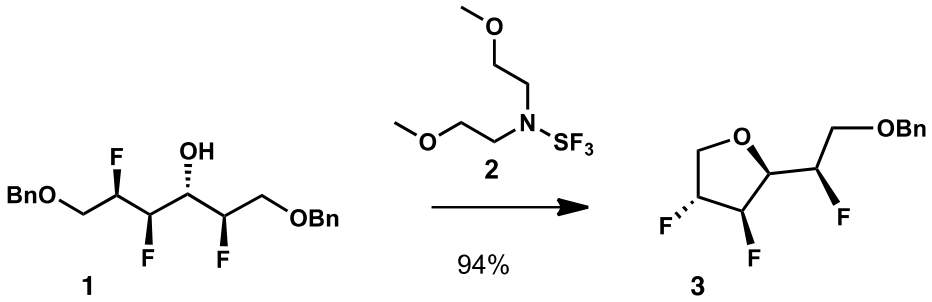
Reactivity in Organic Chemistry Exam
14-01-2016
14:00-17:00, C1

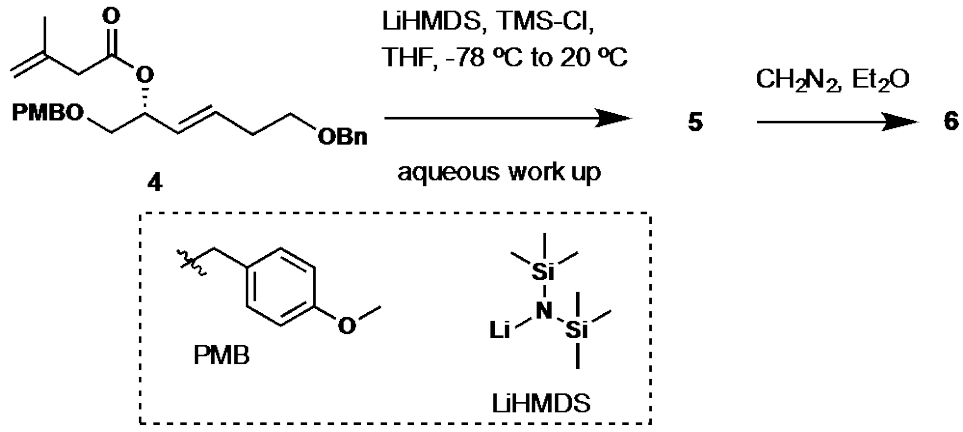
Problem 1 (10 points)

Compound **1** has been treated with an electrophilic reagent **2** to give **3** in high yield. Give a mechanism of this transformation. Explain the regio- and stereochemistry of this reaction.



Problem 2 (20 points)

A) Compound **4** was treated with the strong base LiHMDS and subsequently with TMS-Cl to give product **5**, featuring a carboxylic acid function and two new stereocenters. Give a detailed mechanism for this transformation and account for the stereochemistry of the newly formed chiral centers and the double bond in **5.**
B) Give the structure of **6**.



Problem 3 (40 points)

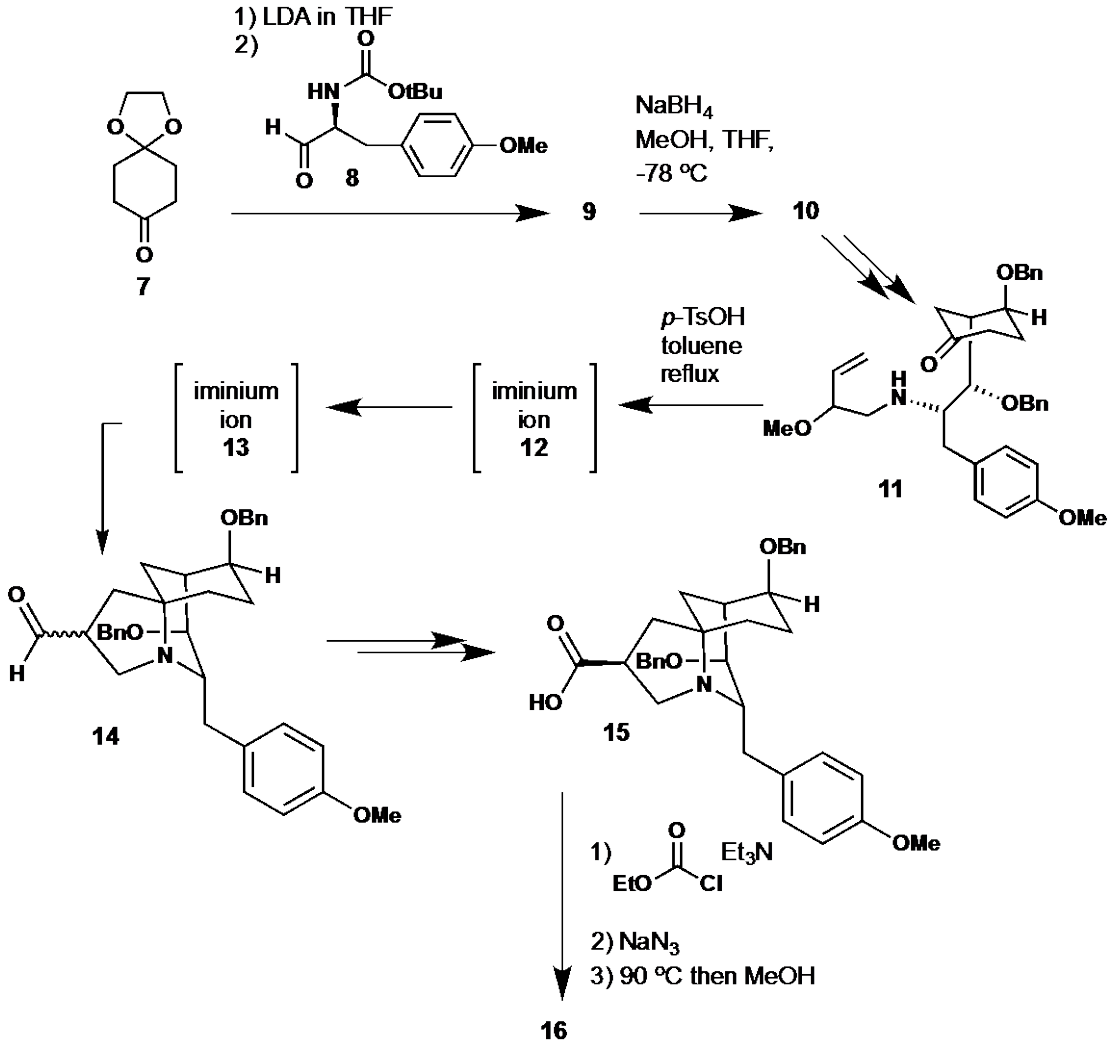
(-)FR901483 is an immunosuppressive agent with a unique tricyclic azaspirane scaffold. Because of its structure it has attracted significant attention from the synthetic community and one of the syntheses is depicted below.

A) Ketone **7** is treated with LDA and subsequently with aldehyde **8** to provide hydroxyketone **9**. Provide the mechanism for this reaction and show which stereoisomer is preferentially formed.

B) Next **9** is treated with $NaBH_4$ to give a **10**. Provide the structure of **10** and rationalize the stereochemistry of the newly formed chiral center.

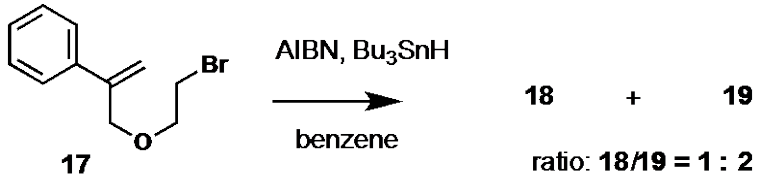
C) After a number of steps intermediate **11** is obtained. This ketone is treated with *p*-TsOH to provide aldehyde **14** (mixture of diastereomers as shown) in a sequence of reactions that proceeds *via* the formation of two iminium ions (**12** and **13**). Give the mechanism for the three steps of this sequence.

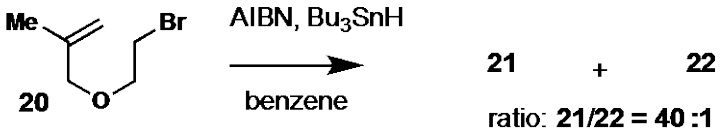
D) After a few steps acid **15** is obtained. This acid is transformed into carbamate **16** through the a three step reaction sequence shown. Give the mechanism for these three reactions and give the structures of the intermediates.



Problem 4 (10 points)

The reaction of bromoalkene **17** with Bu_3SnH and a catalytic amount of AIBN led to a mixture of two products **18** and **19** in the ratio as specified below. In case of bromoalkene **20** the products **21** and **22** (structural analogues of **18** and **19**, respectively) were formed in a different ratio. Provide a mechanism for these transformations and explain the product ratios obtained therein.

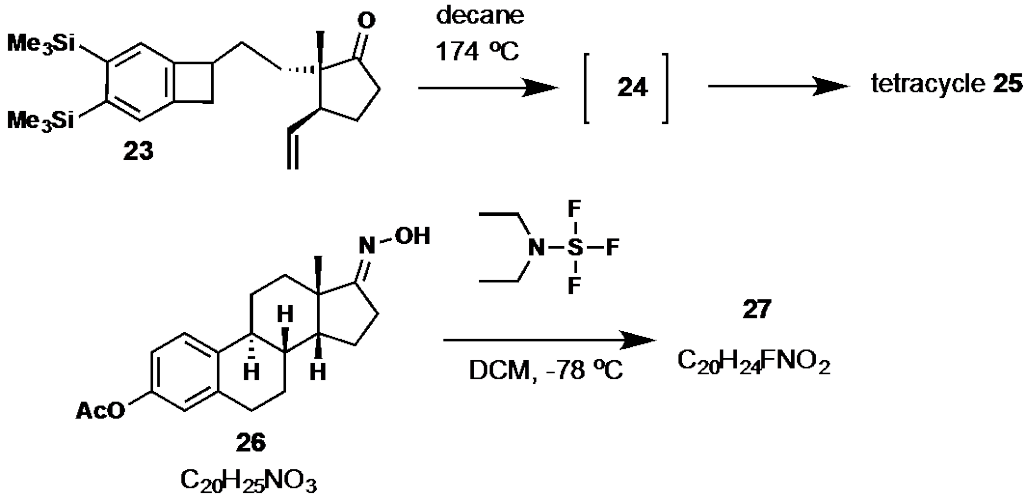




Problem 5 (20 points)

A) Below a part of the synthesis of estrone is given. In this synthesis tricycle **23** was transformed into tetracycle **25** by heating the substrate in decane (a high boiling solvent). Provide the mechanism of this reaction that proceeds via intermediate **24** (you can disregard the stereochemistry of the newly formed chiral centers).

B) In a related synthesis estrone analogue **26** is treated with diethylamino sulfurtrifluoride (DAST, a reagent that is commonly used to transform an alcohol into an fluoride) to give a tricyclic product. Provide the structure of product **27** and a mechanism of the reaction to explain its formation.

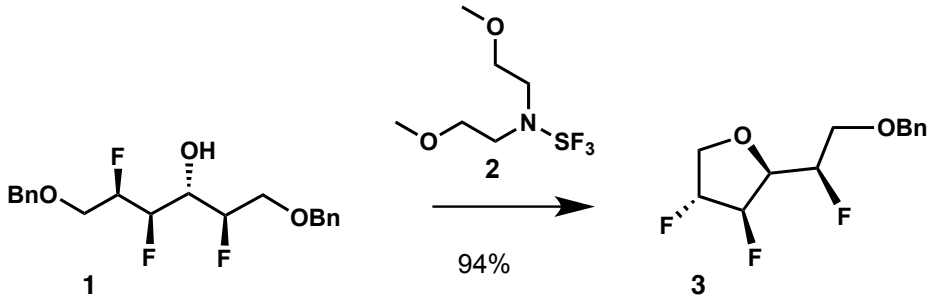


BONUS: Give the stereochemistry of the newly formed chiral centers in **25** and an explanation for this observed stereoselectivity.

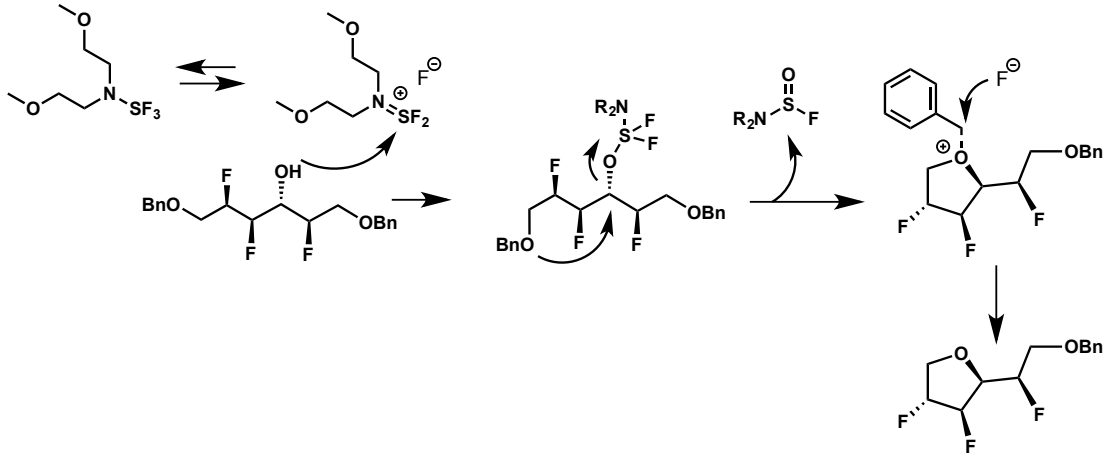
Reactivity in Organic Chemistry Exam
14-01-2016
14:00-17:00, C1

Problem 1 (10 points) JACS 2006, 128, 16422-16423

Compound **1** has been treated with an electrophilic reagent **2** to give **3** in high yield. Give a mechanism of this transformation. Explain the regio- and stereochemistry of this reaction.



Answer:

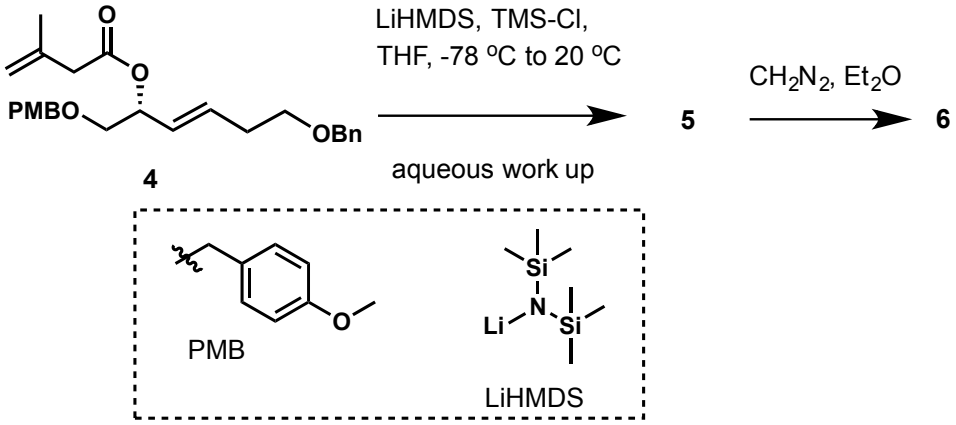


Deoxofluor **2** transforms the alcohol into a leaving group as shown. There is competition between two different nucleophliic displacement reactions: an intramolecular displacement of the O-SR3 leaving by the released fluoride and the intramolecular attack by the benzyl ether oxygen. In this case ring closure by the primary benzyl ether is (apparently) faster. This leads to the species shown, which is a potent electrophile. Attack at the benzylic position by an fluoride anion then provides cyclic ether **3** and benzylfluoride. The corresponding 4-membered ring that could be formed by attack of the other primary benzyl ether is not formed because formation of 4-membered rings is rather unfavorable.

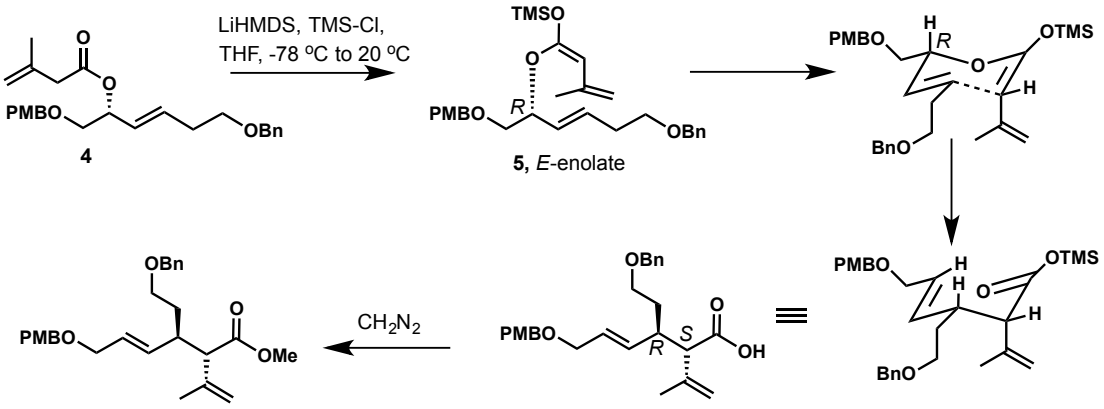
Problem 2 (20 points) JOC, 2013, 78, 3355-3360

A) Compound **4** was treated with the strong base LiHMDS and subsequently with TMS-Cl, warming to room temperature and aqueous work up then gives product **5**, having a carboxylic acid function and two new stereocenters. Give a detailed mechanism for this transformation and account for the stereochemistry of the newly formed chiral centers and the double bond in **5.**

B) Give the structure of **6**.



Answer:



With LIHMDS and TMSCl, the *E*-enolate is generate, through an Ireland t.s. (Esters generally give *E*-enolates*)* The ensuing Claisen rearrangement proceeds through a chair like t.s with the CH_2OPMB group equatorial to give the product shown (the TMS ester is hydrolysed upon aqueous work-up).

Treatment of the acid with diazomethane gives the methyl ester.

Problem 3 (40 points) JOC, 2005, 70, 907-916

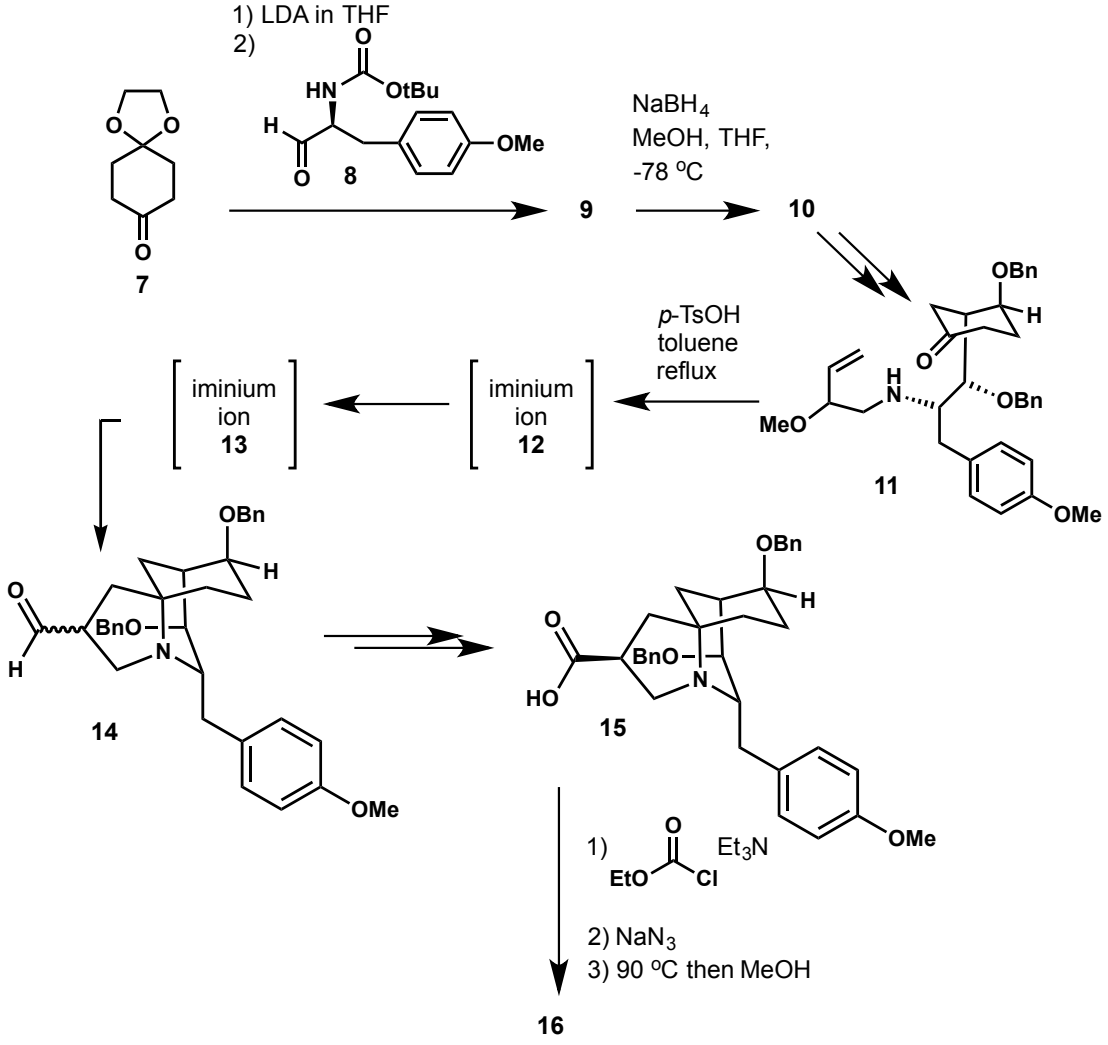
(-)FR901483 is an immunosuppressive agent with a unique tricyclic azaspirane scaffold. Because of its structure it has attracted significant attention from the synthetic community and one of the syntheses is depicted below.

A) Ketone **7** is treated with LDA and subsequently with aldehyde **8** to provide hydroxyketone **9**. Provide the mechanism for this reaction and show which stereoisomer is preferentially formed.

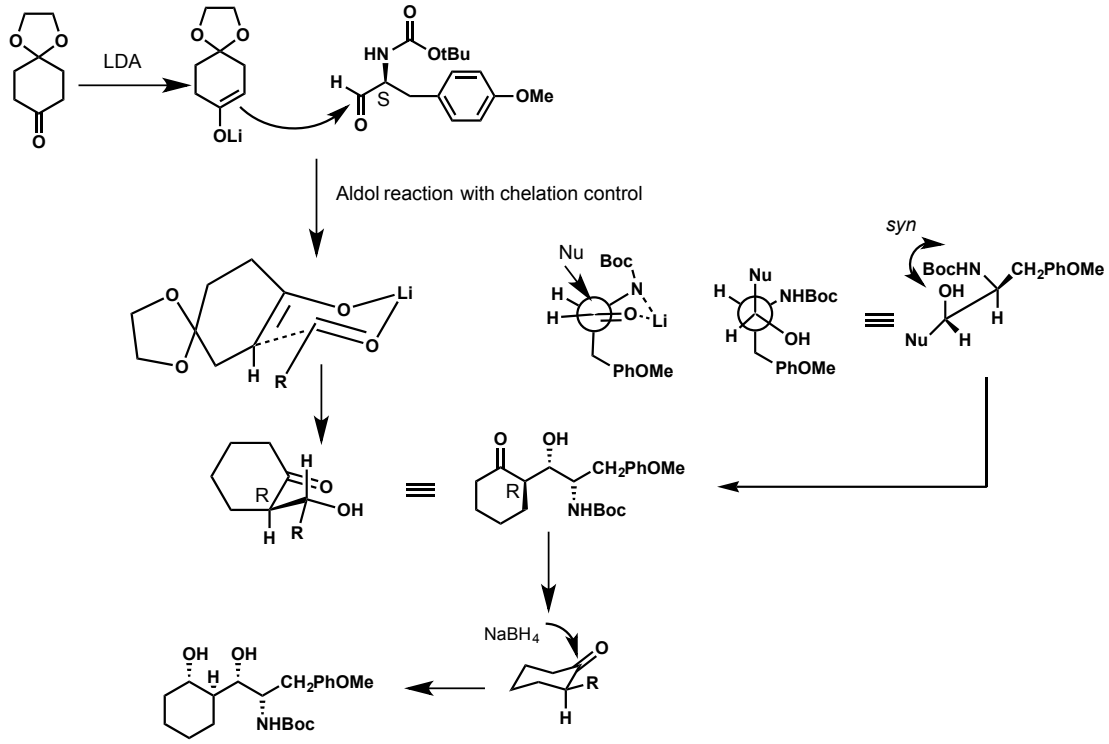
B) Next **9** is treated with $NaBH_4$ to give a **10**. Provide the structure of **10** and rationalize the stereochemistry of the newly formed chiral center.

C) After a number of steps intermediate **11** is obtained. This ketone is treated with *p*-TsOH to provide aldehyde **14** (mixture of diastereomers as shown) in a sequence of reactions that proceeds *via* the formation of two iminium ions (**12** and **13**). Give the mechanism for the three steps of this sequence.

D) After a few steps acid **15** is obtained. This acid is transformed into carbamate **16** through the a three step reaction sequence shown. Give the mechanism for these three reactions and give the structures of the intermediates.



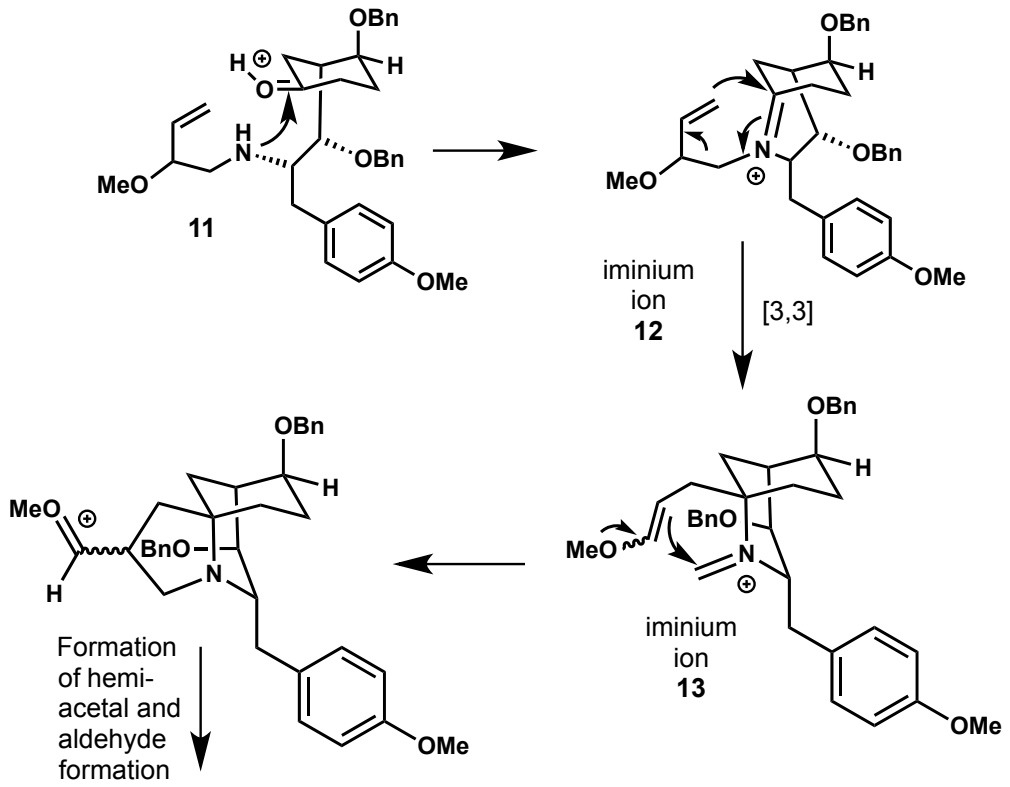
Answer:



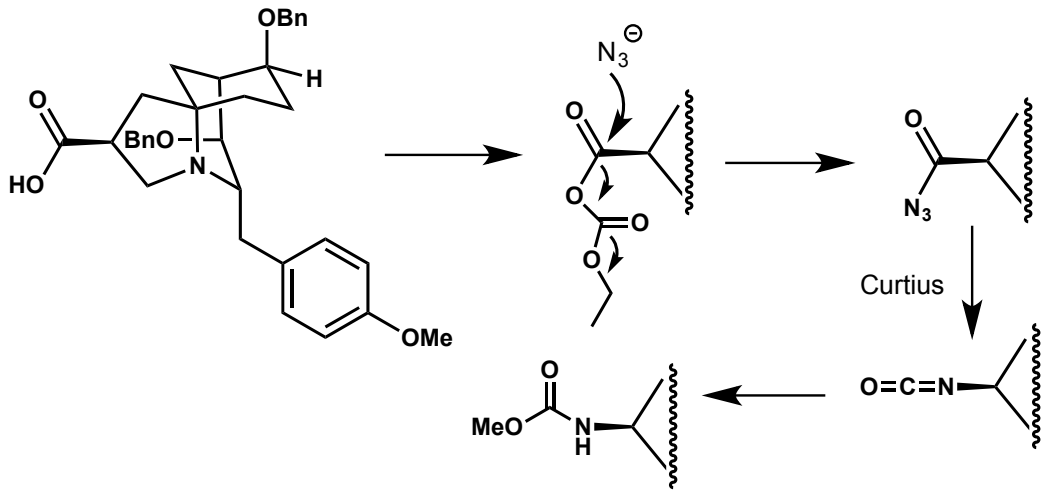
A) LDA deprotonates the ketone to give the *E*-enolate (only possible enolate because it is cyclic). Next an aldol reaction occurs. This can proceed through a chelation controlled Felkin Ahn approach. The *E*-enolate gives the trans-Aldol product (as shown). The alpha-carbon on the aldehyde dictates the absolute stereochemistry. [Note that the mirror image of the chair like aldol t.s. shown would lead to the opposite stereochemistry at the newly formed alcohol]

B) Reduction of the ketone occurs by axial attack (NaBH4 is a relatively small reagent) to give the diol shown.

C)

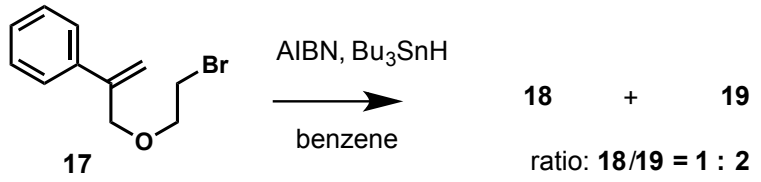


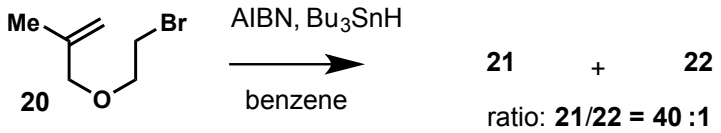
D) Formation of a mixed anhydride (or acid chloride) is followed by generation of the acylazide that undergoes a Curtius rearrangement to give the isocynate. Trapping of this species by MeOH gives the methylcarbamate with retention of stereochemistry on the 5-membered ring.



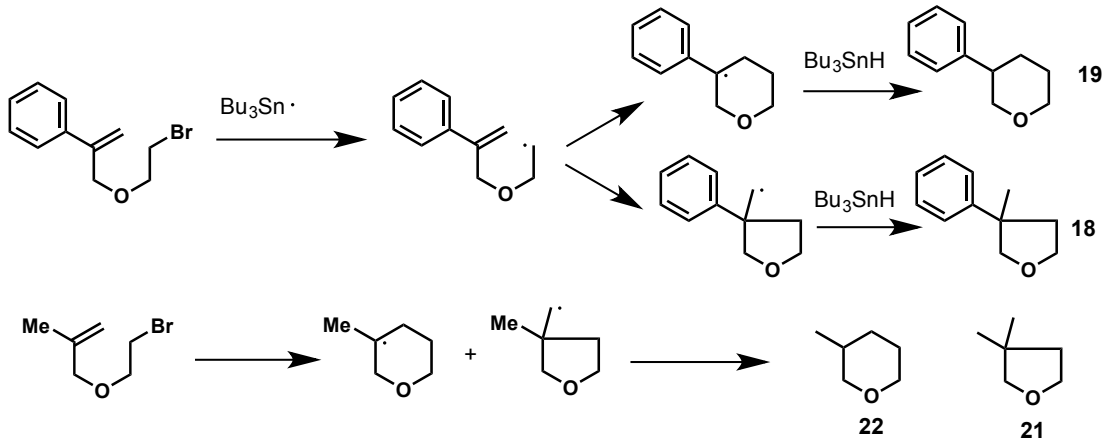
Problem 4 (10 points) JOC, 1978, 40, 6-13

The reaction of bromoalkene **17** with Bu_3SnH and a sub-stoichiometric amount of AIBN led to a mixture of two products **18** and **19** in the ratio as specified below. In case of bromoalkene **20** the products **21** and **22** (structural analogues of **18** and **19**, respectively) were formed in a different ratio. Provide a mechanism for these transformations and explain the product ratios obtained therein.





Answer:



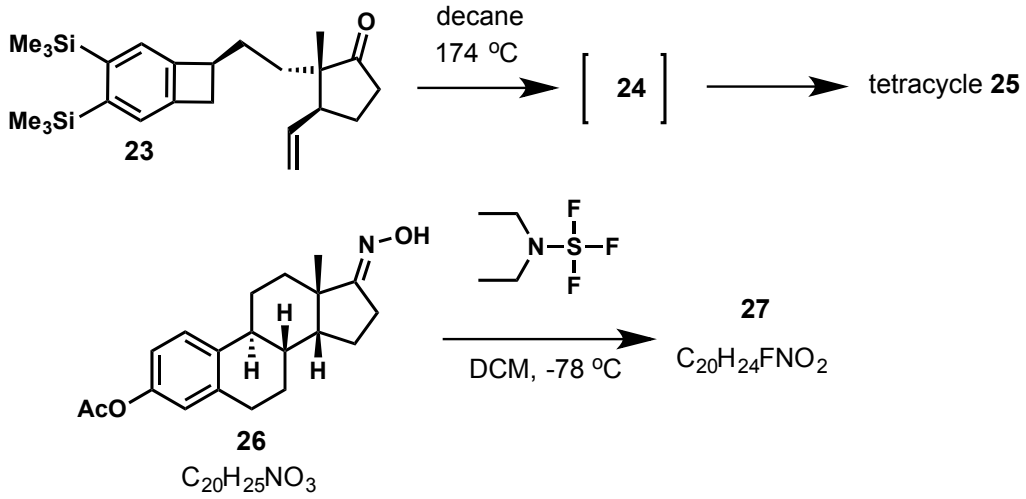
A primary radical is formed from both bromides. This can undergo a ring closure to give either a 5 or a 6-membered ring. Primary radicals are so reactive that they generally provide the kinetic product, that results from 5-membered ring closure. In the case of the **20** this leads to the predominant formation of **21**.
When there is an extra Phenyl ring as in **17**, the radical that is formed by the generation of the 6-memberen ring, is tertiary and benzylic. This is very favorable and now this reaction pathway becomes important as well.

NB: if the stability of the intermediate radical would have been decisive in both cases, you would expect the phenyl substituted system to be more selective!

Problem 5 (20 points) JACS 1980, 102, 5253 + ChemComm, 1997, 599-600)

A) Below a part of the synthesis of estrone is given. In this synthesis tricycle **23** was transformed into tetracycle **25** by heating the substrate in decane (a high boiling solvent). Provide the mechanism of this reaction that proceeds via intermediate **24** (you can disregard the stereochemistry of the newly formed chiral centers).

B) In a related synthesis estrone analogue **26** is treated with diethylamino sulfurtrifluoride (DAST, a reagent that is commonly used to transform an alcohol into an fluoride) to give a tricyclic product. Provide the structure of product **27** and a mechanism of the reaction to explain its formation.

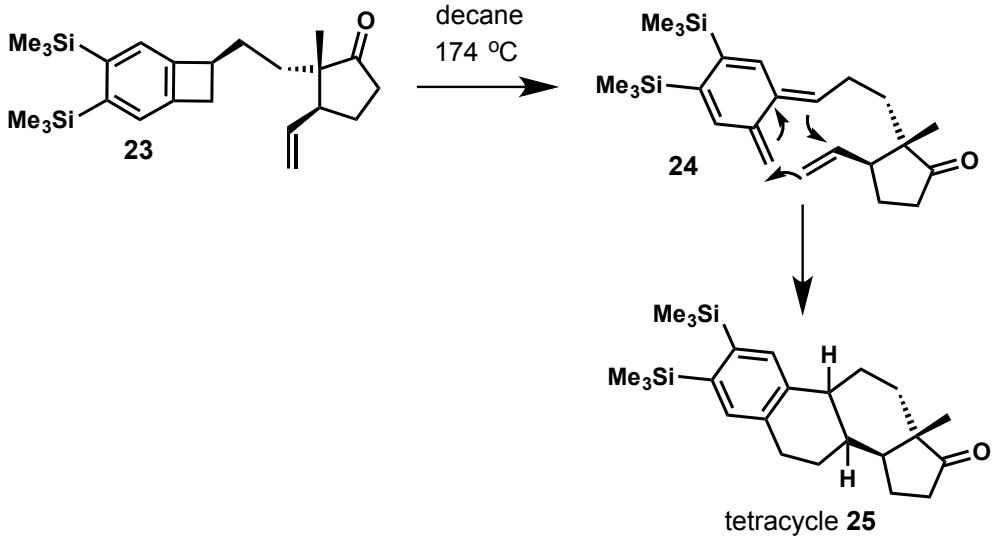


BONUS: Give the stereochemistry of the newly formed chiral centers in **25** and an explanation for the stereoselectivity.

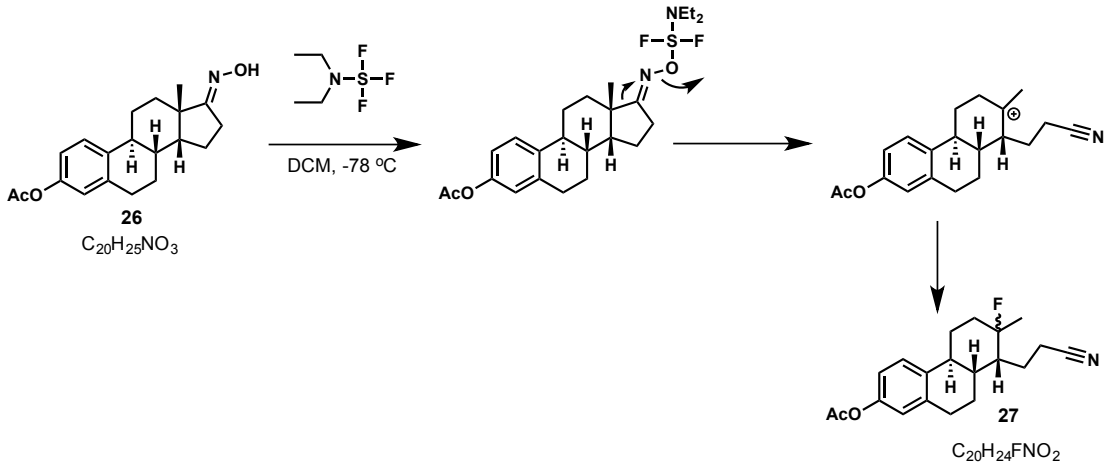
Answer:

A) Conrotatory ring opening of the cyclobutane ring gives **24** as shown. Note that the alkene is formed with the large group pointing "outwards".

An ensuing intramolecular Diels Alder reaction then gives the tetracycle **25**.



B) Reaction of the oxime with DAST provides a molecule that is set-up for a Beckman fragmentation. Formation of the tertiary cation is more favorable and will proceed preferentially. The intermediate carbocation can then be trapped by the fluoride anion released from the DAST.



26
$C_{20}H_{25}NO_3$

27
$C_{20}H_{24}FNO_2$

BONUS:
A plausible t.s. for the D.A reaction is shown below: approach of the dienophile to the diene can happen occur with the tether adopting a chair like structure: