Montogue

Quiz CH204

Organic Chemistry

Ethers and Epoxides

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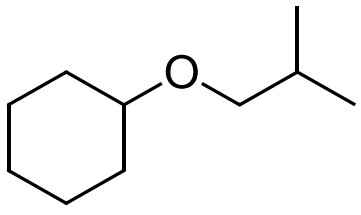
PROBLEMS

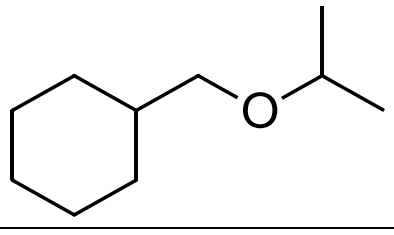
Problem 1 (Klein, 2017)

Show reagents that you could use to prepare each of the following ethers via a Williamson ether synthesis and explain your reasoning.

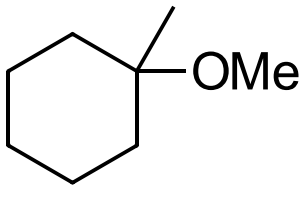
1.1.



1.2.



1.3.



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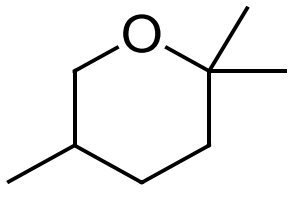
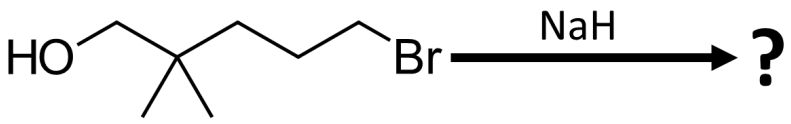


1.5. When 5-bromo-2,2-dimethyl-1-pentanol is treated with sodium hydride, a compound with molecular formula $C_7H_{14}O$ is obtained. Identify the structure of this compound.



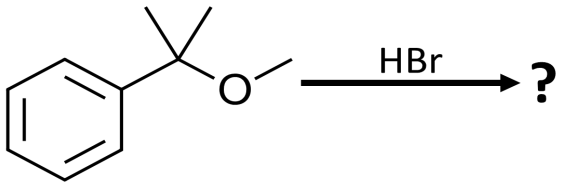
Problem 2 (Carey, 2008)

Outline the steps in the preparation of each of the constitutionally isomeric ethers of molecular formula $C_4H_{10}O$, starting with the appropriate alcohols. Use the Williamson ether synthesis as your key reaction.

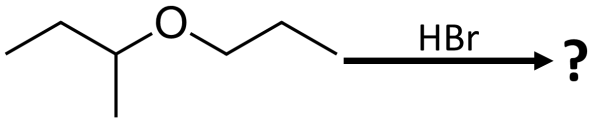
Problem 3 (McMurry, 2008)

Predict the products of the following ether acid cleavage reactions.

3.1.



3.2.

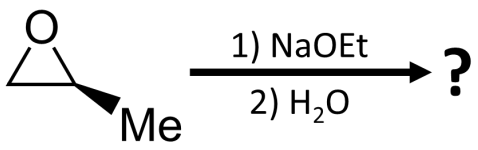


3.3. Why are HI and HBr more effective than HCl in cleaving ethers?

▶ Problem 4

Predict the product of the following reactions involving (*S*)-2-methyloxirane.

4.1.



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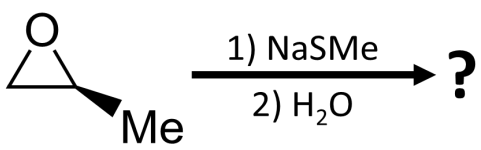

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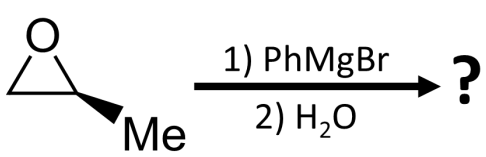

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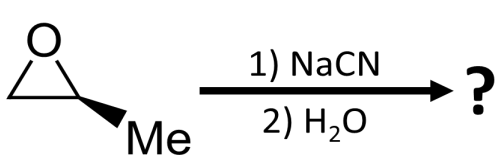
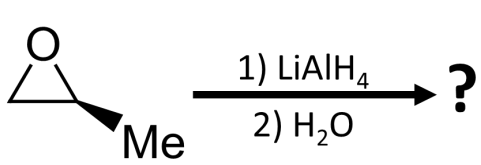


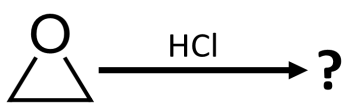
4.5.



▶ Problem 5 (Klein, 2017)

Predict the product of the following acid-catalyzed epoxide ring opening reactions.

5.1.



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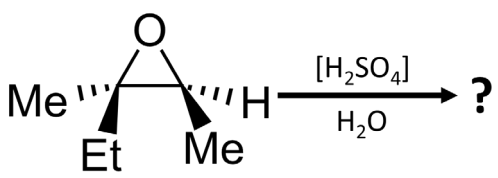

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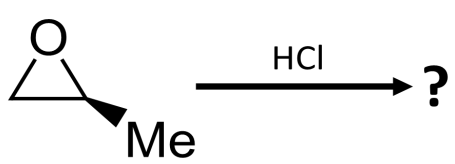

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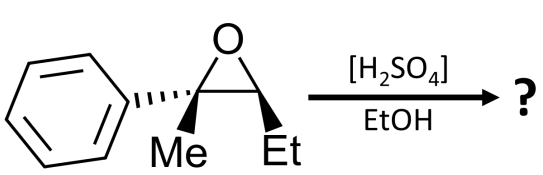
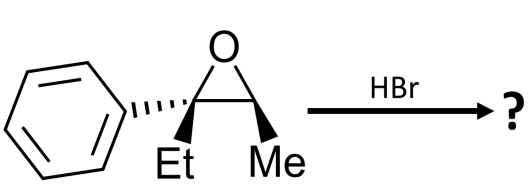
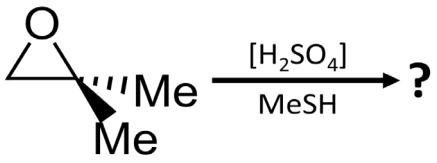


5.5.



5.6.



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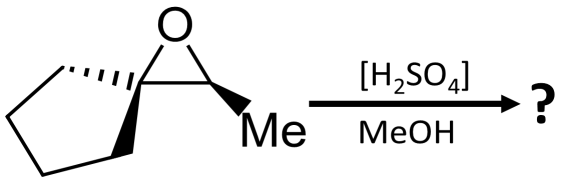
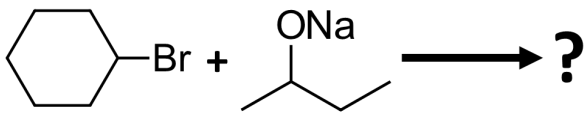


▶ Problem 6

Predict the principal organic product of each of the following reactions.

6.1.



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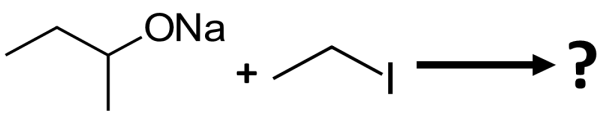

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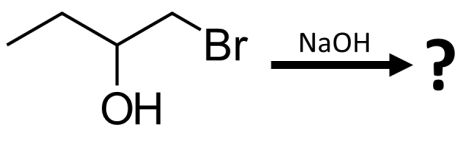
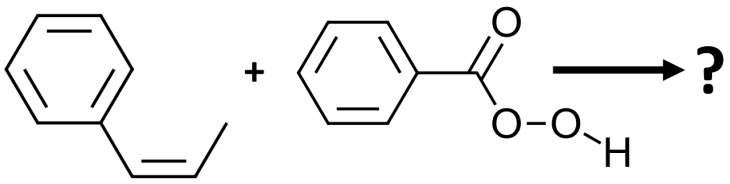
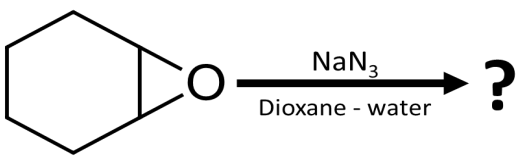


6.4.



6.5.



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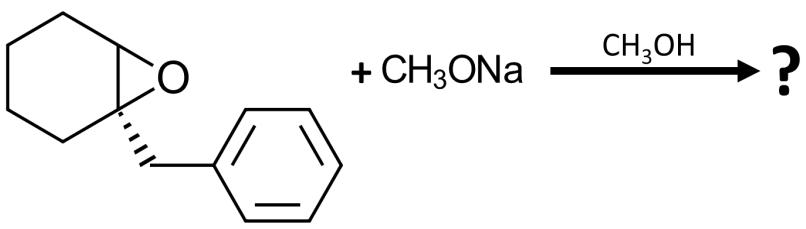
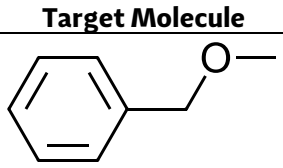
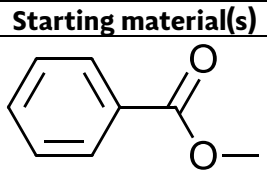
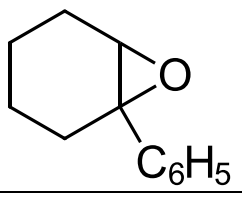
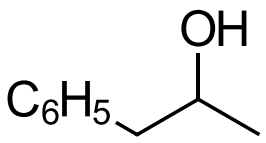
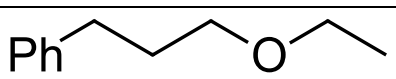
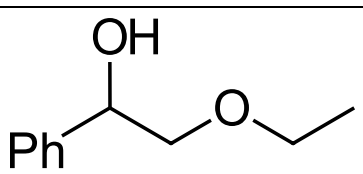


▶ Problem 7 (Carey, 2008)

Suggest short, efficient reaction sequences suitable for preparing each of the following compounds from the given starting materials and any necessary organic or inorganic reagents.

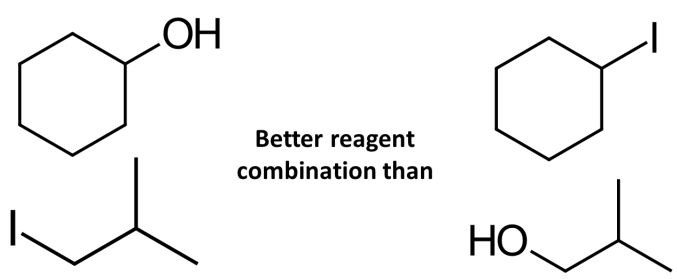
	Target Molecule	Starting material(s)
7.1		
7.2		Bromobenzene and cyclohexanol

7.3		Bromobenzene and isopropyl alcohol
7.4		Benzyl alcohol and ethanol
7.5		Styrene and ethanol

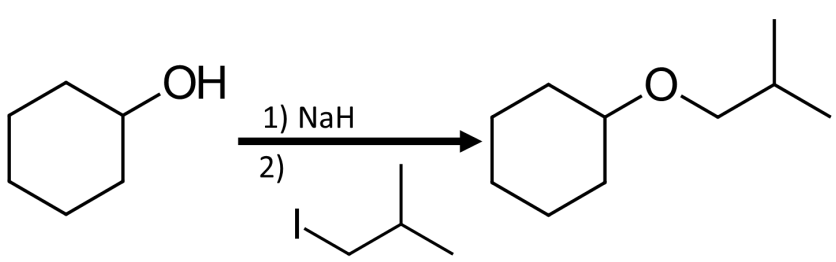
SOLUTIONS

P.1 ➡ *Solution*

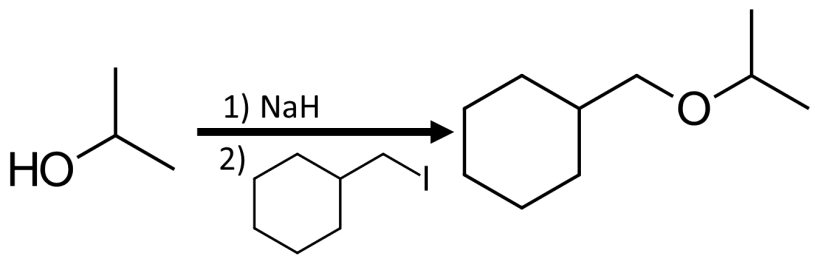
1.1: A Williamson ether synthesis will be more efficient with a less sterically hindered substrate, since the process involves a S_N2 reaction. Therefore, in this case, it is better to start with a secondary alcohol and a primary alkyl halide, rather than a primary alcohol and a secondary alkyl halide.



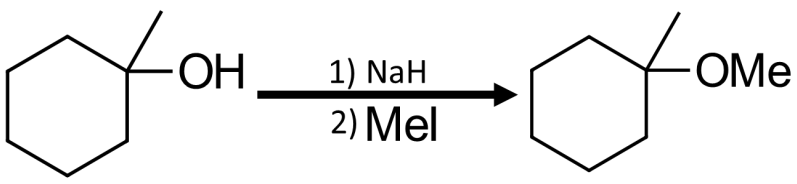
The reaction is outlined below.



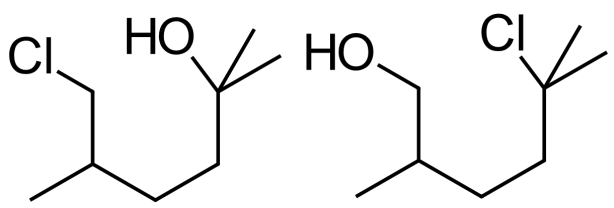
1.2: As before, a combination of secondary alcohol and primary alkyl halide is favored. The reaction is outlined below.



1.3: In this case, the reactants of choice are 1-methylcyclohexanol and methyl iodide.

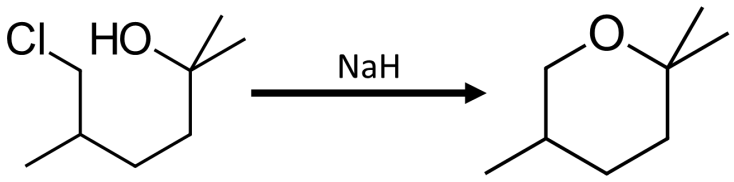


1.4: Cyclic ethers can be formed by intramolecular Williamson reactions. For the reaction to take place, the reactant must contain both and OH group and a halogen group; in this sense, two starting materials are suggested.

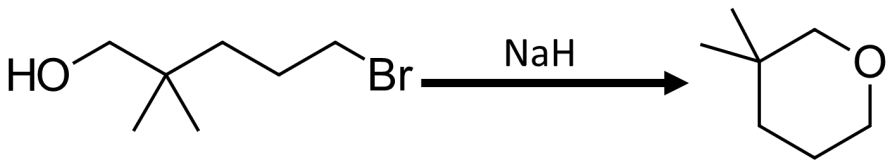


The compound to the right cannot be used because the leaving group – chlorine – is attached to a tertiary position, so a S_N2-type process cannot take place at that location. This leaves us with the molecule to the left. The OH group is deprotonated upon treatment with NaH (a strong base). The resulting

alkoxide ion can then function as a nucleophile in an intramolecular, S_N2-type reaction, expelling chloride as a leaving group and giving a six-membered ring.

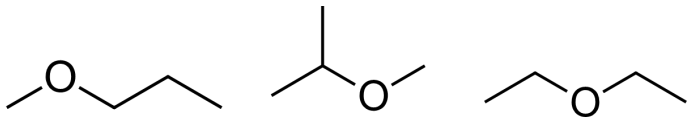


1.5: Upon treatment with NaH (a strong base), the hydroxyl proton is removed, giving an alkoxide ion. This alkoxide ion is tethered to a leaving group (bromide), so an intramolecular, S_N2-type process can occur, forming a cyclic ether.



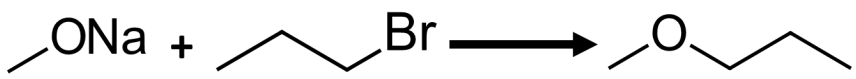
P.2 ➡ *Solution*

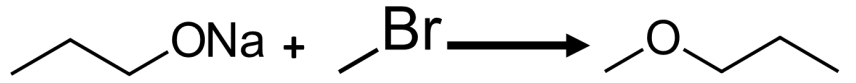
There are three constitutionally isomeric ethers with four carbons.



Methyl propyl ether | Isopropyl methyl ether | Diethyl ether

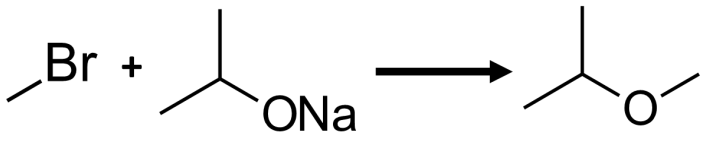
We were told to examine the preparation of each ether by the Williamson method. Methyl propyl ether can be prepared by reacting sodium methoxide with 1-bromopropane or by reacting methyl bromide with sodium propoxide.





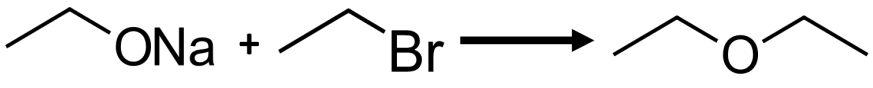
Either combination is satisfactory. Sodium methoxide and sodium propoxide can be prepared by treating methanol and 1-propanol with sodium. Likewise, the haloalkanes in question can be formed by treating the corresponding alcohols with PBr_3 or HBr.

In turn, isopropyl methyl ether is best prepared by reacting methyl bromide and sodium isopropoxide.



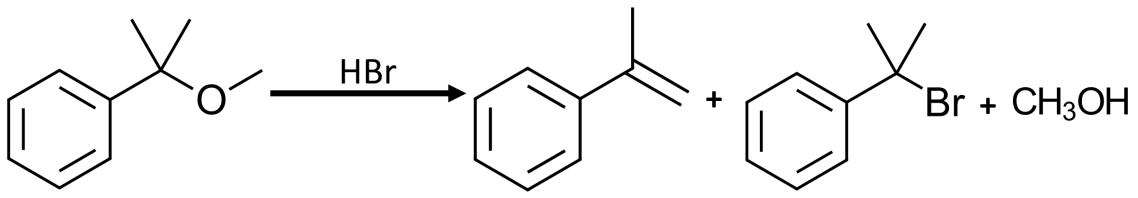
The reaction of sodium methoxide with isopropyl bromide will proceed mainly by elimination. Methyl bromide is prepared as mentioned above, and sodium isopropoxide can be prepared by adding sodium to isopropyl alcohol.

Lastly, diethyl ether can be prepared by reacting sodium ethoxide with ethyl bromide.

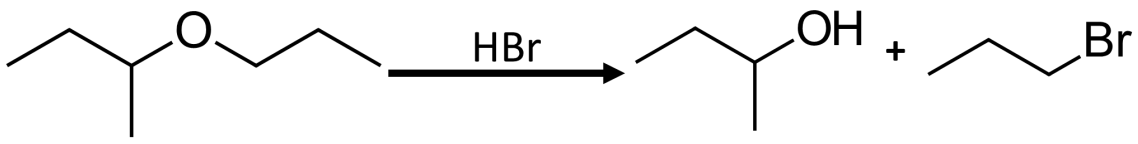


P.3 ➡ *Solution*

3.1: 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.



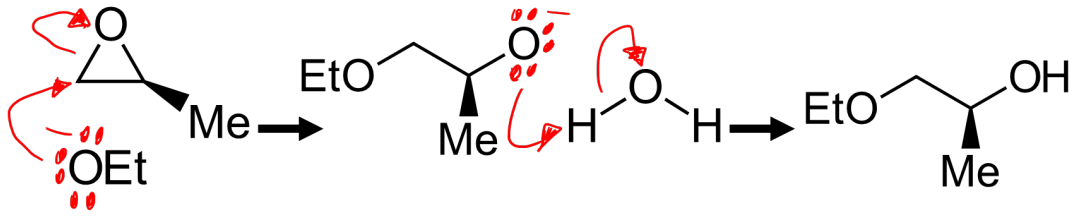
3.2: In this case, linked to the oxygen are primary and secondary alkyl groups. Bromide attacks at the less hindered primary group, and oxygen remains with the secondary group to give a secondary alcohol.



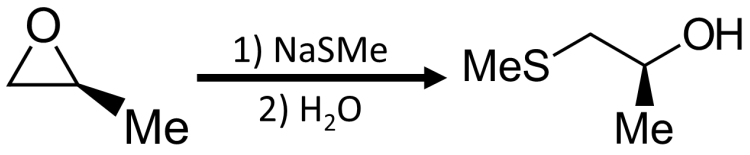
3.3: In acidic cleavage of ethers, HX (X = Cl, Br or I) first protonates the oxygen atom, and the halide then effects a nucleophilic displacement to form an alcohol and an organic halide. The better the nucleophile, the more effective the displacement. Since I^- and Br^- are better nucleophiles than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

P.4 ➡ *Solution*

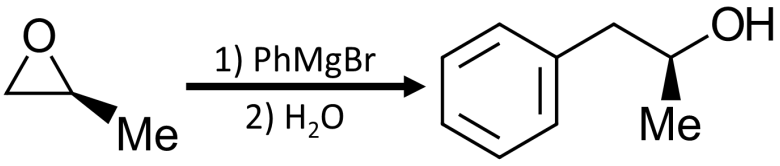
4.1: EtO^- , acting as a nucleophile, attacks the epoxide at the less substituted position. The epoxide is opened, resulting in an alkoxide ion, which is then protonated upon treatment with water. The product is 1-ethoxy-2-propanol.



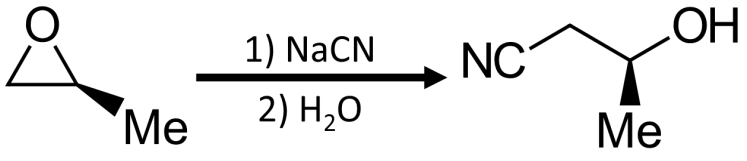
4.2: MeS^-, which is a strong nucleophile, attacks the epoxide at the less substituted position, opening the epoxide and forming an alkoxide ion. Protonation of the alkoxide ion forms a neutral product, which in this case is 1-(methylthio)-2-propanol.



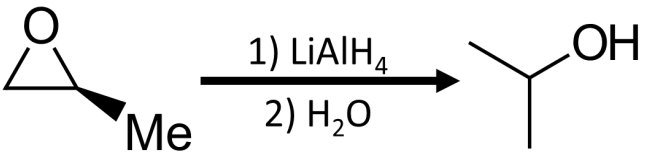
4.3: The nucleophile in this case is a Grignard reagent. Opening of the epoxide ultimately yields 1-phenyl-2-propanol.



4.4: The nucleophile in this case is a cyanide ion. Opening of the epoxide ultimately yields 3-hydroxybutyronitrile.



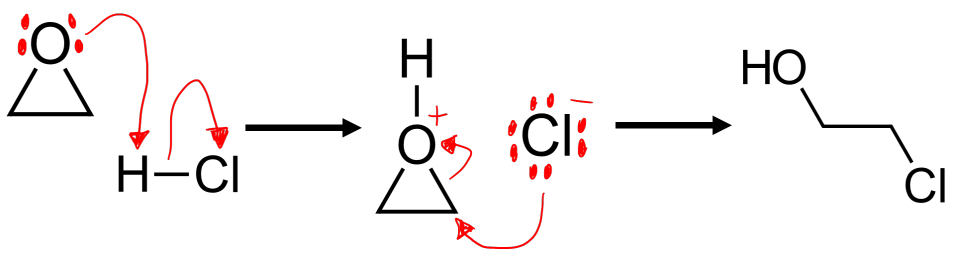
4.5: $LiAlH_4$ is a source of hydride (H^-), which functions as a nucleophile in this case. Opening of the epoxide ultimately yields isopropanol.



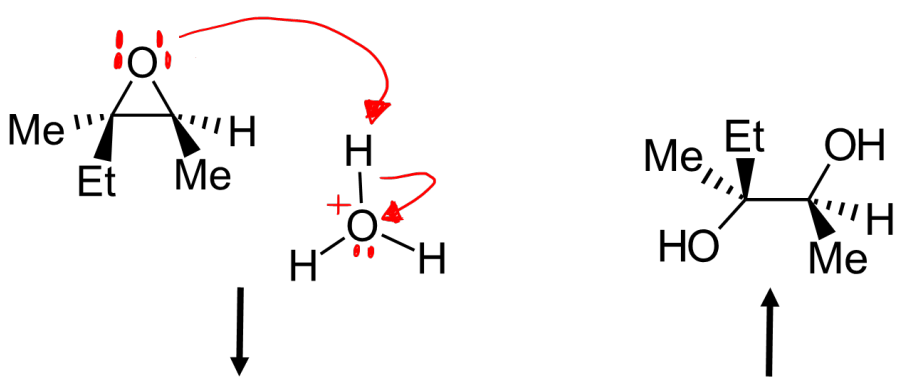
P.5 ➡ *Solution*

5.1: Under acidic conditions, the epoxide is protonated, thereby generating a very powerful electrophile (a protonated epoxide). Since the starting epoxide is symmetrical, regiochemistry is not a concern in this case;

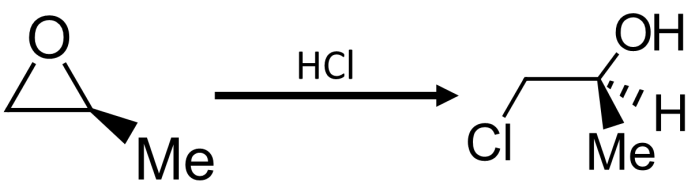
the nucleophile can attack the epoxide at either position, giving the same product either way. Stereochemistry is also not a concern in this case, because the product does not contain any chiral centers. Acid-catalyzed opening of the epoxide yields 2-chloroethanol.



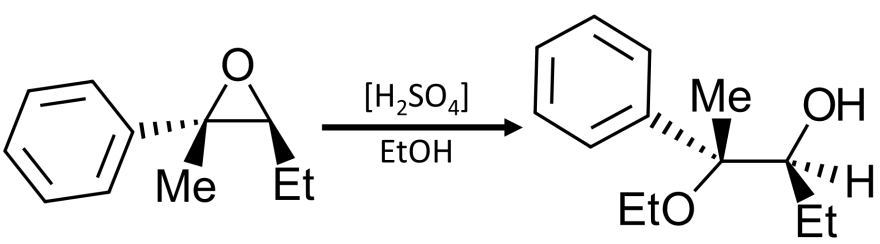
5.2: As in the previous problem, the epoxide is protonated and generates a powerful electrophile. Water functions as a nucleophile and will attack one of the two epoxide carbons. When the epoxide possesses a tertiary position, the electronic effect will be dominant and attack at the more substituted position will be favored; when the epoxide possesses only primary and secondary positions, the steric effect will be dominant and attack at the less substituted position will be favored. In the present case, one position is a tertiary carbon, and the other is secondary. Presence of a tertiary position implies that electronic effects are dominant; as a result, attack at the more substituted position is favored. Back-side attack causes inversion of configuration at the chiral center being attacked. Finally, a proton is removed; the most likely base is the solvent, water.



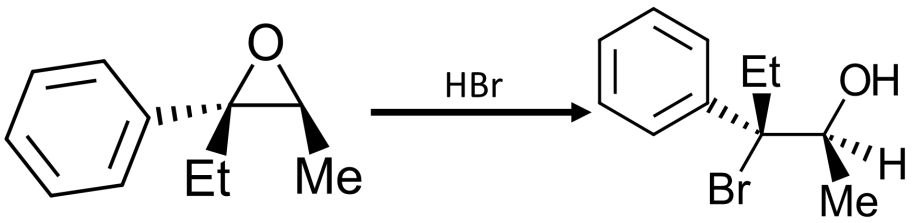
5.3: The nucleophile in this case is ethanol. One of the epoxide carbons is primary, while the other is secondary; accordingly, steric effects dominate and the attack is expected to occur at the less substituted position. There is an existing chiral center, but this position is not attacked; hence, we do not expect the configuration of that chiral center to change.



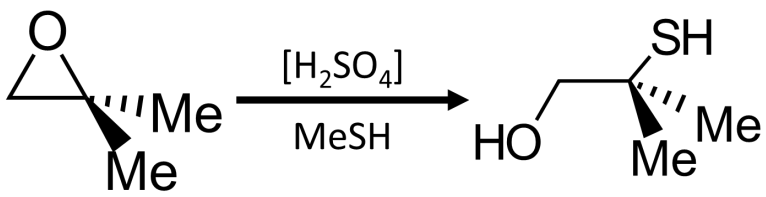
5.4: The nucleophile in this case is ethanol. One of the epoxide carbons is tertiary, while the other is secondary. Presence of a tertiary carbon indicates that electronic factors dominate, and the tertiary carbon should be preferentially attacked. Back-side attack causes inversion of configuration at the chiral center being attacked.



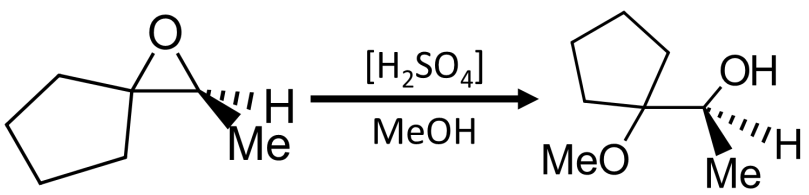
5.5: The nucleophile in this case is bromide. One of epoxide carbons is tertiary, while the other is secondary. Presence of a tertiary carbon indicates that electronic factors dominate, and the tertiary carbon should be preferentially attacked. Back-side attack causes inversion of configuration at the chiral center being attacked.



5.6: The nucleophile in this case is methanethiol. One of the epoxide carbons is primary, while the other is tertiary. Presence of a tertiary carbon indicates that electronic factors dominate, and the tertiary carbon should be preferentially attacked. Back-side attack would cause inversion of configuration at the affected chiral center, but the carbon in question is not asymmetric; thus, stereochemistry is conserved.

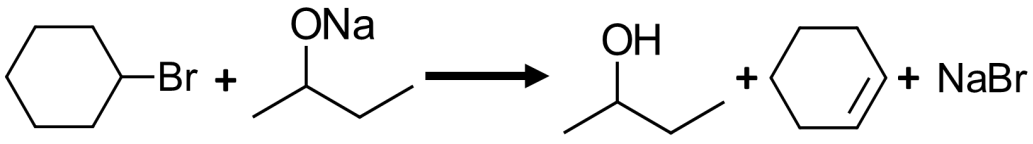


5.7: The nucleophile in this case is methanol. One of the epoxide carbons is secondary, while the other is tertiary. Presence of a tertiary carbon indicates that electronic factors dominate, and the tertiary carbon should be preferentially attacked. Back-side attack causes inversion of configuration at the chiral center being attacked.

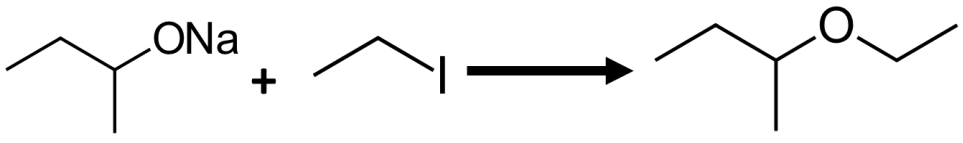


P.6 ➡ *Solution*

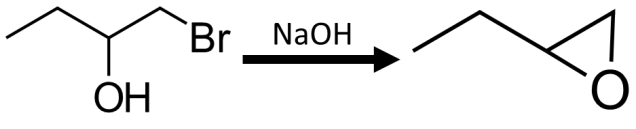
6.1: Secondary alkyl halides react with alkoxide bases by E2 elimination as the major pathway. The Williamson ether synthesis is not a useful process with secondary alkyl halides.



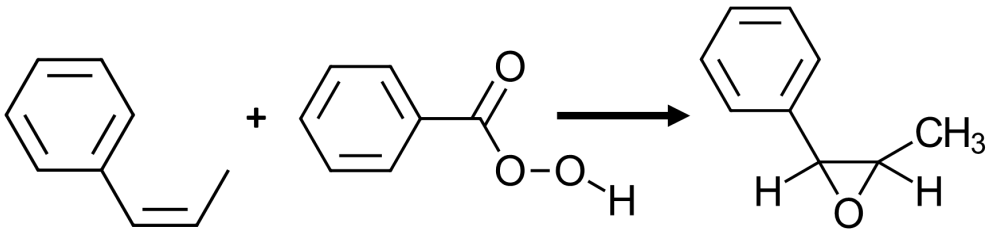
6.2: In this reaction, a sodium alkoxide acts as a nucleophile toward iodoethane to yield 2-ethoxybutane.



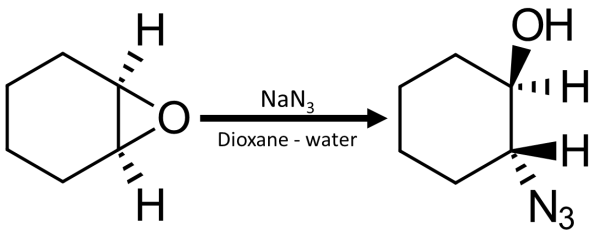
6.3: Treatment of vicinal halohydrins with base leads to the formation of epoxides.



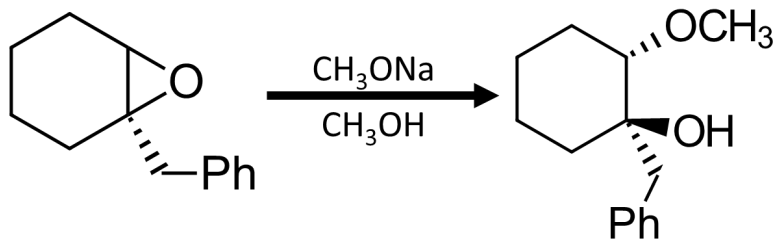
6.4: Reactions of alkenes with peroxycarboxylic acids are used to prepare epoxides. The reaction is a stereospecific *syn* addition of oxygen to the double bond.



6.5: Azide ion is a good nucleophile and attacks the epoxide function. Substitution occurs with inversion of configuration.

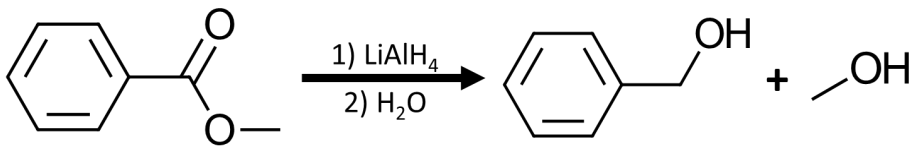


6.6: Methoxide ion attacks the less substituted carbon of the epoxide ring with inversion of configuration.

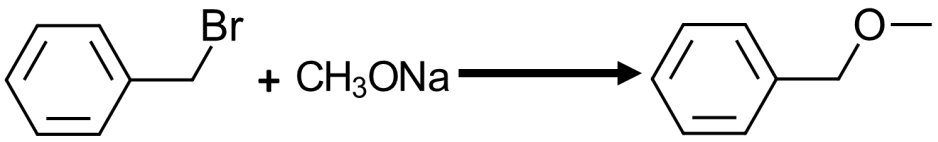


P.7 ➡ *Solution*

7.1: Ethers can be prepared by Williamson ether synthesis involving an alkyl halide and an alkoxide ion. Both the alkyl halide and the alkoxide ion are prepared from alcohols; the problem, then, becomes one of preparing these alcohols. They can be readily obtained by reducing the starting ester with lithium aluminum hydride, followed by an aqueous workup.

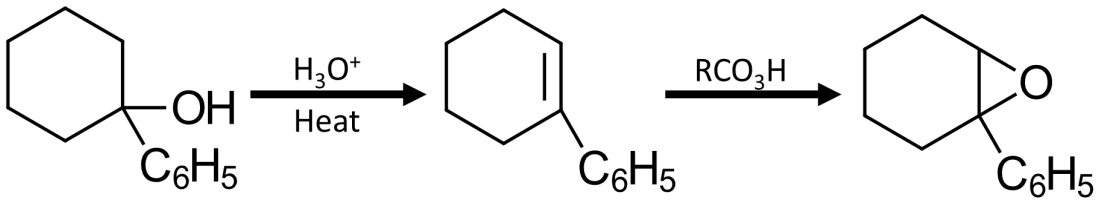


Next, treatment of methanol with sodium yields sodium methoxide, and reaction of benzyl alcohol with HBr or PBr_3 produces benzyl bromide. Combining sodium methoxide and benzyl bromide in a Williamson ether synthesis yields the desired molecule.

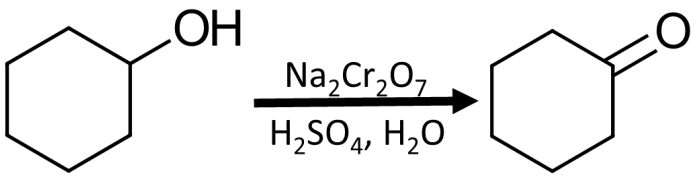


We could just as well have reacted methanol with HBr and benzyl alcohol with sodium.

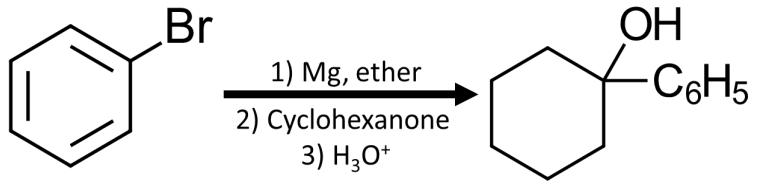
7.2: Let's use retrosynthetic analysis. The target molecule was likely synthesized by epoxidation of an alkene. The alkene, in turn, can be synthesized by dehydration of an alcohol.



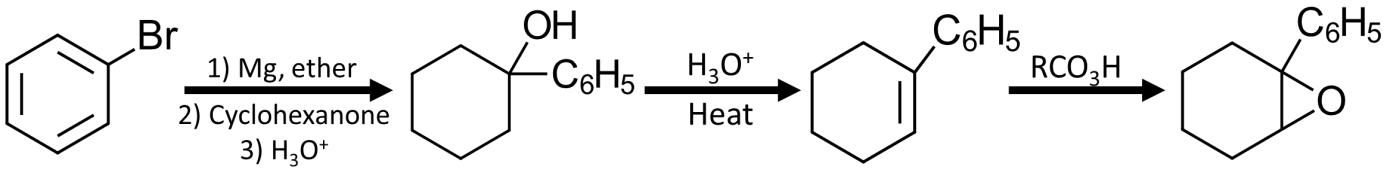
This alcohol, 1-phenylcyclohexanol, can be synthesized with a Grignard reaction involving bromobenzene and cyclohexanone. Bromobenzene is a starting material; cyclohexanone follows from oxidation of cyclohexanol, which is a starting material.



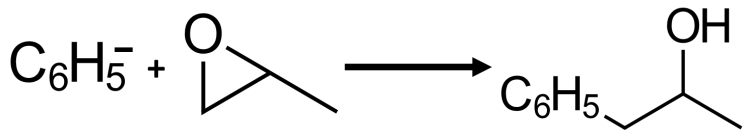
The Grignard reaction in question is outlined below.



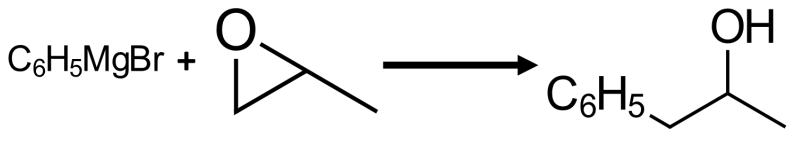
The full synthetic route is shown in continuation.



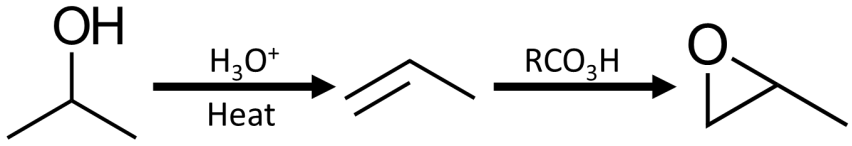
7.3: The necessary carbon skeleton can be obtained through reaction of a Grignard reagent with 1,2-epoxypropane.



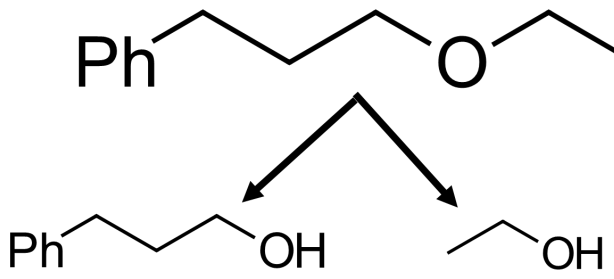
Treatment of bromobenzene, one of the starting materials, with magnesium yields a Grignard reagent. Reaction of this Grignard reagent with 1,2-epoxypropane yields the alcohol we are looking for.



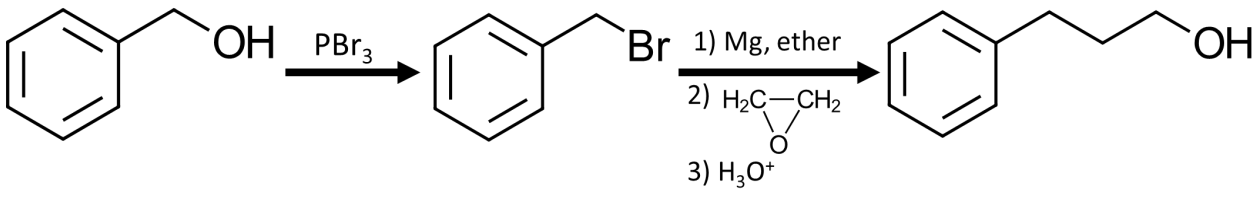
It remains to establish how 1,2-epoxypropane can be obtained. This is where isopropyl alcohol comes in. We first dehydrate the alcohol to propene; then, epoxidation with a peroxycarboxylic acid produces 1,2-epoxypropane.



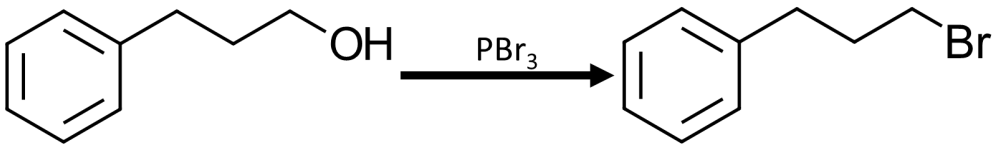
7.4: Because the target molecule is an ether, it ultimately derives from two alcohols.



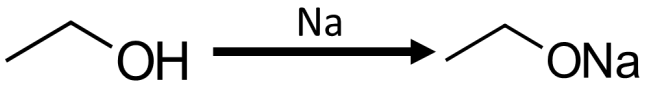
The first task is to produce 3-phenyl-1-propanol from benzyl alcohol, which is one of our starting materials. This requires formation of a primary alcohol with the original carbon chain extended by two carbons. The method Carey proposes to achieve this transformation is to first convert benzyl alcohol to a bromide, then treat it with magnesium to produce a Grignard reagent, and finally react it with ethylene oxide.



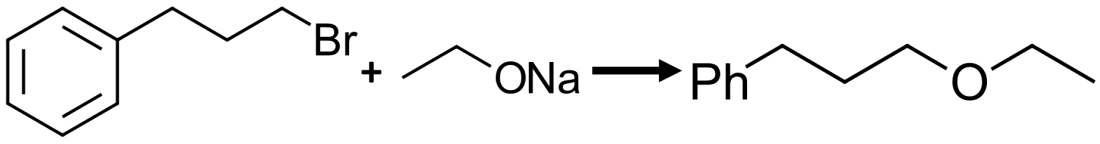
After the alcohol above has been prepared, we convert it back to a bromide.



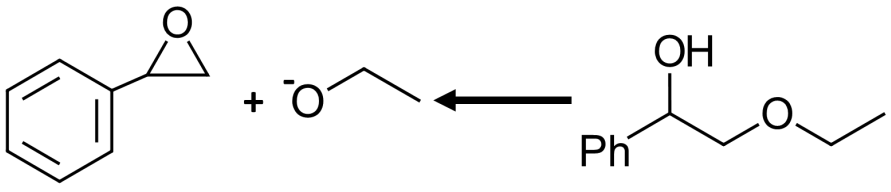
Then, we treat ethanol, another starting material, with sodium.



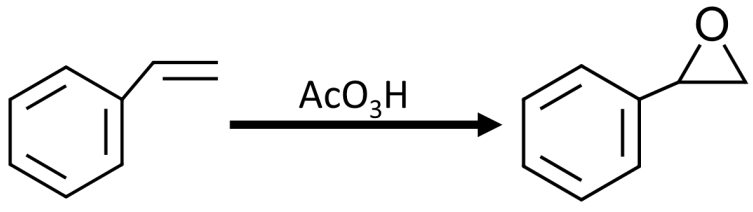
Reaction of the two foregoing products should yield the desired ether.



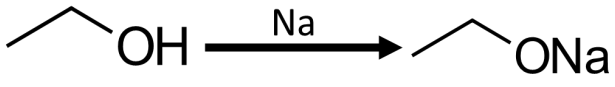
7.5: Retrosynthetic analysis reveals that the desired target molecule may be prepared by reaction of an epoxide with an ethoxide ion.



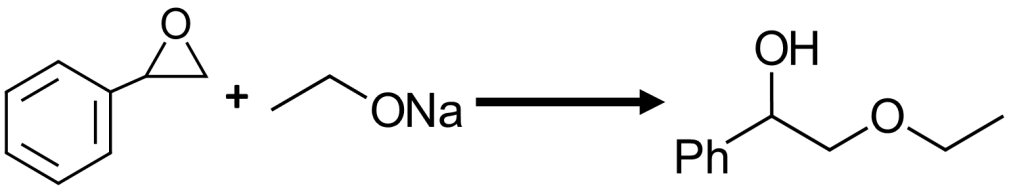
Styrene oxide may be prepared by reaction of styrene, a starting material, with peroxyacetic acid.



Ethanol, also a starting material, can be used to generate sodium ethoxide.



Reaction between the two foregoing products yields the ether we are looking for.



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