Mechanistic Assignment
CHEM 4000A – Medicinal Chemistry
Due at 4:00pm on Friday, March 1st, 2019

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.)

Several derivatives of (±)-$\Delta^{9(12)}$-capnellene (**13**) have shown potential as chemotherapeutic agents. The last three pages of this assignment show Curran's synthesis of (±)-$\Delta^{9(12)}$-capnellene from (±)-norbornenone (**1**).[1] The numbers in the questions below refer to the labeled structures on those diagrams.

1. In the first step of the synthesis, Curran (or, more likely, his graduate student) uses a Baeyer-Villiger reaction to insert an oxygen atom into one of the rings in norbornenone, converting ketone **1** to lactone **2**.

(a) Show the mechanism for this reaction. *Most 2nd year organic texts include the Baeyer-Villiger reaction.*

(b) When this reaction was originally developed, there was concern about a possible side reaction (which, fortunately, turned out to be less favoured than the Baeyer-Villiger reaction for this family of molecules). Which other functional group in norbornenone might you expect to react with a peracid, and what would the expected product be for this undesired side reaction?

2. In the second step of the synthesis, an acid-catalyzed rearrangement converts lactone **2** into lactone **3**. Propose a reasonable mechanism for this acid-catalyzed rearrangement. Comment on the stability of any intermediate carbocations.

Hint: Start by protonating the carbonyl. You will probably also find it helpful to number the carbon atoms.

3. In the third and sixth steps of the synthesis, a copper(I) catalyst is used to promote reaction with a Grignard reagent.

(a) Propose a reasonable mechanism for the reaction of **3** with $(CH_3)_2CuMgBr$ to give **4**. You may assume work-up with aqueous acid.

(b) What is the role of the copper(I) catalyst in this reaction? What could happen if **3** were reacted with CH_3MgBr without the addition of the catalyst?

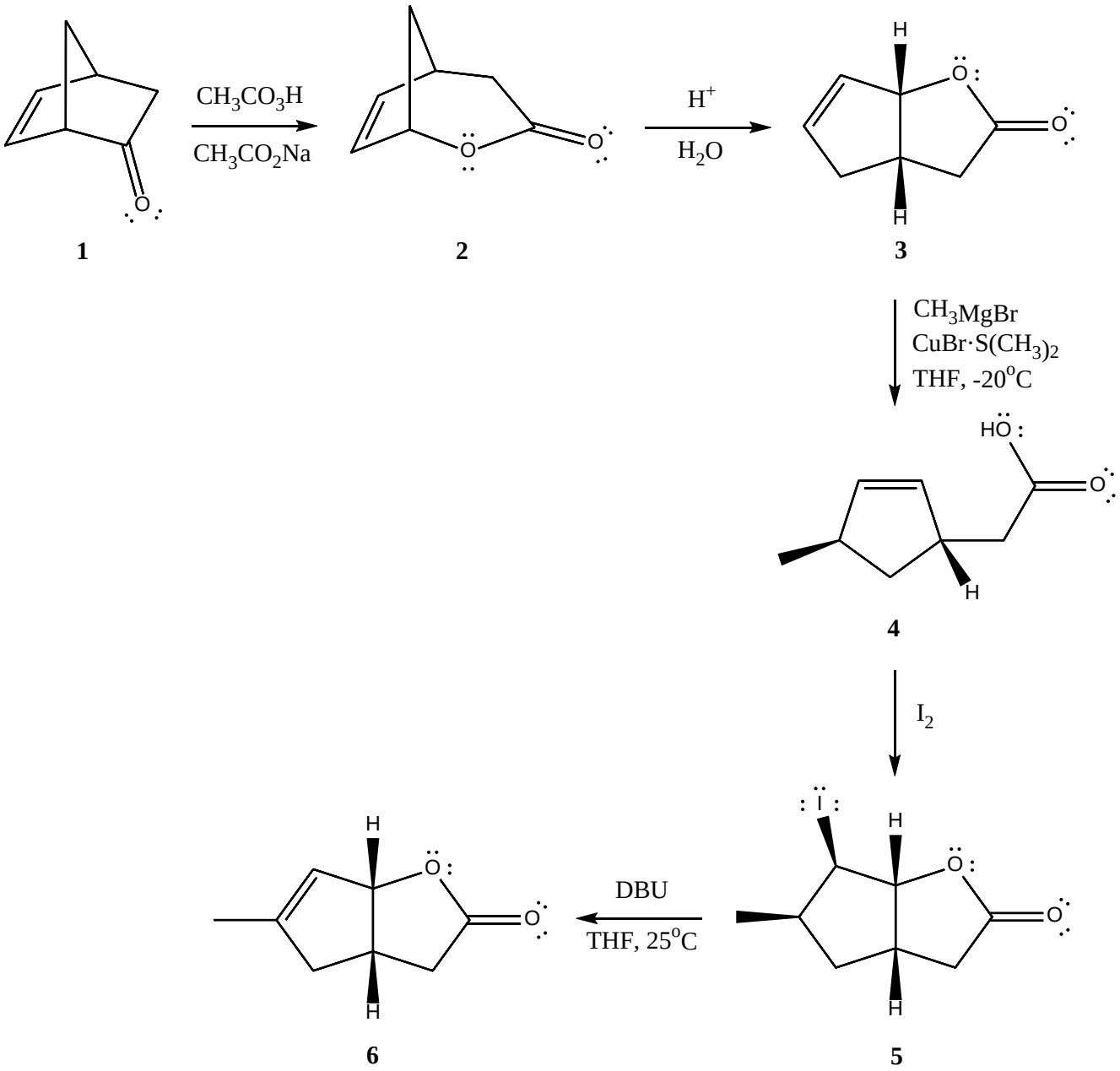
4. An iodolactonization reaction is used to convert **4** into **5**. Use the mechanism for this reaction to demonstrate why only one stereoisomer of **5** can be produced.

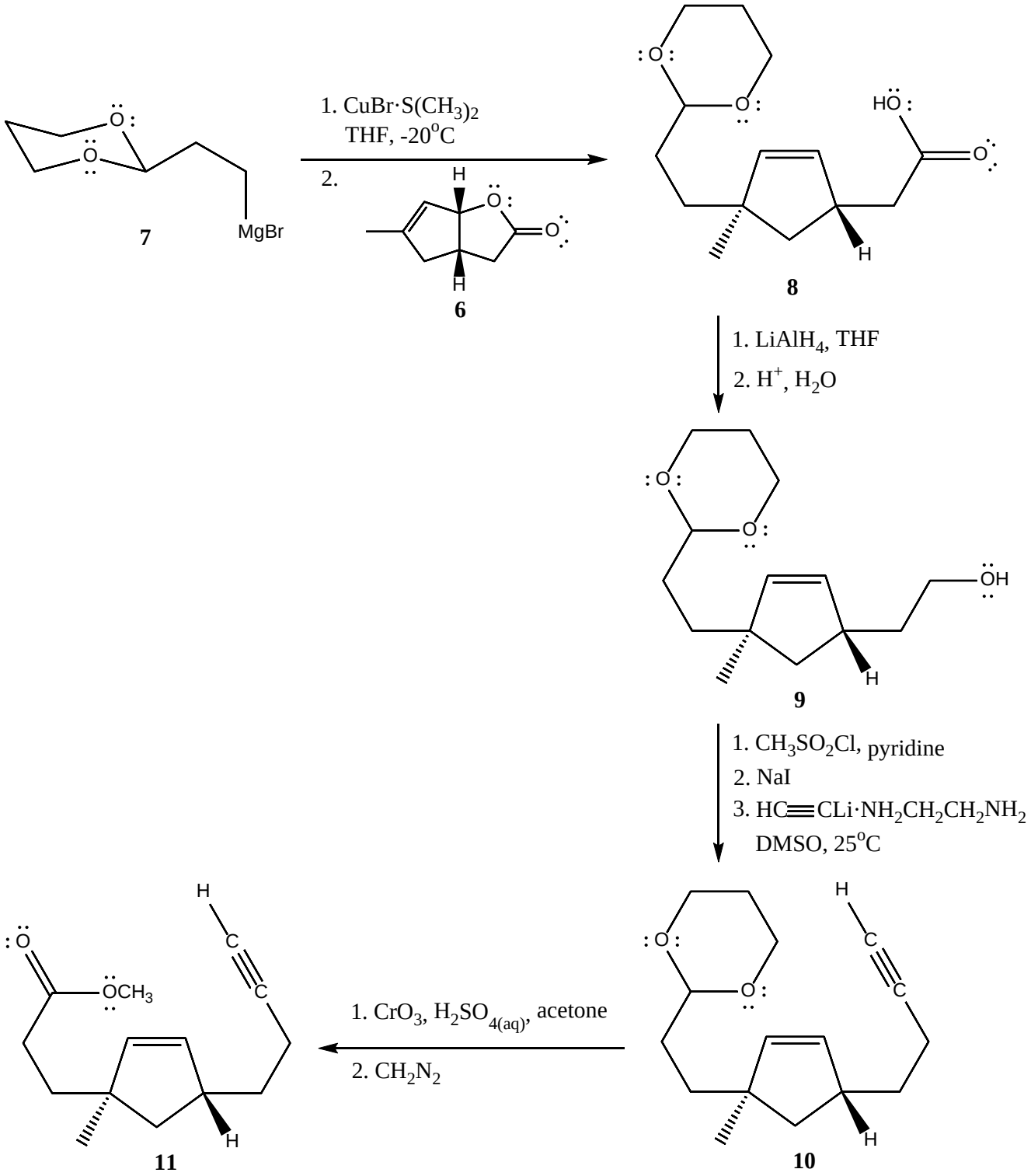
5. DBU stands for 1,8-diazabicyclo[5.4.0]undec-7-ene which is a non-nucleophilic amine base. Briefly explain why only one regioisomer is produced when HI is eliminated from **5**. In other words, why does the double bond only form in one position? *You may abbreviate the base as* R_3N.

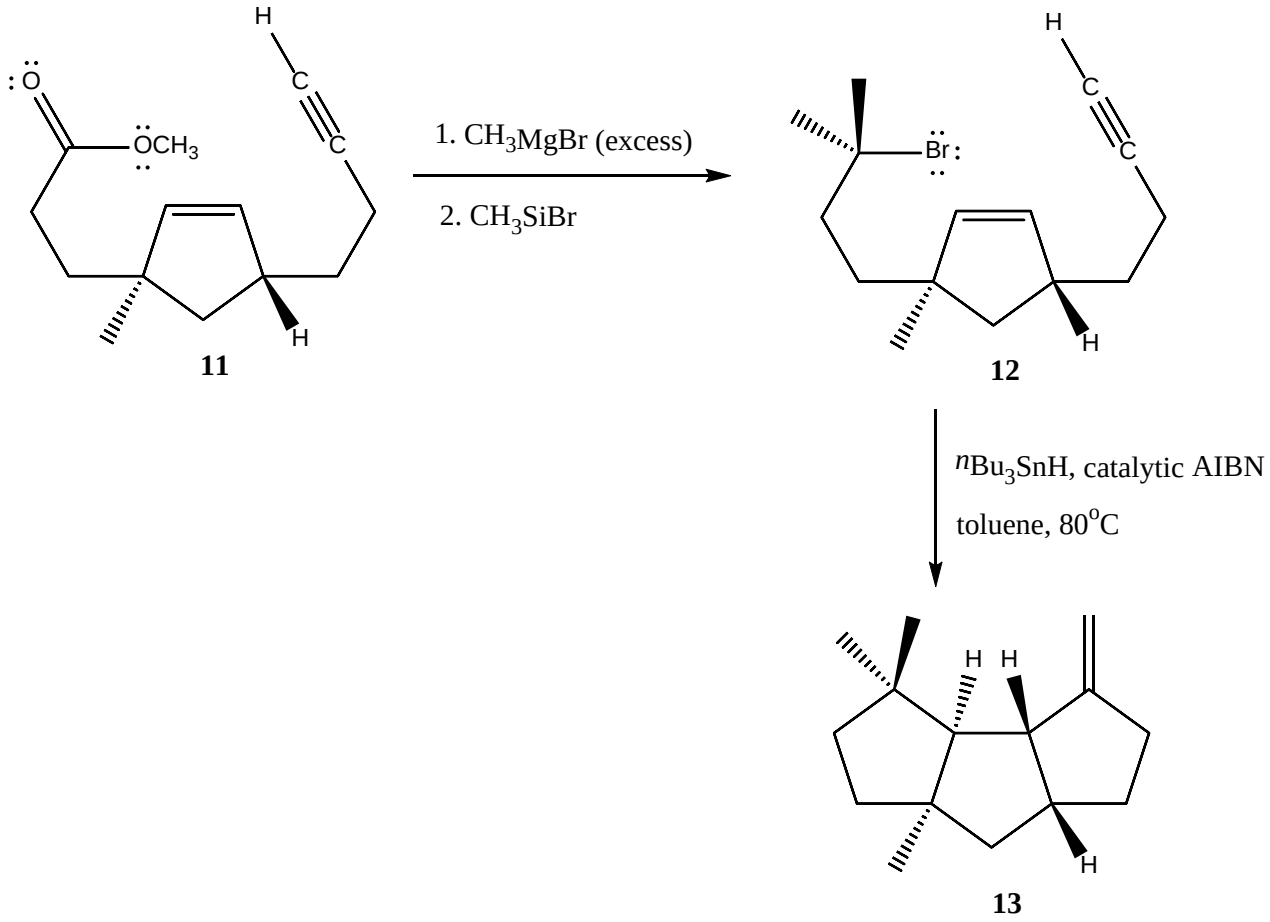
6. Many steps are bundled together over each arrow for the production of **11** from **9**. Expand each of these reaction sequences, showing the product of each numbered step starting with compound **9** and ending with compound **11**. The $CrO_3/H_2SO_{4(aq)}$ step involves two sequential reactions; please show the product of each (with the first one in square brackets to indicate that it's not the final product).

You do <u>not</u> need to show the mechanisms for the reactions in this question.

[1] Nicolaou, K.C.; Sorensen, E.J. *Classics in Total Synthesis*, VCH, Weinheim (Germany), **1996**, pp.413-416.


CH3CO3H
CH3CO2Na
H+
H2O
CH3MgBr
CuBr·S(CH3)2
THF, -20°C
I2
DBU
THF, 25°C
1
2
3
4
5
6


1. CuBr·S(CH3)2
THF, -20°C
2.
7
MgBr
6
8
1. LiAlH4, THF
2. H+, H2O
9
1. CH3SO2Cl, pyridine
2. NaI
3. HC≡CLi·NH2CH2CH2NH2
DMSO, 25°C
10
1. CrO3, H2SO4(aq), acetone
2. CH2N2
11



11 **12** **13**

The last reaction is a radical tandem cyclization. Its mechanism is beyond the scope of this course. But it looks pretty cool!