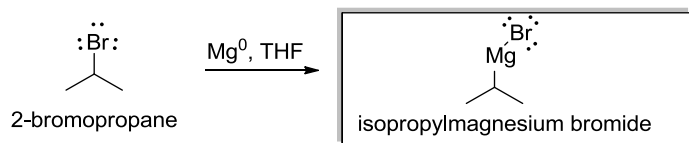


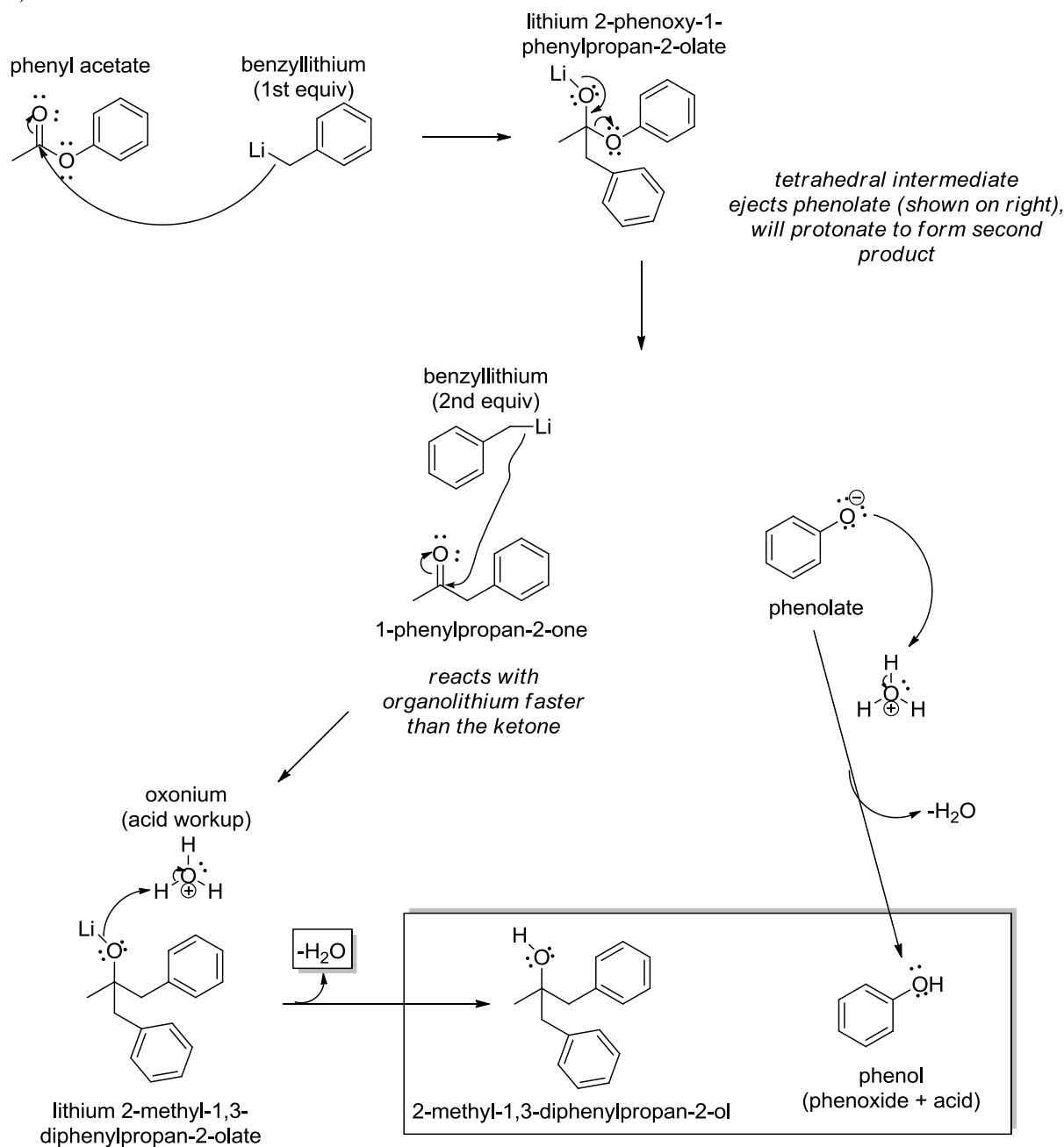
Note : Based on the conventions that we learned in lecture, we do not show any arrow pushing to form organometallic bonds such as in 1a or 1c (for example, $\text{O}-\text{Cl} + \text{Mg} \rightarrow \text{O}-\text{MgCl}$). You will receive full credit whether or not you show any curved arrows when forming those bonds.

1. Carbonyl Addition Reactions (20 points)

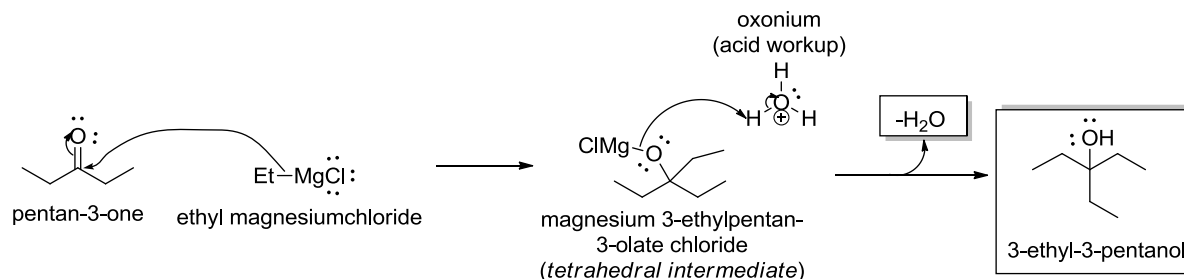
a)



b)



c)

**Part (a): 4 points for product****Part (b): 8 points total;**

2 points for the two major products (final box), 6 points for curved arrow mechanism, -6 overall if the answer does not eject phenoxide (i.e. the ester reacts just like a ketone). No deduction for not writing H_2O as a product.

Part (c): 8 points total;

2 points for product (final box), 6 points for curved arrow mechanism

No deductions at any time for writing Li^+O^- rather than $\text{Li}-\text{O}$.

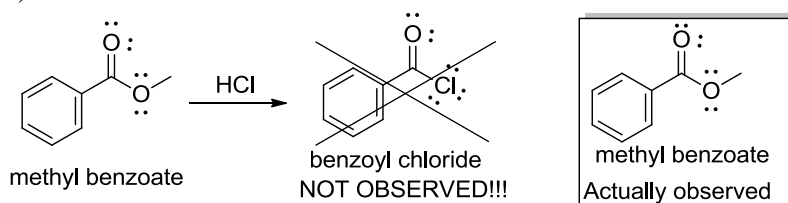
No deduction for not listing H_2O as a product.

-1 per mistake on intermediates (such as incorrect bindings of metals)

NOTE TO GRADERS: the curved arrow mechanisms shown above are suggestions. Some students may start their mechanisms with a resonance structure moving electrons from the carbonyl double bond to the carbonyl oxygen, for example, and that is perfectly fine. (**This only applies if the molecule is drawn as a resonance structure, and not a two-step reaction**) In the mechanisms above, this particular movement of electrons is indicated as reacting simultaneously with attack at the carbonyl carbon. Both versions are correct. Also, protonation can often occur from an outside water (solvent) or from an acid molecule. Either of these mechanisms of protonation is acceptable. As long as the student shows understanding of the underlying mechanism (nucleophilic attack at the carbonyl carbon and subsequent hydrolysis, etc.), full credit should be received. Labels such as “tetrahedral intermediate” are explanatory and are not necessary for full credit.

2. More Carbonyl Additions (15 points)

a)

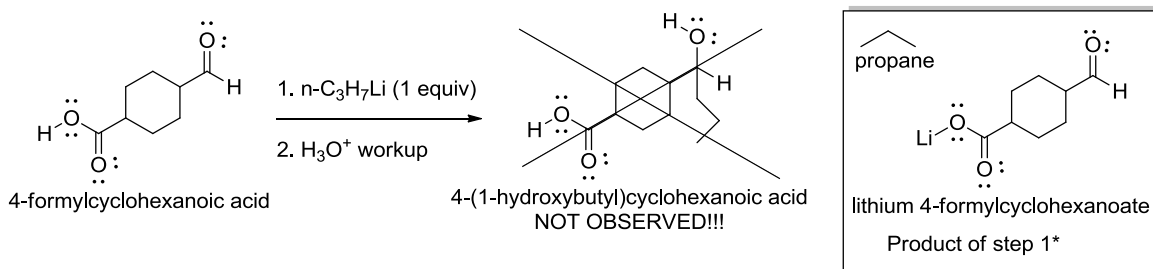


Benzoyl chloride is not observed because **Cl is a better leaving group than OMe**. If any acid chloride were to form, it would react with the MeOH that is generated to revert back to the ester.

Alternate explanation: reacting with HCl, the ester would be protonated at the carbonyl oxygen, and chloride ion can attack the carbonyl carbon. This leaves you with a tetrahedral intermediate, in which you can either eliminate Cl^- or OMe^- . Again, Cl is a better leaving group than OMe, so it will eliminate to reform the starting material.

(3 points for explanation, 4 points for observed product shown in the box)

b)



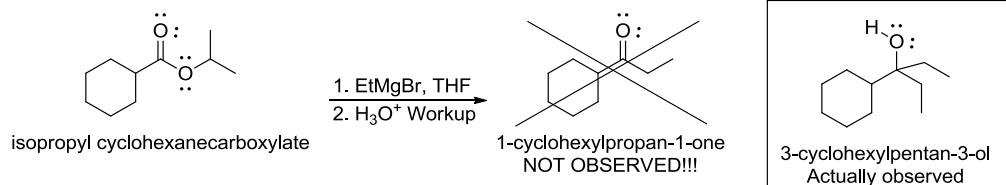
The aldehyde addition product is not observed because propyllithium is a strong base. **The fastest reaction to occur is the acid-base reaction between the carboxylic acid O-H ($\text{pK}_a = 4.8$) and propyllithium.** Thus, the reagent will be consumed generating the lithium carboxylate.

ALTERNATE EXPLANATION: If you state that propane is the product, you would also be correct. However, you would have to explain that the deprotonation is occurring at the carboxylic acid rather than anywhere else on the molecule. (It should be obvious, but you still have to say it. Just drawing propane doesn't actually tell us that!)

(3 points for explanation, 4 points for observed product shown in the box. No deduction for writing $\text{Li}^+ \text{O}^-$ rather than $\text{Li}-\text{O}$. Full credit for propane as a product, but no credit for the explanation unless it explains that the *acid group* is deprotonated)

* Product of step 1? Well, what about step 2? The key here lies in the fact that we specified "1 equivalent" of propyllithium. If we had specified 2, then we would not have just acid-base chemistry. Instead, we could have reactions at the acid's carbonyl group, and the end result would be formation of a ketone group at the end of step 2. But alas, we only have one equivalent, so step 2 doesn't really matter. All that affects is the equilibrium of acid vs. lithium salt.

c)

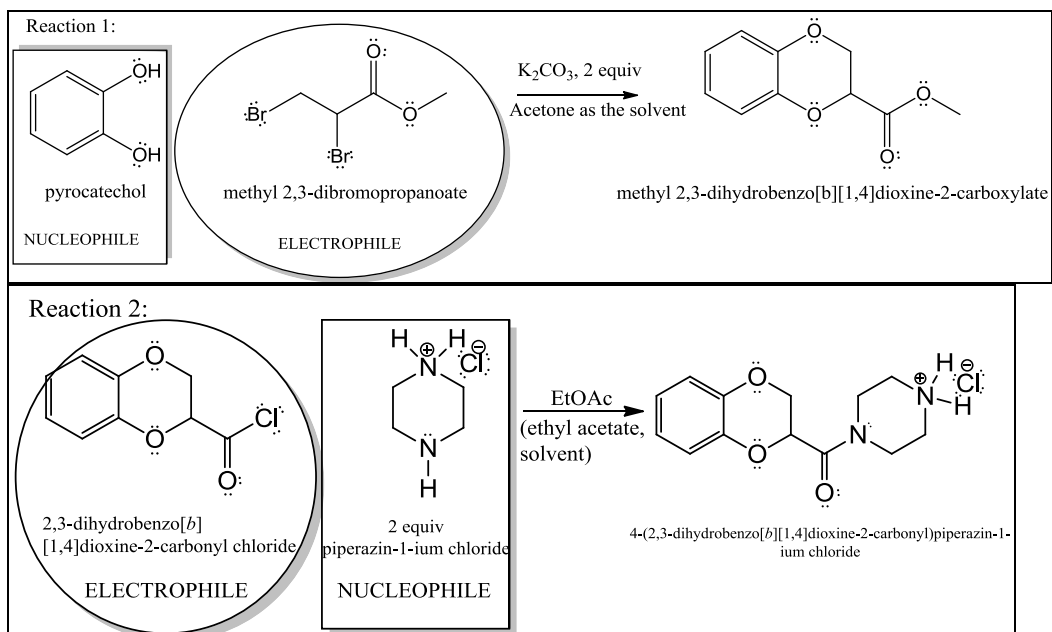


This product is not observed because the starting ester is competent for two successive additions, therefore provides the tertiary alcohol. The intermediate ketone reacts more rapidly with a second equivalent of the Grignard reagent than does the ester. As a result, with one equivalent of EtMgBr, ~1:1 ratio of tertiary alcohol product and starting ester will be recovered.

(3 points for explanation, 4 points for observed product shown in the box)

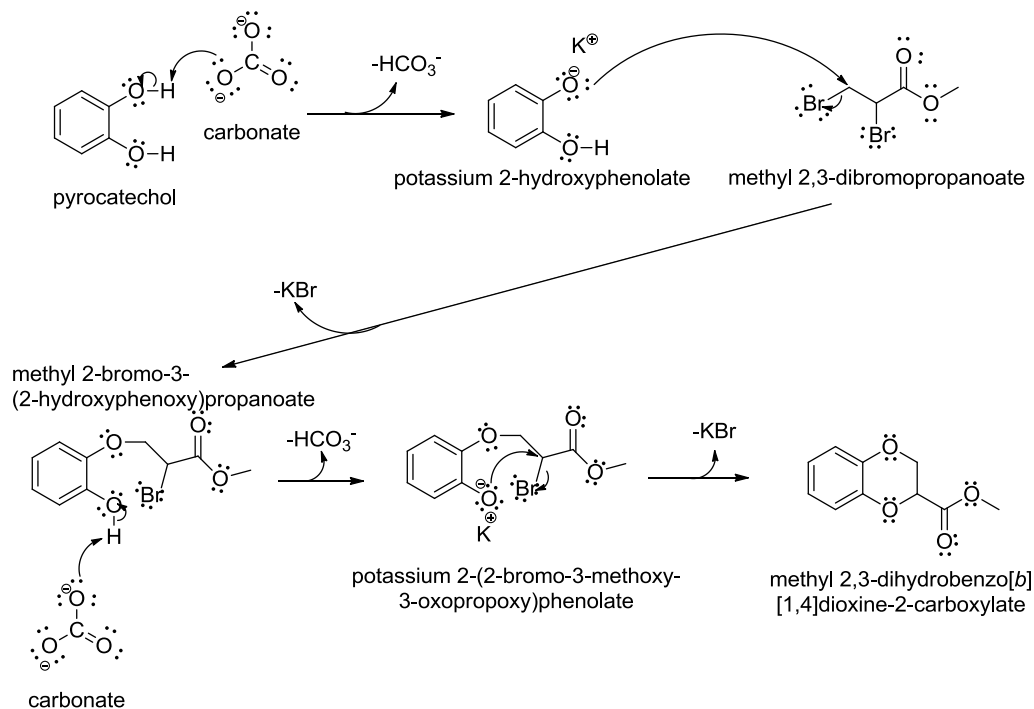
3. Doxazosin (34 points)

(a)



(4 points total; 1 point for correctly identifying each nucleophile, 1 point for correctly identifying each electrophile.)

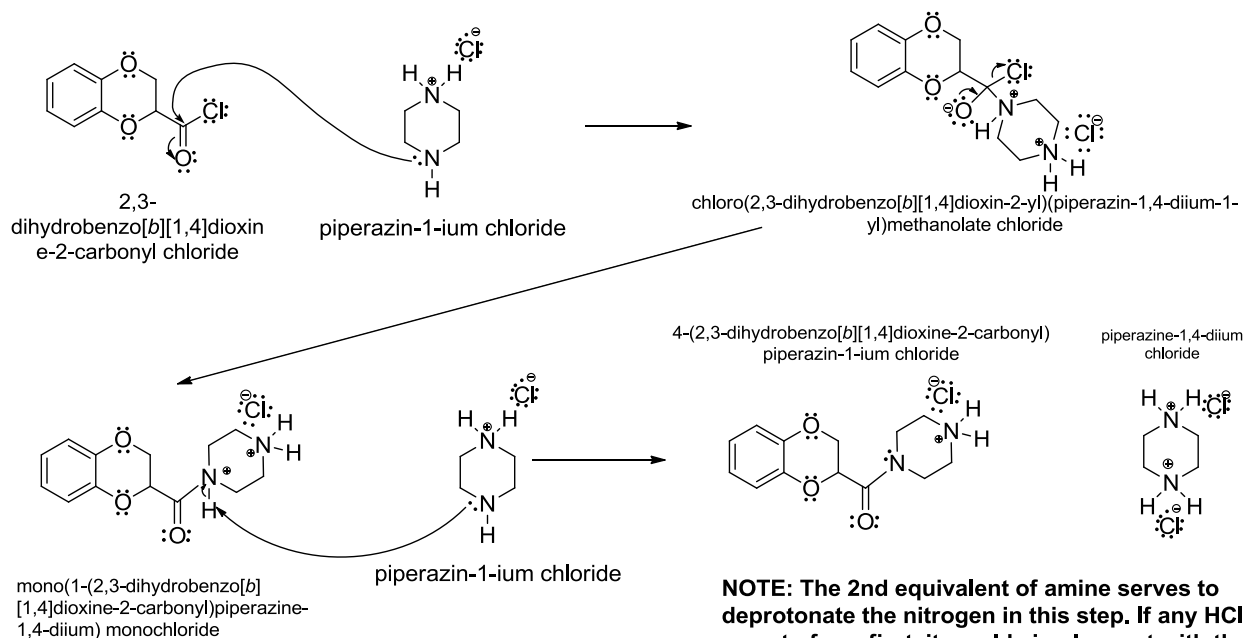
(b) Reaction 1:



Notes: The stepwise mechanism is preferred. However, if you show both steps at once, it's okay as long as your arrows flow in the correct direction.

Technically, the acid-base deprotonation of the phenol by K_2CO_3 probably happens first to give the potassium alkoxide, which could then act as the nucleophile (and a better one at that!). That answer would also receive full credit. You could still easily make the argument that it will take two steps to add the methyl 2,3-dibromopropanoate though, since it would have to approach the deprotonated pyrocatechol at **just** the right angle for simultaneous addition to both oxygens.

Reaction 2:



NOTE: The 2nd equivalent of amine serves to deprotonate the nitrogen in this step. If any HCl were to form first, it would simply react with the amine to generate the HCl salt

Part b, reaction 1: 12 points total

Reaction scheme does not have to be identical to that shown for full credit. The following steps should be shown (3 pts. each):

1. Attack by carbonate anion at the hydroxyl proton.
2. Attack by the alkoxide oxygen at Br-bound carbon of the electrophile, with Br leaving.
3. Attack by carbonate anion at the second hydroxyl proton.
4. Attack by the second alkoxide oxygen at the other Br-bound carbon of the electrophile, with Br leaving.

Notes: both attacks may take place simultaneously; Br may leave as Br^- , rather than KBr, as shown here.

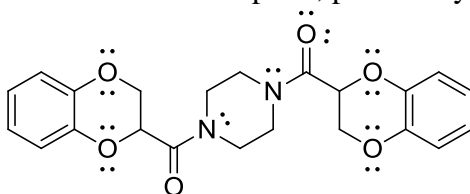
Part b, reaction 2: 12 points total

Reaction scheme does not have to be identical to that shown for full credit. The following steps should be shown (3 pts. each):

1. Attack by the piperazine amine at the carbonyl carbon (this step may be preceded by movement of carbonyl bond electrons to the carbonyl oxygen).
2. Cl^- leaving
3. Movement of electrons from the alkoxy anion to form the carbonyl double bond
4. Deprotonation of the amide nitrogen by a second equivalent of piperazine

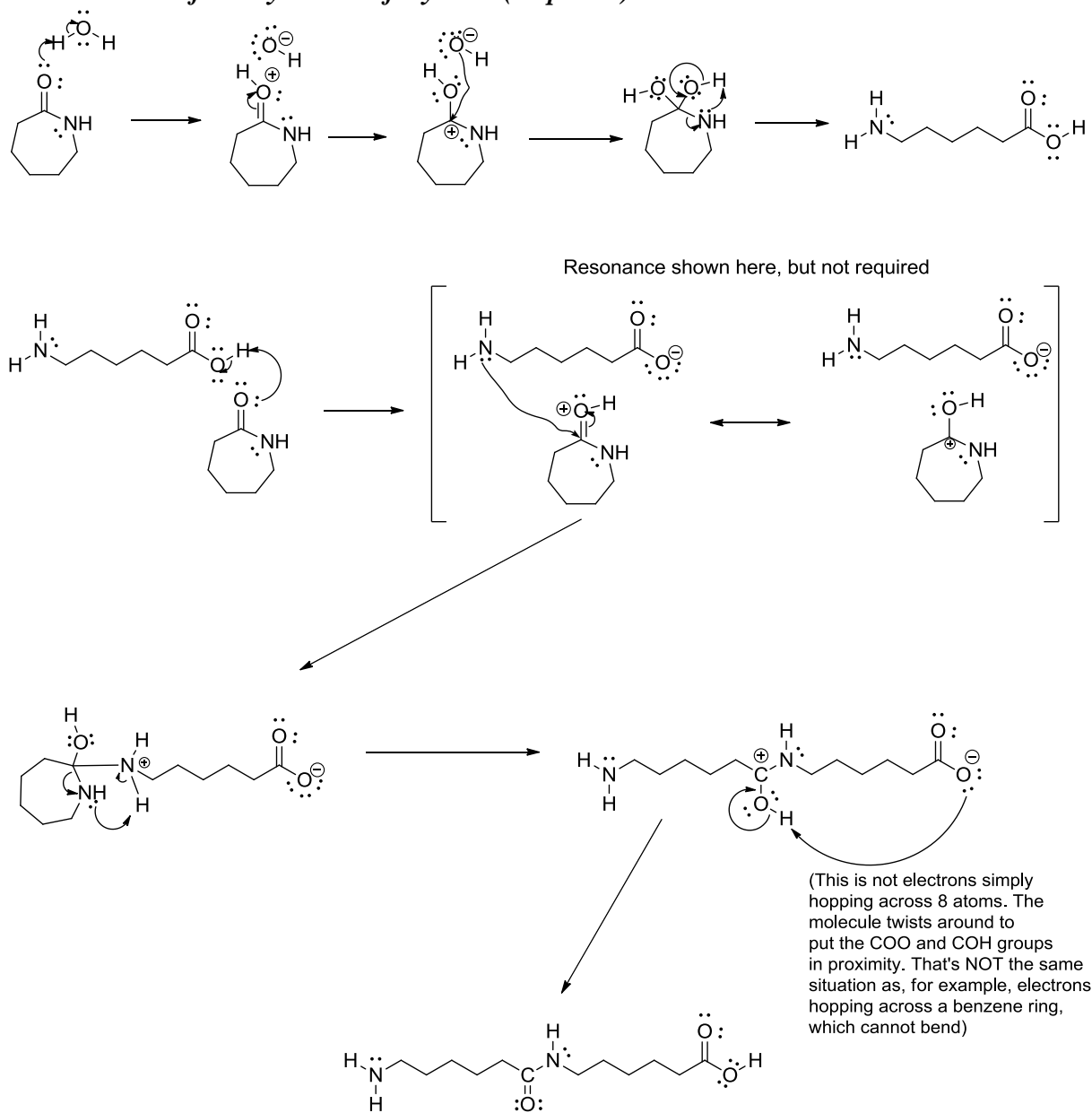
Full credit should be given whether the student draws these steps happening sequentially or simultaneously, within reason (all of the steps cannot happen at the same time!)

c) In piperazine, each amine could act as a nucleophile, potentially creating products of the type:



By using the mono-HCl salt, one of the nitrogens of the piperazine is deactivated towards nucleophilic attack, so mono-addition is favored. There may be some equilibrium between the HCl salts in the mechanism shown in part B, but since there is excess of the piperazine HCl, the double addition adduct should be less prevalent due to concentration differences.

(6 points for realizing that the double addition product could be generated if piperazine is used. It is not necessary to draw the structure of the double addition product for full credit.)

4. Mechanism of the Synthesis of Nylon 6 (35 points)

At this point, it should be apparent that this process can continue *ad infinitum*, leading to the polymer structure given in the problem statement.

5 pts: initial extraction of a proton from water

5 pts: formation of diol because OH^- acts as a nucleophile

5 pts: rearrangement to form 6-aminohexanoic acid

5 pts: stripping of acid proton by a second caprolactam molecule

5 pts recognition that the amine acts as the nucleophile during this cycle

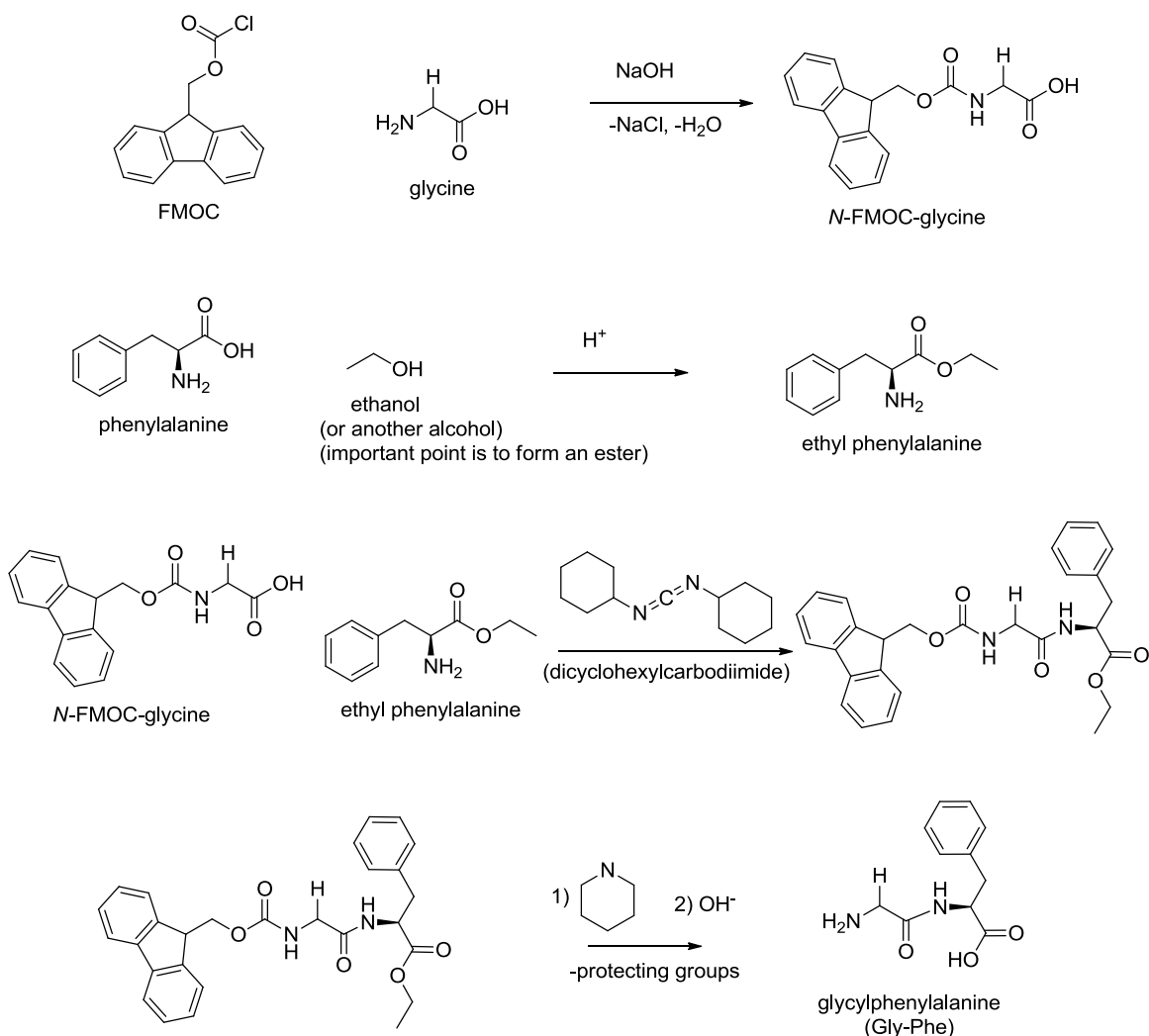
5 pts for opening of ring

5 pts for electron rearrangement to final structure

(Alternate reasonable arrow pushing should be awarded full credit. If a student combines too many steps and the relevant chemistry is therefore unclear, then points should be deducted)

5. Synthesis of a Dipeptide (30 pts)

a) Since the dipeptide is listed as Gly-Phe, we are linking the carboxylic acid end of glycine to the amine end of phenylalanine. We therefore need to protect the other two sides of the amino acids using the first two reactions, then link the two amino acids, and finally remove the protecting groups. (Note that there are MANY different protecting groups, but you learned about Fmoc in lecture)



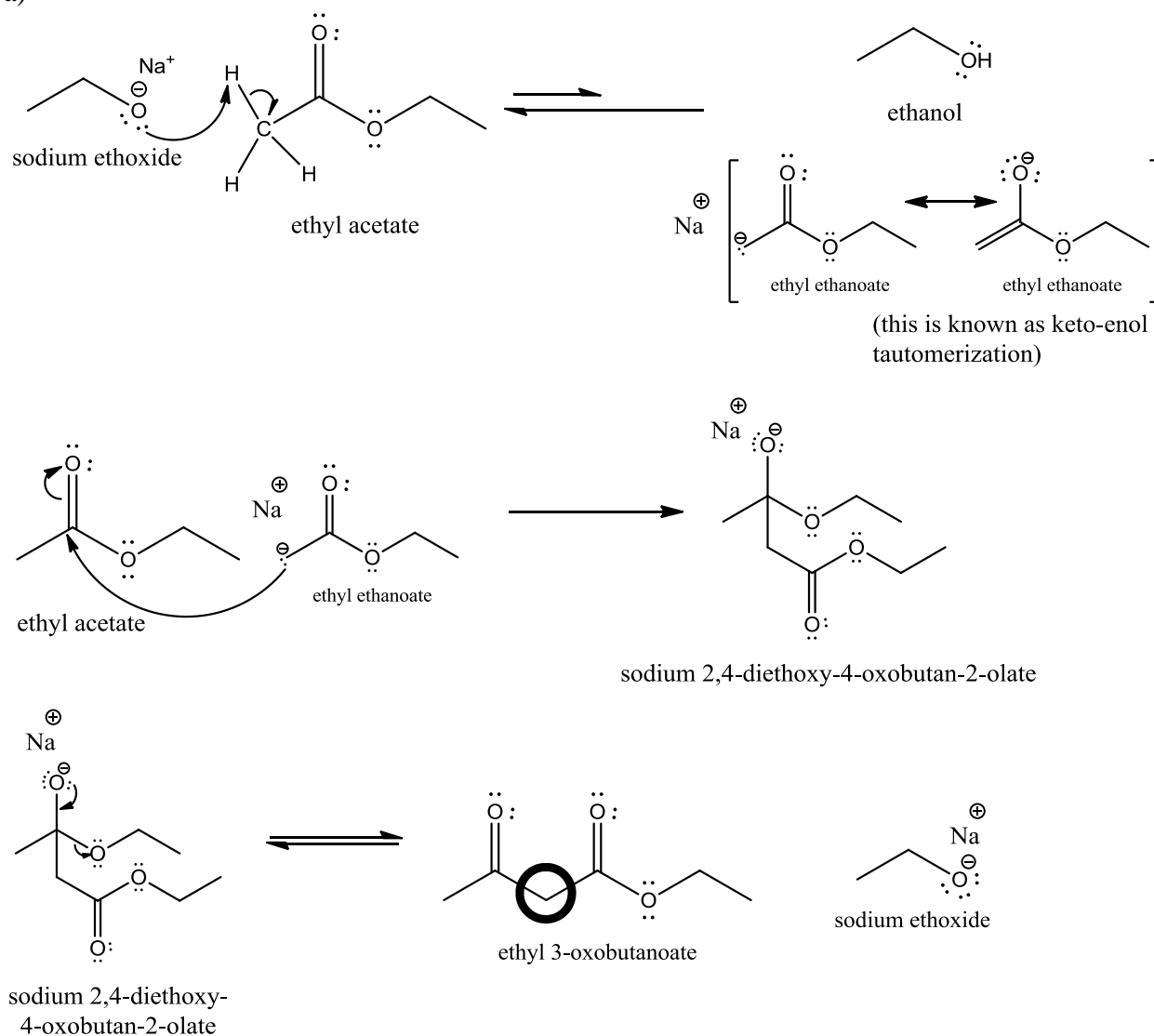
6 pts for protecting glycine with Fmoc or any other reasonable amine protecting group, 6 pts for protecting phenylalanine with any reasonable acid protecting group (ester, substrate linker, etc.), 6 pts for reasonable coupling reaction (piperidine to form a benzotriazole group, dicyclohexylcarbodiimide, etc.), 6 pts. for something related to removal of protecting groups. -8 if acid and amine protecting groups are placed on wrong amino acids.

b) Without protecting groups, you could have any combination of amino acids react with each other (after all, they all have amine and carboxylic acid groups). So you'd end up with Gly-Phe, Phe-Gly, Gly-Gly, Phe-Phe, Gly-Gly-Gly, Gly-Gly-Phe, etc.

(6 points for anything related to mixture of products)

6. The Claisen Condensation Reaction and Mechanism (25 points)

a)



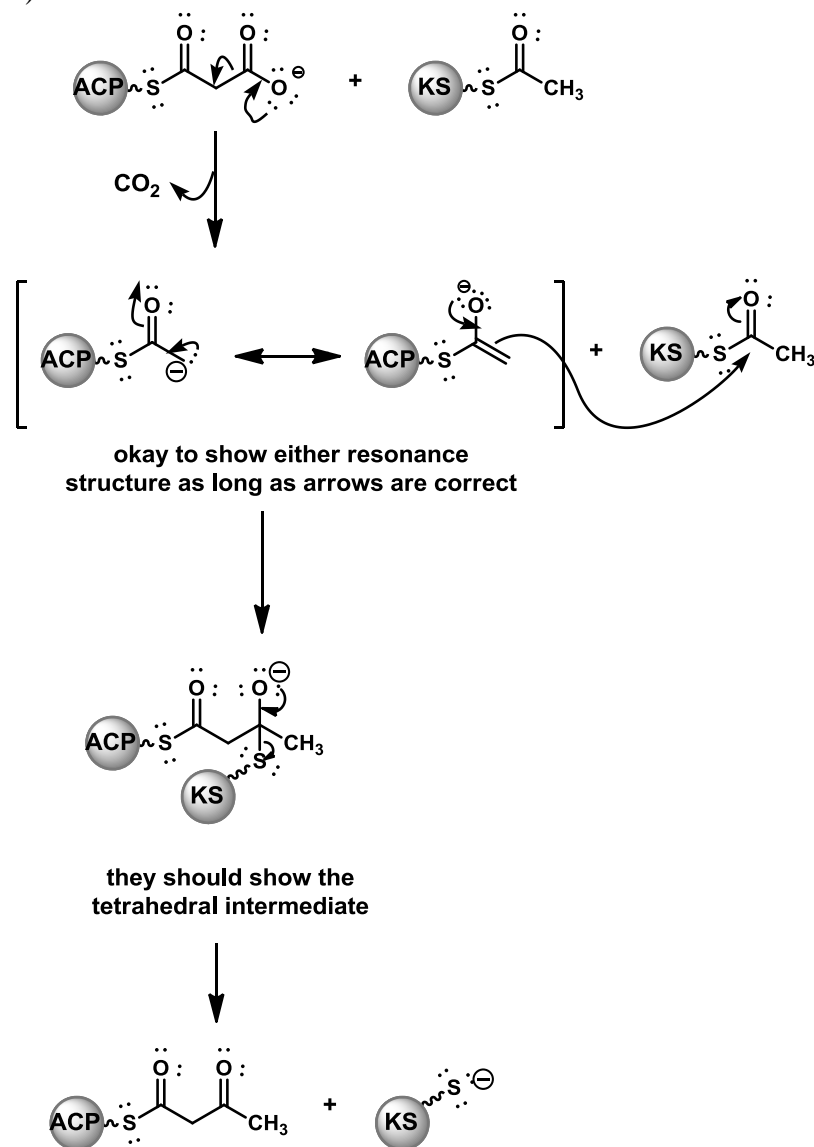
(5 pts per step: 3 for curved arrows and 2 for products. Award full credit for alternate arrow pushings that are reasonable and show the relevant chemistry concepts. Award full credit for deprotonating the circled carbon. However, -5 for any further reactions beyond this deprotonation. No credit for structures without lone pairs or formal charges. Students do not need to name their molecules)

b) The problem here is that the hydrogens on carbon 2 of ethyl 3-oxobutanoate (circled above) are highly acidic (in this case, $pK_a=11$) due to the electron withdrawing effects of the two carbonyl groups, and can be deprotonated by the ethoxide anions. However, the very first step of our synthesis required the sodium ethoxide. If we only used a catalytic amount of sodium ethoxide (as first glance at our mechanism might suggest we need), the $C_2H_5O^-Na^+$ would be depleted, and our reaction would stop.

(5 points for acidity of protons, 5 points for recognizing depletion of a starting material)

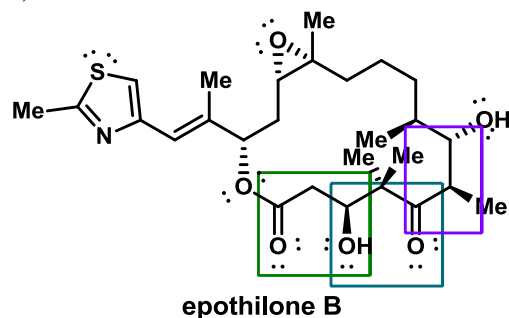
7. A Polyketide Synthesis Step For Epothilones (25 points)

a)



3 pts per correct arrow pushing in steps 1–3, 3 pts for the products of each reaction. –1.5 for not explicitly indicating leaving groups when appropriate.

b)



(7 pts for at least two of the correct boxes. 4 pts total for only one correct box, no credit otherwise)