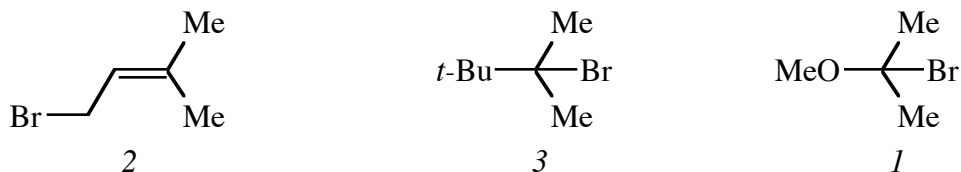
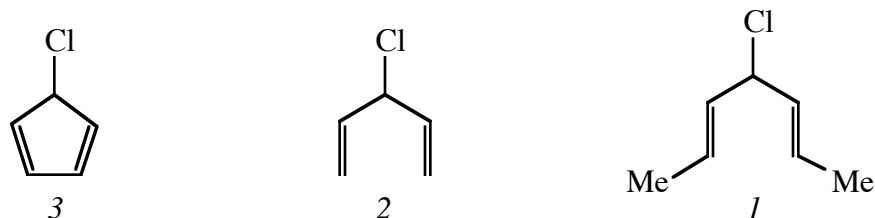


Answers To Chapter 3 Problems.

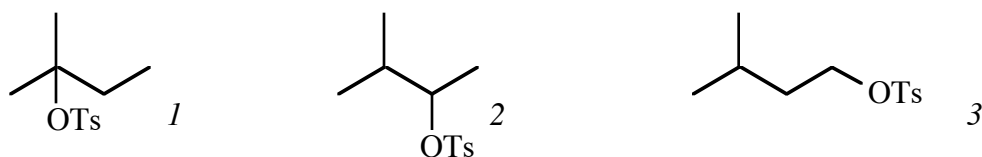
1. (a) In order to compare it directly with the other two carbocations, the carbocation derived from the first compound should be drawn in the resonance form in which the empty orbital is located on the 3° C. It can then clearly be seen that the three carbocations are all 3° carbocations that differ only in the third carbocation substituent. The order of substituent stabilizing ability is lone pair > π bond > σ bonds.



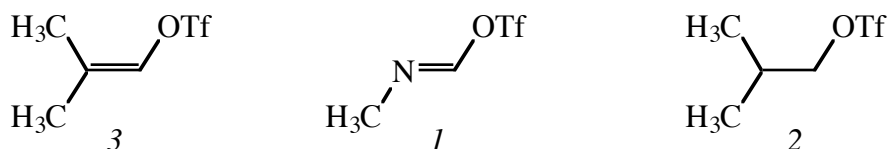
(b) The first compound gives an antiaromatic carbocation. Among the other two, the second compound gives a cation with the electron deficiency delocalized across one 2° and two 1° C's, while the third compound gives a cation with the electron deficiency delocalized across three 2° C's.



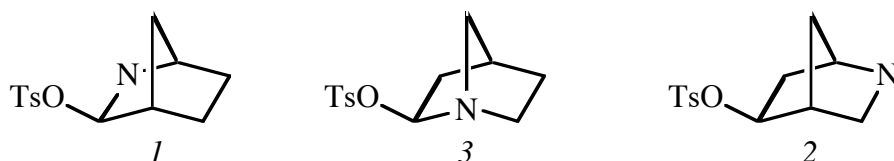
(c) The order of stability of alkyl cations is 3° > 2° > 1°.



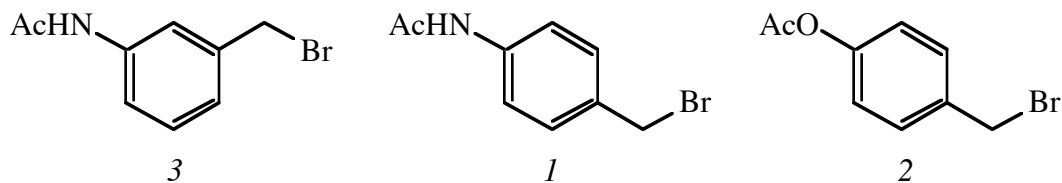
(d) The second compound gives a lone-pair-stabilized carbocation. Among the other two, 1° alkyl carbocations are more stable than 1° alkenyl carbocations.



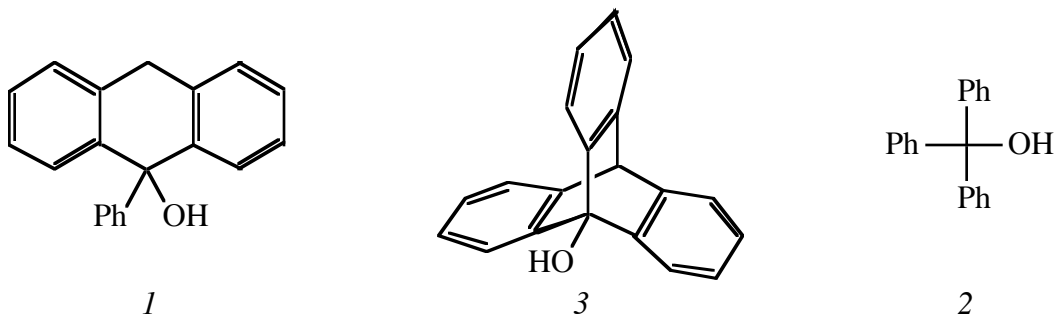
(e) The first compound generates a cation that can be stabilized by the lone pair on N. The second compound generates a cation that cannot be stabilized by the lone pair on N due to geometrical constraints (would form bridgehead π bond, a no-no). Therefore the *inductive* effect of N *destabilizes* the carbocation derived from the second compound relative to the carbocation from the third compound, in which the N is more remote.



(f) The second and third compounds generate cations that can be directly stabilized by resonance with the lone pairs on the heteroatoms, with N more stabilizing than O, while the cation from the first compound isn't stabilized by resonance with the heteroatom at all.



(g) The second compound (a *tritycene*) provides no π stabilization to the corresponding cation, because the p orbitals of the phenyl rings are perpendicular to the empty p orbital. The first compound is more likely to ionize than the third for two reasons. (1) The phenyl rings in first compound are more electron-rich (alkyl-substituted). (2) In the first compound, two of the phenyl rings are held in a coplanar arrangement by the bridging CH_2 , so they always overlap with the empty p orbital of the cation. In the third compound, there is free rotation about the C–Ph bonds, so there is generally less overlap between the Ph π clouds and the empty p orbital of the cationic center.



2.

(a) Excellent carbocation, nucleophilic solvent, \therefore S_N1 . Br^- leaves spontaneously to give a carbocation, which combines with solvent to give a protonated ether, which loses H^+ to give the product.

(b) Excellent carbocation, nucleophilic solvent, \therefore S_N1 . First O is protonated, then OH_2 leaves to give carbocation, Next, the carbonyl O of AcOH adds to the carbocation, and then H^+ is lost from O to give the product.

(c) Excellent carbocation, nonnucleophilic solvent, \therefore E1. First O is protonated, then OH_2 leaves to give carbocation. Finally, H^+ is lost from the C adjacent to the electron-deficient C to give the alkene.

(d) Good carbocation, nucleophilic solvent, \therefore S_N1 . The product is racemic. Br^- leaves spontaneously to give a planar, achiral carbocation; then the carbonyl O of HCO_2H adds to the carbocation from either enantioface. Finally, H^+ is lost from O to give the product.

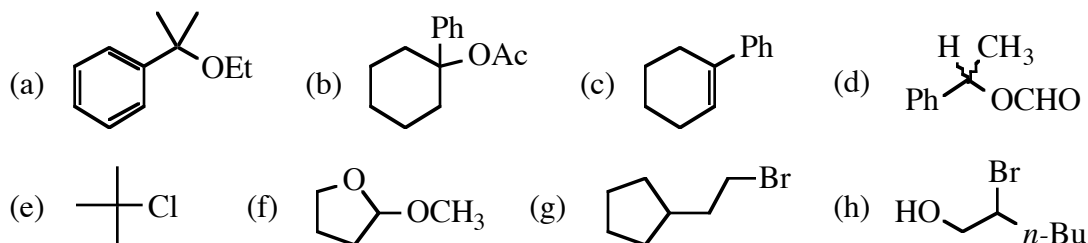
(e) Excellent carbocation, nucleophilic solvent, \therefore S_N1 . Here the nucleophile is Cl^- , because addition of H_2O simply gives back starting material. First O is protonated, then OH_2 leaves to give carbocation, then Cl^- adds to carbocation to give the product.

(f) Excellent carbocation, nucleophilic solvent, \therefore S_N1 . First the O of the OH group is protonated, then OH_2 leaves to give an O-stabilized carbocation. Next, the O of CH_3OH adds to the carbocation, and finally H^+ is lost from the O of OCH_3 group to give the product. Note that the ring oxygen could also act as a leaving group to give an acyclic compound, but entropy favors the loss of the OH group (because two products are formed from one).

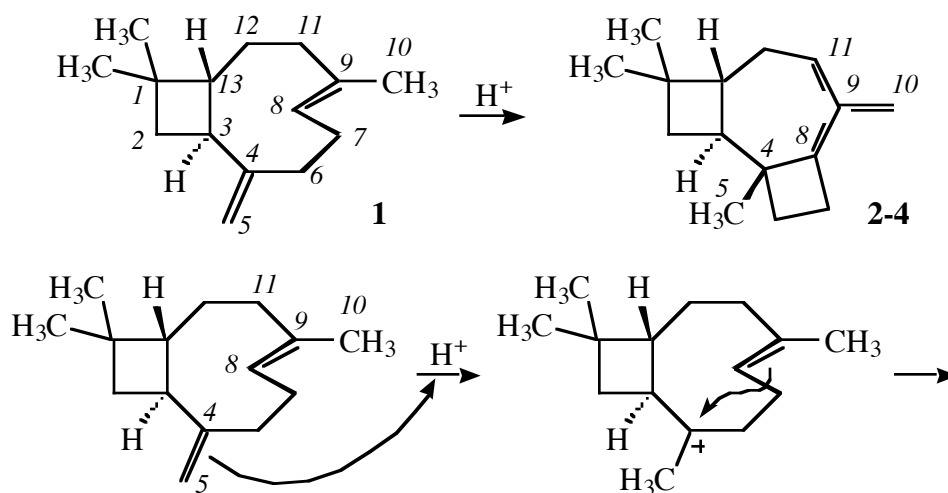
(g) Awful carbocation, so can't be S_N1 . Strongly acidic conditions, excellent nonbasic nucleophile, \therefore S_N2 . First O is protonated, then Br^- does a nucleophilic displacement of OH_2 to give the product.

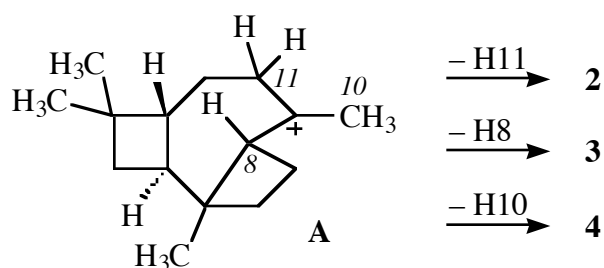
(h) So-so carbocation, excellent nonbasic nucleophile. Could be S_N1 or S_N2 . First O is protonated;

then, *either* Br^- displaces O from C to give product, *or* O leaves to form carbocation, and then Br^- adds to the carbocation. The regiochemistry is determined by the formation of the stabler carbocation. (Even in $\text{S}_{\text{N}}2$ reaction, the central C in the transition state has some carbocationic character, so the more substituted C undergoes substitution under acidic conditions.)

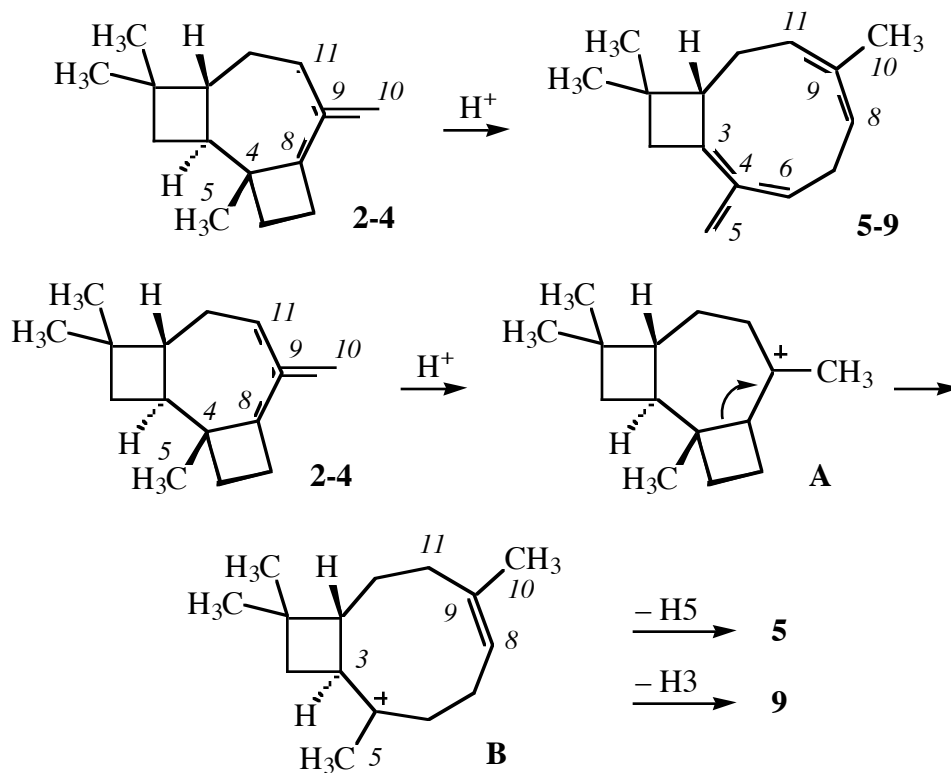


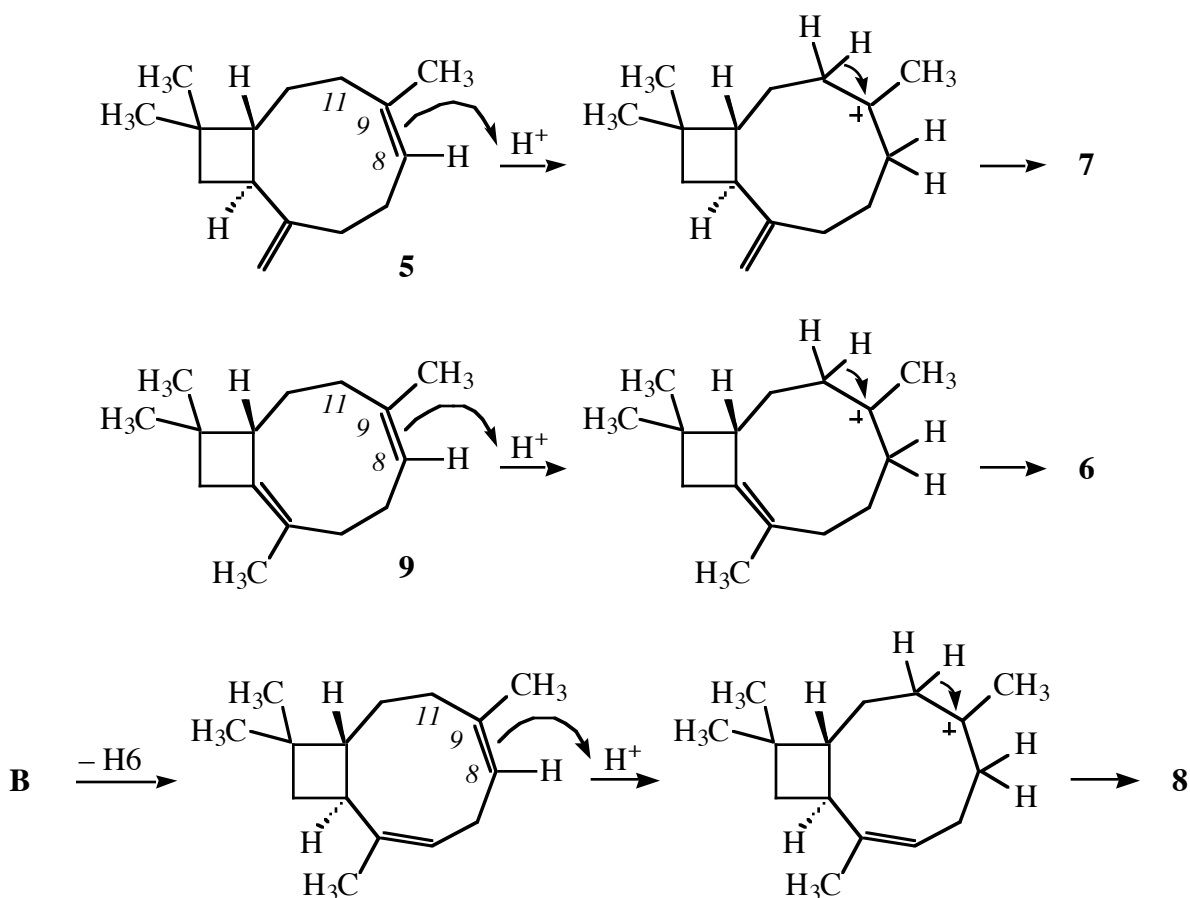
3. Number the C's in **1**. We see that the first set of compounds, **2-4**, are all obtained by formation of a bond between C4 and C8. To make the C4–C8 bond, we could make C4 electrophilic and C8 nucleophilic, or vice versa. If we make C8 electrophilic by protonation of C9, then after attack of C4, we end up with a 1° carbocation on C5 — very unstable and not what we want. On the other hand, if we make C4 electrophilic by protonating C5, then after attack of C8 on C4, we end up with a 3° carbocation on C9. As compounds **2-4** differ only in the location of the π bond to C9, suggesting that loss of H^+ from a C9 carbocation is the last step, this is what we need to do.



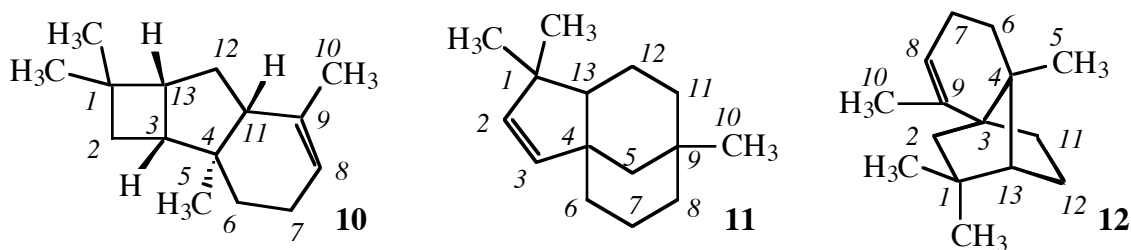


The next set of products, **5-9**, must be formed from **2-4**. To get from **2-4** to **5-9**, we must break the C4–C8 bond again. This is easy to do if we regenerate carbocation **A**. Cleavage of the C4–C8 bond gives a C8=C9 π bond and a carbocation, **B**, at C4. Loss of H⁺ from C5 or C3 of **B** gives product **5** or **9**, respectively. Compounds **5** and **9** can then partly isomerize to compounds **7** and **6**, respectively, by protonation at C8 and loss of H⁺ from C11. Loss of H⁺ from C6 of **B**, followed by protonation at C8 and loss of H⁺ from C11, gives product **8**.



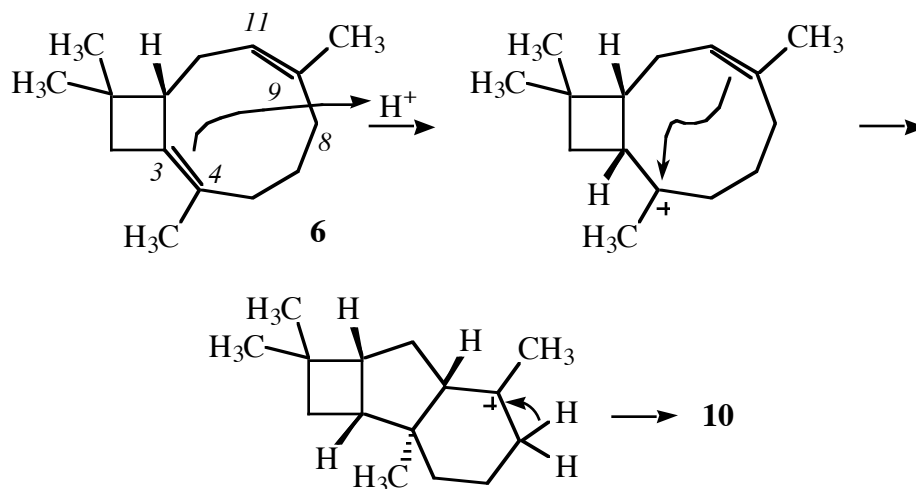


After a while longer, compounds **5-9** are converted into compounds **10-12**. Note that since all of **5-9** are easily interconverted by protonation and deprotonation reactions, any of them could be the precursors to any of **10-12**.

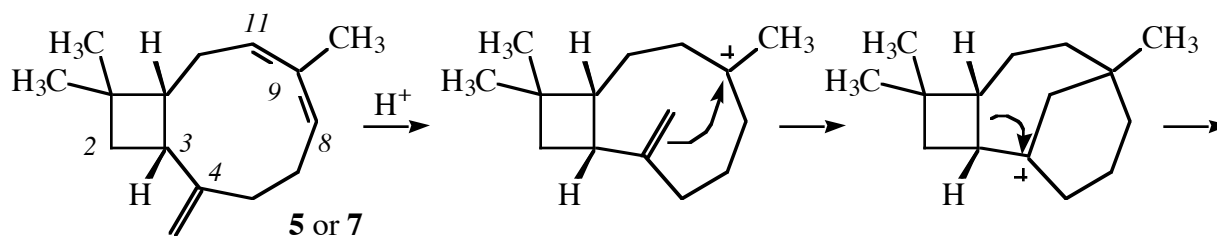


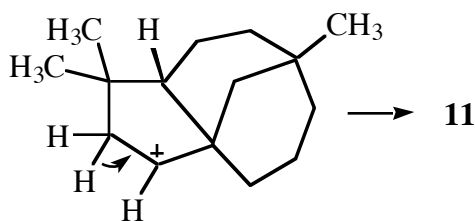
Compound **10** has a new C4-C11 bond. Either C4 is the nucleophile and C11 is the electrophile, or vice versa. Either way, compounds **5** and **9** are excluded as the immediate precursors to **10**, since they both have a saturated C11 that cannot be rendered nucleophilic or electrophilic (except by isomerization to **6**, **7**, or **8**). If C11 is the nucleophile, this would put a carbocation at C9, which is where we want it so that we can deprotonate C8 to form the C8=C9 π bond in **10**. So we might protonate **6**, **7**, or **8** at C3, C5, or C6,

respectively, to make an electrophile at C4. However, note the stereochemistry of the H atom at C3 in **10**. Both **7** and **8** have the opposite stereochemistry at C3. This means that **6** must be the immediate precursor to **10**. Protonation of C3 of **6** from the top face gives a carbocation at C4. Attack of the C11=C9 π bond on C4 gives a new σ bond and a carbocation at C9. Loss of H⁺ from C8 gives **10**.

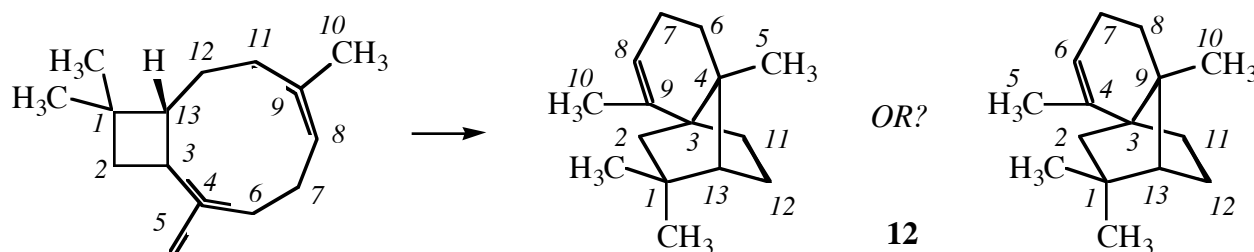


Compound **11** has new bonds at C5–C9 and C13–C4, and the C3–C13 bond is broken. Also, a new C2=C3 π bond is formed. The shift of the C13–C3 bond to the C13–C4 bond suggest a 1,2-alkyl shift. Then loss of H⁺ from C2 can give the C2=C3 π bond. So we need to establish a carbocation at C4. We can do this simply by protonating C5 of **5** or **7**, but if we do this, then we can't form the C5–C9 bond. But allowing C5 to be a nucleophile toward a C9 carbocation will give a similar carbocation at C4 and gives the desired bond. The requisite carbocation at C9 might be generated by protonation of C8 of **5** or C11 of **7**. Addition of the C4=C5 π bond to C9 gives the C5–C9 σ bond and a carbocation at C4. A 1,2-alkyl shift of C13 from C3 to C4 gives a carbocation at C3, which is deprotonated to give **11**.





The key to **12** is numbering its C's correctly. It's relatively easy to number the atoms in the bottom of the compound as C1 to C3 and C11 to C13, but the atoms in the top half of the compound could be labelled as C4 to C9 or the other way around, as C9 to C4. If you label the atoms incorrectly, the problem becomes nearly impossible. How do you decide which is correct?



Make a list of make and break for each compound.

Left make: C3–C9, C3–C11, C4–C13.

Right make: C3–C9, C3–C11, C9–C13.

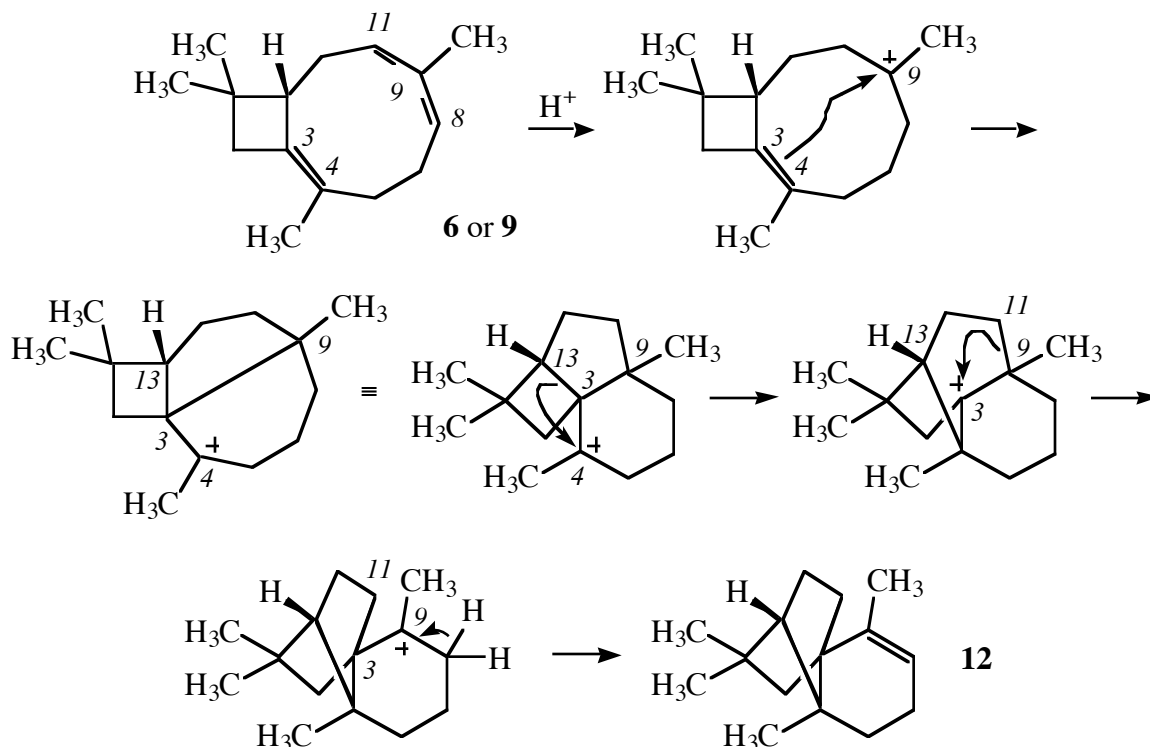
Left break: C3–C13, C9–C11.

Right break: C3–C13, C9–C11.

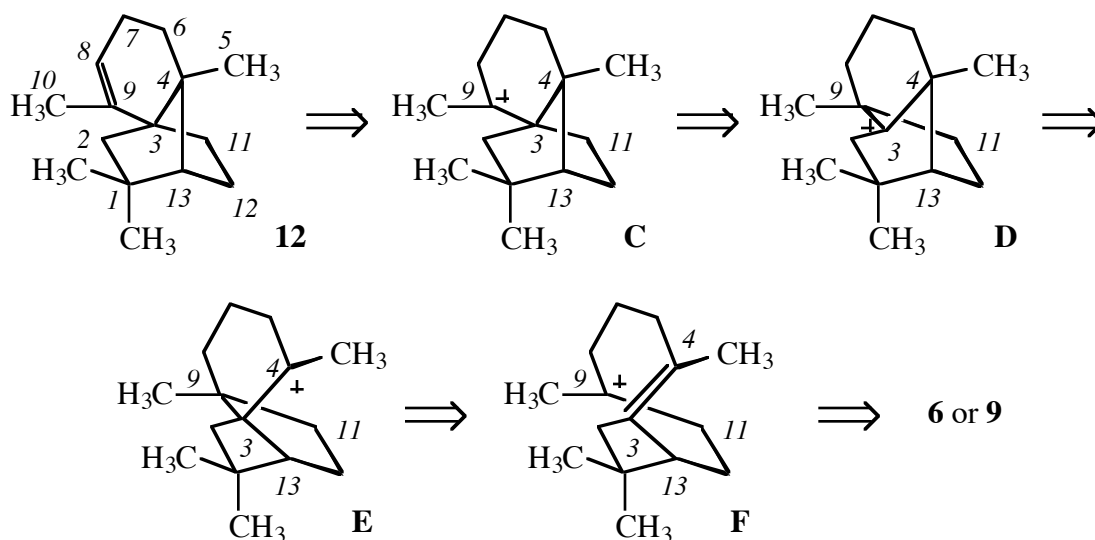
The only difference is that on the right, we need to make C4–C13, while on the left, we need to make C9–C13. Which is better? On the left, the C4–C13 bond can be made and the C3–C13 bond can be broken by a 1,2-shift. This can't be done on the right. Also, in compound **11** we made a C4–C13 bond. Not a lot to go on, but the first numbering seems a little more likely, so we'll go with it. If you were unable to number the atoms correctly, go back and try to solve the problem now.

The broken C13–C3 and new C13–C4 bonds suggest a 1,2-alkyl shift of C13 from C3 to a C4 carbocation, leaving a carbocation at C3. The broken C9–C11 and new C3–C11 bonds suggest a 1,2-shift of C11 from C9 to a C3 carbocation, leaving a carbocation at C9. Since a shift of C11 from C9 to C3 could only occur

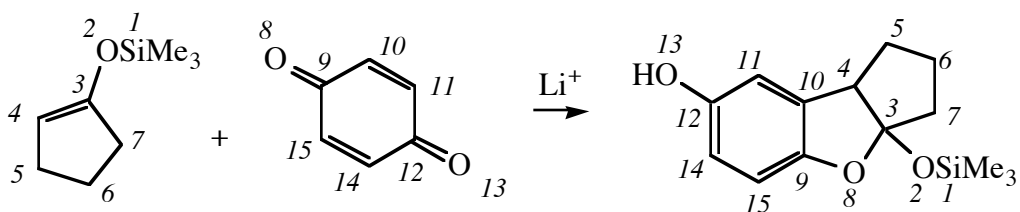
after C3 and C9 were connected, this suggests that the C3–C9 bond is formed *first*. Such a bond would be formed from a C9 carbocation with a C3=C4 π bond. The C9 carbocation could be formed from **6** or **9**. Attack of the C3=C4 π bond on C9 puts a carbocation at C4. Then C13 shifts from C3 to C4. That puts a carbocation at C3. Then C11 shifts from C9 to C3. Finally, deprotonation of C8 gives the product.



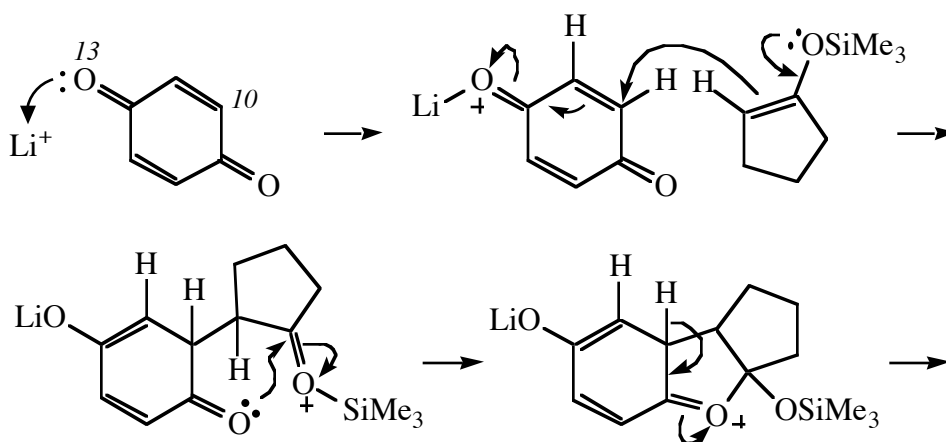
In a deep-seated rearrangement like this, it's sometimes easier to work backwards from the product. The π bond at C8=C9 in **12** suggests that the last step is deprotonation of C8 of a carbocation at C9, **C**. Carbocation **C** might have been formed from carbocation **D** by a 1,2-alkyl shift of C11 from C9 to C3. Carbocation **D** might have been formed from carbocation **E** by a 1,2-alkyl shift of C13 from C3 to C4. Carbocation **E** might have been formed from carbocation **F** by attack of a C3=C4 π bond on a C9 carbocation. The C9 carbocation could have been formed from **6** or **9** by protonation of C11 or C8, respectively.

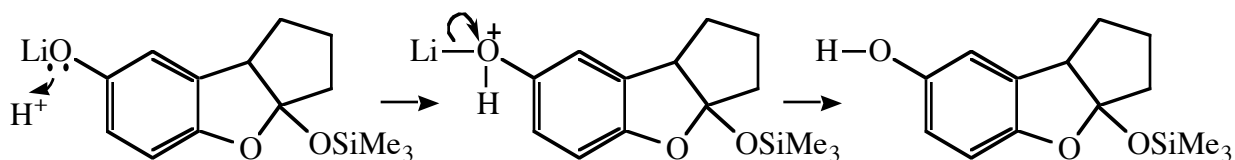


4. (a) Make: C3–O8, C4–C10.

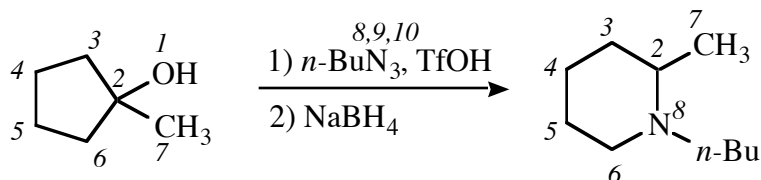


C4 is nucleophilic (enol ether), and C10 is electrophilic. The Lewis acid makes C10 more electrophilic by coordinating to O13. After conjugate addition, O8 traps the C3 carbocation. Proton– Li^+ exchange gives the product.

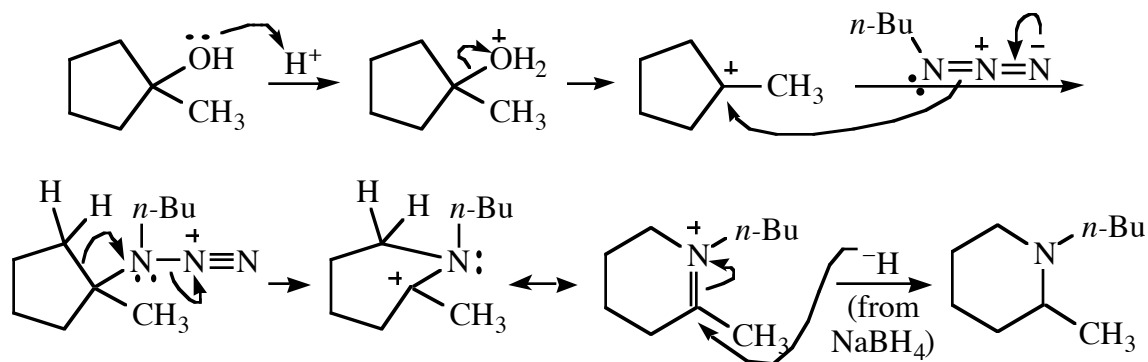




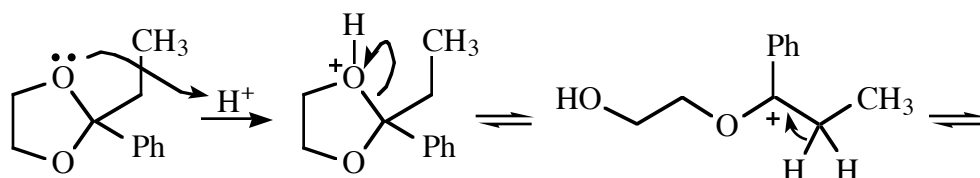
(b) Make: C2–N8, C6–N8. Break: O1–C2, C2–C6.

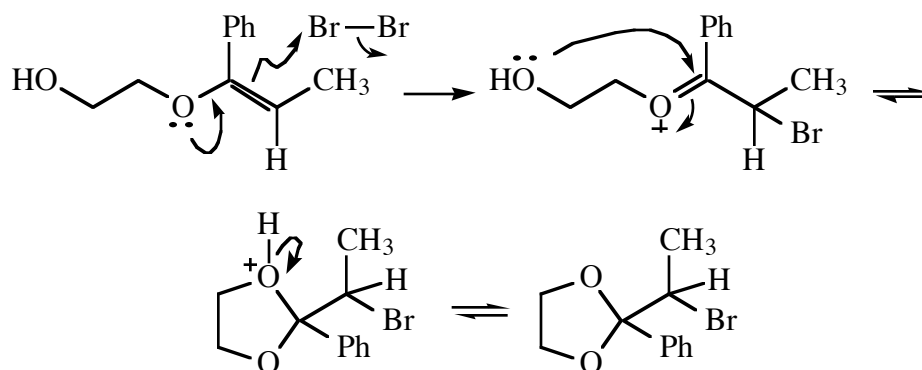


N8 of the azide adds to the carbocation to give an amine with an N_2^+ leaving group attached. Concerted 1,2-migration of C6 from C2 to N8 and expulsion of N_2 gives a N-stabilized carbocation, which is reduced by $NaBH_4$ to give the product.

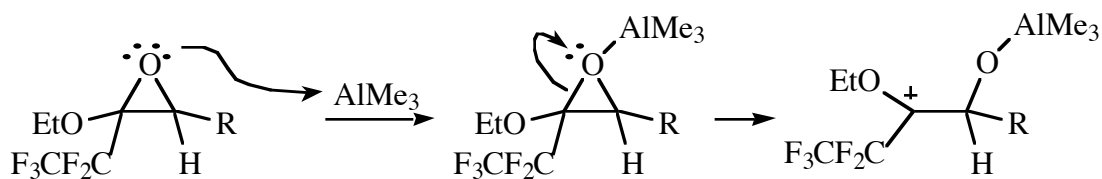


(c) Bromine is an electrophile, so we need to convert the CH_2 group into a nucleophile. This might be done by converting it into an alkene C. There is a leaving group next door, so we can do an E1 elimination to make an enol ether. Another way to look at it: under acidic conditions, acetals are in equilibrium with enol ethers. Either way, after bromination of the enol ether, a new carbocation is formed, which ring-closes to give the product.

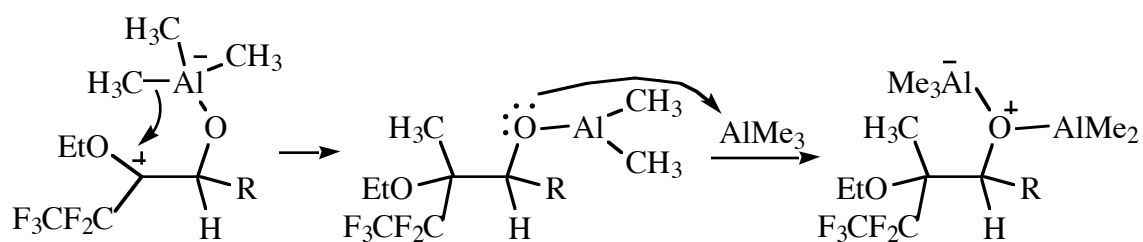




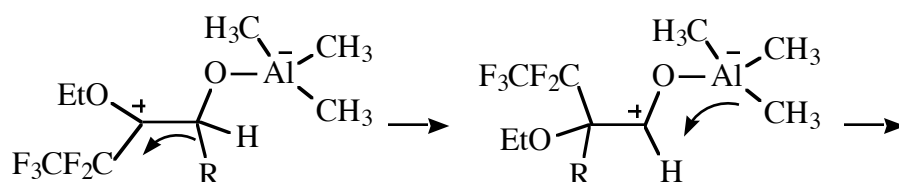
(d) Both reactions begin the same way. AlMe_3 is a Lewis acid, so it coordinates to the epoxide O. The epoxide then opens to a carbocation.

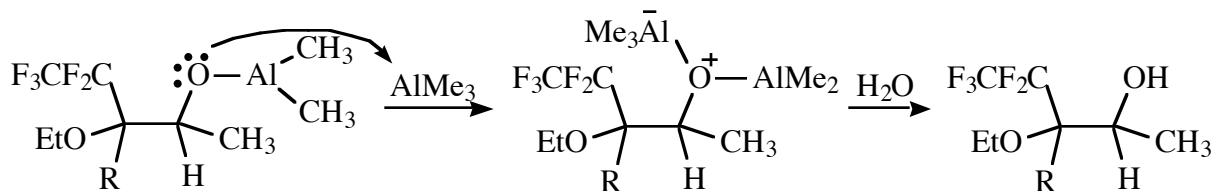


When $\text{R} = \text{CH}_2\text{CH}_2\text{Ph}$, the coordinated Al simply transfers a Me group to the carbocation C (σ bond nucleophile). The O atom then coordinates another equivalent of AlMe_3 before the product is obtained upon workup.

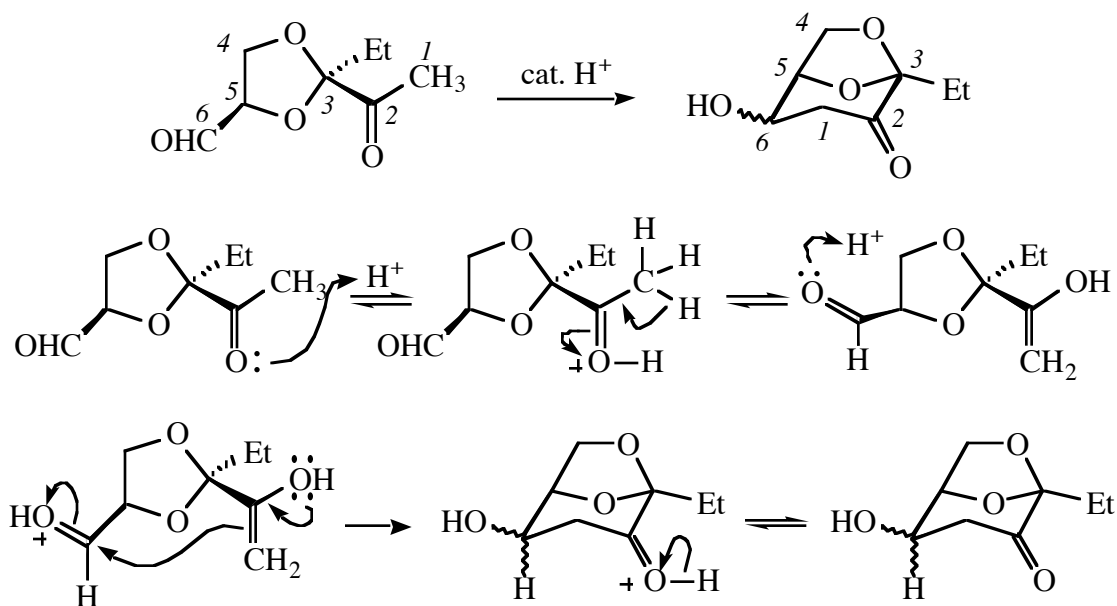


When $\text{R} = \text{cyclohexyl}$, the R group migrates (1,2-alkyl shift) to give a new carbocation. (2° Alkyl groups are more prone to migrate than 1° alkyl groups.) After Me transfer to the new carbocation and coordination of another equivalent of AlMe_3 , workup gives the product.

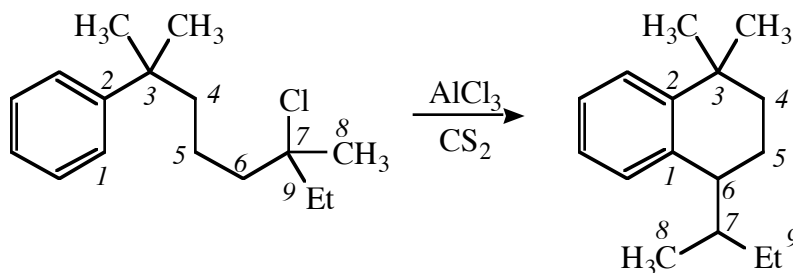




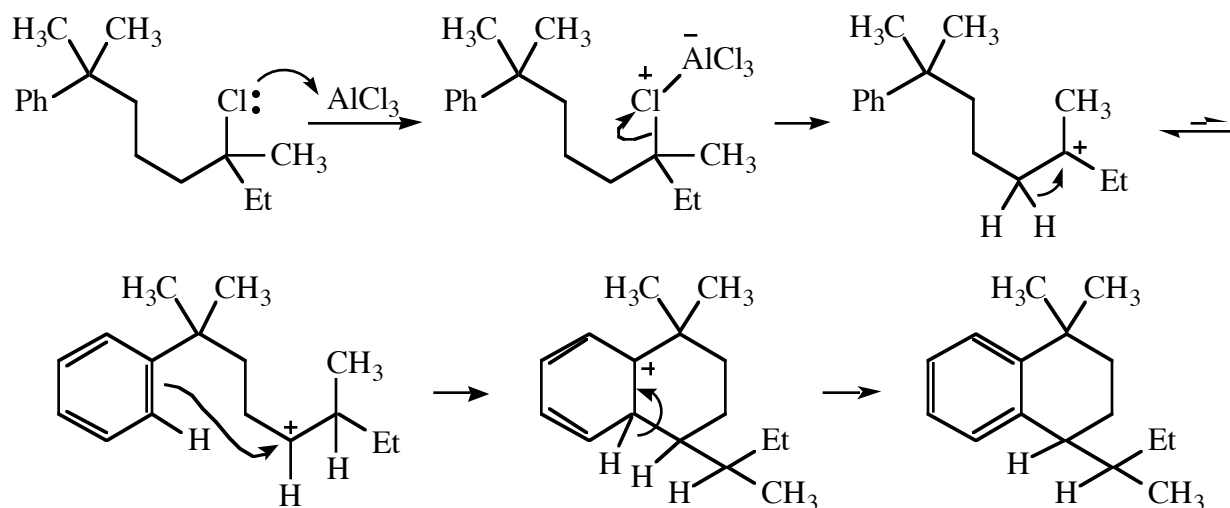
(e) Make: C1–C6. An acid-catalyzed aldol reaction.



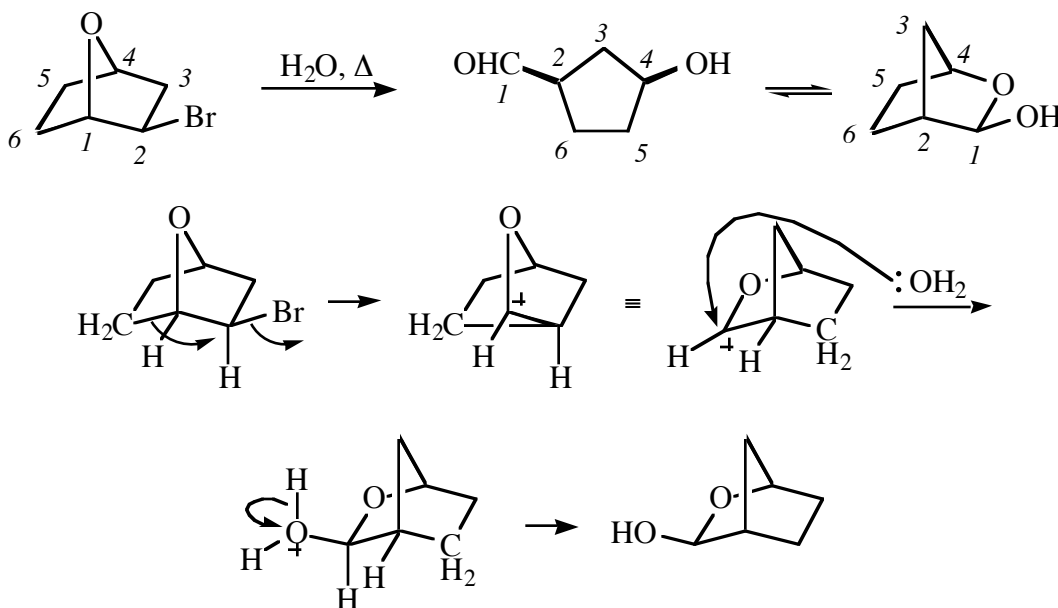
(f) Make: C1–C6. Break: C7–Cl.



The reaction looks like a simple Friedel–Crafts alkylation, but there is a twist — the leaving group is not on the C which becomes attached to the ring. After formation of the C7 carbocation, a 1,2-hydride shift occurs to give a C6 carbocation. The 1,2-hydride shift is energetically uphill, but the 2° carbocation is then trapped rapidly by the arene to give a 6-6 ring system.



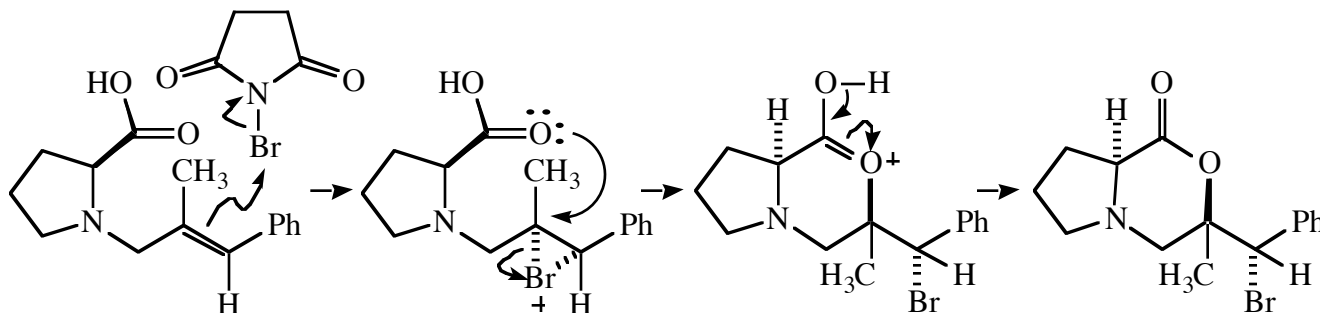
(g) Number the C's! The sequence C2–C3–C4–C5–C6 is identifiable on the basis of the number of H's and O's attached to each C in starting material and product. Make: C2–C6. Break: C1–C6. This pattern is evocative of a 1,2-alkyl shift. The C1–C6 bond is antiperiplanar to the C2–Br bond, so it migrates.



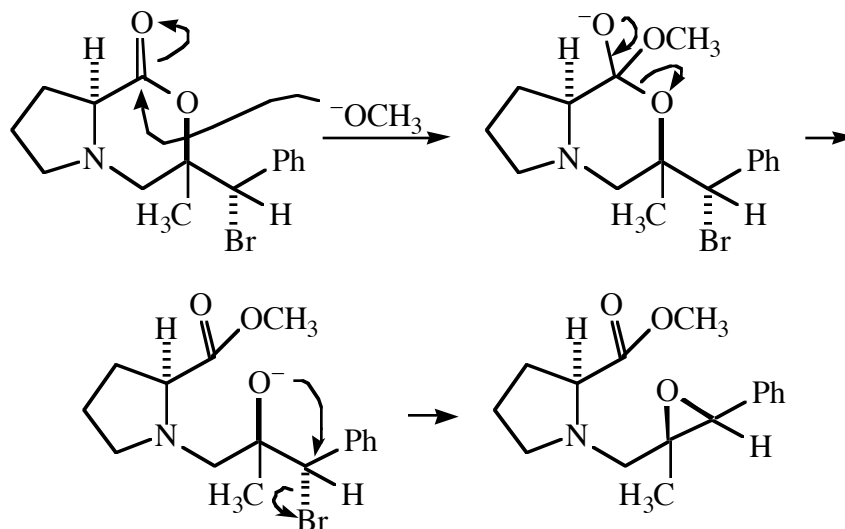
(h) The first step of this two-step reaction takes place under acidic conditions, and the second step takes place under basic conditions. The product from the acidic conditions needs to be a stable, neutral compound.

NBS is a source of Br^+ . It reacts with alkenes to give bromonium ions. Then both C–Br bonds need to be

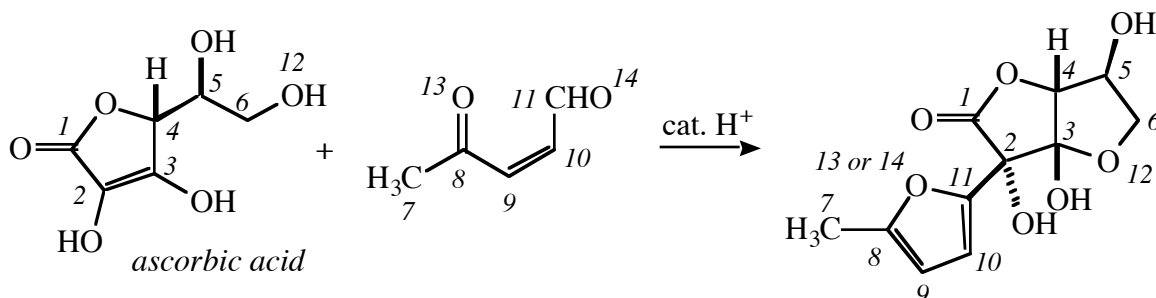
replaced by C–O bonds by single inversions, since the *trans* stereochemistry of the double bond is retained in the epoxide. Under these acidic conditions the bromonium ion is opened intramolecularly by the acid carbonyl O, with inversion at one center; loss of H⁺ gives a bromolactone.



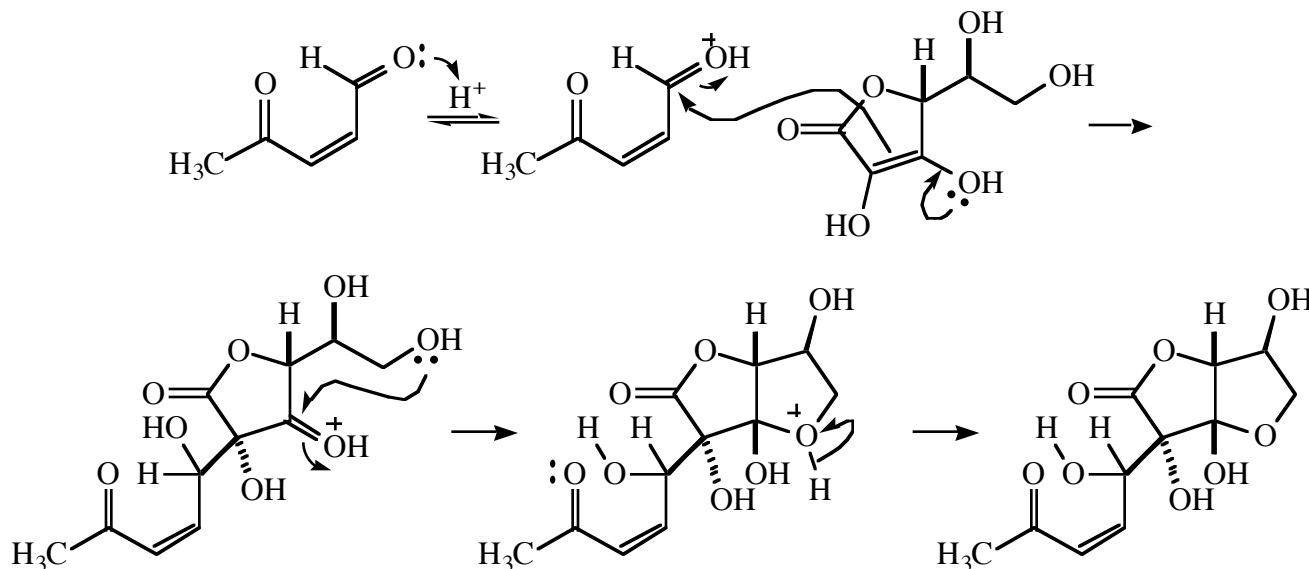
Now MeO[−] is added to begin the sequence that takes place under basic conditions. The MeO[−] opens the lactone to give a 2-bromoalkoxide, which closes to the epoxide, inverting the other center.



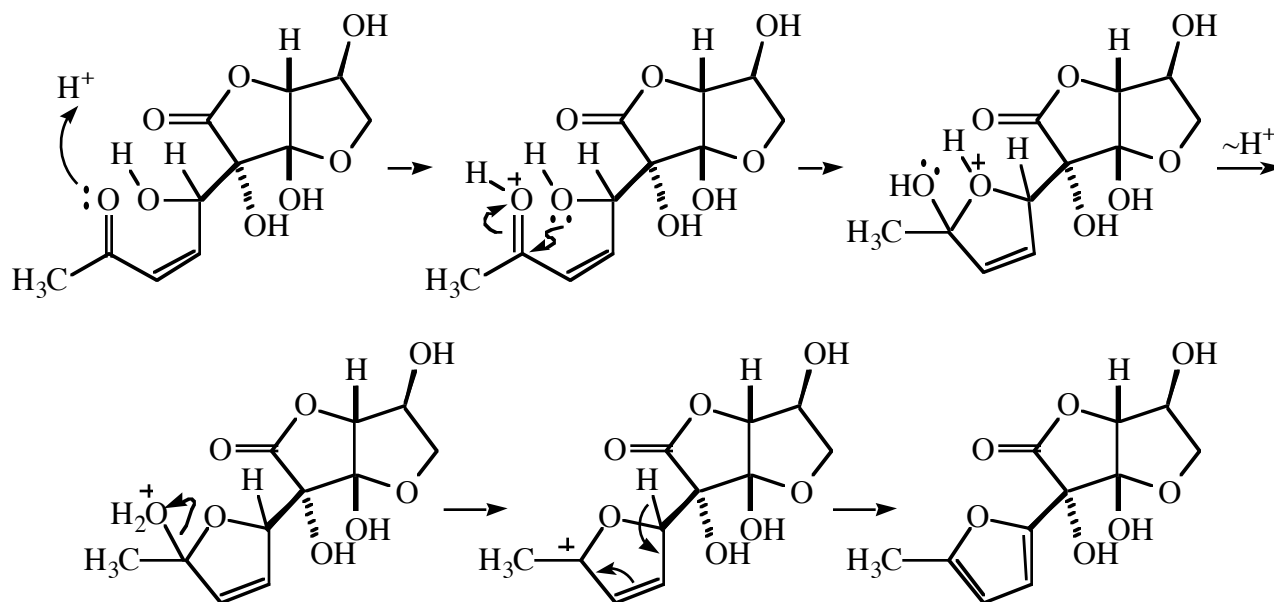
(i) Make: C2–C11, C3–O12, and either C8–O14 or C11–O13. Break: Either C8–O13 or C11–O14.



Both C2 and C3 are β to an OH group, and C3 is also β to a carbonyl. Thus C3 is subject to both pushing and pulling, but C2 is subject only to pushing. The first step then is likely attack of nucleophilic C2 on electrophilic C11. Then the C3 carbocation is trapped by O12.

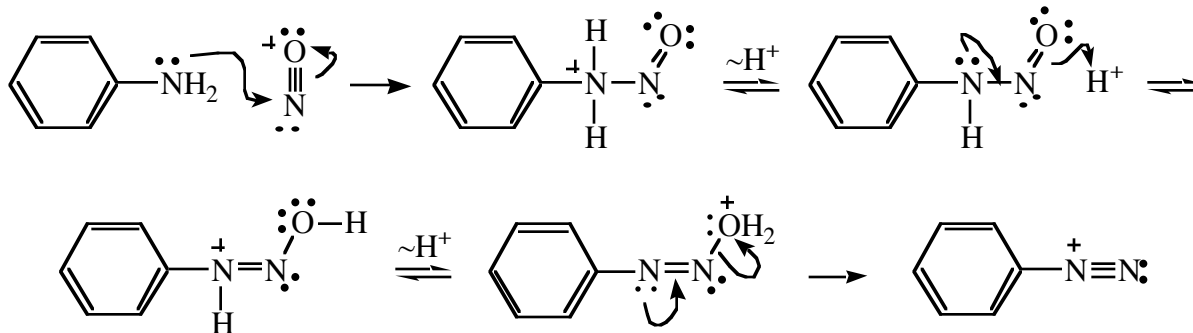


Now the furan ring is formed. Either O13 or O14 must be lost (certainly as H_2O). If O14 is lost, a carbocation at C11 would be required. This carbocation would be destabilized by the electron-withdrawing carbonyl at C18. Better to protonate O14, have O14 attack C8, and then lose O14 as H_2O .

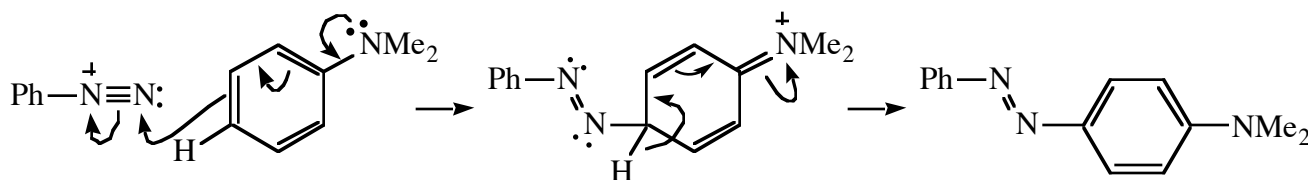


(j) Addition of NaNO_2 and HCl to an aniline always gives a diazonium salt by the mechanism discussed in

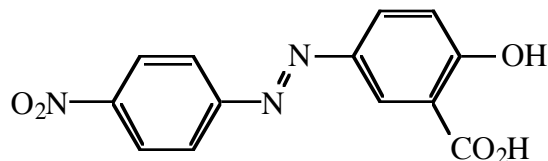
the chapter (Section D.2).



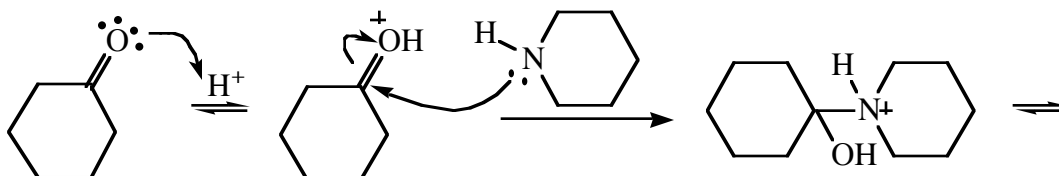
Then the second arene undergoes electrophilic aromatic substitution, with the terminal N of the diazonium salt as the electrophilic atom. When nucleophilic arenes are added to diazonium salts, electrophilic aromatic substitution tends to take place instead of $\text{S}_{\text{N}}1$ substitution of the diazonium salt.

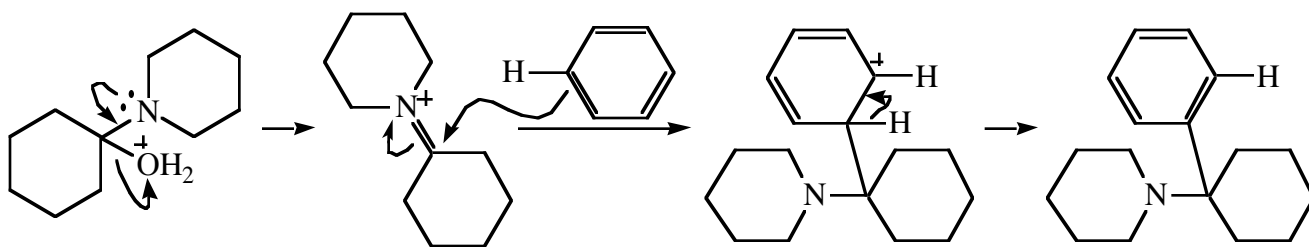


(k) Salicylic acid (as in acetylsalicylic acid, or aspirin) is 2-hydroxybenzoic acid.

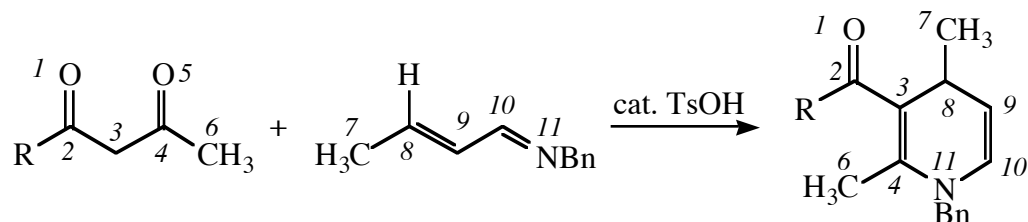


(l) Two new σ bonds are formed in this reaction. In principle either the $\text{N}-\text{C}$ bond or the $\text{C}-\text{C}$ bond could form first. Benzene does not generally react with ketones, while the reaction of an amine with a ketone is very rapid. Therefore the $\text{N}-\text{C}$ bond forms, and iminium ion is generated, and then electrophilic aromatic substitution occurs to give PCP.

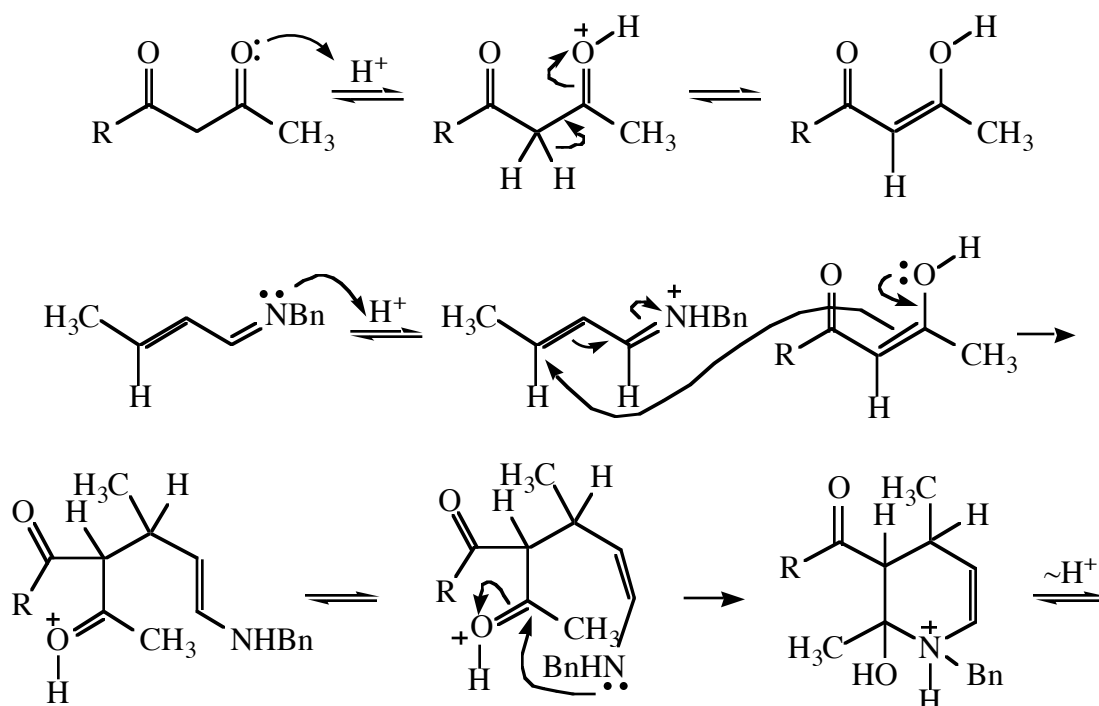


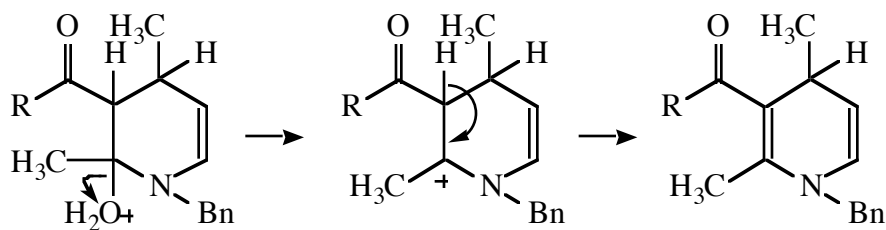


(m) Make: C3–C8, C4–N11. Break: C4–O5.

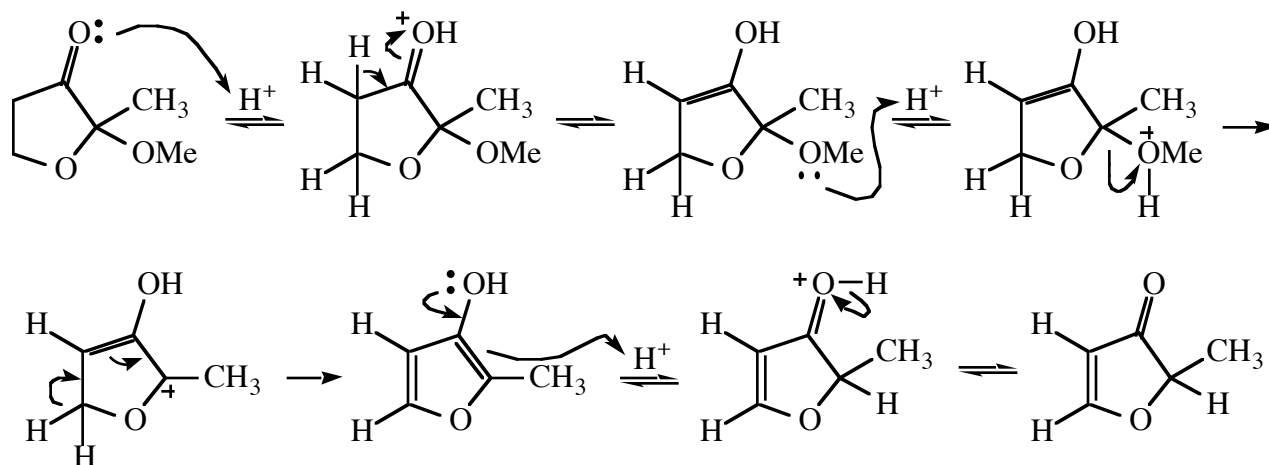


C3 and N11 are nucleophilic, C4 and C8 are electrophilic. Which bond forms first? Once the N11–C4 bond forms, C3 is made much less nucleophilic. So form the C3–C8 bond first (Michael reaction). C3 is made nucleophilic by tautomerization to the enol. The Michael reaction must be preceded by protonation of N11 to make C8 electrophilic enough. After the Michael reaction, the enamine is formed by the mechanism discussed in the text.

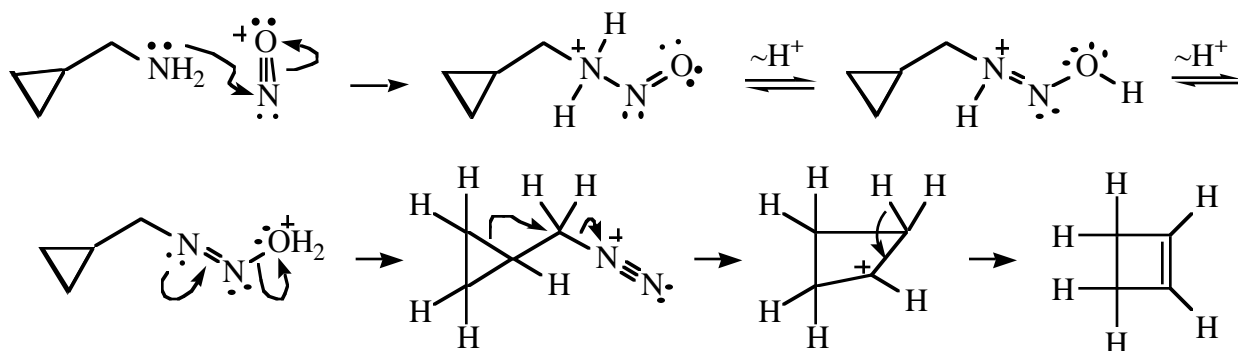




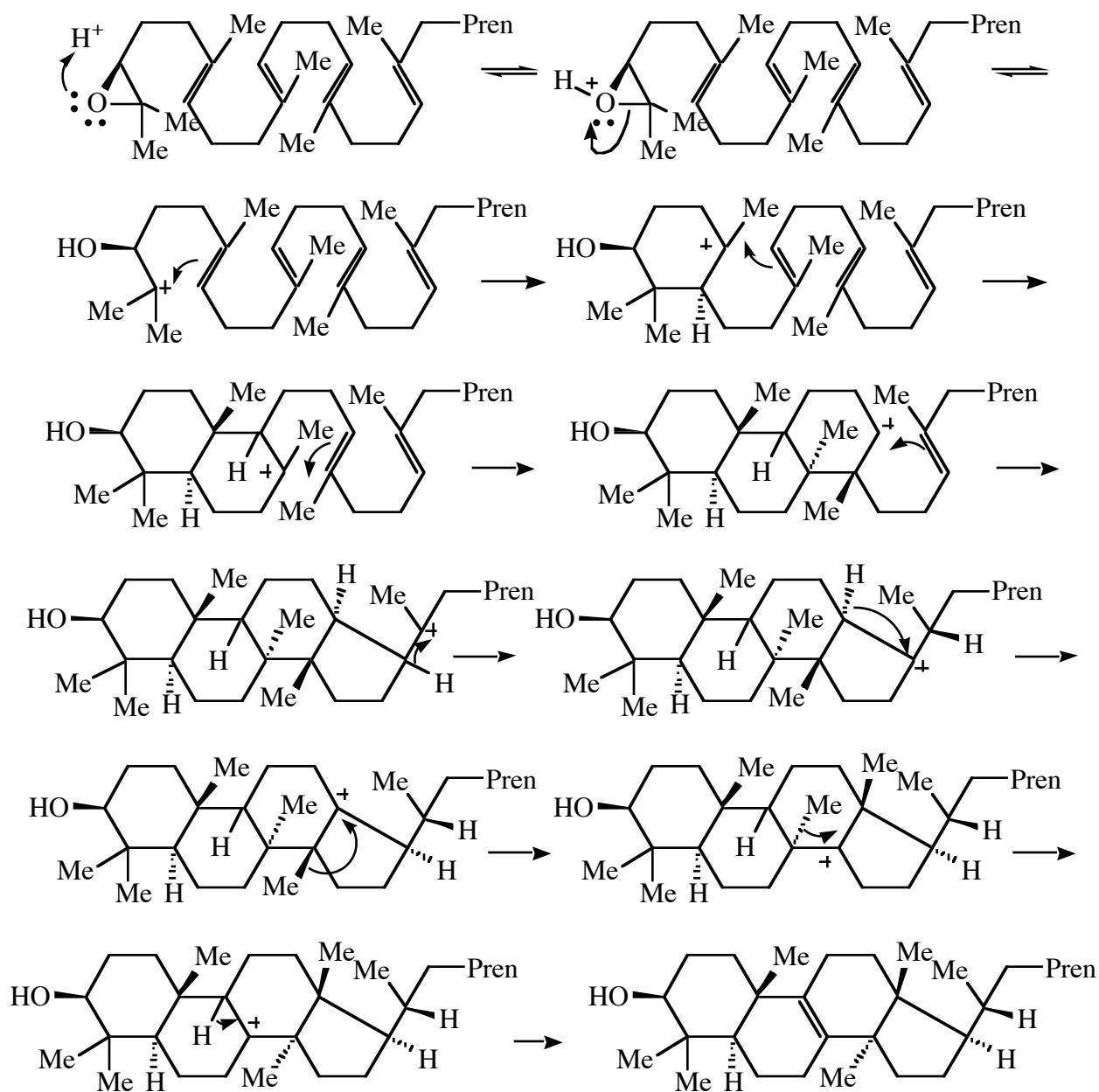
(n) The elements of MeOH are eliminated. However, since there are no H's β to the OMe group, the mechanism must be slightly more complicated than a simple E1. The key is to realize that formation of a carbocation at the acetal C is unlikely to occur with the keto group present. Under acidic conditions, the keto group is in equilibrium with the enol, from which a vinylogous E1 elimination can occur.



(o) Nitrous acid converts primary amines into diazonium salts RN_2^+ . The N_2 group is an excellent leaving group. Formation of the carbocation followed by 1,2-alkyl migration gives a more stable carbocation, which loses H^+ to give cyclobutene. Alternatively, α -elimination could occur from the diazonium ion to give a carbene, which would undergo the 1,2-hydride shift to give the alkene.

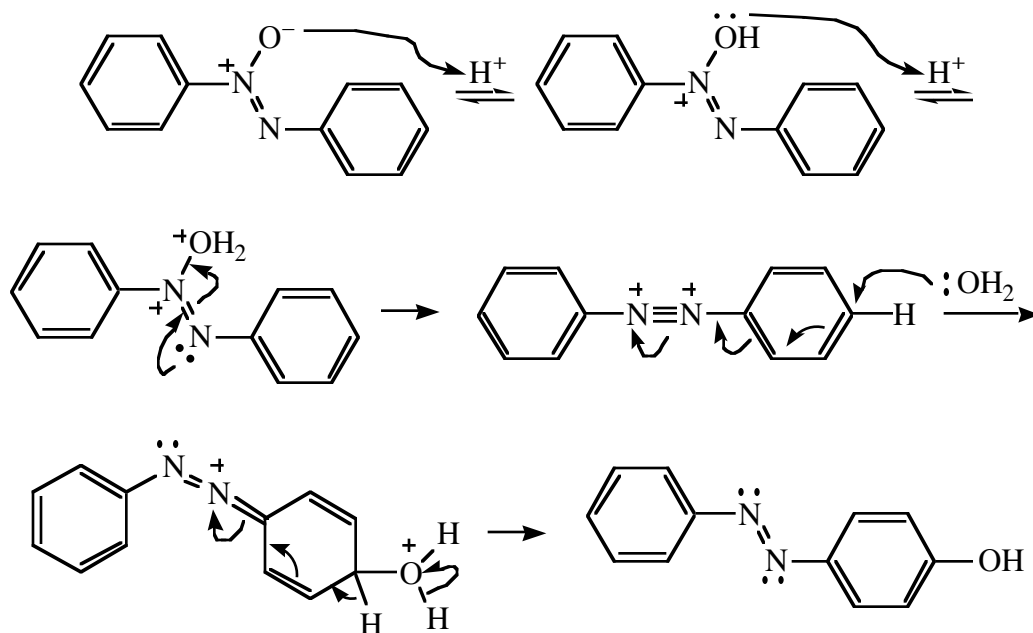


(p) The most basic site is the epoxide O. Protonation followed by a very facile ring opening gives a 3° carbocation. A series of additions of alkenes to carbocations follows, then a series of 1,2-shifts. The additions and 1,2-shifts have been written as if they occur stepwise, but some or all of them might be concerted. In principle, any of the carbocationic intermediates could undergo many other reactions; the role of the enzyme is to steer the reaction along the desired mechanistic pathway.

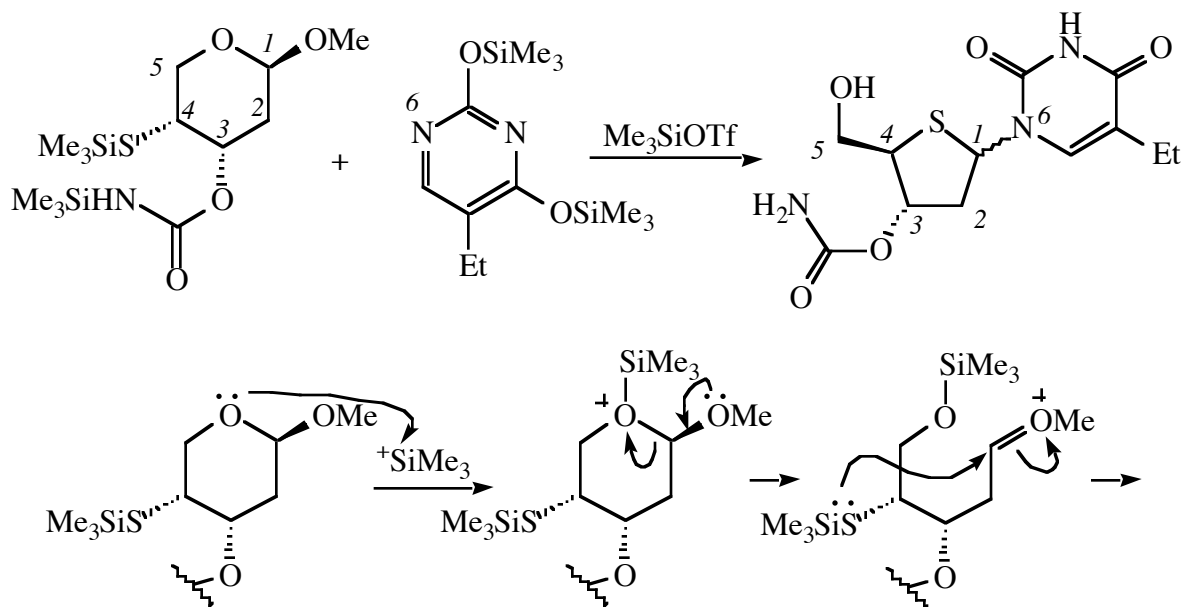


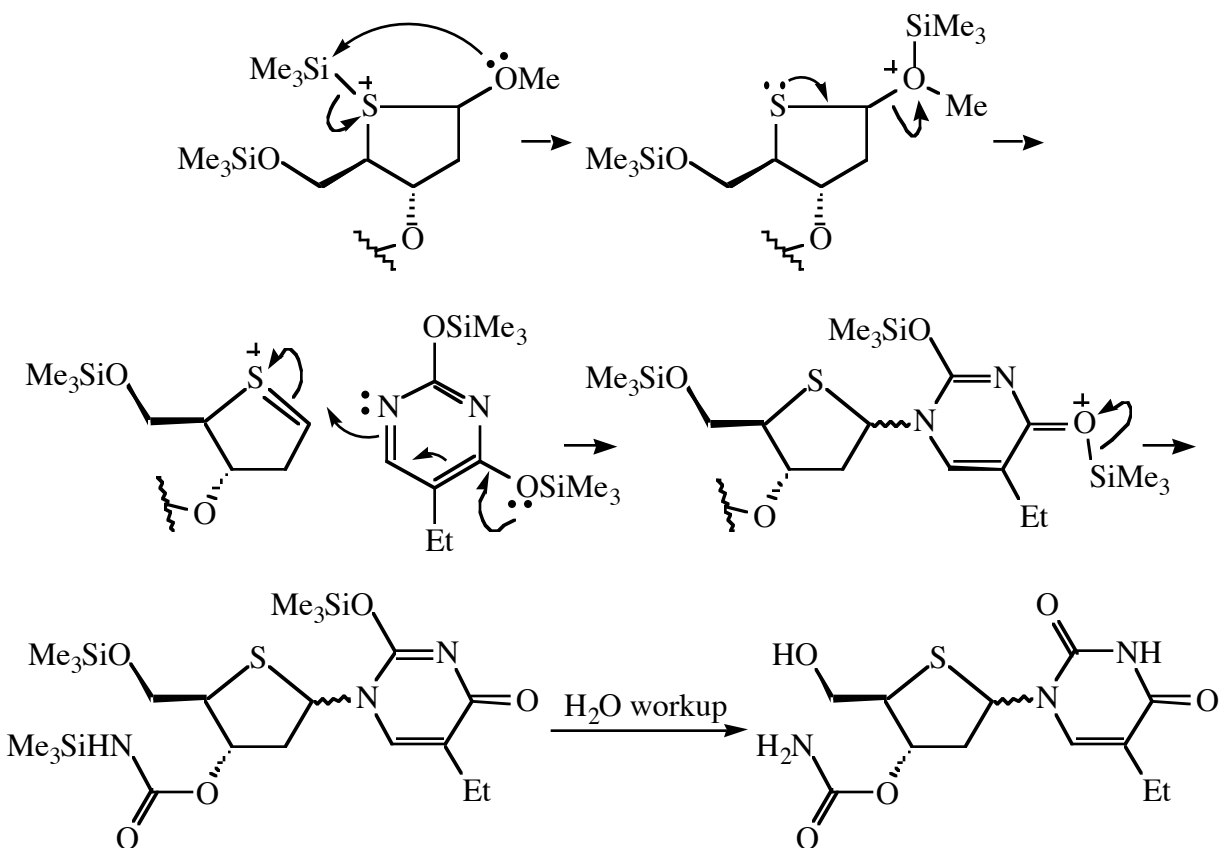
(q) The scrambling of the ^{15}N label suggests a symmetrical intermediate in which the two N's are equivalent. Incorporation of ^{18}O from H_2O suggests that a nucleophilic aromatic substitution is occurring.

Double protonation of O followed by loss of H₂O gives a very electrophilic, symmetrical dicationic intermediate. Water can attack the *para* carbon; deprotonation then gives the product.

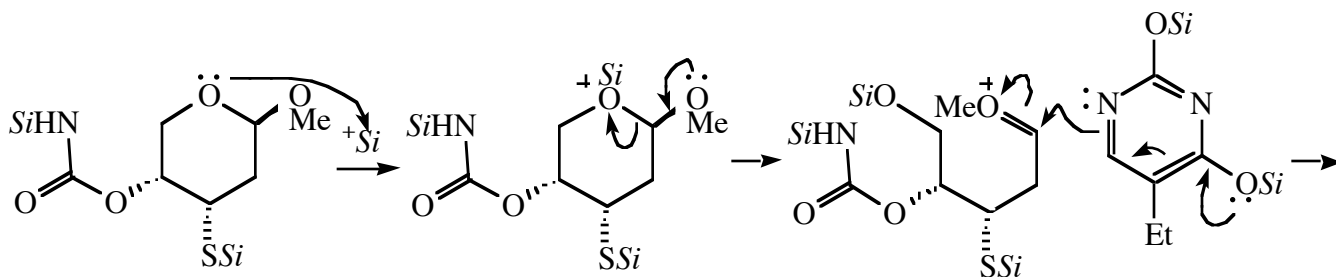


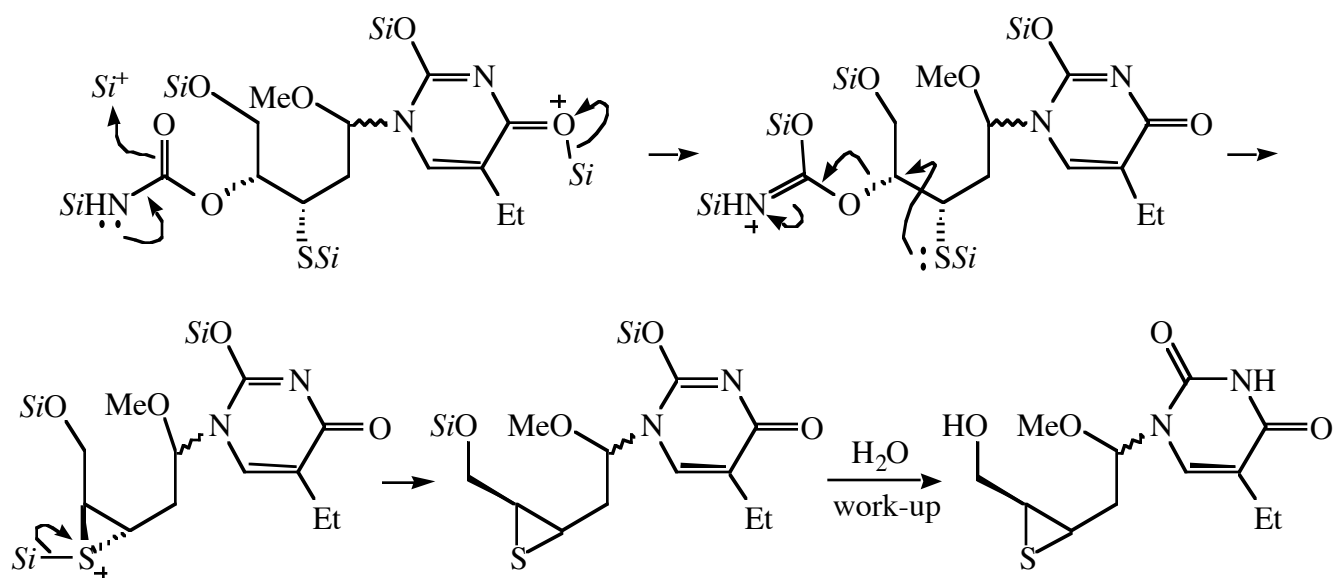
(r) (1) The two C1–O bonds undergo substitution with C1–S and C1–N6 bonds. Under these Lewis acidic conditions, and at this secondary and O-substituted center, the substitutions are likely to proceed by an S_N1 mechanism. The order of the two substitutions is not clear.



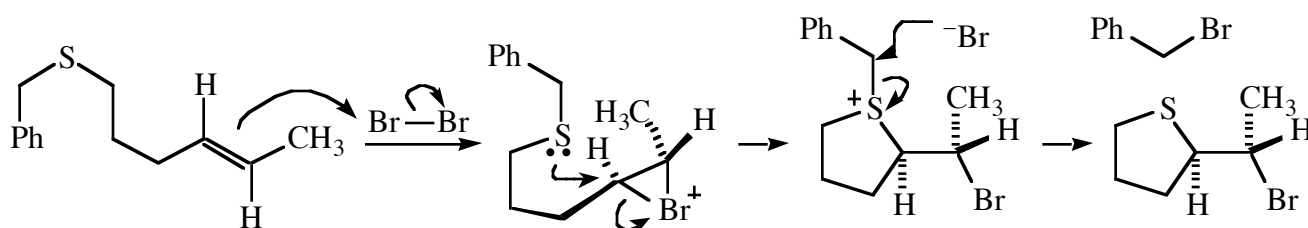


(2) Now only the endocyclic C1–O bond undergoes substitution, but the C4–O bond undergoes substitution with a C–S bond. In the previous problem we had S attack the C1 carbocation to give a five-membered ring. In the present problem, this would result in the formation of a four-membered ring, so the external nucleophile attacks C1 directly. We still need to form the C4–S bond. As it stands, C4 is not terribly electrophilic, but silylation of the urethane carbonyl O makes C4 more electrophilic. Then attack of S on C4 followed by desilylation gives the product. $\text{Si} = \text{SiMe}_3$.

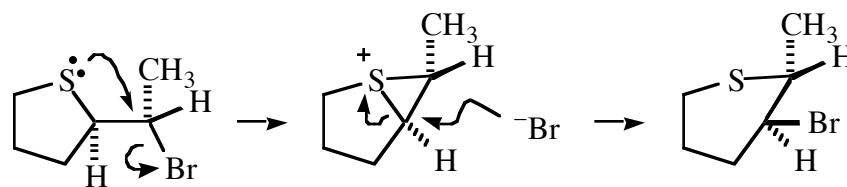




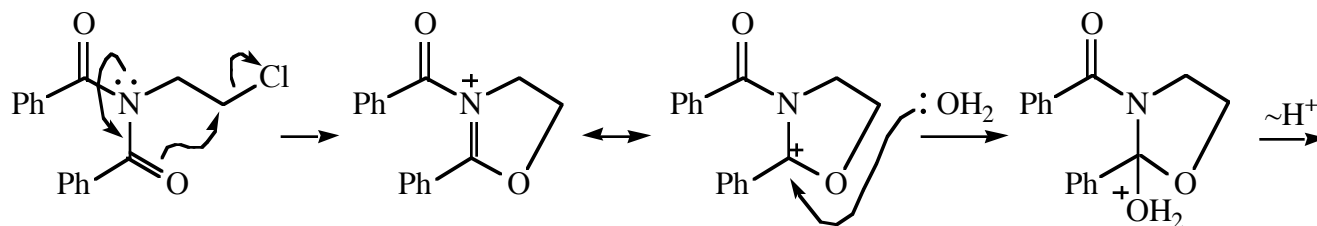
(s) Five-membered ring formation proceeds through a bromonium ion intermediate.

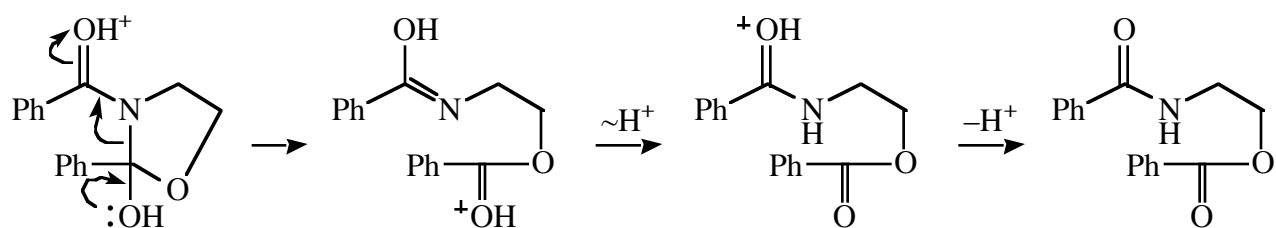


The five-membered ring can convert to the six-membered ring by two S_N2 displacements.

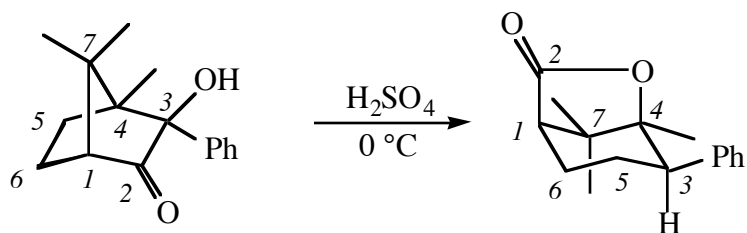


(t) The dependence of the rate of the reaction on the length of the alkyl chain suggests that an *intramolecular* reaction occurs between the nucleophilic O and the electrophilic C attached to Cl.

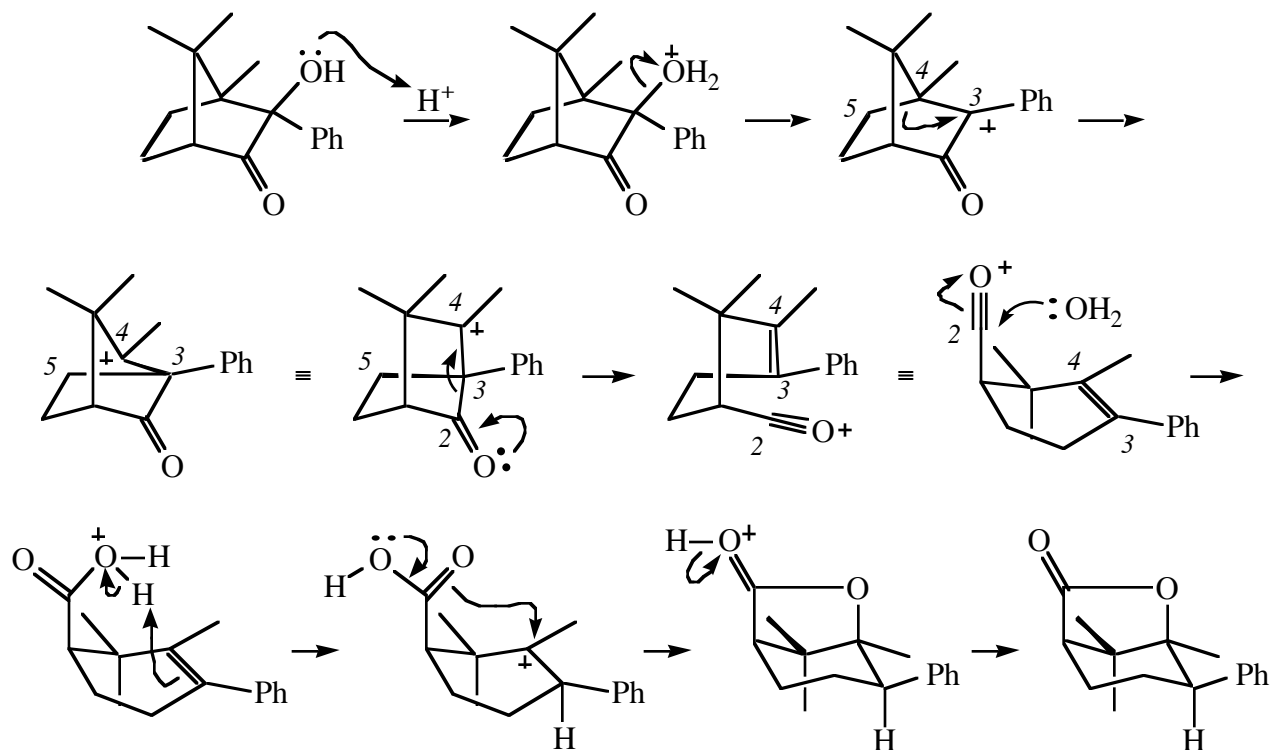




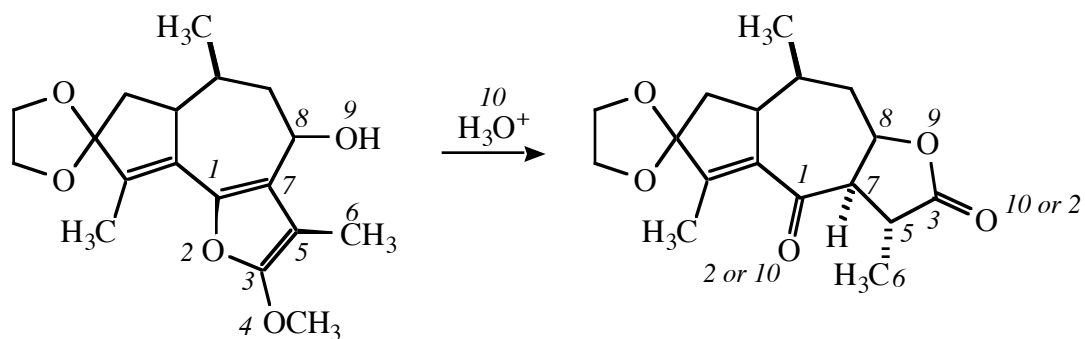
(u) The key atoms to recognize for numbering purposes are C7, C4, and C3. Then the others fall into place. Break: C2–C3, C4–C5. Make: C3–C5.



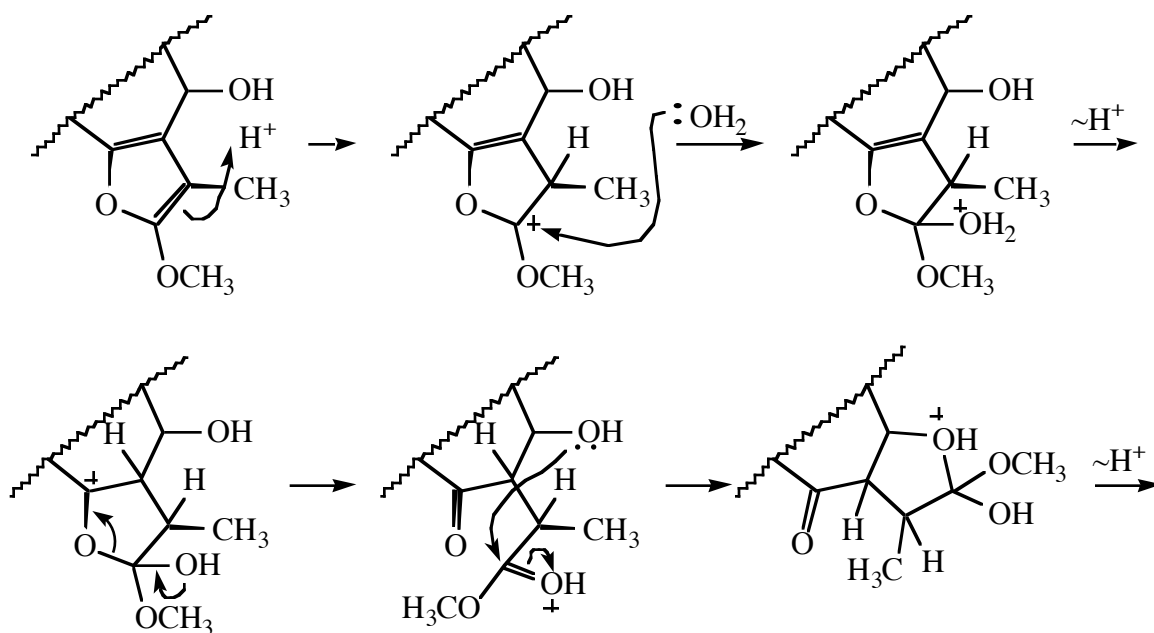
The cleavage of C5–C4 and formation of C5–C3 suggests that we have a 1,2-alkyl migration of C5 from C4 to a cationic C3. Then the electrons in the C2–C3 bond can move to form a new π bond between C3 and C4, leaving a stabilized acylium ion at C2. After addition of H_2O to the acylium ion, an acid-catalyzed electrophilic addition of the resultant carboxylic acid to the alkene occurs to give the final product.

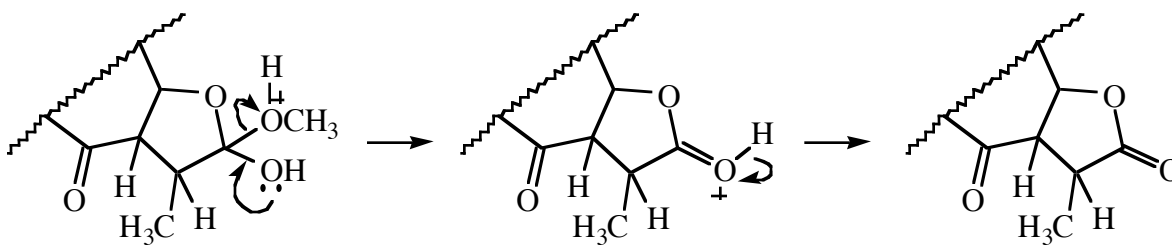


(v) The OCH_3 group is lost, and an OH group is gained. Whereas in the starting material C1 and C3 are attached to the same O, in the product they are attached to different O's. It is not clear whether O2 remains attached to C1 or C3. Make: O9–C3, O10–C3; break: C3–O4, C3–O2. *OR* make: O9–C3, O10–C1; break: C3–O4, C1–O2.

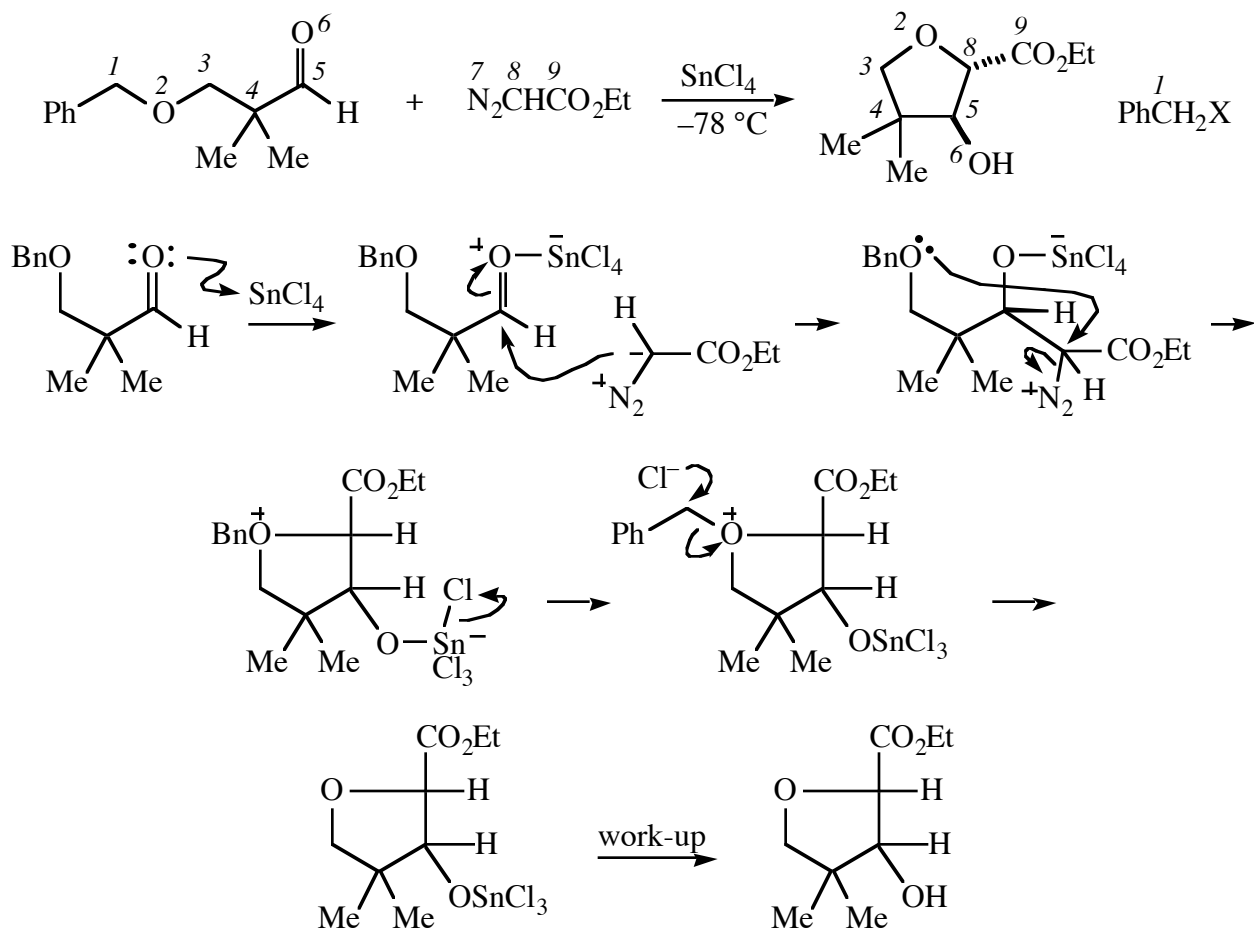


The first step is protonation; since all of the $\text{C}-\text{O}$ bonds to be broken are $\text{C}(\text{sp}^2)-\text{O}$ bonds, the direct ionization of a $\text{C}-\text{O}$ bond won't occur, so protonating O is unproductive. Both C5 and C7 need to gain a bond to H; protonation of C5 gives the better carbocation. Water can add to make the $\text{C3}-\text{O10}$ bond. The rest of the mechanism follows.

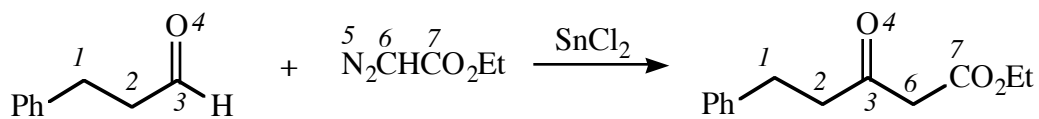




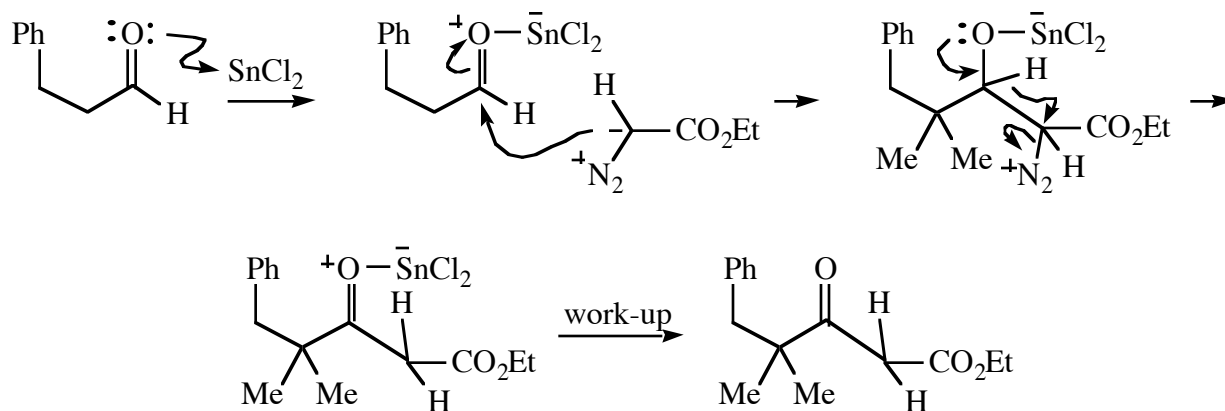
(w) Make: O2–C8, C5–C8. Break: C8–N, C1–O2. C8 is nucleophilic. SnCl₄ coordinates to O6 to make C5 more electrophilic, and C8 attacks C5. Then O2 circles around to displace N₂ from C8. Finally, Cl[–] from SnCl₄ can come back and displace O2 from C1. The stereochemistry of the product is thermodynamically controlled.



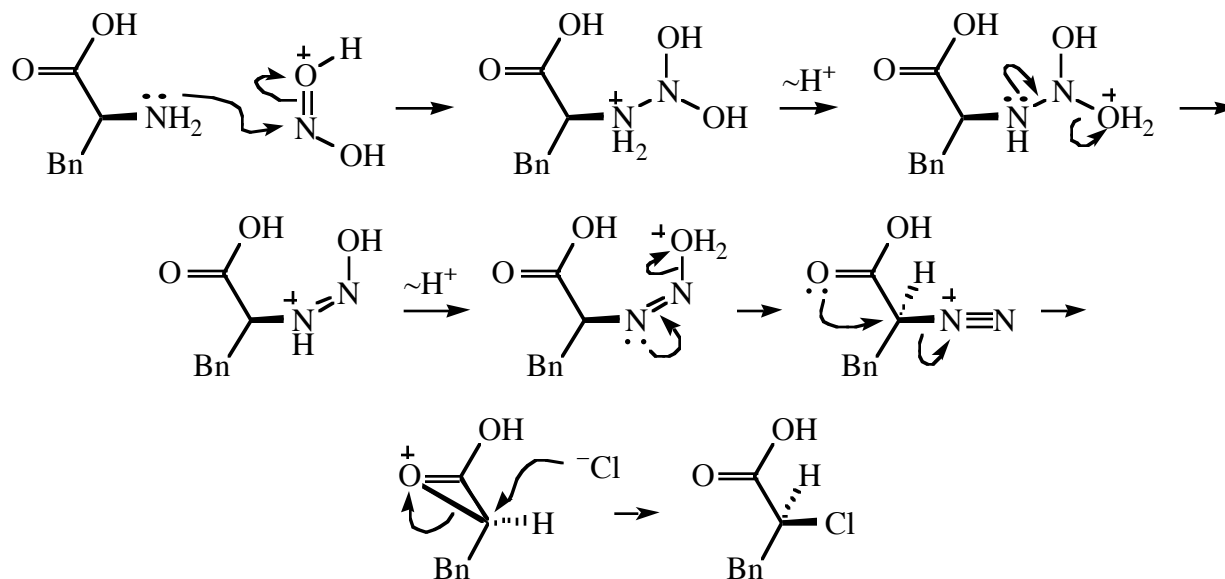
(x) Make: C3–C6. Break: C6–N5.



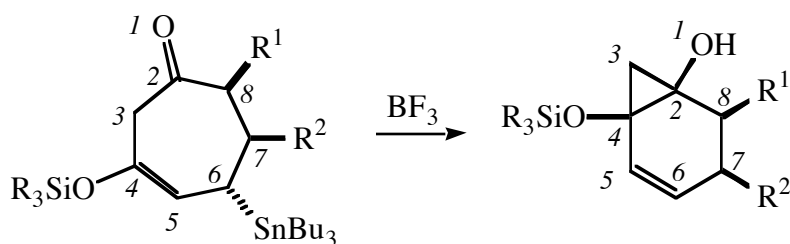
Reaction starts off the same way as last time. After addition to the carbonyl, though, a 1,2-hydride shift occurs with expulsion of N_2 to give the product after workup.



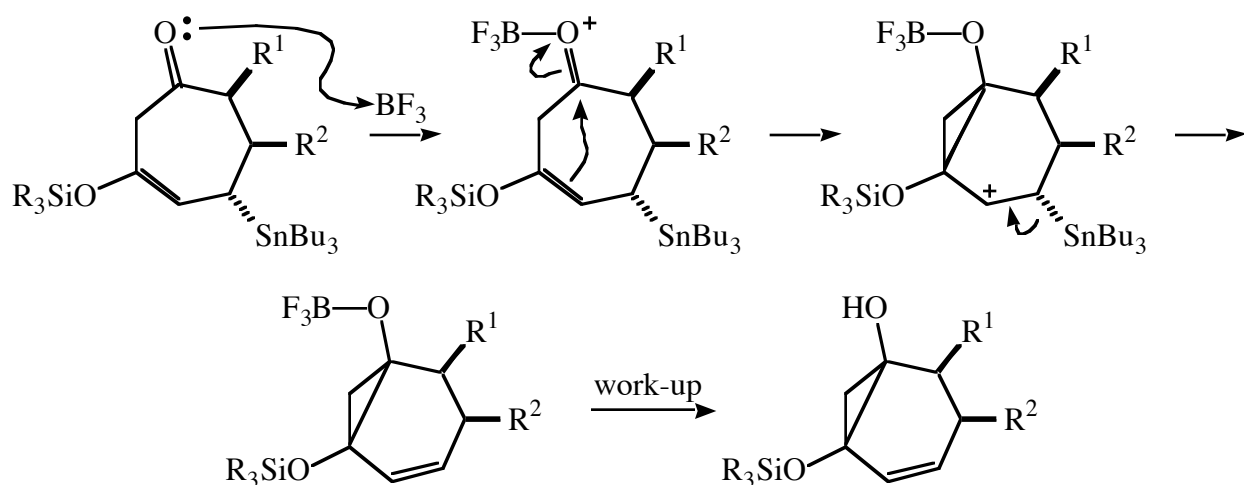
(y) The stereochemistry tells you that neither a simple S_N1 nor an S_N2 mechanism is operative. Two S_N2 substitutions would give the observed result, however. When 1° amines are mixed with HNO_2 , a diazonium ion is formed. Intramolecular S_N2 substitution by the carbonyl O gives a lactone, and then a second S_N2 substitution by Cl^- gives the product.



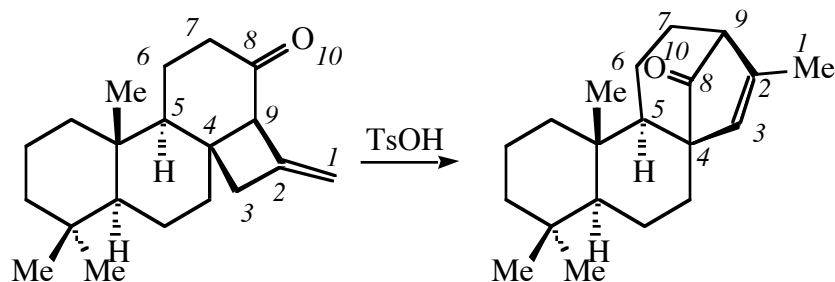
(z) Make: C2–C4. Break: C6–Sn.



C2 is electrophilic, especially after BF_3 coordinates to it. C4 can then act as a nucleophile, making C5 carbocationic. Fragmentation of the C6–Sn bond gives the product.



(aa) Numbering correctly is key. C4 through C7 are clear. The Me group in the product must be C1, and it's attached to C2. The rest follow. Make: C7–C9, C4–C8. Break: C7–C8, C4–C9.



First step is protonation of O10 to make C8 electrophilic. Then a shift of C4 from C9 to C8 occurs to give a cation at C9. This is followed by a shift of C7 from C8 to C9. Deprotonation of O10, protonation of C1, and deprotonation of C3 give the product.

