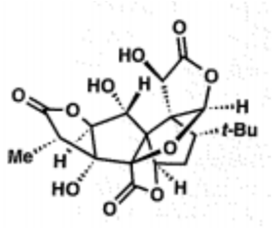
CHEM 4000A: Mechanistic Assignment

13 + 11 + 16 = 40 marks total
Due by 5pm on Thursday, February 29th, 2024

You will likely find it easiest to draw your mechanisms by hand (though you can use a program like ChemDraw if you like). The written parts of your answers can either be hand written or typed. As long as I can read them. ☺

Do not take "short cuts" showing protonation or deprotonation steps that can't actually happen because the basic site can't reach the acidic hydrogen. (Be warned that some textbooks, etc. have this very bad habit because it saves them space.) You may, however, abbreviate parts of the molecule not involved in the reaction as R groups (as I did in Figure 3). Also, please remember to show all lone pairs!

Extracts from leaves of the *Gingko biloba* tree are widely used in traditional medicine in various parts of Asia. The search for the biologically active molecules in these extracts led to the discovery and identification of a family of terpenes now called the ginkgolides. The structure of ginkgolide B is shown below. The first synthesis of (±)-ginkgolide B (**1**) was published in 1983 by the E.J. Corey research group at Harvard.



1: ginkgolide B

The questions on this assignment pertain to reactions in the earlier steps of this synthesis of (±)-ginkgolide B.[1]

1. The synthesis of one of the necessary intermediates begins with reaction between an enamine and an aldehyde, as shown in Figure 1.

(a) How would you prepare enamine **2** from morpholine and one other organic reactant? Draw both organic reactants and identify any other reagents required for this reaction. **[2]**
Most 2nd year organic texts have a section on the preparation of reactions of enamines.

(b) Draw a valid mechanism for the preparation of intermediate **4** from enamine **2** and aldehyde **3**. **[1]**

(c) Draw a valid mechanism for the conversion of intermediate **4** into α,β-unsaturated ketone **5**. **[10]**
You will probably find it easiest to write the acid as H_3O^+. *There are three distinct tasks to be accomplished in this reaction so don't try to cram everything into a couple of steps!*

2. Reaction of an organocuprate with α,β-unsaturated ketone **5** followed by addition of trimethylsilylchloride $(TMSCl = (CH_3)_3SiCl)$ gives silyl enol ether **7**, as shown in Figure 2.

(a) Predict the structure of intermediate **6** of this reaction. Show the mechanism for the conversion of **5** to **6**. **[2]**

(b) There are two electrophilic sites in **5**. Identify both, and explain why the nucleophile selectively reacts with one of them. **[4]**

(c) Draw a valid mechanism for the conversion of **6** to **7**. **[1]**

(d) There are two nucleophilic sites in **6**. Identify both and explain why the electrophile selectively reacts with one of them. **[4]**

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[1] Nicolaou, K.C.; Sorensen, E.J. *Classics in Total Synthesis*, VCH, Weinheim (Germany), **1996**, pp.451-464.

3. Later in the synthesis, a palladium-catalyzed coupling reaction similar to the Suzuki is used to attach an alkyne to the prepared ring system. The resulting alkyne (**8**) is then converted to an alkene and deprotected to give carboxylic acid **10**, as shown in Figure 3.

(a) A hydroboration reaction is used to exclusively generate the *cis*-alkene. Why is only one stereoisomer formed in this reaction? **[1]**

(b) When you studied hydroborations in CHEM 2500, you saw that hydroboration-oxidation reactions can be used to produce alcohols. Why don't you get an alcohol in this hydroboration reaction? **[1]**

(c) Suggest one other reaction that could be used to convert an alkyne stereospecifically to a *cis*-alkene. Clearly identify any required reagents. **[2]**

(d) Propose a valid mechanism for the acid-catalyzed transformation of compound **9** into carboxylic acid **10**. *The original synthesis switches from acidic conditions to basic conditions and back again, presumably to improve yield; however, it is possible to propose a reasonable mechanism for the whole process in aqueous acid (on paper, at least).* **[12]**

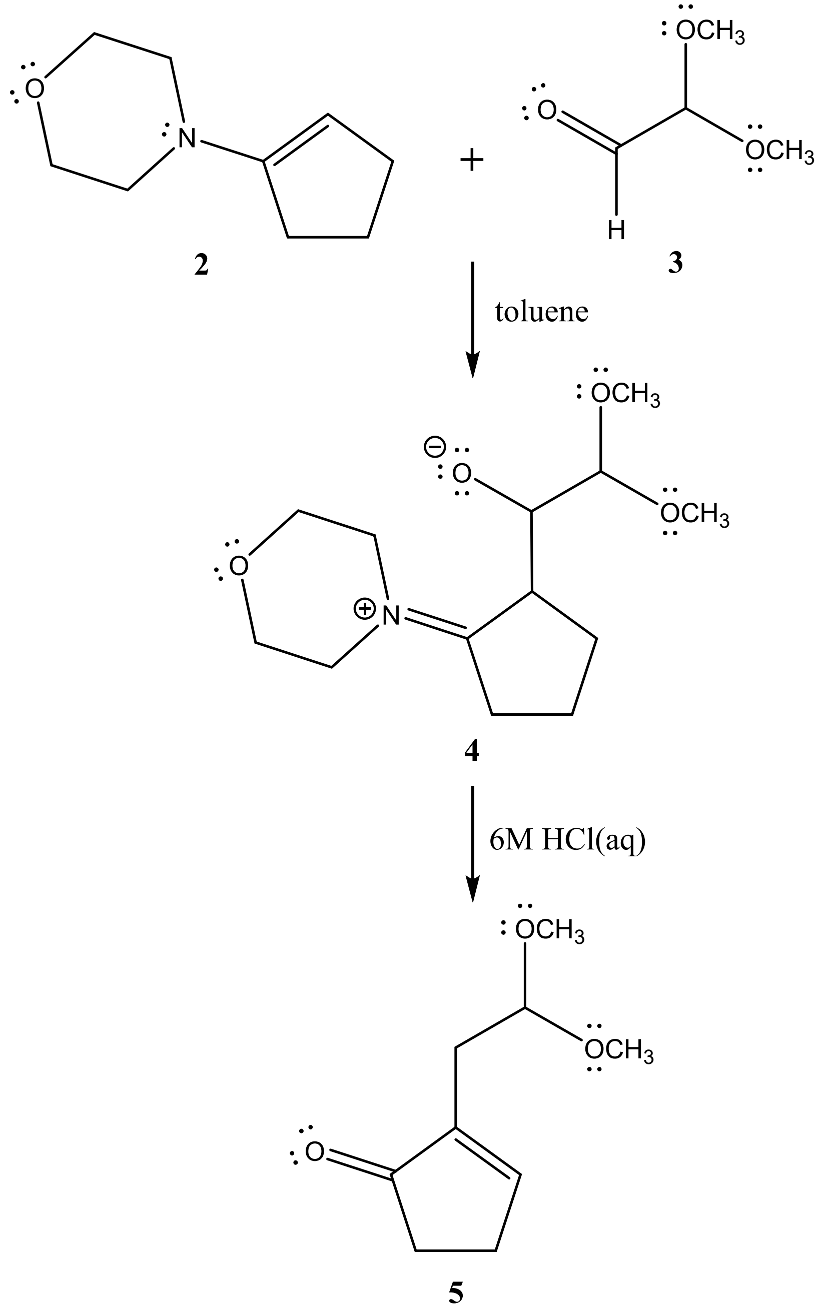

Figure 1: Synthesis of α,β-unsaturated ketone **5** from enamine **2** and aldehyde **3**

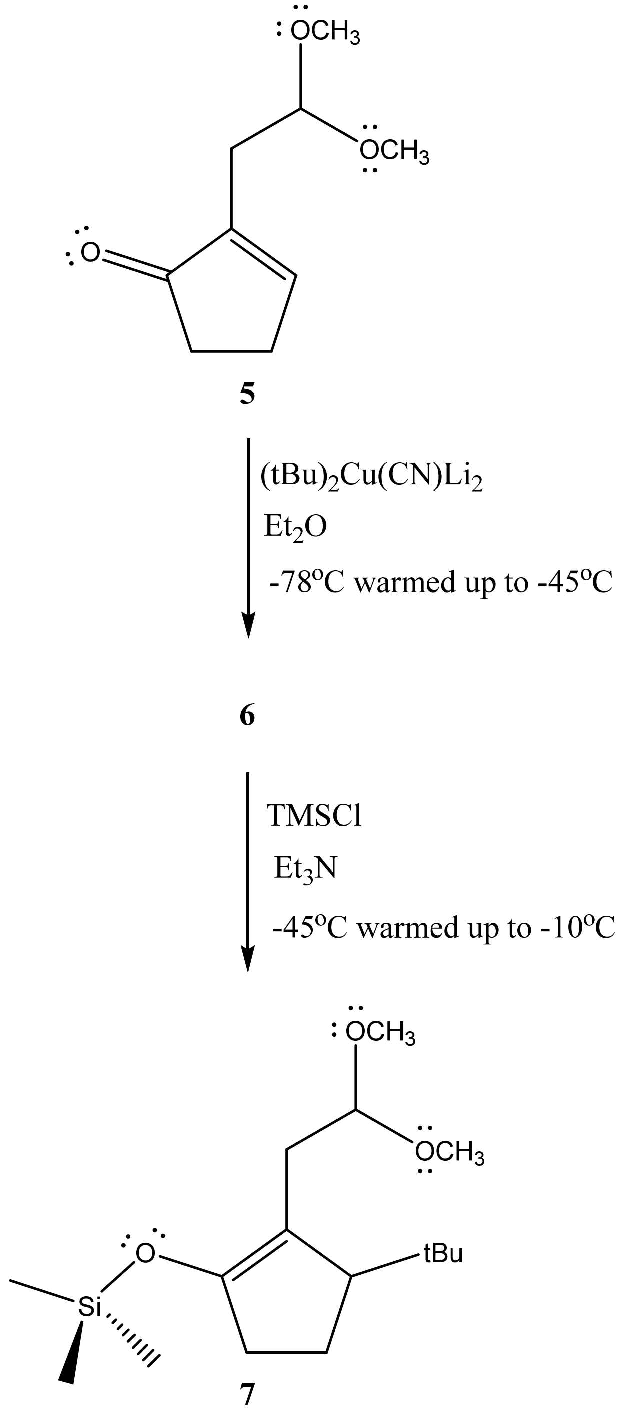

Figure 2: Synthesis of silyl enol ether **7** from α,β-unsaturated ketone **5**

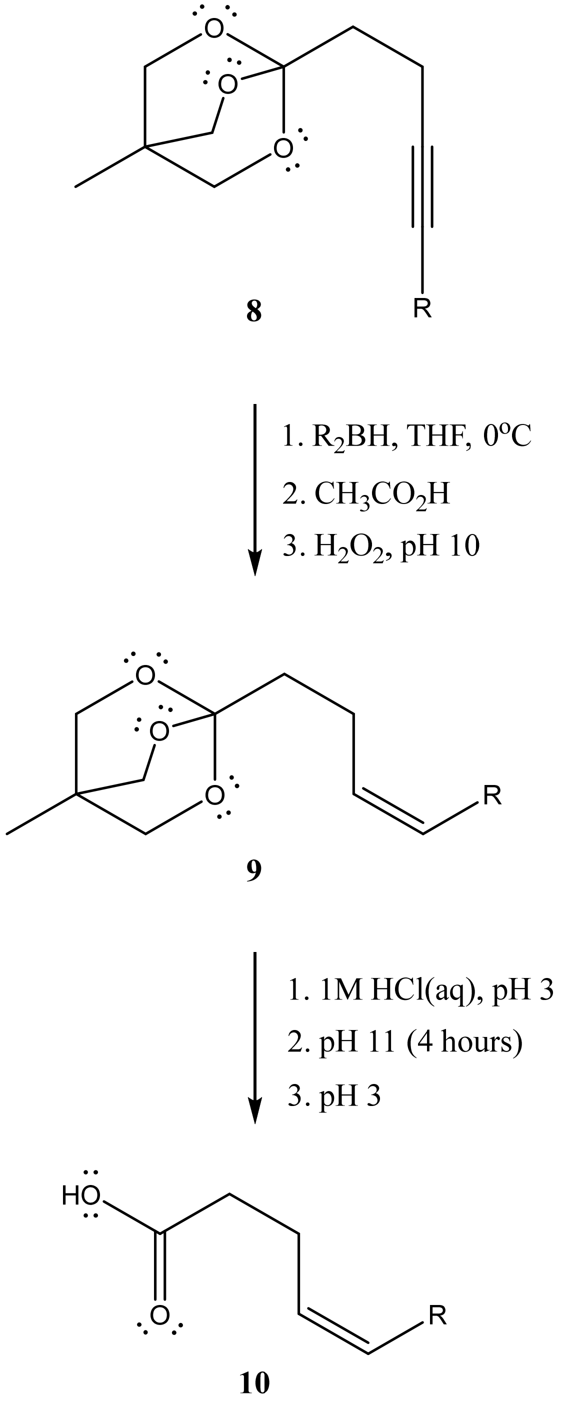

Figure 3: Synthesis of alkene **10** from alkyne **8**