NAME:_____ Section:__A__ Student Number:_____

Spring 2015 **Chemistry 4000 Final** ____/ 70 marks

INSTRUCTIONS:

1) Please read over the test carefully before beginning. You should have 10 pages of questions and a periodic table.
2) Unless otherwise stated in the question, explain all of your answers fully. Use diagrams where appropriate. When invoking any argument based on resonance, you must draw all relevant resonance structures.
3) ALL structures must be drawn showing lone pairs, non-zero formal charges and reasonable bond angles – regardless of whether they are expanded, condensed or line-bond. Marks will be deducted for poorly drawn structures.
4) Marks will be deducted for incorrect information added to an otherwise correct answer.
5) If your work is not legible, it will be given a mark of zero.
6) Calculators are not allowed. You are not permitted to have any electronic devices with you during the exam unless authorized by the instructor.
7) You may use a molecular model kit.
8) You have 3 hours to complete this test.

Confidentiality Agreement:

I agree not to discuss (or in any other way divulge) the contents of this exam until after 1:00 pm Mountain Time on Wednesday, April 29th, 2015. I understand that breaking this agreement would constitute academic misconduct, a serious offense with serious consequences. The minimum punishment would be a mark of 0/70 on this exam; the maximum punishment would include expulsion from this university.

Signature: _____ Date: _____

Course: CHEM 4000A (Medicinal Chemistry)
Semester: Spring 2015
The University of Lethbridge

Question Breakdown

Q1	/ 4
Q2	/ 3
Q3	/ 4
Q4	/ 3
Q5	/ 10
Q6	/ 4
Q7	/ 2
Q8	/ 5
Q9	/ 5
Q10	/ 4
Q11	/ 6
Q12	/ 20

Total	/ 70

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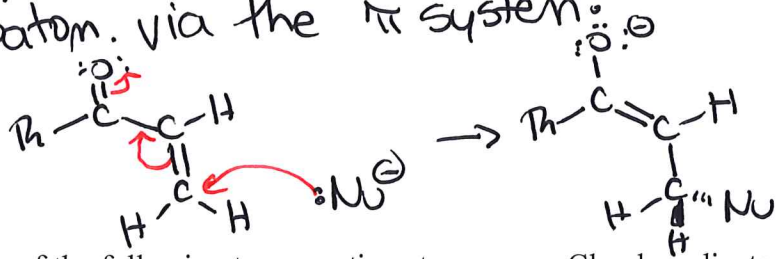
1. Explain why an a^3 synthon is a natural synthon. Your explanation should include an example. **[4 marks]**

In an a^3 synthon, the electrophilic carbon atom is part of an extended π system (usually an α,β-unsaturated carbonyl). Thus, when a nucleophile attacks, electron density can be shifted onto the electronegative heteroatom via the π system:

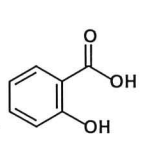


You could also use  or similar as an example.

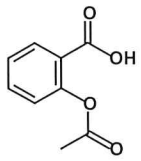
2. Choose one of the following two questions to answer. Clearly indicate which option you chose. If you answer both, only the first answer will be marked. **[3 marks]**

Option A

Aspirin is made from salicylic acid, which can be extracted from willow bark.



salicylic acid



aspirin

When I mentioned we were looking at 'green chemistry', my husband suggested that maybe someone could suggest a method for making aspirin that didn't require cutting down so many willow trees. Evaluate his suggestion using the principles of green chemistry.

My husband would like it noted that he was joking.

Option B

I recently read an article about development of "ball milling" techniques in chemistry. Essentially, the reactants would be put into a reaction vessel with small steel balls and the whole thing would be rotated. The motion of the balls (and associated friction) would create 'hot spots' of localized high temperature and pressure where reactions would occur. Evaluate this technique using the principles of green chemistry.

A Using renewable materials is desirable in green chemistry, so having a starting material that can be extracted in reasonable quantities from a quick-growing plant is good from a green chemistry perspective. Making and using synthetic salicylic acid would not be better.

B This technique would allow for reaction without a solvent - which is very desirable in green chemistry (which aims to minimize solvent use). While it would require some energy to rotate the reaction vessel, it would probably be less than the energy required to heat the whole container to the temperature achieved at the 'hot spots'. As such, this technique sounds 'green'.

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3. Certain elements have another element with which they form particularly strong bonds. These pairs of elements are said to have a strong affinity for each other. We saw several such pairs of elements over the course of the semester. **[4 marks]**

(a) Identify one pair of elements that have this type of strong affinity for each other. *[1 mark]*

silicon and fluorine or phosphorus and oxygen or sulfur and mercury

(b) Explain how this affinity is useful in synthesis. Include a sample reaction equation in your answer (but also explain why the reaction is useful in the "big picture"). *[3 marks]*

See lecture notes for sample equations.
→ Affinity of F for Si allows for selective cleavage of silyl ethers ∴ silyl ethers can be used as protecting groups
→ Affinity of P for O drives the Wittig reaction, allowing conversion of ketones and aldehydes into alkenes
→ Affinity of Hg for S allows for selective cleavage of thioacetals/ketals, allowing them to be used as either protecting groups or auxiliary functional groups

4. List three major factors you must consider when choosing a protecting group. Explain why each factor is important. **[3 marks]**

1. What other functional groups are present when the protecting group is to be attached?
→ Will it attach at the desired site or somewhere else?
→ Will the reaction conditions (eg acid) affect other functional groups in the molecule?
2. What reaction conditions must the protecting group survive? → we don't want it coming off prematurely and having to be reattached!
3. What other functional groups will be present when the protecting group is to be removed?
→ You don't usually want other parts of the molecule to be affected by the removal of the functional group. eg Don't cleave a benzyl ether by hydrogenation if you have an alkene or alkyne that you want to preserve.
4. Is the protecting group really necessary?
→ Could I just do the reactions in a different order? I don't want to add unnecessary steps to the synthesis

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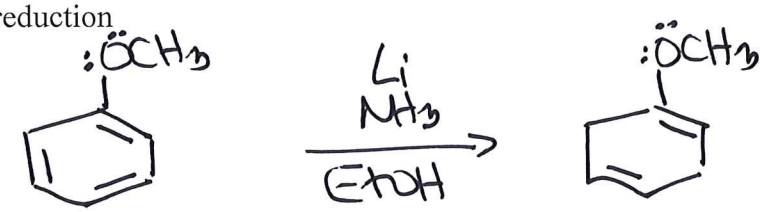
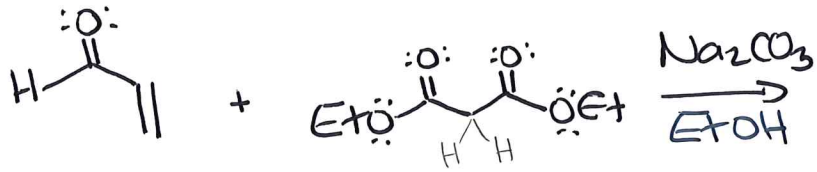
5. Give an example of each of the following reactions. Your example should take the form of a chemical equation including structures of all organic reactants and products. Other necessary reagents should be listed over the arrow. **[10 marks]**

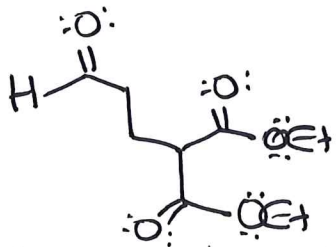
(a) Birch reduction



(b) Michael addition (aka conjugate addition)

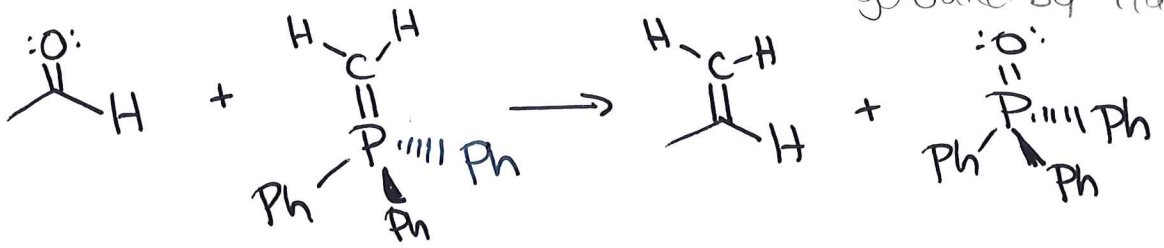


Na_2CO_3 deprotonates one of these two H, making a soft nucleophile.

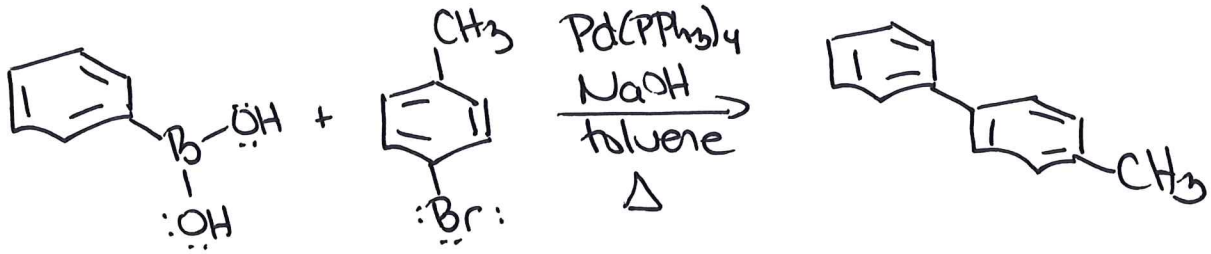


EtOH can act as proton source to protonate anion generated by 1,4 addition.

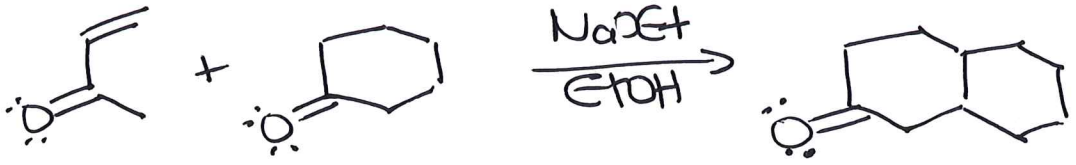
(c) Wittig reaction



(d) Suzuki coupling



(e) Robinson annelation



Since these are all sample reactions, there are many acceptable variations of all of them.

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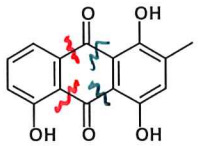
5. The disconnections are at exocyclic bonds (bonds exocyclic to one ring and endocyclic in another).

6. The molecule shown below is islandicin.

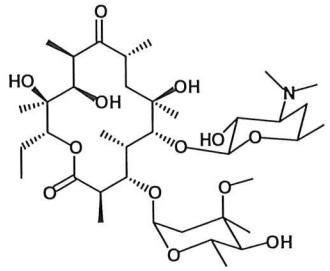


When beginning a retrosynthetic analysis of this molecule, which would be the best bond(s) at which to propose disconnection(s)? Why? Give three reasons for your choice(s). **[4 marks]**

I would start with either the red or green pair of disconnections (or some combination thereof). Either would be a good choice because:

1. It does not require formation of either benzene ring. (Skeleton-based bondset)
2. The C=O in the middle could come from a synthons - which are natural ∴ a good choice.
3. Assuming that the benzene piece acts as the nucleophile, three of the four disconnections shown involve a d^2 synthon - also natural ∴ a good choice.
4. The pair of disconnections gives two synthons of approximately equal size and complexity.

7. The molecule shown below is erythromycin A. What would you consider to be the two greatest synthetic challenges in developing a synthesis for this molecule? **[2 marks]**



You do **not** have to suggest how to overcome these challenges!!!

1. The very large number of chirality centers!
2. Attaching the sugar molecules (which are different) at the correct sites when there are five oxygen atoms that can be part of either an alcohol or hemiacetal.
3. Making a 14 atom ring. (closing the ester with the right oxygen atom in the ring)

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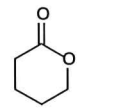
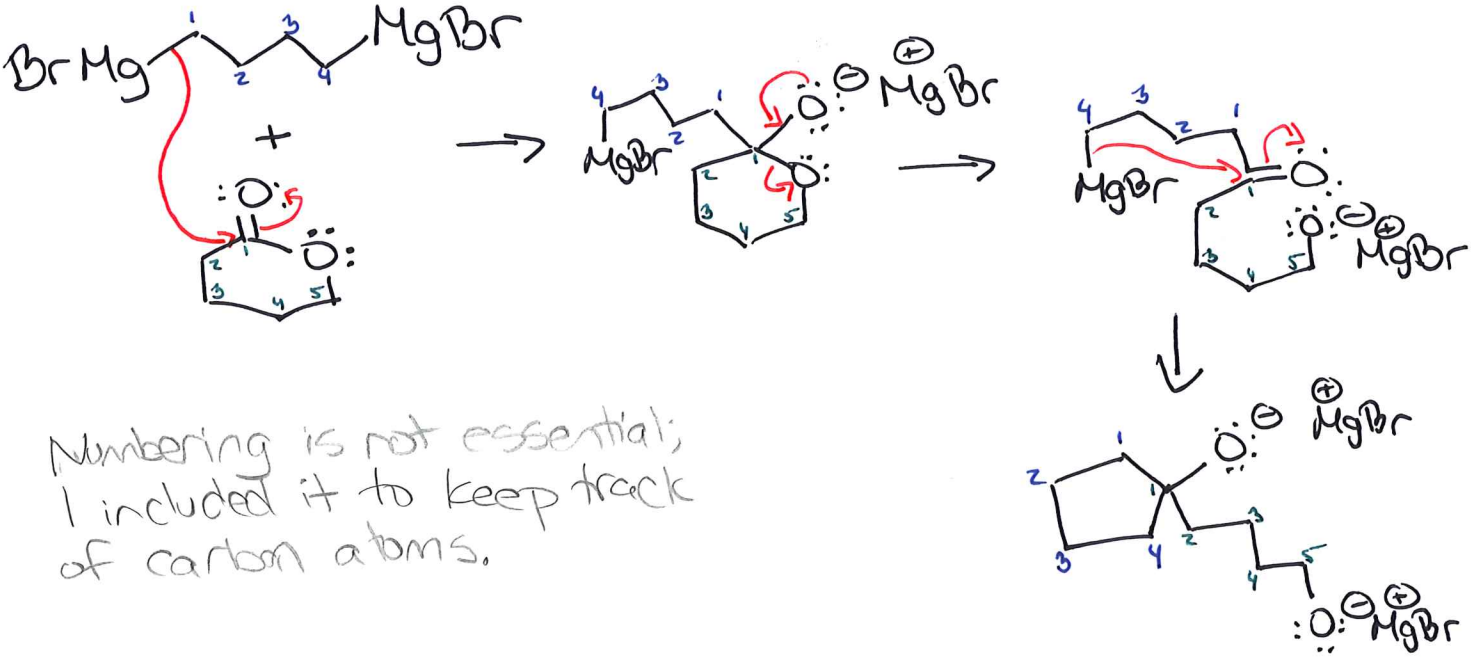
8. When I was working on my PhD, the first step in my synthesis involved making a double Grignard reagent by reacting 1,4-dibromobutane with excess magnesium then adding δ-valerolactone *(shown at right)*. Finally, the reaction was worked up by adding water.

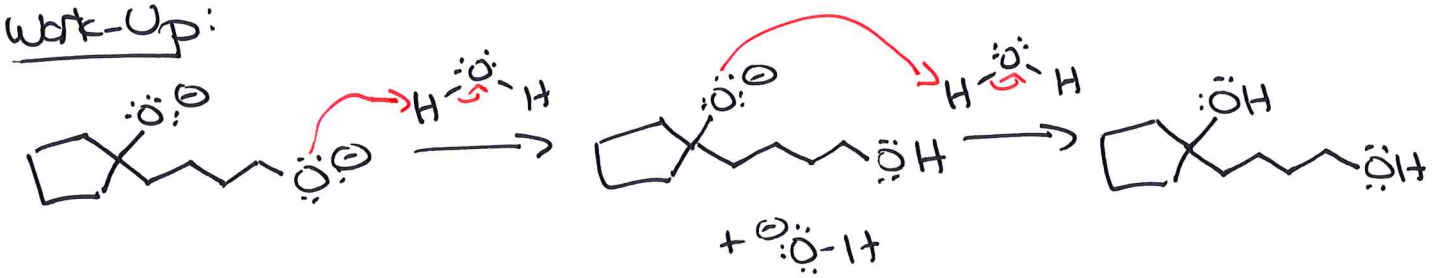


δ-valerolactone

Propose a mechanism for this reaction and identify the final organic product. **[5 marks]**



Numbering is not essential; I included it to keep track of carbon atoms.



Work-Up:

It doesn't matter which O⊖ is protonated first, but shows two separate steps. (The dianion will not collide with two water molecules in the same instant.)

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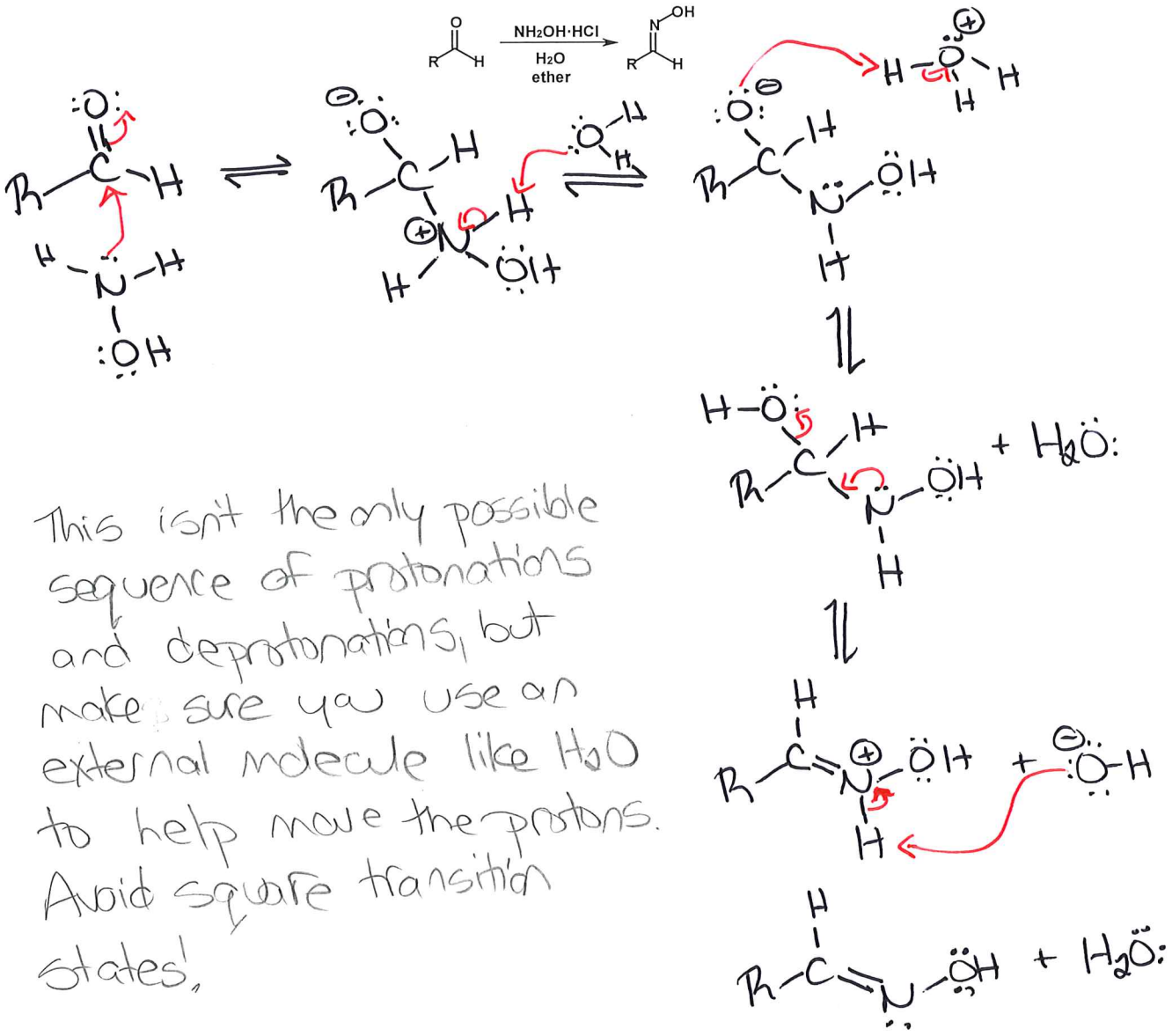
9. Later on in this synthesis, I reacted an aldehyde with hydroxylamine hydrochloride to make the oxime *(see reaction equation below).* Propose a mechanism for that reaction. **[5 marks]**



This isn't the only possible sequence of protonations and deprotonations, but make sure you use an external molecule like H_2O to help move the protons. Avoid square transition states!

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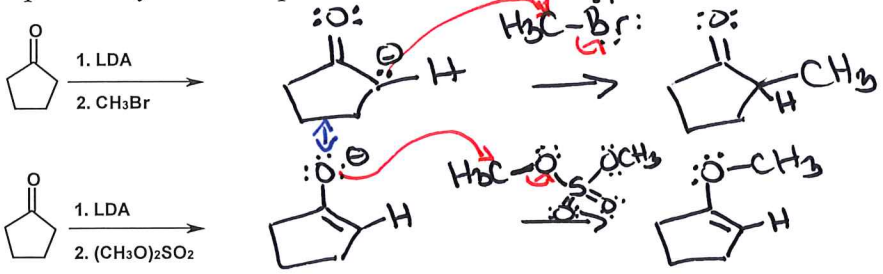
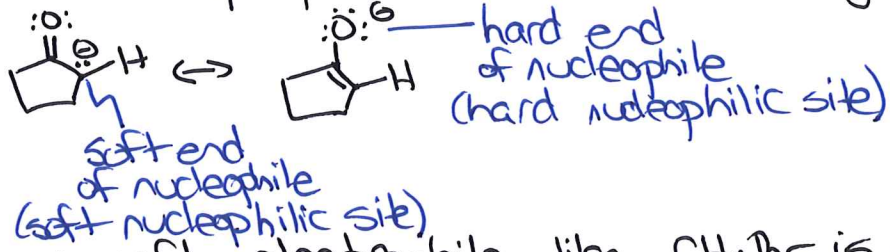
10. Explain why different products are obtained for the two reactions shown below.



As part of your answer, you must also identify the organic product of each reaction. **[4 marks]**

Reaction of cyclopentanone with LDA gives the enolate:



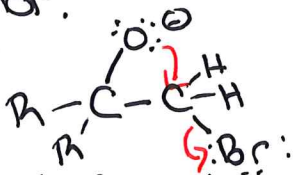
When a soft electrophile like CH_3Br is used, the softer nucleophilic site attacks it. When a harder electrophile like $(CH_3O)_2SO_2$ is used, the harder nucleophilic site attacks it.

11. Some sizes of rings are easier to make than others. **[6 marks]**

(a) Comment on the relative difficulty in making 3-membered rings vs. 4-membered rings. Which is easier to make and why? *[2 marks]*

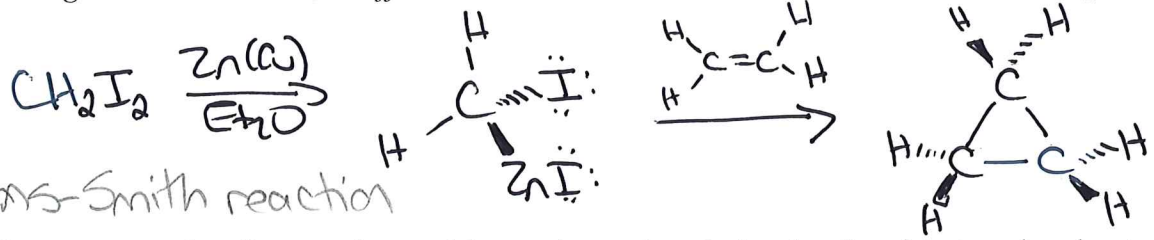
3-membered rings are easier to make because they are kinetically favoured. 4-membered rings are not.

nucleophilic site easily reaches electrophilic site:



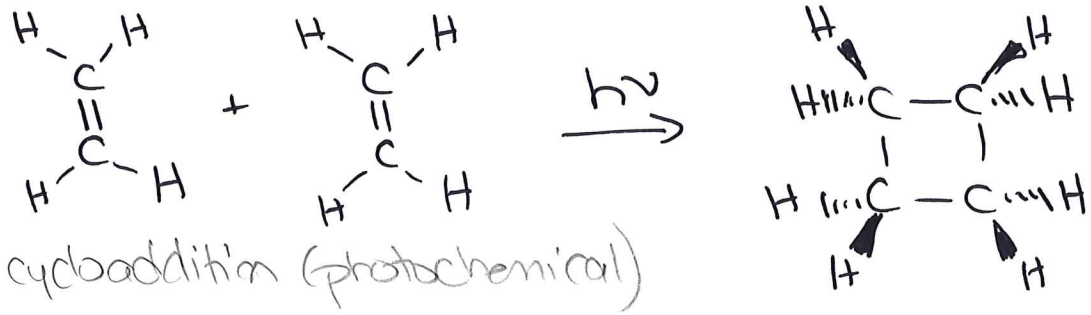
If you add an extra atom between the reacting sites, they are much less likely to be correctly oriented.

(b) Give an example of a reaction making a 3-membered ring by forming two bonds at once. *Naming the reaction is not a sufficient answer! Show how it is done.* *[2 marks]*



Simmons-Smith reaction

(c) Give an example of a reaction making a 4-membered ring by forming two bonds at once. *Naming the reaction is not a sufficient answer! Show how it is done.* *[2 marks]*



[2+2] cycloaddition (photochemical)

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12. Choose **two** of the molecules below and propose a synthetic route to make each. **[20 marks]**

Your answers should take the form of a retrosynthetic analysis followed by chemical equations for the reactions in the synthesis itself. Show all required reagents, and number steps within a reaction if order of addition is important.

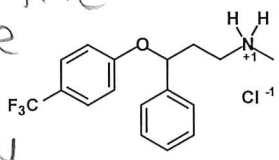
You may use any reagents that you could reasonably expect to be commercially available and that contribute no more than 7 carbon atoms to the final product.

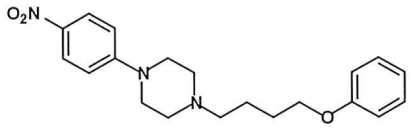
If you are suggesting a multi-step synthesis, write an equation for each step.

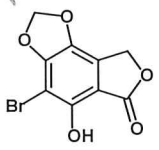
There are two pages after this. Use one of those pages for each synthesis and clearly identify the synthetic target at the top of the page. This page is scrap paper.

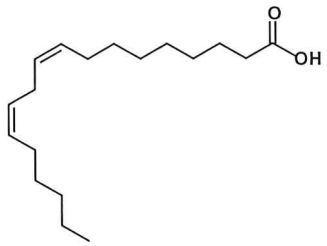
Options

The answers on the next pages are representative. There are many possible reasonable answers. They are taken from (or modified from) actual exams.









If you choose this synthetic target, you may **NOT** use starting materials containing *cis* double bonds.

Generally, I divide the marks for a synthetic proposal as follows: 40% for overall approach (best communicated via a retrosynthetic analysis) and 60% for execution of the approach. For this reason, it is in yar best interest to draw the retrosynthesis. (It is fine if ya realize that it wald be better to do the steps in a different order as ya work forward. Ya don't need to go back and "fix" the retrosynthesis to match.)

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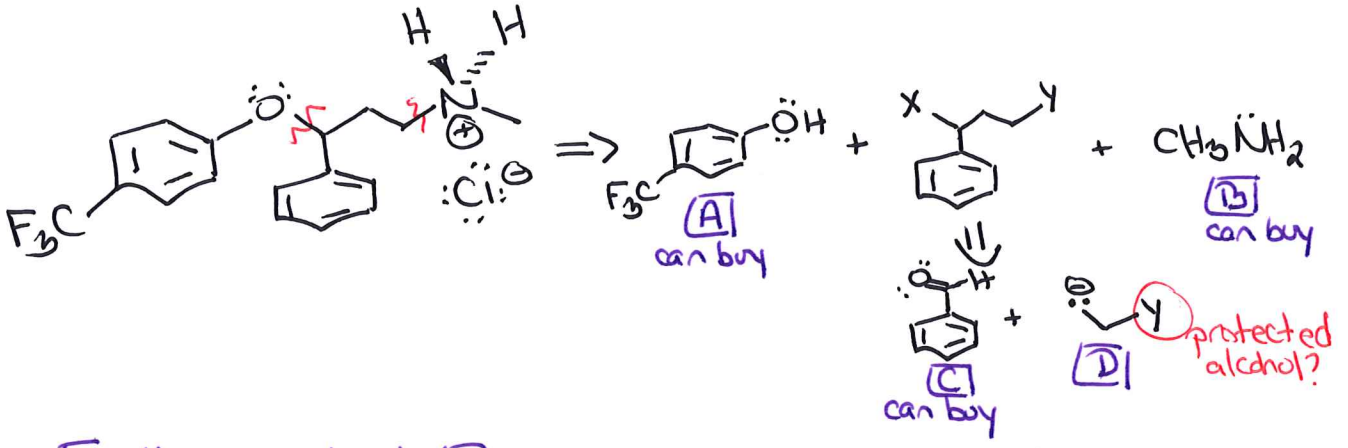
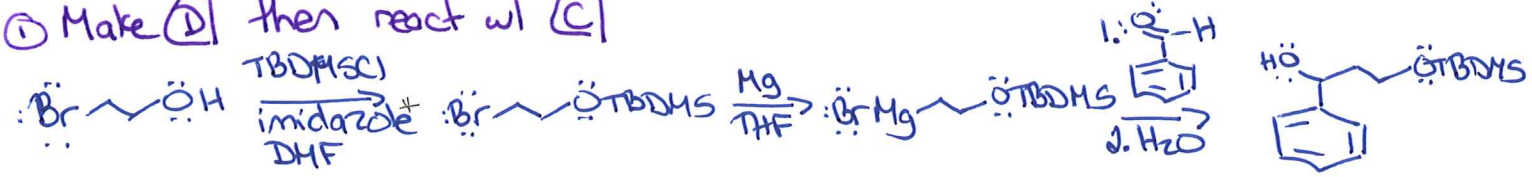
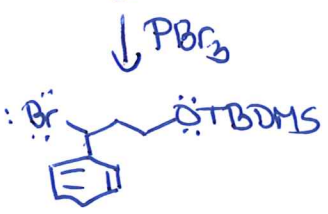
12. *continued...* *[10 marks]*

First Retrosynthesis and Synthetic Proposal

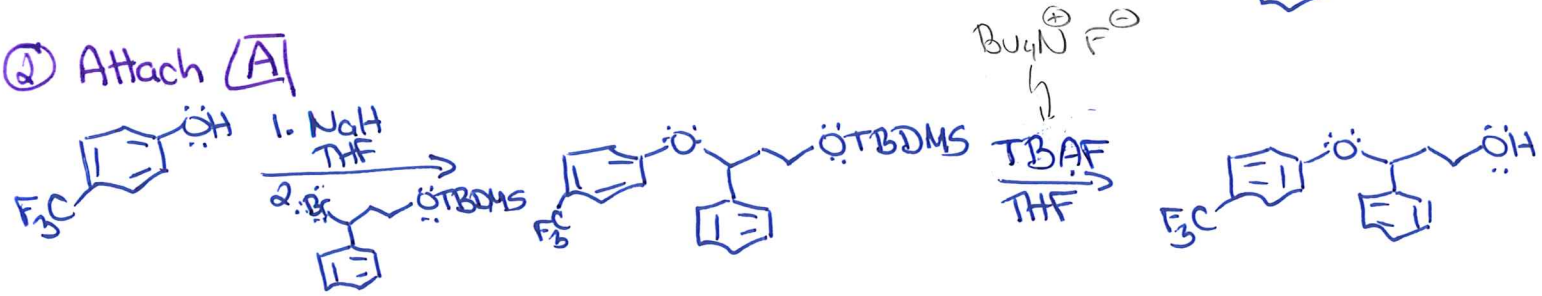


① Make D then react w/ C

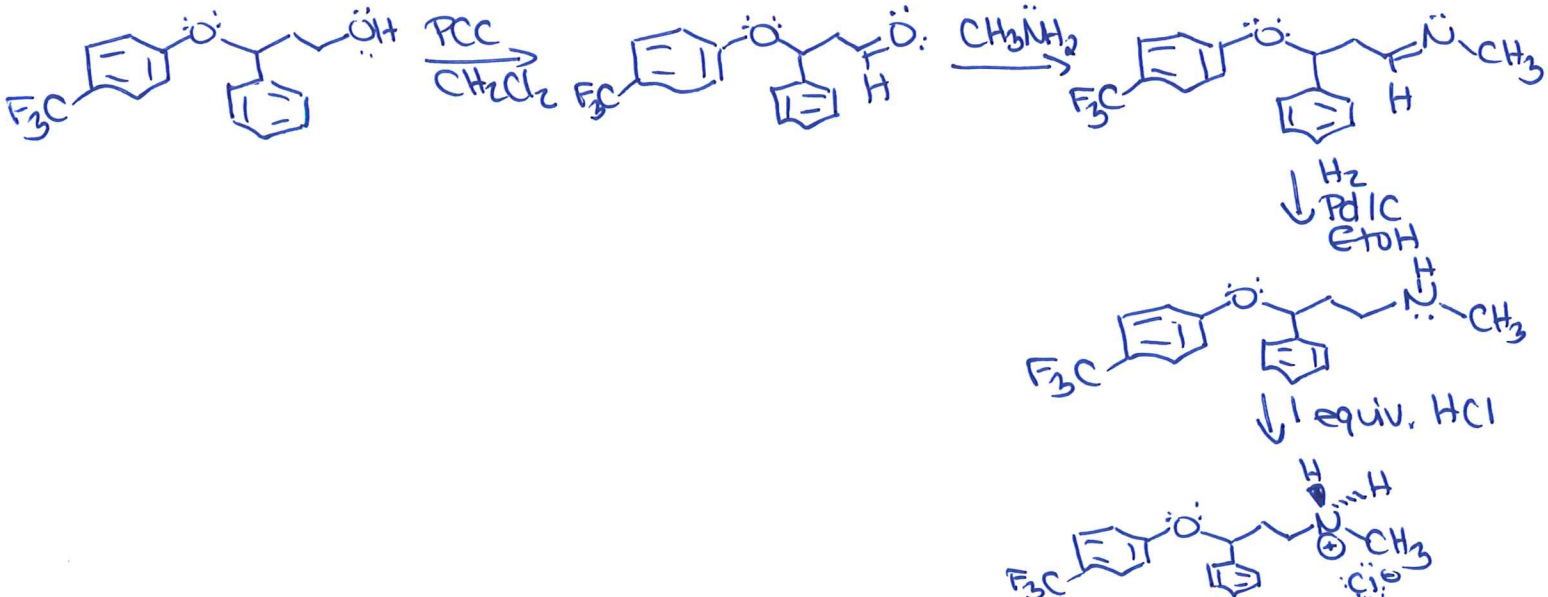




② Attach A



③ Attach B and finish synthesis



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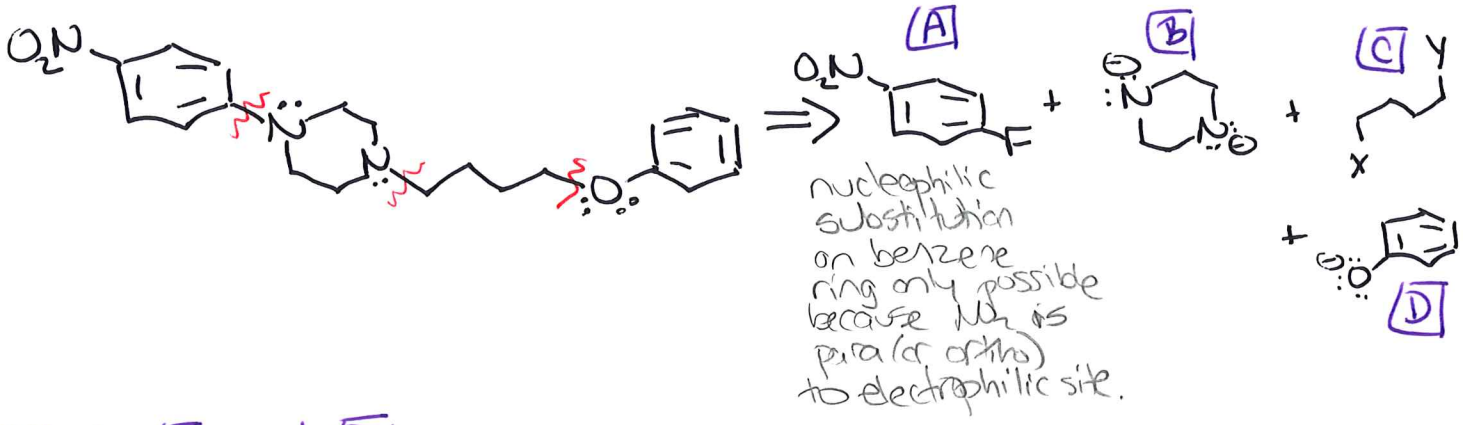
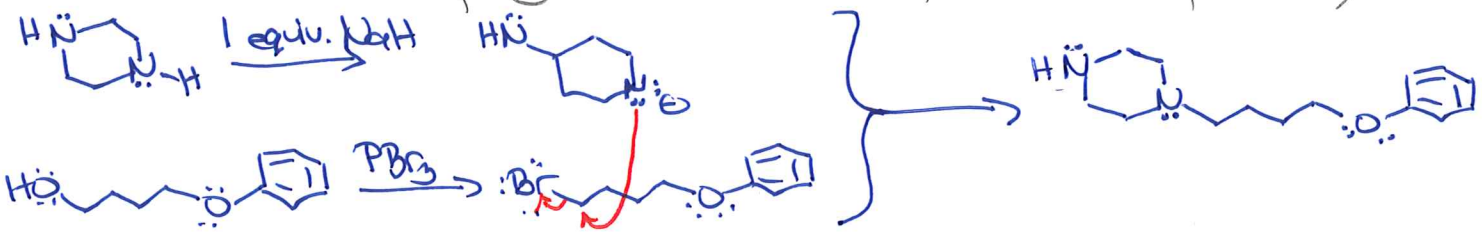
12. *continued...* *[10 marks]*

Second Retrosynthesis and Synthetic Proposal

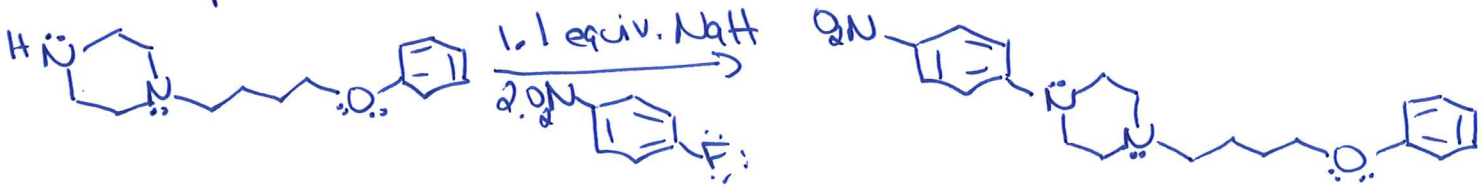


① Attach C and D

② Attach B (While it is more convergent to attach A and B first, that substitution is less favored so offers more opportunity for competing reactions like deprotonation of product.)



③ Attach A



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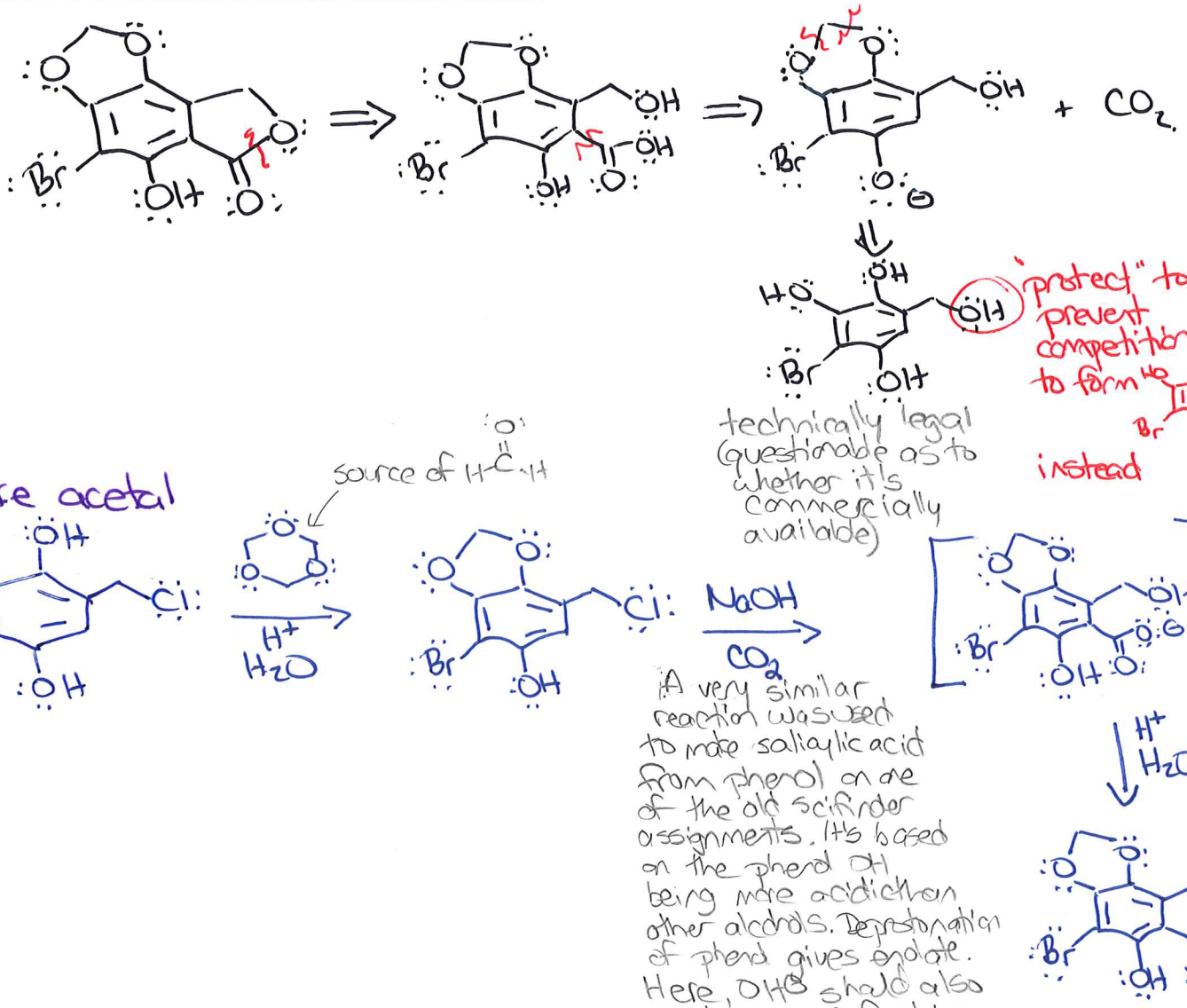
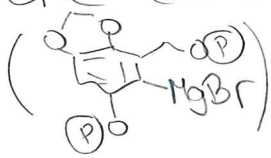
12. *continued...* *[10 marks]*

Third Retrosynthesis and Synthetic Proposal



One could also envision using a Friedel-Crafts reaction to attach the carbonyl to the benzene ring.

One could also envision making a Grignard (), reacting it with CO_2 then attaching the remaining -Br via Br_2 / $FeBr_3$.

cis double bond = either Wittig reaction or partial hydrogenation of alkyne

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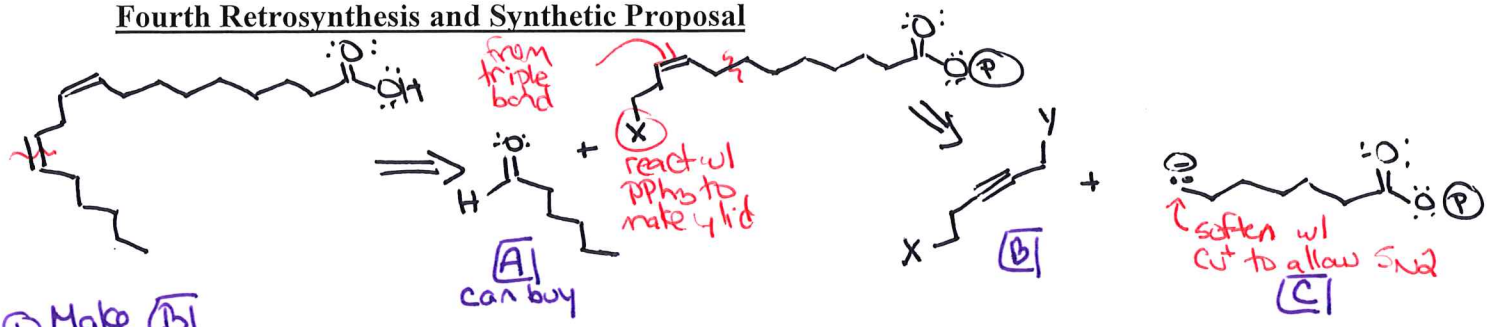
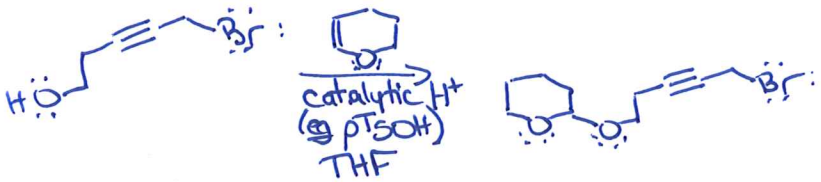
12. *continued...* *[10 marks]*

Fourth Retrosynthesis and Synthetic Proposal

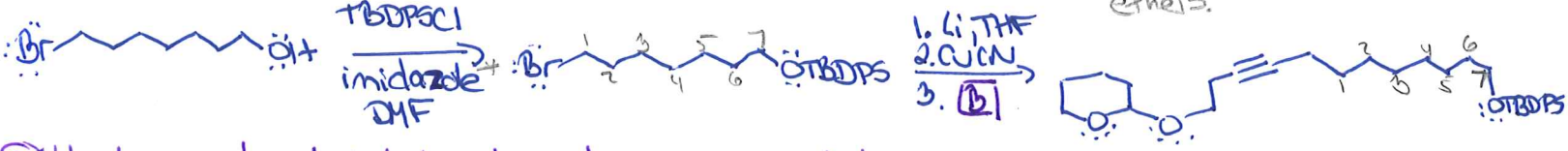


① Make B

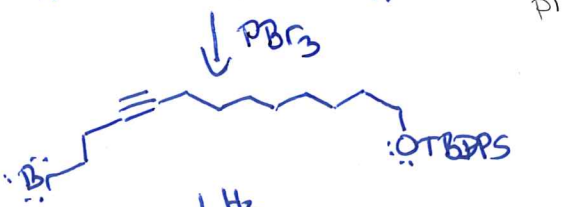


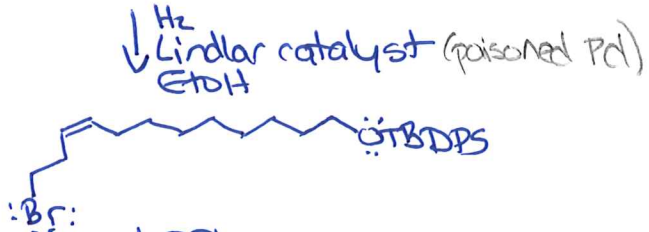
*Imidazole is  . It would be fine to suggest using Et3N or pyridine. Imidazole just happens to be the most common amine to make TBDMS or TBDPS ethers.

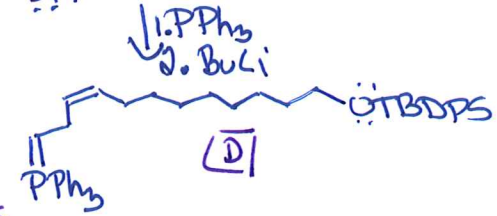
② Make C then react wl B



③ Hydrogenate triple bond and prepare ylid







④ Do Wittig reaction and finish synthesis