Approaching Synthesis Problems

Introduction:

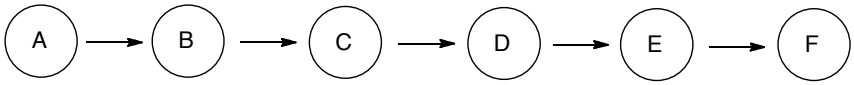
Synthesis can be challenging to study for, as each problem is unique and tricks that work for one question may not work for another. It is helpful to think of studying synthesis as analogous to writing a poem. To write a poem we need to have a good vocabulary (know many reactions), a solid understanding of grammar (mechanisms and basic principles), and a certain amount of inspiration. Like poetry some synthesis can be elegant 100 step convergent epics, while others may be short but serviceable limericks. A synthetic chemist is always learning new reactions and looking for ways to make their synthesis simpler and more elegant, however even the best epic poet had to start writing somewhere. With practice, particular patterns will show up as familiar, and while there is no magic process, there are ways to approach a problem that give a high likelihood of finding the necessary connections. Flexibility of thinking is as important knowing the chemistry.

NOTE: Writing a synthesis of a large molecule may take an afternoon or even a few days, but doing the same synthesis in a lab may take years! It is important for a synthetic chemist to be flexible in the approach to a target molecule and no synthesis written on paper is every truly 'correct' until it's been done with actual materials.

Linear vs. Convergent Synthesis:

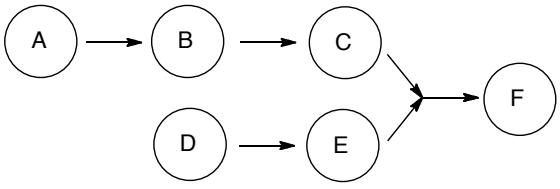
The goal of synthesis is to make as much as possible of the target molecule with minimal waste and expense. To that end synthesis may be linear or convergent. Typically convergent syntheses are preferred as material is lost at each step and convergent synthesis allows portions of the molecule to be built independently, resulting in fewer steps directly between starting material and product and better overall yields. Most syntheses seen in undergraduate classes will be linear synthesis, but the principle of convergence becomes more important as syntheses get longer and more complex.

A Linear Synthesis



A 5 step linear synthesis. If all steps are 90% yield
total yield = (.90 x .90 x .90 x .90 x .90) x 100% = 53%

A Convergent Synthesis



A convergent synthesis (3 step longest linear sequence). If all steps are 90% yield
total yield = (.90 x .90 x .90) x 100% = 73%

Method of Approach A:

A Question Based Process (Starting molecule is given):

Many coursework problems give a particular starting material as well as a target compound to limit the possible ways of synthesis and to guide students towards paths that will work with the reagents that have been learned. If a starting point is given it can be productive to ask series of questions about the molecule.

1) *Look at the target molecule and starting molecule. Find the carbons that are present in both molecules.*
    a. It can help to circle or mark the original atoms to show what is new/old.

2) *Find the changes between the starting material and the product.*
    a. What atoms need to be added (only present in product)?
    b. What atoms need to be removed (only present in starting material)?

3) *Determine which changes are carbon-carbon bond forming reactions, and which are functional group conversions (no additional carbons, just changes in bond order or heteroatoms).*
    a. There are relatively few reactions that form carbon-carbon bonds reactions so this is often a good place to start.
        i. Where do we need to form the new bond?
        ii. Is there a limitation in the question of how many carbons we can add at once?
        iii. What functional group is present in the starting material or formed in the product?
        iv. What reactions do we know that can work with the present/formed functional group?
            1. If no reactions work directly do we need to first make a functional group to add the carbon-carbon bond too? If so go to step 3b then return to step 3aiii.
    b. Functional group conversions are more flexible and can often come after the carbon-carbon bond forming reactions. Exceptions are functional group conversions needed to make the functional group that will make the carbon-carbon bond (e.g. forming a carbonyl to add a Grignard reagent too.)
        i. What functional group is present in the starting material and what functional group needs to be formed?
        ii. Do we need a *syn* or *anti* stereochemistry?
        iii. Do we need a particular regiochemistry? (e.g. Markovnikov or Saytzev?)
        iv. What reactions do we know? Is there a reaction that does this conversion directly?

1. If not what functional groups can we make directly from the starting functional group and can we make one of those into the desired group?

4) *List the reactions that will give the desired conversions from steps 3a and 3b.*

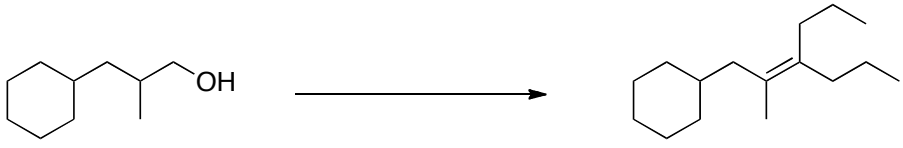
5) *Consider the list of reactions in step 4 and determine the order of reactions.* Do some reactions need to be done first or last? If there are multiple ways to do a particular conversion is one shorter, or easier?
   a. The functional group needed to make the carbon-carbon bonds must be made before the carbon-carbon bond can be made. (i.e. We need to form an alkyne before we can add carbons to an alkynyl anion.)
   b. Friedel-Crafts reactions require an activated ring so must be done before adding deactivating groups.
   c. Conversions of the new carbon-carbon bond must be done after it is formed.
   d. Is there an incompatible functional group (i.e. an alcohol present during a Grignard reaction) that must be converted or protected first?
   e. Keep from making two of the same functional group in the same intermediate unless they are going to undergo the same reactions. (i.e. It is very difficult to pick which alcohol will react with PCC, all primary and secondary alcohols will react).

6) *Write out the steps with their intermediate products in the order determined in step 5.*

7) *CHECK!*
   a. Look for incompatible functional groups.
   b. Look for extra/missing carbons. It is very common to 'lose' a methyl group when writing quickly.
   c. Look for side reactions that could occur with the other functional groups.
   d. Check your stereochemistry. Do the reactions give the desired regiochemistry and stereochemistry?

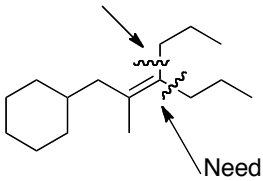
Example: Synthesis of 1-cyclohexyl-2-methyl-3-propyl-2-hexene

Problem A: Synthesize 1-cyclohexyl-2-methyl-3-propyl-2-hexene from 4-cyclohexyl-2-methyl-1-butanol.



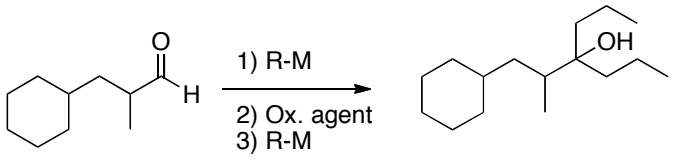
Question Based Analysis:

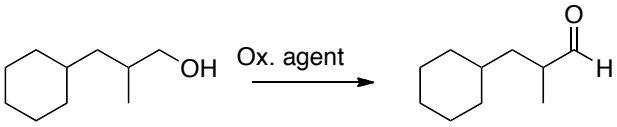
2 Groups of new carbons.



What's new/different? The alcohol has converted to an alkene and two different propyl groups have been added to the carbon that was the alcohol. The presence of the cyclohexane can be used to mark where the original carbons are.

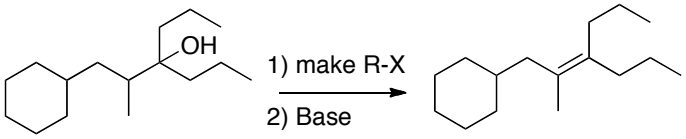
How do we add the carbons? New carbons could be added by addition of an organometallic to a carbonyl. Since there are two groups they can be added in series (or to the ester in 118C).





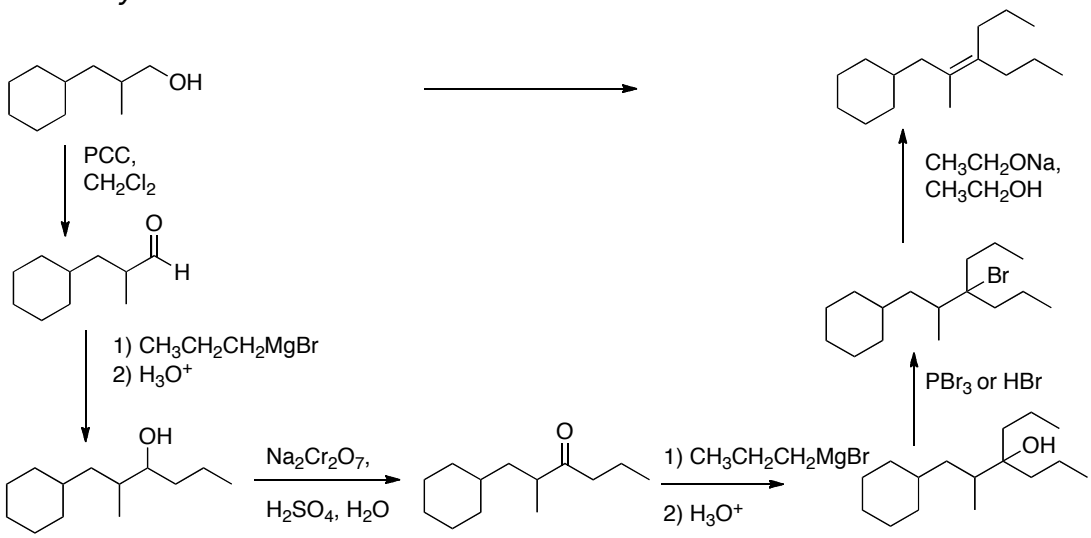
Can we make a carbonyl to add too? The starting material doesn't have a carbonyl, but we can make an aldehyde from the primary alcohol.

How do we make the alkene? By elimination of haloalkanes. We can make the OH a better leaving group (haloalkane) and then eliminate.The product is the most stable alkene, so should form easily by E2 with an unhindered base.



Knowing the reactions we need, we can then decide what reagents we can use in what order to give that particular reaction. For example the oxidizing agent for the first step *must* be PCC since H_2CrO_4 (aq) conditions will give the carboxylic acid, however it doesn't matter for the third step. We can use either the Grignard reagent or the corresponding alkyl lithium to add in steps 2 and 4.

Synthesis:



Method of Approach B:

Retrosynthetic Analysis (Starting molecule is NOT given)

This type of problem is more typical of a real world problem. Any compound could be the starting material, which opens us up to a greater range of possible strategies and reactions that may be used. The lack of a defined starting point allows for greater freedom in putting the molecule together, which means that different people may come up with very different synthesis. Retrosynthetic analysis is commonly also used with convergent synthesis, where several pieces of a molecule are constructed independently and then put together in the last few steps to form the desired product, but it also works for linear synthesis.

If the problem is for a class often there will be a target for the starting material(s) stated such as: no starting material can have more than X carbons. If the problem is real world the target is usually that the starting material(s) are available and relatively inexpensive.

1) *Look at the target molecule.* What functional groups are present? How many carbons are present?

2) *If the carbon skeleton is more than a few carbons, look for places to add carbon-carbon bonds.*
    a. A branch at a functional group may come from addition of an organometallic to a carbonyl.
    b. Branches adjacent to functional groups may be added through enolates.
    c. Remember functional groups can be converted: what was a ketone may be masked as a haloalkane, alcohol, alkene or even an alkane.
    d. Is there particular stereochemistry?

3) *Find a precursor or precursors to the target molecule and repeat step 1-3 with the precursor as the new target until the precursor(s) are small inexpensive molecules.*

4) *You now have a planned retrosynthesis working from the product back to available starting materials.*
    a. Typically a retrosynthesis skips steps and concerns itself with major molecular changes so the full synthesis will need reagents added.

5) *Now using functional group conversions to convert each precursor exactly to its target until you've reached the final target molecule.*
    a. Watch out for incompatible groups (e.g. organometallics with alcohols or leaving groups with nucleophiles)

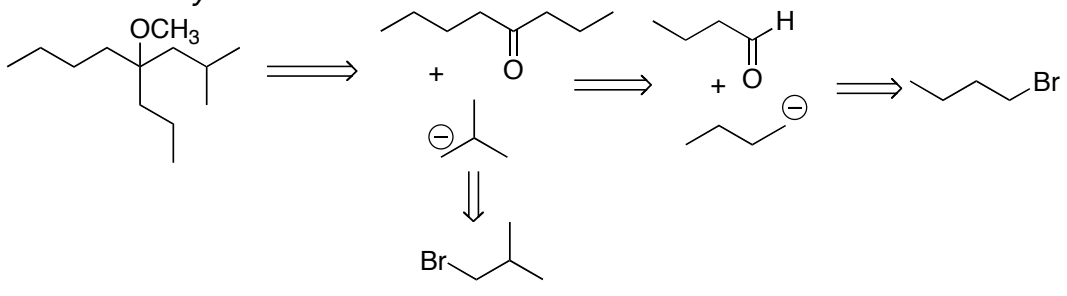
b. Watch out for multiple similar functional groups. If one alkene is reduced by hydrogenation, all alkenes (and alkynes) will likely be hydrogenated.
c. Use protecting groups or functional group conversions to force reaction at only the desired position.
    i. Carbonyls can be masked as acetals or thioacetals
    ii. Alcohols can be masked as ethers
    iii. Amines can be masked as carboxamides
d. Make sure you consider regioselectivity and stereoselectivity in choosing the appropriate reagents.
e. Remember that fewer steps (with reasonable yields) is almost always better than more steps (with equivalent yields).

Example: Synthesis of 4-methoxy-2-methyl-4-propyloctane via Retrosynthetic Analysis

Problem A: Synthesize 4-methoxy-2-methyl-4-propyloctane (compound A) from haloalkanes containing 4 or fewer carbons.

Compound A has twelve carbons in its main alkane skeleton, the methoxy group is easily added as a substituent by functional group conversions so is not included in the count. To get a twelve carbon skeleton from from four carbon or smaller units we'll have to add carbons, and will need at least two carbon-carbon bond forming reactions. Compound A has a branched position at C-4, so C-4 will be a good place to start adding carbons. We can picture adding the four carbons of a 2-methylpropyl group to a 4-octanone. The four carbon fragment (2-methylpropyl anion) can be imagined as coming from 1-bromo-2-methylpropane. We can then break the 4-octanone into two pieces of four carbons each by adding a butyl group to butanal. Both the butanal and the butyl anion can come from 1-bromobutane. The order of adding the two anions is somewhat arbitrary on paper; in reality we'd likely try both options and use whichever gave better overall yields.

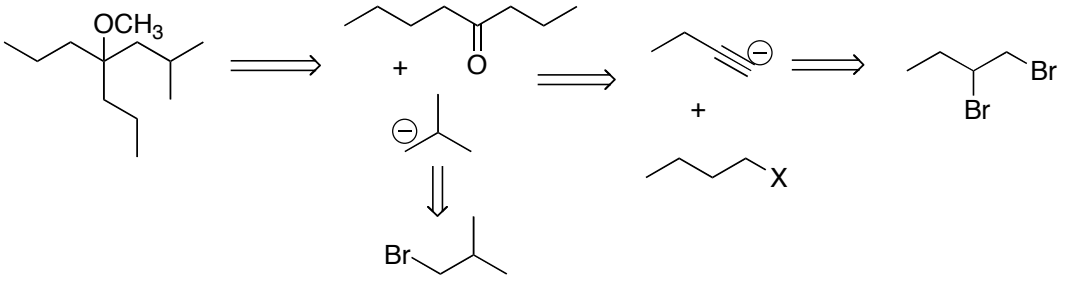
Retrosynthesis I:



An alternative retrosynthesis may use an alkynyl anion to make the 4-octanone. However, this is less ideal, as the functional group conversion from 3-

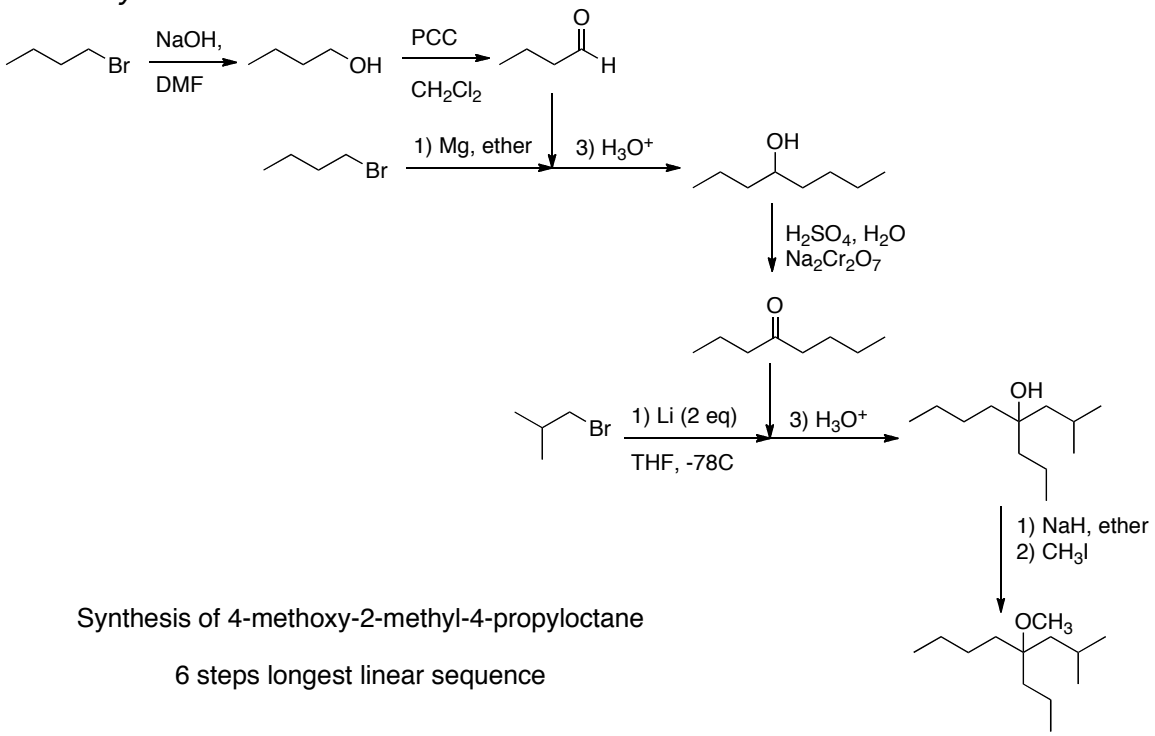
octyne to 4-octanone will actually give an approximately 1:1 mixture of 3-octanone and 4-octanone for a low yield.

Retrosynthesis II:



Once we've found a retrosynthesis we can add in the functional group conversions to complete the total synthesis. 1-bromobutane undergoes S_N2 replacement with hydroxide and the resulting 1-butanol is oxidized to butanal by PCC. The Grignard reagent is made from 1-bromobutane and butanal is added followed by aqueous workup to give 4-octanol. 4-Octanol can be oxidized to 4-octanone and then added to the 2-methylpropyl lithium reagent followed by aqueous work up to give 2-methyl-4-propyl-4-octanol. Full deprotonation of the alcohol by the strong base sodium hydride will give the alkoxide nucloephile , which can undergo Williamson ether synthesis with iodomethane to give the target ether.

Synthesis I:



Synthesis of 4-methoxy-2-methyl-4-propyloctane

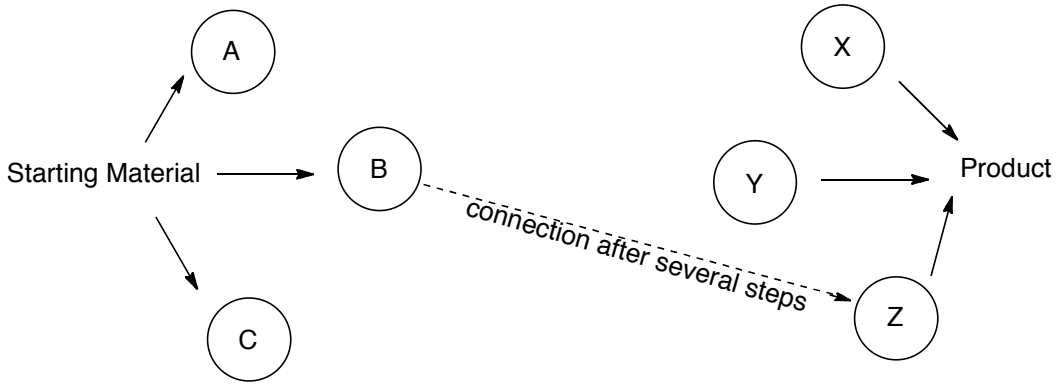
6 steps longest linear sequence

Method of Approach C:

A Combined Process (Starting molecule is given)

It is possible to use retrosynthetic analysis when the starting molecule is given. This can allow us to work straight backwards (product → starting material) as in method B. Or work straight forwards (starting material → product) when the connection between the starting material and product is seen. Or most often both ends can be worked towards the middle.

If the connection between the starting material and product is not clear, find the direct precursor(s) to the product and the direct product(s) of the starting material given different reactions that are known. Are there any connections between those substances? If you can't see any connections, try going out a step further with the most likely product/precursor.



Tricks and Tips:

- *Know your reactions and reagents*. It's very difficult to put together a synthesis if you don't know what functional groups convert to what groups.

- *Carbon-carbon bonds are often the key to the synthesis*. Once you figure out how to add/lose carbons the rest of the synthesis will often fall into place.

- Remember that your *reagents will interact with the whole molecule*, not just the functional group you want them to react with. This can cause side reactions or stop the reaction entirely.

- It is only necessary to *write the intermediate products and reagents.* There is no need to write the mechanism for each reaction. Intermediate products are generally those that are stable enough to purify and identify.

- *Any answer that works is acceptable*, though some are more efficient than others. You are not limited to reactions learned in this course. If it works it works, however, if it doesn't work, it doesn't work so remember the caveats given in lecture.

- It is possible to approach a problem *backwards* (product → starting material) or *forwards* (starting material → product) or *both ends towards the middle.*

- In synthesis questions designed for students *there will be a functional answer that uses the reactions you have learned.* Real world problems may or may not have a solution, but anything you see in this course will.

- *Coursework problems are typically between 3-5 steps* (points where the product can be isolated), though they may be as long as 7 or 8 steps. If you find yourself a dozen steps into a process and not at the answer yet, go back and start over as you're likely going in an unproductive direction.

- *Shorter synthesis are generally preferred* if the product can be obtained in good yield. There are cases where several steps are preferable to one, but these will be cases we talk about specifically.

- When in doubt: think about *what functional groups have been discussed in class recently*? It's likely that they will occur somewhere in the synthesis.

- When in doubt: *look at the rest of an exam.* Often a mechanism or reaction question can remind you of the key step to a synthesis, it may not be the same reaction, but a similar one, or the opposite regio- or stereoselectivity, etc.