NAME:_____ Section:__A__ Student Number:_____

Fall 2017 **Chemistry 4000 Final** ____/ 65 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 12:00 noon Mountain Time on Saturday, December 9th, 2017. I understand that breaking this agreement would constitute academic misconduct, a serious offense with serious consequences. The minimum punishment would be a mark of 0/65 on this exam; the maximum punishment would include expulsion from this university.

Signature: _____ Date: _____

Course: CHEM 4000A (Medicinal Chemistry)
Semester: Fall 2017
The University of Lethbridge

Question Breakdown

Q1	/ 3
Q2	/ 5
Q3	/ 10
Q4	/ 10
Q5	/ 5
Q6	/ 6
Q7	/ 6
Q8	/ 20

Total	/ 65

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1. Supercritical carbon dioxide can be used to extract caffeine from coffee and tea. Coffee beans are soaked in water then put in a sealed vessel with carbon dioxide which is pressurized to approximately 70 atm (70 times atmospheric pressure). Once the caffeine has dissolved in the supercritical carbon dioxide, the solution flows to another chamber in which the pressure is reduced and the carbon dioxide vaporizes.

   This is an alternative to more traditional processes in which solvents like CH_2Cl_2 are used to extract caffeine from coffee.

   Evaluate the use of supercritical fluid as a decaffeinating agent in terms of green chemistry. Suggest at least one benefit, at least one drawback and at least one way in which you could ensure that the process was as green as possible. **[3 marks]**

   Benefits include…

   - Replaces halogenated solvents (which require very high temperatures to burn for disposal)
   - Provides a commercial use for something that might otherwise be a waste product (thereby providing financial incentive for companies to capture waste CO_2 instead of releasing it into the atmosphere)

   Drawbacks include…

   - Requires high pressure (not ambient pressure) which requires energy to attain

   To be as green as possible…

   - Reuse the CO_2. After it vaporizes, capture the CO_2 and use it for repeated rounds of decaffeination.

2. **[5 marks]**

(a) What does it mean for a synthon to be "umpoled" or "umpolung"? *[1 mark]*

An umpoled synthon plays the opposite role to what you would expect given the reactive site's relationship to the nearest heteroatom. In other words, it has "unnatural reactivity".

(b) Circle all the classes of synthon below which would be considered to be umpoled. *[2 marks]*

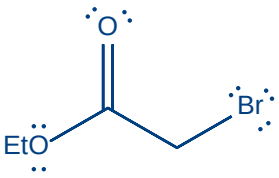
a^1 a^2 a^3 d^1 d^2 d^3

(c) Choose **<u>two</u>** of the classes of umpoled synthon circled above, and give an example of a specific reactant that could be used as an example of each class of synthon. *[2 marks]*

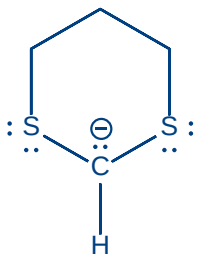
It must be clear which reactant corresponds to which class of synthon.

a^2

or



d^1



or

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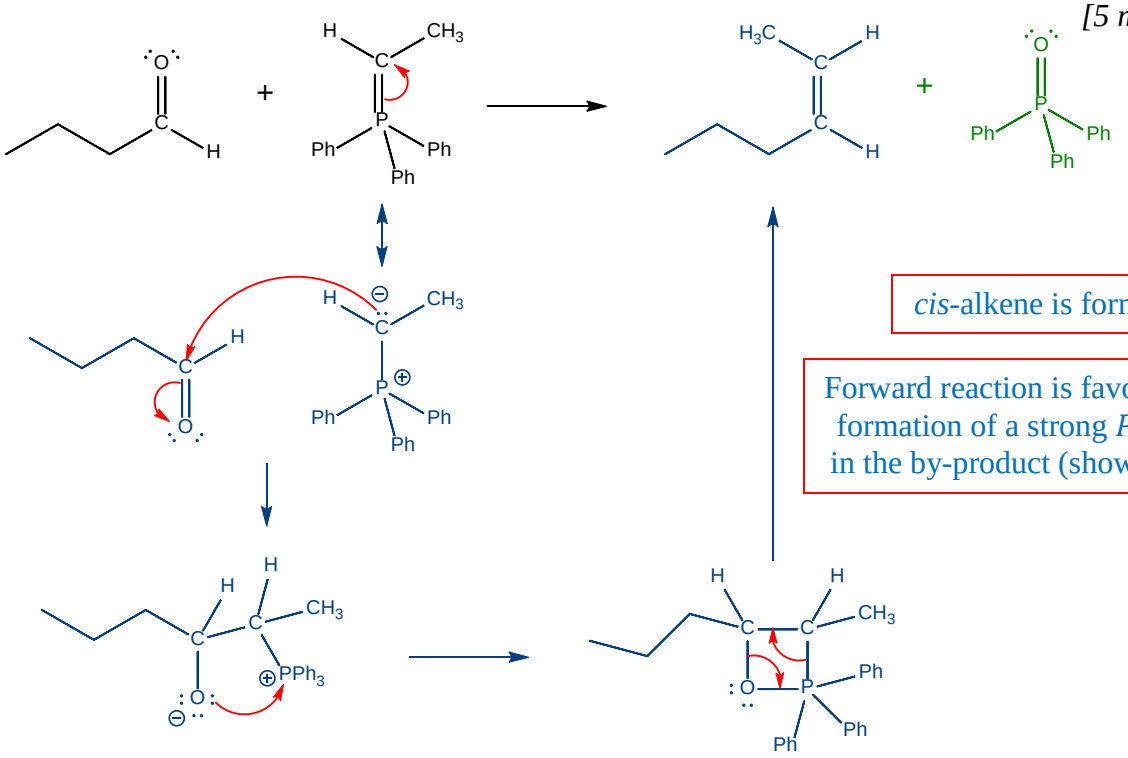
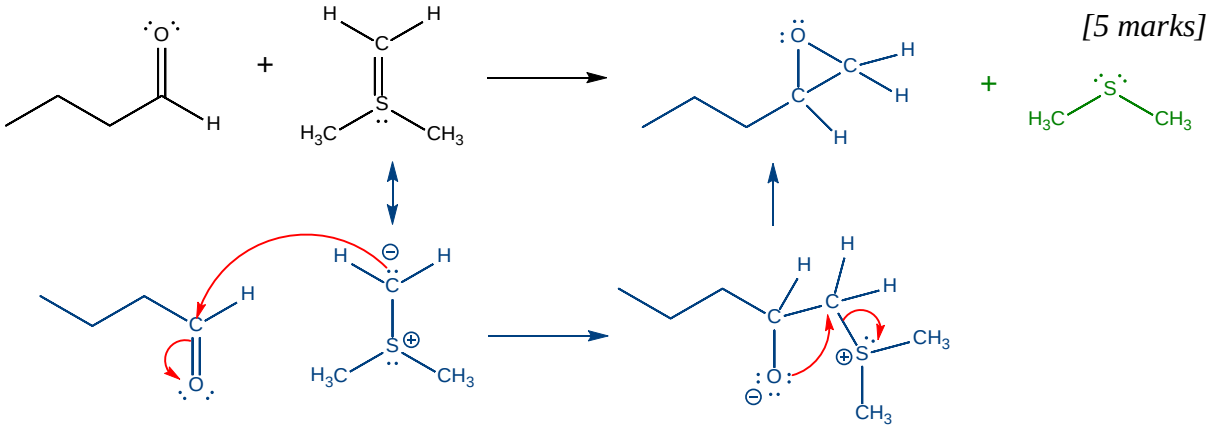
3. We studied two reactions in which a ketone or aldehyde reacts with an ylide. **[10 marks]**
For each reaction:

- draw the final organic product,
- show the mechanism, and
- clearly indicate the driving force pushing the reaction forward.

(a) *[5 marks]*



(b) *[5 marks]*



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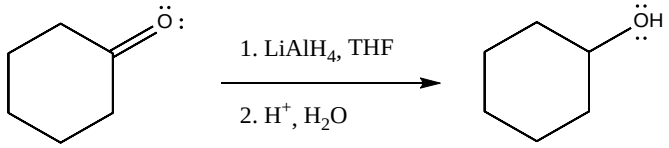
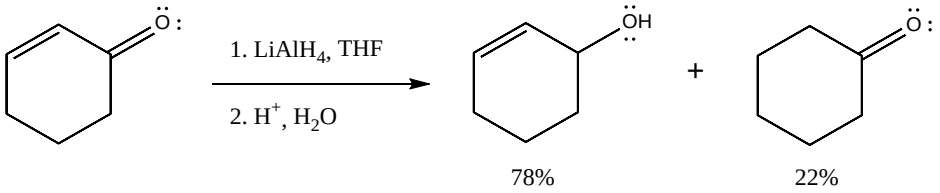
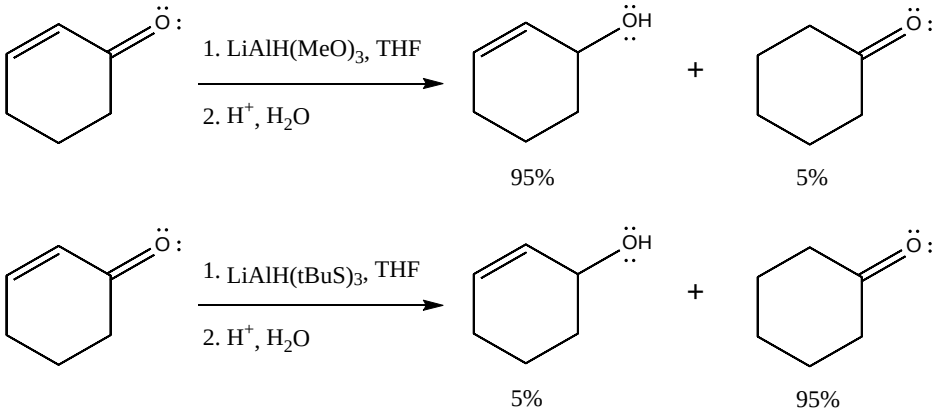
4. Lithium aluminium hydride ($LiAlH_4$) is typically used to reduce carbonyl groups: **[10 marks]**



If 2-cyclohexenone is treated with $LiAlH_4$, two products are observed:

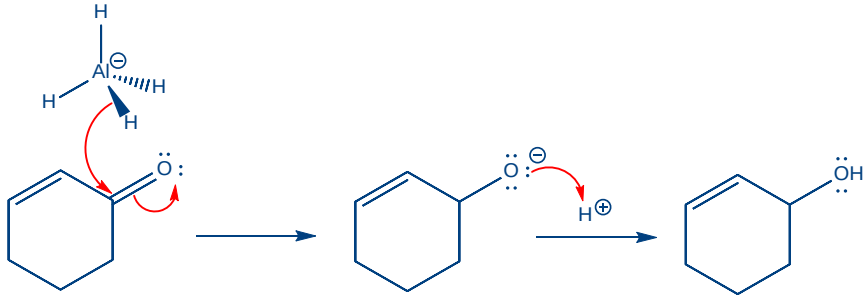


If some of the hydrogen atoms in $LiAlH_4$ are replaced by other groups, the ratio of the two products shifts:

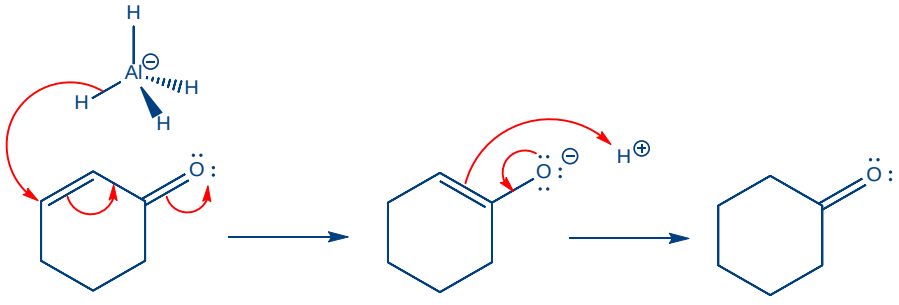


(a) Draw **<u>two</u>** mechanisms – one for the formation of each product made when 2-cyclohexenone reacts with $LiAlH_4$ (followed by work-up with mild aqueous acid). *[5 marks]*

Mechanism 1 ($LiAlH_4$ attacks carbonyl carbon, the harder of the two electrophilic sites)



Mechanism 2 (conjugate addition; $LiAlH_4$ attacks the softer of the two electrophilic sites)



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4. *continued…*

(b) Why do we observe two products when 2-cyclohexenone reacts with $LiAlH_4$? *[1 mark]*

The ketone is part of a conjugated pi system that has two electrophilic sites (shown in the mechanisms in part (a)).

(c) What can you conclude about the three reducing agents ($LiAlH_4$, $LiAlH(MeO)_3$ and $LiAlH(tBuS)_3$) based on the experimental data provided? How do you know? *[4 marks]*

$LiAlH(MeO)_3$ is harder than $LiAlH_4$ while $LiAlH(tBuS)_3$ is softer than $LiAlH_4$.

$LiAlH(MeO)_3$ reacts primarily at the harder electrophilic site (the carbonyl carbon). In the reaction of 2-cyclohexenone with $LiAlH_4$, 78% of the product is the result of attack at the harder electrophilic site. In the reaction of 2-cyclohexenone with $LiAlH(MeO)_3$, 95% of the product is the result of attack at the harder electrophilic site. Since harder nucleophiles tend to favour reaction at harder electrophilic sites, $LiAlH(MeO)_3$ must be harder than $LiAlH_4$.

$LiAlH(tBuS)_3$ reacts primarily at the softer electrophilic site (in a conjugate addition *aka* Michael addition *aka* 1,4-addition). In the reaction of 2-cyclohexenone with $LiAlH_4$, only 22% of the product is the result of attack at the softer electrophilic site. In the reaction of 2-cyclohexenone with $LiAlH(tBuS)_3$, 95% of the product is the result of attack at the softer electrophilic site. Since softer nucleophiles tend to favour reaction at softer electrophilic sites, $LiAlH(tBuS)_3$ must be softer than $LiAlH_4$.

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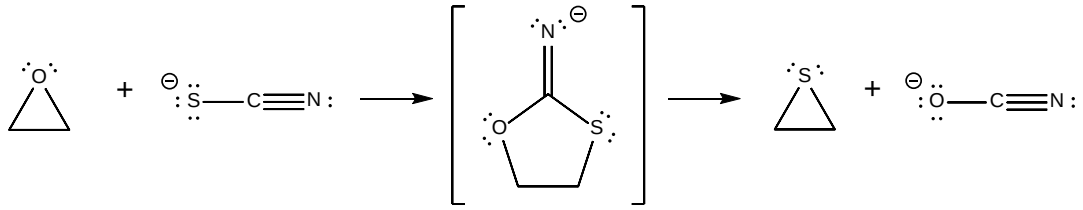
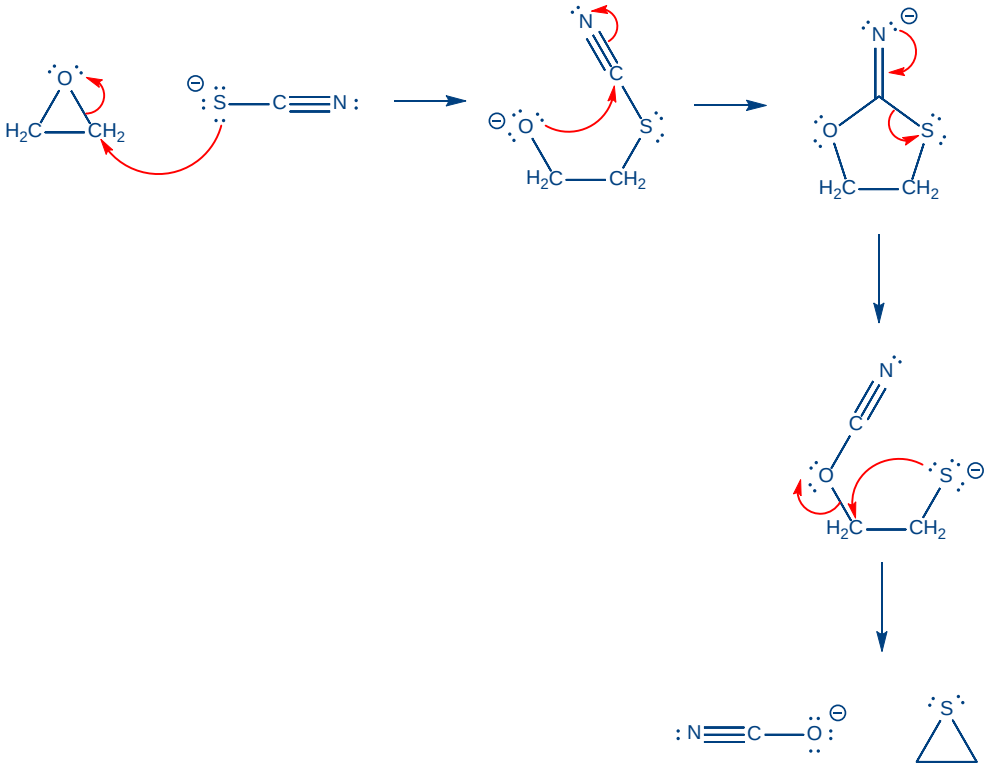
5. Propose a reasonable mechanism for the reaction below. One intermediate is shown. **[5 marks]**





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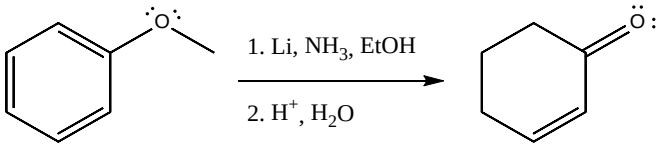
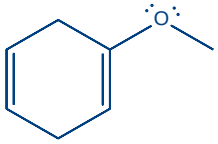
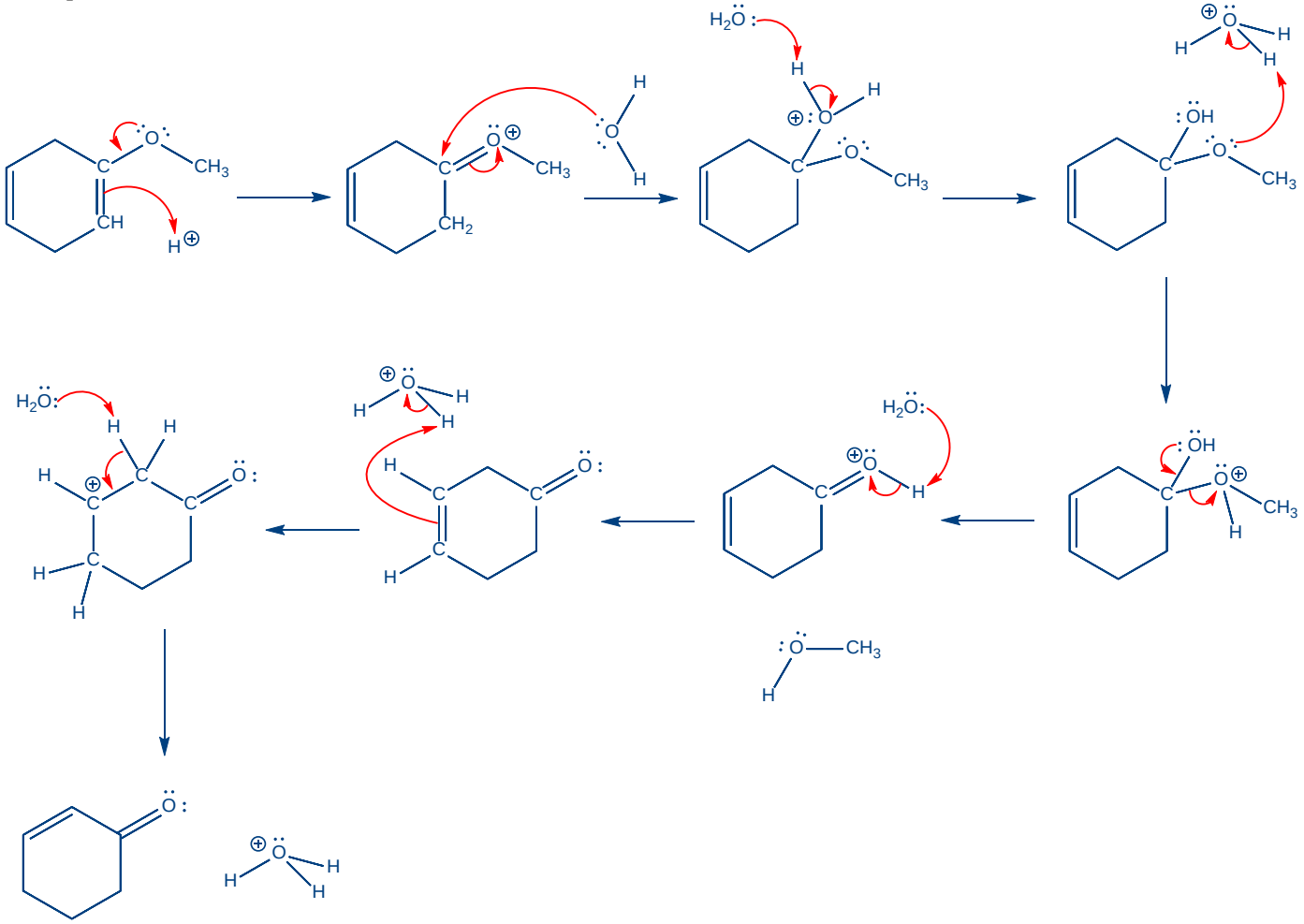
6. We saw that a cyclohexenone can be prepared from a methoxybenzene via a Birch reduction followed by acid-catalyzed hydrolysis of the resulting enol ether: **[6 marks]**



(a) Draw the product of the first step of this reaction sequence. *[1 mark]*
In other words, draw the product of the Birch reduction.



(b) Propose a reasonable mechanism for the second step of this reaction sequence. *[5 marks]*
In other words, propose a mechanism for converting the product of the Birch reduction into the final product show above.



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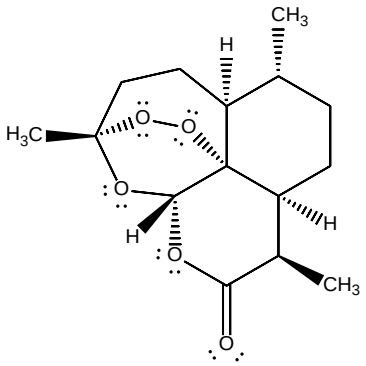
7. The molecule shown below is artemisinin, a component of many treatments for malaria. **[6 marks]**



(a) Identify three features of this molecule that would make it challenging to synthesize. *[3 marks]*

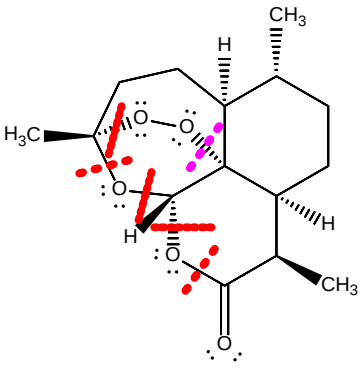
- It contains an $O-O$ bond (they are very reactive so it would be difficult to preserve through many synthetic steps; would need to introduce it near the end of the synthesis)
- It contains 7 chirality centers, 6 of which are contiguous (at connected atoms).
- It contains 4 fused/bridged rings.

(b) If you were going to develop a retrosynthesis for artemisinin, what would be the first disconnection you would propose? Provide at least two reasons for your choice. *[3 marks]*

The marks are for the explanation of why you chose that disconnection.

You do <u>NOT</u> need to propose a whole synthesis of artemisinin!!! You do <u>NOT</u> need to indicate what reaction you would use to make the bond at the disconnection site.

I accepted several disconnections as being reasonable places to start, as long as the rationale was good (and consistent with the proposed disconnections). Several defensible disconnections are shown in red/purple below. (I would be looking for a single answer; not all of those together!)



Points to consider:

- Most of the disconnections shown correspond to formation of an acetal by having an alcohol attack a ketone or aldehyde. The bottom one corresponds to formation of a lactone (cyclic ester) by having an OH group attack a carboxylic acid or derivative thereof. These are relatively straightforward reactions. *(This rationale does not apply to the disconnection shown in purple.)*
- All of the disconnections shown simplify the target by breaking open a ring. In all cases, the ring containing the disconnection is a six-atom ring (easy to form) and the corresponding starting material would not contain any medium sized rings (difficult to form).
- The top four disconnections involve breaking a bond in one of the rings that is fused to the most other rings. That sort of disconnection simplifies the target more than a disconnection in a peripheral ring.

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

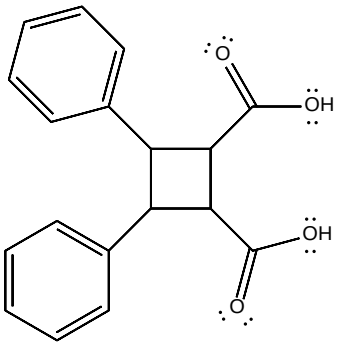
Your answers should take the form of a retrosynthetic analysis followed by chemical equations for the reactions in the synthesis itself. Show all required reagents, and number steps within a reaction if order of addition is important.

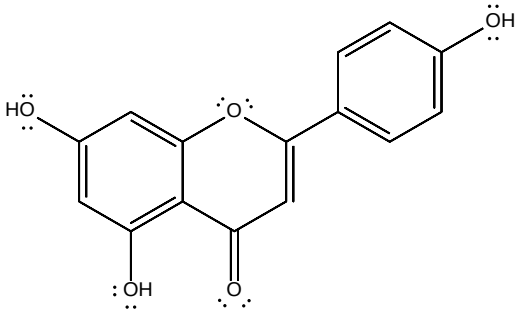
You may use any reagents that you could reasonably expect to be commercially available and that contribute no more than 7 carbon atoms to the final product.

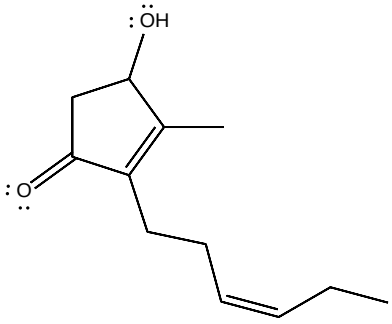
If you are suggesting a multi-step synthesis, write an equation for each step.

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







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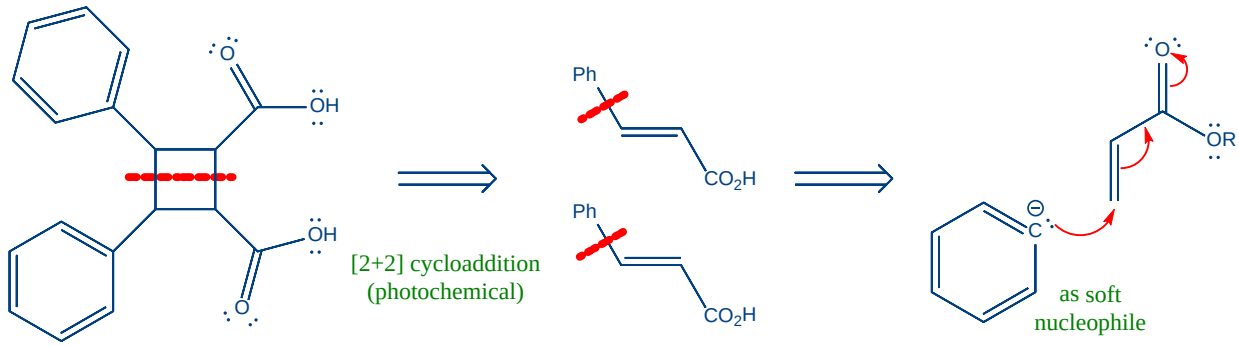
8. *continued…* *[10 marks]*

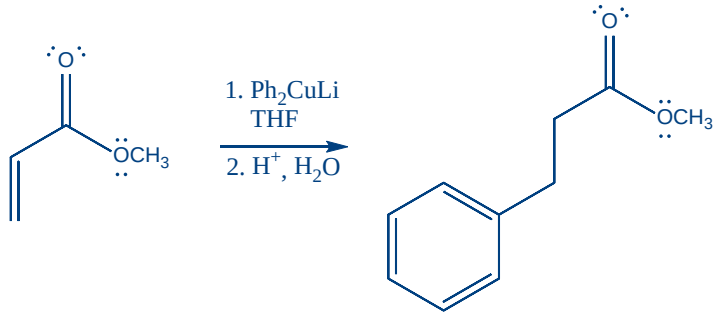
First Retrosynthesis and Synthetic Proposal

Retrosynthetic Analysis

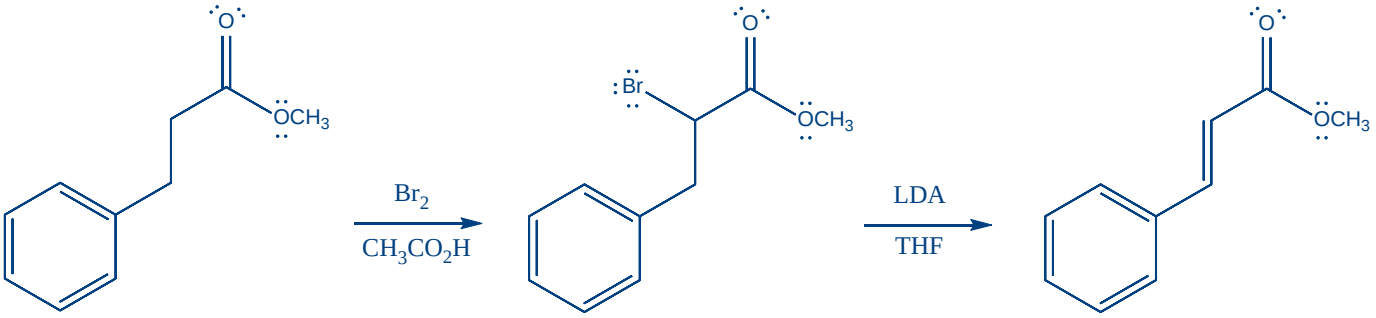


Synthetic Proposal

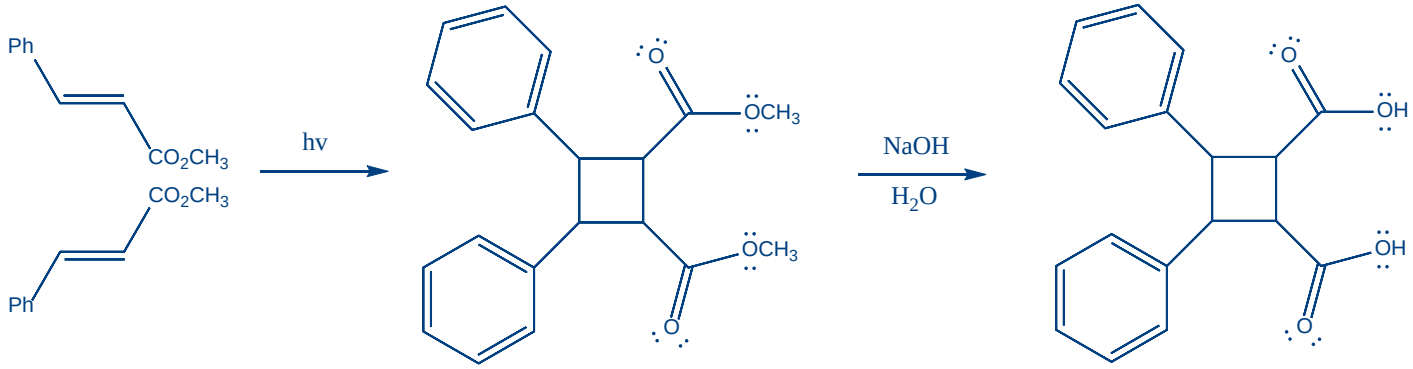
1. Use a cuprate (soft nucleophile) to attach phenyl group via 1,4-addition.



2. Introduce double bond by brominating alpha to carbonyl then eliminating HBr.



3. Perform [2+2] cycloaddition and saponify ester (in either order).



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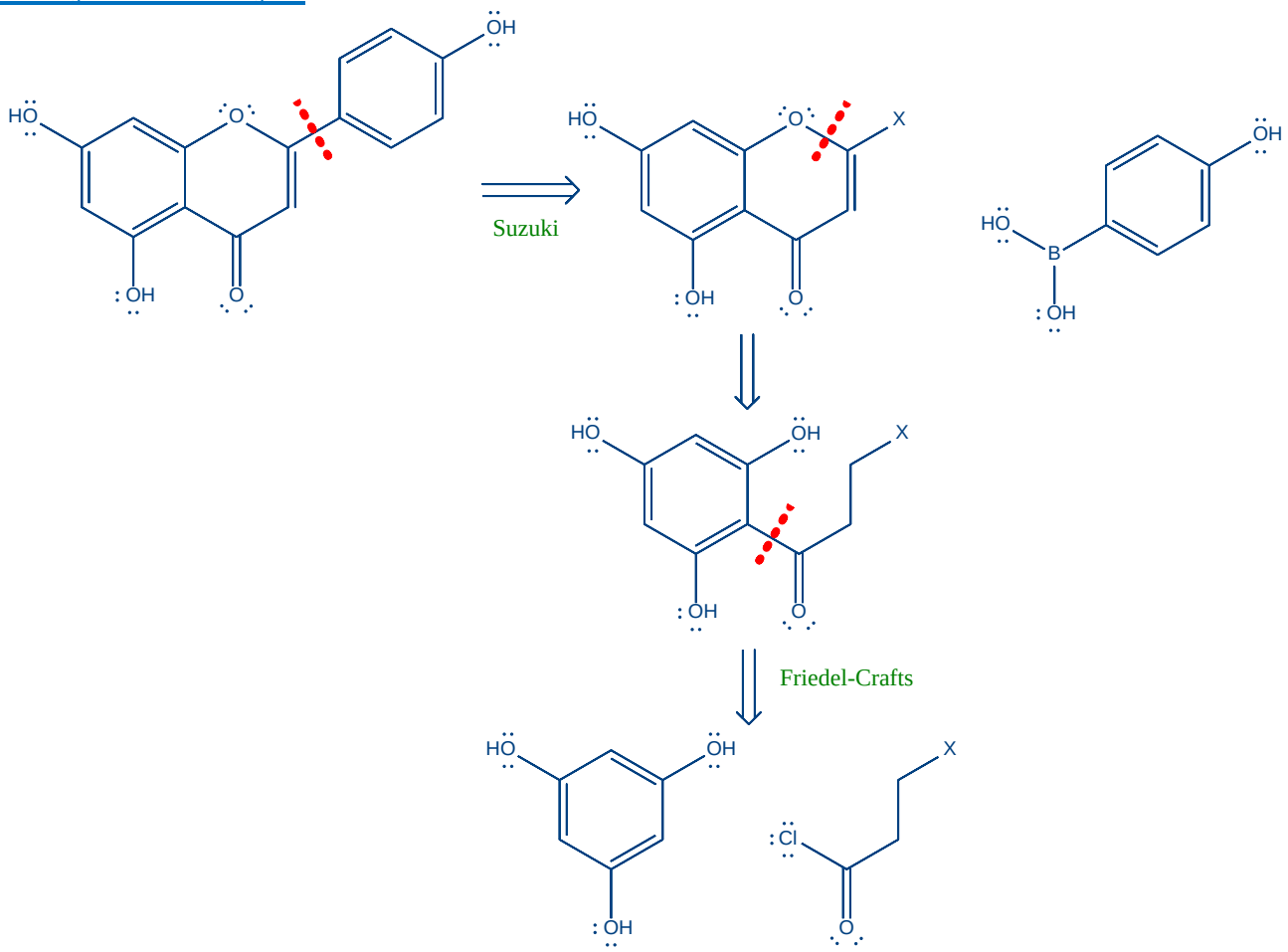
8. *continued…* *[10 marks]*

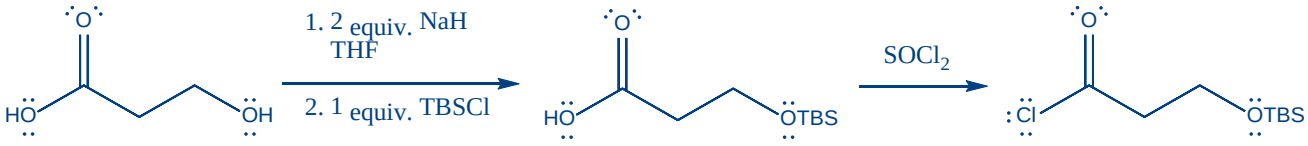
Second Retrosynthesis and Synthetic Proposal

Retrosynthetic Analysis

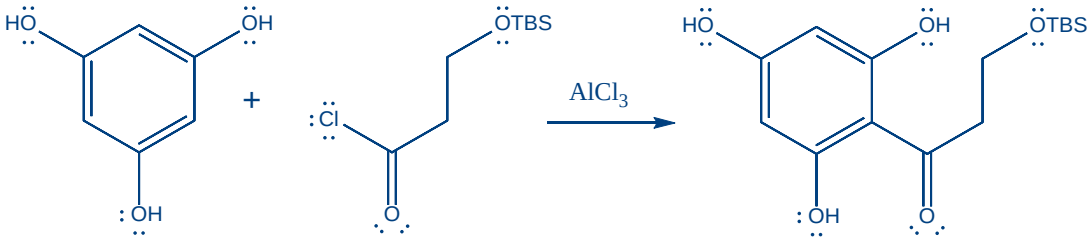


Synthetic Proposal

1. Make acid chloride (with protected alcohol at other end to generate "X" from later).



2. Attach chain to aromatic ring using Friedel-Crafts reaction.



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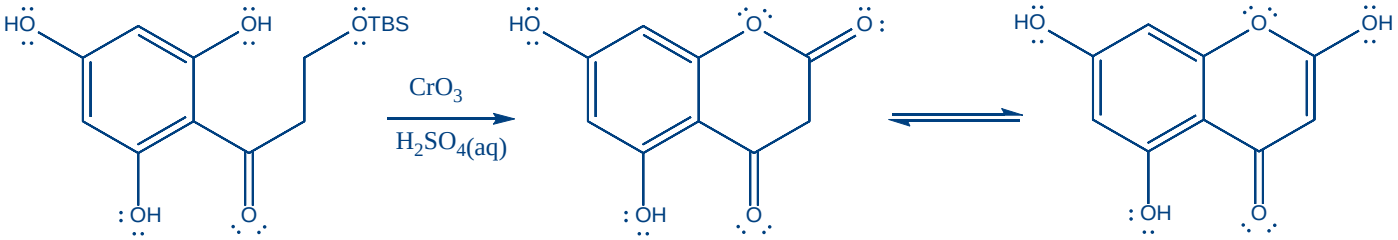
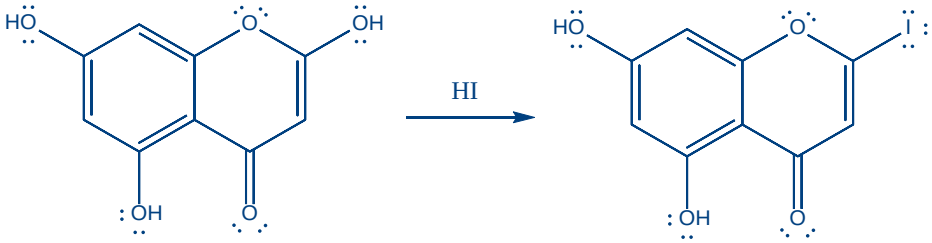
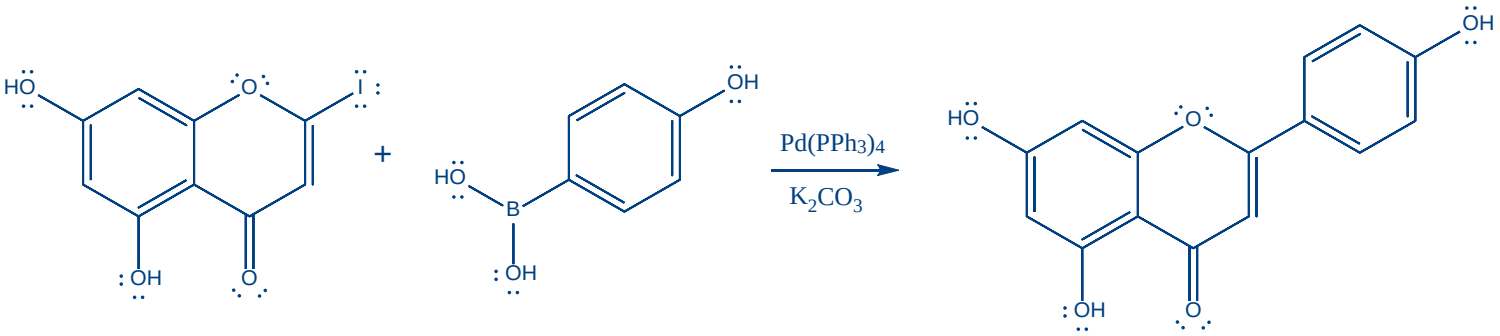
3. Remove protecting group and oxidize alcohol to carboxylic acid. Phenol and carboxylic acid ought to spontaneously form a lactone (cyclic ester) that can tautomerize as shown below.



4. Convert OH into Br or I.



5. Make final product via Suzuki coupling.



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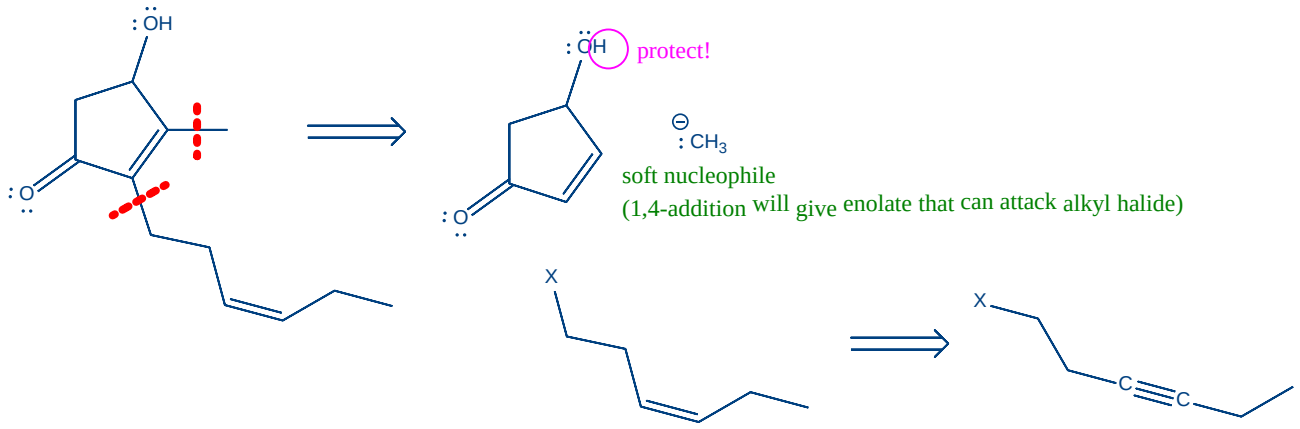
8. *continued…* *[10 marks]*

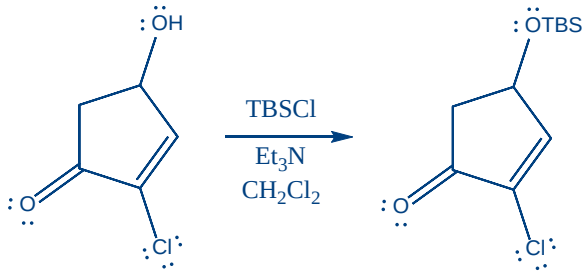
Third Retrosynthesis and Synthetic Proposal

Retrosynthetic Analysis

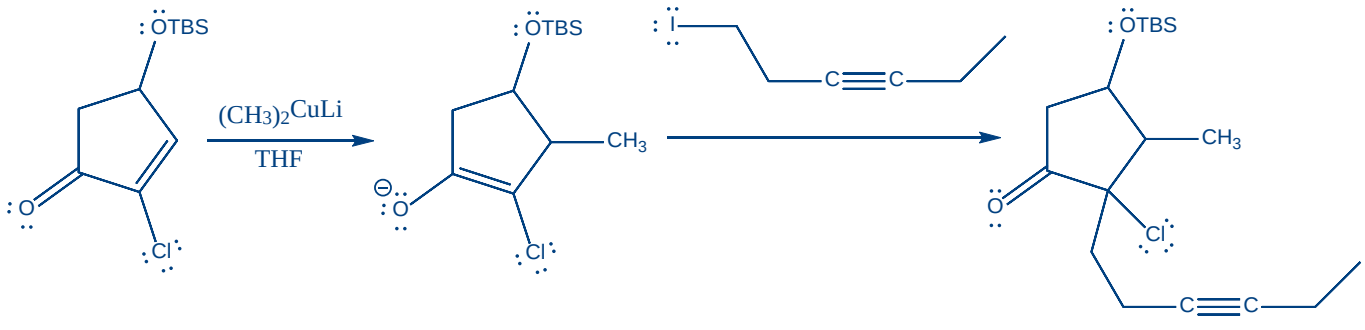


Synthetic Proposal

1. Protect alcohol. (Cl atom was added to starting material generated in retrosynthesis so that an elimination reaction could regenerate the double bond that would be lost in the 1,4-addition but is present in the product. Because Cl is attached to a trigonal planar carbon atom, S_N2 reactions at that site should not compete.)



2. Do 1,4-addition, adding alkyl iodide to resulting enolate (instead of working up immediately with water).



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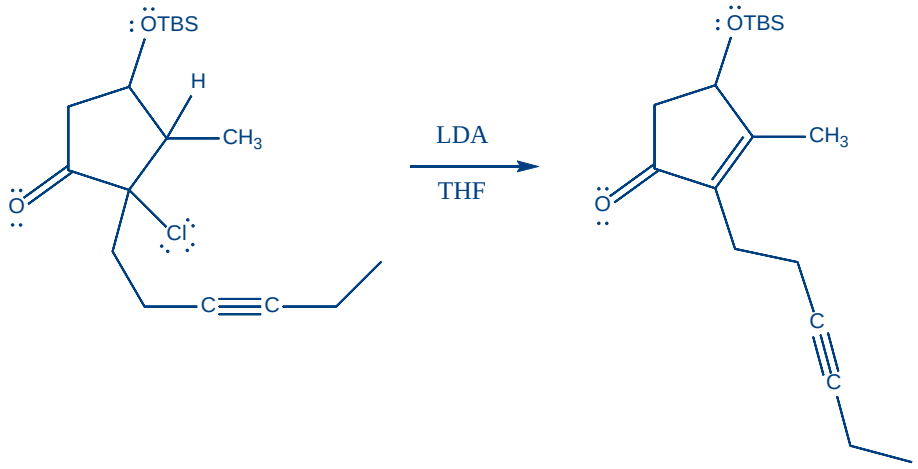
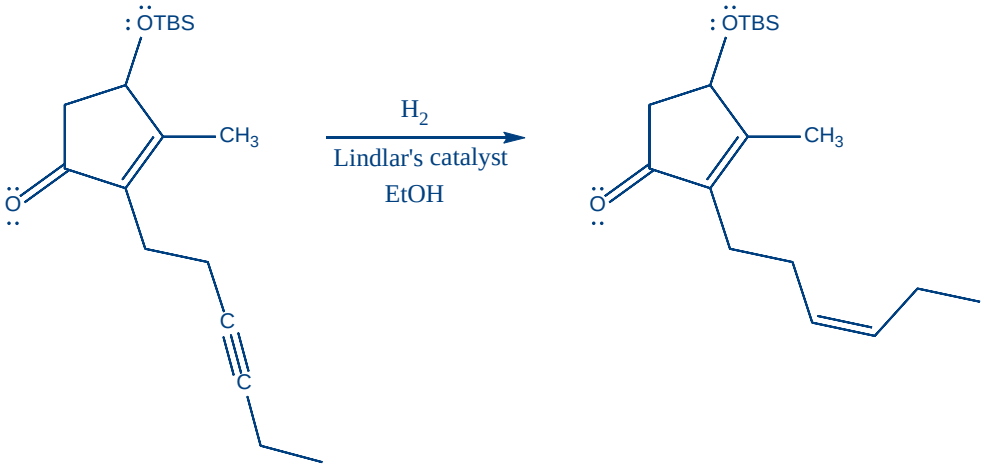
3. Eliminate HCl to regenerate double bond in ring (gives double bond conjugated to C=O; endocyclic double bond is favoured over exocyclic)/



4. Hydrogenated triple bond using poisoned catalyst (to stop at double bond and preserve alkene).



5. Remove protecting group.