CHEM 4000A: Mechanistic Assignment

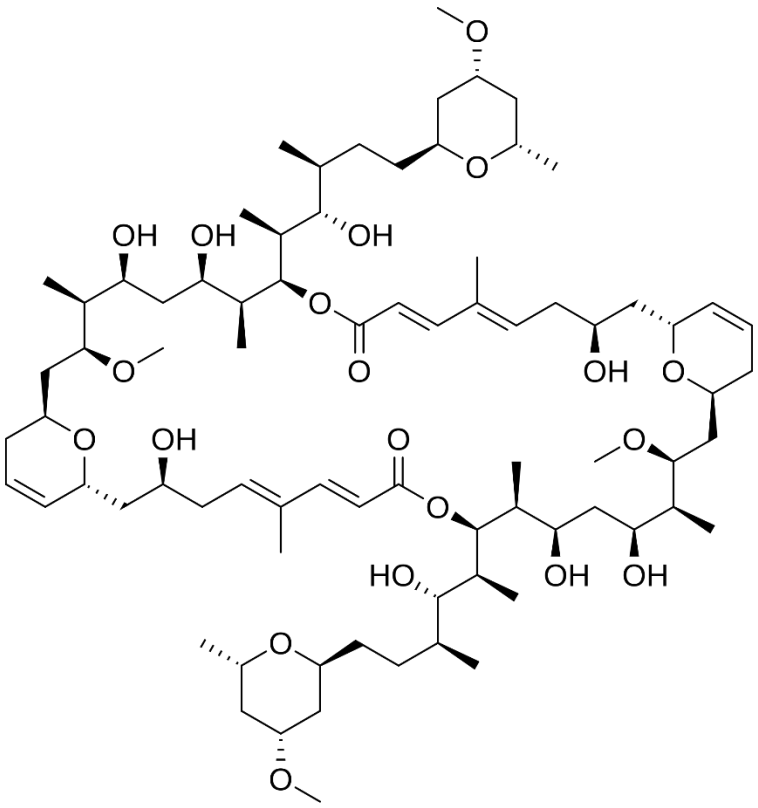
9 + 7 + 20 + 8 + 9 + 15 = 68 marks total

Due at 11:59pm on Friday, October 31st, 2025 (submit via Crowdmark)

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 Question 6). Also, please remember to show all lone pairs!

Swinholide A is one of many biologically active molecules found in *Theonella swinhoei*, a sponge found in the Red Sea. It has been shown to have antifungal activity and was of interest for potential chemotherapeutic activity. The structure of swinholide A is shown below. The first total synthesis of this compound was published in 1994 by the Ian Paterson research group at Cambridge.



The questions on this assignment pertain to reactions in the earlier steps of this synthesis of swinholide A.[1]

At no point in this assignment will you be asked to draw the whole molecule.

[1] Nicolaou, K.C.; Sorensen, E.J. *Classics in Total Synthesis II*, VCH, Weinheim (Germany), **2003**, pp.31-74.

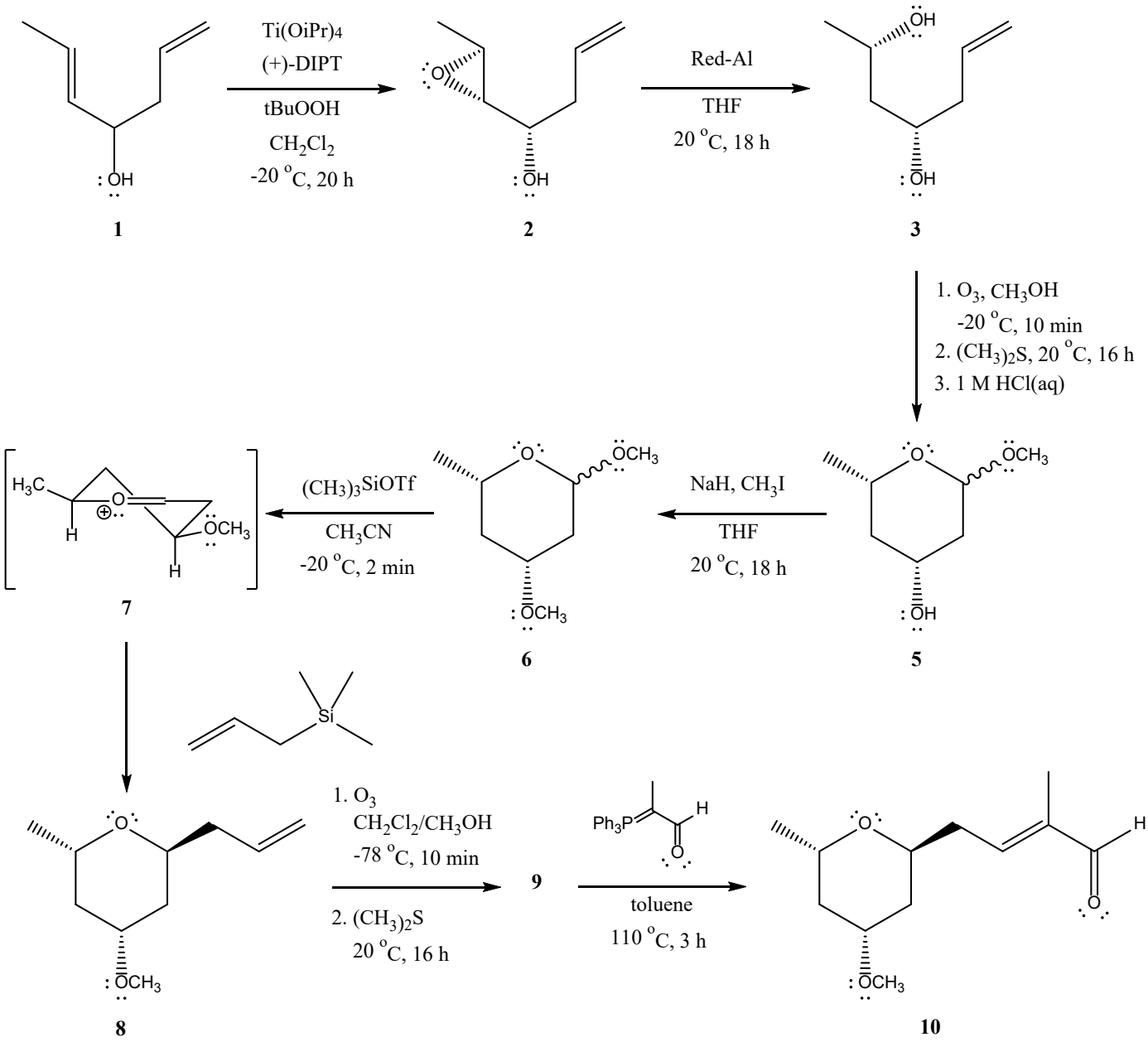

Ti(OiPr)4
(+)-DIPT
tBuOOH
CH2Cl2
-20 °C, 20 h
Red-Al
THF
20 °C, 18 h
1
2
3
1. O3, CH3OH
-20 °C, 10 min
2. (CH3)2S, 20 °C, 16 h
3. 1 M HCl(aq)
NaH, CH3I
THF
20 °C, 18 h
(CH3)3SiOTf
CH3CN
-20 °C, 2 min
5
6
7
1. O3
CH2Cl2/CH3OH
-78 °C, 10 min
2. (CH3)2S
20 °C, 16 h
9
toluene
110 °C, 3 h
8
10

Figure 1

1. As shown in Figure 1, a Sharpless epoxidation was used to convert **1** into **2**.

(a) Compound **1** contains two alkenes but only one of them is converted into an epoxide. What is the key difference between these two alkenes that leads to this difference in reactivity? **[2]**

(b) Epoxide **2** is produced with an enantiomeric excess (ee) of 96%. That means that 98% of the **2** produced was the enantiomer shown while only 2% was the opposite enantiomer. $(98\% - 2\% = 96\%\ ee)$

Which of the reagents is responsible for this enantioselectivity? **[1]**

(c) The yield of this reaction was only 43%; however, because this was a kinetic resolution, that was considered quite good. Explain why, in this context, a sub-50% yield is expected. Your answer should explain what a kinetic resolution is and include structures for all relevant reactants/products. **[6]**

2. Epoxide **2** was reduced to alcohol **3** using Red-Al, a reagent similar to $LiAlH_4$. Propose a reasonable mechanism for this reaction if it had been performed using $LiAlH_4$ followed by workup with aqueous acid. *Hint: You may wish to review the mechanism for reduction of a carboxylic acid by $LiAlH_4$ that we saw in a recent problem set. As in that mechanism, you should plan to use $LiAlH_4$ twice (though this time it makes sense to use the same molecule twice instead of using two different ones).* **[7]**

3. Reaction of alcohol **3** with ozone followed by addition of dimethylsulfide gives compound **4** which is then treated with aqueous acid to give compound **5**.

(a) Draw the structure of compound **4**. **[1]**

(b) Propose a reasonable mechanism for the reaction of **4** with acid to give **5**. Since it was the solvent for the first step in this three-step process, methanol is still present in solution. **[13]**

(c) The drawing of **5** corresponds to two different compounds. Draw them both. Why is it not a problem that **5** exists as a mixture? *Hint: Look at later steps in the synthesis.* **[3]**

(d) Reaction of **5** with NaH and CH_3I gives **6**. Propose a reasonable mechanism for this reaction. **[3]**

4. Compound **8** is converted into compound **9** which is then converted into compound **10**.

(a) Draw the structure of compound **9**. **[1]**

(b) Propose a reasonable mechanism for the conversion of **9** into **10** as shown in Figure 1. **[5]**

(c) Why does the alkene in **10** have an *E* configuration? **[2]**

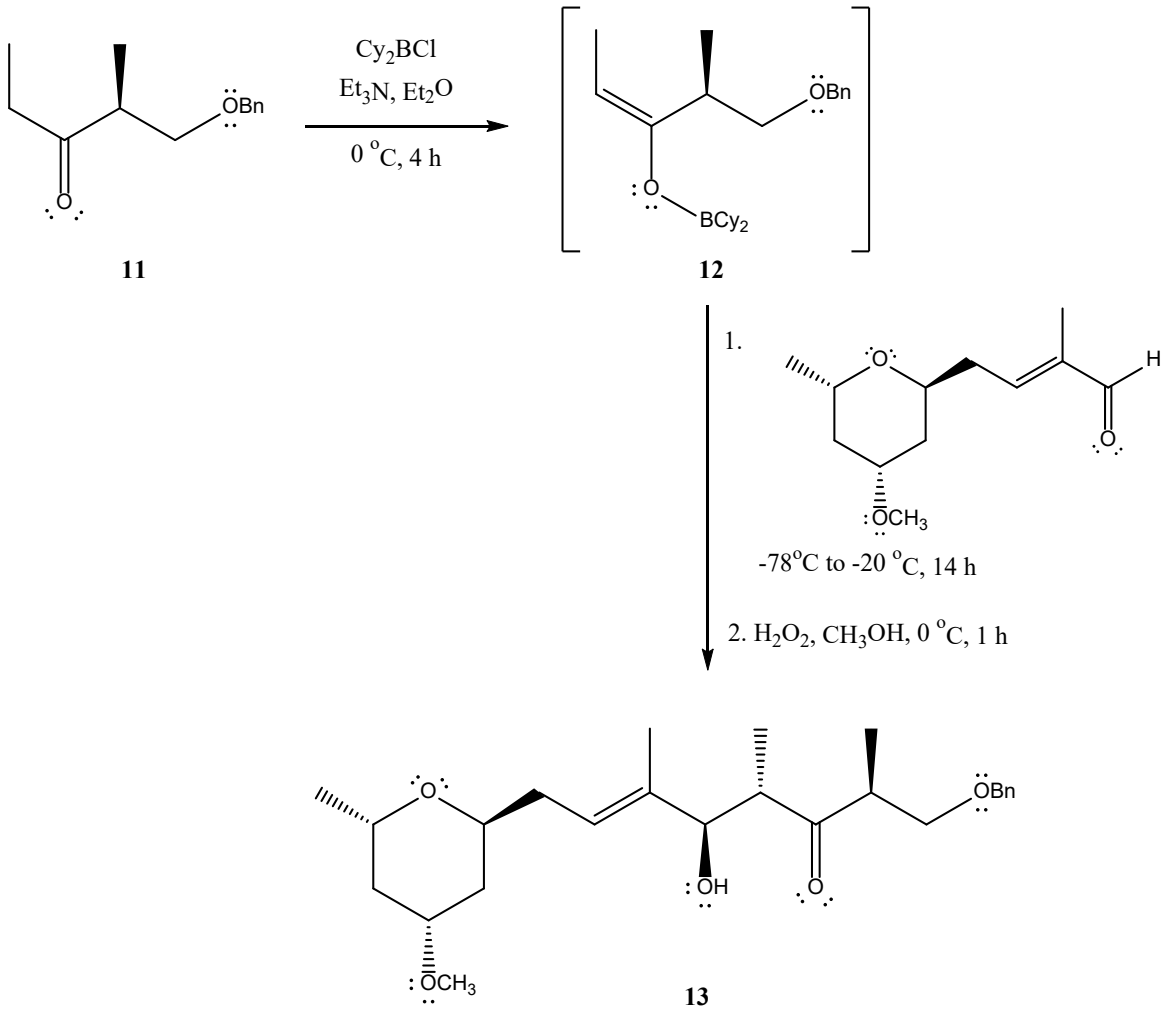


Figure 2

5. Figure 2 shows preparation of boron enolate **12** which is then reacted with compound **10** to give synthetic intermediate **13**.

(a) Propose a reasonable mechanism for formation of **12** from **11** as shown in Figure 2. **[3]**

(b) Propose a reasonable mechanism for reaction between **10** and **12** to give **13**. **[3]**
You are not expected to show how the hydrogen peroxide reacts with the boron-containing by-products.

(c) Explain why a 1,2-addition is observed rather than a 1,4-addition. Your answer must address both the nucleophile and electrophile. **[3]**

6. Synthetic intermediate **13** undergoes several more reactions to produce a primary alcohol which we will call RCH_2OH. This alcohol is subjected to a Swern oxidation. Draw the mechanism and product for Swern oxidation of RCH_2OH. **[15]**