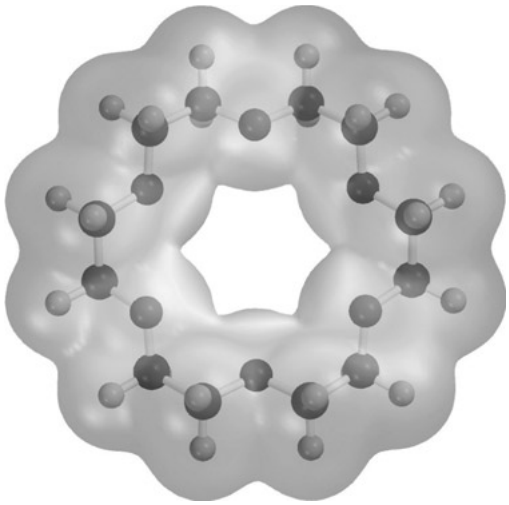
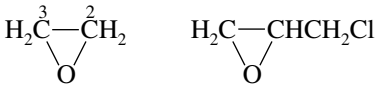


CHAPTER 16

ETHERS, EPOXIDES, AND SULFIDES

SOLUTIONS TO TEXT PROBLEMS

16.1 (*b*) Oxirane is the IUPAC name for ethylene oxide. A chloromethyl group ($ClCH_2$—) is attached to position 2 of the ring in 2-(chloromethyl)oxirane.

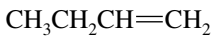


Oxirane

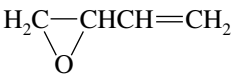
2-(Chloromethyl)oxirane

This compound is more commonly known as **epichlorohydrin.**

(*c*) Epoxides may be named by adding the prefix *epoxy* to the IUPAC name of a parent compound, specifying by number both atoms to which the oxygen is attached.

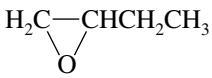


1-Butene



3,4-Epoxy-1-butene

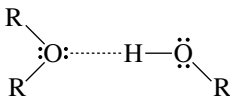
16.2 1,2-Epoxybutane and tetrahydrofuran both have the molecular formula C_4H_8O—that is, they are constitutional isomers—and so it is appropriate to compare their heats of combustion directly. Angle strain from the three-membered ring of 1,2-epoxybutane causes it to have more internal energy than tetrahydrofuran, and its combustion is more exothermic.



1,2-Epoxybutane;
heat of combustion 2546 kJ/mol
(609.1 kcal/mol)

Tetrahydrofuran;
heat of combustion 2499 kJ/mol
(597.8 kcal/mol)

16.3 An ether can function only as a proton acceptor in a hydrogen bond, but an alcohol can be either a proton acceptor or a donor. The only hydrogen bond possible between an ether and an alcohol is therefore the one shown:

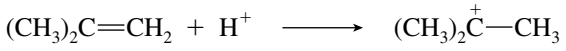


Ether Alcohol

16.4 The compound is 1,4-dioxane; it has a six-membered ring and two oxygens separated by CH_2—CH_2 units.

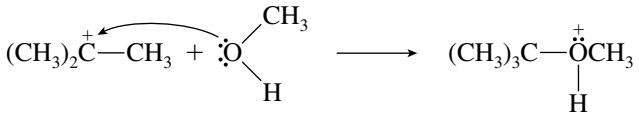
1,4-dioxane
("6-crown-2")

16.5 Protonation of the carbon–carbon double bond leads to the more stable carbocation.

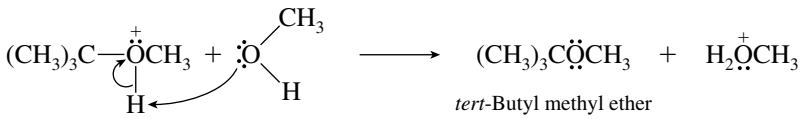


2-Methylpropene *tert*-Butyl cation

Methanol acts as a nucleophile to capture *tert*-butyl cation.



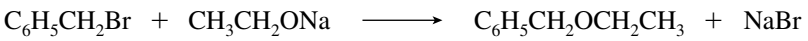
Deprotonation of the alkyloxonium ion leads to formation of *tert*-butyl methyl ether.



tert-Butyl methyl ether

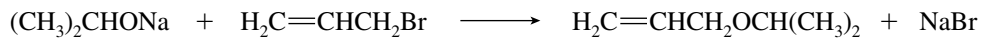
16.6 Both alkyl groups in benzyl ethyl ether are primary, thus either may come from the alkyl halide in a Williamson ether synthesis. The two routes to benzyl ethyl ether are

Sodium benzyloxide Bromoethane Benzyl ethyl ether Sodium bromide



Benzyl bromide Sodium ethoxide Benzyl ethyl ether Sodium bromide

16.7 (*b*) A primary carbon and a secondary carbon are attached to the ether oxygen. The secondary carbon can only be derived from the alkoxide, because secondary alkyl halides cannot be used in the preparation of ethers by the Williamson method. The only effective method uses an allyl halide and sodium isopropoxide.



Sodium isopropoxide Allyl bromide Allyl isopropyl ether Sodium bromide

Elimination will be the major reaction of an isopropyl halide with an alkoxide base.

(*c*) Here the ether is a mixed primary–tertiary one. The best combination is the one that uses the primary alkyl halide.

$$(CH_3)_3COK + C_6H_5CH_2Br \longrightarrow (CH_3)_3COCH_2C_6H_5 + KBr$$

Potassium *tert*-butoxide; Benzyl bromide; Benzyl *tert*-butyl ether; Potassium bromide

The reaction between $(CH_3)_3CBr$ and $C_6H_5CH_2O^-$ is elimination, not substitution.

16.8

$$CH_3CH_2OCH_2CH_3 + 6O_2 \longrightarrow 4CO_2 + 5H_2O$$

Diethyl ether; Oxygen; Carbon dioxide; Water

16.9 (*b*) If benzyl bromide is the only organic product from reaction of a dialkyl ether with hydrogen bromide, then both alkyl groups attached to oxygen must be benzyl.

$$C_6H_5CH_2OCH_2C_6H_5 \xrightarrow[\text{heat}]{\text{HBr}} 2C_6H_5CH_2Br + H_2O$$

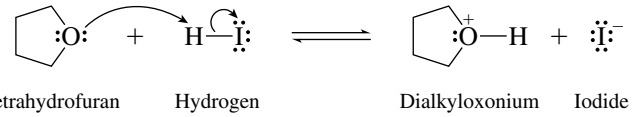
Dibenzyl ether; Benzyl bromide; Water

(*c*) Since *1 mole of a dihalide,* rather than 2 moles of a monohalide, is produced per mole of ether, the ether must be cyclic.

$$\xrightarrow[\text{heat}]{\text{2HBr}} BrCH_2CH_2CH_2CH_2CH_2Br + H_2O$$

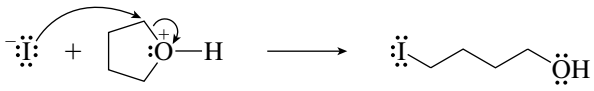
Tetrahydropyran; 1,5-Dibromopentane; Water

16.10 As outlined in text Figure 16.4, the first step is protonation of the ether oxygen to give a dialkyloxonium ion.



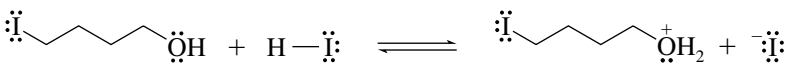
Tetrahydrofuran; Hydrogen iodide; Dialkyloxonium ion; Iodide ion

In the second step, nucleophilic attack of the halide ion on carbon of the oxonium ion gives 4-iodo-1-butanol.



Iodide ion; Dialkyloxonium ion; 4-Iodo-1-butanol

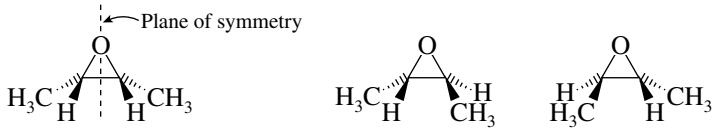
The remaining two steps of the mechanism correspond to those in which an alcohol is converted to an alkyl halide, as discussed in Chapter 4.



4-Iodo-1-butanol; Hydrogen iodide

1,4-Diiodobutane; Water

16.11 The cis epoxide is achiral. It is a meso form containing a plane of symmetry. The trans isomer is chiral; its two mirror-image representations are not superposable.

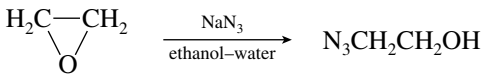


cis-2,3-Epoxybutane (Plane of symmetry passes through oxygen and midpoint of carbon–carbon bond.)

Nonsuperposable mirror-image (enantiomeric) forms of *trans*-2,3-epoxybutane

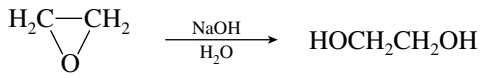
Neither the cis nor the trans epoxide is optically active when formed from the alkene. The cis epoxide is achiral; it cannot be optically active. The trans epoxide is capable of optical activity but is formed as a racemic mixture because achiral starting materials are used.

16.12 (*b*) Azide ion $[:\ddot{N}{=}N{=}\ddot{N}:]^-$ is a good nucleophile, reacting readily with ethylene oxide to yield 2-azidoethanol.



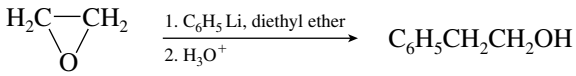
Ethylene oxide — 2-Azidoethanol

(*c*) Ethylene oxide is hydrolyzed to ethylene glycol in the presence of aqueous base.



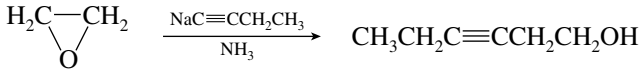
Ethylene oxide — Ethylene glycol

(*d*) Phenyllithium reacts with ethylene oxide in a manner similar to that of a Grignard reagent.



Ethylene oxide — 2-Phenylethanol

(*e*) The nucleophilic species here is the acetylenic anion $CH_3CH_2C{\equiv}C:^-$, which attacks a carbon atom of ethylene oxide to give 3-hexyn-1-ol.

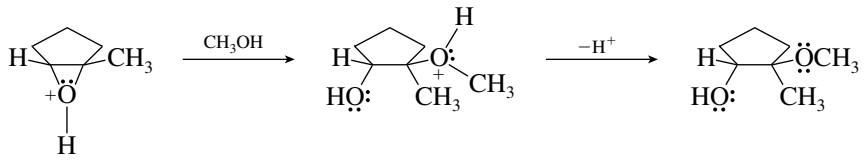


Ethylene oxide — 3-Hexyn-1-ol (48%)

16.13 Nucleophilic attack at C-2 of the starting epoxide will be faster than attack at C-1, because C-1 is more sterically hindered. Compound A, corresponding to attack at C-1, is not as likely as compound B. Compound B not only arises by methoxide ion attack at C-2 but also satisfies the stereochemical requirement that epoxide ring opening take place with inversion of configuration at the site of substitution. Compound B is correct. Compound C, although it is formed by methoxide substitution at the less crowded carbon of the epoxide, is wrong stereochemically. It requires

substitution with retention of configuration, which is not the normal mode of epoxide ring opening.

16.14 Acid-catalyzed nucleophilic ring opening proceeds by attack of methanol at the more substituted carbon of the protonated epoxide. Inversion of configuration is observed at the site of attack. The correct product is compound A.

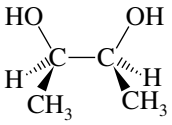


Protonated form of 1-methyl-1,2-epoxycyclopentane

Compound A

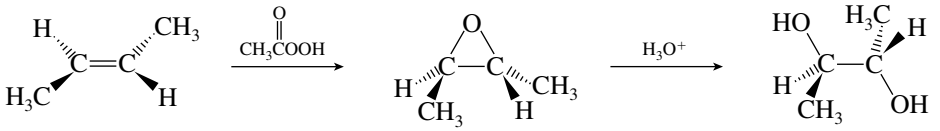
The nucleophilic ring openings in both this problem and Problem 16.13 occur by inversion of configuration. Attack under basic conditions by methoxide ion, however, occurs at the *less* hindered carbon of the epoxide ring, whereas attack by methanol under acid-catalyzed conditions occurs at the *more* substituted carbon.

16.15 Begin by drawing *meso*-2,3-butanediol, recalling that a meso form is achiral. The eclipsed conformation has a plane of symmetry.



meso-2,3-Butanediol

Epoxidation followed by acid-catalyzed hydrolysis results in anti addition of hydroxyl groups to the double bond. *trans*-2-Butene is the required starting material.

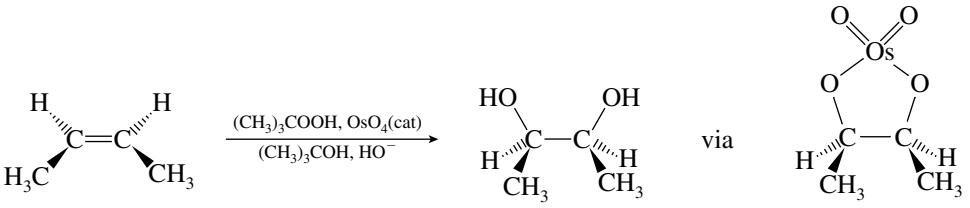


trans-2-Butene

trans-2,3-Epoxybutane

meso-2,3-Butanediol

Osmium tetraoxide hydroxylation is a method of achieving syn hydroxylation. The necessary starting material is *cis*-2-butene.

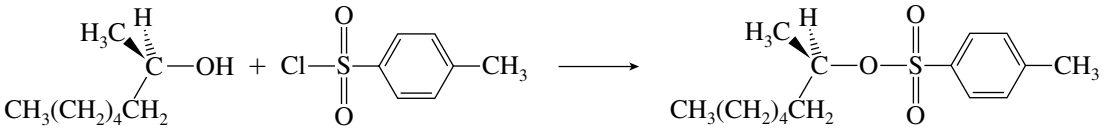


cis-2-Butene

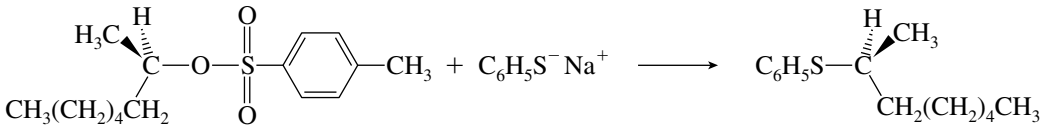
meso-2,3-Butanediol

16.16 Reaction of (*R*)-2-octanol with *p*-toluenesulfonyl chloride yields a *p*-toluenesulfonate ester (tosylate) having the same configuration; the stereogenic center is not involved in this step. Reaction

of the tosylate with a nucleophile proceeds by inversion of configuration in an S_N2 process. The product has the *S* configuration.

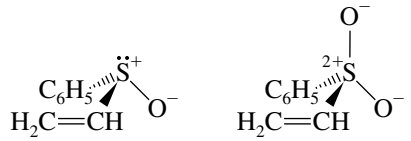


(*R*)-2-Octanol — *p*-Toluenesulfonyl chloride — (*R*)-1-Methylheptyl tosylate



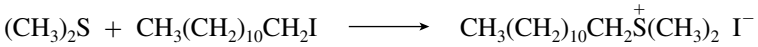
(*R*)-1-Methylheptyl tosylate — Sodium benzenethiolate — (*S*)-1-Methylheptyl phenyl sulfide

16.17 Phenyl vinyl sulfoxide lacks a plane of symmetry and is chiral. Phenyl vinyl sulfone is achiral; a plane of symmetry passes through the phenyl and vinyl groups and the central sulfur atom.



Phenyl vinyl sulfoxide (chiral) — Phenyl vinyl sulfone (achiral)

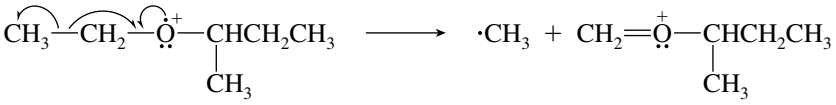
16.18 As shown in the text, dodecyldimethylsulfonium iodide may be prepared by reaction of dodecyl methyl sulfide with methyl iodide. An alternative method is the reaction of dodecyl iodide with dimethyl sulfide.



Dimethyl sulfide — Dodecyl iodide — Dodecyldimethylsulfonium iodide

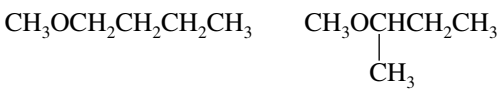
The reaction of a sulfide with an alkyl halide is an S_N2 process. The faster reaction will be the one that uses the less sterically hindered alkyl halide. The method presented in the text will proceed faster.

16.19 The molecular ion from *sec*-butyl ethyl ether can also fragment by cleavage of a carbon–carbon bond in its ethyl group to give an oxygen-stabilized cation of m/z 87.



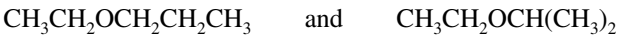
m/z 87

16.20 All the constitutionally isomeric ethers of molecular formula $C_5H_{12}O$ belong to one of two general groups: $CH_3OC_4H_9$ and $CH_3CH_2OC_3H_7$. Thus, we have



Butyl methyl ether — *sec*-Butyl methyl ether

Isobutyl methyl ether — *tert*-Butyl methyl ether

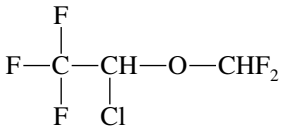


Ethyl propyl ether — Ethyl isopropyl ether

These ethers could also have been named as "alkoxyalkanes." Thus, *sec*-butyl methyl ether would become 2-methoxybutane.

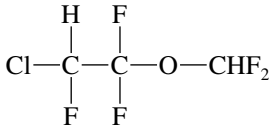
16.21 Isoflurane and enflurane are both halogenated derivatives of ethyl methyl ether.

Isoflurane:



1-Chloro-2,2,2-trifluoroethyl difluoromethyl ether

Enflurane:

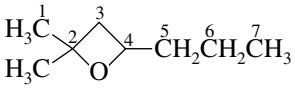


2-Chloro-1,1,2-trifluoroethyl difluoromethyl ether

16.22 (*a*) The parent compound is cyclopropane. It has a three-membered epoxide function, and thus a reasonable name is epoxycyclopropane. Numbers locating positions of attachment (as in "1,2-epoxycyclopropane") are not necessary, because no other structures (1,3 or 2,3) are possible here.

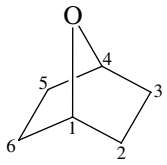
Epoxycyclopropane

(*b*) The longest continuous carbon chain has seven carbons, and so the compound is named as a derivative of heptane. The epoxy function bridges C-2 and C-4. Therefore



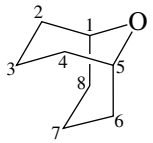
is 2-methyl-2,4-epoxyheptane.

(*c*) The oxygen atom bridges the C-1 and C-4 atoms of a cyclohexane ring.



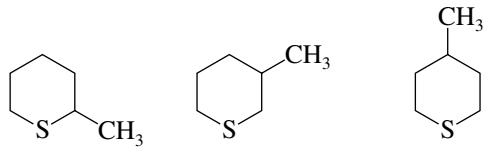
1,4-Epoxycyclohexane

(*d*) Eight carbon atoms are continuously linked and bridged by an oxygen. We name the compound as an epoxy derivative of cyclooctane.



1,5-Epoxycyclooctane

16.23 (*a*) There are three methyl-substituted thianes, two of which are chiral.



2-Methylthiane (chiral) | 3-Methylthiane (chiral) | 4-Methylthiane (achiral)

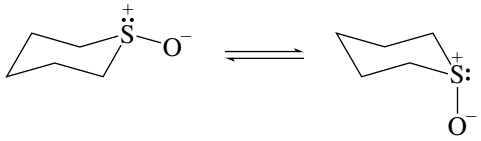
(*b*) The locants in the name indicate the positions of the sulfur atoms in 1,4-dithiane and 1,3,5-trithiane.

1,4-Dithiane | 1,3,5-Trithiane

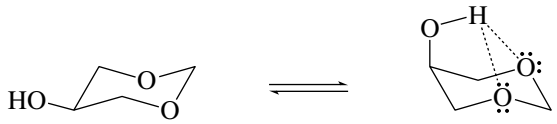
(*c*) Disulfides possess two adjacent sulfur atoms. 1,2-Dithiane is a disulfide.

1,2-Dithiane

(*d*) Two chair conformations of the sulfoxide derived from thiane are possible; the oxygen atom may be either equatorial or axial.



16.24 Intramolecular hydrogen bonding between the hydroxyl group and the ring oxygens is possible when the hydroxyl group is axial but not when it is equatorial.



Less stable conformation; no intramolecular hydrogen bonding | More stable conformation; stabilized by hydrogen bonding

16.25 The ethers that are to be prepared are

$CH_3OCH_2CH_2CH_3$ Methyl propyl ether | $CH_3OCH(CH_3)_2$ Isopropyl methyl ether | and | $CH_3CH_2OCH_2CH_3$ Diethyl ether

First examine the preparation of each ether by the Williamson method. Methyl propyl ether can be prepared in two ways:

$$CH_3ONa + CH_3CH_2CH_2Br \longrightarrow CH_3OCH_2CH_2CH_3$$

Sodium methoxide | 1-Bromopropane | Methyl propyl ether

$$CH_3Br + CH_3CH_2CH_2ONa \longrightarrow CH_3OCH_2CH_2CH_3$$

Methyl bromide | Sodium propoxide | Methyl propyl ether

Either combination is satisfactory. The necessary reagents are prepared as shown.

$$\underset{\text{Methanol}}{CH_3OH} \xrightarrow{Na} \underset{\text{Sodium methoxide}}{CH_3ONa}$$

$$\underset{\text{1-Propanol}}{CH_3CH_2CH_2OH} \xrightarrow[\text{(or HBr)}]{PBr_3} \underset{\text{1-Bromopropane}}{CH_3CH_2CH_2Br}$$

$$\underset{\text{Methanol}}{CH_3OH} \xrightarrow[\text{(or HBr)}]{PBr_3} \underset{\text{Methyl bromide}}{CH_3Br}$$

$$\underset{\text{1-Propanol}}{CH_3CH_2CH_2OH} \xrightarrow{Na} \underset{\text{Sodium propoxide}}{CH_3CH_2CH_2ONa}$$

Isopropyl methyl ether is best prepared by the reaction

$$\underset{\text{Methyl bromide}}{CH_3Br} + \underset{\text{Sodium isopropoxide}}{(CH_3)_2CHONa} \longrightarrow \underset{\text{Isopropyl methyl ether}}{CH_3OCH(CH_3)_2}$$

The reaction of sodium methoxide with isopropyl bromide will proceed mainly by elimination. Methyl bromide is prepared as shown previously; sodium isopropoxide can be prepared by adding sodium to isopropyl alcohol.

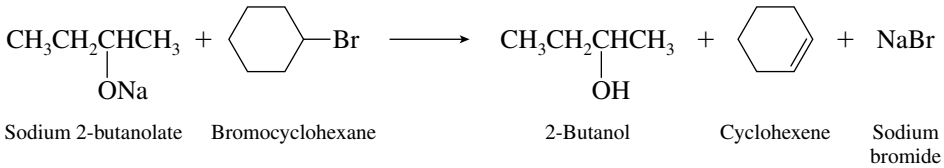
Diethyl ether may be prepared as outlined:

$$\underset{\text{Ethanol}}{CH_3CH_2OH} \xrightarrow{Na} \underset{\text{Sodium ethoxide}}{CH_3CH_2ONa}$$

$$\underset{\text{Ethanol}}{CH_3CH_2OH} \xrightarrow[\text{(or HBr)}]{PBr_3} \underset{\text{Ethyl bromide}}{CH_3CH_2Br}$$

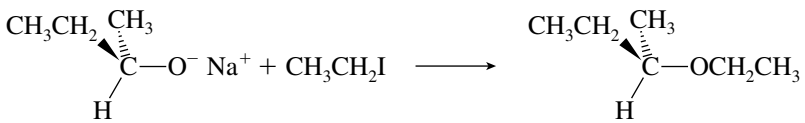
$$\underset{\text{Sodium ethoxide}}{CH_3CH_2ONa} + \underset{\text{Ethyl bromide}}{CH_3CH_2Br} \longrightarrow \underset{\text{Diethyl ether}}{CH_3CH_2OCH_2CH_3} + \underset{\text{Sodium bromide}}{NaBr}$$

16.26 (*a*) Secondary alkyl halides react with alkoxide bases by E2 elimination as the major pathway. The Williamson ether synthesis is not a useful reaction with secondary alkyl halides.



Sodium 2-butanolate — Bromocyclohexane — 2-Butanol — Cyclohexene — Sodium bromide

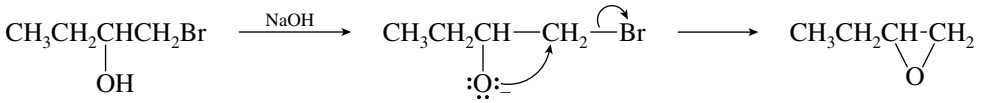
(*b*) Sodium alkoxide acts as a nucleophile toward iodoethane to yield an alkyl ethyl ether.



(*R*)-2-Ethoxybutane

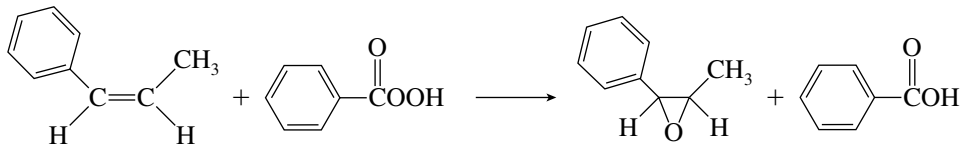
The ether product has the same absolute configuration as the starting alkoxide because no bonds to the stereogenic center are made or broken in the reaction.

(*c*) Vicinal halohydrins are converted to epoxides on being treated with base.



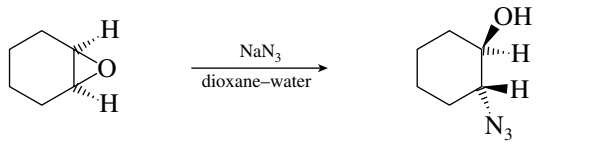
1-Bromo-2-butanol 1,2-Epoxybutane

(*d*) The reactants, an alkene plus a peroxy acid, are customary ones for epoxide preparation. The reaction is a stereospecific syn addition of oxygen to the double bond.



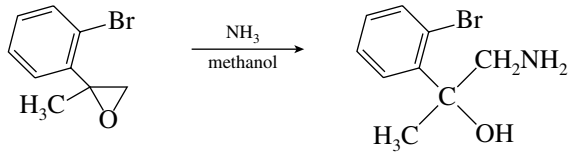
(*Z*)-1-Phenylpropene Peroxybenzoic acid *cis*-2-Methyl-3-phenyloxirane Benzoic acid

(*e*) Azide ion is a good nucleophile and attacks the epoxide function. Substitution occurs at carbon with inversion of configuration. The product is *trans*-2-azidocyclohexanol.



1,2-Epoxycyclohexane *trans*-2-Azidocyclohexanol (61%)

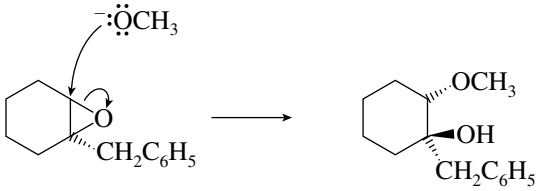
(*f*) Ammonia is a nucleophile capable of reacting with epoxides. It attacks the less hindered carbon of the epoxide function.



2-(*o*-Bromophenyl)-2-methyloxirane 1-Amino-2-(*o*-bromophenyl)-2-propanol

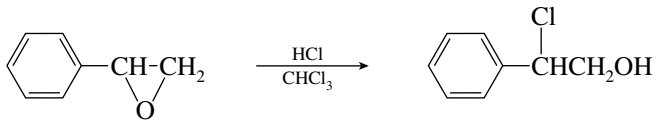
Aryl halides do not react with nucleophiles under these conditions, and so the bromine substituent on the ring is unaffected.

(*g*) Methoxide ion attacks the less substituted carbon of the epoxide ring with inversion of configuration.



1-Benzyl-1,2-epoxycyclohexane 1-Benzyl-*trans*-2-methoxycyclohexanol (98%)

(*h*) Under acidic conditions, substitution is favored at the carbon that can better support a positive charge. Aryl substituents stabilize carbocations, making the benzylic position the one that is attacked in an aryl substituted epoxide.



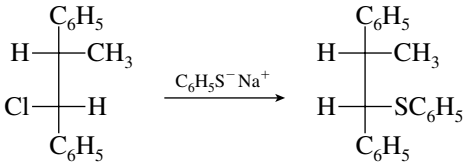
2-Phenyloxirane 2-Chloro-2-phenylethanol (71%)

(*i*) Tosylate esters undergo substitution with nucleophiles such as sodium butanethiolate.

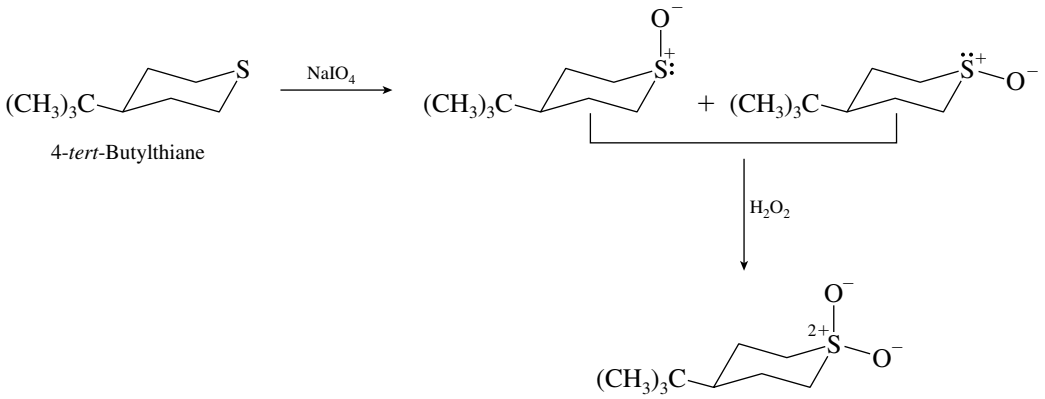
$$CH_3(CH_2)_{16}CH_2OTs + CH_3CH_2CH_2CH_2SNa \longrightarrow CH_3CH_2CH_2CH_2SCH_2(CH_2)_{16}CH_3$$

Octadecyl tosylate Sodium butanethiolate Butyl octadecyl sulfide

(*j*) Nucleophilic substitution proceeds with inversion of configuration.



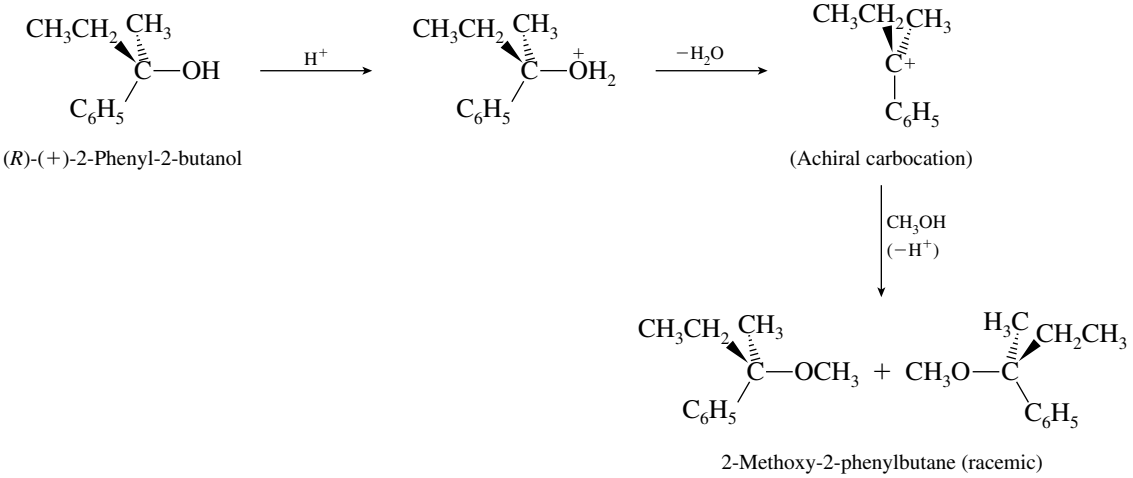
16.27 Oxidation of 4-*tert*-butylthiane yields two sulfoxides that are diastereomers of each other.



4-*tert*-Butylthiane

Oxidation of both stereoisomeric sulfoxides yields the same sulfone.

16.28 Protonation of oxygen to form an alkyloxonium ion is followed by loss of water. The resulting carbocation has a plane of symmetry and is achiral. Capture of the carbocation by methanol yields both enantiomers of 2-methoxy-2-phenylbutane. The product is racemic.

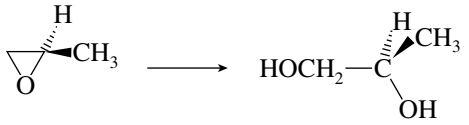


(*R*)-(+)-2-Phenyl-2-butanol (Achiral carbocation)

2-Methoxy-2-phenylbutane (racemic)

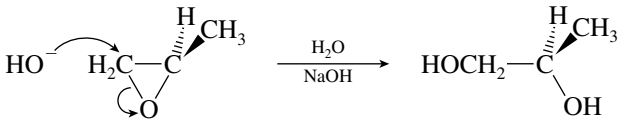
16.29 The proper approach to this problem is to first write the equations in full stereochemical detail.

(*a*)



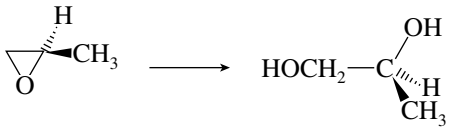
(*R*)-1,2-Epoxypropane (*R*)-1,2-Propanediol

It now becomes clear that the arrangement of groups around the stereogenic center remains unchanged in going from starting materials to products. Therefore, choose conditions such that the nucleophile attacks the CH_2 group of the epoxide rather than the stereogenic center. Base-catalyzed hydrolysis is required; aqueous sodium hydroxide is appropriate.



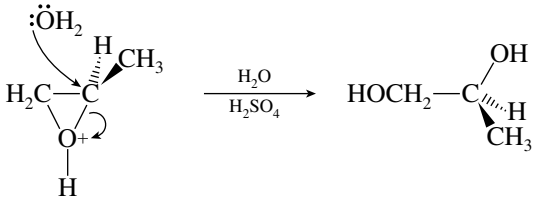
The nucleophile (hydroxide ion) attacks the less hindered carbon of the epoxide ring.

(*b*)



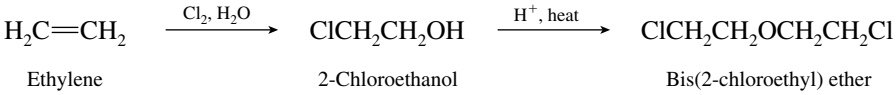
(*S*)-1,2-Propanediol

Inversion of configuration at the stereogenic center is required. The nucleophile must therefore attack the stereogenic center, and acid-catalyzed hydrolysis should be chosen. Dilute sulfuric acid would be satisfactory.



The nucleophile (a water molecule) attacks that carbon atom of the ring that can better support a positive charge. Carbocation character develops at the transition state and is better supported by the carbon atom that is more highly substituted.

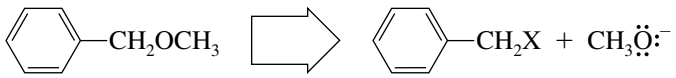
16.30 The key intermediate in the preparation of bis(2-chloroethyl) ether from ethylene is 2-chloroethanol, formed from ethylene by reaction with chlorine in water. Heating 2-chloroethanol in acid gives the desired ether.



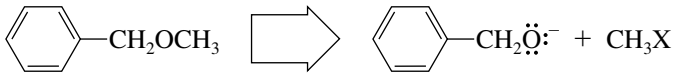
Ethylene 2-Chloroethanol Bis(2-chloroethyl) ether

16.31 (*a*) There is a temptation to try to do this transformation in a single step by using a reducing agent to convert the carbonyl to a methylene group. No reagent is available that reduces esters in this way! The Clemmensen and Wolff–Kishner reduction methods are suitable only for aldehydes and ketones. The best way to approach this problem is by reasoning backward. The desired

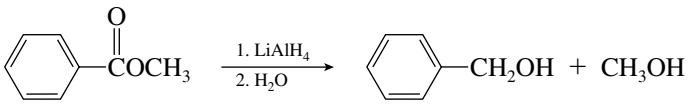
product is an ether. Ethers can be prepared by the Williamson ether synthesis involving an alkyl halide and an alkoxide ion.



or

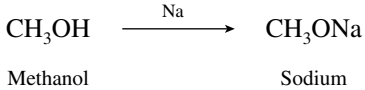


Both the alkyl halide and the alkoxide ion are prepared from alcohols. The problem then becomes one of preparing the appropriate alcohol (or alcohols) from the starting ester. This is readily done using lithium aluminum hydride.

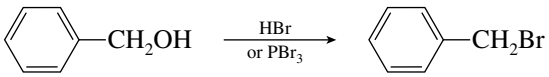


Methyl benzoate — Benzyl alcohol — Methanol

Then

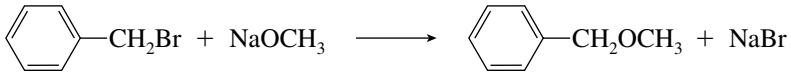


Methanol — Sodium methoxide



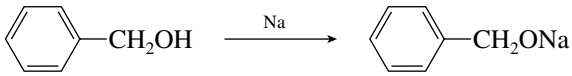
Benzyl alcohol — Benzyl bromide

and

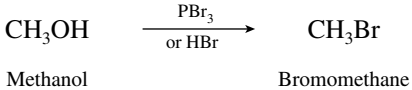


Benzyl bromide — Sodium methoxide — Benzyl methyl ether

The following sequence is also appropriate once methanol and benzyl alcohol are obtained by reduction of methyl benzoate:

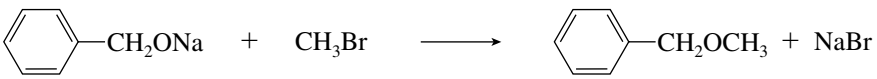


Benzyl alcohol — Sodium benzyloxide



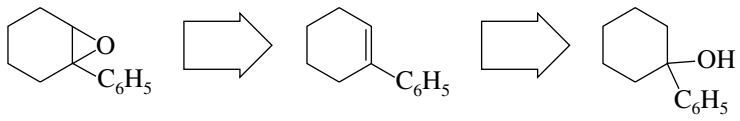
Methanol — Bromomethane

and



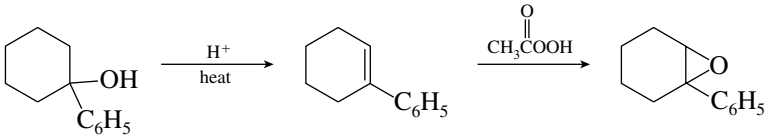
Sodium benzyloxide — Bromomethane — Benzyl methyl ether

(*b*) All the methods that we have so far discussed for the preparation of epoxides are based on alkenes as starting materials. This leads us to consider the partial retrosynthesis shown.

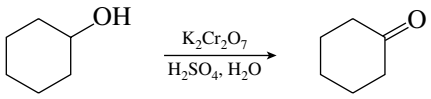


Target molecule Key intermediate

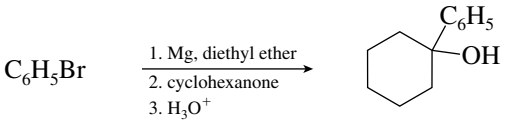
The key intermediate, 1-phenylcyclohexene, is both a proper precursor to the desired epoxide and readily available from the given starting materials. A reasonable synthesis is



Preparation of the required tertiary alcohol, 1-phenylcyclohexanol, completes the synthesis.

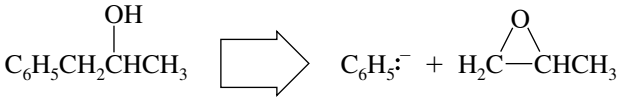


Cyclohexanol Cyclohexanone

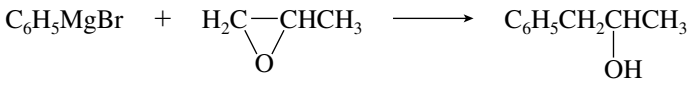


Bromobenzene 1-Phenylcyclohexanol

(*c*) The necessary carbon skeleton can be assembled through the reaction of a Grignard reagent with 1,2-epoxypropane.

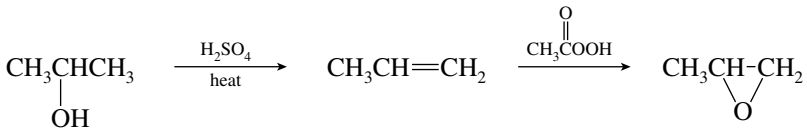


The reaction sequence is therefore



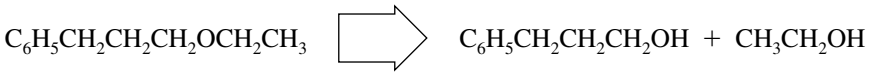
Phenylmagnesium bromide (from bromobenzene and magnesium) 1,2-Epoxypropane 1-Phenyl-2-propanol

The epoxide required in the first step, 1,2-epoxypropane, is prepared as follows from isopropyl alcohol:

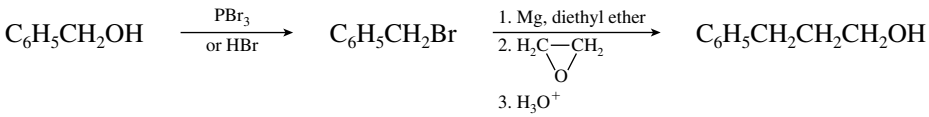


2-Propanol (isopropyl alcohol) Propene 1,2-Epoxypropane

(*d*) Because the target molecule is an ether, it ultimately derives from two alcohols.

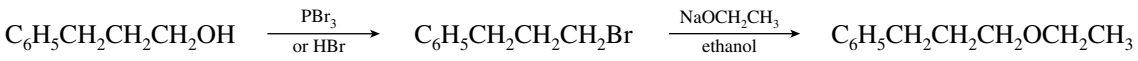


Our first task is to assemble 3-phenyl-1-propanol from the designated starting material benzyl alcohol. This requires formation of a primary alcohol with the original carbon chain extended by two carbons. The standard method for this transformation involves reaction of a Grignard reagent with ethylene oxide.



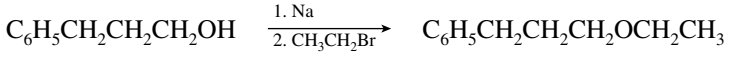
Benzyl alcohol — Benzyl bromide — 3-Phenyl-1-propanol

After 3-phenyl-1-propanol has been prepared, its conversion to the corresponding ethyl ether can be accomplished in either of two ways:



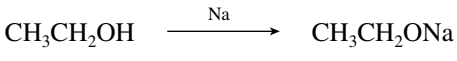
3-Phenyl-1-propanol — 1-Bromo-3-phenylpropane — Ethyl 3-phenylpropyl ether (1-ethoxy-3-phenylpropane)

or alternatively

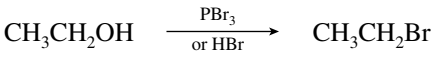


3-Phenyl-1-propanol — Ethyl 3-phenylpropyl ether

The reagents in each step are prepared from ethanol.

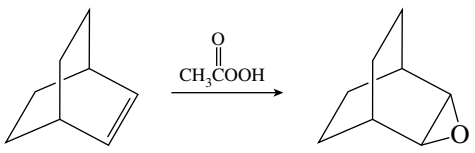


Ethanol — Sodium ethoxide



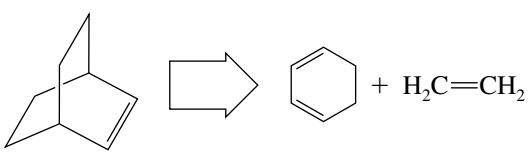
Ethanol — Ethyl bromide

(*e*) The target epoxide can be prepared in a single step from the corresponding alkene.

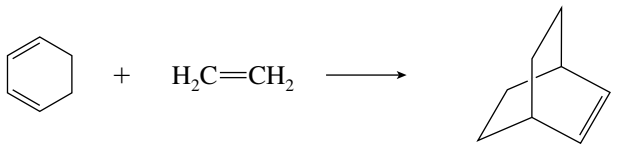


Bicyclo[2.2.2]oct-2-ene — 2,3-Epoxybicyclo[2.2.2]octane

Disconnections show that this alkene is available through a Diels–Alder reaction.

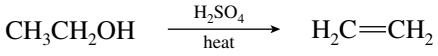


The reaction of 1,3-cyclohexadiene with ethylene gives the desired substance.



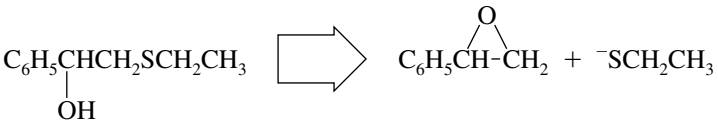
1,3-Cyclohexadiene Ethylene Bicyclo[2.2.2]oct-2-ene

1,3-Cyclohexadiene is one of the given starting materials. Ethylene is prepared from ethanol.

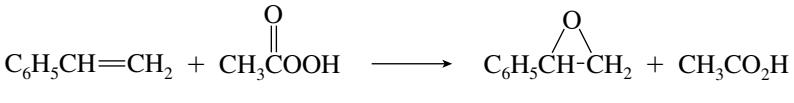


Ethanol Ethylene

(*f*) Retrosynthetic analysis reveals that the desired target molecule may be prepared by reaction of an epoxide with an ethanethiolate ion.

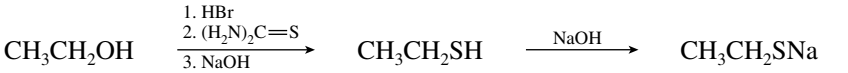


Styrene oxide may be prepared by reaction of styrene with peroxyacetic acid.



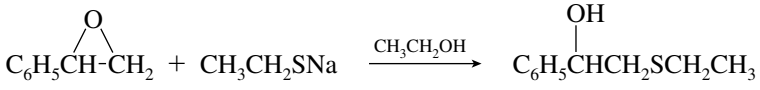
Styrene Peroxyacetic acid Styrene oxide Acetic acid

The necessary thiolate anion is prepared from ethanol by way of the corresponding thiol.



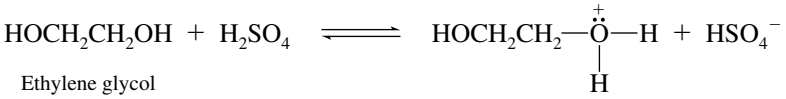
Ethanol Ethanethiol Sodium ethanethiolate

Reaction of styrene oxide with sodium ethanethiolate completes the synthesis.



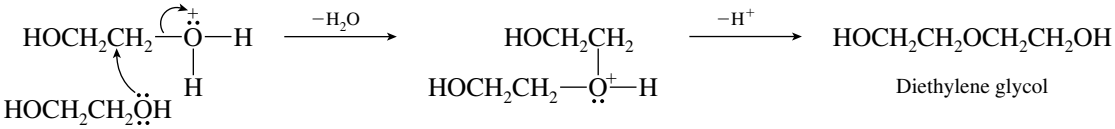
Styrene oxide Sodium ethanethiolate

16.32 (*a*) A reasonable mechanism is one that parallels the usual one for acid-catalyzed ether formation from alcohols, modified to accommodate these particular starting materials and products. Begin with protonation of one of the oxygen atoms of ethylene glycol.



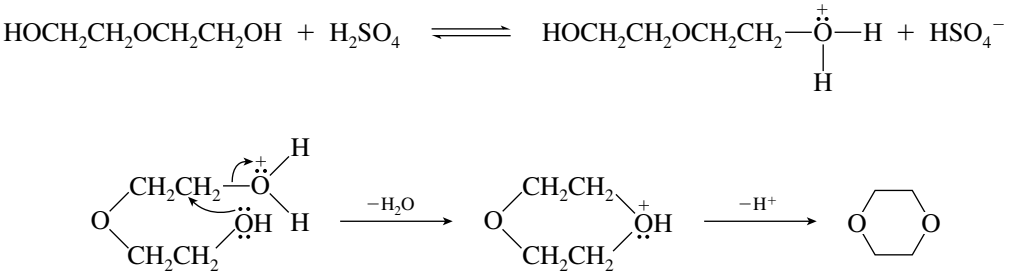
Ethylene glycol

The protonated alcohol then reacts in the usual way with another molecule of alcohol to give an ether. (This ether is known as **diethylene glycol.**)

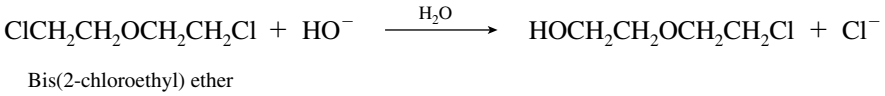


Diethylene glycol

Diethylene glycol then undergoes intramolecular ether formation to yield 1,4-dioxane.

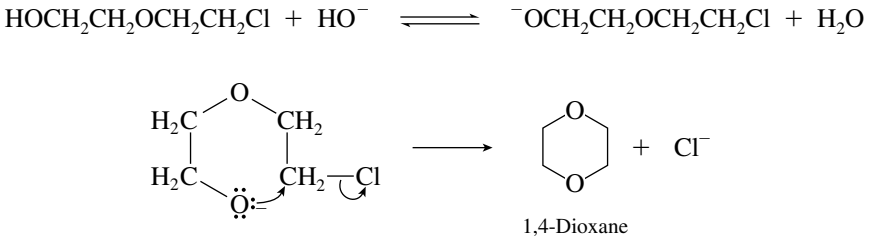


(*b*) The substrate is a primary alkyl halide and reacts with aqueous sodium hydroxide by nucleophilic substitution.



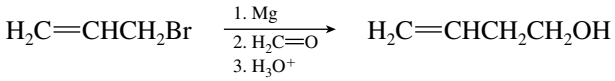
Bis(2-chloroethyl) ether

The product of this reaction now has an alcohol function and a primary chloride built into the same molecule. It contains the requisite functionality to undergo an intramolecular Williamson reaction.



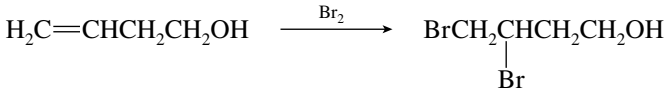
1,4-Dioxane

16.33 (*a*) The first step is a standard Grignard synthesis of a primary alcohol using formaldehyde. Compound A is 3-buten-1-ol.



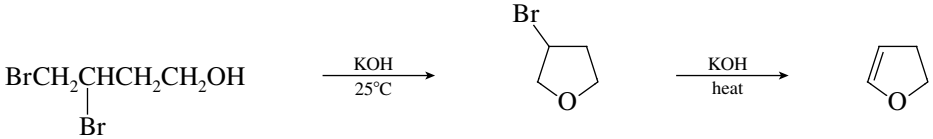
Allyl bromide — 3-Buten-1-ol (compound A)

Addition of bromine to the carbon–carbon double bond of 3-buten-1-ol takes place readily to yield the vicinal dibromide.



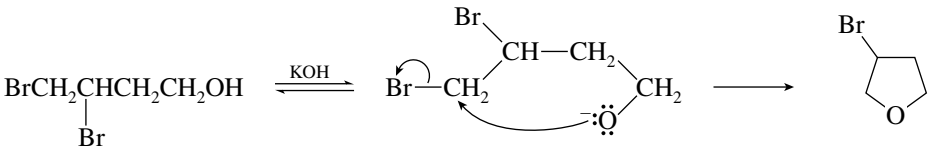
3-Buten-1-ol — 3,4-Dibromo-1-butanol (compound B)

When compound B is treated with potassium hydroxide, it loses the elements of HBr to give compound C. Because further treatment of compound C with potassium hydroxide converts it to D by a second dehydrobromination, a reasonable candidate for C is 3-bromotetrahydrofuran.



3,4-Dibromo-1-butanol (compound B) — 3-Bromotetrahydrofuran (compound C) — Compound D

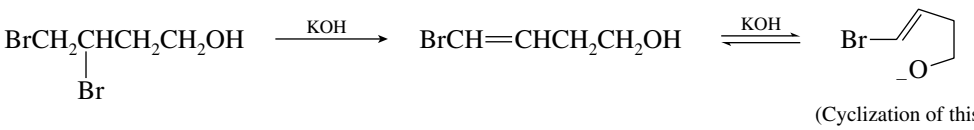
Ring closure occurs by an intramolecular Williamson reaction.



Compound B Compound C

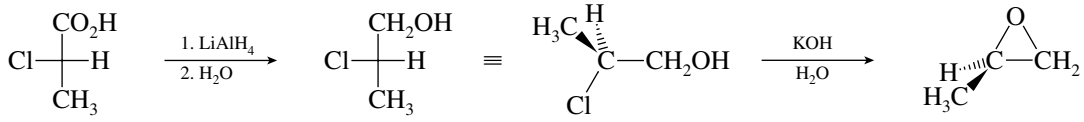
Dehydrohalogenation of compound C converts it to the final product, D.

The alternative series of events, in which double-bond formation proceeds ring closure, is unlikely, because it requires nucleophilic attack by the alkoxide on a vinyl bromide.



(Cyclization of this intermediate does not occur.)

(*b*) Lithium aluminum hydride reduces the carboxylic acid to the corresponding primary alcohol, compound E. Treatment of the vicinal chlorohydrin with base results in formation of an epoxide, compound F.

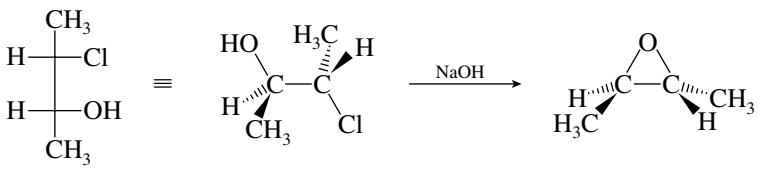


(*S*)-2-Chloro-1-propanol (compound E)

(*R*)-1,2-Epoxypropane (compound F)

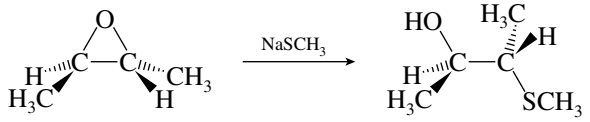
As actually carried out, the first step proceeded in 56–58% yield, the second step in 65–70% yield.

(*c*) Treatment of the vicinal chlorohydrin with base results in ring closure to form an epoxide (compound G). Recall that attack occurs on the side opposite that of the carbon–chlorine bond. Compound G undergoes ring opening on reaction with sodium methanethiolate to give compound H.



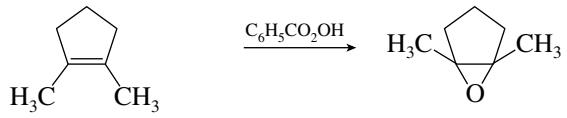
(2*R*,3*S*)-3-Chloro-2-butanol

trans-2,3-Epoxybutane (compound G)



Compound G Compound H

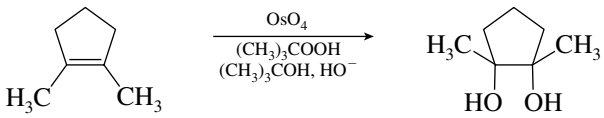
(*d*) Because it gives an epoxide on treatment with a peroxy acid, compound I must be an alkene; more specifically, it is 1,2-dimethylcyclopentene.



1,2-Dimethylcyclopentene (compound I)

1,2-Dimethyl-1,2-epoxycyclopentane (compound K)

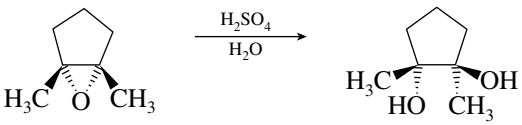
Compounds J and L have the same molecular formula, $C_7H_{14}O_2$, but J is a liquid and L is a crystalline solid. Their molecular formulas correspond to the addition of two OH groups to compound I. Osmium tetraoxide brings about syn hydroxylation of an alkene; therefore compound J must be the cis diol.



1,2-Dimethylcyclopentene (compound I)

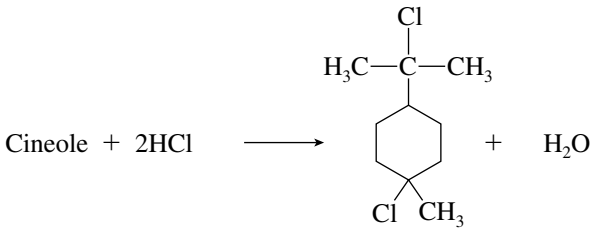
cis-1,2-Dimethylcyclopentane-1,2-diol (compound J)

Acid-catalyzed hydrolysis of an epoxide yields a trans diol (compound L):



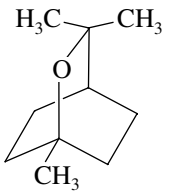
trans-1,2-Dimethylcyclopentane-1,2-diol (compound L)

16.34 Cineole contains no double or triple bonds and therefore must be bicyclic, on the basis of its molecular formula ($C_{10}H_{18}O$, index of hydrogen deficiency = 2). When cineole reacts with hydrogen chloride, one of the rings is broken and water is formed.



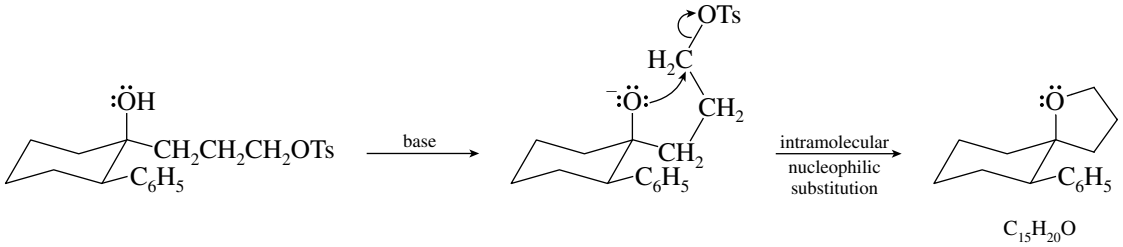
($C_{10}H_{18}O$) ($C_{10}H_{18}Cl_2$)

The reaction that takes place is hydrogen halide-promoted ether cleavage. In such a reaction with excess hydrogen halide, the C—O—C unit is cleaved and two carbon–halogen bonds are formed. This suggests that cineole is a cyclic ether because the product contains both newly formed carbon–halogen bonds. A reasonable structure consistent with these facts is



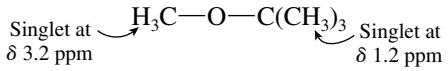
Cineole

16.35 Recall that *p*-toluenesulfonate (tosylate) is a good leaving group in nucleophilic substitution reactions. The nucleophile that displaces tosylate from carbon is the alkoxide ion derived from the hydroxyl group within the molecule. The product is a cyclic ether, and the nature of the union of the two rings is that they are spirocyclic.



$C_{15}H_{20}O$

16.36 (*a*) Because all the peaks in the ^{1}H NMR spectrum of this ether are singlets, none of the protons can be vicinal to any other nonequivalent proton. The only $C_5H_{12}O$ ether that satisfies this requirement is *tert*-butyl methyl ether.

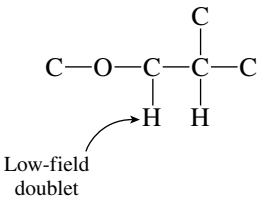


(*b*) A doublet–septet pattern is characteristic of an isopropyl group. Two isomeric $C_5H_{12}O$ ethers contain an isopropyl group: ethyl isopropyl ether and isobutyl methyl ether.

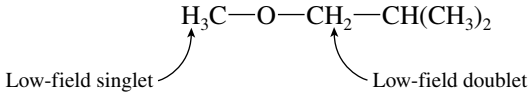
$(CH_3)_2CHOCH_2CH_3$ Ethyl isopropyl ether $\qquad$ $(CH_3)_2CHCH_2OCH_3$ Isobutyl methyl ether

The signal of the methine proton in isobutyl methyl ether will be split into more than a septet, however, because in addition to being split by two methyl groups, it is coupled to the two protons in the methylene group. Thus, isobutyl methyl ether does not have the correct splitting pattern to be the answer. The correct answer is ethyl isopropyl ether.

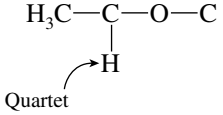
(*c*) The low-field signals are due to the protons on the carbon atoms of the C—O—C linkage. Because one gives a doublet, it must be vicinal to only one other proton. We can therefore specify the partial structure:



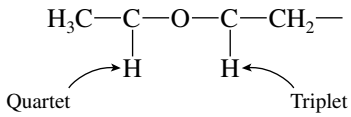
This partial structure contains all the carbon atoms in the molecule. Fill in the remaining valences with hydrogen atoms to reveal isobutyl methyl ether as the correct choice.



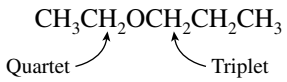
(*d*) Here again, signals at low field arise from protons on the carbons of the C—O—C unit. One of these signals is a quartet and so corresponds to a proton on a carbon bearing a methyl group.



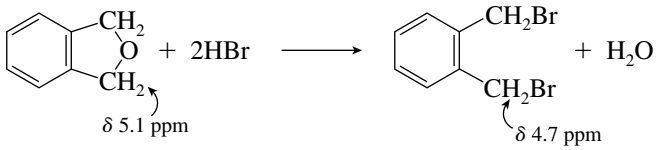
The other carbon of the C—O—C unit has a hydrogen whose signal is split into a triplet. This hydrogen must therefore be attached to a carbon that bears a methylene group.



These data permit us to complete the structure by adding an additional carbon and the requisite number of hydrogens in such a way that the signals of the protons attached to the carbons of the ether linkage are not split further. The correct structure is ethyl propyl ether.



16.37 A good way to address this problem is to consider the dibromide derived by treatment of compound A with hydrogen bromide. The presence of an NMR signal equivalent to four protons in the aromatic region at δ 7.3 ppm indicates that this dibromide contains a disubstituted aromatic ring. The four remaining protons appear as a sharp singlet at δ 4.7 ppm and are most reasonably contained in two equivalent methylene groups of the type $ArCH_2Br$. Because the dibromide contains all the carbons and hydrogens of the starting material and is derived from it by treatment with hydrogen bromide, it is likely that compound A is a cyclic ether in which a CH_2OCH_2 unit spans two of the carbons of a benzene ring. This can occur only when the positions involved are ortho to each other. Therefore



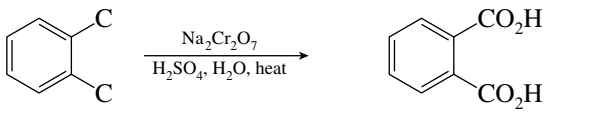
Compound A

16.38 The molecular formula of a compound ($C_{10}H_{13}BrO$) indicates an index of hydrogen deficiency of 4. One of the products obtained on treatment of the compound with HBr is benzyl bromide ($C_6H_5CH_2Br$), which accounts for seven of its ten carbons and all the double bonds and rings. Thus, the compound is a benzyl ether having the formula $C_6H_5CH_2OC_3H_6Br$. The ^1H NMR spectrum includes a five-proton signal at δ 7.4 ppm for a monosubstituted benzene ring and a two-proton singlet at δ 4.6 ppm for the benzylic protons. This singlet appears at low field because the benzylic protons are bonded to oxygen.

$$C_6H_5CH_2OC_3H_6Br \xrightarrow[\text{heat}]{\text{HBr}} C_6H_5CH_2Br + C_3H_6Br_2$$

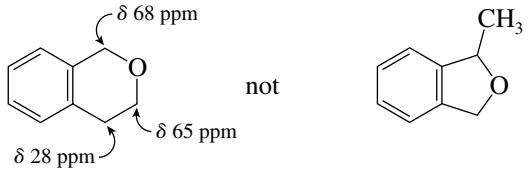
The 6 remaining protons appear as two overlapping 2-proton triplets at δ 3.6 and 3.7 ppm, along with a 2-proton pentet at δ 2.2 ppm, consistent with the unit $—OCH_2CH_2CH_2Br$. The compound is $C_6H_5CH_2OCH_2CH_2CH_2Br$.

16.39 The high index of hydrogen deficiency (5) of the unknown compound $C_9H_{10}O$ and the presence of six signals in the 120–140-ppm region of the ^{13}C NMR spectrum suggests the presence of an aromatic ring. The problem states that the compound is a cyclic ether, thus the oxygen atom is contained in a second ring fused to the benzene ring. As oxidation yields 1,2-benzenedicarboxylic acid, the second ring must be attached to the benzene ring by carbon atoms.



($C_9H_{10}O$) 1,2-Benzenedicarboxylic acid

Two structures are possible with this information; however, only one of them is consistent with the presence of three CH_2 groups in the ^{13}C NMR spectrum. The compound is



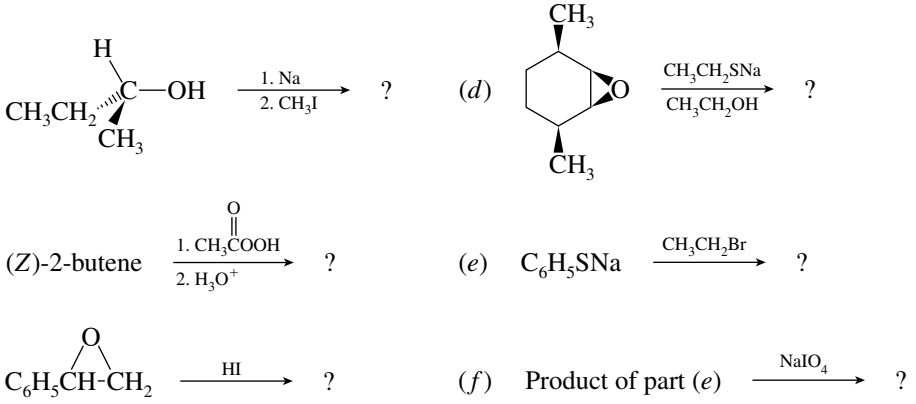
16.40–16.45 Solutions to molecular modeling exercises are not provided in this *Study Guide and Solutions Manual.* You should use *Learning By Modeling* for these exercises.

SELF-TEST

PART A

A-1. Write the structures of all the isomeric ethers of molecular formula $C_4H_{10}O$, and give the correct name for each.

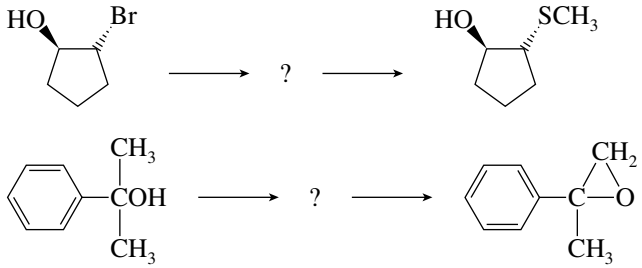
A-2. Give the structure of the product obtained from each of the following reactions. Show stereochemistry where it is important.



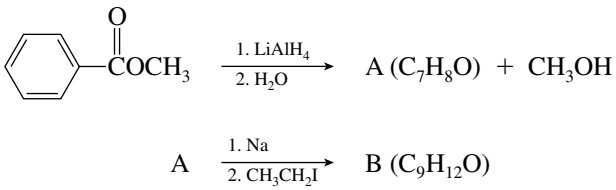
A-3. Outline a scheme for the preparation of cyclohexyl ethyl ether using the Williamson method.

A-4. Outline a synthesis of 2-ethoxyethanol, $CH_3CH_2OCH_2CH_2OH$, using ethanol as the source of all the carbon atoms.

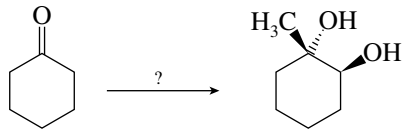
A-5. Provide the reagents necessary to complete each of the following conversions. In each case give the structure of the intermediate product.



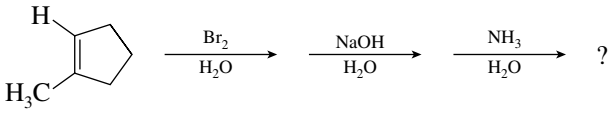
A-6. Provide structures for compounds A and B in the following reaction scheme:



A-7. Using any necessary organic or inorganic reagents, provide the steps to carry out the following synthetic conversion:

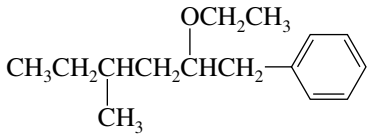


A-8. Give the final product, including stereochemistry, of the following reaction sequence:



PART B

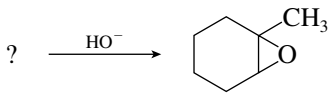
B-1. An acceptable IUPAC name of the compound shown is

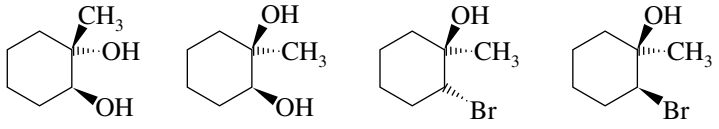


(*a*) 1-Benzyl-3-methylpentyl ethyl ether
(*b*) Ethyl 3-methyl-1-methylphenyl-2-hexyl ether
(*c*) Ethyl 4-methyl-1-phenyl-2-hexyl ether
(*d*) 5-Ethoxy-3-methyl-6-phenylhexane

B-2. The most effective pair of reagents for the preparation of *tert*-butyl ethyl ether is
(*a*) Potassium *tert*-butoxide and ethyl bromide
(*b*) Potassium *tert*-butoxide and ethanol
(*c*) Sodium ethoxide and *tert*-butyl bromide
(*d*) *tert*-Butyl alcohol and ethyl bromide

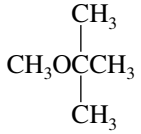
B-3. The best choice of reactant(s) for the following conversion is



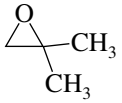


(*a*) (*b*) (*c*) (*d*)

B-4. For which of the following ethers would the ^{1}H NMR spectrum consist of only two singlets?

(*a*) 

(*b*) $CH_3OCH_2CH_2OCH_3$

(*c*) 

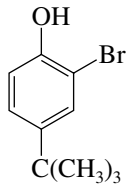
(*d*) All these

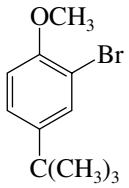
B-5. Heating a particular ether with HBr yielded a single organic product. Which of the following conclusions may be reached?

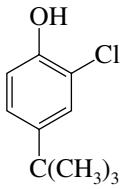
(*a*) The reactant was a methyl ether.
(*b*) The reactant was a symmetric ether.
(*c*) The reactant was a cyclic ether.
(*d*) Both (*b*) and (*c*) are correct.

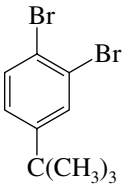
B-6. Treating anisole ($C_6H_5OCH_3$) with the following reagents will give, as the major product,

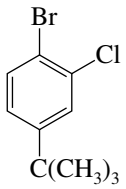
1. $(CH_3)_3CCl$, $AlCl_3$; 2. Cl_2, $FeCl_3$; 3. HBr, heat

(*a*) 

(*c*) 

(*e*) 

(*b*) 

(*d*) 

B-7. What is the product of the following reaction?

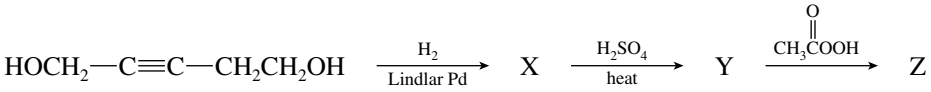
(*a*) $CH_3SCH_2CHC(CH_3)_3$ (OH)

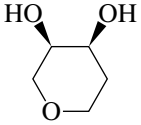
(*c*) $CH_3SCH_2CHC(CH_3)_3$ (OCH_2CH_3)

(*b*) $(CH_3)_3CCHCH_2OH$ (SCH_3)

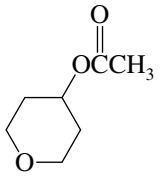
(*d*) $(CH_3)_3CCH_2CHSCH_3$ (OH)

B-8. Identify product Z in the following reaction sequence:

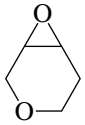




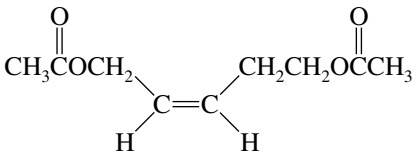
(*a*)



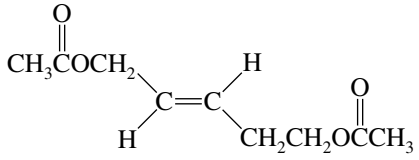
(*b*)



(*c*)

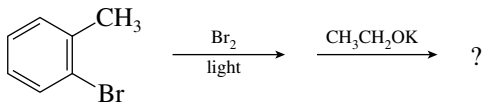


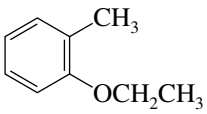
(*d*)

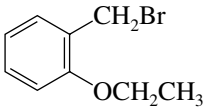


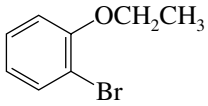
(*e*)

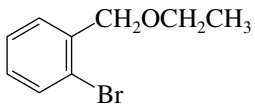
B-9. The major product of the following sequence is

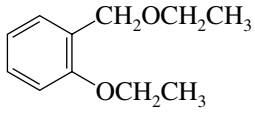


(*a*) 

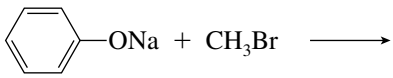
(*b*) 

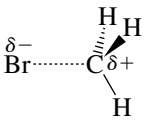
(*c*) 

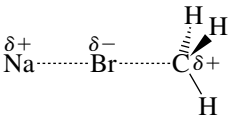
(*d*) 

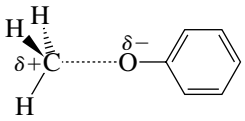
(*e*) 

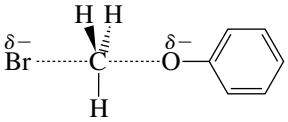
B-10. Which of the following best represents the rate-determining transition state for the reaction shown?



(*a*) 

(*b*) 

(*c*) 

(*d*) 

(*e*)