

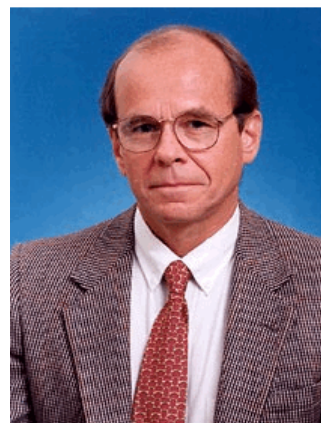
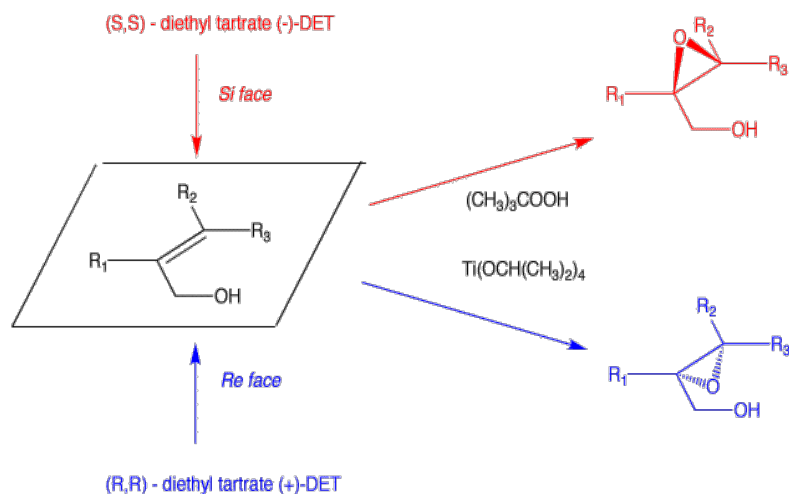
Chem 220 - Organic Chemistry

Problem Set 10

Solution Set

Chapters 11: The Chemistry of Ethers, Epoxides, Glycols and Sulfides

Due: November 28, 2011



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Co-Nobelists 2001

Lecture: [Video Text](#)

Asymmetric Epoxidation and Dihydroxylation

Asymmetric Epoxidation Exemplified

Reading Assignment:

[On the Epoxidation of Alkenes](#)

Enrichment Assignment:

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](#).

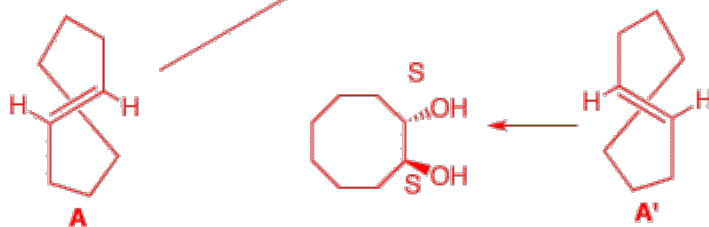
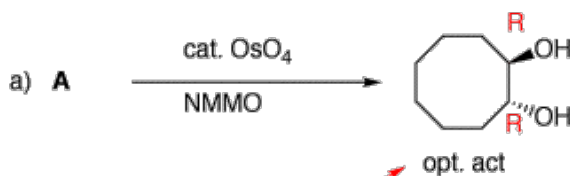
[Theory of Etherification, A. W. Williamson, Quarterly J. Chem. Soc., 1852, 4, 106.](#) [See page 106 in the .pdf file.]

"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, C⁴H¹⁰O." [On Etherification, A. W. Williamson, Quarterly J. Chem. Soc., 1852, 4, 229.](#)

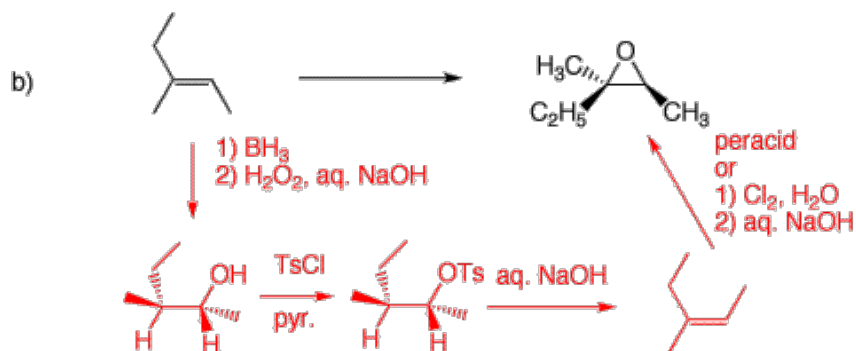
1. Each of the following reactions is missing a reactant, reagent and/or product. Provide the missing items along with an explanation.

a) The diol is optically active (R,

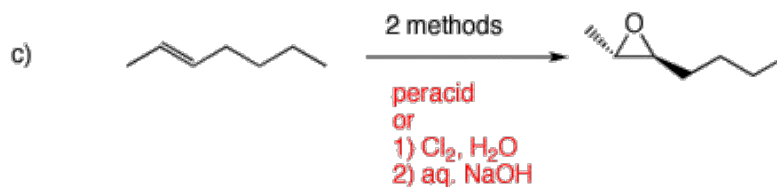
R) and *trans*. Since OsO_4 adds *syn* to a double bond, *A* cannot be *cis*-cyclooctene, which would provide the *cis*-diol. *A* is the enantiomer of *trans*-cyclooctene shown. Its enantiomer, *A'*, would afford the *S,S*-enantiomer. The reaction of OsO_4 with the double bond of *trans*-cyclooctene can only react with the external face.



b) Direct epoxidation would give the diastereomeric epoxide. The alkene geometry must be inverted. Hydroboration adds water *syn* and *anti*-Markovnikov. Removing the elements of water *anti* E2 as TsOH gives the (*Z*)-alkene. Epoxidize by either of two procedures to give the racemic epoxide.

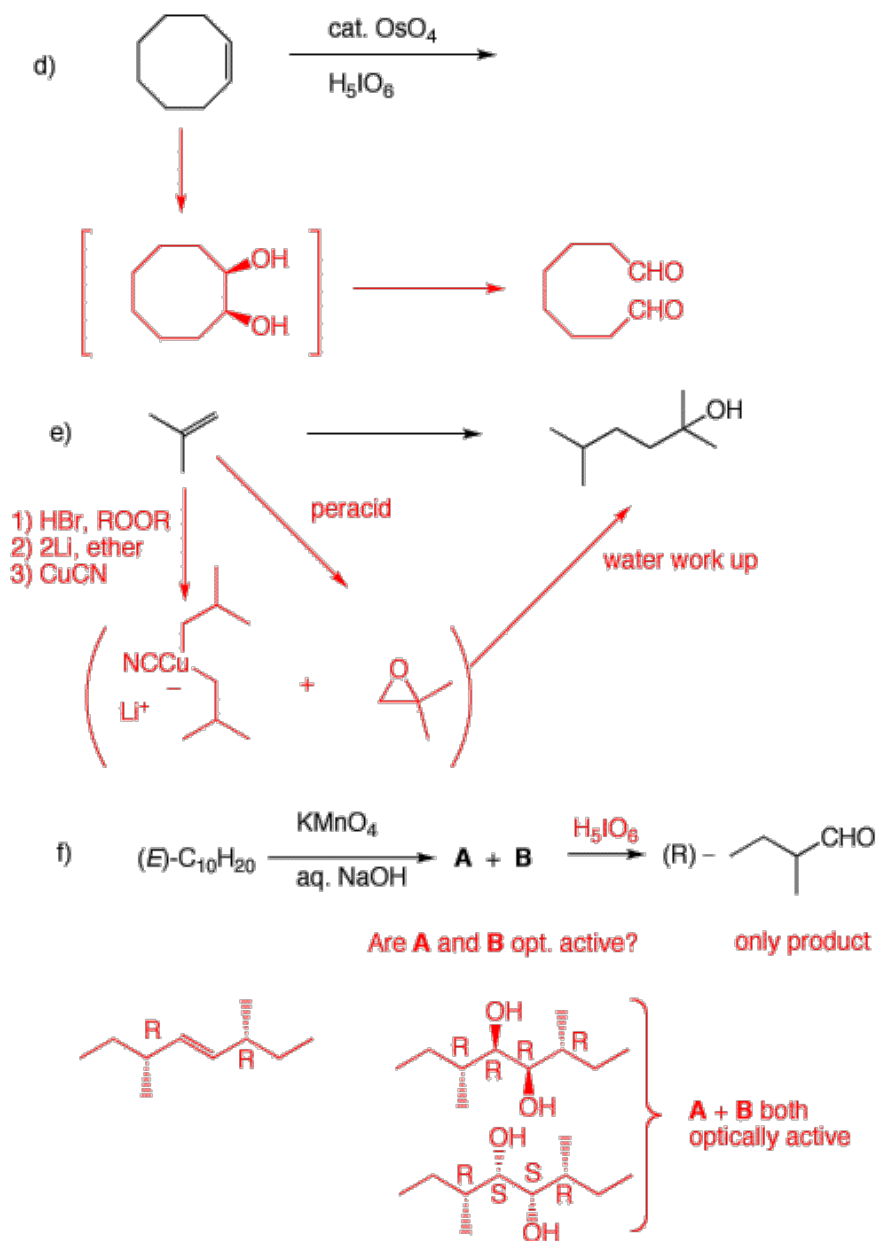


c) See the last step of part b.



d) *cis*-1,2-Cyclooctanediol is formed *in situ*. Cleavage to the dialdehyde occurs. Two equivalents of periodic acid are required. Four electron oxidation.

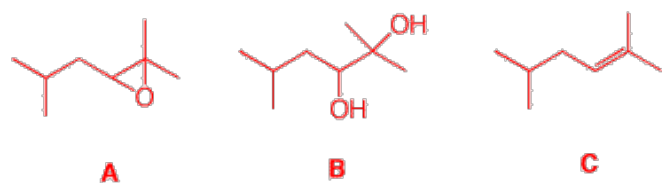
e) Isobutylene must be used twice and a carbon-carbon bond must be formed. The epoxide is the electrophile and the cuprate reagent is the nucleophile. Cuprates may be generated from Grignard reagents (or organolithium reagents). The



problem with magnesium cations, and Grignard reactions with highly substituted epoxides, is that they can effect rearrangement of epoxides. In this instance isobutyraldehyde can form and act as an electrophile toward the magnesium reagents. Attack occurs in an S_N2 fashion at the less substituted carbon of the epoxide.

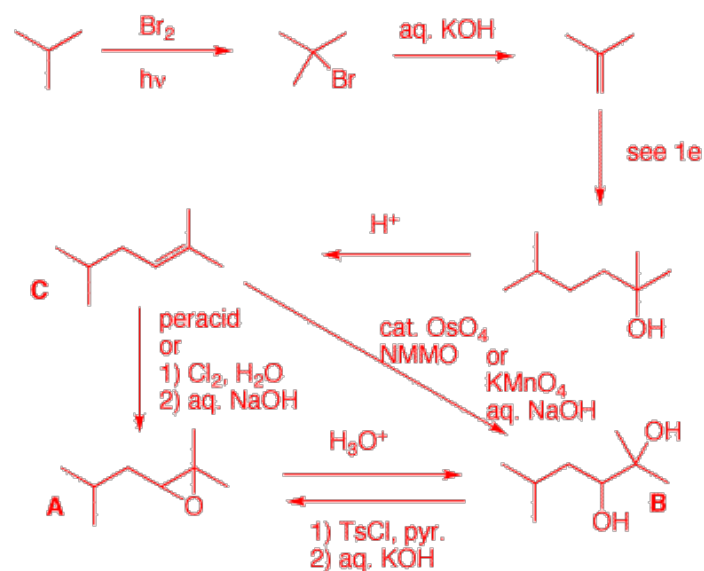
f) Since the aldehyde is opt. act. and a single product, reconstituting the alkene means that both sides of the double bond are substituted equally. Permanganate adds *cis*. Both diols are optically active diastereomers.

2. A graduate student requires two related compounds: (\pm)-2,2-dimethyl-3-isobutyloxirane (**A**) and (\pm)-2,5-dimethylhexan-2,3-diol (**B**). She has available to her isobutane as the only source of carbon. She decides to synthesize 2,5-dimethyl-2-hexene **C**, an alkene that can serve to provide both **A** and **B**.



a) Show her (your) synthesis of **C**. *Free radical bromination is highly selective for tertiary hydrogens over primary ones (~1600:1, tertiary over primary. With 9 primary hydrogens and only one tertiary hydrogen, the selectivity is ~160:1). Elimination gives isobutylene. Carbon-carbon bond formation is provided in 1e. E1 elimination of the tertiary alcohol affords the more substituted alkene C. There are two methods*

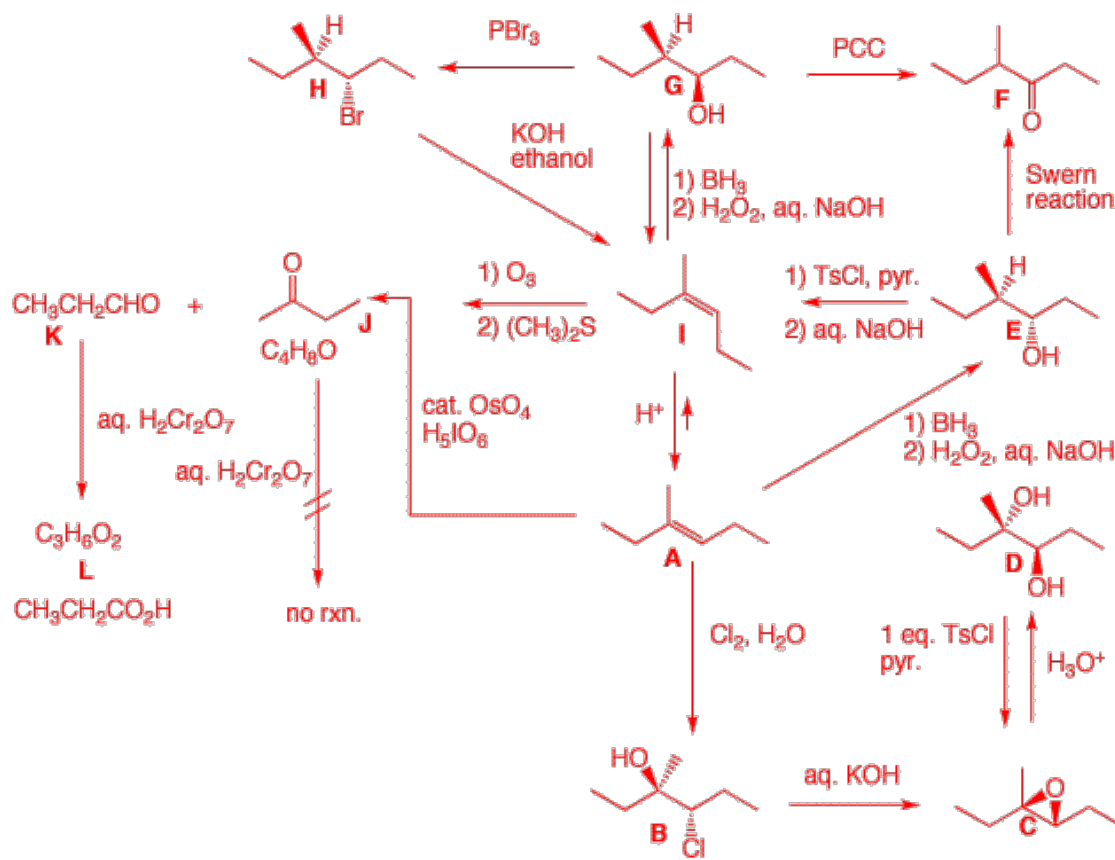
available for forming **A** and **B** from **C**. The conversion of **A** to **B** and **B** to **A** is shown below.



b) Show how she can convert **A** into **B** and **B** into **A**.

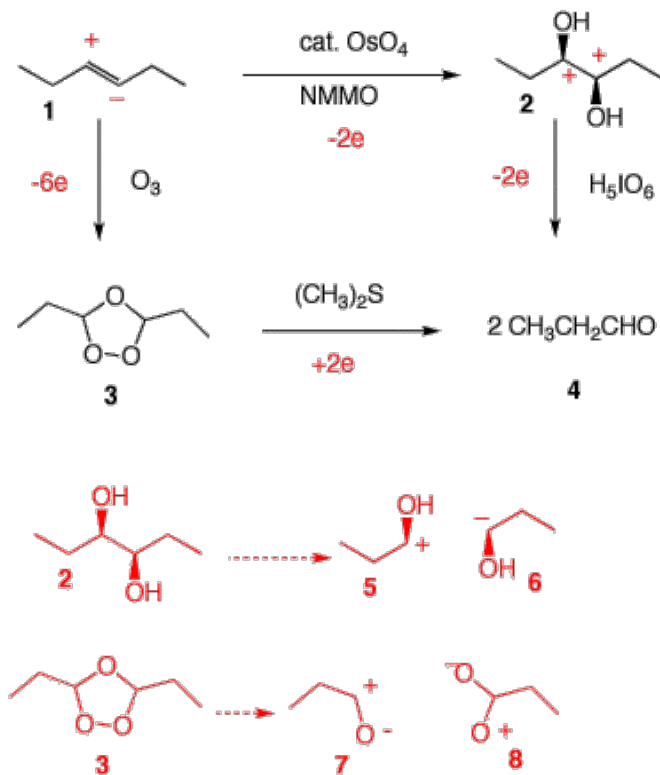
See part a.

3. Identify each of the structures below. Pay attention to stereochemistry. Pay attention to the equilibrium arrows in the equilibrium between **A** and **I**. Ignore any constitutional isomers that may arise. *All compounds are C_7 as seen in the data for **J** and **K**. They are formed from **A** and **I** by reactions that cleave double bonds. **A** and **I** are alkenes. **A** is more stable than **I** based on the position of the equilibrium catalyzed by acid. [Ignore the possibility of formation of the alternative trisubstituted alkenes from the intermediate tertiary cation.] **J** must be a ketone; inert to chromic acid. Only 2-butanone is possible for **J**. **K** is propionaldehyde because it is oxidized to a carboxylic acid **L**, propionic acid. Piecing **J** and **K** together **A** and **I** become (*E*)-3-methyl-3-hexene and (*Z*)-3-methyl-3-hexene, respectively. The rest of the structures fall into place knowing the reactions and stereochemistry.*



4. Two oxidative pathways are shown below for the conversion of (*E*)-3-hexene **1** to propionaldehyde **4**. The total electron change must be the same in both routes. Illustrate the electron change for each of the four steps.

a) Polarize the double bond in alkene 1 as + and -. [Review here.] Carbons 2 and 3 in 2 are $\delta+$ relative to oxygen. Net 2-electron oxidation. Diol 2 to two aldehydes is a two electron oxidation. If the C-2-C-3 bond of diol 2 is broken [mentally] heterolytically, species 5 and 6 are formed. Species 5 is a protonated aldehyde. Species 6 requires the loss of the two electrons to become 5. Break two bonds of ozonide 3 heterolytically to form 7 and 8. Species 7 is an aldehyde while two electrons must be added to the positive oxygen of 8 (and two protons) to give the hydrated form of an aldehyde. Protonation and hydration are electroneutral. Since both routes are 4-electron oxidations, alkene 1 forming ozonide 3 is a 6-electron oxidation.

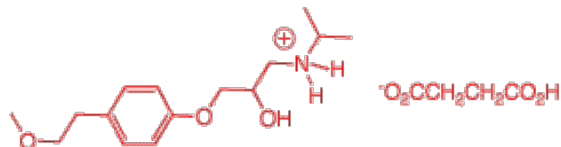


5. Toprol (4; Lopressor; Metoprolol) is a β -blocker for

the treatment of hypertension. It is a 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.

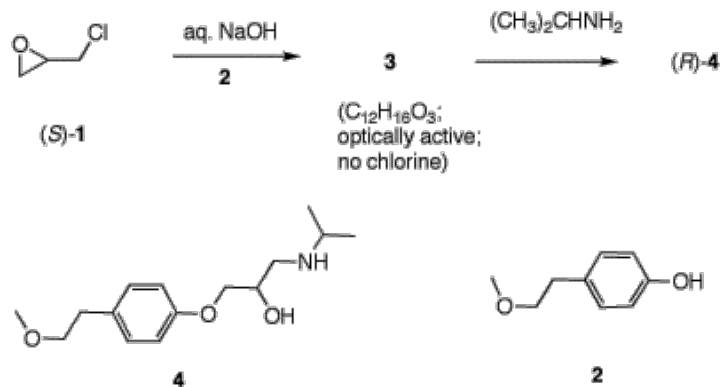
a) Why is Toprol a racemate? *When prepared from racemic 1, 4 is a racemate because the carbon bearing the OH group has both enantiomers present.*

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



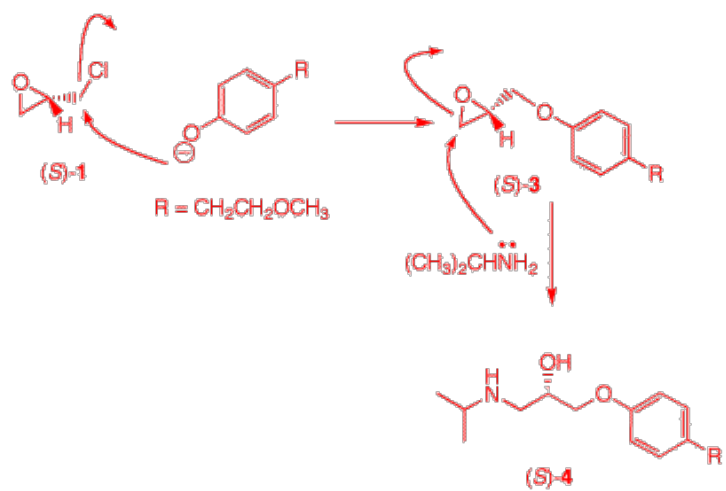
c) What is the role of aq. NaOH? [Check here.](#) *The strong base NaOH forms the anion of the phenol 2.*

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.*



f) How can she prepare (*S*)-4 without resorting to the use of (*R*)-1? *Use the amine as the first nucleophile and then employ the phenoxide.*

Path A



Path B

