As we draw towards the end of the semester, we will be paying more attention to questions regarding synthesis, which is the process by which organic chemists build complex molecules from available starting materials in as few steps as possible. Traditionally, synthesis questions are popular tests of student knowledge since they bring together all of the reactions, reagents, mechanisms and stereochemical concepts learned during your first semester of Organic Chemistry. Learning to master these problems is important both for Chem 232, but also Chem 234, where questions of synthesis become more central. The focus of exam three and the rest of this course will be on synthesis problems. Although many, if not the majority, of students in this class are not destined to become Organic Chemists, the problem solving skills fostered by planning organic syntheses are invaluable in a range of apparently unrelated fields: chemists are a favorite recruitment target of investments banks in the City of London.

Approach these problems then as you might an algebra problem, Sudoku puzzle or chess game. The number of molecules you can make with the chemical transformations you’ve learned so far is literally infinite, just as the number of possible Sudoku puzzles is infinite. Your challenge is to recognize what patterns and logic are operating that will allow you to convert one set of functional groups into another for seemingly different molecules. Like any puzzle or skill, practice makes perfect. I suggest that you attempt all of the synthesis problems that follow. To encourage you to do so, I guarantee that all of the synthesis problems on the next exam will come directly from this handout.

The most common mistake made when approaching a synthetic challenge is to begin with the starting material and try to “find a way” to the product through intense thinking and a lot of trial and error. Although this method may work for simple synthetic problems that require only one or two steps, it is inefficient and usually unsuccessful for more advanced problems. The key is to begin at the end; work backwards from the target, using your knowledge of chemical reactions, until you reach the starting material. This called a retrosynthetic analysis. Let’s work through the synthetic problem below as an example. At first glance you should recognize that there is no one chemical transformation that we’ve learned that is able to convert 1 into 2; therefore, more than one step must be required.

![Reaction Arrow]

Begin the retrosynthetic analysis by first drawing the target, in this case 2. Then, draw the arrow shown below; this arrow is used to represent a retrosynthetic step (reverse thinking step). Each time you draw this arrow, you are asking the question, “What molecule can be converted into the molecule at the beginning of my retrosynthetic arrow using chemistry I know?” In this case the question is, “What molecule can be converted into a secondary alcohol that is trans to the adjacent methyl group in 2?” Alcohols can be prepared from alkenes; specifically, hydroboration/oxidation of 3 is the best choice since this reaction is stereospecific. The –H and –OH groups are both added to the same face of the alkene, which puts the methyl group trans to the –OH group. This transformation is also regioselective and provides the least substituted alcohol (anti-Markovnikov addition). Hydration of 3 with H$_2$SO$_4$/H$_2$O to
give 2 wouldn’t work since that reaction proceeds through a carbocation intermediate and would provide a mixture of cis and trans alcohols. Hydration also provides the most substituted alcohol, which is not what is required. From 3 another retrosynthetic arrow is drawn and another question asked. From what molecule can the alkene in 3 be prepared? Alkenes can be prepared through a number of methods including dehydrohalogenation of alkyl halides. The tertiary alkyl bromide 4 is chosen rather than the secondary alkyl bromide because 4 can be prepared directly from our starting molecule 1 through Markovnikov addition of HBr. This completes the retrosynthetic analysis.

Once the retrosynthesis is complete, the forward reactions can be written including all the required conditions and reagents. Markovnikov addition of HBr across alkene 1 provides alkyl halide 4. Although other conditions may be included such as solvents and temperatures, the most important reagent here is HBr. Dehydrohalogenation of 4 can be accomplished with a strong base. Typically, alkoxide bases such as NaOCH₂CH₃ or NaOC(CH₃)₃ are used. Zaitsev’s rule predicts that the most substituted alkene will result from dehydrohalogenation. However, as we discovered in class large sterically hindered bases such as NaOC(CH₃)₃ may show a preference for deprotonation at the least sterically hindered site. In this case, that would revert 4 back to 1. To avoid this complication, a smaller strong base such as NaOCH₂CH₃ is preferred. Finally, hydroboration of 3 with B₂H₆ followed by oxidation with H₂O₂/OH− gives the target molecule, 2. Other synthetic routes are certainly possible for our target, but this route appears to be the shortest.

Although you may never encounter this exact synthetic target again, you should recognize an important synthetic strategy in this example. Less substituted alkenes such as 1 can be converted into their more substituted isomers through a simple two step sequence: HX addition followed by dehydrohalogenation. This strategy is very powerful and can be used in several of the problems that follow. Look for important patterns and strategies in each of the problems you attempt. Doing so will dramatically increase the speed at which you are able to develop reasonable syntheses.
For each question below, first write out a retrosynthetic analysis. Having done this, design a synthesis of the target molecule including all necessary reaction conditions and reagents for each step. You should be able to devise a synthesis for each target below using chemistry covered through Chapter Six.
For each question below, first write out a retrosynthetic analysis. Having done this, design a synthesis of the target molecule including all necessary reaction conditions and reagents for each step. You should be able to devise a synthesis for each target below using chemistry covered through Chapter Eight.
For each question below, first write out a retrosynthetic analysis. Having done this, design a synthesis of the target molecule including all necessary reaction conditions and reagents for each step. You should be able to devise a synthesis for each target below using chemistry covered through Chapter Nine.
Synthesis

Target Molecule

Retrosynthetic Analysis

Recognize the functional groups in target and their relationship to one another

Disconnect by methods corresponding to known and reliable reactions

Arrive at Starting Materials

Write out plan according to analysis, adding reagents and conditions

Modify plan according to unexpected failures or successes in the laboratory

Repeat as Necessary

Trial & Error

Carry out synthetic steps in laboratory

Synthetic Planning

Repeat as Necessary