of the protecting group furnishes optically pure **411** in 75% overall yield from **409**. A dimerizing cyclization under Mitsunobu conditions forms the macrolide skeleton with inversion of configuration at both chiral centers. Mercury-assisted hydrolysis of the four thioacetals gives (*R,R*)-vermiculin (**413**) as a single enantiomer.



Scheme 54

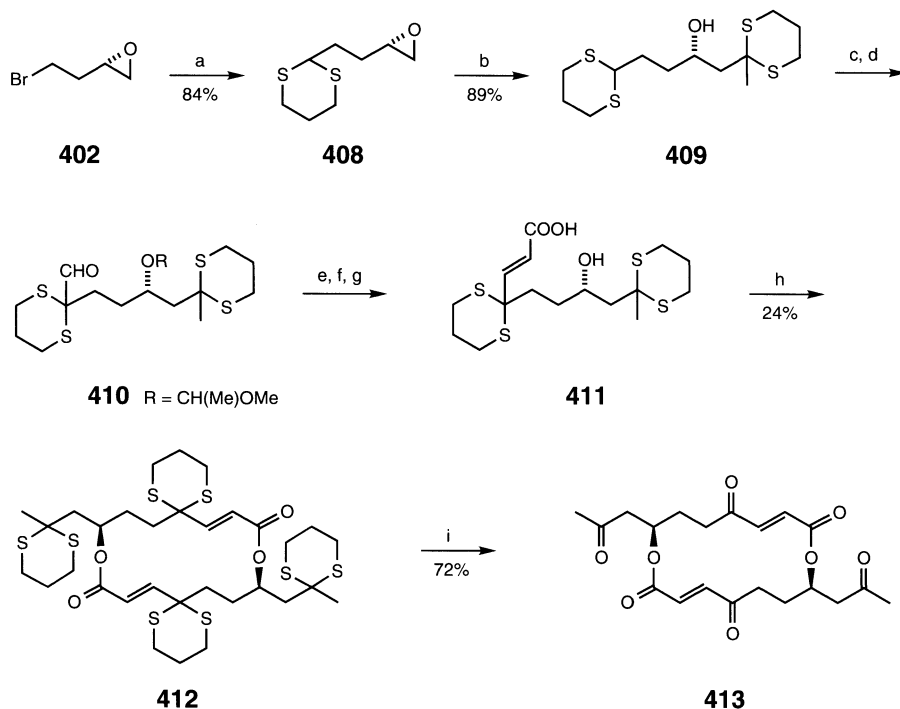
conditions: (a) TsCl, pyridine, then conc. HCl, then CuBr; (b) KOH, H₂O, 40 °C; (c) *n*-BuLi, THF, -78° → -30 °C (93%); (d) LiBHEt₃, THF, -78°C or methyl cuprate, THF, -40 °C; (e) 2N HCl, THF; (f) HgCl₂, MeOH

(2*S*,3*R*)-4-Bromo-1,2-epoxy-3-methylbutane (**416**) is prepared by a route similar to that used for **402**. The alkylated malate **225a** is first protected with an EE group, and the esters are then reduced with lithium aluminum hydride. Conversion of the alcohols to bromides and cyclization under basic conditions affords **416** [86]. The synthetic utility of this very interesting chiral epoxide remains to be explored.

Both enantiomers of 4-iodo-1,2-epoxybutane are available from (*S*)-malic acid as shown in Schemes 57 and 58. Reduction of THP-protected dimethyl or diethyl malate with lithium aluminum hydride gives diol **417**. Immediate mesylation affords **418** in 65–70% overall yield [6,19]. Acidic hydrolysis of the THP ether furnishes the crystalline bis-mesylate **419**, which upon mild base treatment cyclizes to epoxide **420** with retention of configuration. Treatment with sodium iodide gives (*S*)-(-)-4-iodo-1,2-epoxybutane (**421**).

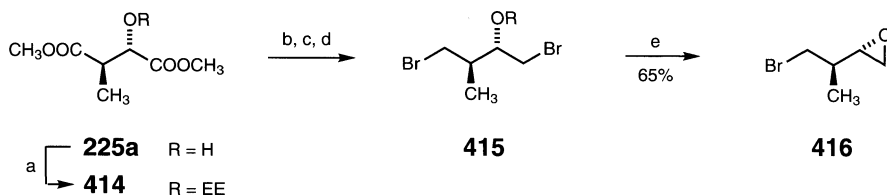
The preparation of (*R*)-(+)-4-iodo-1,2-epoxybutane (**427**) from (*S*)-malic acid requires an inversion of configuration at the hydroxyl-bearing carbon. This can be accomplished by placing the leaving group (OMs) at the site of the secondary alcohol as in **424** instead of at the primary alcohol (**419**). Consequently, base-catalyzed methanolysis of the two acetate groups of **424** gives an intermediate diol that immediately undergoes S_N2 displacement of the mesylate, thus furnishing the (*R*)-epoxy alcohol **425** [6]. Conversion of the alcohol to the iodide **427** proceeds in a manner analogous to the previous example.

The (*S*)-epoxy alcohol **388**, previously synthesized from EE-protected malic acid, can also be prepared from THP-protected malic acid *via* diol **417** (Scheme 59) [107]. When the anion of acetone *N,N*-dimethylhydrazone is sequentially alkylated with (*S*)-1,2-epoxypropane followed by **389** and the resulting product is hydrolyzed under acidic conditions, the result is a mixture of exogonols **430** in 47% yield.



Scheme 55

conditions: (a) 1,3-dithiane, *n*-BuLi, $-100\text{ }^{\circ}\text{C}$; (b) 2-methyl-1,3-dithiane, *n*-BuLi, $-78\text{ }^{\circ}\text{C}$; (c) $\text{CH}_2=\text{CHOCH}_3$, TFA (100%); (d) *n*-BuLi, DMF (100%); (e) methyl-2-(triphenylphosphorandyl)acetate, toluene, $80\text{--}90\text{ }^{\circ}\text{C}$, (90%); (f) 0.5N LiOH; (g) 2N HCl; (h) Ph_3P , DEAD, toluene; (i) $\text{BF}_3\cdot\text{Et}_2\text{O}$, HgO

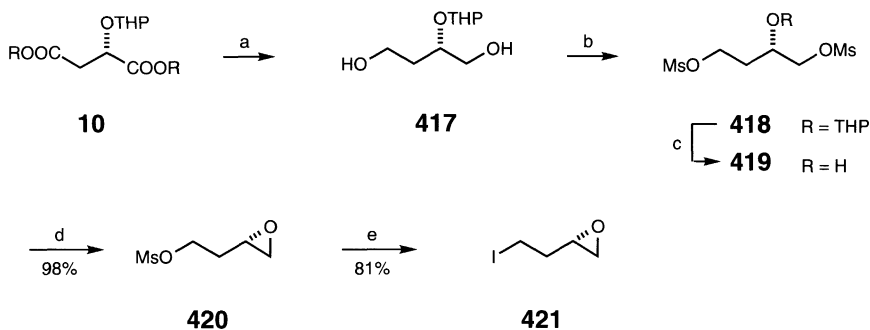


Scheme 56

conditions: (a) $\text{CH}_2=\text{CHOEt}$, TFA (99%); (b) LiAlH_4 , ether, $-10\text{ }^{\circ}\text{C} \rightarrow \text{rt}$ (95%); (c) TsCl, pyridine, CH_2Cl_2 (100%); (d) LiBr, CuBr, NaHCO_3 , acetone (77%); (e) KOH, H_2O

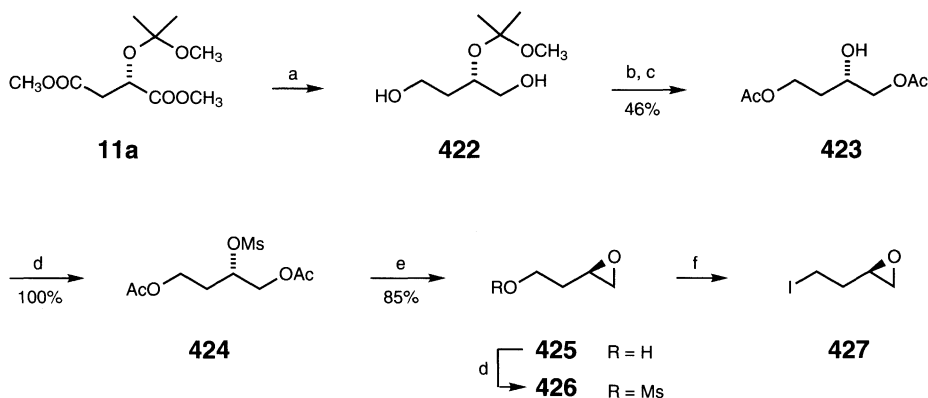
The bis-mesylate **418** serves as a useful difunctional alkylating agent. Treatment of **418** with an excess of lithium sulfide affords protected tetrahydrothiophene **431** in 76% yield. Removal of the THP group under acidic conditions gives (*S*)-3-hydroxytetrahydrothiophene (**432**) in 75% yield [17].

Dibromide **401** has also been used as a four-carbon alkylating agent in the synthesis of the spiro alkaloid sesbanine (**436**) (Scheme 60) [108]. Although the preparation of **401** was previously described starting from EE-protected malic acid, this synthesis utilizes THP-protected malic acid as the starting material [18]. Alkylation of the pyridyl acetate **434** with **401** in ethanol gives cycloannulation product **435** as a single stereoisomer. The configuration



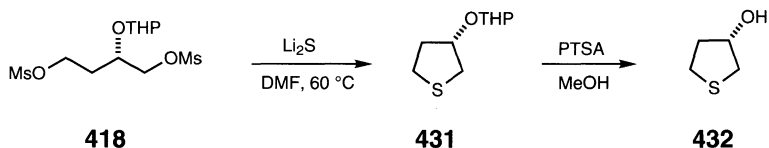
Scheme 57

conditions: (a) LiAlH₄, THF, 55 °C; (b) MsCl, Et₃N, CH₂Cl₂, -15 °C; (c) CH₃SO₃H, EtOH, 50 °C (74%); (d) K₂CO₃, MeOH–THF (1:1); (e) NaI, K₂CO₃, acetone



Scheme 58

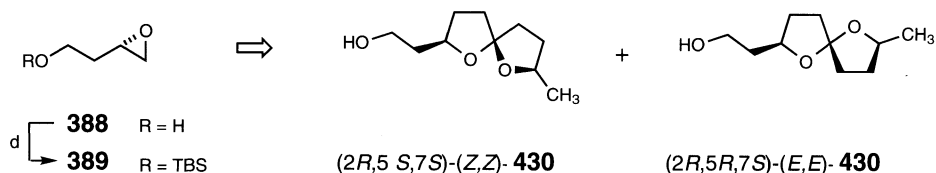
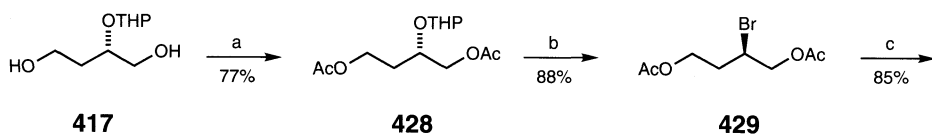
conditions: (a) LiAlH₄, THF, 55 °C; (b) Ac₂O, pyridine, DMAP, THF; (c) 5% HCl; (d) MsCl, Et₃N, CH₂Cl₂, -15 °C; (e) K₂CO₃, MeOH–THF (1:1); (f) NaI, K₂CO₃, acetone



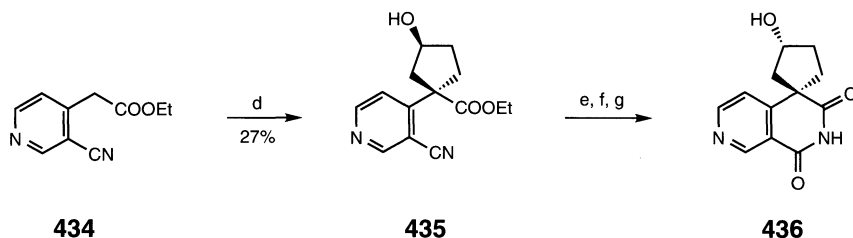
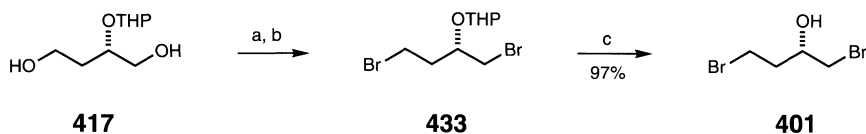
of the hydroxyl group is inverted under Mitsunobu conditions, and the nitrile is selectively hydrolyzed, thus forming the desired cyclic imide **436** in 51% overall yield from **435**.

3.3.1.1 Acetals of (*S*)-1,2,4-Butanetriol

By far the most widely used chiral intermediates derived from malic acid are acetals of 1,2,4-butanetriol. Triol **370** is by its nature capable of forming acetals with either the C-1 and C-2 hydroxyls, thus producing a 5-membered ring, or with the C-2 and C-4 hydroxyls to give a

**Scheme 59**

conditions: (a) Ac₂O, pyridine, DMAP, CH₂Cl₂, 0 °C; (b) HBr, HOAc; (c) K₂CO₃, MeOH; (d) TBS-Cl, Et₃N, DMAP, CH₂Cl₂

**Scheme 60**

conditions: (a) TsCl, pyridine, CH₂Cl₂ (96%); (b) LiBr, NaHCO₃ (90%); (c) 5% HCl, acetone–MeOH; (d) **401**, K₂CO₃, EtOH; (e) DEAD, Ph₃P, HOAc; (f) K₂CO₃, EtOH (83%); (g) NaOH, 30% H₂O₂, EtOH (83%)

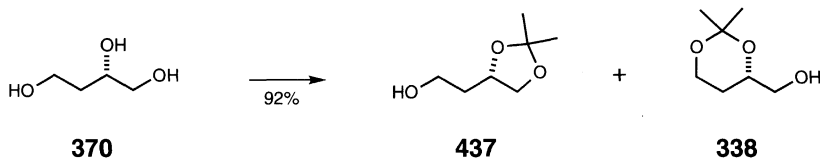
6-membered ring. These differentially protected forms of **370** thereby become highly versatile intermediates that can be used for the introduction of one or more asymmetric centers into a target molecule.

3.3.1.1.1 Five-Membered Acetals

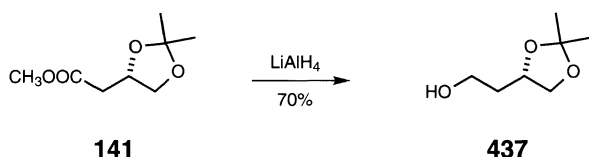
The most straightforward method for the preparation of the 5-membered acetonide **437** is direct treatment of triol **370** with acetone and PTSA [101]. Alternatively, the protected triol **422** (Scheme 58) can be cyclized with boron trifluoride etherate to give **437** in 86% yield [20].

Initially, it was thought that **437** was formed as a pure product, however, it was later discovered [109] that it actually arises as a 9 : 1 equilibrium mixture of the thermodynamic

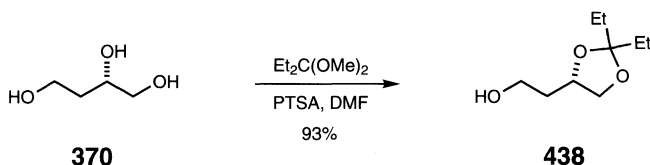
acetone **437** and kinetic 6-membered acetone **338**. This acetone mixture can be purified by separation of the corresponding 3,5-dinitrobenzoate esters by fractional crystallization (41% yield) followed by regeneration of pure **437** through hydrolysis of the ester with potassium carbonate in methanol (83% yield). Alternatively, the acetone mixture can be benzoylated (PhCOCl, Et₃N, DMAP, CH₂Cl₂, 0 °C) and the resulting benzoates separated by column chromatography with methylene chloride as the eluting solvent. Hydrolysis of the ester with sodium hydroxide in methanol furnishes pure **437** in 67% overall yield [8].



The implicit drawbacks in this method can be circumvented by approaching the problem from a different perspective. Thus, reduction of the acetone **141** with lithium aluminum hydride [55,110] produces pure **437** directly, and in good yield.

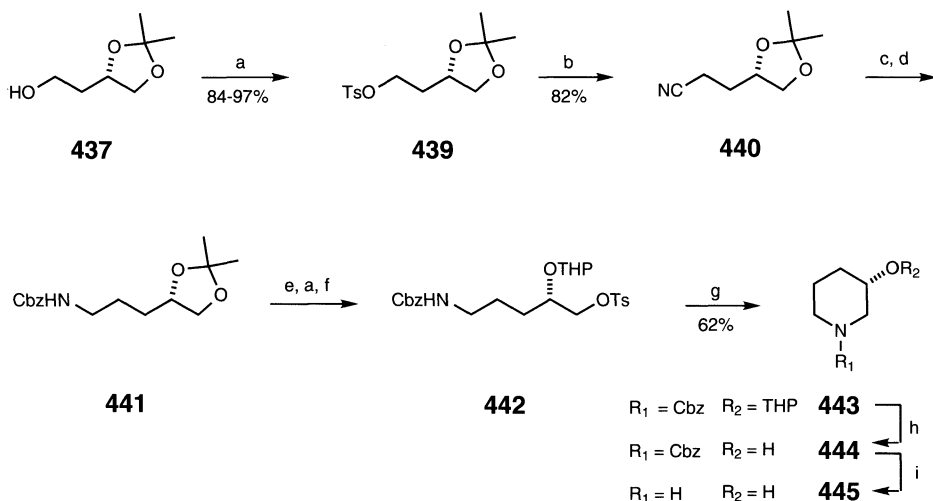


Alternatively, ketalization of **370** with 3,3-dimethoxypropane furnishes **438** as a 45 : 1 mixture of 5- and 6-membered ketals [111]. This dramatic difference can presumably be explained by increased nonbonded interactions that further destabilize the 6-membered ketal with respect to its 5-membered counterpart [112].



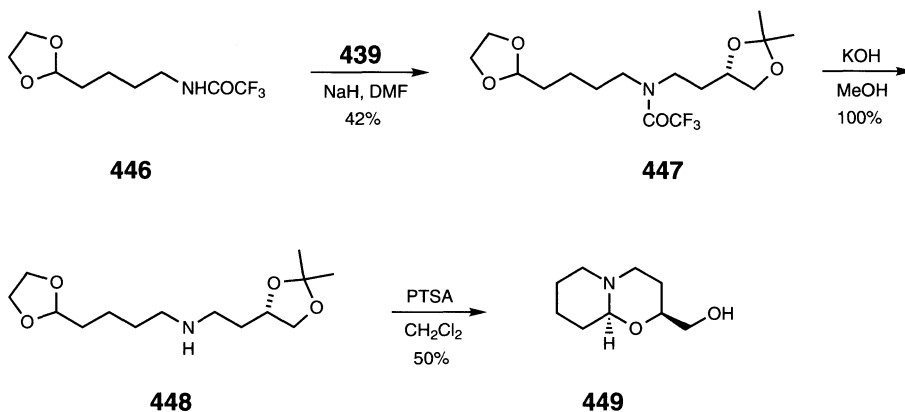
One can now take advantage of the remaining free hydroxyl moiety and convert it into a group that acts as either a nucleophile or an electrophile. Converting the hydroxy substituent into a leaving group provides access to a variety of useful chiral alkylating agents.

Treatment of **437** with tosyl chloride and triethylamine in methylene chloride in the presence of a catalytic amount of DMAP [8], or use of pyridine as both the base and solvent [113,114], affords the tosyloxy derivative **439** in high yield. Displacement of the tosylate group with cyanide gives **440**, and reduction of the nitrile and protection of the resulting amine with a Cbz group then furnishes **441**. Cleavage of the acetone and selective manipulation of the diol gives **442** as an apparent mixture of isomers, only one of which cyclizes to the piperidine **443**. The cyclization is erratic, and gives variable results (37–62% yield). Removal of the protecting groups furnishes (*S*)-(–)-3-hydroxypiperidine (**445**) in an overall yield of 10% from **437** (Scheme 61) [113].

**Scheme 61**

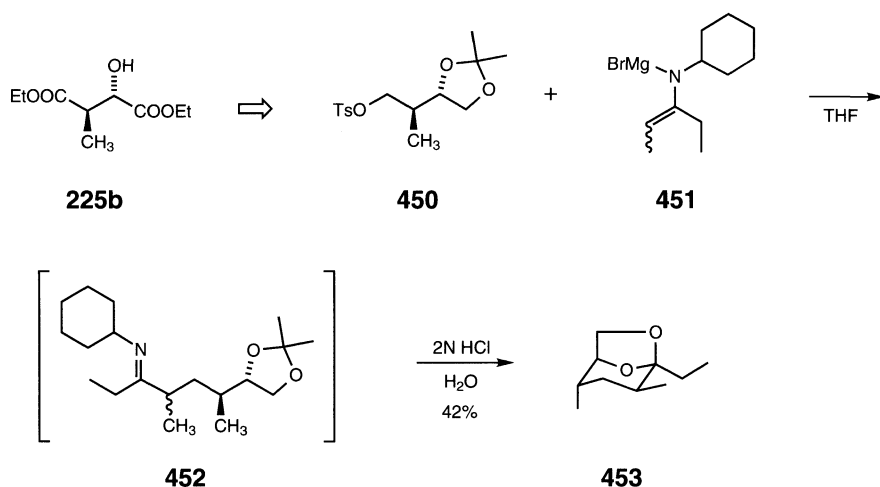
conditions: (a) TsCl, pyridine; (b) NaCN, DMF, 85 °C; (c) LiAlH₄, ether (70%); (d) Cbz-Cl, MgO (93%); (e) CF₃COOH (60%); (f) DHP, PTSA (100%); (g) NaH, THF; (h) HOAc, H₂O (70%); (i) H₂ (50 psi), 10% Pd/C, EtOH (100%)

In model studies directed towards the synthesis of Xestospongine, a marine natural product, the appropriate heterocyclic backbone (an oxaquinolizidine ring system) is easily constructed using tosylate **439** (Scheme 62). Thus alkylation of trifluoroacetone **446** with **439** results in the formation of **447** in moderate yield. Removal of the trifluoroacetyl group under basic conditions followed by removal of the two acid-labile acetal groups produces the desired product **449** directly as a single isomer [8].

**Scheme 62**

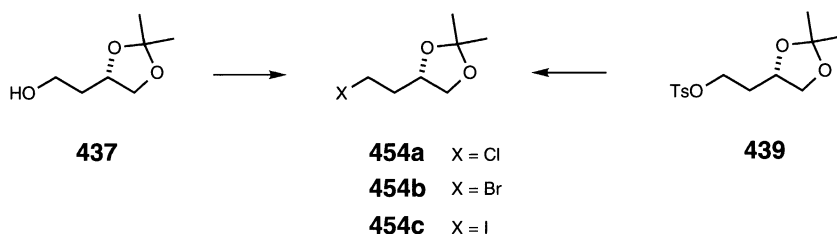
In the synthesis of (–)- δ -multistriatin (**453**), alkylated diethyl (*S*)-malate (**225b**) is converted to the tosyl acetone **450** by the sequence of reactions described previously in this

Section. Alkylation of **451** with **450** produces an intermediate cyclohexyl imine **452**, which upon acid hydrolysis cyclizes to the target compound **453** with 97% isomeric purity (Scheme 63) [115].



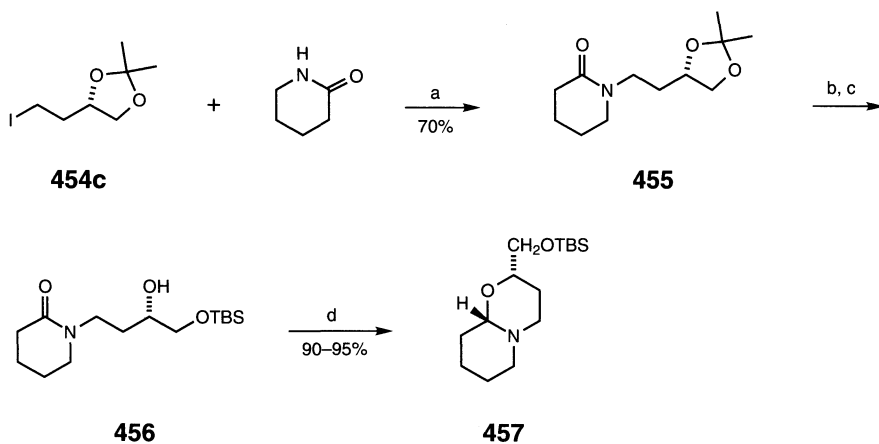
Scheme 63

Halogenated acetonides **454** are readily accessible from either the free alcohol **437** or its tosylate **439**. Treatment of **437** with triphenylphosphine and carbon tetrachloride furnishes the chloro derivative **454a** in 86% yield [116]. A similar reaction of **437** with triphenylphosphine and carbon tetrabromide [117] or *N*-bromosuccinimide [118] produces the bromide **454b** in 77% yield. Alternatively, reaction of tosylate **439** with lithium bromide gives **454b** in 78% yield [114], whereas sodium iodide affords **454c** in 97% yield [55,119].

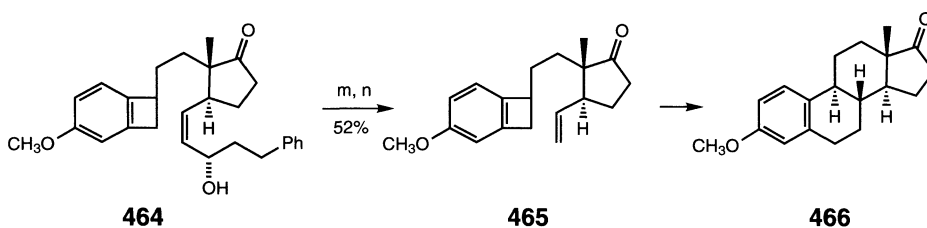
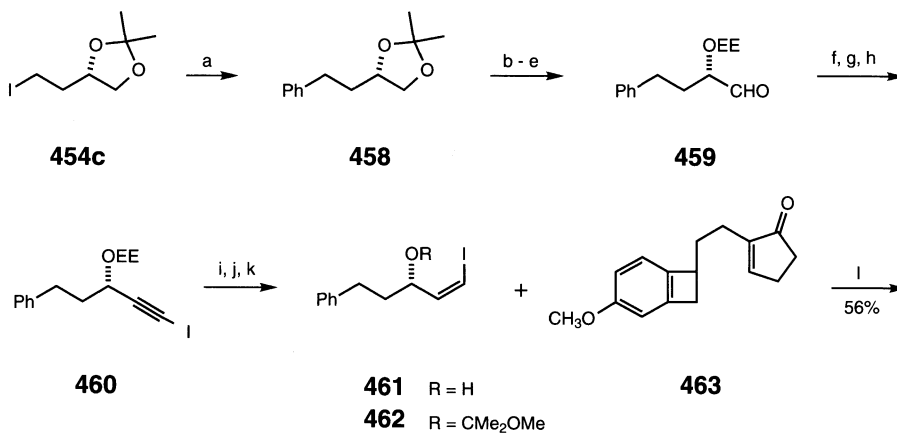


The alkylation of 2-piperidone with iodoacetone **454c** furnishes *N*-alkylated derivative **455**, which in three manipulations is converted to the 1-oxaquinolizidine moiety (**457**) of Xestospongins A (Scheme 64) [55].

In the synthesis of estrone methyl ether (**466**), iodoacetone **454c** is converted to the protected *Z*-vinylidide **462** as shown in Scheme 65 [119]. After conversion of **462** to a phosphine-stabilized organocopper reagent, a 1,4-addition to enone **463** followed by trapping of the resulting enolate with methyl iodide gives **464** as a 95 : 5 mixture of methyl epimers. Oxidative cleavage of the olefin followed by a Wittig olefination furnishes the vinyl derivative **465**, which upon heating at 180 °C in *o*-dichlorobenzene undergoes an intramolecular Diels–Alder reaction to give (+)-estrone methyl ether (**466**) in 70% yield and 96% *ee*.

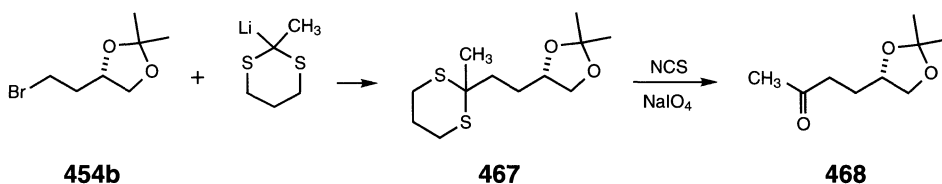
**Scheme 64**

conditions: (a) KO^tBu, THF, 50 °C; (b) PPTS, MeOH (92%); (c) TBS-Cl, imidazole, DMF (90%); (d) LiAlH(*i*-Bu)₂(*n*-Bu), THF-hexane, -20° → 0 °C

**Scheme 65**

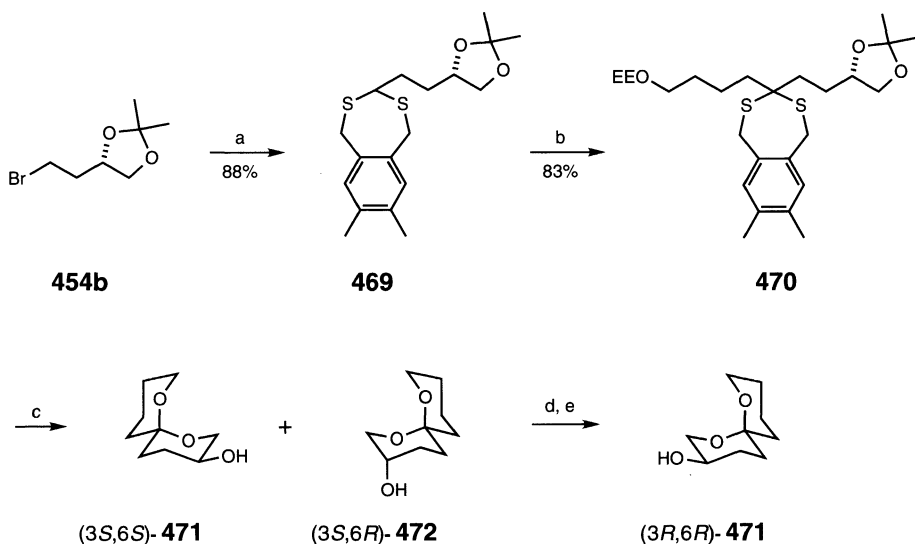
conditions: (a) PhMgBr; (b) *t*-BuCOCl, pyridine; (c) ethyl vinyl ether, H⁺; (d) LiAlH₄; (e) Swern [O]; (f) CBr₄, Ph₃P; (g) *n*-BuLi; (h) I₂; (i) KOOCN=NCOOK; (j) MeOH, H⁺; (k) Me₂NH; (l) *t*-BuLi, CuI, Bu₃P then CH₃I, HMPA; (m) OsO₄, NaIO₄; (n) CH₂=PPh₃, THF, 0 °C

Alkylation of 2-methyl-2-lithio-1,3-dithiane with **454b** affords dialkylated dithiane **467**. Subsequent hydrolysis of the thioacetal furnishes methyl ketone **468** [118].



Both enantiomers of 3-hydroxy-1,7-dioxaspiro[5.5]undecane (**471**), the minor component of the olive fly pheromone, can be synthesized from (*S*)-malic acid *via* acetone **454b** (Scheme 66) [120]. The initial carbon skeleton is constructed by sequential alkylation of **341** with **454b** and then EE-protected 4-iodobutanol. Copper-mediated hydrolysis of the dithiepin ring affords a complex mixture of products, two of which, (*3S,6S*)-**471** and **472**, are isolated in 33% and 18% yields respectively.

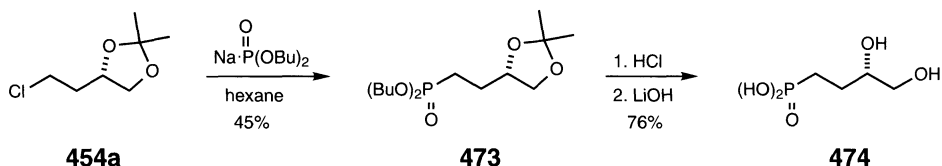
The antipode (*3R,6R*)-**471** is produced from **472** by Mitsunobu inversion (78% yield) followed by hydrolysis of the resulting 3,5-dinitrobenzoate. The (*3S,6S*)-**471** enantiomer can also be converted to (*3R,6R*)-**471** by Mitsunobu inversion of the hydroxyl group (87% yield) followed by equilibration of the spiroacetal with zinc triflate (29% yield).



Scheme 66

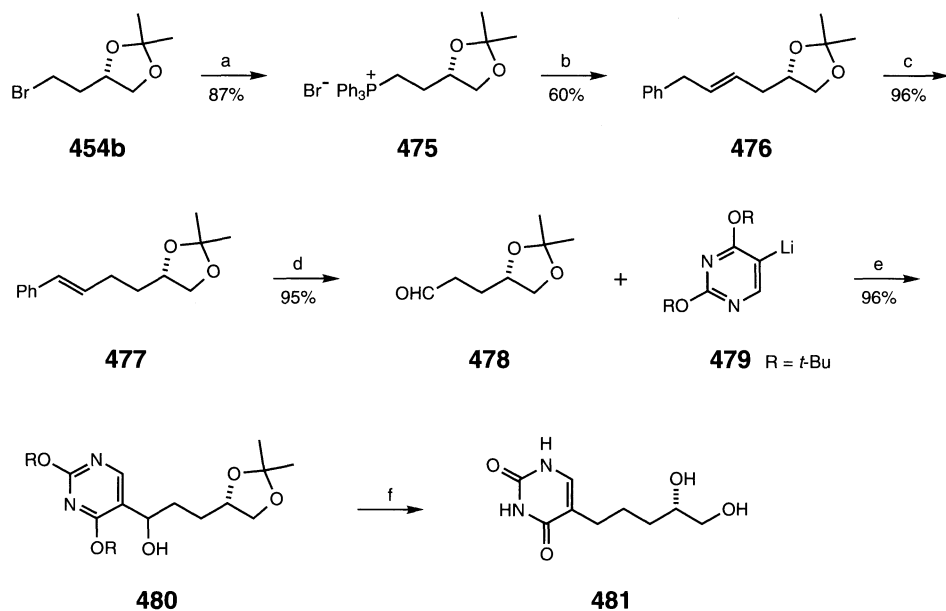
conditions: (a) **341**, *n*-BuLi, THF; (b) I-(CH₂)₄OEE, *n*-BuLi, THF; (c) CuCl₂·2H₂O, CuO, acetone-H₂O, (99:1); (d) 3,5-dinitrobenzoic acid, Ph₃P, DEAD; (e) KOH, THF-MeOH-H₂O

Displacing the chlorine of **454a** with phosphonate provides ready access to the isosteric phosphonic acid analog **474** of glycerol-3-phosphate. This (*S*)-enantiomer is a growth inhibitor of *Escherichia coli* strain 8 and *Bacillus subtilis* BD strains 170 and 1005 [116].



The formation of phosphonium salts with **454** makes them excellent candidates as chiral Wittig reagents for olefination reactions. Several examples are shown in Schemes 67, 68 and 69.

(*S*)-(+)-5-(4',5'-Dihydroxypentyl)uracil (**481**), a modified base that replaces thymine in bacteriophage SP-15 DNA, is synthesized using Wittig reagent **475**, which is readily prepared from **454b** and triphenylphosphine (Scheme 67) [117,121]. Conversion of **475** to a phosphorane and subsequent reaction with phenylacetaldehyde furnishes the *E*-homoconjugated olefin **476**. Isomerization of the double bond to the *trans*-styrene **477** followed by ozonolysis gives aldehyde **478** in approximately 50% overall yield from **454b**. Condensation of the aldehyde with 5-lithio-2,4-*tert*-butylpyrimidine (**479**) affords adduct **480**. Catalytic hydrogenation in moist methanol removes both the benzylic hydroxyl and the remaining protecting groups to give **481** in quantitative yield.

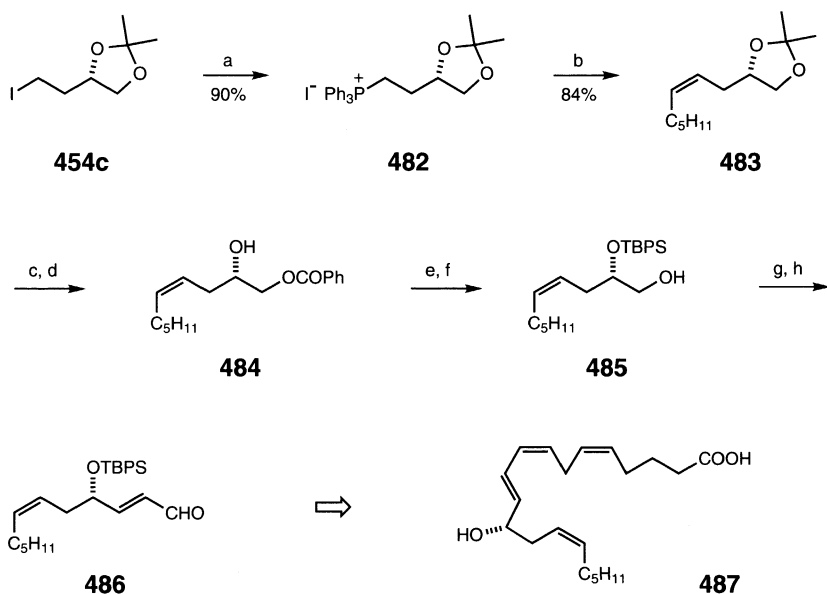


Scheme 67

conditions: (a) Ph_3P , ether, 100 °C (sealed tube); (b) *n*-BuLi, THF then PhCH_2CHO ; (c) KO t -Bu, DMSO; (d) O_3 , MeOH, -70 °C; (e) THF, -70 °C; (f) H_2 , Pd black, MeOH-H $_2$ O

Phosphonium salt **482** supplies the only chiral center (at C-12) in the synthesis of 12-hydroxyeicosatetraenoic acid (12-HETE) (**487**), a biologically important substance formed by the oxidative metabolism of arachidonic acid (Scheme 68) [44].

The lower half of the molecule is constructed by a *cis*-selective Wittig reaction of **482** with hexanal. After protective-group manipulation, the hydroxy group of **485** is oxidized to an aldehyde with Collins reagent and the compound is then homologated to the α,β -unsaturated aldehyde **486**. A second *cis*-selective Wittig reaction couples the bottom fragment with an upper phosphorane fragment to give the desired double bond geometry in the final product, 12(*S*)-HETE (**487**).

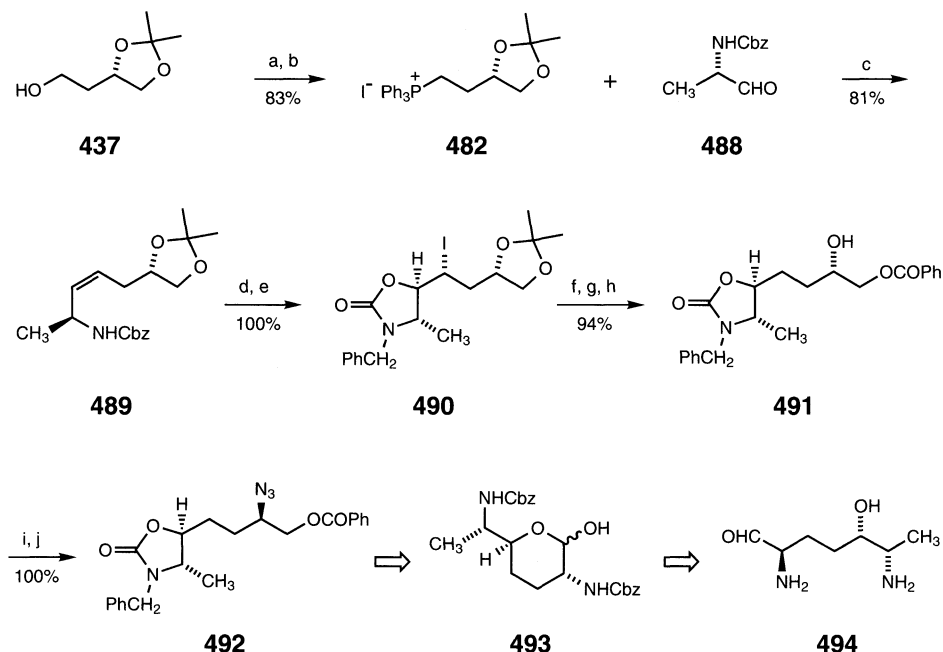


Scheme 68

conditions: (a) Ph_3P , CH_3CN , NaHCO_3 , 40°C ; (b) *n*-BuLi, THF, HMPA, -80°C , *n*- $\text{C}_5\text{H}_{11}\text{CHO}$; (c) 1N HCl, MeOH (100%); (d) PhCOCN , Et_3N , CH_2Cl_2 , 0°C (88%); (e) TBPS-Cl, imidazole, DMF (93–99%); (f) DIBAL, ether, -80°C (96%); (g) $\text{CrO}_3\cdot 2\text{py}$, CH_2Cl_2 , 10°C (71%); (h) $\text{Ph}_3\text{P}^+\text{CH}_2\text{CHO Cl}^-$, Et_3N , CH_2Cl_2 (87%)

Phosphonium salt **482**, which can also be prepared from alcohol **437** by treatment with methyltriphenoxyphosphonium iodide followed by triphenylphosphine, has been used in a stereoselective synthesis of 6-*epi*-D-purpurosamine B (**494**) (Scheme 69) [122]. A Wittig reaction of the ylide generated from **482** and Cbz-L-alaninal (**488**) affords the *Z*-olefin **489**. Iodocyclization gives the *trans*-cyclocarbamate **490** in quantitative yield. Removal of the iodo group, hydrolysis of the acetonide, and benzoylation furnishes **491**.

Introduction of the second nitrogen substituent is accomplished by mesylation of the secondary alcohol and subsequent displacement (with inversion) by sodium azide. Hydrolysis of the carbamate, hydrogenolysis of the *N*-benzyl group with concomitant reduction of the azide group, protection of the newly formed amino group with a Cbz, and ruthenium-catalyzed cyclization gives the hemiacetal **493**, which is then carried on to the target molecule **494**.



Scheme 69

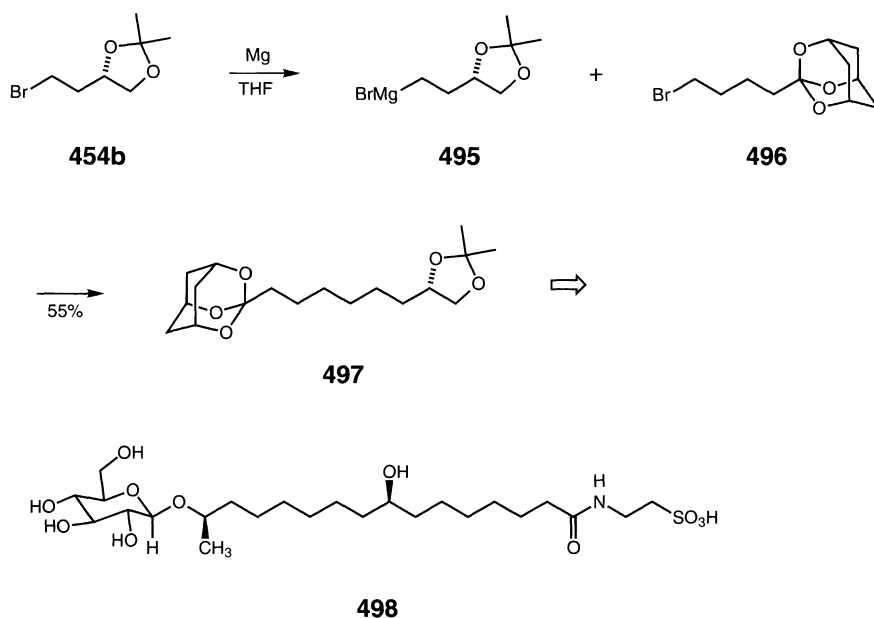
conditions: (a) $(\text{PhO})_3\text{PMel}$, DMF; (b) Ph_3P , ether; (c) KH, THF; (d) PhCH_2Br , NaH; (e) I_2 ; (f) Bu_3SnH , benzene; (g) 1N HCl, THF; (h) PhCOCl , Et_3N , CH_2Cl_2 ; (i) MsCl , Et_3N , CH_2Cl_2 ; (j) NaN_3 , DMF

Treatment of bromide **454b** with magnesium generates Grignard reagent **495** [114], which is readily alkylated with bromide **496**. Acetonide **497** was subsequently converted to **498**, the oviposition-deterrent pheromone of *Rhagoletis cerasi* L. (Scheme 70).

It is not always necessary to use halogenated acetonides **454** in alkylation reactions. Phthalimide can be alkylated with alcohol **438** under Mitsunobu conditions to give **499** in quantitative yield. This intermediate has been used in a synthesis of (+)-Geissman Lactone (**506**) (Scheme 71) [123,124]. Through a series of protecting-group manipulations, **499** is converted to MOM-protected diol **501** in high yield. Swern oxidation of the terminal alcohol affords hemiacetal **502**, and a subsequent Horner–Emmons reaction using Still's modification forms the *Z*-olefin **503** exclusively. Cyclization and MOM cleavage gives **504** with 39 : 1 selectivity. Mesylation of the hydroxyl group, hydrolysis of the ester, and base-catalyzed cyclization produces lactone **505** as the result of an intramolecular $\text{S}_{\text{N}}2$ displacement of the mesylate by carboxylate.

In Section 3.2.4 we briefly introduced epoxide **303** as a useful chiral intermediate. Here, we expand upon the synthetic utility of **303** along with other epoxides. In addition to the previously described synthesis, epoxide **303** can also be prepared from acetals **437** or **438**, as shown in Scheme 72. Silylation of the hydroxy acetonides can be effected with TBPS-Cl in the presence of a variety of bases and solvents. Imidazole in DMF furnishes **507a** in 98% yield [125], DBU in methylene chloride gives **507a** in 86% yield [126], and triethylamine with a catalytic amount of DMAP in methylene chloride affords **507b** in 96% yield [112].

Selective cleavage of the acetonide using either PPTS in methanol or aqueous acetic acid furnishes **301** in 84–88% yield. Mesylation of **301** under standard conditions affords **508a**

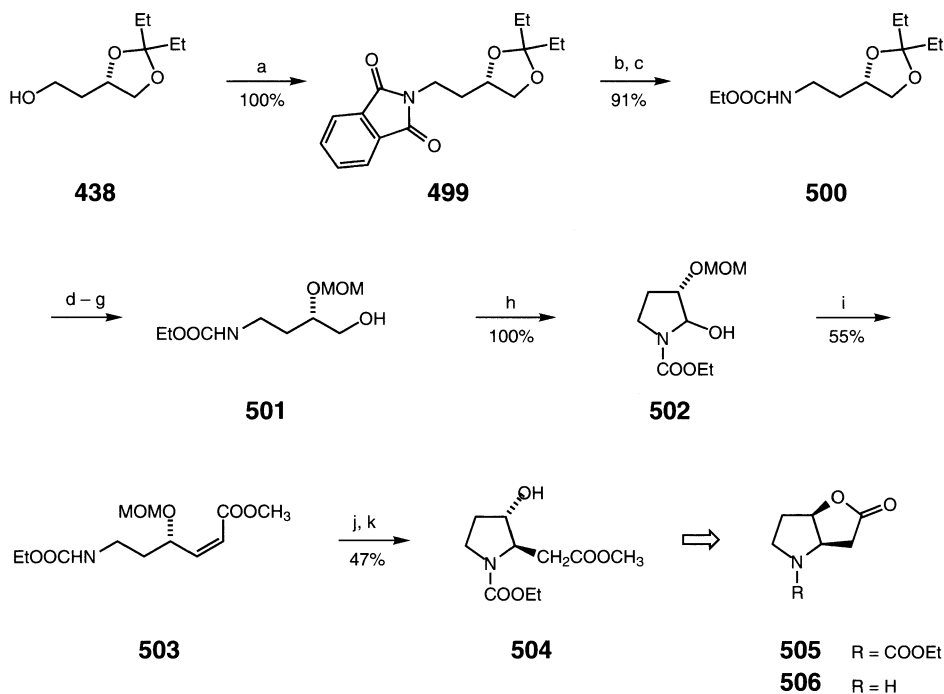


Scheme 70

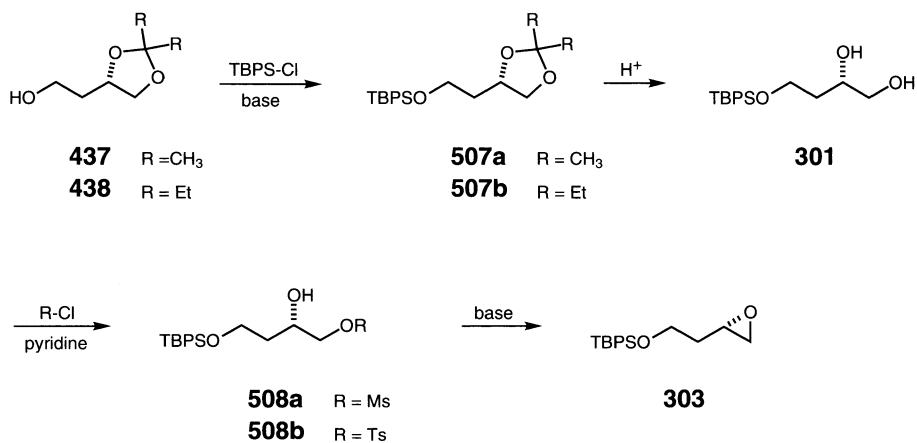
along with a minor amount of the secondary mesylate. This must be separated chromatographically prior to cyclization or else the product will be contaminated with the corresponding (*R*)-epoxide. Treatment of pure **508a** with benzyltrimethylammonium hydroxide affords **303** in 91% yield [112]. Alternatively, tosylation of **301** gives **508b** as a solid that can be recrystallized to the necessary purity. Cyclization of the tosylate with potassium carbonate [125] or potassium hydroxide [126] in methanol gives **303** in 87% and 71% yields respectively from **301**.

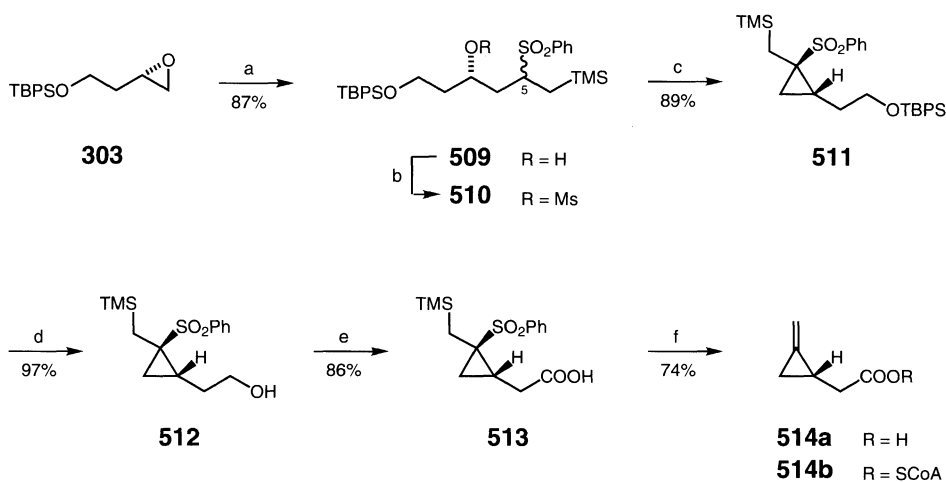
Epoxide **303** has been used as an enantioselective synthesis of the methylenecyclopropylacetic acid (**514a**) portion of (methylenecyclopropyl)acetyl-CoA (**514b**), a mammalian metabolite of hypoglycines A and B. Addition of the anion derived from phenyl 2-(trimethylsilyl)ethyl sulfone to **303** produces a 3 : 1 mixture of *threo* and *erythro* diastereomers **509**. Either diastereomer cyclizes to the same cyclopropane **511** upon treatment with LDA, which suggests that epimerization at C-5 must be occurring prior to cyclization. Selective removal of the TBPS group followed by oxidation of the alcohol to an acid and elimination affords the desired product **514a** (Scheme 73) [126,127].

Under more forcing conditions (sodium hydride in refluxing THF) the adduct **509** undergoes elimination of the benzenesulfonyl group with concomitant migration of the TMS to oxygen giving **515** in good yields (R=H, 80%; R=CH₃, 66%) (Scheme 74) [128,129]. Removal of the more labile silyl group by methanolysis affords **516**. Alternatively, treatment of **303** with dilithium (cyano)divinylcuprate produces **516** (R=H) directly in 96% yield [112]. Iodocarbonation of **516** gives an intermediate cyclic carbonate **517**, which when immediately treated with base cyclizes to epoxide **518** (R=H, 54%; R=CH₃, 69%). When R=CH₃, **518** is obtained as a 20 : 1 mixture of diastereomers, but when R=H, only one diastereomer can be detected by NMR. An iterative reaction of **518** with the anion of phenyl 2-(trimethylsilyl)ethyl sulfone followed by acetonide formation and fluoride-catalyzed elimination (TBAF, CH₃CN, reflux) results in formation of the protected *erythro*-diol **519**.

**Scheme 71**

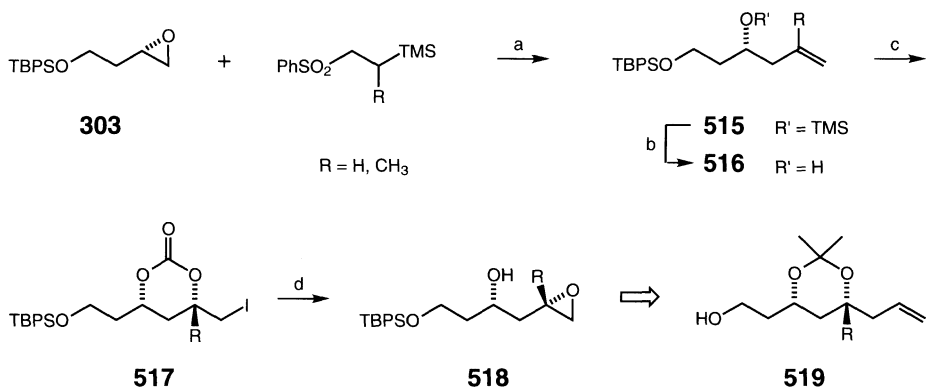
conditions: (a) phthalimide, Ph_3P , DEAD; (b) $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$, EtOH; (c) ClCOOEt, Et_3N ; (d) 6N HCl, THF (100%); (e) TBS-Cl, imidazole, DMAP, CH_2Cl_2 (95%); (f) MOM-Cl, $i\text{-Pr}_2\text{NEt}$ (100%); (g) Bu_4NF , THF (100%); (h) Swern [O]; (i) $(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(\text{O})\text{CH}_2\text{COOCH}_3$, KH, DME; (j) KH, 18-crown-6, DME, 0°C ; (k) EtSH, $\text{BF}_3 \cdot \text{Et}_2\text{O}$

**Scheme 72**



Scheme 73

conditions: (a) $\text{PhSO}_2\text{CH}_2\text{CH}_2\text{TMS}$, BuLi , THF; (b) MsCl , pyridine (95%); (c) LDA , THF, -78°C ; (d) Bu_4NF , THF, rt; (e) Jones [O], acetone; (f) Bu_4NF , CH_3CN , reflux



Scheme 74

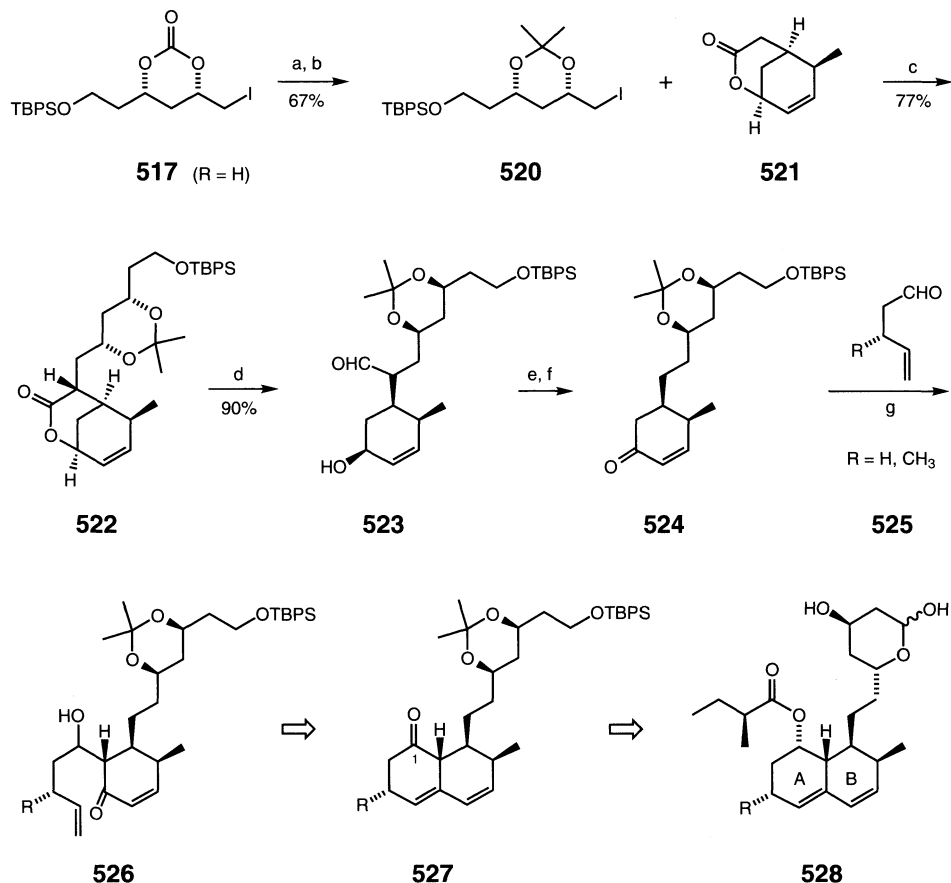
conditions: (a) $n\text{-BuLi}$, THF, $-78^\circ\text{C} \rightarrow \text{rt}$ then NaH , reflux; (b) PPTS, MeOH; (c) $n\text{-BuLi}$, THF, $0^\circ\text{C} \rightarrow \text{rt}$ then CO_2 and I_2 ; (d) K_2CO_3 , MeOH

The arrangement of functional groups as well as the *erythro* configuration of the latent diol makes carbonate **517** an excellent candidate as a “compactin lactone” synthon (**99**) and it has in fact been used in the synthesis of both compactin (**97**) and mevinolin (**98**) (Scheme 75) [112].

The desired synthon, acetonide **520**, is prepared from carbonate **517** by treatment with acetone under acidic conditions. Alkylation of bicyclic lactone **521** with **520** affords **522** as a single isomer. Reduction of the lactone with DIBAL produces an equilibrium mixture of lactol and hydroxy aldehyde **523**. Oxidation of the allylic alcohol and decarbonylation with Wilkinson’s catalyst furnishes the crucial enone intermediate **524** common to both natural products.

Annulation of the A ring is accomplished by reaction of the appropriate 4-pentalenone **525** with the kinetic enolate generated from **524** followed by ozonolysis of the olefin and cyclization of the resulting ketoaldehyde with potassium graphite–titanium trichloride. Oxidation of the alcohol under Swern conditions gives **527**.

The correct stereochemistry of the C-1 hydroxyl is introduced by reducing the carbonyl group of **527** with L-Selectride. Acylation of the alcohol with (*S*)- α -methylbutyric anhydride, oxidation of the TBPS-protected primary alcohol to an aldehyde, and acetone cleavage affords the penultimate lactol **528**. Oxidation of this lactol with Fetizon's reagent ($\text{Ag}_2\text{CO}_3/\text{Celite}$) gives (+)-compactin (**97**) or (+)-mevinolin (**98**).

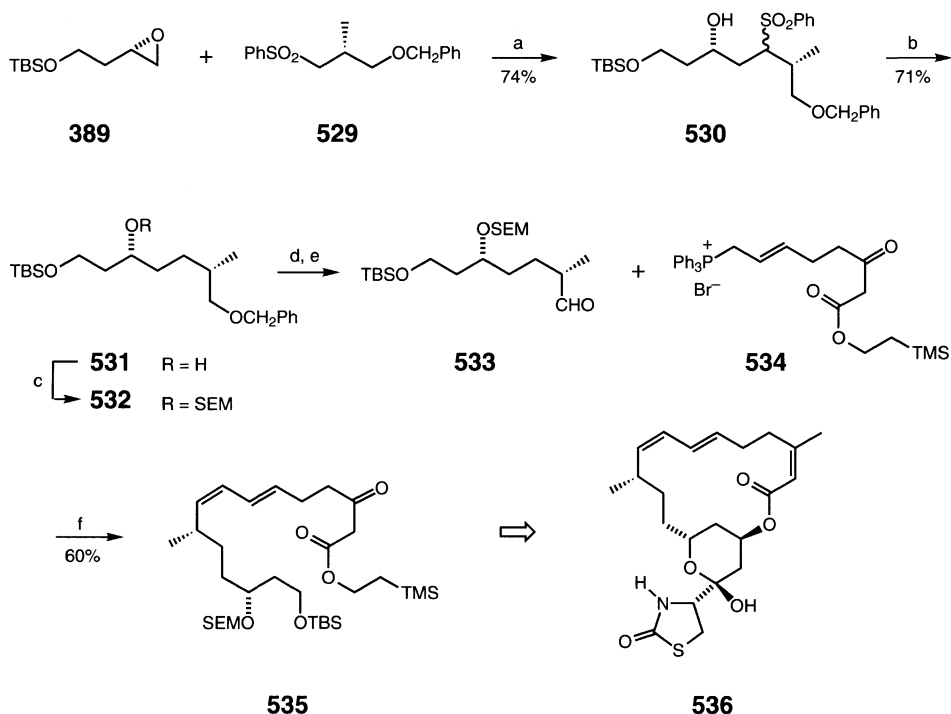


Scheme 75

conditions: (a) PTSA, acetone; (b) TBPS-Cl, Et_3N , DMAP, CH_2Cl_2 ; (c) LDA, THF, HMPA, $-78^\circ\text{C} \rightarrow \text{rt}$; (d) DIBAL, CH_2Cl_2 , -78°C ; (e) MnO_2 , NaOAc, CHCl_3 (78%); (f) $(\text{Ph}_3\text{P})_3\text{RhCl}$, toluene- CH_3CN , reflux (50%); (g) LDA, ether, -78°C

In the synthesis of latrunculin A (**536**), an ichthyotoxin isolated from the Red Sea sponge, the Pacific nudibranch, and the Fijian sponge, the large perimeter macrolide segment incorporates a fragment derived from (*S*)-malic acid (Scheme 76) [130].

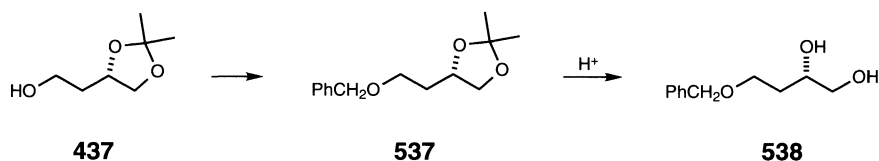
The synthesis begins with alkylation of the anion of phenylsulfone **529** with epoxide **389** to give hydroxy sulfone **530**. In contrast to the previous cases just discussed, in which the phenylsulfonyl group is eliminated to form an olefin, in this instance the group is simply removed reductively to furnish **531**. After protection of the hydroxyl group, hydrogenolysis of the O-benzyl ether and oxidation of the resulting primary alcohol furnishes aldehyde **533**. A Wittig reaction of **533** with the phosphorane derived from **534** produces (*E,Z*)-**535** as the sole diene isomer. Elaboration to the final product **536** requires 9 additional steps.



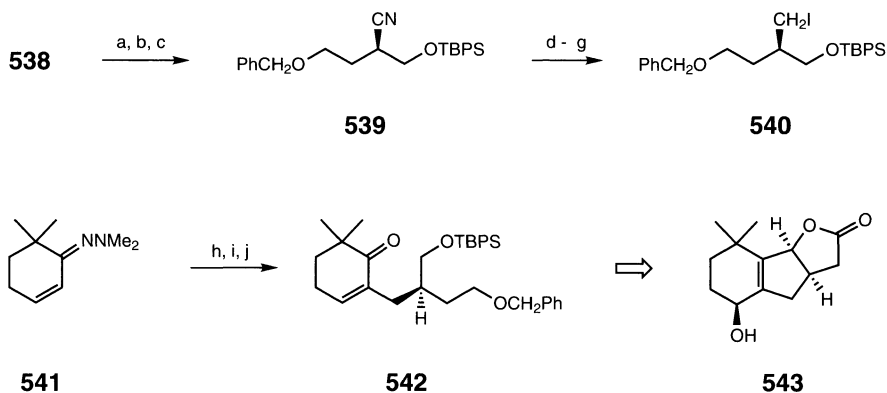
Scheme 76

conditions: (a) *n*-BuLi, THF, HMPA, 0 °C; (b) Na(Hg), EtOH; (c) SEM-Cl, *i*-Pr₂NEt, CH₂Cl₂ (91%); (d) H₂, 10% Pd/C, EtOAc, HCl (cat) (95%); (e) Swern [O]; (f) THF, 0 °C

Benzylating the hydroxyl group of **437** provides access to a wide variety of useful chiral intermediates containing a more robust protecting group capable of withstanding either acidic or basic reaction conditions. The benzylation is typically carried out with benzyl bromide and sodium hydride in THF [110,131,132] under phase-transfer conditions, and it results in formation of the benzyl ether **537** in approximately 95% yield. Cleavage of the acetonide with either PTSA [110,132] or 1M sulfuric acid [131] affords diol **538** in 92% or 98% yield respectively.



The primary hydroxyl of **538** can be selectively silylated, thereby leaving the remaining secondary alcohol free to undergo further reactions. Mesylation and nucleophilic displacement with cyanide gives nitrile **539** with inversion of configuration. Conversion of the cyano group to an iodide (**540**) and alkylation of hydrazone **541** with this iodide furnishes enone **542**, which has been carried on to the tricyclic lactone **543**, a key intermediate in the synthesis of strigol (Scheme 77) [110]. The only problematic step occurs in the conversion sequence of nitrile **539** to iodide **540**, where one of the intermediates is an aldehyde. At this point partial racemization intervenes to varying extents (40–75% *ee*). The optical purity of the final product can be raised to 87% *ee* by recrystallization.



Scheme 77

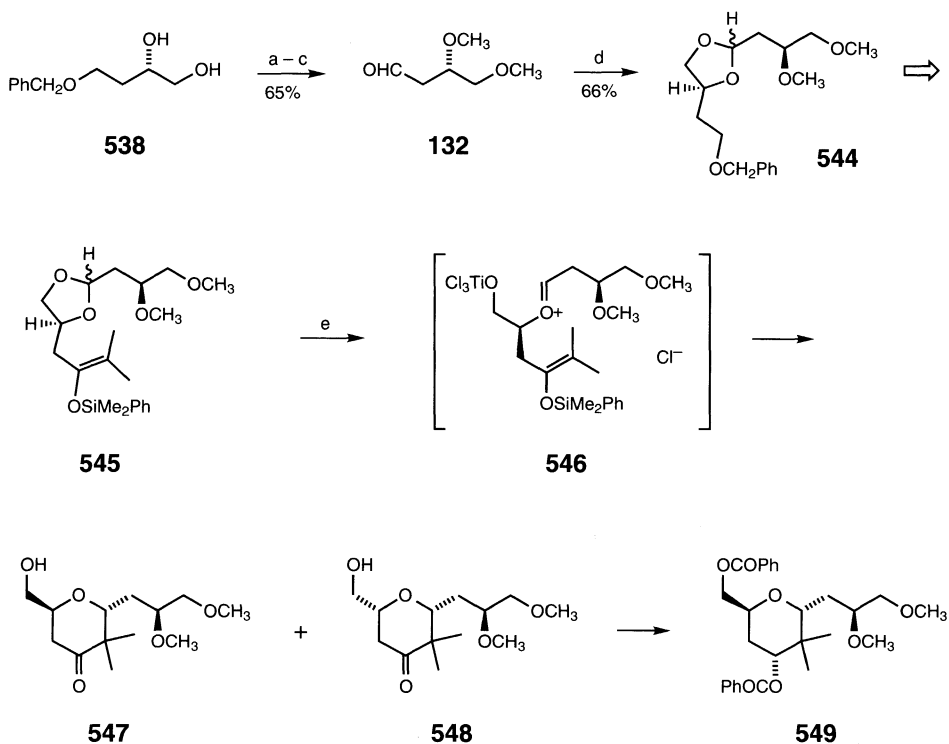
conditions: (a) TBPS-Cl, pyridine (94%); (b) MsCl, Et₃N, CH₂Cl₂ (92%); (c) benzyl tri-*n*-butylammonium cyanide, TMS-CN, CH₃CN, 90 °C (65%); (d) DIBAL, toluene; (e) H⁺; (f) NaBH₄, EtOH; (g) I₂, Ph₃P, imidazole; (h) **540**, LDA, THF; (i) PTSA, ether; (j) Et₃N, MeOH

In the synthesis of pederol dibenzoate (**549**) (Scheme 78), diol **538** is used twice to supply the necessary chiral centers. After conversion of **538** to aldehyde **132** by routine transformations (see also Scheme 17), **132** and **538** are condensed together under acidic conditions to give dioxolan **544** as an inseparable mixture of isomers (75 : 25 *cis/trans*).

In the pivotal reaction, a titanium-mediated aldol condensation of enol silyl ether **545** produces tetrahydropyran-4-ones **547** (11%) and **548** (38%), which are separable by chromatography. Unfortunately, the product with the desired stereochemistry is the minor isomer **547**. The synthesis is completed by benzylation of the primary alcohol, reduction of the ketone with sodium borohydride, and benzylation of the newly formed secondary alcohol [132].

Epoxide **550** is prepared from **538** by converting the primary hydroxyl to a suitable leaving group that can be displaced intramolecularly by the secondary hydroxyl group. Tosylation of **538** with tosyl chloride in pyridine followed by cyclization with DBU gives **550** [131]. Alternatively, treatment of **538** with NBS followed by sodium hydroxide affords **550** in 60% overall yield [133]. In both cases the epoxide is obtained with >98% optical purity (Scheme 79).

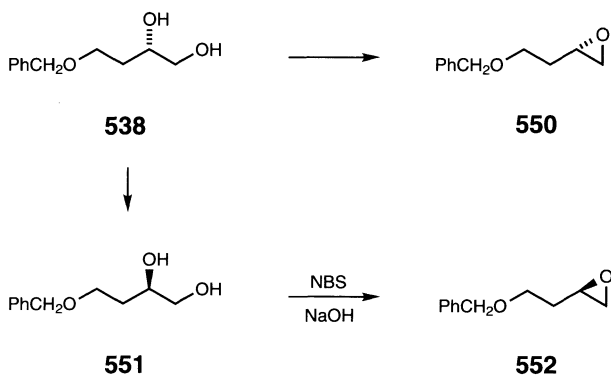
The enantiomeric (*R*)-epoxide **552** can also be prepared from **538** by inverting the hydroxyl stereocenter prior to cyclization. This is accomplished by mesylation of both hydroxy groups,



Scheme 78

conditions: (a) NaI, CH₃I, THF-HMPA; (b) H₂, Pd/C, EtOH; (c) PCC, CH₂Cl₂; (d) **538**, PTSA, MgSO₄, CH₂Cl₂; (e) TiCl₄, CH₂Cl₂, -78 °C

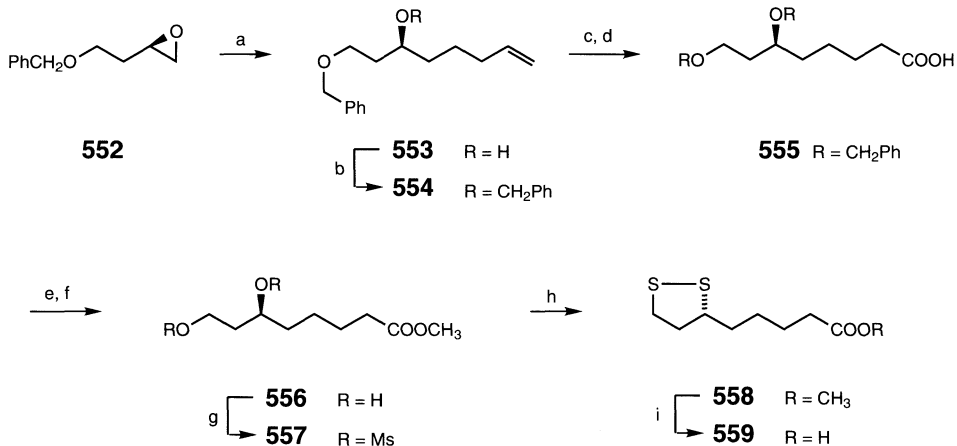
S_N2 displacement of the mesylates by potassium acetate in hot acetic anhydride (the inversion step), and saponification of the resulting diacetate to diol **551** (40% overall yield). Cyclization of **551** with NBS–NaOH gives optically pure **552** [134].



Scheme 79

Addition of organometallics to the epoxide provides ready access to a variety of versatile chiral hydroxyl-bearing intermediates. This is exemplified in Schemes 80–82, where the initial reaction in each sequence is addition of a Grignard reagent to either **550** or **552**.

Both α -(*R*)-lipoic acid (**559**) and its (*S*)-enantiomer have been synthesized from (*S*)-malic acid *via* epoxides **550** and **552**. The synthesis of α -(+)-**559**, the natural form (Scheme 80), begins with the addition of 3-butenylmagnesium chloride to **552**. Since the olefin is later converted to an acid, the original Grignard reagent behaves like a masked form of the organometallic species derived from 4-chlorobutyric acid. The stereochemistry of the final product **559** is the result of two inversions relative to the configuration of (*S*)-malic acid. The first inversion reaction is the conversion of **538** to **551**, and the second is the displacement of the bis-mesylate **557** with sodium sulfide to give methyl lipoate (**558**) [134]. The unnatural (*S*)-enantiomer is prepared by an analogous route starting from the (*S*)-epoxide **550** [135].



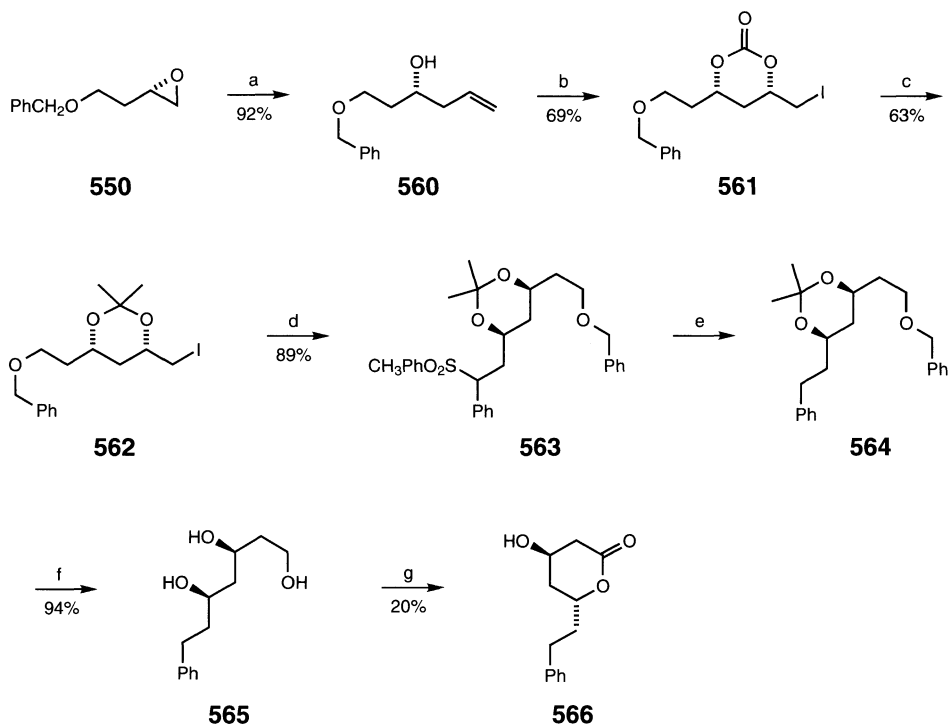
Scheme 80

conditions: (a) CH₂=CHCH₂CH₂MgCl, Li₂CuCl₄, THF; (b) PhCH₂Br, NaH, THF; (c) Sia₂BH, THF then H₂O₂, NaOH; (d) PDC, DMF; (e) MeOH, HCl; (f) H₂ (30 psi), Pd/C, MeOH; (g) MsCl, Et₃N; (h) Na₂S, S, DMF; (i) 1M KOH

In model studies related to the synthesis of compactin (**97**) and mevinolin (**98**), the “upper-half” lactone moiety was constructed from **550** starting with an oxirane ring-opening reaction by vinyl Grignard reagent (Scheme 81) [136]. Iodocarbonation of **560** followed by hydrolysis and ketalization affords isomerically pure acetamide **562**, the “compactin lactone” synthon.

Alkylation of benzyl *p*-tolyl sulfone with **562** followed by desulfonation of **563** with sodium amalgam furnishes **564** in 78% overall yield from **562**. Removal of the protecting groups and oxidation of the primary alcohol of **565** with Fetizon’s reagent affords the optically pure lactone **566** directly. This model demonstrates the feasibility of coupling the “upper-half” lactone unit with a surrogate “bottom-half” fragment *via* alkylation methodology.

The critical C-15 to C-25 spiroacetal-containing fragment of (+)-milbemycin β_3 (**572**) has been constructed from **550**, where the initial step uses 2-propenylmagnesium bromide to open the oxirane ring (Scheme 82) [137]. Unfortunately, the resulting alcohol **567** has the wrong absolute stereochemistry, but this is easily remedied by a Mitsunobu inversion of **568** using 4-nitrobenzoic acid as the nucleophile. Condensation of **569** with tartaric acid-derived *ortho* lactone **570** gives a single diastereomeric spirocyclic *ortho* lactone that is converted in 7 steps to the spiroacetal **571**. Another 10 steps are required to complete the synthesis of **572**.

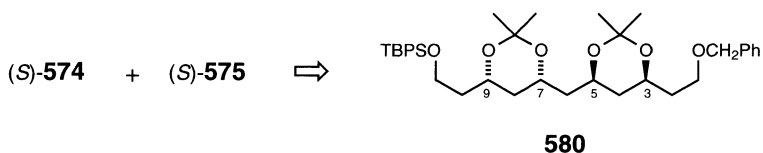
**Scheme 81**

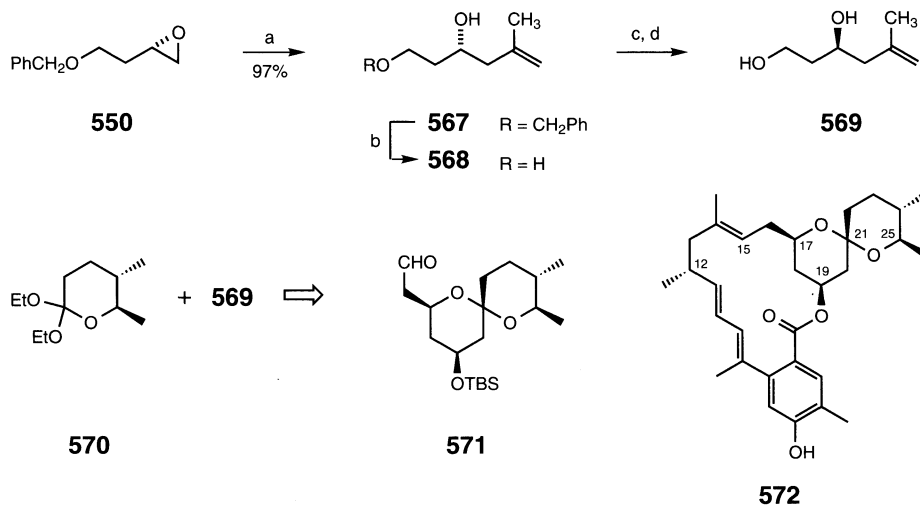
conditions: (a) $\text{CH}_2=\text{CHMgBr}$, THF, rt; (b) $n\text{-BuLi}$, THF then CO_2 then I_2 ; (c) PTSA, acetone; (d) TsCH_2Ph , KH, DMF; (e) Na(Hg) , MeOH, 0°C ; (f) TMSI; (g) Fetizon's reagent

The 1,3-polyol system is prevalent in a variety of marine natural products. This interesting arrangement of hydroxyl groups can be assembled using aldehydes **574**, **575**, and 1,3-dithiane as an acyl anion equivalent (Scheme 83) [138].

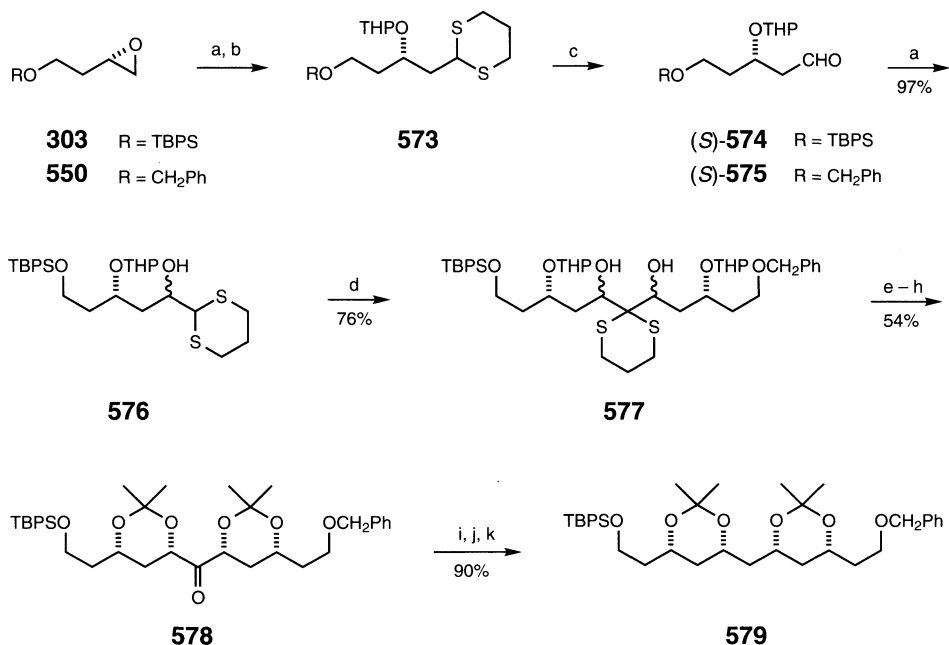
The aldehydes are obtained from either **303** or **550** by opening the oxirane ring with lithiated 1,3-dithiane, protecting the newly formed hydroxyl with a THP group, and hydrolysis of the thioacetal. Silyl-protected (*S*)-**574** is obtained in 76% overall yield, and benzyl-protected (*S*)-**575** is obtained in 60% overall yield. If one begins with (*R*)-epoxide **552**, the enantiomeric (*R*)-**575** is obtained in 69% overall yield. Condensation of **574** with lithiated 1,3-dithiane produces alcohol **576**. Lithiation of **576** with two equivalents of *n*-butyllithium followed by reaction with (*R*)-**575** gives diol **577** as a mixture of isomers. Removal of the THP groups, acetonide formation, hydrolysis of the thioacetal, and epimerization leads to isomerically pure ketone **578**. Reduction of the ketone, xanthate formation, and reduction of the xanthate (with net deoxygenation) affords 3,5,7,9-all-*syn*-tetraol derivative **579**.

A similar sequence of reactions using aldehydes **574** and (*S*)-**575** ultimately produces the 3,5-*syn*-5,7-*anti*-7,9-*syn*-tetraol **580**.



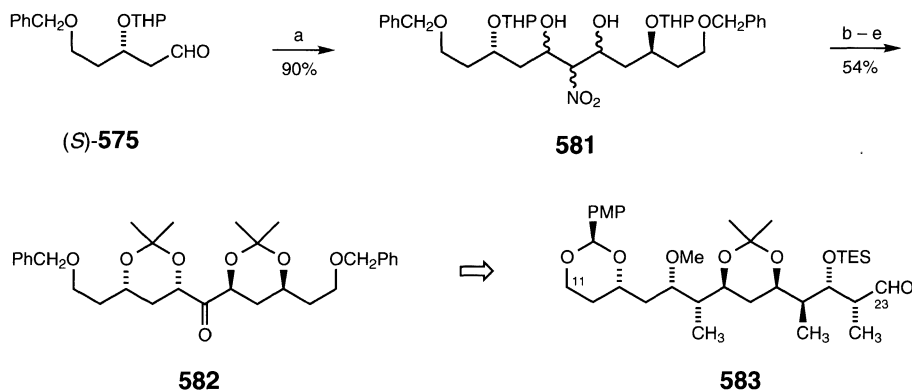
**Scheme 82**

conditions: (a) CH₂=C(CH₃)MgBr, CuI, THF, -30 °C; (b) Na/NH₃ (97%); (c) 4-nitrobenzoic acid, Ph₃P, DEAD, toluene (73%); (d) NaOH, MeOH (88%)

**Scheme 83**

conditions: (a) *n*-BuLi, 1,3-dithiane, THF; (b) DHP, PTSA, CH₂Cl₂; (c) HgO, HgCl₂, acetone; (d) 2 *n*-BuLi, HMPA, THF, -78 °C then (R)-**575**; (e) HOAc-H₂O; (f) Me₂C(OMe)₂, CSA, CH₂Cl₂; (g) NBS, AgNO₃, 2,6-lutidine, CH₃CN-H₂O; (h) K₂CO₃, MeOH; (i) DIBAL, toluene, -48 °C; (j) NaH, CS₂, CH₃, THF; (k) Bu₃SnH, AIBN, toluene, reflux

A related strategy is used in the synthesis of the C-11 to C-23 segment (**583**) of swinholide A, a complex macrolide isolated from the marine sponge *Theonella swinhoi* [139]. The C₂ symmetric ketone **582** is prepared from a single aldehyde, (*S*)-**575**, via a double nitroaldol reaction with nitromethane. High pressure is required to obtain a high yield of **581**, because at atmospheric pressure the product is formed in only 15% yield. Removal of the THP groups, acetonide formation, oxidation of the nitro group to a ketone, and epimerization affords **582** as a single isomer (Scheme 84).



Scheme 84

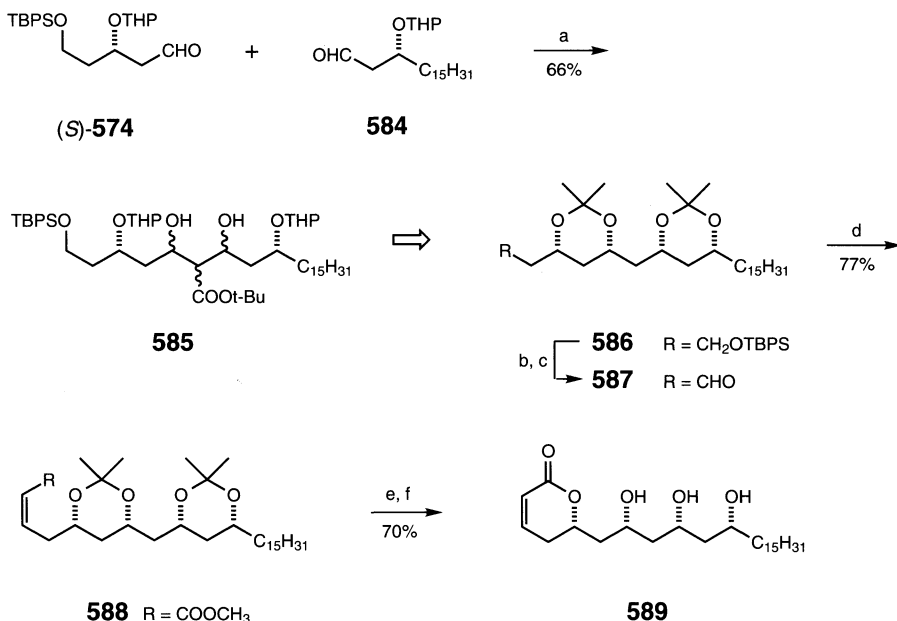
conditions: (a) 1/2 CH₃NO₂, Et₃N, 5.5 kbar; (b) HOAc–H₂O; (c) Me₂C(OMe)₂, CSA, acetone; (d) *t*-BuONa, KMnO₄, MgSO₄, H₂O, benzene; (e) K₂CO₃, MeOH

A synthesis of the δ -lactone of (2*Z*,5*S*,7*S*,9*R*,11*R*)-tetrahydroxyhexacos-2-enoic acid (**589**), a natural product isolated from the aerial parts of *Eupatorium pilosum*, employs a strategically similar approach of coupling two chiral aldehyde pieces via a tandem aldol reaction (Scheme 85) [146]. Aldehyde **584** is prepared from **303** in 4 steps (1: *n*-C₁₄H₂₉MgBr/CuI; 2: DHP, CSA; 3: Bu₄NF; 4: PCC) in 73% overall yield.

Treatment of the lithium enolate of *tert*-butyl acetate with **584** produces a mixture of aldols that is further treated with 2.2 equivalents of LDA and then (*S*)-**574** to give diol **585** as a mixture of isomers. This is subsequently transformed to the all-*syn*-bis-acetonide **586** by conversion of the *tert*-butyl ester to a ketone, epimerization to the desired *syn*-stereochemistry, and removal of the keto group using tactics similar to those described in Scheme 83 (steps h–k). Desilation, oxidation of the primary alcohol to an aldehyde, and *Z*-selective Horner–Emmons-type olefination produces α,β -unsaturated ester **588** (*Z/E* ratio = 91 : 9). Removal of the acetonide protecting groups followed by lactonization affords the natural product **589**.

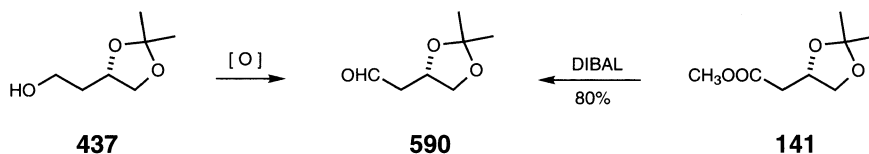
So far, we have explored the chemistry of acetonide **437** in its lowest oxidation state. One can increase the utility of this intermediate by oxidizing the alcohol to an aldehyde. This is readily accomplished under a variety of standard conditions to give **590** in high yield. Reduction of the methyl ester group of **141** with diisobutylaluminum hydride at –78 °C leads directly to **590** in good yield [42,140].

In an interesting synthesis of the bis-nor-4,6-maytansinoid skeleton **53**, the C-1 to C-10 fragment (**597**) is constructed from **590** as illustrated in Scheme 86 [141]. Acidic hydrolysis of **590** produces lactol **591**, which, upon treatment with 1,3-propanedithiol in the presence of boron trifluoride etherate, gives the thioacetal **592**. Conversion to chlorohydrin **593** and



Scheme 85

conditions: (a) CH₃COO*t*-Bu, LDA; (b) Bu₄NF; (c) Swern [O], CH₂Cl₂ (95%);
 (d) (CF₃CH₂O)₂P(O)CH₂COOCH₃, KHMDS, 18-crown-6, THF; (e) PTSA, MeOH;
 (f) PTSA, toluene

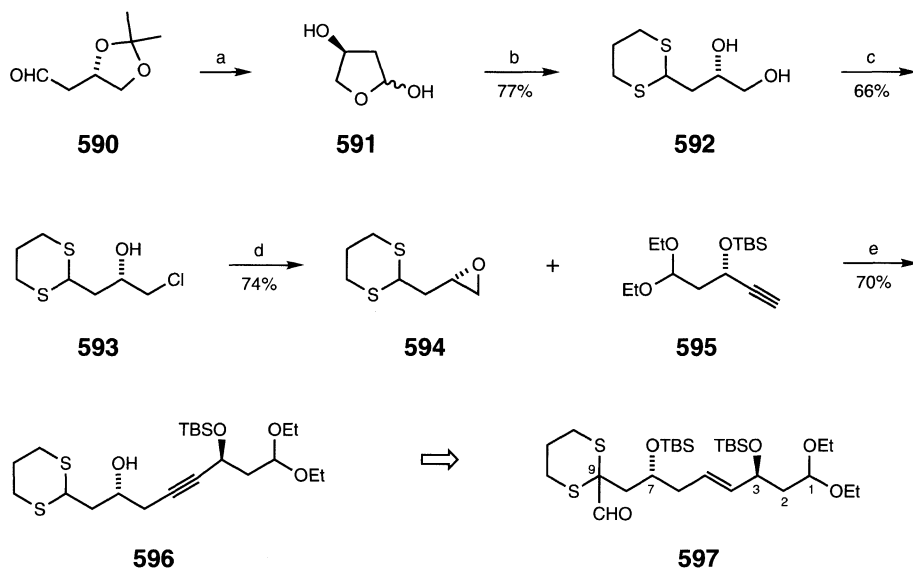


[O] reagents	Yield (%)	Reference
PCC	88	140
PDC	67	141
(COCl) ₂ /DMSO	74	142
CrO ₃ -pyridine	60–99	20, 109, 143

subsequent cyclization leads to epoxide **594**. Transformation of the primary hydroxyl of **592** into a more reactive bromide or tosylate results in intramolecular alkylation on sulfur rather than the desired epoxide.

After coupling of the two chiral fragments **594** and **595**, the TBS group of **596** is removed and the triple bond is reduced to an *E*-olefin with lithium aluminum hydride. Reinstallation of the TBS group affords the desired fragment **597** in 40% overall yield from **596**.

An approach to the 1,3-polyol system complementary to that shown in Schemes 83 and 84 makes use of dithiane **598** as a synthetic equivalent of **603**. Alkylation of the anion generated from **598** with epoxide **303** gives the coupled dithiane **599**. After hydrolysis of the thioacetal, a *syn*-selective reduction of ketone **600** with lithium aluminum hydride in the presence



Scheme 86

conditions: (a) HOAc–H₂O (1:1); (b) HS(CH₂)₃SH, BF₃·Et₂O, CH₂Cl₂; (c) Ph₃P, CCl₄, toluene, 70 °C; (d) NaOCH₃, CH₃OH; (e) BuLi, THF, –78 °C then BF₃·Et₂O

of lithium iodide affords the *syn*-diol **601** with 95 : 5 selectivity. In the absence of lithium iodide the selectivity drops to 79 : 21 (Scheme 87) [125]. Acetonide cleavage yields the all *syn*-polyol **602**.

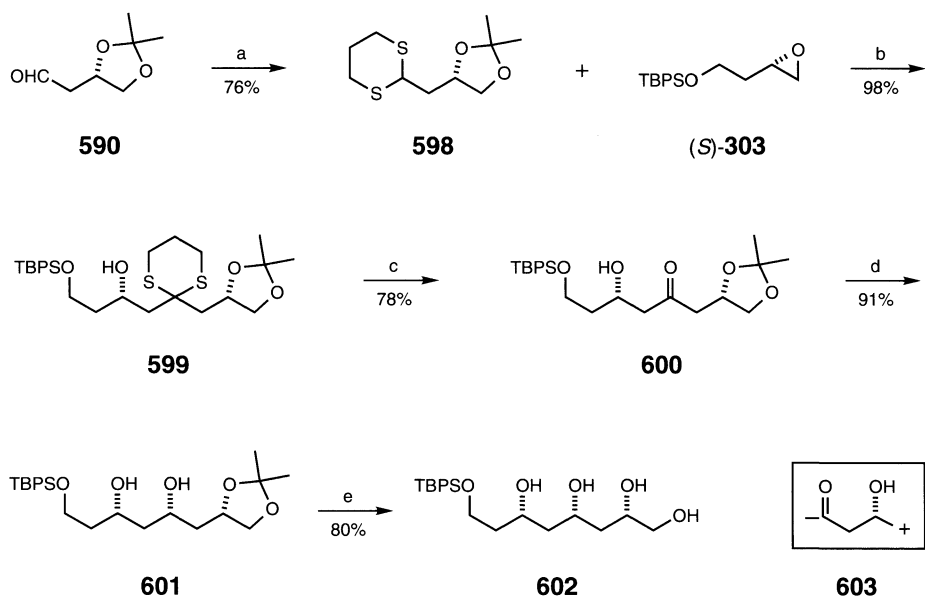
Higher homolog 1,3-polyols are prepared by an iterative procedure (Scheme 88). Acetonide **601** is first protected as the cyclohexylidene ketal **604**. Selective deprotection of the acetonide affords diol **605** in 42% yield, along with unreacted **604** (yield = 89% based on consumed starting material). Conversion of **605** to epoxide **606** followed by reaction of **606** with lithiated **598** in a procedure similar to the sequence outlined in Scheme 87 ultimately produces polyol **607** with 95 : 5 *syn* selectivity.

A parallel sequence of reactions, this time using the enantiomeric (*R*)-**303** epoxide, leads to *anti*-1,3-polyols containing a 1,3-*syn*-3,5-*anti*-triol unit (Scheme 89) [144]. The key reduction of **608** as well as the iterative ketone reaction later in the synthesis requires lithium tri-*tert*-butoxyaluminumhydride–lithium iodide to provide high *syn* selectivity (approximately 95 : 5) with respect to the dioxolane ring.

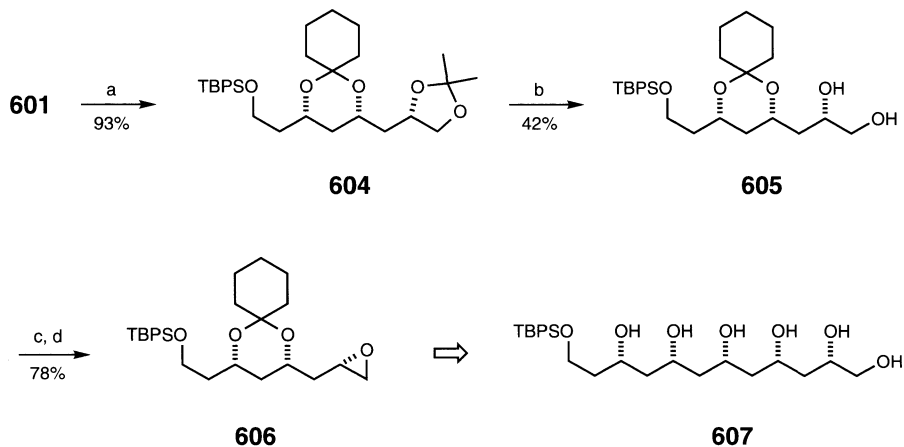
Several α,β -unsaturated δ -lactones are produced by higher plants, and it is speculated that they originate biogenetically from the respective 1,3-polyhydroxylated acids. The synthesis of (–)-tarchonanthuslactone (**615**) exemplifies the utility of asymmetric 1,3-polyols in natural product synthesis (Scheme 90) [145]. All-*syn*-epoxide **606** is transformed into the natural product **615** in good overall yield using only standard synthetic operations.

In the synthesis of the nonamethoxy-1-pentacosene (**622**), a naturally occurring poly-methoxy-1-alkene isolated from the blue–green alga *Tolypothrix conglutinata* var. *chlorata*, the backbone is assembled using two aldehydes (**620** and **621**) (Scheme 91) [146].

The first step in the preparation of aldehyde **620** is addition of the lithium enolate of *tert*-butylacetate to **590**. After reduction of the ester, protection of the primary alcohol as a silyl ether, and oxidation of the remaining secondary alcohol, intermediate **617** is isolated in 60%

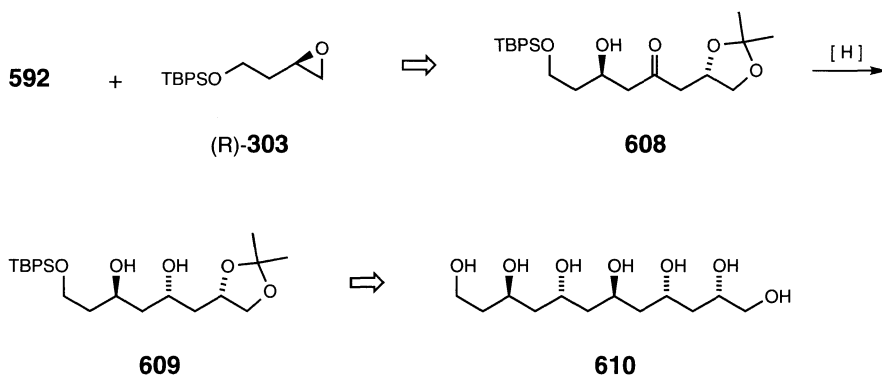
**Scheme 87**

conditions: (a) $\text{HS}(\text{CH}_2)_3\text{SH}$, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 then DMP; (b) *n*-BuLi, THF, -20°C ; (c) NBS, AgNO_3 , 2,6-lutidine, $\text{CH}_3\text{CN}-\text{H}_2\text{O}$; (d) LiAlH_4 , Lil, ether, -100°C ; (e) PPTS, MeOH, 45°C

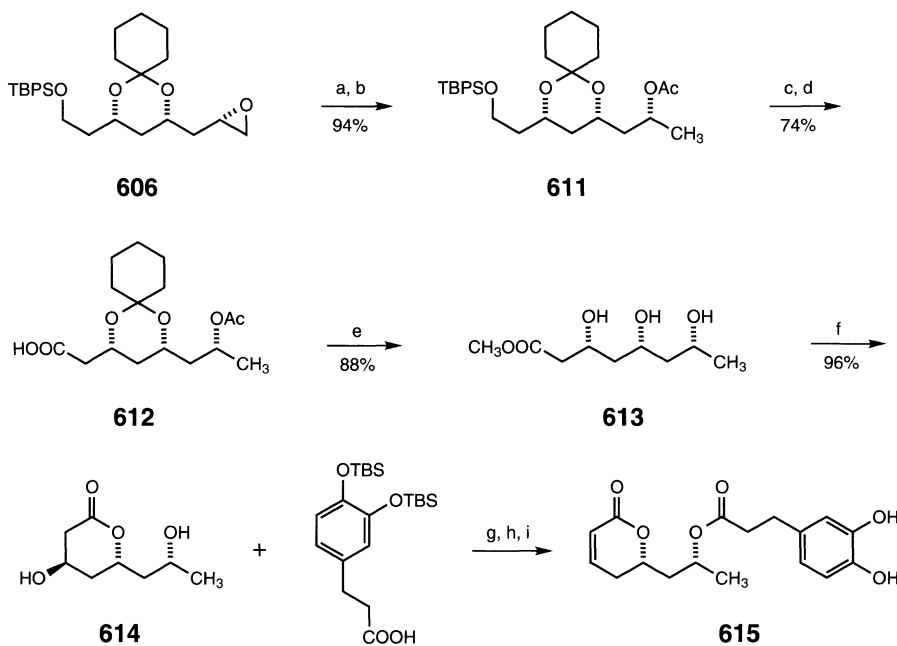
**Scheme 88**

conditions: (a) 1,1-dimethoxycyclohexane, PPTS, CH_2Cl_2 ; (b) 80% HOAc-THF (9:1), -10°C ; (c) TsCl, pyridine, 0°C ; (d) KH, ether-MeOH (5:1), 0°C

overall yield. A *syn*-selective reduction of the ketone with zinc borohydride furnishes **618** (*syn/anti* ratio = 15.4:1) quantitatively. After formation of epoxide **619** by conventional procedures, the epoxide is converted to aldehyde **620** in a fashion analogous to the **303** \rightarrow **574** transformation shown in Scheme 83. Reaction of **620** with the anion of 1,3-dithiane followed



Scheme 89

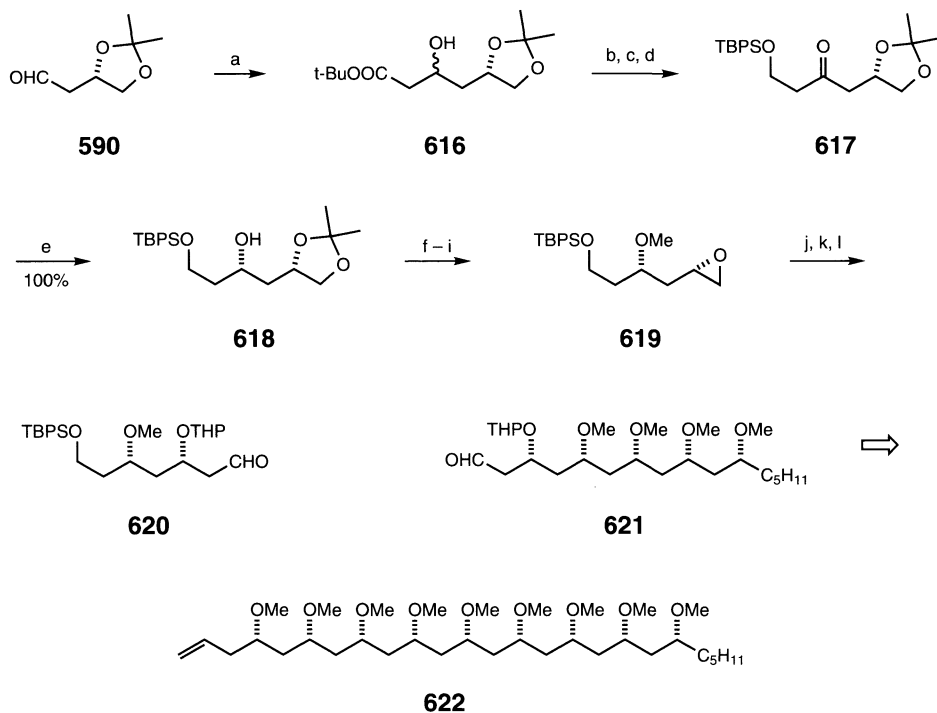


Scheme 90

conditions: (a) LiAlH_4 , ether; (b) Ac_2O , pyridine; (c) Bu_4NF , THF; (d) Jones [O]; (e) 0.1N LiOCH_3 then Amberlyst-15; (f) CSA, CH_2Cl_2 ; (g) DCC, DMAP, CH_2Cl_2 (95%); (h) DBU, benzene (94%)

by alkylation with **621** according to the protocol illustrated in Scheme 83 eventually produces the desired product **622**.

All-*anti*-1,3-polyols are available by a somewhat more laborious route starting again with the **590** \rightarrow **616** reaction (Scheme 92) [147]. The key intermediate in the sequence is the bicyclic acetal **627**, which fixes the conformation of the tetrahydropyran ring so that reduction



Scheme 91

conditions: (a) $\text{CH}_3\text{COO}t\text{-Bu}$, LDA, THF, -78°C ; (b) LiAlH_4 , THF, 0°C ; (c) TBPS-Cl, imidazole, DMF; (d) Swern [O]; (e) $\text{Zn}(\text{BH}_4)_2$, toluene, 0°C ; (f) CH_3I , KH, THF; (g) $\text{HOAc-H}_2\text{O}$; (h) TsCl, pyridine; (i) K_2CO_3 , MeOH; (j) 1,3-dithiane, *n*-BuLi, THF, 0°C ; (k) DHP, CSA, CH_2Cl_2 ; (l) HgO , HgCl_2 , acetone, reflux

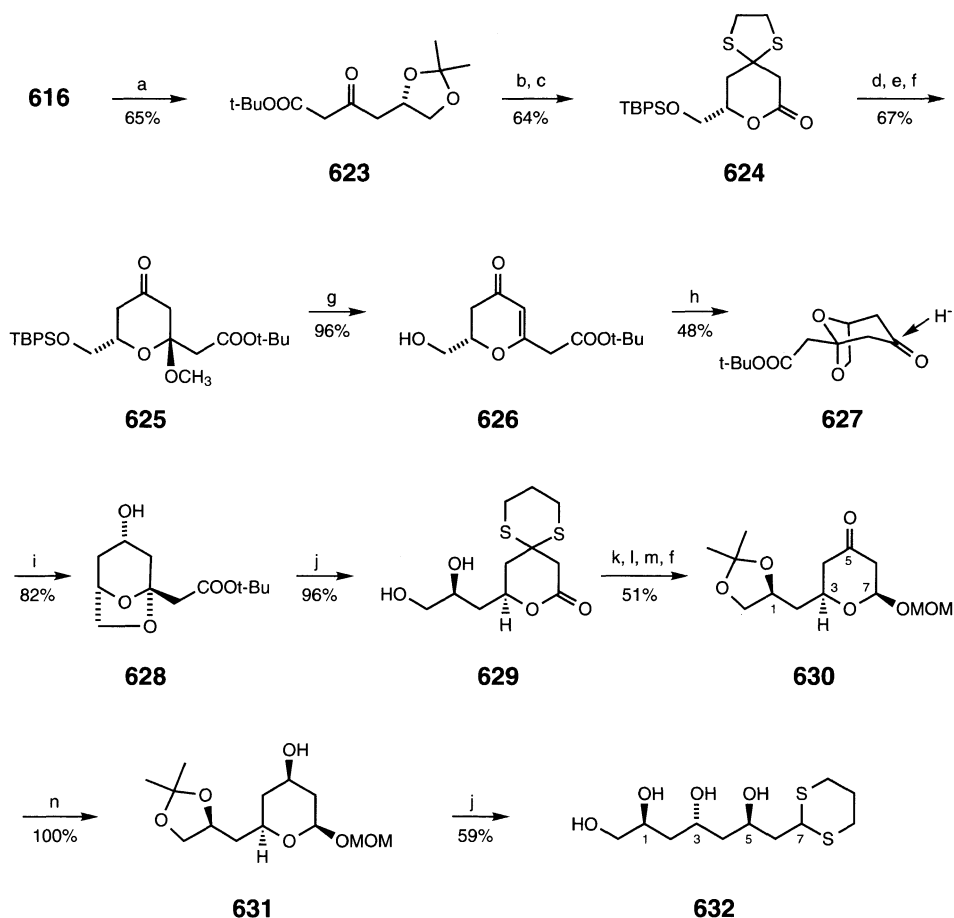
of the carbonyl can take place from the less hindered side of the molecule, thereby producing axial alcohol **628** as a single product that corresponds to a 1,3-*anti*-diol.

A second important feature of the synthesis is introduction of a MOM group into **630**. This positions the anomeric alkoxy group in an equatorial site so that, once again, reduction of the carbonyl group can take place from the less hindered side, introducing complete 3,5-*anti* stereoselection.

Thioacetalization of **631** with 1,3-propanedithiol gives the 1,3,5-all-*anti*-triol **632** as essentially one diastereomer.

A relatively concise synthesis of a “compactin lactone” (**99**) derivative makes use of **590** as the source of chirality (Scheme 93) [142]. Addition of ethyl acetate enolate to **590** produces a 1 : 1 mixture of aldols **633** in 58% yield. After silylation of the hydroxyl group, cleavage of the acetonide furnishes lactone **635** as a crystalline solid. Tosylation of the primary alcohol and separation of the isomers furnishes **636** (47% yield) and **637** (44% yield). The desired isomer **636** is a suitably protected and functionalized version of “compactin lactone”.

The C-12 to C-17 segment (**645**) of (+)-aplasomycin has been synthesized from **590** as shown in Scheme 94 [148]. In the first step, an aldol condensation of isopropyl propionate enolate with **590** produces **638** as a mixture of isomers. After conversion to enone **640**, reduction of the carbonyl with $\text{NaBH}_4\text{-CeCl}_3$ gives alcohol **641** as a single isomer. A second reduction of **642** with zinc borohydride gives a separable mixture of isomers, the major isomer



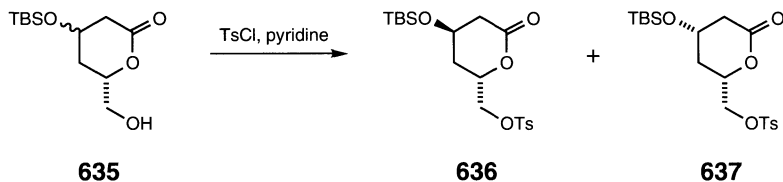
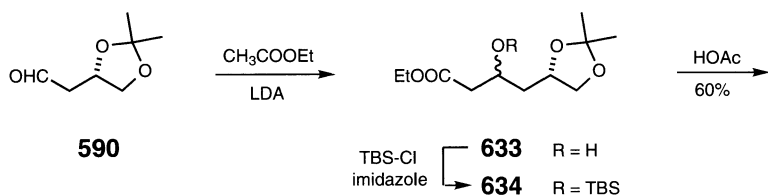
Scheme 92

conditions: (a) PCC, 3Å molecular sieves, CH_2Cl_2 ; (b) $\text{HS}(\text{CH}_2)_2\text{SH}$, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 ; (c) TBPSO-Cl, imidazole, DMF; (d) $\text{CH}_3\text{COO}t\text{-Bu}$, LDA, THF, -78°C ; (e) $\text{CH}(\text{OMe})_3$, CSA, MeOH, CH_2Cl_2 ; (f) NBS, AgNO_3 , Na_2CO_3 , $\text{CH}_3\text{CN}-\text{H}_2\text{O}$; (g) Bu_4NF ; (h) CSA, CH_2Cl_2 ; (i) K-Selectride, THF, -78°C ; (j) $\text{HS}(\text{CH}_2)_3\text{SH}$, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 ; (k) $\text{Me}_2\text{C}(\text{OMe})_2$, CSA, CH_2Cl_2 ; (l) DIBAL, toluene, -78°C ; (m) $\text{BrCH}_2\text{OCH}_3$, $i\text{-Pr}_2\text{NEt}$, CH_2Cl_2 ; (n) LiAlH_4 , ether, 0°C

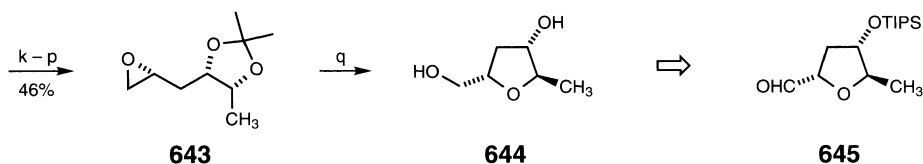
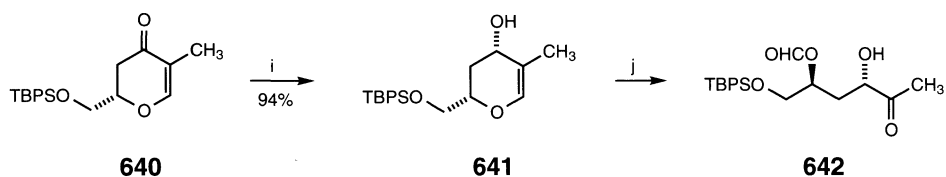
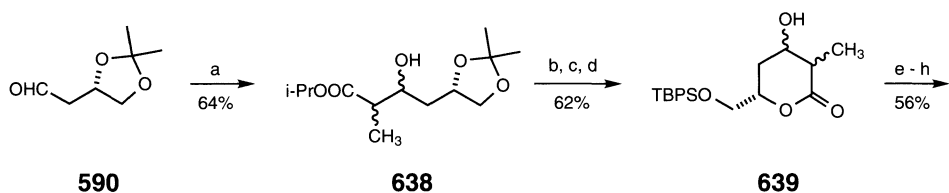
of which (isolated in 66% yield) is converted to epoxide **643**. Upon deprotection of the acetonide, cyclization to tetrahydrofuran derivative **644** occurs smoothly. Standard manipulations convert **644** to **645**.

(+)-Benzoylpedamide (**140**), representing the right half of (+)-pederin (**654**), a potent insect poison isolated from *Paederus fuscipes*, is synthesized from **590** as shown in Scheme 95 [149]. Once again, the initial reaction in the sequence is the addition of an ester enolate to **590**, which produces **646** as a mixture of isomers. Conversion of **646** to δ -lactone **647**, protection of the hydroxyl with an EE group, and treatment with *tert*-butyl acetate enolate gives hemiacetal **648**.

Treatment of **648** with trimethyl orthoformate and CSA simultaneously deprotects the EE group and causes acetalization giving a nearly statistical mixture of **649** (38% yield) and **650**



Scheme 93

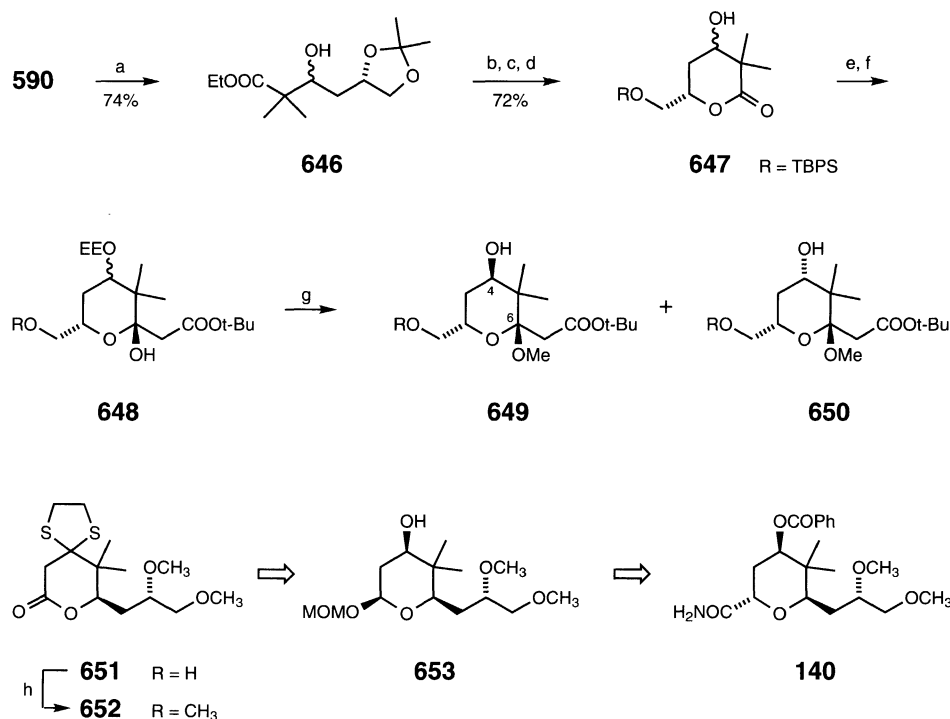


Scheme 94

conditions: (a) $\text{EtCOO}i\text{-Pr}$, LDA , THF , -78°C ; (b) HCl , $\text{MeOH-H}_2\text{O}$; (c) TBPS-Cl , imidazole, DMF ; (d) CSA , benzene; (e) DIBAL , toluene, -78°C ; (f) CSA , $\text{CH}(\text{OMe})_3$, MeOH , CH_2Cl_2 ; (g) PCC , 3Å molecular sieves, CH_2Cl_2 ; (h) NaOCH_3 , THF ; (i) NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, MeOH ; (j) O_3 , MeOH , -78°C ; (k) $\text{Zn}(\text{BH}_4)_2$, ether, -78°C ; (l) K_2CO_3 , MeOH ; (m) PTSA , acetone; (n) MsCl , pyridine; (o) Bu_4NF , THF ; (p) NaOCH_3 , MeOH ; (q) $\text{HOAc-H}_2\text{O}$

(37% yield). The undesired isomer **650** can be converted to the desired **649** by oxidation of the hydroxyl to a ketone with PCC followed by reduction of the ketone to a 4 β -alcohol with L-Selectride (90% yield).

Treatment of **649** with ethanedithiol in the presence of boron trifluoride etherate results in acetal–thioacetal interchange at C-6 and subsequent lactonization of the 4 β -hydroxyl group with the *tert*-butyl ester, thus furnishing **651** in 83% yield. Reduction of the lactone to a lactol, protection with a MOM group, hydrolysis of the thioacetal, and reduction of the ketone with lithium aluminum hydride gives **653** as a single product. After benzoylation of the alcohol, conversion of the OMOM derivative to carboxamide (OMOM \rightarrow OAc \rightarrow CN \rightarrow CONH₂) affords **140** as a 10 : 1 mixture of isomers.

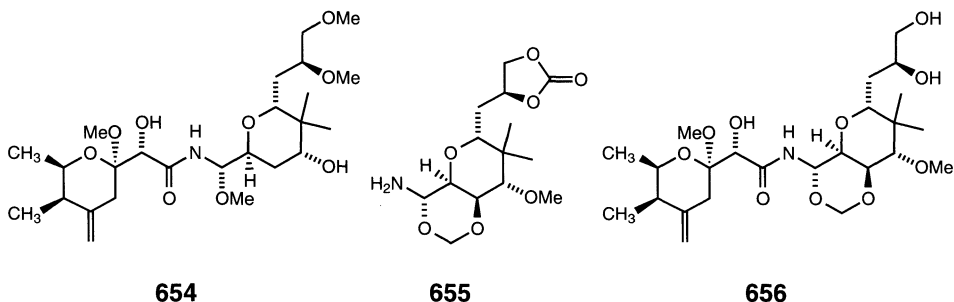


Scheme 95

conditions: (a) Me₂CHCOOEt, LDA, THF, -78 °C; (b) PTSA, MeOH; (c) TBPS-Cl, imidazole, DMF; (d) CSA, benzene; (e) CH₂=CHOEt, PPTS, CH₂Cl₂; (f) CH₃COOt-Bu, LDA, THF, -78 °C; (g) CH(OMe)₃, CSA, CH₂Cl₂, MeOH; (h) CH₂N₂, silica gel, ether, 0 °C (83%)

Benzoylpedamide (**140**) has been employed successfully in the total synthesis of (+)-pederin (**654**) [150]. In addition, intermediate **649** has been used in the synthesis of the right half (**655**) of mycalamide A (**656**), a structurally related marine natural product possessing antiviral and antitumor activity [151].

Addition of olefin-containing Grignard reagents to **590** introduces a site of unsaturation that can be further elaborated to a more synthetically useful functionality. Thus, the synthesis of all four diastereomers of 2-acetamido-2,4-dideoxy-D-hexapyranose (**668–671**) starting from one common intermediate (**590**) makes use of this type of strategy (Scheme 96) [152].



Addition of vinyl Grignard to **590** leads to a 52 : 48 mixture of alcohols **657** and **659**, which are subsequently benzylated (**658** and **660**) and separated by HPLC in 50-g quantities. Ozonolytic cleavage of the olefin of **658** affords **661** quantitatively.

A second non-selective addition of vinyl Grignard to **661** produces a mixture of alcohols **662** and **665**. The hydroxyl center is inverted with phthalimide under Mitsunobu conditions, after which the phthaloyl group is cleaved with hydrazine and the resulting amine acylated to give **664** and **667** (separable by HPLC). Compound **667** is then debenzylated, the acetonide group is hydrolyzed, and the olefin is ozonolyzed to give **668** as a crystalline solid. Likewise, **664** is converted to **669**. By a parallel sequence of reactions, **660** is transformed to **670** and **671**. Ozonolysis as the last step is a critical feature of these syntheses, because the *N*-acetylhexosamines are generated very cleanly, and such compounds are notoriously difficult to purify.

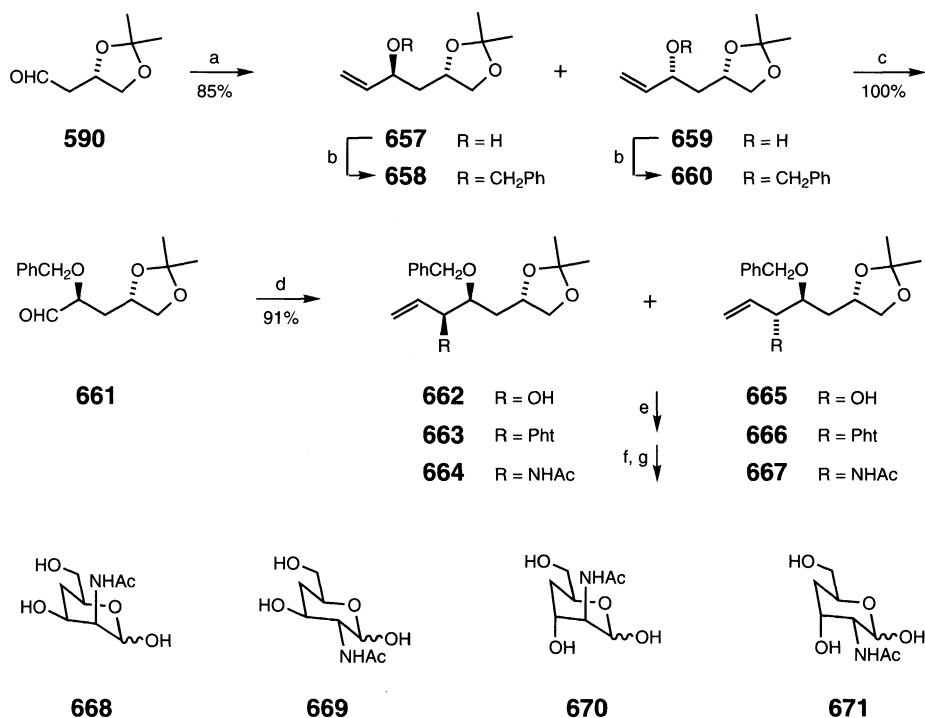
Even though the synthesis illustrated requires two HPLC separations, this potential drawback is outweighed by the advantage of obtaining all four diastereomers fairly rapidly from the single common intermediate **590** in 7.5% overall yield.

The C-15 to C-25 spiroacetal-containing fragment **571** of (+)-milbemycin β_3 (**572**) is constructed from **590** as shown in Scheme 97 [153]. Addition of allylmagnesium chloride to **590** produces a 1 : 1 mixture of diastereomers from which **672** is isolated by column chromatography. The undesired diastereomer is converted to **672** by a Mitsunobu inversion (4-nitrobenzoic acid, DEAD, Ph_3P , then KOH), thus increasing the overall yield of **672** to 85%. Opening the oxirane **673** with a mixed cuprate derived from **674** leads to **675** which, when treated with a trace of CSA, gives the alcohol **676** as a single diastereomer in 70% overall yield from **673**. Resilylation of the alcohol and ozonolysis of the olefin provides the desired aldehyde fragment **571**.

A larger C-11–C-25 fragment of (+)-milbemycin β_3 is prepared by a somewhat similar strategy (Scheme 98) [154]. Addition of phenylthiomethyl lithium to **590** gives a 1 : 3 mixture of diastereomers **678** and **679** that is difficult to separate. Furthermore, the desired diastereomer **678** represents the minor component of the mixture. Consequently, the mixture is transformed to epoxide **680**, which is then allowed to react with aluminate **681** to provide a more easily separable mixture of alcohols. After separation, the major (undesired) alcohol is converted to the desired **682** by Mitsunobu inversion with 4-nitrobenzoic acid.

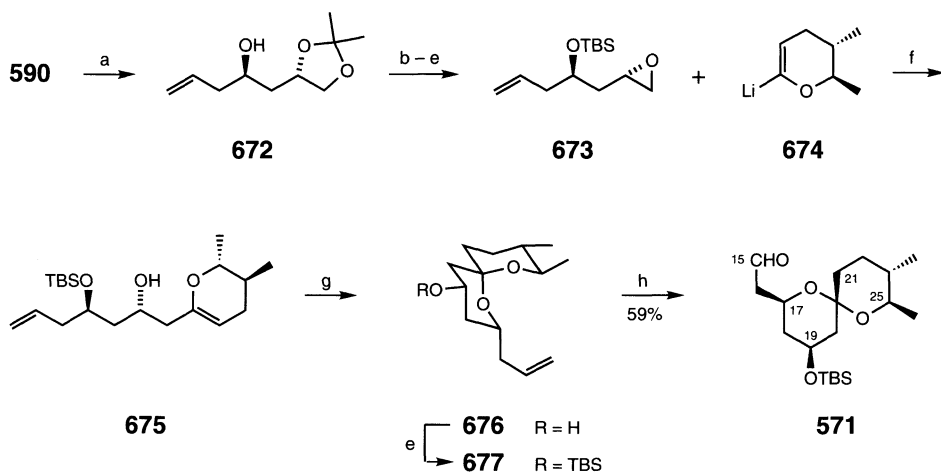
After conversion to aldehyde **683** (acetonide hydrolysis, tosylation, cyclization with K_2CO_3), oxirane ring opening with a mixed cuprate derived from **674** as in the previous synthesis cleanly gives **684**. Acid-catalyzed hydrolysis of **684** forms the spiroacetal framework, and functional group manipulation leads to the desired aldehyde **685**.

The avermectins, which possess potent anthelmintic and insecticidal activities, have structural features similar to the milbemycins. The C-15 to C-28 spiroketal-containing unit (**690**) of avermectin B_{1a} aglycone (**691**) is synthesized in optically pure form by coupling *L*-malic acid-derived lactone **687** with *D*-glucose-derived acetylene **688**. Partial reduction of the



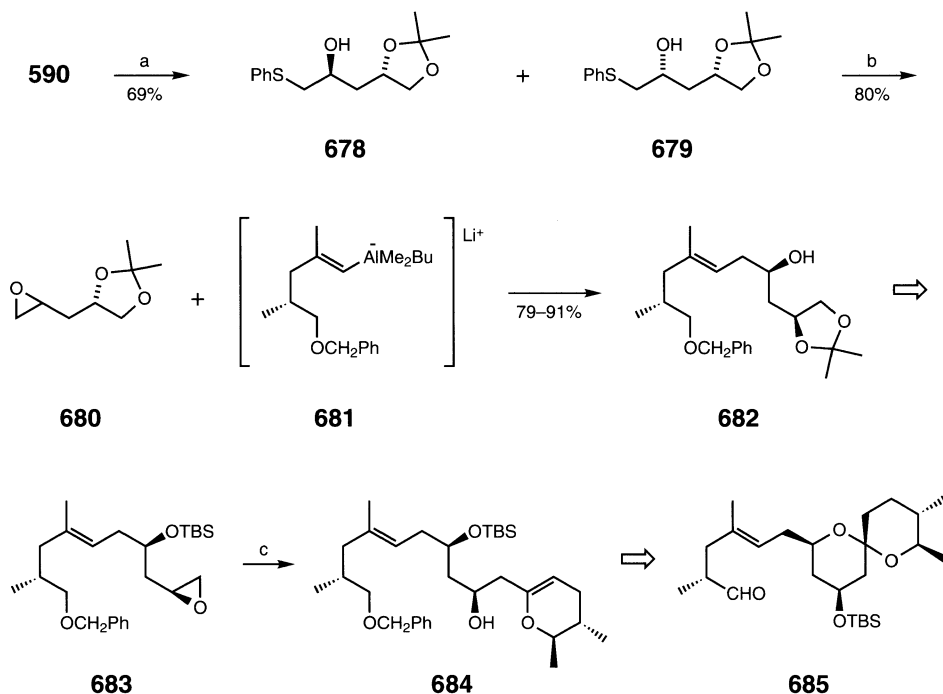
Scheme 96

conditions: (a) CH₂=CHMgCl, THF, 0 °C; (b) NaH, PhCH₂Cl, DMF (91%); (c) O₃, MeOH, -78 °C; (d) CH₂=CHMgBr, THF, 0 °C (91%); (e) DEAD, Ph₃P, phthalimide, THF, -40 °C (56%); (f) N₂H₄, EtOH; (g) Ac₂O, pyridine, DMAP (84%)



Scheme 97

conditions: (a) CH₂=CHCH₂MgCl, ether; (b) Amberlite IR 120 (H⁺) resin, MeOH (100%); (c) mesitylenesulfonyl chloride, pyridine (78%); (d) K₂CO₃, MeOH (92%); (e) TBS-Cl, Et₃N, DMAP, DMF (85%); (f) pentynylcopper (I), THF, rt; (g) CSA, MeOH; (h) O₃, MeOH, pyridine, -78 °C



Scheme 98

conditions: (a) PhSCH₂Li, THF, -70 °C; (b) Me₃OBF₄, 2,6-di-*t*-butylpyridine, CH₂Cl₂, 20 °C then NaOH; (c) **674**, pentynylcopper (I), THF rt

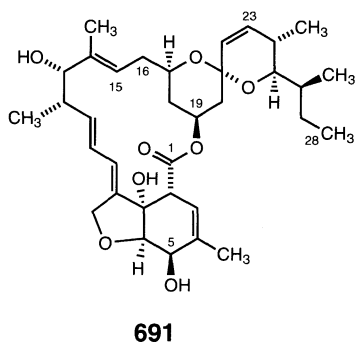
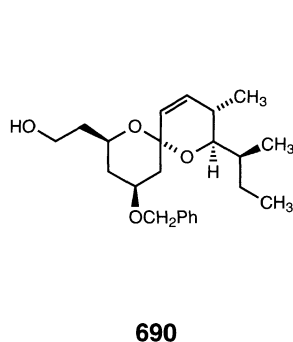
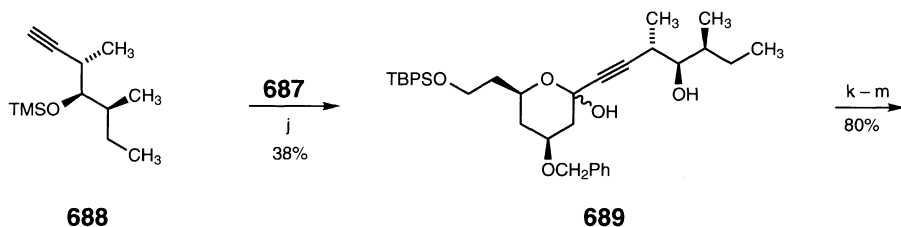
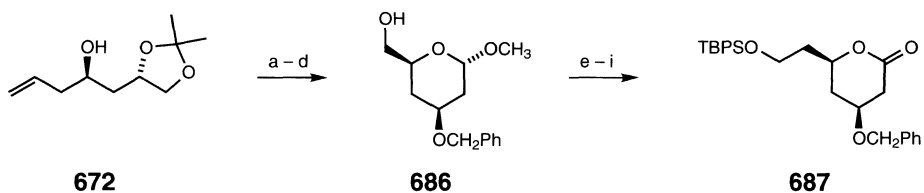
acetylenic linkage produces a *cis*-olefin which, when exposed to boron trifluoride etherate, leads to spiroketal **690** (Scheme 99) [155].

The aldehyde group of **590** serves as a useful “handle” for introducing olefin groups *via* Wittig methodology while maintaining the highly versatile protected diol functionality for later manipulations. This is elegantly demonstrated in the synthesis of prostaglandins F_{3α} and E₃ (Scheme 100) [143]. A Wittig olefination of **590** with propylidene-triphenylphosphorane produces the *Z*-olefin **692** in good yield. Hydrolysis of the acetonide, tosylation of the primary alcohol, and conversion to phosphonium iodide **695** produces an optically pure Wittig reagent which, when reacted with Corey lactone (**696**), affords lactone **697** in modest yield. Protection of the free hydroxyl with a THP group, reduction of the lactone to a lactol, and reaction with a Wittig reagent derived from 5-triphenylphosphonovaleric acid furnishes prostaglandin F_{3α} (**698**). Oxidation of the 9 hydroxy group to a ketone prior to THP-deprotection leads to prostaglandin E₃.

Two different approaches to 12(*S*)-HETE (**703**), a human metabolite of arachidonic acid, make use of a Wittig reaction to couple the top and bottom units.

In the first route (Scheme 101) [20], a Wittig reaction of **590** with 1-hexylidene-triphenylphosphorane gives the *Z*-olefin **699** in satisfactory yield. Conversion to phosphonium iodide **700** and Wittig reaction with aldehyde **701** affords methyl 12(*S*)-HETE (**702**). In this synthesis the upper aldehyde fragment and lower phosphorane fragment are joined at the *E*-olefin.

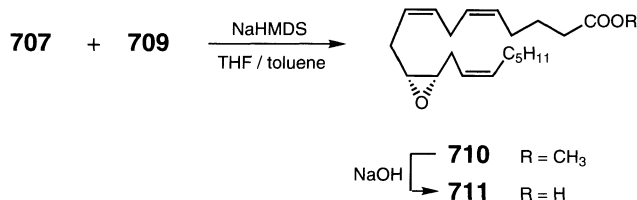
In the second synthesis (Scheme 102) [156], the fragment functionalities are reversed, with an upper phosphorane (**709**) and a lower aldehyde (**708**). The key aldehyde **708** is available

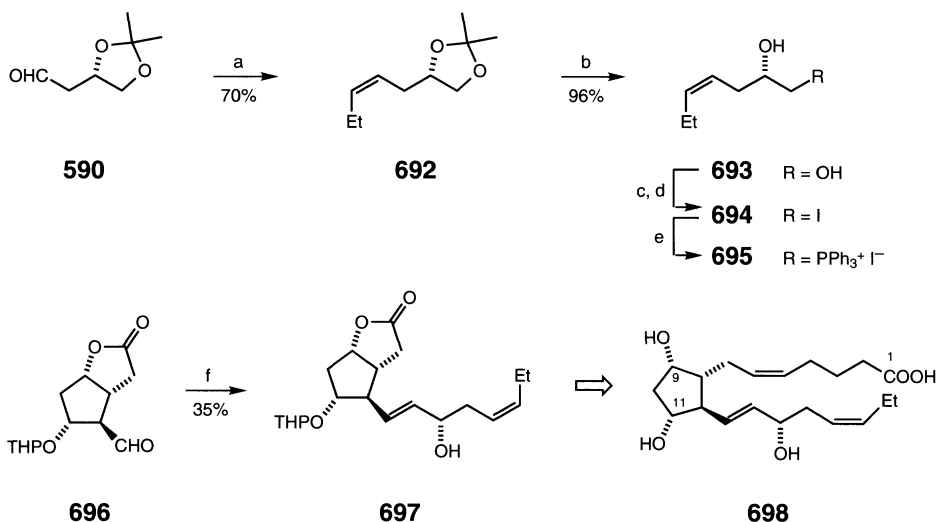
**Scheme 99**

conditions: (a) KH, PhCH₂Br; (b) CF₃COOH; (c) O₃ then Me₂S; (d) MeOH, BF₃•Et₂O; (e) PCC; (f) Ph₃P=CH₂; (g) 9-BBN, NaOH; (h) HOAc-H₂O; (i) TBPS-Cl, pyridine; (j) BuLi, THF, -78 °C, BF₃•Et₂O; (k) H₂, Pd/BaSO₄, EtOAc, pyridine; (l) BF₃•Et₂O, THF; (m) Bu₄NF, THF

from **590** via Wittig olefination. Vanadium-catalyzed epoxidation of **705** produces **706** as a 94 : 6 diastereomeric mixture. Removal of the benzoate group followed by periodate cleavage of the resulting diol furnishes epoxy aldehyde **707**. Isomerization of **707** to *trans*-enal **708** is accomplished with silica gel [157]. A Wittig reaction of **708** with **709** gives methyl 12(*S*)-HETE (**702**) in 65–68% yield.

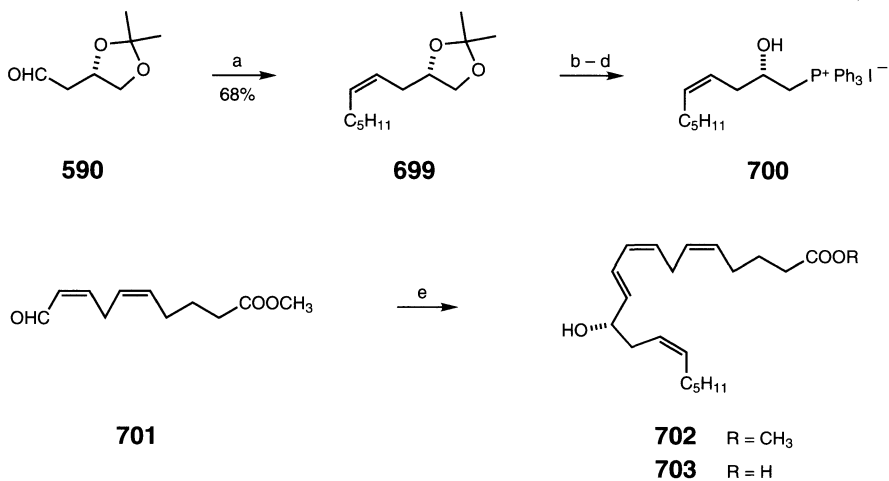
A Wittig reaction of **707** with **709** furnishes methyl 11(*R*),12(*S*)-EET (**710**) directly. The free acid **711** is one of four EET arachidonic acid metabolites found in mammalian tissue and human urine [157].





Scheme 100

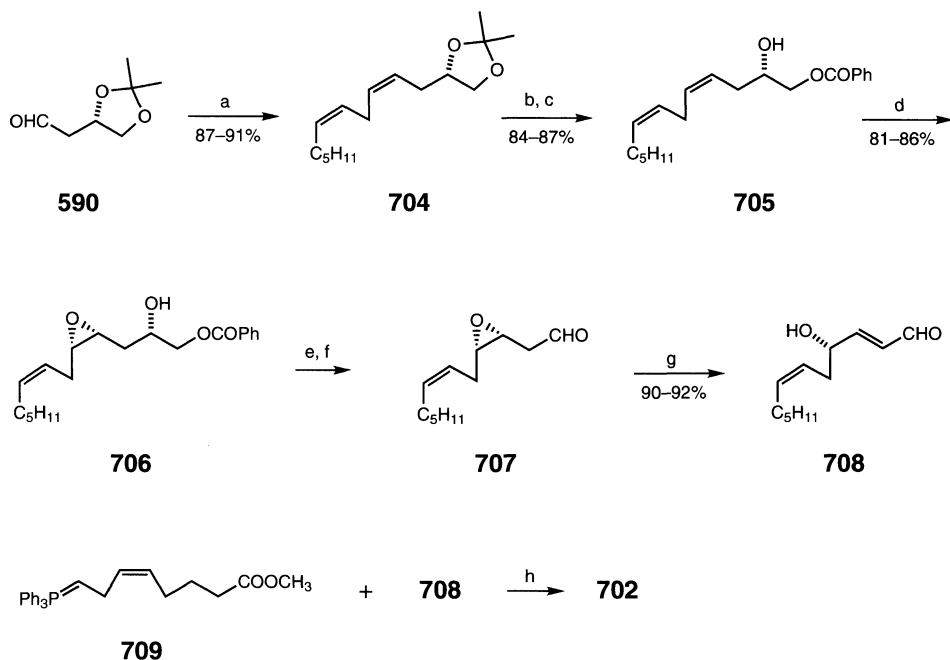
conditions: (a) $\text{EtHC}=\text{PPh}_3$, THF, $-78^\circ \rightarrow 25^\circ \text{C}$; (b) 2N HCl, MeOH; (c) TsCl, pyridine (80%);
 (d) NaI, acetone (96%); (e) PPh_3 , benzene, 40-45 $^\circ\text{C}$; (f) **695**, BuLi, -78°C then **696**



Scheme 101

conditions: (a) $n\text{-C}_5\text{H}_{11}\text{CH}=\text{PPh}_3$, THF, $-78^\circ \rightarrow 25^\circ \text{C}$; (b-d) see Scheme 100, steps c, d, e, use mesitylenesulfonyl chloride; (e) **700**, CH_3Li , THF-toluene, HMPA

Wittig reactions of **590** have played an important role in establishing the absolute stereochemistry of the degradation products of several aglycones of glykenins (Scheme 103) [158]. A Wittig olefination of **590** with phosphoranes **716** followed by hydrogenation and deprotection gives the long-chain triols **717**.



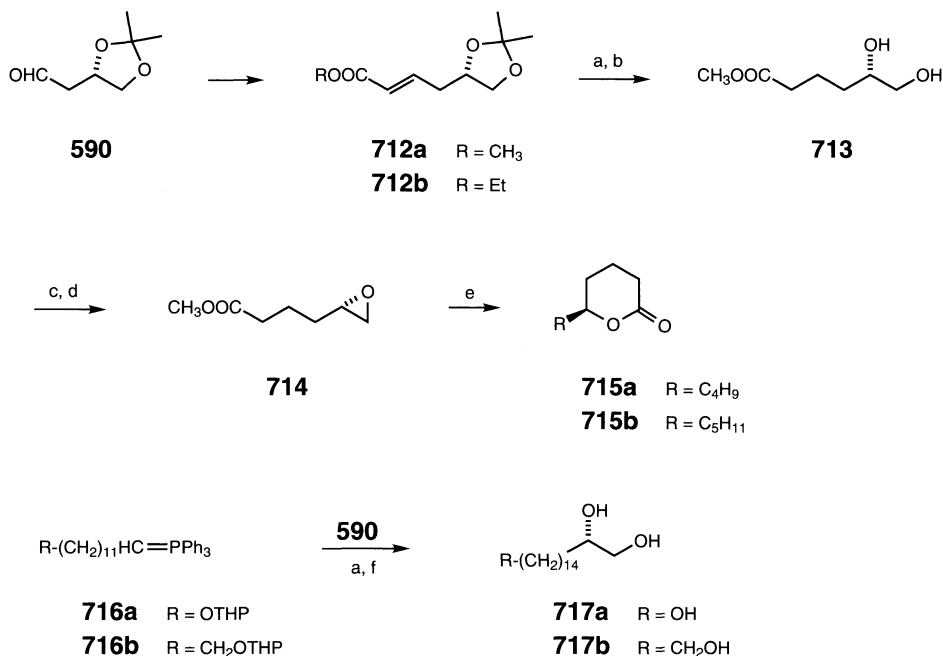
Scheme 102

conditions: (a) 3-(*Z*)-nonenylidene triphenylphosphorane, THF-HMPA (4:1), $-78^{\circ} \rightarrow -20^{\circ} \text{C}$; (b) 1N HCl, MeOH, 4°C ; (c) PhCOCN, Et₃N, CH₂Cl₂, 0°C ; (d) *t*-BuOOH, VO(acac)₂, CH₂Cl₂, 0°C ; (e) KHCO₃, MeOH; (f) NaIO₄, MeOH-H₂O (2:1), Na₂HPO₄; (g) silica gel, ether; (h) THF-HMPA (4:1), $-78^{\circ} \rightarrow -15^{\circ} \text{C}$

Reaction of **590** with either trimethyl phosphonoacetate and sodium hydride in THF [158] or (carbethoxymethylene)triphenylphosphorane in methylene chloride [159] produces the (*E*)- α,β -unsaturated esters **712a** and **712b** in 88% and 84% yields respectively. Catalytic hydrogenation of **712a** followed by acetonide cleavage affords diol **713**. Tosylation of the primary alcohol followed by cyclization gives epoxy ester **714**. Opening the oxirane with organocuprates furnishes lactones **715**.

In an interesting series of transformations, ester **712b** is converted to “compactin lactone” synthon **724** (Scheme 104) [160]. After hydrolysis of the acetonide (**712b** \rightarrow **718**) and silylation of the primary alcohol, treatment of **719** with sodium ethoxide results in silyl migration from primary to secondary hydroxyl as well as Michael addition of the primary alkoxide to the olefin, giving a 2 : 1 mixture of the thermodynamic *trans*-**720** and kinetic *cis*-**721**. The isomers are separated by flash chromatography, and the minor isomer **721** can be recycled to **720** by equilibration with sodium ethoxide [161]. Cleavage of **720** with dimethylboron bromide gives the bromoalcohol **722**, which is then protected with a MOM group and cyclized to epoxide **724**. Attachment of the “compactin lactone” synthon to a lower-half fragment is accomplished by alkylation of the epoxide with a suitable nucleophile. Thus, treatment of **724** with cuprate **725** followed by lactonization and MOM cleavage with dimethylboron bromide furnishes the coupled lactone **726** in 71% overall yield.

A more efficient route to **720** involves an intramolecular iodoetherification of **718**. If the reaction is carried out in THF, a 4.8 : 1 mixture of **727** and **728** is obtained, but if the same reaction is run in ether the ratio increases to 8.5 : 1 (Scheme 105) [159,161]. After silylation, the mixture of isomers can be separated by flash chromatography. Removal of iodine affords

**Scheme 103**

conditions: (a) H₂, 10% Pd/C, EtOAc; (b) Amberlyst-15, MeOH; (c) TsCl, pyridine, 5 °C; (d) LiOCH₃, MeOH; (e) R₂CuLi, ether, -40 °C; (f) 6N HCl, MeOH

720 in high yield. Elaboration of the ester group to acetal **731** followed by opening of the tetrahydrofuran ring with dimethylboron bromide gives bicyclic ketal **733** *via* diol **732**.

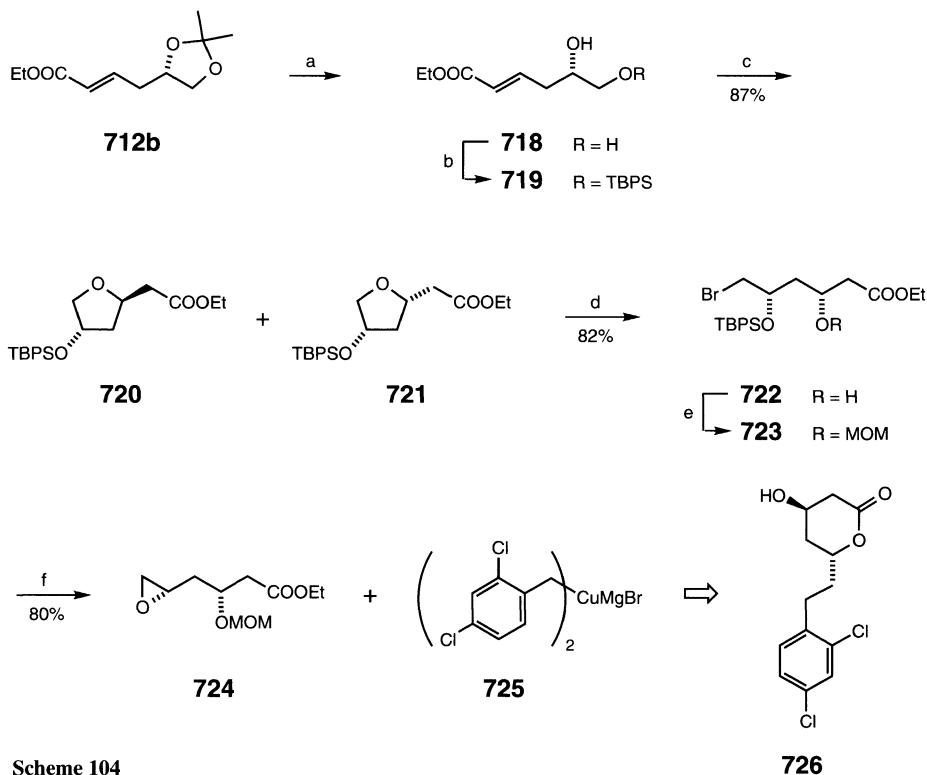
The C-1 to C-12 subunit (**741**) of amphotericin B has been constructed from alcohol **438** by oxidation to the corresponding aldehyde and then transformation *via* common intermediate **736** to chiral fragments **739** and **740**. Alkylation of the anion of **739** with **740** followed by Raney nickel desulfurization gives **741** in approximately 30% yield (Scheme 106) [111].

Through a series of standard manipulations, allylic alcohol **735** is converted to aldehyde **743**, which represents the C-11 to C-15 segment of the 16-membered ring aglycone niddanolide (**744**) (Scheme 107) [162]. The 3-step conversion of **742** to **743** proceeds by reduction of the OTs group to a methyl, removal of the MPM protecting group, and selective oxidation of the allylic alcohol to an aldehyde.

The synthesis of tricholomic acid (**751**), an unusual amino acid isolated from *tricholoma muscarium*, uses an aldol condensation between **590** and **745** (a glycine acyl anion equivalent) to establish the absolute configuration of the amino functionality early in the synthesis (Scheme 108) [140]. The aldol reaction produces a 3 : 2 mixture of diastereomers that can be separated as in the form of the corresponding N-Cbz benzyl esters **746** and **747**.

Hydrolysis of the acetonide and oxidative cleavage of the resulting diol **748** produces acid **749**. Amide formation, mesylation of the alcohol, and hydrogenolysis of the benzyl groups produces an intermediate hydroxamate that intramolecularly displaces the mesylate group with inversion of configuration to form the dihydroisoxazole ring of **751**.

Alcohol **437** can be oxidized to acid **752** with either Jones reagent or potassium permanganate in the presence of 18-crown-6 [22,163]. Hydrolysis of the acetonide yields the



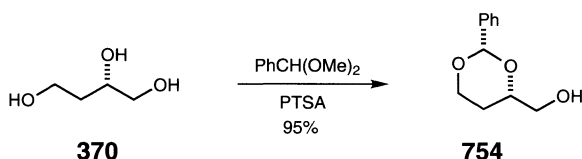
Scheme 104

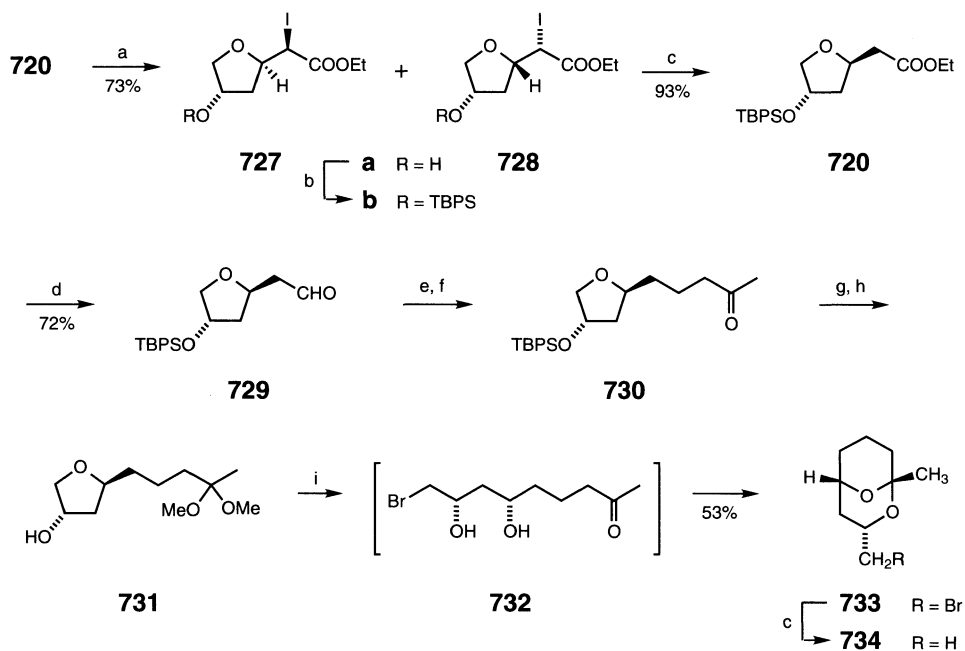
conditions: (a) 1N HCl, THF; (b) TBPS-Cl, Et₃N, DMAP, CH₂Cl₂; (c) NaOEt, EtOH;
 (d) Me₂BBr (2 eq), CH₂Cl₂, 0 °C → rt; (e) MOM-Cl, *i*-Pr₂NEt, DMAP,
 CH₃CN, -3 °C (94%); (f) Bu₄NF (3 eq), THF

hydroxybutyrolactone **149**. Alkylation of the dianion of **149** with a variety of alkylating agents gives **753** as a single diastereomer. The presence of HMPA in the reaction is essential for alkylation to occur.

3.3.1.1.2 C-2 to C-4 Six-Membered Acetals

In contrast to the acetalization of **370** with acetone, which favors the 5-membered acetonide **437** over the 6-membered acetonide **338** (9 : 1), acetalization of **370** with benzaldehyde in the presence of trifluoroacetic acid [164] or transacetalization with benzaldehyde dimethylacetal [102,165,166] produces only the 6-membered acetal **754**. This phenomenon makes it possible for the chemist to conduct operations at the C-1 hydroxyl of **370**.

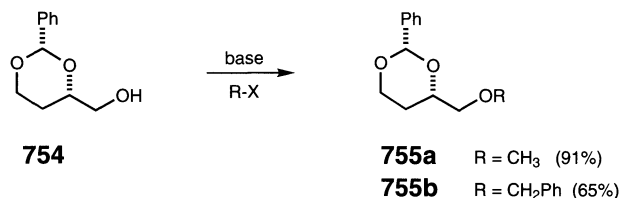




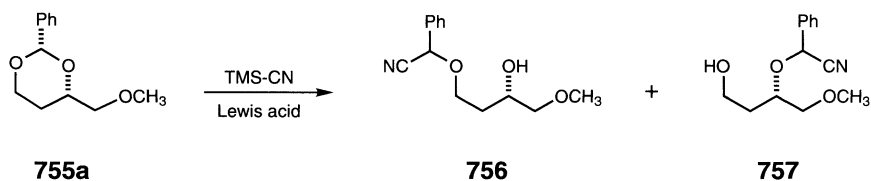
Scheme 105

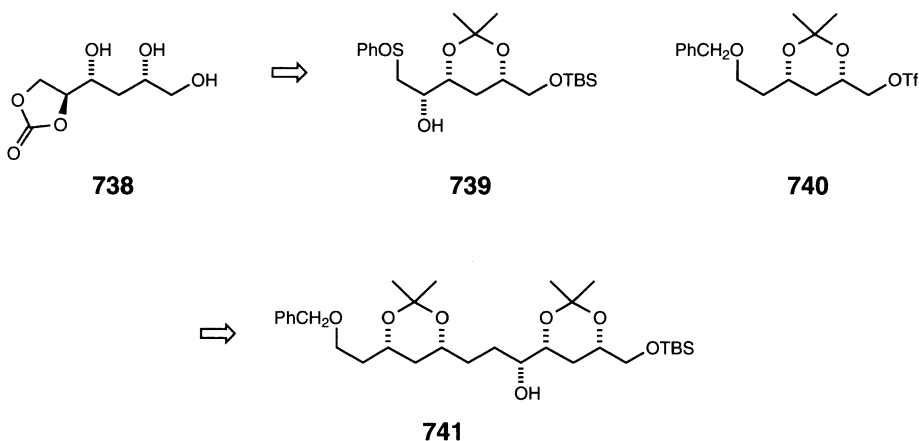
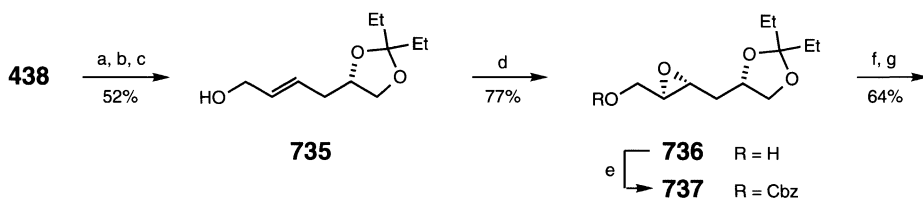
conditions: (a) I_2 , ether, $NaHCO_3$; (b) TBPS-Cl, $i\text{-Pr}_2\text{NEt}$, DMAP, CH_2Cl_2 ; (c) Bu_3SnH , AIBN, hexane; (d) DIBAL, toluene, -78°C ; (e) $Ph_3P=CHCOCH_3$, CH_2Cl_2 ; (f) H_2 , 10% Pd/C, EtOH; (g) $(MeO)_3CH$, HCl (g), MeOH; (h) Bu_4NF ; (i) Me_2BBr

O-Alkylation of **754** is accomplished with either sodium hydride in THF [165] or potassium hydroxide in DMSO [166] to give alkoxy derivatives **755** in good yield.

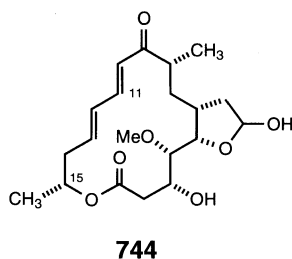
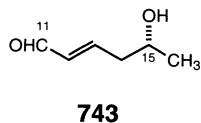
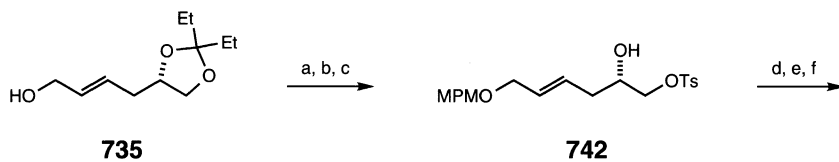


Once alkylated, the acetal can be regioselectively cleaved with trimethylsilyl cyanide in the presence of a Lewis acid. Use of titanium tetrachloride, which is capable of chelation-directed activation of the acetal, affords **756** with $> 250 : 1$ selectivity. Complete reversal of the effect is observed with the non-chelating zinc bromide, which gives **757** with $< 1 : 250$ selectivity. Unfortunately, the diastereoselectivity in both reactions is poor (1.3 : 1 and 2.1 : 1) [165].

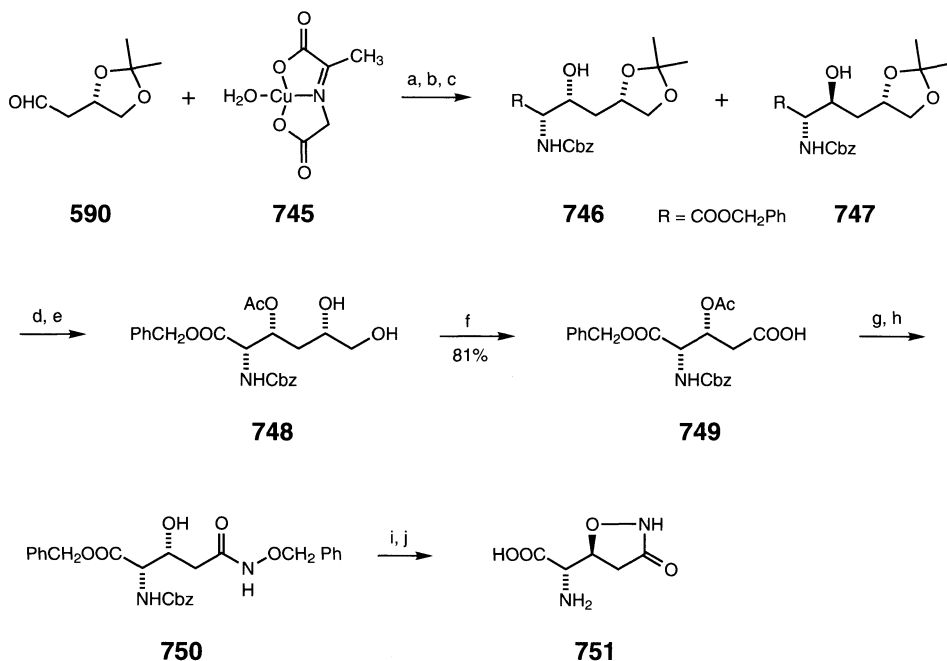


**Scheme 106**

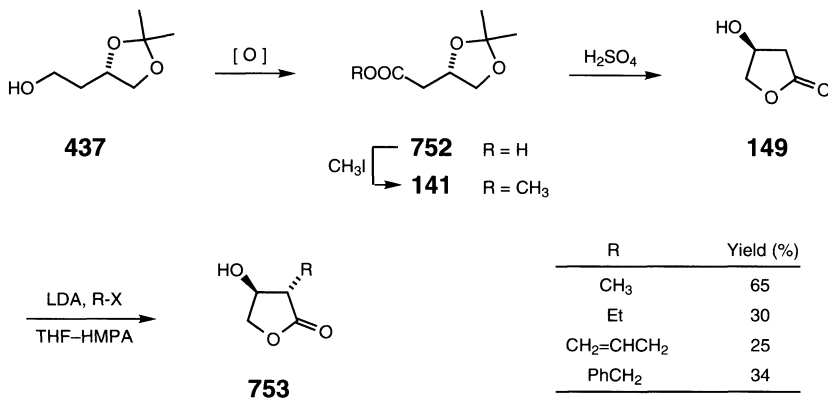
conditions: (a) PCC, CH_2Cl_2 ; (b) $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COOEt}$, NaH, THF-toluene, -20°C ; (c) DIBAL, THF, -40°C ; (d) Sharpless epoxidation; (e) Cbz-Cl, pyridine, THF (90%); (f) AlCl_3 , ether, -20°C ; (g) 1% H_2SO_4 , MeOH

**Scheme 107**

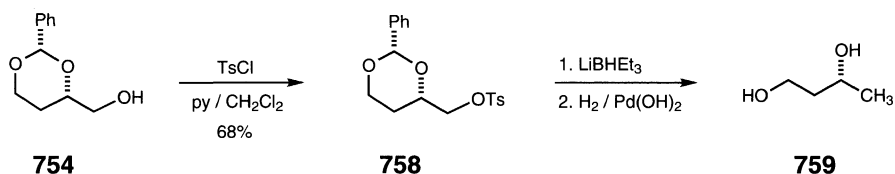
conditions: (a) MPM-Cl, NaH, DMSO-THF (4:3) (94%); (b) 1% H_2SO_4 , MeOH; (c) TsCl, pyridine (70%); (d) LiAlH_4 , ether (94%); (e) DDQ, CH_2Cl_2 - H_2O ; (f) MnO_2 , CH_2Cl_2 (74%)

**Scheme 108**

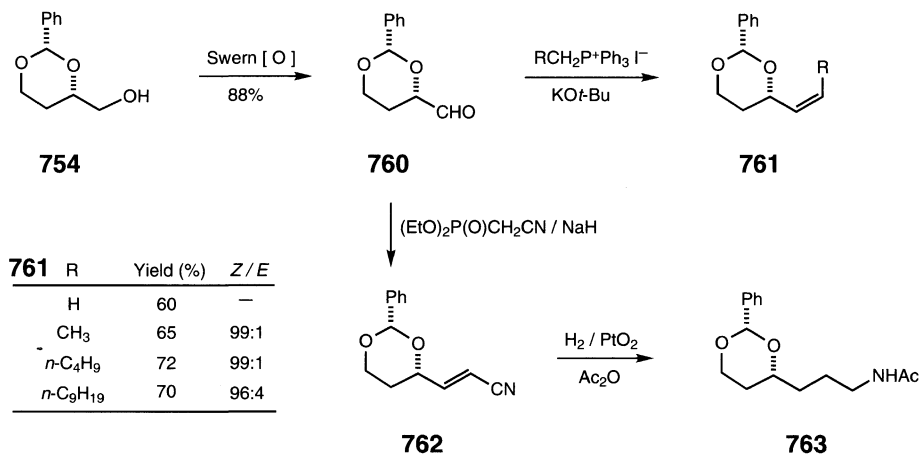
conditions: (a) 2N NaOH (50%); (b) N-Cbz-succinimide, DMF; (c) PhCH₂Br, Et₃N, DMF; (d) Ac₂O, pyridine, DMAP (94%); (e) HOAc (95%); (f) NaIO₄, KMnO₄, acetone-H₂O (10:1); (g) PhCH₂ONH₂, EDAC, DMAP, CH₃CN (80%); (h) LiOCH₂Ph, THF, 0 °C; (i) MsCl, pyridine; (j) H₂, Pd/C, Et₃N

**Scheme 109**

Tosylation of **754** affords tosyloxy acetal **758**. Reductive removal of the tosylate furnishes a methyl derivative (91%), and subsequent hydrogenolytic cleavage of the acetal gives (*R*)-1,3-butanediol (**759**) in 87% yield [164].

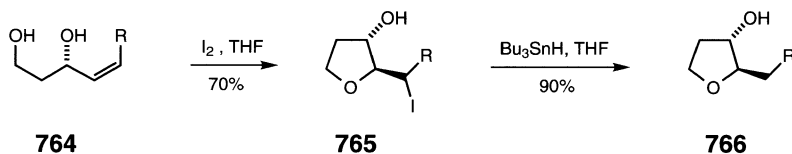


Oxidation of **754** under Swern conditions provides aldehyde **760**. Wittig reaction of **760** with phosphoranes yield *Z*-olefins **761** [166]; phosphonates yield the *E*-olefin **762** (Scheme 110) [102]. Reduction of **762** in acetic anhydride gives *N*-acetyl-protected diol **763**, which is identical to one of the degradation products of the polyene macrolide lienomycin.



Scheme 110

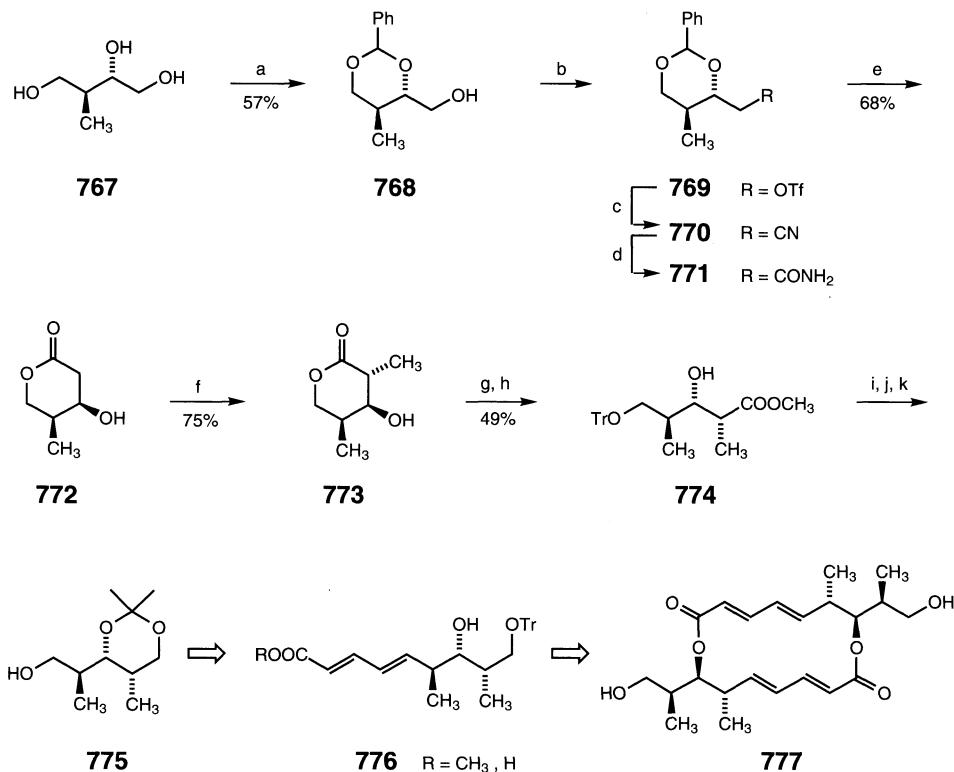
Olefin **761** can be further transformed into *trans*-tetrahydrofuran derivatives (**766**) by iodocyclization followed by dehalogenation. The cyclization to **765** generally proceeds with 84:16 *trans/cis* selectivity, but a significant amount of racemization occurs during the hydrolysis of **761** to **764** (60% *ee*) [166], thus leading to enantiomerically compromised products.



The central ring (**777**) of elaiophylin, a macrodiolide antibiotic isolated from fungi, is synthesized from (*S*)-malic acid via triol **767** as shown in Scheme 111 [167]. Since the ring is C₂-symmetric, only half the molecule need be prepared.

Triol **767** originates from lithium aluminum hydride reduction of alkylated malate **225a**. Acetal formation with benzaldehyde furnishes **768** [86], which is further transformed into amide **771** via the nitrile **770**. Hydrogenolysis of the acetal leads to a diol that is lactonized

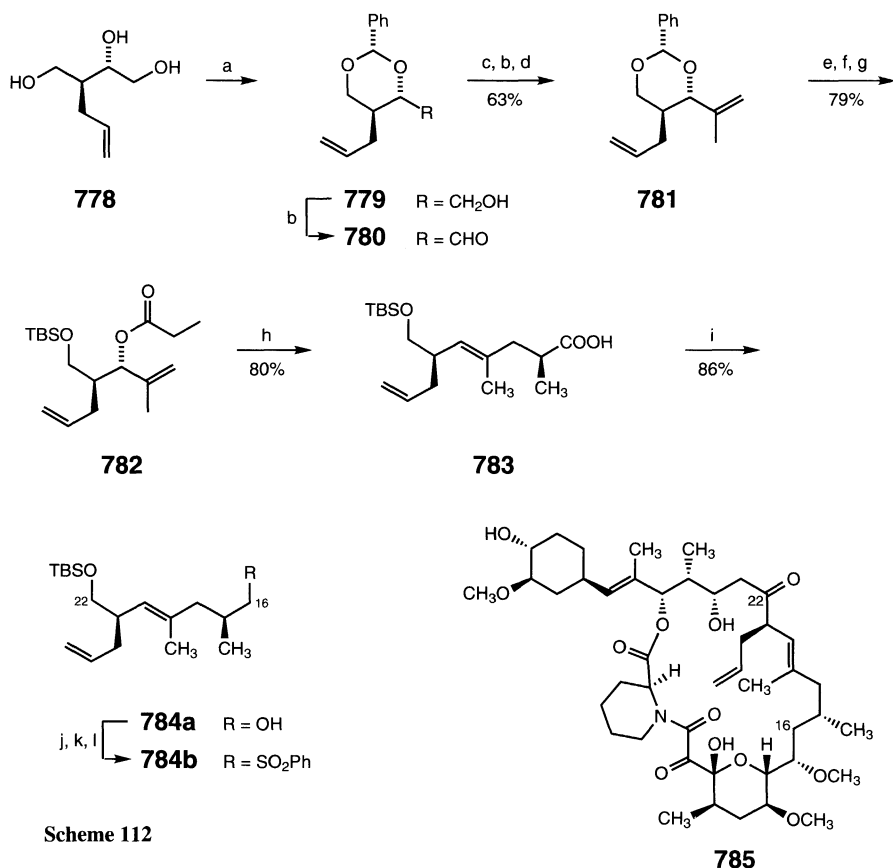
directly to **772**. Alkylation of the lactone proceeds with >99:1 diastereoselectivity to afford the methylated lactone **773**. Opening of the lactone with sodium methoxide followed by tritylation gives ester **774** contaminated with 3% of the epimerized diastereomer. Reduction of the ester, acetone formation, and detritylation furnishes the key intermediate **775**. Swern oxidation of the alcohol to an aldehyde followed by a Wittig reaction to introduce the dienophile portion and protective-group manipulation gives acid **776**, which is then macrolactonized with itself to the macrodiolide **777** [171].



Scheme 111

conditions: (a) PhCHO, ZnCl₂; (b) Tf₂O, pyridine, CH₂Cl₂, 0 °C; (c) NaCN, HMPT (57%); (d) H₂O₂, 1-hexene, Na₂CO₃, MeOH (97%); (e) H₂, Pd(OH)₂, EtOAc then 1N HCl; (f) 2 LDA, THF, HMPT, -60 °C then *n*-BuLi, CH₃I, -78 °C; (g) NaOCH₃, MeOH, 0 °C; (h) tritylpyridinium tetrafluoroborate, CH₃CN; (i) LiAlH₄, ether, 0 °C (98.5%); (j) Me₂C(OMe)₂, PTSA (91%); (k) Li / NH₃ (71%)

The C-16 to C-22 fragment (**784b**) of FK 506 (**785**), a potent immunosuppressant isolated from *Streptomyces tsukubaensis*, is synthesized as shown in Scheme 112 [168]. The initial triol **778** obtained from the reduction of **225e** is converted to the benzylidene acetal **779** and then to olefin **781** via aldehyde **780**. Acidic hydrolysis of the acetal, silylation of the primary alcohol, and acylation of the secondary alcohol produces a substrate (**782**) suitable for a Claisen rearrangement. Treatment of **782** with LDA and TBS-Cl generates an intermediate *Z*-silyl ketene acetal that upon heating undergoes an ester-enolate Claisen rearrangement with complete control of *E*-olefin geometry and high chirality transfer (20:1). Standard manipulations lead to the desired fragment **784b**.



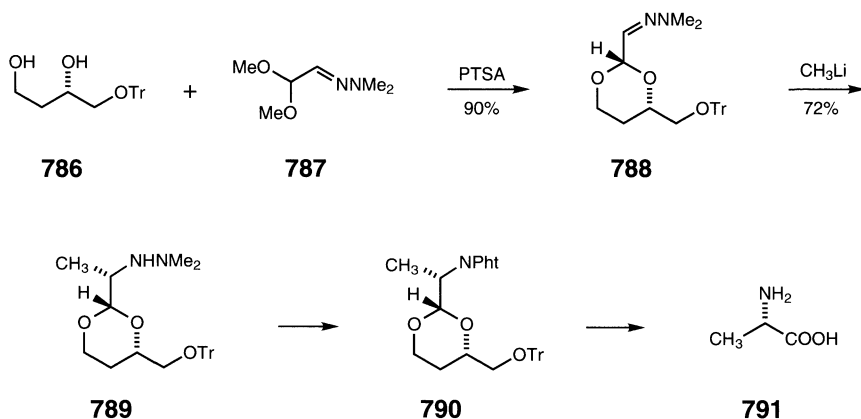
Scheme 112

conditions: (a) PhCH(OMe)₂, CSA, CH₂Cl₂; (b) Swern [O]; (c) CH₃Li, ether; (d) Ph₃P=CH₂, THF; (e) HOAc–THF–H₂O, 60 °C; (f) TBS–Cl, Et₃N, DMAP, CH₂Cl₂; (g) EtCOOH, DCC, DMAP, CH₂Cl₂; (h) LDA, TBS–Cl, HMPA–THF then NaOH; (i) LiAlH₄, THF; (j) MsCl, Et₃N, CH₂Cl₂, 0 °C; (k) NaI, acetone; (l) PhSO₂Na, DMF, 80 °C

An interesting variation on the general theme of 6-membered acetals makes use of hydrazone-acetal **788** in the synthesis of α -amino acids (Scheme 113). Trityl diol **786**, obtained from the lithium aluminum hydride reduction of ester **101**, is transacylated with the glyoxal-derived acetal **787** to give cyclic acetal **788** [169]. Addition of methyl lithium to **788** occurs from the *re* face of the C=N bond to produce **789** with 100% diastereoselectivity. With *n*-butyllithium the diastereoselectivity drops to 92 : 8 [170]. The hydrazino derivative **789** is transformed to L-(+)-alanine (**791**) by reductive cleavage of the N–N bond (H₂, Raney nickel), protection of the resulting amine with a phthaloyl group (**790**), oxidation of the acetal (HClO, H₂O), and cleavage of the phthaloyl group (N₂H₄, H₂O). The desired amino acid is obtained with 97% optical purity. The generality of this synthesis has yet to be explored.

3.3.2 Cyclization

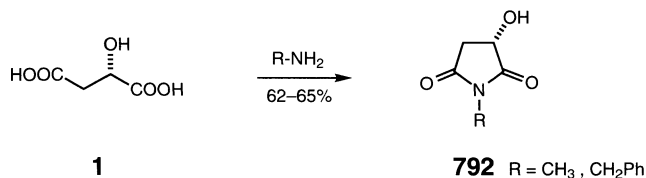
Already in this chapter we have touched sporadically on cyclization reactions of (*S*)-malic acid. These have served primarily as anhydride-forming reactions (e.g. **1** → **21**) whose sole



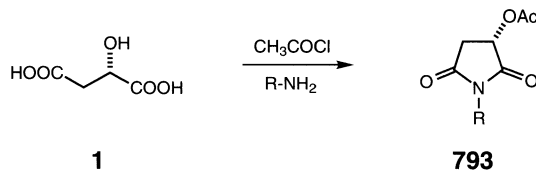
Scheme 113

purpose was to differentiate the carboxylate groups by converting the 1-carboxyl function to an ester (**23**). In this section we focus on cyclization reactions with amines, reactions which in nearly every case leave the skeleton of the newly formed ring intact.

Reaction of (*S*)-malic acid with amines provides (*S*)-*N*-alkyl-3-hydroxy succinimides (**792**). Reactions of this type are typically carried out in ethanol [172] or such aromatic solvents as toluene [173] or xylene [174] at elevated temperature, and they afford **792** in reasonable yields. Water formed in the process can be trapped with 4 Å molecular sieves [175].

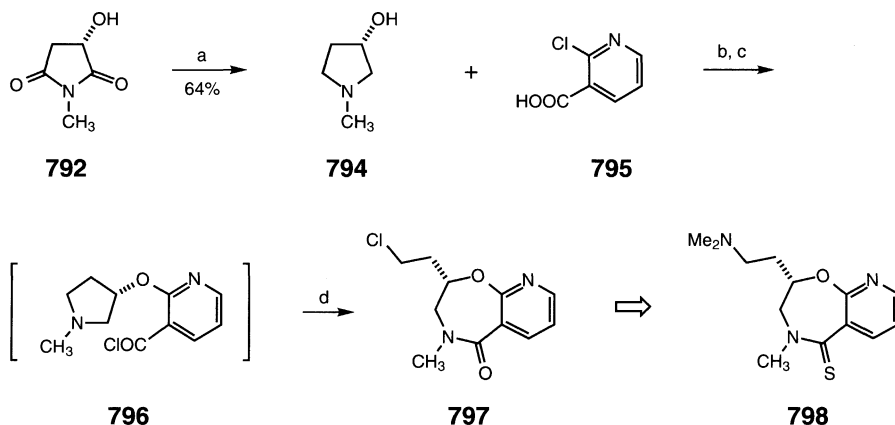


The closely related (*S*)-3-acetoxy succinimides (**793**) are formed by sequential treatment of **1** with acetyl chloride, amine, and acetyl chloride again. Reaction with the amine is best carried out at 20–25 °C in order to avoid any epimerization at the 3-position [176].



793	R	Yield (%)	Ref.
a	H	52	186
b	<i>i</i> -Pr	68	179, 180
c	CH ₂ Ph	83	176, 182, 183
d	CH ₂ COOCH ₃	74	178

The carbonyl groups of **792** (R=CH₃) are easily reduced with Red-Al to afford (*S*)-1-methyl-3-pyrrolidinol (**794**). In an interesting synthesis of the (*S*)-enantiomer of rocastine (**798**), an antihistaminic agent, the hydroxypyrrolidine **794** is coupled with 2-chloronicotinic acid (**795**), and the resulting product is converted to acid chloride **796**. Subsequent treatment with triethylamine results in the formation of the 7-membered oxapine ring **797**. Transformation of the amide to a thioamide (P₂S₅) and displacement of chloride with dimethylamine affords the target molecule **798** (Scheme 114) [173]. The (*R*)-enantiomer of rocastine, similarly derived from (*R*)-malic acid, is 300 times more potent than **798**. It should be noted that this is one of the few cases in which the heterocyclic ring initially generated from malic acid is disrupted.



Scheme 114

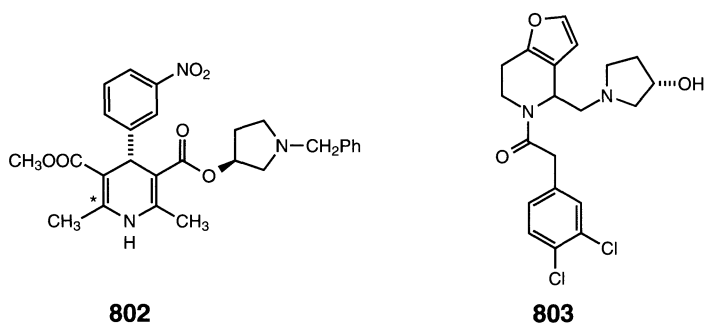
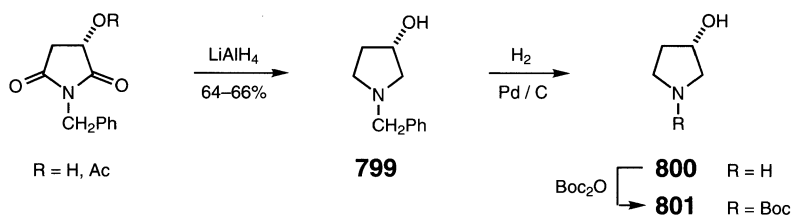
conditions: (a) Red-Al, THF, reflux; (b) NaH, THF, 55–60 °C; (c) CCl₄, Ph₃P; (d) Et₃N

Either **792** (R=CH₂Ph) or **793c** can be completely reduced with lithium aluminum hydride to the *N*-benzyl pyrrolidinol **799**. The benzyl group is easily removed under hydrogenolytic conditions to give **800** in 88% yield [176]. Protection of the nitrogen with a Boc group is accomplished in nearly quantitative yield with Boc anhydride [172]. Pyrrolidinols **799** and **800** have been used in the synthesis of ¹⁴C-labeled YM-09730-5 (**802**), a potent calcium antagonist [177], and **803**, an antinociceptive agent [176].

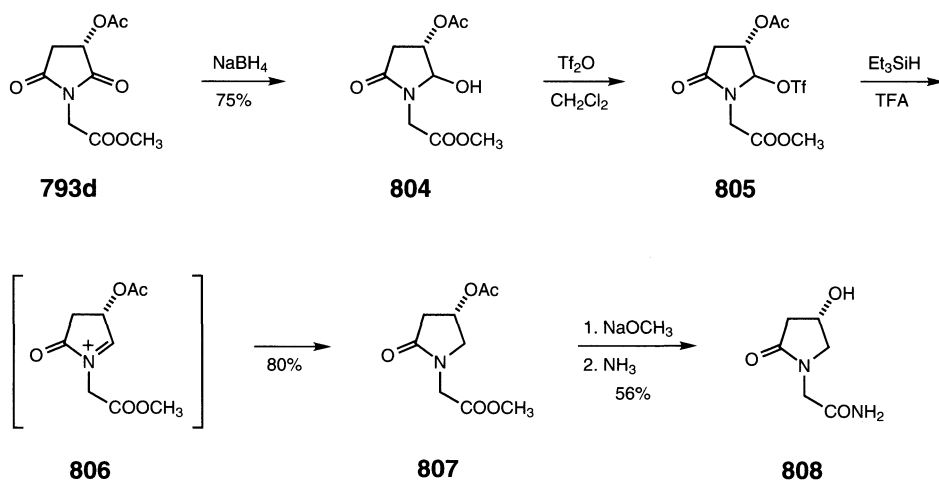
The ability of succinimides **793** to be regioselectively reduced increases the scope of their synthetic utility, as will be shown in the remainder of this section.

Since the C=O in the 2-position is the more electrophilic of the ring carbonyls, selective reduction of this group opens wide vistas for synthesizing asymmetric molecules containing a pyrrolidine nucleus. Take, for example, the synthesis of the nootropic agent oxiracetam (**808**) (Scheme 116) [178]. Of the four carbonyl groups in succinimide **793d**, only the 2-carbonyl is reduced upon treatment with sodium borohydride at –10 °C for 10 minutes. The resulting hydroxy lactam **804** is obtained as a 95 : 5 *cis/trans* mixture. Higher reaction temperatures result in reduction of the methyl ester. Conversion of **804** to triflate **805** and subsequent reduction with triethylsilane in trifluoroacetic acid (via iminium ion **806**) affords pyrrolidinone **807**. Acetate removal and amide formation completes the synthesis of **808** in 21% overall yield.

In the synthesis of peduncularine (**814**), the principal alkaloid of the Tasmanian shrub *Aristolelia peduncularis*, regioselective reduction of **793b** with sodium borohydride followed



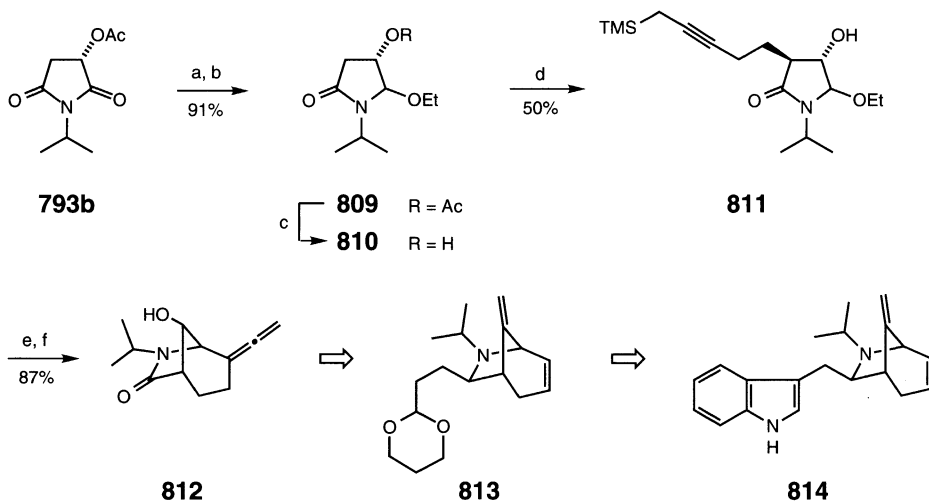
Scheme 115



Scheme 116

by ethanolysis produces ethoxy lactam **809** (Scheme 117) [179,180]. Removal of the acetate function gives alcohol **810** as an 85 : 15 diastereomeric mixture. Alkylation of **810** with 5-iodo-1-(trimethylsilyl)-2-pentyne occurs stereospecifically to afford the 3,4-*trans*-lactam **811**. A temperature of $-117\text{ }^{\circ}\text{C}$ is required in order to prevent competitive hydrogen iodide elimination from the alkylating agent.

The key transformation in the synthesis is the silicon-assisted *N*-acyliminium ion cyclization of **811** to give the bicyclic lactam **812** in high yield [27% overall yield from (*S*)-malic acid]. The remainder of the synthesis requires 11 additional steps.



Scheme 117

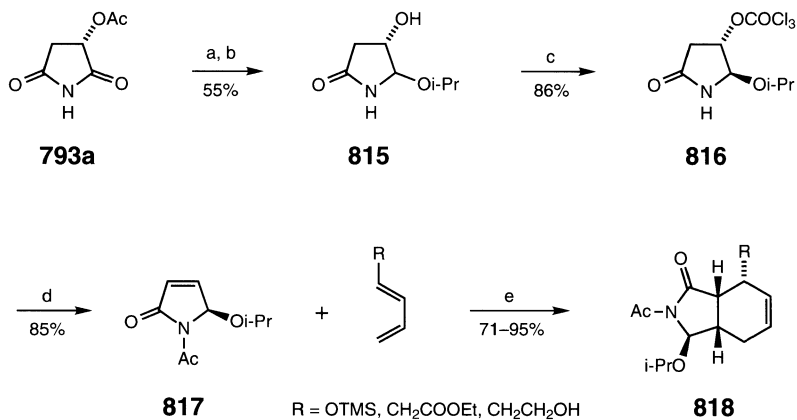
conditions: (a) NaBH_4 , EtOH, -15°C , 15 min; (b) EtOH, H_2SO_4 ; (c) NaOEt, EtOH (99%); (d) 2 LDA, THF, $\text{ICH}_2\text{CH}_2\text{C}\equiv\text{CCH}_2\text{TMS}$, -117°C ; (e) HCOOH ; (f) NH_3 , MeOH

Regio and facial selectivity in the reduction of succinimide **793** can be taken advantage of to introduce a new chiral center at C-5 of the resulting pyrrolidinone. Thus, if succinimide **793a** is reduced with lithium borohydride and the resulting 5-hydroxypyrrolidinone treated with 2-propanone under acidic conditions, the 5-isopropoxy pyrrolidinone **815** results as a 1 : 4 *cis/trans* mixture [181]. Acylation of the hydroxy group with trichloroacetic anhydride gives *trans*-lactam **816** as the sole product as a consequence of epimerization during the reaction. Treatment of **816** with acetic anhydride in pyridine results in N-acetylation followed by elimination of the trichloroacetoxy group, thereby giving the optically pure (*R*)-3-pyrrolidin-2-one derivative **817** in 40% overall yield from **793a**.

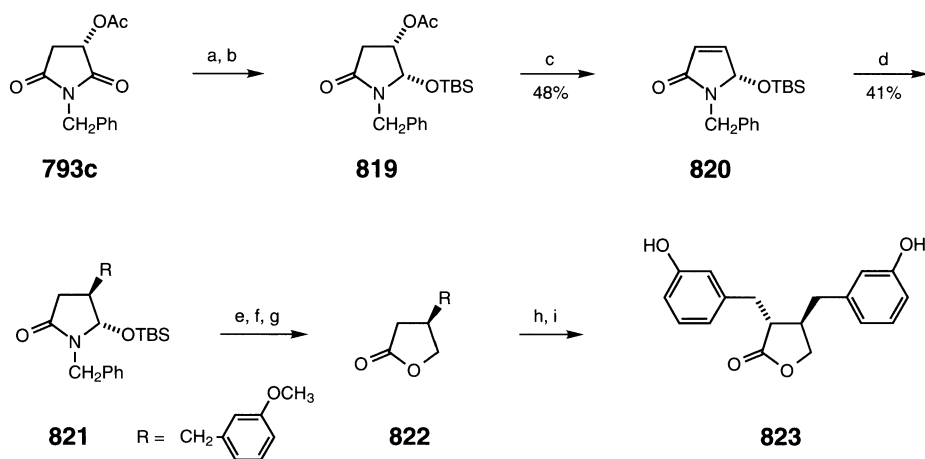
Compound **817** behaves as an excellent chiral dienophile in Diels–Alder reactions. In three selected cases, reaction of **817** with an appropriate butadiene affords adduct **818** with high *endo* selectivity (Scheme 118).

In the synthesis of the lignan lactone (–)-enterolactone (**823**), reduction of succinimide **793c** with sodium borohydride followed by silylation produces the 5-siloxypyrrolidinone **819** as a 78 : 22 mixture of *cis* and *trans* isomers (Scheme 119) [182]. The major *cis* isomer is separable by column chromatography, and when treated with sodium hydride this undergoes elimination of the acetoxy group to furnish the (*S*)-3-pyrrolidin-2-one **820**. Conjugate addition of 3-methoxybenzyl cuprate reagent to **820** affords **821** as the only diastereomer. Desilylation, reductive ring cleavage, and lactonization furnishes butyrolactone derivative **822**, which is then stereoselectively alkylated with 3-methoxybenzyl chloride and demethylated to give **823**.

Two different approaches to (–)-statine (**831**), an unusual amino acid component of pepstatin, both employ **793c** as their starting point. In the first synthesis (Scheme 120) [183], reduction of **793c** with sodium borohydride produces a mixture of two isomeric 5-hydroxypyrrolidinones, from which the pure *cis* product **824** crystallizes in 85% yield. Conversion of bisacetate **825** to thioether **826** followed by removal of the acetate and silylation of the resulting alcohol affords **827**. Radical cyclization of **827** produces a 3 : 2 mixture of isomers **828**. Desilylation and debenzoylation gives **829** as a single diastereomer. The Boc-protected intermediate **830** intersects with a known synthesis of (–)-statine (**831**).

**Scheme 118**

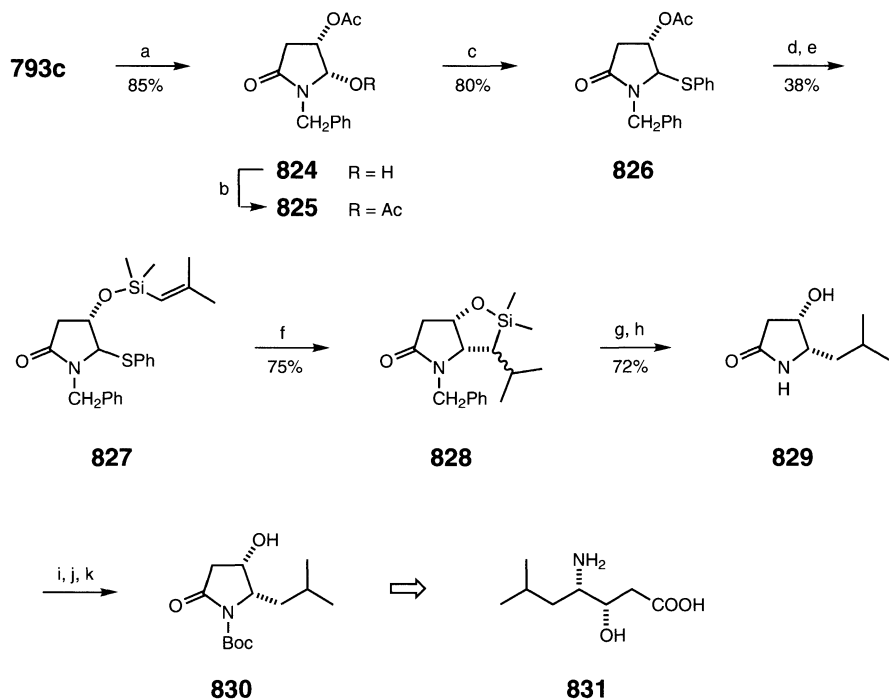
conditions: (a) LiBH₄, THF, -20 °C; (b) H₂SO₄, *i*-PrOH; (c) (Cl₃CCO)₂O, DMAP, ether;
(d) Ac₂O, pyridine, DMAP; (e) toluene, 100–110 °C

**Scheme 119**

conditions: (a) NaBH₄, MeOH, -4 °C (65%); (b) TBS-Cl, imidazole, DMF (60%); (c) NaH, THF;
(d) 3-MeOC₆H₄CH₂MgCl, CuI, TMSCl, THF, -78 °C; (e) Bu₄NF, THF; (f) NaBH₄, EtOH
(71%, 2 steps); (g) PTSA, benzene (89%); (h) LDA, 3-MeOC₆H₄CH₂Cl, THF,
HMPA (84%); (i) BBr₃, CH₂Cl₂

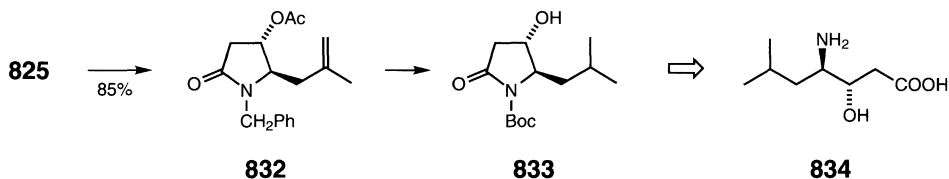
The isomeric 4-*epi*-statine (**834**) is also readily accessible from **825** by alkylation at C-5 with methallyltrimethylsilane in the presence of boron trifluoride etherate *via* an *N*-acyliminium ion intermediate. The resulting lactam **832** is produced as an 11 : 1 mixture of *trans* and *cis* isomers which is readily separable by crystallization. Reduction of the olefin and protective group manipulation furnishes **833**, an intermediate that intersects with a previous synthesis of **834**.

A much shorter synthesis of (-)-statine (**831**) relies on the regiospecific addition of methallylmagnesium chloride to the C-2 carbonyl of **793c** as a way of introducing the



Scheme 120

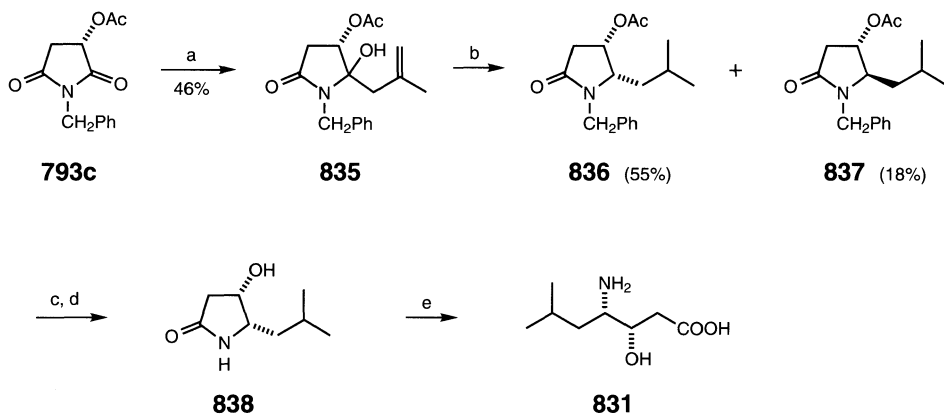
conditions: (a) NaBH_4 , EtOH, -20°C ; (b) Ac_2O , DMAP, pyridine; (c) PhSH, toluene, PTSA; (d) NaOEt, EtOH; (e) $\text{Me}_2\text{C}=\text{CHSi}(\text{Me})_2\text{NMe}_2$, THF, pentane; (f) Bu_3SnH , AIBN, benzene; (g) Bu_4NF , THF, CsF ; (h) Na / NH_3 , -78°C ; (i) TBS-Cl, imidazole, DMF; (j) Boc_2O , Et_3N , DMAP, CH_2Cl_2 ; (k) KF, Bu_4NF , THF



required skeletal components (Scheme 121) [184]. Catalytic hydrogenation of the aminal affords a mixture of **836** and **837** that is separable by column chromatography. Removal of both protecting groups (**838**) followed by acid hydrolysis in a sealed tube gives **831** in 40% overall yield from **836**.

The synthesis of *erythro*-*L*- β -hydroxyglutamic acid (**844**) makes use of the furan heterocycle as a carboxyl equivalent (Scheme 122) [185]. After reduction of **793a** to **839** and acetylation (**840**), the aminal acetate and furan are coupled in the presence of zinc bromide and a catalytic amount of trimethylchlorosilane to give a 67:33 mixture of **841** and **842**. In the absence of silane the reaction requires 12 h at room temperature for completion, but with silane present the reaction time is reduced to 2 h at -15°C .

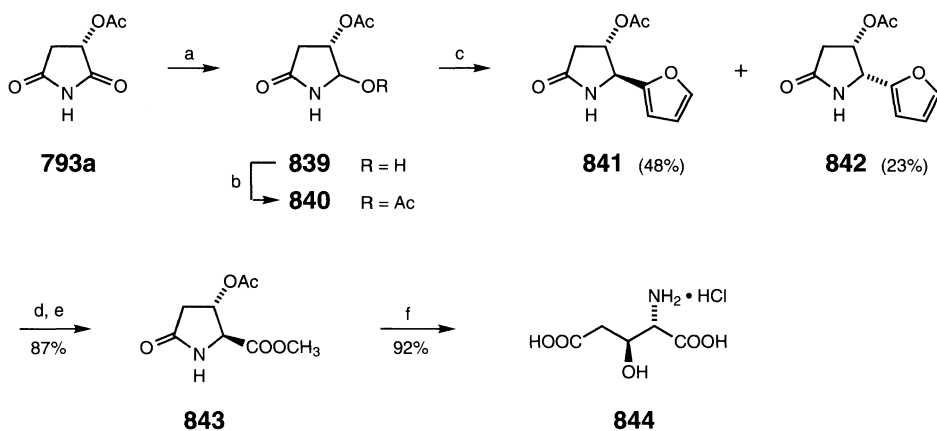
Diastereomers **841** and **842** are easily separable by column chromatography. Ozonolytic cleavage of **841** followed by esterification furnishes methyl (2*S*,3*S*)-3-acetoxypyroglutamate



Scheme 121

conditions: (a) $\text{CH}_2=\text{C}(\text{CH}_3)\text{CH}_2\text{MgCl}$, THF, $-50\text{ }^\circ\text{C}$; (b) H_2 , Pd / C, CH_2Cl_2 ; (c) HCl, MeOH, $60\text{ }^\circ\text{C}$; (d) Na / NH_3 , $-78\text{ }^\circ\text{C}$; (e) 6N HCl, $110\text{ }^\circ\text{C}$

(**843**), and subsequent acidic hydrolysis affords the desired glutamic acid derivative **844**. It is interesting to note that **793a** is not accessible from **793c** by hydrogenolytic cleavage of the benzyl group.



Scheme 122

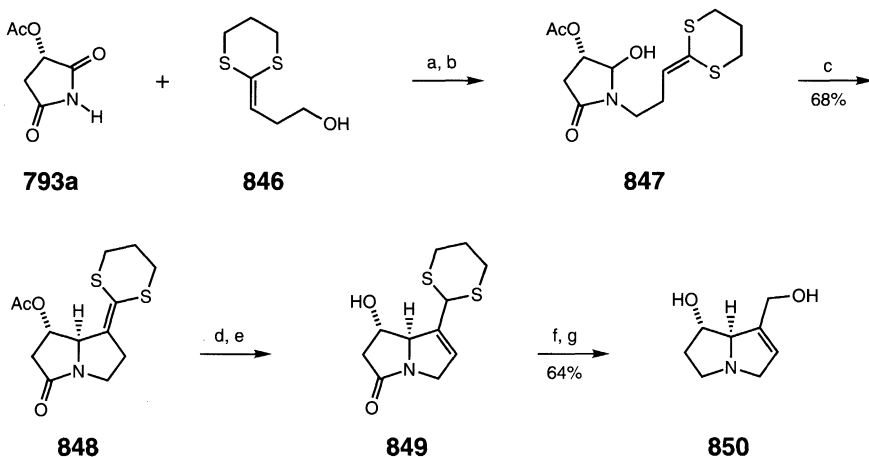
conditions: (a) NaBH_4 , CH_2Cl_2 , MeOH (2:1), $-15\text{ }^\circ\text{C}$; (b) Ac_2O , pyridinium perchlorate; (c) furan, ZnBr_2 , TMSCl, MeNO_2 ; (d) O_3 , MeOH, $-78\text{ }^\circ\text{C}$; (e) CH_2N_2 , $0\text{ }^\circ\text{C}$; (f) 6N HCl

The ability of succinimides **793** to be manipulated at C-2 in conjunction with the location of the acetoxy group makes such compounds ideal candidates for the synthesis of the pyrrolizidine alkaloid framework (**845**). Strategically, this is accomplished by N-alkylation of **793a** with a suitable group followed by regioselective reduction of the C-2 carbonyl and intramolecular acyliminium cyclization.

Several approaches to (+)-heliotridine (**850**) use this strategy, but with variations in the nature of the group attached to nitrogen. For example, alkylation of **793a** with dithiane **846**



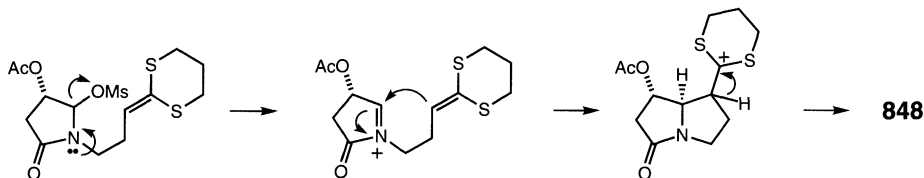
under Mitsunobu conditions followed by sodium borohydride reduction affords the hydroxy lactam **847**. Cyclization to the pyrrolizidine skeleton under nonacidic conditions (MsCl, Et₃N) gives **848** with approximately 97% purity. Removal of the acetyl group and base-induced double-bond migration yields **849**. Mercury-mediated hydrolysis of the dithiane and reduction of the resulting aldehyde and lactam carbonyls furnishes **850** (Scheme 123) [186].



Scheme 123

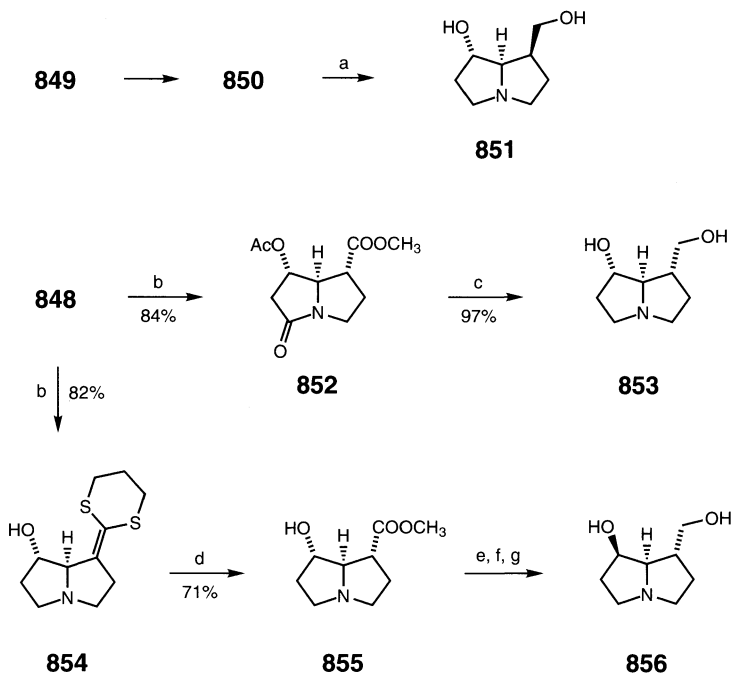
conditions: (a) DEAD, Ph₃P, THF (70%); (b) NaBH₄, MeOH, -4 °C (85%); (c) MsCl, Et₃N, CH₂Cl₂, -20° → 20 °C; (d) K₂CO₃, MeOH, -10 °C (64%); (e) LDA, THF, -30 °C (80%); (f) HgCl₂, CH₃CN, H₂O, CaCO₃; (g) LiAlH₄, THF, reflux

Mechanistically, the cyclization step **847** → **848** proceeds through the acyliminium ion shown below.



Minor adjustment in oxidation level allows rapid entry to other pyrrolizidine alkaloids (Scheme 124) [187]. Catalytic hydrogenation of **850** gives (+)-dihydroxyheliotridane (**851**). Hydrolysis of the dithiane ring of **848** followed by exhaustive reduction of all carbonyls

affords (+)-hastanecine (**853**). Reducing the carbonyl groups of **848** prior to dithiane hydrolysis allows the isolation of ester **855**. Oxidation of the hydroxyl group to a ketone followed by catalytic hydrogenation of the carbonyl effectively inverts the stereochemistry of the 7-hydroxy group. Lithium aluminum hydride reduction of the ester then furnishes (–)-turneforcidine (**856**).



Scheme 124

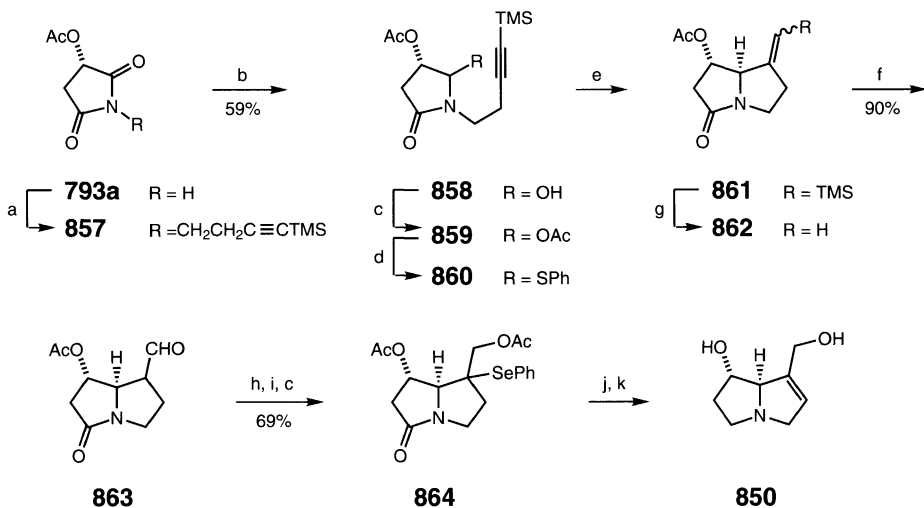
conditions: (a) H_2 , Raney nickel; (b) HgCl_2 , 0.3M HCl, THF; (c) LiAlH_4 , THF, reflux; (d) HgCl_2 , 6N HCl, MeOH; (e) Swern [O] (74%); (f) H_2 , PtO_2 , MeOH; (g) LiAlH_4 (75%)

Two separate syntheses of (+)-heliotridine (**850**) employ the strategy of an intramolecular addition of an α -acylamino radical to an alkyne (Scheme 125) [188,189]. Selective reduction of **857** to **858** followed by acetylation (**859**) and acetoxy–thiophenoxy exchange affords the radical precursor **860**.

Treatment of **860** with tri-*n*-butyltin hydride and AIBN under high dilution conditions leads to cyclized product **861** as a 3 : 1 mixture of *E/Z* isomers (60–71%). Conversion of the TMS-olefin to an aldehyde (**863**), phenylselenation, reduction of the aldehyde, and acetylation furnishes **864**. Oxidation and subsequent elimination of the selenoxide followed by reduction of all carbonyl groups with lithium aluminum hydride gives the natural product **850**.

Alternatively, the exomethylene derivative **862** can be converted directly to a derivative similar to **864** by trifluoroacetoxy phenylselenation, and the product can then be carried on to **850** as in Scheme 125 (steps j, k) [190].

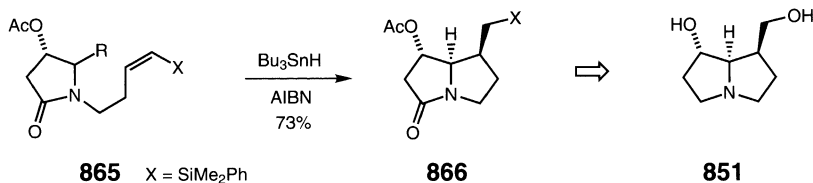
Applying the same concept, vinylsilane **865** ($\text{R}=\text{OH}$) is converted to a radical precursor ($\text{R}=\text{OH} \rightarrow \text{OAc} \rightarrow \text{SPh}$) and cyclized to give a separable 6 : 1 mixture of **866** and its C-1 epimer. Oxidation of the silyl group ($\text{HBF}_4\text{-Et}_2\text{O}$, CH_2Cl_2 ; MCPBA, KF) and reduction of the



Scheme 125

conditions: (a) 4-trimethylsilyl-3-butyne-1-ol, DEAD, Ph₃P (97%); (b) NaBH₄, MeOH, -30 °C; (c) Ac₂O, Et₃N, DMAP, CH₂Cl₂ (100%); (d) PhSH, PTSA (97%); (e) Bu₃SnH, AIBN, benzene, 80 °C; (f) MCPBA, HCOOH, CH₂Cl₂; (g) CF₃COOH, CH₂Cl₂; (h) PhSeNEt₂, CH₂Cl₂ (89%); (i) NaBH₄, EtOH; (j) H₂O₂, THF (97%); (k) LiAlH₄

carbonyl groups gives (–)-dihydroxyheliotridane (**851**) in 23% overall yield from **793a** (7 steps) [191].

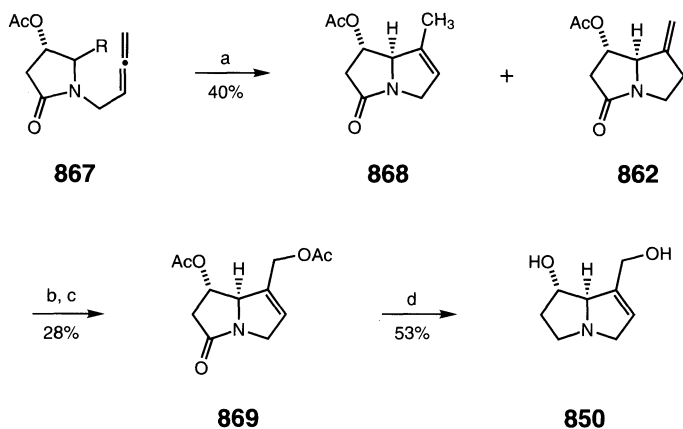


The allene functionality is also useful in radical cyclizations. Radical precursor **867** (R=OH → OAc → SePh) is readily cyclized to a 5 : 1 mixture of **868** and **862** together with two other cyclic compounds. After separation of the desired product **868**, the methyl group is oxidized to an alcohol and then acetylated. Finally, the carbonyl groups are reduced to give (+)-heliotridane (**850**) [191].

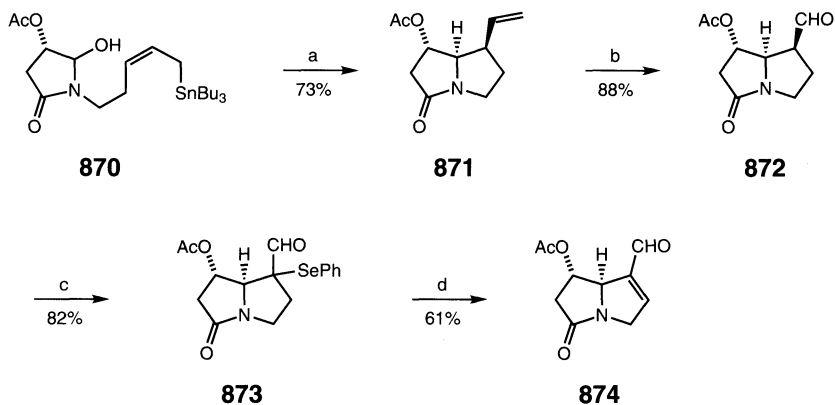
Intramolecular acyliminium-ion cyclization of **870** produces **871** with high stereoselectivity. Ozonolysis of the olefin affords **872** (the totally chiral version of **863**). Lithium aluminum hydride reduction of **872** gives (–)-dihydroxyheliotridane (**851**) in 93% yield.

Introduction of unsaturation (**872** → **873** → **874**) followed by reduction with allane provides (+)-heliotridane (**850**) in 35% yield (Scheme 127) [192].

A slightly different approach to **850** takes advantage of an intermolecular carbenoid displacement and intramolecular alkylation to construct the pyrrolizidine ring (Scheme 128) [193,194]. The precursor is prepared from **875** (R=OH → OEt → SPh) and, for convenience, the protecting acyl group is replaced with a MOM group, which gives **876** as an 8 : 1 mixture of *trans* and *cis* phenylsulfides. The major *trans*-sulfide is subjected to a carbenoid dis-

**Scheme 126**

conditions: (a) Bu_3SnH , AIBN, benzene; (b) SeO_2 , $\text{HOAc}-\text{Ac}_2\text{O}$ (1:1);
(c) Ac_2O , Et_3N , DMAP, CH_2Cl_2 ; (d) LiAlH_4 , THF

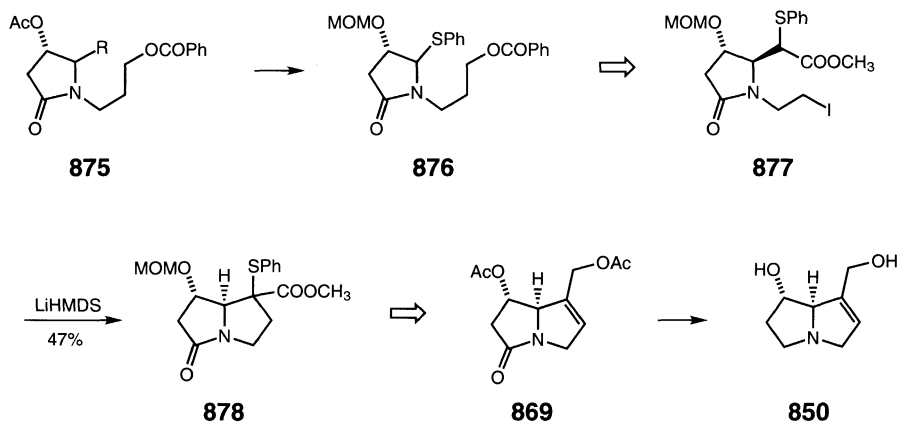
**Scheme 127**

conditions: (a) MsCl , Et_3N , CH_2Cl_2 ; (b) O_3 , MeOH , -78°C ; (c) PhSeNEt_2 , CH_2Cl_2 ; (d) H_2O_2 , THF

placement reaction using methyl *p*-nitrobenzyl α -diazomalonate in the presence of rhodium acetate, and the resulting product is transformed into iodo derivative **877**.

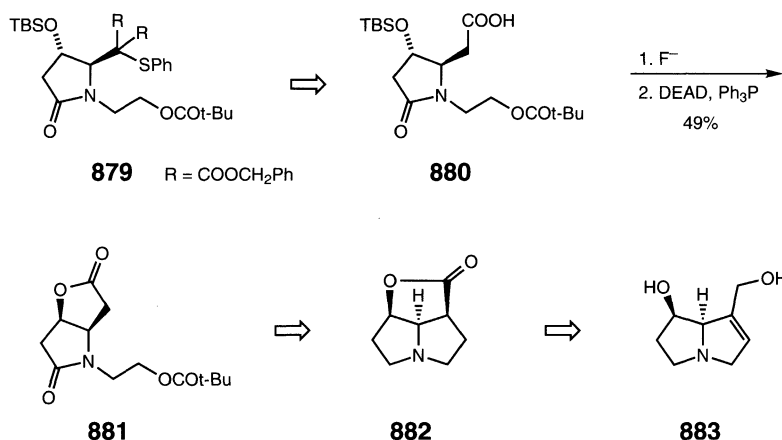
Exposure of **877** to lithium hexamethyldisilazide ($-78^\circ \rightarrow 0^\circ\text{C}$) results in intramolecular alkylation of the ester enolate to afford **878**. Reduction of the ester to an alcohol and oxidation of sulfur followed by elimination of the resulting sulfoxide introduces the unsaturation leading to **869**. This is then converted to (+)-heliotridine (**850**) by reduction of the carbonyl group.

The alkaloid (+)-retronecine (**883**, Scheme 129) is structurally similar to (+)-heliotridine (**850**), with the exception that the stereocenter at C-7 is of opposite configuration. The basic approach to its synthesis involves a carbenoid displacement similar to that in the previous scheme. The acetyl protecting group of the common intermediate **875** ($\text{R}=\text{Sph}$) is changed to a TBS group, and the benzoate is converted to pivalate. Carbenoid displacement with dibenzyl α -diazomalonate in the presence of rhodium acetate gives **879**. Reductive desulfurization



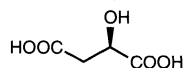
Scheme 128

(Raney Ni) and hydrogenolysis of the benzyl esters provides acid **880** in 83.2% yield from **879**. Removal of the silyl protecting group with fluoride and intramolecular displacement of the secondary hydroxyl under Mitsunobu conditions (inversion) provides lactone **881**. This has been converted to (+)-retronecine (**883**) by known procedures (see Section 3.4).

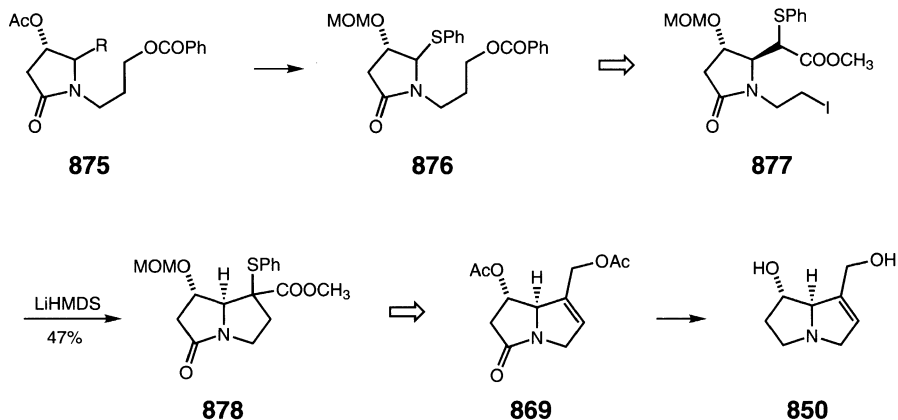


Scheme 129

3.4 (*R*)-Malic Acid

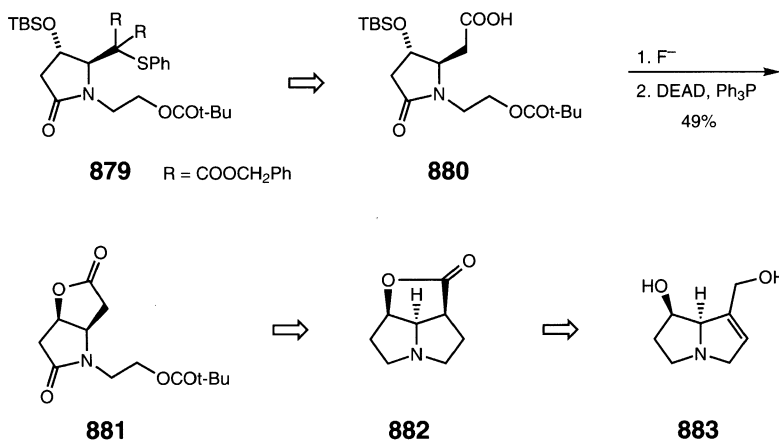
(*R*)-Hydroxybutanedioic Acid

D-Malic acid (**885**), the unnatural form with the (*R*)-configuration, has found its way into the arsenal of the organic chemist as a way of complementing the chemistry of L-malic acid.



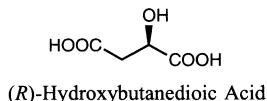
Scheme 128

(Raney Ni) and hydrogenolysis of the benzyl esters provides acid **880** in 83.2% yield from **879**. Removal of the silyl protecting group with fluoride and intramolecular displacement of the secondary hydroxyl under Mitsunobu conditions (inversion) provides lactone **881**. This has been converted to (+)-retroncine (**883**) by known procedures (see Section 3.4).



Scheme 129

3.4 (*R*)-Malic Acid



D-Malic acid (**885**), the unnatural form with the (*R*)-configuration, has found its way into the arsenal of the organic chemist as a way of complementing the chemistry of L-malic acid.

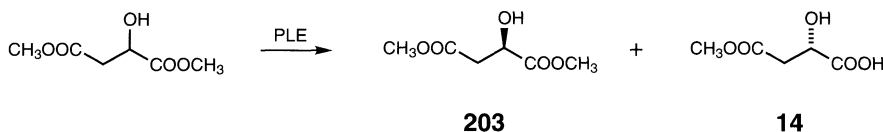
It is not the purpose of this section to reiterate chemical transformations discussed previously in this chapter, since it is quite obvious that virtually all the chemistry associated with L-malic acid can be applied to D-malic acid in order to produce compounds with the opposite configuration. Here we focus instead on the use of D-malic acid in the synthesis of medicinal agents and natural products.

Many of the basic manipulations of D-malic acid and the various derivatives that will be used as starting materials in this section have already been described in detail in terms of the corresponding L-malic acid derivatives. The reader should refer to relevant portions of the chapter for more detailed discussion of their preparation.

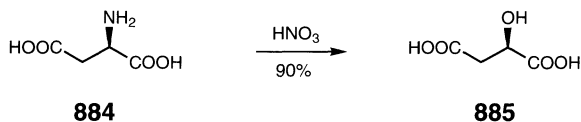
Since D-malic acid is rarer than its L-counterpart, it is also less readily available and consequently significantly more expensive to purchase. Currently the cost of D-malic acid is approximately 30 times that of L-malic acid. When cost is a factor in planning an asymmetric synthesis it may be more advantageous for the chemist to prepare D-malic acid instead of buying it. Numerous methods exist for obtaining D-malic acid.

The most obvious approach is the resolution of DL-malic acid. This is readily accomplished by forming salts of the racemic acid with (*R*)-(+)-1-phenylethylamine. After filtration of the (*R*)-(+)-amine salt of L-malic acid, the filtrate is neutralized and the resulting enriched D-malic acid is exposed to (*S*)-(–)-phenylethylamine to precipitate the (*S*)-(–)-amine salt of D-malic acid. Freeing the acid from the amine affords essentially pure D-malic acid (**885**) in 13% yield [195]. Although the yield is rather low, this resolution can be performed on a large scale, and when one considers that the cost of DL-malic acid is about 60 times less than that of D-malic acid the process is acceptable.

An enzymatic resolution of dimethyl (*R,S*)-malate with pig liver esterase (PLE) relies on selective hydrolysis of the (*S*)-diester to monoacid **14**, leaving dimethyl (*R*)-malate (**203**) behind [10,22]. The reaction is performed at 0 °C in 20% aqueous methanol, and the desired (*R*)-**203** is obtained in 42% yield with 93% *ee* (maximum theoretical yield 50%).

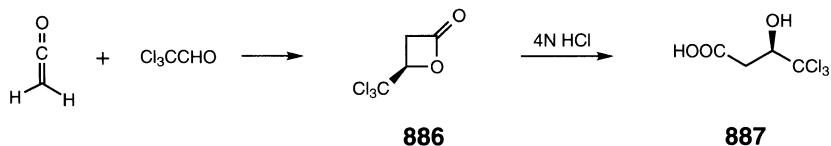


Nitrous acid deamination of D-aspartic acid (**884**) proceeds with retention of configuration to afford D-malic acid (**885**) directly and in high yield with 97% *ee* [2]. The cost of D-aspartic acid is approximately one-fifth that of D-malic acid.



The 2 + 2 cycloaddition of ketene to chloral in toluene at –50 °C in the presence of 4 mol% of cinchonine results in the formation of β -lactone **886** in high yield with 84% *ee*. Recrystallization from methylcyclohexane furnishes optically pure (*R*)-lactone. Mild acid hydrolysis of the lactone to the trichloromethyl hydroxy acid **887** followed by careful basic hydrolysis gives optically pure (*R*)-malic acid (**885**) in 79% overall yield [196].

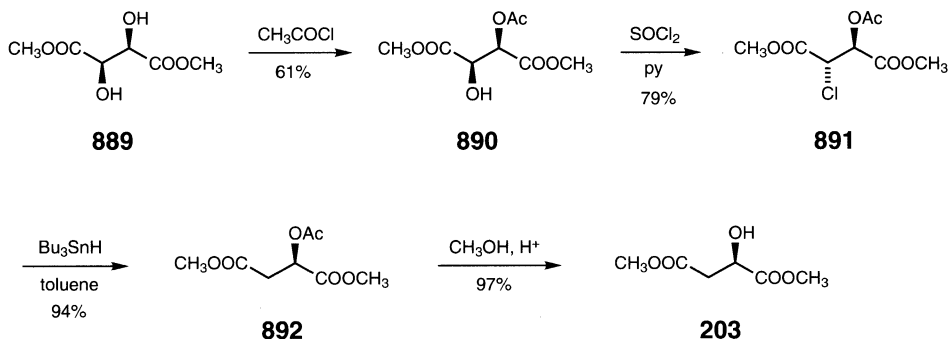
Naturally occurring (*R,R*)-tartaric acid (**888**), currently about 150 times less expensive than (*R*)-malic acid, is an ideal precursor, because the correct absolute configuration at C-2 is



already established. All that remains to be done to complete the synthesis is removal of the offending 3-hydroxyl group.

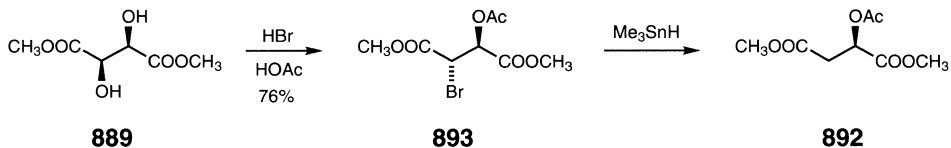


Several syntheses have been reported implementing this strategy for preparing useful quantities of (*R*)-malic acid derivatives. Acylation of dimethyl (*R,R*)-tartrate (**889**) affords **890**. Conversion of the 3-hydroxyl to chloride followed by dehalogenation with tri-*n*-butyltin hydride furnishes the *O*-acetyl (*R*)-malate (**892**). Acidic hydrolysis of the acetyl group gives dimethyl (*R*)-malate itself (**203**) (Scheme 130) [197].



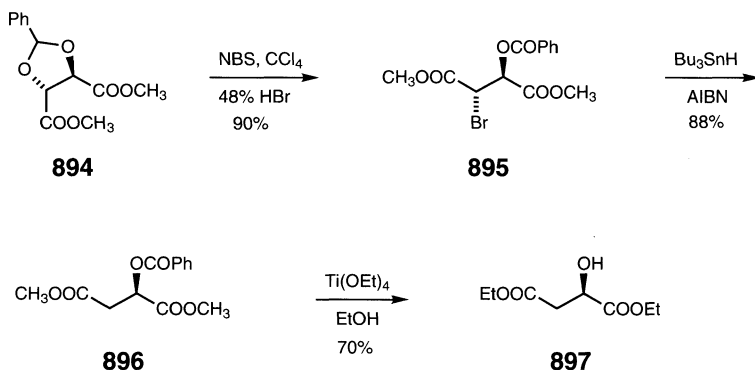
Scheme 130

Similarly, treatment of **889** with 4 equivalents of saturated HBr in acetic acid affords acetoxy bromide **893**. Debromination with a mixture of trimethyltin chloride, AIBN, and sodium borohydride (*in situ* generation of trimethyltin hydride) furnishes **892**, which under acidic hydrolysis gives **203**. The overall yield of **203** from **889** is 56% when the process is carried out on a 0.2-mol scale [198].



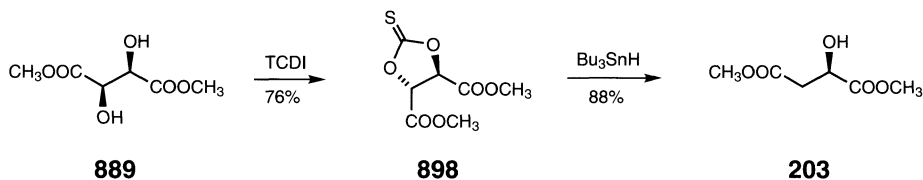
Opening the benzaldehyde acetal of dimethyl (*R,R*)-tartrate (**894**) with *N*-bromosuccinimide furnishes bromide **895**, and dehalogenation with tri-*n*-butyltin hydride gives **896**.

Transesterification of all esters with tetraethyltitanate affords diethyl (*R*)-malate (**897**) (Scheme 131) [199].



Scheme 131

The shortest synthesis of dimethyl (*R*)-malate (**203**) is a two-step process in which **889**, upon treatment with thiocarbonyldiimidazole, is converted to thionocarbonate **898**, which is then reduced with tri-*n*-butyltin hydride to optically pure **203** in 67% overall yield [200].



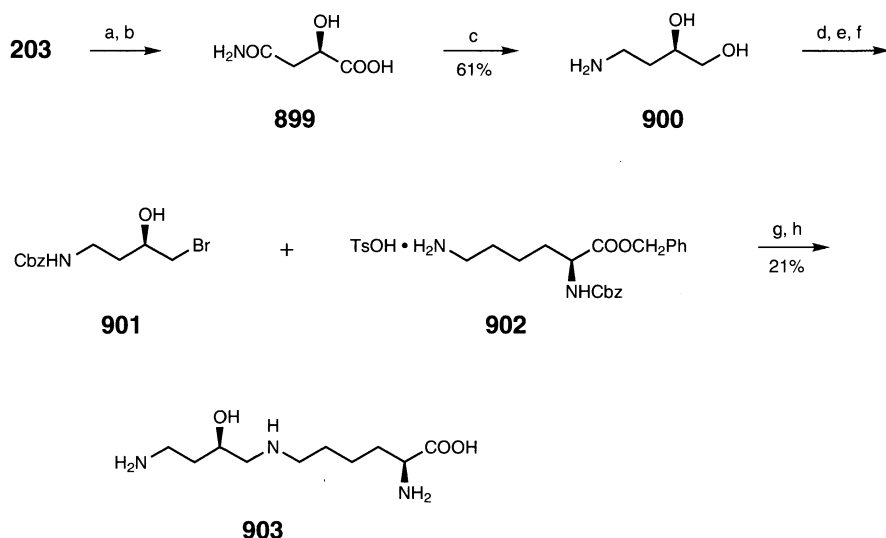
Finally, (*R*)-malates are available from L-malic acid derivatives by inversion reactions of the 2-hydroxyl group with oxygen nucleophiles (see Section 3.2.2.1).

(*R*)-Malic acid supplies one of the integral stereocenters of hypusine (**903**), an unusual amino acid isolated from bovine brain. Its name is derived from the two components hydroxyputrescine and lysine (Scheme 132) [195].

Amidation of **203** followed by partial hydrolysis affords D- β -malamic acid (**899**). Reduction of **899** with diborane furnishes (*R*)-4-amino-1,2-butanediol (**900**). Protection of the amine with a Cbz group and conversion of the primary alcohol to a bromide leads to the critical intermediate **901**. Alkylation of lysine derivative **902** with **901** and removal of the protecting groups under hydrogenolytic conditions gives hypusine (**903**).

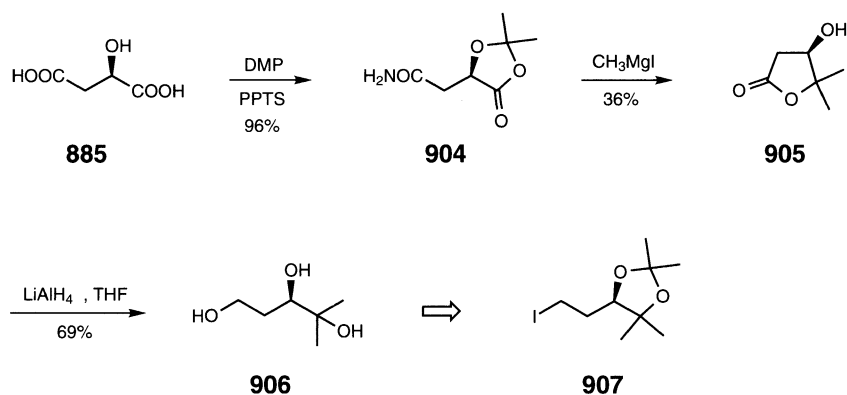
(*R*)-Malic acid can be selectively protected as a dioxolanone (**904**). Treatment of **904** with excess methyl magnesium iodide affords lactone **905** as the result of a completely regioselective reaction of Grignard reagent with the dioxolanone carbonyl followed by lactonization (Scheme 133) [201]. Reduction of the lactone with lithium aluminum hydride gives triol **906**, which is converted to iodoacetone **907** (OH \rightarrow OTs \rightarrow I). This intermediate is used to supply the chiral side chain for the steroid 24,25-dihydroxycholecalciferol.

The presentation of an aspartic acid side chain to an enzyme in a conformationally restricted fashion requires incorporation of the aspartic acid into a fairly rigid framework. The inversion of activated (*R*)-malates with nitrogen nucleophiles produces (*S*)-aspartic acid



Scheme 132

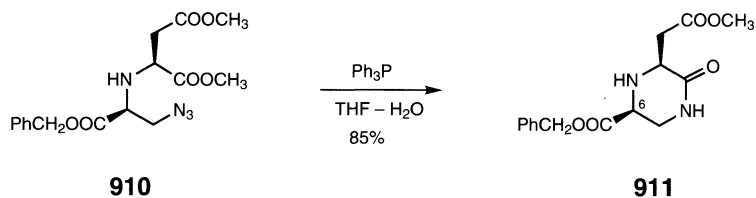
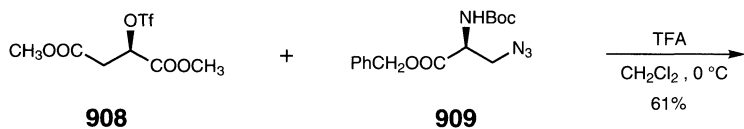
conditions: (a) NH_3 , MeOH; (b) $\text{Ba}(\text{OH})_2$; (c) B_2H_6 , THF, reflux; (d) Cbz-Cl, 4M NaOH, 0 °C (76%); (e) TsCl, pyridine, CH_2Cl_2 (68%); (f) LiBr, acetone (95%); (g) Et_3N , *t*-BuOH, reflux; (h) H_2 , Pd-black



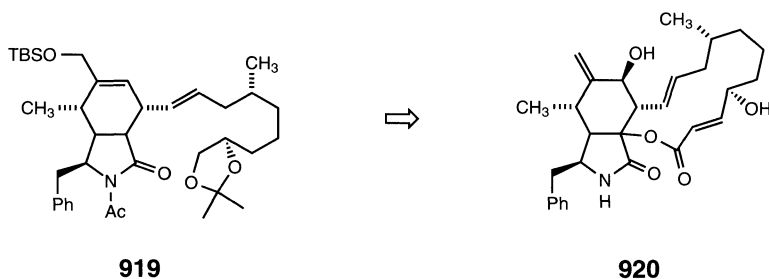
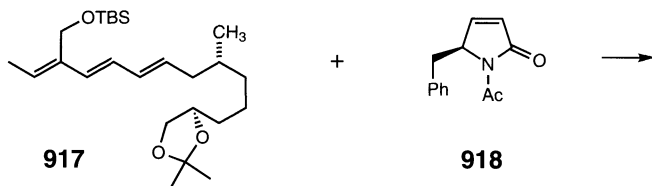
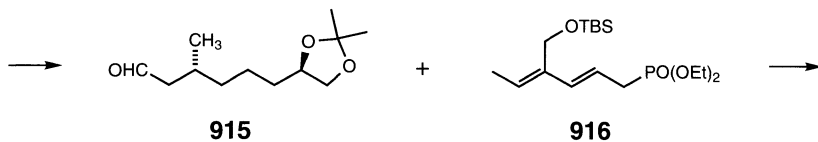
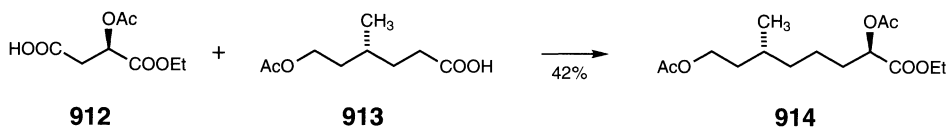
Scheme 133

derivatives directly. The reaction of triflate **908** (generated from **203** with trifluoromethanesulfonic anhydride and 2,6-lutidine) with the (*S*)-serine-derived azide **909** in the presence of trifluoroacetic acid results in both removal of the N-Boc protecting group and $\text{S}_{\text{N}}2$ displacement of triflate by the amine to afford aspartate derivative **910**. Reduction of the azide with triphenylphosphine in moist THF gives the 3-oxopiperazine **911**, which contains the (*S*)-aspartic acid unit in a rigid heterocycle (Scheme 134) [202]. An analogous reaction with an (*R*)-serine-derived azide gives **911** with the opposite configuration at C-6.

In the synthesis of cytochalasin B (**920**), (*R*)-acetoxy malate **912** (available from **885** via anhydride formation followed by reaction with ethanol) is cross-coupled with **913** under



Scheme 134

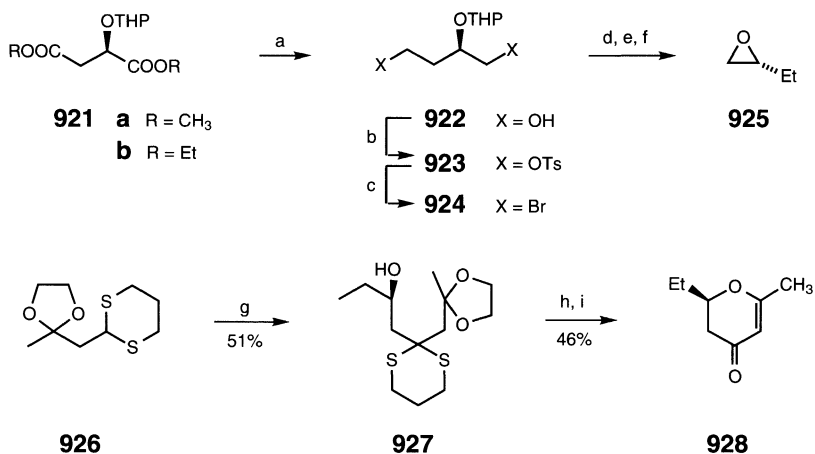


Scheme 135

Kolbe conditions to give **914**. Reduction with lithium aluminum hydride, acetone formation (acetone, PTSA), and Collins oxidation furnishes aldehyde **915**. A Horner–Emmons-type condensation of **915** with diethyl phosphonate **916** affords triene **917** in 50% yield. A Diels–Alder cycloaddition of **917** with L-phenylalanine-derived pyrrolone **918** (xylene, 170 °C, 4 days) produces a separable 4 : 1 mixture of **919** and the undesired regioisomer. Introduction of the methanol functionality and elaboration of the terminal isopropylidene group to a *trans*- α,β -unsaturated system completes the synthesis (Scheme 135) [203].

The synthesis of hepialone (**928**), the principal sex pheromone produced by the male moth *Hepialus californicus*, relies on (*R*)-1,2-epoxybutane (**925**) as the source of chirality (Scheme 136) [204]. Epoxide **925** is in turn synthesized from (*R*)-malic acid by reduction of the THP derivative **921b** with lithium aluminum hydride and conversion of diol **922** to ditosylate **923** and then dibromide **924**. Removal of the protecting group followed by base-catalyzed cyclization results in epoxide formation. Debromination of the primary bromide with tri-*n*-butyltin hydride affords the desired oxirane **925**.

Treatment of **925** with the carbanion derived from **926** yields the dialkylated dithiane **927**. Mercury-mediated hydrolysis of the dithiane ring followed by acid-catalyzed cyclization furnishes the natural product **928**.



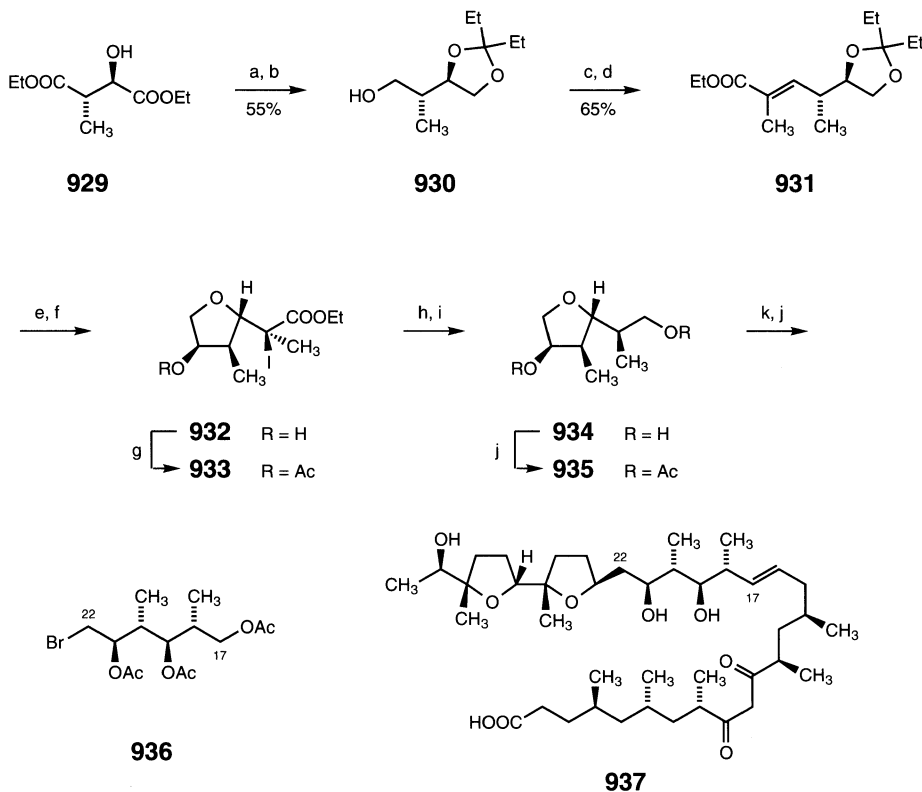
Scheme 136

conditions: (a) LiAlH₄, ether; (b) TsCl, pyridine, CH₂Cl₂; (c) LiBr, NaHCO₃, acetone; (d) HCl, MeOH; (e) KOH; (f) Bu₃SnH; (g) *n*-BuLi, THF, HMPA then **925**, -50° to -30 °C; (h) HgCl₂, CaCO₃, CH₃CN - H₂O; (i) PTSA, benzene

The C-17 to C-22 subunit of ionomycin (**937**) is synthesized by regioselective fragmentation of an appropriately substituted tetrahydrofuran (**935**), which is readily accessible from (*R*)-malic acid (Scheme 137) [205]. Alkylation of the dianion of diethyl (*R*)-malate (**897**) with methyl iodide provides *anti*-**929** in 69% yield with 10 : 1 stereoselectivity. Reduction of the esters, acetal formation, oxidation of the primary alcohol of **930** to an aldehyde, and Wittig olefination furnishes α,β -unsaturated ester **931**.

After hydrolysis of the pentylidene, iodocyclization of the resulting diol under kinetic conditions produces the tetrahydrofuran **932** as a single diastereomer. Removal of iodine with tri-*n*-butyltin hydride in the presence of a catalytic amount of triethylborane followed by reduction of the ester and reacetylation affords the key intermediate **935**. Cleavage of the

tetrahydrofuran ring with Me_2BBr gives exclusively a primary bromo alcohol, which is immediately acetylated to provide the desired C-17 to C-22 fragment **936** in 65% yield.

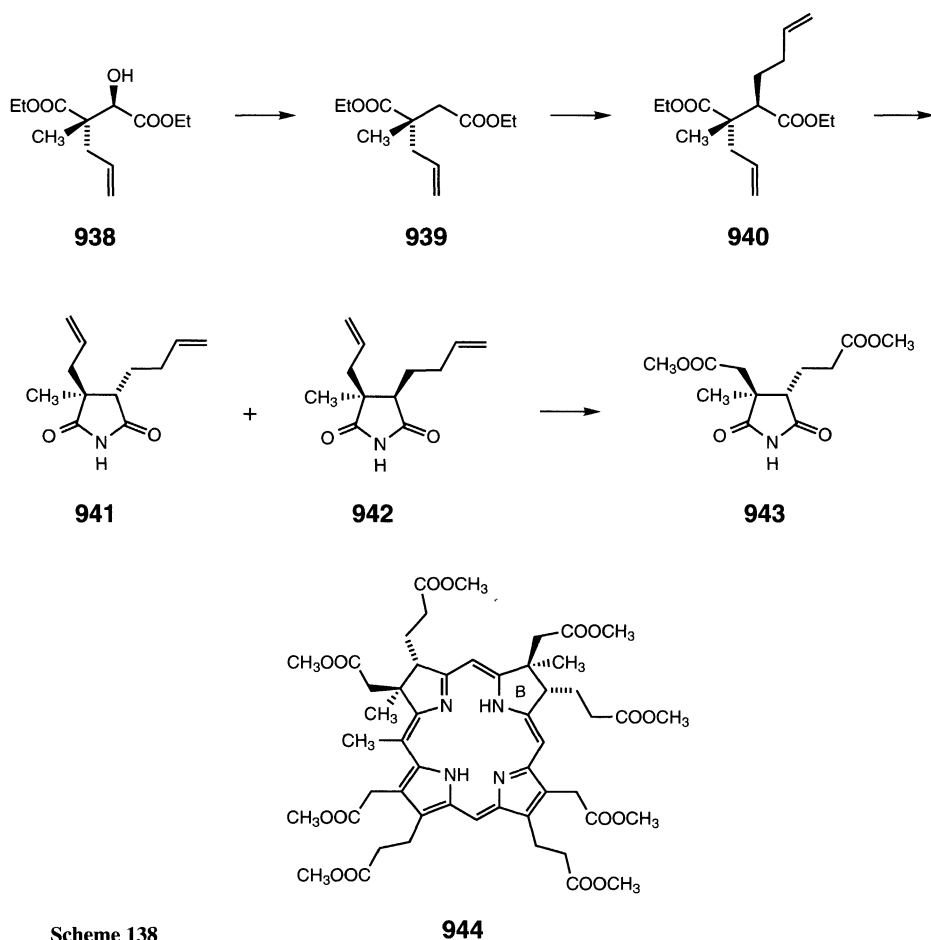


Scheme 137

conditions: (a) BMS, THF, reflux; (b) $\text{Et}_2\text{C}(\text{OMe})_2$, PTSA, DMF; (c) Swern [O]; (d) $\text{Ph}_3\text{P}=\text{C}(\text{CH}_3)\text{COOEt}$; (e) 1N HCl, THF (86%); (f) I_2 , NaHCO_3 , THF; (g) CH_3COCl , pyridine, CH_2Cl_2 ; (h) Bu_3SnH , Et_3B , toluene, -78°C (78%); (i) LiAlH_4 , THF; (j) CH_3COCl , pyridine, THF (87%); (k) Me_2BBr , Et_3N , CH_2Cl_2

The chiral substituents of the (–)-ring-B imide (**943**) of trimethylisobacteriochlorin (**944**), a natural product isolated from the vitamin B_{12} -producing *Propionibacterium shermanii*, are introduced by multiple alkylations of (*R*)-malic acid (Scheme 138) [206].

Sequential alkylation of the lithium enolate of **897** with methyl iodide and then allyl bromide furnishes dialkylated malate **938** with 96 : 4 diastereoselectivity. The hydroxyl group is removed *via* a xanthate ester to give **939**, which is then alkylated with 4-bromo-1-butene to give **940** as the major isomer. The mixture is hydrolyzed with base and heated with urea to yield imides **941** and **942** in a 3 : 1 ratio. After isolation of pure **941** by crystallization, the remaining undesired diastereomer **942** is epimerized to **941** with potassium *tert*-butoxide. Oxidation of **941** with ruthenium tetroxide–sodium periodate and esterification of the resulting acids furnishes imide **943**. This sequence has produced more than 10 g of **943** in a single run.

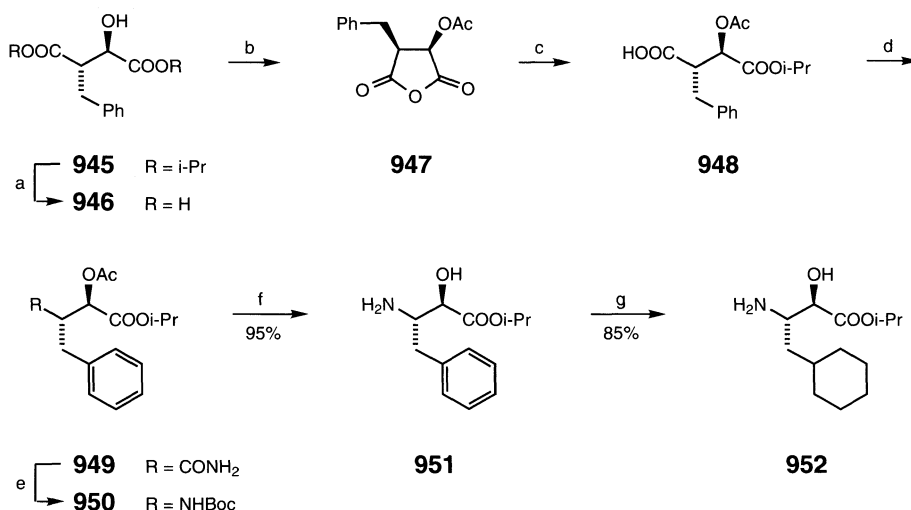


Scheme 138

The structure of the isopropyl ester of nor-C-statine (**952**), a statine mimic used in the synthesis of renin inhibitors, suggests that it should be accessible from (*R*)-malic acid *via* alkylation methodology. Introduction of the cyclohexylmethyl group (as a benzyl) and differentiation of the carboxyl groups allows selective conversion of the C-4 carboxyl to the desired amino group (Scheme 139) [207].

Alkylation of diisopropyl (*R*)-malate with benzyl bromide produces a 10:1 mixture of benzylated product **945** in 80–85% yield. Use of the isopropyl ester results in higher yields than in the case of the corresponding methyl or ethyl esters, presumably due to reduced enolate condensation. Purification of the diastereomeric mixture is accomplished by hydrolysis to diacid **946** and recrystallization from either chloroform or ethyl acetate/hexane [52% overall yield from diisopropyl (*R*)-malate]. Treatment of **946** with acetyl chloride and subsequent reaction with isopropyl alcohol gives monoester **948** in 95% overall yield. Amidation of the free acid followed by Hofmann degradation affords **950** in 90% overall yield. Removal of the Boc group and hydrogenation of the benzene ring provides **952**.

The common feature linking isocitric acid with homoisocitric acid is a malic acid backbone. The only difference between the two compounds is the length of the acid chain attached to the C-3 position.

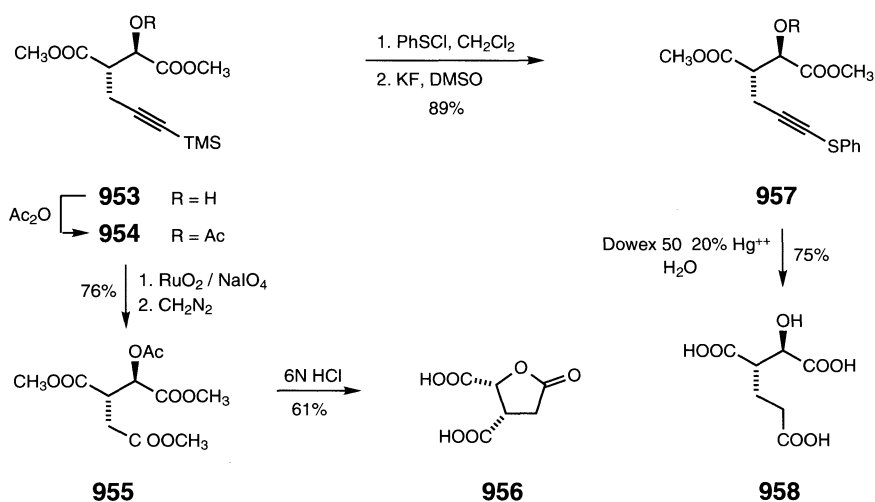


Scheme 139

conditions: (a) KOH; (b) CH₃COCl; (c) *i*-PrOH; (d) EEDQ, CH₃CN, NH₄HCO₃; (e) Pb(OAc)₄, *t*-BuOH; (f) HCl, *i*-PrOH, reflux; (g) HCl, H₂, Rh / C, *i*-PrOH

A short synthesis of (–)-isocitric acid (**956**) relies on alkylation of malic acid to introduce the requisite acetic acid functionality (Scheme 140) [208]. Alkylation of the dianion of dimethyl (*R*)-malate with trimethylsilylpropargyl bromide gives **953** in 51% yield as a 10 : 1 mixture of diastereomers. The mixture is separable by column chromatography after conversion to acetate **954**. Oxidation of the acetylene to an acid followed by esterification furnishes the triester **955**, which upon acid hydrolysis gives the lactone **956**.

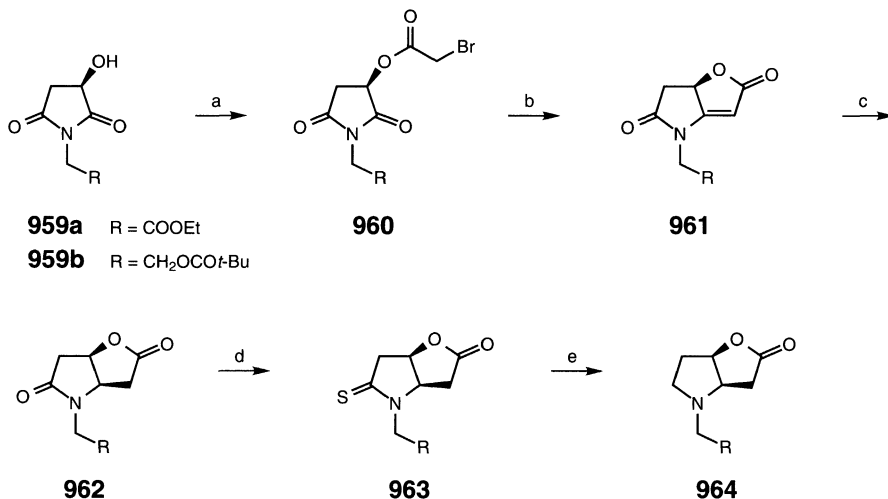
Intermediate **954** can also be used to synthesize (–)-homocitric acid (**958**). Only a modification in oxidation of the acetylene moiety is required. In the synthesis of **955**, oxidation of



Scheme 140

the acetylene results in loss of one carbon atom, thus producing an acetic acid. If the trimethylsilyl group of **954** is replaced by phenylthio (**957**), then hydrolysis using Dowex 50 ion exchange resin impregnated with mercuric sulfate furnishes the desired propionic acid chain of **958**.

Two closely related syntheses of (+)-retronecine (**883**) take advantage of an N-substituted Geissman–Waiss lactone (**964**) as a critical intermediate (Scheme 141). Imide **959a** is prepared by successive treatment of (R)-malic acid with acetyl chloride, glycine ethyl ester, and acetyl chloride again to give a 3-acetoxy imide that is ethanolized to the desired product. Bromoacetylation gives **960a**; phosphonium salt formation followed by intramolecular Wittig reaction in the same pot furnishes the conjugated lactone **961a**. Hydrogenation of the double bond and removal of the lactam carbonyl *via* thiocarbonyl **963a** gives the (–)-N-(ethoxycarbonyl)methyl Geissman–Waiss lactone **964a** with >98% *ee* [209].

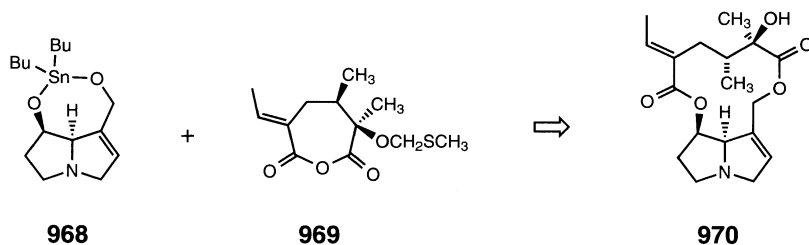


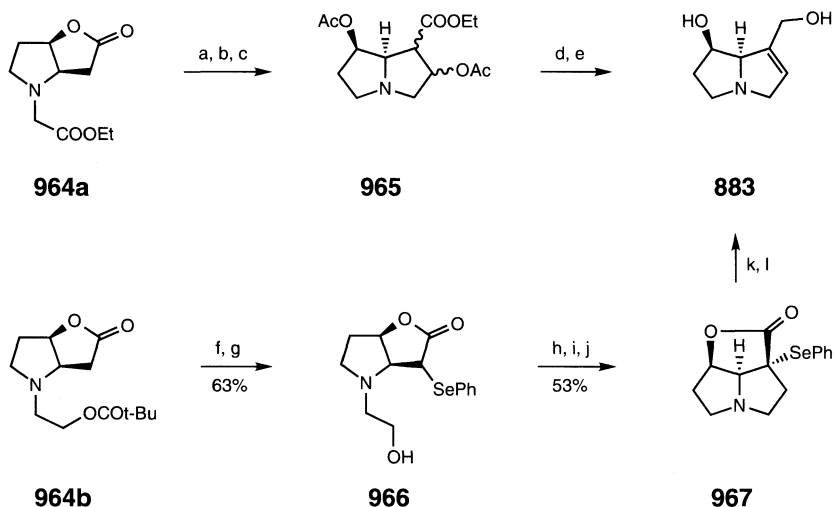
Scheme 141

conditions: (a) BrCH₂COBr, pyridine, ether (**960a**, 97%; **960b**, 94%); (b) Ph₃P, CH₃CN, 50 °C then Et₃N (**961a**, 92%; **961b**, 86%); (c) H₂, 5% Rh / alumina, EtOAc (**962a**, 100%; **962b**, 99%); (d) Lawesson's reagent, toluene; (e) triethyloxonium tetrafluoroborate, NaCNBH₃ (**964a**, 76%; **964b**, 82%)

An identical series of reactions starting with **959b** yields the protected N-(2-hydroxyethyl) Geissman–Waiss lactone **964b** [210]. Either of the lactones **964** is readily converted to (+)-retronecine (**883**), as shown in Scheme 142.

Retronecine, in turn, can be converted to (–)-integerrimine (**970**) by coupling its cyclic stannoxane **968** with anhydride **969** followed by macrolactonization [211].





Scheme 142

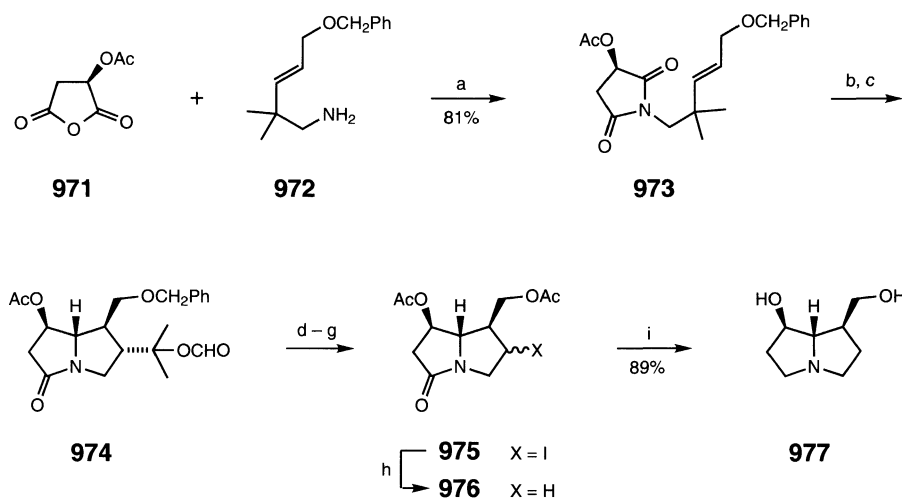
conditions: (a) NaOEt, EtOH; (b) NaBH₄; (c) Ac₂O, pyridine, DMAP; (d) KO^tBu; (e) DIBAL; (f) LDA, THF, -78 °C then PhSeCl; (g) 6N HCl, 50 °C; (h) *n*-BuLi, THF, -78 °C; (i) TsCl, THF, -78 °C; (j) LDA (2 eq), HMPA (2 eq), THF; (k) LiAlH₄, THF, -10 °C; (l) 30% H₂O₂, HOAc

(-)-Hastanecine (**977**) is synthesized by cyclization techniques involving imide **973** as a precursor (Scheme 143) [212]. The imide is prepared by sequential treatment of (*R*)-acetoxysuccinic anhydride (**971**) with amine **972** followed by acetyl chloride. Selective reduction of the 2-carbonyl with sodium borohydride and subsequent rearrangement–cyclization of the resulting hydroxy lactam gives formate **974** (60%) along with a minor amount of deacetylated product. This establishes the basic skeleton of the dihydroxypyrrrolizidine alkaloid. Protective group manipulation, conversion of the alcohol side chain to an iodide (**975**), and dehalogenation with tri-*n*-butyltin hydride furnishes the penultimate intermediate **976**. Reduction of all the carbonyl groups with lithium aluminum hydride leads to (-)-hastanecine (**977**).

Regioselective reduction of the C-1 carboxylate of dimethyl (*R*)-malate (**203**) with BMS–NaBH₄ followed by protection of the diol with either triethylsilyl groups or an acetonide furnishes **978**. Condensation of the ester group with the anion of dimethyl methylphosphonate produces β-ketophosphonate **979** in high yield. Coupling of **979** with (2*S*)-3-hydroxy-2-methylpropionate-derived aldehyde **980** under Horner–Emmons conditions affords **981**, which contains the basic skeletal requirements for the C-16 to C-26 subunit (**982**) of halichondrin B (Scheme 144) [213].

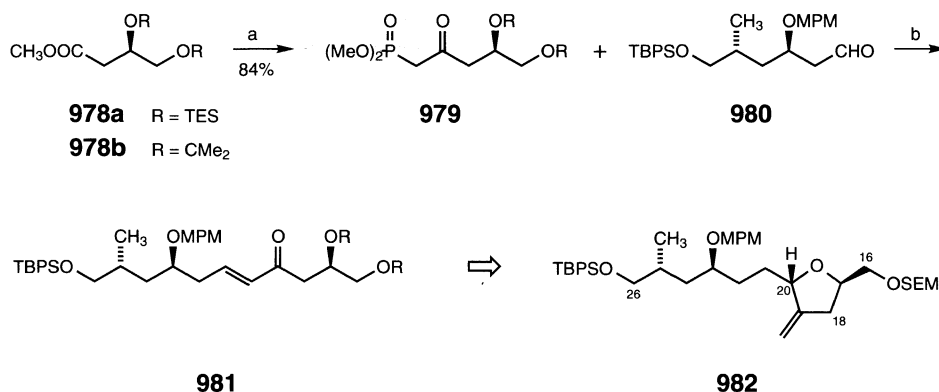
The synthesis of (+)-ipsdienol (**992**), one of the principal components of the pheromone of *Ips* bark beetles, is based on the chirality of (*R*)-(+)-1,2,4-butanetriol (**984**), obtained by the complete reduction of (*R*)-malic acid (Scheme 145) [214].

Triol **984** is converted to acetonide **985** and the free hydroxyl group is sequentially oxidized to an aldehyde (**986**) with pyridinium chlorochromate and then to an acid under Jones conditions. Acidic workup furnishes the hydroxy butyrolactone **987**. Treatment of THP-protected butyrolactone **988** with methyl Grignard reagent affords diol **989**. Removal of the THP group, tosylation of the primary alcohol, and cyclization under basic conditions provides epoxide **990**. Opening the oxirane ring with 2-(1,3-butadienyl)magnesium chloride in the presence of



Scheme 143

conditions: (a) CH_3COCl , CH_2Cl_2 , 40 °C; (b) NaBH_4 , EtOH (83%); (c) HCOOH ; (d) NaOH , $\text{MeOH-H}_2\text{O}$; (e) H_2 , Pd / C, EtOH (96%); (f) Ac_2O , pyridine (94%); (g) HgO , I_2 , CCl_4 (89%); (h) Bu_3SnH (91%); (i) LiAlH_4

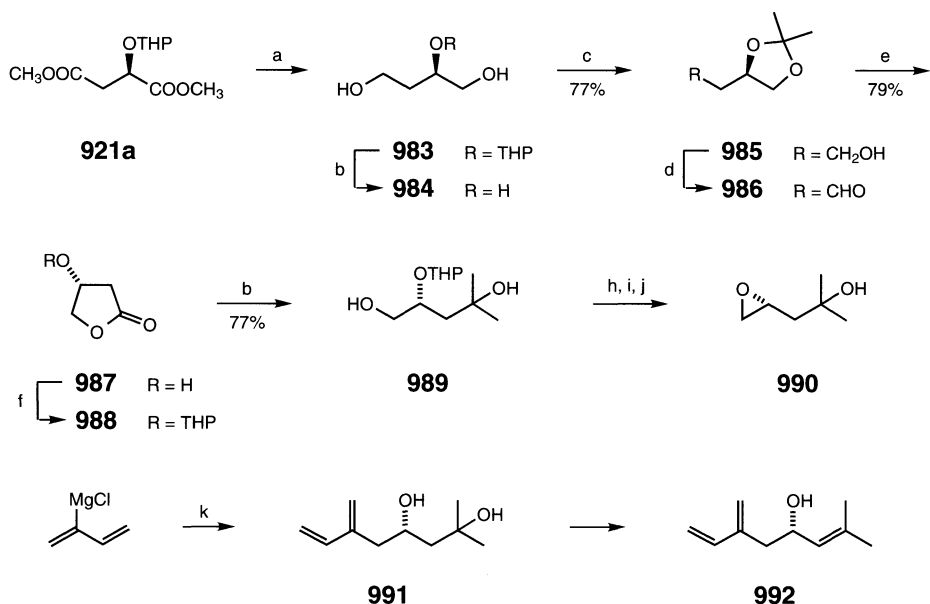


Scheme 144

conditions: (a) $(\text{MeO})_2\text{P}(\text{O})\text{CH}_3$, *n*-BuLi, THF, -78 °C; (b) *n*-BuLi, THF, -78 °C (82%)

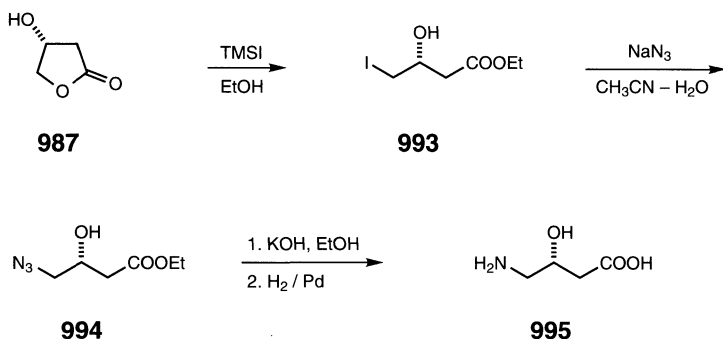
copper iodide affords diol **991**. Acetylation followed by dehydration and removal of the acetyl group with lithium aluminum hydride gives (*S*)-ipsdienol (**992**) with 90% optical purity.

A short and efficient synthesis of (*R*)-GABOB (**995**), a biologically important neuro mediator in the mammalian central nervous system, begins with hydroxybutyrolactone **987** (Scheme 146) [57]. Opening the lactone with trimethylsilyl iodide in ethanol furnishes iodo ester **993**. Displacement of the iodide by azide (**994**) occurs in nearly quantitative yield. Hydrolysis of the ester followed by catalytic reduction of the azido group gives optically pure **995**. If reduction of the ester is attempted prior to hydrolysis of the ester, cyclization of the resulting aminoester occurs to give a lactam.



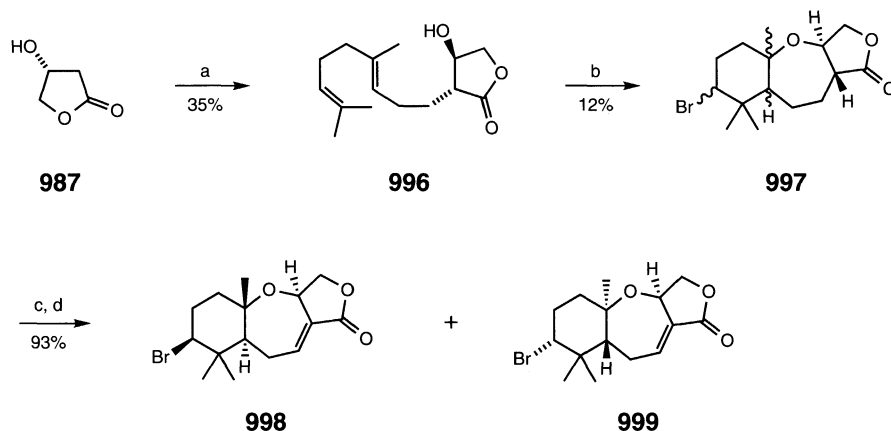
Scheme 145

conditions: (a) LiAlH₄, ether (92%); (b) PTSA, MeOH (91%); (c) acetone, PTSA; (d) PCC, NaOAc, CH₂Cl₂, (46%); (e) Jones CrO₃, acetone; (f) DHP, PTSA, ether (85%); (g) CH₃MgI, ether, -20 °C; (h) 1N HCl, EtOH; (i) TsCl, pyridine (86%); (j) KOH, MeOH, -10 °C (16.5%); (k) **990**, CuI, THF, -50 °C; (l) Ac₂O, pyridine; (m) POCl₃, pyridine (62%); (n) LiAlH₄, ether (97.5%)



Scheme 146

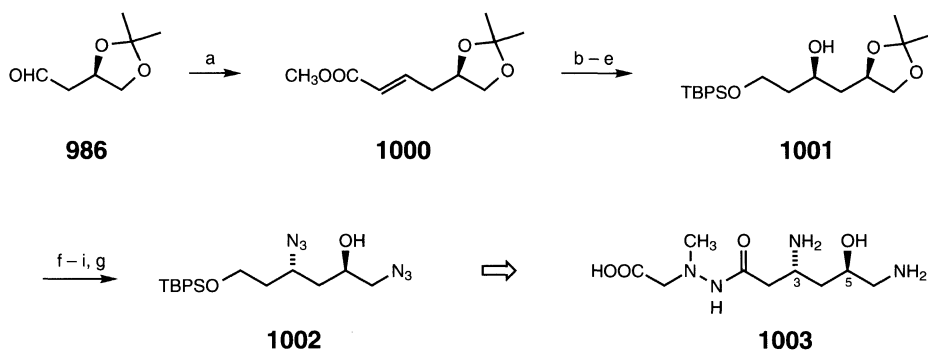
The antineoplastic agent (–)-aplysisstatin (**998**), isolated from the sea hare, is synthesized from (*R*)-malic acid *via* butyrolactone **987** by a biomimetic brominative cyclization of the homoggeranyl-alkylated lactone **996** (Scheme 147) [215]. The cyclization occurs in poor yield, and affords a 19 : 81 mixture of isomeric dihydroaplysisstatins (**997**), the desired isomer being the minor component. The mixture is converted to (–)-aplysisstatin (**998**) and (+)-12-epiaplysisstatin (**999**) by phenylselenation of the lactone enolates followed by oxidative elimination of phenylselenic acid. The mixture (12 : 88) is separated by HPLC to give the pure compounds.



Scheme 147

conditions: (a) 2 LDA, THF, $-78\text{ }^{\circ}\text{C}$ then homogeranyl iodide; (b) 2,4,4,6-tetrabromocyclohexa-2,5-dienone, CH_3NO_2 ; (c) LDA, THF, $-78\text{ }^{\circ}\text{C}$ then PhSeBr; (d) H_2O_2 , THF

The synthesis of (+)-negamycin (**1003**), a naturally occurring inhibitor of Gram-negative bacteria, relies on a Sharpless epoxidation of reduced **1000** followed by a regioselective oxirane ring opening with hydride to introduce the new chiral hydroxyl. This alcohol is ultimately transformed into the 3-amino group of the final product (Scheme 148) [216]. Conversion of the hydroxyl to a mesylate followed by an $\text{S}_{\text{N}}2$ displacement with sodium azide furnishes the azido alcohol **1002** in which the center at C-3 now possesses the correct absolute configuration. The remainder of the synthesis is accomplished by desilylation, oxidation of the primary alcohol to an acid, coupling with benzyl (1-methylhydrazinoacetate), and reduction of the azides to amines. The synthesis of **1003** requires 14 steps with an overall yield of 18% from **1000**.

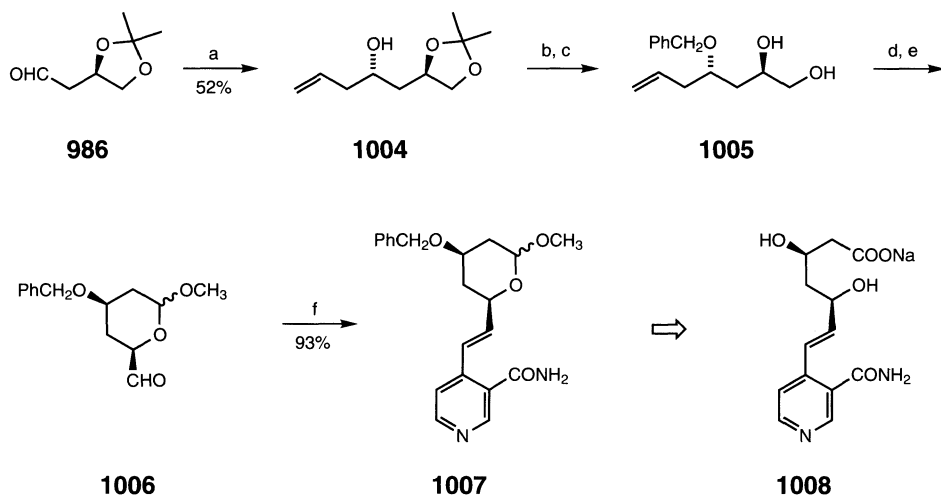


Scheme 148

conditions: (a) $\text{Ph}_3\text{P}=\text{CHCOOCH}_3$; (b) DIBAL, CH_2Cl_2 (96%); (c) Sharpless epoxidation (92%); (d) Red-Al, THF (98%); (e) TBPS-Cl, Et_3N , DMAP, CH_2Cl_2 (89%); (f) MsCl, THF, $0\text{ }^{\circ}\text{C}$ (100%); (g) NaN_3 , 15-crown-5, DMF, $50\text{ }^{\circ}\text{C}$ (99%); (h) $\text{CuCl}_2\cdot 2\text{H}_2\text{O}$, EtOH (87%); (i) TscI, pyridine, $-20\text{ }^{\circ}\text{C}$ (92%)

In an effort to mimic the transition state of the enzymatic reduction of mevaldic acid by NADPH, nicotinamide derivative **1008** was considered a likely candidate as an HMG-CoA reductase inhibitor.

Addition of β -allyldiisocaranylborane to **986** provides allylic alcohol **1004** as a 93:7 mixture of diastereomers. After purification by column chromatography, the alcohol is *O*-benzylated and the acetonide hydrolyzed to furnish diol **1005** in 76.5% overall yield. Ozonolysis of the olefin, etherification of the resulting hemiacetal, and Swern oxidation of the primary alcohol gives the optically pure (5*S*)-epi-“compactin lactone” synthon **1006**. Coupling of aldehyde **1006** with 3-cyano-4-methylpyridine using sodium hydride in DMSO gives **1007** in high yield. Catalytic hydrogenation of the double bond and subsequent functional group manipulation affords the target molecule **1008** (Scheme 149) [217]. Unfortunately, this compound is not active as an HMG-CoA reductase inhibitor.



Scheme 149

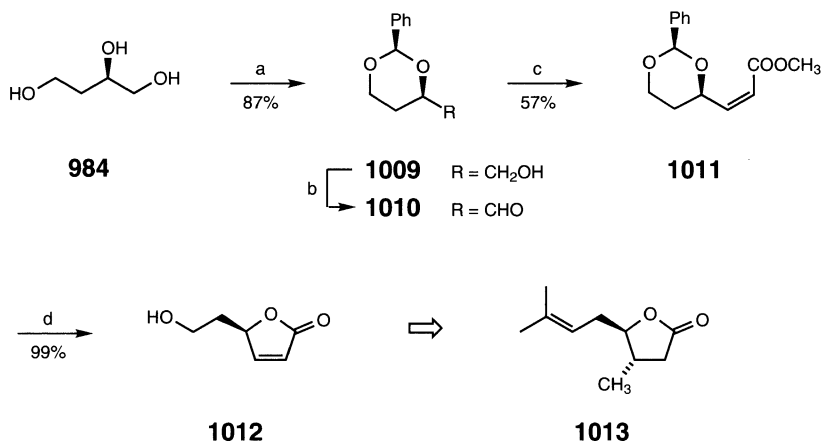
conditions: (a) β -allyldiisocaranylborane, THF; (b) KH, PhCH₂Br, THF (85%); (c) CF₃COOH, THF – H₂O (90%); (d) O₃, CH₂Cl₂ / MeOH (1:1) (75%); (e) Swern [O]; (f) 3-cyano-4-methylpyridine, NaH, DMSO

Butenolide **1012** is a key intermediate in the synthesis of (+)-eldanolide (**1013**), a pheromone of the African sugar-cane borer *Eldana saccharina*. It is synthesized in 5 steps and 48% overall yield from (*R*)-malic acid via (*R*)-1,2,4-butanetriol (**984**) (Scheme 150) [218].

Triol **984** is converted to the 6-membered benzylidene acetal **1009** with benzaldehyde and PTSA, and the remaining hydroxyl group is then oxidized to an aldehyde (**1010**) under Swern conditions. A *Z*-selective Wittig reaction provides a separable mixture of **1011** and its *E*-isomer (92:8). The stereochemical outcome of the Wittig reaction is strongly dependent on the nature of the alkoxyaldehyde and the polarity of the solvent. In this case polar solvents favor the formation of the *Z*-olefin, methanol being optimum. Treatment of **1011** with acetic acid gives the desired butenolide **1012** in nearly quantitative yield.

Acetal **1010** has also been used in the synthesis of (–)-swainsonine (**1024**), a naturally occurring trihydroxyindolizidine alkaloid isolated from fungi and plants (Scheme 151) [219].

A Wittig reaction of **1010** with allyltriphenylphosphonium bromide and potassium *tert*-butoxide produces a 4.3:1 mixture of *Z/E* dienes, the *E*-diene being the desired isomer. Ring opening of the acetal with diisobutylaluminum hydride and subsequent photoisomerization of

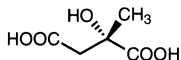


Scheme 150

conditions: (a) PhCHO, PTSA, 4Å molecular sieves, toluene; (b) Swern [O]; (c) Ph₃P=CHCOOCH₃, CH₃OH (1.5 eq), -70 °C → rt; (d) HOAc - H₂O (4:1)

the *Z/E* mixture gives isomerically pure **1015** in 69% overall yield. After conversion of the primary hydroxyl to a hydroxamic acid (**1020**), an intramolecular hetero Diels–Alder reaction of acylnitroso diene **1021** furnishes *trans*-1,2-oxazinolactam **1022**. Performing the cycloaddition in water results in a 4.1 : 1 mixture of *trans* and *cis*-1,2-oxazinolactams, whereas the same reaction in chloroform reduces the extent of diastereoselection to 1.3 : 1. Reductive N–O bond cleavage, silylation of the resulting alcohol, and catalytic osmylation gives diol **1023** with 4 : 1 diastereoselectivity. Intramolecular cyclodehydration and protective group removal furnishes the natural product **1024**.

3.5 Citramalic Acid

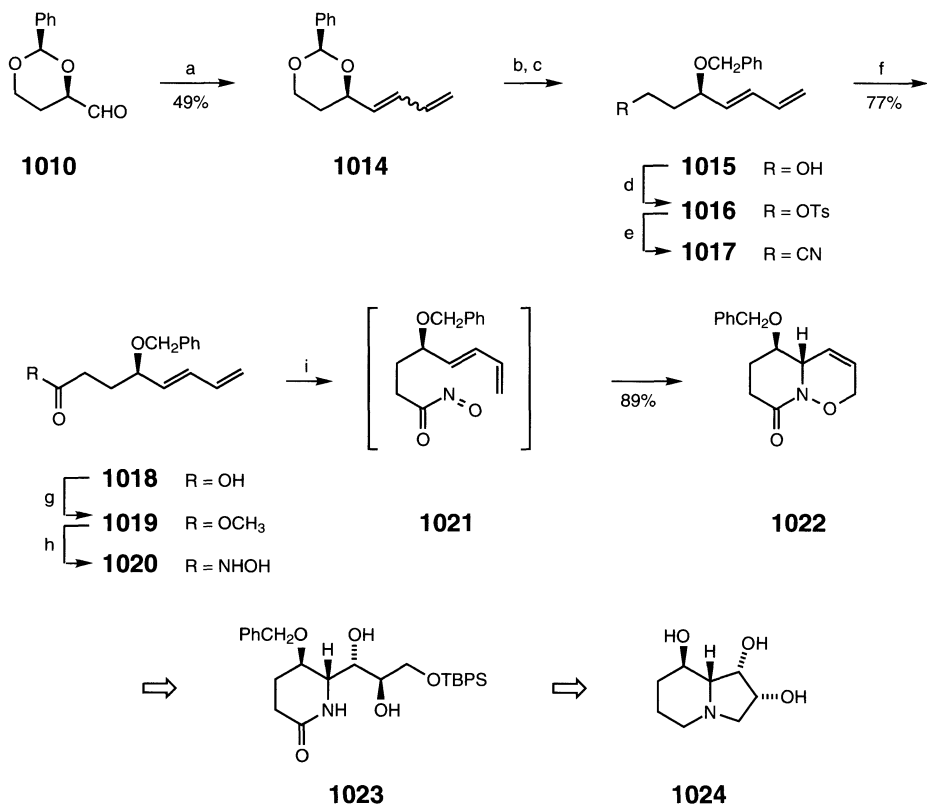


(S)-2-Hydroxy-2-methylbutanedioic Acid

(*S*)-Citramalic acid (also shown below as **1029**), the α -methyl analog of (*S*)-malic acid, has been isolated from a variety of natural sources. It can be produced microbially by incubation of mesaconic acid with an extract from *Clostridium tetanomorphum* cells [220].

Both enantiomers of citramalic acid are commercially available, each selling for approximately \$10.00 per gram. Many synthetic methods exist for the preparation of chiral citramalates, but few produce products of acceptable enantiomeric purity.

Dimethyl (*S*)-2-acetoxycitramalate (**1028**) can be synthesized with high optical purity using the (+)-pulegone-derived oxthianyl ketone **1025** as a conformationally locked chiral electrophile (Scheme 152) [221]. Addition of methyl Grignard reagent to **1025** gives carbinol **1026** as a single diastereomer. Sequential hydrolysis of the auxiliary, oxidation of the resulting aldehyde to an acid, esterification, and acetylation affords **1027** in 65% overall yield.



Scheme 151

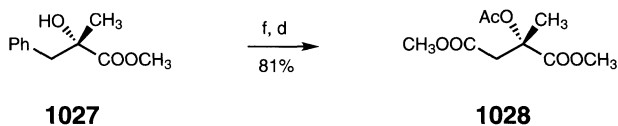
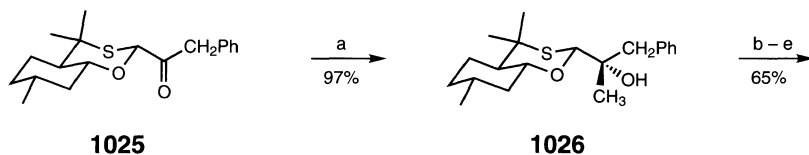
conditions: (a) $\text{Ph}_3\text{P}=\text{CHCH}=\text{CH}_2$; (b) DIBAL, CH_2Cl_2 , 0°C (96%); (c) I_2 , benzene, hv; (d) TsCl, pyridine (95%); (e) NaCN, DMSO (99%); (f) NaOH, MeOH; (g) CH_2N_2 , ether (99%); (h) $\text{NH}_2\text{OH}\cdot\text{HCl}$, KOH, MeOH (96%); (i) NaIO_4 , $\text{Na}_2\text{S}_2\text{O}_3$, H_2O

Oxidation of the phenyl group to an acid with ruthenium tetroxide followed by esterification with diazomethane furnishes the (*S*)-citramalate **1028** with 97.2% *ee*.

(*S*)-Citramalic acid (**1029**) is readily reduced to triol **1030** with either diborane [222] or borane methylsulfide–trimethylborate [223]. Conversion of **1030** to acetone **1031** can be accomplished either with acetone in the presence of a catalytic quantity of perchloric acid (73% yield from **1029**) [222] or with acetone [224] or 2,2-dimethoxypropane [223] in the presence of copper sulfate (48% yield from **1029**). Oxidation of the alcohol with pyridinium chlorochromate furnishes aldehyde **1032** in 72% yield [223].

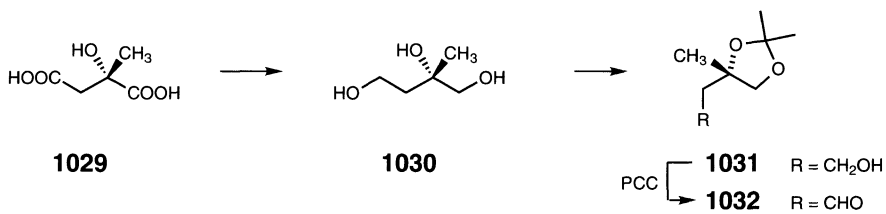
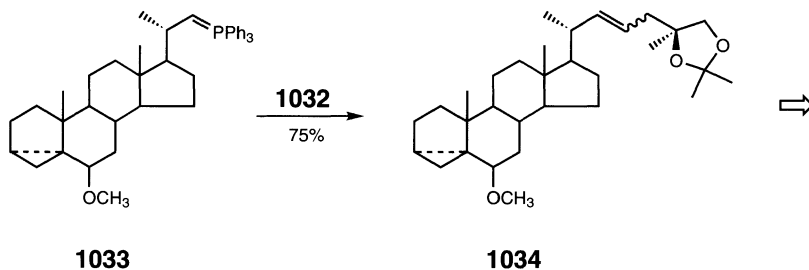
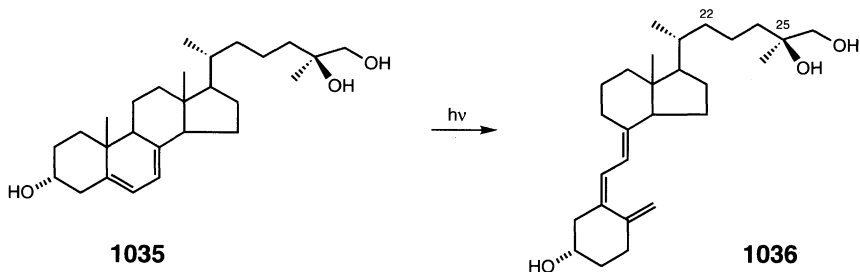
Aldehyde **1032** has been used as a chiral template for the side chain of (25*S*,26)-dihydroxycholecalciferol (**1036**), a metabolite of natural vitamin D_3 (Scheme 153) [225]. The chain is introduced by a Wittig coupling of the stigmaterol-derived phosphorane **1033** with aldehyde **1032** to give olefin **1034** as an *E/Z* isomeric mixture. This is of no consequence, since the double bond is eventually reduced. Transformation of the stigmaterol steroid unit to the 7,8-didehydrocholesterol derivative **1035** followed by photochemical–thermal isomerization furnishes the vitamin D_3 framework.

25-Hydroxyvitamin D_3 26,23-lactone (calciol lactone, **1045**), another metabolite of vitamin D_3 , has also been synthesized by a coupling methodology applied to steroidal ade-



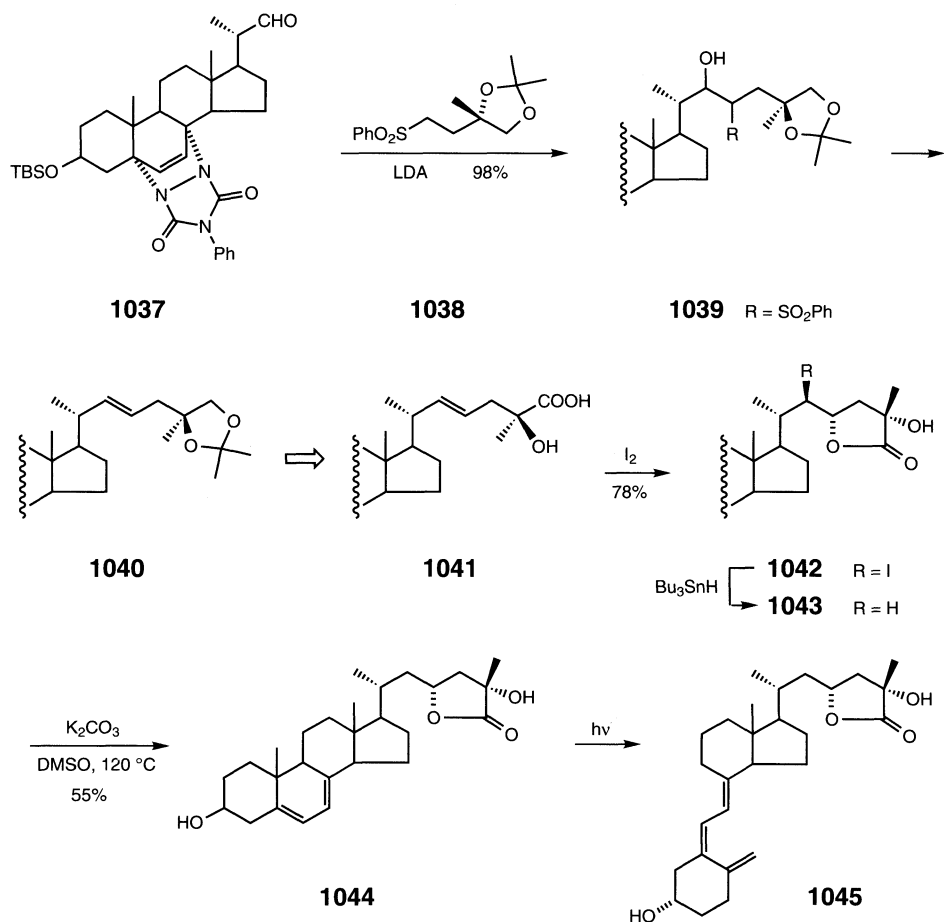
Scheme 152

conditions: (a) CH_3MgBr ; (b) NCS , AgNO_3 , $\text{CH}_3\text{CN-H}_2\text{O}$ (8:2); (c) NaClO_2 , $t\text{-BuOH}$, 2-methyl-2-butene; (d) CH_2N_2 , ether; (e) Ac_2O , DMAP ; (f) RuCl_3 , NaIO_4 , $\text{CH}_3\text{CN-CCl}_4\text{-H}_2\text{O}$

**1029****1030****1031****1032**R = CH_2OH R = CHO **1033****1034****1035****1036**

Scheme 153

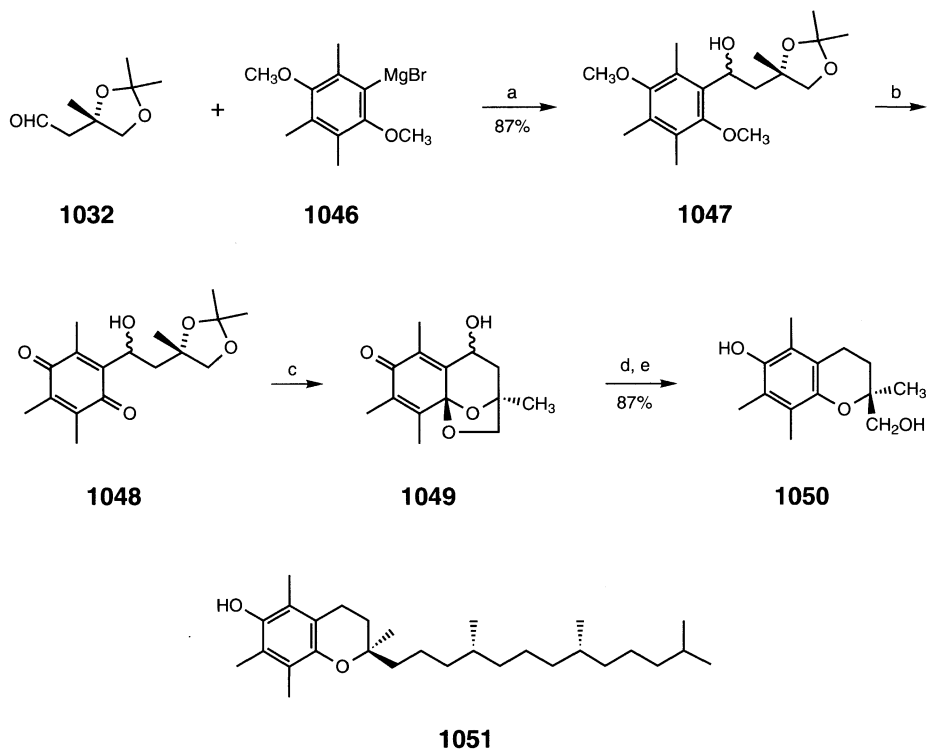
hyde **1037** and citramalate-derived sulfone **1038** (Scheme 154) [226]. The 4-phenylurazole adduct present in **1037** is used as a protecting group for the dienyl system (**1044**) required as a precursor for the vitamin D₃ skeleton. The diene is generated by a retro Diels–Alder reaction. Sulfone **1038** is prepared from the alcohol **1031** by the sequence of transformations: OH → OTs → SPh → SO₂Ph. Coupling the anion of **1038** with **1037** affords **1039** as a mixture of diastereomers. Mesylation of the 22-hydroxy group followed by reductive elimination with sodium amalgam gives the *trans*-olefin **1040** in 77% yield. Hydrolysis of the acetonide and stepwise oxidation of the primary alcohol to an aldehyde then acid furnishes **1041** in 87% yield. Iodolactonization and dehalogenation affords lactone **1043** as an 8.5 : 1 diastereomeric mixture. Removal of the protecting triazolinedione group generates the diene **1044**, which is then photochemically and thermally isomerized to (25*S*)-25-hydroxyvitamin D₃ 26,23-lactone (**1045**).



Scheme 154

The optically active chroman unit (**1050**) of α -tocopherol (vitamin E) (**1051**) is constructed by an initial coupling reaction between aldehyde **1032** and the hydroquinone Grignard reagent

1046 (Scheme 155) [223]. After oxidation of the adduct **1047** to quinone **1048**, treatment with acid removes the acetonide protecting group and subsequently forms a new acetal **1049** in 85% overall yield from **1047**. Catalytic hydrogenolysis serves as a way of both removing the benzylic OH and aromatizing the 6-membered ring to give the chroman **1050**.



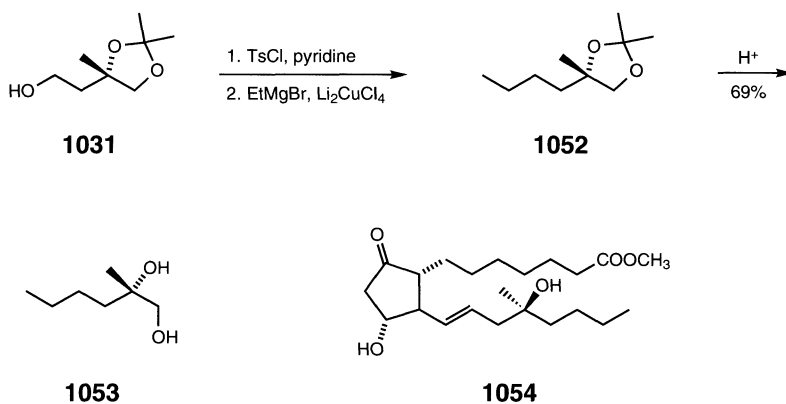
Scheme 155

conditions: (a) THF, 0 °C → rt; (b) CAN, H₂O–CH₃CN; (c) 2N H₂SO₄, dioxane, 70 °C; (d) HClO₄, MeOH, H₂, Pd / BaSO₄; (e) 2N H₂SO₄

The gastric antisecretory properties of 15-deoxy-16-methyl-16- α,β -hydroxyprostaglandin E₁ methyl ester are associated exclusively with the 16(*S*) diastereomer **1054**. Diol **1053**, a key chiral synthon for the synthesis of **1054**, is readily prepared from **1031** by conversion of the primary alcohol to a tosylate, displacement of the tosylate by mixed cuprate to give **1052**, and then hydrolysis of the acetonide (Scheme 156) [222]. The overall yield of the sequence starting from (*S*)-citramalic acid is 50.4%.

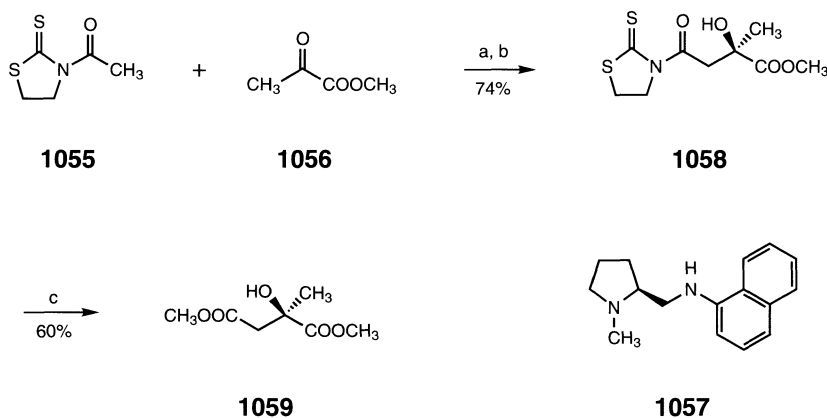
Within the last 10 years, various methods have been employed to synthesize (*R*)-citramalate derivatives with acceptable enantiomeric purity. One of the first methods that produced reasonably enriched product was based on a tin(II) enolate chiral auxiliary-induced asymmetric aldol-type reaction.

Sequential treatment of 3-acetylthiazolidine-2-thione (**1055**) with stannous trifluoromethanesulfonate, diamine **1057**, and methyl pyruvate results in the formation of adduct **1058** with 85% *ee*. The 1-naphthyl group on the pyrrolidine system is essential to ensure high asymmetric induction. Other groups such as cyclohexyl, phenyl, 2,6-xylyl, or 2-naphthyl



Scheme 156

result in diminished optical purity. Methanolysis of **1058** gives dimethyl (*R*)-citramalate (**1059**) (Scheme 157) [227].



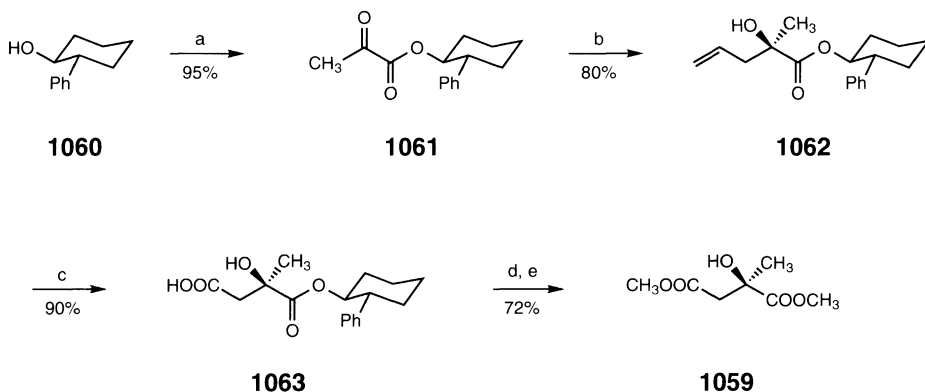
Scheme 157

conditions: (a) $\text{Sn}(\text{OTf})_2$, *N*-ethylpiperidine, CH_2Cl_2 , -78°C ; (b) **1057**; (c) K_2CO_3 , MeOH, 0°C

A second strategy using pyruvate as a source for the C-1 and C-2 carbons of the nascent citramalate is based on an ene reaction with α -ketoesters. Reaction between the pyruvate ester of (–)-*trans*-2-phenylcyclohexanol (**1061**) and allyltrimethylsilane in the presence of tin tetrachloride produces adduct **1062** as a single diastereomer. Oxidation of the alkene to acid **1063** followed by base hydrolysis and esterification gives dimethyl (*R*)-citramalate (**1059**) with 96% optical purity (Scheme 158) [228].

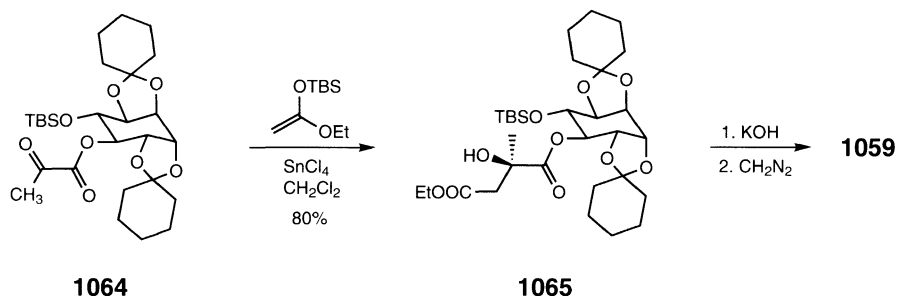
Tin(IV) chloride-mediated aldol reaction of *L*-quebrachitol-derived pyruvate ester **1064** with the ketene silyl acetal of ethyl acetate provides adduct **1065** with 98% *de*. Hydrolysis and esterification affords **1059** [229].

An alternative synthesis of dimethyl (*R*)-citramalate (**1059**) incorporates an enzymatic resolution of racemic dihydroisoxazole **1066** as the key operation (Scheme 159) [230].



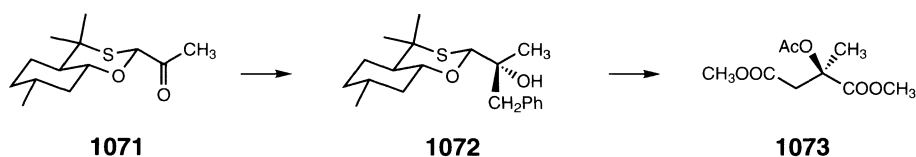
Scheme 158

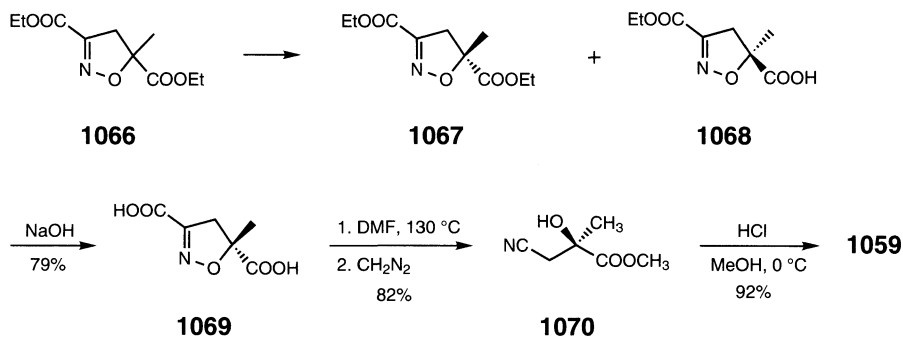
conditions: (a) pyruvic acid, PTSA, benzene; (b) trimethylallylsilane, SnCl_4 , CH_2Cl_2 , -78°C ;
 (c) KMnO_4 , NaIO_4 , H_2O ; (d) KOH , THF, H_2O ; (e) MeOH , HCl



Dihydroisoxazole **1066** is obtained in nearly quantitative yield from the cycloaddition of ethyl methacrylate with ethoxycarbonylformonitrile oxide. Treatment of **1066** with protease from *Aspergillus oryzae* in a two-phase system (toluene and pH 7.0 buffer) results in an enantioselective hydrolysis of the 5-carboxylate group, producing a mixture of (*R*)-**1067** (44.5% yield, 97% *ee*) and (*S*)-**1068** (55% yield, 77% *ee*) when the reaction is terminated at 55% conversion. Hydrolysis of the diester **1067** and thermal decarboxylation of the resulting diacid (**1069**) affords (*R*)-3-cyano-2-hydroxy-2-methylpropanoic acid (**1070**). Acid catalyzed methanolysis of the nitrile group gives **1059** with >97% *ee*.

Dimethyl (*R*)-2-acetoxycitramalate (**1073**) is available using the methodology described previously for the (*S*)-enantiomer (see Scheme 152). All that is required is to reverse the nature of the R-groups on the oxathianyl ketone and Grignard reagent. Addition of benzylmagnesium bromide to methyl ketone **1071** affords adduct **1072** as a single isomer in 97% yield. Using the series of reactions shown in Scheme 152, **1073** is obtained with 96.6% *ee* [221].





Scheme 159

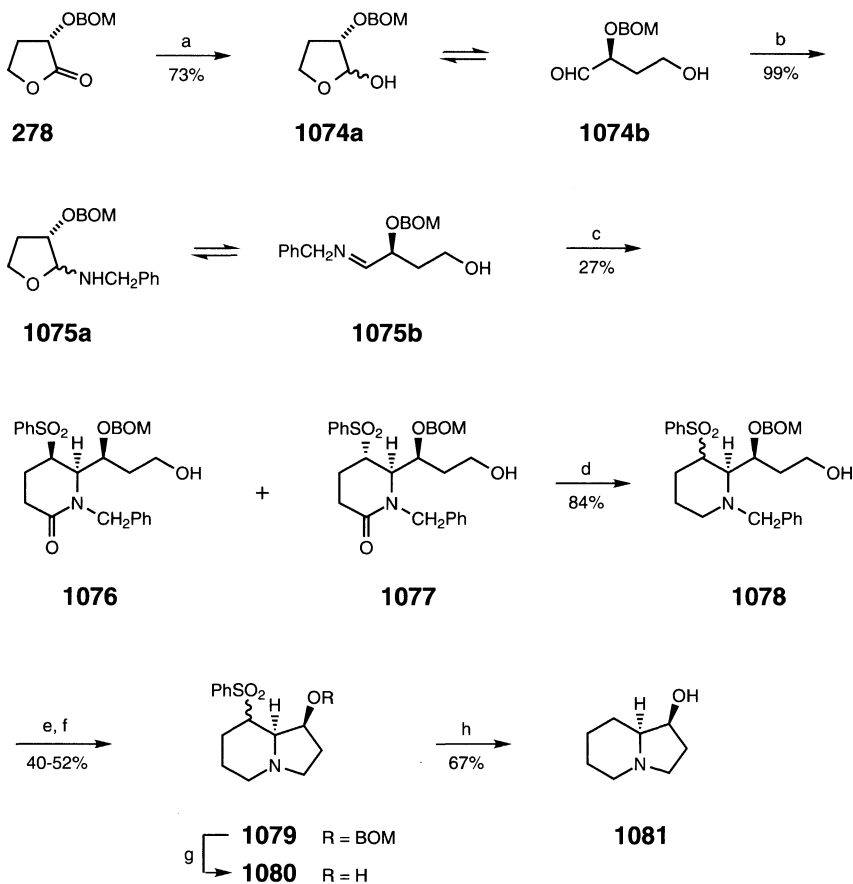
3.6 Addenda

Since the original preparation of the manuscript for this book several interesting articles employing malic acid have appeared in the literature.

The 1-hydroxyindolizidine structure is common to a variety of indolizidine alkaloids, including swainsonine, slaframine, and castanospermine. The asymmetric synthesis of (1*S*,8*aS*)-1-hydroxyindolizidine (**1081**) starting from (*S*)-malic acid-derived butyrolactone **278** is outlined in Scheme 160 [232]. Reduction of the lactone with diisobutylaluminum hydride gives an equilibrium mixture of lactol **1074a** and hydroxy aldehyde **1074b**. The lactol form predominates in solvents such as acetonitrile, ether, acetone, methanol, and chloroform, whereas the aldehyde form is favored in tetrahydrofuran. Condensation of **1074** with benzylamine furnishes an equilibrium mixture of hemiaminal **1075a** and imine **1075b**.

The mixture **1075** is pretreated with boron trifluoride etherate and then reacted with the dianion of 4-(phenylsulfonyl)butanoic acid to give diastereomeric lactams **1076** and **1077** in 29% yield (ratio = 2 : 1). The diastereomers can either be separated at this stage by column chromatography, or the mixture can be carried through the remainder of the sequence. Lactam **1076** or **1077** is reduced to the corresponding piperidine derivative **1078** with diborane. Mesylation of the hydroxyl group results in spontaneous quaternization, leading to the indolizidine skeleton. Hydrogenolysis over Pearlman's catalyst gives the BOM-protected indolizidine **1079**. Sequential removal of the BOM protecting group and the phenylsulfonyl group provides the desired 1-hydroxyindolizidine **1081** with >95% optical purity.

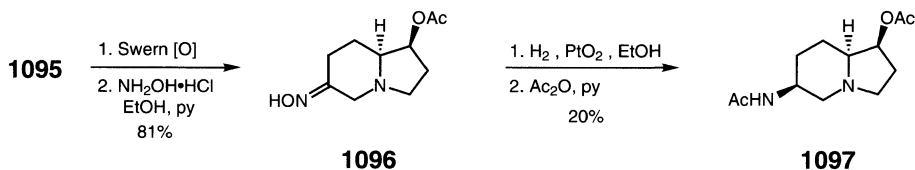
A second approach to indolizidines utilizes (*R*)-malic acid to introduce the chiral hydroxy substituent at position 6 and also to set the stereochemistry of the 8*a* carbon (Scheme 161) [233]. Regioselective silylation of diol **1083** with the bulky TIPS group provides the 4-silyloxy derivative **1084** in 48% yield along with 7% of the 2-silyloxy and 22% of the 2,4-bis silyloxy derivatives. The use of TBS or TBPS groups gives less satisfactory yields of the desired 4-silyloxy derivative. After functional group manipulation, amino alcohol **1087** is reacted with the vinyl tricarbonyl reagent **1088** to give the 3-hydroxypyrrole-2-carboxylate **1089**. Conversion of the terminal OH to Br followed by intramolecular cyclization furnishes bicyclic β -ketoester **1091** and its 8*a* epimer as a 1 : 2 mixture. Lewis acid-assisted reduction of the mixture provides **1092** (and its epimer). Hydrolysis of the ester and subsequent decarboxylation gives a 10 : 1 mixture of **1093** and its 8*a* epimer regardless of whether pure **1092** or its epimer is used. Stereoselective reduction of the carbonyl group with L-Selectride affords

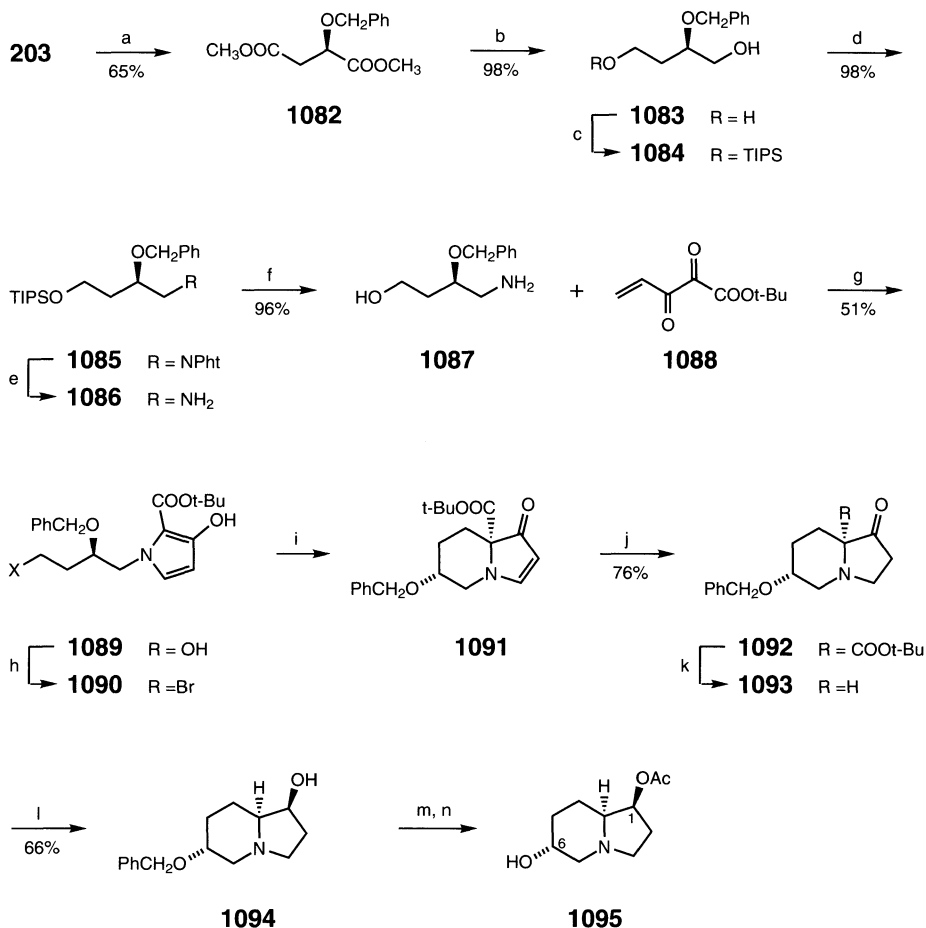
**Scheme 160**

conditions: (a) DIBAL, ether, $-78\text{ }^{\circ}\text{C}$; (b) PhCH_2NH_2 , toluene, rt, 10 h; (c) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (3 eq), THF, $-78\text{ }^{\circ}\text{C}$ then the lithium dianion of 4-(phenylsulfonyl)butanoic acid; (d) $\text{BH}_3 \cdot \text{THF}$, $0\text{ }^{\circ}\text{C} \rightarrow \text{rt}$, 18 h; (e) MsCl , K_2CO_3 , Et_3N , CH_2Cl_2 ; (f) H_2 (39 psi), $\text{Pd}(\text{OH})_2$, MeOH; (g) H_2 , 10% Pd/C, MeOH (54%); (h) Na/Hg, MeOH

1094 with approximately 8 : 1 selectivity. Use of sodium borohydride leads to a statistical 1 : 1 mixture. Acetylation and hydrogenolysis of the benzyl protecting group furnishes the 1-acetoxyindolizidine **1095**.

Oxidation of the hydroxyl group of **1095** followed by treatment with hydroxylamine gives oxime **1096** as a 3 : 1 mixture of *syn* and *anti* isomers. Reduction of the oxime and subsequent acetylation provides *N*-acetylslafamine (**1097**).



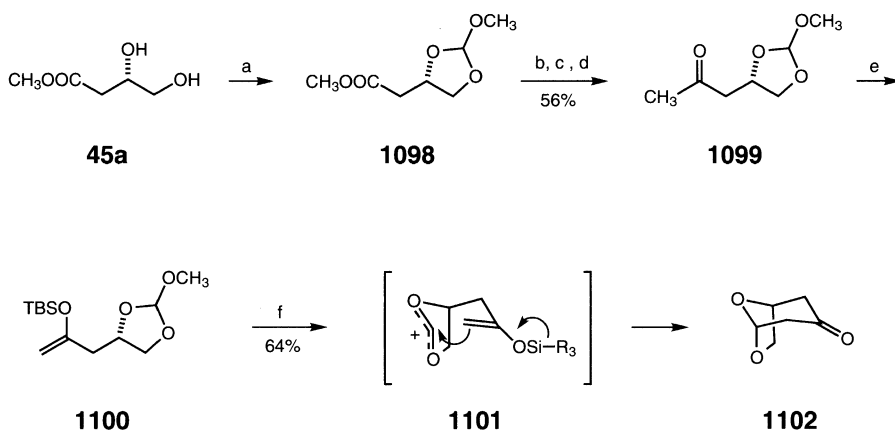


Scheme 161

conditions: (a) PhCH₂Br, Ag₂O, EtOAc, rt, 15h; (b) LiAlH₄, THF, 0 °C, 4 h; (c) TIPS-Cl, imidazole, DMF, rt, 4 h, (48%); (d) DEAD, Ph₃P, phthalimide, THF, rt, 16 h; (e) hydrazine hydrate, EtOH, reflux, 16 h (95%); (f) 2N HCl, EtOH (1:3), reflux, 15 min; (g) CH₂Cl₂, rt, 30 min; (h) CBr₄, Ph₃P, CH₂Cl₂, rt, 30 min (88%); (i) NaH, THF, 0° → 40 °C; (j) BF₃·Et₂O, THF, -78 °C then LiEt₃BH; (k) CF₃COOH, CH₂Cl₂ (85%); (l) L-Selectride, THF, -78 °C, 30 min; (m) Ac₂O, py, rt, 4h (90%); (n) H₂ (1 atm), 10% Pd/C, HOAc, 16 h (88%)

6,8-Dioxabicyclo[3.2.1]octane, the carbon skeleton of 1,6-anhydropyranose, is present in plant extracts and pheromones, and it is a crucial fragment in orally active 5-lipoxygenase inhibitors. The synthon 6,8-dioxabicyclo[3.2.1]octane-3-one (**1102**) is readily prepared from (*S*)-malic acid-derived diol **45a**, as shown in Scheme 162 [234]. Silylation of ketone **1099** with TBS triflate provides the kinetically derived silyl enol ether **1100** (10 : 1 kinetic vs. thermodynamic selectivity) in high yield. Lewis acid cyclization of the cyclic ortho ester **1100** affords the bicyclic ketone **1102** in 25.5% overall yield starting from (*S*)-malic acid.

Stereoselective construction of the C-3 to C-17 fragment of Swinholide A, a 44-membered cytotoxic macrolide, is illustrated in Scheme 163 [235]. Sequential silylation of **45a** with TBSPCl followed by TBS triflate gives the differentially protected diol **1103** via **79**.



Scheme 162

conditions: (a) $\text{HC}(\text{OCH}_3)_3$, H^+ (82%); (b) DIBAL; (c) CH_3Li ; (d) Swern [O]; (e) TBSOTf, $i\text{-Pr}_2\text{NEt}$, 1,2-dichloroethane, 0°C ; (f) Et_2AlCl , CH_2Cl_2 , -20°C , 2h

Asymmetric crotylboration and subsequent methylation furnishes **1105** with $>20:1$ diastereoselectivity. Introduction of the protected terminal hydroxyl group is accomplished by ozonolysis, reductive work-up, and *p*-methoxybenzylolation. The epoxide is formed by intramolecular cyclization of the deprotected primary alcohol with the mesylated secondary alcohol.

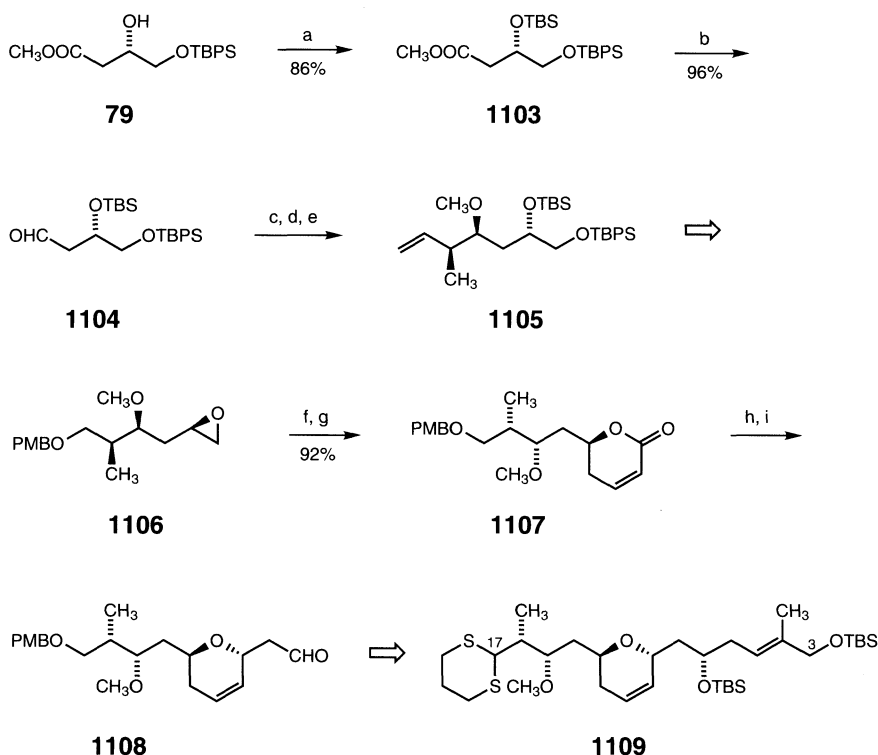
The α,β -unsaturated δ -lactone **1107** is constructed by Ghosez's methodology, which involves treating the epoxide with the lithio anion of methyl-3-phenylsulfonyl orthopropionate followed by acid hydrolysis and DBU-induced elimination. Reduction of the lactone to a lactol with diisobutylaluminum hydride and subsequent C-glycosidation furnishes aldehyde **1108** with a 4:1 epimeric ratio. This is then carried on to the desired fragment **1109**.

The enantioselective synthesis of monoprotected *trans*-2,5-pyrrolidine dialcohol **1119**, a potentially useful intermediate for the construction of pyrrolizidine alkaloids, uses (*S*)-malic acid as the chiral source and radical cyclization to fabricate the heterocycle (Scheme 164) [236]. The crucial intermediate **1112** is prepared from acetonide **454b** by a Mitsunobu reaction of **1110** with oxazolidine-2,4-dione, resulting in inversion of configuration at the hydroxyl-bearing carbon. Reduction of the 4-carbonyl group of heterocycle **1111** with sodium borohydride followed by dehydration of the resulting alcohol furnishes **1112**.

Generation of a radical with tributyltin hydride results in formation of the cyclized product **1114** as a single diastereomer. The high diastereoselectivity can be explained by a transition state that adopts the configuration **1113**, which alleviates severe 1,3-steric crowding due to the amide carbonyl and the bulky CH_2OTBS substituent.

Desilylation affords alcohol **1115**, which can then be converted to ether derivatives **1116** (NaH , CH_3I), **1117** (NaH , PhCH_2Br), or **1118** (MOM-Cl , $i\text{-Pr}_2\text{NEt}$). Cleavage of the carbamate moiety under basic conditions gives the desired monoprotected pyrrolidine analog **1119**.

A synthesis of the functionalized pyrrolidine **1131** makes use of an Eschenmoser sulfide contraction as the key step in the sequence (Scheme 165) [237]. The starting imide **1120** is readily prepared by sequential treatment of (*S*)-malic acid with acetyl chloride, methyl amine, and acetyl chloride again. Protective and functional group manipulations afford **1123**. Treatment of **1123** with allyltrimethylsilane and titanium tetrachloride gives **1124** in 72% yield, accompanied with 12% of the corresponding *trans* isomer.

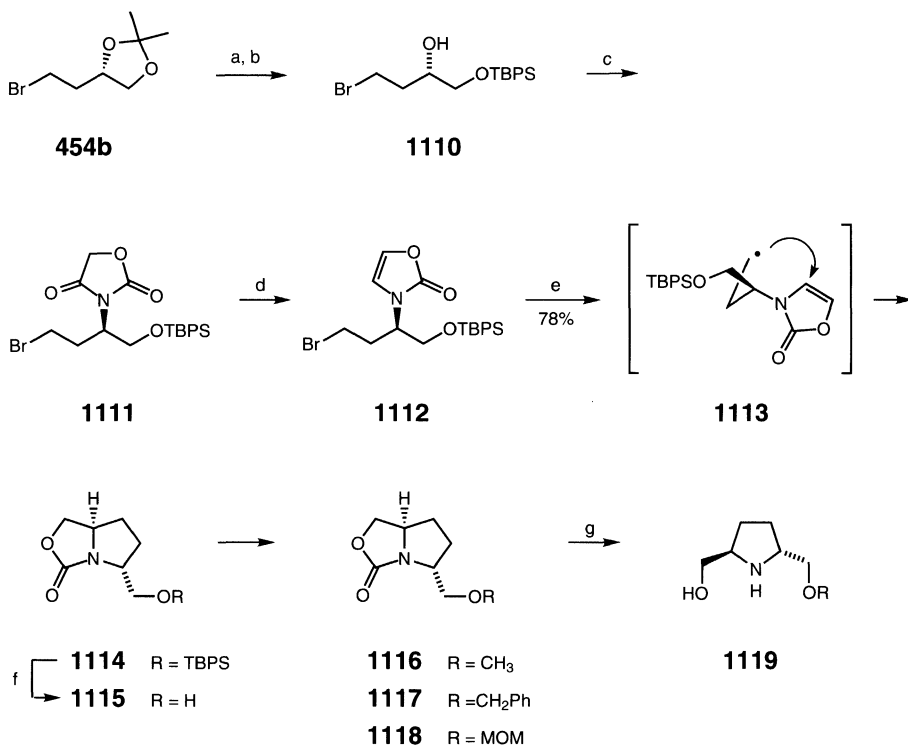
**Scheme 163**

conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2 , rt, 2 h; (b) DIBAL, CH_2Cl_2 , -78°C ; (c) KO \dagger Bu, (Z)-but-2-ene (2 eq), *n*-BuLi, THF, $-78^\circ\text{C} \rightarrow -55^\circ\text{C}$ then (+)- β -methoxydiisopinocampheylborane; (d) NaOH, H_2O_2 (90%); (e) NaH, CH_3I , THF (91%); (f) methyl-3-phenylsulfonfyl orthopropionate, *n*-BuLi, DMPU, THF, $-78^\circ\text{C} \rightarrow -20^\circ\text{C}$; (g) PTSA, CH_2Cl_2 then DBU, Et_3N ; (h) DIBAL, CH_2Cl_2 , -78°C , 30 min (95%); (i) $\text{CH}_2=\text{CHOTBS}$, ZnCl_2 , -20°C , 15 min (65%)

Replacement of the silyl group by benzyl followed by ozonolysis furnishes ester **1127**, which is then converted to thiolactam **1128** with Lawesson's reagent. Eschenmoser sulfide contraction on **1128** gives **1129** in 51% yield. Reduction of the double bond produces a mixture of the desired *all-cis* pyrrolidine **1130** (77%) and 14% of its C-5 epimer. Removal of the benzyl protecting group under hydrogenation conditions furnishes lactone **1131**.

In a potentially more direct route to **1131**, the thiolactam **1135** is prepared in fewer steps and in high yield (Scheme 166). However, the Eschenmoser sulfide contraction fails with **1135** due to competitive β -elimination.

Monobactams such as carmonam fall into the general category of monocyclic β -lactam antibiotics. These β -lactams exhibit pharmacological profiles similar to penicillins and cephalosporins. The key monobactam intermediate (**1143**) of carmonam is synthesized with the correct stereochemistry by way of a ketene-imine cycloaddition (Staudinger reaction) involving a chiral imine derived from (*S*)-malic acid (Scheme 167) [238]. Diol **45b** is fully silylated to **1136** with TBS-Cl, and the primary silyloxy group is regioselectively desilylated under acidic conditions to give **1137**. A Swern oxidation of the resulting alcohol furnishes an intermediate aldehyde [62% overall yield from (*S*)-malic acid], which is then condensed with *p*-anisidine to provide chiral imine **1138**. Without further purification, **1138** is reacted with

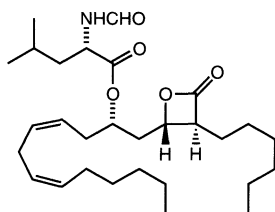


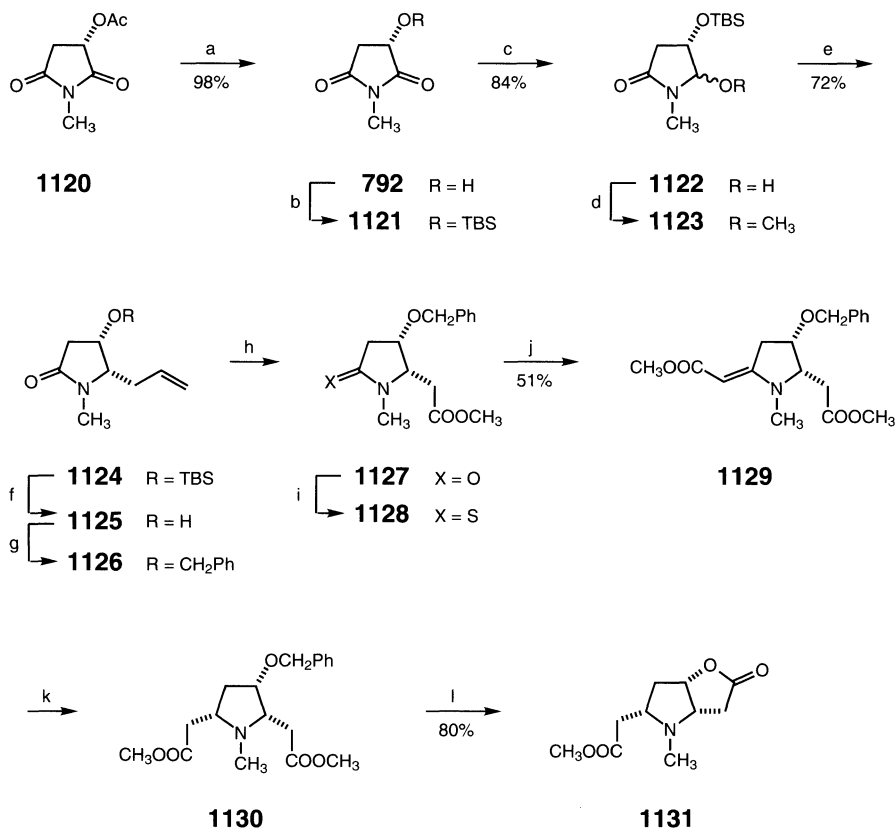
Scheme 164

conditions: (a) TsCl, MeOH; (b) TBPSCI, DMAP, Et₃N; (c) oxazolidine-2,4-dione, DIAD, Ph₃P; (d) NaBH₄, MeOH, then MsCl, Et₃N; (e) Bu₃SnH, AIBN, benzene, reflux; (f) HCl, THF; (g) 10% NaOH, EtOH

either azidoacetyl chloride or phthalimidoacetyl chloride in toluene in the presence of three equivalents of triethylamine at $-78\text{ }^{\circ}\text{C} \rightarrow \text{rt}$ to afford a mixture of (3*S*,4*R*)-*cis*- β -lactam **1139** and (3*R*,4*S*)-**1140** (ratio **1139a**:**1140a** = 95:5; that of **1139b**:**1140b** = 99:1). After purification by column chromatography, **1139a** is transformed to **1143** in 7 steps. The entire synthetic sequence from (*S*)-malic acid requires 14 steps, and is accomplished with an overall yield of 11%.

The first total synthesis of (–)-lipstatin (**1144**), an irreversible inhibitor of pancreatic lipase, has been accomplished in 13 steps with an 8% overall yield from dimethyl (*S*)-malate [239].

**1144**

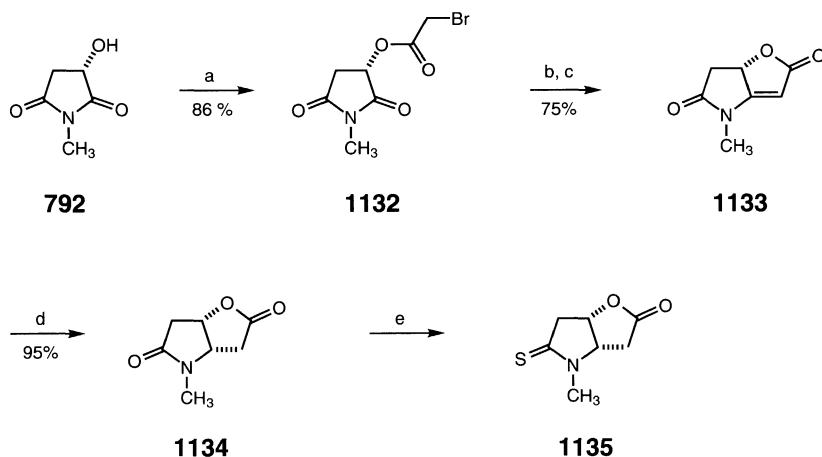


Scheme 165

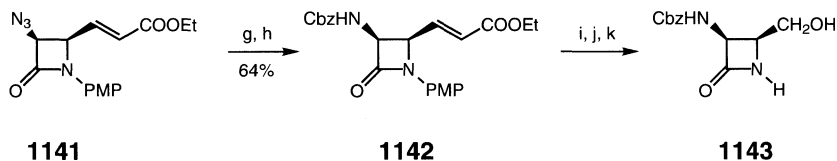
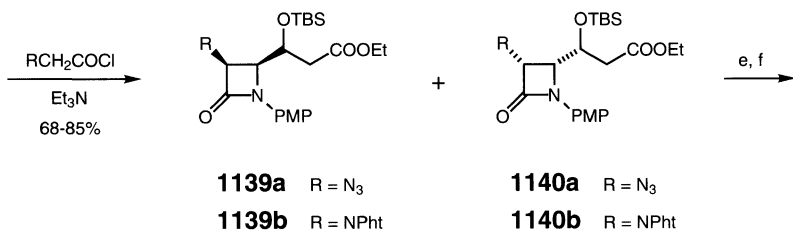
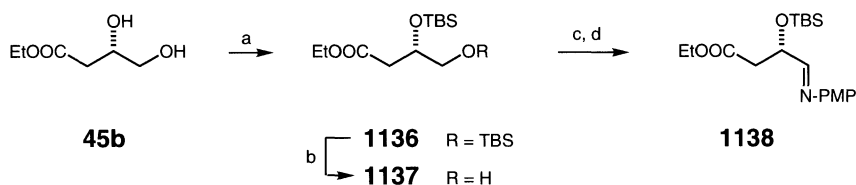
conditions: (a) HCl, EtOH; (b) TBSCl, imidazole, DMF (95%); (c) NaBH₄, MeOH; (d) NaH, CH₃I, THF (96%); (e) TMSCH₂CH=CH₂, TiCl₄, CH₂Cl₂, -78 °C → rt; (f) Bu₄NF, THF (98%); (g) PhCH₂Br, NaH, THF (90%); (h) O₃, MeOH-H₂O-NaOH, CH₂Cl₂ (81%); (i) Lawessons reagent, CH₂Cl₂ (90%); (j) TiOCH₂COOCH₃, Ph₃P, Et₃N, CH₂Cl₂; (k) NaCNBH₃, MeOH (pH 4); (l) H₂, Pd(OH)₂

The key aldehyde **1151** is prepared from the malic acid-derived tosylate **59** as illustrated in Scheme 168. Attempted displacement of the tosyl function of **1145** with carbon nucleophiles fails due to base sensitivity caused by the ester group. Consequently, the ester is instead converted to a diisopropyl acetal, which alleviates the problem. Nucleophilic displacement of the tosylate with cyanide proceeds cleanly in this case to give nitrile **1147**. Conversion of the nitrile to aldehyde **1148** followed by Wittig reaction with **1149** produces the protected (*Z,Z*)-diene **1150** with >95% (*Z*)-stereoselectivity. Hydrolysis of the acetal gives the dienal **1151** in 21% overall yield from dimethyl (*S*)-malate.

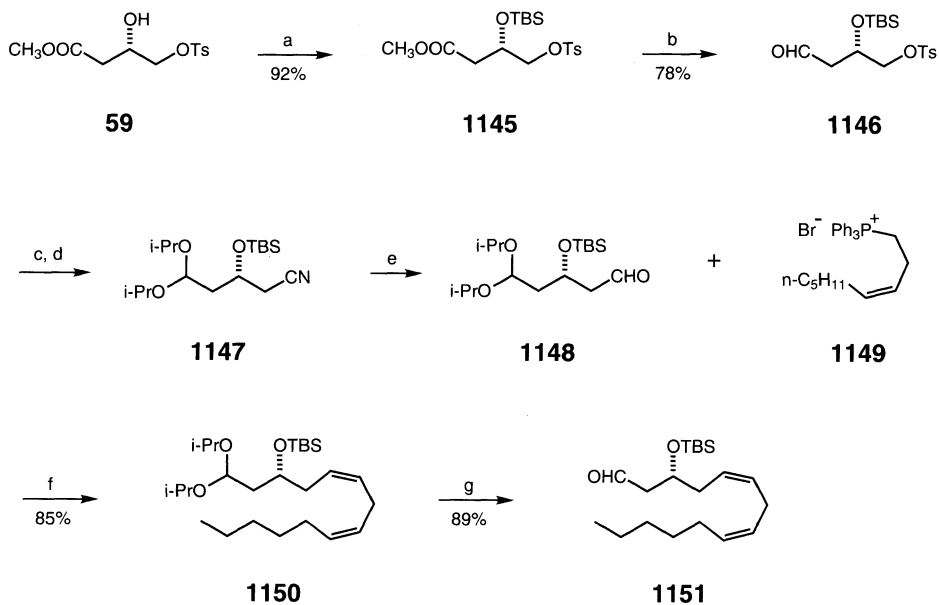
Assembly of the lipstatin framework is effectively accomplished by a diastereoselective Lewis acid-promoted [2 + 2] cycloaddition reaction between silylketene **1152** and aldehyde **1151**. The reaction occurs between -45 °C and -20 °C to give a 9 : 1 mixture of **1153** and the corresponding C-4 epimer. After desilylation and column chromatography, esterification with (*S*)-*N*-formylleucine under Mitsunobu conditions furnishes (-)-lipstatin (**1144**).

**Scheme 166**

conditions: (a) BrCH₂COCl, py, CH₂Cl₂; (b) NaI, acetone; (c) Ph₃P, CH₃CN, then Et₃N;
 (d) H₂, Rh/Al₂O₃, EtOAc; (e) Lawesson's reagent, CH₂Cl₂

**Scheme 167**

conditions: (a) TBS-Cl, imidazole, CH₂Cl₂; (b) 2N HCl, EtOH; (c) Swern [O]; (d) PMP-NH₂, 4Å sieves;
 (e) 36% aq. HF, EtOH (85%); (f) MsCl, Et₃N, CH₂Cl₂ (90%); (g) (NH₄)₂S, MeOH;
 (h) Cbz-Cl, Et₃N, CH₂Cl₂; (i) 5 mol% OsO₄, NaIO₄, dioxane; (j) NaBH₄ (65% for 2 steps);
 (k) CAN, CH₃CN

**Scheme 168**

conditions: (a) TBS-Cl, imidazole, DMF, rt, 12 h; (b) DIBAL, CH_2Cl_2 -toluene, -90°C , 30 min; (c) $(i\text{-PrO})_3\text{CH}$, PTSA, $i\text{-PrOH}$, rt, 2 h (92%); (d) NaCN, DMSO, 90°C , 2 h (83%); (e) DIBAL, CH_2Cl_2 -toluene, -40°C , 2 h (81%); (f) NaHMDS, THF, -90°C →rt; (g) PTSA, THF- H_2O , reflux, 15 min

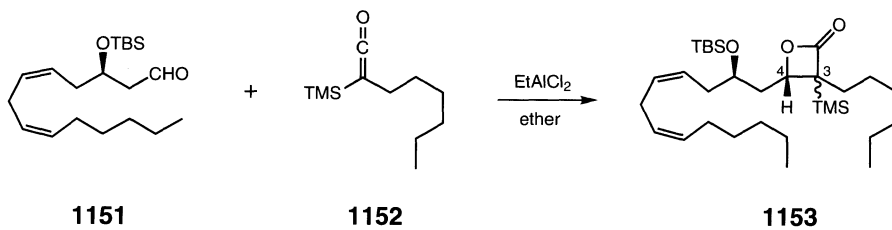
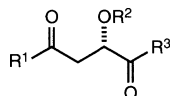


Table 3.1. Physical properties of malic acid derivatives

R ¹	R ²	R ³	[α] _D (°)	Solvent (c)	mp (°C) or bp (°C; pressure in mmHg)	References
OH	H	OH	-31.7	pyridine (1.1)		6
			-28.2	pyridine (5.5)	105	15
OCH ₃	H	OCH ₃	-7.6	neat		6
			-9.2	MeOH (1.3)	105–108 (2.5)	4
			-28.3	pyridine (5)		67
			+1.5	CHCl ₃ (1.8)		22
OEt	H	OEt	-9.3	neat	55 (0.01)	231
			-15.6	acetone (5.3)	106–108 (2.5)	7
			-11.4	EtOH (2.5)		10
			+6.0	CHCl ₃ (2.3)		10
OCH ₂ Ph	H	OCH ₂ Ph	-16	MeOH (1)		46
OH	H	OCH ₃	+5.8	MeOH (9.5)	79–80	27
OH	H	OEt			4–49.5	27
OCH ₃	H	NH ₂	-46.5	EtOH (2.1)	40–42	30
OEt	COCH ₃	OEt	-23.6	EtOH (6.7)	71–72 (0.15)	7
OH	COCH ₃	OEt	-27.1	EtOH (0.7)	43.6–46	34
			-29.6	EtOH (1.1)	50–51	96
			-32.4	CHCl ₃ (0.5)	53	33
			-10	CHCl ₃ (1)	80–81 (0.05)	100
OEt	COCH ₃	OEt	+32.6	CHCl ₃ (1.4)		72
OEt	COPh	OEt	-4.0	neat		231
OCH ₃	CH ₂ Ph	OCH ₃	-68.5	CHCl ₃ (11.4)		13
			-63.0	CHCl ₃ (1.6)		12
OCH ₃	CH ₃	OCH ₃	-50.7	acetone (3.2)	116 (11)	3
OH	CH ₃	OCH ₃	-55.9	acetone (3.8)		3
OCH ₃	CH ₃	OH	-45.8	acetone (3.3)		3
OCH ₃	EE	OCH ₃	-52.4	acetone (6.9)		14
OEt	EE	OEt			99 (0.01)	16
OCH ₃	THP	OCH ₃	-59.0	acetone (6)		6
OEt	THP	OEt	-39.2	CHCl ₃ (1.5)	83 (0.005)	18
			-59.0	acetone (6)	118.5–119 (0.4)	19
OTMS	TMS	OTMS	-43.2	neat	137–140 (11)	21

References

1. I. Takata and T. Tosa, *Bioprocess Technol.* **16**, 53 (1993).
2. S. Henrot, M. Larcheveque, and Y. Petit, *Syn. Commun.* **16**, 183 (1986).
3. G. Odham, B. Pettersson, and E. Stenhagen, *Acta Chem. Scand. B* **28**, 36 (1974).
4. J. L. Bloomer and F. E. Kappler, *J. Chem. Soc., Perkin I Trans.*, 1485 (1976).
5. C. E. Berkman and C. M. Thompson, *Tetrahedron Lett.* **33**, 1415 (1992).
6. D. L. Boger and J. S. Panek, *J. Org. Chem.* **46**, 1208 (1981).
7. S. G. Cohen, Z. Neuwirth, and S. Y. Weinstein, *J. Am. Chem. Soc.* **88**, 5306 (1966).
8. L. Borjesson and C. J. Welch, *Tetrahedron* **48**, 6325 (1992).
9. S. Takano, Y. Iwabuchi, and K. Ogasawara, *Tetrahedron Lett.* **32**, 3527 (1991).
10. E. Santaniello, P. Ferraboschi, P. Grisenti, F. Aragozzini, and E. Maconi, *J. Chem. Soc., Perkin I Trans.*, 601 (1991).
11. K. Freudenberg, *Chem. Ber.* **47**, 2027 (1914).
12. D. H. R. Barton, M. Benechie, F. Khuong-Huu, P. Potier, and V. Reyna- Pinedo, *Tetrahedron Lett.* **23**, 651 (1982).
13. G. E. Keck, M. B. Andrus, and D. R. Romer, *J. Org. Chem.* **56**, 417 (1991).
14. P. A. Bartlett, J. D. Meadows, and E. Ottow, *J. Am. Chem. Soc.* **106**, 5304 (1984).
15. K. Mori and M. Ikonaka, *Tetrahedron* **40**, 3471 (1984).
16. E. Hungerbuhler, R. Naef, D. Wasmuth, and D. Seebach, *Helv. Chim. Acta* **63**, 1960 (1980).
17. A. K. Ghosh, W. J. Thompson, H. Lee, S. P. McKee, P. M. Munson, T. T. Duong, P. L. Darke, J. A. Zugay, E. A. Emimi, W. A. Schlieff, J. R. Huff, and P. S. Anderson, *J. Med. Chem.* **36**, 924 (1993).
18. B. Seuring and D. Seebach, *Helv. Chim. Acta* **60**, 1175 (1977).
19. P. W. Feit and O. Nielsen, *J. Med. Chem.* **9**, 416 (1966).
20. E. J. Corey, H. Niwa, and J. Knolle, *J. Am. Chem. Soc.* **100**, 1942 (1978).
21. T. R. Hoye, B. H. Peterson, and J. D. Miller, *J. Org. Chem.* **52**, 1351 (1987).
22. C. Papageorgiou and C. Benezra, *J. Org. Chem.* **50**, 1144 (1985).
23. T. Miyazawa, E. Akita and T. Ito, *Agr. Biol. Chem.* **40**, 1651 (1976).
24. C. E. Grimshaw and W. W. Cleland, *Biochemistry* **19**, 3153 (1980).
25. R. Andruszewicz, A. Czerwinski and J. Grzybowska, *Synthesis*, 31 (1983).
26. T. Yoneta, S. Shibahara, S. Fukatsu, and S. Seki, *Bull. Chem. Soc. Jap.* **51**, 3296 (1978).
27. M. J. Miller, J. S. Bajwa, P. G. Mattingly and K. Peterson, *J. Org. Chem.* **47**, 4928 (1982).
28. H. Maeda, M. Suzuki, H. Sugano and K. Matsumoto, *Synthesis*, 401 (1988).
29. G. P. Liesen and C. N. Sukenik, *J. Org. Chem.* **52**, 455 (1987).
30. B. Rajashekhar and E. T. Kaiser, *J. Org. Chem.* **50**, 5480 (1985).
31. B. Jones, *J. Chem. Soc.*, 788 (1933).
32. D. H. S. Horn and Y. Y. Pretorius, *J. Chem. Soc.*, 1460 (1954).
33. T. Tashiro, S. Fushiya and S. Nozoe, *Chem. Pharm. Bull.* **36**, 893 (1988).
34. H. Meier, P. Uebelhart and C. H. Eugster, *Helv. Chim. Acta* **69**, 106 (1986).
35. S. Shiuey, J. J. Partridge and M. R. Uskokovic, *J. Org. Chem.* **53**, 1040 (1988).
36. J. Barry and H. B. Kagan, *Synthesis*, 453 (1981).
37. C. J. Burns, C. A. Martin and K. B. Sharpless, *J. Org. Chem.* **54**, 2826 (1989).
38. G. Ryback, *J. Chem. Soc., Chem. Commun.*, 1190 (1972).
39. M. Shibuya, Y. Jinbo and S. Kubota, *Chem. Pharm. Bull.* **32**, 1303 (1984).
40. E. J. Trybulski, R. H. Kramss, R. M. Mangano, H. J. Brabander and G. Francisco, *BioMed. Chem. Lett.* **2**, 827 (1992).
41. G. Guanti, L. Banfi and E. Narisano, *Tetrahedron Lett.* **30**, 5507 (1989).
42. S. Saito, T. Hasegawa, M. Inaba, R. Nishida, T. Fujii, S. Nomizu and T. Moriwake, *Chem. Lett.*, 1389 (1984).
43. R. W. Hoffmann and A. Schlapbach, *Tetrahedron* **48**, 1959 (1992).
44. P. Mosset, P. Pointeau, F. Aubert, J. P. Lellouche, J. P. Beaucourt and R. Gree, *Bull. Soc. Chim. Fr.* **127**, 298 (1990).
45. J. R. Falck, S. Lumin, S. Lee, B. Heckmann, C. Mioskowski, A. Karara and J. Capdevila, *Tetrahedron Lett.* **34**, 4893 (1992).
46. F. D. Bellamy, M. Bondoux and P. Dodey, *Tetrahedron Lett.* **31**, 7323 (1990).
47. S. Saito, T. Ishikawa, A. Kuroda, K. Koga and T. Moriwake, *Tetrahedron* **48**, 4067 (1992).
48. S. Saito, S. Matsumoto, S. Sato, M. Inaba and O. Moriwake, *Heterocycles* **24**, 2785 (1986).
49. H. Kashiwara, H. Suemune, K. Fujimoto and K. Sakai, *Chem. Pharm. Bull.* **37**, 2610 (1989).
50. K. Prasad, K. Chen, O. Repic and G. Hardtmann, *Tetrahedron Asymm.* **1**, 307 (1990).

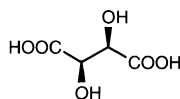
51. G. Wess, K. Kessler, E. Baader, W. Bartmann, G. Beck, A. Bergmann, H. Jendralla, K. Bock, G. Holzstein, H. Kleine and M. Schnierer, *Tetrahedron Lett.* **31**, 2545 (1990).
52. H. Jendralla, E. Granzer, B. V. Kerekjarto, R. Krause, U. Schacht, E. Baader, W. Bartmann, G. Beck, A. Bergmann, K. Kessler, G. Wess, L. J. Chen, S. Granata, J. Herchen, H. Kleine, H. Schussler and K. Wagner, *J. Med. Chem.* **34**, 2962 (1991).
53. F. G. Kathawala, *Med. Chem. Reviews* **11**, 121 (1991).
54. M. Fukui, S. Okamoto, T. Sano, T. Nakata and T. Oishi, *Chem. Pharm. Bull.* **38**, 2890 (1990).
55. K. H. Ahn and S. J. Lee, *Tetrahedron Lett.* **33**, 507 (1992).
56. M. Larcheveque and S. Henrot, *Tetrahedron* **43**, 2303 (1987).
57. M. Larcheveque and S. Henrot, *Tetrahedron* **46**, 4277 (1990).
58. D. W. Knight, D. Shaw and G. Fenton, *Synlett.*, 295 (1994).
59. D. Seebach, R. Naef and G. Calderari, *Tetrahedron* **40**, 1313 (1984).
60. D. Seebach, M. A. Maestro, M. Sefkow, A. Neidlein, F. Sternfeld, G. Adam and T. Sommerfeld, *Helv. Chim. Acta* **74**, 2112 (1991).
61. M. J. Milewska and T. Polonski, *Synthesis*, 475 (1988).
62. D. B. Collum, J. H. McDonald, III and W. C. Still, *J. Am. Chem. Soc.* **102**, 2118 (1980).
63. S. Hanessian, A. Tehim and P. Chen, *J. Org. Chem.* **58**, 7768 (1993).
64. S. Kano, Y. Yuasa and S. Shibuya, *Heterocycles* **26**, 373 (1987).
65. J. L. Bloomer and F. E. Kappler, *J. Org. Chem.* **39**, 113 (1974).
66. M. Sato, J. Sakaki, K. Takayama, S. Kobayashi, M. Suzuki and C. Kaneko, *Chem. Pharm. Bull.* **38**, 94 (1990).
67. G. Lowe and B. V. L. Potter, *J. Chem. Soc., Perkin I Trans.*, 2029 (1980).
68. B. Strijveen and R. M. Kellogg, *J. Org. Chem.* **51**, 3664 (1986).
69. R. V. Hoffman and H. Kim, *Tetrahedron* **48**, 3007 (1992).
70. R. W. Feenstra, E. H. M. Stokkingreef, R. J. F. Nivard and H. C. J. Ottenheijm, *Tetrahedron Lett.* **28**, 1215 (1987).
71. R. W. Feenstra, E. H. M. Stokkingreef, R. J. F. Nivard and H. C. J. Ottenheijm, *Tetrahedron* **44**, 5583 (1988).
72. C. E. Berkman, C. M. Thompson and S. R. Perrin, *Chem. Res. Toxicol.* **6**, 718 (1993).
73. F. Effenberger, U. Burkard and J. Willfahrt, *Liebigs Ann. Chem.*, 314 (1986).
74. U. Burkard and F. Effenberger, *Chem. Ber.* **119**, 1594 (1986).
75. K. Krohn and H. Rieger, *Liebigs Ann. Chem.*, 515 (1987).
76. K. Krohn, H. Rieger, E. Broser, P. Schiess, S. Chen and T. Strubin, *Liebigs Ann. Chem.*, 943 (1988).
77. G. Calderari and D. Seebach, *Helv. Chim. Acta* **68**, 1592 (1985).
78. G. Kneer, J. Mattay, G. Raabe, C. Kruger and J. Lauterwein, *Synthesis*, 599 (1990).
79. D. Seebach and D. Wasmuth, *Helv. Chim. Acta* **63**, 197 (1980).
80. D. Wasmuth, D. Arigoni and D. Seebach, *Helv. Chim. Acta* **65**, 344 (1982).
81. D. Seebach, J. Aebi and D. Wasmuth, *Org. Syn., Coll. Vol. VII*, 153 (1990).
82. B. H. Norman and M. L. Morris, *Tetrahedron Lett.* **33**, 6803 (1992).
83. M. Zuger, T. Weller and D. Seebach, *Helv. Chim. Acta* **63**, 2005 (1980).
84. P. Renaud, M. Hurzeler and D. Seebach, *Helv. Chim. Acta* **70**, 292 (1987).
85. J. S. Bajwa and M. J. Miller, *J. Org. Chem.* **48**, 1114 (1983).
86. J. D. Aebi, M. A. Sutter, D. Wasmuth and D. Seebach, *Liebigs Ann. Chem.*, 2114 (1983).
87. A. B. Smith, III, J. J. W. Duan, K. G. Hull and B. A. Salvatore, *Tetrahedron Lett.* **32**, 4855 (1991).
88. U. Schmidt, R. Meyer, V. Leitenberger, F. Stabler and A. Lieberknecht, *Synthesis*, 409 (1991).
89. H. P. Buser, B. Pugin, F. Spindler and M. Sutter, *Tetrahedron* **47**, 5709 (1991).
90. F. Matsuda, N. Tomiyoshi, M. Yanagiya and T. Matsumoto, *Tetrahedron* **46**, 3469 (1990).
91. Y. Ohfune, M. Tomita and K. Nomoto, *J. Am. Chem. Soc.* **103**, 2409 (1981).
92. M. J. Smith, *Tetrahedron Lett.* **30**, 313 (1989).
93. U. Nubbemeyer, R. Ohrlein, J. Gonda, B. Ernst and D. Bellus, *Angew. Chem., Int. Ed. Engl.* **30**, 1465 (1991).
94. B. Gong and D. G. Lynn, *J. Org. Chem.* **55**, 4763 (1990).
95. K. Mori, T. Uematsu, H. Watanabe, K. Yanagi and M. Minobe, *Tetrahedron Lett.* **25**, 3875 (1984).
96. K. Mori, T. Uematsu, K. Yanagi and M. Minobe, *Tetrahedron* **41**, 2751 (1985).
97. S. Fushiya, Y. Sato and S. Nozoe, *Chem. Lett.*, 1215 (1980).
98. S. Fushiya, Y. Sato, S. Nakatsuyama, N. Kanuma and S. Nozoe, *Chem. Lett.*, 909 (1981).
99. K. G. Paul and F. Johnson, *J. Am. Chem. Soc.* **98**, 1285 (1976).
100. F. Johnson, K. G. Paul, D. Favara, R. Ciabatti and U. Guzzi, *J. Am. Chem. Soc.* **104**, 2190 (1982).
101. S. Hanessian, A. Ugolini, D. Dube and A. Glamyan, *Can. J. Chem.* **62**, 2146 (1984).
102. J. Pawlak, K. Nakanishi, T. Iwashita and E. Borowski, *J. Org. Chem.* **52**, 2896 (1987).
103. V. K. Tandon, A. M. van Leusen and H. Wynberg, *J. Org. Chem.* **48**, 2767 (1983).

104. D. Seebach, B. Seuring, H. Kalinowski, W. Lubosch and B. Renger, *Angew. Chem., Int. Ed. Engl.* **16**, 264 (1977).
105. B. Seuring and D. Seebach, *Liebigs Ann. Chem.*, 2044 (1978).
106. D. Seebach and E. Hungerbuhler, *Modern Synthetic Methods*, Otto Salle Verlag, 1980 p. 141.
107. E. N. Laweson, J. F. Jamie and W. Kitching, *J. Org. Chem.* **57**, 353 (1992).
108. K. Tomioka and K. Koga, *Tetrahedron* **44**, 4351 (1988).
109. A. I. Meyers and J. P. Lawson, *Tetrahedron Lett.* **23**, 4883 (1982).
110. U. Berlage, J. Schmidt, Z. Milkova and P. Welzel, *Tetrahedron Lett.* **28**, 3095 (1987).
111. S. Masamune, P. Ma, H. Okumoto, J. W. Ellingboe and Y. Ito, *J. Org. Chem.* **49**, 2834 (1984).
112. D. L. J. Clive, K. S. Keshava Murthy, A. G. H. Wee, J. Siva Prasad, G. V. J. de Silva, M. Majewski, P. C. Anderson, C. F. Evans, R. D. Haugen, L. D. Heerze and J. R. Barrie, *J. Am. Chem. Soc.* **112**, 3018 (1990).
113. R. K. Olsen, K. L. Bhat, R. B. Wardle, W. J. Hennen and G. D. Kini, *J. Org. Chem.* **50**, 896 (1985).
114. B. Kuchler, G. Vob, and H. Gerlach, *Liebigs Ann. Chem.*, 545 (1991).
115. R. W. Hoffmann and W. Helbig, *Chem. Ber.* **114**, 2802 (1981).
116. K. Tang, B. E. Tropp and R. Engel, *Tetrahedron* **34**, 2873 (1978).
117. H. Hayashi, K. Nakanishi, C. Brandon and J. Marmur, *J. Am. Chem. Soc.* **95**, 8749 (1973).
118. J. A. Schneider, K. Yoshihara and K. Nakanishi, *J. Chem. Soc., Chem. Commun.*, 352 (1983).
119. T. Doi, K. Shimizu, T. Takahashi, J. Tsuji and K. Yamamoto, *Tetrahedron Lett.* **31**, 3313 (1990).
120. K. Mori and H. Watanabe, *Tetrahedron Lett.*, 6025 (1984).
121. H. Hayashi and K. Nakanishi, *J. Am. Chem. Soc.* **95**, 4081 (1973).
122. K. Kamiyama, Y. Urano, S. Kobayashi and M. Ohno, *Tetrahedron Lett.*, 3123 (1987).
123. K. Shishido, Y. Sukegawa, K. Fukumoto and T. Kametani, *Heterocycles* **24**, 641 (1986).
124. K. Shishido, Y. Sukegawa, K. Fukumoto and T. Kametani, *J. Chem. Soc., Perkin I Trans.*, 993 (1987).
125. Y. Mori, A. Takeuchi, H. Kageyama and M. Suzuki, *Tetrahedron Lett.* **29**, 5423 (1988).
126. B. Achmatowicz, M. M. Kabat, J. Karjewski and J. Wicha, *Tetrahedron* **48**, 10201 (1992).
127. M. M. Kabat and J. Wicha, *Tetrahedron Lett.* **32**, 531 (1991).
128. M. M. Kabat and J. Wicha, *Tetrahedron Lett.* **32**, 1073 (1991).
129. B. Achmatowicz and J. Wicha, *Tetrahedron Asymm.* **4**, 399 (1993).
130. J. D. White and M. Kawasaki, *J. Am. Chem. Soc.* **112**, 4991 (1990).
131. J. Mulzer and P. De Lasalle, *J. Chem. Res. (S)*, 10 (1983).
132. K. Isaac and P. Kocienski, *J. Chem. Soc., Chem. Commun.*, 460 (1982).
133. D. A. Howes, M. H. Brookes, D. Coates, B. T. Golding and A. T. Hudson, *J. Chem. Res. (S)*, 9 (1983).
134. M. H. Brookes, B. T. Golding and A. T. Hudson, *J. Chem. Soc., Perkin I Trans.*, 9 (1988).
135. M. H. Brookes, B. T. Golding, D. A. Howes and A. T. Hudson, *J. Chem. Soc., Chem. Commun.*, 1051 (1983).
136. M. Majewski, D. L. J. Clive and P. C. Anderson, *Tetrahedron Lett.* **25**, 2101 (1984).
137. P. J. Kocienski, S. D. A. Street, C. Yeates and S. F. Campbell, *J. Chem. Soc., Perkin I Trans.*, 2171 (1987).
138. T. Nakata, T. Suenaga and T. Oishi, *Tetrahedron Lett.* **30**, 6525 (1989).
139. T. Nakata, T. Komatsu, K. Nagasawa, H. Yamada and T. Takahashi, *Tetrahedron Lett.* **35**, 8225 (1994).
140. S. Hanessian and B. Vanasse, *Can. J. Chem.* **65**, 195 (1987).
141. M. Benechie, B. Delpach, Q. Khuong-Huu and F. Khuong-Huu, *Tetrahedron* **48**, 1895 (1992).
142. T. Rosen, M. J. Taschner and C. H. Heathcock, *J. Org. Chem.* **49**, 3994 (1984).
143. E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu and T. K. Schaaf, *J. Am. Chem. Soc.* **93**, 1490 (1971).
144. Y. Mori and M. Suzuki, *Tetrahedron Lett.* **30**, 4383 (1989).
145. Y. Mori, H. Kageyama and M. Suzuki, *Chem. Pharm. Bull.* **38**, 2574 (1990).
146. T. Nakata, T. Suenaga, K. Nakashima and T. Oishi, *Tetrahedron Lett.* **30**, 6529 (1989).
147. T. Nakata, S. Nagao and T. Oishi, *Tetrahedron Lett.* **26**, 75 (1985).
148. T. Nakata, K. Saito and T. Oishi, *Tetrahedron Lett.* **27**, 6341 (1986).
149. T. Nakata, S. Nagao, N. Mori and T. Oishi, *Tetrahedron Lett.* **26**, 6461 (1985).
150. T. Nakata, S. Nagao and T. Oishi, *Tetrahedron Lett.* **26**, 6465 (1985).
151. T. Nakata, H. Matsukura, D. Jian and H. Nagashima, *Tetrahedron Lett.* **35**, 8229 (1994).
152. J. Mulzer, C. Seilz, P. Luger, M. Weber and W. Reutter, *Liebigs Ann. Chem.*, 947 (1991).
153. P. J. Kocienski, C. Yeates, S. D. A. Street and S. F. Campbell, *J. Chem. Soc., Perkin I Trans.*, 2183 (1987).
154. P. J. Kocienski, S. D. A. Street, C. Yeates and S. F. Campbell, *J. Chem. Soc., Perkin I Trans.*, 2189 (1987).
155. S. Hanessian, A. Ugolini and M. Therien, *J. Org. Chem.* **48**, 4427 (1983).
156. P. Yadagiri, S. Lumin, P. Mosset, J. Capdevila and J. R. Falk, *Tetrahedron Lett.* **27**, 6039 (1986).
157. P. Mosset, P. Yadagiri, S. Lumin, J. Capdevila and J. R. Falk, *Tetrahedron Lett.* **27**, 6035 (1986).
158. F. Nishida, Y. Mori, N. Rokkaku, S. Isobe, T. Furuse, M. Suzuki, V. Meevootisom, T. W. Flegel, Y. Thebtaranonth and S. Intararuangsorn, *Chem. Pharm. Bull.* **38**, 2381 (1990).
159. M. Labelle, H. E. Morton, Y. Guindon and J. P. Springer, *J. Am. Chem. Soc.* **110**, 4533 (1988).

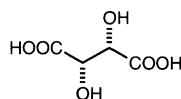
160. Y. Guindon, C. Yoakim, M. A. Bernstein and H. E. Morton, *Tetrahedron Lett.* **26**, 1185 (1985).
161. Y. Guindon, Y. St. Denis, S. Daigneault and H. E. Morton, *Tetrahedron Lett.* **27**, 1237 (1986).
162. N. Nakajima, K. Uoto and O. Yonemitsu, *Heterocycles* **31**, 5 (1990).
163. H. Shieh and G. D. Prestwich, *J. Org. Chem.* **46**, 4319 (1981).
164. D. Seebach and E. Hungerbühler, *Modern Synthetic Methods*, Otto Salle Verlag, 1980 p. 146.
165. R. C. Corcoran, *Tetrahedron Lett.* **31**, 2101 (1990).
166. M. Thiam, A. Slassi, F. Chastrette and R. Amouroux, *Syn. Commun.* **22**, 83 (1992).
167. D. Seebach, H. Chow, R. F. W. Jackson, M. A. Sutter, S. Thaisrivongs and J. Zimmermann, *Liebigs Ann. Chem.*, 1281 (1986).
168. Y. Morimoto, A. Mikami, S. Kuwabe and H. Shirahama, *Tetrahedron Lett.* **32**, 2909 (1991).
169. M. Thiam and F. Chastrette, *Bull. Soc. Chim. Fr.* **129**, 161 (1992).
170. M. Thiam and F. Chastrette, *Tetrahedron Lett.* **31**, 1429 (1990).
171. R. F. W. Jackson, M. A. Sutter and D. Seebach, *Liebigs Ann. Chem.*, 2313 (1985).
172. K. L. Bhat, D. M. Flanagan and M. M. Joulie, *Syn. Commun.* **15**, 587 (1985).
173. M. C. Slevi, A. D. Cale, Jr., T. W. Gero, L. W. Jaques, W. J. Welstead, A. F. Johnson, B. F. Kilpatrick, I. Demian, J. C. Nolan and H. Jenkins, *J. Med. Chem.* **34**, 1314 (1991).
174. T. Poll, A. F. Abdel Hady, R. Karge, G. Linz, J. Weetman and G. Helmchen, *Tetrahedron Lett.* **30**, 5595 (1989).
175. A. Bernardi, F. Micheli, D. Potenza, C. Scolastico and R. Villa, *Tetrahedron Lett.* **31**, 4949 (1990).
176. A. Naylor, D. B. Judd, D. I. C. Scopes, A. G. Hayes and P. J. Birch, *J. Med. Chem.* **37**, 2138 (1994).
177. H. Arima, K. Tamazawa and M. Takeuchi, *J. Label. Compound Radiopharm.* **25**, 161 (1988).
178. J. F. Almeida, J. Anaya, N. Martin, M. Grande, J. R. Moran and M. C. Caballero, *Tetrahedron Asymm.* **3**, 1431 (1992).
179. W. J. Klaver, H. Hiemstra and W. N. Speckamp, *Tetrahedron Lett.* **28**, 1581 (1987).
180. W. J. Klaver, H. Hiemstra and W. N. Speckamp, *J. Am. Chem. Soc.* **111**, 2588 (1989).
181. W. Koot, H. Hiemstra and W. N. Speckamp, *J. Org. Chem.* **57**, 1059 (1992).
182. H. Yoda, H. Kitayama, T. Katagiri and K. Takabe, *Tetrahedron* **48**, 3313 (1992).
183. W. Koot, R. von Ginkel, M. Kranenburg, H. Hiemstra, S. Louwrier, M. J. Moolenaar and W. N. Speckamp, *Tetrahedron Lett.* **32**, 401 (1991).
184. T. Ohta, S. Shiokawa, R. Sakamoto and S. Nozoe, *Tetrahedron Lett.* **31**, 7329 (1990).
185. S. Shiokawa, T. Ohta and S. Nozoe, *Chem. Pharm. Bull.* **40**, 1398 (1992).
186. A. R. Chamberlin and J. Y. L. Chung, *J. Am. Chem. Soc.* **105**, 3653 (1983).
187. A. R. Chamberlin and J. Y. L. Chung, *J. Org. Chem.* **50**, 4425 (1985).
188. J. Choi and D. J. Hart, *Tetrahedron* **41**, 3959 (1985).
189. S. Kano, Y. Yuasa, K. Asami and S. Shibuya, *Chem. Lett.*, 735 (1986).
190. S. Kano, Y. Yuasa and S. Shibuya, *Heterocycles* **27**, 253 (1988).
191. J. M. Dener and D. J. Hart, *Tetrahedron* **44**, 7037 (1988).
192. G. E. Keck, E. N. K. Cressman and E. J. Enholm, *J. Org. Chem.* **54**, 4345 (1989).
193. T. Kametani, H. Yukawa and T. Honda, *J. Chem. Soc., Chem. Commun.*, 685 (1988).
194. T. Kametani, H. Yukawa and T. Honda, *J. Chem. Soc., Perkin I Trans.*, 571 (1990).
195. T. Shiba, H. Akiyama, I. Umeda, S. Okada and T. Wakamiya, *Bull. Chem. Soc. Jap.* **55**, 899 (1982).
196. H. Wynberg and E. G. J. Staring, *J. Am. Chem. Soc.* **104**, 166 (1982).
197. E. Hungerbühler, D. Seebach and D. Wasmuth, *Angew. Chem., Int. Ed. Engl.* **18**, 958 (1979).
198. E. J. Corey, A. Marfat and D. J. Hoover, *Tetrahedron Lett.* **22**, 1587 (1981).
199. E. Hungerbühler, D. Seebach and D. Wasmuth, *Helv. Chim. Acta* **64**, 1467 (1981).
200. M. Alpegiani and S. Hanessian, *J. Org. Chem.* **52**, 278 (1987).
201. J. Sterling, E. Slovin and D. Barasch, *Tetrahedron Lett.* **28**, 1685 (1987).
202. T. P. Kogan and T. E. Rawson, *Tetrahedron Lett.* **33**, 7089 (1992).
203. G. Stork, Y. Nakahara, Y. Nakahara and W. J. Greenlee, *J. Am. Chem. Soc.* **100**, 7775 (1978).
204. K. Uchino, Y. Yamagiwa, T. Kamikawa and I. Kubo, *Tetrahedron Lett.* **26**, 1319 (1985).
205. Y. Guindon, C. Yoakim, V. Gorys, W. W. Ogilvie, D. Delorme, J. Renaud, G. Robinson, J. F. Lavellee, A. Slassi, G. Jung, J. Rancourt, K. Durkin and D. Liotta, *J. Org. Chem.* **59**, 1166 (1994).
206. W. G. Whittingham, M. K. Ellis, P. Guerry, G. B. Henderson, B. Muller, D. A. Taylor, F. J. Leeper and A. R. Battersby, *J. Chem. Soc., Chem. Commun.*, 1116 (1989).
207. R. W. Dugger, J. L. Ralbovsky, D. Bryant, J. Commander, S. S. Massett, N. A. Sage and J. R. Selvidio, *Tetrahedron Lett.* **33**, 6763 (1992).
208. C. Schmitz, A. Rouanet-Dreyfuss, M. Tueni and J. Biellmann, *Tetrahedron Lett.* **33**, 4911 (1992).
209. H. Niwa, O. Okamoto, Y. Miyachi, Y. Uosaki and K. Yamada, *J. Org. Chem.* **52**, 2941 (1987).
210. H. Niwa, Y. Miyachi, O. Okamoto, Y. Uosaki and K. Yamada, *Tetrahedron Lett.* **27**, 4605 (1986).
211. H. Niwa, Y. Miyachi, Y. Uosaki, A. Kuroda, H. Ishiwata and K. Yamada, *Tetrahedron Lett.* **27**, 4609 (1986).

212. D. J. Hart and T. Yang, *J. Chem. Soc., Chem. Commun.*, 135 (1983).
213. K. Horita, M. Nagasawa, S. Hachiya and O. Yonemitsu, *Synlett.*, 40 (1994).
214. K. Mori, T. Takigawa and T. Matsuo, *Tetrahedron* **35**, 933 (1979).
215. H. Shieh and G. D. Prestwich, *Tetrahedron Lett.* **23**, 4643 (1982).
216. D. Tanner and P. Somfai, *Tetrahedron Lett.* **29**, 2373 (1988).
217. M. Barth, F. D. Bellamy, P. Renault, S. Samreth and F. Schuber, *Tetrahedron* **46**, 6731 (1990).
218. B. Herradon, *Tetrahedron Asymm.* **2**, 191 (1991).
219. M. Naruse, S. Aoyagi and C. Kibayashi, *J. Org. Chem.* **59**, 1358 (1994).
220. H. A. Barker and A. H. Blair, *Biochem. Prep.* **9**, 21 (1962).
221. S. V. Frye and E. L. Eliel, *Tetrahedron Lett.* **26**, 3907 (1985).
222. Y. Fujimoto, J. S. Yadav and C. J. Sih, *Tetrahedron Lett.* **21**, 2481 (1980).
223. R. Barner and M. Schmid, *Helv. Chim. Acta* **62**, 2384 (1979).
224. P. A. Stadler, A. J. Frey and A. Hofmann, *Helv. Chim. Acta* **46**, 2300 (1963).
225. R. Barner, J. Hubscher, J. J. Daly and P. Schonholzer, *Helv. Chim. Acta* **64**, 915 (1981).
226. S. Yamada, K. Nakayama and H. Takayama, *Tetrahedron Lett.* **22**, 2591 (1981).
227. R. W. Stevens and T. Mukaiyama, *Chem. Lett.*, 1799 (1983).
228. J. K. Whitesell, K. Naboon and D. Deyo, *J. Org. Chem.* **54**, 2258 (1989).
229. T. Akiyama, K. Ishikawa and S. Ozaki, *Synlett.*, 275 (1994).
230. S. Yang, W. Hayden, K. Faber and H. Griengl, *Synthesis*, 365 (1992).
231. D. Seebach, E. Hungerbuhler, R. Naef, P. Schnurrenberger, B. Weidmann and M. Zuger, *Synthesis*, 138 (1982).
232. D. L. C. Green, J. J. Kiddle, and C. M. Thompson, *Tetrahedron* **51**, 2865 (1995).
233. P. Gmeiner and D. Junge, *J. Org. Chem.* **60**, 3910 (1995).
234. S. Leger, J. Omeara, and Z. Wang, *Synlett.*, 829 (1994).
235. A. P. Patron, P. K. Richter, M. J. Tomaszewski, R. A. Miller, and K. C. Nicolaou, *J. Chem. Soc., Chem. Commun.*, 1147 (1994).
236. Y. Yuasa, J. Ando, and S. Shibuya, *J. Chem. Soc., Chem. Commun.*, 455 (1994).
237. D. J. Hart, L. Sun, and A. P. Kozikowski, *Tetrahedron Lett.* **36**, 7787 (1995).
238. T. Fujisawa, A. Shibuya, D. Sato, and M. Shimizu, *Synlett.*, 1067 (1995).
239. A. Pommier, J. Pons, and P. J. Kocienski, *J. Org. Chem.* **60**, 7334 (1995).

4 Tartaric Acid



(*R,R*)



(*S,S*)

Tartaric acid has played a significant role in the development of organic stereochemistry. In 1848, Louis Pasteur, intrigued by the crystal shapes and optical properties of two substances isolated from the tartar deposits in barrels of maturing wine, achieved the first resolution of a racemic tartrate salt [1]. This in turn led to the discovery of enantiomerism. In 1951, Bijvoet, using X-ray diffraction, made the first determination of the absolute configuration of an optically active substance by establishing the spatial arrangement of the atoms in the sodium rubidium salt of (+)-tartaric acid.

Tartaric acid serves as the stereochemical connection between the carbohydrates and glyceraldehyde, and is a chiral butanediol that exists in three forms. L-(+)-Tartaric acid, (2*R*,3*R*)-2,3-dihydroxybutanedioic acid **1** (R=H), is referred to as the “natural” form, and it is widely distributed in nature and classified as a fruit acid. D-(–)-(2*S*,3*S*)-2,3-dihydroxybutanedioic acid **2** (R=H) is often called “unnatural”, although it does occur in nature as well. It has the same absolute configuration as D-glyceraldehyde. A third form, called *meso*-tartaric acid, possess an internal plane of symmetry and is thus inherently racemic and unresolvable. The name tartaric acid is derived from Tartarus, and is probably of medieval and alchemical origin.

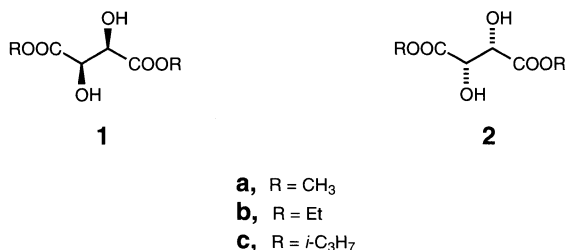
The (*R,R*)- and (*S,S*)-tartaric acids can both be considered as carbohydrates, the “threonic acids”, and they are both inexpensive starting materials for the synthesis of a wide variety of organic molecules. The tartaric acid molecule has a C₂-axis of symmetry, which can be exploited to introduce both possible absolute configurations from a common precursor. Its four functionalized carbon atoms are pairwise homotopic, so that only two types of functional groups are actually present initially. Any transformation in which one of the groups of such a pair reacts, creates a system containing four constitutionally different functional groups. Furthermore, after any “mono- reaction” of this type, the configuration can be inverted such that one of the centers is epimerized and the compound passes from the *threo* to the *erythro* configuration. Seebach and Hungbuhler have prepared an excellent introduction to the chiral utility of the tartaric acids, and this should be consulted for experimental details [2].

In the present chapter we have chosen to be consistent by regarding the chirality of the α -hydroxy-bearing carbon as remaining the same in all the chiral acids discussed. All Fischer projections have been recast into this format. Chiral centers are clearly marked with respect to absolute configuration according to the rules of *R*, *S* nomenclature. Most of the syntheses discussed refer to 2*R*,3*R*-tartaric acid derivatives, but it should be kept in mind that the enantiomers of all chiral structures are accessible as well starting from the 2*S*,3*S*-tartaric acid derivatives and applying exactly the same chemical procedures. This chapter is divided into sections designed to address derivatives of tartaric acid with specific diol protection moieties.

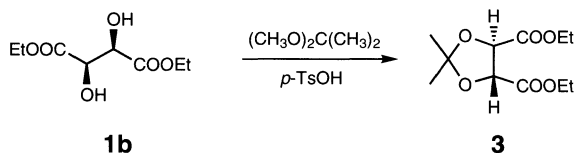
Given the ready availability of these affordable chiral starting materials, the synthetic chemist is in a position to prepare either of the enantiomers of a given chiral target structure. This feature of tartaric acid merits its recognition as a special “vintage” in the wine-cellar of the modern organic chemist.

4.1 2,3-O-Isopropylidene Tartaric Acid Derivatives

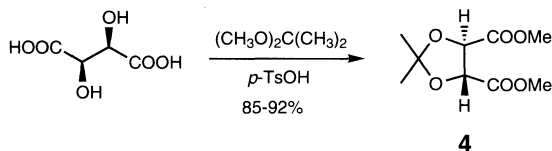
Various diesters (including dimethyl, diethyl, and diisopropyl) of L-(+)-tartaric acid **1a-c** and the corresponding D-(-)-tartaric acid **2a-c**, are commercially available, or can be easily prepared.



Acid-catalyzed reaction of **1b** with acetone and simultaneous azeotropic removal of water provides diethyl (2*R*,3*R*)-2,3-*O*-isopropylidene tartrate **3** in 82–83% yield after distillative purification [3]. However, it has been reported that upon application of this method in petroleum ether as solvent, significant racemate formation was observed [4]. The preferred method for the preparation of **3** involves a transketalization reaction of **1b** with 2,2-dimethoxypropane under acidic catalysis. The yield is nearly quantitative with no loss of optical integrity [5].

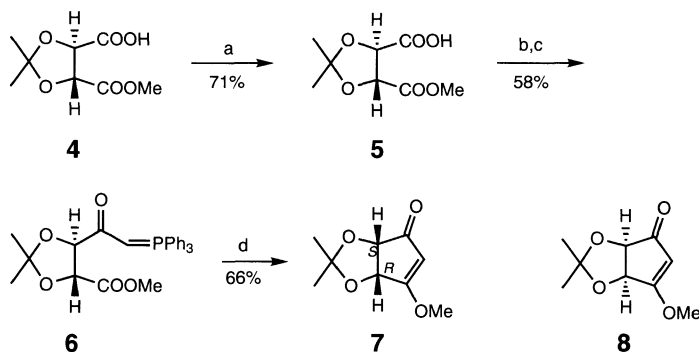


Alternatively, both ketalization and esterification can be accomplished simultaneously. The reaction of 2*R*,3*R*-tartaric acid with 2,2-dimethoxypropane under acidic catalysis provides the corresponding dimethyl ester **4** in 85–92% yield [6].



A salient feature of **4** is its ability to undergo monosaponification to the monoacid **5** in good yield. The presence of free acid and ester groups in the same substrate allows independent functionalization of each chiral carbon. Chiral hydroxylated cyclopentanes are of general interest as building blocks for the synthesis of cyclopentanoid natural products. Conversion of

5 into its methyl trimethylsilyl ester and reaction of this diester with methylenetriphenylphosphorane provides the acyl ylid **6**, which then undergoes epimerization at the C atom bearing the carbonyl ylid group followed by an intramolecular Wittig reaction to afford enantiomerically pure (4*R*,5*S*)-**7**. In this way, 5–10 g of chiral product can be prepared. (2*S*,3*S*)-Tartaric acid provides the corresponding (4*S*,5*R*)-**8** [7] (Scheme 1).

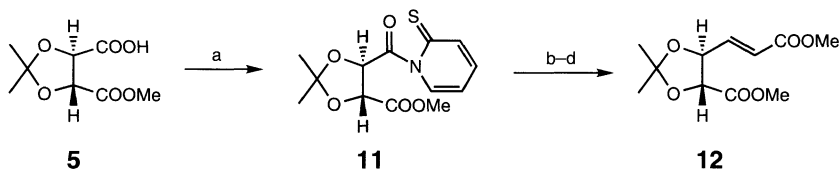


Scheme 1

conditions: (a) KOH, MeOH; (b) EtSH, DCC, DMAP; (c) $\text{Ph}_3\text{P}=\text{CH}_2$; (d) toluene, 110 °C

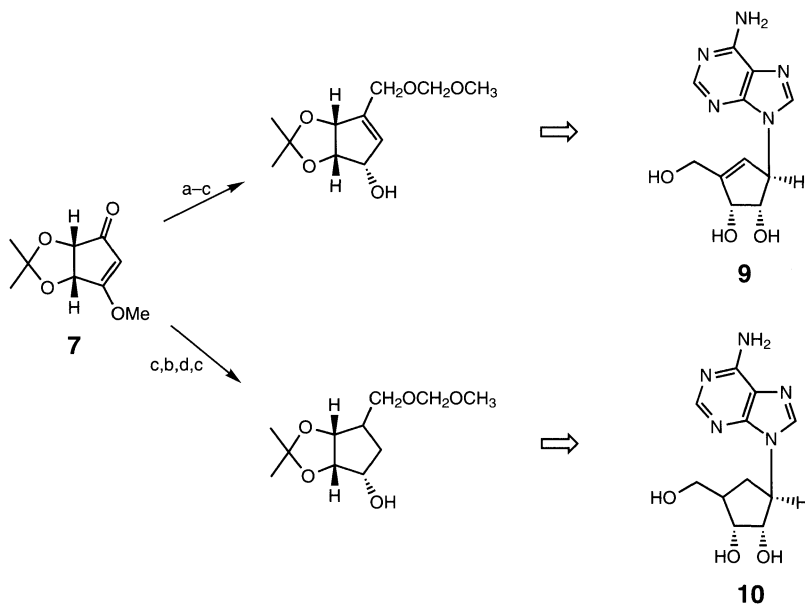
The utility of **7** as a synthetic intermediate is illustrated by its transformation into either (–)-neplanocin A (**9**) [8] or (–)-aristeromycin (**10**) [9], both naturally occurring carbocyclic nucleoside analogs that possess antitumor and antiviral activity. In both cases a highly chemoselective Mitsunobu reaction occurs at the purine N-9 position without need for any protection of the amino group. A recently modified synthesis of **9**, in which a regioselective epoxide ring-opening is followed by an allylic rearrangement to provide the appropriate substrate for the Mitsunobu reaction, is also available [10] (Scheme 2).

Radical decarboxylation of *N*-hydroxy-2-thiopyridone esters in the presence of an olefin results in the formation of a carbon–carbon bond. The monoester **5** is not prone to β -elimination, and the faces of the dioxolane ring are encumbered by the methyl ester, so radical trapping occurs preferentially from the side opposite the methyl ester. This results in overall retention of configuration at the reacting carbon. Irradiation of ester **11** in the presence of methyl acrylate affords the *trans*-alkene **12** after appropriate isolation. Once the first carboxylic acid has been modified, the second can be reacted similarly, whereby the stereochemistry of the first substitution controls the stereochemistry of the second. In this way the resulting product is obtained with overall double retention [11].

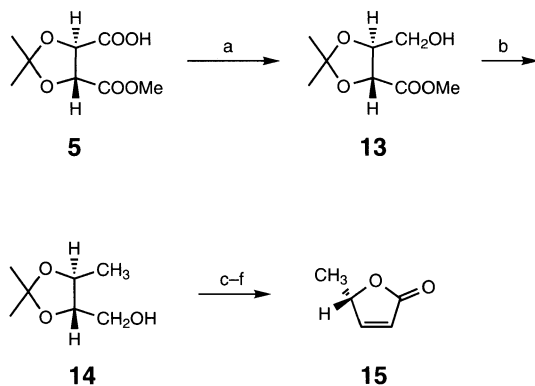


conditions: (a) 2-Thiopyridine, *t*-BuOCCl; (b) methyl acrylate, hv; (c) MCPBA; (d) 110 °C

A synthetically useful feature of **5** is its willingness to undergo monoreduction. Diborane selectively reduces the acid group of **5** to provide the monoalcohol **13**. This alcohol is then converted to a methyl group, which has the chirality found in (*S*)-(+)- β -angelica lactone **15** [12,13] (Scheme 3).

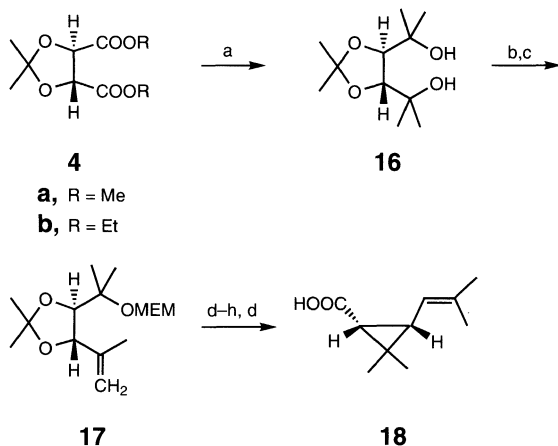
**Scheme 2**

conditions: (a) $\text{LiCH}_2\text{OCH}_2\text{OCH}_3$, -78°C , THF (89%); (b) *p*-TsOH, acetone/ H_2O (91%); (c) $\text{NaBH}_4/\text{CeCl}_3$, MeOH (87%); (d) (2-Thienyl)(MOMOCH₂)CuCNLi₂, THF (89%)

**Scheme 3**

conditions: (a) BH_3 -THF (58%); (b) *p*-TsCl/pyridine then LiAlH_4 , ether (56%); (c) *p*-TsCl/pyridine; (d) NaCN, DMSO (64%); (e) HCl, MeOH (64%); (f) MsCl, Et_3N (94%)

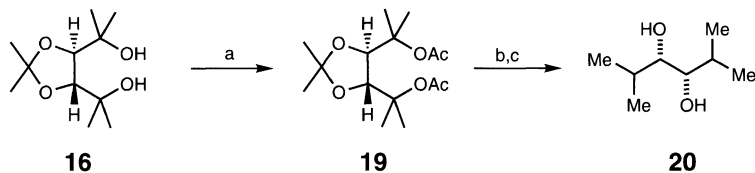
Treating **4a** or **4b** with excess methylmagnesium iodide leads in high yield to the bis-tertiary diol **16**. The inherent C_2 -symmetry of **16** allows for efficient monoprotection of one of the hydroxy groups so that the remaining one can be eliminated to afford olefin **17**. This olefin has been utilized in the preparation of (+)-*cis*-chrysanthemic acid **18**, a pyrethroid with high insecticidal activity [14] (Scheme 4).



Scheme 4

conditions: (a) excess MeMgI (93%); (b) MEMCl, NaH (85%);
 (c) MsCl, Et₃N (88%); (d) Li/NH₃ (71%); (e) *p*-TsNHN=CHCOCl, DMAP, DCM (75%);
 (f) Cu(acac)₂, dioxane (59%); (g) Ac₂O, AcOH, H₂SO₄ then NaOMe, MeOH (64%);
 (h) MsCl, Et₃N DMAP (74%)

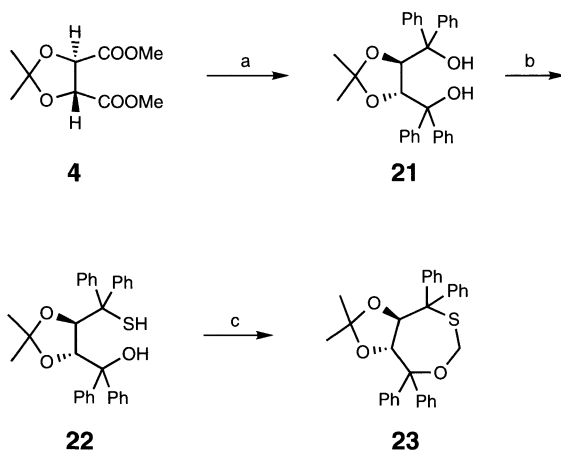
Treatment of the diol **16** with excess trimethylsilyl chloride in acetic anhydride, an efficient acetylating agent, provides the diacetate **19** in nearly quantitative yield. This undergoes efficient pyrolysis on a large scale to generate, after subsequent reduction and hydrolysis, (3*S*,4*S*)-2,5-dimethylhexane-3,4-diol (**20**) [(*S*)-DIPED] [15].



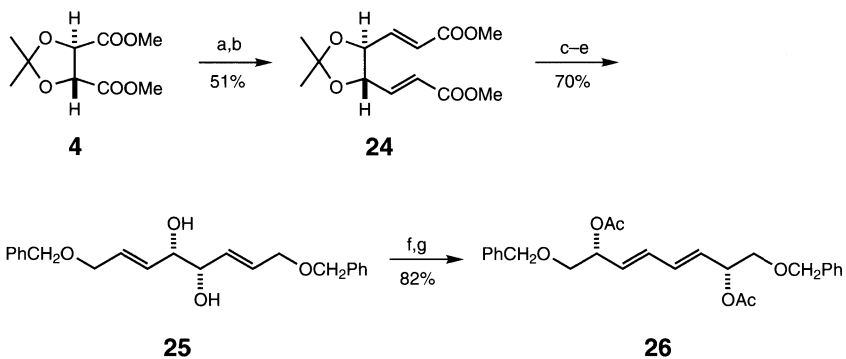
conditions: (a) TMSCl, Ac₂O, 85 °C (100%); (b) 450–470 °C (85%);
 (c) Rh/Al₂O₃, EtOH then 2N HCl (89%)

When **4** is treated with excess phenylmagnesium bromide, good to excellent yields of *trans*-4,5-bis(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxacyclopentane (**21**) are produced. This has been used as an effective optical resolution agent for bicyclic enones [16], and for the preparation of the hydroxythiol **22**, which was transformed into the 1,3-oxathiepane **23** [17] (Scheme 5).

Partial reduction of the two ester groups in **4** with diisobutylaluminum hydride in toluene–hexane at –78 °C provides *in situ* a dialuminatate which, as an aldehyde equivalent, reacts under Wittig–Horner conditions to provide good yields of the diolefin **24**. Subsequent conversion of **24** to (4*R*,5*R*)-1,8-(bisbenzyloxy)-2(*E*),6(*E*)-octadien-4,5-diol (**25**) provides the essential framework for a palladium(II)-catalyzed [3,3]-sigmatropic rearrangement to (2*S*,7*S*)-2,7-(bisacetoxyl)-1,8-(bisbenzyloxy)-3(*E*),5(*E*)-octadiene (**26**) (Scheme 6). The original chirality is completely translated into the dissymmetric 3,5-octadiene framework, which has C₂ chirality [18].

**Scheme 5**

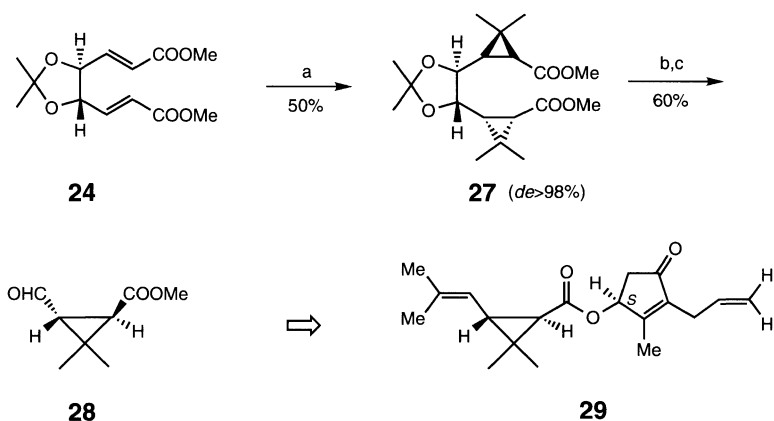
conditions: (a) excess PhMgBr, THF (90%); (b) Lawesson's reagent, toluene, r.t. (30%);
(c) NaH, CH₂Br₂ (100%)

**Scheme 6**

conditions: (a) DIBAL, toluene–hexane, –78 °C; (b) (*i*-PrO)₂P(O)CH₂COOEt, NaH;
(c) DIBAL, THF, –78 ° to 0 °C; (d) PhCH₂Br, NaH, DMF; (e) 2N HCl, MeOH;
(f) Ac₂O, DMAP, DCM; (g) PdCl₂(CH₃CN)₂, THF

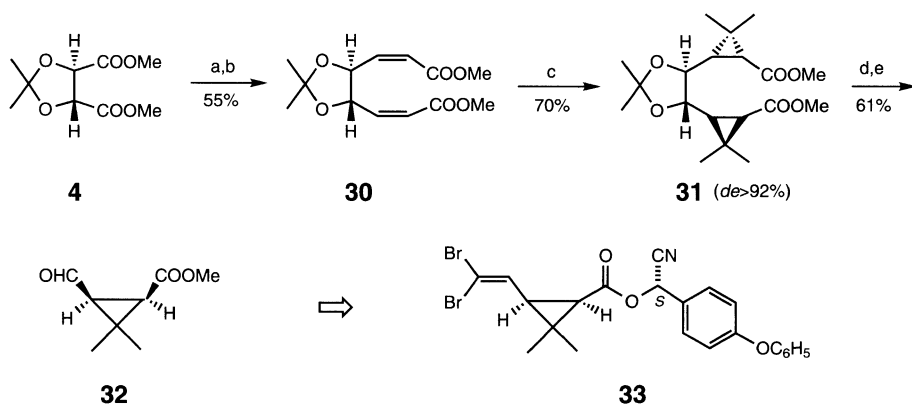
Cyclopropanation of **24** with isopropylidetriphenylphosphorane and subsequent isolation of the predominant isomer provides **27**, which is oxidatively converted to aldehyde **28**, the substrate required for preparation of the biologically active insecticide (*S*)-bioallethrin (**29**) [19,20] (Scheme 7).

In contrast to the Wittig–Horner method, which provides almost exclusively *E*-olefins, Wittig reaction of a suitably stabilized ylid in methanol as solvent with the *in situ* aluminate obtained from DIBAL reduction of **4** provides, after purification and separation of the diastereomers, a 55% yield of **30** with the *Z,Z*-configuration. Subsequent cyclopropanation and oxidative workup leads to aldehyde **32**, which has been used to prepare the biologically active insecticide (*S*)-deltamethrin (**33**) [20] (Scheme 8).



Scheme 7

conditions: (a) $\text{Ph}_3\text{P}=\text{C}(\text{Me})_2$; (b) HClO_4 , THF; (c) NaIO_4 , MeOH, pH=7.2



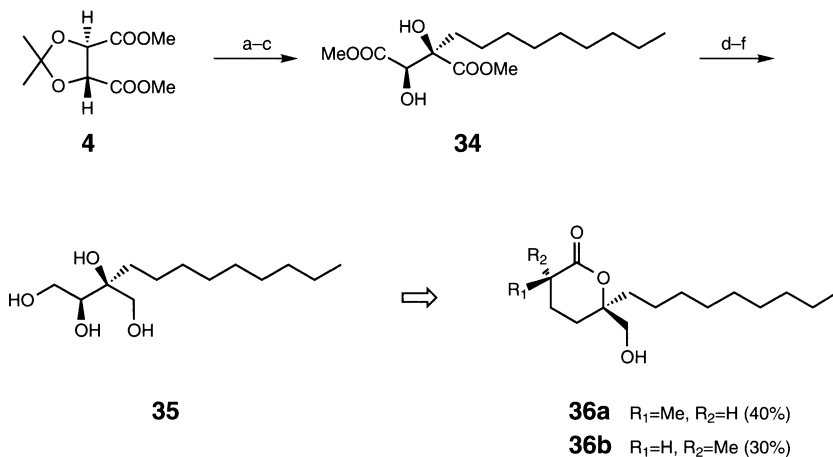
Scheme 8

conditions: (a) DIBAL, toluene-hexane, $-78\text{ }^\circ\text{C}$; (b) $\text{Ph}_3\text{P}=\text{CHCOOMe}$, MeOH; (c) $\text{Ph}_3\text{P}=\text{C}(\text{Me})_2$; (d) HClO_4 , THF; (e) NaIO_4 , MeOH, pH=7.2

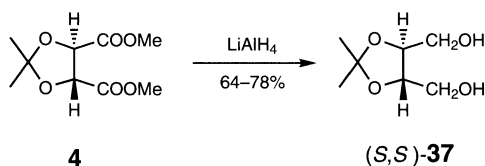
The lithium enolate of **4a** undergoes alkylation with highly reactive electrophiles to provide pentasubstituted *trans/cis* dioxolanes in yields ranging from 40–80%. The stability of the enolate toward allylations and benzylations (but not *n*-alkylations) can be rationalized as due to the rigid acetone skeleton, which holds the enolate π -system and the C–O σ bond perpendicular to each other to prevent β -elimination [21]. The enolate has been utilized in the synthesis of (+)-malyngolide (**36a**) and (–)-epimalyngolide (**36b**), the chiral antipodes of natural (–)-malyngolide and (+)-epimalyngolide [22] (Scheme 9).

The complete reduction of both ester groups in either **4a** or **4b** can be accomplished with lithium aluminum hydride in either diethyl ether or tetrahydrofuran as solvent. Moderate to good yields of 2,3-*O*-isopropylidene-L-threitol (**37**) can be obtained [3,5,6].

When **37** is treated with an excess of methanesulfonyl chloride in pyridine, the 1,4-bis-mesylate **38** is obtained in 86% yield. Acid-catalyzed hydrolysis of **38** proceeds in 90% yield

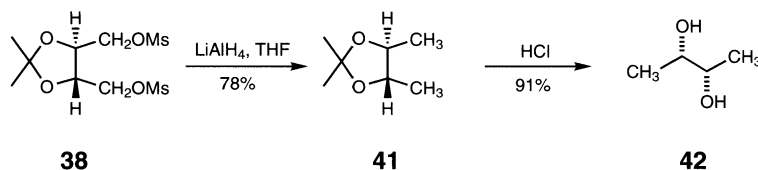
**Scheme 9**

conditions: (a) $CH_3(CH_2)_5CH=CHCH_2Br$, LDA, $-78^\circ C$ (37%); (b) H_2 , Pd/C (90%); (c) $AcOH-H_2O$ (78%); (d) $MsCl$, pyridine (89%); (e) $LiEt_3BH_4$, THF; (f) $NaOH, H_2O_2, H_2O$ (98% for 2 steps)

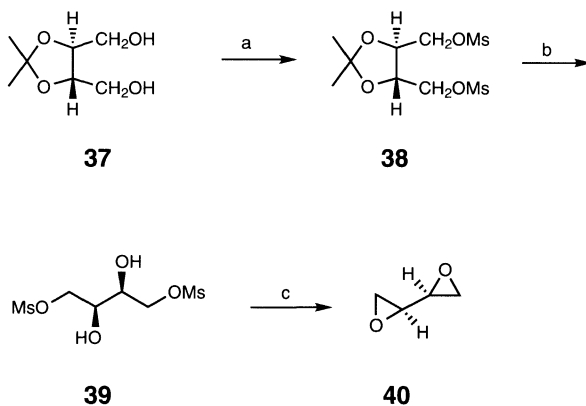


to afford the 1,4-bismethanesulfonate **39**. Treating **39** with potassium hydroxide produces (2*S*,3*S*)-1,2:3,4-diepoxybutane (**40**) in 75% yield [3] (Scheme 10).

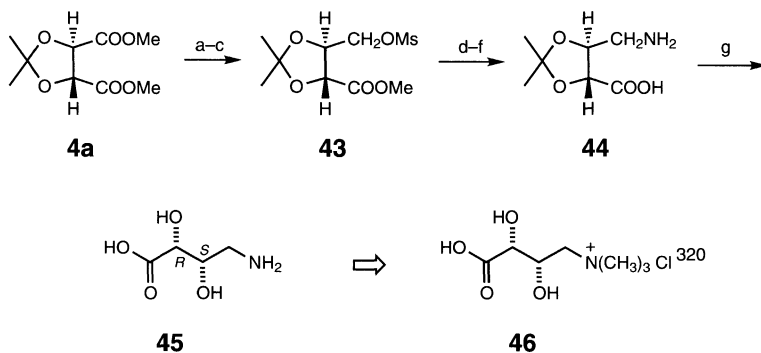
Nucleophilic reduction of **38** with lithium aluminum hydride in tetrahydrofuran provides in 78% yield (2*S*,3*S*)-2,3-*O*-isopropylidenebutanediol (**41**), which after deprotection with mild acid affords (2*S*,3*S*)-(+)-2,3-butanediol (**42**) in 91% yield [23].



The partial hydrolysis of **4a** with methanolic potassium hydroxide followed by selective carboxylic acid reduction with excess borane and treatment of the resulting monoalcohol with methanesulfonyl chloride affords methyl 4-*O*-methanesulfonyl-2,3-*O*-isopropylidene-*L*-threonate (**43**). Facile displacement of the mesylate with azide followed by ester hydrolysis and catalytic reduction to an amine provides 4-amino-4-deoxy-2,3-*O*-isopropylidene-*L*-threonic acid (**44**). Mild acidic deprotection and ion-exchange desalting of **44** yields (2*R*,3*S*)-4-amino-4-deoxy-*L*-threonic acid (**45**), which has been utilized for the preparation of anthopleurine **46**, the alarm pheromone of the sea anemone *Anthopleura elegantissima* [4] (Scheme 11).

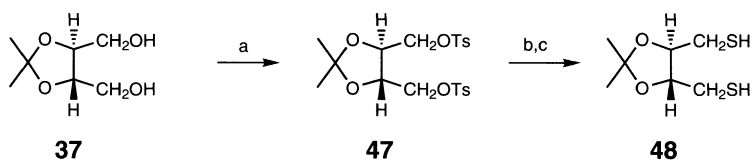
**Scheme 10**

conditions: (a) MsCl, pyridine (86%); (b) HCl, EtOH (90%); (c) KOH, H₂O

**Scheme 11**

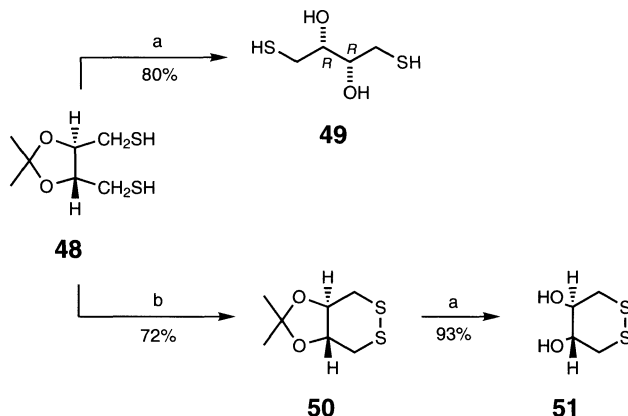
conditions: (a) KOH, MeOH (58%); (b) BH₃-THF (44%); (c) MsCl, Et₃N, DCM (94%);
 (d) NaN₃, DMF, 100 °C (87%); (e) KOH, MeOH (94%); (f) H₂, Pd/C, MeOH (91%);
 (g) 0.1 M HCl (82%)

The bis-tosylate **47** is commonly preferred in synthetic sequences over the bis-mesyate **38**. Treating **37** with excess *p*-toluenesulfonyl chloride in pyridine affords excellent yield of (2*S*,3*S*)-1,4-bis-tosyl-2,3-*O*-isopropylidene-*L*-threitol (**47**) [24]. Nucleophilic displacement of the tosyl groups with potassium thiolacetate followed by deacetylation provides (2*S*,3*S*)-1,4-dithio-2,3-*O*-isopropylidene-*L*-threitol (**48**).



conditions: (a) *p*-TsCl, pyridine (90%); (b) MeCOSK, EtOH (97%); (c) NaOMe, MeOH (100%)

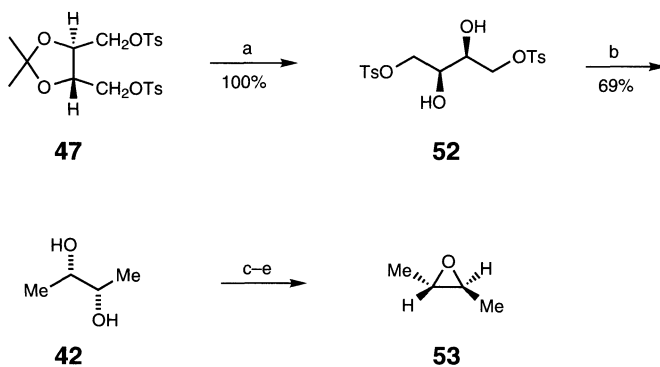
Mild acidic deprotection of **48** leads in good yield to (2*R*,3*R*)-1,4-dithio-L-threitol **49**. Alternatively, **48** can be oxidized with oxygen to **50** which, following deprotection, provides (4*R*,5*R*)-(+)-4,5-dihydroxy-1,2-dithiane (**51**) [5] (Scheme 12).



Scheme 12

conditions: (a) 0.1 N HCl, MeOH; (b) O₂, KOH, MeOH

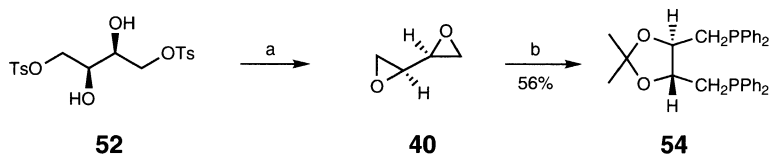
The bis-tosylate functionality in **47** is stable to mild acidic deketalization. The resulting (2*S*,3*S*)-1,4-di-*O*-tosyl-L-threitol (**52**), when reduced with lithium aluminum hydride, provides **42**, which has been converted in three steps to *trans*-(2*S*,3*S*)-epoxybutane (**53**) in an overall yield of 49% from **47** [25] (Scheme 13).



Scheme 13

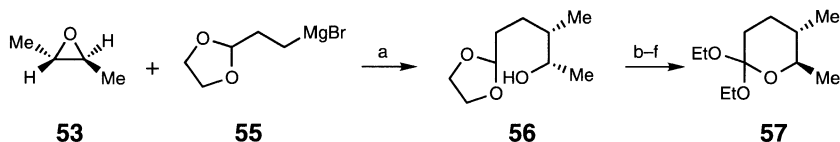
conditions: (a) *p*-TsOH, EtOH-H₂O; (b) LiAlH₄, Et₂O; (c) C₆H₅CHO, *p*-TsOH (96%); (d) CCl₄, NBS (94%); (e) NaOH, diethylene glycol (79%)

(2*S*,3*S*)-1,4-Di-*O*-tosyl-L-threitol (**52**), like the corresponding dimesylate **39**, forms the bisepoxide **40** when treated with pulverized potassium hydroxide. Treating **40** with lithium diphenylphosphine followed by ketalization provides (2*R*,3*R*)-(-)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (**54**) [(-)-DIOP] in a yield of 56% from **40** [26].



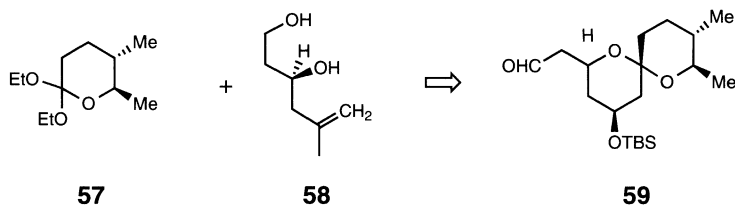
conditions: (a) KOH; (b) LiPPh₂ then Me₂C(OMe)₂

Nucleophilic ring-opening of epoxide **53** with Grignard reagent **55** in the presence of cuprous iodide affords **56**. A Mitsunobu inversion of the free hydroxy group followed by lactonization and conversion to an *ortho*-lactone provides **57**.



conditions: (a) CuI, THF (82%); (b) *p*-NO₂C₆H₄COOH, DEAD, PPh₃, toluene (71%);
 (c) KOH, MeOH (88%); (d) HC-H₂O, THF (90%); (e) Br₂, NaOAc, AcOH, H₂O (72%);
 (f) Et₃OBF₄, DCM then NaOEt, EtOH (71%)

Reaction of **57** with (*S*)-malic acid-derived **58** yields the spiroacetal **59**, which is a key fragment utilized in the total synthesis of (+)-milbemycin β₃ (See Chapter 3, Scheme 82) [27].

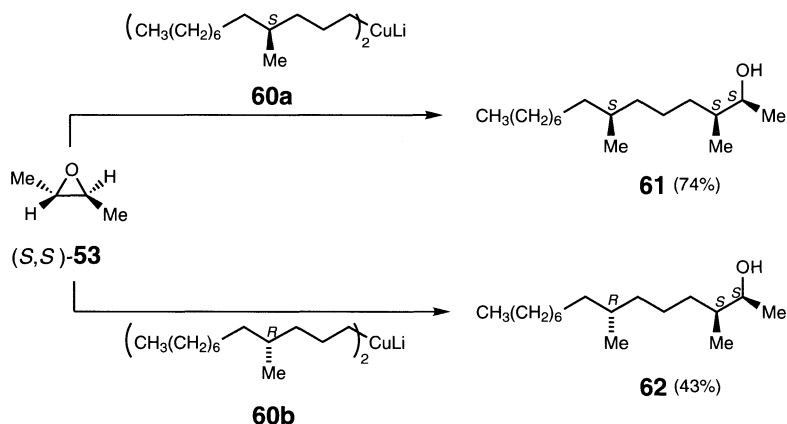


The pine sawfly *Neodiprion sertifer* (Geoffrey, *Diprionidae*) is a pest on Scots pine in the northern parts of Europe, Asia, and North America. The acetate of the female sex pheromone diprionol (**61**) strongly attracts males of several *Neodiprion* species, whereas the propionate is preferred by the genus *Diprion*. Two synthetic approaches, both taking advantage of the high optical purity and *erythro* geometry provided by (2*S*,3*S*)-**53** or (2*R*,3*R*)-**53**, are available for the synthesis of the diastereomeric diprionols required for development of an effective chemical control of this pest.

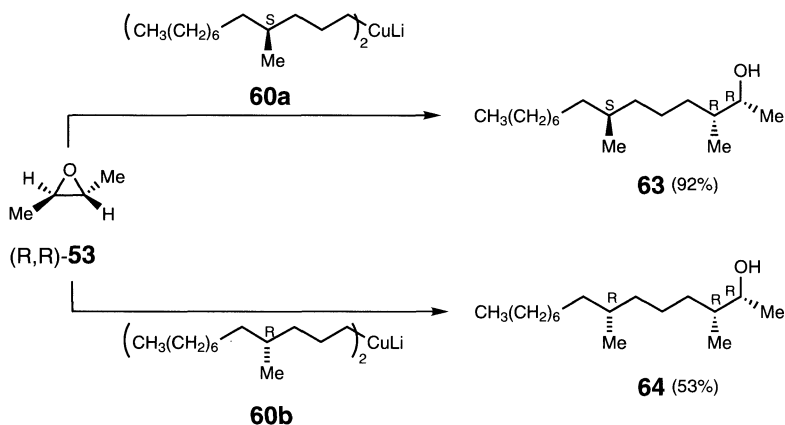
Stereospecific S_N2 oxirane ring-opening of (*S,S*)-**53** with either (*R*)- or (*S*)-cuprates **60a** or **60b**, respectively, provides **61** and **62**, two of the four possible diastereomers of 2,3-*erythro*-3,7-dimethylpentadecan-2-ol (Scheme 14).

The remaining two diastereomers, **63** and **64**, can be similarly obtained from (*R,R*)-**53** (Scheme 15). While either **60a** or **60b** can be prepared from (*R*)-(+)-citronellol, the optical purity of the C-7 methyl group in the final products is uncertain [28].

Pheromone activity is often very selective for one particular stereoisomer over another. Slight contamination by other stereoisomers may have serious consequences with respect to



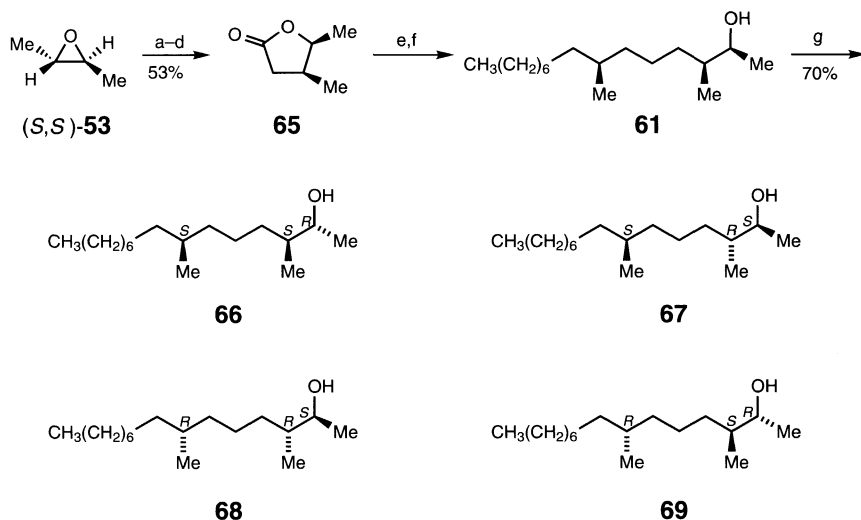
Scheme 14



Scheme 15

the ability of the synthetic material to act as a sex-attractant. The synthesis of all four *erythro*-isomers **61**–**64** and all four *threo*-isomers **66**–**69** is achieved effectively and with high optical purity utilizing stereospecific transformations of intermediates prepared from (*S,S*)- and (*R,R*)-**53**. (*3S,4S*)-*cis*- γ -Butyrolactone (**65**), prepared in an overall yield of 53% with 99% optical purity from **53**, is reacted with (*S*)-1-lithio-2-methyldecane in diethyl ether, and then subjected to Huang–Minlon reduction with hydrazine to furnish (*2S,3S,7S*)-*erythro*-**61** in 72% yield. A Mitsunobu reaction of the hydroxy group of **61** proceeds with complete inversion to provide (*2R,3S,7S*)-*threo*-**66** in 70% yield. A similar set of reactions utilizing (*R*)-1-lithio-2-methyldecane and (*S,S*)-**53** provides **68**. When (*R,R*)-**53** is employed, both **67** and **69** are obtained (Scheme 16). Chemical purities for all stereoisomers are 99% as determined by capillary gas chromatography [29,30].

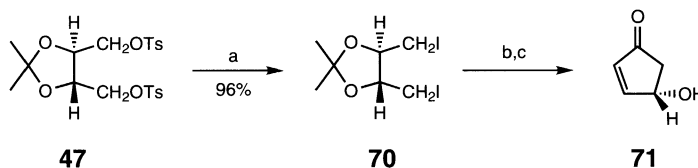
The tosylate groups of **47** readily undergo double nucleophilic displacement with a variety of nucleophiles. Reaction of **47** with sodium iodide in acetone provides (*2S,3S*)-1,4-diiodo-2,3-*O*-isopropylidene-*L*-threitol (**70**) [24]. This is converted in two steps to (*S*)-4-hydroxy-2-



Scheme 16

conditions: (a) $\text{CH}_2(\text{COOMe})_2$, Na, MeOH; (b) KOH, H_2O ; (c) HCl; (d) pyridine, reflux; (e) (*S*)-1-lithio-2-methyldecane, Et_2O , -80°C (53%); (f) N_2H_4 , KOH (76%); (g) $\text{C}_6\text{H}_5\text{COOH}$, DEAD, Ph_3P then hydrolysis

cyclopentenone (**71**), which is 86% optically pure. A similar series of reactions starting from D-tartaric acid provides the corresponding *R* enantiomer with an optical purity of 85% [31].

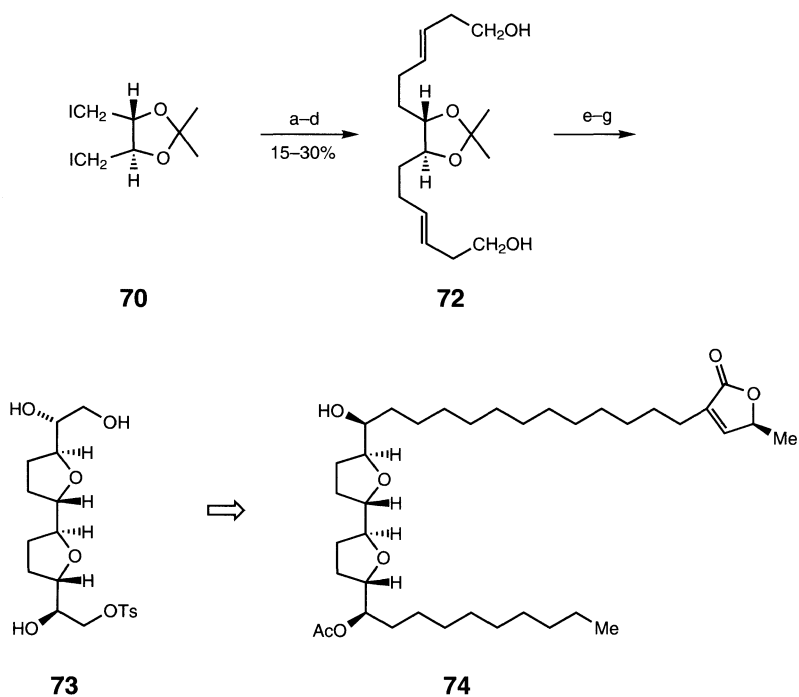


conditions: (a) NaI, acetone; (b) $\text{MeSCH}_2\text{SO}_2\text{Me}$, *n*-BuLi; (c) H_2SO_4

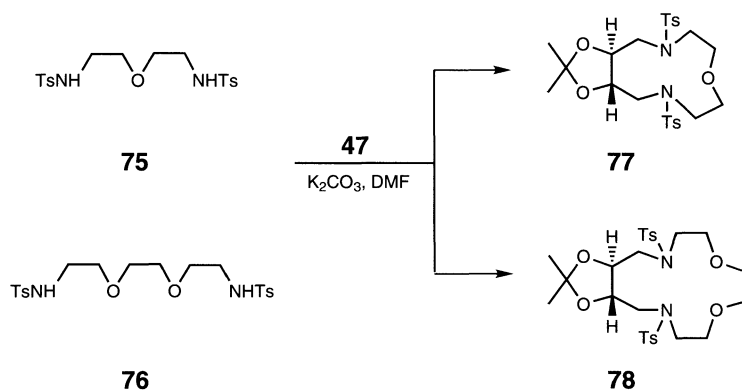
The bis(tetrahydrofuranyl) *Annonaceous* acetogenin (+)-(15,16,19,20,23,24)-hexepta-ricin (**74**), has been synthesized utilizing a polyepoxide cascade reaction. The diiodide **70** is transformed into the bis-allylic alcohol **72**, which is subsequently converted to a C_2 -symmetric diepoxide utilizing the Sharpless asymmetric epoxidation reaction. Selective monotosylation of the primary hydroxyl groups served to desymmetrize the system. An acid-catalyzed deketalization followed by simultaneous epoxide opening affords the *erythro/trans/threo/trans/erythro*-configuration present in the tosylate **73**. Transformation of **73** to the desired **74** completes the synthesis [32] (Scheme 17).

The reaction of **47** with linked nucleophiles, such as **75** or **76**, provides an opportunity to prepare chiral diazocoronands **77** and **78** [33] (Scheme 18).

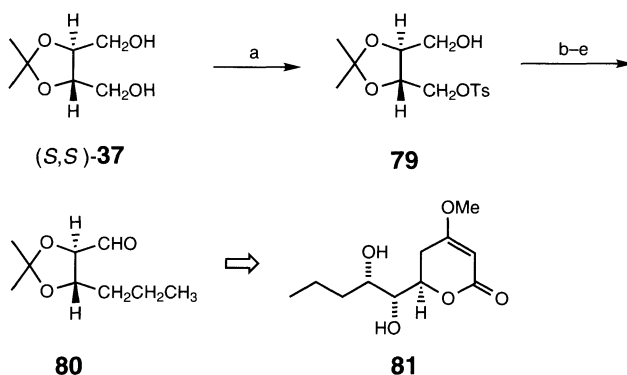
Due to the inherent C_2 -symmetry of **37**, monotosylation occurs in good yield to provide (*2S,3S*)-1-*O*-tosyl-2,3-*O*-isopropylidene-*L*-threitol (**79**). Subsequent protection of the free hydroxyl group, displacement of the tosyl group with lithium diethylcuprate, deprotection,

**Scheme 17**

conditions: (a) *tert*-Butyl acetoacetate, NaH then *n*-BuLi; (b) NaBH₄, MeOH; (c) MsCl, Et₃N then DBU; (d) DIBAL, Et₂O; (e) Sharpless epoxidation, D(-)-DIPT; (f) *p*-TsCl, pyridine; (g) Amberlyst-15, MeOH

**Scheme 18**

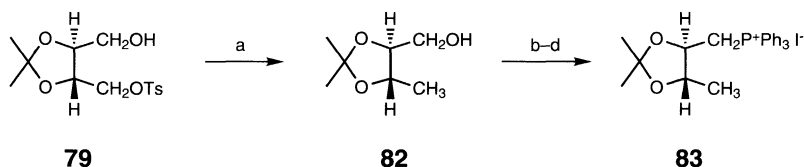
and oxidation of the resulting alcohol provides the somewhat unstable aldehyde **80**. This is converted through a series of chemical transformations to (+)-LLP-880 β (**81**), which is useful for the synthesis of the *Pestalotia cryptomeriaecola* fungal metabolites [34] (Scheme 19).



Scheme 19

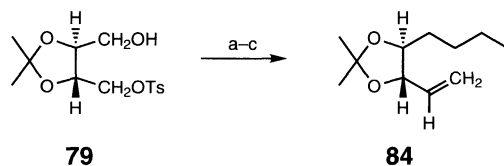
conditions: (a) *p*-TsCl, pyridine (61–75%); (b) $\text{CH}_2=\text{C}(\text{OMe})_2$, POCl_3 (100%);
 (c) $(\text{Et})_2\text{CuLi}$ (55%); (d) AcOH, Et_2O (94%); (e) NCS, Me_2S (40%)

The monotosylate **79** can be reduced to the monoalcohol **82** in good yield with sodium borohydride in acetonitrile. In three steps, **82** is converted to $(4R,5S)$ -(5-methyl-2,2-dimethyl-1,3-dioxolane-4-ylmethyl)phosphonium iodide (**83**). Wittig condensation of **83** with aldehydes proceeds at low temperatures and in good yields, but lacks stereoselectivity [35].



conditions: (a) NaBH_4 , CH_3CN (69%); (b) MsCl , Et_3N (96%); (c) NaI , acetone (45%);
 (d) Ph_3P , CH_3CN (58%)

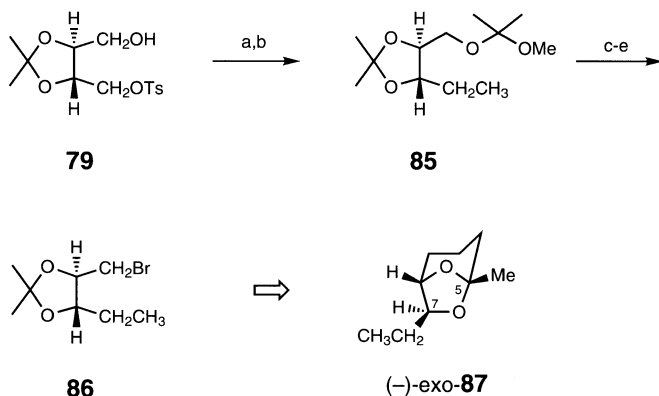
The ability of the tosylate functionality in **79** to undergo facile nucleophilic substitution with alkyl cuprates has been exploited as a way of preparing the chiral acetonide **84**, which has been used to establish the stereochemistry of products obtained from the reaction of aldehydes with chiral γ -(tetrahydropyranyloxy)allylstannanes [36].



conditions: (a) $(n\text{-C}_3\text{H}_7)_2\text{CuLi}$; (b) $(\text{COCl})_2$, DMSO, Et_3N , DCM;
 (c) $\text{Ph}_3\text{PCH}_2\text{Br}$, *n*-BuLi

Brevicomins, first identified by Silverstein [37] have been recognized as aggregation pheromones for the western pine bark beetles, *Dendroctonus brevicomis* Le Conte. $(1S,7S)$ -(-)-*exo*-Brevicomins (**87**) is prepared in high optical purity starting from **79** by selectively

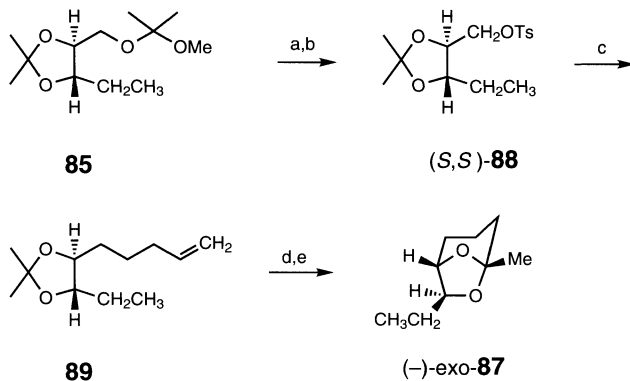
exploiting in turn each of the hydroxyl functionalities derived from carboxyl groups in the parent (+)-tartaric acid. The free alcohol in **79** is protected and the tosylate displaced with lithium dimethylcuprate to provide **85**. Subsequent deprotection and conversion to bromide **86** affords the appropriate chiral substrate for final transformation to (-)-*exo*-brevicomine (**87**) [38] (Scheme 20).



Scheme 20

conditions: (a) $\text{CH}_2=\text{C}(\text{OMe})_2$, POCl_3 , hexanes (100%); (b) LiCuMe_2 , Et_2O (74%); (c) AcOH , Et_2O (91%); (d) *p*- TsCl , pyridine (84%); (e) LiBr , acetone (96%)

A more direct approach to the synthesis of **87** involves first displacing the tosylate in **88** with 3-butenylmagnesium bromide under copper catalysis to afford **89**. Acid hydrolysis followed by Wacker oxidation provides (-)-**87** in an overall yield of 36.5% from **88** (Scheme 21).



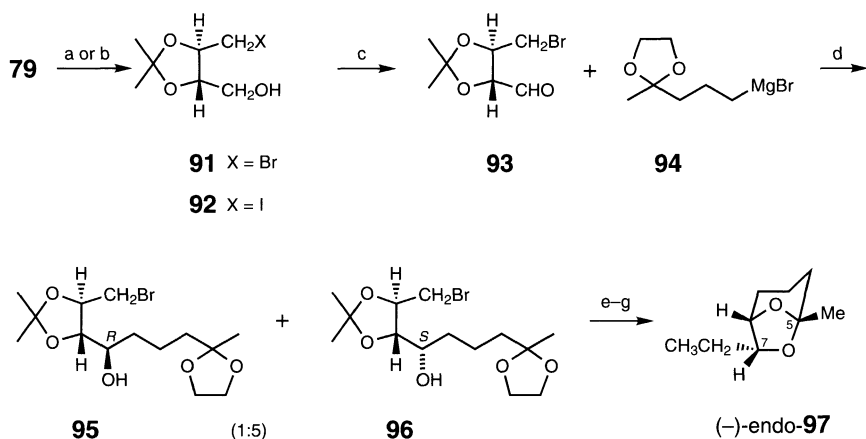
Scheme 21

conditions: (a) AcOH , Et_2O (91%); (b) *p*- TsCl , pyridine (84%); (c) $\text{CH}_2=\text{CHCH}_2\text{CH}_2\text{MgBr}$, CuBr (62%); (d) AcOH (92%); (e) $\text{PdCl}_2\text{-CuCl}_2$, DMF (67%)

A similar set of reactions starting with (4*R*,5*R*)-**88** provides (1*R*,5*S*,7*R*)-(+)-*exo*-brevicomine (**90**) in an overall yield of 37% from (4*R*,5*R*)-**88** [39].



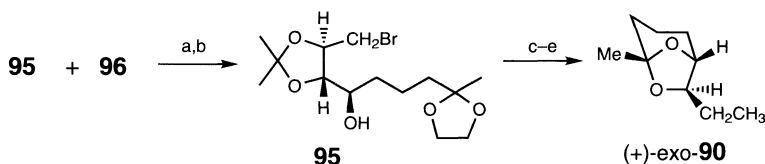
Nucleophilic displacement of the tosylate in **79** with either lithium bromide in acetone to provide [(4*S*,5*R*)-5-bromomethyl-2,2-dimethyl-1,3-dioxolan-4-yl]methanol (**91**) [34] or with sodium iodide in acetone to afford the corresponding (4*S*,5*R*)-5-iodomethyl analog **92** [40] proceeds in excellent yield. Swern oxidation of alcohol **91** and treatment of the resulting aldehyde **93** with Grignard reagent **94** at $-60\text{ }^{\circ}\text{C}$ provides a 1 : 5 mixture of the epimeric alcohols (*R*)-**95** and (*S*)-**96**. The major isomer, (*S*)-**96**, obtained pure by chromatography, undergoes bromine elimination with sodium amalgam. Subsequent catalytic hydrogenation of the resulting olefin and perchloric acid deketalization (with concomitant cyclization) furnishes (–)-*endo*-brevicomine (**97**) (Scheme 22).



Scheme 22

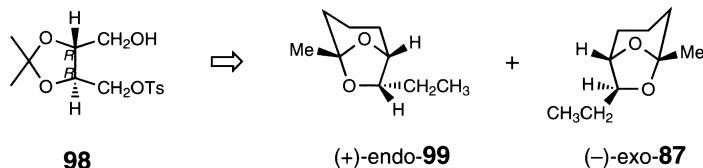
conditions: (a) LiBr, acetone (90%); (b) NaI, acetone (80%); (c) (COCl)₂, DMSO, Et₃N, DCM (96%); (d) Et₂O, $-60\text{ }^{\circ}\text{C}$; (e) Na–Hg, THF–EtOH (71%); (f) H₂, Pd/CaCO₃ (77%); (g) HClO₄, aqueous acetone (91%)

Chromium trioxide oxidation of the epimeric mixture **95** and **96** followed by highly selective reduction of the resulting ketone with K-Selectride in THF provides a 98 : 2 ratio of **95** : **96**. Chromatographic purification provides (*R*)-**95** in 75% yield. This is similarly converted to (+)-*exo*-brevicomine (**90**).

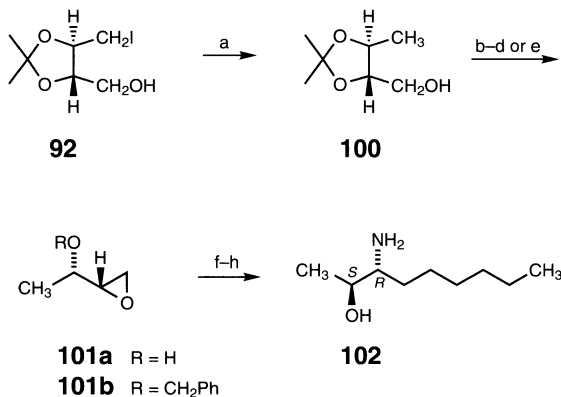


conditions: (a) CrO₃, pyridine; (b) K-Selectride, THF, $-78\text{ }^{\circ}\text{C}$ (75%); (c) Na–Hg, THF–EtOH (71%); (d) H₂, Pd/CaCO₃ (77%); (e) HClO₄, aqueous acetone (91%)

If these reactions are performed with (4*R*,5*R*)-**98**, the enantiomer of **79**, both (+)-*endo*-brevicommin (**99**) and (-)-*exo*-brevicommin (**87**) can be obtained [41].



Catalytic reductive dehalogenation of **92** with palladium on charcoal affords the alcohol **100**. Tosylation, hydrolysis of the isopropylidene group, and epoxide formation with a cold solution of sodium methoxide provides the volatile epoxide **101a**. However, (1*S*)-(2*S*-benzyloxyethyl)oxirane (**101b**) can be prepared directly by treating **100** with two equivalents of sodium hydride followed by immediate benzyl bromide quench. Epoxide-ring opening with lithium di(*n*-pentyl)cuprate, followed by conversion to the azide and catalytic reduction, affords (2*S*)-hydroxy-(3*R*)-nonylamine (**102**) [40] (Scheme 23).

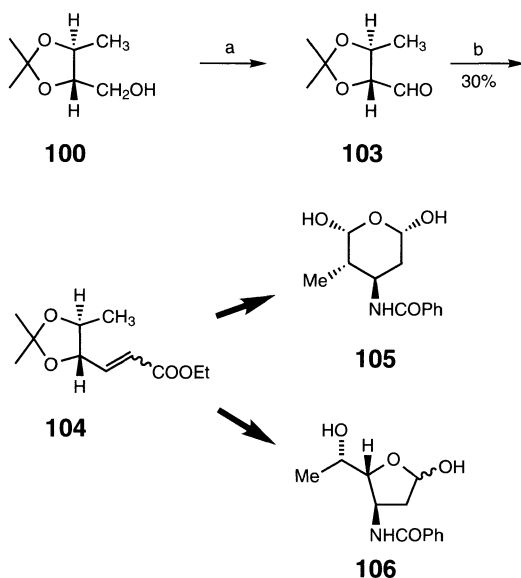


Scheme 23

conditions: (a) 10% Pd/C, EtOH (100%); (b) *p*-TsCl, pyridine; (c) AcOH, H₂O; (d) NaOMe, Et₂O, 0 °C (100%); (e) 2 eq. NaH, PhCH₂Br, DMF; (f) (*n*-C₅H₁₁)₂CuLi, Et₂O; (g) Ph₃P, DEAD, HN₃ (2 eq.); (h) PtO₂, H₂, EtOH

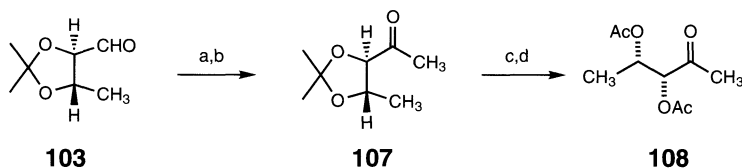
Oxidation of alcohol **100** to aldehyde **103** with PCC followed by treatment of the unpurified aldehyde with (carboethoxyethylidene)triphenylphosphorane affords a poor yield of a mixture of diastereomeric olefins **104** together with substantial amounts of unreacted **100**. This may suggest that PCC oxidation is not the preferred method for optimal oxidation of **100** to **103**. Nevertheless, the diastereomeric mixture **104** has been exploited in the synthesis of *N*-benzoyl-2,3,6-trideoxy-3-amino-*L*-xylo-hexapyranose (**105**) [42]. In three steps, **105** is converted to *N*-benzoyl-*L*-ristosamine (**106**), the aminodeoxy sugar component of the antibiotic ristomycin [43] (Scheme 24).

When aldehyde **103** is reacted with methylmagnesium bromide followed by a Swern oxidation of the resulting alcohol, the ketone **107** is obtained. Subsequent deketalization and treatment with acetic anhydride in pyridine affords (2*R*,3*S*)-**108**, which has been used to determine the absolute configuration of a portion of pumiliotoxin B [44].



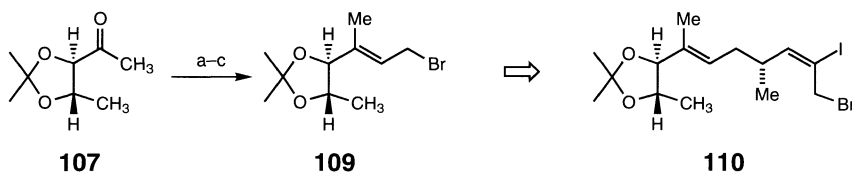
Scheme 24

conditions: (a) PCC, NaOAc, DCM; (b) $\text{Ph}_3\text{P}=\text{CHCOOEt}$



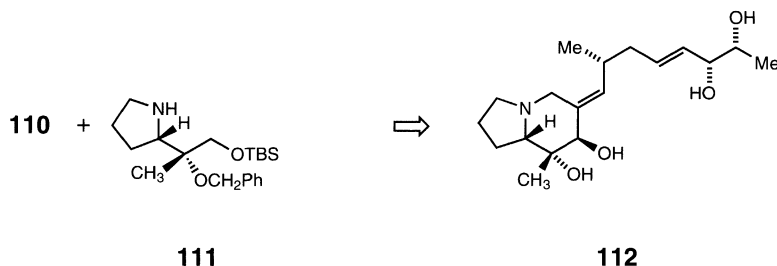
conditions: (a) MeMgBr ; (b) $(\text{COCl})_2$, DMSO, Et_3N , DCM; (c) HCl , MeOH; (d) Ac_2O , pyridine

A novel approach has been developed towards the total synthesis of (+)-allopumiliotoxin 339A (**112**), a minor constituent of skin extracts from the family of Panamanian poison frogs *Dendrobates auratus*, based on an intramolecular chromium(II)-mediated cyclization. Ketone **107**, after a Horner–Emmons condensation, DIBAL reduction, and conversion to the bromide **109**, is homologated based on Evans' alkylation procedure [45] and transformed through a series of efficient reactions into the iodoolefin **110**.

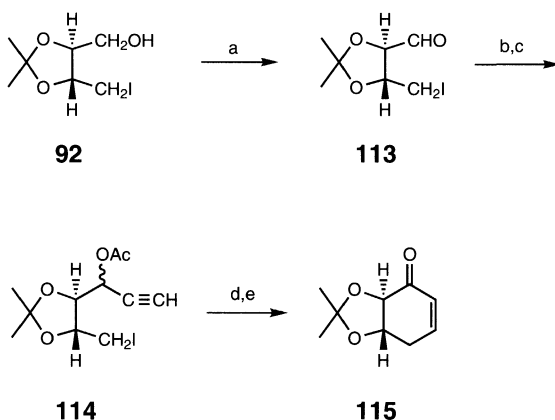


conditions: (a) $(i\text{-PrO})_2\text{P}(\text{O})\text{CH}_2\text{COOEt}$, NaH, C_6H_6 ; (b) DIBAL, DCM–hexanes, -78°C ; (c) CBr_4 , PPh_3 , DCM

Coupling of **110** with the chiral pyrrolidine fragment **111** followed by a chromium(II)-mediated cyclization occurs with complete stereocontrol and good yield. Final clean-up of protecting groups affords **112** in a satisfying overall yield of 71% from the coupling step [46].



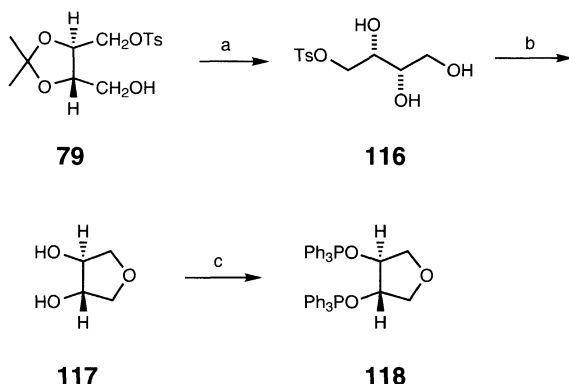
Swern oxidation of **92** provides the iodoaldehyde **113**, which undergoes ethynylmagnesium bromide addition followed by acetylation with acetic anhydride to afford an inseparable mixture of acetates **114** (*anti/syn* = 63/37) in good overall yield. Tributyltin hydride and AIBN-mediated free radical 6-*endo-dig* cyclization of **114**, chromatographic separation of the resulting mixture, and subsequent chemical conversion of the diastereomeric alcohols to cyclohexanone **115** establishes (despite the low diastereomeric excess obtained in forming **114**) the possibility of transforming the corresponding cyclized isomers into a highly functionalized chiral material, which makes this a useful method for preparing chiral intermediates for the synthesis of various cyclitols and other interesting natural products [47] (Scheme 25).



Scheme 25

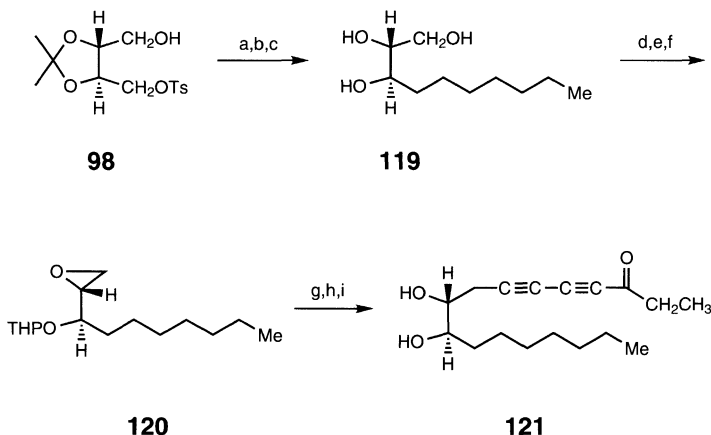
conditions: (a) $(\text{COC})_2$, DMSO, Et_3N , DCM (79%); (b) ethynylMgBr (84%); (c) Ac_2O (90%); (d) $n\text{-Bu}_3\text{SnH}$, AIBN; (e) PDC

Trifluoroacetic acid hydrolysis of the isopropylidene protecting group in **79** without loss of the tosyl group provides (2*S*,3*S*)-1-*O*-tosyl-L-threitol (**116**), which can be cyclized with basic resin to afford (2*S*,3*S*)-1,4-anhydro-L-threitol (**117**) in good overall yield. Treating **117** with triphenylphosphine in pyridine affords the chiral diphosphinite diphin (**118**), which has been utilized as a ligand in asymmetric hydrogenation, hydrocyanation, and hydroformylation reactions [48] (Scheme 26).

**Scheme 26**

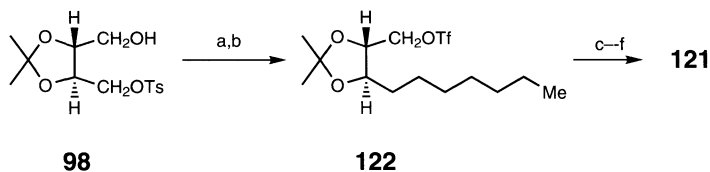
conditions: (a) CF_3COOH ; (b) Amberlite IR45-basic; (c) PPh_3 , pyridine (70%)

Panaxcol (**121**), a cytotoxic polyacetylene isolated from the callus of *Panax ginseng*, has the $9R$, $10R$ absolute configuration at the C-9 and C-10 hydroxyl-bearing carbons. Synthesis of **121** from D -(-)-diethyl tartrate (**2b**) confirmed this *threo* geometry. Treatment of (R,R)-**98** with dihexyllithiumcuprate followed by acidic deketalization affords triol **119** in 66% yield. Subsequent monotosylation, base-catalyzed cyclization, and THP protection of the free hydroxy group provides the epoxide **120**. Nucleophilic ring-opening of the epoxide with the anion of 1,3-heptadiyne-5-ol, deprotection, and Swern oxidation of the diastereomeric C-3 alcohols affords optically pure **121** [49,50] (Scheme 27).

**Scheme 27**

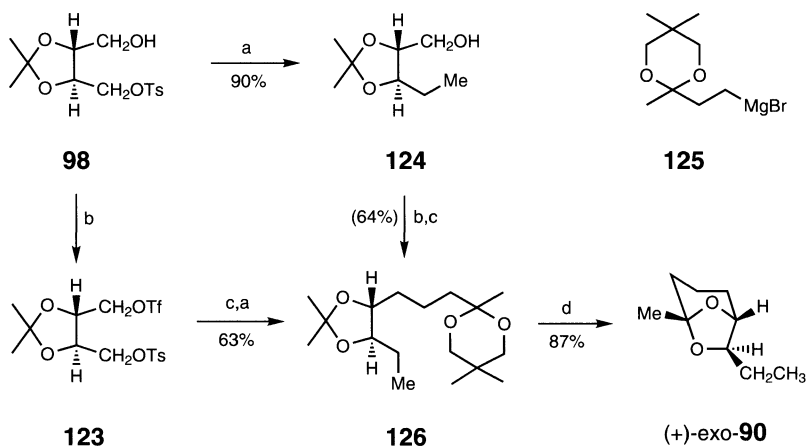
conditions: (a) DHP, C SA, DCM (93%); (b) $(n\text{-C}_6\text{H}_{13})_2\text{CuLi}$, Et_2O ; (c) 2N HCl, MeOH (88%); (d) *p*-TsCl, pyridine (44%); (e) K_2CO_3 , MeOH (76%); (f) DHP, CSA (90%); (g) 1,3-heptadiyne-5-ol, *n*-BuLi; (h) HCl, MeOH (65%); (i) Swern [O]

A concise total synthesis of **121**, accomplished in six steps with an overall yield of 33%, employs an efficient nucleophilic displacement on triflate **122** by the anion of *O*-silyl-protected 1,3-heptadien-5-ol, followed by a Swern oxidation to **121** with high optical purity [51].



conditions: (a) (*n*-C₆H₁₃)₂CuLi, THF, Me₂S (81%); (b) Tf₂O, Et₃N, DCM
 (c) 5-O-TBS-1,3-heptadiyne, *n*-BuLi; (d) *n*-Bu₄NF, THF;
 (e) (COCl)₂, DMSO, Et₃N, DCM; (f) 2N HCl, MeOH

The enhanced leaving ability of the triflate group over the tosylate group, both of which are present in the chiral intermediate **123**, provides the possibility for differentiation between the two hydroxyl functions with respect to nucleophiles. Thus, a first alkylation with copper(I)-catalyzed Grignard reagents replaces the triflate; thereafter, addition of an organocuprate leads to a second alkylation on the tosylate function. The synthesis of (+)-*exo*-brevicomin (**90**), a key component of the aggregation pheromone of the western pine beetle, is achieved either in a sequential manner starting from (4*R*,5*R*)-**98**, or alternatively in a one-pot procedure from tosyltriflate **123** [52,53] (Scheme 28).

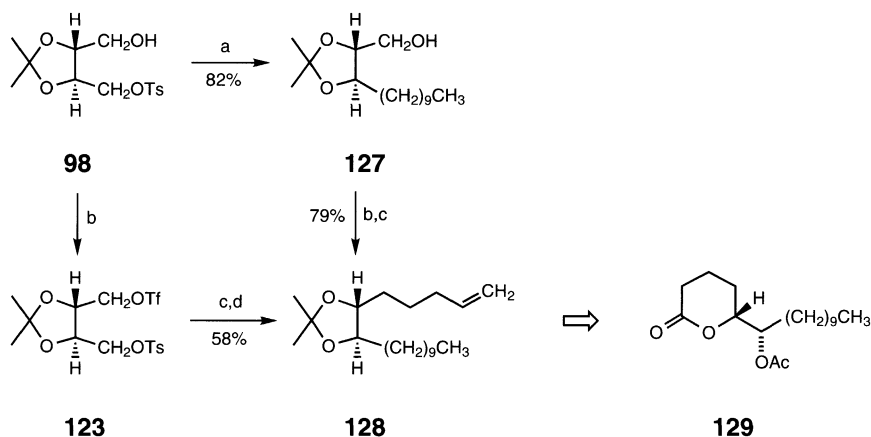


Scheme 28

conditions: (a) Me₂CuLi, ether; (b) Tf₂O, Et₃N; (c) **125**, CuBr; (d) *p*-TsOH, DCM

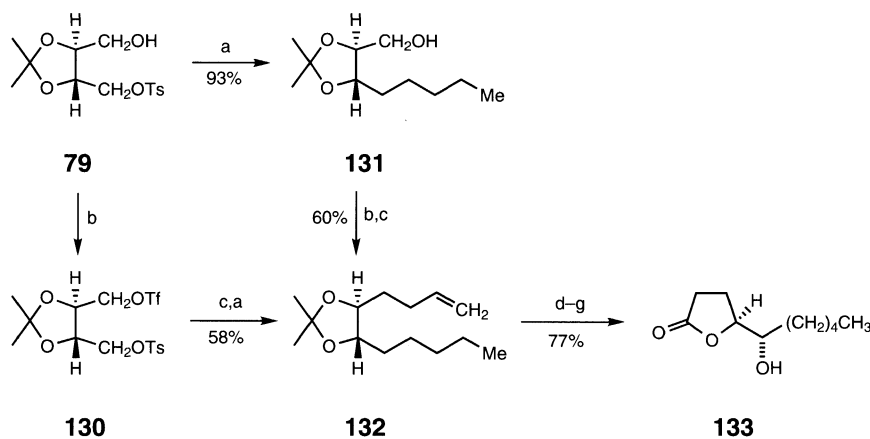
This successful strategy has also been applied to the synthesis of (5*R*,6*S*)-(–)-6-acetoxy-5-hexadecanolide (**129**), the major component of the oviposition-attractant pheromone from apical droplets of eggs of the mosquito *Culex pipiens fatigans*. The opportunity, starting from (*R,R*)-**98**, to carry out this synthesis either sequentially (in which the tosylate of **98** is displaced to provide **127**, which is then converted to a triflate and displaced with a second Grignard reagent) or in a one-pot reaction utilizing **123**, reveals the unique value of these leaving groups [53] (Scheme 29).

L-factor (**133**), isolated from *Streptomyces griseus*, is a biologically inactive γ -lactone whose synthesis from (*S,S*)-**79** is again realized either through sequential displacement of the tosyl and triflate groups or in a one-pot manner, this time utilizing **130** [53] (Scheme 30).



Scheme 29

conditions: (a) $n\text{-C}_9\text{H}_{19}\text{MgBr}$, CuBr; (b) TiF_2O , Et_3N ; (c) 4-butenylMgBr, CuBr; (d) $(n\text{-C}_9\text{H}_{19})_2\text{CuLi}$



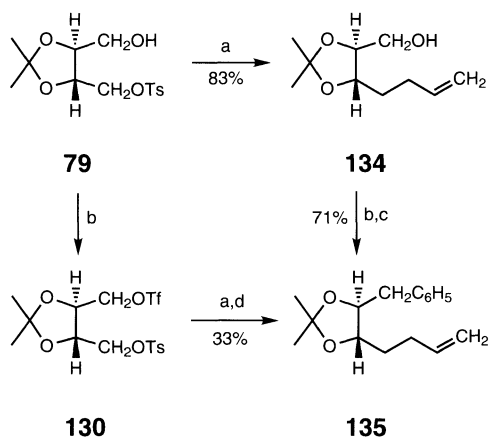
Scheme 30

conditions: (a) $(n\text{-C}_4\text{H}_9)_2\text{CuLi}$; (b) TiF_2O , Et_3N ; (c) allylMgBr, CuBr; (d) O_3 , MeOH, $-78\text{ }^\circ\text{C}$; (e) Me_2S ; (f) AgNO_3 , KOH; (g) $\text{HCl-H}_2\text{O}$, reflux

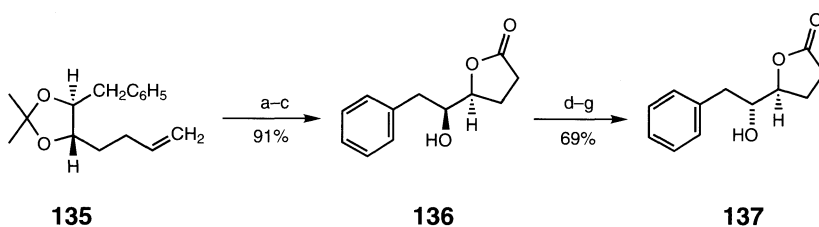
Synthesis of the lateral root-inducing compounds **136** and **137**, isolated from the bacterium *Erwinia quercina*, is another example of efficient carbon-carbon bond homologation by way of triflate and/or tosylate nucleophilic displacements.

Conveniently prepared **135**, derived from either (S,S) -**79** or **130**, is converted in three steps to **136**, which is then inverted at the free hydroxy position in four steps to provide **137** [54].

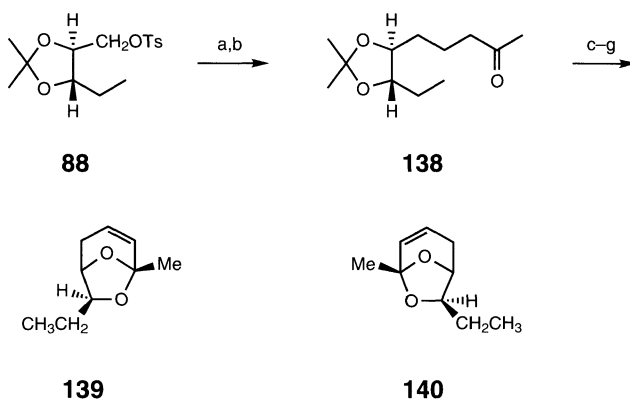
One enantiomer of a volatile pheromone isolated from urine of the male mouse of the species *Mus musculus* has been synthesized from (R,R) -tartaric acid via acetone **88**. Grignard addition and subsequent Wacker oxidation of the resulting olefin provides ketone **138**. This is converted in four steps to $(1S,5R,7S)$ -*exo*-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]oct-3-ene (**139**). Similarly, $(1R,5S,7R)$ -*exo*-**140** is prepared from (S,S) -tartaric acid. The enantiomeric purity of both enantiomers corresponds to 100% *ee* [55] (Scheme 32).

**Scheme 31**

conditions: (a) allylMgBr, CuBr; (b) Tf₂O, Et₃N; (c) C₆H₅MgBr, CuBr;
(d) Ph₂CuLi

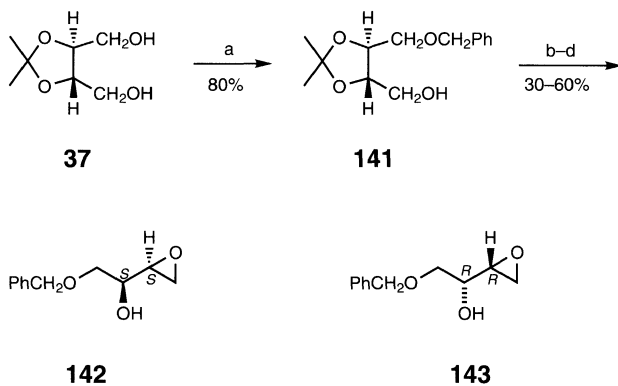


conditions: (a) OsO₄, NaIO₄; (b) AgNO₃, KOH; (c) HCl, H₂O; (d) MsCl, Et₃N;
(e) CsOAc, 18-Crown-6; (f) NaOMe, MeOH; (g) HCl

**Scheme 32**

conditions: (a) HomoallylMgBr, CuBr (62%); (b) PdCl₂-CuCl₂, DMF, NaHCO₃ (84%);
(c) TMSCl, Et₃N, DMF; (d) PhSeCl, pyridine, DCM; (e) SiO₂ chromatography;
(f) *p*-TsOH, Et₂O, H₂O; (g) MCPBA, DCM

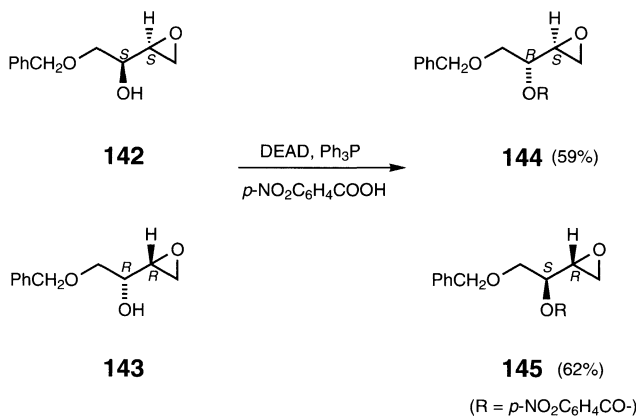
The C_2 -symmetry of **37** is an attractive feature that permits monoprotection of the hydroxy groups, providing **141** in reasonably good yield. This methodology is easily applied to both small- and large-scale reactions. The benzyl protecting group in **141** is preferred because of the mild conditions available for its removal in the presence of relatively sensitive functional groups. A versatile synthetic intermediate easily prepared from **37** is (2*S*,3*S*)-1-*O*-benzyl-3,4-epoxy-2-butanol (**142**). The (2*R*,3*R*)-enantiomer **143** is similarly prepared from D-(-)-tartaric acid. Both are distillable liquids that can be stored in the refrigerator [56,57] (Scheme 33).



Scheme 33

conditions: (a) PhCH₂Br, NaH, DMF; (b) *p*-TsCl, pyridine (97%); (c) 2N HCl (81%);
(d) Ba(OH)₂

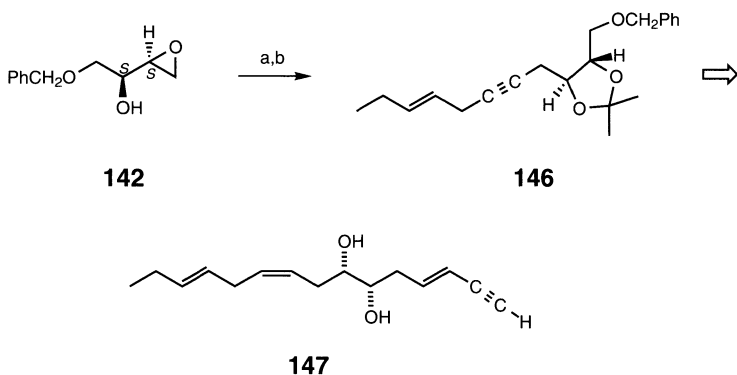
Mitsunobu inversion of (2*S*,3*S*)-**142** in the presence of *p*-nitrobenzoic acid generates (2*R*,3*S*)-**144** in 59% yield. Similarly, (2*R*,3*R*)-**143** is converted to (2*S*,3*R*)-**145** in 62% yield. The *p*-nitrobenzoic acid serves both to stabilize the epoxides and convert them into recrystallizable solids [57] (Scheme 34).



Scheme 34

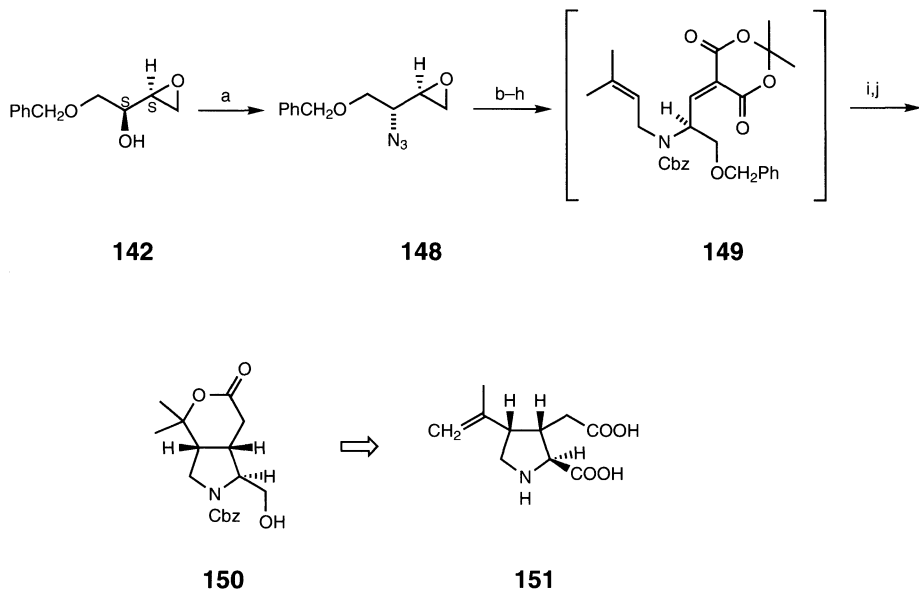
Marine red algae of the genus *Laurencia* provides metabolites that are halogenated cyclic ethers containing enyne or allene side chains. (6*S*,7*S*)-*trans*-Laurediol (**147**), proposed as a biosynthetic precursor of these metabolites, is prepared from **142**. Treatment of **142** with lithium acetylide followed by elongation with (*E*)-2-pentenyl bromide affords undecenyne **146**. A series of functional group manipulations provides **147**. An interesting feature of this synthesis is that Lindlar reduction of **146** with deuterium gas allows introduction of deuterium labelling at the C-9, C-10 olefin positions [58] (Scheme 35).

The anthelmintic, insecticidal, and neuroexcitatory activities of (–)-kainic acid (**151**), isolated from the marine alga *Digenea simplex*, has prompted a variety of synthetic strategies.



Scheme 35

conditions: (a) Lithium acetylide–EDA complex, DMSO, 80 °C (78%); (b) Me₂C(OMe)₂, PPTS (98%)

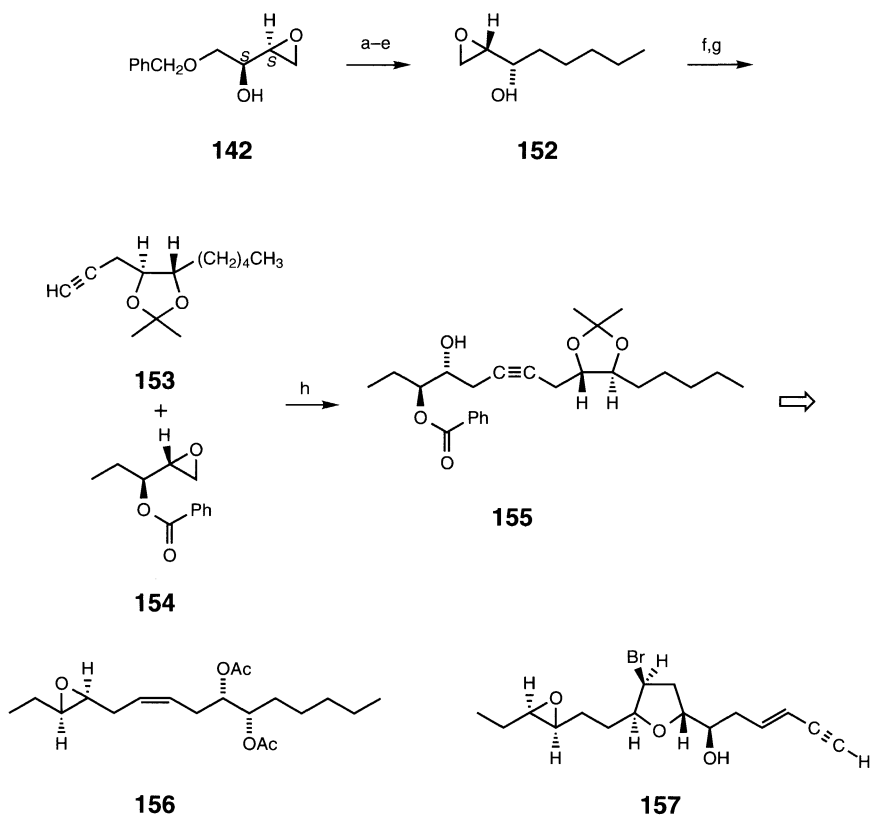


Scheme 36

conditions: (a) (PhO)₂P(O)N₃, DIAD, Ph₃P (61%); (b) acetone, BF₃•Et₂O (81%); (c) LiAlH₄, THF (100%); (d) Cbz–Cl, Et₃N (95%); (e) prenyl chloride, NaH, DMF (92%); (f) 10% HCl, MeOH; (g) NaIO₄, MeOH; (h) Meldrum's acid; (i) dioxane–H₂O; (j) BBr₃, DCM (74%)

One such strategy exploits **142** for construction of the heterodiene **149**, derived from azide **148**, in which the stereochemistry of the intramolecular Diels–Alder cycloadducts is controlled by the configuration of the dienophile olefin. Treatment of **142** with diphenylphosphoryl azide in the presence of diisopropyl azodicarboxylate and triphenylphosphine affords the epoxy azide **148** with inversion of chirality. This is then converted in six steps to the heterodiene intermediate **149**, which undergoes an intramolecular cycloaddition to furnish a single adduct that is subsequently converted to **150**. Transformation of **150** into **151** in seven steps completes the synthesis [59] (Scheme 36).

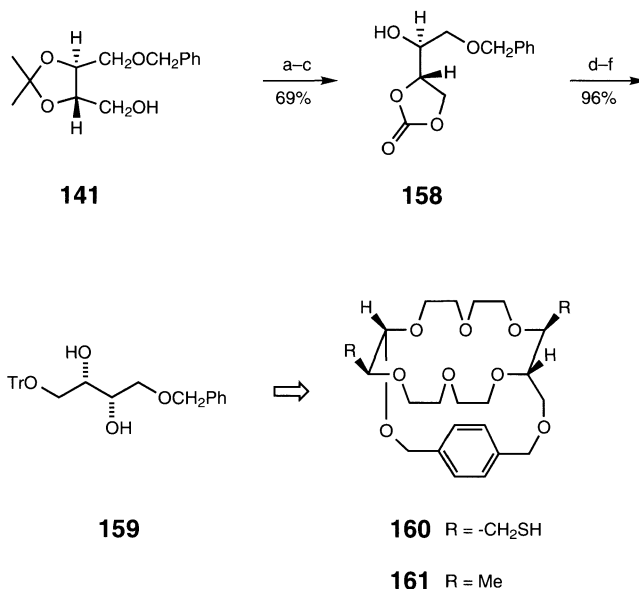
The absolute stereochemistry of the C-12 and C-13 oxirane moiety of laureoxolane (**157**), a colorless unstable bromoether obtained from extracts of *Laurencia nipponica*, was determined on the basis of a chiral synthesis of **156**, a degradative derivative of **157**. The C-5 to C-8 unit with two asymmetric centers at C-6 and C-7 of **157** corresponds to (2*S*,3*S*)-1-benzyloxy-3,4-epoxy-2-butanol (**142**). Elongation of **142** using butyllithium and copper cyanide followed by the creation of a new epoxide provides **152**. Lithium acetylide ethylenediamine complex addition to **152** and subsequent ketalization affords the acetylenic acetonide **153**, which is coupled with (2*R*,3*S*)-1,2-epoxy-3-benzoyloxypentane (**154**) to furnish **155**. Subsequent five-step transformation of **155** provides **156** [60] (Scheme 37).



Scheme 37

conditions: (a) *n*-BuLi–CuCN, THF–45 °C (100%); (b) Me₂C(OMe)₂, PPTS, DCM (79%); (c) Li–NH₃, –78 °C (91%); (d) MsCl, Et₃N, DCM (100%); (e) 2*N* HCl, MeOH then Ba(OH)₂ (80%); (f) Lithium acetylide–EDA, DMSO (83%); (g) Me₂C(OMe)₂, PPTS, DCM (79%); (h) *n*-BuLi, BF₃–Et₂O, –78 °C (51%)

The novel crown thiol **160**, with a *p*-xylenedioxy bridge structure, undergoes intracomplex thiolysis with α -amino acid esters more rapidly than the corresponding structure without a bridge structure, possibly due to increased stability of the **160**-amino acid ester complex during the reaction. The cyclic orthoester **158**, prepared in three steps from **141**, is transformed in three steps to **159**, which is then converted in nine additional steps to **160**. This sequence of reactions can also be used to prepare **161** [61] (Scheme 38).



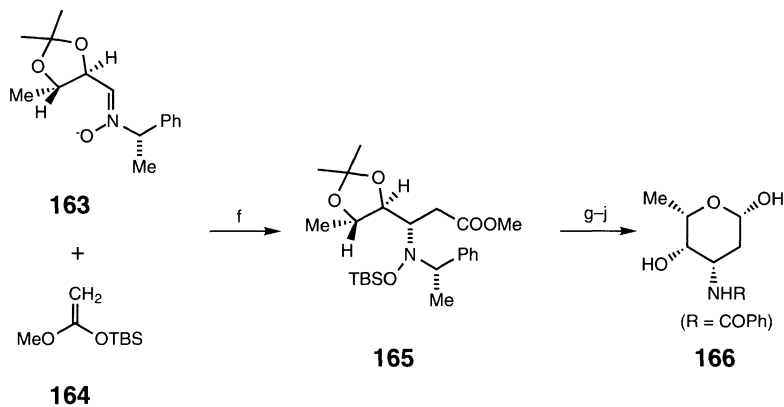
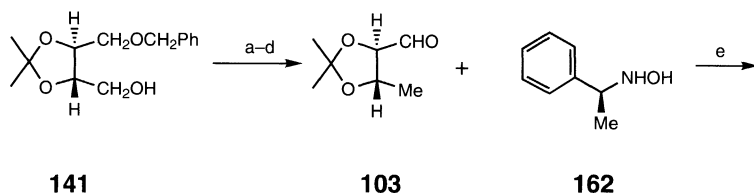
Scheme 38

conditions: (a) PhOCOCl, DCM, pyridine (100%); (b) 4N HCl, THF; (c) K₂CO₃, THF; (d) DHP, PPTS, DCM; (e) 1N NaOH, MeOH; (f) TrCl, pyridine

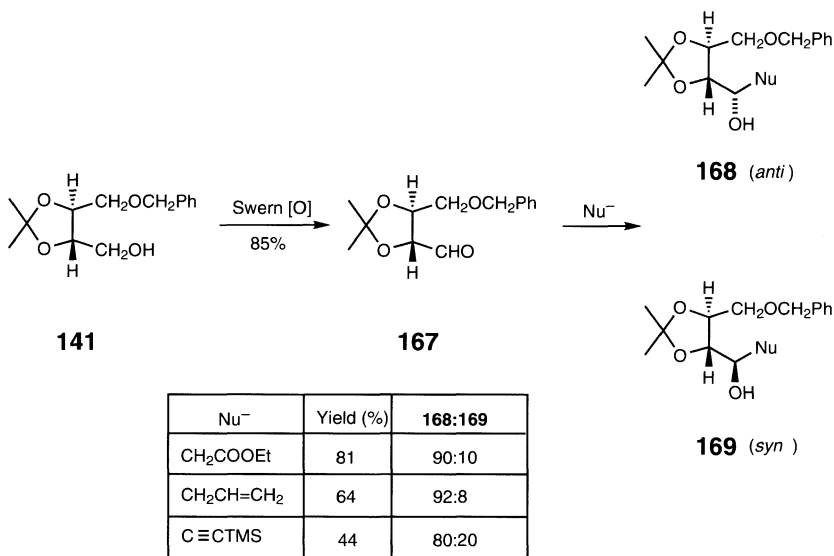
L-Daunosamine (**166**) (R=H), (3-amino-2,3,6-trideoxy-*L*-*lyxo*-hexose), is an essential component of both natural and unnatural anthracycline antitumor agents. The 1,3-addition of ketene silyl acetal **164** to the chiral nitron (*Z*)-[(4*R*)-*trans*-2,2,5-trimethyl-1,3-dioxolan-4-yl]methylene[(1*S*)-1-phenylethyl]amine *N*-oxide (**163**), prepared by the conversion of **141** to **103** [62] and then reaction of **103** with the hydroxylamine **162**, provides the *O*-silylated addition product **165** in quantitative yield with an *anti* relative stereochemistry at C-3 and C-4 (*anti* : *syn* = > 100 : 1). Efficient transformation of **165** to **166** (R=COPh) is achieved in three steps [63] (Scheme 39).

A Swern oxidation of the free hydroxy group in **141** affords in good yields 4-*O*-benzyl-2,3-*O*-isopropylidene-*L*-threose (**167**), which constitutes a new and potentially useful four-carbon building block for the synthesis of L-sugars. In contrast to glyceraldehyde acetonide, **167** is fairly stable and can be stored at room temperature for up to a week. Nucleophilic addition to the aldehyde group occurs with effective 1,2-asymmetric induction to provide in good yield the preferred *anti*-isomer **168**, which can be separated chromatographically from *syn*-**169** [64,65].

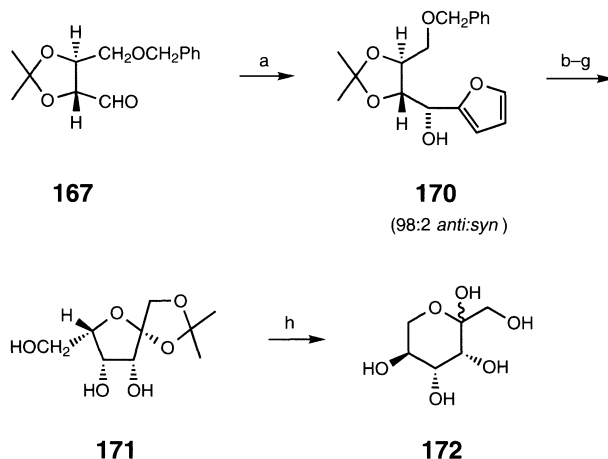
In the presence of zinc bromide (ZnBr₂), the nucleophilic addition of 2-furyllithium to **167** proceeds in a highly stereoselective manner to afford the *anti*-adduct **170**. This observed high stereoselectivity has been attributed to enhanced Felkin selectivity due to the chelation effect

**Scheme 39**

conditions: (a) *p*-TsCl, pyridine; (b) NaBH₄; (c) H₂, Pd/C; (d) (COCl)₂, DMSO, Et₃N, DCM; (e) Na₂SO₄, DCM; (f) MeCN–DCM (1:1), ZnI₂ (cat.) (100%); (g) H₂, Pd/C, AcOH (96%); (h) PhCOCl, pyridine; (i) 80% AcOH, 40 °C (88%); (j) DIBAL, THF, –78 °C (68%)



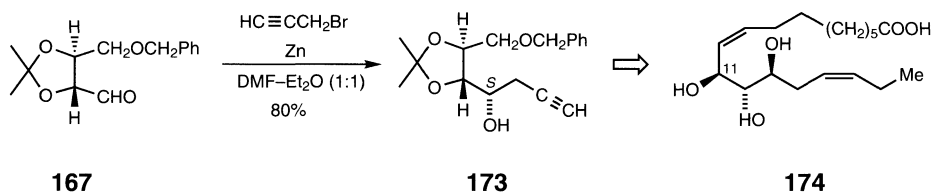
of Zn(II). Diastereomer **170** is utilized for the synthesis of L-tagatose (**172**), the antipode of a naturally occurring ketose of physiological and immunological interest [65,66] (Scheme 40).



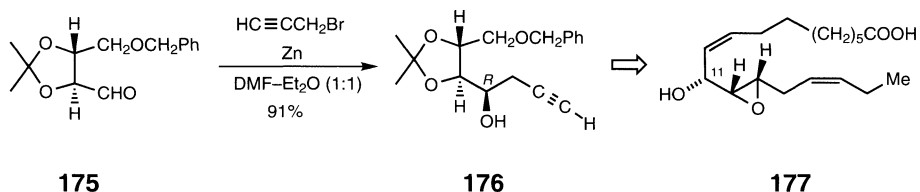
Scheme 40

conditions: (a) 2-furyllithium, ZnBr₂, THF (97%); (b) Br₂, MeOH, -42 °C (83%); (c) Me₂C(OMe)₂, PPTS (56%); (d) O₃, MeOH, -78 °C; (e) NaBH₄; (f) acetone, H₂SO₄ (37% for steps d-f); (g) H₂, Pd/C (100%); (h) HCl-H₂O (85%)

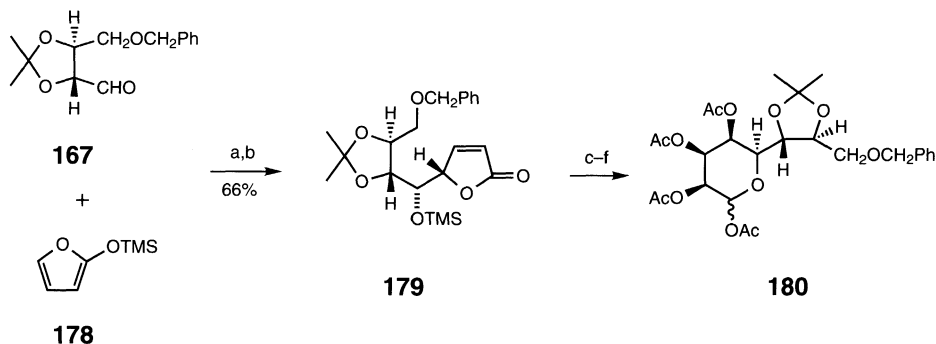
The ability of several oxygenated C₁₈ fatty acids, such as **174** and **177**, isolated from rice plants (including Fukuyuki) suffering from rice-blast disease, to act as self-defense substances against the fungus, has attractive synthetic interest. Zinc-mediated addition of propargyl bromide to (*S,S*)-**167** provides (*S*)-**173**, which is converted in nine steps to (11*S*,12*S*,13*S*)-trihydroxy-(9*Z*,15*Z*)-octadecadienoic acid (**174**) [67].



(*S,S*)-(-)-Tartaric acid provides (*R,R*)-**175**, which is converted in a similar fashion to (*R*)-**176** and transformed also in nine steps to methyl (11*R*,12*S*,13*S*)- (9*Z*,15*Z*)-11-hydroxy-12,13-epoxyoctadecadienoate (**177**) [67].



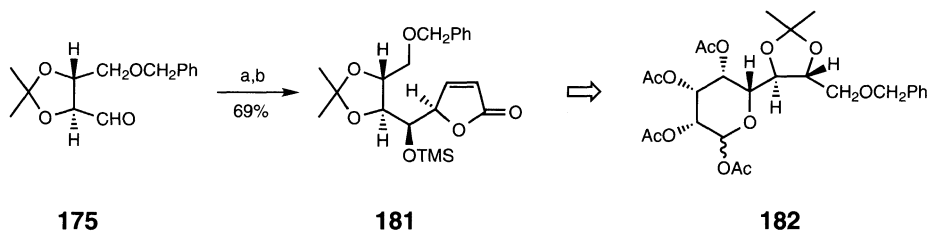
Complex sugars play a central role in biologically active products. The stereoselective elongation of a C_n chiral substrate with BF_3 -mediated addition of 2-(trimethylsiloxy)furan (TMSOF) (**178**) selectively generates C_{n+4} butenolides **179**. By a series of clean reactions these can be converted into multifunctional products by exploiting the strong chiral bias of the butenolide matrix. This methodology has led to a highly stereoselective synthesis of the octopyranose sugar *L-threo-D-talo*-octose (**180**) from (*S,S*)-**167** (Scheme 41).



Scheme 41

conditions: (a) $\text{BF}_3 \cdot \text{Et}_2\text{O}$; (b) TMSCl, pyridine; (c) KMnO_4 , DCH, 18-Crown-6; (d) TMSCl, pyridine; (e) DIBAL; (f) Ac_2O , pyridine, 18-Crown-6

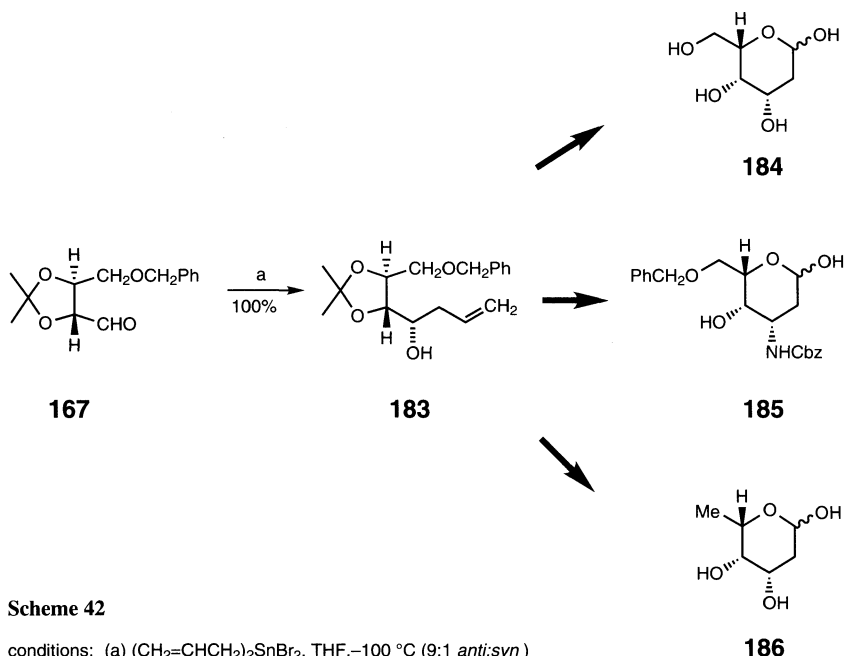
Similar transformation utilizing (*R,R*)-**175** provides *D-threo-L-talo*-octose (**182**). Both **180** and **182** are obtained optically pure in an overall yield of 10% in five steps [68].



conditions: (a) **178**, $\text{BF}_3 \cdot \text{Et}_2\text{O}$; (b) TMSCl, pyridine

“Rare sugars”, such as L-series sugars, deoxy sugars, amino sugars, and branched sugars, possess unique structural features, and they occur in many biologically significant substances. The allylation of **167** with diallyltin(IV) dibromide at -100°C proceeds with high stereoselectivity to afford *anti*-**183** in high yield. A straightforward three-step conversion of **183** provides 2-deoxy-L-galactose (**184**) in an overall yield of 50%. Moreover, selective manipulation of the protecting groups in **183** allows for the preparation of either L-diginose (**185**), a 2,6-dideoxy-L-sugar found in the digitalin cardiac steroids, or 3-amino-2,3-dideoxy-L-xylohexose (**186**), representative of a class of sugars found in the anthracycline antibiotics [65,69] (Scheme 42).

Polyoxins constitute a group of antifungal metabolites produced by *Streptomyces cacaoi* var. *asoensis*, the gross structure of which is divisible into a nucleoside moiety and a dipeptide comprised of a unique functionalized polyhydroxynorvaline known commonly as 5-O- or δ -

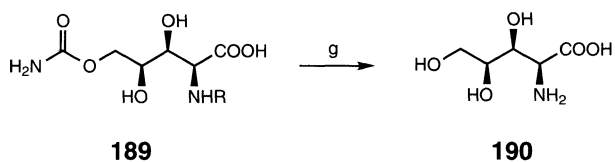
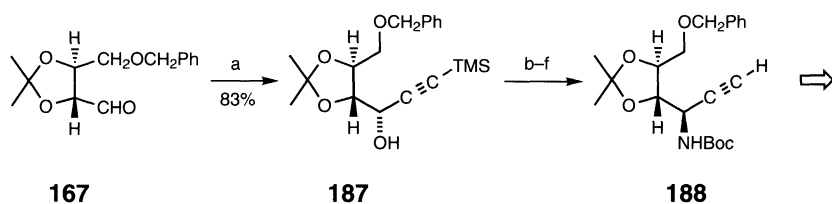


carbamoylpolyoxamic acid (**189**) ($\text{R}=\text{H}$). Highly stereoselective nucleophilic addition of a carboxyl anion equivalent, prepared from lithium trimethylsilylacetylide and 1 : 1 $\text{TiCl}_4\text{-Ti}(\text{O-}i\text{-iso-Pr})_4$, to **167** provides *anti* alcohol **187** (*anti:syn* = 9 : 1). Azide displacement of the tosylate of **187** followed by lithium aluminum hydride reduction and N-Boc protection affords **188**, in which the chiral center has been inverted. Subsequent conversion of **188** in four steps to N-Boc-**189** followed by acidic hydrolysis unfortunately results in carbamoyl cleavage as well as N-Boc deprotection to provide polyoxamic acid (**190**) [70] (Scheme 43).

Utilization of the Overman–Claisen imidate rearrangement as a key synthetic step underlies the strategy for a convenient preparation of not only **189** and **190** but also the corresponding unnatural D-isomers of these acids. Wittig–Horner reaction of aldehyde **167** provides the *E*-acrylate **191**, which is converted to a trichloroacetimidate and thermally rearranged to a chromatographically separable 1 : 1 mixture of diastereomeric amides (*S*)-**192** and (*R*)-**193**. Each is obtained pure in 55-g amounts, and is subsequently hydrolyzed, suitably protected, and carbamoylated prior to a sodium periodate–ruthenium trichloride oxidation to the protected acids. Deprotection affords either the *S*-amino acid **189** or, in an analogous way, the corresponding *R*-amino acid **194** ($\text{R} = \text{carbamoyl}$) contaminated with some decarbamoylated product (**194** $\text{R}=\text{H}$) [71] (Scheme 44).

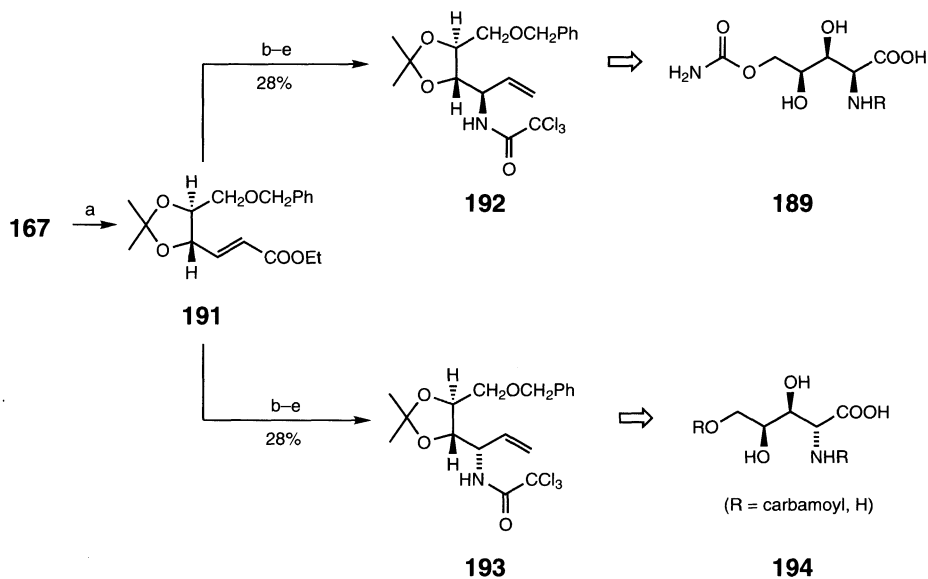
Wittig reaction of **167** with ethyl (triphenylphosphoranyliden)acetate in methanol leads to a high yield of *Z*-olefin **195** containing a minor amount of the *E*-isomer [70,71]. Acid treatment of **195** affords the separable unsaturated lactones **196** and **197** in 78% yield (7 : 1 ratio). Subsequent transformation of **196** provides deoxypoloxin C (**198**), which, when appropriately coupled with **189**, affords Polyoxin J (**199**) [72,73] (Scheme 45).

The macrocyclic lactone (–)-aspicilin (**204**), isolated from the lichen *Aspicilia gibbosa*, contains three contiguous chiral hydroxy groups, of which two can be introduced directly from **167**. A Wittig–Horner chain elongation of **167** with triethylphosphonoacetate followed by DIBAL reduction of the ester to the allylic alcohol **200** provides the appropriate substrate



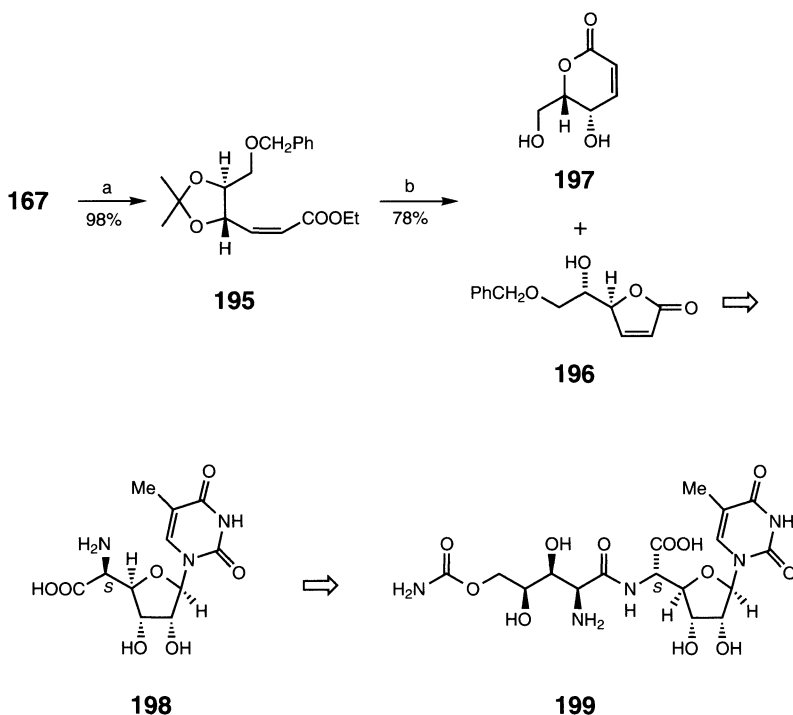
Scheme 33

conditions: (a) Li TMS-acetylide, TiCl_4 - $\text{Ti}(i\text{-Pro})_4$, -78°C ; (b) *p*-TsCl, pyridine (84%); (c) LiN_3 , HMPA (85%); (d) NH_4^+F^- (100%); (e) LiAlH_4 , Et_2O (76%); (f) $(\text{Boc})_2\text{O}$; (g) HCl, H_2O



Scheme 34

conditions: (a) $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COOEt}$, NaH (93%); (b) DIBAL, toluene (85%); (c) CCl_3CN , NaH; (d) xylene, reflux; (e) HPLC



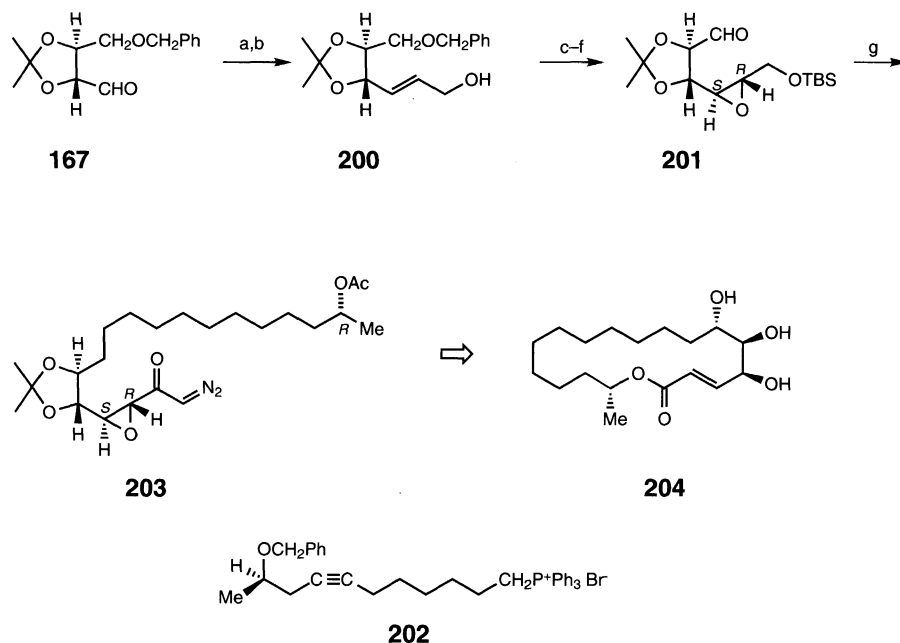
Scheme 45

conditions: (a) $\text{Ph}_3\text{P}=\text{CHCOOEt}$, MeOH; (b) 3N HCl

for a Sharpless epoxidation with (*S,S*)-(-)-diisopropyl D-tartrate as the chiral inductor. Protection of the free hydroxy group, then reductive cleavage of the benzyl group and a Swern oxidation of the resulting primary alcohol, affords aldehyde **201**. Wittig coupling between **202**, prepared from (-)-ethyl L-lactate, and **201**, followed by catalytic reduction, desilylation, and conversion to the α,β -epoxy diazomethyl ketone **203**, provides the required substrate for a photo-induced rearrangement to the (*S*)-4-hydroxyalkenoate. This, upon saponification, macro-lactonization, and deprotection, affords **204** [74] (Scheme 46).

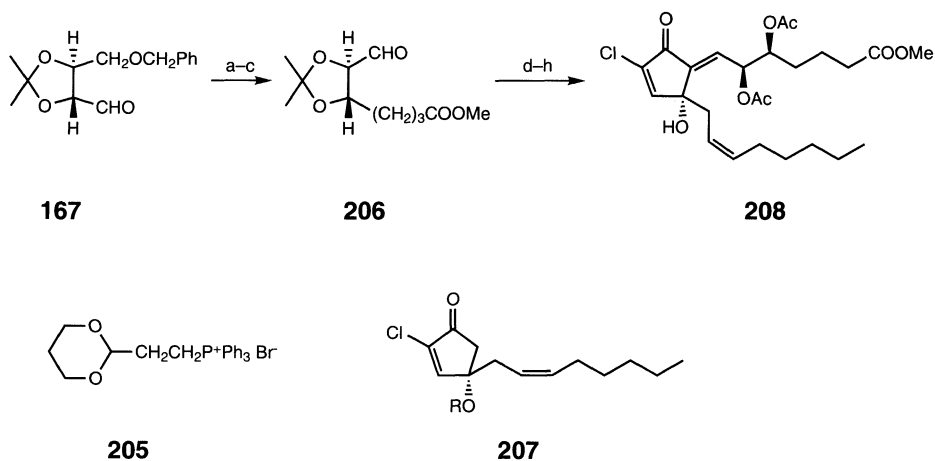
Punaglandin **4** (**208**) is an example of a C-10 chlorinated prostanoid isolated from the Hawaiian octocoral *telesto riisei*. Its potent antitumor activity has attracted considerable synthetic interest. Characteristic of the α -chain is the same familiar dihydroxy stereochemistry found in (*R,R*)-tartaric acid. Wittig reaction of **167** with the phosphorane of [2-(1,3-dioxan-2-yl)ethyl]triphenylphosphonium bromide (**205**) followed by catalytic reduction and simultaneous debenzoylation affords a primary alcohol, which is converted to aldehyde **206** in two oxidative steps. Aldol coupling of **206** with racemic cyclopentenone **207** (R=MOM) provides a statistical mixture of all four possible diastereomers. After chromatographic purification and protective group transformations, the target molecule **208** is obtained in 30–40% yield. The remaining three aldol products have been similarly converted to the diastereomers of **208** [75] (Scheme 47).

An approach to the preparation of chiral **208** utilizes a free-radical chain-elongation reaction for the preparation of **206**. Alcohol **141** is converted in two steps and 92% yield to (4*S*,5*R*)-4-benzoyloxymethyl-5-iodomethyl-2,2-dimethyl-1,3-dioxolane (**209**). Treatment of



Scheme 46

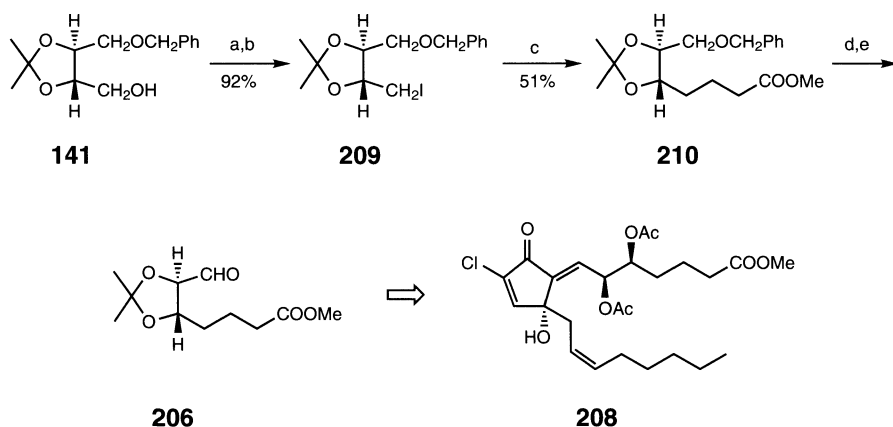
conditions: (a) $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COEt}$, LiCl , $i\text{-Pr}_2\text{NEt}$ (90%); (b) DIBAL (100%); (c) Sharpless epoxidation, D-(-)-DIPT (85%); (d) TBSCl, imidazole, DMF (87%); (e) H_2 , Pd/C (100%); (f) $(\text{COCl})_2$, DMSO, Et_3N , DCM (81%); (g) **202**, $n\text{-BuLi}$



Scheme 47

conditions: (a) **205**, $n\text{-BuLi}$, THF, then H_2 , Pd(black) (63%); (b) O_3 , NaOMe, MeOH (72%); (c) $(\text{COCl})_2$, DMSO, Et_3N , DCM (94%); (d) **207**, LDA, -78°C (53%); (e) MPLC; (f) 80% aq. AcOH, 80°C ; (g) Ac_2O , pyridine, DCM; (h) 80% aq. AcOH, 100°C

209 with tri-*n*-butyltin hydride [generated *in situ* from tri-*n*-butyltin(IV) chloride/ NaBH_4] followed by photoinduction to a radical and addition of the radical to methyl acrylate affords in 51% yield methyl (5*S*,6*S*)-7-benzyloxy-5,6-isopropylidenedioxyheptanoate (**210**). Subsequent debenzoylation and Swern oxidation of **210** affords **206**. Enzymatic resolution of the racemic acetates of **207** (R=Ac) provides, after appropriate protecting group manipulations, homochiral (1*S*,4*R*)-(–)-4-*tert*-butyldimethylsilyloxy-3-chloro-2-cyclopenten-1-ol (**207**) (R=TBDMS) which, when coupled with **206**, yields only two diastereomeric olefins. Chromatographic separation and protecting group transformation affords pure **208** in an overall yield of 13.7% from **207** [76] (Scheme 48).



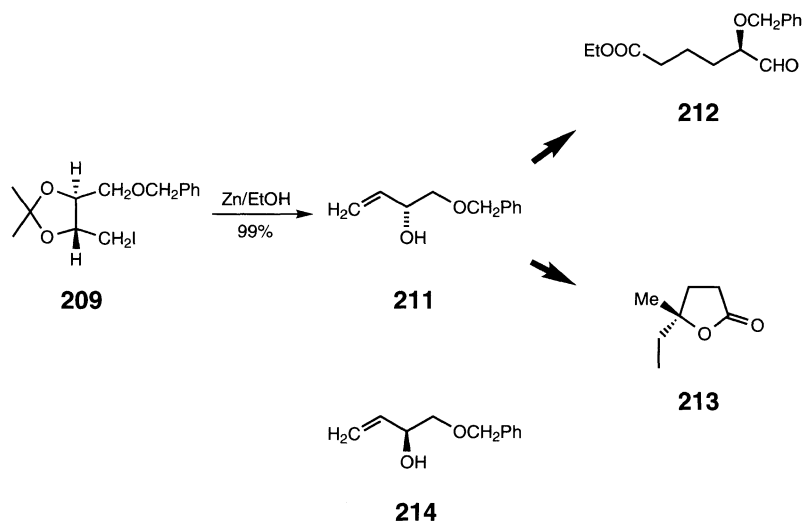
Scheme 48

conditions: (a) MsCl , Et_3N , DCM ; (b) NaI , NaHCO_3 , DMF , 70°C ; (c) $n\text{-Bu}_3\text{SnCl}$, NaBH_4 , $\text{CH}_2=\text{CHCOOMe}$, $h\nu$; (d) $\text{Pd}(\text{black})$, MeOH ; (e) Swern [O]

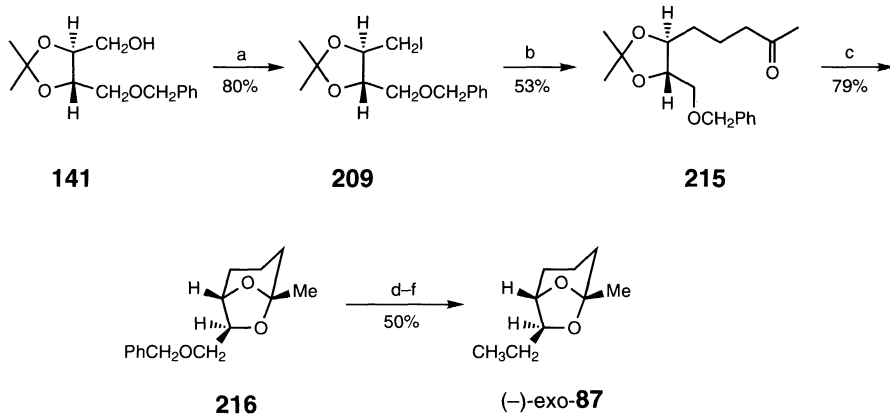
The multi-purpose chiral synthon (*R*)-1-benzyloxy-3-buten-1-ol (**211**) can be prepared in high yield from **209**. Treatment of **209** with activated zinc in refluxing ethanol results in the facile elimination of iodide to provide **211** in nearly quantitative yield. The utility of **211** is illustrated by the synthesis of (*R*)-ethyl-5-benzyloxy-5-formylpentanoate (**212**), a useful synthon for the preparation of arachidonic acid metabolites, and (*R*)- γ -caprolactone (**213**), a pheromone of the *Trogoderma* species. The corresponding (*S*)-**214** is conveniently prepared from D-tartaric acid based on similar transformations [77] (Scheme 49).

A convenient synthesis of (–)-*exo*-brevicomine (**87**) utilizes a radical chain reaction of methyl vinyl ketone with (4*S*,5*R*)-4-benzyloxymethyl-5-iodomethyl-2,2-dimethyl-1,3-dioxolane (**209**), prepared by treating the (*R,R*)-tartaric acid derivative **141** with triphenylphosphonium iodide in the presence of imidazole. Adduct **215**, after acidic hydrolysis of the isopropylidene protecting group, furnishes the bicyclic acetal **216**. Subsequent debenzoylation and tosylation followed by methylation with lithium dimethylcuprate provides **87** in an overall yield of 17% from (*R,R*)-tartaric acid. The optical purity of **87** corresponds to greater than 99% *ee* (Scheme 50). Carrying out a similar series of transformations with (*S,S*)-tartaric acid leads to (+)-*exo*-brevicomine (**90**) [78].

Tosylmethyl isocyanide (TosMIC) (**217**) has the potential to serve as a carbonyl equivalent. Treatment of **209** with the anion of **217** under phase-transfer conditions provides unstable (4*S*,5*S*)-4-benzyloxymethyl-2,2-dimethyl-5-(2'-tosyl-2'-isocyanoethyl)-1,3-dioxolane (**218**), which is treated with lithium in liquid ammonia to afford (4*S*,5*S*)-4-ethyl-5-hydroxymethyl-



Scheme 49

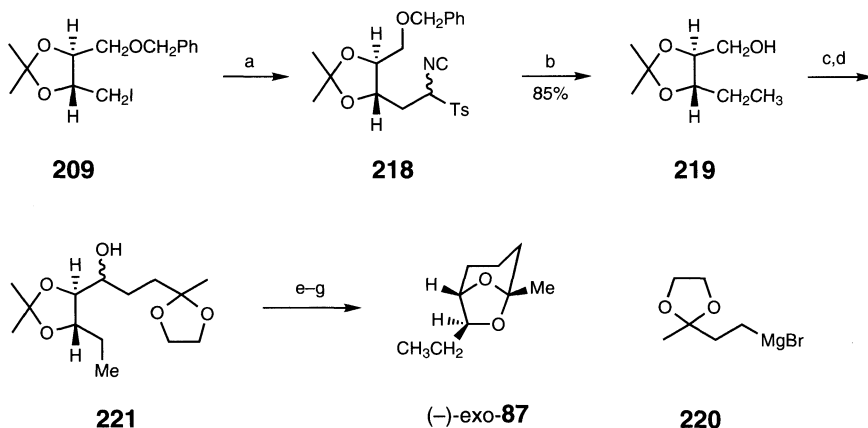


Scheme 50

conditions: (a) I_2 , Ph_3P , imidazole; (b) MVK, $n-Bu_3SnH$, AIBN, C_6H_6 ; (c) Amberlyst-15, DCM; (d) H_2 , Pd/C, Et_2O ; (e) $p-TsCl$, pyridine, DCM; (f) Me_2CuLi , Et_2O

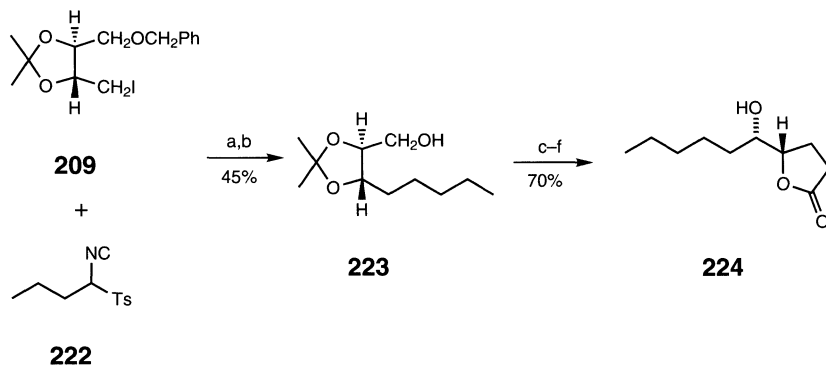
2,2-dimethyl-1,3-dioxolane (**219**) in 85% yield. Subsequent Swern oxidation of **219** to the aldehyde and addition of 3,3-ethylenedioxybutyl magnesium bromide (**220**) provides **221**. Barton–McCombie deoxygenation of the hydroxyl group in **221** followed by acidic hydrolysis of the isopropylidene ring furnishes (–)-*exo*-brevicomine (**87**) [79] (Scheme 51).

Monoalkylated TosMIC **222** reacts with **209** to furnish, after lithium–ammonia deprotection, (4*S*,5*S*)-5-pentyl-4-hydroxymethyl-2,2-dimethyl-1,3-dioxolane (**223**). This is smoothly converted in four steps to (4*S*,5*S*)-5-hydroxy-4-decanolide (L-factor) (**224**), the proposed autoregulator isolated from mutant strains of *Streptomyces grieseus* [79] (Scheme 52).



Scheme 51

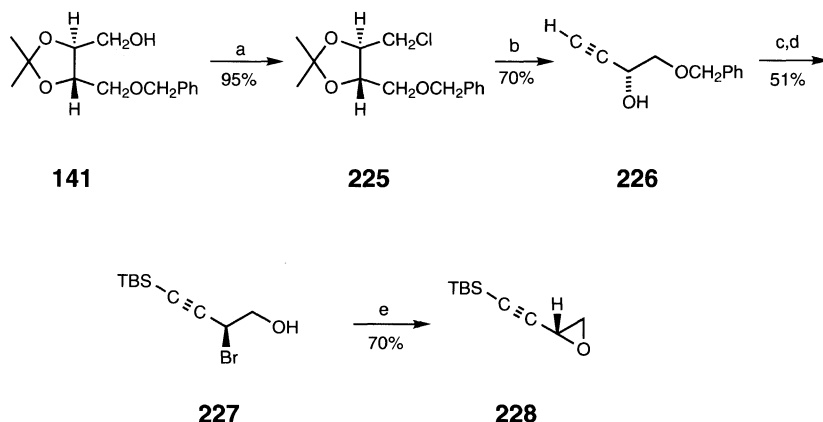
conditions: (a) TsCH₂NC (**217**), NaH; (b) Li, NH₃(l); (c) Swern [O] (70%); (d) **220**, THF (72%); (e) NaH, CS₂, MeI (95%); (f) *n*-Bu₃SnH, AIBN, toluene, 100 °C (97%); (g) PTSA, wet Et₂O (90%)



Scheme 52

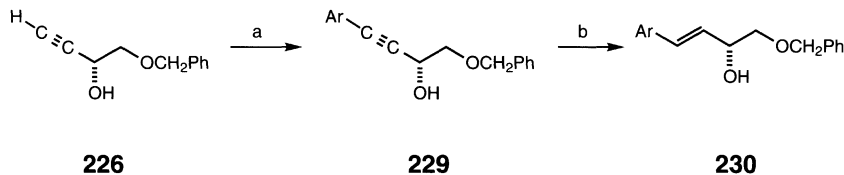
conditions: (a) NaH, DMSO; (b) Li, NH₃(l); (c) Swern [O]; (d) Ph₃P=CHCOOEt, C₆H₆; (e) H₂, Raney Ni; (f) CF₃COOH-H₂O (4:1)

Homochiral epoxides are versatile intermediates for the synthesis of a variety of natural products. The four-carbon bifunctional chiron (*R*)-1-*tert*-butyldimethylsilyl-3,4-epoxybut-1-yne (**228**) is conveniently prepared from **141** as shown in Scheme 53. The conversion of **141** to chloride **225** followed by base-induced chloride elimination in liquid ammonia proceeds without any detectable epimerization (as determined by both hplc and nmr analysis of the corresponding Mosher ester) to provide the *R*-alcohol **226** in good yield. Subsequent silyl protection followed by treatment with boron tribromide results in a highly stereoselective bromination, together with simultaneous debenzoylation to the bromohydrin **227**, which under mild basic conditions is converted to epoxide **228**. The optical purity of **228** (*ee* = 99%) demonstrates the high selectivity in this new bromination reaction [80,81].

**Scheme 53**

conditions: (a) CCl_4 , Ph_3P , 70°C ; (b) LiNH_2 , $\text{NH}_3(\text{l})$, -33°C ; (c) *n*-BuLi, TBSCl (59%);
 (d) BBr_3 , DCM, -70°C (85%); (e) K_2CO_3 , acetone

The cross-coupling reaction of **226** with a variety of aromatic halides proceeds without difficulty in triethylamine in the presence of bis(triphenylphosphine)palladium(II) chloride and copper(I) iodide under sonication conditions to furnish the corresponding arylacetylenes **229** in satisfactory yields. Refluxing these arylacetylenes with lithium aluminum hydride in THF provides in good yields the corresponding allylic alcohols **230** having the *E*-configuration [81].

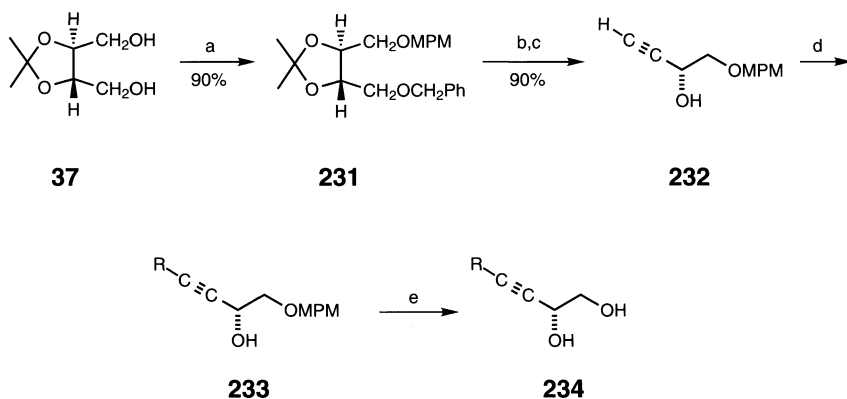



conditions: (a) ArX, $(\text{Ph}_3\text{P})_2\text{PdCl}_2$, CuI, Et_3N ; (b) LiAlH_4 , THF

ArX	Yield 229 (%)	Yield 230 (%)
$\text{C}_6\text{H}_5\text{I}$	90	81
4-Me $\text{C}_6\text{H}_4\text{I}$	93	93
2-FC $_6\text{H}_4\text{I}$	76	80
3-FC $_6\text{H}_4\text{I}$	77	83
4-FC $_6\text{H}_4\text{I}$	77	79
4-MeOC $_6\text{H}_4\text{I}$	70	73
2-IC $_4\text{H}_3\text{S}$	67	90
2-BrC $_5\text{H}_4\text{N}$	83	68

Optically active acetylenic alcohols, such as **234**, are widely encountered in natural product synthesis. The *p*-methoxybenzyloxy (MPM) protected acetylenic alcohol **232**, readily pre-

pared from **231**, offers a practical intermediate for the synthesis of acetylenic diols **234**. The attractive feature of the the MPM protecting group is the ease with which it is cleaved in the presence of DDQ to produce the diols **234** from **233** in good yields [82] (Scheme 54).



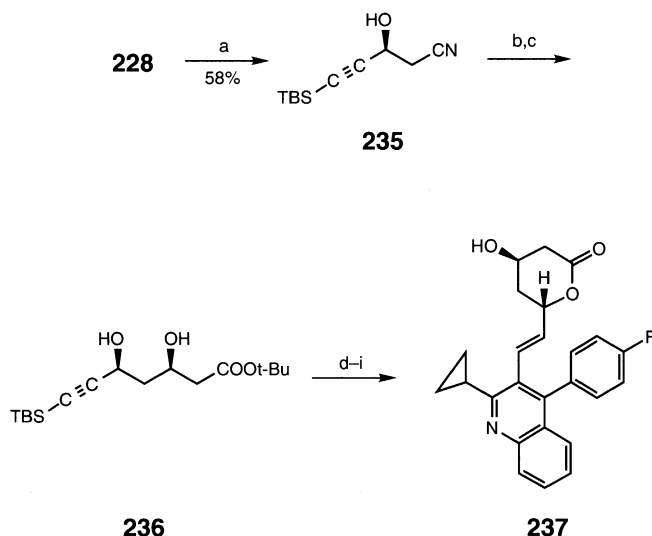
RBr	Yield 233 (%)
<i>n</i> -C ₄ H ₉	81
<i>n</i> -C ₆ H ₁₅	80
-(CH ₂) ₇ COOH	81
-(CH ₂) ₈ OTHP	75
CH ₂ =CH(CH ₂) ₃ -	82
Me(CH ₂) ₃ C≡C(CH ₂) ₃ -	85
 -CH ₂ CH ₂ -	65

Scheme 54

conditions: (a) *p*-MeOC₆H₄CH₂Br, NaH, THF; (b) CCl₄, Ph₃P; (c) LiNH₂, NH₃(l); (d) LiNH₂, RBr; (e) DDQ, DCM-H₂O (17:1)

Regioselective opening of epoxide **228** with potassium cyanide in ethanol–buffer furnishes the β -hydroxy nitrile **235**. This undergoes a Reformatsky reaction [83] with *tert*-butyl bromoacetate/zinc followed by a highly stereoselective ketone reduction with sodium borohydride/diethylmethoxyborane to provide the chiral ester **236**. Subsequently, **236** is converted in four steps to optically active NK-104 (**237**), a highly potent HMG-CoA reductase inhibitor [84] (Scheme 55).

The ability to convert the aldehyde function, present in both **167** and **175**, to an imine has been utilized for the stereoselectively preparation of (2*R*,3*S*)-3-amino-4-cyclohexyl-2-hydroxybutyric acid (cyclohexylnorstatine) (**242**), the C-terminal moiety of a renin inhibitor. Condensation of (2*R*,3*R*)-**175** with benzylamine furnishes imine **238**. While **238** does not undergo Grignard addition with cyclohexylmethylmagnesium bromide, it will undergo a



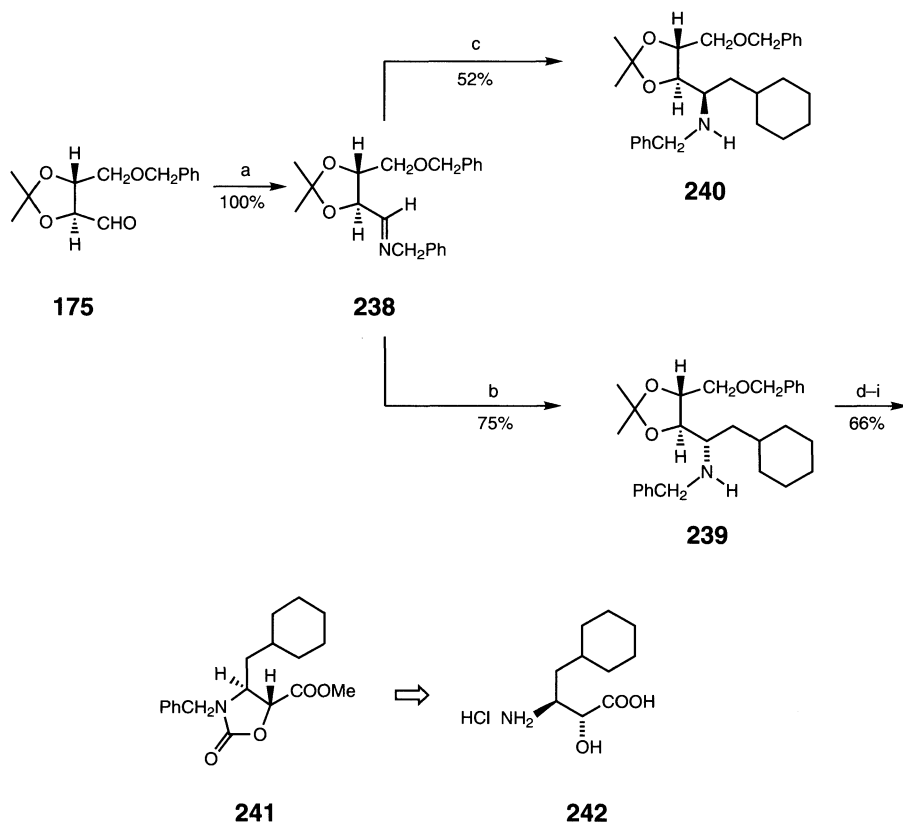
Scheme 55

conditions: (a) KCN, EtOH, buffer at pH=7.0; (b) BrCH₂COO*tert*-Bu, Zn, THF; (c) aq. HCl (60% for 2 steps); (d) NaBH₄, Et₂BOMe, THF–MeOH (82%); (e) TBAF(cat), THF (81%); (f) Me₂C(OMe)₂ *p*-TsOH (95%); (g) Me₂ClSiH, *tert*-Bu₃P–Pt(CH₂=CHSiMe₂)₂O; (h) ArI, TBAF and THF, (allyl)PdCl₂ (60%); (i) CF₃COOH (67%)

highly stereoselective addition with the cerium(III) complex of cyclohexylmethylmagnesium bromide to afford the amine **239** (α -H) in 75% yield. Interestingly, addition of cyclohexylmethylcopper(I) in the presence of boron trifluoride etherate produces only **240** (β -H) in 52% yield. Chelation control may explain the stereoselective formation of **239**, while a dipolar or Felkin–Anh model may explain the formation of **240**. Subsequent methoxycarbonylation of **239** followed by deacetalization, oxazolidin-2-one formation, oxidation to the acid, and esterification furnishes **241**. In five steps **241** is then converted to the hydrochloride of **242** [85] (Scheme 56).

Renin inhibitors, which possess both promising antihypertensive activity as well as oral efficacy, are objects of intense research and development interest. The synthesis of such C-terminal unusual amino alcohols as **245** and **246** illustrates the utility of chelation-controlled addition product **239**. In three steps, **239** is converted in an overall yield of 90% to the oxazolidin-2-one **243**, which is in turn efficiently and stereoselectively converted to epoxide **244**. A highly regioselective epoxide ring opening of **244** with either morpholine or isopropylmagnesium chloride in the presence of copper(I) iodide, followed by a series of functional group manipulations, provides either (2*S*,3*R*,4*S*)-4-*N-tert*-butoxycarbonylamino-5-cyclohexyl-1-morpholin-4-yl-2,3-pentanediol (**245**) or (2*S*,3*R*,4*S*)-*N-tert*-butoxycarbonylamino-1-cyclohexyl-6-methyl-3,4-heptanediol (**246**) in good overall yield [86] (Scheme 57).

Polyhydroxylated indolizidine alkaloids, due to their biological activity, have attracted considerable synthetic interest. The total synthesis of (–)-1-*epi*-swainsonine (**250**) from the chiral imine **238** (Scheme 58) and the parallel synthesis of (+)-2,8,8a-tri-*epi*-swainsonine (**252**) from the enantiomeric threose *N*-benzylimine **251**, prepared from natural L-tartaric acid, provide further examples of the utility of tartaric acid in meeting the challenge of complex syntheses. A stereospecific 4 + 4 homologation utilizing 2-(trimethylsiloxy)furan (**178**) pro-



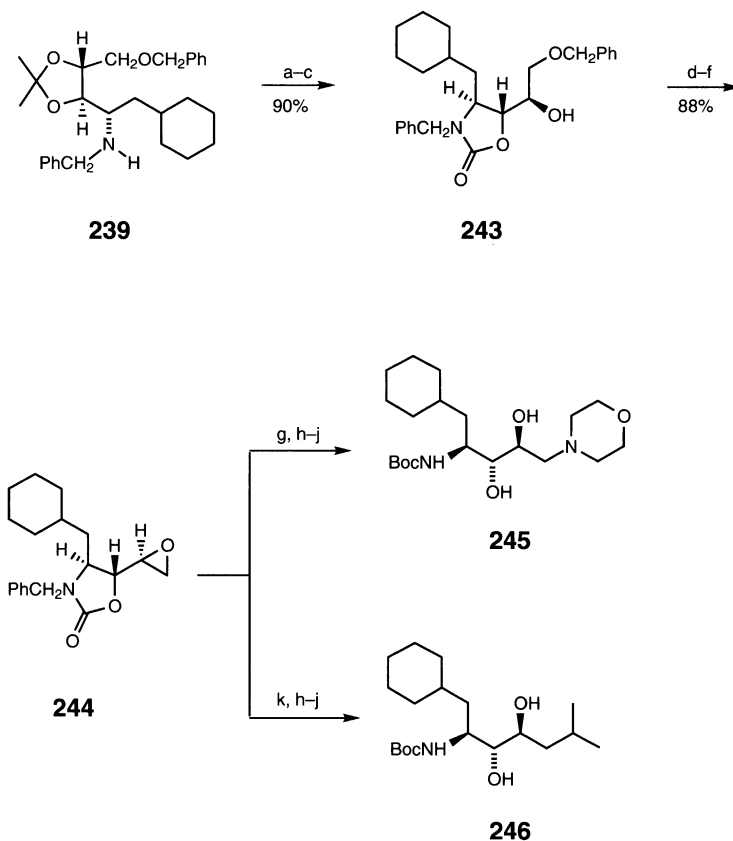
Scheme 56

conditions: (a) PhCH₂NH₂, MgSO₄ (anhydrous), toluene, 0 °C (100%); (b) C₆H₁₁CH₂MgBr–CeCl₃, Et₂O–THF, –30 °C (75%); (c) C₆H₁₁CH₂MgBr–CuI, BF₃·Et₂O, Et₂O–THF, –78 °C to rt (52%); (d) ClCOOMe, K₂CO₃, THF; (e) 80% AcOH, 80 °C; (f) KOH, MeOH (90%); (g) H₂, Pd(OH)₂/C, MeOH (100%); (h) RuCl₃·3H₂O, NaIO₄; (i) TMSOCH₂N₂, MeOH, benzene (73%)

vides the eight-carbon skeleton of the indolizidine triols and installs the proper chirality. Thus, the addition of **178** to **238** provides 5-(*N*-benzylamino)-6,7-*O*-isopropylidene-8-*O*-benzyl-2,3,5-trideoxy-*D*-*talo*-oct-2-enone-1,4-lactone (**247**) in good yield. Reduction of the butenolide double bond in **247** with concomitant reductive cleavage of the C–O and C–N benzylic bonds followed by DBU treatment in benzene furnishes the δ -lactam **248** in very good yield. Subsequent lactam reduction with borane–dimethyl sulfide in THF and intramolecular displacement of the activated primary hydroxyl function provides **250** in an overall yield of 61% yield from **238**.

Further application of this chemistry utilizing **251** leads to **252** in an overall yield of 56% from **251**. A feature of both syntheses is that gram quantities of the two optically pure enantiomers **250** and **252** can be prepared *via* a concise five-step route utilizing inexpensive and readily available imines **238** and **251** [87].

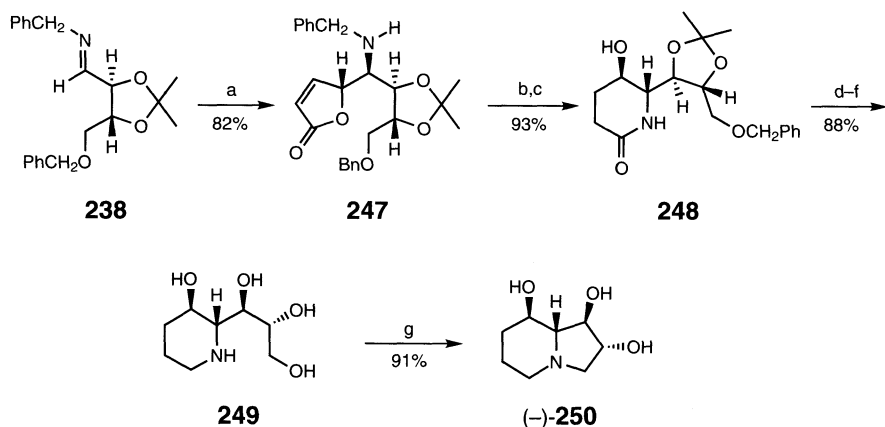
(+)-Hydantocidin (**257**), isolated from the cultured broth of *Streptomyces Hygroscopicus SANK 63584* represents a new class of ribofuranose derivative that possesses both herbicidal and plant-growth regulatory activity. The total synthesis of **257** begins with an aldol con-



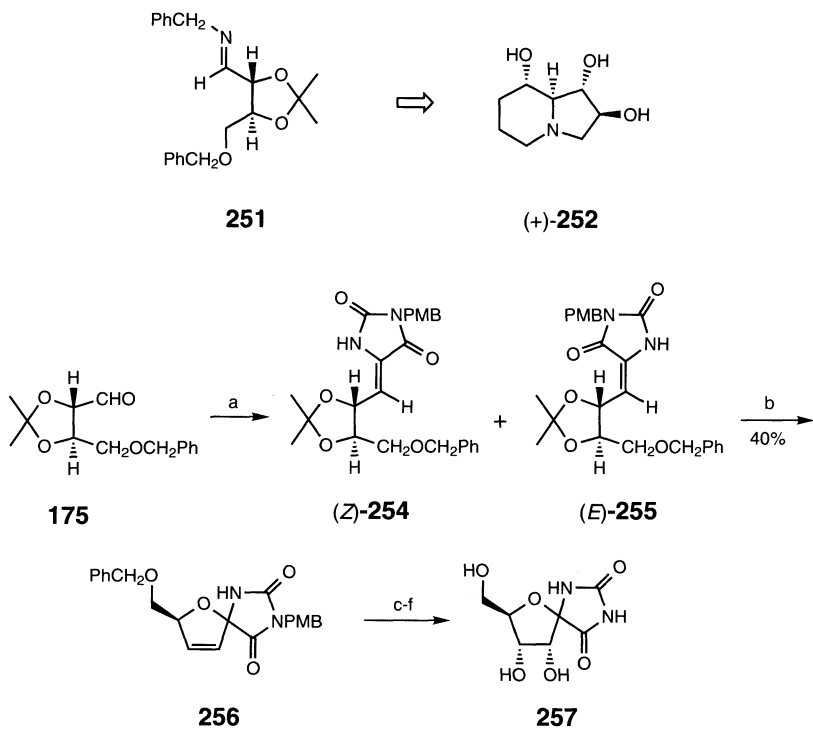
Scheme 57

conditions: (a) ClCOOMe, K_2CO_3 , THF; (b) 10% AcOH, 80 °C; (c) 10% KOH, MeOH; (d) MsCl, pyridine (96%); (e) H_2 , Pd(OH) $_2$ -C, MeOH (98%); (f) NaOMe, THF (97%); (g) morpholine, MeOH (90%); (h) Na, $\text{NH}_3(\text{l})$, -78 °C (78%); (i) conc. HCl (100%); (j) Boc_2O , Et_3N , CHCl_3 (75%); (k) Me_2CHMgCl , CuI, Et_2O (62%)

densation between **175** and 1-acetyl-3-*N*-(4-methoxybenzyl)hydantoin (**253**) to furnish a mixture consisting of 71% (*Z*)-isomer **254** and 14% (*E*)-isomer **255**. Heating this mixture with *p*-toluenesulfonic acid under reflux provides, after chromatographic purification, the spirofuranose **256** in 40% yield. This is then converted in four steps to (+)-**257** [88] (Scheme 59).

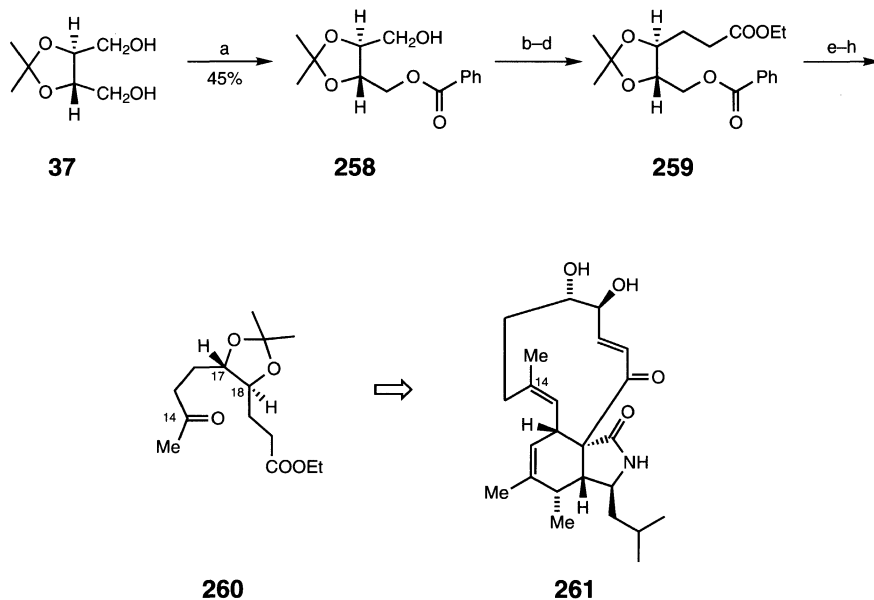
**Scheme 58**

conditions: (a) **178**, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, DCM, -85°C ; (b) H_2 , Pd/C, NaOAc, THF (97%); (c) DBU, C_6H_6 , reflux (96%); (d) $\text{BH}_3\text{-DMS}$, THF; (e) 60% TFAA, rt; (f) Dowex OH^- ; (g) Ph_3P , CCl_4 , Et_3N , DMF

**Scheme 59**

conditions: (a) *tert*-BuOK, dioxane, 0°C ; (b) *p*-TsOH, DCM, reflux, then SiO_2 chromatography; (c) *tert*-BuOK, THF, CbzCl (97%); (d) OsO_4 , NMO, acetone- H_2O (48%); (e) CAN, MeCN- H_2O (94%); (f) H_2 , Pd/C, MeOH (89%)

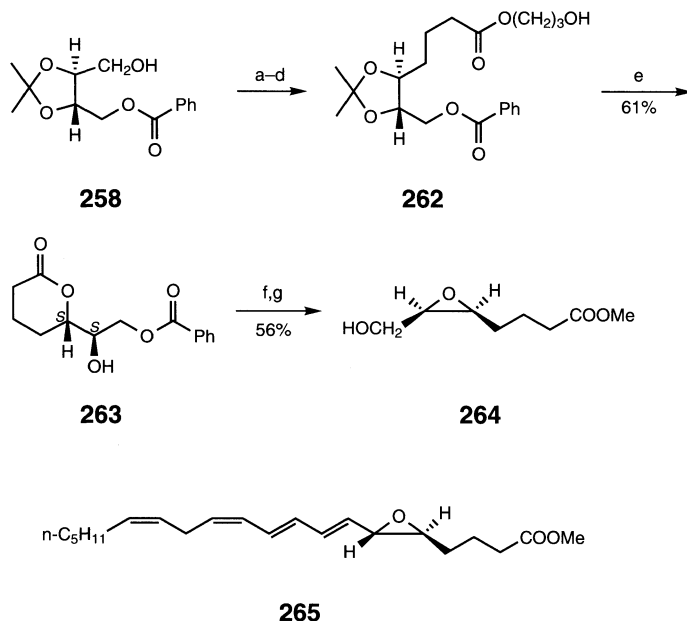
The isomeric 13,14-(*E*)-Aspochalasin C (**261**) is the product of a stereoselective intramolecular Diels–Alder reaction utilized for the simultaneous formation of the large-ring and hydrogenated isoindolone fragments in **261**. Crucial to this synthetic strategy is the C-14 to C-21 fragment **260**, in which the vicinal hydroxy groups possess the absolute configuration of (*R,R*)-tartaric acid. Monoprotection of **37** as the benzoate **258** [89] followed by a Wittig chain elongation of the free hydroxy *via* its aldehyde and subsequent catalytic reduction of the olefin functionality furnishes **259**. Elongation of the remaining hydroxy functionality to methyl ketone results in **260**, in which the absolute geometry of the fragment is determined completely by **37** [90] (Scheme 60).



Scheme 60

conditions: (a) PhCOCl, pyridine; (b) Swern [O] (65%); (c) (EtO)₂P(O)CH₂COOEt, NaH, DME (60%); (d) H₂, Pd/C, EtOH (79%); (e) Na, EtOH (91%); (f) Swern [O]; (g) MeC(O)CH=PPh₃, C₆H₆ (72%); (h) H₂, Pd/C, EtOAc (88%)

Leukotrienes, identified as the slow-reacting substances of anaphylaxis, have attracted an explosion of synthetic interest with the ultimate goal of developing novel compounds for the treatment of bronchial asthma and related conditions of hypersensitivity. Since the pivotal and extremely unstable biosynthetic intermediate leukotriene A₄ (**265**) can be converted to LTB₄, LTC₄, LTD₄, and LTE₄, its synthesis from the “chiral pool” would provide access to synthetic amounts of these leukotrienes. In order to study structure–activity relationships with respect to diastereomeric leukotrienes, the epimeric (5*S*,6*R*)-*cis*-epoxide **264** was prepared as a precursor to the 6*R* diastereomer. Swern oxidation of **258** to the aldehyde followed by Wittig olefination with **205**, subsequent reduction, and ozonolysis, furnishes the diester **262**. Hydrolysis with trifluoroacetic acid provides **263**, which is converted to optically pure *cis*-epoxide **264**. This was in fact not ultimately utilized in the overall synthesis due to a prior disclosure of a synthesis of the 6*R* isomer [89] (Scheme 61).



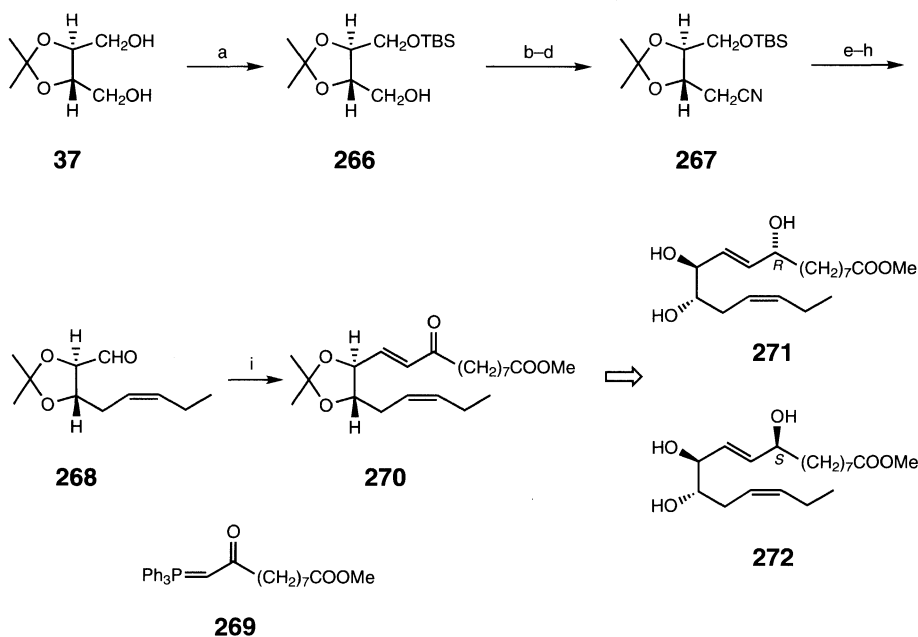
Scheme 61

conditions: (a) Swern [O] (65%); (b) **205**, *n*-BuLi, THF (47%); (c) H₂, PtO₂, EtOAc (98%); (d) O₃, EtOAc, -78 °C (60%); (e) CF₃COOH–H₂O; (f) MsCl, pyridine; (g) K₂CO₃, MeOH

The diversity associated with silyl protecting groups as well as the chemical conditions available for their removal makes them attractive alternatives to benzyl protection of the hydroxy groups of either D- or L-tartaric acid derivatives. *O*-isopropylidene-L-threitol (**37**) is mono-protected with *tert*-butyldimethylsilyl chloride to furnish **266**, which is converted in three steps to the nitrile **267**. Reduction with DIBAL and Wittig olefination followed by desilylation with fluoride and Swern oxidation of the resulting alcohol provides aldehyde **268**, which reacts with methyl 10-(triphenylphosphorane)-9-oxo-decanoate (**269**) to afford enone **270**. Reduction of **270** with subsequent preparative TLC and acetal hydrolysis furnishes (9*R*)-**271** and (9*S*)-**272**, both interesting unsaturated trihydroxy C₁₈ fatty acid metabolites isolated from vegetables [91] (Scheme 62).

“Higher sugars” constitute a special category within the monosaccharides. These relatively uncommon 7–11 carbon carbohydrates, which occur as subunits of several antibiotics, can be prepared from readily available tartrate derivatives. Swern oxidation of **266**, followed by a Horner–Emmons condensation, DIBAL reduction of the (*E*)-ester to the (*E*)-alcohol, and finally Swern oxidation, furnishes (*E*)-(4*S*,5*S*)-6-[(*tert*-butyldimethylsilyl)oxy]-4,5-*O*-(1-methylethylidene)-2-hexenal (**273**). Enal **273** undergoes a highly diastereoselective reagent-controlled addition of (*Z*)-(3*R*)-1-[(*tert*-butyldimethylsilyl)oxy]-3-(tri-*n*-butylstannyl)-1-butene (**274**) in the presence of boron trifluoride etherate to afford the (*S,S*)-allylic diol **276** in 97% yield. Under these conditions the enantiomeric (*Z*)-(3*S*)-stannane **275** affords the corresponding (*R,R*)-allylic diol **277** in 93% yield [92,93,94] (Scheme 63).

Silylation of **276** with TBSOTf furnishes the bis-TBS ether, which undergoes an osmium tetroxide hydroxylation to afford the *syn,anti,syn,anti,syn,anti*-hexol **278** in 73% yield and with high diastereoselectivity. Selective diol oxidative cleavage with periodic acid, PCC oxidation of the resulting epimeric lactols to the lactone, followed by deprotection with *p*-toluene-



Scheme 62

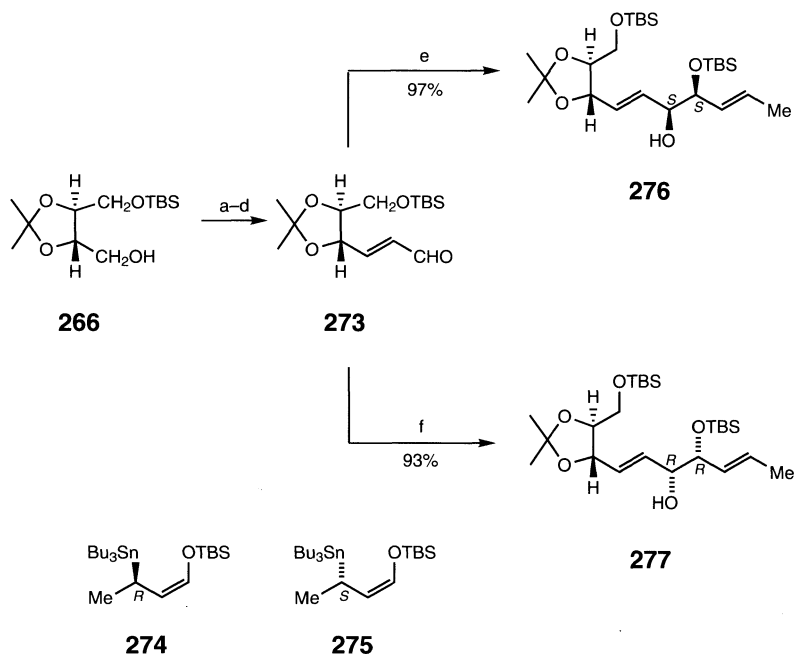
conditions: (a) TBSCl, NaH; (b) MsCl, Et₃N, DCM (90%); (c) NaI, acetone, 80 °C, 80 hr (70%); (d) NaCN, DMF; (e) DIBAL, Et₂O, -50 °C; (f) Ph₃P=CHC₂H₅, THF-HMPA; (g) *n*-Bu₄NF•3H₂O, THF; (h) Swern [O]; (i) **269**, MeCN

sulfonic acid provides (*2R,3S,4S,5R,6R,7S*)-2,3,5,6,7,8-hexahydrooctanoic acid lactone (**279**) first prepared by Fischer [95] and Hudson [96] from D-galactose [92,93] (Scheme 64).

Hydroxylation of either **276** or **277** with osmium tetroxide followed by hydrolysis and exhaustive acetylation provides the nonaacetates **280** and **281**, respectively [92] (Scheme 65).

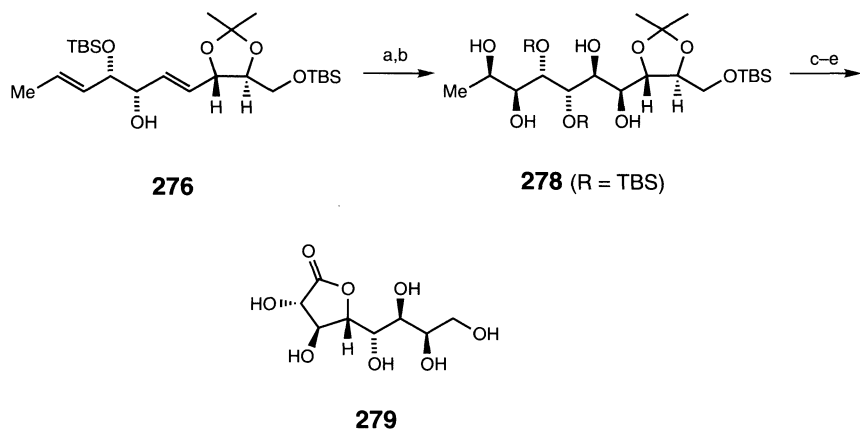
The antibiotics (+)-nojirimycin (**285**), isolated from several strains of *Streptomyces* and *Bacillus*, and (+)-1-deoxynojirimycin (**286**), first isolated from the plants of genus *Morus* (*Mori cortex*) and also *Bacillus*, inhibit various glucosidases. Efficient total syntheses of optically pure **285** and **286** have been realized from the common intermediate **37**. Silylation provides the monosilyl derivative **266**, which is then oxidized to an aldehyde under Swern conditions, chain elongated under Horner–Emmons conditions, and reduced with DIBAL to the (*E*)-allylic alcohol **282**. Sharpless asymmetric epoxidation furnishes **283**, which undergoes a highly regio- and stereoselective epoxide-opening reaction with sodium azide to provide, after protection of the free hydroxy group, **284**. Azide **284** serves as the common intermediate for a six-step synthesis of (+)-**285** as well as a synthesis of (+)-**286** in five steps [97] (Scheme 66).

Regio- and stereoselective ring opening of **283** with Et₂AlN(CH₂Ph)₂, prepared *in situ* from Et₂AlH and dibenzylamine, furnishes in 78% yield the amino alcohol **287**, which is converted in four steps to aldehyde **288**. An aldol reaction of **288** with lithio ethyl acetate proceeds by a nonchelated Felkin–Anh pathway to provide predominantly the *anti*-selective α -hydroxy ester (89:11 diastereomeric mixture), which is tosylated and separated chromatographically to afford **289**. This compound is converted in four steps to (+)-*epi*-castanospermine (**290**) (Scheme 67).



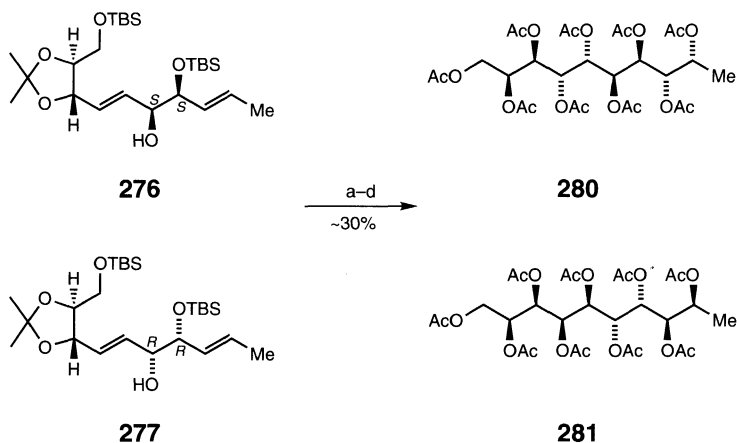
Scheme 63

conditions: (a) Swern [O]; (b) $(\text{Et}_2\text{O})\text{P}(\text{O})\text{CH}_2\text{COOEt}$, NaH, THF (83%); (c) DIBAL (87%);
 (d) Swern [O] (94%); (e) **274**, $\text{BF}_3 \cdot \text{Et}_2\text{O}$; (f) **275**, $\text{BF}_3 \cdot \text{Et}_2\text{O}$



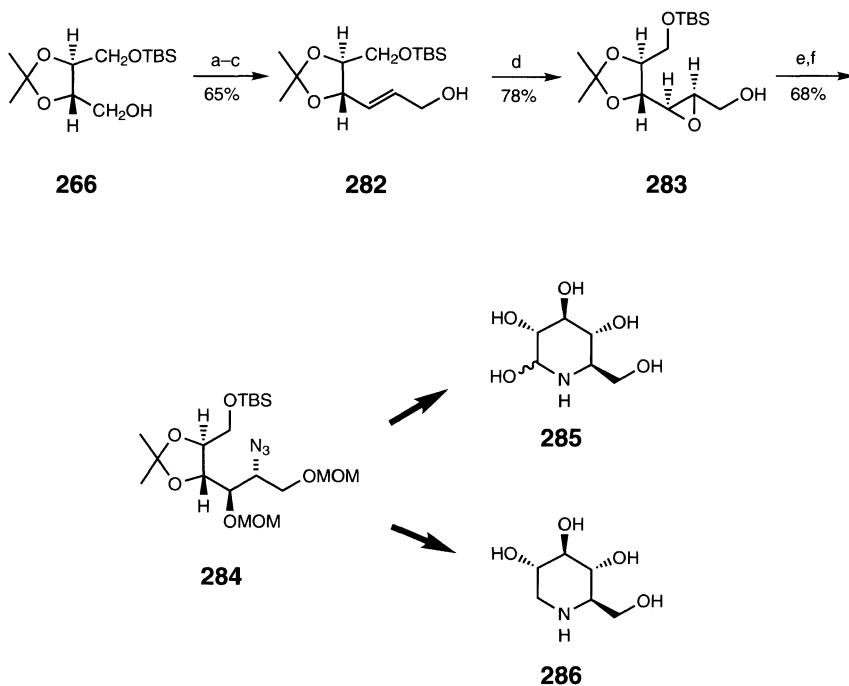
Scheme 64

conditions: (a) TBSOTf, lutidine, DCM (98%); (b) OsO_4 , NMO, acetone (73%);
 (c) H_5IO_6 , THF (86%); (d) PCC, DCM (92%); (e) *p*-TsOH, MeOH (88%)



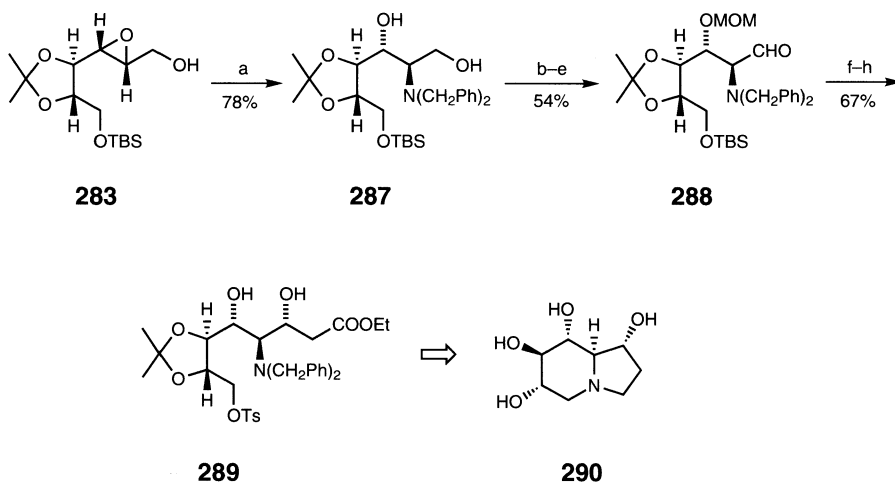
Scheme 65

conditions: (a) TBSOTf, lutidine, DCM; (b) OsO₄, NMO; (c) *p*-TsOH, MeOH; (d) Ac₂O, pyridine, DMAP



Scheme 66

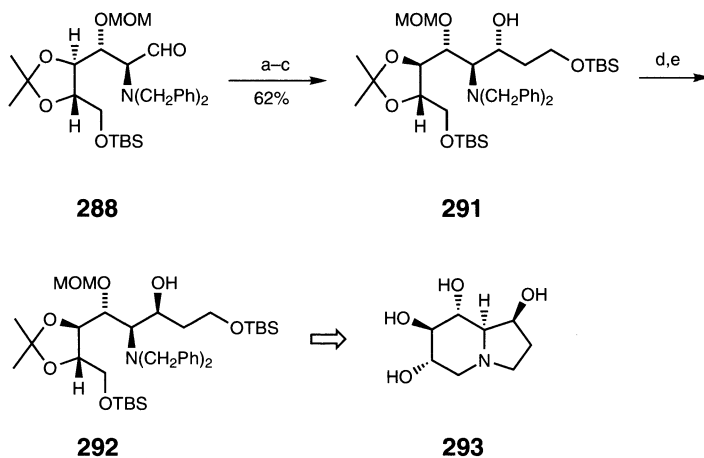
conditions: (a) Swern [O] (85%); (b) (EtO)₂P(O)CH₂COOEt, NaH, C₆H₆ (95%); (c) DIBAL, toluene (81%);
 (d) Sharpless epoxidation, (-)-DET; (e) NaN₃, NH₄Cl, DME, MeOCH₂CH₂OH, H₂O (75%);
 (f) MOMCl, *iso*-Pr₂NEt, CHCl₃ (91%)



Scheme 67

conditions: (a) Et_2AlH , $(\text{PhCH}_2)_2\text{NH}$, DCM; (b) AcCl , Et_3N (88%); (c) MOMCl , $\text{iso-Pr}_2\text{NEt}$ (85%); (d) LiAlH_4 , Et_2O (91%); (e) Swern [O] (80%); (f) $\text{LiN}(\text{TMS})_2$, EtOAc , THF, -80°C (92%, 89:11 α : β); (g) $n\text{-Bu}_4\text{NF}$, THF (94%); (h) i. $p\text{-TsCl}$, pyridine; ii. chromatography (78%)

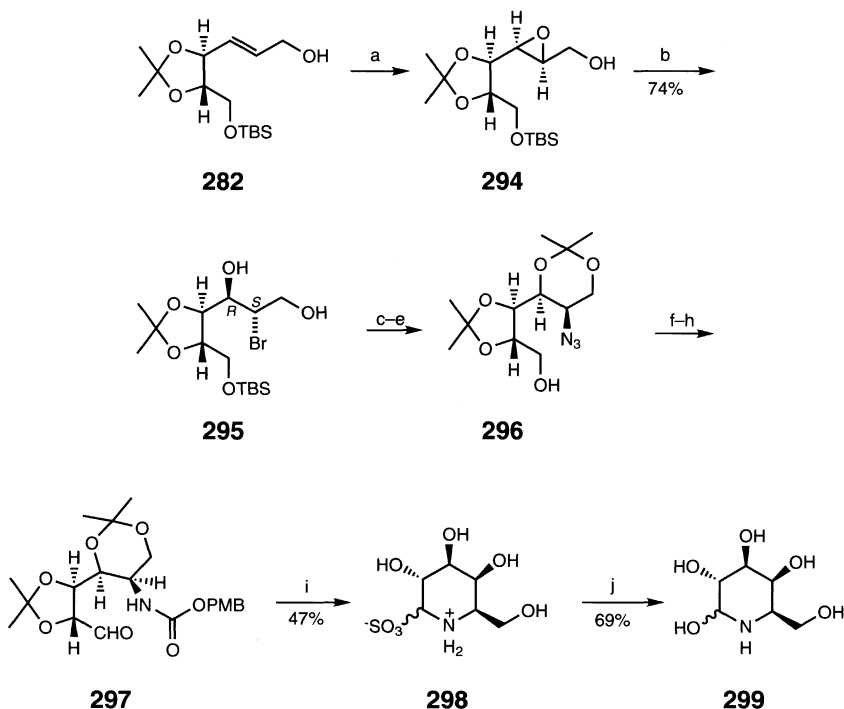
Alternatively, the diastereomeric mixture of aldol adducts undergoes lithium aluminum hydride reduction, primary alcohol silylation, and chromatographic separation to afford **291**. Subsequent Mitsunobu inversion at C-3 to furnish the β -alcohol **292** followed by a deprotective sequence and ring closure provides (+)-castanospermine (**293**). This polyhydroxylated indolizidine alkaloid isolated from *Castanospermum australe* and *Alexa leipetala* is a potent inhibitor of various α - and β -glucosidases [98] (Scheme 68).



Scheme 68

conditions: (a) $\text{LiN}(\text{TMS})_2$, EtOAc , THF, -80°C ; (b) LiAlH_4 , Et_2O (81%); (c) TBSCl , imidazole, DMF, then chromatography (83%); (d) AcOH , DEAD , Ph_3P (54%); (e) LiAlH_4 , Et_2O (86%)

Azahexoses, such as nojirimycin (**285**), are sugar analogues that have been shown to be potent and specific inhibitors of glycosidases. Isolation of the potent β -galactosidases (+)-galactostatin (**299**) and (+)-1-deoxygalactostatin (**302**) from the culture broth of *Streptomyces lydicus* PA-5725 provides another opportunity for the utilization of **282** for the total enantiomeric synthesis of azasugars. Peracid epoxidation of **282** with MCPBA provides *anti*-**294**/*syn*-**283** (65/35) in 95% yield, whereas peracid oxidation with peracetic acid provides *anti*-**294**/*syn*-**283** (71/29) in 81% yield. The *anti*-epoxide **294** undergoes regio- and stereoselective epoxide opening with dilithium tetrabromonickelate(II) in THF to furnish bromohydrin **295**, which is converted to the acetone, desilylated, and subsequently treated with sodium azide to afford azide **296**. Catalytic reduction to the amine, selective N-protection as the carbamate, and a Swern oxidation results in aldehyde **297**. Exposure of **297** to aqueous sulfurous acid accomplishes deprotection and formation of the bisulfite adduct **298**, which is converted to (+)-galactostatin (**299**) by elution on a Dowex 1-X8 (OH^-) resin (Scheme 69).

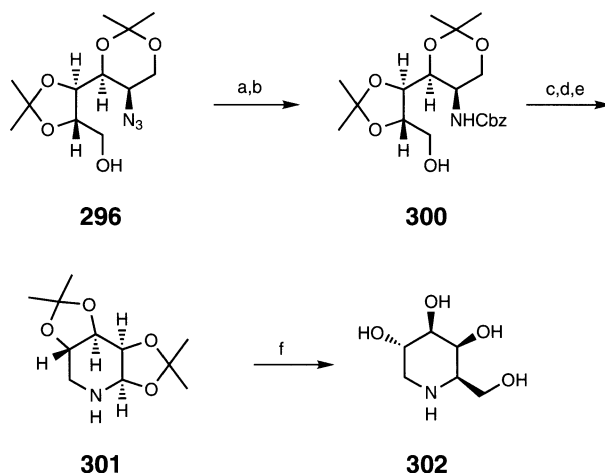


Scheme 69

conditions: (a) RCO_3H ; (b) Li_2NiBr_4 , THF; (c) $\text{Me}_2\text{C}(\text{OMe})_2$, *p*-TsOH (66%); (d) *n*-Bu₄NF, THF (98%); (e) NaN_3 , DMSO (65%); (f) H_2 , Pd/C, MeOH (81%); (g) PMB S-4,6-diMepyrimidin-2-yl thiocarbonate, Et₃N, dioxane (93%); (h) Swern [O] (98%); (i) SO_2 , H_2O ; (j) Dowex 1-X8 (OH^-)

In order to prepare **302**, the azide **296** is catalytically reduced to the amine and protected as the Cbz amide **300**. Subsequent mesylation, hydrogenolysis, and cyclization with tri-

ethylamine provides **301**. Deprotection of **301** with hydrochloric acid in methanol furnishes (+)-1-deoxygalactostatin (**302**) in 89% yield [99,100] (Scheme 70).

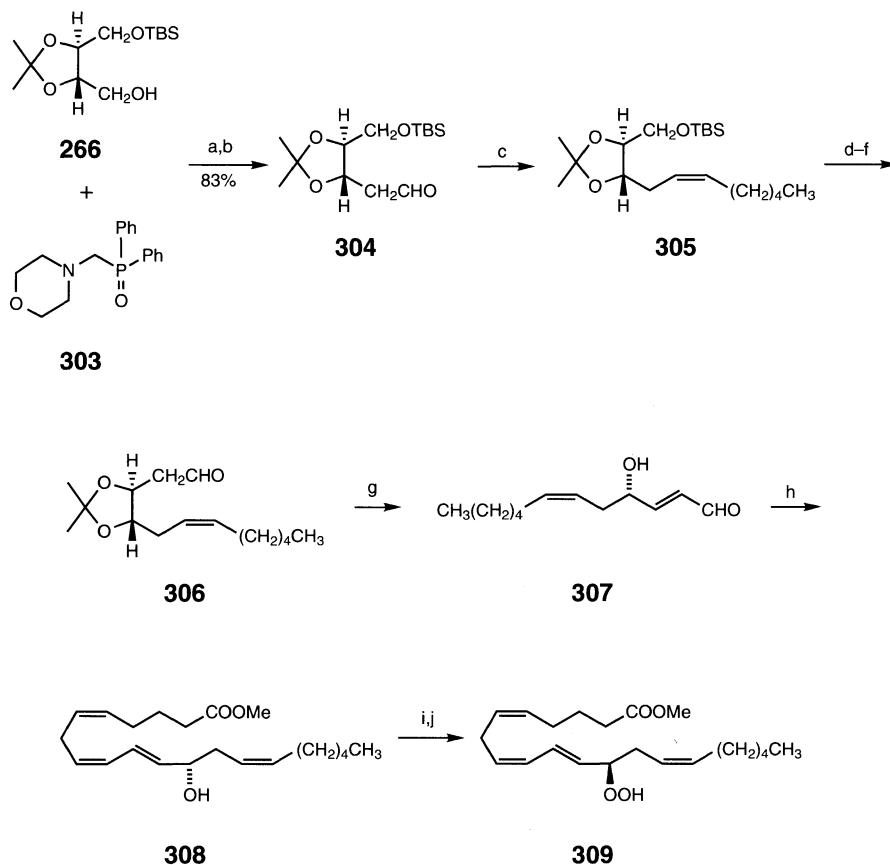


Scheme 70

conditions: (a) H_2 , Pd/C, MeOH (81%); (b) CbzCl, Na_2CO_3 , H_2O (97%); (c) MsCl, Et_3N , DCM (96%); (d) H_2 , Pd/C, MeOH; (e) Et_3N (47%); (f) HCl, MeOH (89%)

Arachidonic acid metabolites 12(*S*)-hydroperoxyeicosatetraenoic acid (**309**) [12(*S*)-HPETE] and the corresponding alcohol 12(*S*)-hydroxyeicosatetraenoic acid methyl ester (**308**), of interest due to their uncertain physiological roles in mammals, have been synthesized utilizing **266** as the chiral starting material. Swern oxidation of **266** to the aldehyde followed by treatment with the anion of phosphine oxide **303** furnishes homologated aldehyde **304**, which is then converted to the *cis*-olefin **305**. Subsequent desilylation and homologation of **305** furnishes aldehyde **306**. Treatment of **306** with activated alumina in acetonitrile results in deprotection of the isopropylidene and loss of water to provide enal **307** in good yield. This in turn undergoes a Wittig reaction to afford 12(*S*)-HETE (**308**). A two-step procedure in which **308** is first treated with chlorodiethylphosphite to furnish quantitatively a phosphite, and this is then treated with anhydrous hydrogen peroxide followed by chromatographic separation of the isomeric mixture, yields *S*-enriched **309** (*S*:*R* = 65:35) to complete the synthesis [101] (Scheme 71).

Optically active propargylic compounds are particularly useful for the preparation of optically active allenes, many of which exhibit biological activity [102,103]. The enantiopure propargylic epoxide (3*R*,4*S*)-1-*tert*-butyldimethylsilyl-3,4-epoxy-1-pentyne (**315**), readily available from **266**, is the type of chiral intermediate versatile enough to provide these chiral propargylic compounds. Swern oxidation of **266** to an aldehyde followed by addition of methyllithium to the crude aldehyde furnishes a 9:1 epimeric mixture of alcohols **310** and **311**, which are easily separated by silica gel chromatography. Subsequent benzylation of **310**, desilylation, and a non-acidic chlorination with carbon tetrachloride and triphenylphosphine provides (2*R*,3*S*,4*S*)-4-benzyloxy-1-chloro-2,3-isopropylidenedioxypentane (**312**). A base-induced elimination of **312** with LDA affords the propargylic alcohol **313** with no detectable epimerization having occurred. Subsequent disilylation and simultaneous debenylation fol-

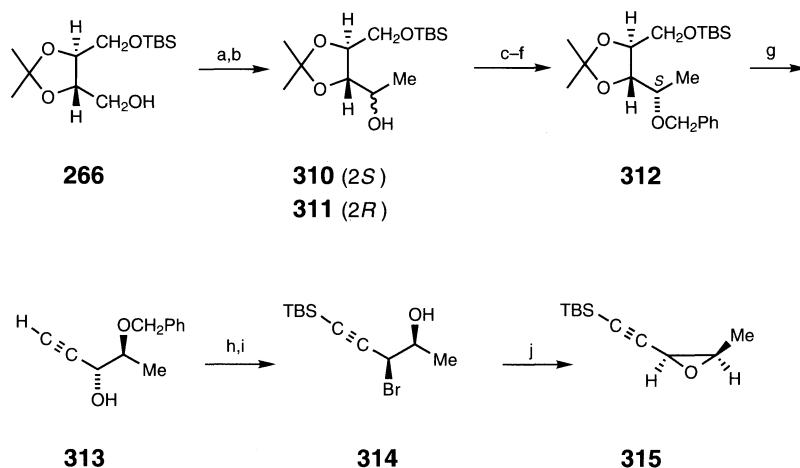


Scheme 71

conditions: (a) Swern [O]; (b) **303**, *n*-BuLi, THF-HMPA; (c) Br⁻ Ph₃P⁺(CH₂)₅CH₃, KHMDS, toluene, -78 °C (81%); (d) *n*-Bu₄NF, THF (98%); (e) Swern [O]; (f) **303**, *n*-BuLi, THF-HMPA; (g) activated alumina, MeCN (63%); (h) I⁻ Ph₃P⁺CH₂CH₂CH=CH(CH₂)₃COOMe, KHMDS, -78 °C (57%); (i) (EtO)₂P(O)Cl, Et₃N, hexane (100%); (j) anhydrous H₂O₂

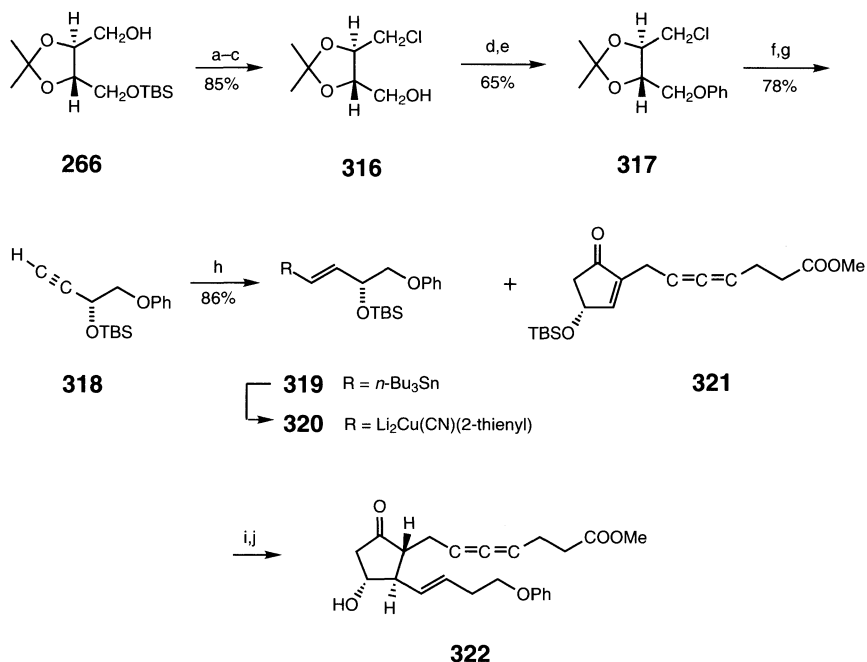
lowed by a highly stereoselective bromination with boron tribromide yields the bromohydrin **314**, which is readily converted in 92% yield to **315** with potassium carbonate in aqueous acetone [104] (Scheme 72).

Enprostil (**322**), an antiulcer prostaglandin analogue, bears an allenic moiety at the 4-position of the α -side chain. Crucial to the synthesis of **322** is introduction of the ω -side chain, which can be prepared optically pure from **266**. Conversion of **266** to the mesylate, followed by lithium chloride displacement and desilylation, furnishes the chloroalcohol **316**. The primary alcohol is activated as a tosylate and nucleophilically displaced with sodium phenoxide to provide **317**, which undergoes a base-induced elimination with LDA to afford, after silyl protection, the propargylic alcohol **318**. This is readily converted to organotin derivative **319**. Subsequent transformation to the organocuprate **320** and coupling with **321** provides, after hydrogen fluoride deprotection, **322** [105] (Scheme 73).



Scheme 72

conditions: (a) Swern [O]; (b) MeLi, THF, -20° to 0° C (79%); (c) Chromatography;
 (d) PhCH₂Br, NaH, *n*-Bu₄Ni, 18-Crown-6, THF (65%); (e) *n*-Bu₄NF, THF (100%);
 (f) Ph₃P, CCl₄, 60° C (80%); (g) LDA, THF, -78° C to 0° C (82%);
 (h) *n*-BuLi, TBSCl, THF (60%); (i) BBr₃, DCM, -78° C (91%); (j) K₂CO₃, acetone/H₂O (92%)

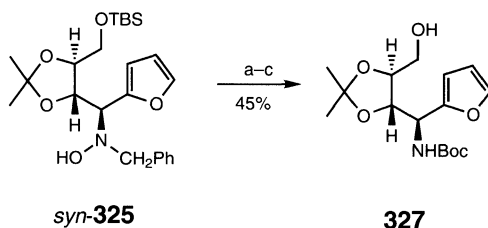


Scheme 73

conditions: (a) MsCl, Et₃N, DCM; (b) LiCl, DMF, 80° C; (c) *n*-Bu₄NF, THF; (d) *p*-TsCl, pyridine, DMAP, DCM;
 (e) PhOH, NaOH, MeOCH₂CH₂OH-H₂O; (f) LDA, THF, 0° C; (g) TBSCl, imidazole, DMF;
 (h) *n*-Bu₃SnH, AIBN, C₆H₆; (i) **320** + **321** (90%); (j) HF, THF (61%)

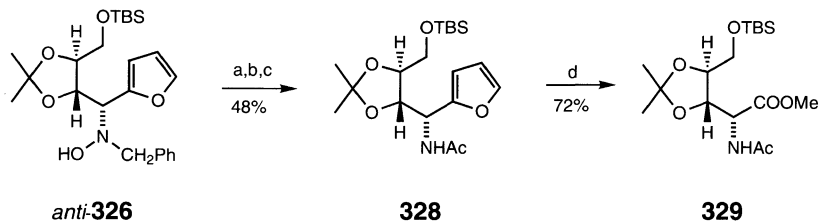
Non-proteinogenic α -amino acids containing one or more hydroxyl groups are not only present in cyclic peptides [106,107] and cyclosporins, but they are also suitable precursors for such biologically active molecules as β -lactams [108], aminosugars [109] and phytosiderophores [110]. Recognition of the fact that furan can be considered a masked carboxylate equivalent has led to the development of a highly diastereoselective addition of 2-lithiofuran to *N*-benzyl nitronne **324**. The reaction of *N*-benzylhydroxylamine with **323**, prepared from the Swern oxidation of **266**, furnishes very good yields of **324** [111]. Freshly generated 2-lithiofuran adds in a highly stereoselective manner to **324** to provide predominantly *syn*-**325** in good to excellent yield. When the addition is performed in the presence of one equivalent of diethylaluminum chloride, the *anti*-adduct **326** is obtained with the same yield and high diastereoselectivity (*syn* and *anti* are defined here relative to the C-3 hydroxy stereochemistry). Presumably the *syn*-adduct arises from a Houk transition-state model of nucleophilic addition to olefins [112], whereas the *anti*-adduct arises from a β -chelated transition-state model. The same results have been observed for addition of the corresponding 2-lithiothiazoles [112,113] (Scheme 74).

Reduction of **325** with titanium(III) chloride in 20% aqueous methanol, followed by treatment of the crude mixture with wet silica gel and Boc protection of the amine, provides **327**, in which the silyl protecting group is lost.

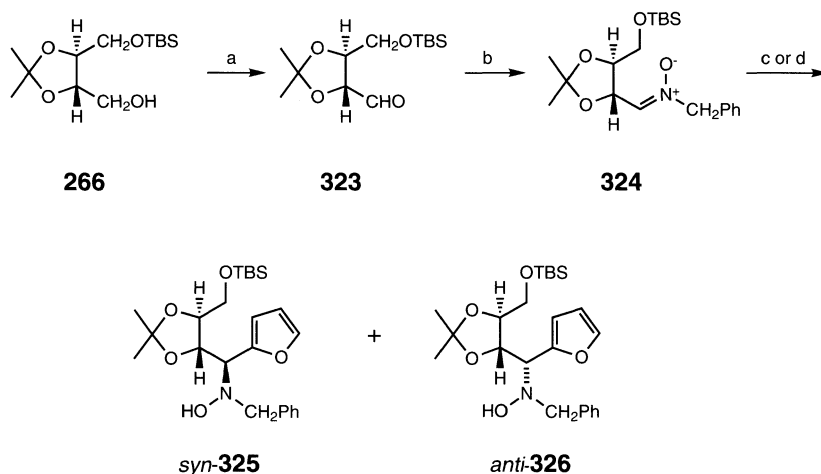


conditions: (a) TiCl_3 , MeOH, H_2O ; (b) SiO_2 , H_2O DCM;
(c) Boc_2O , dioxane

Alternatively, reductive dehydroxylation of **326** with zinc-copper couple followed by *N*-acetylation and debenzylation with lithium in liquid ammonia affords **328**. Ruthenium dioxide-sodium periodate oxidative cleavage of the furyl ring and conversion to the methyl ester with diazomethane affords the (*R*)- α -amino acid ester **329**, which is a fully protected α -epimeric β -alkoxy- α -amino acid [114].



conditions: (a) $\text{Cu}(\text{OAc})_2$, Zn, AcOH, H_2O , 70 °C; (b) Ac_2O , pyridine (71% for 2 steps);
(c) Li, $\text{NH}_3(\text{l})$ (68%); (d) RuO_2 , NaIO_4 , MeCN, CCl_4 , H_2O , then CH_2N_2 , Et_2O

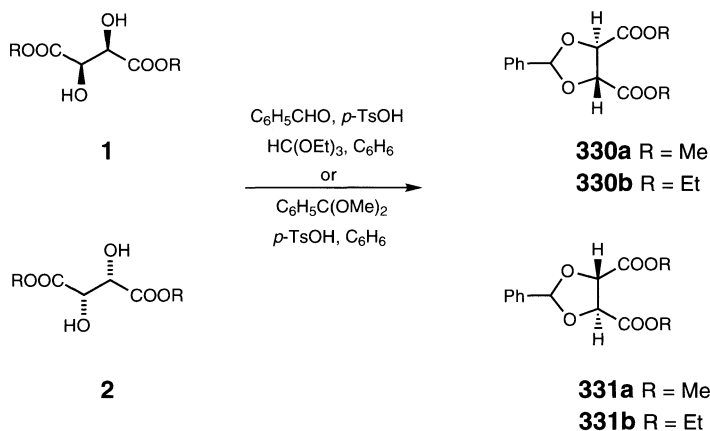


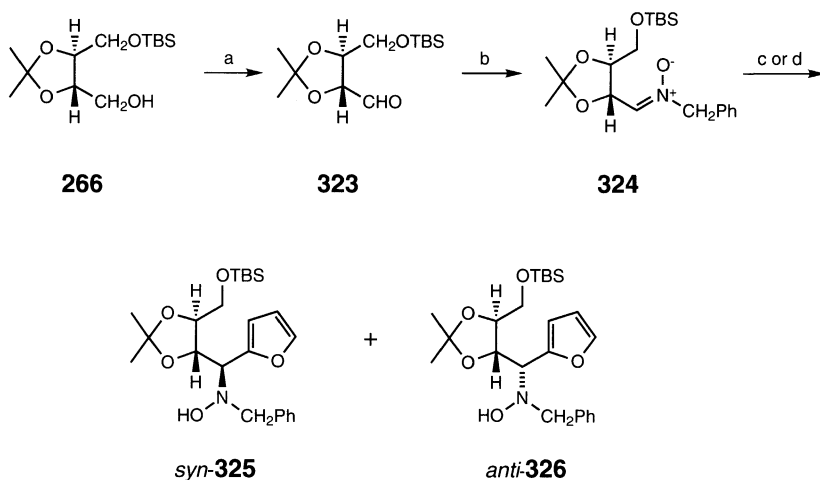
Scheme 74

conditions: (a) Swern [O]; (b) PhCH₂NHOH, MgSO₄(anhydrous), DCM (80%);
 (c) Furan, *n*-BuLi, -78 °C THF (72%, *syn:anti* = 94:6);
 (d) Furan, *n*-BuLi, Et₂AlCl, hexane, -90 ° to -80 °C (70%, *syn:anti* = 8:92)

4.2 2,3-O-Benzylidene Tartaric Acid Derivatives

When either L-tartaric acid esters **1a,b** or D-tartaric esters **2a,b** are treated with benzaldehyde under acidic catalysis with Dean–Stark removal of generated water, good to excellent yields of either (4*R*,5*R*)-(330) or (4*S*,5*S*)-2-phenyl-1,3-dioxolane-4,5-dicarboxylates (**331**) are obtained [115,116]. Acetal exchange, which involves reaction of the tartaric diesters with benzaldehyde dimethyl acetal in the presence of an acid catalyst, is also an excellent protection method [117].





Scheme 74

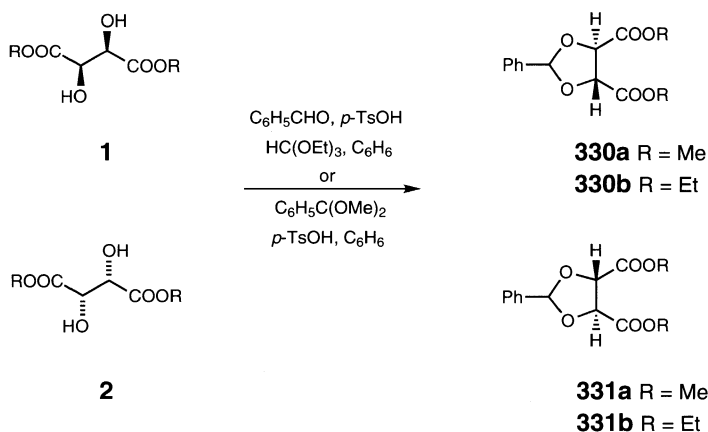
conditions: (a) Swern [O]; (b) PhCH₂NHOH, MgSO₄(anhydrous), DCM (80%);

(c) Furan, *n*-BuLi, -78 °C THF (72%, *syn:anti* = 94:6);

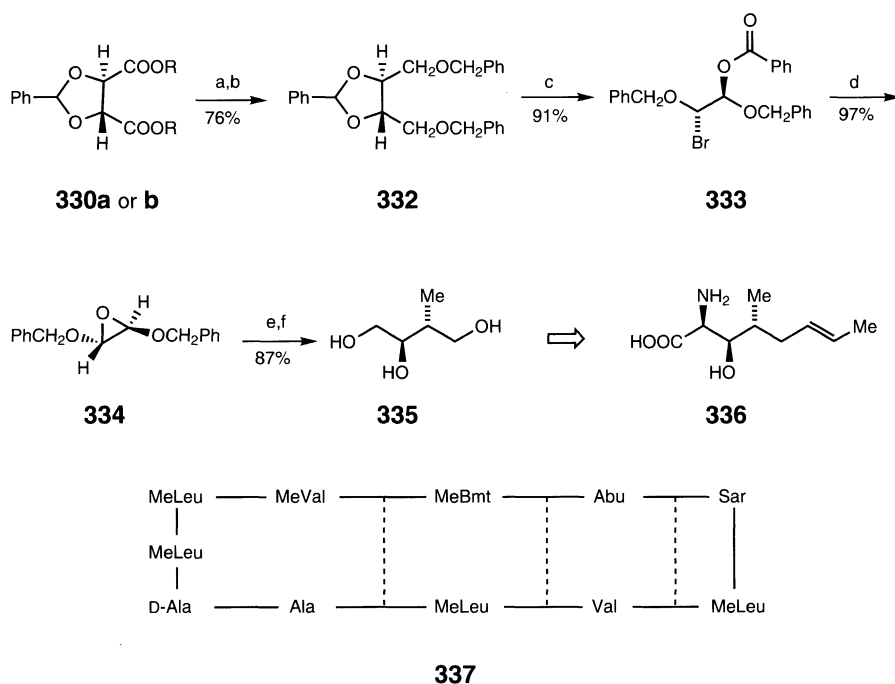
(d) Furan, *n*-BuLi, Et₂AlCl, hexane, -90 ° to -80 °C (70%, *syn:anti* = 8:92)

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Cyclosporin A (**337**) is a cyclic undecapeptide possessing significant immunosuppressant activity. Of the amino acids that comprise the cyclic peptide structure, (2*S*,3*R*,4*R*)-(6*E*)-3-hydroxy-4-methylamino-6-octenoic acid (also known as (4*R*)-4-[(*E*)-2-butenyl]-4, *N*-dimethyl-L-threonine or MeBmt) (**336**), appears as a novel, previously unsynthesized amino acid. Lithium aluminum hydride reduction of **330a** or **330b** followed by dibenzoylation of the hydroxy groups furnishes **332** in 72% overall yield from **1b**. Treatment of **332** with *N*-bromosuccinimide in the absence of light, followed by alkaline ring closure of the resulting bromohydrin **333**, affords the C₂-symmetric epoxide (2*S*,3*S*)-2,3-bis(benzyloxymethyl)-oxirane (**334**). Methyl lithium alkylation of **334** proceeds with complete inversion to afford, after catalytic reductive debenzoylation, the triol (2*R*,3*R*)-3-methyl-1,2,4-butanetriol (**335**). This is converted in eighteen steps to MeBmt (**336**). The overall yield for the 24 step sequence is a remarkable 7.8% [116,118,119] (Scheme 75).

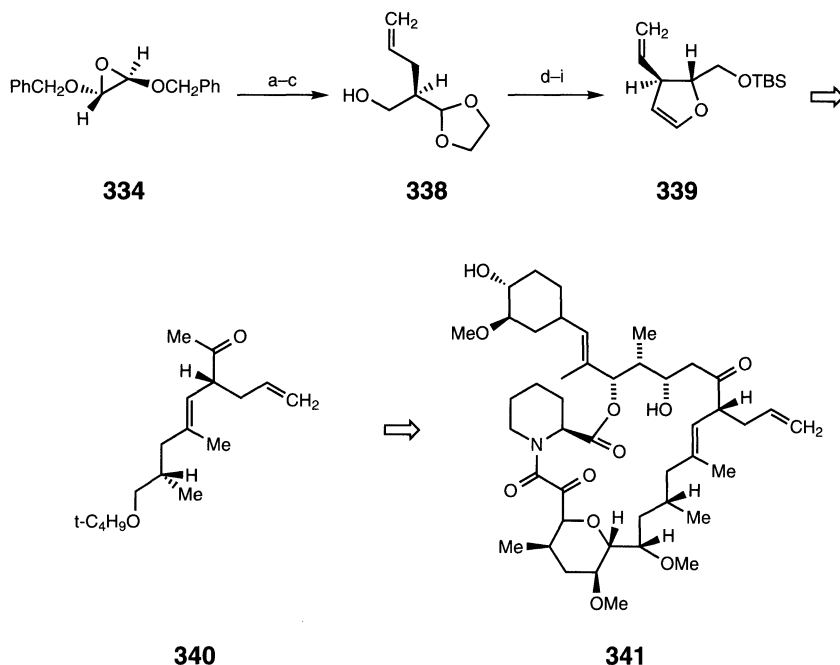


Scheme 75

conditions: (a) LiAlH₄, THF (85%); (b) PhCH₂Br, KOH, toluene (90%); (c) NBS, CCl₄; (d) KOH, EtOH; (e) 2 equiv. MeLi, CuI, Et₂O (89%); (f) H₂, Pd/C, EtOH (98%)

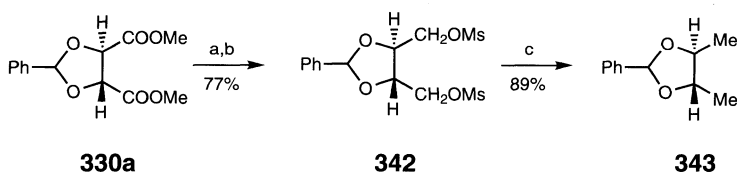
FK-506 (**341**), a macrolide isolated from *Streptomyces tsukubaensis*, has become synthetically interesting due to its potent immunosuppression activity [120]. A convergent synthesis of **341** relies upon effective construction of the appropriate segments. One such segment, the C-16 to C-23 moiety **340**, is prepared from **334**. Nucleophilic epoxide ring-opening of **334** with allylmagnesium bromide followed by debenzoylation and acetonide protection furnishes **338**. This is converted to the enantiomerically pure dihydrofuran **339**. Subsequent transformation of **339** involving a copper-catalyzed migratory insertion reaction furnishes the ketone **340** [121] (Scheme 76).

The versatile enantiomerically pure (2*S*,3*S*)-4,5-dimethyl-2-phenyl-1,3-dioxolane (**343**) can be prepared on an economically large scale from L-tartaric acid in five steps in 63–68%

**Scheme 76**

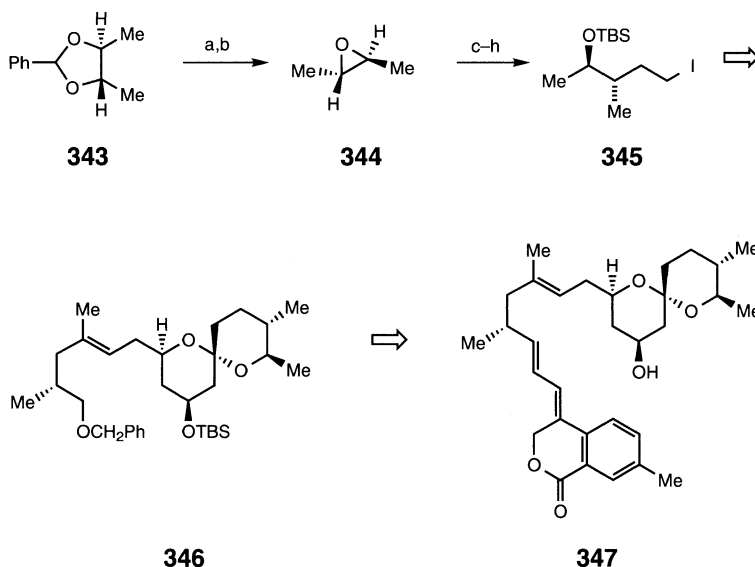
conditions: (a) allylMgBr, THF, $-20\text{ }^{\circ}\text{C}$ (93%); (b) Na, $\text{NH}_3(\text{l})$, THF; (c) acetone, PTSA (63%); (d) *p*-TsCl, pyridine; (e) NaCN, DMSO (75%); (f) 10% HCl, MeOH (74%); (g) TBSCl, imidazole, DCM (98%); (h) DIBAL, $-78\text{ }^{\circ}\text{C}$; (i) MsCl, Et_3N , THF, -30 ° to $50\text{ }^{\circ}\text{C}$ (86%)

overall yield. A principal advantage of this synthesis lies in the ability to reduce the dimethylate **342**, prepared in two steps from **330a**, using sodium borohydride in hot DMSO as opposed to the more costly but comparable use of lithium triethylborohydride to reduce the corresponding ditosylate [117].



conditions: (a) LiAlH_4 , THF (82%); (b) MsCl, Et_3N , DCM (94%); (c) NaBH_4 , DMSO, $100\text{--}140\text{ }^{\circ}\text{C}$ (89%)

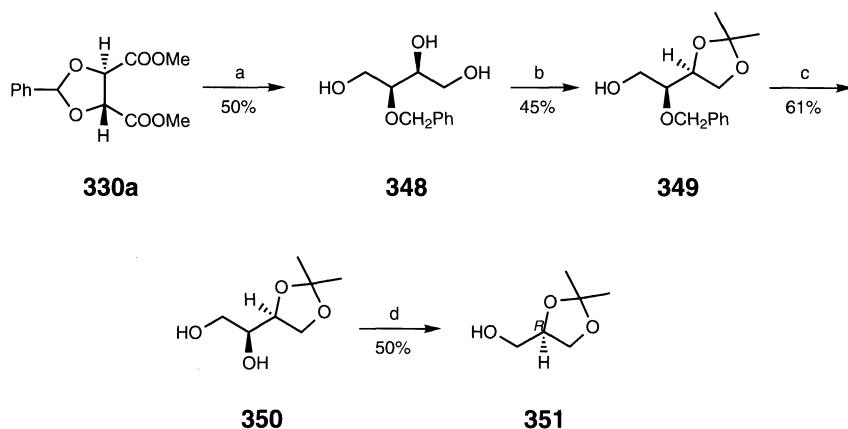
The ability to smoothly convert **343** into the C_2 -symmetric chiral epoxide *trans*-(2*S*,3*S*)-2,3-epoxybutane (**344**) [122] has been exploited for the preparation of (3*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-1-iodo-3-methylpentane (**345**), which is used to prepare the crucial intermediate **346** necessary for the convergent synthesis of Lacrimin A (**347**), a chemically modified Milbemycin having antihypertensive activity [123] (Scheme 77).

**Scheme 77**

conditions: (a) NBS, CCl_4 (99%); (b) NaOH, diethylene glycol, $120\text{ }^\circ\text{C}$; (c) allylMgCl, CuI, $-70\text{ }^\circ\text{C}$, THF (88%); (d) PPh_3 , DEAD, toluene, $p\text{-NO}_2\text{-C}_6\text{H}_4\text{COOH}$ (78%); (e) KOH, $\text{MeOH-H}_2\text{O}$ (90%); (f) TBSCl, imidazole, DCM (82%); (g) O_3 , then NaBH_4 (87%); (h) $p\text{-TsCl}$, pyridine, then NaI, acetone (89%)

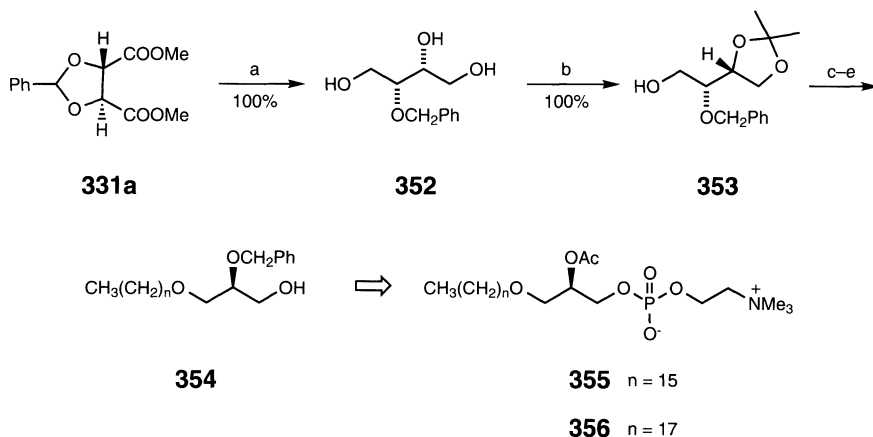
A particularly useful transformation of **330a** exploits the combination of lithium aluminum hydride and aluminum chloride to execute both diester reduction and reductive cleavage of the benzylidene protecting group to furnish triol **348**, which can be converted in modest yields to the acetonide, (3*S*)-3-*O*-benzyl-1,2-*O*-isopropylidene-*L*-threitol (**349**). Catalytic debenzoylation of **349** generates (3*S*)-1,2-*O*-isopropylidene-*L*-threitol (**350**), which is converted to the relatively inaccessible (*R*)-1,2-*O*-isopropylidene-glycerol (**351**) [124] (Scheme 78).

Acetyl glycerol ether phosphorylcholines, also known as platelet-activating factors (PAFs), act as powerful mediators in anaphylaxis and inflammation. Crucial to the biological activity of PAF analogues is the absolute stereochemistry at the C-2 chiral center. In order to evaluate the dependence of biological activity upon C2 chirality, an enantioselective synthesis displaying considerable flexibility has been developed in which either D-(−)- or L-(+)-tartaric acid provides the absolute stereochemistry. Reductive cleavage of **331**, prepared from **2a**, followed by acetonide protection of the vicinal hydroxy groups in **352**, furnishes a nearly quantitative yield of **353** bearing the *R*-configuration at C-3. Subsequent alkylation of the primary alcohol of **353**, removal of the isopropylidene protecting group, lead tetraacetate oxidative cleavage of the resulting glycol, and finally sodium borohydride reduction affords (2*S*)-2-*O*-benzyl-1-*O*-hexadecyl-*syn*-glycerol (**354**) in good overall yield. A four-step sequence completes the synthesis of optically pure *n*- C_{16} -PAF (**355**). The overall synthesis, accomplished in eleven steps, provides **355** in yields of 21–25%. A similar series of reaction affords *n*- C_{18} -PAF (**356**) in an overall yield of 32%. The corresponding (*S*) enantiomers of **355** and **356** are similarly prepared from **350** as the starting chiral intermediate [115,125] (Scheme 79).



Scheme 78

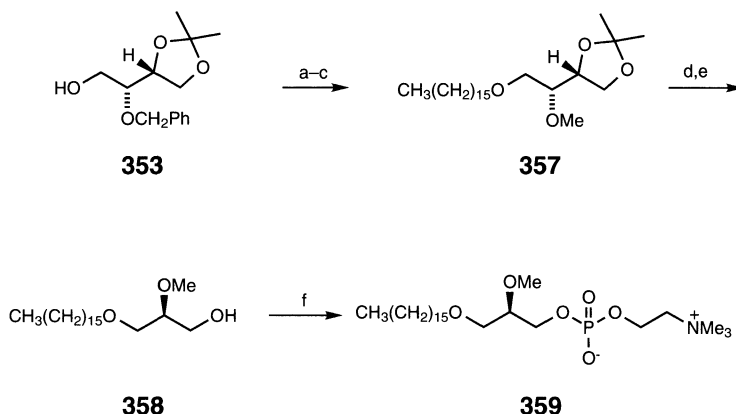
conditions: (a) $\text{LiAlH}_4\text{-AlCl}_3$, $\text{DCM-Et}_2\text{O}$; (b) $\text{Me}_2\text{C}(\text{OMe})_2$, $p\text{-TsOH}$, DCM ;
 (c) H_2 , Pd/C , MeOH ; (d) NaIO_4 , H_2O , 0°C then NaBH_4



Scheme 79

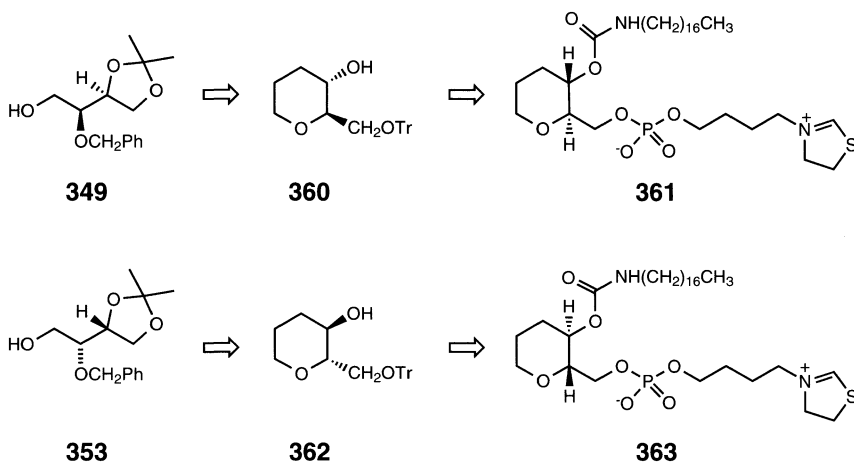
conditions: (a) $\text{LiAlH}_4\text{-AlCl}_3$ (1:1), $\text{Et}_2\text{O-DCM}$; (b) $\text{Me}_2\text{C}(\text{OMe})_2$, $p\text{-TsOH}$; (c) $n\text{-C}_{16}\text{H}_{33}\text{OMs}$, KH , PhH (88%) or $n\text{-C}_{18}\text{H}_{37}\text{OMs}$, KH , PhH (94%); (d) 2N HCl , THF ;
 (e) $\text{Pb}(\text{OAc})_4$, PhH , then NaBH_4 , MeOH

The synthesis of the 2-*O*-methyl analogue **359**, which exhibits growth-inhibitory activity on cultured myeloid leukemia cells, demonstrates the flexibility of this methodology. Alkylation of **353** followed by reductive debenzoylation and alkylation of the secondary hydroxy group with methyl iodide provides 1-*O*-hexadecyl-2-*O*-methyl-D-threitol (**357**). Acidic hydrolysis of the isopropylidene protecting group, oxidative cleavage of the resulting glycol, and sodium borohydride reduction furnishes **358**, which is conveniently converted to 1-*O*-hexadecyl-2-*O*-methyl-*syn*-glycerol-3-phosphocholine (**359**) in an overall yield of 74% for the nine step sequence [125] (Scheme 80).

**Scheme 80**

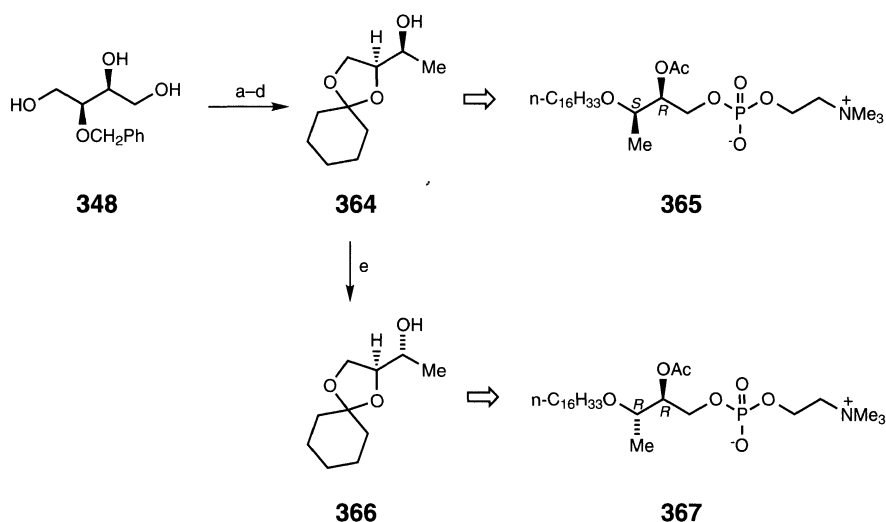
conditions: (a) *n*-C₁₆H₃₃OMs, KH, PhH (88%); (b) H₂, Pd/C, MeOH (87%); (c) MeI, KH, PhH (98%); (d) 6 N HCl, THF (98%); (e) Pb(OAc)₄, PhH then NaBH₄ (90%); (f) Cl₂P(O)OCH₂CH₂Br then Me₃N (75%)

Cyclic PAF analogues, such as the chiral tetrahydropyrans **361** and **363**, represent conformationally restricted glycerol derivatives that exhibit potent PAF antagonistic activity [126]. A twelve-step sequence converts **349** or **353** to (2*R*,3*S*)-(360) (*ee* = 98.8%) or (2*S*,3*R*)-2-triphenylmethoxymethyltetrahydropyran-3-ol (362) (*ee* = 96.8%), respectively. These are then appropriately transformed to the corresponding PAF products **361** and **363** [127].



The design of PAF analogues with selective hypotensive activity but limited ability to cause platelet activation has resulted in development of a highly selective agonist (**365**) with orally-potential antihypertensive activity. The key feature in the synthesis of this agonist is

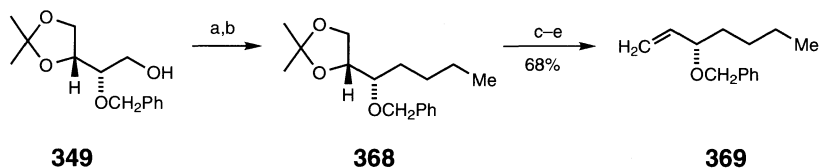
introduction of a methyl group at C-1. This creates a second chiral center in the molecule. The synthesis of both (1*S*)-**365** and (1*R*)-**367** from the common chiral triol intermediate **348** illustrates further the utility of this remarkable tartaric acid derivative. Protection of the vicinal hydroxy groups of **348** as the cyclohexylideneacetal, followed by tosylation of the primary hydroxy group and hydride reduction to the desired methyl group, furnishes the crucial intermediate **364**, in which C-2 has the *S*-configuration while C-3 has the *R*-configuration. In nine steps **364** is converted to 1*S*-Me-PAF (**365**) in an overall yield of 30% from *L*-tartaric acid. A Mitsunobu inversion of the 2*S*-hydroxy group in **364** provides the 2*R*-derivative **366**, which is similarly transformed to the biologically less active 1*R*-Me-PAF (**367**) [128] (Scheme 81).



Scheme 81

conditions: (a) cyclohexyl dimethylacetal, *p*-TsOH, PhH; (b) *p*-TsCl, Et₃N, DCM;
 (c) LiAlH₄, Et₂O; (d) Na, NH₃(l); (e) Ph₃P, DEAD, PhCOOH, THF then hydrolysis

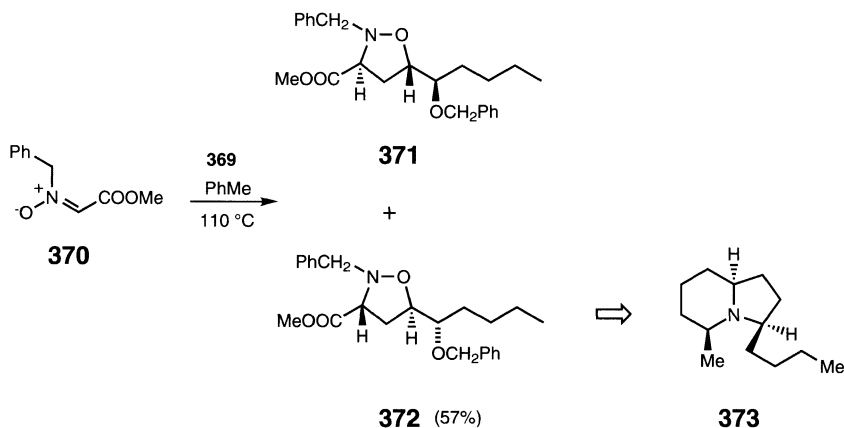
The indolizidine alkaloid (+)-monomorine I (**373**), isolated from Pharaoh's ant *Mono-morium pharaonis*, is the first example of an indolizidine alkaloid found in the animal kingdom. One enantioselective total synthesis of **373** exploits an asymmetric cycloaddition of nitrene **370** to the chiral allylic ether **369**, which is prepared from **349**. The conversion of **349** to a tosylate followed by treatment with *n*-propylmagnesium bromide in the presence of



conditions: (a) *p*-TsCl, DCM, DMAP (97%); (b) *n*-C₃H₇MgBr, Li₂CuCl₄, THF (87%);
 (c) 6*N* HCl, MeOH (98%); (d) Me₂NCH(OMe)₂; (e) Ac₂O, reflux (70%)

dilithium tetrachlorocuprate affords **368** in very good yields. Subsequent acetonide hydrolysis, formation of the *N,N*-dimethylformamide dimethyl acetal, and thermal elimination furnishes the allylic ether **369** in 68% overall yield from **368**.

The thermal reaction of **369** with nitron **370** in refluxing toluene affords a separable 1:3 mixture of C-3,C-5-*trans*-isoxazolidines **371** and **372** in 76% yield. The pure diastereomer [*3R,5R,5(1S)*]-*N*-benzyl-5-[1-(benzyloxy)pentyl]isoxazolidine-3-carboxylate (**372**) is converted in fourteen steps to (+)-monomorine (**373**) [129] (Scheme 82).

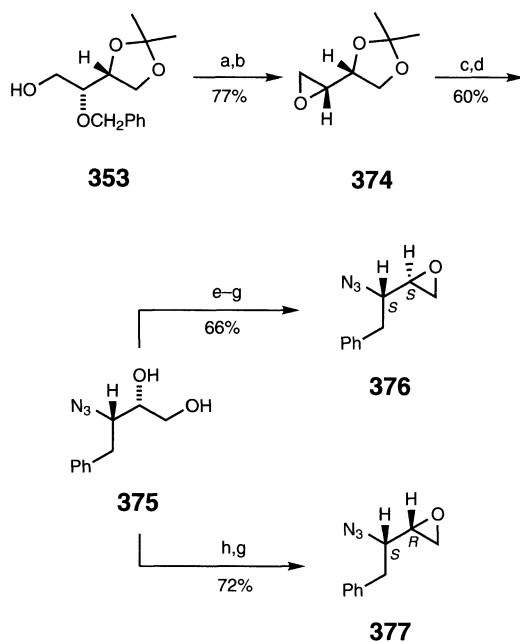


Scheme 82

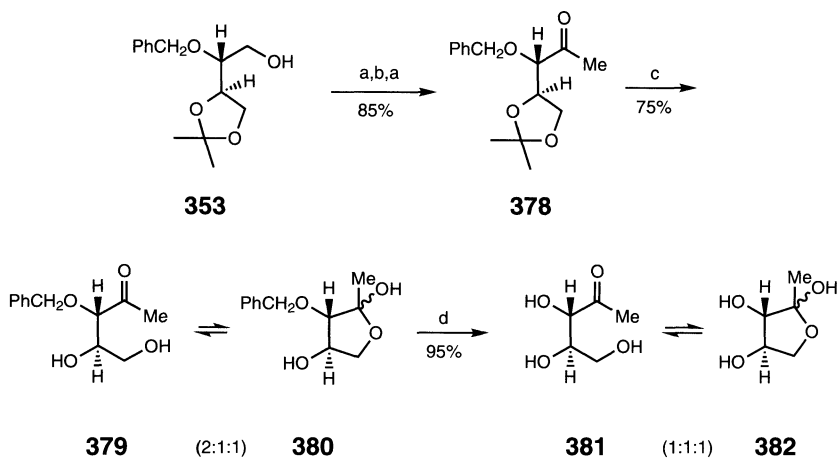
Enantiomerically pure azidoalkyl epoxides **376** and **377**, efficiently synthesized from D-(-)-tartaric acid, are protected aminoalkyl epoxides utilized in the synthesis of potent and selective inhibitors of HIV-1 protease and other aspartic proteases. Catalytic debenzoylation of **353** with Pearlman's catalyst followed by epoxide ring formation with triphenylphosphine–DEAD furnishes in good yield the epoxide **374**. Epoxide ring opening with phenylmagnesium bromide in the presence of a catalytic amount of copper(I) cyanide followed by a Mitsunobu azidation and aqueous acetic acid deketalization provides diol **375**. By selecting either the primary or secondary hydroxy group to effect epoxide ring formation, either 2(*S*)-[1'(*S*)-azido-2-phenylethyl]oxirane (**376**) or 2(*R*)-[1'(*S*)-azido-2-phenylethyl]oxirane (**377**) can be prepared [131] (Scheme 83).

A new stereocontrolled synthesis of 1-deoxy-D-*threo*-2-pentulose (**381**), a biosynthetic precursor to the thiazole moiety of thiamin, utilizes **353** as the chiral intermediate. Dess–Martin oxidation of the primary hydroxy group in **353**, addition of methylmagnesium bromide to the resulting aldehyde, followed by a second Dess–Martin oxidation of the secondary hydroxyl group provides the ketone **378** in good overall yield. Acidic deketalization affords the diol **379**, which exists in equilibrium with the diastereomeric hemiketals **380** (2:1:1 in CDCl_3). The synthesis is completed by hydrogenolysis of the benzyl ethers **379/380** to yield the pentulose **381**, also as an equilibrium mixture of ketone **381** and hemiketals **382** (1:1:1 in CD_3OD) [132] (Scheme 84).

The versatility of **330b** is demonstrated by the systematic transformation of **330b** into a number of protected L-threitol derivatives. Facile sodium borohydride reduction in aqueous ethanol followed by DIBAL reductive cleavage of the resulting diol **383** provides (2*S*,3*S*)-2-*O*-benzyl-L-threitol (**384**) (the enantiomer of **352**) in good yield. In fact, this two-step procedure is preferred, because it is more practical than one-step reductive cleavage (LiAlH_4 –

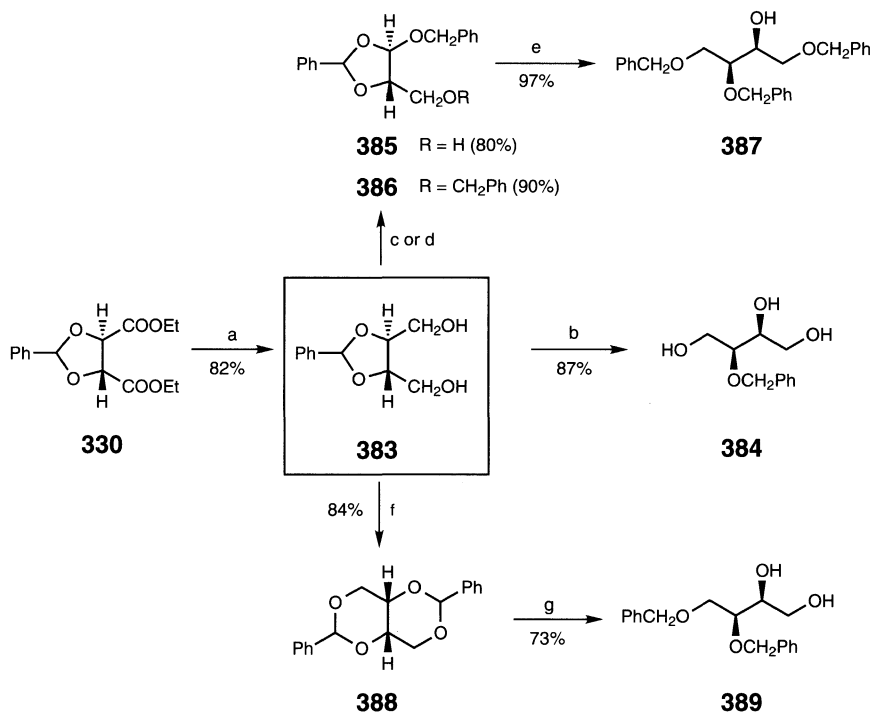
**Scheme 83**

conditions: (a) $H_2, Pd(OH)_2, EtOH$; (b) $Ph_3P, DEAD, PhH$; (c) $PhMgBr, CuCN, THF$;
 (d) $(PhO)_2P(O)N_3, Ph_3P, DEAD, THF$; (e) $C_6H_5COCl, pyridine$;
 (f) $MsCl, pyridine$; (g) $NaOMe, THF$; (h) $MeOOCCH_2CH_2COCl, CHCl_3$

**Scheme 84**

conditions: (a) Dess–Martin [O]; (b) $MeMgBr$; (c) $3N HCl, THF$; (d) $H_2, Pd/C, MeOH$

AlCl_3) for large scale preparations of **384** (or **352**). Treatment of **383** with benzaldehyde results in a concomitant benzylidenation and rearrangement to furnish (2*S*,3*S*)-1,3 : 2,4-di-*O*-benzylidene-L-threitol (**388**). A DIBAL reductive cleavage of **388** affords (2*S*,3*S*)-di-*O*-benzyl-L-threitol (**389**), which is also available from **383** via a monobenylation followed by reductive cleavage of the intermediate **385** with DIBAL. Treatment of **383** with excess benzyl bromide provides the dibenzylated derivative **386**, which undergoes reductive cleavage to afford 1,2,4-tri-*O*-benzyl-L-threitol (**387**) in excellent yield [133] (Scheme 85).

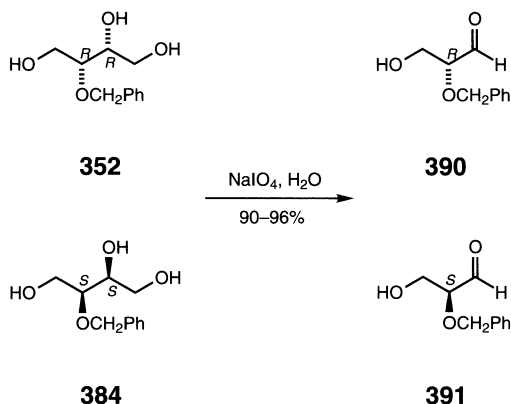


Scheme 85

conditions: (a) NaBH_4 , aq. EtOH, 0 °C; (b) DIBAL, DCM-toluene, rt; (c) PhCH_2Br , NaH, DMF; (d) 5 equiv. PhCH_2Br , NaH, DMF; (e) DIBAL, toluene, 0 °C to rt; (f) $\text{C}_6\text{H}_5\text{CHO}$, *p*-TsOH, PhH; (g) DIBAL, DCM-toluene, rt

The oxidative cleavage of (*R,R*)-**352** or (*S,S*)-**384** with sodium periodate in water proceeds in excellent yield to afford either (*R*)-2-*O*-benzylglyceraldehyde (**390**) or (*S*)-2-*O*-benzylglyceraldehyde (**391**). Both enantiomers can be distilled to a colorless oils with fruit-like odors. However, upon standing, these pure aldehydes become syrupy and are finally transformed into waxy, odorless solids, signifying extensive oligomerization and polymerization (Scheme 86).

Nevertheless, both enantiomers maintain C-2 configurational stability (no racemization) so that C-C bond formation can be achieved without loss of chirality. This is observed, for example, when **390** undergoes a Horner-Wittig reaction with the anion of triethylphosphonoacetate to produce the *E*-pentaenoic ester **392**. High diastereoselectivity (*E/Z* = > 97 : 3) and enantiomeric purity (*S/R* = > 97 : 3) are observed when **390** is added



Scheme 86

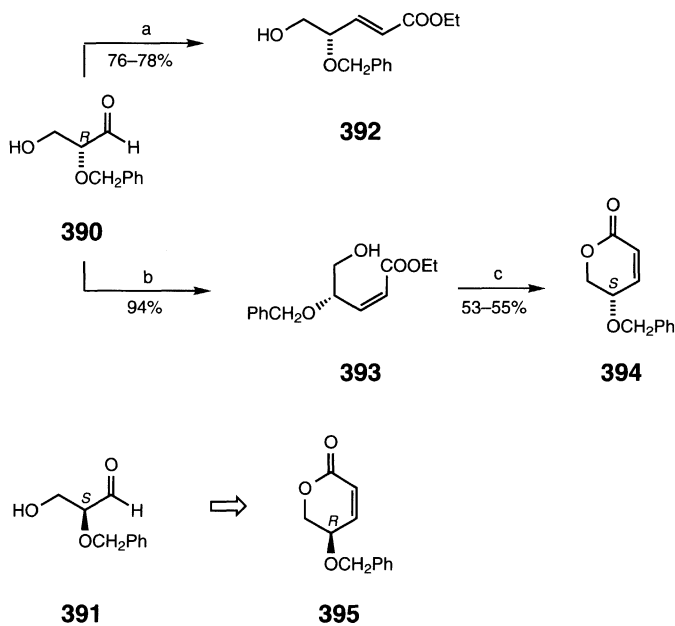
to the preformed anion at -78°C . The *Z*-selective Wittig reaction with ethoxycarbonylmethylenetriphenylphosphorane in acid-free methanol provides a 94% yield of *Z*-pentenoic ester **393** with *E/Z* = 24 : 76 diastereoselectivity. Pure **393** undergoes acid-catalyzed lactonization to provide (*S*)-penten-5-olide **394**. Similarly, use of **391** affords the corresponding (*R*)-**395** [134] (Scheme 87).

The synthetic utility of (*R*)-enoate **392** is illustrated in the stereoselective synthesis of the bengamide E derivative **399** (Scheme 88). Silyl protection of **392**, reduction with DIBAL, and Sharpless epoxidation of the resulting allylic alcohol furnishes epoxy alcohol **396** as a 95 : 5 *anti* : *syn* mixture. Conversion of the primary hydroxyl group of **396** to an iodide under neutral conditions followed by a metallation–elimination and subsequent *in situ* methylation provides the ether **397**. Ozonolysis, desilylation with aqueous acetic acid, and a Dess–Martin oxidation supplies the α,β -dialkoxy aldehyde **398**. This, utilizing stannane S_{E}' addition, is then converted to **399** [135].

4-Hydroxypyrrolidines (1,3,4-trideoxy-1,4-iminoglycitols) represent important intermediates for the synthesis of polyhydroxylated N-bicycles. Conversion of (*S*)-**391** to the chlorohydroxamic acid **400** by oximation/chlorination, followed by cycloaddition of the *in situ* generated nitrile oxide of **400** with allyl chloride, furnishes the 5-chloromethylidihydro-1,2-oxazoles **401** and **402** as a 1 : 1 mixture of diastereomers (Scheme 89).

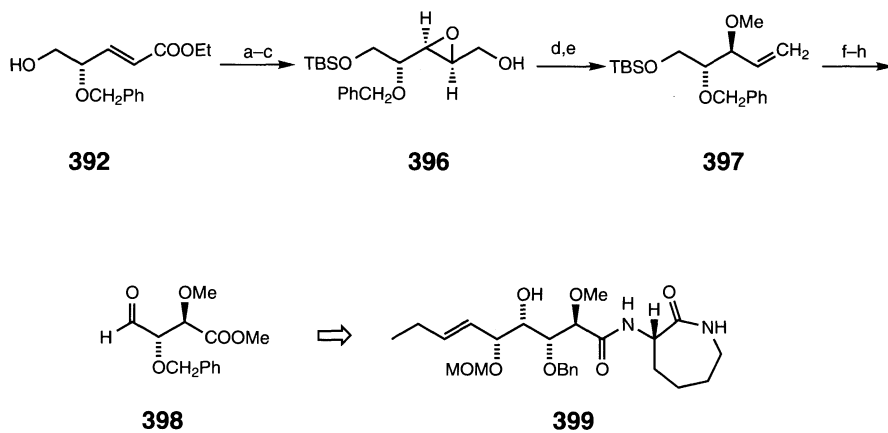
Chromatographic separation of this mixture provides the two diastereomers **401** and **402** in 46% yield and in gram quantities. The highly selective catalytic hydrogenation of **401** in the presence of platinum on charcoal followed by reductive debenzoylation in the presence of palladium on charcoal provides a mixture of *L-ribo*-**403** (3,5-*trans*) and *L-xylo*-**404** (3,5-*cis*) in a diastereomeric ratio of 93 : 7. Similarly, **402** in two steps affords *L-lyxo*-**405** (3,5-*trans*) and *L-arabino*-**406** (3,5-*cis*) in a diastereomeric ratio of 80 : 20. With the ready availability of (*R*)-**390**, the corresponding D-series compounds can be prepared with similar diastereochemical results [136] (Scheme 90).

The quantitative addition of benzylamine to **391** provides *S,O*-benzylglyceraldimine (**407**), which undergoes Grignard addition to afford a mixture of *threo*-**408** and *erythro*-**409** amino alcohols. The product ratio obtained depends on the solvent and metal cation employed. Addition of cerium(III) chloride in THF reverses the stereoselectivity in favor of the *erythro* adduct **409** [137].



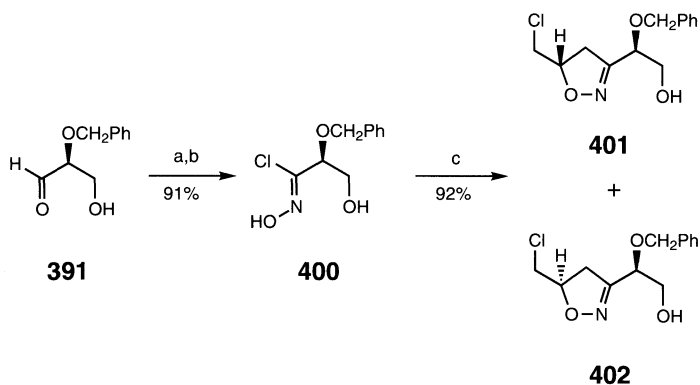
Scheme 87

conditions: (a) $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COOEt}$, NaH, THF, 0 °C then -78 °C and **390**;
 (b) $\text{Ph}_3\text{P}=\text{CHCOOEt}$, MeOH, 0 °C; (c) *p*-TsOH, toluene, H_2O

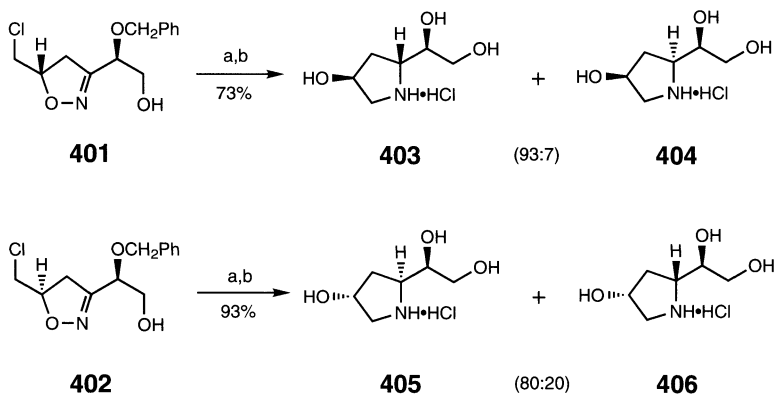


Scheme 88

conditions: (a) TBSCl, imidazole, DMF (99%); (b) DIBAL, -78 °C (76%); (c) D-(-)-DIPT, TBHP, TIP (98%);
 (d) Ph_3P , I_2 , imidazole; (e) *tert*-BuLi, $(\text{MeO})_2\text{SO}_2$ (90%); (f) O_3 , MeOH, NaOH, DCM (72%);
 (g) AcOH, H_2O , THF (88%); (h) Dess-Martin [O] (85%)

**Scheme 89**

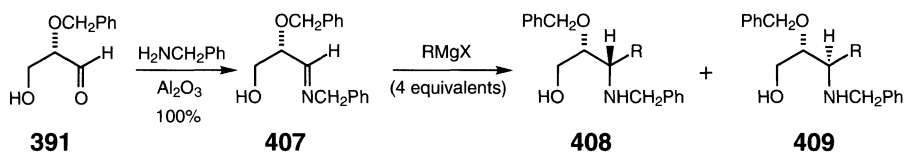
conditions: (a) $\text{NH}_2\text{OH}\cdot\text{HCl}$, Na_2CO_3 , H_2O (95%); (b) NCS , DMF , HCl (cat.) (96%); (c) $\text{ClCH}_2\text{CH}=\text{CH}_2$ (6 equiv.), Et_3N , Et_2O

**Scheme 90**

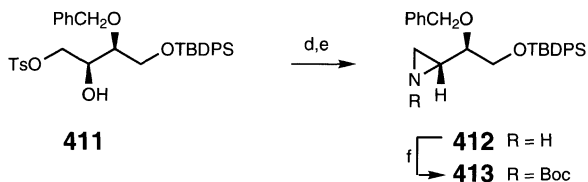
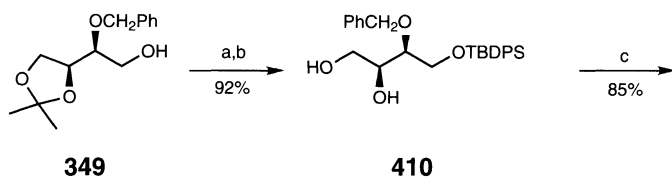
conditions: (a) H_2 , Pt/C , MeOH (100%); (b) H_2 , Pd/C , MeOH , conc. HCl

Sugar-derived chiral functionalized aziridines are extremely useful aminoalkylating intermediates for the synthesis of enantiomerically pure amino derivatives. Silyl protection of the free primary hydroxy group of **349** followed by removal of the isopropylidene protecting group provides the vicinal diol **410**. Regioselective tosylation of the primary hydroxy group is achieved through stannyldiene activation to furnish **411** in 85% yield. Sodium azide treatment of **411** leads to the azido alcohol, which undergoes a triphenylphosphine reductive ring closure to the aziridine **412** that is then protected as its *N*-Boc derivative **413** [138] (Scheme 91).

The utility of **413** is illustrated in the five-step synthesis of 2-amino-2-deoxy-*L*-threitol (**414**), which is oxidized either to 2-amino-2-deoxy-*L*-erythrose (**415**) under Swern conditions or to 2-amino-2-deoxy-*L*-erythronic acid (**416**) under potassium chromate–sulfuric acid conditions (Scheme 92).



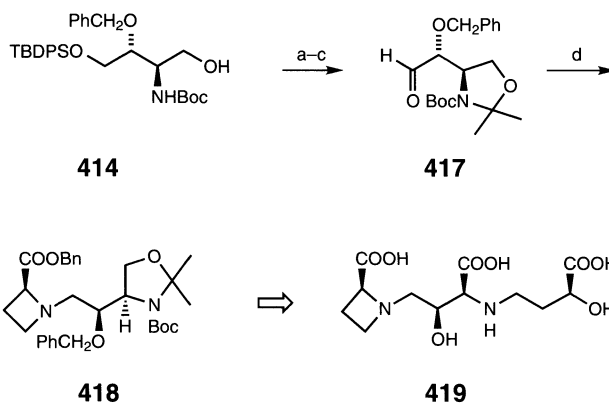
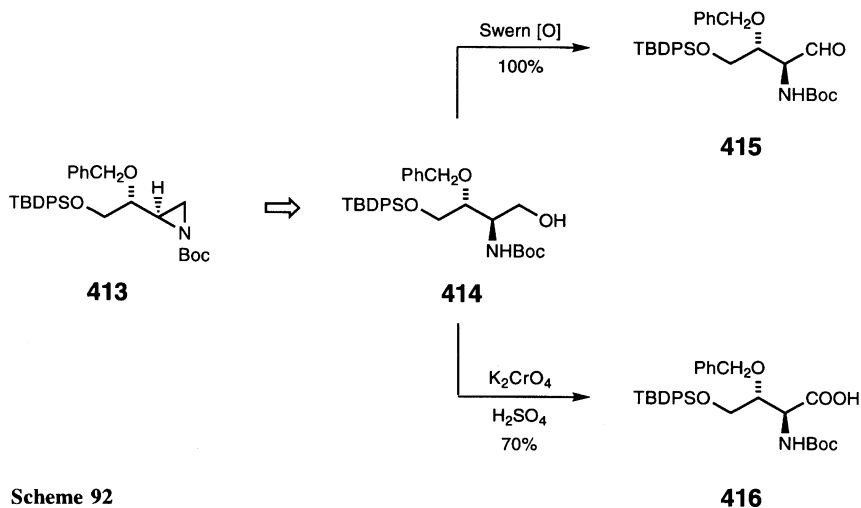
RM	Yield (%)	408:409
MeMgBr	78	63:37
<i>n</i> -C ₄ H ₉ MgBr	73	73:27
<i>n</i> -C ₆ H ₁₁ CH ₂ MgBr	58	>95:5
<i>tert</i> -C ₄ H ₉ MgCl	86	56:44
vinylMgBr	91	83:17
allylMgBr	74	40:60
MeLi	80	46:54
<i>tert</i> -C ₄ H ₉ Li	79	40:60
MeMgCl/CeCl ₃	69	9:91
<i>iso</i> -C ₄ H ₉ MgBr/CeCl ₃	62	<5:95
PhCH ₂ MgBr	87	40:60
PhCH ₂ MgCl/CeCl ₃	70	76:24



Scheme 91

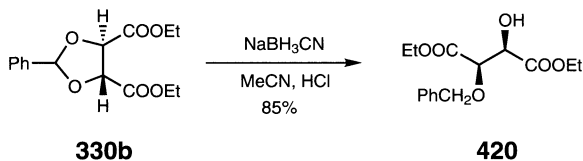
conditions: (a) *tert*-BuPh₂SiCl, imidazole, DMF; (b) 70% AcOH, 40 °C; (c) *n*-Bu₂SnO, PhMe then *p*-TsCl, DCM, reflux; (d) NaN₃, DMSO, 65 °C (90%); (e) PPh₃, PhMe, 100 °C, 2 h; (f) Boc₂O, Et₃N, THF

Alternatively, 414 can be converted to 3-amino-3-deoxy-D-erythrose (417), which is further transformed into γ -azetidyl- β -hydroxy-amino alcohol 418, a precursor to mugineic acid (419) [138] (Scheme 93).

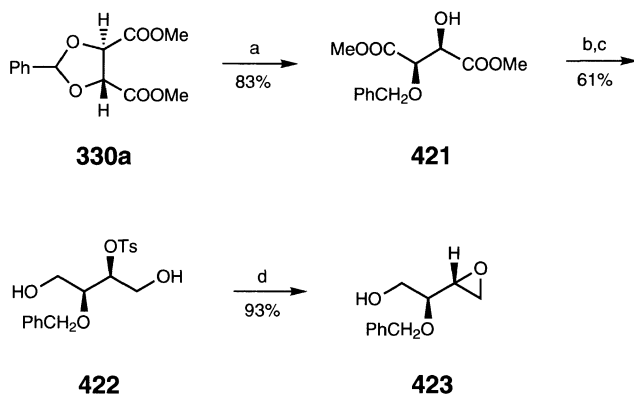


conditions: (a) $\text{Me}_2\text{C}(\text{OMe})_2$, *p*-TsOH, toluene (84%); (b) resin-supported TBAF (90%); (c) Swern [O] (100%); (d) benzyl (*S*)-2-azetidinecarboxylate, NaBH_3CN , MeOH (65%)

The reductive ring opening of **330b** has been accomplished with sodium cyanoborohydride in acetonitrile in the presence of hydrogen chloride to provide efficiently monobenzyl ether **420** in 85% yield [139].



The reductive ring opening of **330a** with sodium cyanoborohydride/titanium tetrachloride in acetonitrile occurs with no ester reduction whatsoever to provide **421** in 83% yield. Subsequent conversion to the tosylate followed by reduction with lithium borohydride/lithium triethylborohydride affords in 61% yield the crystalline diol **422**. Lithium aluminum hydride or sodium borohydride reduction of the tosylate of **422** fails to produce clean reductions to **422**. Epoxide ring closure of **422** is achieved with two equivalents of sodium hydroxide in methanol to furnish in 93% yield (2*S*,3*R*)-2-benzyloxy-3,4-epoxybutan-1-ol (**423**) [140] (Scheme 94).

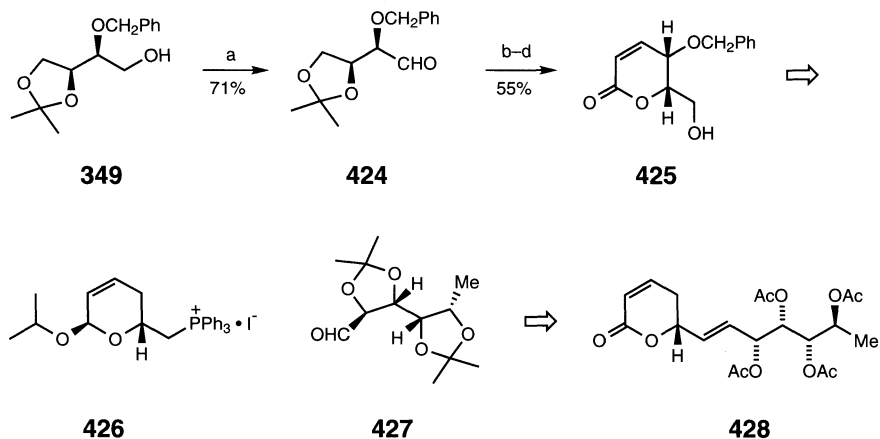


Scheme 94

conditions: (a) $\text{NaBH}_3\text{CN}-\text{TiCl}_4$, MeCN; (b) *p*-TsCl, pyridine, DMAP, DCM; (c) LiBH_4 , LiEt_3BH , THF; (d) NaOH, MeOH, H_2O

A convergent total synthesis of (+)-anamarine (**428**), isolated from the flowers and leaves of an unclassified Peruvian *Hyptis* species, utilizes the chiral diacetonide of 6-deoxyaldehyde-L-glucose (**427**), readily available from D-gulonolactone, and (*R,R*)-6-alkoxy-2-triphenylphosphoniomethylidihydropyran iodide (**426**), prepared from **349** (Scheme 95). Oxidation of **349** with pyridinium chlorochromate/aluminum oxide [141,142] furnishes the aldehyde **424** in 71% yield. Wittig C-2 extension, hydrolysis, and lactonization provides the enelactone **425** in 30% overall yield for the six steps from (*R,R*)-diethyl tartrate (**1b**). A series of six functional group transformations provides **426**, which is coupled in 60% yield with **427**. The resulting condensation product is then deprotected and appropriately functionalized to afford (+)-anamarine (**428**) with high optical purity [143].

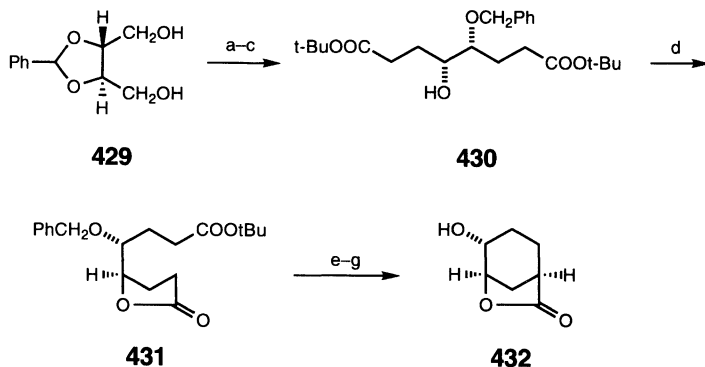
The need to develop efficient strategies for the total synthesis of FK-506 (**341**), an important immunosuppressive agent, as well as its constituent parts, has attracted numerous creative approaches. A key intermediate toward synthesis of the cyclohexyl fragment present in **341** is the bicyclic lactone **432**. The diol **429**, available from **331**, is triflated, then coupled with *tert*-butyllithioacetate (2.5 equivalents) in a mixed solvent of THF and 2,6-dimethylpropyleneurea (DMPU) to provide in 71% yield the diester, which is then reductively cleaved with triethylsilane/ TiCl_4 at -78°C to afford monobenzyl ether **430** in good overall yield. Exposure to trifluoroacetic acid produces (4*R*,5*R*)-5-(benzyloxy)-7-carboxy-4-heptanolide (**431**) in 86% yield. Of the numerous decarboxylative halogenations available, only iodobenzene diacetate in refluxing $\text{CCl}_4-\text{Cl}_2\text{CHCHCl}_2$ containing an equimolar amount of iodine provides a successful route to preparation of the iodide which, following an intramolecular alkylation, furnishes the bicyclic lactone (1*R*,4*R*,5*R*)-4-(benzyloxy)-6-oxabicyclo[3.2.1]octan-



Scheme 95

conditions: (a) PCC–Al₂O₃, NaOAc, DCM; (b) Ph₃P=CHCOOMe, MeOH (71%);
 (c) LiOH, THF, MeOH; (d) TFA–H₂O ((9:1)

7-one (**432**) (Scheme 96). A more practical route for large scale preparation of **431** has been developed utilizing D-mannitol [144].

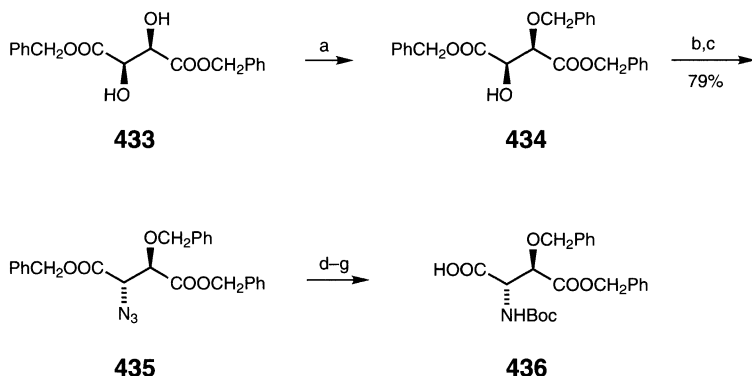


Scheme 96

conditions: (a) Tf₂O, pyridine; (b) LiCH₂COOtBu, THF–HMPA (6:1), –78 °C (71%);
 (c) Et₃SiH, TiCl₄, –78 °C, DCM (88%); (d) TFA–H₂O (7:3);
 (e) PhI(OAc)₂, I₂, CCl₄–CHCl₂CHCl₂ (4:1), hv (66%);
 (f) LiN(TMS)₂, THF, –90 °C (94%); (g) H₂, Pd(OH)₂/C, EtOAc (100%)

Monobenylation can also be accomplished directly on tartrate esters, although yields, despite the C₂-symmetry, tend to be low. Dibenzyl tartrate (**433**) [145] is converted to benzyl ether **434** by treating the diester with sodium hydride and benzyl bromide. The isolated yield of **434** from tartaric acid is 36%. *In situ* generation of the triflate with trifluoromethanesulfonic anhydride in the presence of 2,6-lutidine followed immediately with tetramethylguanidinium azide provides the pure azide **435** in 79% yield. Reduction of this azide with hydrogen sulfide/triethylamine, regioselective saponification of the aminoester, and protection of the free amine as the Boc amide furnishes O⁴-benzyl hydrogen (2*S*,3*R*)-*N*-(*tert*-butoxycarbonyl)-3-

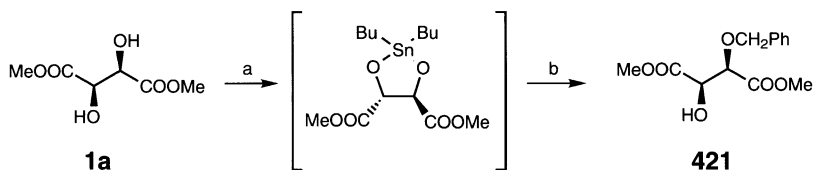
benzyloxyaspartate (**436**) (Scheme 97). This synthesis is amenable to preparation of multi-gram amounts of **436** [146].



Scheme 97

conditions: (a) PhCH₂Br, NaH, DMF; (b) (CF₃SO₂)₂O, 2,6-lutidine, DCM, -78 °C; (c) tetramethylguanadinium azide, -120 ° to 0 °C; (d) H₂S, Et₃N, DCM (62%); (e) CuBr₂, EtOH, NaHCO₃; (f) 1N HCl, EDTA (24%); (g) Boc₂O, Et₃N, DMF (92%)

Selective monoprotection of diols is moderately effective. Fluoride ion-promoted monoalkylation of tartrate diesters that have been activated as the stannylene acetal is an extremely effective method for the efficient monoalkylations of diols. An equimolar mixture of dimethyl tartrate (**1a**) and dibutyltin oxide in toluene, heated under reflux to azeotropically remove the formed water, provides a stannylene acetal. The crude acetal in DMF is treated with cesium fluoride and then benzyl bromide to provide in 85% yield the dimethyl (2*R*,3*R*)-2-*O*-benzyloxytartrate (**421**). Reaction of **1a** with benzyl bromide and CsF in DMF proceeds to provide **421** in only 5% yield. Benzyl iodide is generally a better alkylating agent, providing **421** in 99% yield [147].



conditions: (a) (Bu₂SnO)_n, toluene, reflux; (b) CsF, PhCH₂X

4.3 Miscellaneous Diol-Protected Tartaric Acid Derivatives

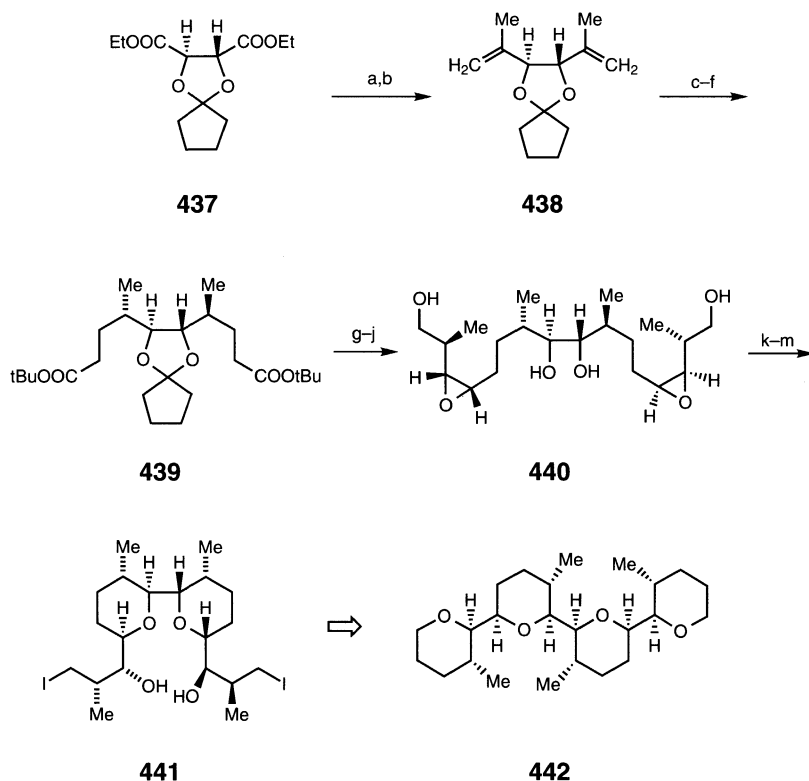
Choice of the appropriate diol protecting group to meet specific synthetic demands often leads to interesting new synthetic advantages. This will be illustrated in the sections that follow.

4.3.1 Cycloalkylidenes

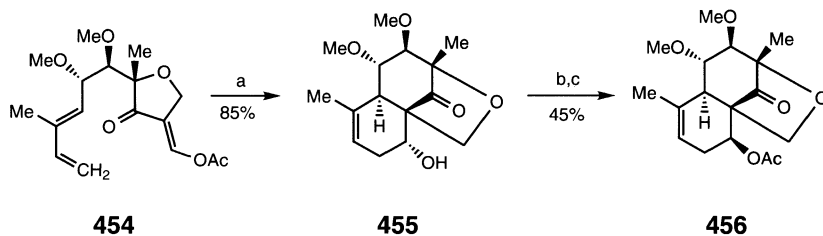
Three-dimensional preorganization, characteristic of effective host molecules, is commonly incorporated into hosts through macrocyclic linkages that restrict conformational space and favor those conformers whose geometries are appropriate for binding. The podand tetraether **442**, prepared from L-(+)-diethyl tartrate (**1b**), is a conformationally homogeneous C₂ ionophore that binds a variety of chiral organic ammonium cations with enantioselectivities corresponding to 34–42% *ee*. The cyclopentylidene protecting group present in **437** is used because of its ease of removal. Treating **437** with excess methyl magnesium bromide and a subsequent double thermal dehydration can be accomplished in a single operation to provide **438** in 35% overall yield. This process can also be carried out stepwise to provide **438** in higher yields (72%). The product was then homologated in four steps to afford the diester **439**. Subsequent *in situ* conversion to the aldehyde with DIBAL followed by a Wittig olefination furnishes the favored *Z*-olefin (*Z*:*E* = 18:1). Epoxidation provides the α -epoxy product **440**. Acid-catalyzed regiospecific epoxide ring opening generates the two tetrahydropyran rings which, after further functionalization, results in the diiodo intermediate **441**. This is finally converted in several steps to the desired podand **442** [148] (Scheme 98).

The cyclohexylidene protecting group has been employed in several syntheses. A preparation of 2,3-*O*-cyclohexylidene-4-deoxy-L-threose (**445**) from L-(+)-diethyltartrate (**1b**) in seven steps illustrates one synthetic application (Scheme 99). Conversion of the monobenzyl protected alcohol **443** to its tosylate followed by reduction with sodium borohydride provides the deoxy intermediate **444**, which is reductively deprotected and Swern oxidized to **445** in good overall yield. Treatment with benzylamine provides an imine that undergoes a stereoselective carbon–carbon bond forming reaction with α -lithio-*N,N*-dimethylacetamide in the presence of the Lewis acid zinc bromide to furnish, after Cbz-amine protection, the β -aminoamide **446**. This is converted in four steps to *N*-acetyl-L-daunosamine (**447**), a sugar moiety particularly important as the carbohydrate constituent of the anthracycline antibiotics [149].

Efforts toward the total synthesis of quassimarin (**453**), a pentacyclic lactone possessing potent antitumor activity, have focused on an *endo*-selective intramolecular Diels–Alder reaction to prepare the chiral tricyclic synthon **452**. Transformation of (+)-(2*S*,3*S*)-3-benzoyloxymethyl-2-hydroxymethyl-1,4-dioxaspiro[4,5]decane (**443**) to the allylic alcohol **448** followed by a manganese dioxide oxidation and Wittig olefination affords the diene **449** in good overall yield. The primary alcohol in **449** is converted in three steps to a methyl ketone, which undergoes a stereoselective addition of α -lithio- α -methoxyallene in the presence of magnesium bromide to furnish, after appropriate hydrolysis, the dihydrofuranone **450**, but in only 16% overall yield. Formylation and acetylation of **450** provides the triene **451** which, after thermolysis in xylene in a sealed tube at 153 °C for 53 hours, basic hydrolysis, and separation of the isomeric alcohols, permits the isolation of **452** (overall yield 18%) as the BCE ring system of **453** [150] (Scheme 100).

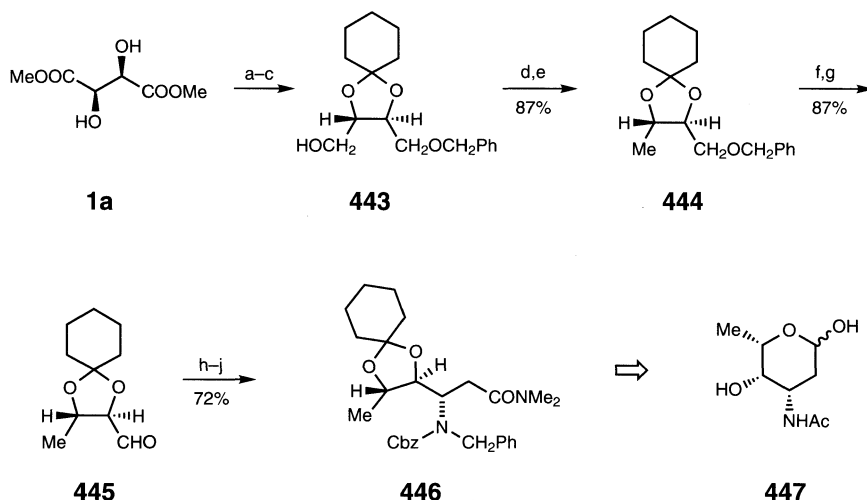
**Scheme 98**

conditions: (a) MeMgBr, Et₂O; (b) SO₂Cl₂, collidine; (c) 9-BBN, THF, then H₂O₂, NaOH (62%); (d) *p*-TsCl, Et₃N; (e) NaI, acetone; (f) LDA, *tert*-BuOAc, THF–HMPA (61%, 3–steps); (g) DIBAL, DCM, –78 °C; (h) (2*S*)-OTMS-2-methylbutylphosphonium bromide, NaN(TMS)₂, MeOH; (i) HCl, H₂O, MeOH (50%, 3–steps); (j) *tert*-BuOOH, VO(acac)₃; (k) CSA, DCM; (l) *p*-TsCl, Et₃N; (m) NaI, acetone (78%)



conditions: (a) toluene, 150 °C, 1 h; (b) MsCl, Et₃N; (c) CsOAc, 18-Crown-6

By contrast, the more flexible 2,3-dimethoxy derivative **454** [151] undergoes thermolysis in toluene within only one hour to provide with high *endo*-selectivity the alcohol **455** in 85% yield (*endo*:*exo* = > 30 : 1). Conversion of **455** to the mesylate followed by treatment with



Scheme 99

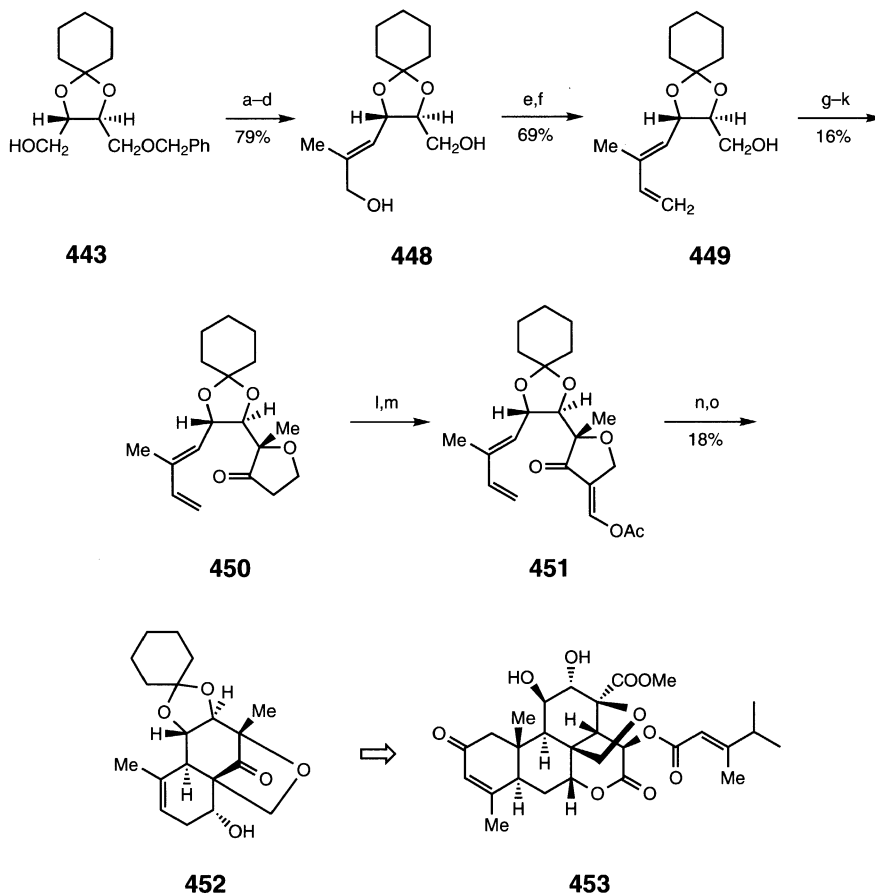
conditions: (a) cyclohexyldimethyl acetal, TsOH; (b) LiAlH_4 (80%, 2 steps); (c) PhCH_2Br , NaH (88%); (d) *p*-TsCl, pyridine; (e) NaBH_4 ; (f) H_2 , Pd/C; (g) Swern [O]; (h) PhCH_2NH_2 ; (i) $\text{LiCH}_2\text{CONMe}_2$, ZnBr_2 ; (j) CbzCl , NaHCO_3

cesium acetate provides **456**, whereby the nucleophilic displacement occurs with complete inversion [150,152,153].

2,3-Bis(mesylate)-1,4-dioxaspiro[4,5]decane (**458**), easily prepared by treating **457** with excess methanesulfonyl chloride in pyridine, undergoes macrocyclization with a variety of dicesium salts derived from either 1, ω -diamides **459a,b** or 1, ω -dithiols **460a-d** to furnish chiral macrocyclic diamines **461a,b** or disulfides **462a-d** (Scheme 101). These macrocyclic products are generally fairly tractable, and they can be purified without excessive effort. However, when examined as possible chiral ligands for nickel-catalyzed Grignard cross-coupling reactions, these ligands provided poor enantiomeric excesses (17% *ee*) [154].

Protection of the 2,3-dihydroxy moiety of tartrates as a cyclized acetal is not limited to alkylidene or benzylidene groups, which often are discarded at some point in the synthesis of a target molecule. The acetal protecting group may also function as an integral component in the synthesis of a more complex molecule that also incorporates the chirality of the tartrates into its structure. (+)-(2*S*,6*S*)-(cis-6-methyltetrahydropyran-2-yl)acetic acid (**468**), a constituent of civet, the glandular secretion of the civet cat *Viverra civetta*, is prepared from diethyl (+)-L-tartrate (**1b**), where the acetal protecting group is transformed into a chiral tetrahydropyran ring system. Acetalization of **1b** with 4-phenylsulfonyl-2-butanone diethyl acetal (**463**) furnishes the sulfone diester **464** in 85% yield. Ester reduction with sodium borohydride, conversion of the resulting diol to the crystalline bis(mesylate) **465**, and a smooth intramolecular alkylation provides the 6,8-dioxabicyclo[3.2.1]octane **466** in good yield. Selective desulfonylation followed by a stereospecific reductive ring opening with aluminum hydride (generated *in situ* with 4:1 AlCl_3 - LiAlH_4) affords the stereochemically homogeneous product **467** in 48% yield for the two steps. This is converted in five steps to **468** [155] (Scheme 102).

The enantiospecific synthesis of (+)-*erythro*-(5*S*,6*R*)-6-acetoxy-5-hexadecanolid (475), an optically active form of the major component of an oviposition attractant pheromone of the mosquito *Culex pipiens fatigans*, exploits the 6,8-dioxabicyclo[3.2.1]octane system to provide

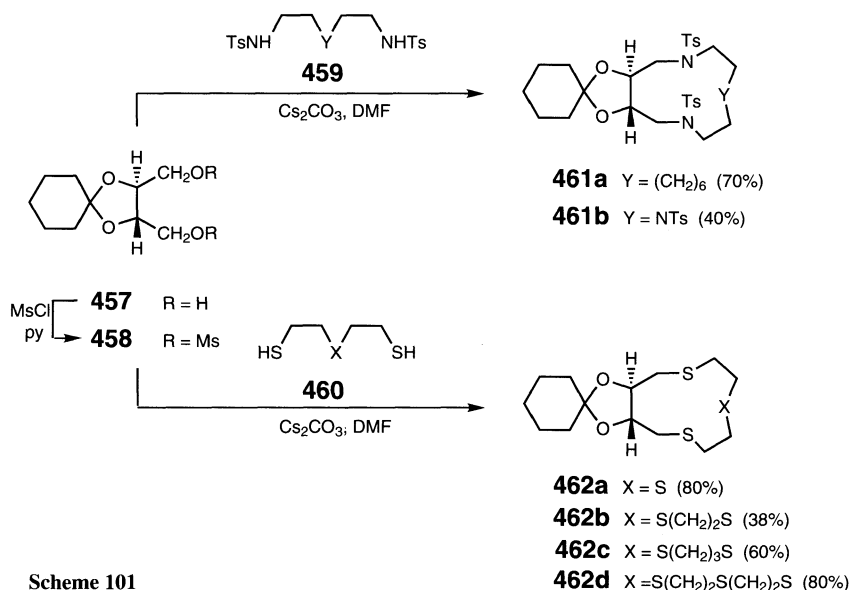


Scheme 100

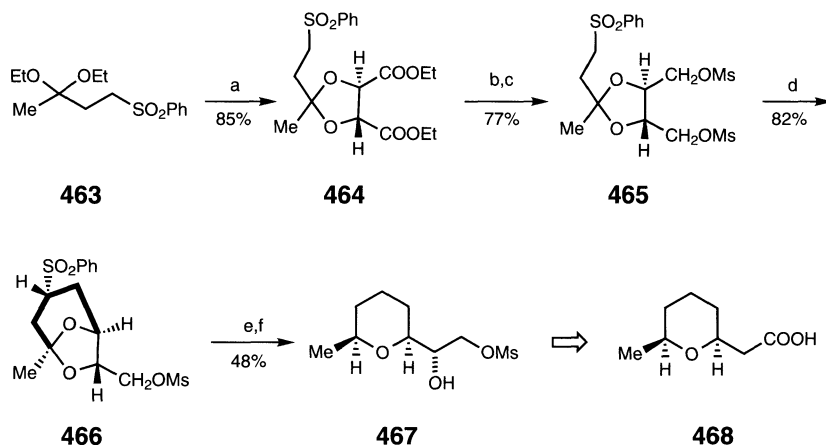
conditions: (a) Swern [O]; (b) $\text{Ph}_3\text{P}=\text{C}(\text{Me})\text{COOMe}$; (c) LiAlH_4 , Et_2O (84%); (d) NaH , THF then Li , $\text{NH}_3(\text{l})$ (93%); (e) MnO_2 , DCM ; (f) $\text{Ph}_3\text{PCH}_2\text{Br}$, $n\text{-BuLi}$; (g) Swern [O]; (h) MeLi , Et_2O (82%); (i) Swern [O]; (j) α -methoxyallene, $n\text{-BuLi}$, MgBr_2 , THF, -78°C ; (k) tert-BuOK , 18-Crown-6, tert-BuOH then HCl ; (l) HCOEt , NaH , DME; (m) Ac_2O , pyridine, DMAP; (n) xylene, 180°C , 53 h; (o) LiOH , aq. MeOH

chirality at C-5 and C-6. Acetalization of **1b** with β -*p*-tosylpropanal diethyl acetal (**469**) provides the acetal **470** in 79% yield. A consecutive three-step sequence of transformations affords the 6,8-dioxabicyclo[3.2.1]octane **471** in an overall yield of 58% from **470**. Alkylation of the sulfonate terminus with $(n\text{-C}_9\text{H}_{19})_2\text{CuLi}$ furnishes the 7-*exo*-decylbicyclic compound **472** in 78% yield. Fission of the dioxolane ring with acetic anhydride–boron trifluoride etherate provides 3,4-dihydro-2*H*-pyran **473**, in which the hydroxyl group is subsequently inverted under Mitsunobu conditions to provide **474** with the correct *R*-configuration at C-6. This was then converted in four steps to the desired chiral product **475** [156] (Scheme 103).

The facile conversion of the 6,8-dioxabicyclo[3.2.1]octanes to chiral pyrans is exploited in steps towards the synthesis of (–)-(6*S*,1′*S*)-pestalotin (**478**), a gibberellin synergist isolated from microorganisms. Treatment of either tosylate **471** or mesylate **476** with lithium di-*n*-



Scheme 101

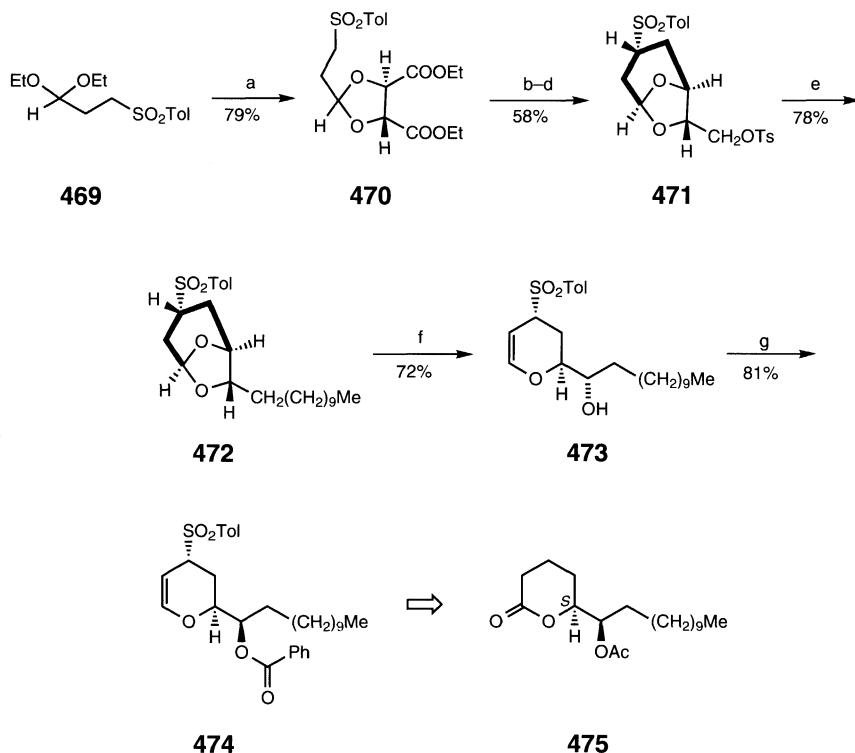


Scheme 102

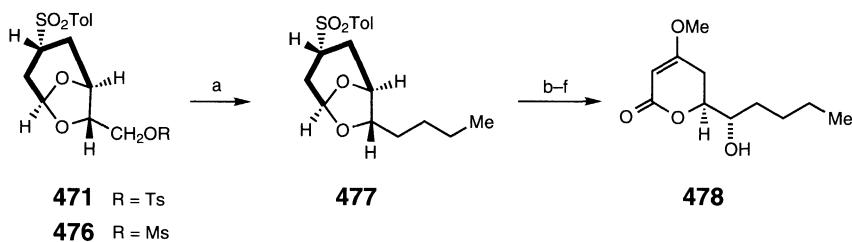
conditions: (a) **1b**, *p*-TsOH, PhH; (b) NaBH₄, EtOH, 0–5 °C; (c) MsCl, pyridine;
 (d) *n*-BuLi, THF, –20°C; (e) Na, EtOH, THF, –20 °C (60%);
 (f) AlCl₃–LiAlH₄ (4:1), Et₂O (80%)

propylcuprate affords in good yields **477**, which is transformed in five steps to **478** [157] (Scheme 104).

Acetalization of diethyl (–)-(*S,S*)-tartarate (**2b**) with **463** affords in 87% yield the syrupy **479**. Nearly quantitative reduction of the ester groups with sodium borohydride followed by ditosylation of the resulting diol and an intramolecular carbon–carbon coupling furnishes **480**.

**Scheme 103**

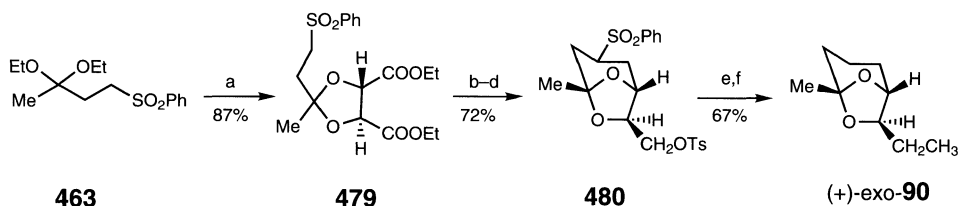
conditions: (a) **1b**, *p*-TsOH, toluene, 120 °C; (b) NaBH₄, EtOH, 0–5 °C; (c) *p*-TsCl, pyridine; (d) *n*-BuLi, THF, –20 °C; (e) (*n*-C₉H₁₉)₂CuLi, Et₂O–DMS; (f) Ac₂O, BF₃·Et₂O, DCM; (g) Ph₃P, DEAD, C₆H₅COOH, THF

**Scheme 104**

conditions: (a) (*n*-C₃H₇)₂CuLi; (b) Br₂, DCM, 0 °C; (c) 5% K₂CO₃, THF; (d) NaOMe, THF (76% for 3 steps); (e) Jones [O], acetone (90%); (f) K₂CO₃, MeOH (70%)

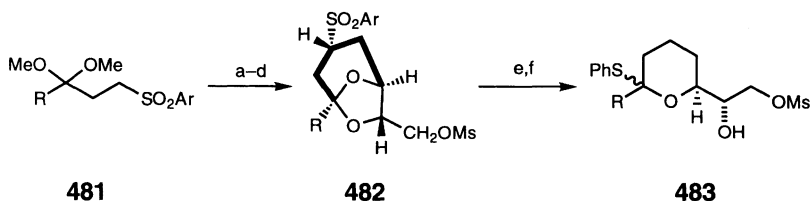
Methylation with lithium dimethylcuprate and reductive desulfonation with sodium in ethanol provides (+)-*exo*-brevicomin (**90**) in 67% yield [158] (Scheme 105).

A particularly attractive feature of the methodology described above is the ability it confers to prepare a variety of 5-alkyl-6,8-dioxabicyclo[3.2.1]octanes useful in natural product

**Scheme 105**

conditions: (a) **2b**, *p*-TsOH, PhH, 80–90 °C, 20 h; (b) NaBH₄, EtOH, 5 °C (100%);
 (c) *p*-TsCl, pyridine (90%); (d) *n*-BuLi, THF, –20 °C (81%);
 (e) Me₂CuLi, Et₂O–DMS (76%); (f) Na, EtOH–THF

syntheses. Acetalization of **1b** with β -arylsulfonyl ketone dimethyl acetals **481a–d** followed by reduction, dimesylation, and intramolecular carbon–carbon coupling furnishes the 5-alkyl-7-mesyloxy-6,8-dioxabicyclo[3.2.1]octanes **482a–d** in good yields. Reductive desulfonation followed by ring fission of **482a–d** with diethylaluminumthiophenoxide in toluene provides the pyranoid monothioacetals **483** in good yields. Attempts to affect similar transformations with thiophenol and boron trifluoride etherate or aluminum chloride failed [159] (Scheme 106).

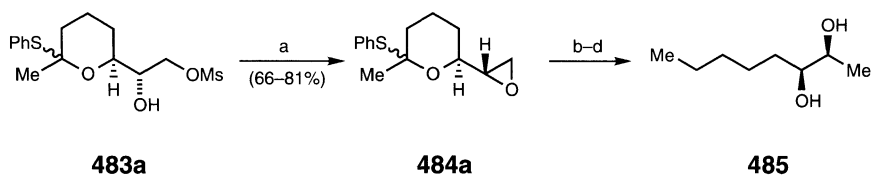


483	R	Yield (%)
a	Me	78
b	C ₂ H ₅	76
c	<i>iso</i> -C ₃ H ₇	87
d	<i>n</i> -C ₆ H ₁₃	89

Scheme 106

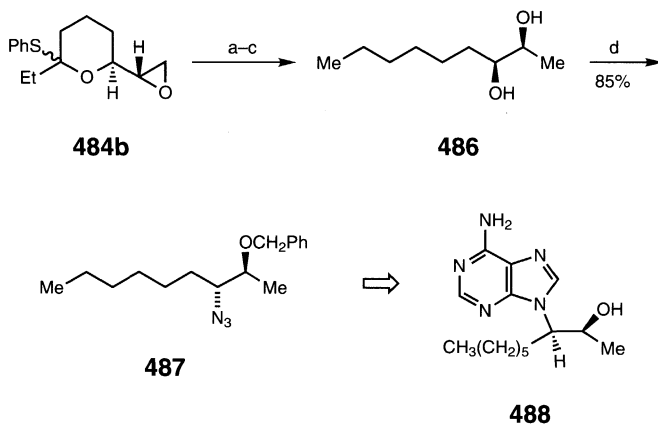
conditions: (a) **1b**, *p*-TsOH, PhH; (b) NaBH₄, EtOH–THF; (c) MsCl, Et₃N;
 (d) *n*-BuLi, THF; (e) Na, EtOH–THF; (f) Et₂AlSPh

The pyranoid monothioacetals **483a–d** may be viewed as selectively functionalized, protected, and homologated building blocks of (+)-tartaric acid ester (**1b**). The utility of these chiral intermediates is derived from the fact that they can be converted to epoxides **484**, which undergo highly regiospecific ring opening with a variety of nucleophiles. In this way **484a** is converted to (–)-(2*S*,3*S*)-octanediol (**485**), a sex pheromone of a grape borer *Xylotrechus pyrrhoderus*. (Scheme 107).

**Scheme 107**

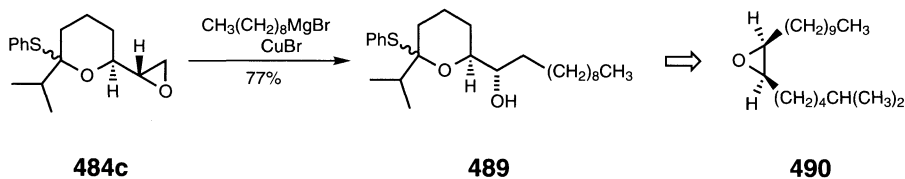
conditions: (a) K_2CO_3 , MeOH, $0\text{ }^\circ\text{C}$; (b) LiAlH_4 , Et_2O (96%); (c) PhSH, AlCl_3 , DCM (71%); (d) Raney Ni (W-2), EtOH (70%)

A similar series of reactions with **484b** provides **486**, which is converted to (2*S*,3*R*)-2-benzyloxy-3-hydrazononane (**487**), a synthetic intermediate for (+)-*erythro*-9-(2*S*-hydroxy-3*R*-nonyl)adenine (**488**) [(+)-EHNA], which is a potent inhibitor of adenosine deaminase (Scheme 108).

**Scheme 108**

conditions: (a) LiAlH_4 , Et_2O (94%); (b) PhSH, AlCl_3 , DCM, then PhCH_2Br , NaH (68%); (c) Raney Ni, EtOH (72%); (d) HN_3 , Ph_3P , DEAD, PhH

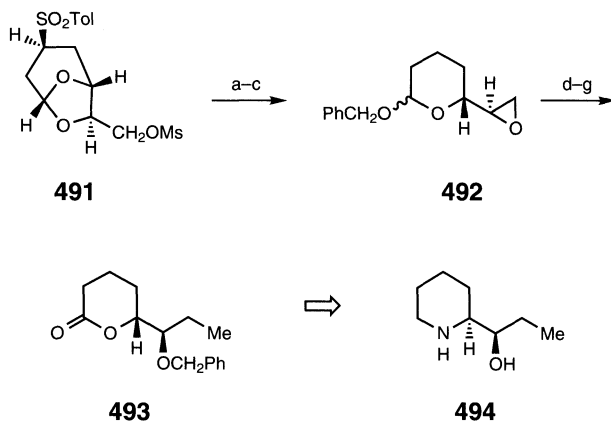
Epoxide ring opening of **484c** with *n*-nonylmagnesium bromide in the presence of copper(I) bromide provides in 77% yield the alcohol **489**, which is transformed into (+)-(7*R*,8*S*)-disparlure (**490**), the sex pheromone of the gypsy moth *Porthetria dispar* [159].



The enantiospecific synthesis of (+)-(2*S*)-[(1'*R*)-hydroxypropyl]piperidine or (+)-conhydrine (**494**), one of the poisonous alkaloids of the hemlock *Conium maculatum*, is accomplished utilizing (+)-(1*R*,5*R*,7*R*)-7-mesyloxy-6,8-dioxabicyclo[3.2.1]octane (**491**),

easily prepared in four steps starting with an acetalization of (–)-(*S,S*)-diethyl tartrate (**2b**) with **469** (see Scheme 103).

Removal of the tosyl group with sodium in ethanol and partial ring opening of **491** followed by potassium carbonate cyclization provides the epoxide **492**. Epoxide ring opening of **492** with lithium dimethylcuprate, benzyl protection of the secondary hydroxy group, and oxidation of the acetal to a lactone affords **493**. Methanolysis of **493** and Mitsunobu inversion of the resulting hydroxy ester with hydrazoic acid, followed by three functional group transformations, provides the desired product **494** in optically pure form [160] (Scheme 109).



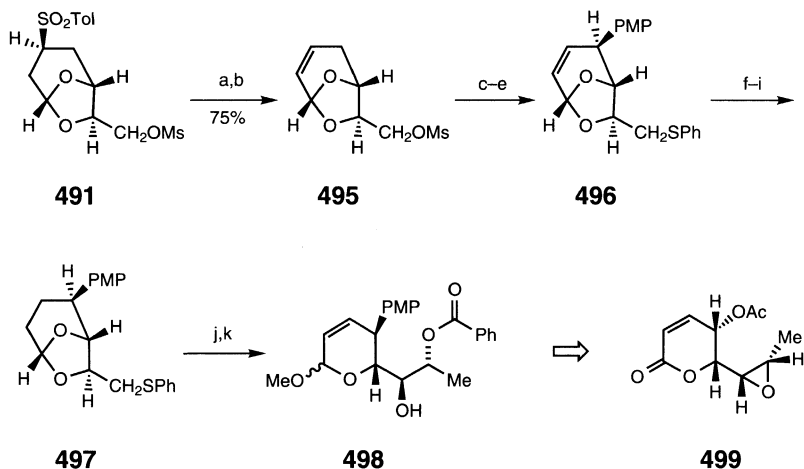
Scheme 109

conditions: (a) Na, EtOH, THF, $-20\text{ }^{\circ}\text{C}$ (78%); (b) PhCH₂OH, BF₃·Et₂O (74%);
 (c) K₂CO₃, MeOH (92%); (d) Me₂CuLi, Et₂O (90%);
 (e) PhCH₂Br, NaH, DME (79%); (f) MCPBA, BF₃·Et₂O; (g) Et₃N (75%)

(+)-(*5S,6S,7S,8R*)-Asperlin (**499**), isolated as a crystalline metabolite from *Aspergillus nidulans*, possesses both antibiotic and antitumor activities. It is structurally the smallest representative of the family of biologically active 5-oxygenated 5,6-dihydro-2-pyrones with the oxygen-functionalized sidechain at the 6-position. Treatment of **491** with bromine followed by zinc–copper couple dehalogenation provides the 3,4-dehydrobicyclic product **495**. Conversion of **495** to the phenylsulfenylated analog followed by a highly regio- and stereoselective bromination affords a bromo olefin, which undergoes stereospecific S_N2' reaction with sodium 4-methoxyphenolate to furnish crystalline (*2R*)-2-*p*-methoxyphenylether **496**. The stereoselective introduction of a 7'-oxygen function (latent epoxide of **499**) is accomplished by methylation of the *in situ* generated 7-carboxyaldehyde to provide, after separation of the 7'*R* (71%) and 7'*S* (15%) alcohols, **497**. Protection of the hydroxy function of **497** as the benzoate and bicyclic ring opening with Amberlyst-15 in methanol provides the pyranoid acetal **498**, which is converted in six steps to the desired product **499**. A similar sequence of reactions starting from (*R,R*)-tartaric acid leads to the chiral antipode of **499** [161] (Scheme 110).

4.3.2 Orthoester Protection

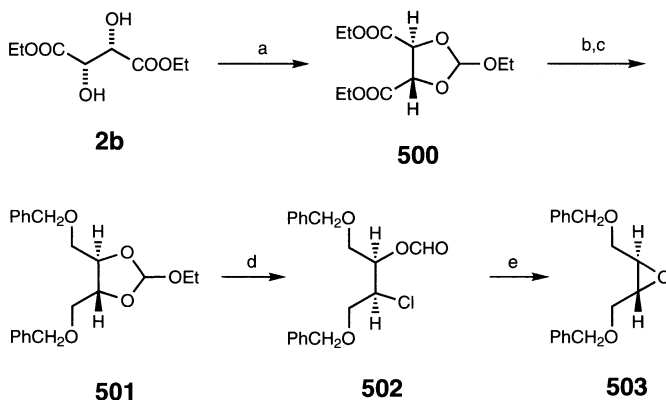
Protection of the 2,3-dihydroxy moiety of either (*S,S*)- or (*R,R*)-tartaric acid derivatives as an orthoester is attractive, because on the one hand the orthoester provides enough protective



Scheme 110

conditions: (a) Br_2 ; (b) Zn-Cu ; (c) PhSNa , DMF, 80 °C (83%); (d) NBS, AIBN, CCl_4 (63%); (e) PMPNa, THF (85%); (f) MCPBA, DCM (92%); (g) Ac_2O , NaOAc (97%); (h) MeLi, THF, -90 °C (71%); (i) SiO_2 chromatography; (j) PhCOCl , pyridine (98%); (k) Amberlyst-15, MeOH (89%)

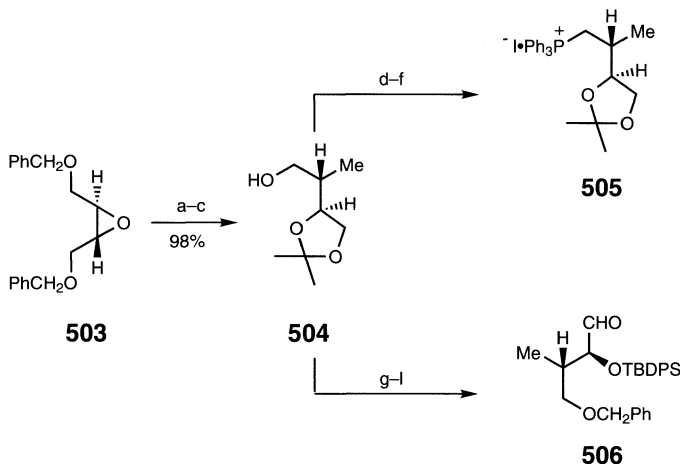
stability to execute reactions under sufficiently rigorous conditions without itself being affected, while on the other hand the orthoester is able to undergo ring opening to furnish, for example, protected halohydrins that themselves constitute extremely useful tartaric derivatives. Treatment of diethyl (–)-D-tartrate (**2b**) with triethyl orthoformate under acidic conditions affords the orthoester **500**. Subsequent reduction of **500** with lithium aluminum hydride followed by benzylation of both of the hydroxy groups furnishes **501**. Phosphorus pentachloride opens the orthoester of **501** to provide chlorohydrin derivative **502**, which can be cyclized to the (*S,S*)-epoxide **503** with methanolic potassium carbonate. Overall yields starting from **2b** range from 70–75% [162] (Scheme 111).



Scheme 111

conditions: (a) $(\text{EtO})_3\text{CH}$, CSA, toluene; (b) LiAlH_4 , THF, 0 °C; (c) PhCH_2Br , NaH, DME; (d) PCl_5 , DCM, 0 °C; (e) K_2CO_3 , MeOH

Antibiotics in the ionophore class have the ability to complex cations and exert a variety of biological activities. The naturally occurring ionophore X-14547A (**513**), isolated from *Streptomyces antibioticus* NRRRL8167, possesses a *trans*-butadienyl moiety, a *trans*-fused tetrahydroindan ring system, and a ketopyrrole group, all of which make **513** a formidable synthetic challenge. The utility of **503** toward the preparation of key intermediates employed in the convergent synthesis of **513** is illustrated in Schemes 112–114. Regiospecific epoxide ring opening of **503** with lithium dimethylcuprate followed by hydrogenolysis of the benzyl ethers provides a nearly quantitative yield of triol that is subsequently protected as the acetonide to afford **504**. The flexibility of this valuable intermediate is demonstrated in its ability to provide both the Wittig salt **505** and the aldehyde **506**.



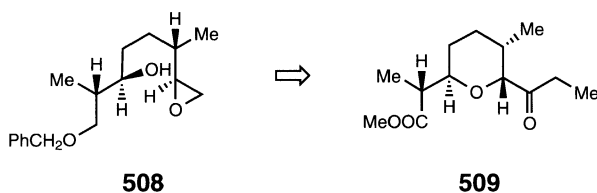
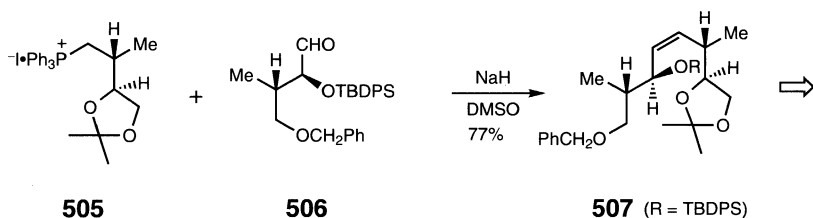
Scheme 112

conditions: (a) Me_2CuLi , Et_2O ; (b) H_2 , Pd/C, EtOH; (c) $\text{Me}_2\text{C}(\text{OMe})_2$, CSA, PhH, then CSA, MeOH (98%); (d) *p*-TsCl, pyridine (100%); (e) NaI, acetone (85%); (f) PPh_3 , $\text{MeCN}-(\text{EtO})_3\text{CH}$ (4:1), 75 °C, 48 h (80%); (g) PhCH_2Br , NaH, DME (90%); (h) Amberlyte IR-120, ethylene glycol–DME (2:1) (80%); (i) Me_2COCl , pyridine; (j) $\text{Ph}_2(\text{tert-Bu})\text{SiCl}$, imidazole, DMF; (k) DIBAL, DCM, -78 °C (3 steps 85%); (l) CrO_3 , HCl, pyridine, DCM 4A sieves (85%)

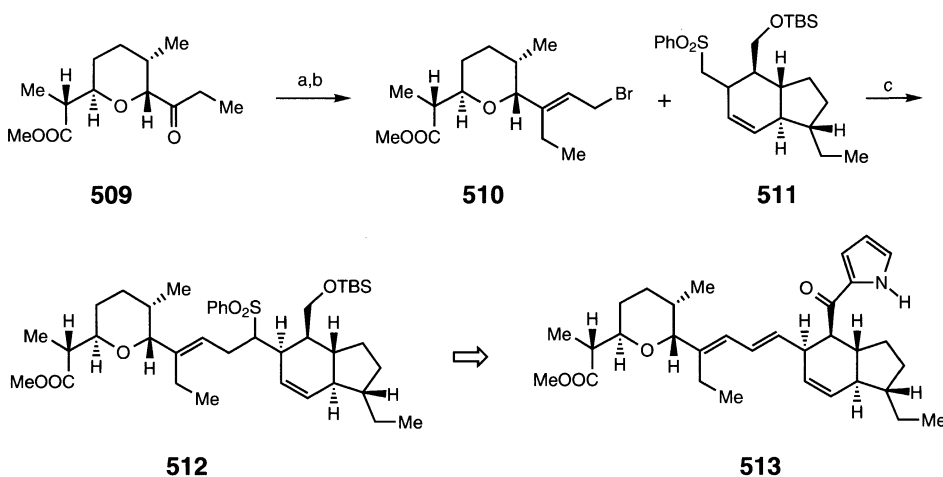
The coupling of **505** and **506** proceeds in 77% yield to furnish olefin **507** as a 2:1 *E*:*Z* mixture. In five steps this is transformed into epoxide **508**. Further manipulation of **508** in six additional steps provides the tetrahydropyran **509** [162].

Vinylmagnesium bromide addition to **509** results in a tertiary alcohol that upon treatment with phosphorus tribromide undergoes rearrangement to furnish a 65% yield of the *E*-allylic bromide **510** (along with 25% *Z*-bromide). This is coupled with the anion of **511** to afford **512**, which is elaborated to the antibiotic **513** [162,163].

A convergent total synthesis of amphotericin B (**517**), with a β -linked mycosamine at the C-19 hydroxyl position, a clinically useful antifungal agent isolated from *Streptomyces nodosus*, and its aglycon, amphoteronolide B (**518**), relies upon the stereocontrolled construction of enantiomerically pure (homochiral) structural units. Retrosynthetic analysis of **517** uncovers certain stereochemical features that allow construction of two of the essential chiral building blocks from **514**, the chiral antipode of **503** and readily available from **1b**, by utilizing similar reaction conditions to those available for the synthesis of **503**. Thus, chiral



Scheme 113

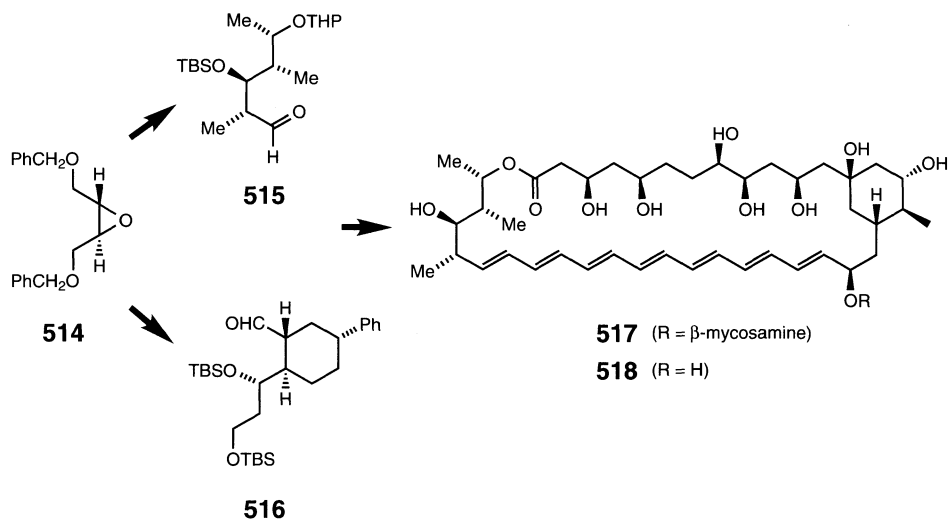


Scheme 114

conditions: (a) $\text{CH}_2=\text{CHMgBr}$, THF, -78°C (95%); (b) PBr_3 , Et_2O , -10°C (65%);
(c) LDA, THF, -78°C then HMPA (99%)

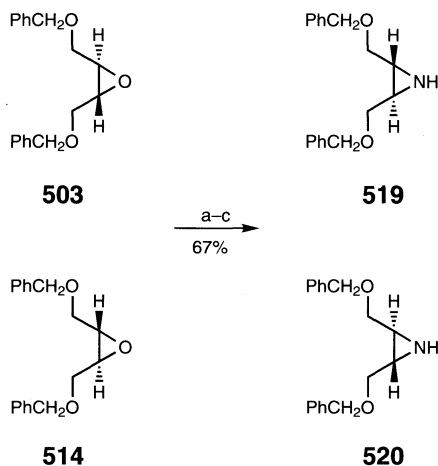
aldehyde **515** is prepared in twelve steps from **514**, while chiral aldehyde **516** is prepared from **514** in six steps [164,165] (Scheme 115).

Whitesell observed that alkylation at the α -carbon of an amide of a C_2 -symmetric amine, in which the amine acts as a chiral auxiliary, should result in effective symmetric induction [166]. The C_2 -symmetric aziridines **519** and **520** are readily accessible from **503** and **514**, respectively. Ring opening of either epoxide with sodium azide, mesyl activation of the free hydroxy group, and lithium aluminum hydride reduction of the azide with concomitant ring



Scheme 115

closure provides the aziridines in good overall yields. Note that inversion has occurred [167] (Scheme 116).

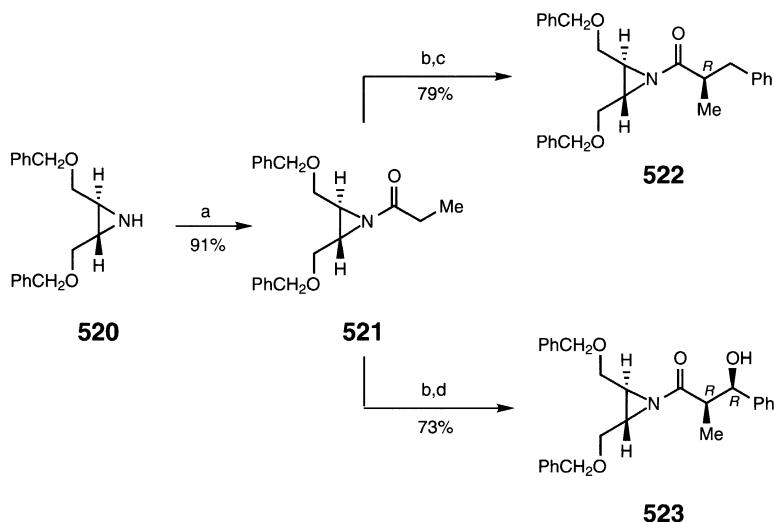


Scheme 116

conditions: (a) NaN_3 , NH_4Cl , $\text{MeO}(\text{CH}_2)_2\text{OH}/\text{H}_2\text{O}$;
 (b) MsCl , Et_3N , DCM ; (c) LiAlH_4 , THF

Amidation of **520** with propionic anhydride provides in 91% yield the aziridine amide **521**. Deprotonation at the amide α - CH_2 position occurs at -78°C with lithium bis(trimethylsilyl)amide. Subsequent treatment of the anion with benzyl bromide results in α -alkylation to furnish in 79% yield the single diastereomer **522**. On the other hand, if this anion is treated with benzaldehyde at -78°C , the aldol reaction proceeds with high *syn*-selectivity

to provide in 73% yield the *syn*-aldol products **523** (ratio = 98 : 2). No detectable *anti*-aldol products are observed. Hydrolysis of the amide products allows recovery of the auxiliaries. Clearly the C_2 -symmetry present in these tartaric acid-derived chiral auxiliaries provides a synthetically useful advantage [167] (Scheme 117).



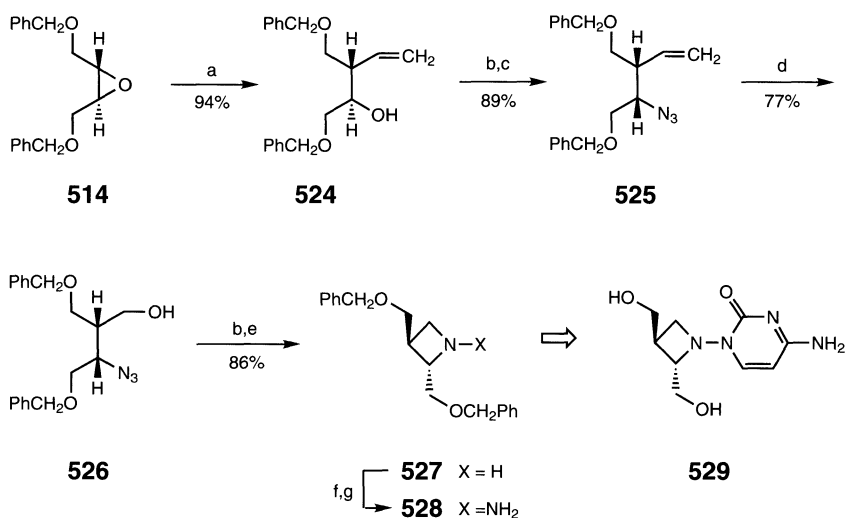
Scheme 117

conditions: (a) $(\text{CH}_3\text{CH}_2\text{CO})_2\text{O}$, Et_3N , DMAP, DCM; (b) $\text{LiN}(\text{TMS})_2$, THF, -78°C ;
(c) PhCH_2Br ; (d) PhCHO

The development of less toxic anti-AIDS agents that are not cross-resistant with existing drugs has led to the design of a new class of nucleoside analogs in which the oxetane ring present in the antiviral antibiotic oxetanocin-A is replaced by an azetidine ring linked to a nucleic base through an N–N bond. Treatment of **514** with vinyl magnesium chloride in the presence of copper(I) iodide provides in 94% yield the vinyl alcohol **524**, which is converted to azide **525** with inversion of configuration. Ozonolysis and *in situ* reduction of the ozonide with sodium borohydride affords the azide alcohol **526** in 77% yield. This one pot, two-step procedure avoids isolation of the rapidly epimerizable aldehyde. While direct reductive cyclization of **526** to the azetidine **527** fails, a two-step procedure provides good yields of **527**, which is converted to the unstable 1-aminoazetidine **528**. This is in turn transformed into (2'*S*,3'*S*)-1-[2',3'-bis(hydroxymethyl)-azetidiny]cytosine (**529**), which has potential antiviral activity [168] (Scheme 118).

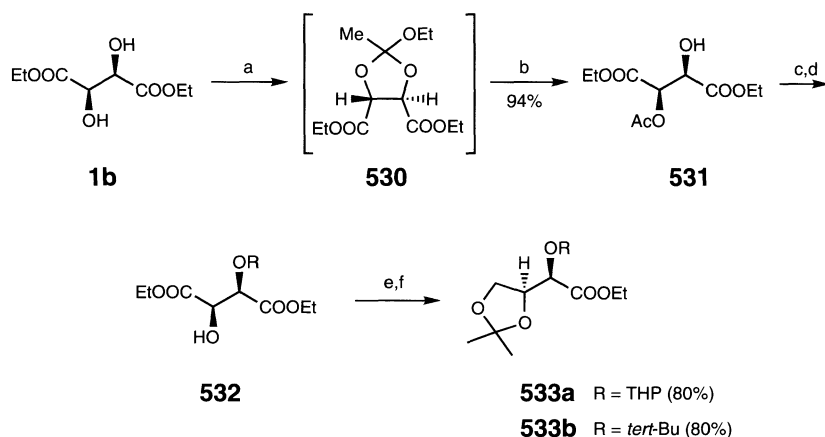
An attractive feature of tartaric acid is the potential for treating each of the two carboxylic moieties as distinct functional groups. Most metal hydride reductions of tartaric acid derivatives afford polyhydroxy compounds. The chemoselective reduction of malic acid (for details see Chapter 3) suggests that tartaric acid, under favorable conditions, might also be susceptible to such a transformation.

Treating diethyl (+)-(*R,R*)-tartrate (**1b**) with triethyl orthoacetate under acidic conditions provides the cyclic orthoester **530**, which is then ring opened with acid to afford the monoacetate **531** in 94% overall yield. Protection of the free hydroxyl group followed by basic hydrolysis of the acetate furnishes **532**. The regioselective reduction of **532** with borane–dimethylsulfide complex and a catalytic amount of sodium borohydride followed by acetamide

**Scheme 118**

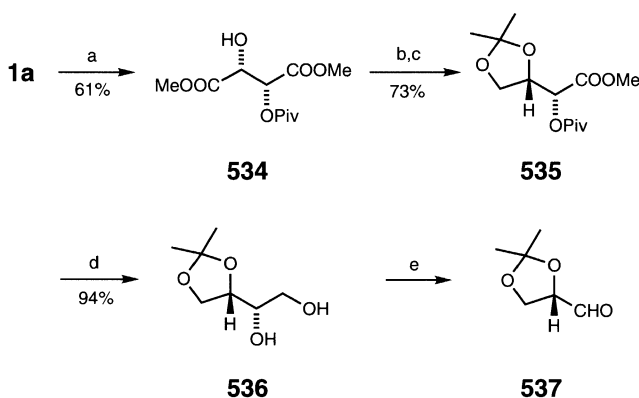
conditions: (a) CH₂=CHMgCl, CuI, Et₂O, -10 °C; (b) MsCl, Et₃N; (c) NaN₃, DMF, 100 °C; (d) O₃, MeOH, -20 °C then NaBH₄, rt; (e) Raney Ni, EtOH; (f) isoamyl nitrite; (g) LiAlH₄, THF, -10 °C (83% 2 steps)

formation of the resulting diols provides compounds **533**, in which the site selectivity ranges from poor to excellent (5-membered acetonide vs. 6-membered acetonide). Clearly in the case of tartaric acid esters, site selectivity seems to depend on a delicate balance between steric and electronic factors [169] (Scheme 119).

**Scheme 119**

conditions: (a) MeC(OEt)₃, *p*-TsOH, THF; (b) *p*-TsOH, EtOH then SiO₂ chromatography; (c) (R = THP) DHP, CSA, DCM (99%), then NaOEt, EtOH (82%); (d) (R = *tert*-Bu) 2-methylpropene, H₂SO₄, **1b** (60%) (e) BMS, NaBH₄; (f) Me₂C(OMe)₂, *p*-TsOH, acetone

Site-selective reduction of the pivaloyl-protected **534** (similarly prepared from **1b** as described in Scheme 119) with BMS–sodium borohydride(catalytic) followed by acetonide formation furnishes a 73% yield of pure **535** after distillation, which can be further purified by recrystallization. The reduction of **535** with lithium aluminum hydride affords 1,2-*O*-sopropylidene-*L*-threitol (**536**) in 94% yield. Oxidative C–C bond cleavage of **536** with sodium periodate furnishes the highly versatile chiral synthon (*S*)-2,3-*O*-isopropylidene-glyceraldehyde (**537**). An attractive feature of both **535** and **536** is high stability, which permits storage in the refrigerator for years [169] (Scheme 120).



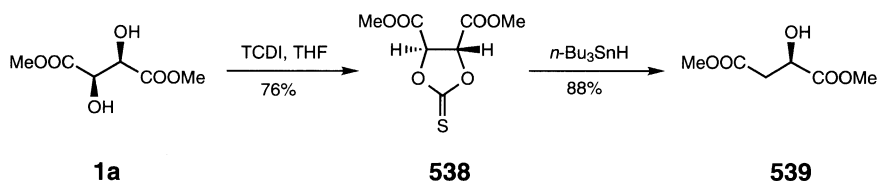
Scheme 120

conditions: (a) pivaloyl chloride, pyridine, $-20\text{ }^{\circ}\text{C}$; (b) BMS, THF then NaBH_4 ;
(c) $\text{Me}_2\text{C}(\text{OMe})_2$, *p*-TsOH, acetone; (d) LiAlH_4 , THF; (e) NaIO_4

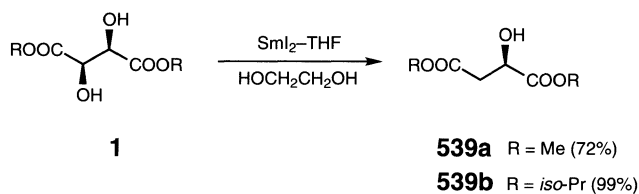
4.3.3 Cyclic Sulfur and Carbonate Derivatives

One attractive feature of the 2,3-dihydroxy groups present in tartaric acid derivatives is the fact that they can be incorporated into cyclic derivatives in which the protecting group also maintains a reactive center, as already discussed in the case of the orthoester protected tartrates. Cyclic carbonates and cyclic sulfur compounds of tartaric acids offer additional opportunities for exploitation of the chirality of the tartaric acids in the preparation of very useful chiral intermediates.

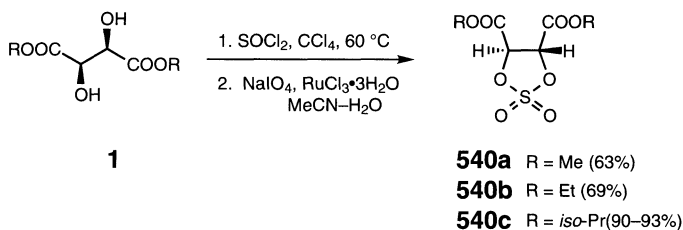
Of the two enantiomeric malic acid methyl esters, the *R*-isomer **539** is considered less accessible and considerably more costly. Several attempts at its synthesis have been made [170,171,172], but a very expedient two-step synthesis from dimethyl (+)-(*R,R*)-tartrate (**1a**) provides (*R*)-dimethylmalate (**539**) in 67% yield. Treatment of **1b** with thiocarbonyldiimidazole affords in 76% yield the thionocarbonate **538** which, when treated with tri-*n*-butyltin hydride furnishes, after facile chromatographic purification, multigram quantities of pure **539** [173].



As an aside, it should also be noted that a highly efficient deoxygenation of tartrate diesters *via* a samarium iodide-induced electron transfer process allows direct conversion to **539**. Ethylene glycol, presumably due to its modest acidity and strong coordinating ability with the samarium cation, provides the best results [174].



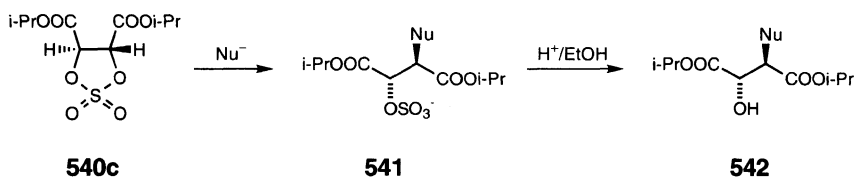
1,2-Cyclic sulfates **540a–c** are conveniently prepared in good yields by a two-step, one-pot transformation of the appropriate diester **1a** or **1b** with thionyl chloride followed by ruthenium tetroxide oxidation. They behave like epoxides in that they simultaneously activate and protect adjacent functionalized carbon atoms from nucleophilic attack. As a consequence of their cyclic nature, they render competing elimination processes stereochemically unfavorable [175].



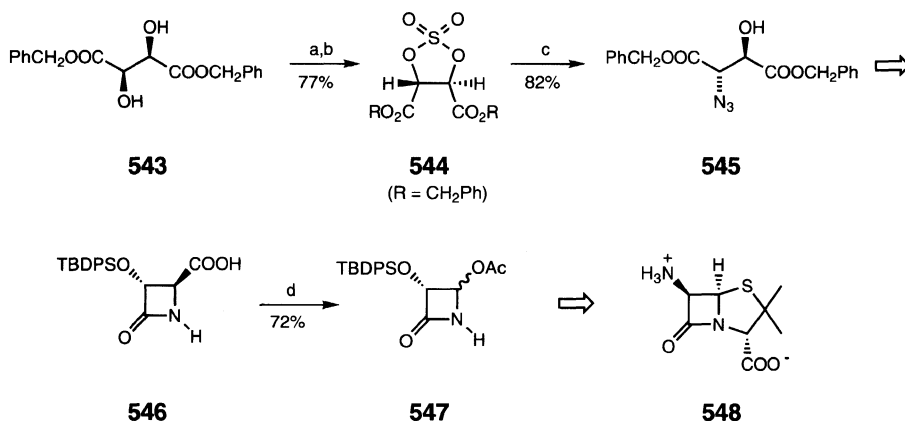
When treated as an electrophile, cyclic sulfate **540c** undergoes facile sulfate ring opening with a variety of nucleophiles to furnish the β -sulfates **541**, which are easily hydrolyzed to the β -hydroxy derivatives **542**. In this sense, cyclic sulfates are synthetically equivalent to epoxides, but unlike the β -hydroxy group that results in epoxide ring openings, the corresponding β -sulfate moiety is still a good leaving group and should be capable of further exploitation in certain synthetic cases [175,176].

The antibacterial activity of β -lactams has stimulated extensive synthetic investigation into the design and assembly of superior penicillins, cephalosporins, carbapenems, monobactams, and numerous unnatural analogs. The synthesis of 6-aminopenicillanic acid (**548**) exploits the capability of the cyclic sulfate **544**, prepared in two steps from (*R,R*)-dibenzyltartrate (**543**) [177], to undergo nucleophilic ring opening with sodium azide to provide, after sulfate hydrolysis, (*2S,3R*)-dibenzyl-2-azido-3-hydroxysuccinate (**545**) in good yield. A four-step sequence converts **545** to the crystalline (*3R,4S*)-3-[(*tert*-butyldiphenylsilyl)oxy]-2-oxo-4-azetidinedicarboxylic acid (**546**). Oxidative decarboxylation of **546** with lead tetraacetate in DMF–acetic acid furnishes the target acetate **547**, which is transformed in 10 steps to 6-aminopenicillanic acid (**548**) [178] (Scheme 121).

Although cyclic sulfites **549** of tartrate esters are less reactive than the corresponding cyclic sulfates **540**, they do react with such good nucleophiles as lithium bromide, lithium chloride, sodium azide, ammonium thiocyanate, or sodium acetate in polar aprotic solvents (DME, THF or DMF) to provide β -substituted-D-malates **550**. Quantitative yields of **549** can be



542	Nu ⁻	Conditions	Yield (%)
a	H	NaBH ₃ CN (pH=4–5) 65 °C, 5 h, THF	55
b	N ₃	NaN ₃ , acetone/H ₂ O 0–25 °C, 1 h	81
c	F	Et ₄ NF•2H ₂ O, acetone 25 °C, 6 h	90
d	NO ₃	Bu ₄ NNO ₃ , acetone 25 °C, 2 h	96
e	PhCH ₂	PhCH ₂ MgCl, Li ₂ CuCl ₄ THF, -78 °C	73
f	SCN	NH ₄ SCN, acetone 25 °C, 5 h	87

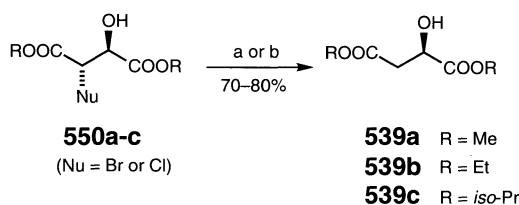
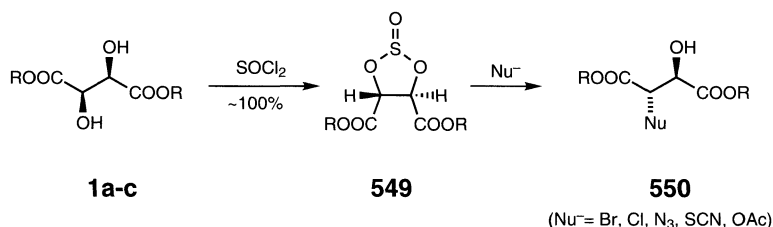


Scheme 121

conditions: (a) SOCl₂, Et₃N, DCM; (b) RuCl₃•3H₂O, MeCN, NaIO₄, H₂O;
(c) NaN₃, acetone, H₂SO₄, H₂O; (d) Pb(OAc)₄, AcOH

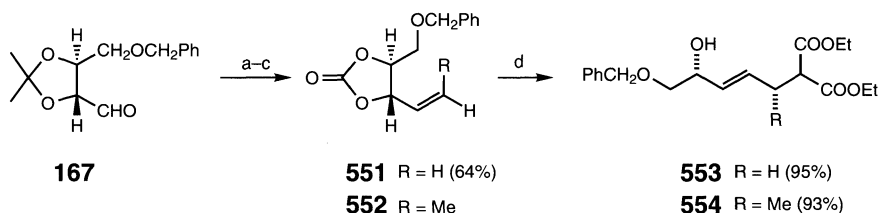
obtained by reacting the L-tartrate esters with a slight excess of thionyl chloride in the absence of base or solvent. These cyclic sulfites are stable to purification by vacuum distillation. Ring opening is usually accomplished by treating 549 with 1.5–2.0 equivalents of the desired nucleophilic salt.

Reduction of 550 (Nu = Br or Cl) with zinc powder or hydrogen in the presence of palladium on carbon and magnesium oxide as an acid scavenger provides D-malates 539 in 70–80% yields with no loss of optical purity [179].



conditions: (a) Zn (2.5–3.0 equiv), H₂O; (b) H₂, Pd/C, MgO, H₂O

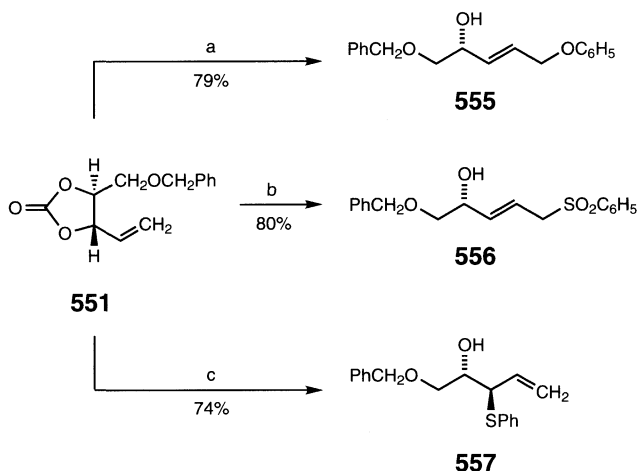
Chiral allylic cyclic carbonates such as **551** or **552** undergo excellent regioselective alkylation reactions with soft nucleophiles in the presence of palladium(0) in refluxing THF to provide (*E*)-allylic alcohols. The reaction of 4-*O*-benzyl-2,3-isopropylidene-*L*-threose (**167**) with the appropriate ylid, followed by deprotection of the isopropylidene ring with acidic resin and cyclic carbonate formation, provides a good overall yield of either **551** or **552**. Ring opening with diethyl malonate in the presence of tetrakis(triphenylphosphine)palladium(0) provides in excellent yield the allylic alcohols **553** or **554**, where the diastereoselectivity exceeds 99%. This reaction represents an efficient method of 1,3-chirality transfer [180] (Scheme 122).



Scheme 122

conditions: (a) Ph₃P⁺CH₂R, *n*-BuLi; (b) Dowex 50 WX8 resin, MeOH;
(c) CDI, DCM; (d) CH₂(COOEt)₂, Pd(Ph₃P)₄ (5 mol%), THF, reflux

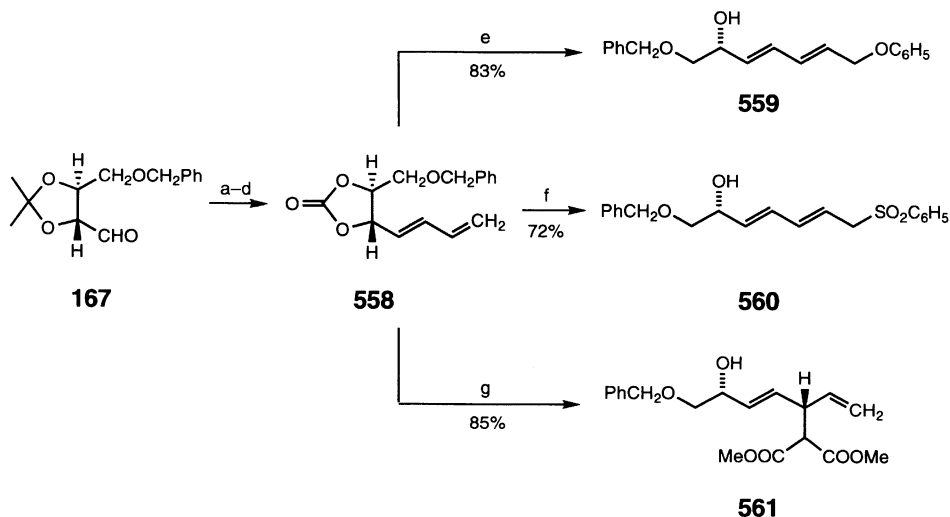
These chiral allylic cyclic carbonates are also capable of reacting with carbon, oxygen, or sulfur nucleophiles to provide products whose regio- and diastereoselectivities depend on the nature of the nucleophile. The reaction of **551** with phenol in the presence of palladium(0) and triethylamine provides in 79% yield **555**, whereas similar reaction with sodium benzene-sulfinate furnishes the (*E*)-allylic alcohol **556** in 80% yield. However, sodium thiophenoxide, under conditions that do not lead to catalyst poisoning, attacks “proximal” to the oxygen atom with inversion to afford the *threo*-β-hydroxy sulfide **557** in 74% yield. This reaction is not observed in the absence of a palladium catalyst [181] (Scheme 123).



Scheme 123

conditions: (a) $\text{C}_6\text{H}_5\text{OH}$, $\text{Pd}(\text{PPh}_3)_4$, Et_3N ; (b) NaSO_2Ph , $\text{Pd}(\text{PPh}_3)_4$, Et_3N ;
(c) NaSC_6H_5 , $\text{Pd}(\text{PPh}_3)_4$, Et_3N

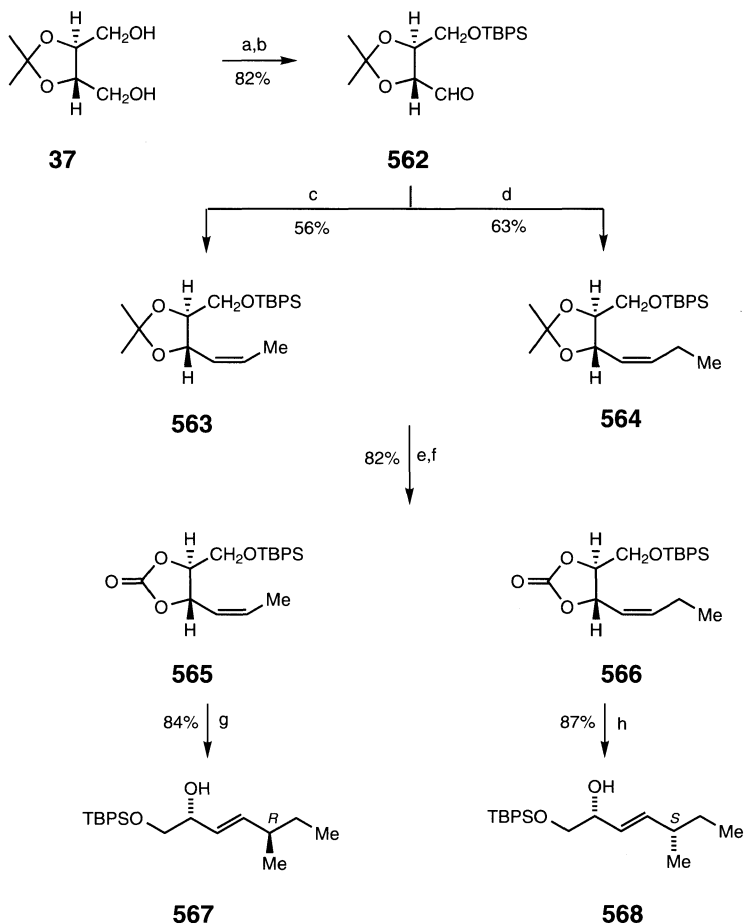
Extension of this reaction to the dienylcyclic carbonate **558**, easily prepared in four steps from **167**, opens the way to useful dienes. While **558** reacts with either phenol or sodium benzenesulfinate in the presence of palladium(0) and triethylamine to produce the expected (*E,E*)-dienes **559** and **560** respectively, the reaction of **558** with dimethylmalonate under neutral conditions provides the γ -alkylated product **561** with 98% diastereoselectivity together with the minor ε -alkylated product ($\gamma : \varepsilon = 6 : 1$) [181] (Scheme 124).



Scheme 124

conditions: (a) $\text{Ph}_3\text{P}=\text{CHCHO}$, C_6H_6 (92%); (b) $\text{Ph}_3\text{P}^+\text{CH}_3\text{Br}^-$, THF (67%); (c) 10% HCl , THF (87%);
(d) CDI , DCM (74%); (e) $\text{C}_6\text{H}_5\text{OH}$, Et_3N , $\text{Pd}(\text{PPh}_3)_4$; (f) NaSO_2Ph , $\text{Pd}(\text{PPh}_3)_4$, Et_3N ;
(g) $\text{CH}_2(\text{COOMe})_2$, $\text{Pd}(\text{PPh}_3)_4$, THF

The reaction of cyclic carbonates with organocuprates, such as $\text{RCu}(\text{CN})\text{Li}-\text{BF}_3$, $\text{RCu}(\text{CN})\text{MgBr}-\text{BF}_3$, or $\text{RMgBr}-\text{CuI}(\text{cat})$ in THF at -78°C , proceeds in an $\text{S}_{\text{N}}2'$ fashion to provide alkylated *E*-allylic alcohols with high diastereoselectivity. Monosilylation and Swern oxidation of **37** affords **562**, which undergoes the Wittig reaction to provide either **563** or **564** in modest overall yield. Subsequent hydrolysis of the isopropylidene protecting group and conversion to a cyclic carbonate furnishes **565** or **566**. Treating **565** with $\text{EtMgBr}-\text{CuI}(\text{cat})/\text{BF}_3$ etherate affords in 84% yield the *R*-allylic alcohol **567**, where the diastereoselectivity is 99 : 1. Similar treatment of **566** with $\text{MeMgBr}-\text{CuI}(\text{cat})/\text{BF}_3$ etherate provides in 87% yield the *S*-allylic alcohol **568**, where the diastereoselectivity is also 99 : 1 [182] (Scheme 125).



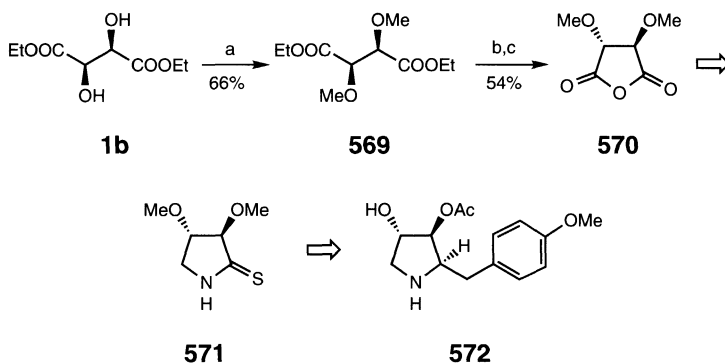
Scheme 125

conditions: (a) TBPSCl, NaH, DME (91%); (b) Swern [O] (98%); (c) $\text{Ph}_3\text{P}^+\text{CH}_3^-\text{Br}^-$, *n*-BuLi, THF; (d) $\text{Ph}_3\text{P}^+\text{CH}_2\text{CH}_3^-\text{Br}^-$, *n*-BuLi, THF; (e) 70% AcOH, THF; (f) CDI, DCM; (g) EtMgBr , CuI, $\text{BF}_3\cdot\text{Et}_2\text{O}$; (h) MeMgBr , CuI, $\text{BF}_3\cdot\text{Et}_2\text{O}$

4.3.4 Di-O-Alkylated Tartrates

A significant portion of this chapter has been devoted to protection of the vicinal dihydroxy functionalities of tartaric acid derivatives with various cyclic protecting groups that may or may not participate in synthesis of the desired product. However, many noncyclic protecting groups are also available. Of these, the dialkylated derivatives will be discussed first.

Perhaps the most direct approach to 2,3-di-*O*-methyl tartrates is to treat the corresponding ester, such as **1b**, with a base like sodium hydride together with excess methyl iodide. Performed on a scale of up to one kilogram, this reaction provides in 66% yield diethyl (+)-2,3-di-*O*-methyltartrate (**569**). Saponification of the diesters followed by anhydride formation with refluxing acetyl chloride furnishes **570**, which is converted to 3,4-dimethoxythiopyrrolidone (**571**). This is the key intermediate for the synthesis of the antibiotic anisomycin (**572**). The synthesis itself is not diastereoselective, and suffers from the tedious methodology required to introduce the correct acetoxy functionality present in **572** [183] (Scheme 126).

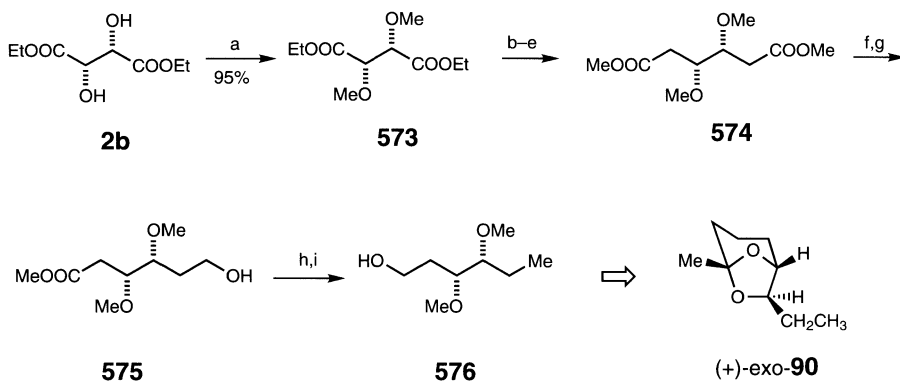


Scheme 126

conditions: (a) NaH, MeI, Et₂O; (b) NaOH, EtOH (64%); (c) MeCOCl, reflux (85%)

A second approach, also suitable for large-scale preparations, reacts diethyl (*S,S*)-tartrate (**2b**) with methyl iodide in the presence of freshly prepared, dry, powdered silver(I) oxide to furnish, after distillative purification, diethyl (2*S*,3*S*)-(–)-2,3-dimethoxysuccinate (**573**) in 95% yield. Subsequent reduction with lithium aluminum hydride, conversion of the resulting diol to the dinitrile *via* tosylate displacement with cyanide, and methanolysis provides dimethyl (3*R*,4*R*)-(+)-dimethoxyadipate (**574**). Controlled saponification with potassium hydroxide affords the half acid, which is reduced with diborane to **575**. This is in turn converted to the tosylate and reduced with lithium aluminum hydride to provide (3*R*,4*R*)-(+)-3,4-dimethoxyhexan-1-ol (**576**), which is converted in several steps to (+)-*exo*-brevicomine (**90**) (Scheme 127). The *O*-methyl groups were oxidatively unmasked with chromium trioxide, although in poor yields. Boron trichloride proves fruitless in performing this unmasking [184].

Disparlure, [*cis*-(7*R*,8*S*)-(+)-7,8-epoxy-2-methyloctadecane] (**490**) is the sex pheromone of the female gypsy moth *Prothetria dispar* L. Its stereoselective synthesis utilizes the *threo* configuration present in diethyl (2*R*,3*R*)-(+)-tartate (**1b**). Conversion of **577**, prepared



Scheme 127

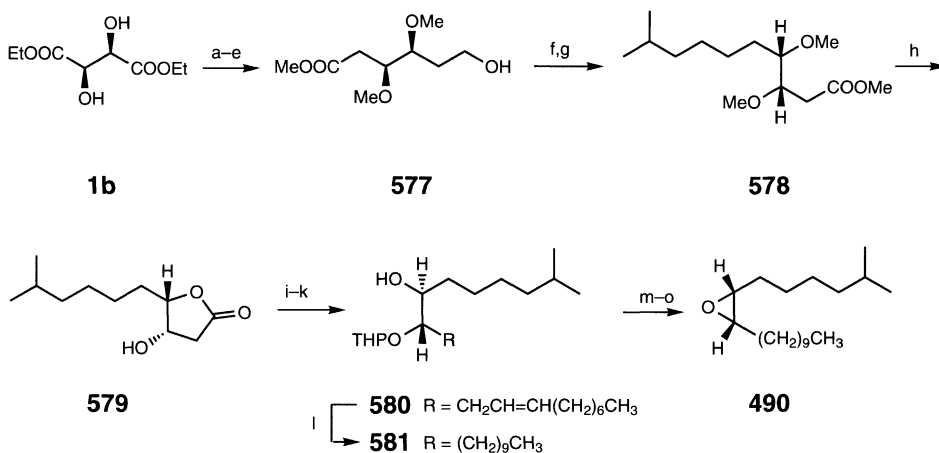
conditions: (a) Ag_2O , MeI; (b) LiAlH_4 , Et_2O (70%); (c) *p*-TsCl, pyridine (79%); (d) NaCN, DMSO (66%); (e) HCl(g), MeOH (84%); (f) KOH, MeOH (72%); (g) B_2H_6 , THF (54%); (h) *p*-TsCl, pyridine (81%); (i) LiAlH_4 , Et_2O (75%)

similarly to **575** [184], to the tosylate followed by a nucleophilic displacement with diisooamyl lithium cuprate in ether provides in 65% yield the dimethoxy ester **578**. Demethylation with boron trichloride in methylene chloride affords the diol, which lactonizes *in situ* to **579** in 56% yield. After THP protection of the free hydroxy group, DIBAL reduction to a lactol, Wittig olefination, and catalytic hydrogenation of the resulting olefin, **580** is obtained in good overall yield. The free hydroxy group is tosylated, THP protection is removed, and ring closure is effected with dilute potassium hydroxide in methanol to give (+)-**490** [185] (Scheme 128).

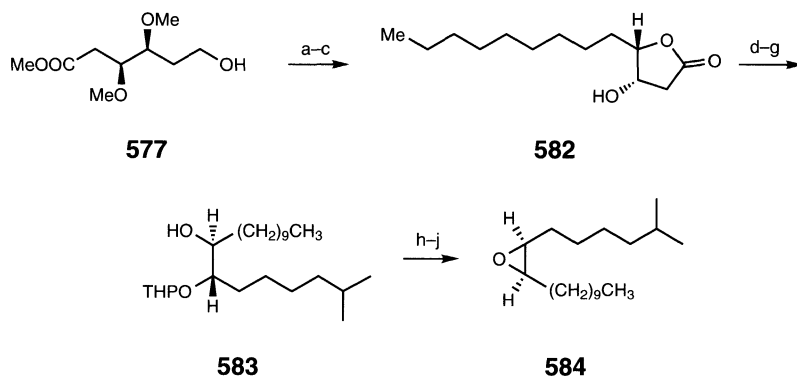
A particularly useful feature of the above-described synthesis for (7*R*,8*S*)-(+)-**490** is the possibility of preparing the enantiomeric (7*S*,8*R*)-(–)-disparlure (**584**) from **577** by simply reversing the order of alkyl group introduction. Treatment of the tosylate of **577** with di-*n*-octyllithium cuprate in ether followed by boron trichloride demethylation provides the lactone **582**. This is converted to **583**, where the isoamyl group is introduced in the Wittig olefination step. Subsequent group transformations provide (7*S*,8*R*)-(–)-disparlure (**584**) (Scheme 129). Both (7*R*,8*S*)-(+)-**490** and (7*S*,8*R*)-(–)-**584**, prepared in quantities up to one gram, are 98% optically pure [185] (Scheme 129).

Passing dry ammonia through a solution of the dimethoxy anhydride **570** produces an amide-acid [186] which, when heated at 200 °C for several minutes, cyclizes to (2*R*,3*R*)-2,3-dimethoxysuccinimide (**585**) in 60% yield. Coupling **585** with *Z*-3-hexenol provides **586**, which undergoes a highly stereoselective sodium borohydride reduction under acidic conditions to provide the α -OH lactam **587**. Treatment of **587** with formic acid generates an α -acyliminium ion that cyclizes to **588** in nearly quantitative yields. The geometry of the double bond determines the stereochemistry of the products [187]. Similar chemistry is observed utilizing (3*R*,4*R*)-3,4-bis(benzyloxy)succinimide (**589**) [188] (Scheme 130).

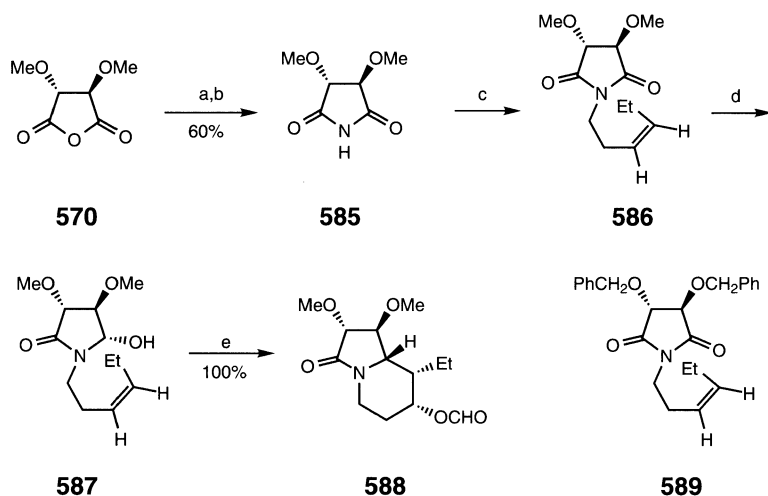
A variant of the Williamson reaction for the preparation of ethers utilizes thallium ethoxide to convert the vicinal hydroxy groups in tartaric esters to the thallium(I) oxide derivative **590**, which upon treatment with alkyl halides provides excellent yields of dialkylated tartaric esters **569** [189].

**Scheme 128**

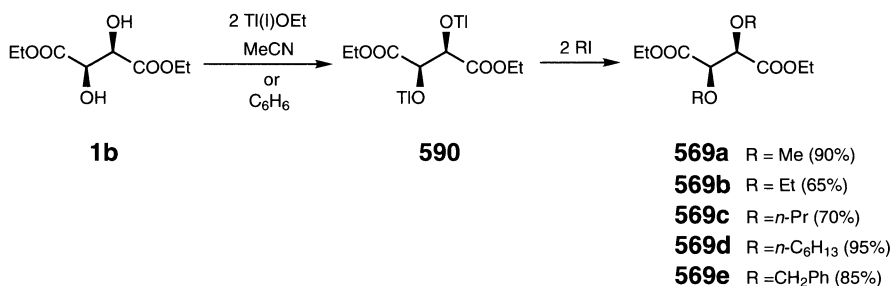
conditions: (a) Ag₂O, MeI (95%); (b) LiAlH₄, ether (70%); (c) TsCl, pyridine (79%) then NaCN, DMSO (66%); (d) HCl, MeOH (84%) then KOH, MeOH (72%); (e) B₂H₆, THF (54%); (f) *p*-TsCl, pyridine (81%); (g) (*iso*-amyl)₂CuLi, Et₂O, -78 °C (65%); (h) BCl₃, DCM then MeOH (56%); (i) DHP, *p*-TsOH; (j) DIBAL, THF-toluene (1:1), -78 °C (100%); (k) *n*-C₈H₁₇PPh₃Br, *n*-BuLi, THF (69%); (l) H₂, Pd/C, EtOH (90%); (m) *p*-TsCl, pyridine (78%); (n) *p*-TsOH, MeOH (67%); (o) 0.25N KOH, MeOH (85%)

**Scheme 129**

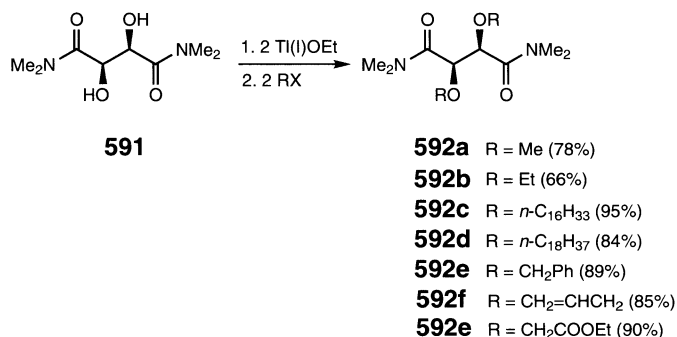
conditions: (a) *p*-TsCl, pyridine (81%); (b) (*n*-C₈H₁₇)₂CuLi, Et₂O (74%); (c) BCl₃, DCM (44%); (d) DHP, *p*-TsOH; (e) DIBAL, toluene (94%); (f) Me₂CHCH₂CH=PPh₃ (90%); (g) H₂, Pd/C, EtOH (90%); (h) *p*-TsCl, pyridine; (i) *p*-TsOH, MeOH (76%); (j) 0.25N KOH, MeOH (90%)

**Scheme 130**

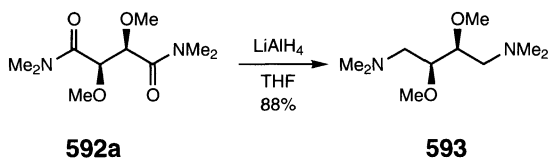
conditions: (a) NH_3 , Et_2O ; (b) $200\text{ }^\circ\text{C}$; (c) PPh_3 , DEAD , $\text{HO}(\text{CH}_2)_2\text{CH}=\text{CH:Et}$; (d) NaBH_4 ; (e) HCOOH



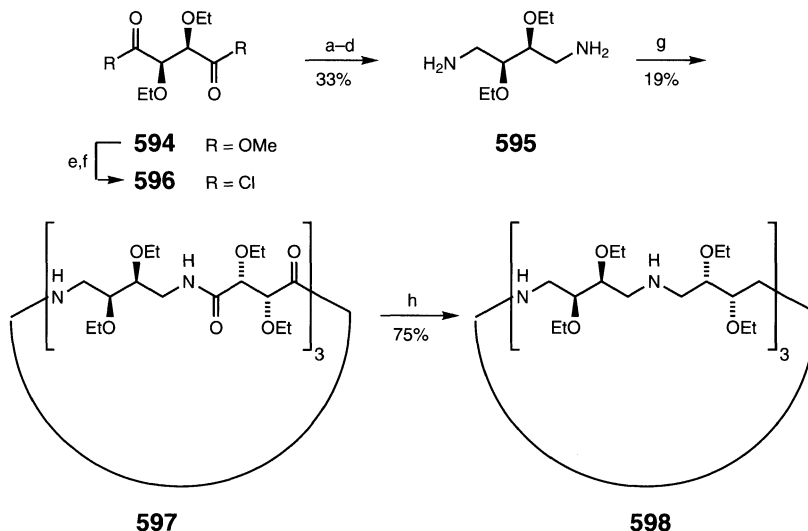
Conversion of **1b** to the dimethylamide **591** [190] and introduction of thallium ethoxide followed by treatment with an appropriate alkyl halide generates in good to excellent yield the di-O-alkylated tartaramides **592** [189].



The asymmetric solvent (*S,S*)-(+)-1,4-bis(dimethylamino)-2,3-dimethoxybutane (**593**) can be easily prepared in 88% yield from **592a** by lithium aluminum hydride reduction of both amides. Interestingly, **592a** is prepared from **591** by bis-alkylation with dimethyl sulfate under phase-transfer conditions [191].



The reduction of dimethyl 2,3-di-*O*-ethyltartrate (**594**) with lithium aluminum hydride, followed by a three-step transformation of the free hydroxyl groups into amines, provides **595** in an overall yield of 33% from **594**. Saponification of **594** to the diacid followed by treatment with thionyl chloride in the presence of a catalytic amount of DMF furnishes the diacid chloride **596**. High-dilution condensation of **595** with **596** in benzene containing triethylamine followed by chromatographic purification of the resulting macrocyclic polyamide mixture provides the glassy hexaamide **597** in 19% yield. Reduction of **597** with diborane in THF provides after work-up the free hexaamine **598** in 75% yield. This 30-membered hexaamine, possessing one C_6 symmetry axis and six C_2 axes (dihedral axes) perpendicular to it, or D_6 , is the first organic molecule prepared with this symmetry [192] (Scheme 131).

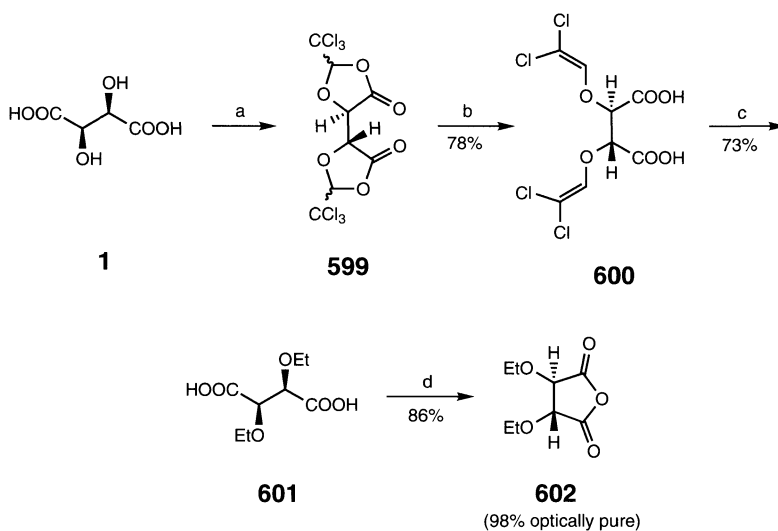


Scheme 131

conditions: (a) LiAlH_4 ; (b) *p*-TsCl, pyridine; (c) potassium phthalimide, DMF; (d) $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$; (e) NaOH; (f) SOCl_2 , DMF, C_6H_6 ; (g) **596**, Et_3N , C_6H_6 ; (h) B_2H_6 , THF

A somewhat unusual but effective method for the preparation of (2*R*,3*R*)-2,3-di-*O*-ethyl-tartaric acid (**601**) involves the use of chloral hydrate. Treatment of tartaric acid with chloral hydrate affords **599**, which is reductively converted to (2*R*,3*R*)-2,3-di-*O*-(2,2-dichloro-

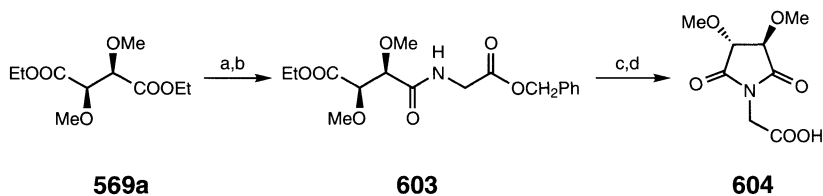
vinyl) tartaric acid (**600**) in 78% yield. Pure **600** is difficult to isolate, but it is stable for weeks in the refrigerator. It is also stable to dilute alkaline solution, and can be extracted after acidification. Attempted reduction of **600** with sodium borohydride or Raney nickel proved unsuccessful. Total reduction with hydrogen over palladium/carbon in methanolic solution using potassium carbonate as acid scavenger yields **601** in 73% yield. Reaction of **601** with acetyl chloride provides (2*R*,3*R*)-2,3-di-*O*-ethyltartaric anhydride (**602**) in 86% yield [193] (Scheme 132).



Scheme 132

conditions: (a) Cl_3CCHO , H_2O , H_2SO_4 ; (b) Zn , AcOH ; (c) H_2 , Pd/C , K_2CO_3 , MeOH ; (d) MeCOCl , EtOAc

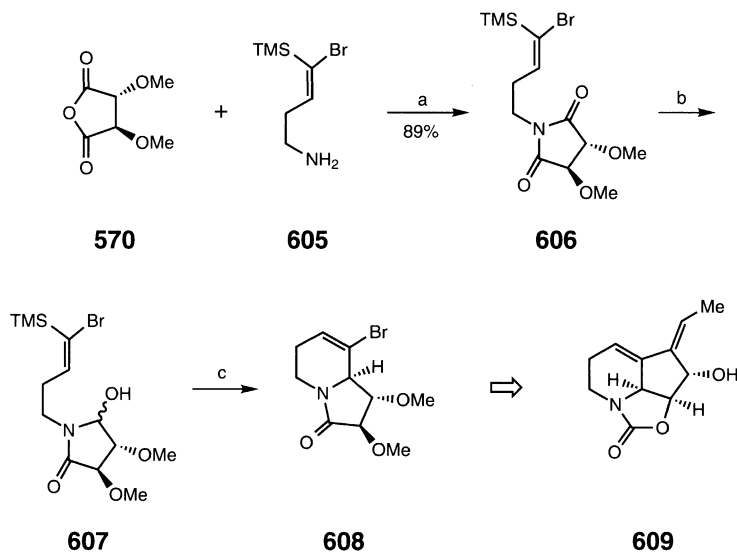
Monosaponification of **569a** with aqueous sodium hydroxide followed by coupling of the free acid with the ester *O*-benzyl glycine provides amide **603**, which is cyclized in two steps to the tartarimide **604** in 40% overall yield (Scheme 133). This compound has been utilized as a chiral auxiliary in the preparation of chiral lactams by a cycloaddition reaction. The asymmetric induction under appropriate conditions can be as high as 96% [194].



Scheme 133

conditions: (a) aq. NaOH ; (b) glycine-*O*-benzyl ester, $p\text{-TsOH}$, $(\text{EtO})_2\text{P(O)CN}$, Et_3N ; (c) Na (powder), toluene; (d) H_2 , Pd/C , EtOH

The enantioselective total synthesis of streptazolin (**609**), a neutral lipophilic antibiotic isolated from cultures of *Streptomyces viridochromogenes*, utilizes a tandem iminium ion–vinylsilane cyclization of the tartrate-derived **607** together with intramolecular acylation as a way of achieving high stereoselectivity. Heating a mixture of **570** and (*E*)-4-bromo-4-(trimethylsilyl)-3-buten-1-amine (**605**) followed by dehydration with acetyl chloride provides the imide (**606**) in reproducible yields of 90%. Reduction of **606** with sodium borohydride affords **607**, which is refluxed in trifluoroacetic acid to provide, after careful purification, the single bicyclic adduct **608** in 74% yield. This is then transformed in four steps to the desired streptazolin (**609**) [196] (Scheme 134).



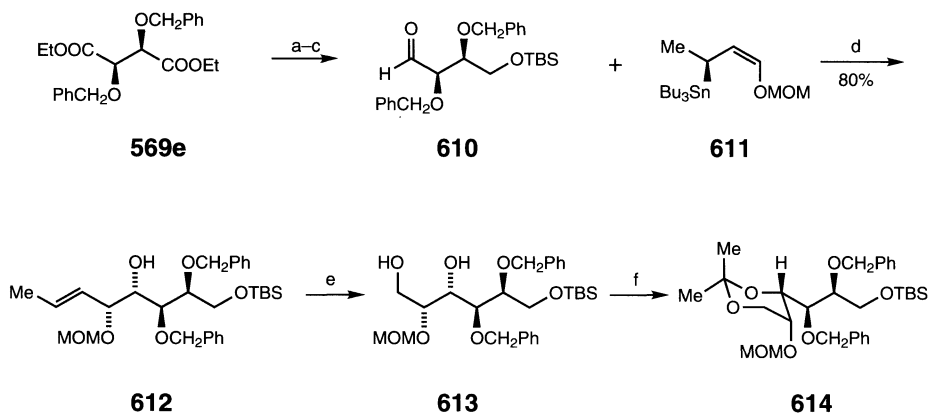
Scheme 134

conditions: (a) DCM, rt, overnight then 90 °C, toluene, then AcCl; (b) NaBH₄, MeOH; (c) CF₃COOH, reflux 6 h (87%)

The reduction of **569e** with lithium aluminum hydride followed by monoprotection with *tert*-butyldimethylsilyl chloride and Dess–Martin oxidation of the free hydroxyl group to an aldehyde affords **610**. An aldol reaction of **610** with (*S*)-(γ-alkoxyallyl)stannane (**611**) in the presence of boron trifluoride etherate provides exclusively, in 80% yield, the alcohol **612**. Ozonolysis of the olefin followed by sodium borohydride reduction affords diol **613**, which is converted to acetonide **614** (Scheme 135). Interestingly, alcohol **612**, the double bond of which is susceptible to stereocontrolled introduction of hydroxyl groups, could lead to ω-deoxy sugars [197].

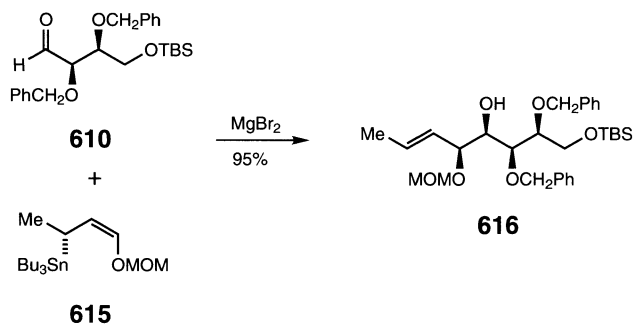
Reaction of aldehyde **610** with the corresponding (*R*)-(γ-alkoxyallyl)stannane (**615**) in the presence of magnesium bromide affords exclusively the alcohol **616** in 95% yield [197].

(–)-Hikizimycin (anthelmycin) (**622**) is a nucleoside disaccharide isolated from the fermentation broth of *Streptomyces A-5* and *Streptomyces longissimus*. Possessing significant anthelmintic activity against a variety of parasites, **622** represents the most structurally complex member of the long-chain carbohydrate class of natural products. It is comprised of a cytosine base, a 3-amino-3-deoxyglucose sugar (kanosamine), and a 4-aminoundecose sugar

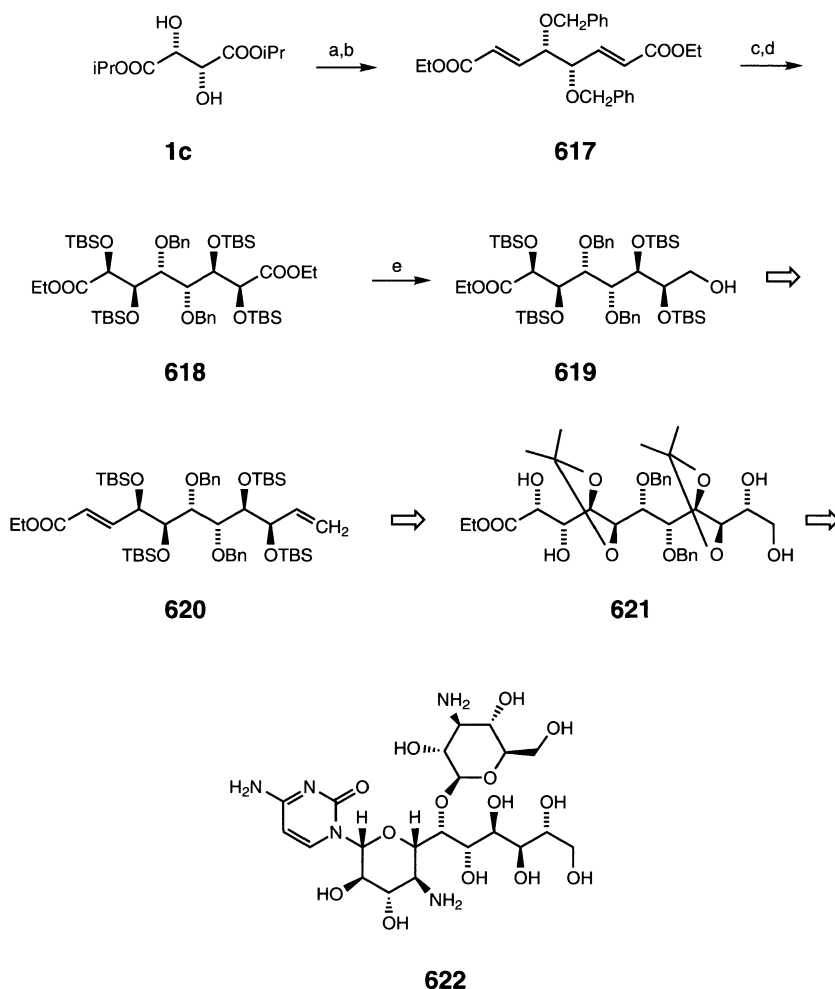


Scheme 135

conditions: (a) LiAlH_4 ; (b) TBSCl, imidazole, DMF; (c) Dess–Martin [O]; (d) $\text{BF}_3 \cdot \text{Et}_2\text{O}$; (e) O_3 , DMS, then NaBH_4 ; (f) $\text{Me}_2\text{C}(\text{OMe})_2$, *p*-TsOH



(hikosamine). One of the features of the total synthesis of **622** is utilization of a two-directional chain synthesis that exploits the C_2 -axis of symmetry present in the appropriate tartrate starting synthon. Benzylation of the hydroxy groups of L-(+)-diisopropyl tartrate (**1c**) followed by a one-pot reduction/homologation procedure furnishes the α,β -unsaturated ester **617**. Bis-hydroxylation with catalytic osmium tetroxide and excess *N*-methylmorpholine *N*-oxide occurs with high selectivity. Recrystallization of the reaction mixture easily removes the minor *E,Z* isomer. Protection of the hydroxy groups then furnishes tetraol **618**. This sequence of reactions was used to prepare over 100 g of **618**. Terminus differentiation of the C_2 -symmetric chain is exploited to furnish the monoalcohol **619**, which is subsequently converted in five steps to **620**. As a result of the loss of stereoselectivity in osmylation reactions of **620**, the compound is desilylated and then protected as the bis-acetonide, which then affords good diastereoselectivity when catalytic osmylation is carried out in the presence of a dihydroquinine *p*-chlorobenzoate. Thus, in 11 steps, all accomplished on a multigram scale, the undecose chain **621** has been constructed at the appropriate oxidation level and with the correct stereochemistry at each carbon (Scheme 136). Construction of the remaining fragments and a convergent synthetic route provides **622** [198].



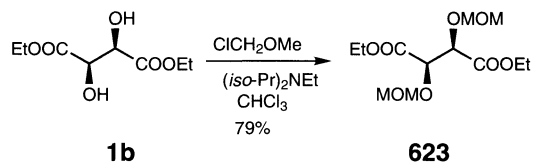
Scheme 136

conditions: (a) PhCH_2Br , NaH (2.1 equiv.), $n\text{-Bu}_4\text{NI}$, THF (53%); (b) $(\text{EtO})_2\text{P}(\text{O})\text{CH}(\text{Li})\text{COOEt}$, DCM, DIBAL (53%); (c) OsO_4 (cat), NMO, acetone– H_2O (71%); (d) TBSOTf, 2,6-lutidine, DCM (100%); (e) DIBAL, DCM, -78°C (82%)

4.3.5 Methoxymethyl Ether (MOM) Protection

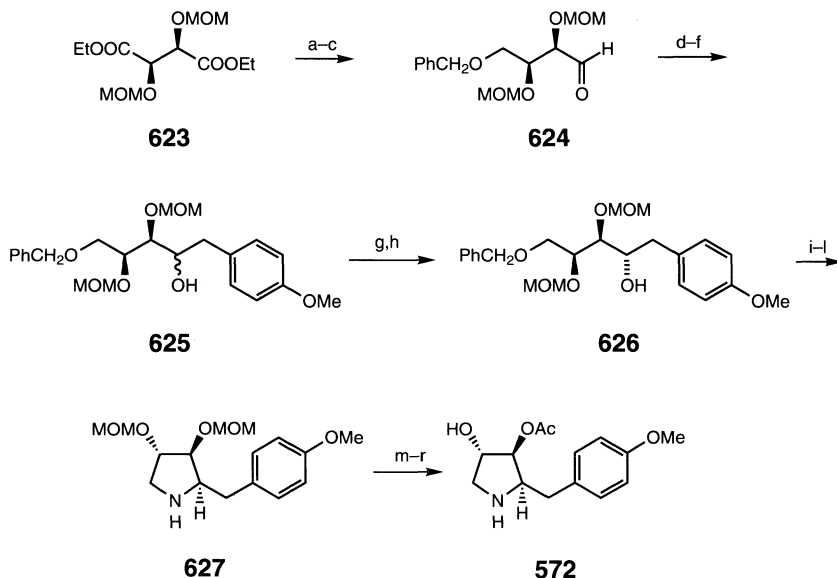
Easily prepared and removed under mild acidic conditions, the methoxymethyl ether (MOM) protecting group has been widely utilized with a variety of tartarate derivatives. Treatment of diethyl tartrate (**1b**) with excess chloromethyl methyl ether in the presence of *N,N*-diisopropylethylamine furnishes in 79% yield diethyl 2,3-*O*-bis(methoxymethyl)-*L*-tartrate (**623**). This reaction is easily performed on a scale greater than 100 g [199,200].

Anisomycin (**572**), an antibiotic isolated from fermentation broth filtrates of various species of *Streptomyces*, possesses strong and selective activities against pathogenic protozoa and



fungi, apparently by blocking ribosomal peptide synthesis. Lithium aluminum hydride reduction of **623** followed by monobenzylation and Swern oxidation affords 4-*O*-benzyl-2,3-*O*-bis(methoxymethyl)-*L*-threose (**624**) in good overall yield. The Grignard addition of *p*-methoxybenzylmagnesium chloride provides a mixture of *xylo* and *lyxo* alcohols **625**, which can be oxidized to a ketone and reduced with zinc borohydride to afford (2*S*,3*S*,4*S*)-5-benzyloxy-3,4-[bis(methoxymethyl)oxy]-1-(4-methoxyphenyl)-2-propanol (**626**), where the reduction takes place with almost complete diastereofacial control. The *anti* selectivity of this hydride addition is consistent with formation of a five-membered α -chelate rather than the β -chelate model, which leads to *syn* selectivity [201].

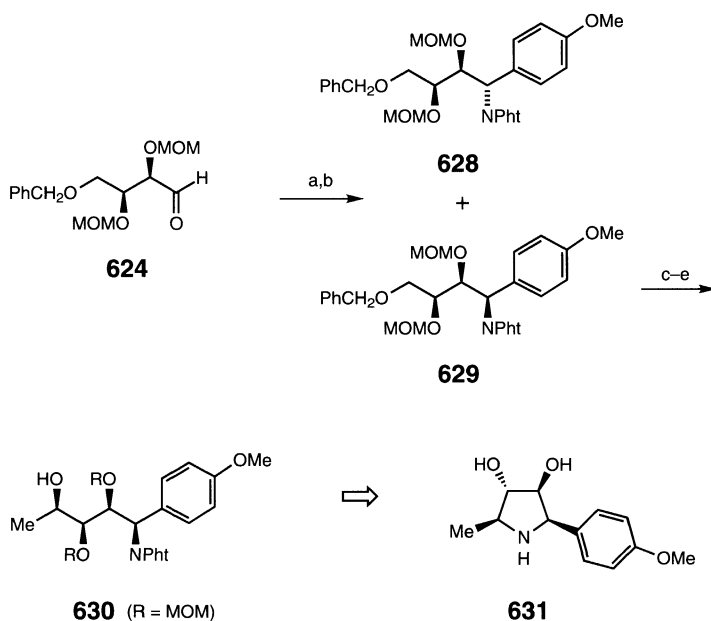
Debenzylation of **626** followed by conversion to a dimesylate, selective displacement with azide ion at the primary position, and catalytic azide reduction with simultaneous cyclization produces the pyrrolidine **627**. Mild acidic removal of the methoxymethyl ether protecting groups, Cbz protection of the nitrogen, and selective protection of the less hindered secondary hydroxyl group with the bulky *tert*-butyldimethylsilyl protecting group allows acetylation of the remaining hydroxy group. Appropriate deprotection completes the synthesis of **572** [200] (Scheme 137).



Scheme 137

conditions: (a) LiAlH_4 , Et_2O (94%); (b) PhCH_2Cl , NaOH , $n\text{-Bu}_4\text{NBr}$, DCM (74%); (c) Swern [O] (82%); (d) H_2 , Pd/C , MeOH (91%); (e) PMBMgCl , THF (69%); (f) PhCH_2Cl , NaOH , $n\text{-Bu}_4\text{NBr}$, DCM (69%); (g) Swern [O] (91%); (h) $\text{Zn}(\text{BH}_4)_2$, Et_2O (91%); (i) H_2 , Pd/C , MeOH (100%); (j) MsCl , DCM , Et_3N (87%); (k) NaN_3 , DMF , 80°C (45%); (l) H_2 , Pd/C , CHCl_3 (95%); (m) $\text{HCl-H}_2\text{O}$ (1:1) (81%); (n) CbzCl , Na_2CO_3 , H_2O , DCM (72%); (o) TBSCl , imidazole, DMF (80%); (p) Ac_2O , pyridine (96%); (q) $n\text{-Bu}_4\text{NF}$, THF (85%); (r) H_2 , Pd/C , EtOH (95%)

(+)-Codonopsinine (**631**) is the enantiomer of the naturally occurring (–) form of this pyrrolidine alkaloid isolated from *Codonopsis clematidea* (*Campanulaceae*). The reaction of **624** with *p*-methoxyphenylmagnesium bromide provides in 83% yield a 1:1 mixture of *threo*:*erythro* alcohols, which undergoes a Mitsunobu reaction with phthalimide to afford, after chromatographic separation of the 1:1 mixture, *anti*-**628** and *syn*-**629**. Debenzylation of **629** followed by Swern oxidation and a highly stereoselective chelation-controlled addition of methylmagnesium bromide provides the *threo* alcohol **630**, which is converted in five steps to (+)-(2*R*,3*S*,4*S*,5*S*)-codonopsinine (**631**) [199] (Scheme 138).

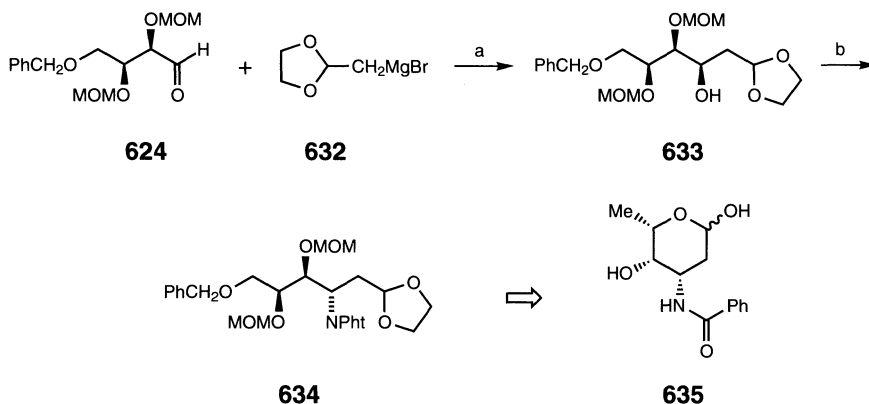


Scheme 138

conditions: (a) *p*-MeOC₆H₄MgBr, THF, –10 °C (83%); (b) phthalimide, DEAD, PPh₃, THF (64%); (c) H₂, Pd/C, MeOH (70%); (d) Swern [O] (83%); (e) MeMgBr, Et₂O, –78 °C (62%)

Chelation-controlled addition of a Grignard reagent to **624** is exploited in the efficient and completely stereocontrolled synthesis of *N*-benzoyl-L-daunosamine (**635**), the common sugar moiety of such anthracyclin antitumor agents as daunorubicin and adriamycin. The addition of [(1,3-dioxolan-2-yl)methyl]magnesium bromide (**632**) to **624** provides in 70% yield the single *syn* (*xylo*) adduct **633**. This *syn* stereoselection is consistent with a cyclic α -chelation model. The stereoselectivity of Grignard addition is dependent on the nucleophile used. Presumably the acetal oxygens of **632** contribute toward the stabilization of a cyclic transition state. Subsequent Mitsunobu inversion of **633** with phthalimide occurs stereospecifically to provide **634**, which is converted in nine steps to *N*-benzyl-L-daunosamine (**635**) [202] (Scheme 139).

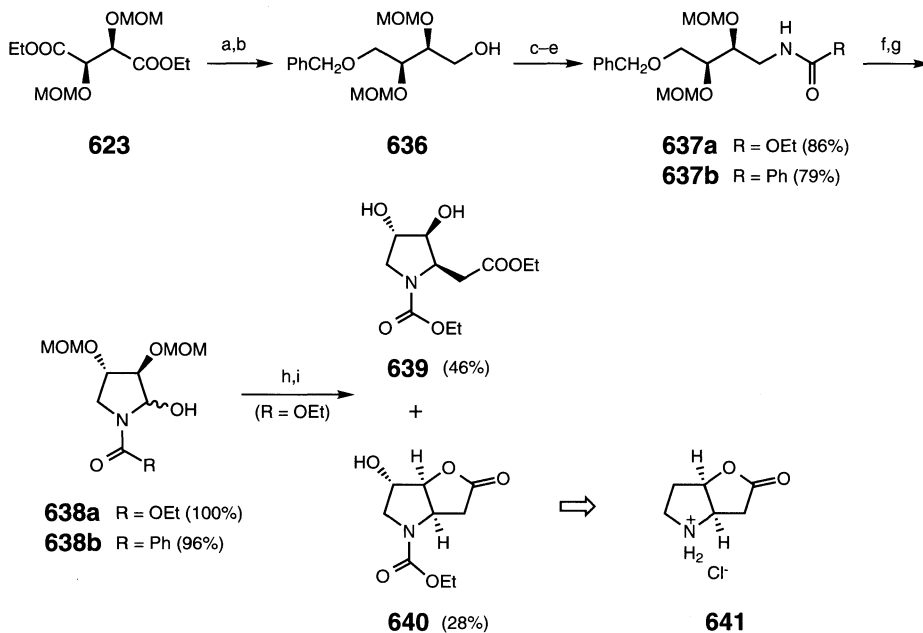
The intramolecular Michael reaction is useful for the preparation of nitrogen-containing heterocycles. Crucial to the success of this Michael reaction is the accessibility of substrates and nucleophilicity on the part of the nitrogen atom. The ability to control 1,2-asymmetric induction during formation of the heteroring is realized when the substrates are derived from tartaric acid derivatives.



Scheme 139

conditions: (a) THF (70%); (b) phthalimide, DEAD, PPh₃, THF (94%)

Lithium aluminum hydride reduction of **623** followed by monoprotection provides the benzyl ether **636**. Mitsunobu introduction of phthalimide, hydrazinolysis, and acetylation yields either **637a** or **637b**. Hydrogenolysis of the benzyl protecting group and subsequent Swern oxidation of the free hydroxy group affords in good yield the hemiacetals **638a** or

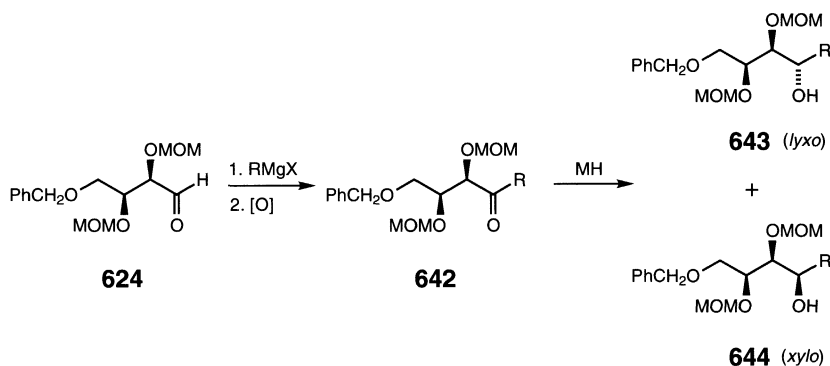


Scheme 140

conditions: (a) LiAlH₄, THF (85%); (b) PhCH₂Br, NaH, DMF (99%); (c) phthalimide, DEAD, PPh₃, THF (92%); (d) hydrazine hydrate, EtOH (89%); (e) RCOCl, Et₃N, DCM; (f) H₂, Pd/C, EtOH (100%); (g) Swern [O] (100%); (h) (EtO)₂P(O)CH₂COOEt, NaH, DME (70%); (i) EtSH, BF₃·Et₂O, DCM

638b. A Horner–Emmons reaction of **638a** with triethyl phosphonoacetate leads to an α,β -unsaturated ester that under the basic conditions of the reaction undergoes intramolecular Michael reaction. Cleavage of the MOM ethers with ethanethiol/boron trifluoride etherate provides a readily separable mixture of ester **639** and lactone **640**. Lactone **640** is transformed in three steps to the Geissman lactone **641**, also available from *S*-malic acid [203] (Scheme 140).

The α -chelation-controlled addition of Grignard reagents to aldehyde **624** to provide in some cases exclusively *syn* addition products suggests the possibility of utilizing either α - or β -chelation-controlled addition of hydride to the ketone derivative **642** for efficient and stereoselective preparation of either the *L*-lyxo (*anti*)-**643** or *L*-xylo (*syn*)-**644** alcohols [201] (Scheme 141).



R	MH	Yield (%)	643:644
Me	NaBH ₄	94	79:21
	Vitride	82	86:14
	Zn(BH ₄) ₂	78	93:7
	L-Selectride	75	23:72
<i>n</i> -C ₃ H ₇	NaBH ₄	93	80:20
	Vitride	87	95:5
	L-Selectride	75	8:92
<i>p</i> -MeOC ₆ H ₄ CH ₂	NaBH ₄	99	72:28
	Vitride	78	95:5
	Zn(BH ₄) ₂	91	>99:1
	L-Selectride	74	5:95
	LiAlH ₄	66	64:36

Scheme 141

The diastereoselective hydride addition of a chiral metal hydride reagent to a ketone substrate bearing a stereogenic center is called a substrate-controlled process, and it leads to 1,2-asymmetric induction. Enantioselective hydride addition to a prochiral ketone by metal

hydride reagents modified with chiral ligands is referred to as reagent-controlled. The ability to selectively prepare both enantiomers of a desired synthetic target from a single, readily available and inexpensive enantiomeric source by exploiting either type of hydride addition is illustrated by the highly stereocontrolled syntheses of naturally occurring (+)-indolizide 195B (bicyclic gephyrotoxin 195B) (**654**) and (-)-pinidine (**661**).

When first isolated from extracts from the skin of the Columbian poison frog *Dendrobates histrionicus* as a new alkaloid component, indolizidine 195B's (**654**) absolute stereochemistry needed to be established. Consequently, both enantiomers were synthesized.

Addition of *n*-butylmagnesium bromide to **624** followed by Swern oxidation affords the ketone **642**. Zinc borohydride addition occurs with almost exclusive *anti*-selectivity (>99:1), leading to **646** in accordance with an α -coordinated transition-state model in which the *re*-face of the carbonyl is exposed to the reagent. Presumably the MOM-ethers display a "crown ether effect" to facilitate α -chelation. In marked contrast, L-Selectride shows excellent *syn*-selectivity to provide **645** (92:8), consistent with a β -chelation and/or Felkin-Anh model. The *anti*-adduct **646** is converted in five steps to ketone **647**, which undergoes a similar highly selective hydride reduction with zinc borohydride to yield the *anti,syn,syn*-alcohol **648** (96:4). This product is converted in six steps to the *trans*-(2*R*,5*R*)-pyrroline **649**, which undergoes a Wacker oxidation followed by catalytic reduction to (-)-indolizidine 195B (**650**) and its C-5 epimer (86:14) (Scheme 142).

Exposing **645** to a similar reaction sequence results in ketone **651**, which is reduced with L-Selectride almost exclusively to **652**. Subsequent functional group transformations of **652** to *trans*-(2*S*,5*S*)-pyrroline **653** followed by Wacker oxidation and reductive deprotection with concomitant cyclization affords (+)-indolizidine 195B (**654**) and its C-5 epimer (86:14). A comparison with the natural product established the absolute configuration of natural (+)-**654** to be 3*S*,5*S*,9*S* [204] (Scheme 143).

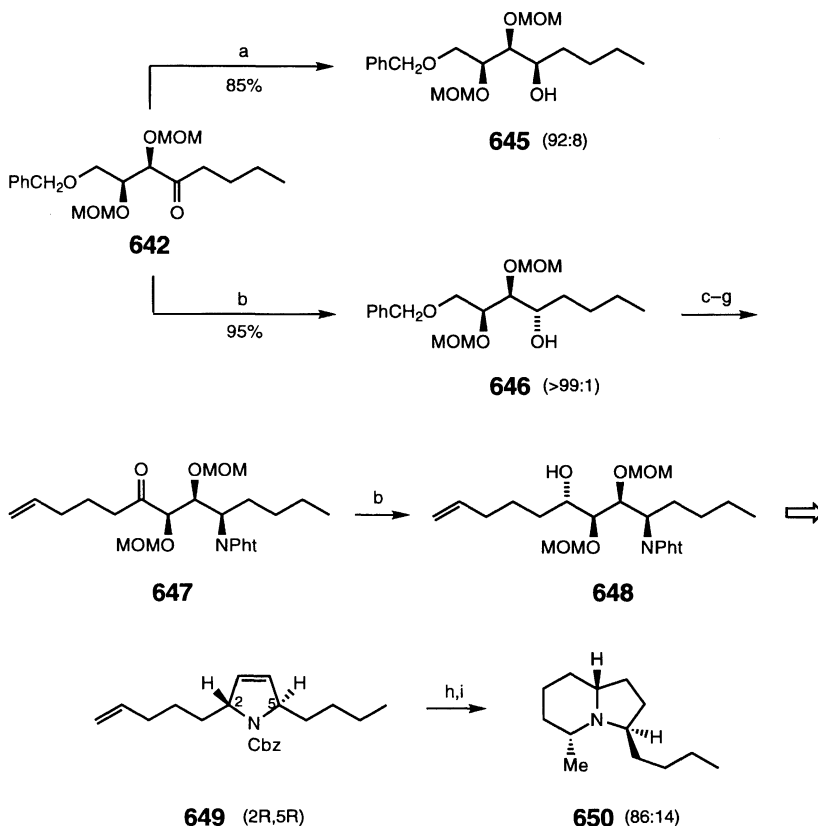
Diastereoselective hydride addition is quite versatile, and it provides facile synthetic access to (-)-pinidine (**661**), an alkaloid isolated from several species of *Pinus*, as well as its unnatural isomer (+)-pinidine (**660b**). The unstable aldehyde **655**, prepared in four steps from **624** [202], undergoes Grignard addition with 4-pentenylmagnesium bromide followed by Swern oxidation to afford ketone **656** in 90% yield for the two steps. Stereoselective hydride addition with L-Selectride provides the *syn*-alcohol **657** (91:9), while zinc borohydride reduction provides almost exclusively the *anti*-alcohol **658** (>99:1) (Scheme 144).

The *syn* alcohol **657** contains the stereochemistry required for a synthesis of (+)-**660b**. The 2,6-disubstituted piperidine **659** is prepared from **657** in seven steps. Conversion of **659** to the cyclic thionocarbonate followed by heating with trimethylphosphite produces the *E*-olefin **660a** which undergoes a Birch desylation to afford (+)-**660b** (Scheme 145).

A similar synthetic route utilizing **658** allows preparation of (-)-**661** [204].



(+)-Monomorine (**664**), isolated from the cosmopolitan ant *Monomorium pharaonis* (*L.*) as a major component displaying attracting and trail-initiating activity, is another example in which stereoselective hydride addition to a prochiral ketone creates easy access to crucial stereogenic centers. L-Selectride reduction of **647** affords, with high *syn* selectivity, alcohol **662** (98:2). This is similarly converted in six steps to the (2*S*,5*R*)-pyrroline **663** which, after



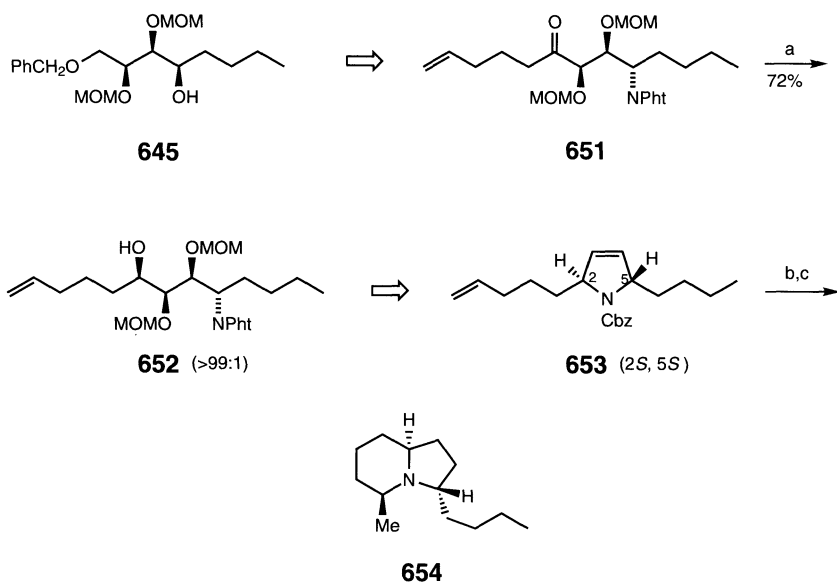
Scheme 142

conditions: (a) L-Selectride, THF -78°C ; (b) $\text{Zn}(\text{BH}_4)_2$, Et_2O , -20°C ; (c) phthalimide, DEAD, Ph_3P (61%);
 (d) H_2 , Pd/C, MeOH; (e) Swern [O] (67% for 2 steps); (f) $\text{CH}_2=\text{CH}(\text{CH}_2)_3\text{MgBr}$, THF;
 (g) Swern [O], (78% for 2 steps); (h) O_2 , PdCl₂, CuCl₂, DMF–H₂O (79%); (i) H_2 , Pd/C,
 MeOH (91%)

Wacker oxidation followed by reductive deprotection and cyclization, affords (+)-**664** [205] (Scheme 146).

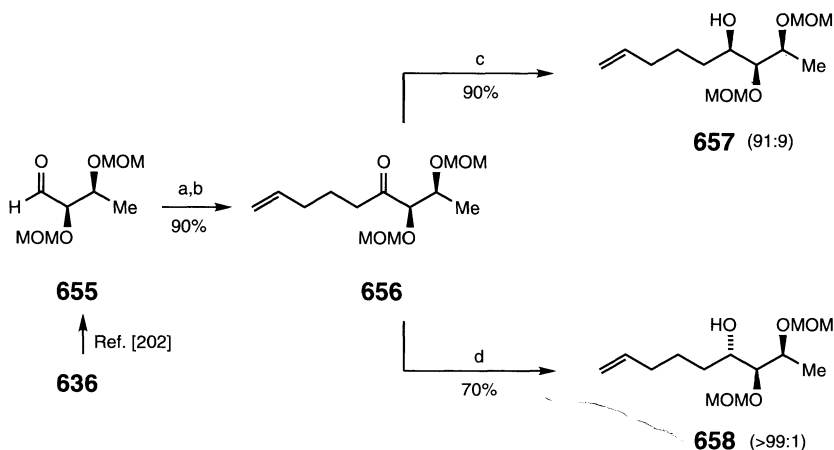
The addition of benzylamine to aldehyde **624** results in the Schiff base **665**, which undergoes preferential *syn* addition of phenyllithium to provide in 68% yield an 86 : 14 mixture of *syn*-**667** and *anti*-**666**. This result suggests that α -chelation is responsible for the observed stereochemistry. Subsequent acidic deprotection of the MOM ethers in **667**, N-Boc protection, and glycol cleavage with periodic acid followed by a reductive work-up affords the alcohol **668**. Removal of the Boc protecting group, then reductive debenzoylation with palladium(II) chloride and reprotection as the N-Boc derivative yields **669**. This is converted in three steps in 47% yield to N-Boc-(*S*)- β -phenyl- β -alanine (**670**), which is utilized in the enantioselective total synthesis of (+)-(*S*)-dihydroperiphylline (**671**), a 13-membered-ring spermidine alkaloid isolated from the leaves of *Peripterygia marginata* [206] (Scheme 147).

Treating **624** with methylene iodide, zinc, and trimethylaluminum in THF provides a good yield of the 4-benzyloxy-1-pentene derivative **672**. Hydrogenation of the olefin and simul-



Scheme 143

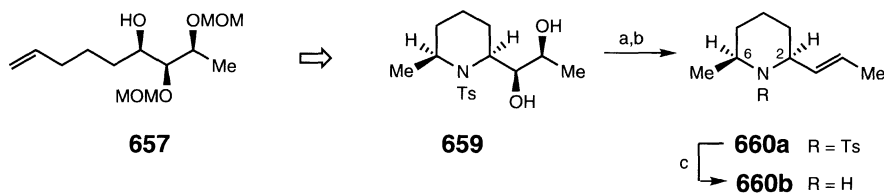
conditions: (a) L-Selectride, THF, -78°C ; (b) O_2 , PdCl_2 , CuCl_2 , $\text{DMF-H}_2\text{O}$ (79%);
(c) H_2 , Pd/C , MeOH (83%)



Scheme 144

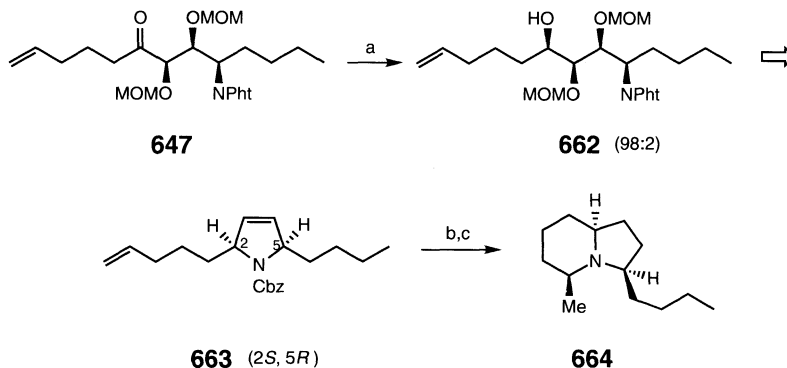
conditions: (a) $\text{CH}_2=\text{CH}(\text{CH}_2)_3\text{MgBr}$, THF; (b) Swern [O]; (c) L-Selectride, THF, -78°C ;
(d) $\text{Zn}(\text{BH}_4)_2$, Et_2O , -20°C

taneous debenzylation followed by Swern oxidation of the primary hydroxy group to the corresponding aldehyde and conversion to the phenylhydrazone provides **673**. Condensation of 5,6-diamino-3-methyluracil (**674a**) with **673** followed by oxidation with potassium ferricyanide in the presence of potassium iodide yields (*S*)-6-(1-hydroxypropyl)-3-methyluracil (**675**) in a yield of 21% for these two steps. Similarly prepared from the *N*-methyl derivative



Scheme 145

conditions: (a) Thionocarbonyldiimidazole, EtN(*i*-Pr)₂, DCM (84%); (b) (MeO)₃P (97%);
 (c) Na, NH₃(l), EtOH, -78 °C (81%)



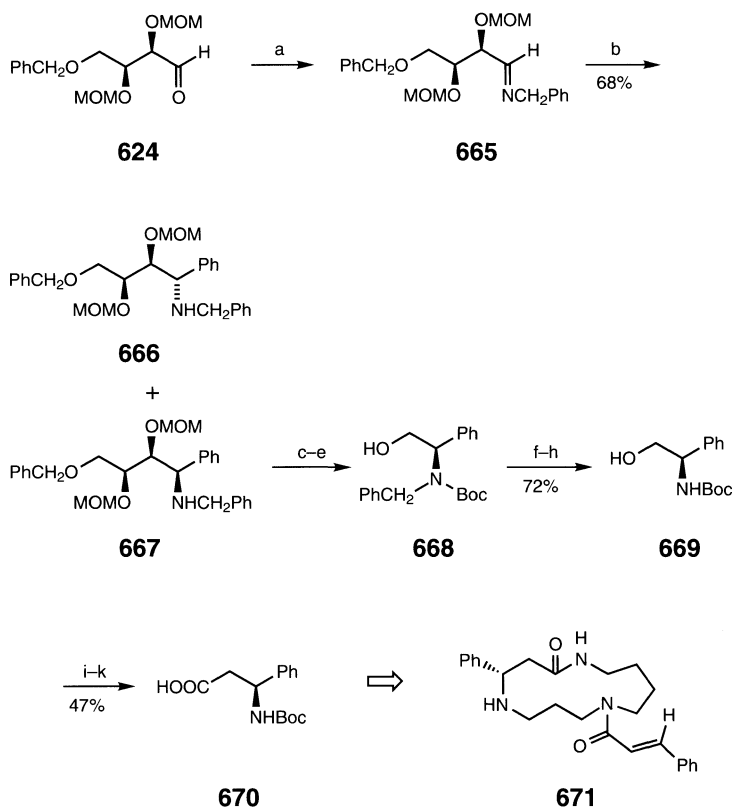
Scheme 146

conditions: (a) L-Selectride, THF, -78 °C (67%); (b) O₂, PdCl₂, CuCl₂, DMF-H₂O (81%);
 (c) H₂, Pd/C, MeOH (76%)

674b is (*S*)-6-(1-hydroxypropyl)-1,3-dimethylumazine (**676**). Both are isolated from the luminescent marine polychaete *Odontosyllis undecimdonta*. The optical purity as determined by proton nmr is 83% *ee* [207] (Scheme 148).

Syringolide I (**681**) and Syringolide 2 (**682**) are both C-glycosides possessing a new ring system acting as specific elicitors from *Pseudomonas syringae* *pv.* *tomato*. Diethyl D-tartrate (**2b**) is converted almost quantitatively to **677**, which is monosilylated, Swern oxidized to the aldehyde, and converted to the protected D-xylulose **678** by addition of (1-ethoxyethoxy)-methylolithium followed by Swern oxidation to the ketone. Selective deprotection and esterification with 3-oxodecanoic acid affords **679**, which undergoes a Knoevenagel condensation simply upon mixing **679** with silica gel in hexane-ethyl acetate to afford **680**. While the direct conversion of **680** to **682** using aqueous acidic conditions fails, a two step procedure in which **680** is treated with Dowex 50-X8 or Amberlyst-15E in dry methanol followed by treatment of the resulting intermediate with *p*-toluenesulfonic acid in acetone affords pure **682** in modest yields. A similar reaction sequence could be utilized to prepare **681** [208] (Scheme 149).

The ethoxyethoxy protecting group (OEE), a close analog of the OMOM protecting group, is easily introduced at the vicinal hydroxy centers of tartaric acids by employing ethyl vinyl ether under acidic conditions. A total synthesis of the macrolide antibiotic (+)-colletodiol (**688**) from diethyl D-(-)-tartrate (**2b**) utilizes this OEE protecting group (Scheme 150). The monobenzyl ether (**683**), prepared in three steps from **2b** in excellent overall yield, is converted to the (*R,R*)-epoxide **143**, which is protected as the methoxyisopropylether (MI), then



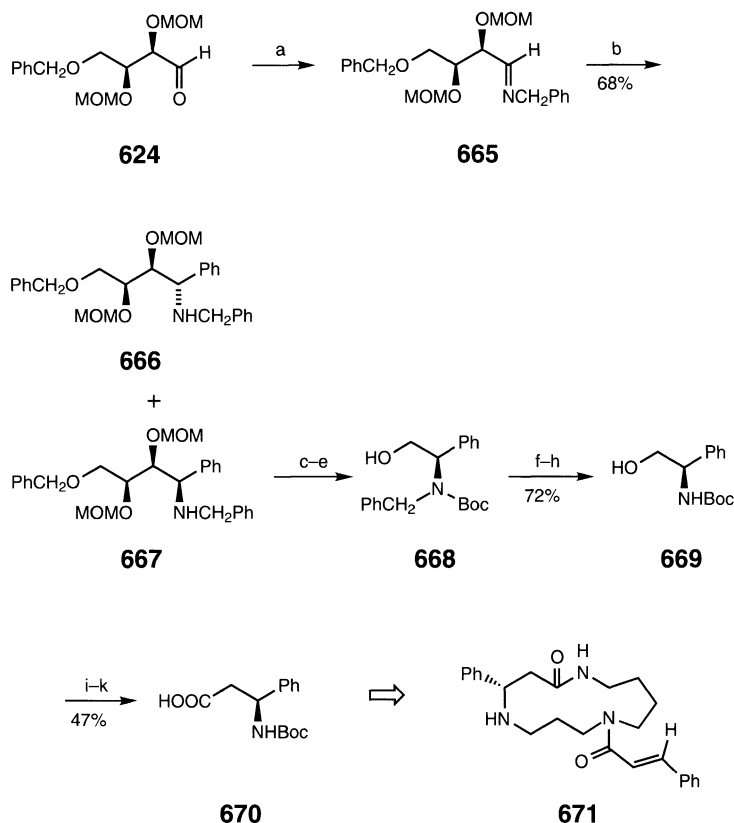
Scheme 147

conditions: (a) PhCH₂NH₂, Et₂O; (b) 2 equiv. PhLi, THF, -60 °C; (c) HCl, MeOH; (d) Boc₂O, toluene (63% 2 steps); (e) HIO₄, MeOH then NaBH₄, MeOH (66%); (f) CF₃COOH, DCM; (g) H₂, PdCl₂, MeOH; (h) Boc₂O, toluene; (i) *p*-TsCl, DMAP, DCM; (j) NaCN, DMSO, 90 °C; (k) 2N HCl, EtOH

treated with 2-lithio-2-methyl-1,3-dithiane, and hydrolyzed with mercury(II) chloride to provide ketone **684**, where the MI protecting group undergoes loss of methoxy, resulting in simultaneous protection of the vicinal hydroxy groups as the acetonide. Hydride reduction of **684** with either lithium tri-*tert*-butoxyaluminum hydride or sodium borohydride is non-selective, and affords a chromatographically separable 1 : 1 mixture of diastereomers **685** and **686**. Esterification of the *R*-isomer **685** with retention followed by Mitsunobu esterification of the *S*-isomer **686** with inversion provides **687**, which is utilized in the total synthesis of **688** [209].

4.3.6 Silyl-Protected Tartaric Acids

The commercial availability of numerous silyl chlorides, the ease of their attachment, and their selectivity toward removal under mild conditions, makes silyl protection extremely attractive.

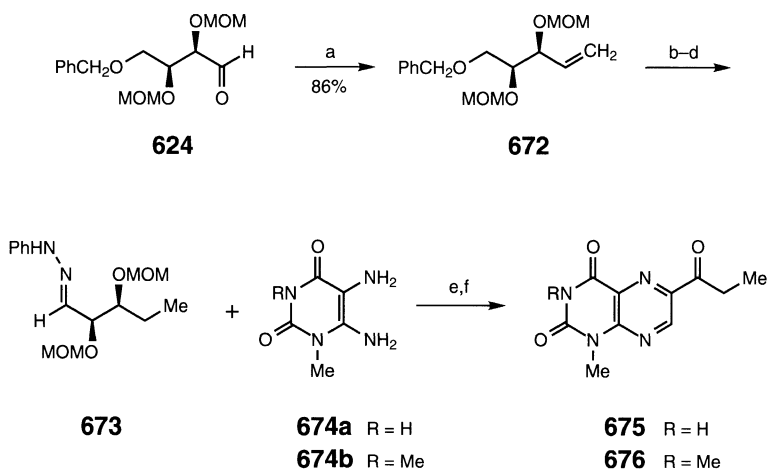
**Scheme 147**

conditions: (a) PhCH₂NH₂, Et₂O; (b) 2 equiv. PhLi, THF, -60 °C; (c) HCl, MeOH; (d) Boc₂O, toluene (63% 2 steps); (e) HIO₄, MeOH then NaBH₄, MeOH (66%); (f) CF₃COOH, DCM; (g) H₂, PdCl₂, MeOH; (h) Boc₂O, toluene; (i) *p*-TsCl, DMAP, DCM; (j) NaCN, DMSO, 90 °C; (k) 2N HCl, EtOH

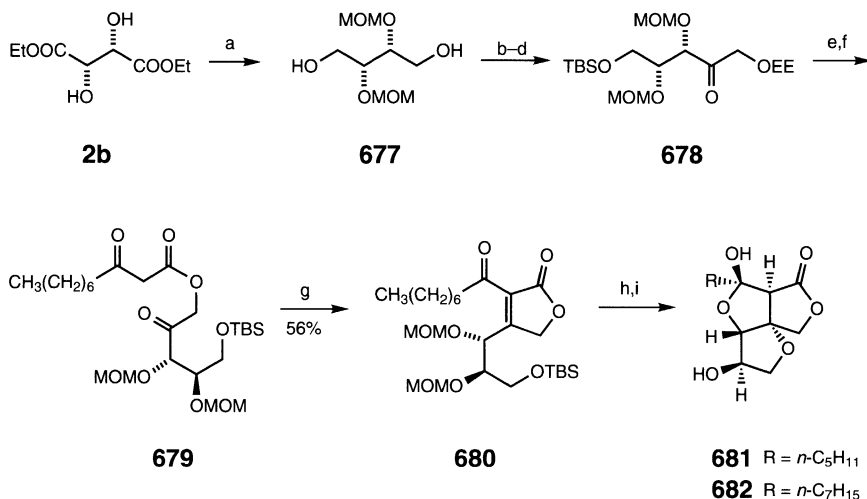
treated with 2-lithio-2-methyl-1,3-dithiane, and hydrolyzed with mercury(II) chloride to provide ketone **684**, where the MI protecting group undergoes loss of methoxy, resulting in simultaneous protection of the vicinal hydroxy groups as the acetonide. Hydride reduction of **684** with either lithium tri-*tert*-butoxyaluminum hydride or sodium borohydride is non-selective, and affords a chromatographically separable 1 : 1 mixture of diastereomers **685** and **686**. Esterification of the *R*-isomer **685** with retention followed by Mitsunobu esterification of the *S*-isomer **686** with inversion provides **687**, which is utilized in the total synthesis of **688** [209].

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The commercial availability of numerous silyl chlorides, the ease of their attachment, and their selectivity toward removal under mild conditions, makes silyl protection extremely attractive.

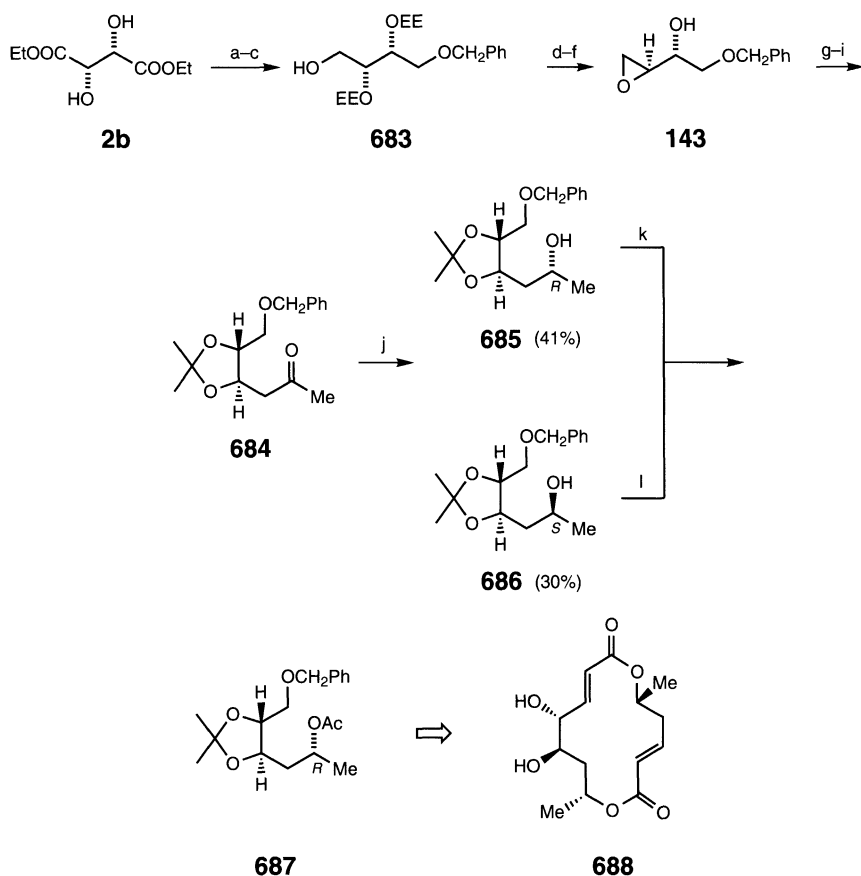
**Scheme 148**

conditions: (a) CH_2I_2 , Zn, Me_3Al , THF; (b) H_2 , Pd/C, 50% AcOH–MeOH; (c) Swern [O];
 (d) PhNHNH_2 , AcOH, MeOH; (e) 4N H_2SO_4 , aq. MeOH; (f) $\text{K}_3[\text{Fe}(\text{CN})_6]$,
 KI, 35% H_2O_2

**Scheme 149**

conditions: (a) MOMCl, (*iso*-Pr)₂NEt, CHCl_3 then LiAlH_4 ; (b) TBSCl, NaH (91%); (c) Swern [O];
 (d) *n*-Bu₃SnCH₂OEE, *n*-BuLi, -78°C then Swern [O] (70% 2 steps); (e) PPTS, EtOH (90%);
 (f) 3-oxodecanoic acid, DCC, DMAP, DCM; (g) SiO_2 , hexane–EtOAc (8:1);
 (h) Dowex 50W-X8, MeOH (36%); (i) *p*-TsOH, H_2O (51%)

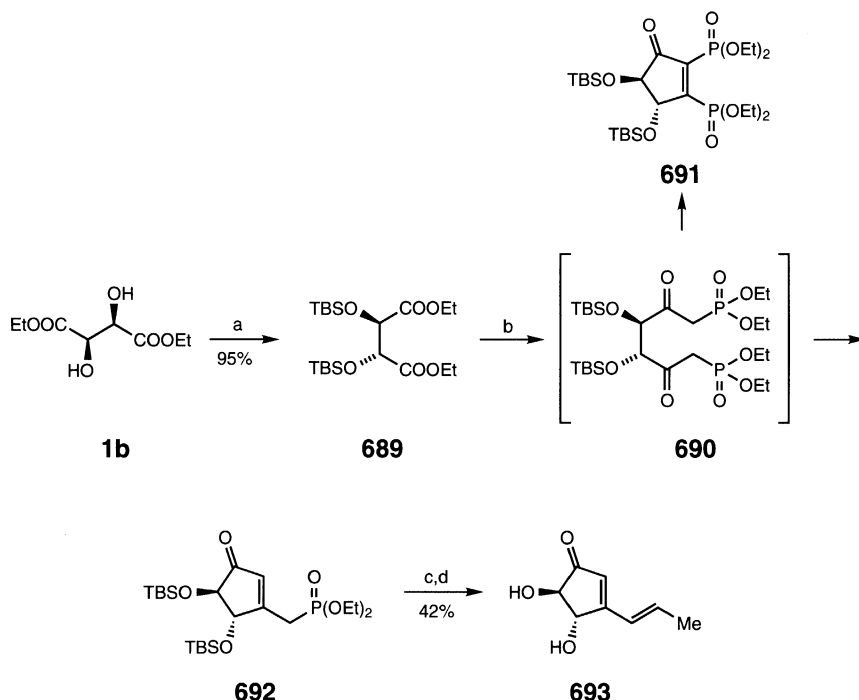
(+)-Terrein (**693**), a metabolic product of several types of fungi, is highly sensitive to both acids and bases. The absolute configuration of the *threo* vicinal hydroxy groups present in **693** is such that the compound is accessible from L-tartaric acid. Protecting both hydroxy groups as *tert*-butyldimethylsilyl ethers permits subsequent deprotection under mild conditions that



Scheme 150

conditions: (a) ethyl vinyl ether, *p*-TsOH (100%); (b) LiAlH₄, Et₂O (95%); (c) PhCH₂Br, NaH, DMF (96%); (d) MsCl, Et₃N, toluene (97%); (e) HCl, H₂O, acetone (95%); (f) Ba(OH)₂, H₂O, acetone (61%); (g) isopropenyl methyl ether, picric acid (90%); (h) 2-methyl-1,3-dithiane, *n*-BuLi, THF (89%); (i) HgCl₂, CaCO₃, MeCN, H₂O (82%); (j) NaBH₄, MeOH; (k) Ti(OEt)₄, EtOAc (89%); (l) Ph₃P, DEAD, AcOH C₆H₆-toluene (64%)

avoid possible isomerization (and racemization) to the undesirable *cis*-configuration (isoterein). Treatment of **1b** with *tert*-butyldimethylsilyl chloride and imidazole in DMF provides in 95% yield **689**, which undergoes reaction with four equivalents of diethyl lithiomethylphosphonate to afford the Knoevenagel product **691** and a small amount of the desired intramolecular Wittig–Horner product **692**. Highest yields of **692** (61% after chromatographic purification) could be obtained when two equivalents of acetic acid were added after addition of the lithiomethylphosphonate, followed by stirring the reaction at room temperature for 20 h. Both **691** and **692** are derived from the bisketophosphonate **690**. Reaction of **692** with acetaldehyde followed by desilylation with tetraethylammonium fluoride (generated *in situ* from tetraethylammonium chloride and KF–H₂O) provides in 42% yield (+)-terrein (**693**) [210] (Scheme 151).



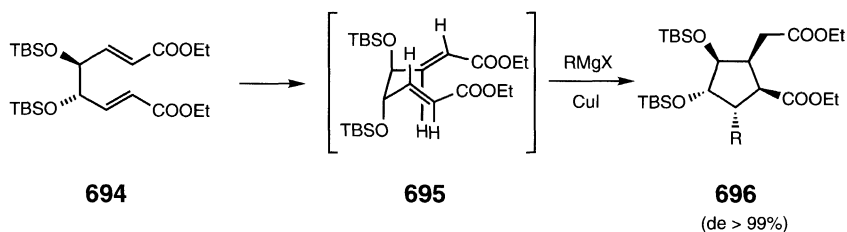
Scheme 151

conditions: (a) TBSCl, imidazole, DMF; (b) $\text{LiCH}_2\text{P}(\text{O})(\text{OEt})_2$ (4 equiv.), then AcOH (2 equiv.), $-20\text{ }^\circ\text{C}$ to rt, 20 h (61%); (c) CH_3CHO , NaH, THF; (d) Et_4NCl , $\text{KF}\cdot\text{H}_2\text{O}$, MeCN

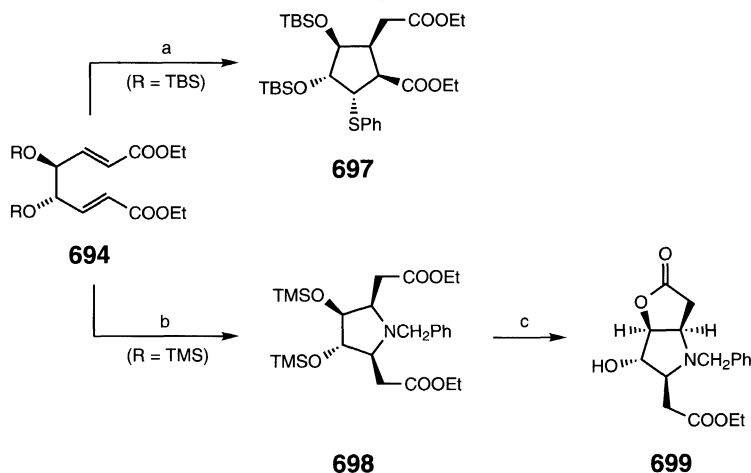
The spatial bulk of vicinal *tert*-butyldimethylsilyloxy protection exerts a significant role in controlling rotational isomeric population. Diethyl (4*S*,5*S*)-4,5-bis(*tert*-butyldimethylsilyloxy)-(2*E*,6*E*)-octadienedioate (**694**), prepared from **24** [18] by acidic deprotection followed by reprotection with *tert*-butyldimethylsilyl triflate in the presence of triethylamine [211], exists as the conformer **695** even at room temperature. Nucleophilic attack at the β -carbon of the enoate moiety of **695** should occur only toward the two π -faces, which are exposed to the outside of the molecule. Michael addition of several Grignard reagent–cuprous iodide mixtures (1 : 1) results in the isolation of a single enantiomer **696a–d** in every case.

This methodology for π -face differentiation through rotamer-distribution control is promising for double Michael reactions mediated by such heteroatom nucleophiles as thiolate and amine. Lithium benzenethiolate reacts with **694** to provide exclusively **697** in quantitative yield. Benzylamine even at elevated temperatures and prolonged reaction times fails to react with **694**. Interestingly, switching from TBS to TMS protecting groups in **694** results in a reaction with benzylamine to furnish the pyrrolidine **698** as a single isomer, which on exposure to silica gel suspended in hexane leads to the unstable monolactone **699** with no trace of the bis-lactone detected [211,212] (Scheme 152).

The highly diastereoselective osmylation of **694** or **700** with osmium tetroxide (5 mol%) and two equivalents of *N*-methylmorpholine-*N*-oxide (NMO) provides either **701** in 94% yield or **702** in 87% yield. When four equivalents of NMO are utilized, the corresponding 2,3,6,7-tetrahydroxylated product **703** or **704** is isolated in 88% or 93% yield, respectively. All products are obtained as single isomers [213] (Scheme 153).



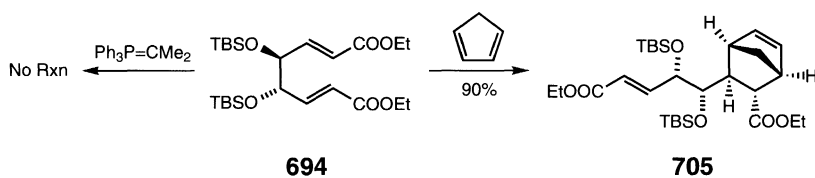
696	R	Yield (%)
a	CH ₂ =CH	94
b	Me	92
c	Et	77
d	C ₆ H ₅	40

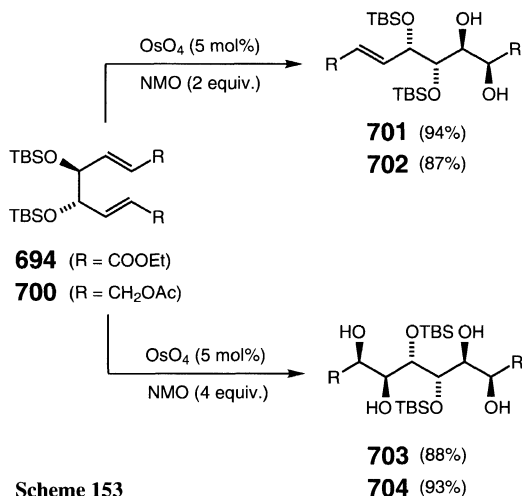


Scheme 152

conditions: (a) PhSLi (100%); (b) PhCH₂NH₂, EtOH, 80 °C, 48 h; (c) SiO₂, hexane

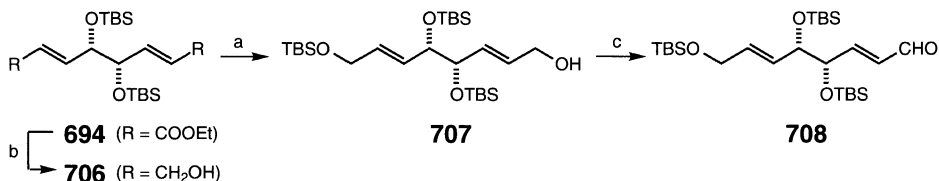
The Diels–Alder reaction of **694** with cyclopentadiene is a relatively slow process that proceeds to give in 90% the single product **705**, where only one outside face undergoes the cycloaddition reaction. Cyclopropanation of **694** with isopropylidetriphenylphosphorane does not take place, presumably due to steric crowding [212].





Scheme 153

The unique facial bias present in **694** is further exploited by the $\text{S}_{\text{E}}2$ -addition of chiral stannanes to aldehyde **708**. Treating **694** with excess DIBAL provides in 91% yield the dialcohol **706**, which is selectively monoprotected as the *tert*-butyldimethylsilyl ether **707**. Swern oxidation of the allylic alcohol occurs in excellent yield to provide **708** [214] (Scheme 154).

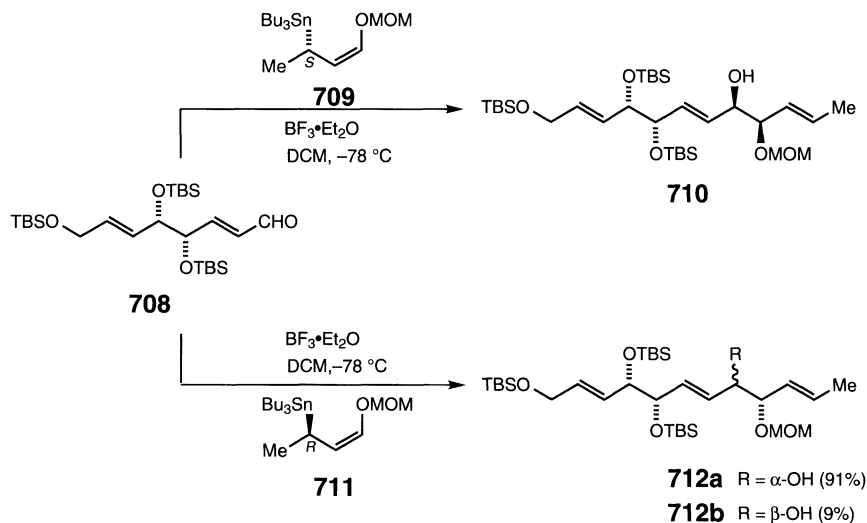


Scheme 154

conditions: (a) DIBAL (91%); (b) TBSCl, *n*-BuLi (75%); (c) Swern [O] (94%)

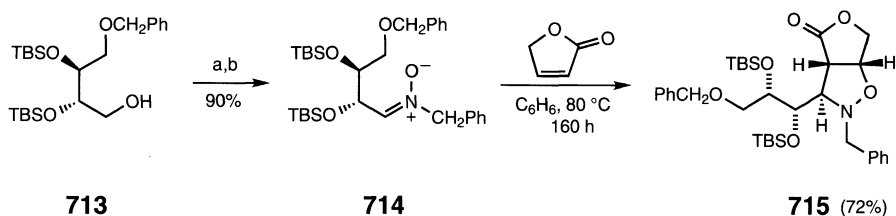
Addition of (*S*)-stannane **709** to **708** in the presence of boron trifluoride etherate furnishes in 90% yield the *syn* adduct **710** as the only detectable product. Less successful is addition of the (*R*)-stannane **711** under similar conditions to **708**. Product **712** is obtained in only 68% yield as a 91 : 9 mixture of *syn*-**712a** and *anti*-**712b** adducts [214] (Scheme 155).

Nitrone–olefin [3 + 2] cycloaddition reactions are capable of introducing simultaneously both latent amino and hydroxy functionalities while at the same time lengthen the carbon chain by one or more units. The possibility of utilizing the silyl-protected diol controller, permitting the shielding of one of the π -(C=N) diastereofaces found in **714**, would allow absolute stereochemical control, and this demonstrates another valuable synthetic example of such tartaric derivatives. Swern oxidation of 1-*O*-benzyl-2,3-*O*-bis(*tert*-butyldimethylsilyl)-L-threitol (**713**) [57] leads to an aldehyde that readily condenses with *N*-(benzyl)hydroxylamine to furnish the stable nitrone **714** as a single isomer in 90% overall yield. While the reaction of **714** with γ -butenolide proceeds to give a 17 : 1 *endo/exo* ratio (89% *de*) of **715**, other olefins such as dimethyl malate or dimethyl fumarate give 1 : 1 mixtures. Thus, [3 + 2]



Scheme 155

cycloaddition of **714** with various olefins results in perfect discrimination between the nitron faces [215] (Scheme 156).



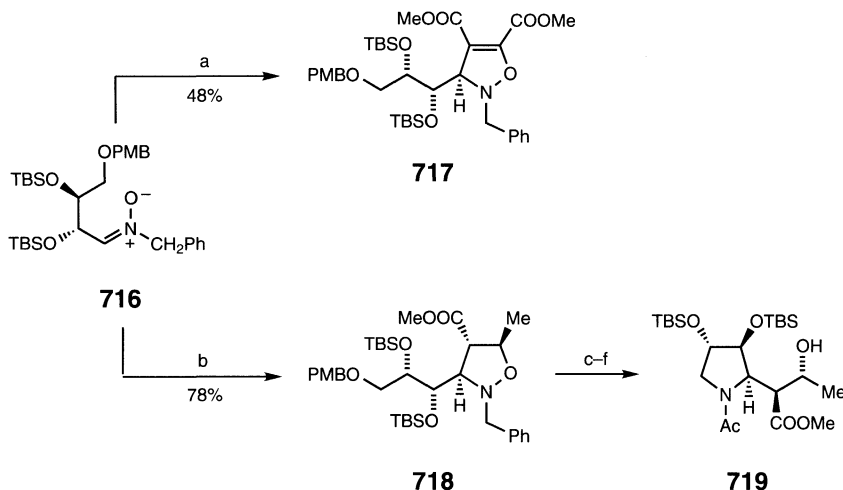
Scheme 156

conditions: (a) Swern [O]; (b) PhCH_2NHOH , DCM, 40°C

Interestingly, **716**, in which a *p*-methoxybenzyl ether replaces the benzyl ether as a protecting group, undergoes the [3+2] cycloaddition with dimethyl acetylene dicarboxylate to provide exclusively and in 48% yield the cycloadduct **717**, whose absolute configuration was established by an NOE difference spectral analysis of a synthesized pyrrolidine derivative. The reaction of **716** with methyl crotonate provides a 10 : 1 separable mixture of cycloadducts **718** which are converted to the pyrrolidine **719** [215] (Scheme 157).

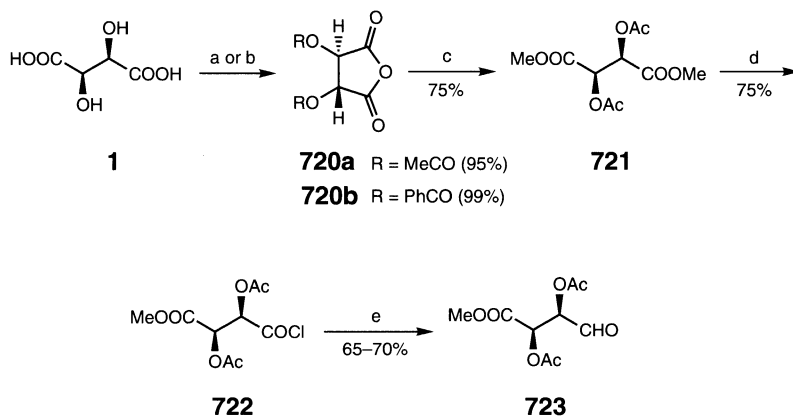
4.3.7 Vicinal Dihydroxy Ester-Protected Tartaric Acid Derivatives

When tartaric acid (**1**) is heated with acetic anhydride or benzoyl chloride, the diacetyl tartaric anhydride **720a** or the dibenzoyl tartaric anhydride **720b** is obtained in excellent yield.

**Scheme 157**

conditions: (a) DMAD, C₆H₆, 25 °C, 3 h; (b) *trans*-methylcrotonate, C₆H₆, 80 °C, 36 h; (c) DDQ; (d) MsCl, Et₃N, DCM; (e) H₂, Pd/C; (f) Ac₂O, Et₃N, DCM

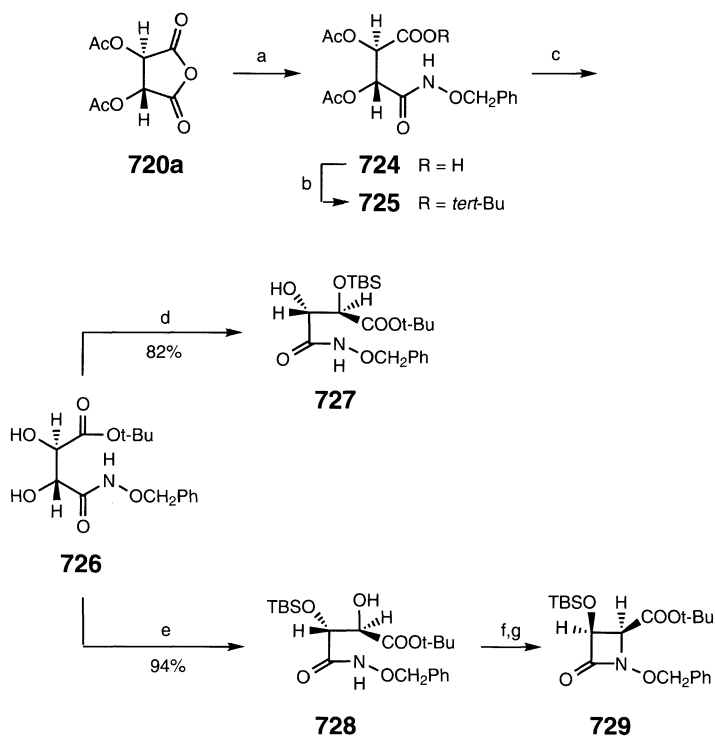
Treatment of **720a** with methanol provides in 75% yield the crystalline monomethyl tartrate **721** which is converted in 75% yield to the crystalline acid chloride **722** with thionyl chloride. Rosenmund reduction of **722** in xylene at 130–135 °C affords the crystalline methyl diacetyl-L-threonate (**723**) in 65–70% yield [216] (Scheme 158).

**Scheme 158**

conditions: (a) Ac₂O; (b) C₆H₅COCl; (c) MeOH; (d) SOCl₂, 60 °C; (e) H₂, xylene, Pd/BaSO₄, 130–135 °C

When **720a** is treated with *O*-benzylhydroxylamine at 0 °C, the hydroxamic acid **724** is produced. The remaining carboxyl group is converted to a *tert*-butyl ester by the reaction of **725** with *tert*-butyl acetate and perchloric acid. Overall yields for these two steps range from 50–75%. Methanolysis quantitatively removes the two acetate protecting groups to afford diol

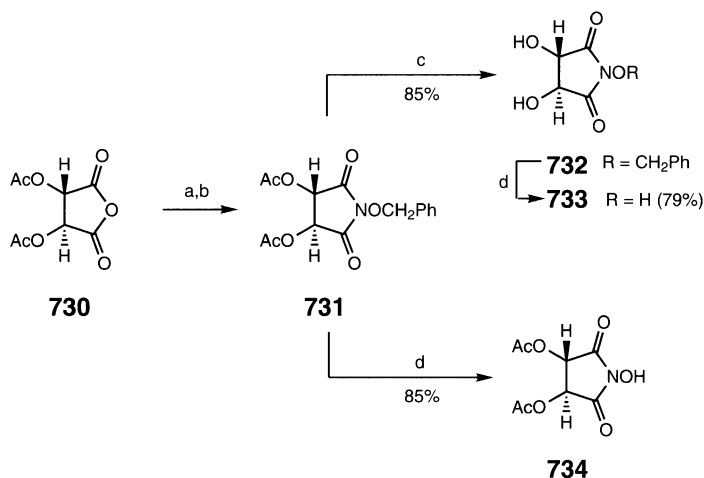
726, which undergoes a selective monoprotection with 100 mol% *tert*-butyldimethylsilyl chloride and 100 mol% imidazole to provide exclusively the desired *O*-benzyl 3-(*O*-*tert*-butyldimethylsilyl)-4-*tert*-butyl-L-tartarohydroxamate (**728**). Interestingly, reaction of **726** with 100 mol% of *tert*-butyldimethylsilyl chloride and 200 mol% of imidazole affords exclusively the *O*-benzyl 2-(*O*-*tert*-butyldimethylsilyl)-4-*tert*-butyl-L-tartarohydroxamate **727**. Cyclization of **728** to the β -lactam **729** under Mitsunobu conditions is moderately successful if dimethyl azodicarboxylate is employed. DEAD and diisopropyl azodicarboxylate are less effective. A more successful alternative is to treat the mesylate of **728** with triethylamine in ethanol. In this way, a nearly quantitative conversion of **728** to 3-*tert*-butyldimethylsilyloxy-4-*tert*-butoxycarbonyl-2-azetidinone (**729**) is achieved. The corresponding tosylate is far less effective [217,218] (Scheme 159).



Scheme 159

conditions: (a) PhCH₂ONH₂, 0 °C, 3 h; (b) *tert*-BuOAc, HClO₄; (c) MeOH, DMAP (99%); (d) 100 mol% TBSCl, 200 mol% imidazole, DMF; (e) 100 mol% TBSCl, 100 mol% imidazole, DMF; (f) MsCl, pyridine (95%); (g) Et₃N, EtOH, rt, 5 d (100%)

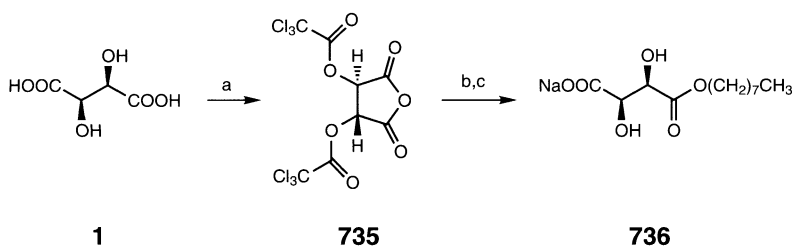
The reaction of (*S,S*)-**730**, derived from **2**, with *O*-benzyloxyamine followed by heating in acetic anhydride at 90 °C for three hours affords in good yields the diacetylated *N*-benzyloxytartramide **731**. Subsequent acidic methanolysis of the acetate protecting groups provides **732** which undergoes hydrogenolytic debenzylation to give the *N*-hydroxytartramide **733**. A similar debenzylation reaction of **731** affords **734** in 85% yield. These are useful for enantioselective peptide synthesis [219] (Scheme 160).



Scheme 160

conditions: (a) PhCH₂ONH₂, THF, 0 °C, 3 h (69%); (b) Ac₂O, 90 °C, 3 h (94%);
 (c) *p*-TsOH, MeOH, reflux, 5 h (85%); (d) H₂, Pd/C, EtOH

The anhydride of unprotected tartaric acid is difficult to prepare and almost impossible to isolate. Stable anhydrides such as **720a** and **720b**, where the hydroxy groups are esterified, do not permit reactions with alcohols in the absence of ester hydrolysis. The ability of a trichloroacetate protecting group to activate the anhydride towards nucleophilic attack, while proving less labile to nucleophilic attack and subject to removal without ester cleavage, makes this a useful protecting group. Heating tartaric acid with trichloroacetic anhydride in dioxane at 75 °C provides (after sublimation) a 85% yield of analytically pure **735**. Reaction of **735** with 1-octanol in dry THF at room temperature is complete in less than 4 h to afford the monoester, which when stirred with water at room temperature effectively loses the trichloroacetate protecting groups. Subsequent addition of 3N NaOH while maintaining the pH > 10 provides **736** as the sodium salt [220] (Scheme 161).

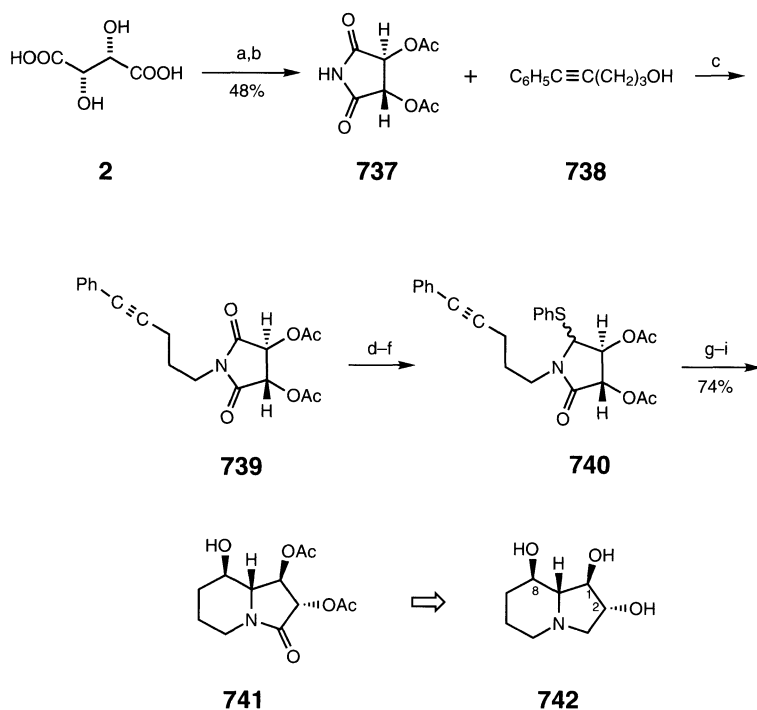


Scheme 161

conditions: (a) (Cl₃CCO)₂O, dioxane, 75 °C (>85%); (b) CH₃(CH₂)₇OH, THF (70–90%);
 (c) H₂O, rt, 18 h, then 3N NaOH

Swainsonine (**742**), a polyhydroxylated indolizidine alkaloid first isolated from the fungus *Rhizoctonia leguminicola* and later found in the legume *Swainsona canescens* and the spotted locoweed *Astragalus lentiginosus*, is believed to be responsible for locoism, a disease of range animals that ingest these plants. The synthesis of **742** is realized through utilization of an α -acylamino radical cyclization in which the free radical precursor **740** is obtained from D-tartaric acid (**2**).

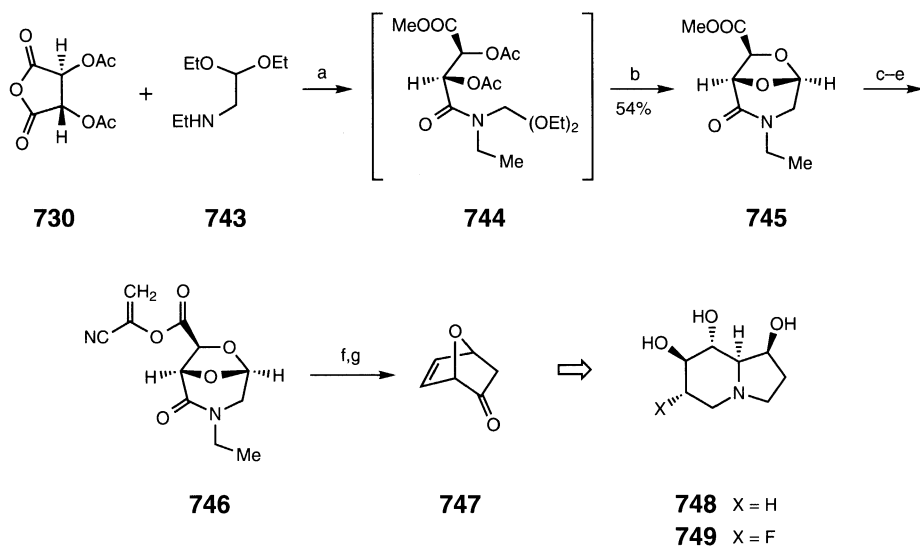
D-Tartaric acid (**2**) is converted in three steps to multigram quantities of (3*S*,4*S*)-3,4-diacetoxy-2,5-pyrrolidinedione (**737**) in 48% overall yield. Mitsunobu coupling of **737** with 5-phenyl-4-pentyn-1-ol (**738**) occurs in 96% yield to furnish acetylene **739**, which is converted in three steps to the radical precursor **740** in 79% overall yield. Radical cyclization of **740** with tri-*n*-butyltin hydride and AIBN in refluxing benzene provides an 80–85% yield of a mixture of indolizidines that is ozonolyzed and reduced with sodium borohydride to afford (1*R*)-(1 β ,2 α ,8 β ,8 $\alpha\beta$)-1,2-diacetoxy-8-hydroxyhydro-3(2*H*)-indolizidine (**741**) in 74% yield. The required stereochemical inversion at C-1 is achieved by adjusting the protecting groups so that the free hydroxy group can be inverted by a nucleophilic substitution reaction. This total synthesis of **742** involves 15 steps and is accomplished in 14% overall yield from **737** [221] (Scheme 162).



Scheme 162

conditions: (a) CH_3COCl , reflux; (b) $\text{NH}_3(\text{g})$, DCM, then CH_3COCl , reflux; (c) Ph_3P , DEAD, THF (96%); (d) NaBH_4 , MeOH (91%); (e) Ac_2O , NEt_3 , DMAP, DCM (96%); (f) *n*- Bu_3P , PhSSPh , C_6H_6 (77%); (g) *n*- Bu_3SnH , AIBN, C_6H_6 , reflux; (h) O_3 , MeOH, DMS; (i) NaBH_4 , MeOH

The stereoselective, total synthesis of (+)-6-deoxycastanospermine (**748**) and (+)-6-deoxy-6-fluorocastanospermine (**749**) starting from (-)-(1*S*,4*S*)-7-oxabicyclo[2.2.1]hept-5-en-2-one (**747**), a “naked sugar”, illustrates the utility of D-tartaric acid to act as a chiral auxiliary. Di-*O*-acetyl-(*S,S*)-tartaric anhydride (**730**) reacts with ethylaminoacetaldehyde diethyl acetal (**743**) to provide after acidic hydrolysis the ester **745** in 54% yield. Acid hydrolysis to the acid, conversion to the crystalline acid chloride, and coupling with pyruvonnitrile provides the optically pure ketene equivalent **746**. A ZnBr₂-induced Diels–Alder addition of **746** to furan provides a mixture of diastereomers from which the desired optically pure diastereomer is obtained in 35% yield after two recrystallizations. Saponification of the chiral auxiliary affords pure **747** in 96% yield. Subsequent transformations of **747** lead to either **748** or **749**. Interestingly, the fluoride present in **749** is introduced by an HF–Et₃N stereoselective epoxide ring opening [222,223] (Scheme 163).

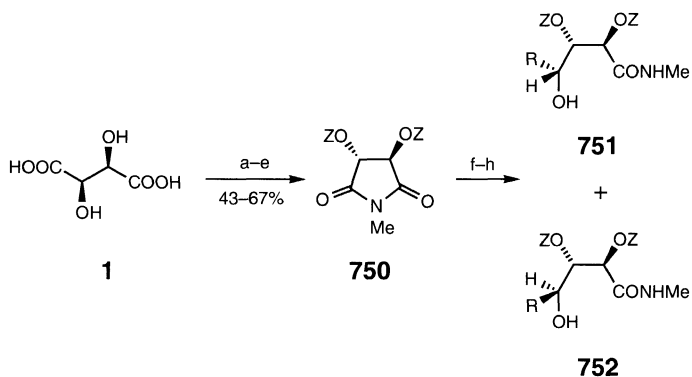


Scheme 163

conditions: (a) 20 °C, 1 h, then SOCl₂, MeOH, 20 °C, 24 h; (b) H₂SO₄–SiO₂, DCM; (c) HCl–H₂O (100%); (d) SOCl₂, 75 °C (92%); (e) pyruvonnitrile, pyridine, DCM (86%); (f) furan, ZnBr₂, 20 °C, 7 d, then recrystallization (35%); (g) 1 N NaOH, 40% aq CH₂O, 20 °C, 4 h (96%)

Compounds possessing a C₂-axis of symmetry often serve as chiral intermediates for the synthesis of other chiral substances. Consecutive treatment of L-tartaric acid (**1**) with acetyl chloride, methylamine, and acetyl chloride again, followed by hydrolysis of the acetate groups and subsequent silyl protection provides the C₂-symmetric imides **750** in 43–67% yields. The reaction of **750** with Grignard reagents in THF at –78 °C occurs from either of the two symmetrical sides bearing a *trans* relationship with respect to the silyloxy protecting groups to afford unstable carbinolamides that are reduced with sodium borohydride to provide with high diastereoselectivity the two hydroxyamide **751** contaminated with a minor amount of **752**. The stereoselectivity of the Grignard addition increases with increasing steric bulk of the silyloxy protection (Scheme 164).

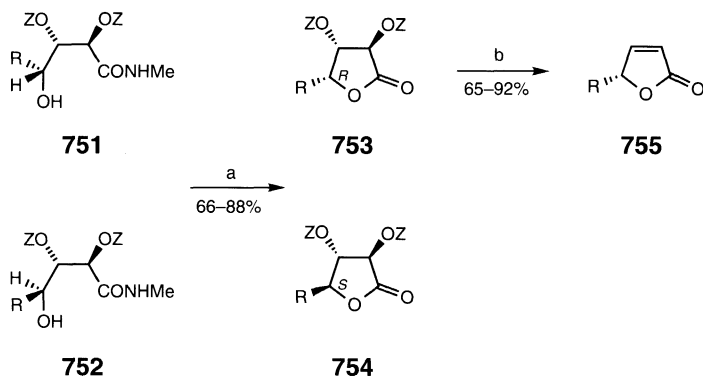
Refluxing each of the isolated amides **751** or **752** with 3N HCl in dioxane yields the chiral γ -lactones (*R*)-**753** or (*S*)-**754**, containing three stereogenic centers, in good yields. Treating (*R*)-



R	Z	Yield (%)	751:752
<i>n</i> -C ₁₃ H ₂₇	TBS	64	92:8
<i>n</i> -C ₁₃ H ₂₇	TIPS	74	>99:1
<i>n</i> -C ₈ H ₁₇	TBS	52	94:6
PhCH ₂	TBS	82	96:4

Scheme 164

conditions: (a) AcCl; (b) MeNH₂; (c) AcCl; (d) AcCl, EtOH; (e) ZSiCl or ZSiOTf;
 (f) RMgBr, THF, -78 °C; (g) NaBH₄, EtOH; (h) SiO₂ chromatography

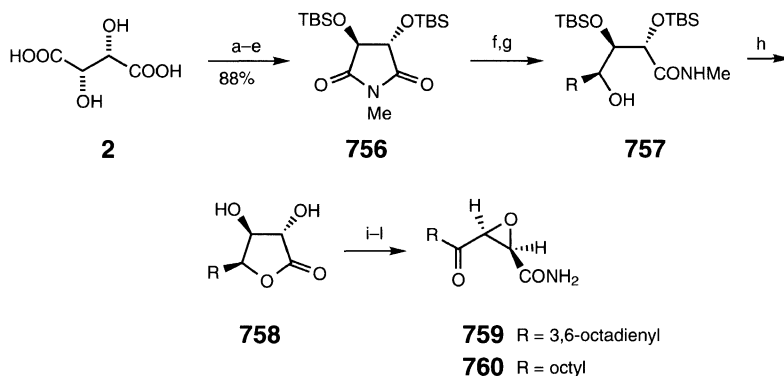
**Scheme 165**

conditions: (a) 3 M HCl, dioxane, reflux; (b) imidazole-1₃, Ph₃P, Zn, toluene

753 with triiodoimidazole, triphenylphosphine, and zinc in toluene affords the synthetically useful (*R*)-butenolides **755** in good yield [224,225] (Scheme 165).

The utility of this methodology is illustrated by the stereoselective synthesis of (+)-cerulenin (**759**), an antifungal antibiotic first isolated from the culture filtrate of *Cephalosporium caerulens*. Its ability to inhibit lipid biosynthesis in *Escherichia coli* by irreversibly binding β -keto-acyl-carrier protein synthetase, the enzyme responsible for the chain lengthening reaction in fatty acid synthesis, has attracted interest in its mechanism of action. D-Tartaric acid

(2) is converted in five steps to **756**, which is treated with 3,6-octadienylmagnesium bromide followed by sodium borohydride to afford exclusively **757** in 73% yield. Cyclization and concomitant desilylation occurs in 83% yield with 3N HCl in refluxing dioxane to provide γ -lactone **758**. Regioselective tosylation at the β -hydroxy group, ammonolysis of the lactone, potassium carbonate cyclization, and PCC oxidation provides in 63% yield (+)-(2*R*,3*S*)-cerulenin (**759**). Use of octylmagnesium bromide in the above sequence allows similar preparation of (+)-(2*R*,3*S*)-tetrahydrocerulenin (**760**) [226] (Scheme 166).

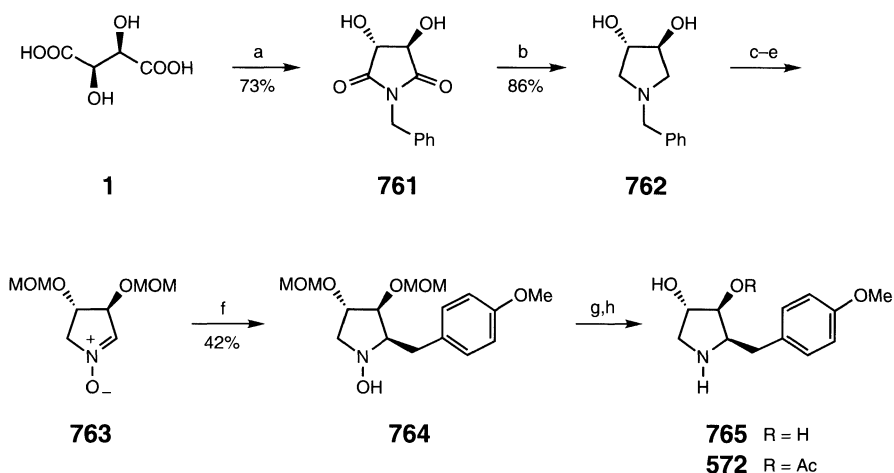


Scheme 166

conditions: (a) AcCl, reflux; (b) MeNH₂; (c) AcCl, reflux; (d) AcCl, 60 °C; (e) TBSCl, imidazole, DMF; (f) RMgBr, THF, -78 °C to rt, [R = 3,6-octadienyl (73%); R = *n*-octyl (86%)]; (g) NaBH₄, EtOH; (h) 3M HCl, dioxane, reflux [R = 3,6-octadienyl (83%); R = *n*-octyl (87%)]; (i) *p*-TsCl, pyridine, 0 °C, 2 d (62%); (j) NH₄OH, MeOH 0 °C (100%); (k) K₂CO₃, MeOH (91%); (l) PCC, NaOAc, DCM (63%)

The antibiotic (–)-anisomycin (**572**) is a fermentation product of various species of streptomyces, and it exhibits strong and selective activity against pathogenic protozoa and fungi. A formal synthesis of **572** exploits a nitronone-based strategy in which the vicinal hydroxy groups of tartaric acid affect the enantioselectivity of the Grignard reaction. Treating tartaric acid (**1**) with benzylamine in refluxing xylene provides in 73% yield (3*R*,4*R*)-1-benzyl-3,4-dihydroxy-2,5-pyrrolidindione (**761**). Subsequent reduction of **761** with sodium borohydride in the presence of boron trifluoride etherate affords in 86% yield (3*S*,4*S*)-1-benzyl-3,4-pyrrolidinediol (**762**) [227]. MOM protection of the diols followed by a catalytic debenzoylation and hydrogen peroxide–selenium dioxide *N*-oxidation yields the unstable (3*S*,4*S*)-3,4-bis(methoxymethoxy)-1-pyrroline *N*-oxide (**763**). The reaction of **763** with *p*-methoxybenzylmagnesium chloride in the presence of magnesium bromide etherate provides a chromatographically separable mixture of diastereomers (7 : 3) from which the major diastereomer **764** is obtained in 42% yield. Hydrogenolysis of the oxime and MOM deprotection of **764** leads in 75% yield to (2*R*,3*S*,4*S*)-2-(4-methoxybenzyl)pyrrolidine-3,4-diol (**765**), which is employed in the synthesis of **572** [228] (Scheme 167).

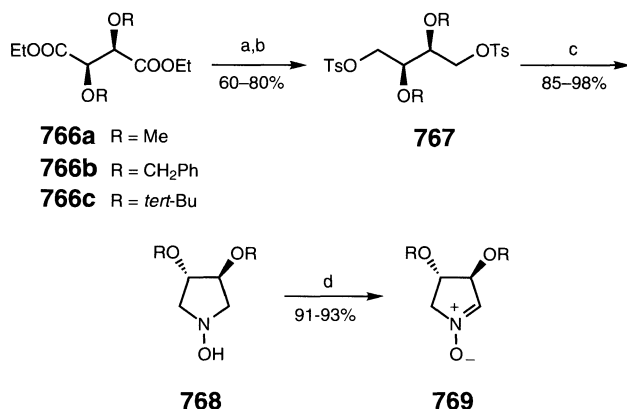
An alternative synthesis of five-membered cyclic nitronones such as **763** differs from the previous one in the choice of substrates for hydroxy group protection and pyrrolidine ring formation. Lithium aluminum hydride reduction of **766a–c** followed by tosylation affords the ditosylate **767** in good yield. These threitols are cyclized to the *N*-hydroxypyrrolidines **768** with hydroxylamine in refluxing ethanol. Oxidation of **768** with yellow mercury(II) oxide in dichloromethane affords the nitronones **769** in quantitative yield. This methodology avoids the



Scheme 167

conditions: (a) PhCH₂NH₂, xylene, reflux; (b) NaBH₄, BF₃•Et₂O; (c) CH₂(OMe)₂, P₂O₅, DME (75%); (d) H₂, Pd(OH)₂, MeOH (85%); (e) H₂O₂, SeO₂, acetone (60%); (f) *p*-MeOC₆H₄CH₂MgCl, MgBr₂•Et₂O, DCM, THF; (g) H₂, Raney Ni, MeOH (85%); (h) 6N HCl, MeOH (75%)

difficulty of hydroxyl group protection in the presence of a reactive nucleophilic nitrogen, and it allows protection of the hydroxyl groups as benzyl ethers. Moreover, the approach is unique in that it employs hydroxylamine as a nucleophile for the synthesis of cyclic hydroxylamines on the route to cyclic nitrones. The synthetic advantage is that higher yields are obtained [229] (Scheme 168).

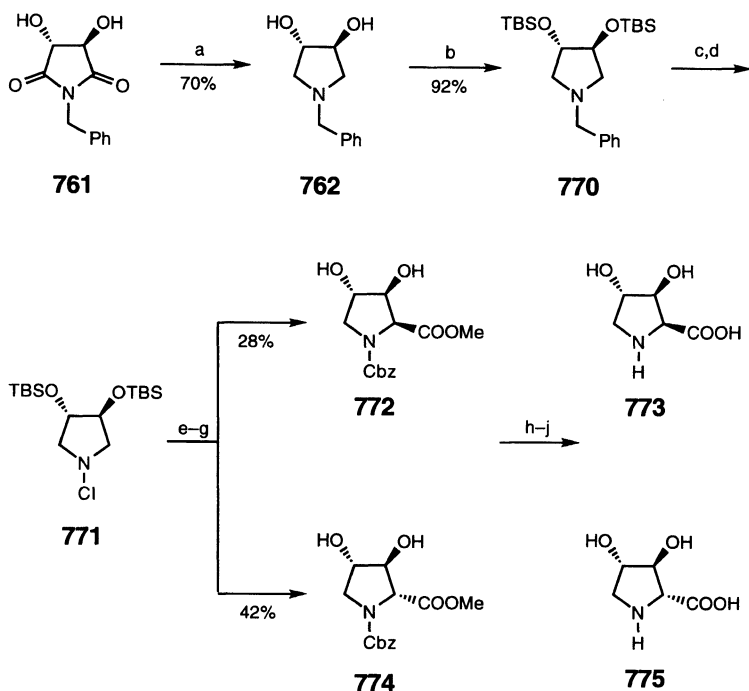


Scheme 168

conditions: (a) LiAlH₄; (b) *p*-TsCl, pyridine; (c) NH₂OH•HCl, Et₃N, EtOH; (d) HgO (yellow), DCM

(3*S*,4*S*)-1-Benzyl-3,4-dihydropyrrolidine (**762**), prepared in 70% yield by a lithium aluminum hydride reduction of **761**, undergoes efficient disilyl protection to afford **770** in 83% yield. Debonylation of **770** with palladium hydroxide followed by treatment with

N-chlorosuccinimide provides (3*S*,4*S*)-3,4-bis(TBSO)-1-chloropyrrolidine (**771**). Dehydrochlorination with DBU in benzene affords a cyclic imine that reacts with cyanotrimethylsilane in the presence of catalytic zinc iodide to afford an epimeric mixture of aminonitriles. Acidic hydrolysis of the nitrile, esterification of the resulting acid, Cbz-protection of the basic amine, and chromatographic separation affords **772** in 28% yield and **774** in 42% yield. These are converted respectively to either (2*S*,3*S*,4*S*)-3,4-dihydroxyproline (**773**) or (2*R*,3*S*,4*S*)-3,4-dihydroxyproline (**775**) [230] (Scheme 169).

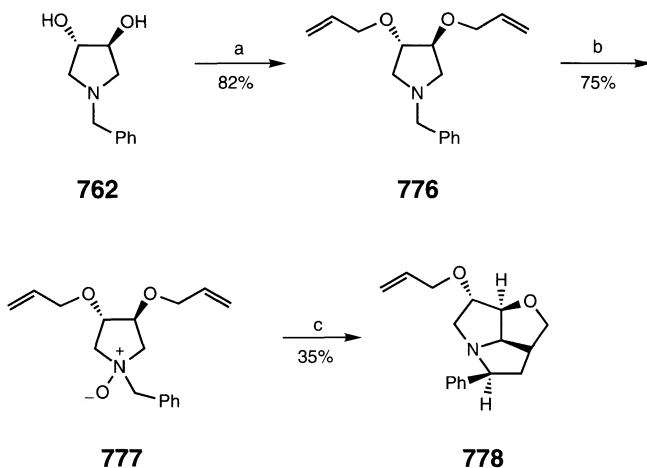


Scheme 169

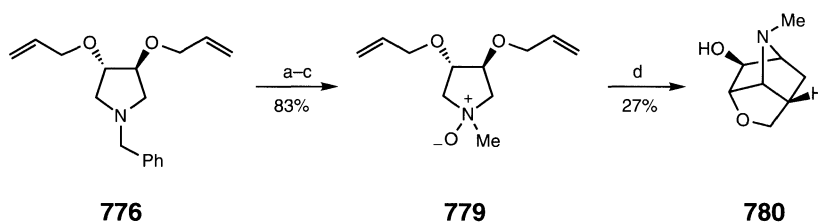
conditions: (a) LiAlH_4 , THF; (b) TBSCl, NaH, THF; (c) H_2 , 20% $\text{Pd}(\text{OH})_2$, AcOH (83%); (d) NCS, Et_2O (92%); (e) DBU, C_6H_6 then TMSCN, ZnI_2 , dioxane- H_2O (90%); (f) 6N HCl, AcOH; (g) SOCl_2 , MeOH then CbzCl, dioxane, aq NaHCO_3 and chromatography; (h) 1N KOH, MeOH; (i) Amberlite 200C (H^+), Et_2O ; (j) H_2 , Pd/C, EtOH

Treatment of **762** with allyl bromide and sodium hydride provides in 82% yield the C_2 -symmetric pyrrolidine **776**. Chemoselective *N*-oxidation with *tert*-butylhydroperoxide in the presence of vanadyl acetylacetonate affords in 75% yield the *N*-oxide **777** which, when treated with LDA, forms a benzylideneazomethine ylid (having the *Z*-configuration) that undergoes an intramolecular 1,3-dipolar cycloaddition to afford the *endo*-phenyl adduct **778** as the only isolable product in 35% yield (Scheme 170).

The corresponding *N*-methyl derivative **779**, prepared from **776** in three steps with an overall yield of 83%, fails to undergo any reaction with LDA. However, intramolecular 1,3-dipolar cycloaddition does occur with trimethylaluminum followed by *tert*-butyllithium at -90°C to furnish in 27% yield **780** [231] (Scheme 171).

**Scheme 170**

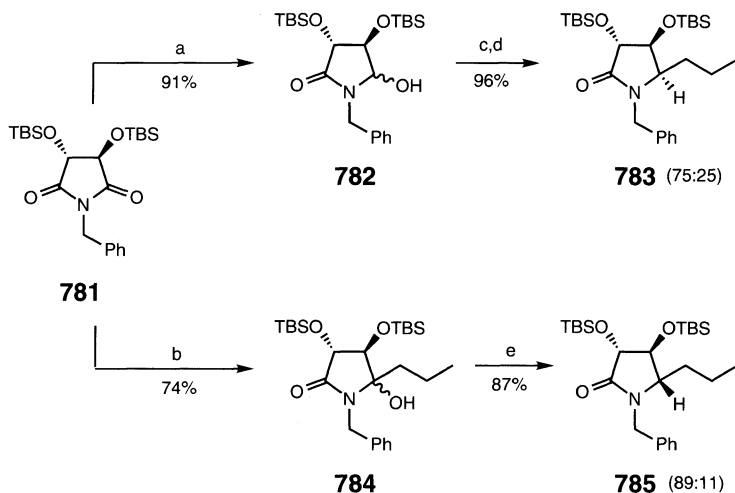
conditions: (a) allyl bromide, NaH, DMF-THF, *n*-Bu₄Nl; (b) *tert*-BuOOH, VO(acac)₂, DCM; (c) LDA, THF

**Scheme 171**

conditions: (a) ClCOOMe, C₆H₆, rt; (b) LiAlH₄, THF; (c) *tert*-BuOOH, VO(acac)₂, DCM; (d) Me₃Al then *tert*-BuLi, -90 °C

The sodium borohydride reduction of **781** [225] provides a mixture of two stereomeric hydroxylactams **782** produced *via* an N-acyliminium intermediate upon treatment with allyltrimethylsilane in the presence of boron trifluoride etherate this affords, after catalytic reduction, **783** characterized by a 75:25 *cis*-selectivity. The addition of allylmagnesium bromide to **781** followed by reduction of lactams **784** with triethylsilane in the presence of boron trifluoride etherate proceeds *via* a reverse deoxygenation to afford **785** with 89:11 *trans*-selectivity. By choosing the appropriate protecting groups, temperature, and Grignard reagents, diastereoselectivities of 99:1 can be achieved for this reductive deoxygenation of quarternary α -hydroxy lactams [232] (Scheme 172).

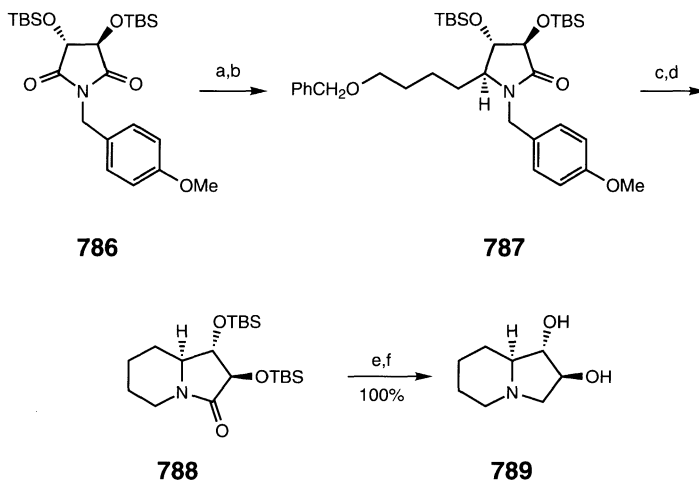
Lentiginosine (**789**) is a *trans*-dihydroxyindolizidine alkaloid first isolated from the spotted locoweed *Astragalus lentiginosus* var. *diphysus* and indicated to be the first inhibitor of the fungal α -glucosidase, amyloglucosidase. The *trans* selectivity observed in asymmetric deoxygenation of the quarternary α -hydroxylactam derived from a Grignard addition to **786** facilitates the envisioned synthetic strategy toward total synthesis of **789**. 4-Benzyloxybutylmagnesium bromide addition to **786** followed by reductive deoxygenation with tri-



Scheme 172

conditions: (a) NaBH₄, MeOH, -15 °C; (b) allylMgBr, THF, -78 °C; (c) allylTMS, BF₃•Et₂O, DCM, 0 °C (96%); (d) H₂, Pd/C, EtOH (100%); (e) Et₃SiH, BF₃•Et₂O, DCM

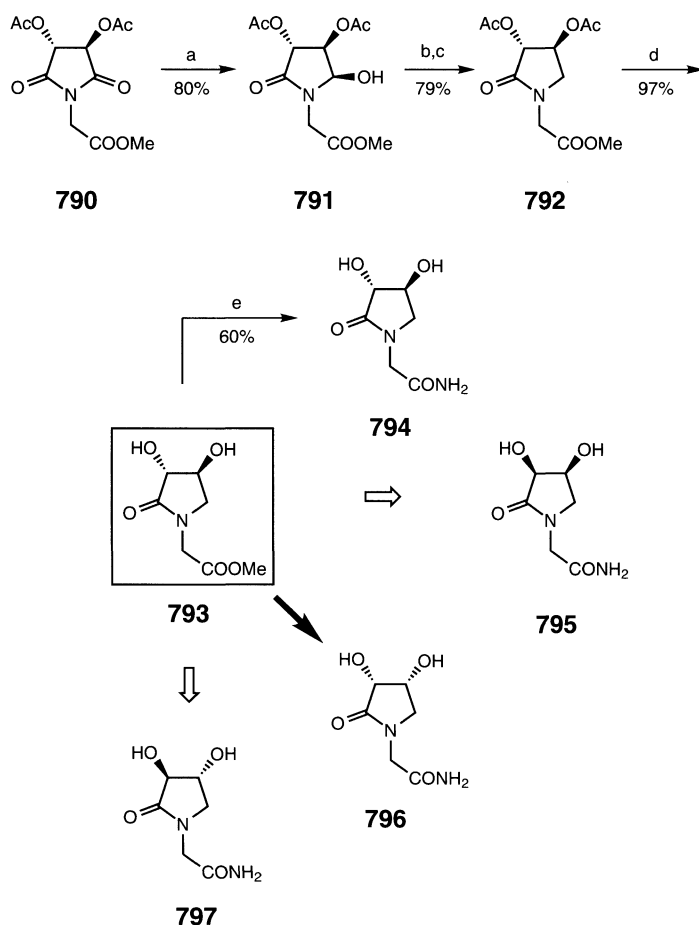
thylsilane in the presence of boron trifluoride etherate affords lactam **787** (96 : 4). Deprotection with CAN and palladium black, mesylation, and cyclization yields the bicyclic amide **788** in good yield. Desilylation occurs readily under acidic conditions, and a final lithium aluminum hydride reduction of the amide affords **789**, which was determined to have a 92% *de* at C-8a [233] (Scheme 173).



Scheme 173

conditions: (a) PhCH₂O(CH₂)₄MgBr, THF, -78 °C (85%); (b) Et₃SiH, BF₃•Et₂O, DCM (95%); (c) CAN, MeCN-H₂O then Pd (black), HCOOH, *iso*-PrOH (27% 2 steps); (d) MsCl, Et₃N, DCM then NaH, THF (90% 2 steps); (e) HCl, MeOH; (f) LiAlH₄, THF

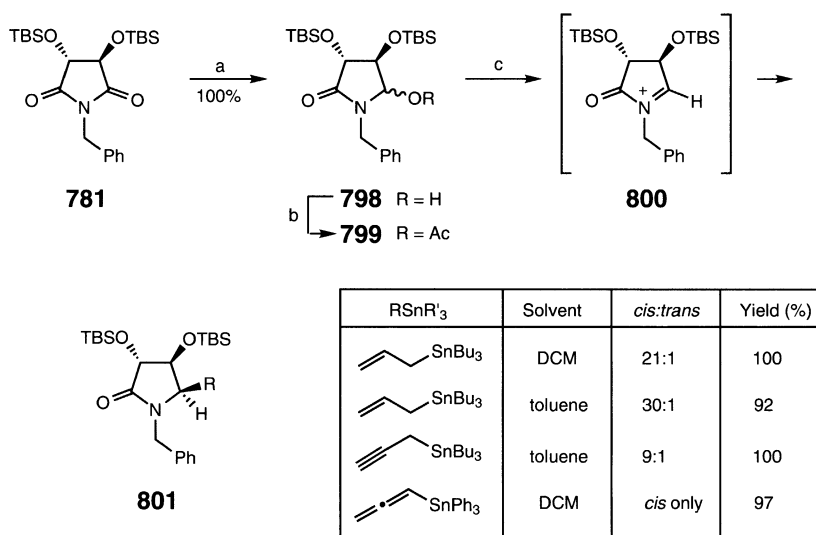
3,4-Dihydroxypyrrolidinones, which can be considered as cyclic GABA derivatives, are potential nootropic drug candidates. All four possible diastereomers **794–797**, as shown in Scheme 174, can be prepared from tartaric acid. Treating L-tartaric acid sequentially with acetyl chloride, methyl glycinate, and then acetyl chloride provides in 81% overall yield the C₂-symmetric succinimide **790**. In order not to reduce the methyl ester, the very mild treatment with sodium borohydride at $-40\text{ }^{\circ}\text{C}$ is employed to prepare the *cis*-hydroxylactam **791** in an 80% isolated yield. Esterification of **791** with trifluoroacetic anhydride followed by triethylsilane reduction yields to the extent of 79% the pyrrolidinone **792**. This is deprotected with sodium methoxide to provide in 97% yield (3*R*,4*S*)-3,4-dihydroxy-*N*-methoxycarbonylmethyl-2-pyrrolidinone (**793**). Ammonolysis of **793** affords (3*R*,4*S*)-3,4-dihydroxy-2-oxopyrrolidine-*N*-acetamide (**794**) in 60% yield. Subsequent modifications to **793** allow for the preparation of (3*S*,4*S*)-3,4-dihydroxy-2-oxopyrrolidine-*N*-acetamide (**795**), (3*R*,4*R*)-3,4-dihydroxy-2-oxopyrrolidine-*N*-acetamide (**796**) and (3*S*,4*R*)-3,4-dihydroxy-2-oxopyrrolidine-*N*-acetamide (**797**) [234].



Scheme 174

conditions: (a) NaBH₄, THF, H₂O, $-40\text{ }^{\circ}\text{C}$; (b) TFAA, CHCl₃; (c) Et₃SiH, Et₃N, CHCl₃; (d) NaOMe, MeOH; (e) MeOH, NH₃(g)

(3*R*,4*R*)-3,4-Bis[(*tert*-butyldimethylsilyl)oxy]-1-benzyl-2,5-pyrrolidinedione (**781**), available in large quantities from *L*-tartaric acid [235], provides the chiral starting material for a practical and divergent route toward the preparation of trihydroxylated pyrrolidine derivatives, many of which may be potential glycosidase inhibitors. Reduction of **781** to the β -hydroxylactam **798** with sodium borohydride–tin(II) chloride occurs quantitatively. This is converted to acetate **799**, which is then treated with magnesium bromide and an appropriate organotin reagent to provide in excellent yields **801**, in which the *syn*-selectivity is very high. This result suggests that favorable orbital interactions over steric interactions experienced during *syn* approach of the tin nucleophiles to the resident OTBS group in **800** determine the stereochemical result [236] (Scheme 175).



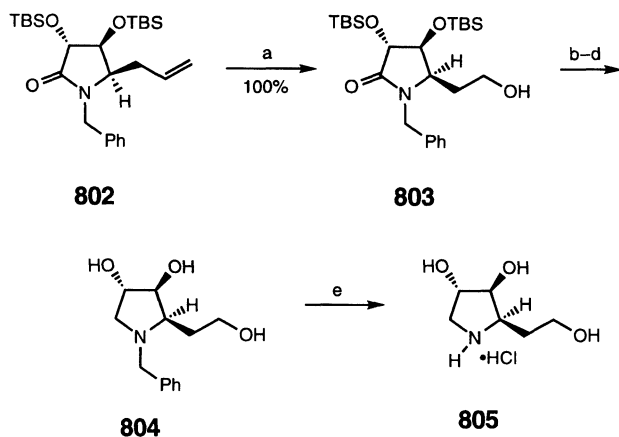
Scheme 175

conditions: (a) NaBH_4 , SnCl_2 , EtOH, DCM; (b) Ac_2O , pyridine (100%); (c) MgBr_2 , RSnR'_3 , 0 °C

Preparation of the *xylo*-configured deoxyimino sugars **805** and **807** from **802** or **806** illustrates the value of tartaric acid in enantiospecific syntheses of valuable target molecules. Ozonolysis of **802** followed by reduction with sodium borohydride in methanol provides **803**. Subsequent borane–dimethylsulfide–THF complex reduction, OTBS deprotection with 60% aqueous acetic acid, and purification with Amberlite IRA400(OH) resin provides, after acidification, **804** in 75% yield. Catalytic debenzoylation in the presence of palladium hydroxide occurs quantitatively to afford (2*R*,3*R*,4*R*)-2-(2-hydroxyethyl)-3,4-dihydroxypyrrolidine hydrochloride (**805**) in an overall yield of 53% (Scheme 176).

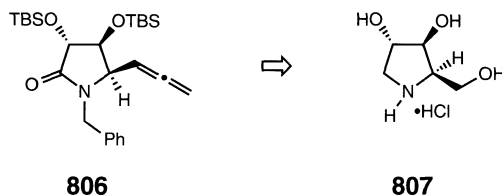
A similar sequence of reactions utilizing **806** provides in 54% overall yield (2*R*,3*R*,4*R*)-2-(hydroxymethyl)-3,4-dihydroxypyrrolidine hydrochloride (**807**) [236].

Inversion of the C-4 hydroxyl group on **805** and **807** would provide either of the *lyxo*-deoxyimino sugars **810** or **813**. Deprotection of the OTBS groups on **802** followed by ozonolysis and oxidation with silver carbonate on Celite of the resulting anomeric mixture provides in 89% yield the lactone (1*R*,5*R*,8*R*)-6-benzyl-8-hydroxy-2-oxa-6-azabicyclo-[3.3.0]octane-3,7-dione (**808**), determined by proton NMR of the MTPA ester to have 96% *ee*.



Scheme 176

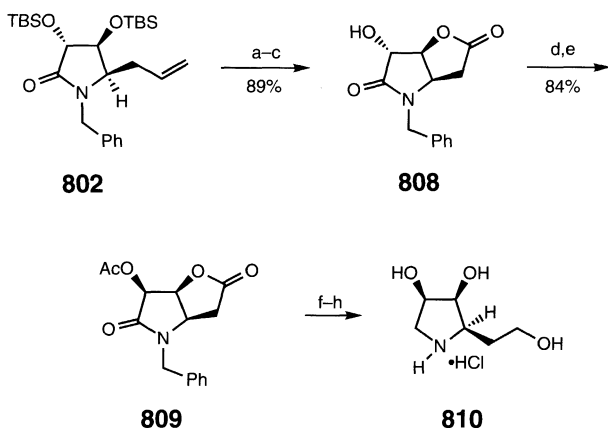
conditions: (a) O_3 , MeOH, DMS then $NaBH_4$; (b) $BH_3 \cdot DMS$, THF; (c) 60% aq. AcOH; (d) Amberlite IRA 400 (OH); (e) H_2 , $Pd(OH)_2/C$, MeOH



The inversion of stereochemistry occurs in a two-step sequence. Exposure of **808** to triflic anhydride and then treating the resulting triflate with potassium acetate and 18-crown-6 ether in DMF generates **809** in 84% yield. This is converted in three steps to L-dihydroxyhomoprolinol (**810**). The overall yield in the 11 steps from tartaric acid is a remarkable 48% [236] (Scheme 177).

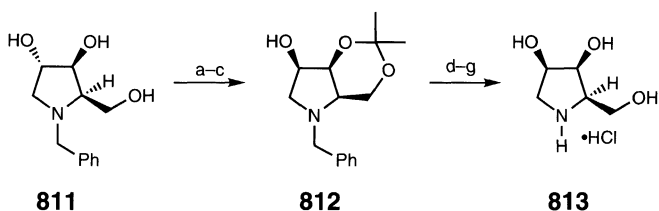
The corresponding *cis* L-dihydroxyprolinol (**813**) is conveniently prepared from **811**. Selective protection of the C-3 and C-5 hydroxyl groups with 2,2-dimethoxypropane, Swern oxidation of the remaining hydroxyl group to a ketone, and K-Selectride reduction results in inversion to provide **812**. Hydride attack occurs exclusively from the convex face. Deprotection and reductive debenzoylation of **812** affords **813** in an overall yield of 41% for the 14-step synthesis [236] (Scheme 178).

Due to the fragility of the ester groups, many *O,O*-diacyltartrimidates cannot be prepared by heating the corresponding anhydride with ammonia. A mild and general preparative method involves treating anhydride **814** with methanol to provide the monoacid **815**, which is converted to its acid chloride **816** by gentle heating in thionyl chloride. The crude acid chloride **816** is subsequently treated with ammonia in THF followed by deprotonation with sodium hydride to provide, after an intra-molecular cyclization, the tartrimidates **817a-c** in good overall yields. Interestingly, the poorest yield occurs with the diacetate **817a** [237] (Scheme 179).



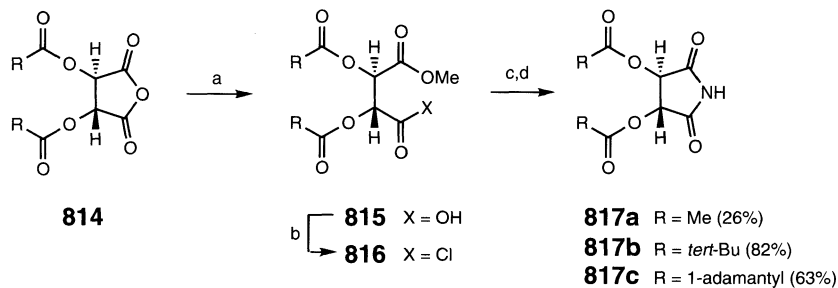
Scheme 177

conditions: (a) 60% AcOH; (b) O₃, MeOH, DMS; (c) Ag₂CO₃, Celite, toluene; (d) Tf₂O, pyridine; (e) KOAc, 18-crown-6, DMF; (f) BH₃•DMS, THF; (g) HCl, MeOH; (h) H₂, Pd(OH)₂/C, MeOH



Scheme 178

conditions: (a) Me₂C(OMe)₂, *p*-TsOH, DMF (97%); (b) Swern [O] (97%); (c) K-Selectride, THF, -78 °C (79%); (d) 80% AcOH, 100 °C, 30 min; (e) Amberlite IRA-400(OH); (f) 2N HCl (99% 3 steps); (g) 90% aq. MeOH, H₂, Pd(OH)₂ then 2N HCl (99%)



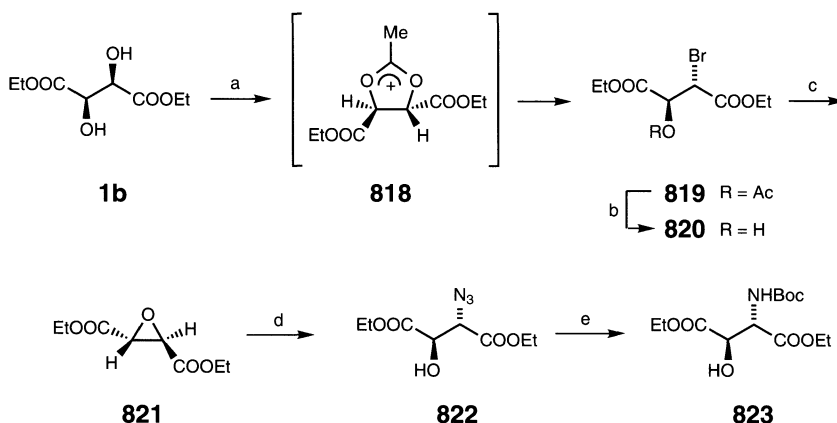
Scheme 179

conditions: (a) MeOH, 60 °C, 1 h (99%); (b) SOCl₂, 40 °C; (c) NH₃(g), THF, 0 °C (85–96%); (d) NaH, THF, rt, 3 h

4.3.8 Halohydrins from Tartaric Acids

Chiral β -hydroxy- α -amino acids are important constituents of biologically active peptides and precursors to β -lactam antibiotics. Diethyl L-tartrate (**1b**) provides the starting material for a practical and large-scale synthesis of diethyl *erythro*-3-hydroxy-*N*-(*tert*-butoxycarbonyl)-L-aspartrate (**823**) in high optical purity. Reaction of diethyl L-tartrate (**1b**) with 30% hydrobromic acid in acetic acid provides the bromo acetate **819**, which undergoes facile hydrolysis with acetic acid in refluxing ethanol to afford diethyl (2*S*,3*S*)-2-bromo-3-hydroxysuccinate (**820**) in 72–76% overall yield. The observed inversion presumably occurs by bromide ion capture of the intermediate 1,3-dioxolan-2-ylum ion **818**. Ring closure of **820** to diethyl (2*R*,3*R*)-2,3-epoxysuccinate (**821**) is best carried out using sodium ethoxide in ethanol. Such bases as potassium hydroxide in ethanol, sodium or potassium carbonate in ethanol, or benzyltriethylammonium hydroxide in ethanol provide complex mixtures of decomposition products.

Azide cleavage of **821**, utilizing a modification in which trimethylsilylazide first forms a reactive complex with DMAP that allows the reaction to occur at room temperature, affords in 85% yield diethyl (2*S*,3*R*)-2-azido-3-hydroxysuccinate (**822**). An advantage of this synthesis is that hazardous hydrazoic acid (HN₃) is avoided. A one-pot two-step conversion of **822** involving hydrogenation over palladium on charcoal in the presence of di-*tert*-butyl dicarbonate provides enantiomerically pure **823** in 66–73% yield [238,239] (Scheme 180).

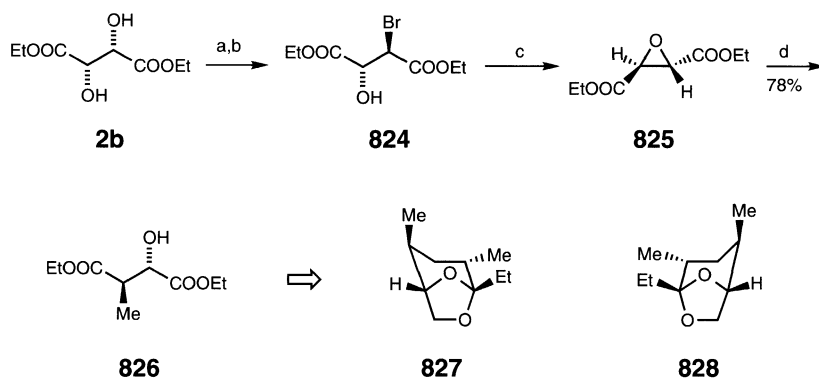


Scheme 180

conditions: (a) 30% HBr, AcOH; (b) AcCl, Et₃N, reflux (72–76% 2 steps); (c) NaOEt, EtOH (85–90%); (d) DMAP, DMF, EtOH, TMSN₃ (96–98%); (e) H₂, Pd/C, EtOAc, Boc₂O (66–73%)

Diethyl D-tartrate (**2b**), treated similarly with 30% hydrobromic acid in acetic acid followed by acidic hydrolysis, is converted to diethyl *erythro*-(2*R*,3*R*)-2-bromo-3-hydroxysuccinate (**824**) in an overall yield of 73%. Sodium ethoxide cyclization affords (2*S*,3*S*)-2,3-epoxysuccinate (**825**), which is the enantiomeric epoxide of **821**. Epoxide cleavage with lithium dimethylcuprate provides in 78% yield diethyl (2*S*,3*R*)-*erythro*-3-methylmalate (**826**), which is converted in eight steps to (–)-(1*S*,2*S*,4*S*,5*R*)-2,4-dimethyl-5-ethyl-6,8-dioxobicyclo-[3.2.1]octane or (–)- δ -multistriatin (**827**), one of the eight possible stereoisomeric forms for this pheromone component responsible for the aggregation of the North American

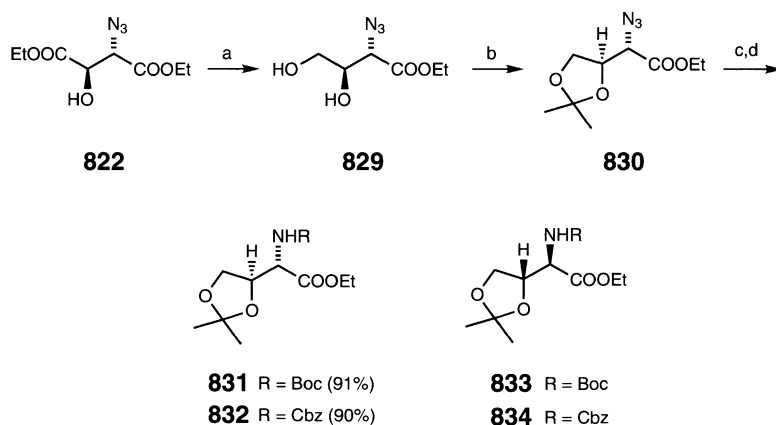
population of the smaller European elm bark beetle *Scolytus multistriatus* Marsham. The enantiomeric (+)-(1*R*,2*R*,4*R*,5*S*) **828** can be prepared similarly from diethyl L-tartrate (**1b**) [240] (Scheme 181).



Scheme 181

conditions: (a) 30% HBr, AcOH; (b) AcCl, EtOH; (c) NaOEt, EtOH; (d) Me₂CuLi

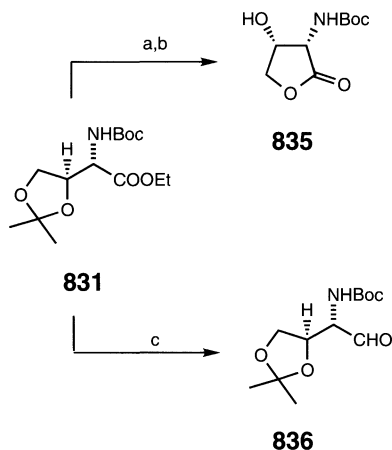
Regioselective reduction of the α -hydroxy ester group in **822** to the highly labile dihydroxy azido ester **829** is accomplished with borane–dimethylsulfide complex and a catalytic amount of sodium borohydride. Immediate treatment of **829** with dimethoxypropane affords the isolable ethyl 2-azido-3,4-*O*-isopropylidene-3,4-dihydroxybutanoate (**830**) in 59% yield for the two steps. Subsequent catalytic reduction of the azido group followed by either N-Boc or N-Cbz protection provides either **831** or **832** in excellent yield. These are equivalent to *erythro*- β -hydroxymethyl-L-serine. The enantiomeric **833** and **834** are readily available from diethyl D-tartrate through a similar series of transformations [239] (Scheme 182).



Scheme 182

conditions: (a) BH₃•DMS, cat. NaBH₄, THF; (b) Me₂C(OMe)₂, *p*-TsOH, acetone; (c) H₂, Pd/C, EtOAc; (d) Boc₂O, CHCl₃, rt, 10 h or CbzCl, NaHCO₃/H₂O 0 °C, 2 h

When **831** is treated with *p*-toluenesulfonic acid in methanol for six hours followed by stirring for six hours in methylene chloride, deprotection and subsequent lactonization occurs to provide the γ -lactone **835**. Alternatively, DIBAL reduction of **831** at $-78\text{ }^\circ\text{C}$ in toluene affords the fully protected aldehyde **836** [239] (Scheme 183).



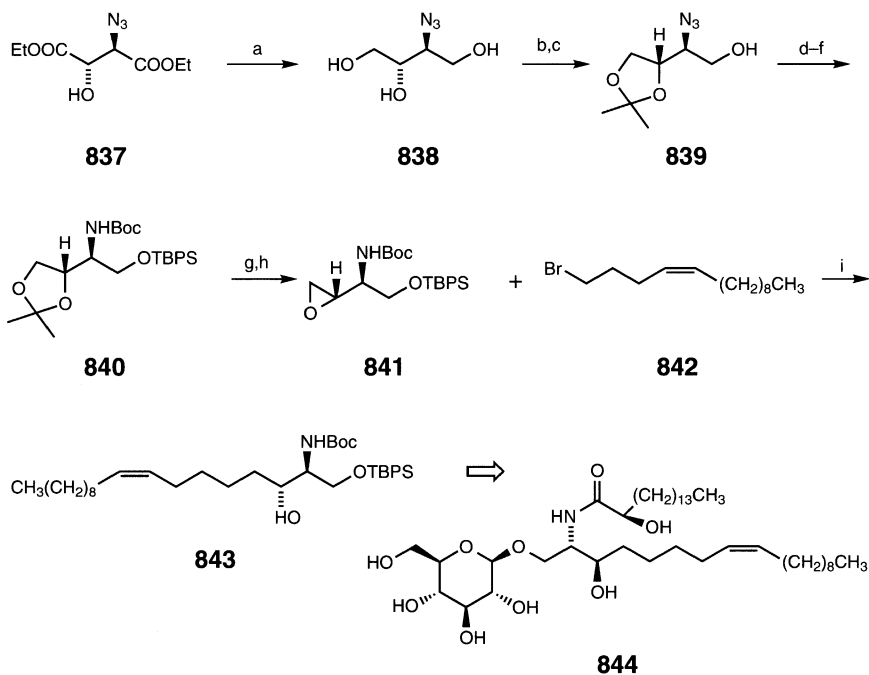
Scheme 183

conditions: (a) *p*-TsOH, MeOH, 6 h; (b) DCM, 6 h, rt;
(c) DIBAL, $-78\text{ }^\circ\text{C}$, toluene

Treatment of azido alcohol **837**, easily prepared from diethyl D-tartrate (**2b**) under conditions similar to those used for the preparation of **822**, with excess sodium borohydride, results in reduction of both ester groups to provide (2*S*,3*S*)-3-azido-1,2,4-butanetriol (**838**) in 90% yield. Isopropylidene protection affords a mixture of 1,2- and 2,4-protected triols, which after acid-catalyzed equilibration affords the 1,3-dioxolane **839** as a single isomeric product. Silyl protection of the free hydroxy group, catalytic reduction of the azido function to an amine, and N-Boc protection yields **840** in an overall yield of 82%. Removal of the isopropylidene protecting group followed by selective monotosylation of the primary hydroxy group and potassium carbonate cyclization affords in good yield the epoxide **841**. Addition of the Grignard reagent prepared from (*Z*)-1-bromo-4-tetradecene (**842**) to a mixture of copper(I) iodide and **841** in THF furnishes (2*S*,3*R*,8*Z*)-2-*N*-Boc-1-*O*-*tert*-butyldiphenylsilyl-8-sphingene (**843**) in 80% yield. This is converted in six steps to (2*S*,3*R*,8*Z*)-1-*O*-(β -D-glucopyranosyl)-*N*-hexadecanoyl-8-sphingene (**844**), a wheat grain cerebroside possessing fruiting-inducing effects on the mushroom *Schizophyllum commune* (Scheme 184). The corresponding (*E*)-isomer can be prepared similarly [241].

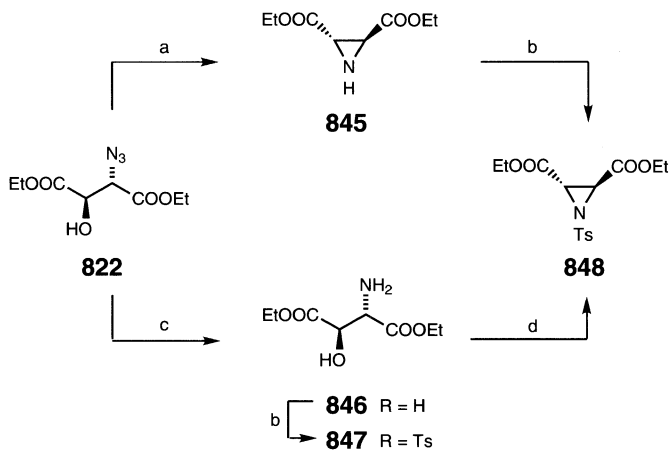
The ability of non-racemic C_2 -symmetric aziridines **848** and **849** to undergo rapid nucleophilic ring-opening to provide synthetic equivalents for the β -cation of aspartic acid illustrates the utility of the azide **822**. Treatment of **822** with triphenylphosphine in refluxing benzene results in reduction of the azide to an amine that readily undergoes ring closure to aziridine **845**. Subsequent tosylation of the secondary nitrogen affords **848** in 73% yield for the two steps.

Alternatively, **848** can be prepared sequentially by first treating **822** with triphenylphosphine in benzene at room temperature to provide the aminoalcohol **846**. This is then tosylated to **847** followed by an intramolecular Mitsunobu cyclization to provide **848** in an overall yield of 61% (Scheme 185).



Scheme 184

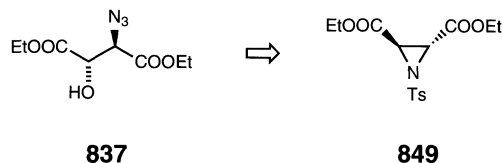
conditions: (a) excess NaBH_4 , EtOH (83%); (b) $\text{Me}_2\text{C}(\text{OMe})_2$, *p*-TsOH, acetone; (c) NaHCO_3 , acetone, 50 °C, 18 h (90% 2 steps); (d) TBPSCI, imidazole, DMF (99%); (e) H_2 , PtO_2 , EtOH (100%); (f) Boc_2O , DCM (92%); (g) Amberlyst-15, MeOH (95%); (h) *p*-TsCl, pyridine, then K_2CO_3 , MeOH (82%); (i) **842**, Mg, CuI, THF (80%);



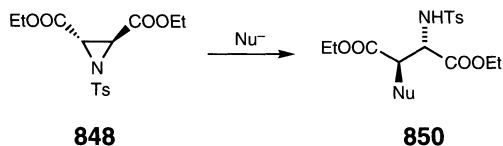
Scheme 185

conditions: (a) PPh_3 , C_6H_6 , reflux; (b) *p*-TsCl, pyridine; (c) PPh_3 , C_6H_6 , rt; (d) PPh_3 , DEAD, THF, rt

A similar series of reactions utilizing **837** provides the enantiomeric **849** [242].



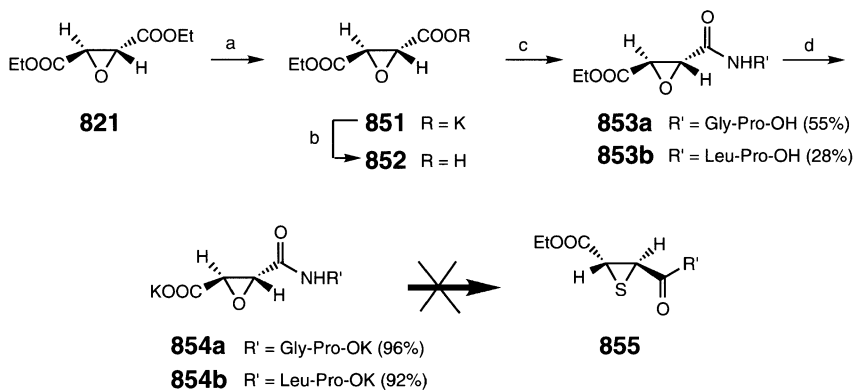
Nucleophilic ring-opening of **848** with a variety of nucleophiles occurs with clean inversion to provide the compounds **850** in moderate yields. The C_2 -symmetric nature of **848** conserves both the stereochemical and enantiomeric purity. Moreover, the two ester groups as well as the tosyl moiety presumably activate the aziridine toward nucleophilic attack [242].



Nu ⁻ reagent	Solvent	Temp (°C)	Nu	Yield (%)
LiMe ₂ Cu	Et ₂ O	-78	Me	68
LiBu ₂ Cu	Et ₂ O	-78	Bu	54
NaN ₃	DMF	30	N ₃	81
MgI ₂	THF	0	I	72
MgBr ₂	THF	0	Br	76

Increased interest in the ability of the epoxysuccinyl moiety to serve as a reactive handle for the design of specific inhibitors of the cysteine-proteases has stimulated efforts to incorporate it or the corresponding epithiosuccinyl moiety into peptides. Saponification of **821** with a stoichiometric amount of potassium hydroxide in ethanol at 0 °C provides in 79% yield ethyl (2*R*,3*R*)-*trans*-2,3-epoxysuccinate potassium salt (**851**). Subsequent treatment of **851** with a 5% solution of potassium bisulfate affords a 77% yield of ethyl (2*R*,3*R*)-*trans*-2,3-epoxy-succinate (**852**). N^x -acylation of suitably protected amino acid or peptide derivatives with **852** is best performed using *N*-hydroxysuccinimide or pentafluorophenol as a coupling reagent to provide **853a,b**. The remaining ester in **853** can be saponified with potassium hydroxide to generate the potassium salts **854** in good yield. These salts are stable on storage in the cold. Unfortunately, all attempts to convert epoxide **854a** to an epithiosuccinyl analog **855** failed [243] (Scheme 186).

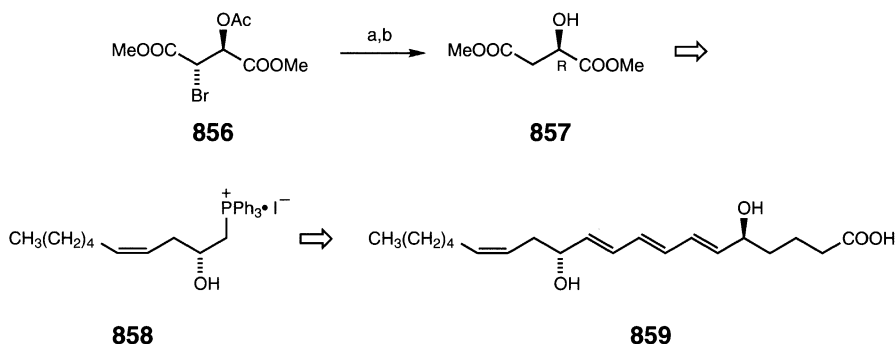
The radical debromination of **856**, prepared from (+)-dimethyl tartrate (**1a**) as described for **819**, with trimethyltin chloride in the presence of AIBN and sodium borohydride in ethanol below 10 °C followed by deacetylation with 3% hydrochloric acid affords (*R*)-(+)-



Scheme 186

conditions: (a) KOH, EtOH, 0 °C, 2 h (79%); (b) 5% KHSO₄, NaCl (77%); (c) R'NH₂, pentafluorophenol, DCC, DMF; (d) 2 equiv. KOH, EtOH, 0 °C, 2 h

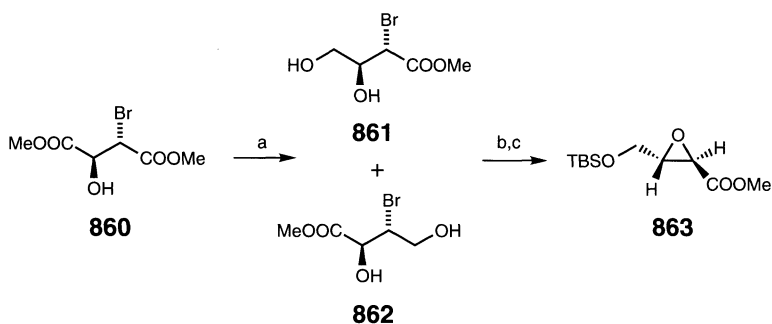
dimethylmalate (**857**). The overall yield from **1a** is 56% on a 0.2 mol scale. This is in turn converted to **858**, which is used to synthesize the 12-(*R*) form of 6-*trans*-leukotriene B (**859**) [244] (Scheme 187).



Scheme 187

conditions: (a) Me₃SnCl, AIBN, NaBH₄; (b) HCl, MeOH

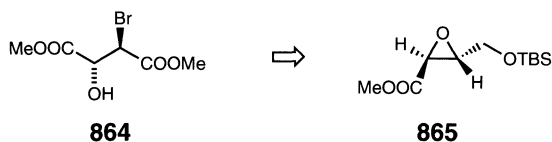
One of the most potent frameworks for the synthesis of two contiguous stereochemically defined asymmetric centers is the chiral epoxy functionality. Prepared in molar-scale quantity from dimethyl L-tartrate (**1a**), bromohydrin **860** is a shelf-storable solid that undergoes selective reduction at the α -hydroxy ester function with borane–dimethylsulfide complex in the presence of catalytic sodium borohydride to provide a 4 : 1 mixture of methyl (2*S*,3*S*)-2-bromo-3,4-dihydroxybutanoate (**861**) and methyl (2*R*,3*R*)-3-bromo-2,4-dihydroxybutanoate (**862**). Without purification this mixture is treated with *tert*-butyldimethylsilylchloride and then exposed to sodium methoxide, which results in conversion to the single epoxide methyl (2*R*,3*S*)-4-(*tert*-butyldimethylsilyloxy)-2,3-epoxybutanoate (**863**) in 95% yield and with 99% optical purity (Scheme 188).



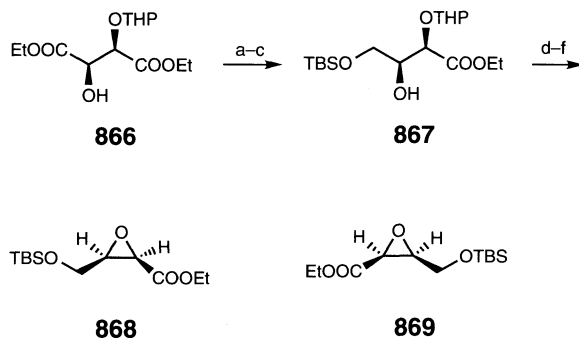
Scheme 188

conditions: (a) $\text{BH}_3 \cdot \text{DMS}$, THF, NaBH_4 ; (b) TBSCl, imidazole, THF (76%); (c) NaOMe, MeOH (95%)

Similar chemistry utilizing **864**, derived from dimethyl D-tartrate (**2a**), affords the antipode **865** [245].



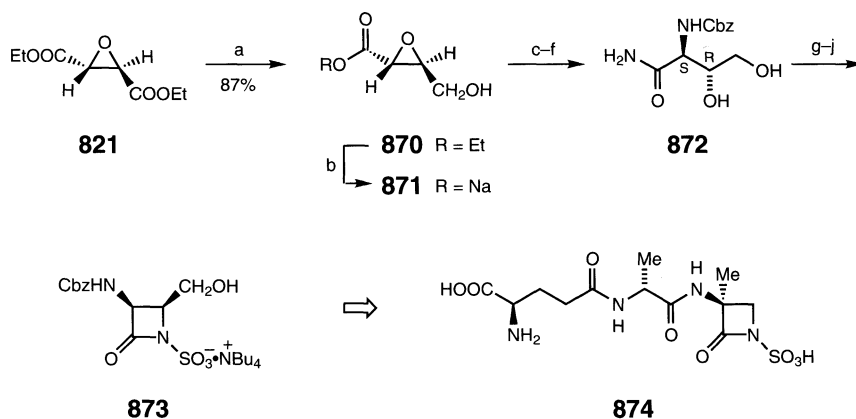
In order to prepare the corresponding enantiomeric *cis*-epoxides **868** and **869**, an alternative synthesis is utilized. The mono-*O*-THP-(+)-diethyl tartrate (**866**) undergoes exclusive α -hydroxyester reduction with borane–dimethylsulfide and catalytic sodium borohydride [see [246]] to provide, after chromatographic purification and silyl protection of the primary hydroxy group, a 71% yield of **867**. Sulfonylation of the secondary hydroxyl group with mesyl chloride, selective THP deprotection, and exposure to sodium ethoxide in ethanol affords the *cis*-epoxide **868** in moderate yields. The antipode **869** can be prepared similarly from diethyl D-tartrate (**2b**) [245] (Scheme 189).



Scheme 189

conditions: (a) $\text{BH}_3 \cdot \text{DMS}$, THF, NaBH_4 ; (b) TBSCl, imidazole, THF; (c) SiO_2 chromatography; (d) MsCl, Et_3N , Et_2O , 0 °C, 2 h (95%); (e) 2 equiv. Me_2AlCl , hexane–DCM (1:4), –25 °C to rt (94%); (f) NaOEt, EtOH (43%)

The *trans*-epoxide diethyl (2*R*,3*R*)-2,3-epoxysuccinate (**821**) can be mono reduced with sodium borohydride in ethanol at 0 °C to provide in 87% yield ethyl (2*R*,3*S*)-4-hydroxy-2,3-epoxybutyrate (**870**), determined to be 98% pure by gas chromatography. Treatment of the sodium salt **871**, derived from **870**, with ammonia leads to stereo- and regiospecific opening of the oxirane ring to give, after esterification, amide formation, and Cbz-amino group protection, (2*S*,3*R*)-2-(*N*-Cbz)-3,4-dihydroxybutanamide (**872**) in 44% overall yield. Conversion of **872** to tetrabutylammonium (3*S*,4*S*)-3-(*N*-Cbz)-4-(hydroxymethyl)-2-oxoazetidine-1-sulfonate (**873**) is accomplished by selective protection of the primary hydroxy group with chloroacetyl chloride, mesylation, sulfonation with 2-picoline-SO₃ (prepared *in situ*), and ring closure with potassium bicarbonate [247] (Scheme 190). This monobactam is a precursor of the antibiotic carumonam (**874**) [248,249].



Scheme 190

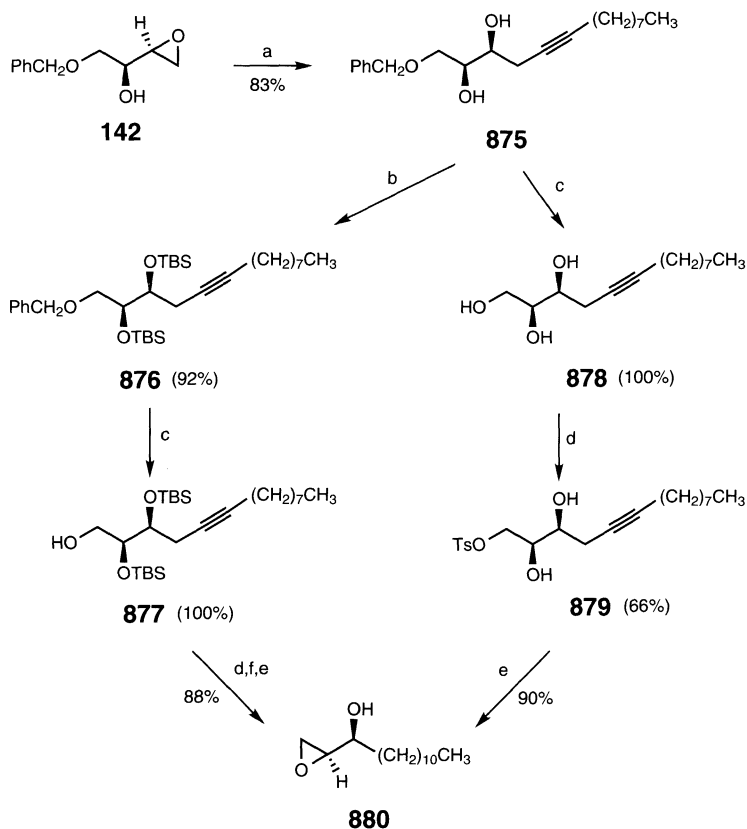
conditions: (a) NaBH₄, EtOH, 0 °C; (b) NaOH, MeOH (90%); (c) NH₄OH, 50–55 °C, 45 h; (d) HCl(g), MeOH; (e) NH₃(g), MeOH; (f) NaHCO₃, CbzCl; (g) ClCH₂COCl, DMA (91%); (h) MeOCH₂CH₂OMe, MsCl, Et₃N (74%); (i) TMSCl, SO₃, 2-picoline, CCl₄, DCM; (j) KHCO₃, ClCH₂CH₂Cl, 70 °C (83% from **872**)

4.3.9 Addenda

During the writing of this chapter a number of complex molecules have been synthesized in which a tartaric acid derivative has played a crucial role for the introduction of stereo- and enantiochemistry. It is the purpose of this addendum to bring these exciting applications to the attention of the reader.

Optically active epoxides, such as **882** and **884**, bearing both an unsaturated and a saturated side chain in a *cis* relationship, are encountered as sex pheromones of the Lepidoptera pest *Phragmatobia fuliginosa*. Due to the low reactivity of leaving groups adjacent to an epoxide, direct displacement of either an α -bromide or α -tosylate with unsaturated organometallic nucleophiles is ineffective. A general method for the synthesis of chiral *cis*-epoxides involves the tartrate-derived epoxide (2*S*,3*S*)-1,2-epoxy-3-hydroxy-4-benzyloxybutane (**142**) as a readily available chiral starting material. Two different routes are available for the preparation of (2*S*,3*S*)-1,2-epoxy-3-hydroxytetradecane (**880**), the common precursor for the divergent

synthesis of either (–)-**882** or (+)-**884**. However, the direct pathway through the tosylate **879** requires stringent regard to reaction conditions, and at best provides **879** in 66% yield, whereas improved overall yields are obtained by prior silyl protection of the free hydroxy groups in **875** to generate **876**. Subsequent debenzoylation, tosylation, fluoride desilylation, and base cyclization provides the epoxide **880** (Scheme 191).

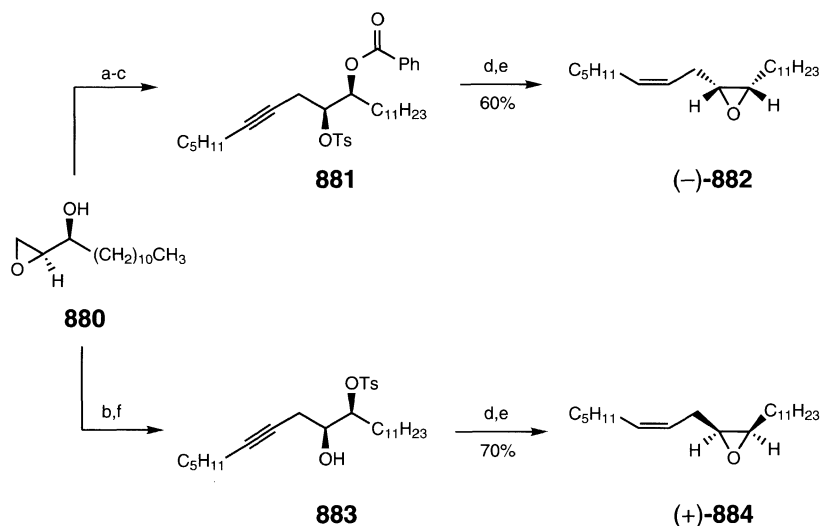


Scheme 191

conditions: (a) 1-lithio-1-decyne, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, -70°C ; (b) TBSCl, DMAP, DCM, Et_3N ;
 (c) H_2 , Pd/C, MeOH; (d) *p*-TsCl, pyridine, -20°C , DCM; (e) K_2CO_3 , MeOH;
 (f) *n*- Bu_4NF , THF

The free hydroxy group in **880** is first protected as a benzoate, ring opened with the lithium anion of 1-heptyne, and finally tosylated to afford **881**, which is deprotected and cyclized to the epoxide with potassium carbonate in methanol. A Lindlar reduction of the triple bond provides the *cis*-olefin present in (–)-(6*Z*,9*R*,10*S*)-9,10-epoxyheneicosadec-6-ene (**882**). In order to prepare the enantiomer **884**, **880** is directly ring opened with the lithium anion of 1-heptyne, and then tosylated to afford **883**, which is cyclized and selectively reduced to (+)-(6*Z*,9*S*,10*R*)-9,10-epoxyheneicosadec-6-ene (**884**) [250] (Scheme 192).

Annonaceous acetogenins, potent bioactive secondary metabolites from several species of *Annonaceae*, usually contain 35 or 37 carbon atoms, one or two tetrahydrofuran rings, and a γ -lactone with five to eight carbinol asymmetric centers. Corosolone (**890**), a naturally



Scheme 192

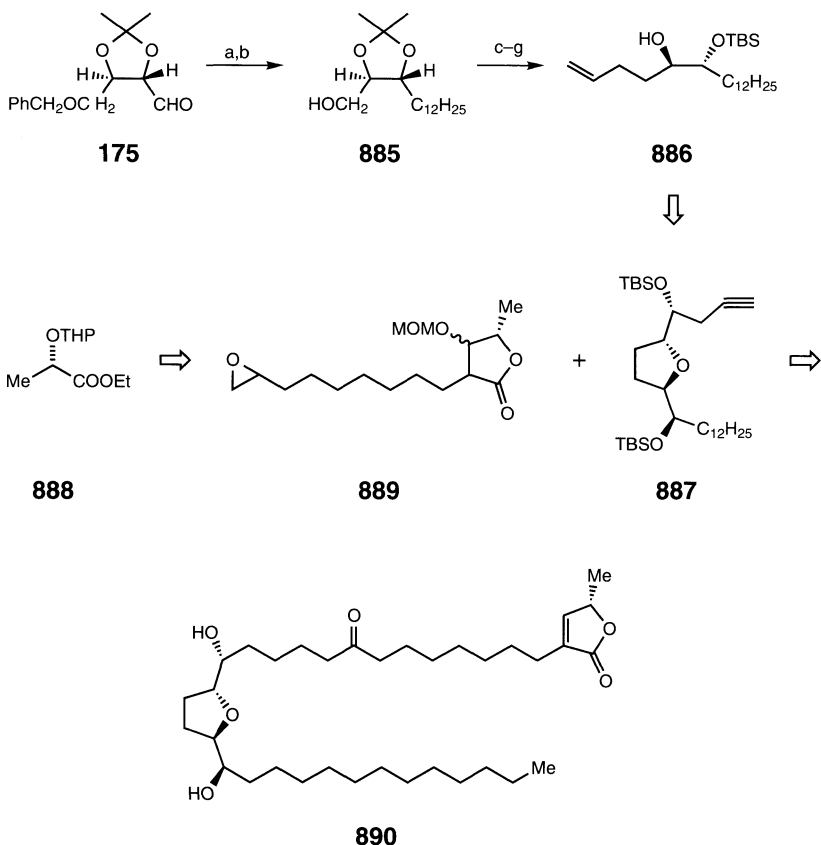
conditions: (a) $PhCOCl$, pyridine (92%); (b) 1-lithio-1-heptyne, $BF_3 \cdot Et_2O$, $-70^\circ C$, THF (86%); (c) $p-TsCl$, DMAP, Et_3N , DCM (86%); (d) K_2CO_3 , MeOH; (e) H_2 , Lindlar catalyst, MeOH; (f) $p-TsCl$, pyridine, $0^\circ C$, 2 d (85%)

occurring cytotoxic annonaceous acetogenin isolated from *Annona muricata*, is the subject of a diastereoselective and convergent synthesis starting with the tartrate-derived aldehyde **175**. The Wittig reaction of **175** with undecylphosphonium bromide/butyllithium in THF at $-60^\circ C$ affords a 95:5 *Z:E* mixture of olefins that is catalytically reduced to provide (2*R*,3*R*)-2,3-*O*-isopropylidene-pentadec-1-ol (**885**) in 86% yield. Reductive cleavage of the benzyl protecting group is incomplete, thus requiring additional treatment with lithium in liquid ammonia to finish the task. Tosylation of **885**, removal of the isopropylidene protecting group, and treatment with potassium carbonate provides the epoxide, which, after silyl protection of the free hydroxy group, undergoes ring opening with allylmagnesium chloride in the presence of cuprous bromide to provide (5*R*,6*R*)-5-hydroxy-6-[(*tert*-butyldimethylsilyloxy)-1-octadecene (**886**) in good overall yield. Subsequent transformation of **886** affords the chiral tetrahydrofuran **887**, which is coupled with **889**, the second segment derived from the protected lactate **888**, to provide, after appropriate functional group manipulations, corosolone (**890**) [251] (Scheme 193).

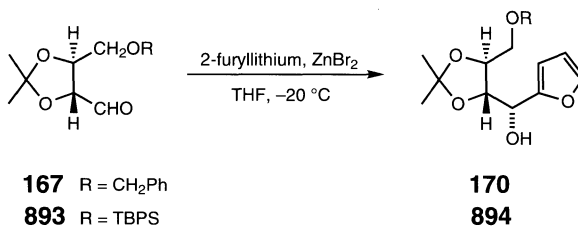
The synthesis of higher sugars containing more than six carbon atoms is of intense interest, since these complex chiral structures are components of lincomycins, ezoaminuroic acids, 3-deoxy-D-*manno*-2-octulosonic acid (KDO), and *N*-acetylneuraminic acid (Neu5Ac). The C_2 -symmetric bis-phosphonate **891**, prepared from diethyl 2,3-*O*-isopropylidene-L-tartrate (**4**), undergoes the Wadsworth–Emmons reaction with various sugar aldehydes to provide the corresponding C_2 -symmetric bis-enones **892a–c** in moderate yields. Use of the base cesium carbonate in isopropanol provides cleanly the *trans* olefins [252] (Scheme 194).

The stereoselective addition of 2-furyllithium to aldehydes **167** or **893** in the presence of excess zinc bromide in THF at $-20^\circ C$ proceeds with 98% stereoselectivity to provide either **170** or **894**. In both cases the *R*-geometry of the carbinol is obtained.

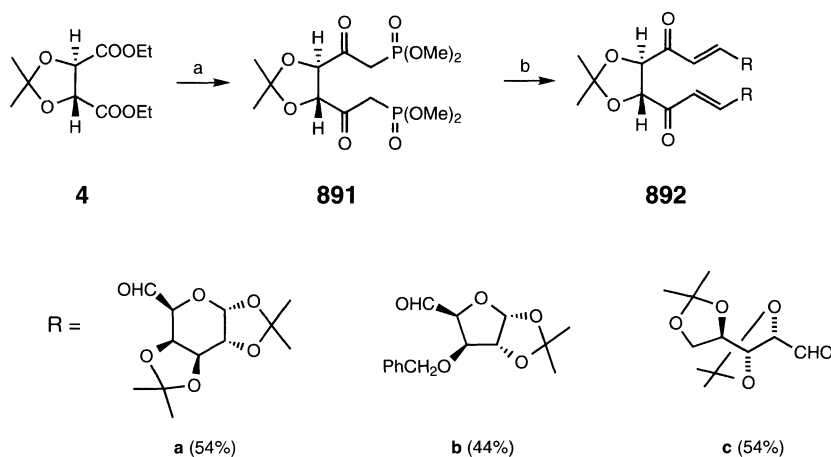
A three-step conversion of **894** provides the tetrahydropyran intermediate **895**, which can be converted to the azide **896**. Reduction of the azide group and cyclization of an intermediate amino mesylate yields 1-deoxy-8,8a-di-*epi*-castanospermine (**897**) [253] (Scheme 195).

**Scheme 193**

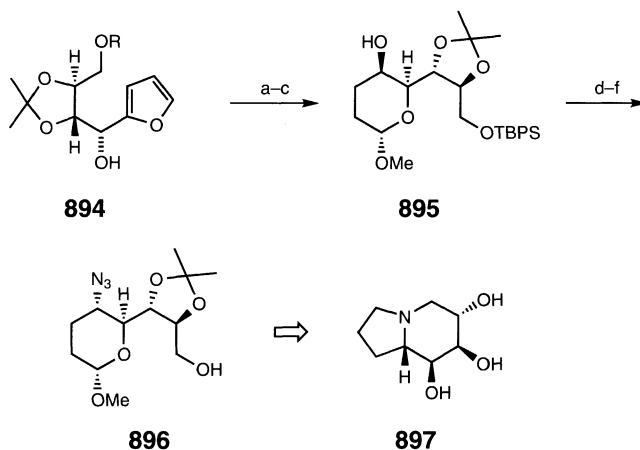
conditions: (a) $C_{10}H_{21}CH=PPh_3$, THF; (b) H_2 , Pd/C (86%); (c) TsCl, Et_3N , DMAP, DCM (96%); (d) TsOH, MeOH; (e) K_2CO_3 , MeOH (75%); (f) TBSCl, $AgNO_3$, pyridine, THF (93%); (g) allylMgCl, CuBr, THF-ether (84%)



(3*Z*)- and (3*E*)-Dactomelynes (**905**) and (**906**), isolated from the digestive glands of the sea hare *Aplysia dactylomela*, represent nonisoprenoid ethers characterized by a unique pyranopyran skeleton with ethyl and pentenynyl substituents. A characteristic feature of their structure is the chlorine substituent oriented on the sterically hindered side, whereas the bromine substituent avoids steric congestion. Construction of the pyranopyran skeleton *via*

**Scheme 194**

conditions: (a) $\text{LiCH}_2\text{P}(\text{O})(\text{OMe})_2$; (b) RCHO

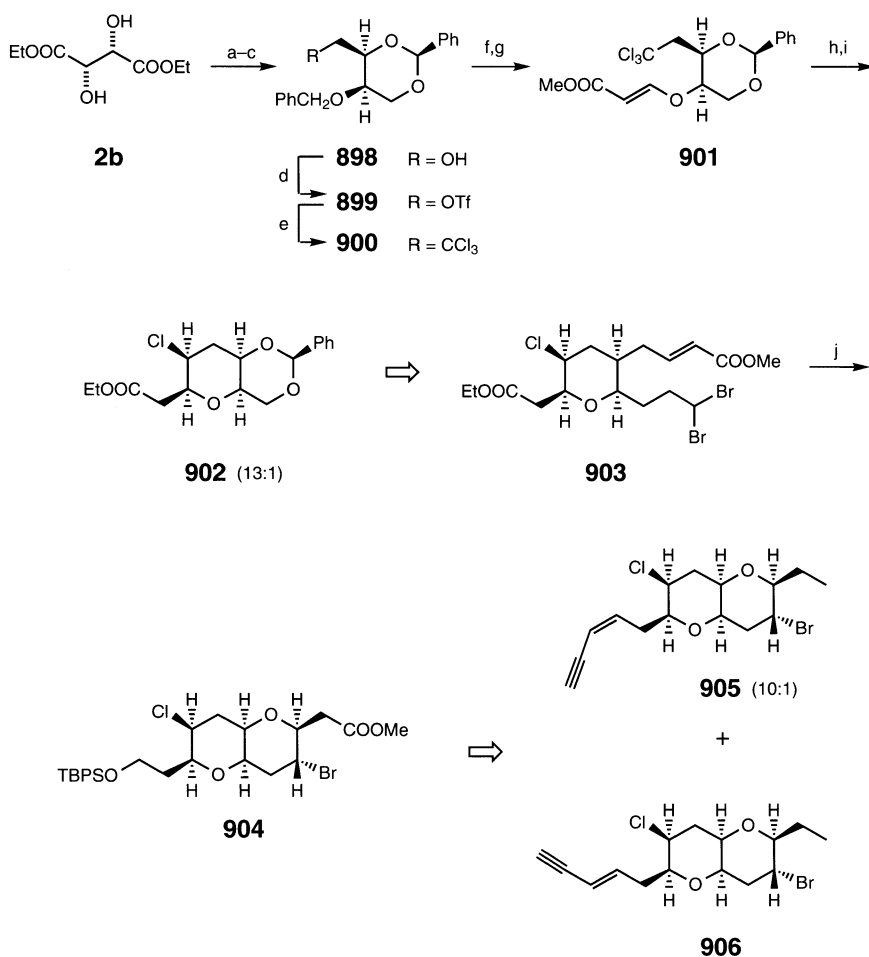
**Scheme 195**

conditions: (a) *tert*-BuOOH/ $\text{VO}(\text{acac})_2$; (b) MeI, Ag_2O ; (c) K-Selectride, EtOH; (d) MsCl, Et_3N , DMAP; (e) NaN_3 , DMF; (f) Bu_4NF

two independent radical cyclization reactions of β -alkoxyacrylate substrates prepared ultimately from diethyl D-tartrate (**2b**) exemplifies the synthetic utility of this readily available chiral precursor for the synthesis of a very complex natural product.

Cyclic acetal **898**, prepared from **2b** in three steps, is converted to the triflate **899** and reacted with excess (trichloromethyl)lithium at -110°C to provide the trichloro derivative **900**. Hydrogenolysis and a Michael addition to ethyl propiolate provides the first β -alkoxyacrylate **901**. This is treated with tricyclohexylstannane under high-dilution conditions to afford, as the main product in 67% yield, the dichloro product, which is stereoselectively

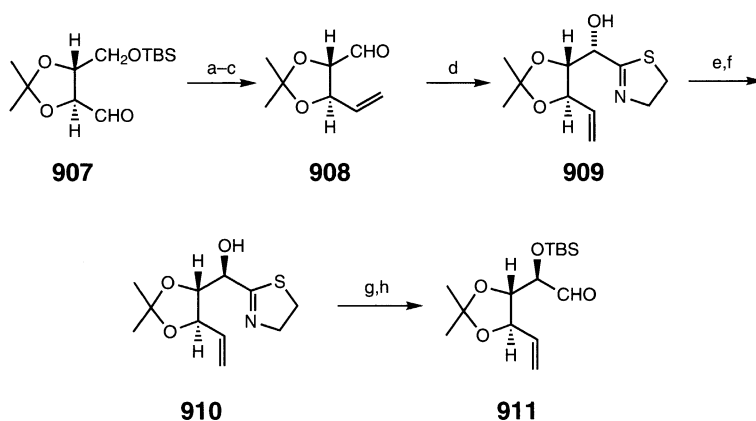
dechlorinated with tri(trimethylsilyl)silane in the presence of triethylborane to provide the monochloro product **902**. A 9-step chemical transformation of **902** provides the second β -alkoxyacrylate **903**, which under high-dilution radical conditions with tributylstannane and AIBN in hot benzene affords exclusively the pyranopyran **904**. Final elaboration of **904** provides a 10 : 1 mixture of **905** and **906**. This is a marvelous synthesis of a complex natural product that takes advantage of a radical-mediated reaction to introduce the required stereochemistry [254] (Scheme 196).



Scheme 196

conditions: (a) PhCHO, acid; (b) LiAlH₄-AlCl₃ (1:1) (91%); (c) PhCH(OMe)₂, acid (83%); (d) Tf₂O, pyridine; (e) LDA, CHCl₃, THF-ether-HMPA (1:1:0.2), -110 °C (60%); (f) H₂, Pd/C (75%); (g) ethyl propiolate, N-Me-morpholine (100%); (h) c-Hex₃SnH, AIBN (67%); (i) (TMS)₃SiH, Et₃B (98%); (j) Bu₃SnH, AIBN (75%)

(-)-Depudecin (**918**), a fungal metabolite discovered in the culture broth of *Alternaria brassicicola*, reverts the rounded phenotype of NIH3T3 cells doubly transfected with *v-ras* and *v-src* oncogenes to the flat phenotype of the non-transformed parental cells. It is therefore necessary that sufficient quantities of this material be prepared for further study. The synthetic strategy leading to the sensitive bis-*trans*-epoxide moiety of **918** utilizes the Sharpless stereoselective conversion of *syn*-vicinal diols to *trans*-epoxides. To prepare the key tetraol **916**, the D-threose derivative (**907**), available from ethyl D-tartrate (**2b**) by isopropylidene protection, lithium aluminum hydride reduction, mono silylation, and Swern oxidation, is utilized as the chiral starting material. Methylenation, TBS-deprotection, and Swern oxidation of **907** provides aldehyde **908**, which condenses in a non-chelation manner with 2-TMS-thiazole to afford *anti*-alcohol **909** (85 : 15). Inversion of the hydroxyl group is achieved through an oxidation–reduction sequence to provide the *syn*-alcohol **910** (79 : 21). Silylation of the free hydroxy group followed by thiazole ring cleavage results in aldehyde **911** (Scheme 197).

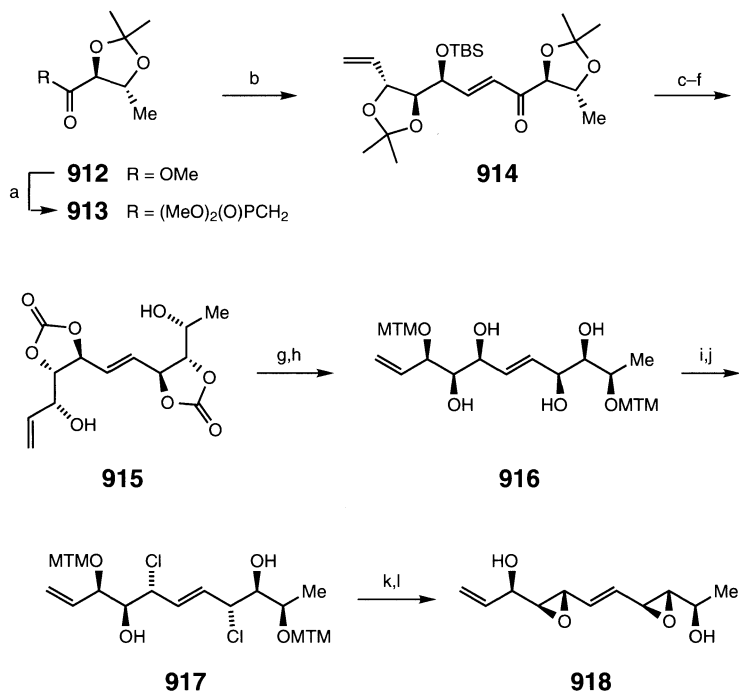


Scheme 197

conditions: (a) Ph_3PCl_3 , *tert*-BuOK, 23 °C (91%); (b) TBAF, THF (99%); (c) Swern [O] (100%); (d) 2-TMS-thiazole, THF, 23 °C then TBAF (71%); (e) Swern [O] (76%); (f) NaBH_4 , MeOH, -78 ° to -20 °C (99%); (g) TBSCl, imidazole, DMF, 70 °C (100%); (h) MeI, MeCN, reflux, NaBH_4 then CuO, CuCl_2 , MeCN-H₂O (88%)

Condensation of **911** with ketophosphonate **913**, prepared in 92% yield from **912**, provides enone **914** in 88% yield. Subsequent functional group transformation converts **914** to the labile bis-cyclic carbonate **915**. Treatment of **915** with a large excess of dimethyl sulfide in the presence of benzoyl peroxide followed by basic hydrolysis provides the tetraol **916**. When **916** is treated with trimethylorthoacetate in the presence of catalytic PPTS followed by trimethylsilyl chloride in a triethylamine buffer, the exclusive product is the diacetoxy dichloride **917**. Base-mediated saponification of crude **917** results in spontaneous cyclization to the bis-*trans*-epoxide, which after treatment with a large excess of mercury(II) chloride affords (-)-depudecin (**918**) in 52% yield. The total synthesis involves 22 steps, and provides **918** in 1.4% overall yield [255] (Scheme 198).

The indolizidine alkaloid lentiginosine (**789**) possesses stereochemical features that suggest as a precursor for the dihydroxylated portion of the molecule the readily available chiral nitrone **763**. Reverse addition of nitrone **763** to 2 equivalents of [4-(benzyloxy)-butyl]-magnesium bromide provides a 95 : 5 chromatographically separable mixture of diastereomers in which the 2,3-*trans*-**919** predominates. Raney nickel reduction of the hydroxylamine



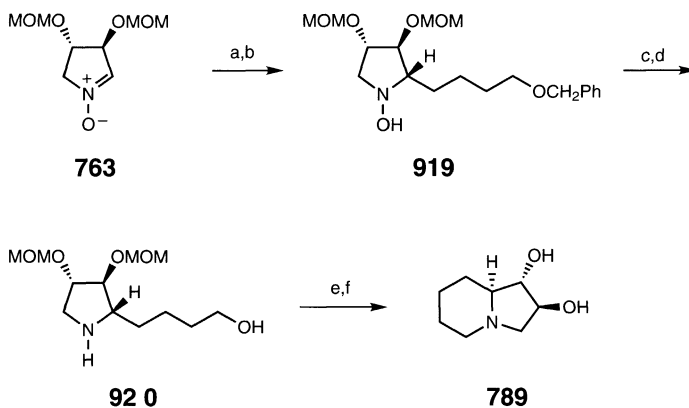
Scheme 198

conditions: (a) LiCH₂P(O)(OMe)₂, THF (92%); (b) NaH, THF, 23 °C then **911** (88%); (c) NaBH₄-CeCl₃-7H₂O, MeOH, -78 ° to -20 °C (96%); (d) TBAF then separation of diastereomers (74%); (e) ClCO₂CH₂CCl₃, 2,6-lutidine, DCM (99%); (f) HCl(g), MeOH (44%); (g) Me₂S, benzoyl peroxide, MeCN (34%); (h) 1 M LiOH, THF (93%); (i) MeC(OMe)₃, PPTS; (j) TMSCl, Et₃N; (k) K₂CO₃, MeOH (74% 3 steps); (l) 50 equiv. HgCl₂-CaCO₃, MeCN-H₂O (52%)

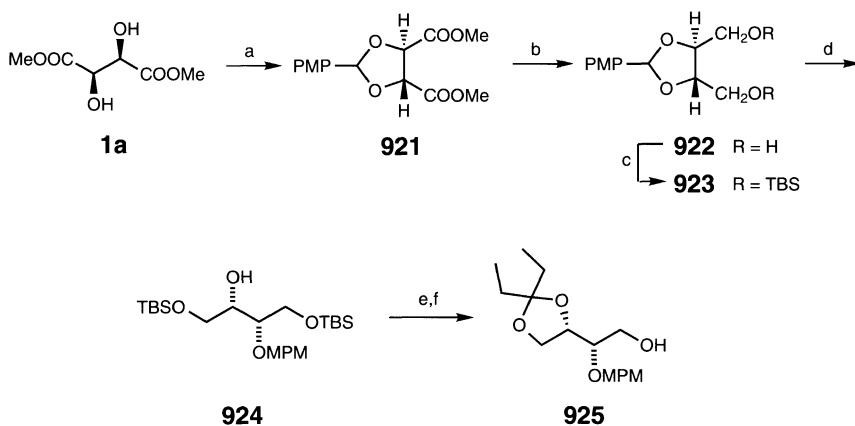
followed by debenzoylation using a catalytic-transfer hydrogenolysis affords in 76% yield the amino alcohol **920**. This undergoes ring closure by intramolecular displacement of the activated hydroxyl group followed by MOM-deprotection to give (1*S*,2*S*,8*aS*)-1,2-dihydroxy-indolizidine (**789**) or lentiginosine [256] (Scheme 199).

(2*S*,3*S*)-2-(4-methoxybenzyloxy)-3,4-*O*-(3-pentylidene)-1,3,4-butanetriol (**925**) is a versatile chiral building block readily prepared in large scale from dimethyl *L*-tartrate (**1a**). Treatment of **1a** with *p*-anisaldehyde dimethyl acetal in the presence of *p*-toluenesulfonic acid provides a nearly quantitative yield of **921**. Reduction of **921** with lithium aluminum hydride provides the diol **922**, which is protected as the TBS ether **923**. Initial attempts at a reductive cleavage of **921** with lithium aluminum hydride-aluminum chloride provided a mixture of products. Silyl protection prior to reductive cleavage of **923** to **924** with DIBAL in methylene chloride at -78 °C also avoids the water-soluble triol obtained if **922** is reductively cleaved. Subsequent treatment of **924** with CSA followed by addition of 3,3-dimethoxypentane in the presence of *p*-toluenesulfonic acid provides **925** in excellent yield. For large scale syntheses of **925** it is recommended that all chromatographic purifications be avoided [257] (Scheme 200).

The C-27 to C-36 fragment **928** of halichondrin B can be prepared from **925**, whereby an efficient acid-catalyzed C-glycosylation to generate the F ring is the key step. In four reac-

**Scheme 199**

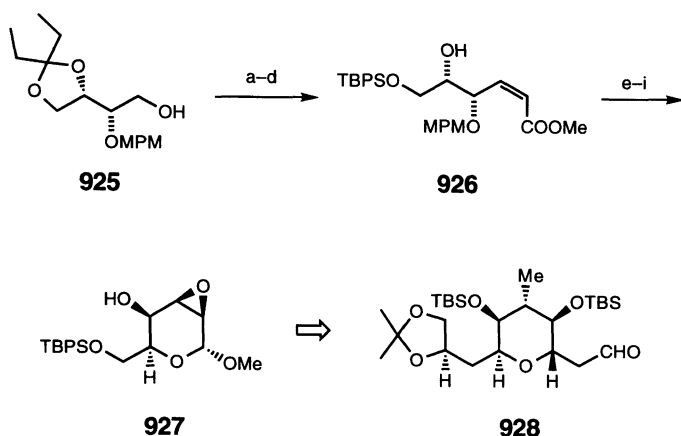
conditions: (a) $\text{PhCH}_2\text{O}(\text{CH}_2)_4\text{MgBr}$, THF (82%, 90% de); (b) chromatography; (c) H_2 , Raney-Ni; (d) HCONH_4 , Pd/C (76% 2 steps); (e) Ph_3P , CCl_4 , Et_3N , DMF (88%); (f) HCl, MeOH (91%)

**Scheme 200**

conditions: (a) $\text{PMPCH}(\text{OMe})_2$, TsOH, benzene, reflux (97%); (b) LiAlH_4 , THF, 0 °C (91%); (c) TBSCl, imidazole, DCM (87%); (d) DIBAL, DCM, -78 °C (87%); (e) CSA, MeOH, rt; (f) $\text{Et}_2\text{C}(\text{OMe})_2$, TsOH, benzene, rt (92% 2 steps)

tions, **925** is converted to **926**. Treatment of **926** with tosic acid provides an α,β -unsaturated lactone that is immediately reduced with DIBAL and methylated. MPM-deprotection, followed by a rigorous MCPBA oxidation, provides the epoxide **927**. This, following an epoxide ring opening with methylmagnesium chloride, is converted to the TBS ether, which is transformed in several steps into the C-27 to C-36 subunit **928** (Scheme 201). The TBS-ether protection step is essential for efficient C-glycosylation [258].

(+)-Altholactone (**933**), an unusual *cis*-fused tetrahydrofuran-2-pyrone independently isolated from an unnamed *Polyalthia* species as well as from *Goniothalamus giganteus*, is of synthetic interest due to its activity against P388 leukemia (*in vivo*) as well as its *in vitro*



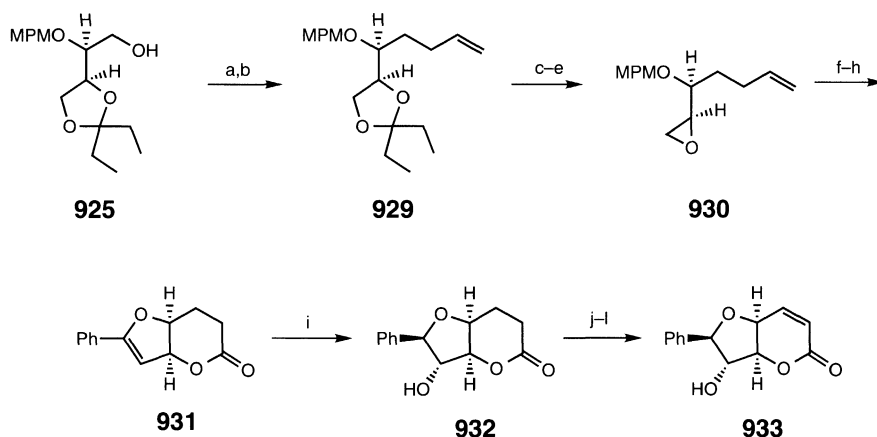
Scheme 201

conditions: (a) Swern [O], $-60\text{ }^{\circ}\text{C}$; (b) $(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(\text{O})\text{CH}_2\text{COOMe}$, 18-crown-6, $\text{KN}(\text{TMS})_2$, THF, $-78\text{ }^{\circ}\text{C}$ (90% 2 steps); (c) 1N HCl, MeOH; (d) TBPSCI, imidazole, DCM (94% 2 steps); (e) TsOH, benzene; (f) DIBAL, toluene, $-78\text{ }^{\circ}\text{C}$; (g) CSA, MeOH (86% 3 steps); (h) DDQ, DCM–MeOH, buffer (97%); (i) MCPBA, radical scavenger, DCM, reflux (74%)

cytotoxic activity. Tosylation of **925** followed by copper-catalyzed addition of allylmagnesium chloride provides the olefin **929** in 78% overall yield. This is deprotected, selectively tosylated at the primary hydroxyl position, and cyclized with potassium carbonate in methanol to provide epoxide **930**. Higher-order organocuprate addition to **930** followed by ozonolysis, MPM deprotection, and PCC oxidation without acetate buffer and acid-catalyzed elimination of the ketone hemiacetal affords the unstable dihydropyran **931**, which resists purification. However, hydroboration of **931** proceeds from the sterically less hindered α -face to furnish in good yield the alcohol **932**. This is converted in three steps to (+)-alcoholactone (**933**) [259] (Scheme 202).

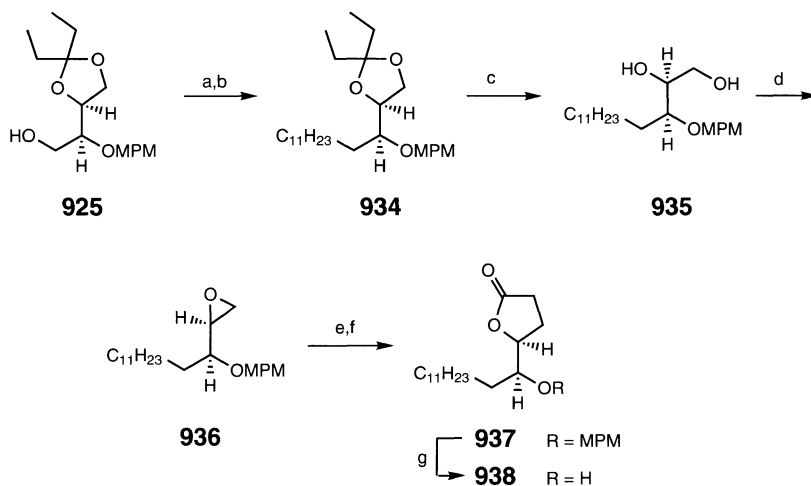
(+)-Muricatacin (**938**), an acetogenin-related γ -lactone recently isolated from the seeds of *Annona muricata*, possesses activity against various tumor cell lines. This has sparked a synthetic interest in the molecule. An enantiospecific total synthesis of **938** can be achieved conveniently utilizing **925**. The tosylate of **925** is subjected to a copper-catalyzed addition of undecylmagnesium bromide (freshly prepared) in THF at $-30\text{ }^{\circ}\text{C}$ to afford **934** in an overall yield of 82%. Dilute sulfuric acid unmasks the acetal protective group to furnish the diol **935** in 91% yield. Selective tosylation of the primary hydroxyl group followed by potassium carbonate cyclization in methanol furnishes the epoxide **936**, which is ring opened with the lithium anion of ethoxyacetylene to afford after hydrolysis and lactone formation the γ -lactone **937**. Oxidative deprotection with DDQ provides the final product **938** [260] (Scheme 203).

An organometallic approach to **938**, in which there is an acetylenic–vinylidene rearrangement of a chiral β -hydroxylactone without loss of stereochemical integrity, provides an interesting alternative to the synthesis of this natural product. Treatment of **40**, derived from **39**, with 2.2 equivalents of lithium acetylide–ethylenediamine complex provides crystalline diol **939** in 57% yield. However, this synthesis is problematic, because **40** is not easily prepared or isolated. A more practical route involves *in situ* generation of the bis-mesyate **39** and trapping with lithium acetylide–ethylenediamine complex to afford **939** in 87% overall



Scheme 202

conditions: (a) TsCl, pyridine (93%); (b) allylMgCl, CuI, $-30\text{ }^{\circ}\text{C}$, THF (84%); (c) H_2SO_4 , MeOH (96%); (d) TsCl, pyridine; (e) K_2CO_3 , MeOH (84% 2 steps); (f) 1-lithio-1-phenylethylene, CuCN, THF, $-78\text{ }^{\circ}\text{C}$ (87%); (g) O_3 , acetone, $-78\text{ }^{\circ}\text{C}$ then DMS; (h) PCC, DCM; (i) $\text{BH}_3\cdot\text{THF}$ then NaOH, H_2O_2 , H_2SO_4 (57–65% 3 steps); (j) TBPSOTf, pyridine, DCM (87%); (k) LDA, PhSeBr, THF, $-78\text{ }^{\circ}\text{C}$, then H_2O_2 , $\text{CH}_2\text{ClCH}_2\text{Cl}$, $60\text{ }^{\circ}\text{C}$ (79%); (l) Bu_4NF , THF (91%)

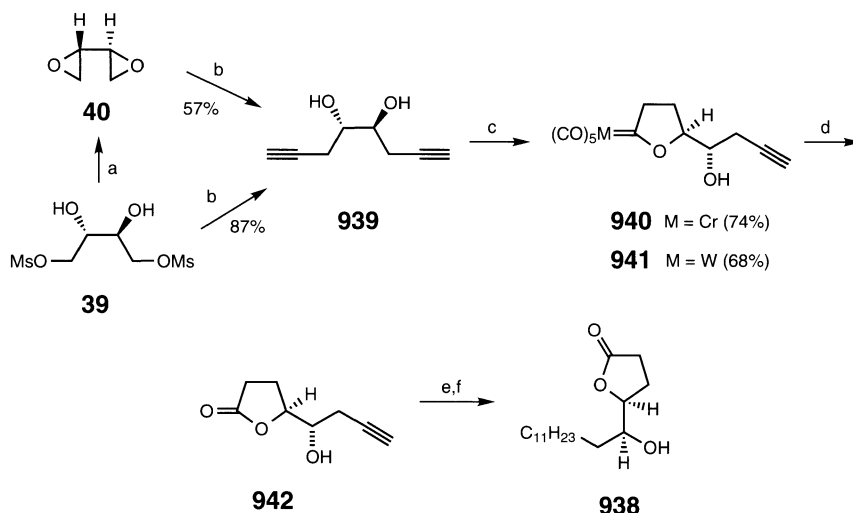


Scheme 203

conditions: (a) TsCl, pyridine; (b) $\text{C}_{11}\text{H}_{23}\text{MgBr}$, CuI, THF, $-30\text{ }^{\circ}\text{C}$ (82% 2 steps); (c) 2% aq. H_2SO_4 , MeOH (91%); (d) TsCl, pyridine then K_2CO_3 , MeOH (83%); (e) ethoxyacetylene, BuLi, THF, $-78\text{ }^{\circ}\text{C}$ (79%); (f) heat, xylenes (79%); (g) DDQ, DCM, water (89%)

yield and 95% *ee*. Treatment of **939** with a preformed solution of either pentacarbonyl chromium in THF or pentacarbonyl tungsten in THF generates the stable carbene complexes **940** and **941**, respectively. These complexes are oxidized with cerium ammonia nitrate to the γ -lactone **942** in good overall yields (68% and 74% respectively). The γ -lactone **942** is formed

in preference to any δ -lactone, and no protection of the hydroxy group is necessary. Final palladium coupling of **942** with 1-iodo-1-nonyne followed by catalytic reduction of the bis-acetylene provides **938** [261] (Scheme 204).



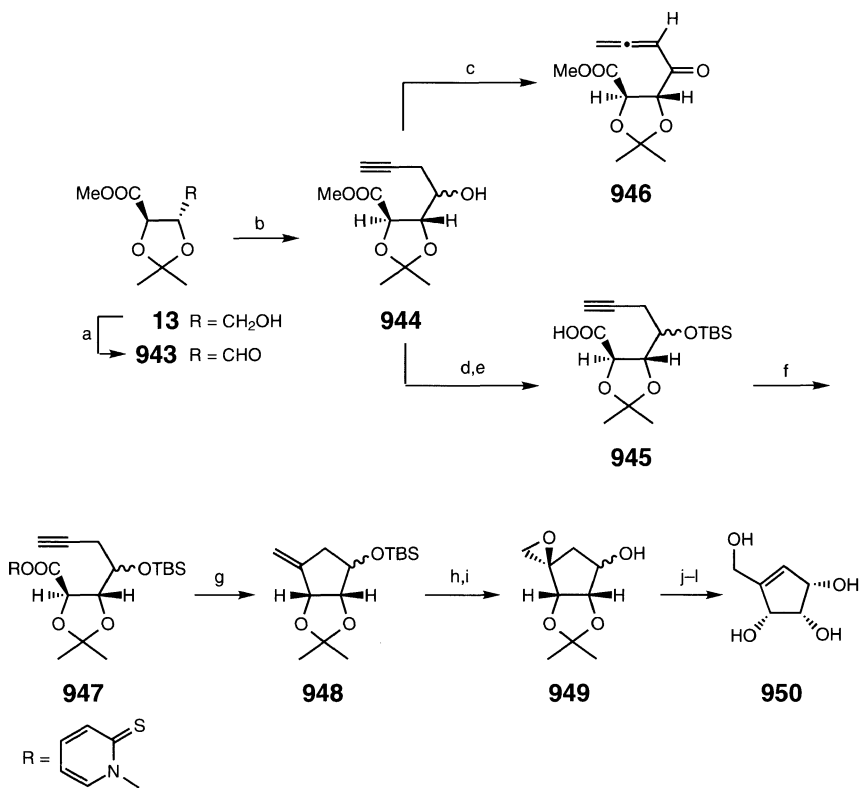
Scheme 204

conditions: (a) 2.2 equiv. KOH, ether, 20 °C (79%); (b) Lithium acetylide–EDA complex, THF–DMSO, (1:10), 0 °C; (c) Cr(CO)₅, THF, 20 °C or W(CO)₅, THF; (d) CAN, acetone, 20 °C; (e) 1-iodo-1-nonyne, (Ph₃P)₂PdCl₂ (3 mol%), DIPA, THF, 45 °C, (82%); (f) H₂, Pd/C, EtOAc, 20 °C, 16 h (94%)

Naturally occurring (1*S*,2*S*,3*R*)-4-hydroxymethylcyclopent-4-ene-1,2,3-triol (**950**) plays a central role in the ability of a non-aristeromycin producing mutant strain of *Streptomyces citricolor* to support production of both aristeromycin and neplanocin. Swern oxidation of readily available **13** from L-tartaric acid provides the aldehyde **943** which, when treated with an excess of propargyl zinc bromide, leads to a 2.3 : 1 diastereomeric mixture of acetylenic alcohols **944**. Silylation of the hydroxyl group with TBSOTf and subsequent saponification of the ester group yields the carboxylic acid **945** in 74% overall yield from **13**. Interestingly, Dess–Martin oxidation of **943** provides the allenic ketone **946**, which is unstable to base and cannot be used in the subsequent radical cyclizations.

Transformation of **945** into the thiohydroxamate ester **947** followed by visible-light photolysis in the presence of tributyltin hydride allows large scale preparation of the methylene cyclopentane **948**. The overall yield of **948** from **945** after chromatographic purification on silica gel is 55–65%. Desilylation of **948** and subsequent epoxidation of the exocyclic olefin with freshly prepared dimethyldioxirane solution provides the epoxyalcohol **949** in high yield. A Dess–Martin oxidation to the epoxyketone followed by rearrangement on silica gel to the enone, a Luche reduction from the convex face, and a final isopropylidene ketal hydrolysis provides **950** as a single diastereomer [262] (Scheme 205).

Chiral auxiliaries are particularly important in asymmetric synthesis. A bicyclic orthoester derived from dimethyl-L-tartrate (**1a**) provides a novel auxiliary with useful applications. Treating **1a** with phenylmagnesium bromide followed by reaction with methyl 2-methoxy-2,2-dichloroacetate (commercially available) affords in greater than 75% yield the methyl

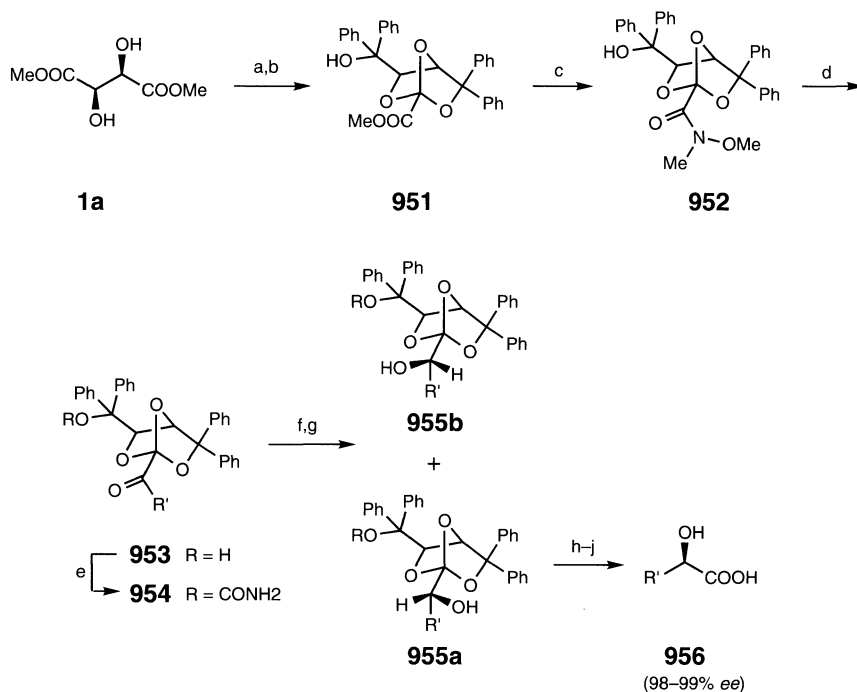


Scheme 205

conditions: (a) Swern [O]; (b) propargyl bromide, Zn/Hg, THF, rt; (c) Dess–Martin [O] (90%); (d) TBSOTf, DCM, 0 °C (74% from **13**); (e) LiOH, aq. THF (100%); (f) 2,2'-dithiobis(pyridine N-oxide), Bu₃P, THF, 0 °C to rt, 30 min.; (g) Bu₃SnH, (1.2 equiv.), slow addition, hv (55–65% 2 steps); (h) TBAF, THF (90–92%); (i) dimethyldioxirane, aq. acetone (88%); (j) Dess–Martin [O] (89%); (k) NaBH₄, CeCl₃·6H₂O, MeOH (86%); (l) aq. HCl, THF (83%)

ester **951**. The required ketones **953** are prepared by addition of an alkylmagnesium or aryllithium reagent to the corresponding *N,O*-dimethylamide **952**, prepared from **951** in good yield using the magnesium salt of *N,O*-dimethylhydroxylamine. Optimum selectivity in the asymmetric reduction of ketones **953** to the alcohols **955a** and **955b** is obtained with *L*-Selectride in THF at –78 °C. While bulky α -substituted ketones experience maximum stereoselection in the presence of the unprotected tertiary alcohol, selectivity decreases proportionately with the size of these α -substituents. On the other hand, diastereoselection in the reduction of the corresponding carbamate **954** is excellent for all ketones. The carbamate is easily removed with catalytic sodium ethoxide in ethanol. Following cleavage of the chiral auxiliary with mild aqueous trifluoroacetic acid in THF–methanol and lithium hydroxide saponification of the esters, the α -hydroxy acids **956** are obtained in 71–95% yields without any observed racemization [263] (Scheme 206).

D-erythro-Sphingosine (**961**) is an important component of all sphingolipids of the glyco-sphingolipid and phosphosphingolipid types. Glycosphingosines, as well as sphingosine



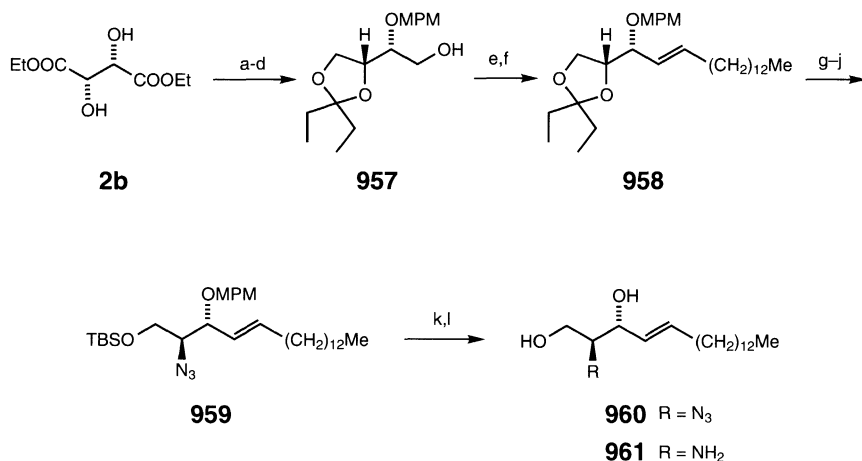
R'	ratio 955a : 955b
methyl	97:3
ethyl	>99:1
benzyl	>99:1
<i>iso</i> -propyl	>99:1
phenyl	>99:1
2-furyl	>99:1

Scheme 206

conditions: (a) PhMgBr (84%); (b) MeO(Cl)₂CCOOMe, pyridine (90%); (c) MeO(Me)NMgBr, THF, –78 °C; (d) R'MgX, or RLi, THF (83–92% 2 steps); (e) CCl₃CONCO then NH₃(g), MeOH (75–85%); (f) L-Selectride, THF, –78 °C; (g) NaOEt, EtOH (81–92% 2 steps); (h) Ac₂O, DMAP; (i) THF:MeOH:H₂O:TFA (4:4:1:0.1); (j) LiOH, THF (71–95% 2 steps)

itself, are important in cell–cell recognition and in signalling within and between cells. The enantiospecific formal synthesis of **960** from diethyl D-tartaric acid (**2b**) is an important utilization of **2b** for the introduction of the absolute stereochemistry present in **961**. A four-step sequence starting from **2b** is invoked for the preparation of acetal (*2R,3R*)-1,2-*O*-pentylidene-3-(4-methoxybenzyl)-1,2,3,4-butanetetrol (**957**), the enantiomer of **925**. Swern oxidation of **957** provides an aldehyde prone to epimerization, a problem overcome by subjecting the crude aldehyde to a Schlosser modification of the Wittig olefination to furnish **958** as a single isomer in 62% yield for the two steps. As an alternative, the Julia–Lythgoe olefination procedure affords low yields of **958** as an *E/Z* mixture of isomers. Mild acidic hydrolysis of

the acetal, selective protection of the primary hydroxyl group, mesylation of the free secondary hydroxyl group, and displacement with sodium azide affords the fully protected azidosphingosine derivative **959** in good overall yield. Oxidative cleavage of **959** with DDQ occurs without any concomitant oxidation of the allylic alcohol; desilylation then affords **960**, which has been previously converted to **961** [264,265]. Thus, this constitutes a formal synthesis of **961** [266] (Scheme 207).

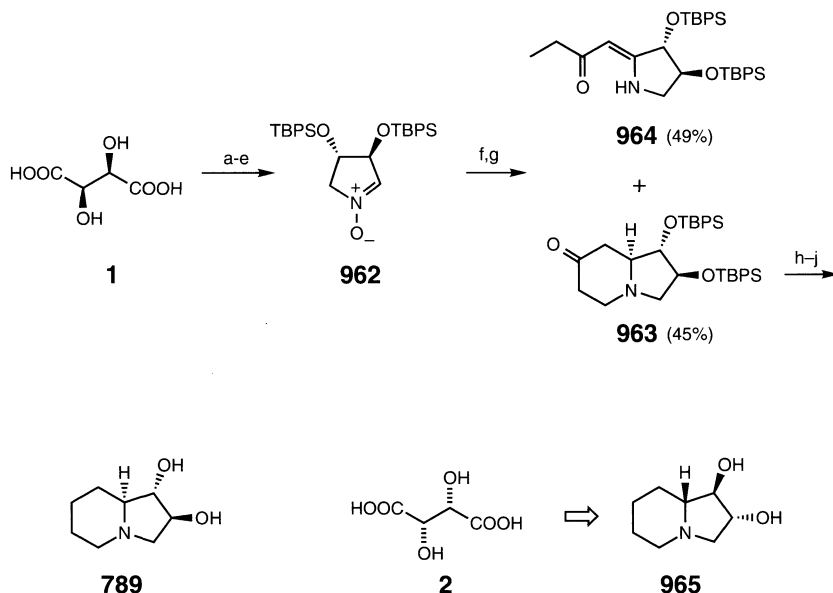


Scheme 207

conditions: (a) *p*-MeOC₆H₄CH(OMe)₂, TsOH, DMF (99%); (b) NaBH₄, LiCl, EtOH (100%); (c) BH₃•THF, reflux (94%); (d) 3-pentanone, TsOH, THF (89%); (e) Swern [O]; (f) Ph₃PCH₂(CH₂)₁₂MeBr, Ph Li, toluene, -30 °C then MeOH–water (62% 2 steps); (g) 2% aq. H₂SO₄, MeOH (93%); (h) TBSCl, Et₃N, DMAP, DCM (91%); (i) MsCl, pyridine, 0 °C; (j) NaN₃, 18-crown-6, DMF, 75 °C (87%); (k) DDQ, DCM–water (87%); (l) Bu₄NF, THF (94%)

Inhibitors of α -glucosidases are useful drugs for controlling non-insulin-dependent diabetes mellitus by preventing a rise in blood glucose. They are also interesting for their potential use in treating obesity and hyperlipoproteinemia. The need to discriminate between chiral antipodes of a particular enzyme inhibitor challenges the synthetic chemist to prepare these crucial enzyme substrates in a highly enantioselective manner. Lentiginosine exists as the (+)-(1*S*,2*S*,8*aS*)-form (**789**) as well as the (-)-(1*R*,2*R*,8*aR*)-form (**965**). The preparation of (+)-**789** from L-tartaric acid (**1**) and (-)-(**965**) from D-tartaric acid (**2**) via a highly stereo- and regioselective 1,3-dipolar cycloaddition is a marvelous example of the synthetic utility of these readily available natural chiral sources.

A five-step sequence starting from **1** provides (3*S*,4*S*)-3,4-bis[(*tert*-butyldiphenylsilyl)oxy]-1-pyrroline-*N*-oxide (**962**), which undergoes a 1,3-dipolar cycloaddition to methylenecyclopropane, followed by a thermal rearrangement of the adduct to provide (1*S*,2*S*,8*aS*)-1,2-[(*tert*-butyldiphenylsilyl)oxy]octahydroindolizidin-7-one (**963**) in modest yield. A competing 1,5-hydrogen-atom transfer followed by double-bond migration affords the enone **964** in 49% yield. Column chromatography easily separates these products. Reduction of the ketone in **963** via its tosylhydrazone followed by fluoride desilylation affords optically pure (+)-**789**. A similar sequence of reactions starting from **2** provides **965**, also in optically pure form (Scheme 208). Interestingly, with amyloglucosidase from *Aspergillus niger*, (+)-**789** is the most potent and specific competitive inhibitor among azasugars and their analogs [267].



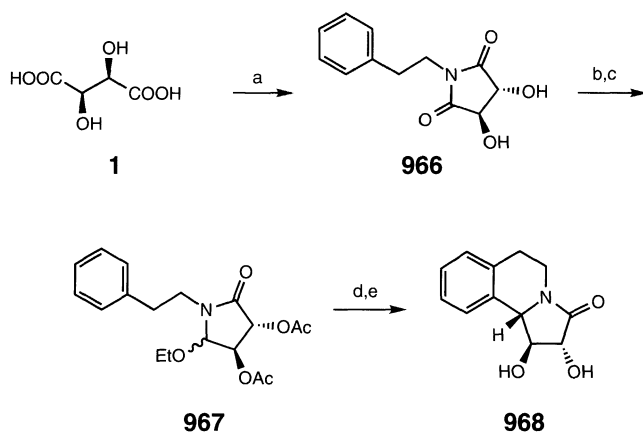
Scheme 208

conditions: (a) PhCH_2NH_2 ; (b) BF_3 , NaBH_4 ; (c) TBPSCl , imidazole, DMF (100%); (d) H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, MeOH (71%); (e) H_2O_2 , cat. SeO_2 , acetone (53%); (f) methylenecyclopropane, C_6H_6 , 35°C , sealed tube, 8 d (94% mixture); (g) xylene, reflux, 100 min. then separation; (h) TsNHNH_2 , sieves, MeOH, reflux; (i) NaBH_4 , MeOH (45% 2 steps); (j) MeCN–aqueous 40% HF (7:3), 46 h (85%)

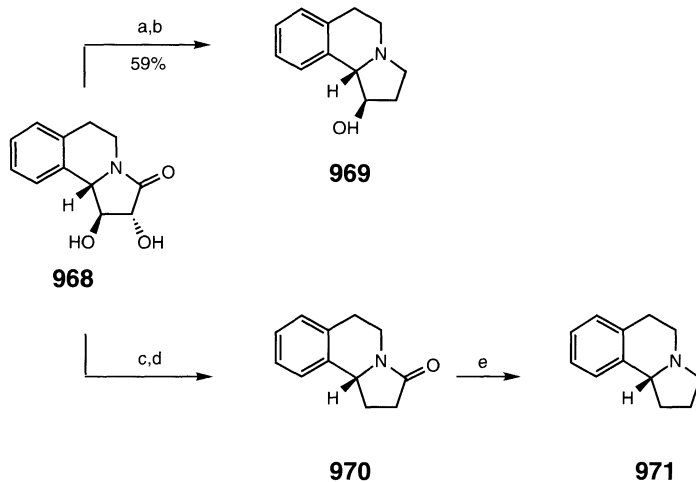
Pyrrolidinoisoquinoline alkaloids are abundant in plant products, and they exhibit interesting biological activity. The synthesis of isoquinolinopyrrolidinone **968** with complete stereocontrol of the ring juncture using an acyliminium ion cyclization illustrates the synthetic utility of L-tartaric acid in alkaloid synthesis. The chiral imide **966**, obtained in 84% yield by treating L-tartaric acid with phenethylamine in refluxing xylene, is reductively converted to the diastereomeric mixture of lactams **967** which undergoes an acid-catalyzed acyliminium ion cyclization to provide **968** as a single diastereomer. The efficiency of this cyclization is high and rapid if the free hydroxy groups in **967** are protected [268] (Scheme 209).

Regioselective tosylation of the less hindered C-2 hydroxyl group in **968** followed by reductive deoxygenation and lactam reduction with lithium aluminum hydride furnishes in 59% overall yield (+)-(1*R*,10*bS*)-1-hydroxy-1,2,3,5,6,10*b*-hexahydropyrrolo[2,1-*a*]isoquinoline (**969**). As a result of this steric hindrance, exploited for the preparation of **969**, the C-1 hydroxy group does not undergo tosylation, so it cannot be removed *via* this route. However, thioacylation of **968** followed by radical cleavage of the resulting thioester provides in moderate yields **970** which, after lithium aluminum hydride reduction of the lactam, affords (+)-(10*bR*)-1,2,3,5,6,10*b*-hexahydropyrrolo[2,1-*a*]isoquinoline (**971**). Interestingly, the optical antipodes of both **969** and **971** can be similarly prepared from readily available L-malic acid [269] (Scheme 210).

The total synthesis of (+)-bullatacin (**979**), a representative of potent antitumor *Annonaceous acetogenins*, and its stereoisomer, (+)-(15,24)-*bisepi*-bullatacin (**977**), from diethyl 2,3-*O*-isopropylidene-D-tartrate (**972**) illustrates the wonderful versatility of this remarkably simple chiral molecule. In a “one-pot” sequence of transformations involving DIBAL

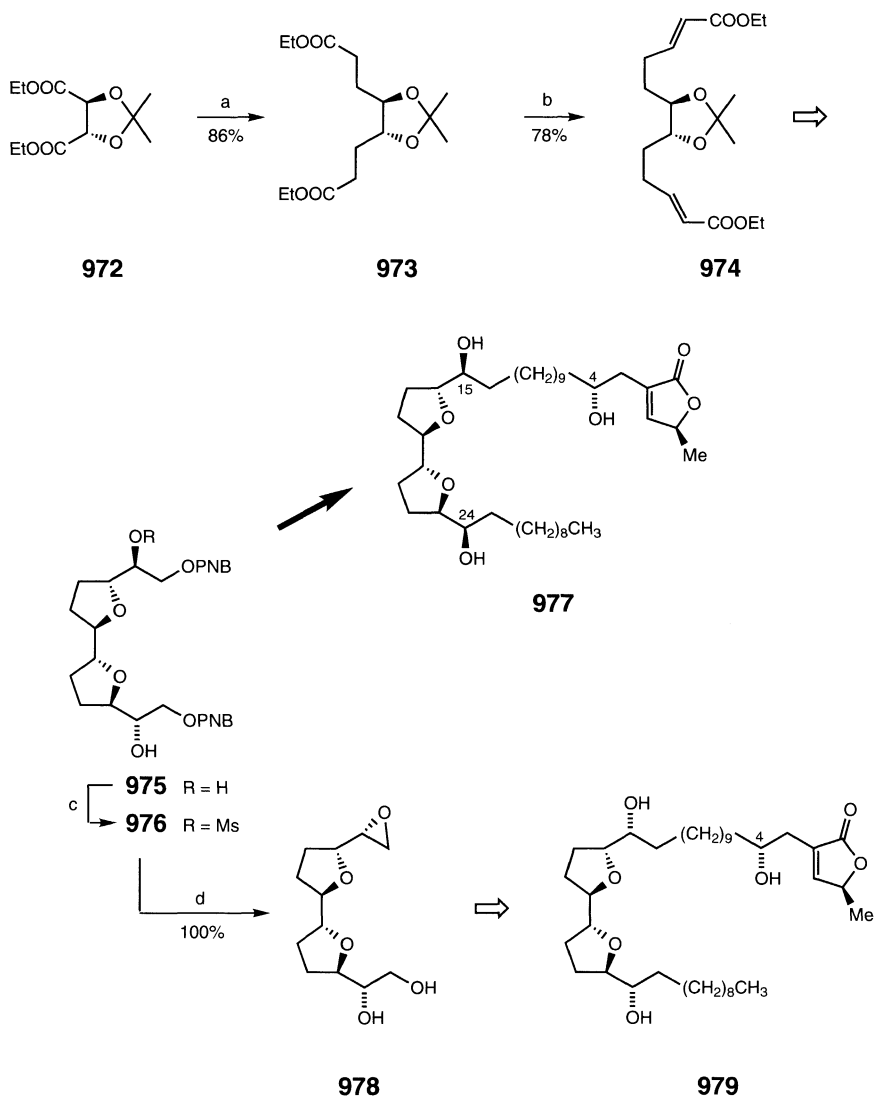
**Scheme 209**

conditions: (a) $\text{PhCH}_2\text{CH}_2\text{NH}_2$, refluxing xylene (84%); (b) NaBH_4 , EtOH then 1N H_2SO_4 , EtOH (88%); (c) Ac_2O , DMAP, DCM (100%); (d) HCOOH , reflux, 17 h; (e) AcCl , EtOH (90% 2 steps)

**Scheme 210**

conditions: (a) TsCl , DMAP, Et_3N , DCM (77%); (b) LiAlH_4 , THF (76%); (c) phenyl chlorothionoformate, DMAP, MeCN (41%); (d) $n\text{-Bu}_3\text{SnH}$, AIBN, toluene, reflux; (e) LiAlH_4 , THF (40% 2 steps)

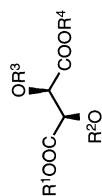
reduction at $-78\text{ }^{\circ}\text{C}$ to a dialdehyde followed by a Wittig–Horner olefination and finally a catalytic hydrogenation, **972** is converted to diethyl (+)-(4*R*,5*R*)-4,5-*O*-isopropylidene-4,5-dihydroxyoctanedioate (**973**) in 86% overall yield. The same sequence of reactions, but without catalytic reduction, performed on **973** provides the *trans,trans*-diester **974** in 78% purified yield. Subsequent reduction to a bis-allylic alcohol, Sharpless epoxidation using L-(+)-DIPT as the chiral ligand, then a series of transformations leading to the construction of the tetrahydrofuran rings, furnishes (–)-(2*S*,3*R*,6*R*,7*R*,10*R*,11*S*)-1,12-*O*-bis-(4-nitrobenzoyl)-3,6:7,10-diepoxy-1,2,11,12-tetrahydroxydodecane (**975**). This intermediate possesses the *erythro-trans-threo-trans-erythro* configuration and C_2 -symmetry. In order to prepare **979**, a stereochemical inversion at the C-15 or C-24 hydroxy groups in **975** is required. Monomesylation of **975** furnishes, after a three-fold repeat of the reaction on recovered starting material, **976** in 86% yield. Having the correct configuration present in **977**, **976** is efficiently converted, through a series of transformations, to (+)-(15,24)-*bisepi*-bullatacin (**977**). Hydrolysis of the PNB ester of **976** with tetrabutylammonium hydroxide in THF simultaneously forms the epoxide **978** with the desired *threo-trans-threo-trans-erythro* configuration present in **979**. The required (4*R*)-hydroxy group in both **977** and **979** is obtained *via* Brown's asymmetric allylation, and it possesses 92% *ee* (as determined by nmr). A series of transformations provides (+)-bullatacin (**979**). It is unclear what the final optical purities of **977** and **979** are [270] (Scheme 211).



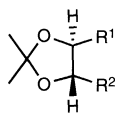
Scheme 211

conditions: (a) DIBAL, toluene, $-78\text{ }^{\circ}\text{C}$ then $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COOEt}$, NaH, DME, $-78\text{ }^{\circ}\text{C}$ to rt, followed by H_2 , 5% Pd/C, EtOH, rt; (b) DIBAL, toluene, $-78\text{ }^{\circ}\text{C}$ then $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COOEt}$, NaH, DME, $-78\text{ }^{\circ}\text{C}$ to rt; (c) MsCl, TEA, THF, $0\text{ }^{\circ}\text{C}$ (86%); (d) Bu_4NOH , THF, $0\text{ }^{\circ}\text{C}$

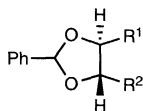
Table 4.1 Physical properties of L-(+)-tartaric acid derivatives



R ¹	R ²	R ³	R ⁴	[α] _D (°)	Solvent (c)	mp, °C or bp, °C (mmHg)	Reference
Me	H	Me	Me	+ 39	CHCl ₃ (1.07)	oil	147
Me	H	allyl	Me	+ 34.1	CHCl ₃ (1.28)	oil	147
Me	H	<i>p</i> -MeOC ₆ H ₄ CH ₂	Me	+ 84.0	CHCl ₃ (1.72)	oil	147
Me	H	<i>p</i> -NO ₂ C ₆ H ₄ CH ₂	Me	+ 68.1	CHCl ₃ (1.03)	74.5–75.5	147
Me	H	PhCH ₂	Me	+ 87.5	CHCl ₃ (1.17)	69–70	147
Et	Me	Me	Et	+ 84	neat	98 (0.012–0.013)	183
Et	Et	Et	Et	+ 93.5	neat	96–97 (0.6)	189
Et	<i>iso</i> -Pr	<i>iso</i> -Pr	Et	+ 49.3	neat	93–94 (0.1)	189
Et	PhCH ₂	PhCH ₂	Et	+ 79.5	neat	95–98 (0.03)	189
Et	MOM	MOM	Et	+ 142.7	neat	40–48 (1.2)	189
Me	Ac	Ac	H	–18.4	MeOH (1.57)	152–154 (0.6)	200
PhCH ₂	H	PhCH ₂	PhCH ₂	+ 59.9	MeOH (2.32)	124.7	216
H	Me	Me	H	+ 84	MeOH (1.1)	54.5–55.5	146, 147
H	Et	Et	H	+ 67.1	neat	154–156	183
					H ₂ O	125–126.5	192

Table 4.2 Physical properties of 2,3-*O*-isopropylidene-L-tartrate derivatives

R ¹	R ²	[α] _D (°)	Solvent (c)	mp, °C or bp, °C (mmHg)	Reference
COOMe	COOMe	− 49.4	neat	82–90 (0.02)	5
		− 53.7	neat	80 (0.1)	4
COOMe	COOH	− 53.3	MeOH (0.52)	75–80 (0.02)	4
COOMe	CH ₂ OH	− 19.2	MeOH (0.55)	80–85 (0.1)	4
COOMe	CH ₂ OMs	− 25.7	acetone (0.82)	100 (0.03)	4
COOMe	CH ₂ OTs	− 22.12	MeOH (0.68)	47–49	13
COOMe	COOTMS	− 53.7	THF (0.5)	65 (0.05)	7
COOEt	COOEt	− 48.8	neat	80 (0.05)	4
				85–96 (0.5)	5
CH ₂ OH	CH ₂ OH	+ 4.1	CHCl ₃ (5)	49.5–51	3
CH ₂ OH	CH ₂ OTs	− 12.2	CHCl ₃ (21.8)		34
CH ₂ OTs	CH ₂ OTs	− 12.4	CHCl ₃ (8.8)	90.5–92	5
CH ₂ OH	CH ₂ OCH ₂ Ph	+ 9	CHCl ₃ (0.99)		57
CHO	CH ₂ OCH ₂ Ph	+16.8	CHCl ₃ (1.10)	121 (0.4)	65
CH ₂ OH	CH ₂ OH	+17.6	CHCl ₃ (1.15)		93

Table 4.3 Physical properties of 2,3-*O*-benzylidene-L-tartrate derivatives

R ¹	R ²	[α] _D (°)	Solvent (c)	mp, °C or bp, °C (mmHg)	Reference
COOMe	COOMe	− 47.26	MeOH (1.02)	70–71	115, 117
CH ₂ OH	CH ₂ OH	+ 11.7	MeOH (2.14)	69.1– 69.4	117
CH ₂ OMs	CH ₂ OMs	− 14.85	acetone (1.98)	113.9– 114.6	117
Me	Me	+ 28.7	neat	65 (0.25)	117

References

1. R. A. Sheldon, *Chirotechnology: Industrial Synthesis of Optically Active Compounds*, Marcel Dekker Inc., New York, 1993, p. 2–3.
2. D. Seebach and E. Hungebuhler in *Modern Synthetic Methods*, vol. 2, R. Scheffold Ed., Otto Salle Verlag, Frankf./M., 1980, p. 91.
3. P. W. Feit, *J. Med. Chem.* **7**, 14 (1964).
4. J. A. Musich and H. Rapoport, *J. Am. Chem. Soc.* **100**, 4865 (1978).
5. M. Carmack and C. J. Kelley, *J. Org. Chem.* **33**, 2171 (1968).
6. E. A. Mash, K. A. Nelson, S. V. Deusen and S. B. Hemperly, *Org. Syn.* **68**, 92 (1989).
7. H. J. Bestmann and T. Moenius, *Angew. Chem. Int. Ed. Engl.* **25**, 994 (1986).
8. H. J. Bestmann and D. Roth, *Angew. Chem. Int. Ed. Engl.* **29**, 99 (1990).
9. H. J. Bestmann and D. Roth, *Synlett.*, 751 (1990).
10. J. Nokami, H. Matsuura, H. Takahashi and M. Yamashita, *Synlett.*, 491 (1994).
11. D. H. R. Barton, A. Gateau-Olesker, S. D. Gero, B. Lacher and C. Tachdjian, *J. Chem. Soc., Chem. Commun.*, 1790 (1987).
12. R. M. Ortuno, D. Alonso and J. Font, *Tetrahedron Lett.* **27**, 1079 (1986).
13. R. M. Ortuno, D. Alonso, J. Cardellach and J. Font, *Tetrahedron* **43**, 2191 (1987).
14. J. S. Yadav, S. V. Mysorekar and A. V. Rama Rao, *Tetrahedron* **45**, 7353 (1989).
15. D. S. Matteson, E. C. Beedle and A. A. Kandil, *J. Org. Chem.* **52**, 5034 (1987).
16. F. Toda and K. Tanaka, *Tetrahedron Lett.* **29**, 551 (1988).
17. O. De Lucchi, P. Maglioli, G. Delogu and G. Valle, *Synlett.*, 841 (1991).
18. S. Saito, S. Hamano, H. Moriyama, K. Okada and T. Moriwake, *Tetrahedron Lett.* **29**, 1157 (1988).
19. A. Krief, w. Dumont and P. Pasau, *Tetrahedron Lett.* **29**, 1079 (1988).
20. A. Krief, W. Dumont, P. Pasau and Ph. Lecomte, *Tetrahedron* **45**, 3039 (1989).
21. R. Naef and D. Seebach, *Angew. Chem. Int. Ed. Engl.* **20**, 1030 (1981).
22. Y. Tokunaga, H. Nagano and M. Shiota, *J. Chem. Soc., Perkin Trans. I*, 581 (1986).
23. J. J. Plattner and H. Rapoport, *J. Am. Chem. Soc.* **93**, 1758 (1971).
24. L. J. Rubin, H. A. Lardy and H. O. L. Fischer, *J. Am. Chem. Soc.* **74**, 425 (1952).
25. V. Schurig, B. Koppenhoefer and W. Buerkle, *J. Org. Chem.* **45**, 538 (1980).
26. S. Zhang, S. Zhang and R. Feng, *Tetrahedron: Asymmetry* **2**, 173 (1991).
27. P. J. Kocienski, S. D. A. Street, C. Yeates and S. F. Campbell, *J. Chem. Soc., Perkin Trans. I*, 2171 (1987).
28. K. Mori and S. Tamada, *Tetrahedron* **35**, 1279 (1979).
29. S. Bystrom, H.-E. Hogberg and T. Norin, *Tetrahedron* **37**, 2249 (1981).
30. H.-E. Hogberg, E. Hedenstrom, A.-B. Wassgren, M. Hjalmarsson, G. Bergstrom, J. Lofqvist and T. Norin, *Tetrahedron* **46**, 3007 (1990).
31. K. Ogura, M. Yamashita and G. Tsuchihashi, *Tetrahedron Lett.*, 759 (1976).
32. T. R. Hoye, P. R. Hanson, A. C. Kovelesky, T. D. Ocain and Z. Zhuang, *J. Am. Chem. Soc.* **113**, 9369 (1991).
33. J. Jurczak, R. Ostaszewski, G. D. Andreetti and G. Calestani, *Heterocycles* **31**, 397 (1990).
34. H. Meyer and D. Seebach, *Liebigs Ann. Chem.*, 2261 (1975).
35. S. Valverde, B. Herradon, R. M. Rabanal and M. Martin-Lomas, *Can. J. Chem.* **65**, 332 (1987).
36. Y. Yamamoto, K. Kobayashi, H. Okano and I. Kadota, *J. Org. Chem.* **57**, 7003 (1992).
37. R. M. Silverstein, R. G. Brownless, T. E. Bellas, D. L. Eood and L. E. Browne, *Science* **159**, 889 (1968).
38. H. H. Meyer, *Liebigs Ann. Chem.*, 732 (1977).
39. K. Mori and Y.-B. Seu, *Liebigs Ann. Chem.*, 205 (1986).
40. E. Abushanab, M. Bessodes and K. Antonakis, *Tetrahedron Lett.* **35**, 3841 (1984).
41. B. Achmatowicz and J. Wicha, *Liebigs Ann. Chem.*, 1135 (1988).
42. G. Fronza, C. Fuganti, P. Grasselli and G. Marinoni, *Tetrahedron Lett.* **40**, 3883 (1979).
43. G. Fronza, C. Fuganti and P. Grasselli, *Tetrahedron Lett.* **21**, 2999 (1980).
44. M. Uemura, K. Shimada and T. Tokuyama, *Tetrahedron Lett.* **23**, 4369 (1982).
45. D. A. Evans, M. D. Ennis and D. J. Mathre, *J. Am. Chem. Soc.* **104**, 1737 (1982).
46. S. Aoyagi, T. Wang and C. Kibayashi, *J. Am. Chem. Soc.* **114**, 10653 (1992).
47. J. Marco-Contelles, M. Bernabe, D. Ayala and B. Sanchez, *J. Org. Chem.* **59**, 1234 (1994).
48. W. R. Jackson and C. G. Lovel, *Aust. J. Chem.* **35**, 2069 (1982).
49. Y. Fujimoto, M. Satoh, N. Takeuchi and M. Kirisawa, *Chem. Lett.*, 619 (1989).
50. Y. Fujimoto, M. Satoh, N. Takeuchi and M. Kirisawa, *Chem. Pharm. Bull.* **38**, 1447 (1990).
51. H. Kotsuki, I. Kadota and M. Ochi, *Tetrahedron Lett.* **32**, 4609 (1990).
52. H. Kotsuki, I. Kadota and M. Ochi, *Tetrahedron Lett.* **30**, 3999 (1989).

53. H. Kotsuki, I. Kadota and M. Ochi, *J. Org. Chem.* **55**, 4417 (1990).
54. H. Kotsuki, A. Miyazaki, M. Ochi and J. J. Sims, *Bull. Chem. Soc. Jpn.* **64**, 721 (1991).
55. K. Mori and Y.-B. Seu, *Tetrahedron* **42**, 5901 (1986).
56. E. Hungerbuhler, D. Seebach and D. Wasmuth, *Angew. Chem Int. Ed. Engl.* **18**, 958 (1979).
57. E. Hungerbuhler and D. Seebach, *Helv. Chim. Acta* **64**, 687 (1981).
58. A. Fukuzawa, H. Sato, M. Miyamoto and T. Masamune, *Tetrahedron Lett.* **27**, 2901 (1986).
59. S. Takano, T. Sugihara, S. Satoh and K. Ogasawara, *J. Am. Chem. Soc.* **110**, 6467 (1988).
60. A. Fukuzawa, M. Aye, Y. Takaya, H. Fukui, T. Masamune and A. Murai, *Tetrahedron Lett.* **30**, 3665 (1989).
61. T. Yasukata, S. Sasaki and K. Koga, *Chem. Pharm. Bull.* **39**, 530 (1991).
62. T. Mukaiyama, Y. Goto and S.-I. Shoda, *Chem. Lett.*, 671 (1983).
63. Y. Kita, F. Itoh, O. Tamura and Y. Y. Ke, *Tetrahedron Lett.* **28**, 1431 (1987).
64. T. Mukaiyama, K. Suzuki and T. Yamada, *Chem. Lett.*, 929 (1982).
65. T. Mukaiyama, K. Suzuki, T. Yamada and F. Tabusa, *Tetrahedron* **46**, 265 (1990).
66. T. Mukaiyama, Y. Yuki and K. Suzuki, *Chem. Lett.*, 1169 (1982).
67. W.-L. Wu and Y.-L. Wu, *Tetrahedron Lett.* **33**, 3887 (1992).
68. G. Rassu, P. Spanu, G. Casiraghi and L. Pinna, *Tetrahedron* **47**, 8025 (1991).
69. T. Mukaiyama, T. Yamada and K. Suzuki, *Chem. Lett.*, 5 (1983).
70. F. Tabusa, T. Yamada, K. Suzuki and T. Mukaiyama *Chem. Lett.*, 405 (1984).
71. A. K. Saksena, R. G. Lovey, V. M. Girjavalabhan, A. K. Ganguly and A. T. McPhail, *J. Org. Chem.* **51**, 5024 (1986).
72. H. Kuzuhara and E. Emoto, *Tetrahedron Lett.*, 5051 (1973).
73. H. Kuzuhara, S. Ohrui and E. Emoto, *Tetrahedron Lett.*, 5055 (1973).
74. P.P. Waanders, L. Thijs and B. Zwanenburg, *Tetrahedron Lett.* **28**, 2409 (1987).
75. H. Sasai and M. Shibasaki, *Tetrahedron Lett.* **28**, 333 (1987).
76. K. Mori and T. Takeuchi, *Tetrahedron* **44**, 333 (1988).
77. A. V. Rama Rao, E. R. Reddy, B. V. Joshi and J. S. Yadav, *Tetrahedron Lett.* **28**, 6497 (1987).
78. B. Giese and R. Rupaner, *Synthesis*, 219 (1988).
79. J. S. Yadav, P. Satyanarayana Reddy and B. V. Joshi, *Tetrahedron* **44**, 7243 (1988).
80. M. Lopp, T. Kanger, A. Muraus, T. Pehk and U. Lille, *Tetrahedron: Asymmetry* **2**, 943 (1991).
81. S. Takano, M. Akiyama, T. Sugihara and K. Ogasawara, *Heterocycles* **33**, 831 (1992).
82. J. S. Yadav, M. C. Chander and B. V. Joshi, *Tetrahedron Lett.* **29**, 2737 (1988).
83. S. M. Hannick and Y. Kishi, *J. Org. Chem.* **48**, 3833 (1983).
84. K. Takahashi, T. Minami, Y. Ohara and T. Hiyama, *Tetrahedron Lett.* **34**, 8263 (1993).
85. T. Matsumoto, Y. Kobayashi, Y. Takemoto, Y. Ito, T. Kamijo, H. Harada and S. Terashima, *Tetrahedron Lett.* **29**, 4175 (1990).
86. Y. Kobayashi, T. Matsumoto, Y. Takemoto, K. Nakatani, Y. Ito, T. Kamijo, H. Harada and S. Terashima, *Chem. Pharm. Bull.* **39**, 2550 (1990).
87. G. Casiraghi, G. Rassu, P. Spanu, L. Pinna and F. Ulgheri, *J. Org. Chem.* **58**, 3397 (1993).
88. S. Mio, R. Ichinose, K. Goto, S. Sugai and S. Sato, *Tetrahedron Lett.* **47**, 2111 (1991).
89. N. Cohen, B. L. Banner, R. J. Lopresti, F. Wong, M. Rosenberger, Y. Liu, E. Thom and A. A. Liebman, *J. Am. Chem. Soc.* **105**, 3661 (1983).
90. A. P. Craven, H. J. Dyke and E. J. Thomas, *Tetrahedron* **45**, 2417 (1989).
91. B. Gosse-Kobo, P. Mosset and R. Gree, *Tetrahedron Lett.* **30**, 4235 (1989).
92. J. A. Marshall, S. Beaudoin and K. Lewinski, *J. Org. Chem.* **58**, 5876 (1993).
93. J. A. Marshall and S. Beaudoin, *J. Org. Chem.* **59**, 6614 (1994).
94. J. A. Marshall and S. Beaudoin, *J. Org. Chem.* **59**, 7833 (1994).
95. E. Fischer, *Liebigs Ann. Chem.* **288**, 150 (1895).
96. W. D. MacLay, R. M. Hann and C. S. Hudson, *J. Amer. Chem. Soc.* **60**, 1035 (1938).
97. H. Iida, N. Yamazaki and C. Kibayashi, *J. Org. Chem.* **52**, 3337 (1987).
98. H. Ina and C. Kibayashi, *J. Org. Chem.* **58**, 52 (1993).
99. S. Aoyagi, S. Fujimaki, N. Yamazaki and C. Kibayashi, *Heterocycles* **30**, 783 (1990).
100. S. Aoyagi, S. Fujimaki, N. Yamazaki and C. Kibayashi, *J. Org. Chem.* **56**, 815 (1991).
101. R. Nagata, M. Kawakami, T. Matsuura and I. Saito, *Tetrahedron Lett.* **30**, 2817 (1989).
102. J. Huguet and M. Carmen Reyes, *Tetrahedron Lett.* **31**, 4279 (1990).
103. O. W. Gooding, C. C. Beard, D. Y. Jackson, D. L. Wren and G. F. Cooper, *J. Org. Chem.* **56**, 1083 (1991).
104. T. Kanger, M. Liiv, T. Pehk and M. Lopp, *Synthesis*, 91 (1993).
105. N. Ono, Y. Kawanaka, Y. Yoshida and F. Sato, *J. Chem. Soc., Chem. Commun.*, 1251 (1994).
106. M. C. DiGiovanni, D. Misiti, G. Zappia and G. D. Monache, *Tetrahedron* **49**, 11321 (1993).
107. T. Sunazuka, T. Nagamitsu, H. Tanaka, S. Omura, P. A. Spengler and A. B. Smith III, *Tetrahedron Lett.* **34**, 4447 (1993).

108. M. J. Miller, *Acc. Chem. Res.* **19**, 49 (1986).
109. A. Golebiowski and J. Jurczack, *Synlett.*, 241 (1993).
110. F. Matsuura, Y. Hamada and T. Shioiri, *Tetrahedron Lett.* **50**, 265 (1994).
111. A. Dondoni, S. Franco, F. Junquera, F. Merchan, P. Merino and T. Tejero, *Syn. Commun.* **24**, 2537 (1994).
112. A. Dondoni, S. Franco, F. L. Merchan, P. Merino and T. Tejero, *Tetrahedron Lett.* **34**, 5475 (1993).
113. A. Dondoni, F. Junquera, F. L. Merchan, P. Merino and T. Tejero, *Tetrahedron Lett.* **33**, 4221 (1992).
114. A. Dondoni, F. Junquera, F. L. Merchan, P. Merino and T. Tejero, *Synthesis*, 1450 (1994).
115. K. Fujita, H. Nakai, S. Kobayashi, K. Inoue, S. Nojima and M. Ohno, *Tetrahedron Lett.* **23**, 3507 (1982).
116. R. M. Wenger, *Helv. Chim. Acta* **66**, 2308 (1983).
117. P. Kocienski and S. D. A. Street, *Syn. Commun.* **14**, 1087 (1984).
118. R. M. Wenger, *Angew. Chem. Int. Ed. Engl.* **24**, 77 (1985).
119. J.-O. Durand and J.-P. Genet, *Bull. Soc. Chim. Fr.* **131**, 612 (1994).
120. H. Tanaka, A. Kuroda, H. Marusawa, H. Hatanaka, T. Kino, T. Goto, M. Hashimoto and T. Taga, *J. Am. Chem. Soc.* **109**, 5031 (1987).
121. M. Stocks, P. Kocienski and D. K. Donald, *Tetrahedron Lett.* **31**, 1637 (1990).
122. D. Seebach and E. Hungerbuhler, *Modern Synthetic Methods*, vol. 2, R. M. Wenger, ed., Salle and Saurlander, Frankf./M., 1980, pp. 113–171.
123. A. Takle and P. Kocienski, *Tetrahedron* **46**, 4503 (1990).
124. A. H. Al-Hakim, A. H. Haines and C. Morley, *Synthesis*, 207 (1985).
125. M. Ohno, K. Fujita, H. Nakai, S. Kobayashi, K. Inoue and S. Nojima, *Chem. Pharm. Bull.* **33**, 572 (1985).
126. H. Miyazaki, N. Ohkawa, N. Kakamura, T. Ito, T. Sada, T. Oshima and H. Koike, *Chem. Pharm. Bull.* **37**, 2379 (1989).
127. H. Miyazaki, N. Nakamura, T. Ito, T. Sada, T. Oshima and H. Koike, *Chem. Pharm. Bull.* **37**, 2391 (1989).
128. M. Ohno, K. Fujita, M. Shiraiwa, A. Izumi, S. Kobayashi, H. Yoshiwara, I. Kudo, K. Inoue and S. Nojima, *J. Med. Chem.* **29**, 1812 (1986).
129. M. Ito and C. Kibayashi, *Tetrahedron Lett.* **35**, 5065 (1990).
130. M. Ito and C. Kibayashi, *Tetrahedron* **47**, 9329 (1991).
131. A. K. Ghosh, S. P. McKee, H. Y. Lee and W. J. Thompson, *J. Chem. Soc., Chem. Commun.*, 273 (1992).
132. A. D. Backstrom, R. Austin, S. McMordie and T. P. Begley, *J. Carbohydrate Chem.* **14**, 171 (1995).
133. S. Takano, A. Kurotaki, Y. Sekiguchi, S. Satoh, M. Hiramata and K. Ogasawara, *Synthesis*, 811 (1986).
134. V. Jager and V. Wehner, *Angew. Chem. Int. Ed. Engl.* **28**, 469 (1989).
135. J. A. Marshall and G. Luke, *Synlett.*, 1007 (1992).
136. R. Muller, T. Leibold, M. Patzel and V. Jager, *Angew. Chem. Int. Ed. Engl.* **33**, 1295 (1994).
137. T. Franz, M. Hein, U. Veith, V. Jager, E.-M. Peters, K. Peters and H. G. von Schnering, *Angew. Chem. Int. Ed. Engl.* **33**, 1298 (1994).
138. F. Carreaux, A. Dureault and J. C. Depezay, *Synlett.*, 527 (1992).
139. A. Gateau-Olesker, J. Cleophax and S. D. Gero, *Tetrahedron Lett.* **27**, 41 (1986).
140. G. Adam and D. Seebach, *Synthesis*, 373 (1988).
141. S. Valverde, B. Herradon and M. Martin-Lomas, *Tetrahedron Lett.* **26**, 3731 (1985).
142. D. R. Williams and F. D. Klinger, *Tetrahedron Lett.* **28**, 869 (1987).
143. K. Lorenz and F. D. Lichtenthaler, *Tetrahedron Lett.* **28**, 6437 (1987).
144. H. Kotsuki, H. Nishikawa, Y. Mori and M. Ochi, *J. Org. Chem.* **57**, 5036 (1992).
145. K. Furuata, Q. Gao and H. Yamamoto, *Org. Syn.* **72**, 86 (1993).
146. R. Wagner, J. W. Tilley and K. Lovey, *Synthesis*, 785 (1990).
147. N. Nagashima and M. Ohno, *Chem. Pharm. Bull.* **39**, 1972 (1991).
148. T. Iimori, S. D. Erickson, A. L. Rheingold and W. C. Still, *Tetrahedron Lett.* **30**, 6947 (1989).
149. T. Mukaiyama, Y. Goto and S. Shoda, *Chem. Lett.*, 671 (1983).
150. K. Shishido, K. Takahashi, Y. Oshio, K. Fukumoto, T. Kametani and T. Honda, *Heterocycles* **27**, 495 (1988).
151. I. Felner and K. Schenker, *Helv. Chim. Acta* **53**, 754 (1970).
152. K. Shishido, K. Takahashi, Y. Oshio, K. Fukumoto, T. Kametani and T. Honda, *Tetrahedron Lett.* **27**, 1339 (1986).
153. K. Shishido, K. Takahashi, K. Fukumoto, T. Kametani and T. Honda, *J. Org. Chem.* **52**, 5704 (1987).
154. B. K. Vriesema, M. Lemaire, J. Buter and R. M. Kellogg, *J. Org. Chem.* **51**, 5169 (1986).
155. Y. Masaki, Y. Serizawa, K. Nagata and K. Kaji, *Chem. Lett.*, 1601 (1983).
156. Y. Masaki, K. Nagata and K. Kaji, *Chem. Lett.*, 1835 (1983).
157. Y. Masaki, K. Nagata, Y. Serizawa and K. Kaji, *Tetrahedron Lett.* **25**, 95 (1984).
158. Y. Masaki, K. Nagata, Y. Serizawa and K. Kaji, *Tetrahedron Lett.* **23**, 5523 (1982).
159. Y. Masaki, Y. Serizawa, K. Nagata, H. Oda, H. Nagashima and K. Kaji, *Tetrahedron Lett.* **27**, 231 (1986).
160. Y. Masaki, T. Imaeda, K. Nagat, H. Oda and A. Ito, *Tetrahedron Lett.* **30**, 6395 (1989).
161. Y. Masaki, T. Imaeda, H. Oda, A. Itoh and M. Shiro, *Chem. Lett.*, 1209 (1992).

162. K. C. Nicolaou, D. P. Papahatjis, D. A. Claremon and R. E. Dolle, III, *J. Am. Chem. Soc.* **103**, 6967 (1981).
163. K. C. Nicolaou, D. P. Papahatjis, D. A. Claremon, R. L. Magolda and R. E. Dolle, *J. Org. Chem.* **50**, 1440 (1985).
164. K. C. Nicolaou, R. A. Daines, J. Uenishi, W. S. Li, D. P. Papahatjis and T. K. Chakraborty, *J. Am. Chem. Soc.* **109**, 2205 (1987).
165. K. C. Nicolaou, R. A. Daines, J. Uenishi, W. S. Li, D. P. Papahatjis and T. K. Chakraborty, *J. Am. Chem. Soc.* **110**, 4672 (1988).
166. J. K. Whitesell, *J. Org. Chem.* **42**, 1663 (1977).
167. D. Tanner and C. Birgersson, *Tetrahedron Lett.* **32**, 2533 (1991).
168. F. Hosono, S. Nishiyama, S. Yamamura, T. Izawa, K. Kato and Y. Terada, *Tetrahedron* **50**, 13335 (1994).
169. S. Saito, T. Ishikawa, A. Kuroda, K. Koga and T. Moriwake, *Tetrahedron* **48**, 4067 (1992).
170. E. Hungerbuhler, D. Seebach and D. Wasmuth, *Helv. Chim. Acta* **64**, 1467 (1981).
171. H. Wynberg and G. J. Staring, *J. Amer. Chem. Soc.* **104**, 166 (1982).
172. S. Henrot, M. Larcheveque and Y. Petit, *Chem. Soc., Perkin Trans. I Synth. Commun.* **16**, 183 (1986).
173. M. Alpegiani and S. Hanessian, *J. Org. Chem.* **52**, 278 (1987).
174. K. Kusuda, J. Inanaga and Y. Yamaguchi, *Tetrahedron Lett.* **30**, 2945 (1989).
175. Y. Gao and K. B. Sharpless, *J. Am. Chem. Soc.* **110**, 7538 (1988).
176. B. M. Kim and K. B. Sharpless, *Tetrahedron Lett.* **30**, 655 (1989).
177. T. G. Hansson and J. O. Kihlberg, *J. Org. Chem.* **51**, 4490 (1986).
178. A. G. M. Barrett and S. Sakadarat, *J. Org. Chem.* **55**, 5110 (1990).
179. Y. Gao and C. M. Zepp, *Tetrahedron Lett.* **32**, 3155 (1991).
180. S.-K. Kang, S.-G. Kim and J.-S. Lee, *Tetrahedron: Asymmetry* **3**, 1139 (1992).
181. S.-K. Kang, D.-C. Park, J.-H. Jeon, H.-S. Rho and C.-M. Yu, *Tetrahedron Lett.* **35**, 2357 (1994).
182. S.-K. Kang, D.-H. Lee, H.-S. Sim and J.-S. Lim, *Tetrahedron Lett.* **34**, 91 (1993).
183. I. Felner and K. Schenker, *Helv. Chim. Acta* **53**, 755 (1970).
184. K. Mori, *Tetrahedron* **30**, 4223 (1974).
185. K. Mori, T. Takigawa and M. Matsui, *Tetrahedron Lett.*, 3953 (1976).
186. C. R. Young, *J. Chem. Soc.* **105**, 1228 (1914).
187. B. P. Wijnberg and W. N. Speckamp, *Tetrahedron Lett.* **21**, 1987 (1980).
188. J. Ohwada, Y. Inouye, M. Kimura and H. Kakisawa, *Bull. Chem. Soc. Jpn.* **63**, 287 (1990).
189. H.-O. Kalinowski, G. Crass and D. Seebach, *Chem. Ber.* **114**, 477 (1981).
190. D. Seebach, H.-O. Kalinowski, B. Bastani, G. Crass, H. Daum, H. Dorr, N. P. DuPreez, V. Ehrig, W. Langer, C. Nussler, H.-A. Oei and M. Schmidt, *Helv. Chim. Acta* **60**, 301 (1977).
191. D. Seebach, H.-O. Kalinowski, W. Langer, G. Crass and E.-M. Wilka, *Organic Synthesis* **61**, 24 (1983).
192. K. Naemura, Y. Kanda, M. Yamanaka and H. Chikamatsu, *Chem. Lett.*, 283 (1989).
193. G. Uray, W. Lindner and F. Reiter, *Synthesis*, 194 (1989).
194. N. Ikota and A. Hanaki, *Heterocycles* **22**, 2227 (1984).
195. N. Ikota, *Chem. Pharm. Bull.* **38**, 1601 (1990).
196. C. J. Flann and L. E. Overman, *J. Am. Chem. Soc.* **109**, 6115 (1987).
197. J. A. Marshall and G. P. Luke, *J. Org. Chem.* **56**, 483 (1991).
198. N. Ikemoto and S. L. Schreiber, *J. Am. Chem. Soc.* **114**, 2524 (1992).
199. H. Iida, N. Yamazaki and C. Kibayashi, *Tetrahedron Lett.* **26**, 3255 (1985).
200. H. Iida, N. Yamazaki and C. Kibayashi, *J. Org. Chem.* **51**, 1069 (1986).
201. H. Iida, Y. Yamazaki and C. Kibayashi, *J. Org. Chem.* **51**, 3769 (1986).
202. H. Iida, N. Yamazaki and C. Kibayashi, *J. Org. Chem.* **51**, 4245 (1986).
203. K. Shishido, Y. Sukegawa, K. Fukumoto and T. Kametani, *J. Chem. Soc., Perkin Trans. I*, 993 (1987).
204. N. Yamazaki and C. Kibayashi, *J. Am. Chem. Soc.* **111**, 1396 (1989).
205. N. Yamazaki and C. Kibayashi, *Tetrahedron Lett.* **29**, 5767 (1988).
206. T. Kaseda, T. Kikuchi and C. Kibayashi, *Tetrahedron Lett.* **30**, 4539 (1989).
207. H. Tanino, H. Takakura, H. Kakoi, K. Okada and S. Inoue, *Heterocycles* **38**, 971 (1994).
208. S. Kuwahara, M. Moriguchi, K. Miyagawa, M. Konno and O. Kodama, *Tetrahedron Lett.* **36**, 3201 (1995).
209. P. Schnurrenberger, E. Hungerbuhler and D. Seebach, *Liebigs Ann. Chem.*, 733 (1987).
210. H.-J. Altenbach and W. Holzappel, *Angew. Chem. Int. Ed. Engl.* **29**, 67 (1990).
211. S. Saito, Y. Hirohara, O. Narahara and T. Moriwake, *J. Am. Chem. Soc.* **111**, 4533 (1989).
212. S. Saito, O. Narahara, T. Ishikawa, M. Asahara, T. Moriwake, J. Gawronski and F. Kazmierczak, *J. Org. Chem.* **58**, 6292 (1993).
213. S. Saito, Y. Morikawa and T. Moriwake, *J. Org. Chem.* **55**, 5424 (1990).
214. J. A. Marshall and S. Beaudoin, *J. Org. Chem.* **59**, 7833 (1994).
215. S. Saito, T. Ishikawa, N. Kishimoto, T. Kohara and T. Moriwake, *Synlett.*, 282 (1994).
216. H. J. Lucas and W. Baumgarten, *J. Am. Chem. Soc.* **63**, 1653 (1941).
217. T. Kolasa and M. J. Miller, *Tetrahedron Lett.* **28**, 1861 (1987).

218. T. Kolasa and M. J. Miller, *Tetrahedron* **45**, 3080 (1989).
219. T. Teramoto, M. Deguchi, T. Kurosaki and M. Okawara, *Tetrahedron Lett.* **22**, 1109 (1981).
220. G. P. Liesen and C. N. Suenik, *J. Org. Chem.* **52**, 455 (1987).
221. J. M. Denner, D. J. Hart and S. Ramesh, *J. Org. Chem.* **53**, 6022 (1988).
222. J.-L. Reymond and P. Vogel, *Tetrahedron: Asymmetry* **1**, 729 (1990).
223. J.-L. Reymond and P. Vogel, *J. Chem. Soc., Chem. Commun.*, 1070 (1990).
224. H. Yoda, K. Shirakawa and K. Takabe, *Chem. Lett.*, 489 (1991).
225. H. Yoda, K. Shirakawa and K. Takabe, *Tetrahedron Lett.* **32**, 3401 (1991).
226. H. Yoda, T. Katagiri and K. Takabe, *Tetrahedron Lett.* **32**, 6771 (1991).
227. U. Nagel, E. Kinzel, J. Andrade and G. Prescher, *Chem. Ber.* **119**, 3326 (1986).
228. R. Ballini, E. Marcantoni and M. Petrini, *J. Org. Chem.* **57**, 1316 (1992).
229. S. Cicchi, I. Hold and A. Brandi, *J. Org. Chem.* **58**, 5274 (1993).
230. Y. Arakawa and S. Yoshifuji, *Chem. Pharm. Bull.* **39**, 2219 (1991).
231. S. Takano, Y. Sugihara and K. Ogasawara, *Heterocycles* **34**, 1519 (1992).
232. H. Yoda, H. Kitayama, W. Yamada, T. Katagiri and K. Takabe, *Tetrahedron: Asymmetry* **4**, 1451 (1993).
233. H. Yoda, H. Kitayama, T. Katagiri and K. Takabe, *Tetrahedron: Asymmetry* **4**, 1455 (1993).
234. J. F. Almeida, M. Grande, J. R. Moran, J. Anaya, M. L. Mussons and M. C. Caballero, *Tetrahedron: Asymmetry* **4**, 2483 (1993).
235. U. Nagel, E. Kinzel, J. Andrade and G. Pescher, *Chem. Ber.* **119**, 3326 (1986).
236. Y. Ryu and G. Kim, *J. Org. Chem.* **60**, 103 (1995).
237. L. Duhamel, T. Herman and P. Angibaud, *Syn. Commun.* **22**, 735 (1992).
238. R. K. Boeckman, Jr. Ed. *Org. Synthesis* **73**, 184 (1995).
239. S. Saito, N. Bunya, M. Inaba, T. Moriwake and S. Tori, *Tetrahedron Lett.* **26**, 5309 (1985).
240. K. Mori and H. Iwasaw, *Tetrahedron* **36**, 87 (1980).
241. K. Mori and T. Kinsho, *Liebigs Ann. Chem.*, 1309 (1991).
242. D. Tanner, C. Birgerisson and H. K. Dhaliwal, *Tetrahedron Lett.* **31**, 1903 (1990).
243. A. Korn, S. Rudolph-Bohner and L. Moroder, *Tetrahedron* **50**, 8381 (1994).
244. E. J. Corey, A. Marfat and D. J. Hoover, *Tetrahedron Lett.* **22**, 1587 (1981).
245. S. Saito, Y. Nagao, M. Miyazaki, M. Inaba and T. Moriwake, *Tetrahedron Lett.* **27**, 5249 (1986).
246. S. Saito, T. Hasegawa, M. Inaba, R. Nishida, T. Fujii, S. Nomizu and T. Moriwake, *Chem Lett.*, 1389 (1984).
247. P. S. Manchand, K.-C. Luk, P. S. Belica, S. C. Choudhry, C. C. Wei and M. Soukup, *J. Org. Chem.* **53**, 5507 (1988).
248. S. Kishimoto, M. Sendai, S. Hashiguchi, M. Tomimoto, Y. Satoh, T. Matsuo, M. Kondo and M. Ochiai, *J. Antibiot.* **36**, 1421 (1983).
249. M. Sendai, S. Hashiguchi, M. Tomimoto, S. Kishimoto, T. Kondo and M. Ochiai, *J. Antibiot.* **38**, 346 (1985).
250. J. Soulie and J. Y. Lallemand, *Tetrahedron: Asymmetry* **6**, 625 (1995).
251. Z.-J. Yao and Y.-L. Wu, *J. Org. Chem.* **60**, 1170 (1995).
252. K. Narkunan and M. Nagarajan, *J. Org. Chem.* **59**, 6386 (1994).
253. S. F. Martin, H.-J. Chen and V. M. Lynch, *J. Org. Chem.* **60**, 276 (1995).
254. E. Lee, C. M. Park and J. S. Yun, *J. Am. Chem. Soc.* **117**, 8017 (1995).
255. J. Shimada, H. J. Kwon, M. Sawamura and S. L. Schreiber, *Current Biology* **2**, 517 (1995).
256. R. Giovannini, E. Marcantoni and M. Petrini, *J. Org. Chem.* **60**, 5706 (1995).
257. K. Horita, Y. Sakurai, S. Hachiya, M. Nagasawa and O. Yonemitsu, *Chem. Pharm. Bull.* **42**, 683 (1994).
258. K. Horita, Y. Sakurai, M. Nagasawa, S. Hachiya and O. Yonemitsu, *Synlett.*, 43 (1994).
259. P. Somfai, *Tetrahedron* **50**, 11315 (1994).
260. P. Somfai, *J. Chem. Soc., Perkin Trans I*, 817 (1995).
261. P. Quayle, S. Rahman and J. Herbert, *Tetrahedron Lett.* **36**, 8087 (1995).
262. F. E. Ziegler and P. G. Harra, *Synlett.*, 493 (1995).
263. D. Dube, D. Deschenes, J. Tweddell, H. Gagnon and R. Carlini, *Tetrahedron Lett.* **36**, 1827 (1995).
264. R. R. Schmidt and P. Zimmermann, *Angew. Chem. Int. Ed. Engl.* **25**, 725 (1988).
265. P. Zimmermann and R. R. Schmidt, *Liebigs Ann. Chem.*, 663 (1988).
266. P. Somfai and R. Olsson, *Tetrahedron* **49**, 6645 (1993).
267. A. Brandi, S. Cicchi, F. M. Cordero, R. Frignoli, A. Goti, S. Picasso and P. Vogel, *J. Org. Chem.* **60**, 6806 (1995).
268. Y. S. Lee, D. W. Kang, S. J. Lee and H. Park, *Syn. Commun.* **25**, 1947 (1995).
269. Y. S. Lee, D. W. Kang, S. J. Lee and H. Park, *J. Org. Chem.* **60**, 7149 (1995).
270. H. Naito, E. Kawahara, K. Maruta, M. Maeda and S. Sasaki, *J. Org. Chem.* **60**, 4419 (1995).

Appendix A Protection of Functional Groups

"Naked" group	Protected group	Conditions	Structure	Page		
1,2-diol	acetonide	DMP, CSA, benzene	504	396		
		DMP, CSA, acetone	556	77		
		DMP, CuSO ₄ , PTSA (cat), acetone	1031	293		
		DMP, PPTS	141	187		
		acetone, PTSA	985	288		
		acetone, HClO ₄	1031	293		
		acetone, CuSO ₄	1031	293		
		acetone, PTSA	141	187		
		CH ₂ =CHOCH ₃ , PPTS	141	187		
		CONH	CONAc	Ac ₂ O, pyridine, DMAP	817	268
CONH	CONBoc	Boc ₂ O, Et ₃ N, DMAP, CH ₂ Cl ₂	830	269		
COOH	COOCH ₂ Ph	PhCH ₂ Br, Et ₃ N, DMF	746	260		
NH	NBoc	Boc ₂ O, Et ₃ N, CH ₂ Cl ₂	801	266		
NH ₂	NHAc	Ac ₂ O, pyridine, DMAP	667	251		
NH ₂	NHBoc	Boc ₂ O, dioxane	30	174		
NH ₂	NHCbz	Cbz-Cl, NaHCO ₃ , acetone	965	127		
		Cbz-Cl, MgO, H ₂ O	441	224		
		Cbz-Cl, 4M, NaOH, 0 °C	901	279		
		Cbz-Cl, dioxane, 1N NaOH	267	204		
		Cbz-Cl, Na ₂ CO ₃ , H ₂ O	300	364		
		Cbz-Cl, Et ₃ N, THF	1142	305		
		N-Cbz-succinimide, DMF	746	260		
		NH ₂	NHCOPh	PhCOCl, NaHCO ₃	719	99
		NH	NTBS	TBS-Cl, Et ₃ N, CH ₂ Cl ₂	762	104
		OH	OAc	Ac ₂ O, DMAP, CH ₂ Cl ₂	967	469
CH ₃ COCl	222			32		
CH ₃ COCl, pyridine	935			282		
Ac ₂ O, DMAP, pyridine, THF	423			221		
Ac ₂ O, DMAP, pyridine, CH ₂ Cl ₂ , 0 °C	428			222		
Ac ₂ O, DMAP, pyridine	748			260		
Ac ₂ O, DMAP, pyridine	825			269		
Ac ₂ O, pyridine	6			169		
Ac ₂ O, pyridine	611			245		
TMS-Cl, Ac ₂ O, 85 °C	19			317		
OH	OBoc	2-[[(<i>tert</i> -Butoxycarbonyl)oxy]- imino]-2-phenylacetoneitrile, THF, Bu ₃ SnH, THF, 40 °C	375	216		
		OH	OBOM	BOM-Cl, <i>iso</i> -Pr ₂ NEt, CH ₂ Cl ₂	282	39
BOM-Cl, NaH, THF, DMF	590	82				
BOM-Cl, <i>iso</i> -Pr ₂ NEt	278	205				
BOM-Cl, <i>iso</i> -Pr ₂ NEt	283	206				

(continued)

"Naked" group	Protected group	Conditions	Structure	Page		
OH	OC(Me) ₂ OCH ₃	CH ₂ =C(CH ₃)OCH ₃ , POCl ₃ , CH ₂ Cl ₂	11	170		
		CH ₂ =C(OCH ₃) ₂ , POCl ₃ , hexane	85	328		
		CH ₂ =C(CH ₃)OCH ₃ , PPTS	335	211		
OH	OCbz	Cbz-Cl, pyridine, THF	737	259		
OH	OCH ₂ Ph	PhCH ₂ Br, NaH, DMF	137	186		
		PhCH ₂ Br, NaH, DMF	141	337		
		PhCH ₂ Br, NaH, Bu ₄ NI, 18-crown-6, THF	312	366		
		PhCH ₂ Br, NaH, THF	554	238		
		PhCH ₂ Br, KOH, toluene	332	369		
		PhCH ₂ Br, KH, THF	1005	290		
		PhCH ₂ Br, Ag ₂ O, ether	271	38		
		PhCH ₂ Br, Ag ₂ O, ether	928	124		
		PhCH ₂ Br, Ag ₂ O, EtOAc	7	169		
		PhCH ₂ Cl, NaH, THF, 0 °C	465	67		
		PhCH ₂ Cl, NaH, DMF, 40 °C	860	116		
		PhCH ₂ Cl, NaH, DMF	658	251		
		Cl ₃ C(NH)OCH ₂ Ph, CF ₃ COOH (cat)	271	38		
		Cl ₃ C(NH)OCH ₂ Ph, CF ₃ COOH	7	169		
		Cl ₃ C(NH)OCH ₂ Ph, CF ₃ COOH	305	208		
		OH	OCOCCl ₃	(Cl ₃ CCO) ₂ O, dioxane, 75 °C	735	433
				PhCOCl, pyridine	733	100
OH	OCOPh	PhCOCl, pyridine	881	455		
		PhCOCl, pyridine, CH ₂ Cl ₂	145	187		
		PhCOCl, Et ₃ N, CH ₂ Cl ₂	491	230		
		PhCOCN, Et ₃ N, CH ₂ Cl ₂ , 0 °C	705	255		
		CH ₂ =CHOEt, PTSA	683	426		
		CH ₂ =CHOEt, 36% HCl	310	43		
OH	OEE	CH ₂ =CHOEt, PPTS	11b	45		
		CH ₂ =CHOEt, PPTS, CH ₂ Cl ₂	348	47		
		CH ₂ =CHOEt, PPTS, CH ₂ Cl ₂	9	169		
		CH ₂ =CHOEt, PPTS, CH ₂ Cl ₂	648	249		
		CH ₂ =CHOEt, CF ₃ COOH	414	220		
		MEM-Cl, <i>iso</i> -Pr ₂ NEt, CH ₂ Cl ₂ , 0 °C	372	49		
		MEM-Cl, <i>iso</i> -Pr ₂ NEt, CH ₂ Cl ₂	376	51		
OH	OMOM	MEM-Cl, Et ₃ N, CH ₃ CN	92	181		
		MOM-Cl, <i>iso</i> -Pr ₂ NEt, CH ₂ Cl ₂	377	51		
		MOM-Cl, <i>iso</i> -Pr ₂ NEt, CH ₂ Cl ₂	391	53		
		MOM-Cl, <i>iso</i> -Pr ₂ NEt, CH ₂ Cl ₂	71	179		
		MOM-Cl, <i>iso</i> -Pr ₂ NEt, CHCl ₃	623	416		
		MOM-Cl, <i>iso</i> -Pr ₂ NEt, DMAP, CH ₃ CN, -3 °C	723	257		
		CH ₂ (OCH ₃) ₂ , P ₂ O ₅	377	51		

"Naked" group	Protected group	Conditions	Structure	Page		
OH	OMPM	4-CH ₃ OC ₆ H ₄ CH ₂ Br, NaH, THF	231	352		
		MPM-Cl, NaH, DMSO/THF (4 : 3)	742	259		
OH	Ot-Bu	isobutylene, H ₂ SO ₄	28	174		
OH	OTBPS	TBPS-Cl, imidazole, THF	427	59		
		TBPS-Cl, imidazole, DMF	299	208		
		TBPS-Cl, imidazole, DMF	507	232		
		TBPS-Cl, Et ₃ N, DMAP, CH ₂ Cl ₂	507	232		
		TBPS-Cl, DBU, CH ₂ Cl ₂	507	232		
		TBPS-Cl, Et ₃ N, DMAP, CH ₂ Cl ₂	719	257		
		TBPS-Cl, Et ₃ N, DMAP, CH ₂ Cl ₂	1001	289		
		TBPS-Cl, Et ₃ N, THF, AgNO ₃ (1.5 eq)	65	179		
		TBPS-Cl, HMPA, pyridine, CH ₂ Cl ₂ , 0 °C	79	180		
		OH	OTBS	TBS-Cl, imidazole, DMF	689	427
				TBS-Cl, NaH, THF	770	439
				TBSOTf, 2,6-lutidine, CH ₂ Cl ₂ , rt, 2 h	1103	302
				TBSOTf, 2,6-lutidine, CH ₂ Cl ₂	278	360
				TBSOTf, 2,6-di- <i>tert</i> -butyl-4- methylpyridine, CH ₂ Cl ₂ , 0 °C	34	143
				TBS-Cl, imidazole, DMF	401	55
				TBS-Cl, imidazole, DMF	284b	206
TBS-Cl, imidazole, DMF	456			226		
TBS-Cl, Et ₃ N, DMAP, THF	401			55		
TBS-Cl, Et ₃ N, DMAP, CH ₂ Cl ₂ , 0 °C	71			179		
OH	OTES	TBS-Cl, Et ₃ N, DMAP, CH ₂ Cl ₂	389	217		
		TBS-Cl, Et ₃ N, DMAP, DMF	673	251		
		TBS-Cl, Et ₃ N, DMAP, CH ₂ Cl ₂	389	222		
		TBS-Cl, Et ₃ N, DMAP, CH ₂ Cl ₂	782	263		
OH	OTHP	Et ₃ SiOTf, 2,6-lutidine, CH ₂ Cl ₂	29	142		
OH	OTHP	Et ₃ SiCl, DMF, 0 °C	118	185		
		DHP, PPTS, CH ₂ Cl ₂	251	35		
OH	OTHP	DHP, PPTS, CH ₂ Cl ₂	794	108		
		DHP, PTSA, CH ₂ Cl ₂ , 0 °C	289	207		
		DHP, PTSA, CH ₂ Cl ₂	89	150		
		DHP, PTSA, ether	10	169		
		DHP, PTSA, ether	442	224		
		DHP, PTSA, ether	988	288		
		DHP, 12N HCl	450	62		
		DHP, conc HCl	10	169		
		DHP, Amberlyst-15, hexane	390	217		
		OH	OTIPS	TIPS-triflate, <i>iso</i> -Pr ₂ NEt, CH ₂ Cl ₂ , 0 °C	166	190
OH	OTMS	HMDSH, TMSCl	12	170		

(continued)

"Naked" group	Protected group	Conditions	Structure	Page
OH	OTr	TrCl, DBU, CH ₂ Cl ₂	463	64
		TrCl, pyridine, CH ₂ Cl ₂	101	182
		tritylpyridinium tetrafluoroborate, CH ₃ CN	774	262

Appendix B Protective Group Removal

Protected group	“Naked” group	Conditions	Structure	Page
CONCH ₂ Ph acetoneide	CONH	Na/NH ₃ , –78 °C	838	270
	1,2-diol	CF ₃ COOH-H ₂ O (9 : 1)	558	77
		CF ₃ COOH	442	224
		CF ₃ COOH	116	333
		CF ₃ COOH, THF/H ₂ O	1005	290
		HOAc	748	260
		70% HOAc, 40 °C	410	381
		PPTS, MeOH	456	226
		PPTS, MeOH, 45 °C	602	244
		PTSA, MeOH	145	187
		0.1N HCl, MeOH	49	322
		1N HCl, THF	718	257
		2N HCl, MeOH	693	254
		6N HCl, THF	358	373
		1M H ₂ SO ₄	538	235
		Amberlite IR120(H ⁺) resin, MeOH	673	251
		Amberlyst-15, MeOH	713	256
		Amberlyst-15, CH ₂ Cl ₂	215	349
		Dowex 50WX8 resin, MeOH	551	404
		CuCl ₂ ·2H ₂ O, EtOH	1002	289
N-Cbz	NH	H ₂ (350 kPa), 10% Pd/C, EtOH	445	224
	NH	CAN, CH ₃ CN/H ₂ O, –10 °C	576	80
N-DAM	NH	CAN, CH ₃ CN/H ₂ O, 0 °C	753	104
N-PMP	NH	CAN, CH ₃ CN/H ₂ O, 0 °C	820	111
		CAN, CH ₃ CN, –5 °C	762	104
		CAN, CH ₃ CN, –20 °C	762	104
		CAN, CH ₃ CN	1143	305
NCH ₂ Ph	NH	H ₂ , Pd(OH) ₂ /C, MeOH	810	445
		H ₂ (480 kPa), Pd/C, EtOH/HOAc	800	266
		Na/NH ₃ , –78 °C	829	269
NCOCF ₃	NH	KOH, MeOH	448	224
NBoc	NH	CF ₃ COOH, CH ₂ Cl ₂	669	424
NTBS	NH	Bu ₄ NF, HOAc/THF	804	108
NHBoc	NH ₂	4N HCl, dioxane	32	174
		HCl, <i>iso</i> -PrOH	951	284
NHCbz	NH ₂	H ₂ (1 atm), 10% Pd/C, water	806	108
		H ₂ , Pd/C	751	260
		H ₂ , Pd black	903	279
NHDAM	NH ₂	H ₂ , 5% Rh/Al ₂ O ₃ , HOAc	126	156
NPh _t	NH ₂	N ₂ H ₄ ·H ₂ O, EtOH	500	232
OAc	OH	NaOCH ₃ , MeOH	793	442
		NaOEt, EtOH	810	267
		CH ₃ COCl, EtOH	750	436
		CH ₃ COCl, EtOH	968	469

(continued)

Protected group	“Naked” group	Conditions	Structure	Page
		MeOH, DMAP	726	432
		MeOH, PTSA, reflux	732	433
		LiOH, THF/MeOH/H ₂ O	266	37
		LiAlH ₄ , THF (reflux)	799	266
OBOM	OH	H ₂ (1 atm), 10% Pd/C, MeOH	302	42
		Li/NH ₃ , THF, aniline	593	83
		Li/NH ₃	280b	205
		Li/NH ₃ , -78 °C	285	206
OC(Me) ₂ OCH ₃	OH	5% HCl	423	221
OCH ₂ Ph	OH	H ₂ (0.3 MPa), 10% Pd/C, MeOH	864	116
		10% Pd/C, cyclohexene, EtOH, reflux	151	160
		HCONH ₄ , Pd/C	920	461
		H ₂ , 10% Pd/C, EtOAc, HCl (cat)	533	235
		H ₂ , Pd/C, MeOH	350	372
		H ₂ (1 atm), Pd(OH) ₂ , THF	503	71
		H ₂ , Pd(OH) ₂ /C, EtOAc	432	384
OCOCCL ₃	OH	H ₂ O, rt, 18 h	736	433
OCOPh	OH	K ₂ CO ₃ , MeOH	882	455
OCOt-Bu	OH	6N HCl, 50 °C	966	286
OEE	OH	30% H ₂ SO ₄ , MeOH	260	86
		96% H ₂ SO ₄ , MeOH	312	43
		PPTS, EtOH	330	46
		PPTS, EtOH	356	48
		PPTS, MeOH	373	216
		1M HCl, dioxane	360	49
		2N HCl, THF/H ₂ O (5 : 2)	370	215
		2N HCl, THF	406	219
		HOAc/H ₂ O/THF (3 : 1 : 1)	622	87
		Amberlyst-15, THF/H ₂ O (98 : 2)	957	127
OMEM	OH	catechol boron bromide, CH ₂ Cl ₂	2	50
OMOM	OH	EtSH, BF ₃ ·Et ₂ O, CH ₂ Cl ₂	639	418
		HCl, THF/EtOH	76	179
OMPM	OH	DDQ, CH ₂ Cl ₂ -H ₂ O	743	259
		DDQ, CH ₂ Cl ₂ -H ₂ O (17 : 1)	234	352
		DDQ, CH ₂ Cl ₂ -H ₂ O	938	463
		DDQ, CH ₂ Cl ₂ -H ₂ O	960	467
OTBPS	OH	Bu ₄ NF, THF	442	61
		Bu ₄ NF, THF	93	181
		48% HF-CH ₃ CN, CH ₂ Cl ₂ (5 : 95)	306	208
OTBS	OH	conc. HF-CH ₃ CN (1 : 20 v/v), rt	9	138
		Et ₄ NCl, KF-H ₂ O, CH ₃ CN	693	427
		HOAc/THF/H ₂ O	423	58
		HOAc/THF/H ₂ O (1 : 1 : 1)	720	100
		1N HCl, MeOH	691	96
		Bu ₄ NF, THF	787	107
		KF, Bu ₄ NF, THF	830	269

Protected group	“Naked” group	Conditions	Structure	Page
		HF, THF	322	366
		CSA, MeOH	925	461
OTES	OH	5% aq HOAc, THF	120	185
OTHP	OH	PTSA, MeOH	861	116
		PTSA, MeOH	984	288
		CH ₃ SO ₃ H, EtOH, 50 °C	419	221
		5% HCl, acetone/MeOH	401	222
OTIPS	OH	Bu ₄ NF, THF	169	190
		2N HCl- EtOH (1 : 3), reflux, 15 min	1087	300
OTr	OH	CF ₃ COOH, CH ₂ Cl ₂	104	182

Appendix C Functional Group Manipulation (Sorted by Product Group)

From	To	Conditions	Structure	Page		
COOH	Br	HgO, Br ₂ , CCl ₄	273	204		
OH	Br	BBr ₃ , CH ₂ Cl ₂ , -70 °C	227	351		
		HBr, HOAc	39	5		
		HBr, HOAc	387	217		
		Ph ₃ P, CBr ₄ , CH ₂ Cl ₂ , 0 °C	66	179		
		Ph ₃ P, CBr ₄ , CH ₂ Cl ₂	454	225		
		Ph ₃ P, CBr ₄ , CH ₂ Cl ₂ , rt, 30 min	1090	300		
		Ph ₃ P, NBS	454	225		
		Ph ₃ P, Br ₂ , Et ₃ N	284	39		
		MsCl, Et ₃ N, then LiBr, acetone, rt, 1 h	454b	303		
		OMs	Br	LiBr, THF	866	116
OTHP	Br	HBr, HOAc	429	222		
OTs	Br	LiBr, acetone	901	279		
		LiBr, acetone	91	329		
		LiBr, NaHCO ₃ , acetone	433	222		
		LiBr, NaHCO ₃ , acetone	924	281		
		LiBr, THF	454	225		
		conc. HCl then CuBr	401	219		
		LiBr, CuBr, NaHCO ₃ , acetone	415	220		
		CHOH	C=O	MnO ₂ , NaOAc, CHCl ₃	524	234
		CHOH	C=O	PCC, 3 Å molecular sieves, CH ₂ Cl ₂	623	247
		CN	CH ₂ NH ₂	H ₂ , PtO ₂ , EtOH	19	172
CONH ₂	CH ₂ NH ₂	LiAlH ₄ , THF (reflux)	29	174		
		B ₂ H ₆ , THF (reflux)	900	279		
C=C	CH ₂ OH	O ₃ , CH ₂ Cl ₂ , MeOH, -78 °C, NaBH ₄	844	113		
CH ₃	CH ₂ OH	SeO ₂ , HOAc/Ac ₂ O (1 : 1)	869	274		
CHO	CH ₂ OH	NaBH ₄ , EtOH	864	273		
COOCH ₃	CH ₂ OH	LiAlH ₄ , ether	152	188		
		LiAlH ₄ , ether, 0 °C	371	215		
		LiAlH ₄ , THF	853	272		
		DIBAL, CH ₂ Cl ₂ , -78 °C	66	179		
		DIBAL, THF, 0 °C	776	106		
		LiAlH ₄ , ether	311	43		
COOEt	CH ₂ OH	LiAlH ₄ , ether	451	63		
		LiAlH ₄ , THF	934	282		
		BMS, THF (reflux)	930	282		
		BMS, (CH ₃ O) ₃ B, THF	370	215		
		B ₂ H ₆ , THF	234	200		
COOH	CH ₂ OH	O ₃ , CH ₂ Cl ₂ , -78 °C	814	110		
		O ₃ , CH ₂ Cl ₂ , -60 °C	888	118		
		O ₃ , CH ₂ Cl ₂ , -78 °C	137	186		
		O ₃ , CH ₂ Cl ₂ , -78 °C	181	24		

From	To	Conditions	Structure	Page
CH ₂ OH	CHO	O ₃ , MeOH, -78 °C	872	274
		(COCl) ₂ , DMSO, CH ₂ Cl ₂ , -65 to -70 °C	606	85
		(COCl) ₂ , DMSO, CH ₂ Cl ₂ , -78 °C	260	203
		(COCl) ₂ , DMSO, CH ₂ Cl ₂	587	242
		(COCl) ₂ , DMSO, CH ₂ Cl ₂	590	242
		(COCl) ₂ , DMSO	760	261
		(COCl) ₂ , DMSO	780	263
		(COCl) ₂ , DMSO, CH ₂ Cl ₂ , Et ₃ N	93	329
		(COCl) ₂ , DMSO	1010	291
		PCC, CH ₂ Cl ₂	464	66
		PCC, NaOAc, Celite, CH ₂ Cl ₂	503	71
		PCC, CH ₂ Cl ₂	132	237
		PCC, 4 Å molecular sieves, CH ₂ Cl ₂	105	182
		PCC, NaOAc, CH ₂ Cl ₂	986	288
		PCC-Al ₂ O ₃ , NaOAc, CH ₂ Cl ₂	424	384
		PDC, CH ₂ Cl ₂	307	208
		PDC, 3 Å molecular sieves, CH ₂ Cl ₂	590	242
		(Cl ₃ CO) ₂ O, DMSO, CH ₂ Cl ₂ , -78 °C	689	96
		(Cl ₃ CO) ₂ O, DMSO, CH ₂ Cl ₂	826	111
		Collins reagent, CH ₂ Cl ₂ , 0 °C	658	91
CrO ₃ ·2Py, CH ₂ Cl ₂	589	82		
CrO ₃ ·2Py	590	242		
CrO ₃ ·2Py, CH ₂ Cl ₂ , 10 °C	486	229		
Dess-Martin periodinane, Et ₃ N, CH ₂ Cl ₂	378	376		
COCl	CHO	H ₂ , Pd/BaSO ₄ , xylene, 130 - 135 °C	723	431
CONMe ₂	CHO	Vitride, THF, 0 °C	464	67
COOCH ₃	CHO	Vitride, toluene, THF, 0 °C	589	82
		DIBAL, hexane, -78 °C	808	109
		DIBAL, hexane/ether (3 : 1), -78 °C	929	124
		DIBAL, MgBr·Et ₂ O, CH ₂ Cl ₂ , -95 °C	50	176
		DIBAL, ether, -78 °C	119	185
		DIBAL, toluene, -78 °C	132	186
		DIBAL, THF, -78 °C	316	209
		DIBAL, toluene, -78 °C	590	242
COOEt	CHO	DIBAL, CH ₂ Cl ₂ /hexane (3 : 1), -78 °C	178	24
C=O	CHOH	DIBAL, toluene, -78 °C	729	258
		NaBH ₄ , EtOH, -15 °C	809	267
		NaBH ₄ , MeOH, -4 °C	819	268
OH	Cl	Ph ₃ P, CCl ₄ , CH ₂ Cl ₂	454	225
		Ph ₃ P, CCl ₄ , toluene, 70 °C	593	243
OMs	Cl	LiCl, DMF, 80 °C	316	366
CONH ₂	CN	Ac ₂ O, pyridine	18	172
OMs	CN	PhCH ₂ N(Bu) ₃ CN, TMS-CN, CH ₃ CN, 90 °C	539	236
OTf	CN	NaCN, HMPT	770	262

(continued)

From	To	Conditions	Structure	Page
OTs	CN	NaCN, DMF, 85 °C	440	224
		NaCN, DMSO	1017	292
COOH	COCl	SOCl ₂ , CHCl ₃	900	120
		SOCl ₂ (reflux)	265	203
		SOCl ₂ , 40 °C	816	445
		(COCl) ₂ , DMF, CH ₂ Cl ₂	126	18
		(COCl) ₂ , DMF, CH ₂ Cl ₂ , 20 °C	74	148
		Ph ₃ P, CCl ₄	796	265
COOTBS	COCl	(COCl) ₂ , DMF, CH ₂ Cl ₂	310	209
CN	CONH ₂	H ₂ O ₂ , 1-hexene, Na ₂ CO ₃ , MeOH	771	262
COOCH ₃	CONH ₂	NH ₃	6	2
		NH ₃ (g), MeOH	808	266
COOEt	CONH ₂	NH ₃ , MeOH	408	56
COOH	CONH ₂	CDI, THF then NH ₃	275	38
COOCH ₃	CONHOH	NH ₂ OH·HCl, KOH, MeOH	1020	292
COOH	COOCH ₃	CH ₃ OH, HCl	2	168
		CH ₃ OH, CH ₃ COCl, 60 °C	253	202
		CH ₂ N ₂ , MeOH/ether, 0 °C	267	204
		CH ₂ N ₂ , ether	1019	292
		EtOH, PTSA, benzene	88	150
COOH	COOEt	CH ₃ CHN ₂ , ether	222	32
		EtI, CsF, DMF	2	1
		EtBr, Et ₃ N, toluene, 100 °C	220	198
		RuO ₂ , NaIO ₄	769	105
2-furan	COOH	RuO ₂ ·H ₂ O, NaIO ₄ , CCl ₄ /H ₂ O/CH ₃ CN (2 : 2 : 3)	912	121
		O ₃ , MeOH, -78 °C	843	270
		KMnO ₄ , NaIO ₄ , K ₂ CO ₃ , <i>tert</i> - BuOH/H ₂ O (7 : 3)	938	125
C=C	COOH	NaIO ₄ , H ₂ O, K ₂ CO ₃ , KMnO ₄	252	202
		KMnO ₄ , NaIO ₄ , H ₂ O	1063	297
		PDC, DMF	864	116
CH ₂ OH	COOH	PCC, CH ₂ Cl ₂	1032	293
		NaIO ₄ , RuO ₂ (cat), CCl ₄ /CH ₃ CN/H ₂ O (2 : 2 : 3)	982	129
CHO	COOH	CrO ₃ , H ₂ SO ₄ , H ₂ O/acetone	181	24
		Ba(OH) ₂ , H ₂ O	16	171
		HCl (g), CH ₃ CN-H ₂ O (4 : 1), 60 – 70 °C	85	150
CONH ₂	COOH	H ₂ (1 atm), 5% Pd/C, MeOH	198	27
CONMe ₂	COOH	H ₂ , 10% Pd/C, MeOH	63	178
COOCH ₂ Ph	COOH	KOH, MeOH	13	171
COOCH ₃	COOH	1M KOH	559	238
		5% H ₂ SO ₄	189	193
COOCH ₃	COOH	1N NaOH, EtOH	250	201
		1N HCl	255	202
		Ba(OH) ₂ , H ₂ O	8	169
		LiOH, THF/H ₂ O, 0 °C	125	185

From	To	Conditions	Structure	Page
COOt-Bu	COOH	15% HCl dioxane	905	120
		CF ₃ COOH	357	212
phenyl COOH	COOH	RuCl ₃ , NaIO ₄ , CH ₃ CN/CCl ₄ /H ₂ O	1028	293
	COO <i>tert</i> -Bu	<i>tert</i> -BuOAc, 60% HClO ₄	265	37
		<i>tert</i> -BuOAc, HClO ₄	725	432
CONH ₂ OH	CSNH ₂	Lawesson's reagent, dioxane	238	34
	F	DAST, CHCl ₃ , 0 °C	188	193
		DAST, CH ₂ Cl ₂	324	210
OTs	F	CsF, triethylene glycol, 110 °C	90	150
Br	H	H ₂ , Pd/C, HOAc	181	192
I	H	Bu ₃ SnH, THF, 40 °C	377	216
		Bu ₃ SnH	1043	294
OH	H	thiocarbonyldiimidazole, CH ₂ Cl ₂ then	541	76
		Bu ₃ SnH, AIBN		
OMs	H	LiAlH ₄ , THF	41	320
OTs	H	NaBH ₄ , CH ₃ CN	82	327
OH	I	(PhO) ₃ P, CH ₃ I	277	38
		I ₂ , Ph ₃ P, imidazole	209	349
OMs	I	NaI, K ₂ CO ₃ , acetone	421	221
OTs	I	NaI, acetone	457	64
		NaI, DME, 80 °C	799	108
		NaI, acetone	153	188
		NaI, NaHCO ₃ , acetone	340	211
		NaI, acetone	392	217
		NaI, acetone	454	225
		NaI, acetone	694	254
		NaI, acetone	70	325
		OTf	N(Boc) ₂	(Boc) ₂ NH, <i>n</i> -BuLi, THF, -28 °C
OTs	N ⁺ Me ₃	Me ₃ N, toluene	62	178
N-C=O	N-C=S	Lawesson's reagent, toluene	963	285
I	N ₃	NaN ₃ , CH ₃ CN-H ₂ O, 80 °C	994	288
OH	N ₃	DPPA, DBU, toluene	96	12
		ZnN ₆ ·2Py, DEAD, Ph ₃ P, toluene	96	14
OMs	N ₃	NaN ₃ , 15-crown-5, DMF, 50 °C	1002	289
ONs	N ₃	NaN ₃ , DMSO	99	13
NHCHO	NC	(Cl ₃ CO) ₂ O, Et ₃ N, CH ₂ Cl ₂ , 0 °C	823	111
N-C=S	NCH ₂	(Et) ₃ OBf ₄ , NaCNBH ₃	964	285
COOH	NCO	DPPA, benzene	24	173
NOH	NH	Cu(OAc) ₂ , Zn, HOAc, H ₂ O, 70 °C	328	367
COCl	NH ₂	NaN ₃ , acetone, -20 °C then benzene (reflux)	17	203
CONH ₂	NH ₂	NaOCl, NaOH, H ₂ O	17	171
N ₃	NH ₂	Ph ₃ P, benzene, rt	846	449
		H ₂ , PtO ₂ , EtOH	840	449
		H ₂ , Pd/C, EtOH	242	34
		H ₂ , Pd/C, MeOH/H ₂ O	995	288

(continued)

From	To	Conditions	Structure	Page
NHCOPh	NH ₂	MeOH, NaHCO ₃ (cat)	719	124
NHTs	NH ₂	Na-naphthalene, THF, -78 °C	95	151
NO ₂	NH ₂	H ₂ , 10% Pd/C, MeOH, HCl	558	112
CONH ₂	NHBoc	Pb(OAc) ₄ , <i>tert</i> -BuOAc	950	284
N(Boc) ₂	NHBoc	CF ₃ COOH (1.5 eq), CH ₂ Cl ₂	197	27
NH ₂	NHCHO	Ac ₂ O, HCOOH	822	111
NO ₂	NHCOPh	H ₂ , RaNi, MeOH, (PhOC) ₂ O	932	124
OH	NPh _t	phthalimide, DEAD, Ph ₃ P, THF	112	15
		phthalimide, DEAD, Ph ₃ P, THF, -40 °C	663	251
COCH ₃	OAc	MCPBA, EtOAc, 50 °C	755	103
		MCPBA, CHCl ₃	968	127
NH ₂	OAc	NaNO ₂ , HOAc	123	17
OMs	OAc	CsOAc, 18-crown-6	456	387
OTf	OAc	CH ₃ COOK, CH ₃ CN	200	28
OH	OCH ₂ Ph	PhCH ₂ Br, Ag ₂ O, EtOAc, rt, 15 h	1082	300
OH	OCH ₃	CH ₃ I, Ag ₂ O (neat)	7	169
		CH ₃ I, Ag ₂ O, DMF, rt	141	159
		CH ₃ I, Ag ₂ O, reflux	573	408
		CH ₂ N ₂ , silica gel, ether	131	186
		CH ₂ N ₂ , silica gel, ether, 0 °C	652	249
OTf	OCHO	DMF	202	195
OH	OCNH ₂	ClSO ₂ NCO, CH ₂ Cl ₂ , -20 °C	721	100
OCH ₃	OH	BCl ₃ , CH ₂ Cl ₂	579	409
OH	OMs	MsCl, Et ₃ N, CH ₂ Cl ₂ , 0 °C	156	21
		MsCl, Et ₃ N, CH ₂ Cl ₂	338	47
		MsCl, Et ₃ N, CH ₂ Cl ₂	781	107
		MsCl, Et ₃ N, CH ₂ Cl ₂ , -15 °C	418	221
OH	ONs	NsCl, Et ₃ N, DMAP	98	13
OH	OTf	Tf ₂ O, pyridine, CH ₂ Cl ₂	189	26
		Tf ₂ O, 2,6-lutidine, CH ₂ Cl ₂ , -78 °C	197	194
		Tf ₂ O, pyridine, CH ₂ Cl ₂ , 0 °C	769	262
		Tf ₂ O, CH ₂ Cl ₂	805	266
OH	OTs	Bu ₂ SnO, toluene, then TsCl, CH ₂ Cl ₂	411	381
		TsCl, Et ₃ N (neat)	120	17
		TsCl, pyridine	37	5
		TsCl, pyridine	120	17
		TsCl, pyridine	439	224
		TsCl, pyridine	59	178
		TsCl, pyridine, DMAP, CH ₂ Cl ₂	157	188
		TsCl, pyridine, CH ₂ Cl ₂	758	261
		TsCl, pyridine	694	254
Cl	SAc	KSAc, acetone	133	18
OH	SAc	CH ₃ COSH, DIAD, Ph ₃ P, THF, 0 °C	102	13
OMs	SAc	CH ₃ COSH, Et ₃ N, CH ₃ CN	781	107
		CsSAc, DMF	168	23
		CsSAc, DMF	192	193

From	To	Conditions	Structure	Page
OTs	SAc	KSAc, acetone	133	18
OMs	SePh	PhSeNa, EtOH/H ₂ O	177	24
SAc	SH	3% HCl, EtOH	169	23
		3% HCl, EtOH	193	193

Appendix D Abbreviations

A-15	Amberlyst-15
Ac	Acetyl
acac	Acetylacacetate
AIBN	Azobisisobutyronitrile
Alloc	Allyloxycarbonyl
9-BBN	9-Borabicyclo[3.3.0]nonane
BMS	Borane–methyl sulfide complex
Boc	<i>tert</i> -Butoxycarbonyl
BOM	Benzyloxymethyl
Bu	Butyl
CAN	Ceric ammonium nitrate
Cb	<i>N,N</i> -Diisopropylcarbonyl
Cbz	Benzyloxycarbonyl
CDI	<i>N,N'</i> -Carbonyldiimidazole
CSA	Camphorsulfonic acid
DABCO	1,4-Diazabicyclo[2.2.2]octane
DAM	Di- <i>p</i> -anisylmethyl
DAST	Diethylaminosulfur trifluoride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCB	2,6-Dichlorobenzyl
DCC	1,3-Dicyclohexylcarbodiimide (dicyclohexylcarbodiimide)
DCM	Dichloromethane
<i>de</i>	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DET	Diethyltartrate
DHP	Dihydropyran
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminum hydride
DIPA	Diisopropylamine
DIPT	Diisopropyltartrate
DMAD	Dimethyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	<i>N,N</i> -Dimethylformamide
DMP	2,2-Dimethoxypropane
DMS	Dimethyl sulfide
DPPA	Diphenylphosphoryl azide
<i>ds</i>	Diastereoselectivity
EDAC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
<i>ee</i>	Enantiomeric excess
EE	1-Ethoxyethyl
EEDQ	Ethyl 1,2-dihydro-2-ethoxy-1-quinolinecarboxylate
Et	Ethyl
HMDSH	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HMPT	Hexamethylphosphoric triamide
HOBT	1-Hydroxybenzotriazole

HYTRA	2-Hydroxy-1,2,2-triphenylethyl acetate
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
MCPBA	<i>m</i> -Chloroperoxybenzoic acid
Me	Methyl
MEM	(Methoxyethoxy)methyl [(methoxyethoxy)methyl]
MOM	Methoxymethyl
MPM	(<i>p</i> -Methoxyphenyl)methoxymethyl
Ms	Methanesulfonyl
MSA	Methanesulfonic acid
MSH	<i>O</i> -(Mesitylenesulfonyl)hydroxylamine
MTM	Methoxythiomethyl
MVK	Methyl vinyl ketone
Nap	Napthalene
NBS	<i>N</i> -Bromosuccinimide
NCS	<i>N</i> -Chlorosuccinimide
NMM	<i>N</i> -Methylmorpholine
NMO	<i>N</i> -Methylmorpholine <i>N</i> -oxide
Ns	4-Nitrobenzenesulfonyl
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl
Pht	Phthaloyl
Piv	Pivaloyl
PLE	Pig liver esterase
PMB	<i>p</i> -Methoxybenzyl
PMP	<i>p</i> -Methoxyphenyl
PNB	<i>p</i> -Nitrobenzyl
PPTS	Pyridinium <i>p</i> -toluenesulfonate
Pr	Propyl
PTSA	<i>p</i> -Toluenesulfonic acid
PTSCl	<i>p</i> -Toluenesulfonyl chloride
Py	Pyridine
rt	Room temperature
SEM	2-(Trimethylsilyl)ethoxymethyl
Sia ₂	Disiamyl
TBAF	Tetrabutylammonium fluoride
TBHP	<i>tert</i> -Butyl hydroperoxide
TBPS	<i>tert</i> -Butyldiphenylsilyl
TBS	<i>tert</i> -Butyldimethylsilyl
TCDI	Thiocarbonydiimidazole
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl (Triflate)
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TIP	Triisopropyl
TIPS	Triisopropylsilyl
TMSI	Trimethylsilyl iodide

TMSO	Trimethyl trifluoromethanesulfonate
Tol	Tolyl
TosMIC	Tosylmethyl isocyanide
Tr	Triphenylmethyl (Trityl)
Troc	Trichloroethoxycarbonyl
Ts	<i>p</i> -Toluenesulfonyl (Tosyl)
WSC	Water-soluble carbodiimide

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