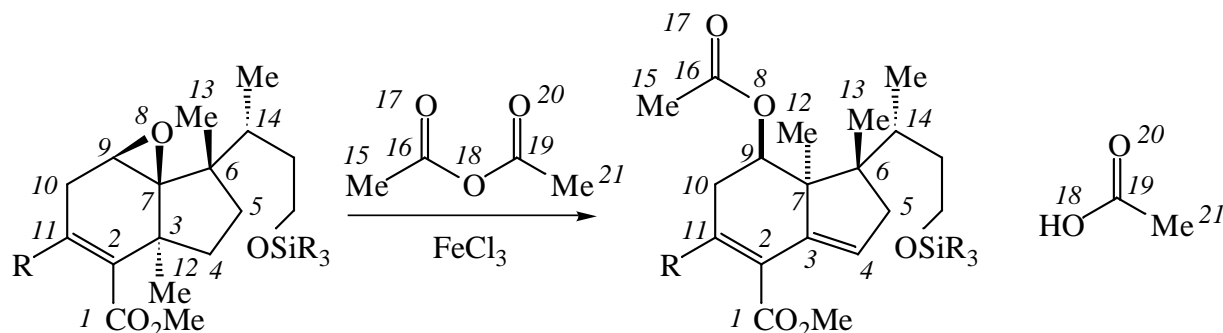
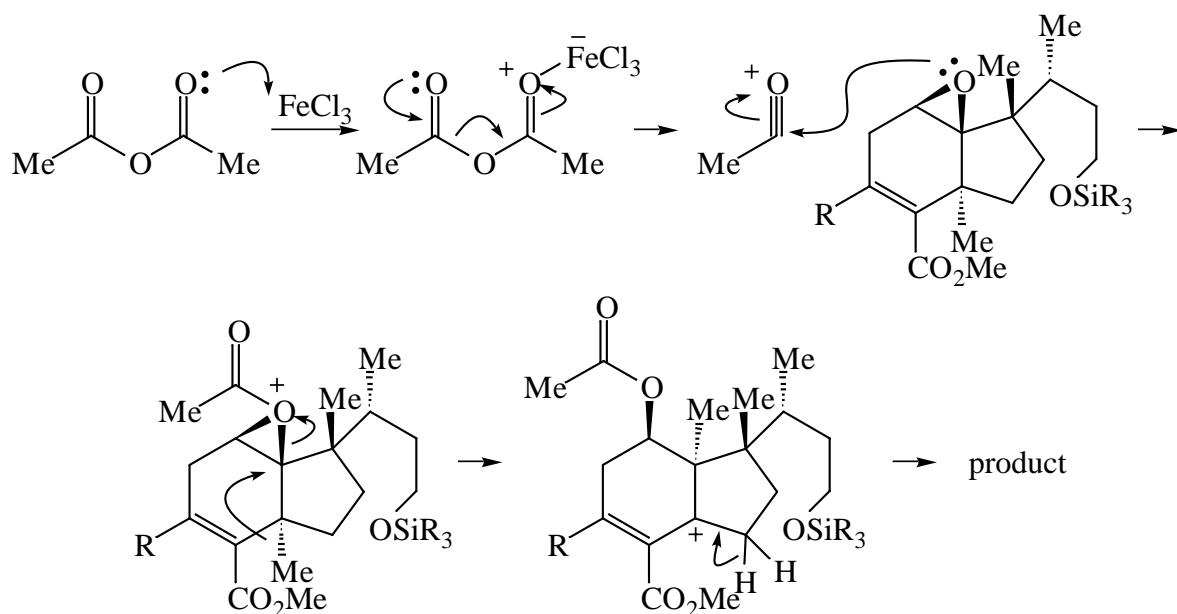


Answers To Chapter 3 In-Chapter Problems.

3.1. The by-product is AcOH. It is important in this problem to draw out the structure of Ac_2O and label all the atoms. Make: C7–C12, O8–C16. Break: C3–C12, C16–O18.



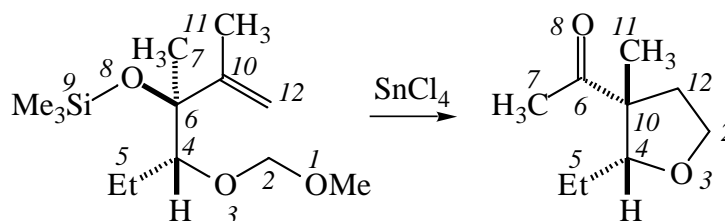
The fact that C12–C3 breaks and C12–C7 makes is a signal that a 1,2-alkyl shift occurs. The shift requires that a carbocation be formed at C7, which could be accomplished by cleaving the C7–O8 bond. Before the C7–O8 bond cleaves, something else must attach to O8 to give it a formal positive charge. Because we need to make an O8–C16 bond, that something could be C16. The role of the FeCl_3 is to encourage the ionization of the O18–C16 bond by coordinating to O20. (Alternatively, the FeCl_3 can coordinate to O17, and O8 can be acetylated with C16 by an addition–elimination mechanism.)



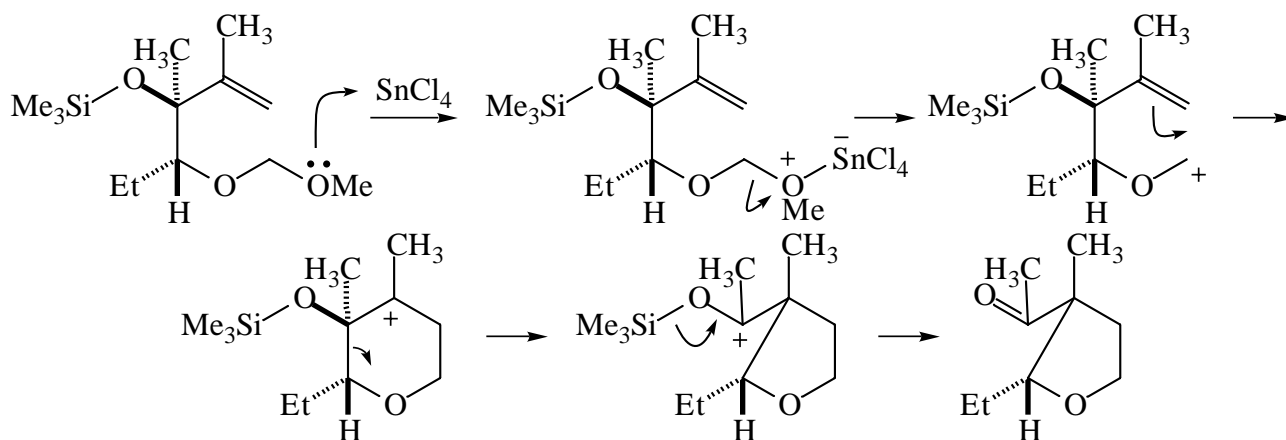
Why do we draw cleavage of the C7–O8 bond concerted with migration of C12? If the two steps were nonconcerted, then a C7 carbocation would intervene, and other 1,2-shifts could occur. For example, C13 or C14 could shift from C6 to C7. In a 1,2-shift that is concerted with leaving group departure, the migrating group must be antiperiplanar to the leaving group, and only C12 fulfills this condition.

3.2. Make: C2–C12, C4–C10. Break: O1–C2, C4–C6, O8–Si9. Neither O1 nor Si9 are incorporated

into the product.

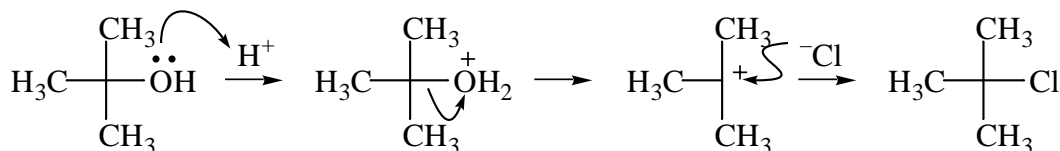


The role of the Lewis acid is either to make a π bond electrophile more electrophilic or to promote the departure of a leaving group. There is no π bond electrophile in the starting material, but O1 is a leaving group, so the first step must be coordination of SnCl_4 to O1. Cleavage of the O1–C2 bond gives a carbocation at C2 (although it is primary, it is well-stabilized by O3), and the C2 carbocation is attacked by nucleophilic C12 to give a C10 carbocation. Now a 1,2-shift of C4 from C6 to C10 can occur to give a new carbocation at C6. Finally, fragmentation of the O8–Si9 bond gives the product.

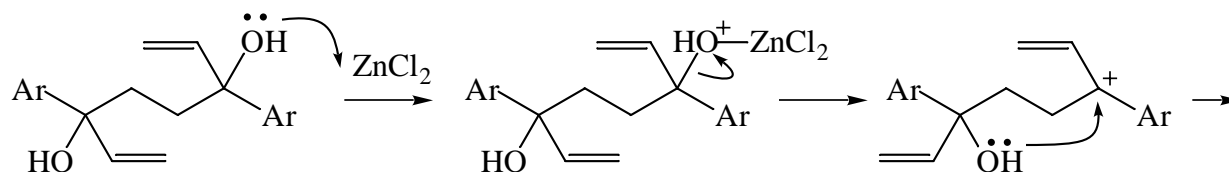


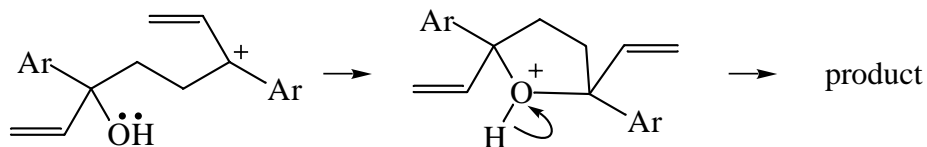
3.3.

(a)



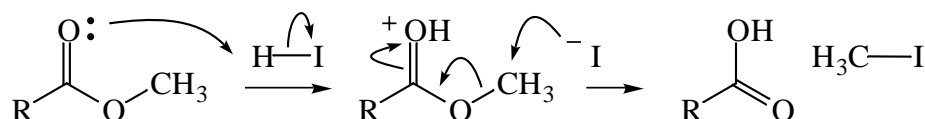
(b)



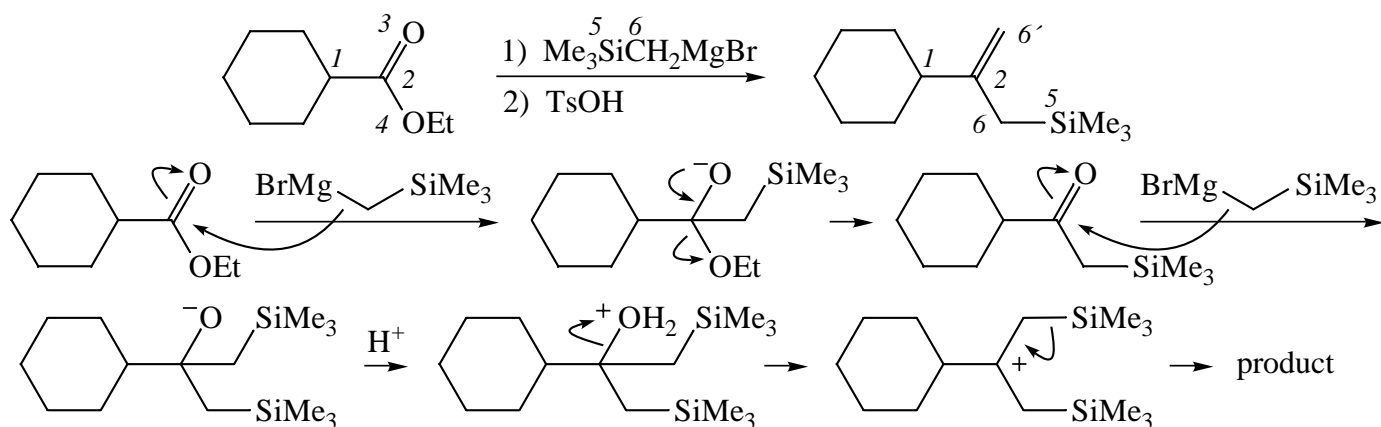


3.4. Because the carbocations derived from aryl and alkenyl halides are extremely high in energy.

3.5. The carbonyl O of esters, amides, and the like is always more nucleophilic than any other heteroatom attached to the carbonyl C. The first protonation occurs at the carbonyl O. An $\text{S}_{\text{N}}2$ attack of I^- on CH_3 then gives the free carboxylic acid.

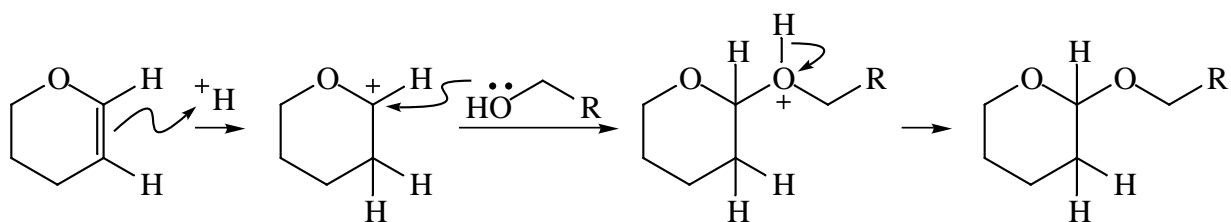


3.6. A few things about this reaction may have caught you off guard. First, the first step is a polar reaction under basic conditions, involving the Grignard reagent; only the second step is a polar reaction under acidic conditions. Second, *two* equivalents of the Grignard are required for the product; the second equivalent explains whence comes the terminal alkene C (labelled $\text{C6}'$) in the product. (Remember that Grignards react with esters by addition–elimination–addition to give tertiary alcohols, and that it is not possible under normal circumstances to stop the reaction after one Grignard adds.) Make: C2-C6 , $\text{C2-C6}'$. Break: C2-O3 , C2-O4 , $\text{Si5'-C6}'$.

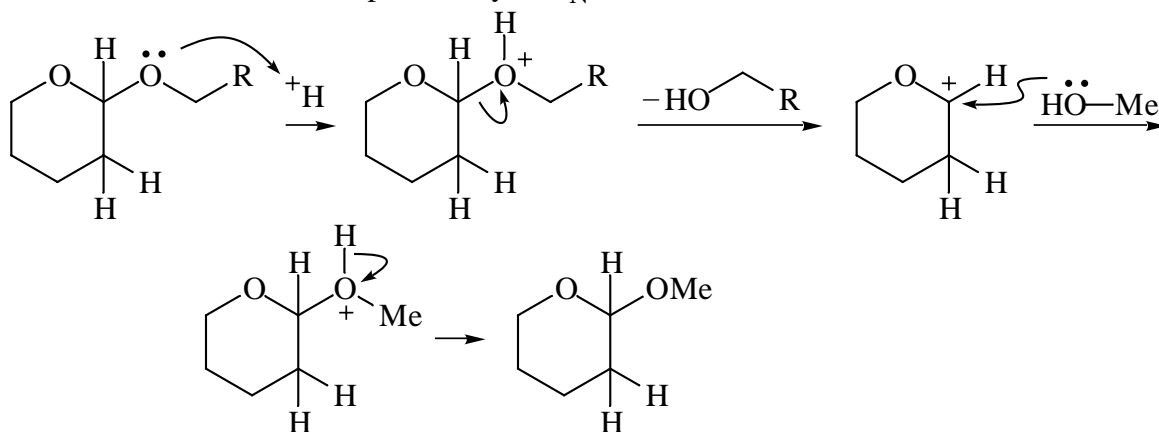


3.7.

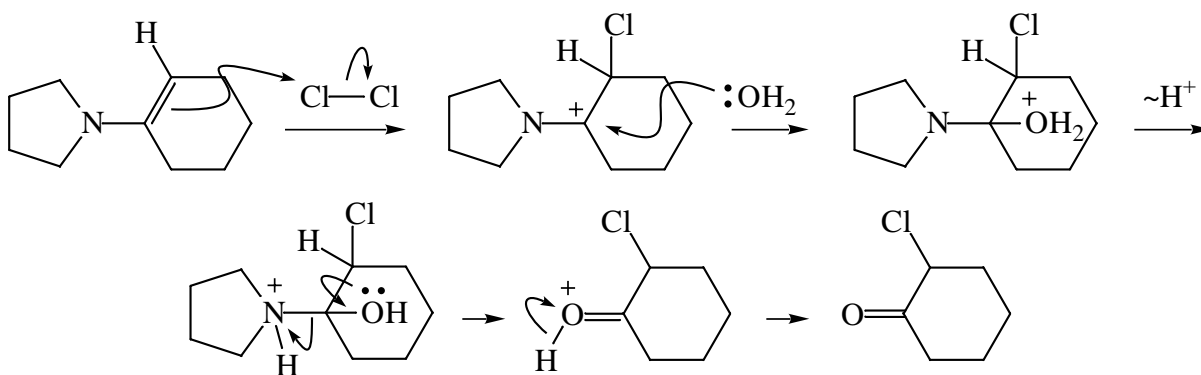
(a)



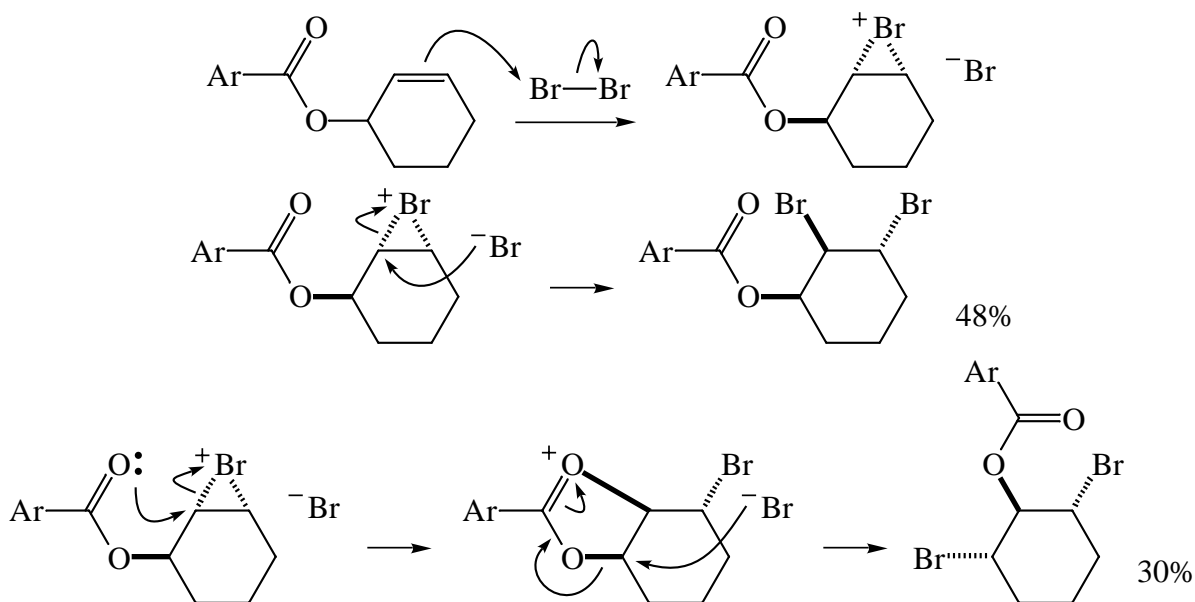
(b) This substitution reaction must proceed by an S_N1 mechanism.

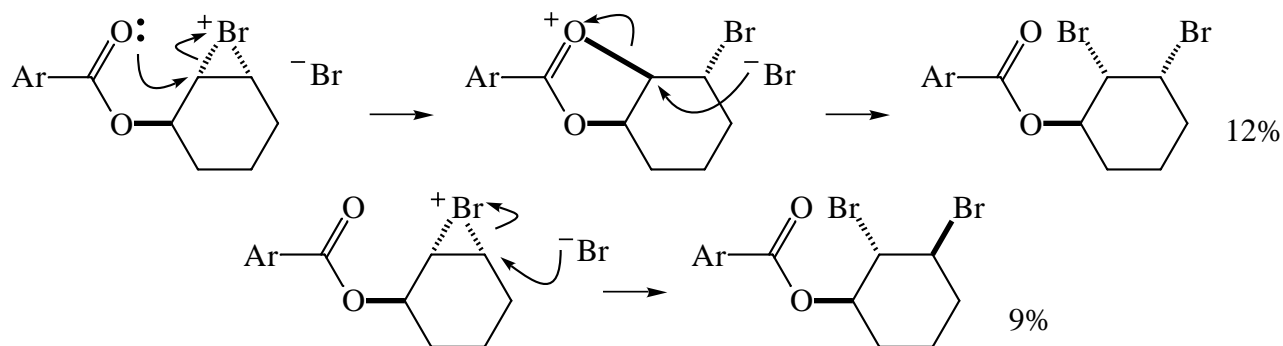


3.8. The N atom so strongly stabilizes cations that a β -halocarocation is the likely intermediate, not a halonium ion.



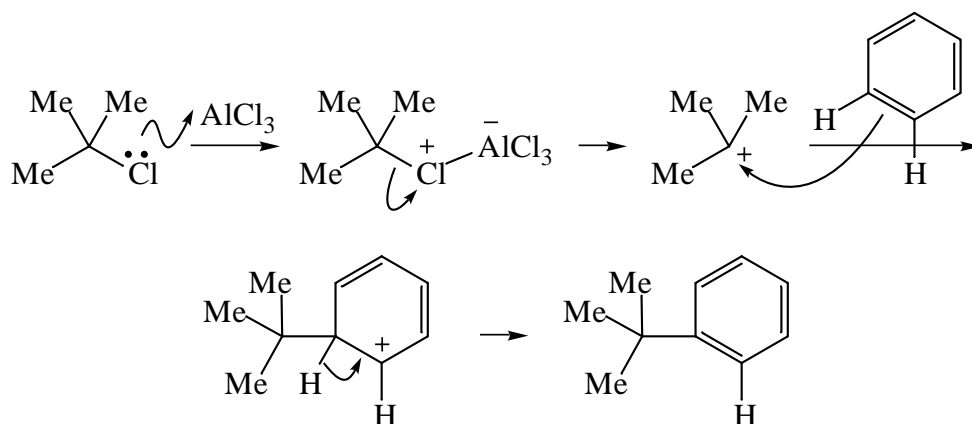
3.9. The products have in common a bromonium ion that is formed by attack of Br_2 on the face of the double bond *opposite* the acyloxy substituent. The two products not consistent with simple anti addition across the π bond are obtained via neighboring group participation of the acyloxy group.



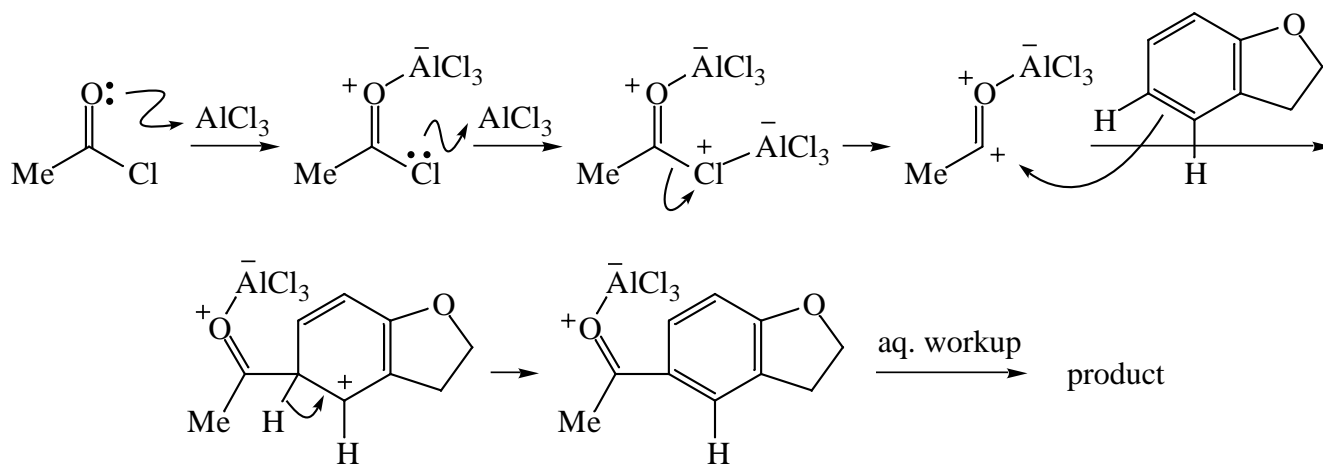


3.10.

(a) The role of AlCl_3 is to turn the Cl of $t\text{-BuCl}$ into a better leaving group. Ionization of the $\text{C}-\text{Cl}$ bond gives a carbocation, which reacts with benzene by the standard addition–fragmentation mechanism.

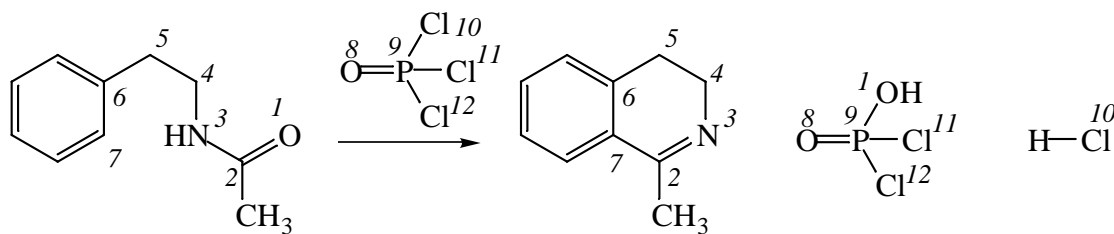


(b) Unlike a Friedel–Crafts alkylation, which requires only a catalytic amount of AlCl_3 , a Friedel–Crafts acylation requires more than a stoichiometric amount of AlCl_3 . The first equivalent coordinates to the carbonyl O ; the remaining catalytic amount catalyzes the ionization of the $\text{C}-\text{Cl}$ bond. The final product is obtained after addition–fragmentation and aqueous workup.

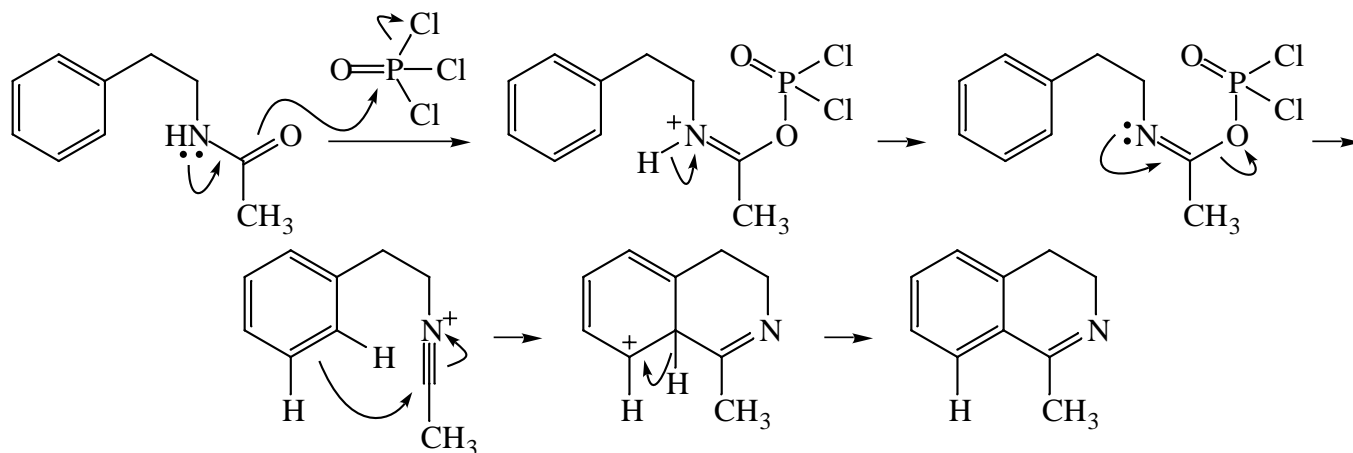


(c) The starting material loses the elements of water, but if water is the by-product, what is the role of the

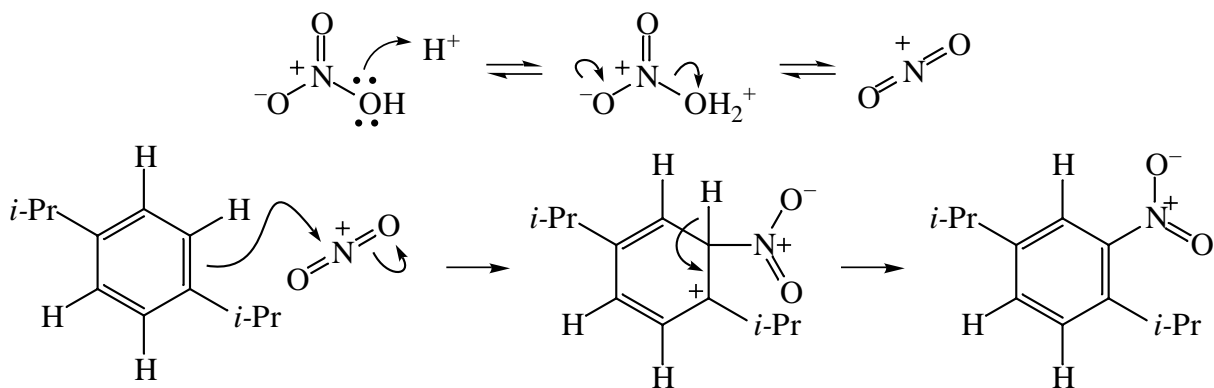
POCl_3 ? It is not a Lewis acid; it is a σ bond electrophile at P. Because P9 is electrophilic and O1 is nucleophilic, the first step must be formation of O1–P4 bond. If this is true, the P-containing by-product has an O–P bond. Make: O1–P9, C2–C7. Break: O1–C2, P9–Cl10.

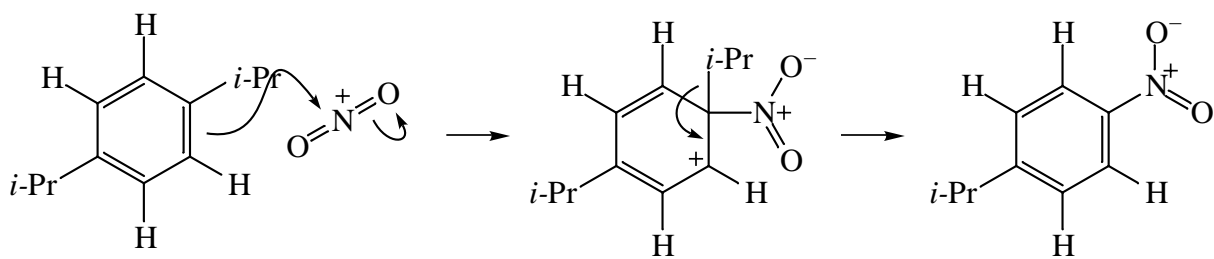


In the first step, O1 attacks P9 and displaces Cl10. After deprotonation of N3, a carbocation at C2 (stabilized by resonance with N4) is formed. Addition–elimination then gives the product. An alternative and reasonable mechanism would have C7 attack C2 before the C2–O1 bond cleaves (addition–elimination type mechanism), but the conventional wisdom is that the reaction proceeds through the nitrilium ion intermediate.



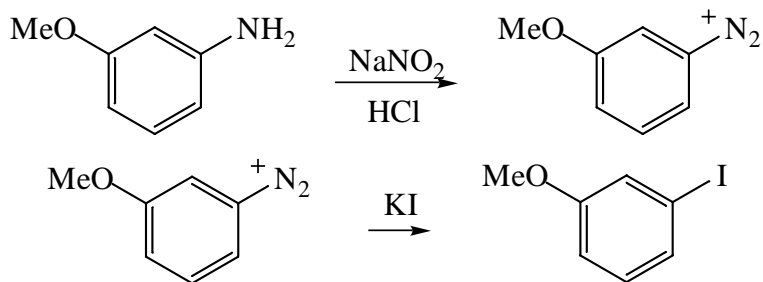
3.11. The first product is derived from a normal electrophilic aromatic substitution reaction of the kind described in the text. The second product is derived from ipso electrophilic aromatic substitution. The mechanism is exactly the same, but in the last step $i\text{-Pr}^+$ is lost instead of H^+ .



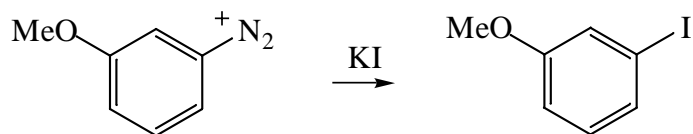


3.12.

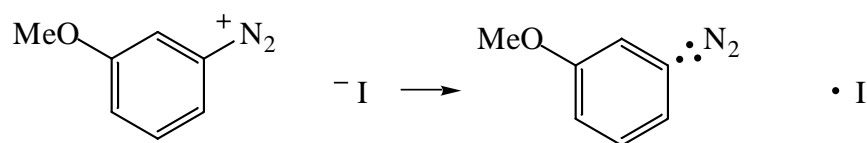
(a) The initial part, formation of a diazonium ion, proceeds by the mechanism described in the book.



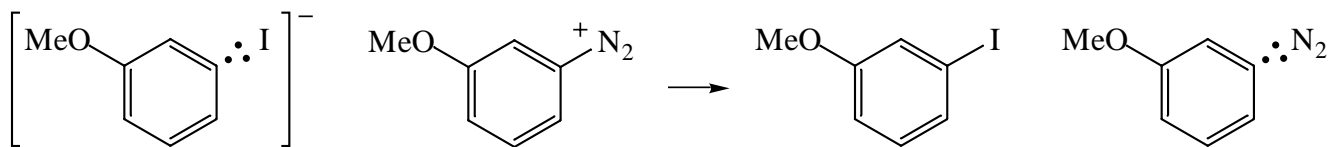
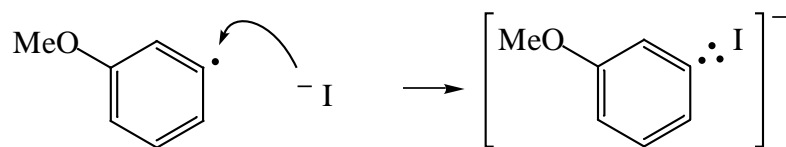
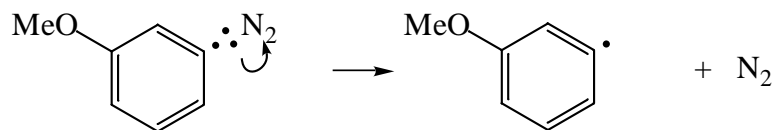
The second part, substitution of N_2 by I^- , proceeds by the $S_{RN}1$ mechanism.



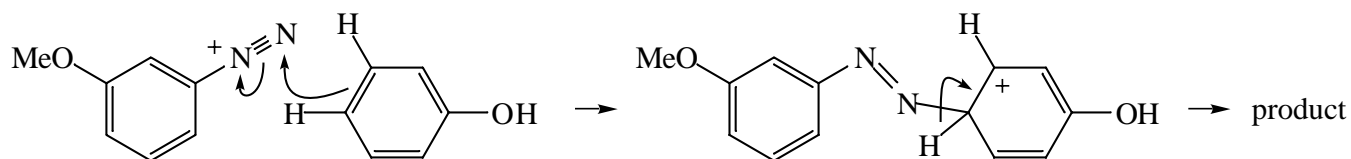
Initiation:



Propagation:

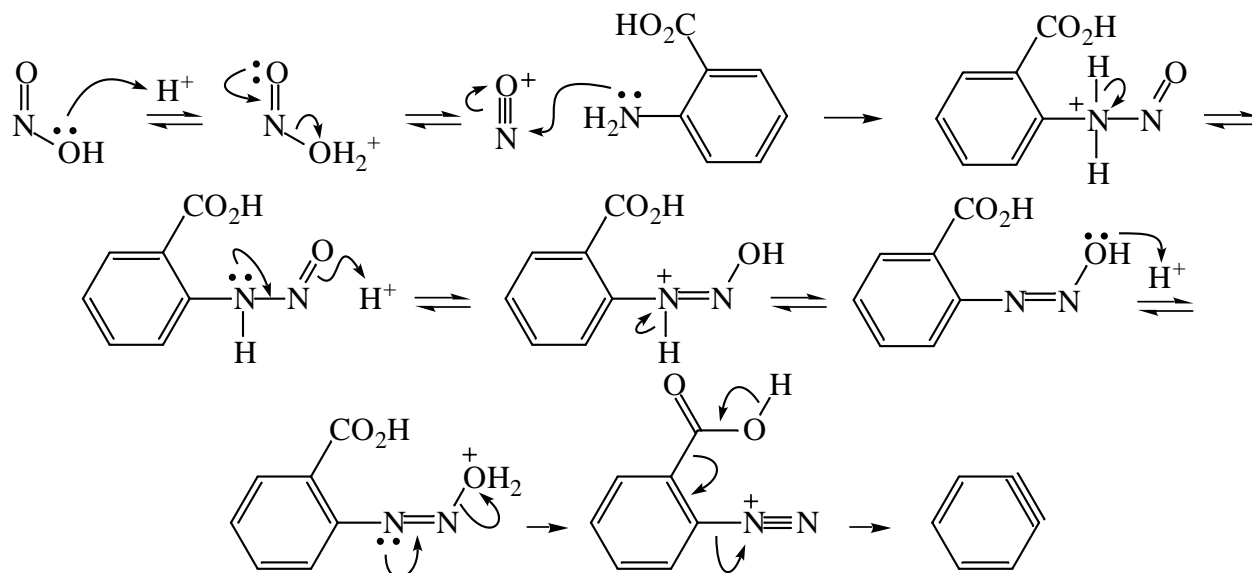


(b) Here the diazonium ion forms again, but now, an electrophilic aromatic substitution occurs, with the terminal N of the diazonium ion acting as the electrophile.

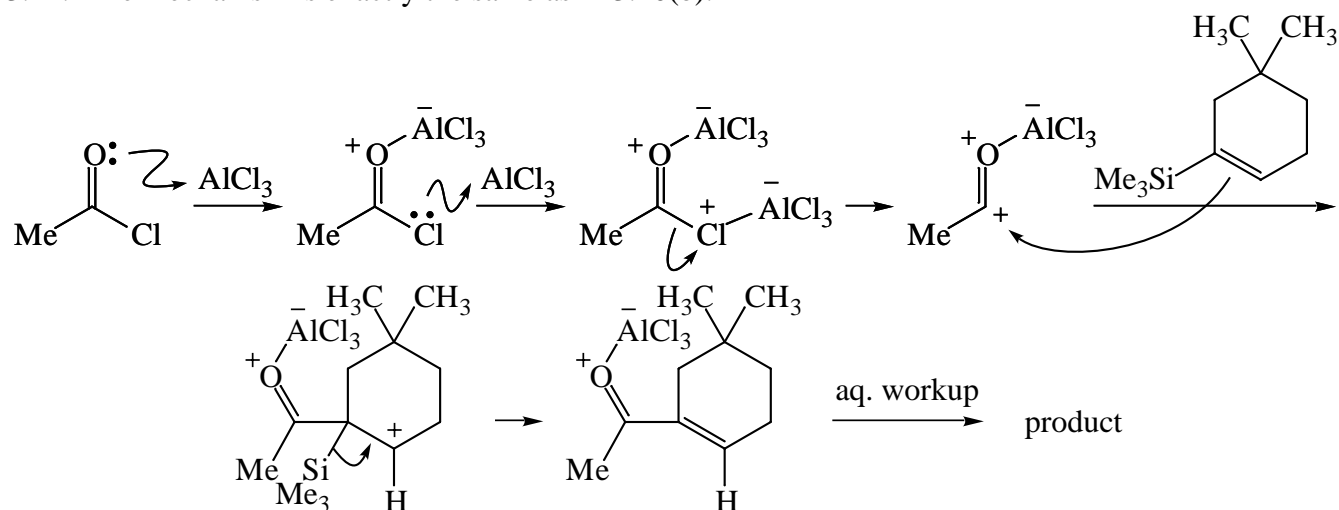


3.13.

(a) Only an N–N bond is made, and one C–C bond is broken. When an amine is combined with NaNO_2 and HCl , a diazonium ion is formed. An elimination reaction then ensues with loss of CO_2 .



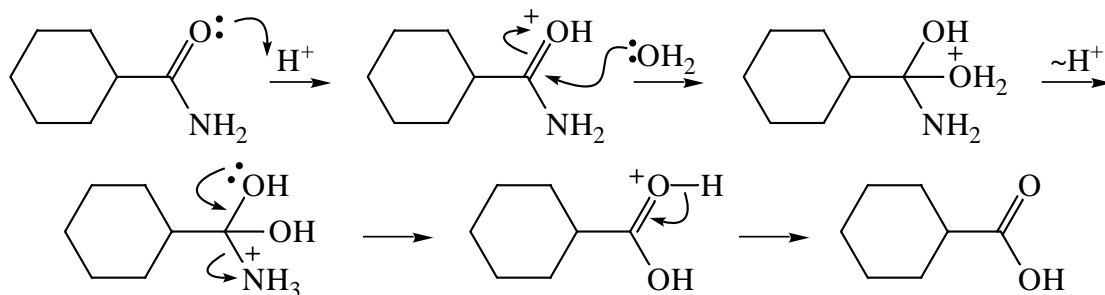
3.14. The mechanism is exactly the same as in 3.10(b).



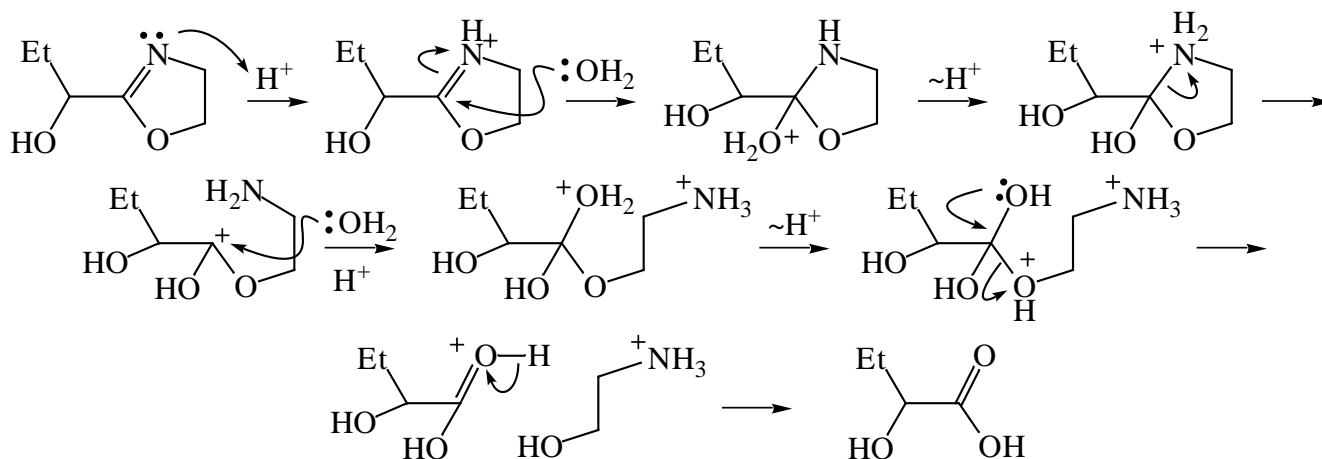
3.15.

(a) The mechanism proceeds by addition–elimination. *However*, both the addition and elimination steps

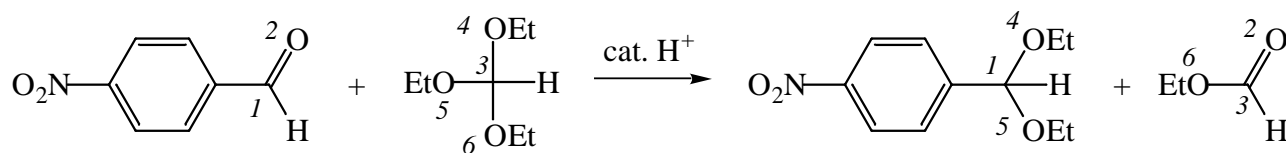
are preceded by protonation and followed by deprotonation. It is very important that these proton transfer steps are drawn properly!



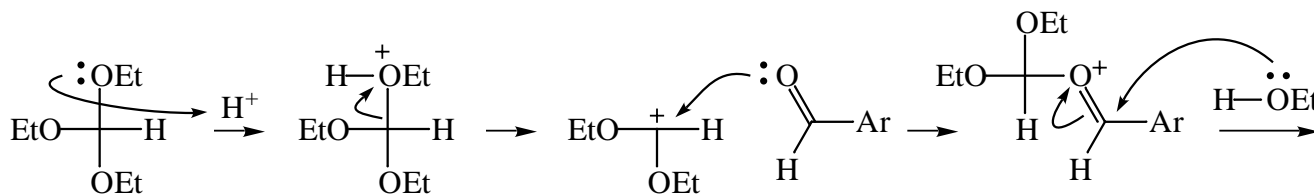
(b) It is unlikely that the $\text{CH}_2\text{-O}$ bond in the starting material will break under aqueous acidic conditions (can't form a carbocation, and $\text{S}_{\text{N}}2$ is unlikely unless conditions are very harsh). Therefore the $\text{CH}_2\text{-O}$ bond is preserved in the product, which means that *both* O's of the carboxylic acid product come from H_2O .

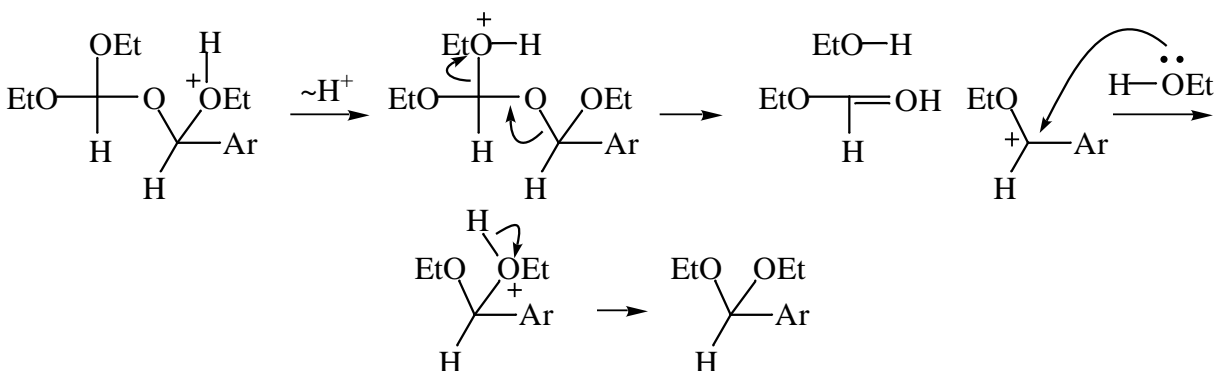


3.16. Make: C1–O4, C1–O5, O2–C3. Break: C1–O2, C3–O4, C3–O5.

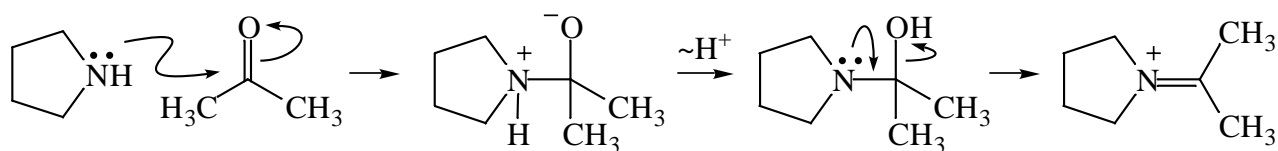


There are a number of ways this reaction could proceed, but the key step in any of them is attack of O2 on a carbocation at C3.

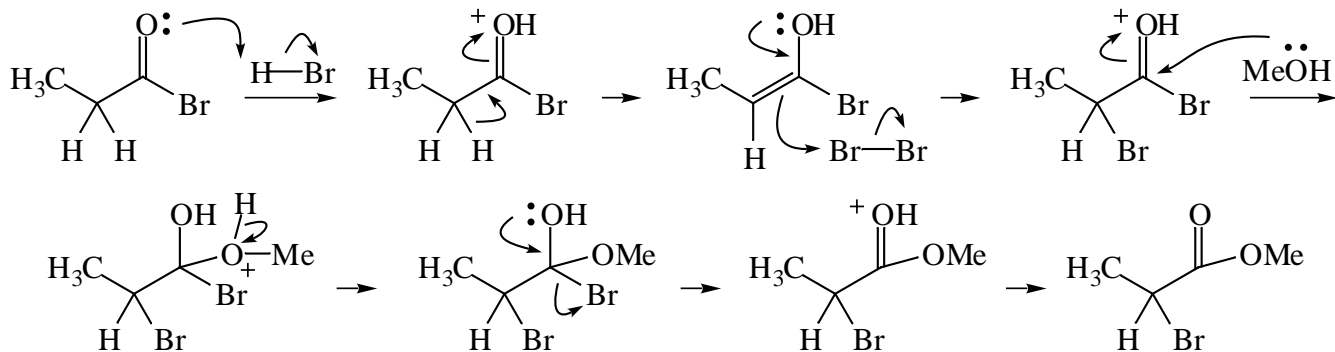




3.17. Under these nearly neutral conditions, it is unclear whether the carbonyl O is protonated before or after attack of N. Either way is acceptable.

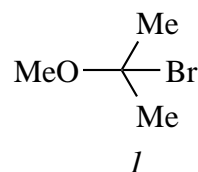
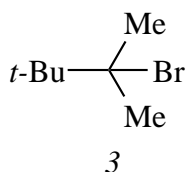
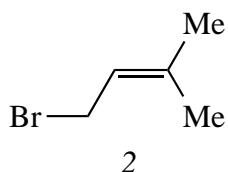


3.18. Two substitutions are occurring here: H to Br, and Br to MeO. Looking at the order of reagents, the first substitution is H to Br. Br_2 is electrophilic, so the α -C of the acyl bromide must be made nucleophilic. This is done by enolization. The substitution of Br with MeO occurs by a conventional addition-elimination reaction under acidic conditions.

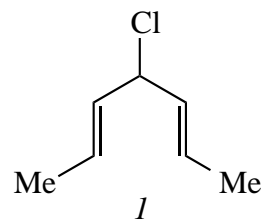
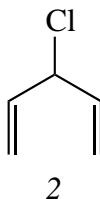
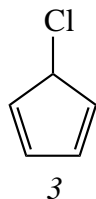


Answers To Chapter 3 End-of-Chapter Problems.

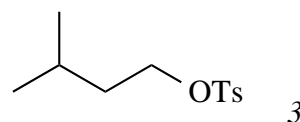
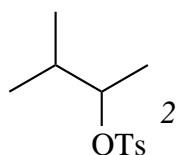
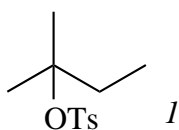
1. (a) In order to compare it directly with the other two carbocations, the carbocation derived from the first compound should be drawn in the resonance form in which the empty orbital is located on the 3° C. It can then clearly be seen that the three carbocations are all 3° carbocations that differ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



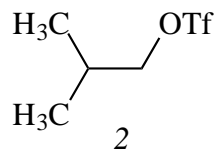
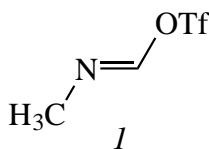
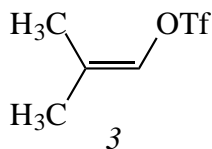
(b) The first compound gives an antiaromatic carbocation. Among the other two, the second compound gives a cation with the electron deficiency delocalized across one 2° and two 1° C's, while the third compound gives a cation with the electron deficiency delocalized across three 2° C's.



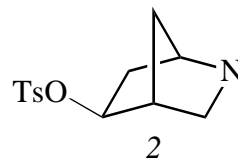
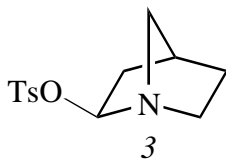
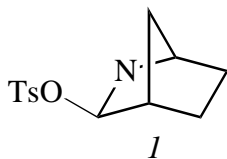
(c) The order of stability of alkyl cations is $3^\circ > 2^\circ > 1^\circ$.



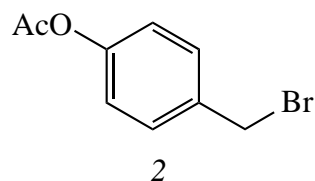
(d) The second compound gives a lone-pair-stabilized carbocation. Among the other two, 1° alkyl carbocations are more stable than 1° alkenyl carbocations.



(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.

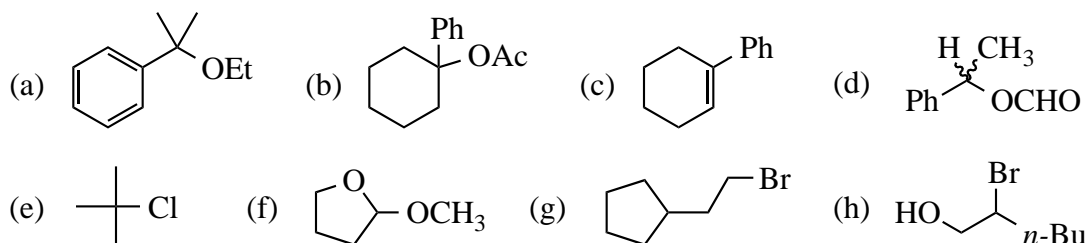

$$\begin{array}{c} \text{Ph} \\ | \\ \text{Ph} - \text{C} - \text{OH} \\ | \\ \text{Ph} \end{array}$$

(f) Excellent carbocation, nucleophilic solvent, \therefore S_N1. First the O of the OH group is protonated, then OH₂ leaves to give an O-stabilized carbocation. Next, the O of CH₃OH adds to the carbocation, and finally H⁺ is lost from the O of OCH₃ group to give the product. Note that the ring oxygen could also act

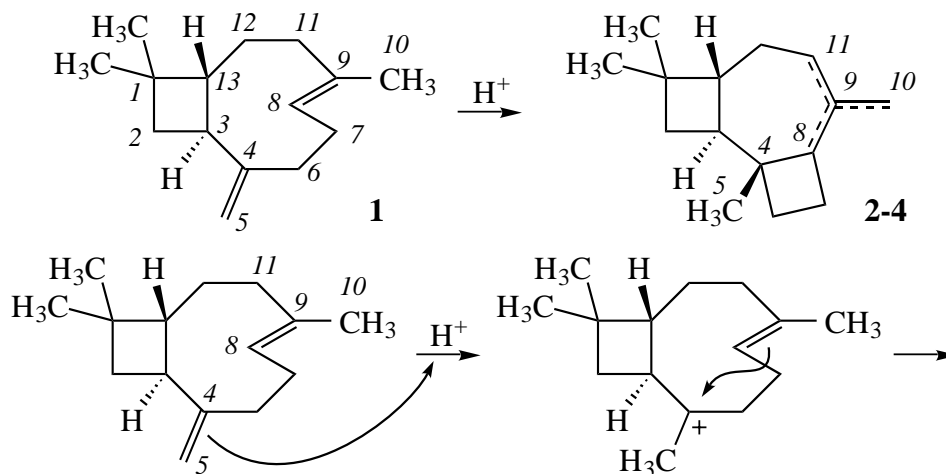
as a leaving group to give an acyclic compound, but entropy favors the loss of the OH group (because two products are formed from one).

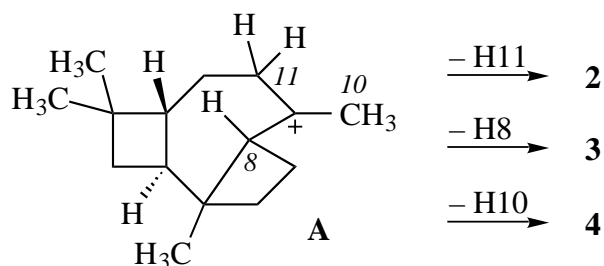
(g) Awful carbocation, so can't be S_N1 . Strongly acidic conditions, excellent nonbasic nucleophile, $\therefore S_N2$. First O is protonated, then Br^- does a nucleophilic displacement of OH_2 to give the product.

(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 S_N2 reaction, the central C in the transition state has some carbocationic character, so the more substituted C undergoes substitution under acidic conditions.)

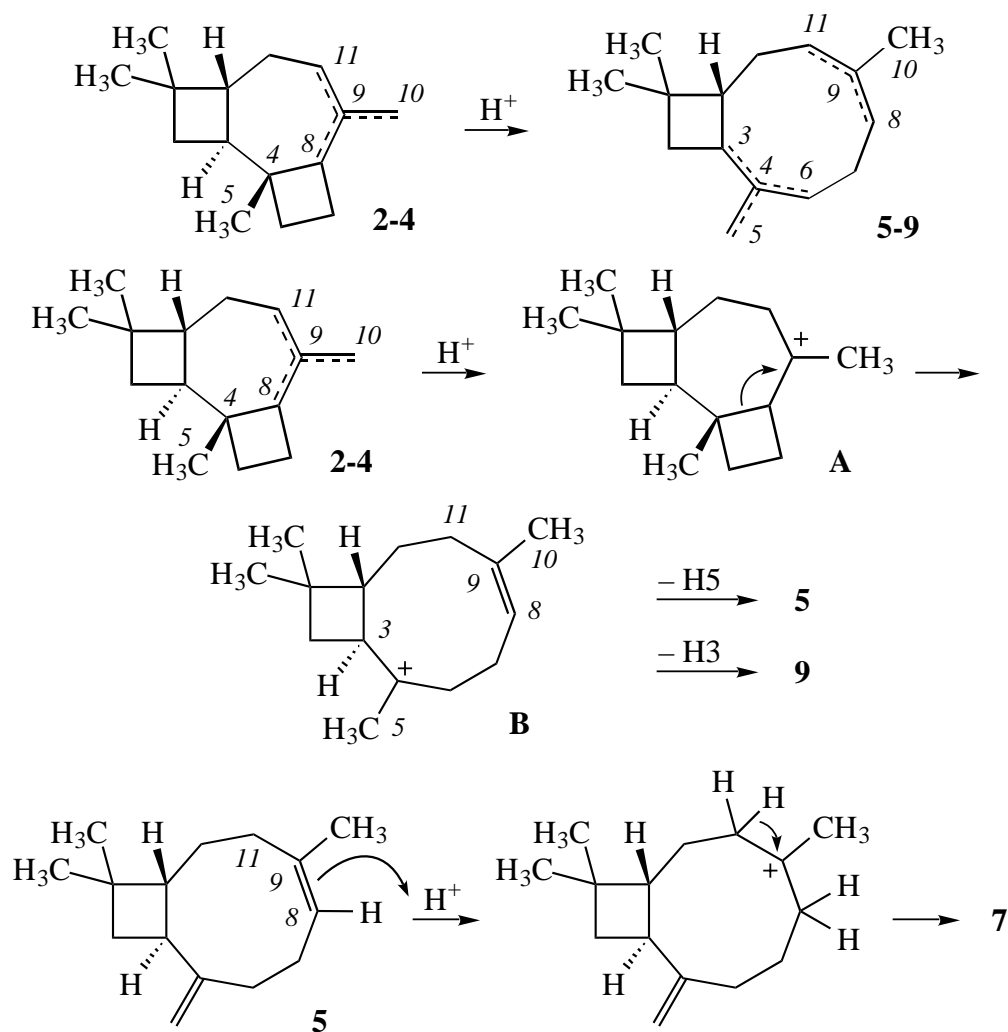


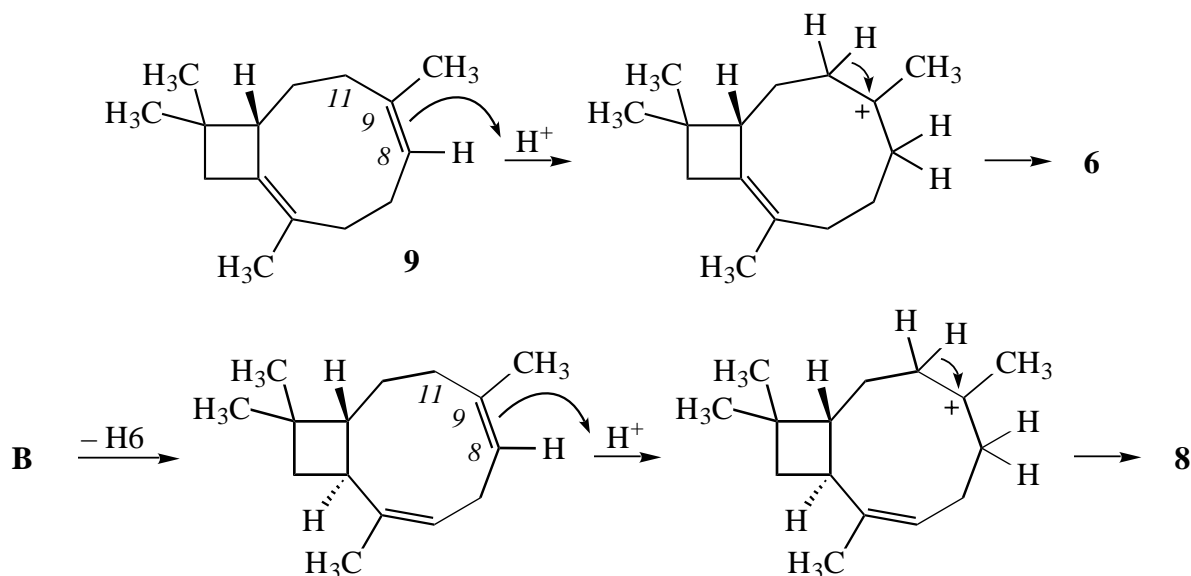
3. Number the C's in **1**. We see that the first set of compounds, **2-4**, are all obtained by formation of a bond between C4 and C8. To make the C4–C8 bond, we could make C4 electrophilic and C8 nucleophilic, or vice versa. If we make C8 electrophilic by protonation of C9, then after attack of C4, 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.



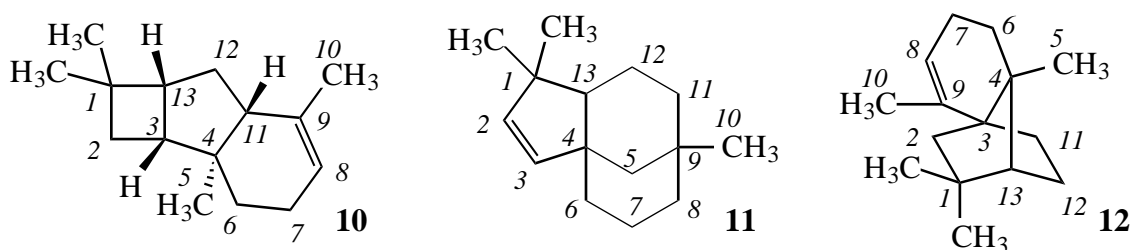


The next set of products, **5-9**, must be formed from **2-4**. To get from **2-4** to **5-9**, we must break the C4–C8 bond again. This is easy to do if we regenerate carbocation **A**. Cleavage of the C4–C8 bond gives a C8=C9 π bond and a carbocation, **B**, at C4. Loss of H^+ from C5 or C3 of **B** 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**.

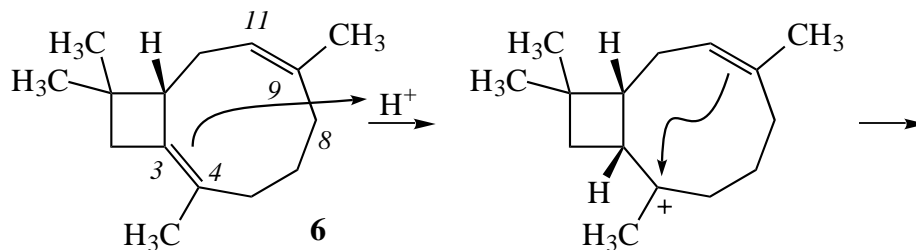


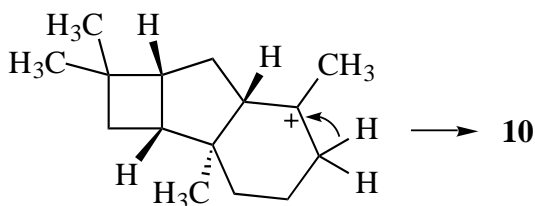


After a while longer, compounds **5-9** are converted into compounds **10-12**. Note that since all of **5-9** are easily interconverted by protonation and deprotonation reactions, any of them could be the precursors to any of **10-12**.

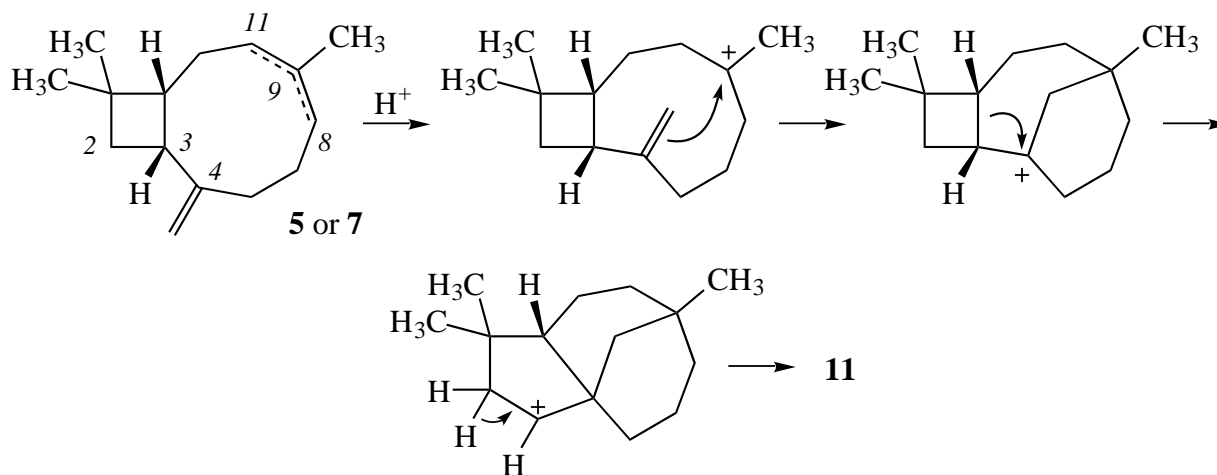


Compound **10** has a new C4-C11 bond. Either C4 is the nucleophile and C11 is the electrophile, or vice versa. Either way, compounds **5** and **9** are excluded as the immediate precursors to **10**, since they both have a saturated C11 that cannot be rendered nucleophilic or electrophilic (except 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**.

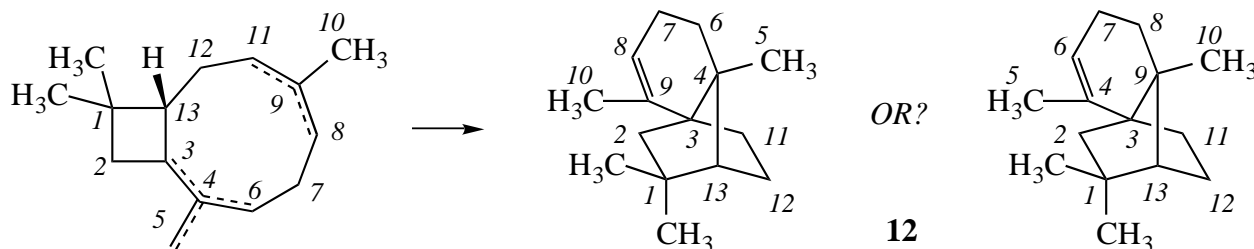




Compound **11** has new bonds at C5–C9 and C13–C4, and the C3–C13 bond is broken. Also, a new C2=C3 π bond is formed. The shift of the C13–C3 bond to the C13–C4 bond suggests a 1,2-alkyl shift. Then loss of H⁺ from C2 can give the C2=C3 π bond. So we need to establish a carbocation at C4. We can do this 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.

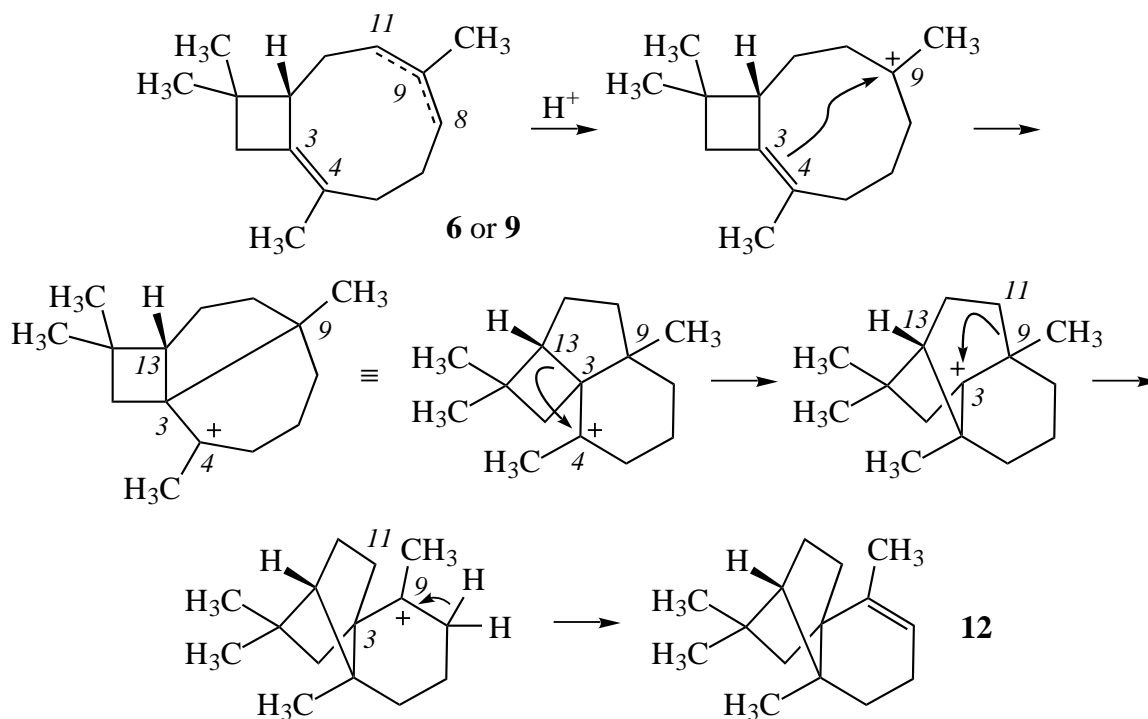
Right make: C3–C9, C3–C11, C9–C13.

Left break: C3–C13, C9–C11.

Right break: C3–C13, C9–C11.

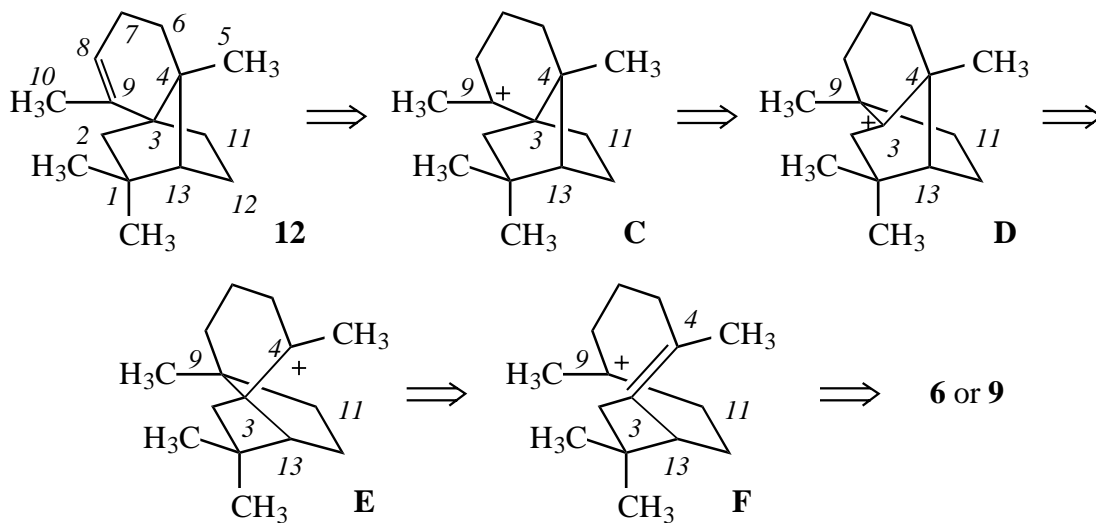
The only difference is that on the right, we need to make C4–C13, while on the left, we need to make C9–C13. Which is better? On the left, the C4–C13 bond can be made and the C3–C13 bond can be broken by a 1,2-shift. This can't be done on the right. Also, in compound **11** we made a C4–C13 bond. Not 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.

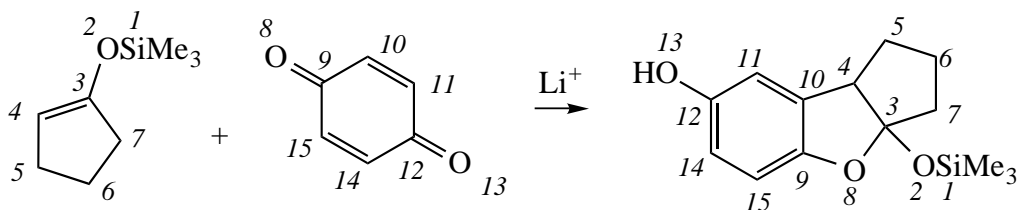


In a deep-seated rearrangement like this, it's sometimes easier to work backwards from the product. The π bond at C8=C9 in **12** suggests that the last step is deprotonation of C8 of a carbocation at C9, **C**. Carbocation **C** might have been formed from carbocation **D** by a 1,2-alkyl shift of C11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

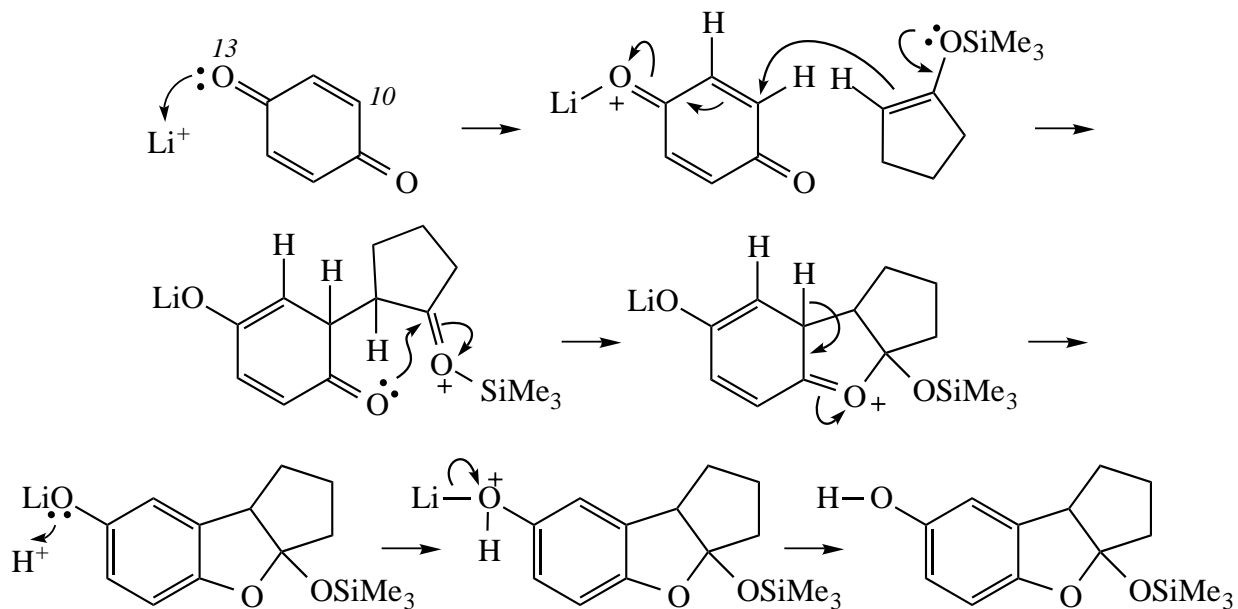
carbocation. The C9 carbocation could have been formed from **6** or **9** by protonation of C11 or C8, respectively.



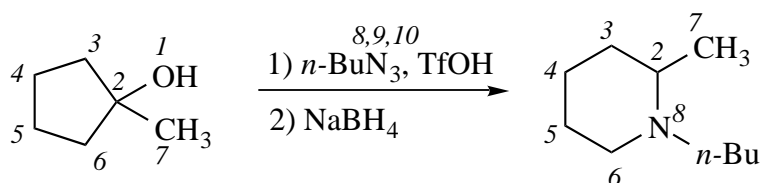
4. (a) Make: C3–O8, C4–C10.



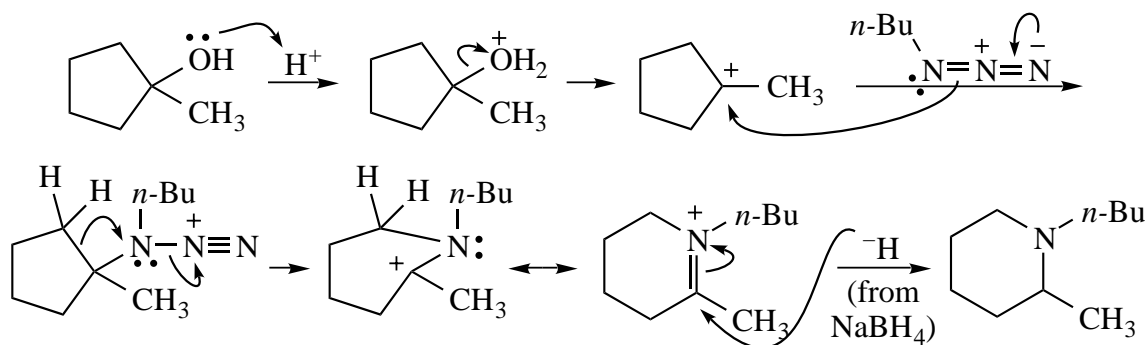
C4 is nucleophilic (enol ether), and C10 is electrophilic. The Lewis acid makes C10 more electrophilic by coordinating to O13. After conjugate addition, O8 traps the C3 carbocation. Proton–Li⁺ exchange gives the product.



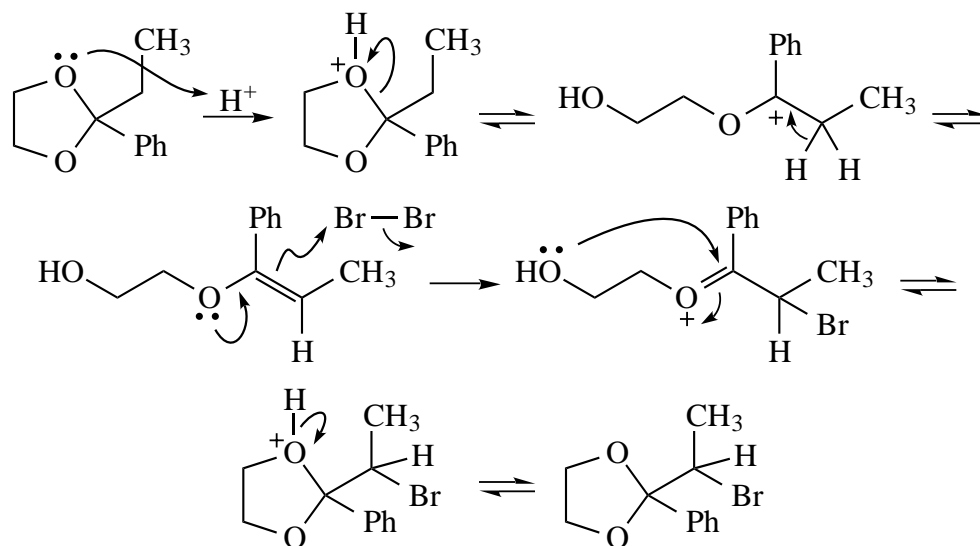
(b) Make: C2–N8, C6–N8. Break: O1–C2, C2–C6.



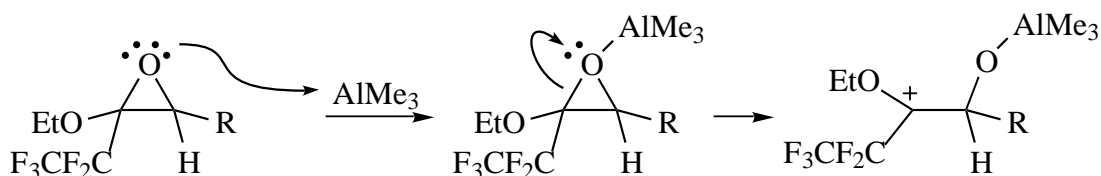
N8 of the azide adds to the carbocation to give an amine with an N_2^+ leaving group attached. Concerted 1,2-migration of C6 from C2 to N8 and expulsion of N_2 gives a N-stabilized carbocation, which is reduced by NaBH_4 to give the product.



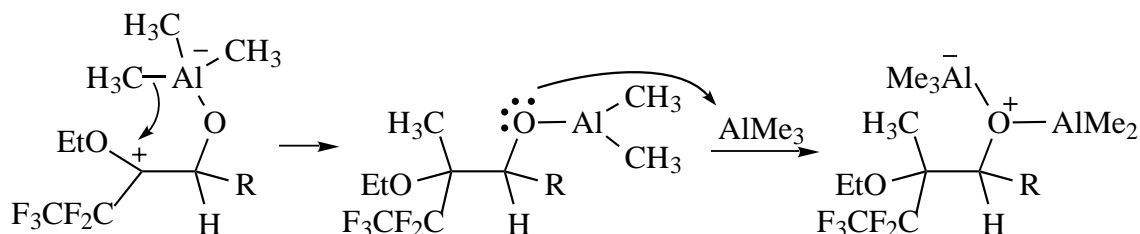
(c) Bromine is an electrophile, so we need to convert the CH_2 group into a nucleophile. This might be done by converting it into an alkene C. There is a leaving group next door, so we can do an E1 elimination to make an enol ether. Another way to look at it: under acidic conditions, acetals are in equilibrium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



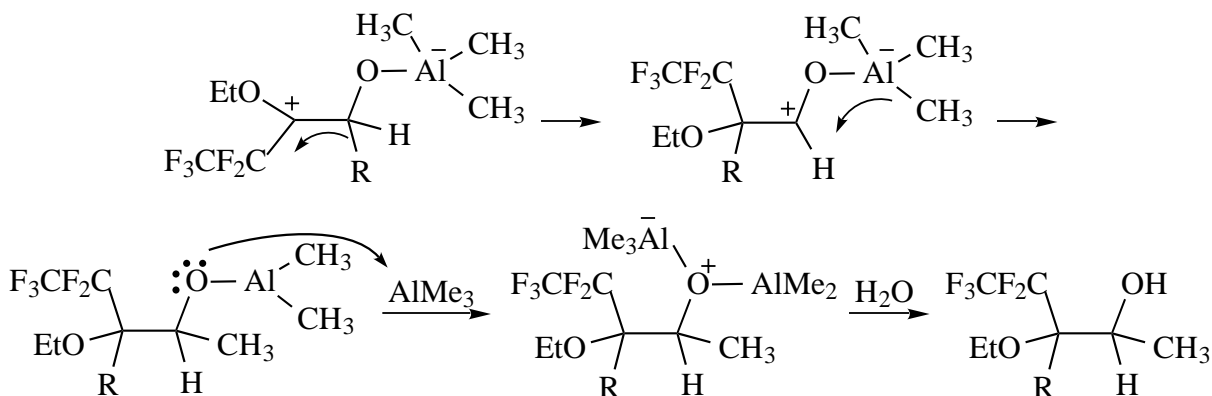
(d) Both reactions begin the same way. AlMe_3 is a Lewis acid, so it coordinates to the epoxide O. The epoxide then opens to a carbocation.



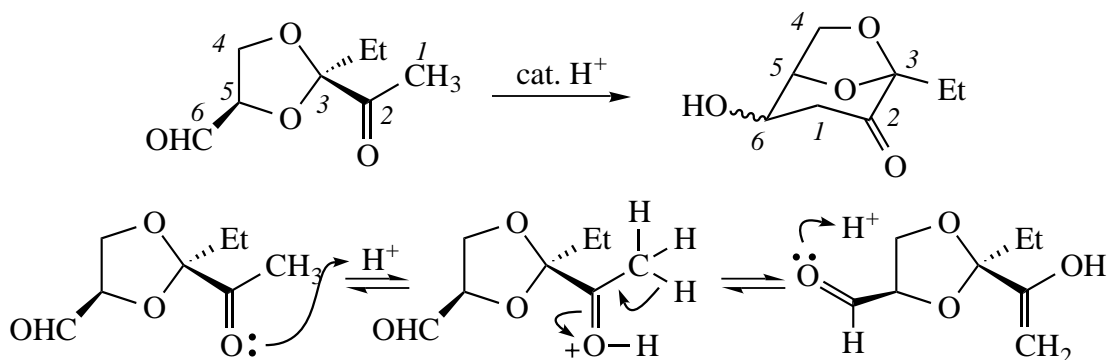
When $R = \text{CH}_2\text{CH}_2\text{Ph}$, the coordinated Al simply transfers a Me group to the carbocation C (σ bond nucleophile). The O atom then coordinates another equivalent of AlMe_3 before the product is obtained upon workup.

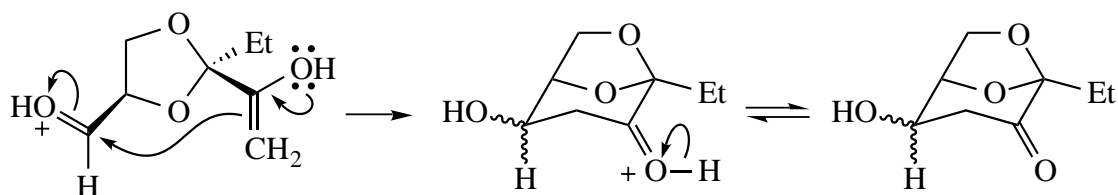


When $R = \text{cyclohexyl}$, the R group migrates (1,2-alkyl shift) to give a new carbocation. (2° Alkyl groups are more prone to migrate than 1° alkyl groups.) After Me transfer to the new carbocation and coordination of another equivalent of AlMe_3 , workup gives the product.

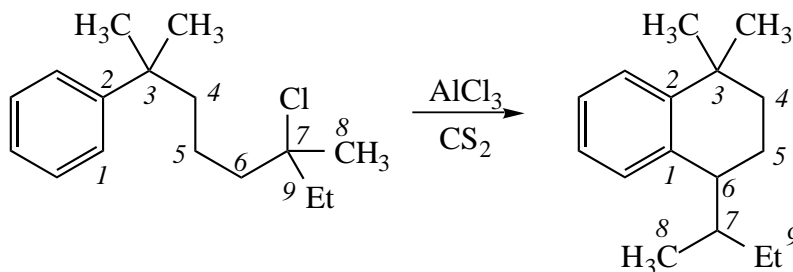


(e) Make: C1–C6. An acid-catalyzed aldol reaction.

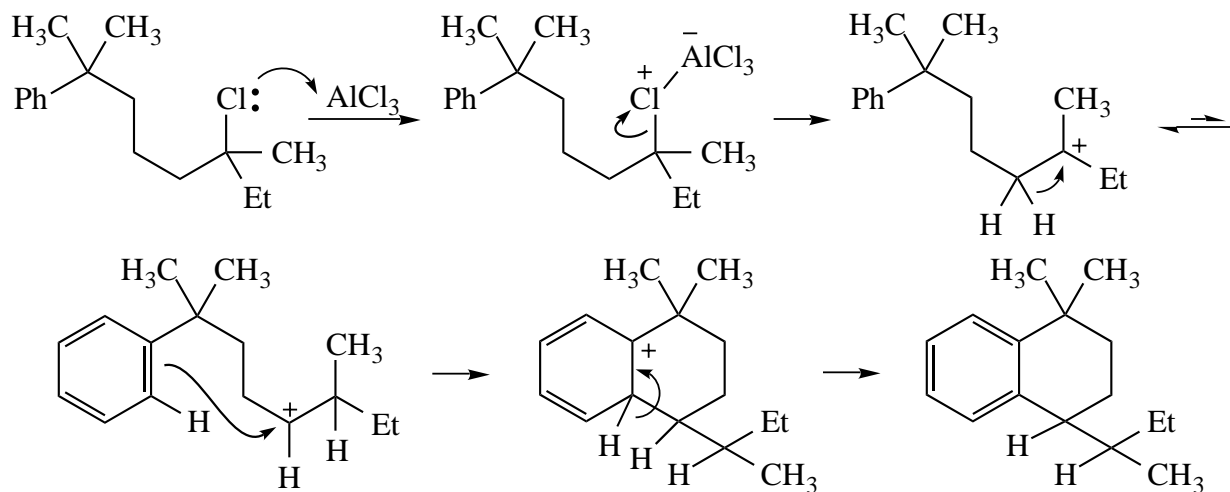




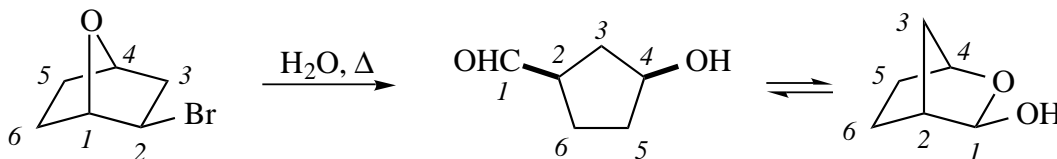
(f) Make: C1–C6. Break: C7–Cl.

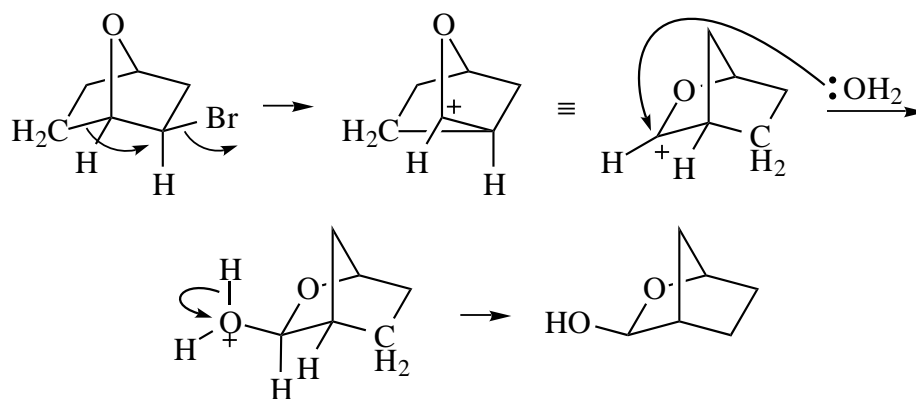


The reaction looks like a simple Friedel–Crafts alkylation, but there is a twist — the leaving group is not on the C which becomes attached to the ring. After formation of the C7 carbocation, a 1,2-hydride shift occurs to give a C6 carbocation. The 1,2-hydride shift is energetically uphill, but the 2°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



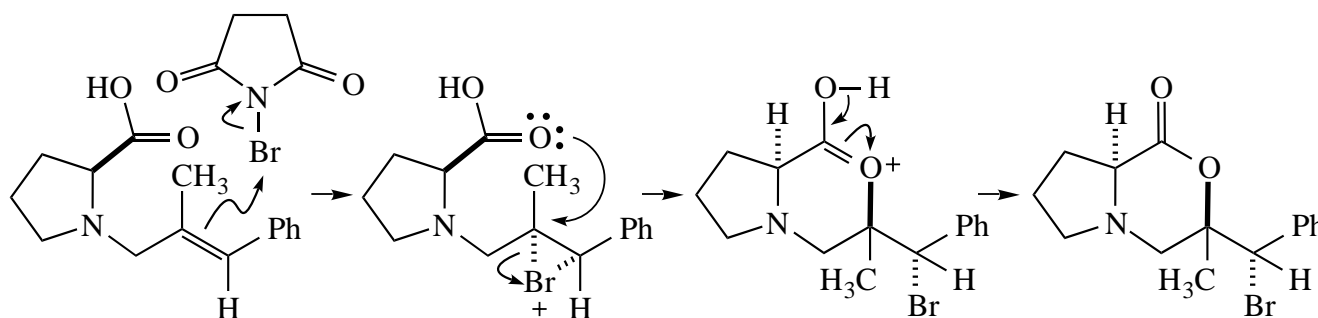
(g) Number the C's! The sequence C2–C3–C4–C5–C6 is identifiable on the basis of the number of H's and O's attached to each C in starting material and product. Make: C2–C6. Break: C1–C6. This pattern is evocative of a 1,2-alkyl shift. The C1–C6 bond is antiperiplanar to the C2–Br bond, so it migrates.



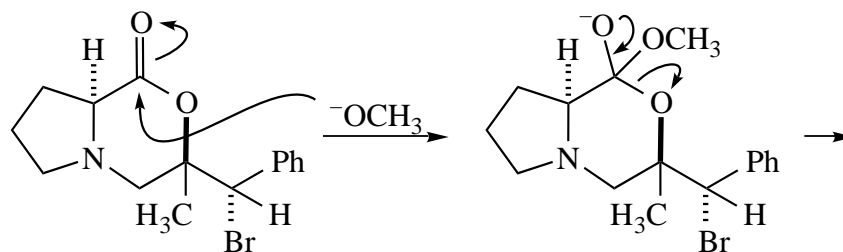


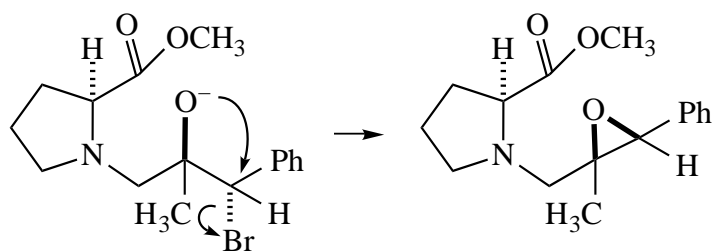
(h) The first step of this two-step reaction takes place under acidic conditions, and the second step takes place under basic conditions. The product from the acidic conditions needs to be a stable, neutral compound.

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.

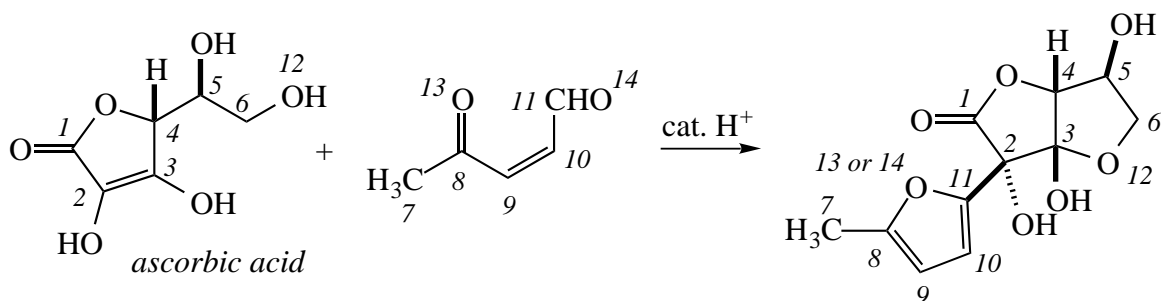


Now MeO^- is added to begin the sequence that takes place under basic conditions. The MeO^- opens the lactone to give a 2-bromoalkoxide, which closes to the epoxide, inverting the other center.

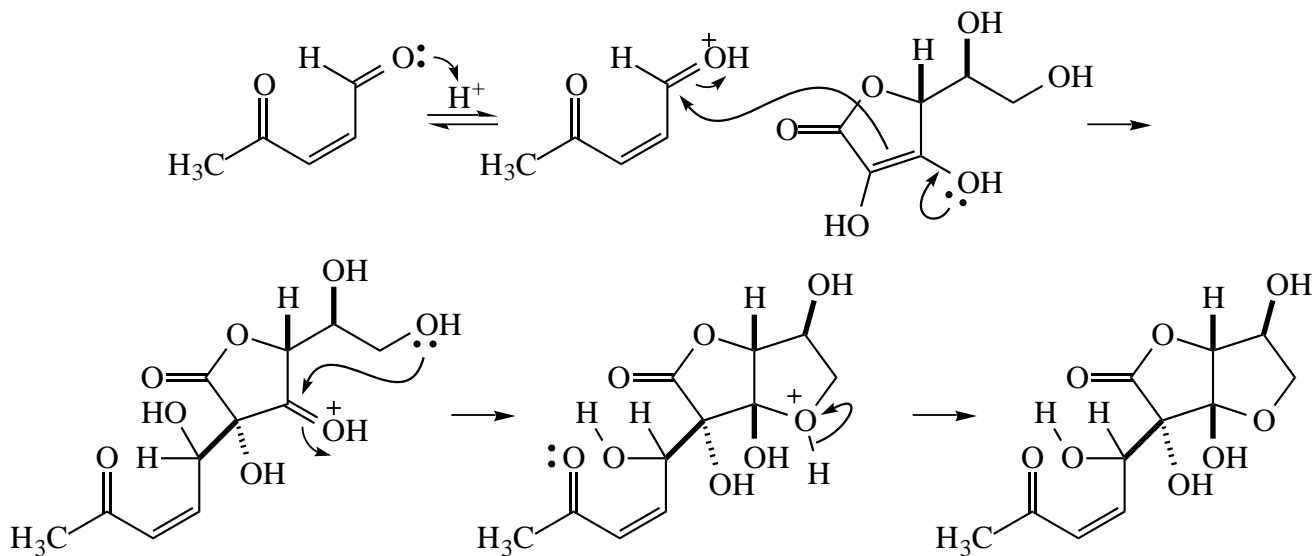




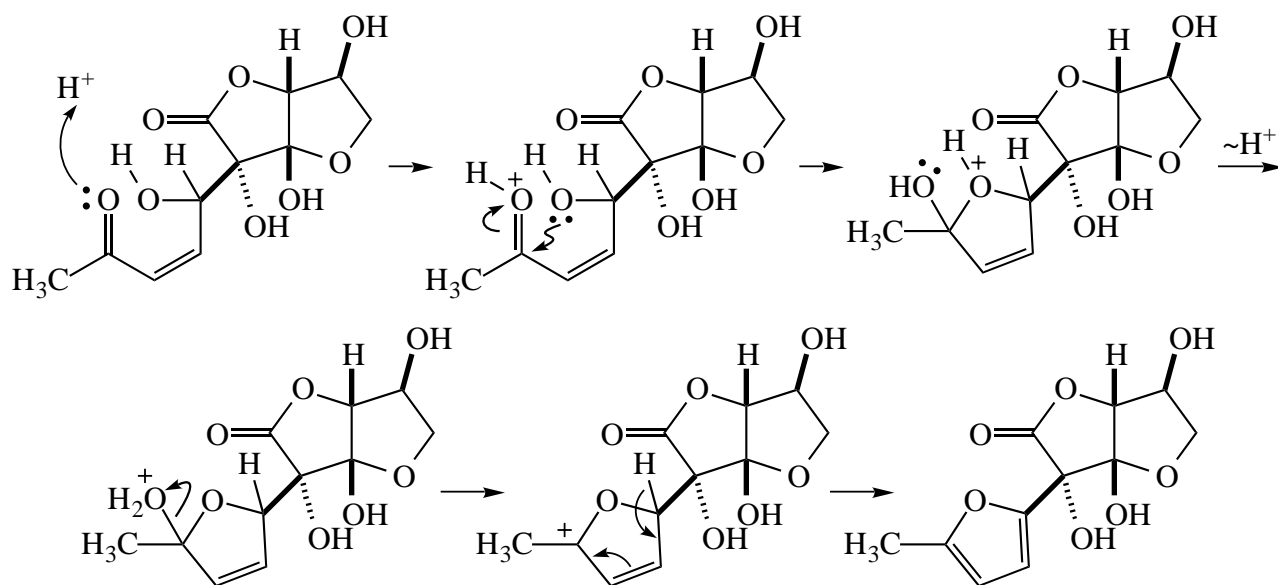
(i) Make: C2–C11, C3–O12, and either C8–O14 or C11–O13. Break: Either C8–O13 or C11–O14.



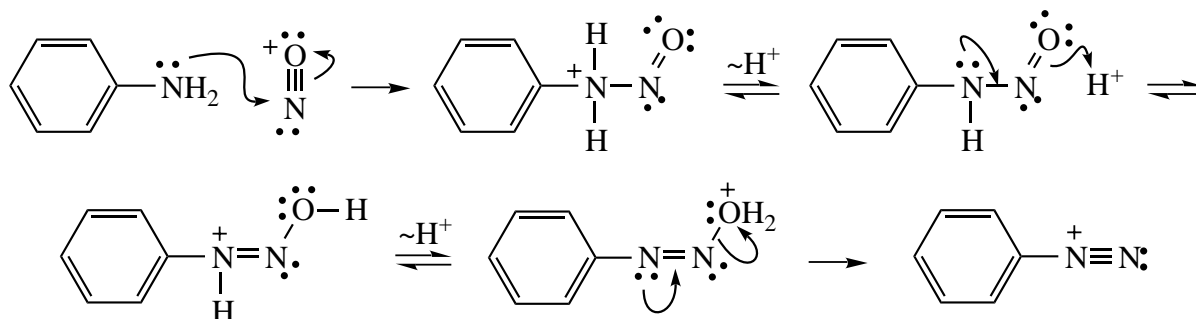
Both C2 and C3 are β to an OH group, and C3 is also β to a carbonyl. Thus C3 is subject to both pushing and pulling, but C2 is subject only to pushing. The first step then is likely attack of nucleophilic C2 on electrophilic C11. Then the C3 carbocation is trapped by O12.



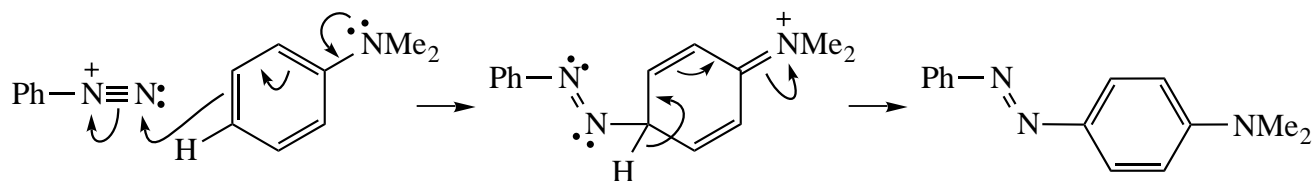
Now the furan ring is formed. Either O13 or O14 must be lost (certainly as H_2O). If O14 is lost, a carbocation at C11 would be required. This carbocation would be destabilized by the electron-withdrawing carbonyl at C18. Better to protonate O14, have O14 attack C8, and then lose O14 as H_2O .



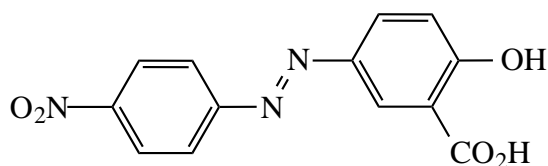
(j) Addition of NaNO_2 and HCl to an aniline always gives a diazonium salt by the mechanism discussed in the chapter (Section D.2).



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.

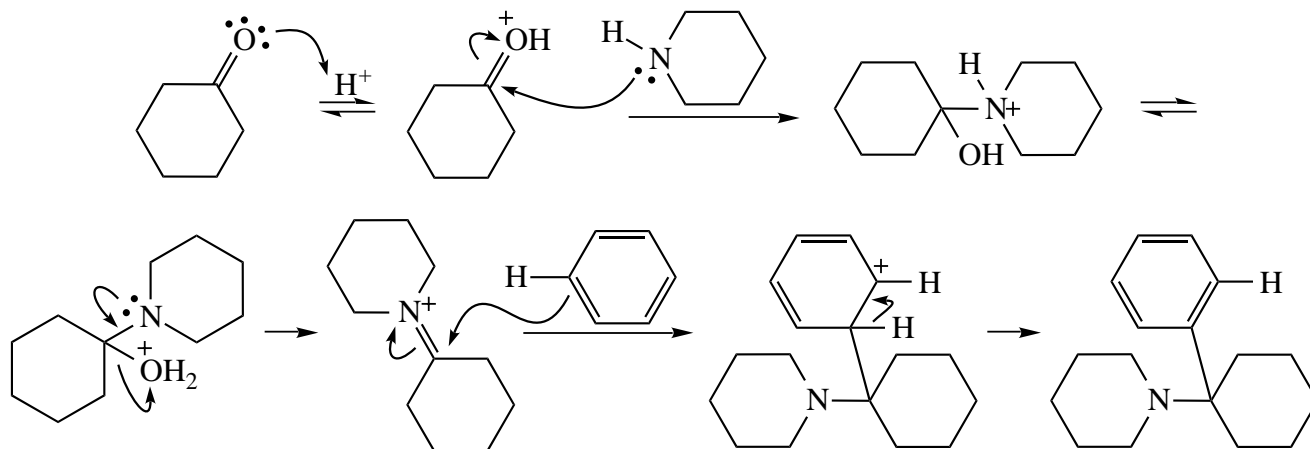


(k) Salicylic acid (as in acetylsalicylic acid, or aspirin) is 2-hydroxybenzoic acid.

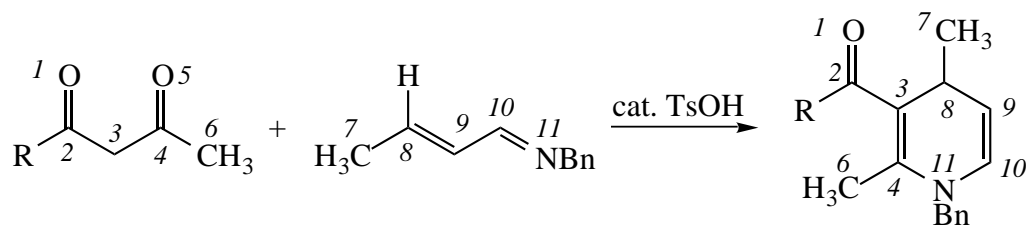


(l) Two new σ bonds are formed in this reaction. In principle either the N–C bond or the C–C bond could

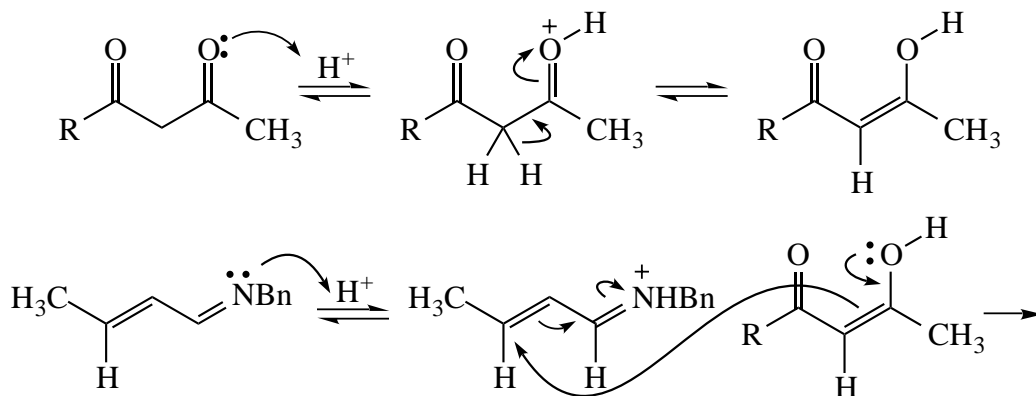
form first. Benzene does not generally react with ketones, while the reaction of an amine with a ketone is very rapid. Therefore the N–C bond forms, and iminium ion is generated, and then electrophilic aromatic substitution occurs to give PCP.

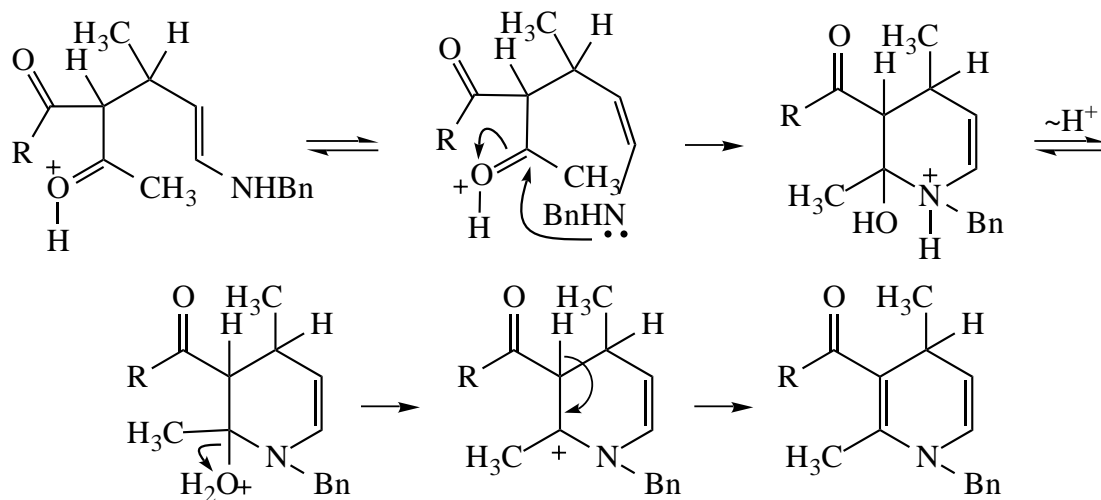


(m) Make: C3–C8, C4–N11. Break: C4–O5.

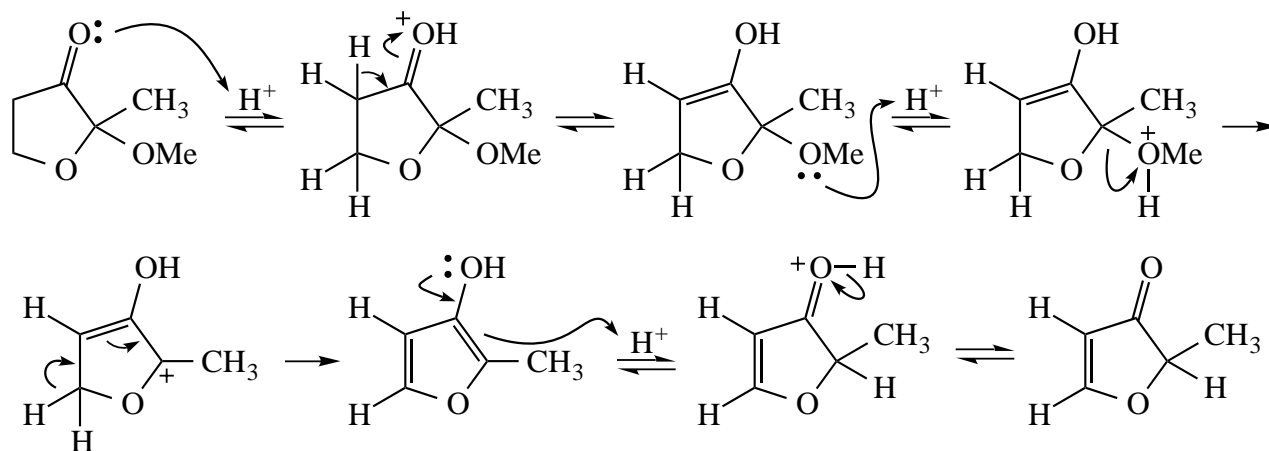


C3 and N11 are nucleophilic, C4 and C8 are electrophilic. Which bond forms first? Once the N11–C4 bond forms, C3 is made much less nucleophilic. So form the C3–C8 bond first (Michael reaction). C3 is made nucleophilic by tautomerization to the enol. The Michael reaction must be preceded by protonation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

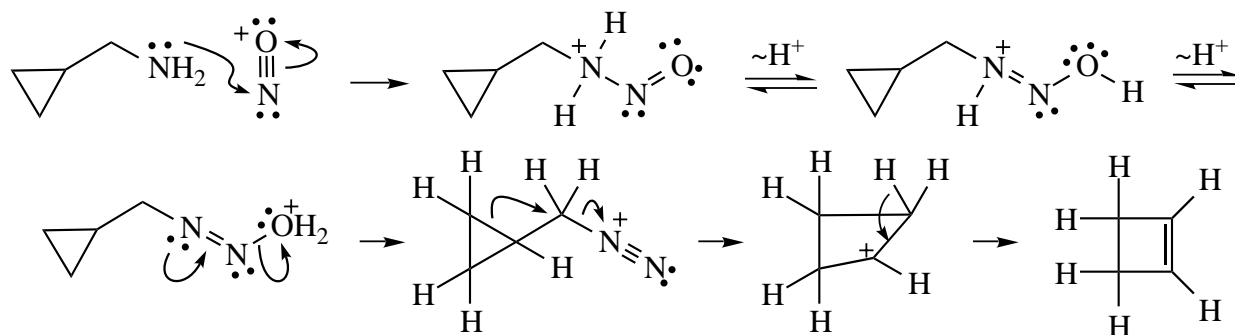




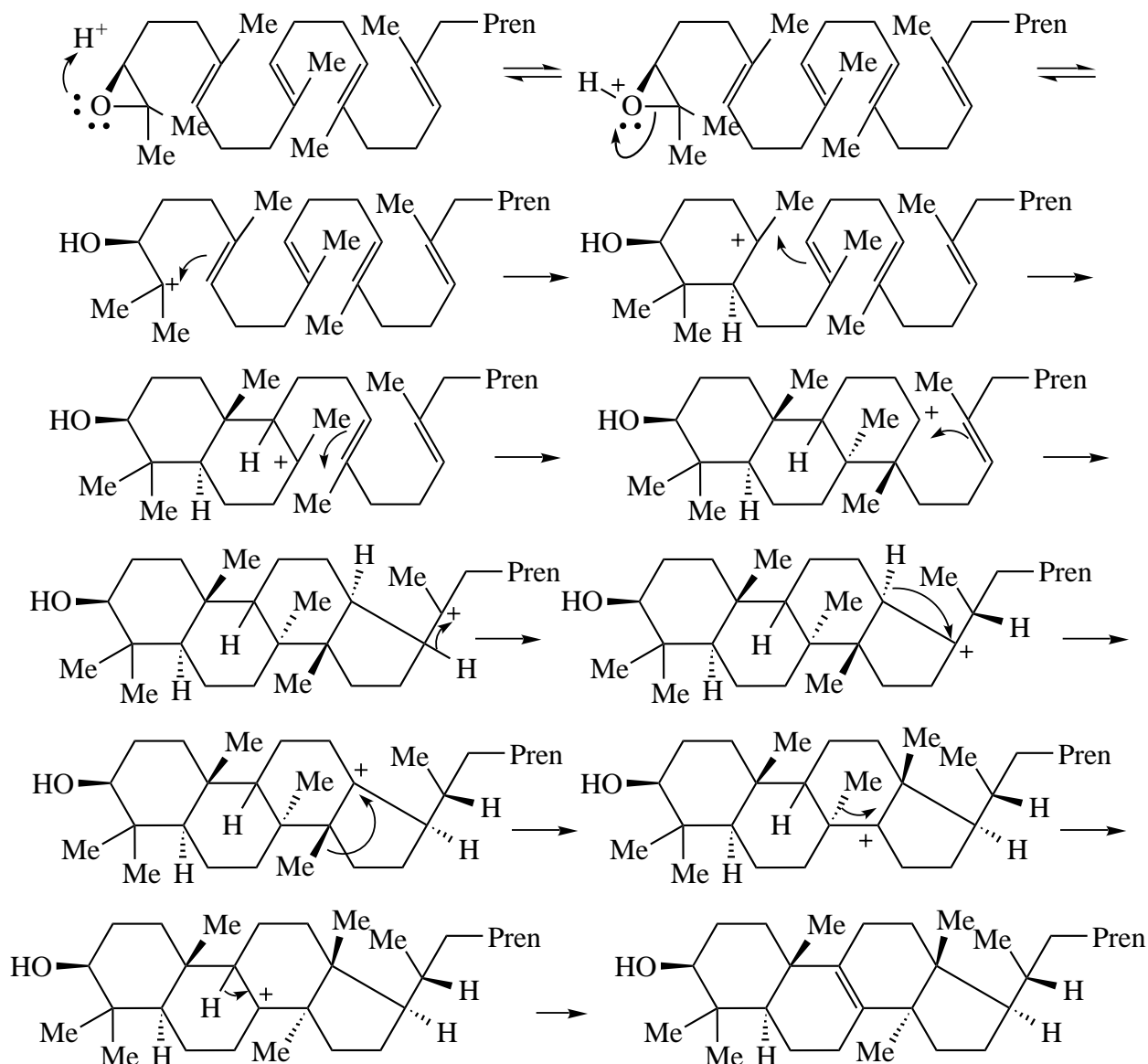
(n) The elements of MeOH are eliminated. However, since there are no H's β to the OMe group, the mechanism must be slightly more complicated than a simple E1. The key is to realize that formation of a carbocation at the acetal C is unlikely to occur with the keto group present. Under acidic conditions,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



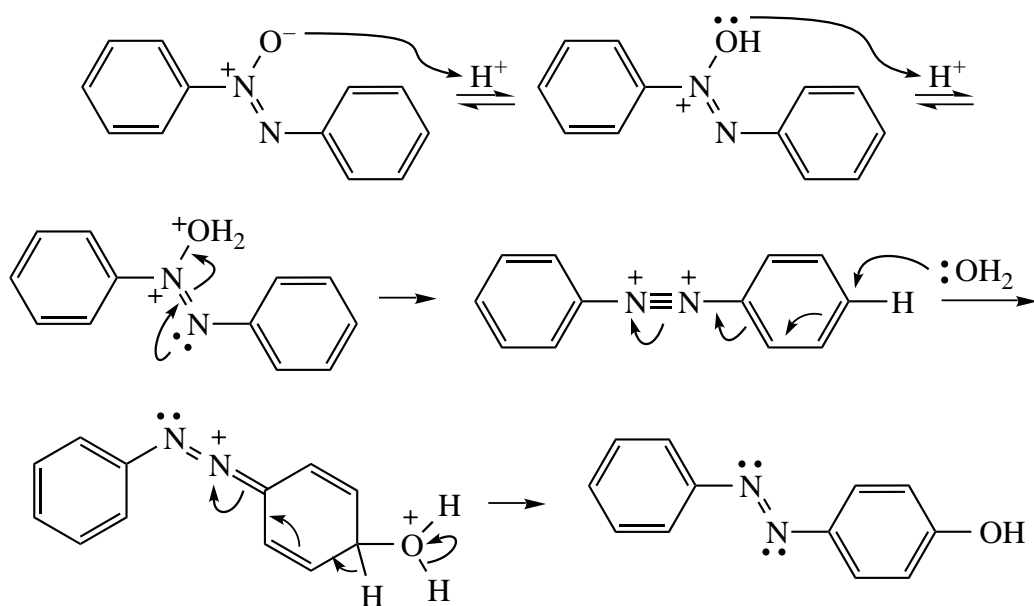
(o) Nitrous acid converts primary amines into diazonium salts RN_2^+ . The N_2 group is an excellent leaving group. Formation of the carbocation followed by 1,2-alkyl migration gives a more stable carbocation, which loses H^+ to give cyclobutene. Alternatively, α -elimination could occur from the diazonium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



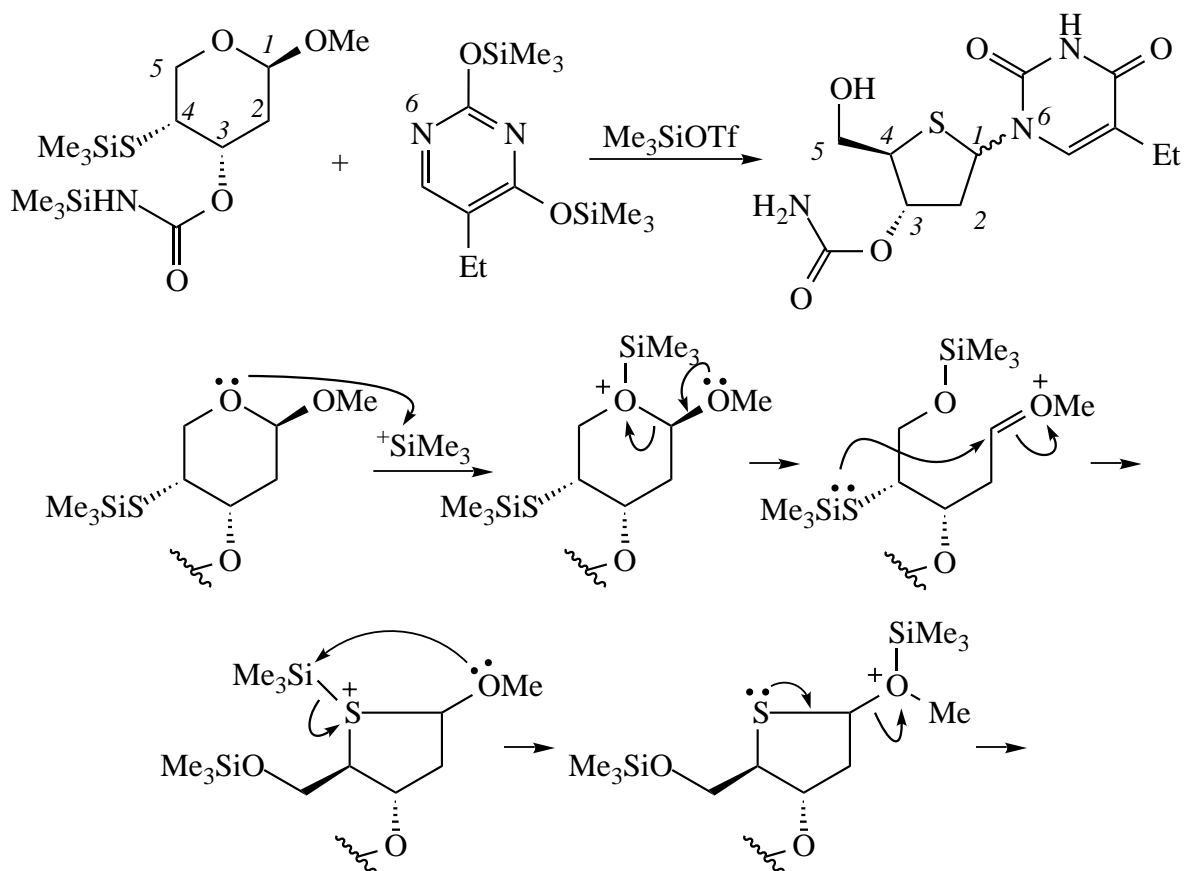
(p) The most basic site is the epoxide O. Protonation followed by a very facile ring opening gives a 3° carbocation. A series of additions of alkenes to carbocations follows, then a series of 1,2-shifts. The additions and 1,2-shifts have been written as if they occur stepwise, but some or all of them 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.

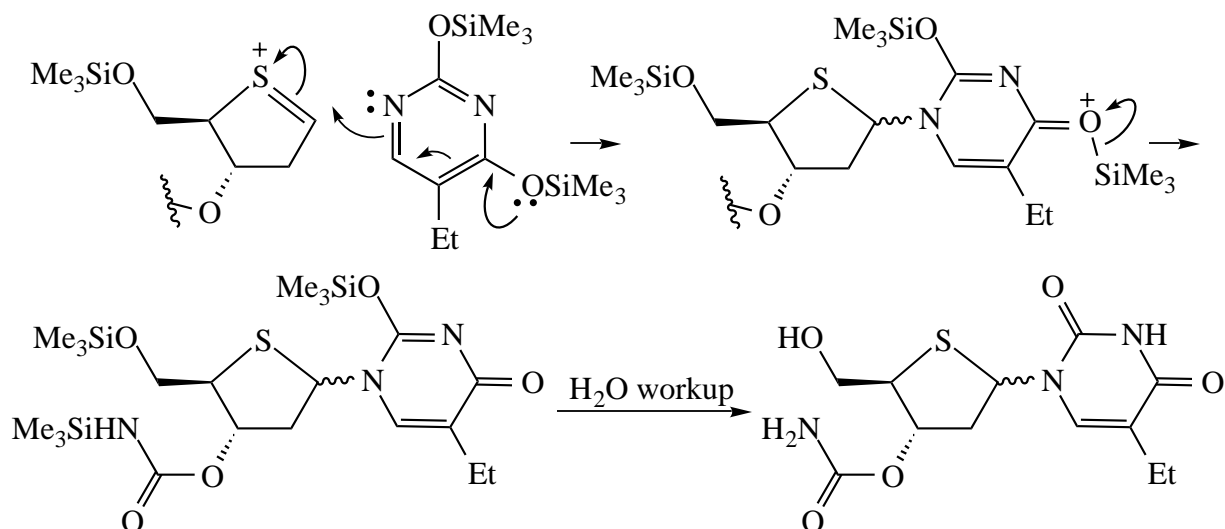


(q) The scrambling of the ^{15}N label suggests a symmetrical intermediate in which the two N's are equivalent. Incorporation of ^{18}O from H_2O suggests that a nucleophilic aromatic substitution is occurring. Double protonation of O followed by loss of H_2O gives a very electrophilic, symmetrical dicationic intermediate. Water can attack the *para* carbon; deprotonation then gives the product.

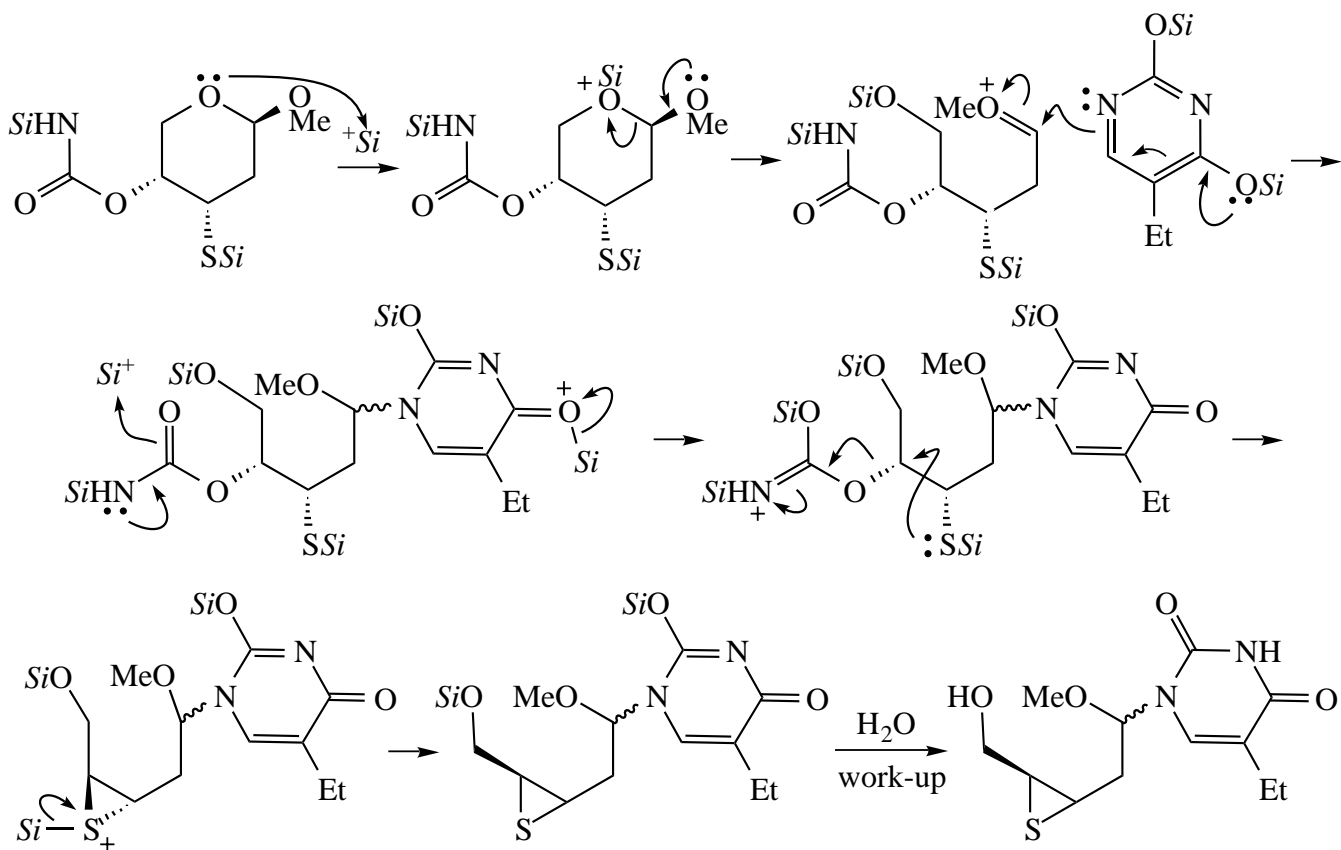


(r) (1) The two C1–O bonds undergo substitution with C1–S and C1–N6 bonds. Under these Lewis acidic conditions, and at this secondary and O-substituted center, the substitutions are likely to proceed by an $\text{S}_{\text{N}}1$ mechanism. The order of the two substitutions is not clear.

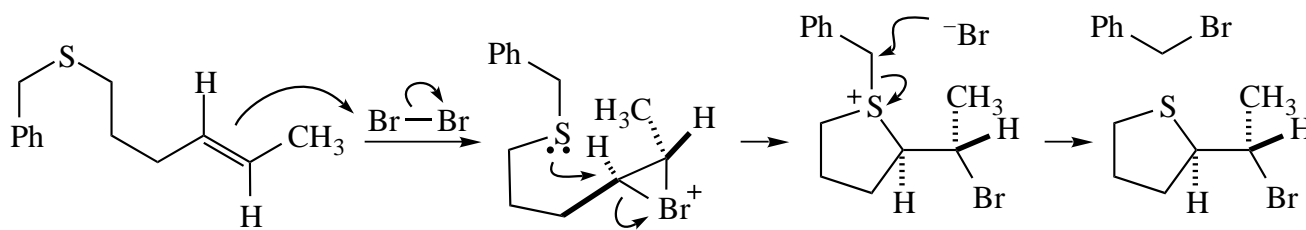




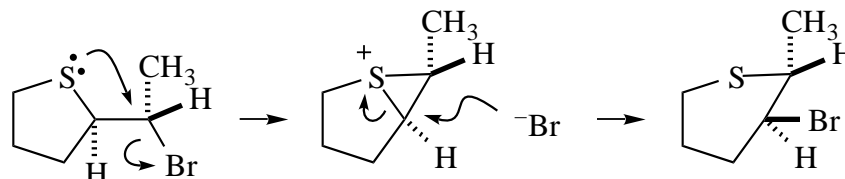
(2) Now only the endocyclic C1–O bond undergoes substitution, but the C4–O bond undergoes substitution with a C–S bond. In the previous problem we had S attack the C1 carbocation to give a five-membered ring. In the present problem, this would result in the formation of a four-membered ring, so the external 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. $Si = SiMe_3$.



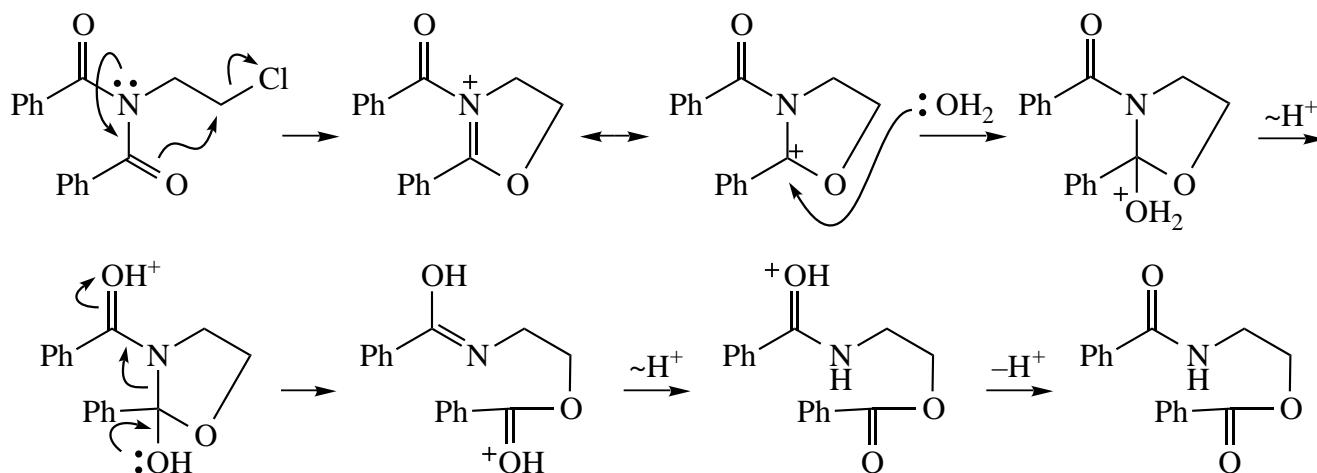
(s) Five-membered ring formation proceeds through a bromonium ion intermediate.



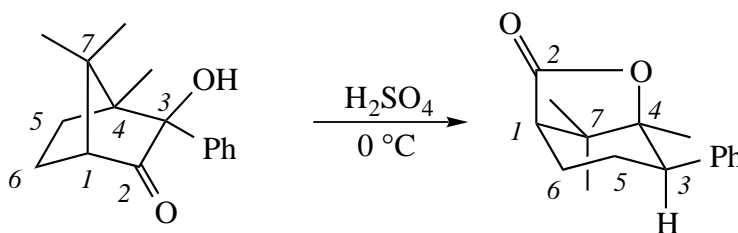
The five-membered ring can convert to the six-membered ring by two S_N2 displacements.



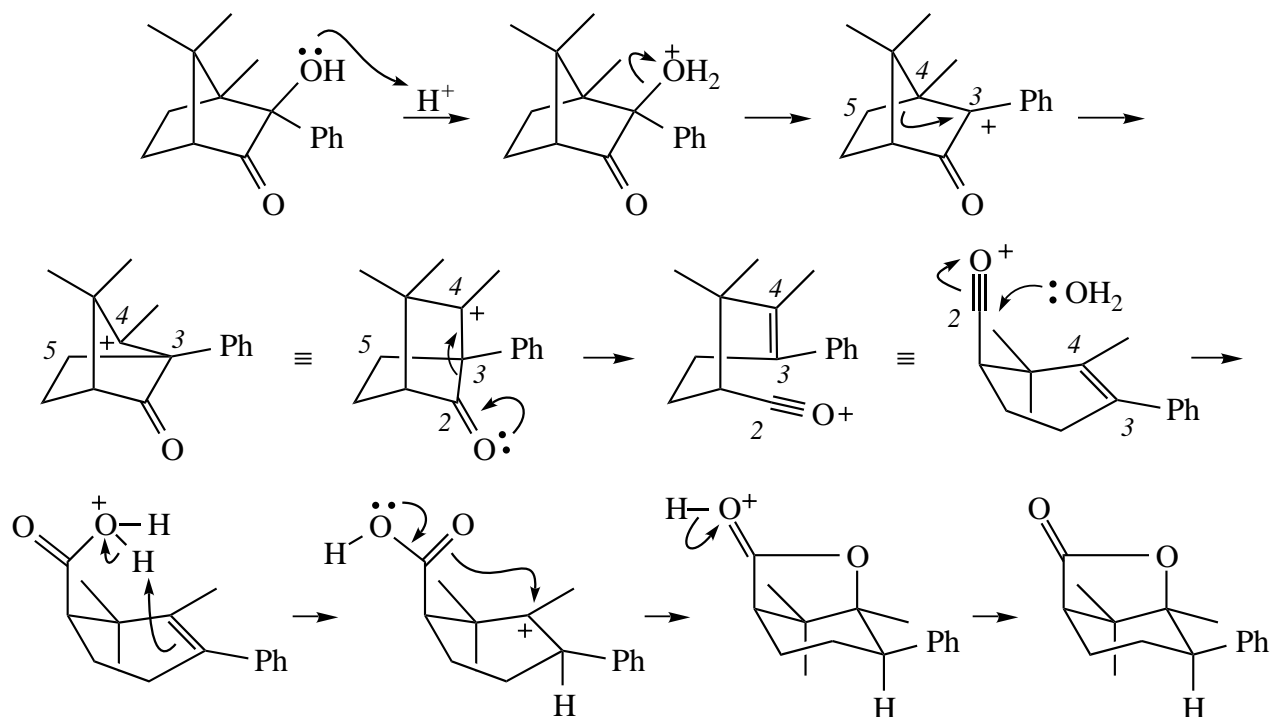
(t) The dependence of the rate of the reaction on the length of the alkyl chain suggests that an *intramolecular* reaction occurs between the nucleophilic O and the electrophilic C attached to Cl.



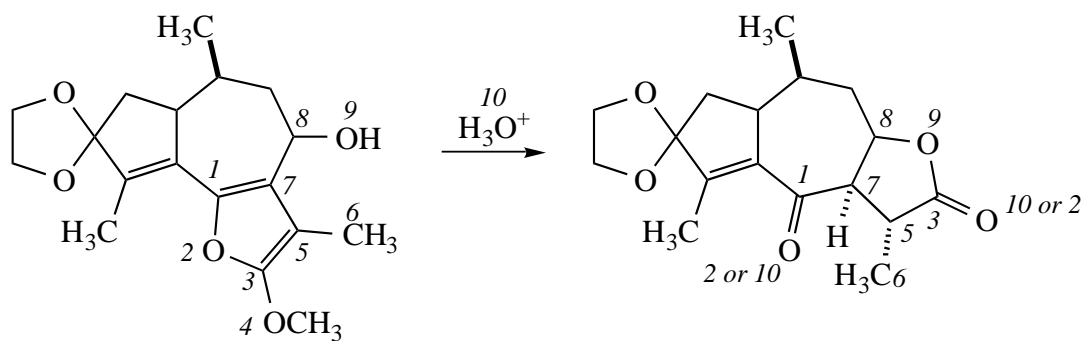
(u) The key atoms to recognize for numbering purposes are C7, C4, and C3. Then the others fall into place. Break: C2–C3, C4–C5. Make: C3–C5.



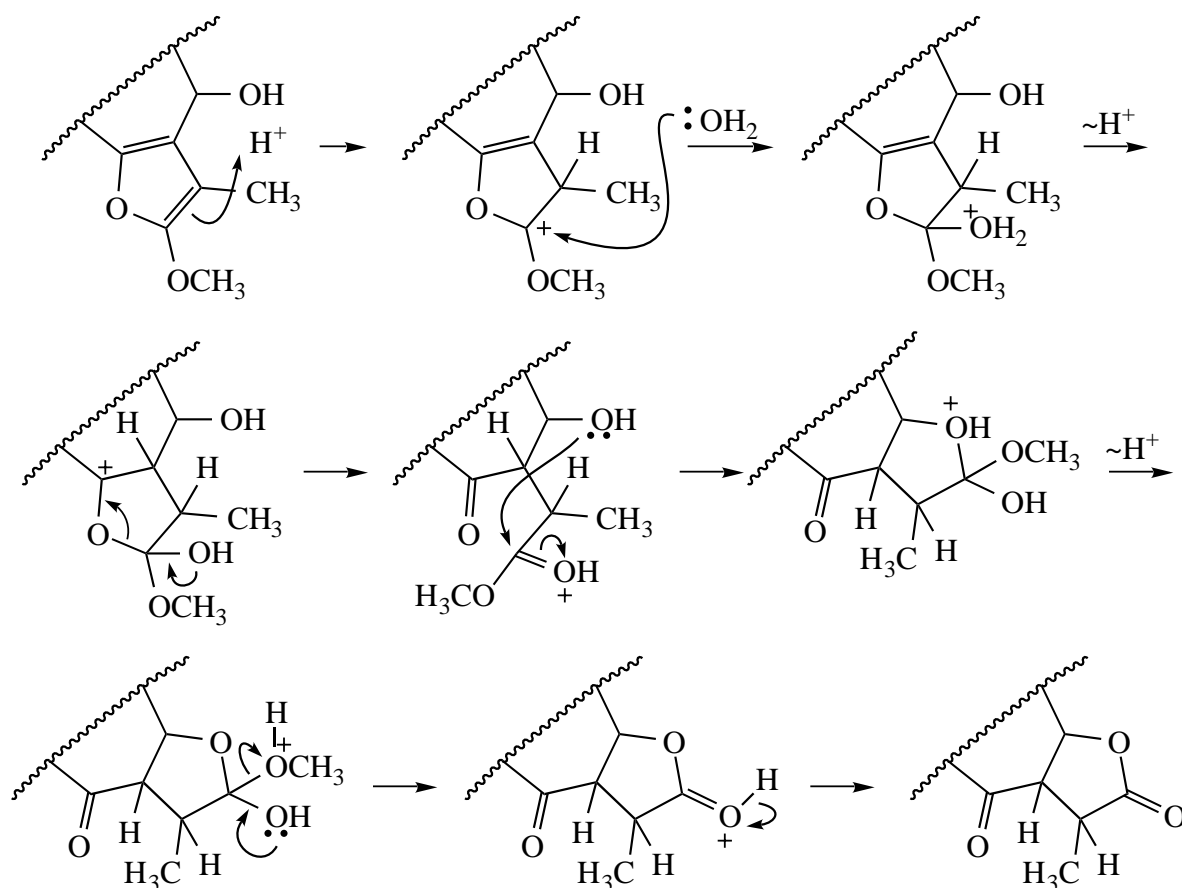
The cleavage of C5–C4 and formation of C5–C3 suggests that we have a 1,2-alkyl migration of C5 from C4 to a cationic C3. Then the electrons in the C2–C3 bond can move to form a new π bond between C3 and C4, leaving a stabilized acylium ion at C2. After addition of H_2O to the acylium ion, an acid-catalyzed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



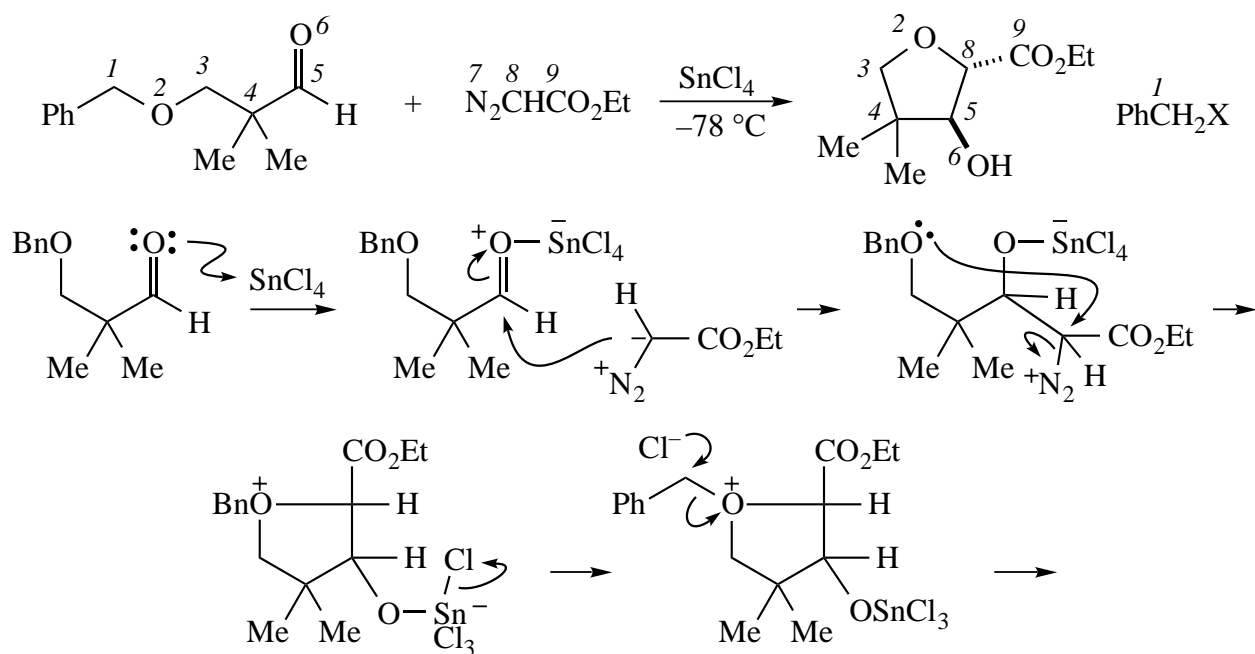
(v) The OCH_3 group is lost, and an OH group is gained. Whereas in the starting material C1 and C3 are attached to the same O, in the product they are attached to different O's. It is not clear whether O2 remains attached to C1 or C3. Make: O9–C3, O10–C3; break: C3–O4, C3–O2. *OR* make: O9–C3, O10–C1;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

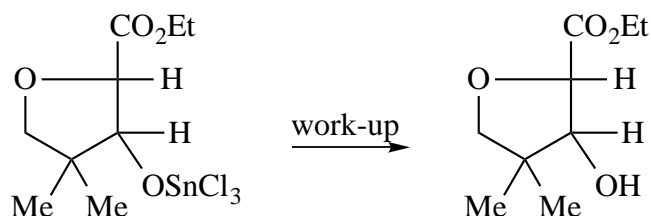


The first step is protonation; since all of the C–O bonds to be broken are $C(sp^2)$ –O bonds, the direct ionization of a C–O bond won't occur, so protonating O is unproductive. Both C5 and C7 need to gain a bond to H; protonation of C5 gives the better carbocation. Water can add to make the C3–O10 bond.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

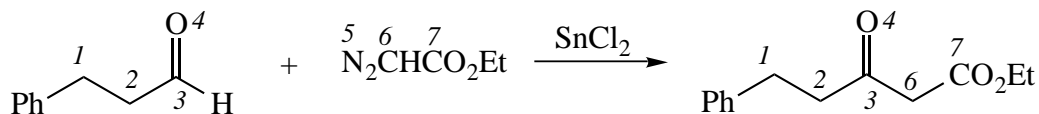


(w) Make: O2–C8, C5–C8. Break: C8–N, C1–O2. C8 is nucleophilic. $SnCl_4$ coordinates to O6 to make C5 more electrophilic, and C8 attacks C5. Then O2 circles around to displace N_2 from C8. Finally, Cl^- from $SnCl_4$ can come back and displace O2 from C1. The stereochemistry of the product is thermodynamically controlled.

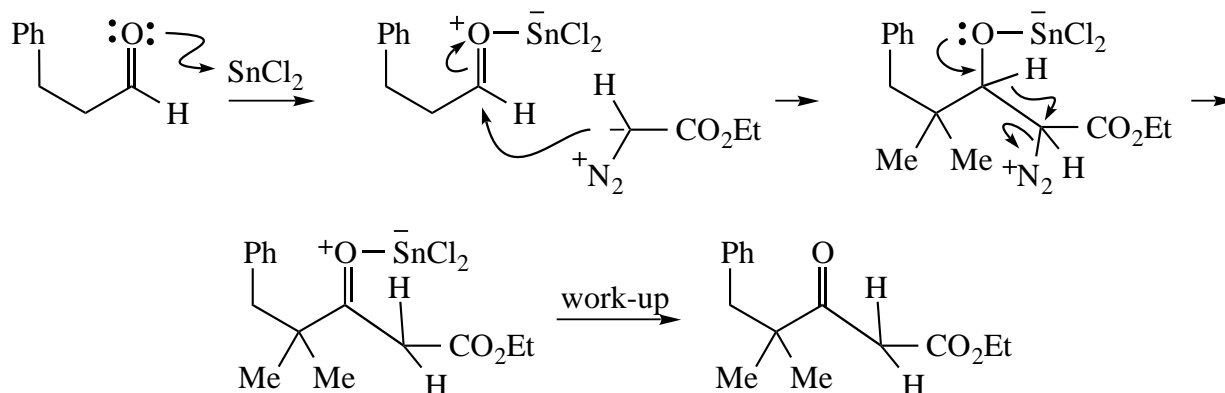




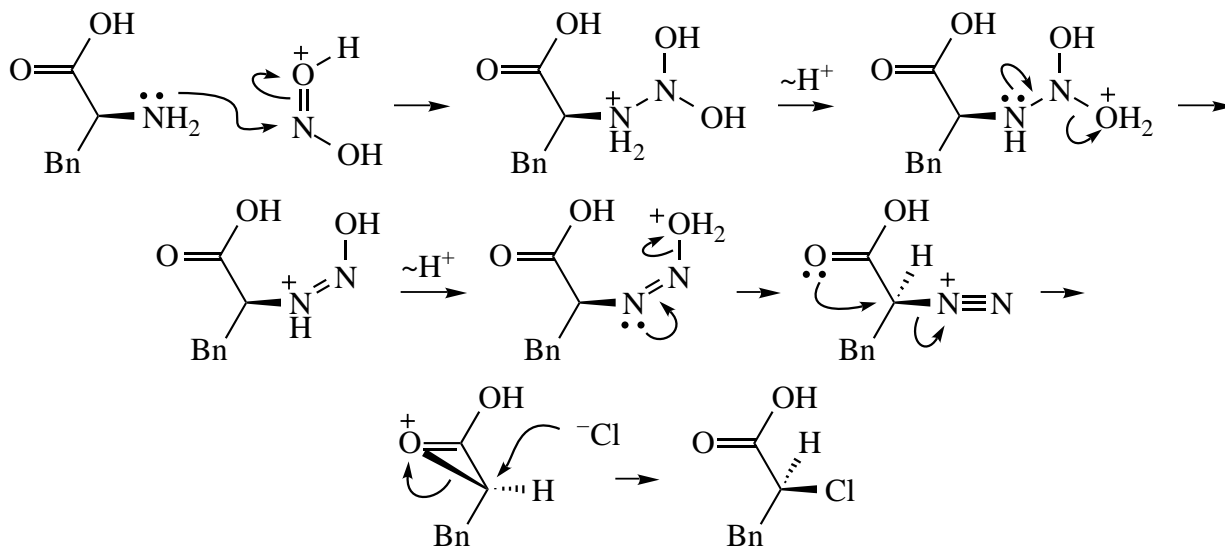
(x) Make: C3–C6. Break: C6–N5.



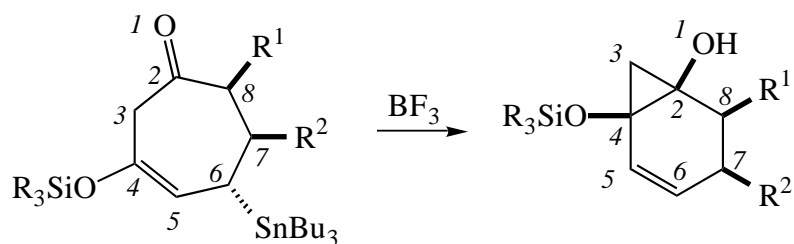
Reaction starts off the same way as last time. After addition to the carbonyl, though, a 1,2-hydride shift occurs with expulsion of N_2 to give the product after workup.



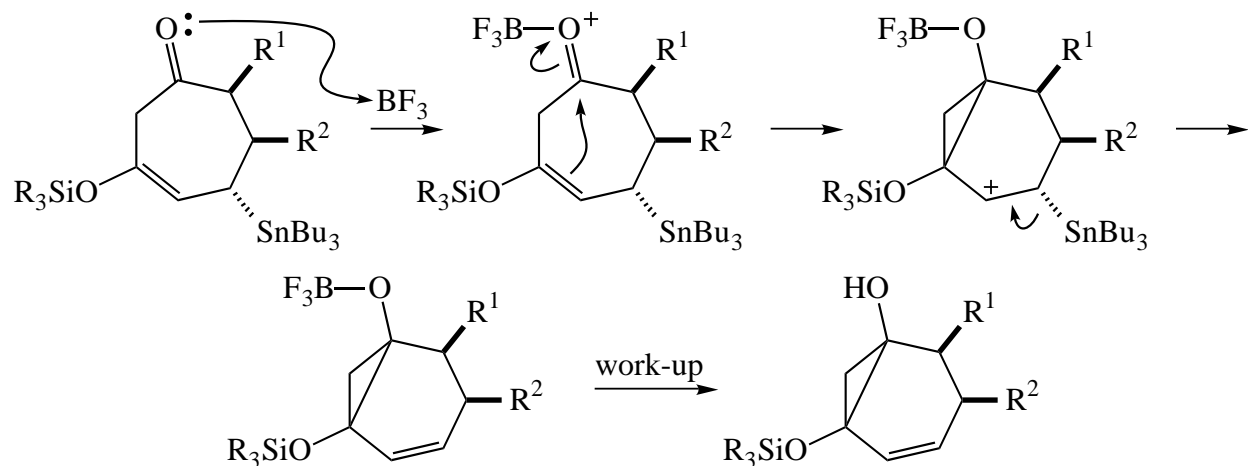
(y) The stereochemistry tells you that neither a simple $\text{S}_{\text{N}}1$ nor an $\text{S}_{\text{N}}2$ mechanism is operative. Two $\text{S}_{\text{N}}2$ substitutions would give the observed result, however. When 1° amines are mixed with HNO_2 , a diazonium ion is formed. Intramolecular $\text{S}_{\text{N}}2$ substitution by the carbonyl O gives a lactone, and then a second $\text{S}_{\text{N}}2$ substitution by Cl^- gives the product.



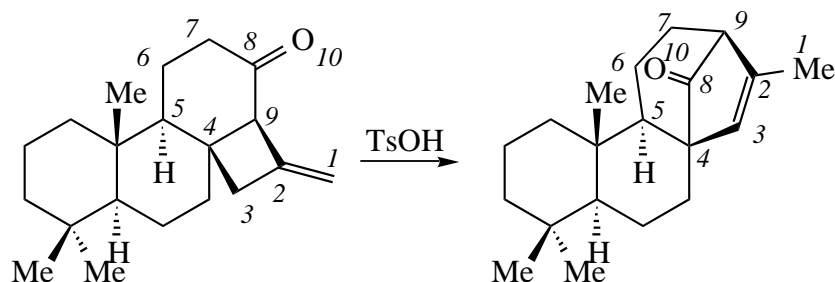
(z) Make: C2–C4. Break: C6–Sn.



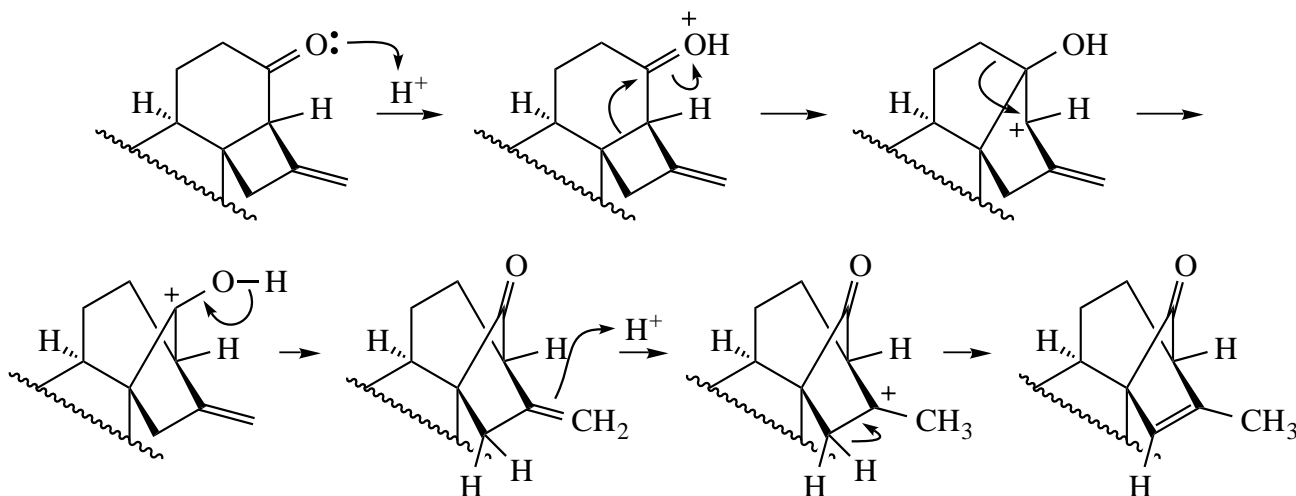
C2 is electrophilic, especially after BF_3 coordinates to it. C4 can then act as a nucleophile, making C5 carbocationic. Fragmentation of the C6–Sn bond gives the product.



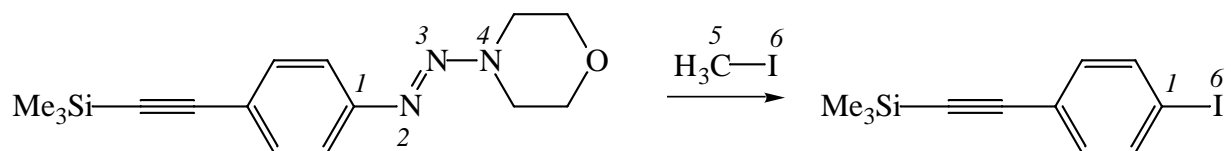
(aa) Numbering correctly is key. C4 through C7 are clear. The Me group in the product must be C1, and it's attached to C2. The rest follow. Make: C7–C9, C4–C8. Break: C7–C8, C4–C9.



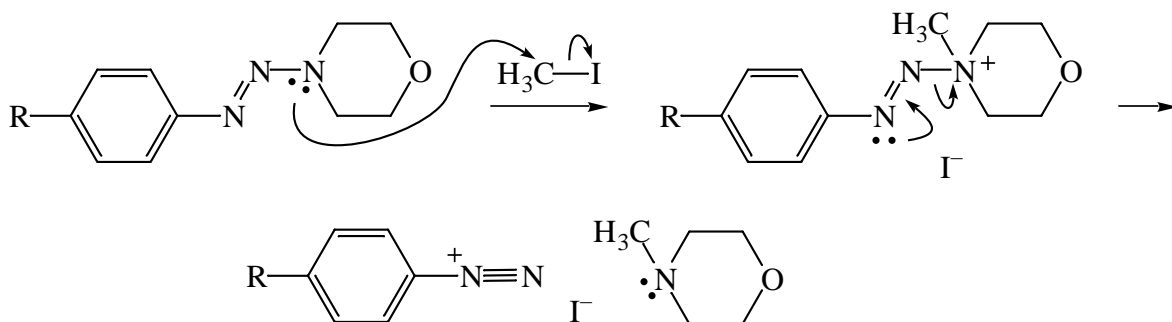
First step is protonation of O10 to make C8 electrophilic. Then a shift of C4 from C9 to C8 occurs to give a cation at C9. This is followed by a shift of C7 from C8 to C9. Deprotonation of O10, protonation of C1, and deprotonation of C3 give the product.



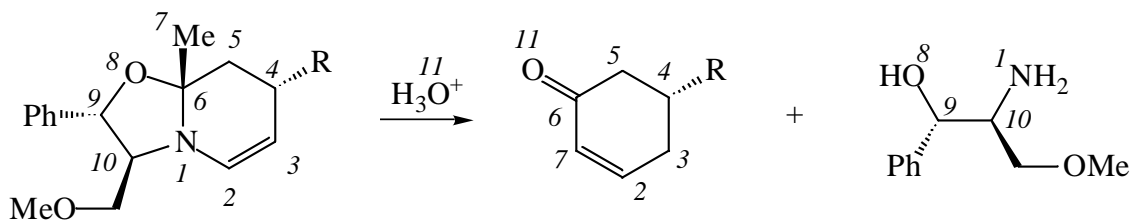
(bb) Make: C1–I6. Break: C1–N2, C5–I6.



Hold on! What happened to N2, N3, N4, and C5? One possibility is that the new product has an N2–C5 bond. But this doesn't seem too likely, because it seems that this compound would want to form N₂. If we assume N₂ is formed, then there must be a new N4–C5 bond. Make: C1–I6, N4–C5. Break: C1–N2, C5–I6. The first step is attack of N4 on C5, displacing I6. Cleavage of the N3–N4 bond then gives a diazonium ion, which undergoes S_{RN}1 substitution as in in-chapter problem 3.12.

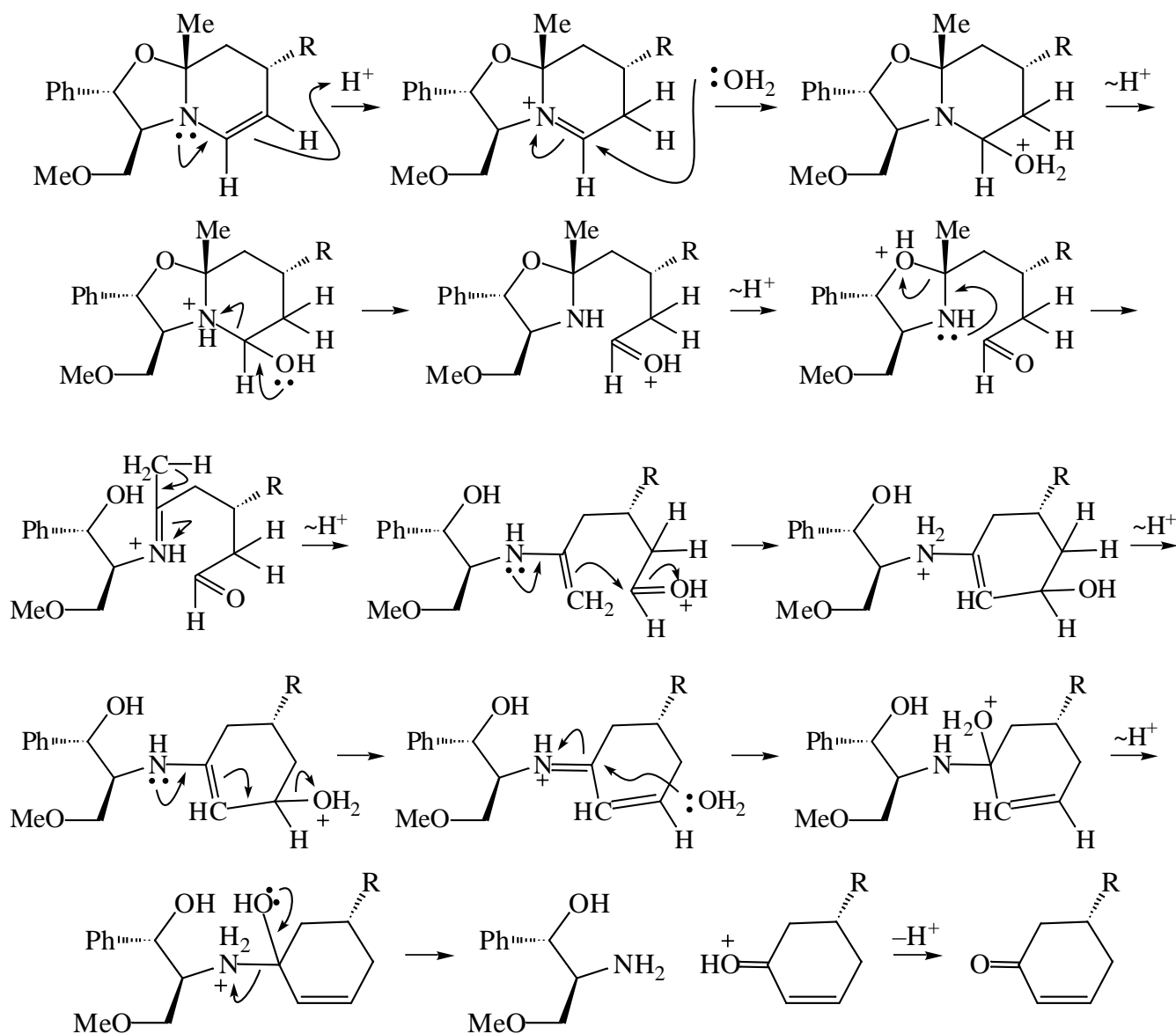


(cc) Make: C2–C7, C6–O11. Break: N1–C2, N1–C6, C6–O8.



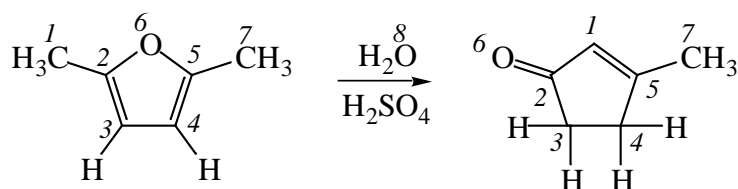
The first step must be protonation to form a nice stable carbocation. The first protonation can occur on C3

to give a C2 carbocation or on O8 so it can leave to form a C6 carbocation. Let's assume the former for now. Protonation on C3 gives a carbocation to which O11 can add. Proton transfer to N1 is followed by cleavage of the N1–C2 bond. Another proton transfer from O11 to O8 is followed by cleavage of the O8–C6 bond to give a C6 carbocation. At this point, we have the opportunity to turn C7 into a nucleophile by H^+ transfer from C7 to O11 to give an enamine. Attack of C7 on C2 is now followed by H^+ transfer from N1 to O11 and cleavage of the O11–C3 bond. Finally, O11 attacks C2, and H^+ transfer from O11 to N1 is followed by cleavage of the N1–C6 bond to give the products.

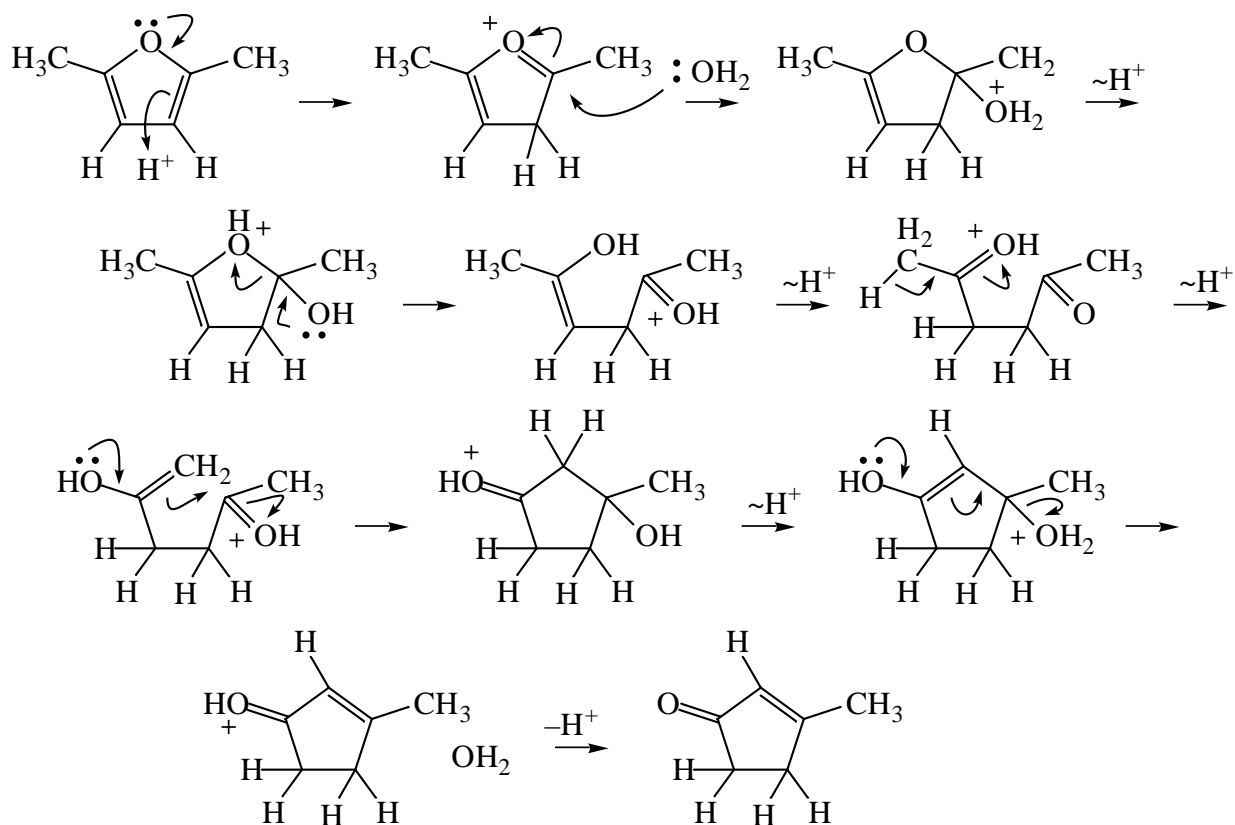


A similar mechanism can be drawn if O8 is protonated first (not shown). Cleavage of the O8–C6 bond gives a C6 carbocation to which O11 adds. After cleavage of the N1–C6 bond, H^+ transfer from C7 to C3 occurs to give an enol and an iminium ion. C7 then attacks C2, and elimination of the amine follows to give the products.

(dd) Make: C1–C5. Break: C5–O6.



The first step is protonation. Because both C3 and C4 need to pick up protons, we protonate on C4. At this point, there's not much we can do except allow H_2O to add to the carbocation, even though this is not a bond that is in our list of bonds that need to be made; we will need to cleave it later. Addition of O8 to C5, H^+ transfer from O8 to O6, and cleavage of the C5–O6 bond follow. At this point we still need to make the C1–C5 bond. C5 is clearly electrophilic, so C1 needs to be made nucleophilic. Proton transfer from O8 to C3 and another H^+ transfer from C1 to O8 gives the C1 enol, which attacks the C5 carbocation. Another H^+ transfer from C1 to O8 is followed by cleavage of the O8–C5 bond, and loss of H^+ gives the product.



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