

Chapter 18 – Ethers and Epoxides; Thiols and Sulfides

Chapter Outline

I. Acyclic ethers (Sections 18.1 – 18.4)

A. Naming ethers (Section 18.1).

1. Ethers with no other functional groups are named by citing the two organic substituents and adding the word "ether".
2. When other functional groups are present, the ether is an alkoxy substituent.

B. Properties of ethers.

1. Ethers have the same geometry as water and alcohols.
2. Ethers have a small dipole moment that causes a slight boiling point elevation.
3. Ethers can react slowly with oxygen to give explosive peroxides.

C. Preparation of ethers (Section 18.2).

1. Symmetrical ethers can be synthesized by acid-catalyzed dehydration of alcohols.
2. Williamson ether synthesis.

- a. Metal alkoxides react with primary alkyl halides and tosylates to form ethers.
- b. The alkoxides are prepared by reacting an alcohol with a strong base, such as NaH.

Reaction of the free alcohol with the halide can be achieved with Ag_2O .

- c. The reaction occurs via an $\text{S}_{\text{N}}2$ mechanism.
 - i. The halide component must be primary.
 - ii. In cases where one ether component is hindered, reaction should occur between the alkoxide of the more hindered reagent and the halide of the less hindered reagent.

3. Alkoxymercuration of alkenes.

- a. Ethers can be formed from the reaction of alcohols with alkenes.
- b. The reaction is catalyzed by mercuric trifluoroacetate.
- c. The mechanism is similar to that for hydration of alkenes.
 NaBH_4 is used for demercuration of the intermediate.
- d. Many different types of ethers can be prepared by this method.

D. Reactions of ethers (Sections 18.3 – 18.4).

1. Acidic cleavage (Section 18.3).

- a. Strong acids can be used to cleave ethers.
- b. Cleavage can occur by $\text{S}_{\text{N}}2$ or $\text{S}_{\text{N}}1$ routes.
 - i. Primary and secondary alcohols react by an $\text{S}_{\text{N}}2$ mechanism, in which the halide attacks the ether at the less hindered site.
This route selectively produces one halide and one alcohol.
 - ii. Tertiary, benzylic and allylic ethers react by either an $\text{S}_{\text{N}}1$ or an $\text{E}1$ route.

2. Claisen rearrangement (Section 18.4).

- a. The Claisen rearrangement is specific to allyl aryl ethers.
- b. The result of Claisen rearrangement is an *o*-allyl phenol.
- c. The reaction takes place by a pericyclic mechanism.

Inversion of the allyl group is evidence for this mechanism.

II. Cyclic ethers (Sections 18.5 – 18.7).

A. Epoxides (Sections 18.5 – 18.6).

1. The three-membered ring of epoxides gives them unique chemical reactivity (Section 18.5).
2. The nonsystematic name *-ene oxide* describes the method of formation.
3. The systematic prefix *epoxy-* describes the location of the epoxide ring.

4. Preparation of epoxides.
 - a. Epoxides can be prepared by reaction of an alkene with a peroxyacid RCO_3H .
The reaction occurs in one step with syn stereochemistry.
 - b. Epoxides are formed when halohydrins are treated with base.
This reaction is an intramolecular Williamson ether synthesis.
5. Ring-opening reactions of epoxides (Section 18.6).

- a. Acid-catalyzed ring opening.
 - i. Acid-catalyzed ring opening produces 1,2 diols.
 - ii. Ring opening takes place by back-side attack of a nucleophile on the protonated epoxide ring.
A *trans*-1,2-diol is formed from an epoxycycloalkane.
 - iii. When both epoxide carbons are primary or secondary, attack occurs primarily at the less hindered site.
 - iv. When one epoxide carbon is tertiary, attack occurs at the more highly substituted site.
 - v. The mechanism is midway between $\text{S}_{\text{N}}2$ and $\text{S}_{\text{N}}1$ routes.
The reaction occurs by back-side attack ($\text{S}_{\text{N}}2$), but positive charge is stabilized by a tertiary carbocation-like transition state ($\text{S}_{\text{N}}1$).
- b. Base-catalyzed ring-opening.
 - i. Base-catalyzed ring opening occurs because of the reactivity of the strained epoxide ring.
 - ii. Ring-opening also occurs when epoxides react with Grignard reagents, forming a product with two more carbons than the starting alkyl halide.
 - iii. Ring-opening takes place by an $\text{S}_{\text{N}}2$ mechanism, in which the nucleophile attacks the less hindered epoxide carbon.

B. Crown ethers (Section 18.7).

1. Crown ethers are large cyclic ethers.
2. Crown ethers are named as *x*-crown-*y*, where *x* = the ring size and *y* = # of oxygens.
3. Crown ethers are able to solvate metal cations.
 - a. Different sized crown ethers solvate different cations.
 - b. Complexes of crown ethers with ionic salts are soluble in organic solvents.
 - c. This solubility allows many reactions to be carried out under aprotic conditions.
 - d. The reactivity of many anions in $\text{S}_{\text{N}}2$ reactions is enhanced by crown ethers.

IV. Thiols and sulfides (Section 18.8).

A. Naming thiols and sulfides.

1. Thiols (sulfur analogs of alcohols) are named by the same system as alcohols, with the suffix *-thiol* replacing *-ol*.
The $-\text{SH}$ group is a mercapto- group.
2. Sulfides (sulfur analogs of ethers) are named by the same system as ethers, with *sulfide* replacing *ether*.
The $-\text{SR}$ group is an alkylthio- group.

B. Thiols.

1. Thiols stink!
2. Thiols may be prepared by $\text{S}_{\text{N}}2$ displacement with a sulfur nucleophile.
 - a. The reaction may proceed to form sulfides.
 - b. Better yields occur when thiourea is used.
3. Thiols can be oxidized by Br_2 or I_2 to yield disulfides, RSSR .
The reaction can be reversed by treatment with zinc and acid.

C. Sulfides.

1. Treatment of a thiol with base yields a thiolate anion, which can react with an alkyl halide to form a sulfide.
2. Thiolate anions are excellent nucleophiles.
3. Dialkyl sulfides can react with alkyl halides to form trialkylsulfonium salts, which are also good alkylating agents.

Many biochemical reactions use trialkylsulfonium groups as alkylating agents.

4. Sulfides are easily oxidized to sulfoxides (R_2SO) and sulfones (R_2SO_2).

Dimethyl sulfoxide is used as a polar aprotic solvent.

III. Spectroscopy of ethers (Section 18.9).

A. IR spectroscopy.

1. Ethers are difficult to identify by IR spectroscopy because many other absorptions occur at $1050\text{--}1150\text{ cm}^{-1}$, where ethers absorb.

B. NMR spectroscopy.

1. 1H NMR spectroscopy.

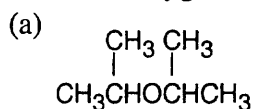
- a. Hydrogens on a carbon next to an ether oxygen absorb downfield ($3.4\text{--}4.5\ \delta$).
- b. Hydrogens on a carbon next to an epoxide oxygen absorb at a slightly higher field ($2.5\text{--}3.5\ \delta$).

2. ^{13}C NMR spectroscopy.

Ether carbons absorb downfield ($50\text{--}80\ \delta$).

Solutions to Problems

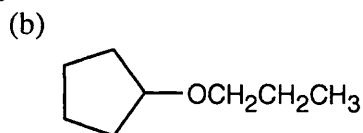
- 18.1** Ethers can be named either as alkoxy-substituted compounds or by citing the two groups bonded to oxygen, followed by the word "ether".



2-Isopropoxypropane

or

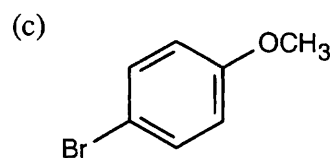
Diisopropyl ether



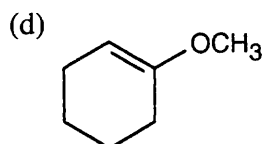
Propoxycyclopentane

or

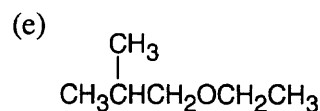
Cyclopentyl propyl ether

*p*-Bromoanisole

or

p-Bromomethoxybenzene

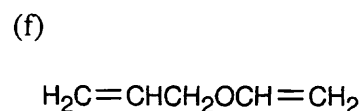
1-Methoxycyclohexene



1-Ethoxy-2-methylpropane

or

Ethyl isobutyl ether

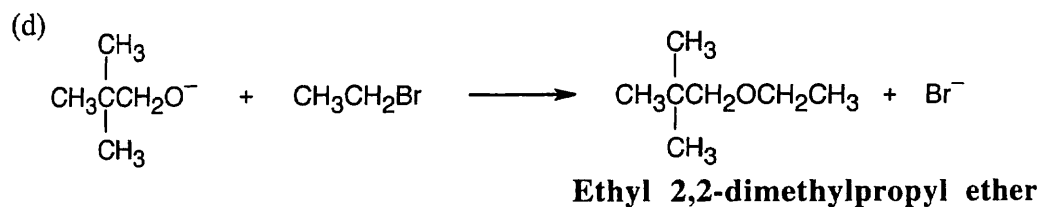
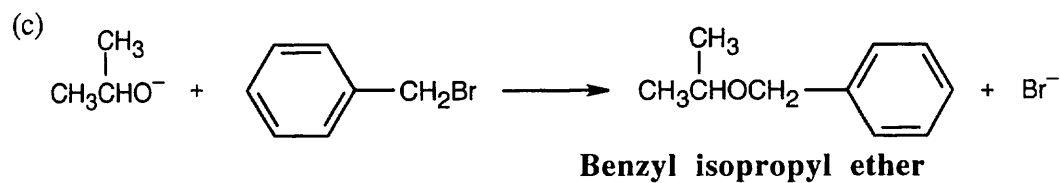
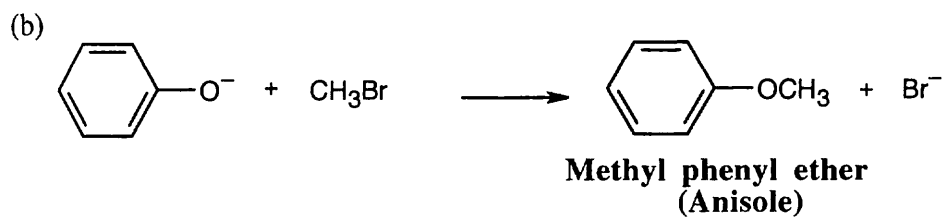
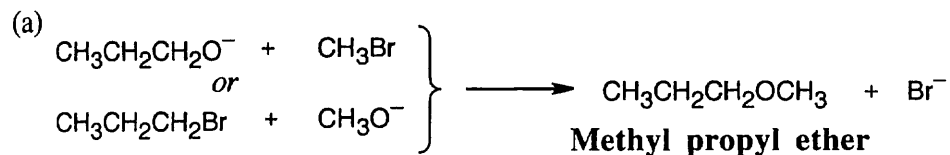


Allyl vinyl ether

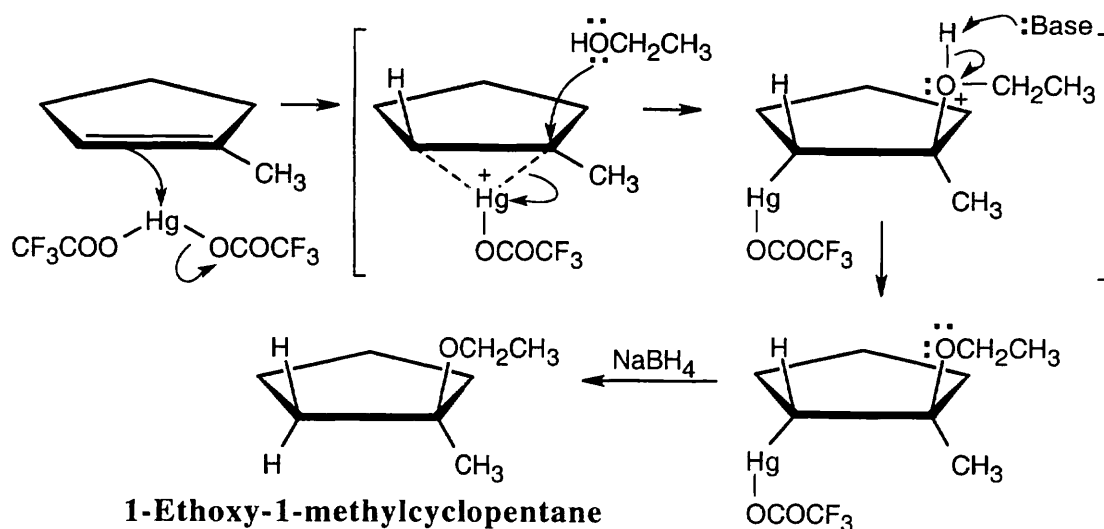
- 18.2** The first step of the dehydration mechanism is protonation of an alcohol. Water is then displaced by another molecule of alcohol to form an ether. If two different alcohols are present, either one can be protonated and either one can displace water, yielding a mixture of products.

If this procedure were used with ethanol and 1-propanol, the products would be diethyl ether, ethyl propyl ether, and dipropyl ether. If there were equimolar amounts of the alcohols, and if they were of equal reactivity, the product ratio would be diethyl ether : ethyl propyl ether : dipropyl ether = 1:2:1.

18.3 Remember that the halide in the Williamson ether synthesis should be primary or methyl, in order to avoid competing elimination reactions. The alkoxide anions shown are formed by treating the corresponding alcohols with NaH.



18.4



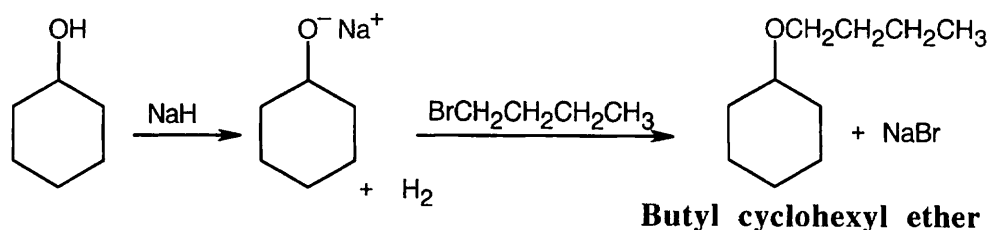
The reaction mechanism of alkoxymercuration/demercuration of an alkene is similar to other electrophilic additions we have studied. First, the cyclopentene π electrons attack Hg^{2+} with formation of a mercurinium ion. Next, the nucleophilic alcohol displaces mercury. Markovnikov addition occurs because the carbon bearing the methyl group is better able to stabilize the partial positive charge arising from cleavage of the carbon-mercury bond. The ethoxyl and mercuric groups are trans to each other. Finally, removal of mercury by NaBH_4 by a mechanism that is not fully understood results in the formation of 1-ethoxy-1-methylcyclopentane.

- 18.5 Strategy:** Use the Williamson synthesis when one of the ether components can be a primary or benzylic halide. Use alkoxymercuration when one or both components are branched.

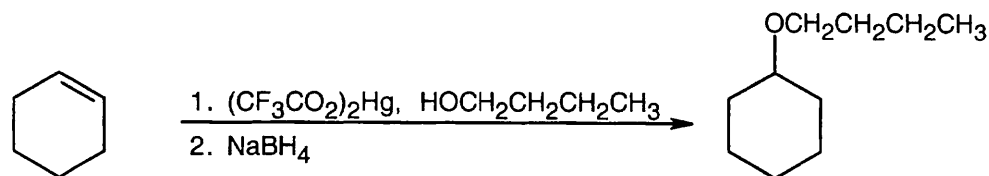
Solution:

(a) Either method of synthesis is appropriate.

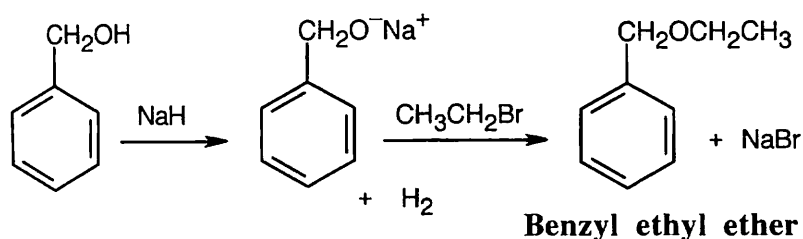
Williamson:



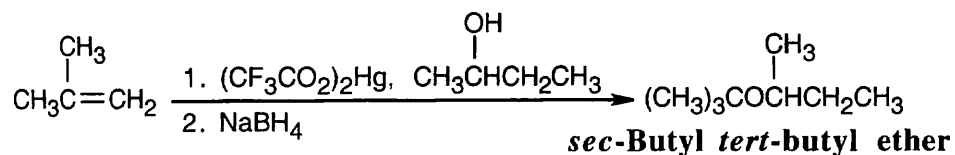
Alkoxymercuration:



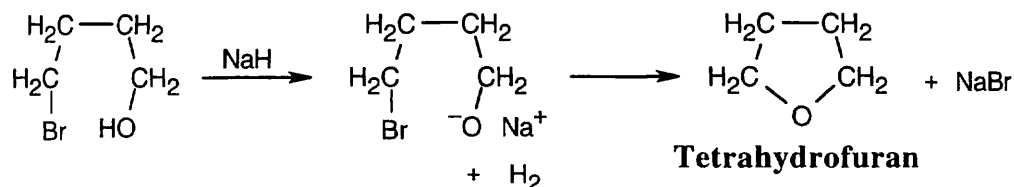
(b) Either method is possible, but the Williamson synthesis is simpler.



(c) Because both parts of the ether are branched, use alkoxymercuration.

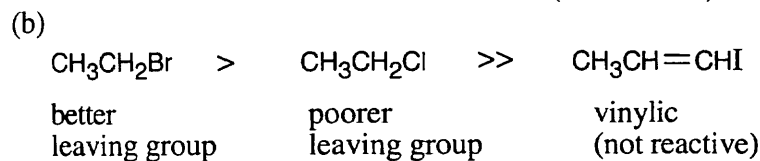
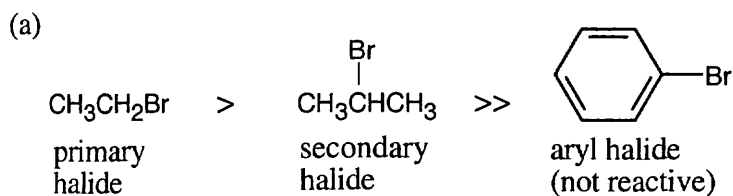


(d) The Williamson synthesis must be used.

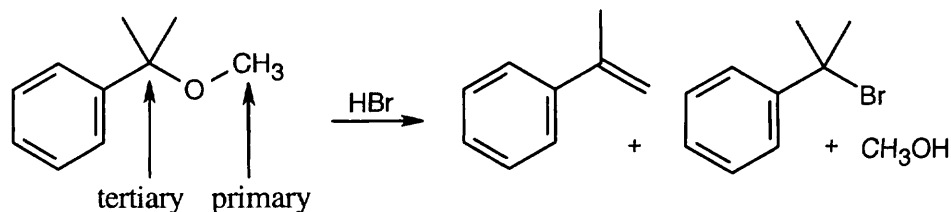


18.6 The compounds most reactive in the Williamson ether synthesis are also most reactive in any $\text{S}_\text{N}2$ reaction (review Chapter 11 if necessary).

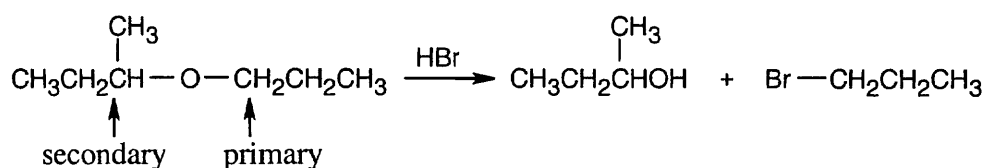
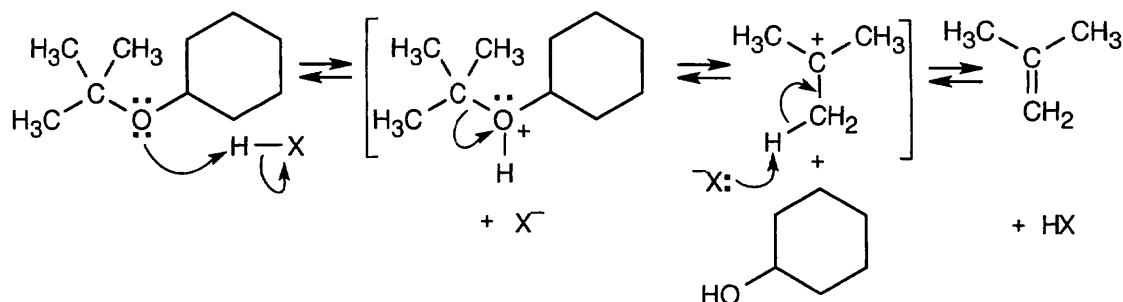
Most reactive \longrightarrow *Least reactive*



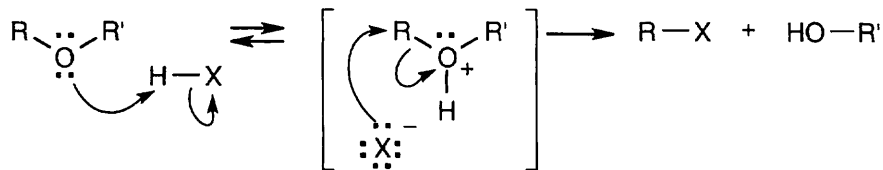
- 18.7** (a) First, notice the substitution pattern of the ether. Bonded to the ether oxygen are a primary alkyl group and a tertiary alkyl group. When one group is tertiary, cleavage occurs by an S_N1 or $E1$ route to give either an alkene or a tertiary halide and a primary alcohol.



- (b) In this problem, the groups are primary and secondary alkyl groups. Br^- attacks at the less hindered primary group, and oxygen remains with the secondary group, to give a secondary alcohol.

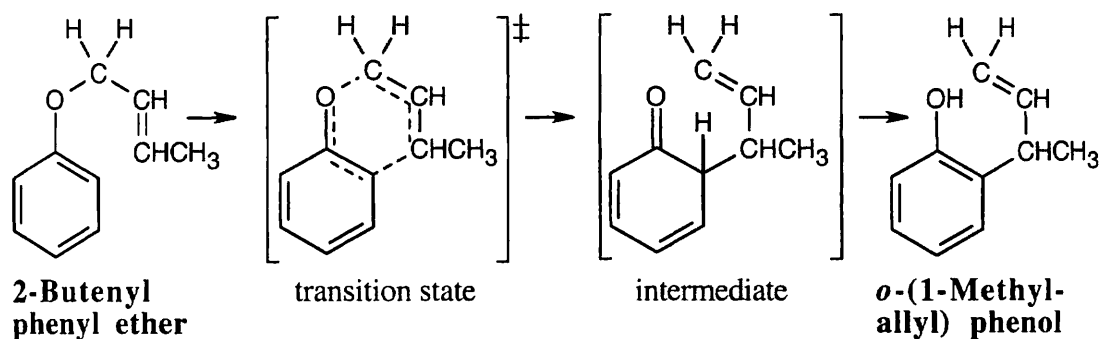
**18.8**

The first step of acid-catalyzed ether cleavage is protonation of the ether oxygen to give an intermediate oxonium ion, which collapses to form an alcohol and a tertiary carbocation. The carbocation then loses a proton to form an alkene, 2-methylpropene. This is an example of $E1$ elimination. The acid used for cleavage is often trifluoroacetic acid.

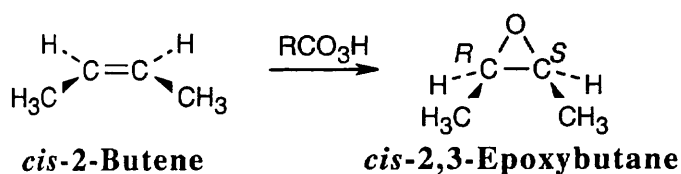
18.9

HX first protonates the oxygen atom, and halide then effects a nucleophilic displacement to form an alcohol and an organic halide. The better the nucleophile, the more effective the displacement. Since I^- and Br^- are better nucleophiles than Cl^- , ether cleavage proceeds more smoothly with HI or HBr than with HCl .

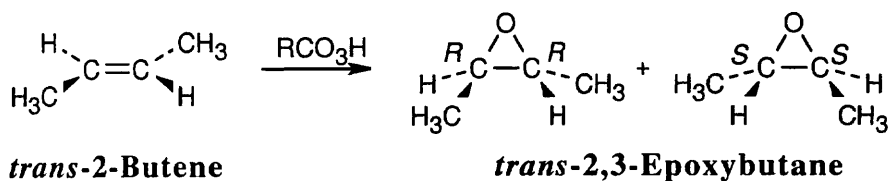
- 18.10** Draw the ether with the groups involved in the rearrangement positioned as they will appear in the product. Six bonds will either be broken or formed in the product; they are shown as dashed lines in the transition state. Redraw the bonds to arrive at the intermediate enone, which rearranges to the more stable phenol.



- 18.11** Epoxidation by use of *m*-chloroperoxybenzoic acid (RCO_3H) is a syn addition of oxygen to a double bond. The original bond stereochemistry is retained, and the product is a meso compound.



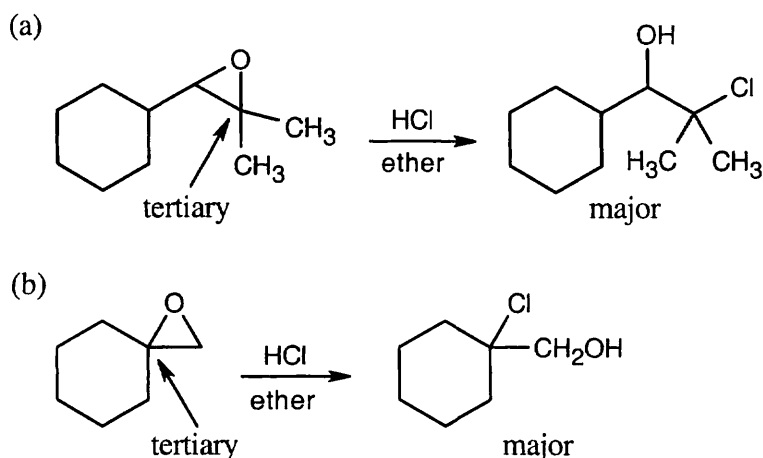
In the epoxide product, as in the alkene starting material, the methyl groups are *cis*.



Reaction of *trans*-2-butene with *m*-chloroperoxybenzoic acid yields *trans*-2,3-epoxybutane. A mixture of enantiomers is formed because the peroxyacid can attack either the top or bottom of the double bond.

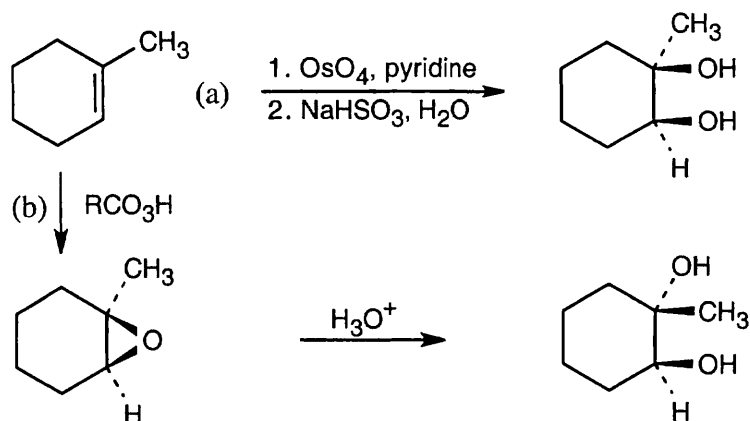
18.12 Strategy: As discussed in this section, acid-catalyzed epoxide ring opening occurs primarily at the more hindered carbon when one of the epoxide carbons is tertiary. In both parts of this problem, one epoxide carbon is tertiary.

Solution:

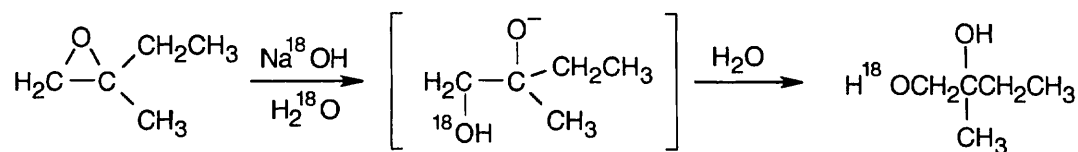


18.13 Strategy: Notice the relationship of the hydroxyl groups in the two diols. In diol (a), the two hydroxyls are *cis*, and in (b) they are *trans*. Since ring-opening of epoxides forms *trans*-1,2-diols, only diol (b) can be formed by this route. The *cis*-1,2-diol in (a), results from treatment of 1-methylcyclohexene with OsO_4 . The enantiomers of the diols are also formed.

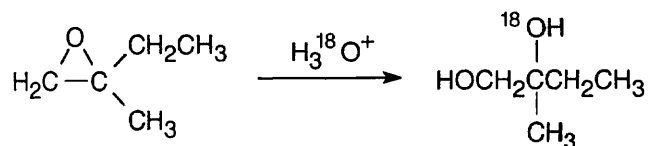
Solution:



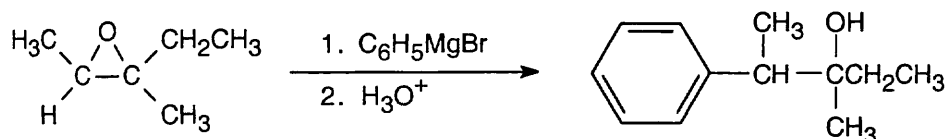
18.14 (a) Attack of the basic nucleophile occurs at the less substituted epoxide carbon.



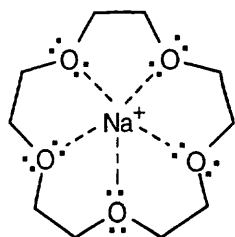
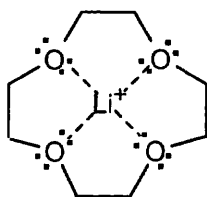
(b) Under acidic conditions, ring-opening occurs at the more substituted epoxide carbon when one of the carbons is tertiary.



(c) Addition of a Grignard reagent takes place at the less substituted epoxide carbon.

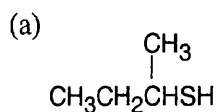
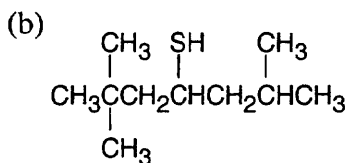
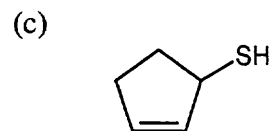
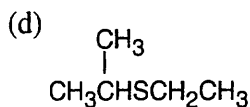
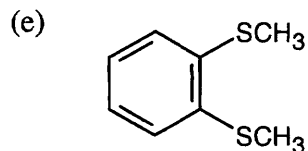
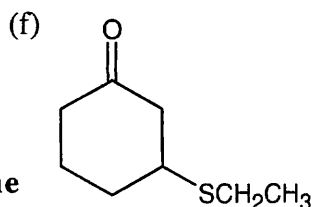


18.15

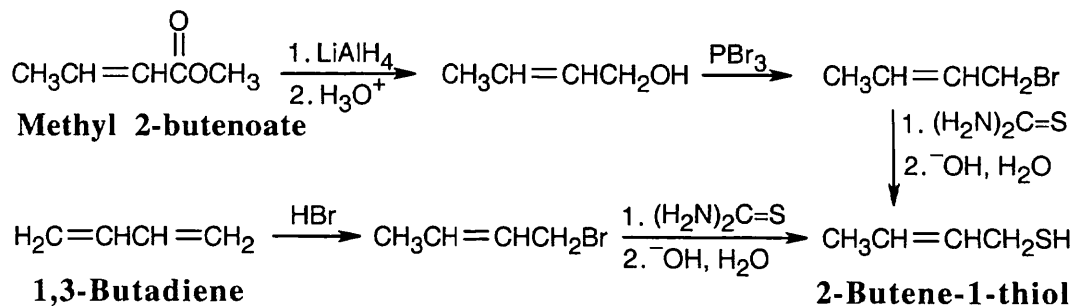
**15-Crown-5****12-Crown-4**

The ion-to-oxygen distance in 15-crown-5 is about 40% longer than the ion-to-oxygen distance in 12-crown-4.

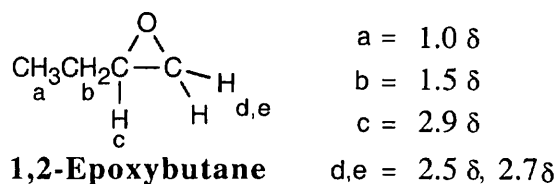
18.16 Thiols are named by the same rules as alcohols, with the suffix -ol replaced by the suffix -thiol. Sulfides are named by the same rules as ethers, with "sulfide" replacing "ether".

**2-Butanethiol****2,2,6-Trimethyl-4-heptanethiol****2-Cyclopentene-1-thiol****Ethyl isopropyl sulfide****o-(Dimethylthio)benzene****3-(Ethylthio)cyclohexanone**

18.17 Thiourea is used to prepare thiols from alkyl halides.



18.18



Visualizing Chemistry

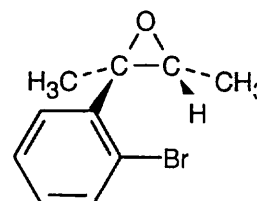
18.19

(a)



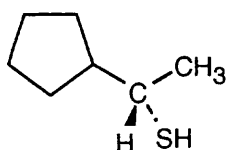
cis-1-Ethoxy-3-methylcyclohexane

(b)



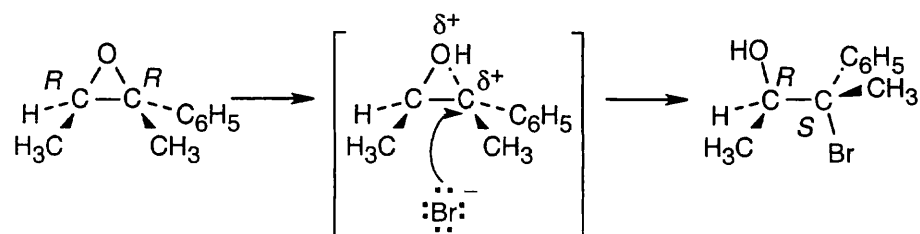
E-2-(*o*-Bromophenyl)-2,3-epoxybutane

(c)

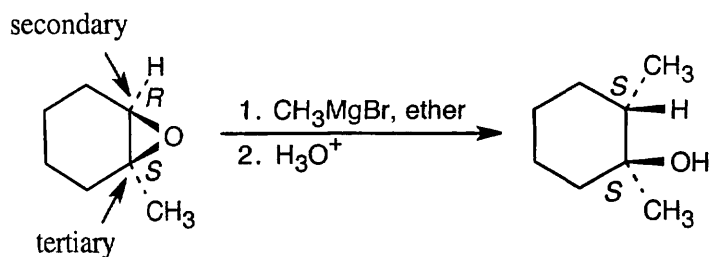


(*S*)-1-Cyclopentylethanethiol

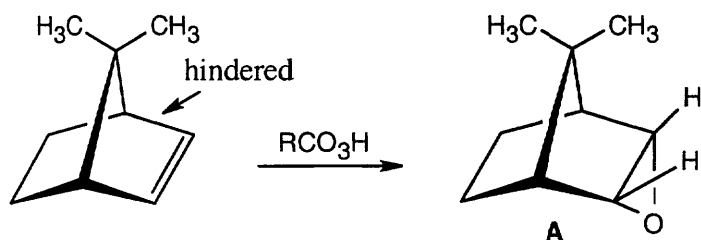
18.20 Ring-opening occurs at the tertiary carbon to give the transition state carbocation-like stability. Bromine approaches 180° from the C–OH bond, as it would in an S_N2 reaction.



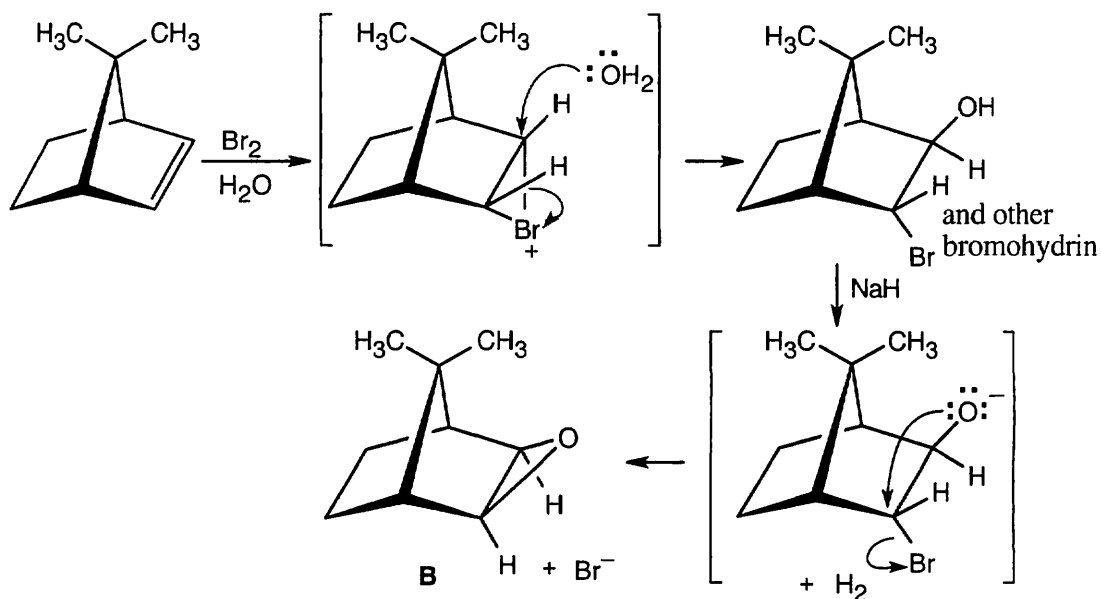
18.21 The Grignard reagent attacks the epoxide at the less hindered carbon in an S_N2 reaction. The oxygen remains bonded to the tertiary carbon.



18.22 A molecular model shows that approach to the upper face of the double bond is hindered by a methyl group. Reaction with RCO_3H occurs at the lower face of the double bond to produce epoxide **A**.



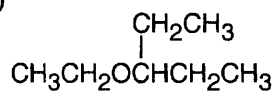
In the reaction of Br_2 and H_2O , the intermediate bromonium ion also forms at the lower face. Reaction with water yields a bromohydrin which, when treated with base, forms epoxide **B**.



Additional Problems

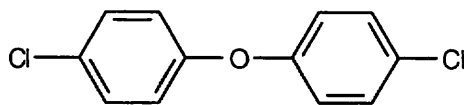
18.23

(a)

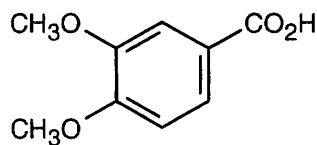


Ethyl 1-ethylpropyl ether

(b)

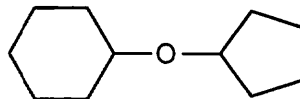
Di(*p*-chlorophenyl) ether

(c)



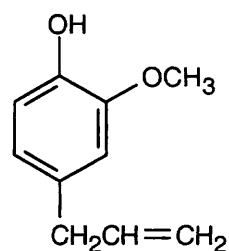
3,4-Dimethoxybenzoic acid

(d)



Cyclopentyloxycyclohexane

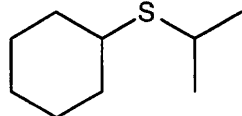
(e)



4-Allyl-2-methoxyphenol

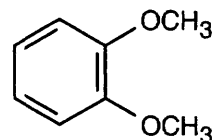
18.24

(a)

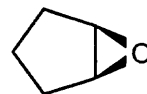


Cyclohexyl isopropyl sulfide

(b)

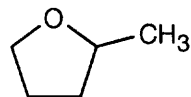
*o*-Dimethoxybenzene

(c)



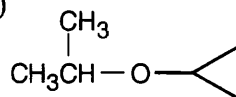
1,2-Epoxycyclopentane

(d)

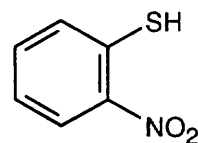


2-Methyltetrahydrofuran

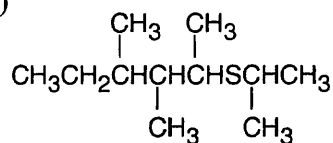
(e)

Cyclopropyl isopropyl ether
or
Isopropoxycyclopropane

(f)

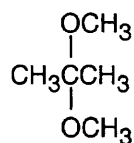
*o*-Nitrobenzenethiol

(g)



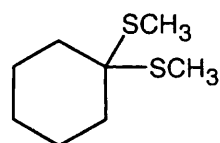
2-(Isopropylthio)-3,4-dimethylhexane

(h)



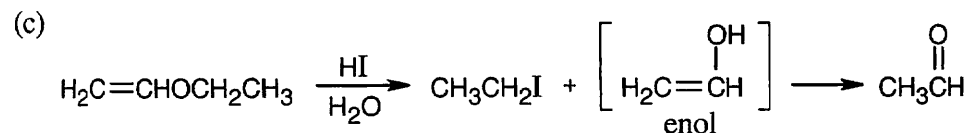
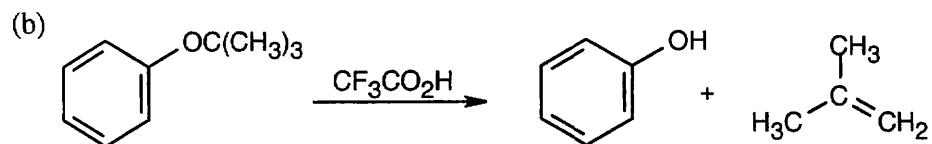
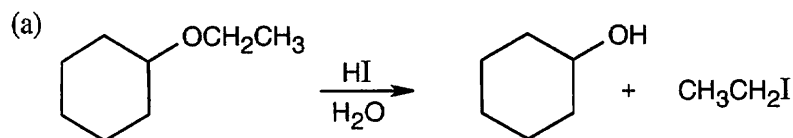
2,2-Dimethoxypropane

(i)

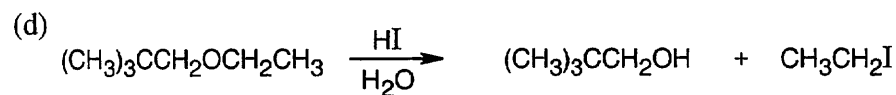


1,1-(Dimethylthio)cyclohexane

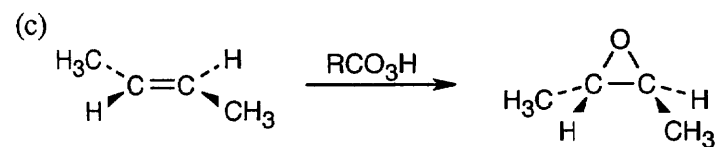
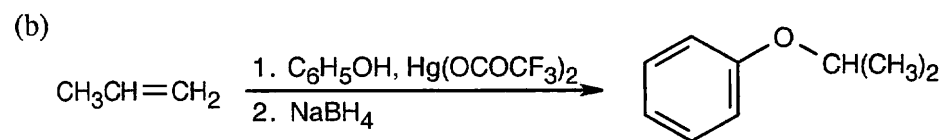
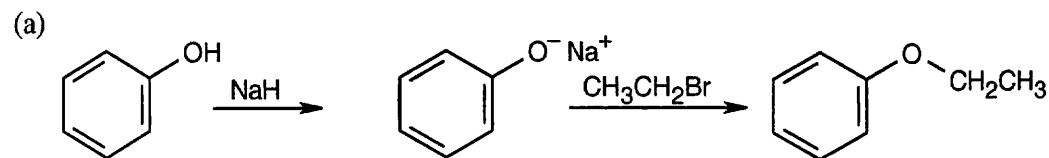
18.25

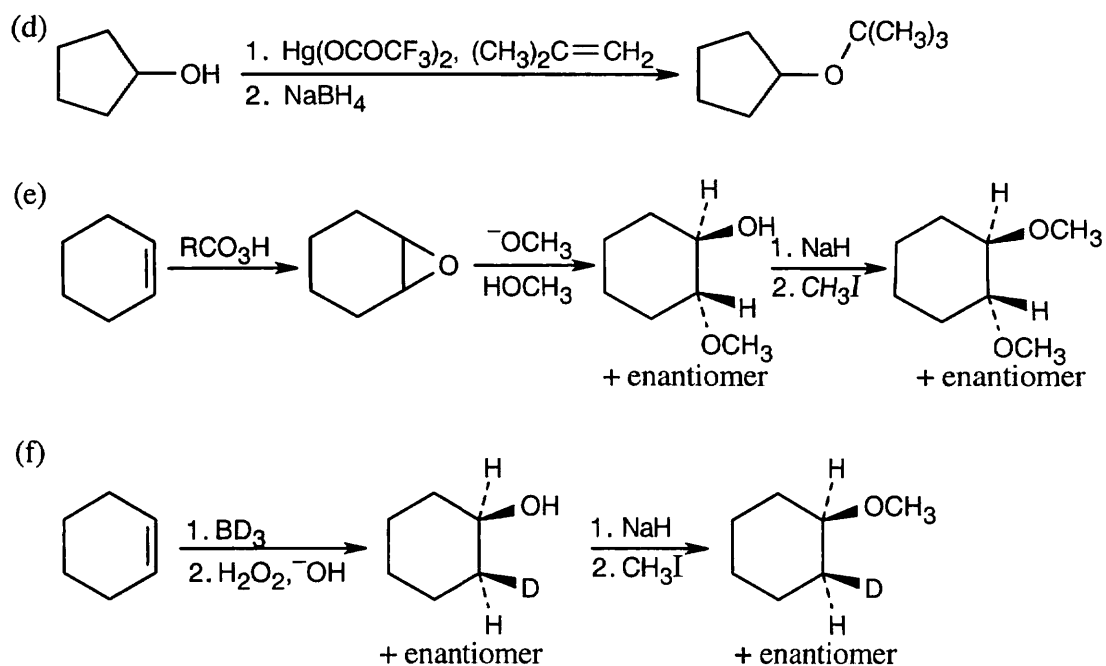


The enol tautomerizes to an aldehyde.

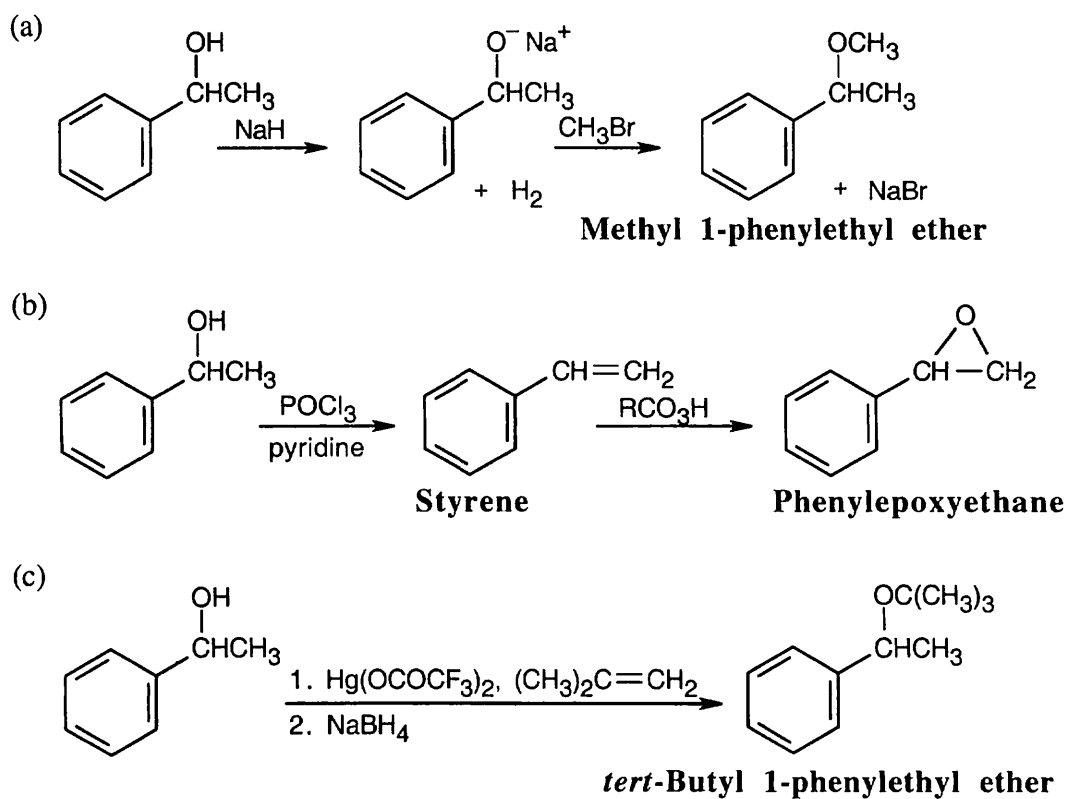


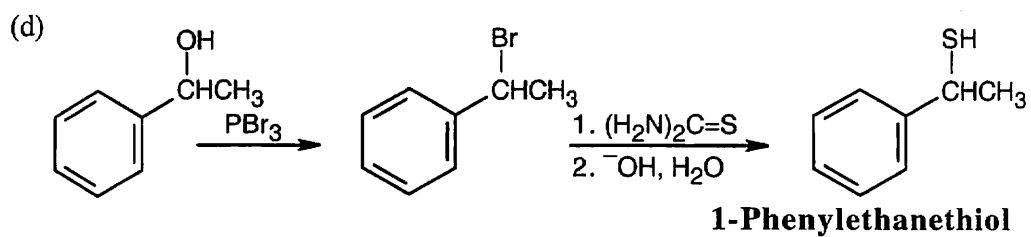
18.26



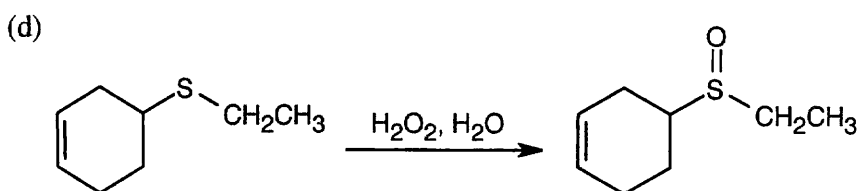
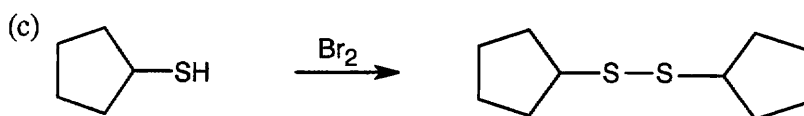
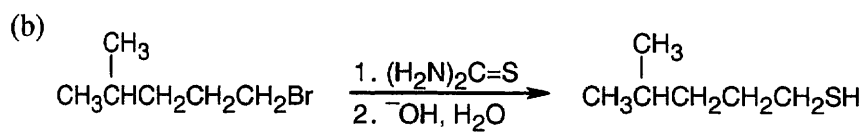
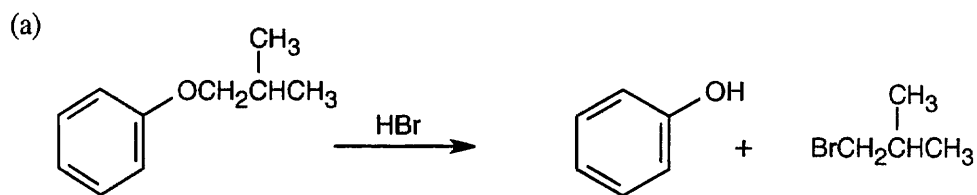


18.27

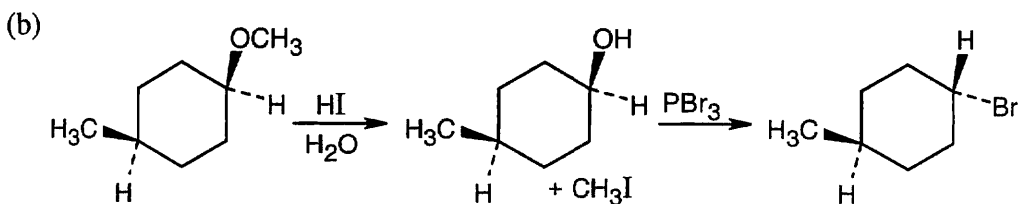
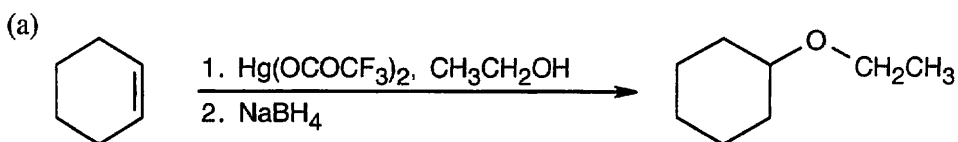




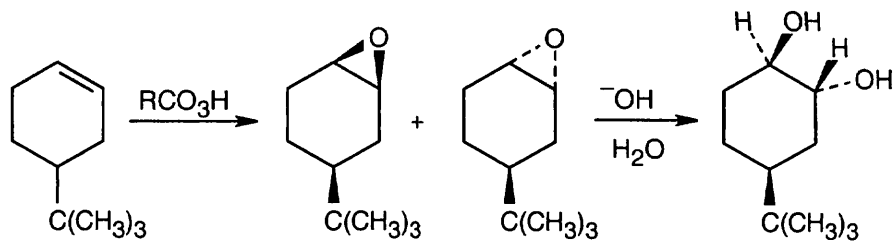
18.28



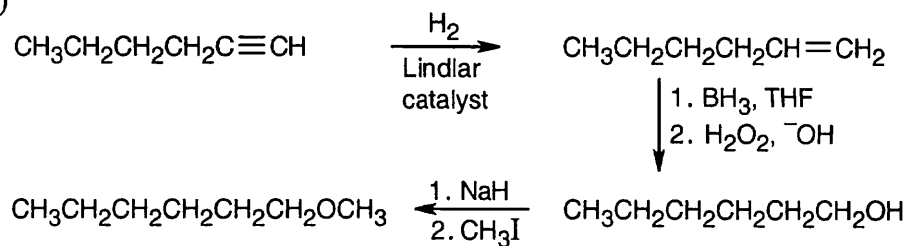
18.29



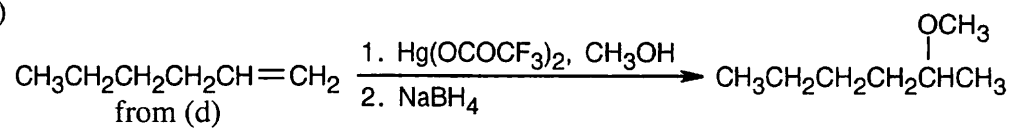
(c)



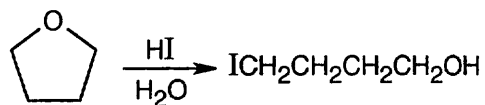
(d)



(e)

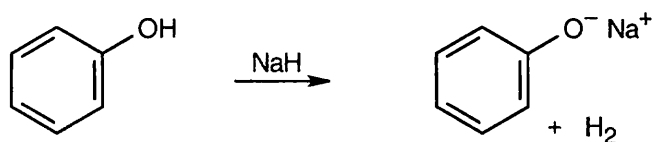


18.30

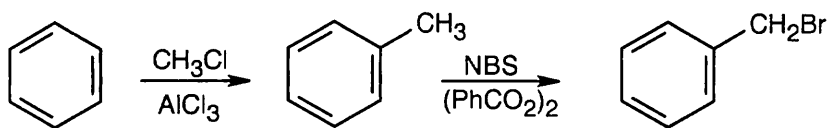


18.31

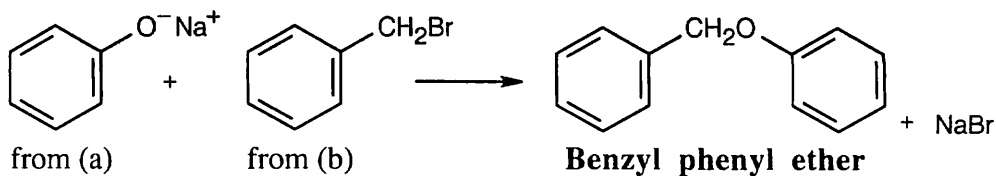
(a)



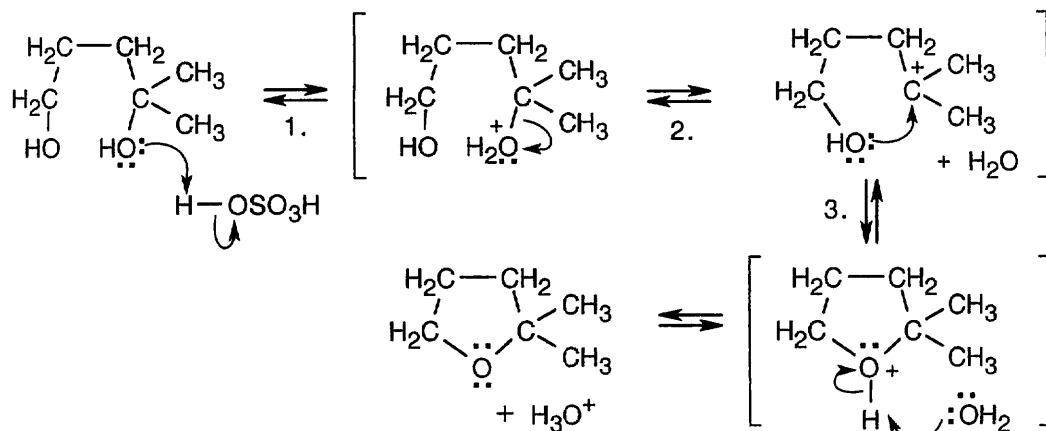
(b)



(c)

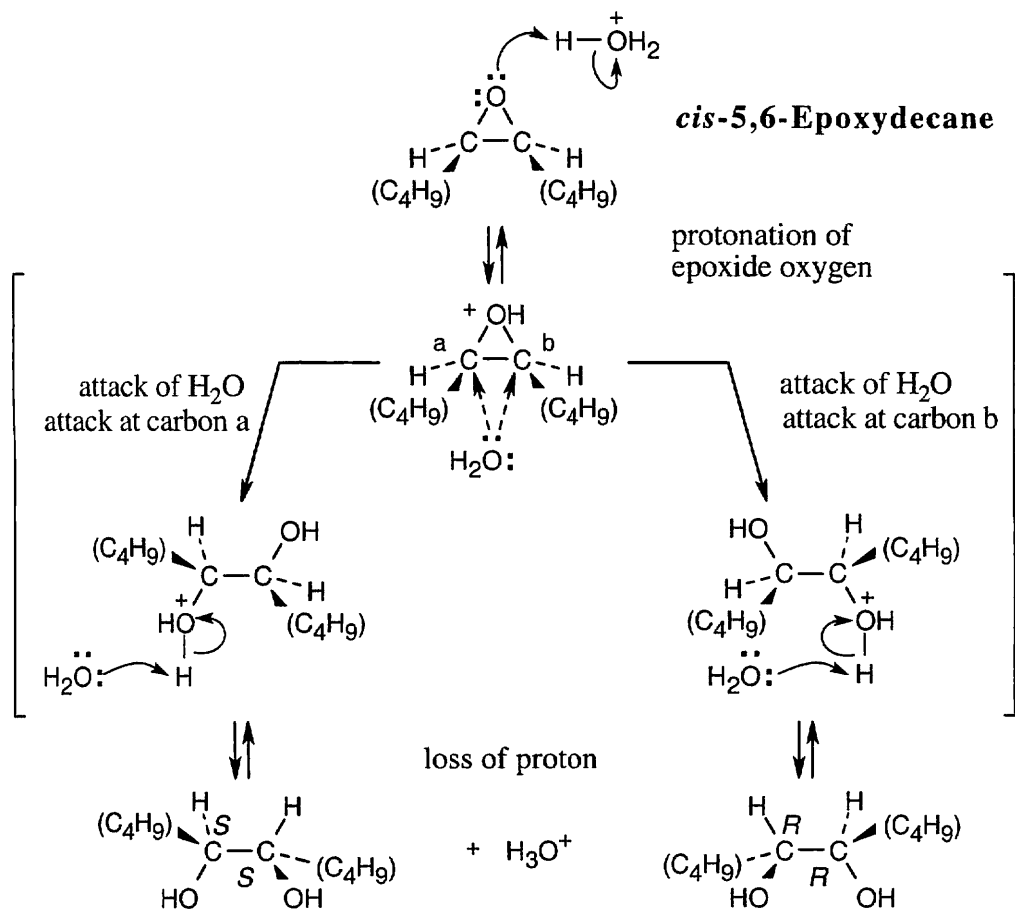


18.32



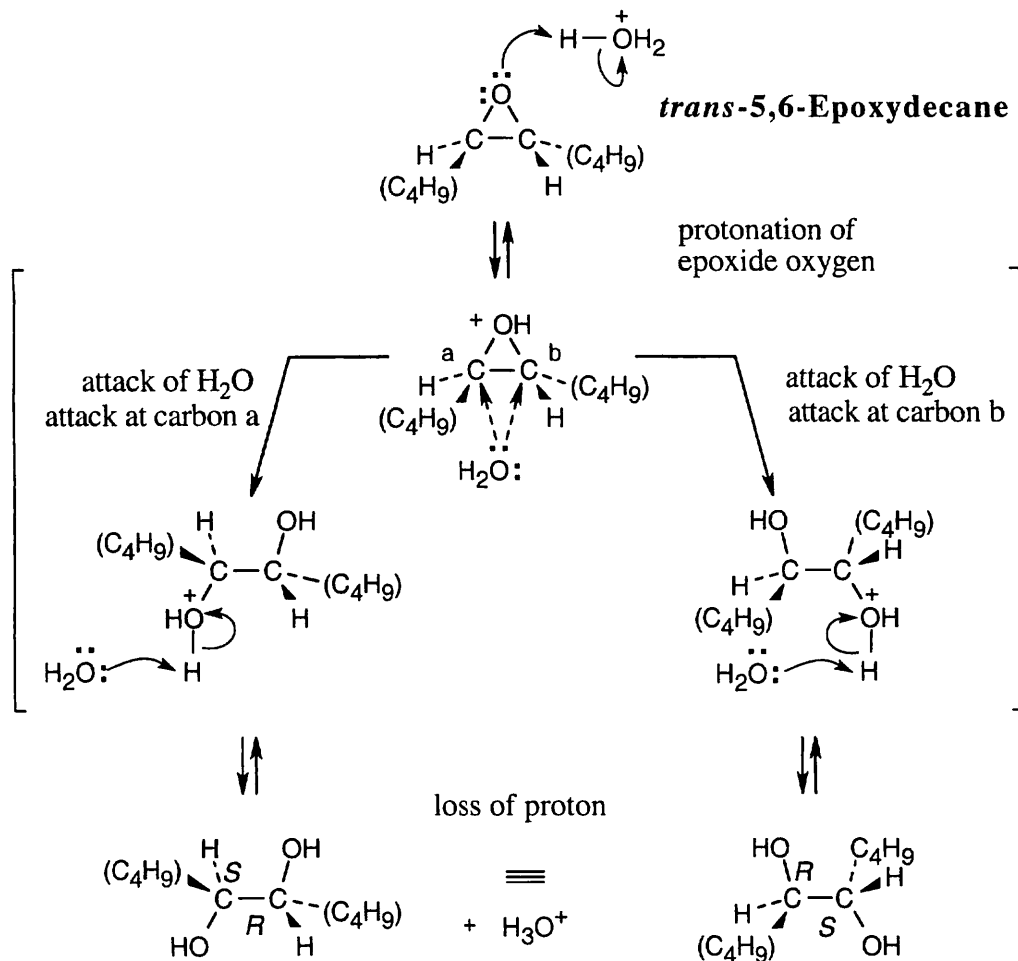
The reaction involves: (1) protonation of the tertiary hydroxyl group; (2) loss of water to form a tertiary carbocation; (3) nucleophilic attack on the carbocation by the second hydroxyl group. The tertiary hydroxyl group is more likely to be eliminated because the resulting carbocation is more stable.

18.33



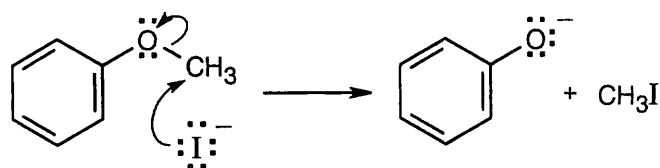
The product of acid hydrolysis of *cis*-5,6-epoxydecane is a racemic mixture of *R,R* and *S,S* diols.

18.34



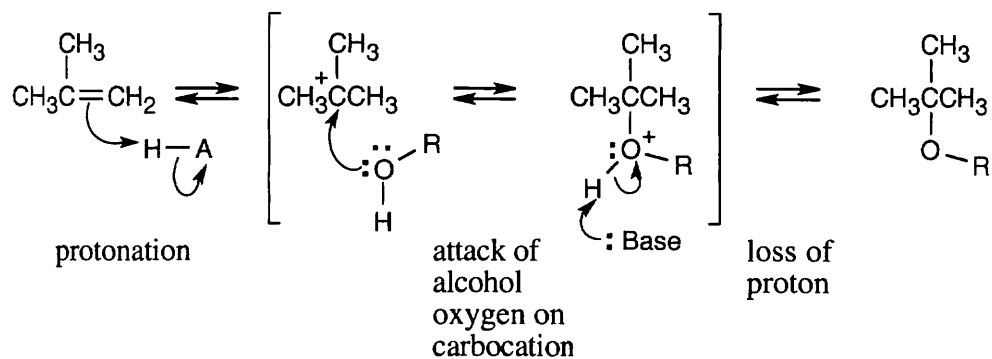
The product of acid hydrolysis of *trans*-5,6-epoxydecane is a meso compound that is a diastereomer of the products formed in the previous problem.

18.35



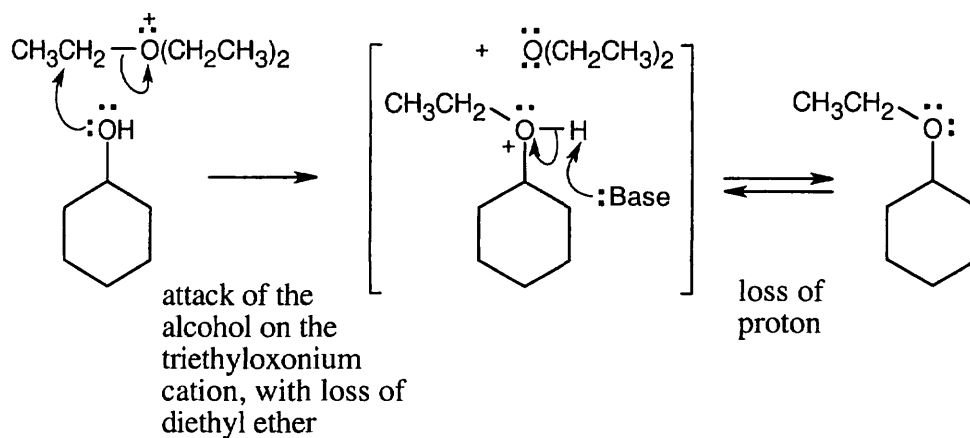
This reaction is an S_N2 displacement and can't occur at an aryl carbon. DMF is a polar aprotic solvent that increases the rate of an S_N2 reaction by making anions more nucleophilic.

18.36



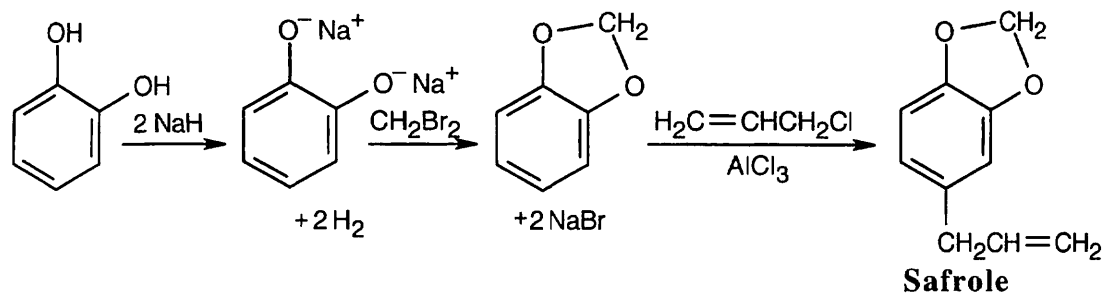
Notice that this reaction is the reverse of acid-catalyzed cleavage of a tertiary ether (Problem 18.8).

18.37

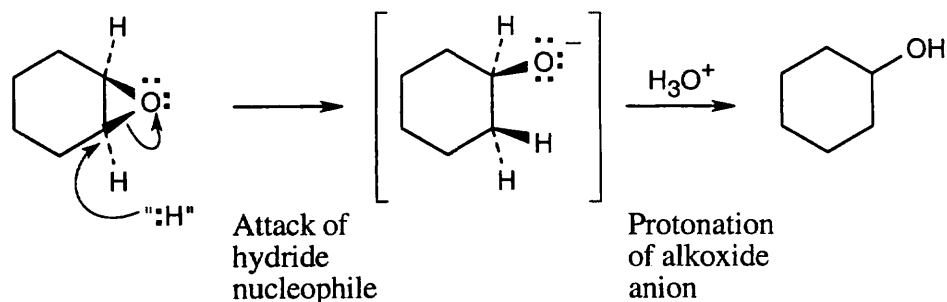


Trialkyloxonium salts are more reactive alkylating agents than alkyl iodides because a neutral ether is an even better leaving group than an iodide ion.

18.38

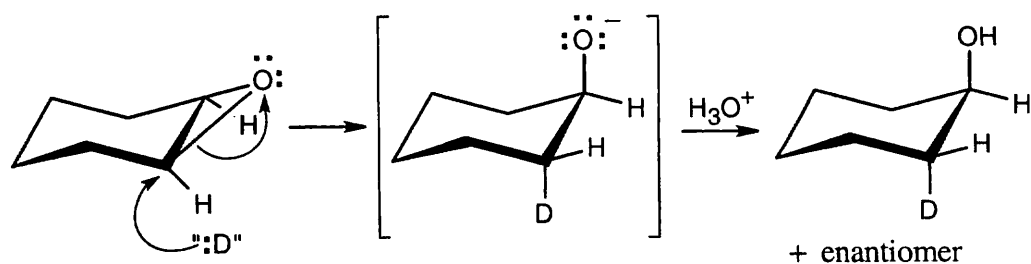


18.39



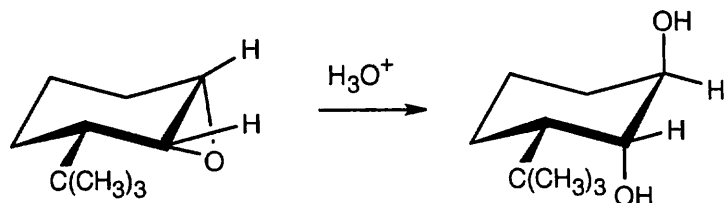
The reaction is an $\text{S}_{\text{N}}2$ epoxide cleavage with :H^- as the nucleophile. The exact nature of the attacking nucleophile is not clear.

18.40



Deuterium and -OH have a trans-diaxial relationship in the product.

18.41

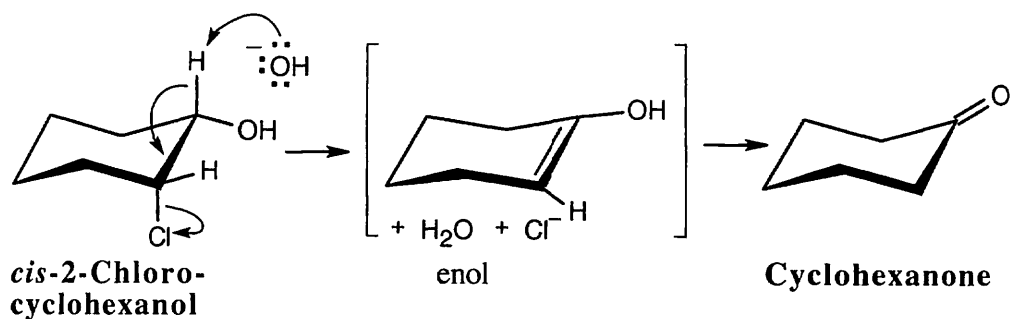
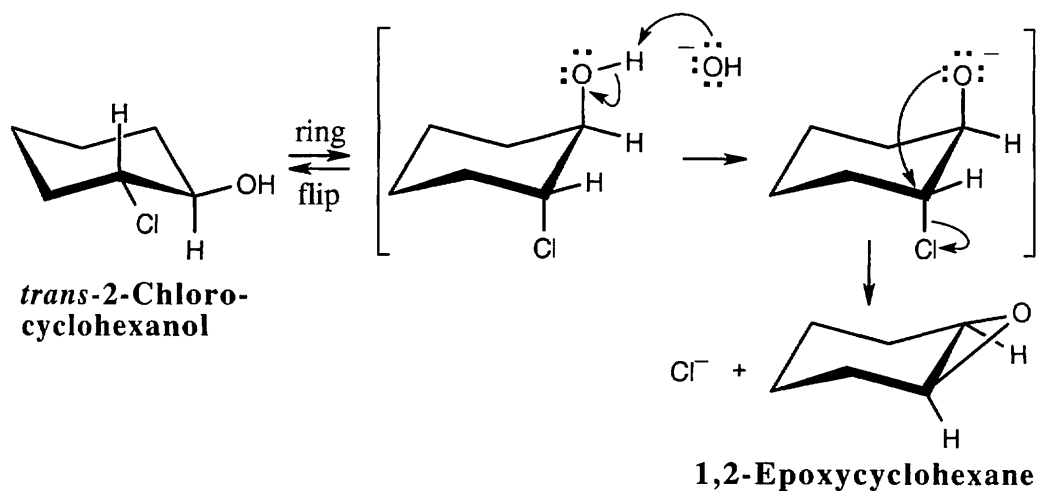


***cis*-3-*tert*-Butyl-1,2-epoxycyclohexane**

The hydroxyl groups in the product have a trans-diaxial relationship.

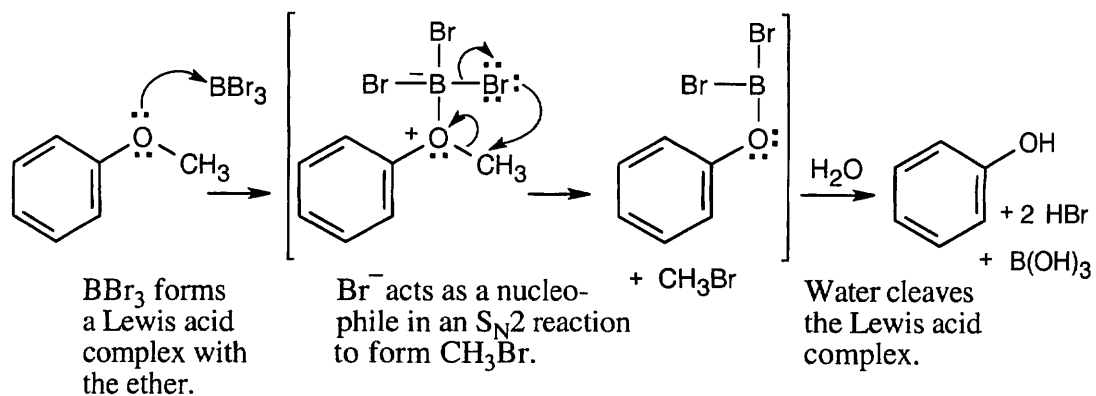
18.42 The mechanism of Grignard addition to oxetane is the same as the mechanism of Grignard addition to epoxides, described in Section 18.6. The reaction proceeds at a reduced rate because oxetane is less reactive than ethylene oxide. The four-membered ring oxetane is less strained, and therefore more stable, than the three-membered ethylene oxide ring.

18.43



In the trans isomer, the -OH and -Cl are in the trans orientation that allows epoxide formation to occur as described in Section 18.5. Epoxidation can't occur for the cis isomer, however. Instead, the base OH^- brings about E2 elimination, producing an enol, which tautomerizes to cyclohexanone.

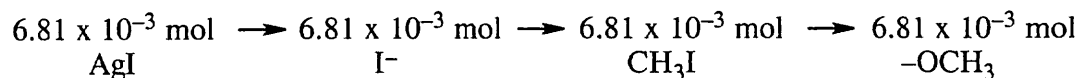
18.44



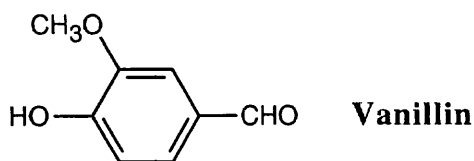
18.45

$$\frac{1.06 \text{ g vanillin}}{152 \text{ g/mol}} = 6.97 \times 10^{-3} \text{ mol vanillin}$$

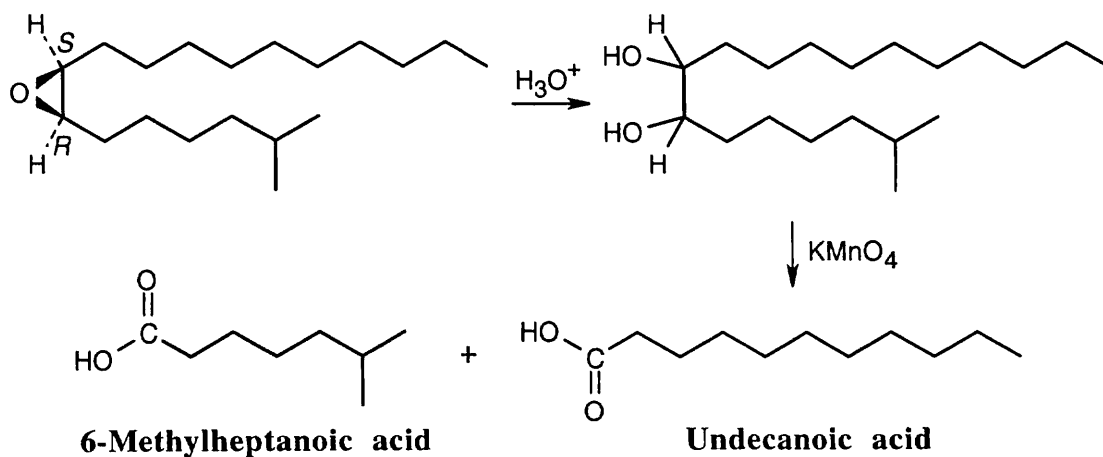
$$\frac{1.60 \text{ g AgI}}{234.8 \text{ g/mol}} = 6.81 \times 10^{-3} \text{ mol AgI}$$



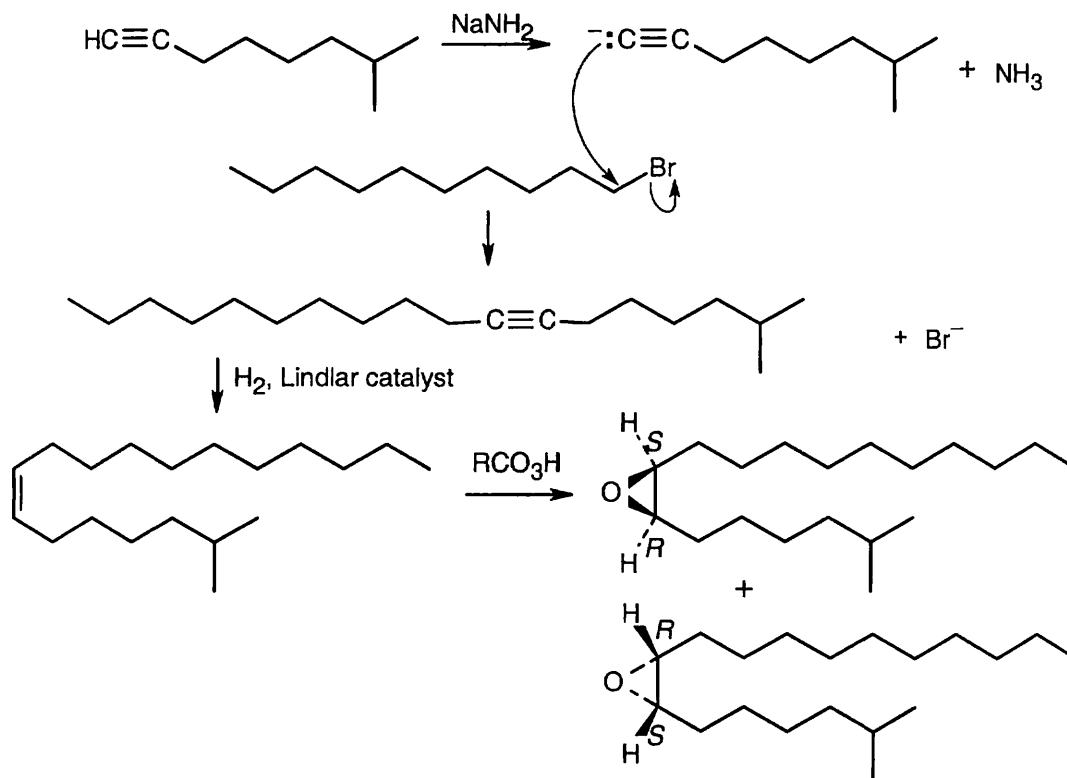
Thus, 6.97×10^{-3} mol of vanillin contain 6.81×10^{-3} mol of methoxyl groups. Since the ratio of moles vanillin to moles methoxyl is approximately 1:1, each vanillin contains one methoxyl group.



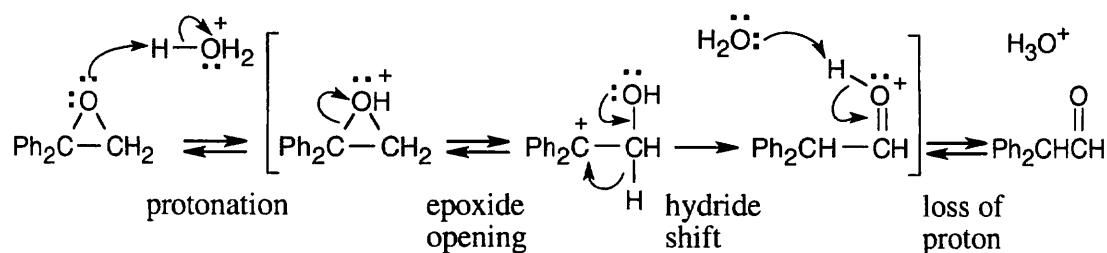
18.46 Disparlure, $\text{C}_{19}\text{H}_{38}\text{O}$, contains one degree of unsaturation, which the ^1H NMR absorption at 2.8 δ identifies as an epoxide ring.



18.47

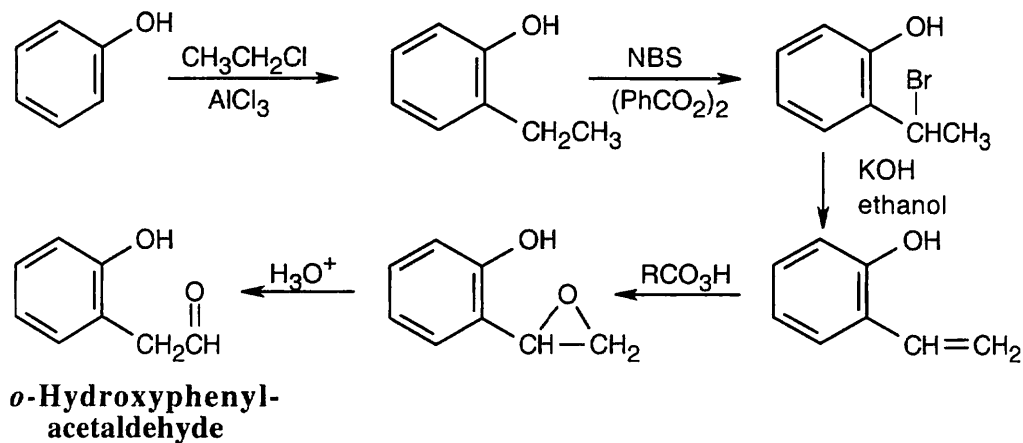


18.48



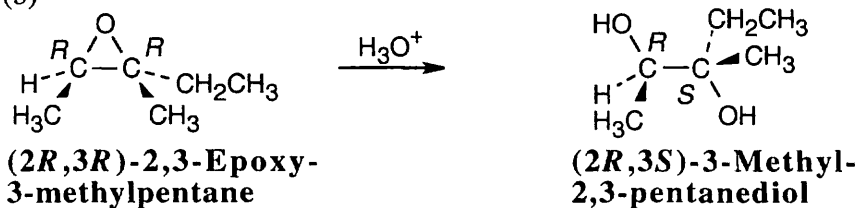
Reaction occurs by this route because of the stability of the intermediate carbocation.

18.49 Use the reaction shown in the previous problem.



18.50

(a) (b)

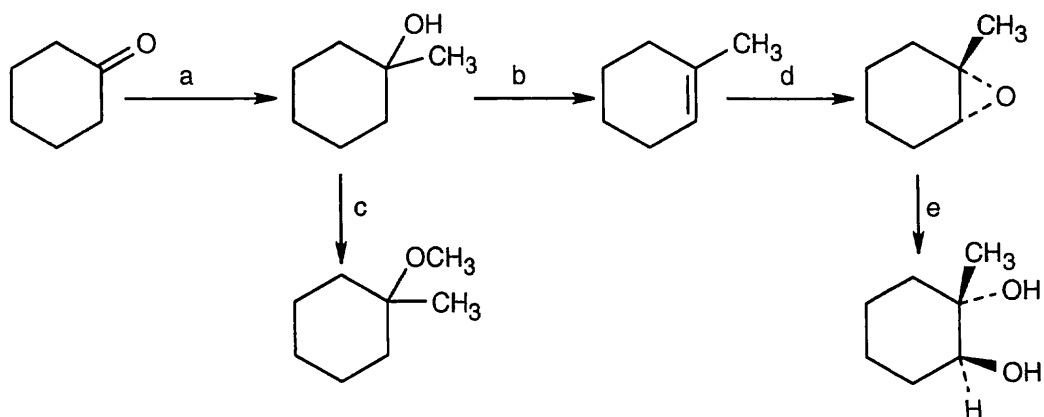


Reaction with aqueous acid causes ring opening to occur at C3 because the positive charge of the transition state is more stabilized at the tertiary carbon.

(c) If ring opening occurs exclusively at C3, the product is the 2*R*,3*S* isomer and is chiral. (If ring opening occurred equally at either carbon, the product would be a mixture of chiral enantiomers).

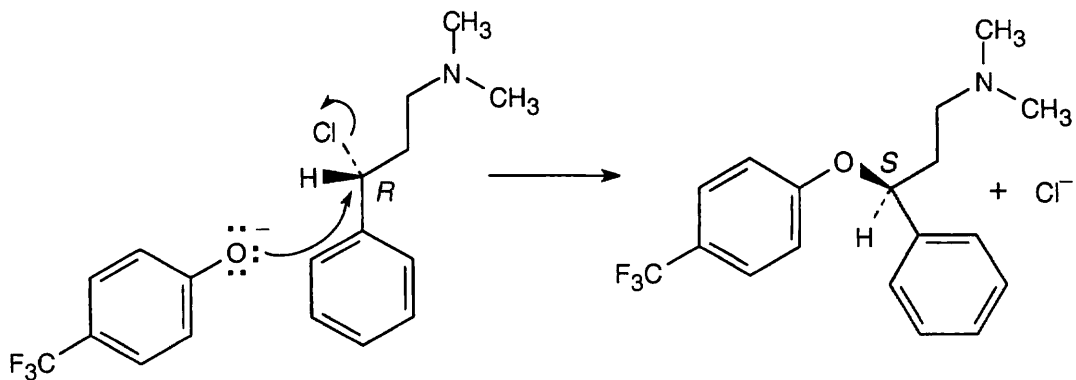
(d) The product is optically active because only one enantiomer is produced.

18.51

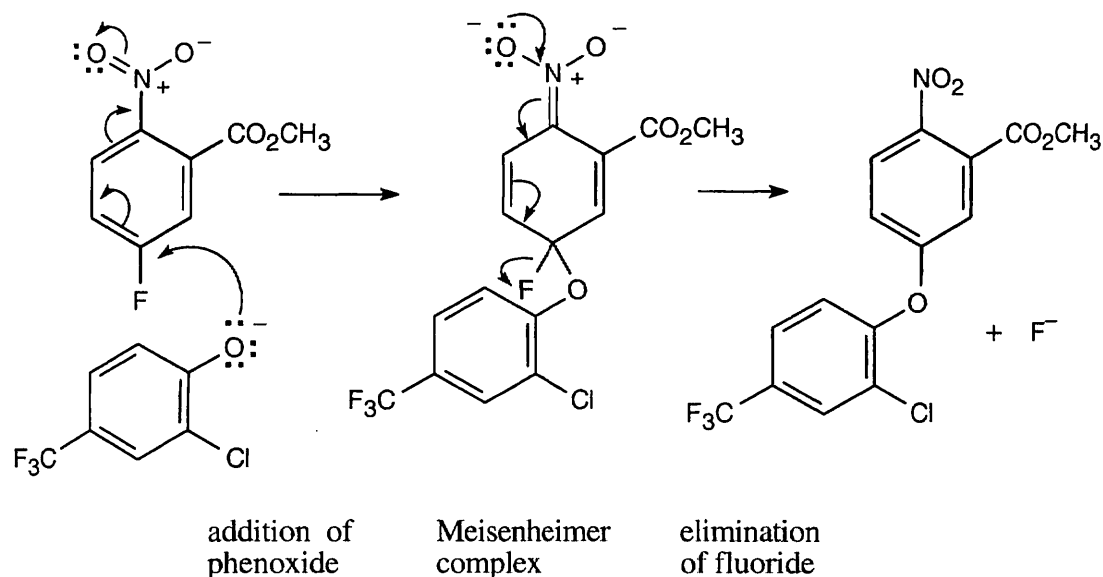


(a) CH_3MgBr , ether; (b) H_2SO_4 , H_2O ; (c) NaH , then CH_3I ; (d) $m\text{-ClC}_6\text{H}_4\text{CO}_3\text{H}$; (e) ^-OH , H_2O .

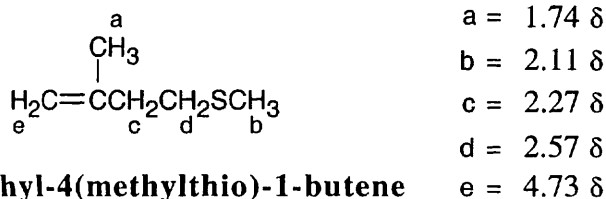
18.52 (a), (b) This S_N2 reaction is a Williamson ether synthesis, in which an alkoxide displaces a halogen. In this reaction, $NaOH$ is used to form the phenoxide anion.



18.53 The reaction is a nucleophilic aromatic substitution. The intermediate Meisenheimer complex is stabilized by the $-\text{NO}_2$ group.

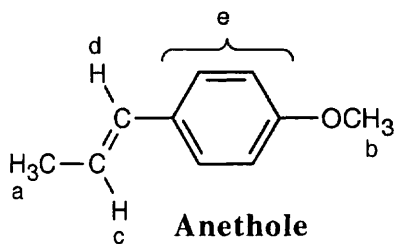


18.54 $M^+ = 116$ corresponds to a sulfide of molecular formula $\text{C}_6\text{H}_{12}\text{S}$, indicating one degree of unsaturation. The IR absorption at 890 cm^{-1} is due to a $\text{R}_2\text{C}=\text{CH}_2$ group.

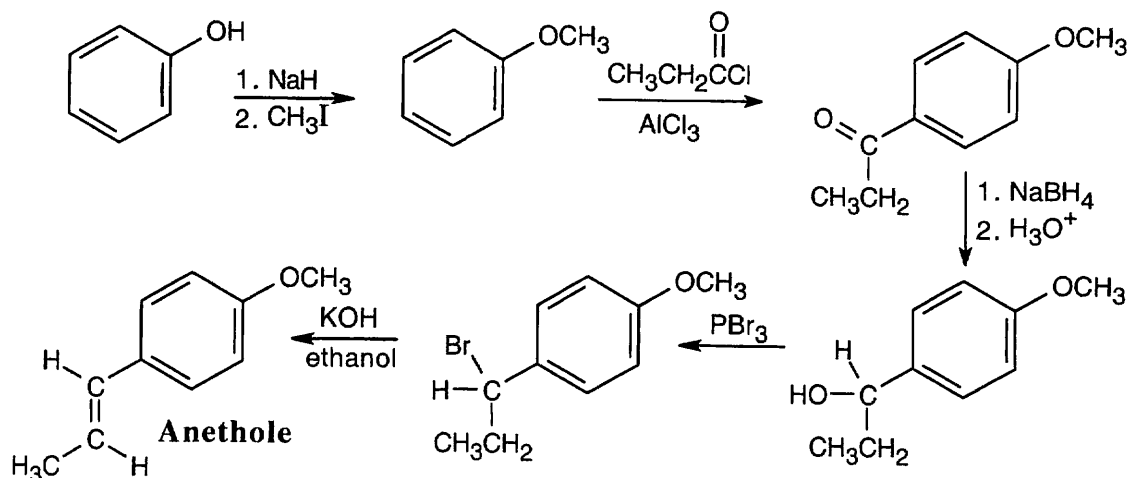


18.55

Peak	Chemical shift	Multiplicity	Split by:
a	1.83 δ	doublet	c
b	3.75 δ	singlet	
c	6.08 δ	two quartets	a, d
d	6.28 δ	doublet	c
e	6.80 δ , 7.23 δ	multiplet	

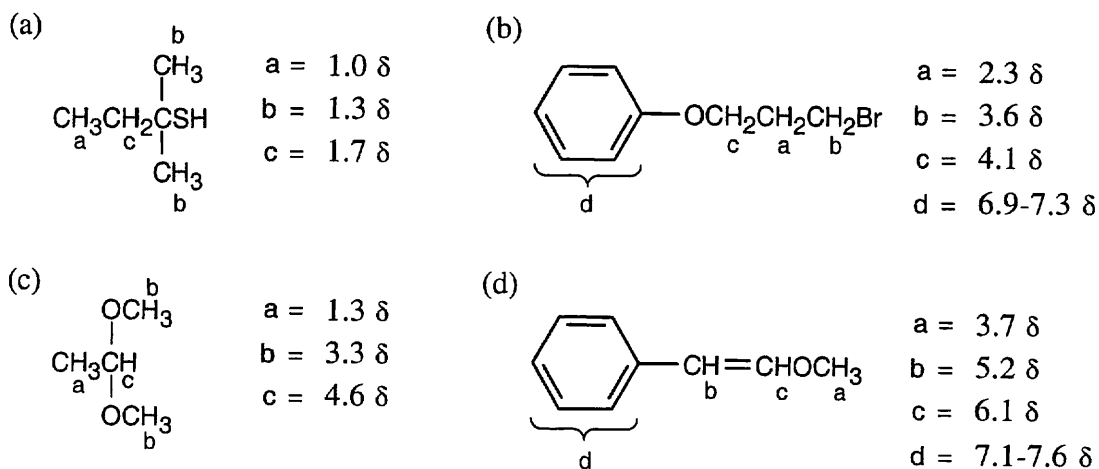


18.56

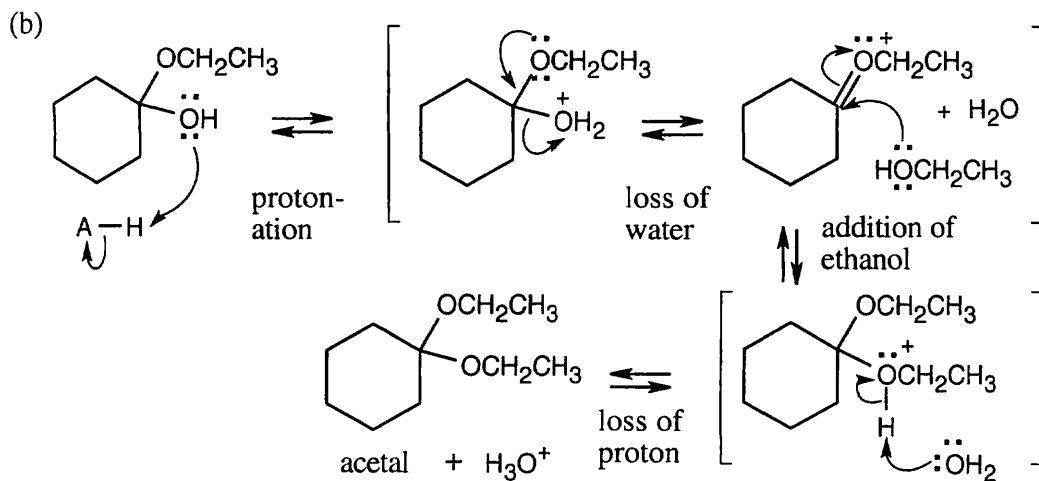
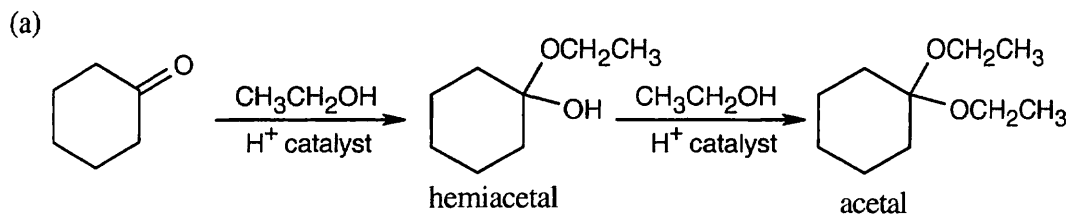


The anethole ring has two functional groups – an ether and a hydrocarbon side chain with a double bond. The ether is synthesized first – by a Williamson ether synthesis from phenol and CH₃I. The hydrocarbon side chain results from a Friedel–Crafts acylation of the ether. Reduction of the ketone, bromination and dehydrohalogenation are used to introduce the double bond.

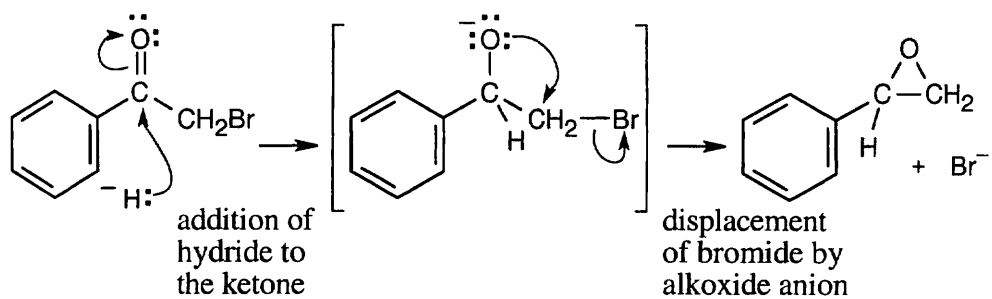
18.57



18.58



18.59



The intermediate resulting from addition of H^- is similar to the intermediate in a Williamson ether synthesis. Intramolecular reaction occurs to form the epoxide.

Review Unit 7: Alcohols, Ethers, and Related Compounds

Major Topics Covered (with vocabulary):

The -OH group:

alcohol phenol glycol wood alcohol hydrogen bonding alkoxide ion phenoxide ion
acidity constant

Alcohols:

Grignard Reagent pyridinium chlorochromate tosylate protecting group TMS ether

Phenols:

cumene hydroperoxide quinone hydroquinone ubiquinone

Acyclic ethers:

Williamson ether synthesis Claisen rearrangement

Cyclic ethers:

epoxide oxirane vicinal glycol peroxyacid crown ether 18-crown-6

Thiols and sulfides:

Thiol sulfide mercapto group alkylthio group disulfide thiolate ion trialkylsulfonium salt
sulfoxide sulfone

Types of Problems:

After studying these chapters, you should be able to:

- Name and draw structures of alcohols, phenols, ethers, thiols and sulfides.
- Explain the properties and acidity of alcohols and phenols.
- Prepare all of the types of compounds studied.
- Predict the products of reactions involving alcohols, phenols and ethers.
- Formulate mechanisms of reactions involving alcohols, phenols and ethers.
- Identify alcohols, phenols and ethers by spectroscopic techniques.

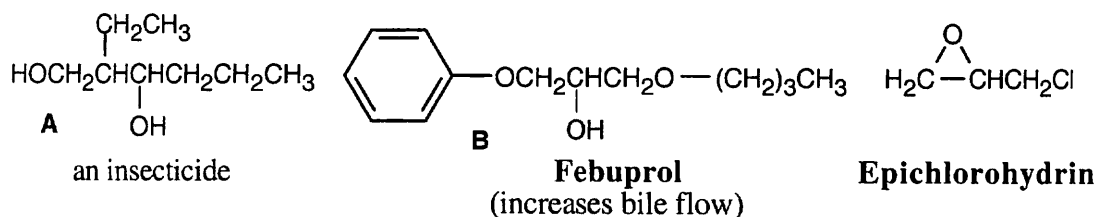
Points to Remember:

- * The great biochemical importance of hydroxyl groups is due to two factors: (1) Hydroxyl groups make biomolecules more soluble because they can hydrogen-bond with water. (2) Hydroxyl groups can be oxidized to aldehydes, ketones and carboxylic acids. The presence of a hydroxyl group in a biological molecule means that all functional groups derived from alcohols can be easily introduced.
- * Carbon-carbon bond-forming reactions are always more difficult to learn than functional group transformations because it is often difficult to recognize the components that form a carbon skeleton. The product of a Grignard reaction contains a hydroxyl group bonded to at least one alkyl group (usually two or three). When looking at a product that might have been formed by a Grignard reaction, remember that a tertiary alcohol results from the addition of a Grignard reagent to either a ketone or an ester (the alcohol formed from the ester has two identical -R groups), a secondary alcohol results from addition of a Grignard reagent to an aldehyde, and a

primary alcohol results from addition of a Grignard reagent to formaldehyde or to ethylene oxide. Remember that any molecule taking part in a Grignard reaction must not contain functional groups that might also react with the Grignard reagent.

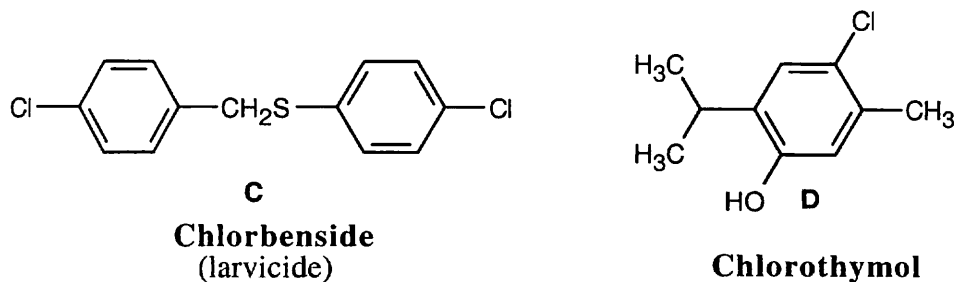
- * Ethers are quite unreactive, relative to many other functional groups we study, and are often used as solvents for that reason. Concentrated halogen acids can cleave ethers to alcohols and halides. Remember that the halide is bonded to the less substituted alkyl group when the ethers are primary or secondary alkyl ethers.
- * Epoxide rings can be opened by both acid and base. In basic ring-opening of an unsymmetrical epoxide (and in ring-opening using a Grignard reagent), attack occurs at the less substituted carbon of the epoxide ring. In acidic ring opening, the position of attack depends on the substitution pattern of the epoxide. When one of the epoxide carbons is tertiary, attack occurs at the more substituted carbon, but when the epoxide carbons are both primary or secondary, attack occurs at the less substituted carbon.
- * The most useful spectroscopic data for these compounds: (1) A broad IR absorption in the range 3300 cm^{-1} – 3600 cm^{-1} shows the presence of the -OH group of an alcohol or a phenol. (2) Hydrogens bonded to the -O-C- carbon of an alcohol or ether absorb in the range $3.5\text{--}4.5\text{ }\delta$ in an ^1H NMR spectrum or in the range $50\text{--}80\text{ }\delta$ in a ^{13}C NMR spectrum.

Self-Test:



Provide a IUPAC name for **A** and identify chiral carbons. Would you expect **A** to be water-soluble? Label the hydroxyl groups of **A** as primary, secondary or tertiary. What products are formed when **A** reacts with: (a) CrO_3 , H_3O^+ ; (b) PBr_3 ; (c) $(\text{CH}_3)_3\text{SiCl}$, Et_3N .

Name **B** by IUPAC rules. Show the three components that comprise **B**. The synthesis of **B** involves a ring-opening reaction of the epoxide epichlorohydrin. Use this information to propose a synthesis of **B** from epichlorohydrin and any alcohol or phenol.



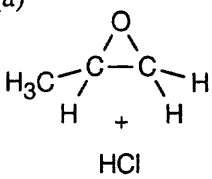
What type of compound is **C**? Name **C**. Synthesize **C** from benzenethiol and benzene. What products are formed when **C** is treated with: (a) CH_3I ; (b) H_2O_2 , H_2O ; (c) product of (b) + $\text{CH}_3\text{CO}_3\text{H}$.

Synthesize **D** from *m*-cresol; assume that isomeric product mixtures can be separated. Describe the IR and ^1H NMR spectrum of **D**.

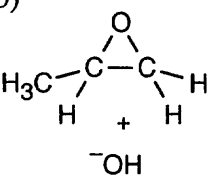
Multiple Choice:

- Hydrogen bonding affects all of the following except:
(a) boiling point (b) solubility (c) position of -OH absorption in IR spectrum (d) chemical shift of -C-O- carbon in ^{13}C NMR.
- Which of the following alcohols can't be synthesized by a Grignard reaction?
(a) Benzyl alcohol (b) Triphenylmethanol (c) 3-Bromo-1-hexanol (d) 1-Hexanol
- Which of the following reactions of a chiral alcohol occurs with inversion of configuration?
(a) reaction with NaH (b) reaction with PBr_3 (c) reaction with tosyl chloride (d) reaction with $(\text{CH}_3)_3\text{SiCl}$
- How many diols of the formula $\text{C}_4\text{H}_{10}\text{O}_2$ are chiral?
(a) 2 (b) 3 (c) 4 (d) 5
- Which alcohol is the least acidic?
(a) 2-Propanol (b) Methanol (c) Ethanol (d) 2-Chloroethanol
- Which of the following compounds can't be reduced to form $\text{C}_6\text{H}_5\text{CH}_2\text{OH}$?
(a) $\text{C}_6\text{H}_5\text{CO}_2\text{H}$ (b) $\text{C}_6\text{H}_5\text{CHO}$ (c) $\text{C}_6\text{H}_5\text{CO}_2\text{CH}_3$ (d) $\text{C}_6\text{H}_5\text{OCH}_3$
- The reagent used for dehydration of an alcohol is:
(a) PCl_3 (b) POCl_3 (c) SOCl_2 (d) PCC
- All of the following are products of oxidation of a thiol except:
(a) a sulfide (b) a disulfide (c) a sulfoxide (d) a sulfone
- In which of the following epoxide ring-opening reactions does attack of the nucleophile occur at the more substituted carbon of the epoxide ring?

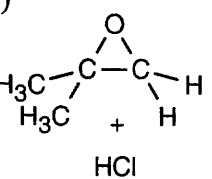
(a)



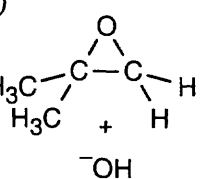
(b)



(c)



(d)


- Ethers are stable to all of the following reagents except:
(a) nucleophiles (b) bases (c) strong acids (d) dilute acids