Practice Questions for Chapters 1-3
CHEM 4000A – Medicinal Chemistry

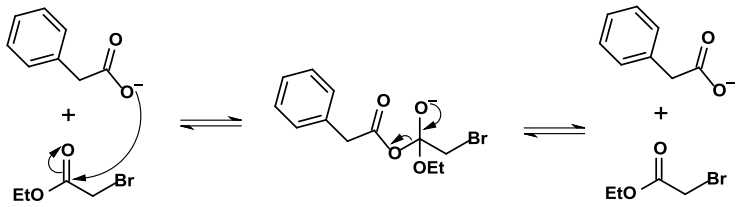
1. …

At the time, we did not have a good explanation for why the nucleophile attacked the carbon attached to bromine instead of the carbonyl carbon.

Use concepts discussed in class since then to suggest potential reasons for this behavior.

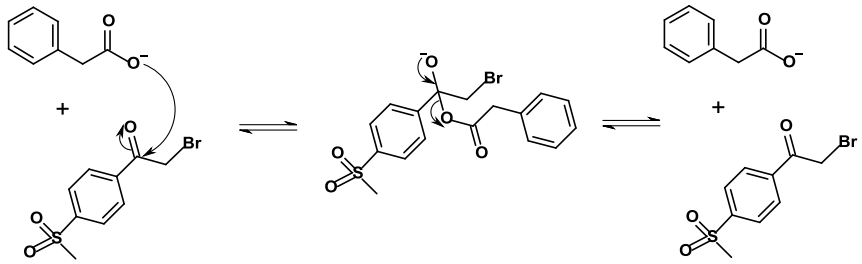
The observed reactivity makes most sense after following the chain of events that is most likely to occur if the nucleophile attacks the carbonyl carbon in each case.

- In the first example, attack at the carbonyl will be followed by reformation of the C=O pi bond, displacing the best leaving group. The carboxylate group (RCO_2^-) is a better leaving group than EtO^- and, thus, the ethyl 2-bromoethanoate is reformed:



On the other hand, when the nucleophile attacks the carbon attached to bromine, the reverse process is less favourable (since Br^- is a better leaving group than RCO_2^-). So, the equilibrium is driven toward the product shown in the original question.

- In the second example, attack at the carbonyl will be followed by reformation of the C=O pi bond, displacing the best leaving group. In this example, the carboxylate group (RCO_2^-) is the only reasonable option as a leaving group. Again, the original electrophile is reformed.



Again, when the nucleophile attacks the carbon attached to bromine instead, the reverse process is less favourable (since Br^- is a better leaving group than RCO_2^-). So, the equilibrium is driven toward the product shown in the original question.

The key factors in both cases are therefore:

1. equilibrium – attack can occur at the carbonyl but it does not give the final product as the intermediate collapses, returning to starting materials
2. leaving group ability – Br^- is better than RCO_2^- which is better than EtO^-

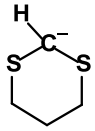
2.

(a) Give an example of an a^1-synthon.

There is an enormous number of possible answers to this question. Many of them involve carbonyl compounds (which are good electrophiles at the carbon of the carbonyl). Nitriles and imines are also good choices.

(b) Give an example of a d^1-synthon.

These are less common, but two good choices would be the cyanide ion (NC^-) or the dithiane anion shown at the right.

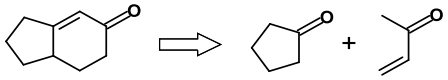


(c) Explain why an a^1-synthon is usually a better choice than a d^1-synthon in retrosynthetic analysis.

A carbon atom in either ran a^1-synthon or a d^1-synthon is, by definition, bonded to a heteroatom. The majority of common heteroatoms in organic compounds are more electronegative than carbon (N, O, S, P, F, Cl, Br, I). Thus, the carbon-heteroatom bond will be polarized such that the carbon is partially positive and therefore somewhat electrophilic. a^1-synthons are 'acceptor' synthons and therefore represent electrophiles.

3. Demonstrate how a Robinson annelation could be used to make the molecule below.

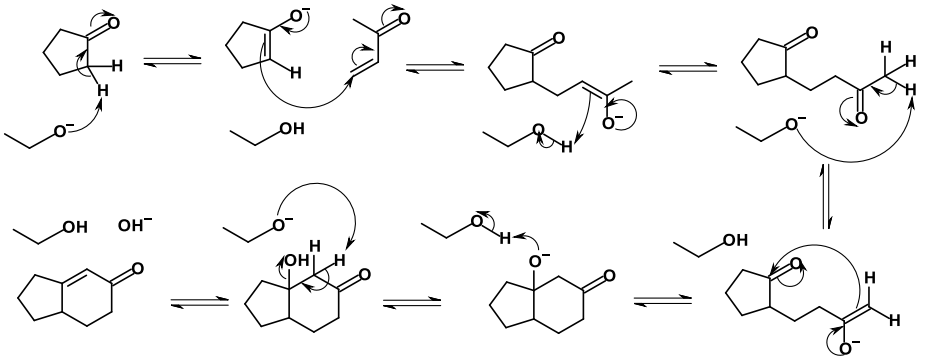
Your answer should indicate all required reagents and include the mechanism for this reaction.



A Robinson annelation consists of a Michael addition followed by an aldol condensation (including elimination of water). The six-carbon ring contains four carbons from the α,β-unsaturated ketone plus two carbons from the other ketone (the carbonyl carbon and one α carbon). The new double bond must appear where the carbonyl has "disappeared" as that carbonyl is the electrophile in the aldol reaction.

This reaction requires a base strong enough to deprotonate α to a carbonyl in order to generate an enolate. Expect the pK_a of those protons to be ~20 so the base must have a conjugate acid with a pK_a no less than ~15. There must also be a proton source available to protonate intermediates; it will have to have a pK_a no more than ~25 (and must be able to coexist with the base – which limits how strong a base is feasible for this reaction; something too strong – like LDA – would just deprotonate the proton source).

For these reasons, alkoxide bases in the corresponding alcohol solvent are typically used. While alcohols only have pK_a values of ~15 and the alkoxide bases are therefore quite weak (relatively speaking), the stability of the final product drives the reaction to completion.

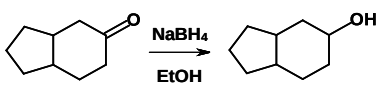


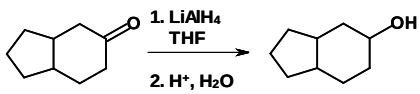
Your mechanism should indicate that you recognize the role of the carbonyl group in stabilizing the α anion. The way that I have drawn the arrows here shows this directly.

4. We discussed $LiAlH_4$ and $NaBH_4$ several times during problem sets.

(a) In what way are these reagents similar? Give an example of a reaction that could be done using either reagent.

Both reagents serve as sources of nucleophilic H^-. As such, they are both reducing agents capable of reducing ketones, aldehydes, imines and nitriles.

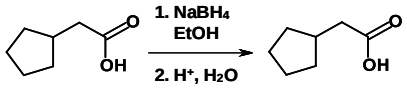




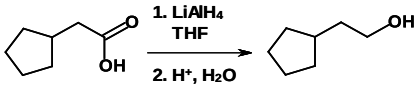
(b) In what way are these reagents different? Give an example of a reaction that could only be done using one of these two reagents (and clearly indicate which one).

$LiAlH_4$ is a stronger nucleophile than $NaBH_4$. It is capable of reducing groups which are unreactive toward $NaBH_4$.

e.g. When a carboxylic acid is treated with $NaBH_4$, it is deprotonated to give its conjugate base. $NaBH_4$ is not nucleophilic enough to reduce the carboxylate anion (which is a poor electrophile) so the carboxylic acid is recovered when the reaction is worked up.



When a carboxylic acid is treated with $LiAlH_4$, it is deprotonated to give its conjugate base. $LiAlH_4$ is nucleophilic enough to reduce the carboxylate anion (in part because Al acts as a Lewis acid and co-ordinates to the anion) so an alcohol is recovered when the reaction is worked up.



5.

(a) Under what circumstances is it helpful (or even necessary) to use an auxiliary functional group?

It is helpful to use an auxiliary functional group when:

- the target molecule does not contain any functional groups in appropriate locations to impart nucleophilicity to a planned donor synthon (or electrophilicity to a planned acceptor synthon)
- the planned synthon contains more than one reactive site (e.g. deprotonation of an α hydrogen could occur on either side of an unsymmetrical ketone) and, if used as-is, will lead to a mixture of regioisomeric products
- the planned nucleophile will be too hard to attack the preferred electrophilic site (or will attack both the preferred electrophilic site and another electrophilic site, leading to a mixture of regioisomeric products)

(b) Give an example of a reaction using an auxiliary functional group (in which it would have been necessary).

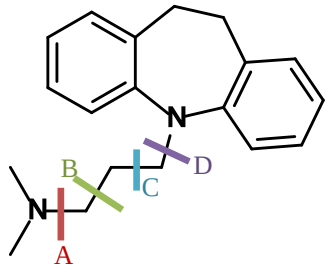
There are many many possible examples. We saw several in the lecture notes. The example in Scheme 3.5 of your text comes to mind. Anything of that nature would be reasonable.

(c) Demonstrate how to remove the auxiliary functional group you used in your answer to part (b).

The two main auxiliary functional groups we looked at were :

- *introducing an ester β to a ketone or aldehyde; this can be removed by hydrolyzing the ester to the carboxylic acid then heating to decarboxylate; a good answer would include reaction equations with all required reagents*
- *introducing an arylsulfone; this can be removed by reductive cleavage with an electron source such as an alkali metal in ammonia or, if it was used to attack a carbonyl, an alkene can be formed by treatment with Na(Hg) in ethanol or with SmI_2*

6. Imipramine (Tofranil®) has the structure shown below:



Where is/are the best place(s) to disconnect between the two nitrogen atoms? Explain your choice(s).

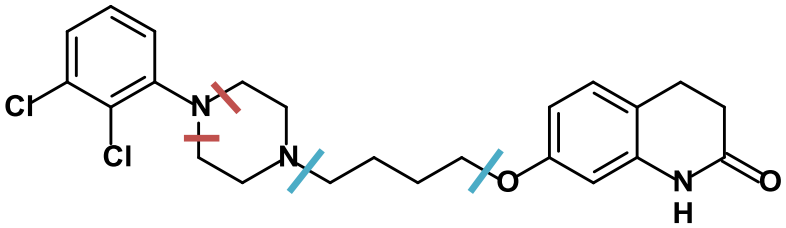
The four possible disconnections are shown above. In terms of reactivity, A and D are equivalent and will therefore be discussed together. B and C are equivalent and will therefore be discussed together.

Disconnection A leads to either a nucleophilic nitrogen atom attacking an a^3 synthon or a d^3 synthon attacking an electrophilic nitrogen atom. Since we do not know of any electrophilic nitrogen reagents, we will discard that option. Amines, however, are good nucleophiles so a nucleophilic nitrogen atom seems like a reasonable choice, and a^3 synthons are natural synthons so that also seems like a good choice. Identical logical applies to disconnection D. The main difference between those two disconnections is the size of the pieces. Disconnection D breaks the target molecule into pieces of more equivalent size and is therefore likely a better choice.

Disconnection B leads to either a d^1 and a^2 synthon or to an a^1 and d^2 synthon. a^1 and d^2 are both natural synthons. d^1 and a^2 are both umpoled synthons. So, a^1 and d^2 would be the better combination. Identical logic applies to disconnection C. Again, I would tend to prefer the disconnection that leads to pieces of more equivalent size (it's usually easier to make two medium-sized pieces than a small one and a large one).

Personally, I'd go with disconnection D if I was going to make this molecule but I'd entertain solid arguments for any of the four options.

7. Aripiprazole (Abilify®) has the structure shown below:

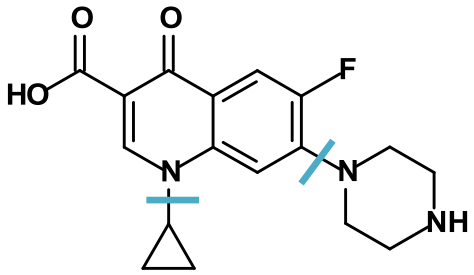


Which of the four main approaches to retrosynthesis would dominate your analysis of this molecule? Justify your choice.

In my opinion, the structure of this molecule (a series of rings attached to each other with one chain in the middle) suggests a skeleton-oriented approach to retrosynthesis. I would tend to start with the two disconnections shown in blue. Assuming that 2,3-dichloroaniline was available as a starting material then the two disconnections shown in red may also be feasible.

Again, I'm looking for a solid argument (not necessarily an argument for the approach that I chose).

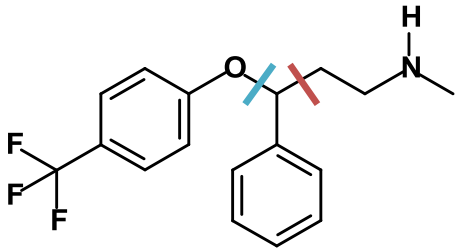
8. Ciprofloxacin (Cipro®) has the structure shown below:



If you wished to take a skeleton-oriented approach to retrosynthesis of this molecule, what disconnections would you make?

The two disconnections shown in blue break the molecule between rings. In a skeleton-oriented approach, it is favourable to disconnect at branches and/or rings to reduce complexity. Your choice of disconnections should show this.

9. Fluoxetine hydrochloride (Prozac®) has the structure shown below:

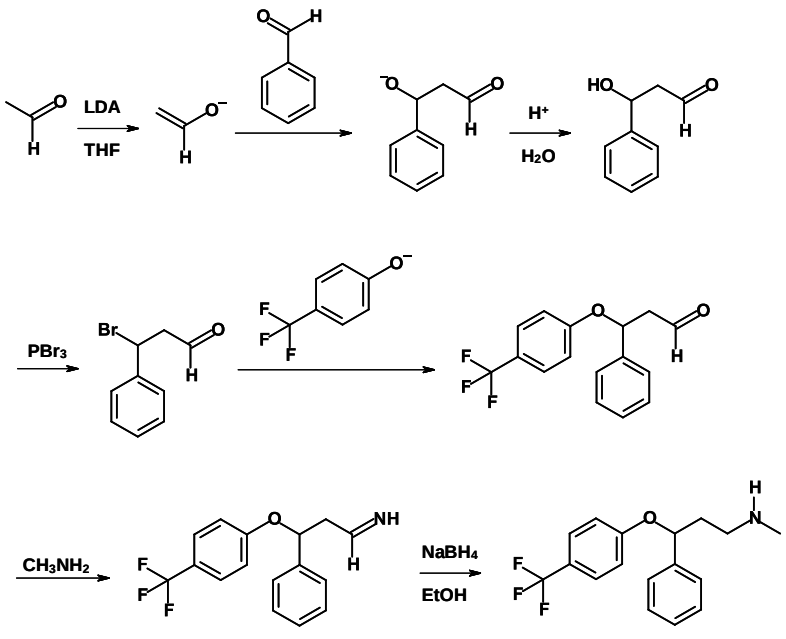


Propose a synthesis of fluoxetine hydrochloride.

4-(trifluoromethyl)phenol is commercially available (and affordable). You may use any other reactants and reagents that you could reasonably expect to be commercially available.

There will be a lot of different ways to approach this question. I include one suggestion at the right (limiting myself to reactions that you have seen in either this course or CHEM 2500/2600); however, that does not mean that it is the best approach. The only disconnection I'd expect to be common to all answers is the one shown by the blue line above, suggested by the availability of 4-(trifluoromethyl)phenol.

I'm suggesting the next disconnection as a d^2-a^1 disconnection between the C-O and the C-N (shown with the red line). This leads us to three pieces of manageable size.



The phenoxide anion was made by treating the 4-(trifluoromethyl)phenol with sodium hydride. I chose that base so as not to provide any alternative nucleophiles to add to either the alkyl bromide or the aldehyde groups.