Midterm 2 – Chem 3A, Fall 2020

Monday, 10/26/2020 5 pm – Tuesday 10/27/2020 5 pm

Time limit: = **120 minutes** from when the file is accessed on the Gradescope site

Technology problems when submitting the exam? (Wi-fi, scanning, uploading, power outages, etc.)
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Academic Integrity:
I acknowledge the following academic integrity guidelines for this exam:

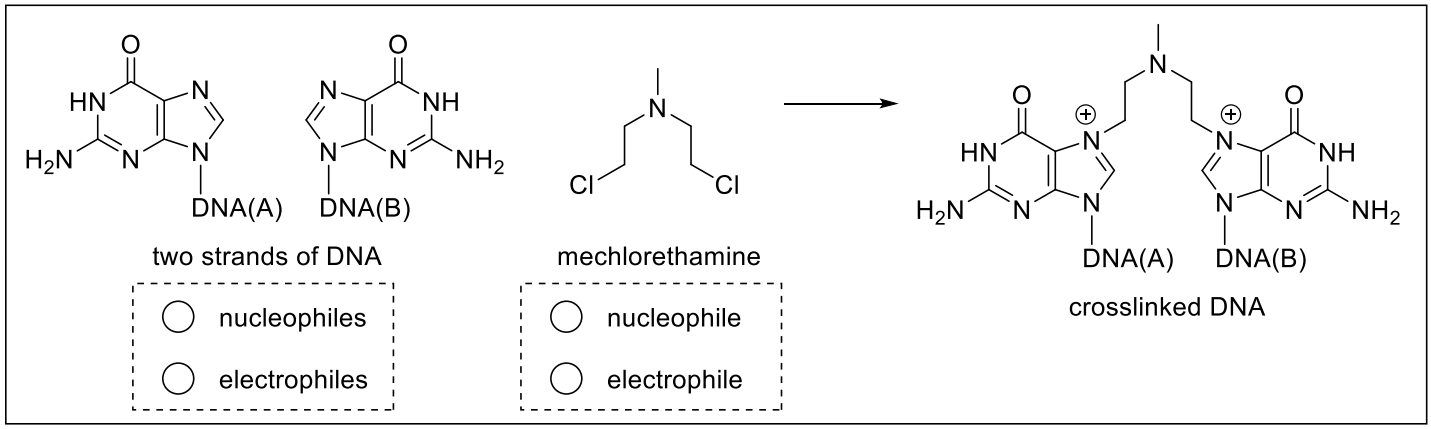
- If I submitted an "Exam Notes" assignment on bCourses for this exam, I **AM** allowed to use those notes for this exam. I am **NOT** allowed to use any other notes or resources during the exam (including materials posted on the course website or ANY other websites.)
- I am **NOT** allowed to communicate about the questions or content of the exam with anyone other than Chem 3A instructors, directly or indirectly, until **9:00 am PST on Thursday, 10/29/2020.**
- I am **NOT** allowed to post files or images of any part of this exam on ANY website, even after the deadline above has passed, with the exception of the Fall 2020 Chem 3A Piazza site.

Name_____ Student ID #_____ Signature: _____

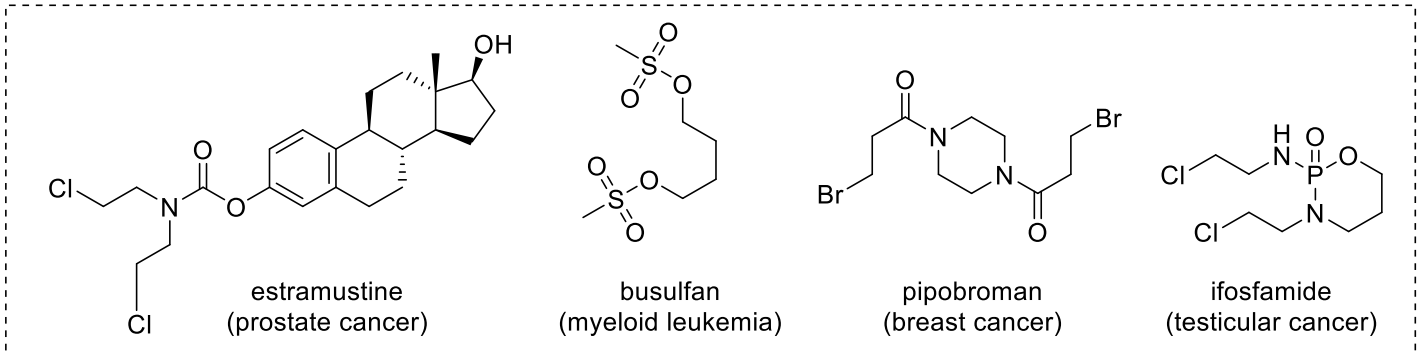
1. **Chemotherapy Drugs: DNA Crosslinking**

Many drugs have been developed to treat cancer that act as "alkylating" agents with DNA. For example, mechlorethamine reacts with guanine residues on DNA to cause crosslinking between the complementary DNA strands, blocking DNA replication and eventually leading to apoptosis.

a. Classify the **reactant roles** in the scheme below. (4 pt)



b. Each of the chemotherapy drugs pictured below could participate in a similar DNA crosslinking reaction to the one shown above with mechlorethamine. **Circle the reactive (nucleophilic or electrophilic) sites** in each drug that would participate in this crosslinking reaction. (4 pt)



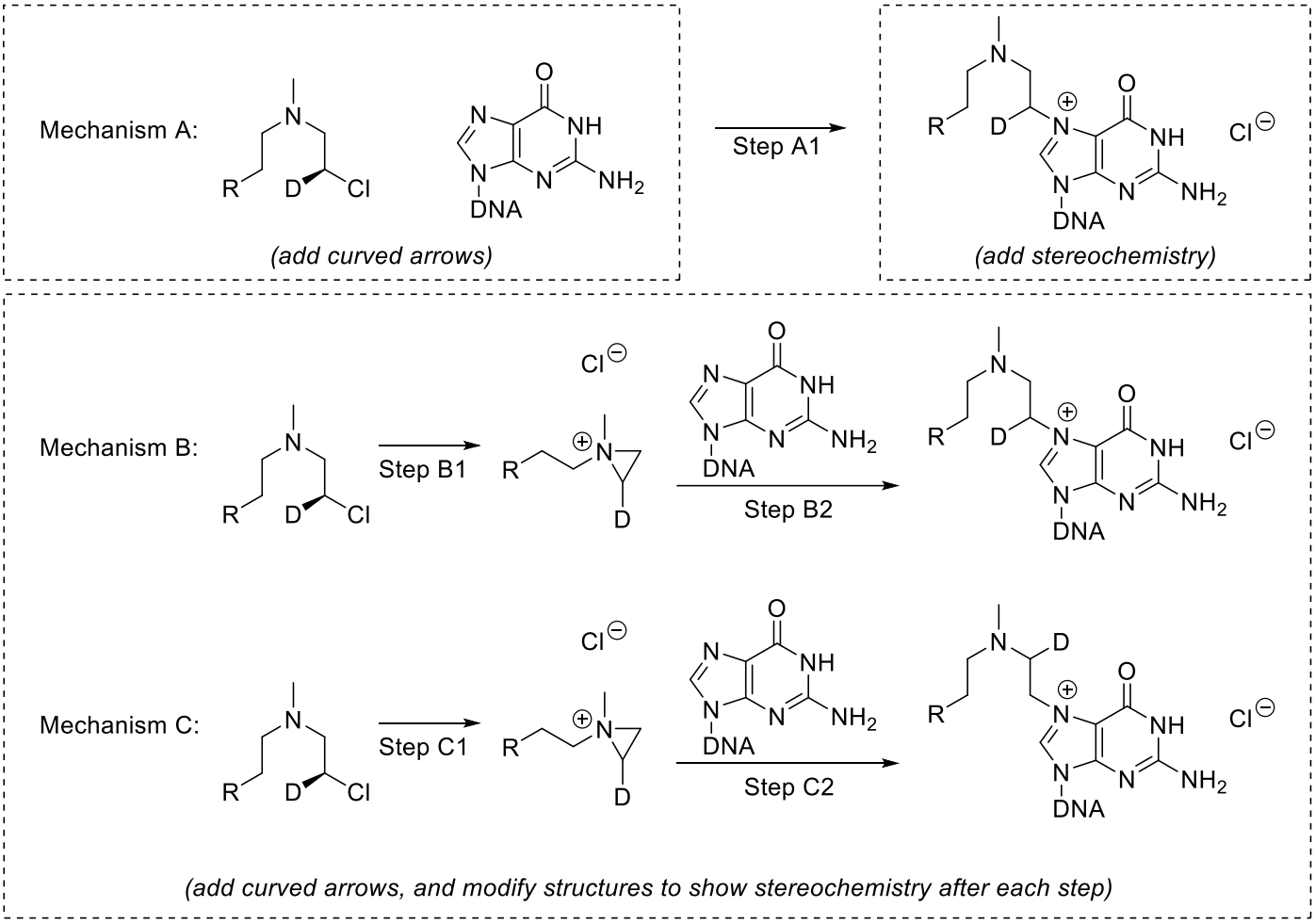
2. **DNA Crosslinking Mechanisms**

Researchers studying the mechanism of the DNA crosslinking reaction using the chemotherapy drug mechlorethamine have described cyclization to form a 3-membered ring intermediate.

a. Consider the following three possible mechanisms. All intermediates and products are shown.

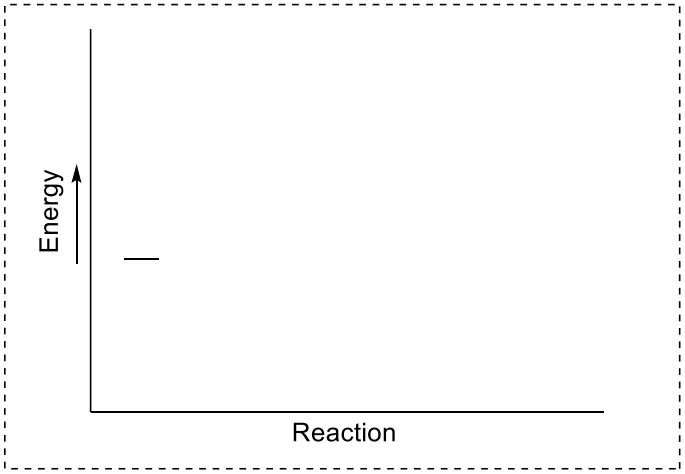
i. **Add curved arrows** to complete each mechanism. (8 pt)

ii. Modify the intermediate and product structures to show the expected **stereochemistry**. (8 pt)



b. Draw a reaction coordinate diagram comparing mechanisms A and B (from above), taking into account the following data: (8 pt)

- "Mechanism B" is faster than "Mechanism A".
- Each step in Mechanism B is favorable.
- The second step of Mechanism B is the rate-limiting step.



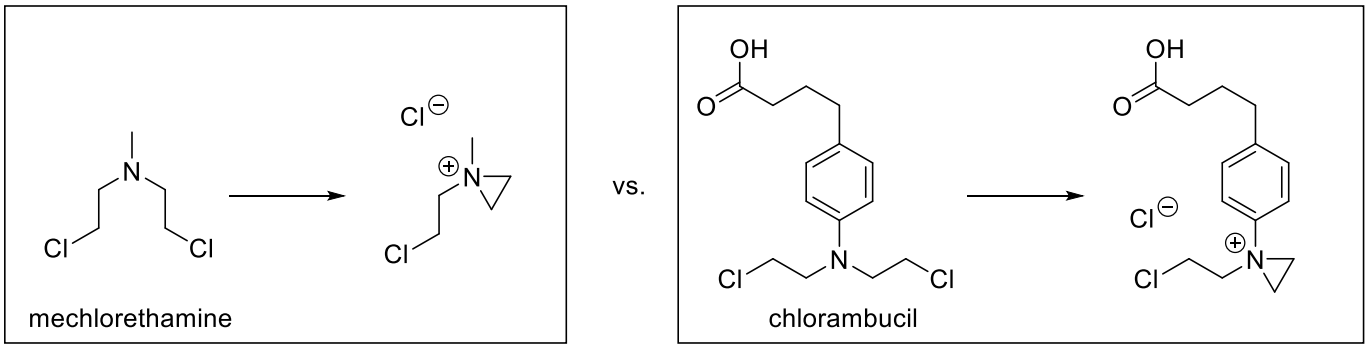
- Account for the energy/rate data described above.

- Use the same starting material line (provided) for both reaction mechanisms.

- Label the transition states with the following labels: $A1^{\ddagger}$ $B1^{\ddagger}$ $B2^{\ddagger}$

(continued from previous page)

c. The cyclization reactions of mechlorethamine and chlorambucil have significantly different energetic favorability from each other. Predict which cyclization is more favorable, and explain your prediction using pictures and a few words. (4 pt)

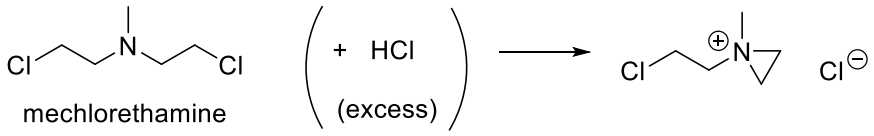


The cyclization of ◯ mechlorethamine ◯ chlorambucil is more favorable because:

(pictures and a few words)

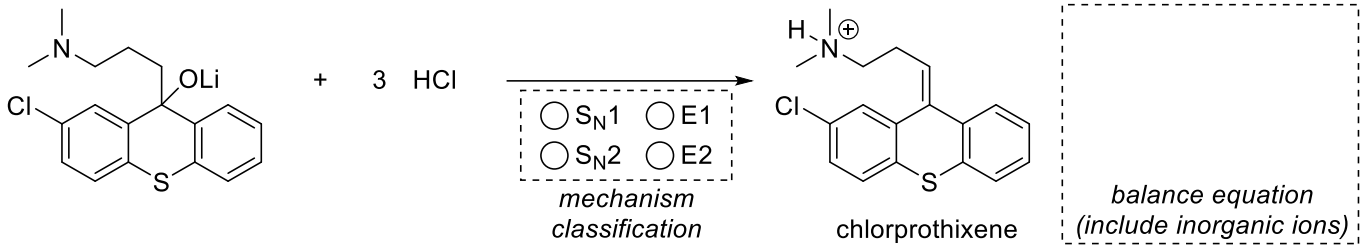
d. The presence of acids or bases can have a significant effect on the rate of a reaction. Would adding excess strong acid to the reaction mixture make the cyclization of mechlorethamine faster or slower? Use a reaction mechanism picture and a few words to explain. (4 pt)

The cyclic intermediate would form ◯ faster ◯ slower if excess HCl was added to the reaction mixture because:

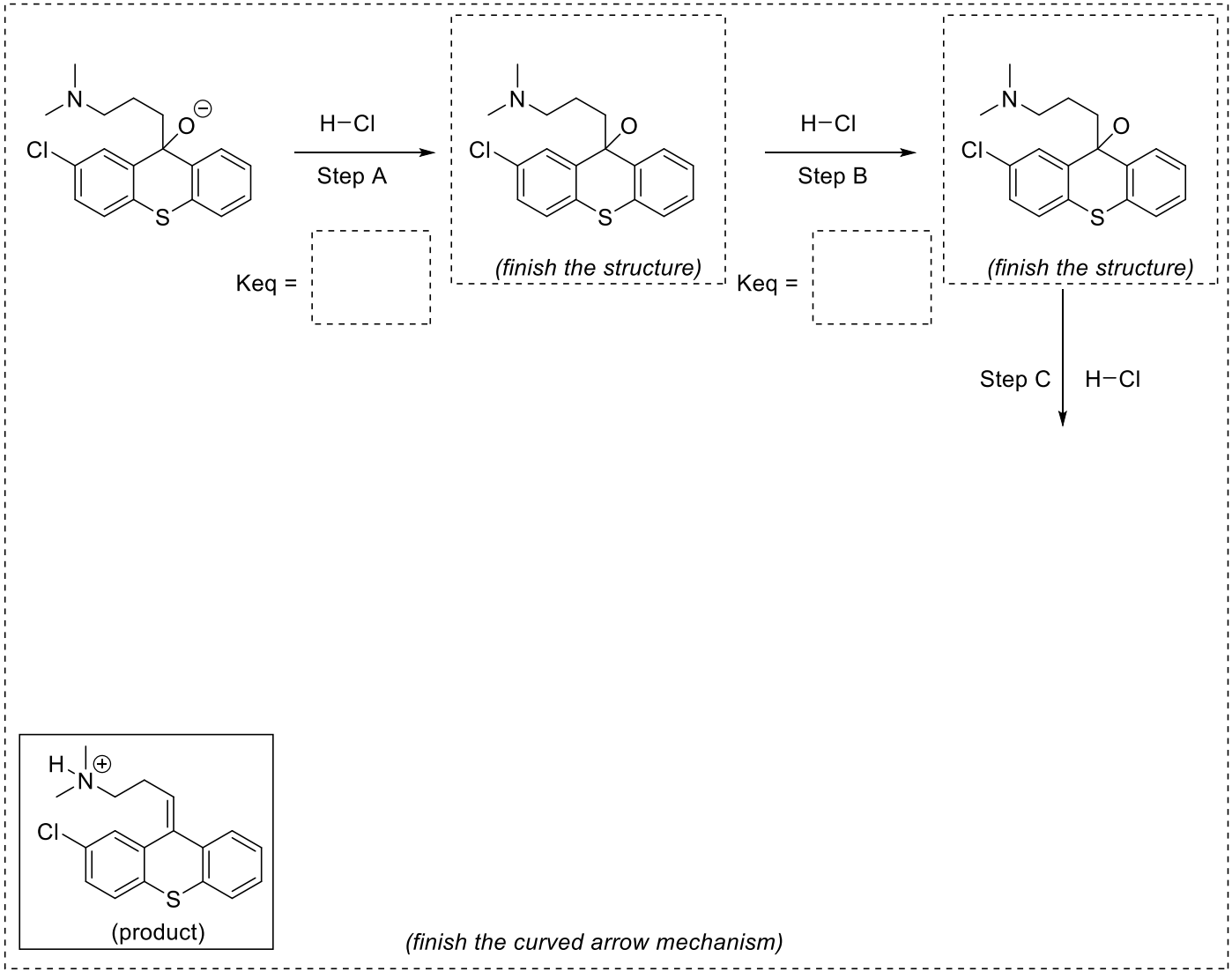


(mechanism pictures and a few words)

3. Chlorprothixene is a medication used to treat schizophrenia. One method for its synthesis ends with the reaction shown below.
   a. Classify the reaction mechanism (multiple choice). (2 pt)
   b. Fill in the box on the product side to balance the equation, taking into account the HCl stoichiometry shown (3 equivalents of HCl). (2 pt)



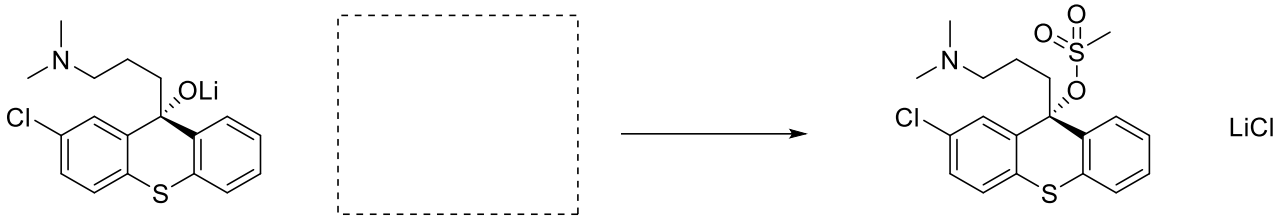
   c. **The mechanism of the reaction above begins with three sequential acid-base steps.** (6 pt)
      i. Assuming the acid-base steps take place in order of reactivity (the most basic site protonated first, etc.), **add hydrogens and formal charges to finish the structures** of the intermediates.
      ii. Add **curved arrows** for each acid-base step.
      iii. Calculate the **equilibrium constants** for Steps A and B.
   d. Finish drawing the reaction mechanism. (6 pt)



4. **Stereoselective alkene formation**

The reaction on the previous page is NOT stereoselective. This question examines the possible stereoselective synthesis of the same product from related starting materials.

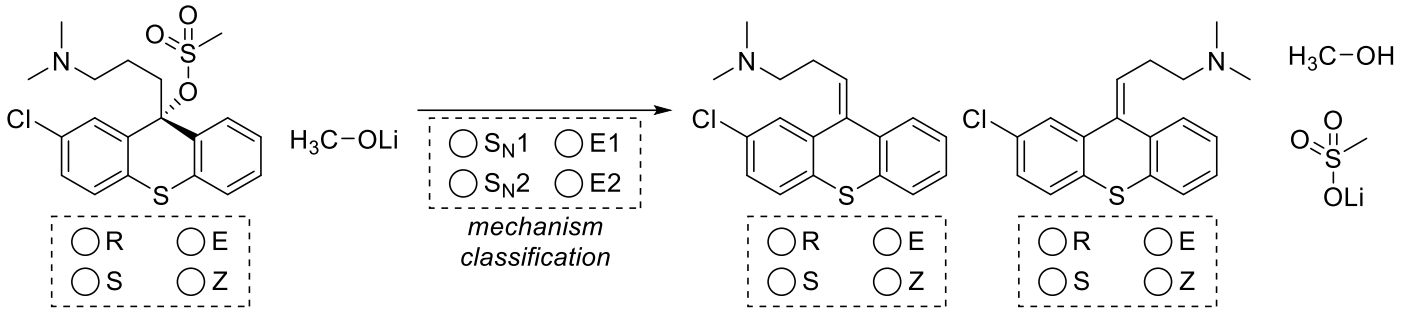
a. Fill in the missing reactant. (3 pt)



b. Choose a configuration label for each structure (6 pt)

c. Classify the mechanism of the reaction. Make sure you take into account the strength of the base. (2 pt)

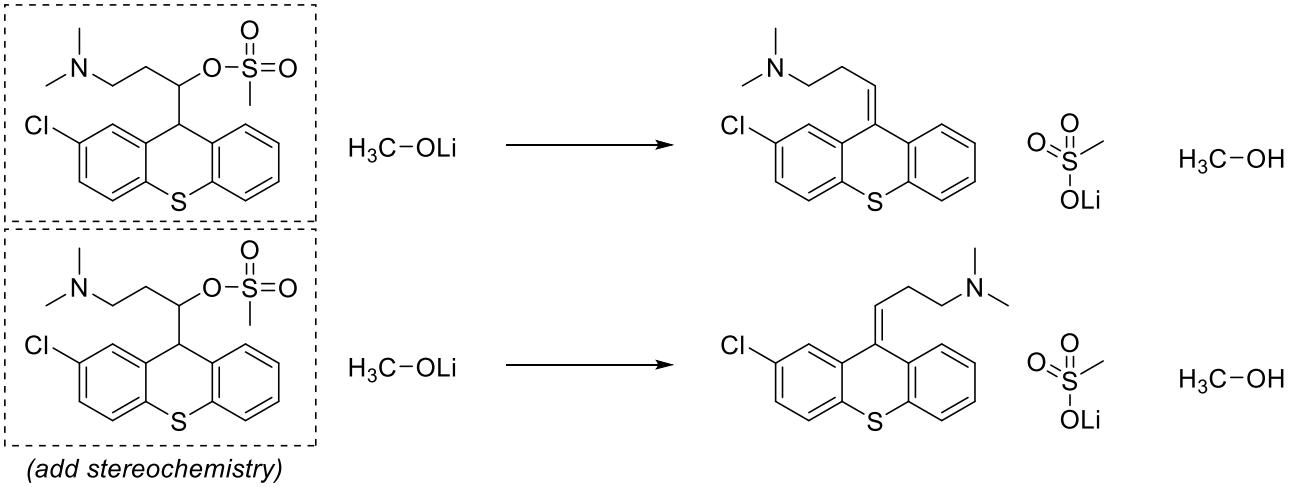
d. Draw a curved arrow mechanism that clearly demonstrates why the reaction is NOT stereoselective. Include comments in the mechanism as needed to explain that stereochemistry. (8 pt)



mechanism:

(add comments with the mechanism to explain why the reaction is NOT stereoselective)

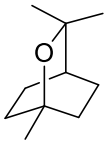
e. Add stereochemistry to the starting materials resulting in stereoselective synthesis of each alkene. (6 pt)



(add stereochemistry)

5. Terpenoid Cyclization

a. A bicyclic terpenoid structure is shown at the left, drawn using a perspective drawing that is related to the "chair" and "boat" cyclohexane conformation drawings. Translate this to the "flat" drawing on the right by adding the missing substituents. (3 pt)

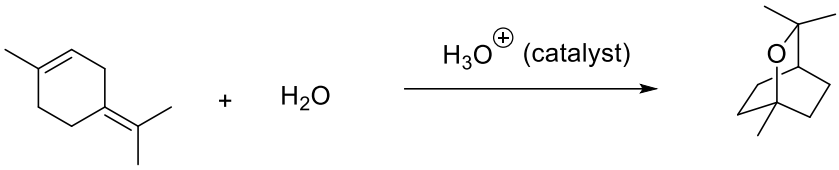


perspective drawing

(add substituents to finish this drawing)

(two different drawings of the same molecule)

b. Draw a curved arrow mechanism for the reaction below. (8 pt)



6. Draw a curved arrow mechanism for the reaction. Ignore stereochemistry. (8 pt)