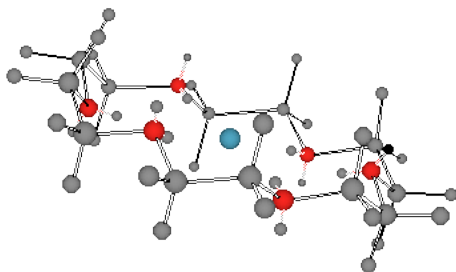


Chem 220 - Organic Chemistry

Problem Set 10, Solution Set

Chapter 14 - Ethers and Epoxides

Due: Monday, November 30, 2009



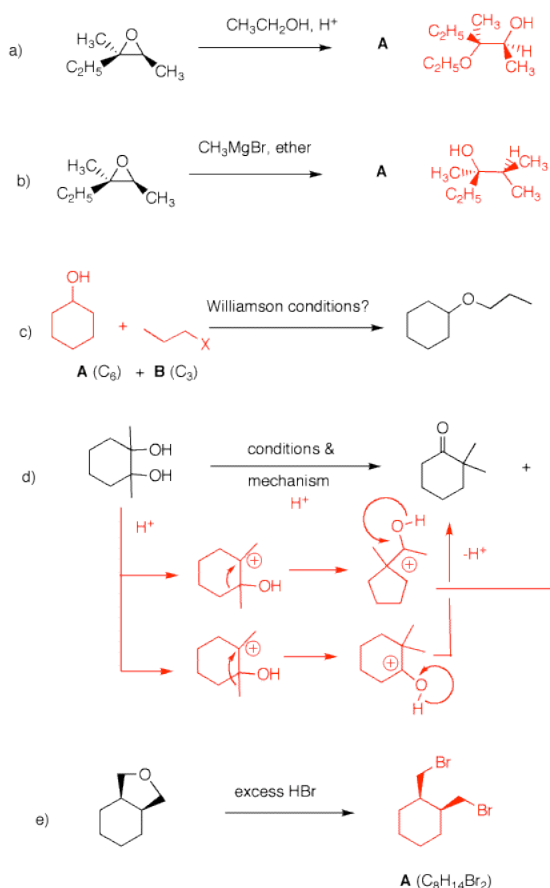
- Potassium cation solvated by the cyclic polyether, 18-crown-6 [18-membered ring; 6 oxygen atoms]. Each of the ethano groups is in a staggered conformation with each of the O-C-C-O dihedral angles at $\sim 60^\circ$ [gauche]. For a dynamic version, [click here](#). Note that the six oxygen atoms occupy the same spatial arrangement as do the six carbon atoms in chair cyclohexane. The discovery of the crown ethers by [Charles Pedersen](#) of DuPont earned him a share in the 1987 Nobel Prize in Chemistry.
- Diethyl ether (ether) may well be the first organic compound prepared that does not appear in Nature. For a chemical history of ether [click here](#). A different Powerpoint version is [here](#).
- [Theory of Etherification](#), A. W. Williamson, *Quarterly J. Chem. Soc.*, **1852**, *4*, 106. [See page 23 in the [pdf file](#).]

"The following experiments were made with the view of obtaining new alcohols, by substituting carburetted hydrogen for hydrogen in a known alcohol. Iodide of potassium was readily formed on the application of a gentle heat, and the desired substitution was effected; but, contrary to expectation, the compound thus formed had none of the properties of an alcohol -- it was nothing else than common ether, $C^4H^{10}O$."

- [On Etherification](#), A. W. Williamson, *Quarterly J. Chem. Soc.*, **1852**, *4*, 229.

1. In the following problems, provide the missing information. Provide explanations for your choices. **Pay attention to stereochemistry.**

1a) Acid-catalyzed opening of epoxides in hydroxylic solvent occurs at the more substituted end of the epoxide with S_N2 control. In the transition state of the protonated epoxide has some of the positive charge on a carbon attached to the oxygen of the epoxide. This charge is better at the tertiary



to occur at the tertiary carbon rather than at the secondary one.

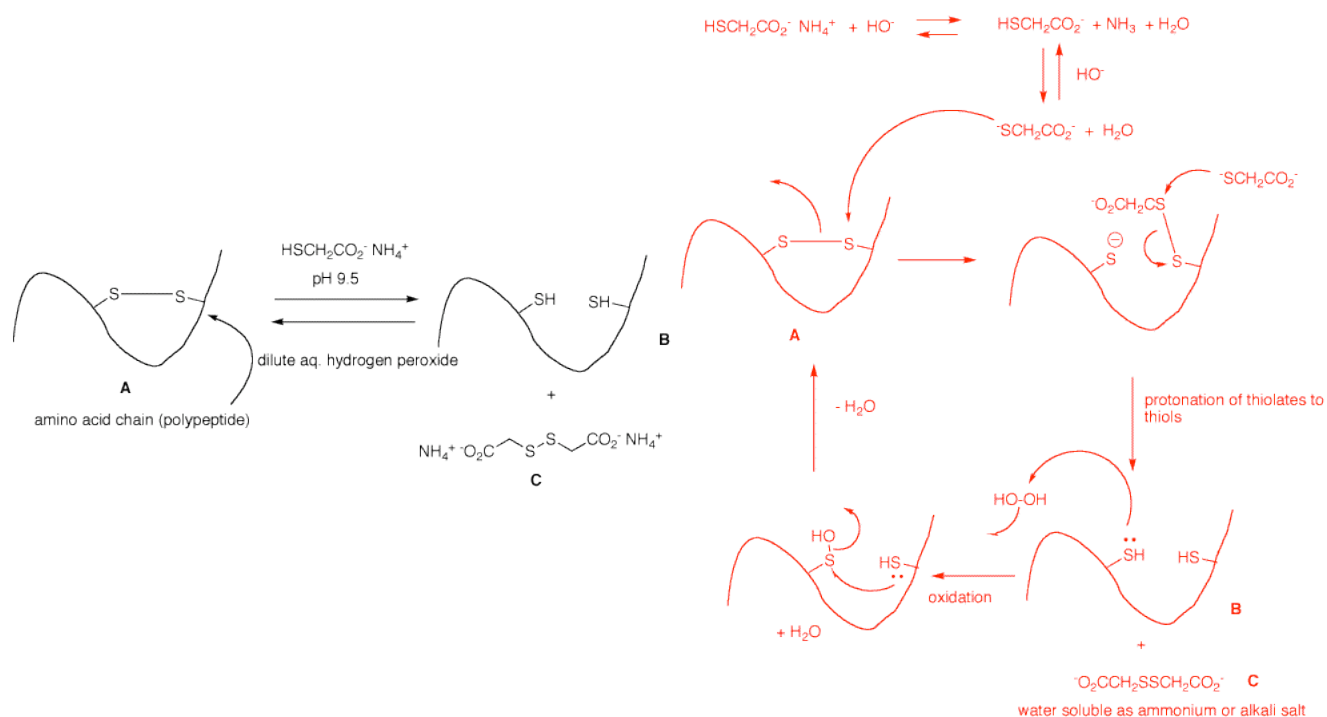
1b) Grignard reagents behave in the traditional sense of nucleophiles. S_N2 attack at the less substituted site.

1c) The alkoxide of cyclohexanol and 1-halopropane (halo = Cl, Br, I). The primary halide favors an S_N2 reaction. The alternative, the alkoxide of 1-propanol and a cyclohexylhalide invites E₂ elimination. Cf. Ethers #1 in ORGO.

1d) Protonation of either equivalent alcohol affords a tertiary carbocation. Migration of a ring bond leads to ring contraction. Migration of a methyl group retains the 6-membered ring. The rearrangement is favorable because a tertiary carbocation is going to a tertiary cation where one of the carbons has been replaced by oxygen. Resonance stabilization of the cation by an electron pair on oxygen is possible, this stabilized species is nothing more than a protonated carbonyl group.

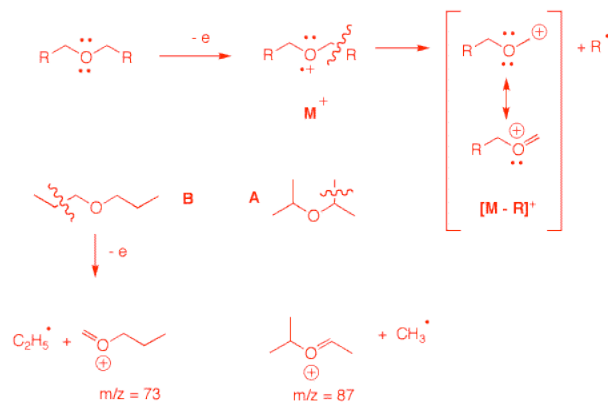
1e) The ether is protonated and then bromide effects an S_N2 displacement to give a bromo alcohol. The process is repeated on the alcohol to give the dibromide.

2. Cartoon A represents the cross-linking a disulfide bond in hair. This property gives hair its natural curl or an artificial "permanent wave". When a solution of ammonium thioglycolate at alkaline pH is applied to the hair, it goes straight to form a dithiol (cartoon B) and disulfide C, which is water soluble and is rinsed away. To restore the curl, the hair is washed with a mild oxidant. Provide a mechanism for the formation of B and C from A, and the formation of A from B. *At pH 9.5 ammonium thioglycolate is in equilibrium with ammonia and the carboxylate and the thiolate carboxylate. It is this species that behaves as a nucleophile to reduce the disulfide bonds in hair and form a new, water soluble disulfide C. Hydrogen peroxide reforms the disulfide A, putting the "bounce" back.*



3. Compounds **A** and **B** (0 Degrees of Unsaturation) are symmetrical, isomeric monoethers (see spectra). Compound **A** cannot be prepared by the Williamson method. Why? Compound **B** can be prepared only one way by the Williamson method and conveniently by classical acid catalysis. The molecular ion of **B** is $m/z = 102$. Since **A** and **B** are isomers, the weaker $m/z = 102$ in **A** is also the molecular ion. Because both of them are saturated, monoethers and have 0 DU, then $12n + 1(2n + 2) + 16 = 102$; $14n = 84$; $n = 6$. The formulas are $\text{C}_6\text{H}_{14}\text{O}$. Symmetrical ethers reduce the choices to diisopropyl ether and di-*n*-propyl ether. The branched ether cannot be made by the Williamson ether synthesis because E_2 elimination will prevail. There are two disconnections for the Williamson route to di-*n*-propyl ether but they are identical. Symmetrical, primary ethers can be prepared by acid catalysis.

a) What are the structures of **A** and **B**? Explain how the spectra distinguish them. **A** is diisopropyl ether; **B** is di-*n*-propyl ether. The principle mode of fragmentation of ethers is shown below. Using electron impact mass spectroscopy, an electron is removed from the oxygen to give the molecular ion, M^+ . Fragmentation leaves a detectable, resonance stabilized cation $[M-R]^+$ and the undetectable radical, R . There is an $m/z = 73$ [$M^+ - 29$] peak for **B** but none for **A**. **A** cannot lose 29 mass units. **A** readily loses a methyl group [$m/z = 87$], which is weak in the spectrum of **B**.

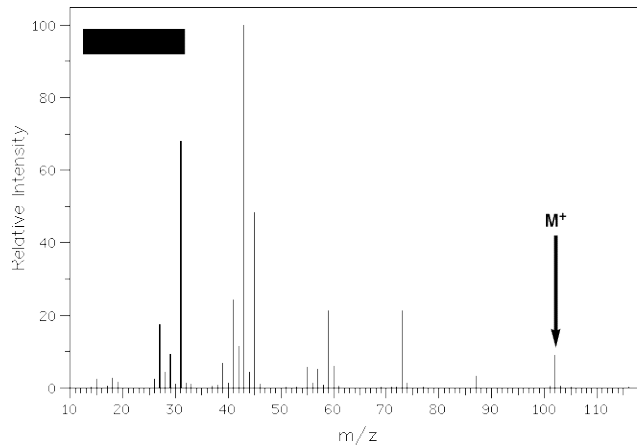
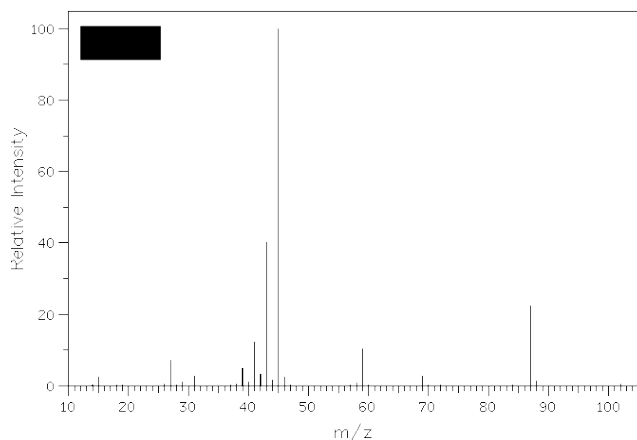


b) Show how you would best prepare the mixed ether **C** that is related to **A** and **B**.

Use the sodium salt of 2-propanol and 1-bromopropane to optimize $\text{S}_{\text{N}}2$ displacement. Use of 2-bromopropane and the sodium salt of 1-propanol will lead to E_2 elimination.

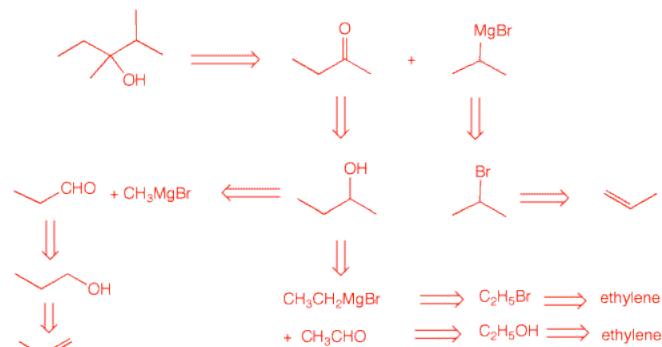
Spectrum A: ([larger version](#))

Spectrum B: ([larger version](#))

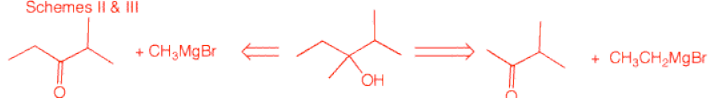


4. Design three independent syntheses of 2,3-dimethyl-3-pentanol using three different disconnections. Your sources of carbon contained in the product are limited to methanol, ethylene and propene. All other reagents are available to you. What can you say about the optical rotation of 4-ethyl-4-octanol in each of your syntheses? *The Schemes show only the retrosynthetic analysis. You supply the reagents for the forward reactions. Tertiary alcohols arise from any one of three retrosyntheses involving Grignard additions to ketones. Scheme I shows one of these routes in detail. Schemes II and III show only the first steps. Follow the logic in Scheme I. A fourth option utilizes an epoxide as shown in detail in Scheme IV.*

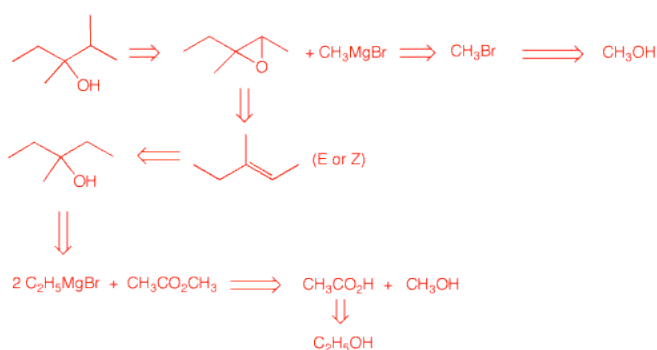
Scheme I



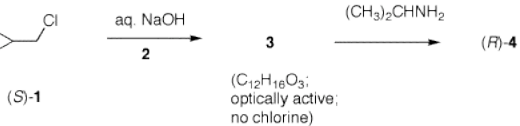
Schemes II & III



Scheme IV

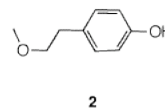
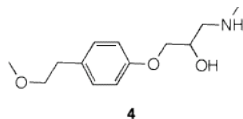
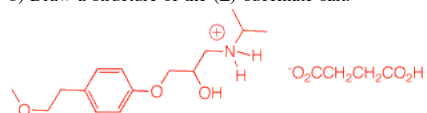


5. Toprol (**4**; Lopressor; Metoprolol) is a β -blocker for the treatment of hypertension. It is racemic drug sold as its monosuccinate salt. A seasoned chemist wants to prepare Toprol as its (*R*)-enantiomer using the synthesis of the racemate. She follows the steps shown on the right.



a) Why is Toprol a racemate? *When prepared from racemic 1, 4 is a racemate because the carbon bearing the OH group is asymmetric.*

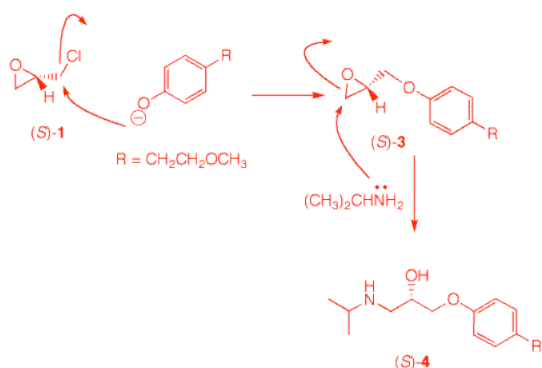
b) Draw a structure of the (\pm)-succinate salt.



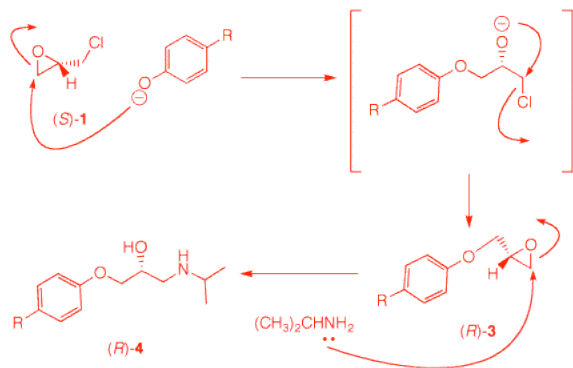
c) What is the role of aq. NaOH? [Check here](#). *The strong base NaOH forms the anion of the phenol 2.*

d) What does the sequence of reactions and their chirality tell you about the mechanism of the double S_N2 reaction sequence? Write mechanisms for the two reactions. *There are 2 sites for S_N2 reactions to occur; on the C-Cl bond and the less substituted end of the epoxide ring. If Path A is followed, the phenoxide anion displaces chloride on (S)-1 to give epoxide (S)-3. Subsequent use of isopropylamine as a nucleophile would lead to (S)-4, the wrong enantiomer of toprol. On the other hand, if Path B is followed, phenoxide opens the epoxide first to yield a chlorohydrin anion which closes to the epoxide which is now (R)-3. Opening of this epoxide with the amine gives the correct enantiomer of toprol, (R)-4. The epoxide, and not the C-Cl entity, is the better electrophile.*

Path A



Path B



e) What is the structure and CIP designation for 3? *See above.*

f) How can she prepare (S)-4 without resorting to the use of (R)-1?

Use the amine as the first nucleophile and the phenoxide second.