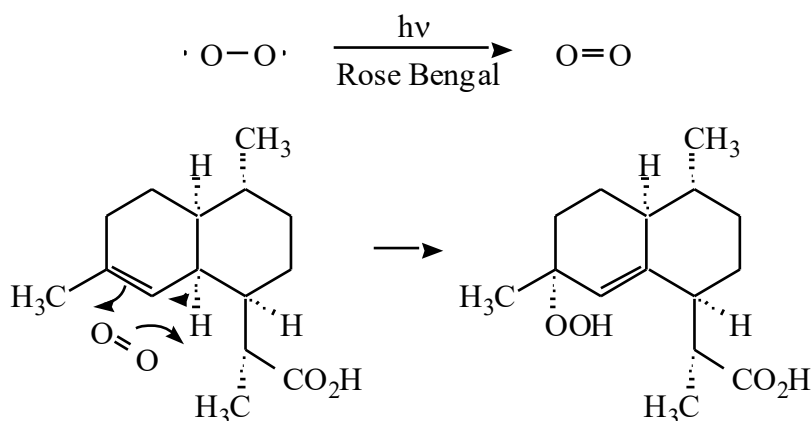
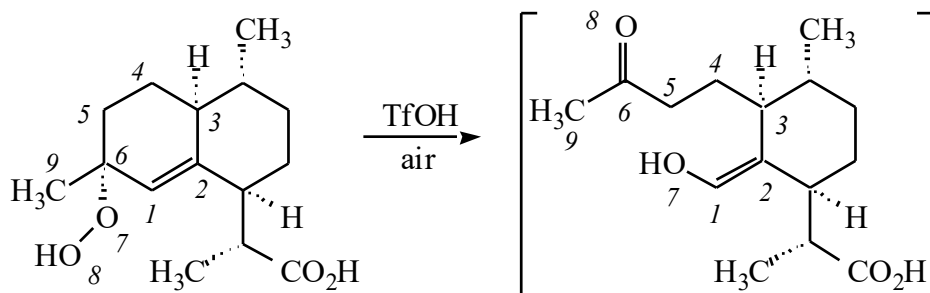


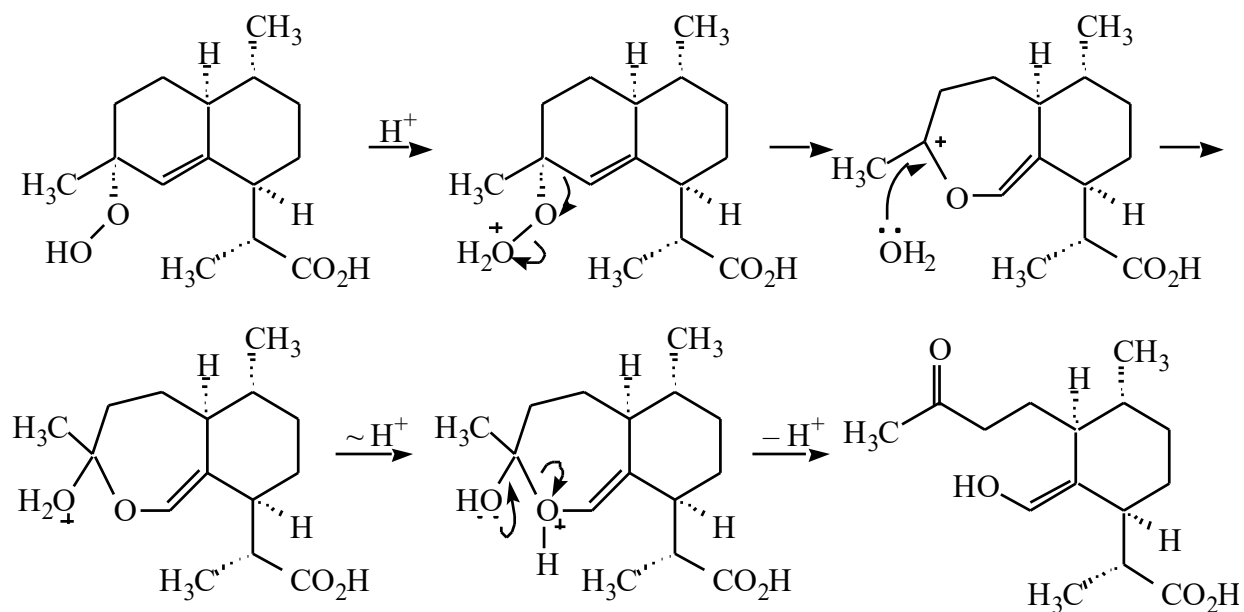
Answers to Chapter 7 Problems.

- Most of the Chapter 1 problems appear as end-of-chapter problems in later chapters.
- The first reaction is an ene reaction. When light shines on O_2 in the presence of light and Rose Bengal, singlet oxygen is obtained. This compound can do cycloadditions or ene reactions. If the reaction were a free-radical autoxidation, neither light nor Rose Bengal would be required.

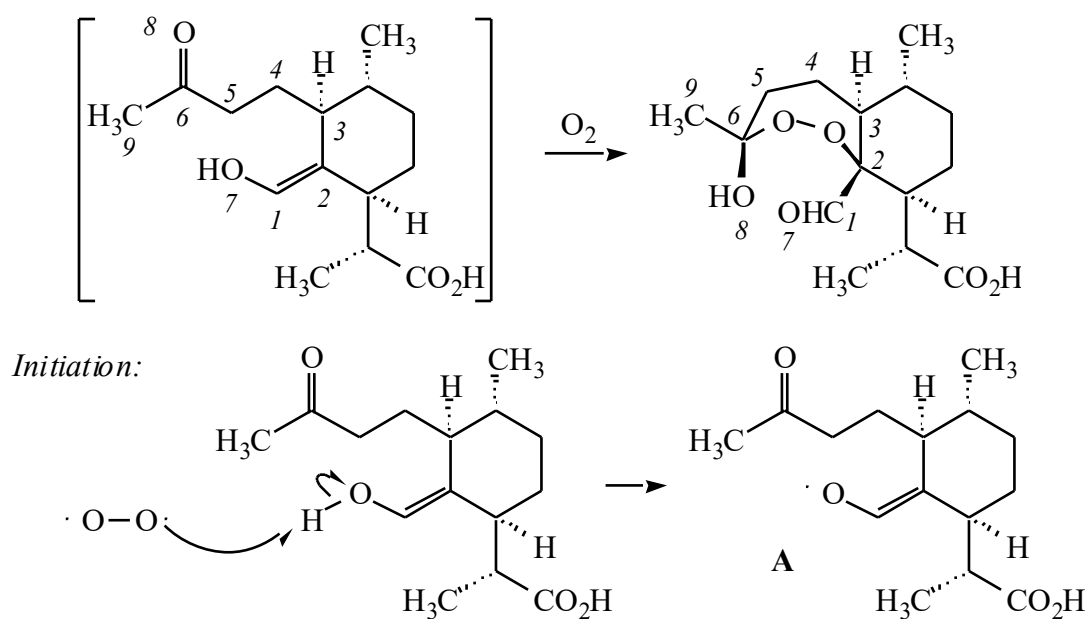


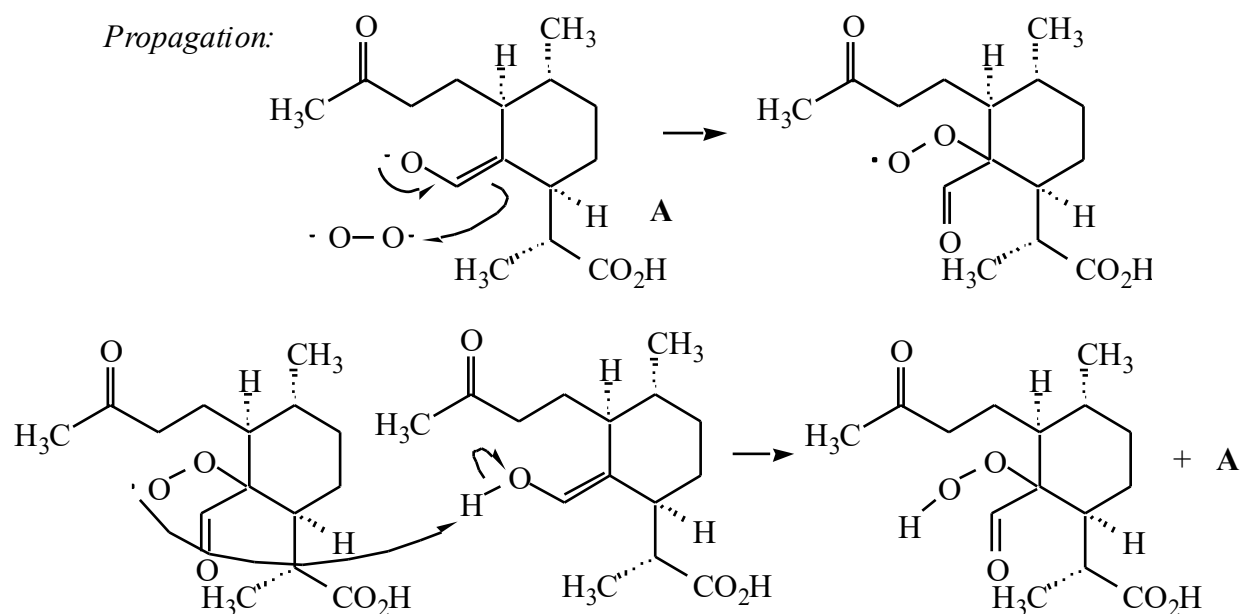
Second reaction. Air is not required for formation of the keto-enol. The C1–C6 and O7–O8 bonds are broken, and a new C1–O bond is made. It makes sense that the driving force for breaking the C1–C6 bond should be provided by migrating C1 from C6 to O7 (note: a 1,2-shift) and expelling O8. Then O8 can add back to C6 to give a hemiketal which can open up to the ketone.



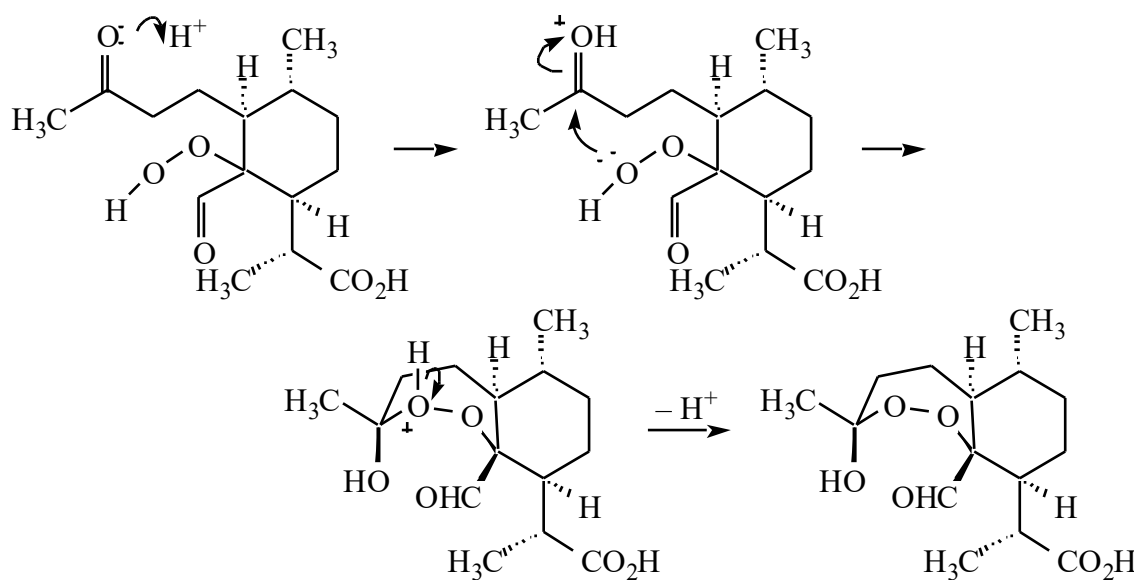


Air is required for conversion of the keto-enol to the endoperoxide. The most likely reaction is autoxidation. The O_2 makes bonds to C2 and C6, neither of which has an H atom attached for abstraction. But abstraction of $\text{H}\cdot$ from O7 gives a radical, **A**, that is delocalized over O7 and C2. Addition of O_2 to C2 gives a hydroperoxy radical, which abstracts $\text{H}\cdot$ from O7 of the starting material to give a hydroperoxide and **A** again. The hydroperoxide thus obtained can then add to the C6 ketone in a polar fashion to give the observed hemiketal.

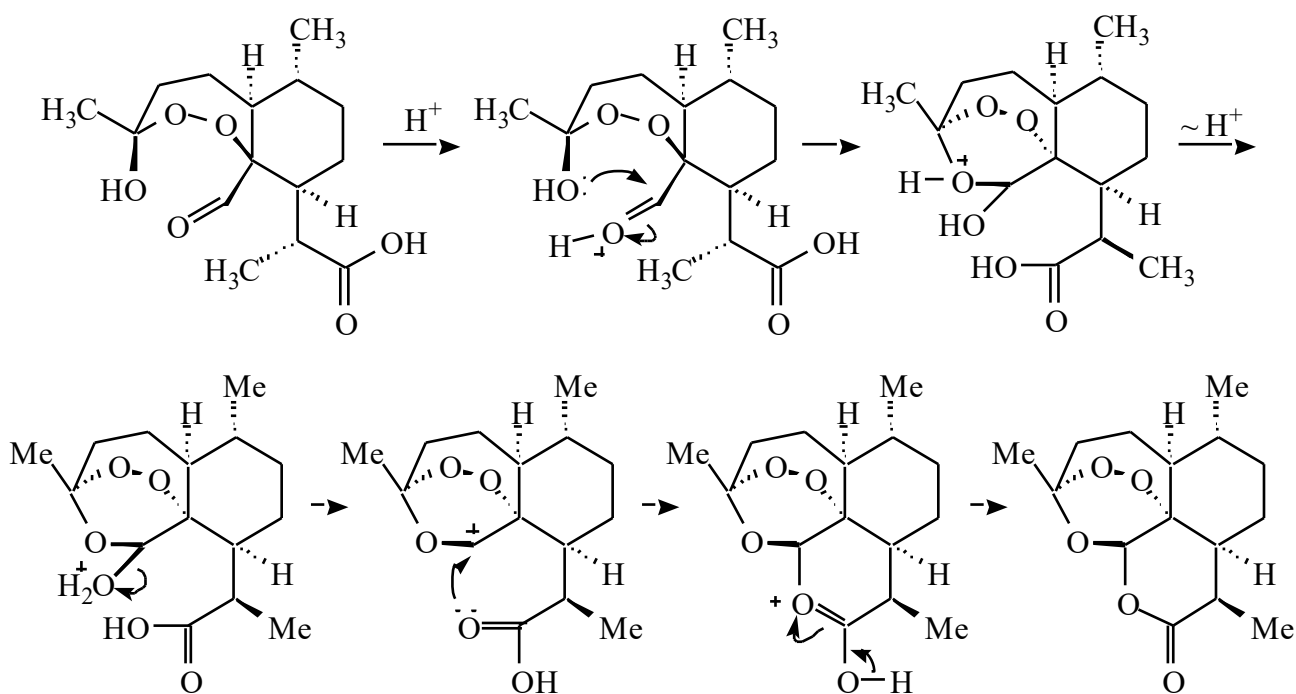




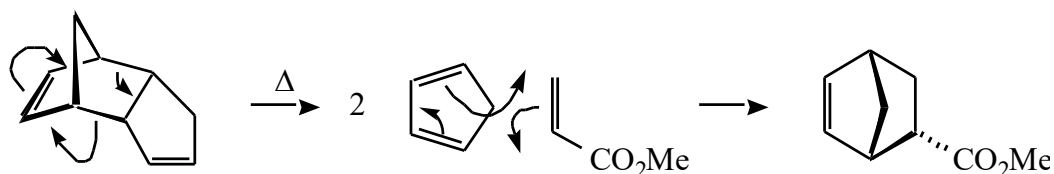
Polar reaction (acid is still present):



The fourth reaction is transformation of the aldehyde into an acetal. This proceeds by acid-catalyzed addition of an alcohol to the carbonyl, loss of H_2O , and then addition of the acid O to the carbocation. Other perfectly correct sequences of steps could be written here.

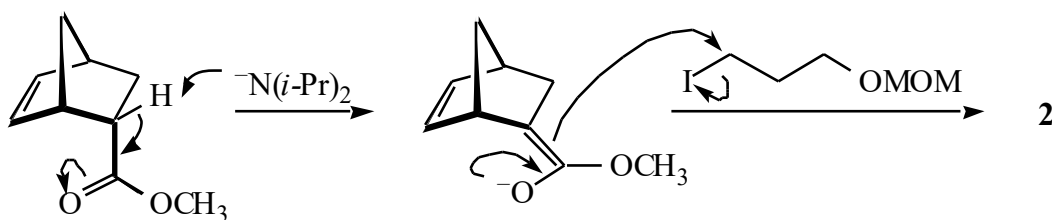


3. (a) Compound **1** is obviously made by a Diels–Alder reaction between cyclopentadiene and methyl acrylate. Cyclopentadiene is made from the starting material by a retro-Diels–Alder reaction. The product is obtained stereoselectively because of *endo* selectivity in the Diels–Alder reaction.

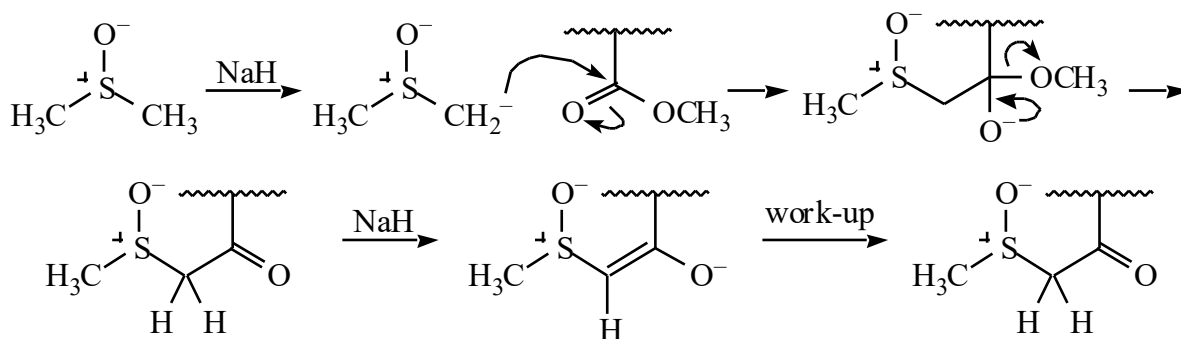


The starting material is called “dicyclopentadiene”. Cyclopentadiene itself is not stable: it dimerizes to dicyclopentadiene slowly at room temperature by a Diels–Alder reaction. It does this even though it is not an electron-deficient dienophile, demonstrating the enormous reactivity of cyclopentadiene as a diene in the Diels–Alder reaction.

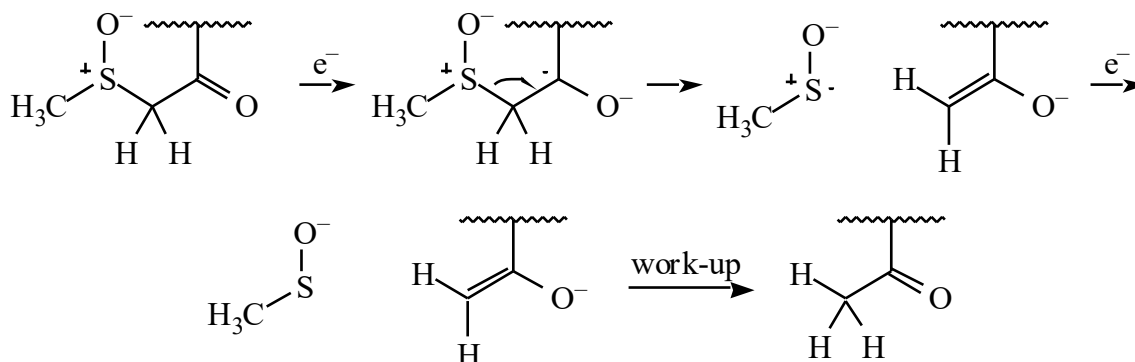
(b) LDA is a strong base. Compound **2** is obtained from the enolate of **1** by a simple S_N2 substitution reaction.



Now DMSO is treated with NaH, then with **2**, then with Zn and NaOH, to give overall substitution of CH₃ for CH₃O. The CH₃ group must come from DMSO, so we need to make a new bond between the DMSO C and the C=O carbon. NaH is a good base; it deprotonates DMSO to give the *dimsyl* anion. This adds to the carbonyl C, and then loss of MeO⁻ occurs to give the β-ketosulfoxide. This is a very good acid (like a 1,3-dicarbonyl), so it is deprotonated under the reaction conditions to give the enolate. Workup gives back the β-ketosulfoxide. This part of the mechanism is directly analogous to a Claisen condensation.

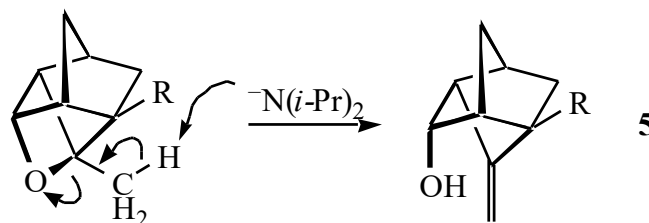


To get to **3**, we need to cleave the S–C bond. Zn is an electron donor, like Na or Li. Electron transfer to the ketone gives a ketyl, which undergoes fragmentation to give the enolate. The second electron from the Zn goes to the S leaving group to give MeSO⁻. Workup gives the methyl ketone.

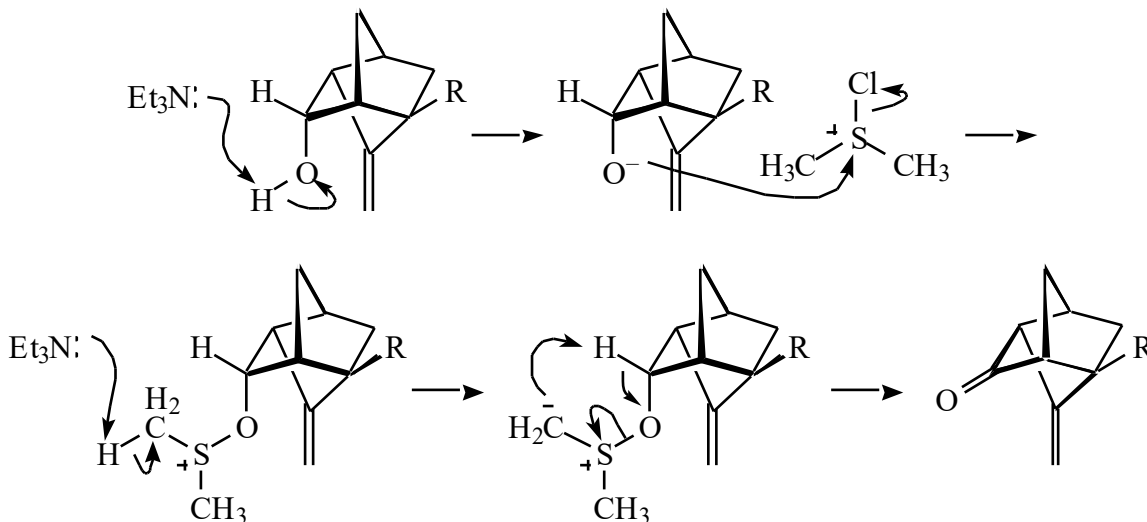
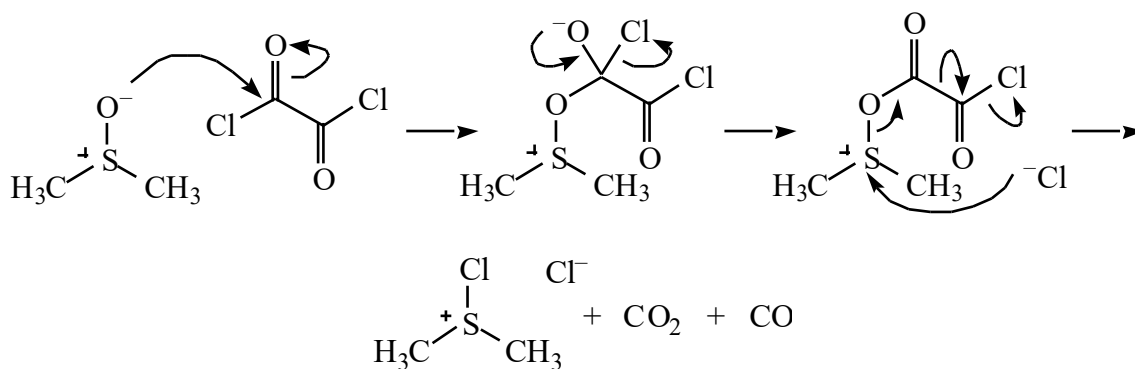


(c) The conversion of **3** to **4** is a [2+2] cycloaddition, the Paterno–Büchi reaction. This four-electron reaction proceeds photochemically.

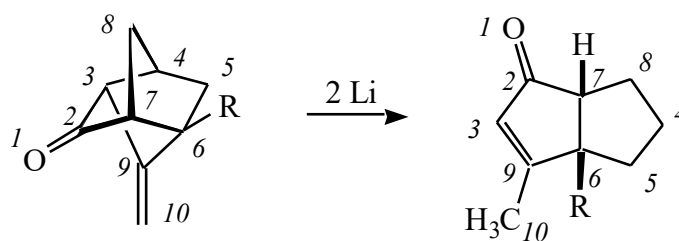
(d) The conversion of **4** to **5** is an E2 elimination.



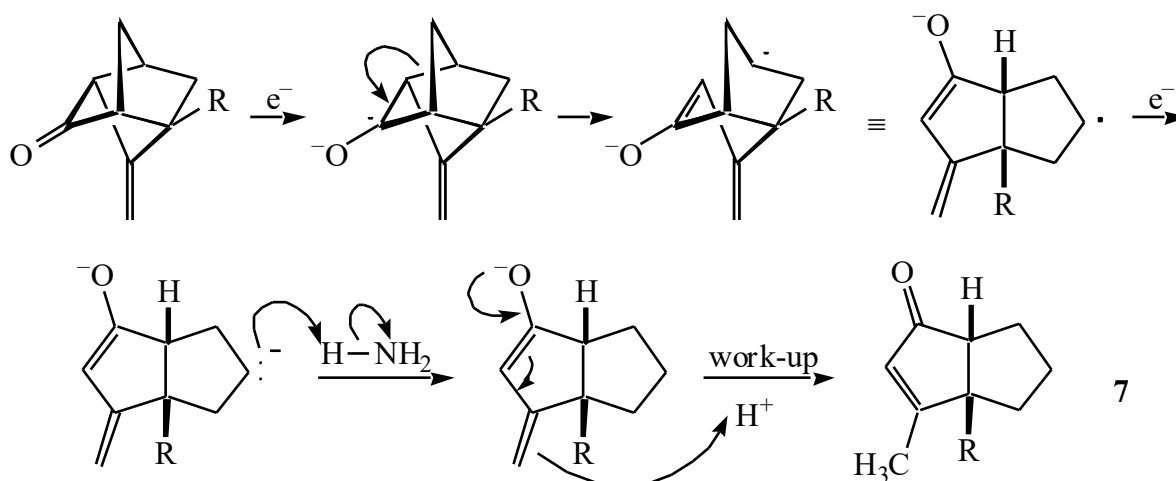
The conversion of **5** to **6** is a Swern oxidation. The O of DMSO is nucleophilic, and it reacts with oxalyl chloride. Cl^- then comes back and displaces O from S to give a S electrophile. The OH of **5** is then deprotonated, whereupon it attacks S, displacing Cl^- . Then deprotonation of a Me group and a retro-hetero-ene reaction occur to give the ketone.



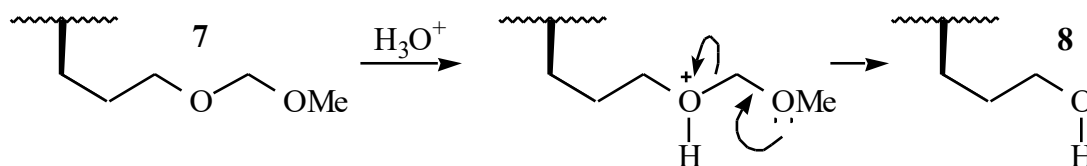
The conversion of **6** to **7** is a dissolving metal reduction. Number the atoms. The key atoms are O1, C2, C6, C10, and C9. Make: none. Break: C3–C4.



The first step is formation of the ketyl of **6**. This species can undergo fragmentation to form the C2–C3 enolate and a radical at C4. A second electron transfer gives a carbanion at C4, which deprotonates NH_3 . Upon workup, C10 is protonated to give **7**.

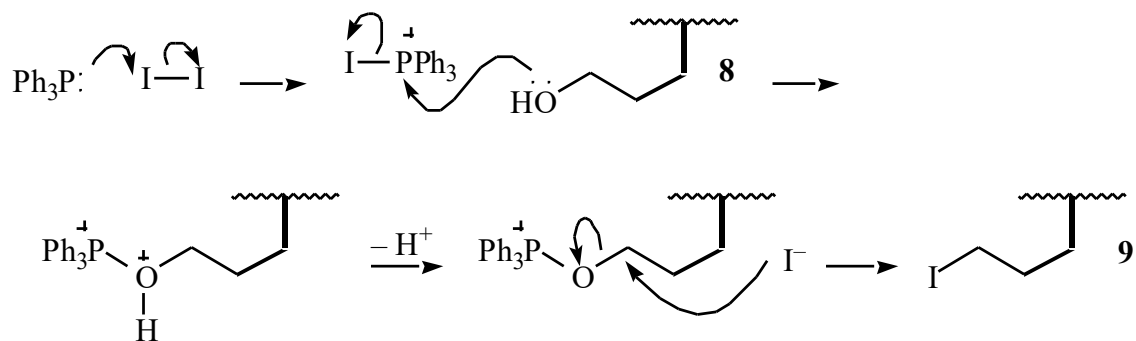


The conversion of **7** to **8** is a simple hydrolysis of an acetal. Acetals are functionally equivalent to alcohols + carbonyls and can be interconverted with them under acidic conditions. Several reasonable mechanisms can be drawn for this transformation, but all must proceed via $\text{S}_{\text{N}}1$ substitutions.

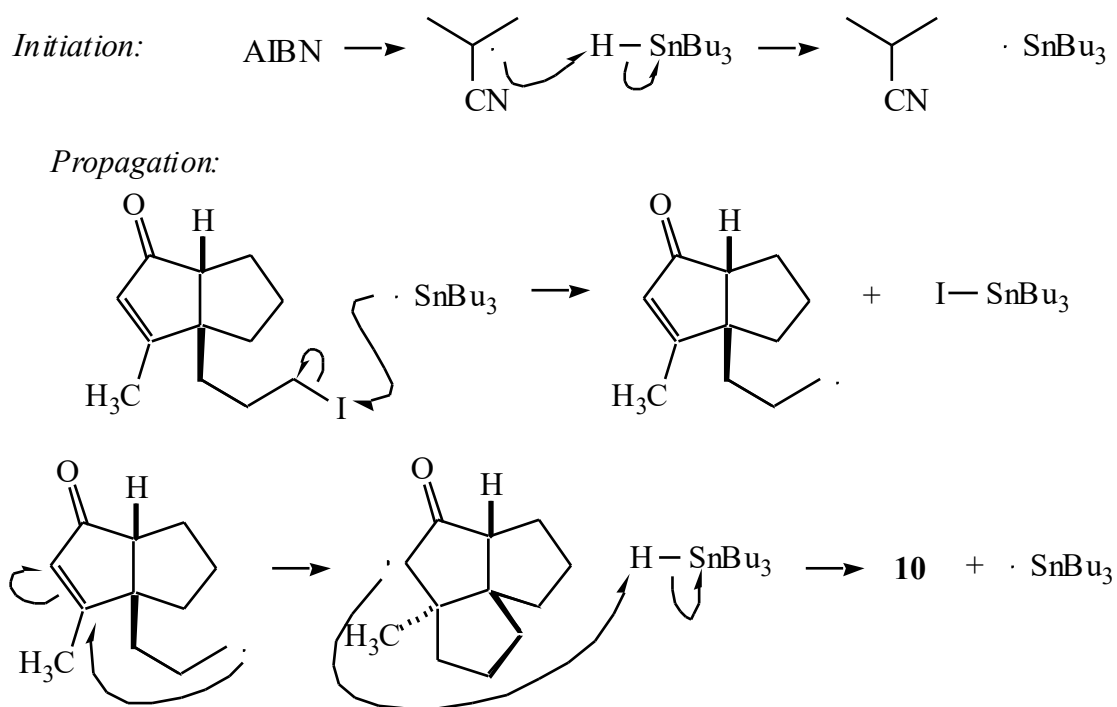


The conversion of **8** to **9** uses PPh_3 and I_2 . The former is a nucleophile, the latter is an electrophile, so they react to give $\text{Ph}_3\text{P}^+\text{I}^-$. The P is attacked by the alcohol to give an O–P bond, and the I^- then

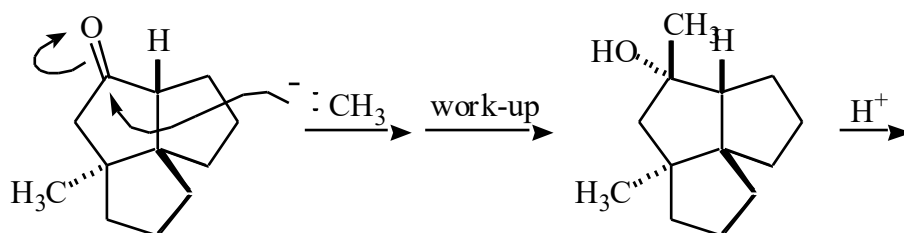
displaces Ph_3PO from C to give the alkyl iodide.

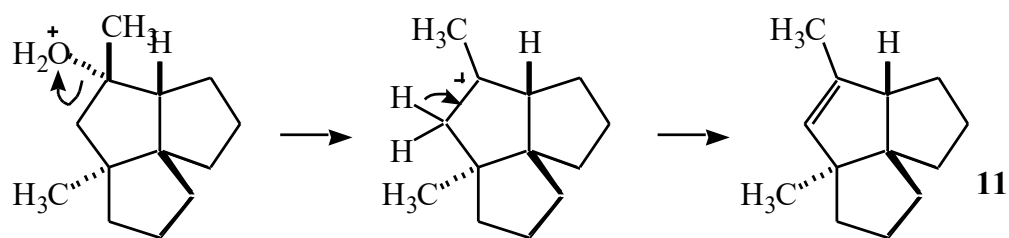


The next reaction is obviously a free-radical chain reaction.



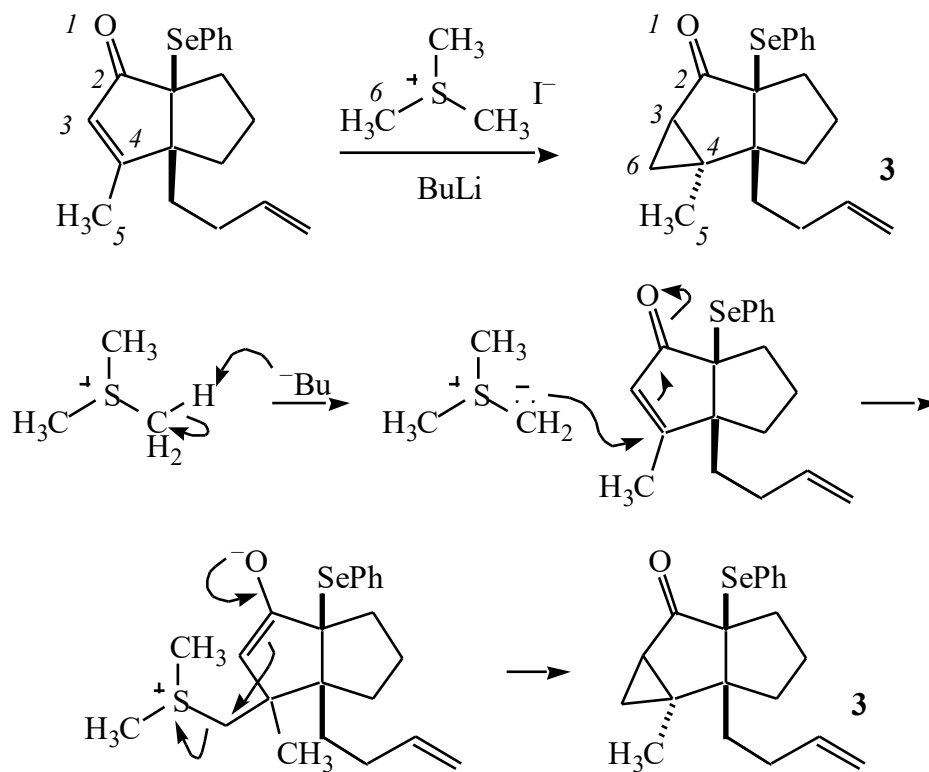
Finally, conversion of **10** to **11** involves addition of the very nucleophilic MeLi to the ketone; workup gives the alcohol. Then E1 elimination promoted by the acid TsOH gives the alkene.





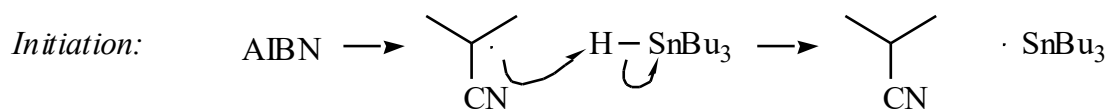
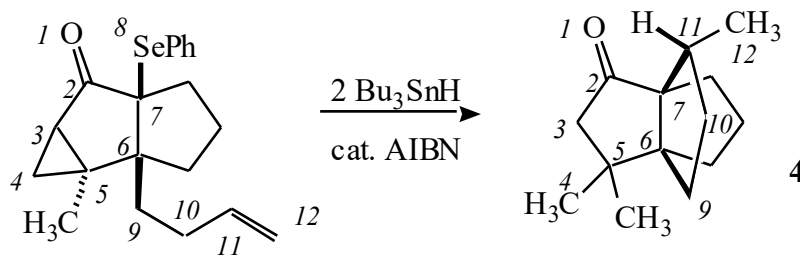
4. (a) The transformation of **1** to **2** (not shown) is a simple deprotonation with LDA, followed by S_N2 substitution on Se, displacing $-\text{SePh}$.

The conversion of **2** to **3** requires making C3–C6 and C4–C6, and breaking C6–S. The BuLi deprotonates C6 to give a sulfur ylide. This makes C6 nucleophilic. It adds to C4, making an enolate and making C3 nucleophilic. The enolate at C3 then attacks C6, displacing Me_2S to give the product.

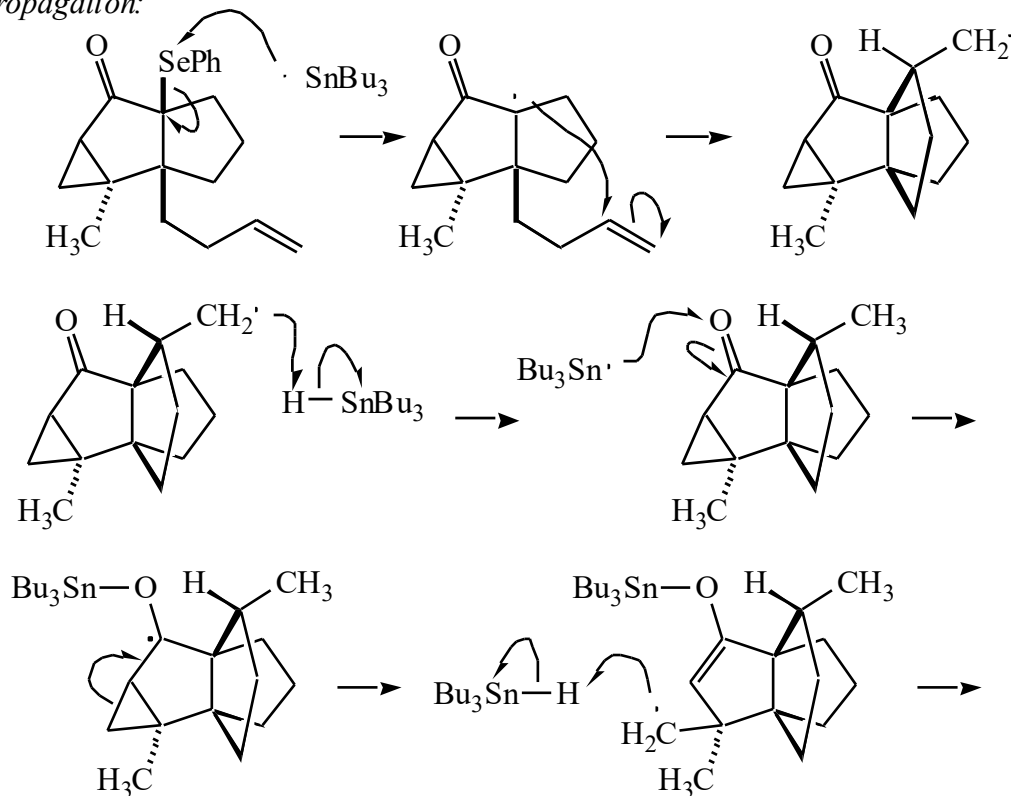


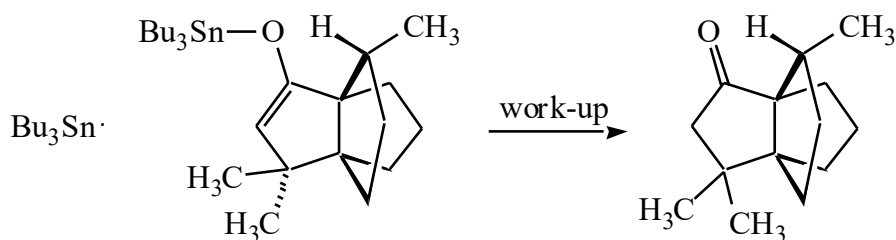
The conversion of **3** to **4** is a free-radical chain process. Note two equivalents of Bu_3SnH are required. Make: C7–C11, Sn–Se8. Break: Se8–C7, C3–C4. Let's deal with the Se first. After initiation, $\text{Bu}_3\text{Sn}\cdot$ abstracts SePh from C7. The C7 radical then adds to C11, giving a radical at C12 which abstracts H

from Bu_3SnH to regenerate $\cdot\text{SnBu}_3$. The C3–C4 bond still needs to be broken, and C3 and C4 both need to have H attached to them. We know that a cyclopropane ring cleaves very easily if a radical is generated at a C attached to it, e.g. at C2. We can generate a radical at C2 by having $\text{Bu}_3\text{Sn}\cdot$ add to O1. Then the C3–C4 bond cleaves, making a C4 radical and a tin enolate at C3–C2–O1. The C4 radical abstracts H from Bu_3SnH to propagate the chain. The tin enolate is protonated upon workup to give **4**.

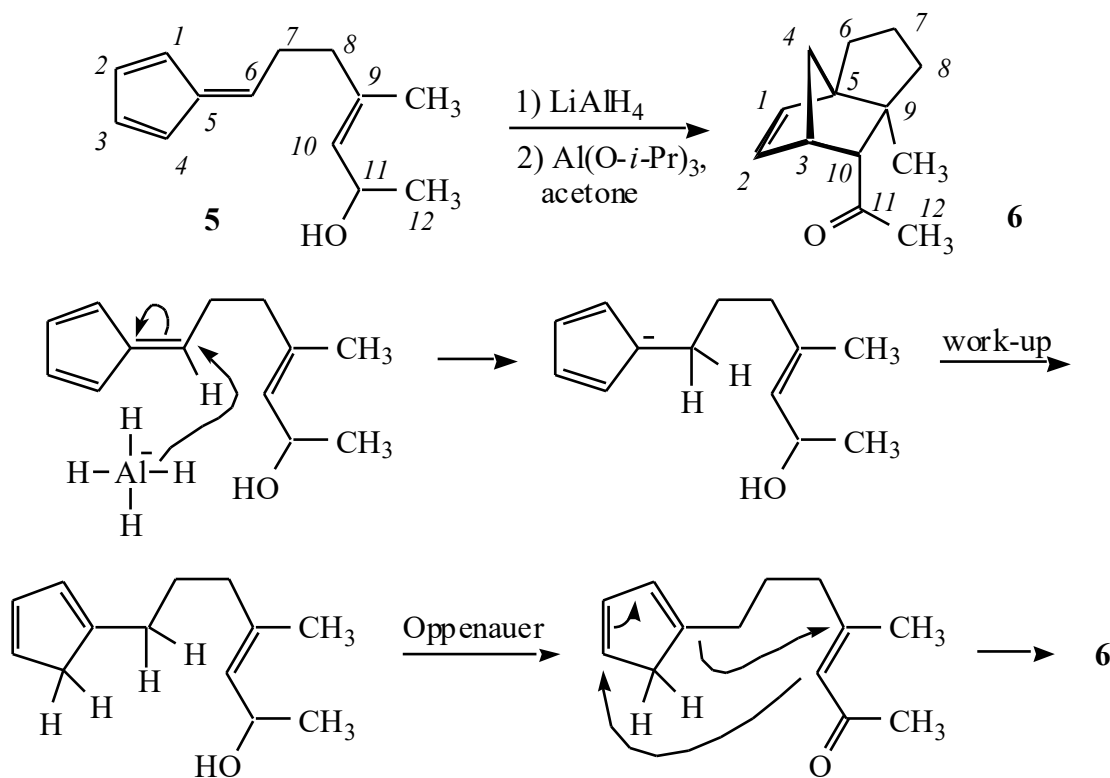


Propagation:



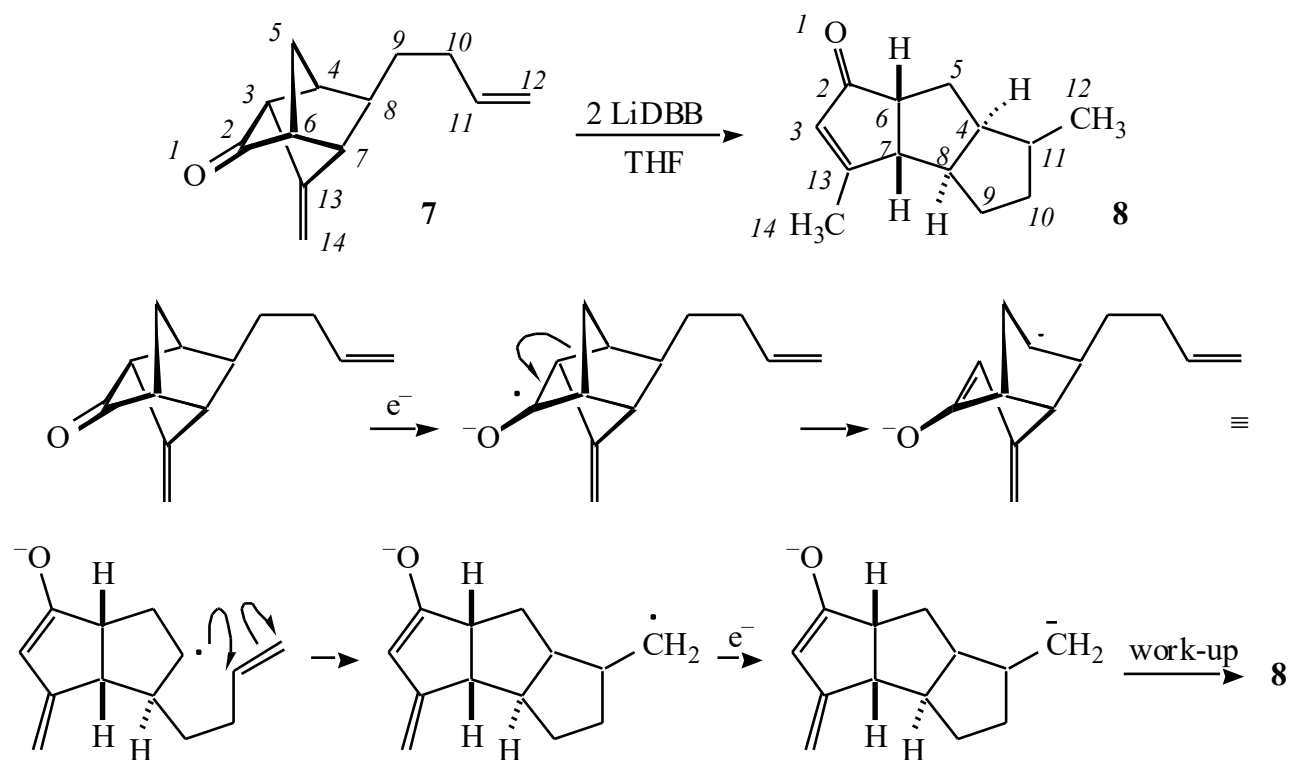


(b) LiAlH_4 is a source of very nucleophilic H^- . It must add to an electrophilic C. If you obey Grossman's Rule, you will see that C4 and C6 in the product have extra H's. Of these two only C6 is electrophilic, because when H^- adds to C6, a very stable (aromatic) cyclopentadienyl anion is obtained. This anion is protonated at C4 upon workup to give the alcohol. (Actually, the anion can be protonated on C3, C4, or C5, but all three isomers are in equilibrium with one another, and only the isomer protonated on C4 is able to undergo the subsequent Diels–Alder reaction.) When the alcohol is oxidized to the ketone, the $\text{C9}=\text{C10}$ π bond becomes electron-deficient and electronically suitable to undergo an intramolecular Diels–Alder reaction with the cyclopentadiene to give **6**.

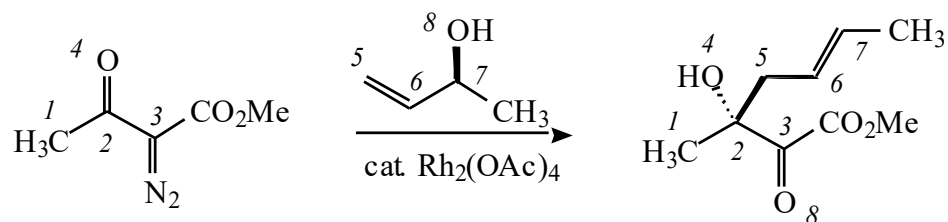


(c) Make: C4–C11. Break: C3–C4. The first step is electron transfer to form the ketyl. Fragmentation of the C3–C4 bond occurs to give a radical at C4, which can add to C11 to make the C4–C11 bond and

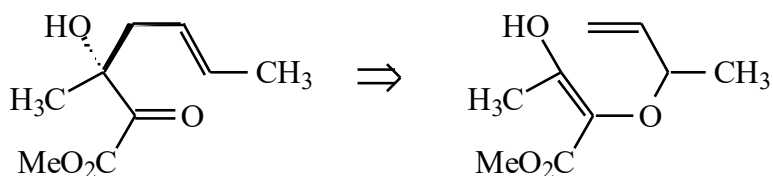
put the radical on C12. A second electron transfer gives a carbanion at C12. Upon workup it is protonated, as is C14, to give **8**.



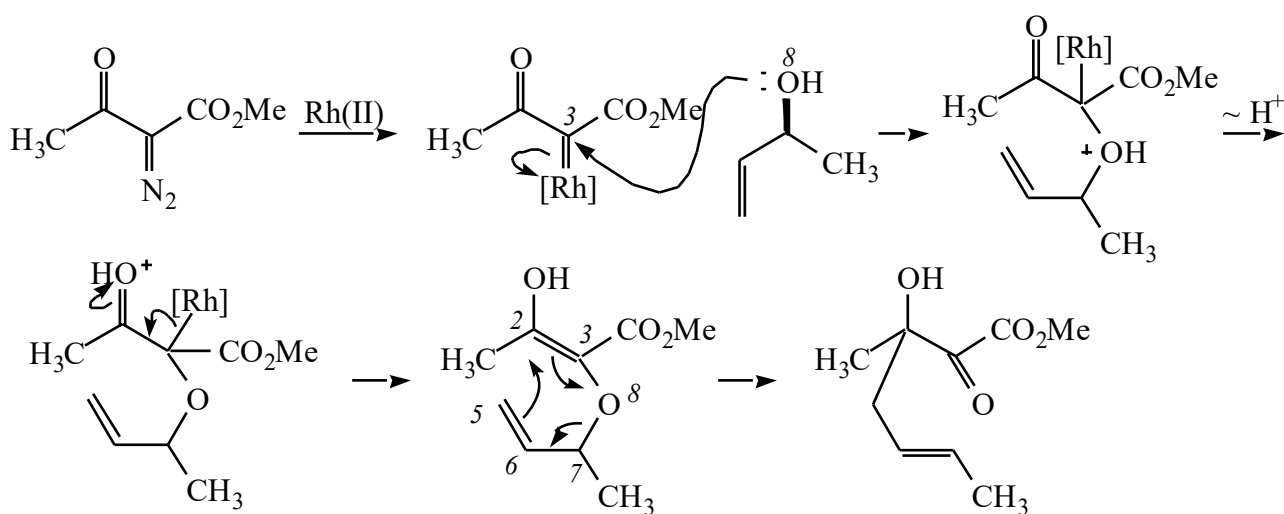
5. First step. Make: C3–O8, C2–C5. Break: C7–O8.



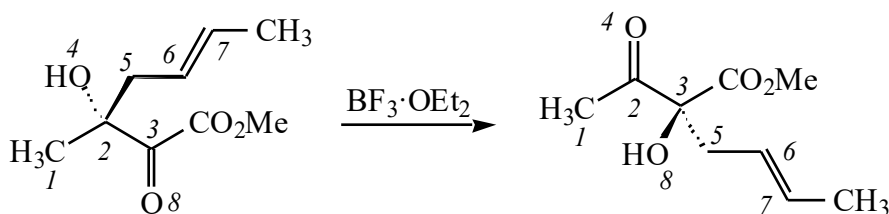
The product is a γ,δ -unsaturated carbonyl compound (a 1,5-diene), hinting that the last step is a Claisen rearrangement.

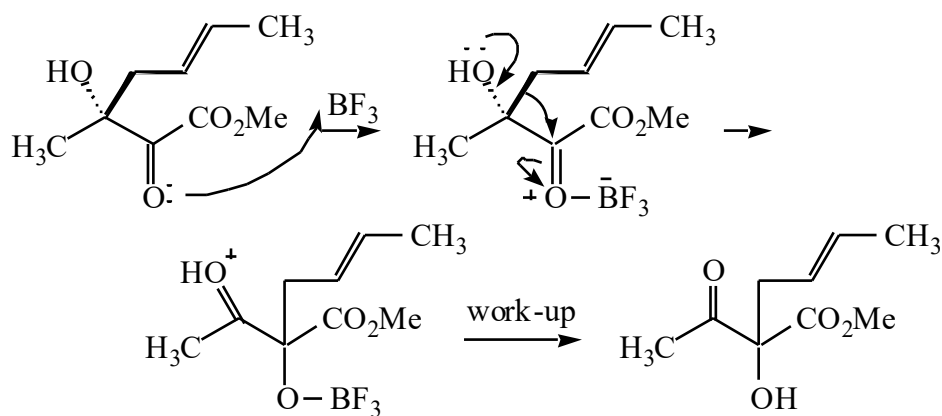


The diazo compound combined with the Rh(II) salt tells you that a carbenoid is involved. The carbenoid can be drawn in the Rh=C form or as its synthetic equivalent, a singlet carbene. In either case, C3 can undergo one of the typical reactions of carbenes, addition of a nucleophile, to form the C3–O8 bond. After proton transfer to O4 and loss of [Rh], a Claisen rearrangement can occur to give the product.

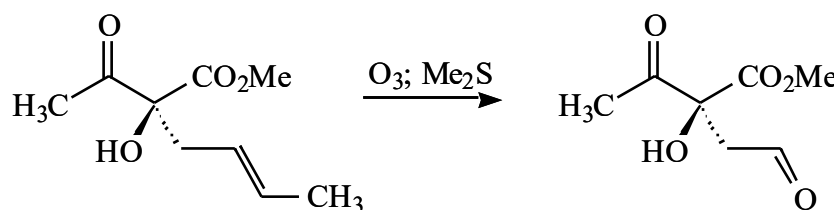


Second step. Make C3–C5. Break C2–C5. The reaction proceeds by a 1,2-shift.

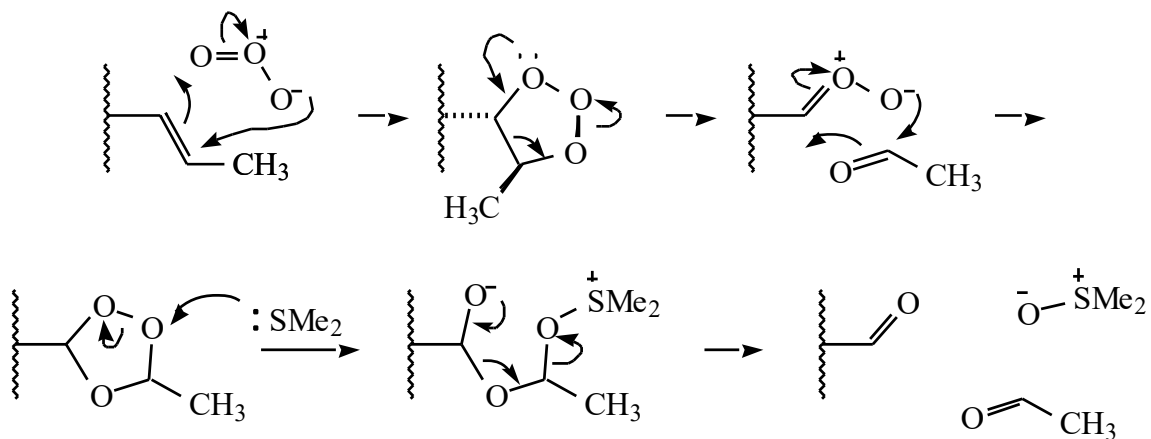




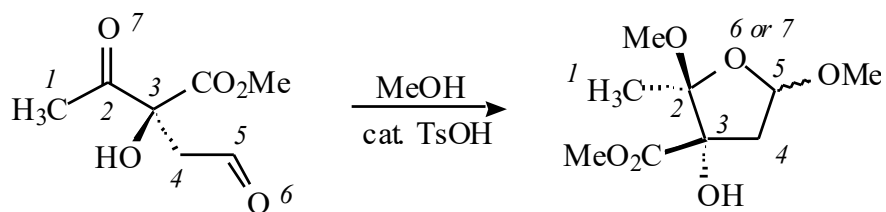
Third step. Standard ozonolysis with Me_2S workup.



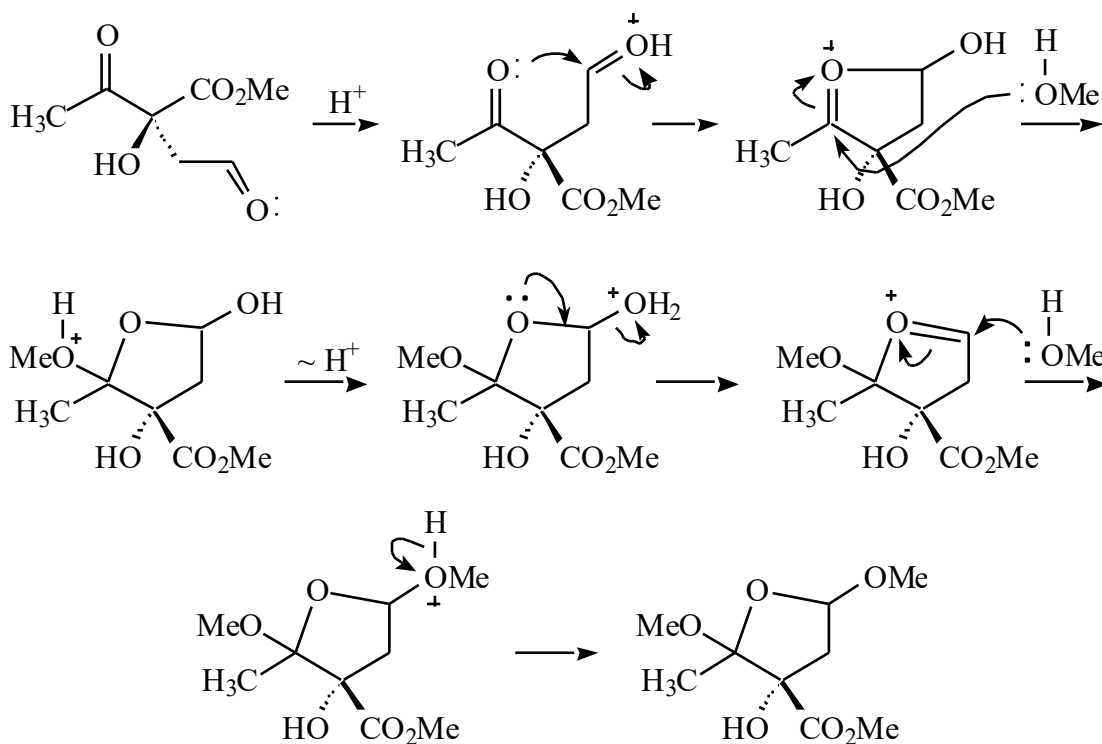
The Criegee mechanism should be drawn. The initially formed 1,2,3-trioxolane can be split up in two ways, one of which gives the desired aldehyde, but the mechanism can't stop there.



Fourth step. It is not clear whether the ring O is O6 or O7. If the ring O is O6, then make: C2-OMe, C2-O6, C5-OMe, and break: C2-O7. If the ring O is O7, then make: C2-OMe, C5-O7, C5-OMe, and break: C5-O6.

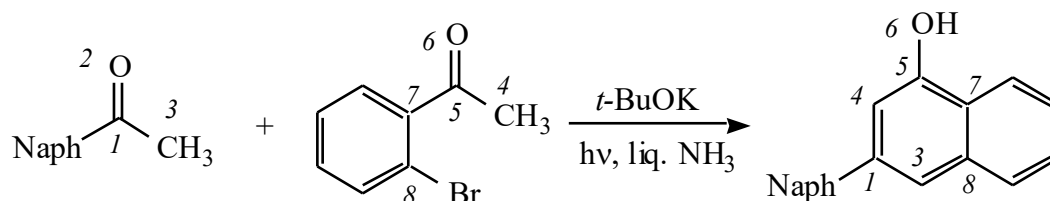


First step is protonation of one of the carbonyl O's. An intramolecular addition is likely to occur faster than an intermolecular one. Because a better carbocation can be formed at C2 than at C5, addition of O7 to O5 is more likely than addition of O6 to C2.

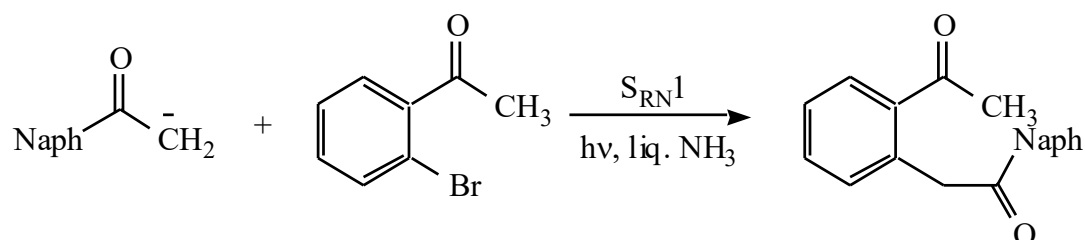


It should be stressed that this mechanism is not the only reasonable one for this reaction. Any reasonable mechanism should avoid an S_N2 substitution, however.

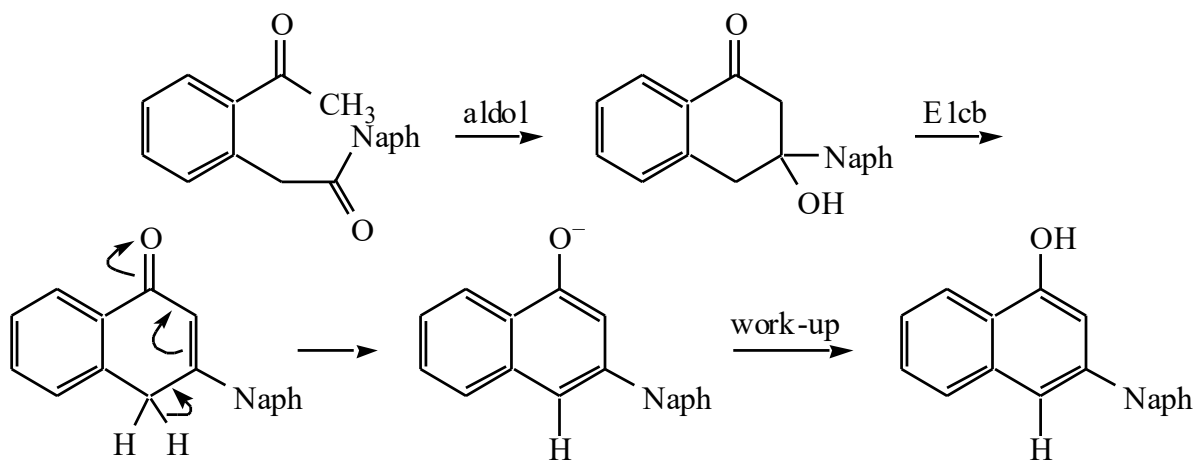
6. Make: C1–C4, C3–C8. Break: C1–O2, C8–Br. The light suggests a free-radical or pericyclic reaction is operative in at least part of the mechanism.



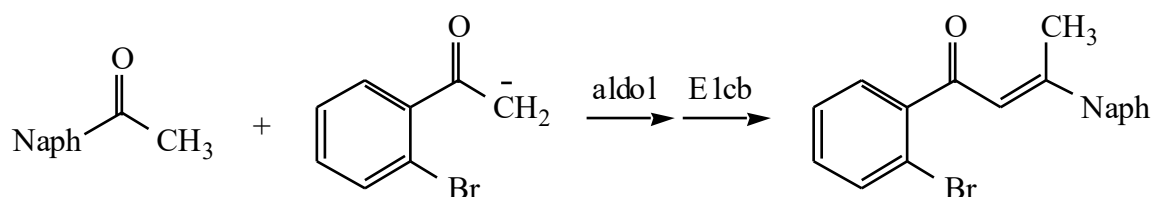
The base may deprotonate either C3 or C4. Deprotonation of C3 makes it nucleophilic. We need to form a new bond from C3 to C8 via substitution. The mechanism of this aromatic substitution reaction could be addition–elimination or $S_{RN}1$. The requirement of light strongly suggests $S_{RN}1$. See Chap. 2, section C.2, for the details of drawing an $S_{RN}1$ reaction mechanism.



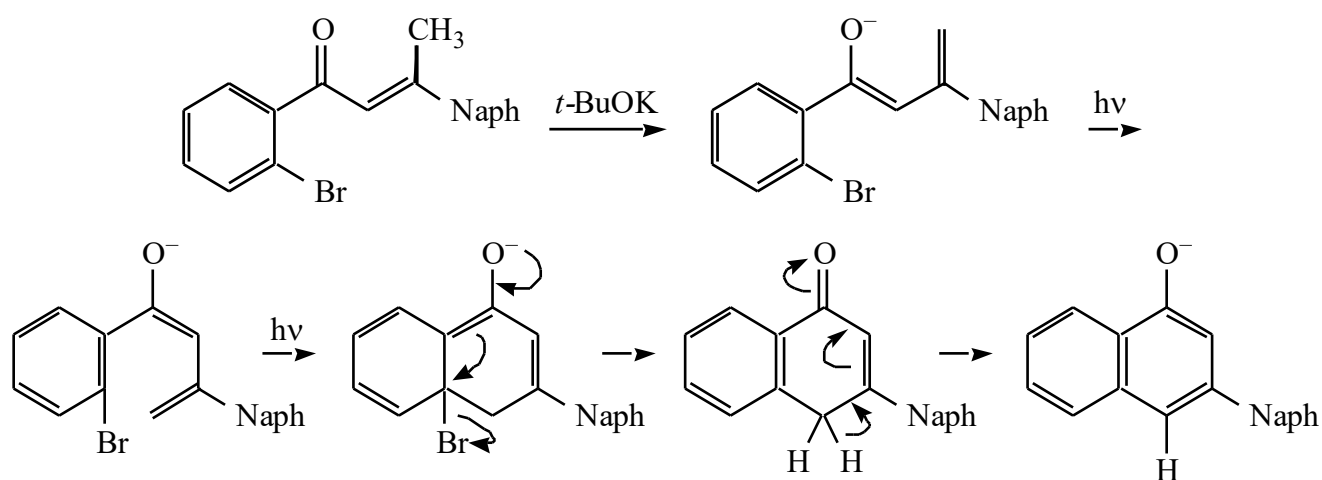
After the substitution is complete, all that is required is an aldol reaction, dehydration by E1cb, and deprotonation. Workup then gives the product.



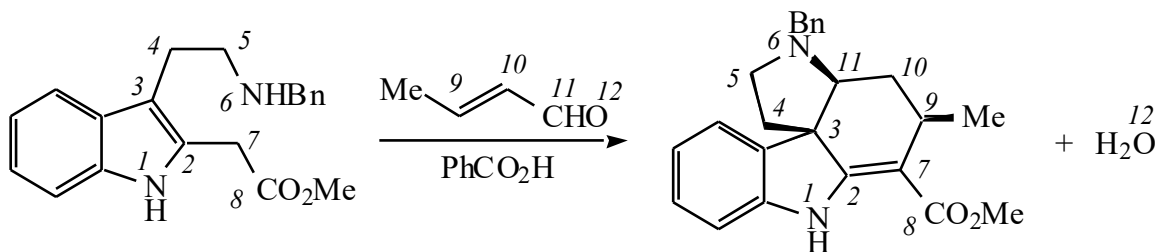
Alternatively, deprotonation of C4 makes it nucleophilic, and an aldol reaction and dehydration by E1cb gives an enone.



We still need to form C3–C8. Deprotonation of C3 gives a dienolate. The more stable, (*E*) isomer will form. Light causes this isomer to isomerize to the (*Z*) isomer. An electrocyclic ring closing, which may also require light because it destroys aromaticity, gives the C3–C8 bond. Expulsion of Br[−] and deprotonation gives the conjugate base of the product.

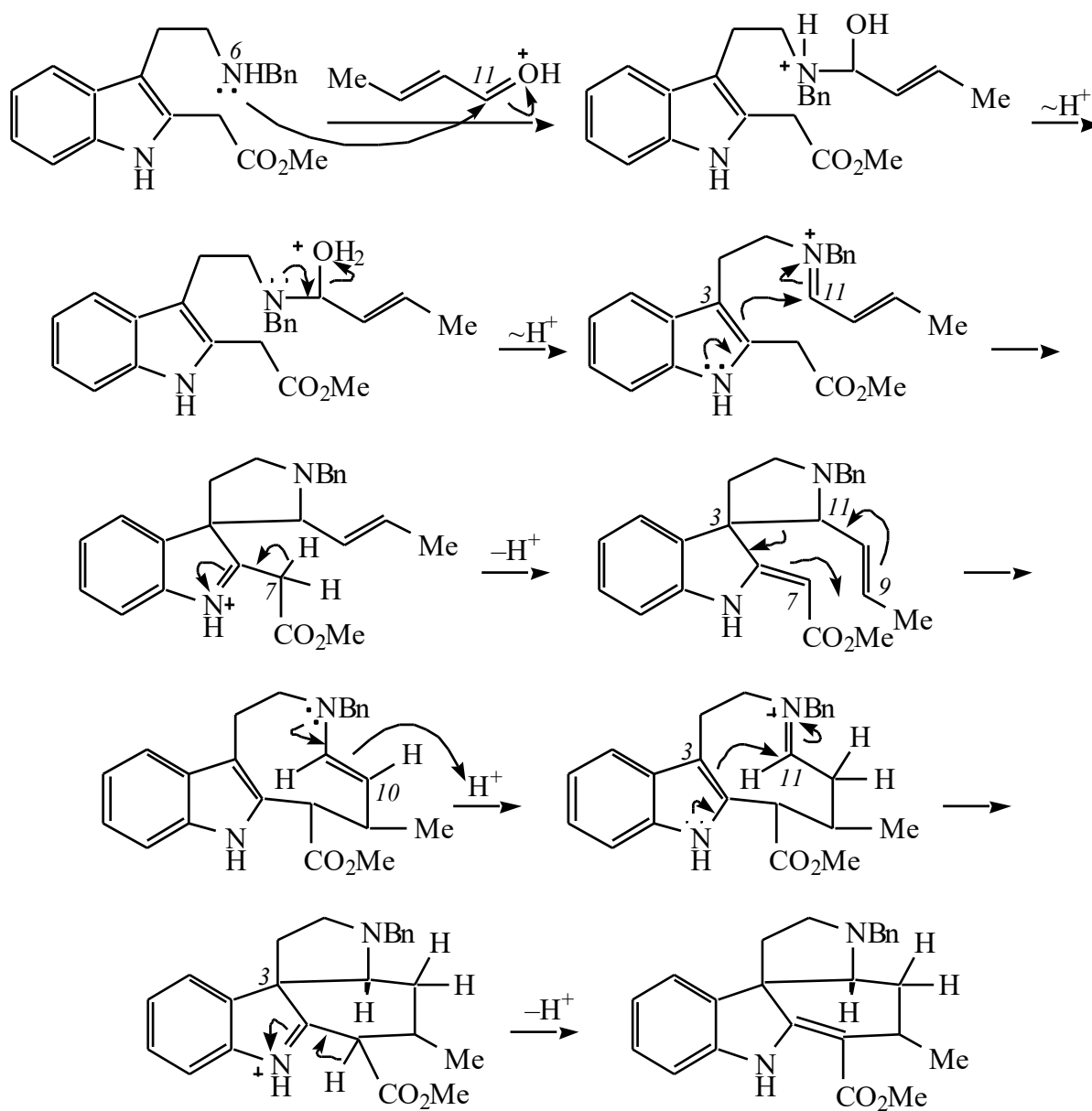


7. Make: C3–C11, N6–C11, C7–C9. Break: C11–O12.

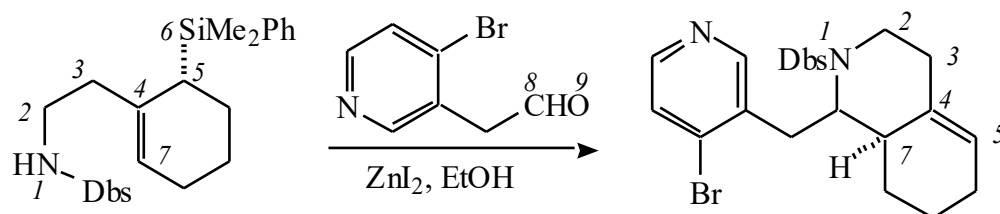


The combination of an amine and an aldehyde under weakly acidic conditions almost always gives an iminium ion very rapidly. Such a reaction forms the N6–C11 bond. Nucleophilic C3 can then attack this iminium ion to give a new iminium ion. We still need to make C7–C9. Deprotonation of C7 gives

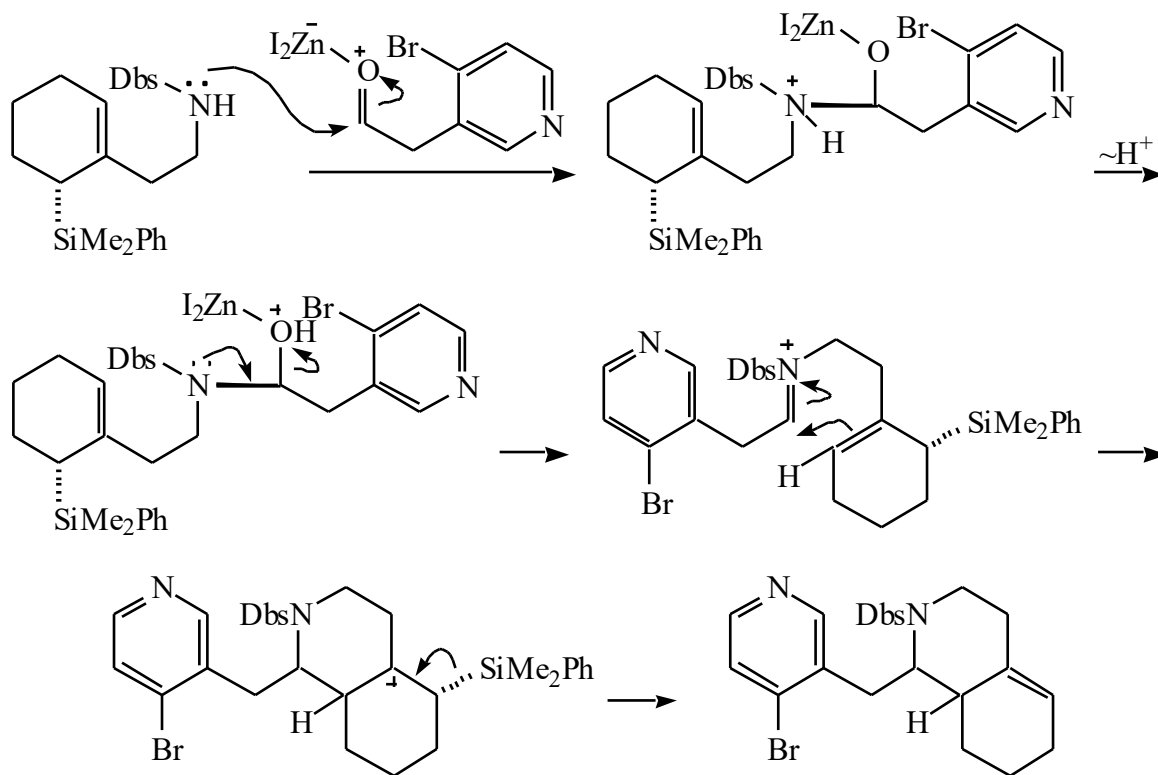
a neutral enamine and a 1,5-diene. Cope rearrangement of the diene gives the C7–C9 bond, but it breaks the C3–C11 bond that was just formed! However, C11 can be made electrophilic again by protonation of C10. Attack of nucleophilic C3 on C11 gives an iminium ion again, and deprotonation of C7 gives the product.



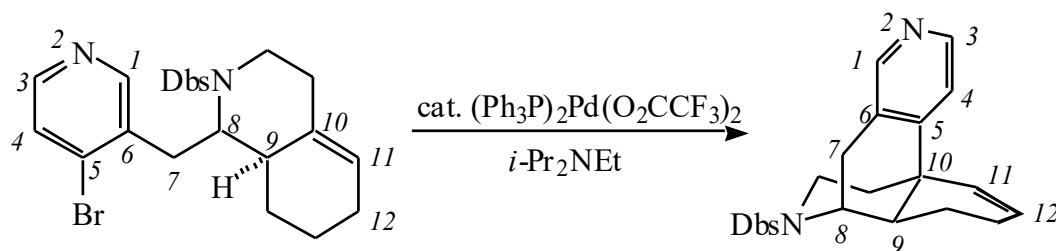
8. First reaction. Make: N1–C8, C7–C8. Break: C5–Si6, C8–O9.



The combination of an amine and an aldehyde under weakly acidic conditions almost always gives an iminium ion very rapidly. Such a reaction forms the N1–C8 bond. Nucleophilic C7 can then attack this iminium ion to give a carbocation. Fragmentation of the C5–Si6 bond gives the product.



Second step. Make: C5–C10. Break: C5–Br.



The catalytic Pd complex and the aryl bromide together suggest the first step is oxidative addition of

Pd(0) to the C5–Br bond. (The reduction of Pd(II) to Pd(0) can occur by coordination to the amine, β -hydride elimination to give a Pd(II)–H complex and an iminium ion, and deprotonation of Pd(II)–H to give Pd(0).) The C10–C11 π bond can then insert into the C5–Pd bond to give the C5–C10 bond. β -Hydride elimination then gives the C11–C12 π bond and a Pd(II)–H, which is deprotonated by the base to regenerate Pd(0). The overall reaction is a Heck reaction.

