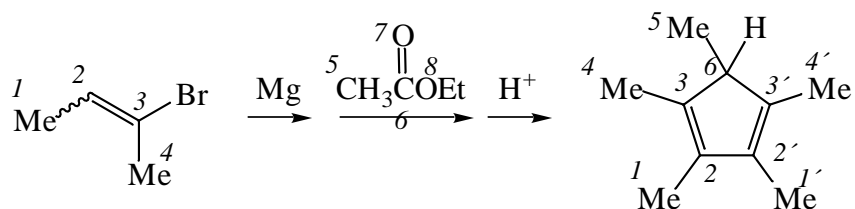
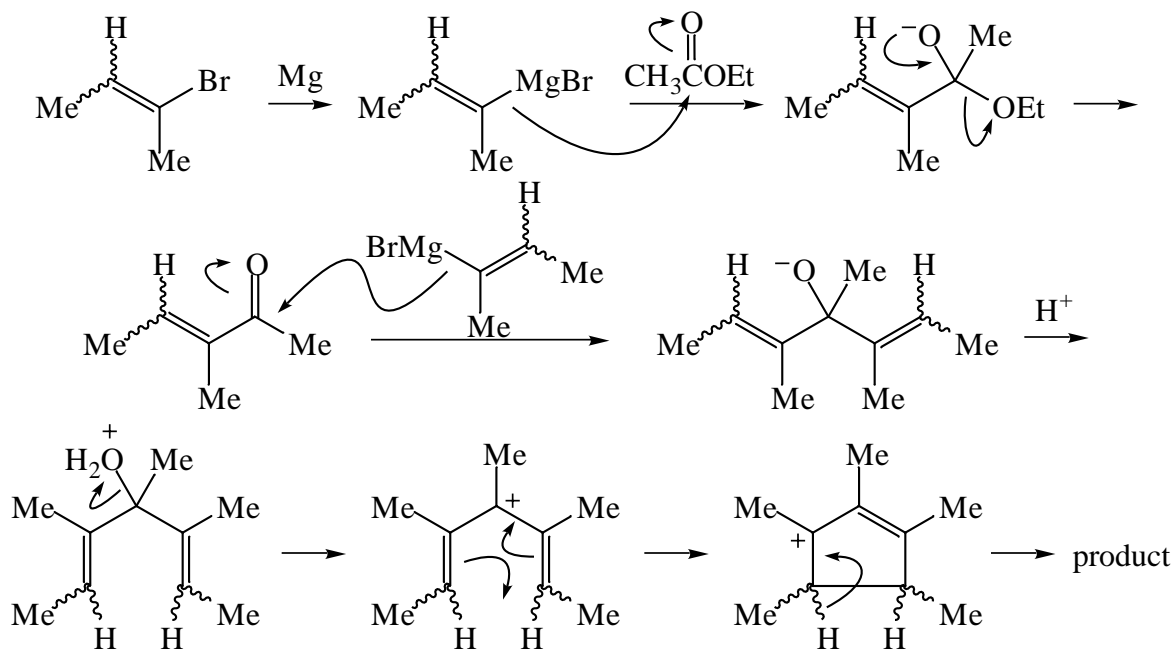


Answers To Chapter 4 In-Chapter Problems.

4.1. The numbering of the atoms is quite difficult in this problem. The number of Me groups in the product suggests that at least two equivalents of the bromide are incorporated into the product. But which ring atoms are C3 and which one is C6? And even if one of the ring carbons is arbitrarily chosen as C6, there is still the question of whether C3 or C2 becomes attached to C6. This problem is solved by noting that step 1 turns the bromide into a Grignard reagent, which is nucleophilic at C3, so it is likely to attack C6, and electrophilic atom. Make: C3–C6, C3'–C6, C2–C2'. Break: C6–O7, C6–O8, C3–Br, C3'–Br.

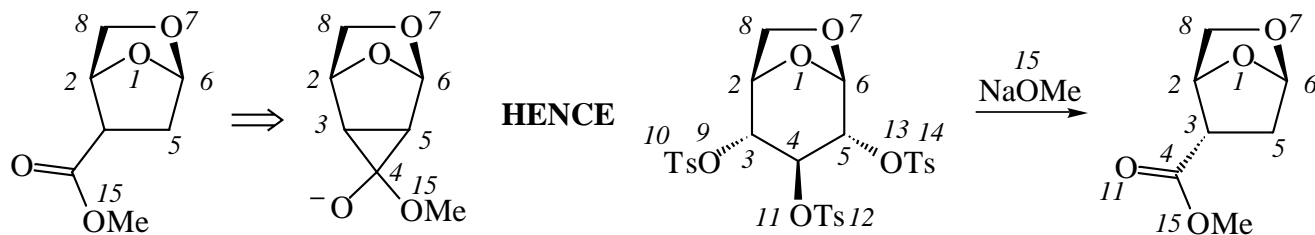


In the first step, the bromide is converted to a Grignard reagent. In the second step, two equivalents of the Grignard reagent react with the ester by addition–elimination–addition. (Remember, the ketone that is initially obtained from reaction of a Grignard reagent with an ester by addition–elimination is more electrophilic than the starting ester, so addition of a second Grignard reagent to the ketone to give an alcohol is faster than the original addition to give the ketone.) In the last step, addition of acid to the tertiary, doubly allylic alcohol gives a pentadienyl cation that undergoes electrocyclic ring closure. Loss of H^+ gives the observed product.



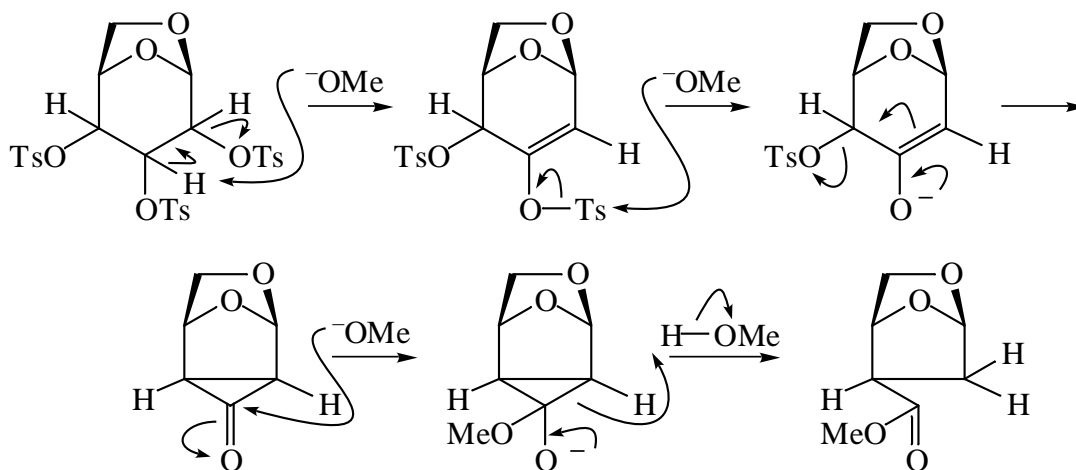
4.2. As usual, the key to this problem is numbering correctly. The main question is whether the ester C in the product is C3 or C4. Because a ring contraction from 6- to 5-membered is likely to proceed by a Favorskii rearrangement, where the last step is cleavage of a cyclopropanone, it makes sense to label the

ester C as C4. Make: C3–C5, C4–C15. Break: C3–O9, C4–C5, C5–O13, O11–Ts12.

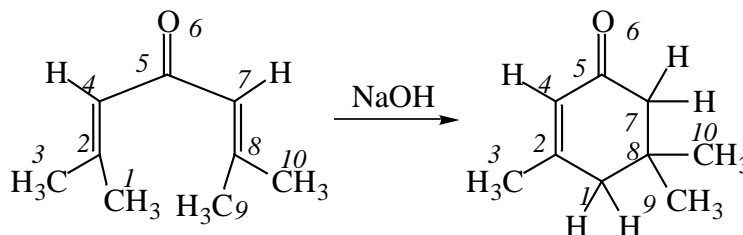


Hold on! If the O11–Ts12 bond is broken, and the electrons go to O (as seems reasonable), what happens to the Ts? Some nucleophile must form a bond to it. The only nucleophile in the mixture is MeO^- , so let's add Ts12–O15 to our make list.

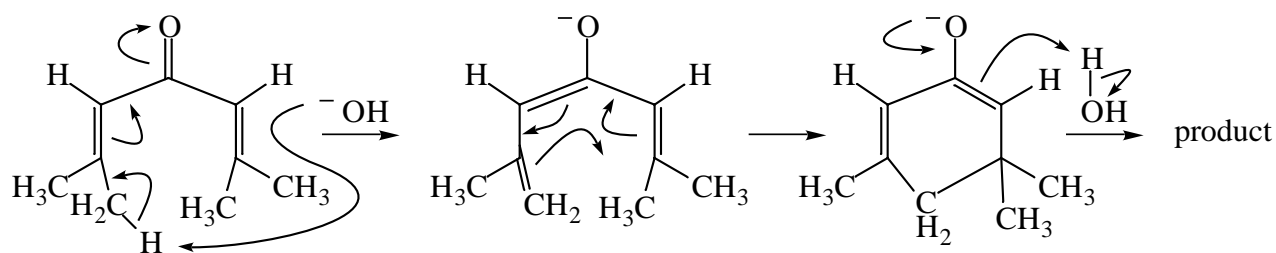
NaOMe is a good base, and with all these TsO groups, an E2 elimination reaction to break a C–OTs bond seems reasonable. Either the C3–O9 or the C5–O13 bond can be cleaved; we choose the C5–O13 bond here, but cleavage of the other bond works, too. The product is an enol tosylate. A second elimination reaction is not possible, but at this point we can form the Ts12–O15 bond and cleave the O11–Ts12 bond by having MeO^- attack Ts 12, displacing O11 to make an enolate. Electrocyclic ring closing with concurrent cleavage of the C3–O9 bond gives a cyclopropanone. Addition of O15 to C4 and then C4–C5 bond cleavage with concurrent protonation of C5 by solvent gives the product.



4.3. Make: C1–C8. Break: none.

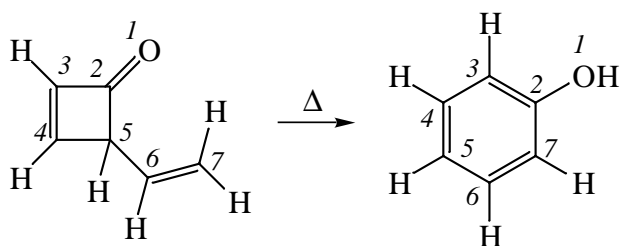


Deprotonation of C1 gives an enolate ion, which in this compound is actually a 1,3,5-hexatriene. As such it can undergo an electrocyclic ring closing. Protonation gives the product.

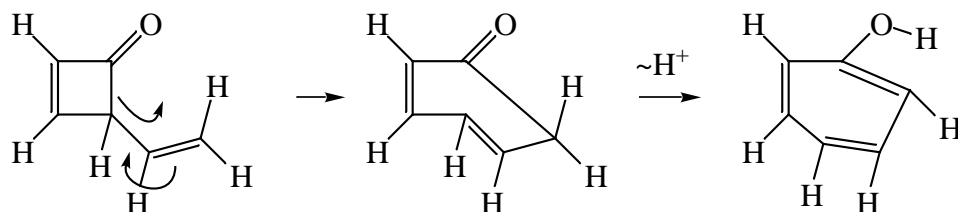


You may have been tempted to draw the C1–C8 bond-forming reaction as a conjugate addition. However, once C1 is deprotonated, the carbonyl group is no longer electrophilic, because it is busy stabilizing the enolate. It is much more proper to think of the bond-forming reaction as an electrocyclic ring closure. This problem illustrates why it is so important to consider *all* the resonance structures of any species.

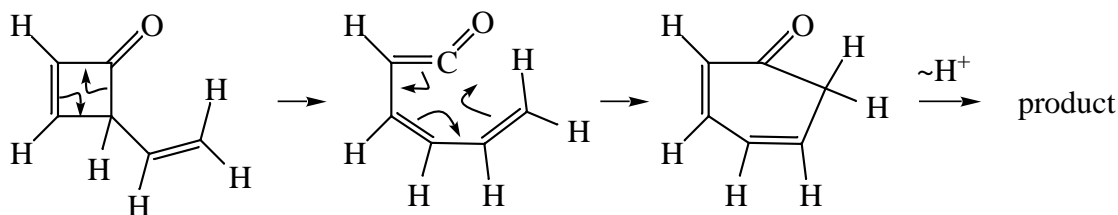
4.4. Make: C2–C7. Break: C2–C5.



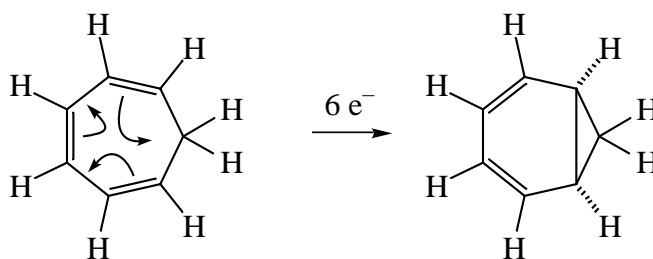
You may be very tempted to draw the following mechanism for the reaction:



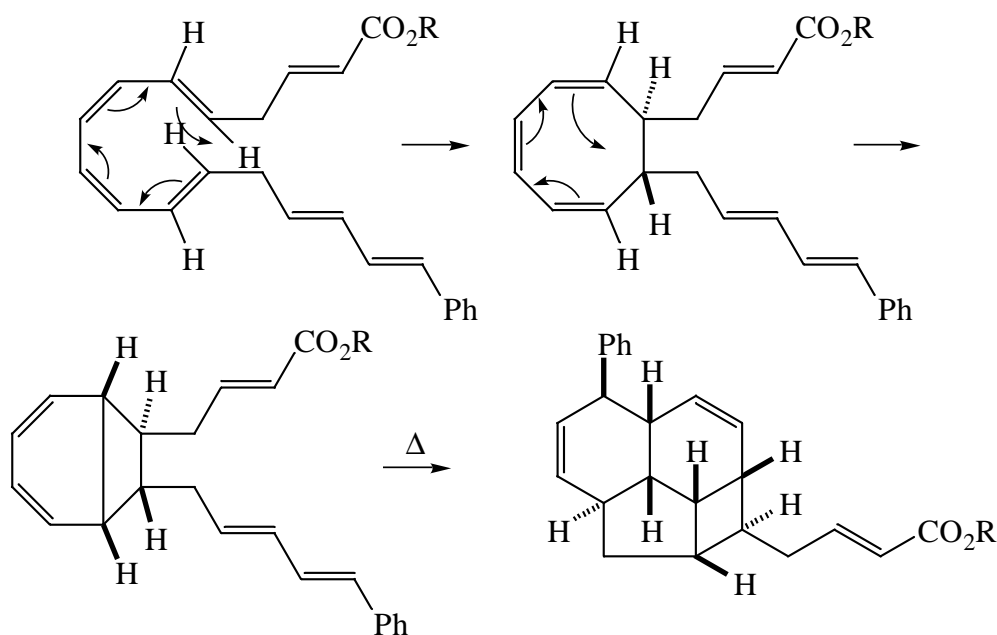
However, this mechanism is not correct. It is a [1,3]-sigmatropic rearrangement, and for reasons which are discussed in Section 4.4.2, [1,3]-sigmatropic rearrangements are very rare under thermal conditions. A much better mechanism can be written. The C2–C5 bond is part of a cyclobutene, and cyclobutenes open very readily under thermal conditions. After the electrocyclic ring opening, a 1,3,5-hexatriene is obtained, and these compounds readily undergo electrocyclic ring closure under thermal conditions. Tautomerization then affords the product.



4.5. The product has a cis ring fusion.

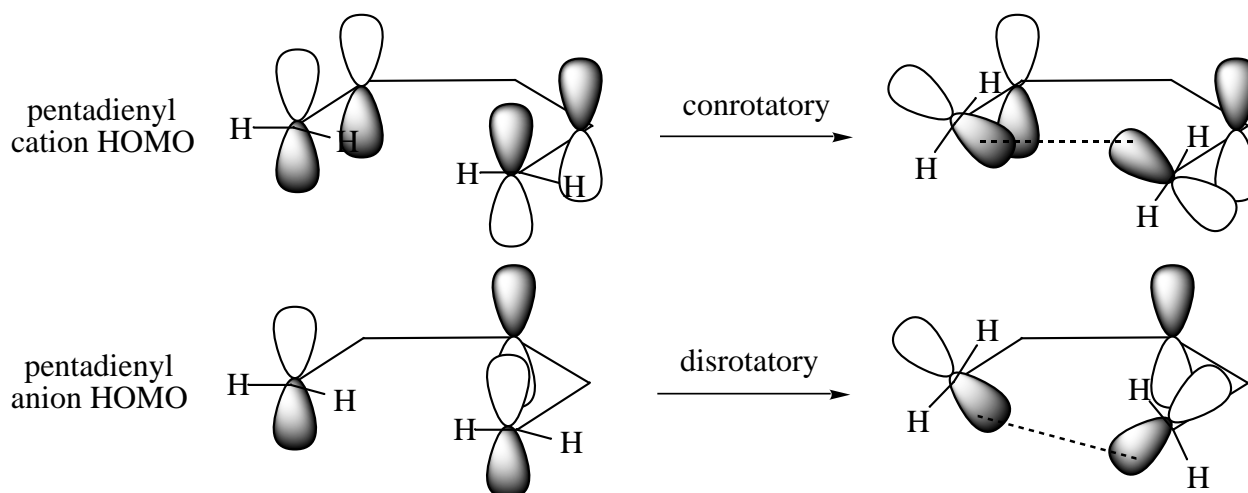


4.6. The first electrocyclic ring closure involves eight electrons, so it is conrotatory under thermal conditions, and the two hydrogen atoms at the terminus of the tetraene, which are both in, become trans. The second electrocyclic ring closure involves six electrons, so it is disrotatory under thermal conditions, and the two hydrogen atoms at the terminus of the triene, which are both out, become cis. This is the arrangement observed in the natural product.

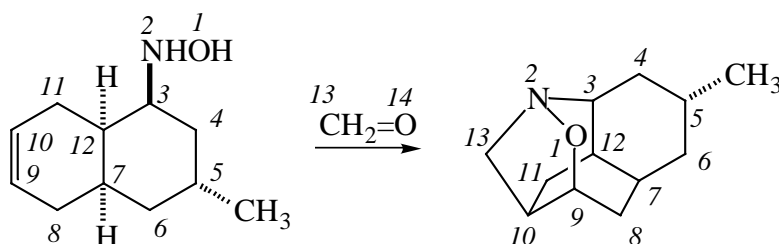


4.7. The HOMO of the pentadienyl cation is ψ_1 , which is antisymmetric, so a conrotatory ring closure occurs, consistent with the four electrons involved in this reaction. The HOMO of the pentadienyl anion is ψ_2 , which is symmetric, so a disrotatory ring closure occurs, consistent with the six electrons involved in this reaction.

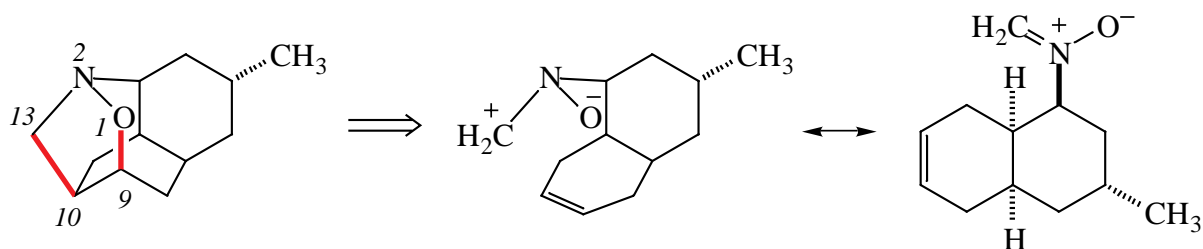
						pentadienyl cation	pentadienyl anion
<i>MOs of the pentadienyl π system</i>	ψ_4	+	-	+	-	+	—
	ψ_3	+	-	.	+	-	—
	ψ_2	+	.	-	.	+	—
	ψ_1	+	+	.	-	-	—
	ψ_0	+	+	+	+	+	—



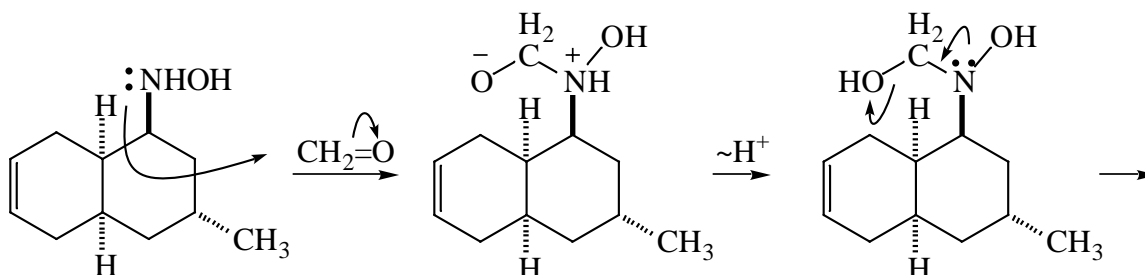
4.8. Make: O1–C9, N2–C13, C10–C13. Break: C13–O14.

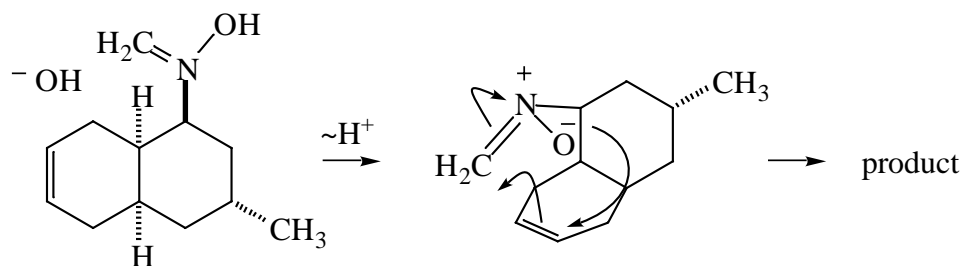


The new five-membered, heterocyclic ring clues you in to the fact that a 1,3-dipolar cycloaddition has occurred here to form bonds O1–C9 and C10–C13. Disconnect these bonds, putting a + charge on C13 and a – charge on O1, to see the immediate precursor to the product.

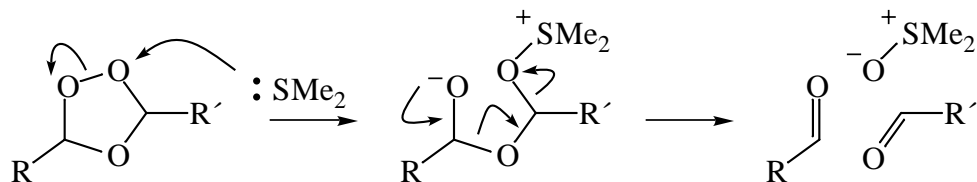


When this disconnection is written in the forward direction along with some curved arrows, it is the last step in the reaction. Now all you have to do is make N2–C13 and break C13–O14. This is easy to do: N2 attacks C13, proton transfer occurs, N2 expels O14, and deprotonation gives the nitrone.

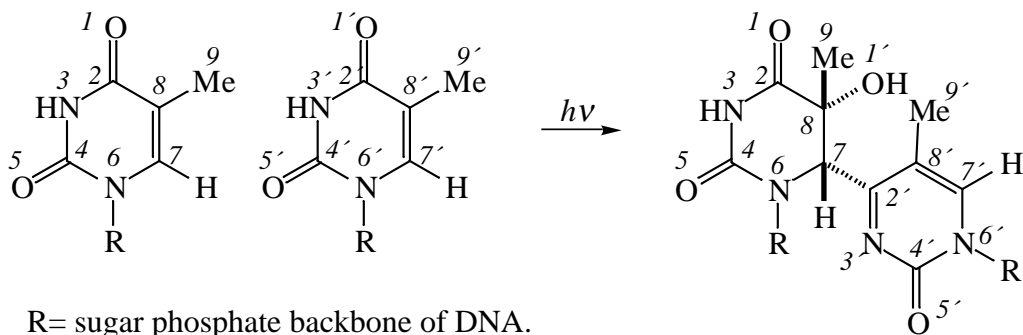




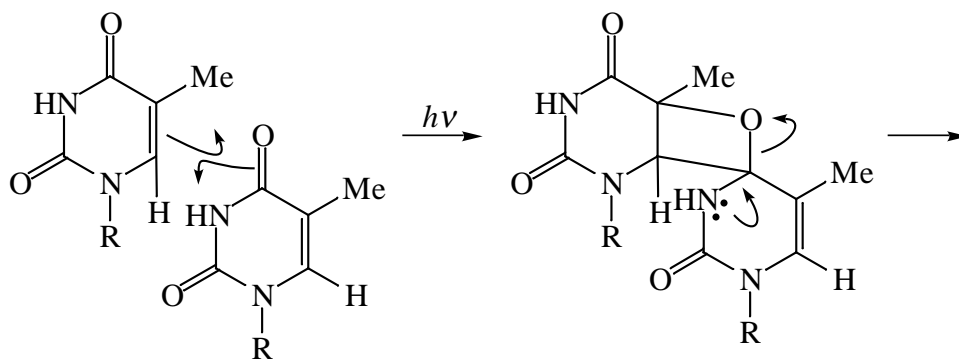
4.9. Me_2S attacks one of the O atoms involved in the O–O bond, displacing O^- . Hemiacetal collapse to the carbonyl compounds then occurs.

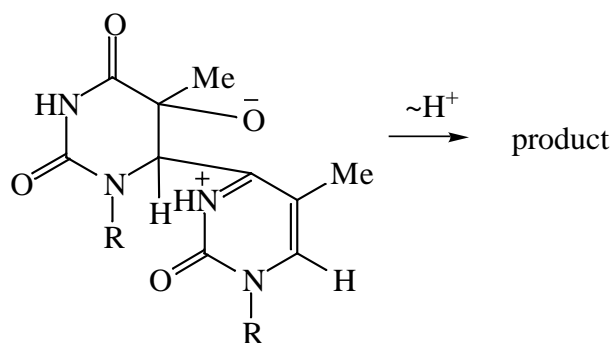


4.10. Make: C7–C2', C9–O1'. Break: C2'–O1'.

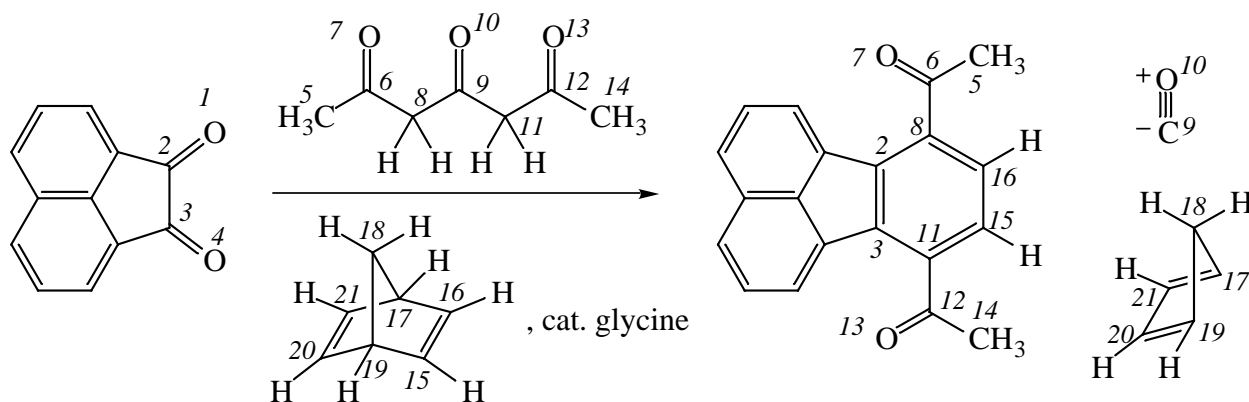


Making the C7–C2' and C9–O1' suggests a [2 + 2] photocycloaddition. Then the lone pair on N3' expels O1' from C2' to give the observed product (after proton transfer).



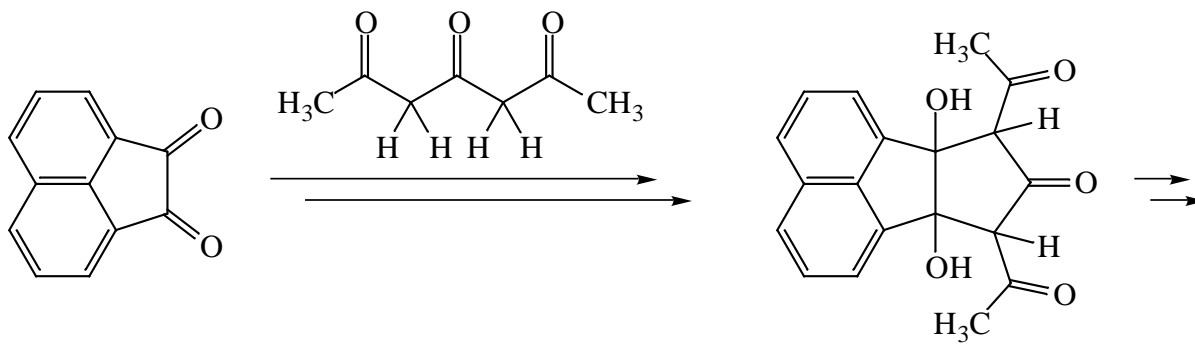


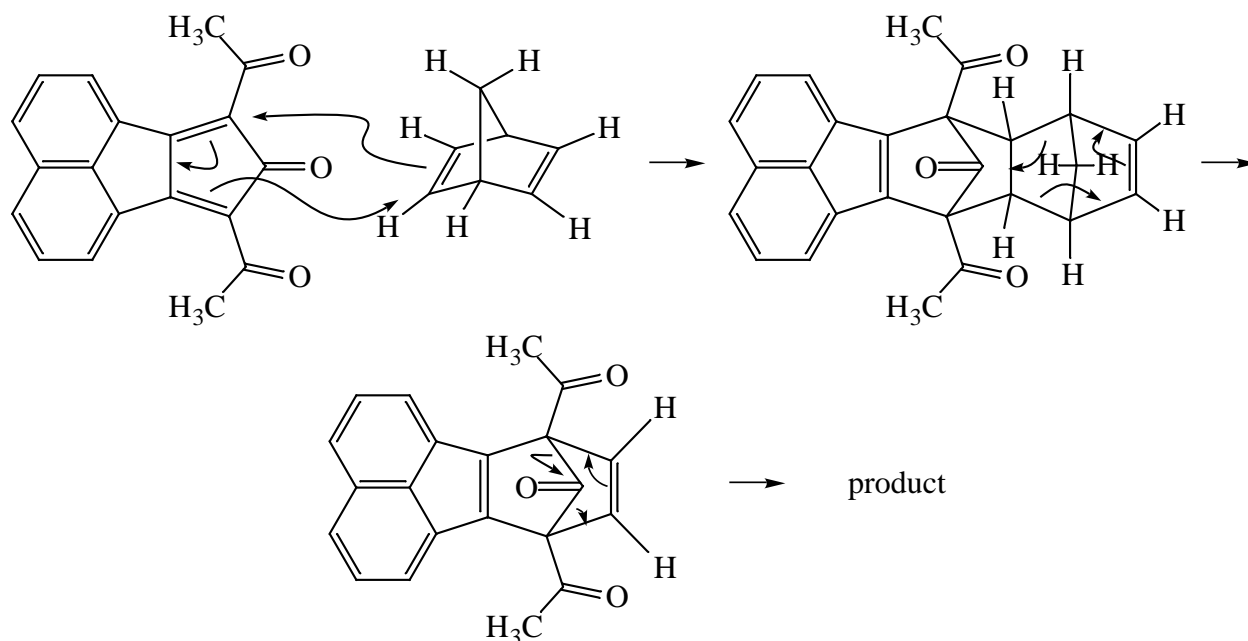
4.11. The numbering is not straightforward in this reaction, but if you draw in the H atoms you can see that the two CH groups in the new benzene ring in the product probably come from two CH groups in norbornadiene. Atoms unaccounted for in the written product include C9 and O10 (can be lost as CO), C17 to C21 (can be lost as cyclopentadiene), and O1 and O4 (can be lost as H₂O). Make: C2–C8, C3–C11, C8–C16, C11–C15. Break: O1–C2, C3–O4, C8–C9, C9–C11, C15–C19, C16–C17.



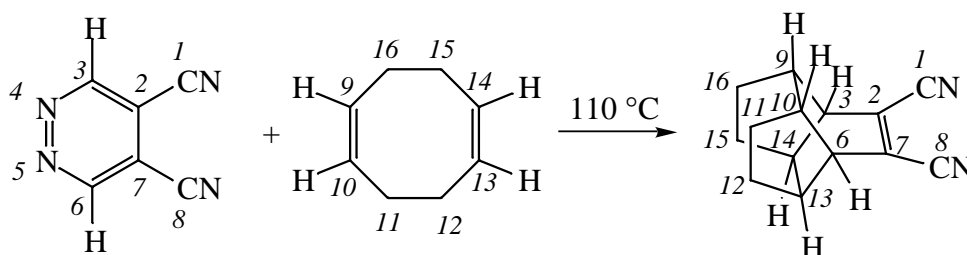
Glycine acts as an acid–base catalyst in this reaction. C8 and C11 are very acidic, and once deprotonated they are very nucleophilic, so they can attack C2 and C3 in an aldol reaction. Dehydration gives a key cyclopentadienone intermediate. (The mechanism of these steps is not written out below.)

Cyclopentadienones are antiaromatic, so they are very prone to undergo Diels–Alder reactions. Such a reaction occurs here with norbornadiene. A retro-Diels–Alder reaction followed by a [4 + 1] retrocycloaddition affords the product.

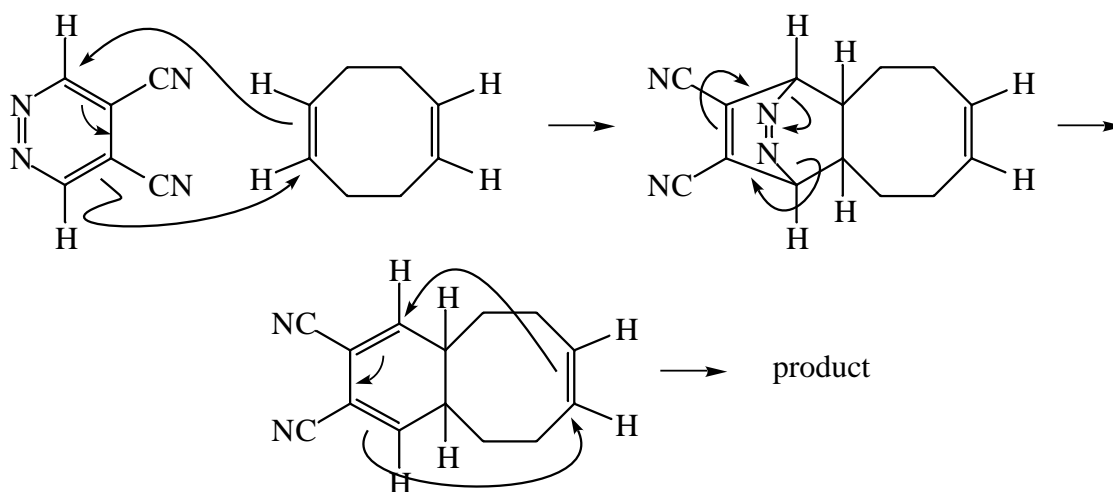




4.12. Make: C3–C9, C3–C14, C6–C10, C6–C13. Break: C3–N4, N5–C6.



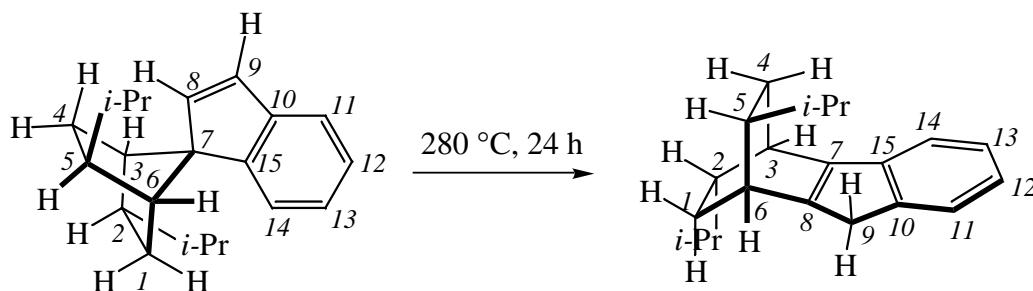
The C3–C9 and C6–C10 bonds can be made by a Diels–Alder reaction. Then loss of N_2 and cleavage of the C3–N4 and N5–C6 bonds can occur by a retro-Diels–Alder reaction. This step regenerates a diene, which can undergo another, intramolecular Diels–Alder reaction with the C13–C14 π bond to give the product.



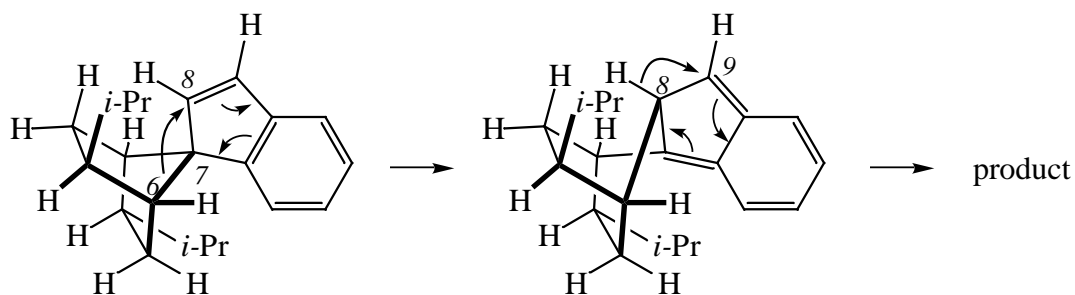
4.13. The [6+4] cycloaddition involves five pairs of electrons (an odd number), so it is thermally

allowed. The [4+3] cationic cycloaddition involves three pairs of electrons, so it is also thermally allowed.

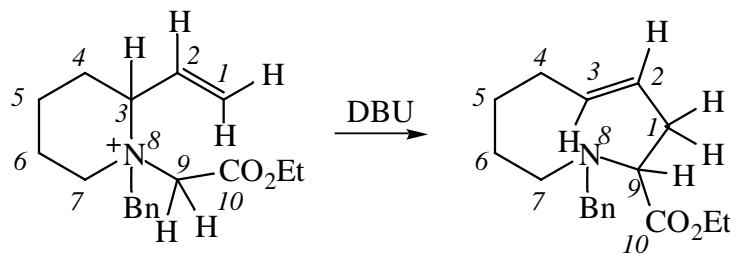
4.14. Make: C6–C8. Break: C6–C7.



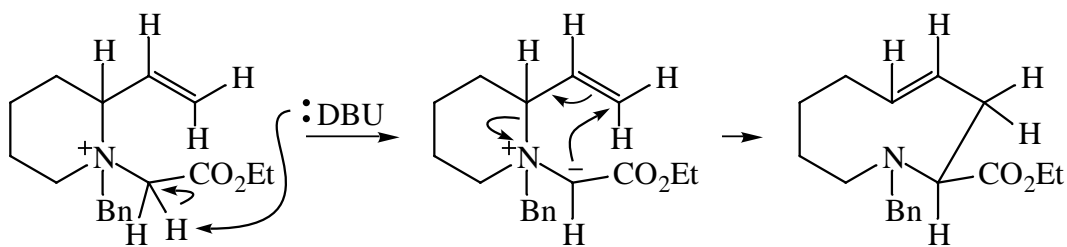
Making and breaking bonds to C6 suggests a [1,n] sigmatropic rearrangement, and a [1,5] sigmatropic rearrangement, one of the most common types, is possible here. Once the rearrangement is drawn, however, the mechanism is not complete, even though all bonds on the make & break list have been crossed off. C8 still has one extra H and C9 has one too few. Both these problems can be taken care of by another [1,5] sigmatropic rearrangement. This step, by the way, reestablishes the aromatic ring.



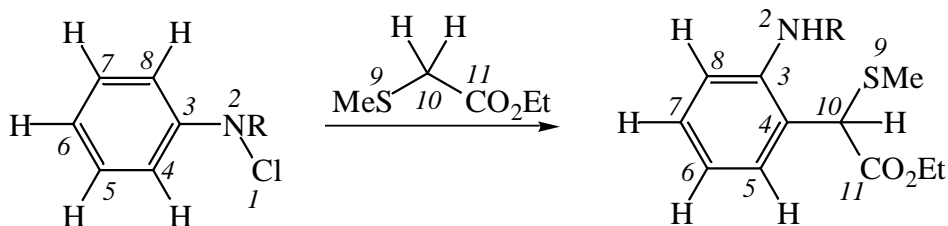
4.15. Make: C1–C9. Break: C3–N8.



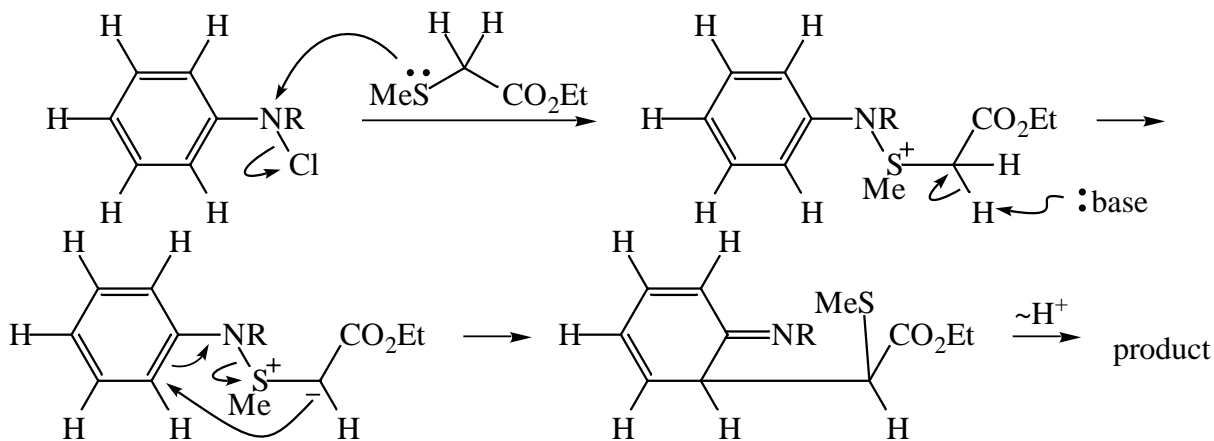
Deprotonation of C9 by DBU gives an ylide (has positive and negative charges on adjacent atoms that cannot quench each other with a π bond), a compound which is particularly prone to undergo [2,3] sigmatropic rearrangements when an allyl group is attached to the cationic center, as is the case here. Esters are not normally acidic enough to be deprotonated by DBU, but in this ester the N^+ stabilizes the enolate by an inductive effect.



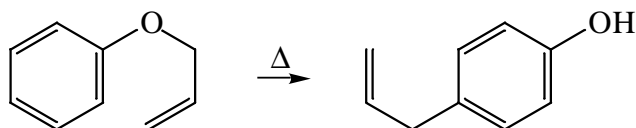
4.16. Make: C4–C10. Break: C11–N2.



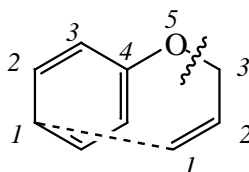
The most unusual bond in this system is the N–Cl bond. The nucleophilic substitution step must involve cleavage of this bond. No base is present, but S is an excellent nucleophile, even in its neutral form, so the first step probably entails formation of an S9–N2 bond. Now we have to make the C4–C10 bond and make the S9–N2 bond. Deprotonation of C4 gives an ylide, which as discussed in problem 4.15 is likely to undergo a [2,3] sigmatropic rearrangement. Tautomerization to rearomatize then gives the product.



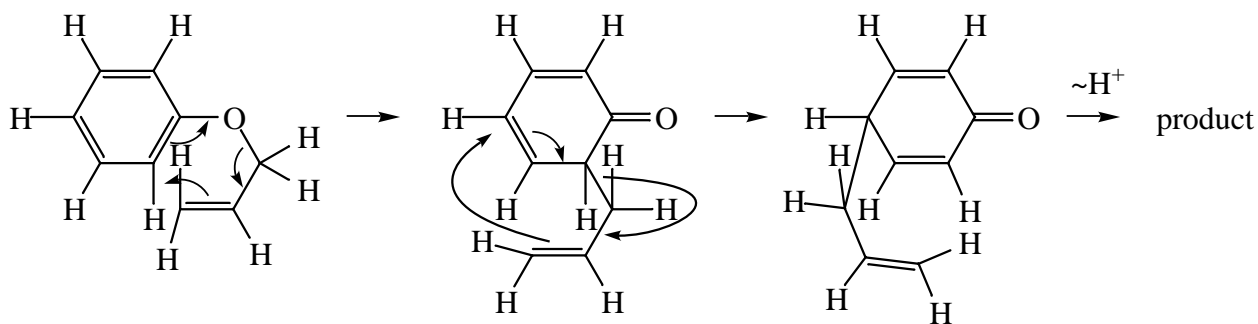
4.17. The reaction in question is:



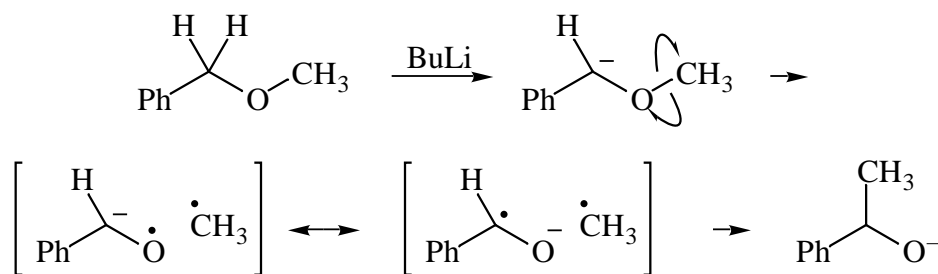
To name the reaction, draw a dashed line where the new bond is made, draw a squiggly line across the bond that is broken, and count the number of atoms from the termini of the dashed bond to the termini of the squiggly bond.



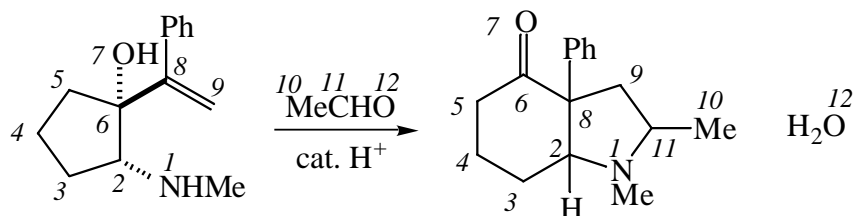
This reaction would be a [3,5] sigmatropic rearrangement, an eight-electron reaction, and hence would require that one component be antarafacial. Not likely! A more reasonable mechanism begins with the same [3,3] sigmatropic rearrangement that gives 2-allylphenol. However, instead of tautomerization to give the aromatic product, a second [3,3] sigmatropic rearrangement occurs. Then tautomerization gives the product.



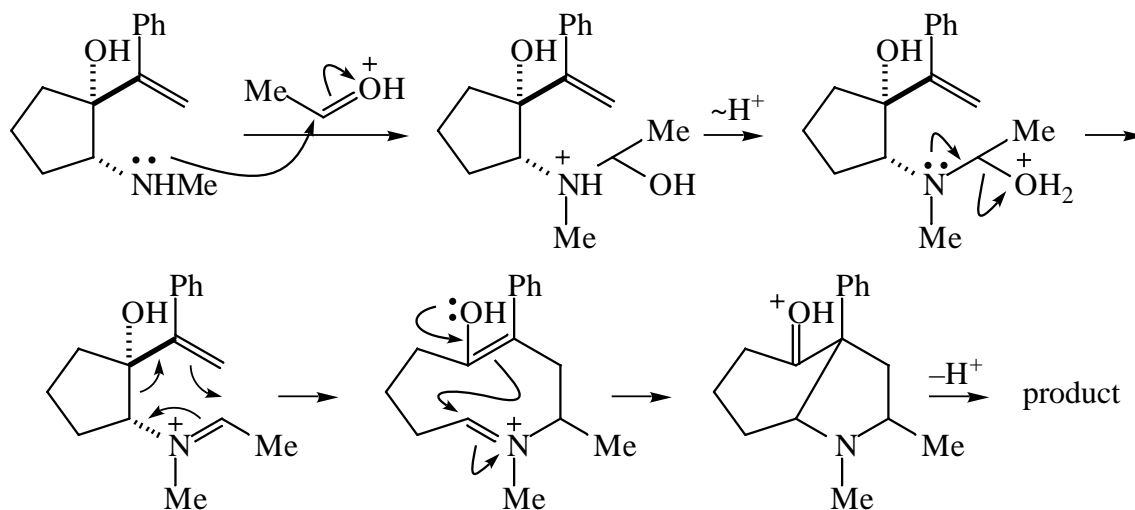
4.18. Both the Stevens rearrangement and the nonallylic Wittig rearrangement begin with deprotonation of the C atom next to the heteroatom followed by an anionic [1,2] sigmatropic rearrangement. Both involve four electrons, an even number of electron pairs, and hence if either is concerted then one of the two components of the reaction must be antarafacial. This condition is extremely difficult to fulfill, and hence it is much more likely that both reactions are nonconcerted. Both the Stevens rearrangement and the nonallylic Wittig rearrangement are thought to proceed by homolysis of a C–S or C–O bond and recombination of the C radical with the neighboring C atom.



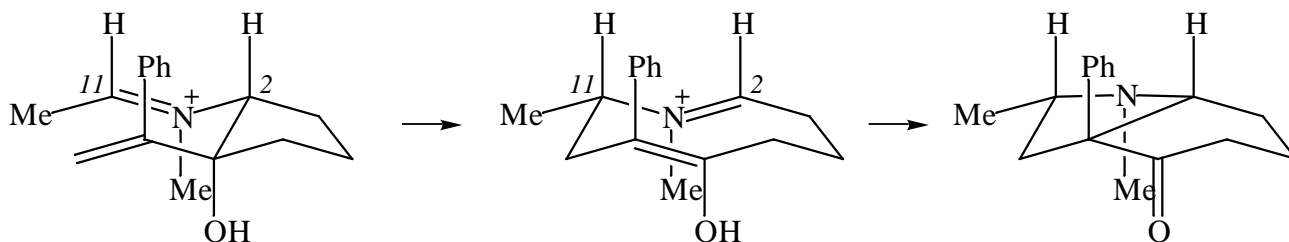
4.19. Make: N1–C11, C2–C8. Break: C2–C6, C11–O12.



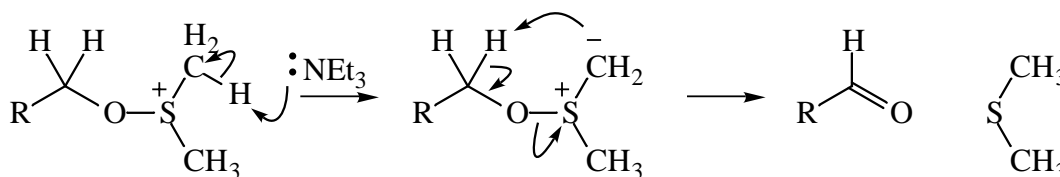
The N1–C11 bond is easily made first. Cleavage of the C11–O12 bond gives an iminium ion that is also a 1,5-(hetero)diene. The Cope rearrangement occurs to give a new iminium ion and an enol. Attack of the enol on the iminium ion (the Mannich reaction) affords the product.



Now the stereochemistry. Assume the thermodynamically more stable iminium ion forms (Me groups cis). The Cope rearrangement occurs from a chair conformation. This puts the Ph, H2, and H11 all pointing up both before and after the rearrangement. Assuming the Mannich reaction occurs without a change in conformation (a reasonable assumption, considering the proximity of the nucleophilic and electrophilic centers), the Ph, H2, and H11 should all be cis in the product.



4.20. Deprotonation of one of the Me groups adjacent to S gives an ylide which can undergo a retro-hetero-ene reaction to give the observed products.



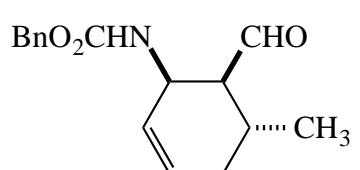
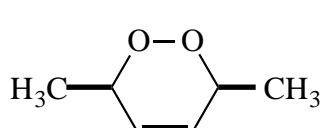
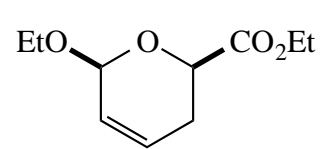
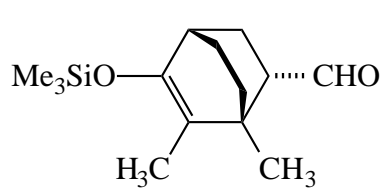
If $(\text{CD}_3)_2\text{SO}$ (deuterated DMSO) is used for the Swern reaction, the E2 mechanism predicts that the sulfide product should be $(\text{CD}_3)_2\text{S}$; the retro-hetero-ene mechanism predicts that it should be $(\text{CD}_3)\text{S}(\text{CHD}_2)$. Guess which product is actually found?

Answers To Chapter 4 End-of-Chapter Problems.

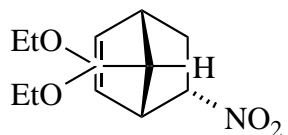
1.

- (a) An eight-electron [4+4] cycloaddition. It proceeds photochemically.
- (b) A four-electron conrotatory electrocyclic ring opening. It proceeds thermally.
- (c) A six-electron ene reaction. (Note the transposition of the double bond.) It proceeds thermally.
- (d) A six-electron [1,5] sigmatropic rearrangement. It proceeds thermally.
- (e) A ten-electron [8+2] cycloaddition. It proceeds thermally.
- (f) A six-electron [2,3] sigmatropic rearrangement. It proceeds thermally.
- (g) A six-electron disrotatory electrocyclic ring opening. It proceeds thermally.
- (h) A four-electron disrotatory electrocyclic ring closing. It proceeds photochemically.
- (i) A six-electron disrotatory electrocyclic ring closing. It proceeds thermally.
- (j) A six-electron [3+2] (dipolar) cycloaddition. It proceeds thermally.
- (k) A four-electron [2+2] cycloaddition. It proceeds photochemically.
- (l) A six-electron conrotatory electrocyclic ring opening. It proceeds photochemically.

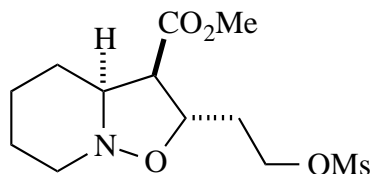
2.

<p>(a) Regio: RNH and CHO are 1,2. Stereo: CHO and CH₃ remain <i>trans</i>; NHR is <i>out</i>, CHO is <i>endo</i>, so they are <i>cis</i> in product.</p> 	<p>(b) The two CH₃ groups are both <i>out</i> groups, so they are <i>cis</i> in product.</p> 
<p>(c) Regio: C4 of diene is nucleophilic, so it makes a bond to electrophilic C of dienophile. Stereo: EtO is <i>out</i>, CO₂Et group is <i>endo</i>, so they are <i>cis</i> in product.</p> 	<p>(d) Regio: CHO and OSiMe₃ are 1,4. Stereo: the CH₂CH₂ bridge is <i>in</i> at both ends of the diene, CHO is <i>endo</i>, so they are <i>trans</i> in product.</p> 

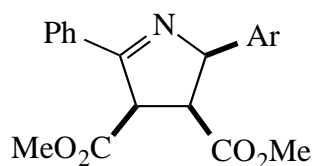
(e) Dienophile adds to less hindered face of diene. C(sp³) of five-membered ring is *in*, NO₂ is *endo*, so they are *trans* in product.



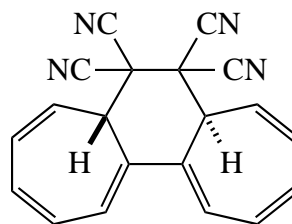
(f) Regio: Nucleophilic O adds to electrophilic β C of unsaturated ester. Stereo: alkyl and CO₂Me groups remain *trans*; H is *in*, CO₂Me is *endo*, so they are *trans* in product.



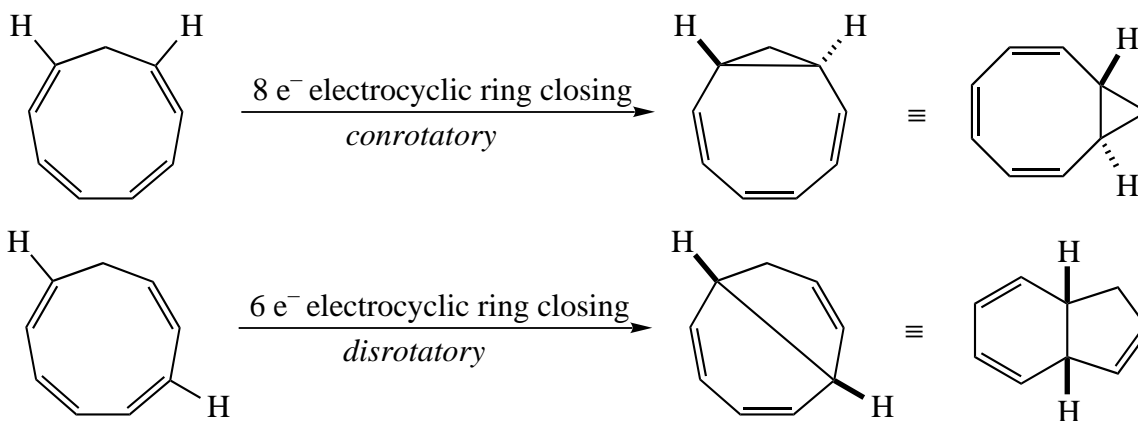
(g) Stereo: CO₂Me groups remain *trans*. Ar group is probably *out* for steric reasons, CO₂Me is *endo*, so the two are *cis* in the product.

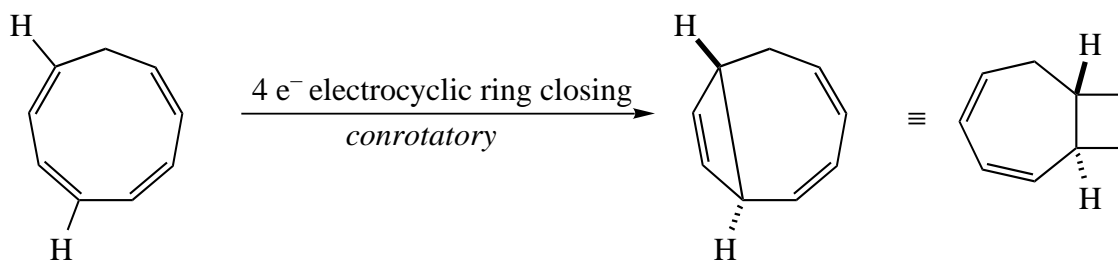


(h) The [14+2] cycloaddition must be antarafacial with respect to one component. The two *in* groups of the 14-atom component become *trans* in the product.



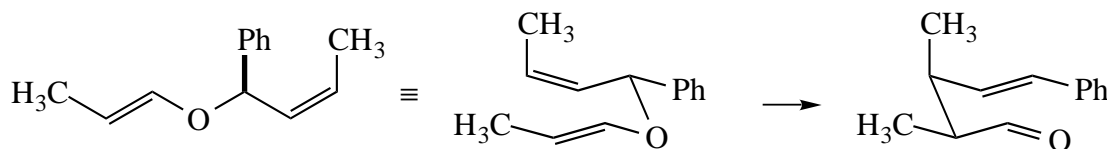
3. 1,3,5,7-Cyclononatetraene can theoretically undergo three different electrocyclic ring closures.



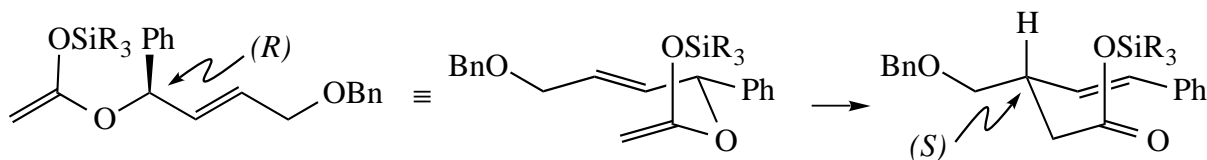


When small rings are fused to other rings, the *cis* ring fusion is almost always much more stable than the *trans* ring fusion. The opposite is true only for saturated 6-6 or larger ring systems. (Make models to confirm this.) The order of stability of the three possible products shown above is: *cis*-6-5 > *trans*-7-4 > *trans*-8-3.

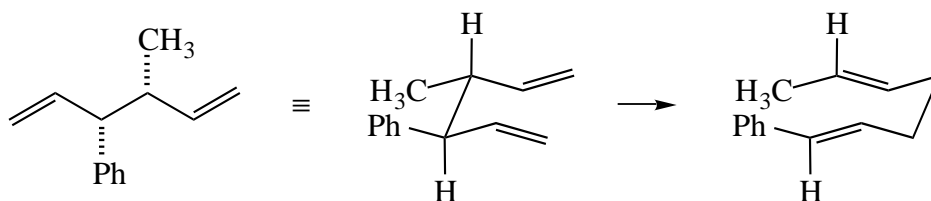
4. (a) Chair TS, with the Me on the C(sp³) equatorial.



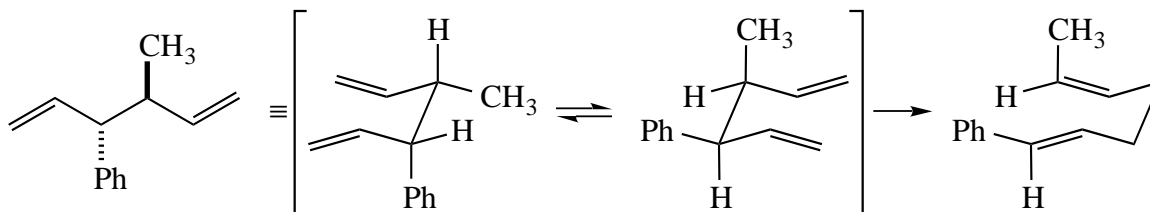
(b) Chair TS, with the Ph equatorial.



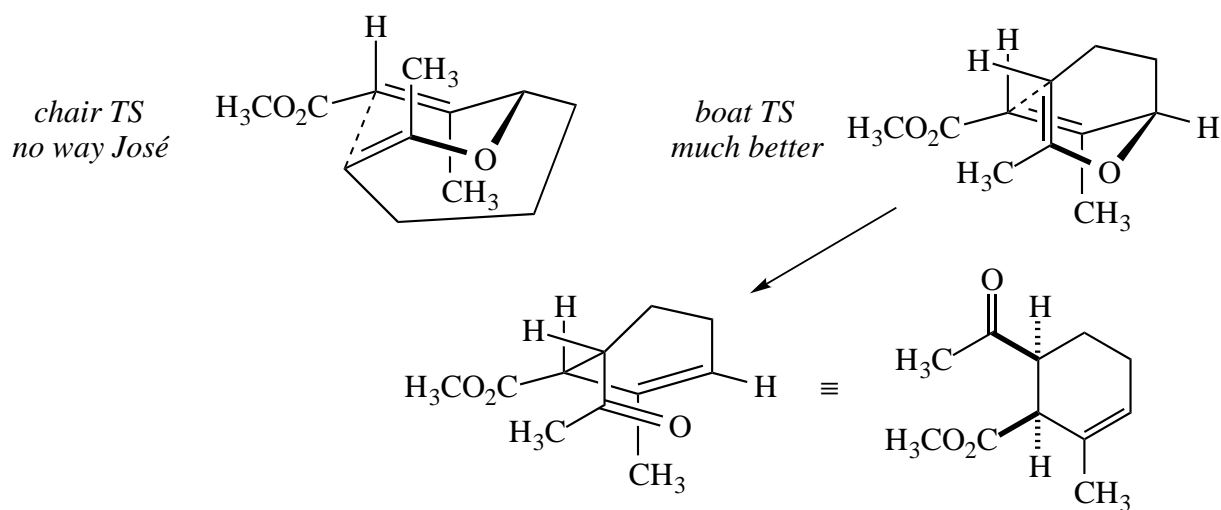
(c) Chair TS, with both substituents equatorial.



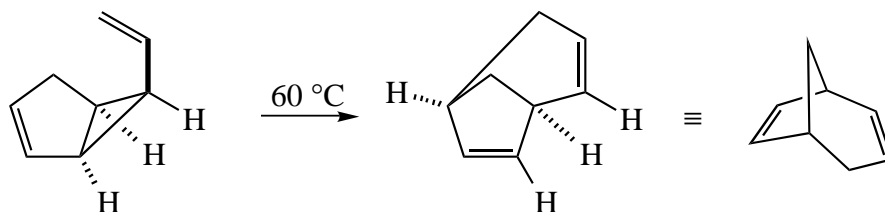
(d) Two different chairs are possible, but one (Ph equatorial) is lower in energy than the other.



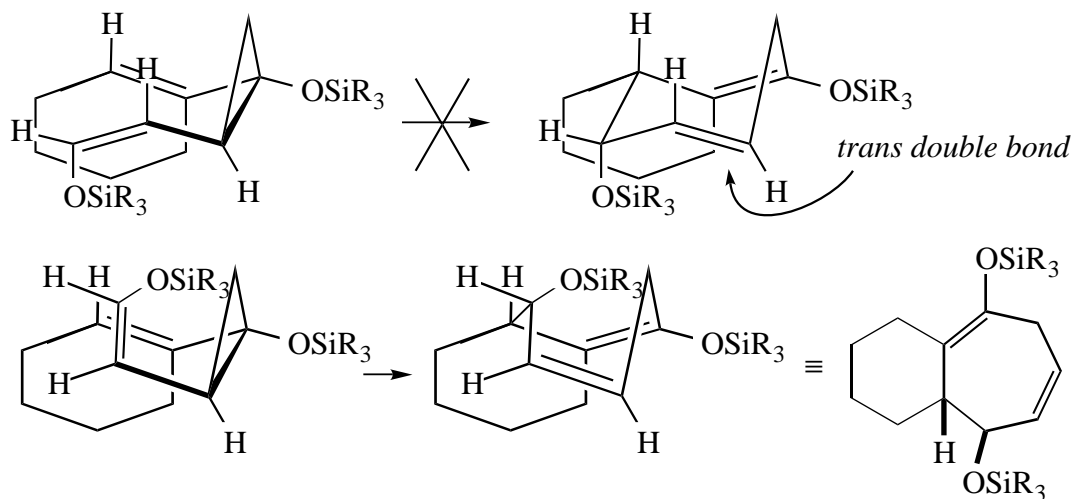
(e) A chair TS is not possible, so it goes through a boat TS.



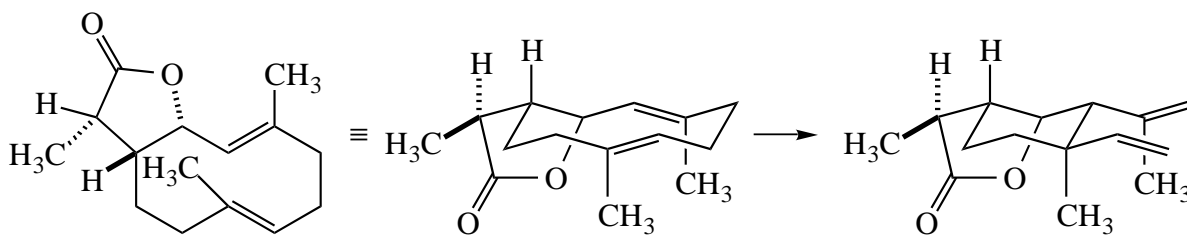
(f) Again, a boat TS is necessary.



(g) A chair TS would produce a trans double bond in the seven-membered ring, so the boat TS is operative, and the H and OSiR₃ groups on the two stereogenic atoms are *cis* to one another.



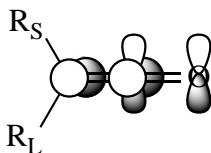
(h) The chair TS is enforced in this macrocyclic compound.



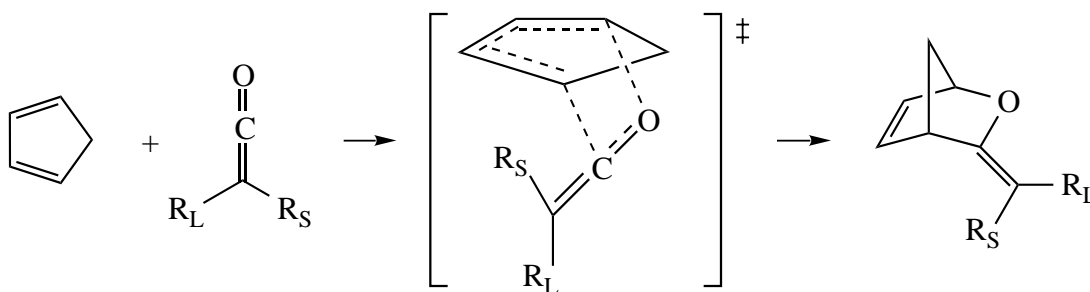
5. (a) First step: hetero-Diels–Alder reaction (six-electron, [4+2] cycloaddition). Second step: Claisen rearrangement (six-electron, [3,3] sigmatropic rearrangement).

(b) The diene is electron-rich, so it requires an electron-poor dienophile for a normal electron demand Diels–Alder reaction. The C=C bond of ketenes is pretty electron-rich, due to overlap with the lone pairs on O: $\text{H}_2\text{C}=\text{C}=\ddot{\text{O}} \leftrightarrow \text{H}_2\text{C}^--\text{C}=\ddot{\text{O}}^+$. Only the C=O bond of the ketene is of sufficiently low energy to react with the diene at a reasonable rate.

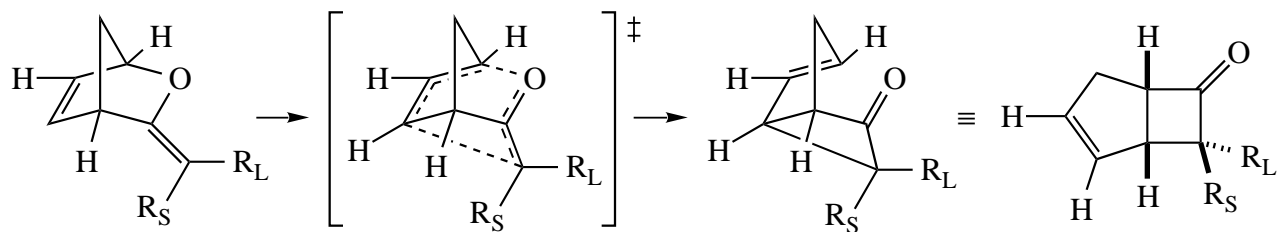
(c) First, it is important to remember that in ketenes, the p orbitals of the C=O bond are coplanar with the substituents on the terminal C.



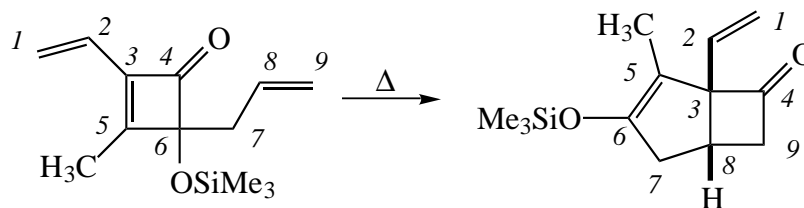
Because of the ketene's geometry, in the TS of the hetero-Diels–Alder reaction, either R_S or R_L must point directly at the diene. The lower energy approach towards R_S is chosen, and the product in which R_S points back toward the former diene portion of the compound is obtained.



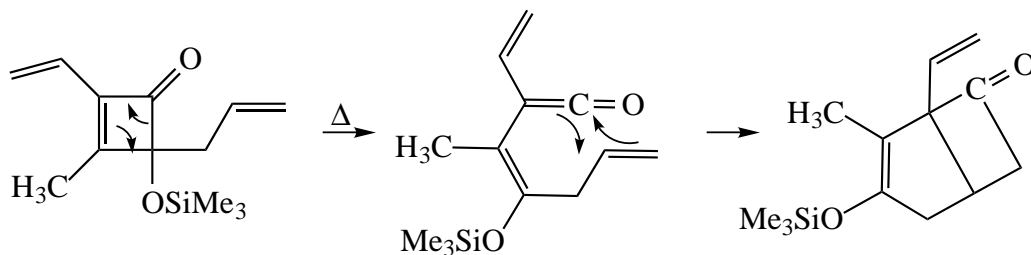
Second step: The new σ bond forms between the bottom face of the double bond on the left and the bottom face of the double bond on the right, giving the observed, less thermodynamically stable product.



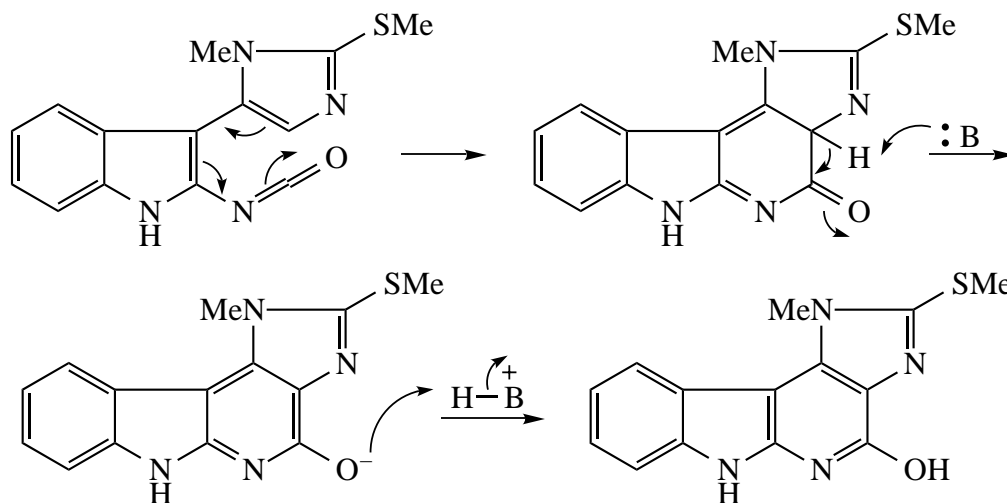
6. (a) Number the C's. C1, C2, C5 and C6 are clear in both starting material and product. The rest follows.



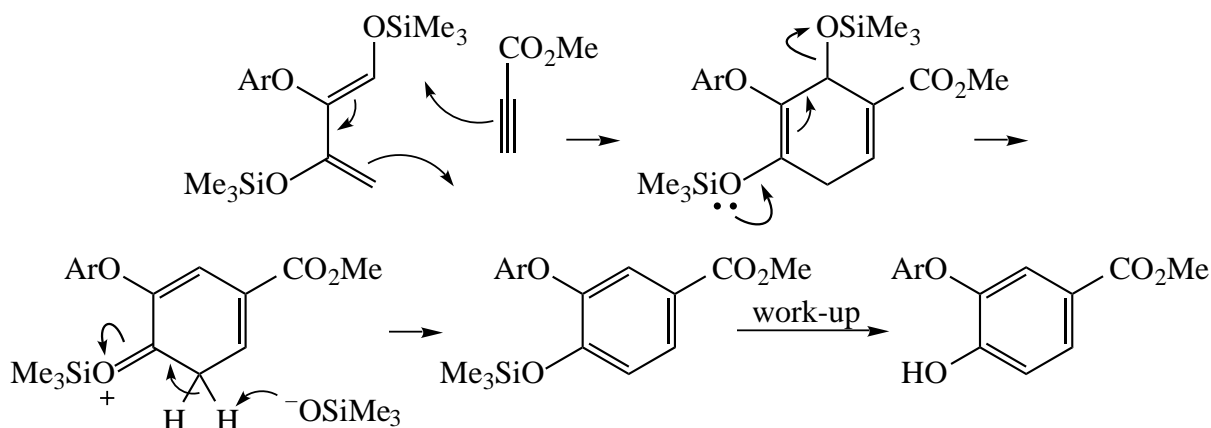
We break the C4–C6 bond, and we form C3–C8 and C4–C9. The formation of the latter two bonds and the fact that we're forming a cyclobutanone suggests a [2+2] cycloaddition between a ketene at C3=C4=O and the C8=C9 π bond. We can generate the requisite C3=C4 π bond by electrocyclic ring opening of the cyclobutene ring in the S.M.



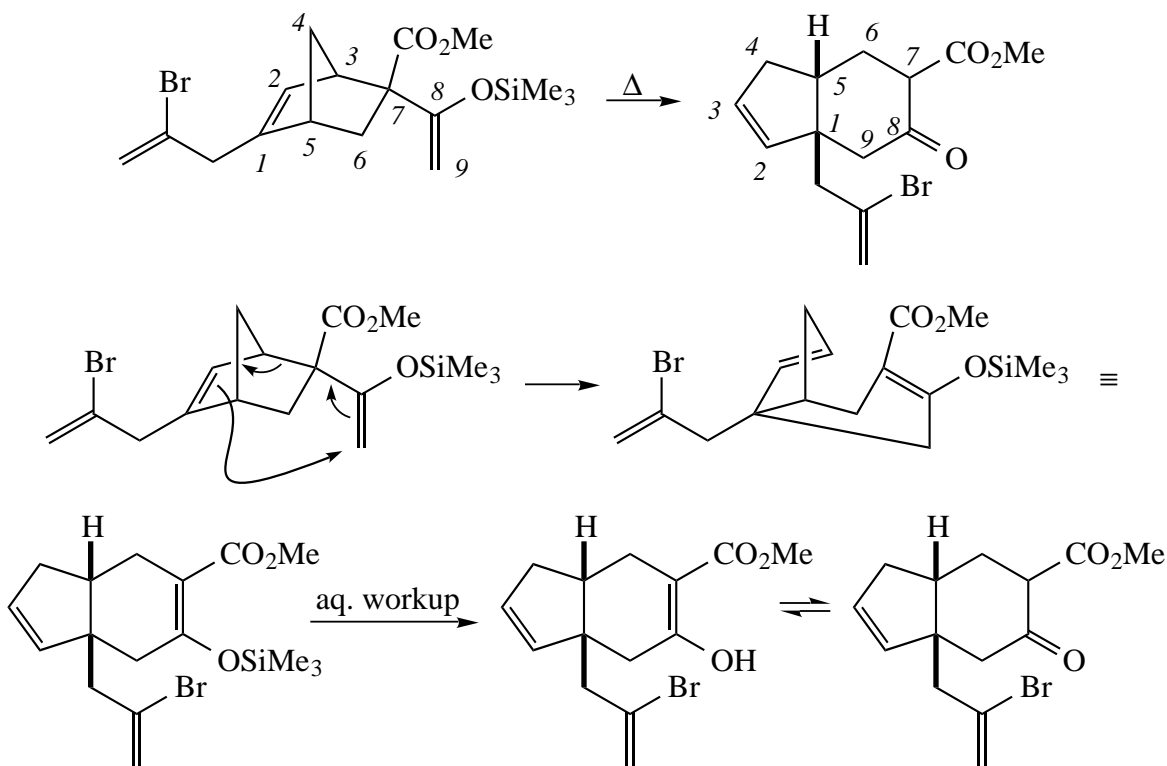
(b) Electrocyclic ring closing followed by base-catalyzed tautomerization (both starting material and product are bases) gives the product.



(c) Diels–Alder reaction followed by spontaneous elimination of Me_3SiO^- and aromatization gives the product. Loss of Me_3SiO^- occurs so readily because the Me_3Si group is a π electron withdrawer like a carbonyl group.

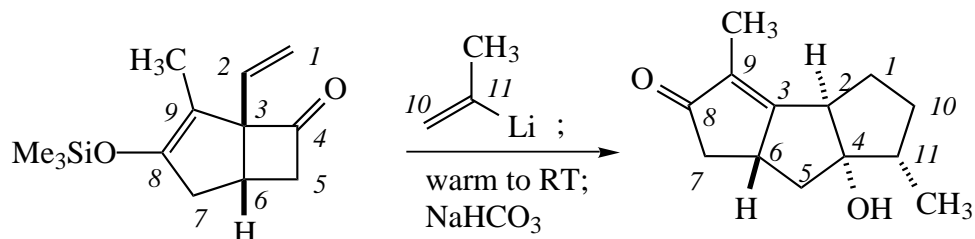


(d) The key atoms for numbering the C's are C1 (with the 2-bromoallyl group attached), C7 (ester group attached), and C8 (O attached). We form bond C1–C9 and break bond C3–C7. Since C3–C7 is the central bond of a 1,5-diene system terminating in C1 and C9, i.e. $\text{C1}=\text{C2}-\text{C3}-\text{C7}-\text{C8}=\text{C9}$, this must be a Cope rearrangement.

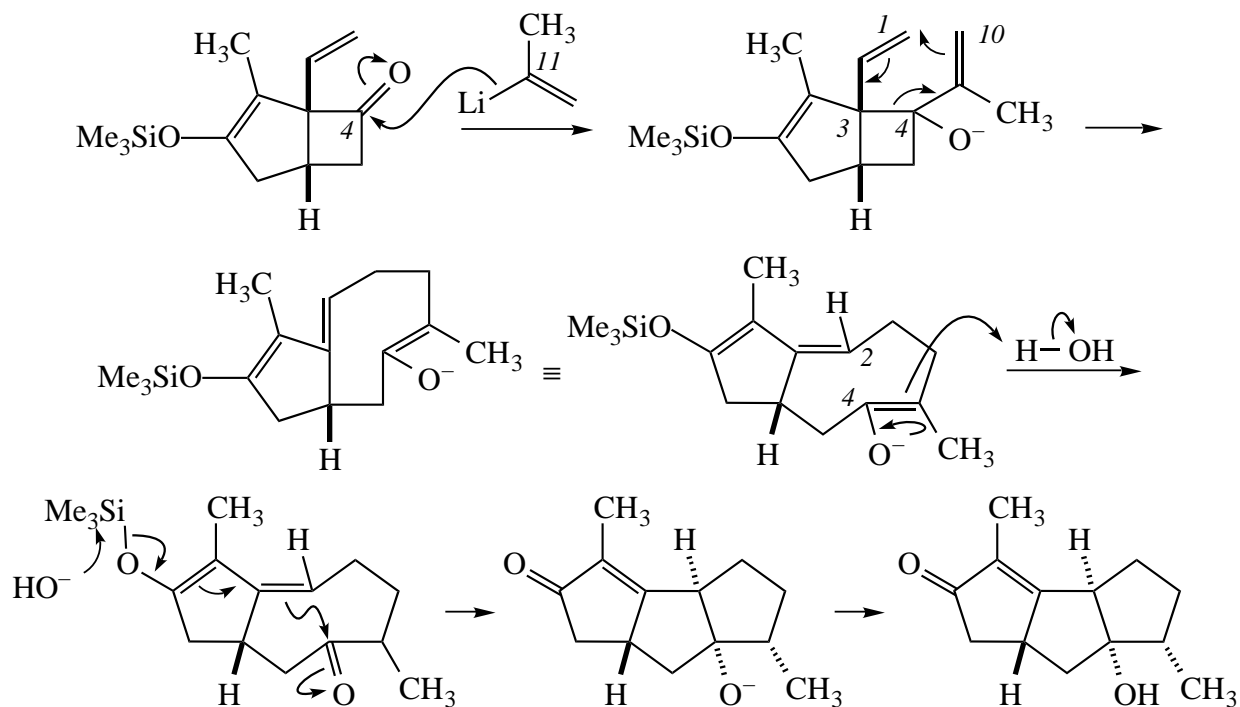


(e) Numbering the carbons is made easier by C9, C8, and C4. These atoms make it easy to label C4 through C9. Since C11 is a carbanion, we can expect that it will add to C4, the only electrophilic C in the starting material, and since C11 has a CH_3 group attached, we can identify it and C10 in the product as the

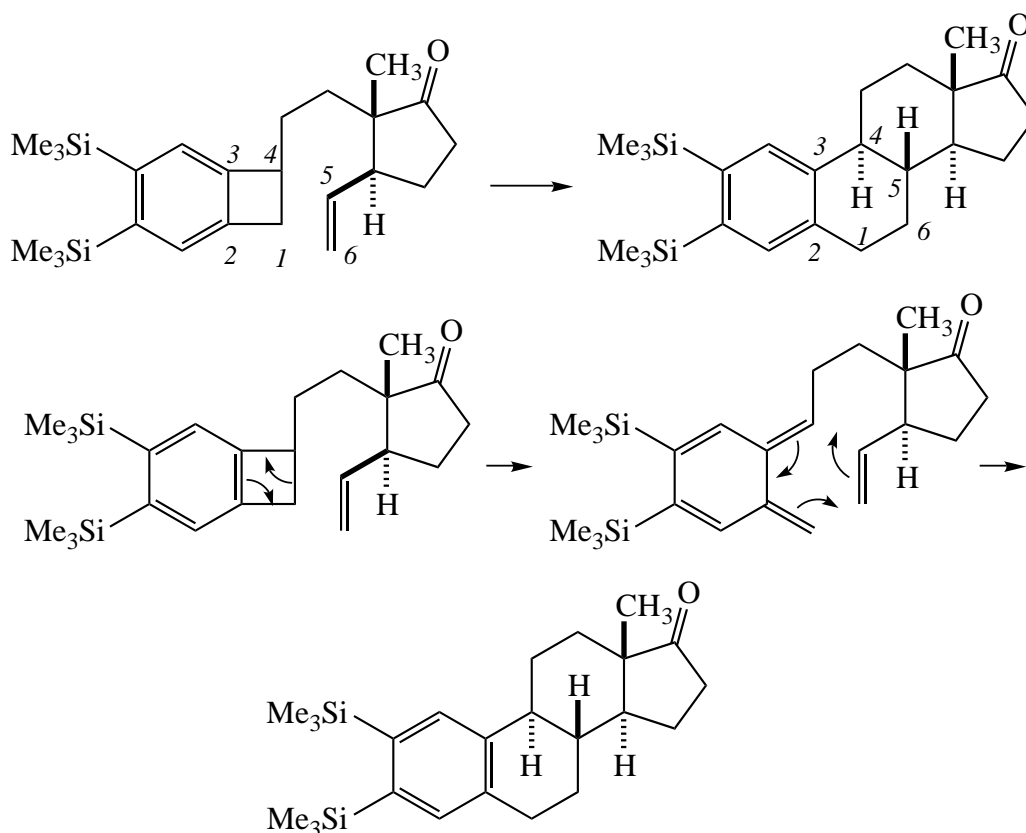
easternmost C's, with C11 attached to C4. For C1 to C3, we preserve the most bonds if we retain the C9–C3–C2–C1 sequence. So overall, we form C4–C11, C4–C2, and C10–C1, and we break C4–C3.



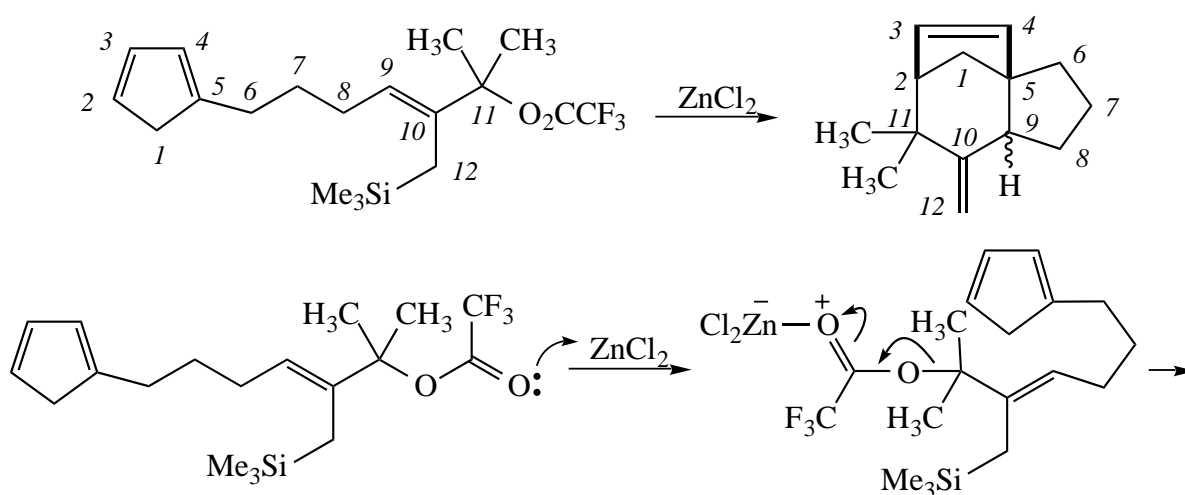
The first step is addition of C11 to C4. We still need to form C10–C1 and break C4–C3. Since we have a 1,5-diene (C11=C10–C4–C3–C2=C1), we can do an oxy-Cope rearrangement. This gives a 5-8 system in which we only have to form the C4–C2 bond. C4 is neither nucleophilic nor electrophilic, while C11 is nucleophilic (conjugation from OSiMe₃). Upon quenching with water, however, C4 becomes an electrophilic carbonyl C, whereupon C11 attacks with concomitant desilylation of O to give the product.

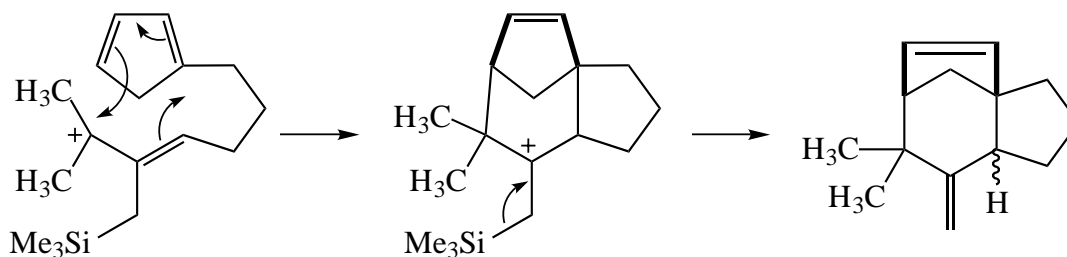


(f) It's clear that we form C4–C5 and C1–C6 bonds, and we break C1–C4. The strained C1–C4 bond can be opened by an electrocyclic ring opening to give an *o*-xylylene, which undergoes an [8+2] cycloaddition to give the observed product.

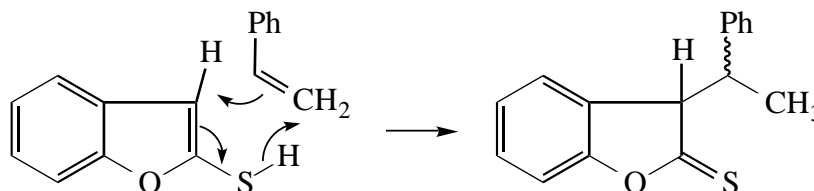


(g) We form C2–C11 and C5–C9 bonds, and we eliminate the elements of $\text{Me}_3\text{SiO}_2\text{CCF}_3$. The ZnCl_2 is a Lewis acid, so it coordinates to the carbonyl O and causes the cleavage of the carboxylate–C11 bond to give the nice stable allylic cation C9–C10–C11. This cation can undergo a six-electron, [4+3] cycloaddition with the C2=C3–C4=C5 diene to give a new carbocation at C11. Loss of the Me_3Si^+ group from C12 then gives the product.

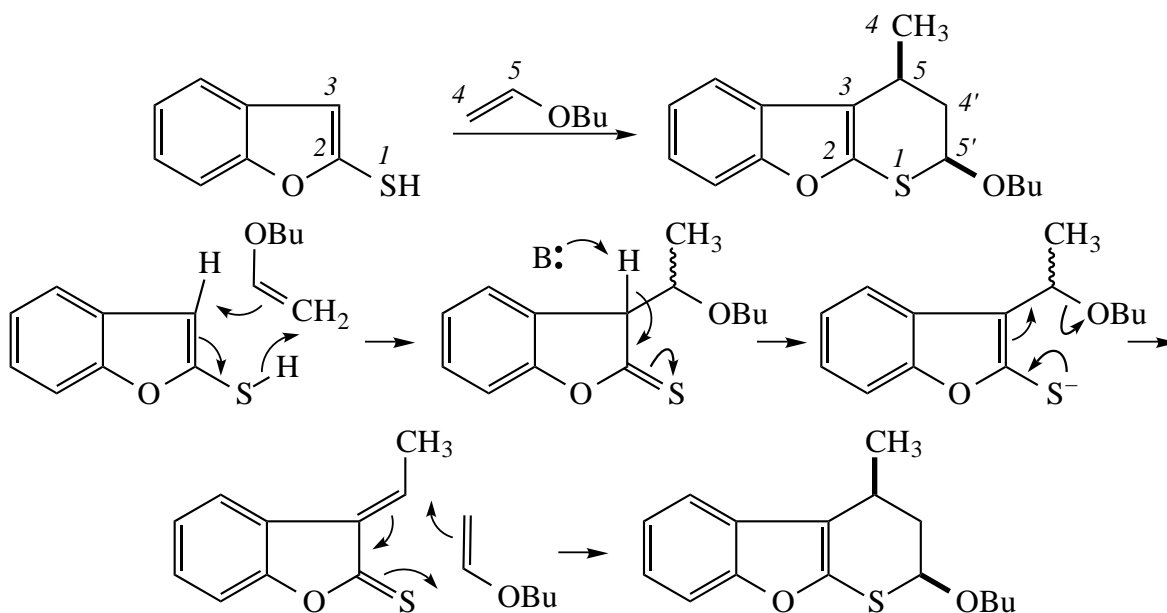




(h) The first product is formed by a hetero-ene reaction, with transfer of the H attached to S to the terminal C of styrene.

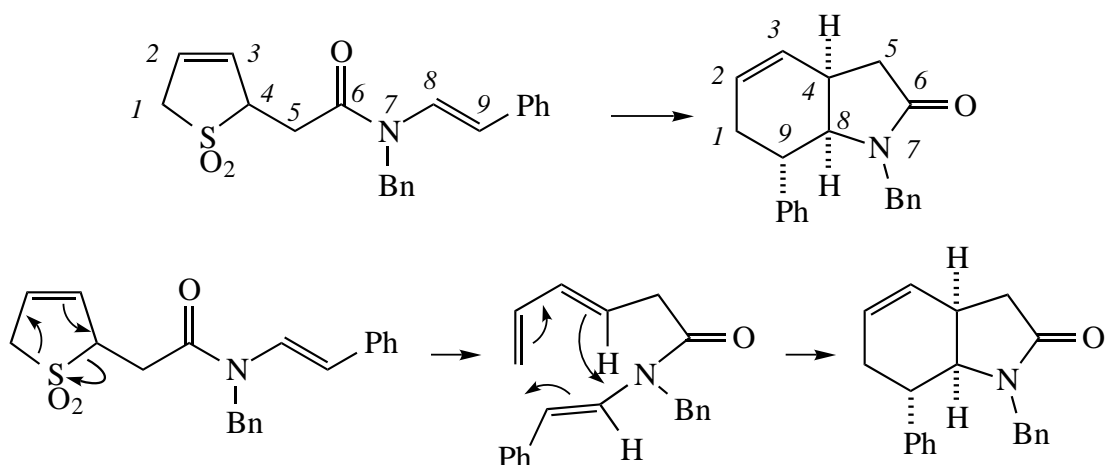


The second product must incorporate two equivalents of the enol ether. We form C3–C5, C5–C4', and C5'–S1 bonds, and we transfer a H from S1 to C4. A hetero-ene reaction forms the C3–C5 bond and transfers the H. As for the other two bonds, since S1 and C5 are at the ends of a four-atom unit, we might expect a Diels–Alder reaction. We can get to the requisite diene by eliminating the elements of BuOH by an E1cb mechanism. The hetero-Diels–Alder reaction gives the product with *endo* stereoselectivity and the expected regioselectivity.

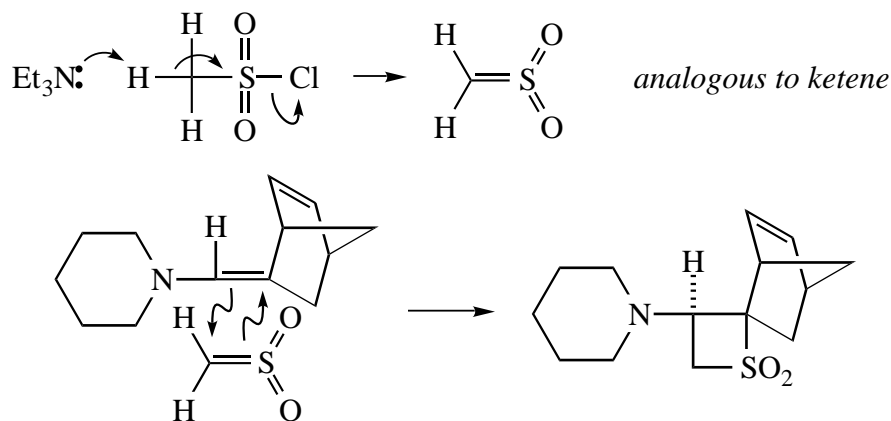


(i) We form C9–C1 and C4–C8 bonds, and we break C1–S and C4–S bonds. Since C1 and C4 are the ends of a four-carbon unit, we can expect a Diels–Alder reaction. The cyclohexene in the product should also tip you off. We can obtain the requisite diene by doing a [4+1] retro-cycloaddition, eliminating SO₂ to give the C1=C2–C3=C4 diene. Stereospecific and *endo*-selective Diels–Alder reaction then gives the

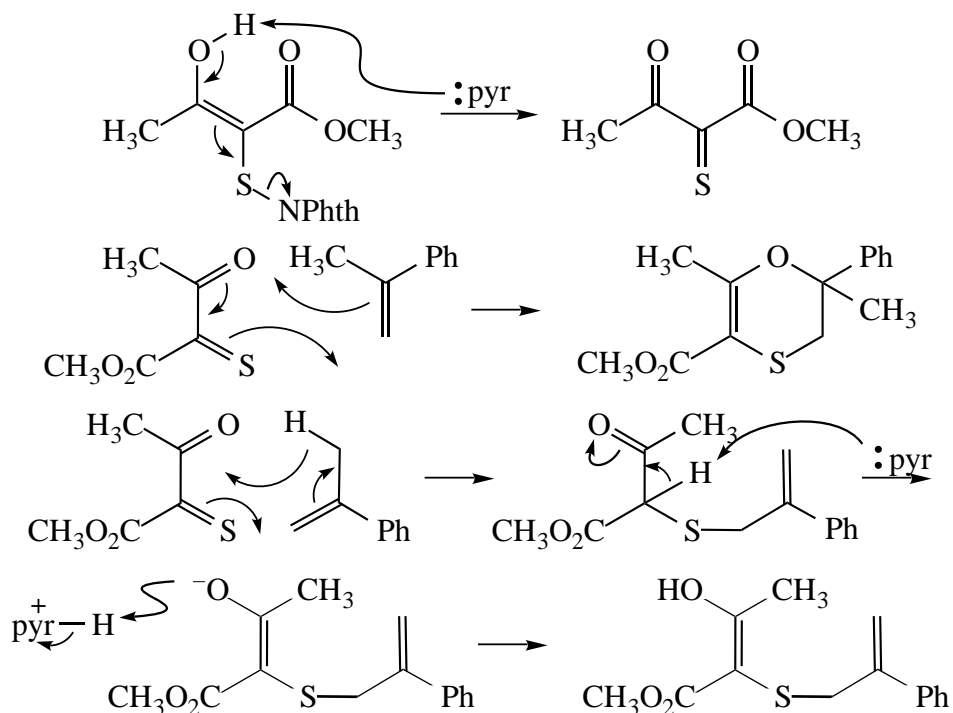
product.



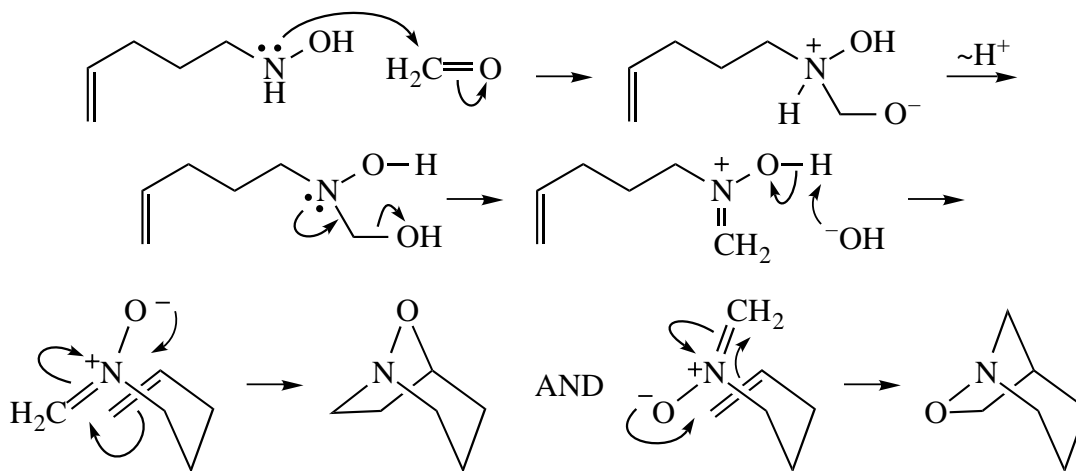
(j) When an acyl chloride is treated with Et_3N , β -elimination takes place to give a ketene. When a sulfonyl chloride is treated with Et_3N , β -elimination takes place in the same way. The intermediate undergoes [2+2] cycloadditions just like ketenes do to give the saturated four-membered ring.



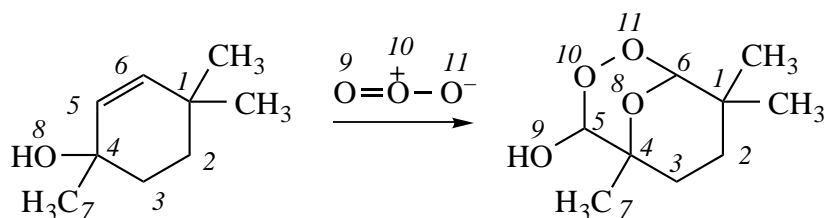
(k) The second product provides the key. It is a six-membered ring with a single double bond, probably the product of a hetero-Diels–Alder reaction. The requisite diene can be made from the starting material by a vinylogous β -elimination, with NPhth as the leaving group. The same diene intermediate can undergo a hetero-ene reaction to give the *other* observed product. An alternative mechanism for formation of the first product, i.e. direct attack of the alkene (nucleophile) on S (electrophile, NPhth as leaving group) to give a carbocation, followed by loss of H^+ , is also possible, but is less likely, especially since we know the $\text{C}=\text{S}$ compound is formed under the conditions. If this mechanism were operative it's also likely that H^+ would be lost from the *other* C of the carbocation to give the more substituted and more stable isomeric alkene.



(l) Whenever you see a five-membered heterocycle, think 1,3-dipolar cycloaddition. The heterocyclic rings shown can be made from an intramolecular cycloaddition of a nitron and the alkene. The nitron must be made from the hydroxylamine and formaldehyde.

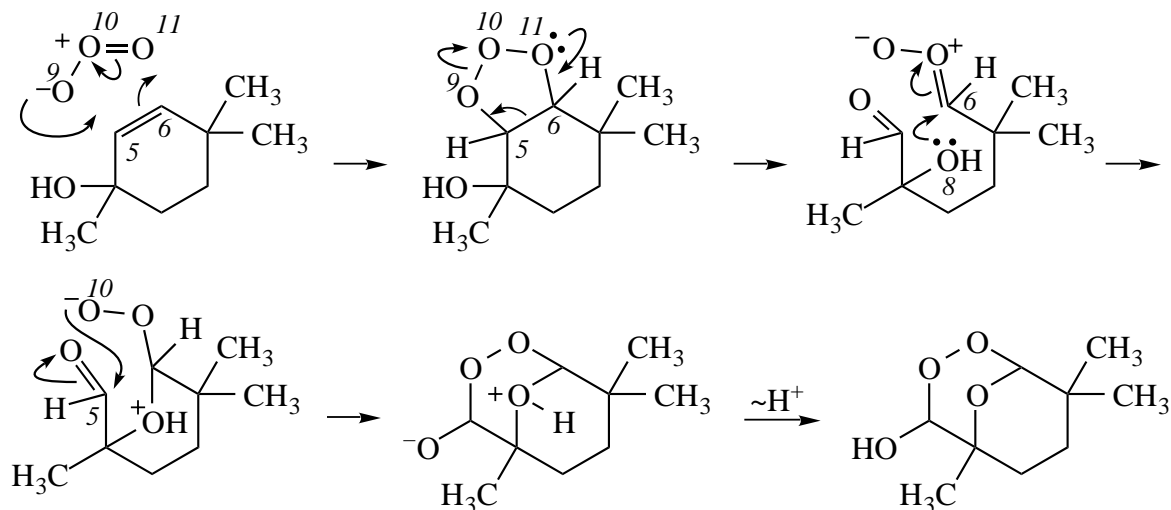


(m) Make: C5–O10, C5–O9, C6–O8, C6–O11. Break: C5–C6, C9–O10.

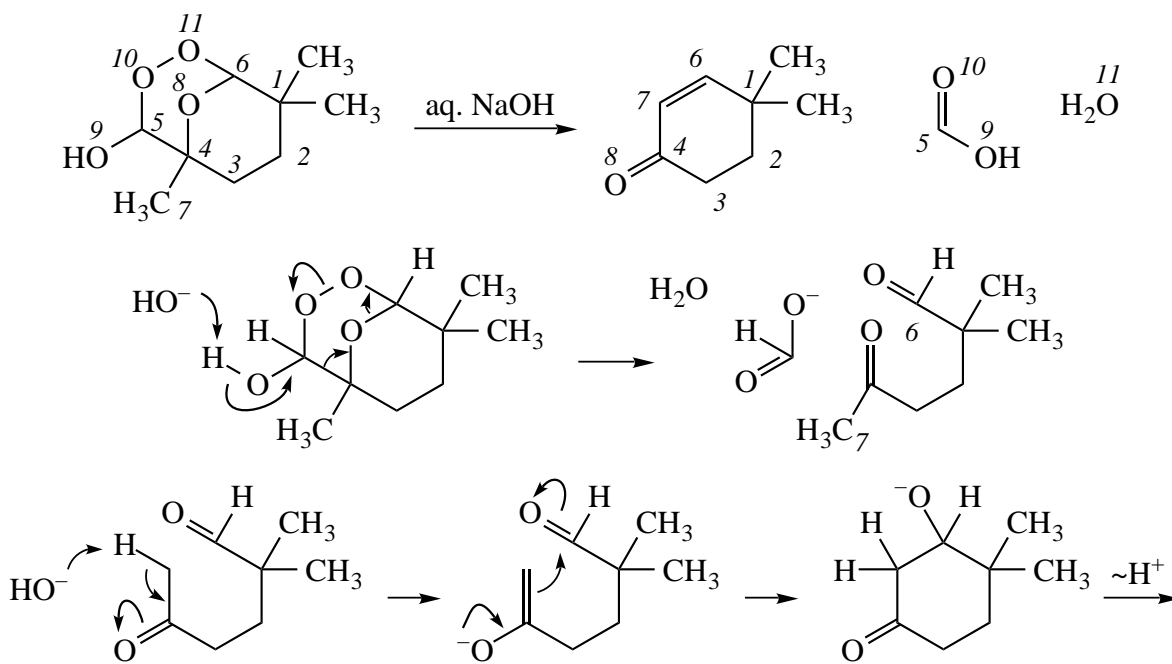


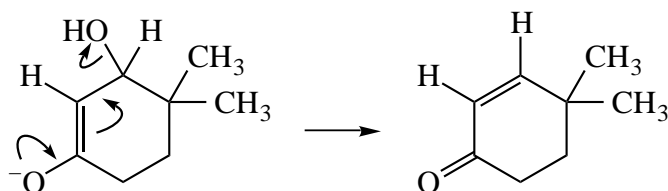
Ozone lives to do 1,3-dipolar cycloadditions. After the cycloaddition to give the C6–O11 and C5–O9

bonds, retro 1,3-dipolar cycloaddition occurs to break the C9–O10 and C5–C6 bonds. Then O8 can attack C6 and O10 can attack C5 to give the observed intermediate (after proton transfer).

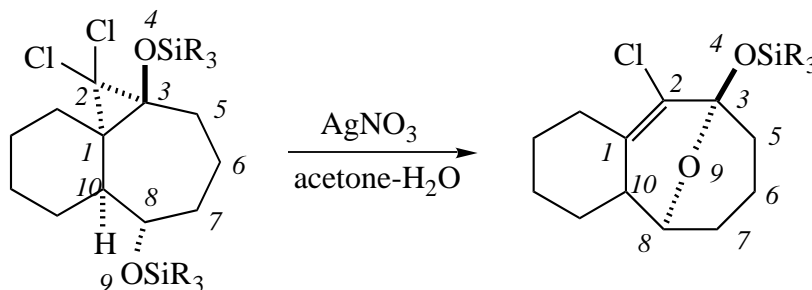


Second step. The elements of CH_4O_3 are eliminated. The most likely by-products are H_2O and HCOOH . Make: None. Break: C4–C5, C6–O8, O10–O11. The base can deprotonate the OH on C5, and the lone pair on O can then push down to form a π bond with C5, causing the C4–C5 bond to break. The electrons keep getting pushed around until they end up on O again and the O–O bond is broken, providing the driving force for the step. A keto-aldehyde and formate anion are obtained. Now C7 (deprotonated) is nucleophilic and C6 is electrophilic, so an aldol reaction followed by dehydration gives the observed product.

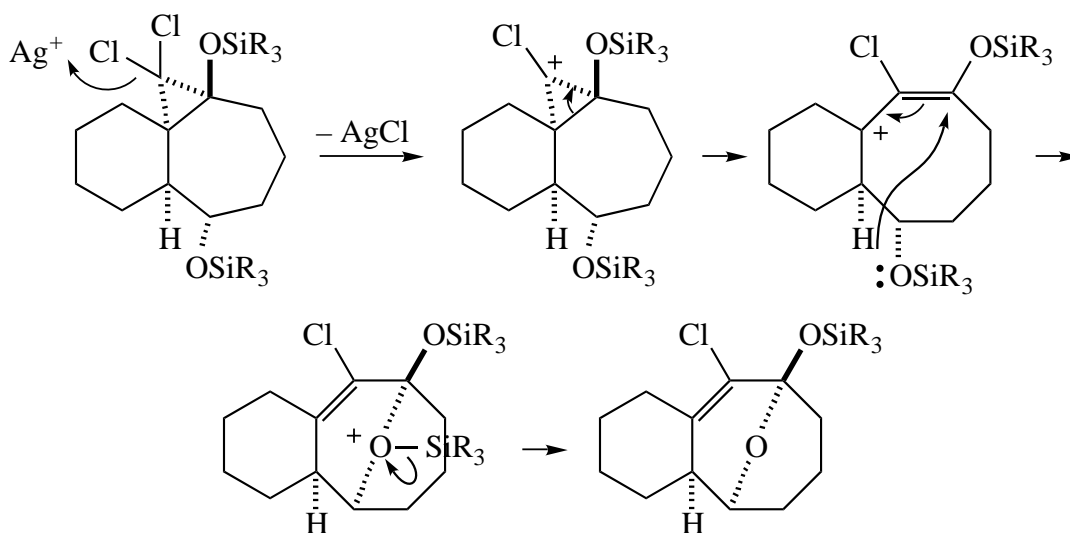




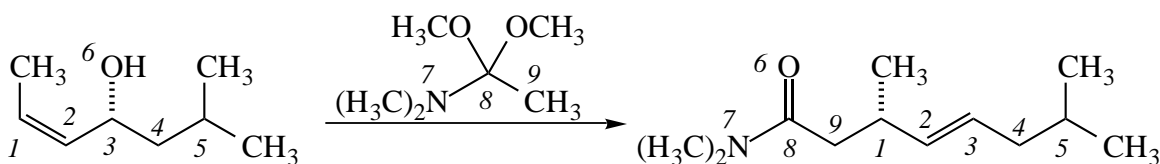
(n) Make: O9–C3. Break: C1–C3. Since O9 is nucleophilic, we must turn C3 into an electrophilic center.

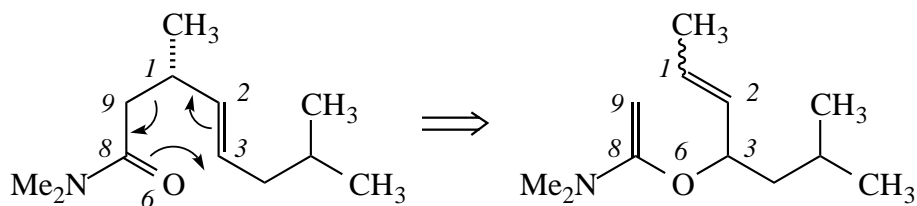


In the first step, Ag^+ promotes the departure of Cl^- to give a cyclopropyl carbocation. This undergoes two-electron disrotatory electrocyclic ring opening to give the chloroallylic cation, in which the empty orbital is localized on C1 and C3. Then O9 can add to C3; desilylation then gives the product.

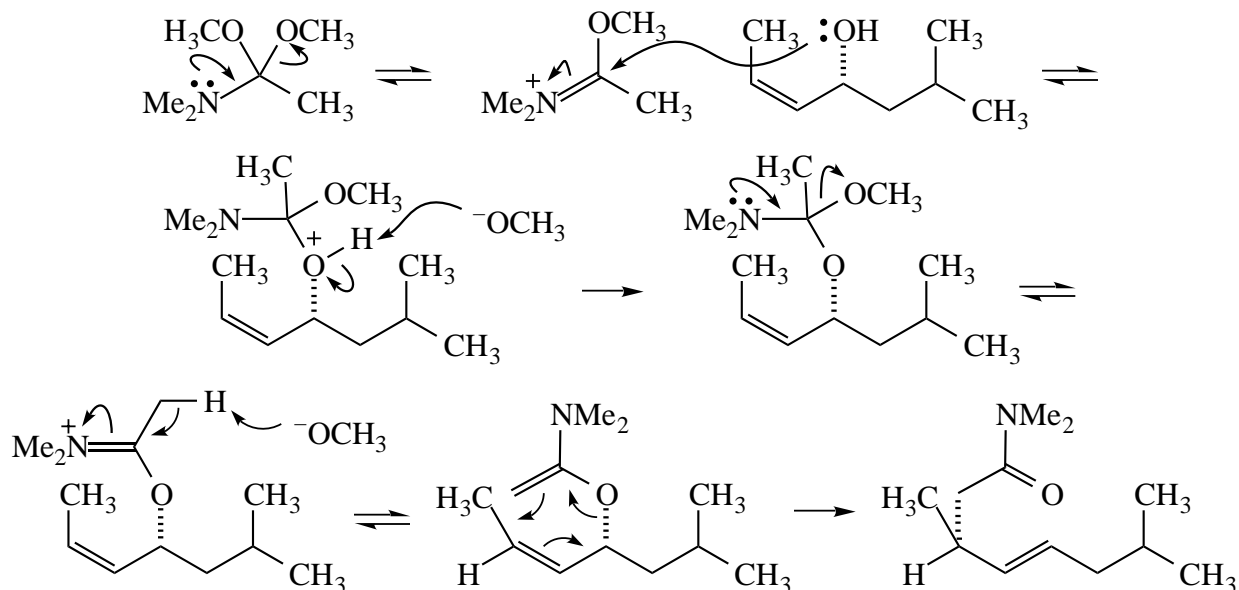


(o) The product is a 1,5-diene, specifically a γ,δ -unsaturated carbonyl, suggesting a Claisen rearrangement. Work backwards one step from the product.

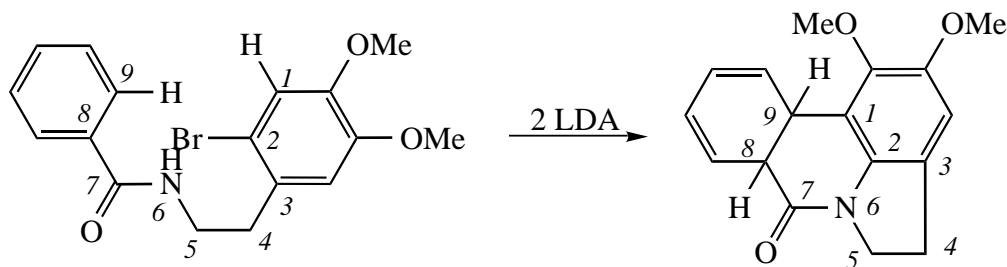




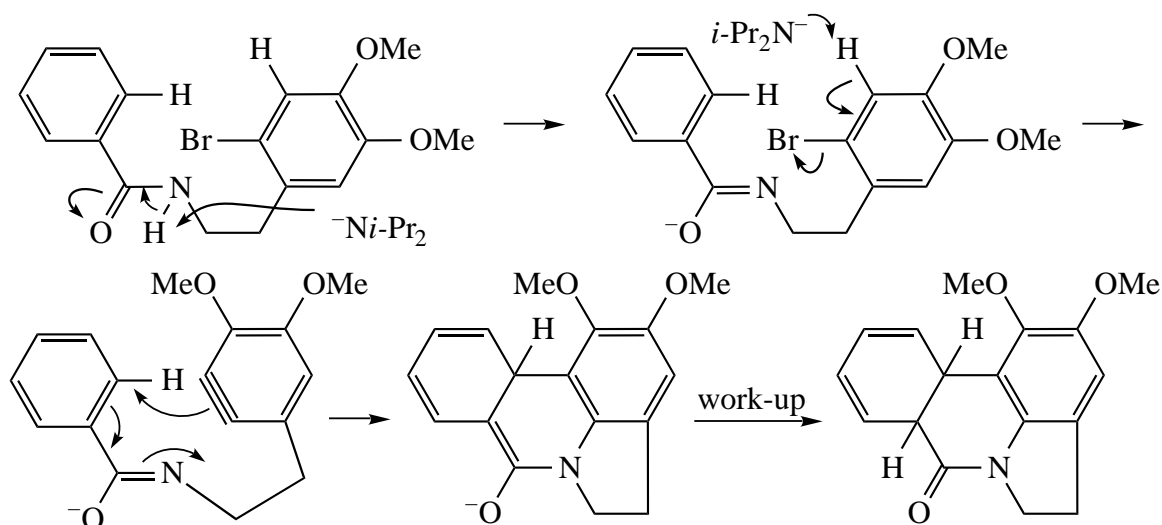
The immediate precursor retains the O6–C3 bond and would have a C8–O6 bond and a C8=C9 π bond. This calls for an S_N1 substitution at C8 to replace the C8–OMe bond with a C8–O6 bond and an E1 elimination to make the C8=C9 π bond. The overall reaction is an orthoamide Claisen rearrangement.



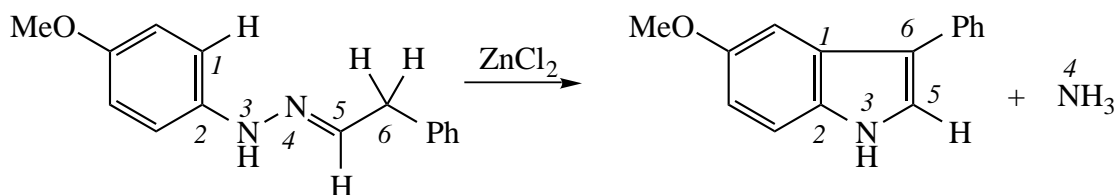
(p) Make: C1–C9, C2–N6.



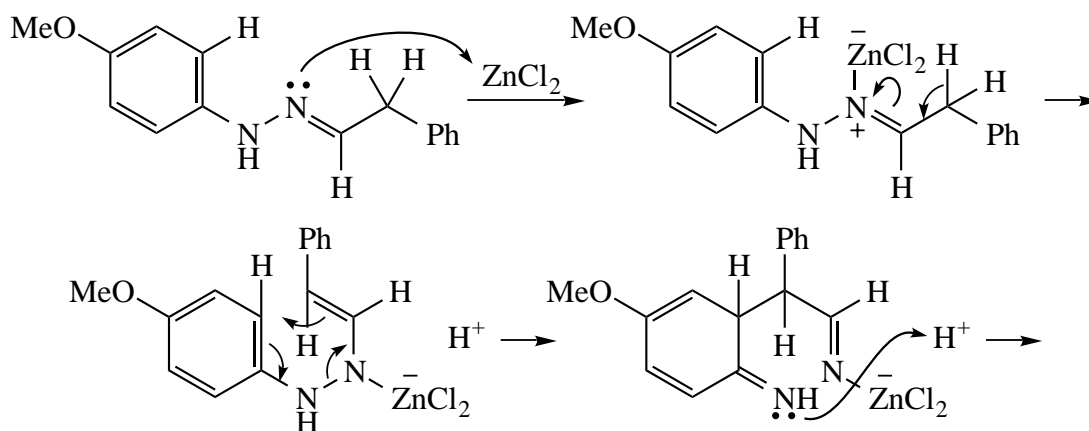
Since N6 and C9 are at the ends of a four-atom chain, we might expect a Diels–Alder reaction. The dienophile in such a reaction would be benzyne; the key is the benzene ring fused to the new six-membered ring and the fact that the H on C1 is gone in the product. (You could alternatively draw the π bond of the aromatic ring participating in the Diels–Alder reaction, but this is unlikely, because the π bonds of aromatic rings are very bad dienophiles.) The first equivalent of LDA deprotonates N to make the 1,3-diene across N6=C7–C8=C9; the second equivalent induces an E2 elimination across C1–C2 to give an aryne. Cycloaddition gives the enolate, which is protonated on C8 to give the observed product. In fact, this compound is not very stable, and it is oxidized by air to give the fully aromatic product.

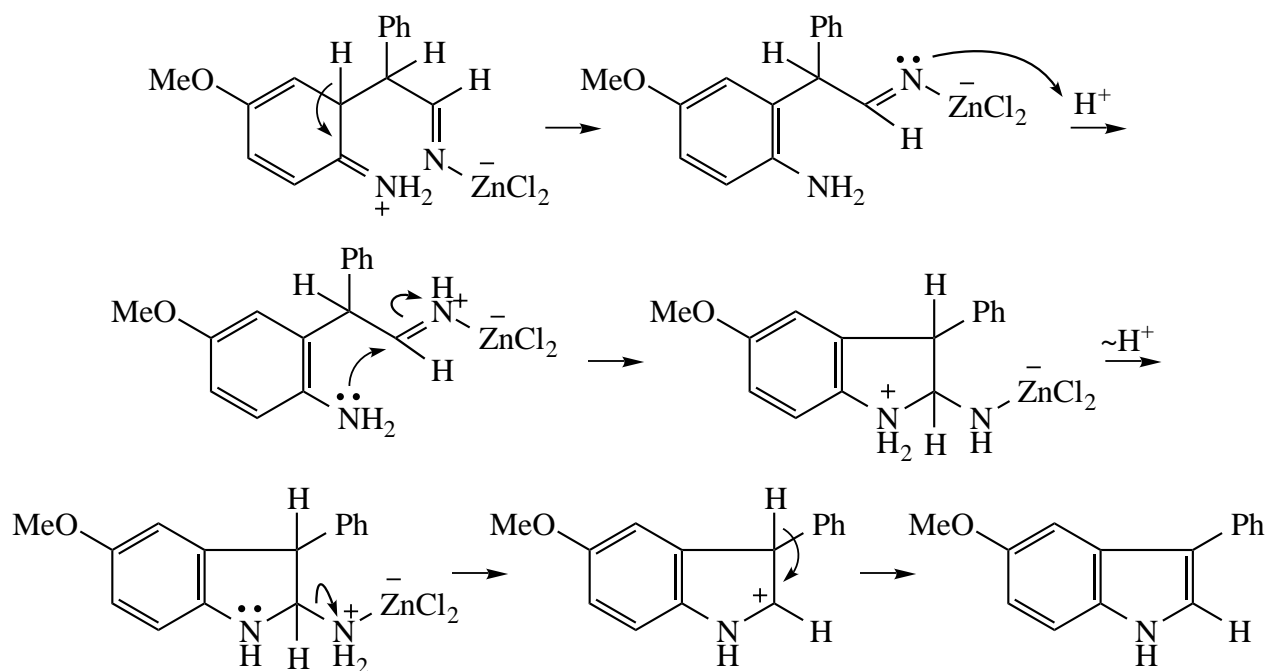


(q) Break: N3–N4, N4–C5. Make: C1–C6, N3–C5. We lose the elements of NH₃.

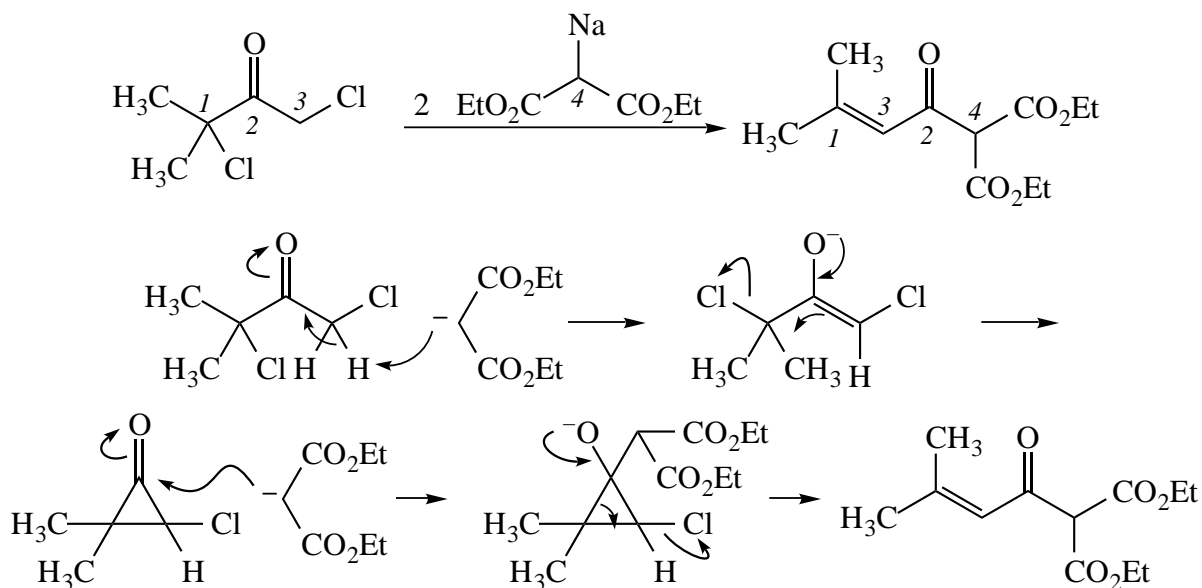


Since we are forming a σ bond at the end of a six-atom chain and breaking the σ bond in the middle, we might expect a Cope rearrangement. To do this, we must make a C5=C6 π bond. We can do this by transposing the N4=C5 π bond. This transposition converts an imine to an enamine, which is exactly analogous to converting a ketone to an enol. The enamine then undergoes Cope rearrangement to give the C1–C6 bond. (Note how this Cope rearrangement is analogous to the Claisen rearrangement of *O*-allylphenols.) After reestablishing aromaticity by tautomerization, nucleophilic N3 attacks electrophilic C5 to form the N3–C5 bond. Finally, E1 elimination of NH₃ gives the indole.

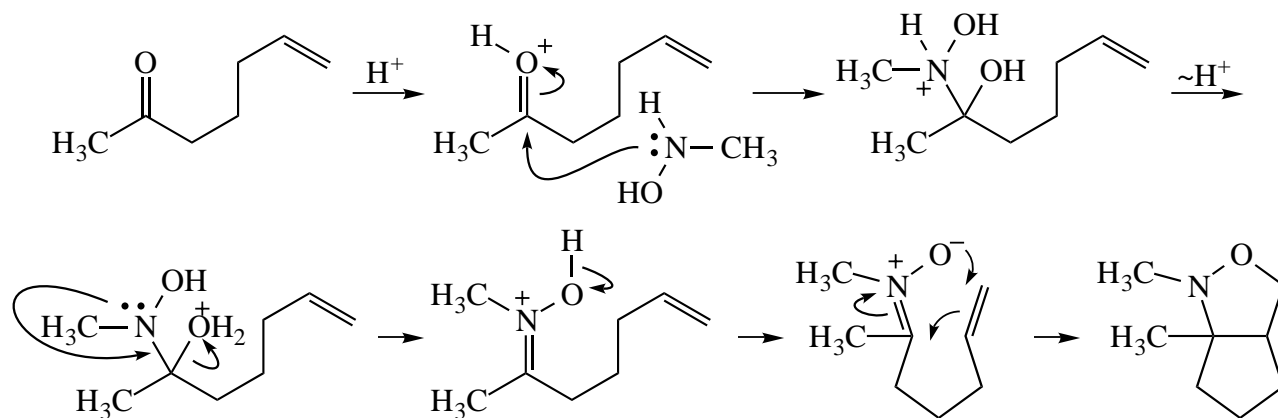




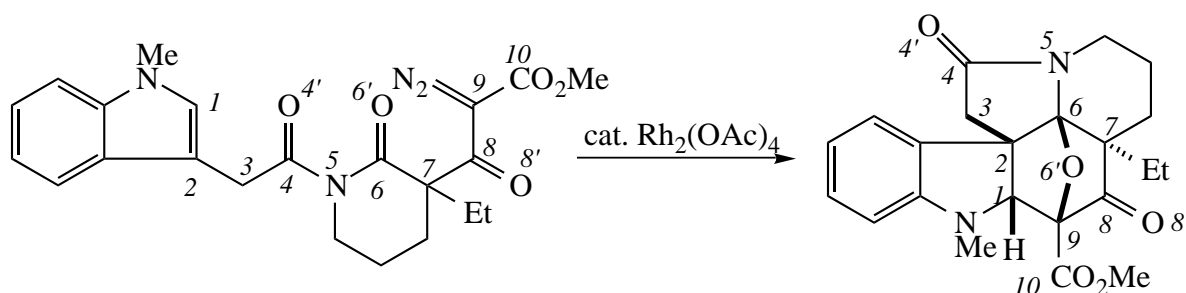
(r) Make: C2–C4, C1–C3. Break: C1–C2. Since only one equivalent of malonate is incorporated into the molecule, the other equivalent must act as a base. The migration of C1 from C2 to C3 is a 1,2-alkyl shift. Under these basic conditions, it is likely to proceed by a Favorskii mechanism. Deprotonation of C3 by malonate gives the enolate. Two-electron electrocyclic ring closing with expulsion of Cl^- gives the cyclopropanone. Attack of malonate on C2 gives a tetrahedral intermediate; fragmentation of this with expulsion of Cl^- gives the observed product. Other reasonable mechanisms can be drawn, some of which do not involve an electrocyclic ring closing.



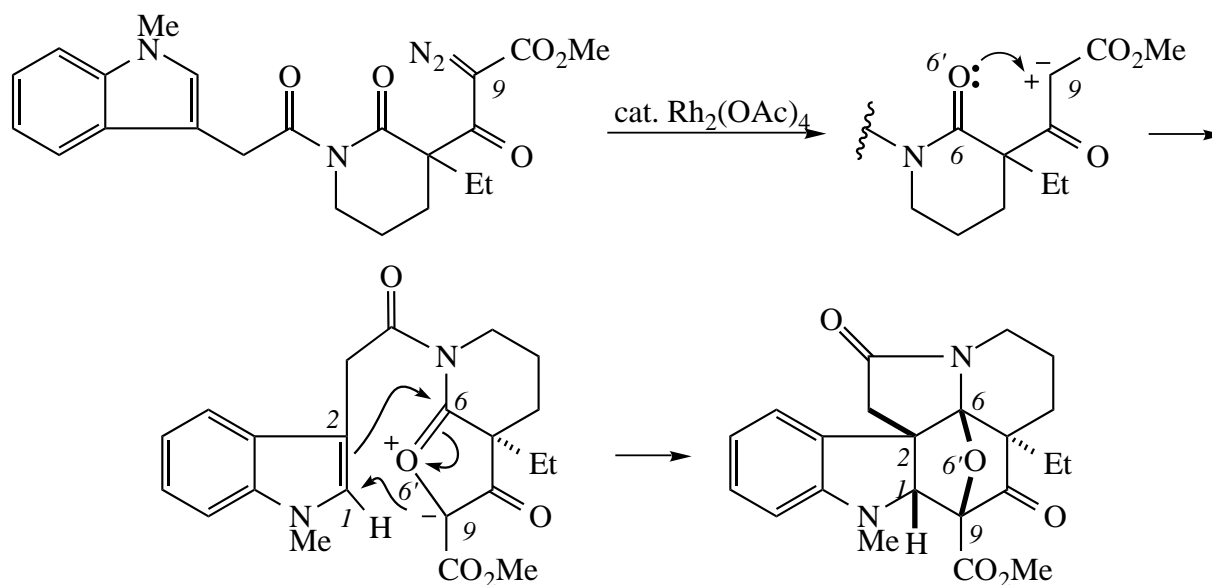
(s) The five-membered heterocycle should alert you to a 1,3-dipolar cycloaddition.



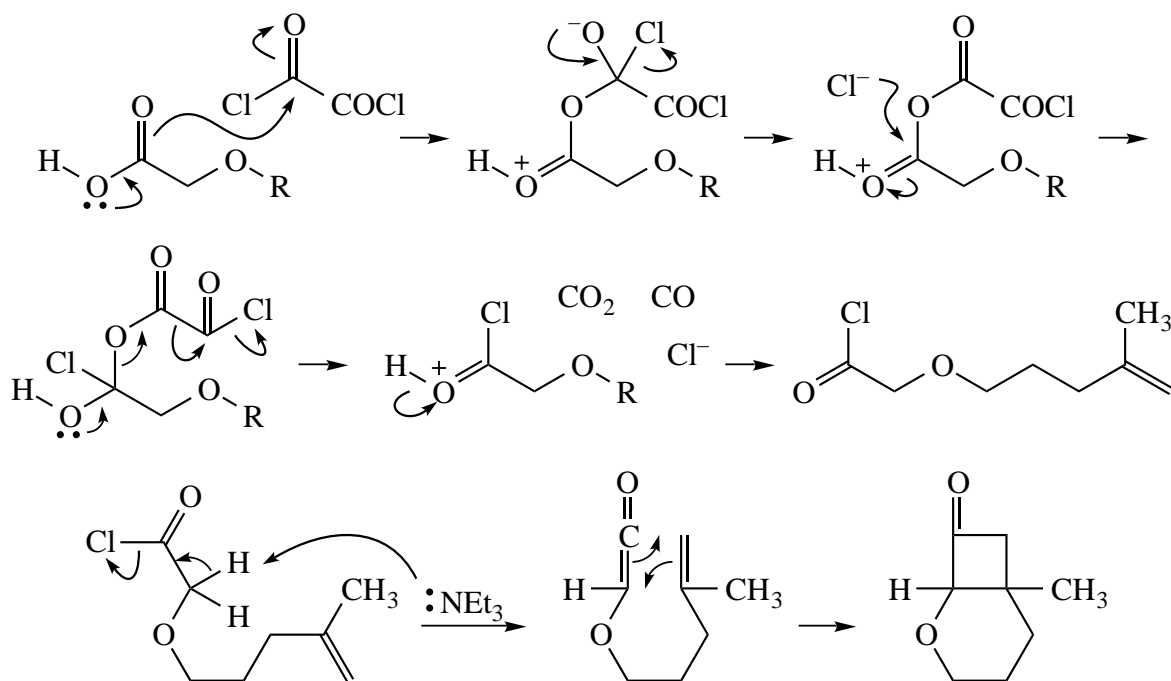
(t) Make: C1–C9, C2–C6, O6'–C9. Break: C9–N₂.



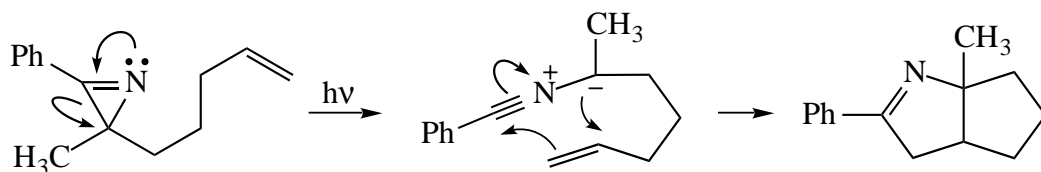
C6 and C9 are at opposite ends of a four-carbon unit, but since one of these atoms (C7) is saturated and quaternary, a Diels–Alder reaction is unlikely (can't make diene). The combination of a diazo compound with Rh(II) generates a carbenoid at C9. The nucleophile O6' can add to the empty orbital at C9, generating the O6'–C9 bond and a carbonyl ylide at C6–O6'–C9. Carbonyl ylides are 1,3-dipoles (negative charge on C9, formal positive charge on O6', electron deficiency at C6), so a 1,3-dipolar cycloaddition can now occur to join C2 to C6 and C1 to C9, giving the product. Note how a relatively simple tricyclic starting material is transformed into a complex hexacyclic product in just one step!



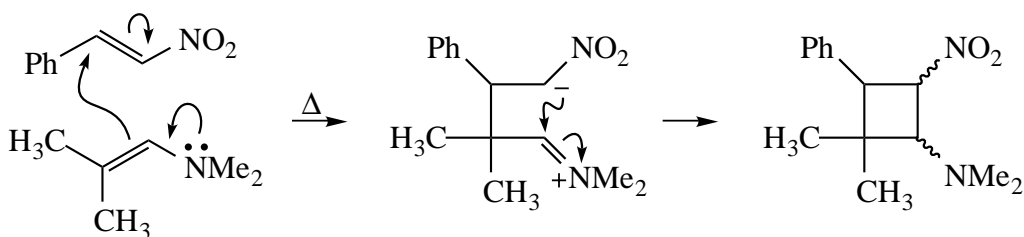
(u) The cyclobutanone should tip you off to a ketene–alkene cycloaddition. Ketenes are generally made by Et_3N -catalyzed elimination of HCl from acyl chlorides. Oxalyl chloride ClCOCOCl serves to convert the acid into an acid chloride.



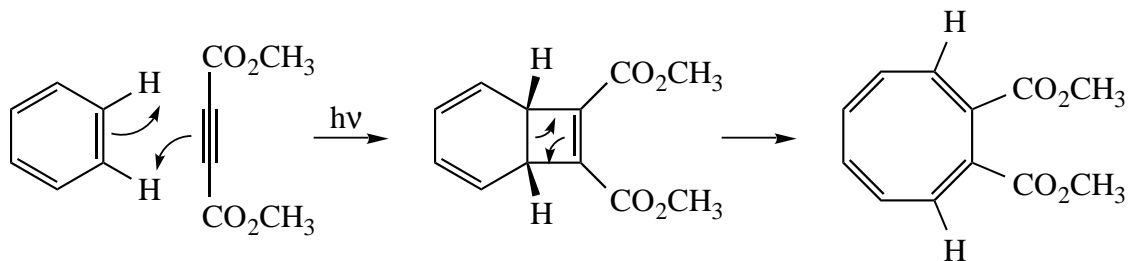
(v) Another five-membered heterocycle, another 1,3-dipolar cycloaddition. The first step is formation of the requisite 1,3-dipole, a nitrile ylide, by a two-electron electrocyclic ring opening. Then dipolar cycloaddition occurs.



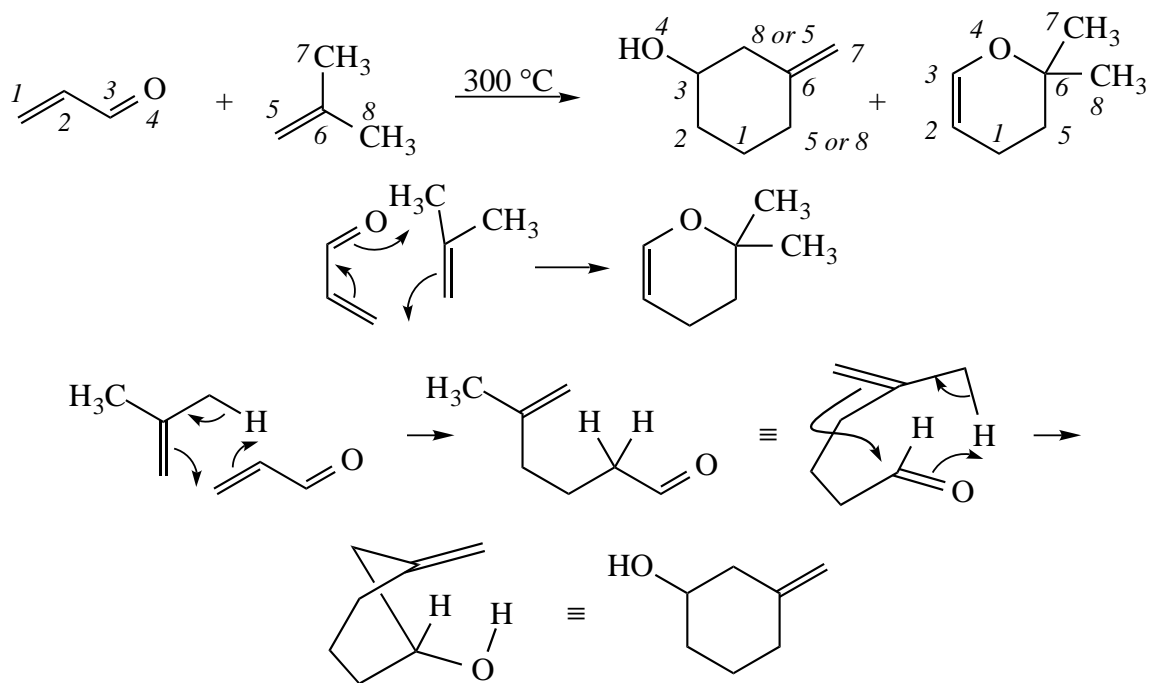
(w) *Formally* this reaction is a $[2+2]$ cycloaddition. In practice, concerted $[2+2]$ cycloadditions occur under thermal conditions *only* when one of the components is a ketene or has a π bond to a heavy element like P or a metal. Neither of the alkenes in this reaction fits the bill. However, one of these alkenes is very electron rich and the other is very electron poor, so a *nonconcerted*, two-step polar mechanism is likely.



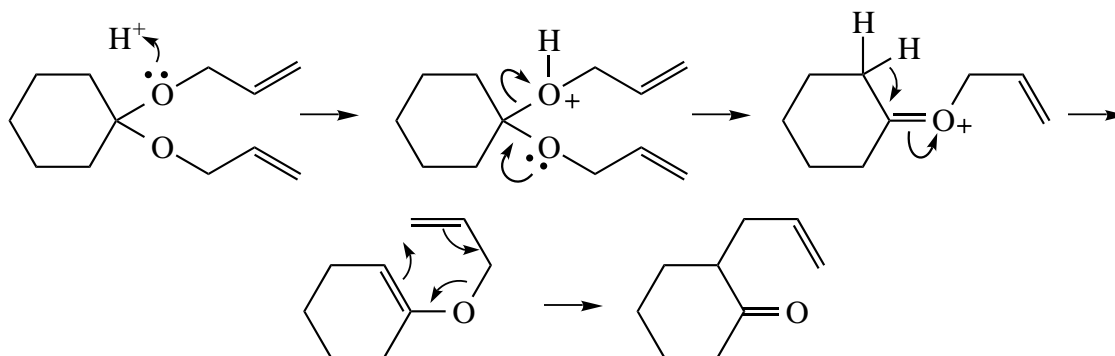
(x) The extra six C's must come from benzene. A photochemically allowed [2+2] cycloaddition between the alkyne and benzene gives an intermediate that can undergo disrotatory electrocyclic ring opening to give the observed product (after bond alternation). (Either two or three arrows can be drawn for the electrocyclic ring opening, but the TS for the reaction involves all eight π electrons, so to be disrotatory the reaction must be promoted photochemically.) Benzene does not usually undergo cycloaddition reactions, but here it evidently does.



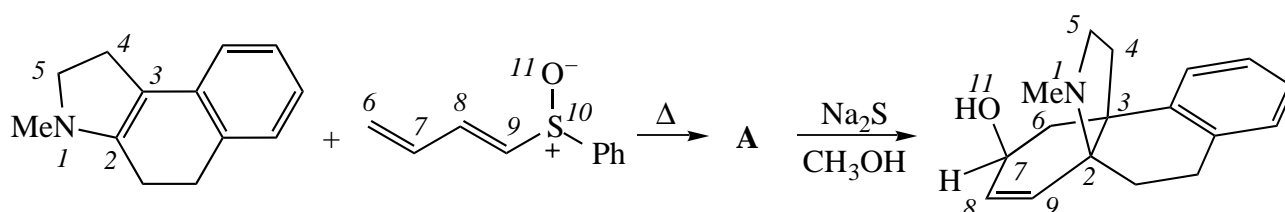
(y) The second product is clearly obtained by a hetero-Diels–Alder reaction between acrolein and isobutylene. The first product is less obvious. Two new C–C bonds are formed, and H atoms are transferred from C7 and C8 to C2 and O4. This suggests two ene reactions.



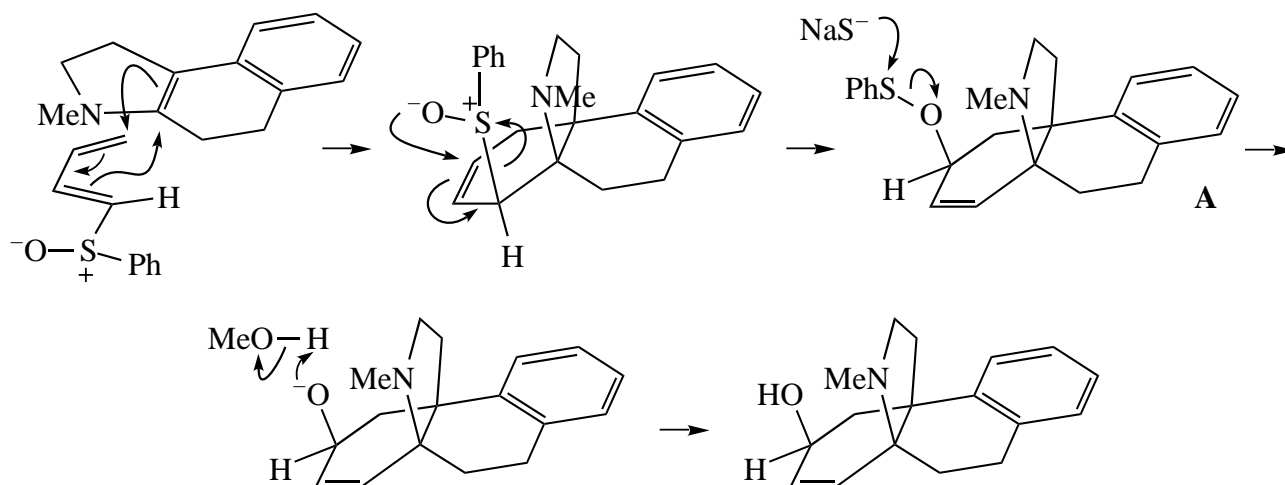
(z) Elimination of allyl alcohol occurs by an E1 mechanism. Then a Claisen rearrangement gives the product.



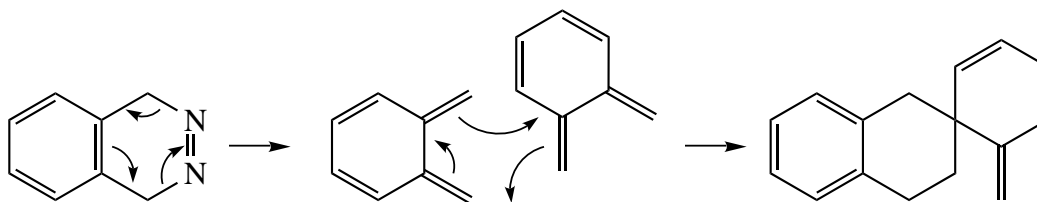
(aa) The C6 to C9 unit in the product is numbered by virtue of the two H's on C6. Make: C2–C9, C3–C6, C7–O11. Break: C9–S10, S10–O11.



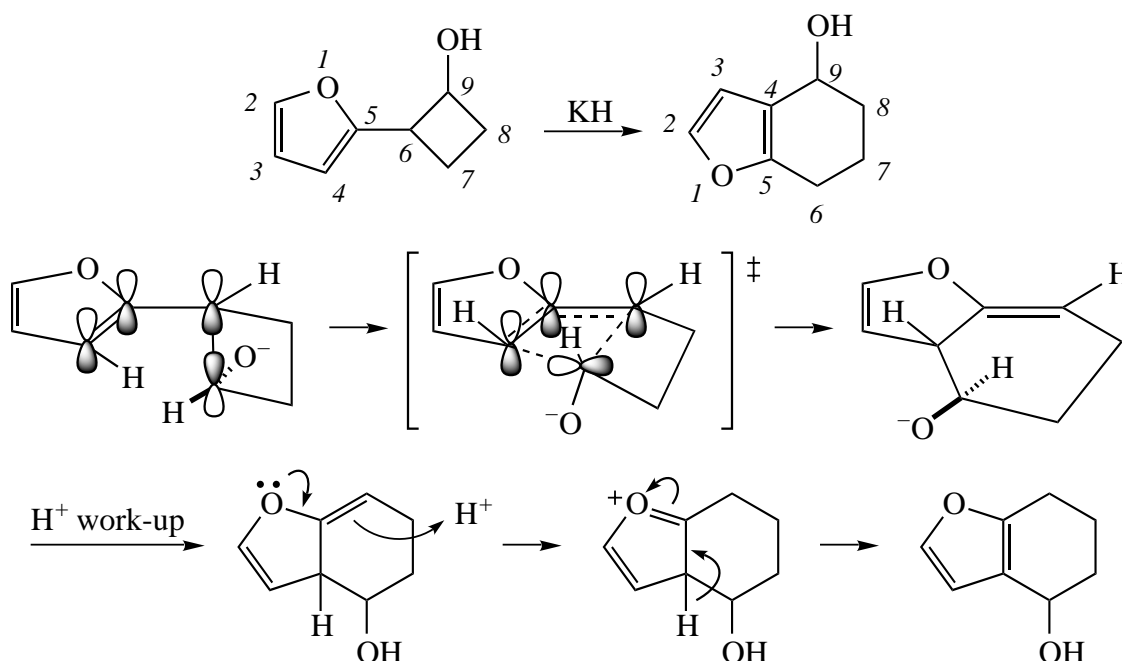
Formation of C2–C9 and C3–C6 suggests a Diels–Alder reaction, this one of the inverse electron demand flavor. The regioselectivity follows the *ortho-para* rule and the stereoselectivity is *endo*. The C7–O11 bond can now be formed and the C9–S10 bond cleaved by a [2,3] sigmatropic rearrangement to give compound A. All that is left is to cleave the S10–O11 bond. Na₂S attacks S, with RO[−] acting as the leaving group, and protonation gives the final product.



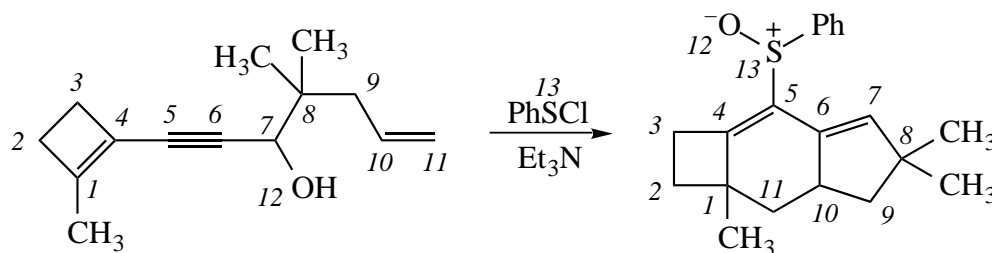
(bb) Retro Diels–Alder reaction gives off N₂ and an *ortho*-xylylene. With no other substrates available, this extremely reactive substance dimerizes in another Diels–Alder reaction to give the product.



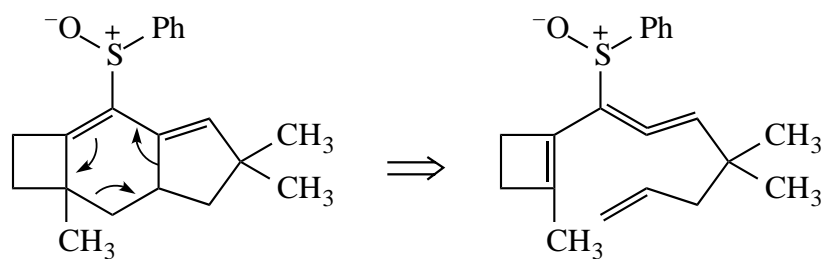
(cc) The product is formally the result of a [1,3] sigmatropic rearrangement. **STOP!** [1,3] sigmatropic rearrangements are very rare, and they should be viewed with suspicion. They are thermally allowed only when one of the components is antarafacial. Sometimes an apparent [1,3] shift is actually the result of two sequential reactions (polar or pericyclic). In this case, the presence of KH suggests an oxyanion-accelerated concerted process. The one-atom component can be antarafacial if the *back* lobe of the sp^3 orbital used to make the old bond to C6 is then used to make the new bond to C4. After workup, aromaticity is reestablished by protonation-deprotonation.



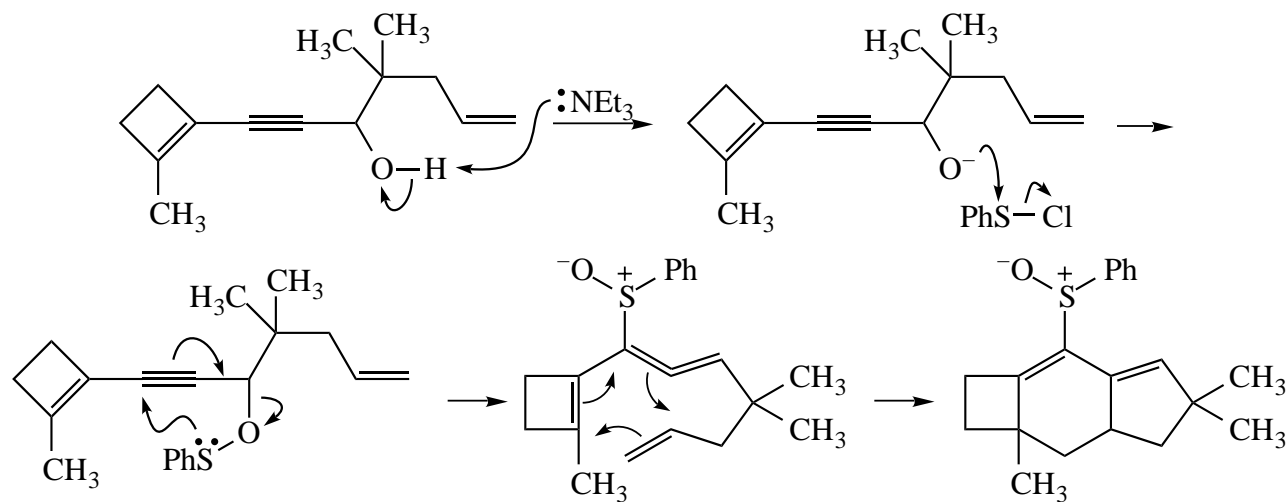
(dd) Make: C1–C11, C5–S13, C6–C10, O12–S13. Break: C7–O12, S13–Cl.



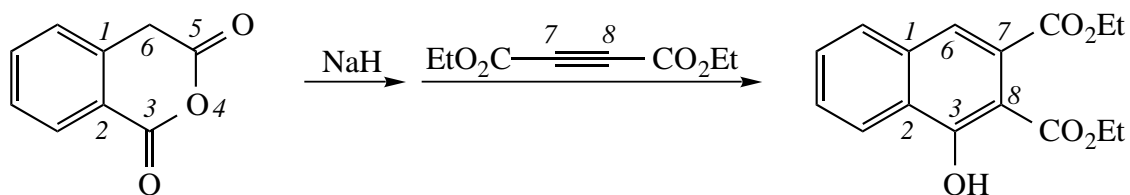
The product looks very much like the result of a Diels–Alder reaction that forms the C1–C11 and C6–C10 bonds. Work backwards one step from the product.



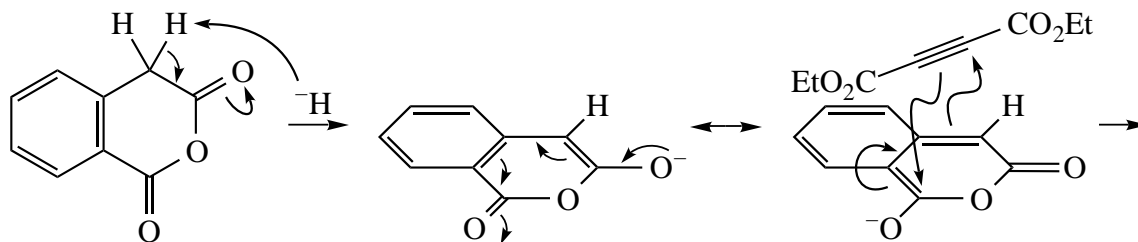
The intermediate might be made by a [2,3] sigmatropic rearrangement of an RO–SPh compound.

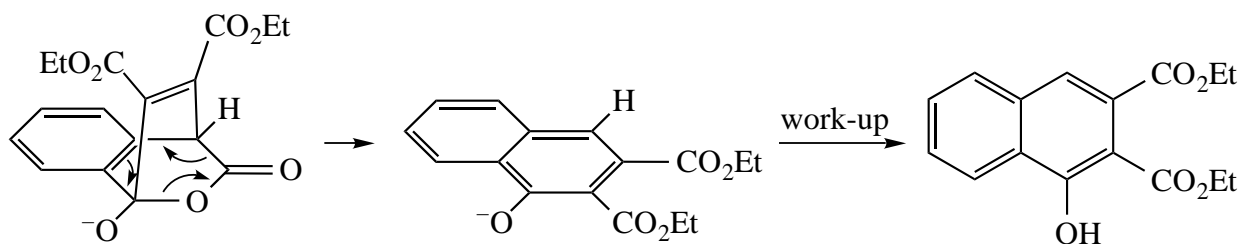


(ee) Make: C6–C7, C3–C8. Break: C5–C6, C3–O4.

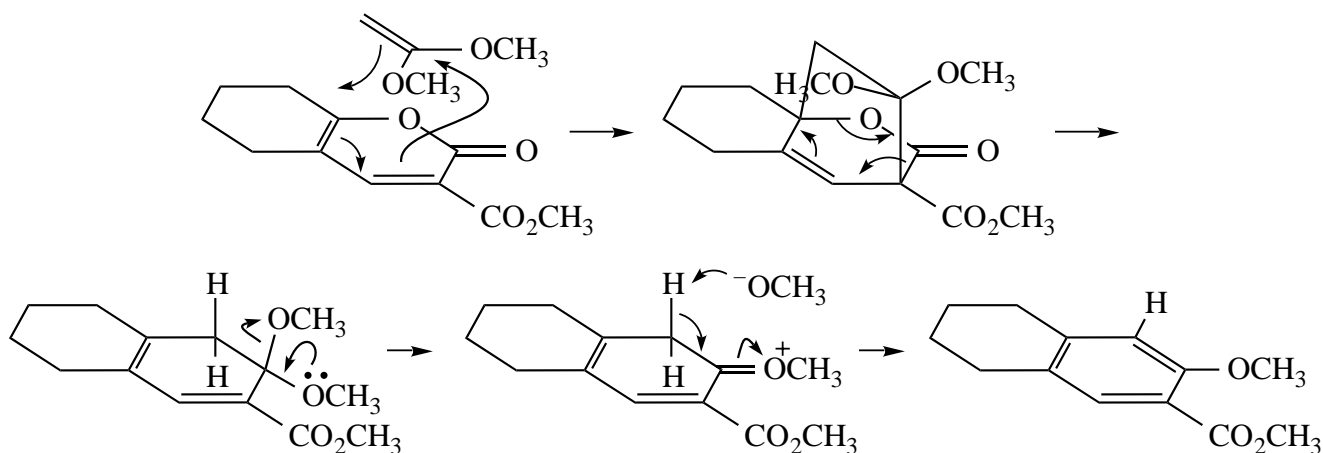


The two new bonds can be obtained by a Diels–Alder reaction. First, deprotonation gives an enolate that has an *ortho*-xylylene resonance structure. Diels–Alder reaction followed by retro-Diels–Alder reaction gives the product.

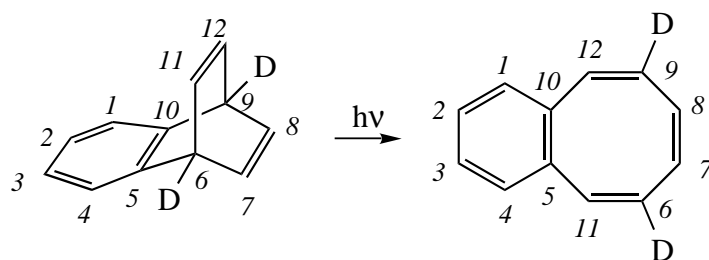




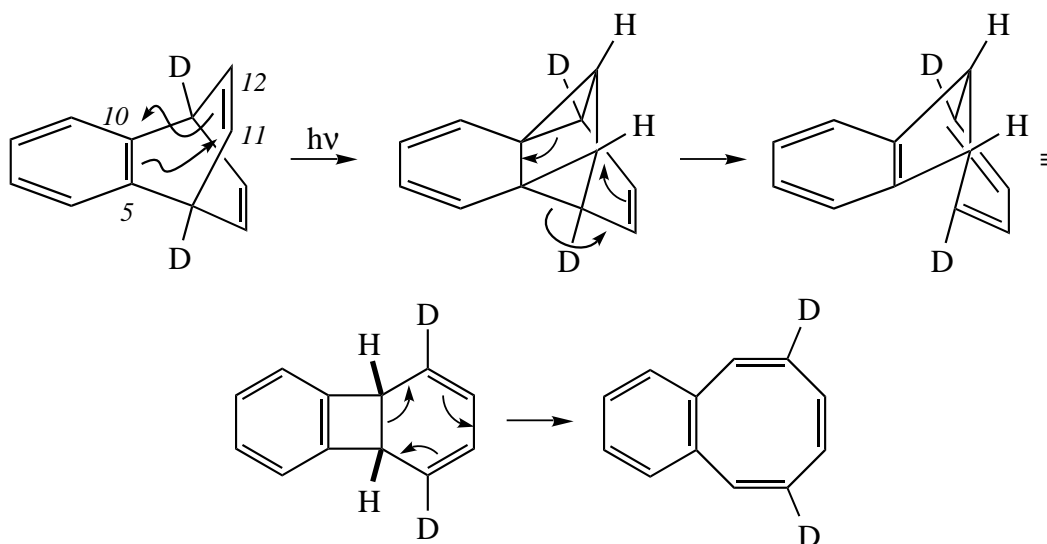
(ff) As in the previous problem, Diels–Alder reaction followed by retro-Diels–Alder reaction establishes the desired C–C bonds. Then E1 elimination of CH_3OH gives the desired product. (An E1cb mechanism for elimination is also reasonable, but less likely in the absence of strong base.)



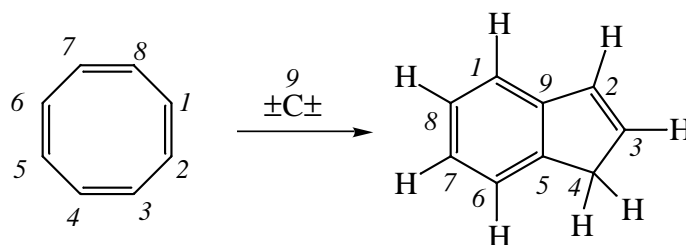
(gg) The D atoms give major clues to the numbering. Break: C5–C6, C9–C10, C11–C12. Make: C5–C11, C10–C12.



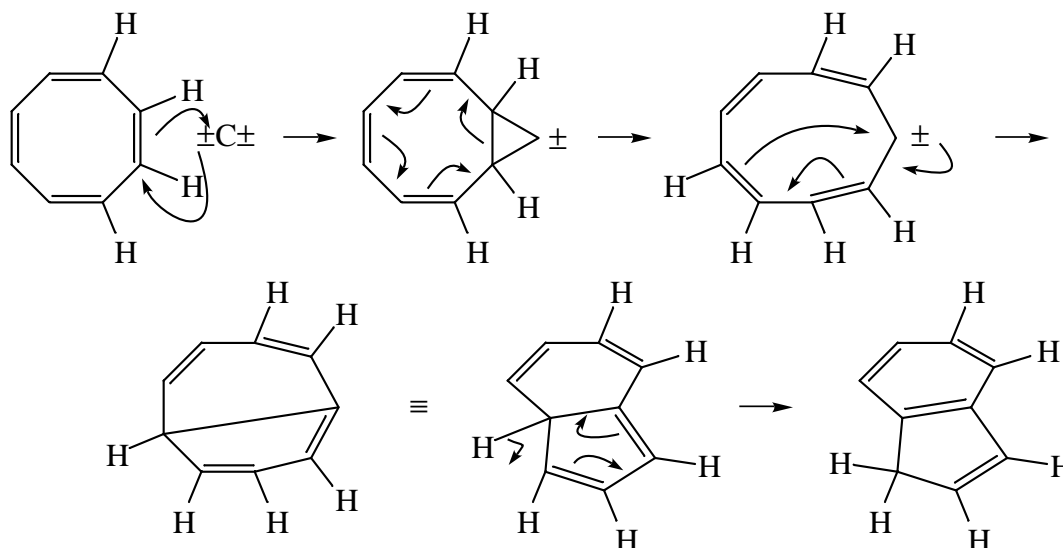
If we break the C5–C6 and C9–C10 bonds by a retro-Diels–Alder reaction first, we get two molecules of benzene. But irradiation of benzene doesn't give the observed product, so this can't be right. Instead, let's form the C5–C11 and C10–C12 bonds first by a (photochemically allowed) $[2+2]$ cycloaddition. This gives the strained polycyclic compound shown. Now the C5–C6 and C10–C9 bonds can be broken by a $[4+2]$ retro-cycloaddition (thermal, supra with respect to both components) to give the tricyclic compound. This compound can then undergo disrotatory six-electron electrocyclic ring opening (thermal) to give the observed product. Note that only the first reaction in this series requires light.



(hh) Numbering the product is difficult. Because C9 in the starting material has no H atoms, let's make it one of the C's in the product that has no H atoms. Make: C1–C9, C2–C9, C5–C9. Break: C1–C2.

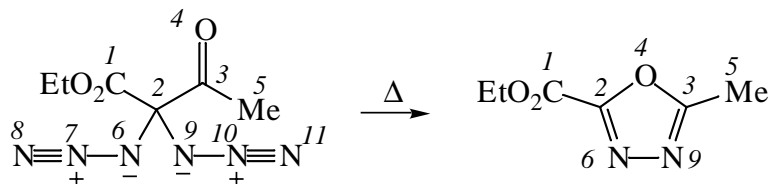


Carbenes like to do [2 + 1] cycloadditions to alkenes. Such a cycloaddition between C9 and the C1=C2 π bond gives a product which can undergo an 8-electron electrocyclic ring opening to cleave the C1–C2 bond, then a 6-electron electrocyclic ring closing to form the C5–C9 bond. All that is left to do is a [1,5] sigmatropic rearrangement to move the C5 H to C4.

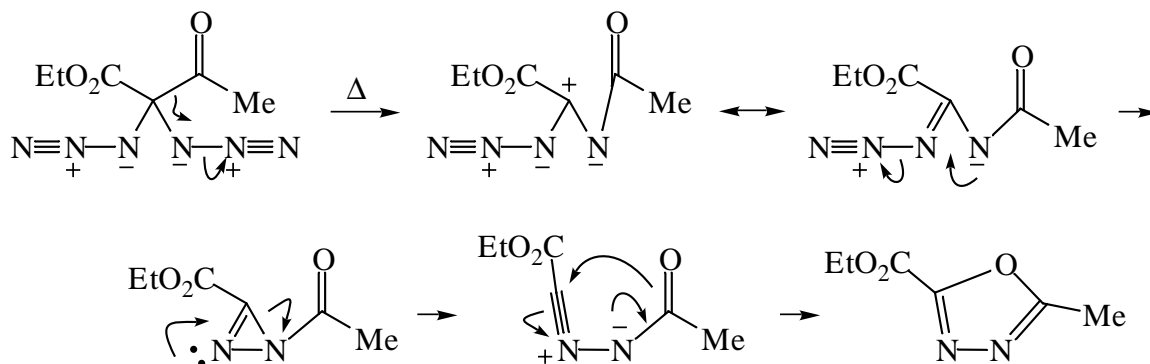


(ii) Following the instructions, we number all the N atoms. The byproducts are 2 N₂. Make: C2–O4,

C3–N9, N6–N9. Break: C2–N9, N9–N10.



The thermal reaction that azides undergo is the Wolff rearrangement (Chapter 2). In the present case, the Wolff rearrangement allows us to make the C3–N9 bond and cleave the N9–N10 bond. A resonance structure can be drawn in which N9 has a negative charge. This lone pair is used to attack N6, displacing N₂. Next, the C2–N9 bond is cleaved by a 4-electron electrocyclic ring opening to give a nitrilimine, which then undergoes a 6-electron electrocyclic ring closure to give the product.



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The Art of Writing Reasonable Organic Reaction
Mechanisms

Grossman, R.B.

2003, XVI, 360 p. 34 illus., Hardcover

ISBN: 978-0-387-95468-4