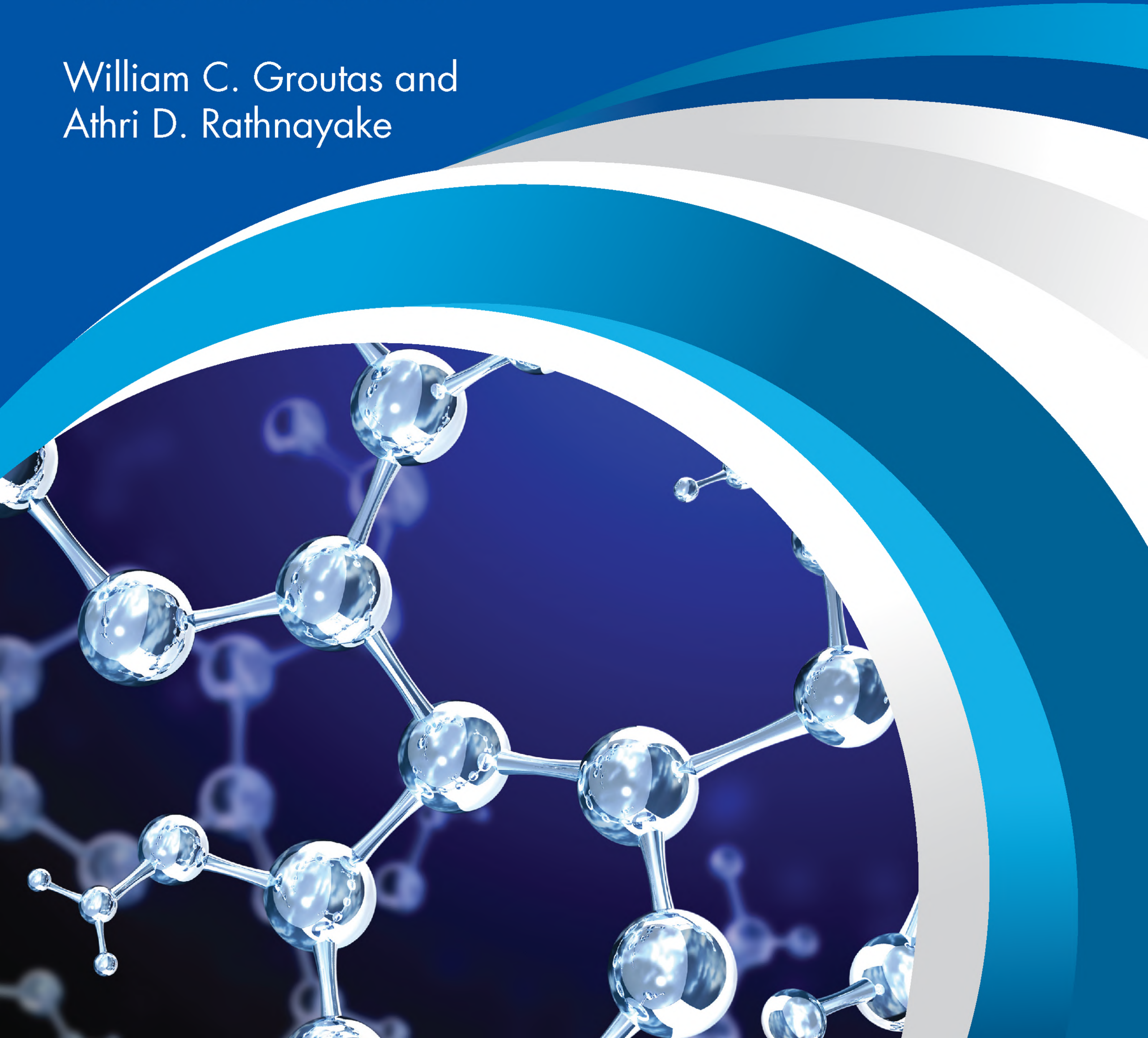
CRC Press
Taylor & Francis Group

Organic Reaction Mechanisms, Selected Problems, and Solutions

Second Edition

William C. Groutas and
Athri D. Rathnayake



ORGANIC REACTION MECHANISMS

Selected Problems and Solutions

William C. Groutas
Athri D. Rathnayake

First edition published 2023
by CRC Press
6000 Broken Sound Parkway NW, Suite 300, Boca Raton, FL 33487-2742

and by CRC Press
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN

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CRC Press is an imprint of Taylor & Francis Group, LLC
First edition published by Wiley, 1996

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ISBN: 978-1-032-48343-6 (HB)
ISBN: 978-1-032-48825-7 (PB)
ISBN: 978-1-003-39096-1 (EB)

DOI: 10.1201/9781003390961

Typeset in Arial
by William C. Groutas and Athri D. Rathnayake

To Susan, Mark, Christopher, Kalyn, Toby, Kindsey

and the memory of Mom and Dad

To Mom, Dad and Uncle

PREFACE TO THE FIRST EDITION

The primary goal of this book is to use organic reaction mechanisms as a means of facilitating the mastery and understanding of the fundamental principles of organic chemistry, while at the same time sharpening a student's reasoning ability and critical thinking. This is achieved through the judicious selection and use of a large number of problems selected from the chemical literature. Each question is meant to illustrate one or more fundamental principles of mechanistic organic chemistry. The level of difficulty and suitability of the questions in this book have been tested by including them in exams and/or as homework assignments in the undergraduate organic chemistry course (Part A), or the first year graduate-level course in organic chemistry (Part B).

Special emphasis has been placed on the organization of the book. Part A contains questions geared toward students taking the sophomore-level organic chemistry course. The questions and principles illustrated thereof, are organized in the same sequence as they are normally discussed in a standard textbook of organic chemistry. A series of minireviews that summarize and reinforce fundamental principles that underlie a particular set of related problems have been included at the beginning of each set of questions. Thus, Part A can serve as a supplement to a standard textbook used in the first year organic chemistry course, and is intended to meet an existing need, since only a token number of end-of-chapter mechanism questions is included in most textbooks of organic chemistry.

The questions included in Part B are suitable for students in an honors course in organic chemistry, and beginning graduate students in chemistry, medicinal chemistry, biochemistry and related disciplines. A limited number of applied problems has been included (Part C) to demonstrate how a knowledge of basic organic reaction mechanisms can be used to understand problems related to everyday life.

I am deeply indebted to professor Richard A Bunce (Oklahoma State University) for his diligence in reviewing the manuscript, and his many valuable comments. I am also grateful to Jennifer Yee for her editorial assistance, guidance and constant encouragement throughout the preparation of the workbook. Any errors that may have crept in is the responsibility of the author.

PREFACE TO THE SECOND EDITION

As in the first edition, our overarching goal is to use organic reaction mechanisms to help students master the fundamental principles of organic chemistry and sharpen their thinking and reasoning skills. In doing so, we have focused on mechanisms that involve Lewis acid/Lewis base reactions. The revised book is aimed at undergraduates and beginning graduate students in organic and medicinal chemistry, biochemistry, and related disciplines, and the questions are organized in the same general sequence as in a standard textbook of organic chemistry.

The second edition contains several important changes. The scope of each minireview has been expanded and the number of problems has been increased considerably (from 210 to 500 problems). The questions are graded in difficulty with part A containing questions aimed at students taking the sophomore-level organic chemistry class while part B contains questions of somewhat greater difficulty suitable for students taking an honors course in organic chemistry and beginning graduate students. Special emphasis has been placed on the selection of questions to ensure that each question illustrates one or more fundamental principles of organic chemistry.

We hope that the second edition will enhance the understanding of organic reaction mechanisms and minimize rote learning. Finally, we would like to thank Hilary LaFoe for her editorial assistance and encouragement, and Sukirti Singh and the CRC press production team for their help and support.

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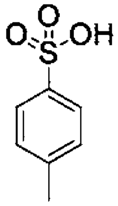
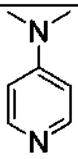
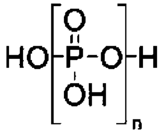
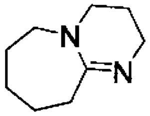
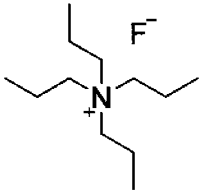
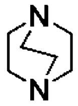
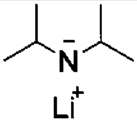
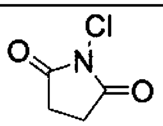
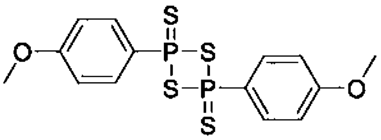
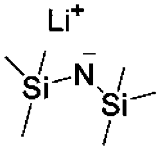
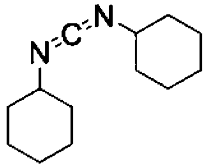
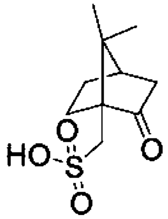
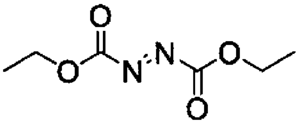
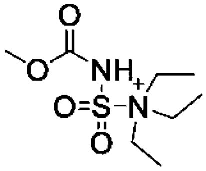
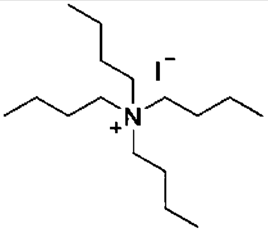
GLOSSARY

Name	Abbreviation	Structure
p-Toluenesulfonic acid	p-TSA/p-TsOH	
4-Dimethylaminopyridine	DMAP	
Polyphosphoric acid	PPA	 $HO{-}\left[P(=O)(OH){-}O\right]_n{-}H$
1,8-Diazabicyclo[5.4.0]undec-7-ene	DBU	
Tetra n-butyl ammonium fluoride	TABF	
1,4-Diazabicyclo[2.2.2]octane	DABCO	
Lithium diisopropylamide	LDA	
N-Chlorosuccinimide	NCS	
2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide	Lawesson's reagent	

Sulfonic acid polymer resin (strongly acidic cation exchanger)	Amberlyst-15	
Lithium bis(trimethylsilyl)amide	LHMDS	
N,N′-Dicyclohexylcarbodiimide	DCC	
(7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonic acid	CSA	
Diethyl azodicarboxylate	DEAD	
1-methoxy-N-(triethylazaniumyl)sulfonylmethanimidate	Burgess reagent	
Tetrabutylammonium iodide	TBAI	

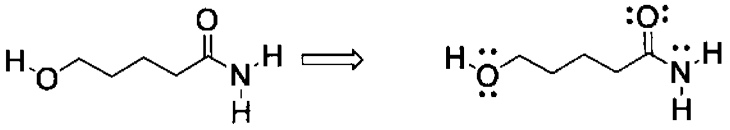
A NOTE ON WRITING MECHANISMS

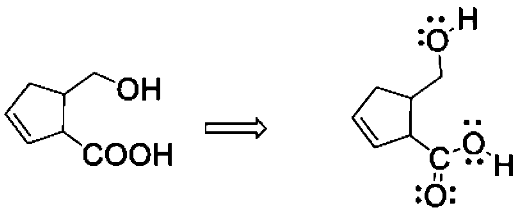
The majority of organic reactions can be viewed as being Lewis acid/Lewis base reactions. Recall that a *Lewis base* (LB) is any substance that can donate a pair of non-bonded or pi electrons to a *Lewis acid* (LA) to form a covalent bond, and a *Lewis acid* is any substance that can accept a pair of electrons to form a covalent bond (see Minireviews 1 and 2 for a general discussion of Lewis structures, Lewis acids and Lewis bases, and Lewis acid/ Lewis base reactions).

In writing mechanisms, the following general approach should be followed:

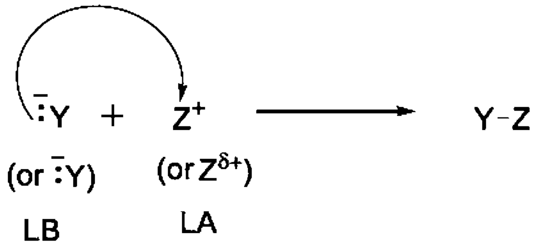
(a) *add a sufficient number of non-bonded electrons pairs on any heteroatoms* (atoms other than carbon, such as, O, N, S, etc.) *to complete their octets,* since chemical structures are customarily drawn without the non-bonded electron pairs shown. By doing so, you will immediately identify the atom(s) in a given reactant that, in principle, can donate a pair of electrons to a Lewis acid. With just a little practice this will turn out to be a trivial task and, furthermore, in many cases you'll only be needing to add non-bonded electron pairs to the atoms that are *directly* involved in the reaction.

EXAMPLES



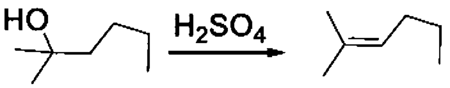


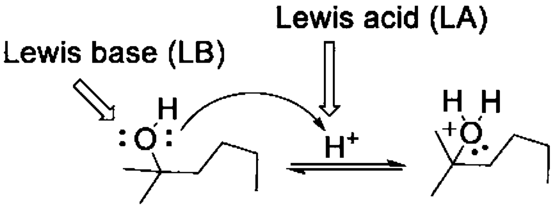
(b) *Identify the reactant that functions as a Lewis base, and the reactant that functions as a Lewis acid in a given reaction and use curved arrows to indicate the flow of electrons from the atom that donates the pair of non-bonded or pi electrons to the receiving electron deficient atom*, as illustrated below. The reactant that acts as a Lewis acid (LA) typically has an atom that is electron deficient, namely, it may have a positive charge, or a partial positive charge (δ^+) if it is bonded to one or more electronegative atoms, or it may have an atom that lacks an octet of electrons.



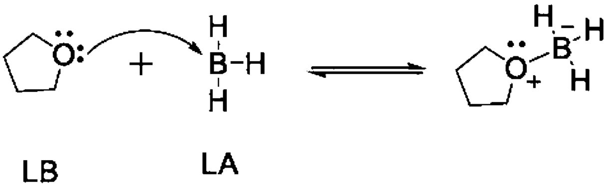
Examples illustrating these ideas are shown below.

EXAMPLE 1



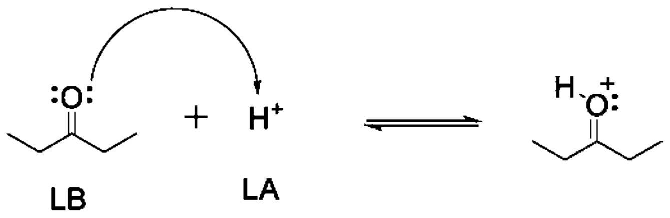


EXAMPLE 2

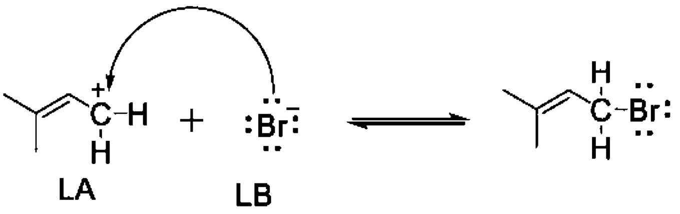


Note In general, compounds of group IIIA elements (B, Al, etc.) typically have an incomplete octet of electrons and invariably function as Lewis acids. Examples include boron trifluoride (BF_3), aluminum chloride ($AlCl_3$), boron tribromide (BBr_3), etc.

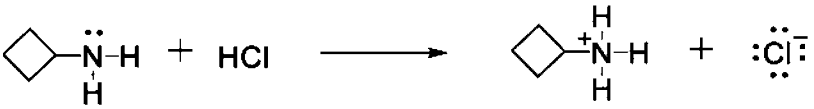
EXAMPLE 3



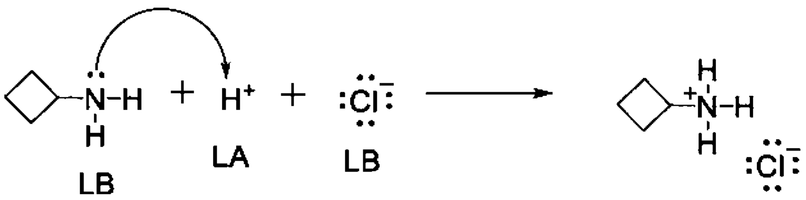
EXAMPLE 4



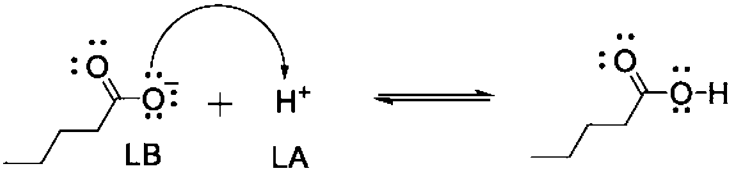
EXAMPLE 5



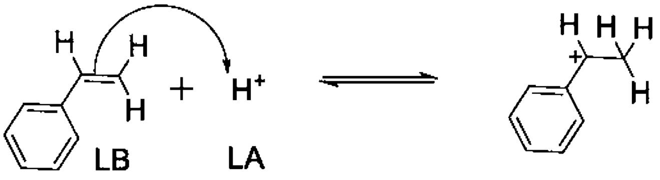
It is helpful to remember that strong mineral acids (HCl, HBr, HNO_3, etc.) or strong organic acids (for example RSO_3H, CF_3COOH) are fully or predominantly ionized in solution. Thus, the reaction shown above can be viewed as shown below, making it easier to identify the Lewis acid(s) and Lewis base(s).



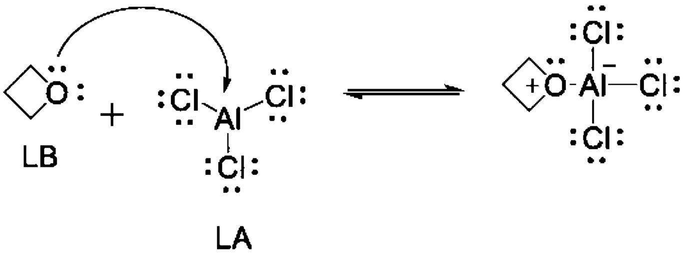
EXAMPLE 6



EXAMPLE 7



EXAMPLE 8



(c) *Assign formal charges to the atoms directly involved in the reaction* (the formal charges on atoms that are not *directly* involved in the reaction do not change). Recall that the formal charge can be readily determined as follows:

Formal charge on an atom = X - Y - Z

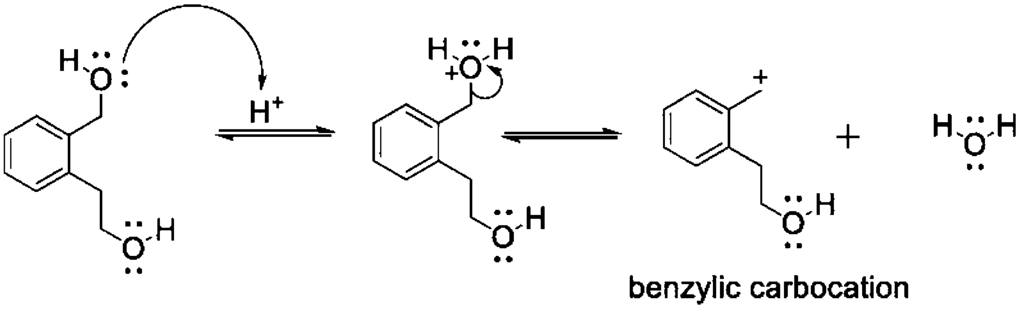
where X = number of valence electrons

Y = number of non-bonded electrons

Z = half the number of bonded electrons

The number of valence electrons for an atom corresponds to its group number in the periodic table. For example, sulfur is in group VI in the periodic table, therefore it has six valence electrons (see also Minireview 1).

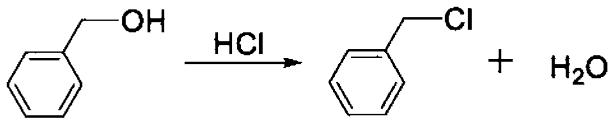
(d) If a reactant has more than one functional group which can donate a pair of non-bonded or pi electrons, then inspection of the structures of the reactant and product will usually reveal which functional group will react initially. Other considerations coming into play in deciding which functional group in a reactant is involved in the first step of a reaction include, for example, the stability of the initial carbocation. *The more stable a carbocation is, the easier it is to form* (see Minireview 4 for a discussion of carbocation chemistry). In the example shown below, while a pair of non-bonded electrons can be donated from either hydroxyl group, reaction takes place preferentially at the one that leads to the formation of the more stable benzylic carbocation, as opposed to the less stable primary carbocation.



(e) Most mechanisms, particularly those involving skeletal rearrangements, may involve several sequential steps. Most of the steps are *consecutive Lewis acid/Lewis base reactions which can be intermolecular* (reaction involves two separate molecules that can be the same or different) or *intramolecular* (reaction takes place within the same molecule) in nature. The *driving force* behind these steps is the *resulting gain in stability* in going from one transient species to another such as, for example, from a less stable carbocation to a more stable carbocation, relief of ring strain, etc.

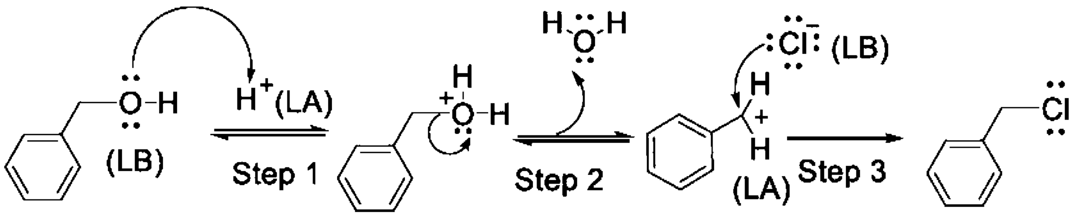
The following examples are meant to serve as a guide on how to write a reasonable mechanism for a reaction you may have never seen before using the Lewis acid/Lewis base approach. The same approach can be used to understand and explain how a reagent mediates a particular transformation. The thought processes underlining the general approach used in writing mechanisms are explicitly stated.

EXAMPLE 1 Write a mechanism for the following reaction.



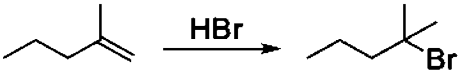
Answer

The first step in writing a mechanism for any chemical reaction is the *identification of the Lewis acid and Lewis base.* This can be readily accomplished by placing a sufficient number of non-bonded electron pairs on the heteroatom (oxygen in this case) in a reactant to complete its octet. This immediately reveals that the alcohol will function as a Lewis base and the oxygen atom of the hydroxyl group will donate a pair of non-bonded electrons to the Lewis acid. Since mineral assets are fully ionized in solution, the second reactant can be viewed as existing as H^+ (a Lewis acid) and Cl^- (a Lewis base) ions. Therefore, the first step of the mechanism for this reaction involves a Lewis base /Lewis acid reaction to yield a protonated alcohol. The second step involves the loss of a molecule of water via the cleavage of the C-O bond (the pair of electrons ends up on the oxygen atom of water as a pair of non-bonded electrons), at the same time relieving the positive charge on the electronegative atom. The second step in this mechanism is the rate-determining step, namely, the step with the highest free energy of activation (see Minireview 4 for a full discussion of carbocation chemistry). The third step completes the mechanism of the reaction. It involves a straightforward Lewis acid/Lewis base reaction between the carbocation (LA) and the chloride ion (LB).



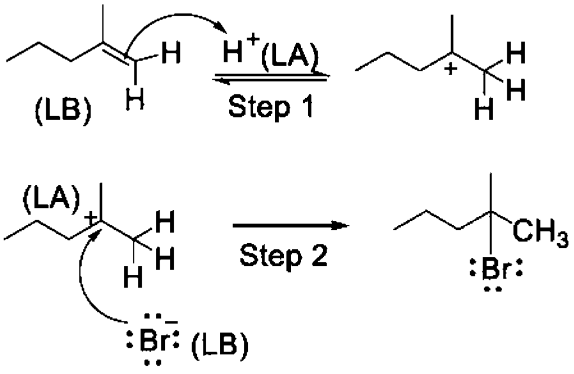
benzylic carbocation

EXAMPLE 2 Write a mechanism for the following reaction.

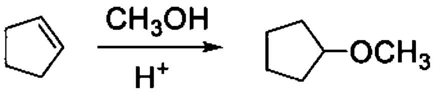


Answer

By definition, any substance that can donate a pair of *non-bonded* or *pi electrons* is a Lewis base. Thus, alkenes (as well as alkynes) invariably function as Lewis bases by donating a pair of pi electrons to a Lewis acid. In the first step of this reaction, the pair of pi electrons in the C=C bond is donated to H^+ (Lewis acid) to form a covalent bond yielding a carbocation (a Lewis acid). Notice that in this instance the pair of pi electrons can potentially be used to form a covalent bond with either one of the carbon atoms of the C=C bond. Recall that, *the reaction of an alkene with H^+ always leads to the initial formation of the most stable carbocation. In order to form the most stable carbocation, the H^+ will have to bond to the carbon of the C=C bond that bears the greater number of hydrogens (Markovnikov's rule).* The second step of the mechanism involves the reaction of a carbocation (LA) with a Lewis base (bromide ion).

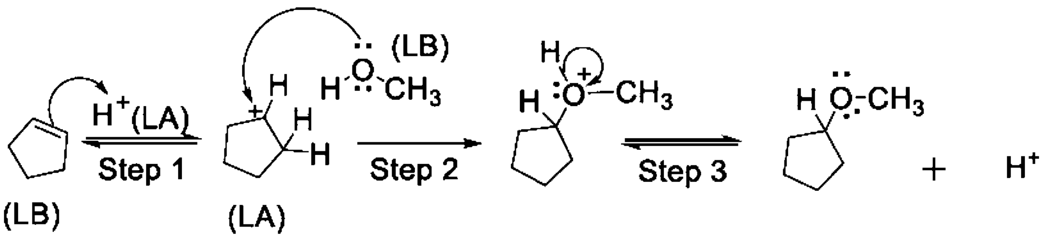


EXAMPLE 3 Write a mechanism for the following reaction.

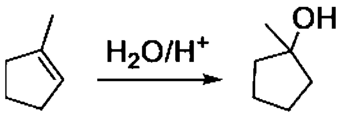


Answer

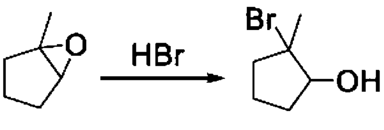
Unlike examples 1 and 2 which involve the reaction of either an alcohol or an alkene with a Lewis acid, this example involves the participation of two Lewis Bases (an alkene and an alcohol) and a Lewis acid (H^+), leading to the formation of an ether. Prior to writing a mechanism for this reaction the following question must be addressed: which one of the two Lewis bases will react with H^+ and how do you go about deciding that? While the alcohol (LB) can potentially react with H^+ (LA), this is an unproductive process (it cannot lead to the formation of the observed product). Note also that methyl carbocations are highly unstable (see Minireview 4). Thus, the reaction is initiated via a Lewis base/Lewis acid reaction between the alkene and H^+ forming a secondary carbocation. Further reaction of the carbocation (a Lewis acid) with the alcohol (a Lewis base) leads to the formation of a protonated ether (Step 2). Loss of a H^+ yields the observed product (step 3). The hydrogen in the protonated ether is *acidic*, consequently step 3 is essentially an ionization step.



<u>Exercise</u> Write a mechanism for the following reaction

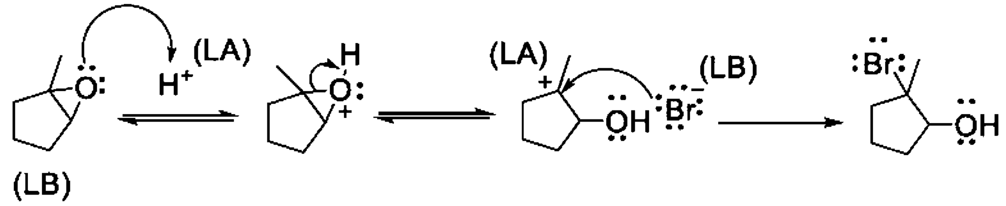


<u>EXAMPLE 4</u> Write a mechanism for the following reaction.

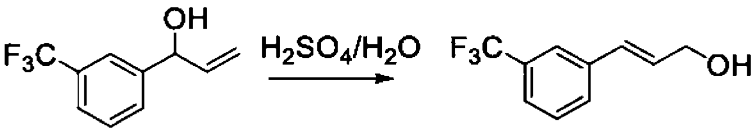


<u>Answer</u>

Once the appropriate number of pairs of non-bonded electrons are placed on the oxygen to complete its octet, it can be readily seen that ethers (like alcohols), can function as Lewis bases. Thus, the first step of this reaction is a Lewis acid/Lewis base reaction leading to the formation of a protonated ether. This is followed by cleavage of the C-O bond *in a way that yields the most stable carbocation* (tertiary vs secondary). A Lewis acid/Lewis base reaction between the carbocation and bromide ion completes the mechanism for this reaction. Note Three and four-membered cyclic ethers readily undergo ring-opening reactions in the presence of Lewis acids. The relief of ring strain serves as the driving force for these reactions (see Minireview 7).



EXAMPLE 5 Write a mechanism for the following reaction.

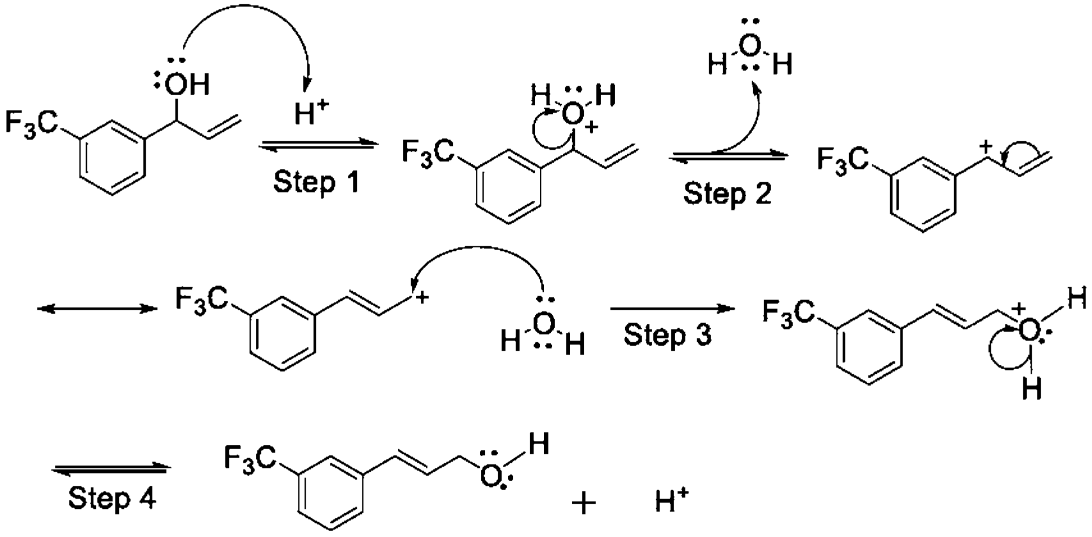


Answer

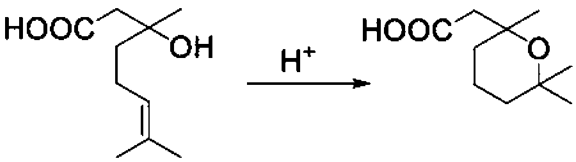
Once the Lewis acid and the Lewis base are identified, casual inspection of the Lewis base indicates that, in principle, three different functional groups (OH, alkene C=C bond and aromatic ring C=C bonds) can act as a Lewis base, namely, donate a pair of non-bonded or pi electrons to the Lewis acid (H^+). At this point a decision has to be made as to which of these will react with the Lewis acid. *As a general rule, it is useful to remember that (a) non-bonded electrons are more available for donation than pi electrons (since pi electrons are held by two nuclei) and, (b) an alkene C=C bond is more reactive than the C=C bond of an aromatic ring,* since reaction of an aromatic ring C=C bond results in the loss of the aromatic character of the ring (30 kcal/mol loss in resonance stabilization energy).

Thus, in step 1 of this reaction the hydroxyl group of the Lewis base donates a pair of non-bonded electrons to the Lewis acid, which is then followed by cleavage of the C-

O bond and the loss of a molecule of water (step 2), leading to the formation of a carbocation (notice that when the C-O bond is cleaved, the pair of electrons making up the bond goes with the oxygen). Step 1 (LB/LA reaction) and step 2 (loss of water) are common to all reactions involving an alcohol and acid. The carbocation formed in step 2 is resonance-stabilized, thus, reaction of the carbocation (LA) with water (LB) gives rise to a protonated alcohol (step 3). The final step (Step 4) in this reaction involves the loss of hydrogen ion (H^+) to give the observed product. Step 4 is a simple ionization step, analogous to the ionization of the hydronium ion ($H_3O^+ = H_2O + H^+$).



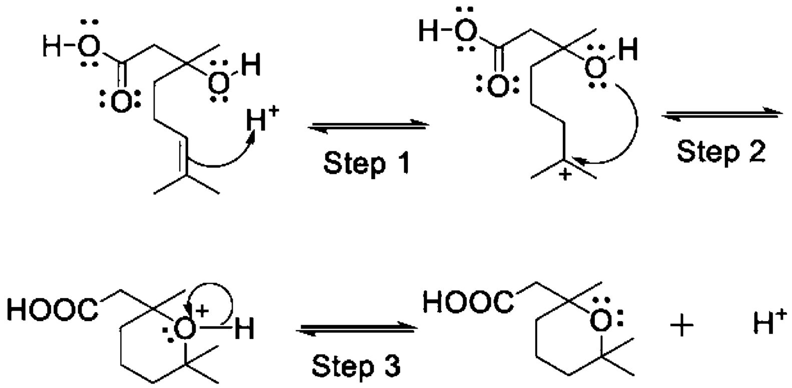
EXAMPLE 6 Write a mechanism for the following reaction.



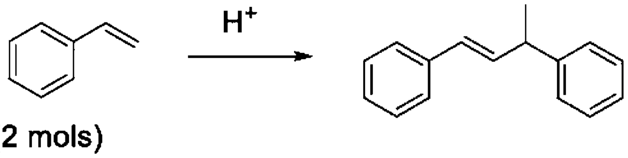
Answer

It is always a good idea to inspect the structures of the starting material and product, since in many instances this will quickly reveal which functional group(s) are involved in the reaction. In this instance, it is evident that it's the hydroxyl group and C=C bond, and not the carboxyl group. With the non-bonded electrons added on the heteroatoms, and recalling the fundamental definition of a Lewis base, it is apparent that either the hydroxyl group or the C=C bond can donate a pair of electrons to the Lewis acid. In example 5, it was stated that, as a general rule, a pair of non-bonded electrons is *more* available for donation than a pair of pi electrons. This example was chosen to (a) demonstrate that this is not always true, and (b) emphasize the need for you to keep an open (flexible) mind as you consider plausible mechanistic pathways. In other words, organic reactions frequently follow an unpredictable course, and the task on hand is to use fundamental principles to account for the formation of the observed product. Indeed, herein lies the pedagogical value of writing mechanisms. In so doing, you will be forced to look at a situation in many ways and consider plausible pathways within a framework of principles. Thus, in step 1 of this reaction, a Lewis base (C=C)/Lewis acid (H^+) reaction gives rise to the 3^0 carbocation (Markovnikov's rule). In step 3, the carbocation (LA) accepts a pair of non-bonding electrons from the Lewis base to form a product that ionizes to give the observed product.

Notice that an initial reaction between the hydroxyl group and H^+, followed by loss of a molecule of water *also* leads to the formation of 3^0 carbocation, however, this pathway cannot account for the observed product (unproductive pathway).

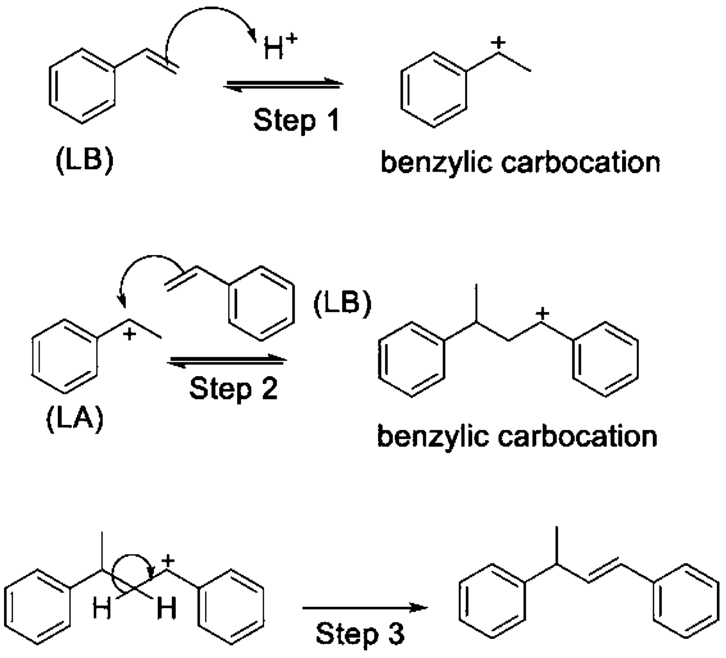


EXAMPLE 7 Write a mechanism for the following reaction.

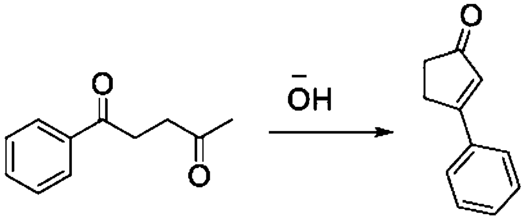


Answer

As stated previously (example 2), the C=C bond of an alkene functions as a Lewis base by donating a pair of pi electrons to a Lewis acid. However, in this instance the pi bonds in the phenyl (aromatic) ring could potentially behave the same way. Since the reaction of a ring C=C with a Lewis acid would result in the formation of a much less stable non-aromatic species, the alkene C=C bond reacts preferentially (step 1). The carbocation formed is a Lewis acid which then reacts with a second molecule of the alkene (a Lewis base) to give rise to a second benzylic carbocation (step 2). Besides reacting with a Lewis base, a carbocation can lose a H$^+$ from an adjacent carbon atom to form an alkene (Minireview 3). Thus, step 3 leads to the formation of a new alkene.

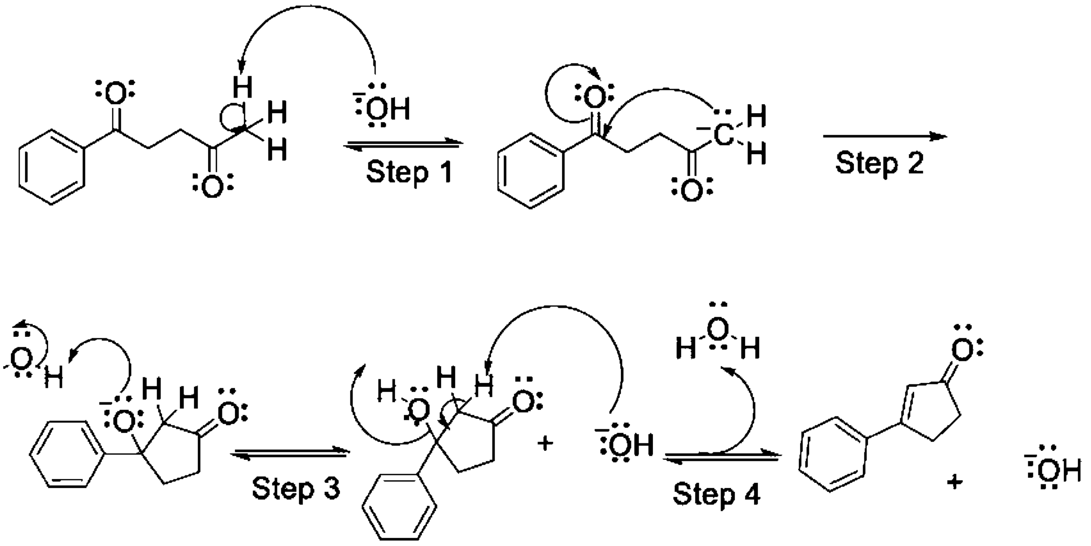


EXAMPLE 8 Write a mechanism for the following reaction.

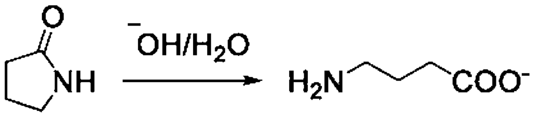


Answer

A mechanism question must always be approached from first principles, namely, it is not necessary for you to be able to realize that this particular reaction is an example of an *aldol condensation reaction*, in order to write a reasonable mechanism. Thus, the approach is always the same: first add non-bonded electron pairs to the two reactants, and classify each as a Lewis base and a Lewis acid. The stronger Lewis base (^{-}OH, since it has a negative charge) is going to react with the second reactant which, by necessity, must function as a Lewis acid (LA). The carbon of the C=O group is electron-deficient (oxygen is more electronegative than carbon, consequently the electrons connecting the carbon and oxygen are not equally shared, and hence the carbon has a partial positive charge and oxygen a partial negative charge, $^{\delta+}C{=}O^{\delta-}$). Thus, one possibility is for the hydroxide ion to donate a pair of electrons to the electron deficient carbon (*nucleophilic addition*) or, since the hydrogens on the alpha carbon of a ketone are acidic, an acid-base reaction can take place instead, yielding an anion (a Lewis base or nucleophile). *As a general rule, Bronsted acid-base reactions are faster than most other types of organic reactions*. Thus, a Bronsted acid-base reaction in step 1 yields an anion, which then reacts in a Lewis base/Lewis acid reaction (step 2) to form the product. This product is the conjugate base of an alcohol and can be viewed as being in equilibrium with the acid (step 3). Step 4 is a β-elimination reaction that leads to the formation of the product. Step 4 is facile because it leads to the formation of a highly stable *conjugated system* (a system that consists of an array of *alternating* double and single bonds).

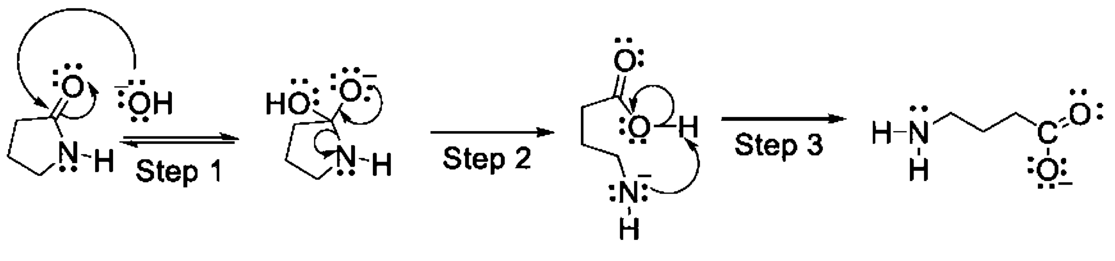


EXAMPLE 9 Write a mechanism for the following reaction.

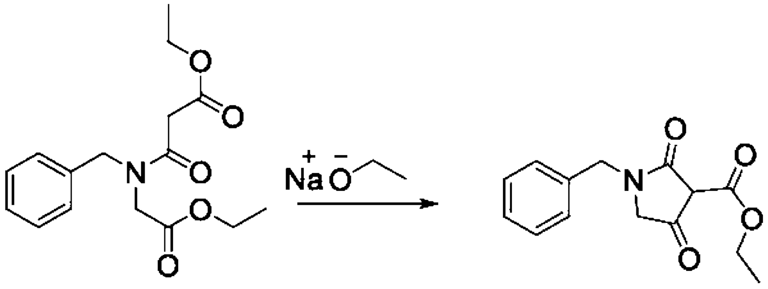


Answer

The carbonyl carbon is electron deficient, i.e., has a partial positive charge, because it is bonded to two electronegative atoms. Any atom that bears either a full positive charge (such as a carbocation, for example) or partial positive charge, is capable of accepting a pair of electrons from a Lewis base to form a covalent bond. Thus, an initial LA/LB reaction leads to the formation of a tetrahedral intermediate (step 1). Subsequent collapse of this intermediate leads to a ring-opened product (step 2). The ring-opened product has an acidic group (COOH) and a basic group, thus a fast Lewis acid/base reaction (H^+ transfer) takes place, leading to the formation of the final product (step 3).

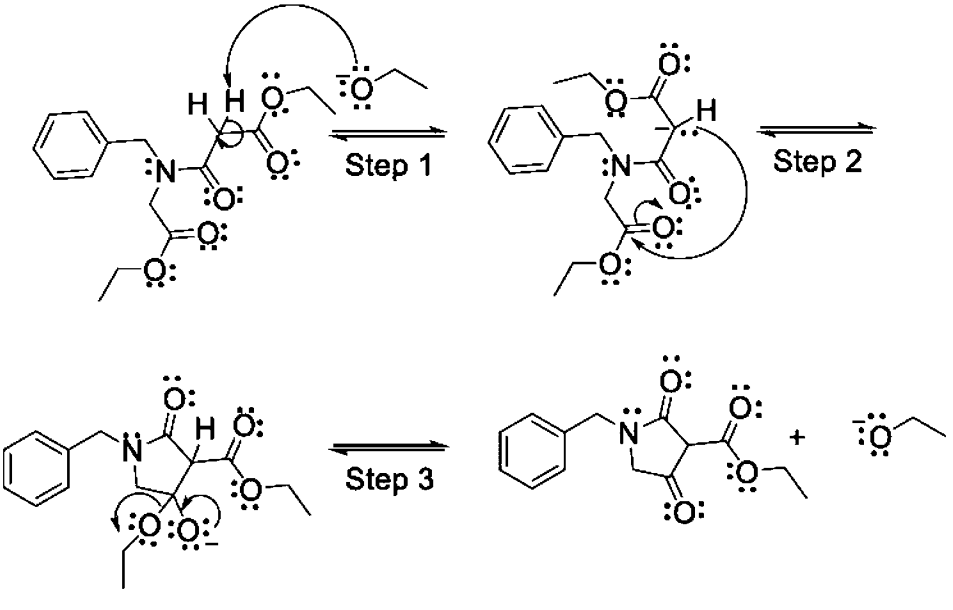


<u>EXAMPLE 10</u> Write a mechanism for the following reaction.



<u>Answer</u>

The Lewis base (ethoxide ion, $CH_3CH_2O^-$) reacts with the reactant to generate an anion (step 1). Notice that the ethoxide ion reacts with the *most acidic hydrogen* (see Minireview 5 for a discussion of acidity). The pKa of the reactant acid is ~11, while that of the product acid ($HOCH_2CH_3$) is ~16. Thus, the equilibrium lies to the right, i.e., favors the formation of the anion derived from the stronger acid. Once the anion (nucleophile) is formed, an intramolecular LB/LA reaction (*nucleophilic acyl substitution*) takes place (Steps 2 and 3), forming the product.



Minireviews 1-4 are intended to provide a quick review of the fundamental principles related to Lewis structures, Lewis acid/Lewis base reactions, and carbocation chemistry. These should be studied prior to attempting questions 1-34, Part A.

PART A

Minireview 1

1. Lewis Structures

A sound understanding of mechanistic organic chemistry requires a proficiency in writing Lewis structures. Without the ability to draw Lewis structures correctly and with facility, a student is so severely handicapped that he or she will ultimately resort to learning organic chemistry by rote (a tedious, frustrating, and minimally-successful endeavor). The importance of this will become apparent momentarily.

A *Lewis structure* is a type of structural formula that shows the way in which the atoms are bonded together and depicts the bonding between atoms using pairs of non-bonded electrons (shown as dots) and bonded electrons (shown as dashes). In writing Lewis structures, the general approach outlined below should be followed.

1. ***Determine the total number of valence electrons***.

For neutral molecules, this is simply accomplished by adding up the valence electrons of the individual atoms. In the case of ions, an electron is added for each negative charge (anions), and an electron is subtracted for each positive charge (cations). *Recall that the number of valence electrons for an element corresponds to the group number of that element in the periodic table*. For example, nitrogen has five valence electrons (nitrogen is located in group five of the periodic table), fluorine has seven valence electrons (fluorine is located in group seven), etc.

2. ***Connect the atoms in the given molecular formula using single lines (dashes)***.

It's helpful to remember that in the case of polyatomic molecules or ions, the atom of lower electronegativity is typically the central atom. Recall that electronegativity follows the order F > O > Cl, N > Br > C, H.

3. ***Place a sufficient number of non-bonded electron pairs on each atom to give each atom an octet of electrons (octet rule)*** (keep in mind that hydrogen can only share a pair of electrons). If at this point the total number of valence electrons used is greater than that computed in step 1 above, use double or triple bonds or rings to arrive at a Lewis structure that has the correct total number of valence electrons and all the atoms have an octet electrons.

4. **Determine the formal charge on each atom**.

As stated earlier, the formal charge can be readily determined as follows (see sidebar).

Minireview 1

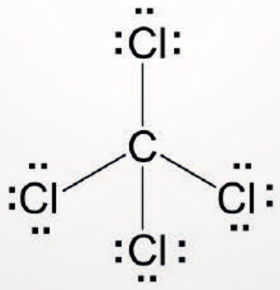
Formal charge = X -Y- Z

where,

X= number of valence electrons (of atom under consideration)

Y= number of non-bonded electrons, and

Z= half the number of bonded electrons



CCl_4

1 C 1 X 4 = 4

4 Cl 4 X 7= 28

32 Total number of valence electrons

Minireview 1

Summary

Species that lack an octet of electrons (electron-deficient species) have two distinct characteristics: they function as Lewis acids and are highly reactive (vide infra).

Notes

a) The Lewis structures of compounds derived from group IIIA elements (B, Al, etc.), have an incomplete octet (six electrons). As expected, these compounds invariably function as Lewis acids and are also highly reactive (because of their incomplete octet, they tend to readily accept a pair of electrons from a Lewis base, thereby acquiring an octet of electrons).

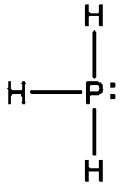
b) Many chemical reactions proceed through the transient formation of highly reactive species. For example, carbocations, as well as other species that lack an octet of electrons, have high energy (low stability) and, consequently, are highly reactive.

c) Lewis structures in which all the atoms have an octet of electrons cannot be written for molecules and ions that have an *odd* total number of valence electrons (for example, nitric oxide, NO). As might be expected, such species also exhibit high chemical reactivity.

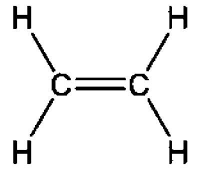
d) The atoms of elements that have empty d orbitals can expand their octets, namely, they can accommodate more than eight electrons. Sulfur and phosphorus are the two elements most commonly encountered in organic chemistry capable of accommodating more than eight electrons.

Examples

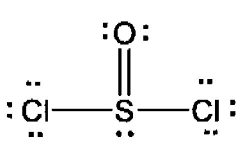
PH_3
P = 1 X 3 = 5
H = 3 X 1 = 3
8



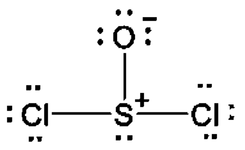
C_2H_2
C = 2 X 4 = 8
H = 4 X 1 = 4
12



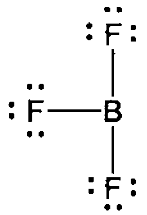
$SOCl_2$
S = 1 X 6 = 6
O = 1 X 6 = 6
Cl = 2 X 7 = 14
26



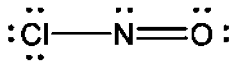
or



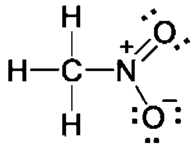
BF_3
B = 1 X 3 = 3
F = 3 X 7 = 21
24



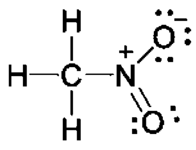
NOCl
N = 1 X 5 = 5
O = 1 X 6 = 6
Cl = 1 X 7 = 7
18



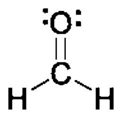
CH_3NO_2
C 1 X 4 = 4
H 3 X 1 = 3
N 1 X 5 = 5
O 2 X 6 = 12
24



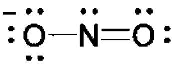
or



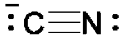
CH_2O
C 1 X 4 = 4
H 2 X 1 = 2
O 1 X 6 = 6
12



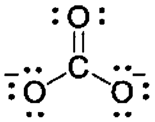
NO_2^-
N 1 X 5 = 5
O 2 X 6 = 12
= 1 (one negative charge)
18



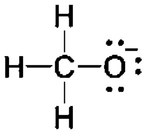
CN^- C 1 X 4 = 4
N 1 X 5 = 5
= 1 (one negative charge)
10



CO_3^{2-} C 1 X 4 = 4
O 3 X 6 = 18
= 2 (two negative charges)
24

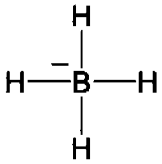


CH_3O^- C 1 X 4 = 4
H 3 X 1 = 3
O 1 X 6 = 6
= 1 (one negative charge)
14



$NaBH_4$ This is the same as Na^+ BH_4^-. Thus, the Lewis structure that we want is that of BH_4^-

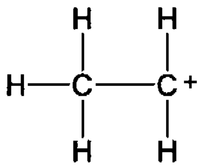
B 1 X 3 = 3
H 4 X 1 = 4
1 (one negative charge)
8



NO^+ N 1 X 5 = 5
O 1 X 6 = 6
11
-1 (subtract one electron for each positive charge)
10

Formal charge on O
6 - 2 - 3 = +1

$C_2H_5^+$ C 2 X 4 = 8
H 1 X 5 = 5
13
-1 (subtract one electron for each positive charge)
12



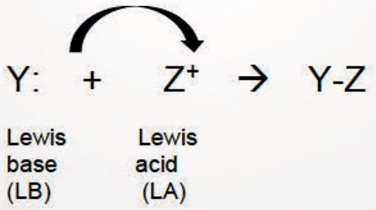
Notes

1) Compounds having a molecular formula that includes a group I or group II element are ionic compounds, namely, they consist of a cation and an anion. For example, $NaBH_4$, NaCN, $BaSO_4$, etc. In drawing a Lewis structure for an ionic compound, write the cation and anion first, and then draw the Lewis structure of the non-metallic component (usually the anion). By way of illustration, $BaSO_4$ consists of Ba^{2+} and SO_4^{2-} and you simply draw the Lewis structure of the sulfate ion.
2) On occasion, instead of being asked to draw the Lewis structure of a compound, you may be asked to deduce its relative stability, in which case you draw the Lewis structure and deduce its stability using the octet rule.

Minireview 2

1. Lewis acids
2. Lewis bases
3. Lewis acid/Lewis base reactions

A Lewis acid/Lewis base reaction can be generally described as shown below.



When organic reactions are described this way, the product of an organic reaction can be readily predicted, *without recourse to memorization.*

A Lewis base is substance that can donate a pair of non-bonded or pi electrons to a Lewis acid to form a covalent bond. Lewis bases that have a negative charge are stronger Lewis bases than those without a negative charge. For example, CH_3O^- is a stronger Lewis base than CH_3OH and, consequently, will react faster with a Lewis acid.

Furthermore, Lewis basicity is directly related to the availability of the pair of non-bonded electrons. A pair of non-bonded electrons on a *less* electronegative atom is more available for donation than a pair of non-bonded electrons on a *more* electronegative atom. This is the reason, for example, why amines are stronger Lewis bases than alcohols and ethers. Likewise, aliphatic amines are stronger Lewis bases than aromatic amines because the pair of non-bonded electrons on the nitrogen in aromatic amines is delocalized over the aromatic ring via resonance and, consequently, is not as available for donation.

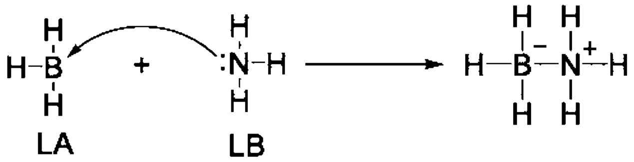
In Lewis acid/Lewis base reactions where a Lewis acid can bond to either of two atoms that differ in electronegativity, the stability of the product determines the site of the reaction. For example, the reaction of an amide ($R(C{=}O)NH_2$) with H^+ takes place on the O (more electronegative atom) than nitrogen (less electronegative atom) because the product is resonance-stabilized (vide infra).

A Lewis acid is a substance that can accept a pair of non-bonded or pi electrons from a Lewis base to form a covalent bond. Lewis acids are electron deficient, namely, an atom in a Lewis acid may have a positive charge, or it may have a *partial positive charge* because it is bonded to one or more electronegative atoms. An atom with an incomplete octet of electrons also acts as a Lewis acid, readily accepting a pair of electrons from a Lewis base. Recall that group IIIA elements are *trivalent*, namely, form compounds with three covalent bonds and, consequently, they lack an octet of electrons.

Example 1

$$BH_3 + NH_3 \longrightarrow H_3\overset{-}{B}\text{-}\overset{+}{N}H_3$$

or



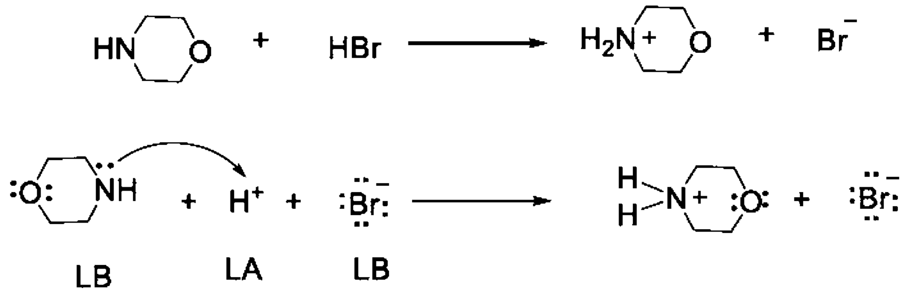
Note that the overall process involved in a Lewis acid/Lewis base reaction entails

(a) writing the Lewis structures of the two reactants and identifying the reactant which functions as a Lewis acid and the reactant that functions as a Lewis base;

(b) using a curved arrow to show how the non-bonded or pi electron pair of electrons in the Lewis base is used to form a covalent bond with the electron-deficient atom in the Lewis acid and

(c) determining the formal charges on the two atoms involved in the formation of the new covalent bond.

Example 2



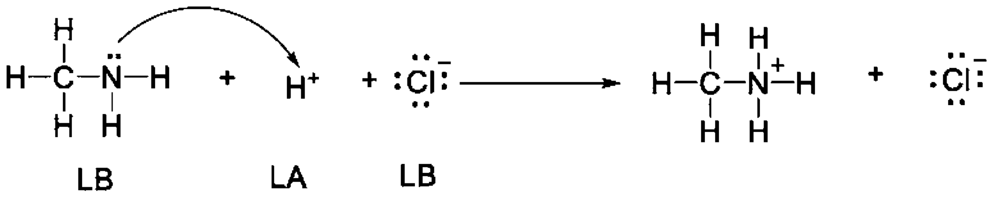
Notes

(a) As mentioned earlier, strong mineral acids (HCl, HBr, HNO_3, etc.) and strong organic acids (RSO_3H, RCOOH, etc.) are *ionized* in solution, therefore it's best to represent them as ions (*for the sake of simplicity, H^+ instead of H_3O^+ is used throughout the book*). When written that way, it can be readily ascertained which is the Lewis acid and which is the Lewis base. Strong bases and ionic compounds should be treated the same way.

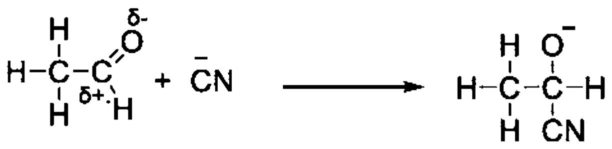
(b) Recall that a Lewis base will only react with a Lewis acid, but *not* with another Lewis base.

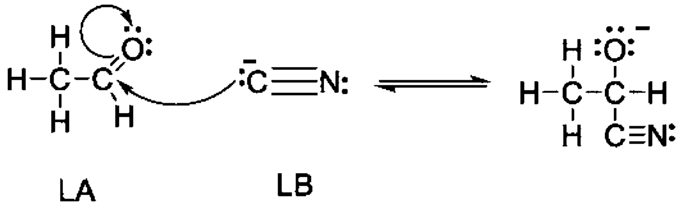
Example 3

$$CH_3NH_2 + HCl \longrightarrow CH_3NH_3^+ + Cl^-$$



Example 4





Notice that in this example the carbonyl carbon is electron-deficient because it is bonded to an electronegative atom and, consequently, has a partial positive charge; Thus, the molecule can behave as a Lewis acid and accept a pair of electrons from the Lewis base. In general, an atom that is bonded to one or more electronegative atoms will have a partial positive charge and can, in principle, function as a Lewis acid by accepting a pair of electrons from a Lewis base.

Minireview 3

Resonance

Resonance involves the alternate placement of non-bonded or pi electrons over the same atomic skeleton, without any change in the position of the atoms.

A general familiarity with the concept of resonance and a facility in writing resonance structures is very helpful in

a) assessing the *stability* of an individual species (anion, cation, or radical)

b) assessing the *relative stability* of two similar species, thereby enabling one to predict the pathway that a reaction will likely to follow and/or which species is likely to form (since the greater the stability of a species is, the easier it is to form) and,

c) predicting the *site* of reaction in a molecule.

When a molecule or ion can be represented by two or more Lewis structures that differ only in the position of the electrons,

a) none of those Lewis structures represents the *actual* structure of the molecule or ion and,

b) the actual structure of the molecule or ion is best represented by a hybrid (called *resonance hybrid*) of these resonance structures.

In writing resonance structures, the following *general rules* should be followed:

a) the greater the number of resonance structures that can be written for a species, the more stable the species is;

b) resonance structures in which all the atoms have an octet of electrons are more stable;

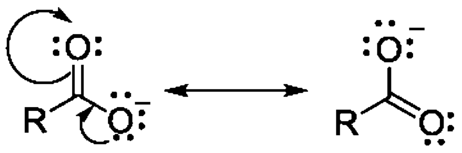
c) other things being equal, a resonance structure with a negative charge on the most electronegative atom will have greater stability. Conversely, a resonance structure with a positive charge on the least electronegative atom will be more stable;

d) maximum stabilization of a species (anion or cation) is achieved when the contributing resonance structures are *equivalent*, namely, they have the same energy.

Examples illustrating these rules are given below.

Resonance structures involving anions

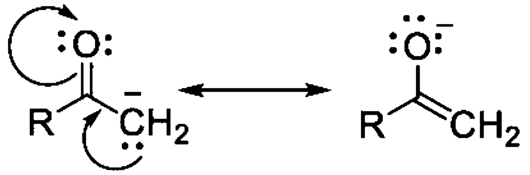
Example 1



The two resonance structures that can be written for the carboxyl anion ($RCOO^-$) are shown here *(in writing resonance structures for anions, the movement of the electrons is initiated from the atom bearing the negative charge toward the pi bond and the other electronegative atom)*.

Note that these structures are *equivalent*, namely, they have the same energy (they both have a negative charge on the same kind of atom) [Rule 4]. Notice also that the delocalization of the negative charge over the two oxygen atoms via resonance stabilizes the anion and is the reason for the acidity of carboxylic acids. In other words, the hydrogen ion in a carboxylic acid (RCOOH) is acidic and readily donated to a base because a resonance-stabilized anion is formed in the process (see also Minireview 5 for a full discussion of the relationship between acid strength and resonance stabilization of the conjugate base).

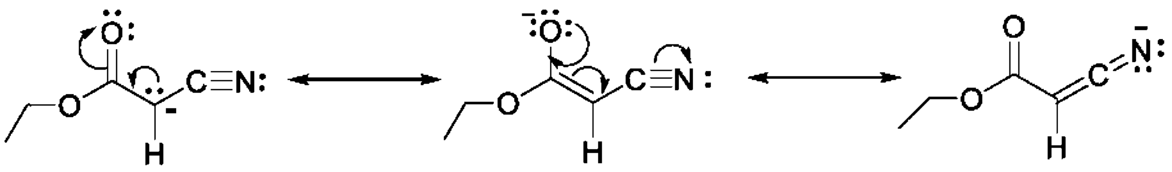
Example 2



The resonance structures shown here are *non-equivalent*, since the negative charge is on two different atoms (carbon and oxygen). The resonance structure with the negative charge on the more electronegative atom is more stable [Rule 3].

Recall that electronegativity follows the order F > O > N, Br > Cl > C, H.

Example 3



(I) (II) (III)

The order of stability in resonance structures (I) to (III) parallels the order of electronegativity of the three atoms bearing the negative charge [Rule 3]. Thus,

(II) > (III) > (I)

←

Increasing stability

O > N > C

←

Increasing electronegativity

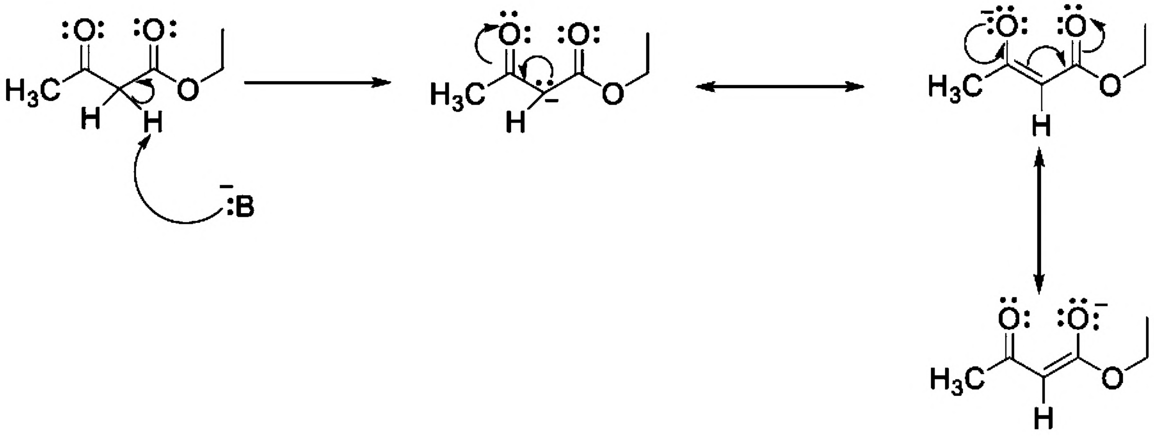
As stated earlier, the greater the number of resonance structures that can be written for an anion, the greater the stability of the anion [Rule 1]. Put differently, *the greater the delocalization of the negative charge, the greater the stability of an anion.* Consequently, in comparing the relative stability of two anions, the more stable anion will be the one for which a greater number of resonance structures can be written.

Corollary

Resonance-stabilized anions have higher stability and, therefore, are easier to form. Thus, the relative acidity of a acid is determined by the stability of the corresponding anion.

Example 4

When ethyl acetoacetate is treated with base it readily forms the resonance-stabilized anion shown below:



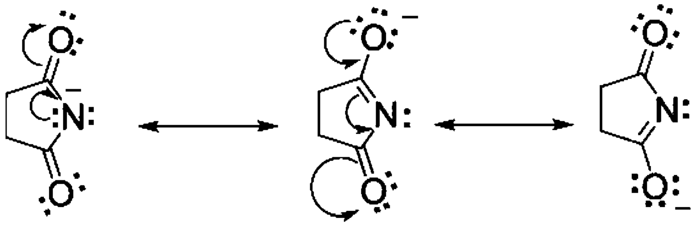
Exercise

a) Rank the resonance structures in example 4 in order of decreasing stability (most stable first).

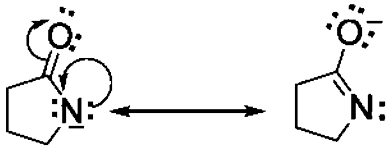
b) The three methyl hydrogens in ethyl acetoacetate are less acidic than the two methylene hydrogens. Why?

Example 5 Assess the relative stability of anions A and B below:

A



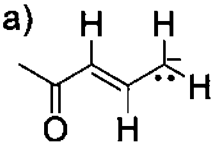
B



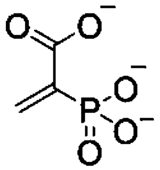
Three resonance structures can be written for anion A versus two resonance structures for anion B. Hence, anion A is more stable than anion B [Rule 1].

Exercise Write all the major resonance structures for the following anions.

a)



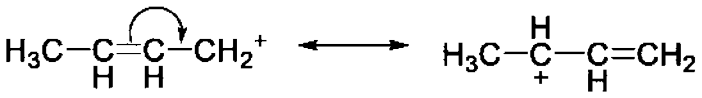
b)



Resonance structures involving cations

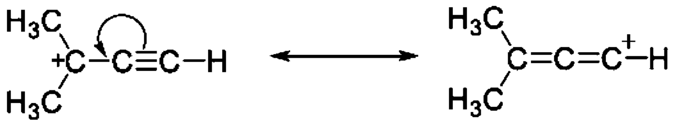
Allylic and benzylic carbocations, as well as carbocations having a heteroatom directly bonded to the carbon bearing the positive charge, are stabilized by resonance. When writing resonance structures for cations, *the movement of the non-bonded or pi electrons is toward the positively charged atom* (electrons are negatively-charged and are therefore attracted to the positive charge).

Example 1

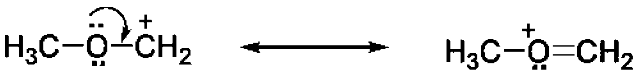


$$H_3C-\underset{H}{C}=\underset{H}{C}-CH_2^+ \longleftrightarrow H_3C-\overset{H}{\underset{+}{C}}-\underset{H}{C}=CH_2$$

Example 2

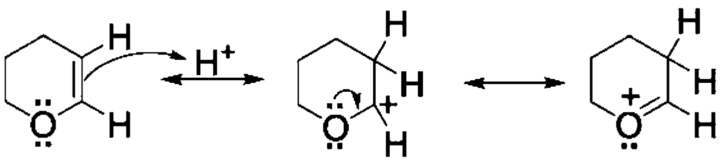


Example 3

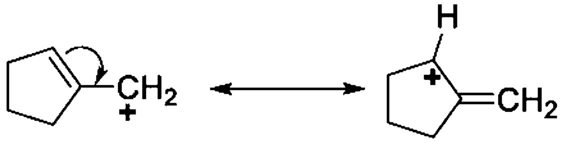


$$H_3C-\overset{..}{\underset{..}{O}}-\overset{+}{C}H_2 \longleftrightarrow H_3C-\overset{+}{\underset{..}{O}}=CH_2$$

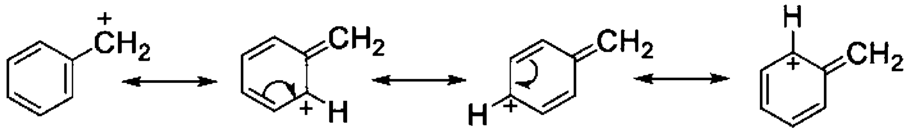
Example 4



Example 5

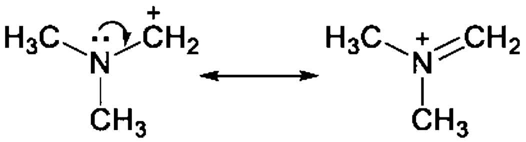


Example 6

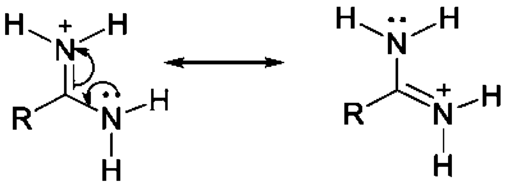


In this example, the first resonance structure is more stable than the others because the ring is aromatic, which is not the case with the other three structures.

Example 7

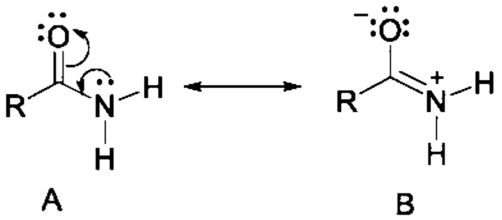


Example 8



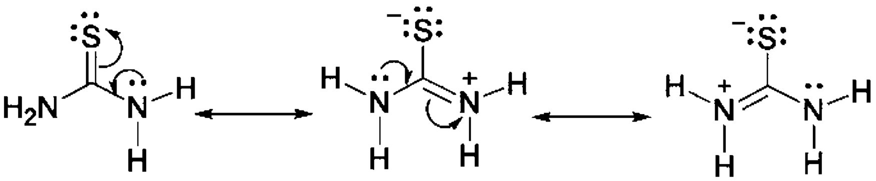
Resonance structures involving neutral molecules

Example 1

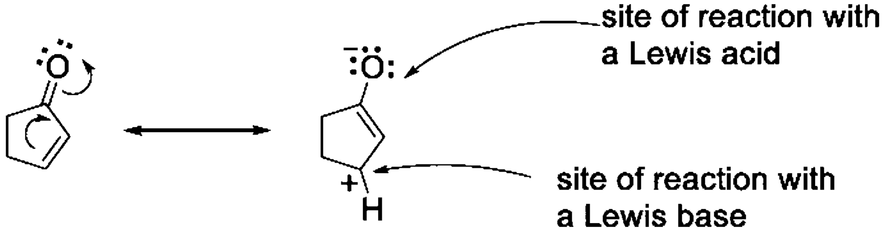


Structure A is more stable than structure B, however, structure B is a significant contributor that accounts for a) the observed *restricted rotation* around the C-N bond in amides and peptides and, b) the *decreased Lewis basicity* of amides verses amines (arising from the lower availability of the non-bonded electron pair on the nitrogen in amides).

In thiourea and thioamides, S_N2 reactions occur at sulfur because of the contribution of the resonance structures shown below and the high nucleophilicity of sulfur (see Minireview 6 for a discussion of nucleophilicity).



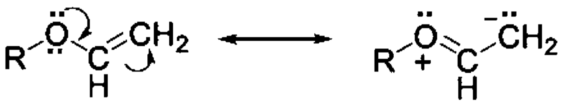
Resonance structures can be used to predict the *site* of reaction in neutral molecules. For example, the course of the reaction of α,β-unsaturated compounds with a Lewis base (*Michael addition reaction*) can be predicted by considering the resonance structure shown below. The resonance structure clearly indicates that the β carbon is electron-deficient (Lewis acid) and can accept a pair of electrons from a nucleophile (Lewis base).

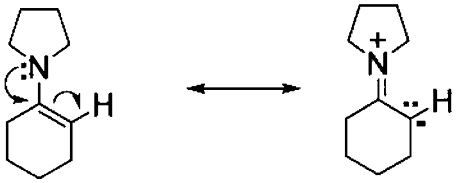


site of reaction with a Lewis acid

site of reaction with a Lewis base

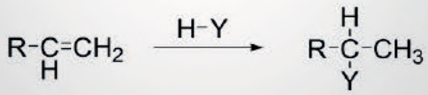
Likewise, the following resonance structures identify the sites of reaction of vinyl ethers and enamines with Lewis acids and provide a better understanding of the chemical behavior of these classes of compounds.





Minireview 4

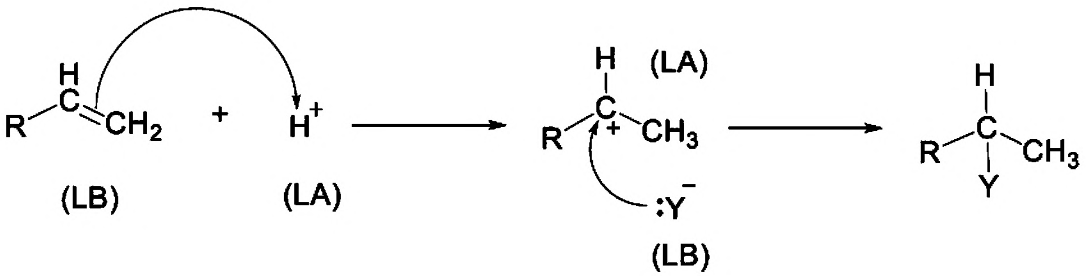
Carbocation Chemistry



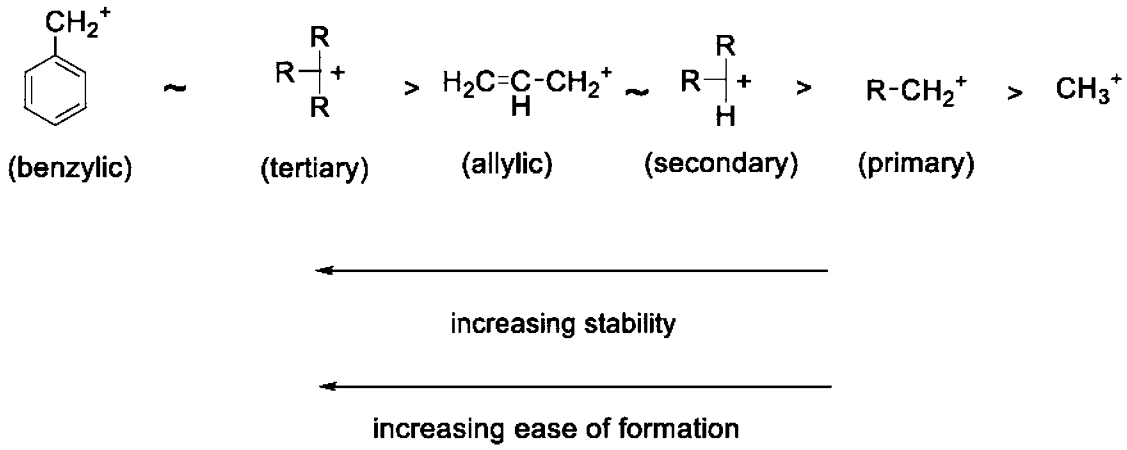
$$\mathrm{R{-}\underset{H}{C}{=}CH_2 \xrightarrow{H{-}Y} R{-}\overset{H}{\underset{Y}{C}}{-}CH_3}$$

The reaction of alkenes, alkynes, or alcohols (all Lewis bases) with H^+ (a strong Lewis acid) leads to the initial formation of a carbocation. *Carbocations are transient, electron-deficient, and highly-reactive species*. Once formed, they function as Lewis acids that react rapidly with Lewis bases (in the process the carbon atom bearing the positive charge completes its octet).

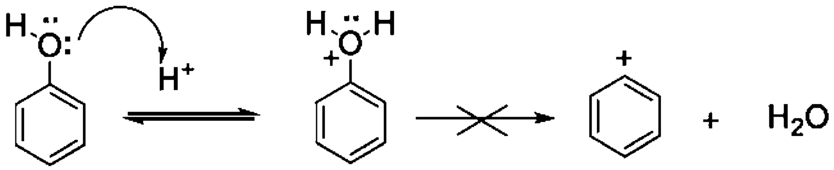
Some noteworthy characteristics of carbocations are the following:



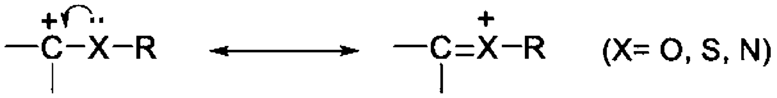
1) Carbocations vary in stability depending on their structure. *The greater the stability of a carbocation is, the easier it is to form*. Thus, the initial carbocation formed in a given reaction is invariably the one with the highest stability. The *order of stability of* carbocations is as follows:



Methyl, vinyl and phenyl carbocations are highly unstable. Consequently, although the hydroxyl group of a phenol can, in principle, function as a Lewis base (just like the hydroxyl group of an alcohol), it never yields a phenyl carbocation.



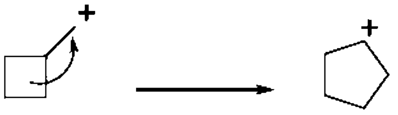
As mentioned earlier, carbocations that have a positive charge on a carbon atom which is bonded to a heteroatom (O, N, S) are stabilized by resonance.



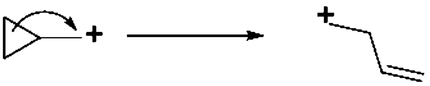
2) *Carbocations frequently undergo rearrangements via 1,2-hydride or 1,2-alkyl shifts to form carbocations of equal or greater stability.* These carbocations may on occasion arise via consecutive 1,2-hydride and/or 1,2-alkyl shifts. Further reaction with a Lewis base, or loss of a H^+ from an adjacent carbon (E_1), ultimately yields the observed product(s).

In certain cases, initial formation of a carbocation is followed by *ring expansion* to form a new carbocation. The driving force behind the observed ring expansion is the relief of ring strain and the formation of a more stable species. *Recall that as ring size decreases, ring strain increases*. Thus, 3- and 4-membered rings have considerable ring strain and tend to undergo ring expansion. *Recall also that as ring strain increases, chemical reactivity increases.*

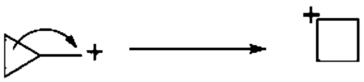
An interesting variation of this theme involves the cyclopropylmethyl carbocation.



(relief of ring strain via ring expansion)



(homoallylic carbocation)

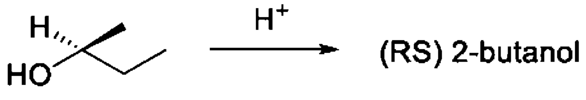


(ring expansion)

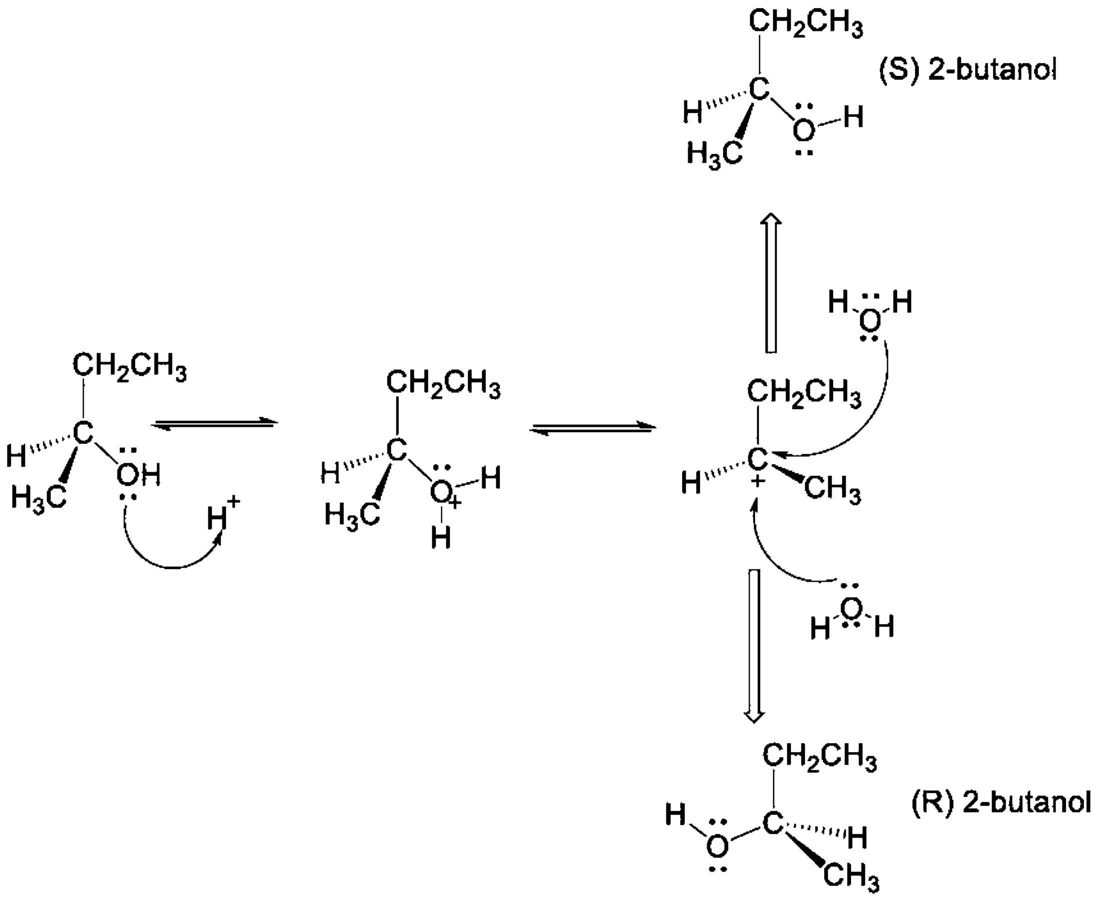
3) *Carbocations are planar (flat), since the carbon bearing the positive charge is* sp^2 *hybridized*. Consequently, *a carbocation derived from an optically active reactant will ordinarily yield an optically inactive product (a racemic mixture) upon reaction with a Lewis base*. Since attack on an sp^2 hybridized carbon by a Lewis base is equally likely from either side, this leads to a 1:1 mixture of the R and S isomers.

Example

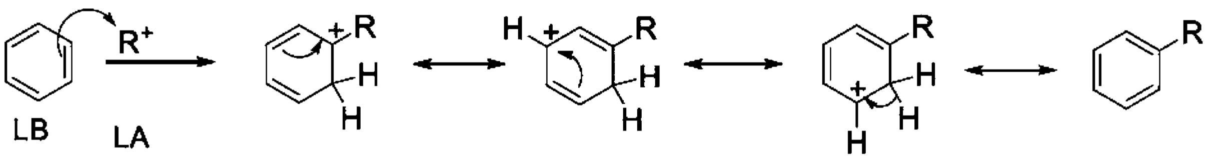
When (S) 2-butanol is treated with a trace amount of acid, it undergoes racemization. Write a plausible mechanism that accounts for this observation.



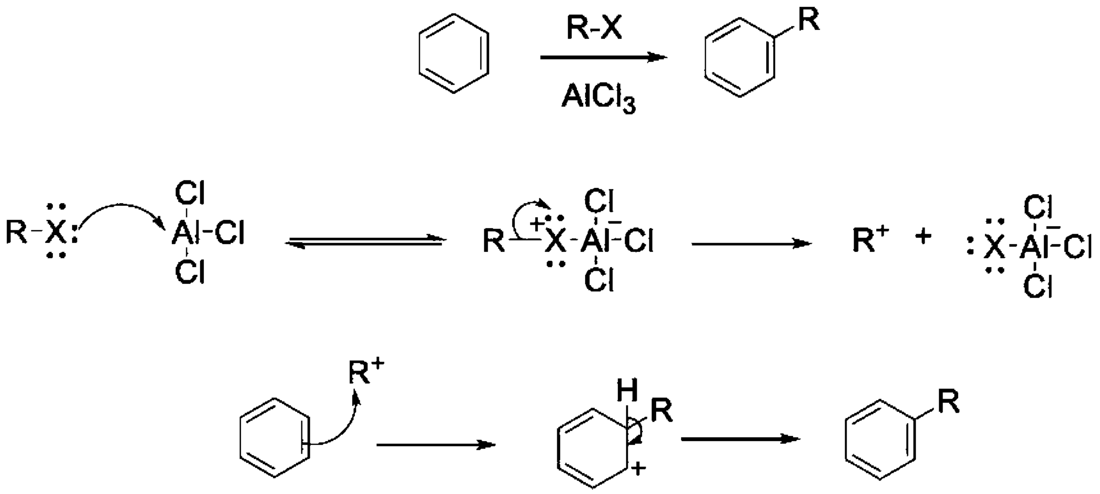
(R)



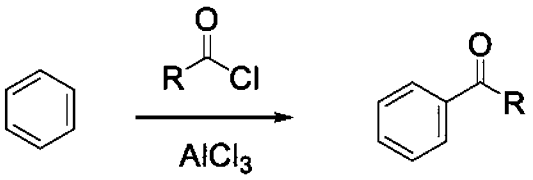
4) An *electrophilic aromatic substitution* reaction can be viewed as a two-step Lewis base/Lewis acid reaction involving an aromatic compound (acting as a Lewis base) and a transiently-generated Lewis acid (also called an *electrophile*). Recall that the first step in an electrophilic aromatic substitution reaction is the *rate-determining* step (has the highest free energy of activation). Typical transient Lewis acids include carbocations and other electron-deficient species such as NO_2^+, R^+, etc.



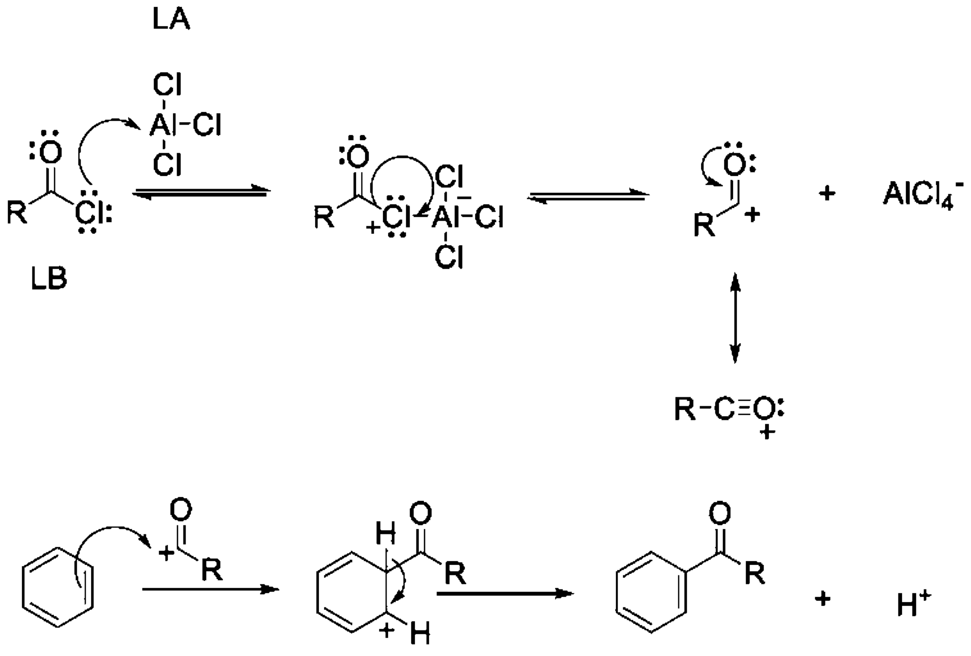
In the familiar *Friedel-Craft alkylation reaction* a carbocation is generated by mixing an alkyl halide (RX) with a Lewis acid (AlX_3), or by mixing an alcohol (ROH) or alkene with acid. As expected, the formation of a carbocation in this reaction may lead to the formation of rearranged products.



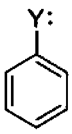
The reaction of an aromatic compound with an acid chloride (RCOCl) in the presence of a Lewis acid is referred to as the *Friedel-Craft acylation reaction*. An initial Lewis acid/ Lewis base reaction leads to the transient formation of a resonance-stabilized carbocation (also called an *acylium ion*) which then reacts with the aromatic compound (illustrated below). In contrast to ordinary carbocations, *acylium ions do not undergo rearrangements*.



Mechanism

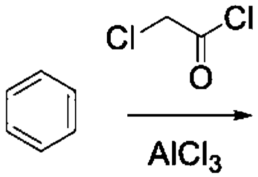


In the nitration and halogenation reactions the Lewis acid (electrophile) is transiently generated via a sequence of Lewis acid/ Lewis base reactions using concentrated HNO_3/H_2SO_4 and Br_2 (or Cl_2) with $FeBr_3$ (or $FeCl_3$), respectively. Recall that the presence and nature of substituent on the aromatic ring has a profound effect on *reactivity* and *orientation*. *Electron-donating groups* (R, OR, NHCOR, OH, NH_2, etc.) enhance Lewis basicity and, hence, the reactivity of an aromatic compound. Furthermore, these groups direct the Lewis acid (electrophile) to the *ortho* and *para* positions. In contrast, *electron-withdrawing groups* (NO_2, CN, CHO, COR, COOR, etc.) decrease reactivity and direct the electrophile to the *meta* position. Halogens are deactivating, but *ortho* and *para*-directing. *Activating groups have one or more pairs of non-bonded elctrons on the attom that is directly bonded to an aromatic carbon.*



Exercise 1 Is the nitroso group (-NO) an activating or deactivating group?

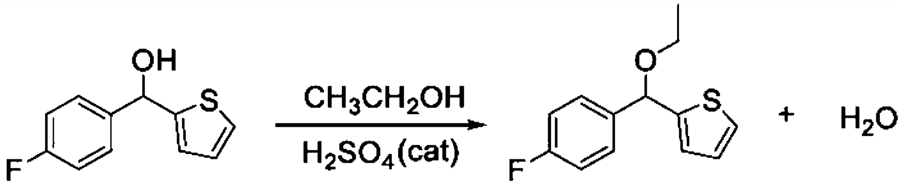
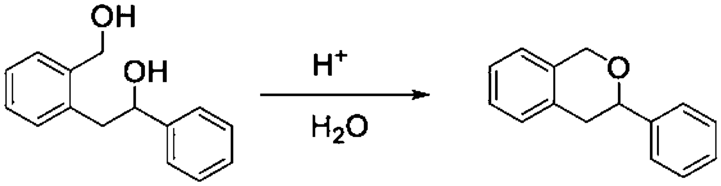
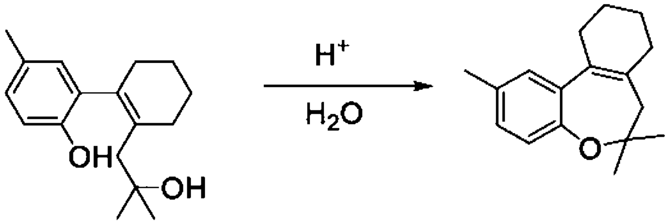
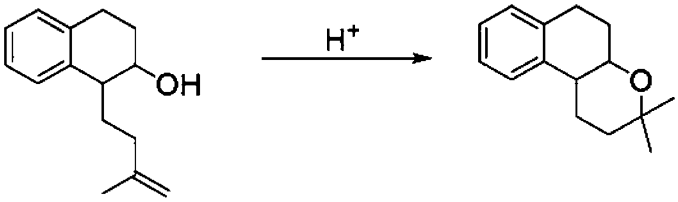
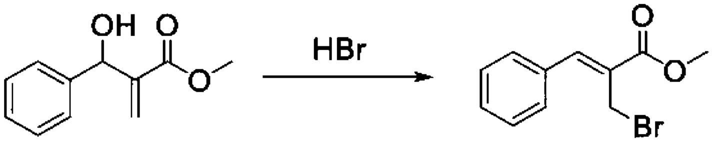
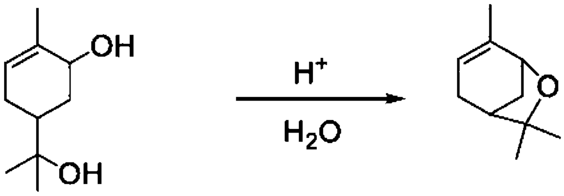
Exercise 2 Predict the product of the following reaction

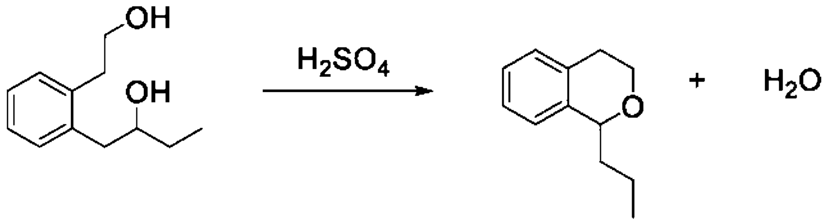
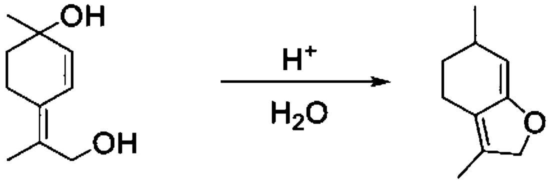
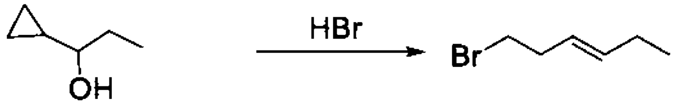
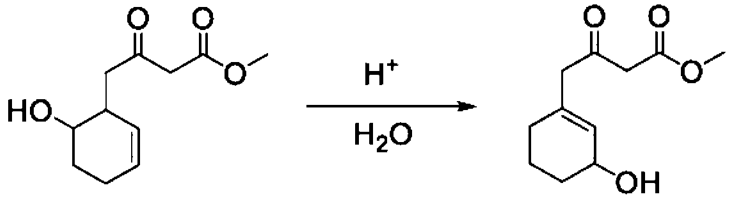
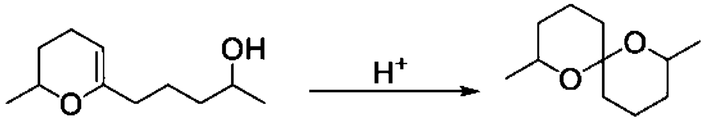
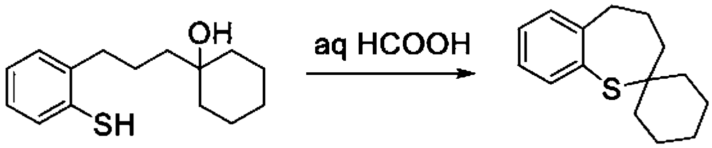


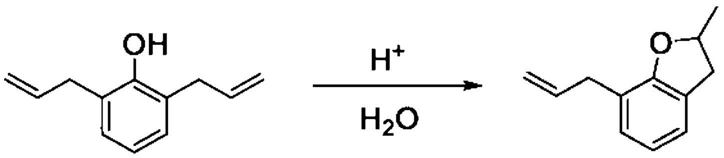
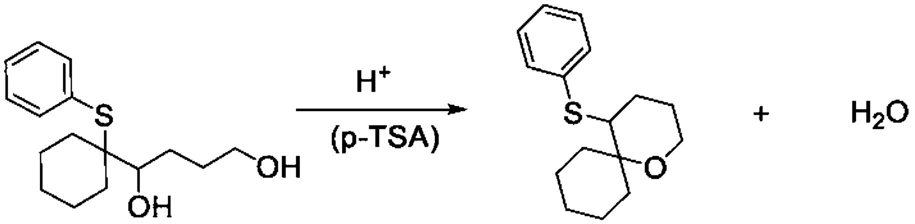
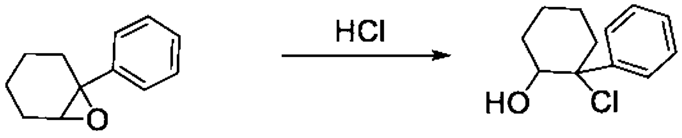
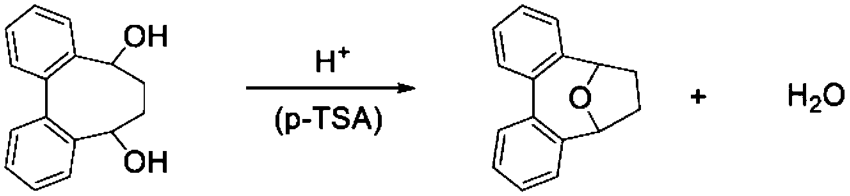
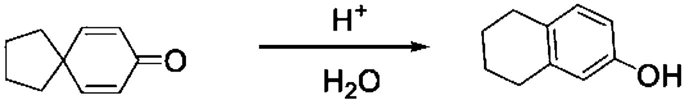
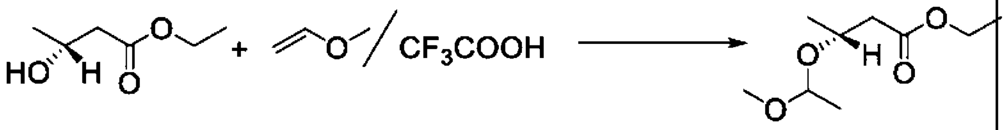
Questions 1 – 34

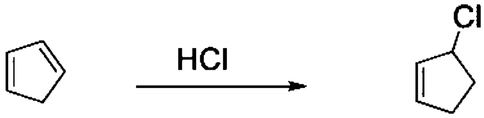
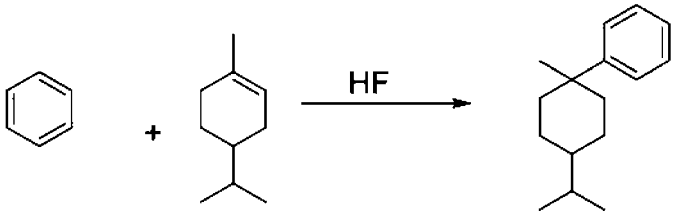
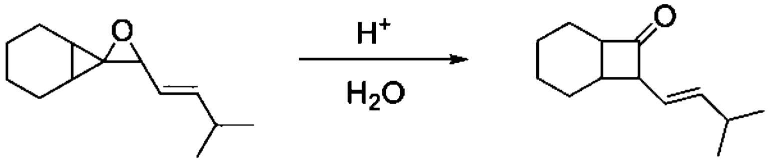
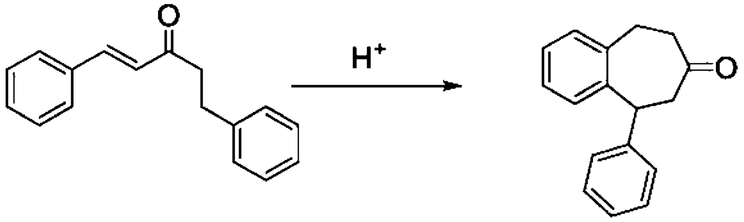
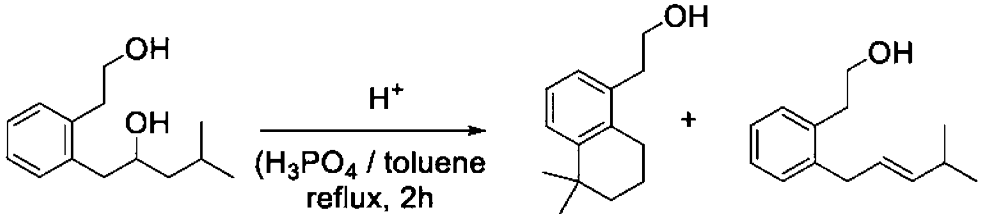
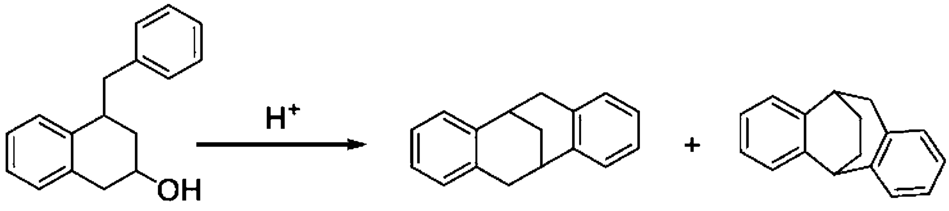
Questions 1-34 aim at reviewing and gaining a better understanding of the following topics.

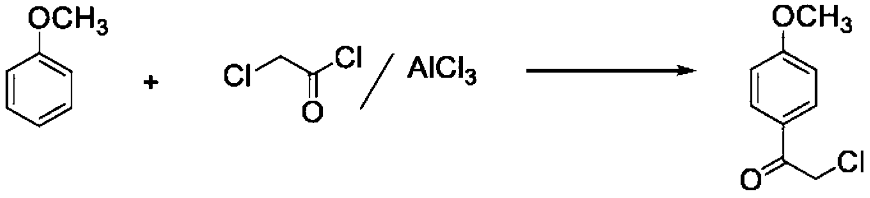
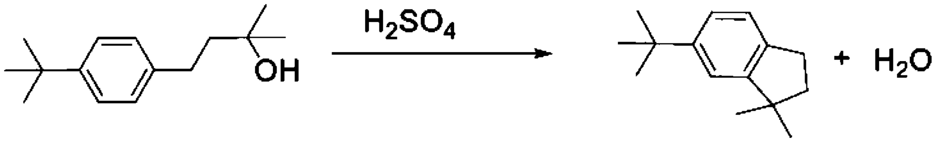
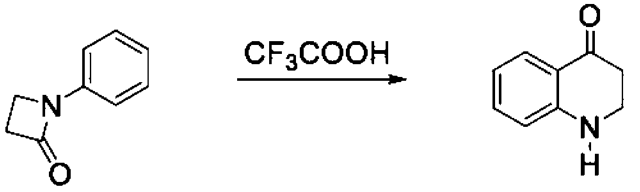
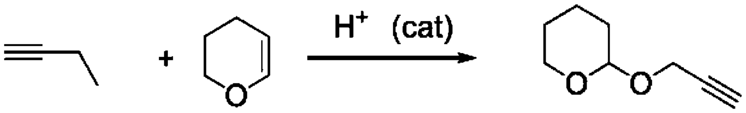
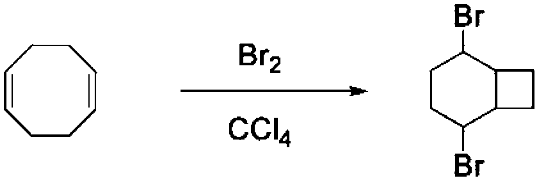
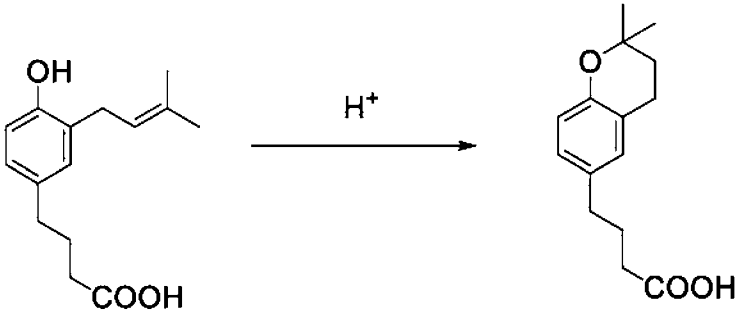
- Lewis structures
- Lewis acids and Lewis bases
- Lewis acid/ Lewis base reactions
- Resonance (rules of resonance, writing resonance structures, assessment of relative stability of anions and cations using resonance)
- Carbocation chemistry (formation, stability, rearrangements, stereochemistry, and reactions of carbocations)
- Lewis acid/ Lewis base reactions of alcohols, alkenes, alkynes, and epoxides
- Lewis acid/ Lewis base reactions involving aromatic rings (electrophilic aromatic substitution reactions, including Friedel-Craft alkylation and acylation reactions)

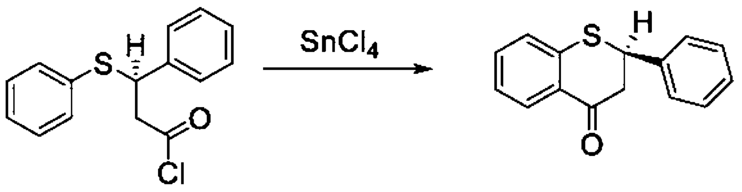
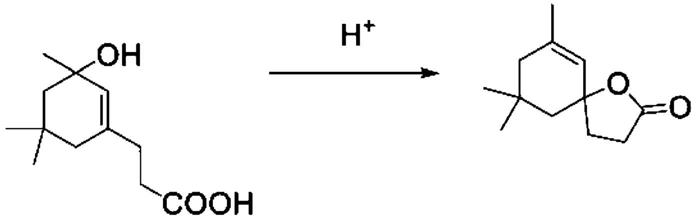
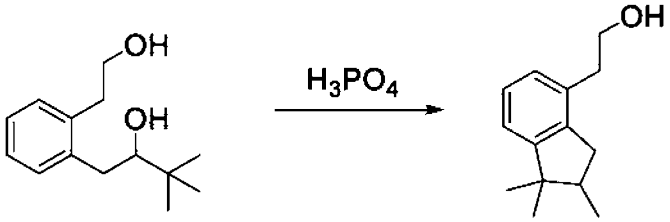
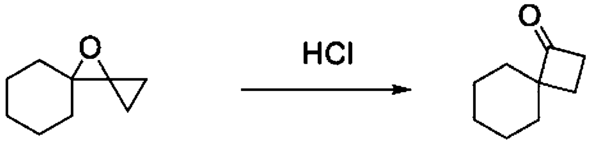
1	 OH S F CH3CH2OH H2SO4(cat) O S F + H2O
2	 OH OH H+ H2O O
3	 OH OH H+ H2O O
4	 OH H+ O
5	 OH O O HBr O O Br
6	 OH OH H+ H2O O

7	 OH OH H_2SO_4 O + H_2O
8	 OH OH H^+ H_2O O
9	 OH HBr Br
10	 O O O HO H^+ H_2O O O O OH
11	 O OH H^+ O O
12	 OH SH aq HCOOH S

13	
14	
15	
16	
17	
18	

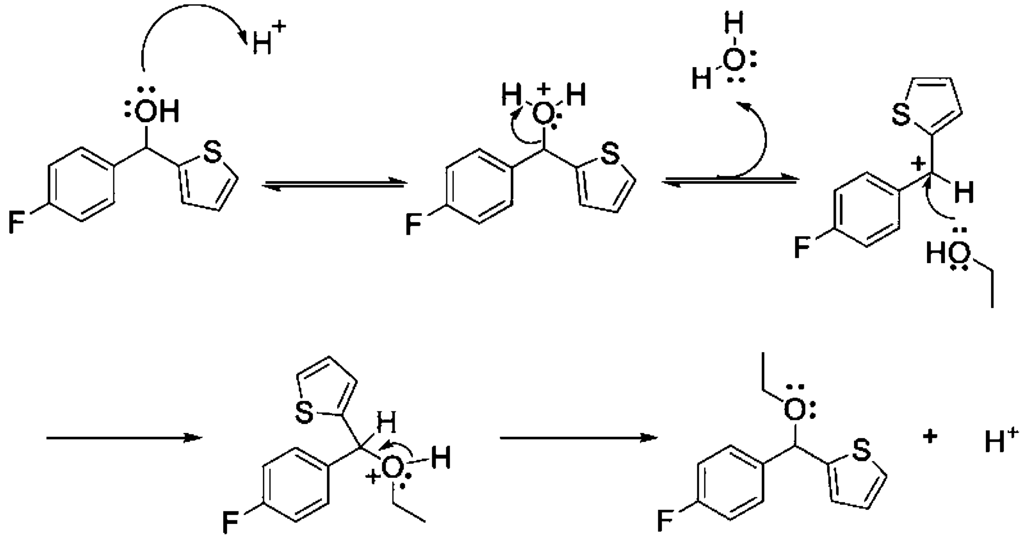
19	
20	
21	
22	
23	
24	

25	
26	
27	
28	
29	
30	

31	
32	
33	
34	

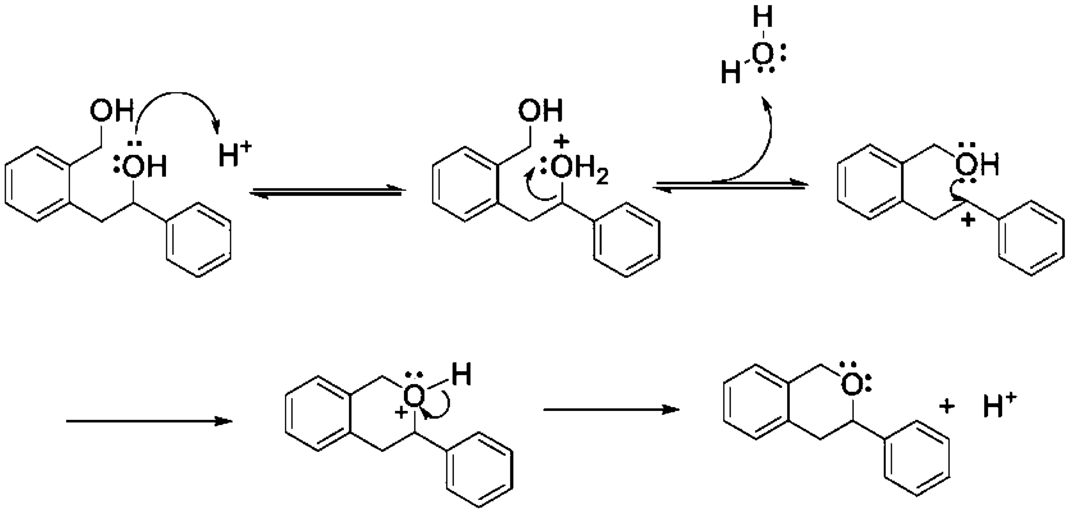
Answers to Questions 1-34

1



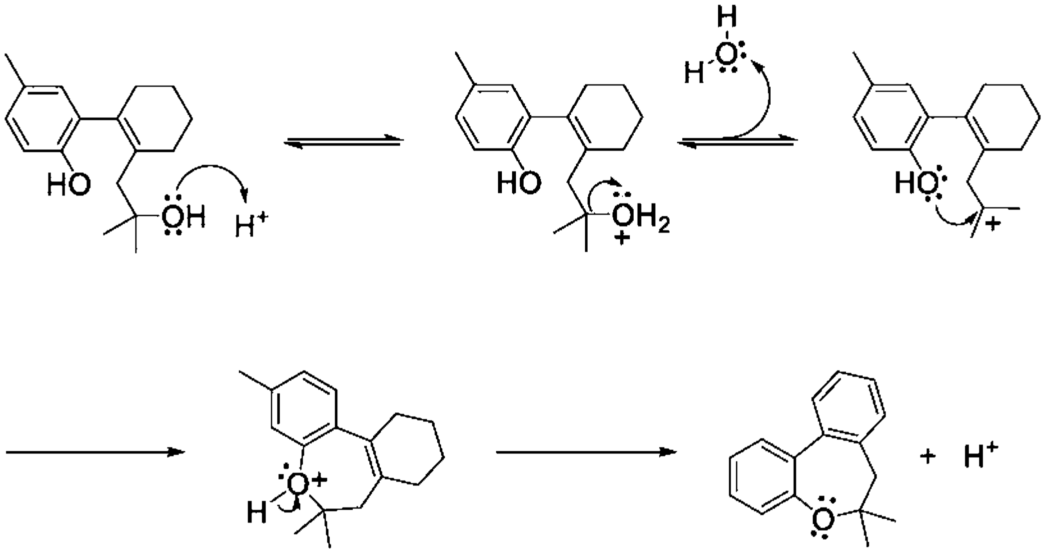
An initial LA/LB reaction leads to the formation of a resonance stabilized benzylic carbocation (a Lewis acid), which then reacts with ethyl alcohol (a Lewis base) to form the product. Recall that (a) non-bonded electrons are more available for donation than bonded electrons (pi electrons); (b) reaction of the LA with either aromatic ring would result in the formation of a non-aromatic species and the loss of resonance stabilization energy.

2



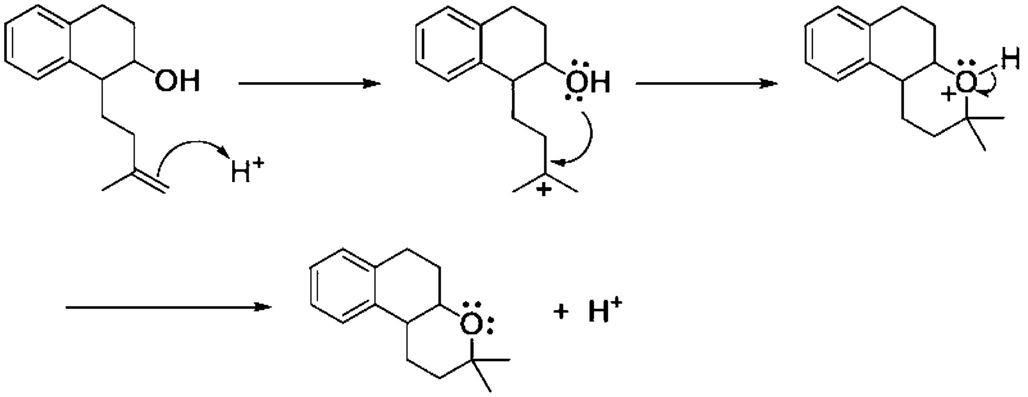
Although either oxygen atom can donate a pair of electrons to the Lewis acid, initial formation of the more stable species (a 2° benzylic carbocation) is preferred. A subsequent intramolecular LA/LB reaction leads to the formation of the product.

3



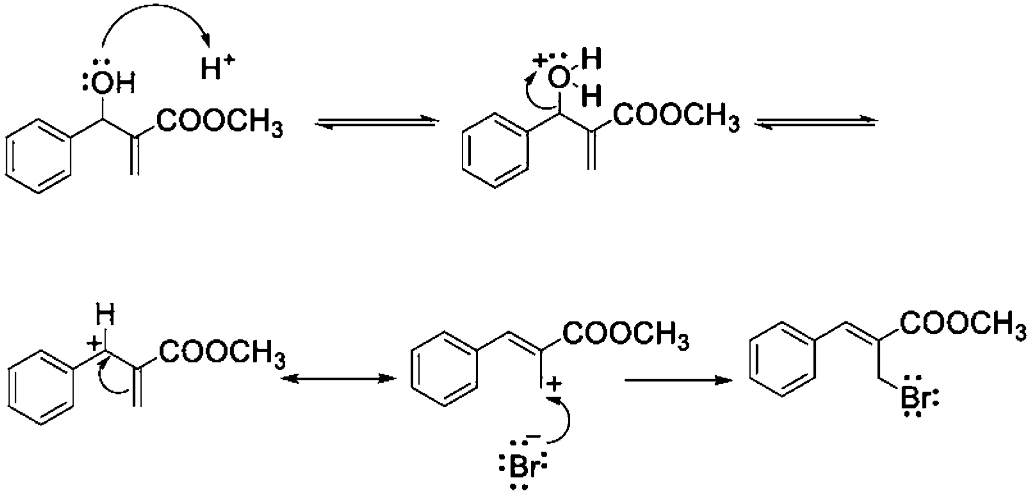
Note that although the phenolic-OH can, in principle, react with the Lewis acid, formation of a phenyl carbocation does not take place because of the low stability of this carbocation. Consequently, only the much more stable tertiary carbocation is formed. This is then followed by an intramolecular LA/LB reaction to form the product.

4



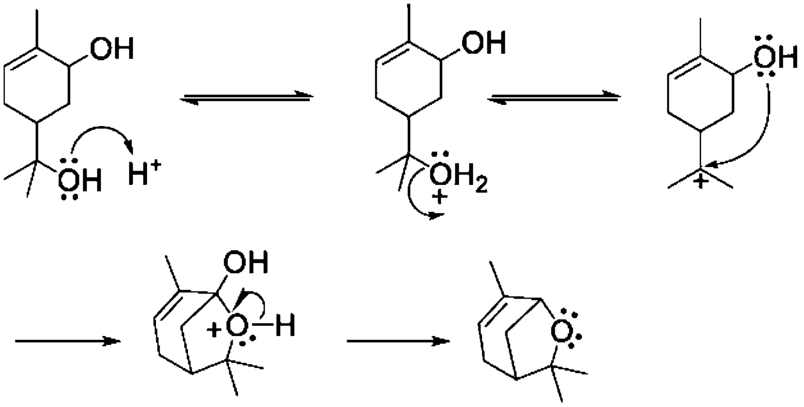
A LA/LB reaction between the pi-bond and the hydrogen ion (LA) yields a tertiary carbocation. This is followed by an intramolecular LA/LB reaction, leading to the formation of the observed product. As stated earlier, non-bonded electrons are more available for donation than pi electrons, however, in this instance donation of a pair of pi electrons results in the formation of a highly stable 3^{o} carbocation.

5



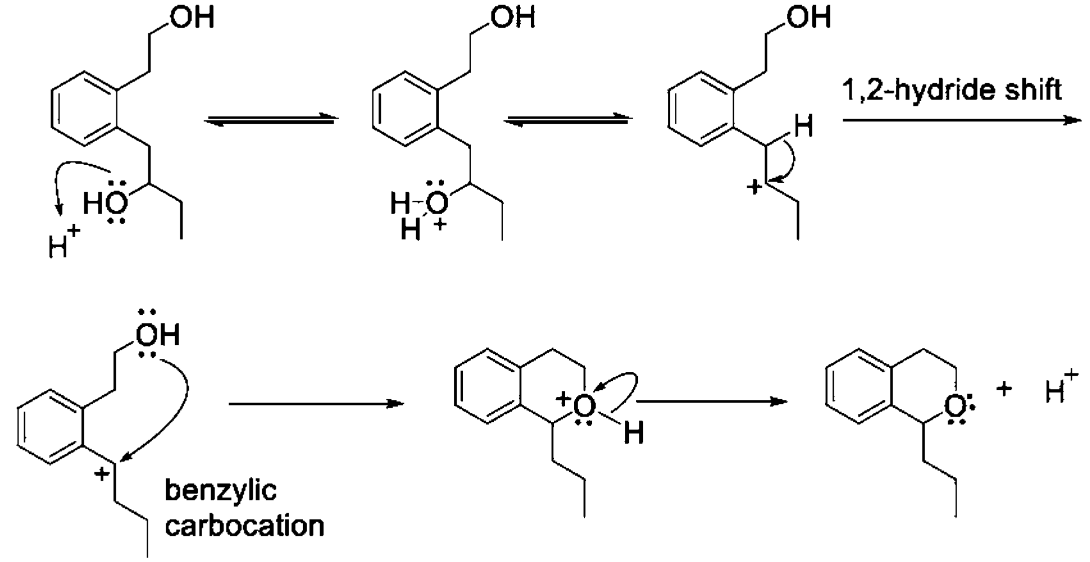
Recall that strong acids are fully ionized in solution. Formation of the resonance-stabilized benzylic and allylic carbocation is followed by a LA/LB reaction to form the product.

6



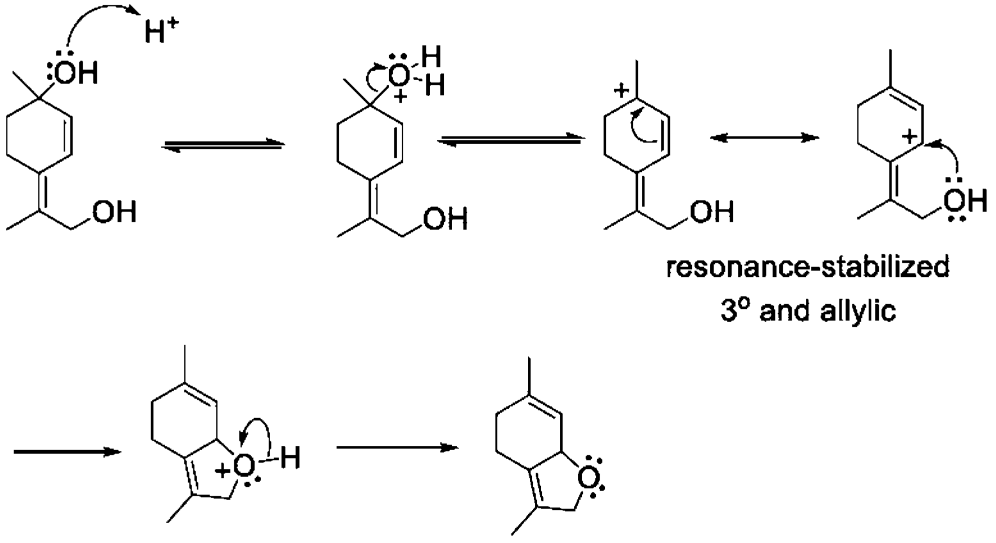
Although either -OH group can react in a LA/LB reaction, the one that leads to formation of the more stable carbocation reacts preferentially (General principle to remember: most organic reactions proceed through the formation of the more stable intermediate species and, ultimately, the more stable final product). A subsequent intramolecular LA/LB reaction leads to the formation of the product

7

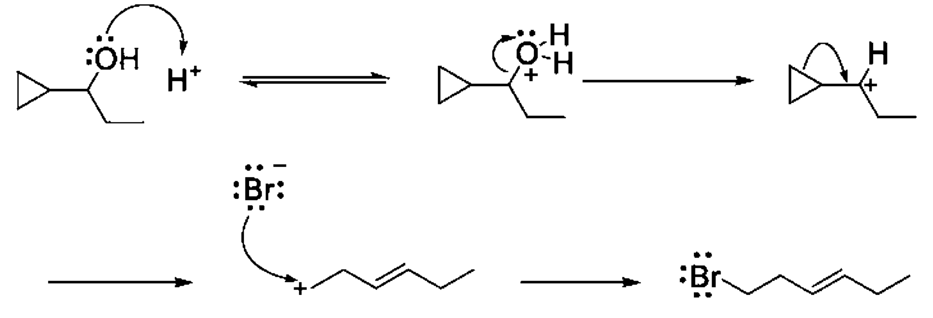
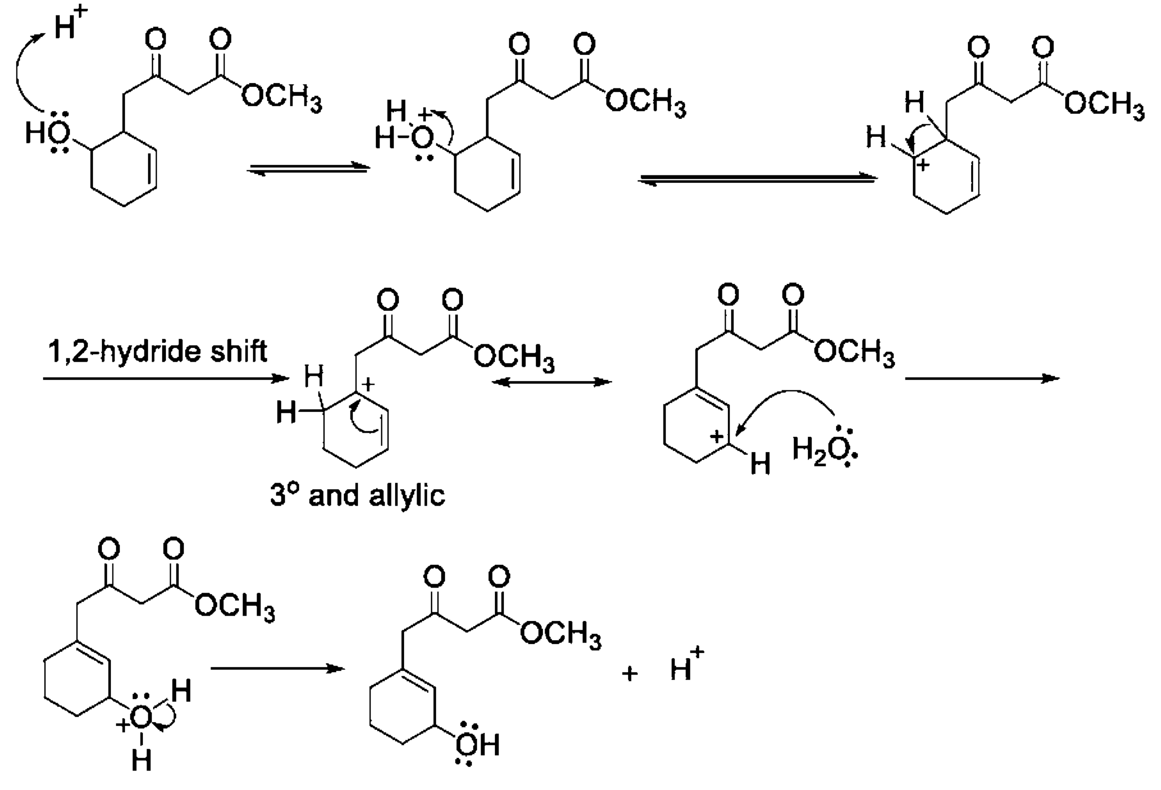


Initial formation of the more stable 2° carbocation is followed by a 1,2-hydride shift to yield a benzylic carbocation. This is followed by an intramolecular LA/LB reaction to yield the product.

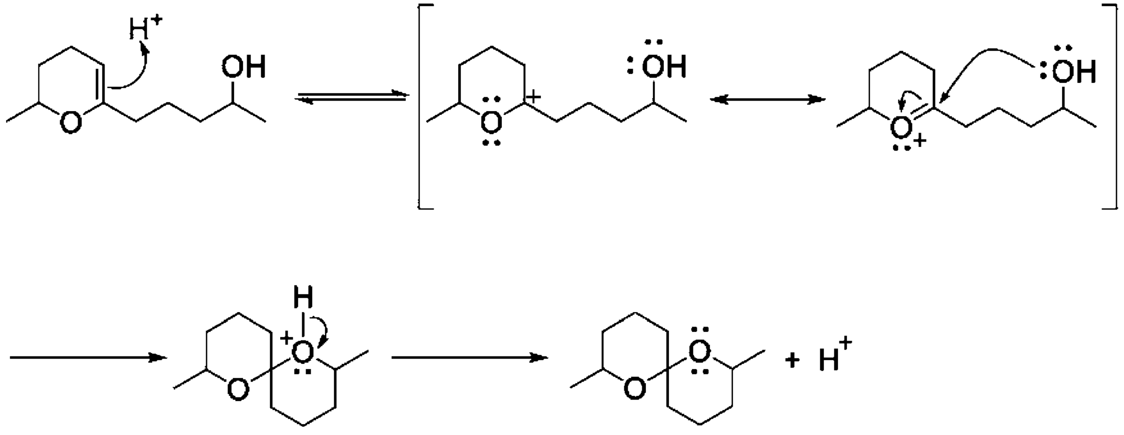
8



Initial formation of a resonance-stabilized 3° and allylic carbocation is followed by an intramolecular LA/LB reaction to yield the product.

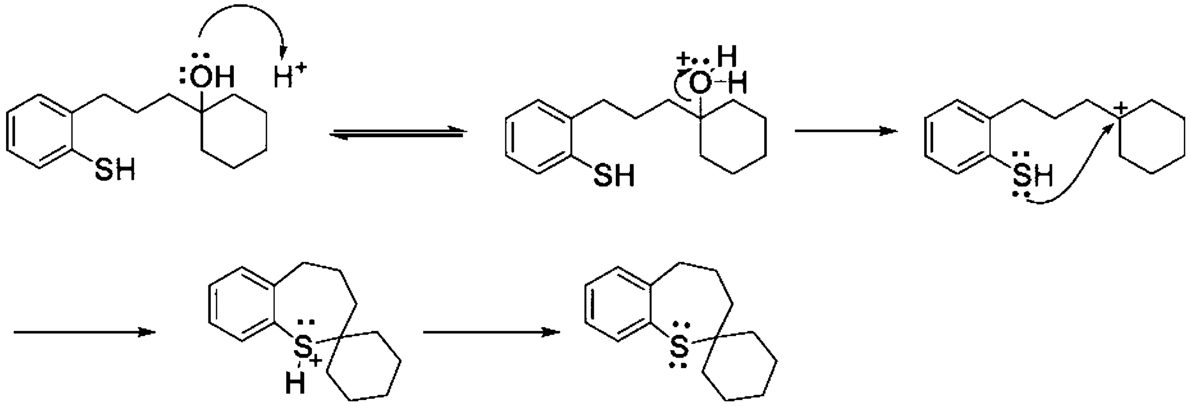
9	
	See Minireview 4 for a discussion of cyclopropyl methyl carbocations.
10	
	While the initial LA/LB reaction can also take place at the carbonyl oxygens, that's an unproductive process, namely, it does not lead to the formation of the observed product

11



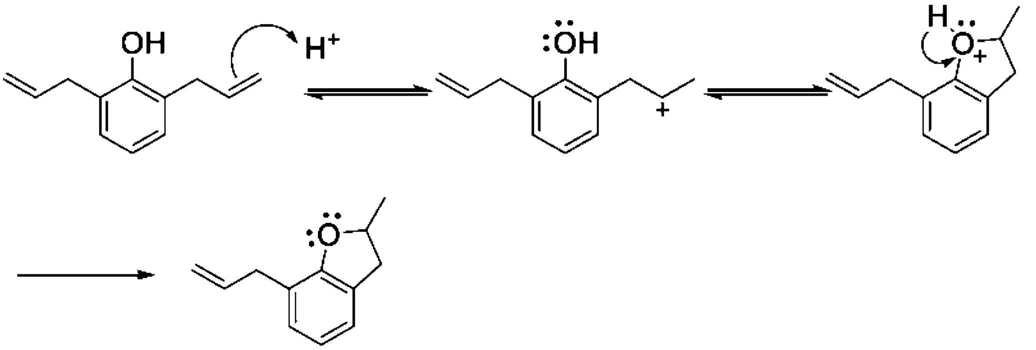
Although the starting material has three functional groups or reactive sites where a LA/LB reaction can take place, the more stable resonance-stabilized cation is initially formed preferentially.

12



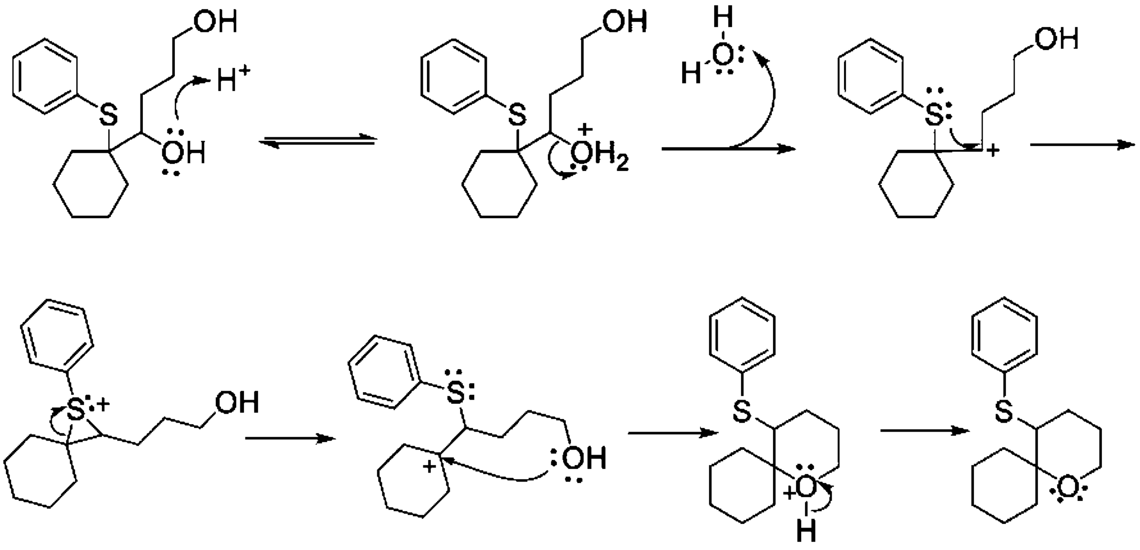
Formation of the 3° carbocation is followed by an intramolecular LA/LB reaction to yield the product.

13



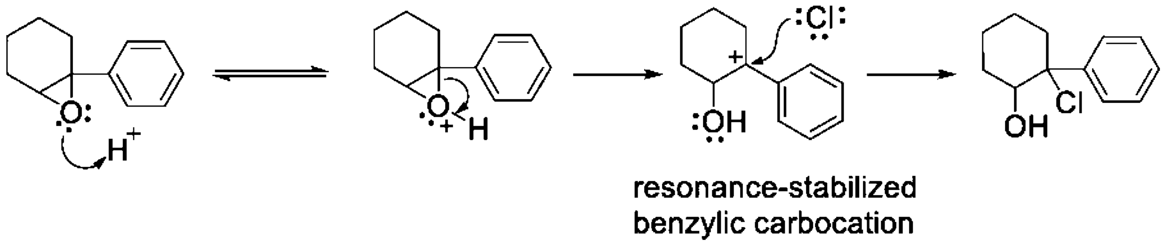
Either one of the two alkene double bonds can react to form a secondary carbocation (notice that simultaneous reaction of both double bonds would give rise to a highly unstable species having two positive charges, therefore, it never happens). As noted earlier, while the aromatic ring can react in a LA/LB reaction, this is energetically unfavorable (loss of aromaticity).

14



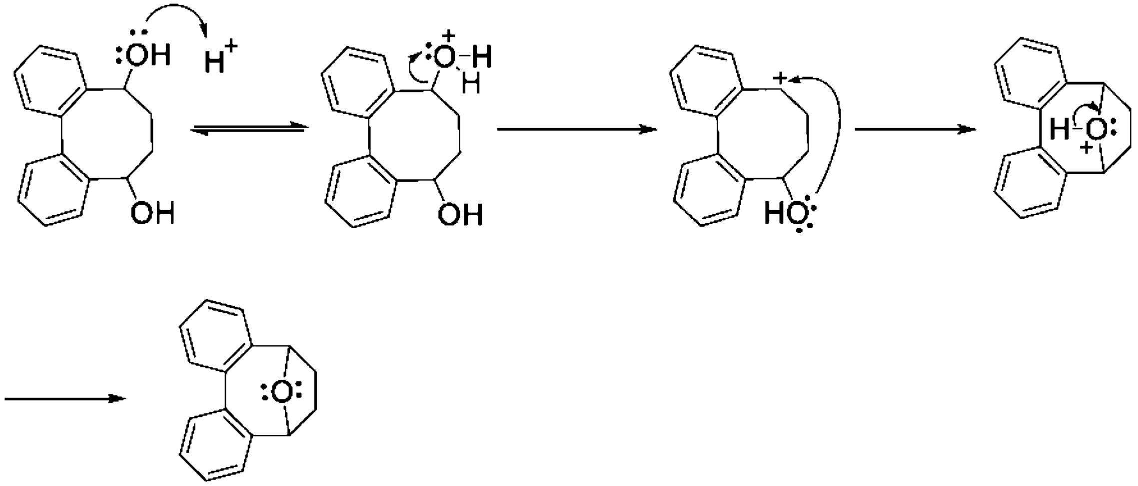
Initial formation of the 2° carbocation is followed by a LA/LB reaction to form a highly reactive episulfonium ion. Ring opening leads to the formation of a 3° carbocation which subsequently undergoes an intramolecular LA/LB reaction to form the observed product.

15



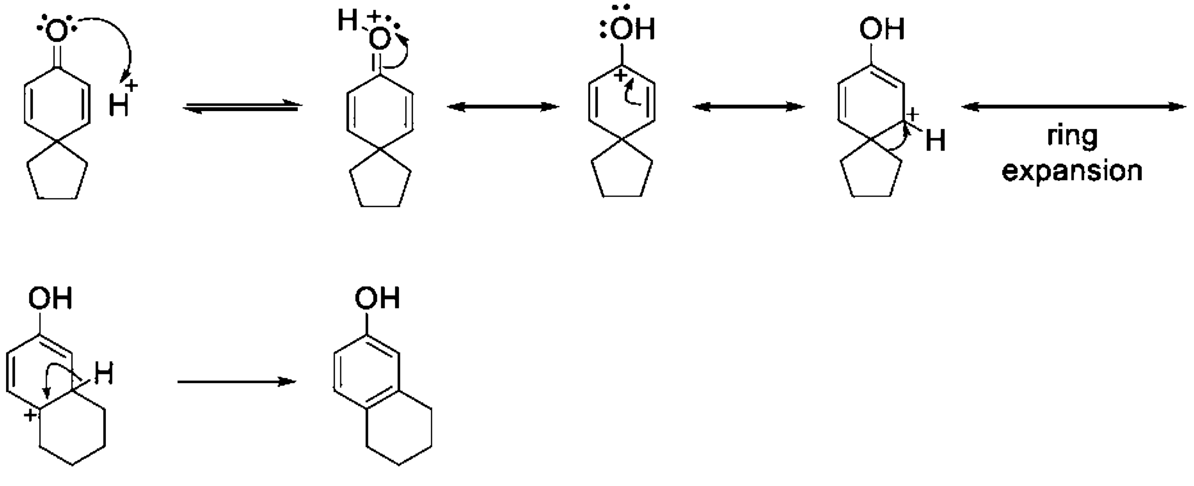
This is an example of acid-catalyzed ring opening of an epoxide. A LA/LB reaction is followed by ring-opening to yield the most stable carbocation (benzylic instead of the less stable secondary carbocation). A second LA/LB reaction yields the observed product.

16



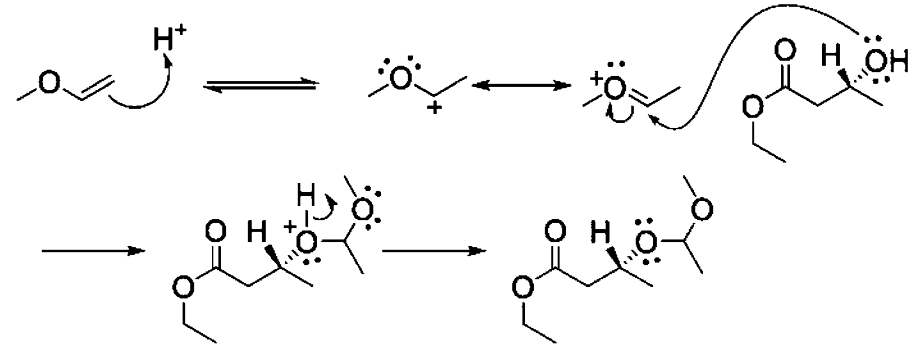
Both alcohols are benzylic, consequently, either one can form a benzylic carbocation which can form the product following an intramolecular LA/LB reaction.

17



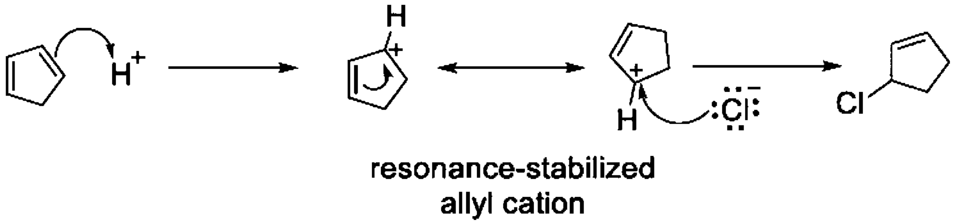
The driving force for this reaction is primarily due to the formation of the aromatic ring. Recall that aromatic compounds are cyclic, planar, satisfy Huckel's 4n+2 rule, where n is the number of pi and non-bonded electron pairs, and can sustain a ring current in a magnetic field.

18



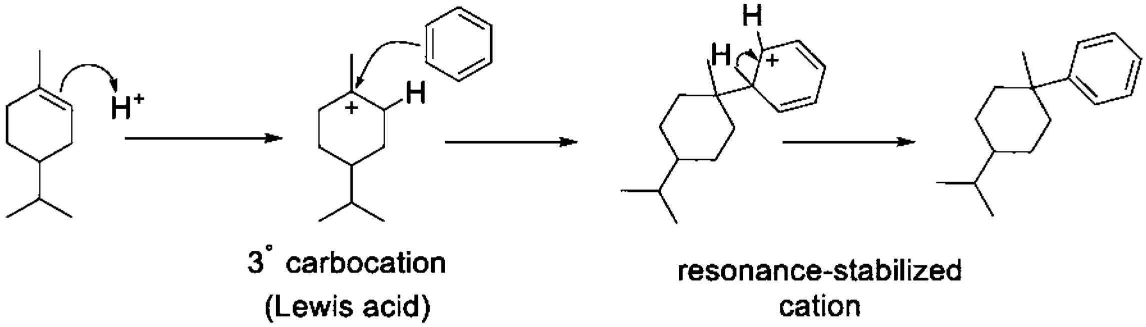
A LA/LB reaction yields the most stable carbocation, which then reacts in a second LA/LB reaction to furnish the product. Note that this reaction proceeds with *retention of configuration*, namely, the atoms or groups bonded directly to the stereogenic (chiral) center are oriented in space the same way in the product, as in the starting material, since none of the bonds to the stereogenic center is broken during the course of the reaction.

19



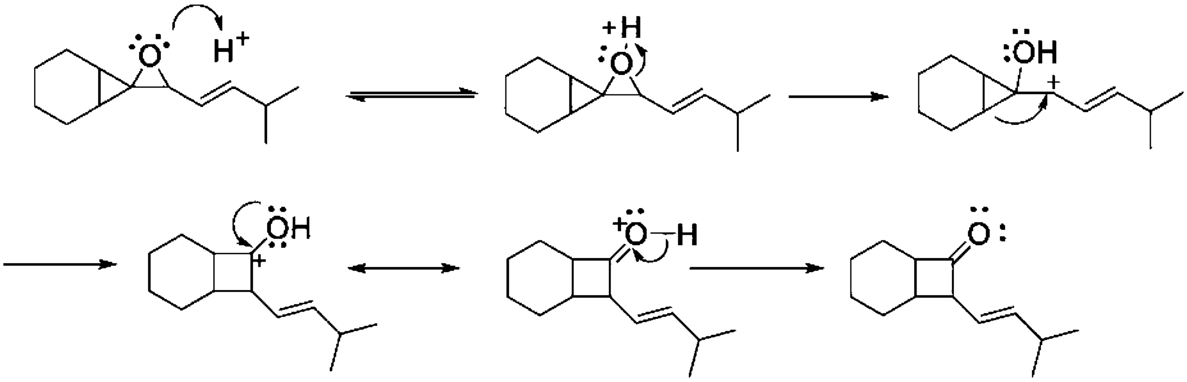
Conjugated dienes undergo electrophilic addition reactions to yield 1,2- and 1,4-addition products. In this example, the 1,2- and 1,4-addition products are the same.

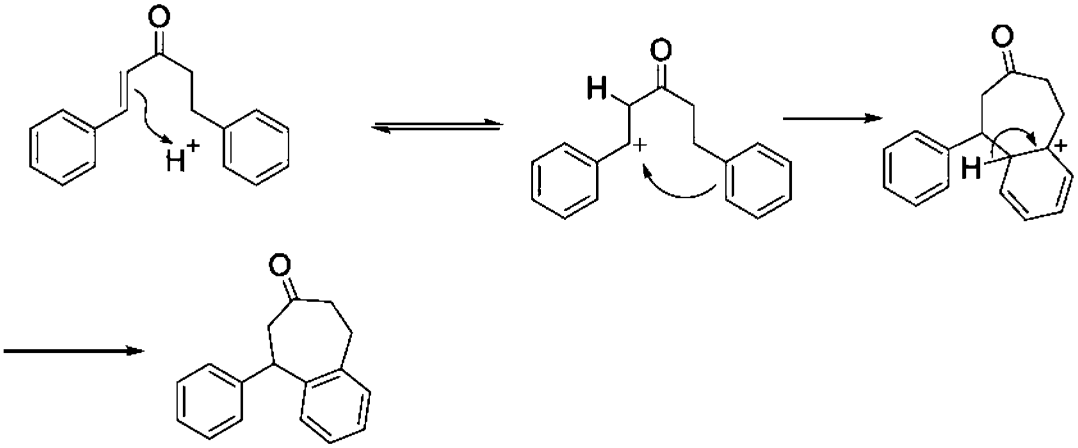
20



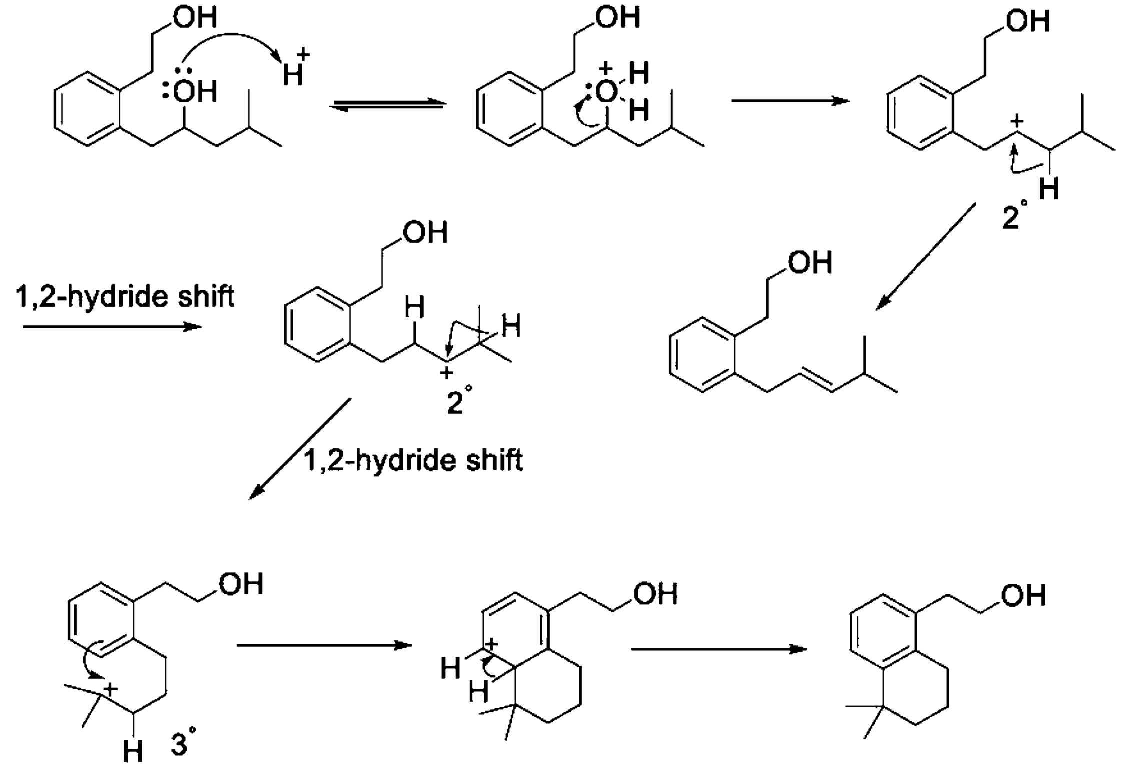
A LA/LB reaction leads to the formation of the most stable carbocation. This is followed by an electrophilic aromatic substitution reaction, specifically, a Friedel-Craft's alkylation reaction (see Minireview 4).

21



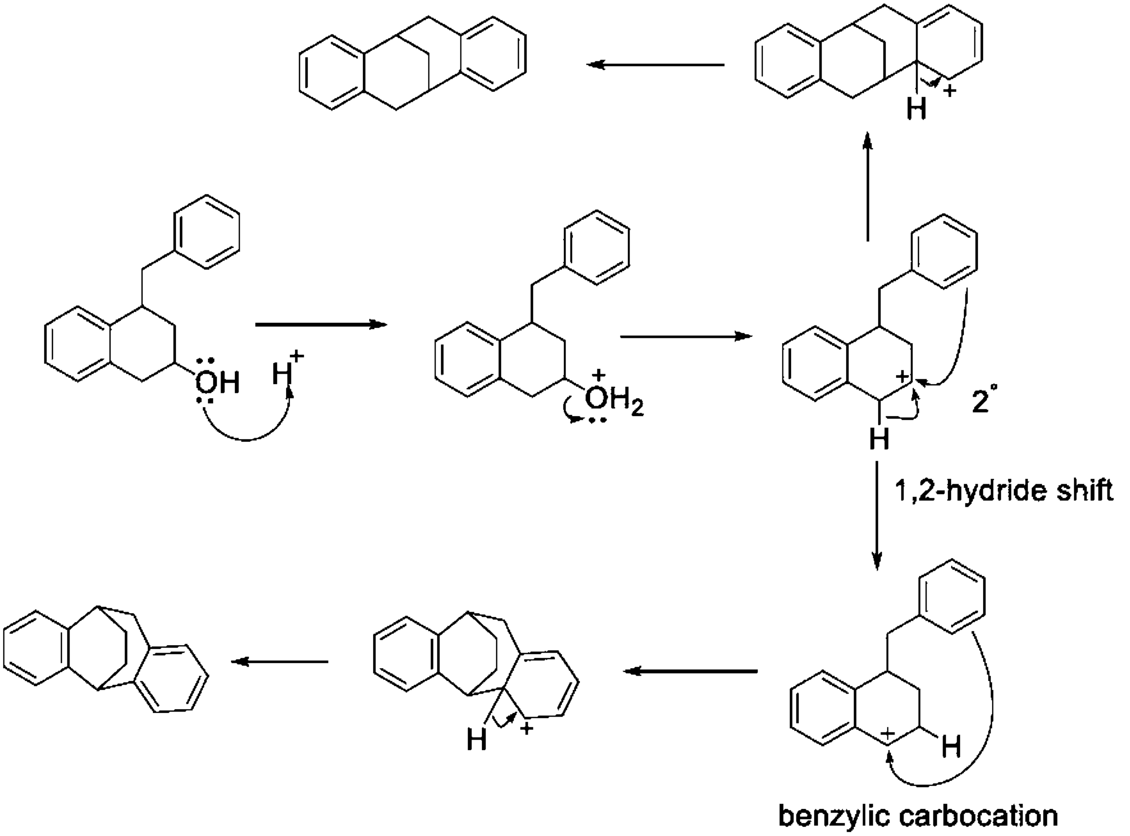
A LA/LB reaction is followed by ring opening of the epoxide (oxirane) ring to form a resonance-stabilized allyl carbocation. Ring expansion results in the relief of ring strain and the formation of a resonance-stabilized carbocation.	
22	
An initial LA/LB reaction yields the most stable carbocation (note that carbocations with a positive charge on a carbon alpha to a carbonyl group are highly unstable because the positive charge is next to the partial positive charge on the carbonyl carbon. Repulsion of the adjacent positive charges raises the energy). This is followed by an intramolecular Friedel-Craft alkylation reaction.	

23



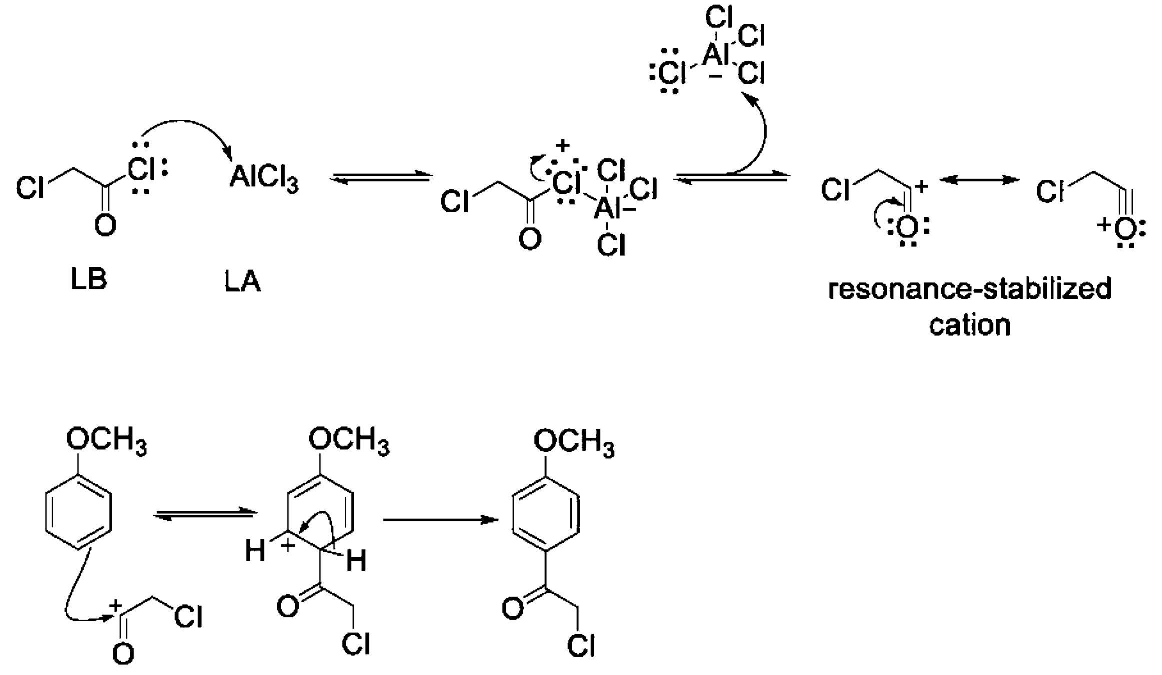
Formation of the 2° carbocation is followed by a 1,2-hydride shift to form a more stable 3° carbocation which undergoes an *intramolecular* Friedel-Craft alkylation reaction.

24



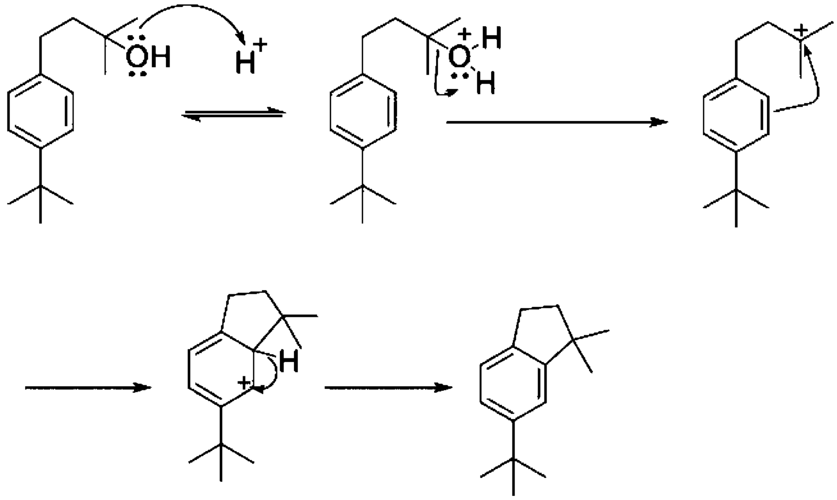
The initial 2° carbocation follows two pathways in forming the observed products.

25



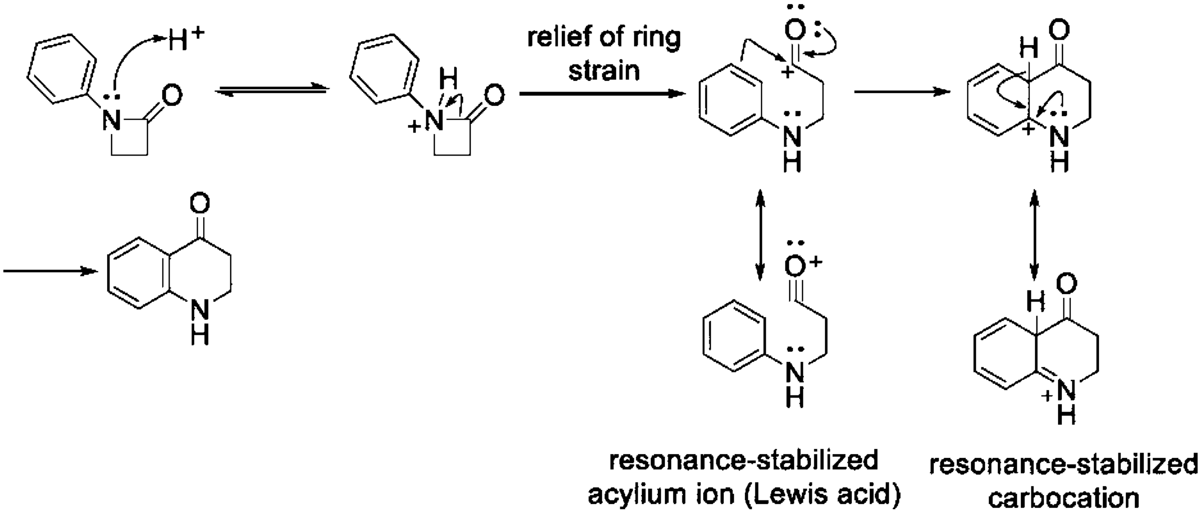
This is an example of the *Friedel-Craft acylation reaction* (see Minireview 4). Since the methoxy group is an activating, *o*- and *p*-directing group, the major product formed is that shown above. Note also that while either chlorine can function as Lewis base by donating a pair of electrons to the Lewis acid, the more stable species is formed (a resonance-stabilized acylium ion).

26



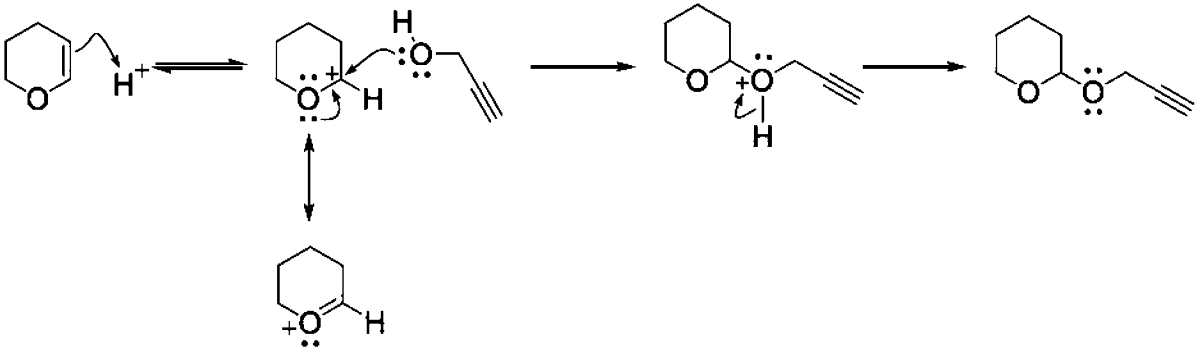
A LA/LB reaction leads to the formation of a 3° carbocation, which is followed by an intramolecular Friedel-Craft alkylation reaction.

27

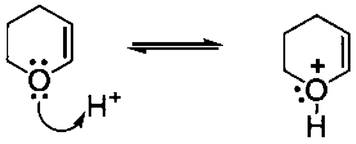


The pair of non-bonded electrons on the nitrogen is more available for donation than in acyclic amides because of ring strain.

28



Two consecutive LA/LB reactions lead to the formation of the product. Note that a LA/LB reaction at the oxygen atom of the starting material is an unproductive process.



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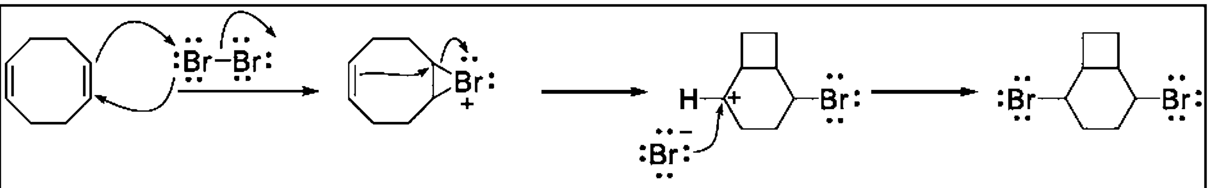
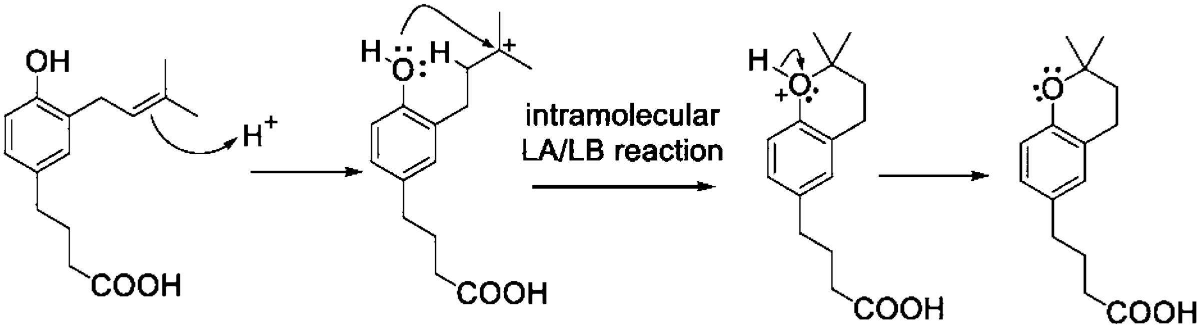
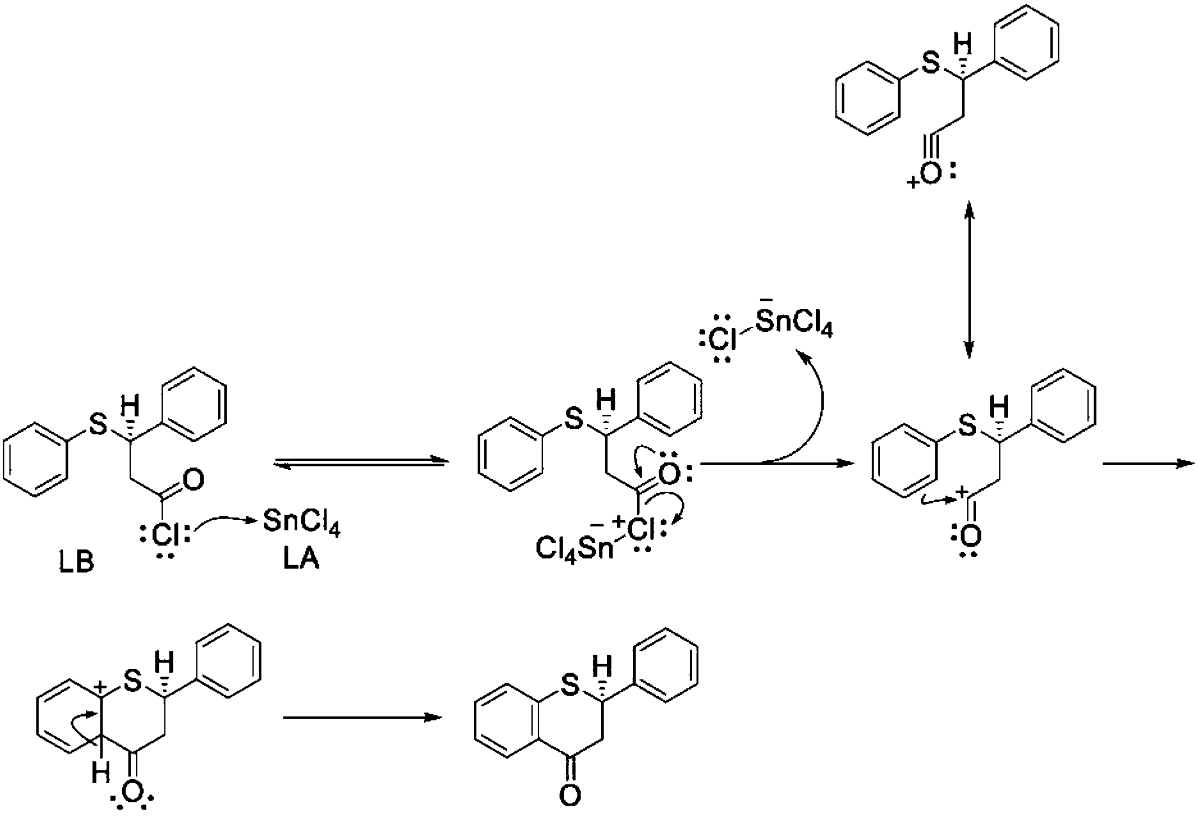
<tr><td>29</td><td></td></tr>
<tr><td colspan="2">Formation of the highly reactive bromonium ion is followed by a transannular LA/LB reaction to form a 2° carbocation. A subsequent LA/LB reaction yields the observed product.</td></tr>
<tr><td>30</td><td> </td></tr>
<tr><td>31</td><td> </td></tr>
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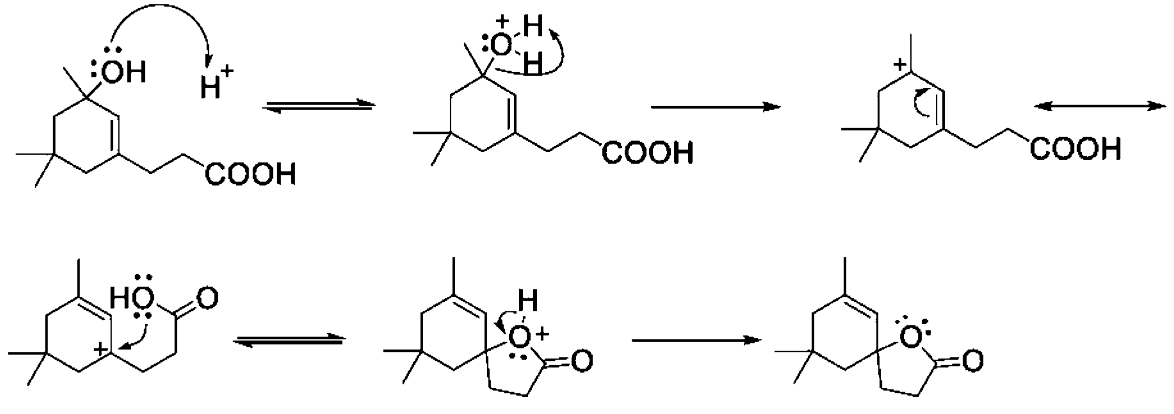
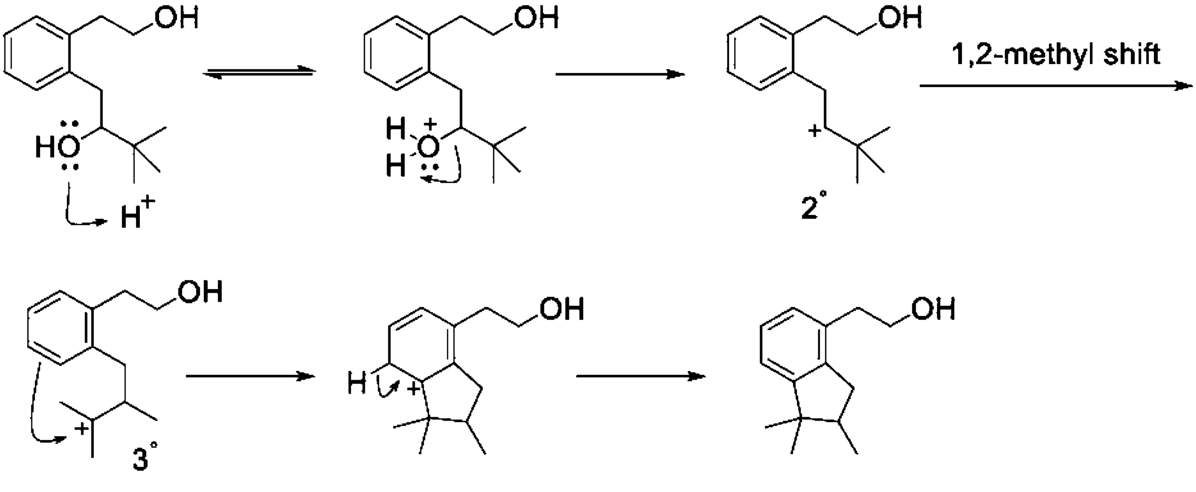
SnCl$_4$ behaves as a Lewis acid (Sn has a partial positive charge), like AlCl$_3$ and related compounds, initiating the formation of an acylium ion that subsequently undergoes an intramolecular Friedel-Craft acylation reaction.

32



Formation of the 3° and allylic carbocation is followed by a LA/LB reaction to form the product.

33



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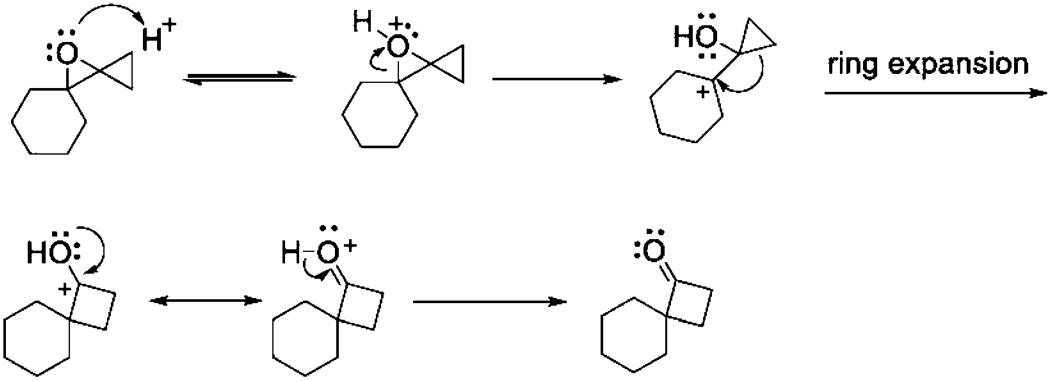
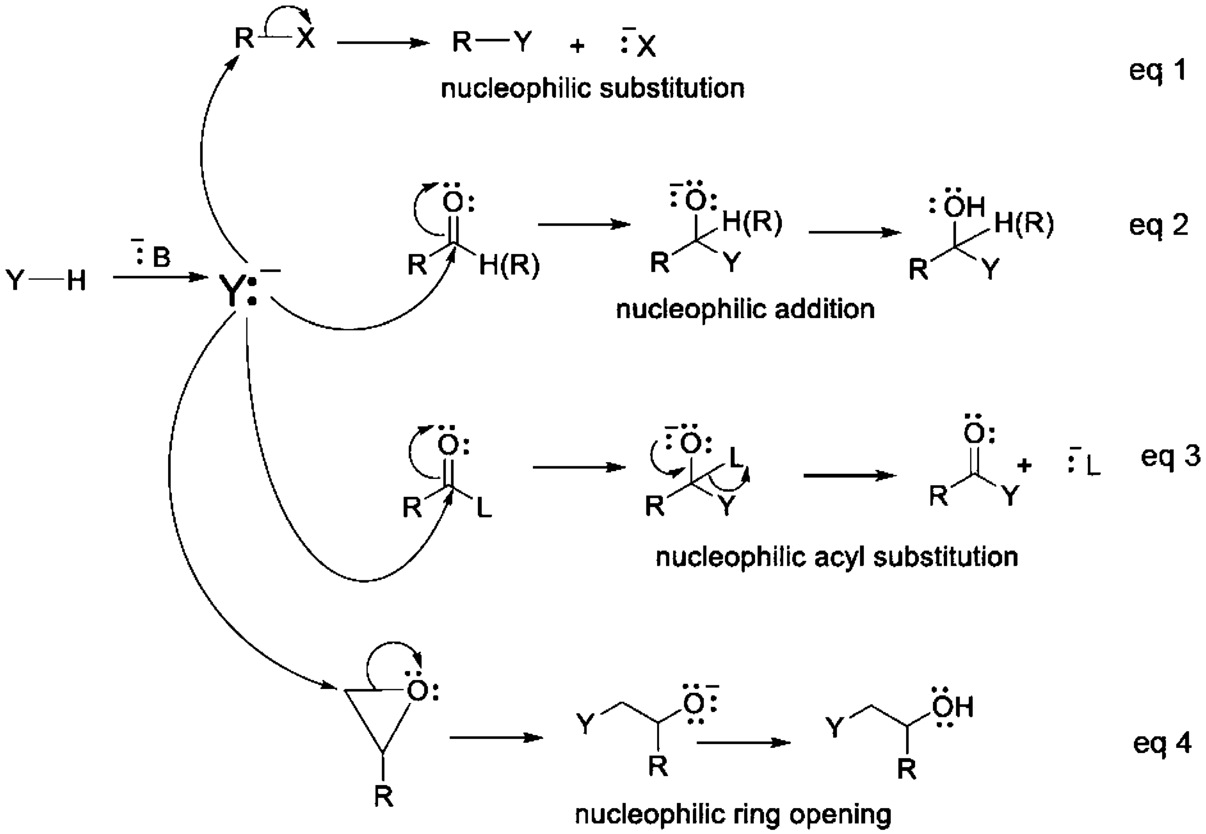


Minireviews 5-7 discuss briefly some basic principles related to the formation of anions (nucleophiles), nucleophilic substitution (S_N2) and elimination (E_2) reactions, chemical reactivity and ring strain. These should be studied prior to attempting questions 35-50.

Minireview 5

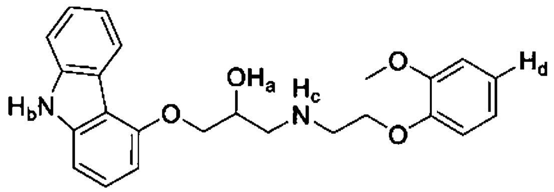
Formation of Anions (Nucleophiles)

Before discussing anions (Lewis bases/ nucleophiles), it is helpful to remember that the chemistry of alkyl halides, aldehydes and ketones, carboxylic acid derivatives (acid halides, anhydrides, thioesters, esters, amides and epoxide) can be simply described and best understood by equations (1-4) below, without recourse to memorization. Thus, the typical reaction of alkyl halides is *nucleophilic substitution* (S_N2) (eq 1) (see Minireviews 6 and 7 for more details and some variations of the same theme), the typical reaction of aldehydes and ketones is *nucleophilic addition* (eq 2) (Minireview 8), and the typical reaction of carboxylic acid derivatives is *nucleophilic acyl substitution* (eq 3) (Minireview 9). Nucleophilic ring opening reactions of epoxides are illustrated by eq 4. These four general reactions can be viewed as Lewis base/Lewis acid reactions and are discussed in greater detail in Minireviews 6-9. Recall that S_N2 reactions proceed most readily when the Lewis base (nucleophile) has a negative charge. In the case of S and P nucleophiles and amines, because of their large size and high basicity, respectively, they can participate in S_N2 reactions as such. *Anions ($Y:^-$) are typically generated by reacting a molecule with an acidic hydrogen (Y-H) with an appropriate base ($B:^-$) for subsequent use in reactions of the type shown below.*

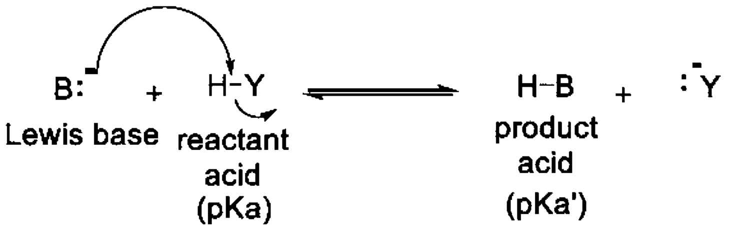


Factors to consider prior to generating an anion include the relative acidity of the starting material (HA) and type of base (B^-) to use. Acid strength is dependent on the following factors: a) ***electronic effects: resonance and inductive effects***. Anions (Y:-) that are stabilized by resonance and/or inductive effects are more stable and easier to form; b) ***size***. The greater the size of the atom (Y) to which the hydrogen is bonded, the higher the acidity of a hydrogen; c) ***electronegativity***. The higher the electronegativity of Y, the higher the acidity of a hydrogen. The following examples illustrate the aforementioned factors and acid strength.

Exercise 1 Rank the hydrogens in the structure shown below in order of decreasing acidity.



It can be readily shown that the equilibrium constant (K_{eq}) for the general acid/base reaction shown below (equation 5) is given by equation 6, where pK_a is the acidity constant of the reactant acid (HY) and pK_a' is the acidity constant of the product acid (HB). Since the pK_as of a large number of acids have been determined and are readily available, an approximate K_{eq} for any acid-base reaction can be readily calculated using equation 6 (*vide infra*). In order for the aforementioned reactions to proceed readily, a high concentration of the anion (nucleophile) is desirable. Hence, *a sufficiently strong base is typically selected to generate* (Y^-) *rapidly and quantitatively.*



eq 5

$$K_{eq} = 10^{pKa' - pKa} \qquad \text{eq 6}$$

Recall that the pK_a of an acid is an index of the relative strength of the acid. *The lower the* pK_a *is, the stronger the acid.* Table 1 lists the pK_a values of some common types of organic compounds

Table 1: pK_a values of some common classes of organic compounds *

	pK_a
RSO_3H	-6.5
RCOOH	4-6
ArSH	6-8
RSH	10-11
ArOH	8-11
ROH	16-18
$RCONH_2$	17
RCH_2CHO	19-20
RCH_2COR	19-20
RCH_2COOR	25

*values are approximate

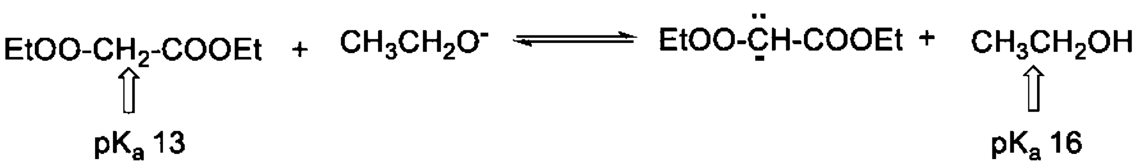
The acidity of substances is greatly affected by the presence of one or more functional groups capable of delocalizing the negative charge in the corresponding anion via resonance (Minireview 3). Common functional groups that enhance acidity include NO_2, COR, CN, COOR, SO_2R and phenyl (Ph). These groups differ in their ability to delocalize the negative charge in the anion, hence the extent to which acidity is affected is dependent on the *nature* and *number* of such functional groups. For example, in a series of compounds of the type RCH_2X, the pK_a varies as follows: X= NO_2 (10), (C=O)R (20), CN (25), COOR (25) and SO_2R (29). The presence of two such groups reduces the pK_a further.

Selection of Base

In selecting a base to be used in the generation of an anion, the *strength* of the base and its *compatibility* with any other functional groups that might present in the molecule, are factors of paramount importance. In general, a sufficiently strong base is selected so that the desired anion is generated rapidly and quantitatively. Secondly, depending on the structure of the acidic molecule (HY), the base used may have to be *non-nucleophilic* (vide infra). Common bases used to generate anions include the following:

a) Alkoxide ions (RO^-M^+, where $M^+ = Na^+$ or K^+)

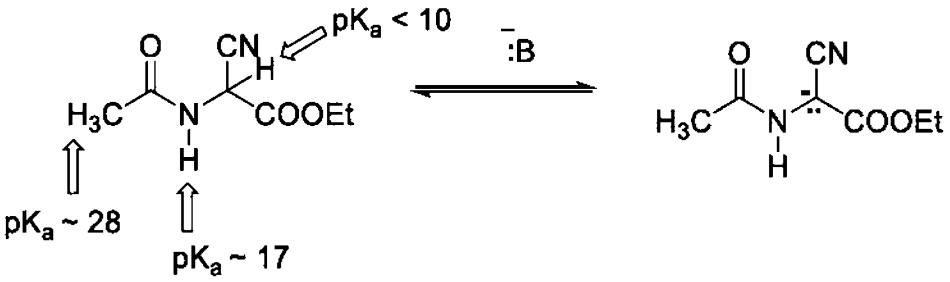
Alkoxide ions are conveniently generated by reacting dry methanol (pK_a ~15.5), ethanol (pK_a ~16), or t-butyl alcohol (pK_a ~18) with sodium or potassium metal under a nitrogen atmosphere. The generated base is then used in situ (in the flask, without isolation). *Note that alkoxides can function as both bases and nucleophiles.*

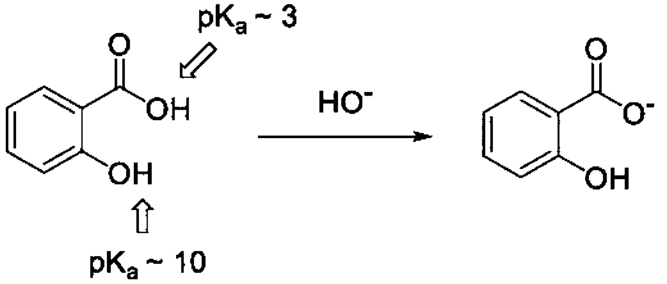


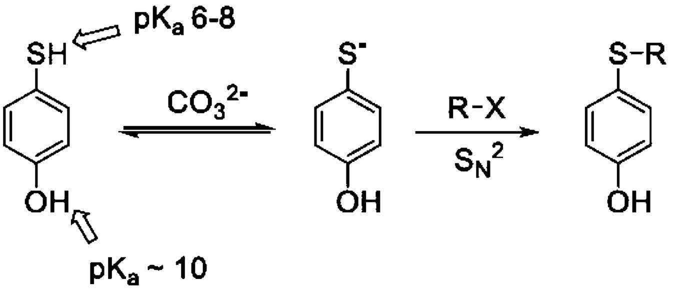
$$\underset{\substack{\Uparrow \\ pK_a\ 13}}{EtOO\text{-}CH_2\text{-}COOEt} + CH_3CH_2O^- \rightleftharpoons EtOO\text{-}\ddot{C}H\text{-}COOEt + \underset{\substack{\Uparrow \\ pK_a\ 16}}{CH_3CH_2OH}$$

Using equation (6), $K_{eq} = 10^{16-13} = 10^3$, therefore the formation of the anion ($:Y^-$) is greatly favored (equilibrium lies to the right).

In cases where a reactant having more than one acidic hydrogen is treated with base, *the most acidic hydrogen will react faster, since it leads to the formation of the more stable anion*. The following examples illustrate this concept.





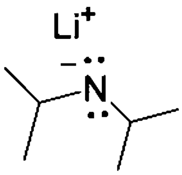


b) Alkyl lithium reagents (:R^- Li^+)

Alkyl lithium bases, such as methyl lithium, n-butyl lithium, and t-butyl lithium, are *strongly basic* and *nucleophilic*. Because alkyl lithium reagents are the conjugate bases of the corresponding hydrocarbons ($pK_a \sim 50$), their high basicity and reactivity requires the use of an inert atmosphere and anhydrous conditions. Recall that the lower the pK_a is, the stronger the acid and the weaker the conjugate base. Conversely, the higher the pK_a is, the weaker the acid and the stronger the conjugate base.

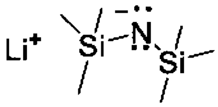
c) If a much stronger, non-nucleophilic base is needed, then use of one of the following bases is preferred:

- Lithium diisopropyl amide (LDA)



LDA can be generated *in situ* by treating diisopropyl amine with n-butyl lithium (the pK_a of diisopropyl amine is ~ 36), however, it is also commercially available.

- Lithium hexamethyldisilane (LHMDS)



- Sodium or potassium hydride NaH or KH (:H^-)
- Sodium amide ($NaNH_2$)

d) Amines

Recall that the basicity of amines follows the order

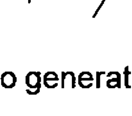
$$3^0 > 2^0 > 1^0 > NH_3 > Ar\text{-}NH_2$$

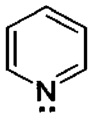
$$\longleftarrow$$

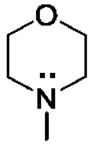
Increasing base strength

(in other words, aliphatic amines are more basic than aromatic amines and, secondly, 3° aliphatic amines are more basic than 2° aliphatic amines which in turn are more basic than 1° amines).

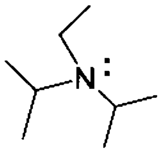
Triethylamine (TEA), pyridine and N-methylmorpholine (NMM) are organic bases that are widely used in organic synthesis.



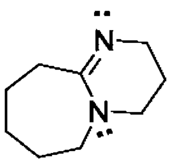




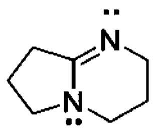
When the objective is to generate an anion via an acid-base reaction, or to induce an E2 elimination reaction (vide infra), the use of a *sterically hindered, non-nucleophilic* *base*, such as diisopropylethyl amine (DIEA), 1,8-diazabicyclo[5.4.0]undecen-7-ene (DBU), or 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) should be considered.



DIEA

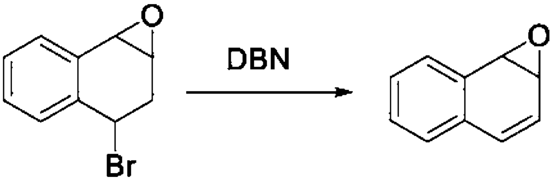


DBU



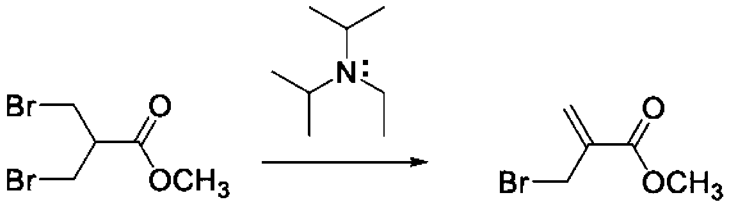
DBN

Example 1



The following transformation was successfully achieved using a bulky and non-nucleophilic base, greatly minimizing competing S_N2 and ring-opening reactions between the base and the highly reactive functionalities in the starting material and product.

Example 2



The objective here was to induce an E_2 elimination only, leading to the formation of the desired product. The selection of base was critical for the success of this reaction because of the high reactivity of the product. The latter is an allylic bromide (highly reactive in S_N2 reactions), thereby necessitating the use of a bulky and non-nucleophilic base.

e) Miscellaneous bases

These include bases such as sodium or potassium bicarbonate, carbonate or hydroxide. The pK_a values of carbonic acid, bicarbonate and water are 6.4, 10.3 and 15.7, respectively. Consequently, base strength follows the order $HO^- > CO_3^{2-} > HCO_3^-$.

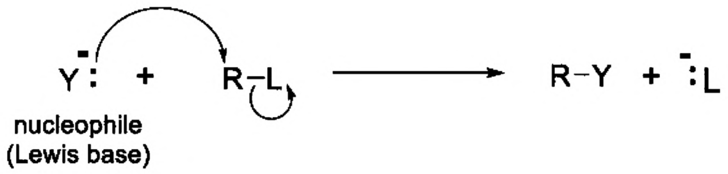
Examples illustrating the *rationale* underlying the selection of a particular base are given below. See Minireview 5 for additional examples. It would be very beneficial to consider the logic behind the use of a particular base, or reaction conditions, as you work through the problems in this workbook.

Minireview 6

- Nucleophilic Substitution Reactions (S_N2)
- Elimination Reactions (E_2)

The S_N2 reaction is *a concerted, one-step reaction involving backside attack by a strong Lewis base (nucleophile) on an sp^3-hybridized carbon bearing a partial positive charge (δ+) (Lewis acid) and a leaving group (L). The reaction proceeds with inversion of configuration* (eq 1).

S_N2 reactions are greatly influenced by the nature of the alkylating agent (R-L), nucleophile ($^-$:Y), leaving group (L), and solvent.



eq 1

a) Alkylating agent (R-L)

The order of reactivity of halides in S_N2 reactions is

Unreactive

benzyl halide > CH_3X ~ allyl > 1^0 > 2^0 > 3^0 > vinyl halide, aryl halide, R-F

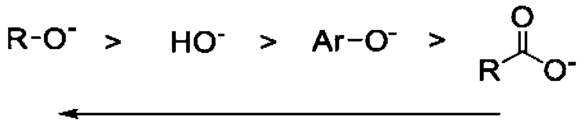
increasing reactivity

Note:

1) Tertiary alkyl halides undergo E2 reactions, while vinyl, aryl halides, and alkyl fluoride do *not* undergo S_N2 reactions.
2) The reactivity profile of α-haloesters, α-haloethers and α-haloketones is similar to that of benzylic halides.

b) Strength and Nature of Lewis Base (Nucleophile)

In general, *nucleophilicity increases with increasing basicity, provided nucleophiles with a common nucleophilic atom are compared.* Thus, a nucleophile with a negative charge (Y:⁻) will always be more basic and, therefore, more nucleophilic than a neutral nucleophile (Y:). With the exception of amine, phosphorus, and sulfur nucleophiles, nucleophiles used in S_N2 reactions are anions, namely, they have a negative charge (Y:⁻). As pointed out earlier, the lower the pK_a is, the stronger the acid and the weaker the conjugate base.



$$R\text{-}O^- > HO^- > Ar\text{-}O^- > RCOO^-$$

$$\longleftarrow$$

increasing base strength

The *size* of the atom that donates the pair of electrons has a profound effect on its nucleophilicity. *The larger the atom is, the greater its nucleophilicity.* Thus,

$$:PH_3 > :NH_3$$

$$RSe^- > R\text{-}S^- > R\text{-}O^-$$

$$I^- > Br^- > Cl^- > F^-$$

$$\longleftarrow$$

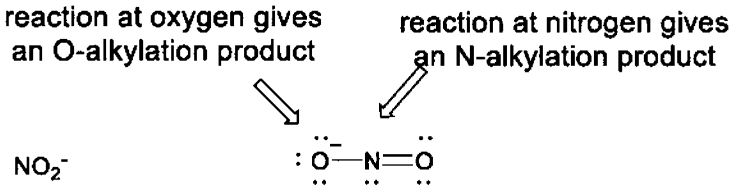
increasing size

$$\longleftarrow$$

increasing nucleophilicity

Nucleophiles that are capable of reacting at more than one atom, thereby giving rise to two different products, are referred to as *ambident nucleophiles*. The site of reaction in ambident nucleophiles is primarily determined by the nature of the solvent used in an S_N2 reaction, and the size of the atom. Some examples of ambident anions are shown below.

NO_2^-

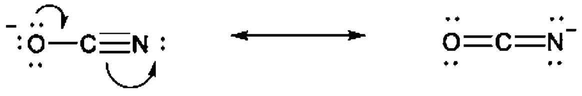


$$R{-}X \; + \; NO_2^- \longrightarrow R{-}NO_2 \; + \; R{-}O{-}N{=}O$$

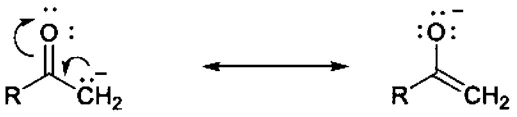
a nitro compound (N-alkylation)

an alkyl nitrite (O-alkylation)

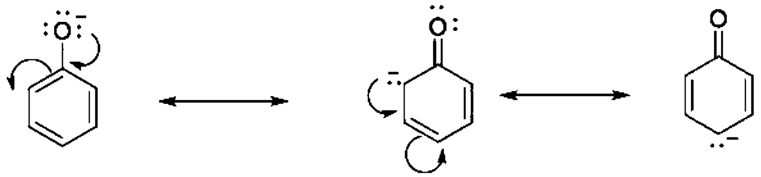
OCN^-



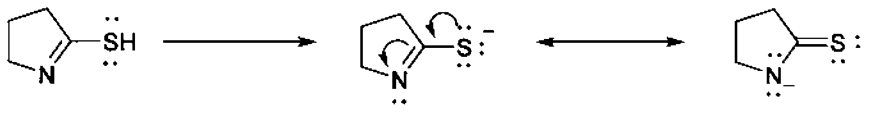
(N and O-alkylation)



(O and C-alkylation)



(O and C-alkylation)*

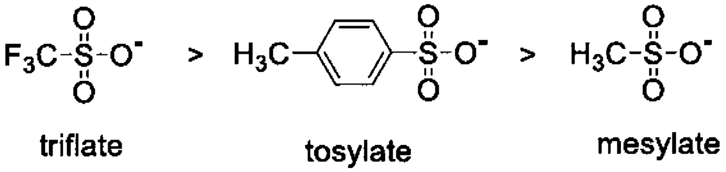


(N and S-alkylation,
S-alkylation predominates. Why?)

* Note that C-alkylation leads to loss of aromaticity

c) Nature of the Leaving Group (L)

The group that is displaced by the nucleophile (Y:⁻) in an SN2 reaction is referred to as the *leaving group*. *Good leaving groups are stable anions, namely, they are* *conjugate bases derived from strong acids*. For example, halide ions (I^-, Br^-, Cl^-, except F^-) are good leaving groups since they are the conjugate bases of strong acids. Many other good leaving groups are derived from strong organic acids and are stabilized by resonance (Minireview 3). These include the triflate, mesylate and tosylate groups (vide infra). The hydroxyl group of an alcohol (a poor leaving group that is not displaced by any nucleophile) is frequently transformed into one of these leaving groups prior to carrying out an S_N2 reaction (Scheme I below).



$CF_3COO^- > CH_3COO^-$

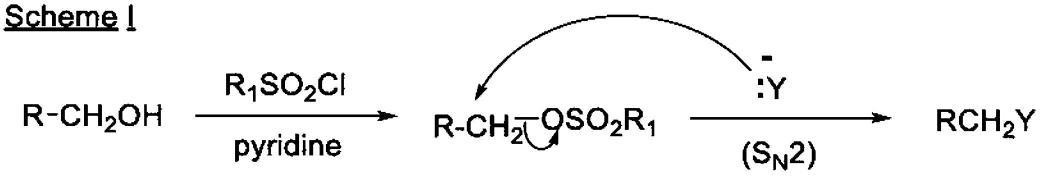
$CF_3SO_3^- > CH_3SO_3^-$

$I^- > Br^- > Cl^- > F^-$

$\longleftarrow$

increasing leaving group ability

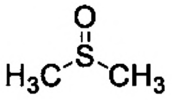
Scheme I



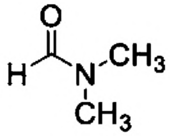
$$R\text{-}CH_2OH \xrightarrow[\text{pyridine}]{R_1SO_2Cl} R\text{-}CH_2\text{-}OSO_2R_1 \xrightarrow[(S_N2)]{:\overset{-}{Y}} RCH_2Y$$

d) Nature of the Solvent

The nature of the solvent used in carrying out an S_N2 reaction can have a dramatic effect on the rate and success of the reaction. S_N2 reactions are greatly facilitated by dipolar aprotic solvents such as dimethyl sulfoxide (DMSO), dimethyl fornamide (DMF) and acetonitrile. These solvents enhance the nucleophilicity of anions by solvating the cation (solvation refers to the clustering of solvent molecules around the anion or cation).



DMSO

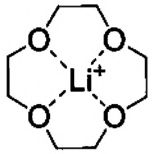


DMF

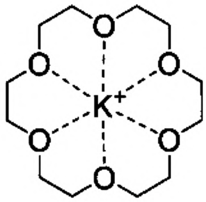
CH_3CN

acetonitrile

The nucleophilicity of an anion can also be enhanced by using a *crown ether* that complexes with the cation, as shown below. The size of the cavity in a polyether determines the type of cation that is complexed. Inorganic reagents, such as potassium permanganate, which are ordinarily insoluble in organic solvents, become soluble in organic solvents in the presence of a crown ether.



12-crown-4



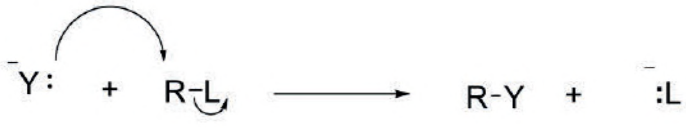
18-crown-6

Note:

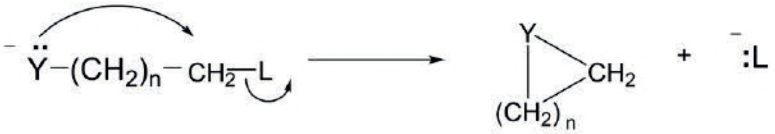
S_N2 reactions can be *intermolecular* (eq 2) or *intramolecular* (eq 3). Intramolecular S_N2 reactions take place within the same molecule. Reactions in which the nucleophile and reactive center are tethered together, are favored entropically and proceed at a much higher rate than the corresponding intermolecular reactions.

Note:

Intramolecular reactions lead to the formation of cyclic structures, consequently, 5- and 6-membered ring structures are favored since they are free of ring strain.



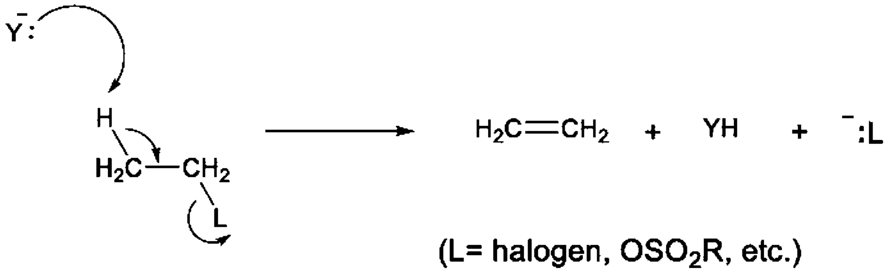
eq 2



eq 3

Elimination (E_2) Reactions

As mentioned earlier, when an alkyl halide or similar type of compound (R-L, where L= halogen or other good leaving group) is treated with a strong base ($:Y^-$), an S_N2 reaction take place. This is the course that an S_N2 reaction typically follows when a methyl, allylic, or benzylic halide is used. However, when a 3° R-L is used, the reaction follows a different cause due to steric reasons. An E_2 elimination reaction takes place, leading to a formation of a C=C bond (eq 4). *An E_2 reaction is a concerted 1,2- or β-anti elimination reaction* (the term *anti* means that the β-hydrogen removed by the base and the leaving group are opposite to each other). Secondary alkyl halides undergo competing substitution (S_N2) and elimination (E_2) reactions. The rate of an E_2 reaction increases with increasing base strength, leaving group ability, and the relative stability of the product(s). Typical bases used in E_2 reactions include HO^-, RO^-, and bulky organic bases such as diisopropyl ethyl amine, DBU, and DBN.

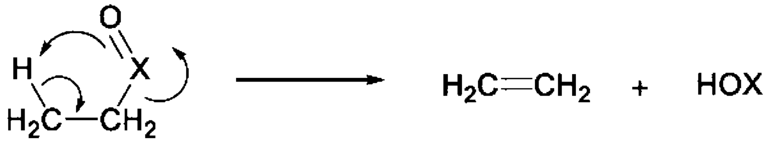


eq 4

(L= halogen, OSO_2R, etc.)

Thermal Syn Elimination Reaction

Thermal *syn elimination* reactions constitute another somewhat less common type of β-elimination reaction. This type of reaction proceeds thermally through a cyclic transition state, and does not require the use of base (the term syn means that the β-hydrogen and the leaving group are on the same side). Syn eliminations involving sulfoxides and selenoxides are widely used in the facile formation of C=C bonds. While other leaving groups have been used in the past (acetate, amine oxide, etc.), elimination occurs at a much higher temperature.



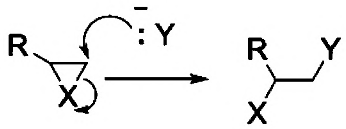
eq 5

(X= SR or SeR)

Minireview 7

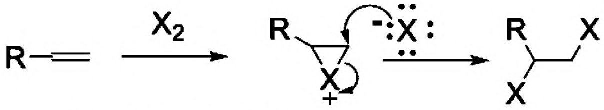
- Chemical Reactivity and Ring Strain

Three and four membered rings have considerable *ring strain*, namely, the ring bonds are weak because of poor overlap of the atomic orbitals and, consequently, exhibit high reactivity. They are highly reactive toward Lewis bases (nucleophiles), giving rise to ring-opened products. Note that *nucleophilic ring opening of an epoxide, for example, involves back-side attack at the least substituted (least congested) carbon, and proceeds with inversion of configuration* (eq 1). Transient 3-membered species, such as halonium and selinarium ions, behave similarly (eq 2 and 3).



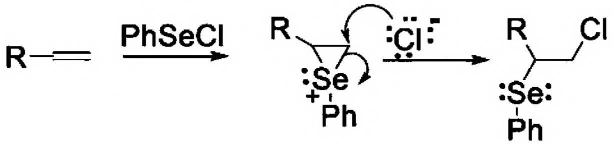
X= O (epoxide), S (episulfide)

eq 1



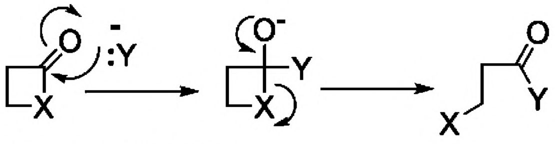
(X_2= Cl_2, Br_2, I_2)

eq 2



eq 3

3-and 4- membered cyclic esters (lactones) and cyclic amides (lactams) also react rapidly with nucleophiles (eq 4).

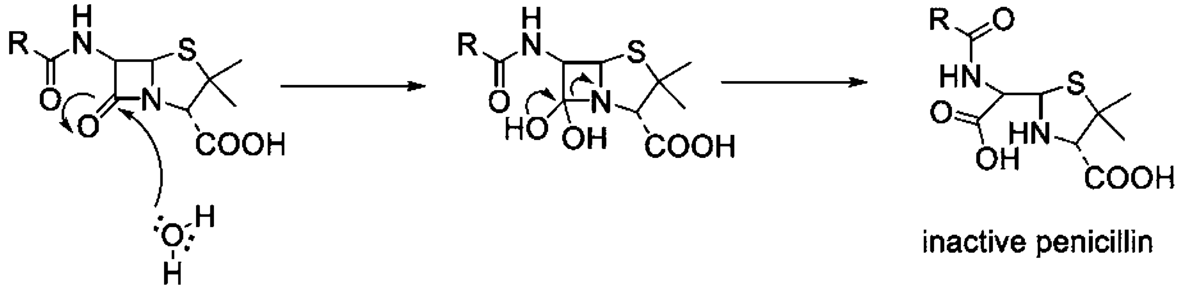


(X= O, NH, NR)

eq 4

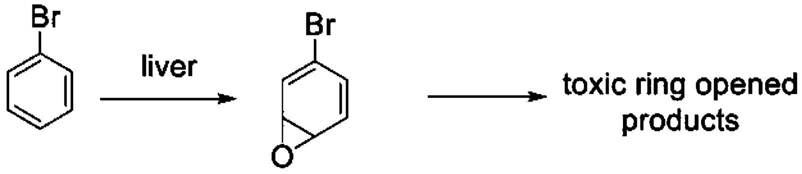
Example 1

The highly reactive β-lactam ring of penicillins and related antibacterial agents undergoes ring opening rapidly. Hydrolysis of the β—lactam ring in penicillins results in total loss of antibacterial activity (in practical terms, suspensions of penicillins, such as pivampicillin, are kept refrigerated in order to slow down the hydrolysis reaction. They are thrown away after a week or so since they contain mostly inactive penicillin).



Example 2

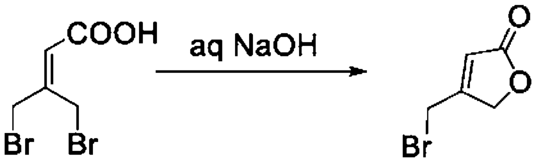
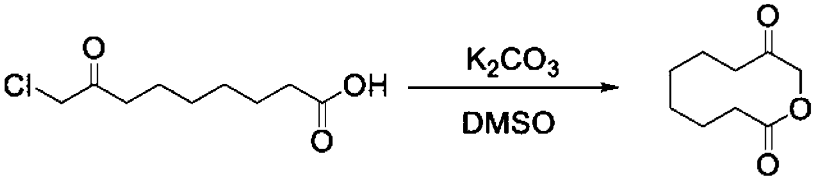
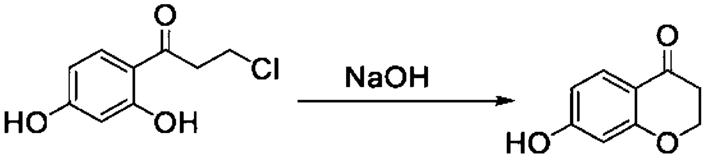
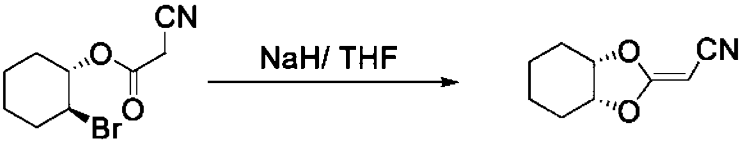
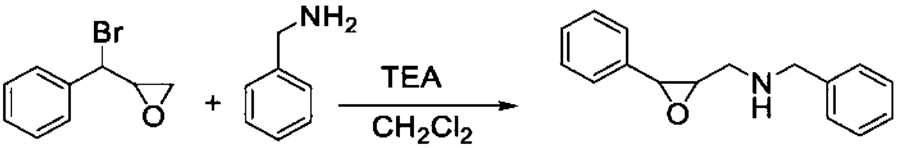
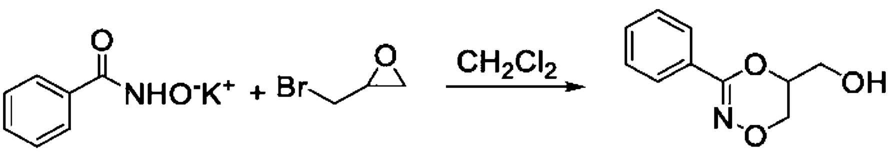
The toxicity associated with a drug or substance is frequently due to the formation of a highly reactive metabolite. For example, the toxicity and carcinogenicity of polycyclic aromatic hydrocarbons and other aromatic compounds is attributed to the formation of highly reactive epoxides by liver-metabolizing enzymes, and their subsequent reaction with nucleophilic cellular components, including DNA.



Questions 35 - 50

Questions 35-50 are meant to help you gain a better understanding of following topics.

- Generation of anions/acidity
- S_N2 reactions (mechanism, nucleophilicity, ambident nucleophiles, leaving groups, stereochemistry, solvent effects, etc.)
- E_2 reactions (anti and thermal syn elimination reactions)
- Nucleophilic ring-opening reactions

35	
36	
37	
38	
39	
40	

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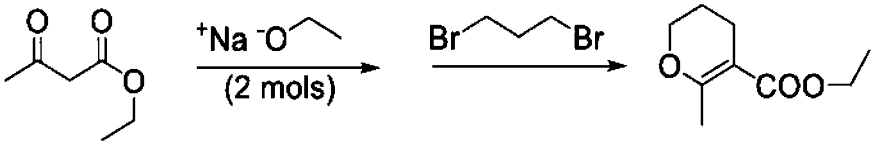
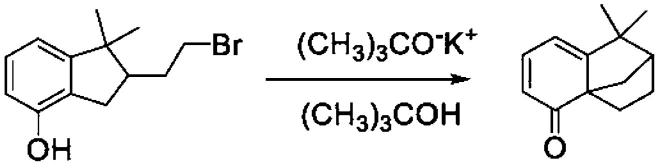
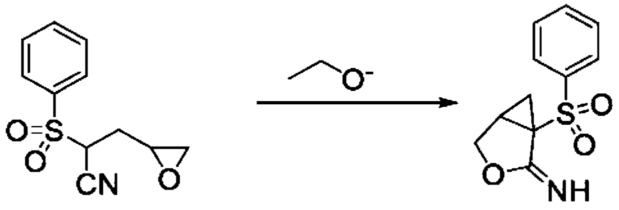
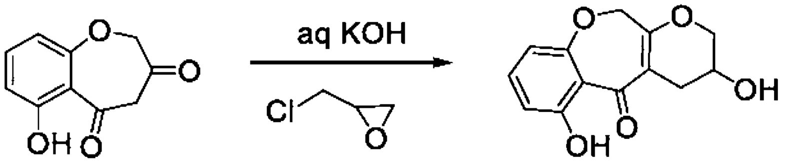
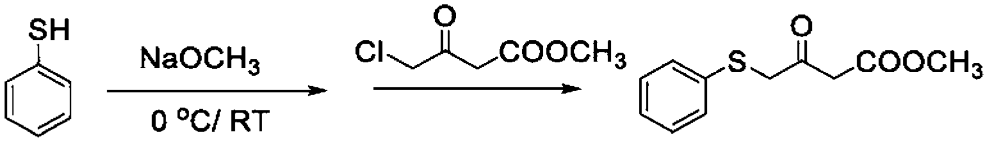
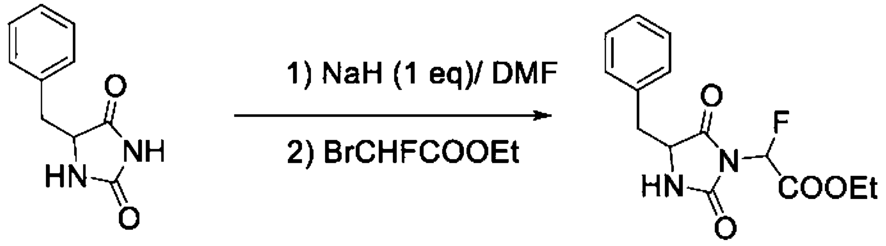
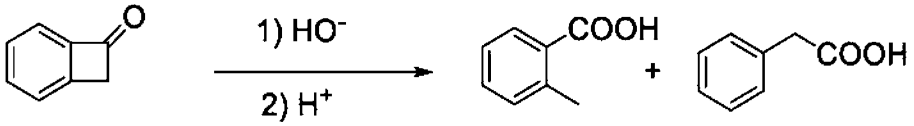
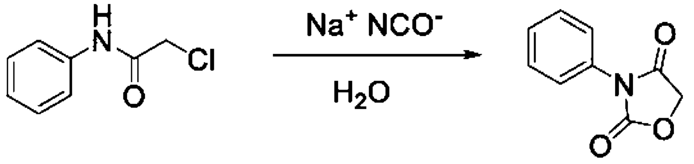
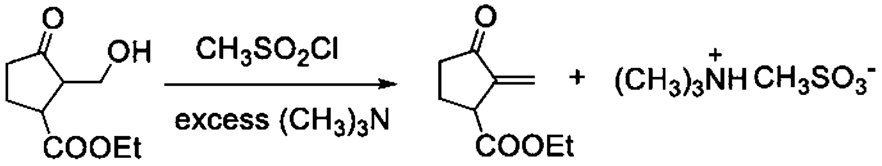
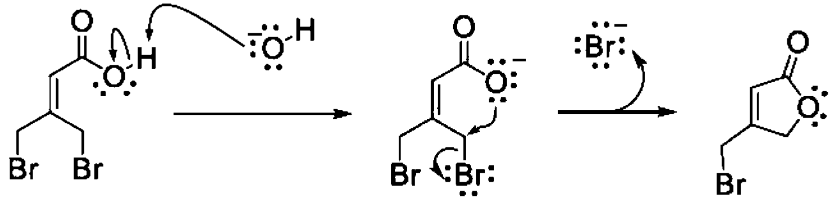
42	
43	
44	
45	
46	

47	 O NH HN O 1) NaH (1 eq)/ DMF 2) BrCHFCOOEt O F N HN COOEt O
48	 O 1) HO⁻ 2) H⁺ COOH + COOH
49	 H N Cl O Na⁺ NCO⁻ H₂O O N O O
50	 O OH COOEt CH₃SO₂Cl excess (CH₃)₃N O COOEt + (CH₃)₃N⁺H CH₃SO₃⁻

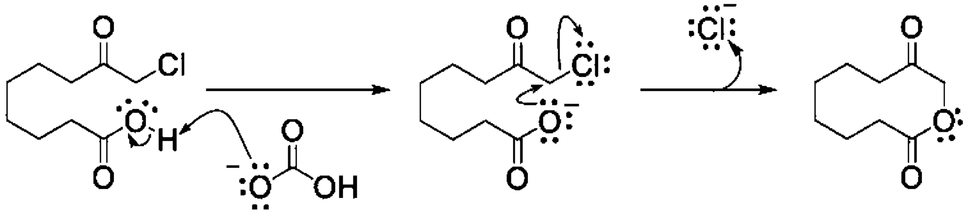
Answers to Questions 35-50

35



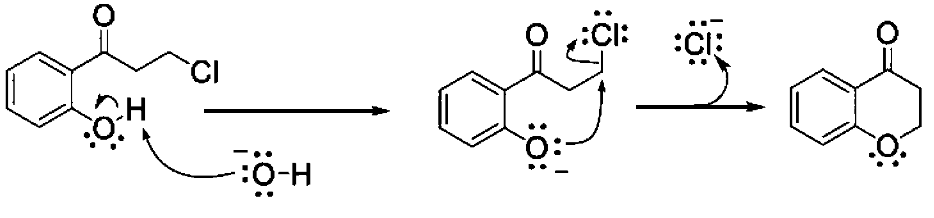
An initial fast acid-base reaction yields the anion (LB or nucleophile). This is followed by an intramolecular SN2 reaction. The reaction proceeds readily at room temperature despite the fact that the carboxylate anion is a weak nucleophile because (a) the reaction is intramolecular (reaction takes place within the same molecule) and is therefore favored entropically; (b) the reacting groups are arranged in a favorable geometric alignment and, (c) the reaction involves a highly reactive allyl bromide (Minireview 6).

36



Formation of the anion is followed by an intramolecular SN2 reaction. In general, intramolecular ring formation (cyclization) is favored when the reaction is carried out in *high dilution*. The relative ease of ring formation is dependent on many factors, including the stability of the ring to be formed, with lowest yields obtained with medium size (8 to 11-membered) rings.

37



Formation of the anion of phenol (pKa~10) is rapid and quantitative. This is followed by an intramolecular SN2 reaction. Note that the hydroxide ion could, in principle, displace the chloride first. It should be remembered, however, that the rates of acid/base reactions are extremely fast

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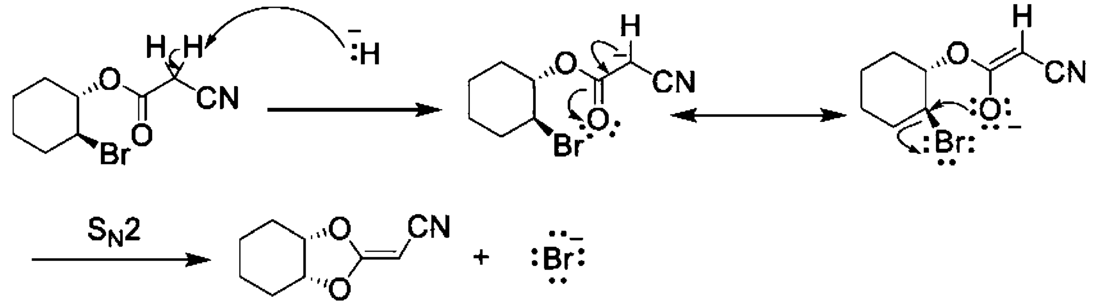

Rapid and quantitative formation of the anion using sodium hydride is followed by an intramolecular SN2 reaction. As expected, the reaction proceeds with inversion of configuration, accounting for the observed stereochemistry. See Minireview 5 for a discussion of acidity and anion formation.

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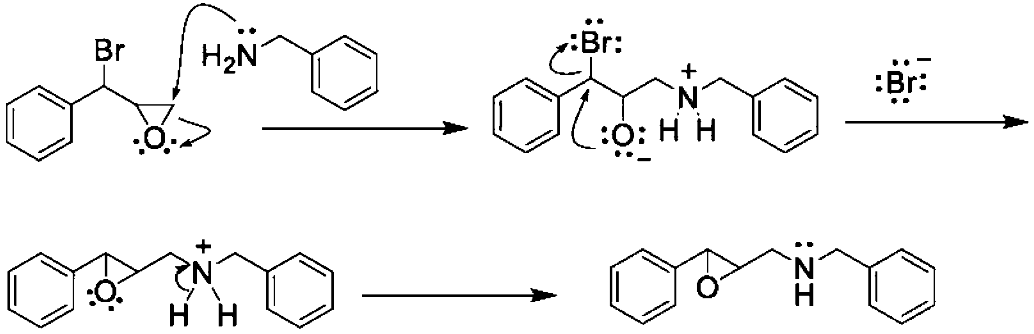

Epoxide (oxiranes) are highly reactive because of ring strain and, consequently, undergo ring opening reactions with the nucleophile attacking the least substituted (least congested) carbon.

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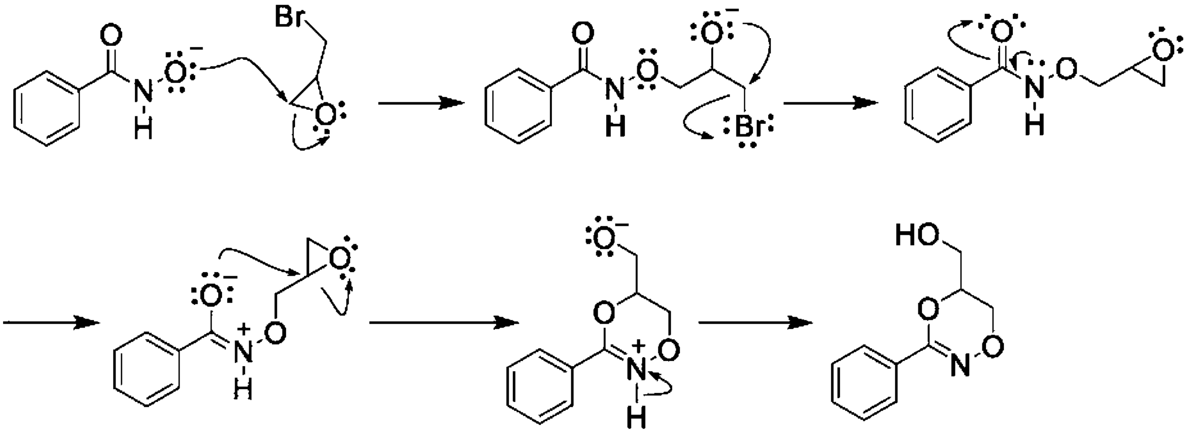

Epoxides are more reactive toward nucleophiles than 1° halides. Thus, nucleophilic ring opening is followed by epoxide formation which undergoes ring opening to form the observed product.

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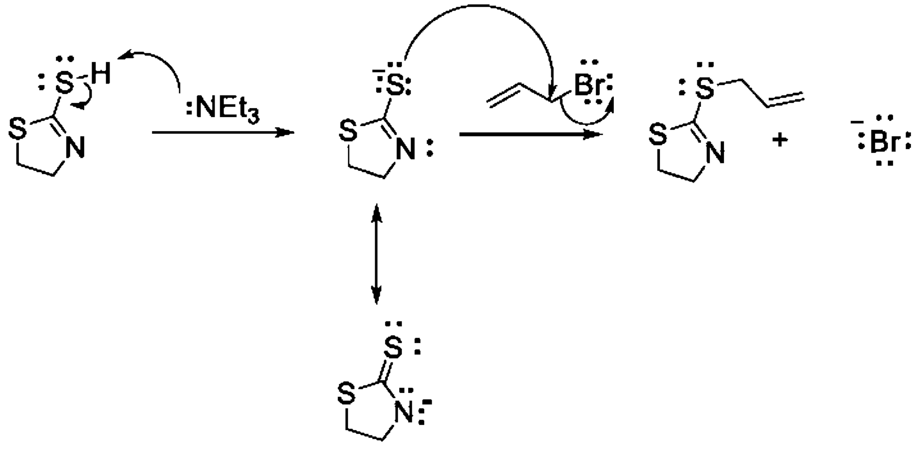
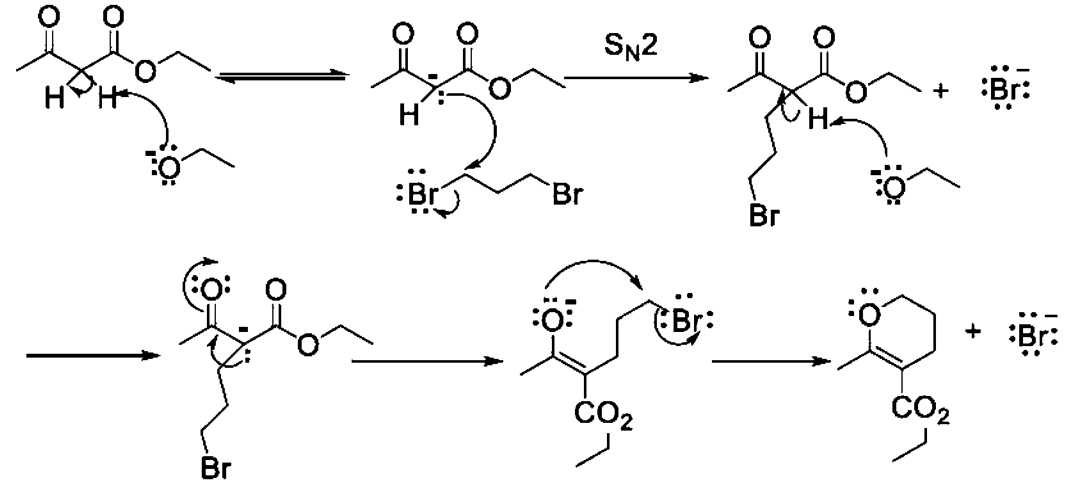


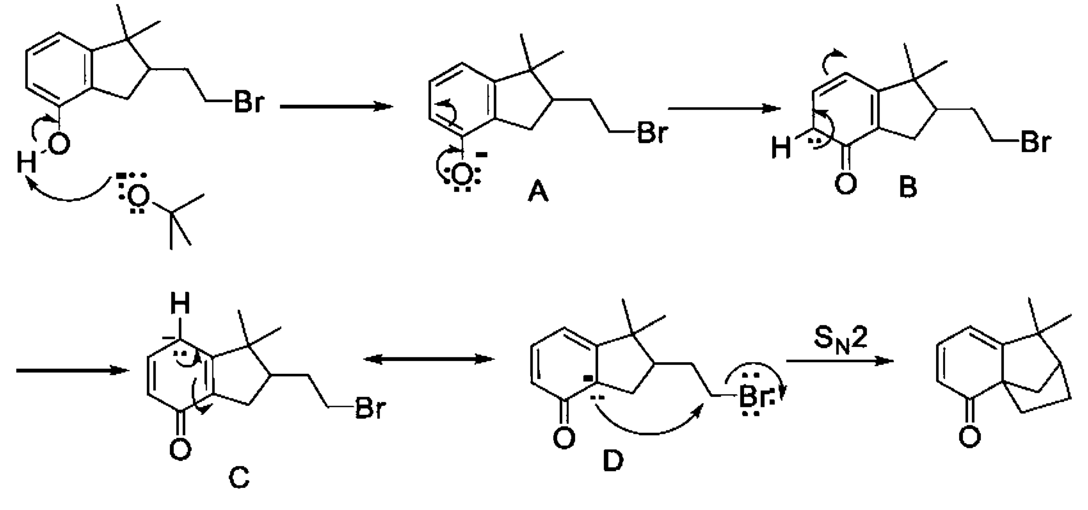
The anion generated in the first step (see Minireview 5) is an ambident anion, i.e., it can react at either the N or S atom. The S_N2 reaction takes place on S (the larger atom), attesting to the greater nucleophilicity of sulfur (see Minireview 6). Recall that size trumps basicity in S_N2 reactions.

42

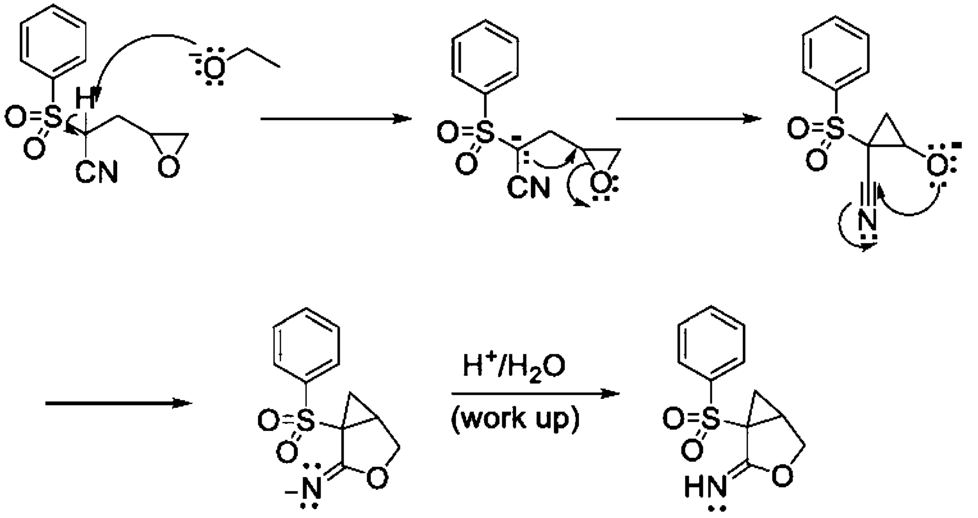
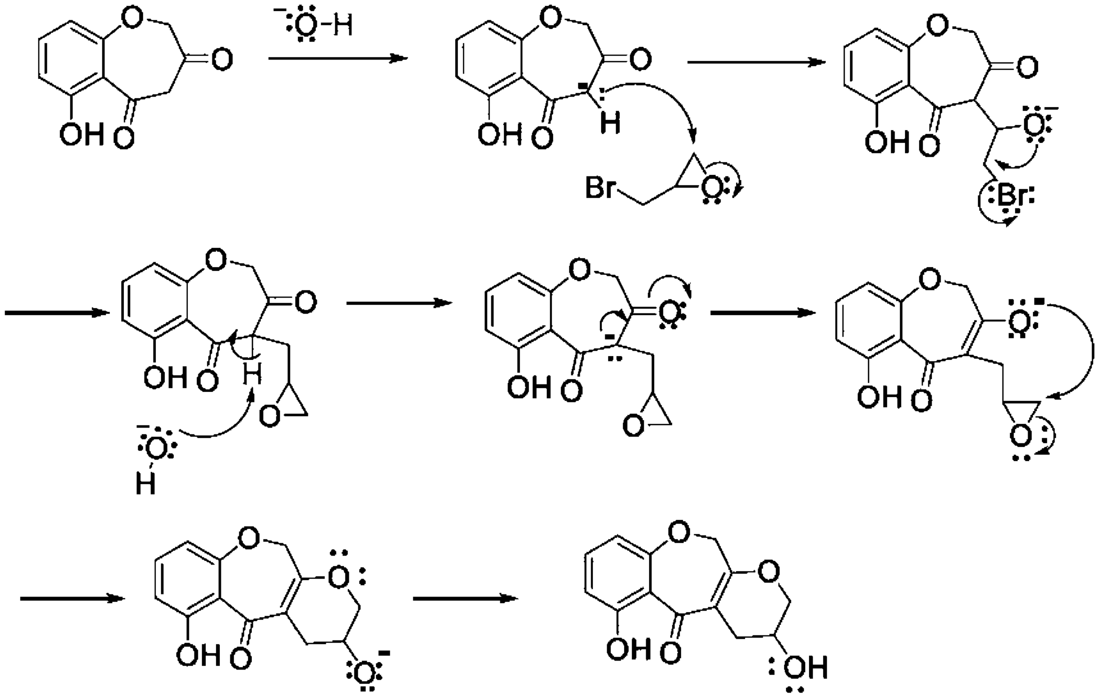
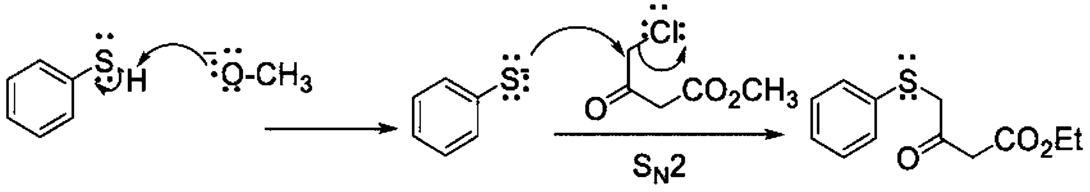


Formation of the ambident anion is followed by C-alkylation. A subsequent acid/base reaction leads to a second ambident anion which undergoes O-alkylation, leading to the formation of the observed cyclic product. Note that C-alkylation would be less favorable since it would result in the formation of a highly-strained 4-membered ring.

43



The first step involves a rapid and quantitative formation of a resonance-stabilized ambident anion. A subsequent intramolecular S$_N$2 reaction (C-alkylation) leads to the observed tricyclic non-aromatic product. As pointed out earlier, the nature of the product formed in reactions involving ambident anions is dependent on a range of factors.

44	
45	
46	

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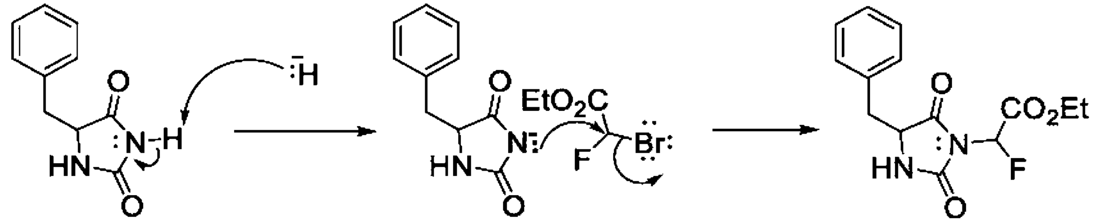
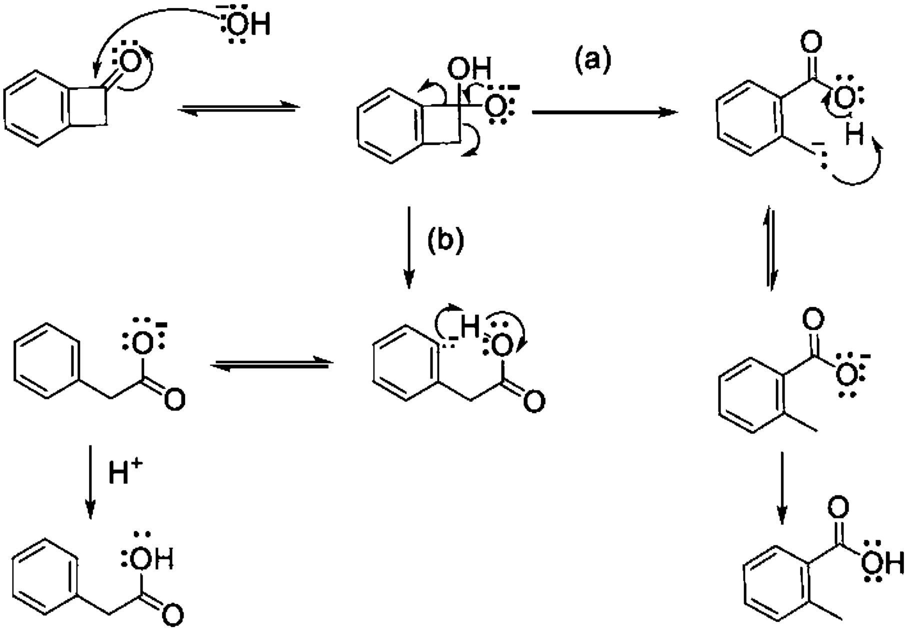
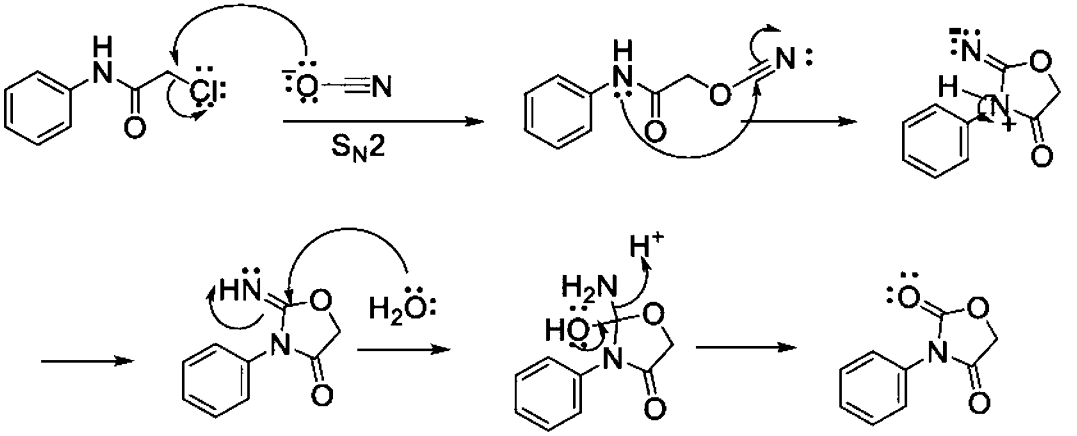
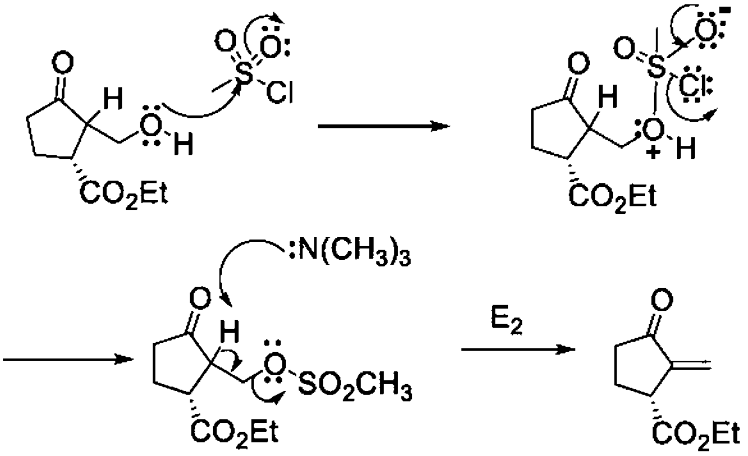


The base reacts preferentially with the more acidic hydrogen leading to the formation of the more stable anion (3 resonance structures). Removal of the less acidic hydrogen would result in the formation of a less stable anion (2 resonance structures). Note also that the nucleophile displaces the bromide ion (better leaving group) instead of the fluoride anion (a poor leaving group).

48



The driving force for the reaction is the ring opening of the cyclobutane ring and the relief of ring strain.

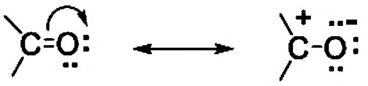
49	
50	
Formation of the sulfonate ester transforms the hydroxyl group from a poor leaving group into a good leaving group (see also Minireview 6).	

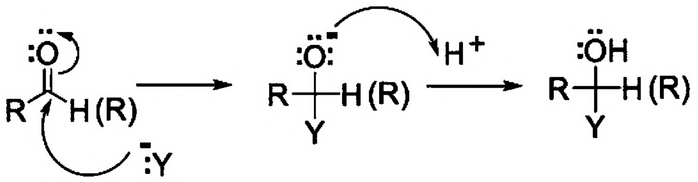
Minireview 8 focuses on nucleophilic addition reactions (the typical reaction of aldehydes and ketones). This should be studied prior to attempting questions 51-70.

Minireview 8

- Nucleophilic Addition Reactions of Aldehydes and Ketones

The typical reaction of aldehydes and ketones is *nucleophilic addition*. Notice that the nucleophilic addition reaction is essentially a Lewis acid/Lewis base reaction involving a Lewis base (:Y$^-$ or :Y) with the electron-deficient carbon (Lewis acid) of the carbonyl group. The addition product arising from strong nucleophiles is then protonated (typically during the workup of the reaction) and the final product isolated (eq 1). Typical strong nucleophiles including Grignard reagents (RMgX or R:$^-$ Mg^{2+}X$^-$), alkyl lithium reagents (RLi or R:$^-$ Li$^+$), cyanide ion, alkyne anions ($RC\equiv C:^-$), reducing agents that deliver hydride (H:$^-$) ions, etc.

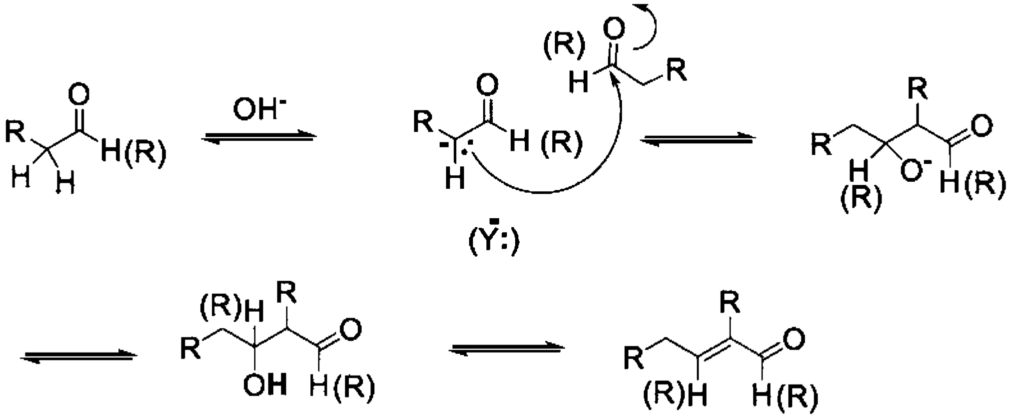




eq 1

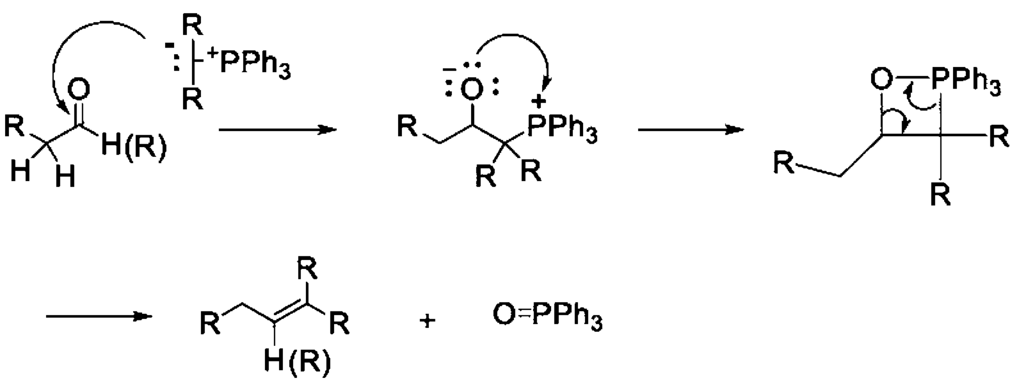
In the familiar aldol *condensation reaction*, an aldehyde or ketone having an acidic α-hydrogen reacts with dilute base to yield a carbon anion (Lewis base), which then adds to the carbonyl carbon of a second molecule of the aldehyde or ketone, leading to the formation of a β-hydroxy aldehyde or ketone (an α,β-unsaturated aldehyde or ketone may also form depending on the reaction conditions) (Scheme I).

Scheme I



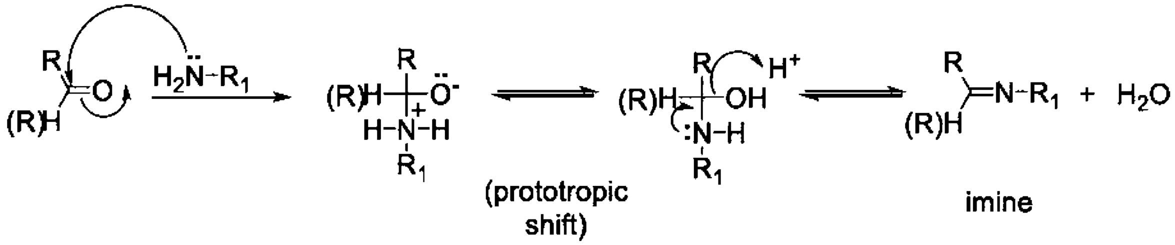
In the case of some nucleophilic addition reactions, the initial nucleophilic addition product reacts further to yield a more stable product. For example, the reaction of an aldehyde or ketone with a *Wittig reagent* involves an initial nucleophilic addition reaction. An intramolecular Lewis acid/base reaction yields a 4-membered intermediate which collapses, forming an alkene (Scheme II).

Scheme II

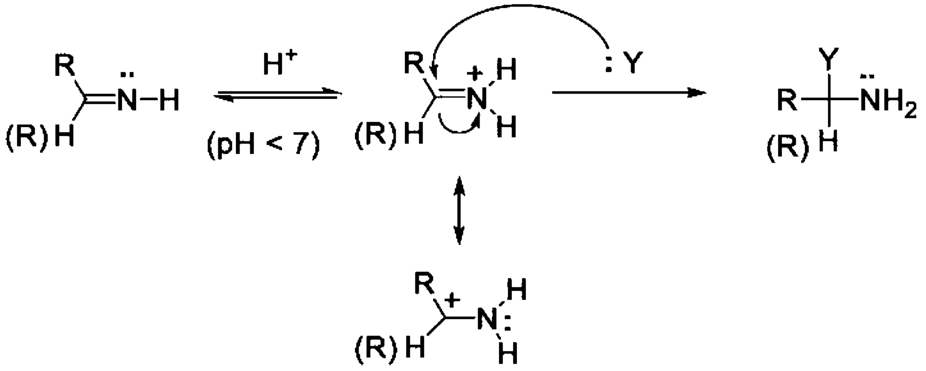


Likewise, *primary* amines react rapidly with aldehydes and ketones, however, the initial adduct loses a molecule of water to form an *imine* (Scheme III). Imines undergo addition reactions with Lewis bases. These reactions proceed readily when the imine is protonated (Scheme IV). *Secondary* amines react with aldehydes and ketones to form enamines (Scheme V).

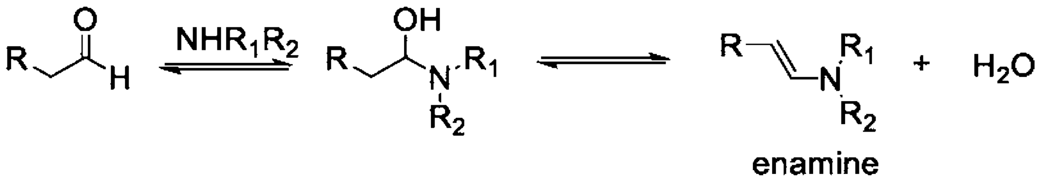
Scheme III



Scheme IV

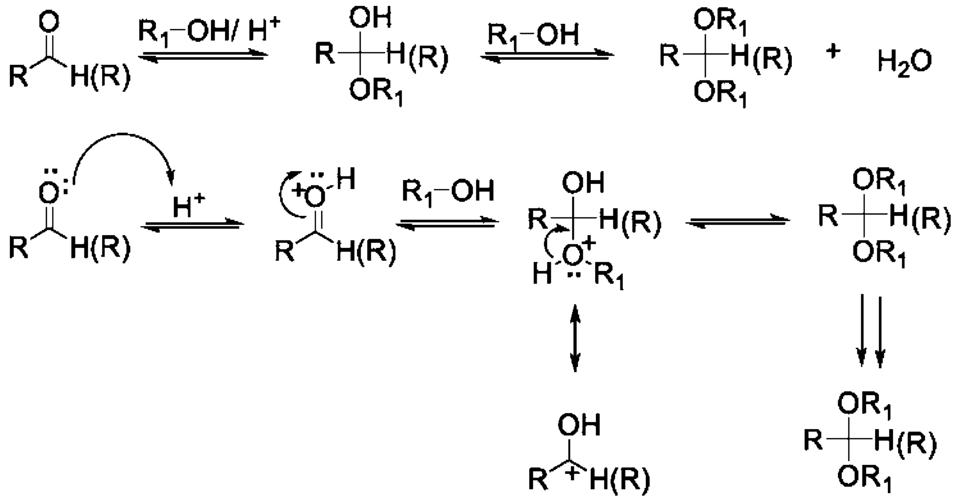


Scheme V



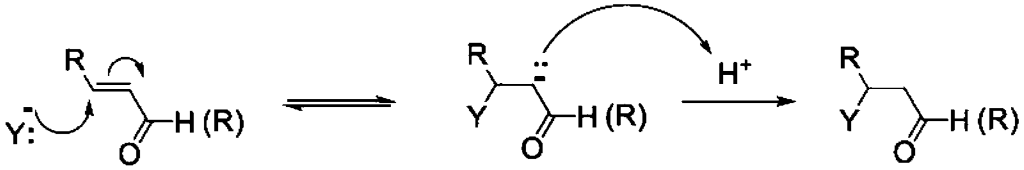
The reaction of aldehydes and ketones with weak nucleophiles (:Y), such as alcohols, requires acid catalysis (Scheme VI). Recall that the reaction of two mols of an alcohol with an aldehyde or ketone in the presence of acid (dry HCl) leads to the formation of an acetal or ketal, respectively (Scheme VI).

Scheme VI



α,β-Unsaturated aldehydes and ketones undergo the *Michael addition reaction* with Lewis bases (nucleophiles) (Scheme VII). Related conjugated systems, R-CH=CH-X, where X=COOR, CN, SO_2R and NO_2, behave similarly.

Scheme VII

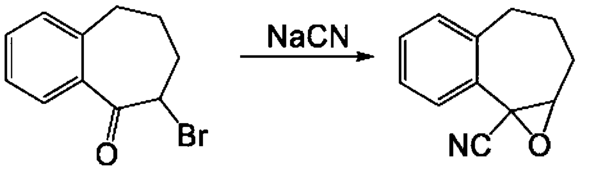
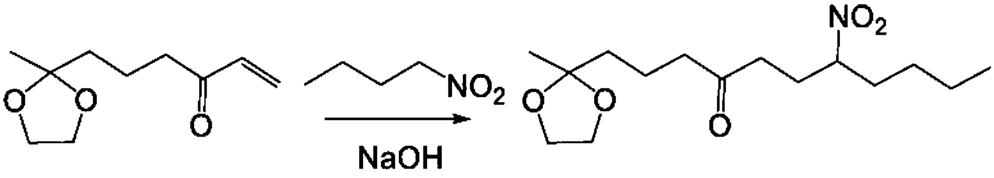
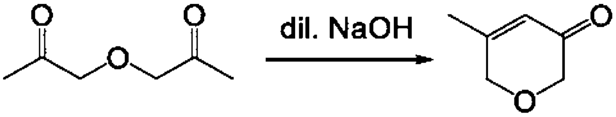
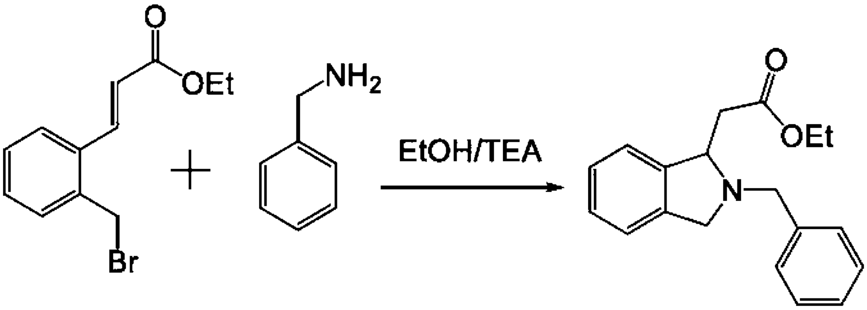
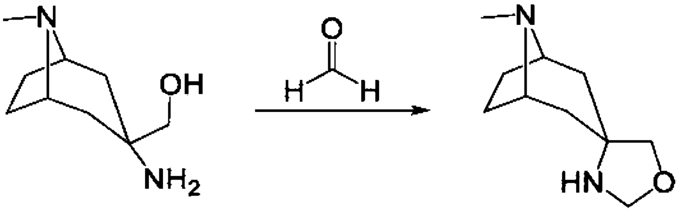
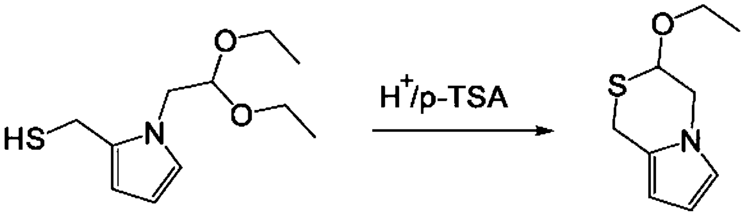


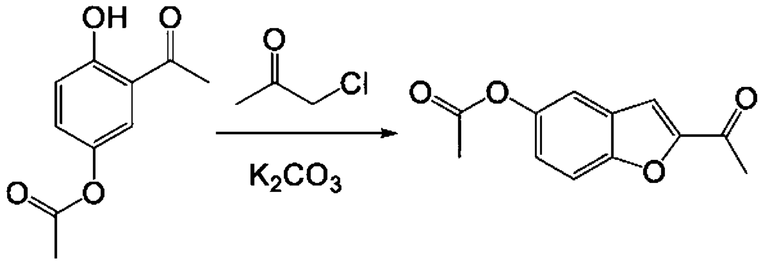
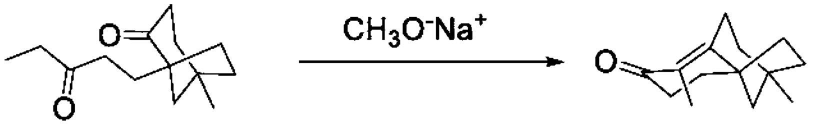
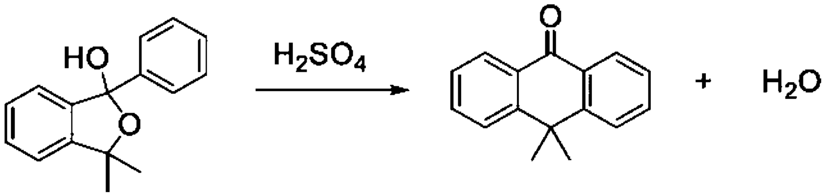
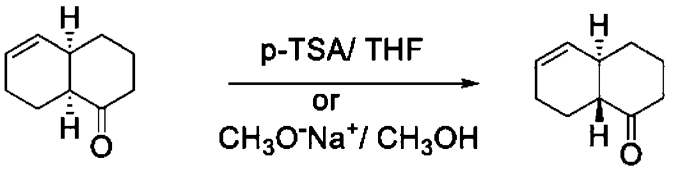
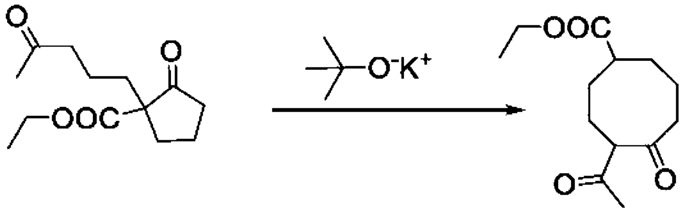
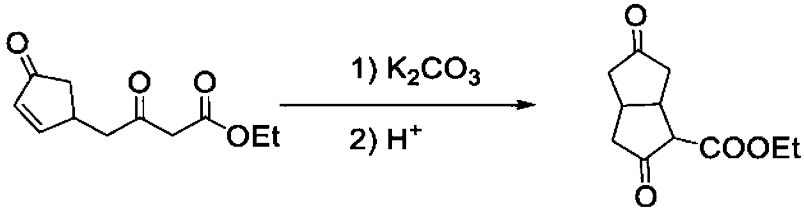
Lastly, the pK_a of the α-hydrogens in aldehydes and ketones is about 20. Consequently, treatment with a strong base leads to the formation of the corresponding anion (a Lewis base or nucleophile). The anion can then participate in nucleophilic displacement reactions (S_N2), nucleophilic addition reactions, or nucleophilic substitution reactions (see Minireview 6).

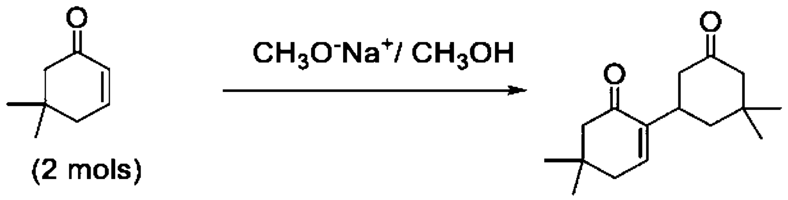
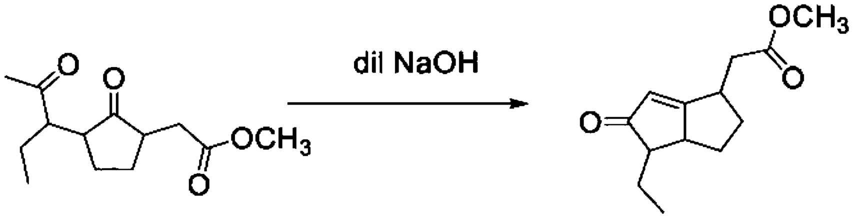
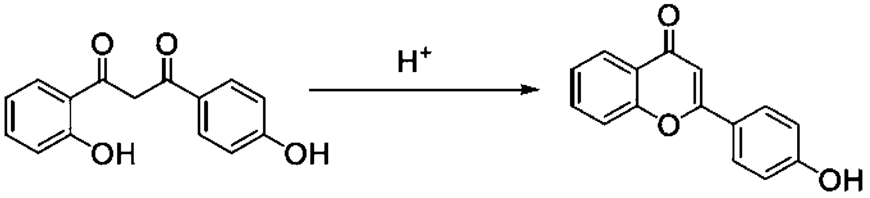
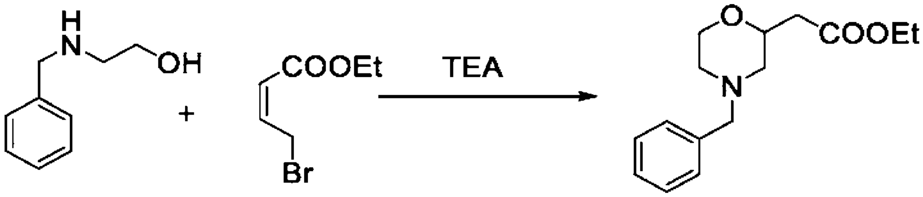
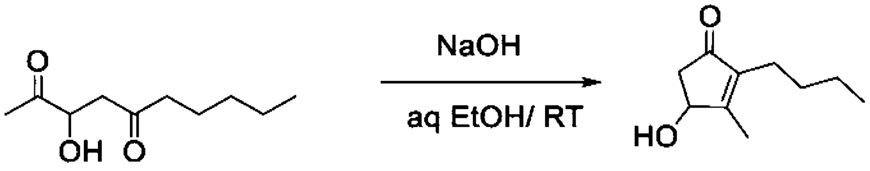
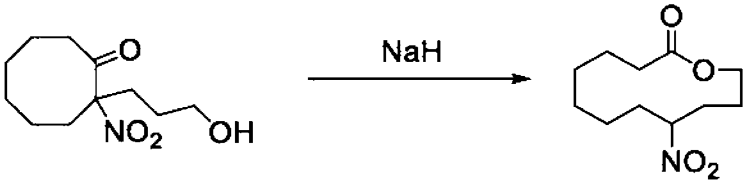
Questions 51 - 70

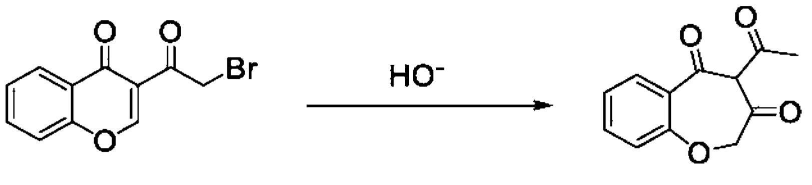
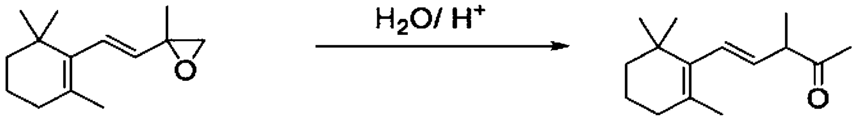
Questions 51-70 are meant to help you gain a better understanding of following topics.

- Acid and base-catalyzed addition reactions
- Aldol condensation reactions
- Michael addition reactions
- Keto-enol tautomeric equilibria

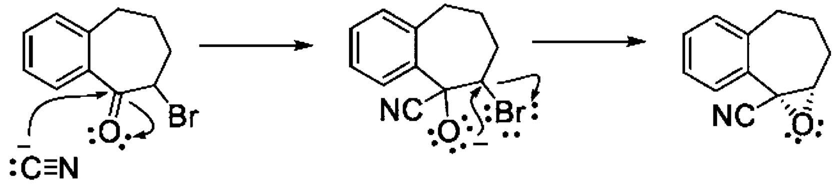
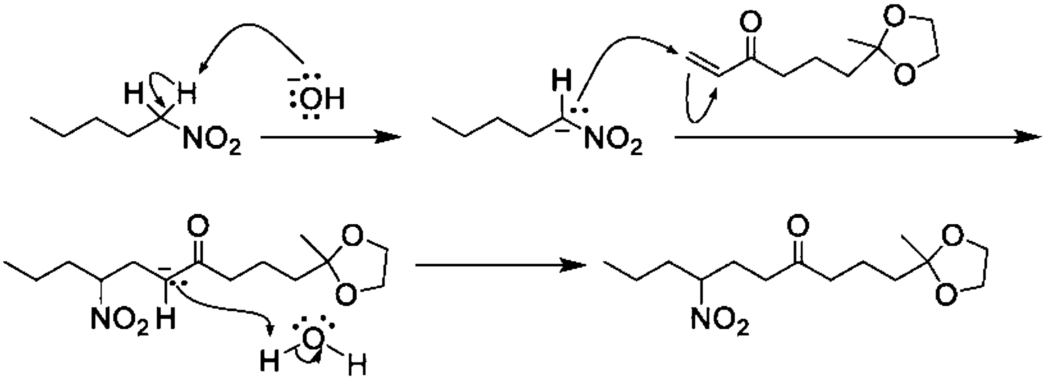
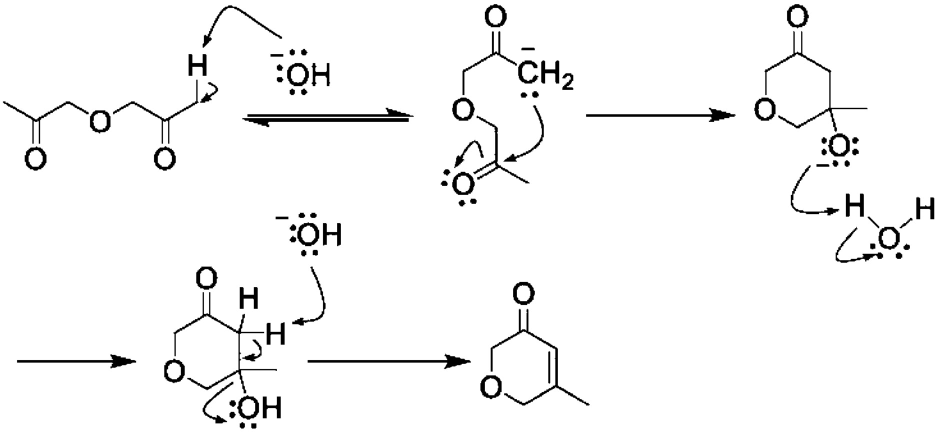
51	
52	
53	
54	
55	
56	

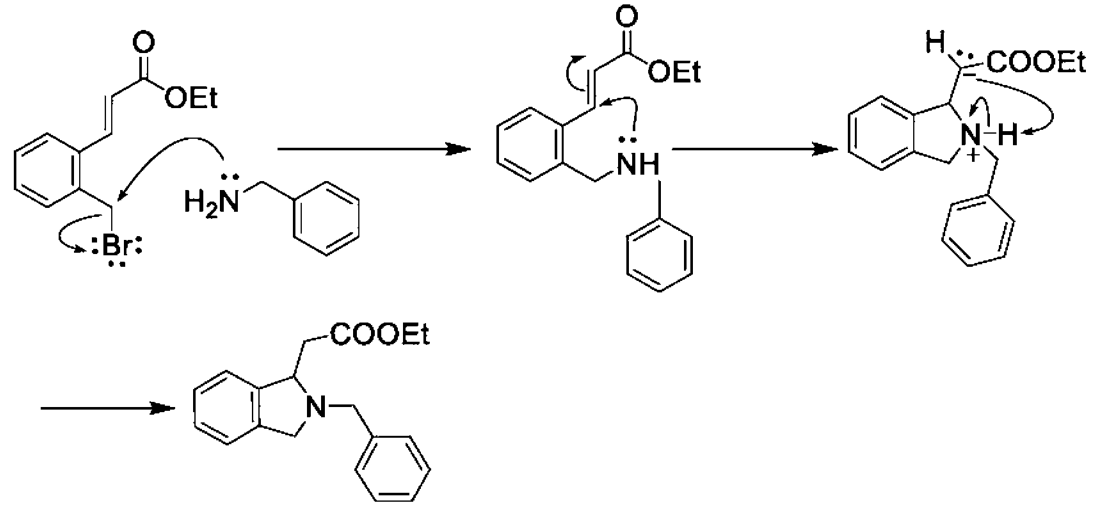
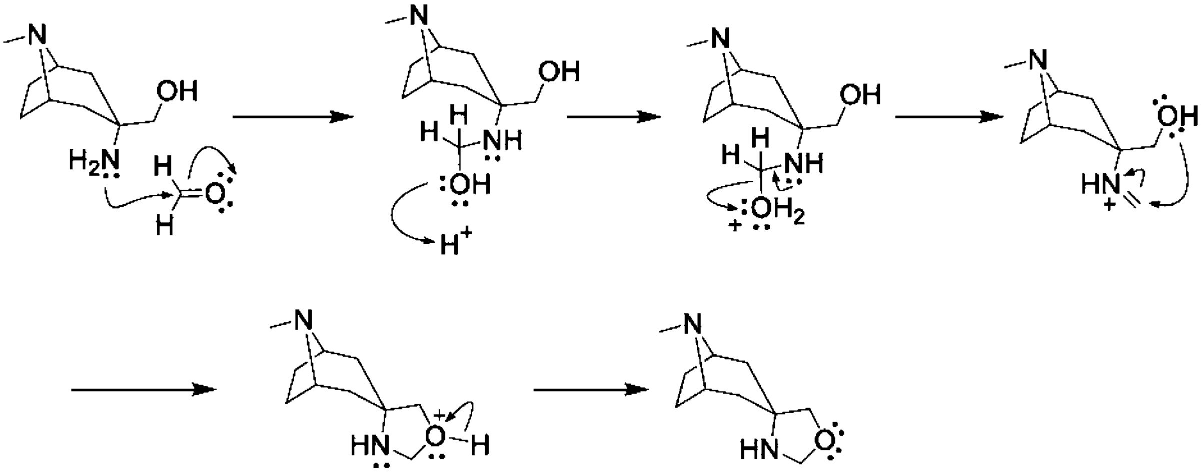
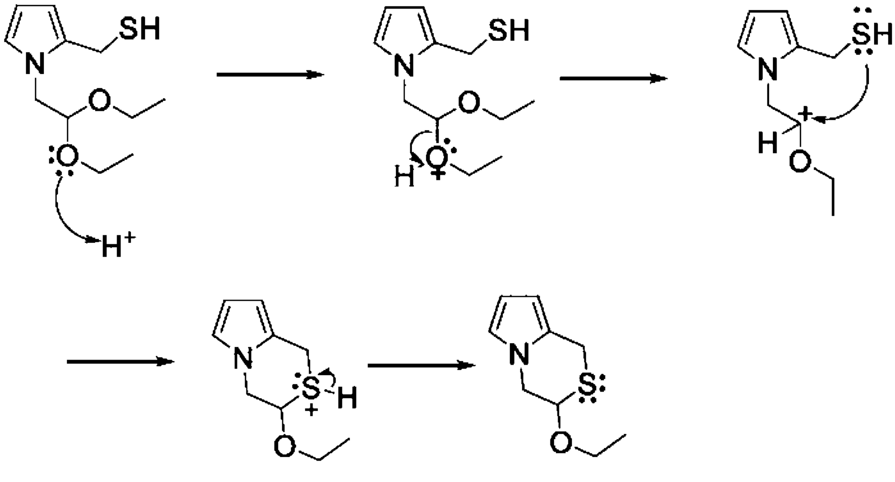
57	
58	
59	
60	
61	
62	

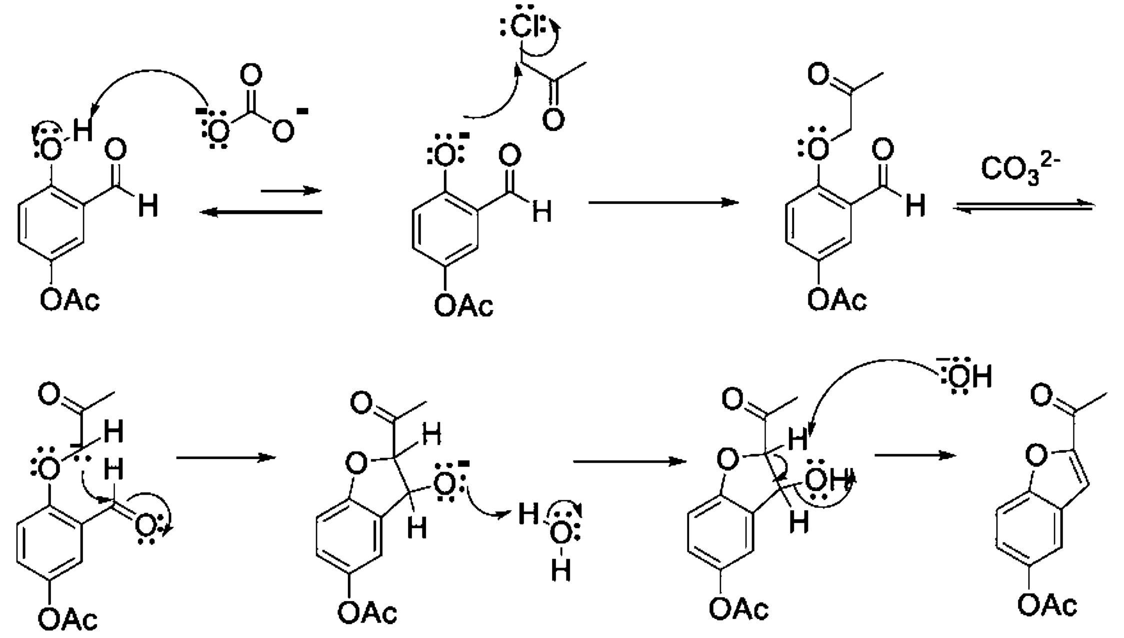
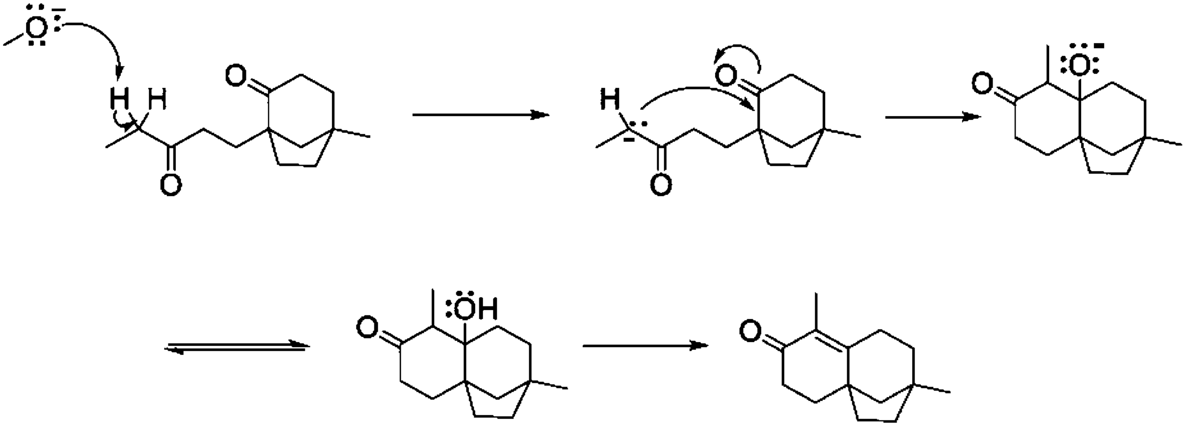
63	
64	
65	
66	
67	
68	

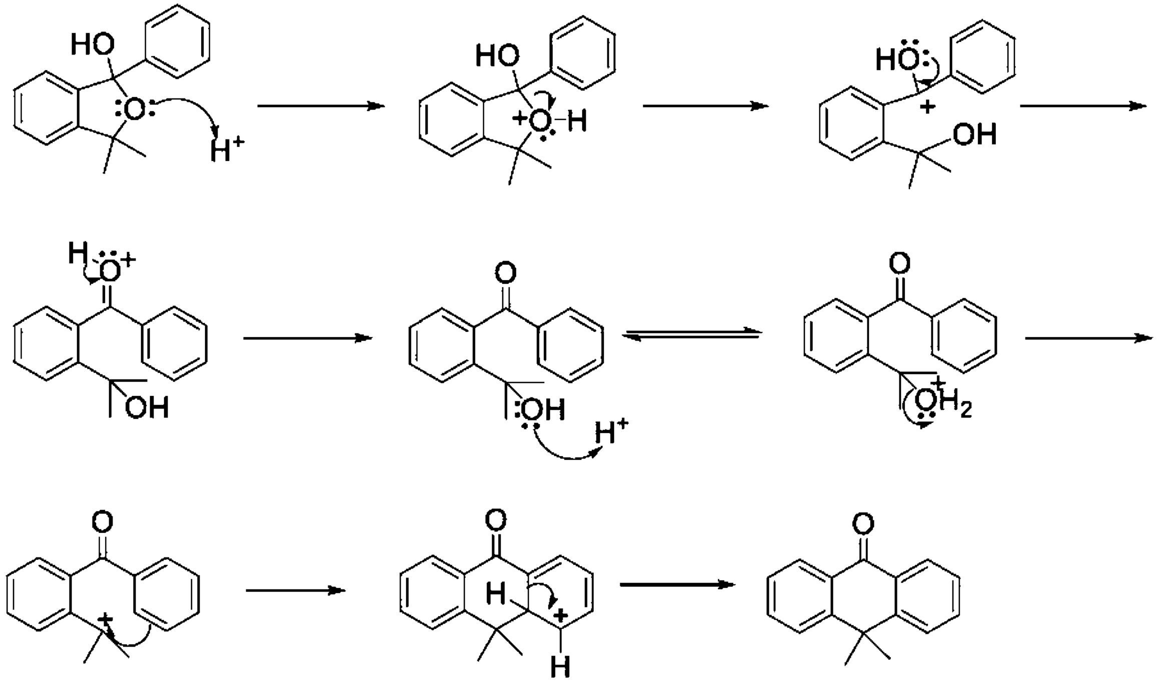
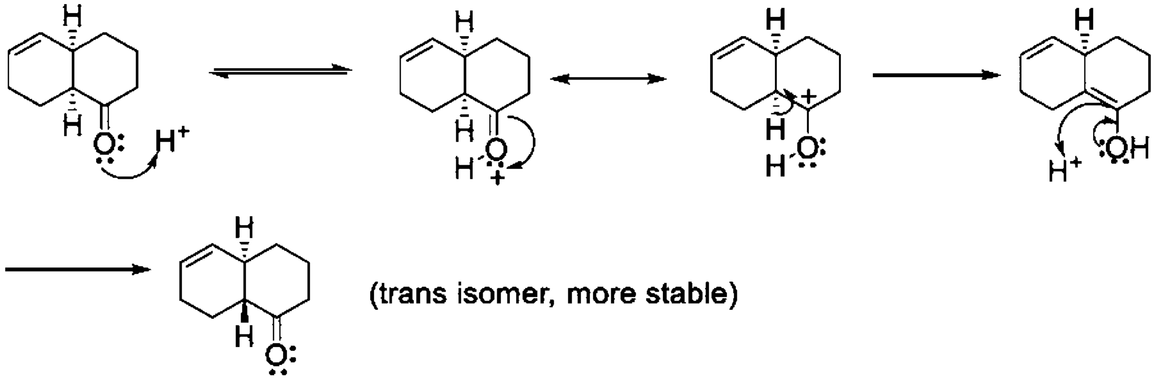
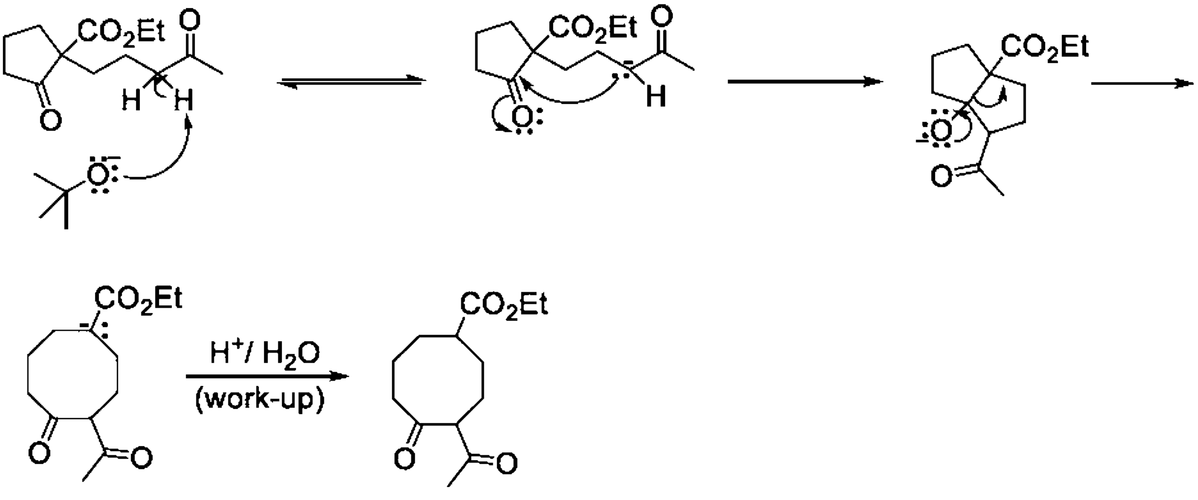
69	
70	

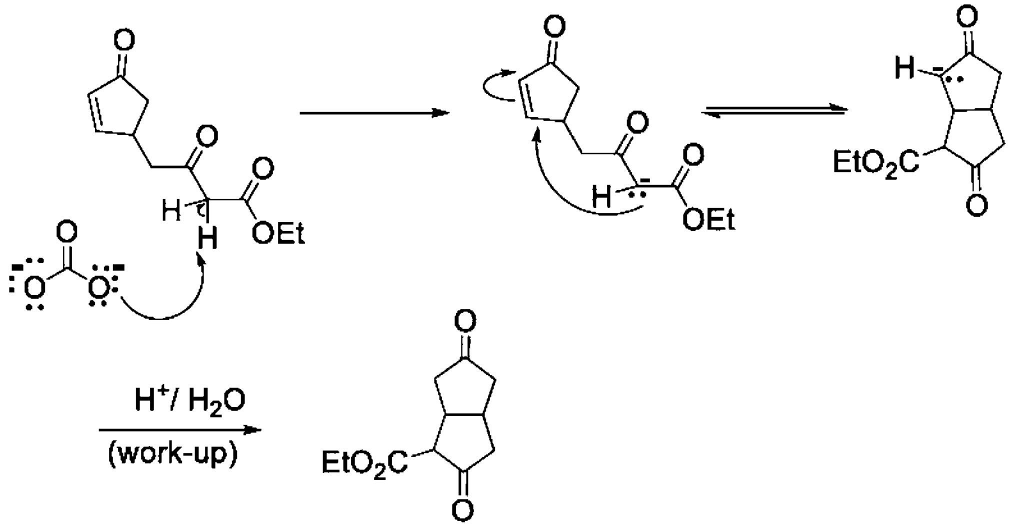
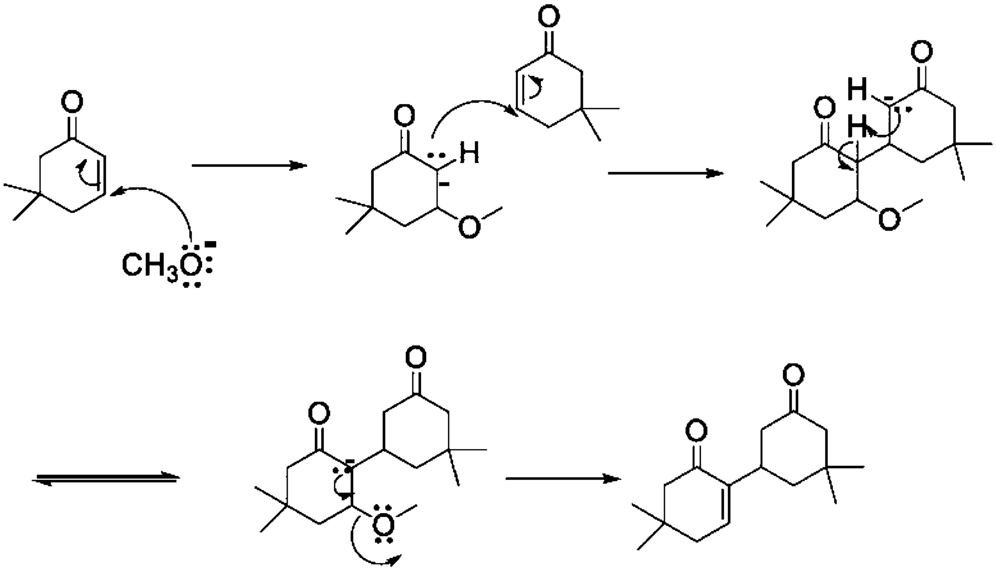
Answers to Questions 51-70

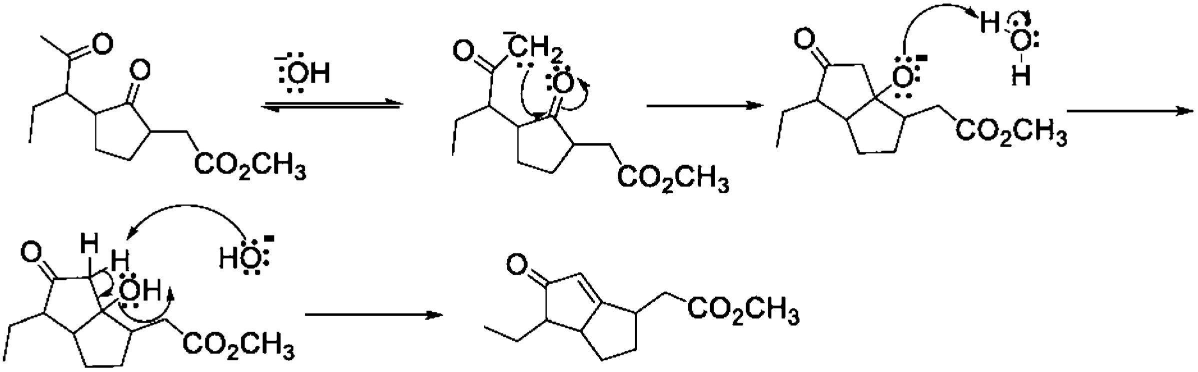
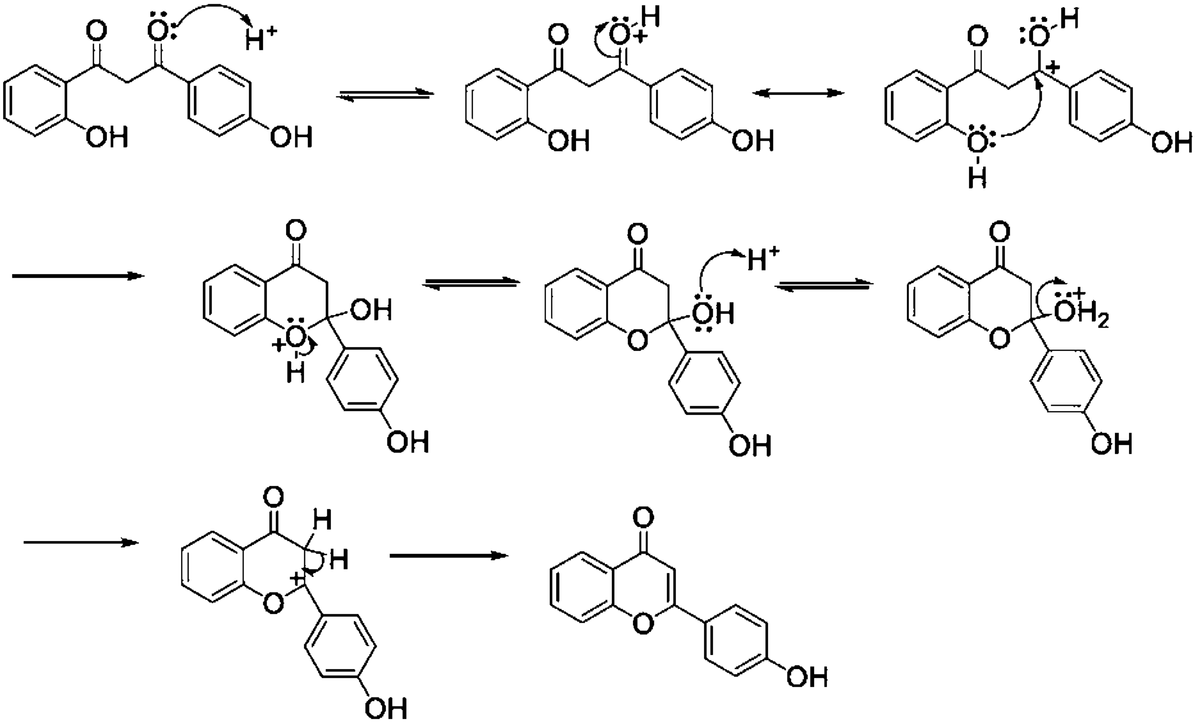
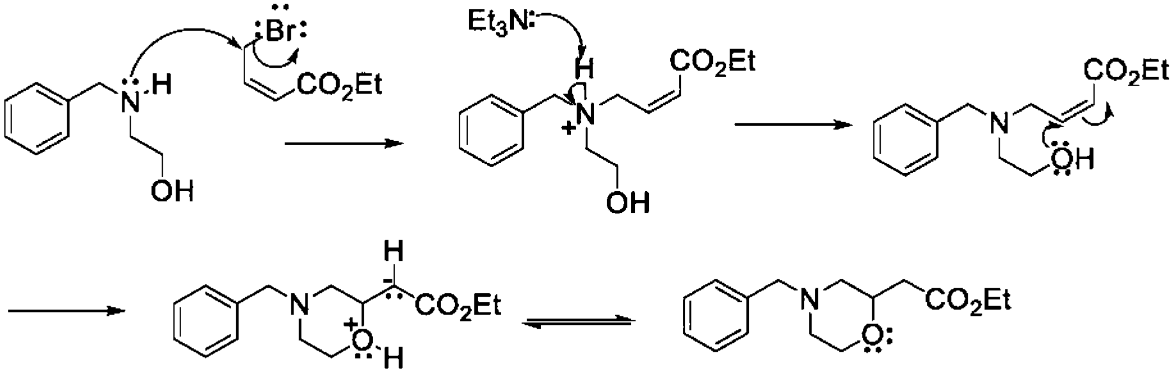
51	
	A straightforward nucleophilic addition is followed by an intramolecular S_N2 reaction.
52	
	Note that once the anion is generated, what happens next is determined by the nature of the other reactant (see Minireview 5). Since the reactant in this case is a conjugated carbonyl compound, a Michael addition reaction takes place.
53	
	This is an example of an intramolecular aldol condensation reactio

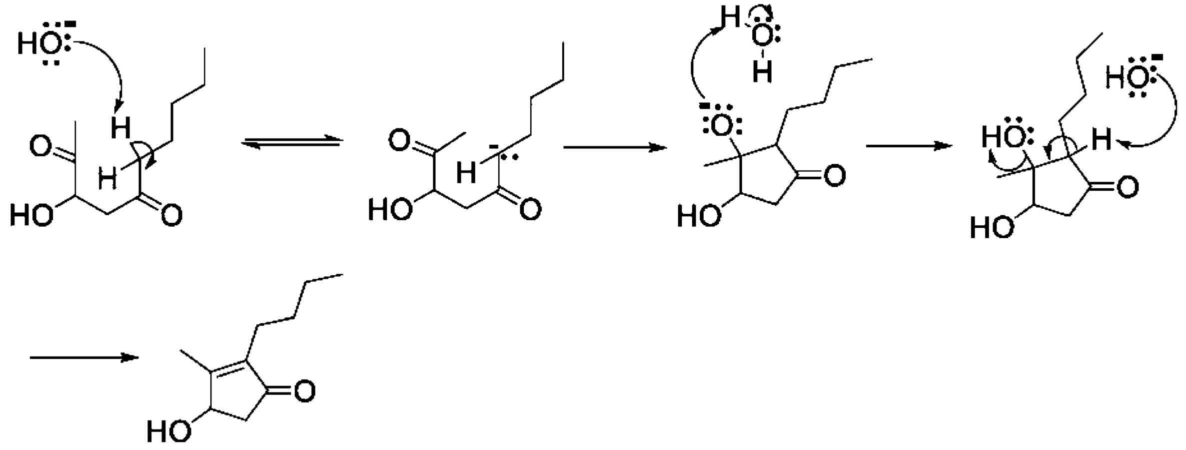
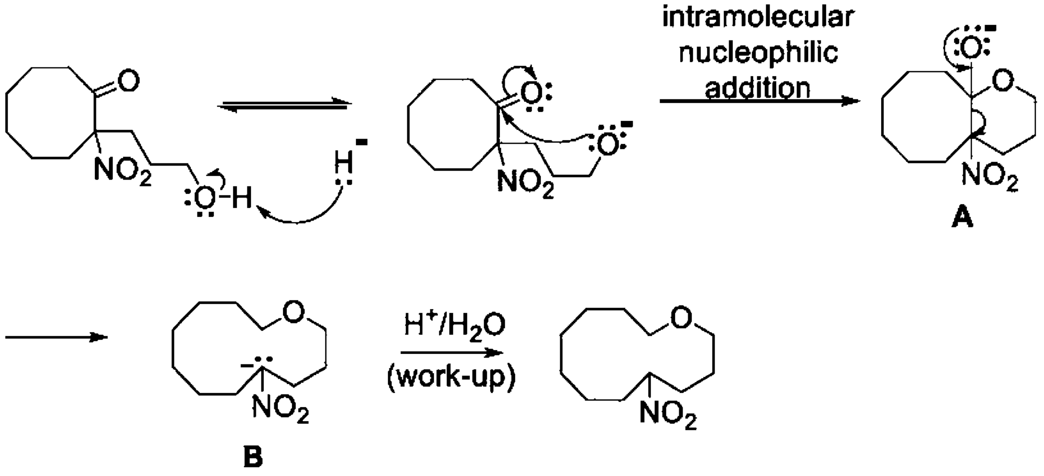
54	
An S_N2 reaction is followed by an intramolecular Michael addition reaction.	
55	
56	

57	
58	

59	
60	 (trans isomer, more stable)
61	

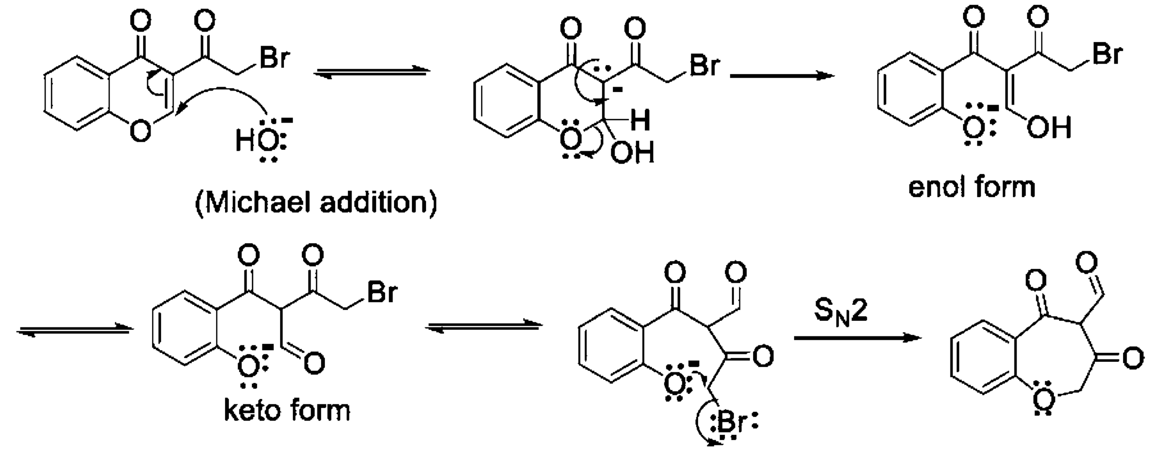
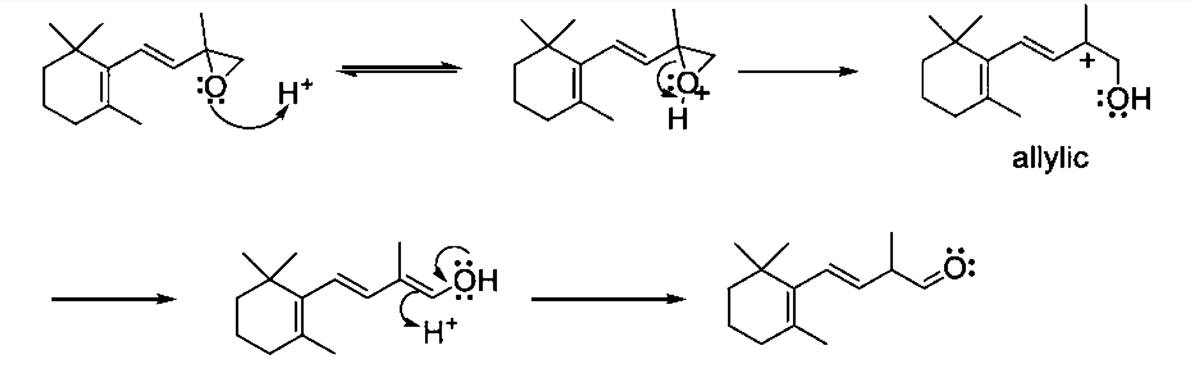
62	
63	
Two consecutive Michael addition reactions are followed by a prototropic shift (an acid-base reaction) and elimination of the methoxide ion to yield the product	

64	
65	
66	

67	
68	

Species A is the expected nucleophilic addition product, however, instead of becoming protonated, A reforms the strong carbonyl bond, yielding a highly stable anion B.

Exercise: Write all the resonance structures that can be written for anion B.

69	
70	

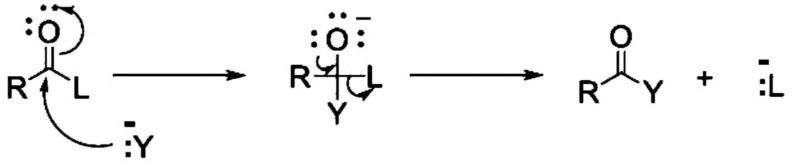
Minireview 9 focuses on nucleophilic acyl substitution reactions, the typical reaction of carboxylic acid derivatives. This should be studied prior to attempting questions 71-200.

Minireview 9

- Nucleophilic Acyl Substitution Reactions

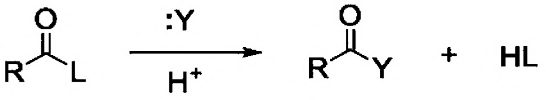
The typical reaction of carboxylic acid derivatives (acid halides, anhydrides, esters, thioesters, and amides) with Lewis bases is *nucleophilic acyl substitution*. The mechanism of this reaction is shown below (eq 1).

Mechanism



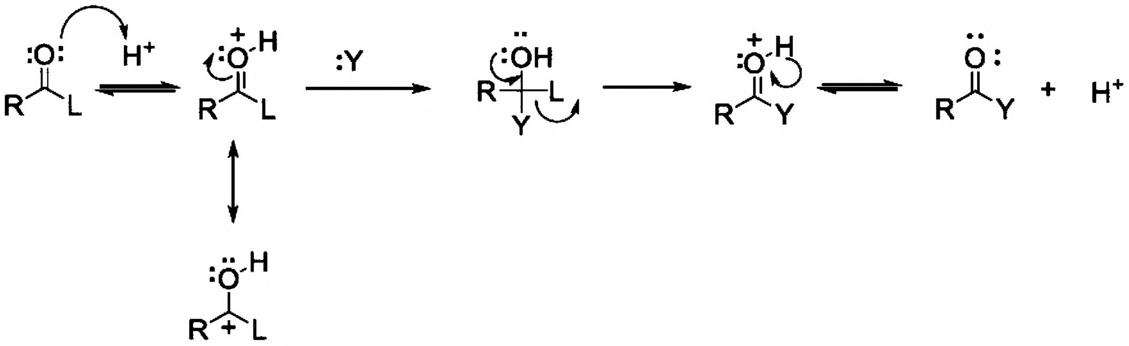
eq 1

Reactions involving weak nucleophiles (:Y) can be speeded up by acid catalysis (eq 2). With the exception of amines and phosphorus nucleophiles, nucleophiles that do not bear a negative charge (:Y) are classified as weak, while those having a negative charge are classified as strong nucleophiles.



eq 2

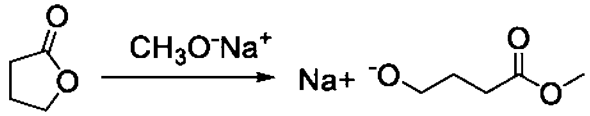
Mechanism



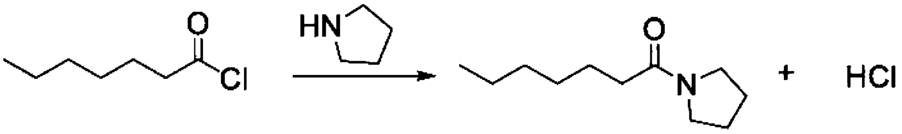
Exercise

1) Using general mechanistic principles, write a mechanism for each of the following reactions

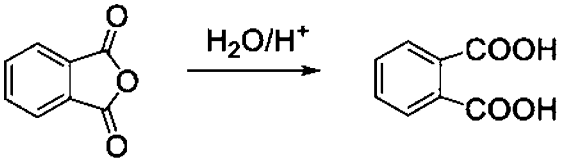
a)



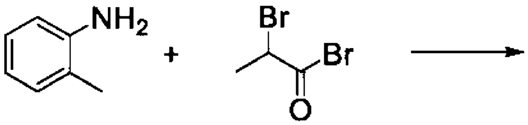
b)



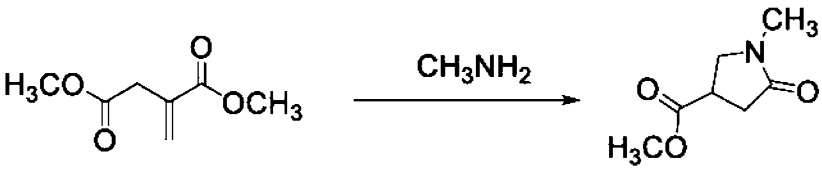
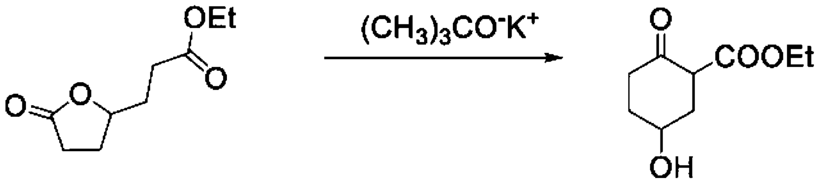
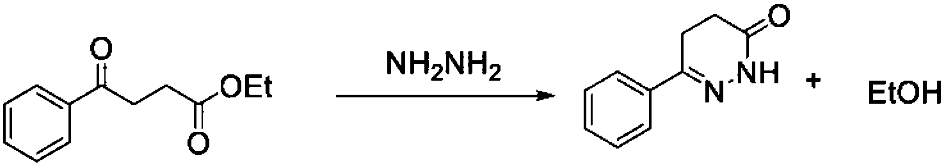
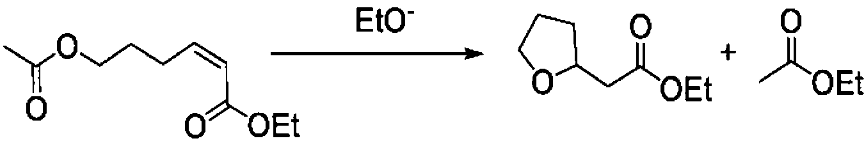
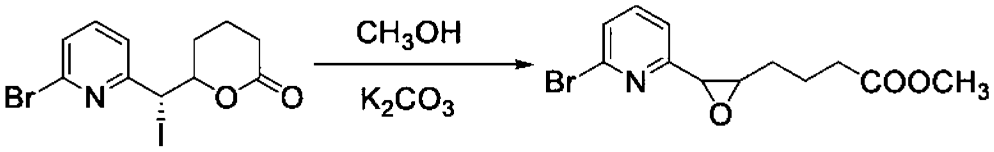
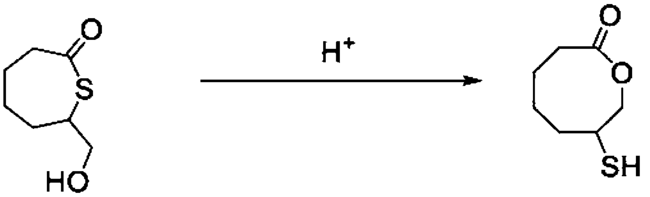
c)

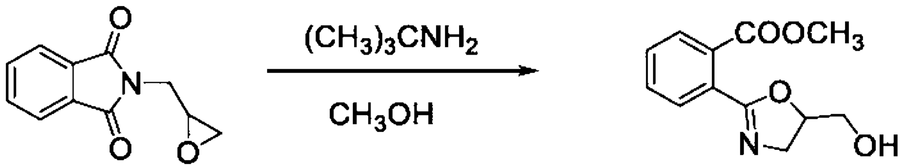
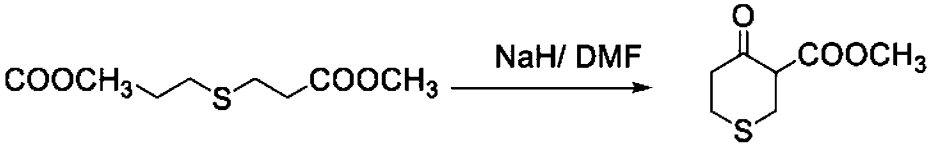
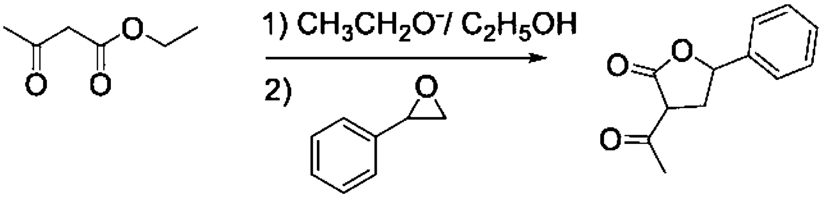
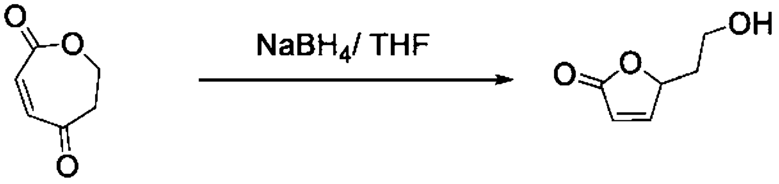
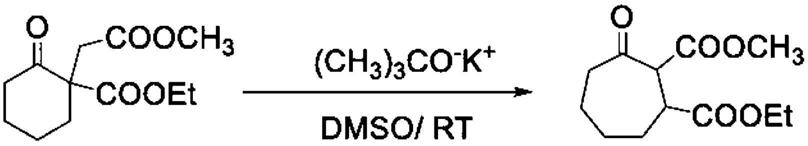
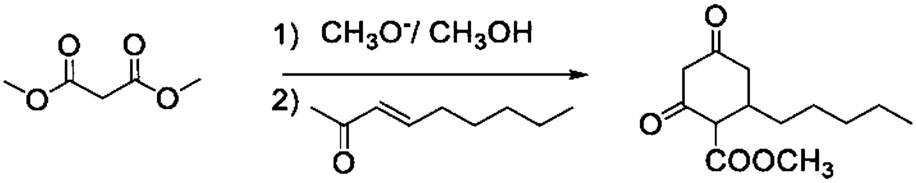


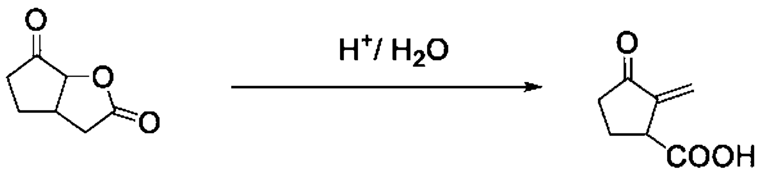
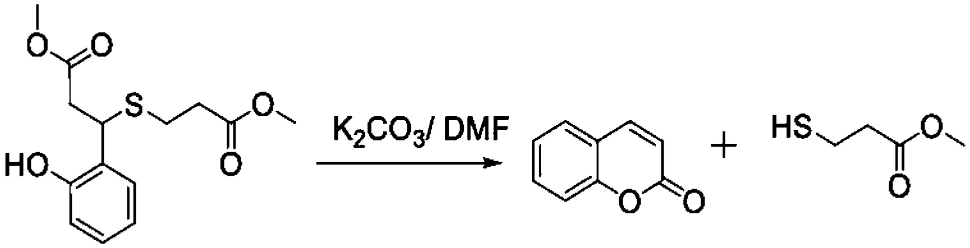
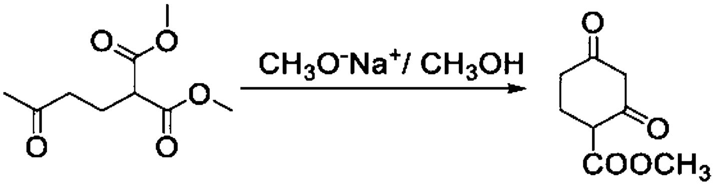
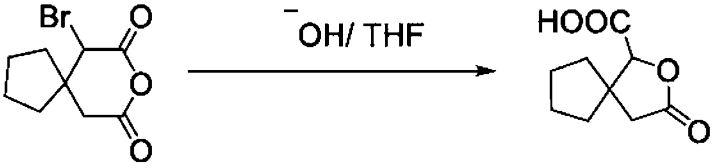
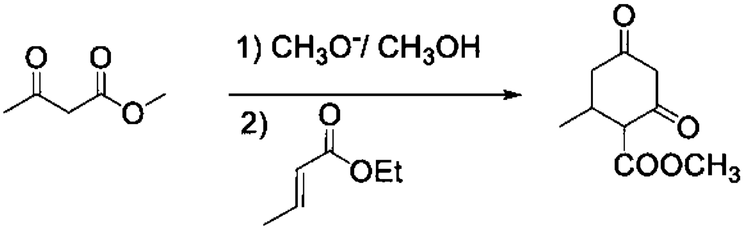
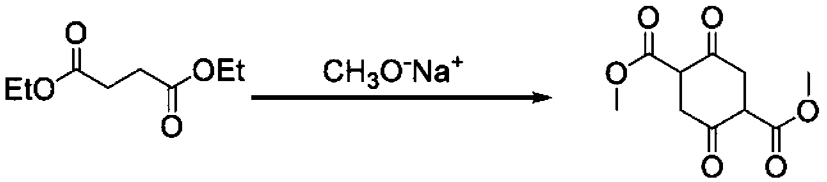
2) Predict the product of the following reaction:

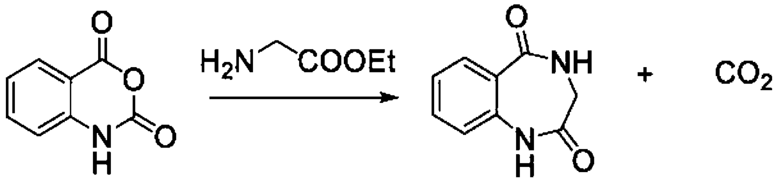
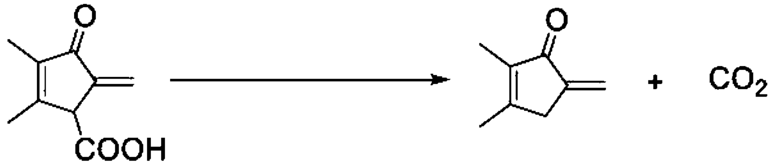
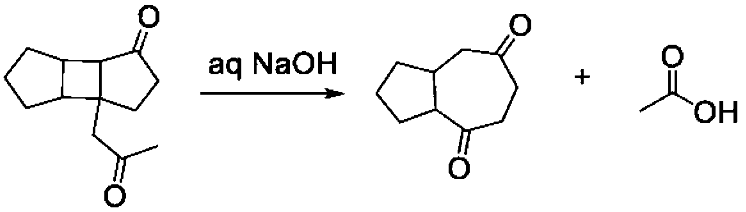
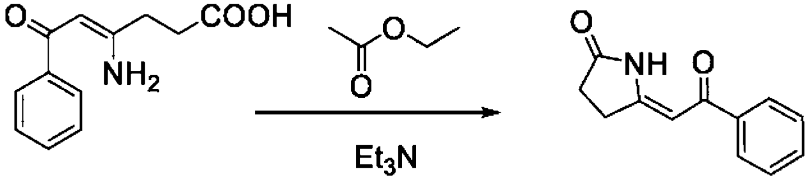
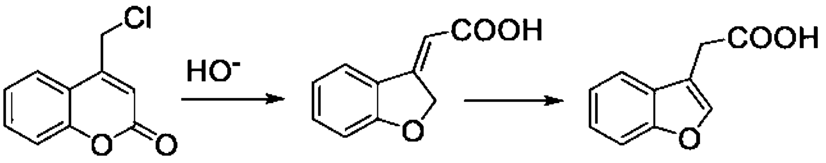
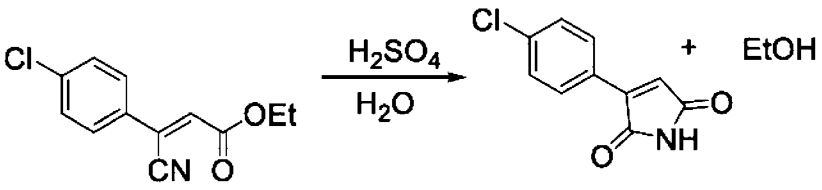


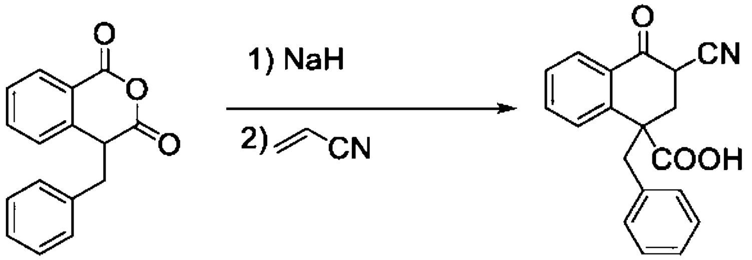
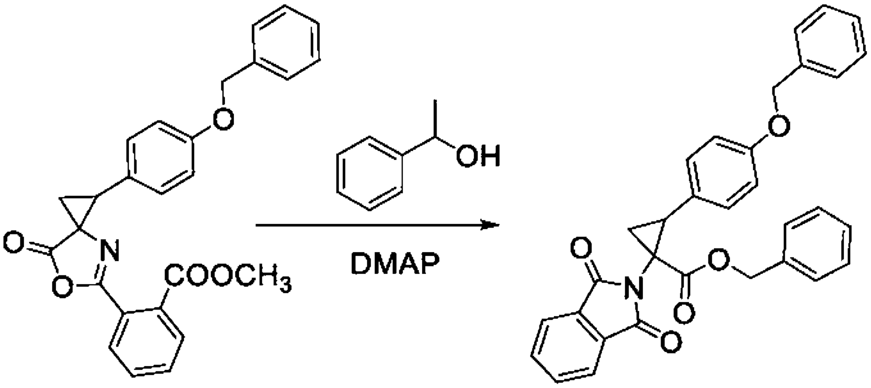
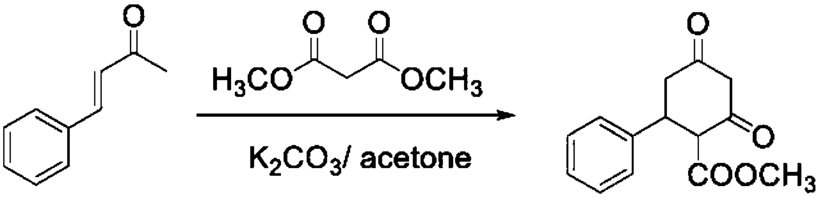
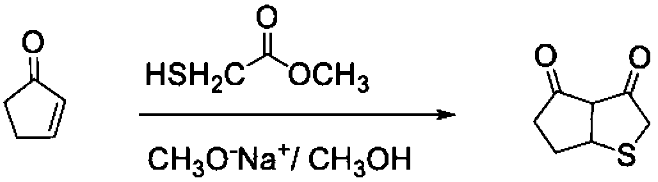
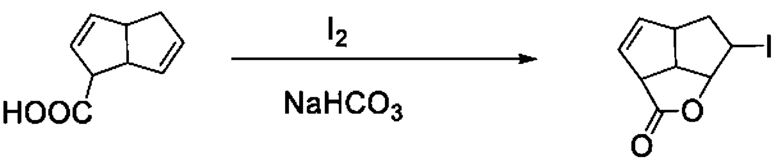
Questions 71-200

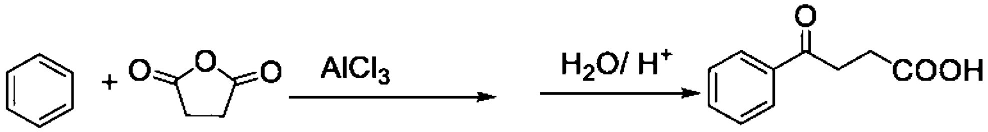
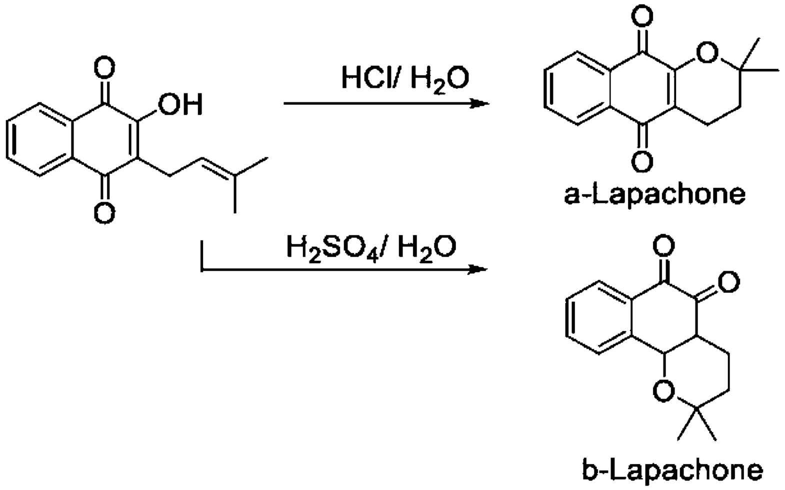
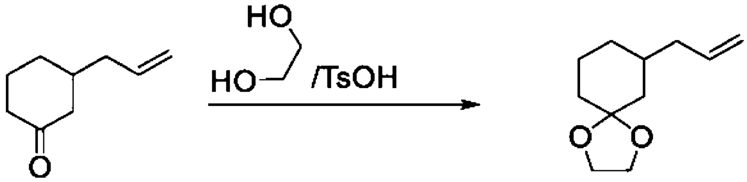
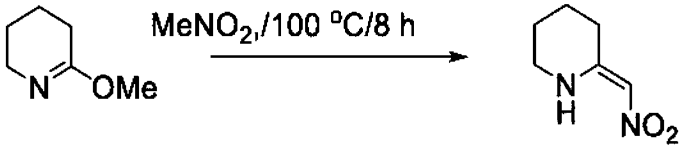
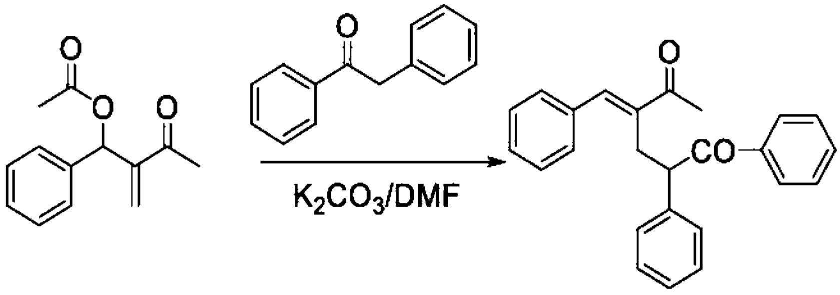
71	
72	
73	
74	
75	
76	

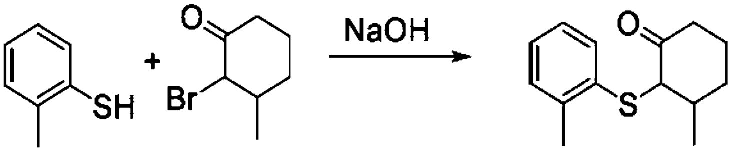
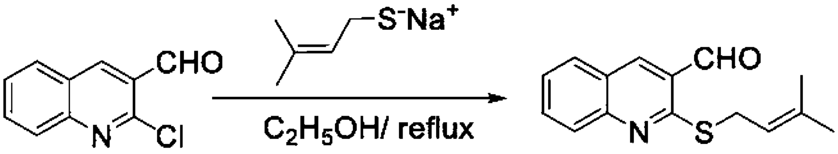
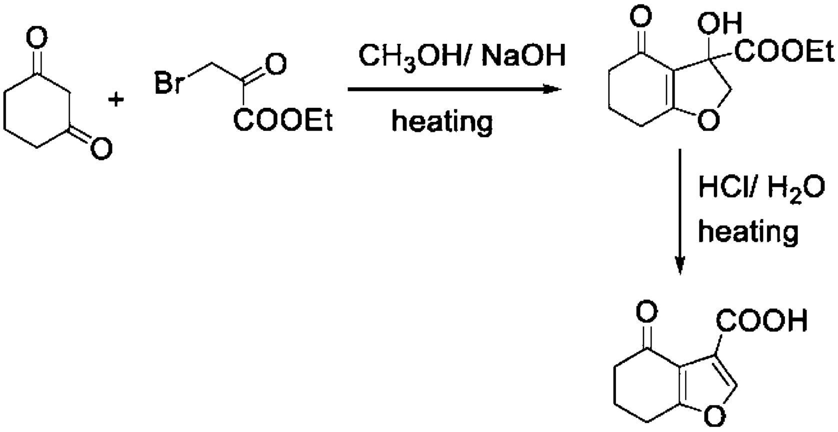
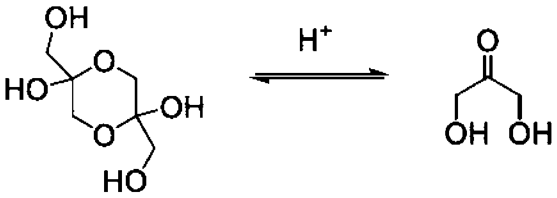
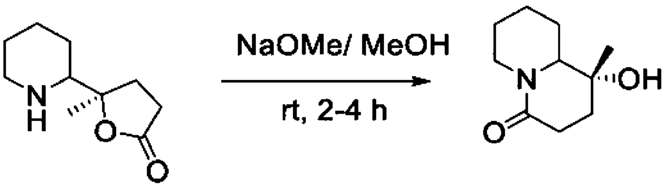
77	
78	
79	
80	
81	
82	

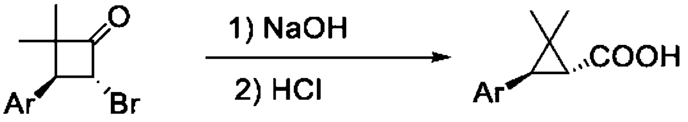
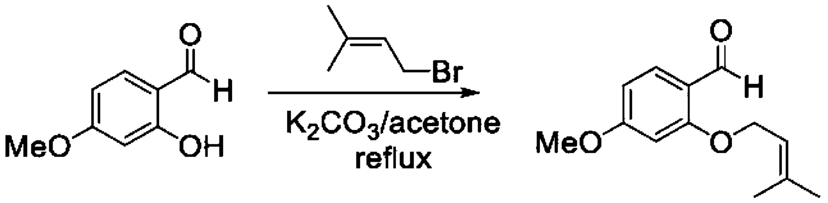
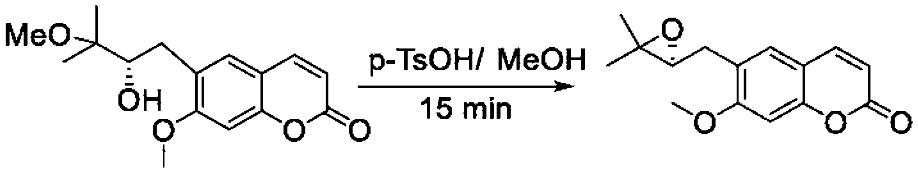
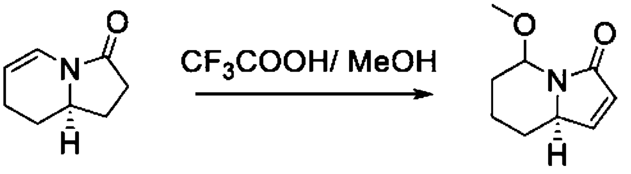
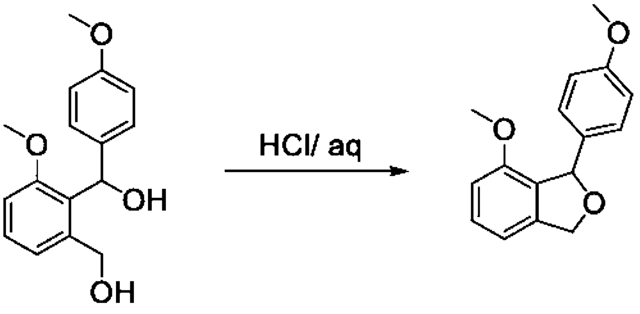
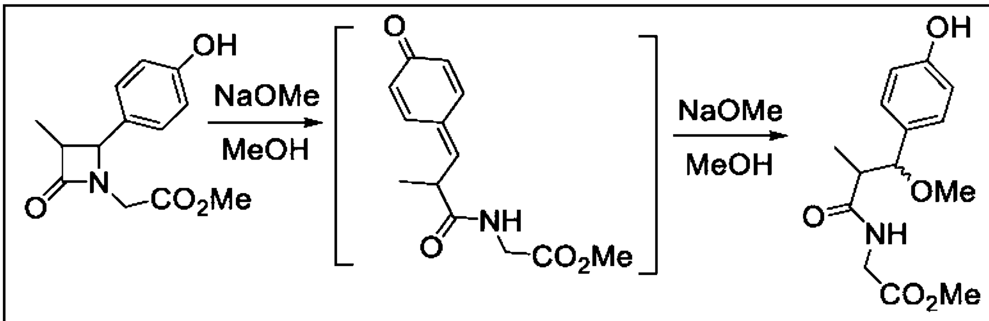
83	
84	
85	
86	
87	
88	

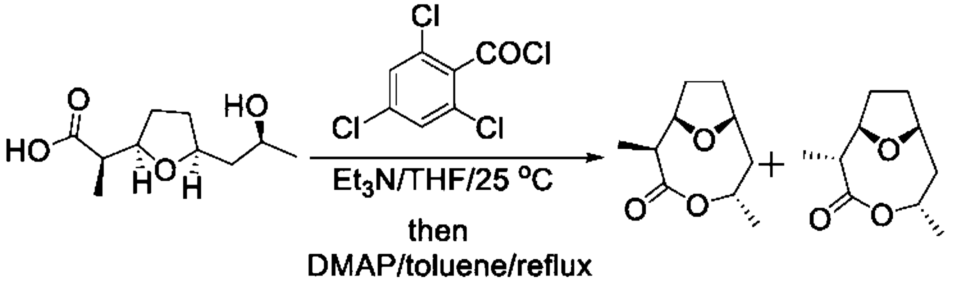
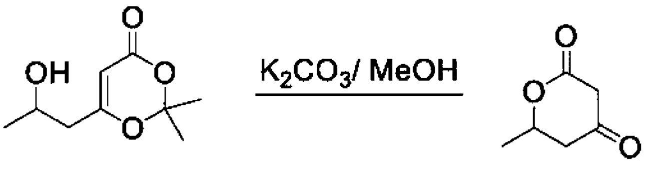
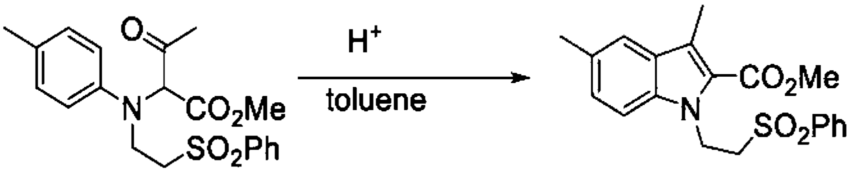
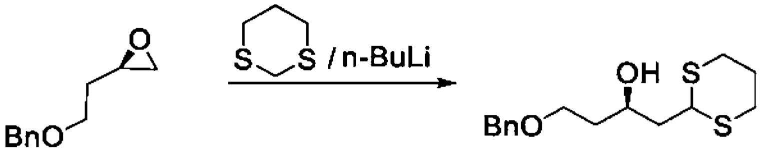
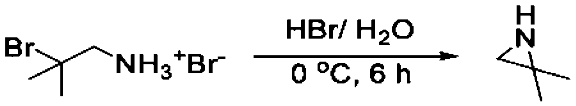
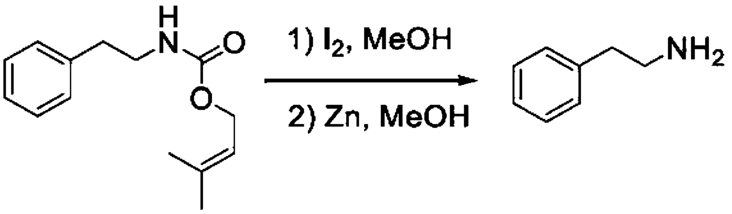
89	
90	The following decarboxylation occurs spontaneously. Explain. 
91	
92	
93	
94	

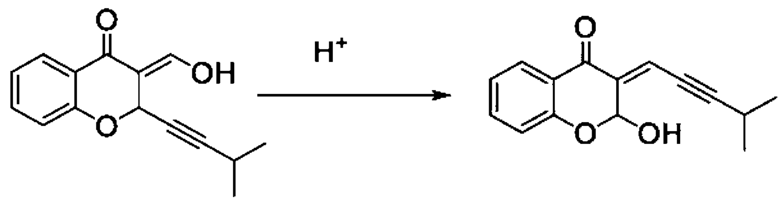
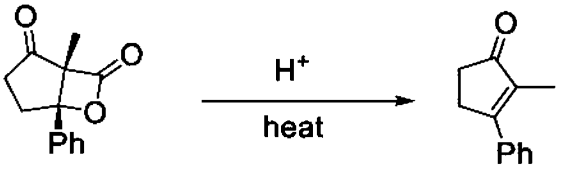
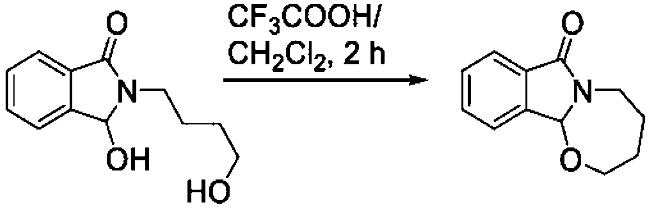
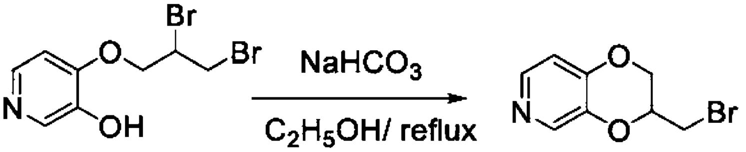
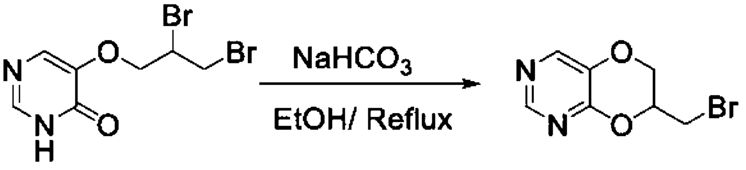
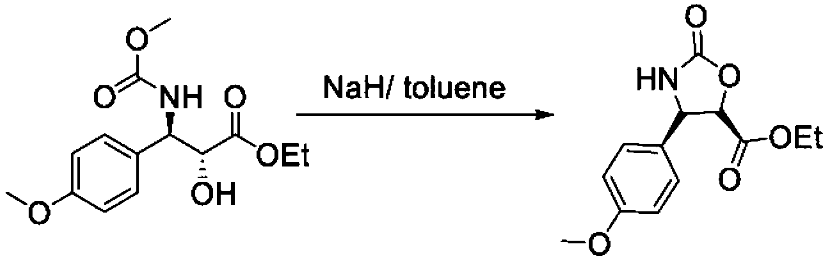
95	 1) NaH 2) CN CN COOH
96	 OH DMAP COOCH$_3$
97	 H$_3$CO OCH$_3$ K$_2$CO$_3$/ acetone COOCH$_3$
98	 HSH$_2$C OCH$_3$ CH$_3$O$^-$Na$^+$/ CH$_3$OH S
99	 HOOC I$_2$ NaHCO$_3$ I

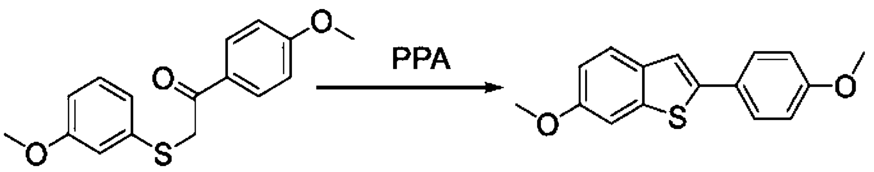
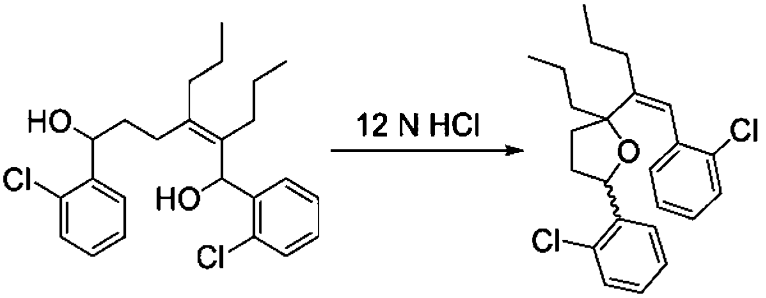
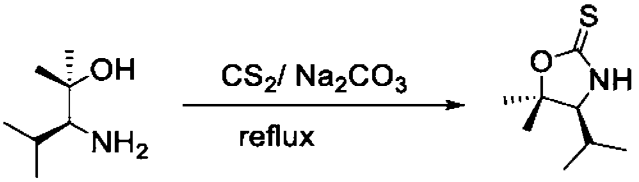
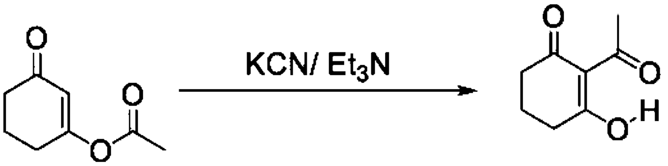
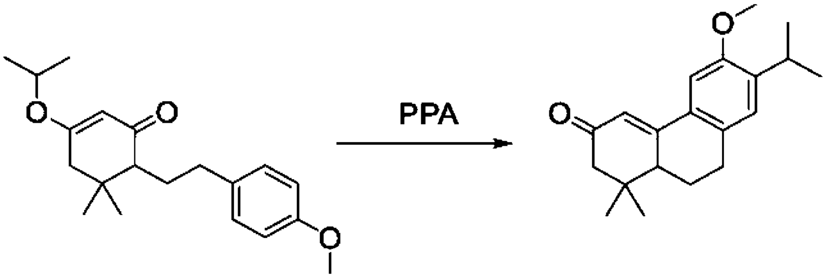
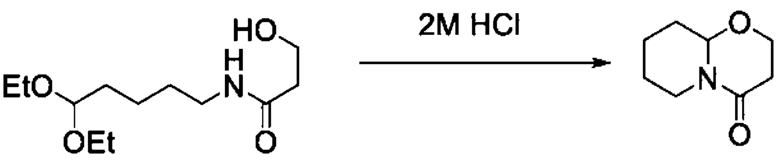
100	
101	
102	
103	
104	

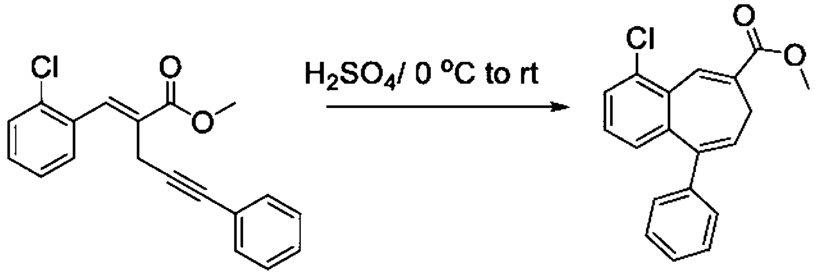
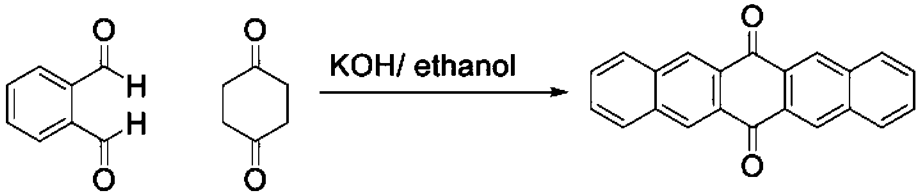
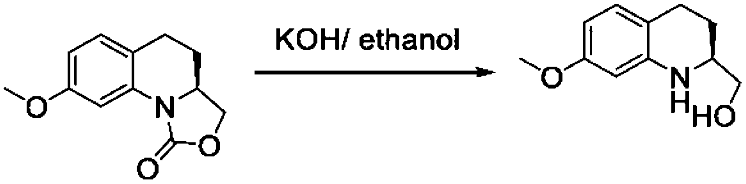
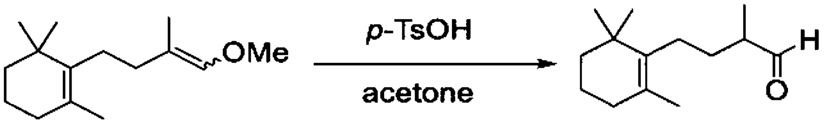
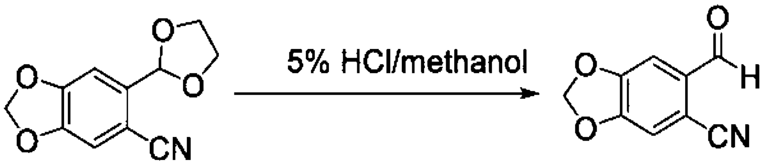
105	
106	
107	
108	
109	

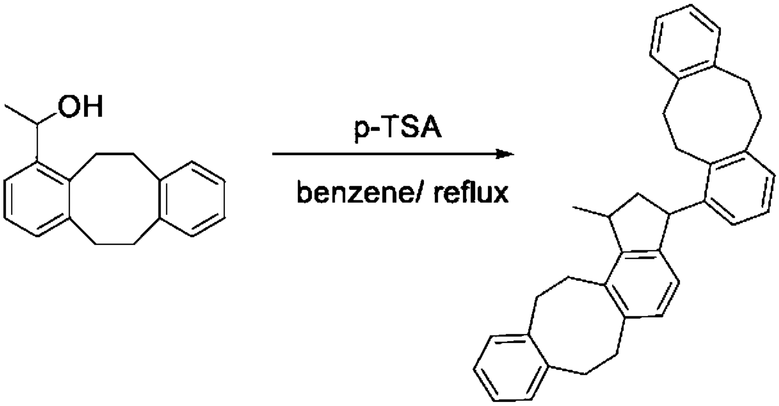
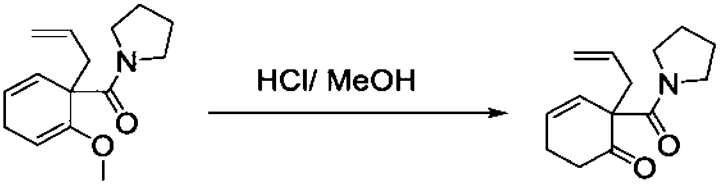
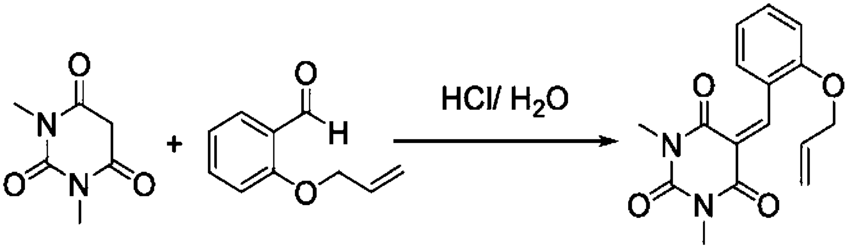
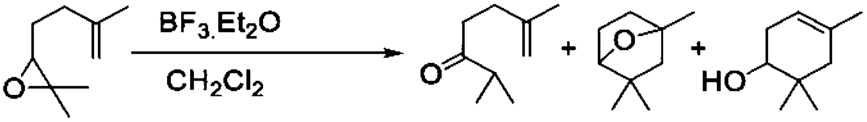
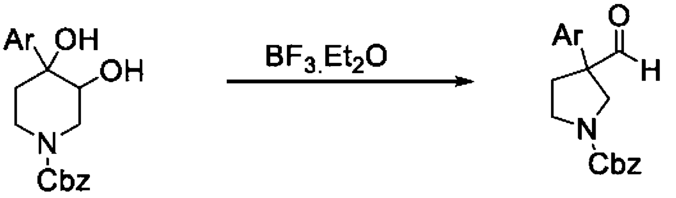
110	
111	
112	
113	
114	
115	

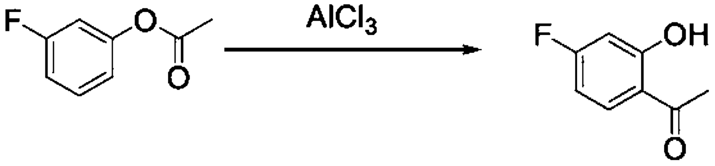
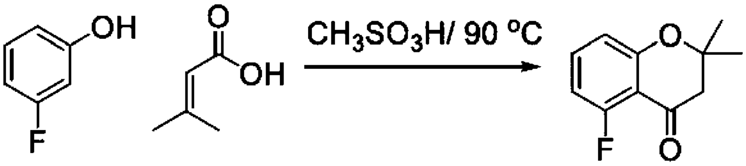
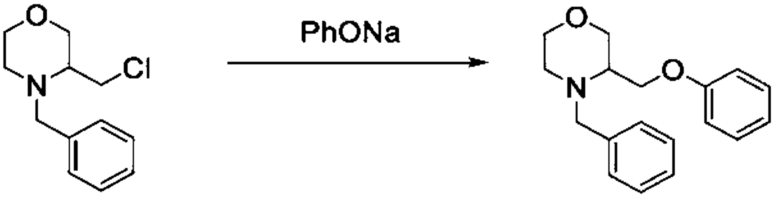
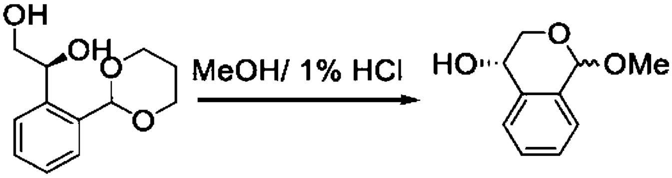
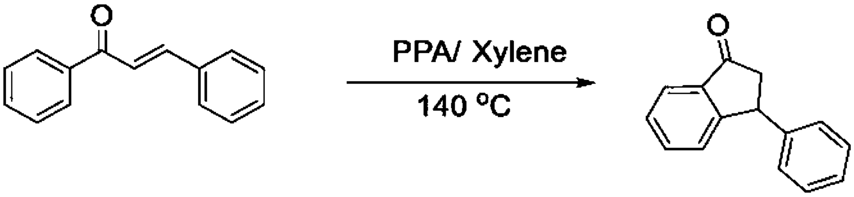
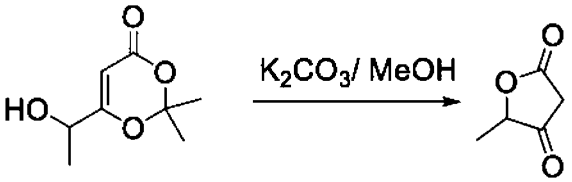
116	
117	
118	
119	
120	
121	

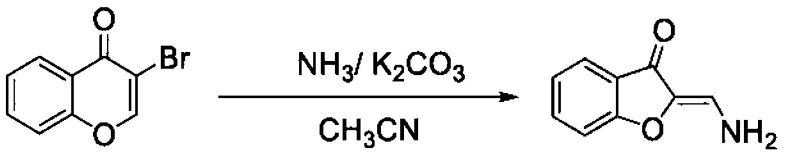
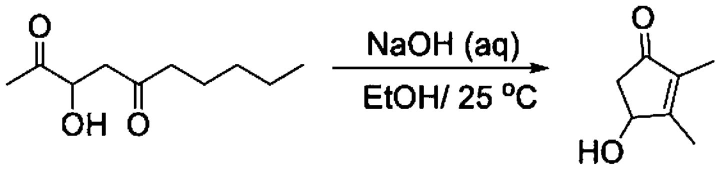
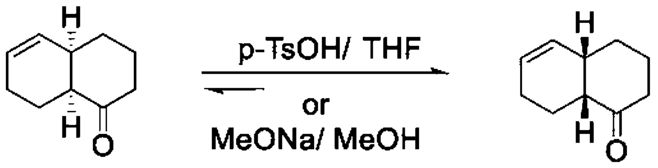
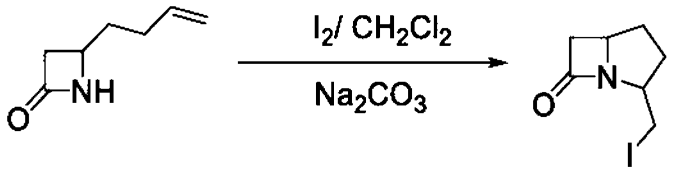
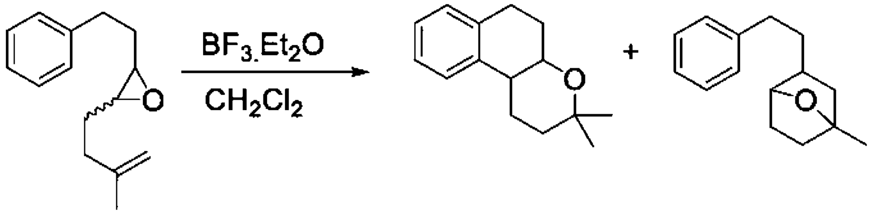
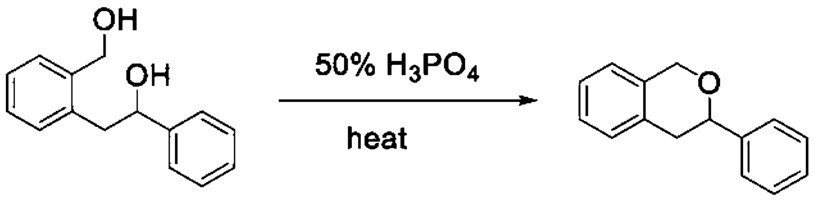
122	
123	
124	
125	
126	
127	

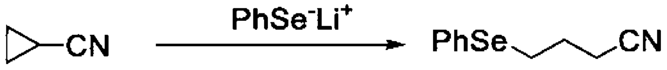
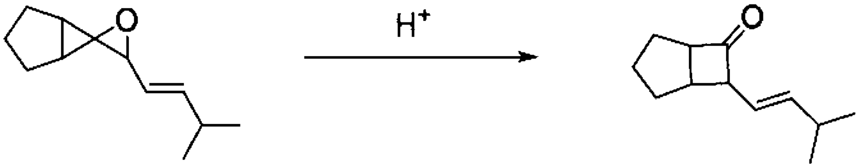
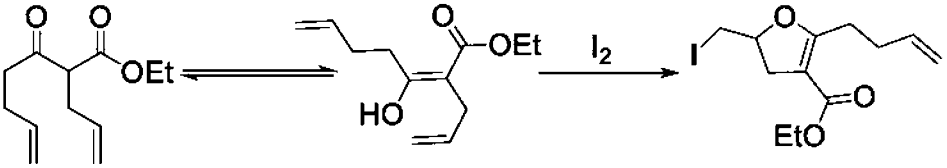
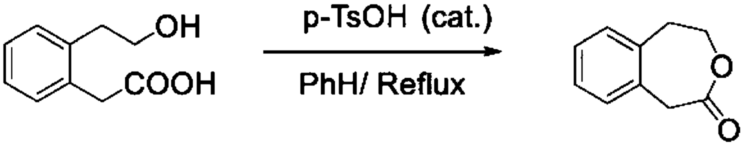
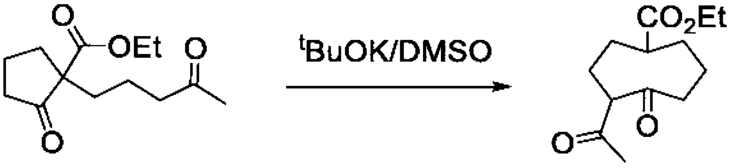
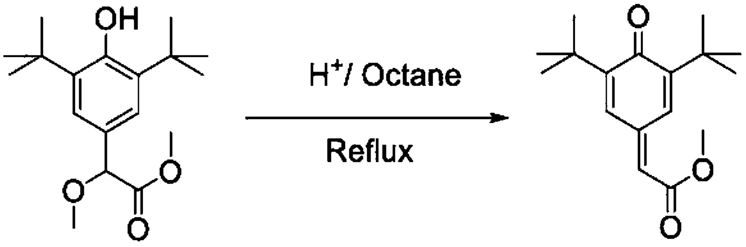
128	
129	
130	
131	
132	
133	

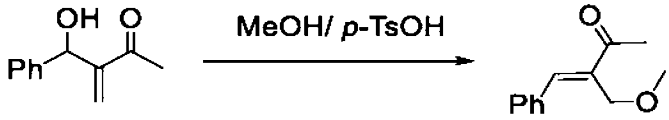
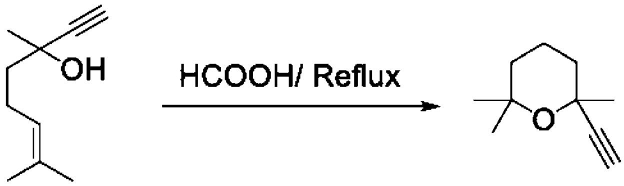
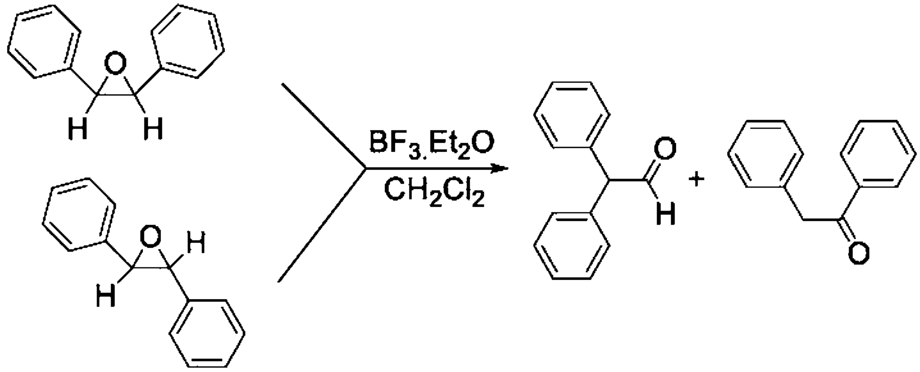
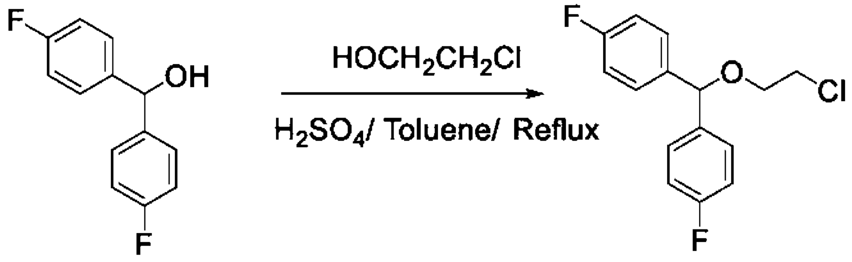
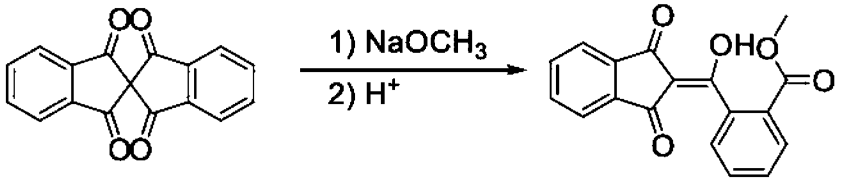
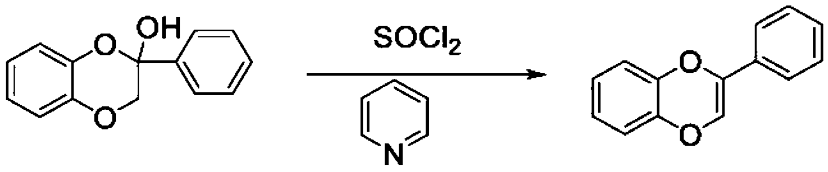
134	
135	
136	
137	
138	

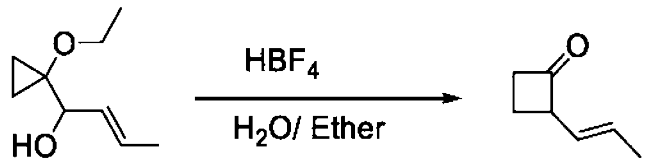
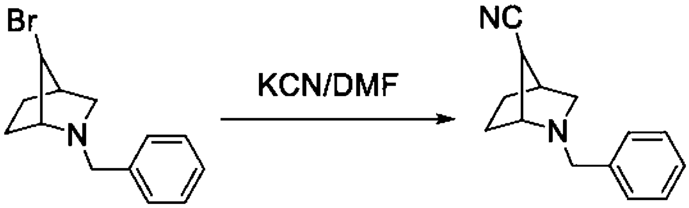
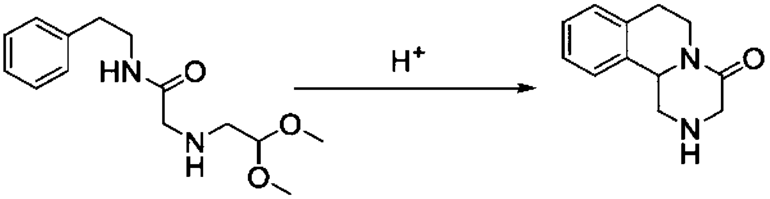
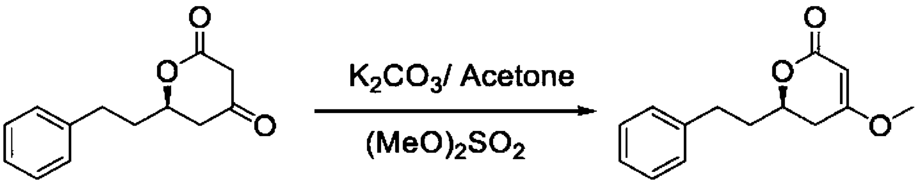
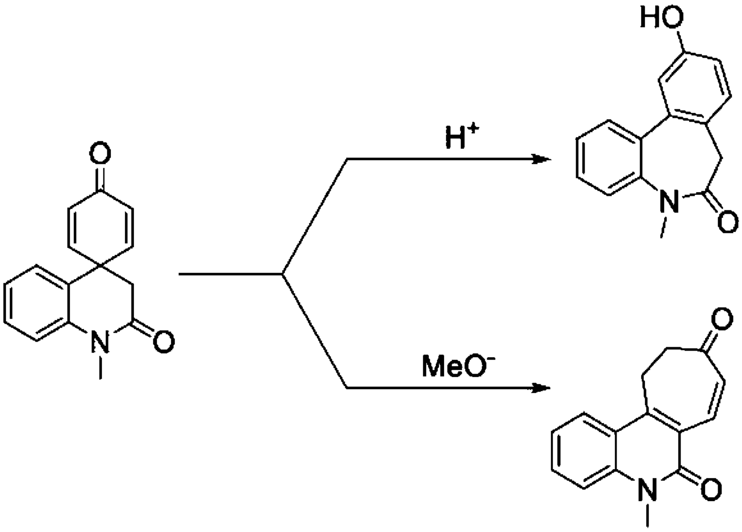
139	
140	
141	
142	
143	

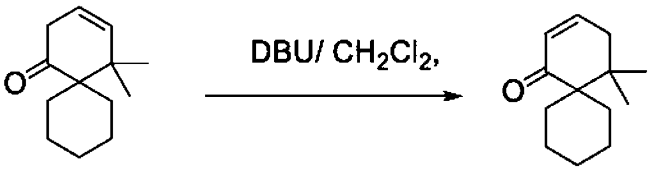
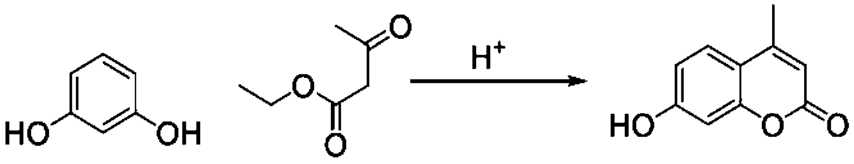
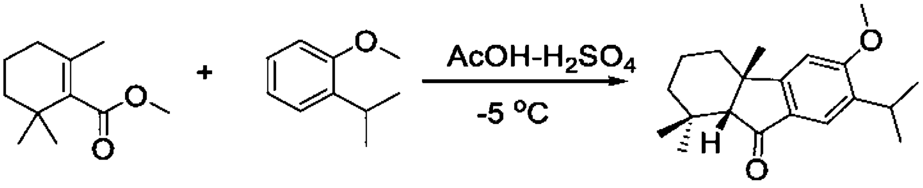
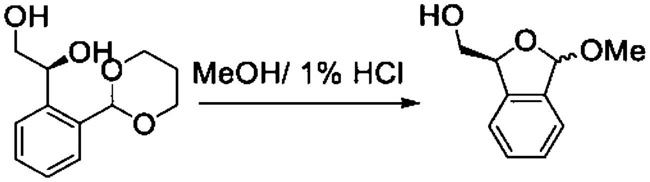
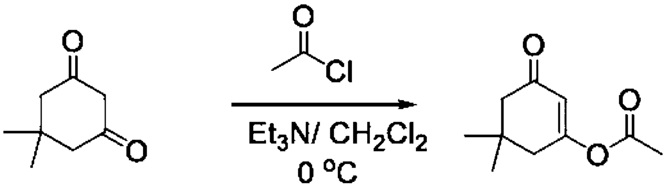
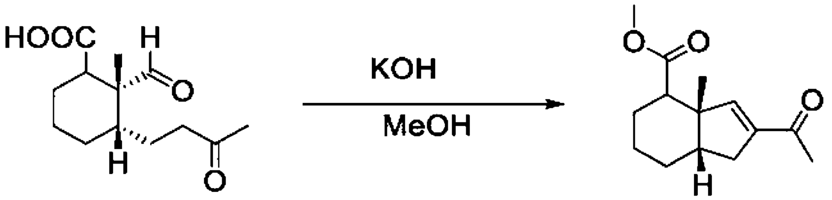
144	
145	
146	
147	
148	
149	

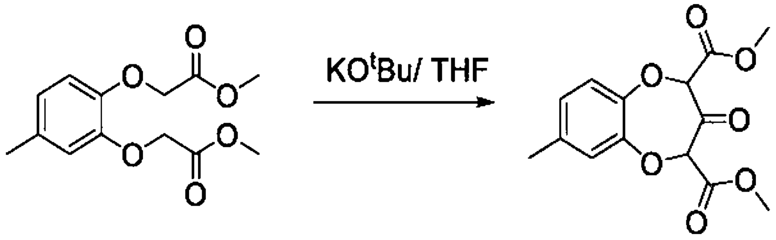
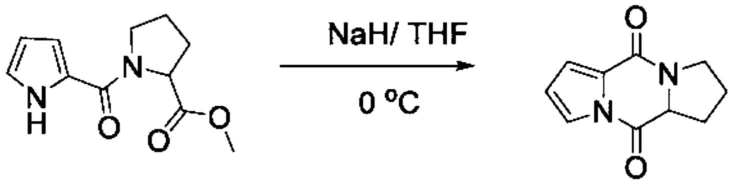
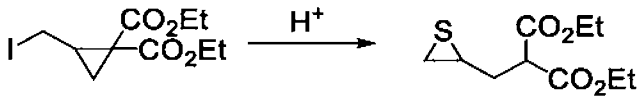
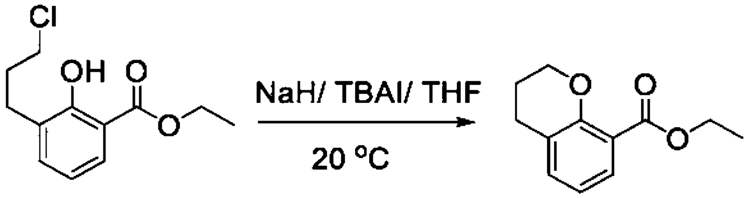
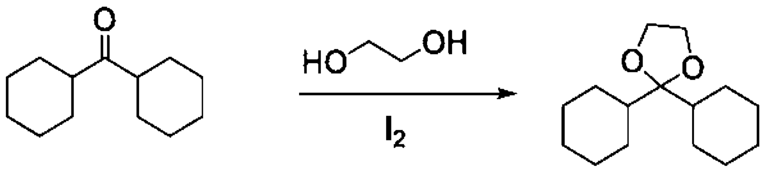
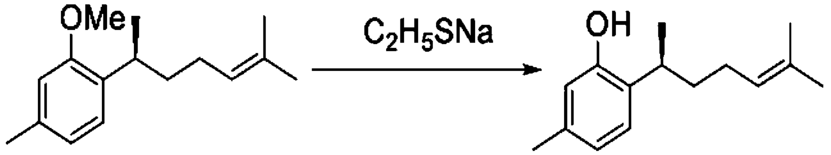
150	
151	
152	
153	
154	
155	

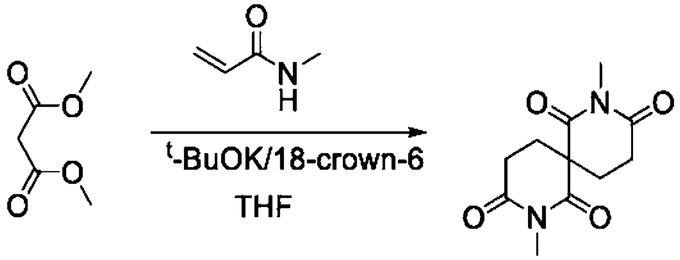
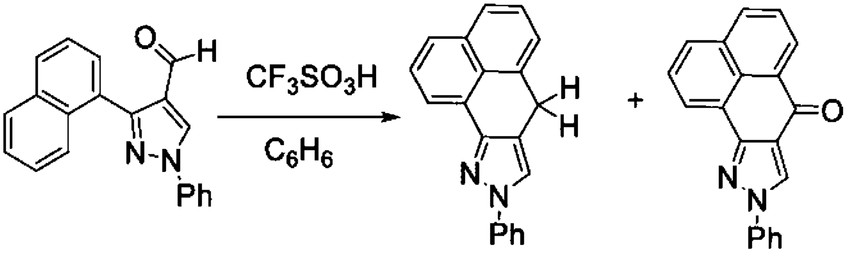
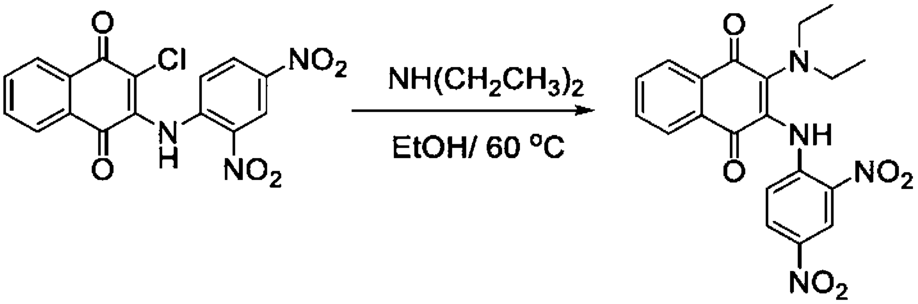
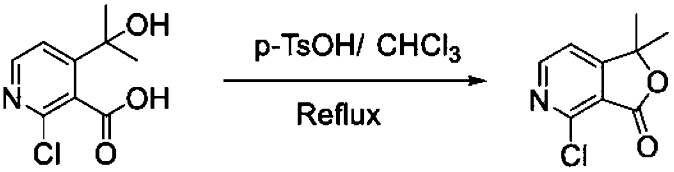
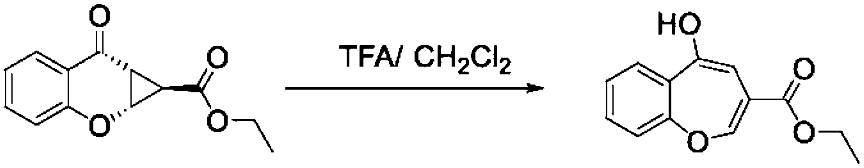
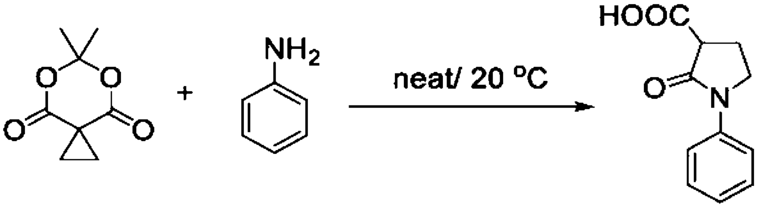
156	Simple cyclopropanes do not react with nucleophilic reagents. In contrast, "activated" cyclopropanes undergo nucleophilic cleavage. Write a mechanism that accounts for this observation. 
157	
158	
159	
160	
161	

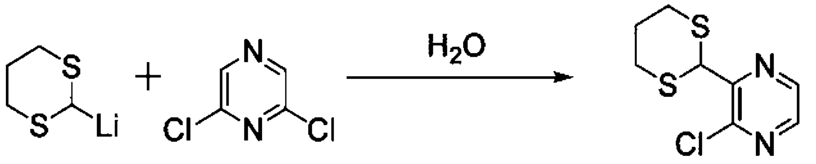
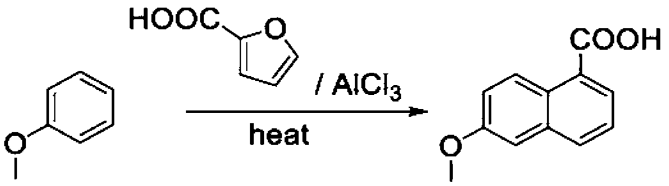
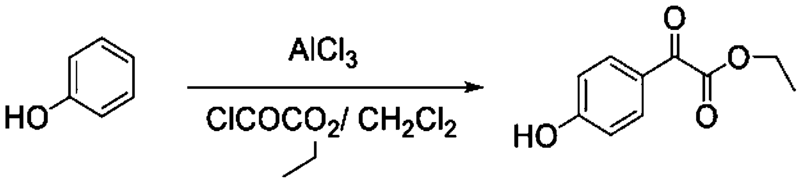
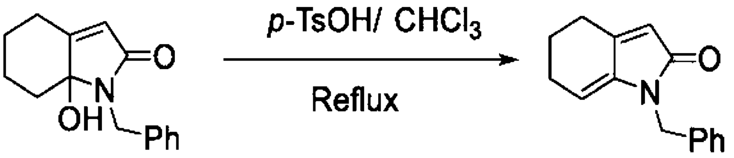
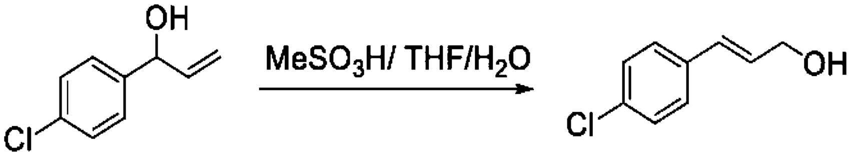
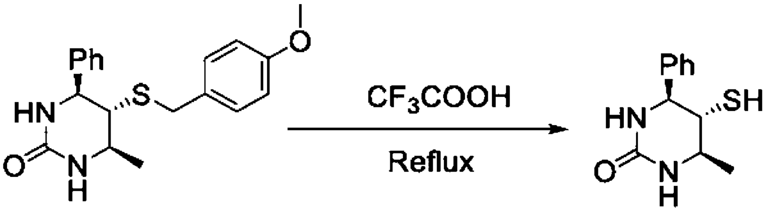
162	
163	
164	
165	
166	
167	

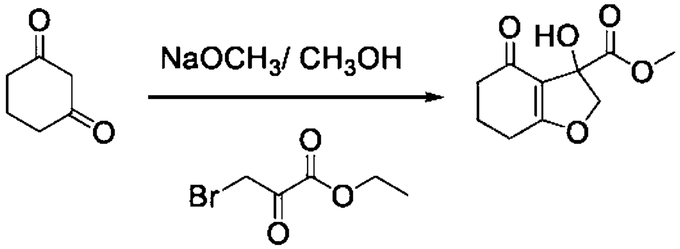
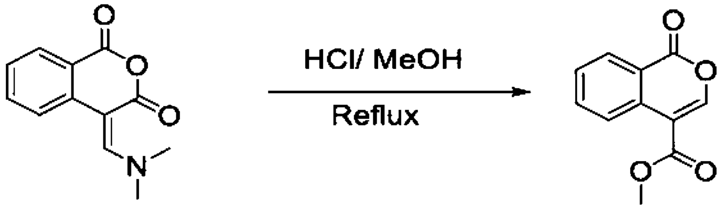
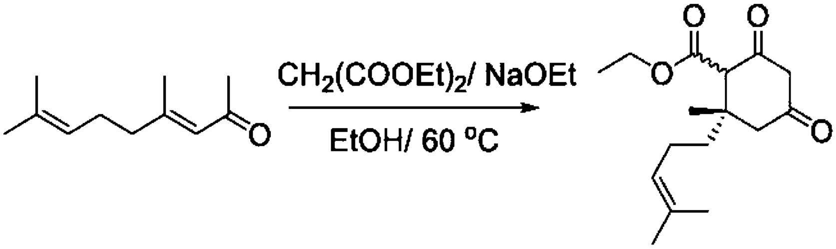
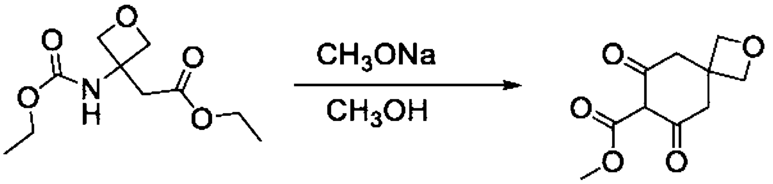
168	
169	
170	
171	
172	

173	
174	
175	
176	
177	
178	

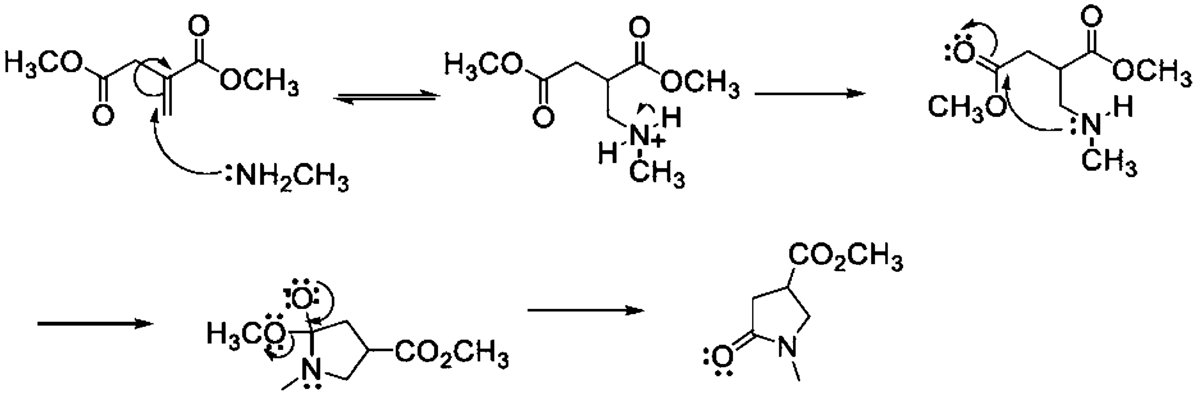
179	
180	
181	
182	
183	
184	

185	
186	
187	
188	
189	
190	

191	
192	
193	
194	
195	
196	

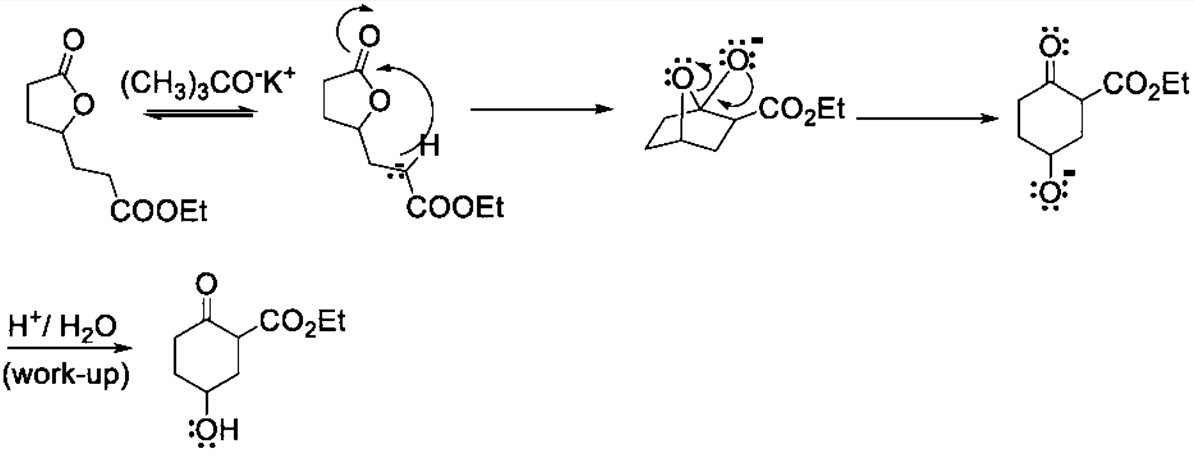
197	
198	
199	
200	

Answers to Questions 71-200

71	

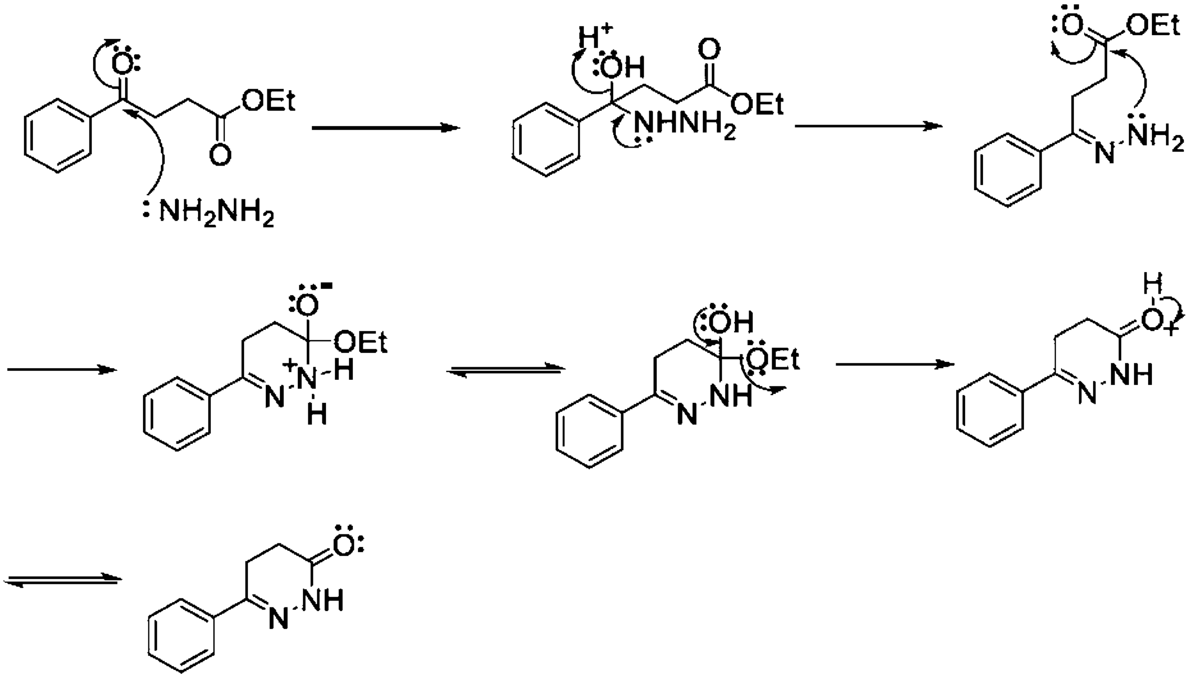
A Michael addition reaction is followed by an intramolecular nucleophilic acyl substitution reaction to yield the product.

72



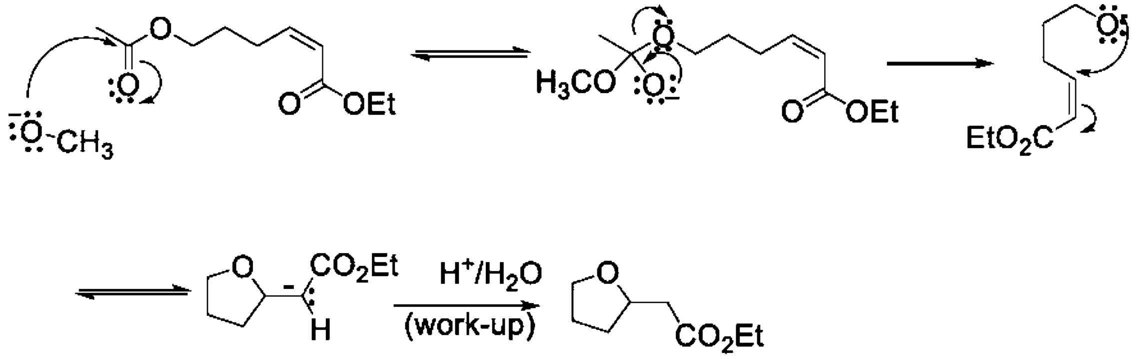
Rapid formation of the anion is followed by an intramolecular acyl substitution reaction.

73



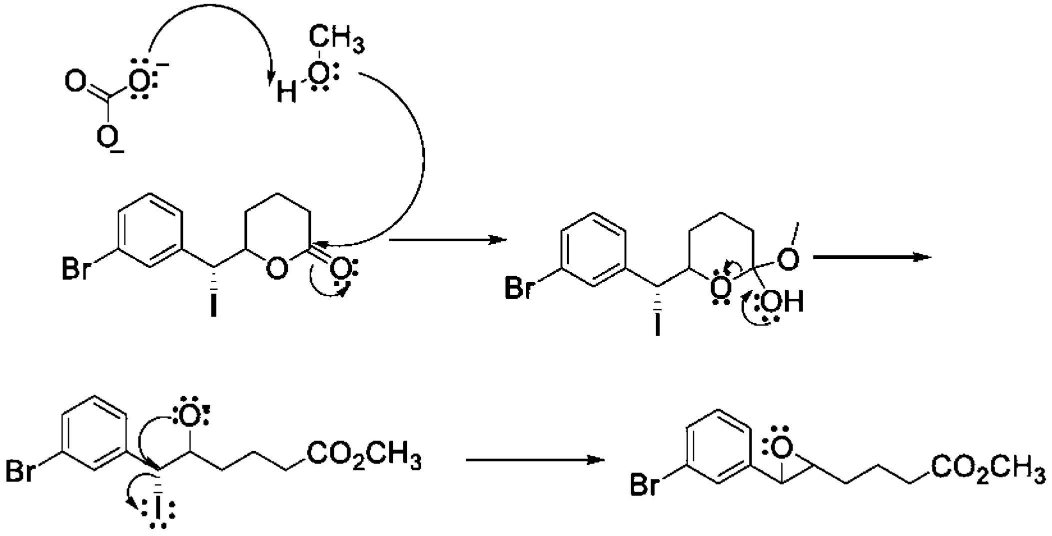
In the first step of this reaction, the nucleophile attacks the ketone carbonyl instead of the ester carbonyl. Why?

74



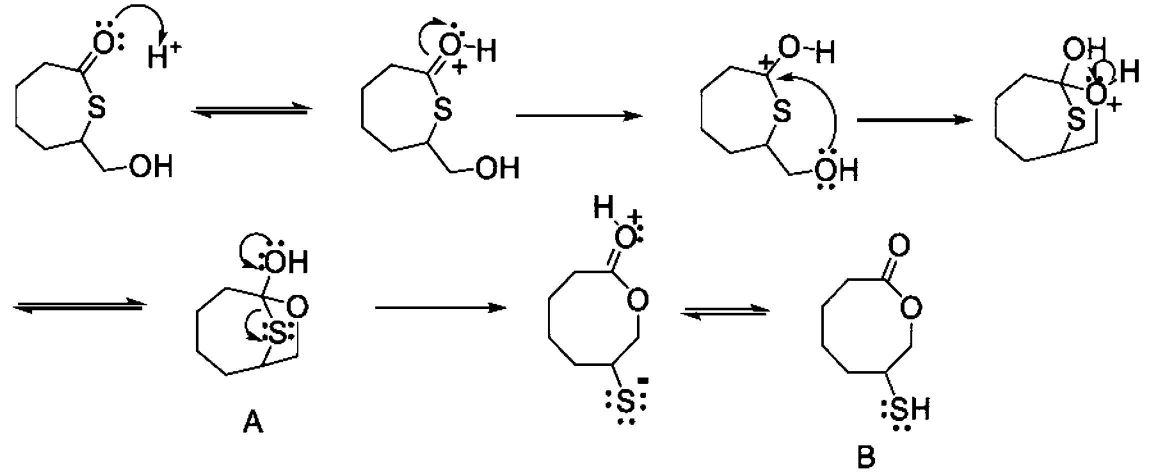
A nucleophilic acyl substitution reaction is followed by an intramolecular Michael addition reaction.

75

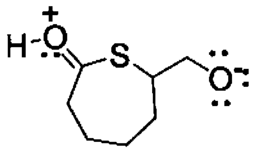


An acid-catalyzed acyl substitution reaction is followed by epoxide formation.

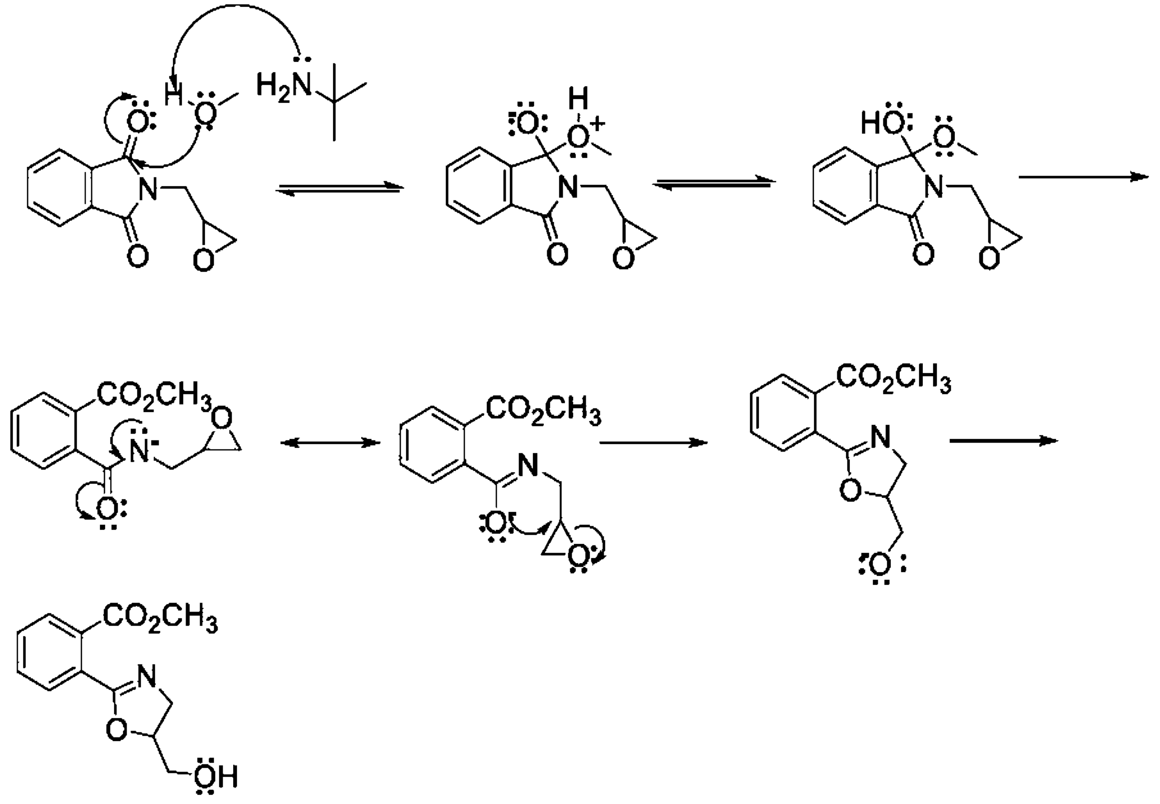
76



When tetrahedral intermediate A reforms the strong C=O bond, it yields B instead of the compound shown below. Why?

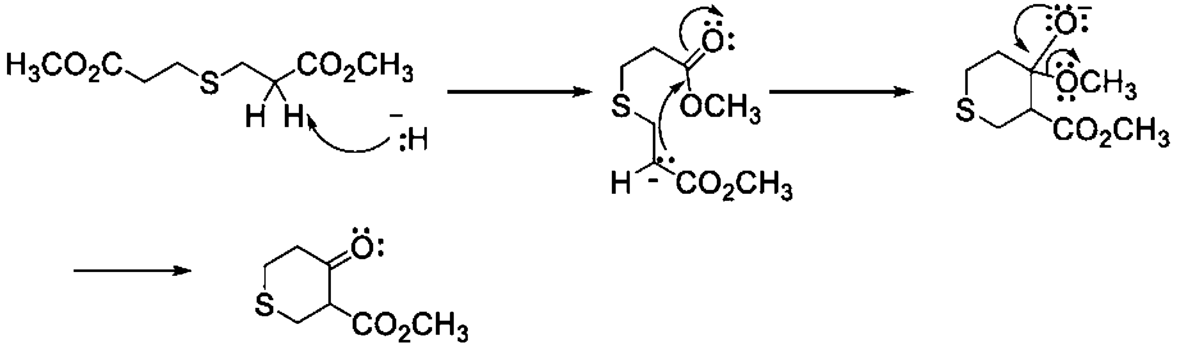


77



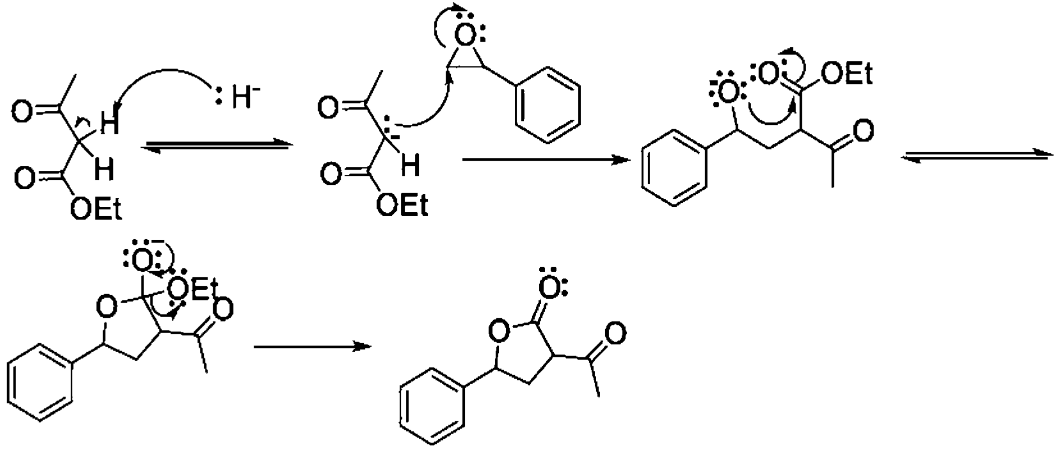
An acyl substitution reaction is followed nucleophilic ring opening of the epoxide to form an oxazolidine.

78



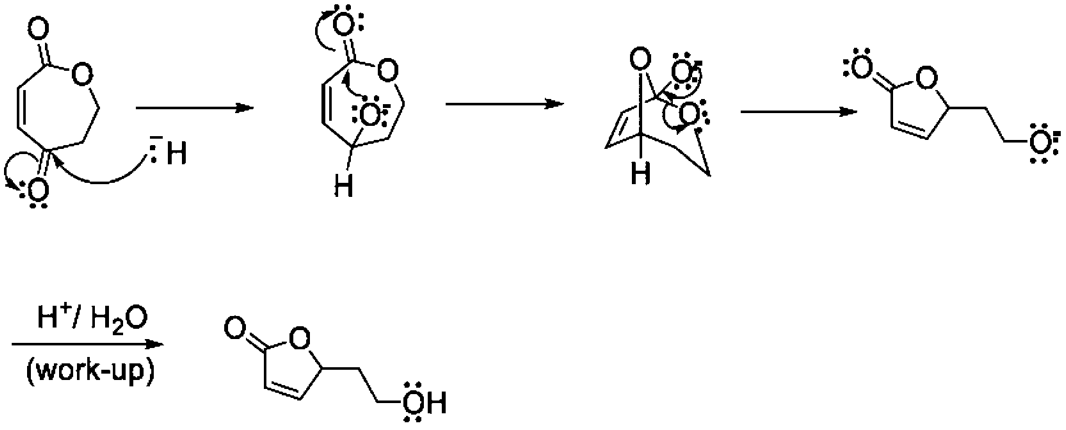
Formation of the anion is followed by an intramolecular acyl substitution reaction.

79

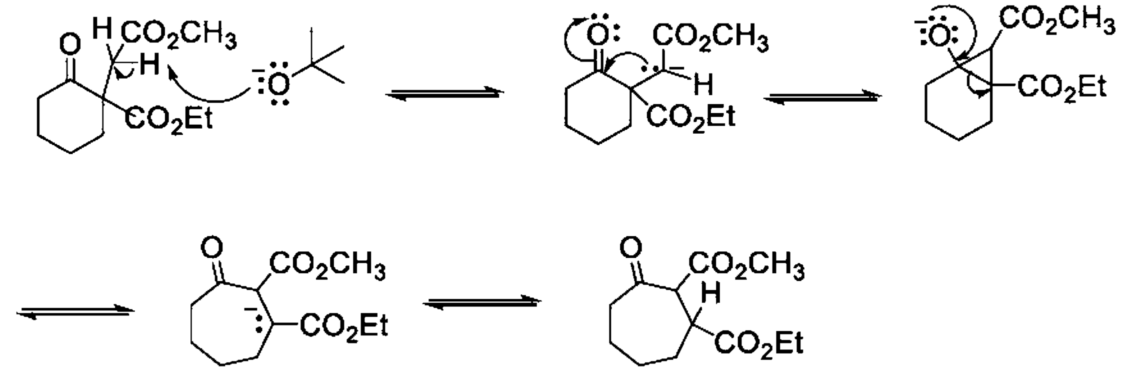
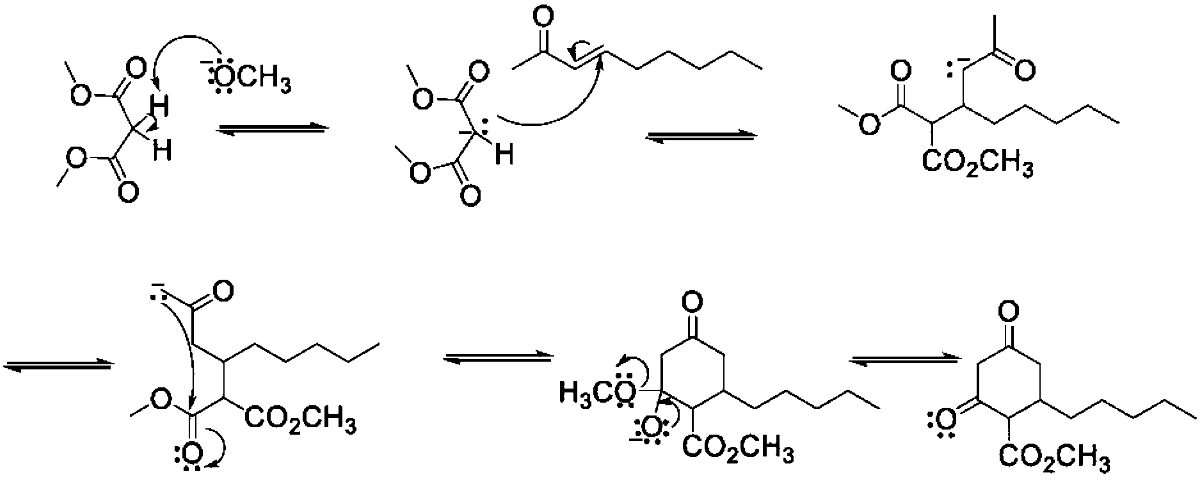


Formation of the anion (nucleophile) is followed by nucleophilic ring opening of the epoxide (note that attack is on the least congested carbon of the epoxide ring) and a subsequent intramolecular acyl substitution reaction.

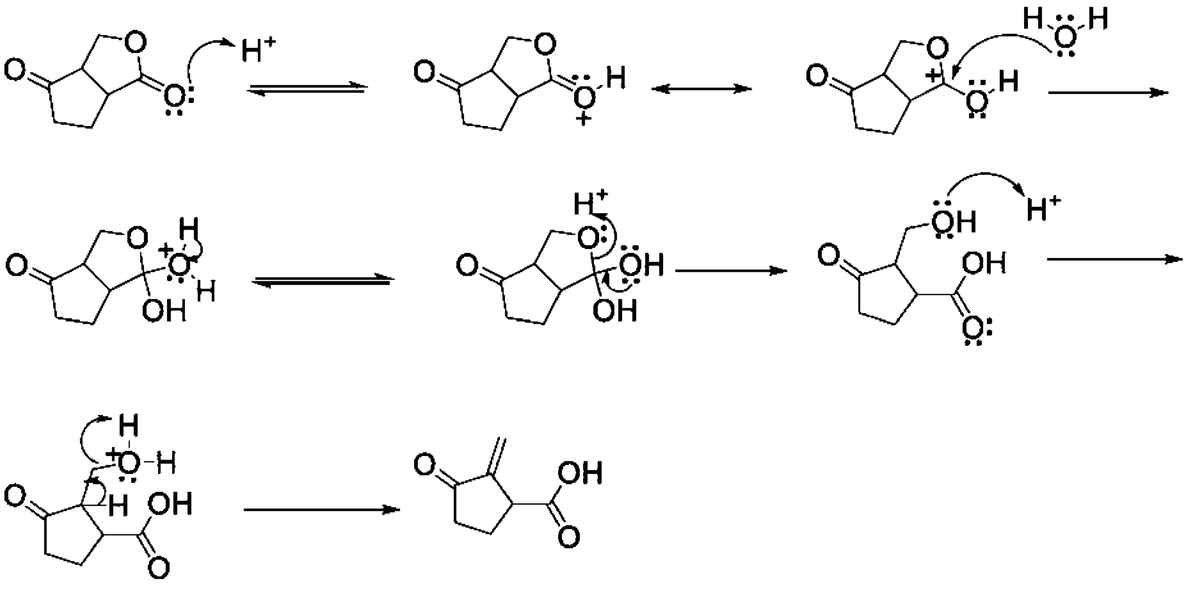
80



Reducing agents, such as $NaBH_4$, $LiAlH_4$, etc. function by delivering hydride (⁻:H) ions. Addition of the hydride to the ketone carbonyl is followed by a transannular nucleophilic acyl substitution reaction.

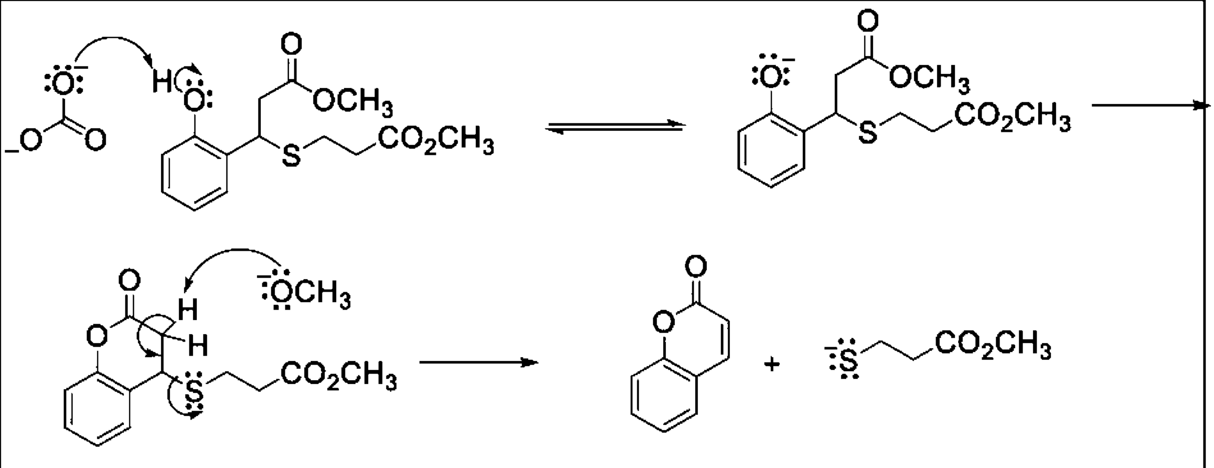
81	
82	
	Initial formation of the anion is followed by a Michael addition reaction. A prototropic shift yields a new anion that undergoes an intramolecular acyl substitution reaction .

83



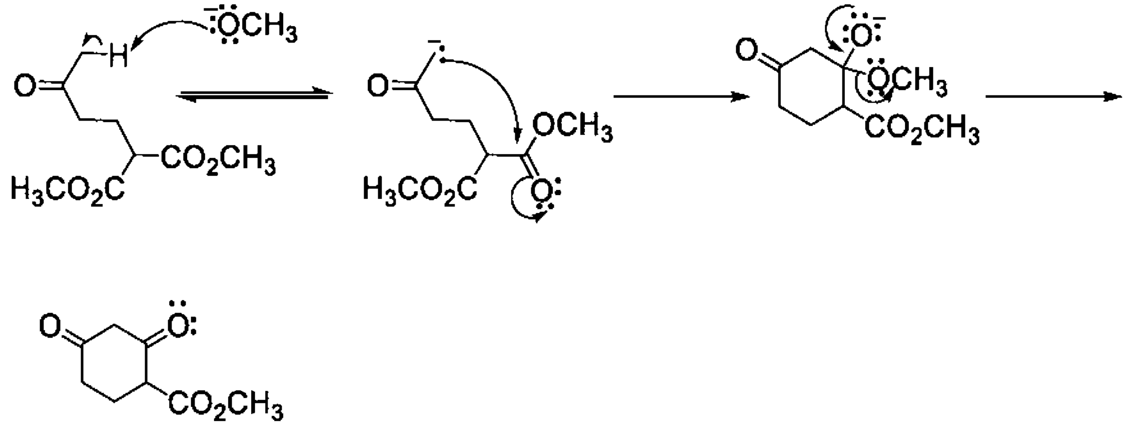
Acid-catalyzed hydrolysis of the lactone yields an α-hydroxymethyl ketone which undergoes elimination of water to form the α-methylene ketone.

84



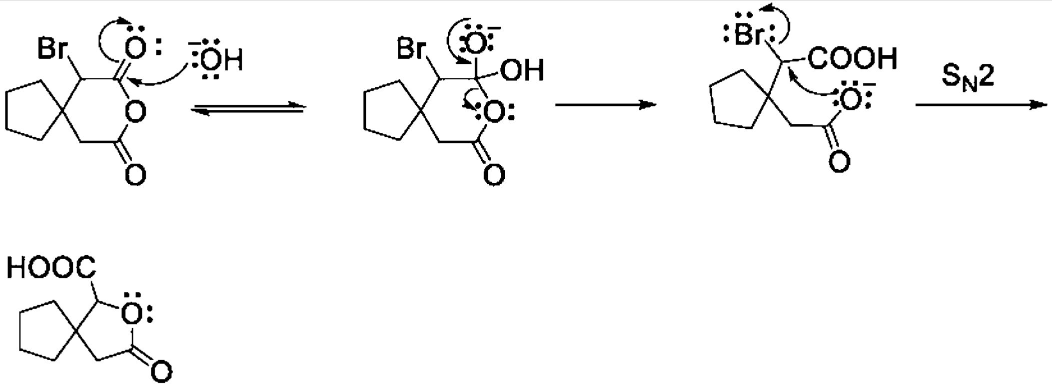
Reaction of the most acidic hydrogen yields an anion that participates in a nucleophilic acyl substitution reaction. This is followed by a base-catalyzed β-elimination reaction to form the α,β-unsaturated lactone.

85



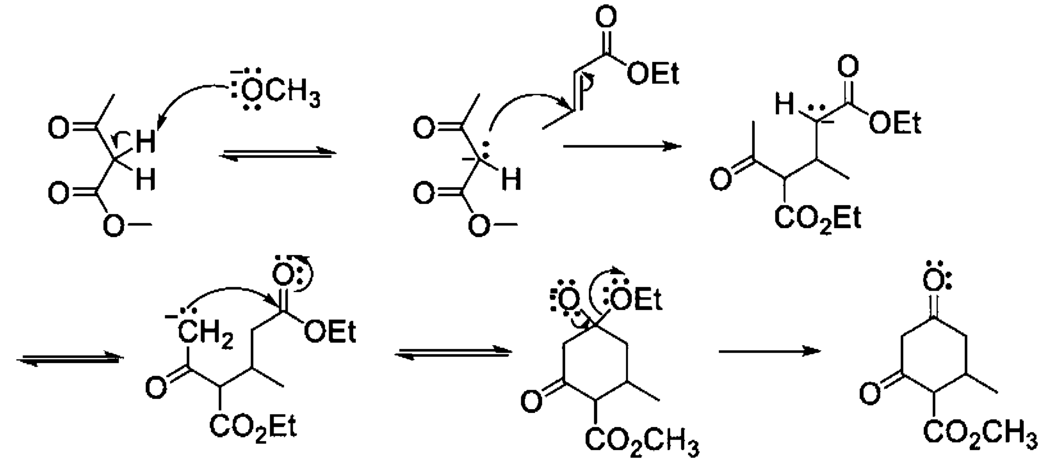
The pK_a of malonic ester is ~13 and the α-H of the ketone is ~18. Why do you think the reaction proceeds as shown?

86



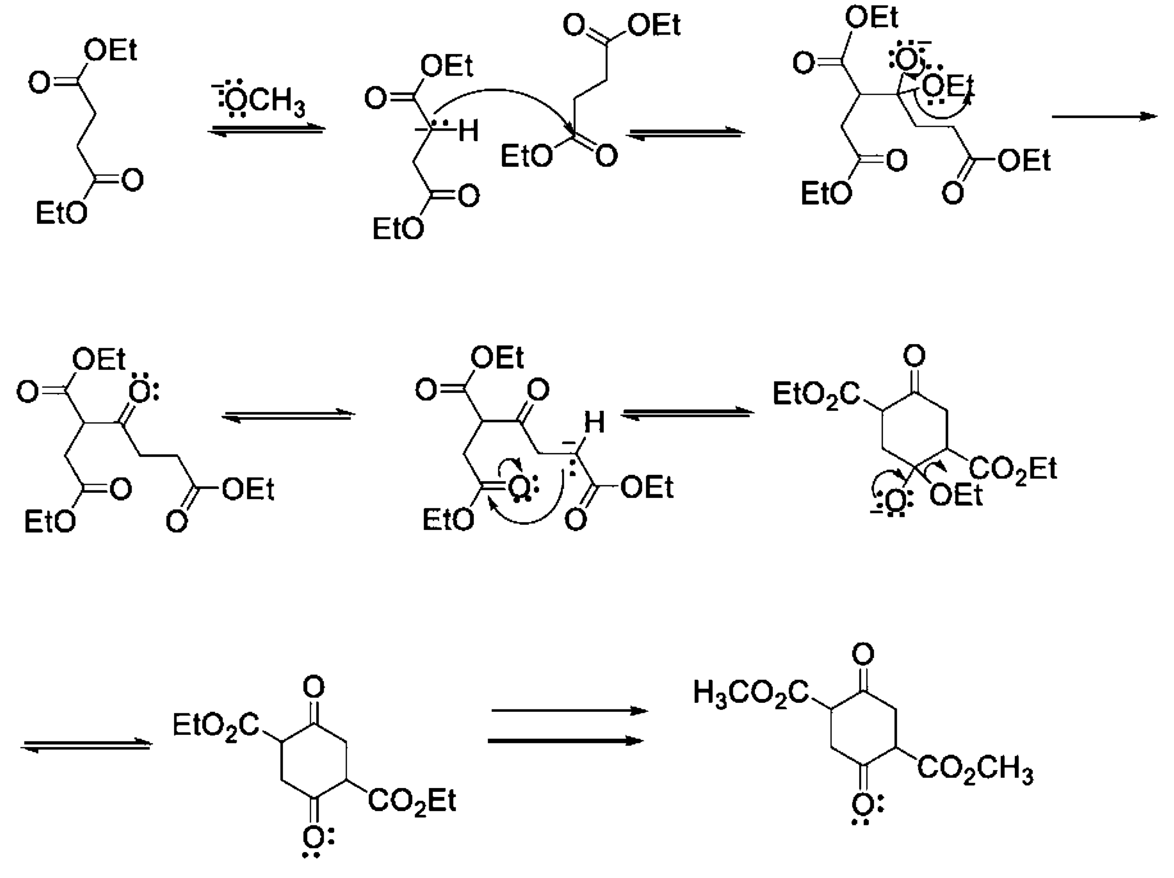
Note that in the first step of the reaction the Lewis base (nucleophile) attacks the most electron-deficient (most electrophilic) carbonyl carbon. The electron-withdrawing inductive effect of the electronegative atom (Br) renders the top carbonyl group more electrophilic (higher partial positive charge).

87



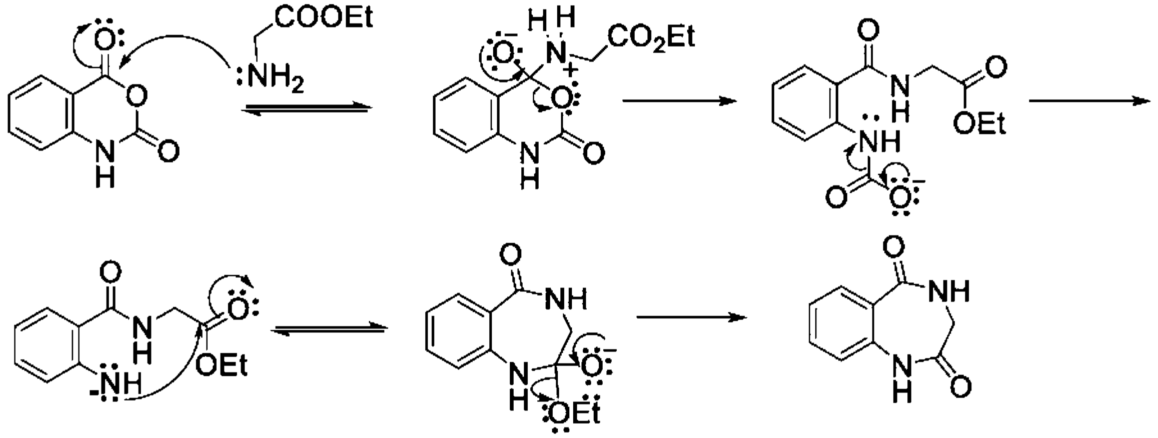
Formation of the anion is followed by a Michael addition reaction, a prototropic shift and an intramolecular acyl substitution reaction.

88



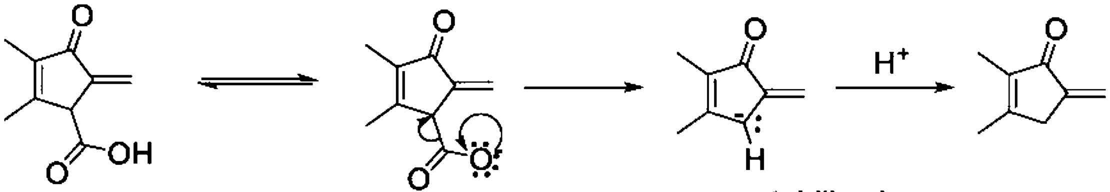
An intermolecular Claisen condensation reaction is followed by an intramolecular condensation reaction (*a Dieckman condensation*). A double transesterification reaction yields the final product.

89



Exercise The top carbonyl carbon in this mixed anhydride is more reactive than the bottom one. Explain.

90

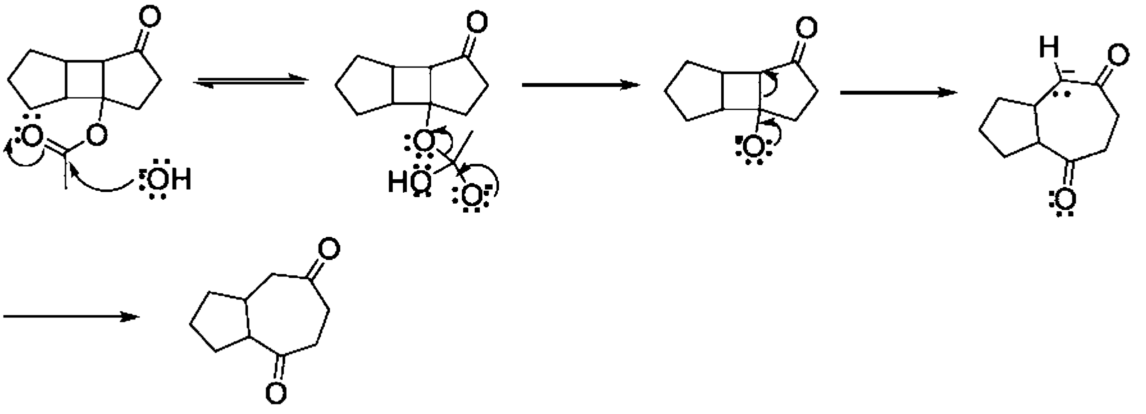


resonance-stabilized anion

Recall that, unlike ordinary carboxylic acids, β-ketoacids and *gem*-dicarboxylic acids (malonic acids) undergo facile loss of CO_2 to form a stable product (a resonance-stabilized anion). This unusual keto acid loses CO_2 for the same reason.

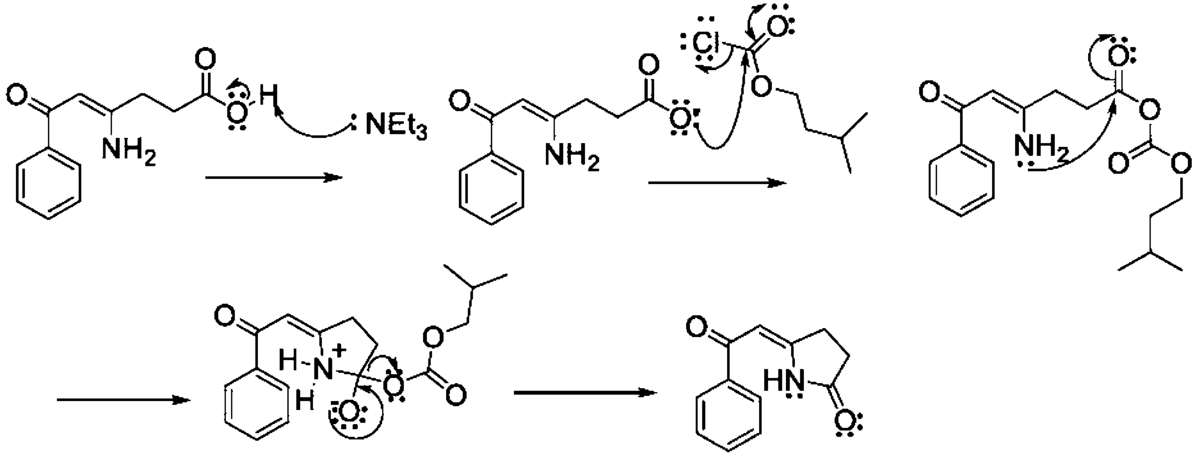
Exercise Draw all the resonance structures of the anion shown above.

91

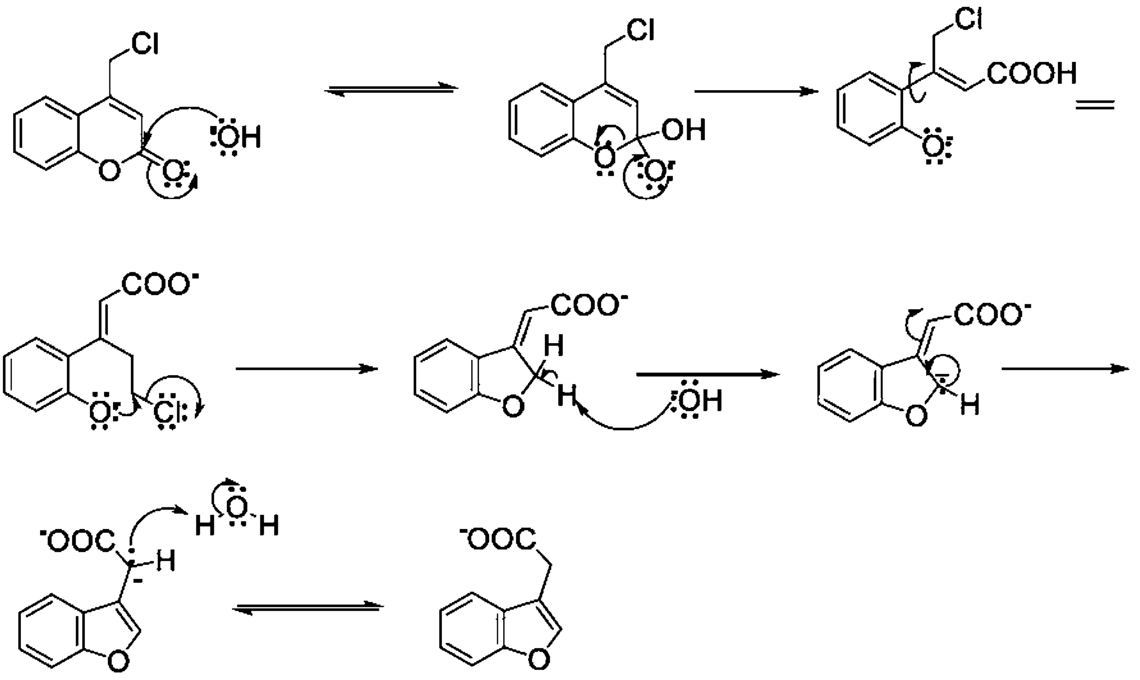
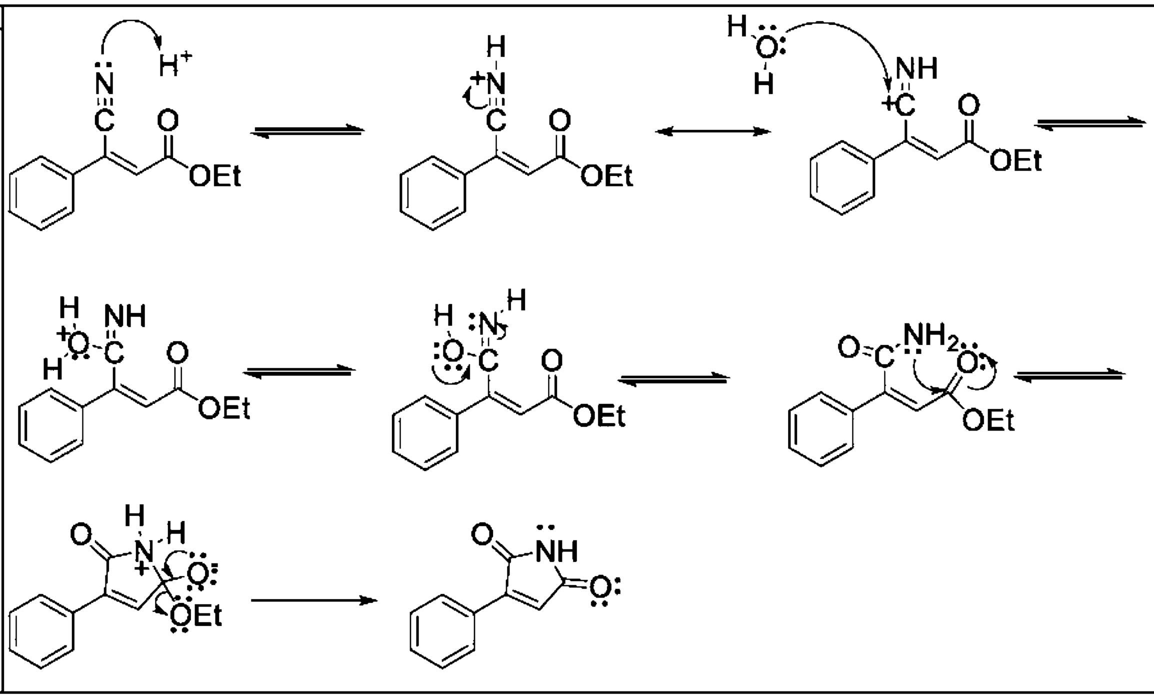


Base-catalyzed hydrolysis of the ester yields an anion that undergoes a retro aldol reaction (recall that the aldol condensation reaction is reversible).

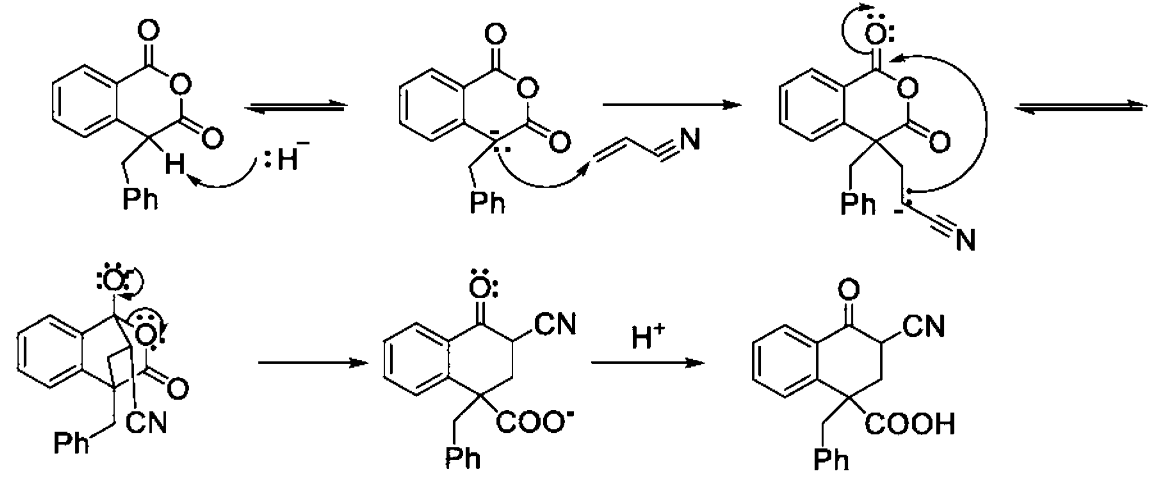
92



Activation by the acid (changing the hydroxyl group from a poor leaving group to a good leaving) is followed by an intramolecular acyl substitution reaction.

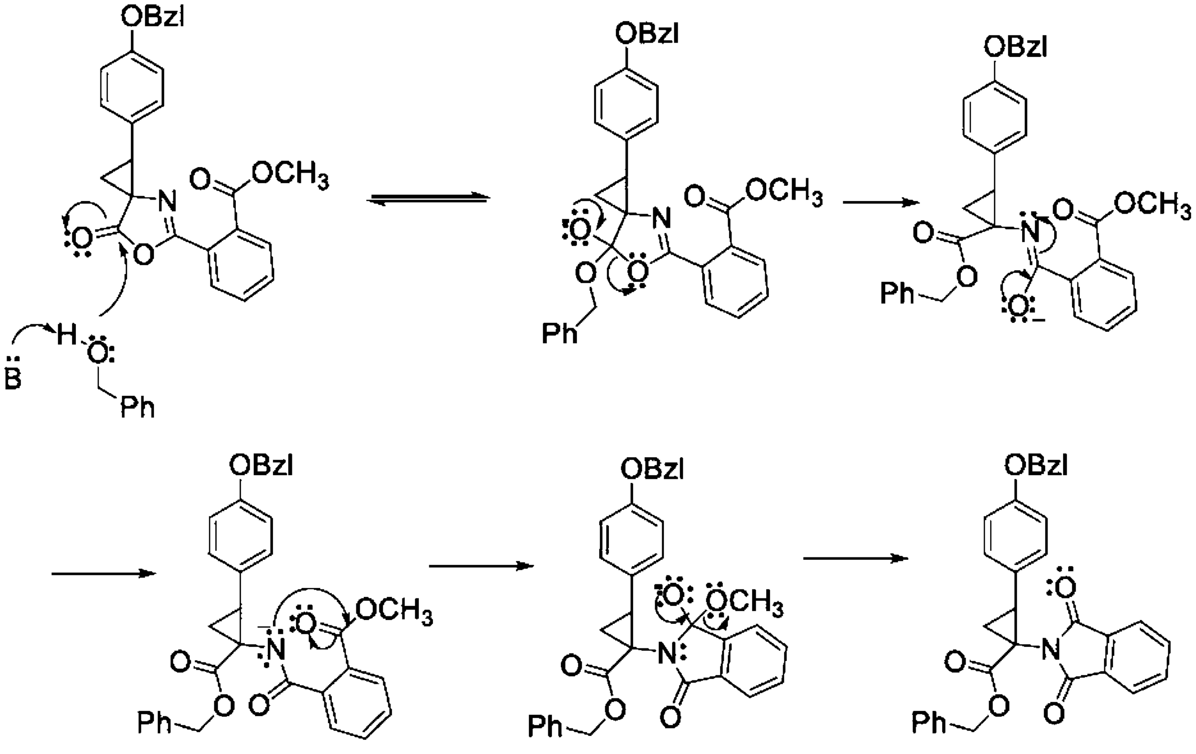
93	
Base-catalyzed hydrolysis of the lactone yields an oxygen nucleophile that undergoes an S_N2 reaction with the allyl chloride. This is followed by a base-catalyzed isomerization to form the product.	
94	

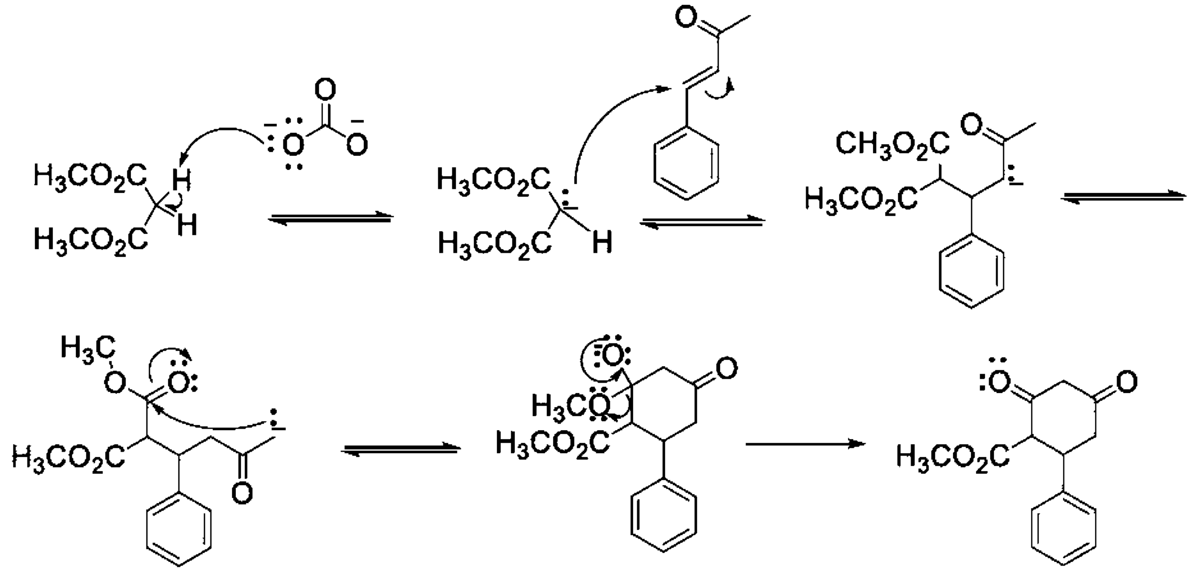
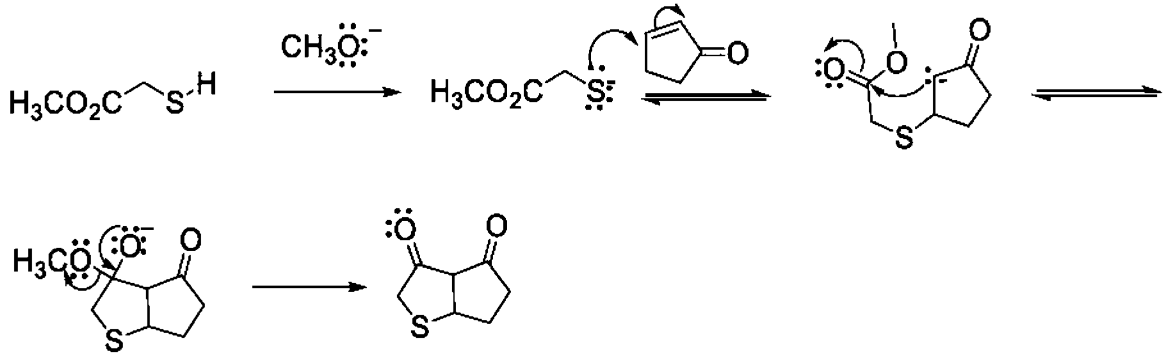
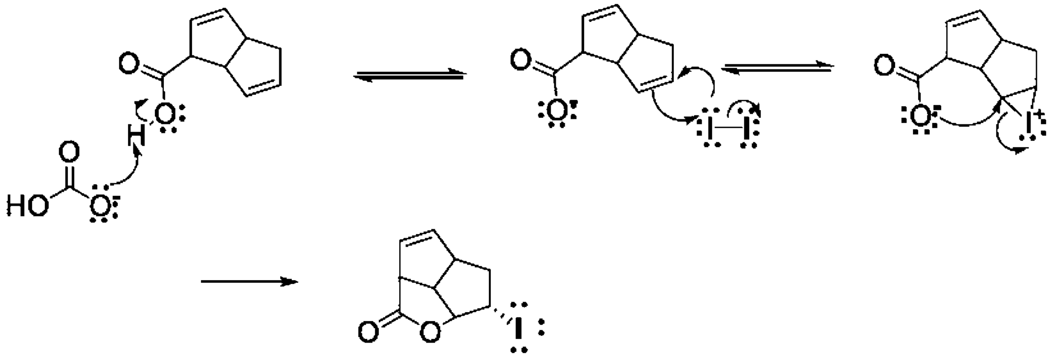
95

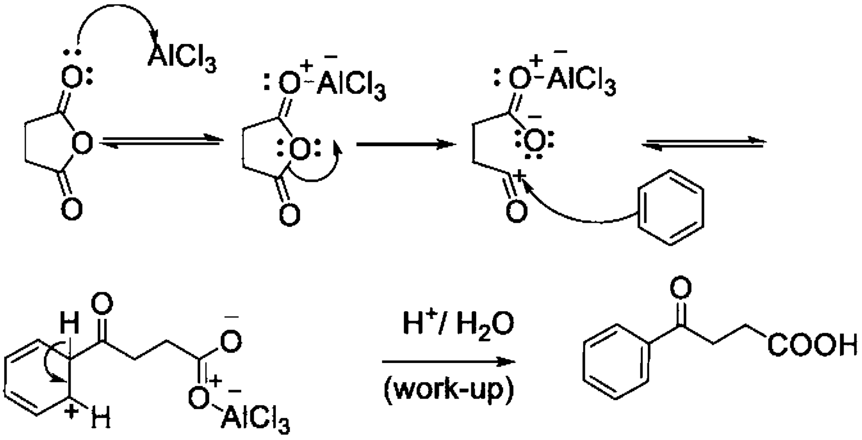


Formation of the anion is followed by a Michael addition reaction and trapping of the anion via reaction with the mixed anhydride.

96

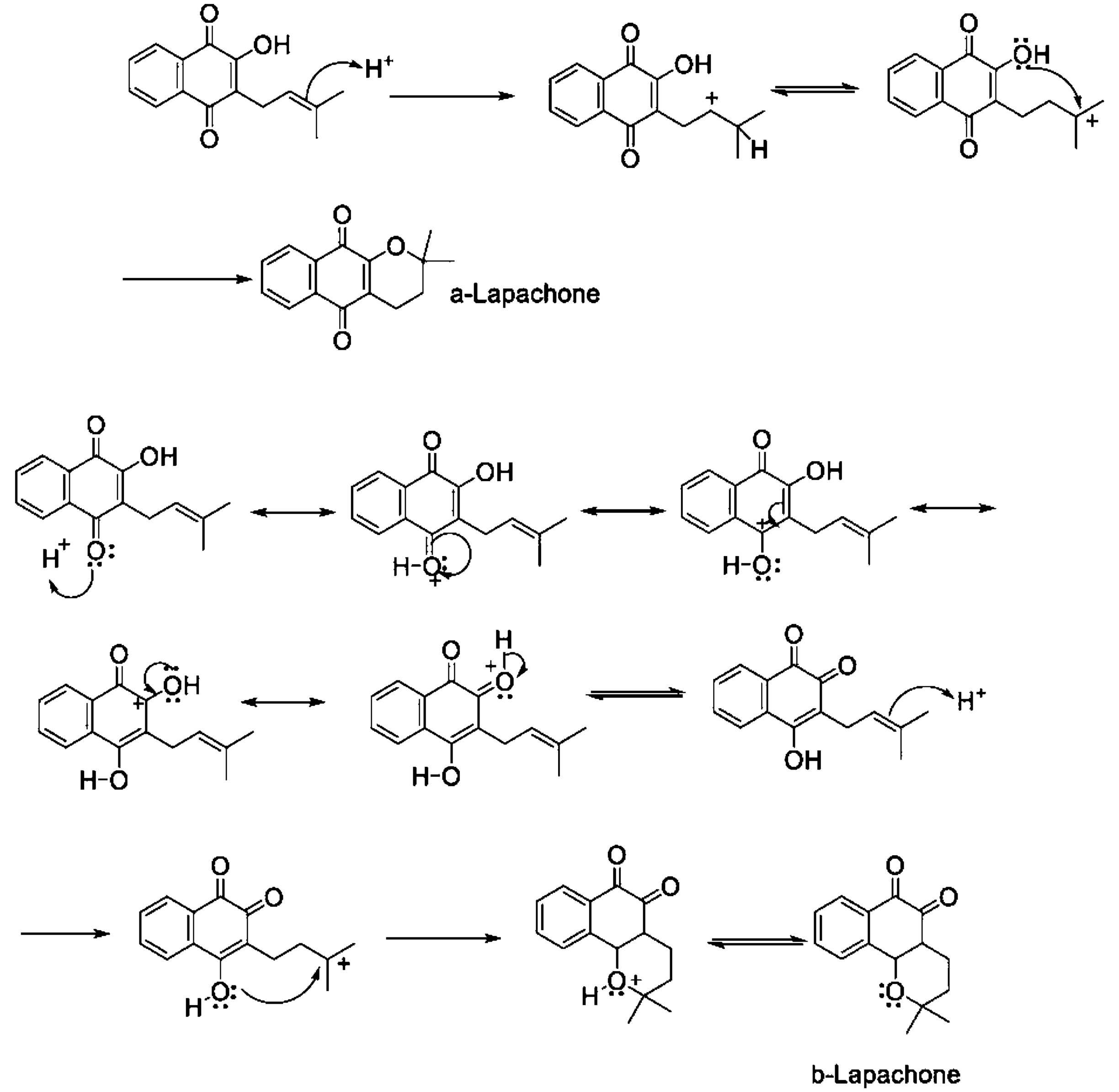


97	
98	
99	
	This is an example of the *iodolactonization reaction*.
100	



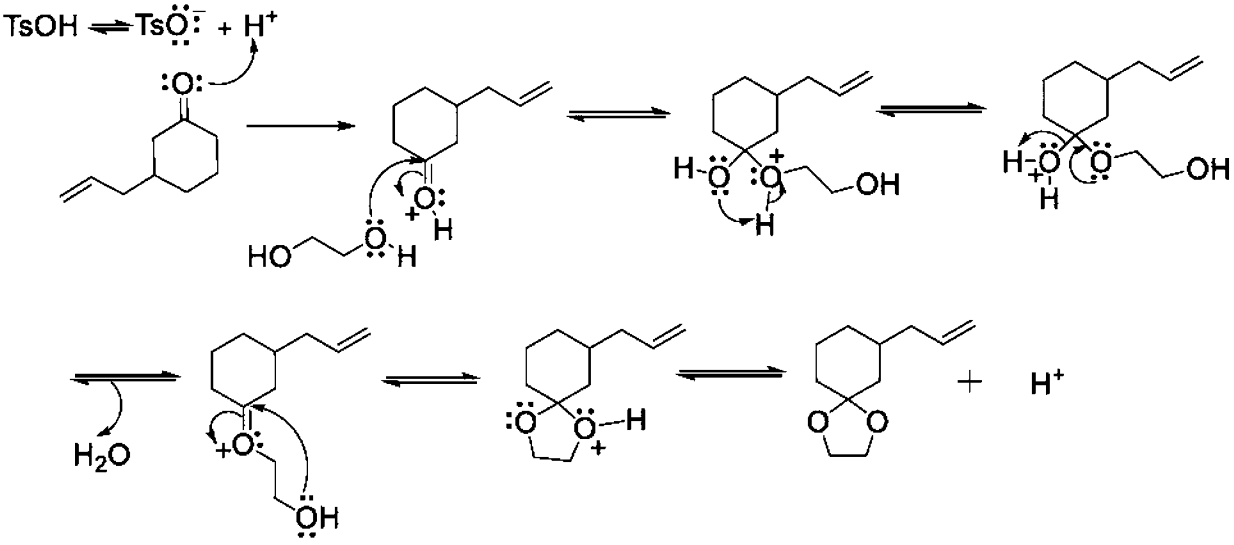
This is a variant of the *Friedel-Craft acylation reaction*.

101

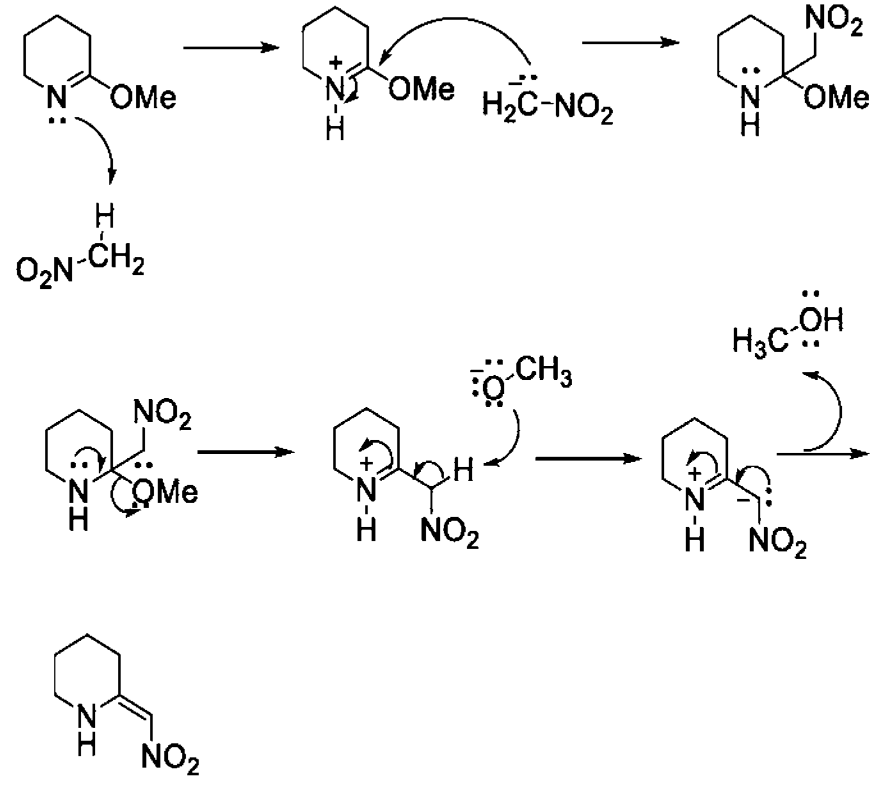


The starting material can exist in two enol forms each capable of reacting with the 3^{o} carbocation in a LA/LB reaction to form two different products.

102



103



104

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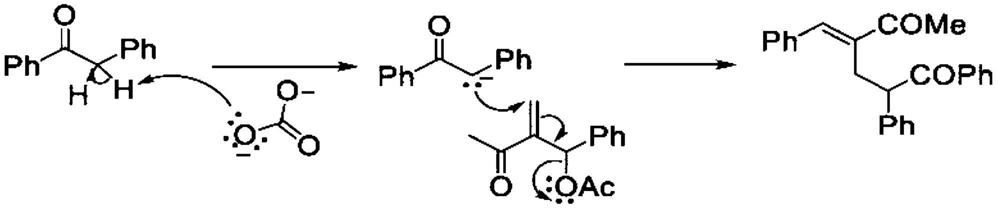
<tr><td></td></tr>
<tr><td>Formation of the anion is followed by a Michael addition reaction and tandem elimination.</td></tr>
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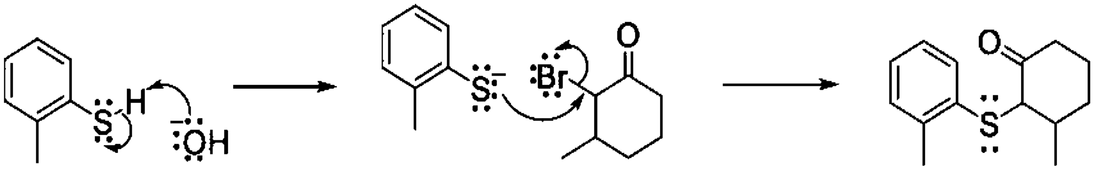
<tr><td></td></tr>
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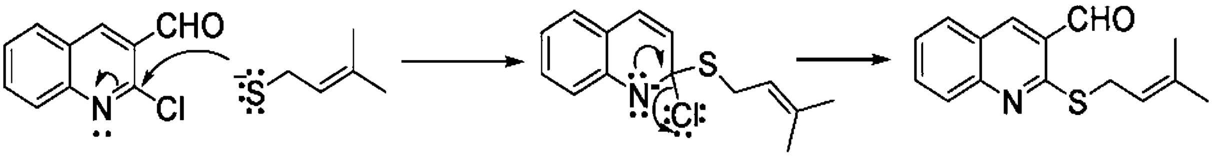
<tr><td></td></tr>
<tr><td>This is a two-step substitution reaction at an electron-deficient sp² hybridized carbon.</td></tr>
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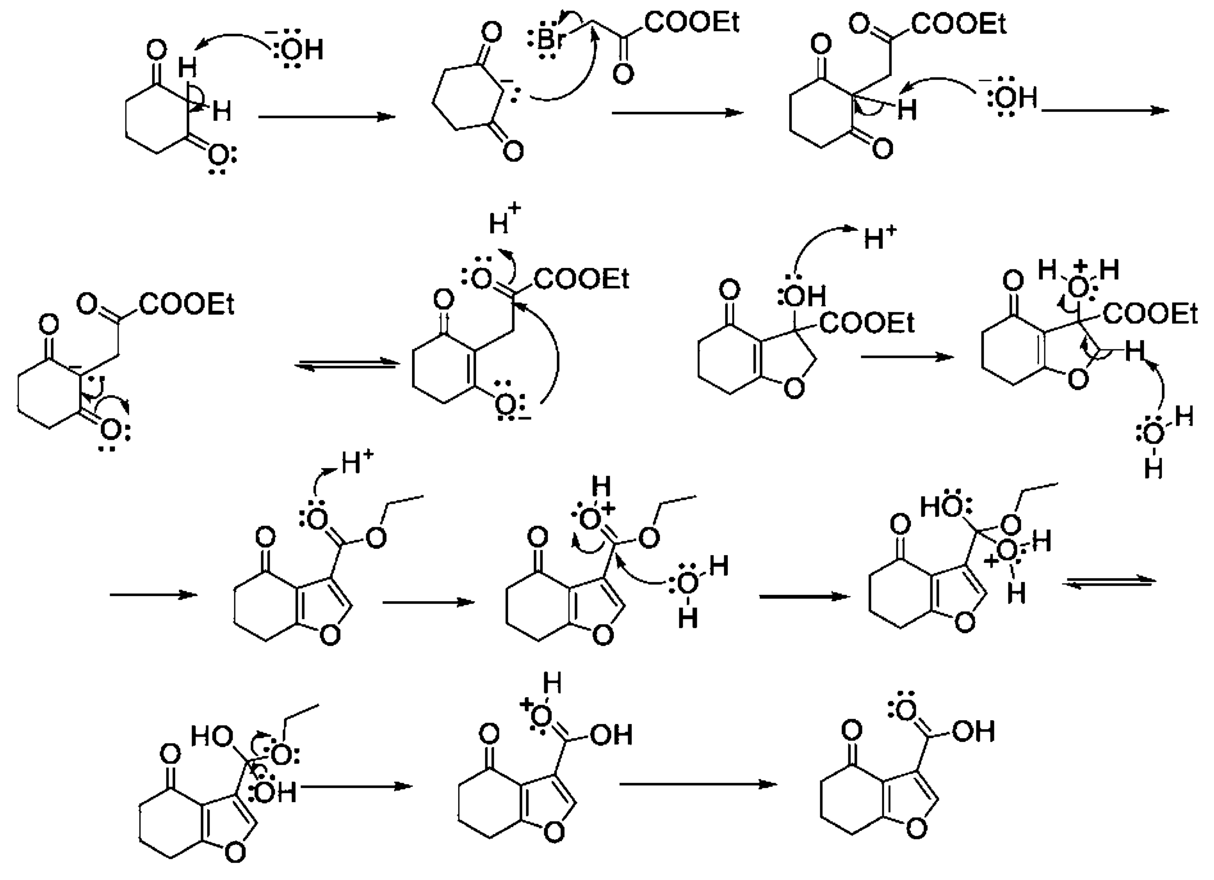
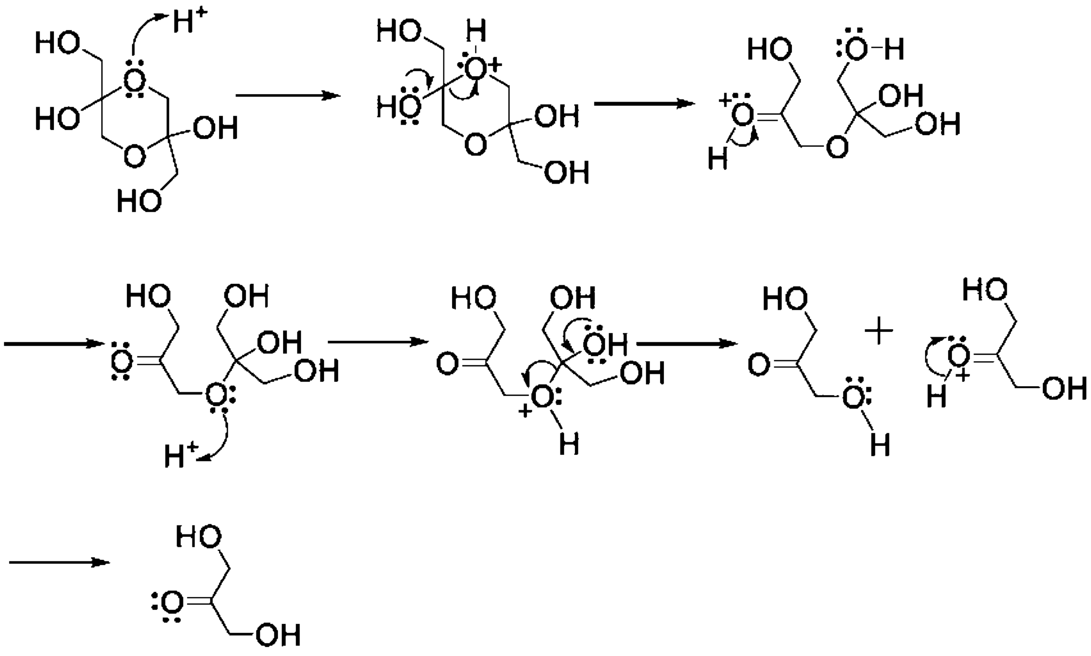
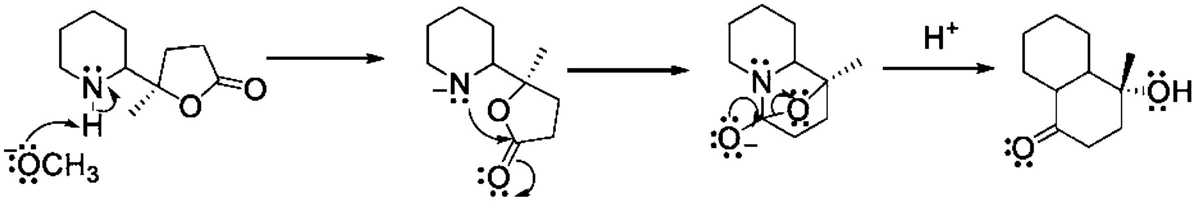


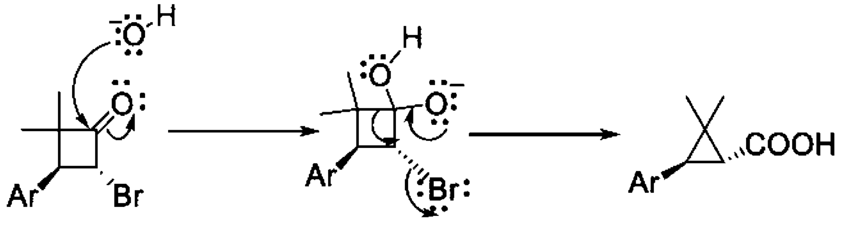
108



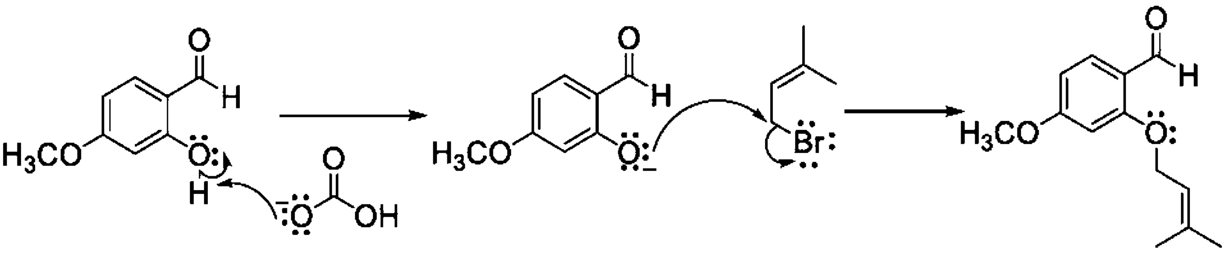
109



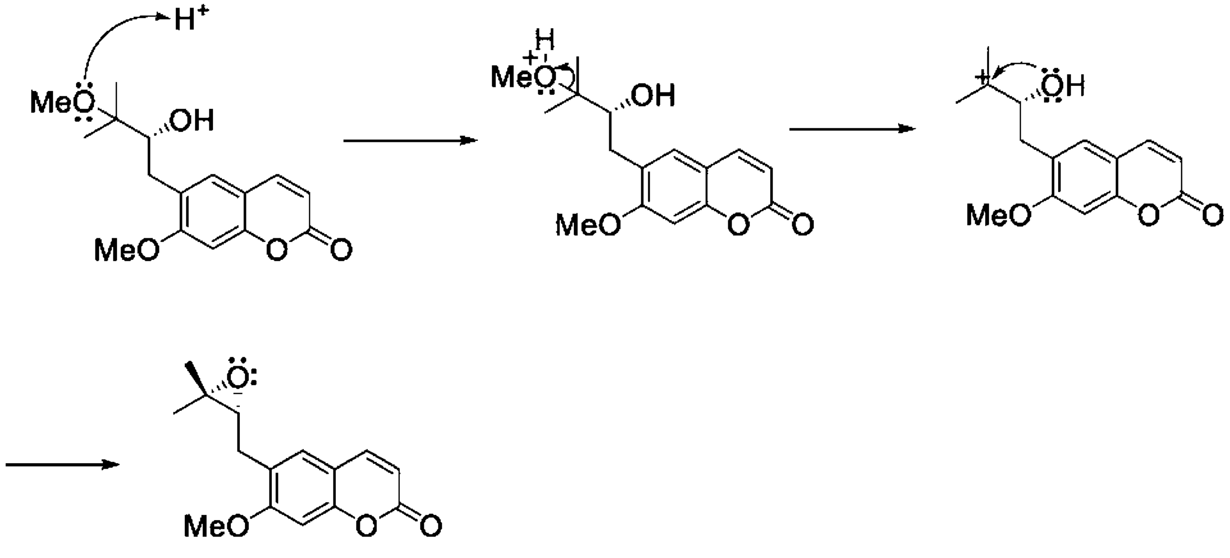
110



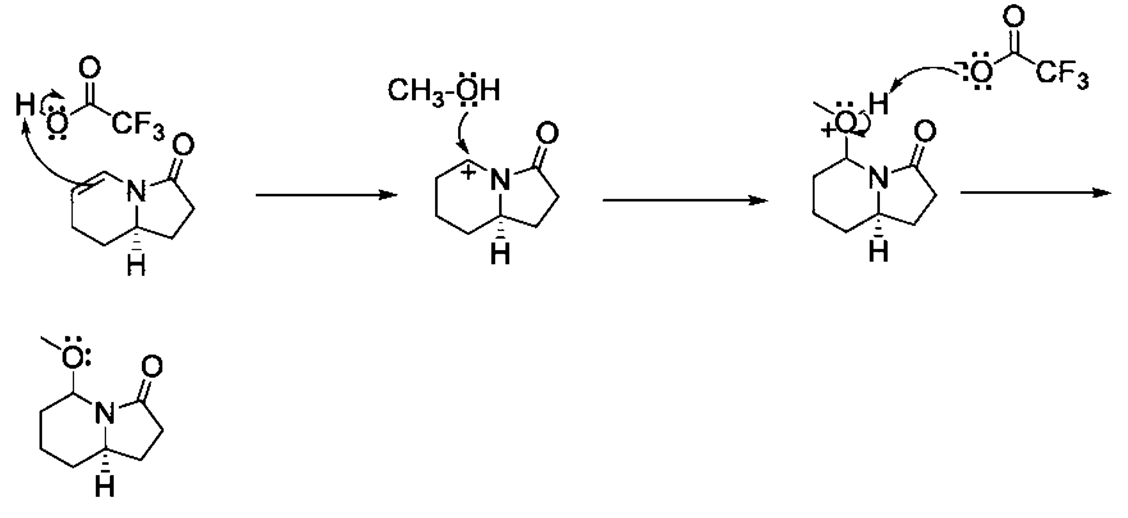
111


H₃CO
H
O
OH
Br
H₃CO
H
O

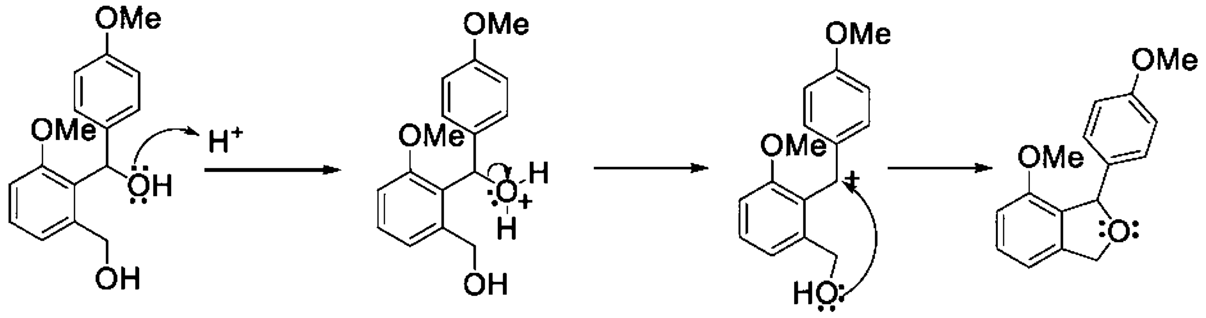
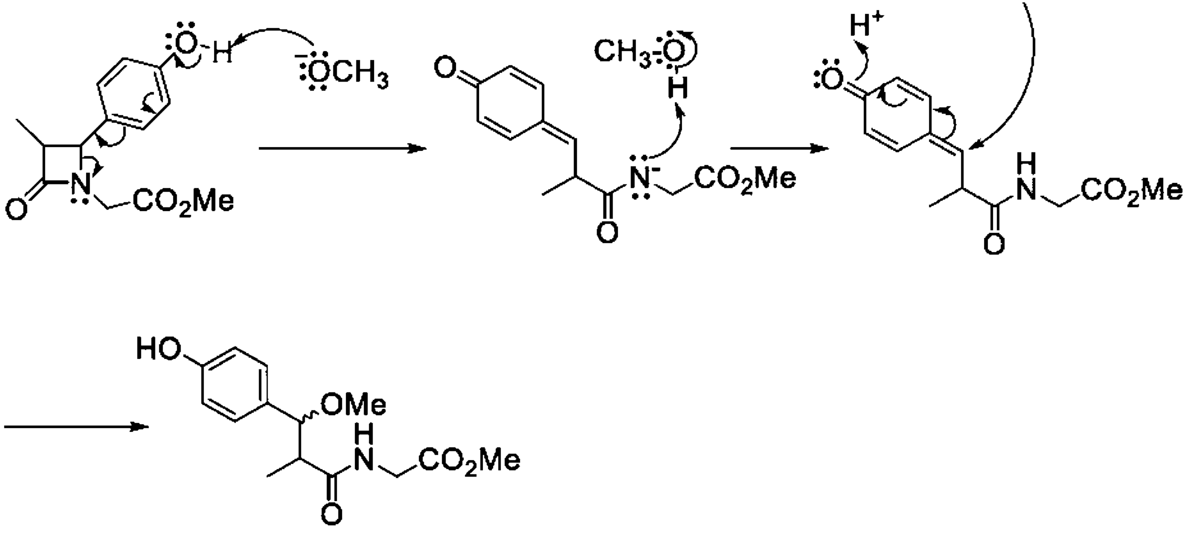
112

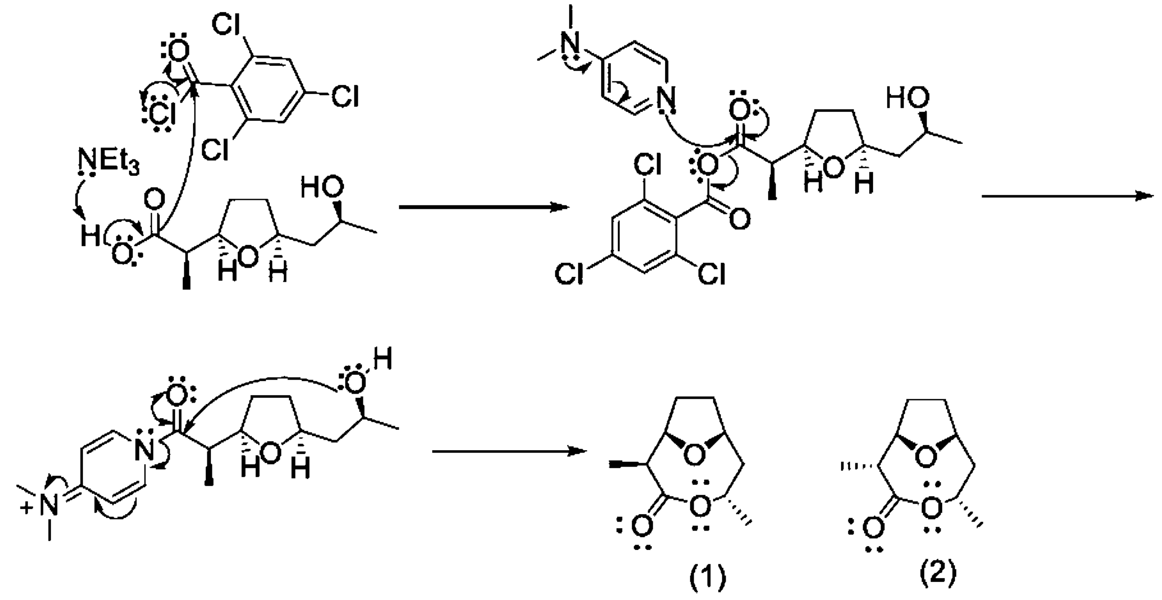

H⁺
MeO
OH
MeO
O
O
H
MeO
OH
MeO
O
O
OH
MeO
O
O
O
MeO
O
O

113

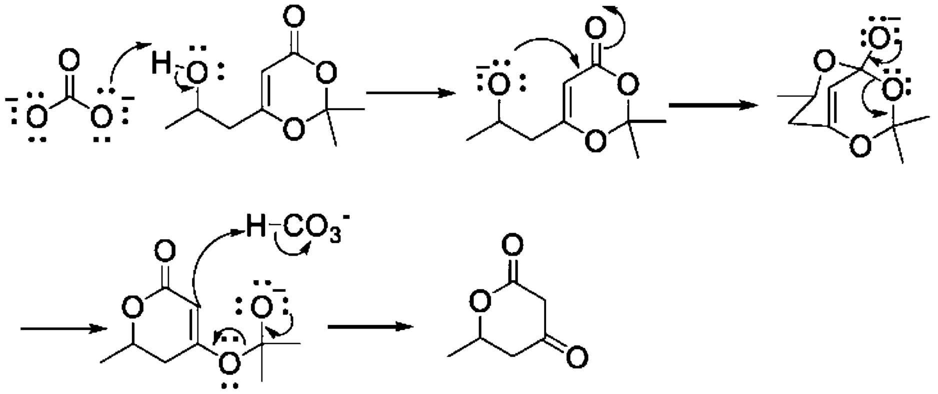

H
O
O
CF₃
O
N
H
CH₃-OH
+
N
O
H
O
CF₃
O
H
+O
N
O
H
O
N
O
H

114

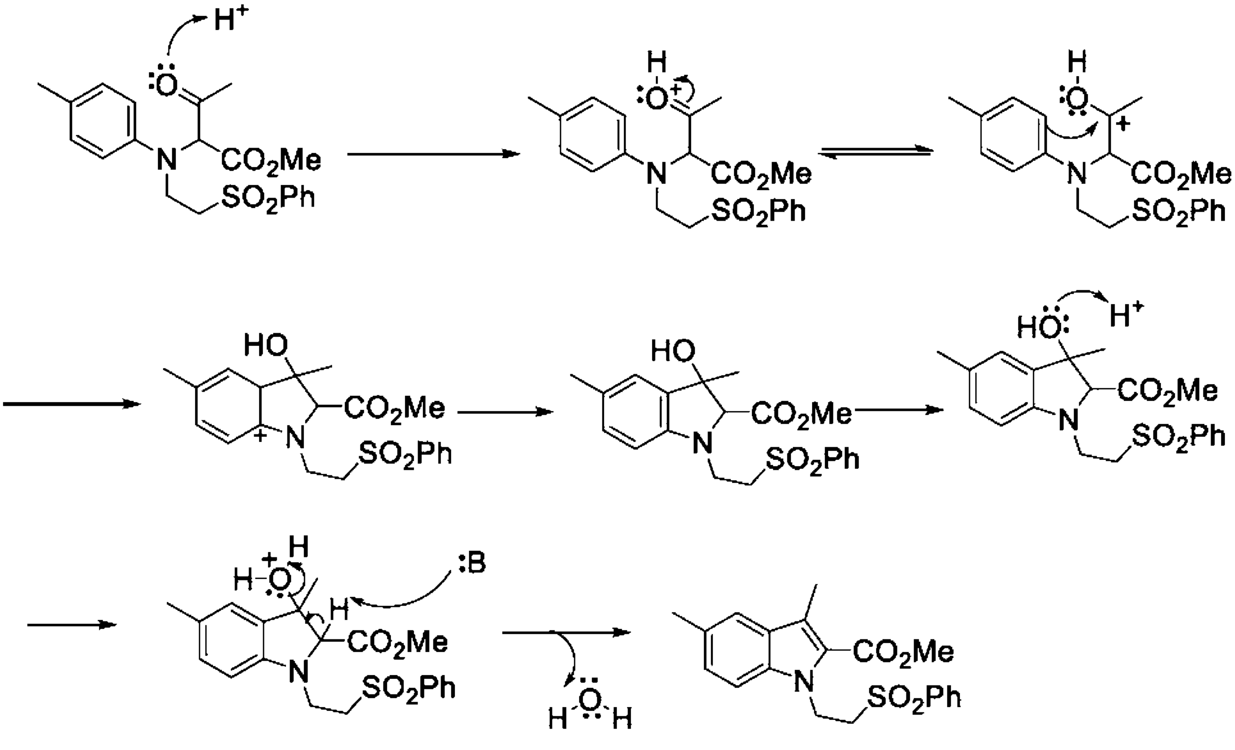

115

116



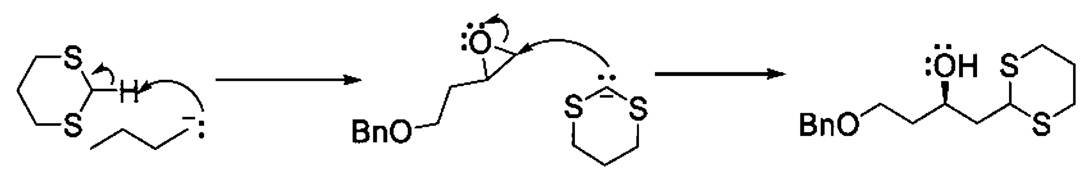
117



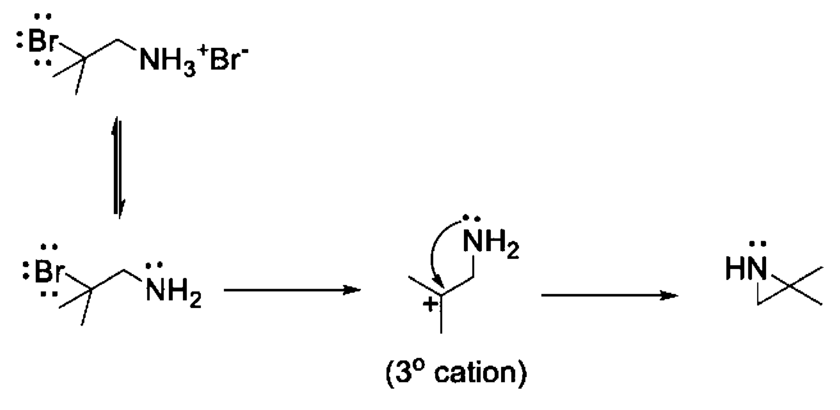
118



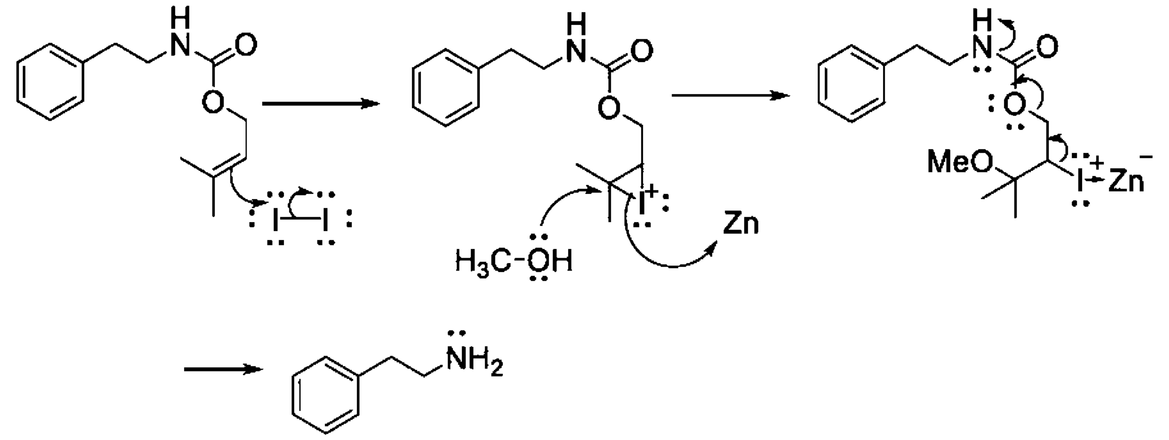
119



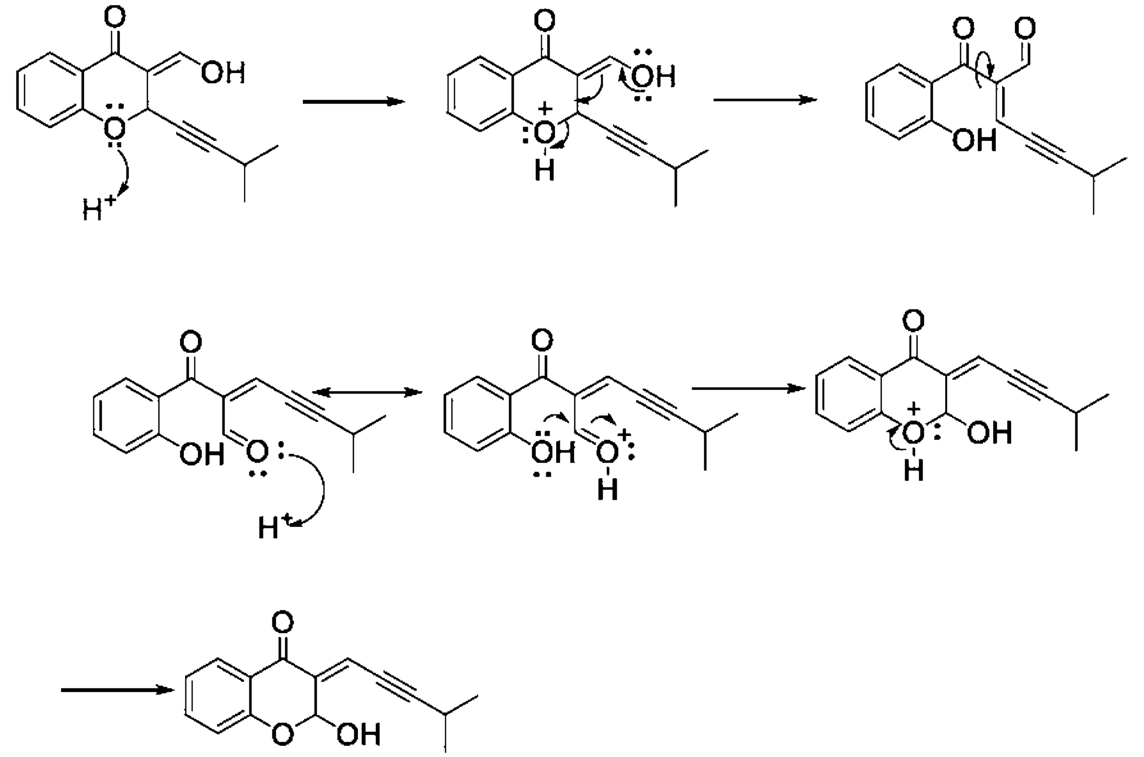
120



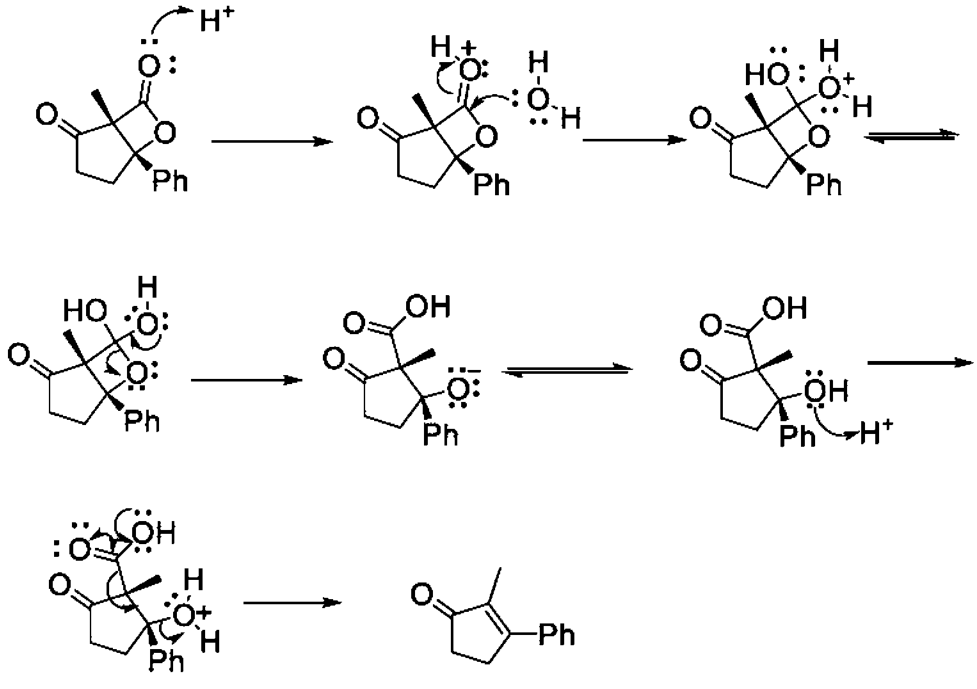
121


H
N
O
O
I
I
H
N
O
O
I+
H3C-OH
Zn
H
N
O
O
MeO
I+
Zn−
NH2

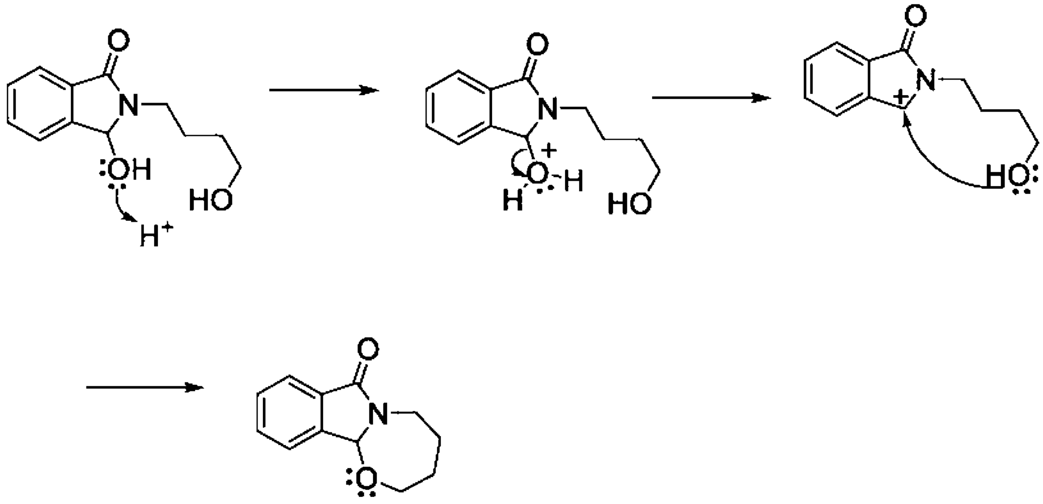
122


O
OH
O
H+
O
OH
O+
H
O
O
OH
O
OH
O
H+
O
OH
O+
H
O
O+
H
OH
O
O
OH

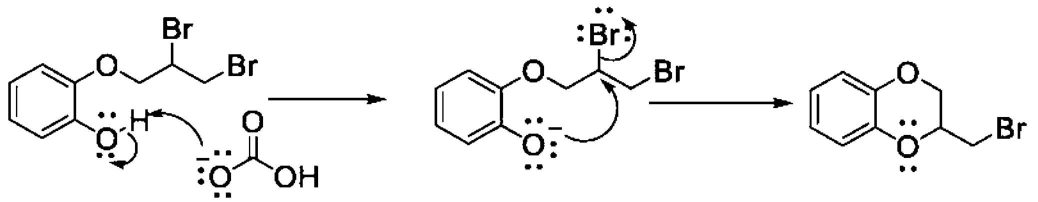
123



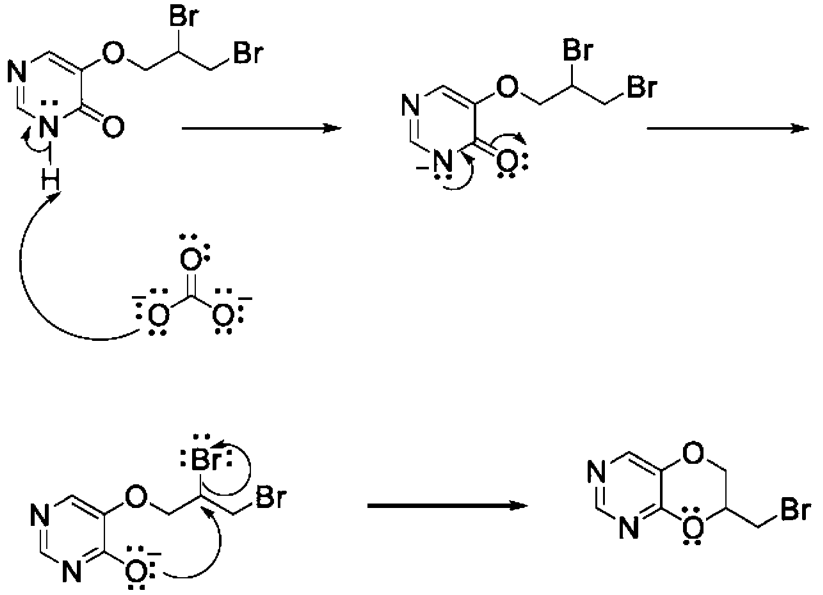
124



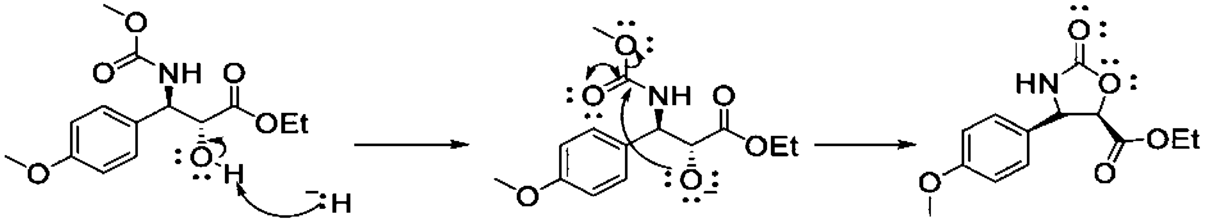
125


Br
O
Br
H
O
OH
Br
O
Br
O
Br

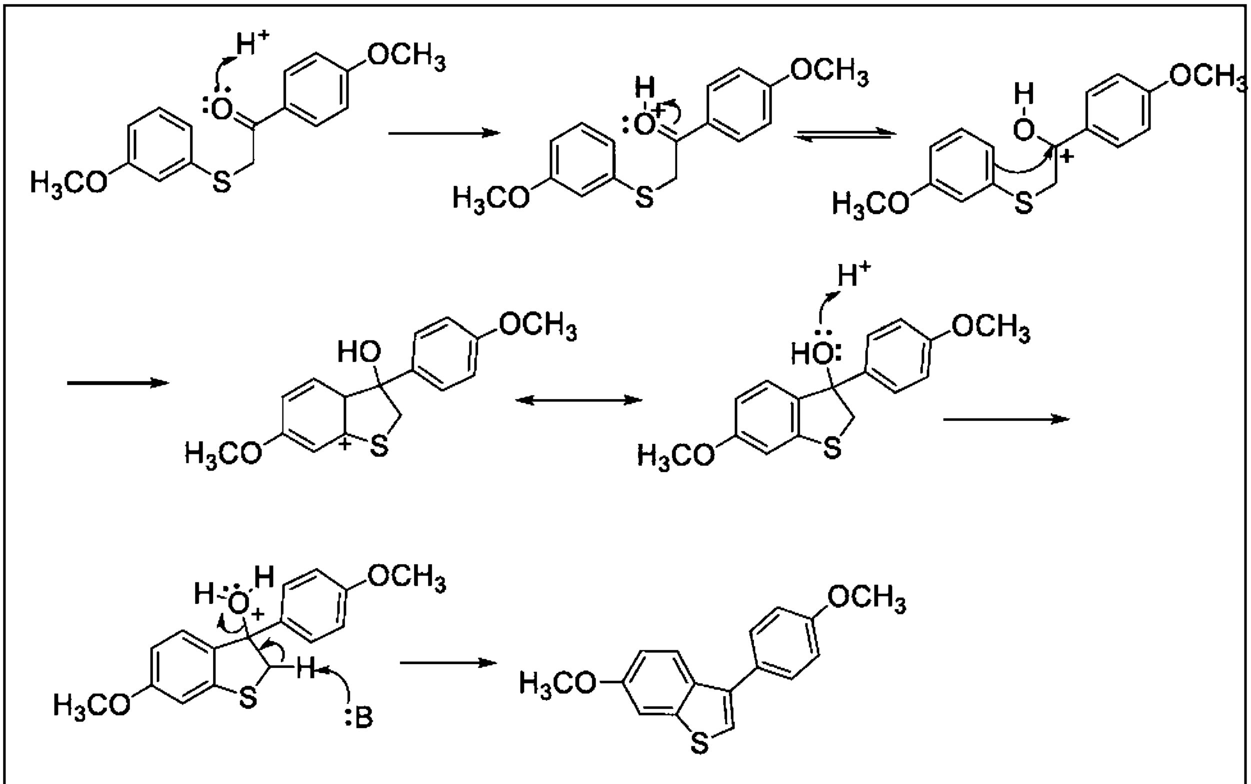
126


Br
N
O
Br
N
O
H
O
Br
N
O
Br
N
O
O
Br
N
Br
N
O
N
O
N
O
Br

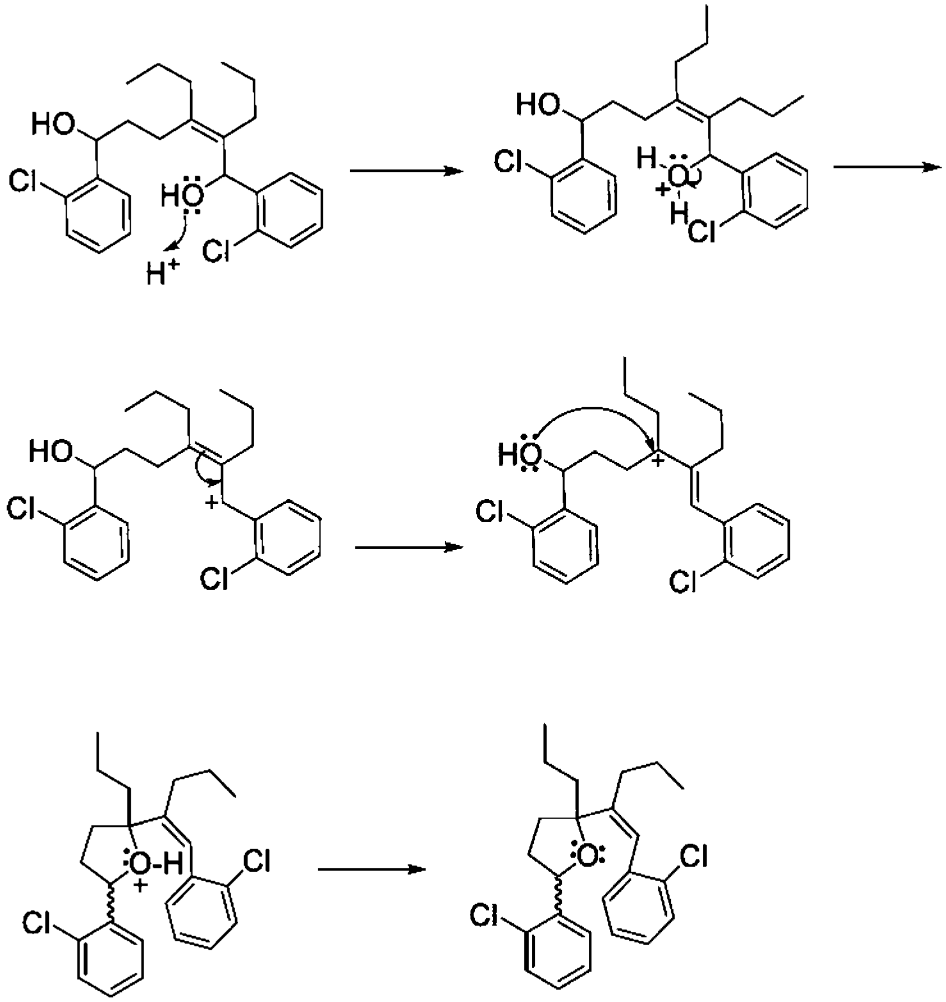
127


O
O
NH
O
OEt
O
H
H
O
O
NH
O
OEt
O
O
O
HN
O
OEt
O
O

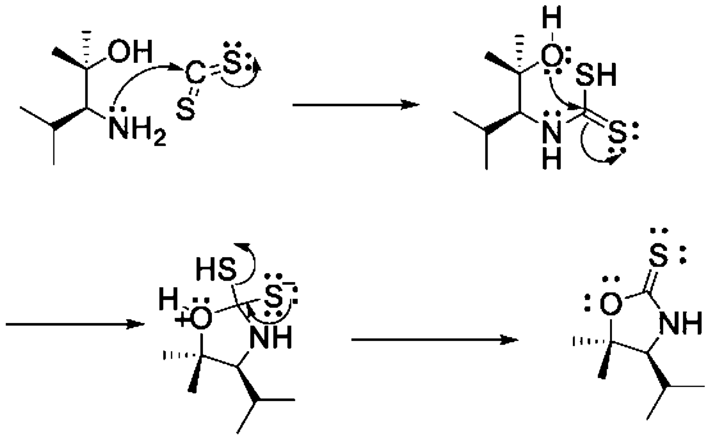
128



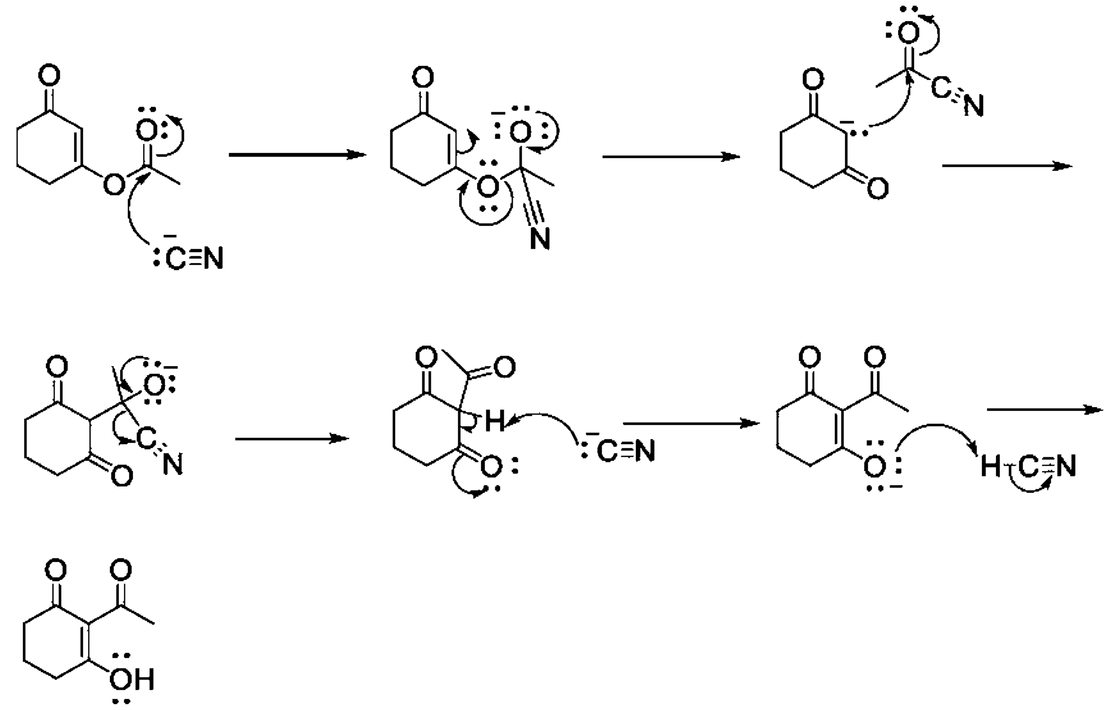
129



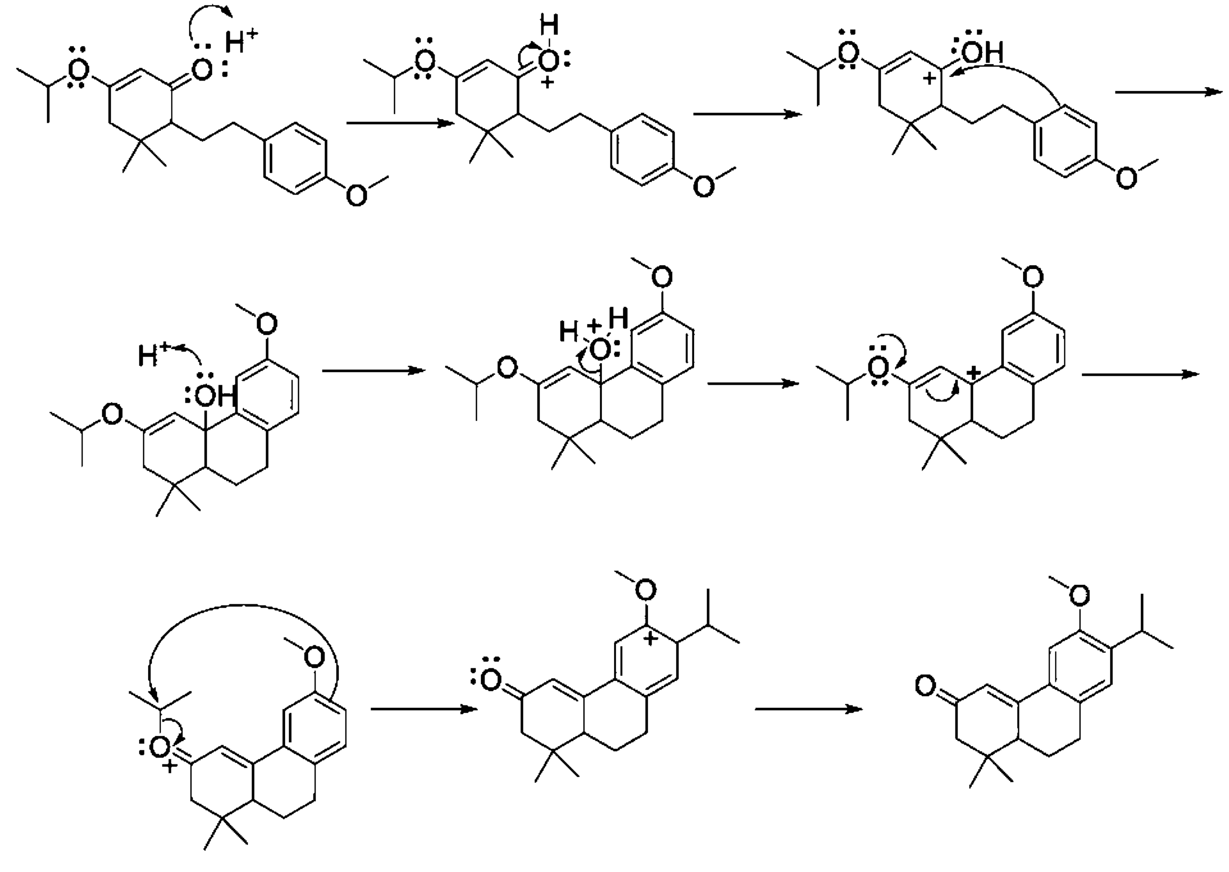
130



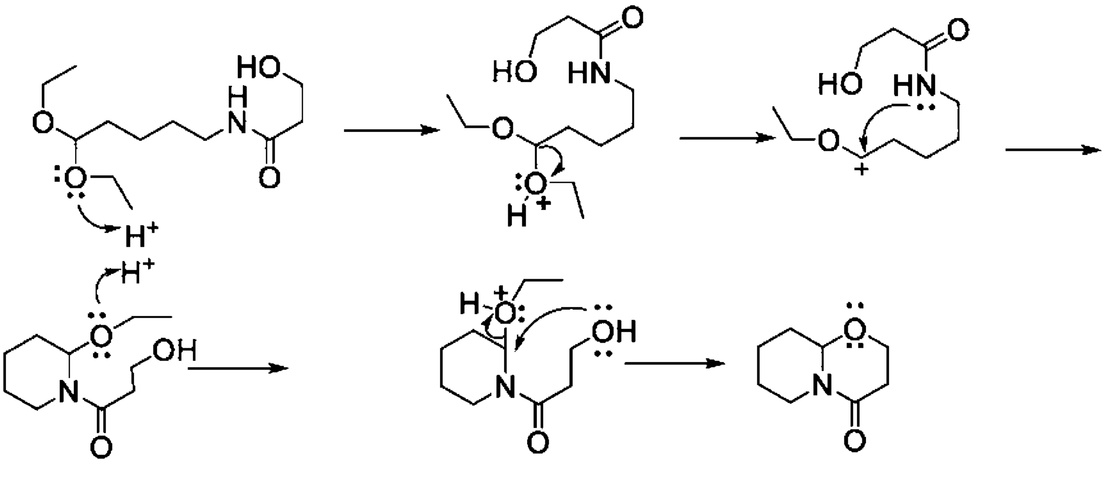
131



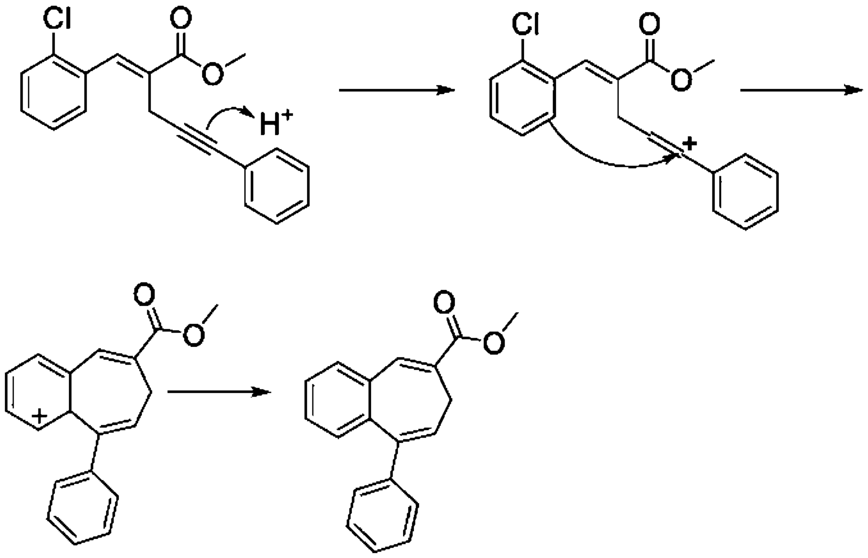
132



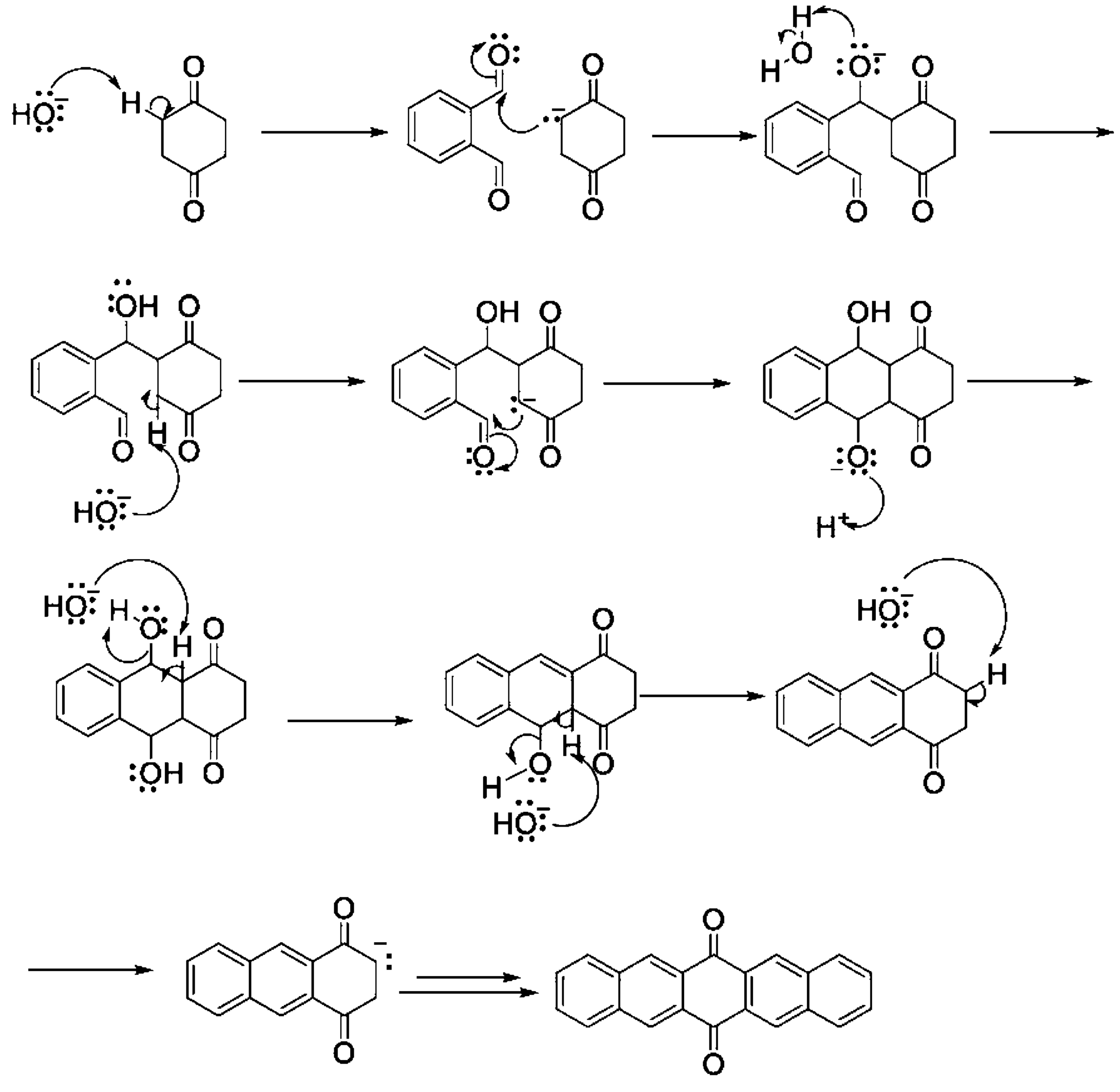
133



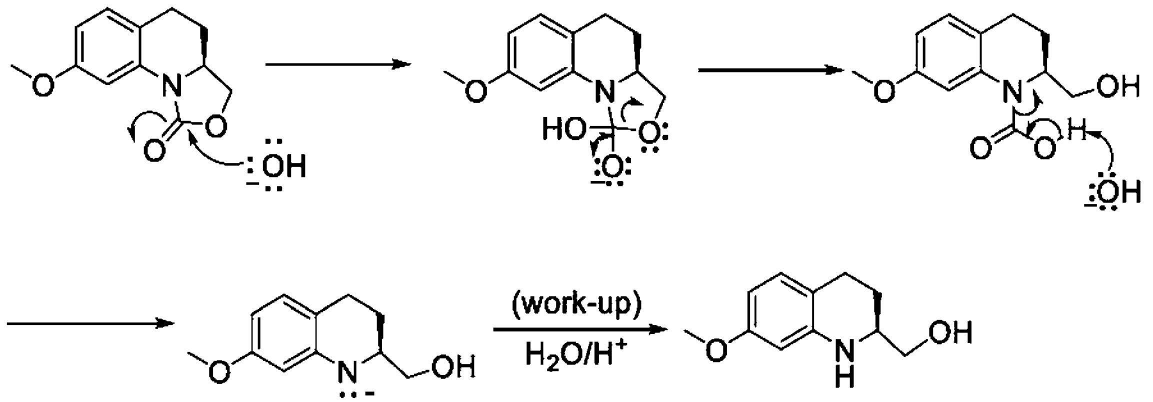
134



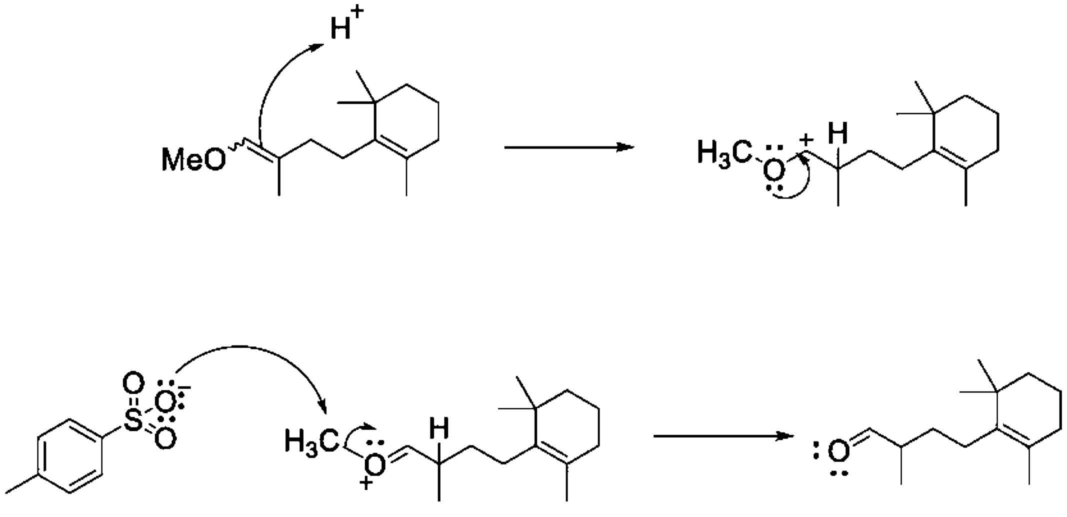
135



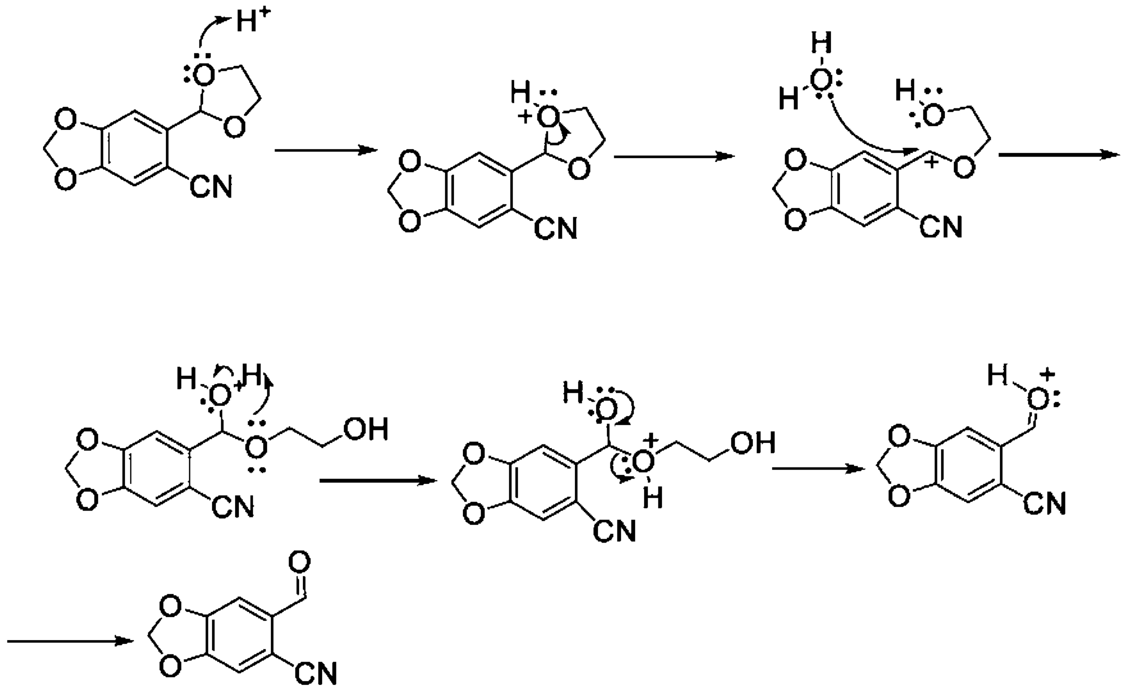
136



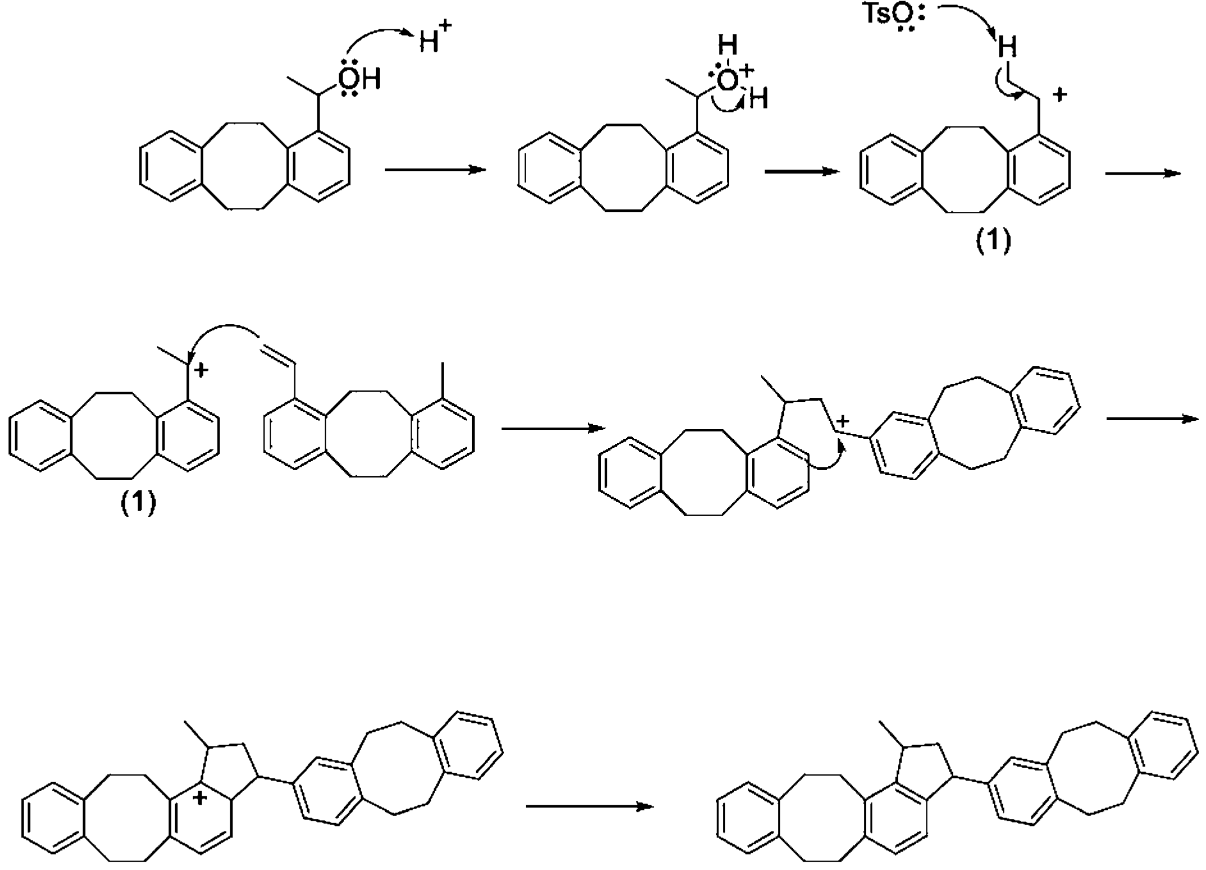
137



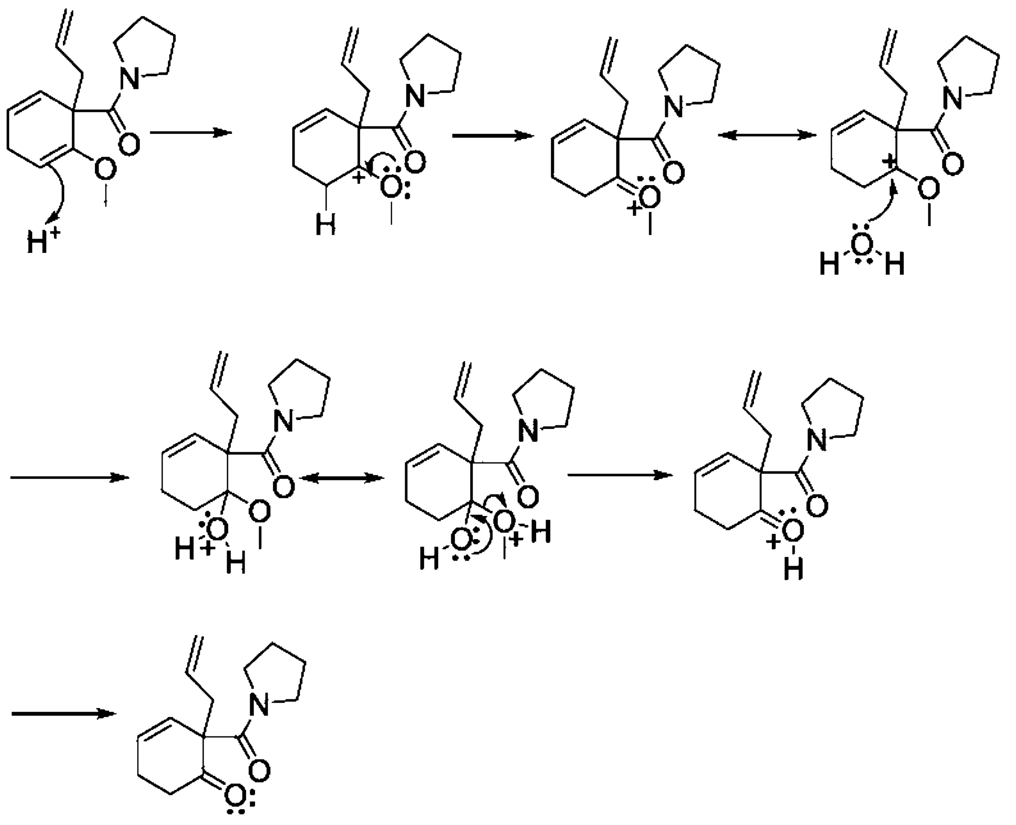
138



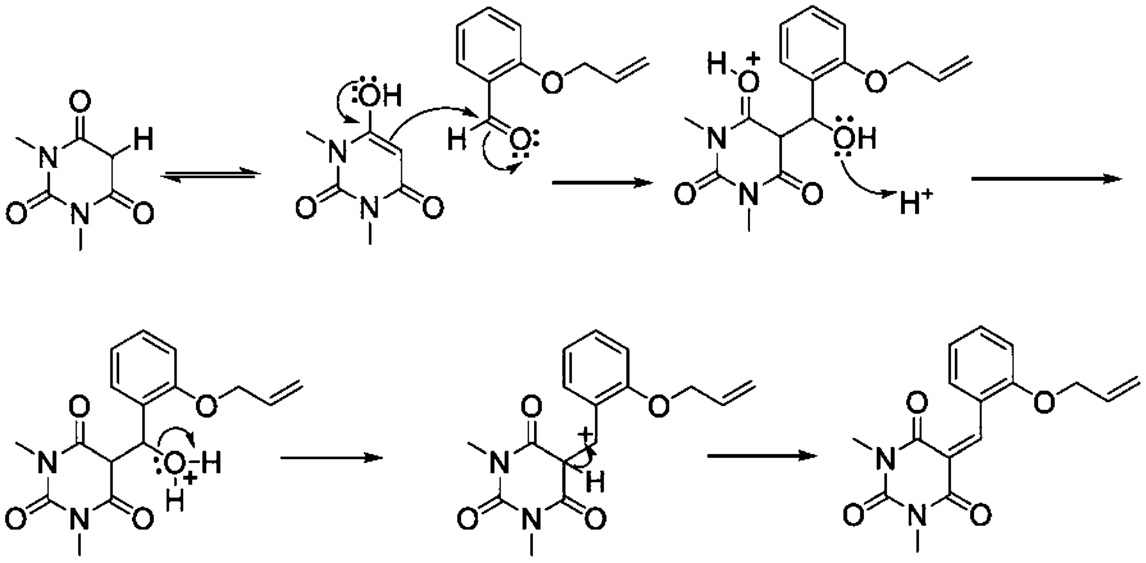
139



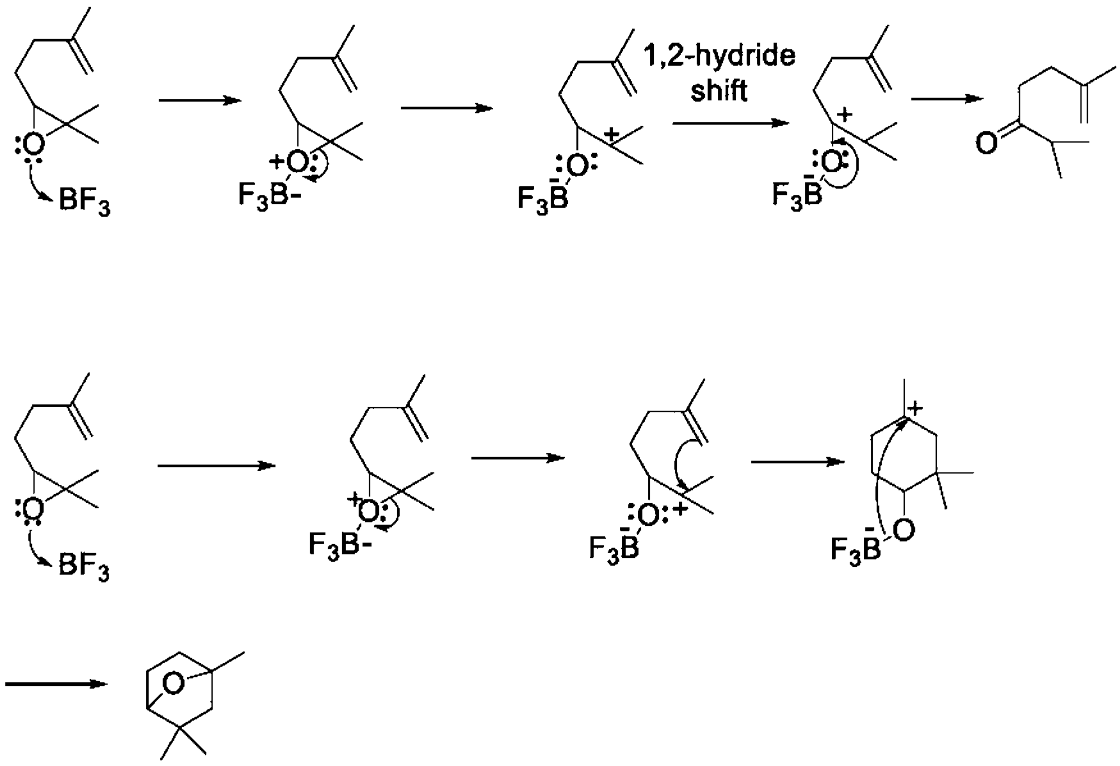
140



141

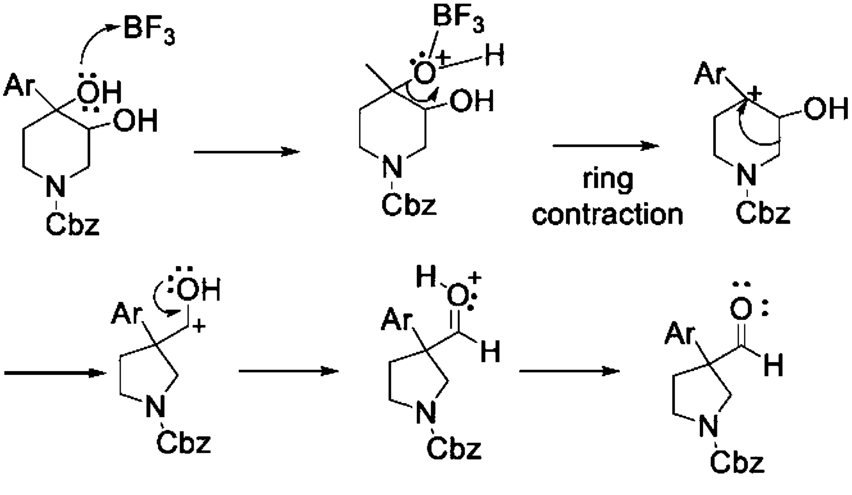


142



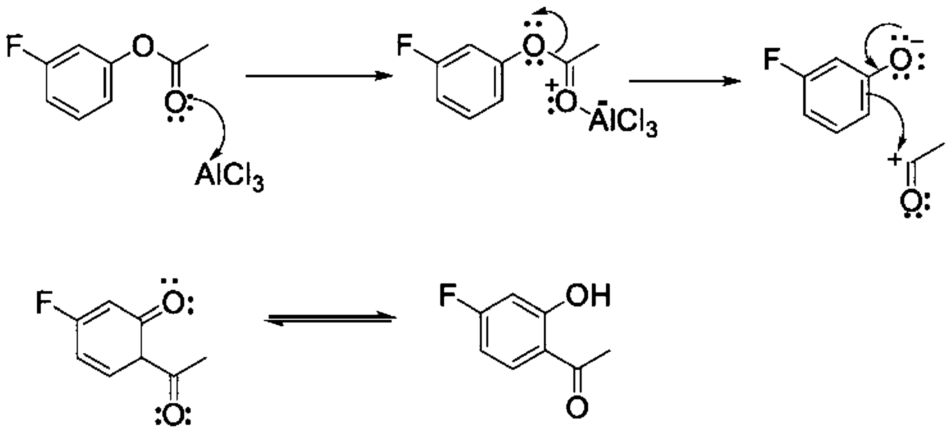
BF3
F3B-
1,2-hydride shift
F3B
O

143



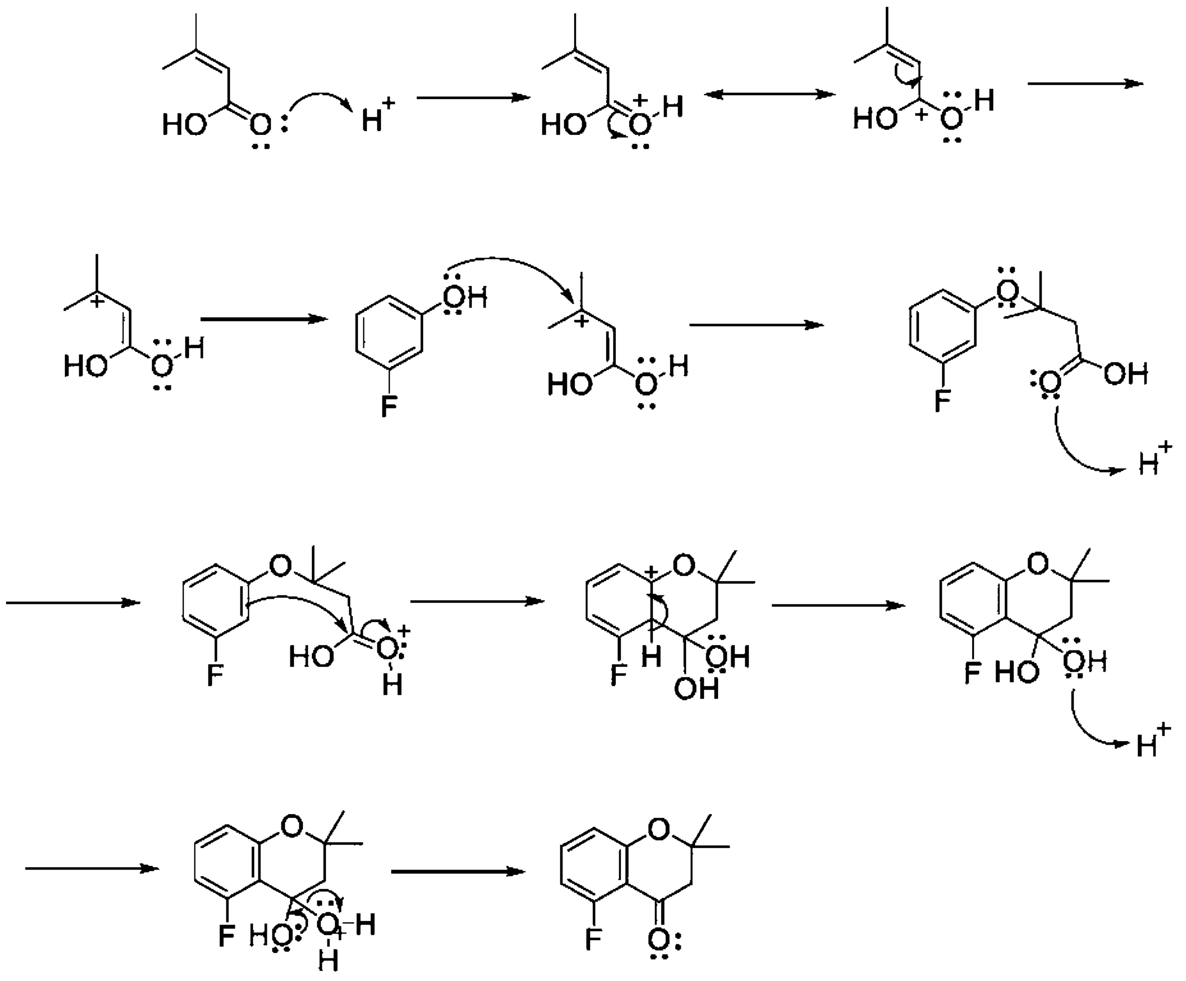
BF3
Ar
OH
OH
N
Cbz
H
ring contraction

144

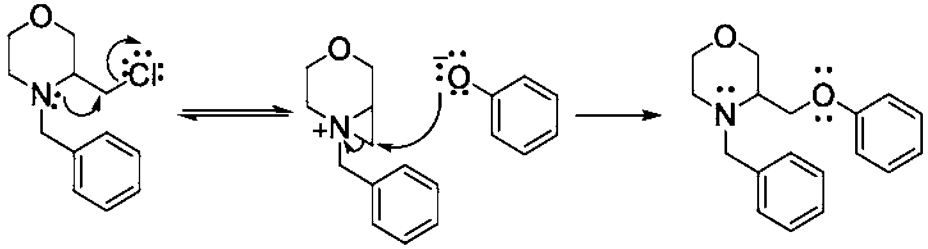


This is an example of the *Fries rearrangement*

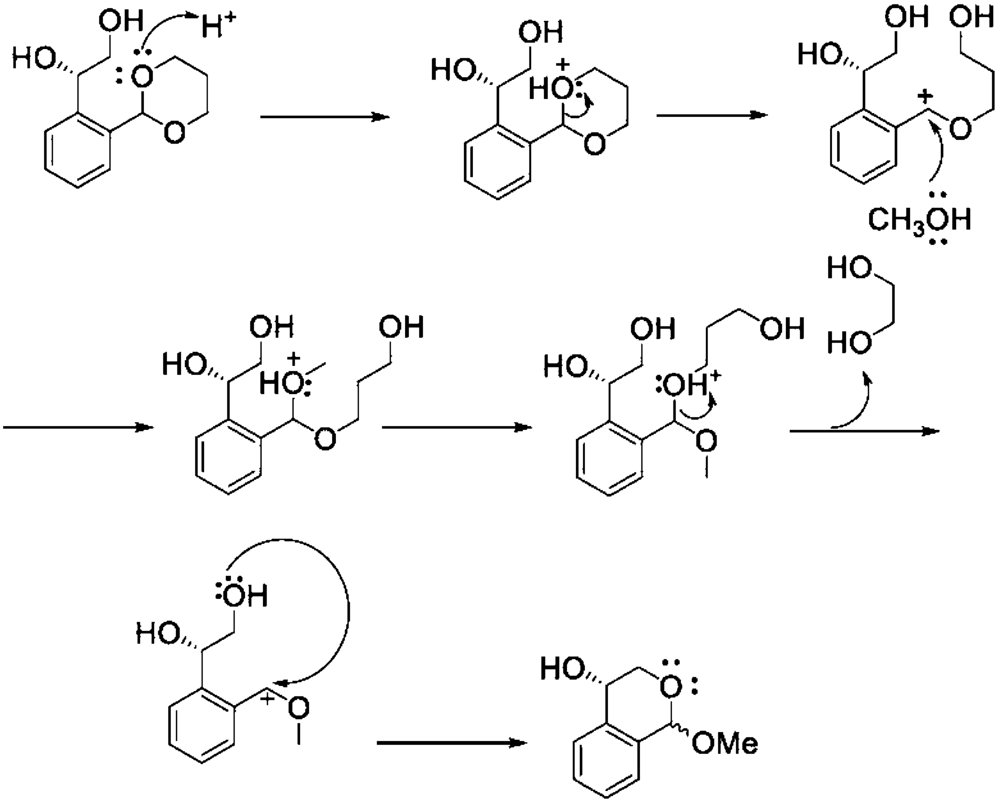
145



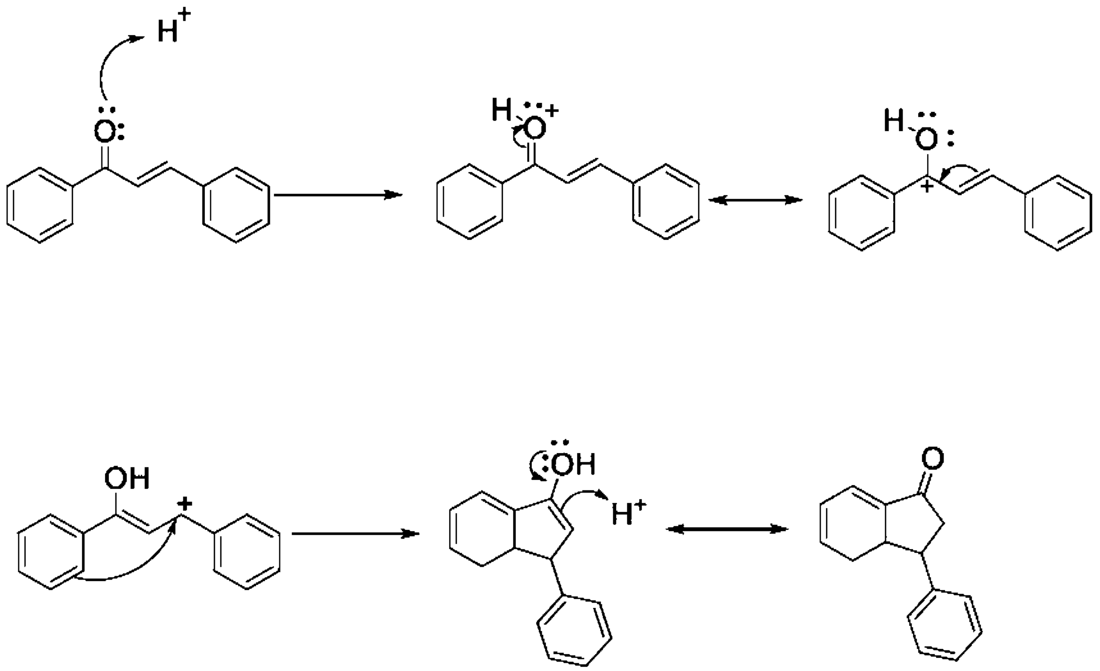
146



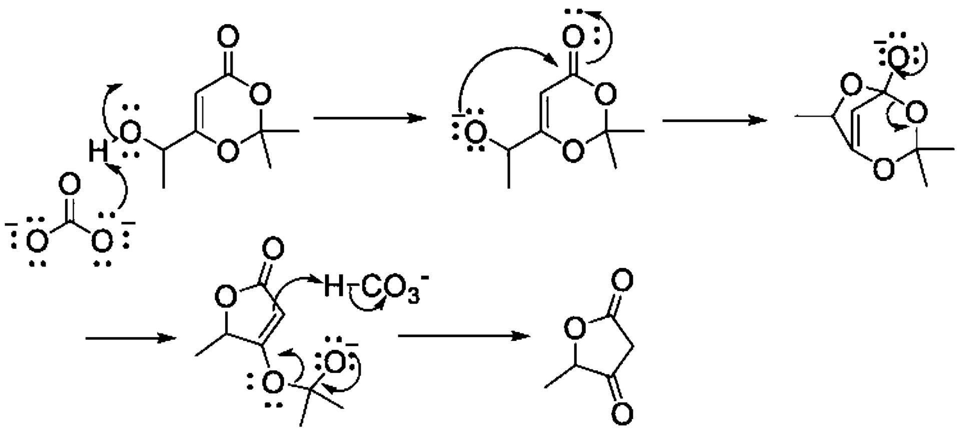
147



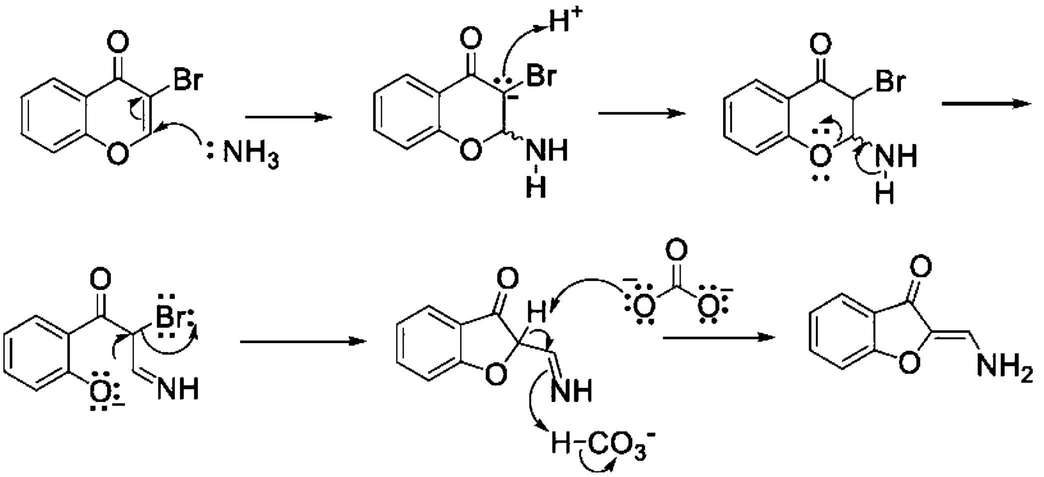
148



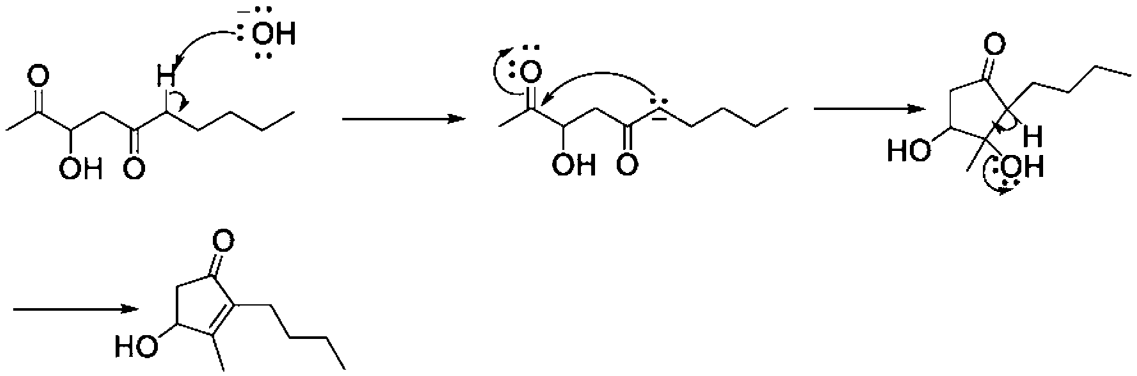
149



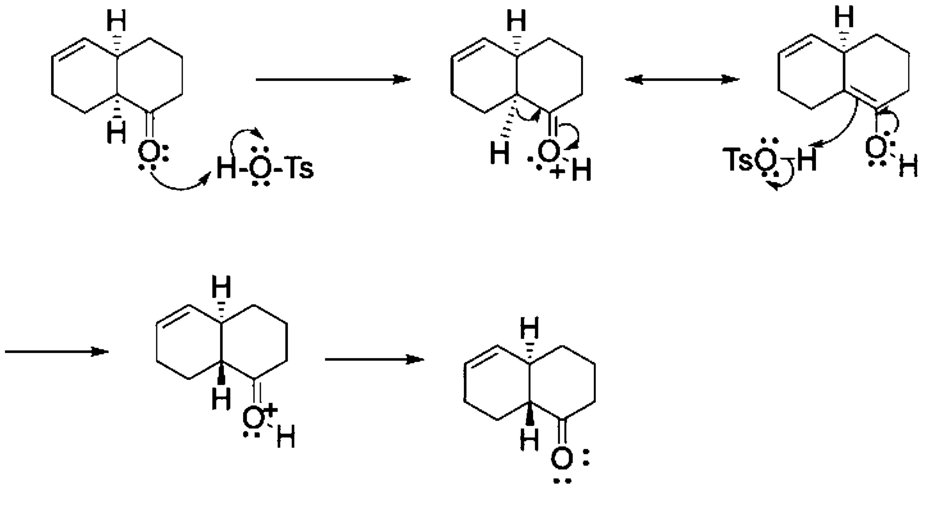
150

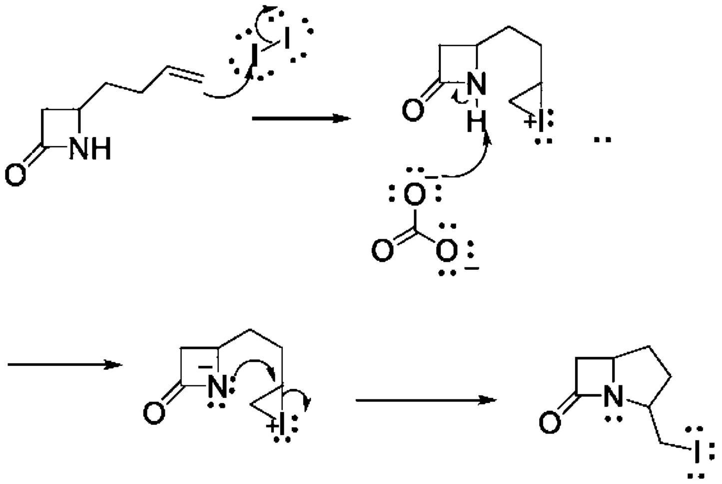


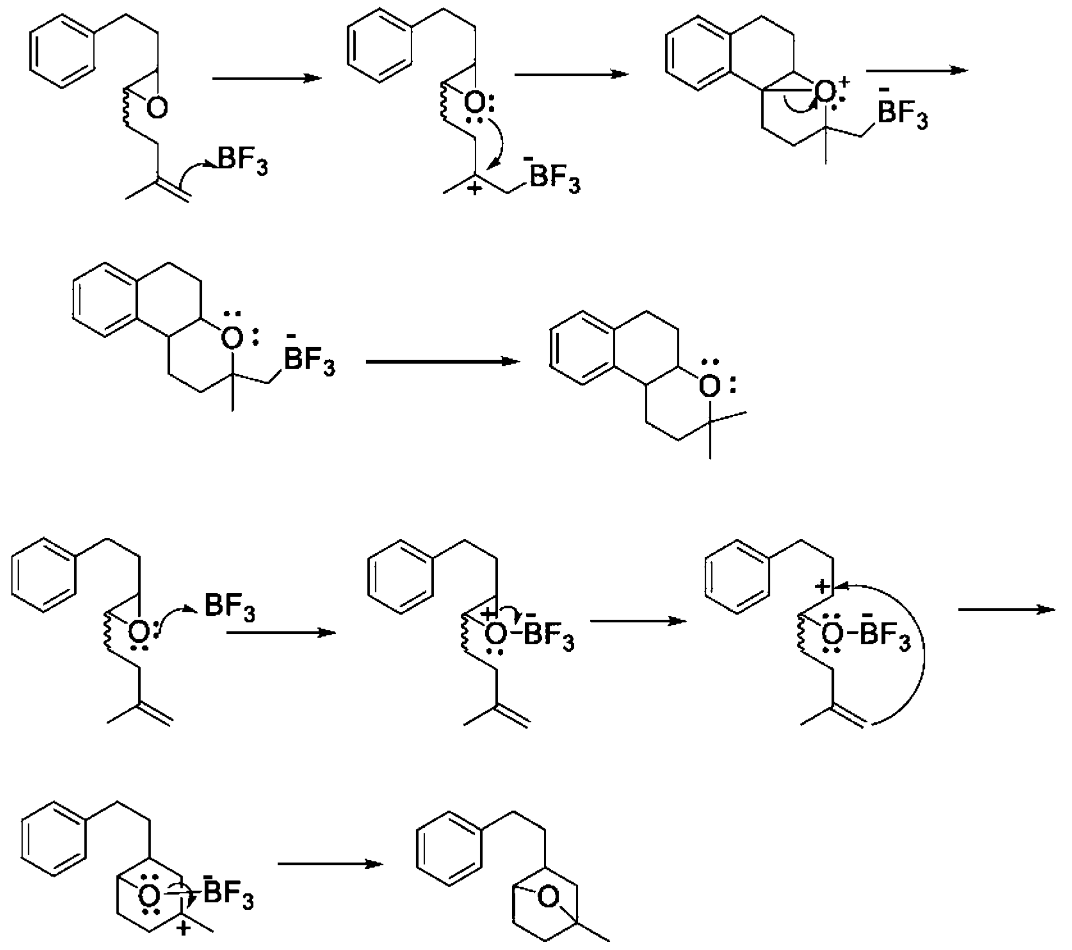
151



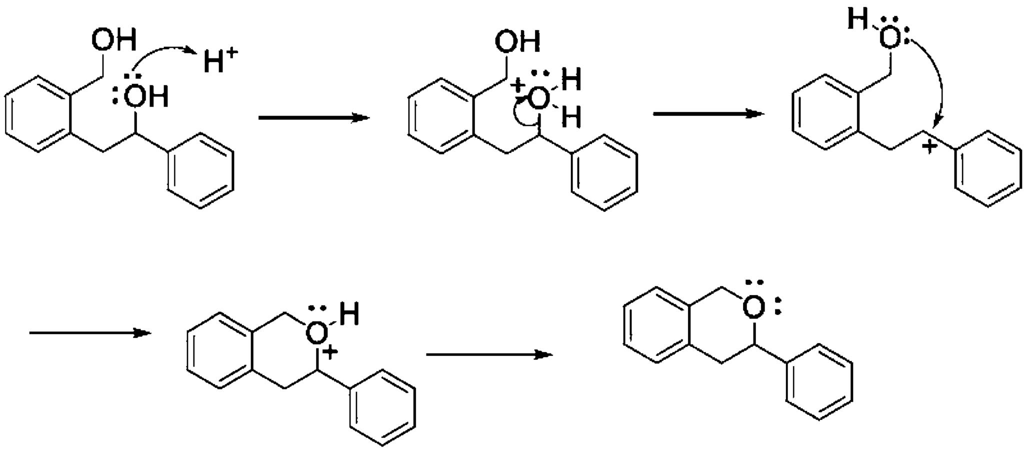
152



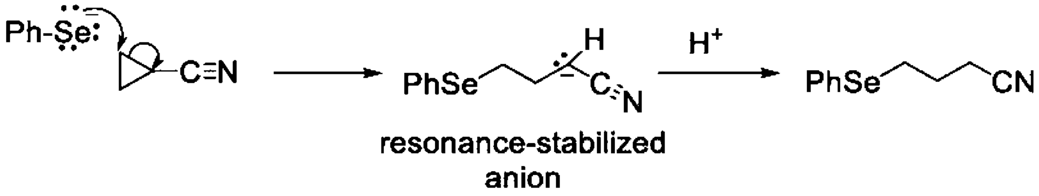
Acid-catalyzed isomerization to the more stable trans isomer
153

154



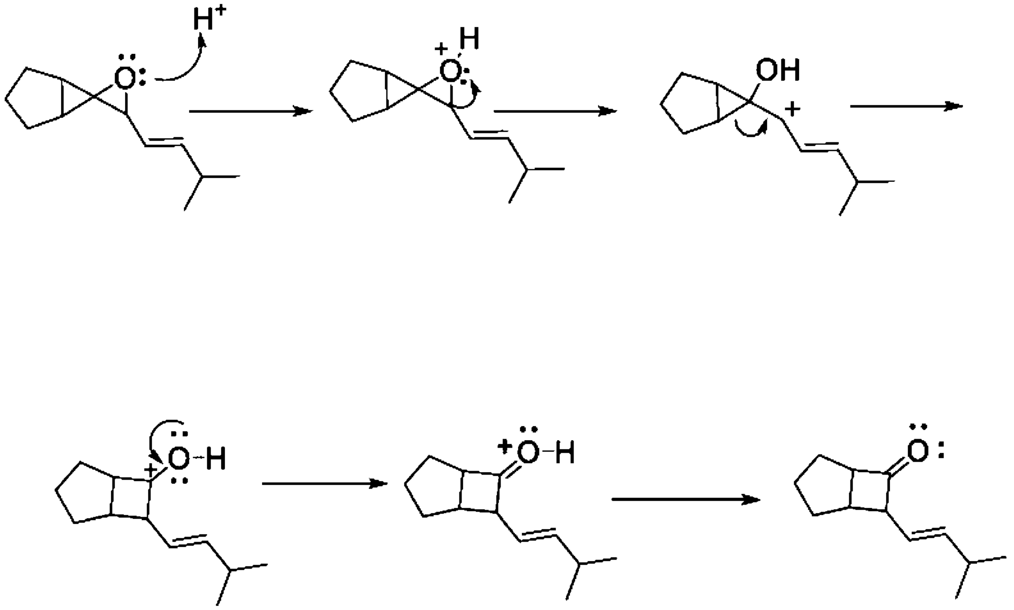
155



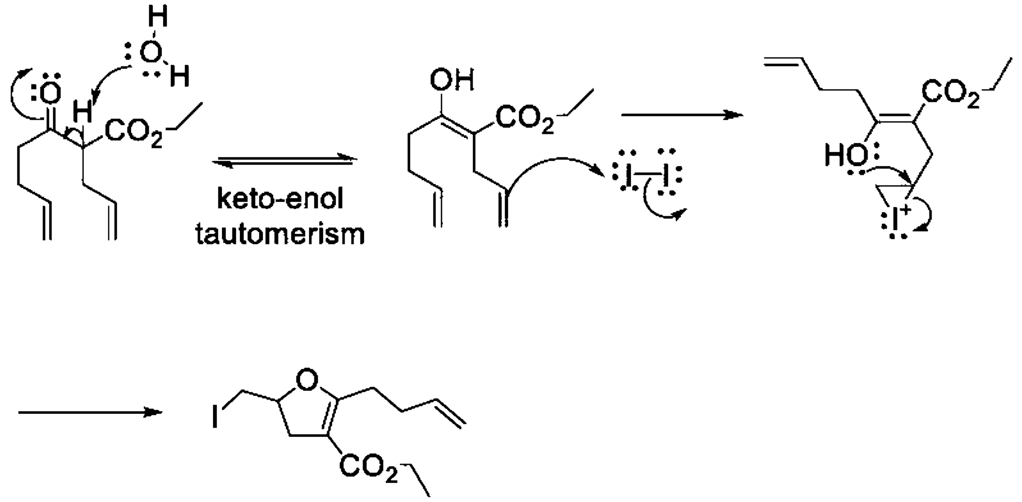
156


Ph-Se:
C≡N
PhSe
H
C
N
H^+
PhSe
CN
resonance-stabilized
anion

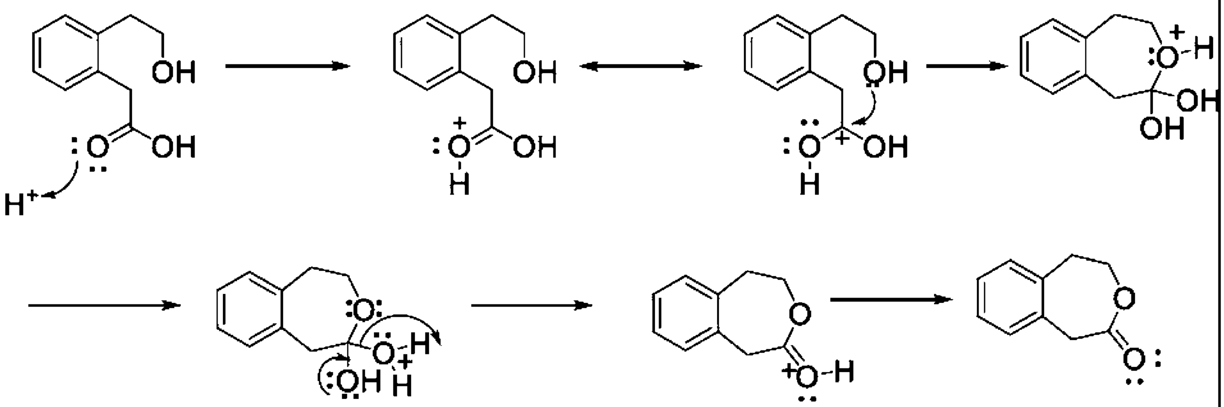
157


H^+
O:
+ H
O:
OH
+
+
O-H
+O-H
O:

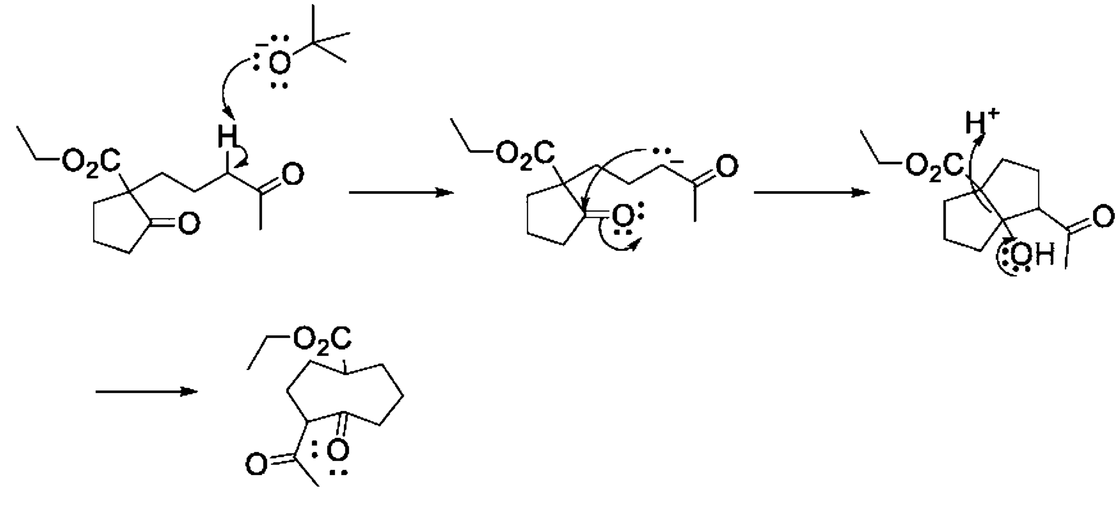
158


H
:O
H
:O
H
CO_2
keto-enol
tautomerism
OH
CO_2
:I–I:
CO_2
HO:
:I+
I
O
CO_2

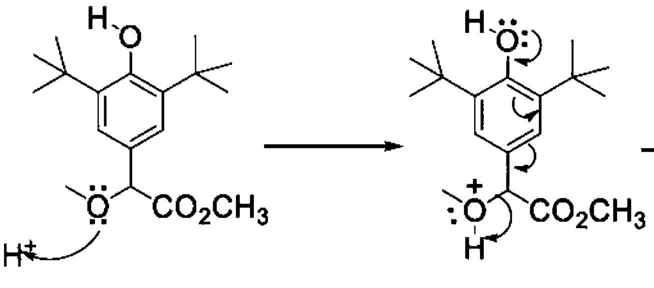
159



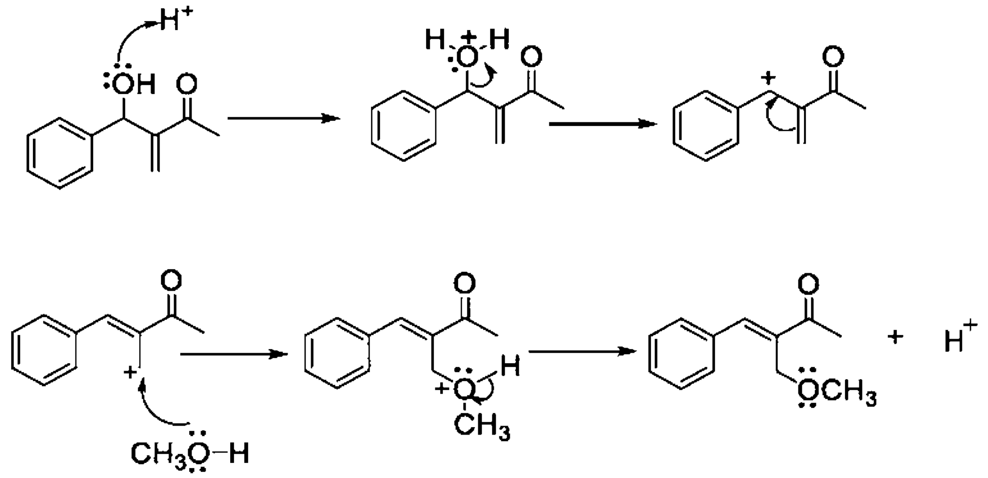
160



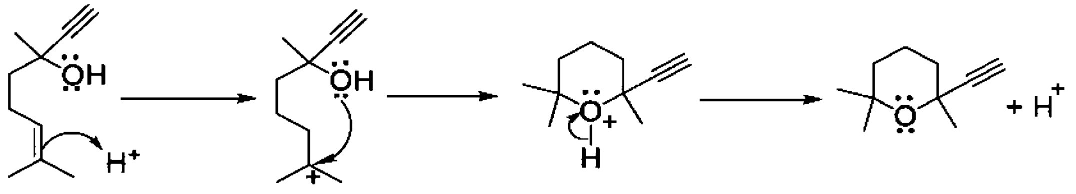
161



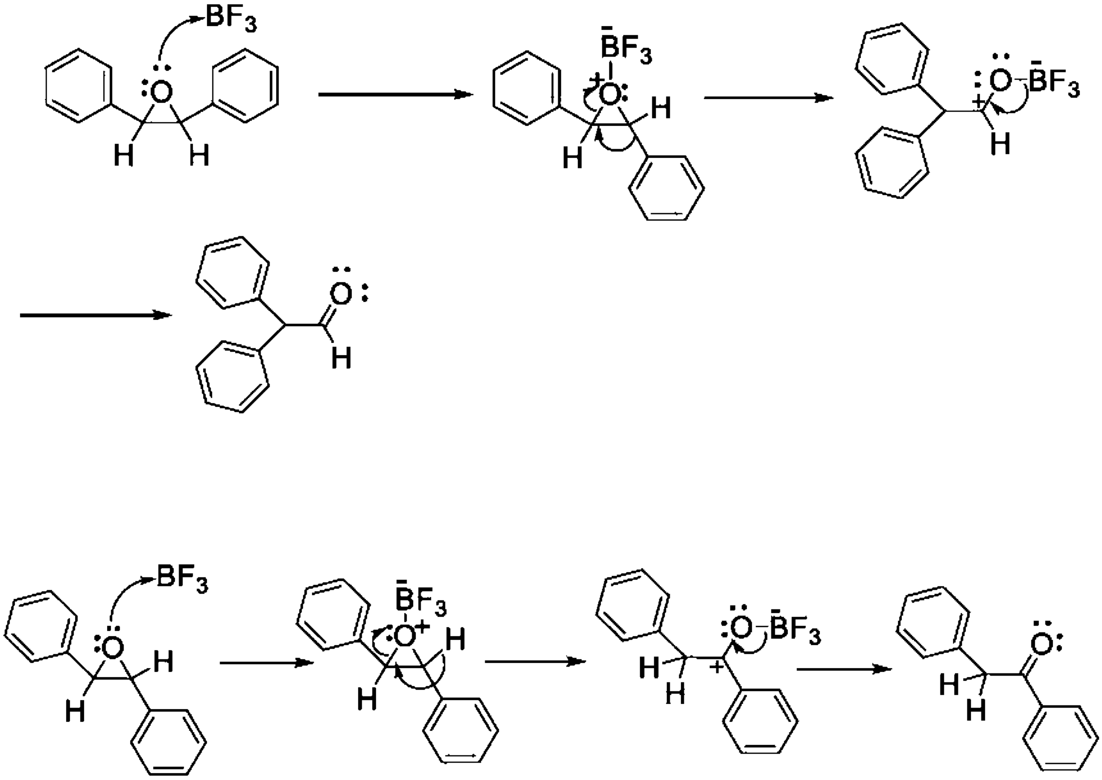
162



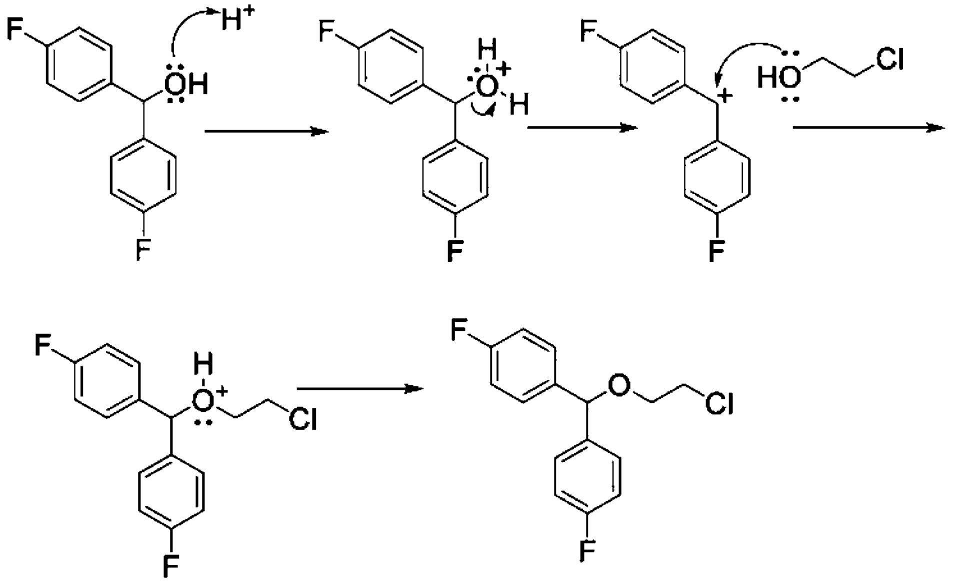
163



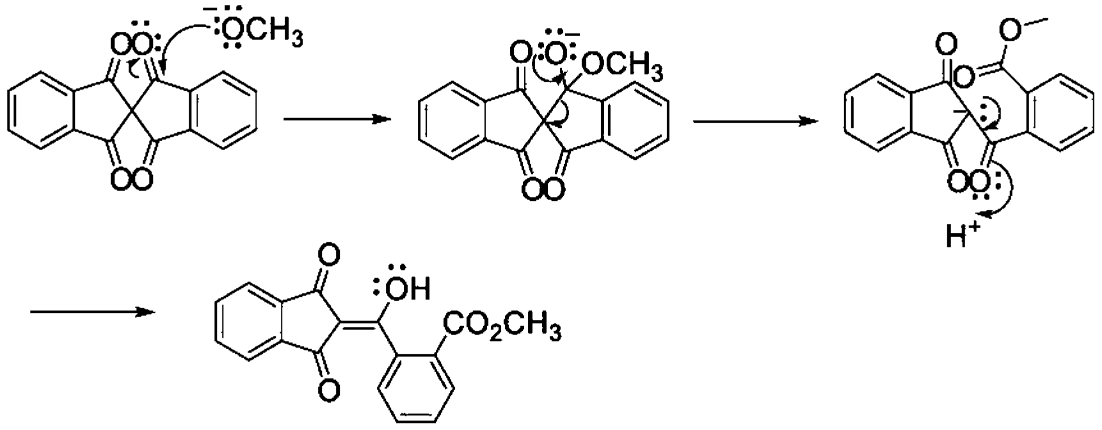
164


BF3
H
H
BF3
H
H
BF3
H
H
BF3
H
H
BF3
H
H
BF3
H
H

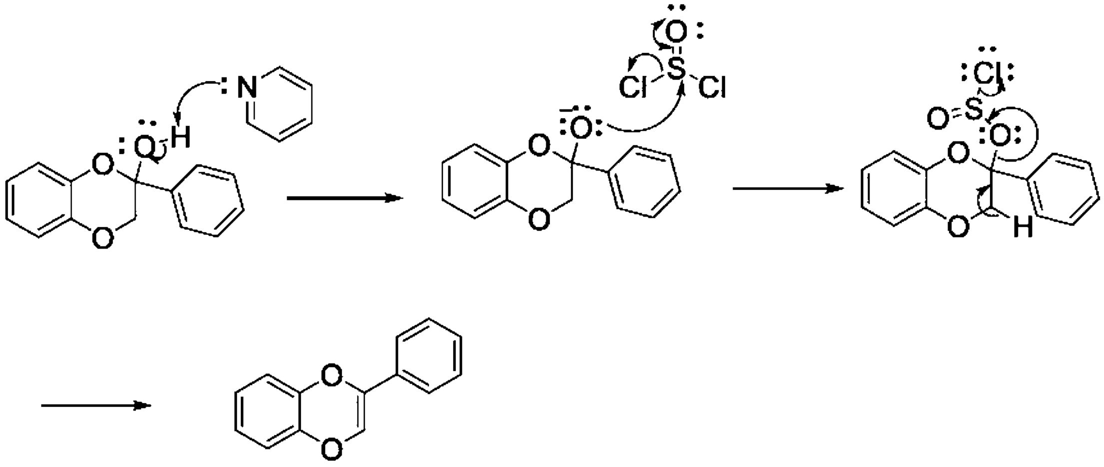
165


F
OH
H+
F
F
H
O
H
F
F
+
HO
Cl
F
F
H
O+
Cl
F
F
O
Cl
F

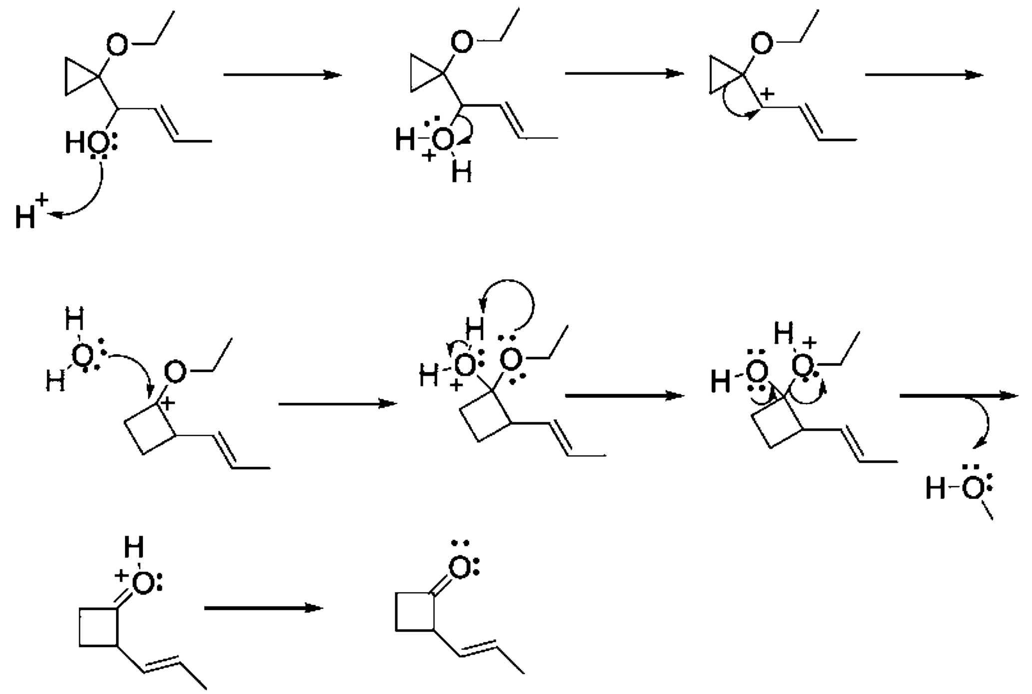
166



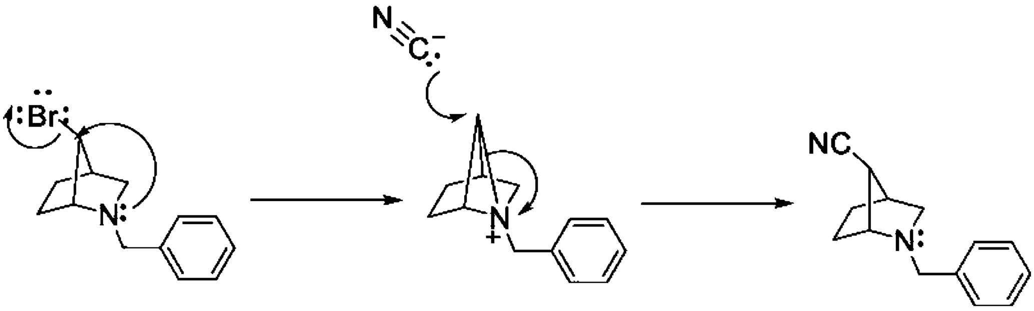
167



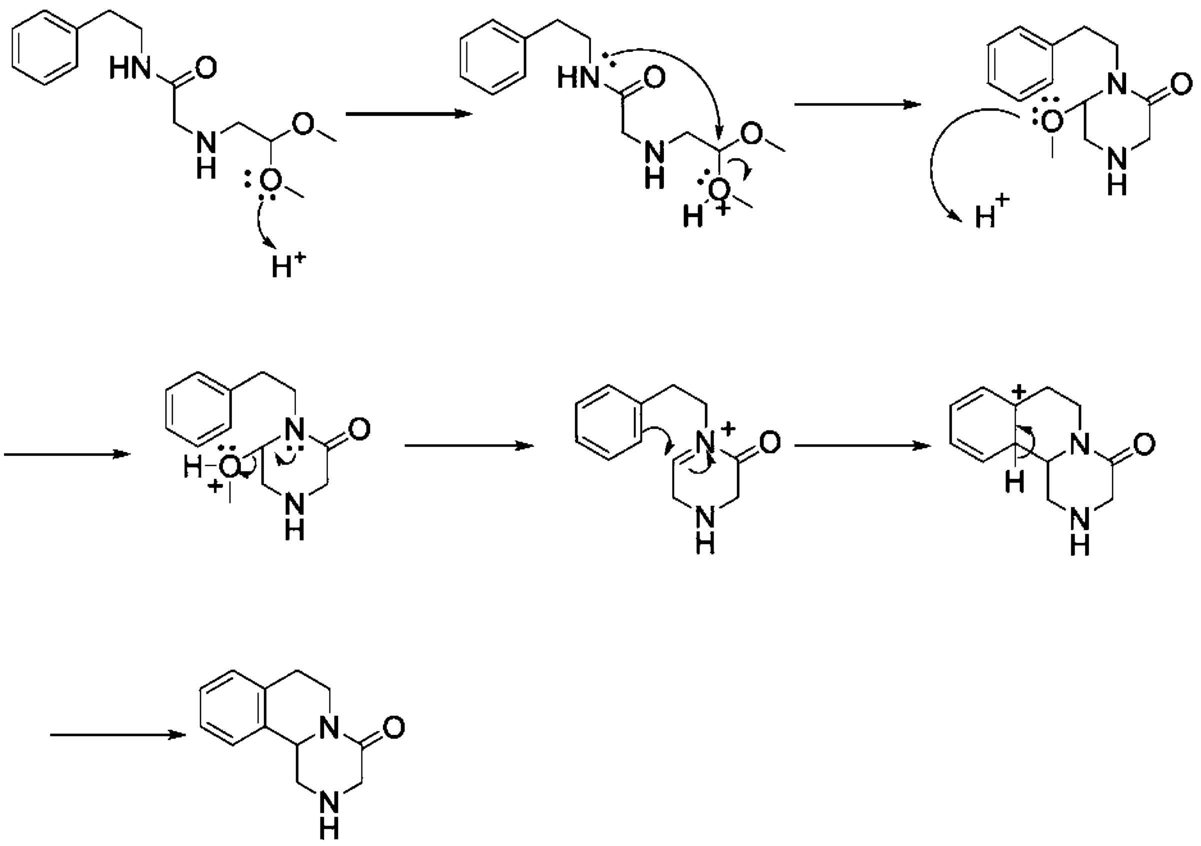
168



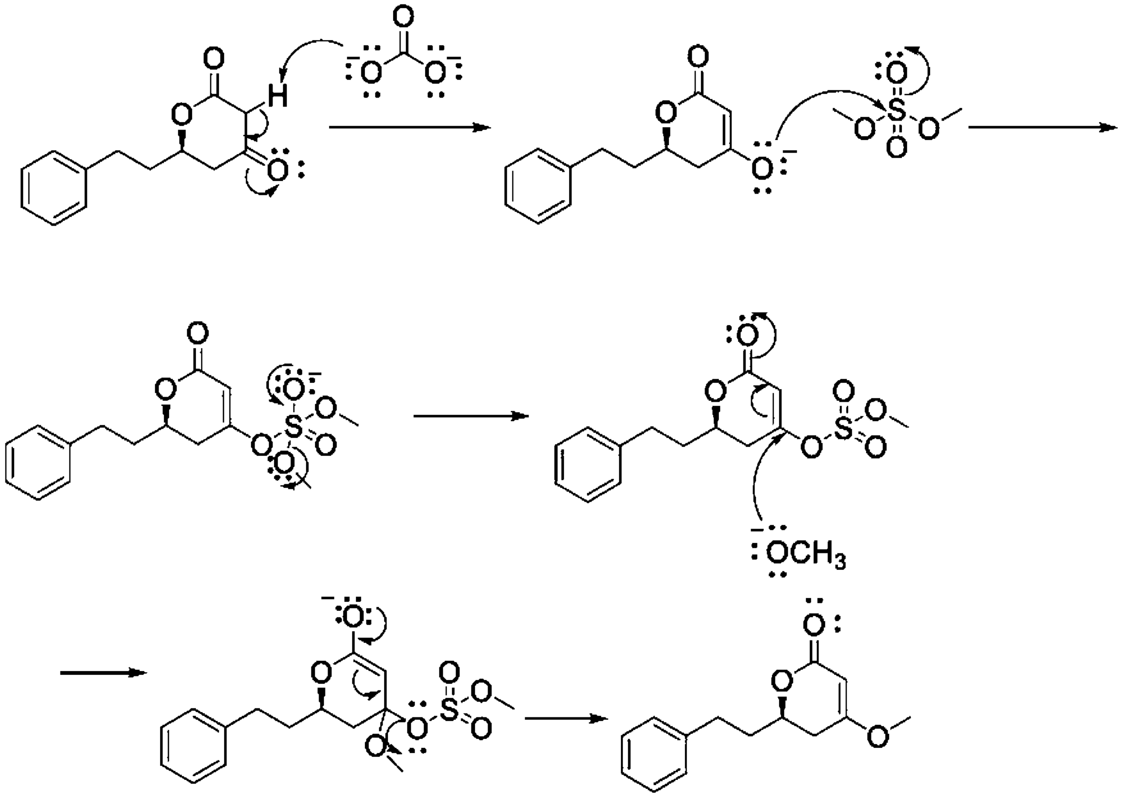
169



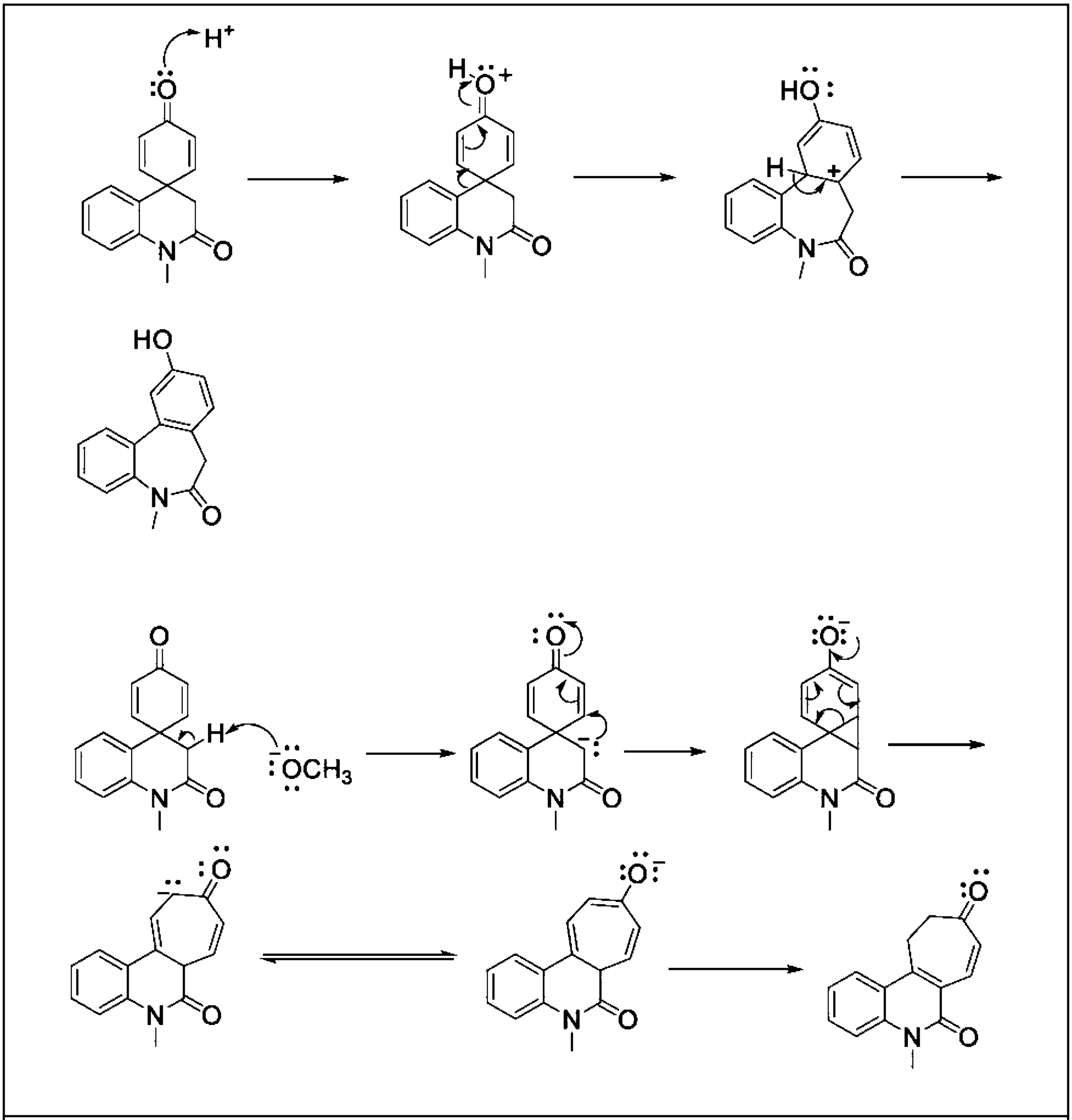
170



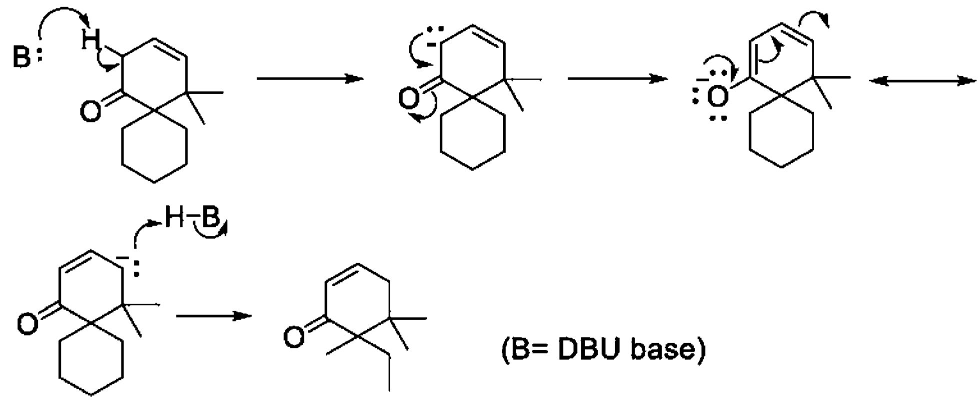
171

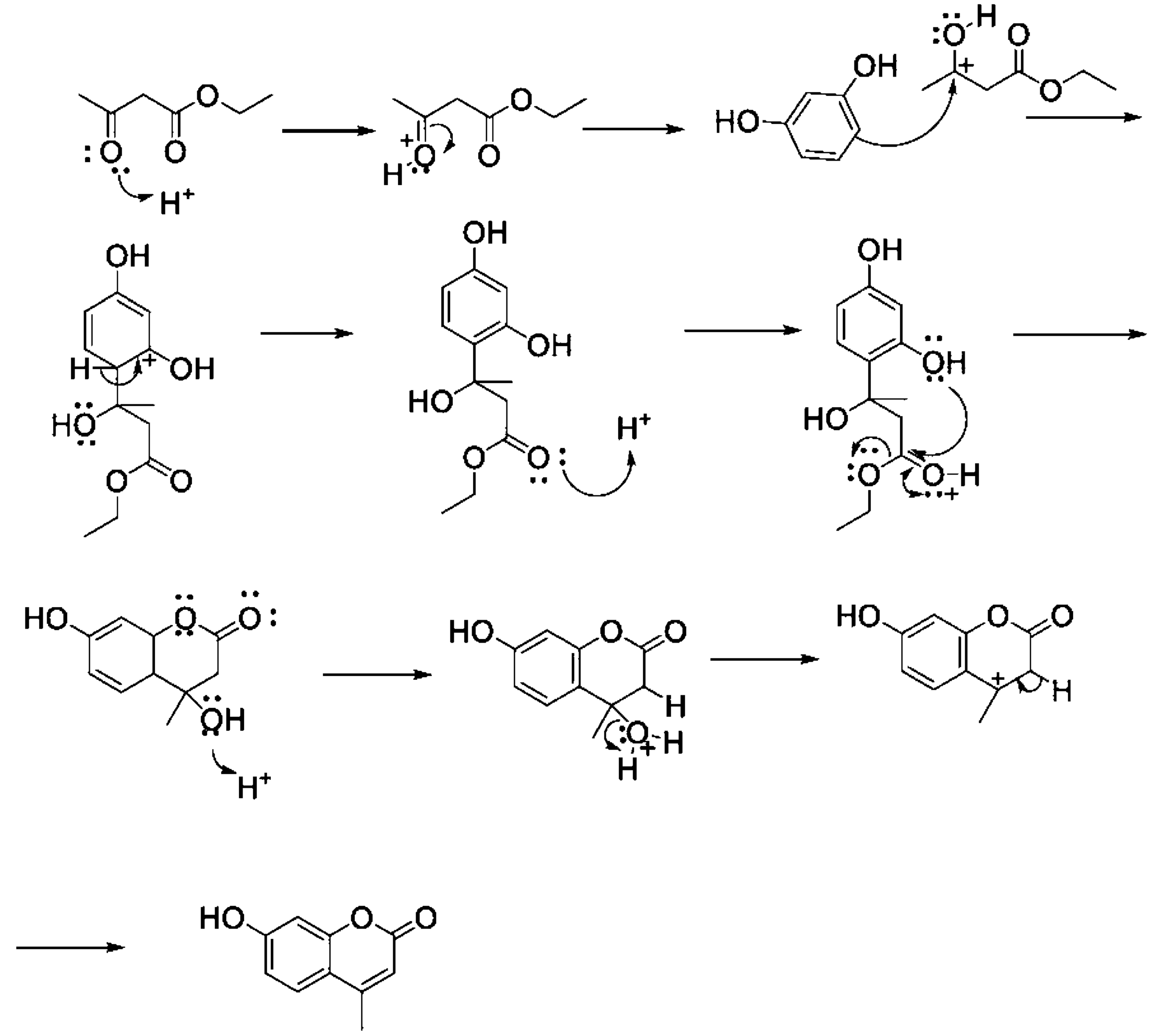


172



173


Base-catalyzed isomerization to form the more stable conjugated product.
174



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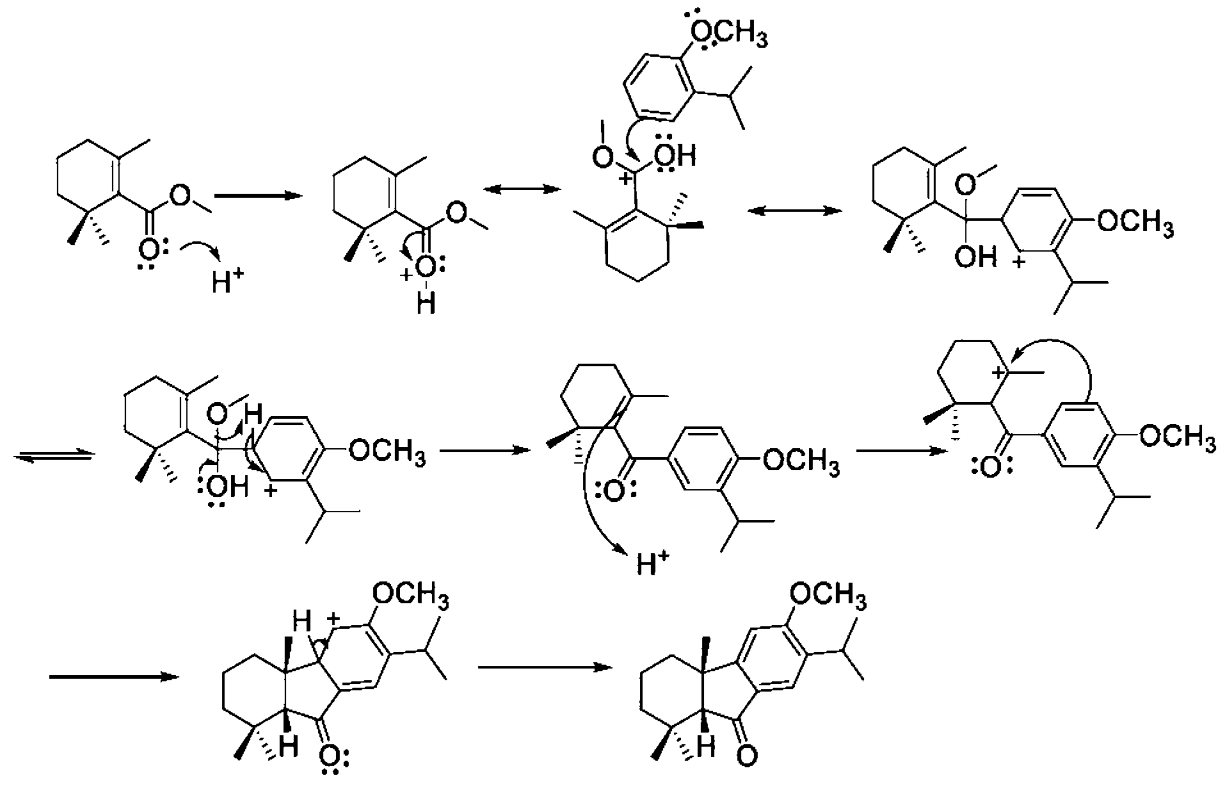

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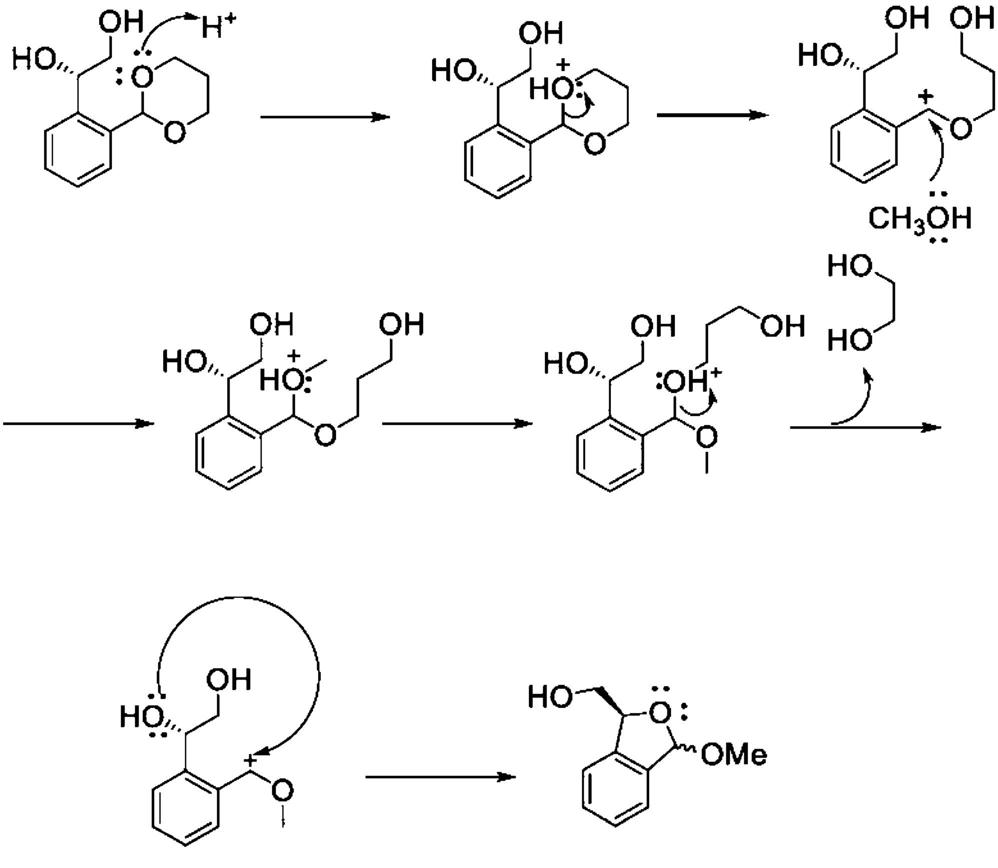
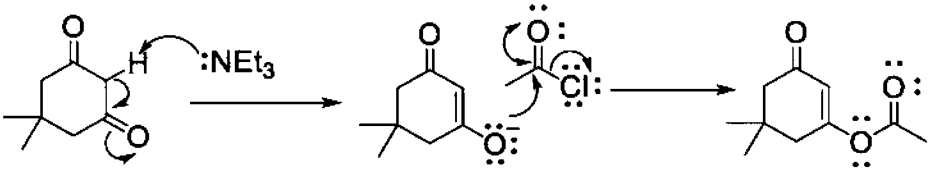


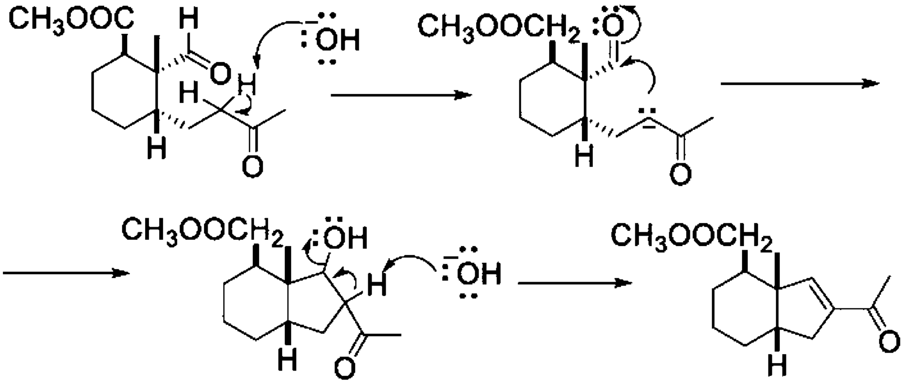
(Resonanace stabilized carbocation)

177



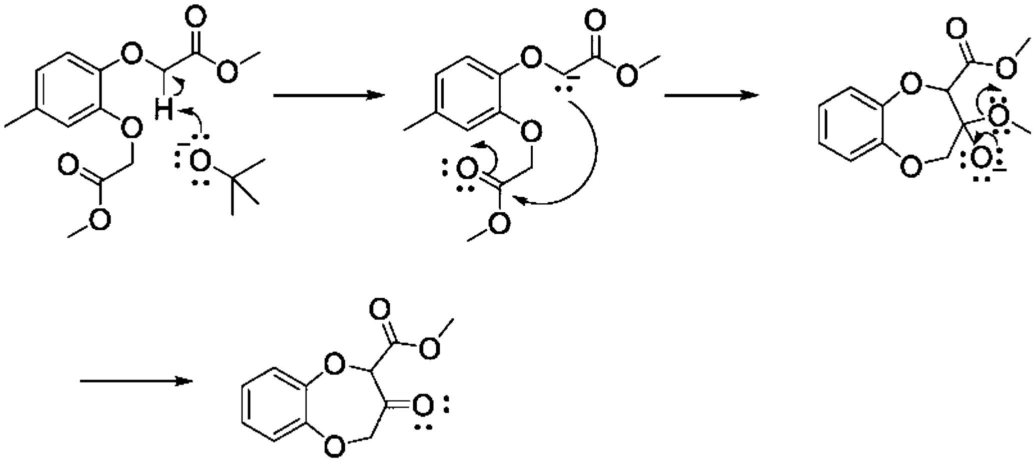
Formation of the ambident anion and subsequent reaction with the acid chloride yields the product.

178



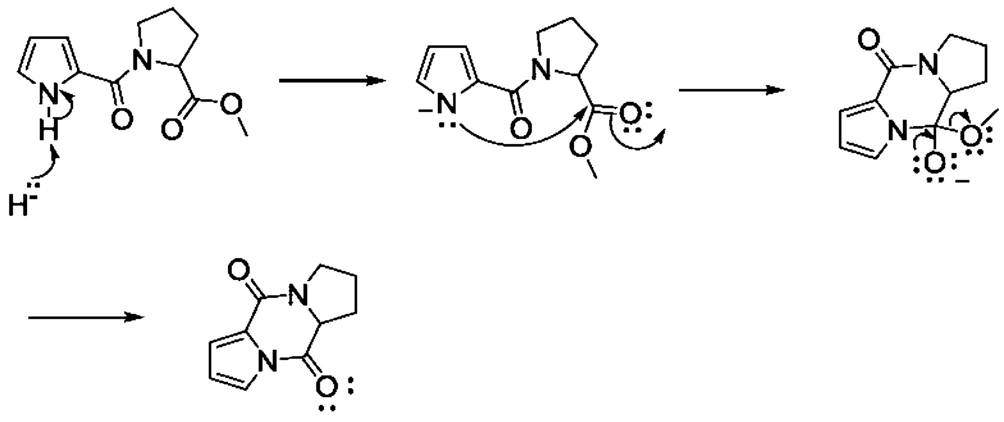
This is an example of an intramolecular aldol condensation reaction.

179



This is a *Dieckmann condensation reaction* (the intramolecular counterpart of the *intermolecular Claisen condensation reaction*)

180



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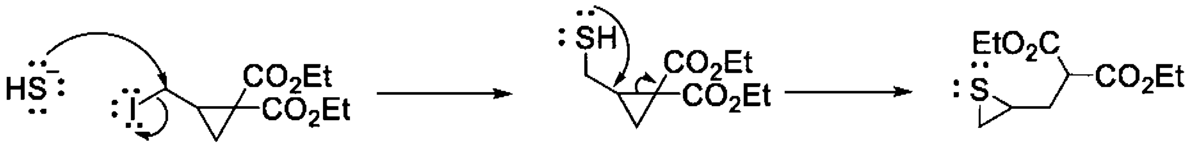

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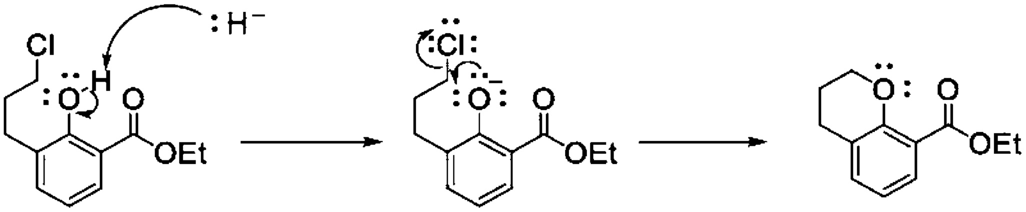

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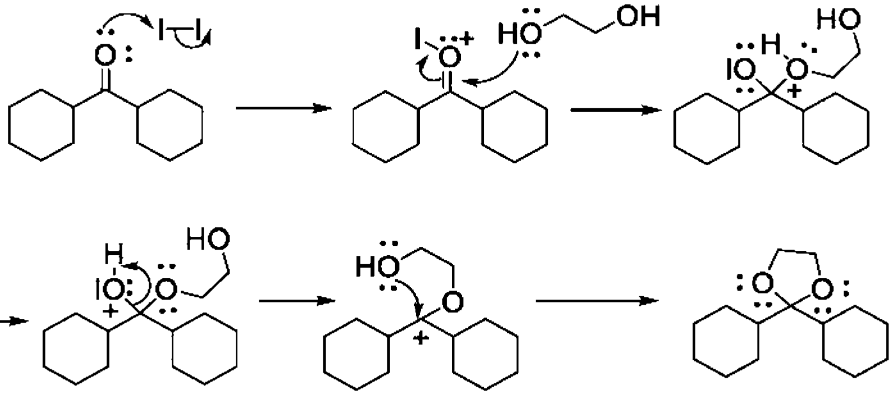

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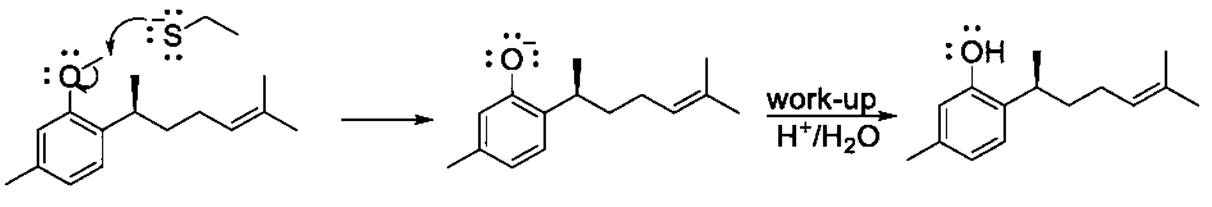
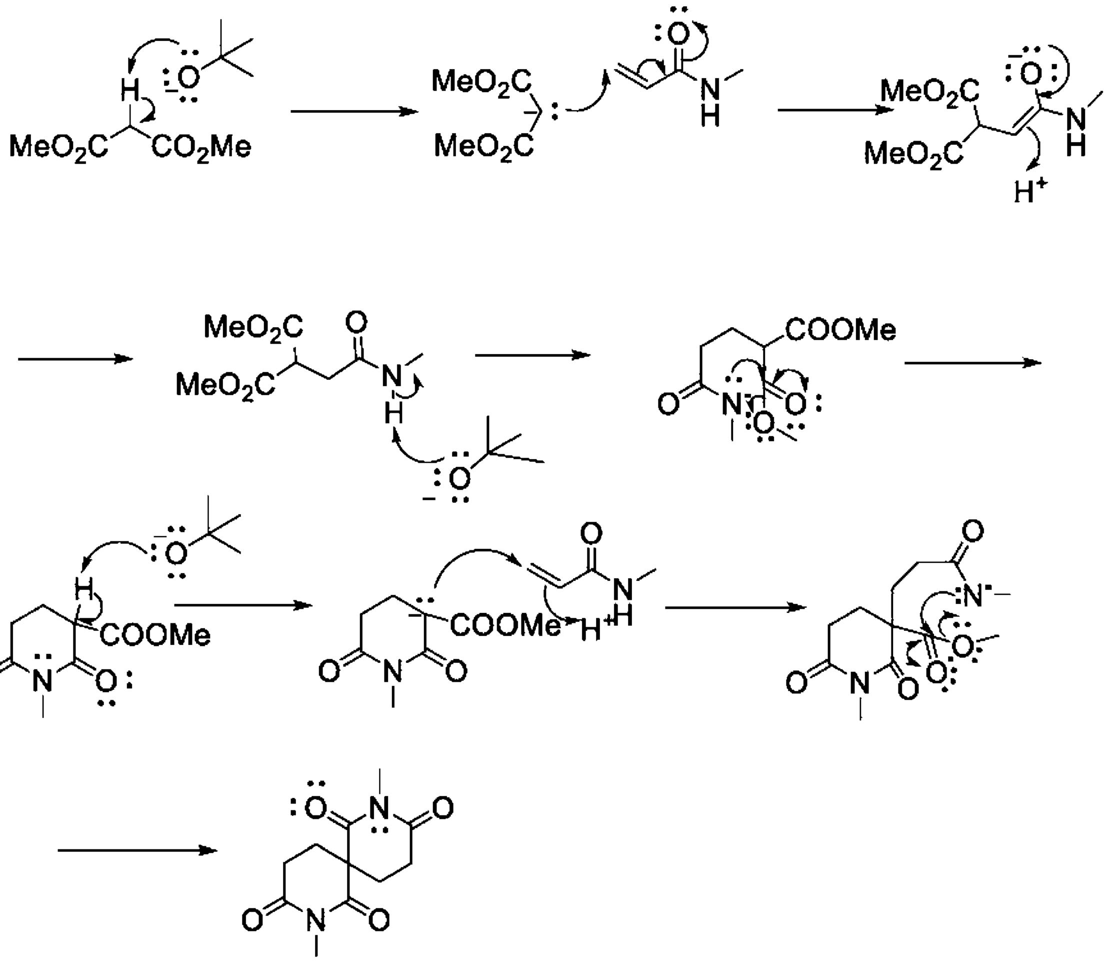


This is a general reaction involving the cleavage of an aryl alkyl ether.

185



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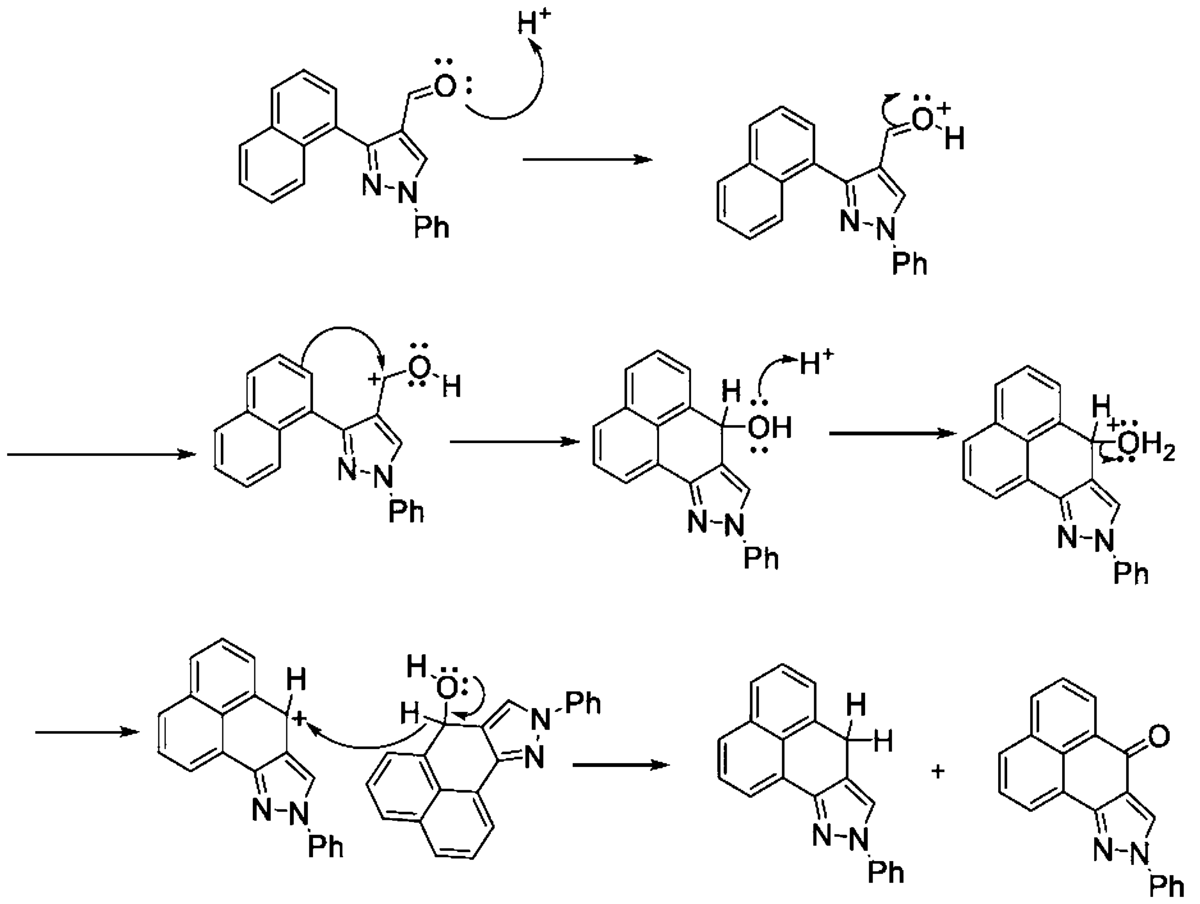

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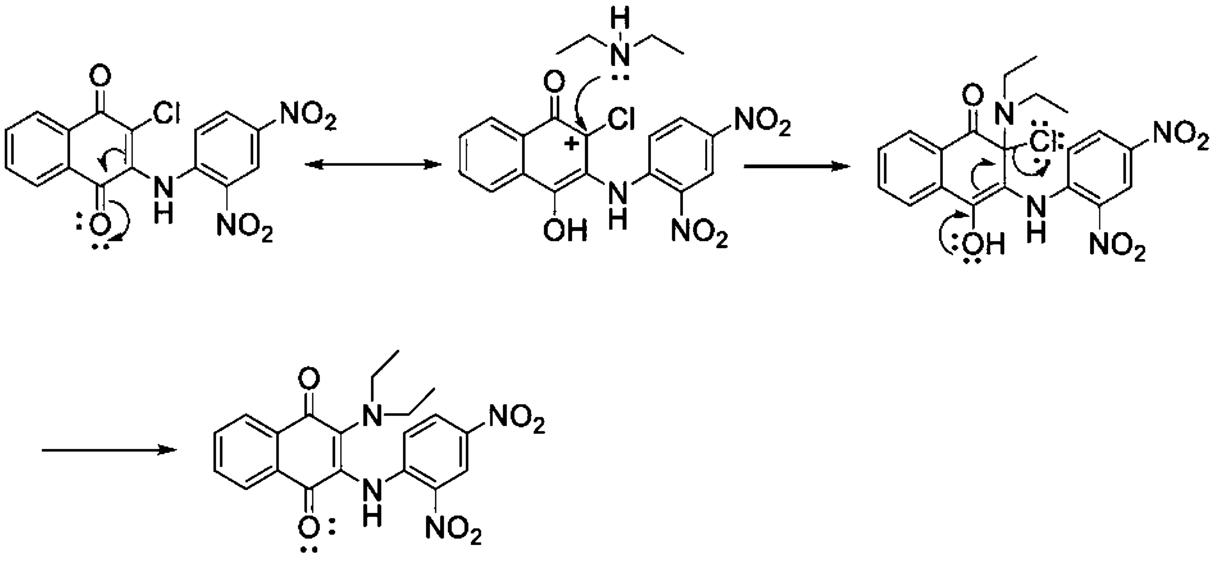

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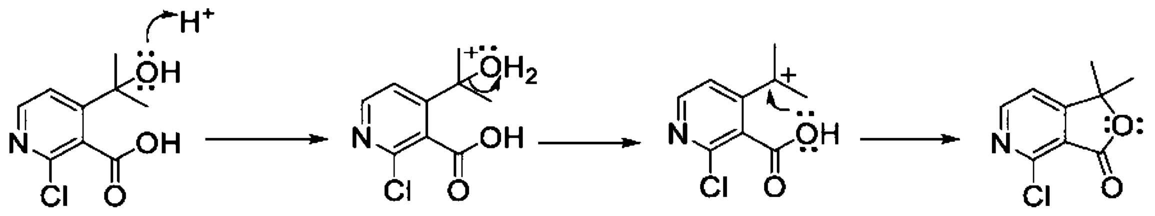

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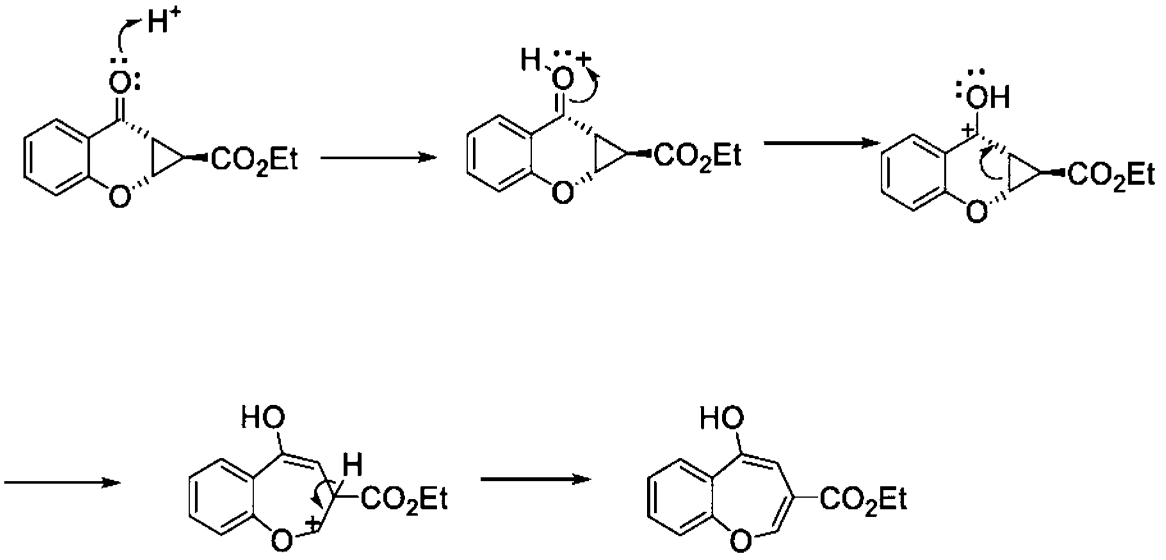

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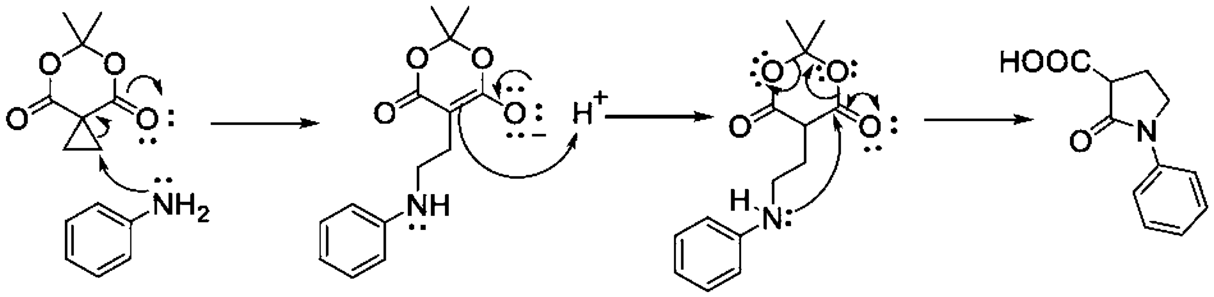

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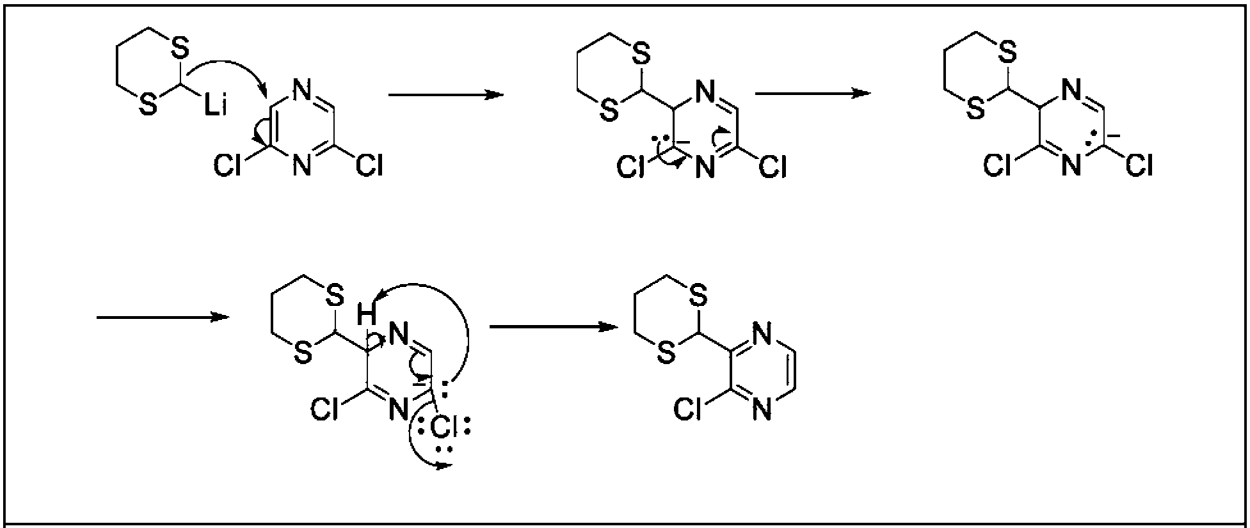

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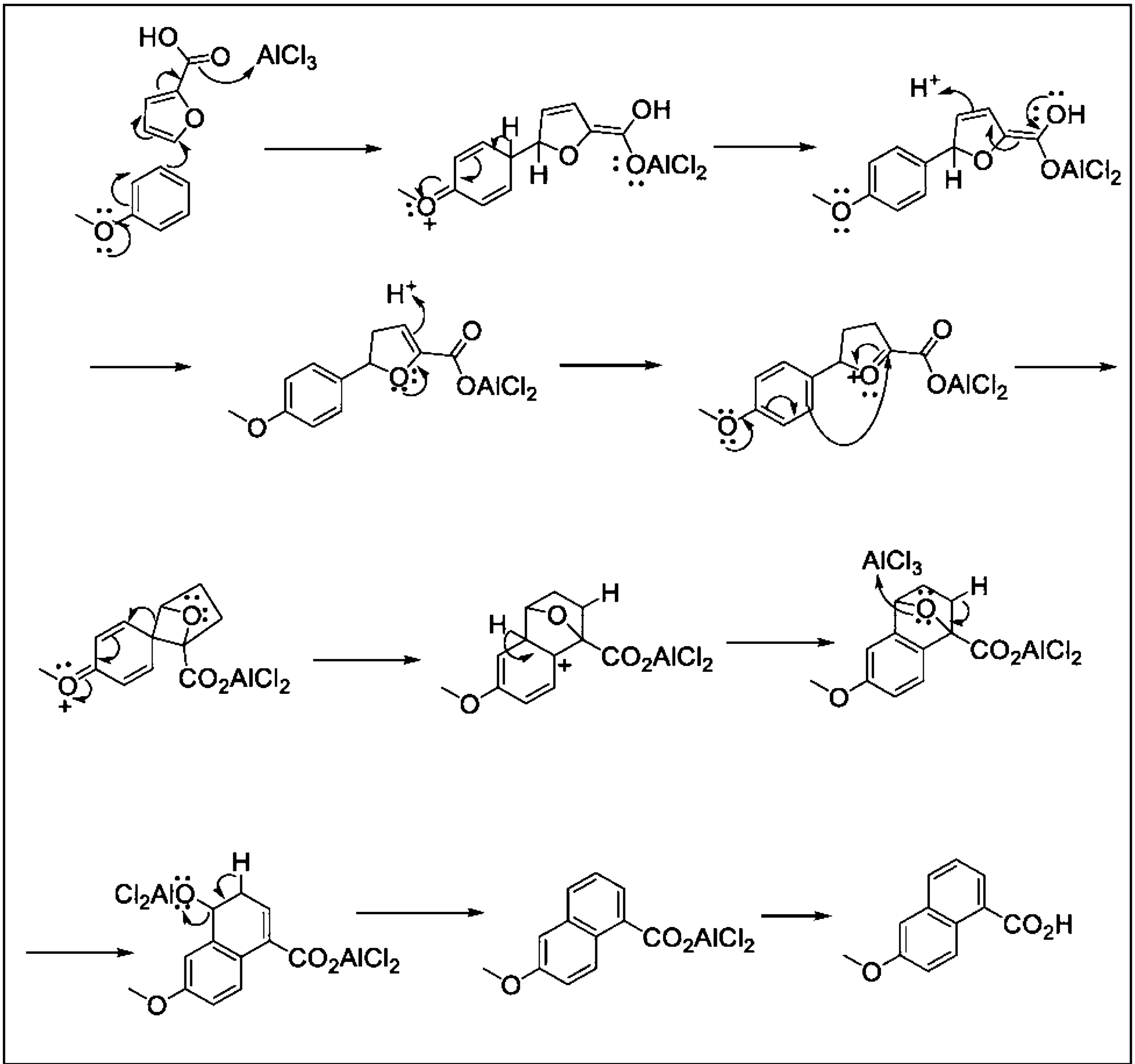

HO
O
AlCl3
O
O
H
H
O
OH
OAlCl2
O
H+
OH
O
H
OAlCl2
O
H+
O
O
OAlCl2
O
O
+O
O
OAlCl2
O
O
O
CO2AlCl2
+
H
O
H
+
O
CO2AlCl2
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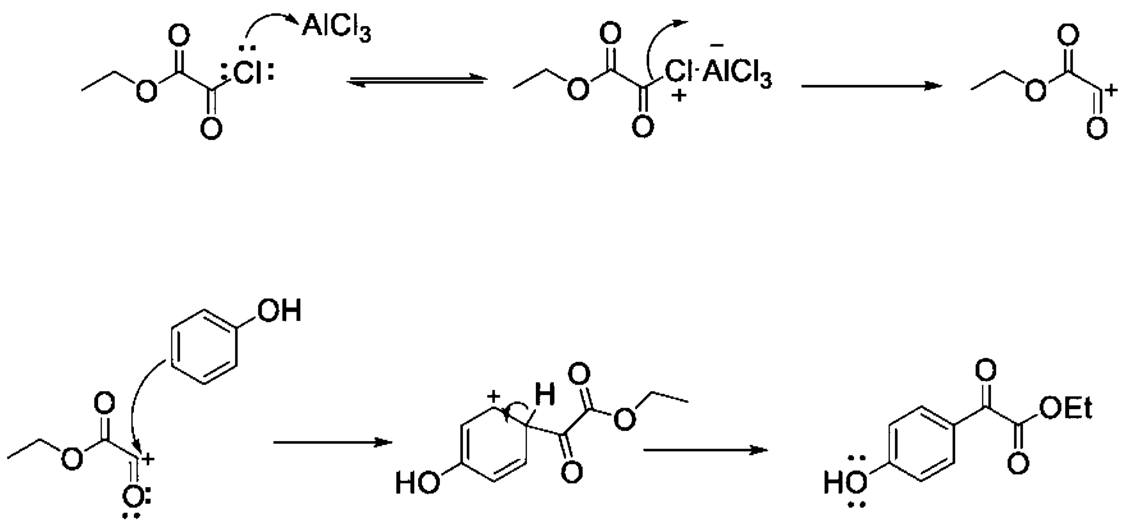
O
CO2H
O

193



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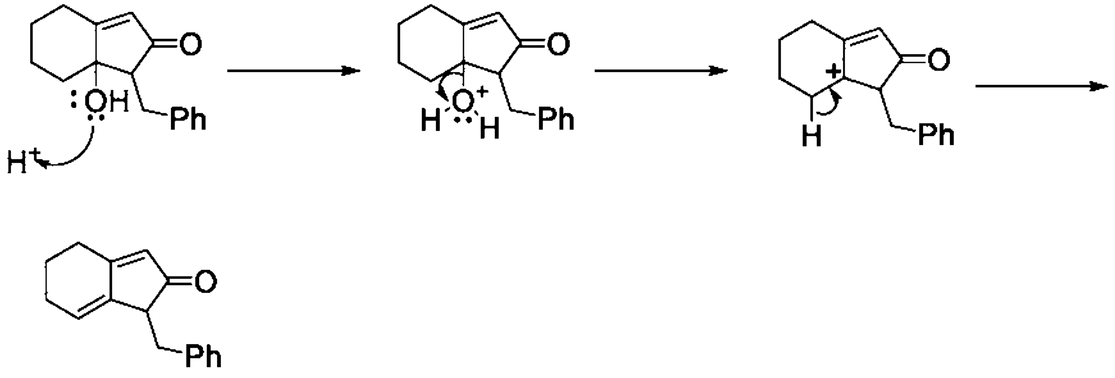

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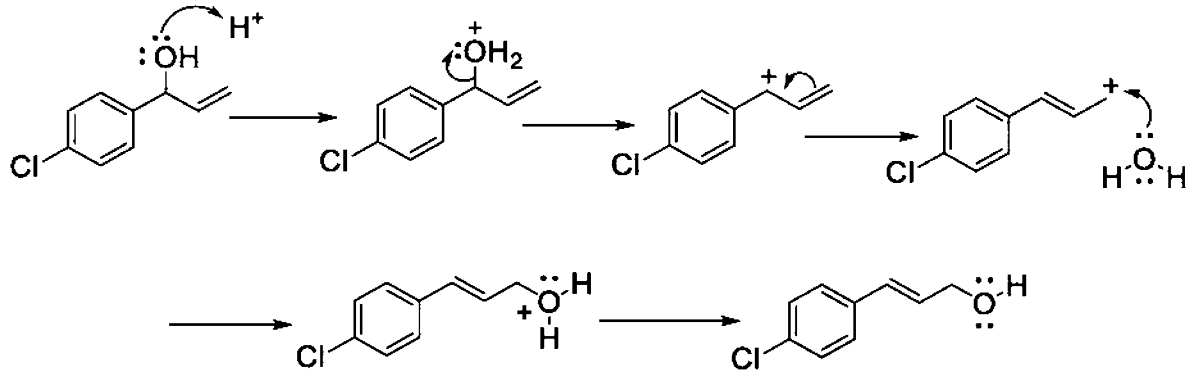

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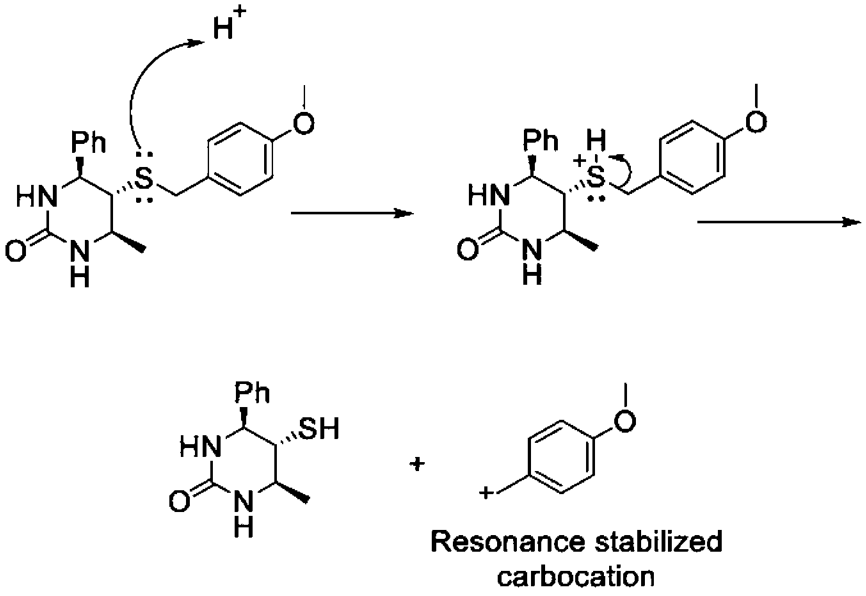
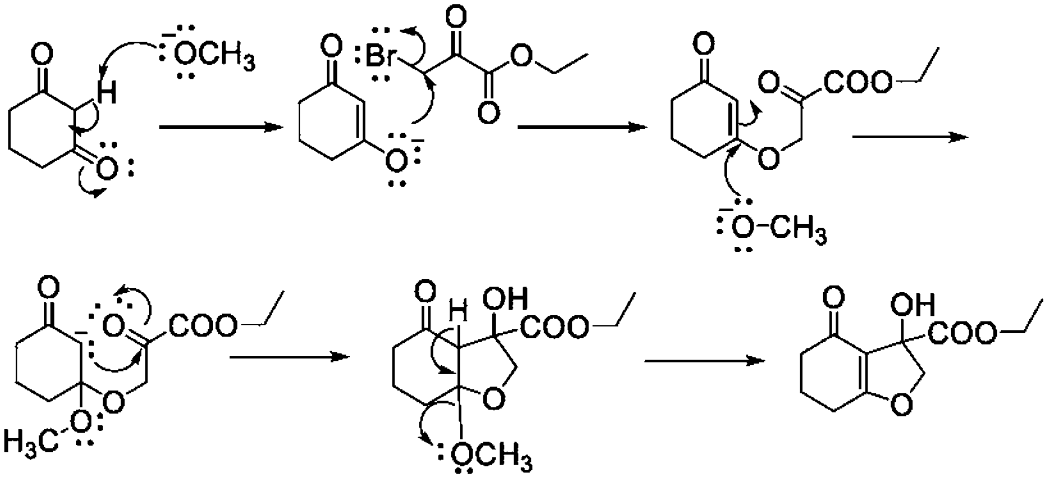


Exercise Draw all the resonance structuers of the *p*-methoxybenzyl carbocation.

197



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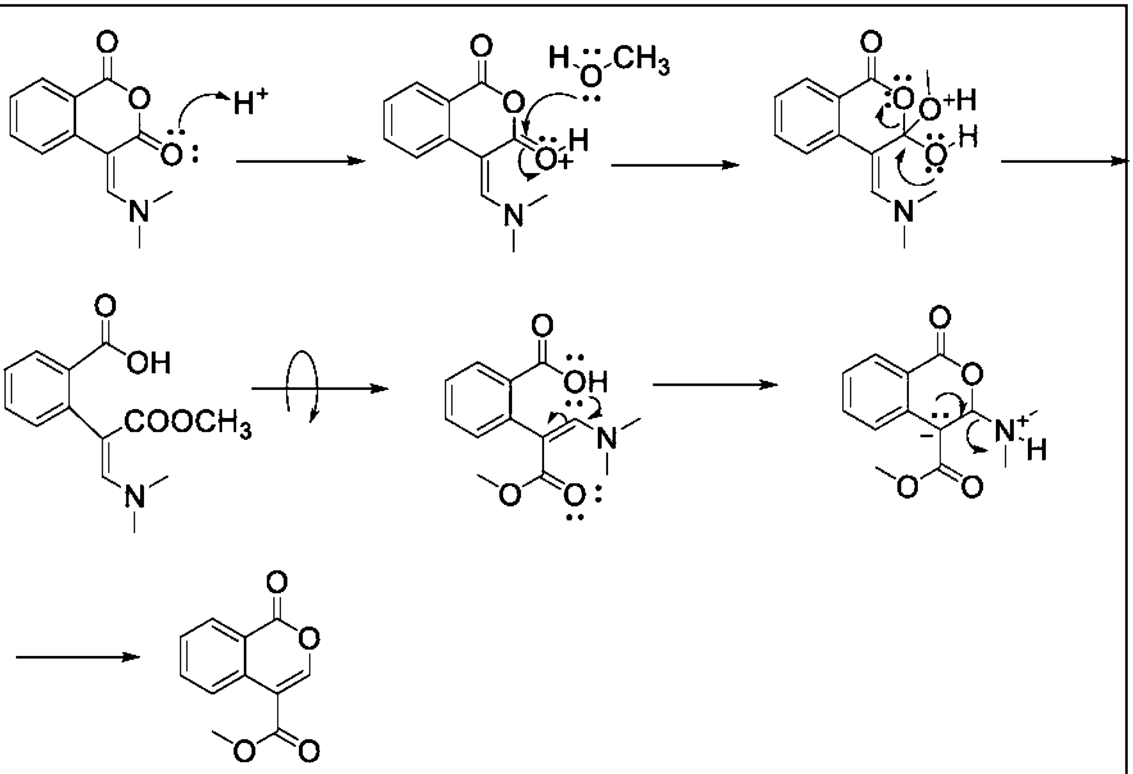

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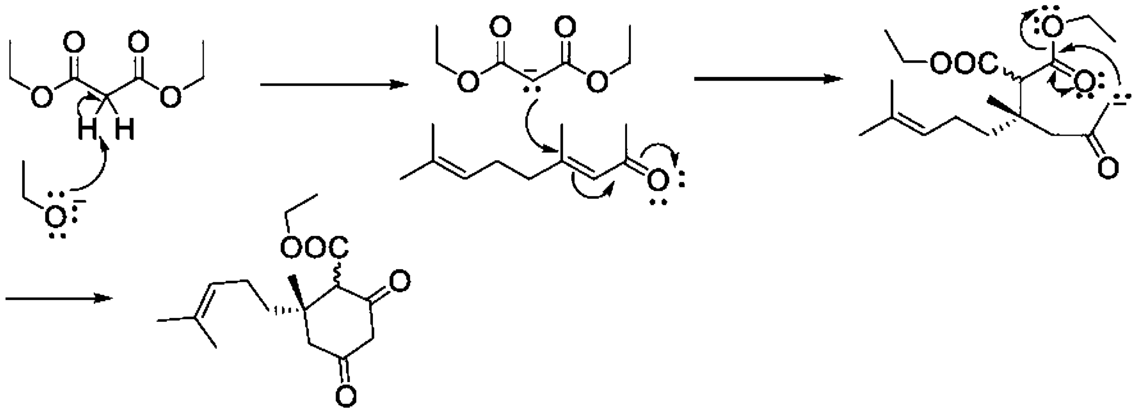

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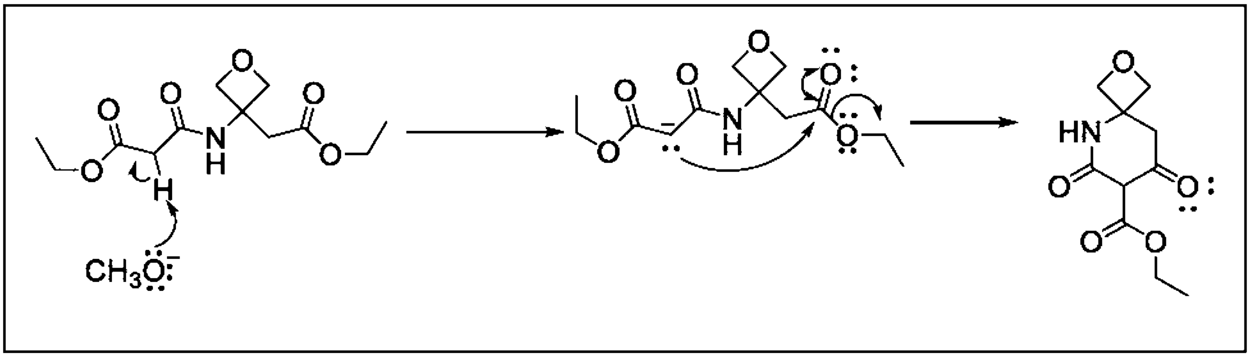
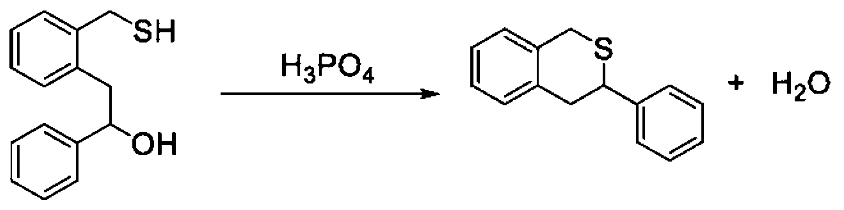
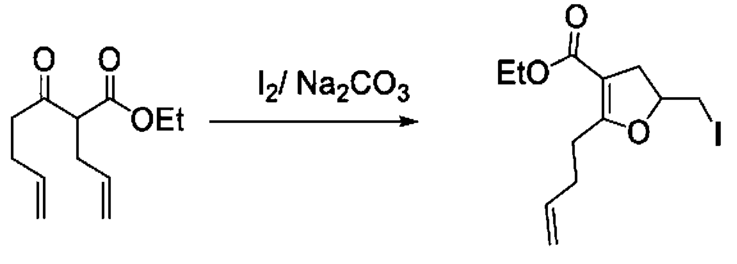
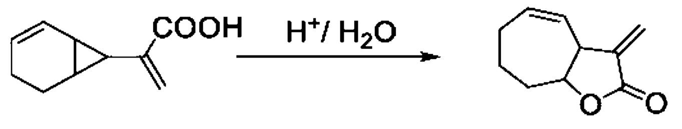
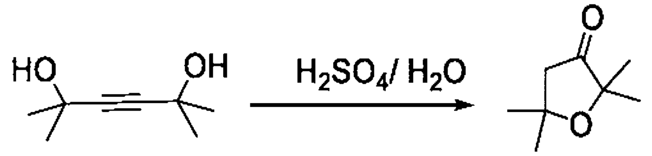
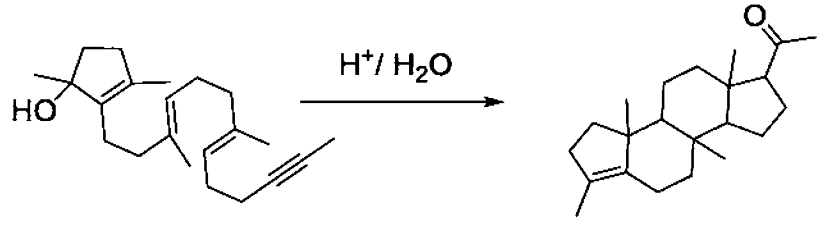
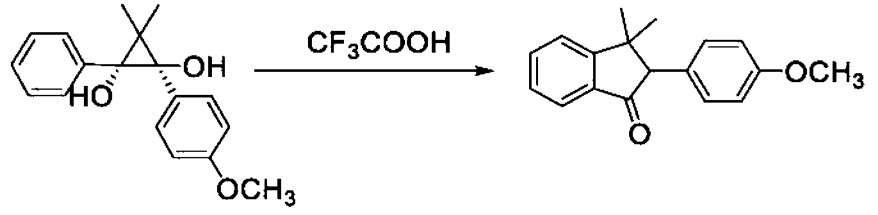
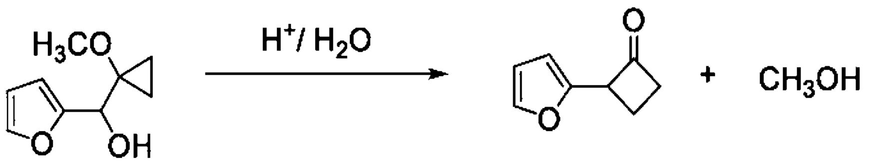
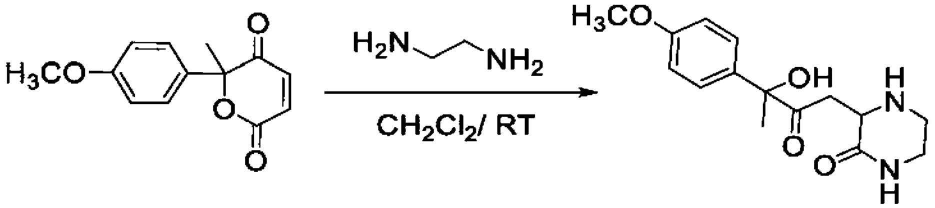
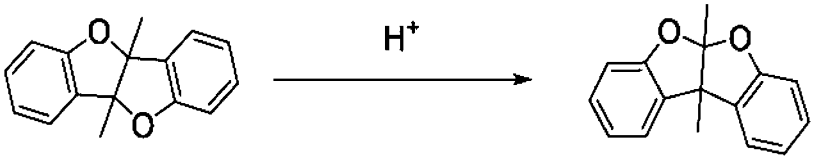
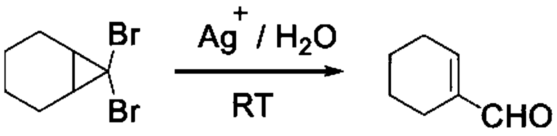
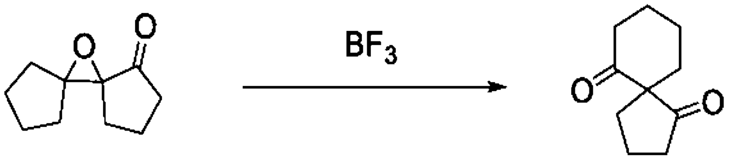
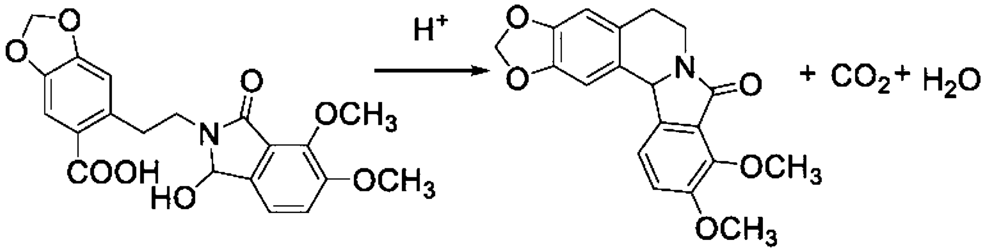
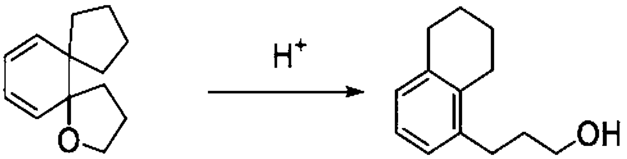
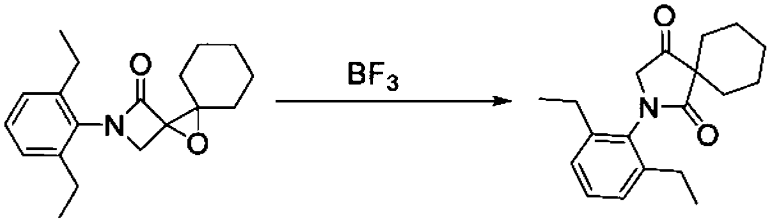
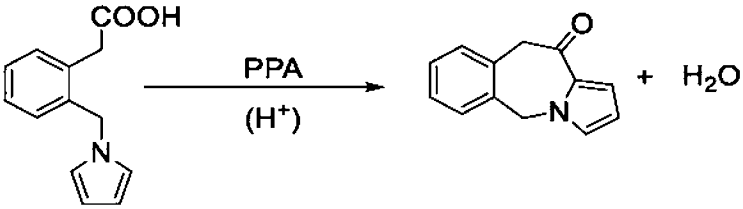
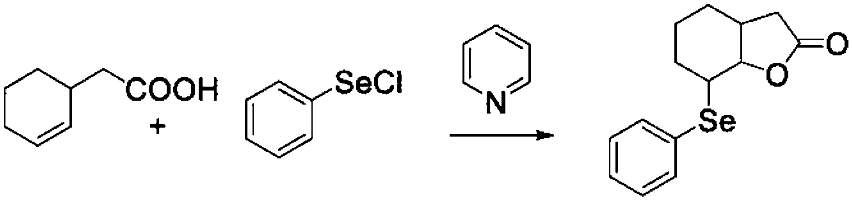
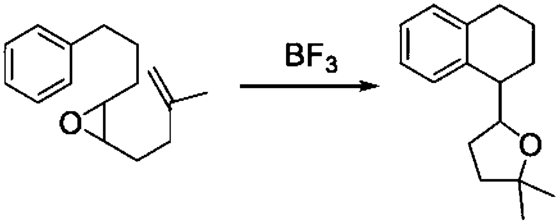
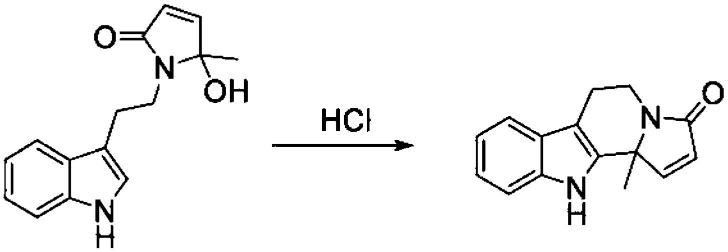

CH3O−
HN

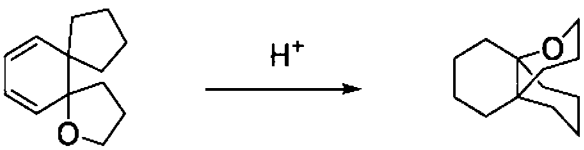
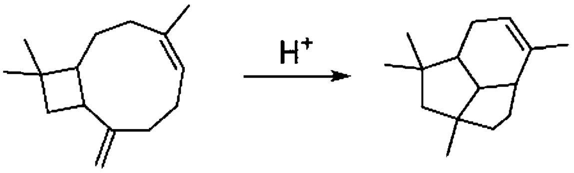
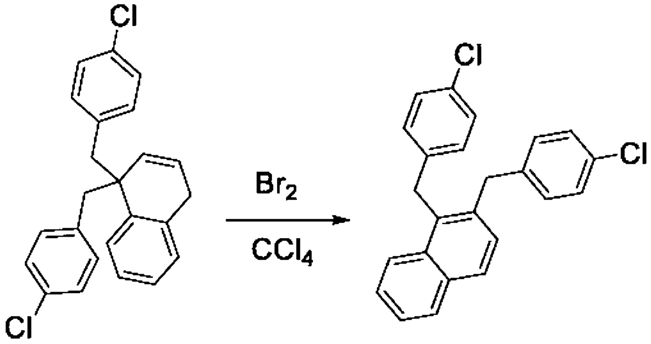
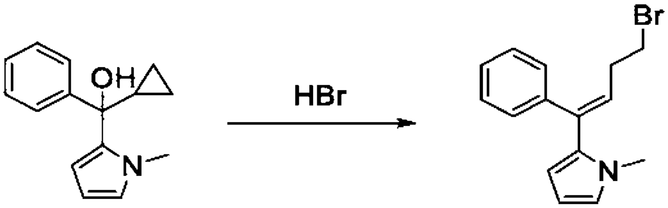
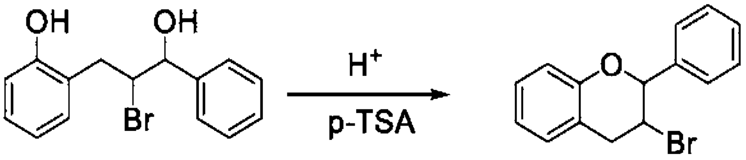
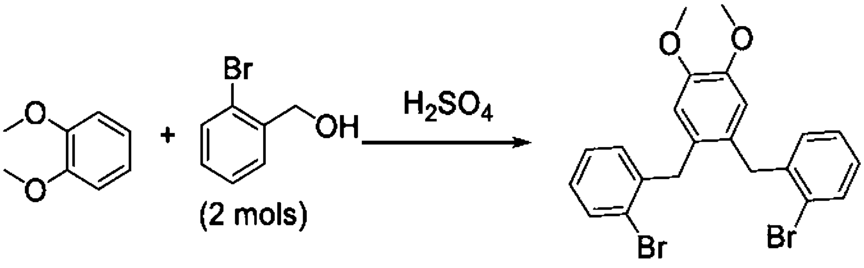
PART B

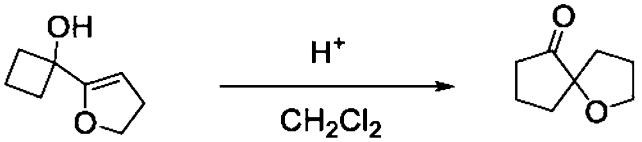
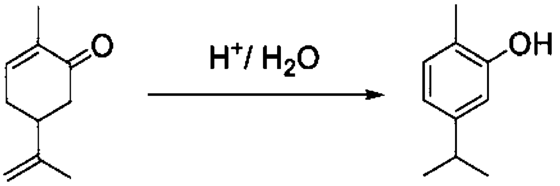
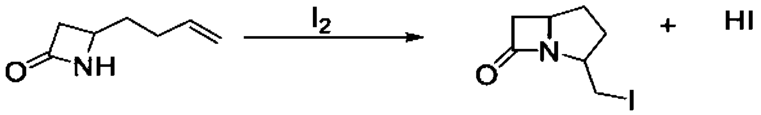
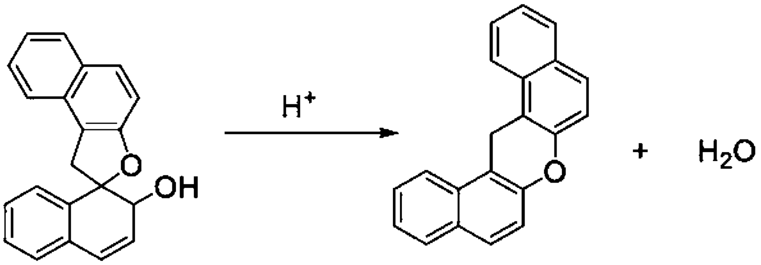
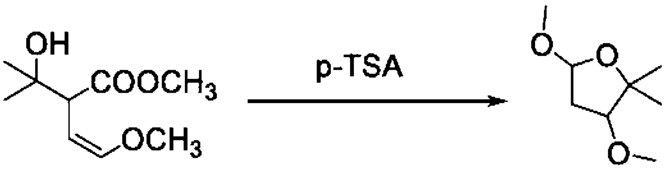
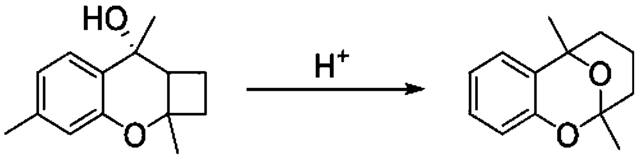
Questions 201-490

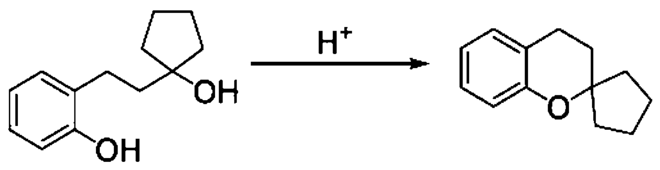
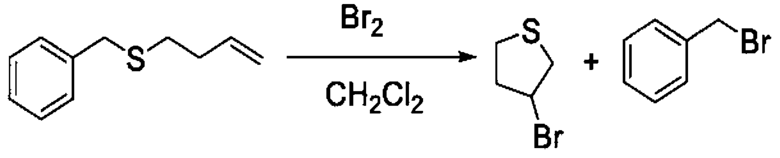
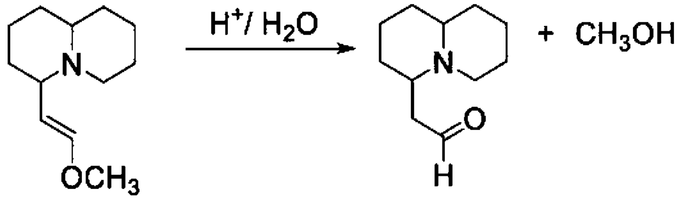
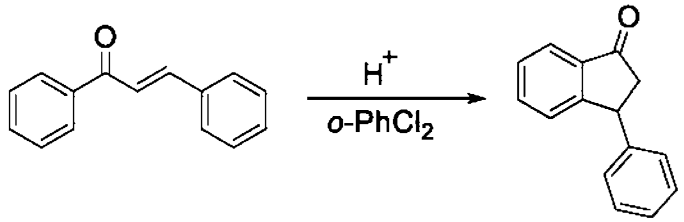
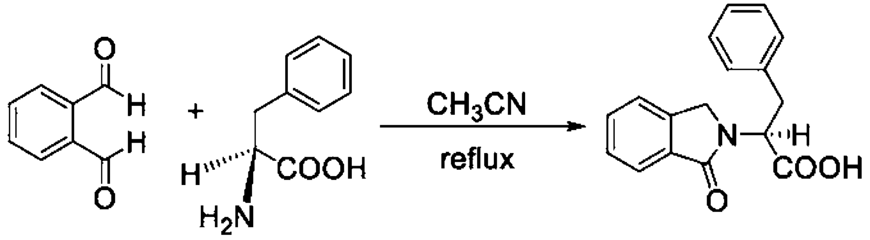
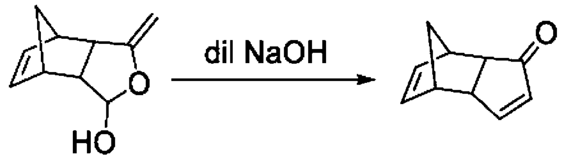
201	
202	
203	
204	
205	
206	

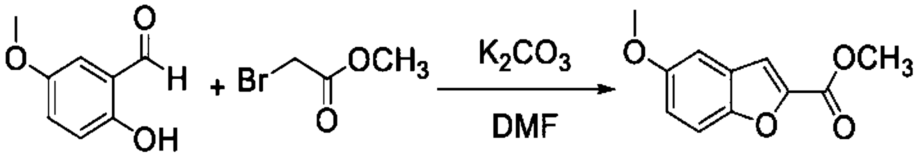
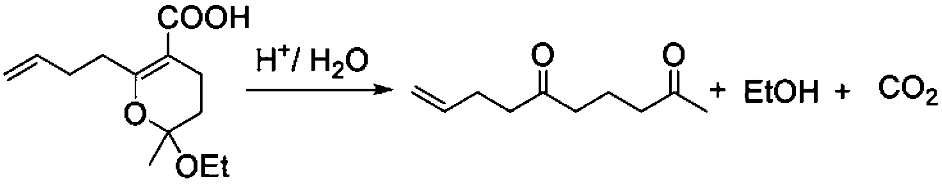
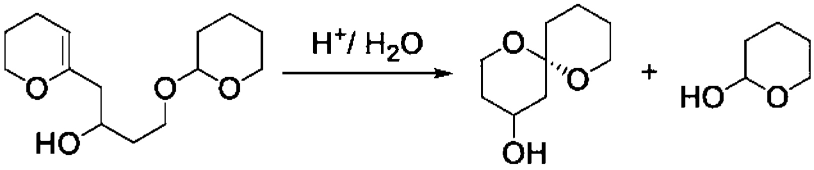
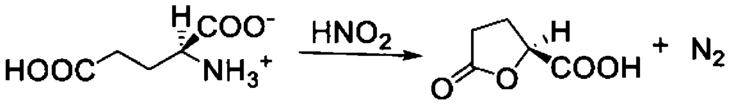
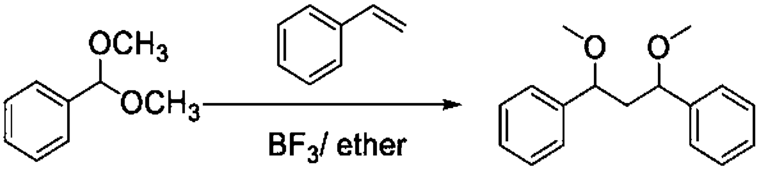
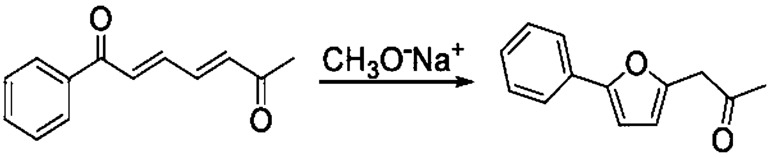
207	
208	
209	
210	
211	
212	

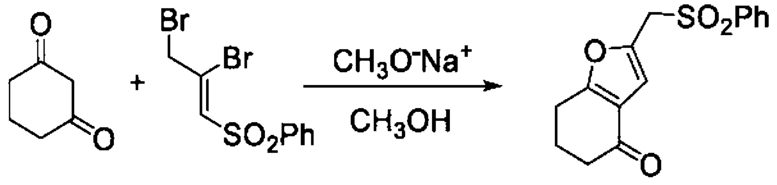
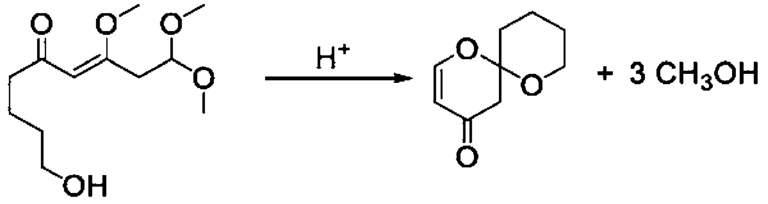
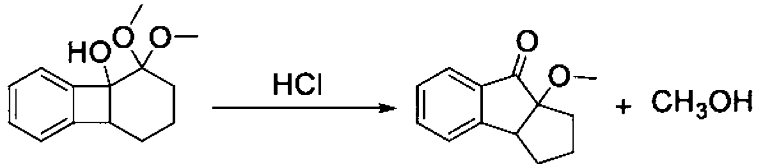
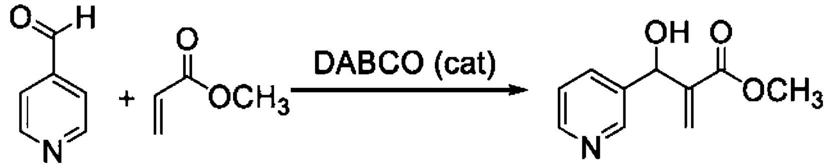
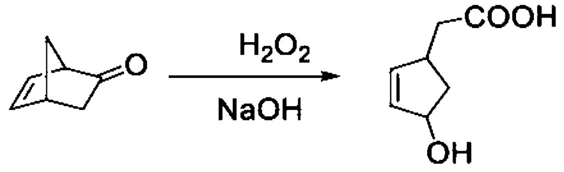
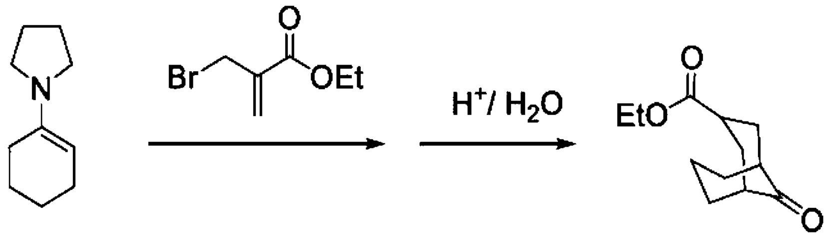
213	
214	
215	
216	
217	
218	

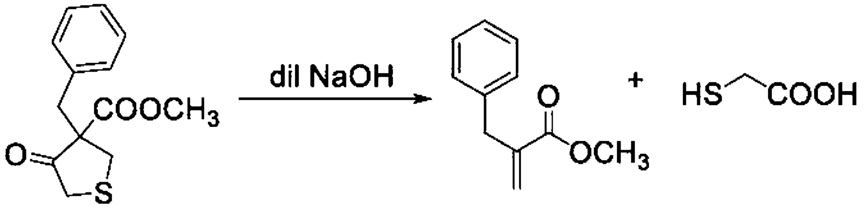
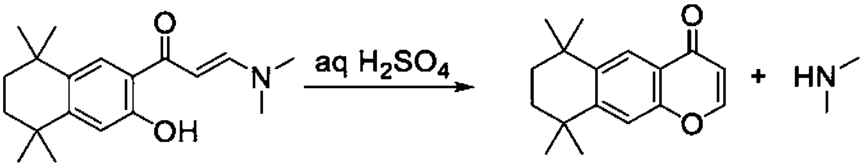
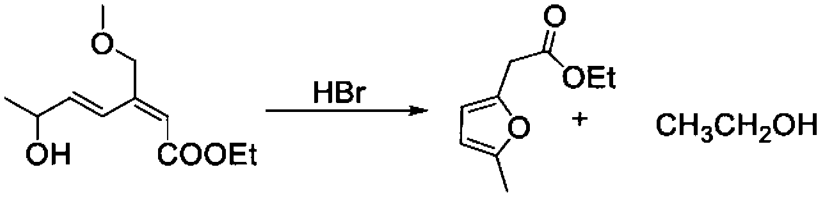
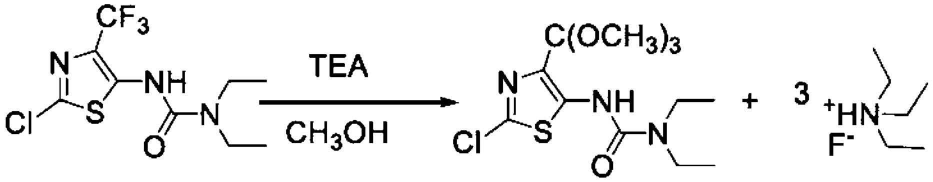
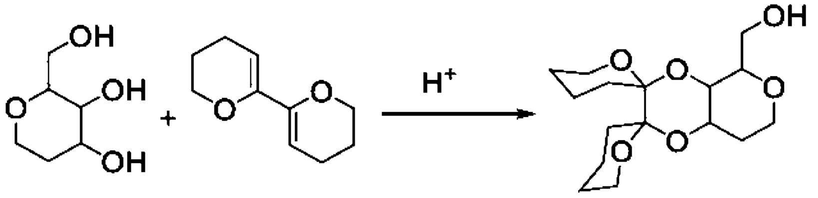
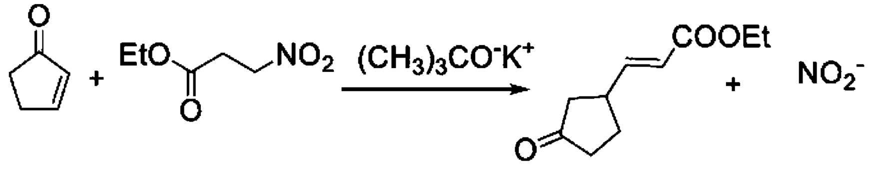
219	
220	
221	
222	
223	
224	

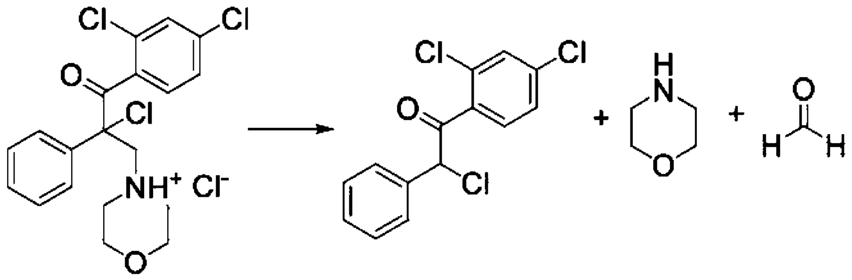
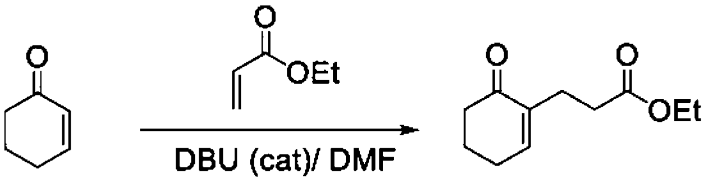
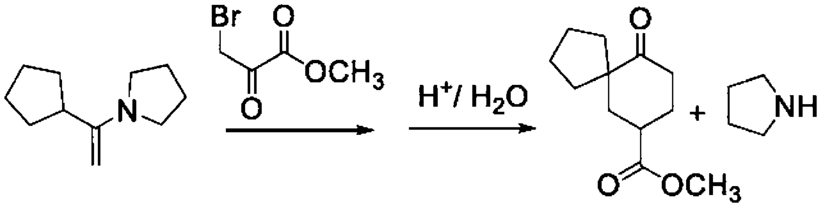
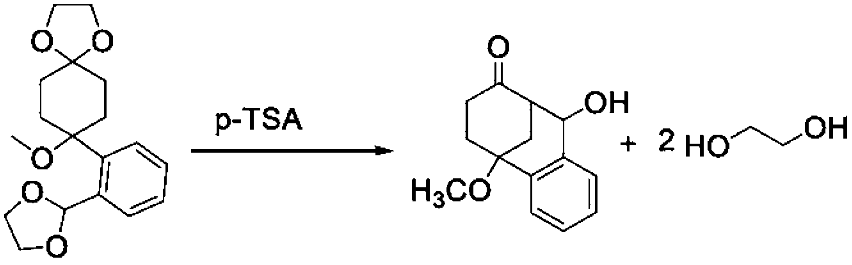
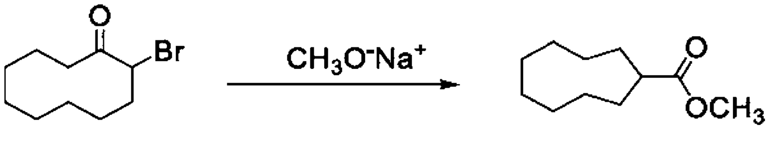
225	
226	
227	
228	
229	
230	

231	
232	
233	
234	
235	
236	

237	
238	
239	
240	
241	
242	

243	
244	
245	
246	
247	
248	

249	
250	
251	
252	
253	
254	

255	The compound shown below is stable when isolated as the hydrochloride salt. However, chromatography on silica gel yields the products shown below. Write a mechanism that explains the formation of these products (Hint: silica gel tends to absorb moisture) 
256	
257	
258	
259	

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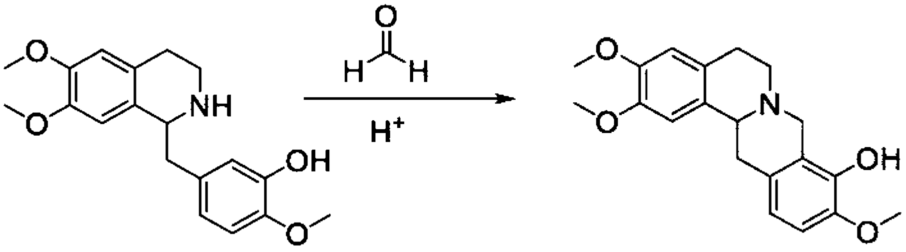
<tr><td>260</td><td>
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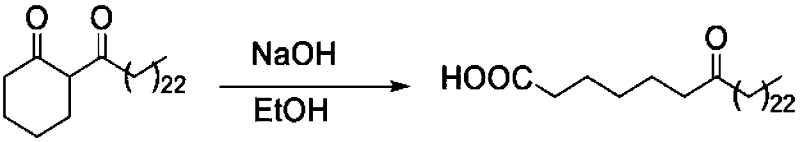
<tr><td>261</td><td>
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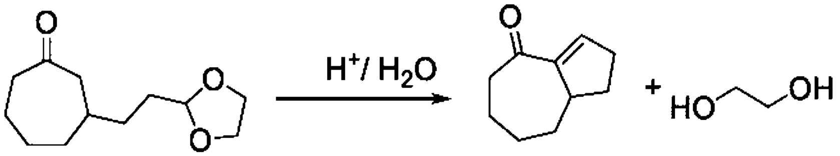
<tr><td>262</td><td>
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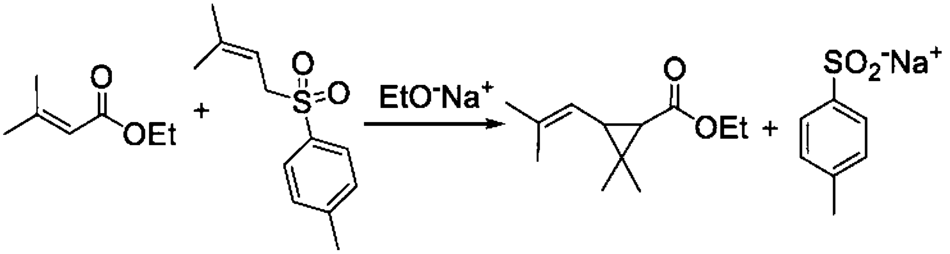
<tr><td>263</td><td>
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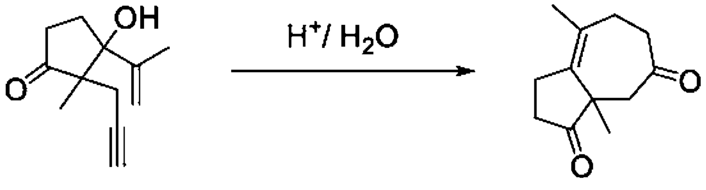
<tr><td>264</td><td>
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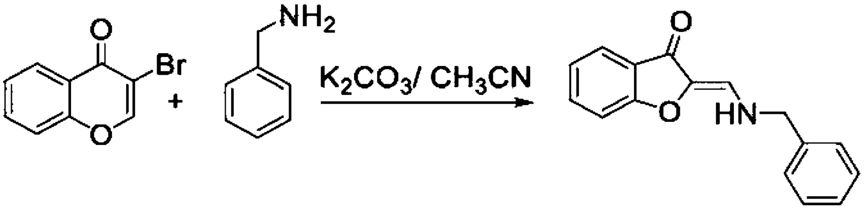
<tr><td>265</td><td>
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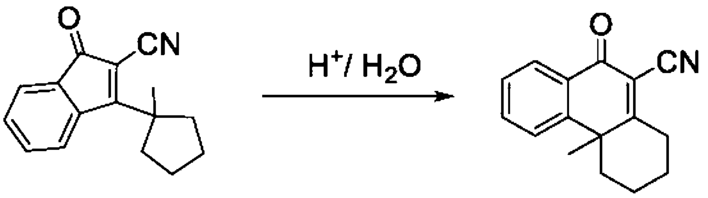
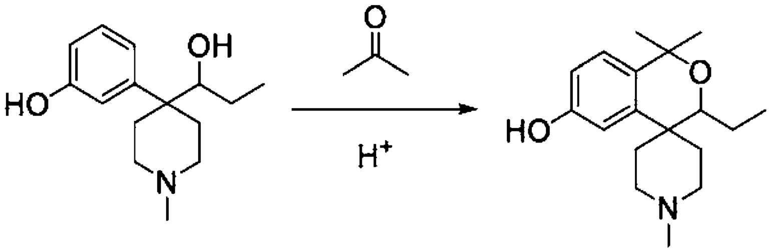
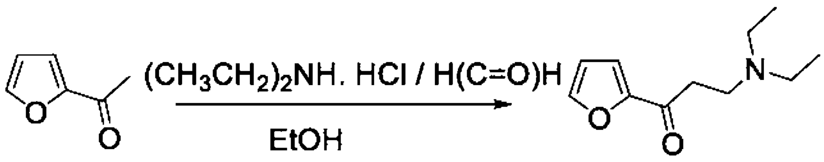
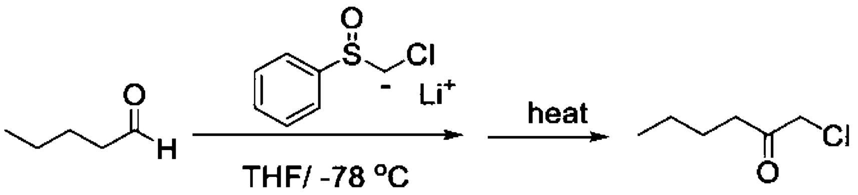
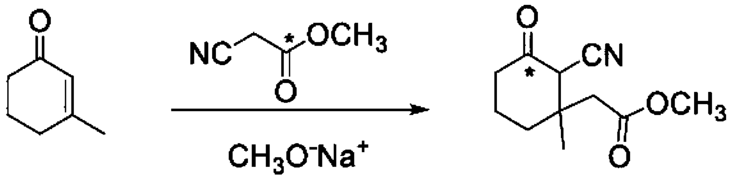
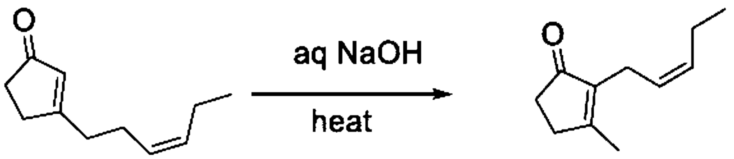
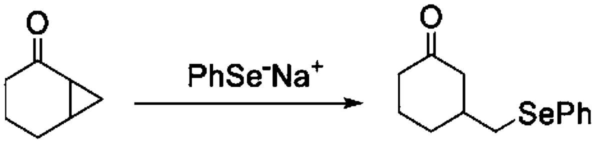
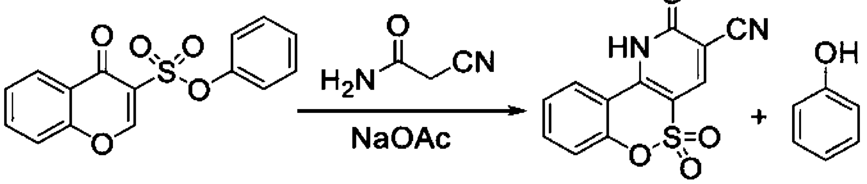
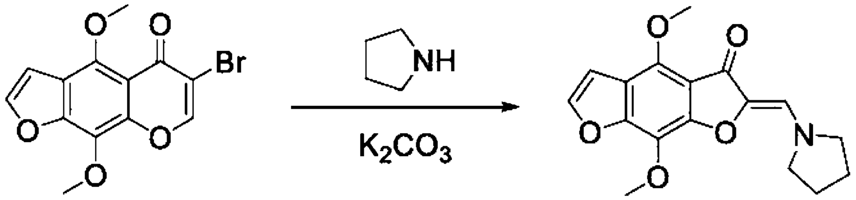
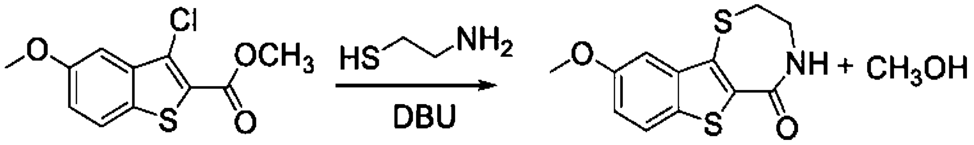
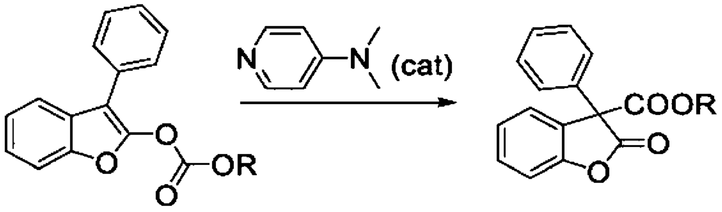
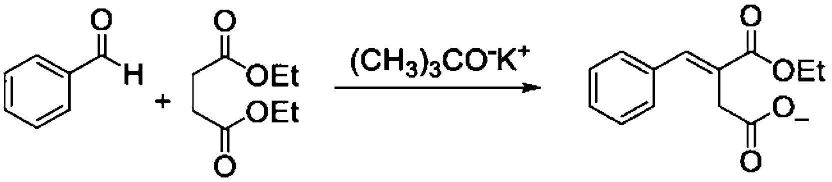
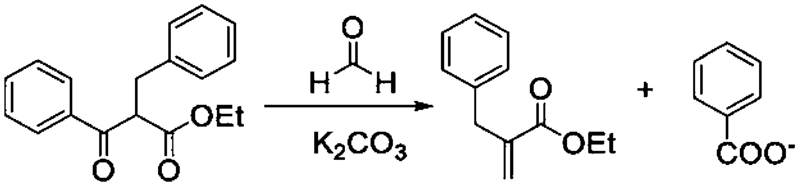
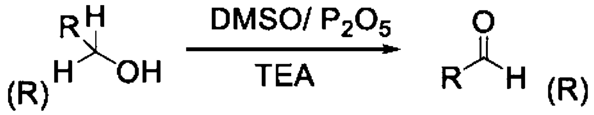
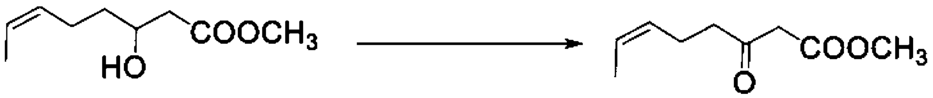
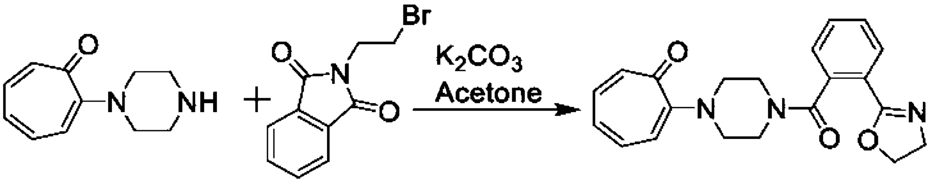
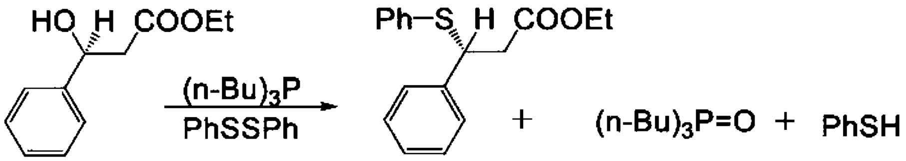
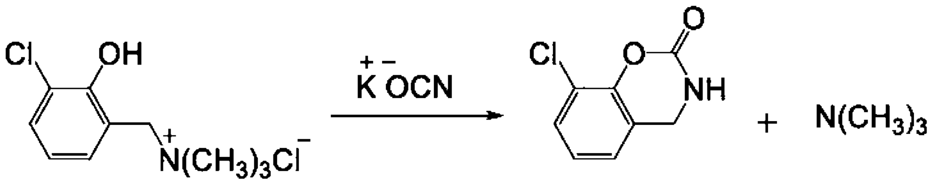
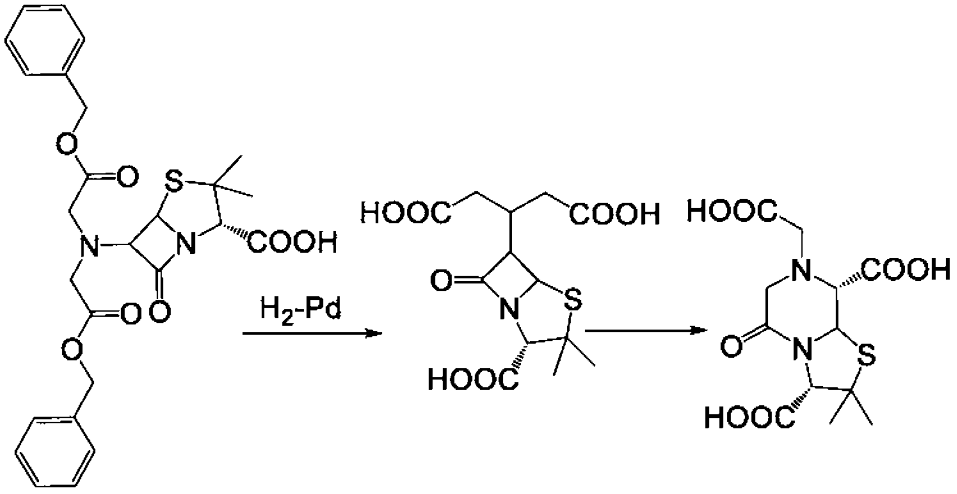
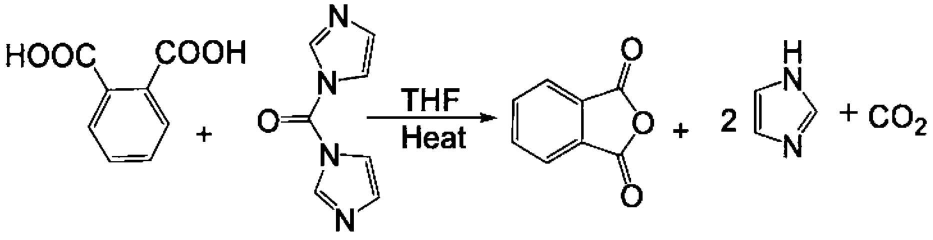
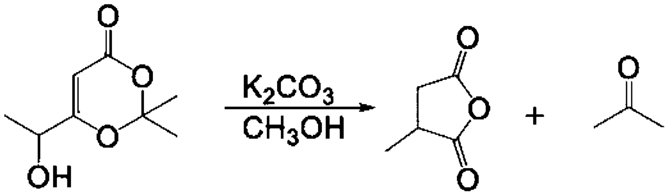
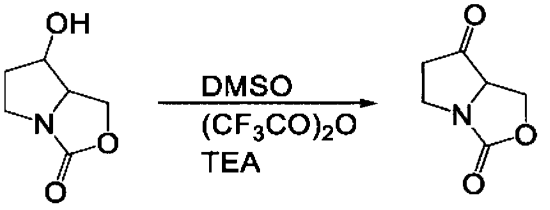
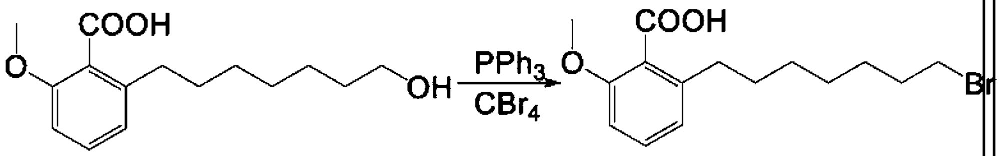
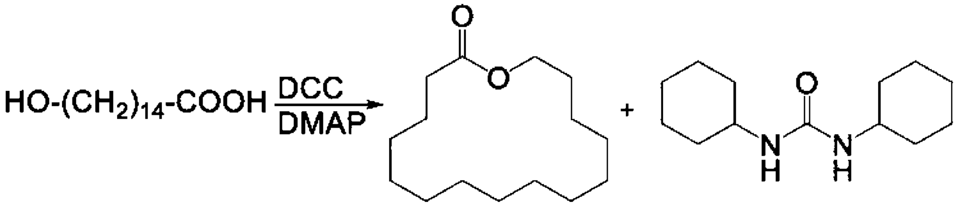
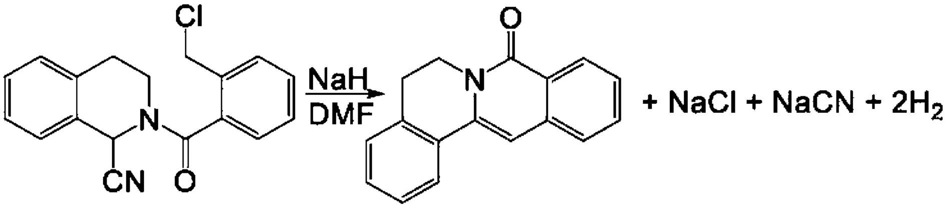
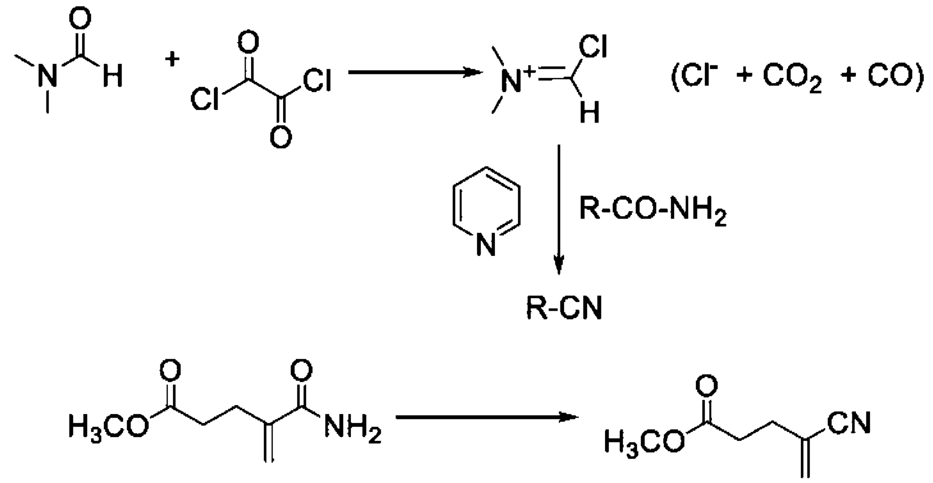
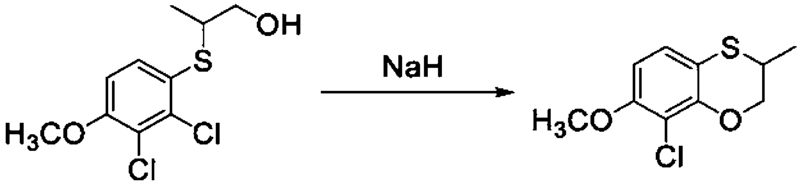
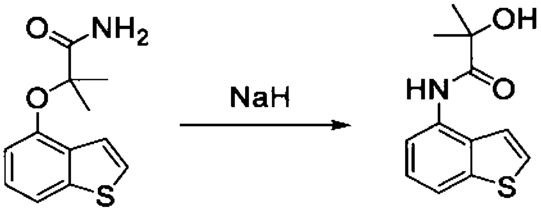
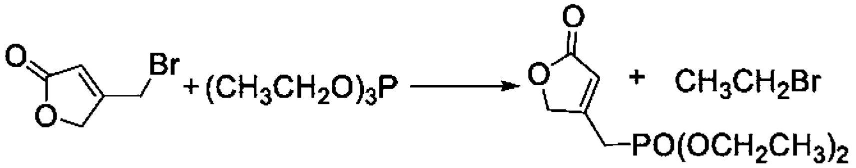
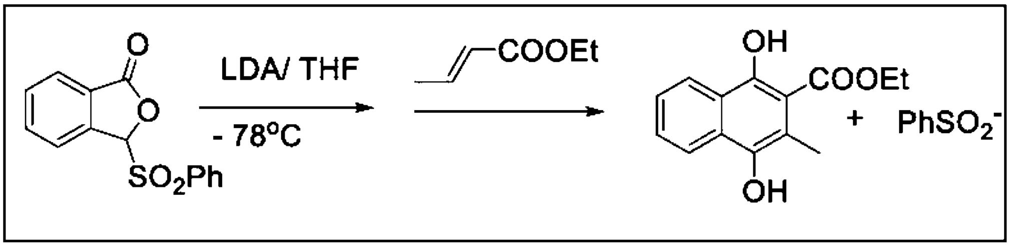
266	
267	
268	
269	Aldehydes can be converted into alpha-chloromethyl ketones by reacting an aldehyde with the reagent shown below, and refluxing the product formed in toluene. Write a mechanism for this transformation. 
270	 (mechanism must account for the location of (*) carbon)

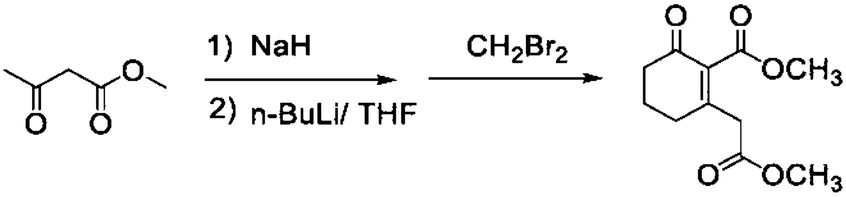
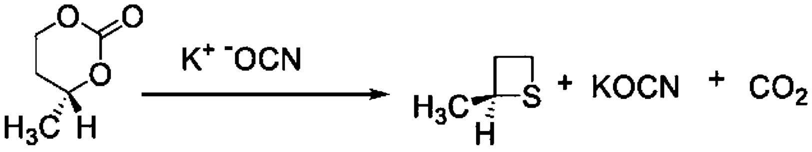
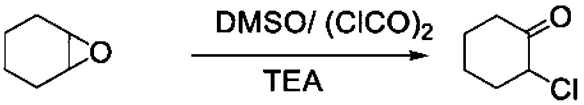
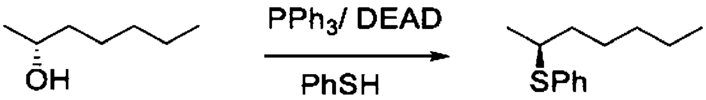
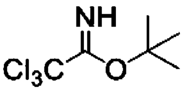
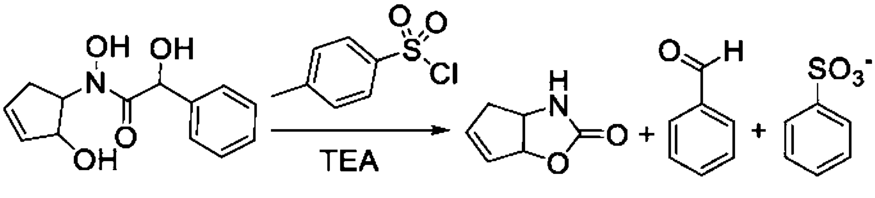
271	
272	
273	
274	
275	
276	

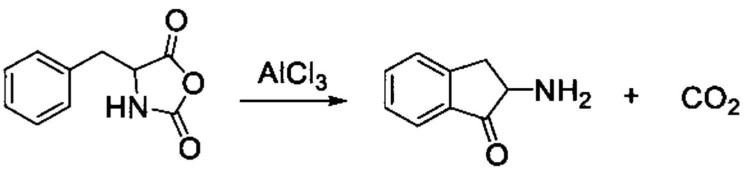
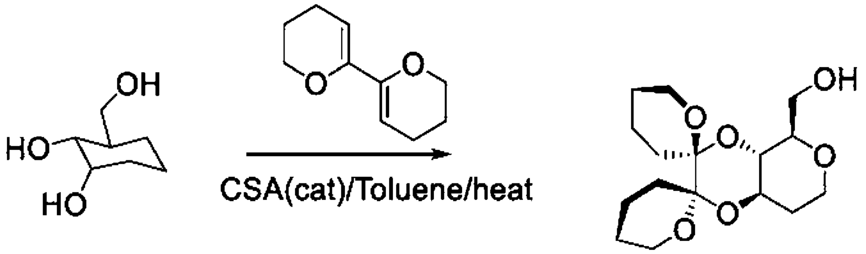
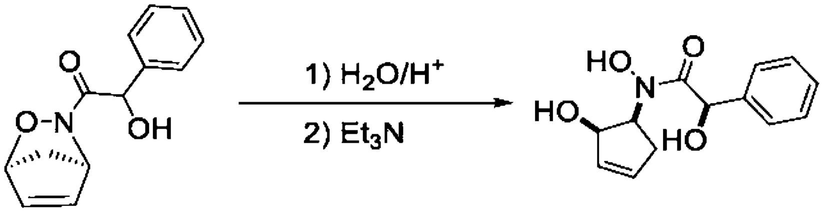
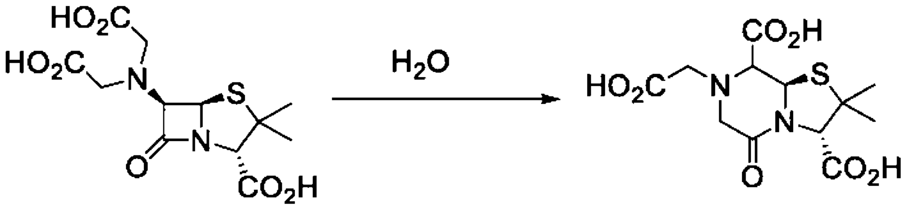
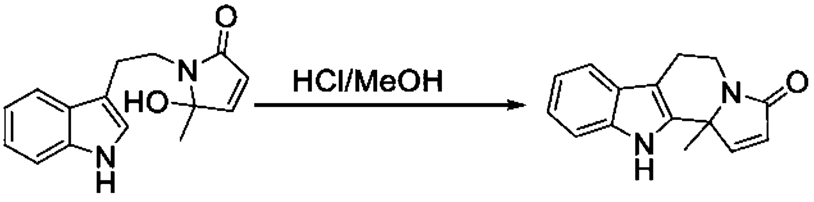
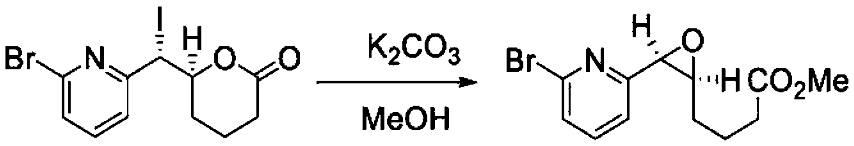
277	
278	
279	Primary and secondary alcohols can be readily oxidized by dimethyl sulfoxide/phosphorus pentoxide/triethylamine under mild conditions (an example is shown below). Use your knowledge of Lewis structures and Lewis acid/base reactions to write a reasonable mechanism for this reaction.  
280	
281	

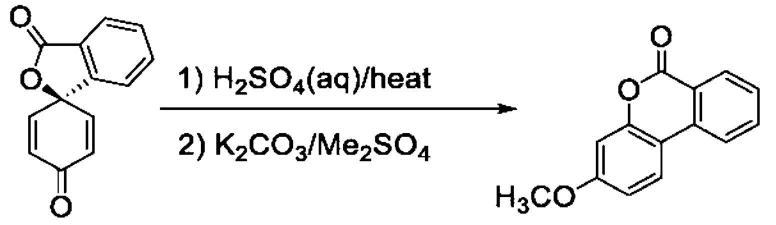
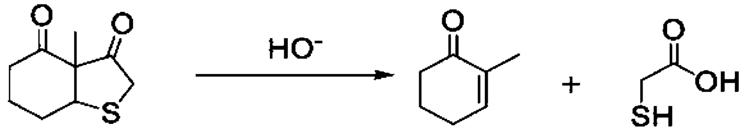
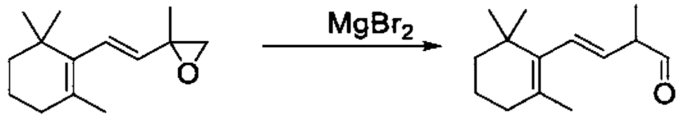
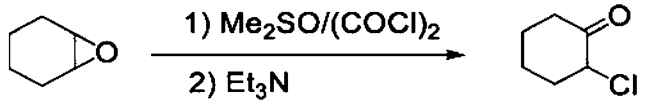
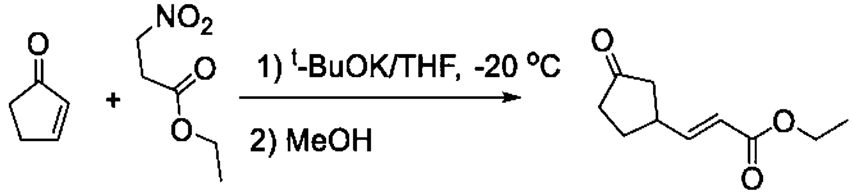
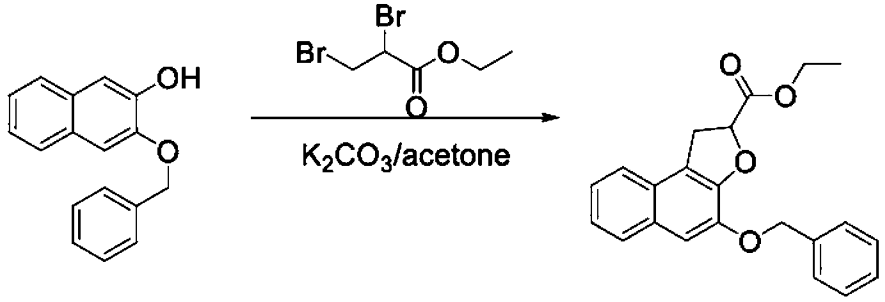
282	
283	
284	
285	
286	

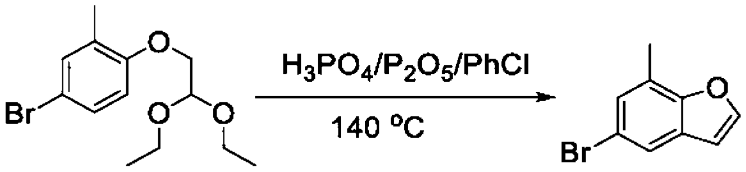
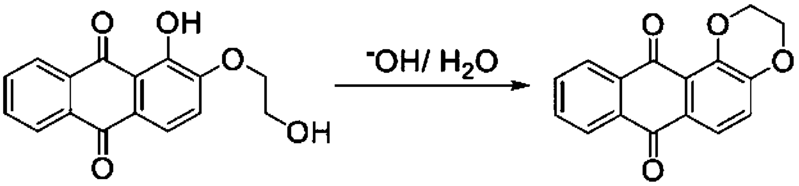
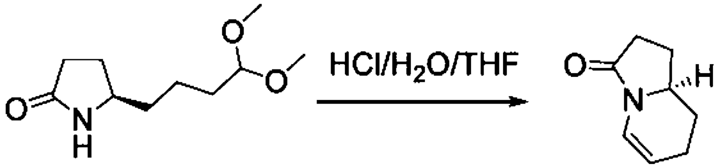
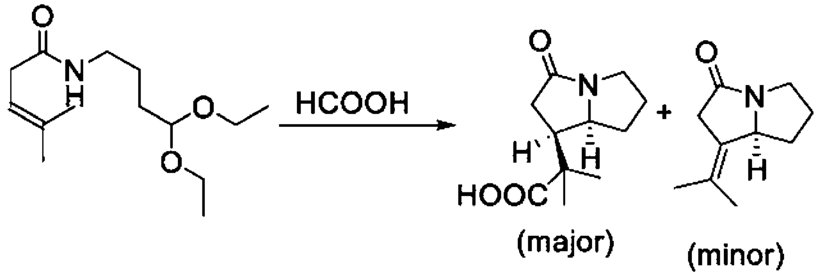
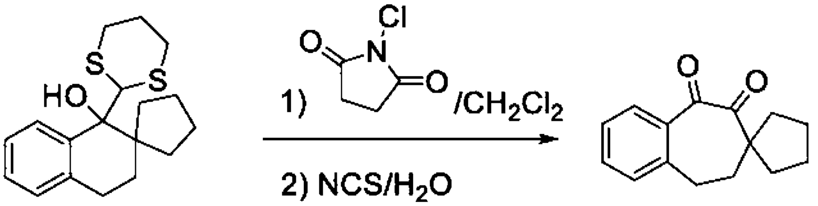
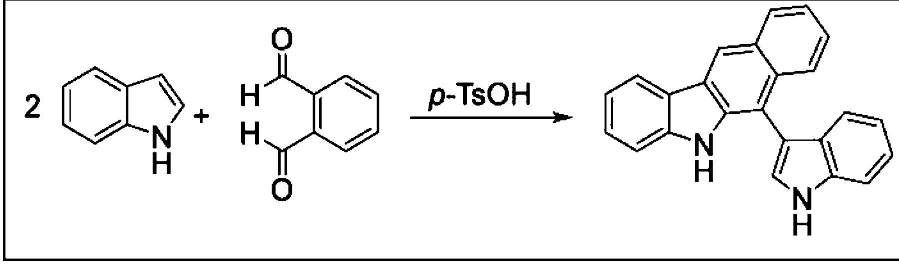
287	Alcohols can be readily converted to alkyl chlorides or bromides under mild conditions using PPh_3 /CCl_4 or PPh_3/$CHBr_3$, respectively (a specific example is shown below). Write a mechanism for this transformation $R\text{-}CH_2\text{-}OH \xrightarrow[CX_4]{PPh_3} R\text{-}CH_2\text{-}X + O{=}PPh_3$ (X=Cl. Br) 
288	
289	
290	Primary amides can be readily dehydrated under mild conditions using chloromethylene iminium salts called *Vilsmeier reagents* to form the corresponding nitriles. When dimethyl formamide (DMF) is treated with oxalyl chloride it forms a *Vilsmeier* reagent which is then reacted with primary amines in the presence of pyridine to yield the corresponding nitrile as shown below. Write a mechanism for the formation of the Vilsmeier reagent and a second mechanism for the formation of the nitrile.

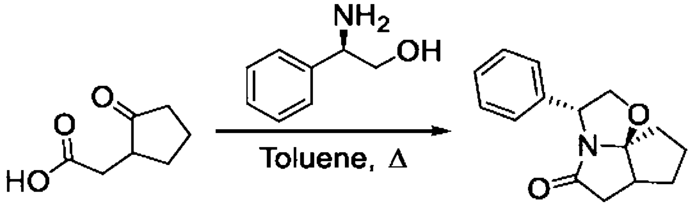
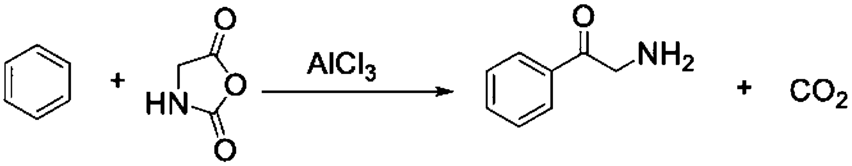
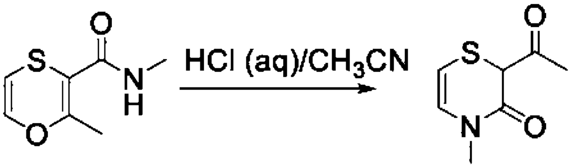
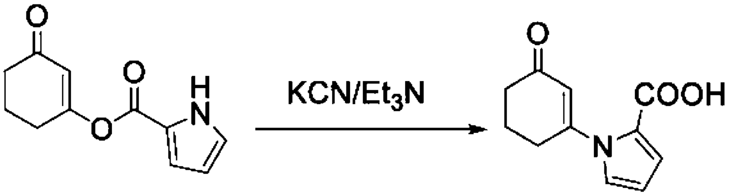
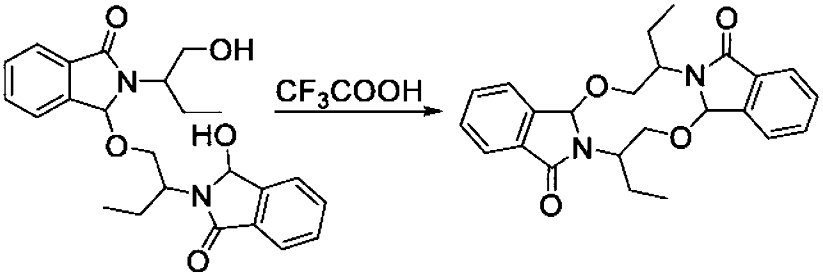
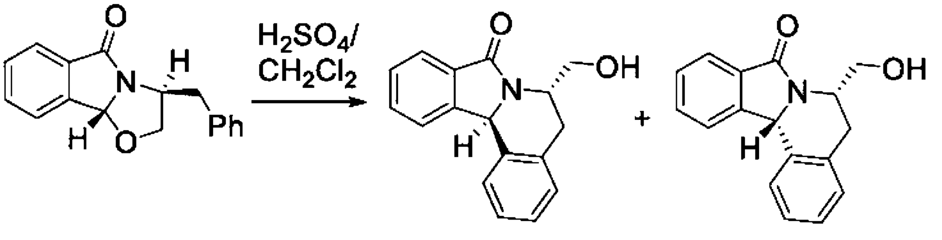
	
291	
292	
293	
294	

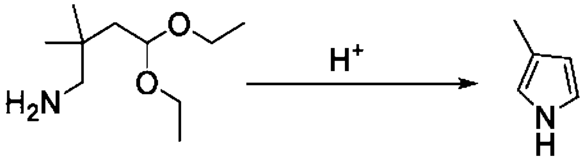
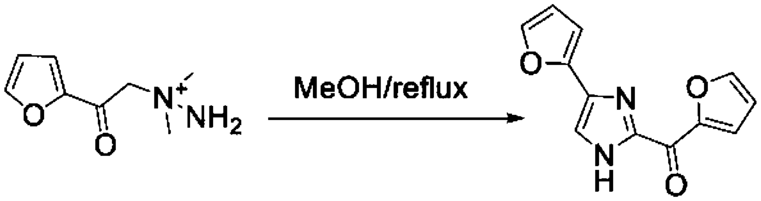
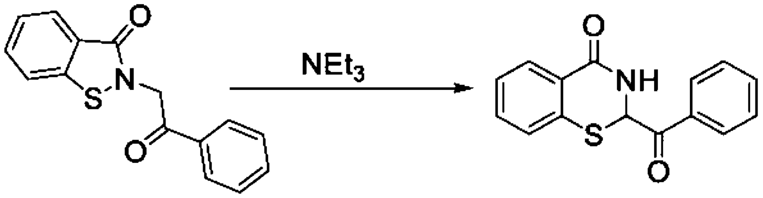
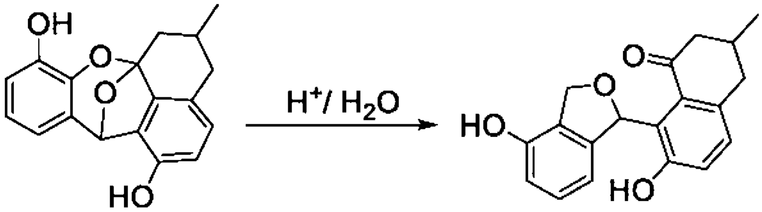
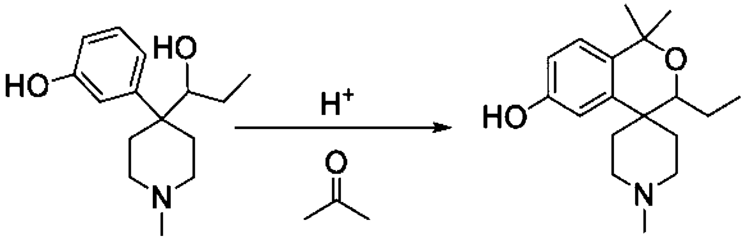
295	
296	
297	
298	
299	t-Butyl ethers and esters can be readily made from the corresponding alcohols and carboxylic acids by mixing the reagent shown below with t-butanol in the presence of a catalytic amount of BF_3 etherate. Write a mechanism for these transformations. 
300	

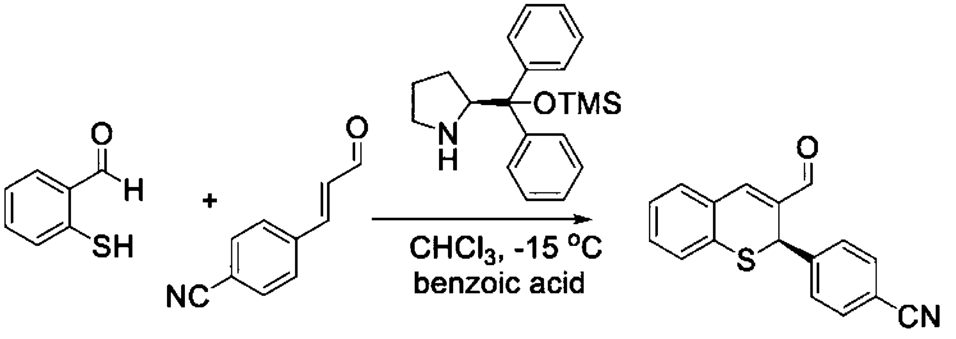
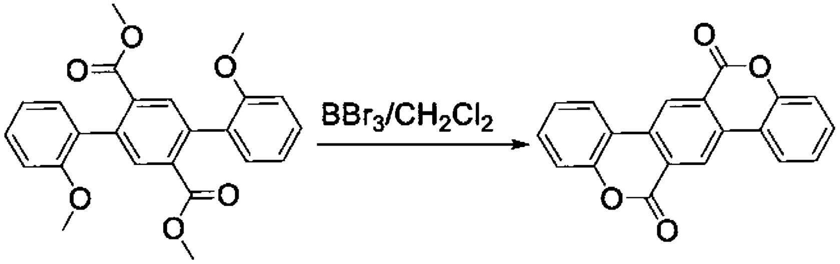
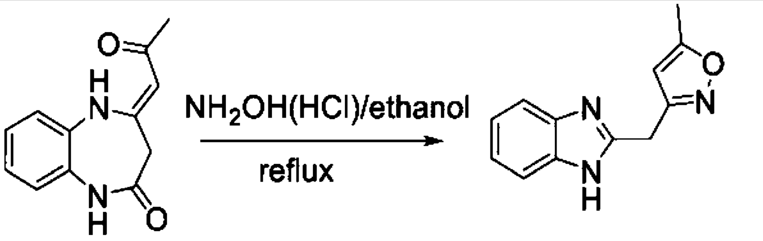
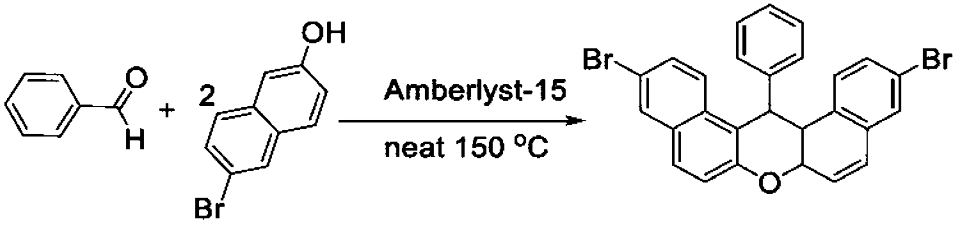
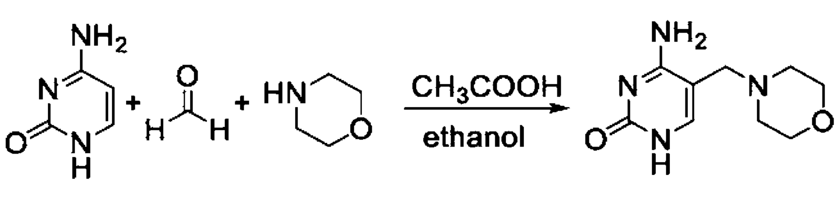
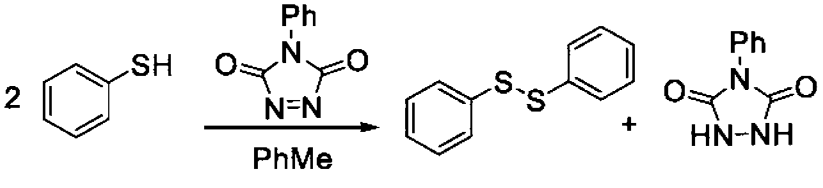
301	
302	
303	
304	
305	
306	

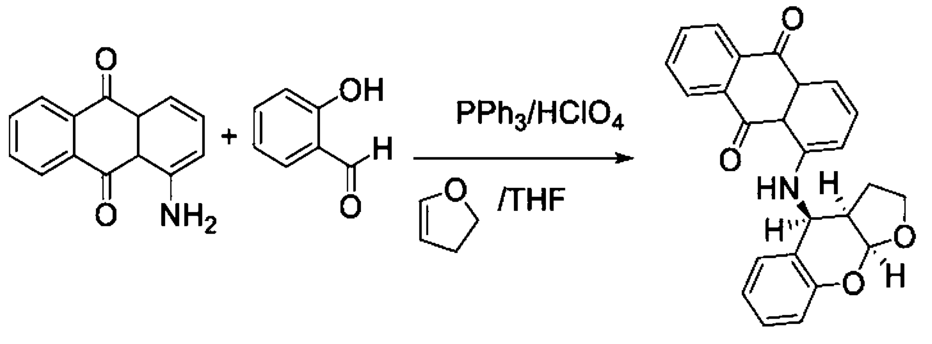
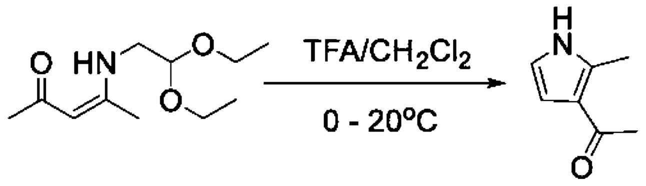
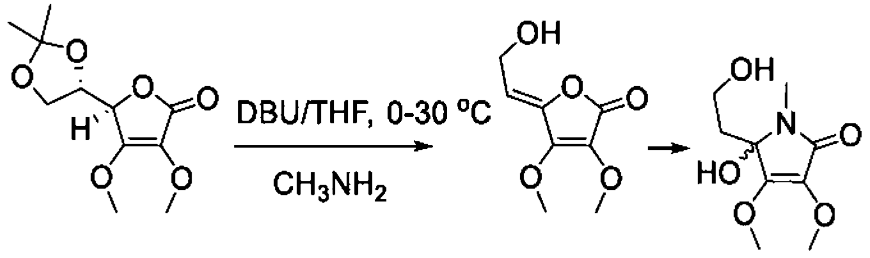
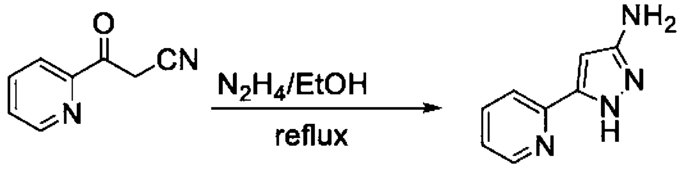
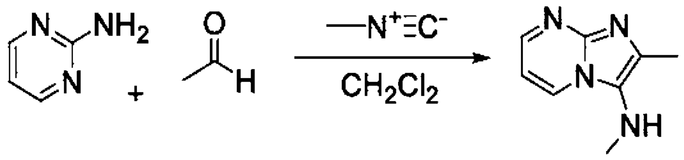
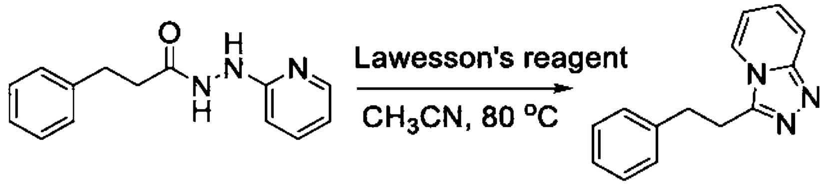
307	
308	
309	
310	
311	
312	

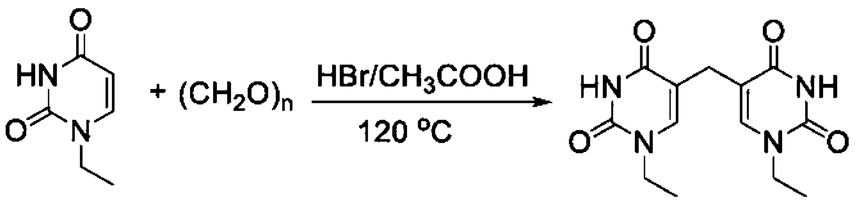
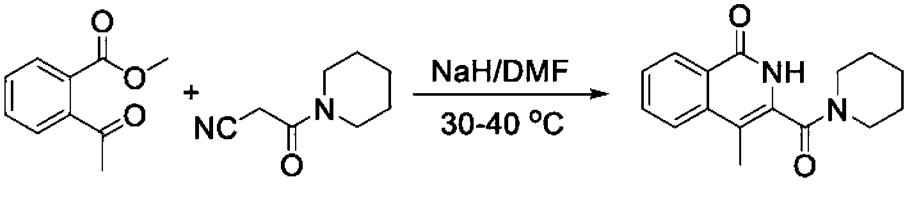
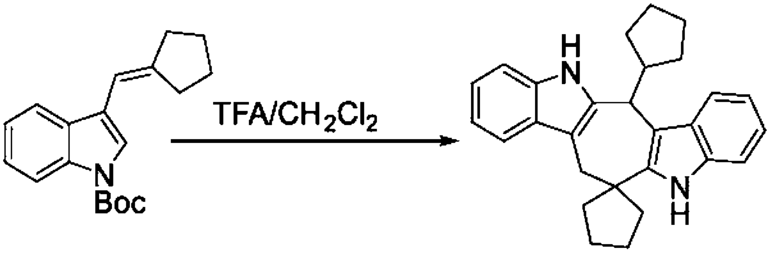
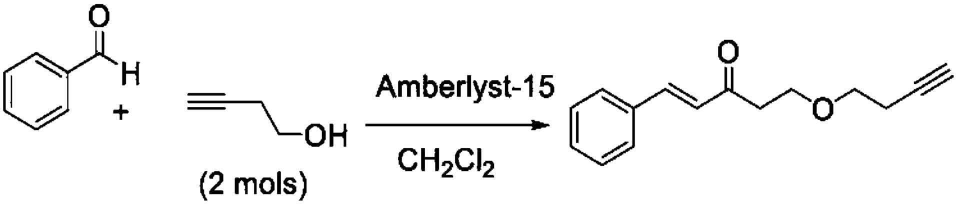
313	
314	
315	
316	
317	
318	

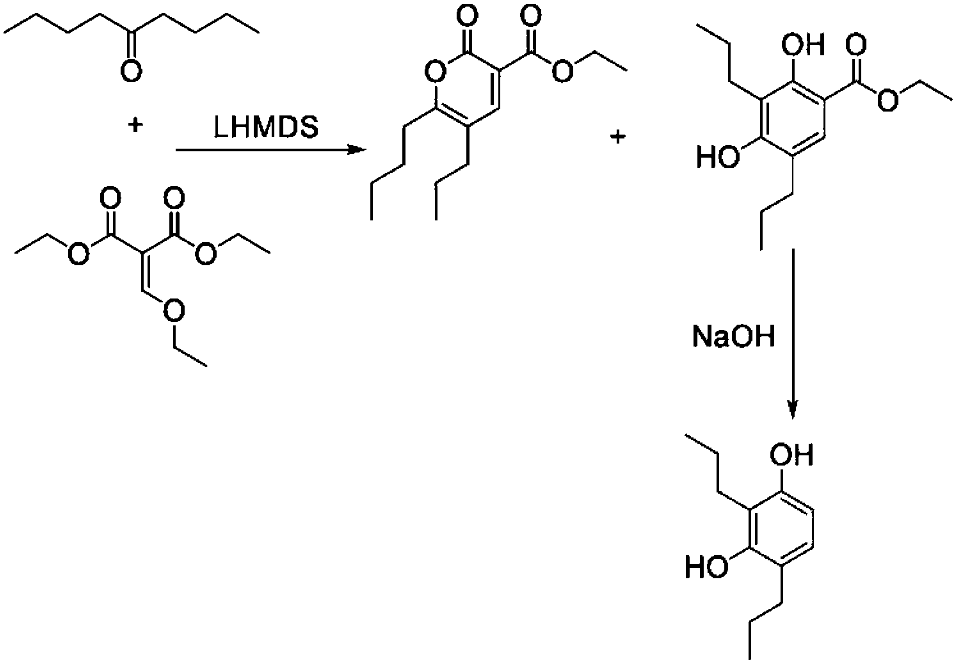
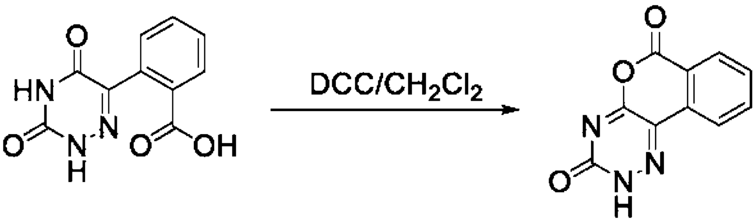
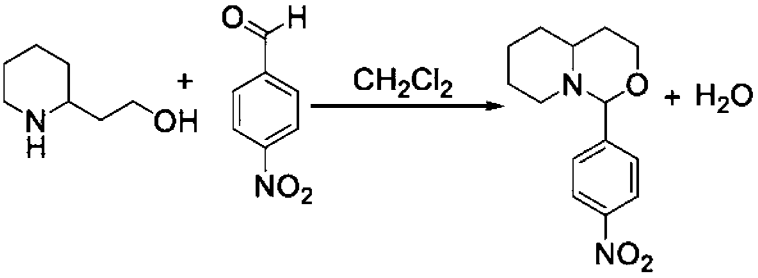
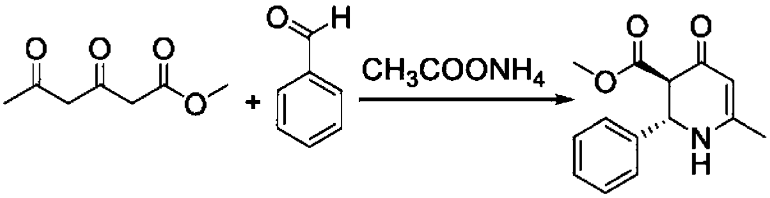
319	
320	
321	
322	
323	
324	 (major) (minor)

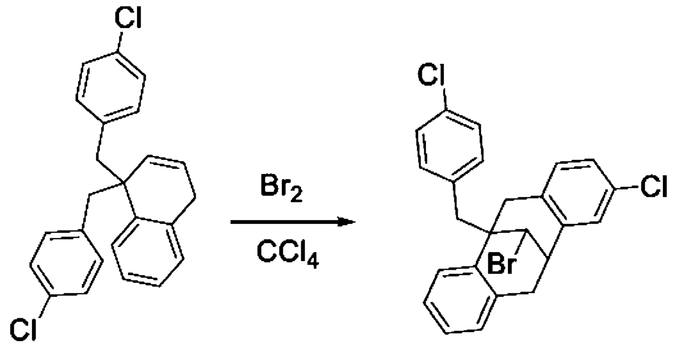
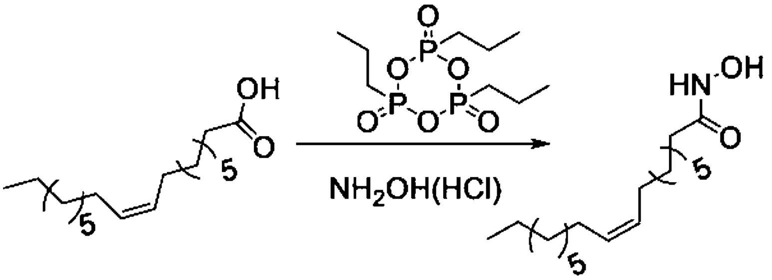
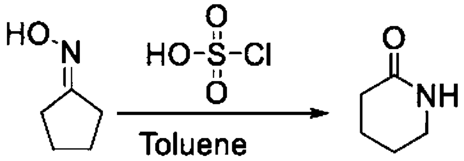
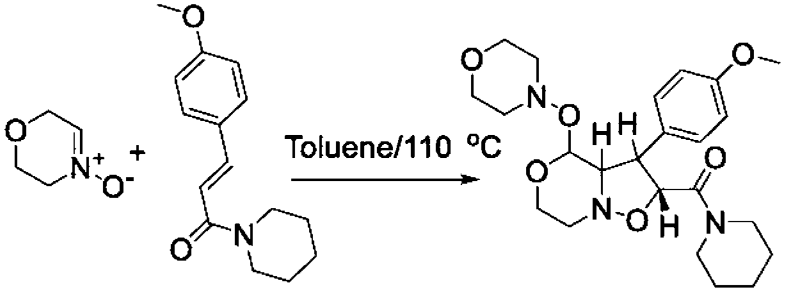
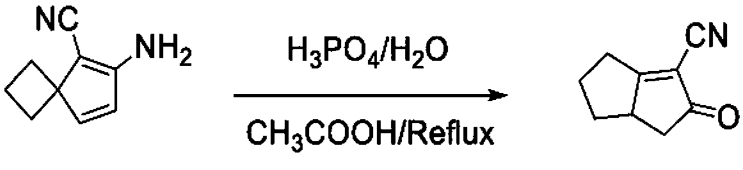
325	
326	
327	
328	When the antibiotic Emycin F is treated with acid, it rearranges to Emycin E. Write a mechanism for this transformation.  Emycin F Emycin E
329	

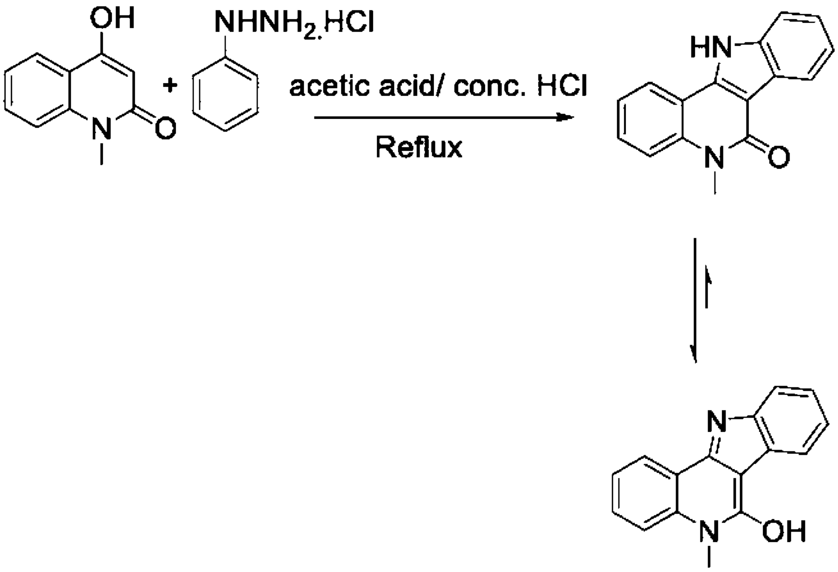
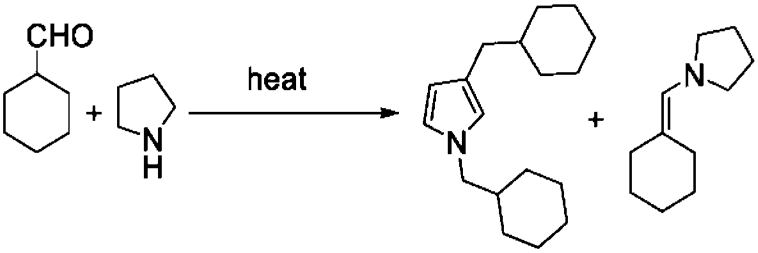
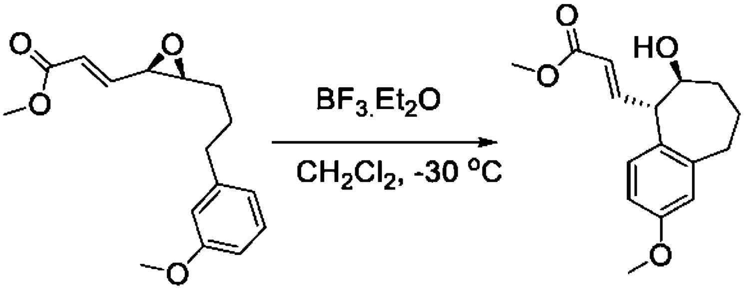
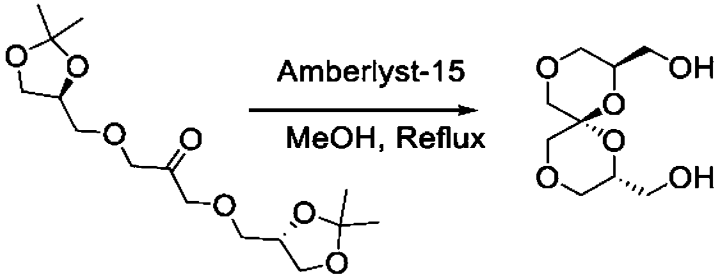
330	
331	
332	
333	
334	
335	

336	
337	
338	
339	
340	
341	

342	
343	
344	
345	

346	
347	
348	
349	

350	
351	
352	
353	
354	

355	
356	
357	
358	

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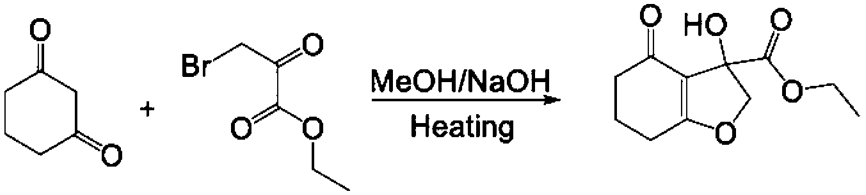
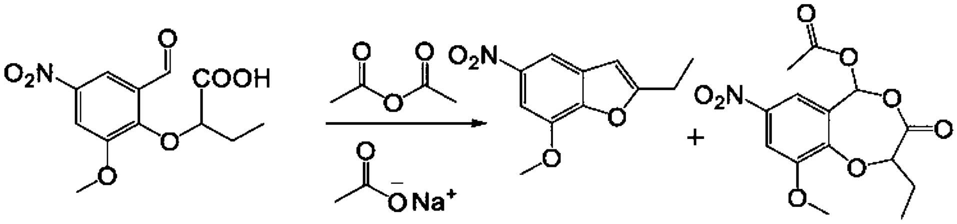
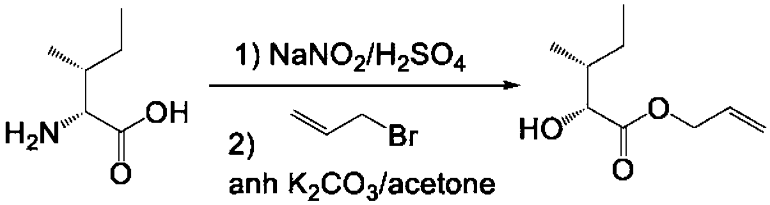
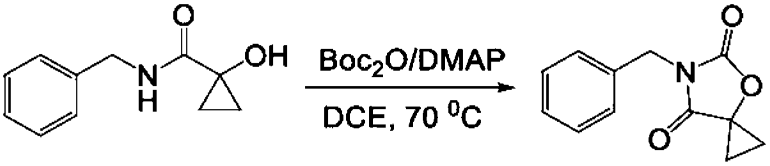
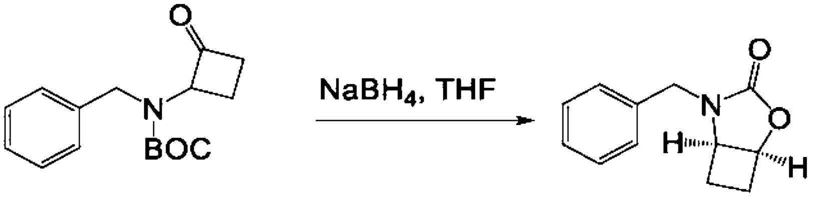
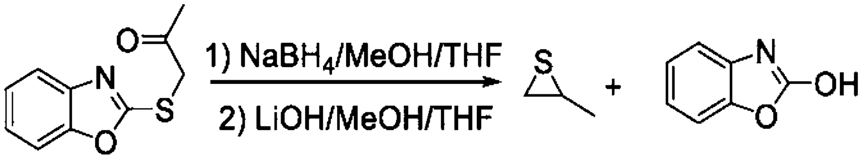
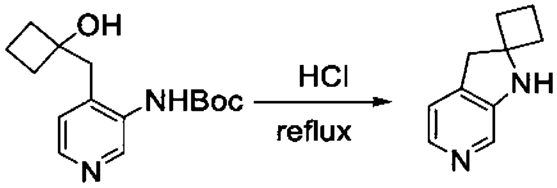
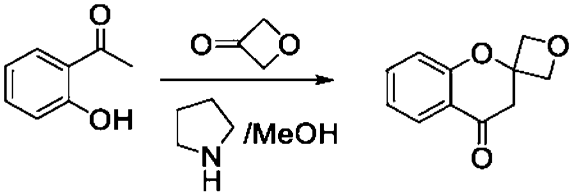
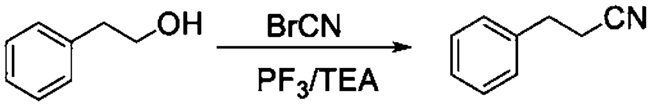
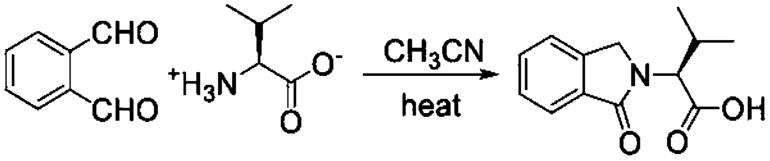
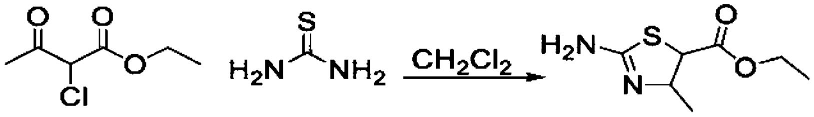
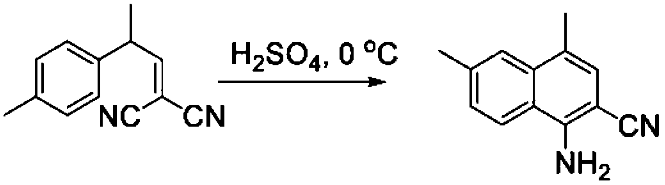
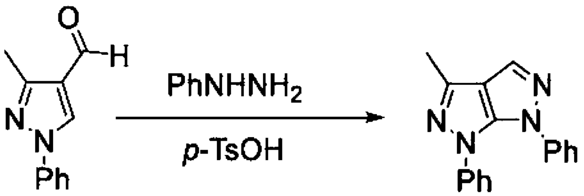
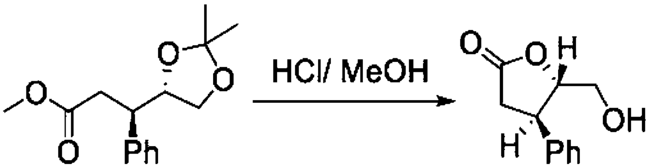
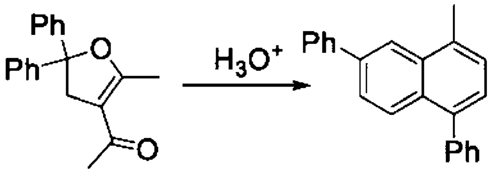
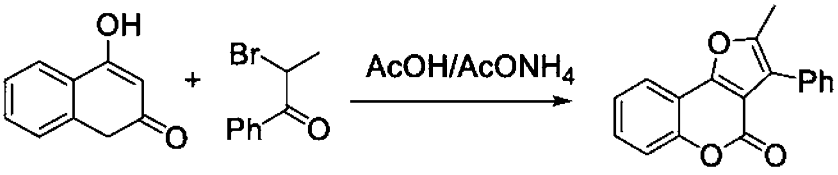
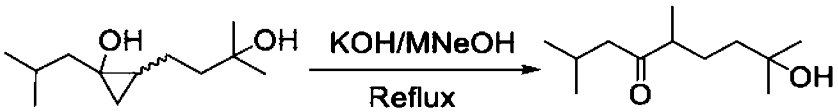
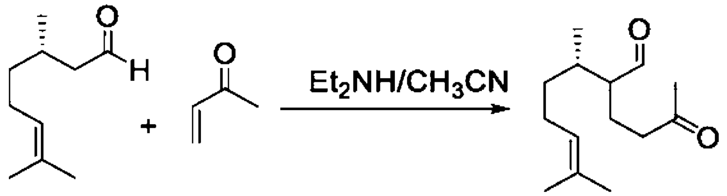
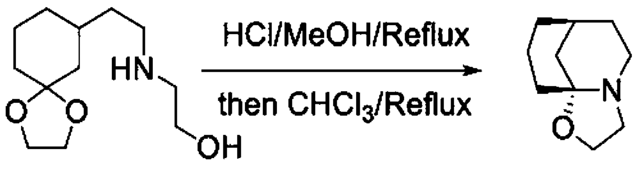
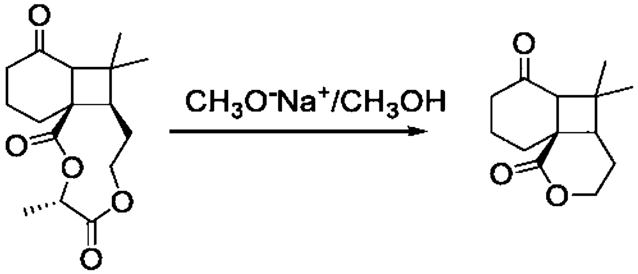
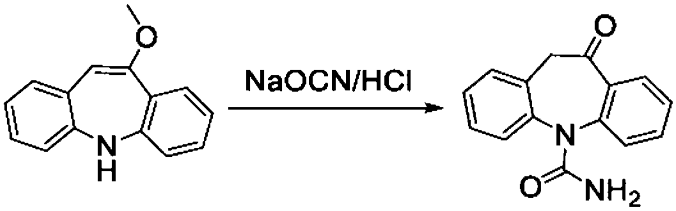
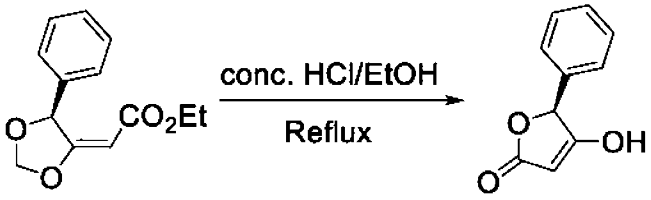
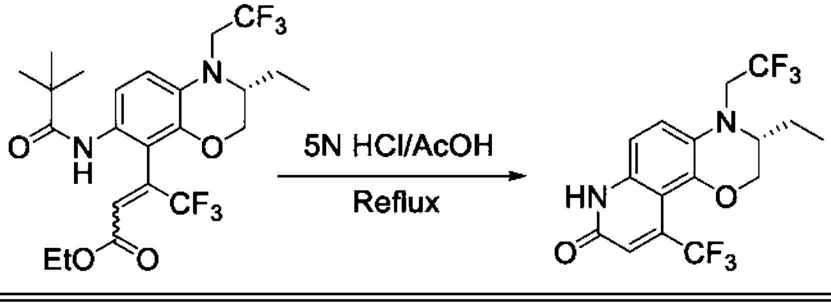
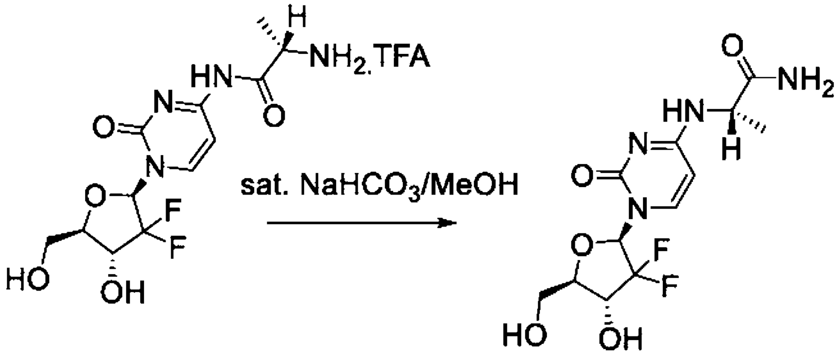
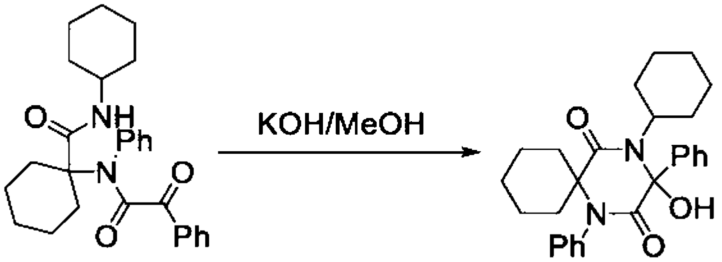
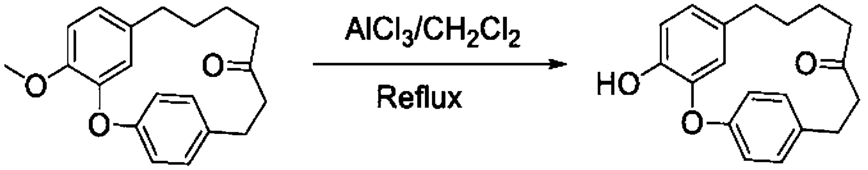
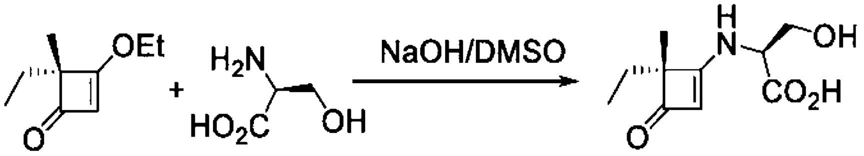
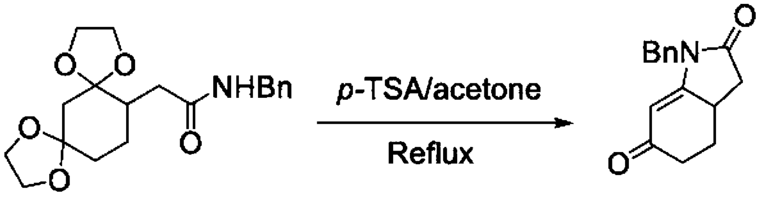
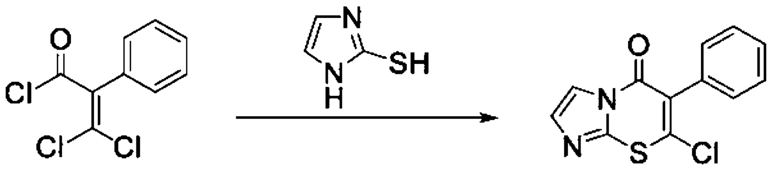
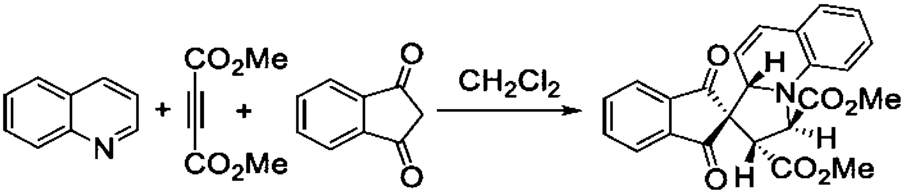
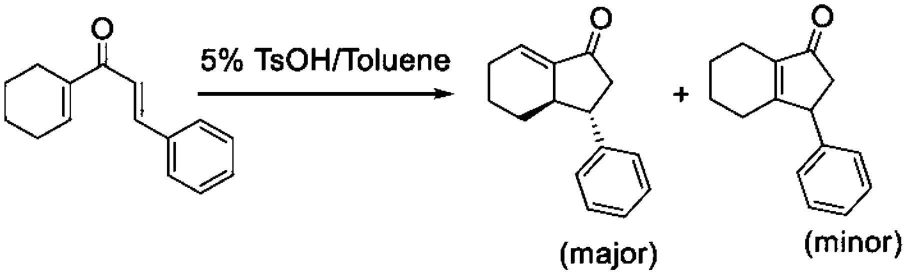
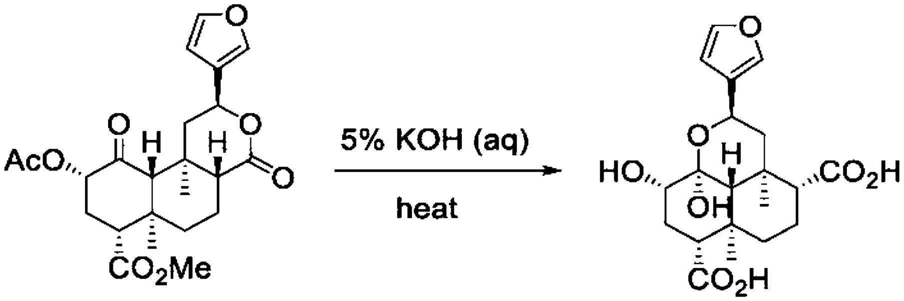
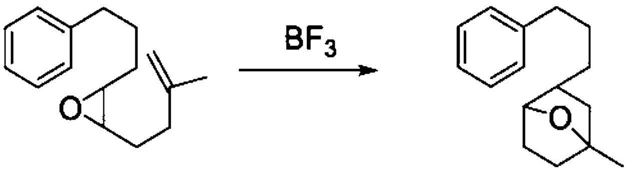
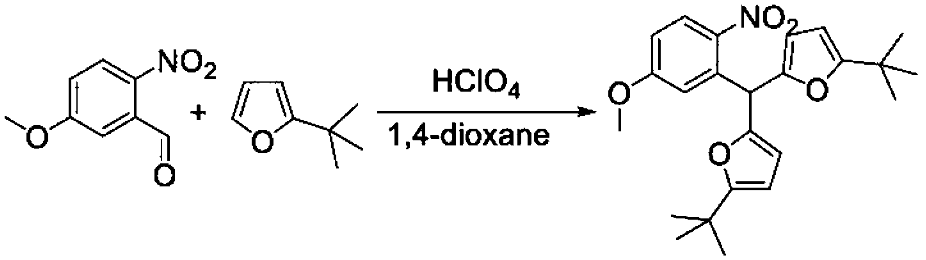
360	
361	
362	
363	
364	

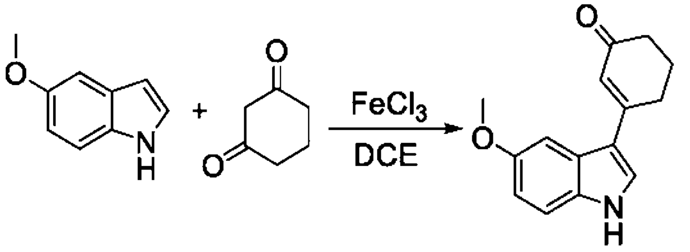
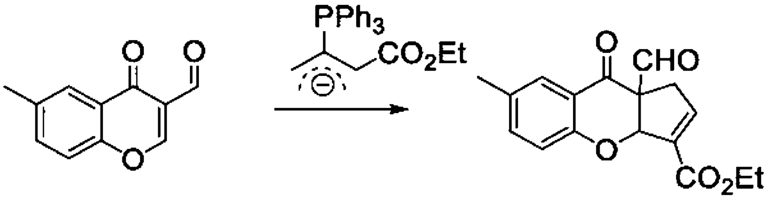
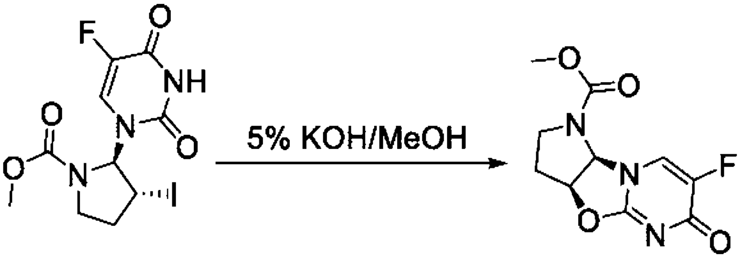
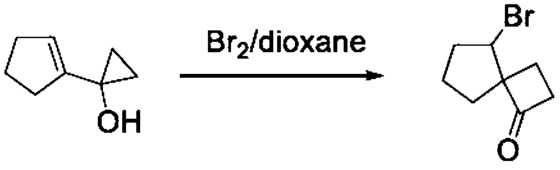
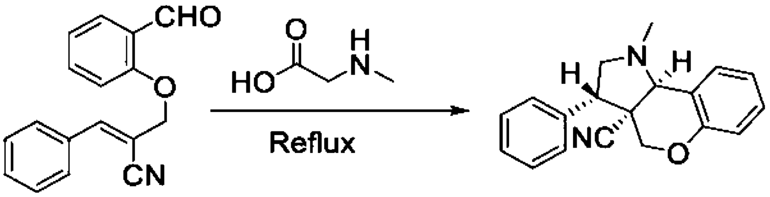
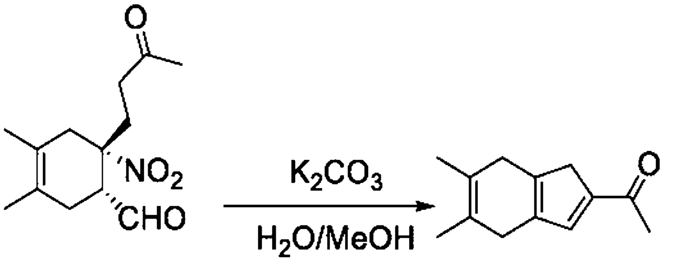
365	
366	
367	
368	
369	
370	

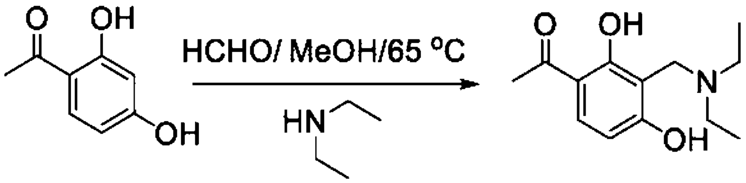
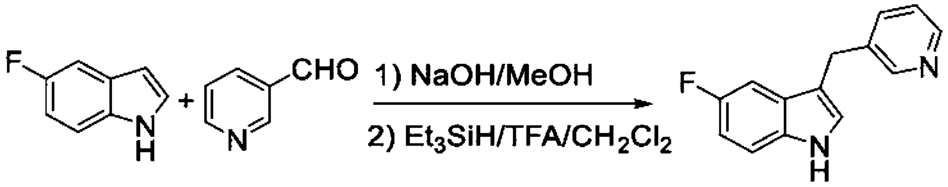
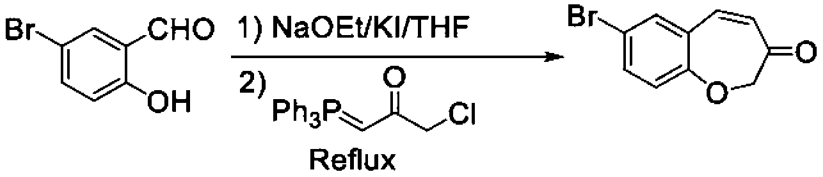
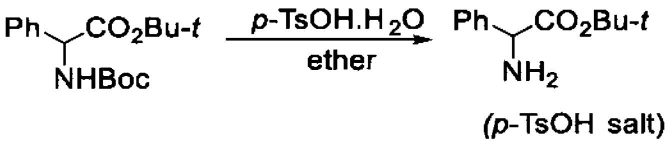
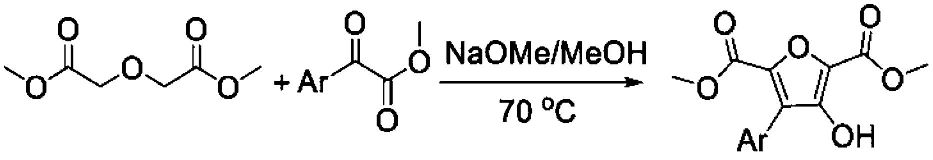
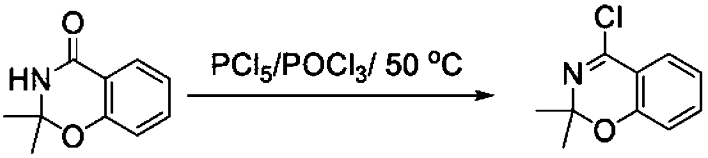
371	
372	
373	
374	
375	
376	

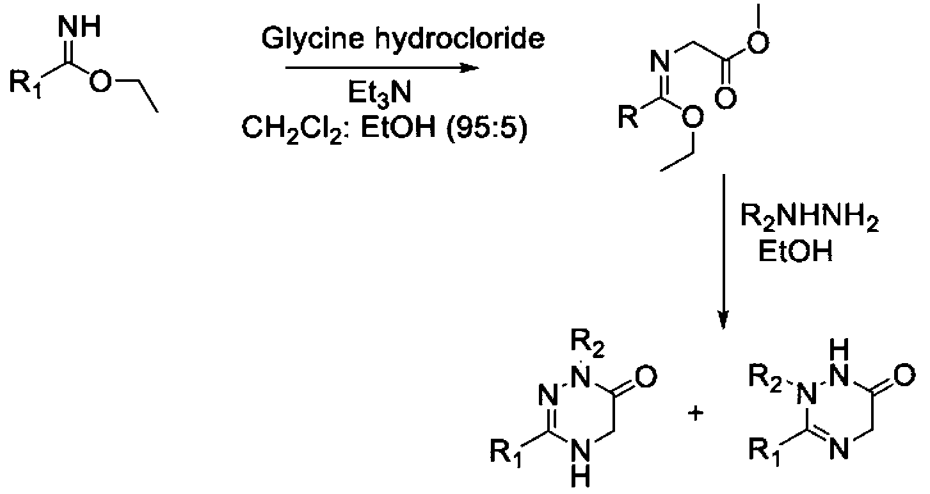
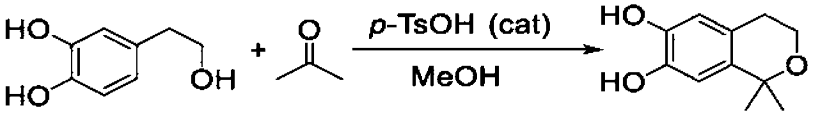
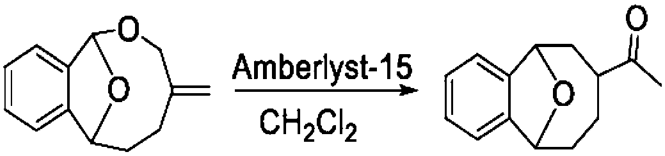
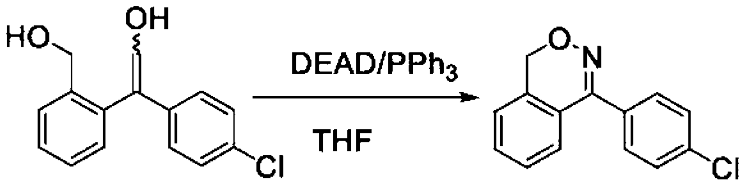
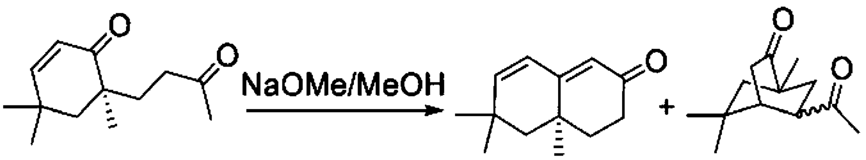
377	
378	
379	
380	
381	
382	

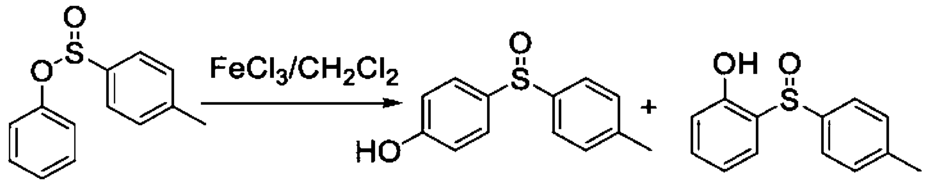
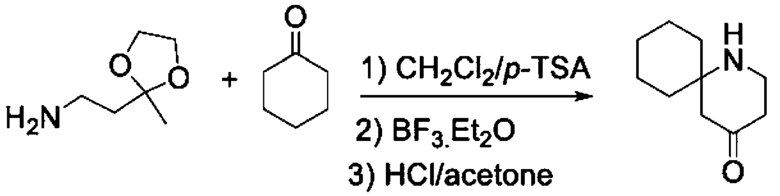
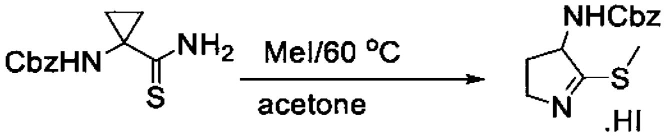
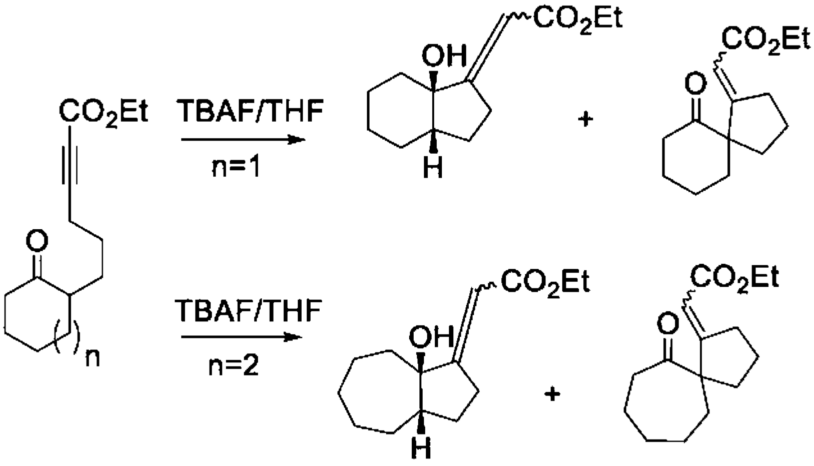
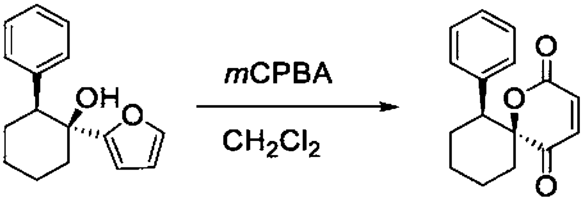
383	
384	
385	
386	
387	
388	

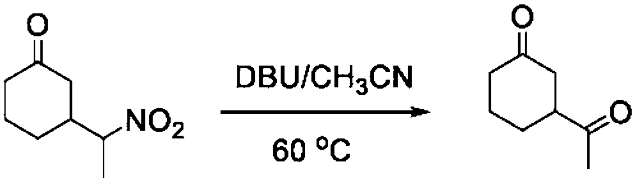
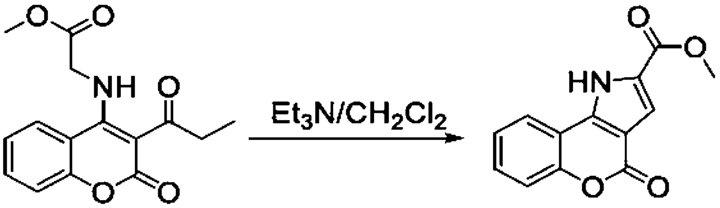
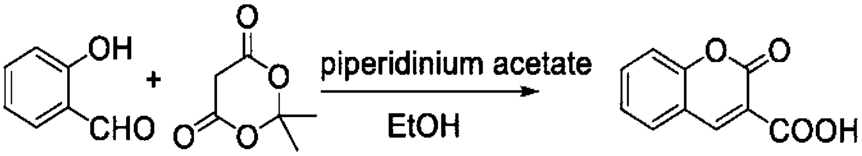
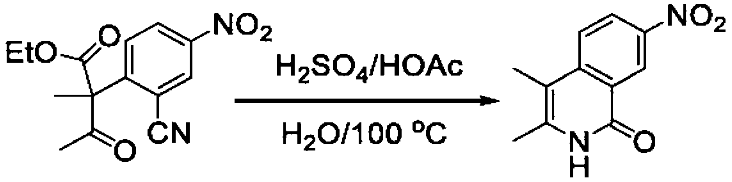
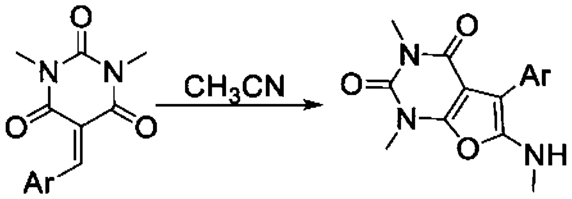
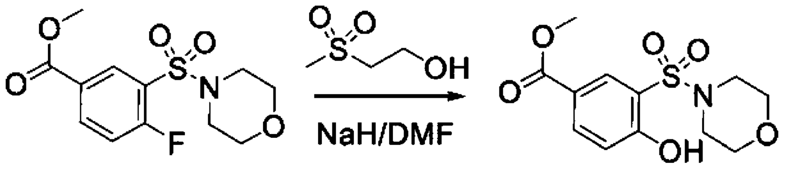
389	
390	
391	
392	
393	

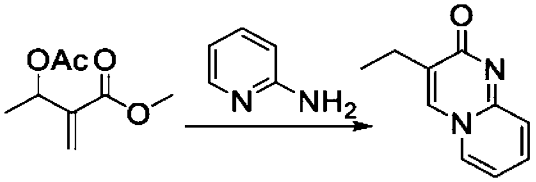
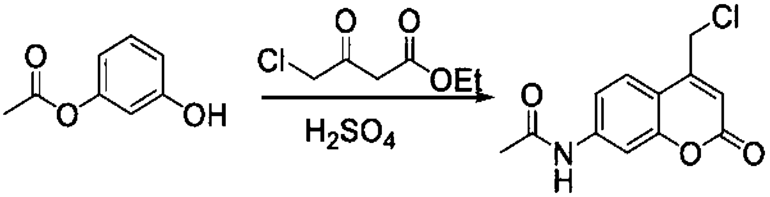
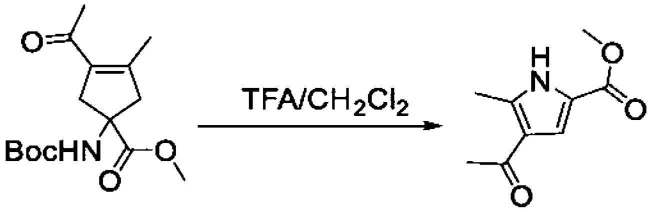
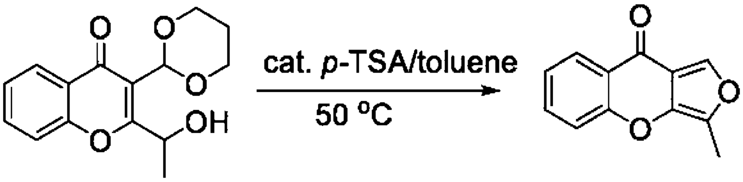
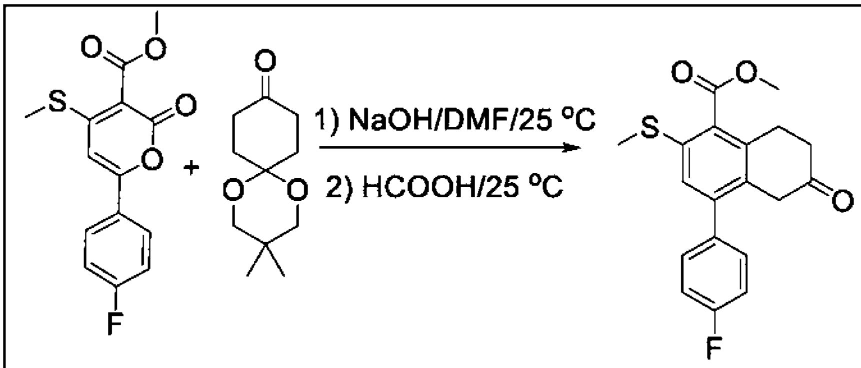
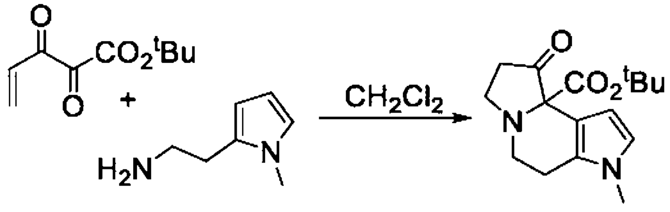
394	
395	
396	
397	
398	
399	

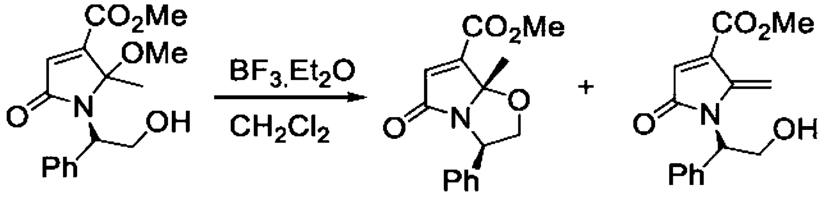
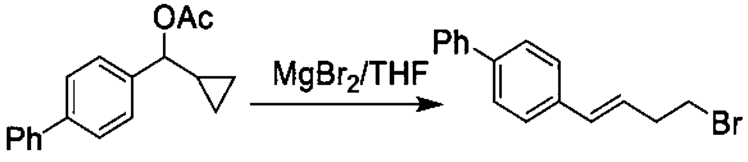
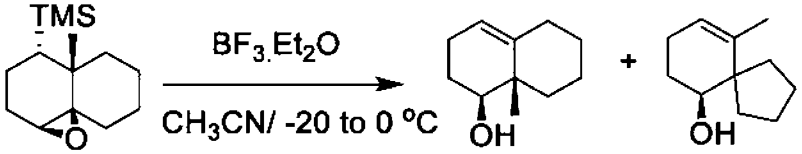
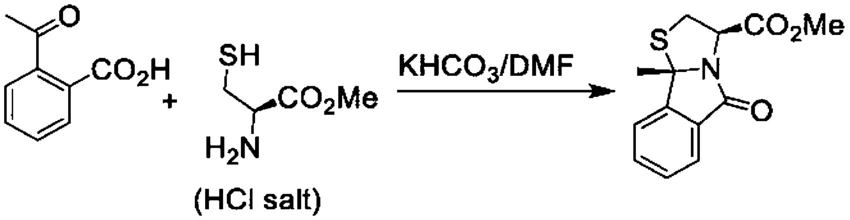
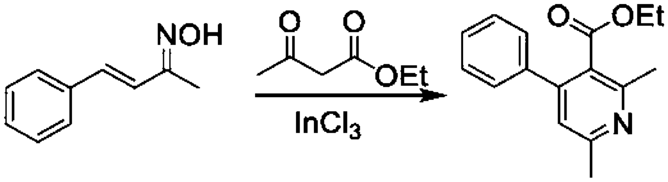
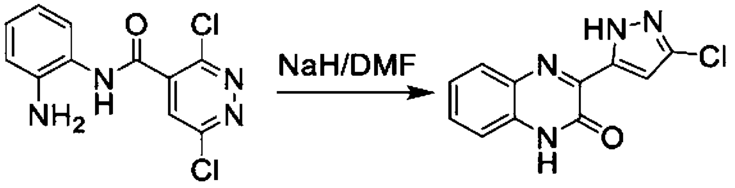
400	
401	
402	
403	
404	
405	

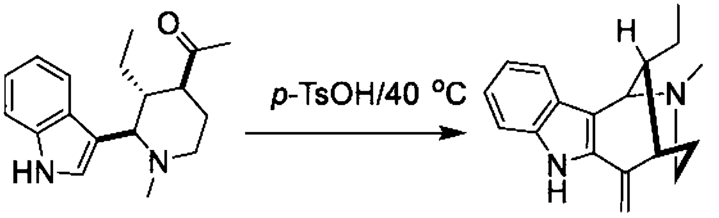
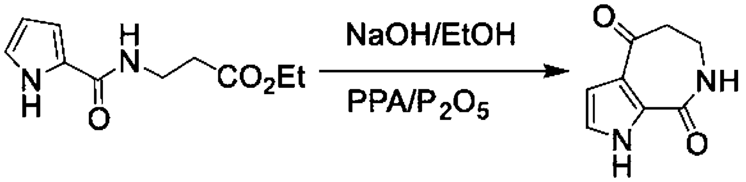
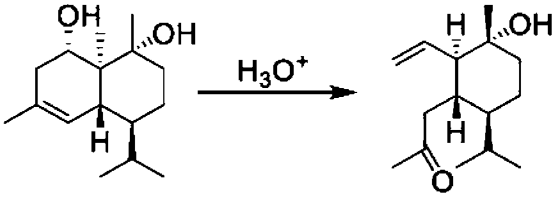
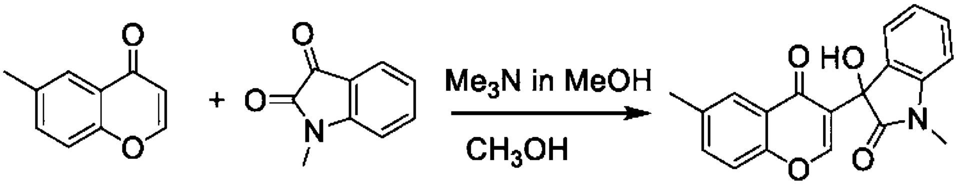
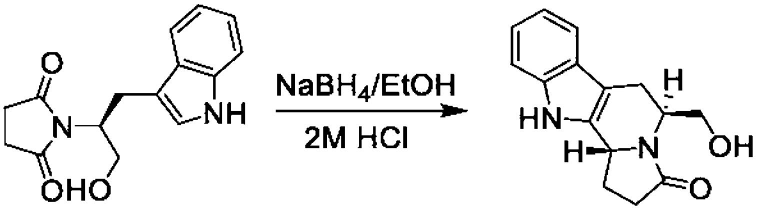
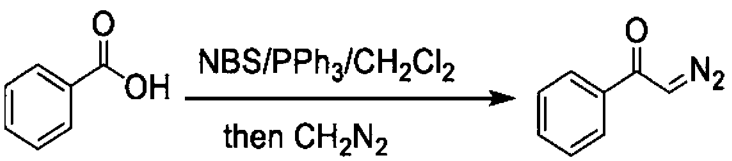
406	
407	
408	
409	
410	

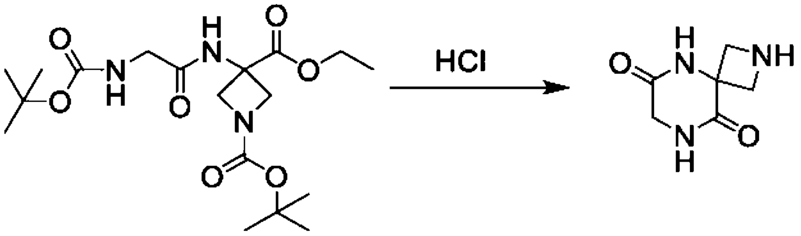
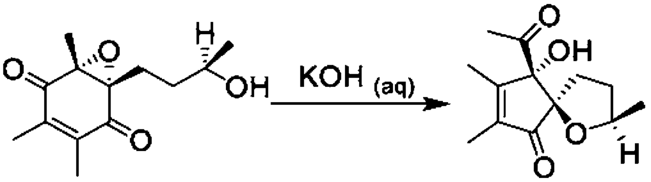
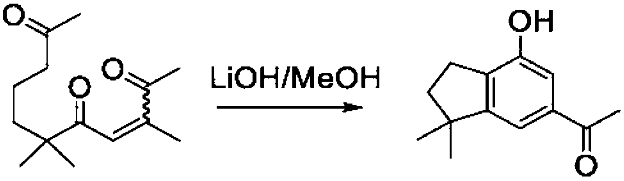
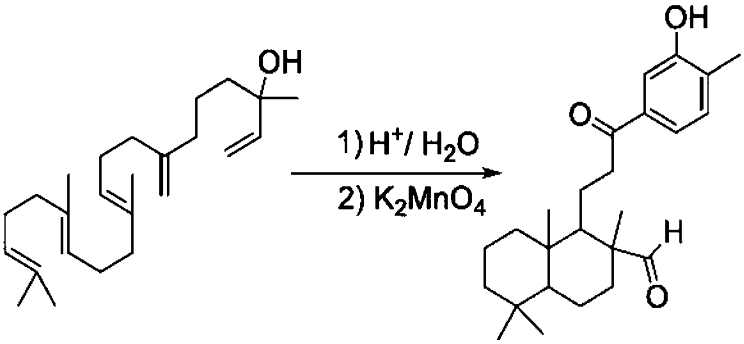
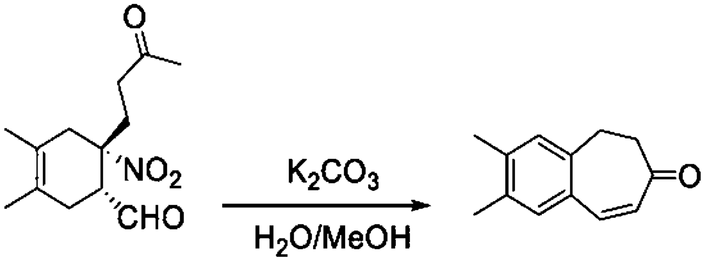
411	
412	
413	
414	
415	

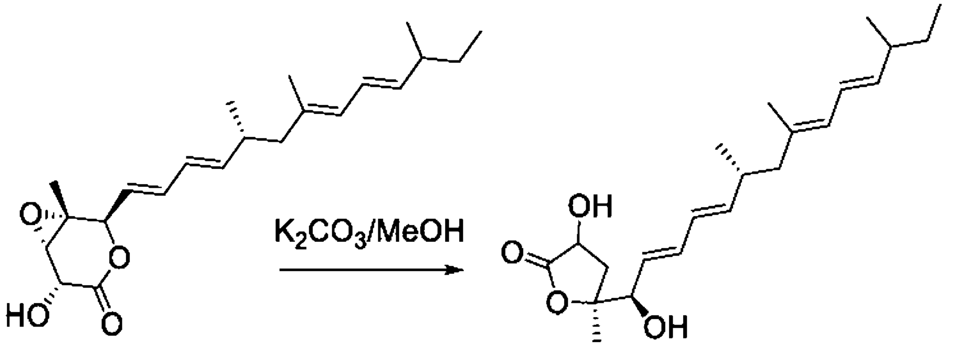
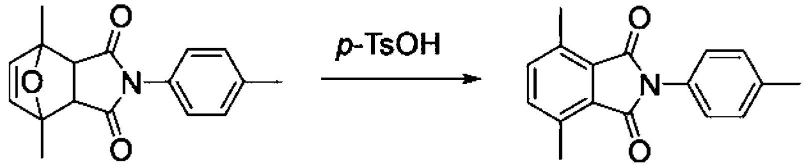
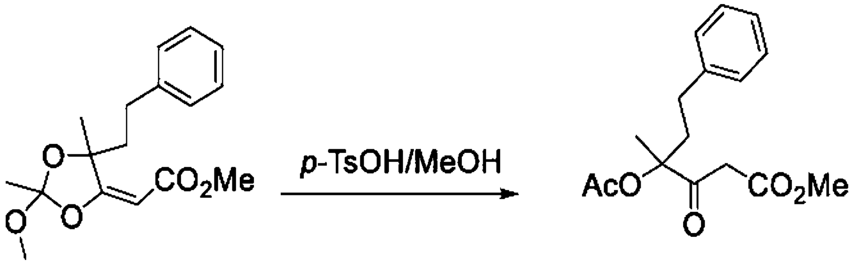
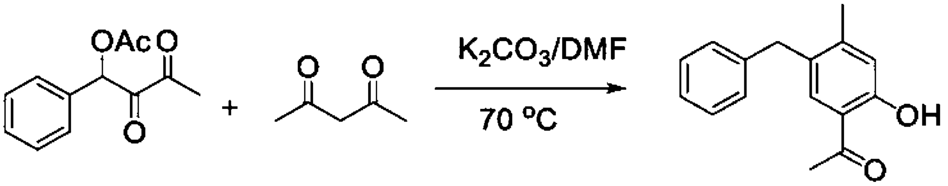
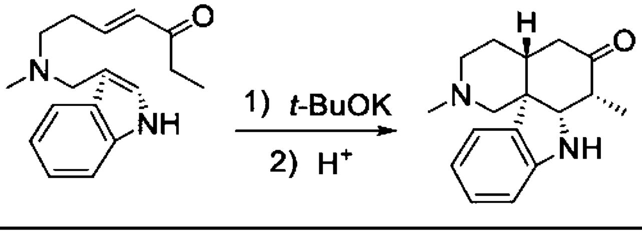
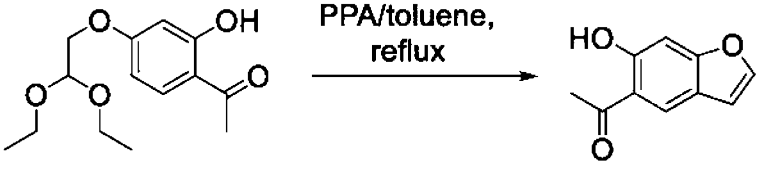
416	
417	
418	
419	
420	
421	

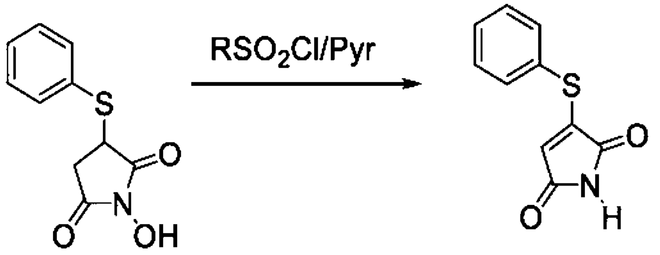
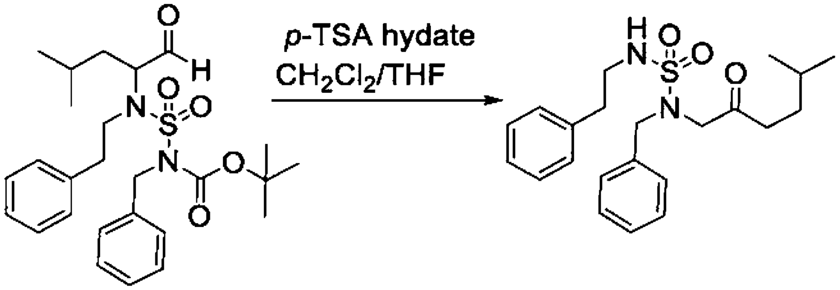
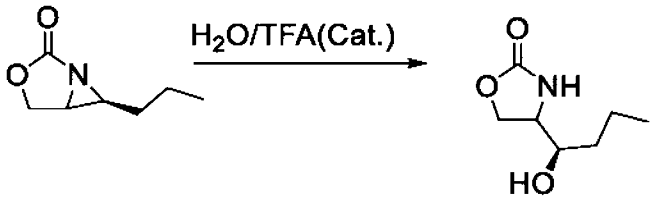
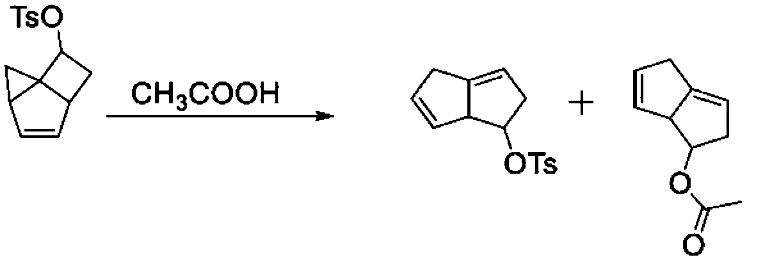
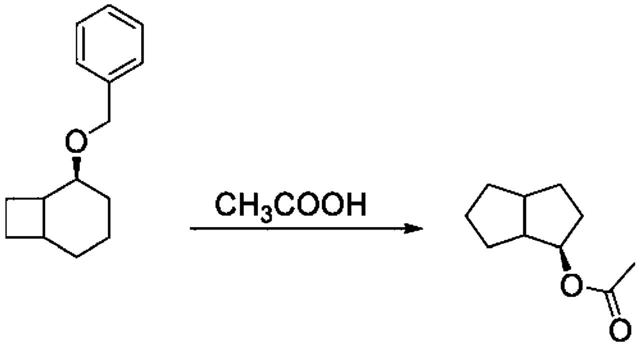
422	
423	
424	
425	
426	
427	

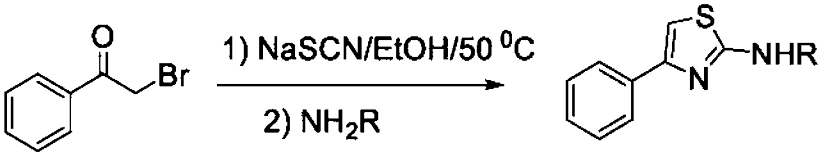
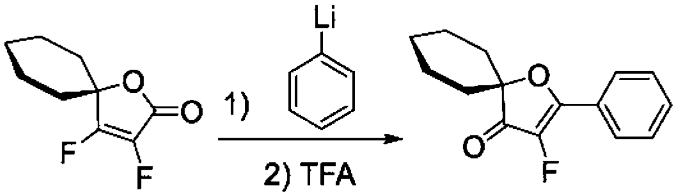
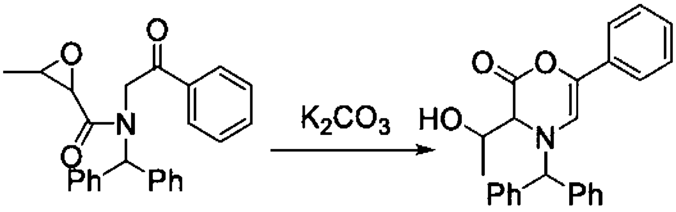
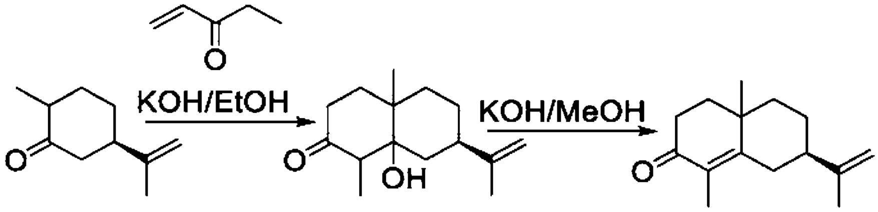
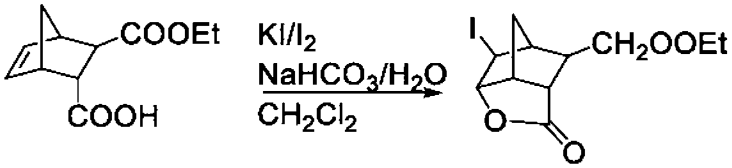
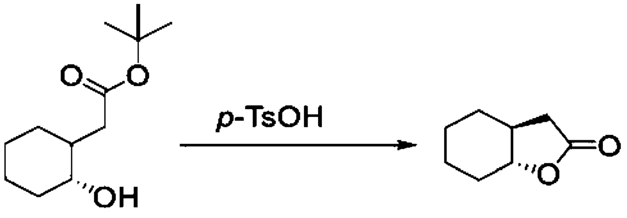
428	
429	
430	
431	
432	
433	

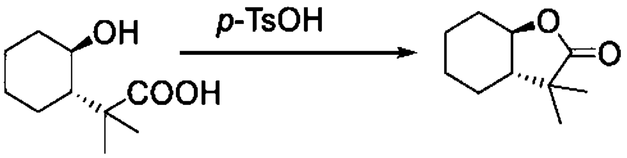
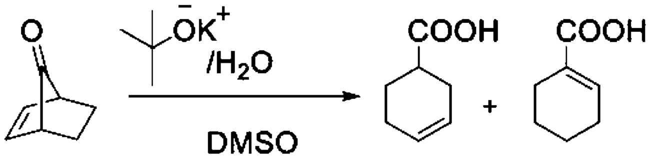
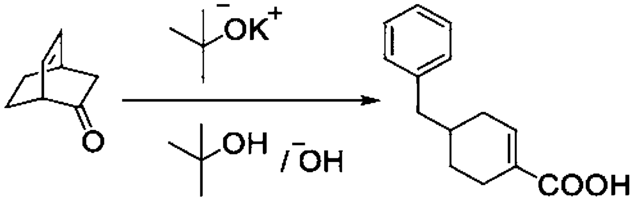
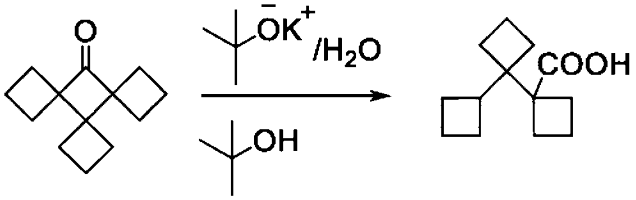
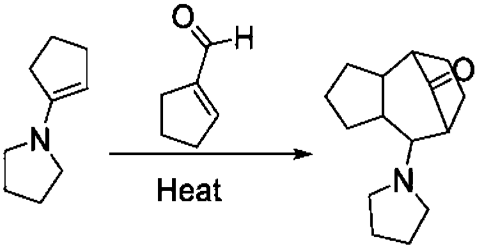
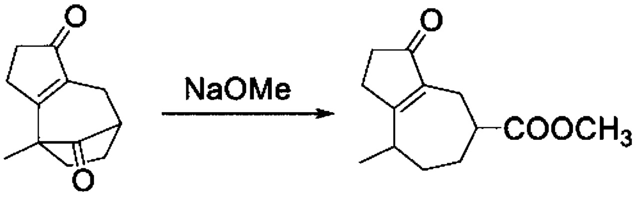
434	 Epiuleine
435	
436	
437	
438	
439	

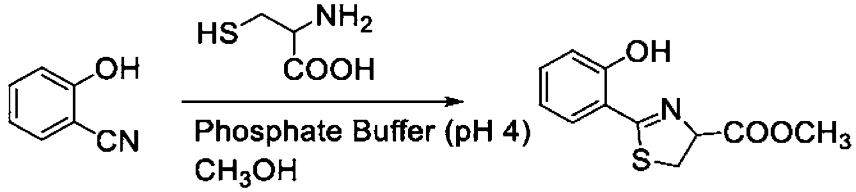
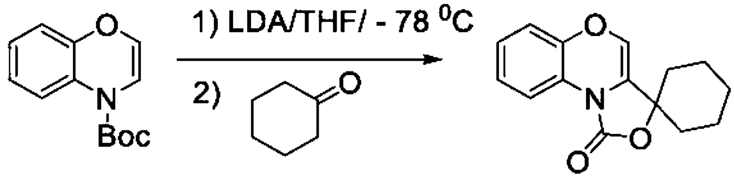
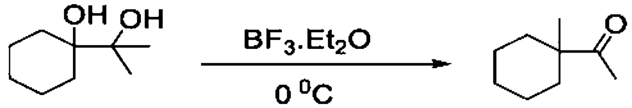
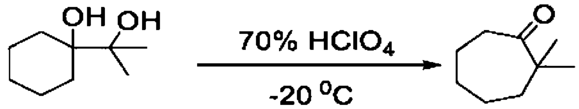
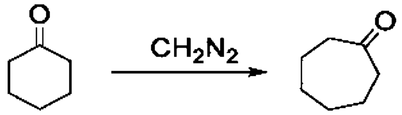
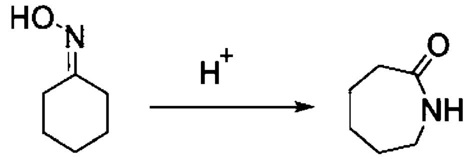
440	
441	
442	
443	
444	

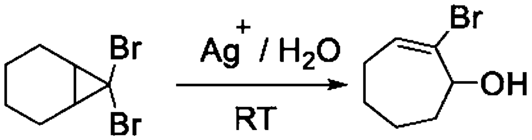
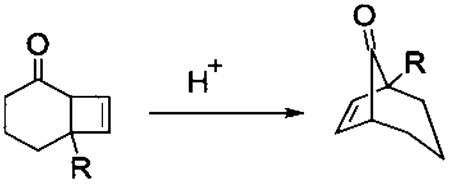
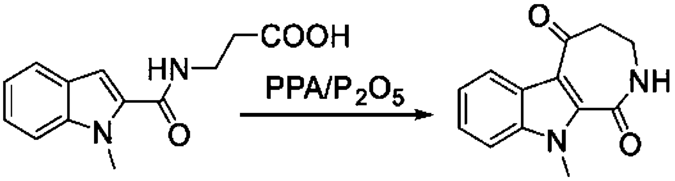
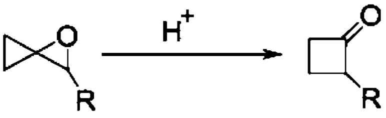
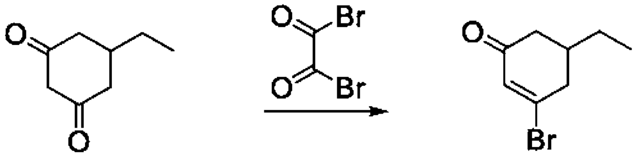
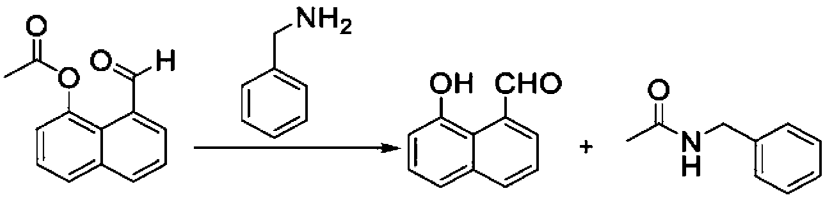
445	
446	
447	
448	
449	
450	

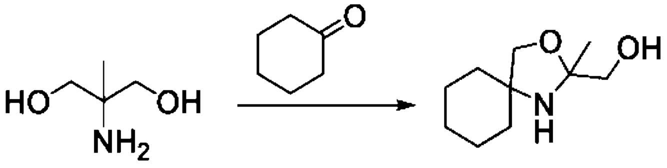
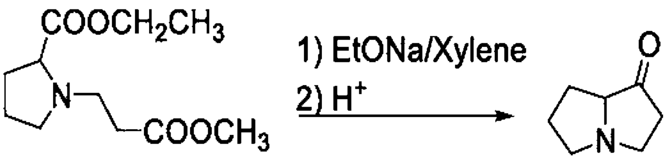
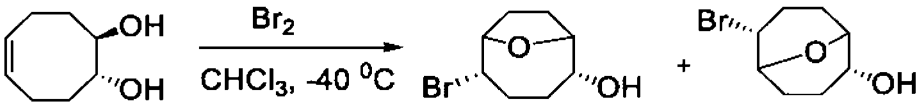
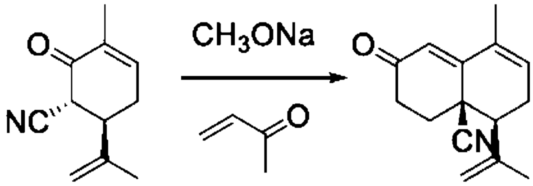
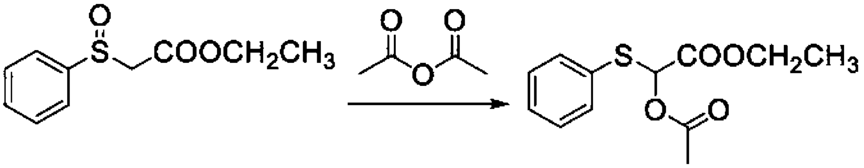
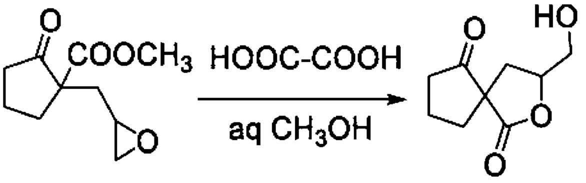
451	
452	
453	
454	
455	

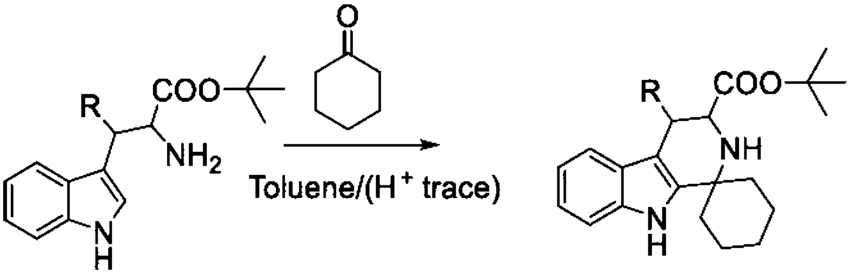
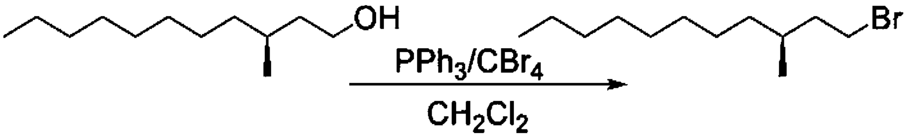
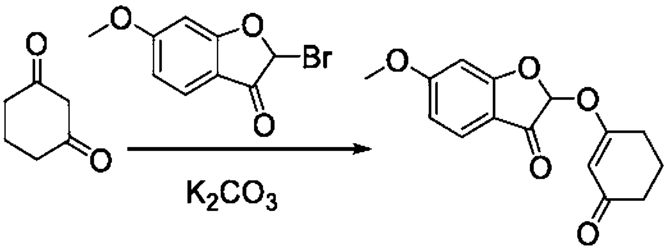
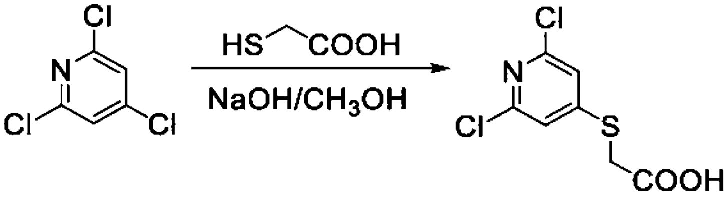
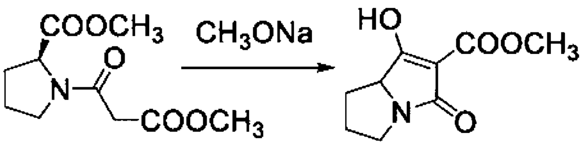
456	
457	
458	
459	
460	
461	

462	
463	
464	
465	
466	
467	

468	
469	
470	
471	
472	
473	

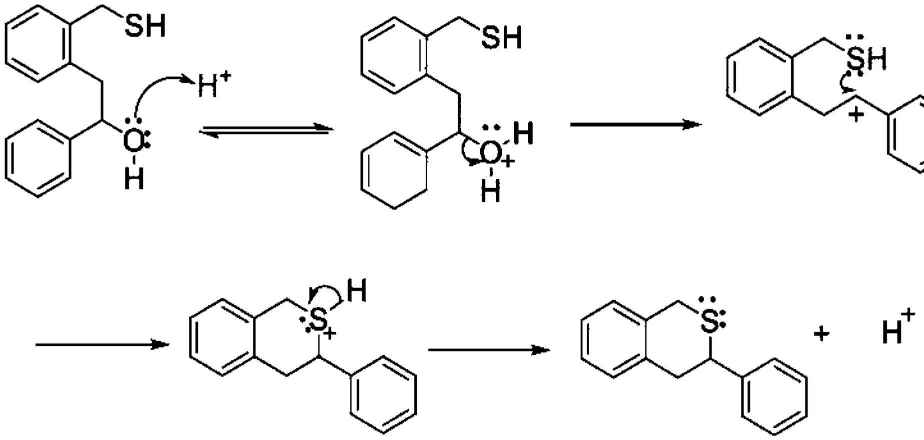
474	
475	
476	
477	
478	
479	

480	
481	
482	
483	
484	
485	

486	
487	
488	
489	
490	

Answers to Questions 201-490

201



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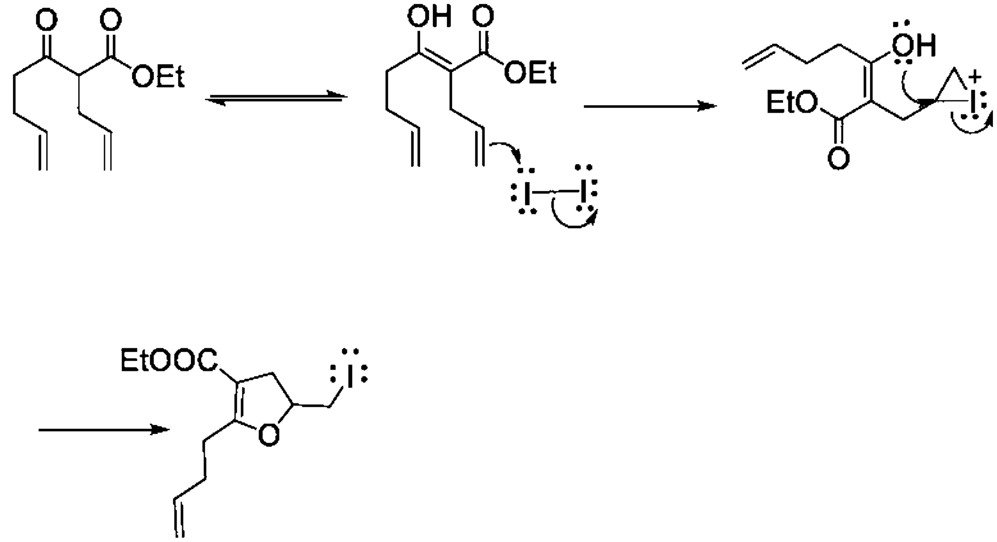

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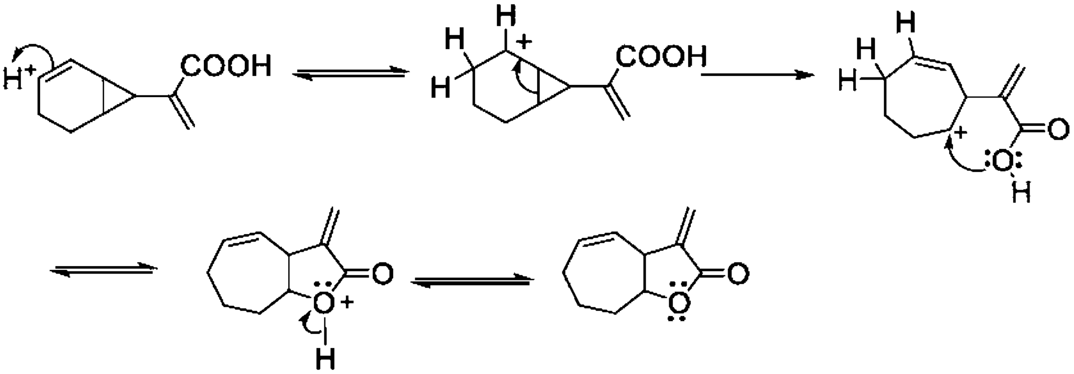

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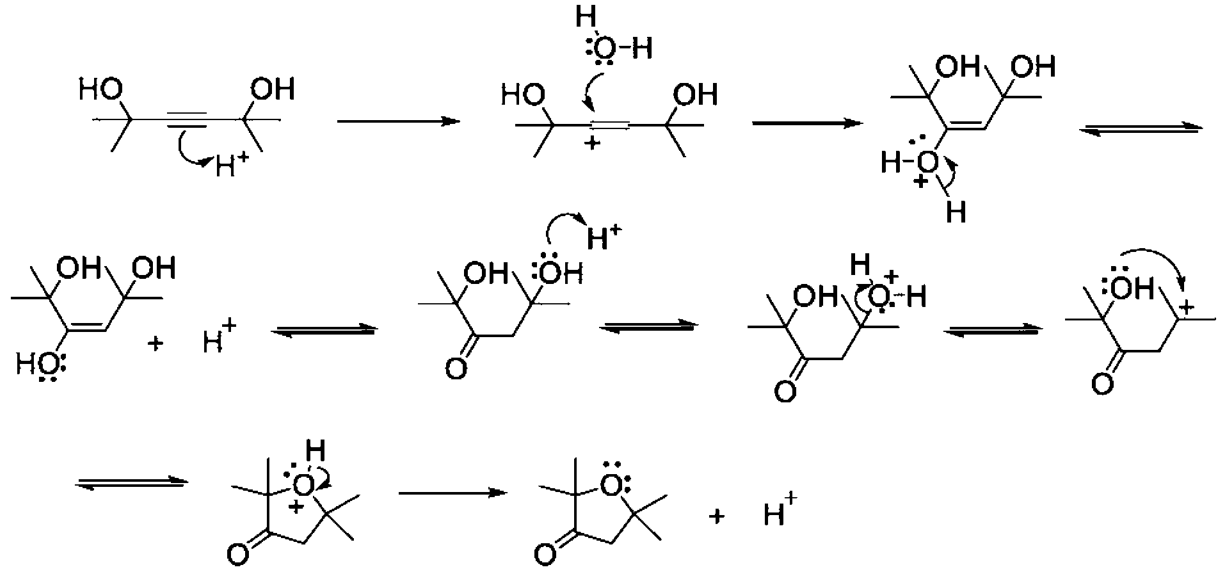

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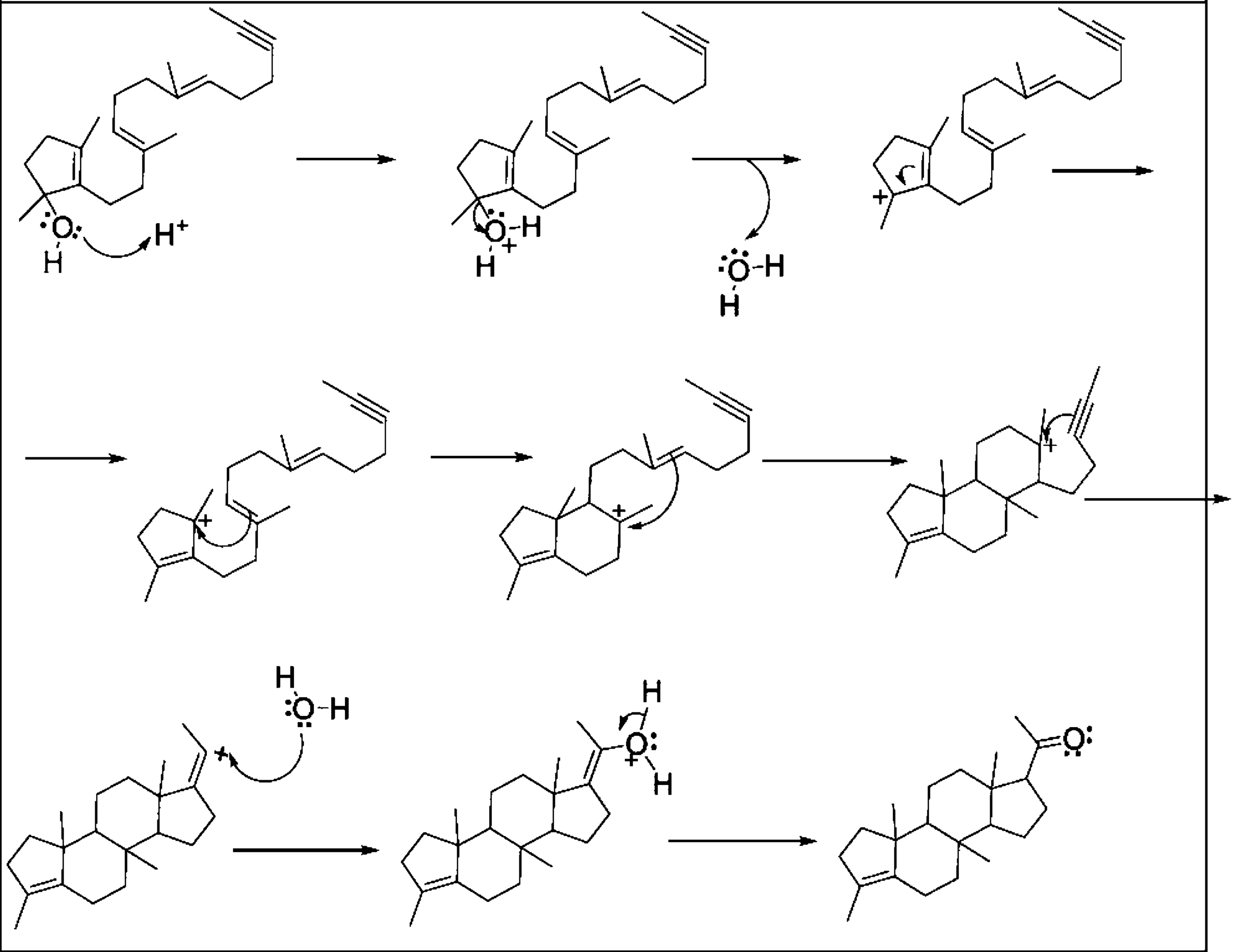

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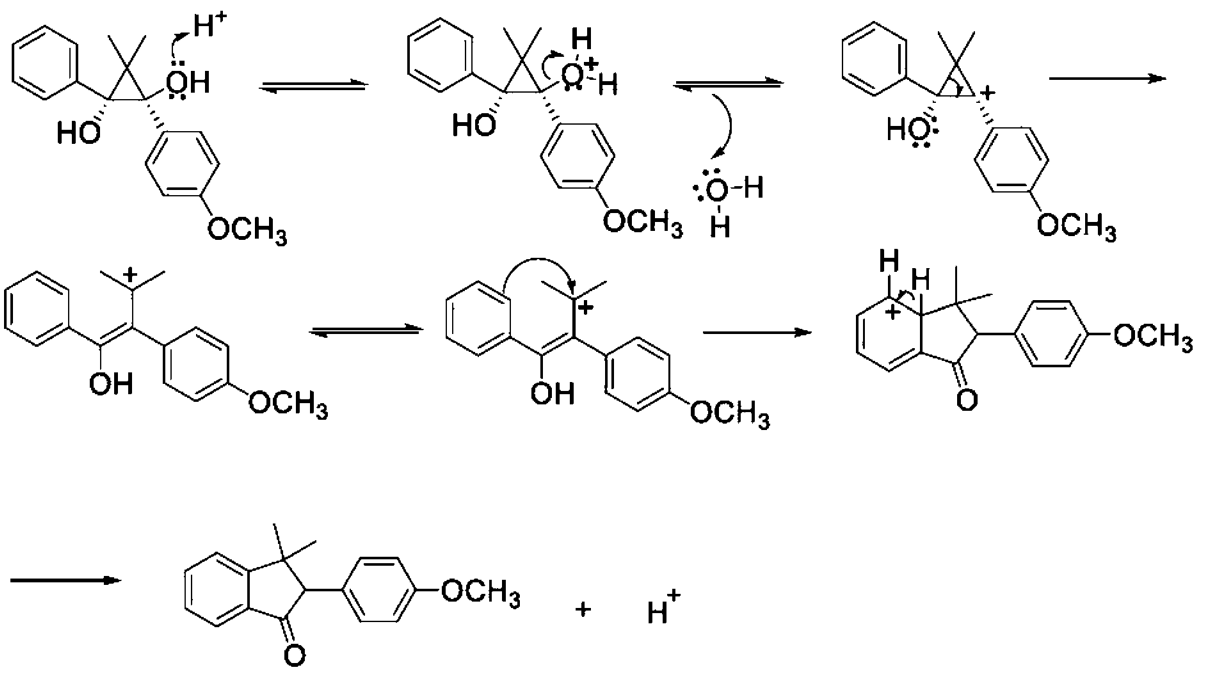

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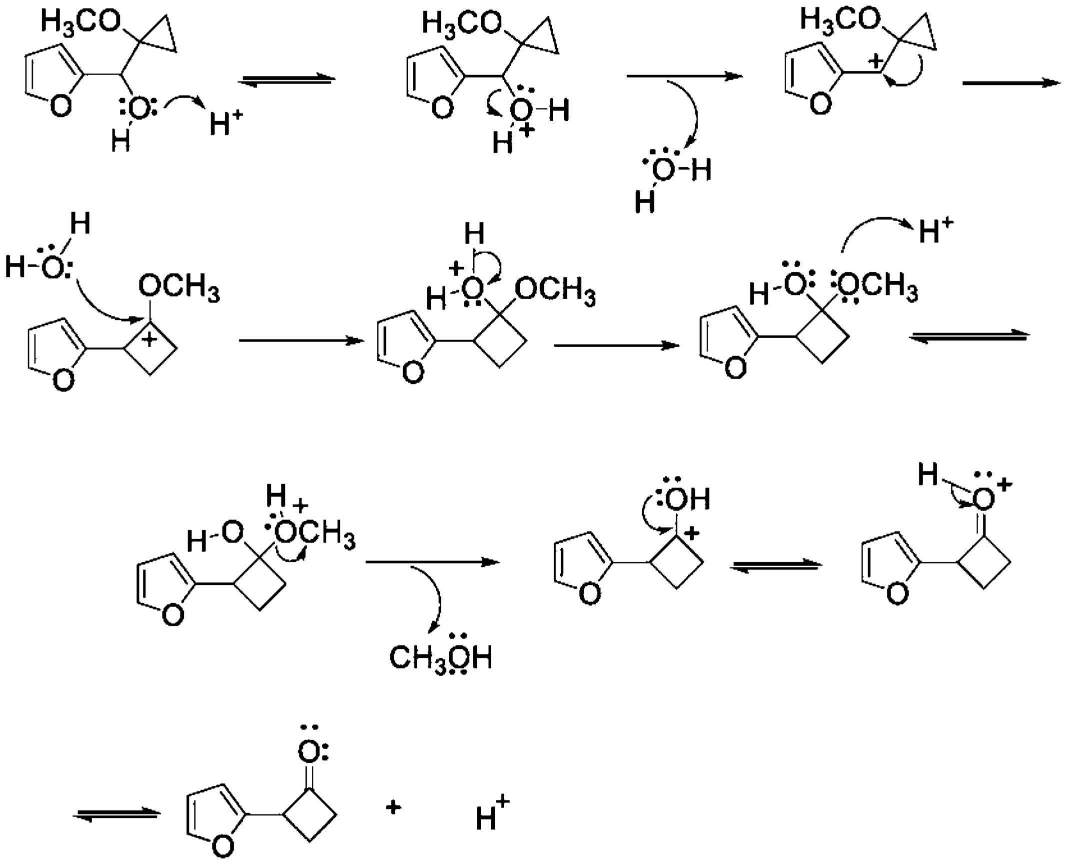

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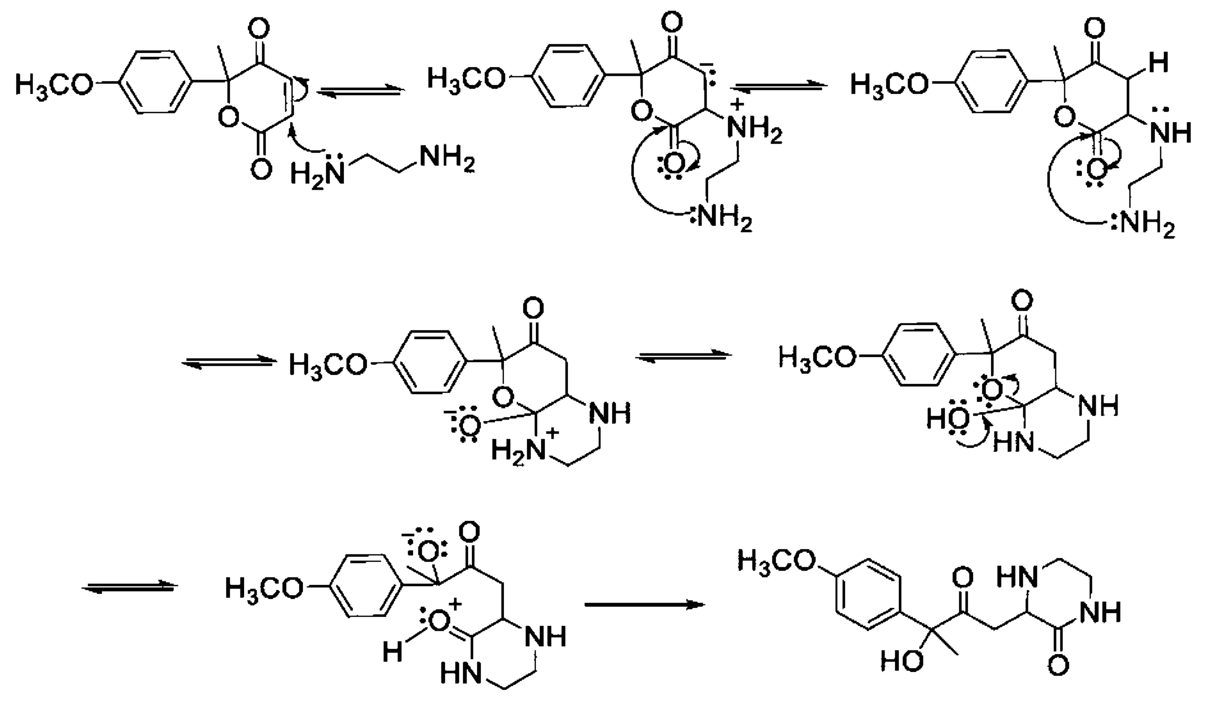

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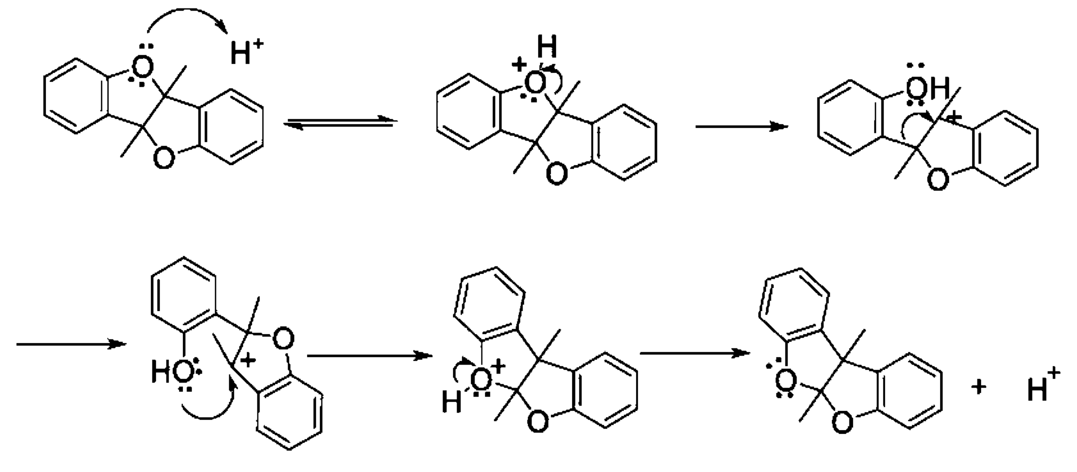

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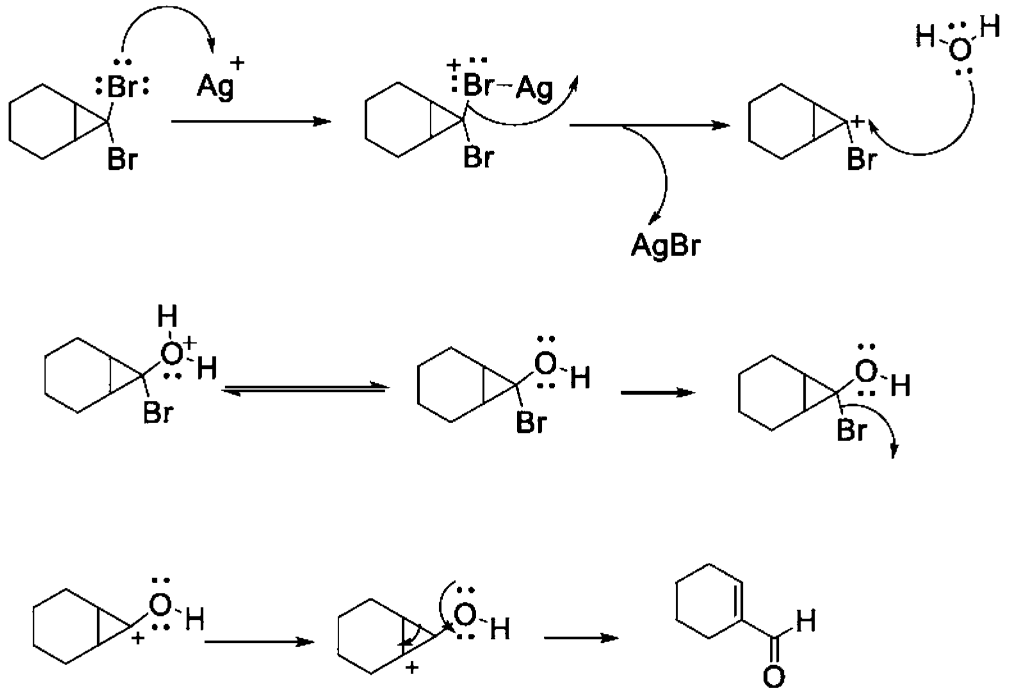

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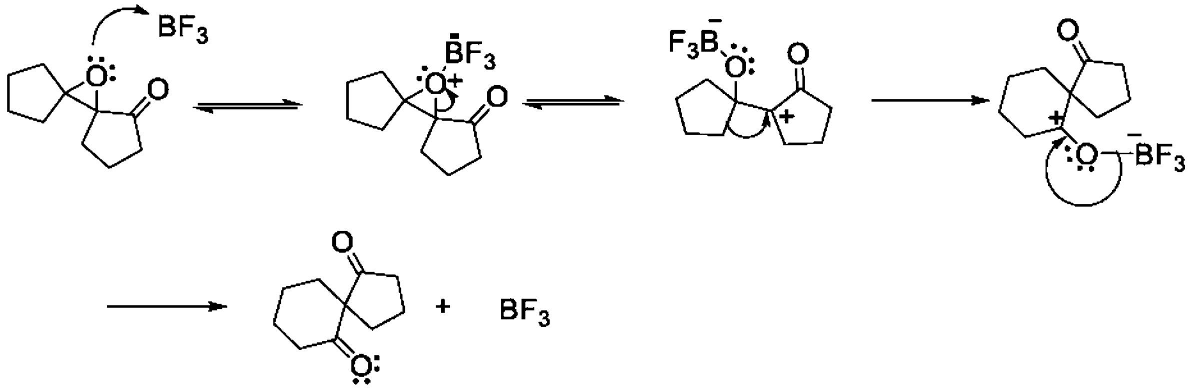

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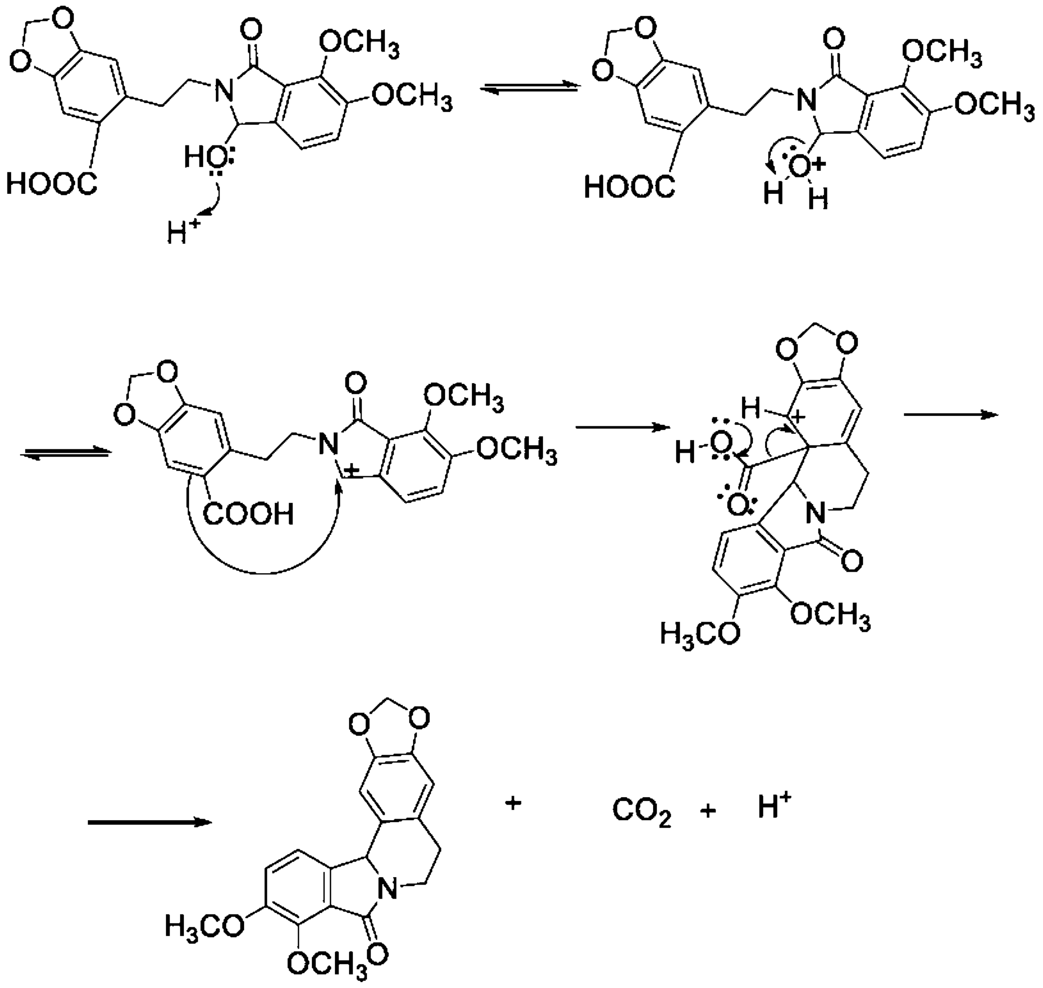

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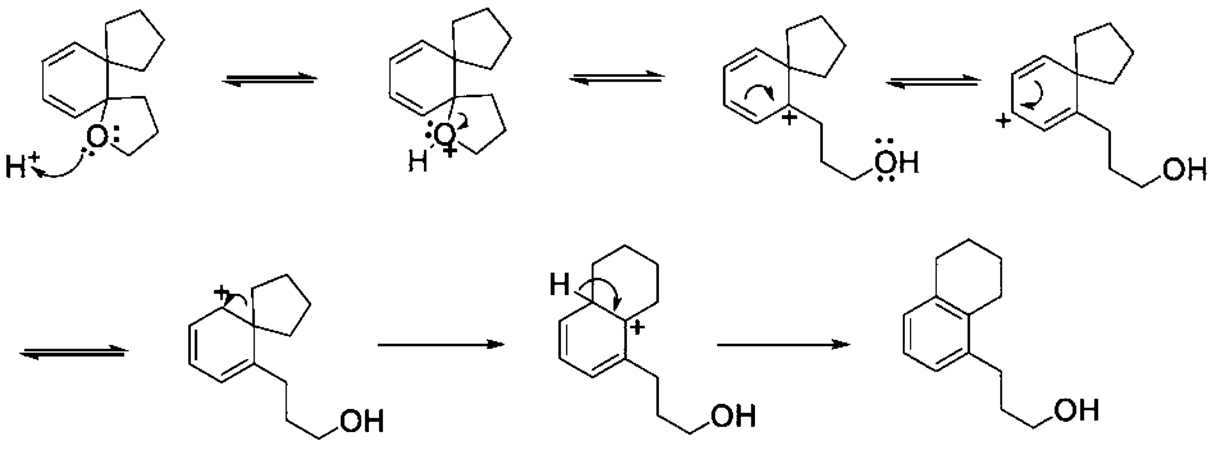

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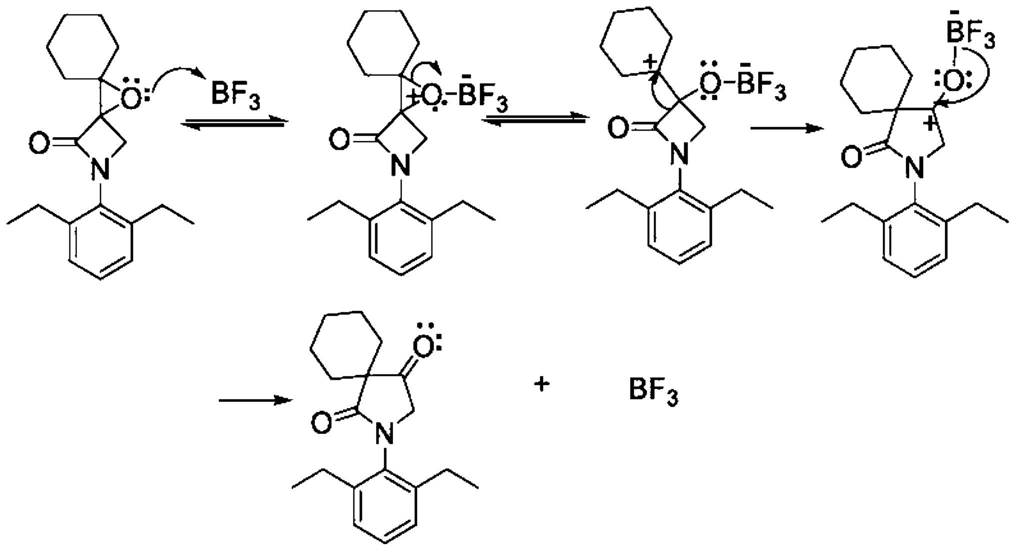

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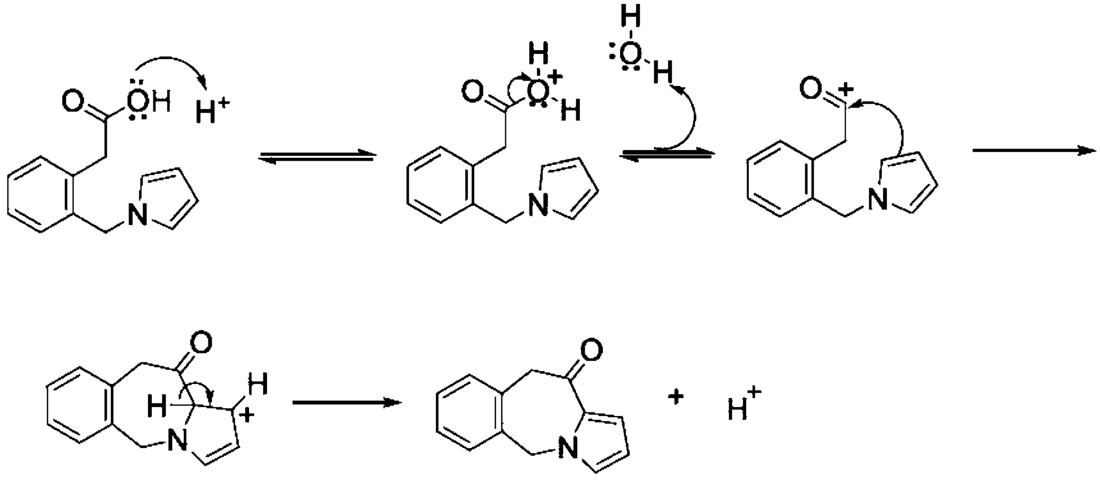

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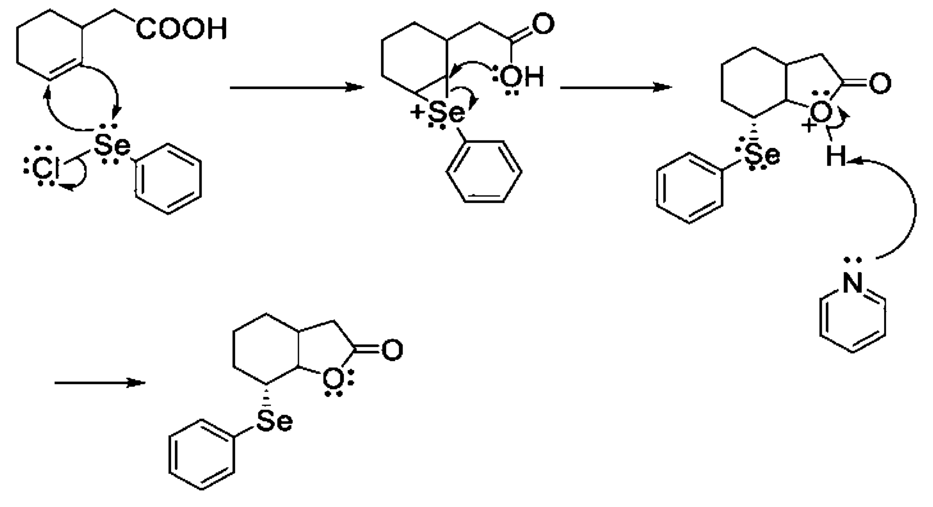
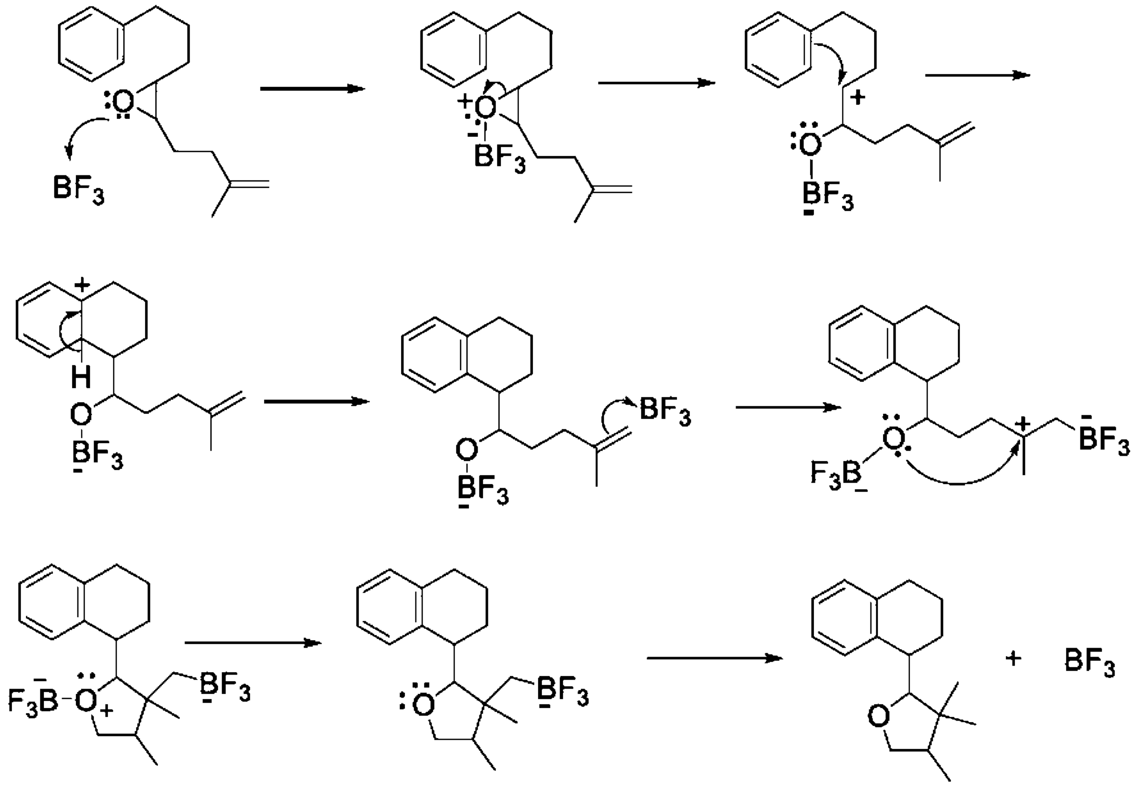

COOH
Cl
Se
O
OH
+Se
O
+
Se
H
N
O
O
Se

217


O
BF3
+O
-
BF3
+
O
BF3
-
+
H
O
BF3
-
O
BF3
-
BF3
O
F3B
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+
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BF3
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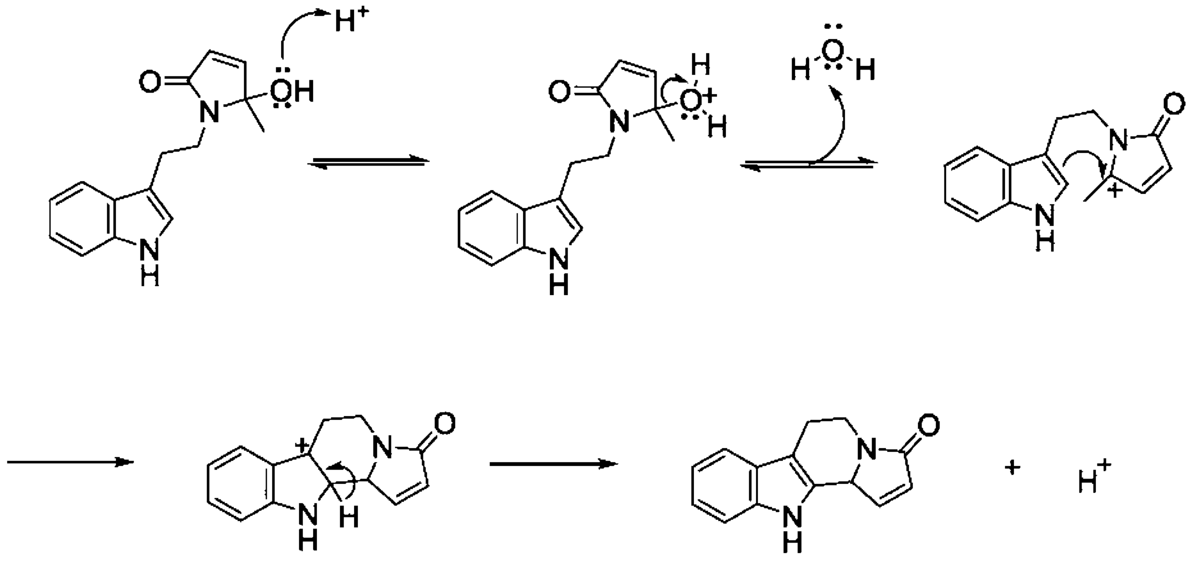
O
+
-
BF3
O
-
BF3
O
+
BF3

218



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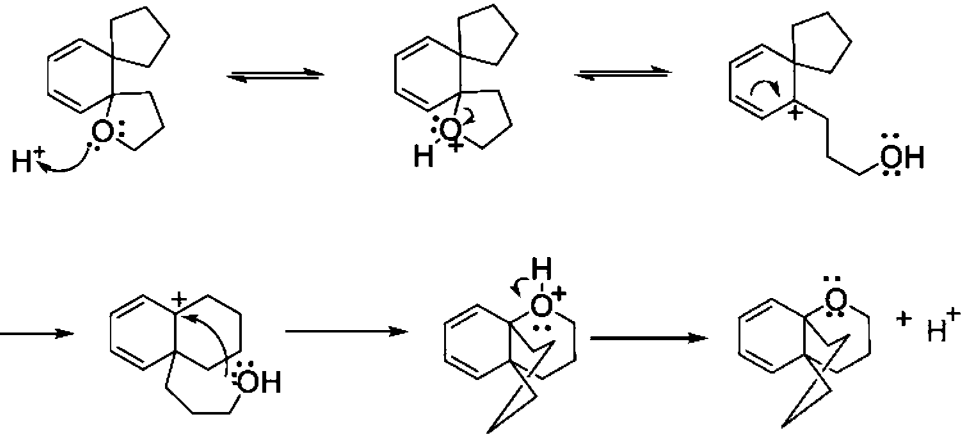

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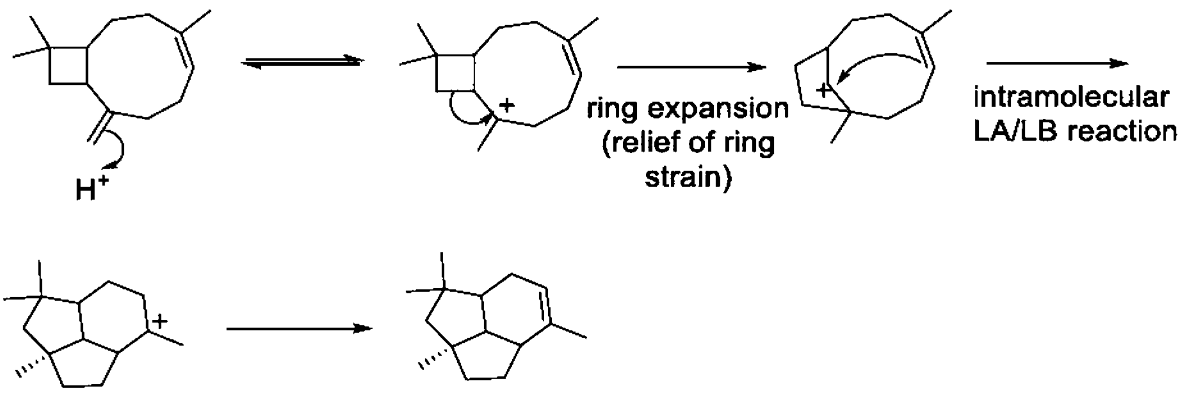
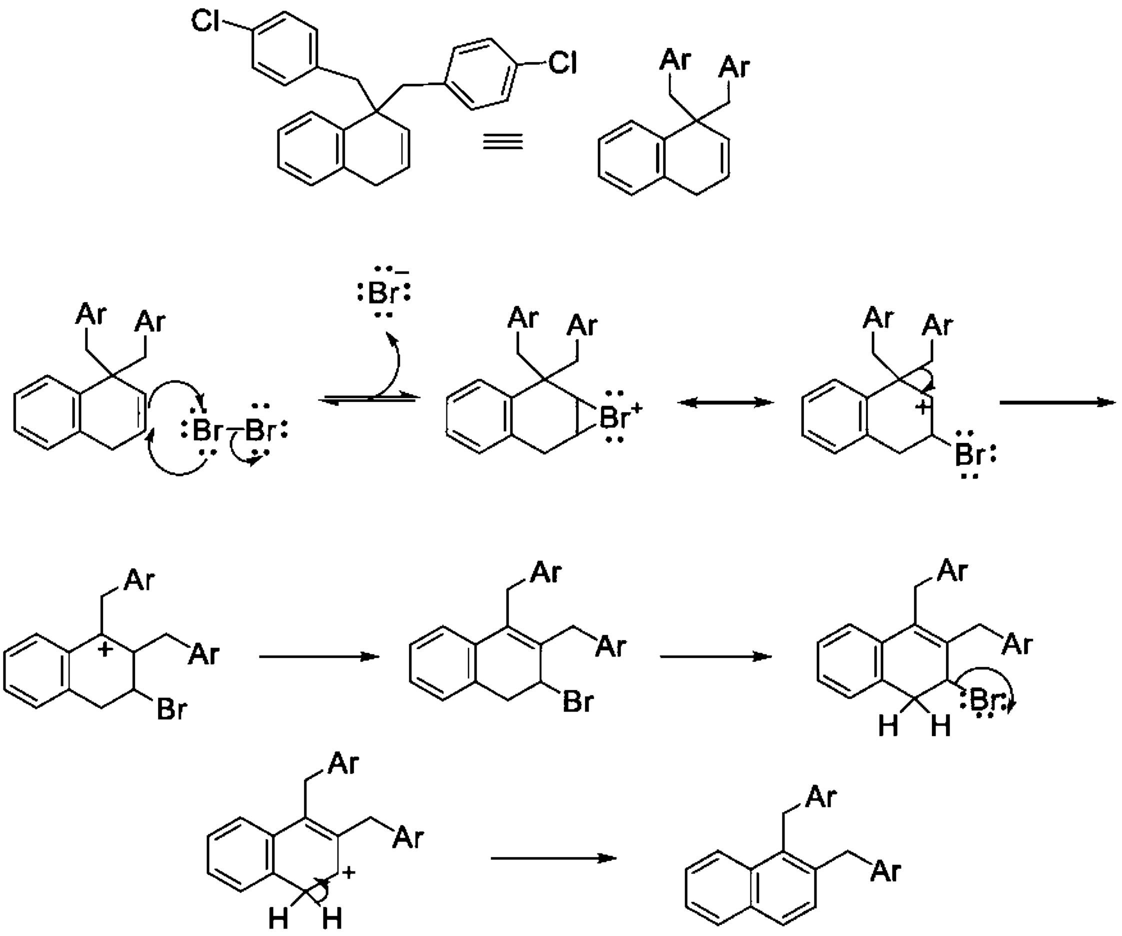

ring expansion (relief of ring strain)
intramolecular LA/LB reaction

221



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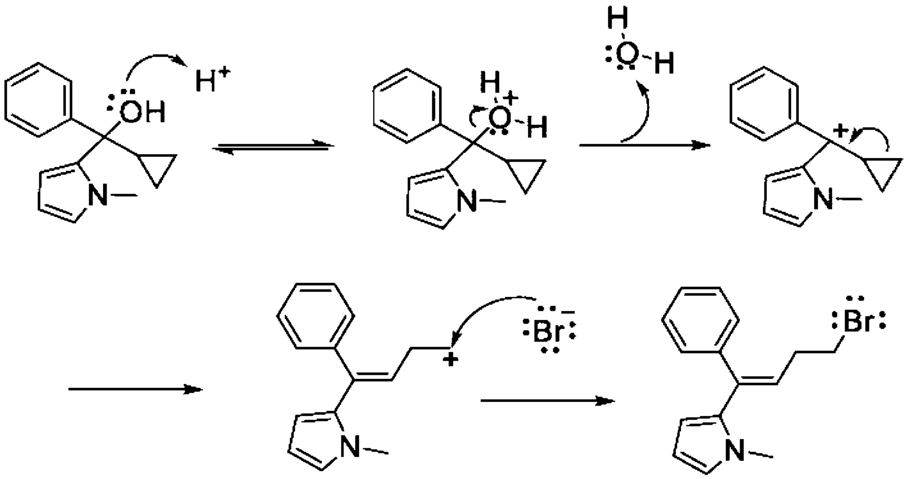

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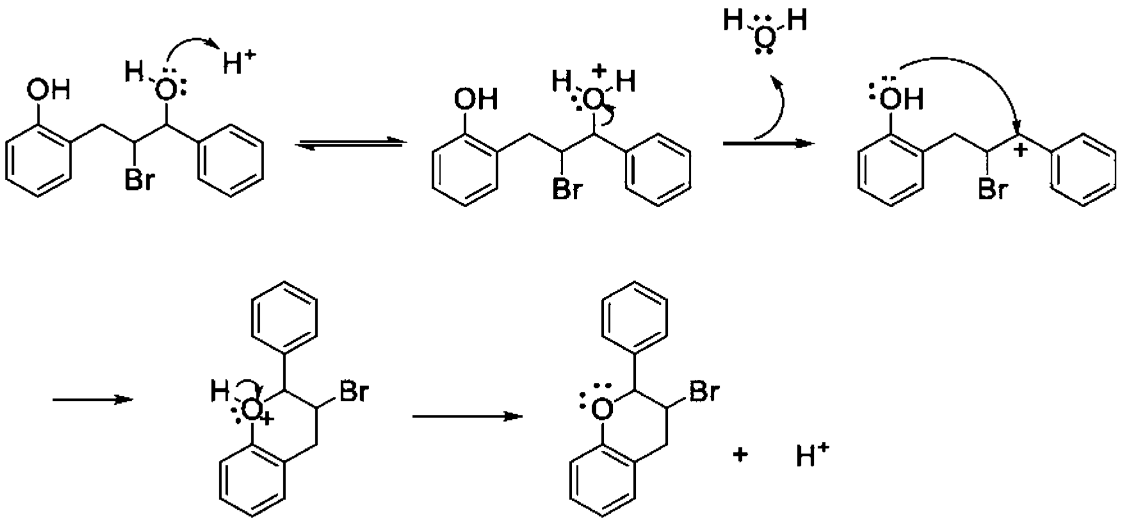

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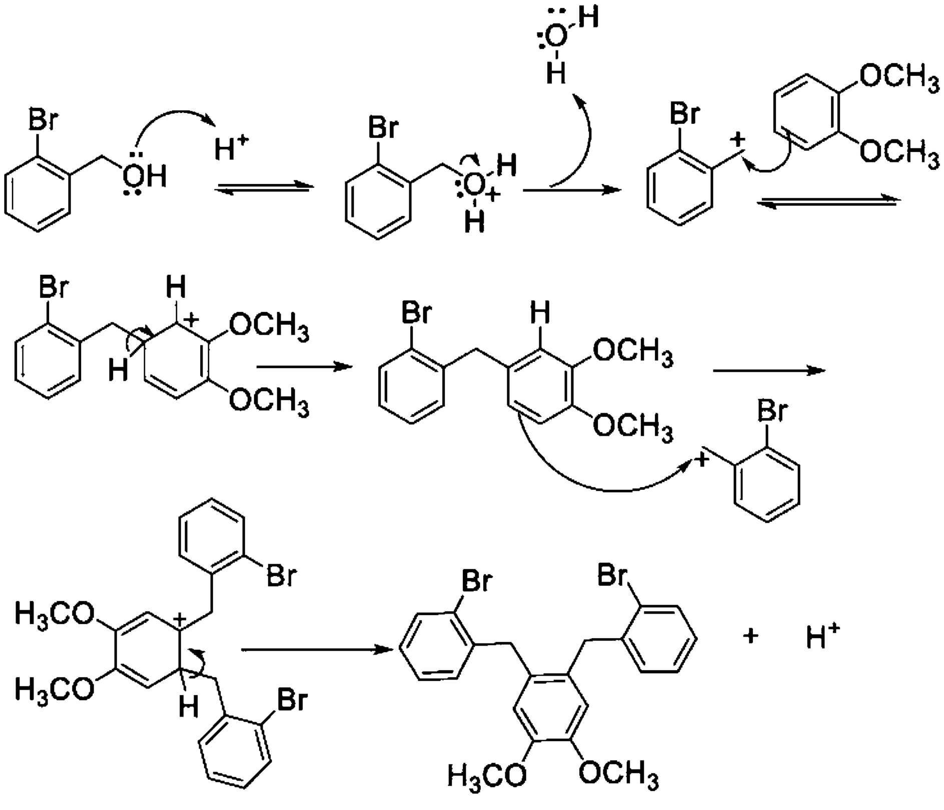

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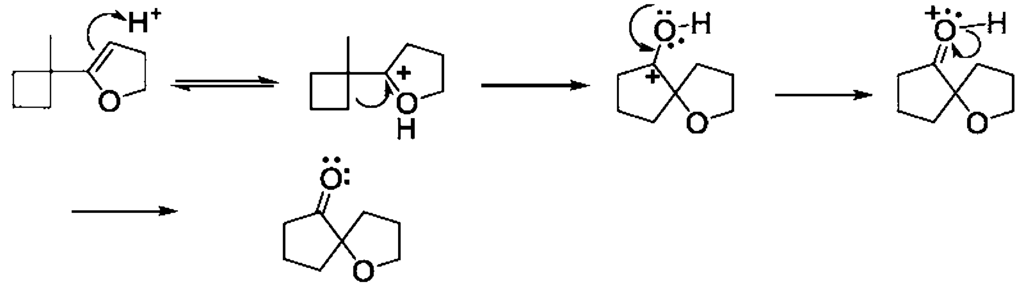

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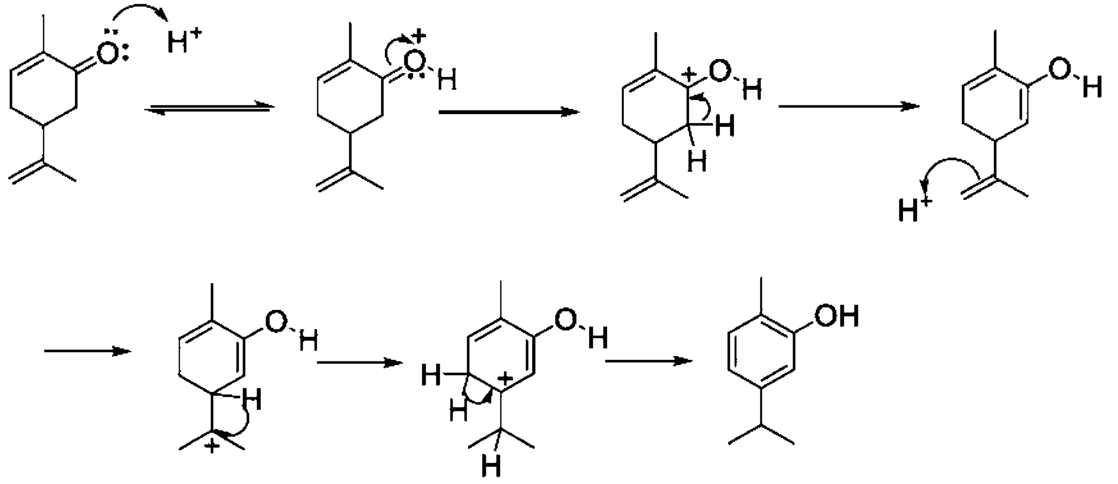

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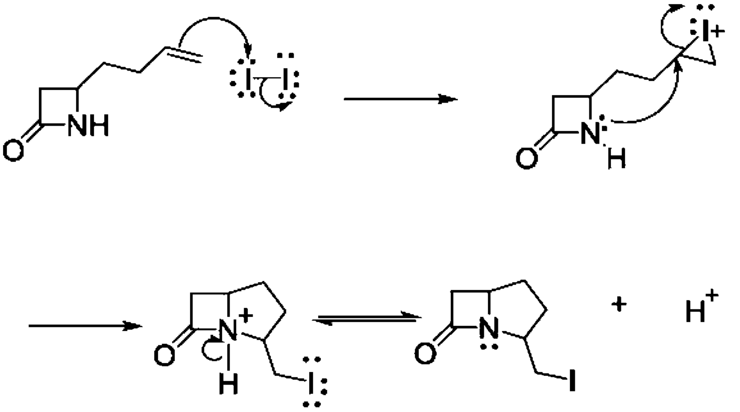
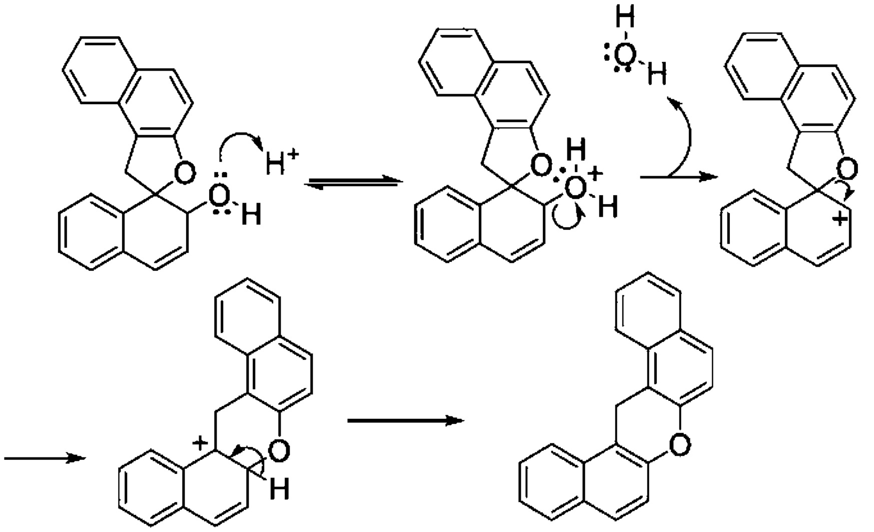


__Note__ The reactivity of the nitrogen is higher than in an acyclic amide because it cannot engage in resonance (ring strain)

228



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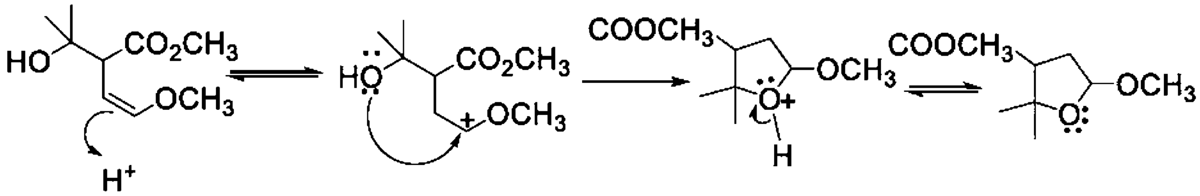
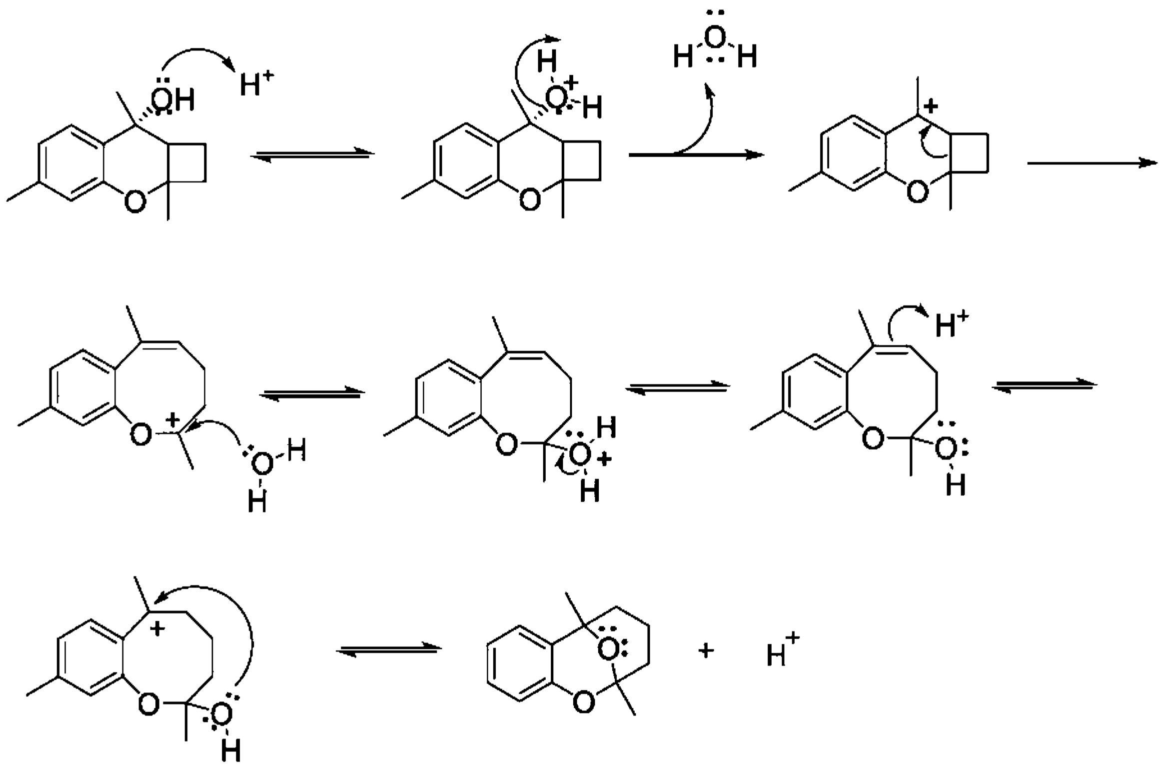


<u>Exercise</u> Why is the carbocation on the carbon next to the oxygen formed?

230



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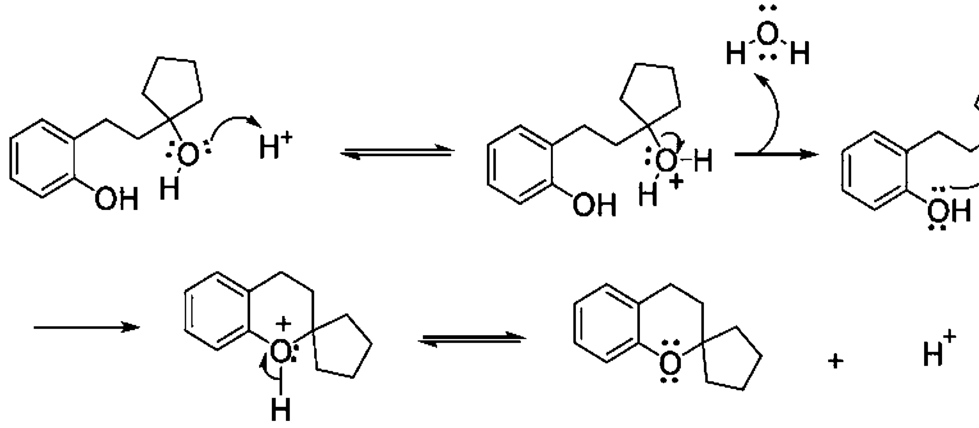

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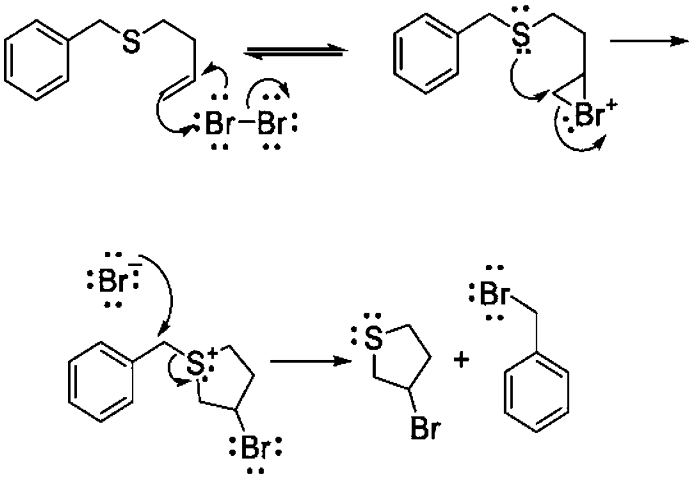
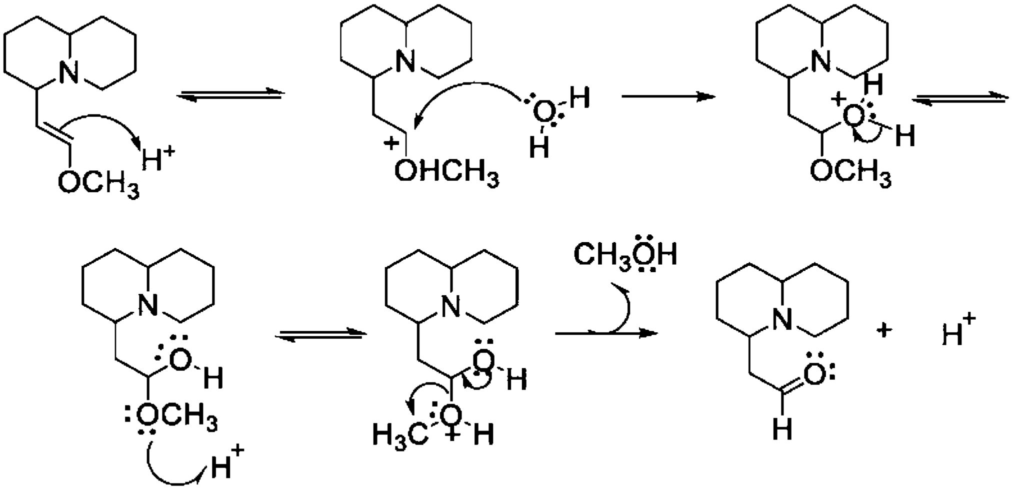
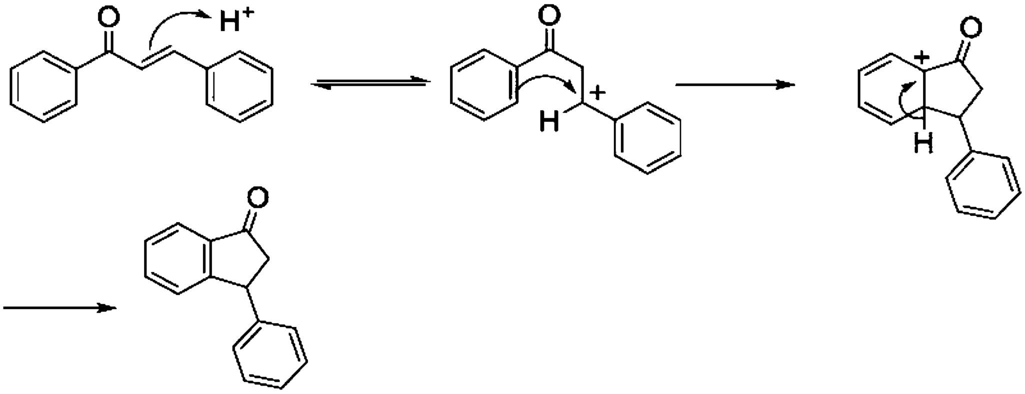

S
Br–Br
S
Br+
Br−
S+
Br
S
+
Br
Br

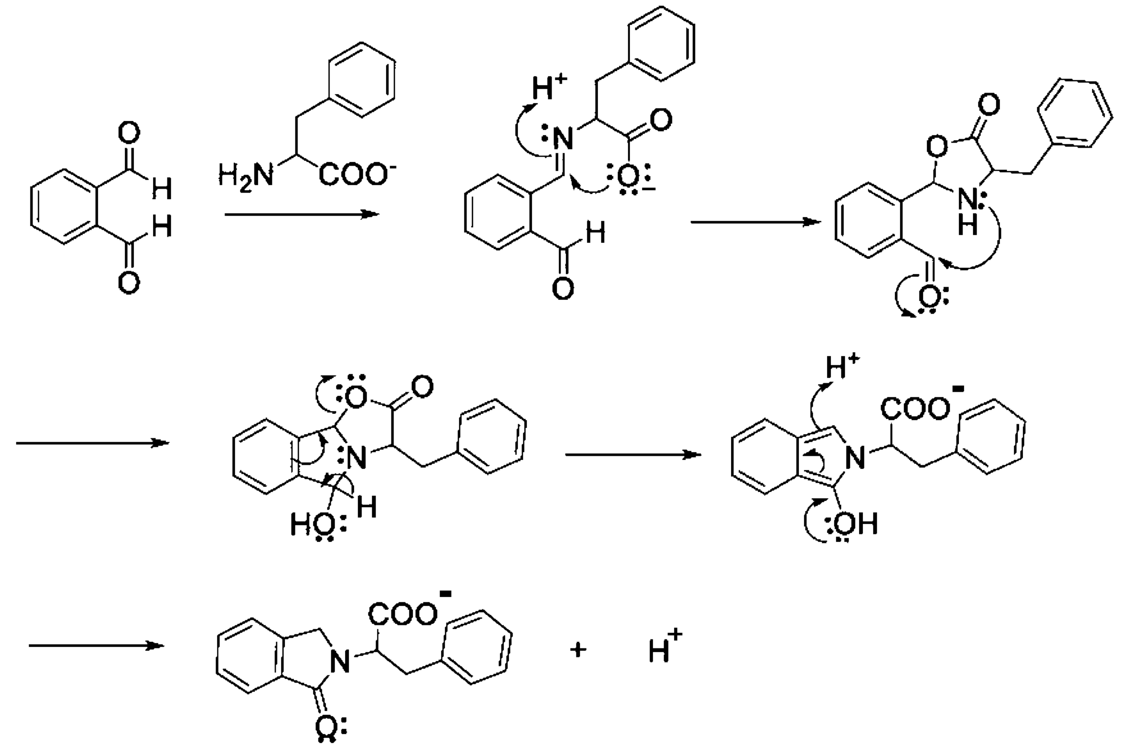
233


N
H+
OCH3
N
+
OHCH3
O
H
H
N
+
O
H
H
OCH3
N
O
H
OCH3
H+
N
O
H
H3C
+
O
H
CH3OH
N
O
H
+
H+

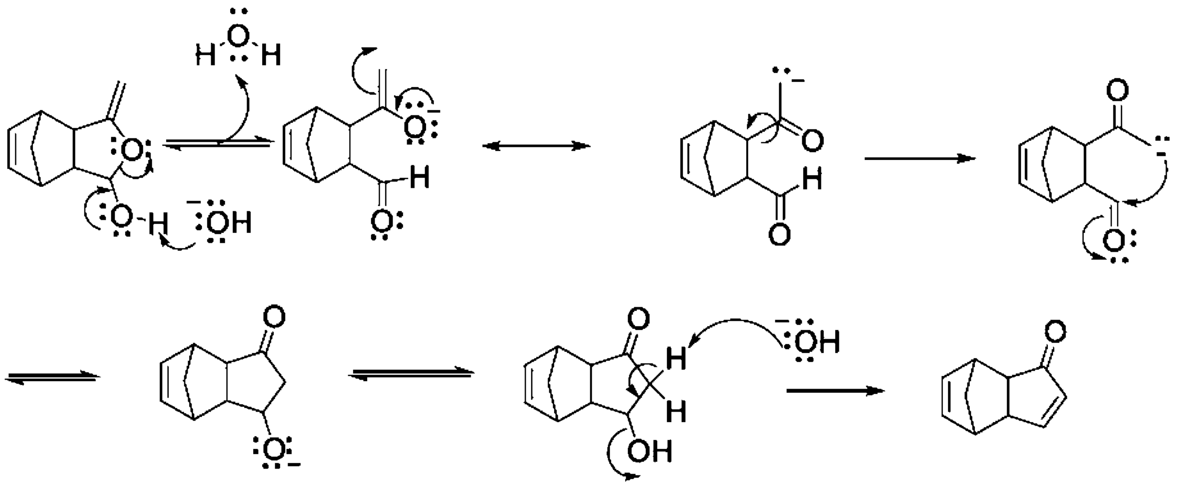
234


O
H+
O
+
H
O
+
H
O

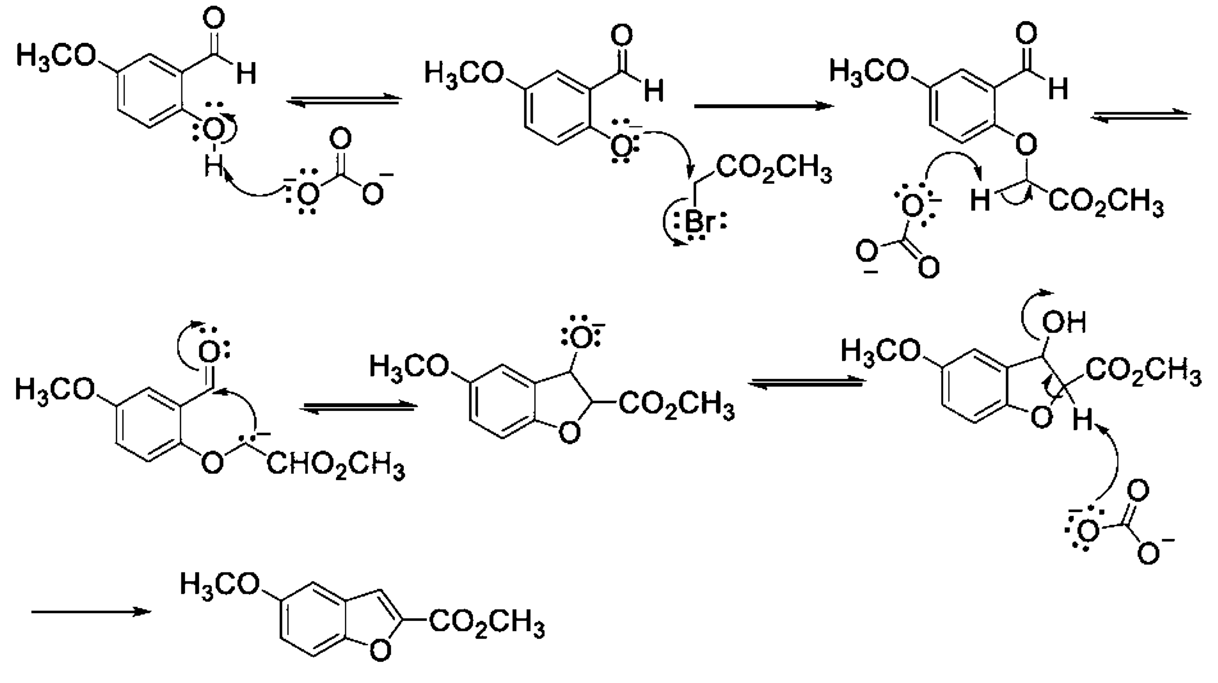
235


H
H
O
O
H₂N
COO⁻
H⁺
N
O
O
H
O
O
N
H
O
O
O
N
H
HO
H⁺
COO⁻
N
OH
COO⁻
N
O
+
H⁺

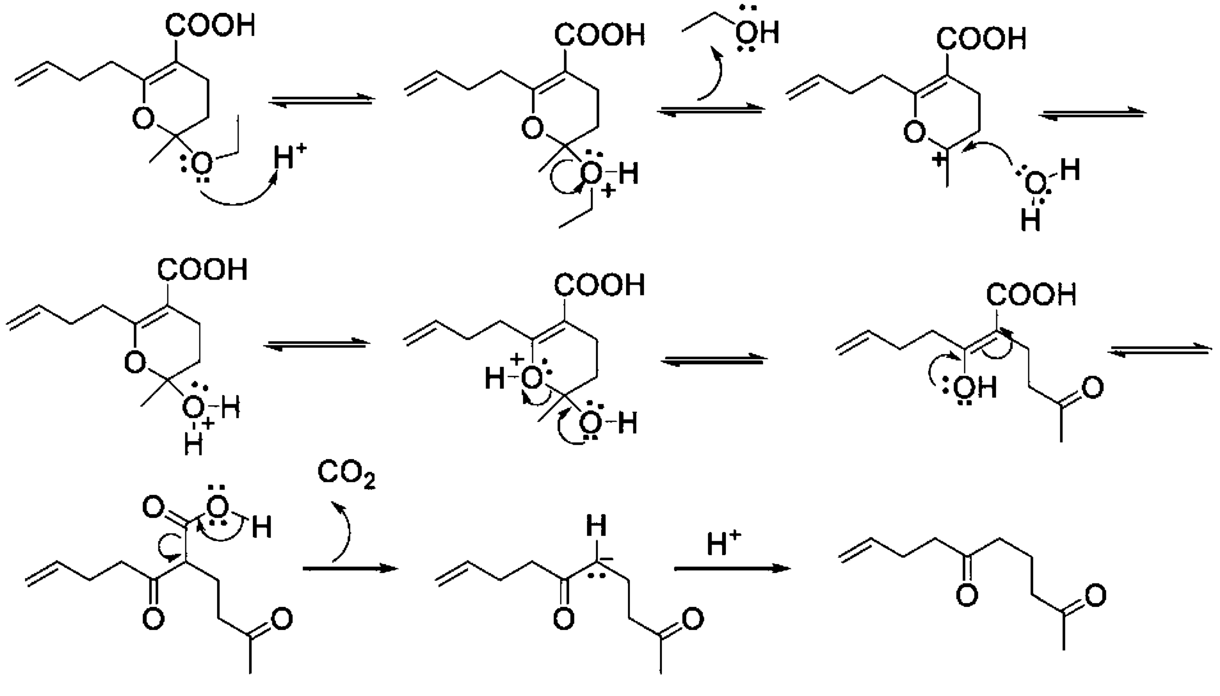
236


H O H
O
O-H
OH
O
H
O
O
H
O
O
O
O
O
O
H
OH
H
OH
O

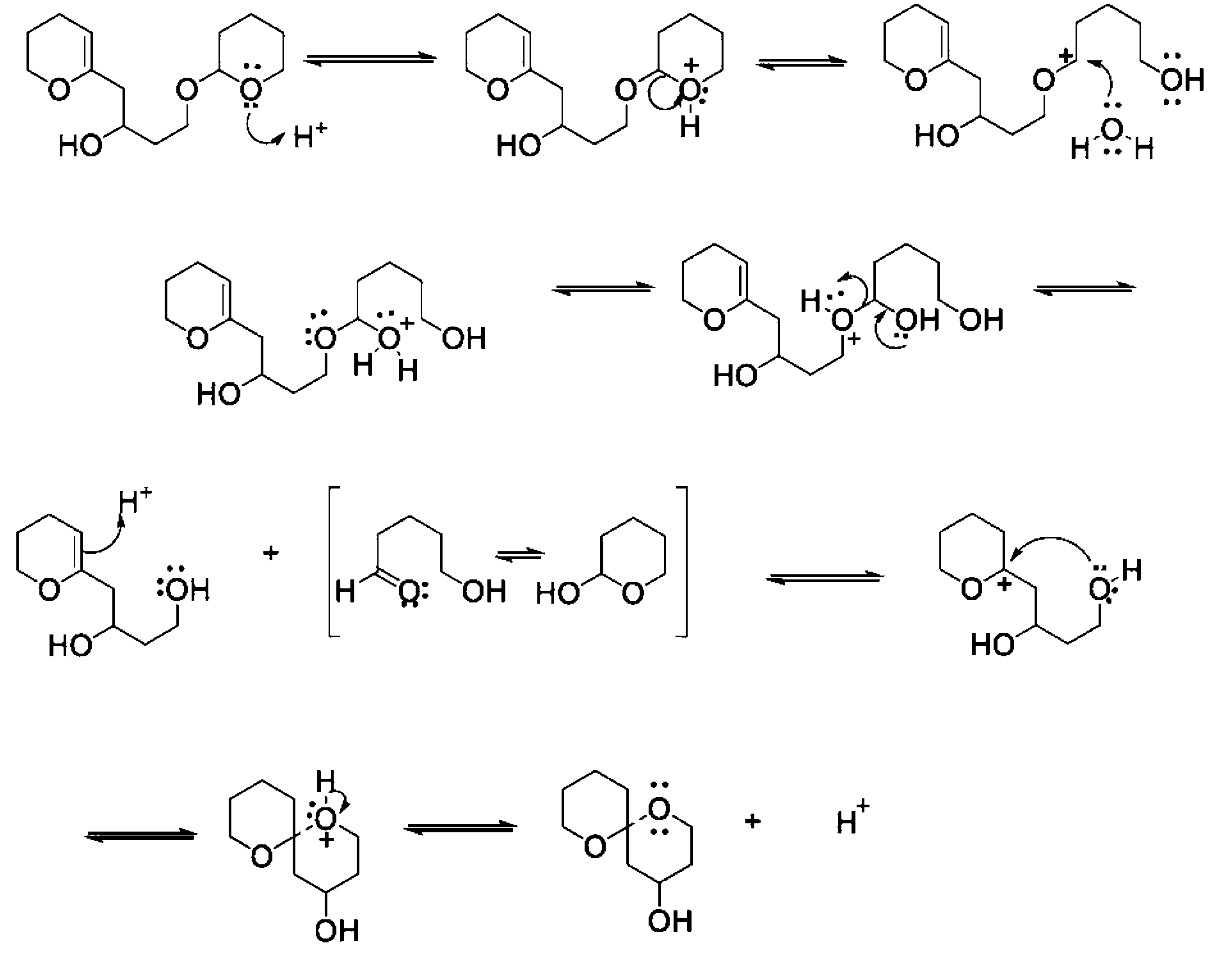
237



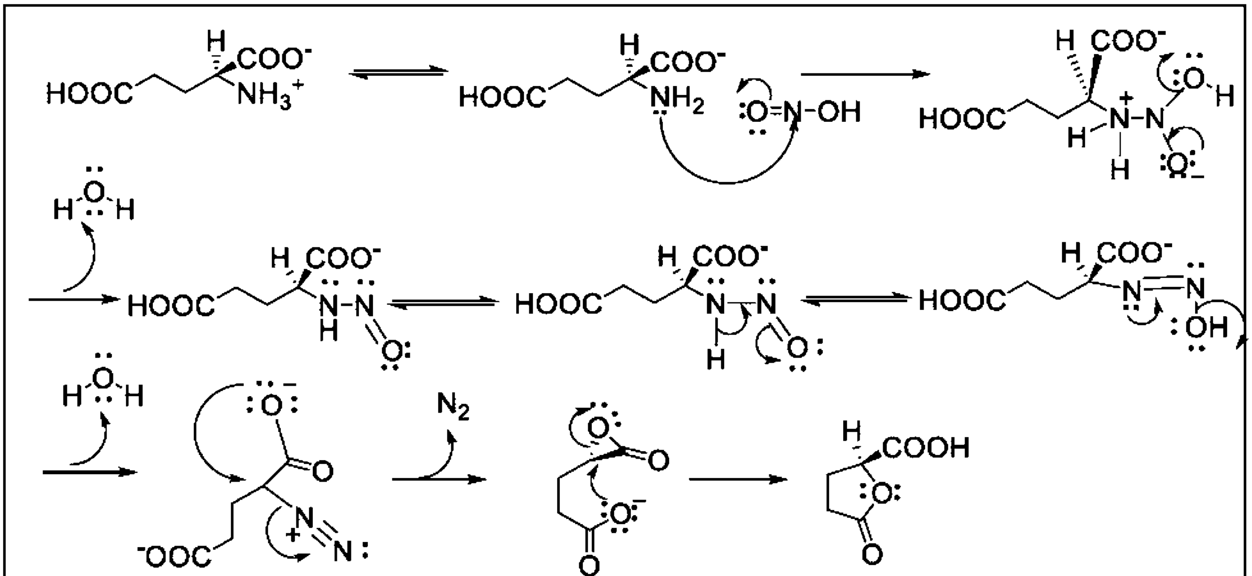
238



239



240



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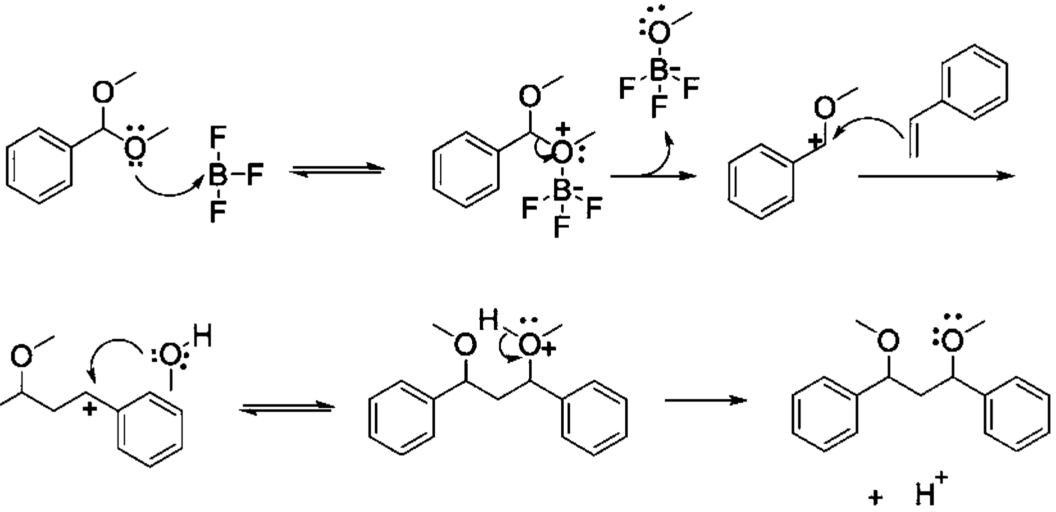
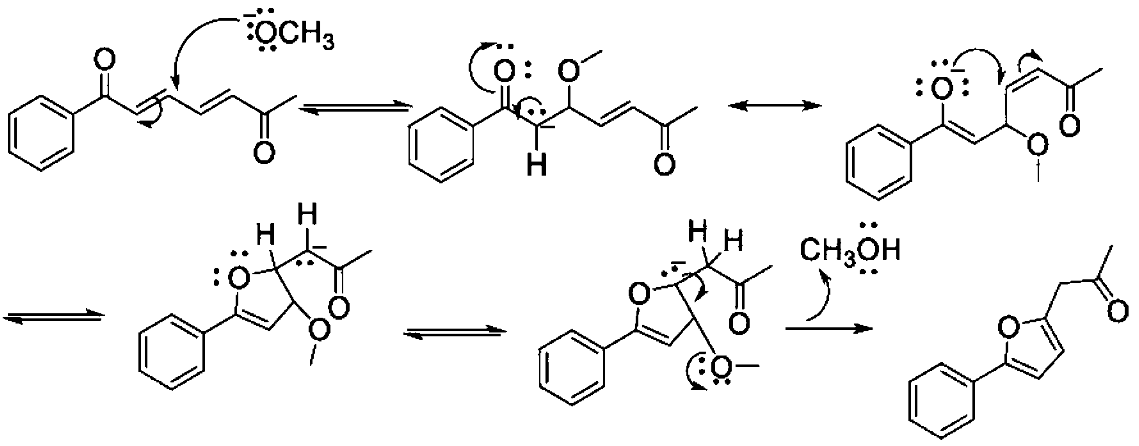
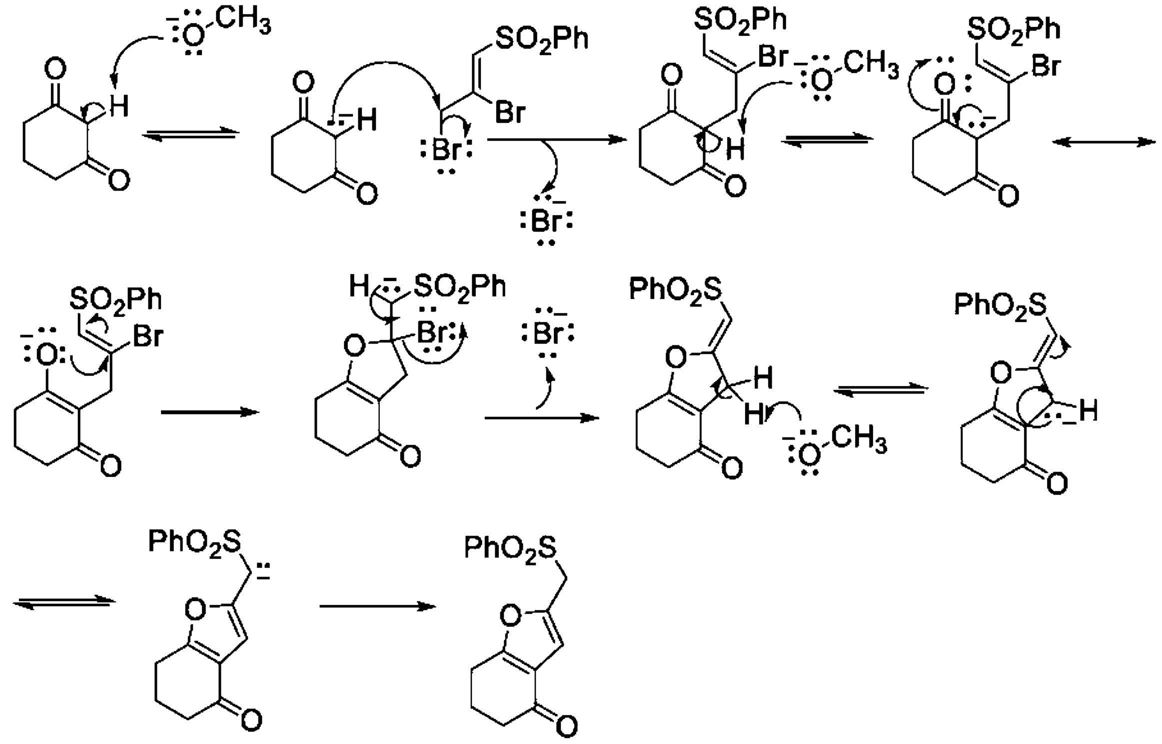


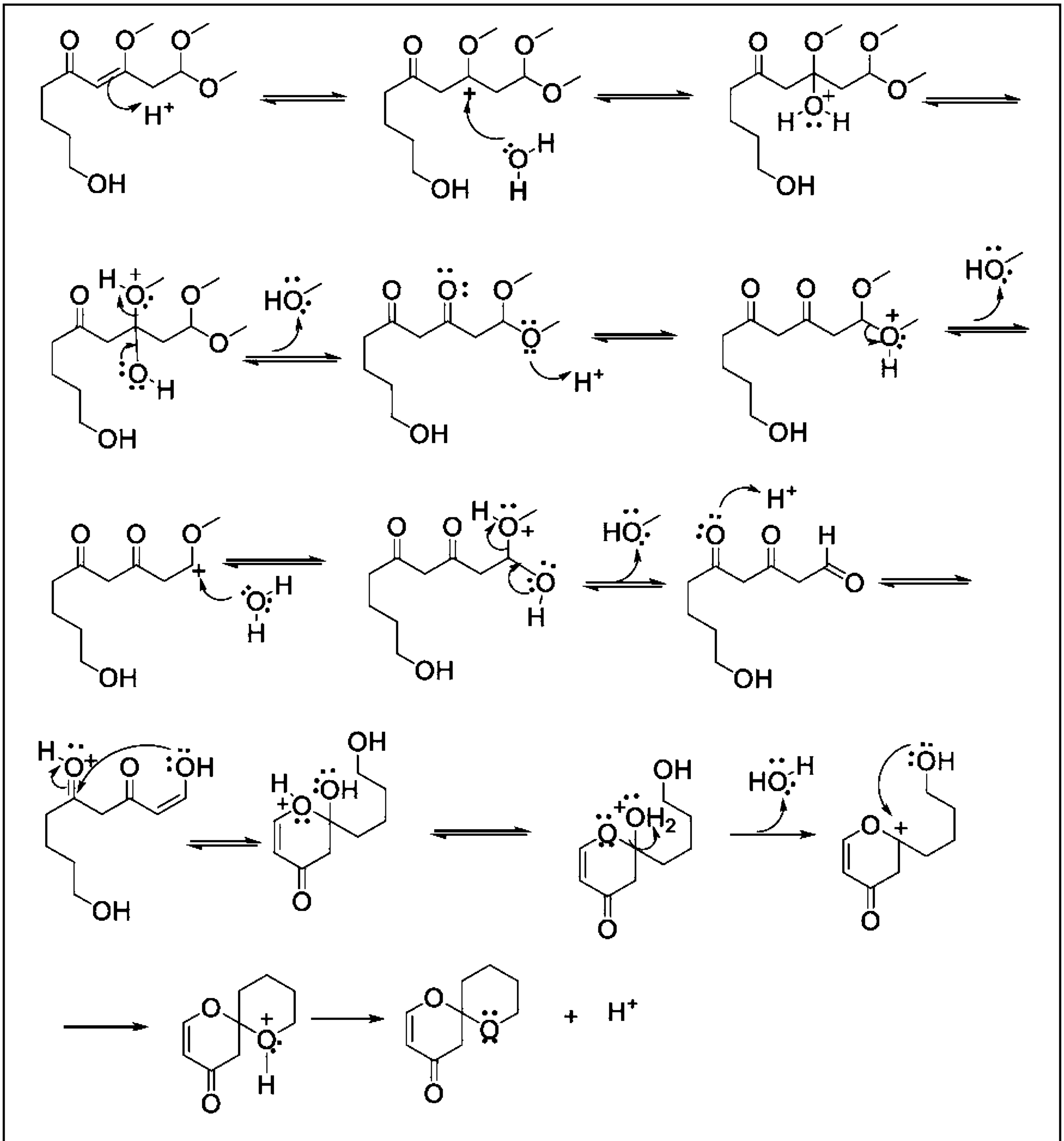
242



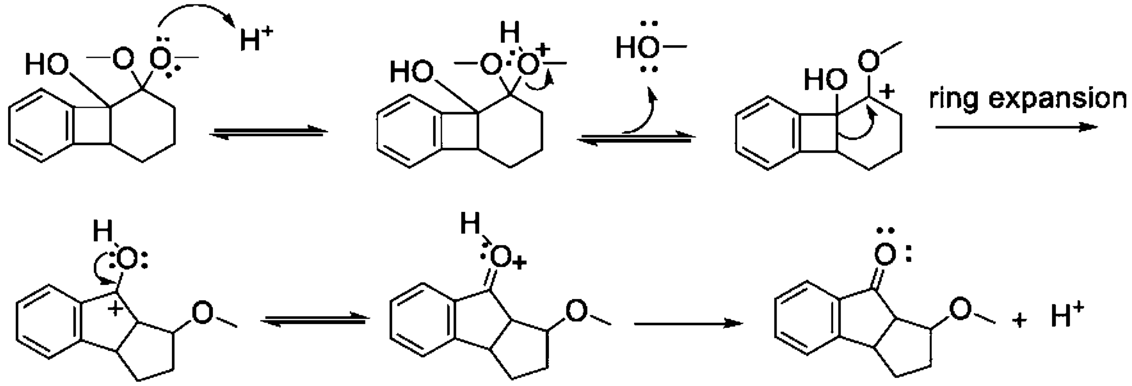
243



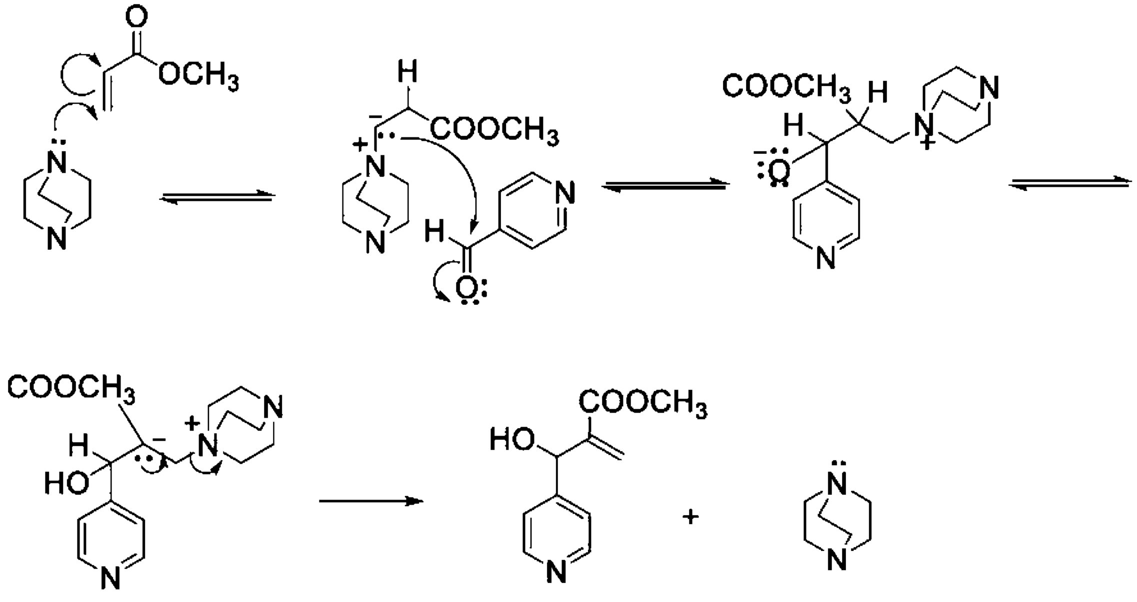
244



245

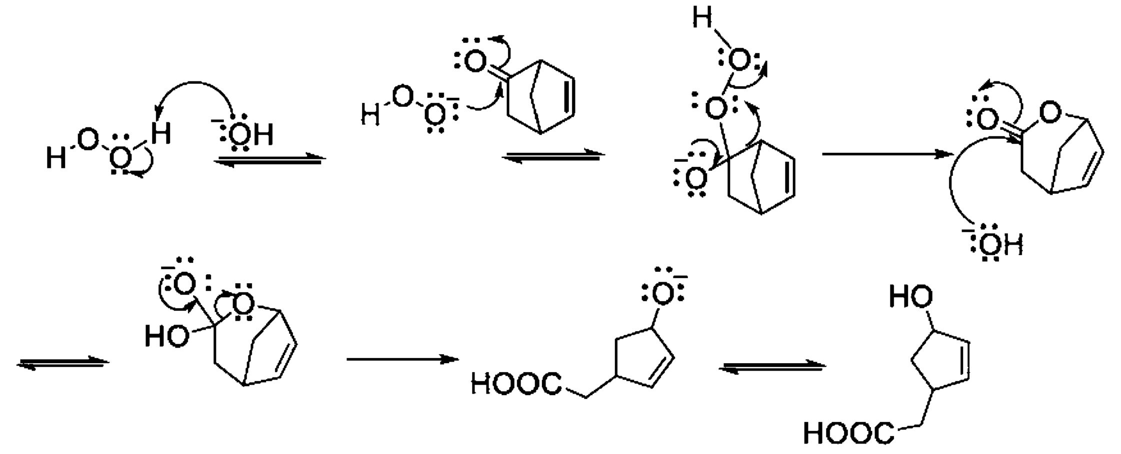


246

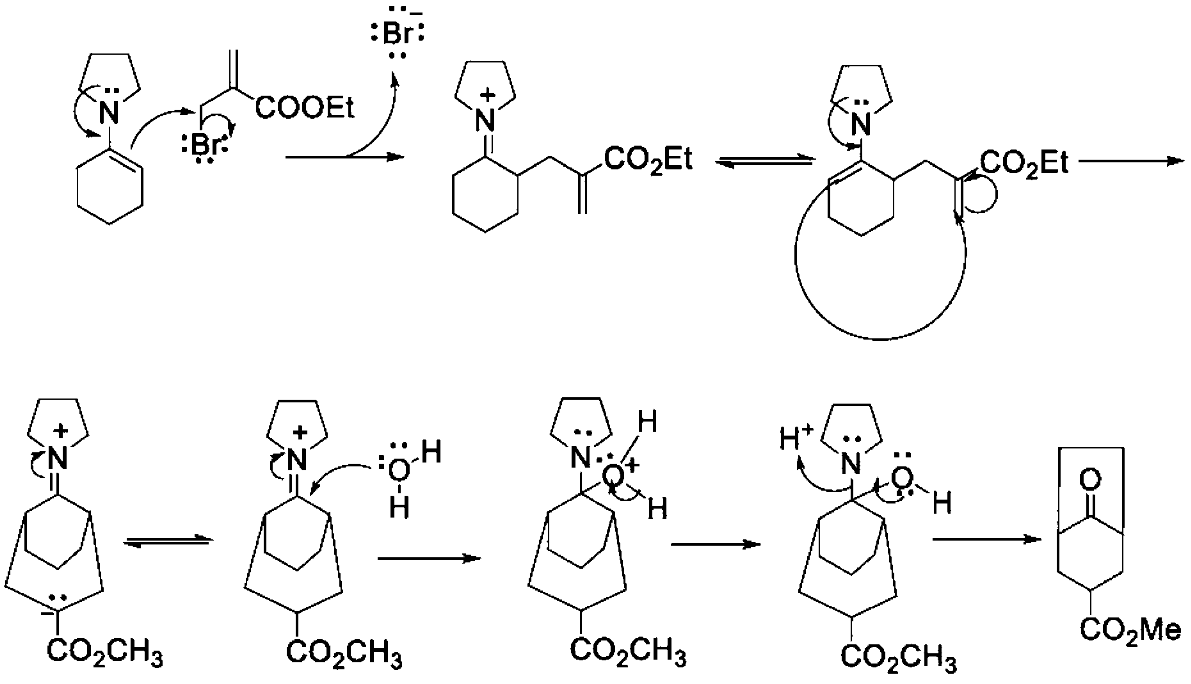


This is an example of the *Bayliss-Hill reaction*

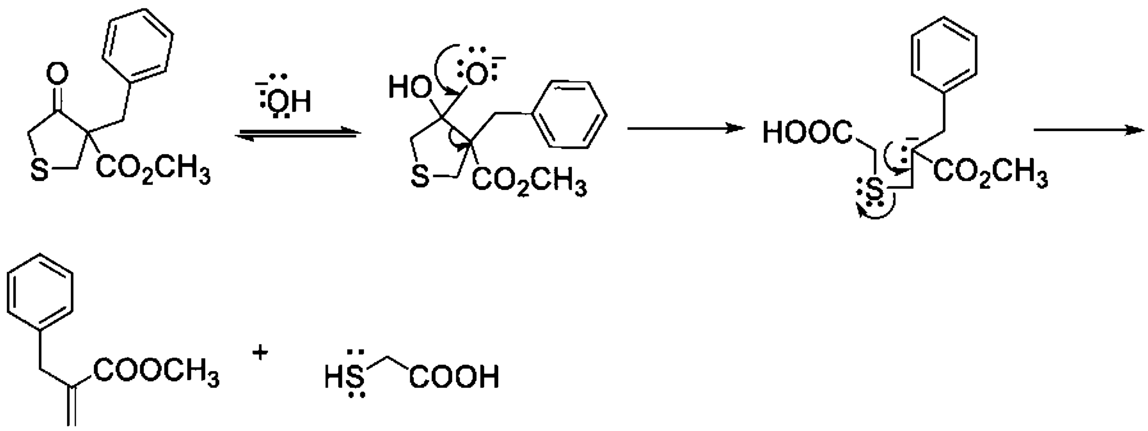
247


H
O
H
OH
H
O
O
O
H
O
O
O
O
O
OH
O
O
HO
O
HOOC
HO
HOOC

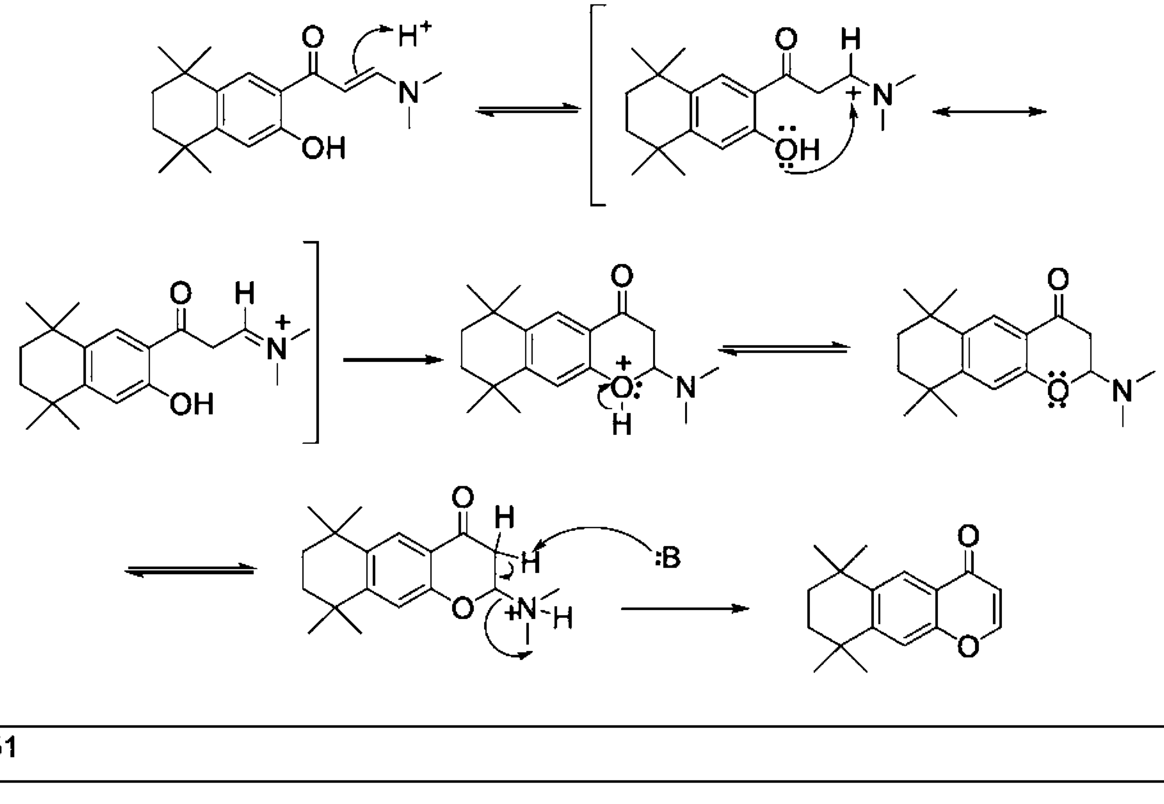
248


N
Br
COOEt
Br
N
+
CO_2Et
N
CO_2Et
+
N
CO_2CH_3
+
N
O
H
H
CO_2CH_3
N
O
+
H
H
CO_2CH_3
H^+
N
O
H
CO_2CH_3
O
CO_2Me

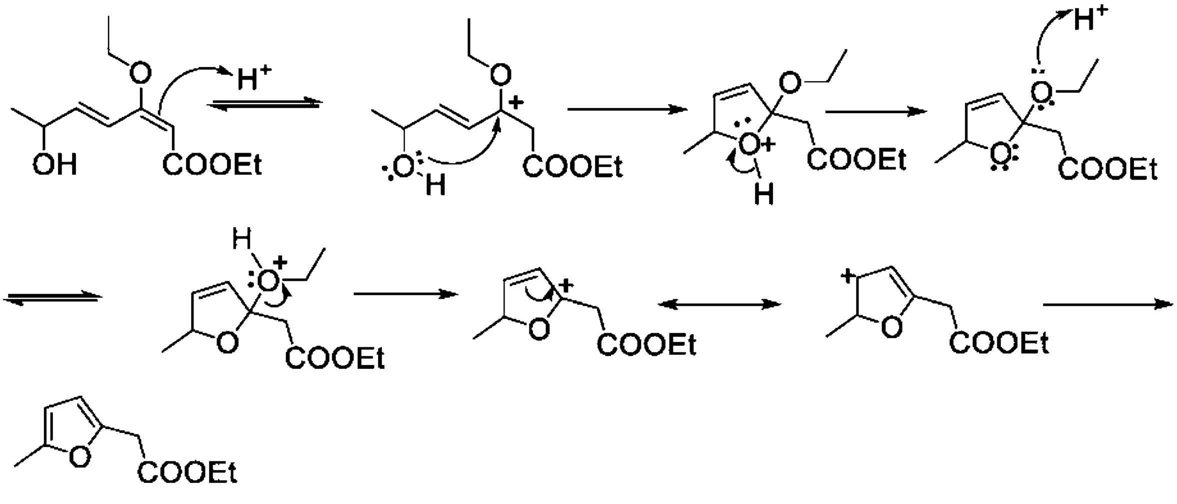
249


O
:ÖH
HO
:Ö:
S
CO2CH3
HOOC
COOCH3
+
HS
COOH

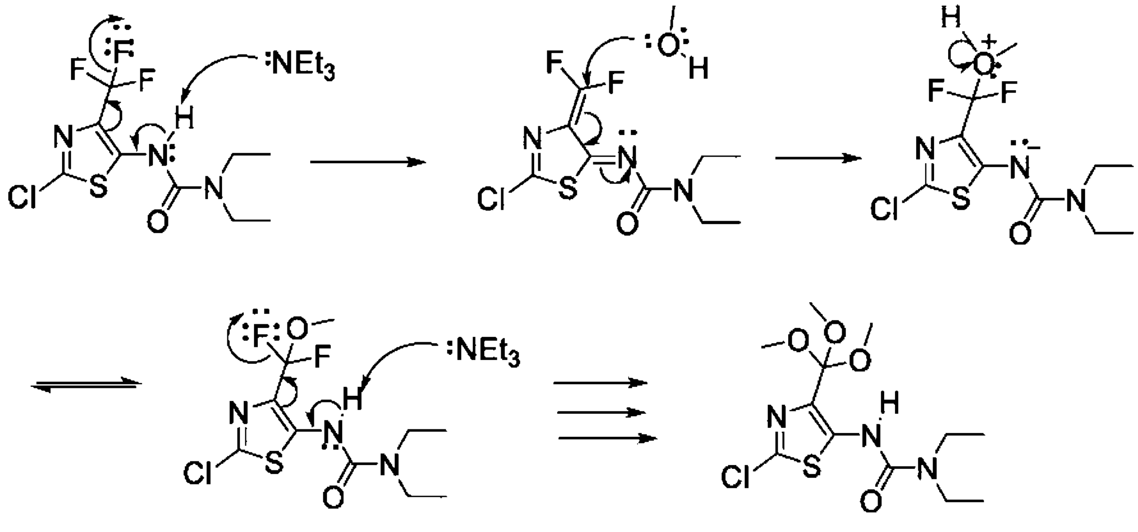
250


O
H+
N
OH
H
+
ÖH
O
H
+
N
OH
O
+
O:
H
N
O
Ö
N
O
H
H
:B
O
+N
H
O
O

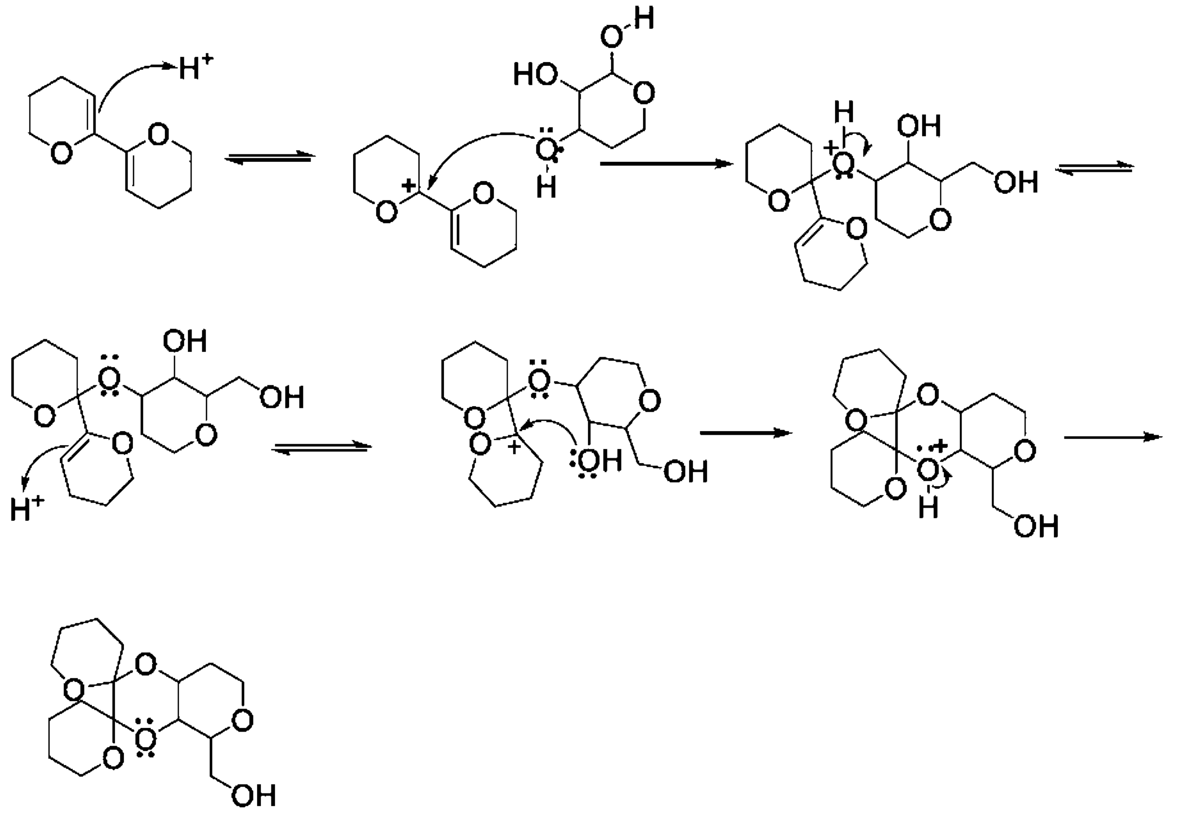
251


H+
OH
COOEt
O
+
H
COOEt
COOEt
COOEt
COOEt
COOEt
COOEt
COOEt

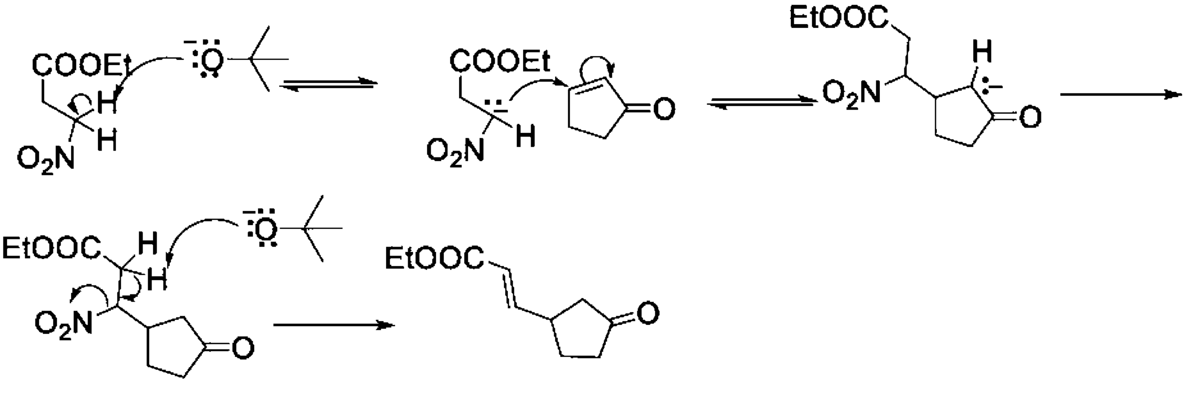
252


F
F
F
:NEt3
H
N
N
Cl
S
O
N
:O
H
H
+
:NEt3
O
O
O

253



254

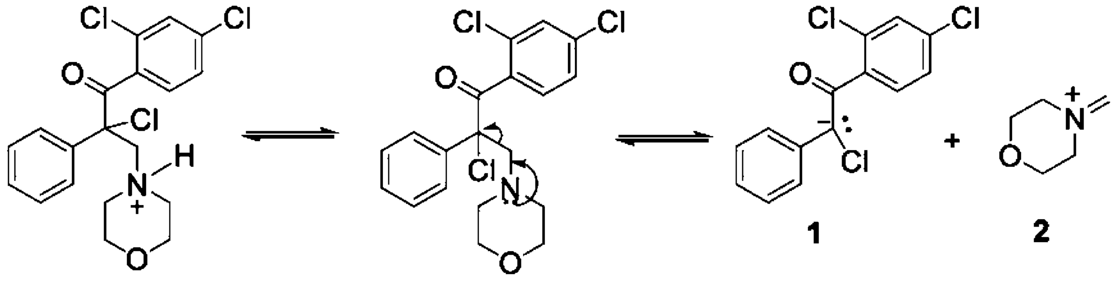


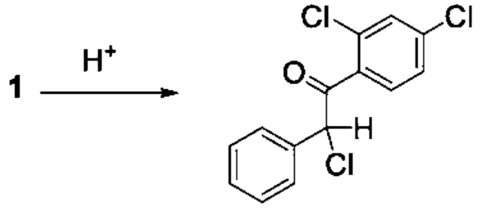
Exercise

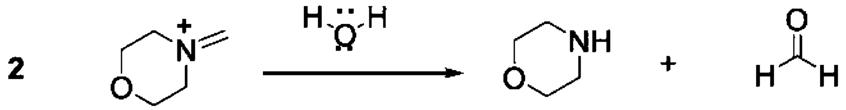
a) Why did the initial proton abstraction happen on the carbon next to the nitro group?

b) Why is NO_2^- a good leaving group?

255

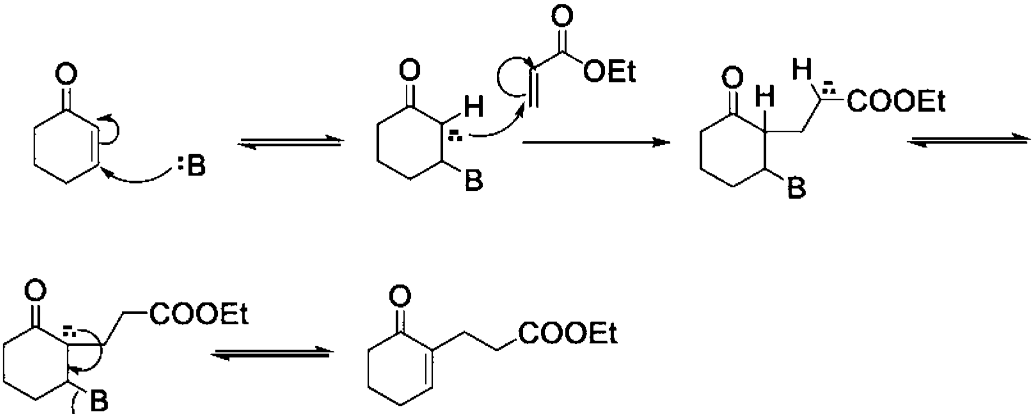




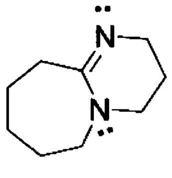


Exercise Write a mechanism for step 2

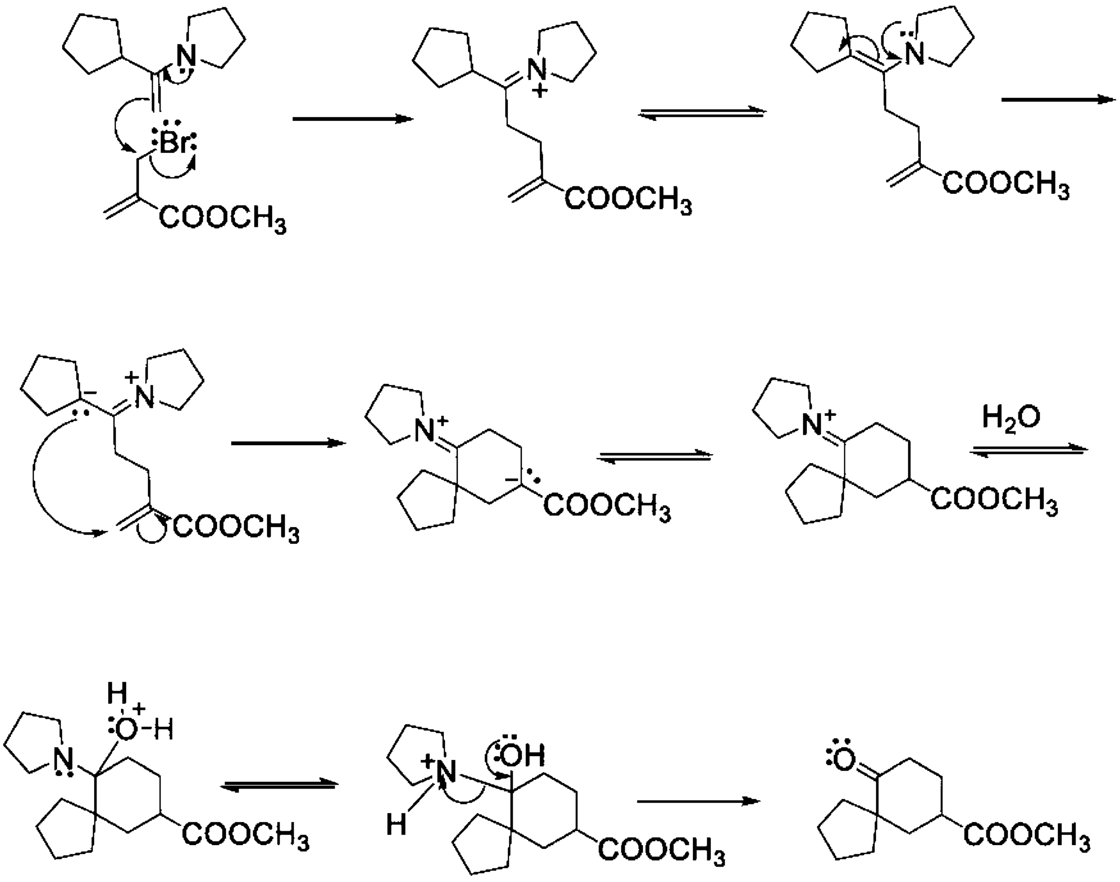
256



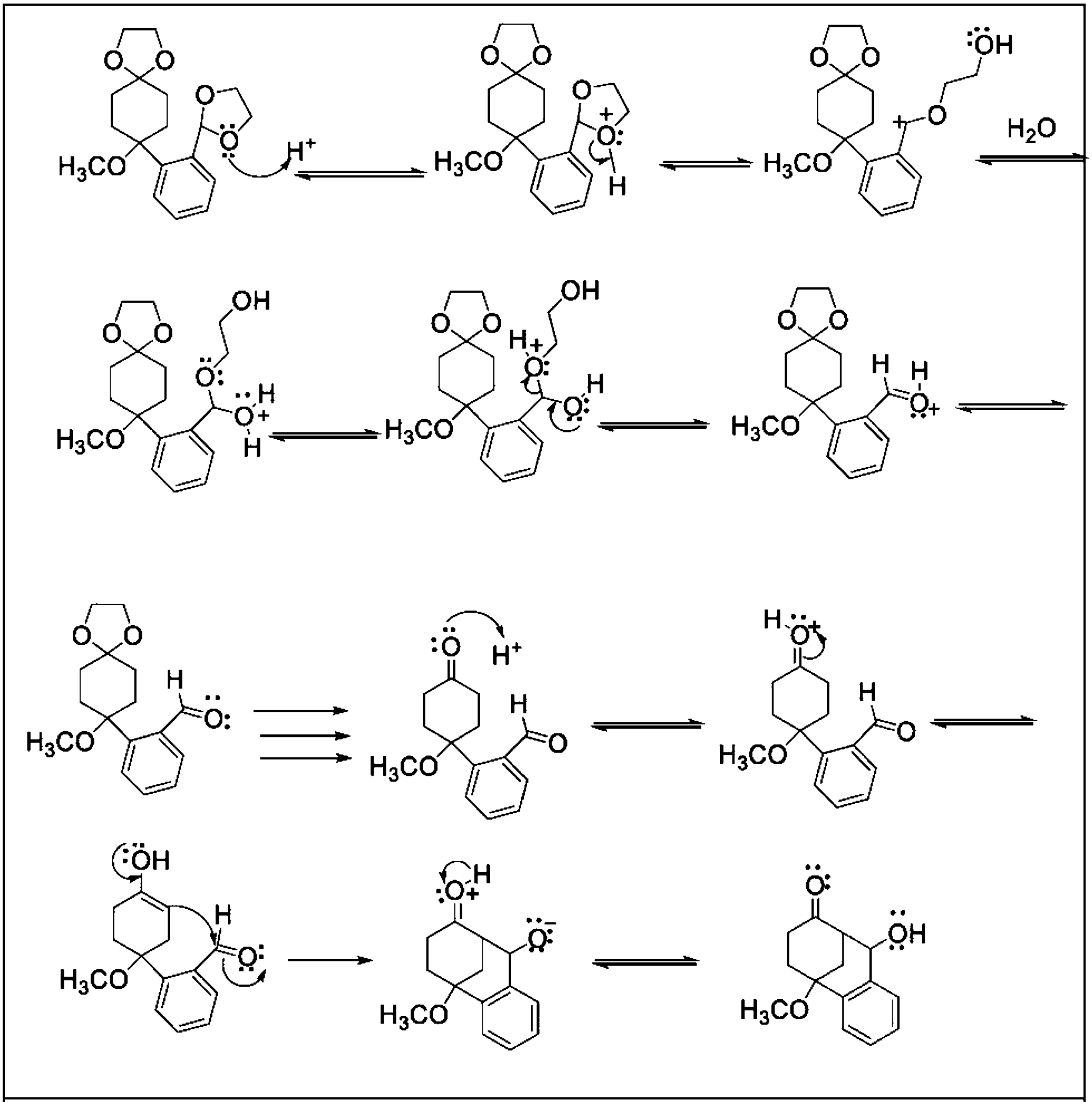
B = DBU =



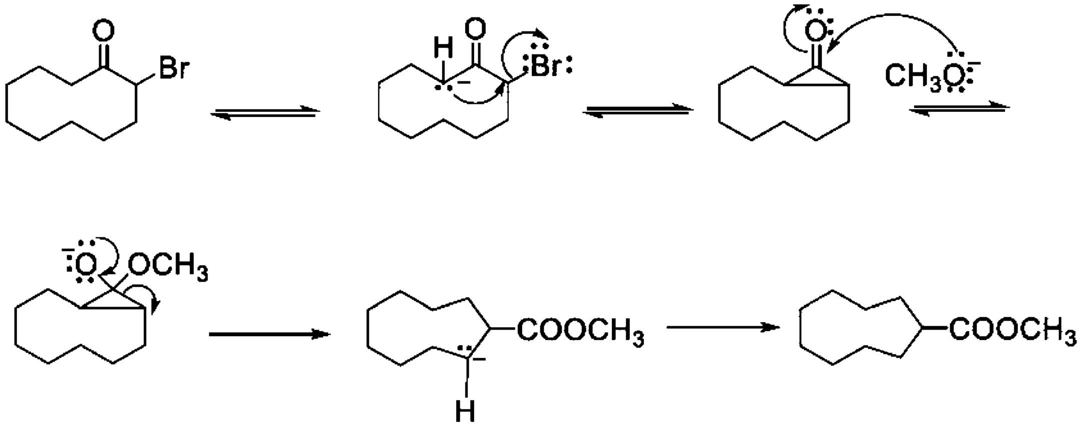
257


N
Br
COOCH$_3$
N
+
COOCH$_3$
N
COOCH$_3$
−
+
N
COOCH$_3$
N
+
−
COOCH$_3$
N
+
COOCH$_3$
H$_2$O
H
+
O-H
N
COOCH$_3$
+
N
H
OH
COOCH$_3$
O
COOCH$_3$

258

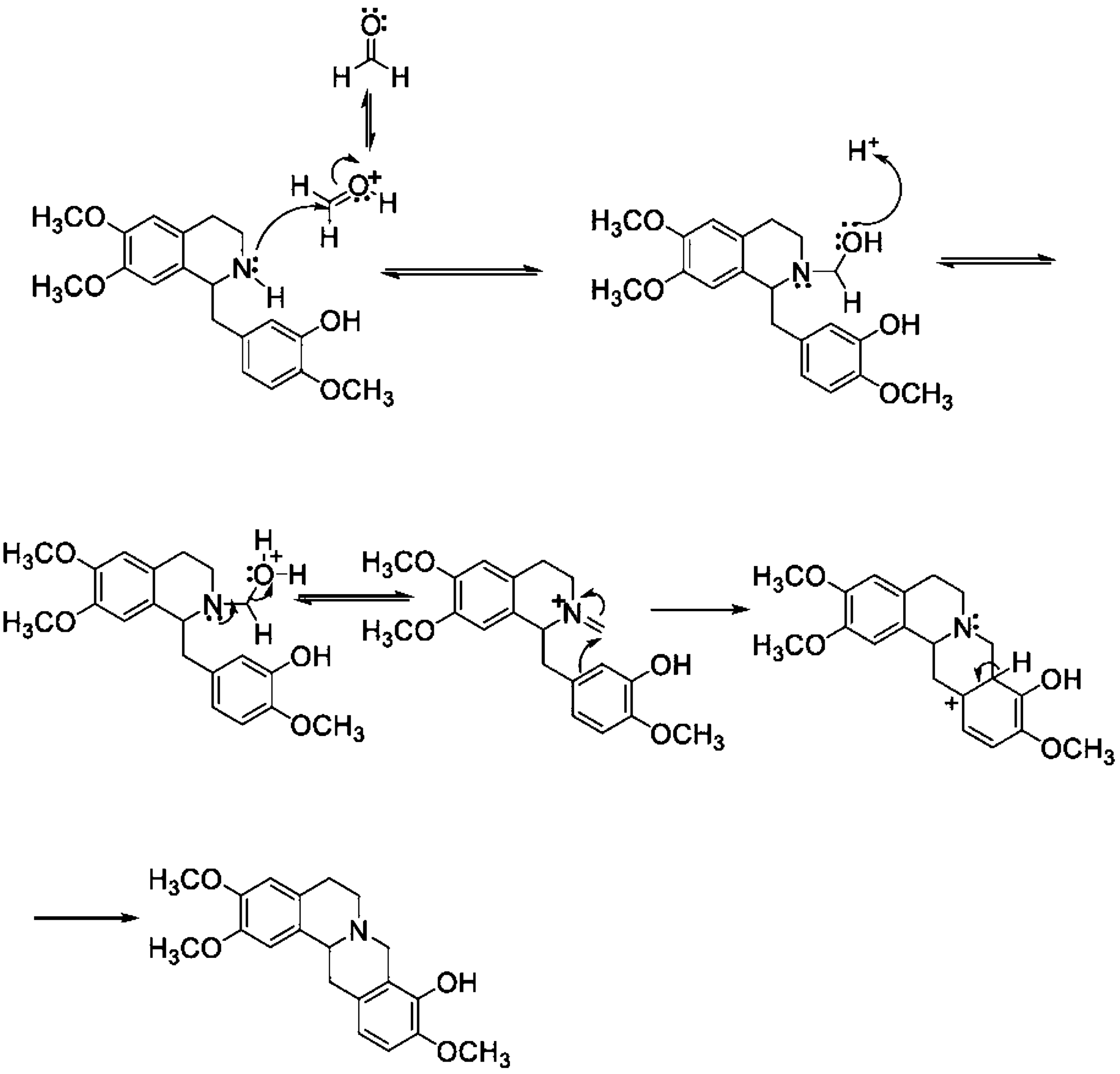


259



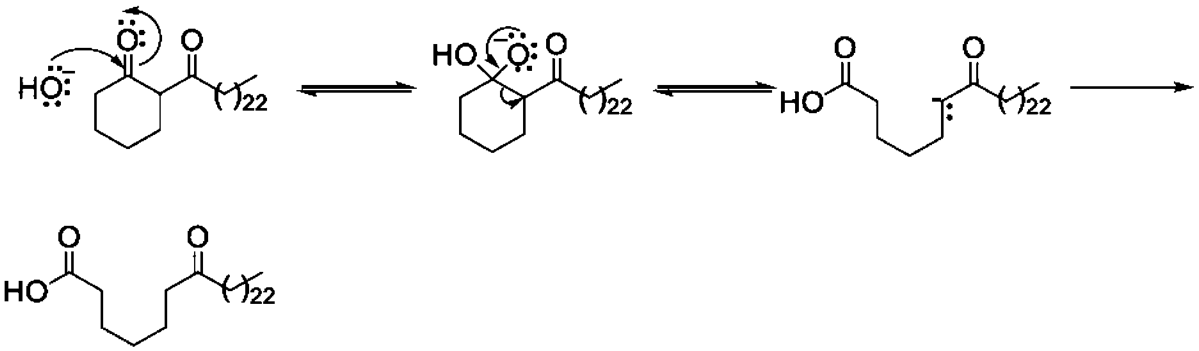
This is an example of the *Favorskii rearrangement*

260

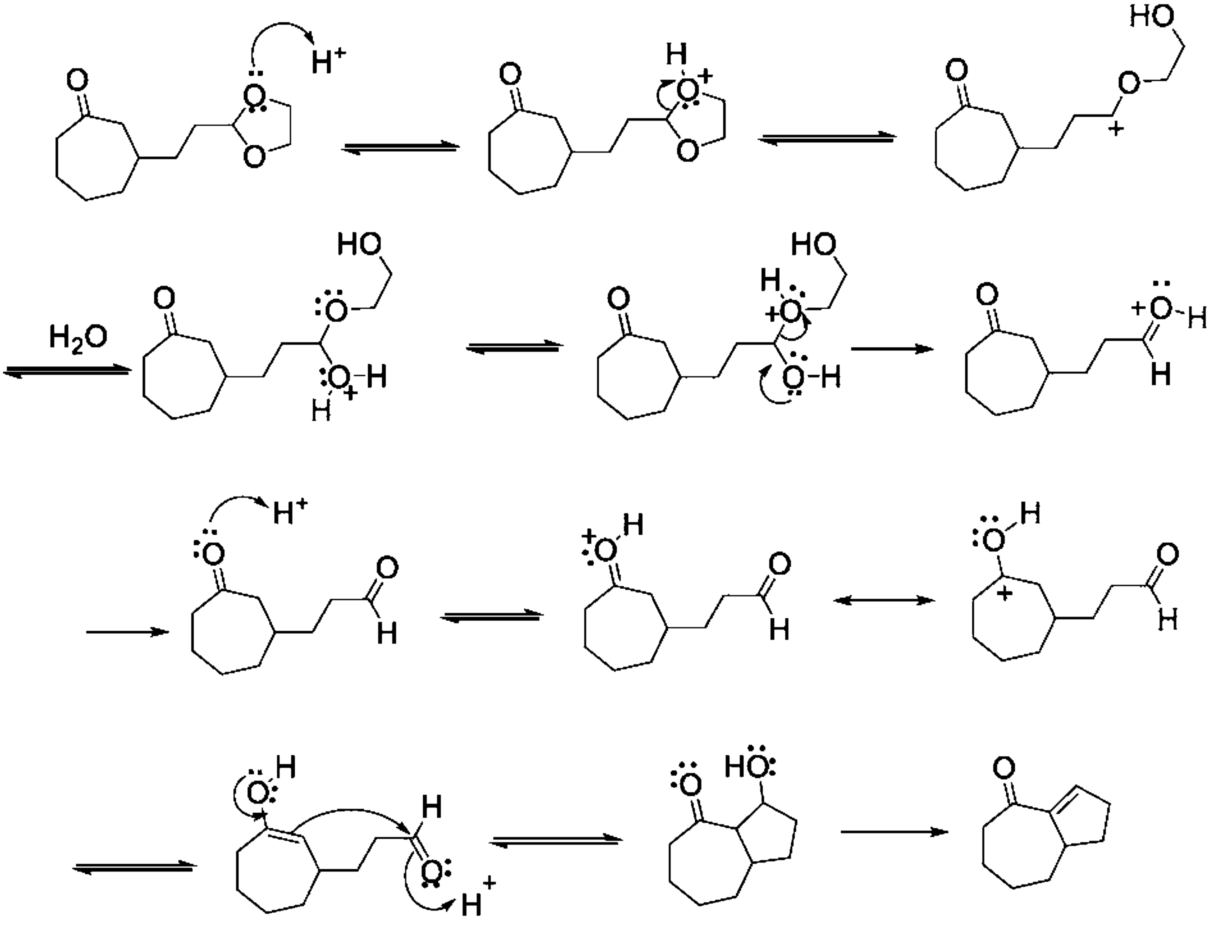


This is an example of the *Pictet-Spengler reaction*

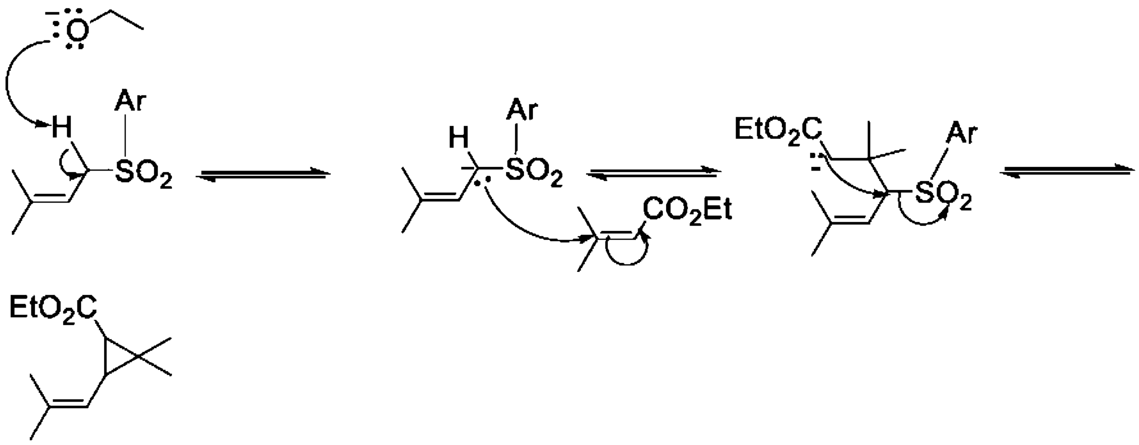
261



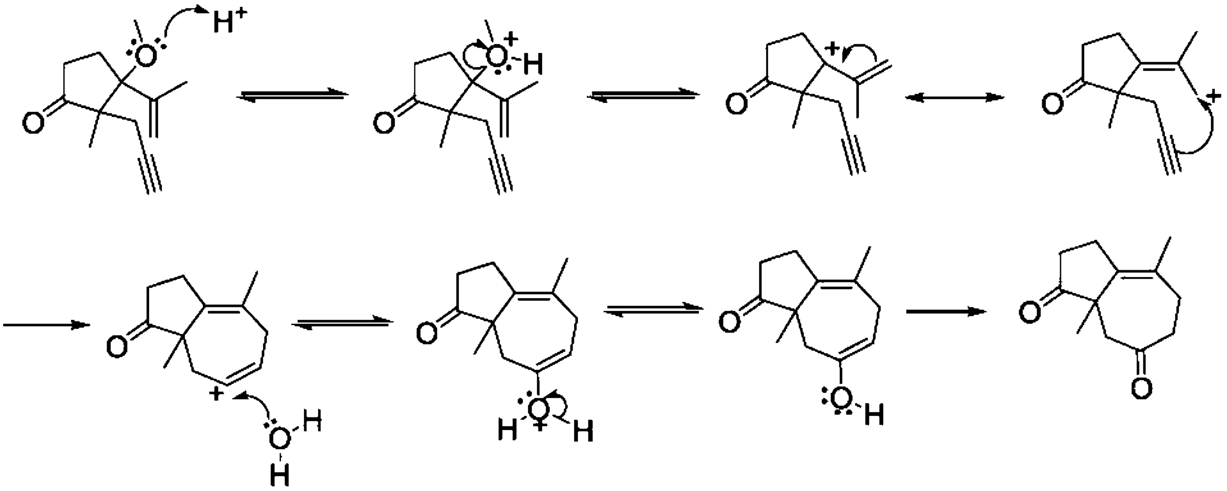
262



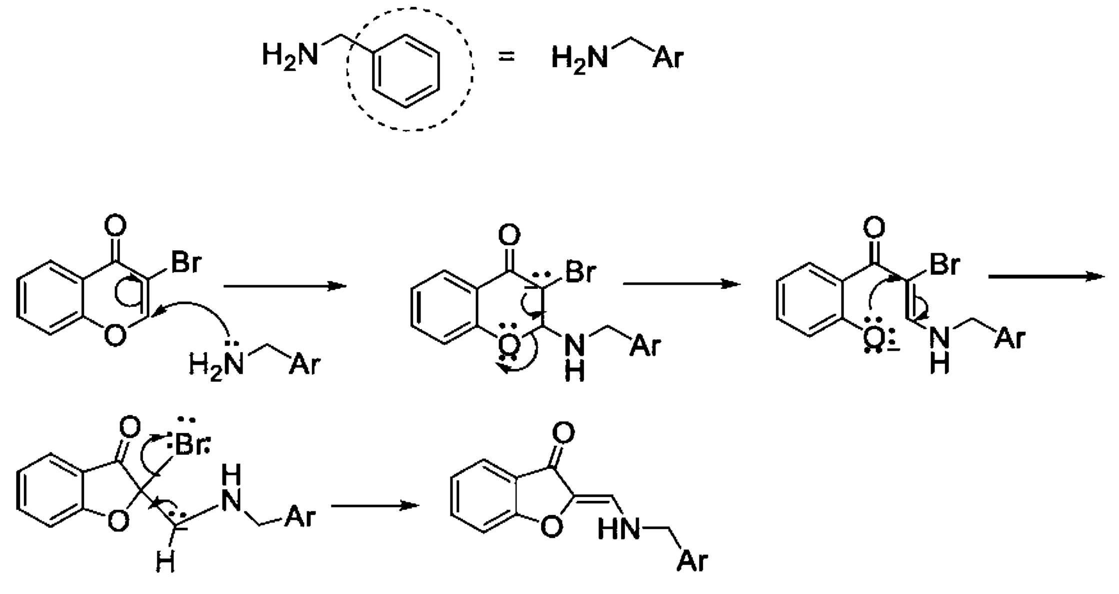
263


O
H
Ar
SO2
H
Ar
SO2
CO2Et
EtO2C
Ar
SO2
EtO2C

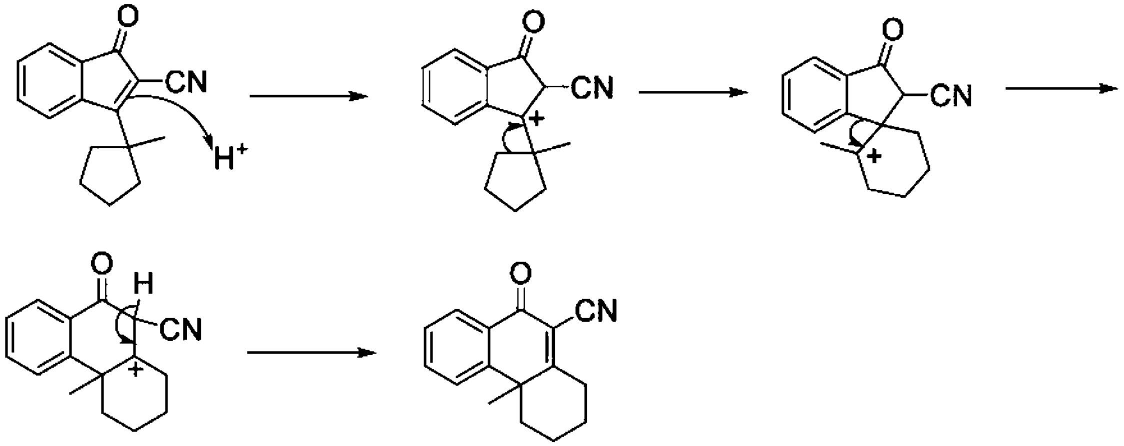
264


O
O
H+
O
O
H
O
O
O
O
O
O
H
H
O
H
H
O
O
O
H
O
O

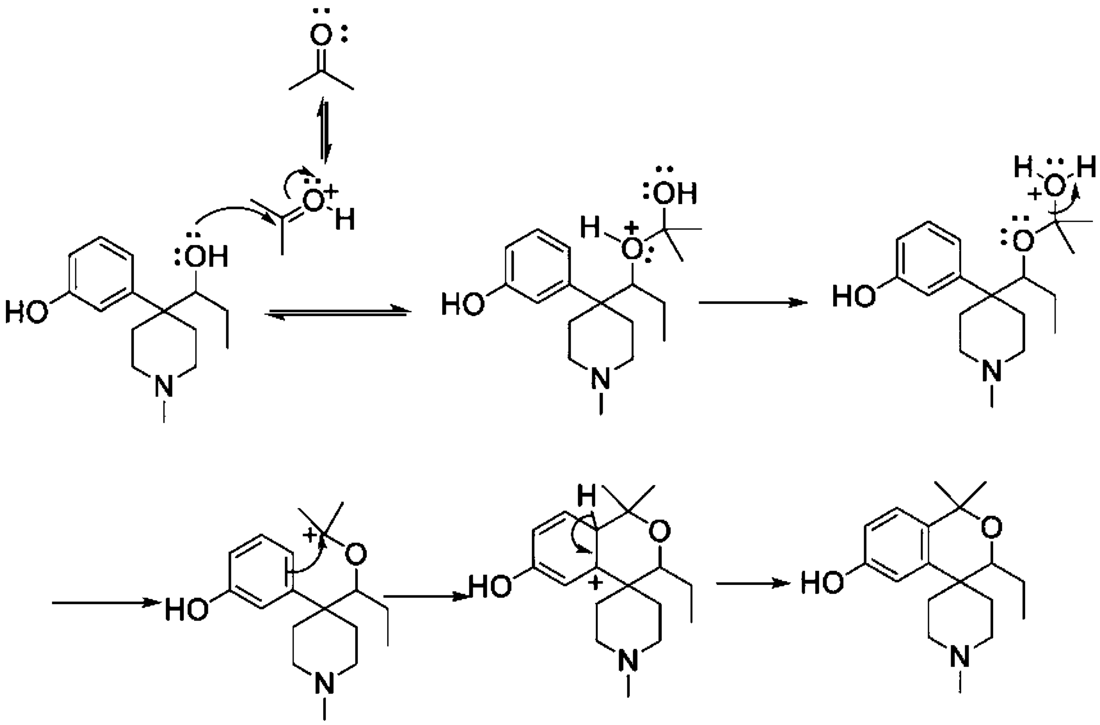
265



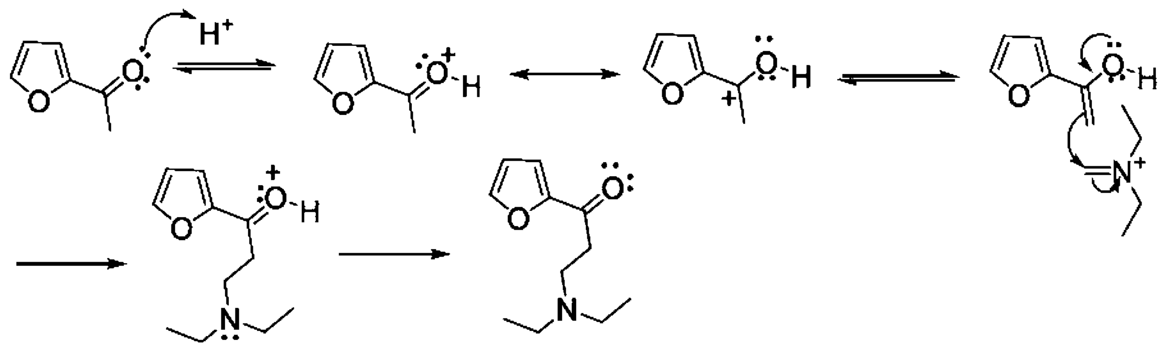
266

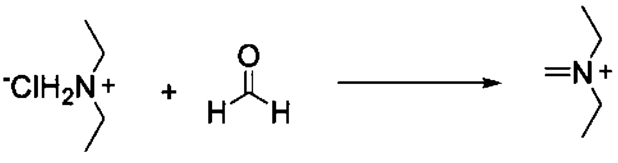


267



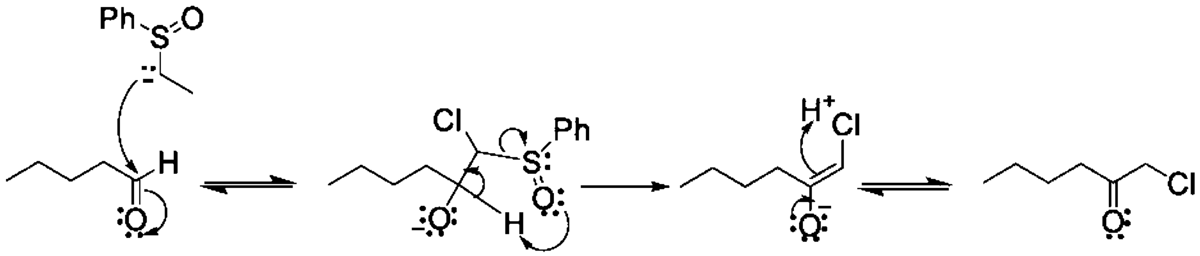
268





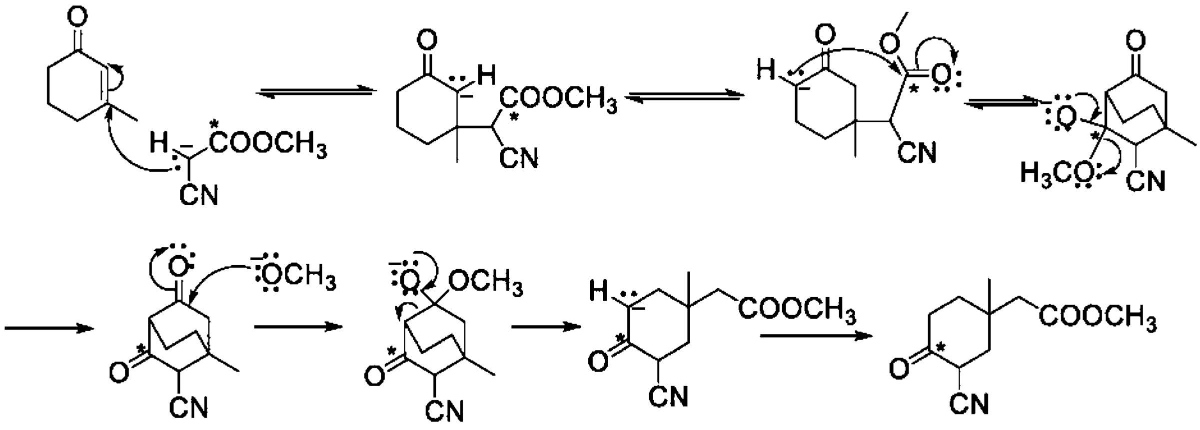
<u>Exercise</u> Write a mechanism for the formation of the imine.

269



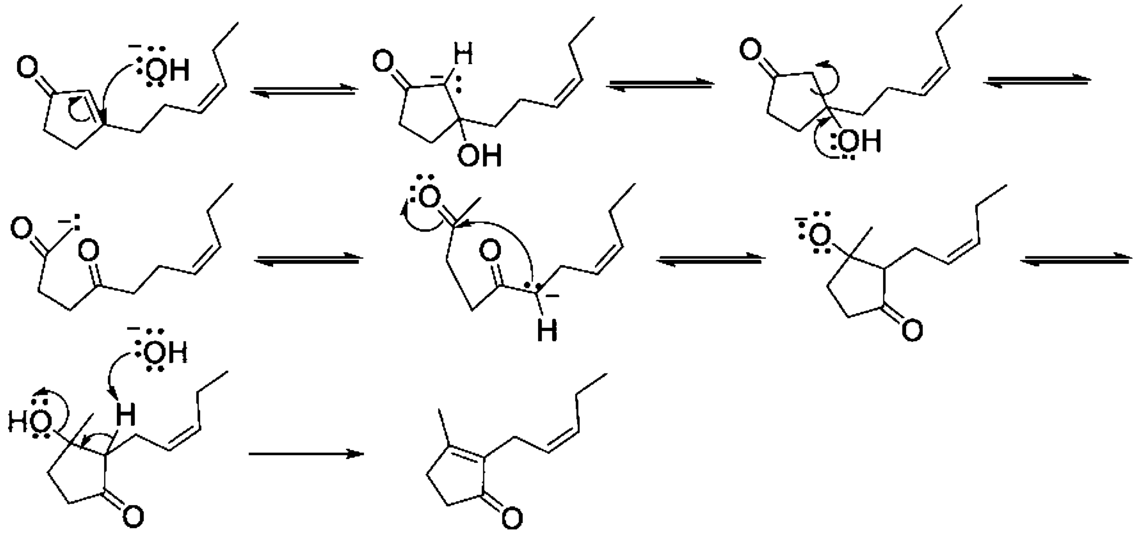
This is an example of a sulfoxide *syn elimination reaction*

270

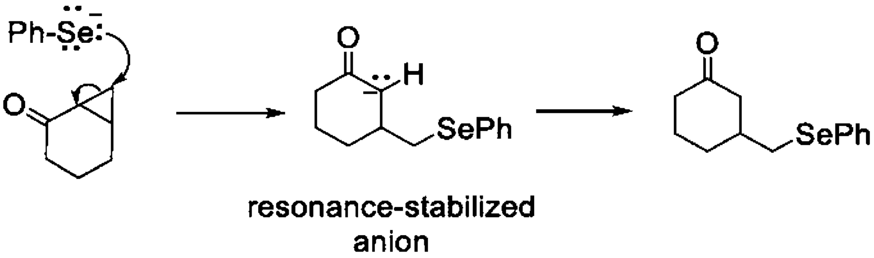


(prototropic shift refers to the equlibration of two anions with equal stability)

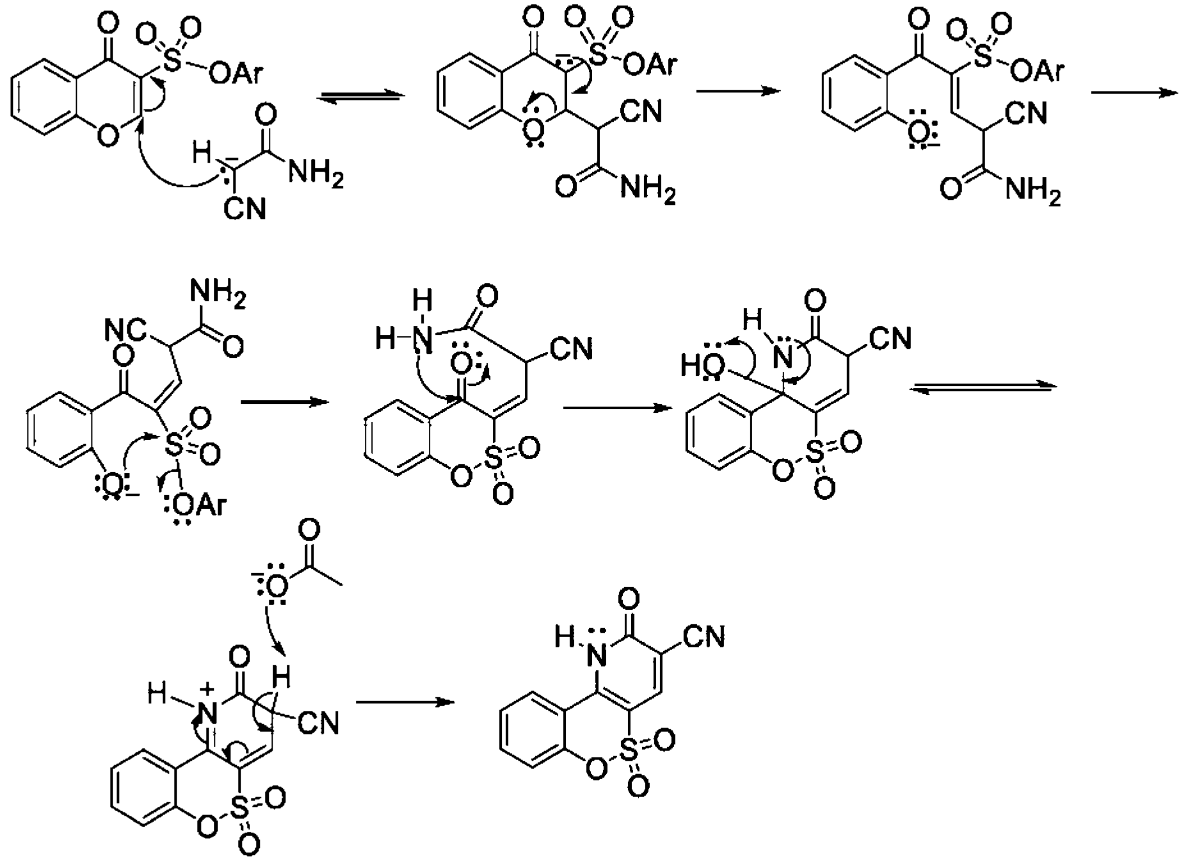
271



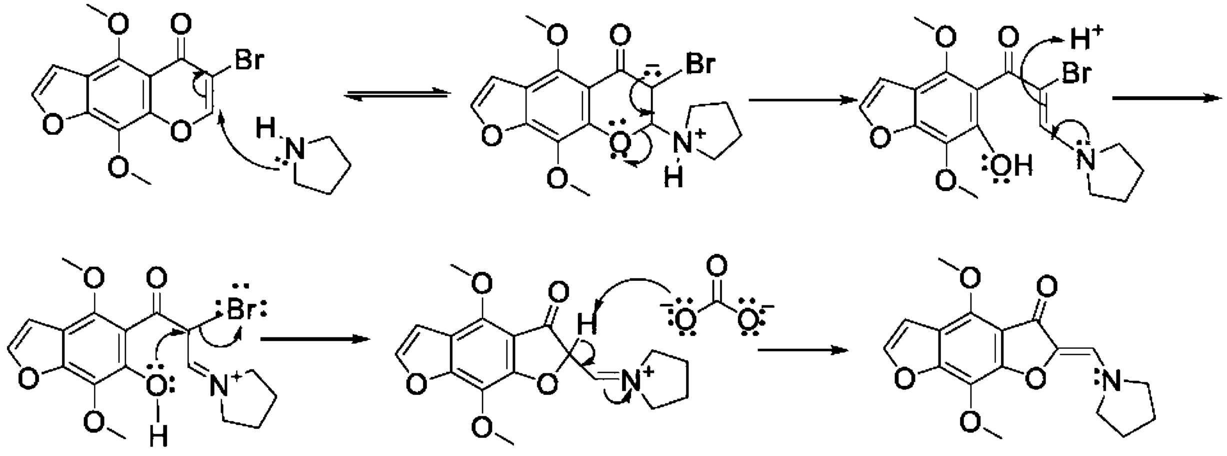
272



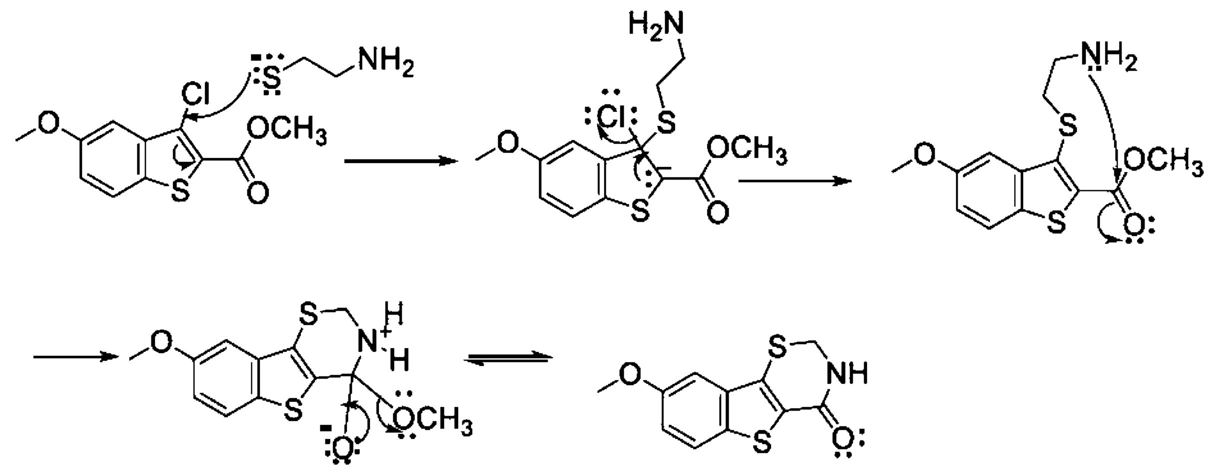
273



274



275



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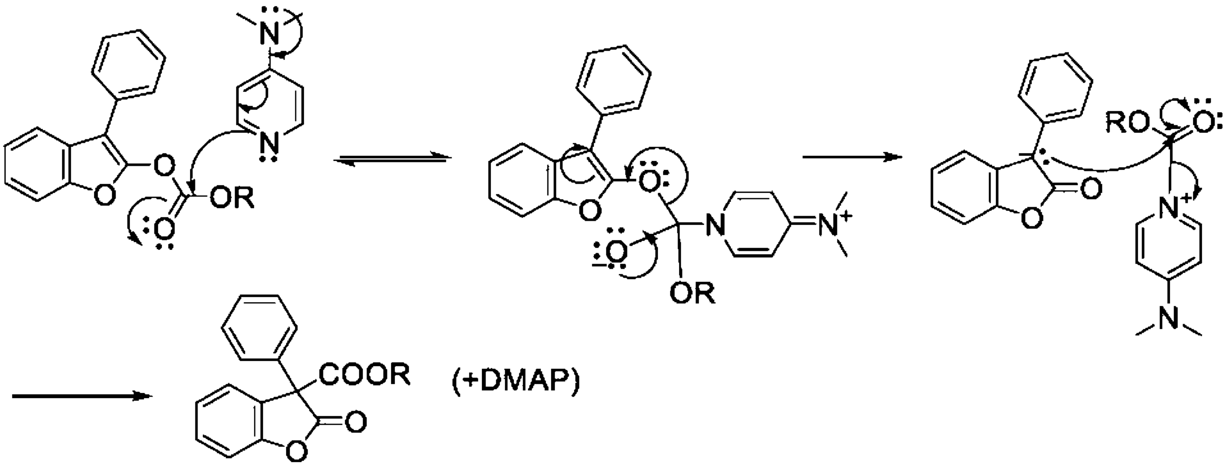
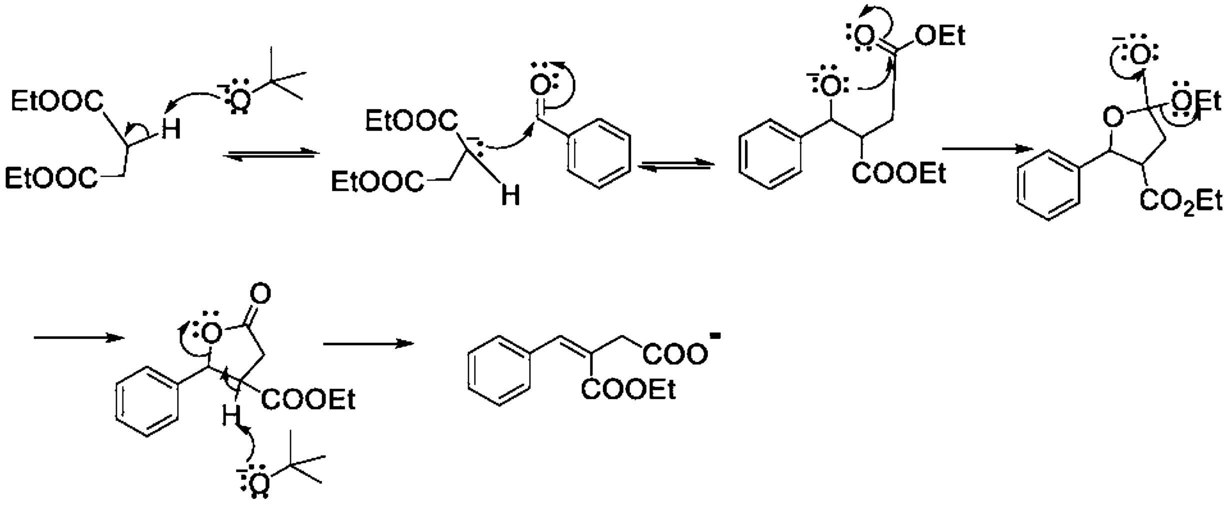
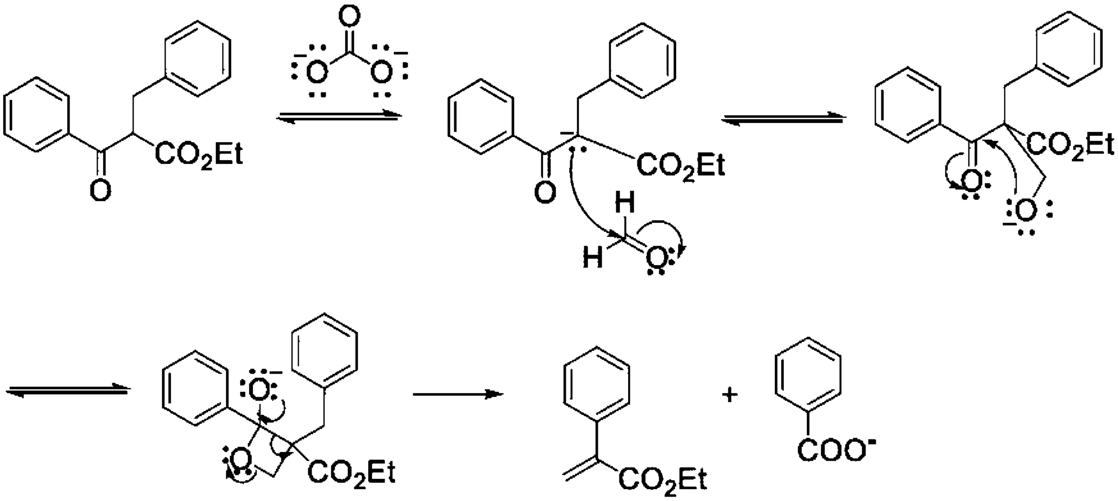


277

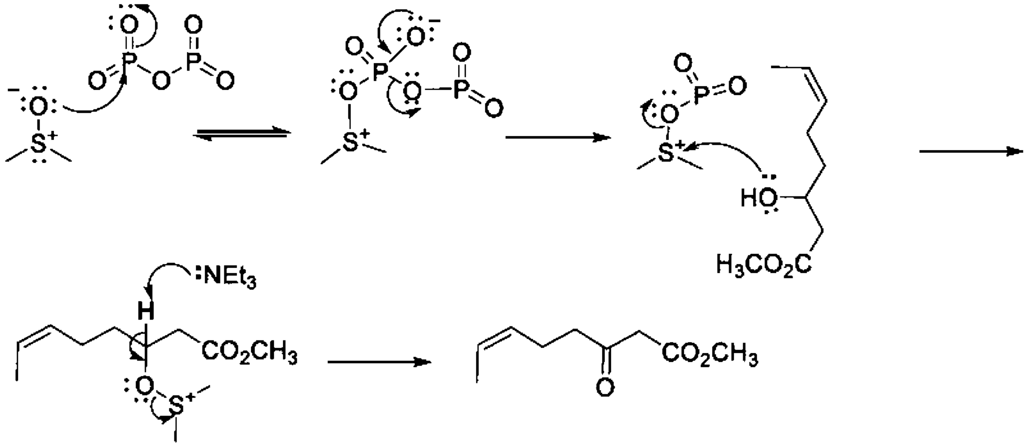


This is an example of the *Stobbe condensation* reaction

278

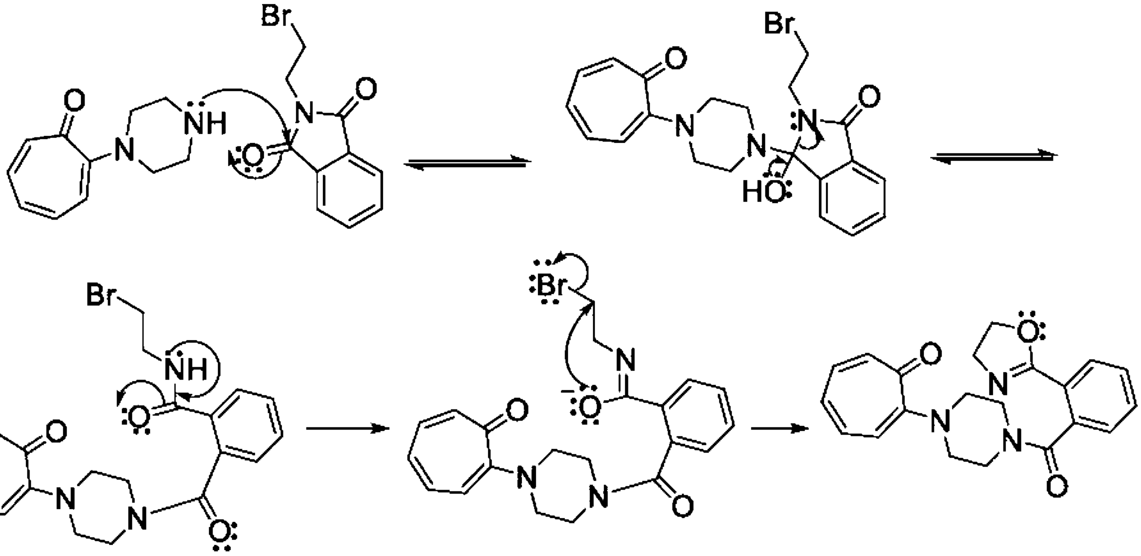


279

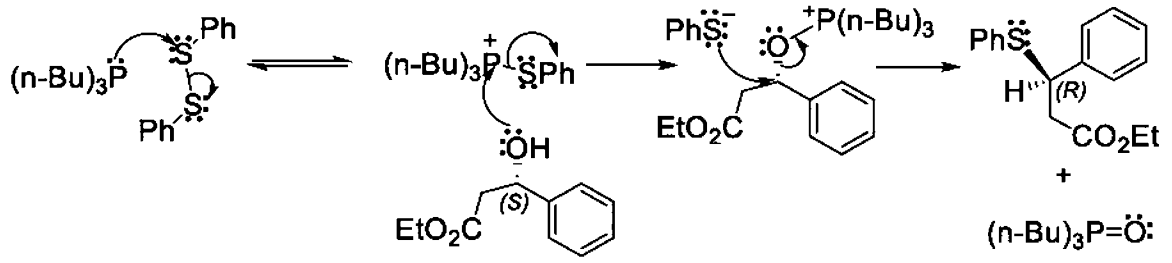


This is a variant of the *Swern oxidation* reaction

280

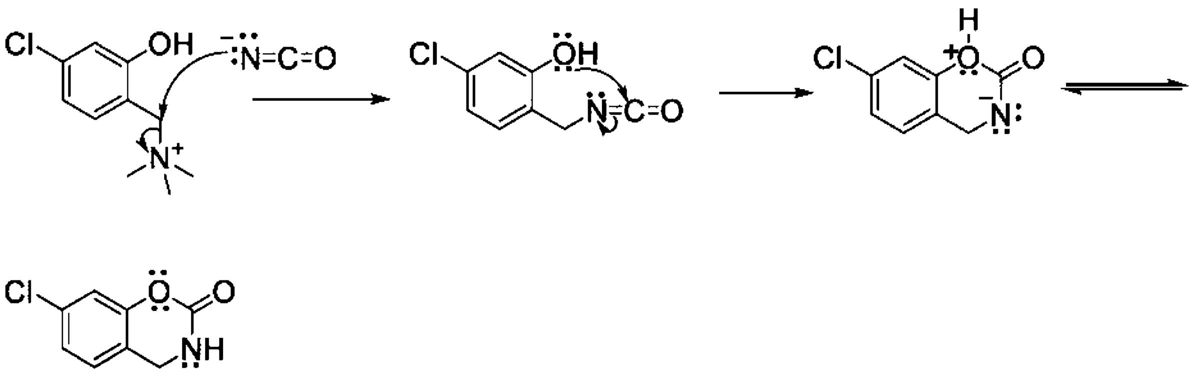


281

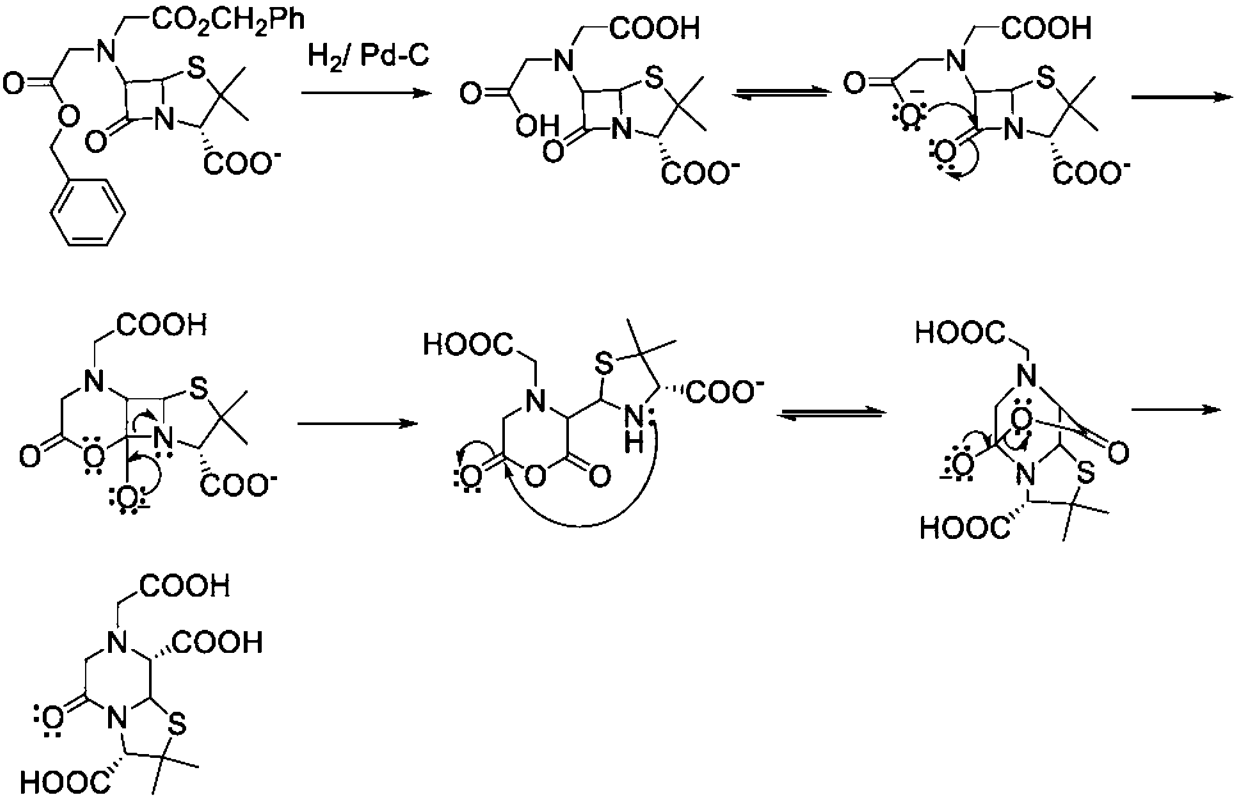


This is an example of the *Mitsunobu* reaction

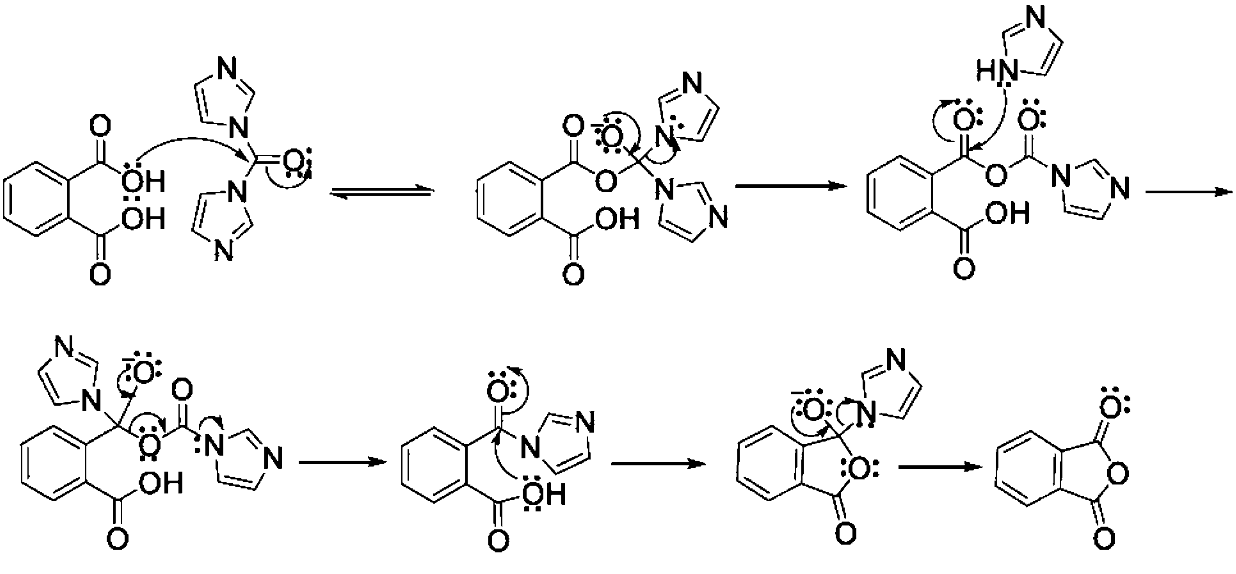
282



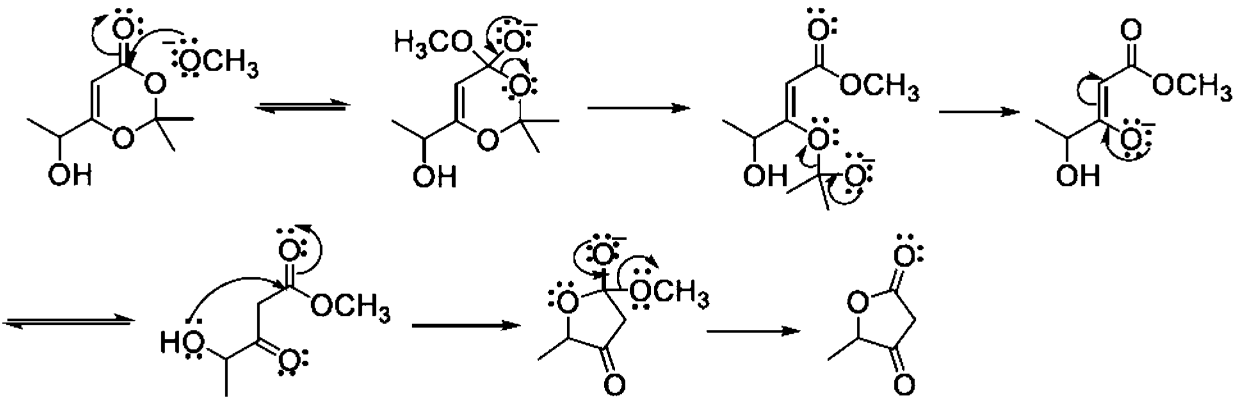
283



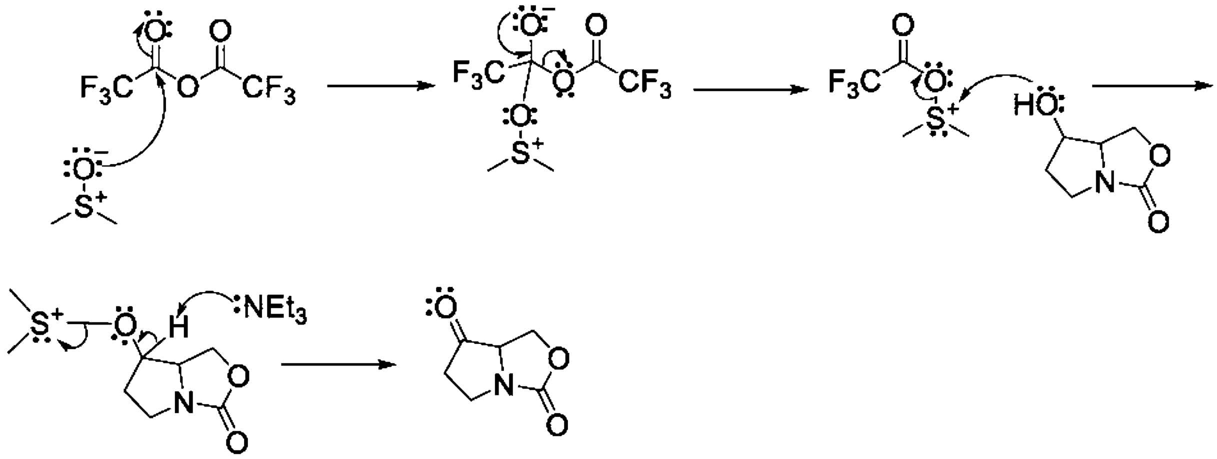
284



285

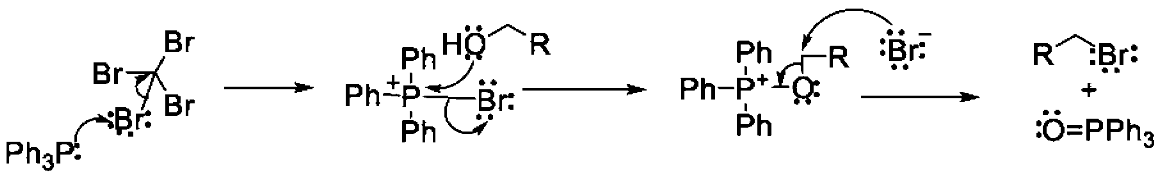


286

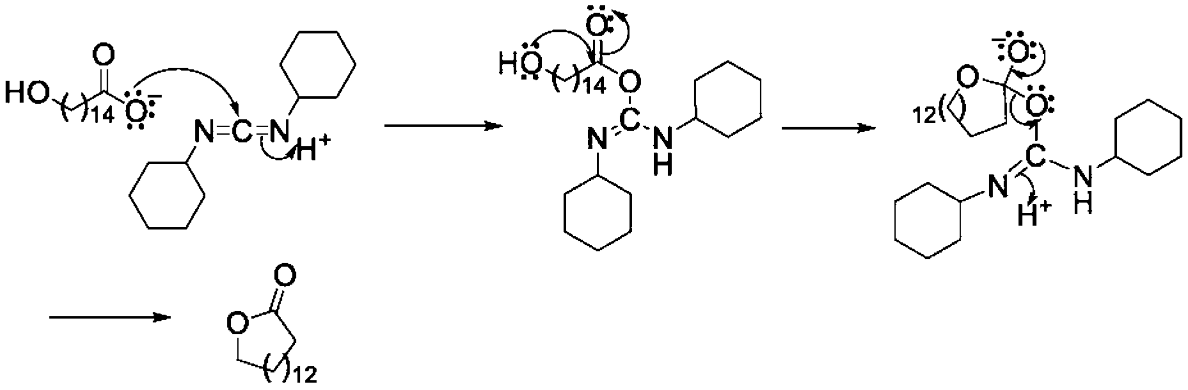


This is a variant of the *Swern oxidation* reaction

287

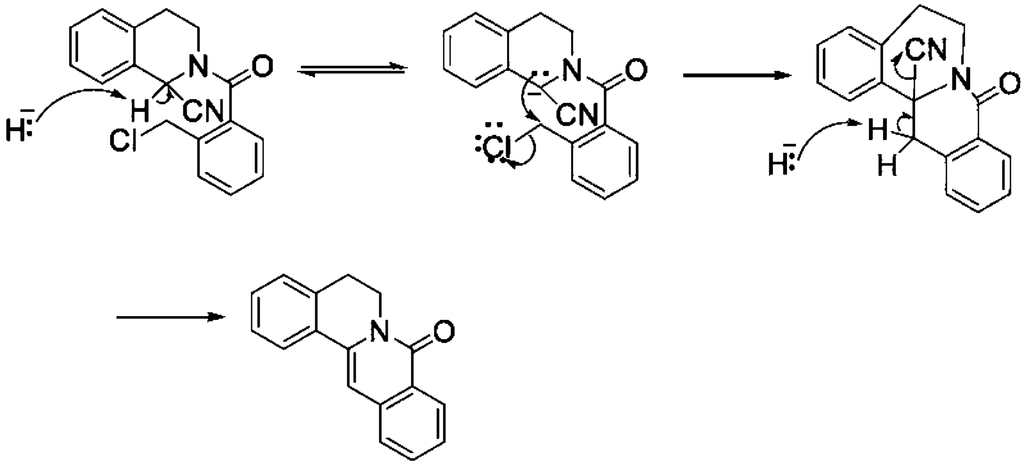


288

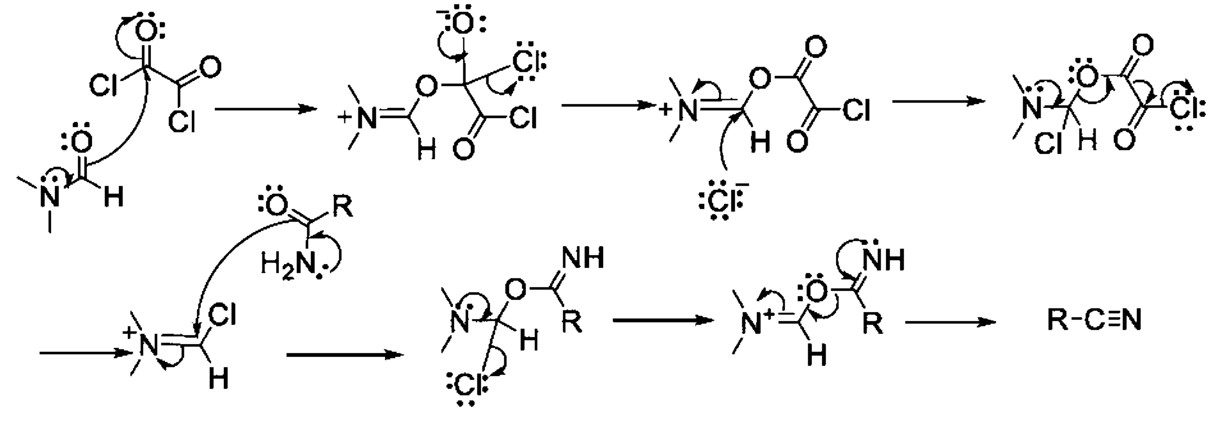


This is an example of a *macrolactonization reaction*

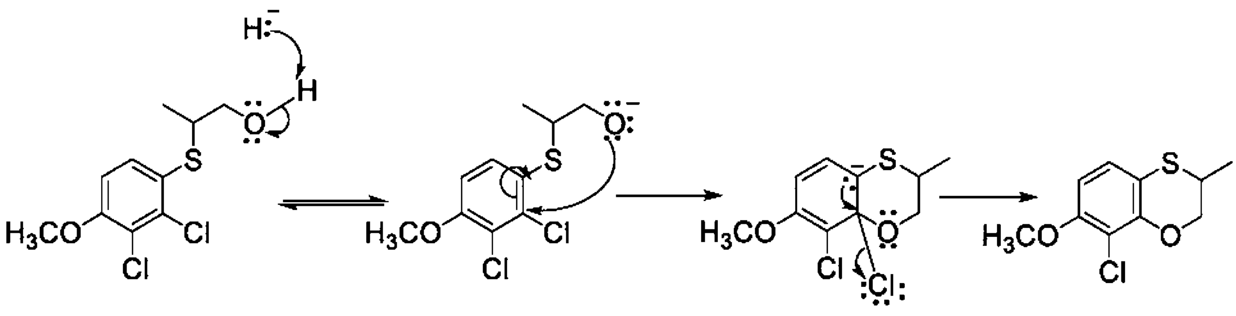
289



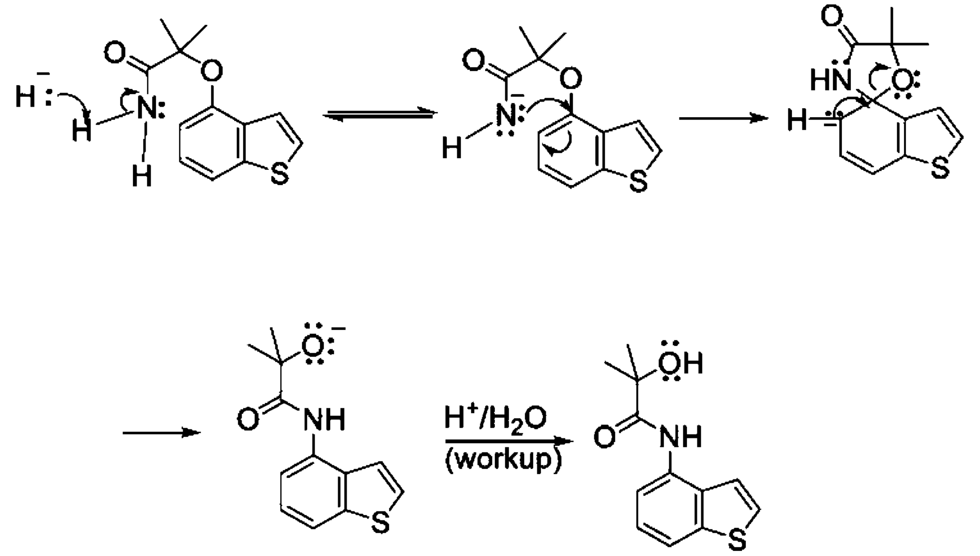
290



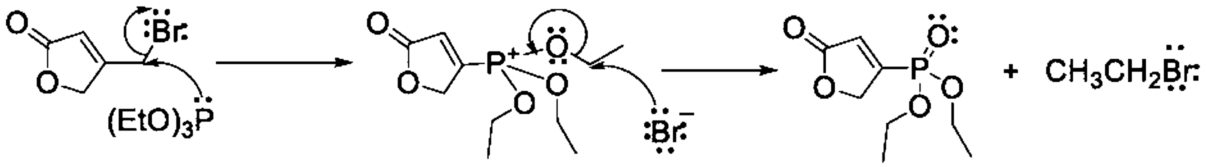
291



292

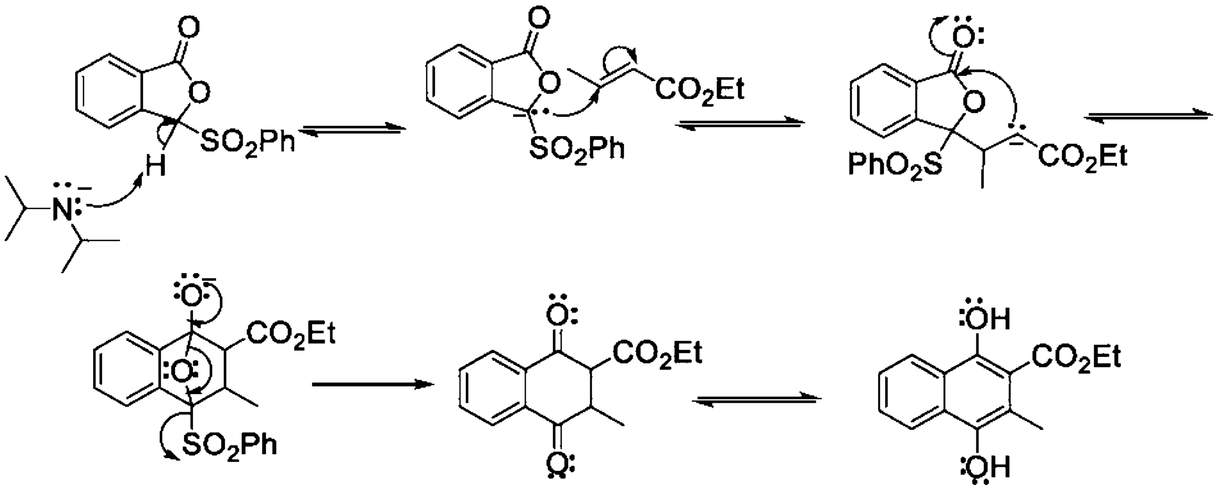


293



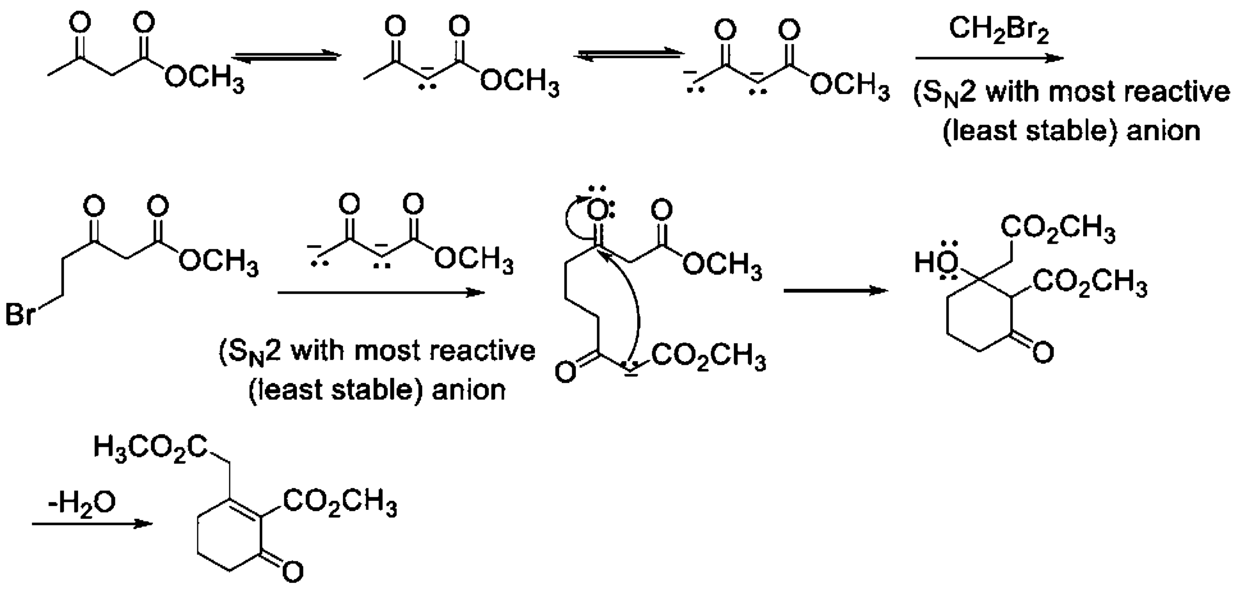
This is an example of the *Arbusov reaction*

294

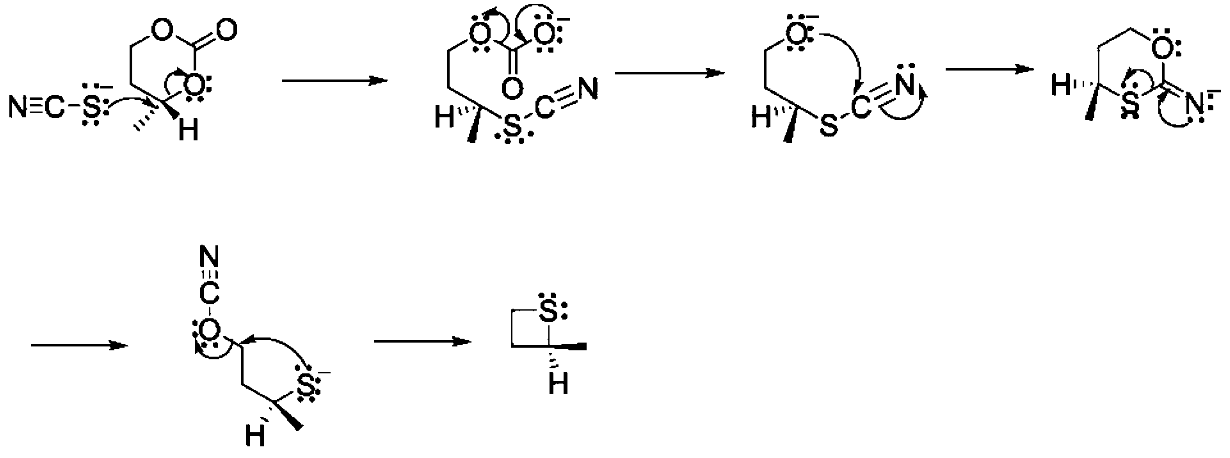


Exercise The keto tautomer is ordinarily more stable than the enol form. In this example, the enol form is favored. Why?

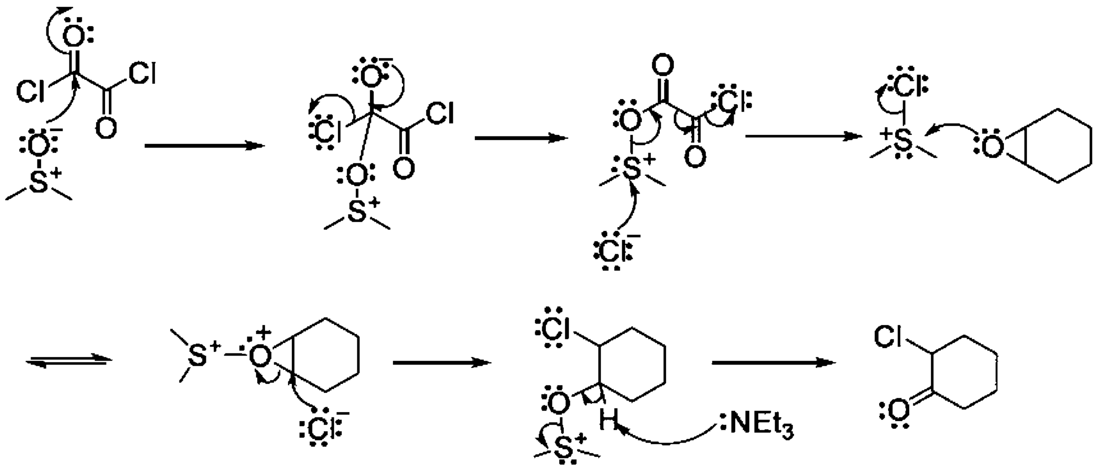
295


CH$_2$Br$_2$
(S$_N$2 with most reactive
(least stable) anion
(S$_N$2 with most reactive
(least stable) anion
-H$_2$O

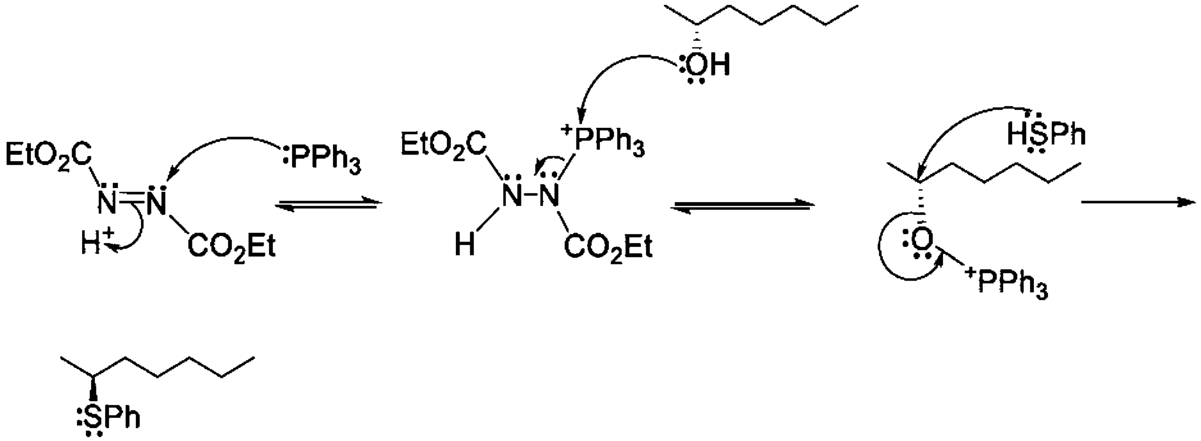
296



297

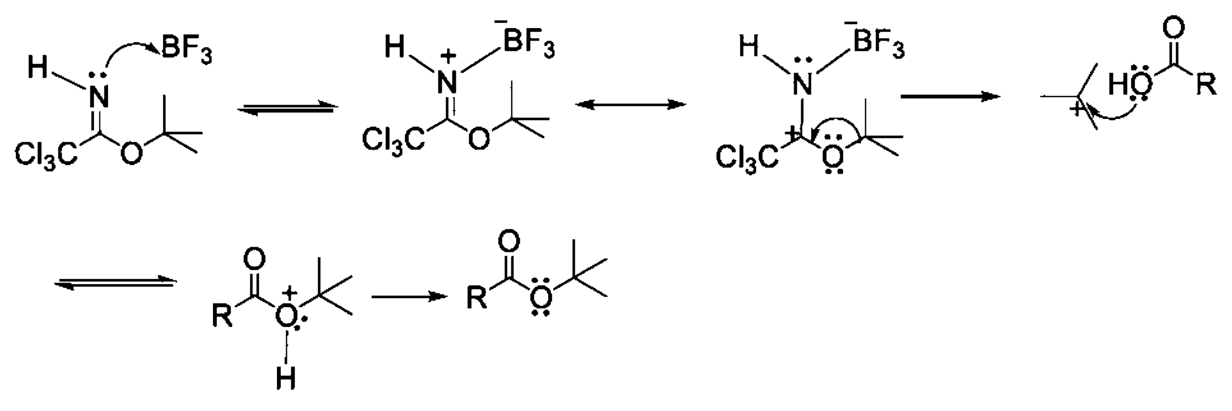


298

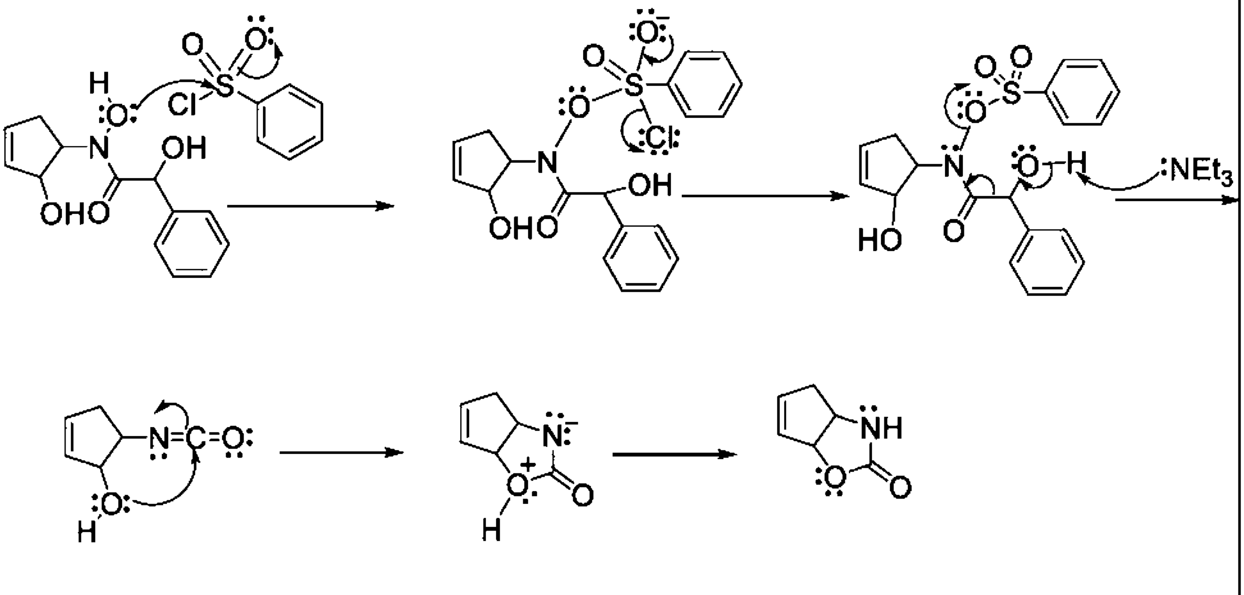


This is an example of the *Mitsonobu reaction*

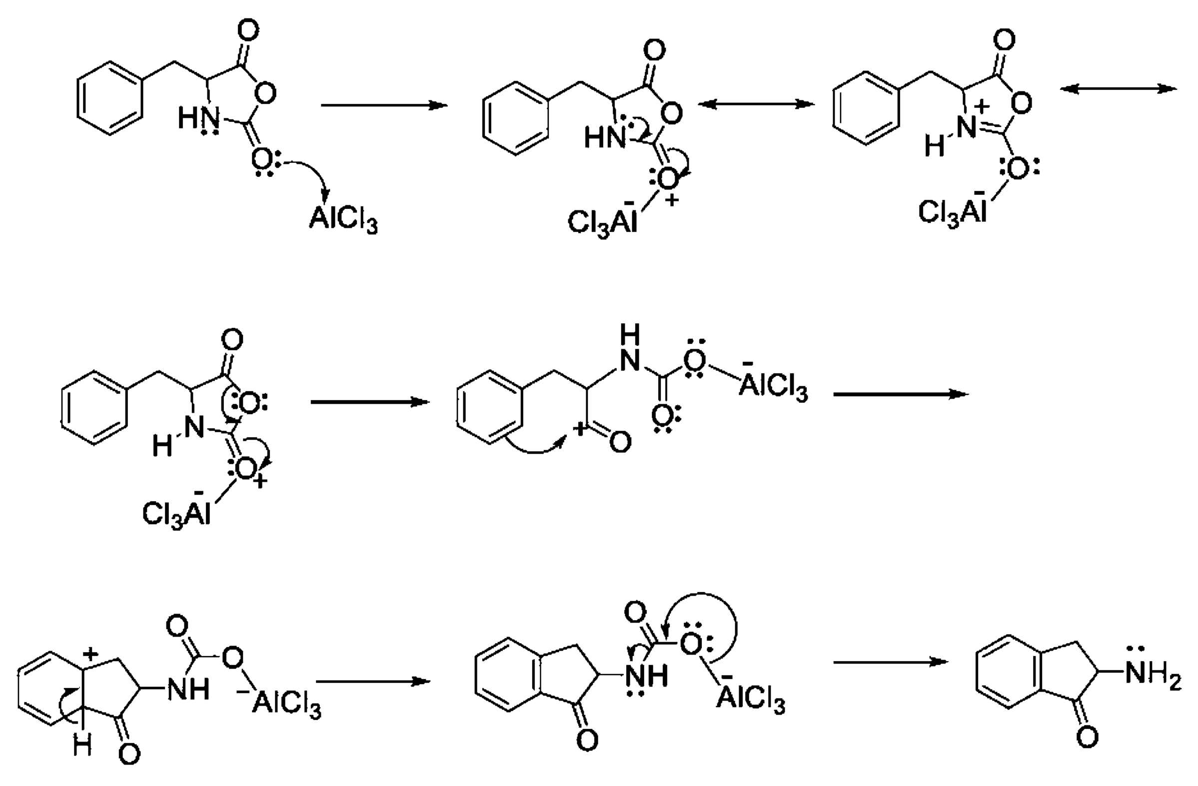
299


H
BF$_3$
N
Cl$_3$C
O
H
+
N
BF$_3$
Cl$_3$C
O
H
N
BF$_3$
Cl$_3$C
+
O
+
HO
O
R
R
O
+
O
H
R
O
O

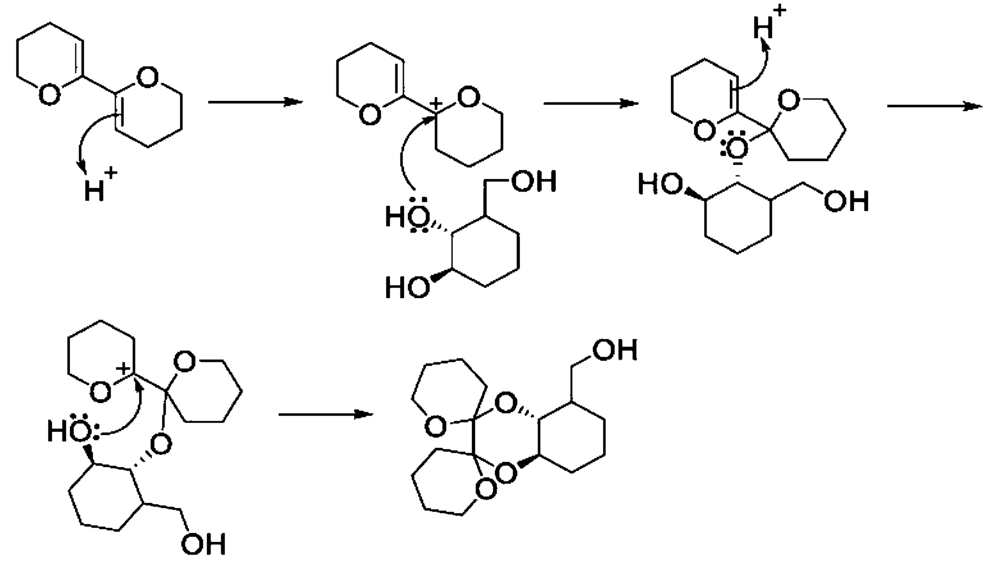
300


H
O
O
O
S
Cl
N
OH
OH
O
O
O
O
S
O
Cl
N
OH
OH
O
O
O
O
S
N
O
H
NEt$_3$
HO
O
N
C
O
O
H
N
+
O
H
O
NH
O
O

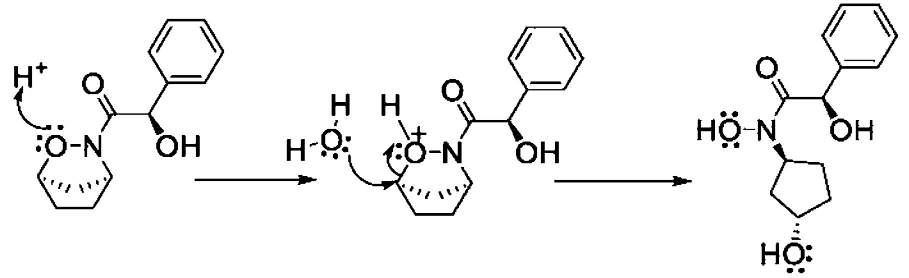
301



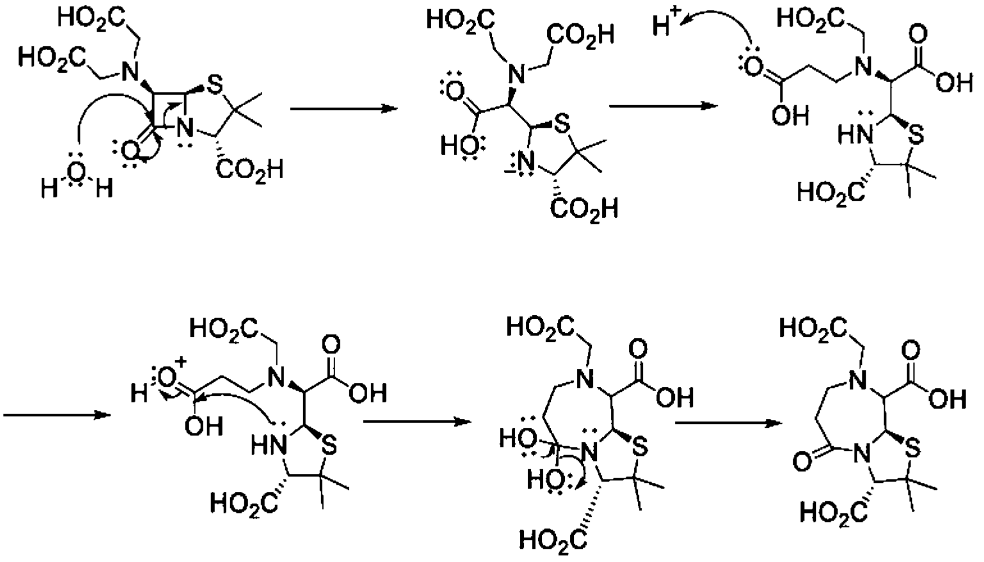
302



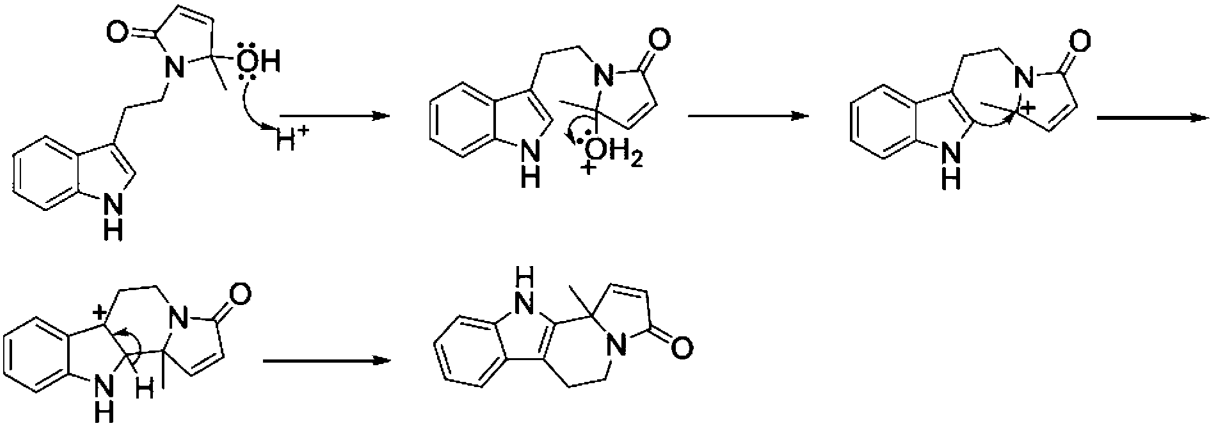
303



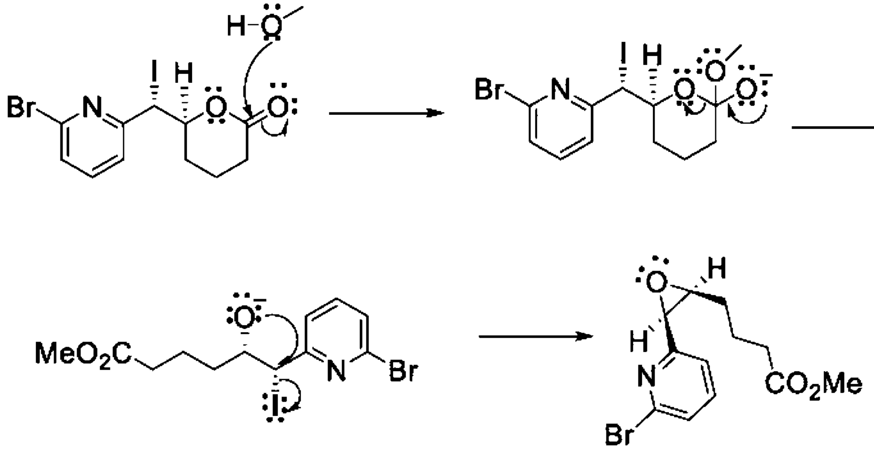
304



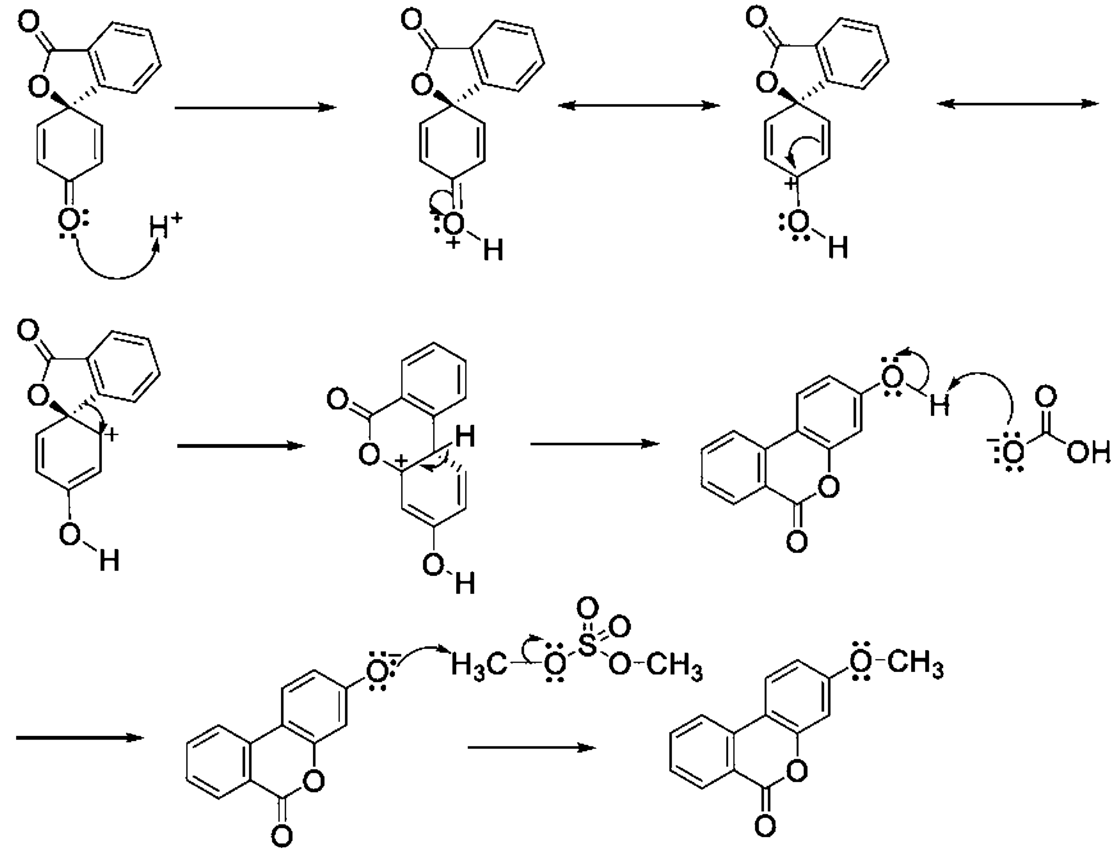
305



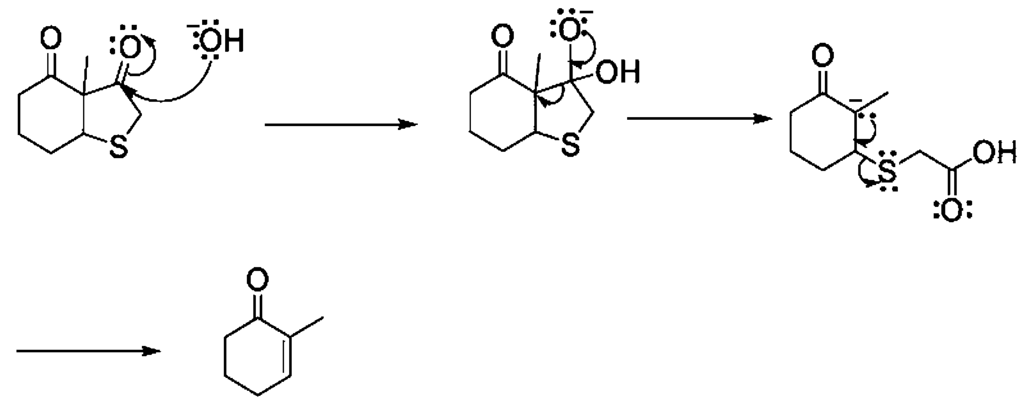
306



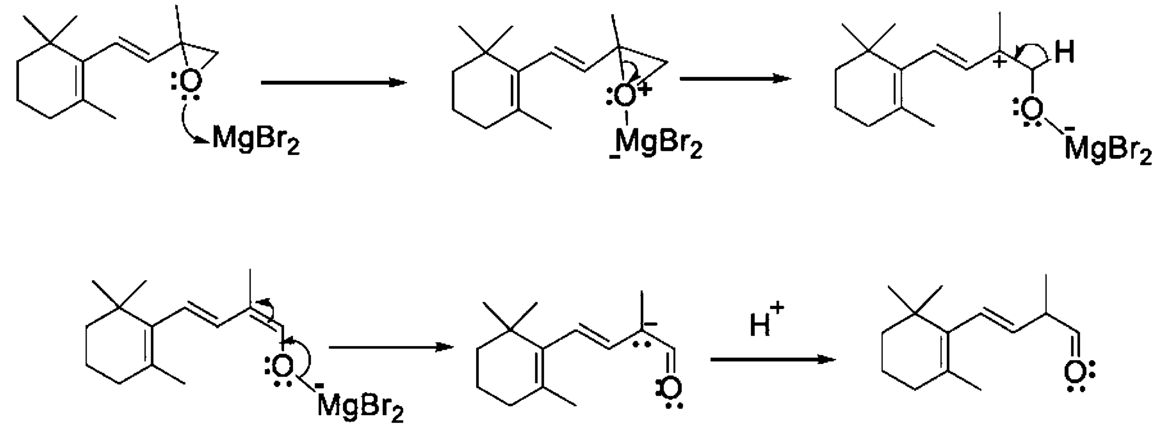
307



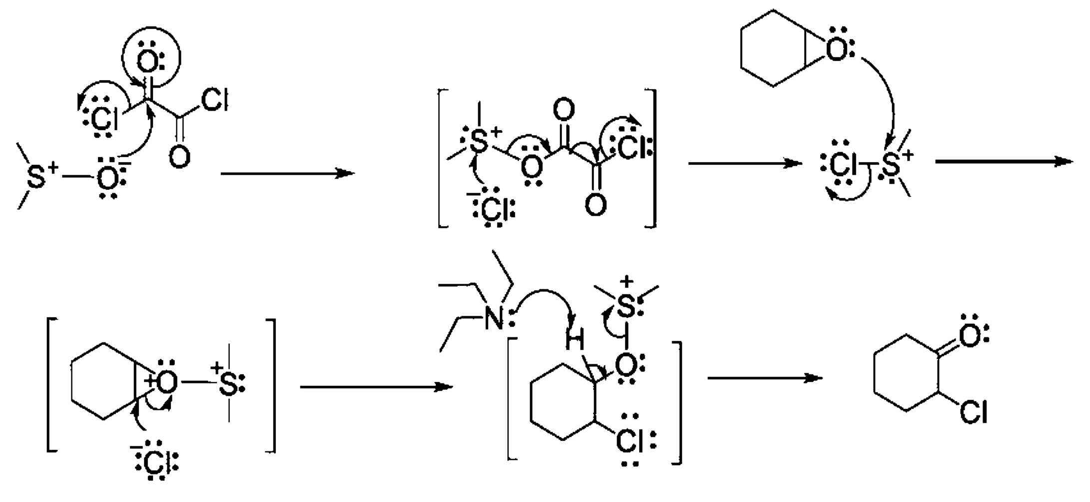
308



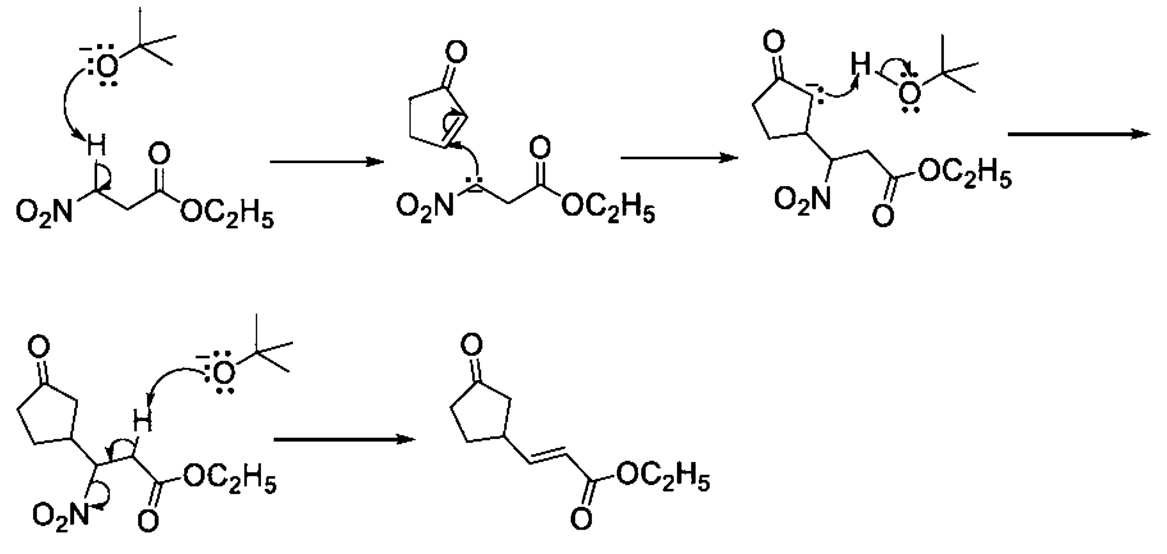
309



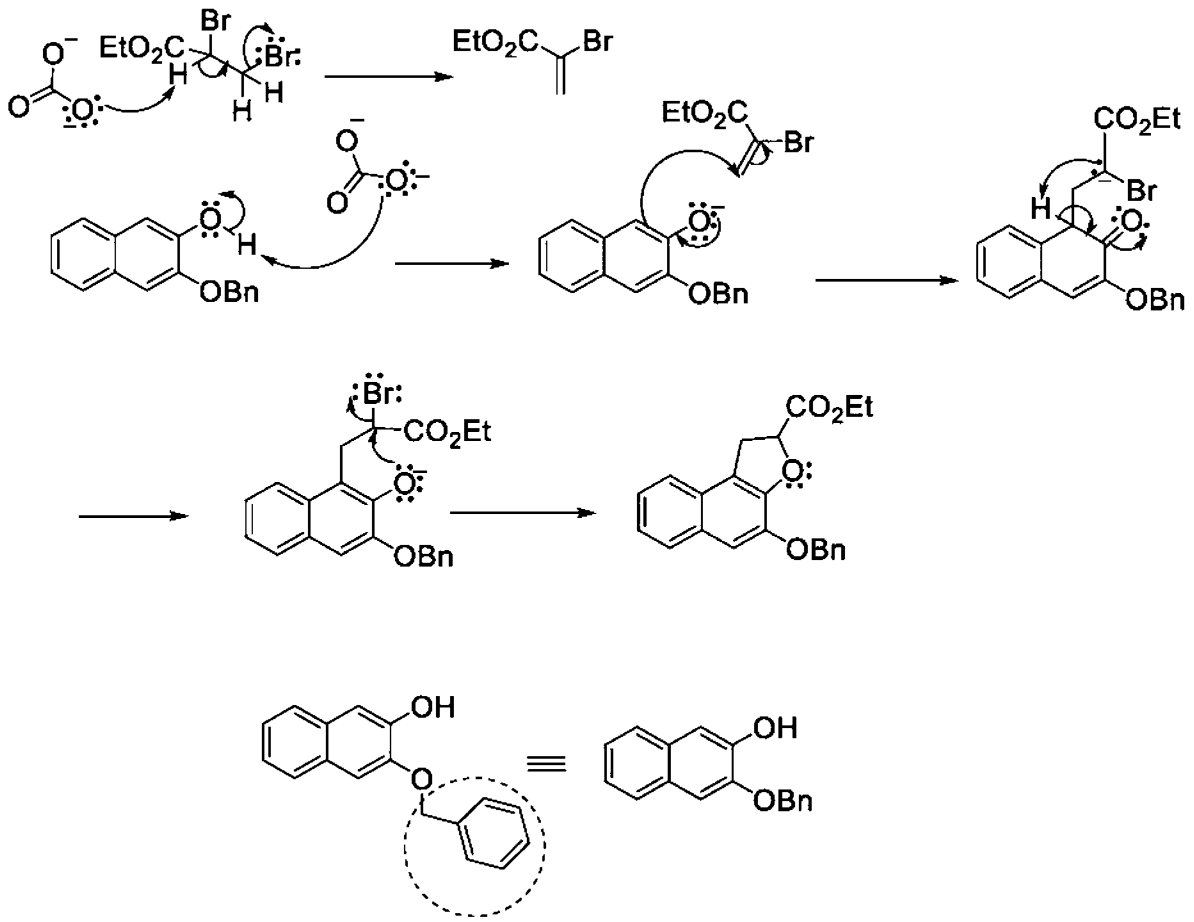
310



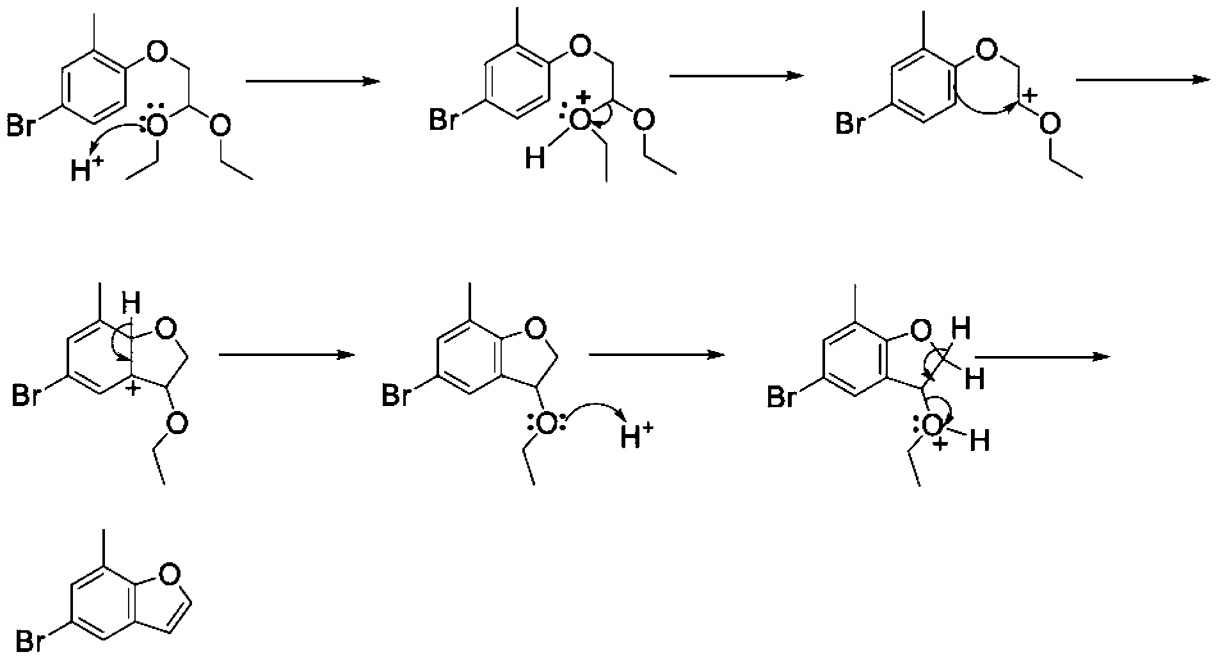
311



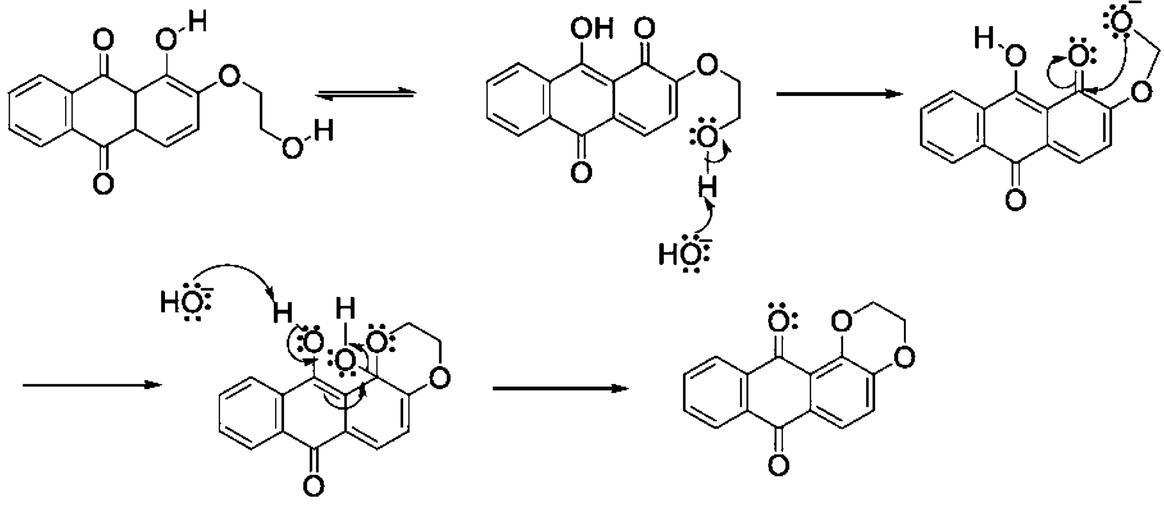
312



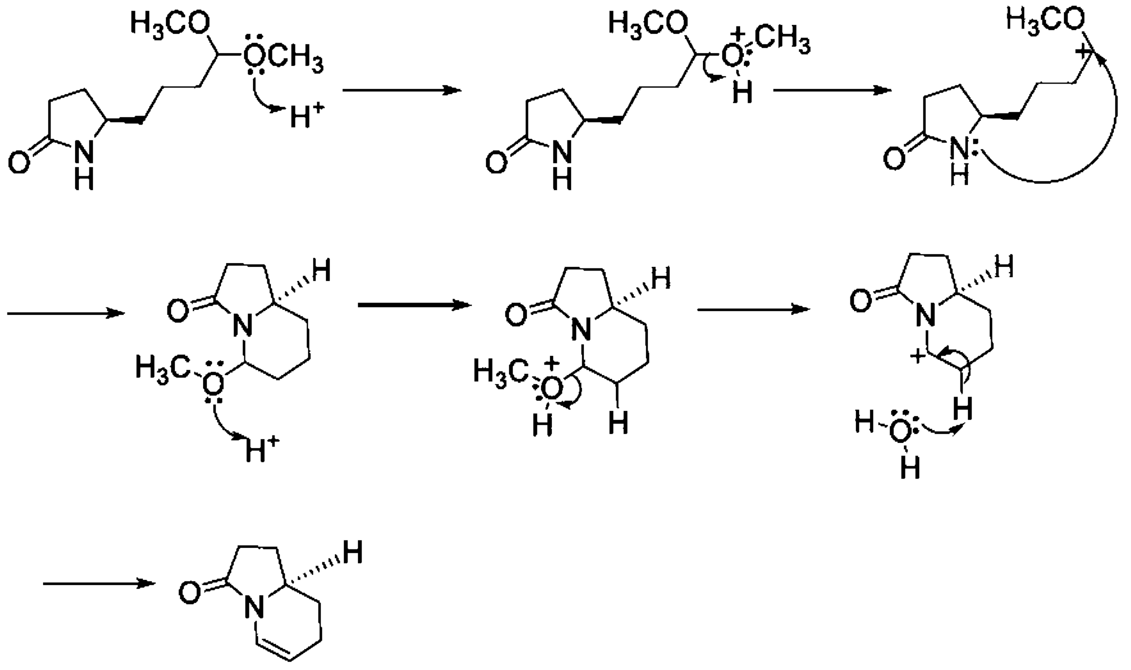
313



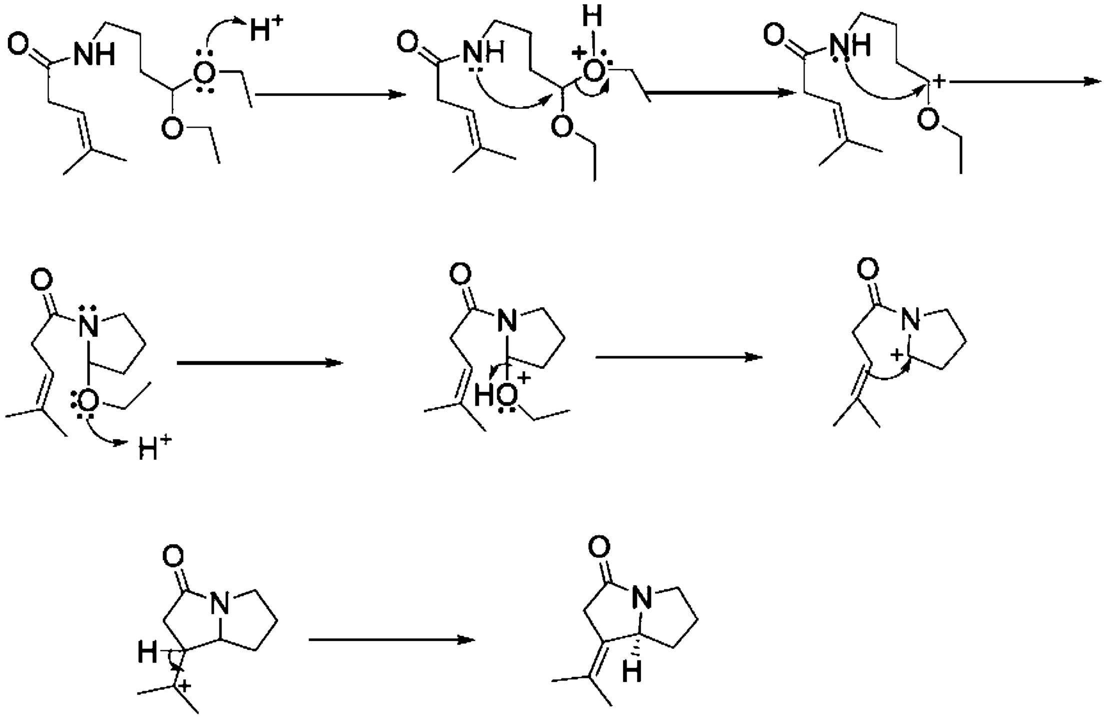
314



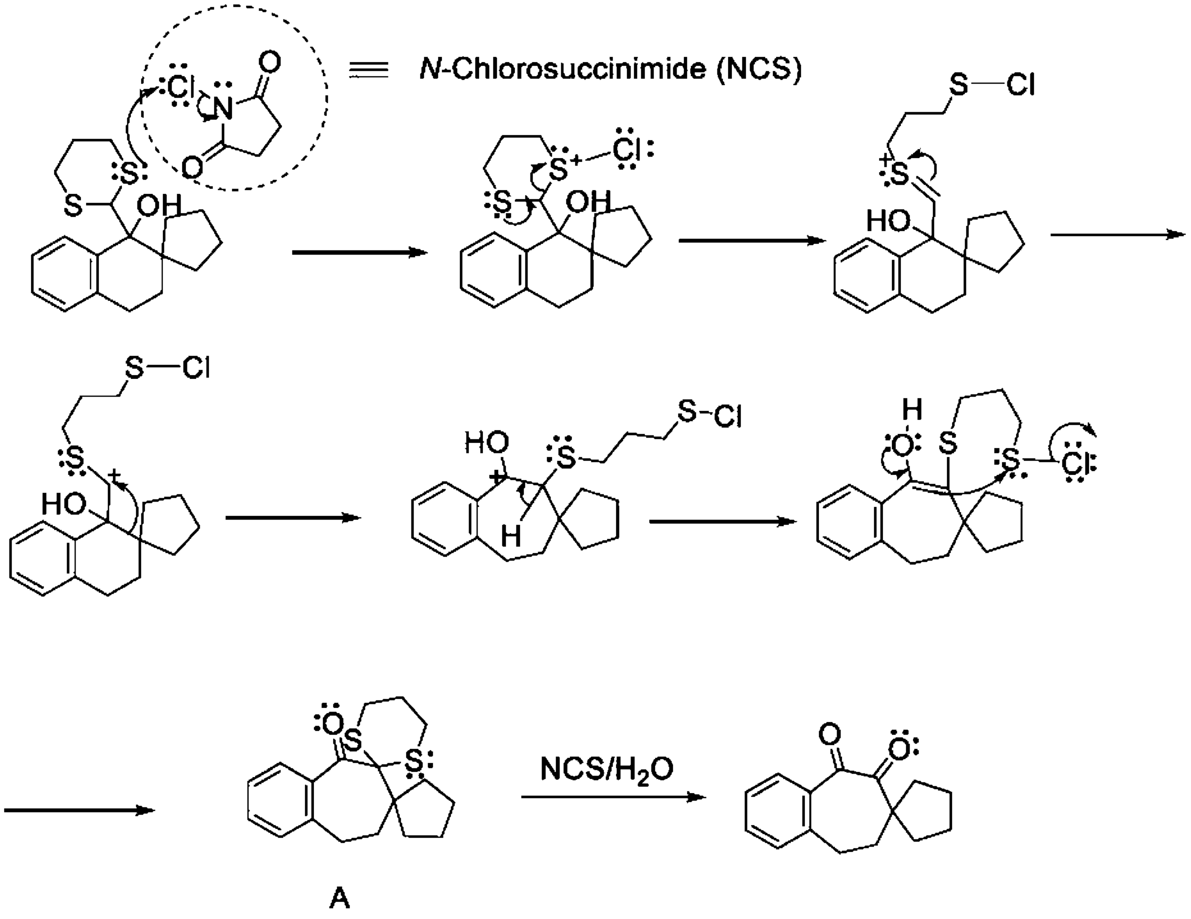
315



316

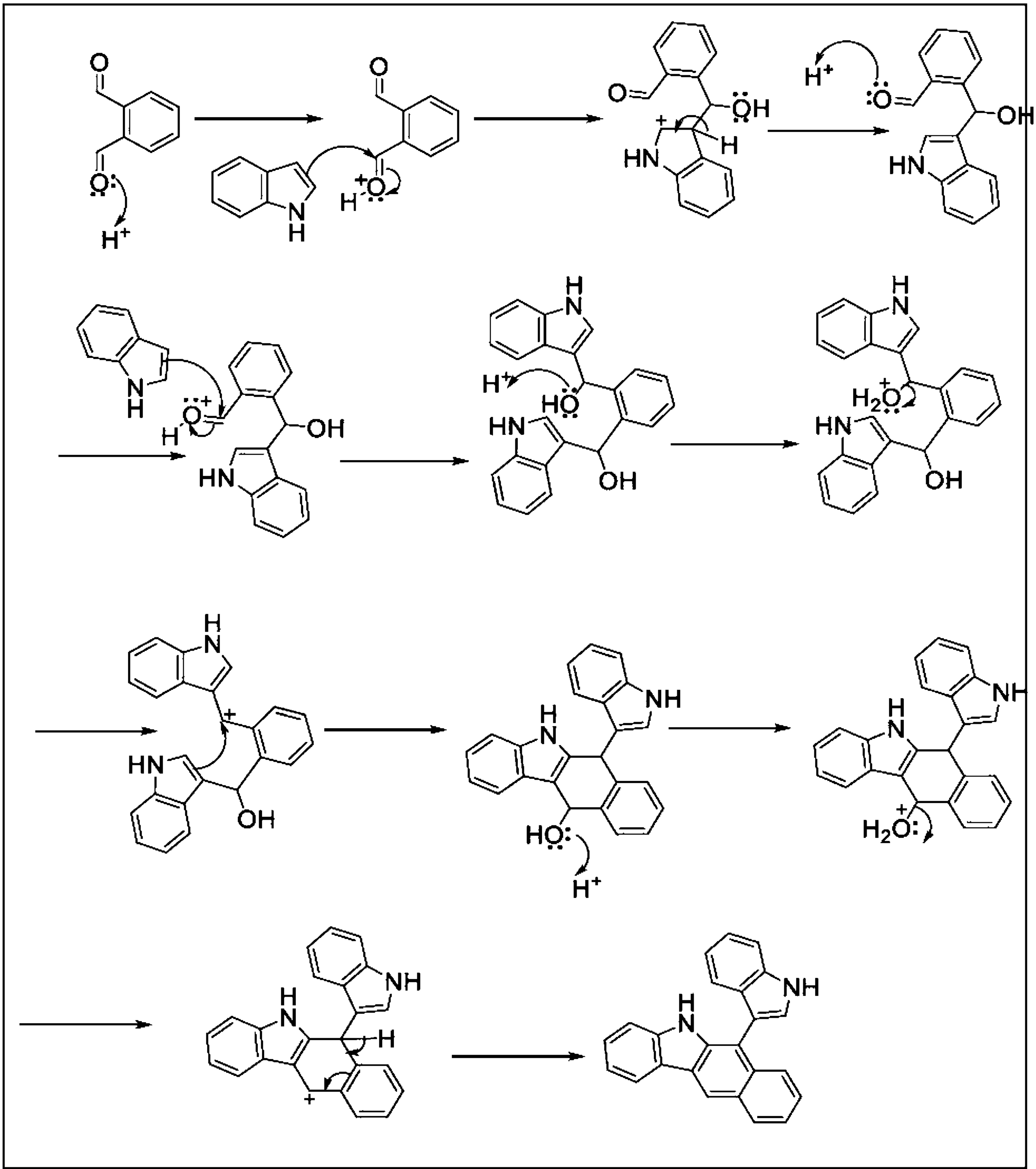


317

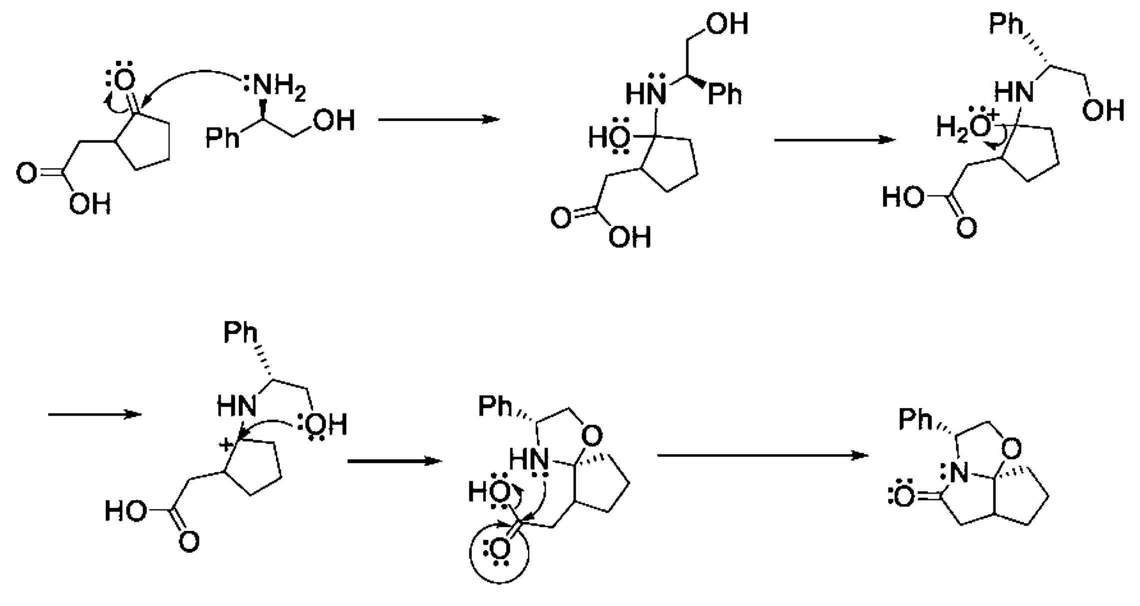


Exercise Write the mechanism for the conversion of A to the final product

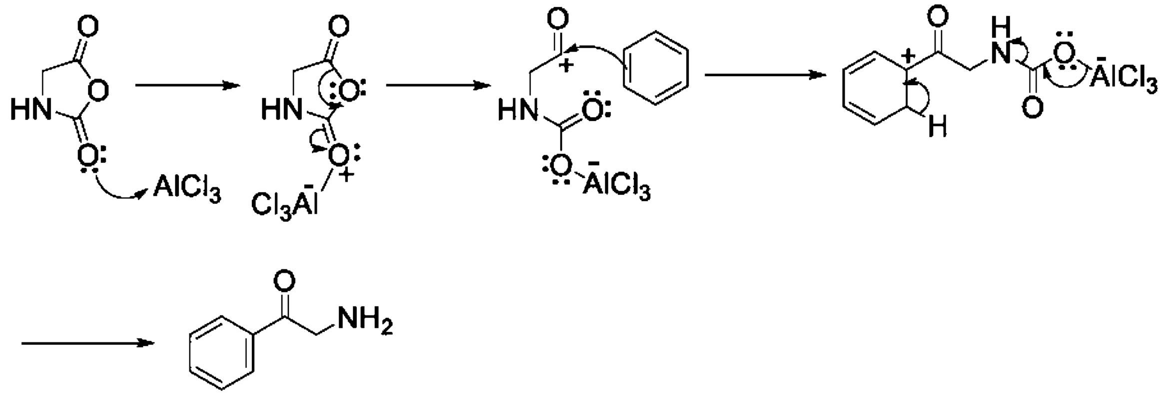
318



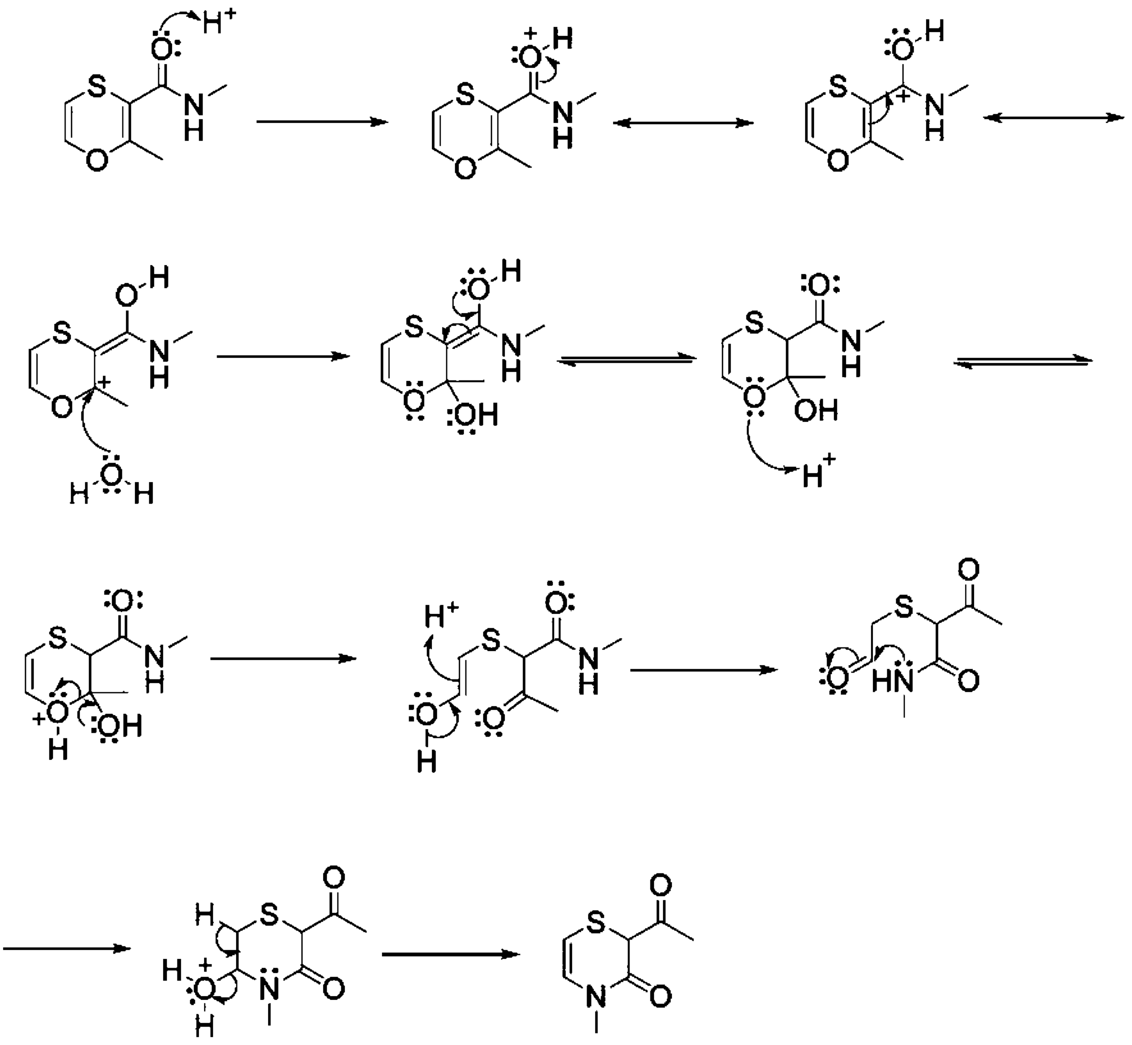
319



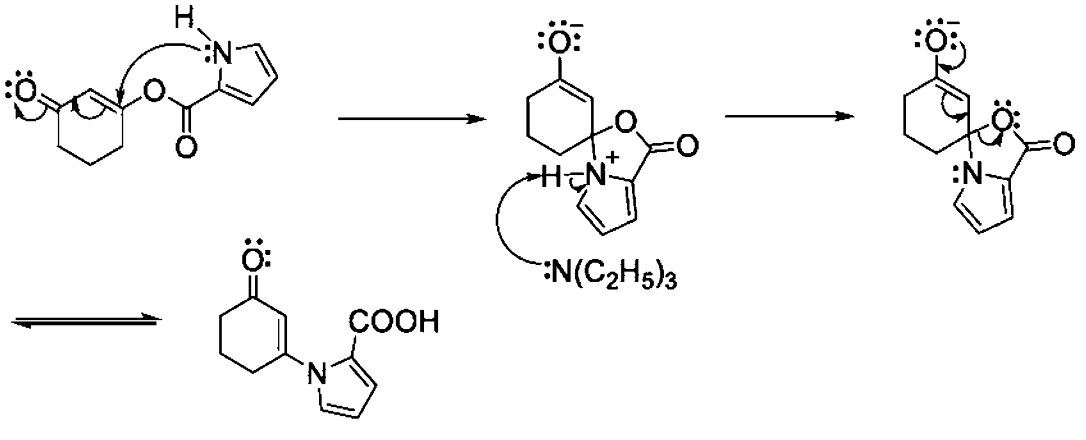
320

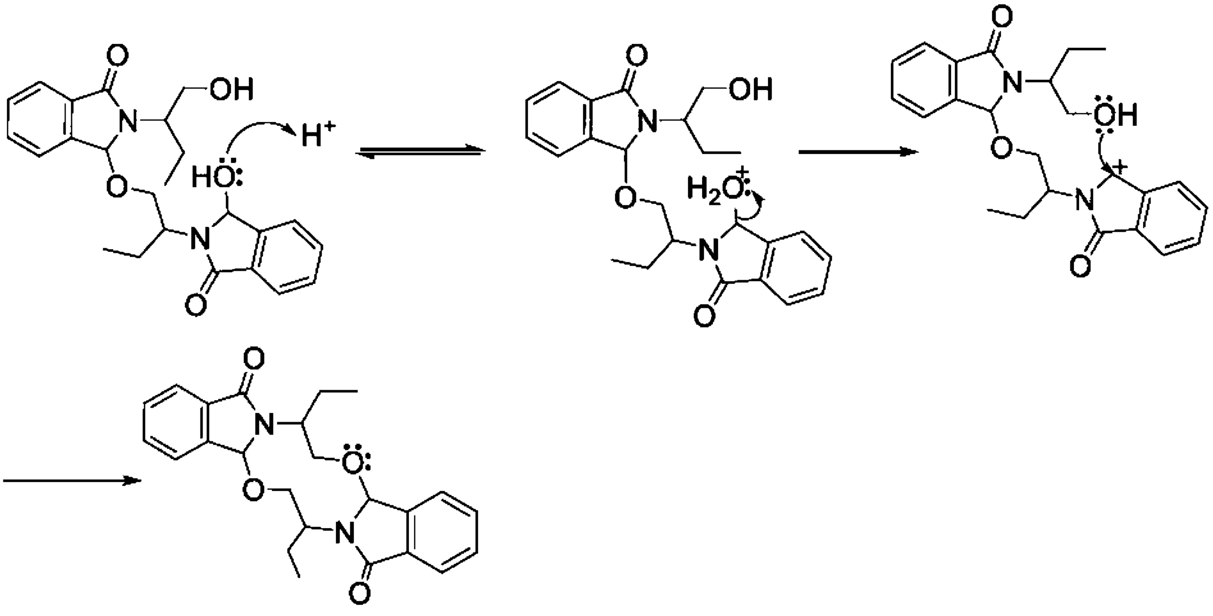
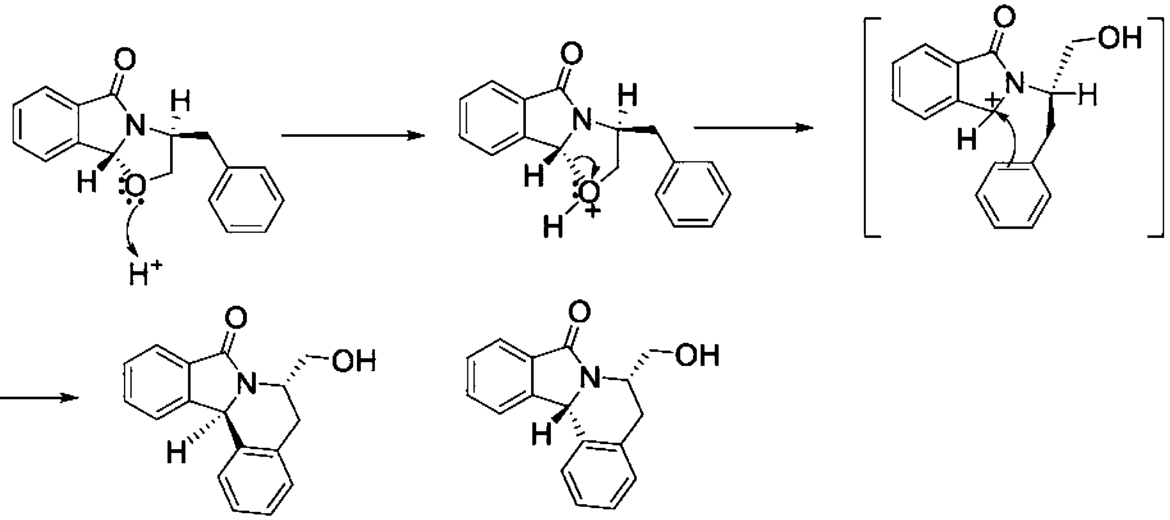


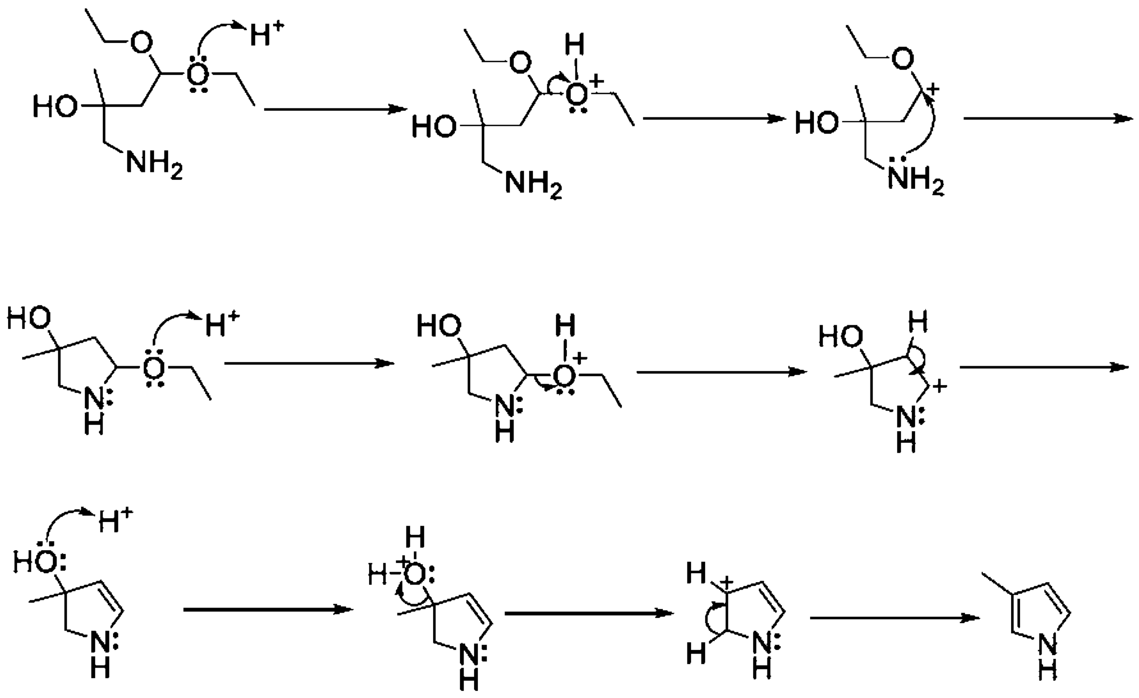
321



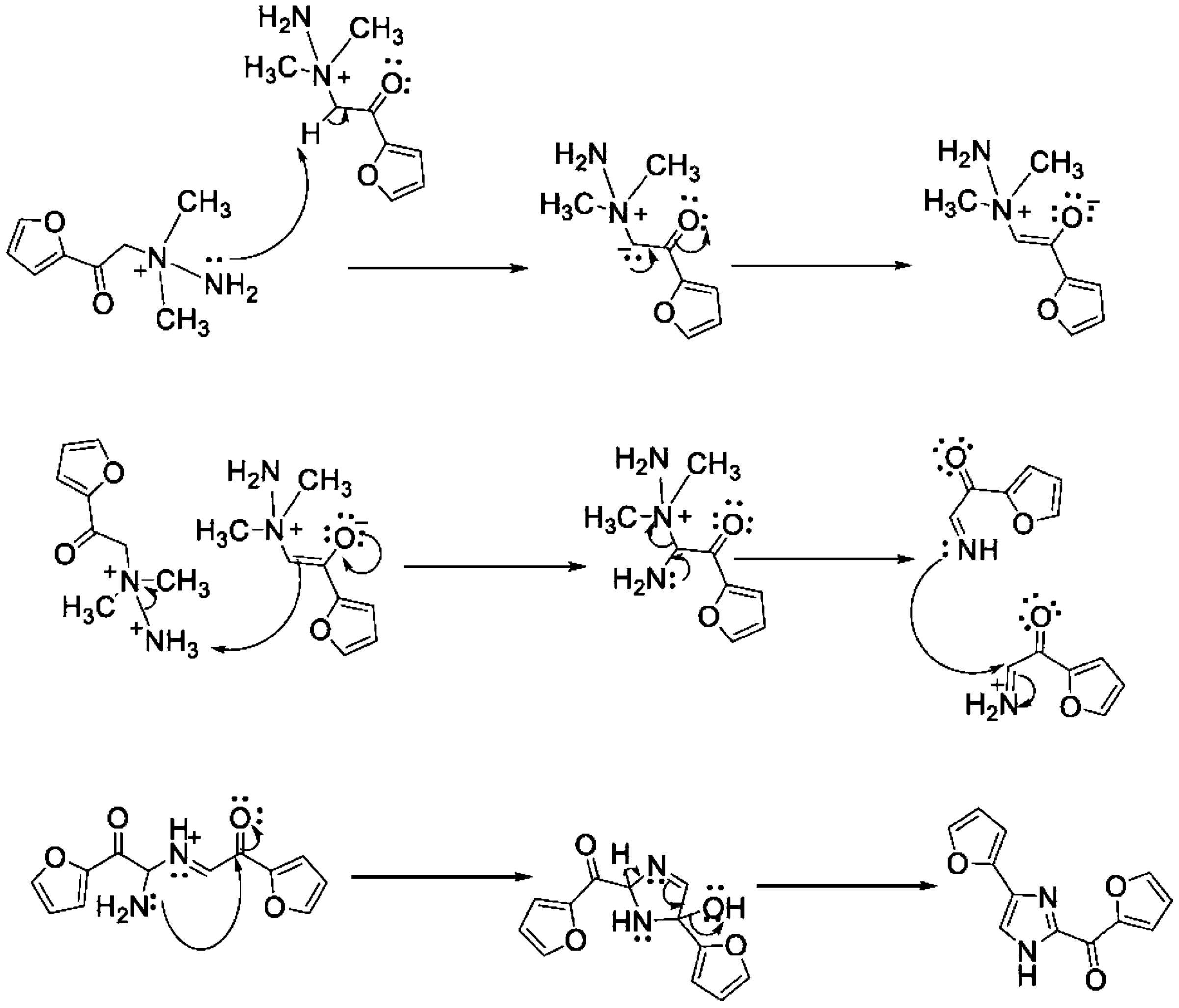
322



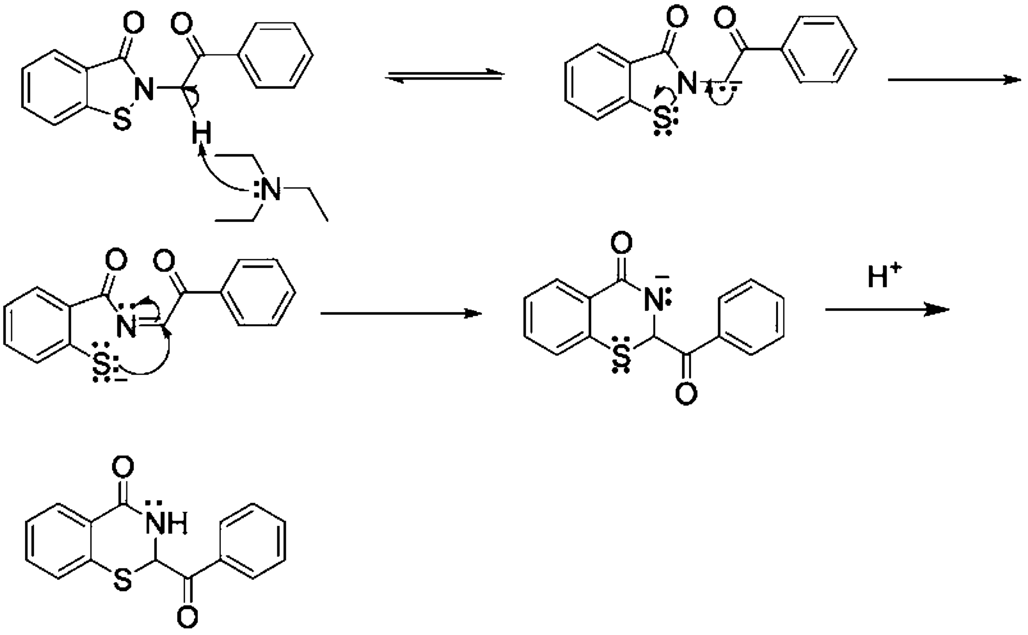
323

324
 (major) (minor)
325



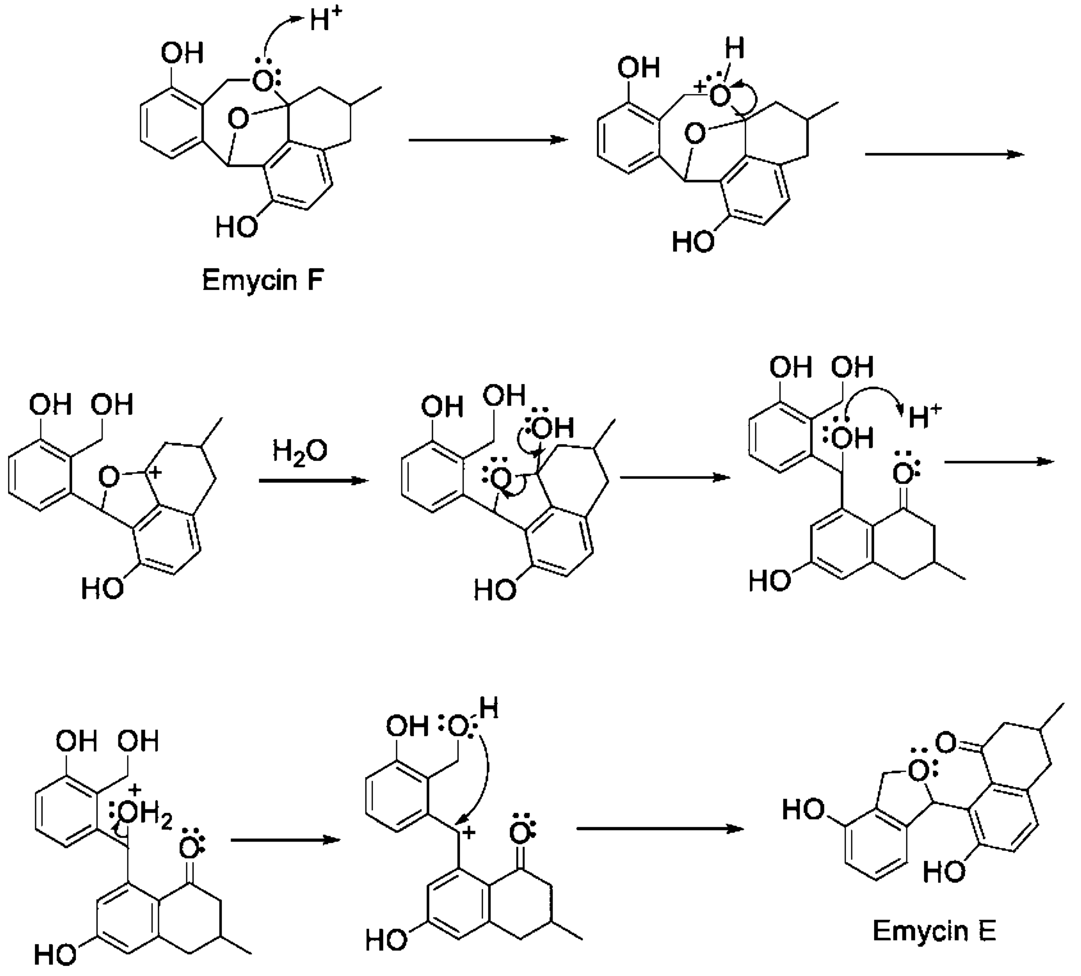
326



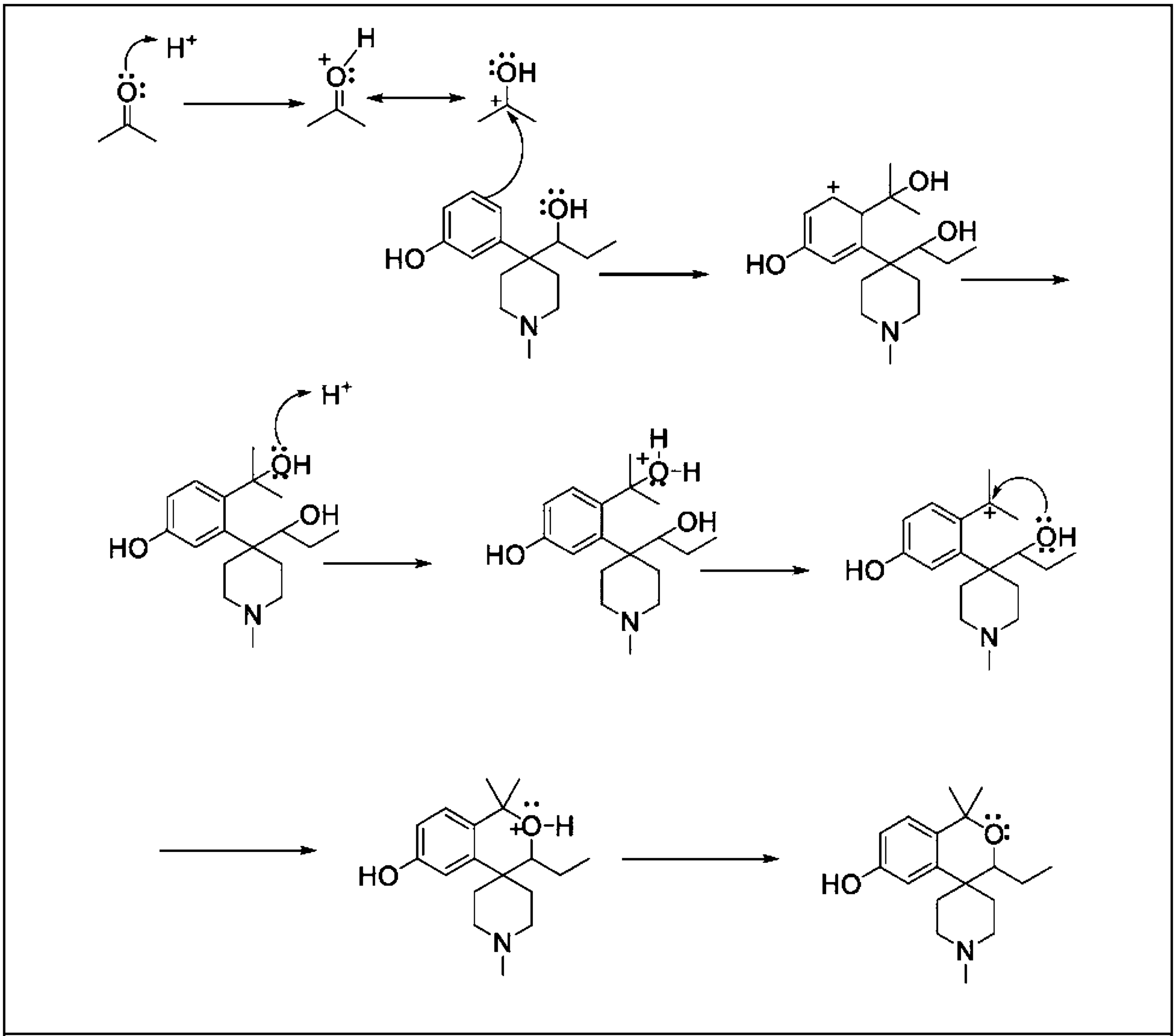
327



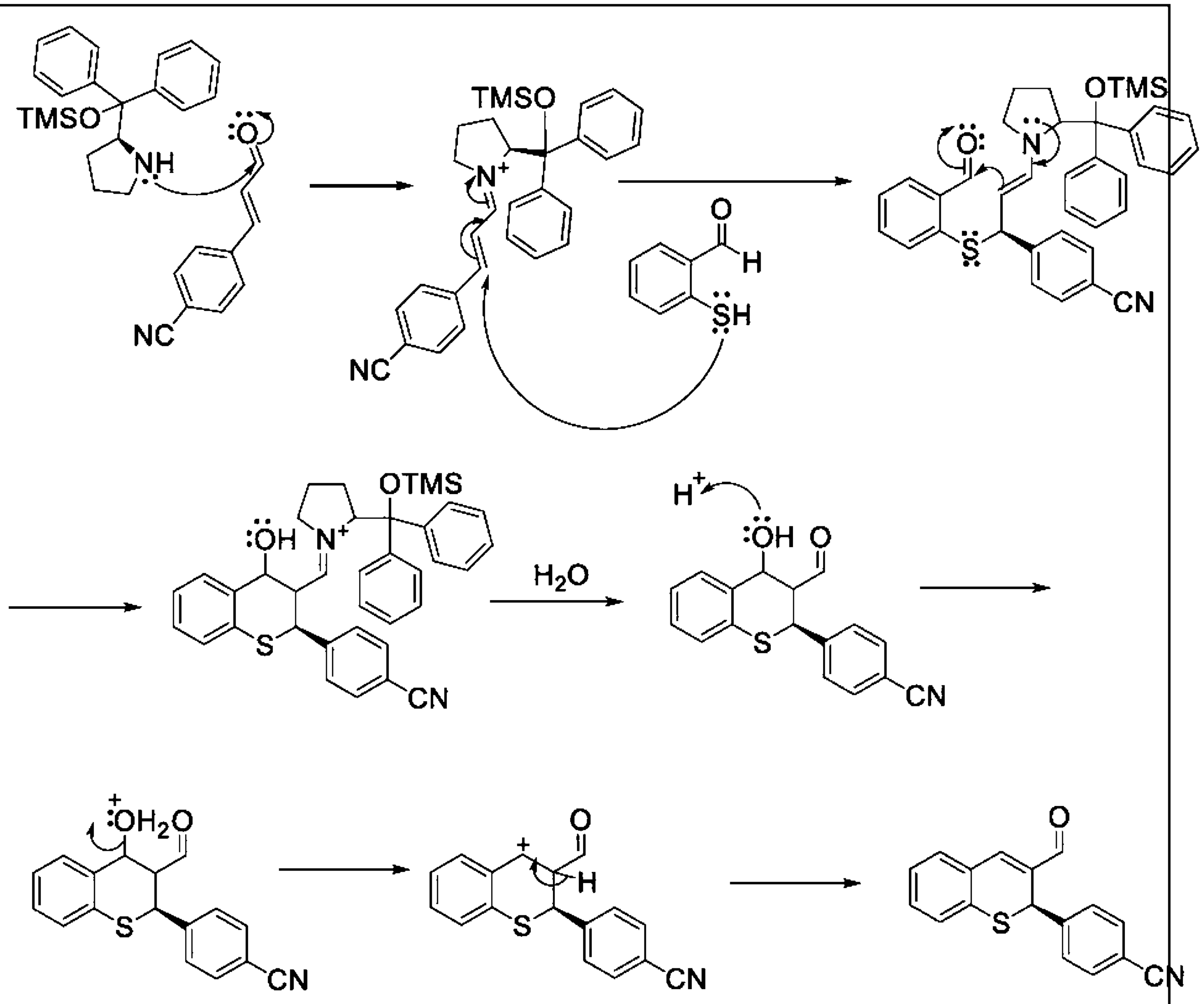
328



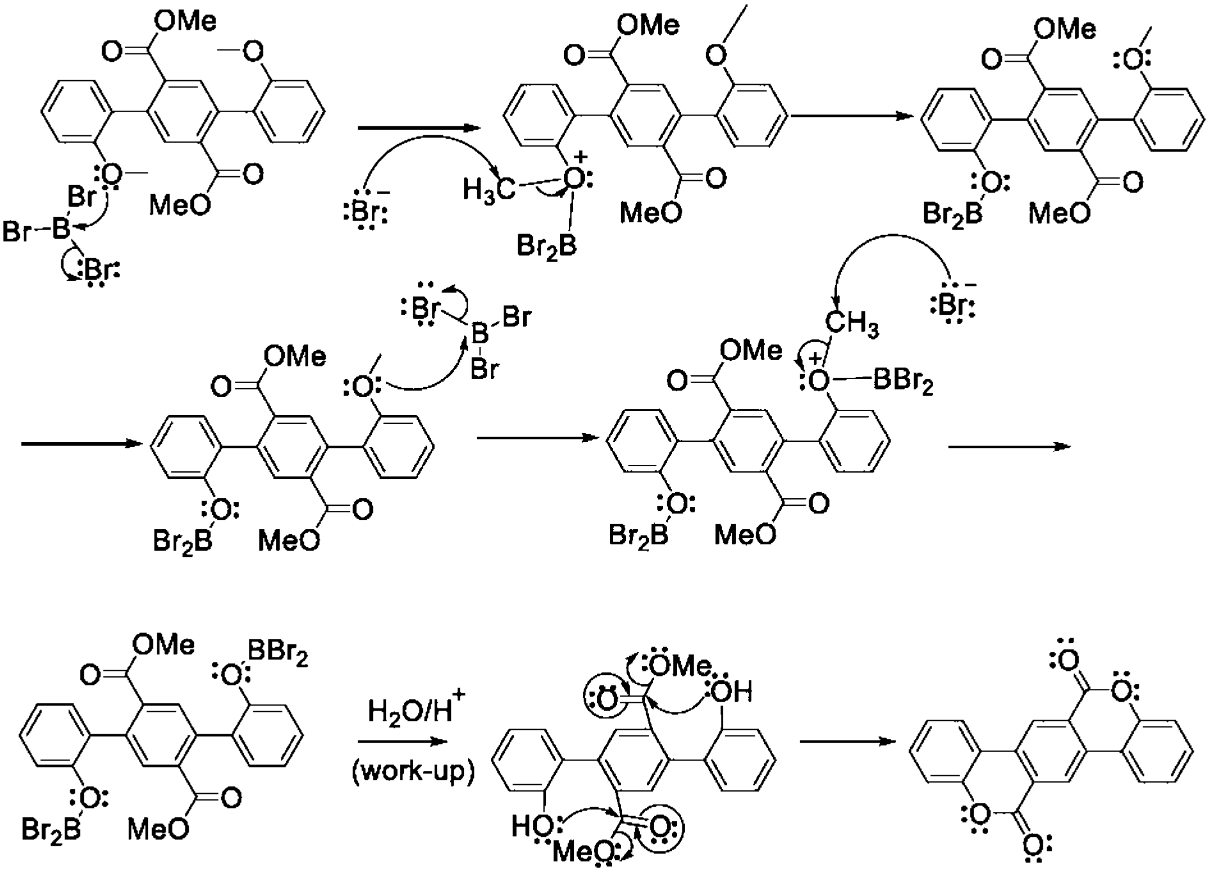
329



330

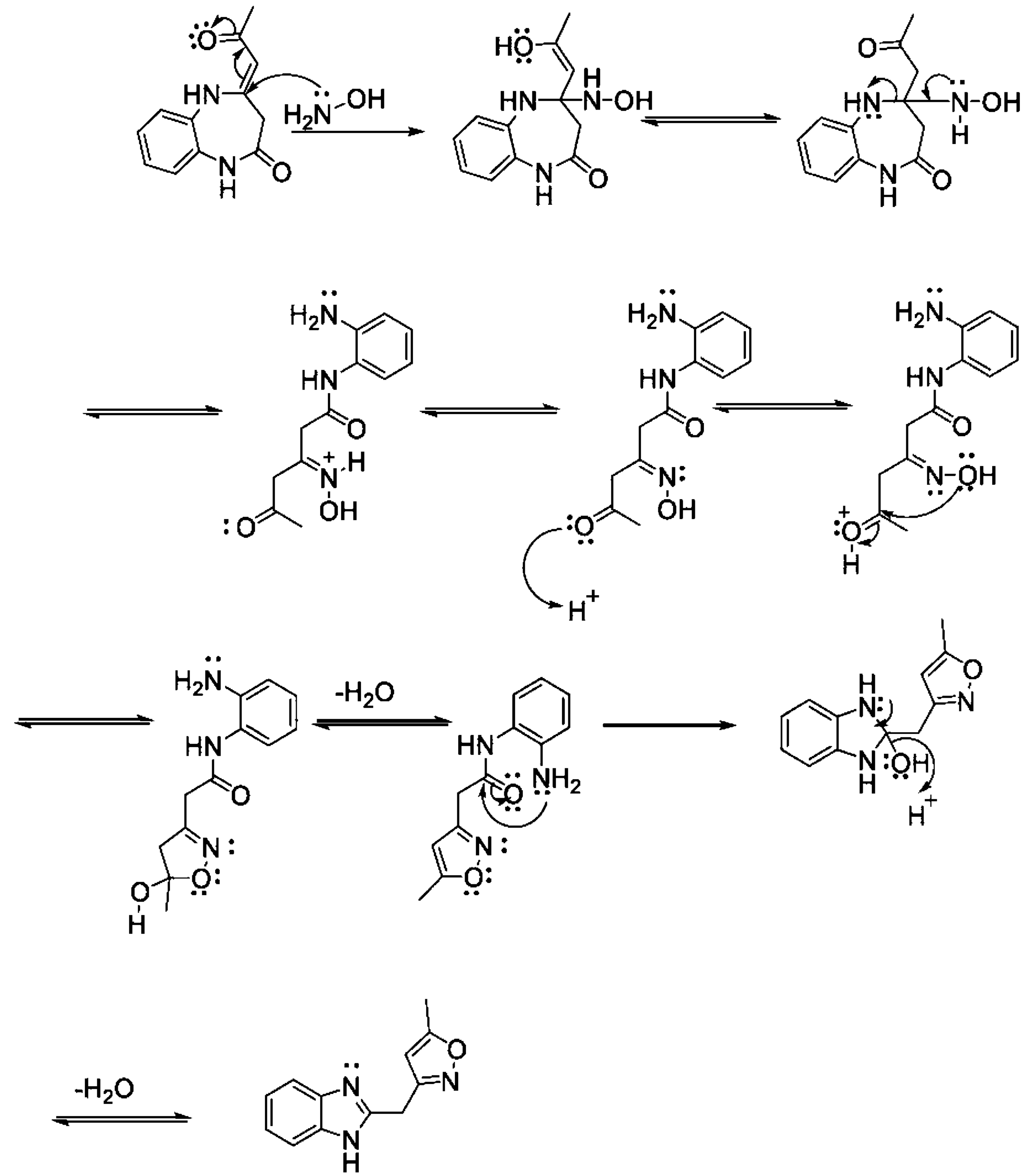

TMSO
NH
O
NC
TMSO
N+
NC
O
H
SH
OTMS
O
N
S
CN
OH
N+
OTMS
S
CN
H2O
H+
OH
O
S
CN
+
OH2
O
S
CN
+
O
H
S
CN
O
S
CN

331

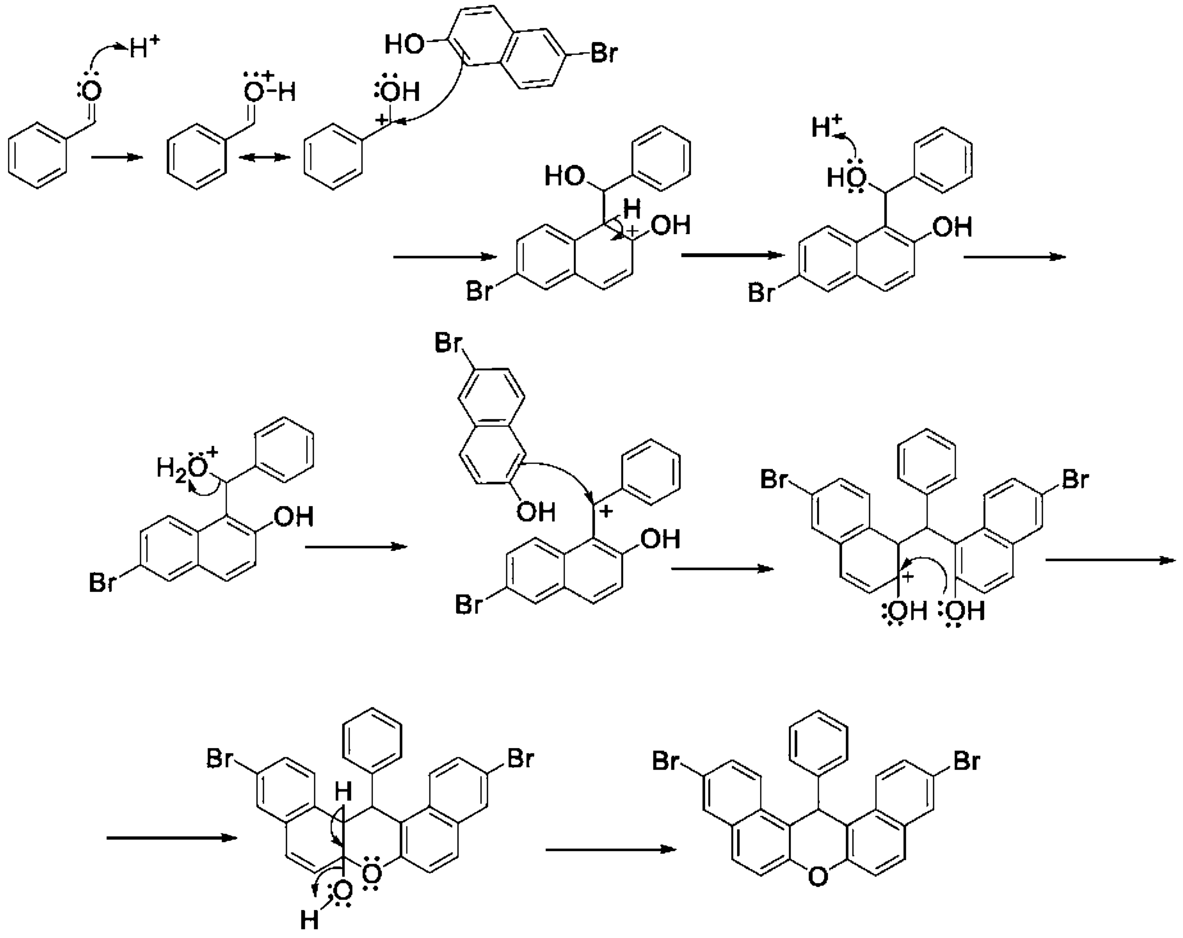


(two consecutive intramolecular transesterification reactions yield the final product)

332

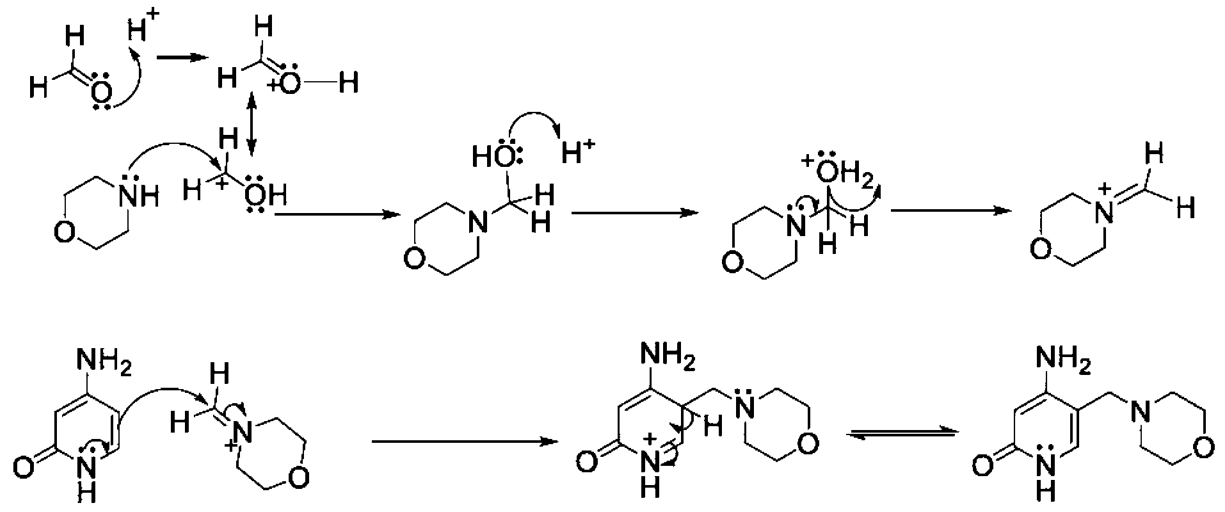


333

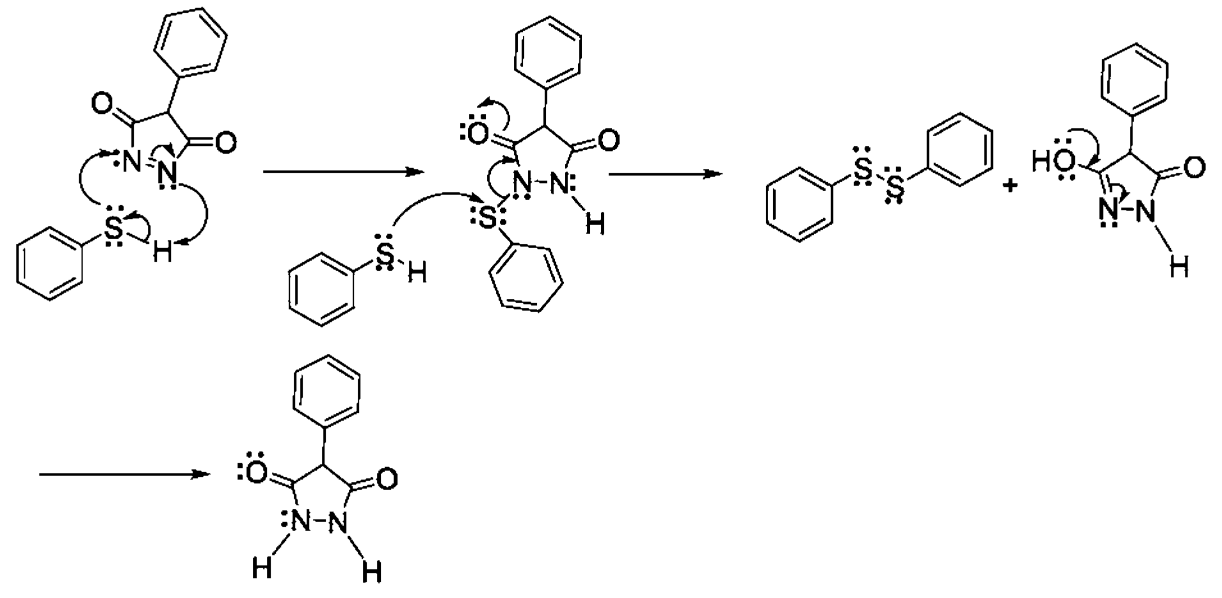


(Amberlyst-15 is a sulfonic acid polymer resin)

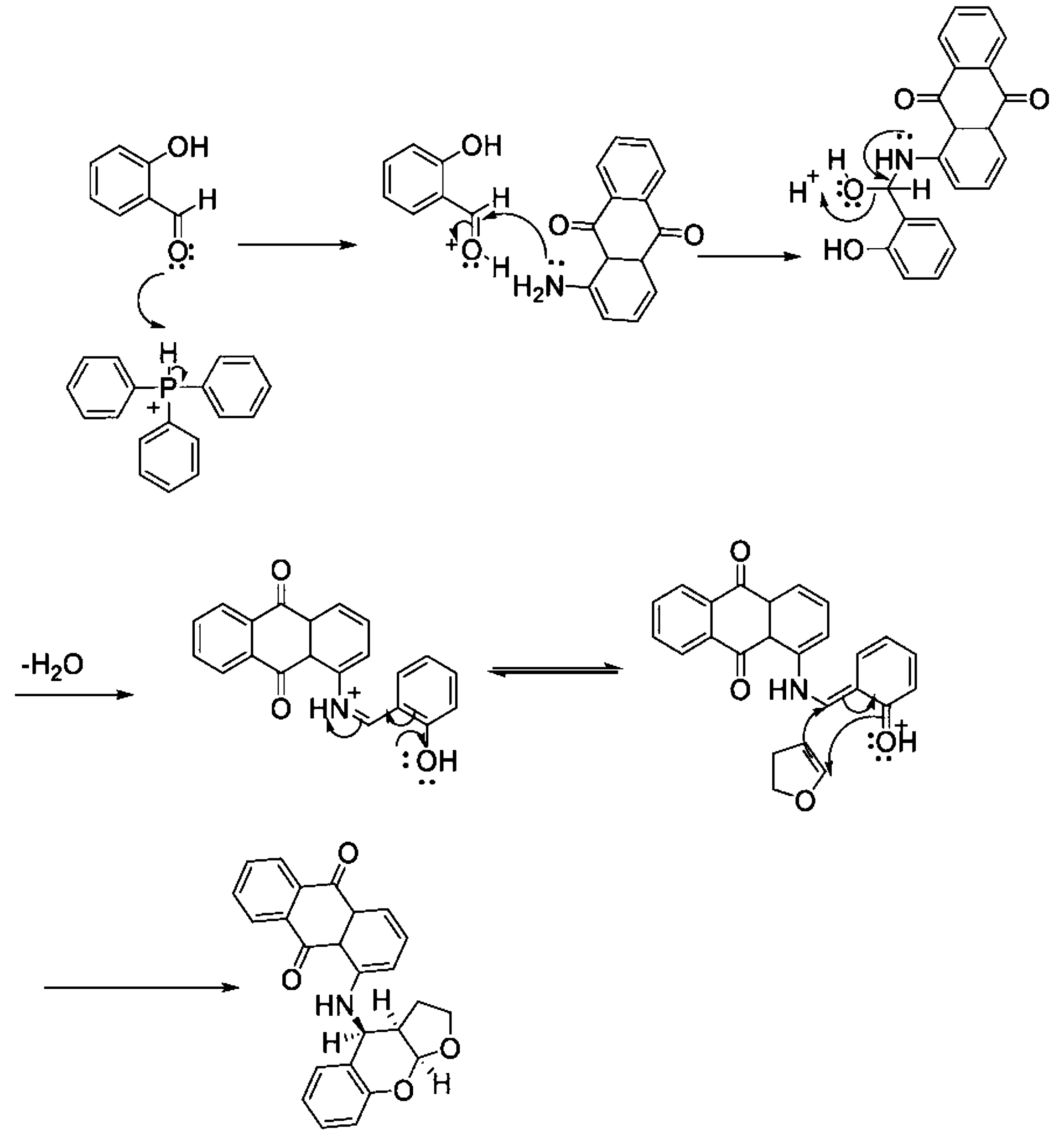
334



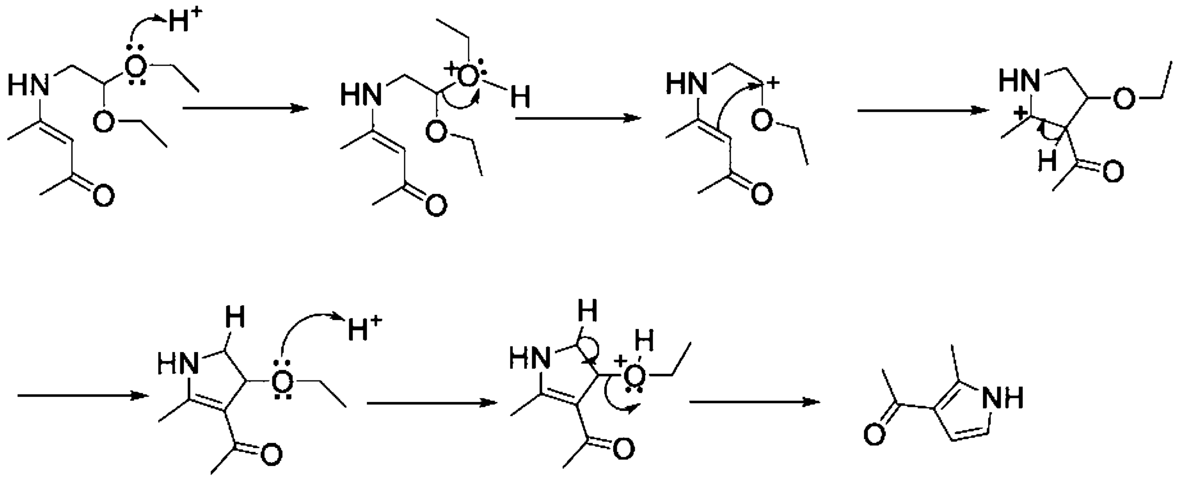
335



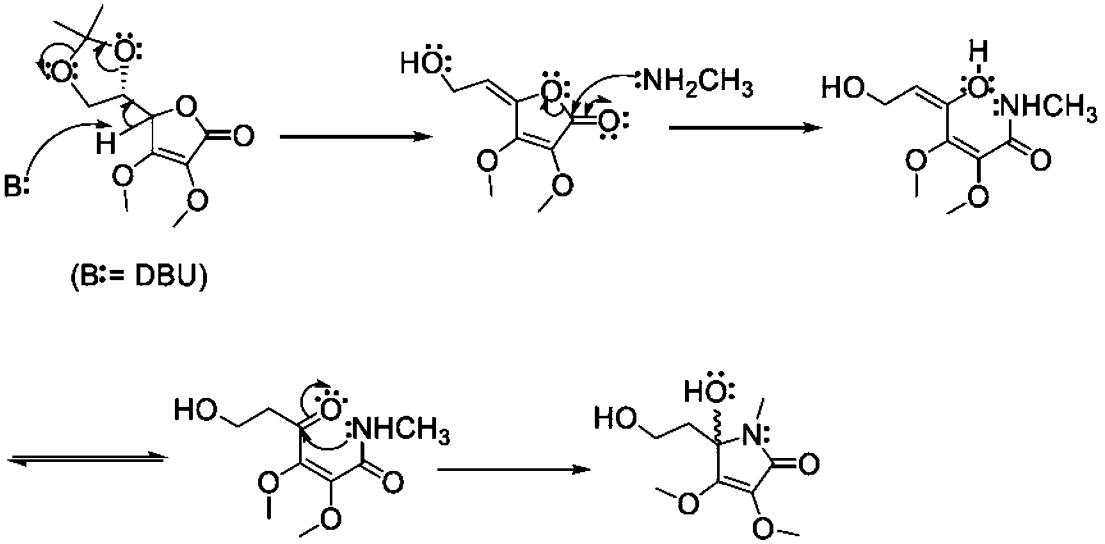
336


OH
H
O:
H
P
+
OH
H
+O
H
H2N
O
O
O
O
H
HN
H+
O
H
HO
-H2O
O
O
HN+
:OH
O
O
HN
O
:OH+
O
O
HN
H
H
O
O
H

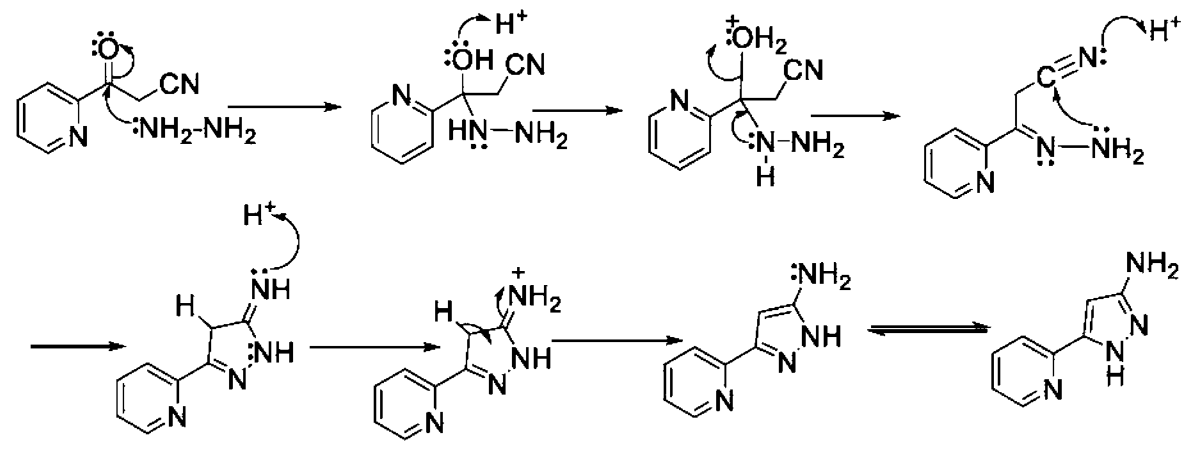
337



338

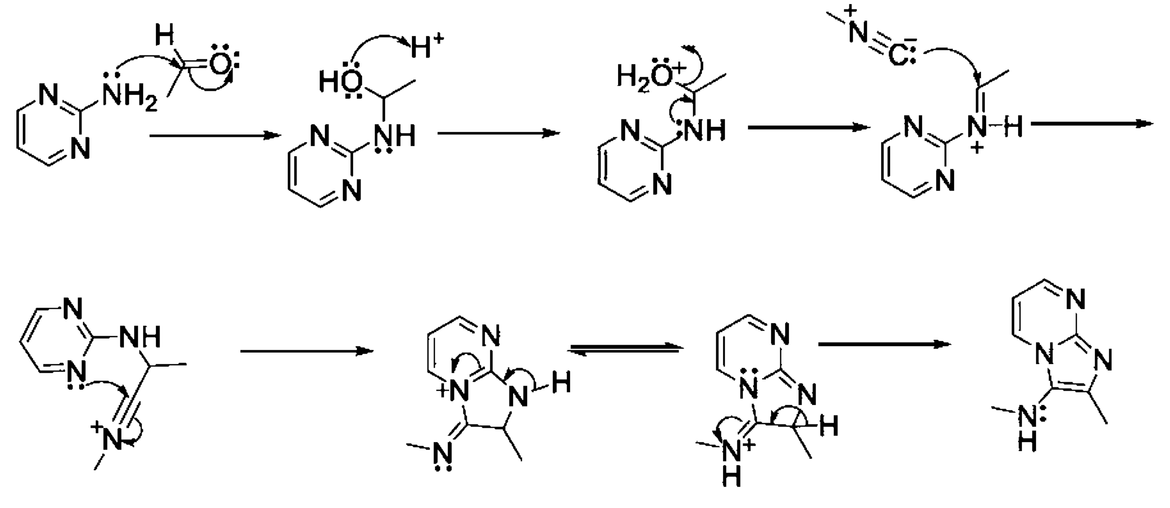


339



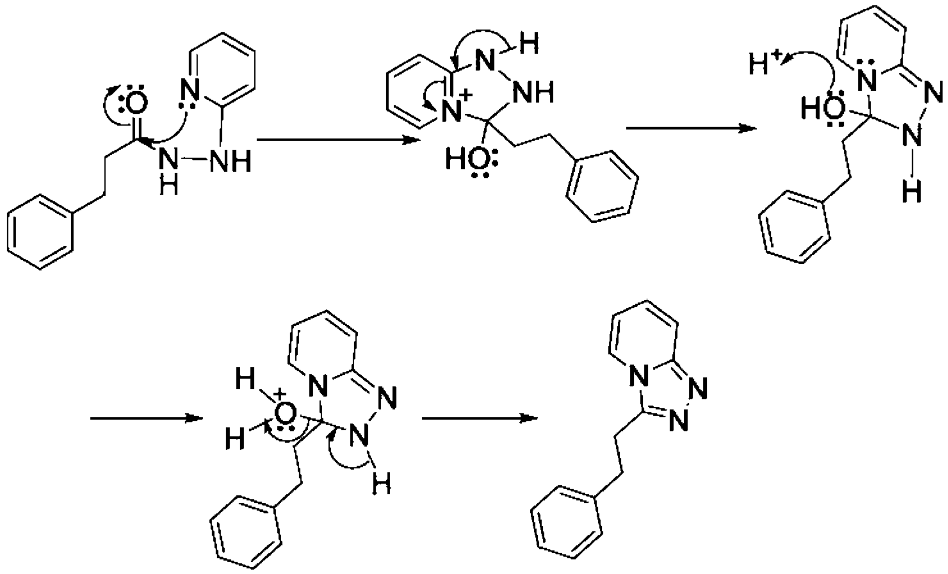
CN
NH2-NH2
H+
OH
HN-NH2
OH2
N-NH2
H
C≡N
N-NH2
H
NH
NH2
N
NH

340

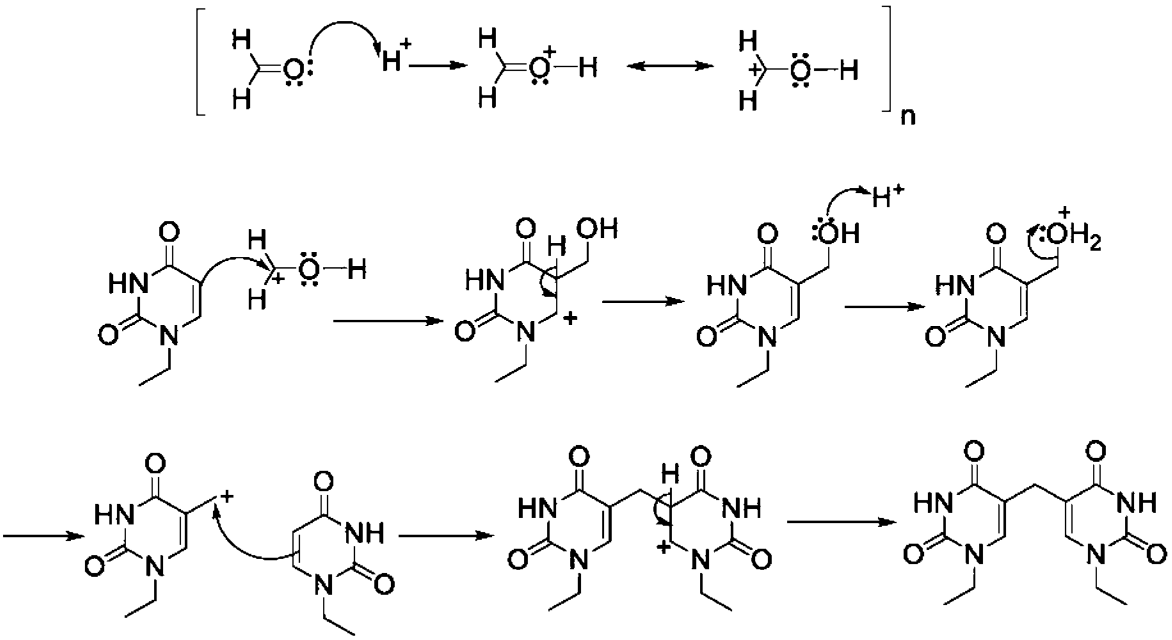


H
O
NH2
N
HO
NH
H+
H2O+
N≡C
N-H
+
NH
N
H

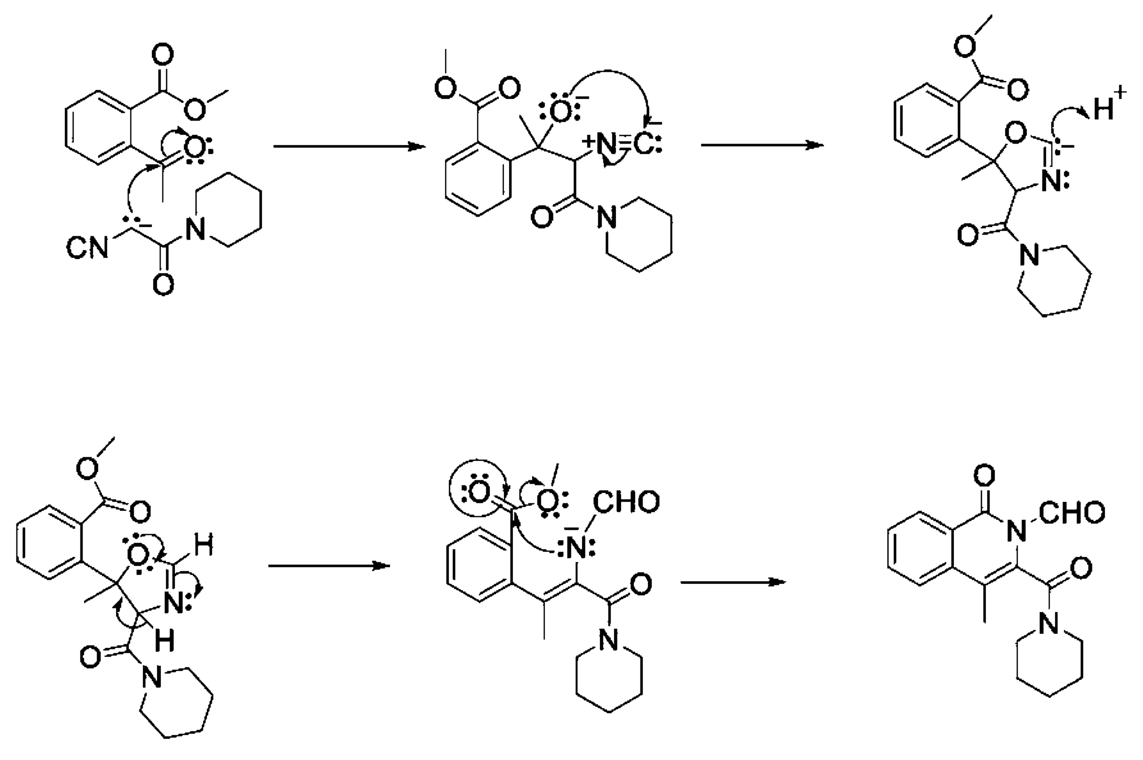
341



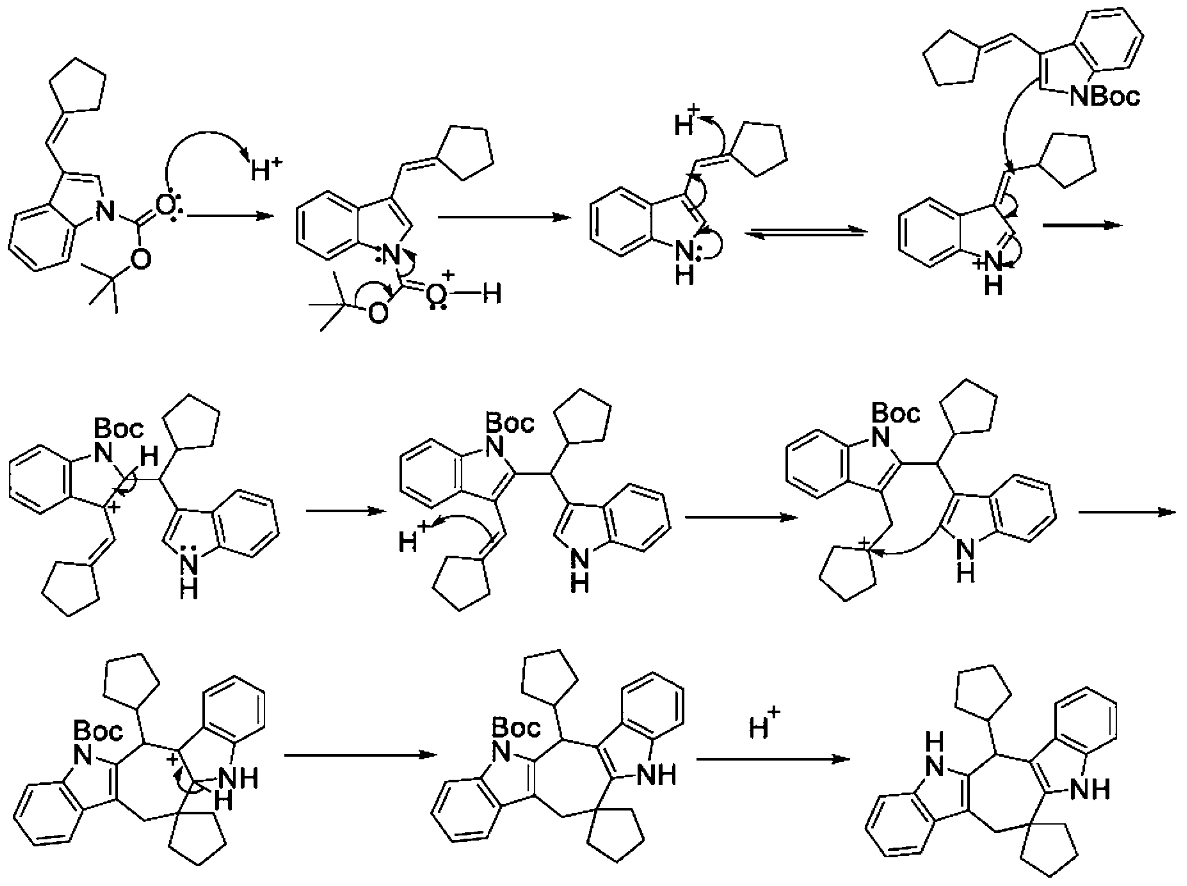
342



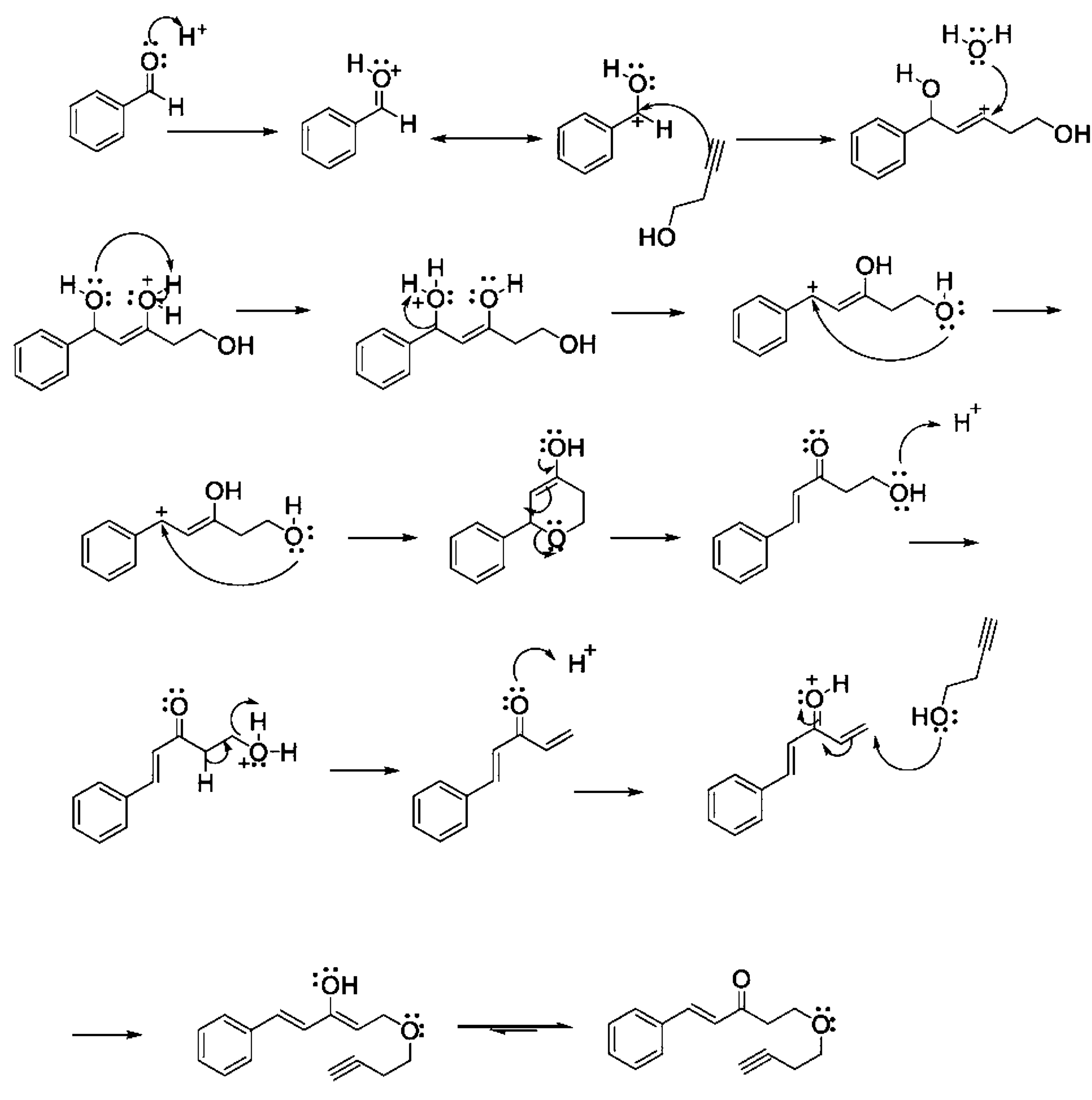
343



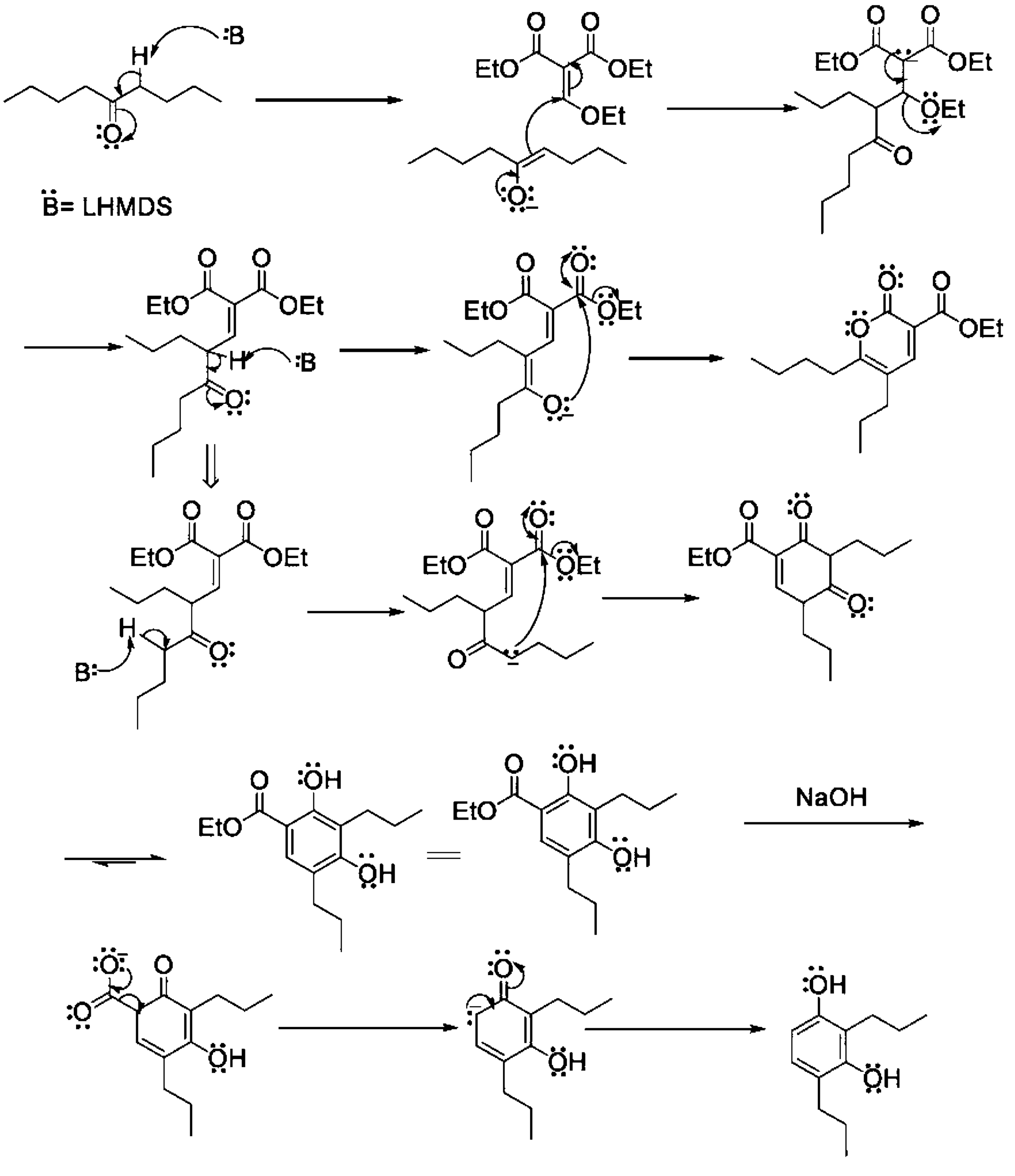
344


N
O
O
H+
N
O
O
H
H+
N
H
N
H
NBoc
Boc
N
H
N
H
Boc
N
H+
N
H
Boc
N
N
H
Boc
N
NH
H
Boc
N
NH
H+
H
N
NH

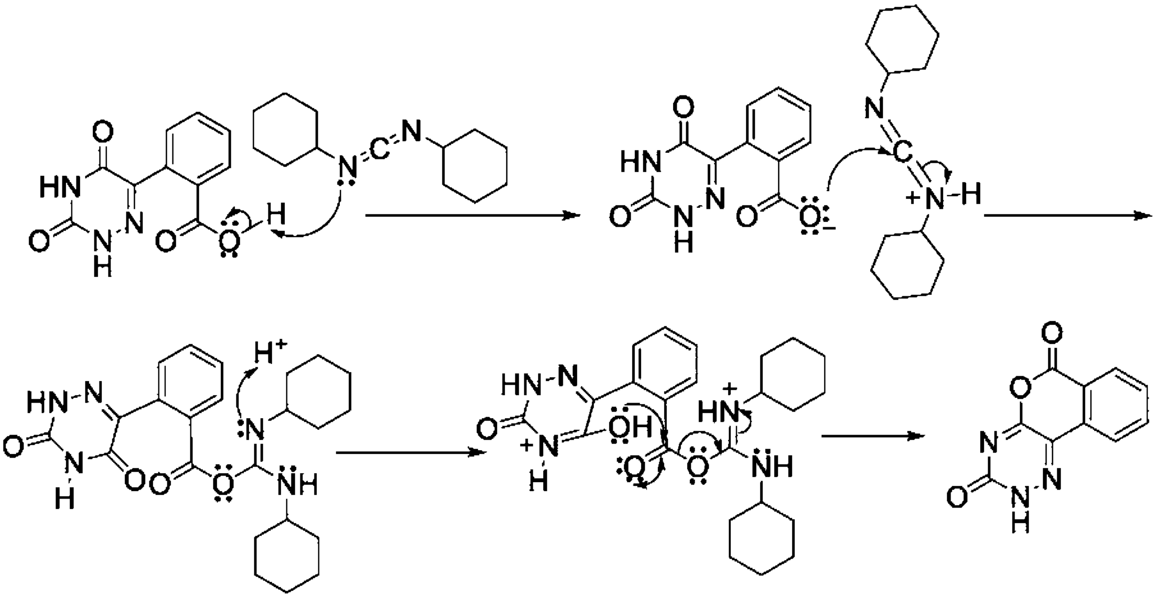
345



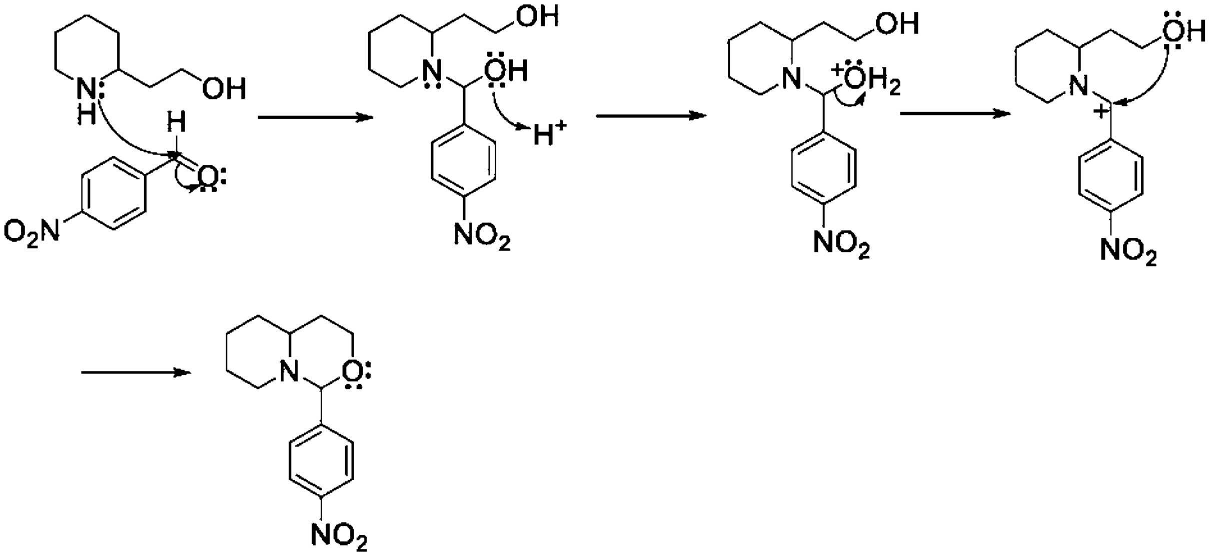
346



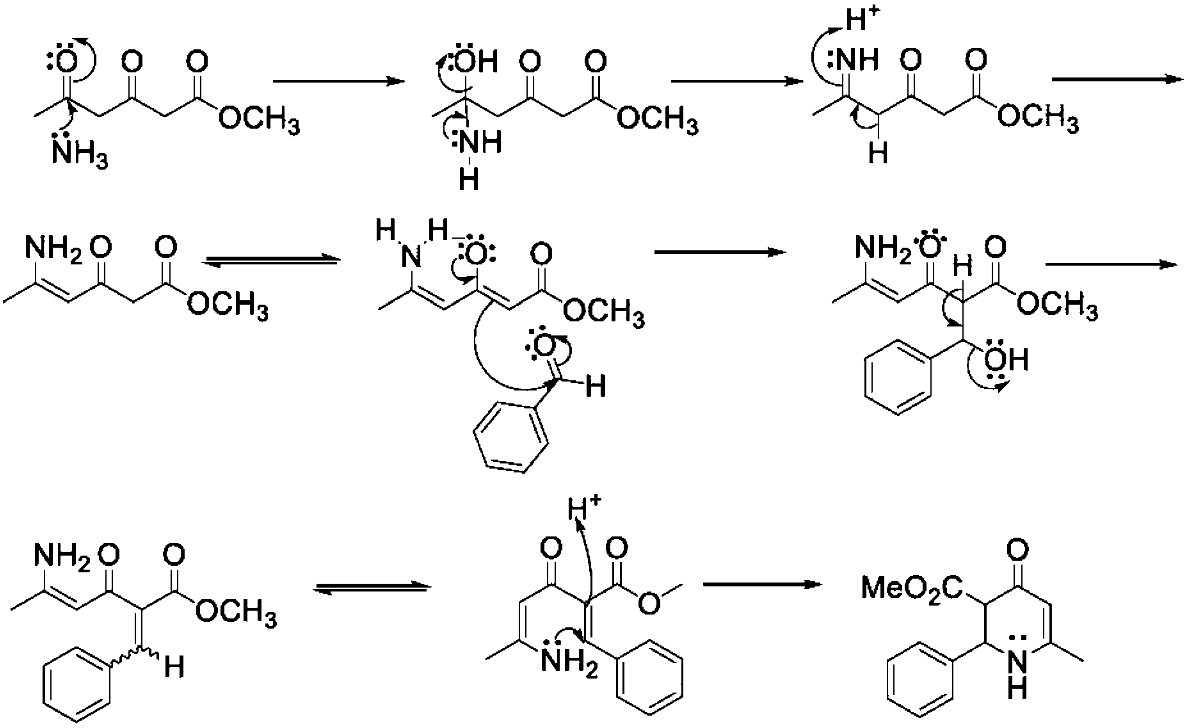
347



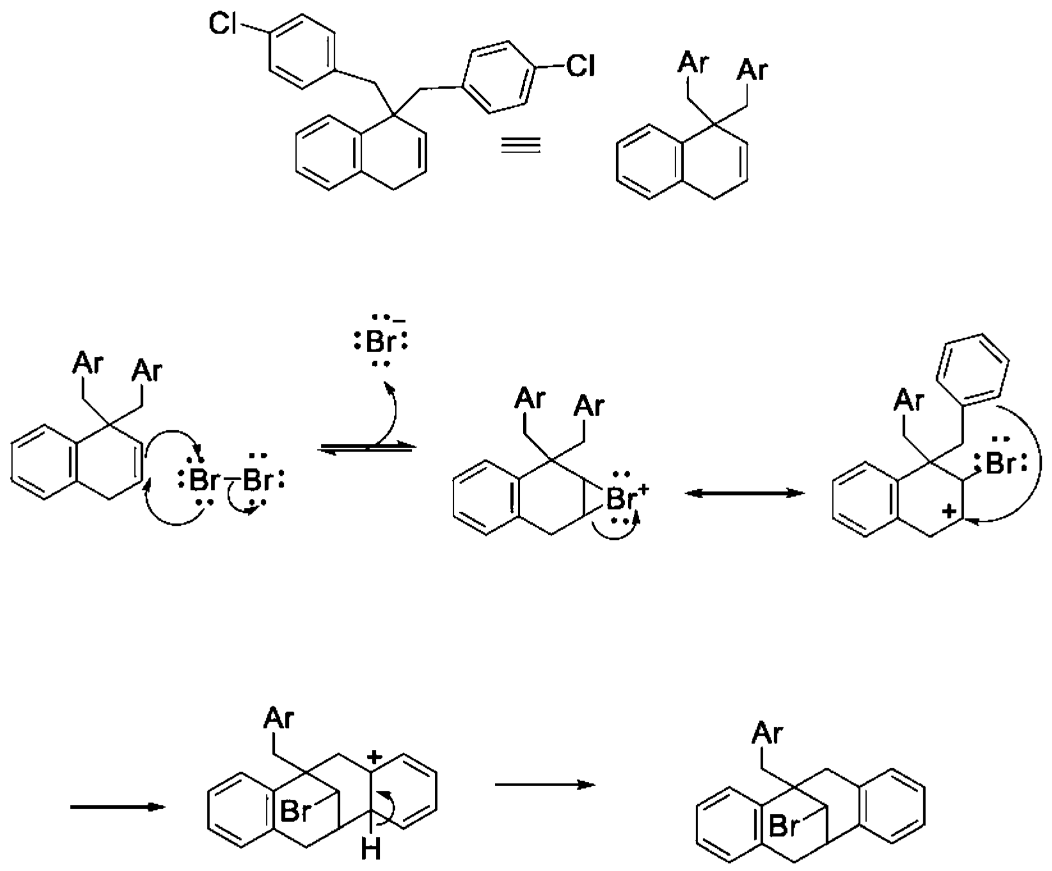
348



349

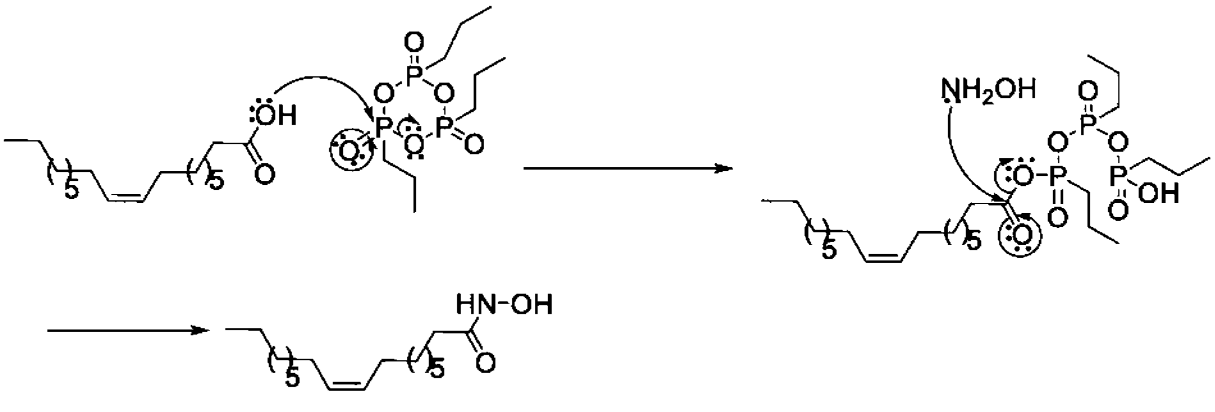


350



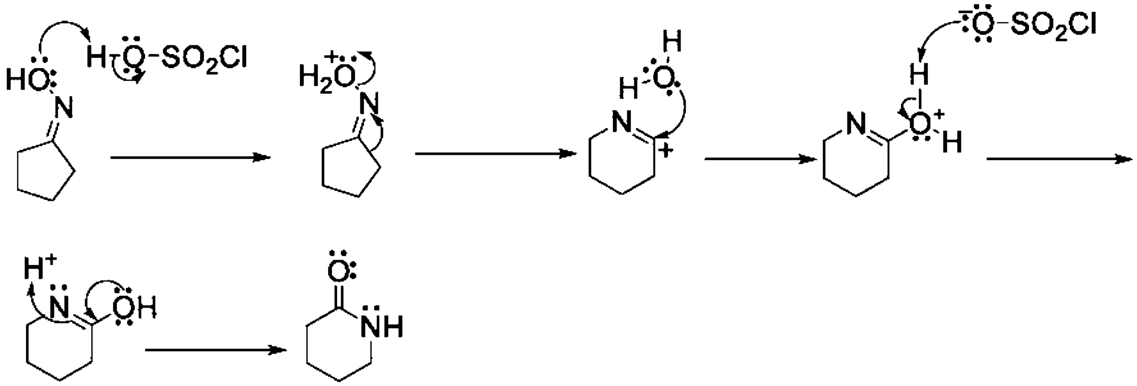
Cl
Cl
≡
Ar
Ar
:Br:
:Br:
:Br:−
Br+
:Br:
+
+
Br
H
Br

351



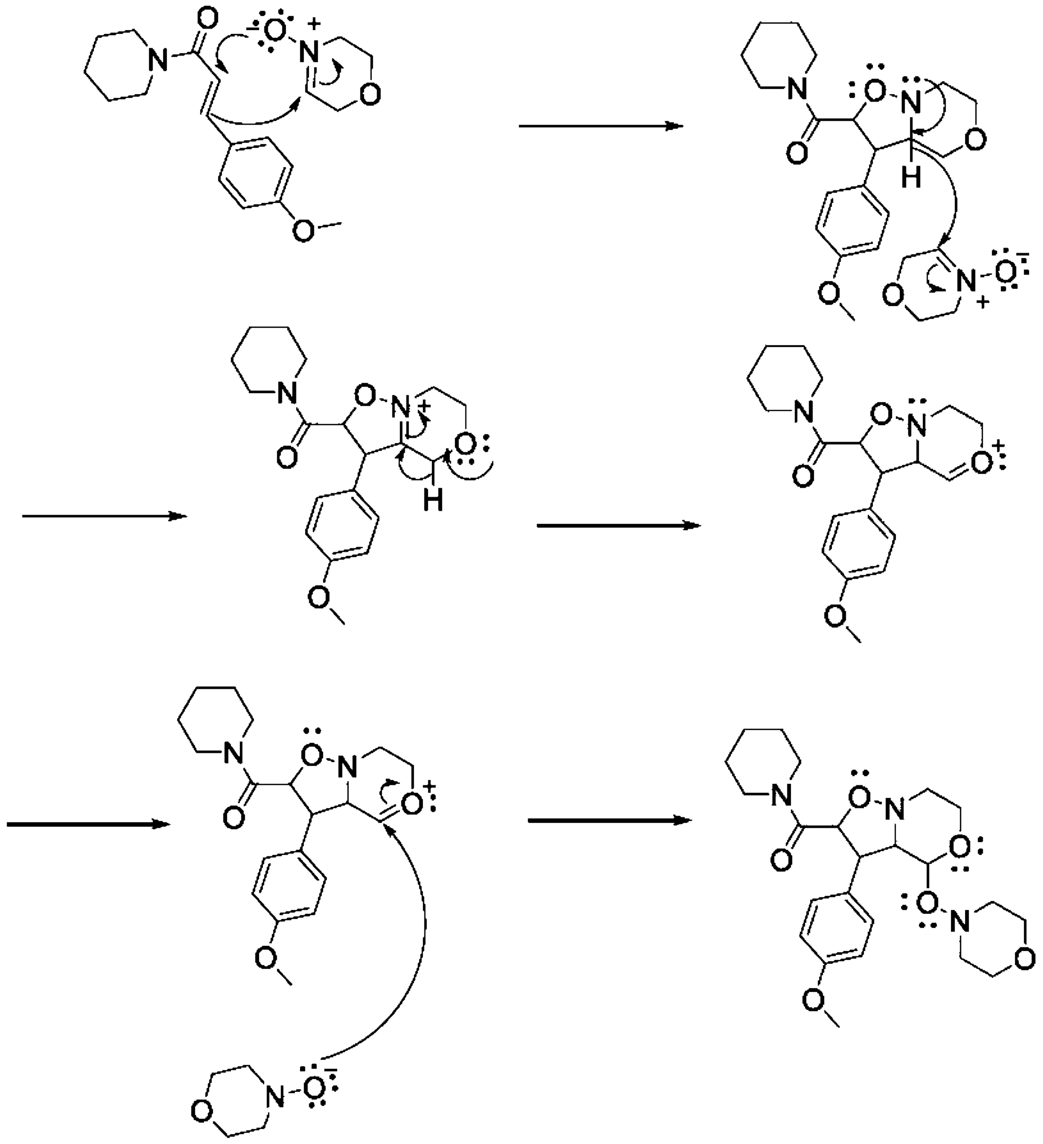
:ÖH
O
5
5
O
P
O
O
P
O
P
O
O
O
NH2OH
O
P
O
O
O
P
P
O
O
O
OH
O
5
5
HN-OH
5
5
O

352

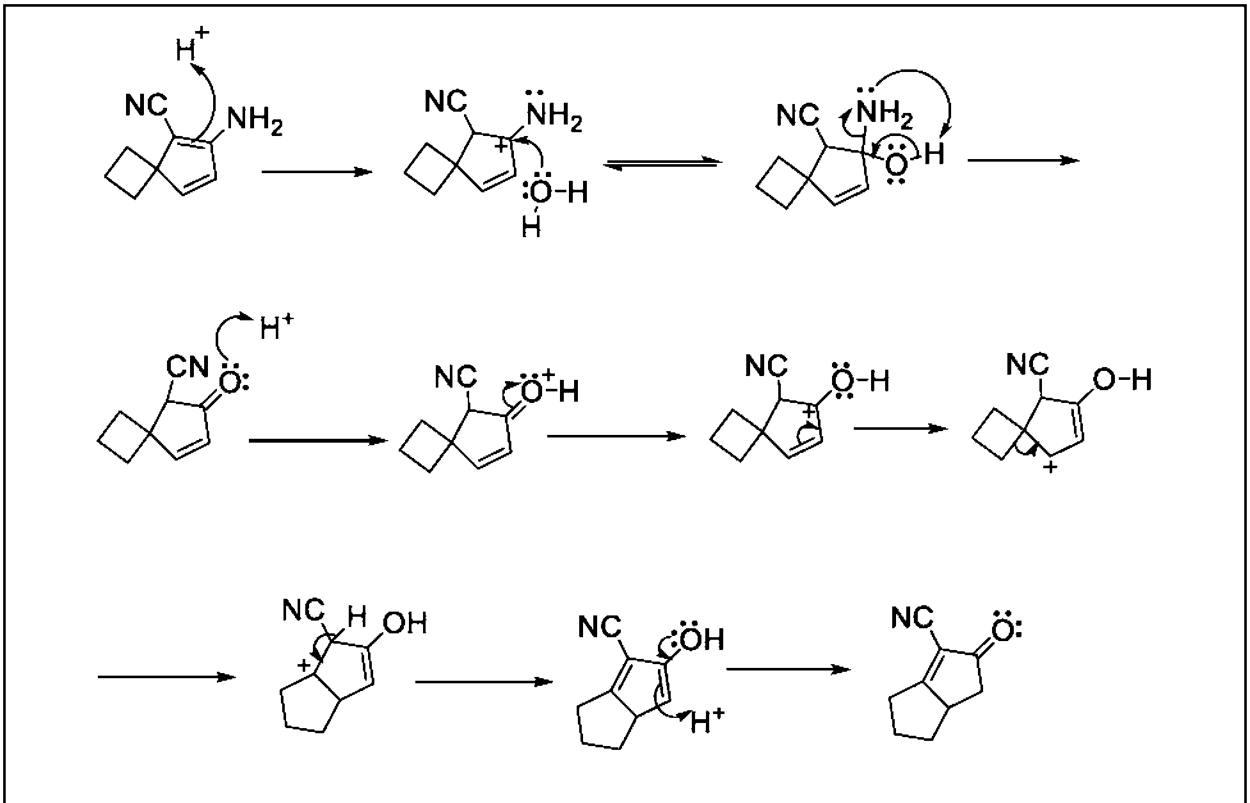


This is an example of the *Beckman rearrangement*

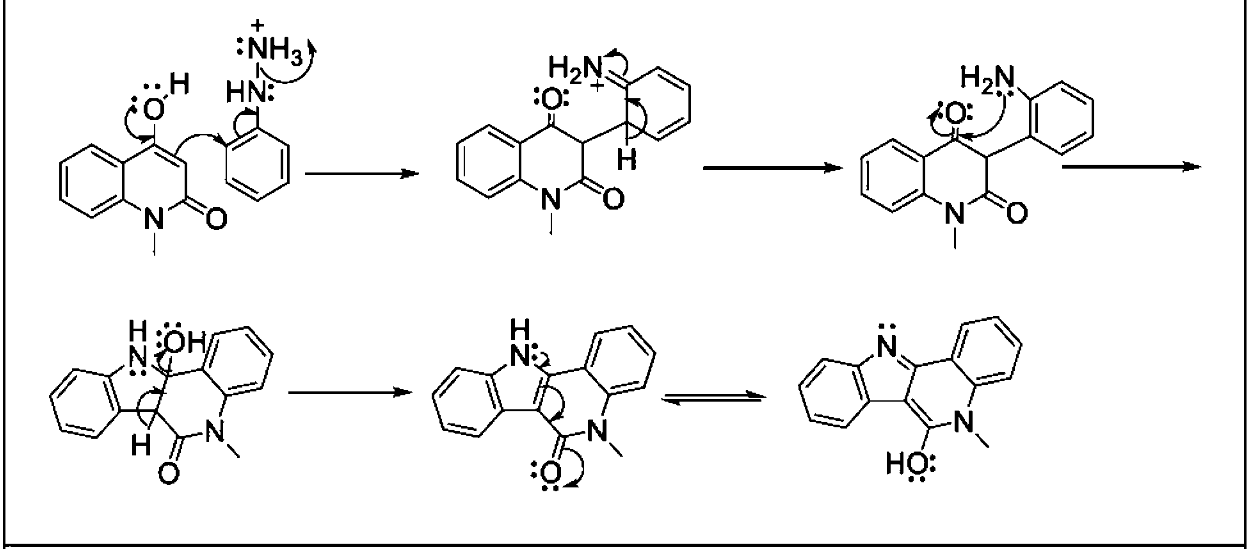
353



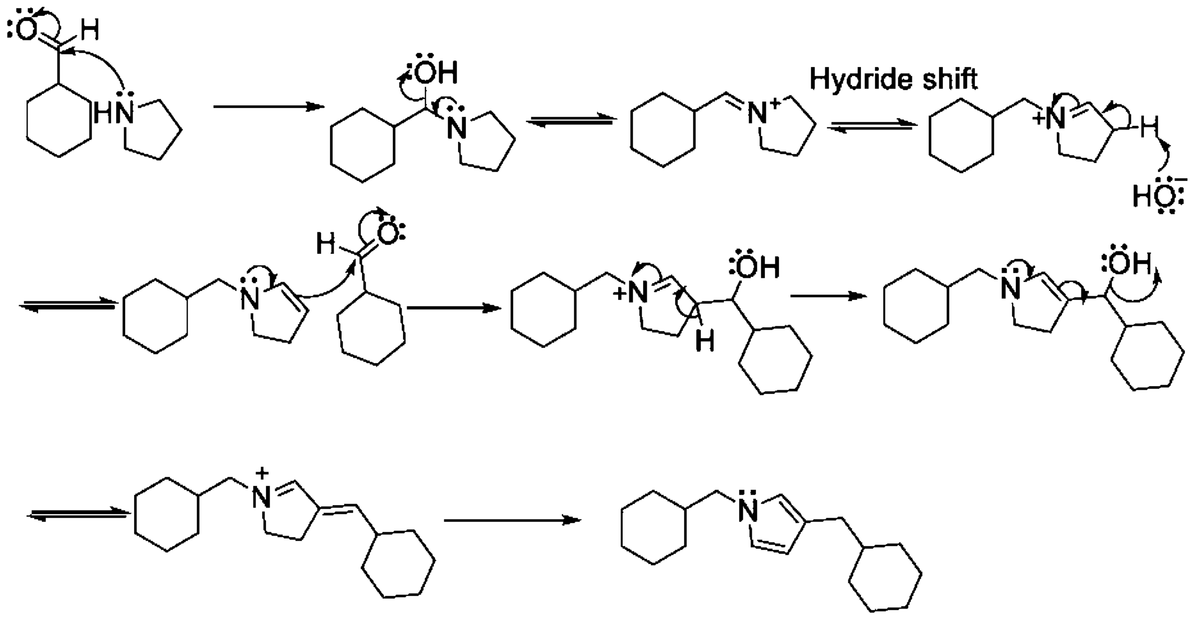
354


H+
NC
NH2
+
O-H
H
NH2
O
H
H+
CN
O
NC
O+-H
O-H
+
NC
H
OH
+
OH
H+
O

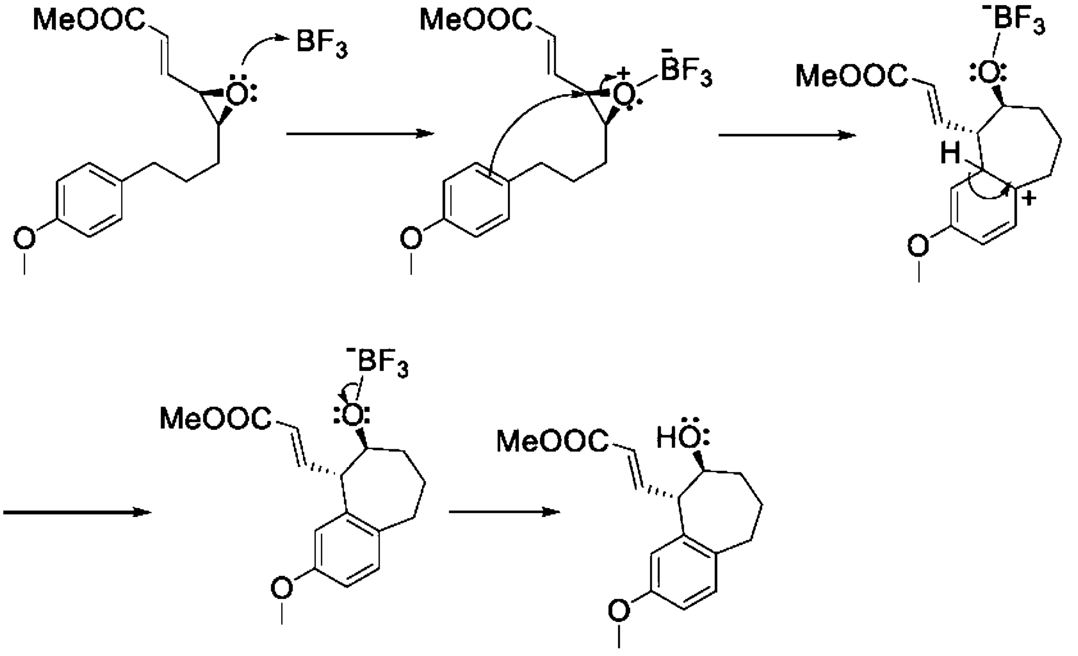
355


O
H
+
NH3
HN
N
O
H2N
+
H
O
N
O
H2N
O
N
O
H
N
OH
H
O
N
H
N
O
N
N
N
HO

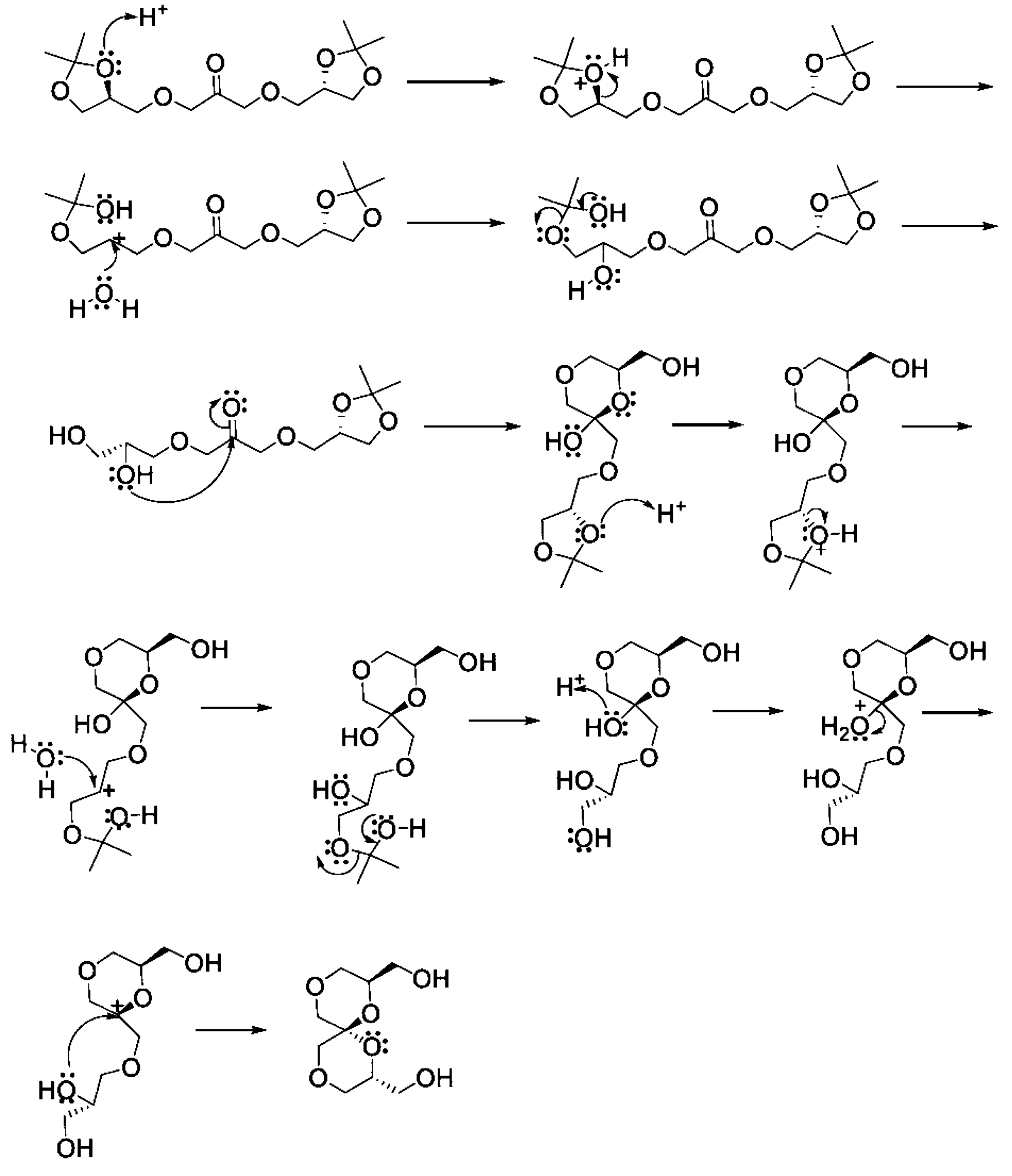
356



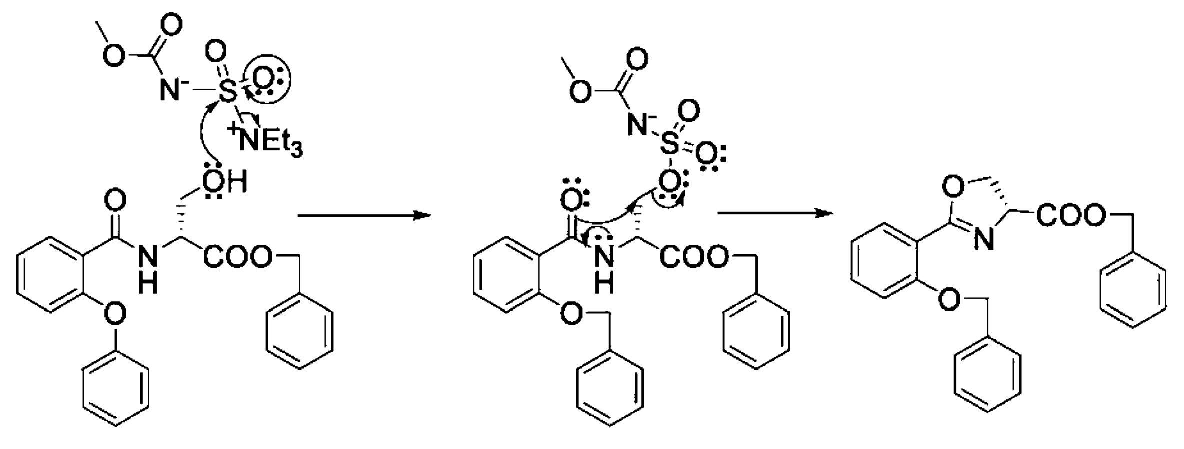
357



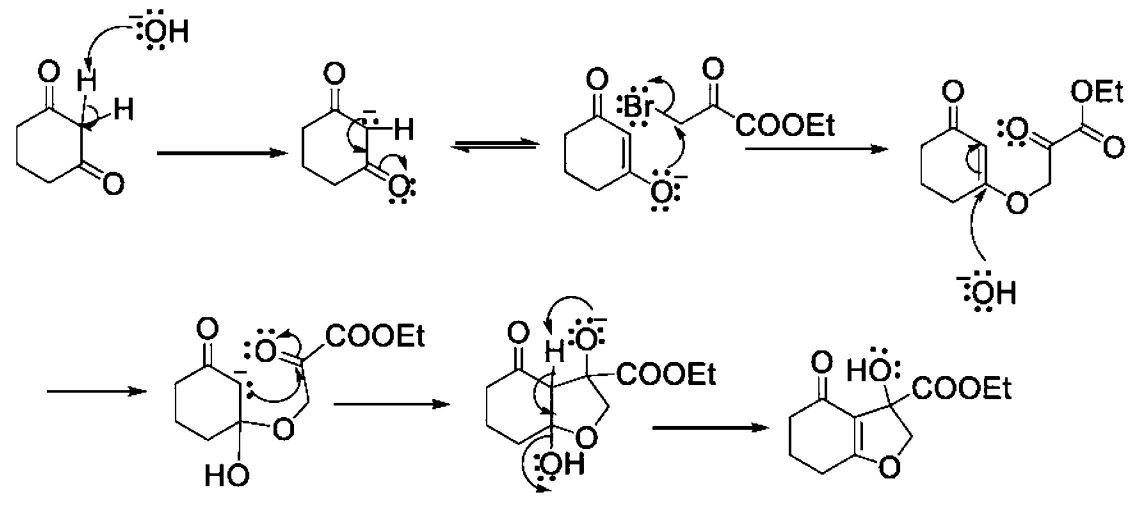
358



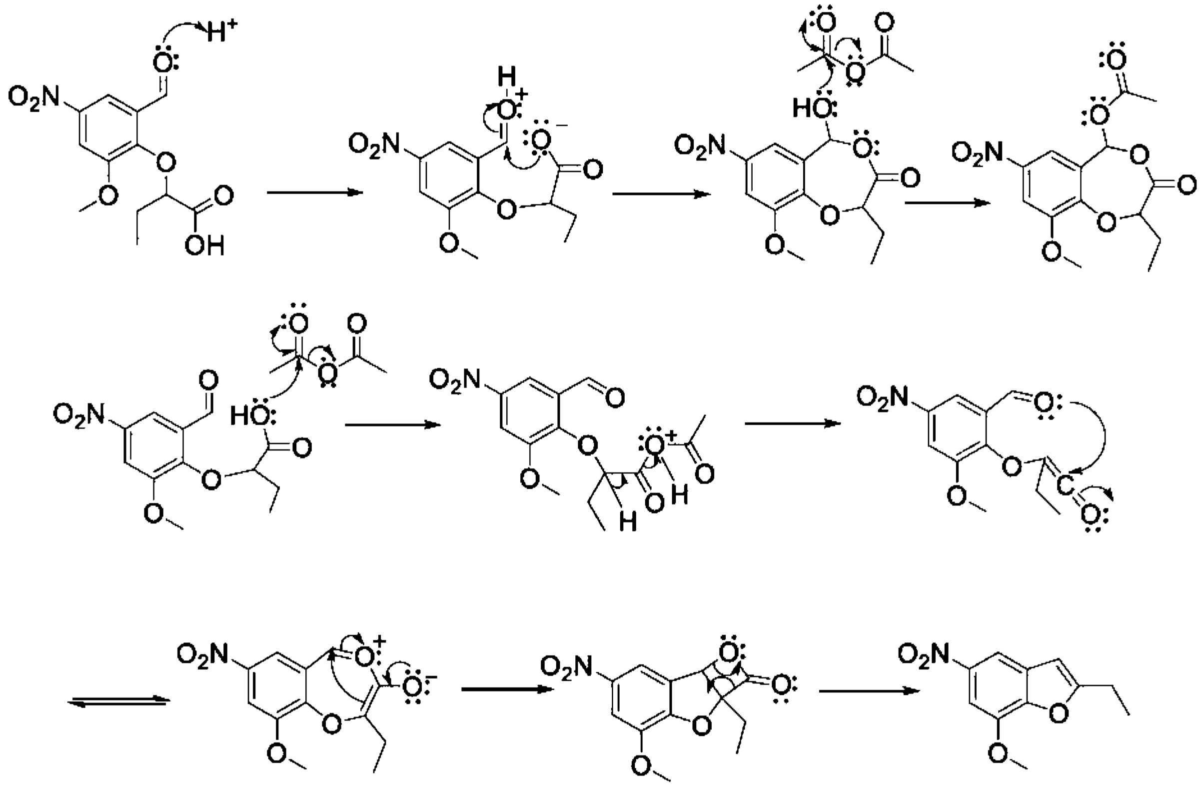
359



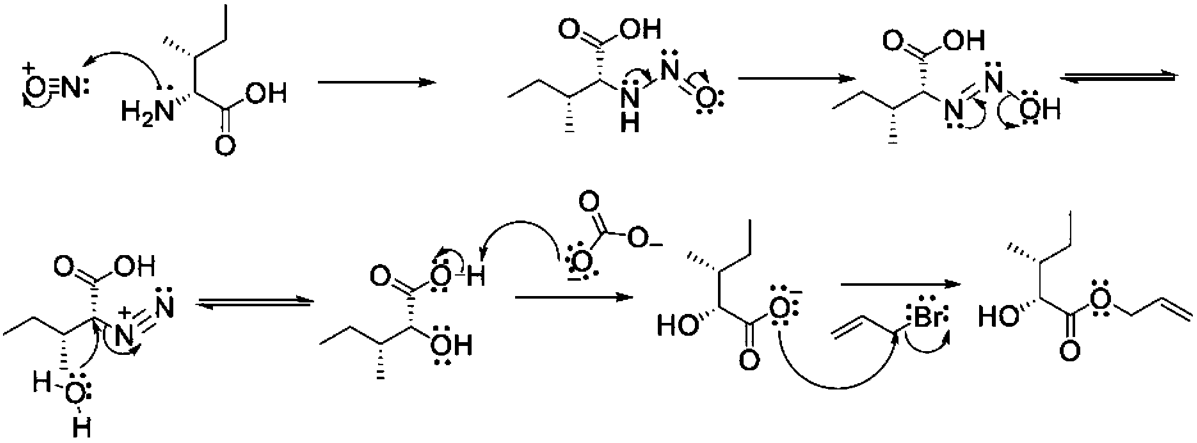
360



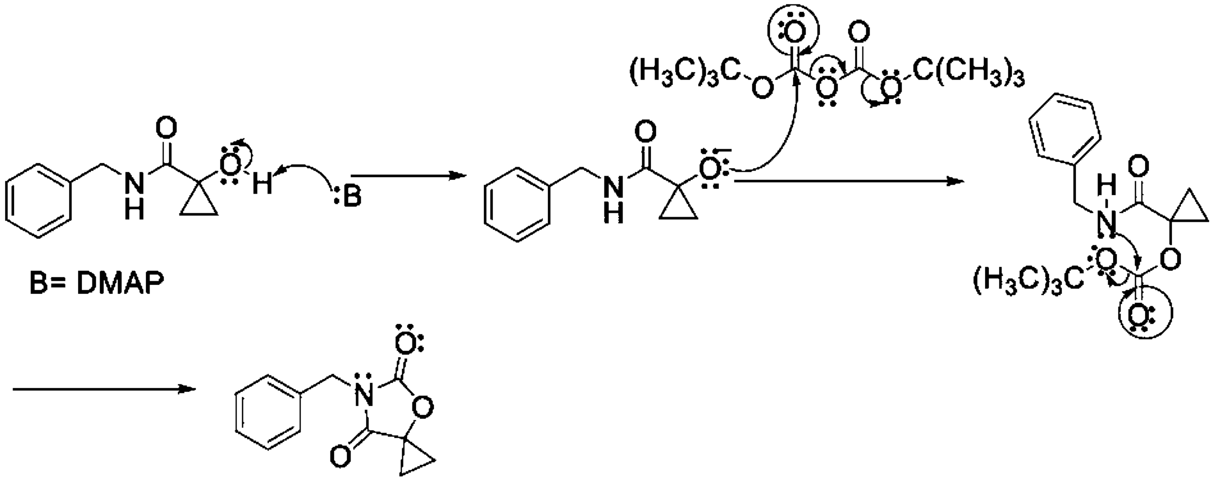
361



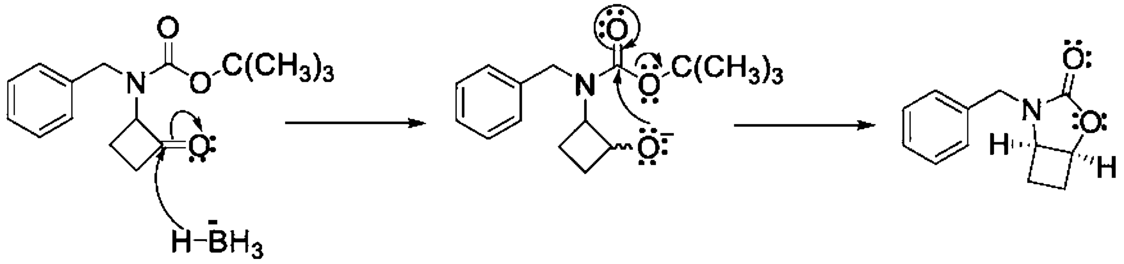
362



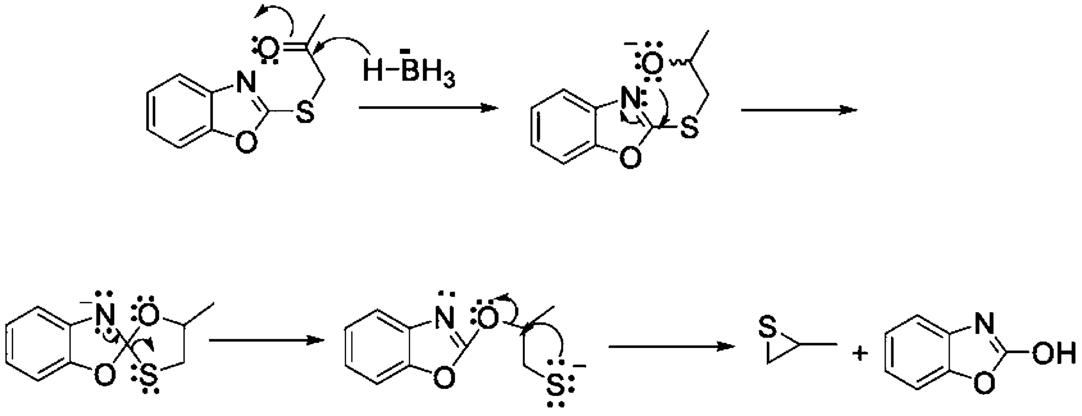
363



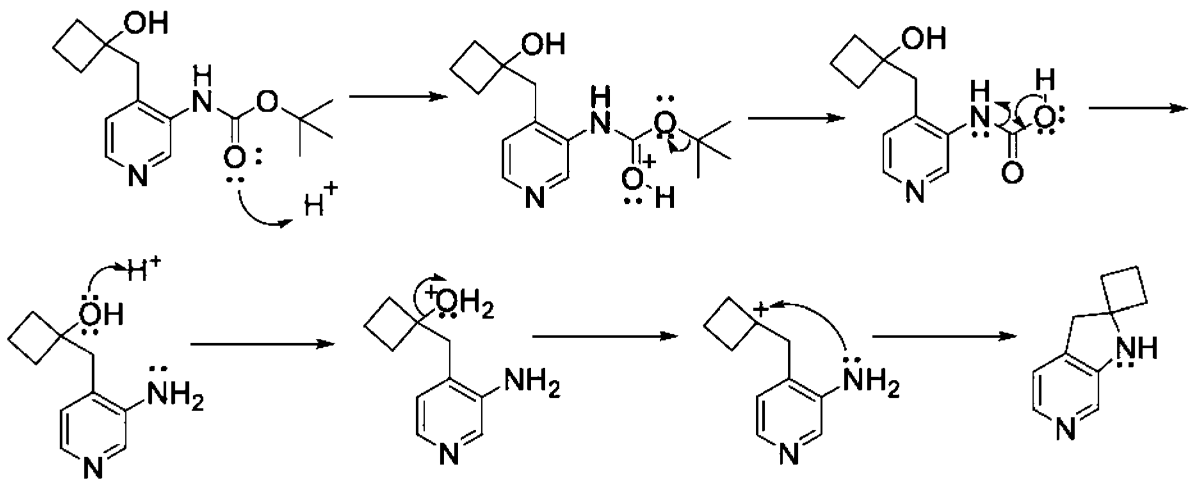
364

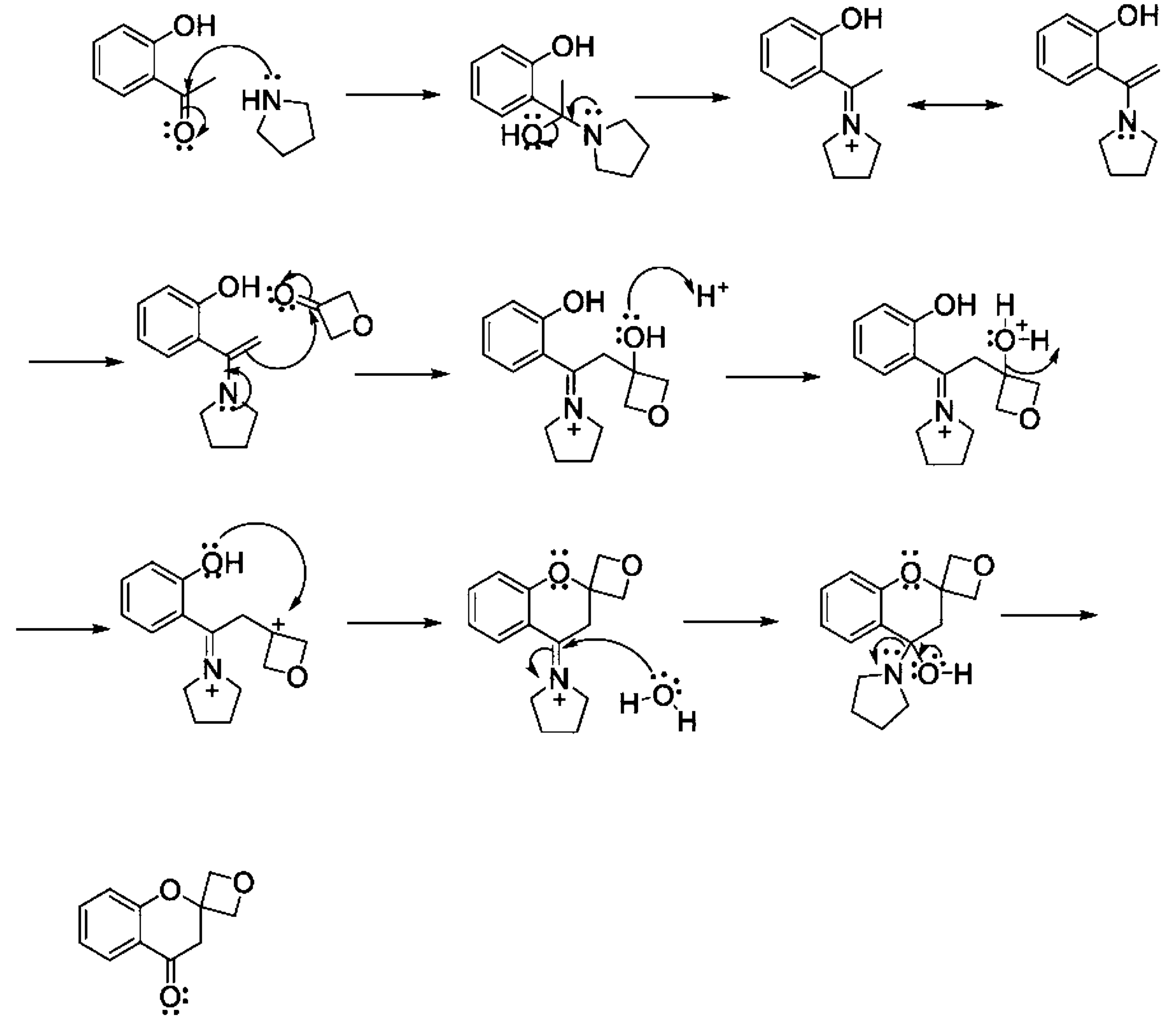


365

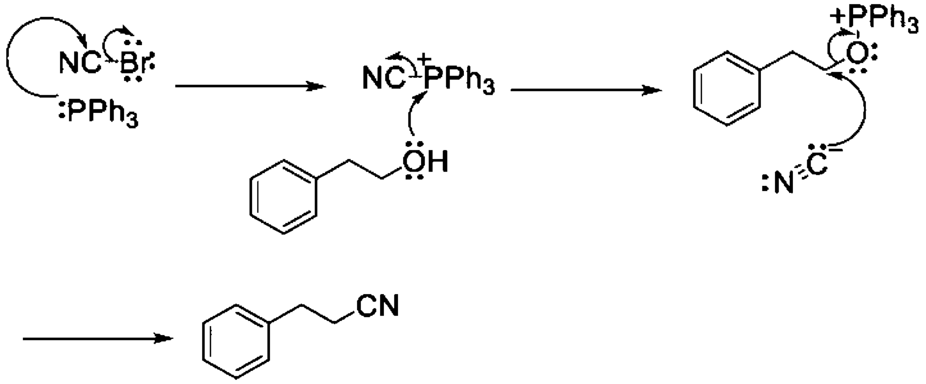


366

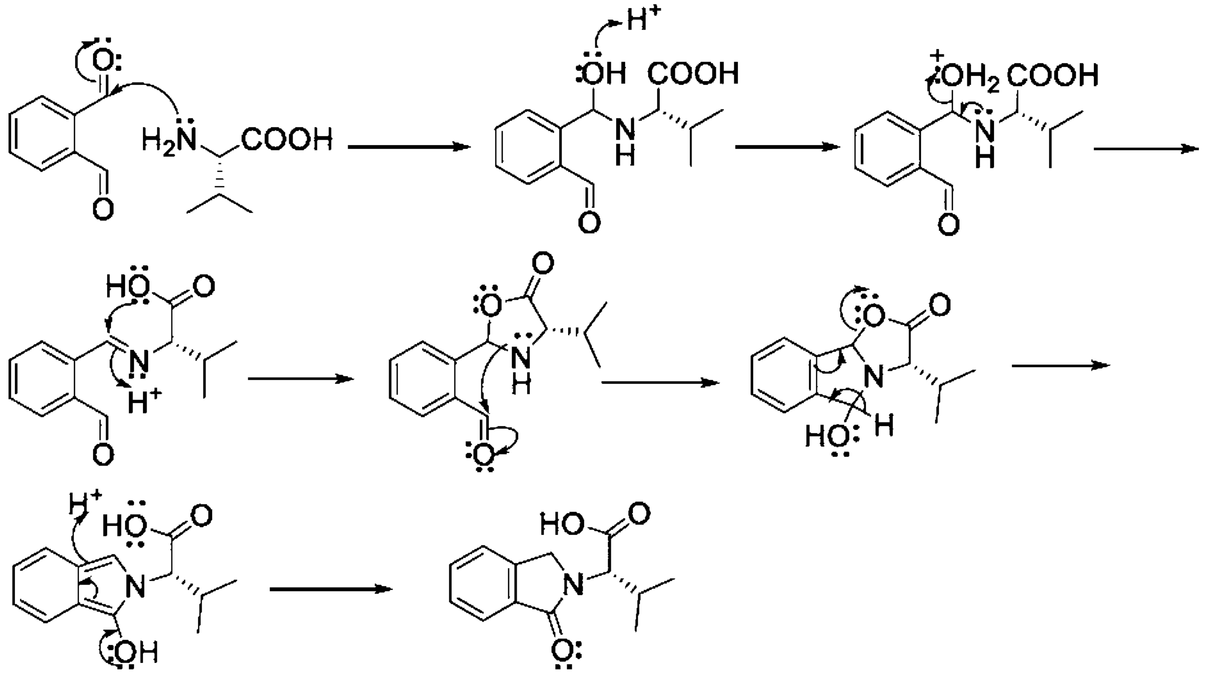

367



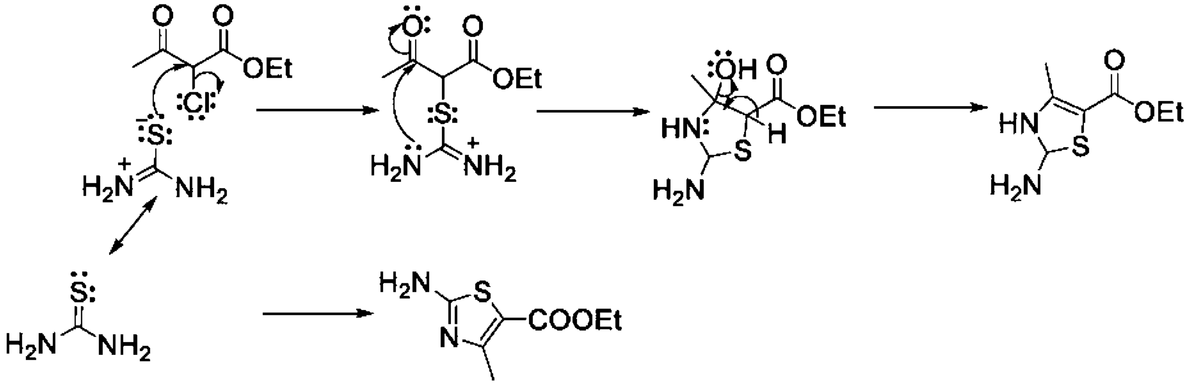
368



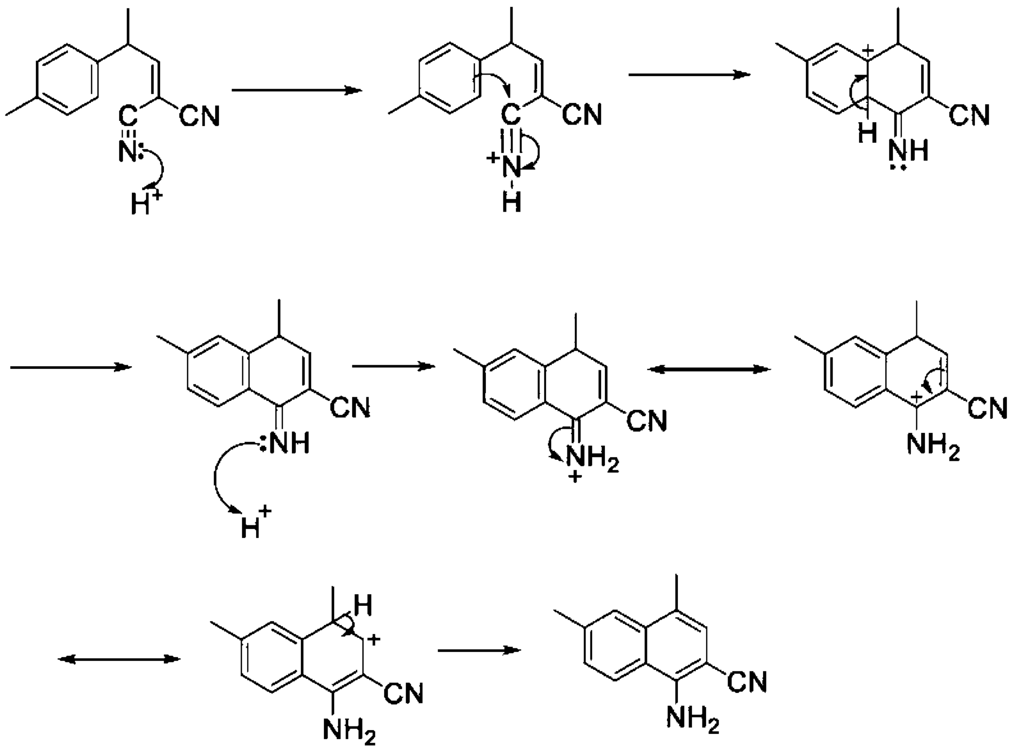
369



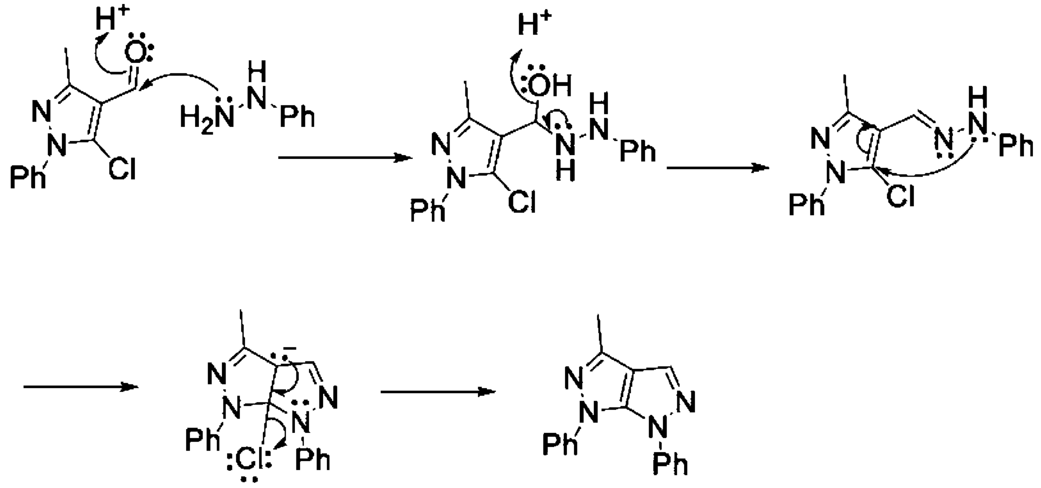
370



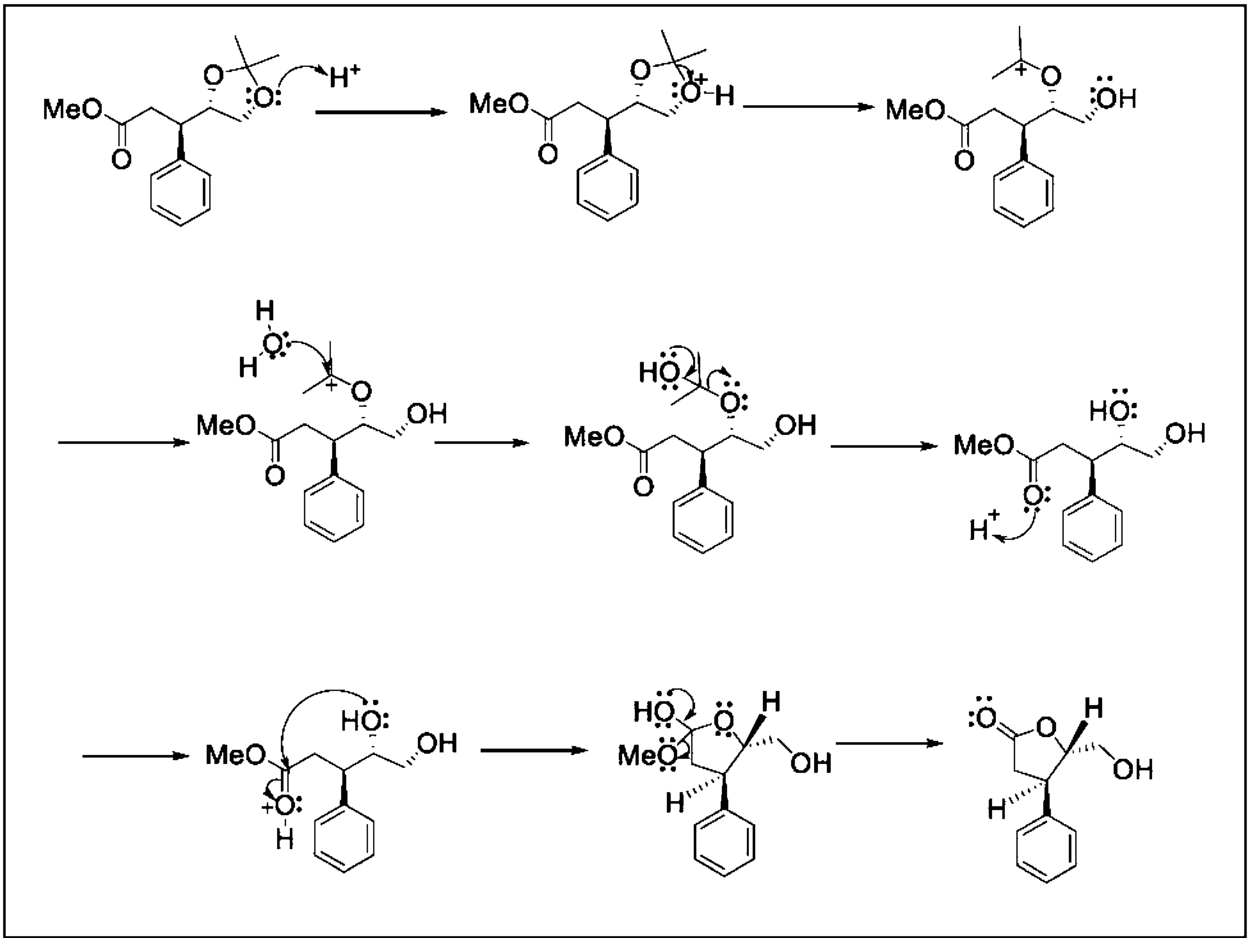
371



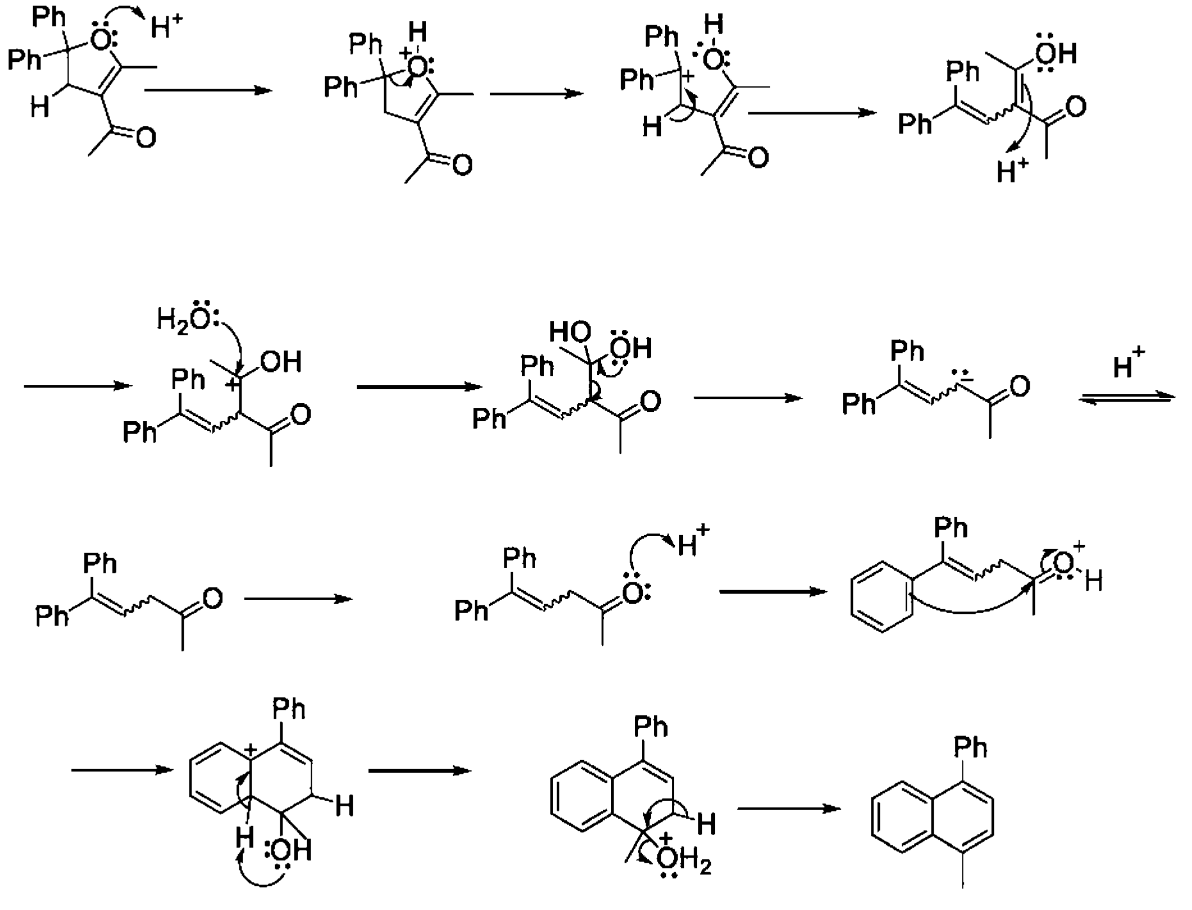
372



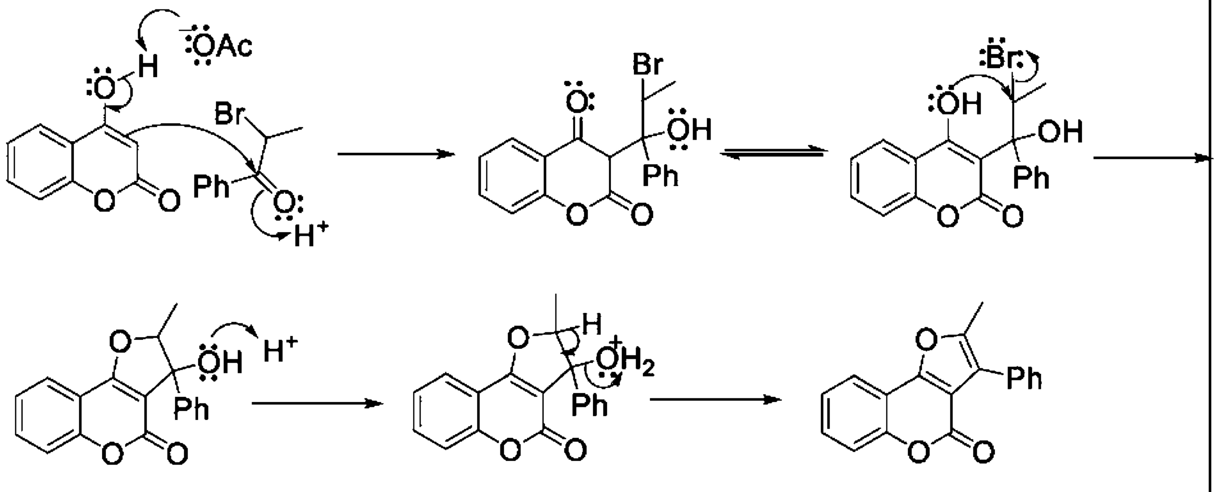
373



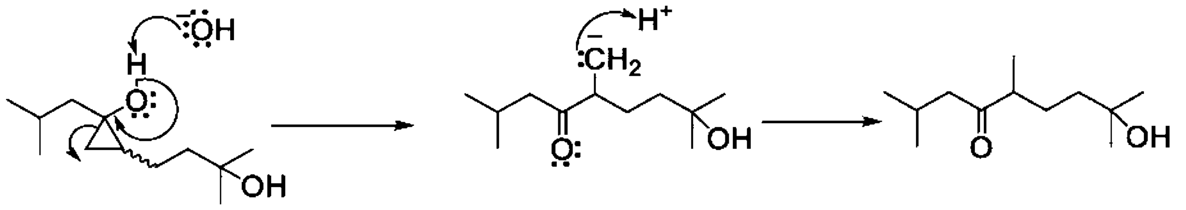
374



375

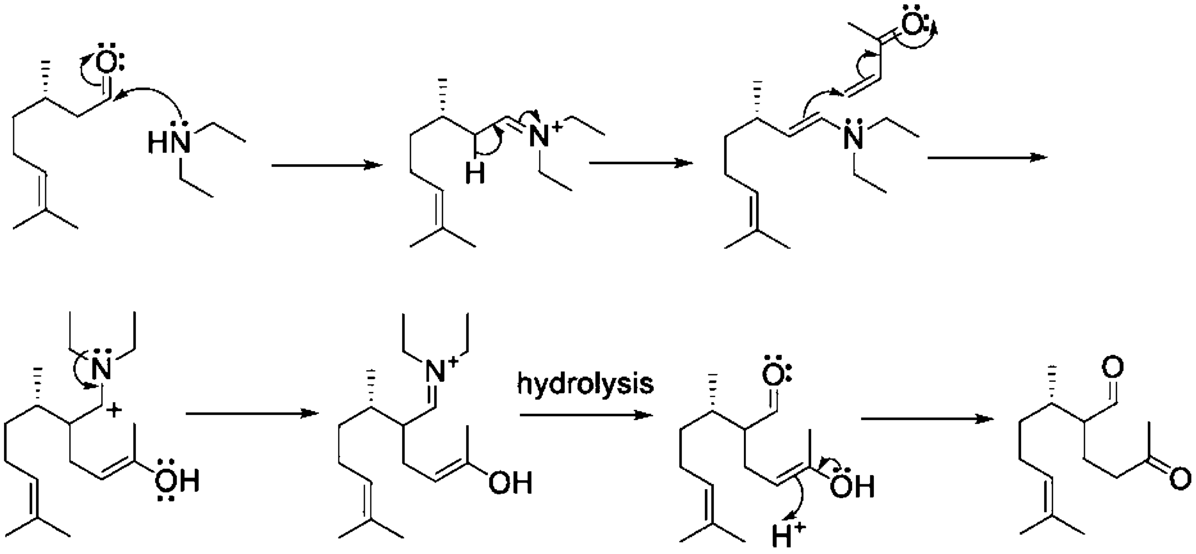


376



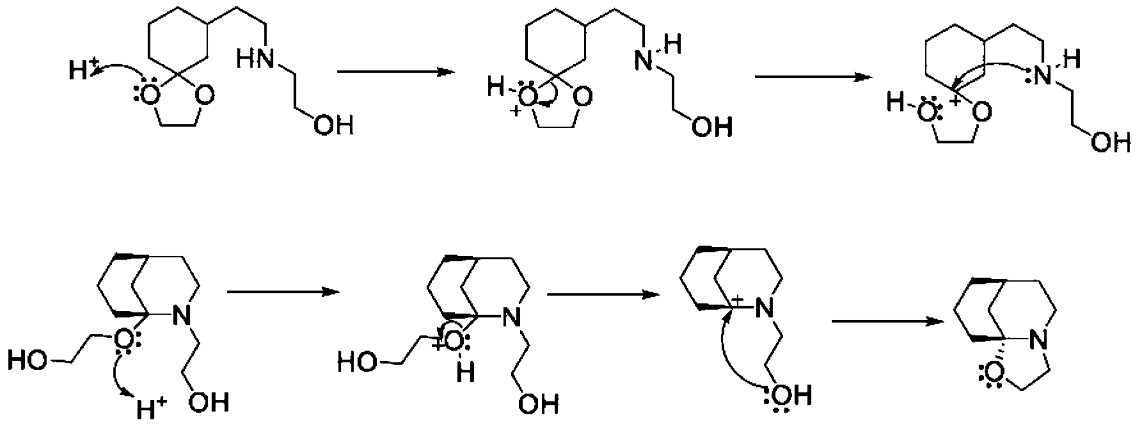
⁻:ÖH
H
:Ö:
OH
H⁺
:CH₂
:Ö:
OH
O
OH

377



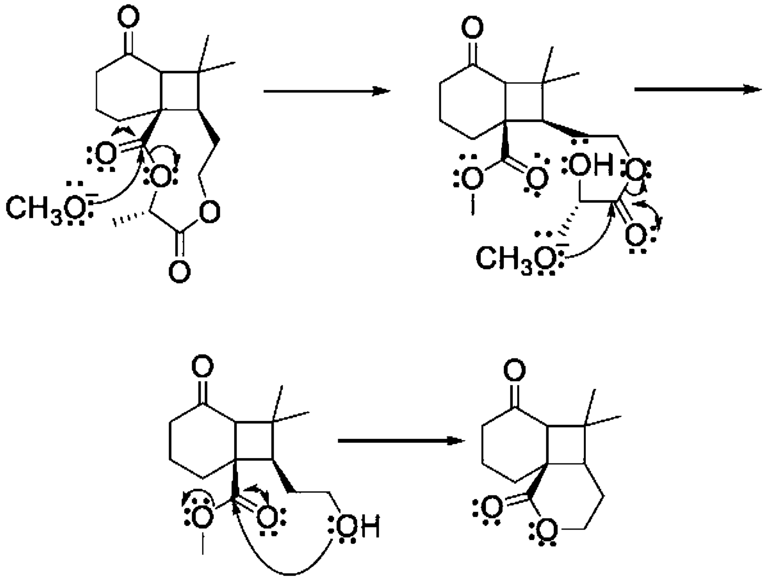
:Ö:
HN
N⁺
H
:O:
N
N
+
:ÖH
N⁺
OH
hydrolysis
:Ö:
:ÖH
H⁺
O
O

378



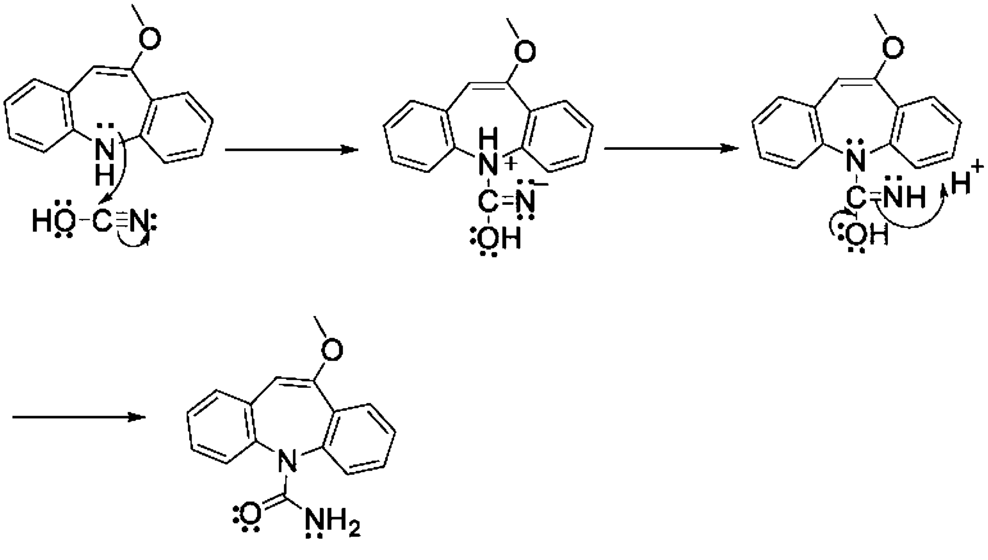
H⁺
:O
O
HN
OH
H
O⁺
O
N
H
OH
H
O
O
:N
H
OH
HO
:O:
N
H⁺
OH
HO
O:
H
N
OH
N
:OH
N
:O:

379

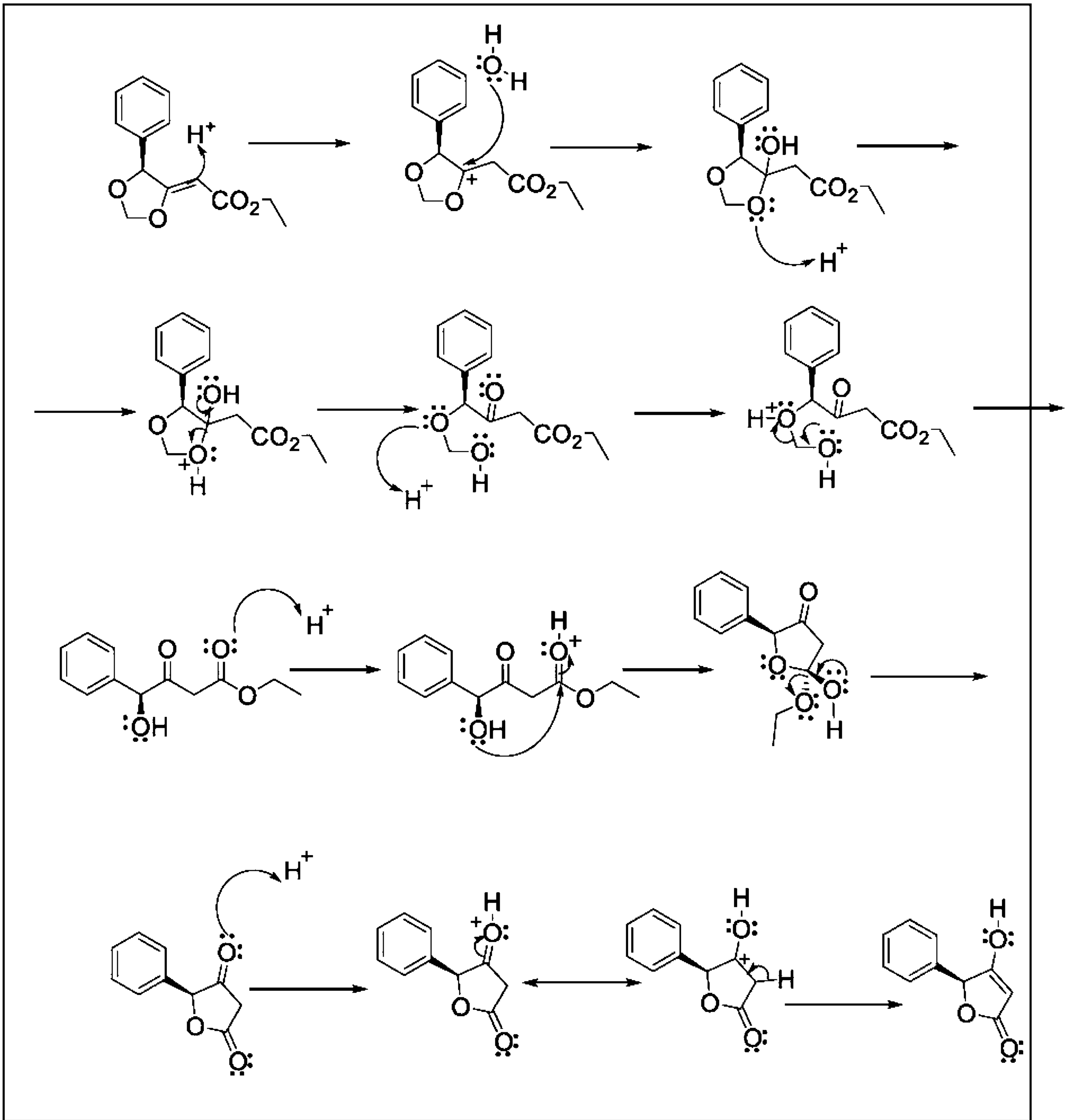


Three consecutive transesterification reactions give the final product

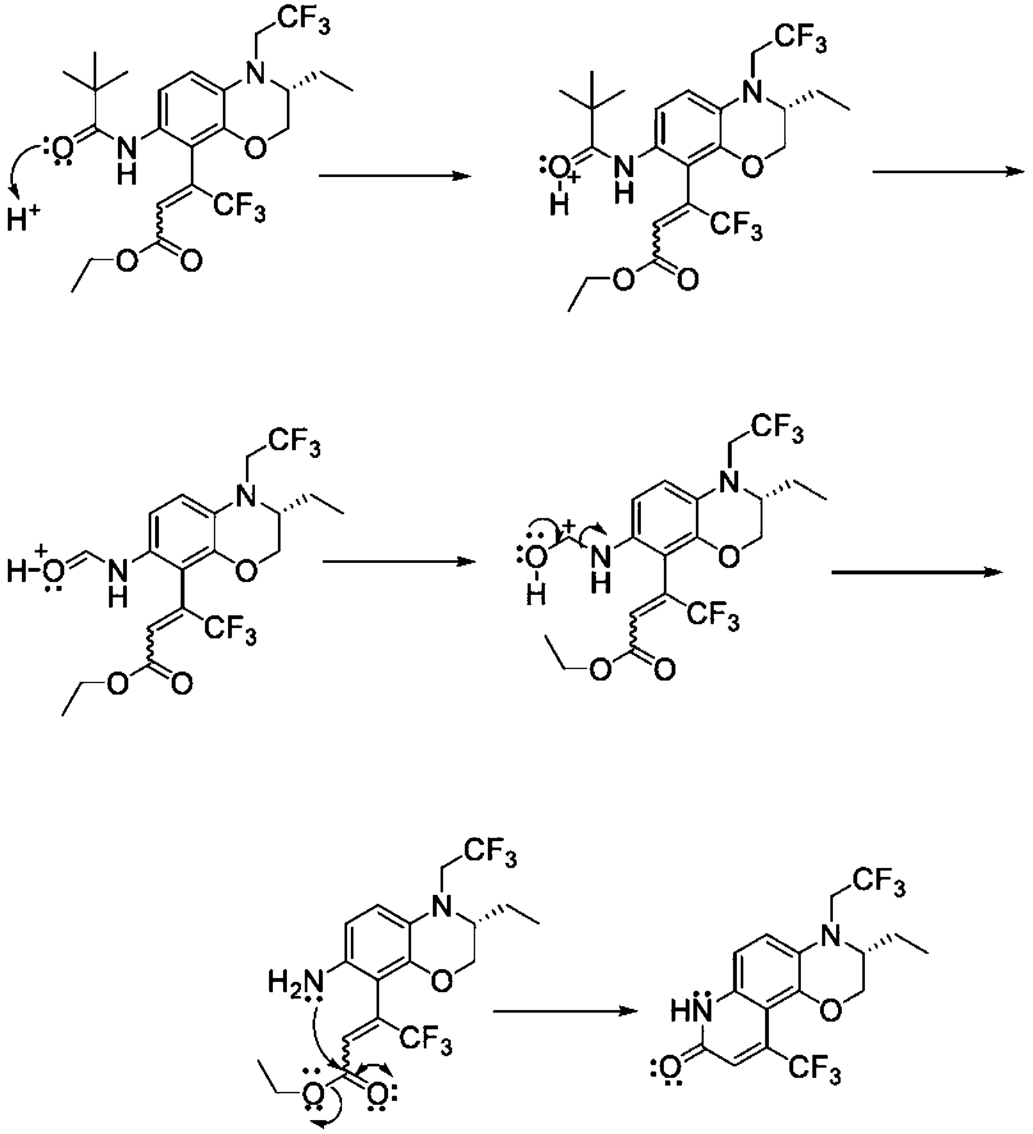
380



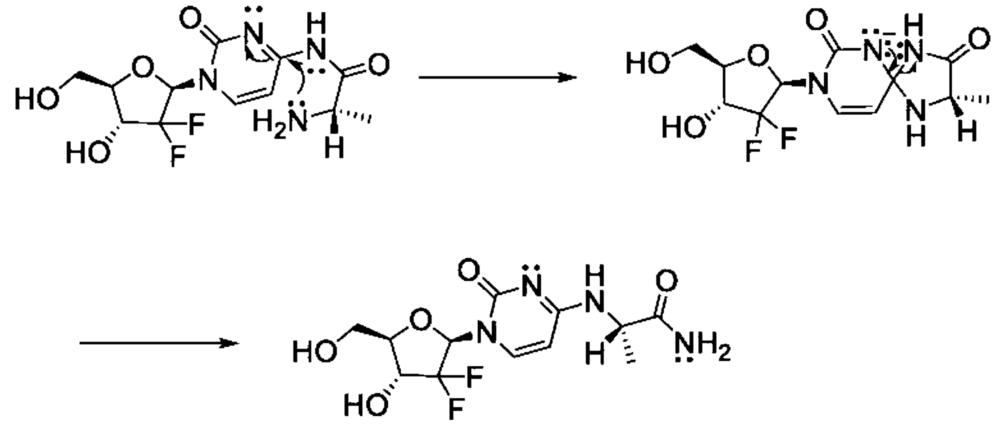
381



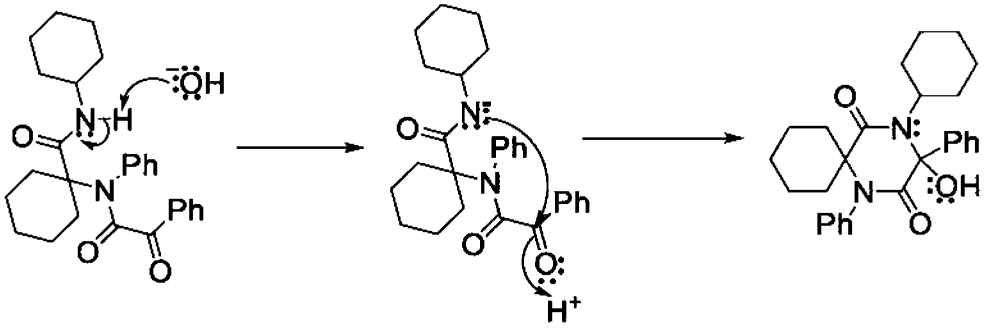
382



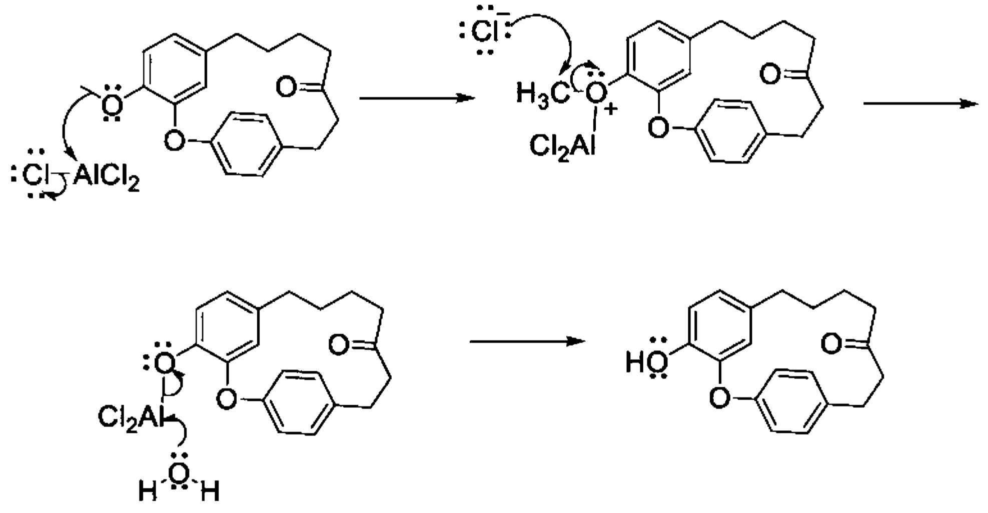
383



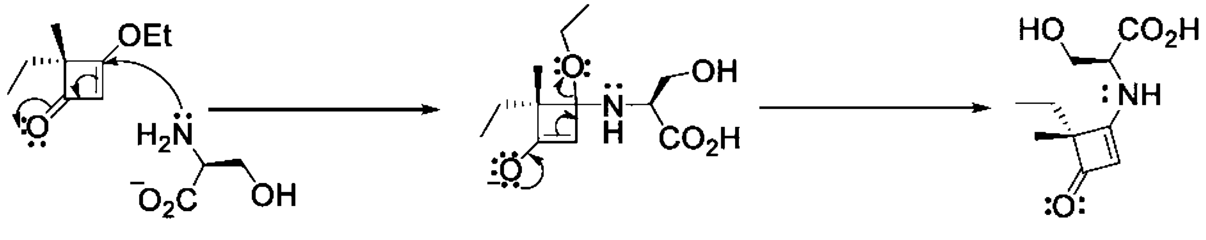
384



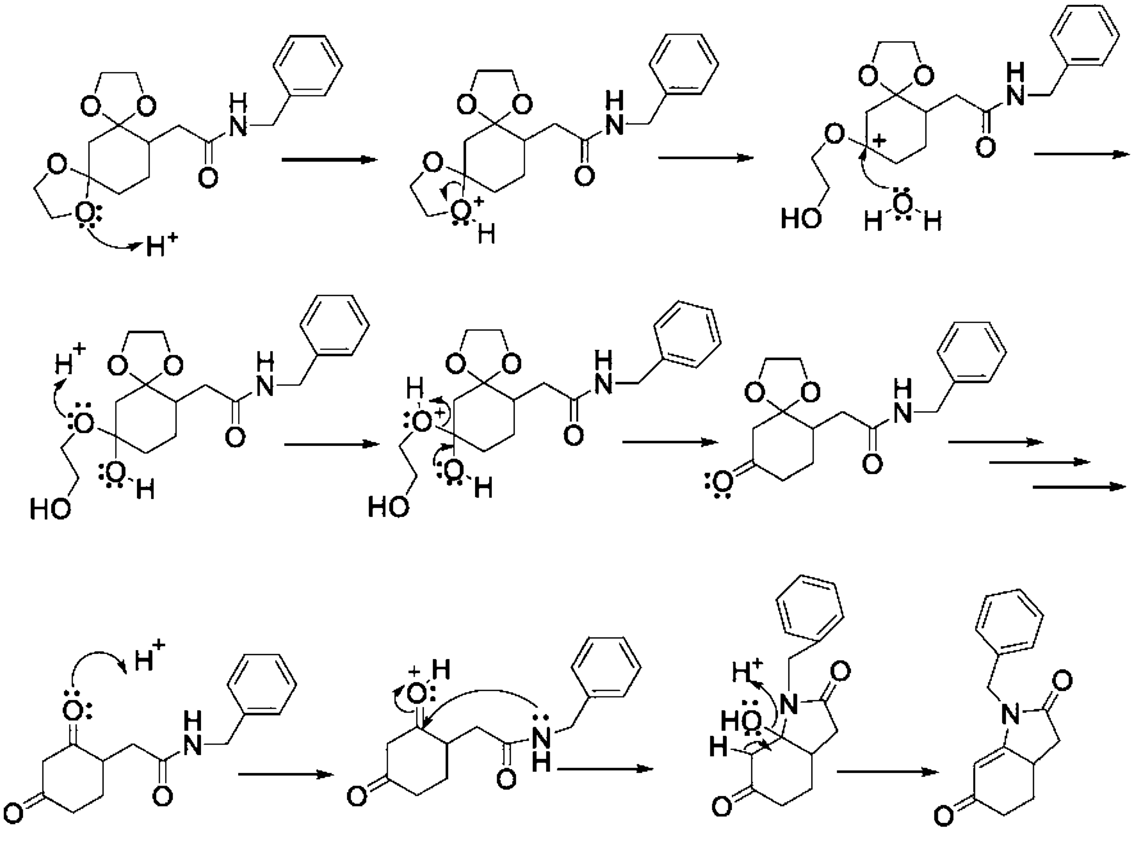
385



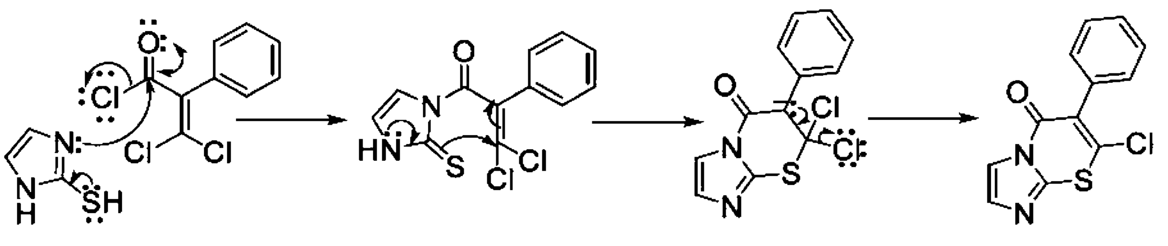
386



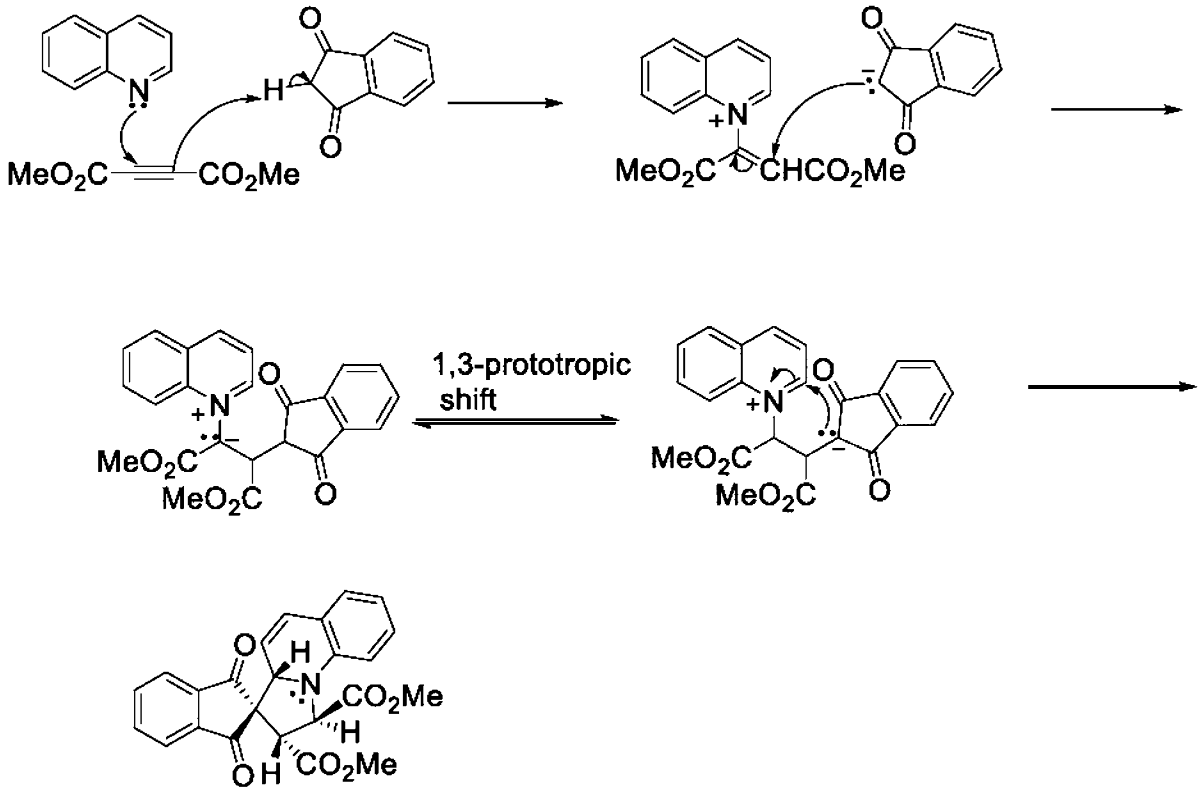
387



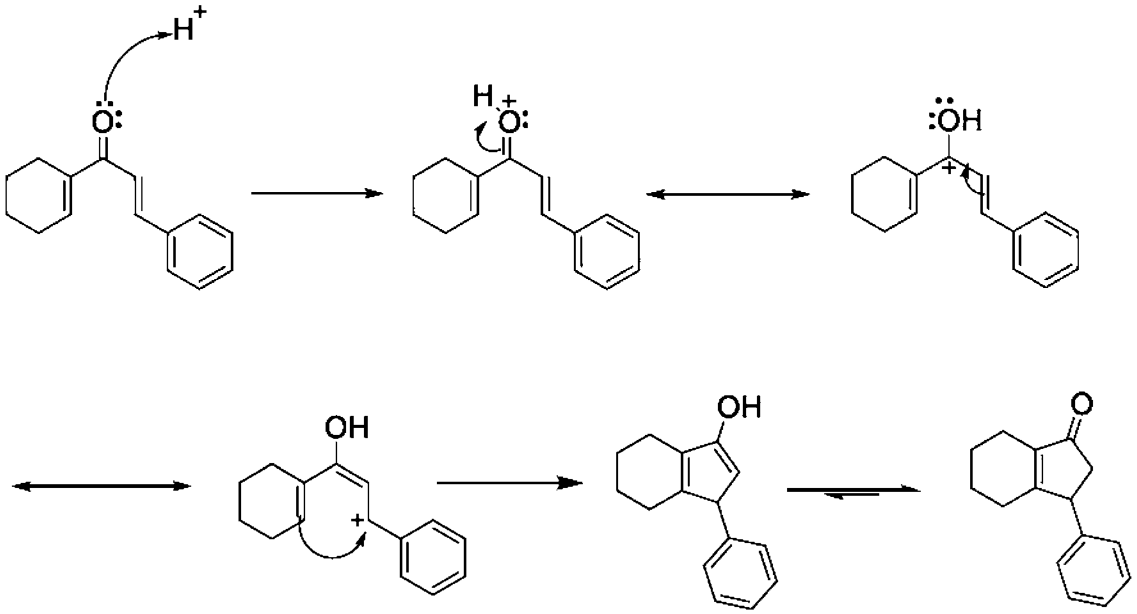
388



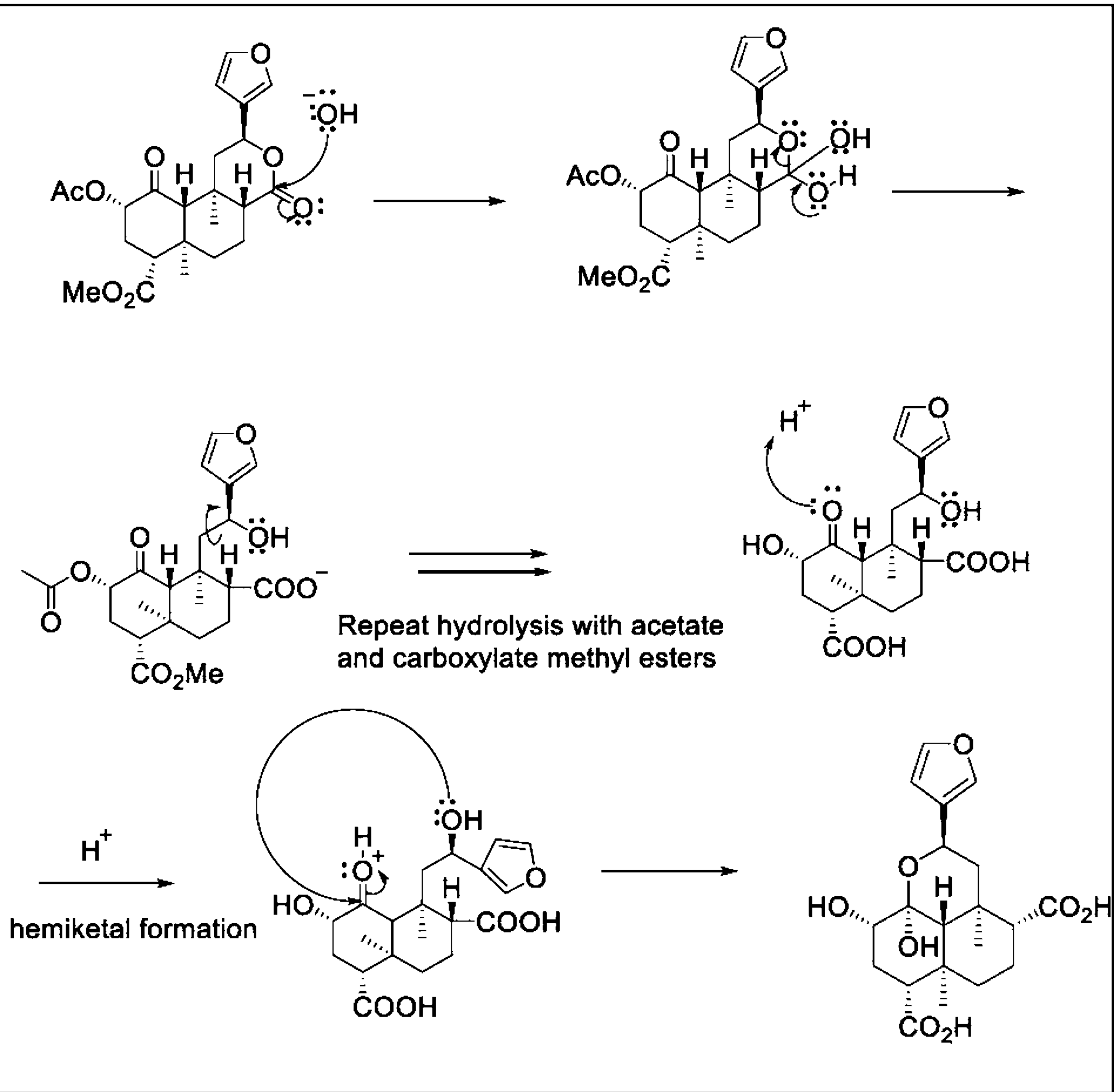
389


MeO2C
CO2Me
H
O
MeO2C
CHCO2Me
1,3-prototropic shift
MeO2C
MeO2C
N
H
CO2Me
CO2Me

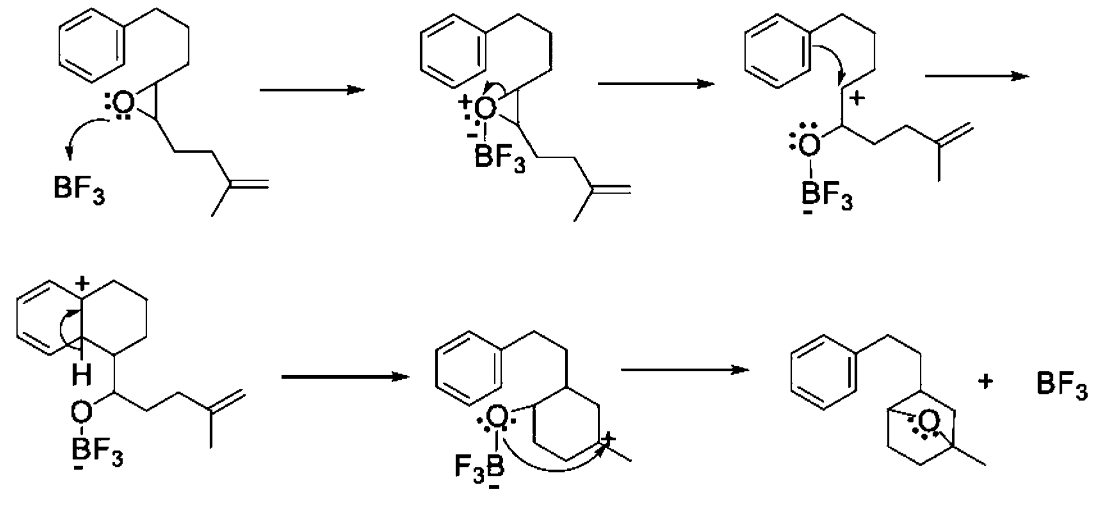
390


H+
O:
OH
OH
OH
O

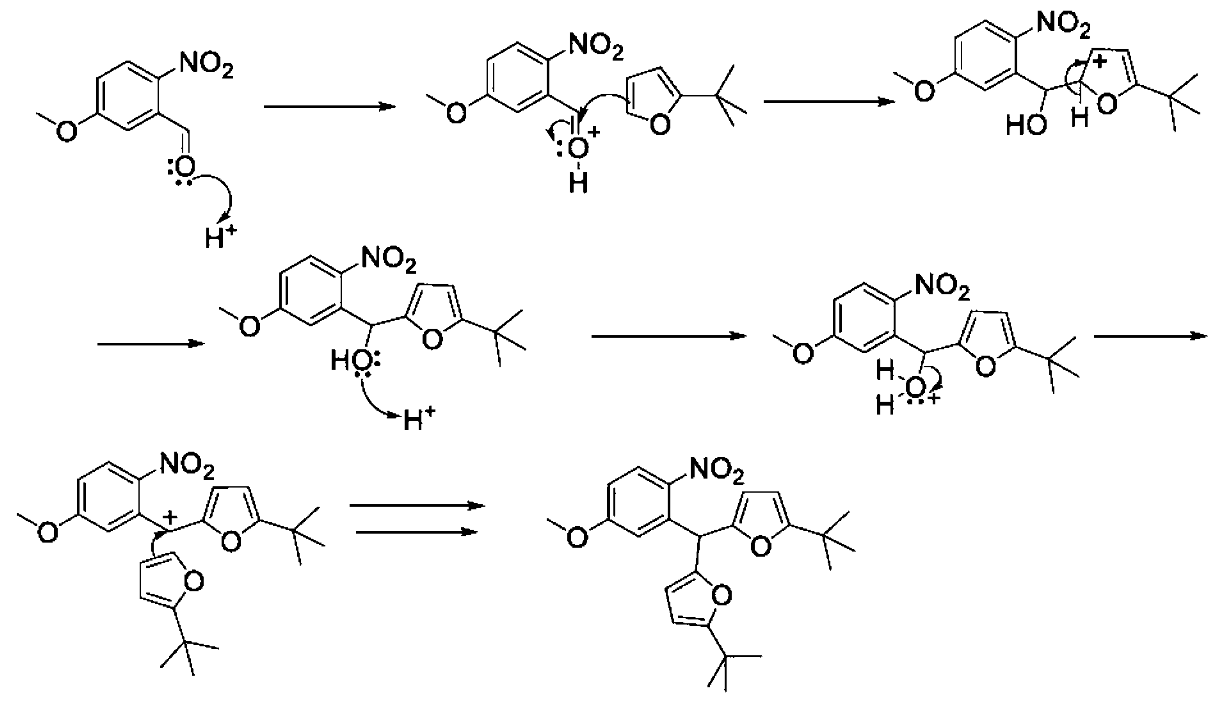
391


Repeat hydrolysis with acetate and carboxylate methyl esters
H+
hemiketal formation

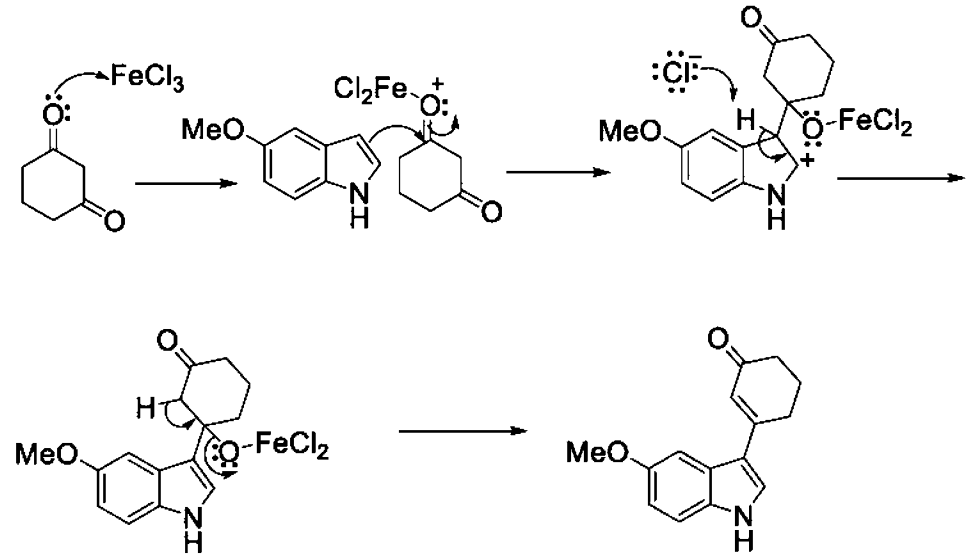
392



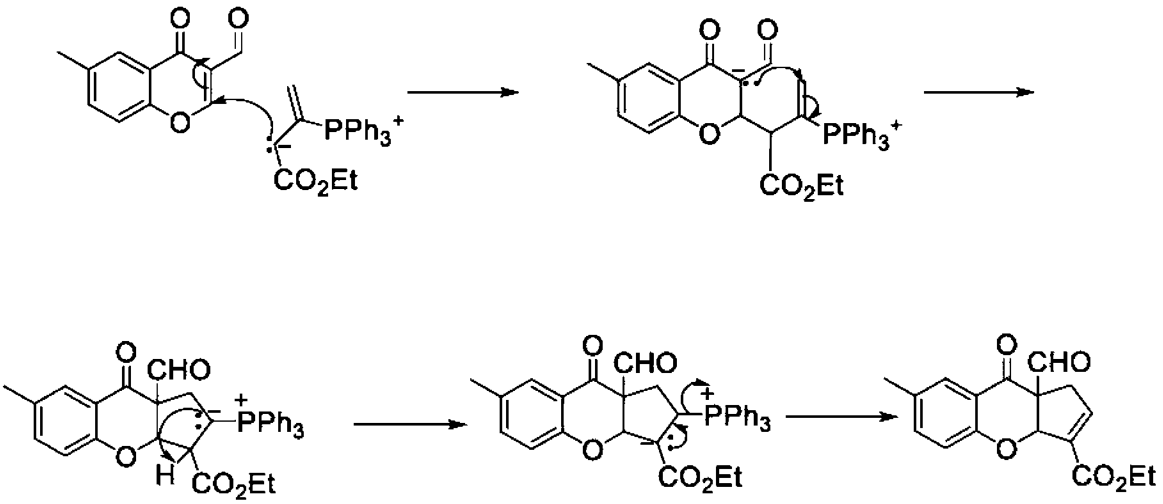
393



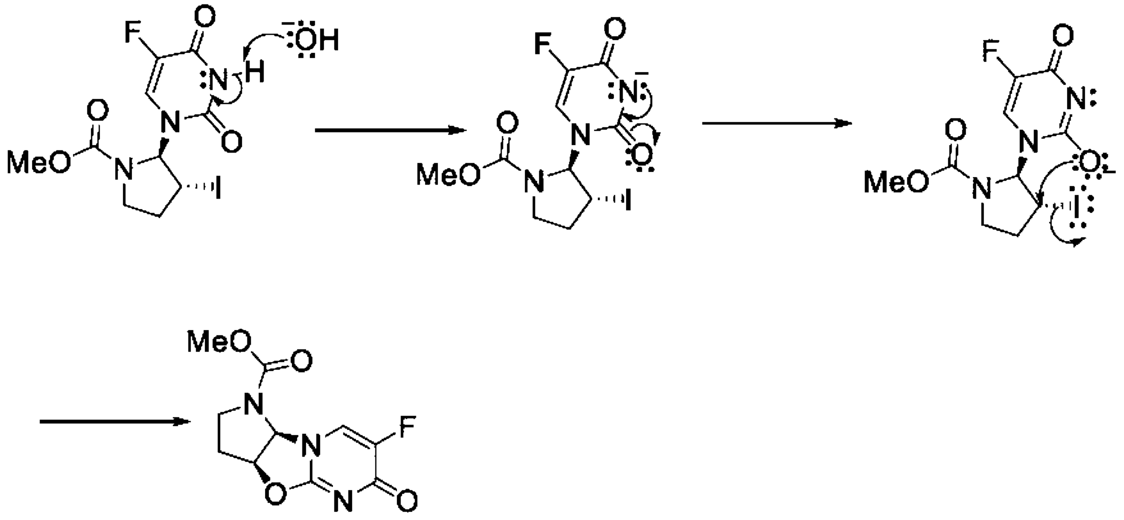
394



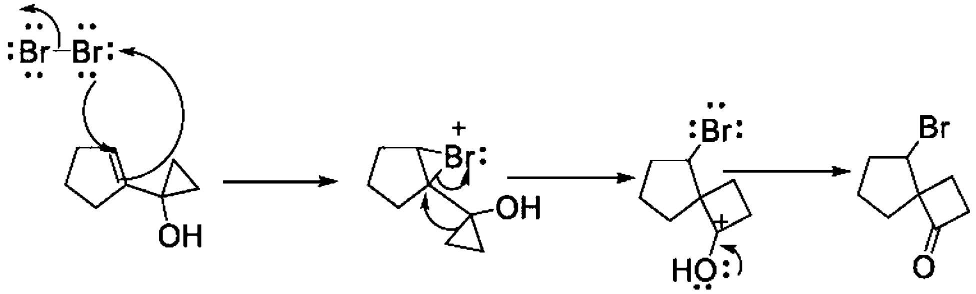
395



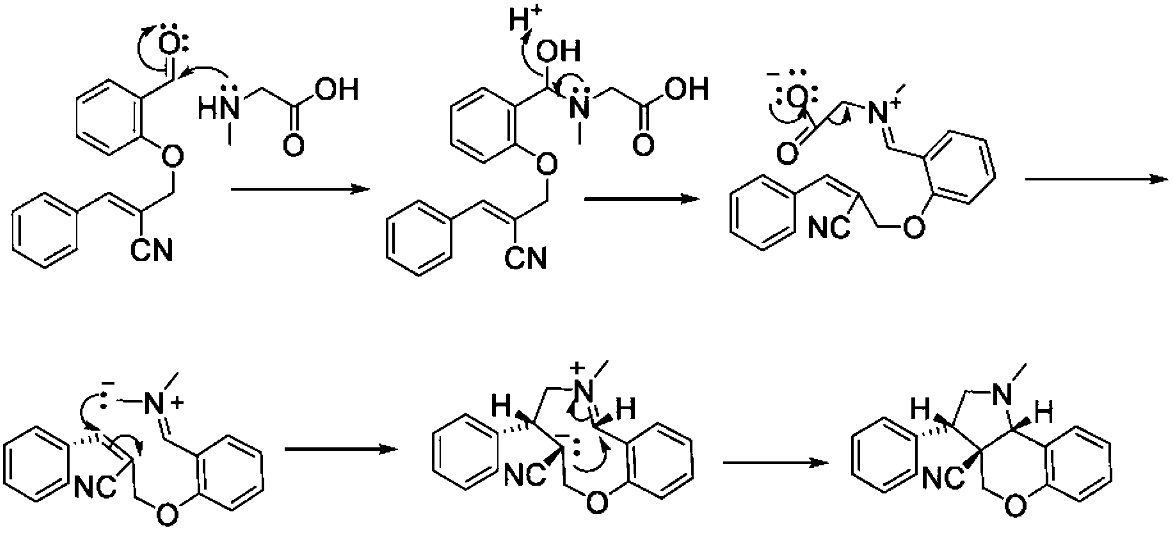
396



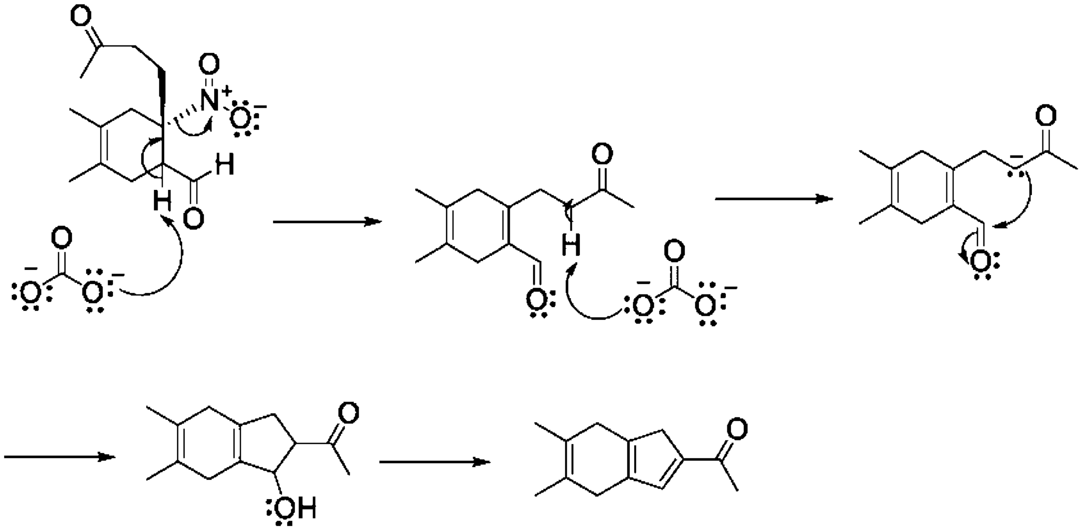
397



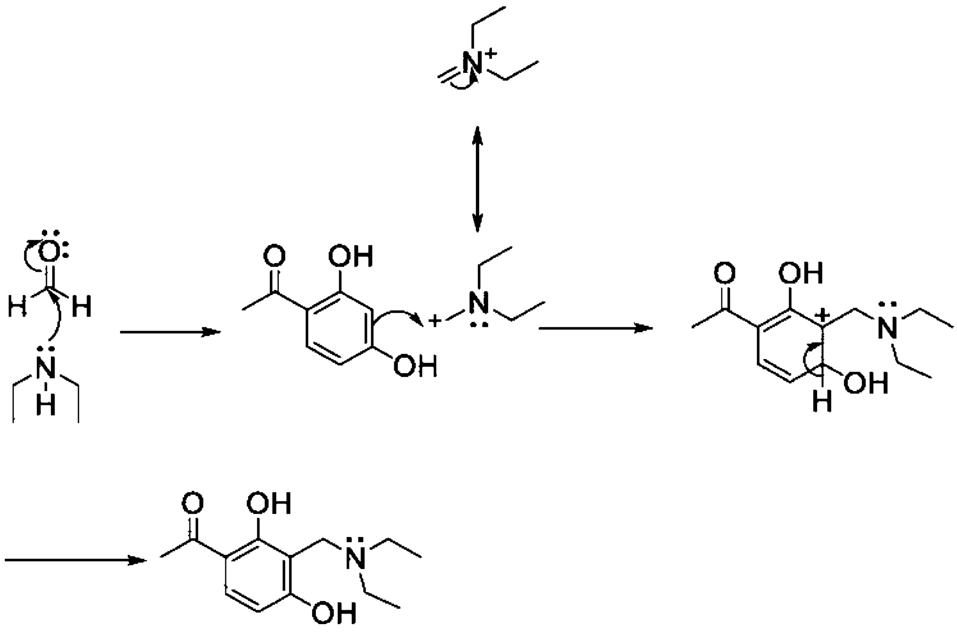
398



399

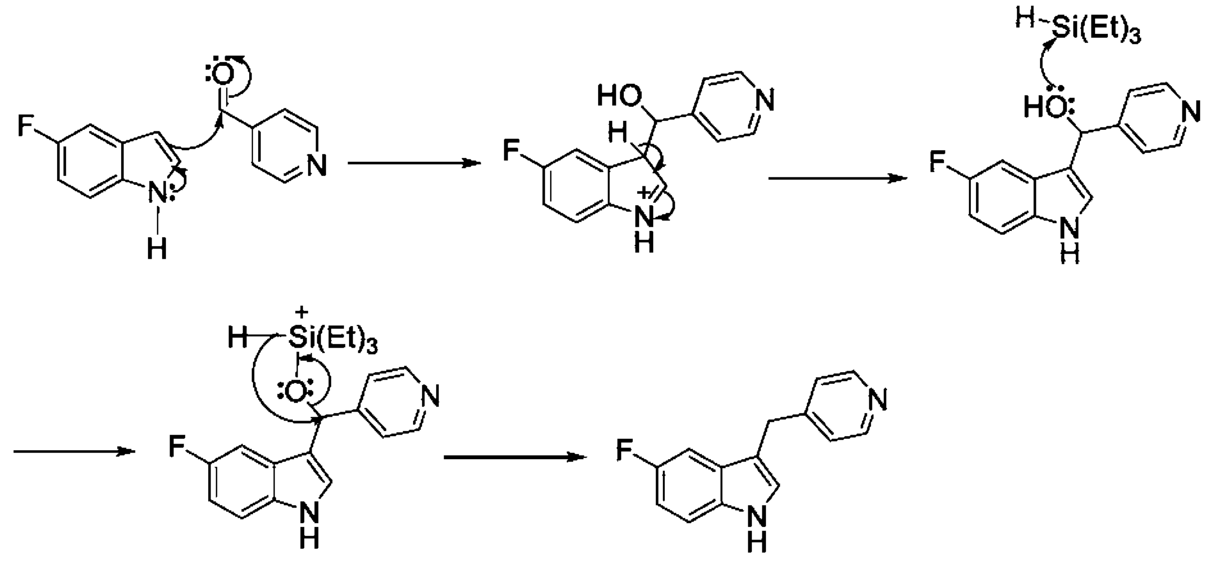


400

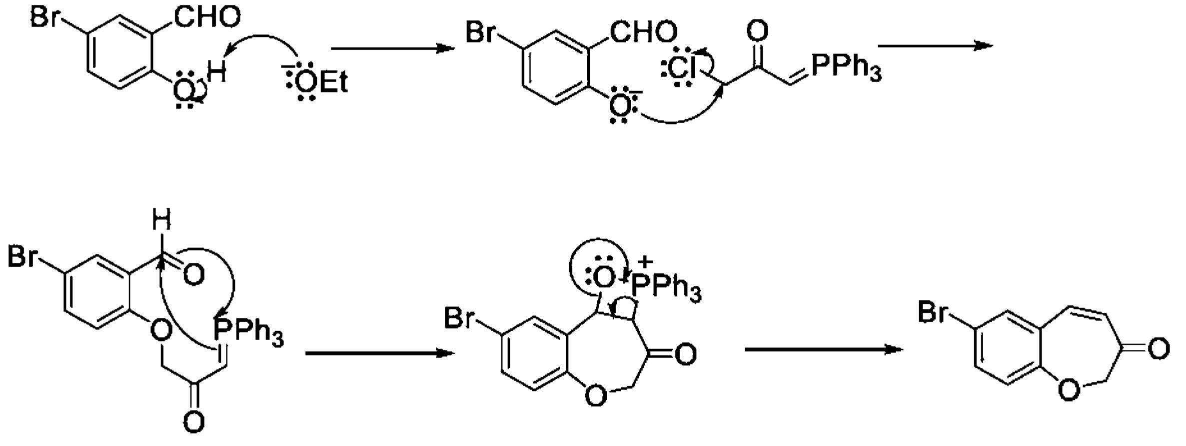


This is an example of the *Mannich reaction* (an aminoalkyl fragment introduced directly onto an aromatic ring)

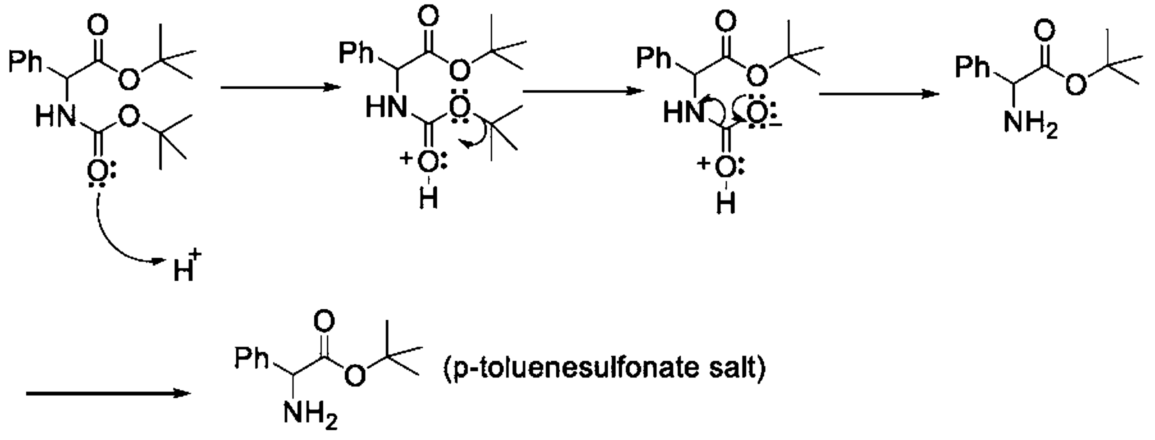
401



402

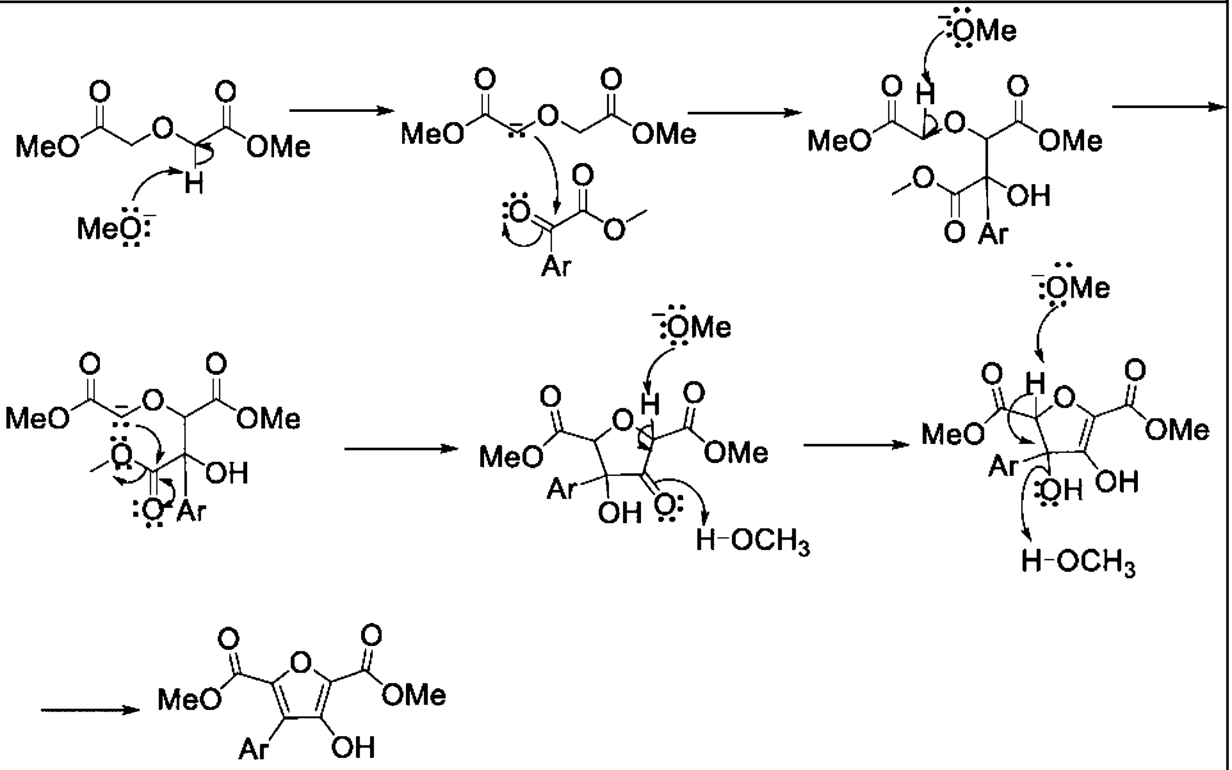


403

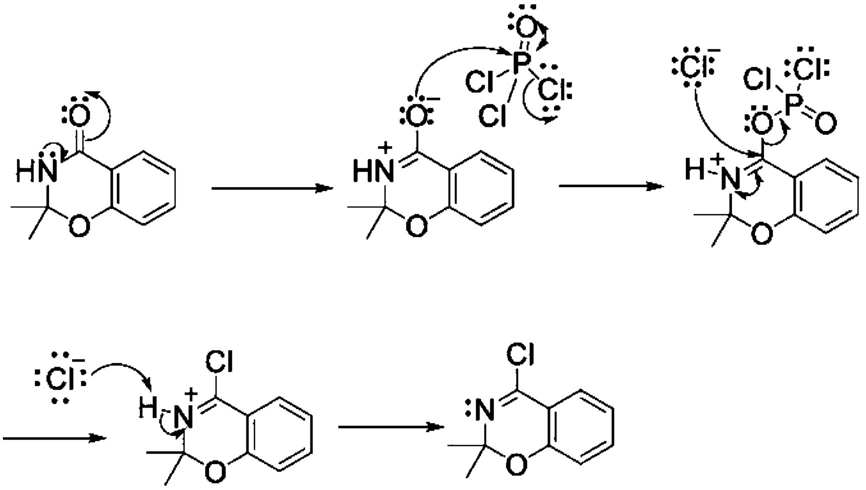


Exercise Provide an explanation for the observed selectivity

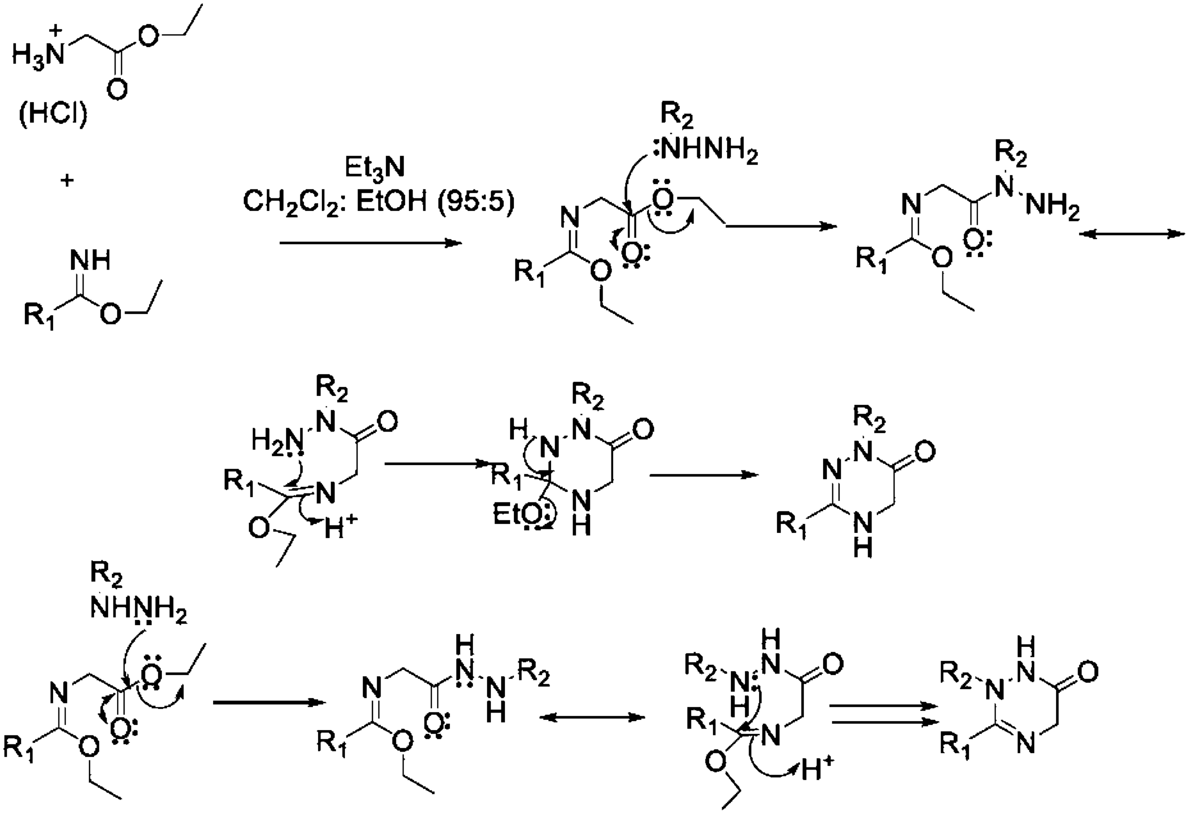
404



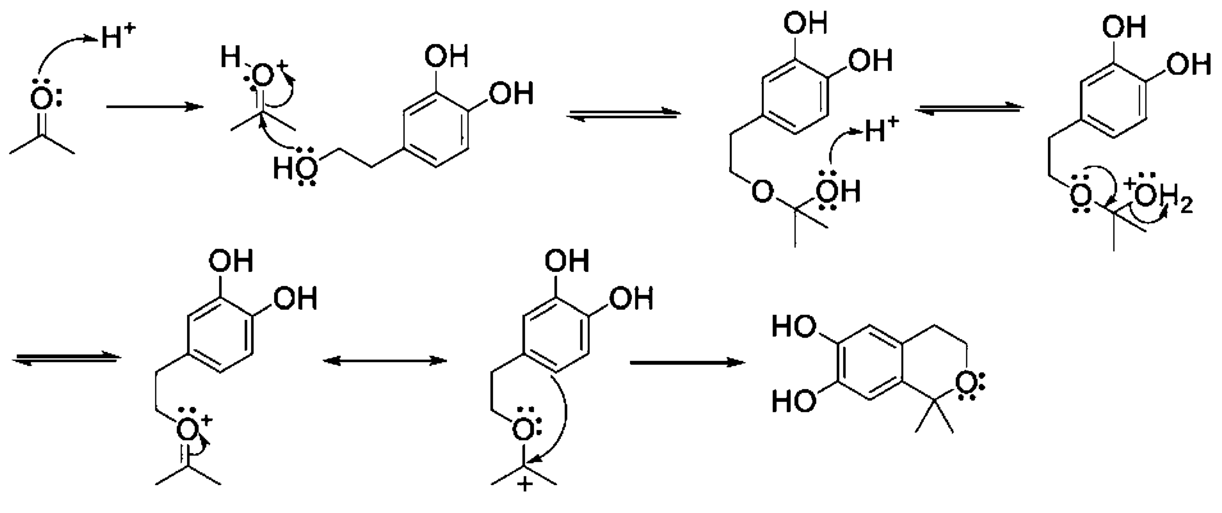
405



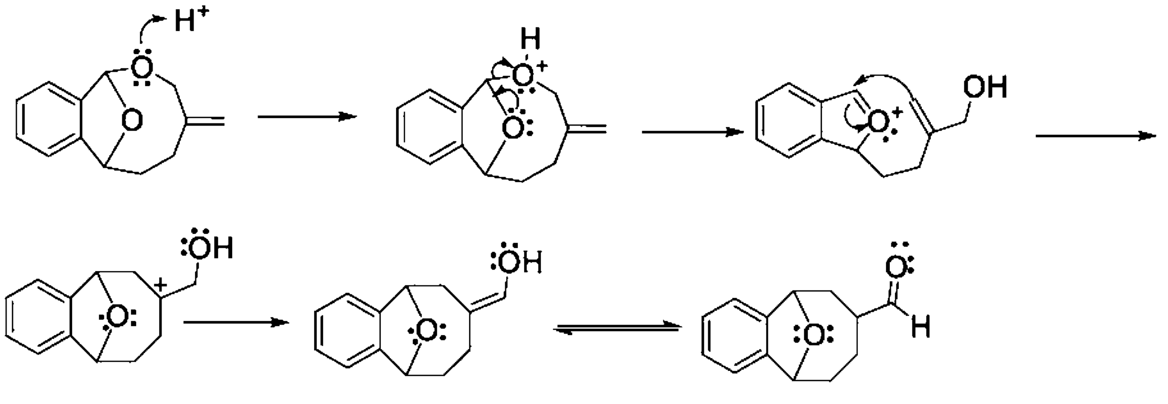
406



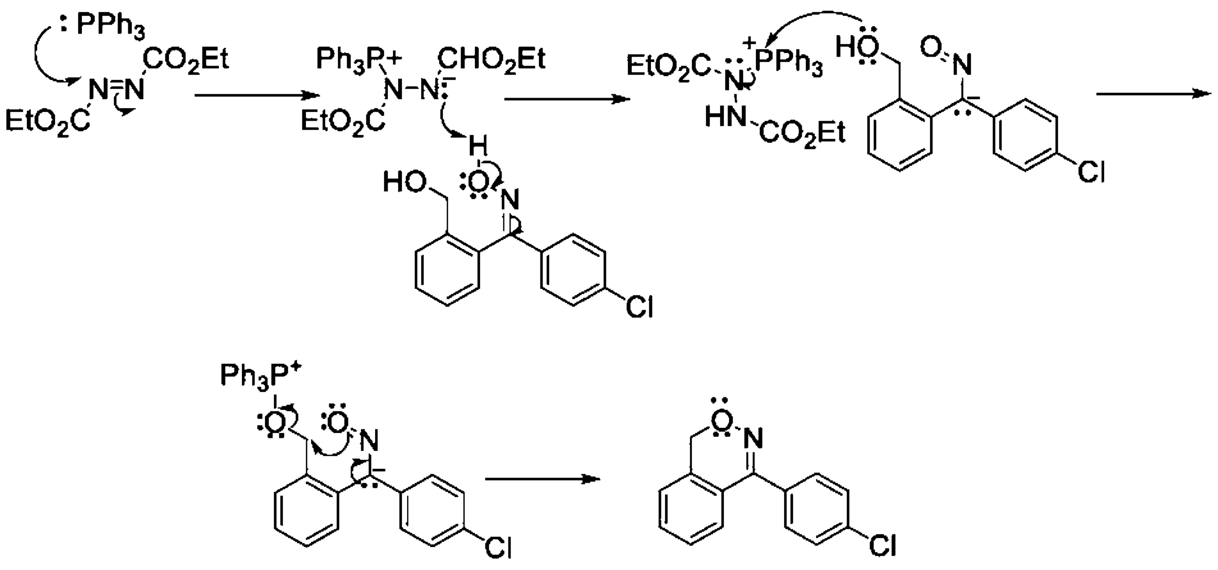
407



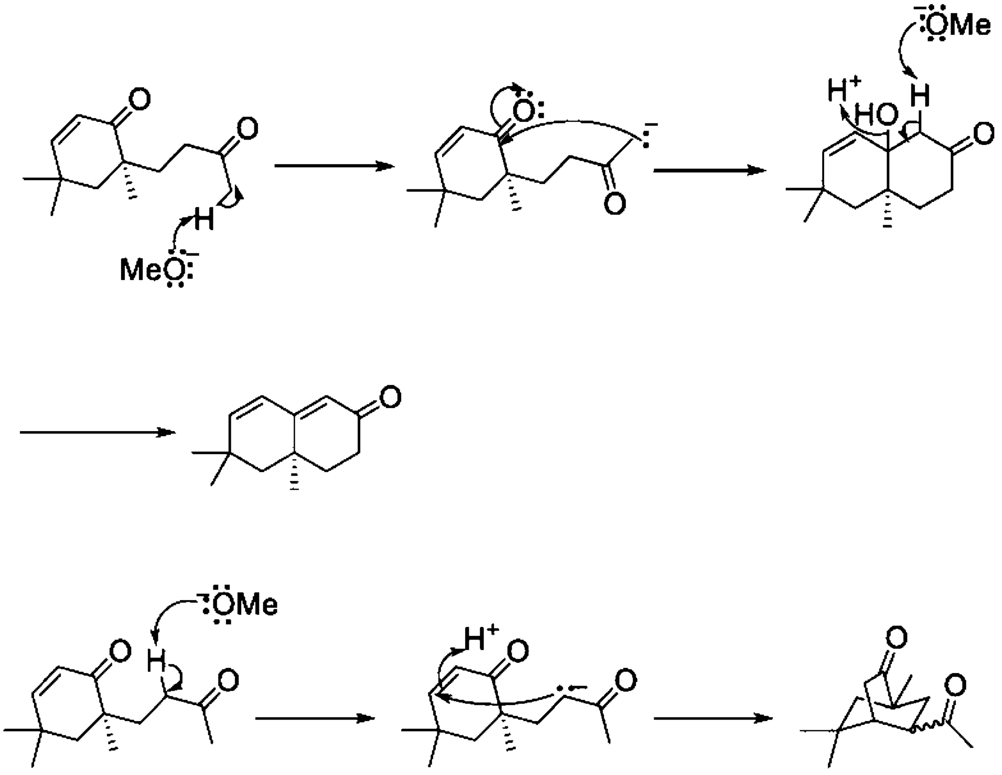
408



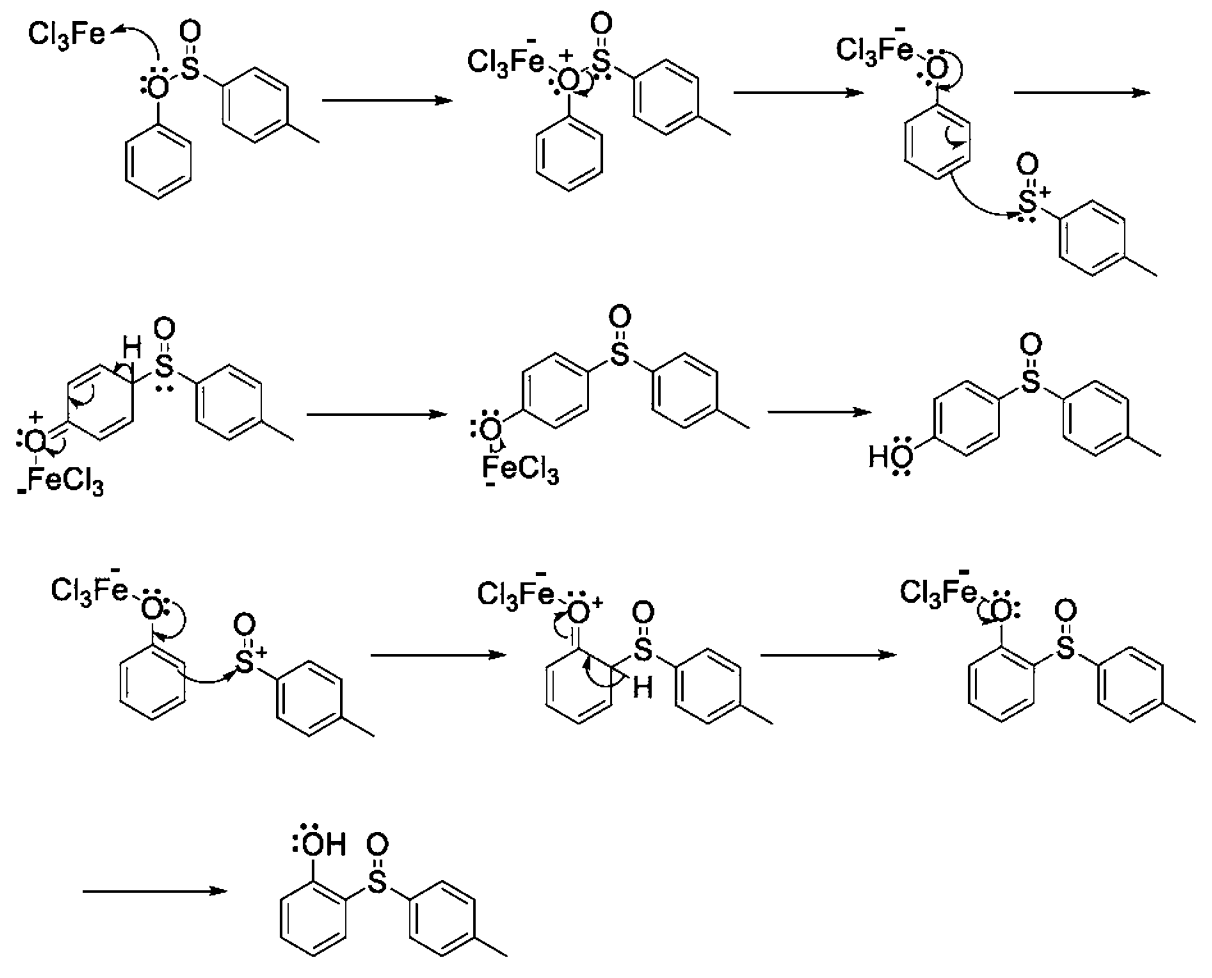
409


:PPh3
CO2Et
EtO2C
Ph3P+
CHO2Et
EtO2C
H
HO
Cl
EtO2C
PPh3
HN
CO2Et
HO
Cl
Ph3P+
Cl
Cl

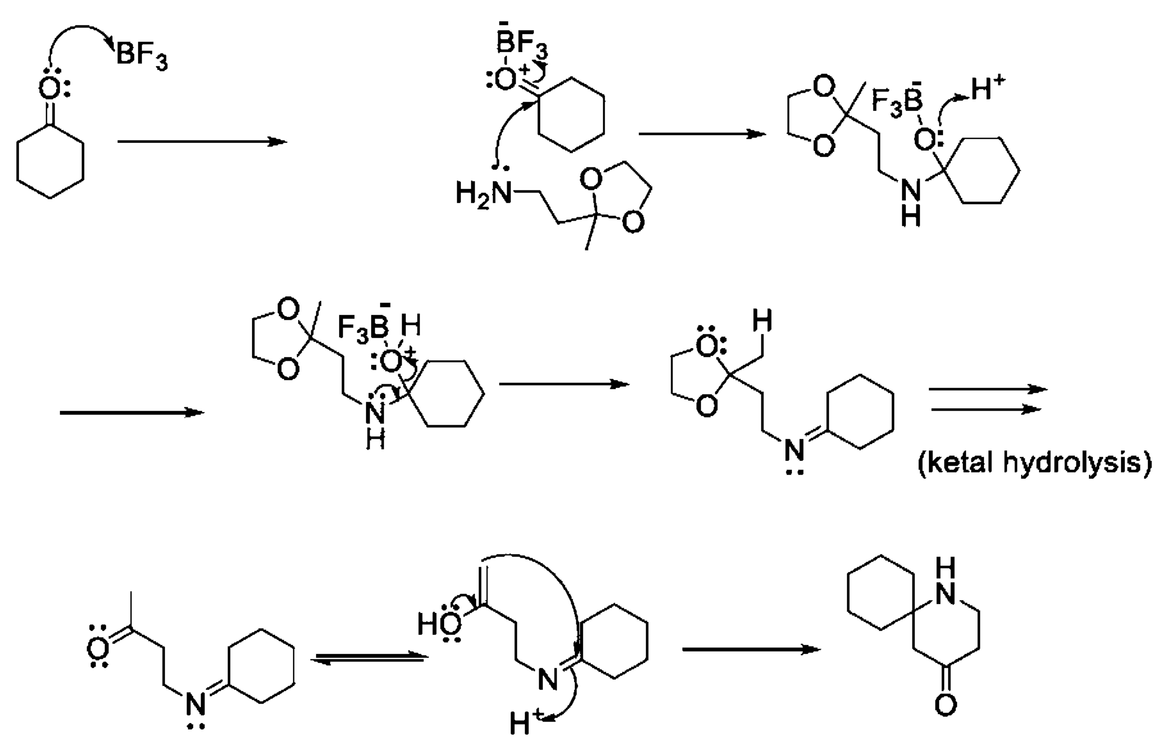
410


MeO
H
OMe
H+
HO
H
OMe
H
H+

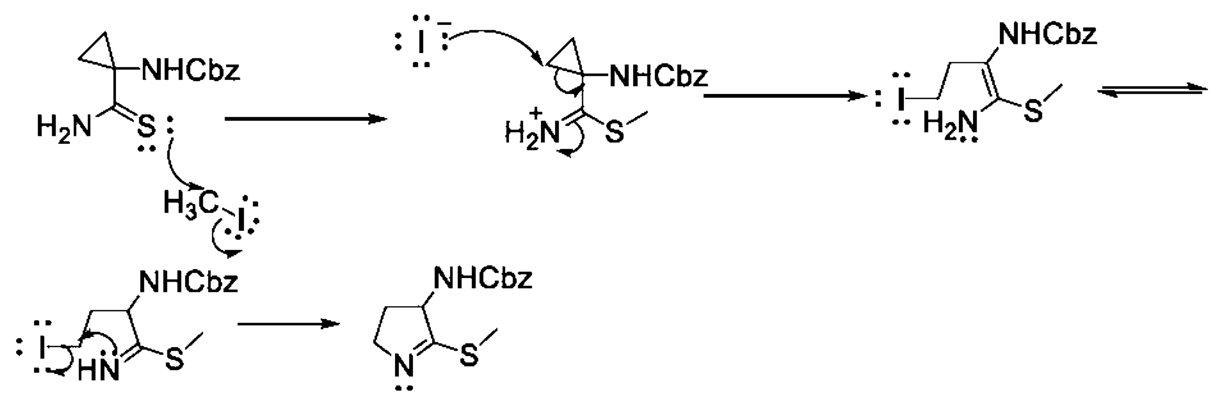
411


Cl3Fe
O
S
O
Cl3Fe
+
O
S
O
Cl3Fe
O
O
S+
H
O
S
+
O
FeCl3
O
S
O
FeCl3
O
S
HO
Cl3Fe
O
O
S+
Cl3Fe
O+
O
S
H
Cl3Fe
O
O
S
OH
O
S

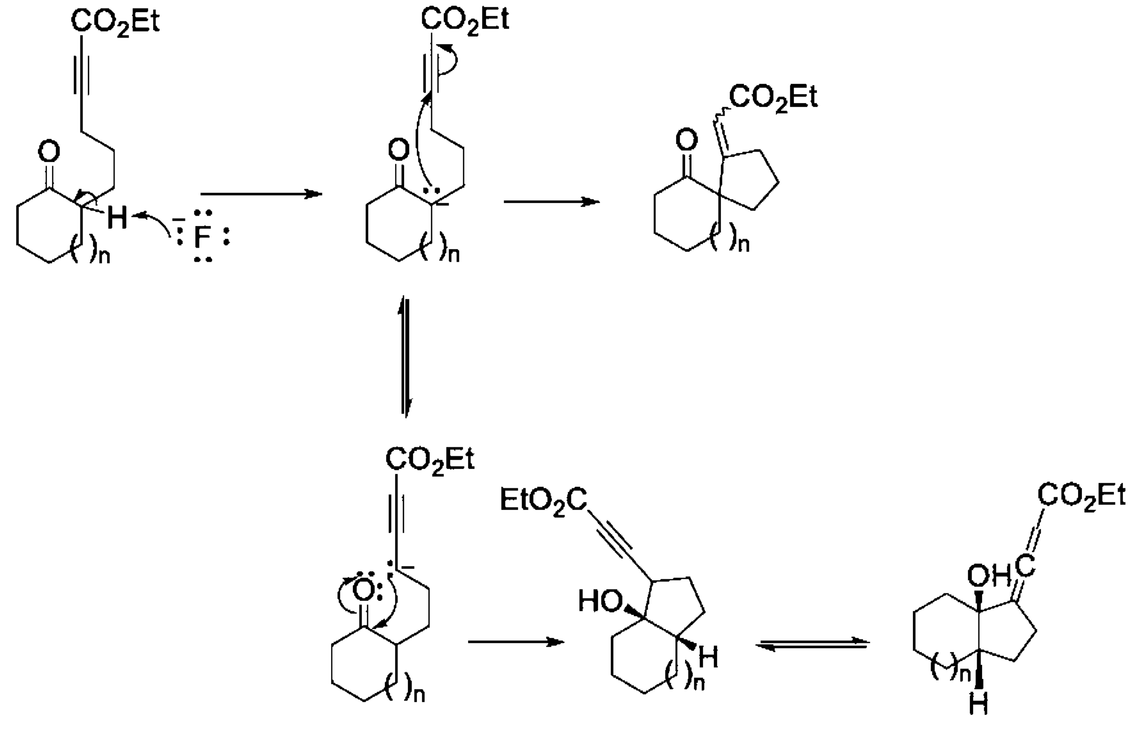
412



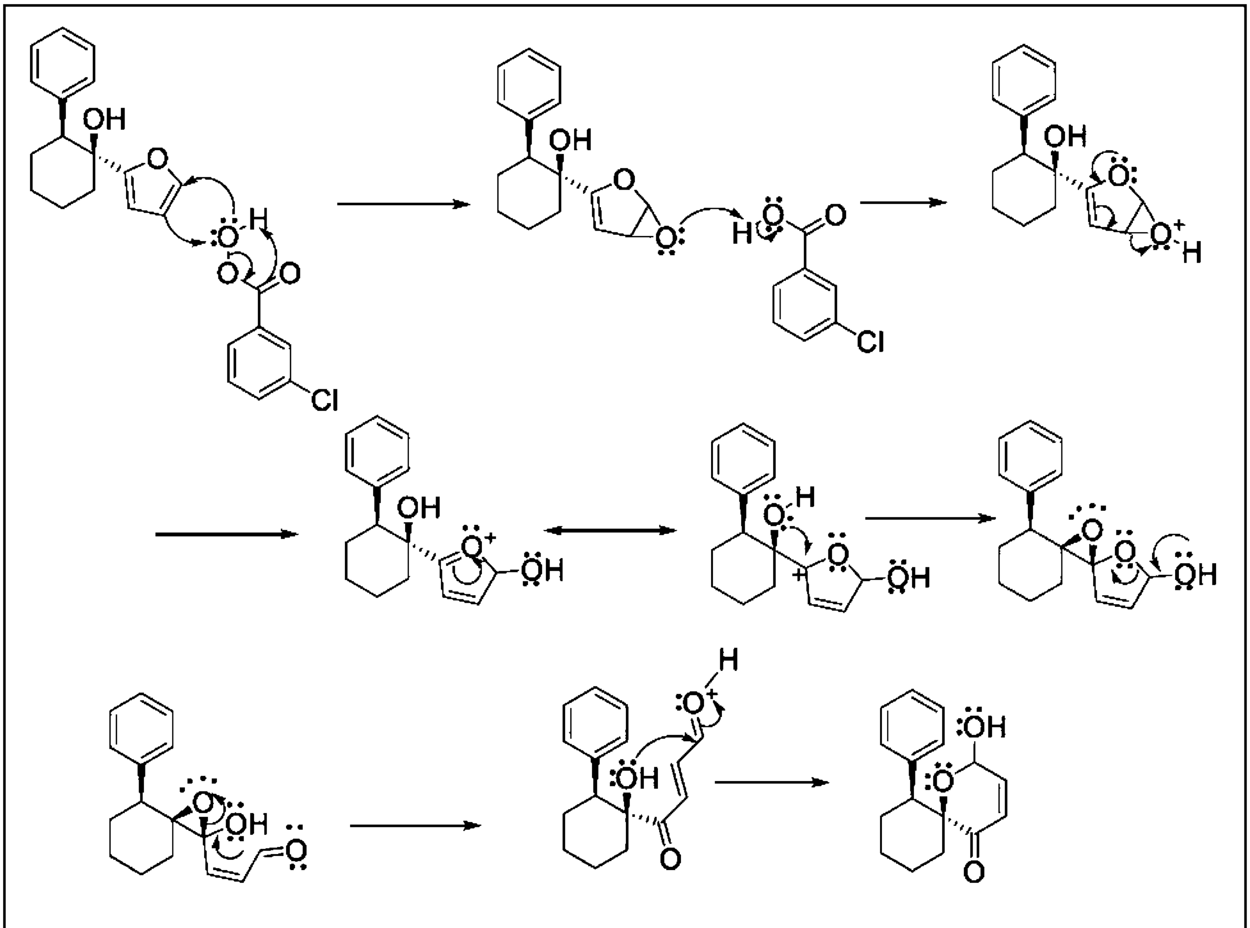
413



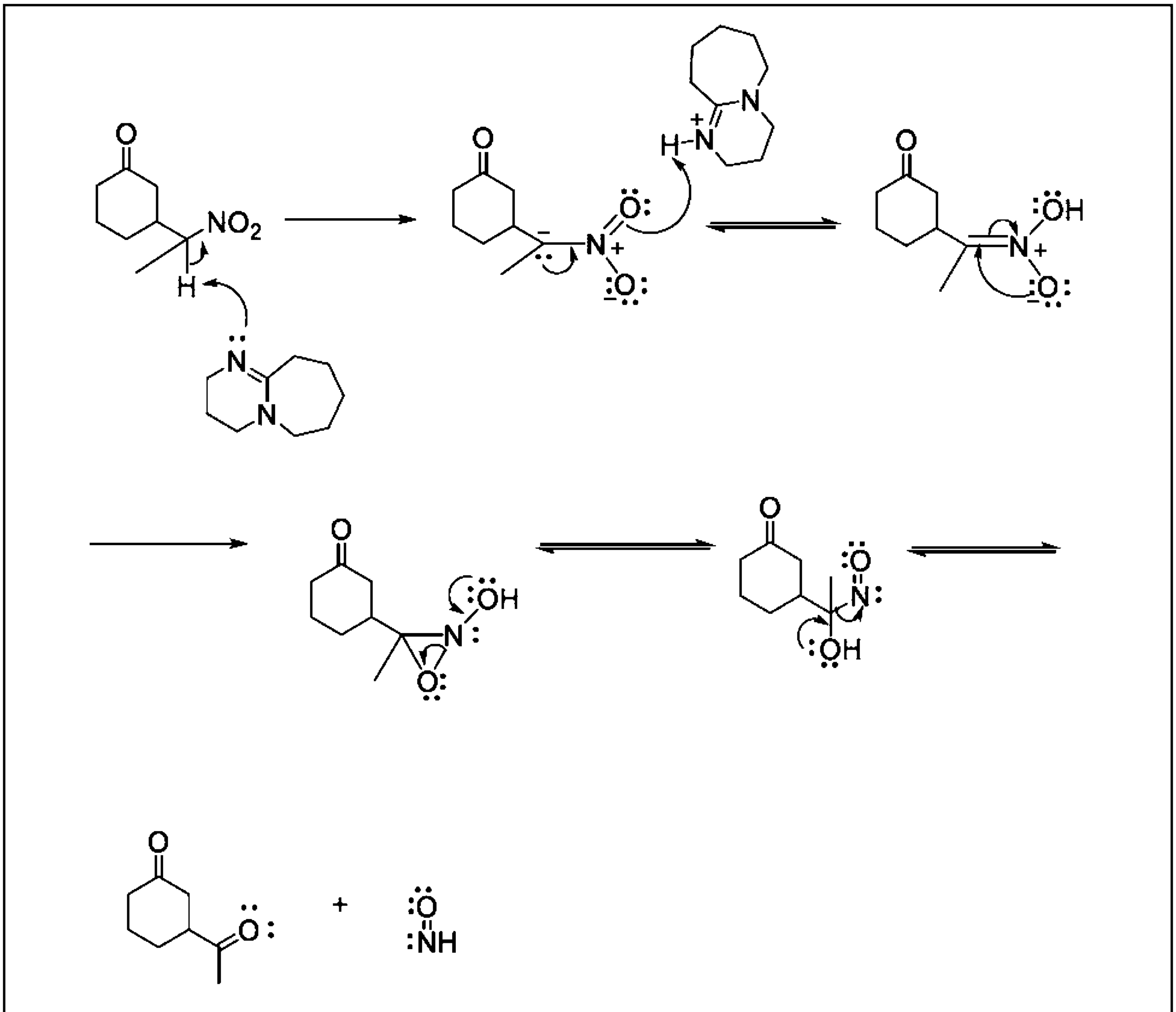
414



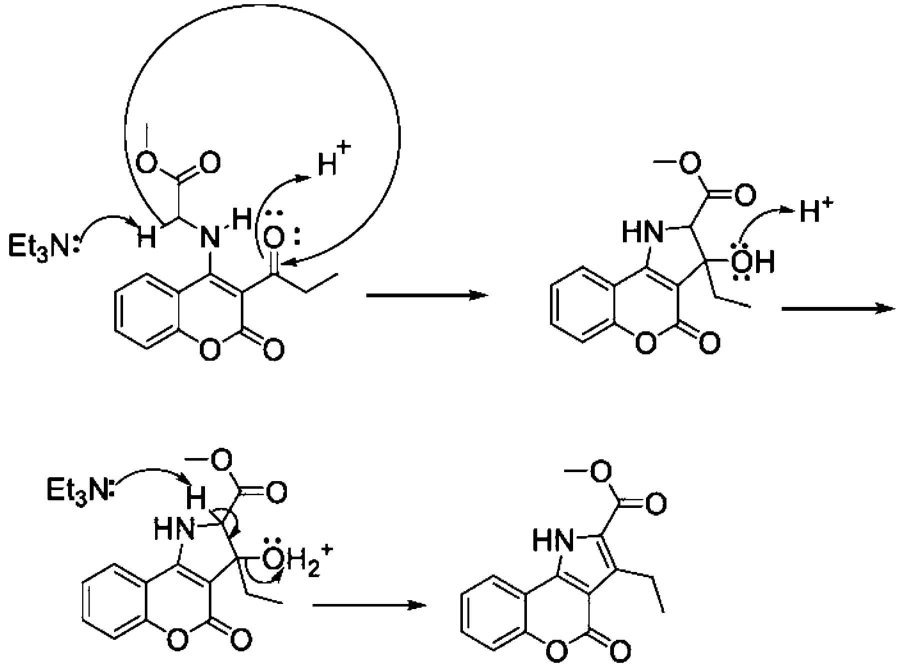
415


OH
O
H
O
O
O
Cl
OH
O
O
H
O
O
Cl
OH
O
O
H
OH
O
OH
O
H
O
OH
O
O
OH
O
OH
O
H
O
OH
O
O
OH
O
O

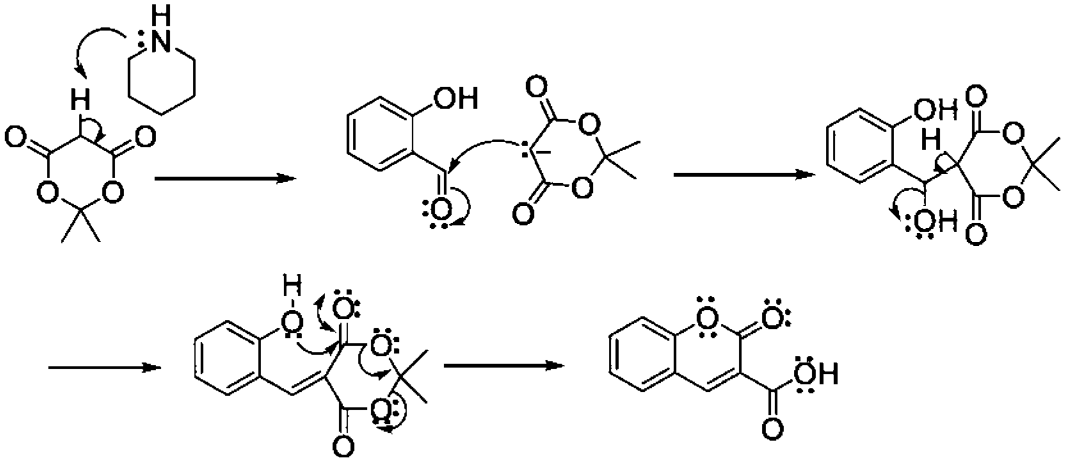
416



417



418



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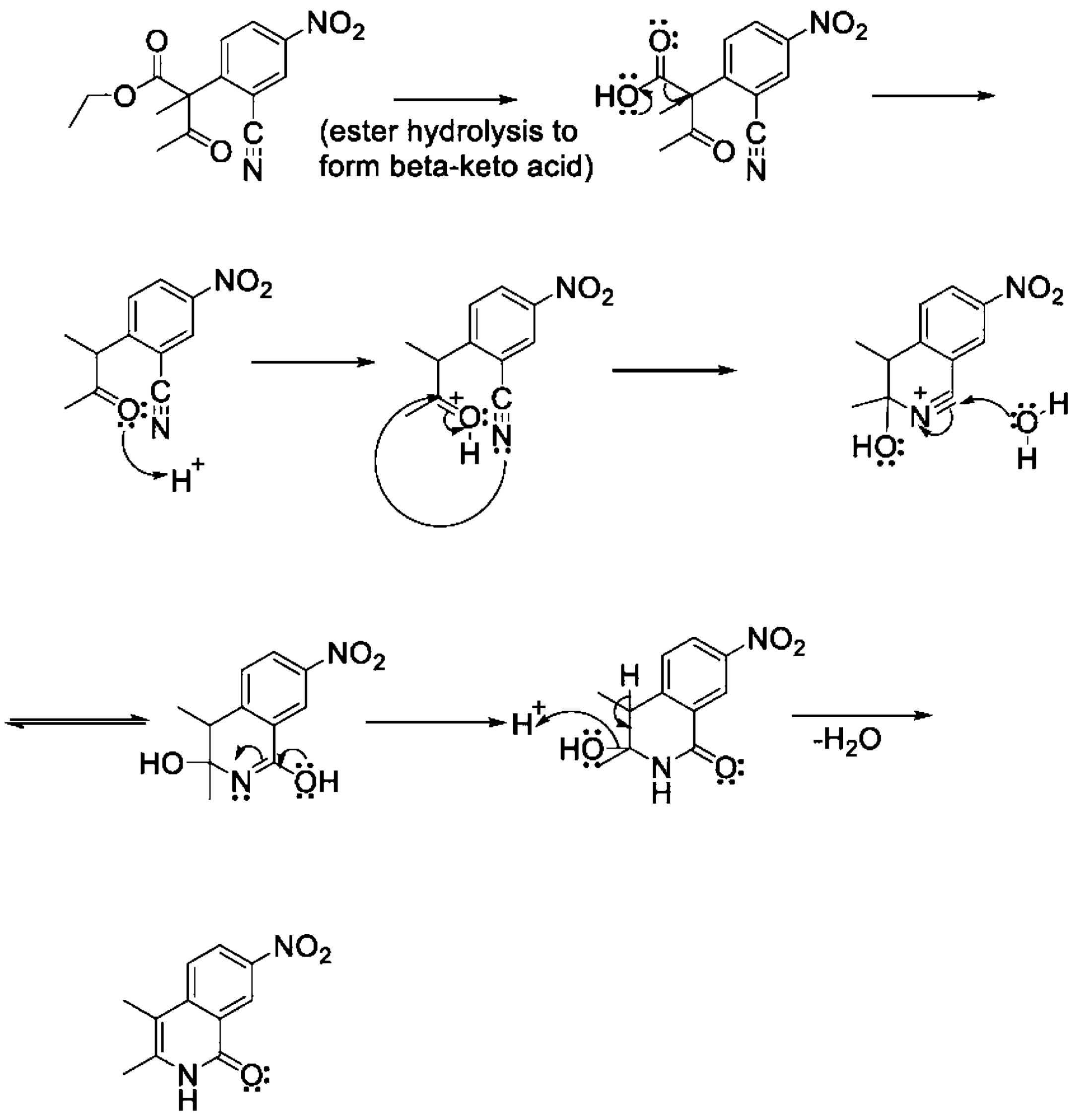
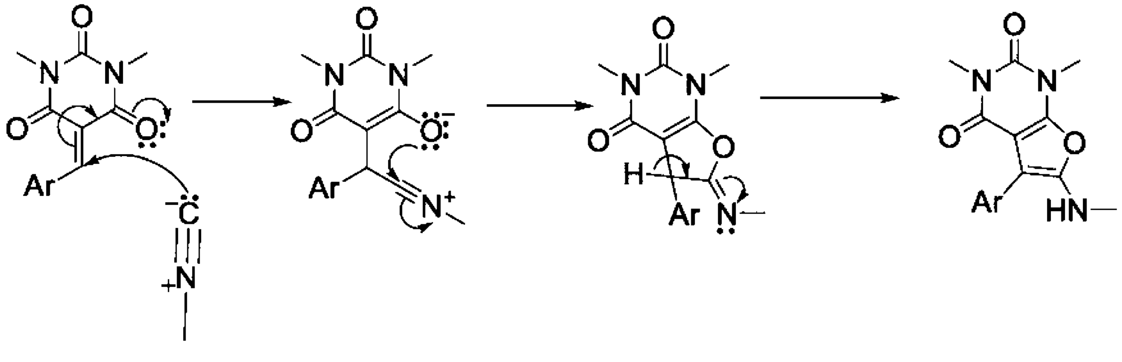
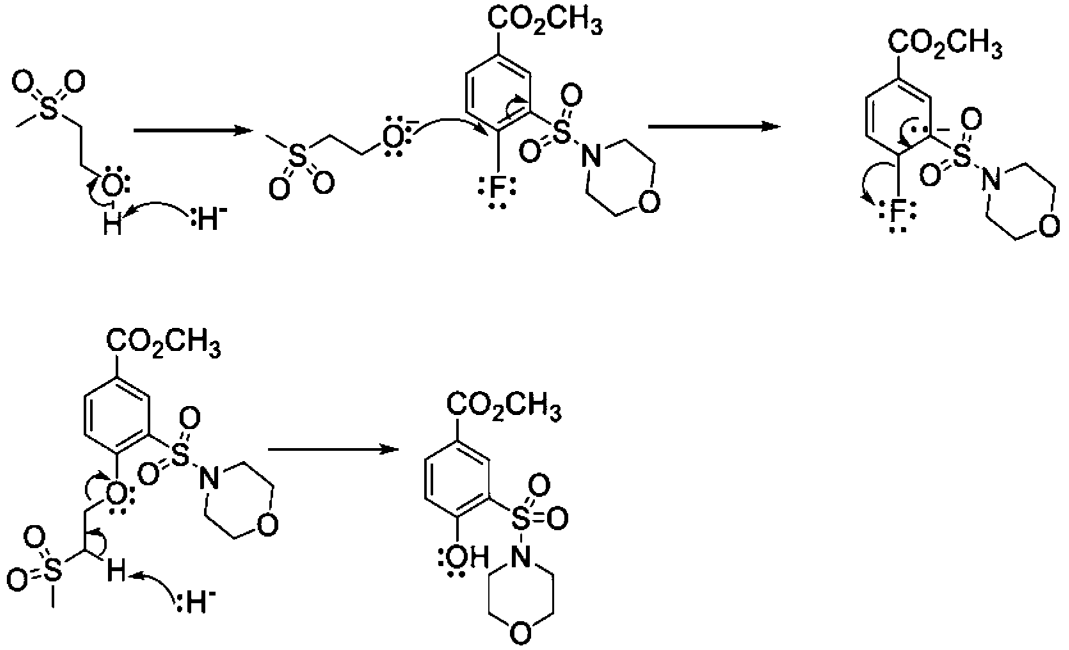


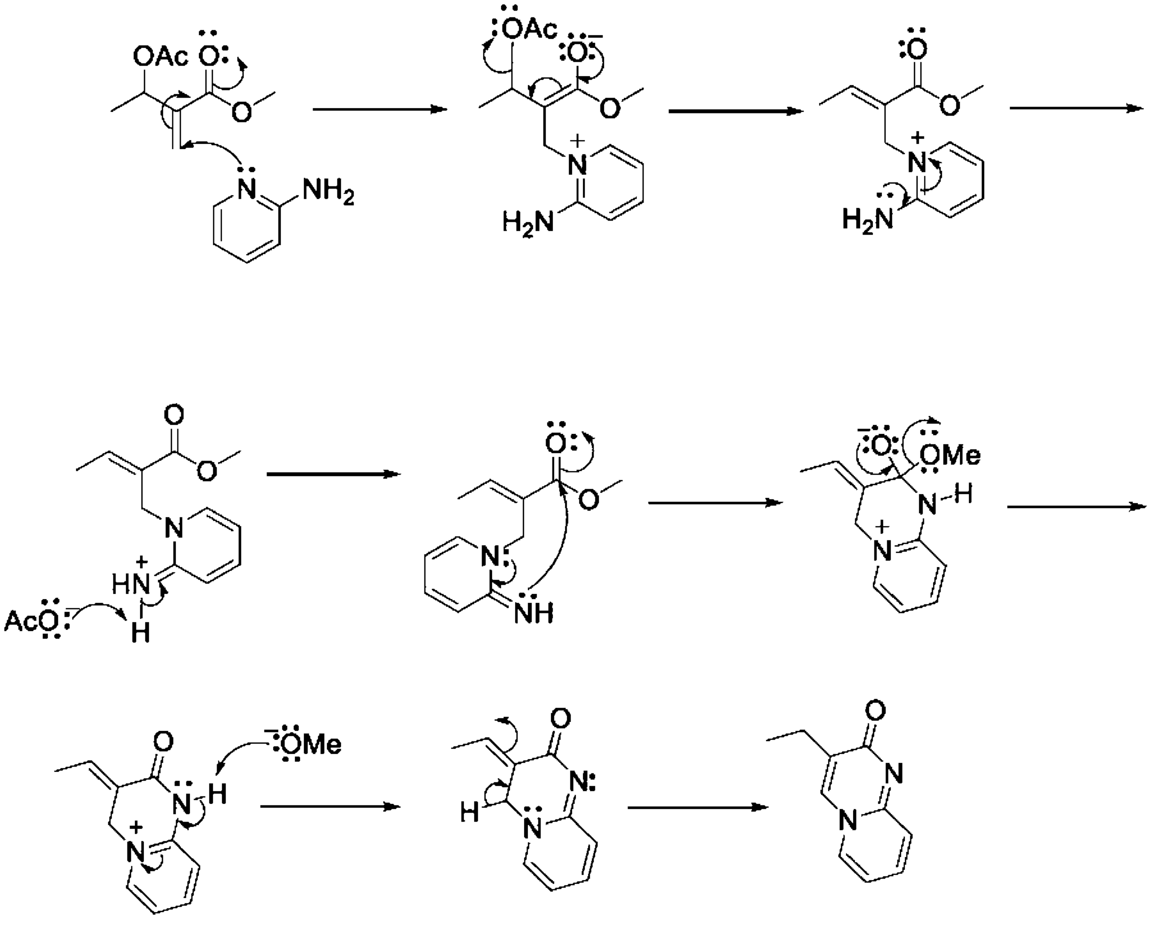
420



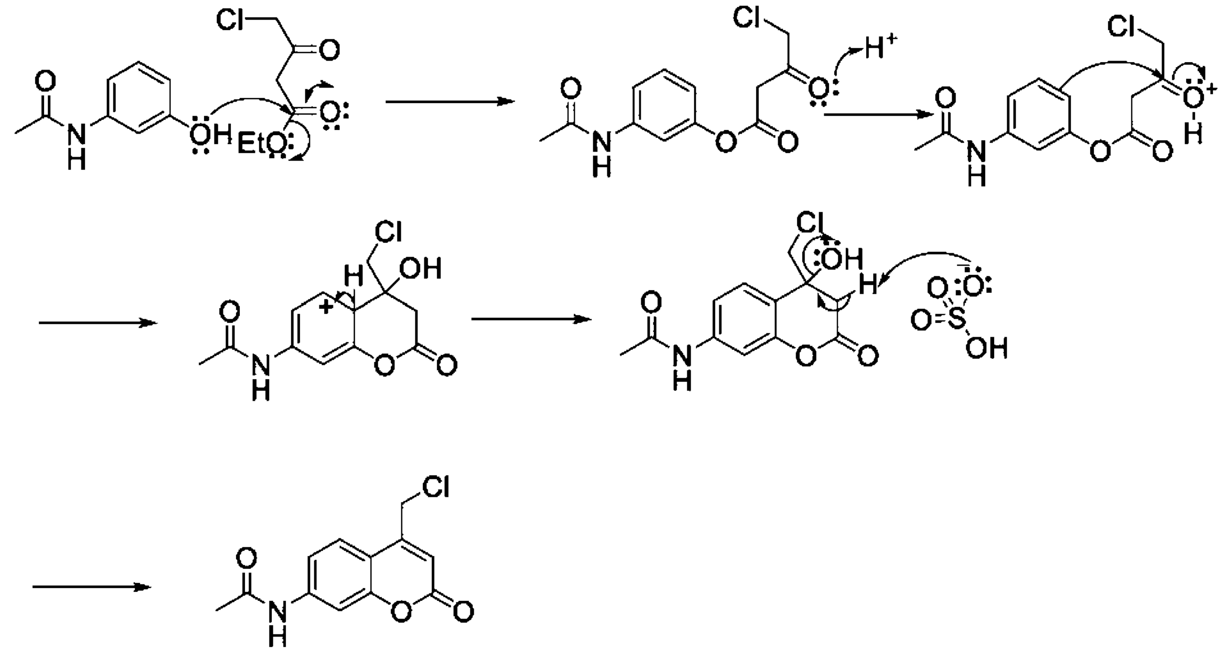
421



422

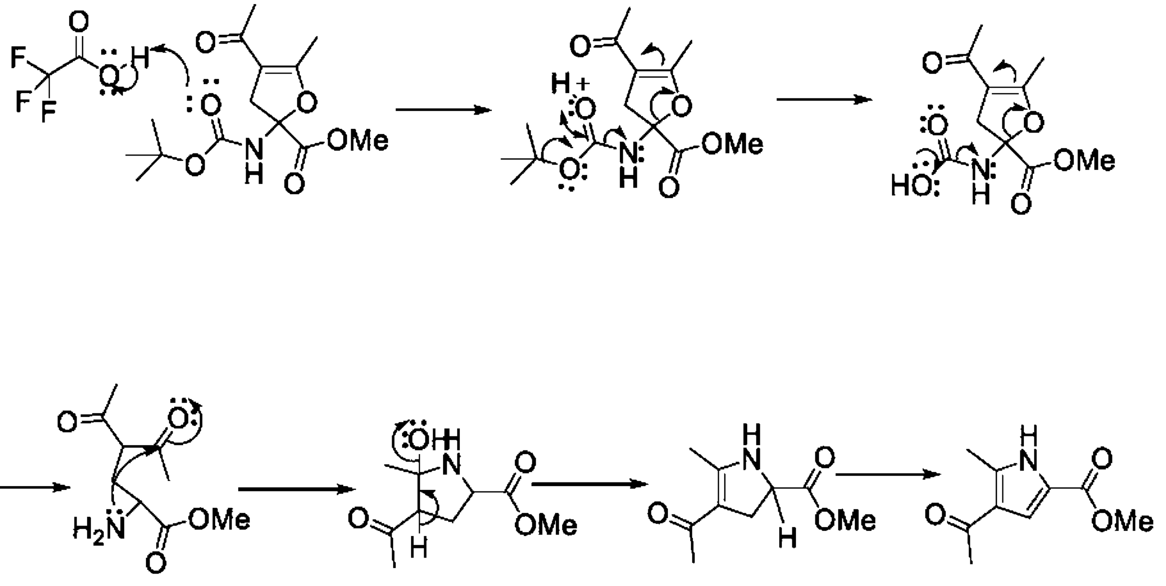


423



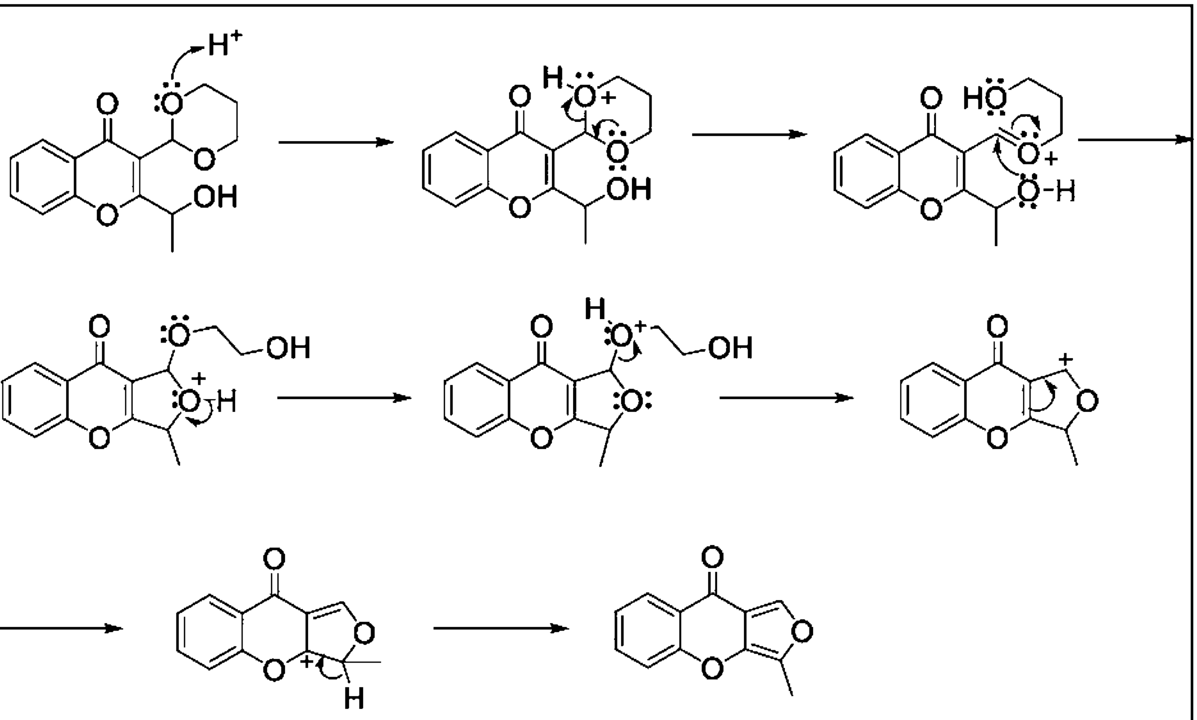
Cl
O
N
H
ÖH
EtO
Cl
H+
O
Cl
O
H
+
H
Cl
OH
OH
O
S
OH
O

424

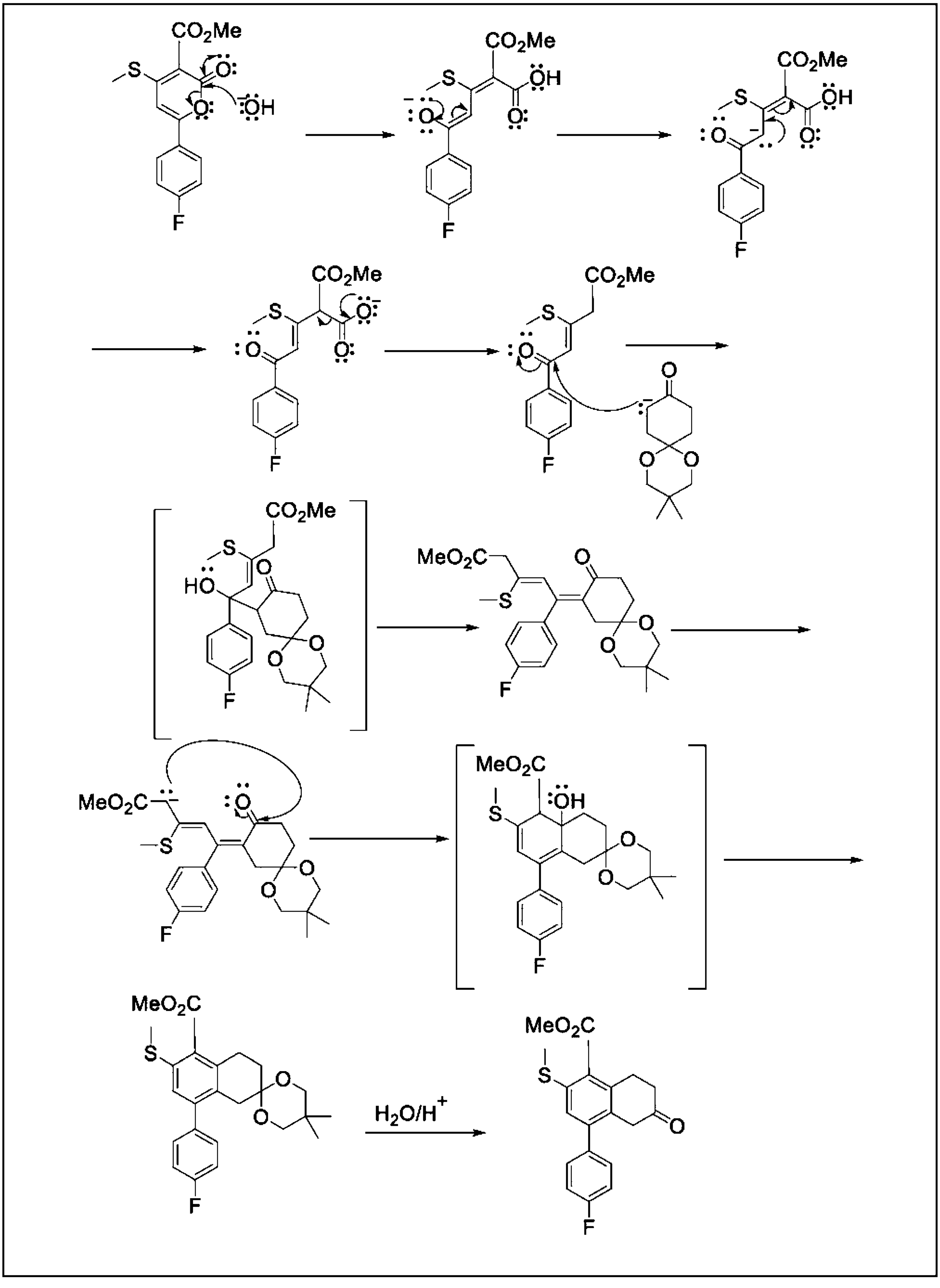


F
F
F
O
O
H
O
O
O
N
H
OMe
H+
HO
H₂N
OH
H
N
H
OMe

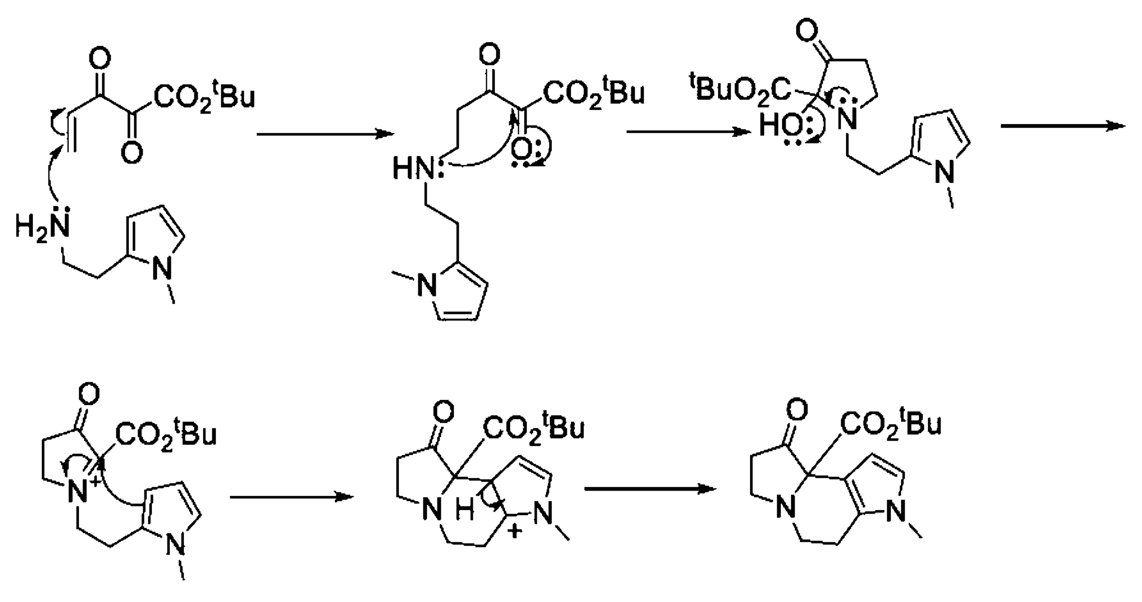
425



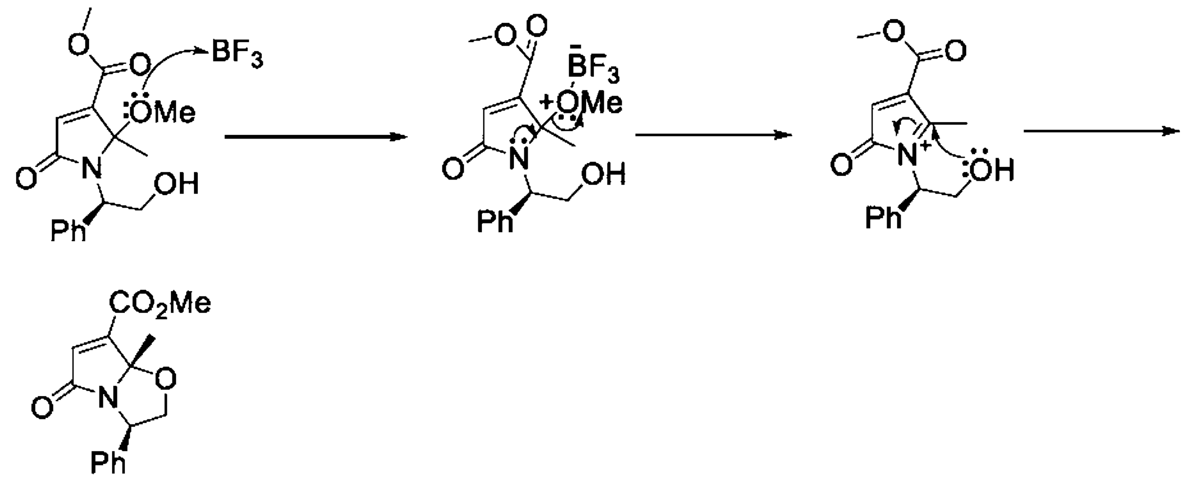
426

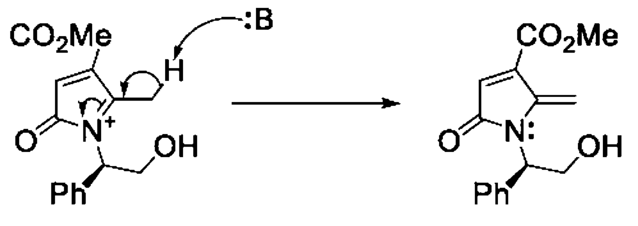

CO2Me
S
O
OH
F
MeO2C
H2O/H+

427

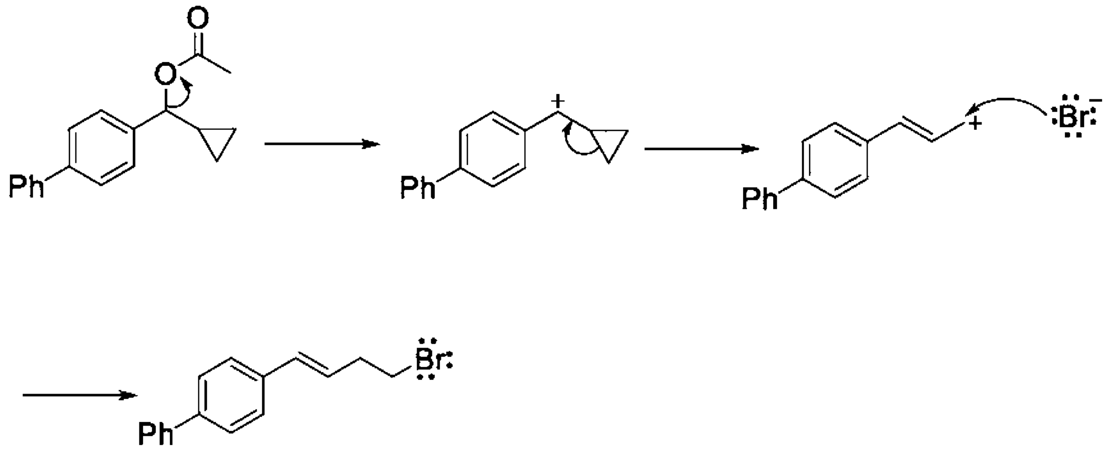


428

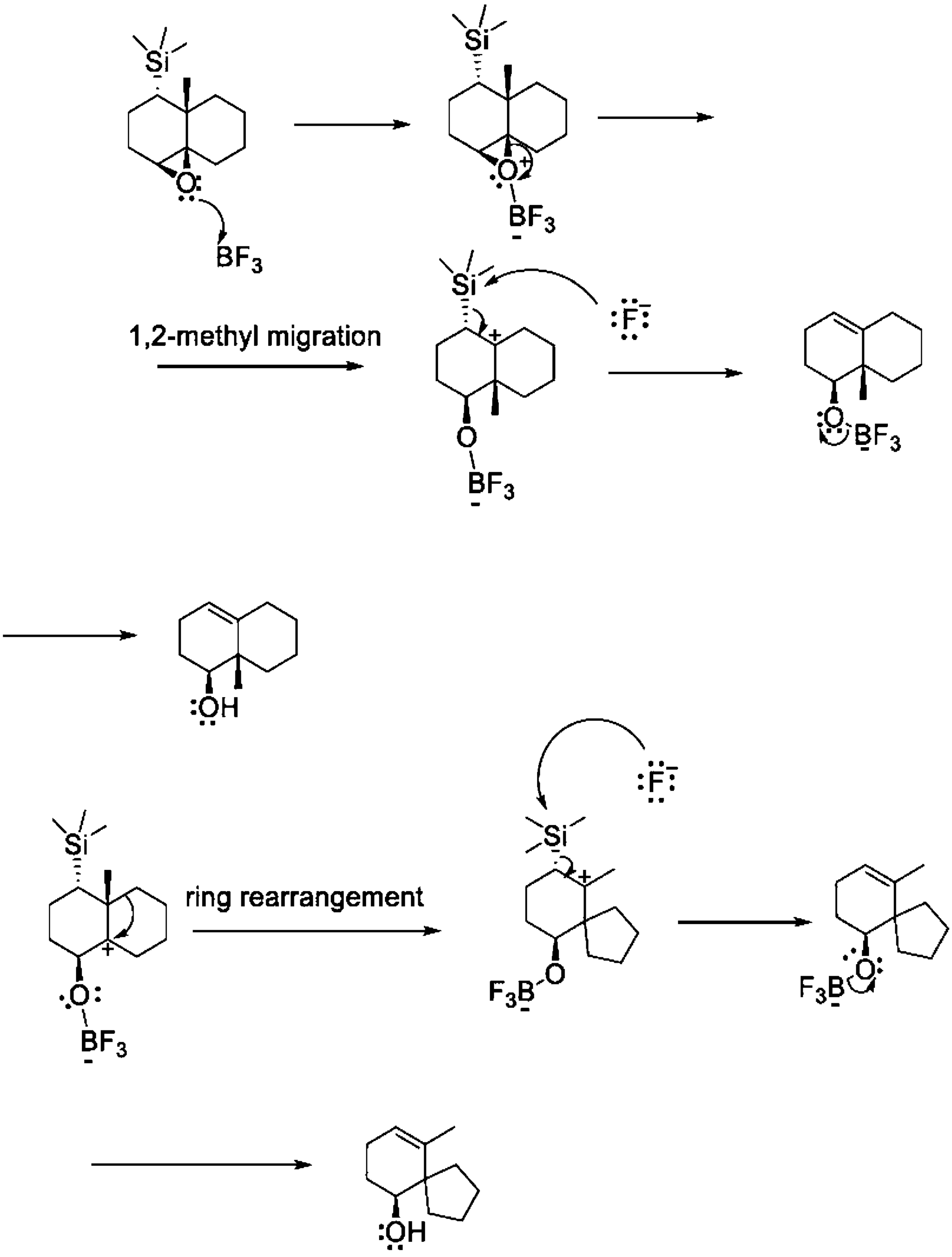




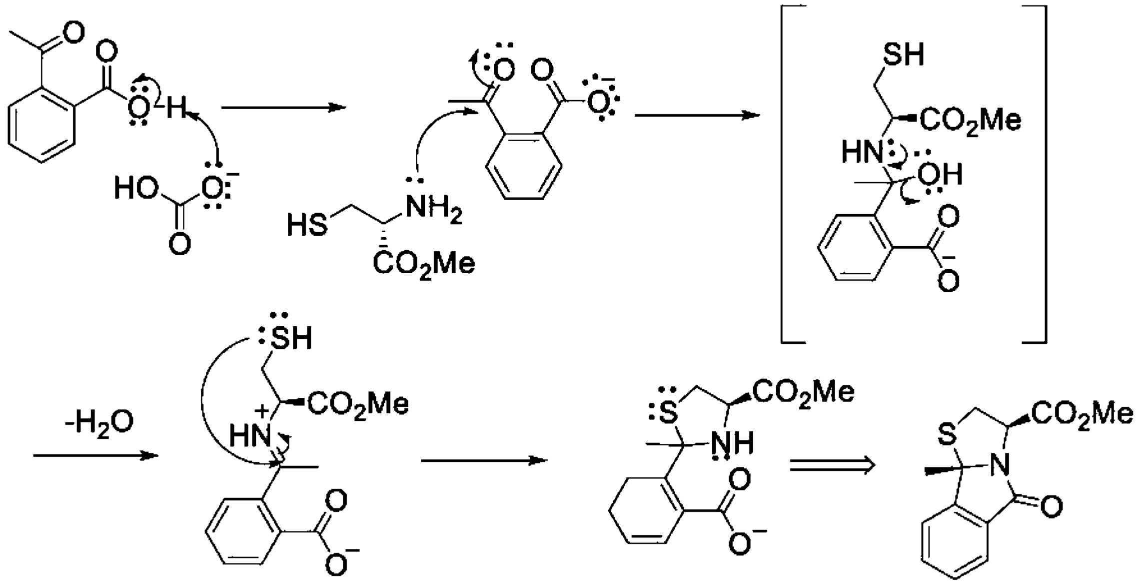
429



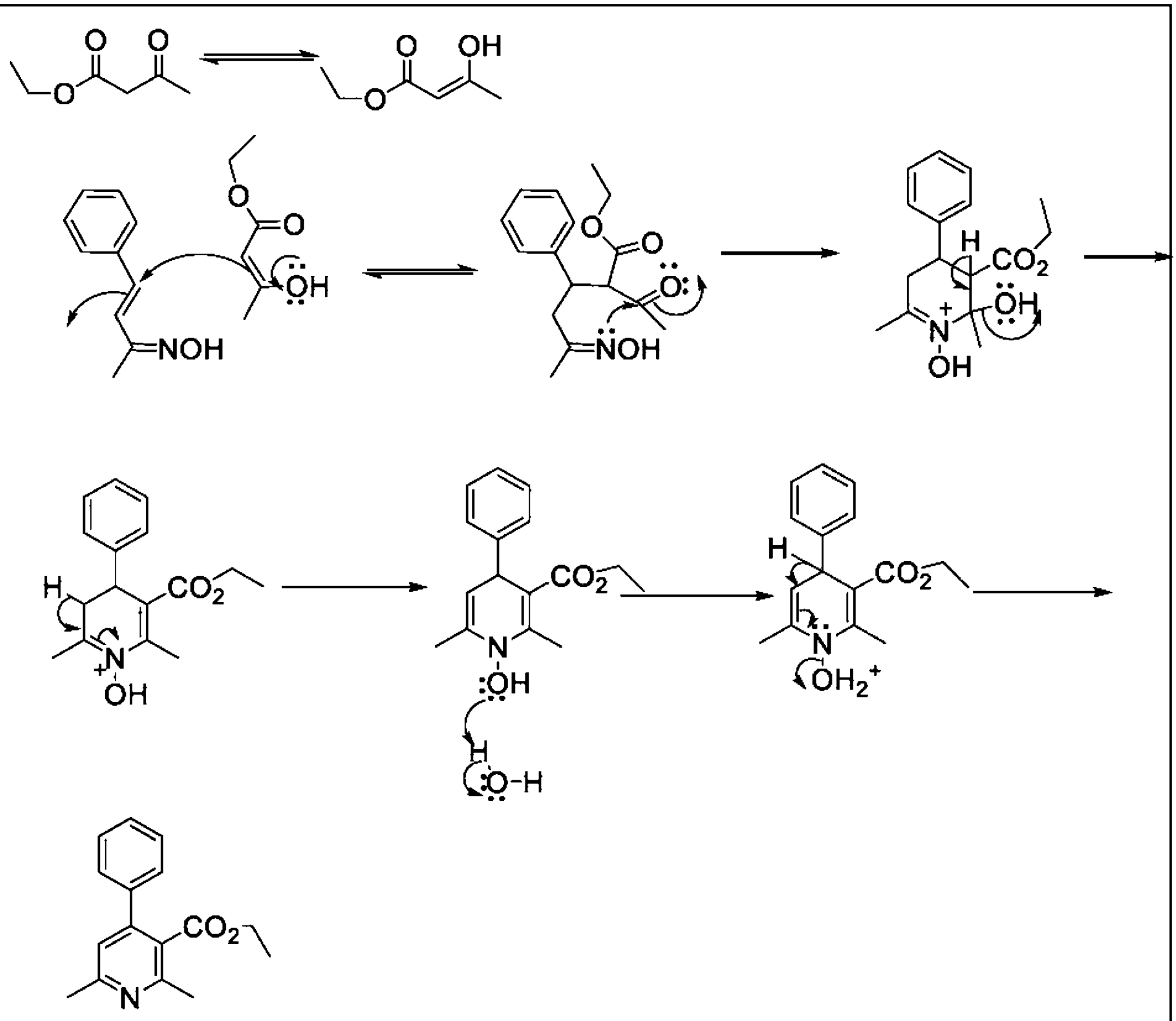
430


Si
O
BF$_3$
O+
BF$_3$
1,2-methyl migration
Si
+
F
O
BF$_3$
BF$_3$
OH
Si
+
O
BF$_3$
ring rearrangement
F
Si
+
F$_3$B
O
F$_3$B
O
OH

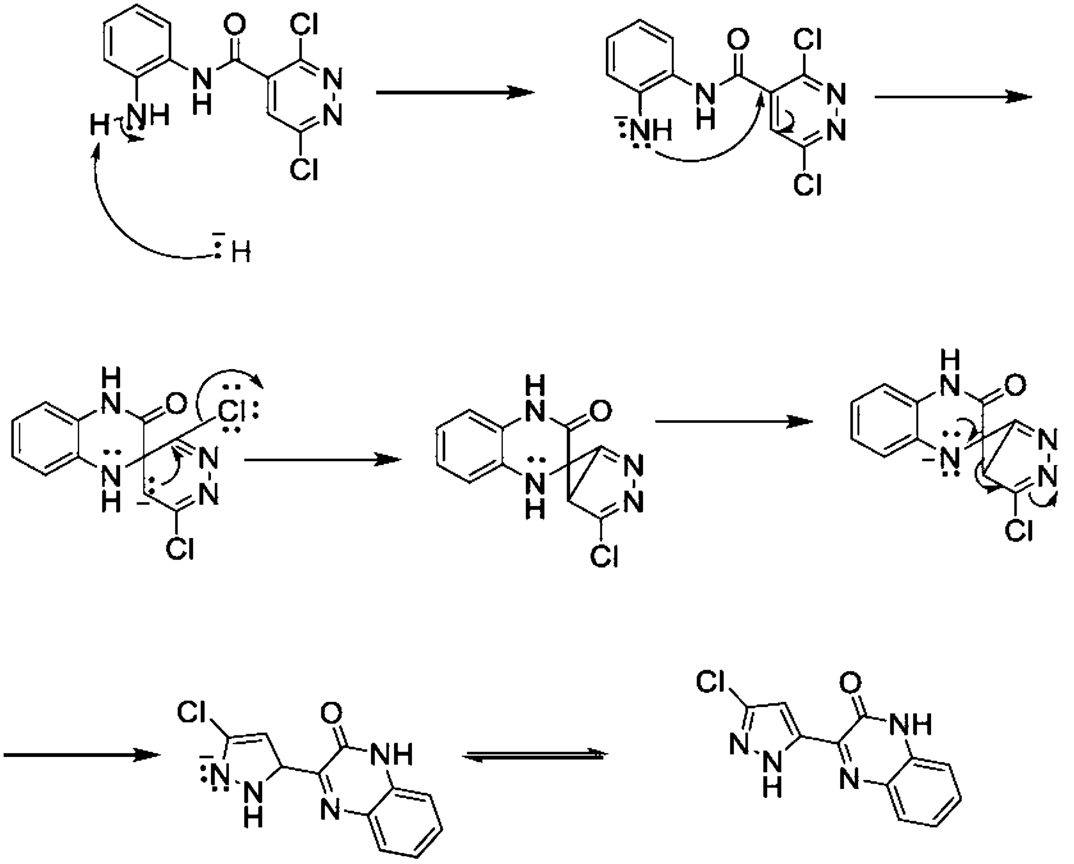
431



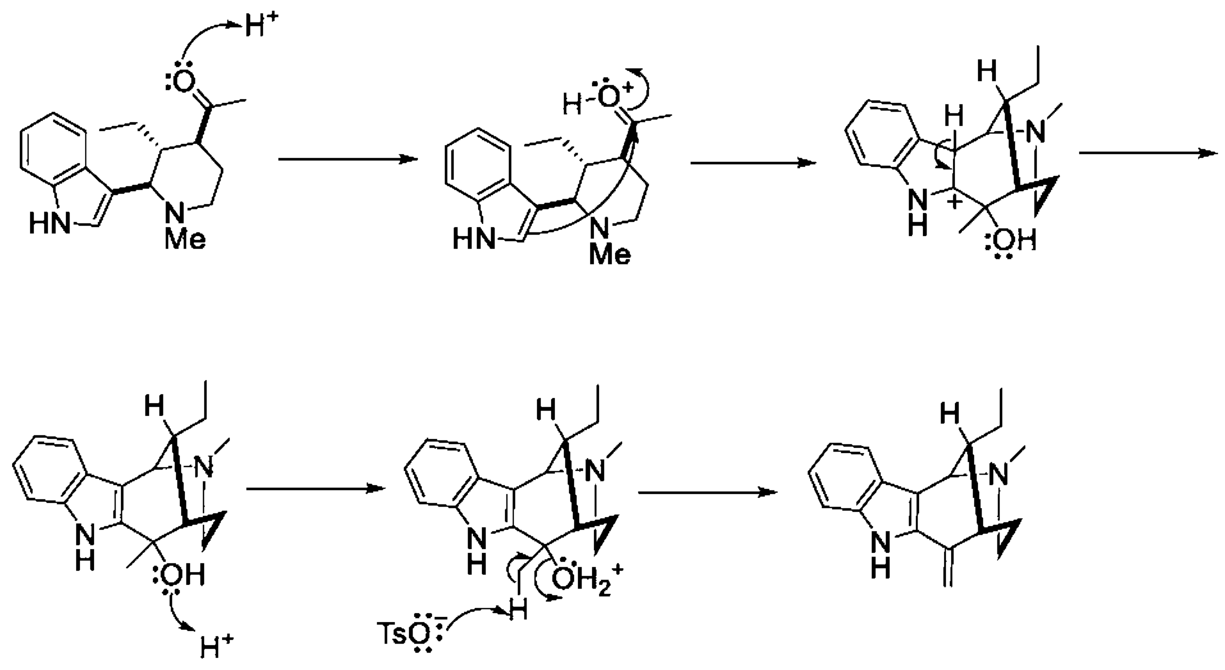
432


O
O
OH
O
O
O
OH
NOH
O
O
O
NOH
H
CO2
OH
N
OH
H
CO2
N
OH
CO2
N
OH
H
O-H
H
CO2
N
OH2+
CO2
N

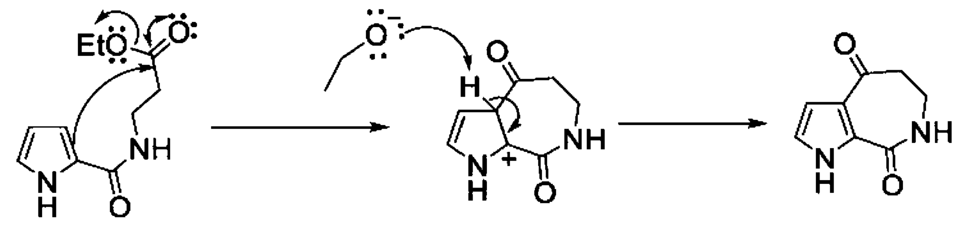
433



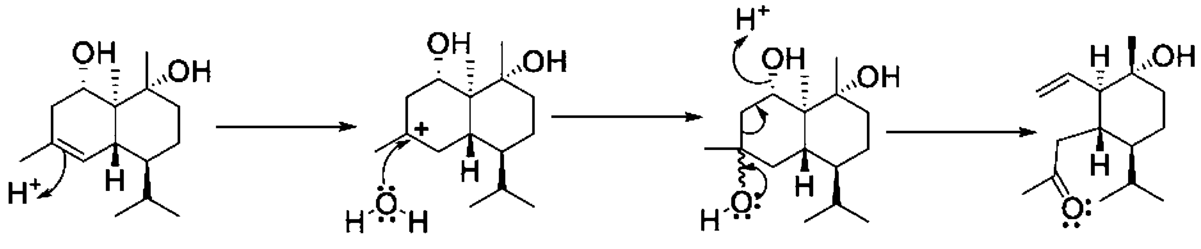
434



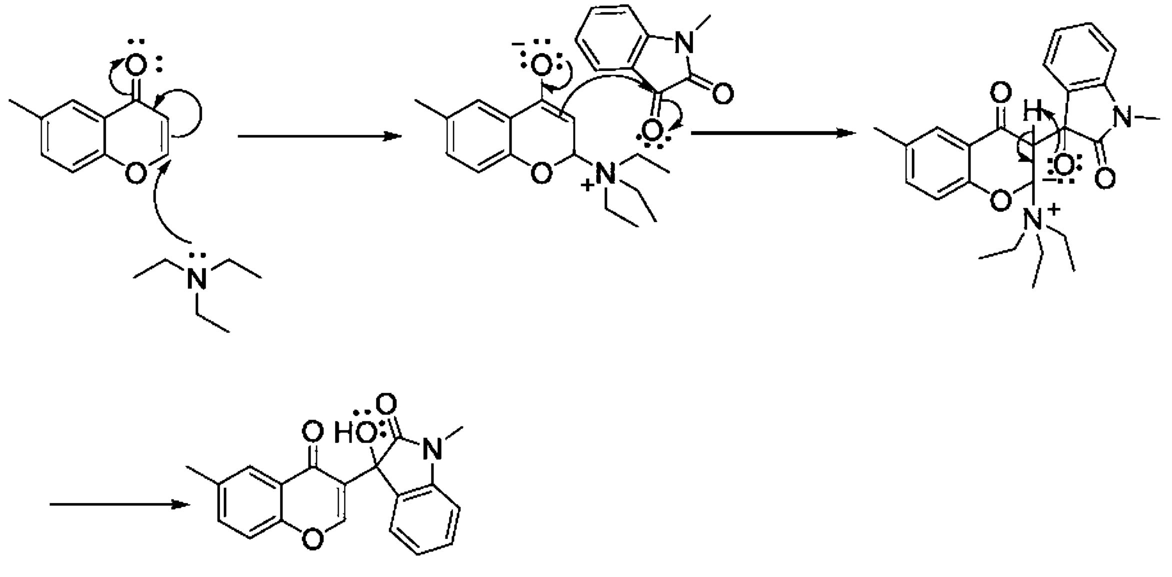
435



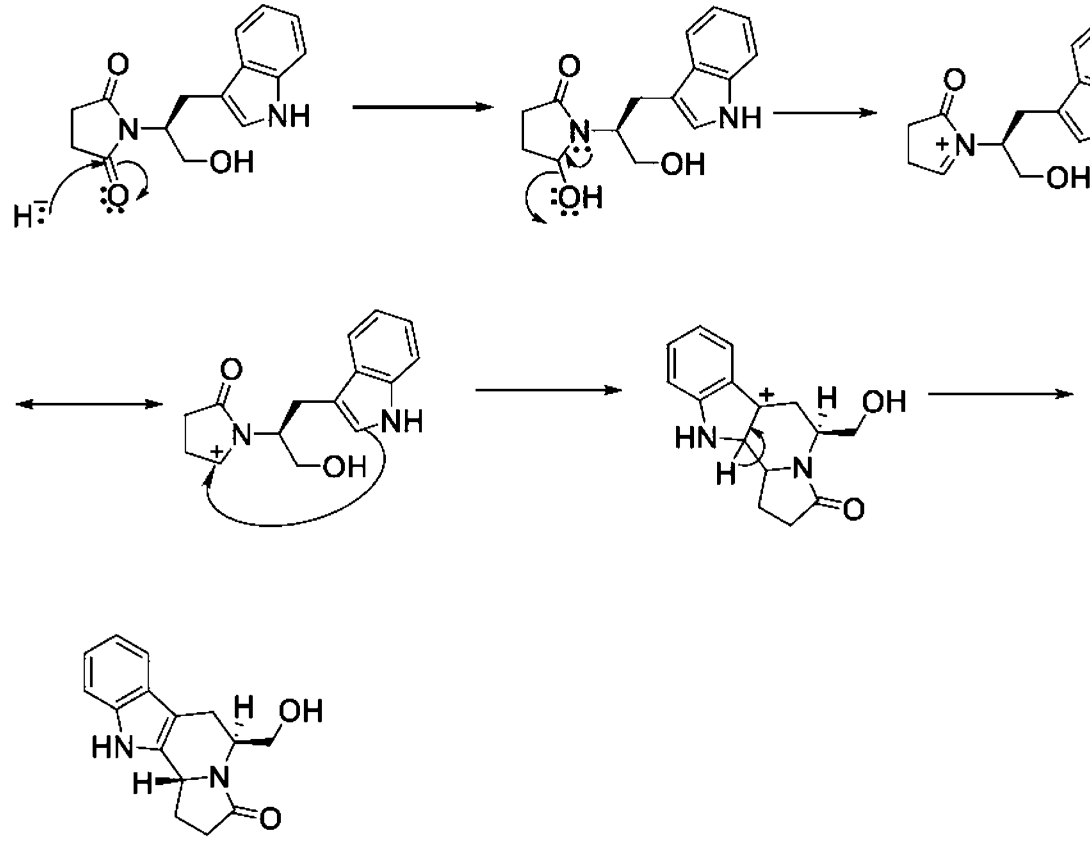
436



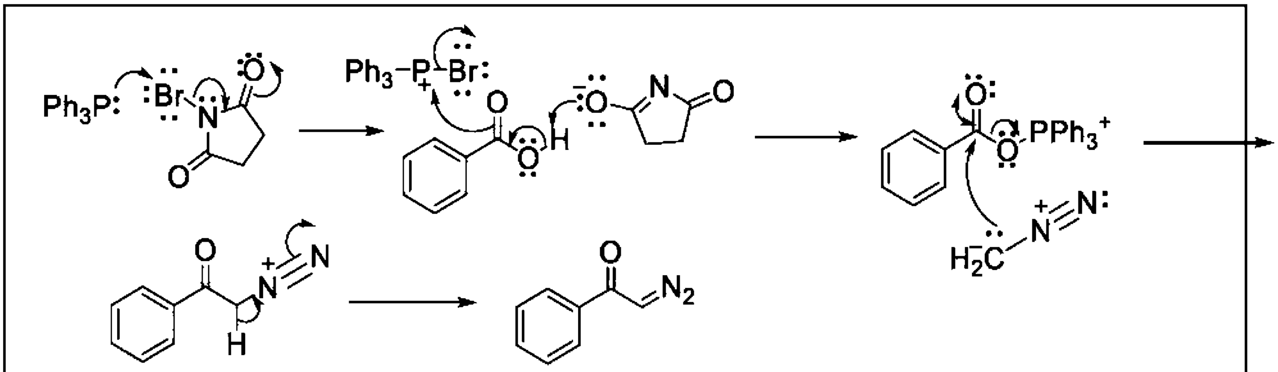
437



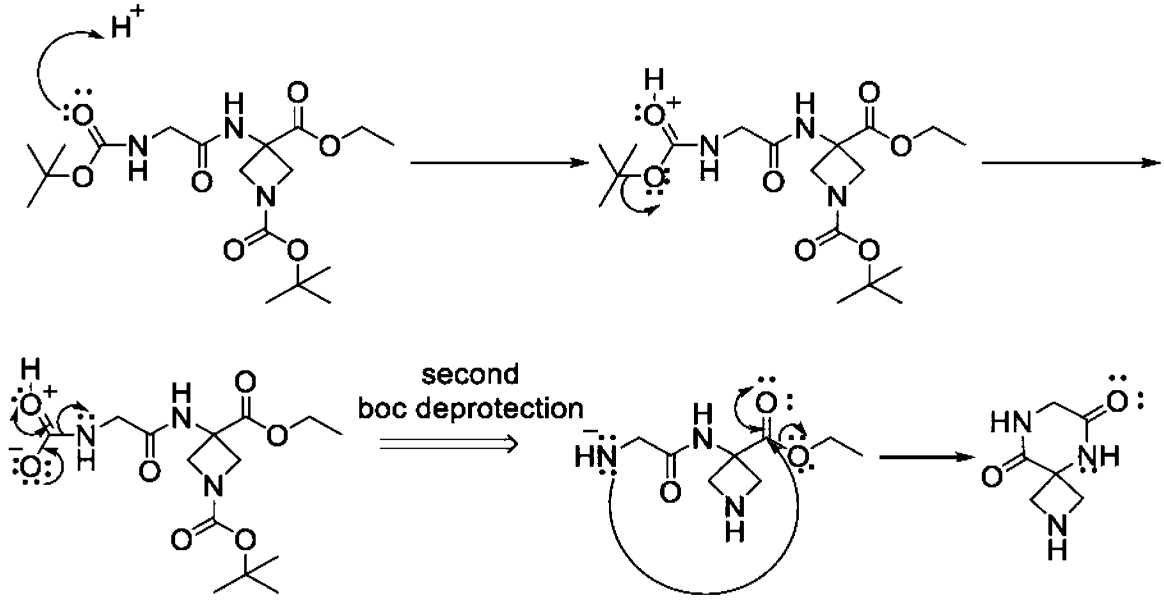
438



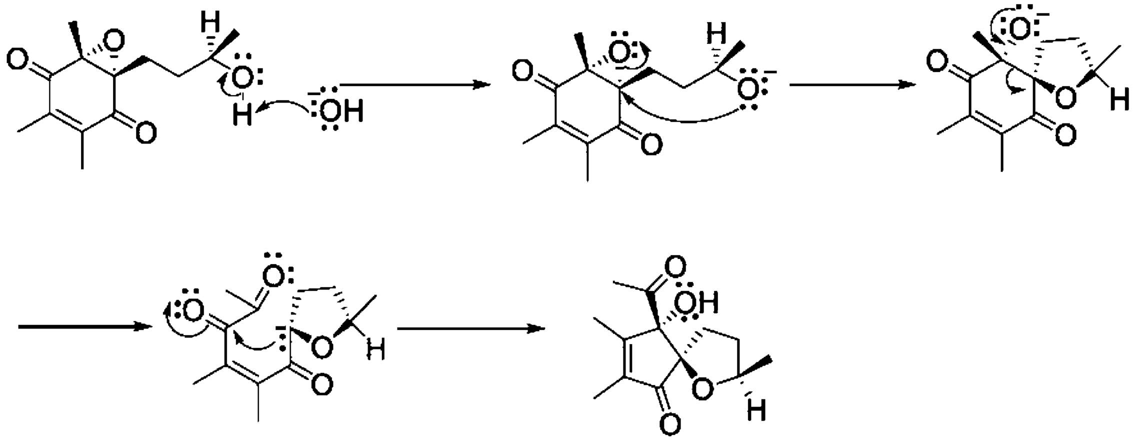
439



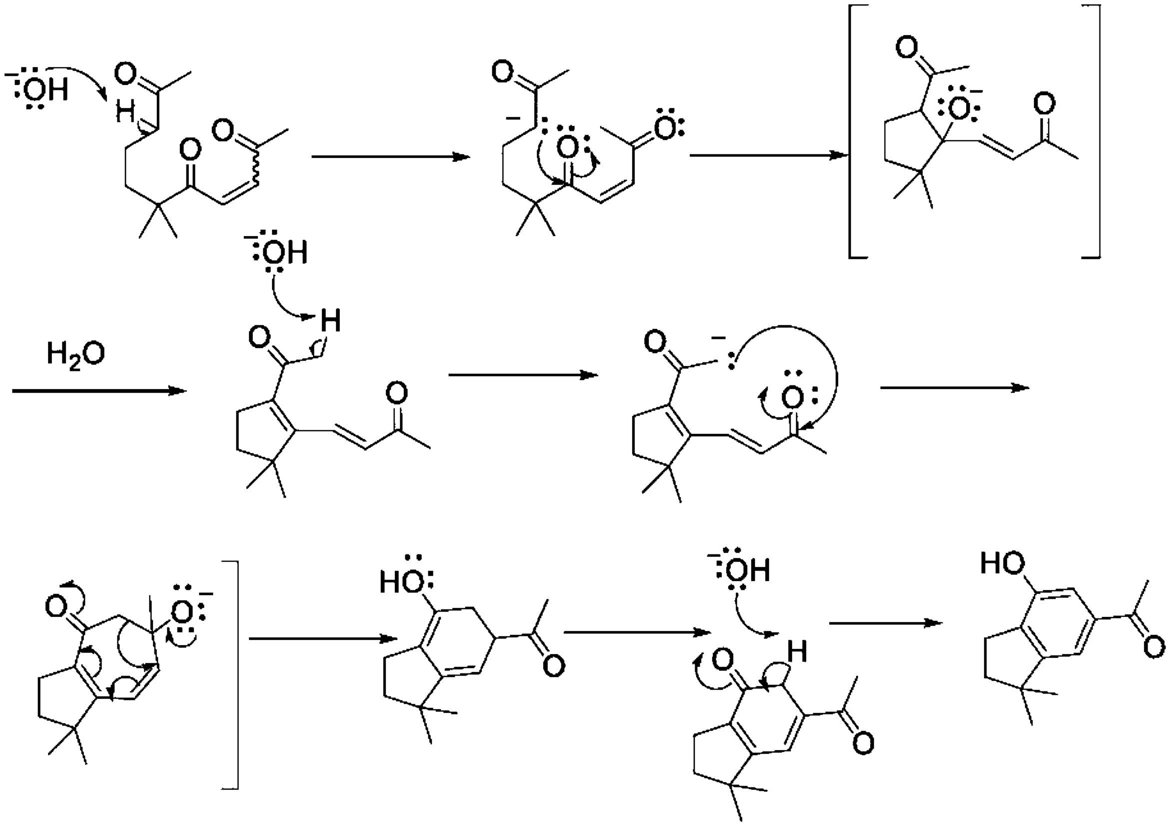
440



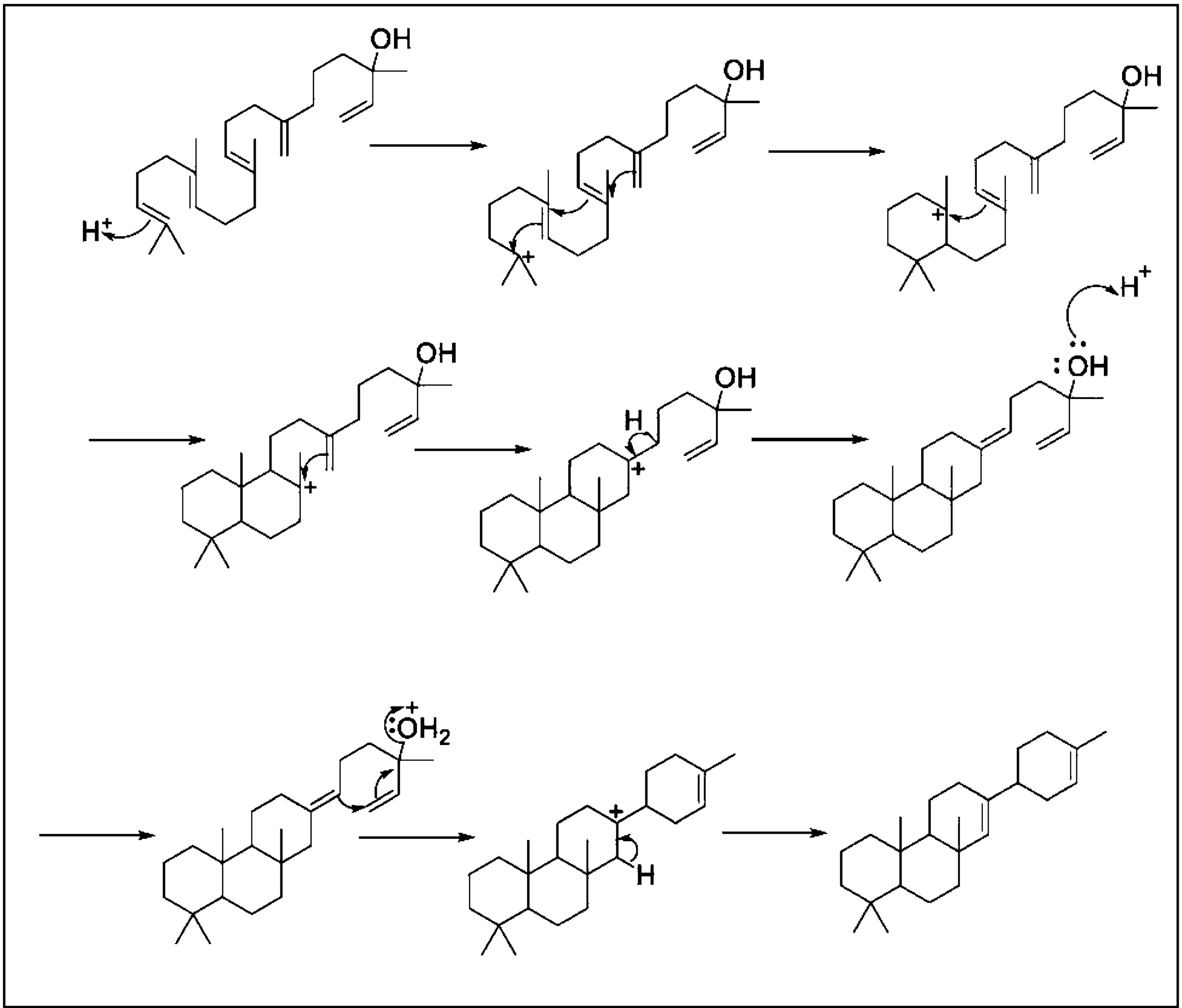
441



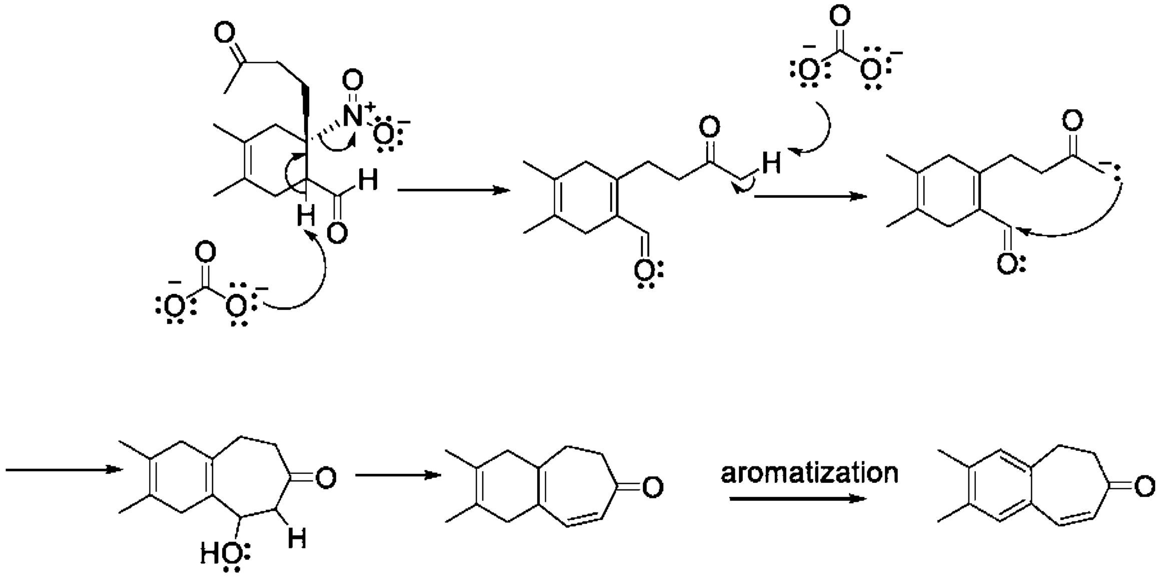
442



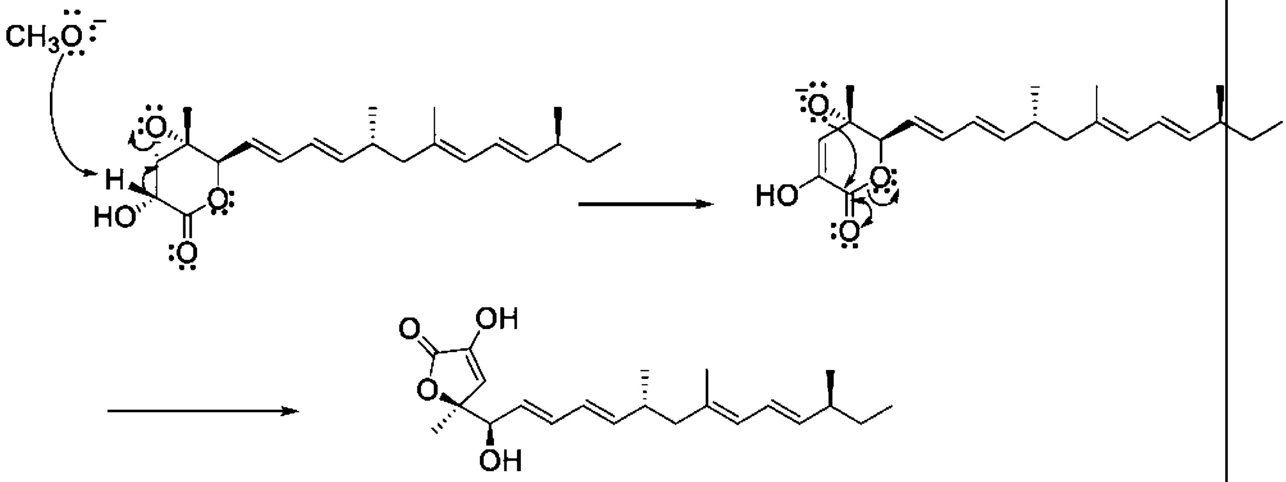
443



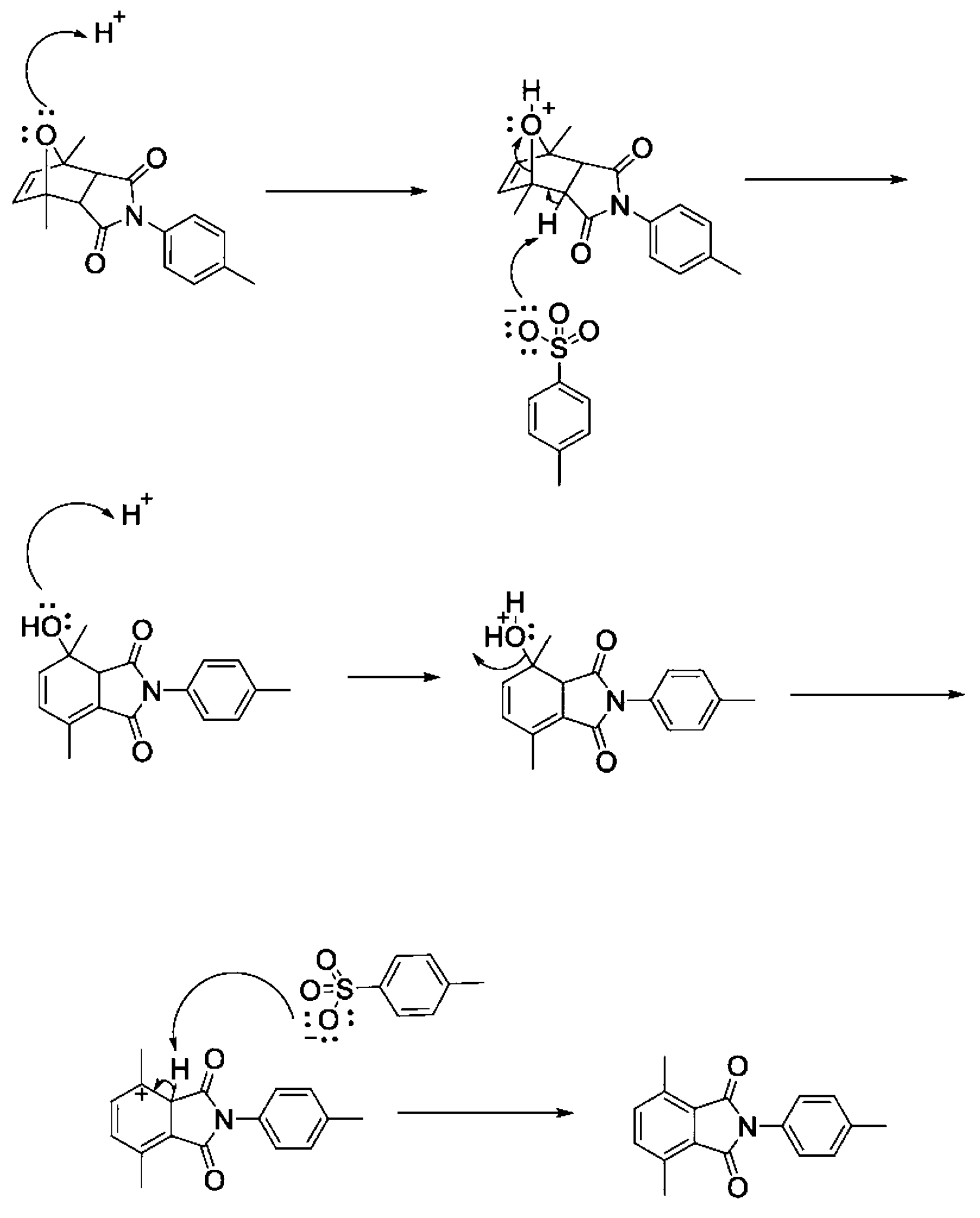
444



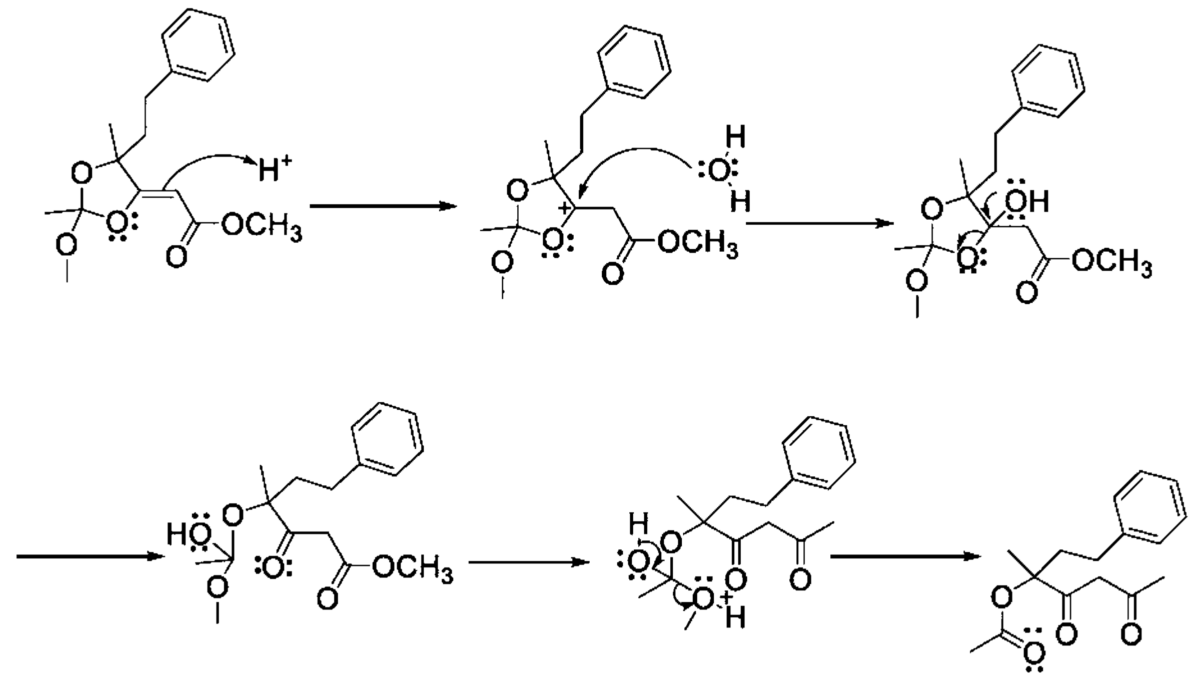
445



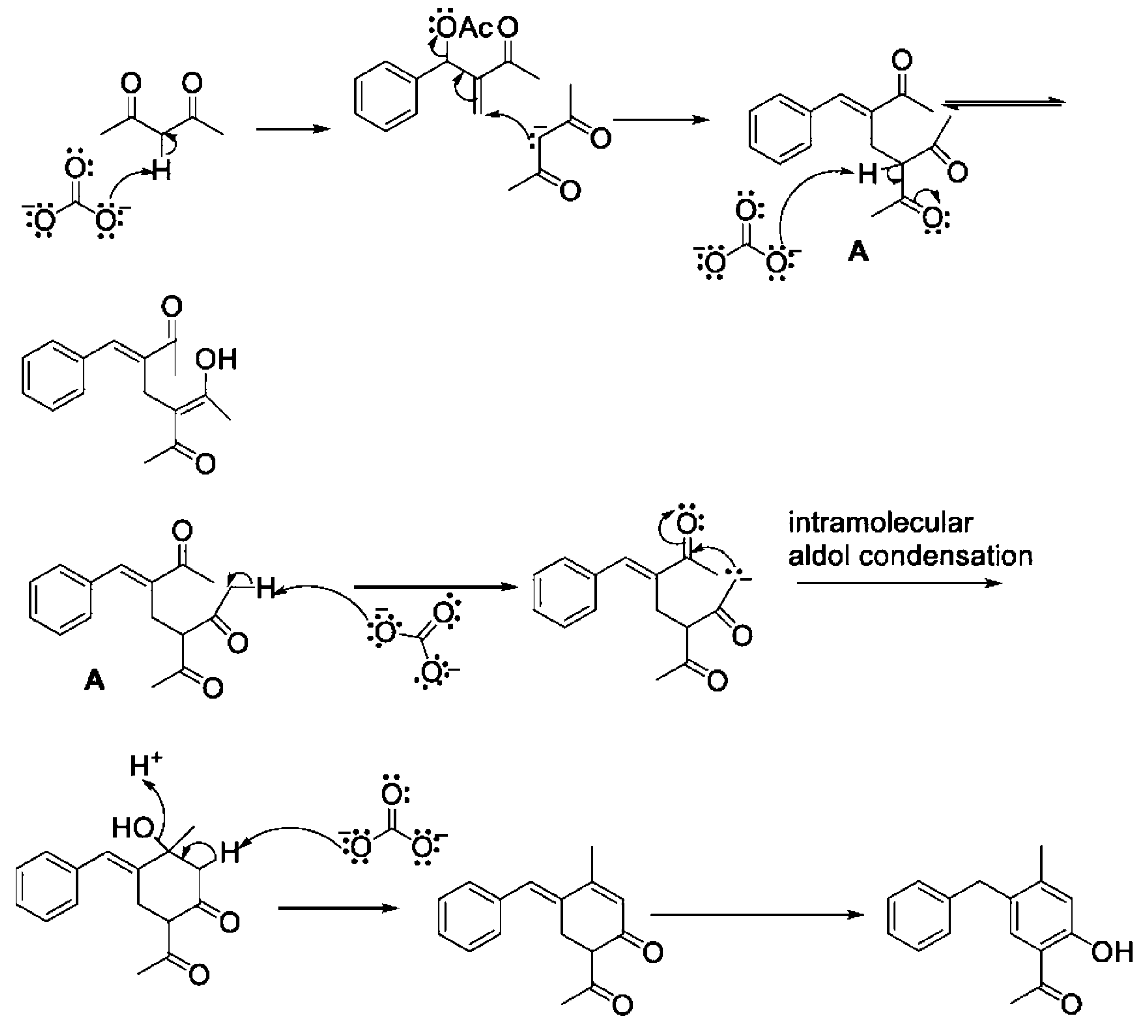
446



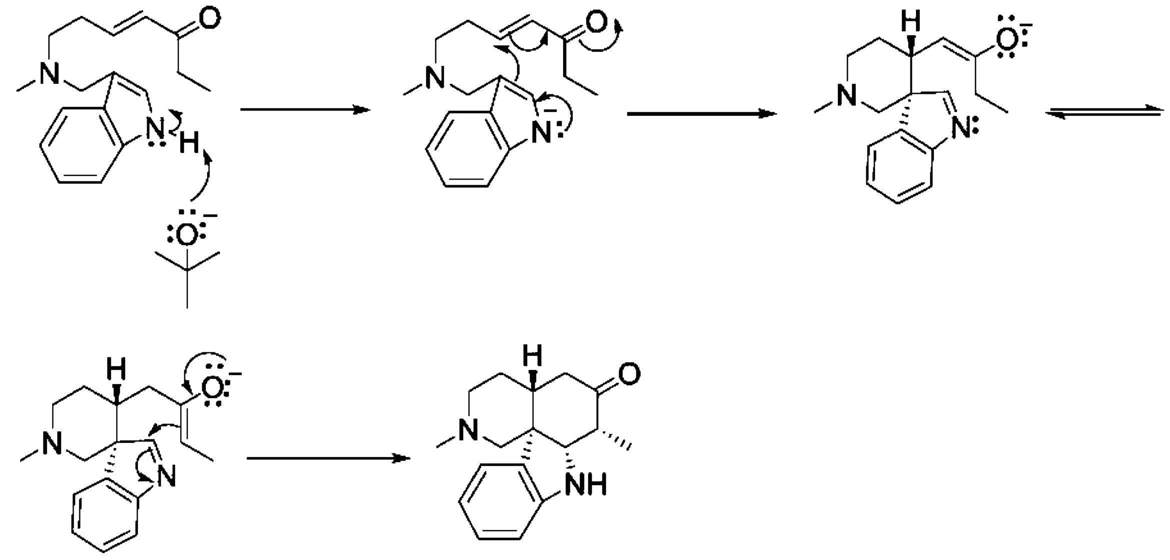
447



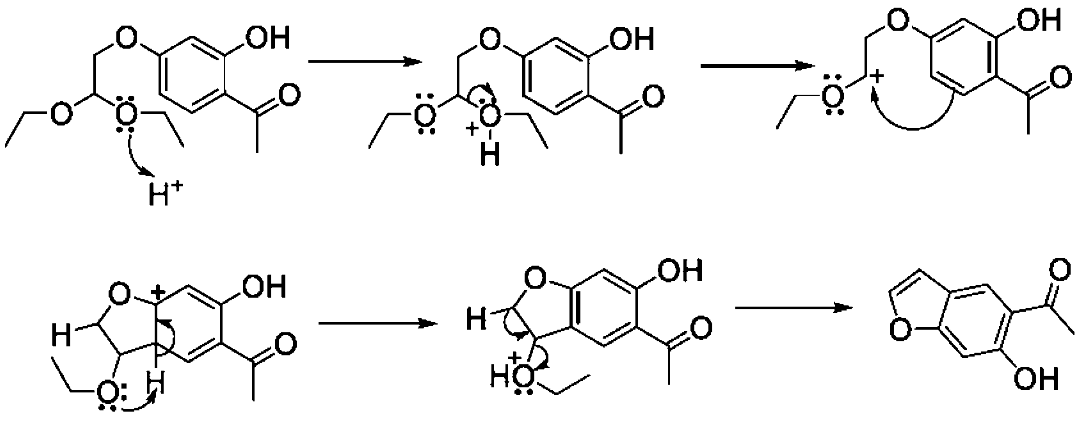
448



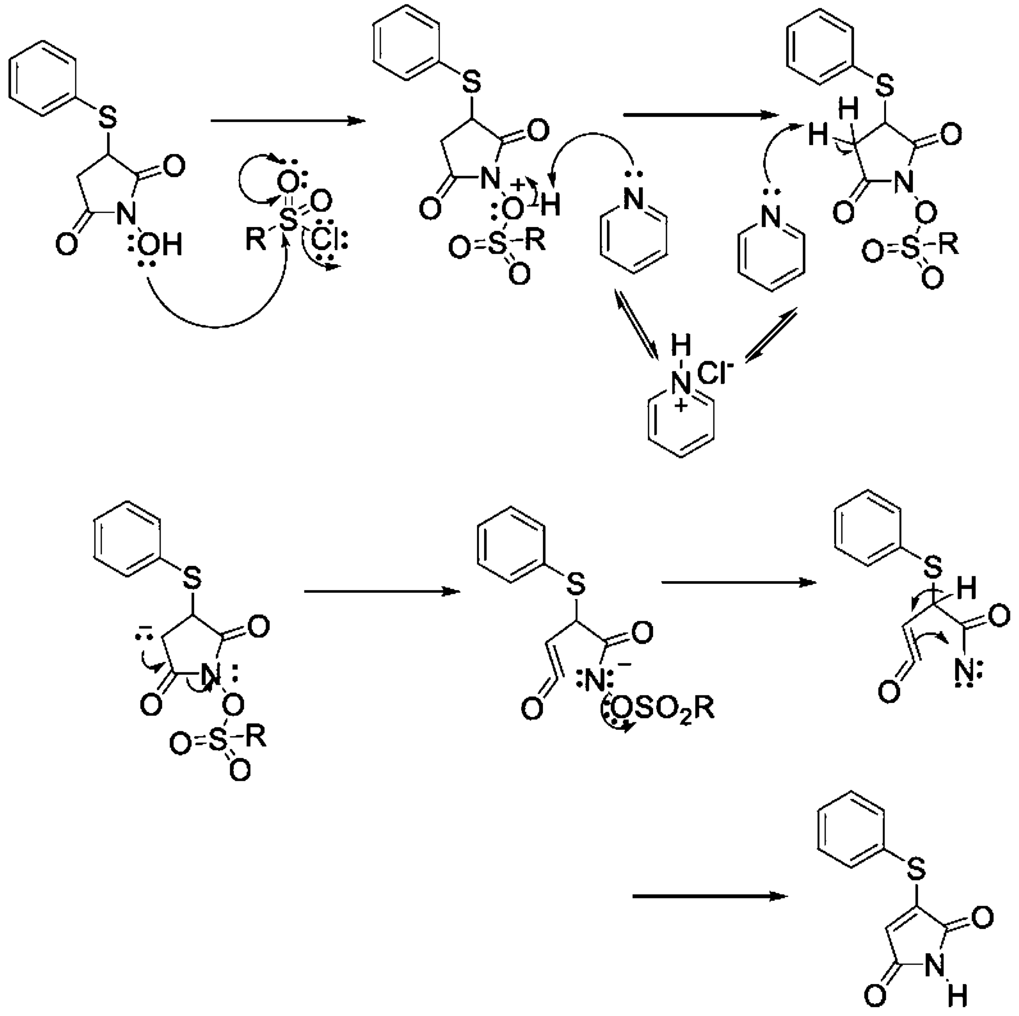
449



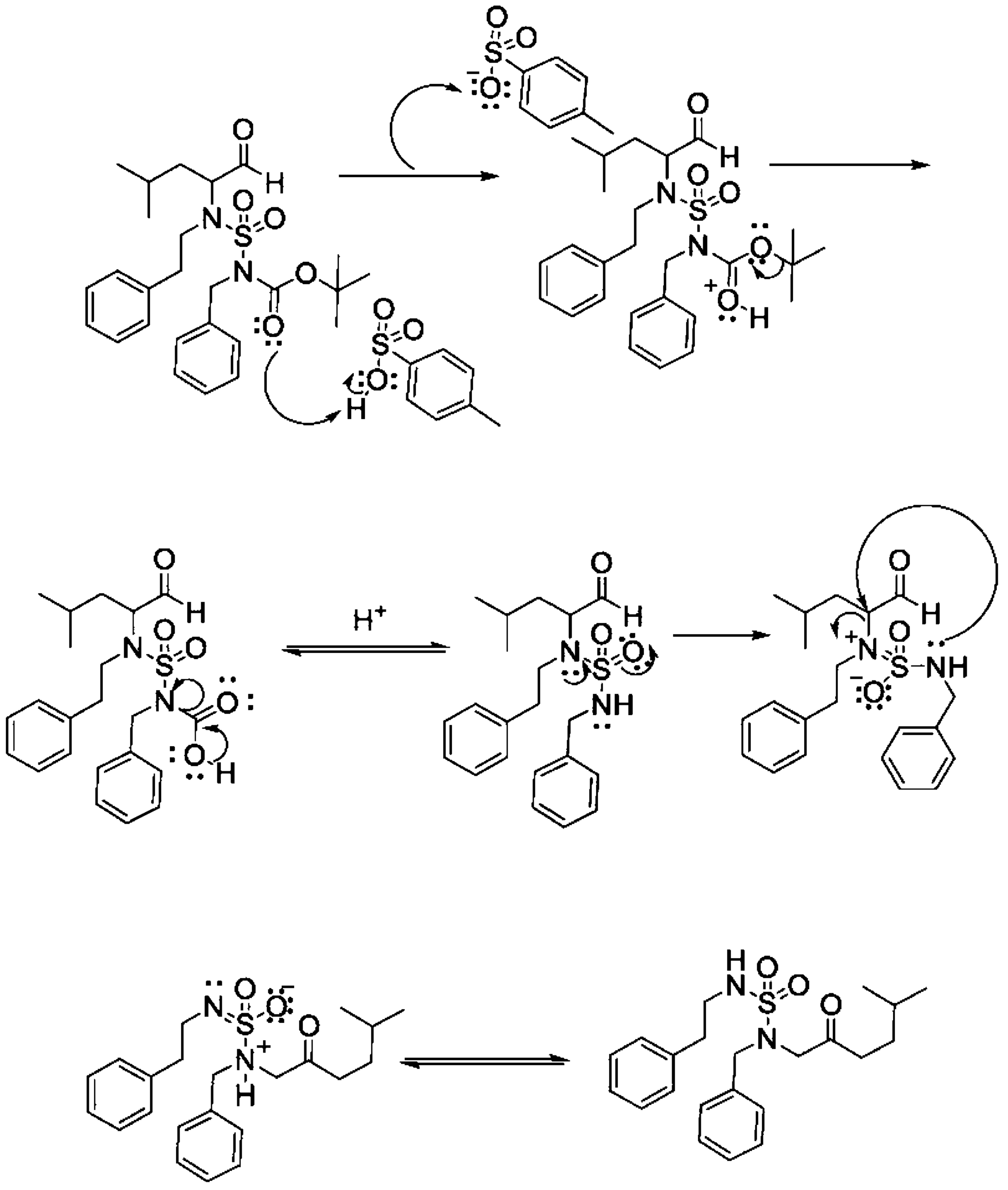
450



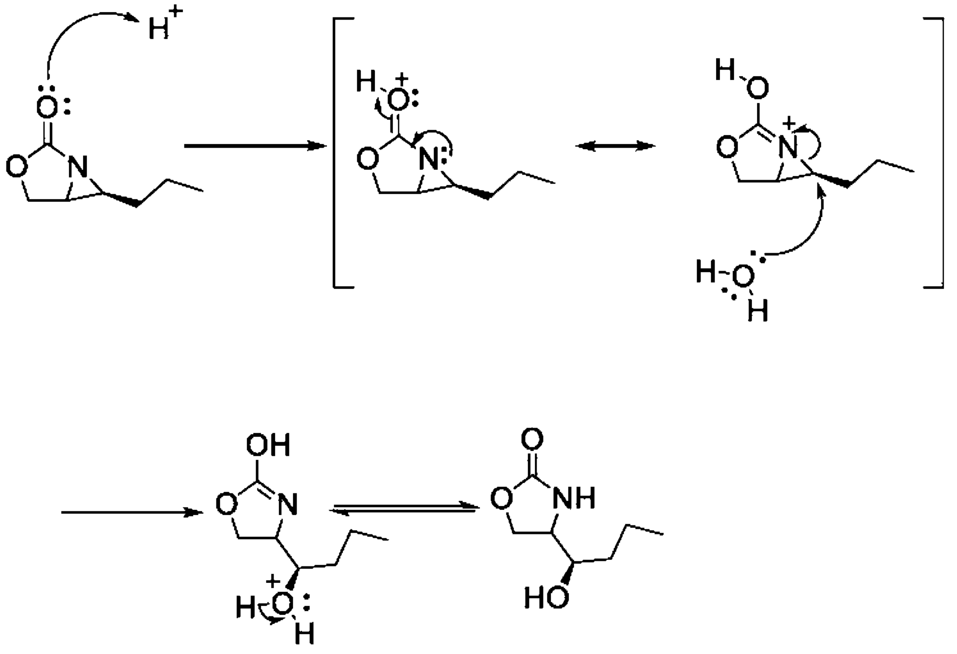
451



452

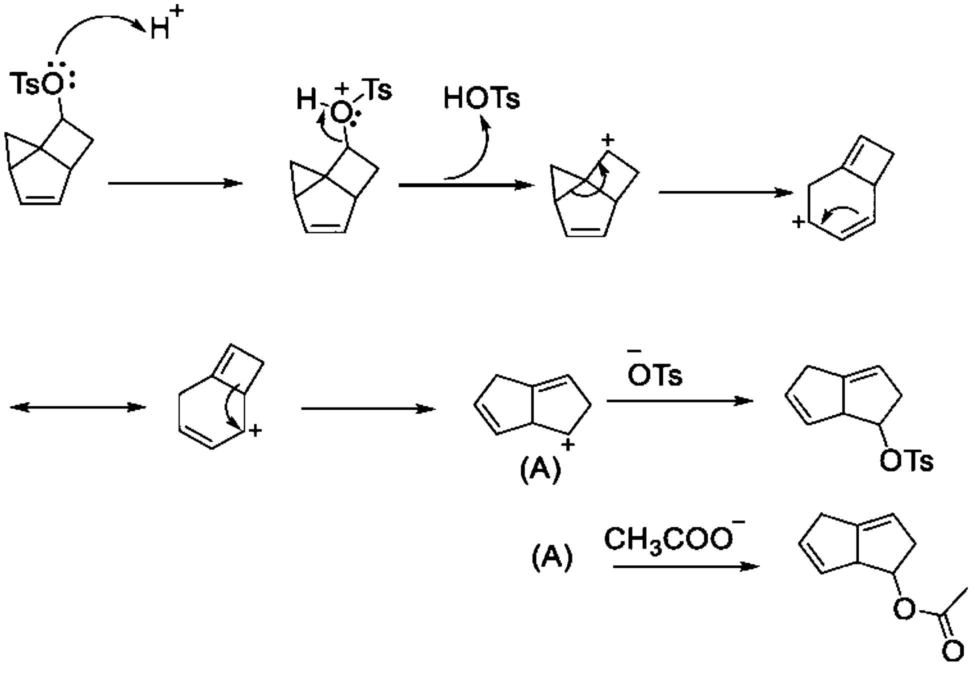


453



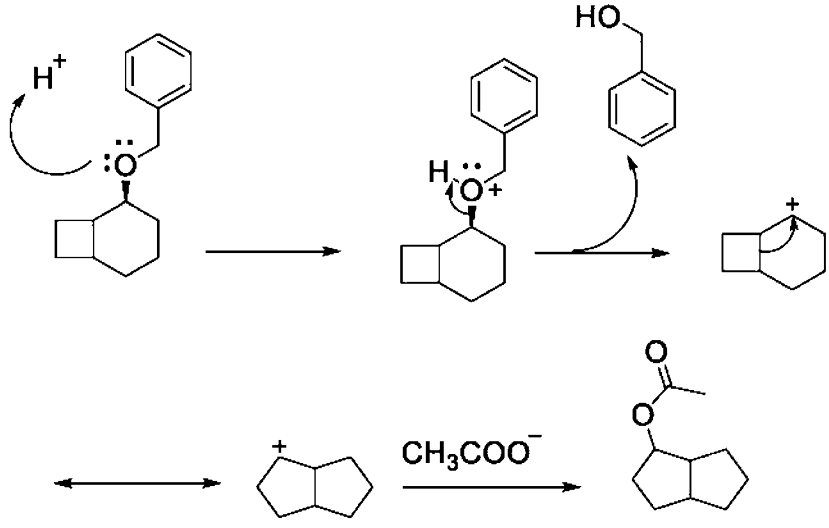
454

$$CH_3COOH \rightleftharpoons CH_3COO^- + H^+$$

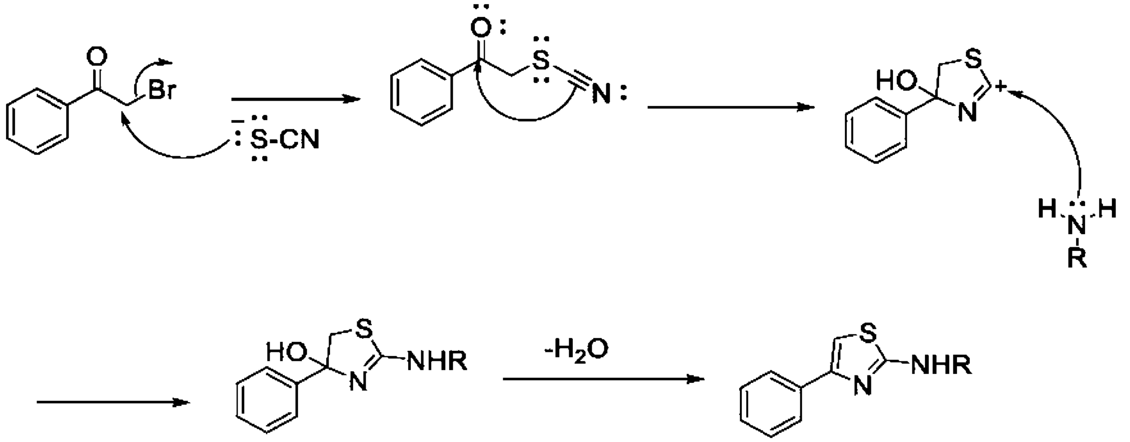


455

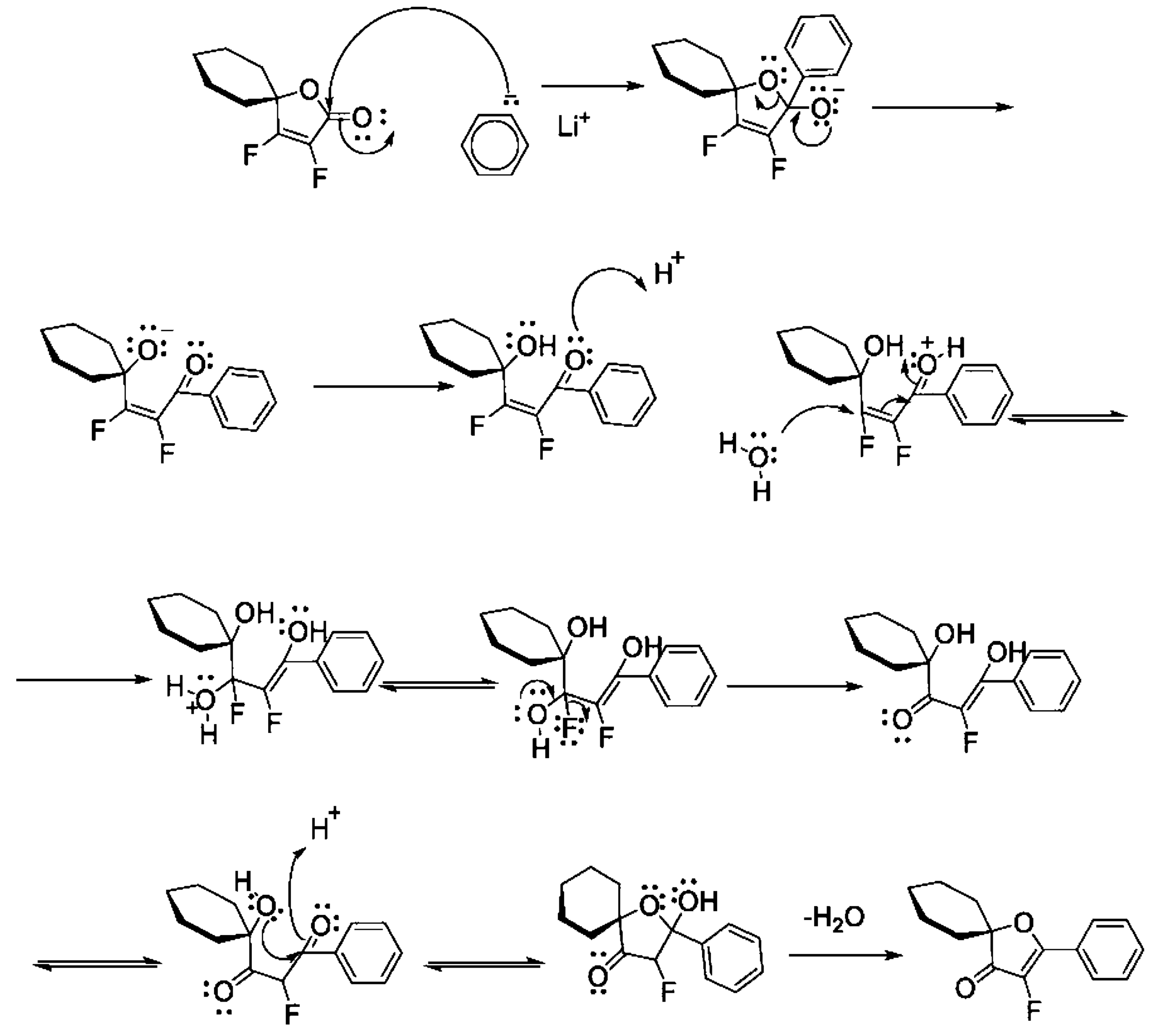
$$CH_3COOH \rightleftharpoons CH_3COO^- + H^+$$



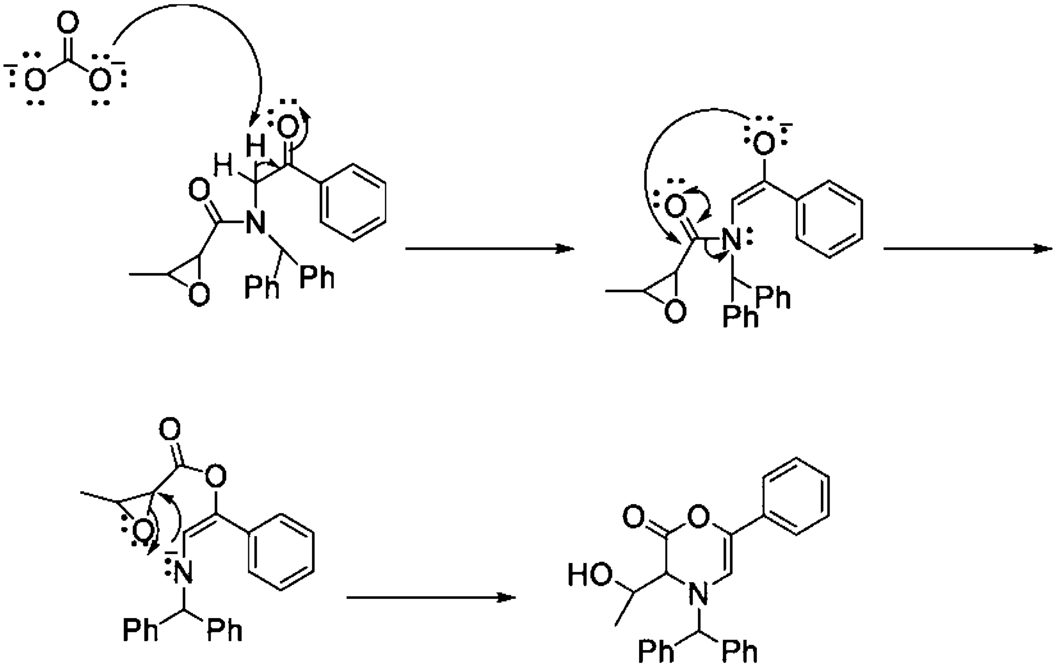
456



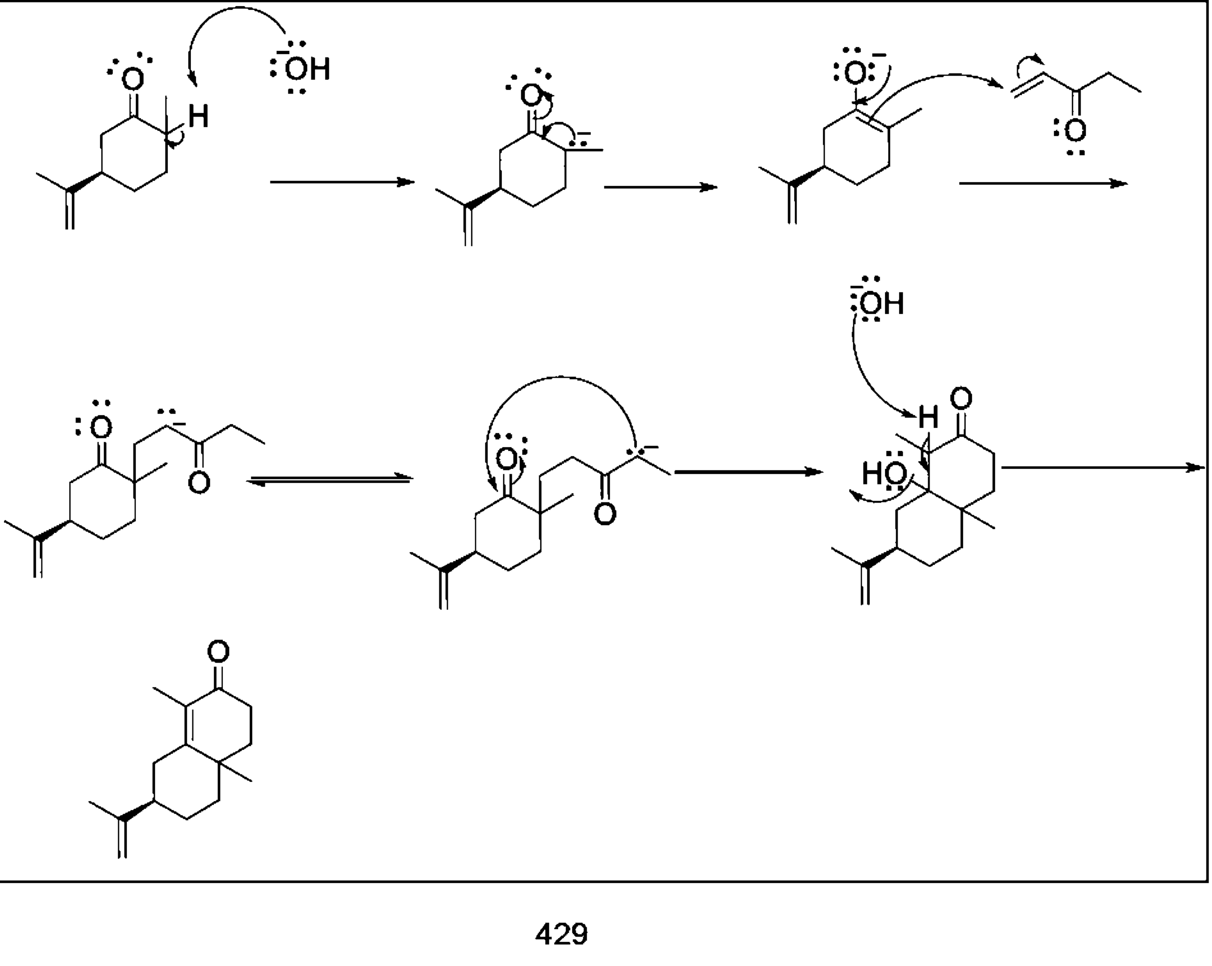
457



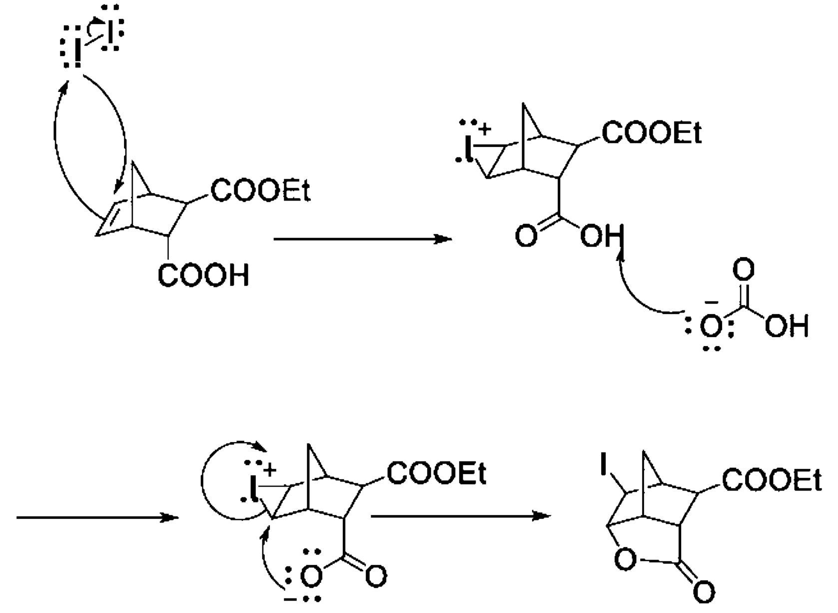
458



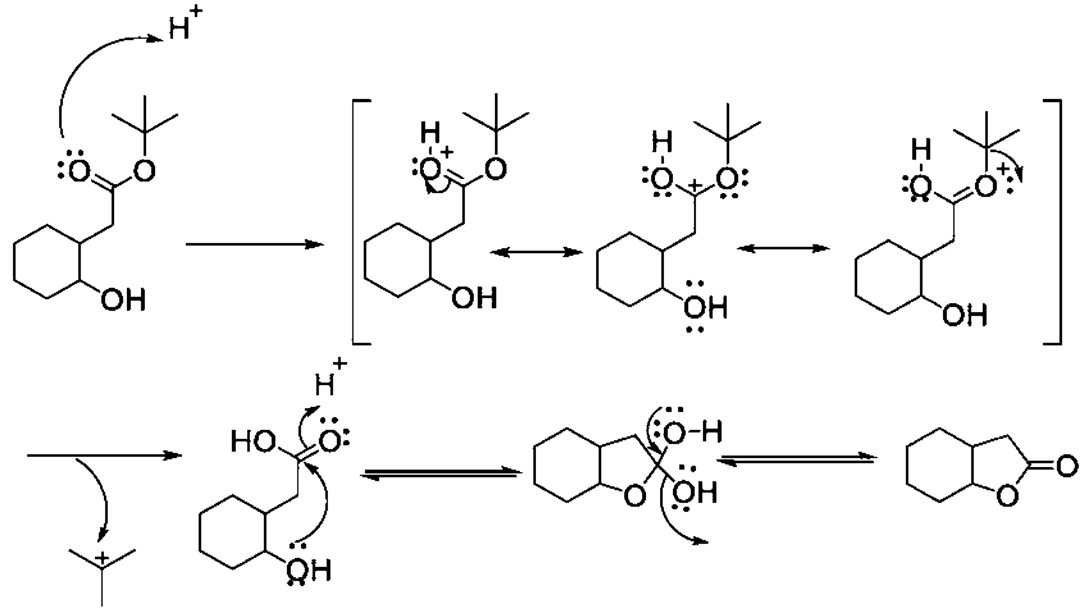
459



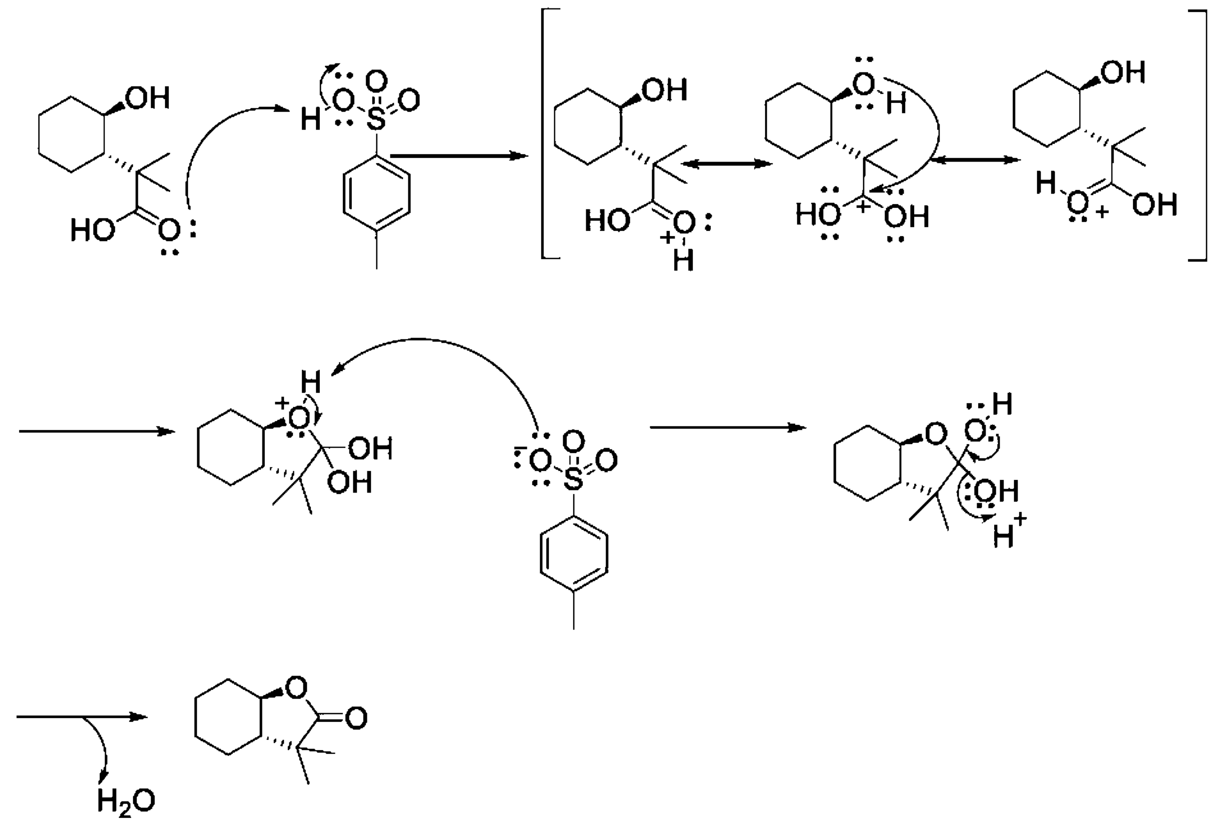
460


I
I
COOEt
COOH
I+
COOEt
O
OH
O
O–
OH
I+
COOEt
O–
O
I
COOEt
O
O

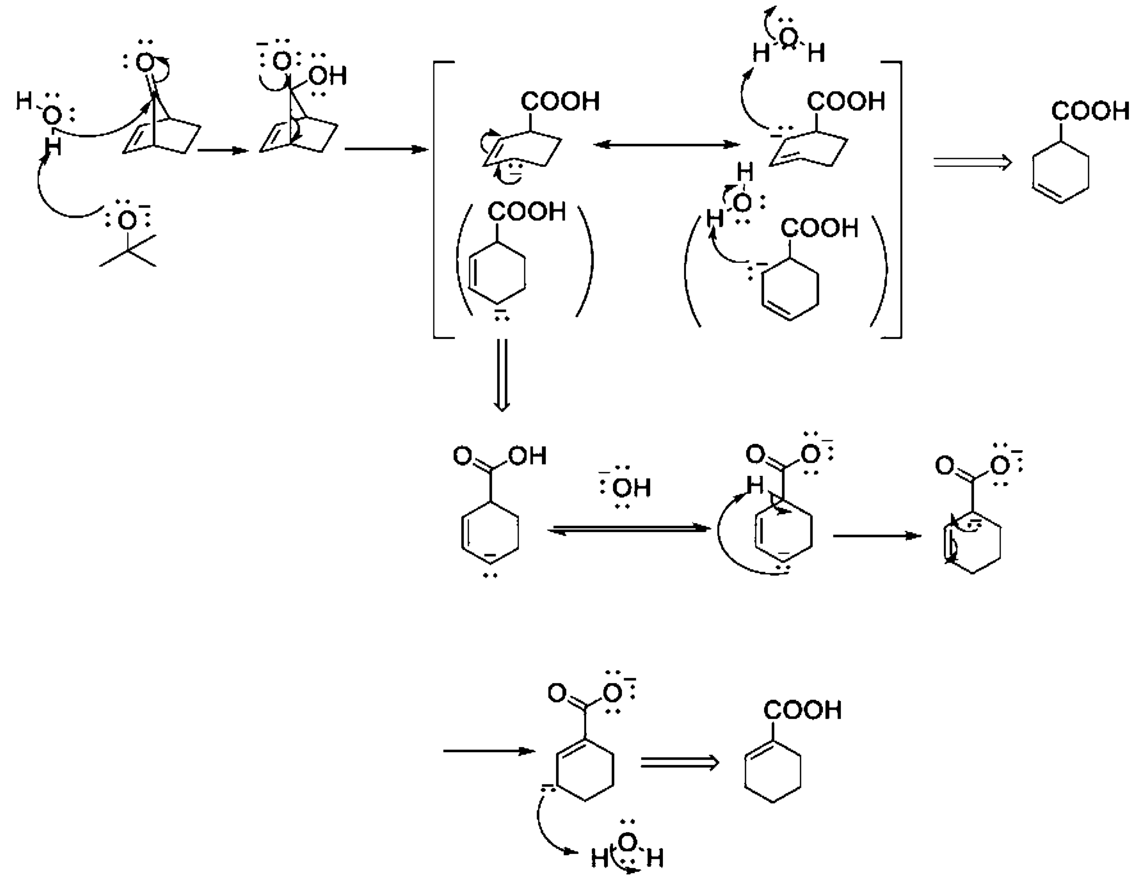
461


H+
O
O
OH
H
O+
O
OH
H
O
+
O
OH
H
O
O+
OH
+
HO
O
H+
OH
O
O-H
OH
O
O

462



463


H
O
H
O
O
OH
COOH
COOH
H
O
H
COOH
COOH
H
O
H
COOH
COOH
O
OH
OH
O
O
H
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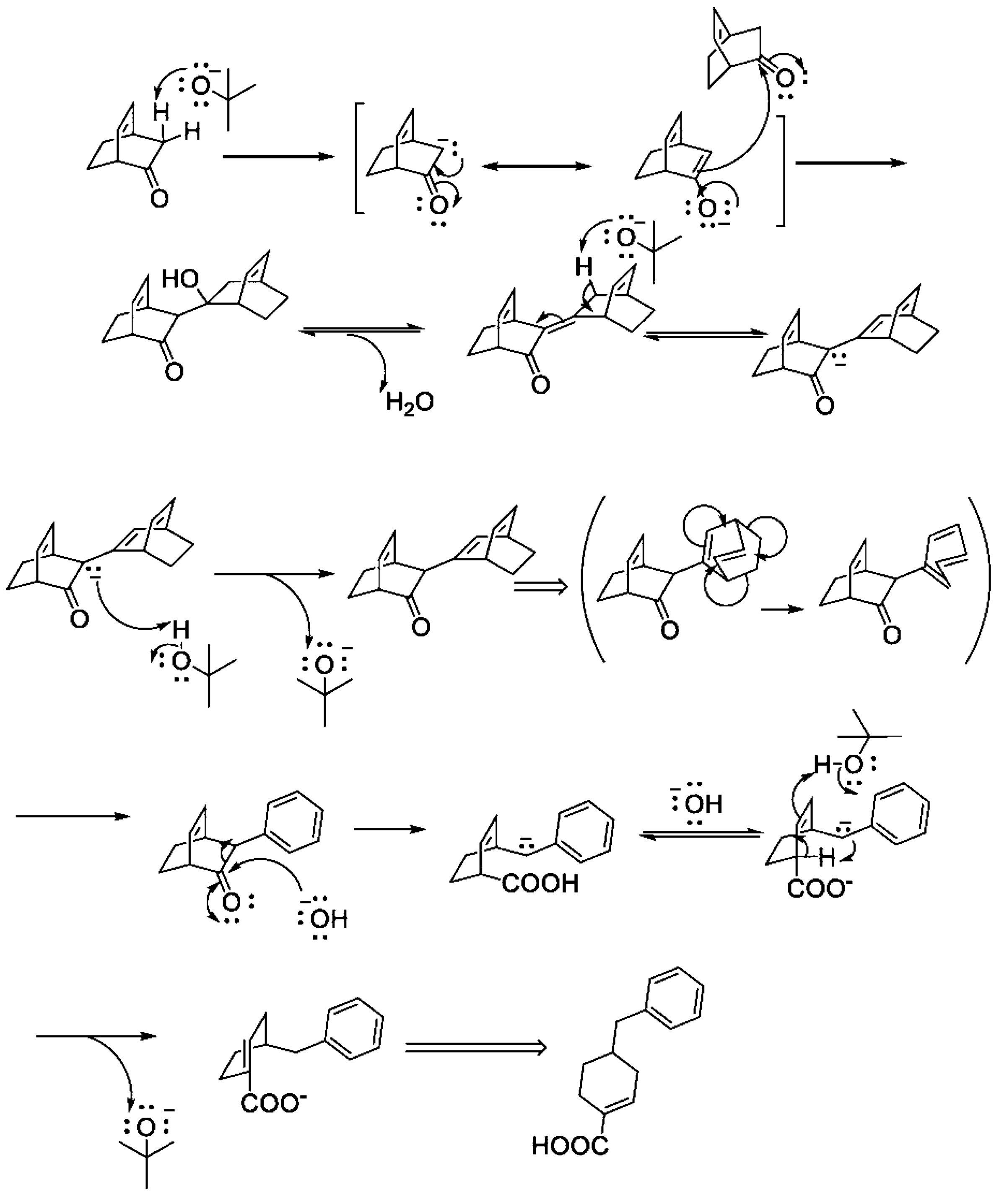
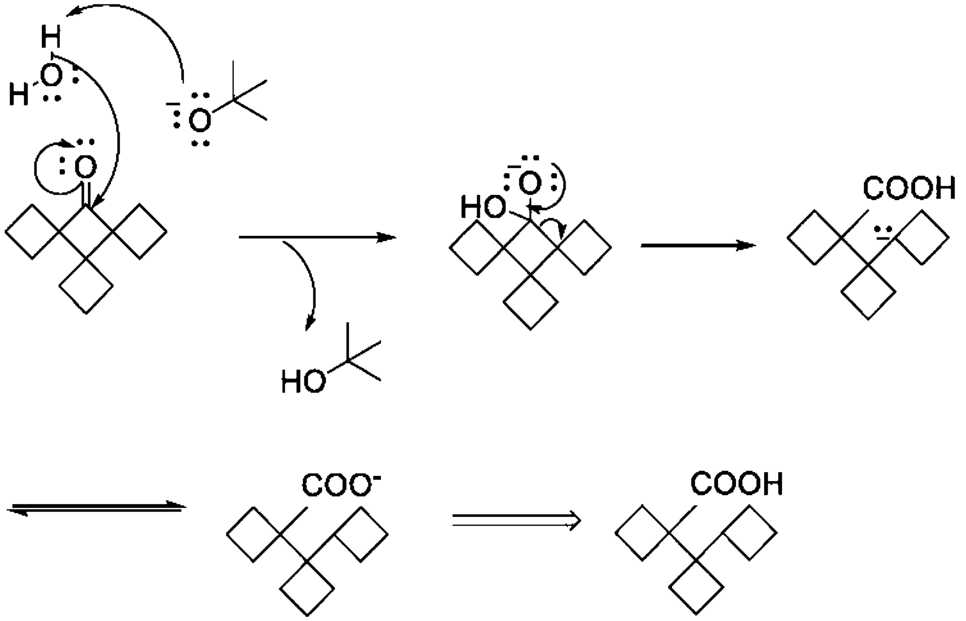
O
O
COOH
H
O
H

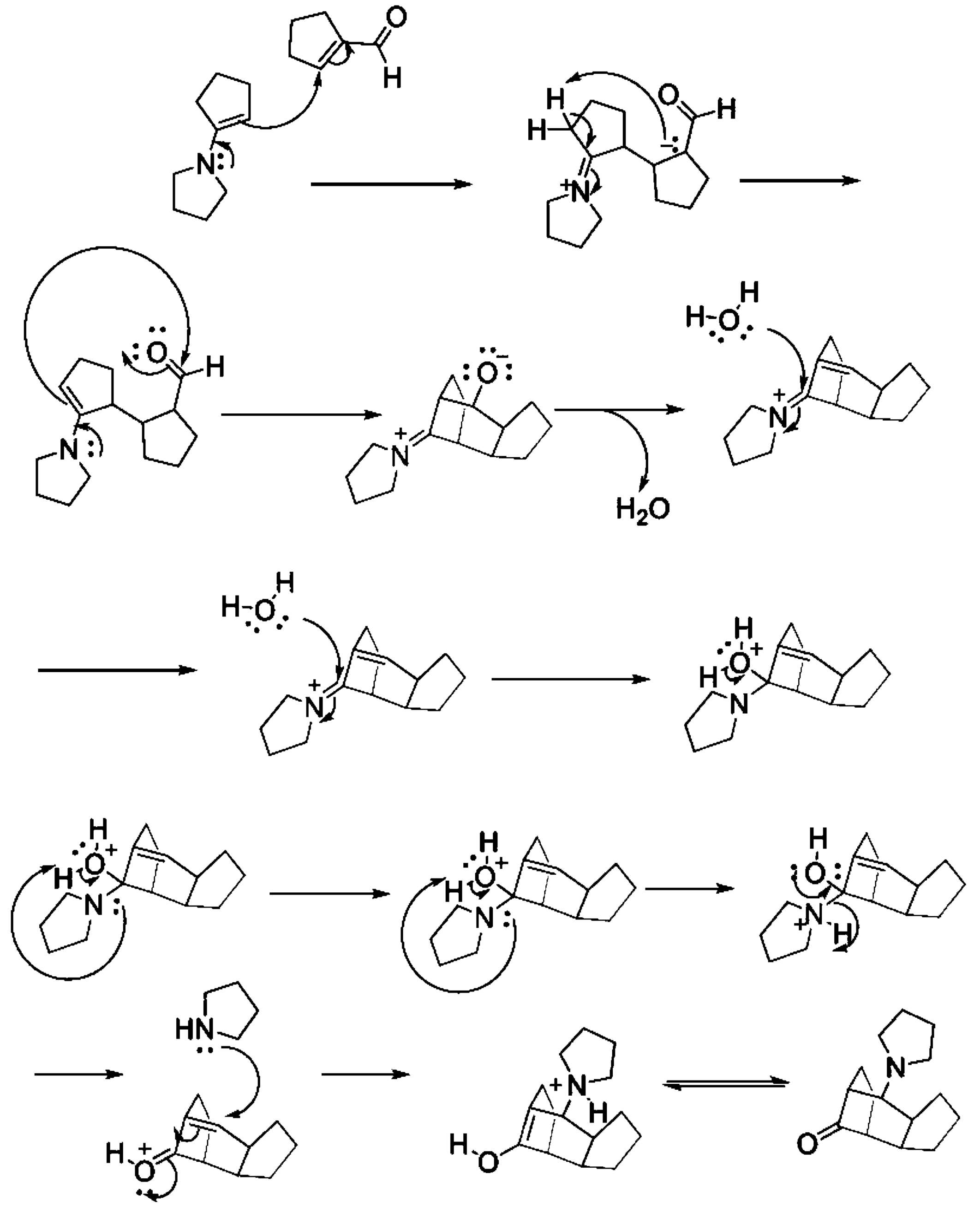
464



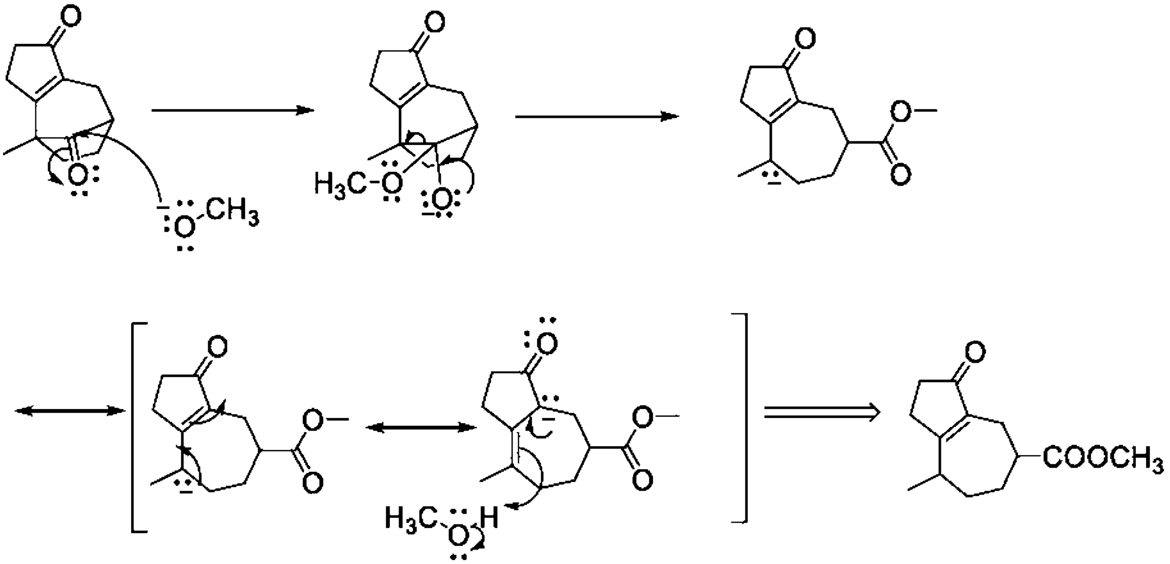
465



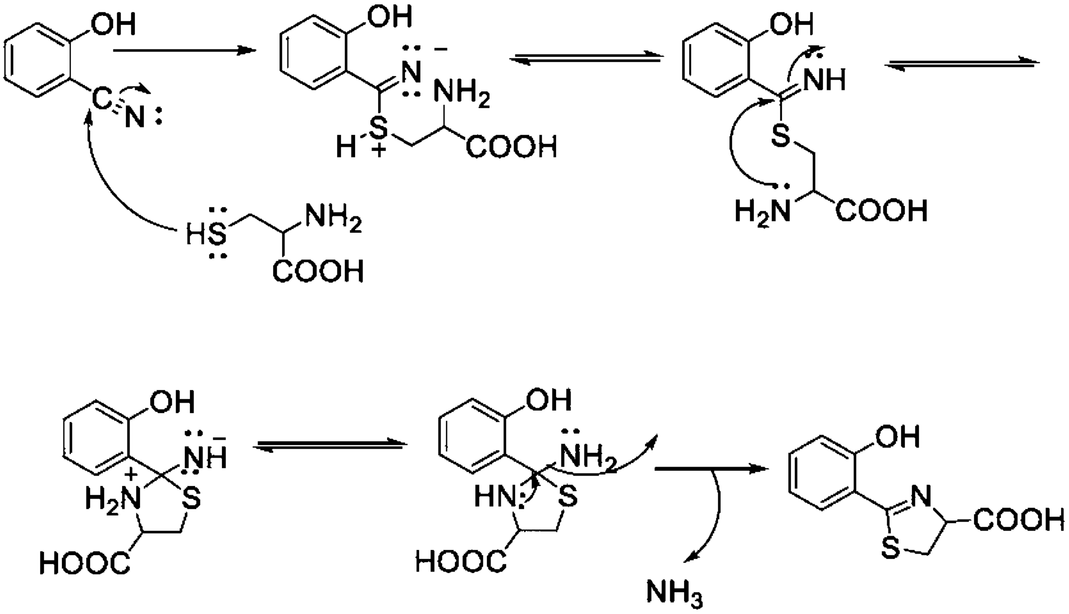
466



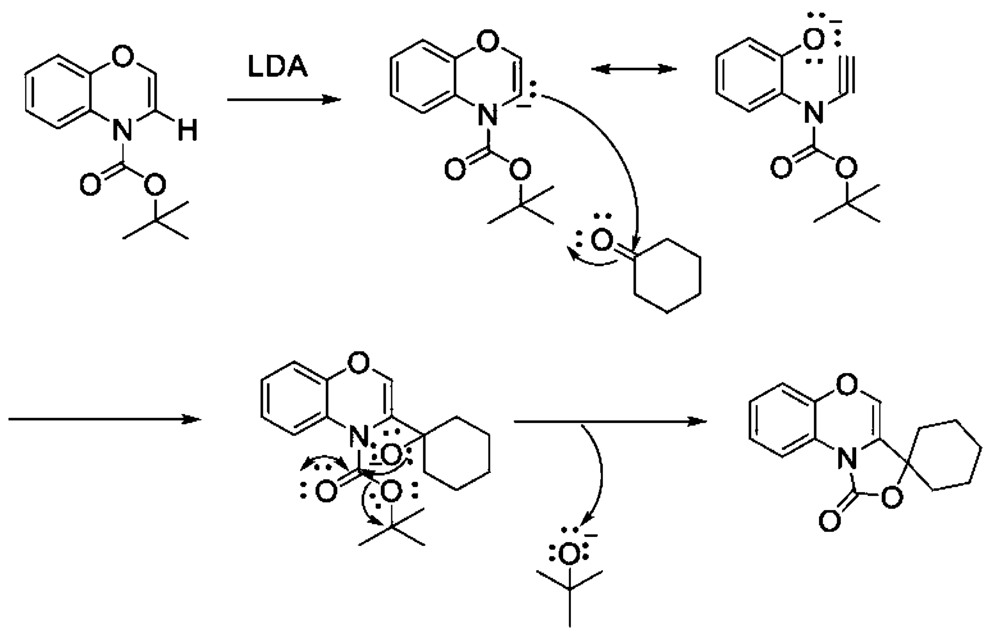
467



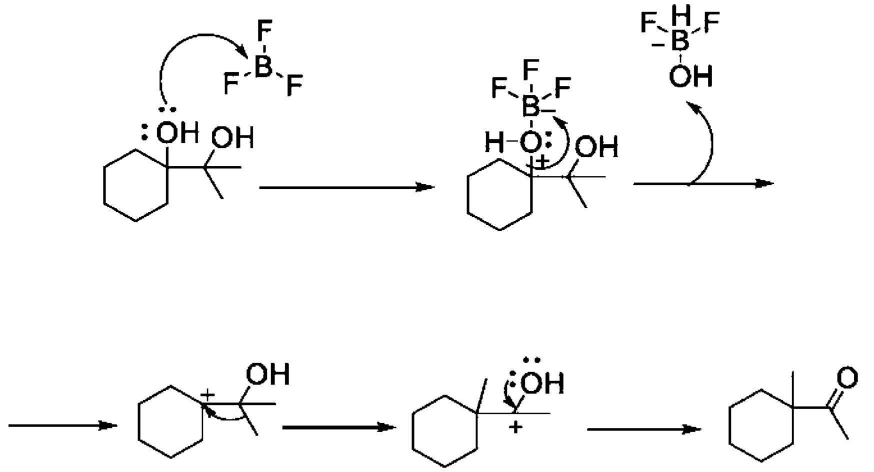
468



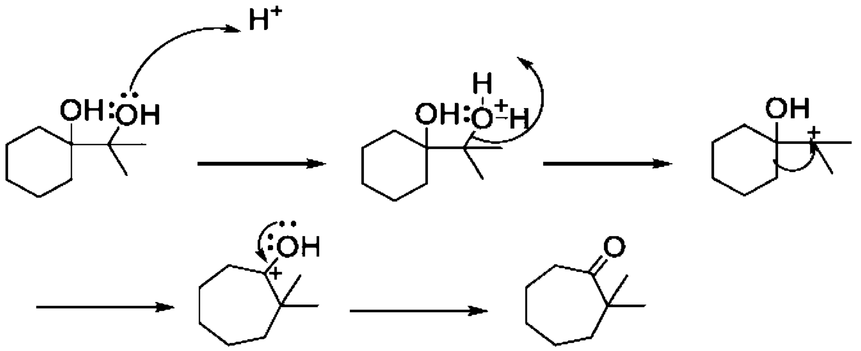
469



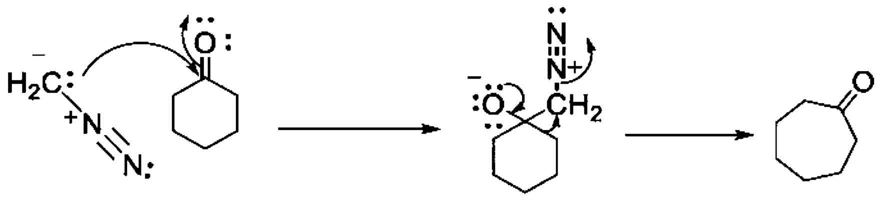
470



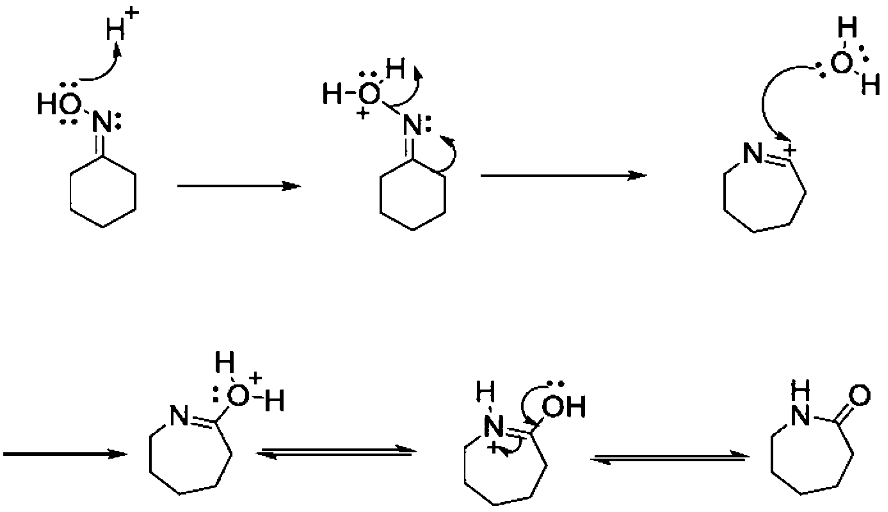
471



472

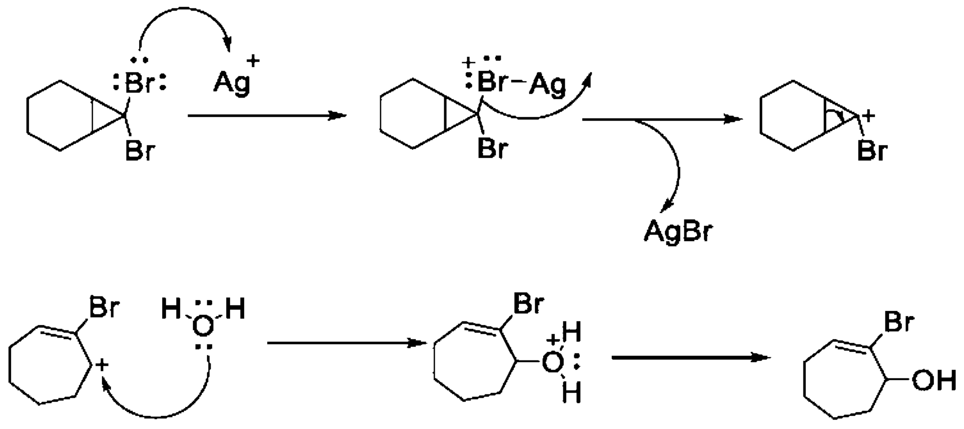


473

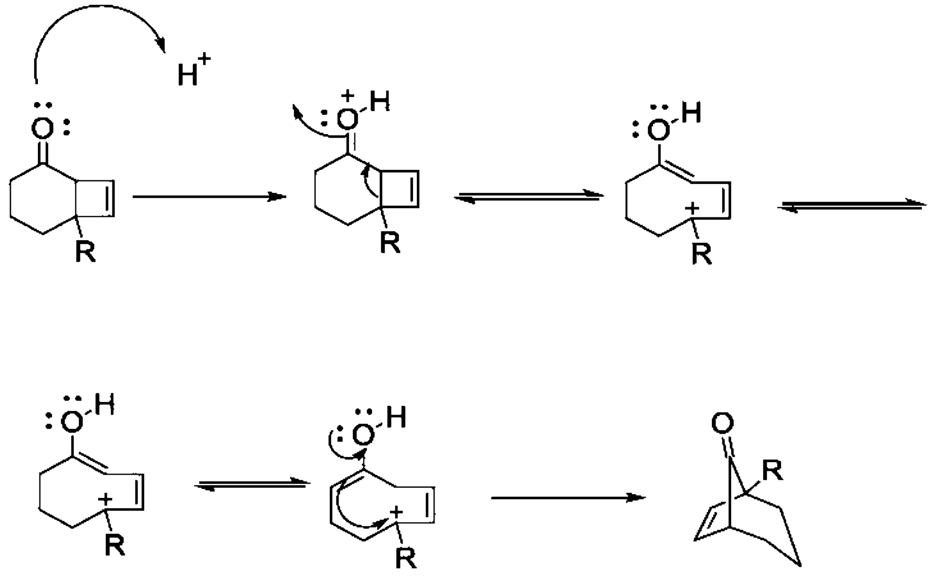


This is an example of the *Beckman rearrangement*

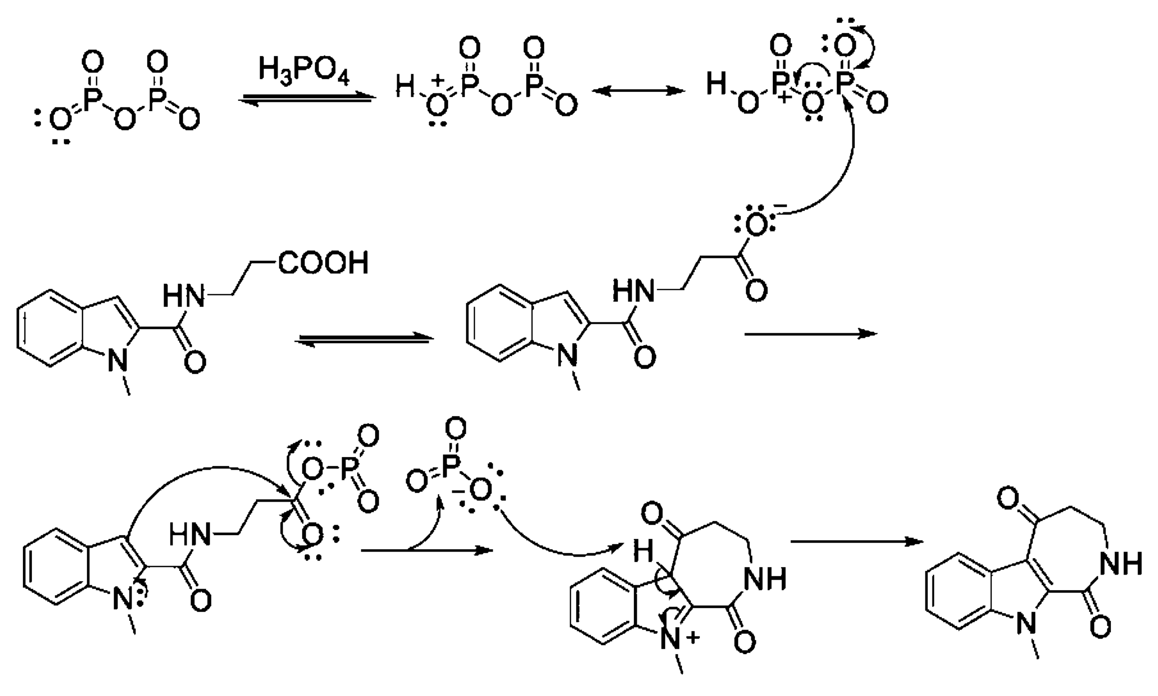
474



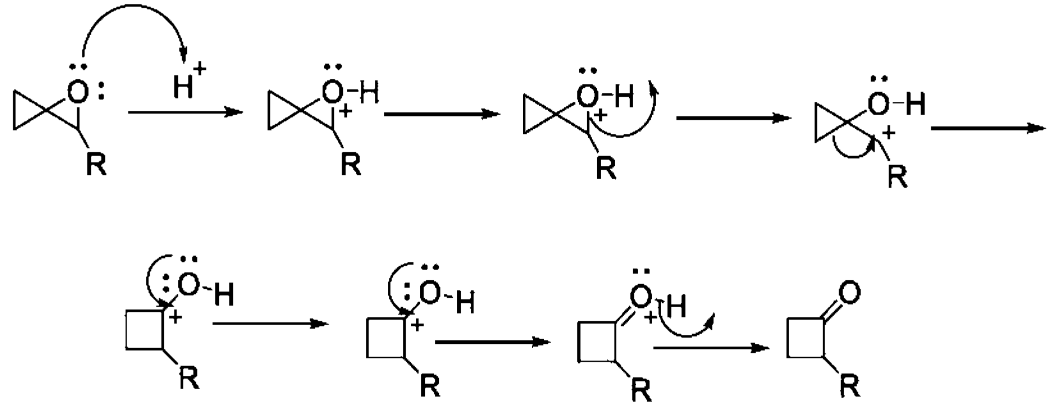
475



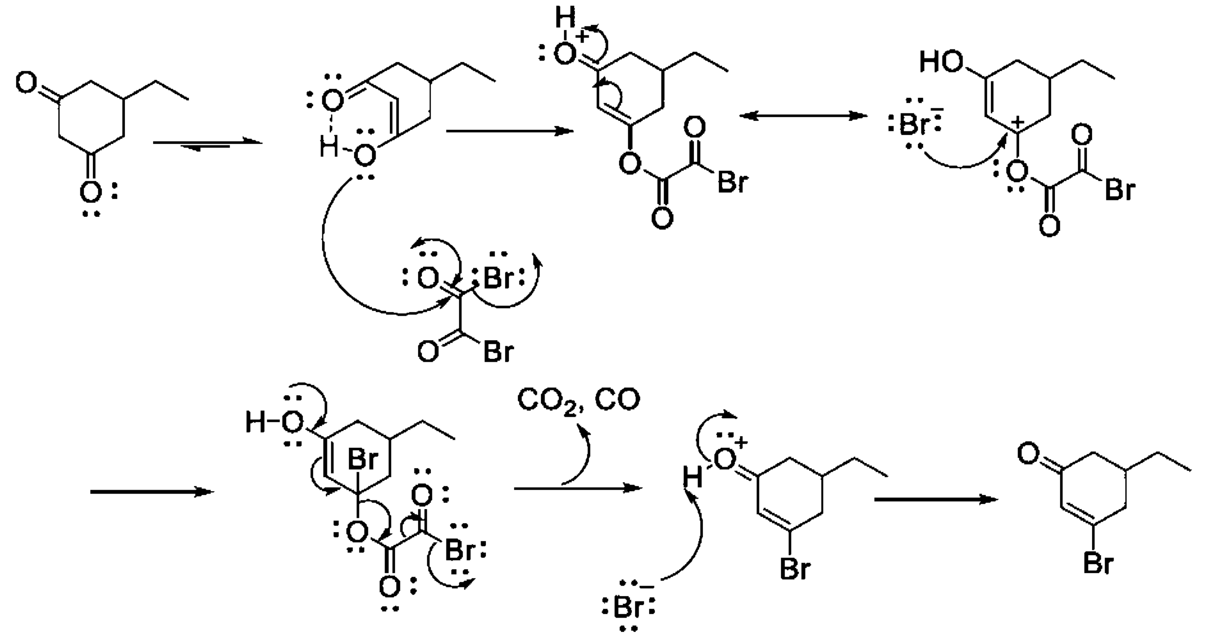
476



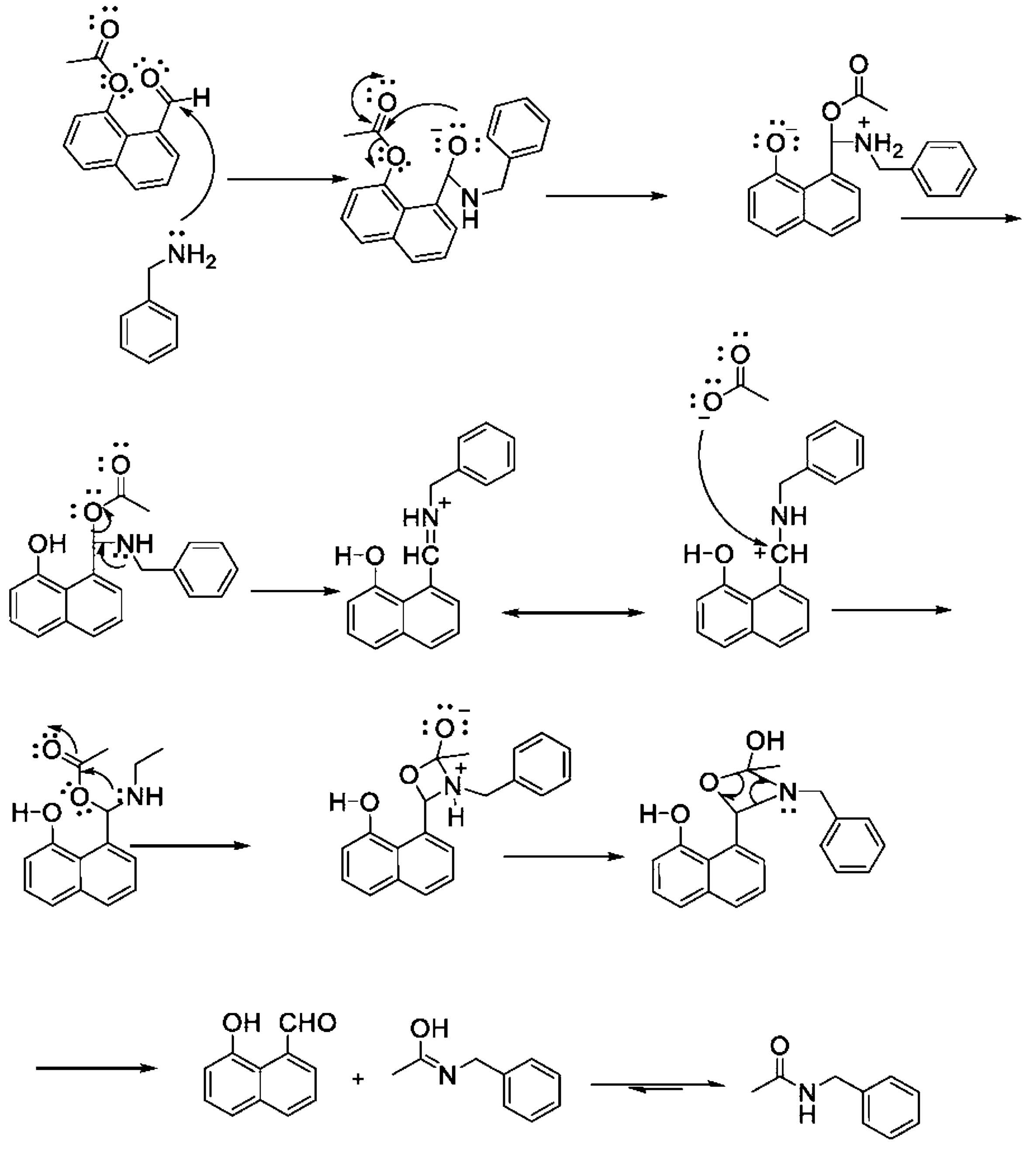
477



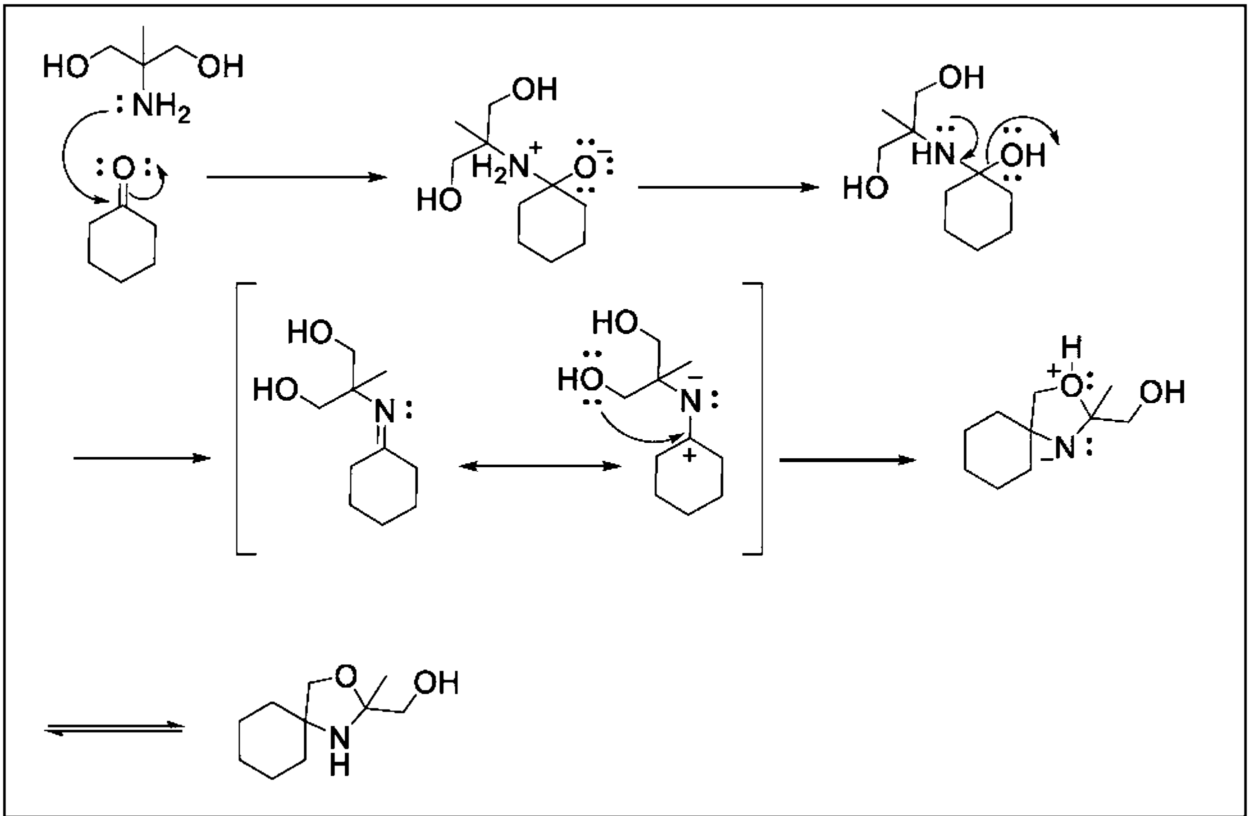
478



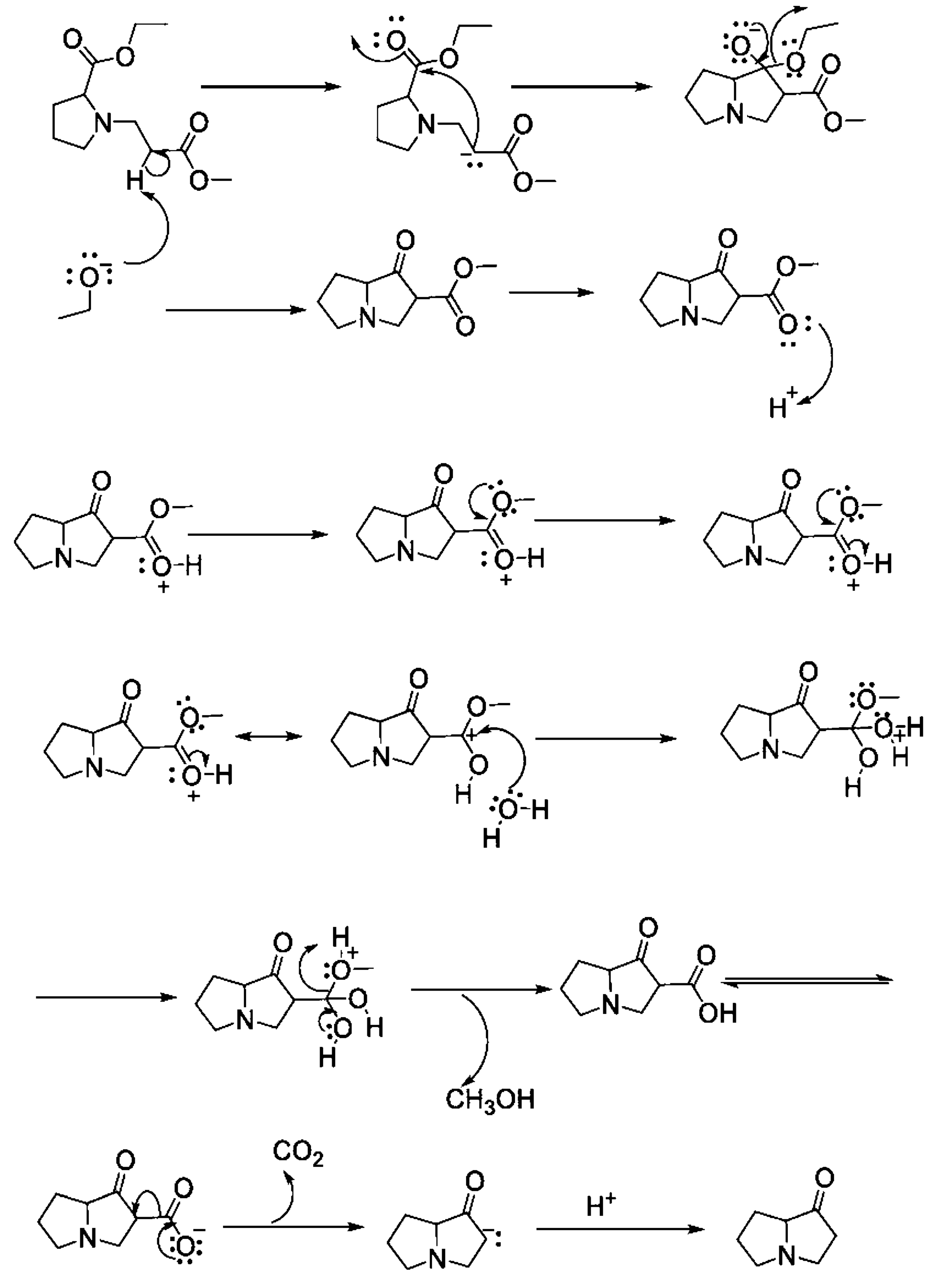
479



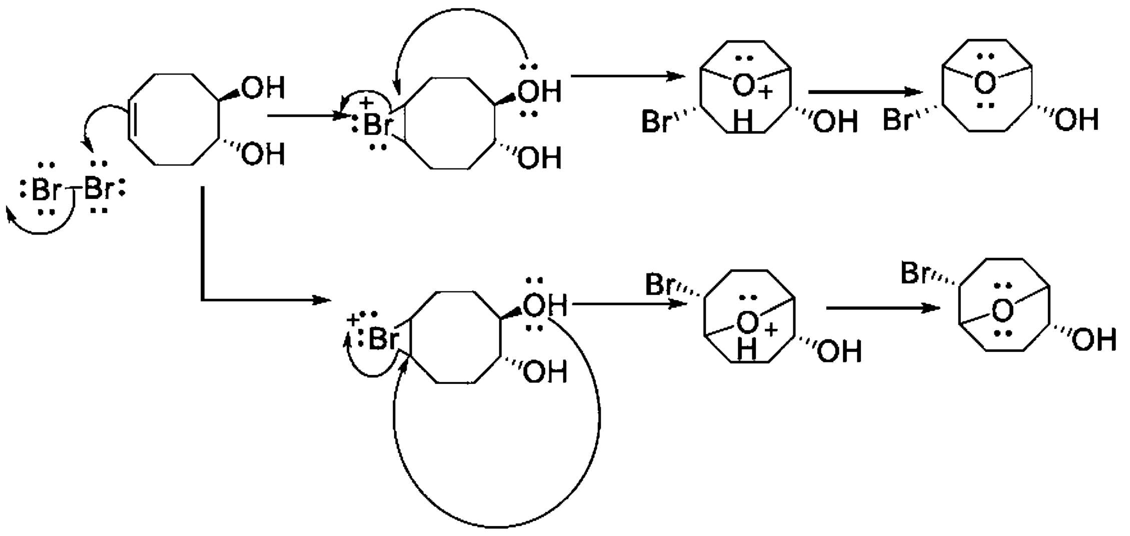
480



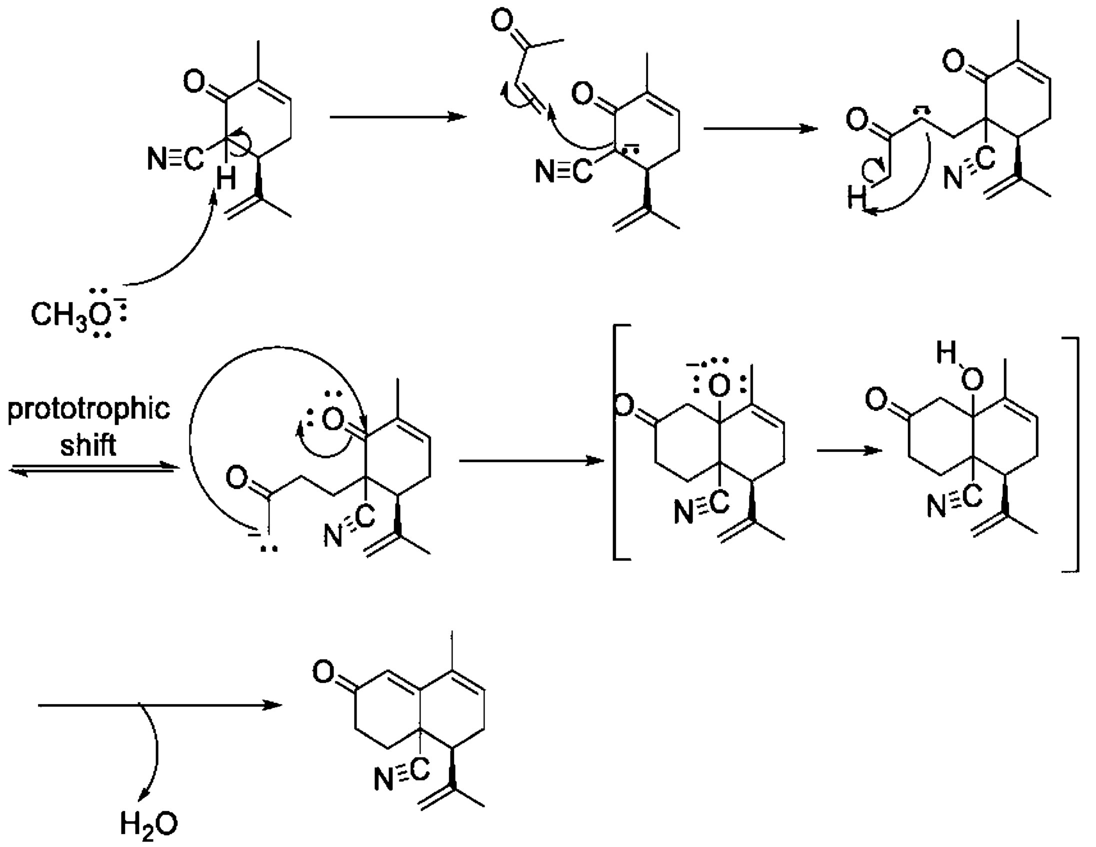
481



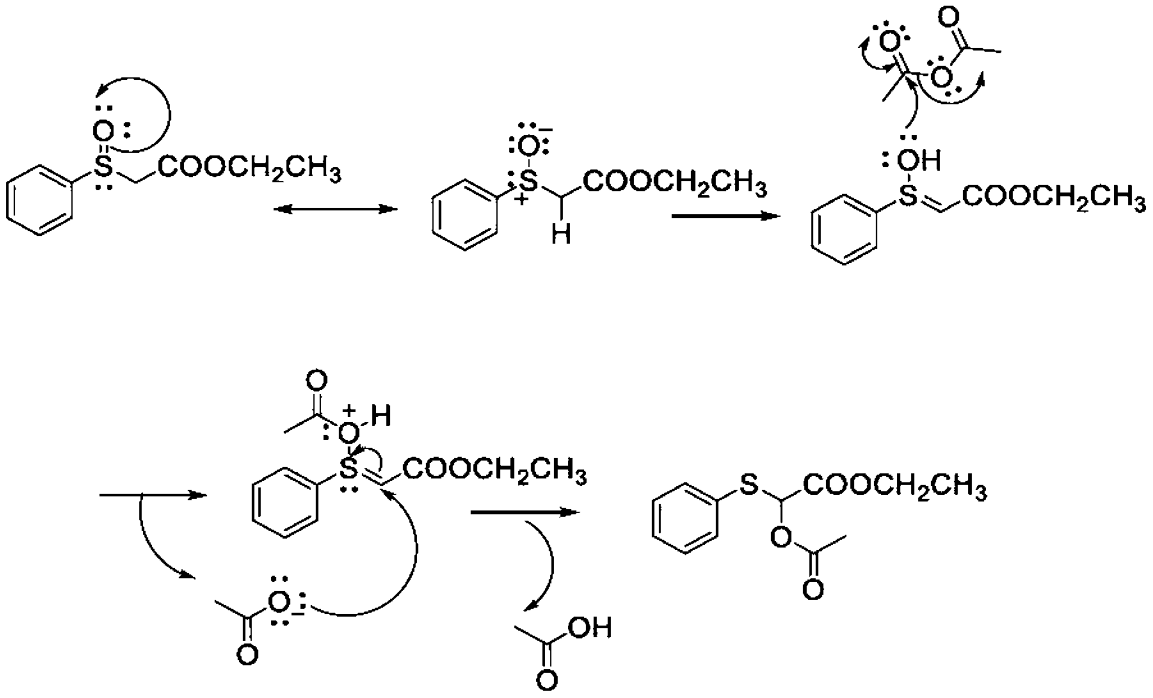
482



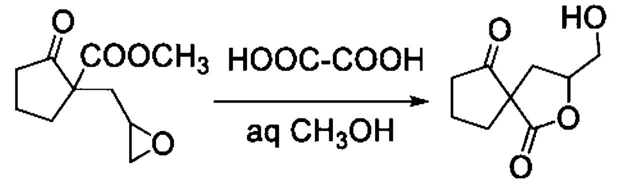
483

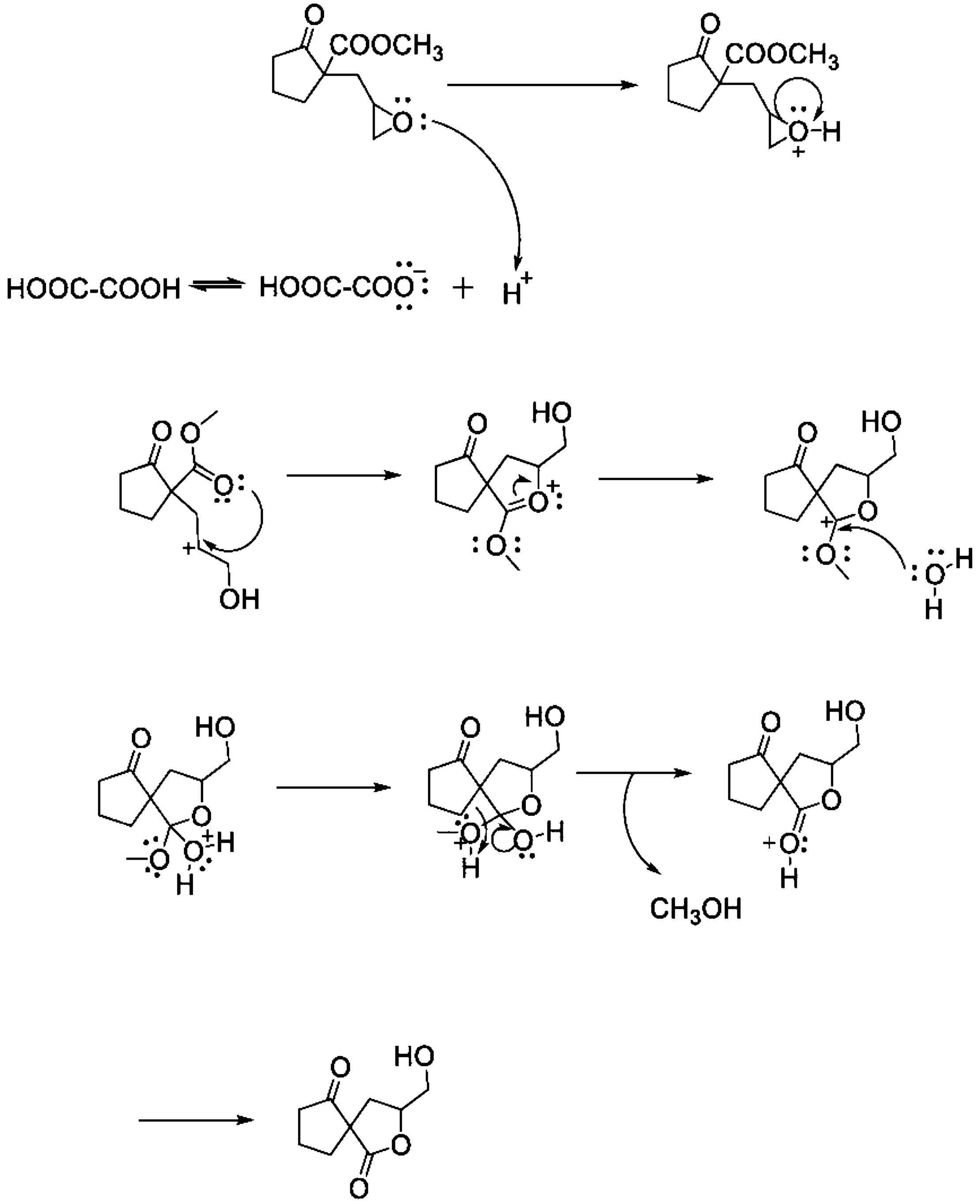


484

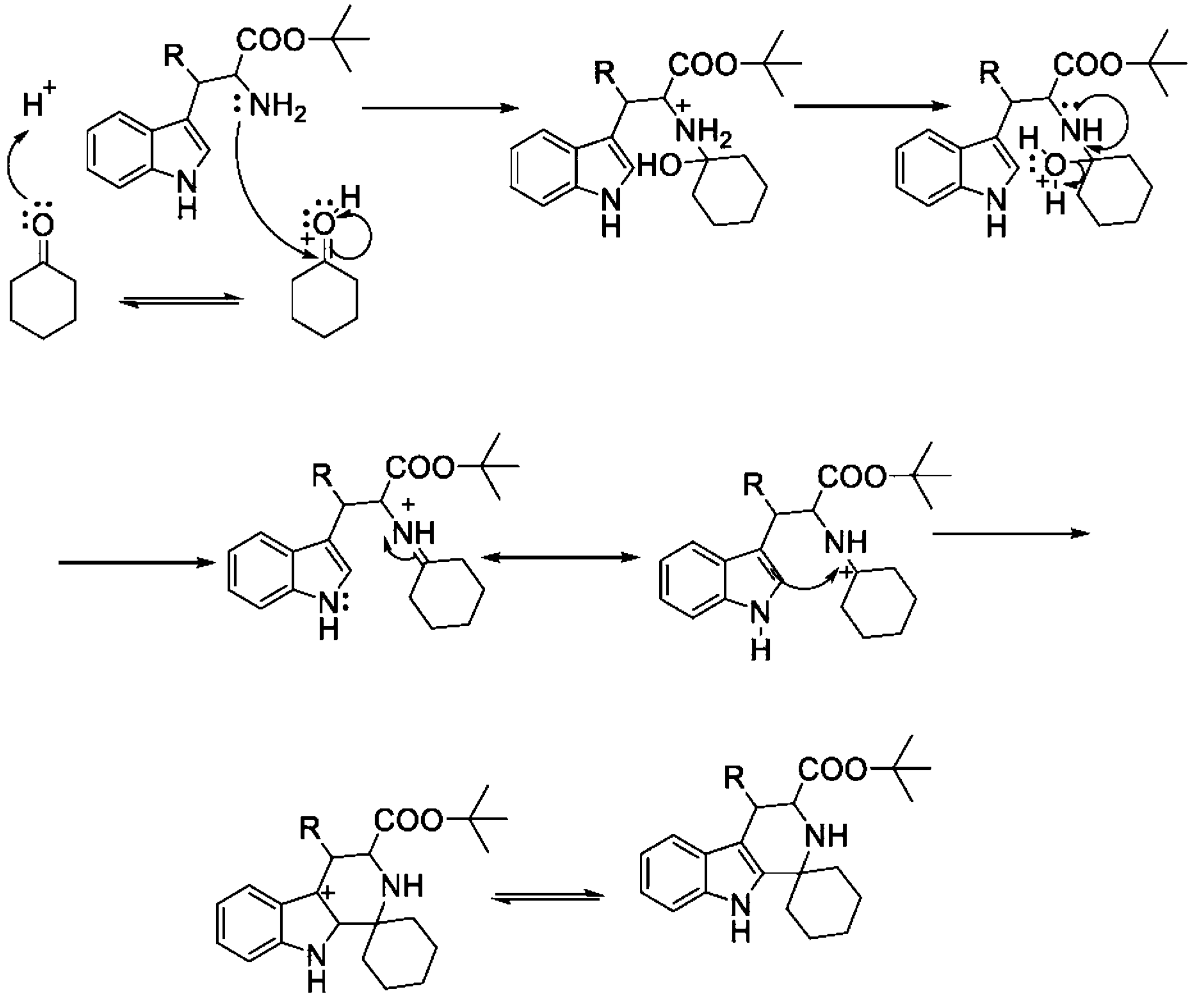


485

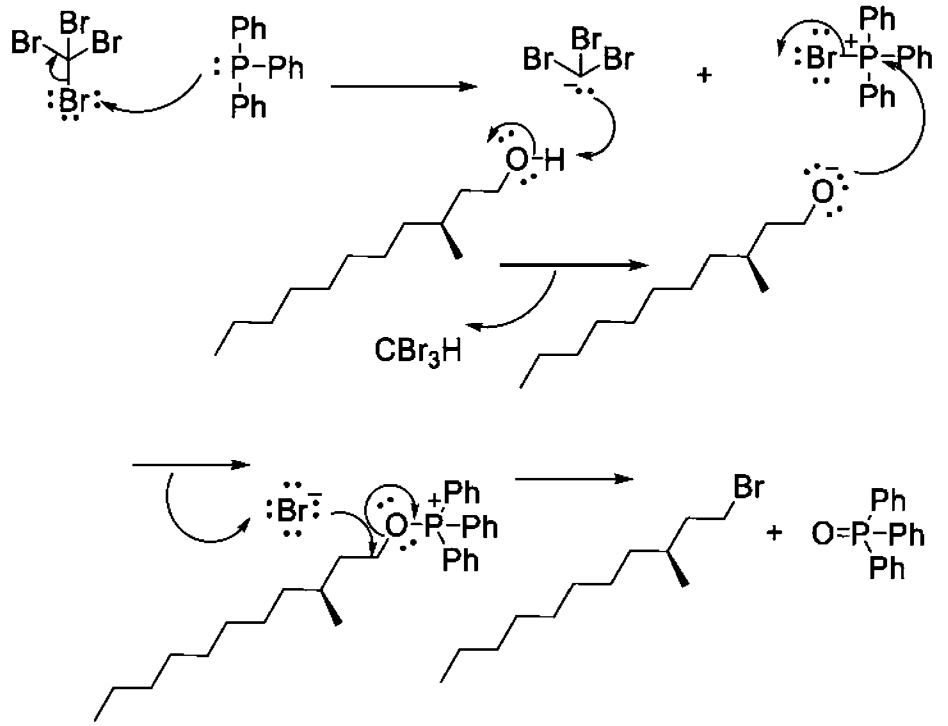

COOCH3
HOOC-COOH
aq CH3OH
HO


COOCH3
HOOC-COOH
HOOC-COO⁻
H⁺
HO
OH
CH3OH

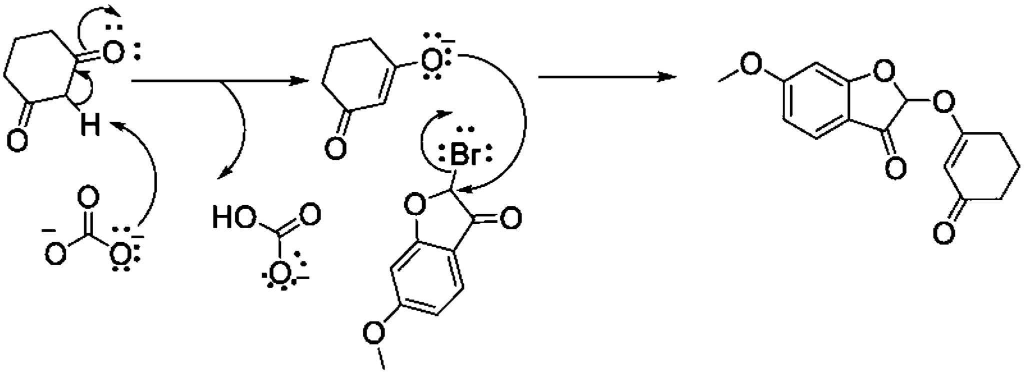
486



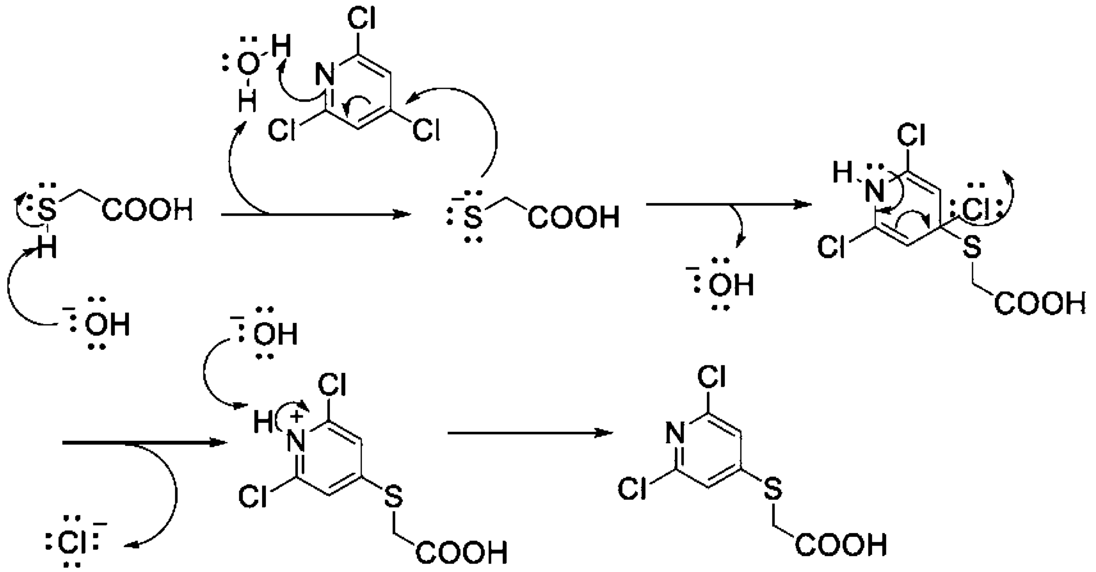
487


Br
Br
Br
Br
Ph
P–Ph
Ph
Br
Br
Br
+
Br
P
Ph
Ph
Ph
O–H
O
CBr3H
Br
O–P–Ph
Ph
Ph
Br
+
O=P–Ph
Ph
Ph

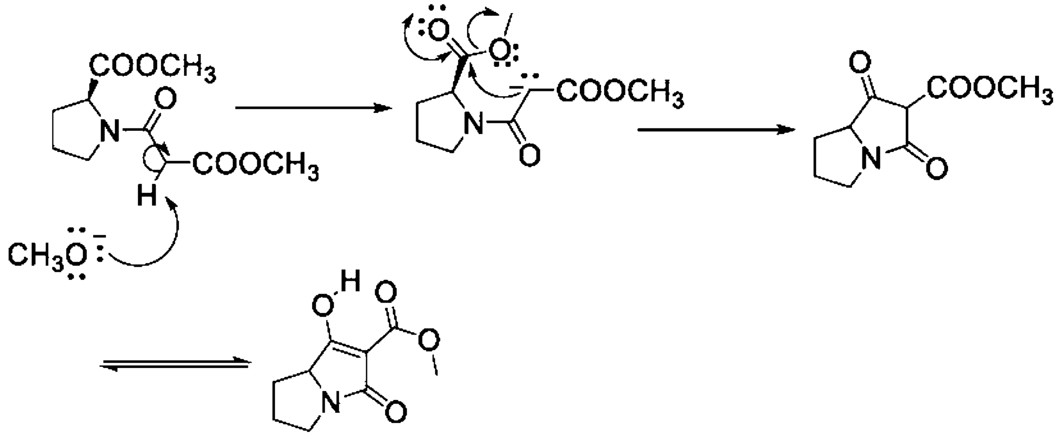
488


O
O
H
O
O
O
O
HO
O
O
O
O
Br
O
O
O
O
O
O
O
O
O

489

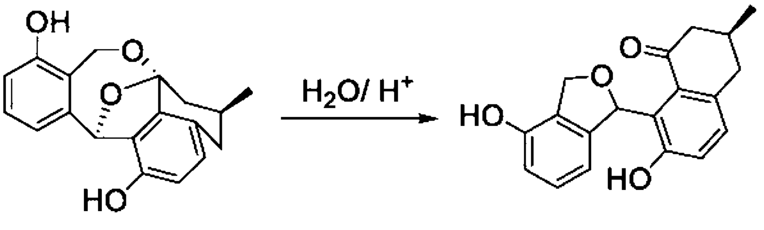
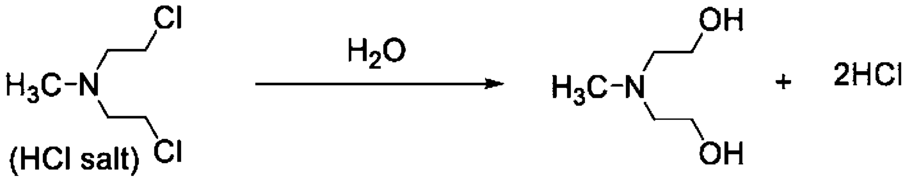


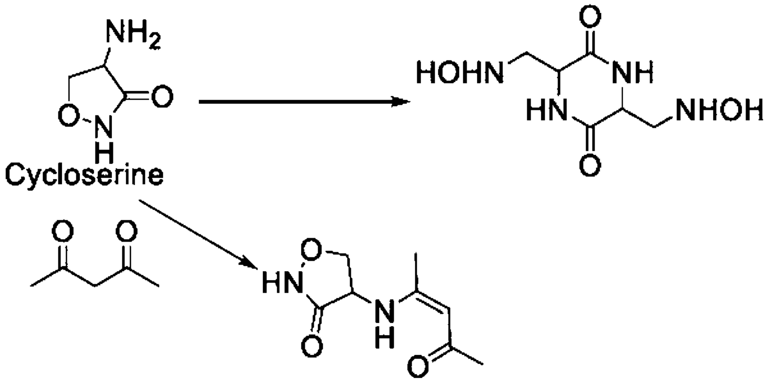
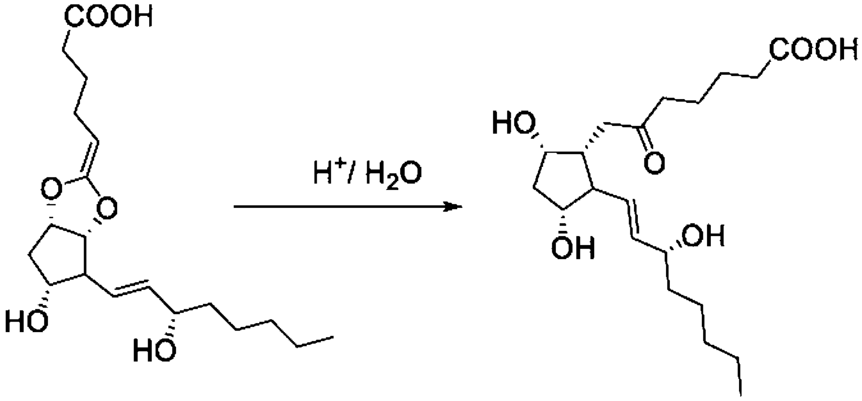
490

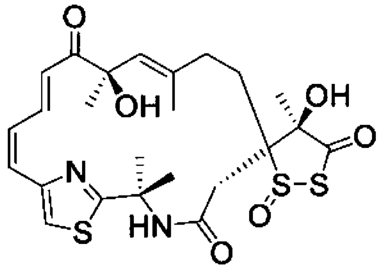
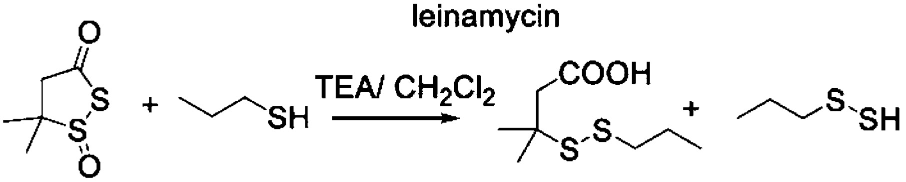
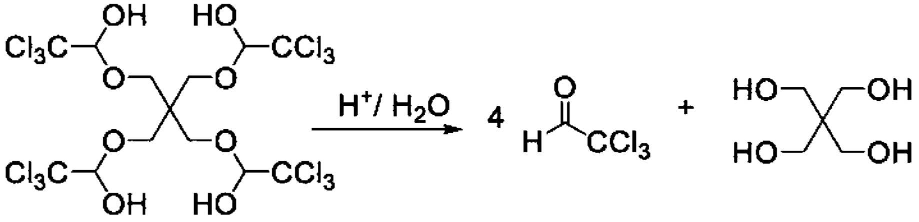


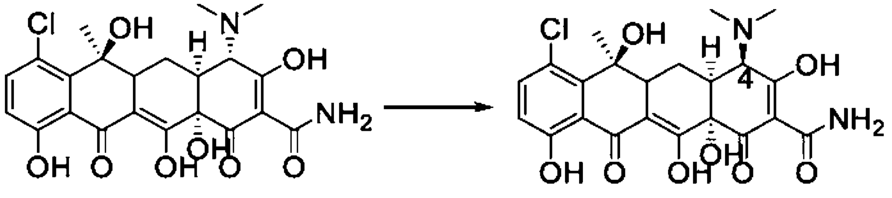
PART C

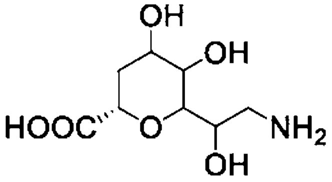
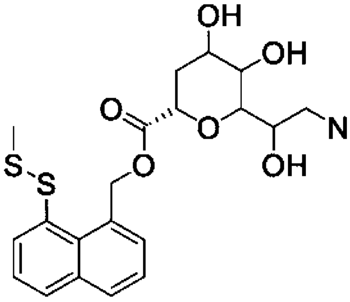
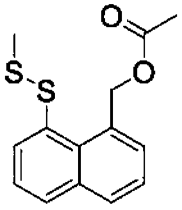
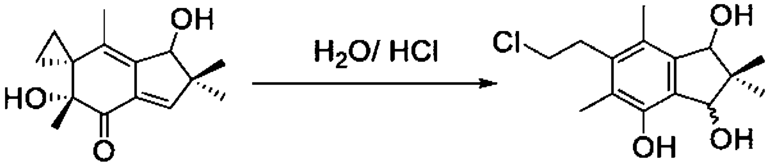
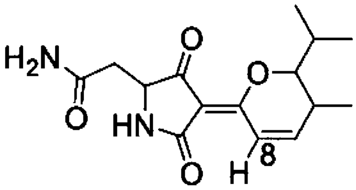
Questions 491-500

491	When the antibiotic emycin F is treated with acid, it rearranges to emycin E. Write a mechanism for this transformation.  emycin F emycin E
492	Mechlorethamine hydrochloride (Mustargen) is a drug used in the treatment of Hodgkins disease and lymphosarcoma. Mustargen is administered intravenously, and its action lasts for only a few minutes. Its short duration of action is due to its rapid non-enzymatic hydrolysis. Write a mechanism that accounts for its rapid hydrolysis (recall that ordinary alkyl halides do not react with weak nucleophiles, such as water). 
493	*A prodrug* is a biologically inactive form of a drug that in vivo yields the active form of the drug. The liberation of the drug from the prodrug can be a non-enzymatic or enzyme-catalyzed process. Prodrugs are typically used because of their greater chemical stability, better transport and/or lower toxicity. The antibiotic cycloserine has a tendency to dimerize, forming an inactive dimer (see below). In order to lower the instability of cycloserine the prodrug shown below was synthesized. It was found to be an efficacious prodrug of increased stability. The prodrug releases the active ingredient in phosphate buffer, pH 7.0. Write a mechanism for the hydrolysis of the prodrug to the formation of the cycloserine and a mechanism for the formation of the cycloserine dimer.

	
494	Mammalian cells produce a range of bioactive substances, including prostaglandins, prostacyclins, thromboxanes, and leukotrienes. These hormone-like substances act as mediators of inflammation, pain, fever, blood clotting, etc. Prostacyclin is a potent vasodilator and inhibitor of platelet aggregation produced by vascular endothelial cells. Decreased production of prostacyclin is associated with platelet aggregation and the formation of blood clots (thrombosis). The latter is the primary cause of heart attacks and stroke. Prostacyclin is transformed into the compound shown below in vivo. Write a mechanism for this reaction.  Prostacyclin

495	The antitumor antibiotic leinamycin cleaves DNA, however, it does so only in the presence of added thiols. The precise mechanism of action of leinamycin is not known. It has been suggested that nucleophilic attack of a thiol on the 1,2-dithiolan-3-one 1-oxide heterocycle present in leinamycin triggers DNA cleavage. The thiol-activated DNA-cleavage chemistry of leinamycin was probed using 1,2,-dithiolan-3-one 1-oxide as a model compound and n-propane thiol (see reaction below).Write a plausible mechanism for this reaction.  leinamycin 
496	The prodrug shown below yields the active ingredient (chloral, a sedative) in the stomach. Write a mechanism for this transformation. 
497	Solutions of the broad-spectrum antibiotic chlortetracycline hydrochloride lose their therapeutic potency with time. This is due to rapid epimerization at the C-4 position, forming an epimerized product having greatly reduced antibiotic activity. Write a mechanism for the epimerization reaction.

	 Chlortetracycline hydrochloride (Aureomycin)
498	The intracellular enzyme CMP-KDO synthetase is the key enzyme in the biosynthesis of the lipopolysaccharide (LPS) of gram-negative bacteria. Compounds that inhibit this enzyme are of potential therapeutic value as antibacterial agents. Compound 1 is a potent inhibitor of CMP-KDO synthetase in vitro but is inactive as an antibacterial agent in vivo. In an effort to circumvent this problem a series of simple esters were synthesized and investigated for their antibacterial activity. None of the esters showed any activity. Ultimately, compound 2 was conceived which was found to be a highly effective antibacterial agent. The design of prodrug 2 was based on the following biological and chemical considerations. (a) gram-negative bacteria contain significant quantities of glutathione (gama-glu-cys-gly); (b) in vitro disulfide exchange reactions are facile; (c) the disulfide exchange was expected to be irreversible because of the "peri" effect; (d) when model compound 3 was reacted with n-propanethiol in the presence of triethylamine at room temperature, compound 4 [($C_{11}H_8S$; ^{1}H NMR: 4.78 (S,2H), 7.20-7.60 (m,4H)] was formed. Write a mechanism for the in vivo conversion of 2 to 1, and comment on the biochemical and chemical rationale underlying the design of compound 2.

	 1  2  3
499	Isoilludin M behave as a bifunctional alkylating agent, yielding the aromatic product shown below. Write a plausible mechanism for this reaction.  isoilludin M
500	The natural product Bripiodionen is an inhibitor of human cytomegalovirus protease. When dissolved in methanol for a prolonged period of time, bripiodionen undergoes geometric isomerization to compound X. The chemical shift of H-8 in bripiodionen is 7.45 and 7.61 in compound X. What is the structure of X? Write a mechanism for the formation of X.  Bripiodionen

Answers to Questions 491-500

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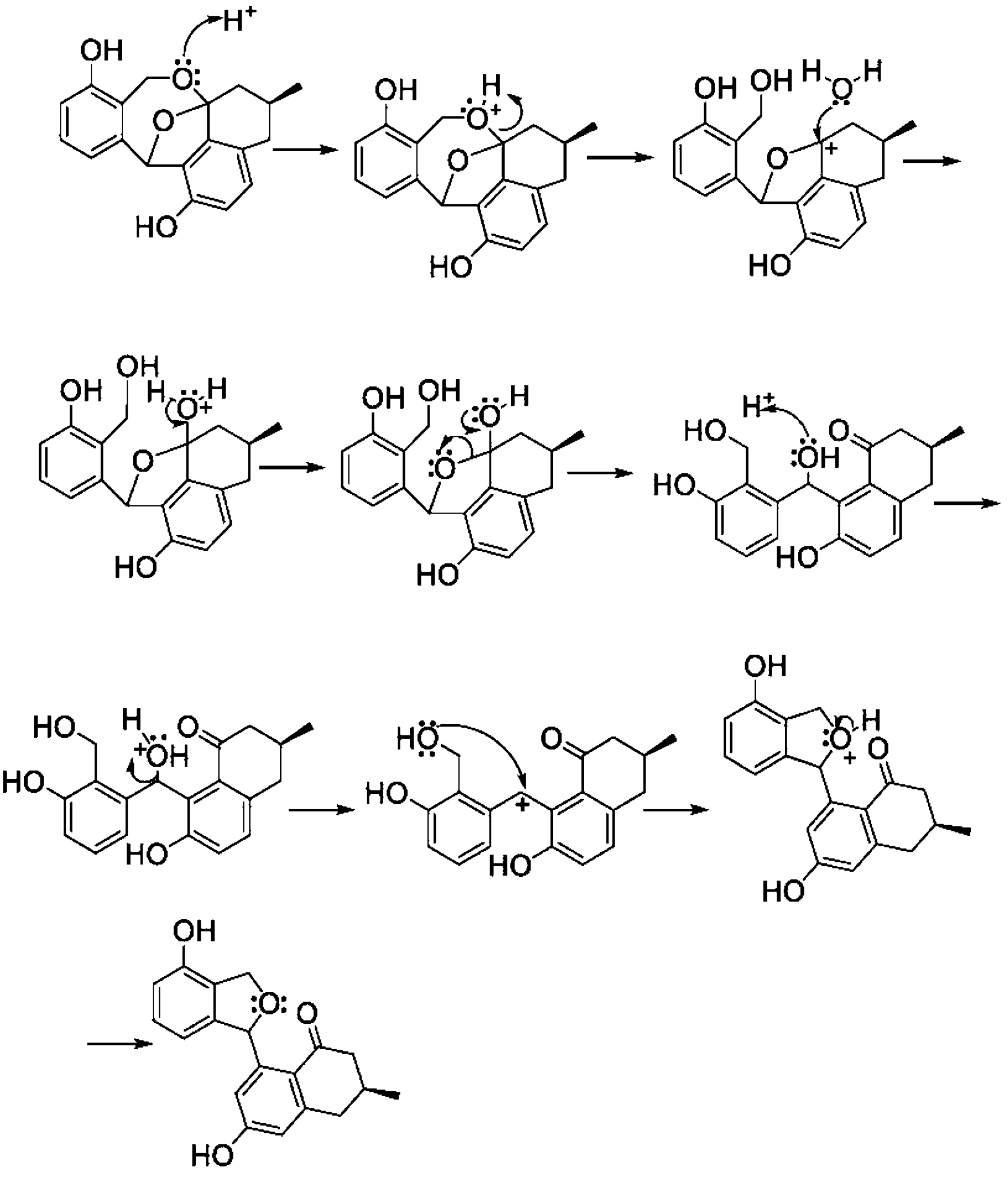

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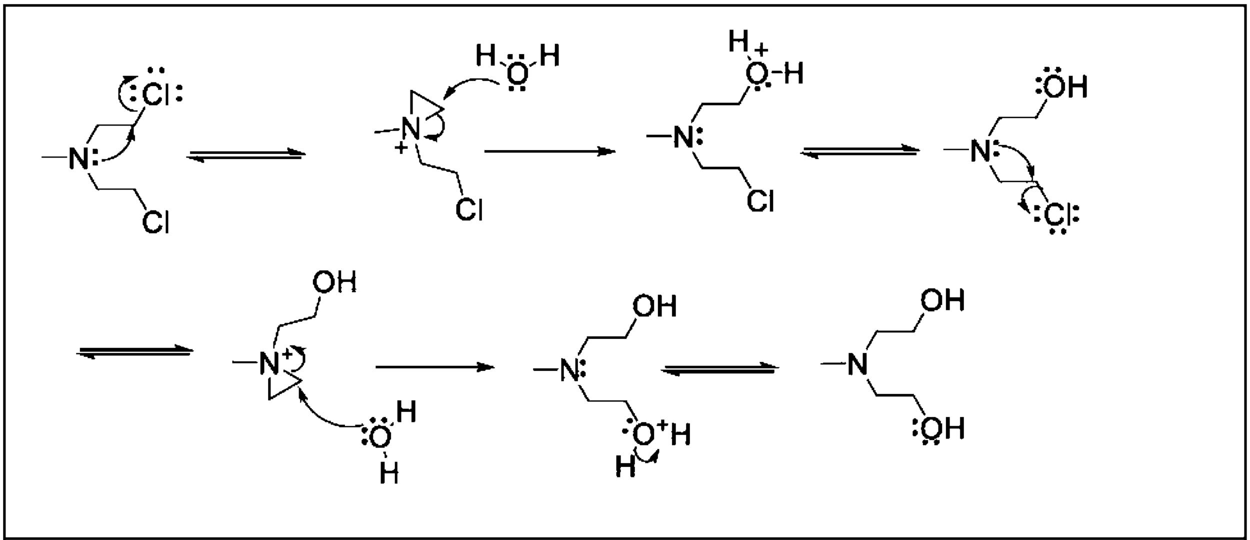

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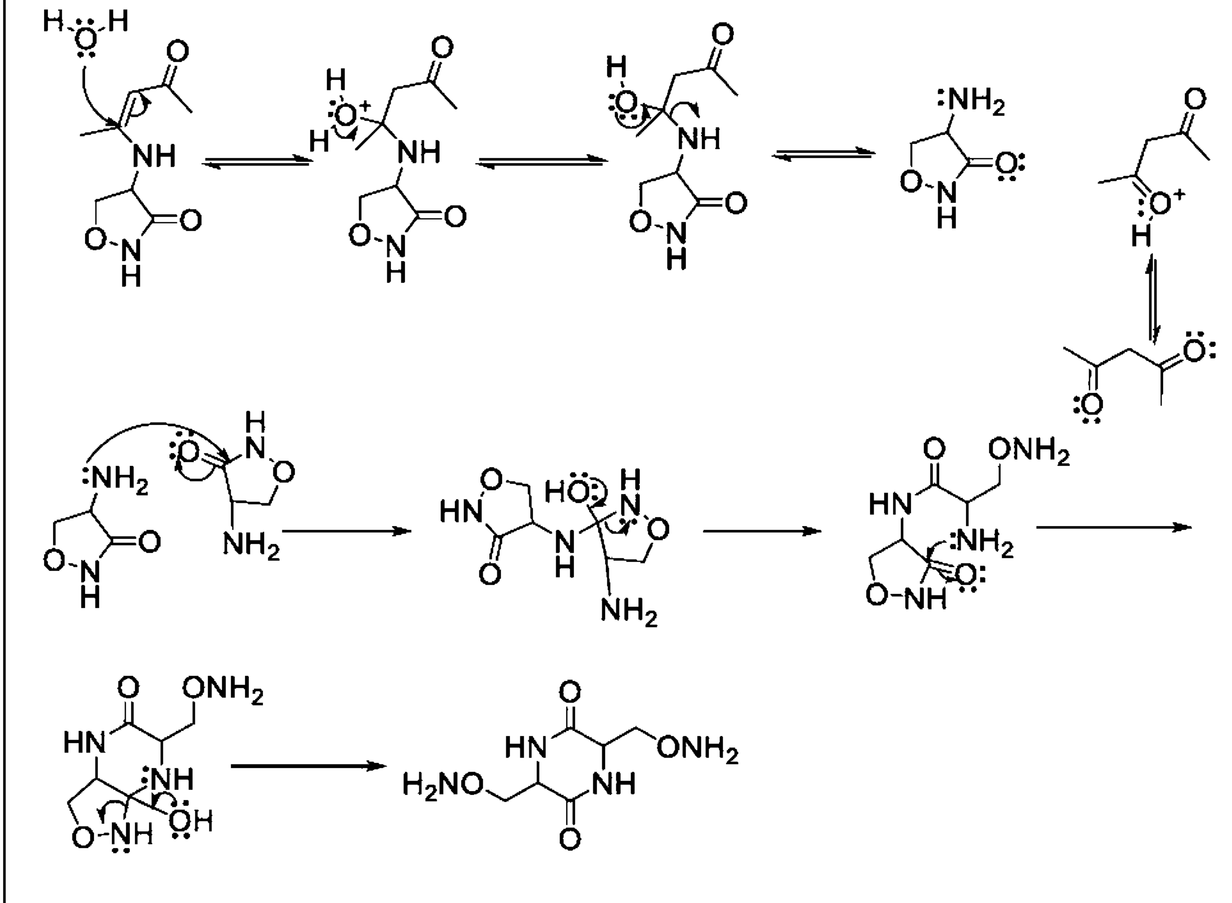

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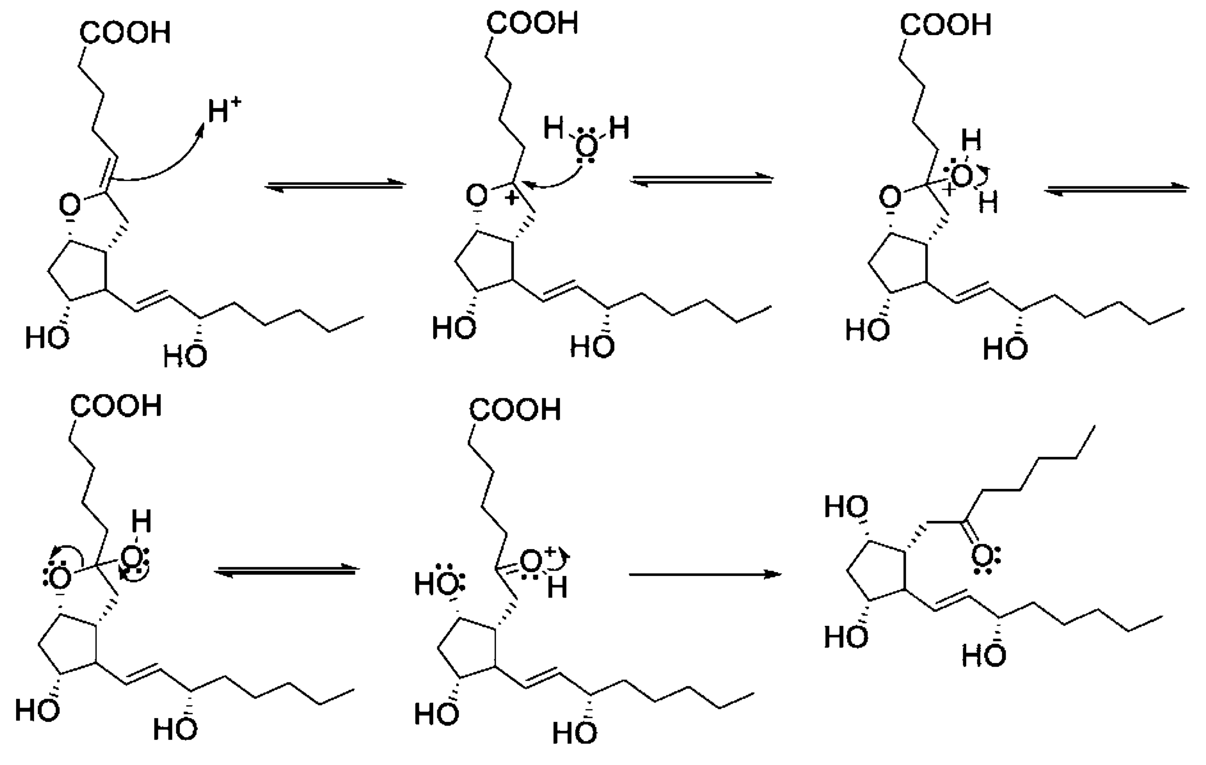

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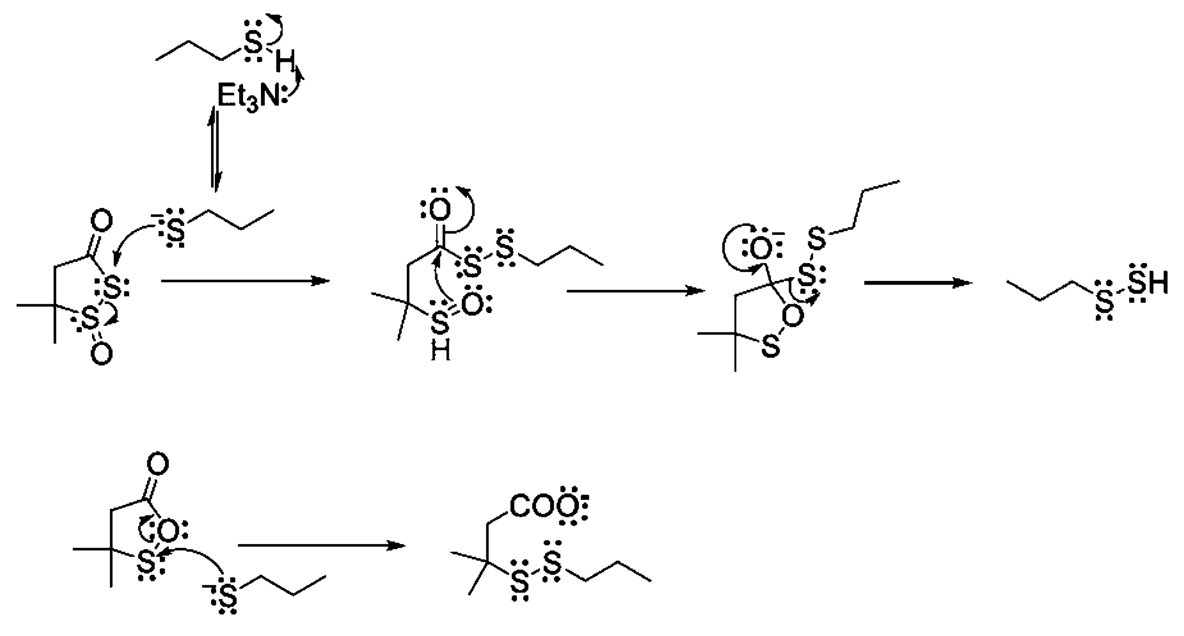

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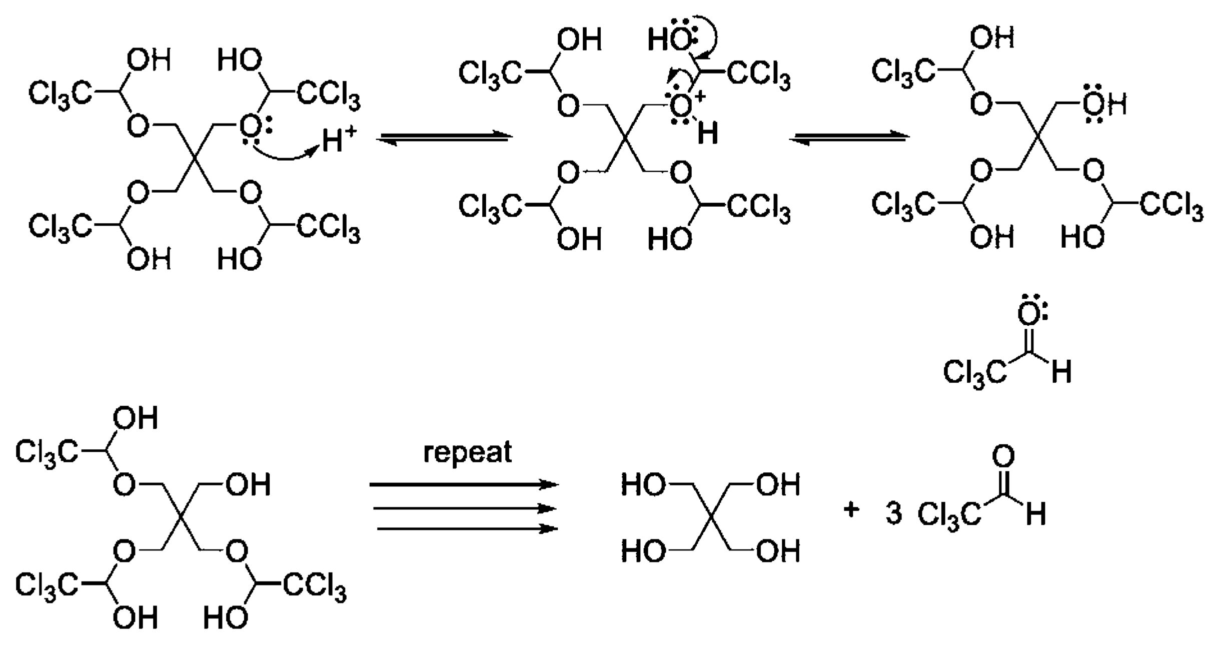

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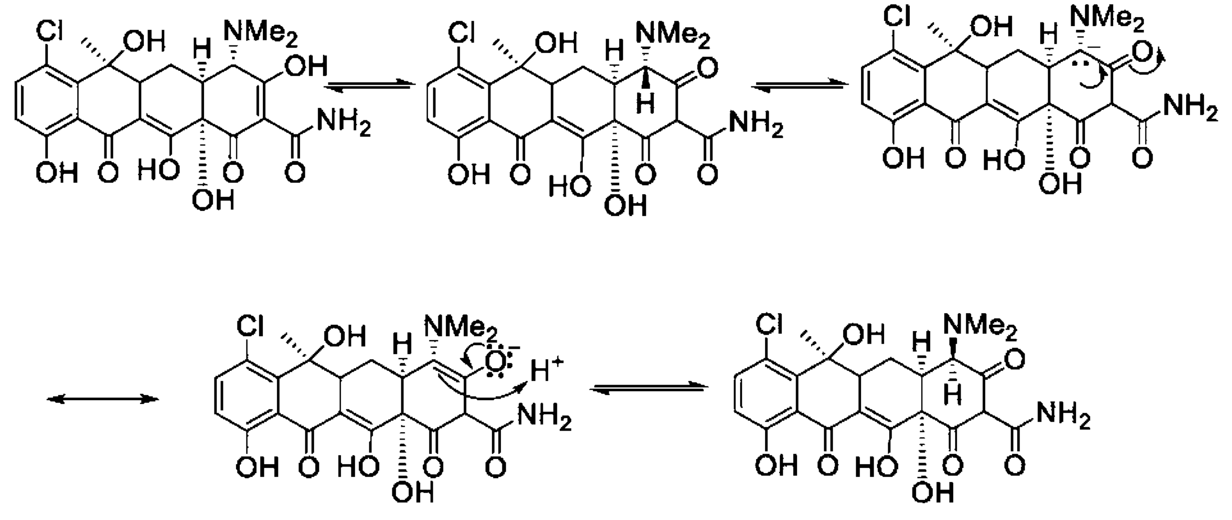

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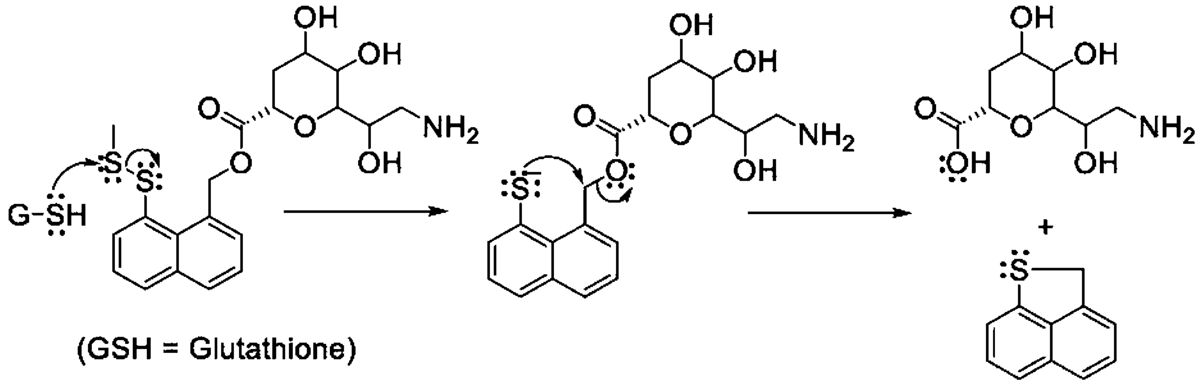

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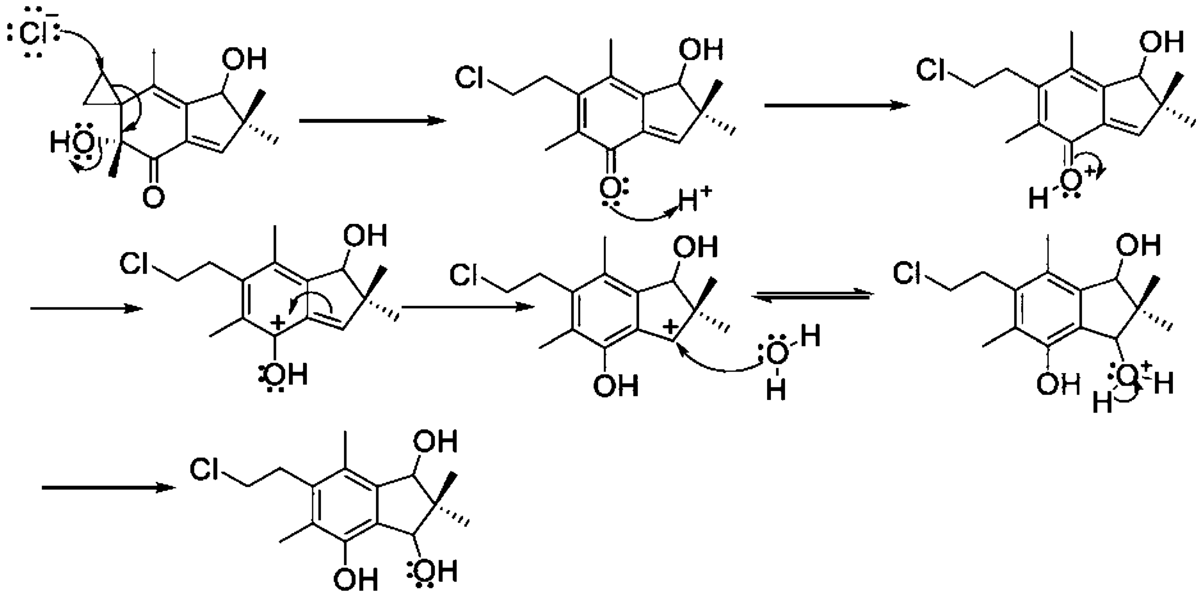

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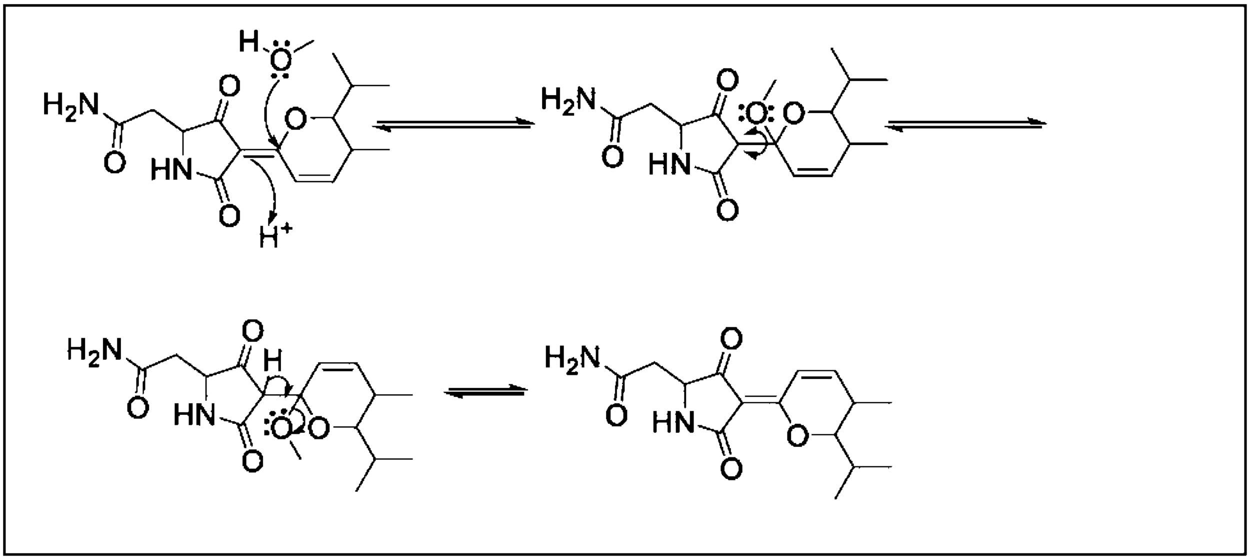
H₂N
O
HN
O
H
O
H⁺

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