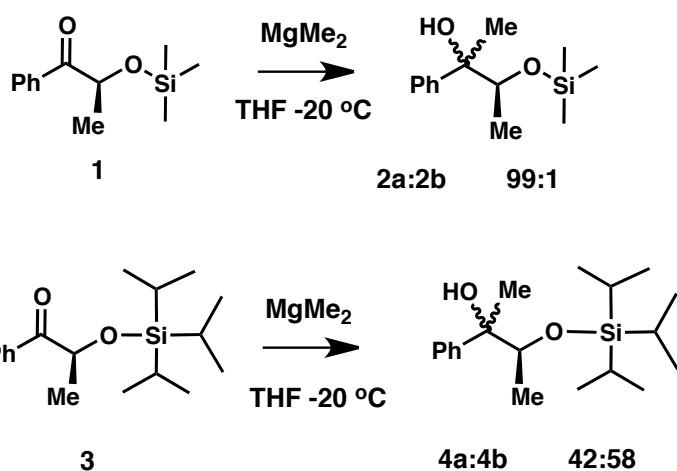


Problem 1 (10 points)

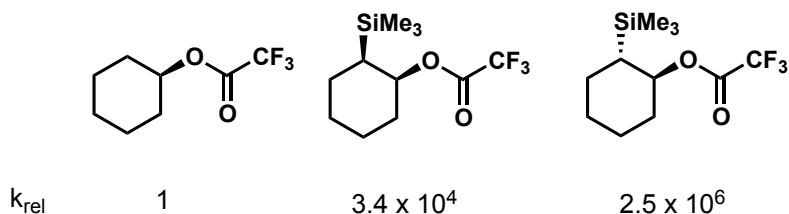
Chiral silyloxyketon **1** was treated with dimethylmagnesium to obtain tertiary alcohol **2** virtually as a single diastereoisomer. When silyloxyketon **3** was subjected to the same reaction conditions the stereoselectivity severely diminished. Two diastereomeric products were obtained in a ratio 42:58.

- A. Predict the stereochemistry of **2a** (the major diastereomer) and justify your answer.
 B. Give an explanation for the loss of stereoselectivity in the transformation of **3** into **4**.



Problem 2 (10 points)

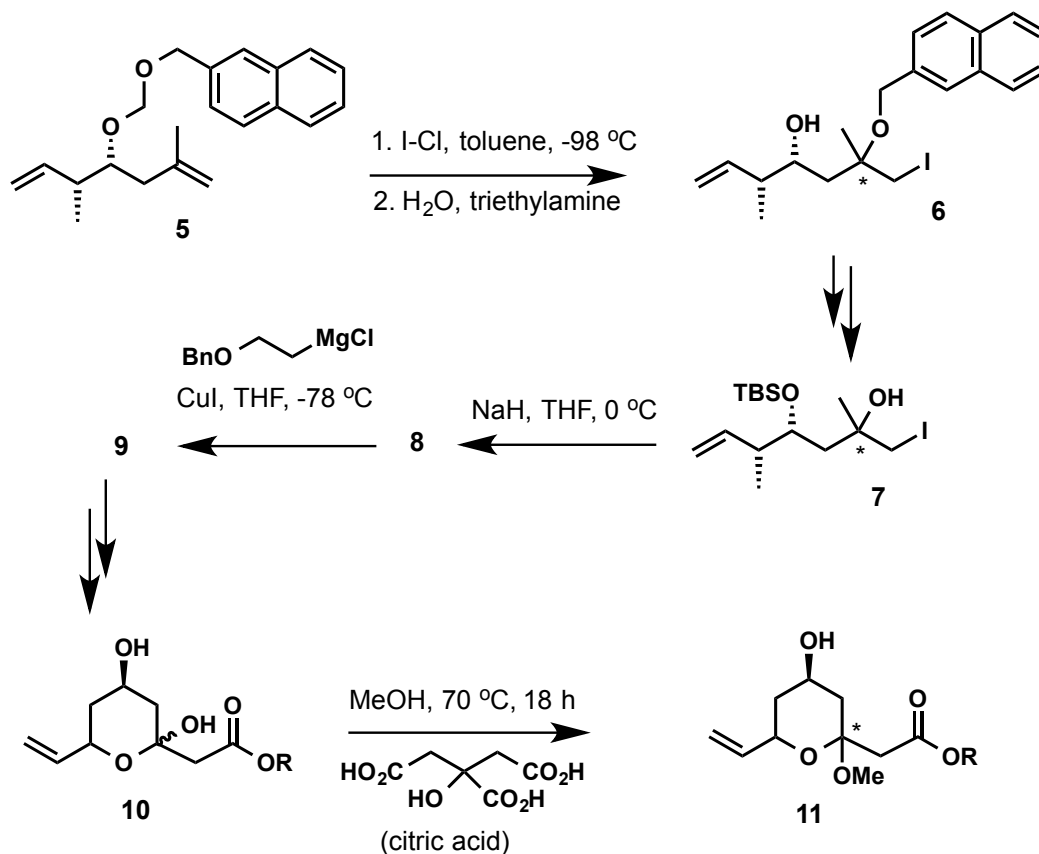
The solvolysis of the trifluoroacetates, depicted below, in trifluoroethanol proceeds with the relative rate constants given. Explain the trend observed for the rate constants.



Problem 3 (30 points)

Below part of the synthesis of Lyngbyaloside C, a classic macrolide exhibiting anti cancer activity, is depicted.

In the beginning of the synthesis an ether transfer is performed in which compound **5** is transformed into compound **6** using I-Cl, followed by treatment with a weak aqueous base.



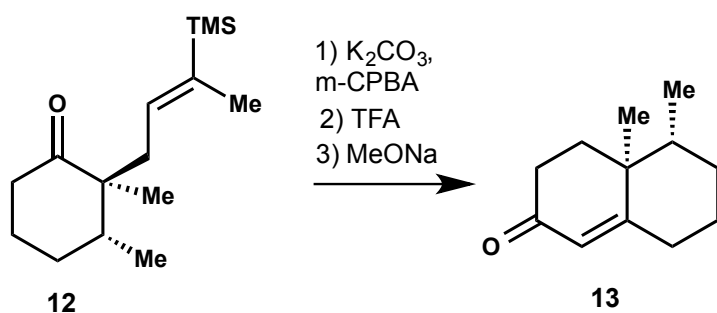
A) Give the mechanism for this reaction. Indicate the stereochemistry of the newly formed stereocenter (*) and provide a rationale for the stereoselectivity. Explain the regio chemistry of reaction.

B) After a few steps intermediate **7** is transformed into **9** using a two step sequence as depicted. Give the structure of **8** and **9**.

C) After several steps cyclic intermediate **10** is transformed into methylketal **11**. Provide the mechanism for this reaction. Which stereoisomer (indicated with an *) is formed and why?

Problem 4 (20 points)

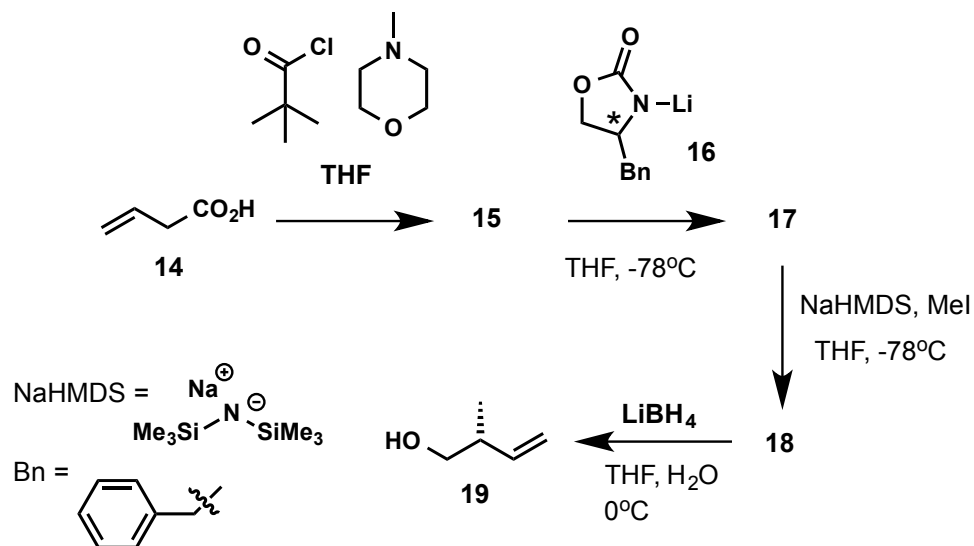
Compound **12** was subjected to a sequence of reactions as outlined below. Give the mechanism of all transformations involved and depict the product in the proper chair(-like) structure.



Problem 5 (30 points)

Provide the structures and the mechanism of formation for compounds **15**, **17**, and **18**. Pay attention to the stereochemistry of the products.

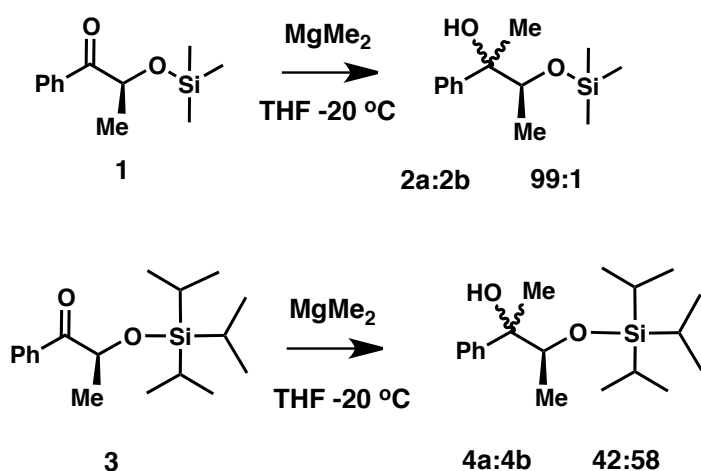
Give the correct stereochemistry of compound **16** (chiral center is indicated with an asterisk *) and justify your answer.



Problem 1 (10 points)

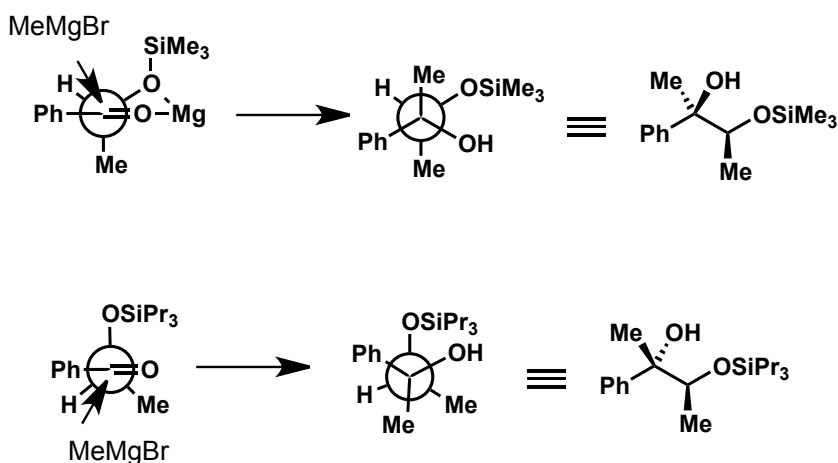
Chiral silyloxyketon **1** was treated with dimethylmagnesium to obtain tertiary alcohol **2** virtually as a single diastereoisomer. When silyloxyketon **3** was subjected to the same reaction conditions the stereoselectivity severely diminished. Two diastereomeric products were obtained in a ratio 42:58.

- A. Predict the stereochemistry of **2a** (the major diastereomer) and justify your answer.
 B. Give an explanation for the loss of stereoselectivity in the transformation of **3** into **4**.



Answer:

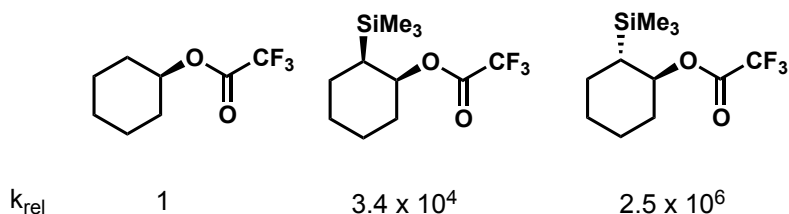
For the prediction of the stereochemistry of **2a** see below. Chelation with the Mg^{2+} ions is possible so the Felkin-Ahn model with chelation can be used.



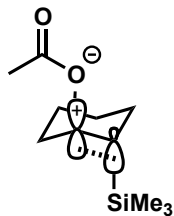
The tri-isopropyl silyl group in **3** is too bulky to allow for effective chelation, therefore the second t.s. having the OSiPr_3 perpendicular to the plane of the $\text{C}=\text{O}$ group also comes into play.

Problem 2 (10 points)

The solvolysis of the trifluoroacetates, depicted below, in trifluoroethanol proceeds with the relative rate constants given. Explain the trend observed for the rate constants.

**Answer**

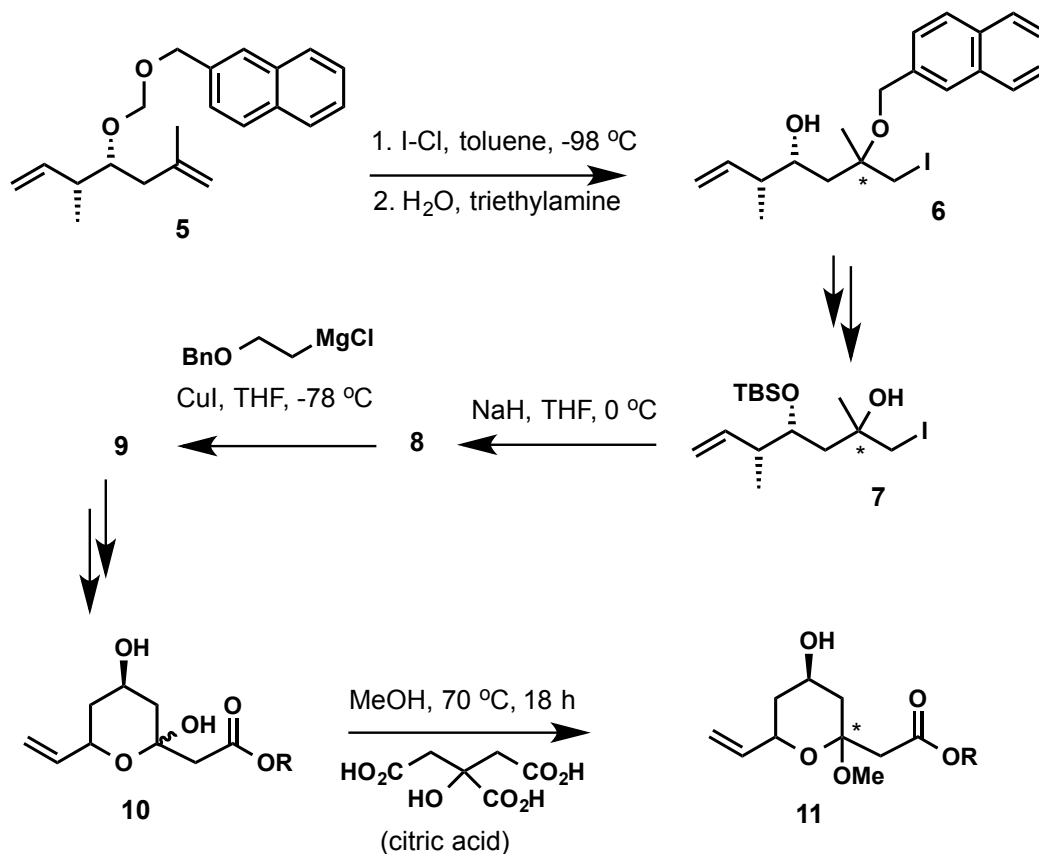
The order of relative rate constants can be explained by the fact that the solvolysis of the compounds occurs through an S_N1 mechanism (poor nucleophile, polar solvent) and formation of the secondary cyclohexane carbocation will be the rate-determining step. β -silicon groups can stabilize a β -positive charge through efficient hyperconjugation. Therefore the two cyclohexanes bearing silyl groups will react faster. The product with the silyl group trans with respect to the leaving group will react fastest because it can directly stabilize the developing positive charge (in an empty p-orbital) because it is perfectly aligned (anti periplanar) with the leaving group:



Problem 3 (30 points)

Below part of the synthesis of Lyngbyaloside C, a classic macrolide exhibiting anti cancer activity, is depicted.

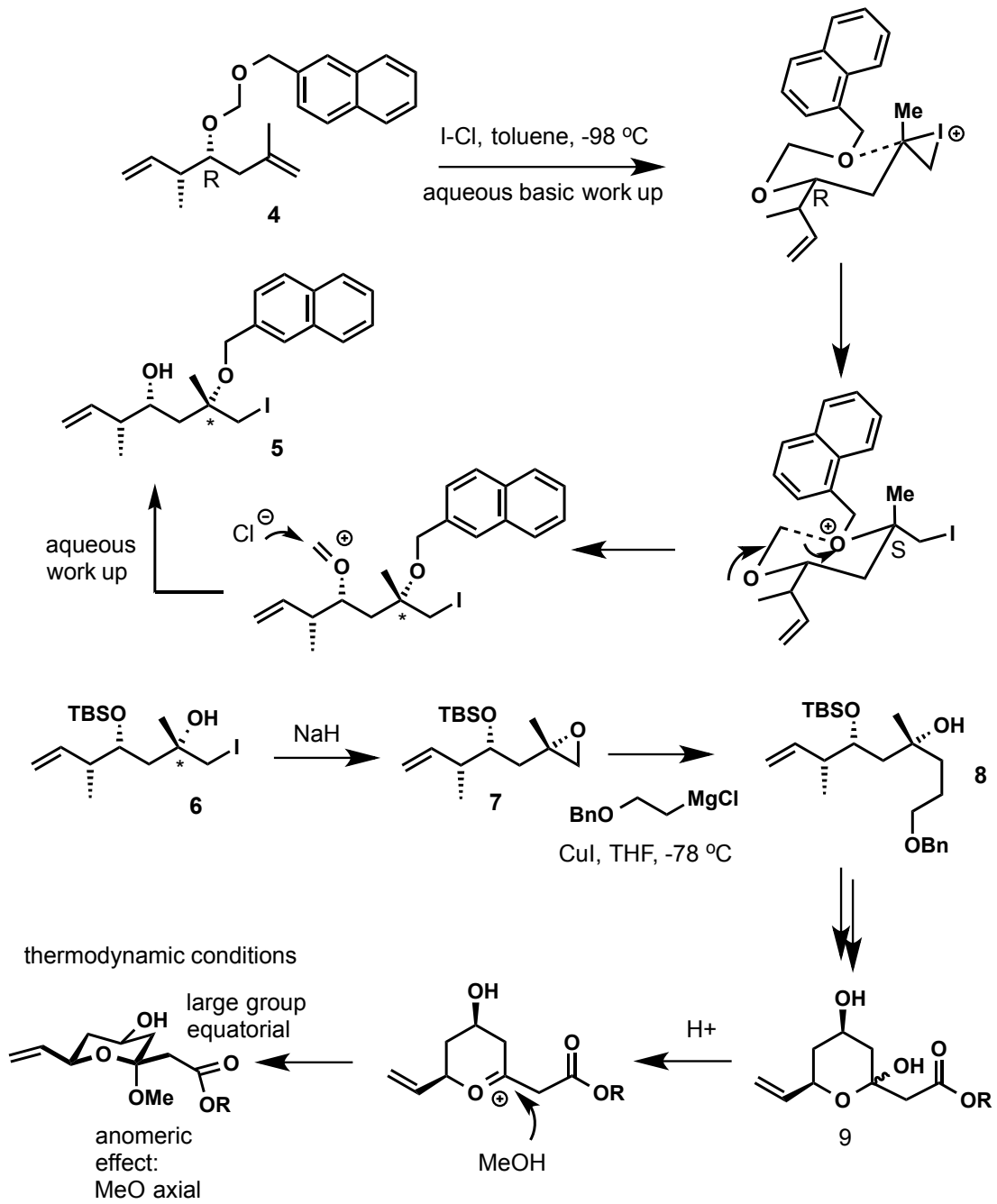
In the beginning of the synthesis an ether transfer is performed in which compound **5** is transformed into compound **6** using I-Cl, followed by treatment with a weak aqueous base.



A) Give the mechanism for this reaction. Indicate the stereochemistry of the newly formed stereocenter (*) and provide a rationale for the stereoselectivity. Explain the regio chemistry of reaction.

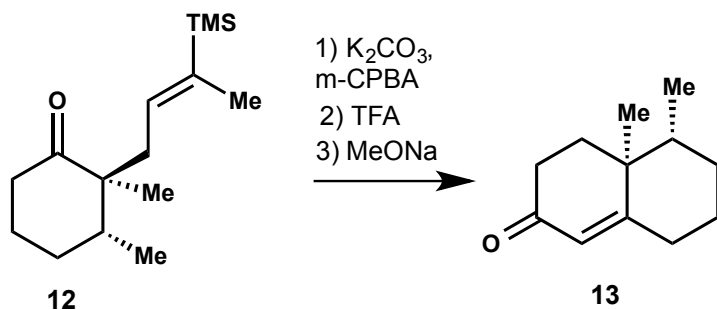
B) After a few steps intermediate **7** is transformed into **9** using a two step sequence as depicted. Give the structure of **8** and **9**.

C) After several steps cyclic intermediate **10** is transformed into methylketal **11**. Provide the mechanism for this reaction. Which stereoisomer (indicated with an *) is formed and why?

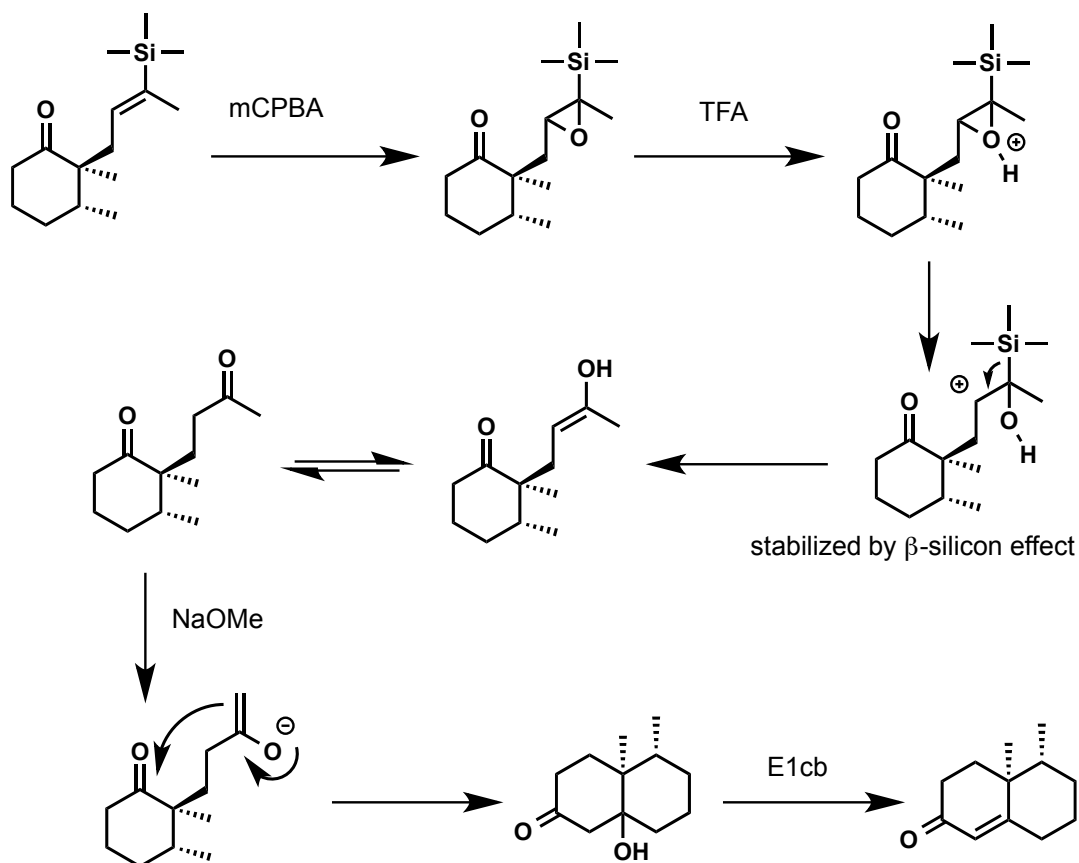


Problem 4 (20 points)

Compound **12** was subjected to a sequence of reactions as outlined below. Give the mechanism of all transformations involved and depict the product in the proper chair(-like) structure.



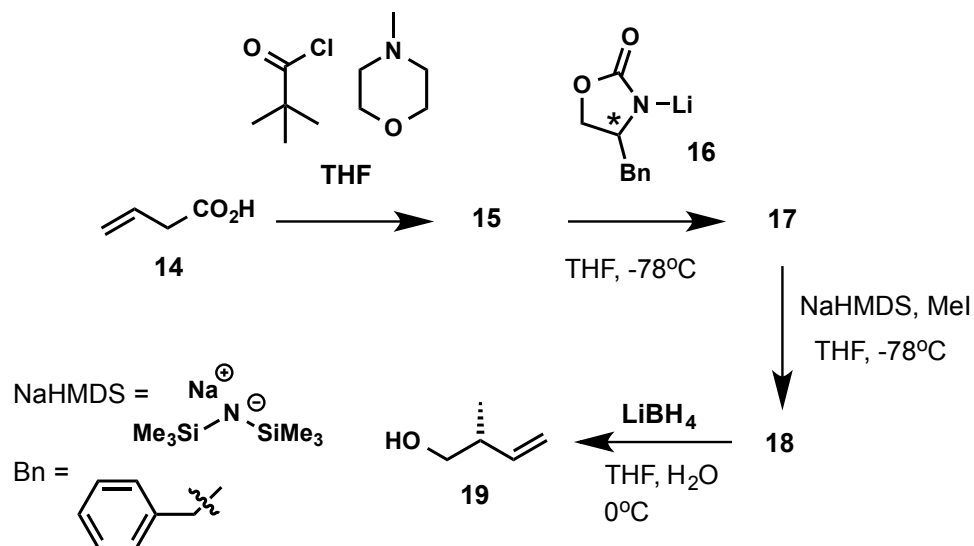
Answer:



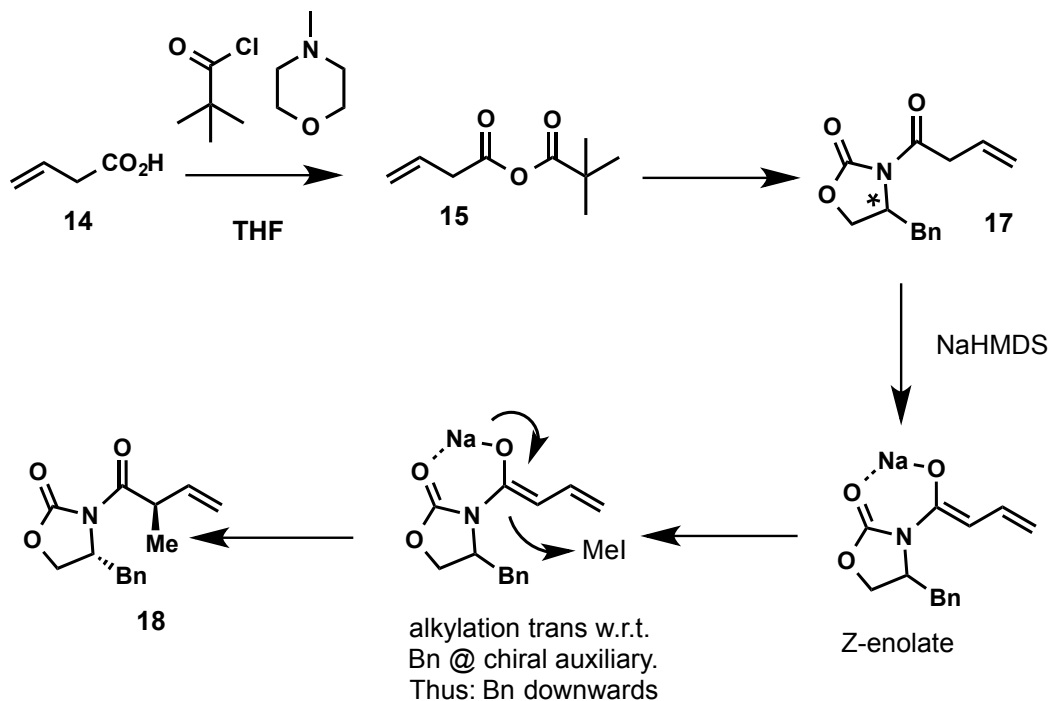
Problem 5 (30 points)

Provide the structures and the mechanism of formation for compounds **15**, **17**, and **18**. Pay attention to the stereochemistry of the products.

Give the correct stereochemistry of compound **16** (chiral center is indicated with an asterisk *) and justify your answer.



Answer:



First a mixed anhydride is formed (deprotonation of the acid by *N*-methylmorpholine and attack on the acid chloride by the formed carboxylate). This mixed anhydride reacts with the lithium imide to give **17** by attack at the least hindered

C=O, the pivaloylate acts as a leaving group). HMDS deprotonates **17** to give the Z-enolate through a Ireland-Claisen transition state. The carbamate chiral auxiliary is bulky and forces the enolate to be Z. Alkylation then occurs *trans* with respect to the Bn-group on the chiral auxiliary. This means that the Bn group had to be upwards. Finally the chiral auxiliary is removed by reduction to provide the primary alcohol (**19**).