## Multistep Organic Synthesis

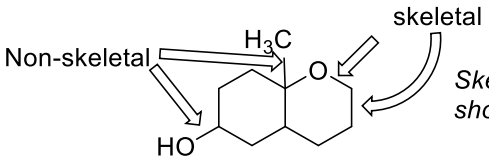
We have presented a cross-section of classical organic reactions in this course, but their real importance is seen when they are put together into a sequence of steps to create a useful substance. Synthesis is not the only goal of organic chemistry, but it is central to everything else. Synthesis allows us to build molecular structures on demand, to satisfy our needs or our curiosity. By synthesizing new compounds we frequently discover new fundamental principles of chemistry that might have gone unnoticed otherwise.

In order to identify a viable sequence of reactions that can turn a small, simple and available material into something much more complex, you must first know what kinds of reactions are possible. Learn what each kind of reaction does in a schematic way: what kind of product does it make, what kind of starting compound does it use, what conditions are employed. You should be able to choose a structural feature at random, and list off all the ways that it could be formed. Likewise, you should be able to list off all the reactions that could start with that structural feature.

## Retrosynthetic analysis

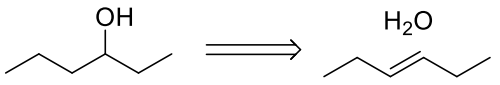
Planning a multistep synthesis is a systematic process based on working backwards from the ultimate target. This is called "retrosynthetic analysis". Klein's textbook covers this topic in a general way in Chapter 12. Section 12.5 gives you an introduction to the material I have discussed in the last couple of lectures. There are a few simple practice problems at the end of Chapter 12 that are worth doing, and you will also find other problems in the various reaction chapters that ask you to "propose a synthesis".

Start by examining the target structure. Identify all functional groups that are present, including alkenes and alkynes as functional groups. Define the bonds as *skeletal* or *non-skeletal*.

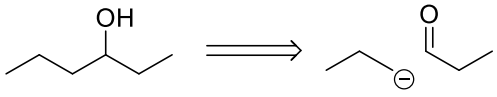



*Skeletal bonds are those internal to the structure; Synthesis should focus on constructing skeletal bonds.*

Functional groups *may* be simply substituents that can be added on after the skeleton is constructed. HOWEVER: don't assume that this is the best analysis. Remember that functional groups are the essential triggers for most chemical reactions, so a functional group in your target can be a suggestion of how a skeletal bond was made.



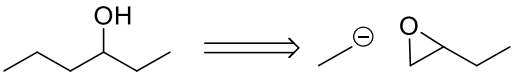

*Alcohol treated as a substituent to be added.*




*Alcohol treated as indicating a C-C bond-forming reaction such as a Grignard.*

Note in the second example, the disconnection might correspond to a Grignard addition to an aldehyde. However, the nucleophile has been represented by a propyl anion. Obviously, this does not mean that we have a bottle of "propyl anion" in the lab! In retrosynthetic analysis it is often better not to get too fixated on a specific reagent, so we represent the nucleophile by the kind of reactivity we require. We call this kind of representation a *synthon*. That is, the *synthon* $CH_3CH_2CH_2-$ could represent a variety of kinds of carbon nucleophiles, such as $CH_3CH_2CH_2MgBr$ or $CH_3CH_2CH_2Li$.

There is yet another way we might disconnect the alcohol shown above.




*Ethyl nucleophile attacking an epoxide*

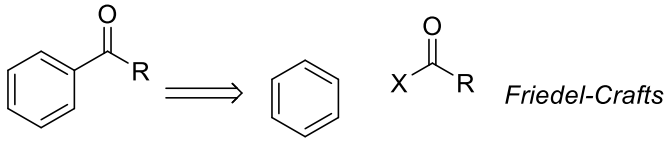
So, you see that there are likely to be quite a few options you can consider. How do you choose which pathway is best to follow?

The goal of retrosynthetic analysis is to reduce a complex target to a simple starting compound in as few steps as possible. *The greatest simplification per step is usually obtained by dividing the target in half by the disconnection – if that is possible.* Don't "nibble around the edges" any more than is absolutely necessary. In the synthesis of 3-hexanol shown above, the Grignard approach is probably most efficient because it cuts the molecule into two roughly equal pieces each containing only one functional group, propanal and (perhaps) propyl bromide.

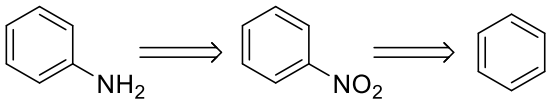
## Structure targets that correspond to specific reactions

Some of the reactions we have covered have very specific applications. Not every molecule target will be appropriate for a given kind of reaction, but if you know what kinds of targets these reactions make you can save a lot of time. Here are a few examples.

- Substituted aromatic rings. Bonds to aryl rings can often be made easily by electrophilic aromatic substitution (halogenation, nitration, Friedel-Crafts) followed by other reactions. Thus, we can disconnect these bonds retrosynthetically.

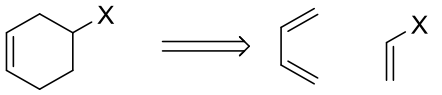



*Friedel-Crafts*



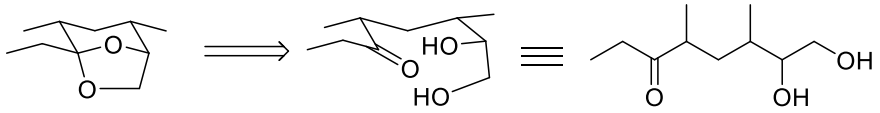

*Nitration followed by reduction*

- Cyclohexenes or cyclohexanes. The Diels-Alder reaction is often ideal for making these structures. Remember that catalytic hydrogenation of a cyclohexene gives a cyclohexane.




*Diels-Alder*

- Acetals. Acetals are not always simply protecting groups, but they are always the product of a pair of alcohols and a carbonyl. They should be disconnected as such.

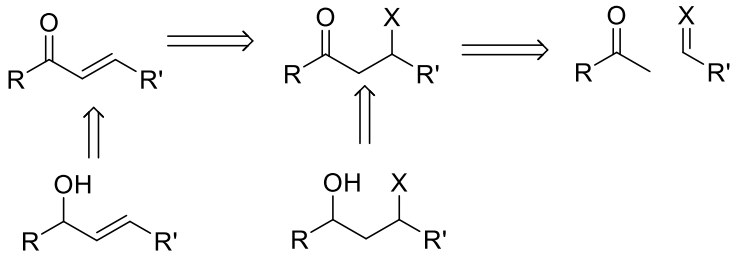


*Acetal/carbonyl/diol*

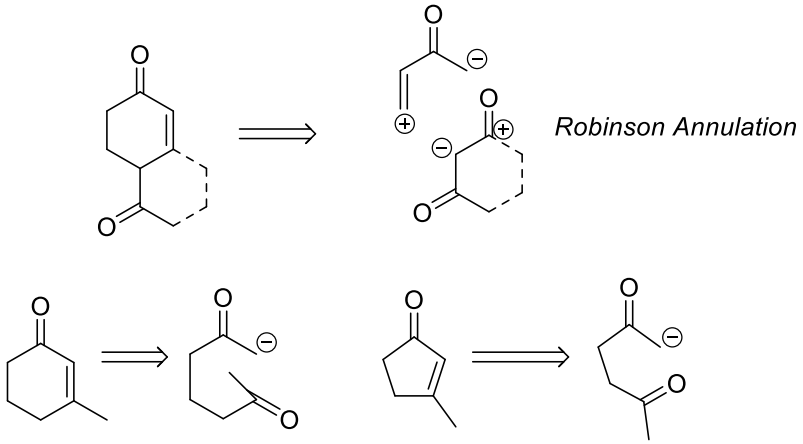
## Disconnections indicated by two functional groups

Many of the most powerful methods for skeletal construction are signalled by a pair of functional groups in the products in a very specific relationship.

- The Aldol disconnection. The aldol forms a beta-hydroxycarbonyl product, or it can form an α,β-unsaturated carbonyl product. Also, remember that many other C-X bonds can be made from C-OH. Note that carbonyls can be reduced to alcohols so 1,3-diols or allylic alcohols can arise from the product of an aldol.



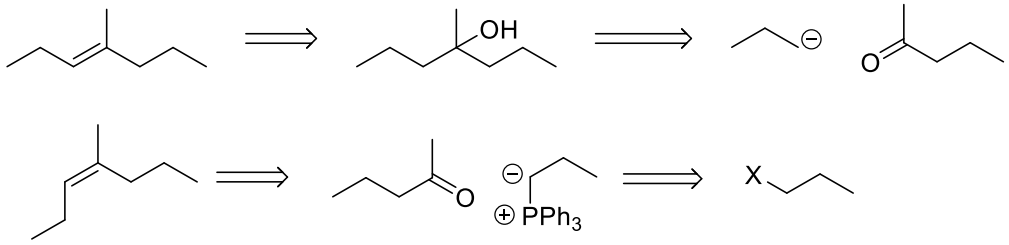

- Cyclohexenones and cyclopentenones. The Robinson Annulation makes cyclohexenones, but in general you can see the preparation of these cyclic α,β-unsaturated ketones as special cases of the intramolecular aldol condensation.



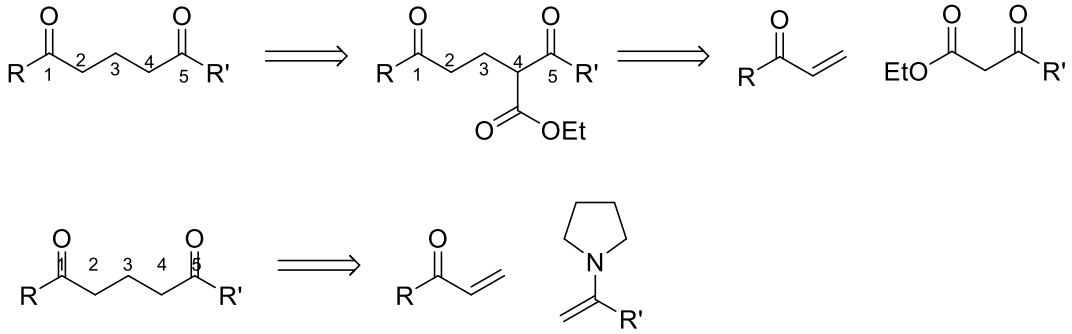
*Robinson Annulation*

- Alkenes (not conjugated). If you can combine making the alkene with forming a skeletal bond it will be more efficient. The Wittig reaction is an obvious candidate since it forms an alkene immediately. Remember that "ordinary" Wittigs favour the Z (cis) alkene, while "stabilized" Wittigs give the E (trans) product. Grignard addition to an aldehyde or ketone followed by

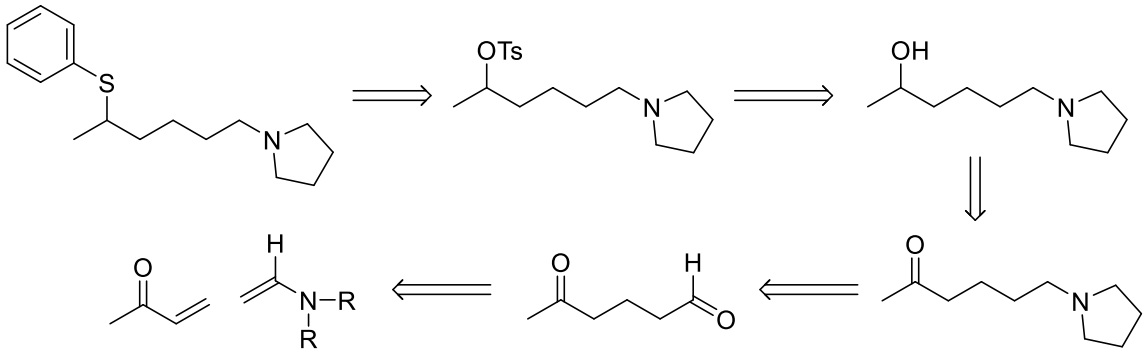
dehydration is also a good strategy.




- "5 = 2 + 3". This is the key arithmetic of the Michael or Stork enamine reactions. Two carbonyls in a 1,5 relationship might suggest formation of the chain of carbons between them by conjugate addition.




Furthermore, we can extend this to other 1,5-functional patterns if we think about converting carbonyls into alcohols, which can then be turned into various other functional groups. Alternatively, carbonyls can be reductively aminated to lead us into amines and their derivatives.

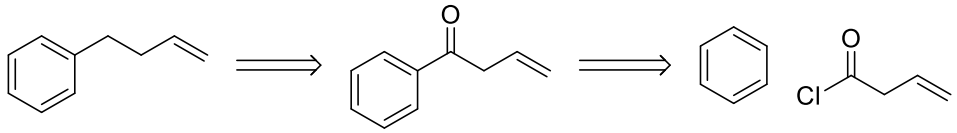



## Warning: Selectivity and the order of steps

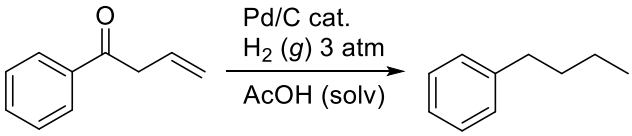
When you are working out a multi-step sequence, you have to pay attention to the fact that some functional groups are incompatible with specific reactions. For example, you cannot form a Grignard reagent or alkyllithium from a halide precursor that contains an OH, NH or C=O group. These are fairly simple limitations that follow from understanding the properties of the various compounds. A somewhat trickier issue is that of *selectivity*.

We have commented on selectivity a few times during the course. One case was the reduction of benzylic ketones all the way to a $CH_2$ group. Clemmensen reduction is the classic method for this, but in class I also pointed out that catalytic hydrogenation is sometimes an alternative. However, C=O groups

are harder to hydrogenate than most C=C groups, usually requiring higher hydrogen pressure and the use of acetic acid as a solvent. We noted that if there was an alkene elsewhere in the molecule, it would also be hydrogenated under such conditions. This would be a situation where the Clemmensen procedure would be better than the catalytic hydrogenation.

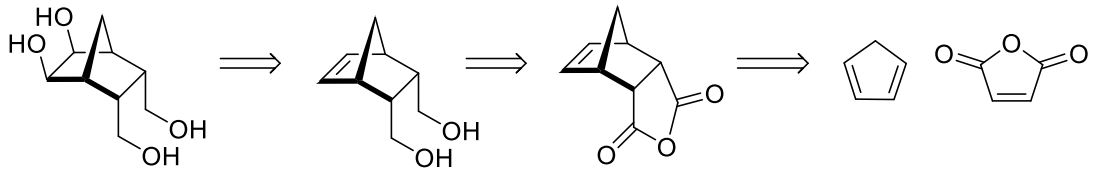



*Clemmensen*




*Not selective! Can't use this method.*

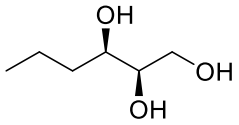
The order in which steps are performed also matters. Consider the following case involving a Diels-Alder reaction.




We could likely form the cis diol from the alkene in the final step as shown ($OsO_4$), or we could do it immediately after the Diels-Alder and before reducing the anhydride to the primary alcohols. BUT: we need the carbonyls on our dienophile, so we cannot start with a compound containing the $CH_2OH$ groups.

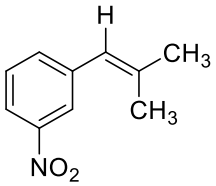
Here are two worked examples. Note that there are usually several possible correct answers to any synthesis question, although some routes are undoubtedly better than others in practice.

Propose a route to prepare the following triol. Note the relative stereochemistry. You may use any monofunctional organic compound of 4 or fewer carbons as your starting point, plus any other reagents you need.



(racemic)

Starting from BENZENE, suggest at least one route to make



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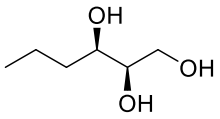


(racemic)

Retrosynthetic Analysis

1. *How many carbons are there in the target? Do we need to form new C-C bonds?*

There are 6 carbons in the target. Since we must start with no more than 4 carbons, we have to make at least 1 new C-C bond.

2. *We must install at least some of the hydroxyls since we have to begin with a monofunctional compound. What methods do we know that can form alcohol groups?*

Acid-catalyzed hydration of alkenes.

Reduction of carbonyls.

Grignard addition to carbonyls.

Hydrolysis of epoxides.

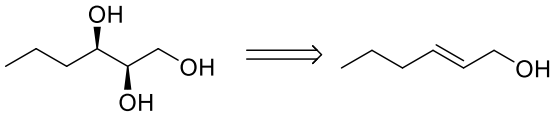
Nucleophilic opening of epoxides.

Osmium tetroxide oxidation of alkenes.

3. *The target has a specific stereochemistry. Of the methods we know, which could form a syn 1,2-diol?*

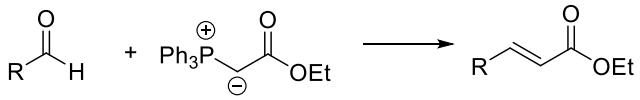
**Osmium tetroxide oxidation of an E-alkene would form the desired syn diol.**

So, perhaps the first retrosynthetic disconnection should be:



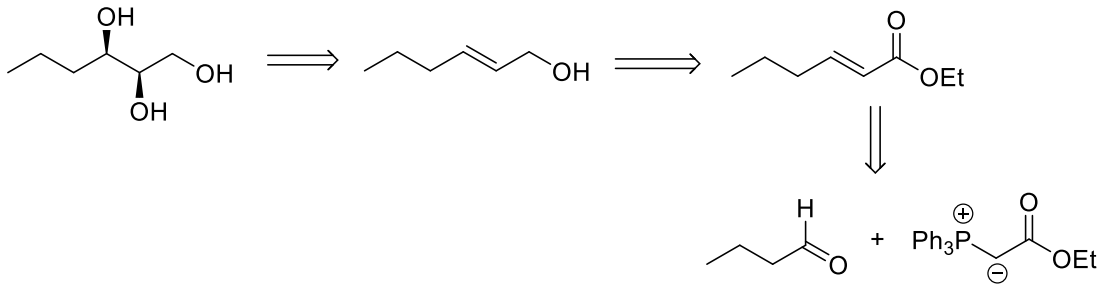

4. *Now, how could we obtain this alkene? Note that it is part of an allylic alcohol. Do we know any chemistry that could prepare an E-alkene with oxygen functionality next door?*

**Reaction of a carbonyl-stabilized Wittig reagent with an aldehyde - as used in lab!**

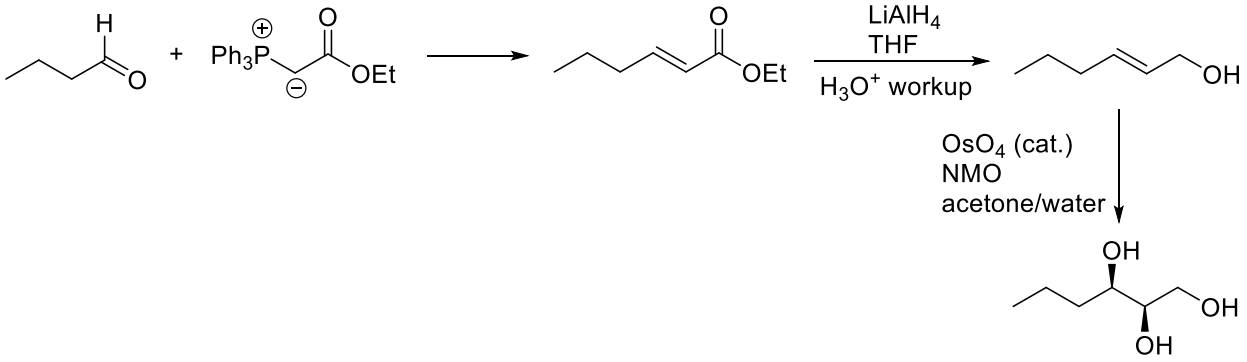


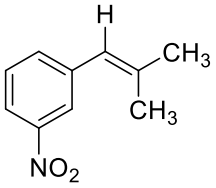

5. *But that's the wrong kind of oxygen functionality! Can we turn an ester into a primary alcohol?*

**YES! $LiAlH_4$ reduction will do this.**

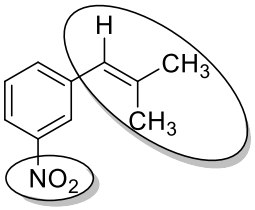



The synthetic route that corresponds to this retrosynthetic analysis is:



Starting from BENZENE, suggest at least one route to make 


Retrosynthetic Analysis:
1. *Observe where the designated starting compound is present in the target. What must be added to it to get the target compound?*




Our synthesis must add these two groups to benzene somehow.

2. *What kinds of reactions do we know that might add one of these groups to benzene?*

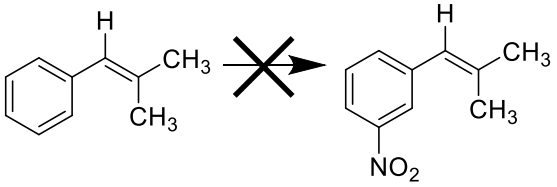
Electrophilic aromatic substitution - NO2 group

**We do not know any reaction that can directly add an alkene to an aromatic ring!**
But we do know that Friedel-Crafts alkylation or acylation can form other C-C bonds to aromatic rings.

We also know that Grignard reagents can be made from aryl halides and can make C-C bonds by reaction with aldehydes or ketones.

3. *What do we know about NO2 groups and electrophilic aromatic substitution?*

Reagent: $HNO_3/H_2SO_4$; product is strongly deactivated towards further reaction; $NO_2$ is a meta director; alkyl and alkenyl groups are ortho/para directors.
It is unlikely that we could successfully perform the following reaction:

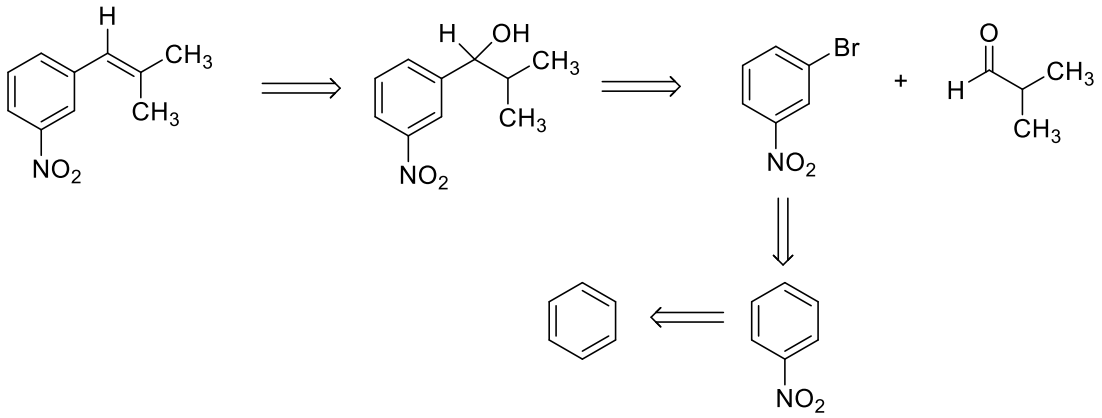



4. *We can conclude two things: We need a way to construct the alkene, and we should have the nitro group in place before the alkene is completed.* ***HOW can we construct an alkene?***

Elimination of an alcohol, tosylate or halide

Wittig reaction

5. *Consider the possibilities. Perhaps the elimination route looks promising, since in step 2 above we observed the possibility of using a Grignard reaction to make the C-C bond. The product of a Grignard reaction is an alcohol.*



Remember, in retrosynthesis you are working backwards, so the first retrosynthetic disconnection is the last step in the synthesis. Observe here that we nitrate first, then brominate, because we want the bromine and nitro groups to be meta to one another.

So what is the actual synthetic route implied by this retrosynthetic analysis?