

One of the things that makes chemistry unique among the sciences is synthesis. Chemists make things. New pharmaceuticals, food additives, materials, agricultural chemicals, coatings, adhesives and all sorts of other useful new molecules are prepared from simpler more readily available starting materials. There are two aspects to organic synthesis, first the development of a synthetic strategy or plan of action and second the actual implementation of that plan in a chemical laboratory. This exercise addresses the first aspect of the problem, the development of strategies for synthesis. The second aspect, the actual synthesis, requires real skill and training, something that you can start to acquire by taking an organic laboratory course. At Stony Brook we offer two such courses, CHE 327, a course that meets the minimum requirements for biology majors, and CHE 383, a course that meets the requirements for chemistry majors and others interested in a research career. Students who master such skills readily find jobs in the chemistry, pharmaceutical and other industries that employ chemists.



This figure shows a distillation apparatus that you would use in the organic chemistry laboratory. For example you might use it to purify a new ester that you synthesized from a carboxylic acid and an alcohol. For more information go to the organic chemistry laboratory web site at: <http://www.sinc.sunysb.edu/Class/orgolab/index.html>

The three questions:

When planning an organic synthesis there are usually different questions that one must ask.

1. How can I build the desired carbon skeleton?
2. How do I introduce the necessary functional groups?
3. How do I control the regio- and stereochemistry of my reactions?

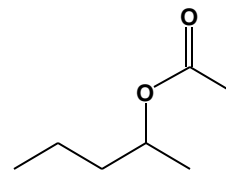
In the real world one needs to know a vast amount of organic chemistry to plan a successful and efficient synthesis of a complex molecule. There are thousands of known reactions; regio and stereochemistry are very difficult to control. However, in this exercise we have simplified things by limiting our universe of reactions to the ones shown on the last page. All the molecules we discuss can be synthesized using this limited set of reactions. However, with this limited set of reactions we can still write out syntheses of an *infinite* set of possible molecules. And we must still consider each of the three questions stated above.

How do you plan a synthesis?

The simple answer is to work backwards, one step at a time, implementing known reactions. Often there will be more than one possible reaction sequence. A little thought devoted to each of the three questions above will lead you to the proper reaction sequence more quickly.

How about an example?

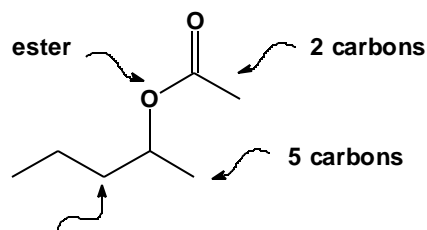
Ok. How would you synthesize the molecule shown at the right starting with organic compounds containing three carbons or less?



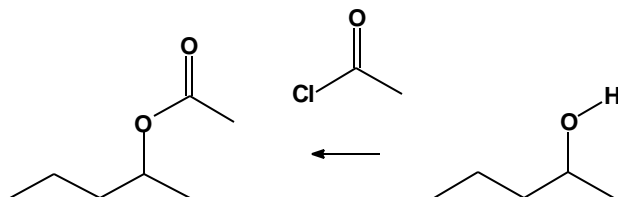
How do I start?

Count the carbon atoms and identify your functional groups. You need to know the functional groups so you know which reactions in your reaction library can be used to yield the given molecule. It is useful to count the carbon atoms so you will know the minimum number of carbon-carbon bond forming reactions you will eventually need in your synthesis.

In this case recognize that the compound is an ester and that it is made from two fragments, a 2 carbon piece and a 5 carbon piece. Since we have to make the 5 carbon piece from starting materials of 3 carbons or less it would be nice if we could eventually figure out a way to make a C-C bond in the middle of the fragment by combining two smaller molecules. But that step is not yet obvious so let start with the ester synthesis.



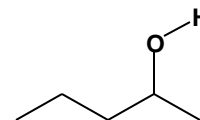
It would be nice if we could figure out how to make a C-C bond some where about here



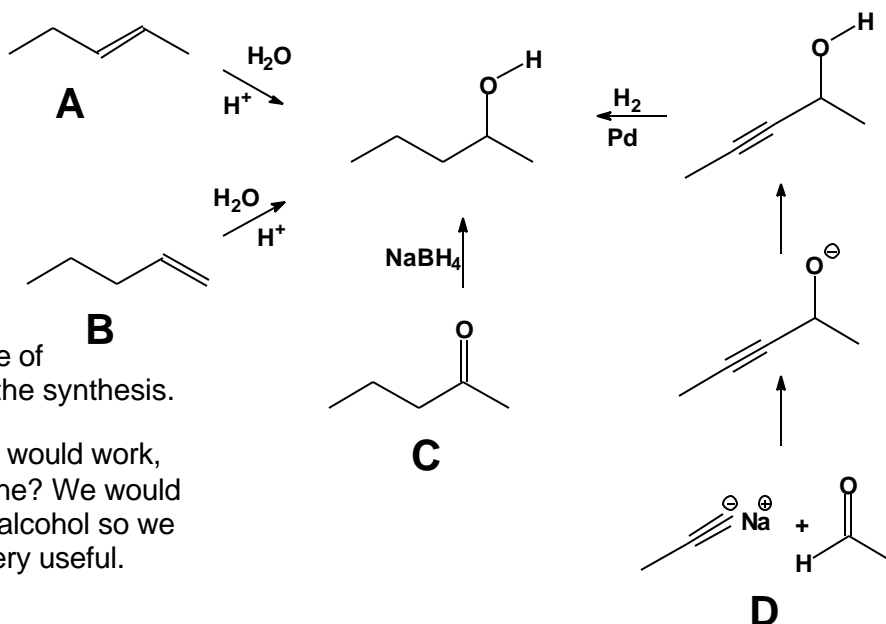
The ester synthesis is easy. You need an alcohol and an acid chloride. The acid chloride has 2 carbon atoms only, so it is a legal starting material, but the alcohol has 5 carbon atoms. This molecule must be synthesized. It becomes out new target molecule.

So how do you synthesize an alcohol?

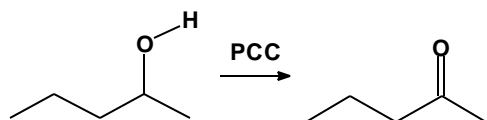
For the ester you only had one reaction to choose from, but for the alcohol your reaction library has several different reactions that yield alcohols. This gives you multiple alternatives for this step. You could use an acid catalyzed addition of water to an alkene. Hydroboration is not appropriate, in this case, but it would be a good choice if we needed a primary alcohol. You could use a substitution reaction starting with an alkyl bromide, but those reactions also work best if you want a primary alcohol. You could reduce a ketone with NaBH_4 . The alcohol could be the product of an acetylide reaction with an aldehyde followed by hydrogenation. How do you choose? Let us not choose yet, we will write out the best possibilities.



We have identified four possible routes to our alcohol and have labeled them. Let us consider each possibility in turn. **A** and **B** both involve the acid catalyzed addition of water to a double bond. **B** is obviously better than **A**, because path **A** would also give 3-pentyl alcohol, something we do not want. This is an example of controlling the regiochemistry of the synthesis.



Path **C**, the reduction of a ketone would work, but how would we make the ketone? We would make it from the oxidation of the alcohol so we would have a circular path, not very useful.

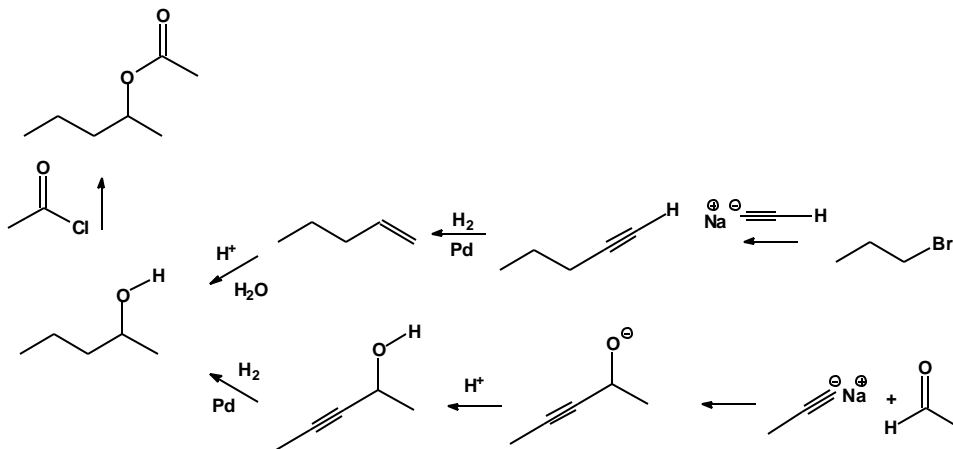


Path **D** requires more insight, but it gives us everything we need, the alcohol functionality and the needed C-C bond forming reaction. Thus of the four possible paths either **B** or **D** would work. Path **D** is finished because it starts with molecules with three carbon atoms or less, but path **B** needs to be completed. Path **D** is an example of a somewhat hidden solution. Your last step to a molecule may involve the hydrogenation of a double or triple bond.

How would we make 1-pentene, the alkene we need for path **B**? We could make it by eliminating water from an alcohol, but that would lead to a circular path since we would need to make the alcohol from the alkene. Instead we can make the alkene by adding hydrogen to an alkyne. This naturally leads us to the necessary C-C bond forming reaction using an acetylide substitution reaction.

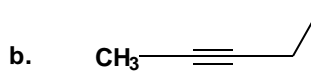
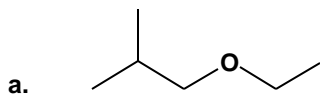


So we have two paths for the final total synthesis. Let us write them both down. Both are correct answers to the original question. Which path is better? That is a decision you would make in the actual laboratory. It would depend upon such things as actual reaction yields and availability of the starting materials. On an exam you would need to give only one of these two paths.

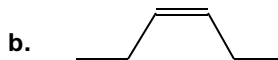
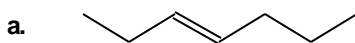


Problems. Use the reactions given on the last page of this exercise.

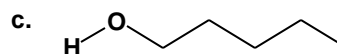
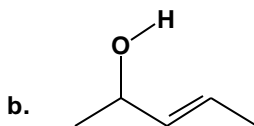
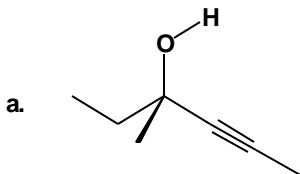
1. For each of the following molecules give **two** synthetic routes starting with molecules containing four carbons or less.



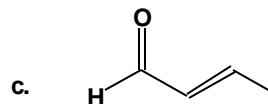
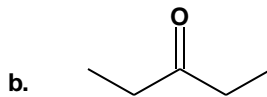
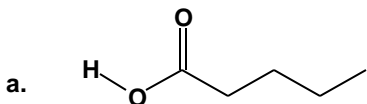
2. Show how you could synthesize the following alkenes starting with molecules containing four carbons or less. More than one step is required.



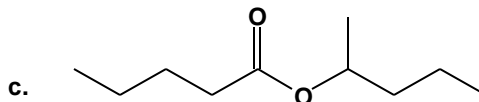
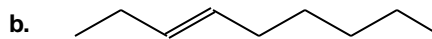
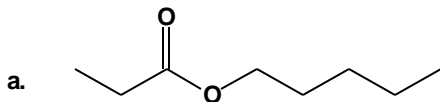
3. Show how you could synthesize the following alcohols starting with molecules containing four carbons or less. More than one step is required.



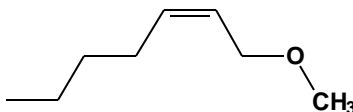
4. Give syntheses for the following molecules starting with molecules containing four carbons or less. Hint: Make an alcohol first and then do an oxidation.



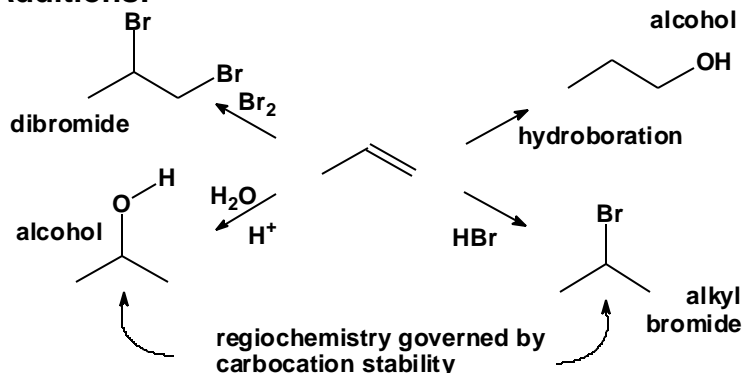
5. Give syntheses for each of the following molecules starting with molecules containing four carbons or less. Multiple steps will be required.



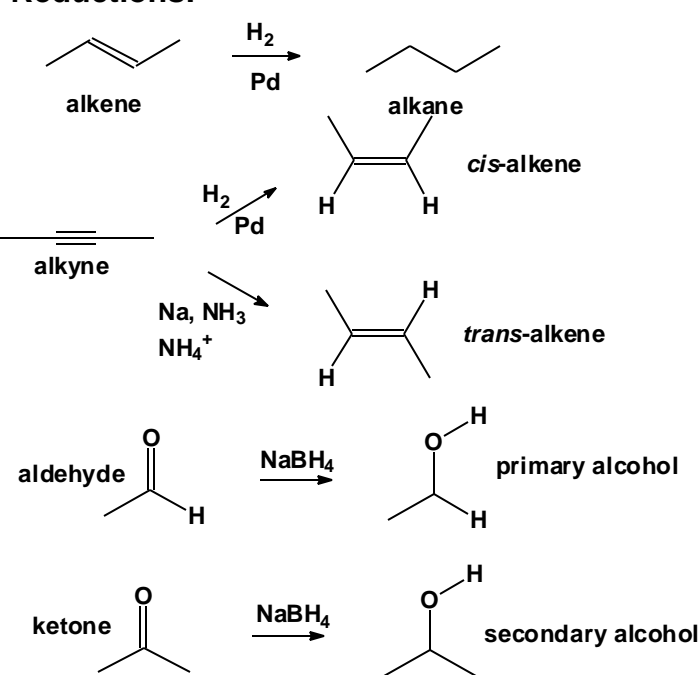
6. Give a synthesis of the following molecule using starting materials containing **three** carbons or less. **Note:** This problem was the final problem on the last CHE 321 exam. Some of the organic students thought it was hard. It is not really hard, but it is long and requires about nine steps.



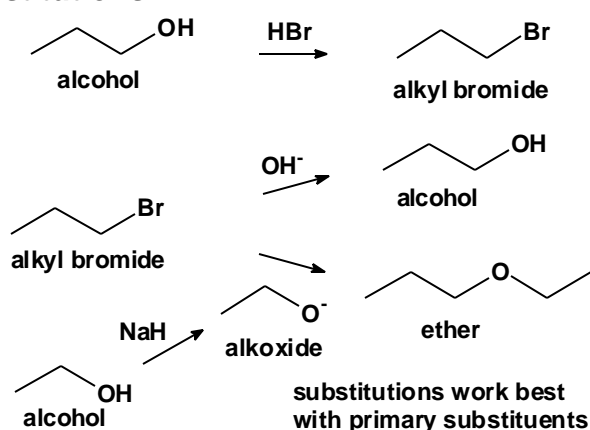
Additions:



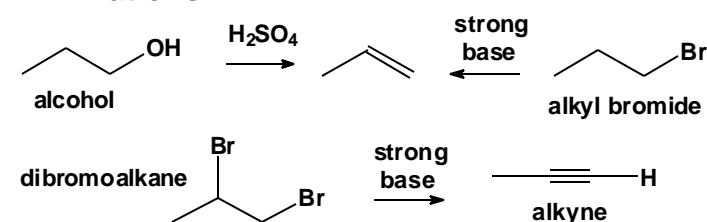
Reductions:



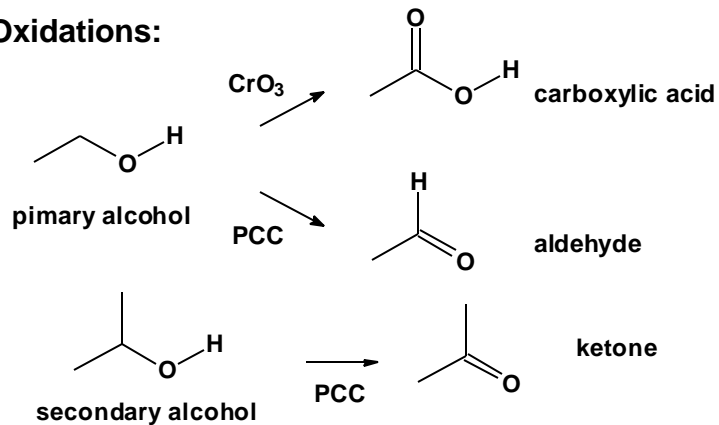
Substitutions:



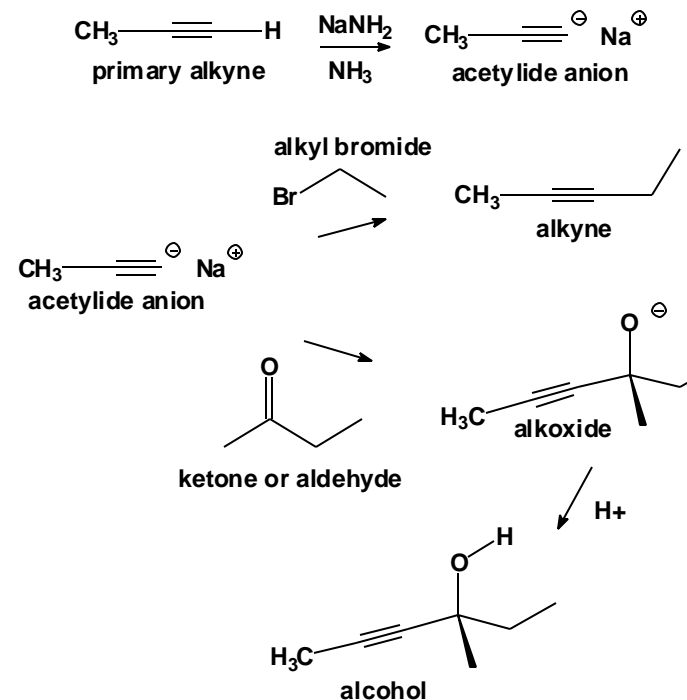
Eliminations:



Oxidations:



Acetylide Chemistry:



Carboxylic acid derivatives:

