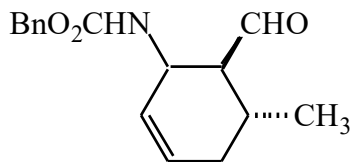# Answers to Chapter 4 Problems.

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.

| (a) Regio: RNH and CHO are 1, 2. Stereo: CHO and CH_3 remain trans; NHR is out, CHO is endo, so they are cis in product.	(b) The two CH_3 groups are both out groups, so they are cis in product.
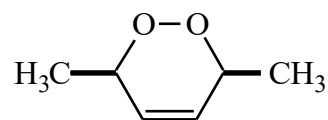
(c) Regio: C4 of diene is nucleophilic, so it makes a bond to electrophilic C of dienophile. Stereo: EtO is out, CO_2Et group is endo, so they are cis in product.
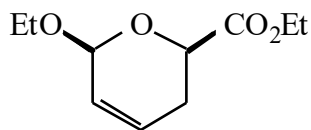

(d) Regio: CHO and $OSiMe_3$ are $1, 4$. Stereo: the CH_2CH_2 bridge is in at both ends of the diene, CHO is endo, so they are trans in product.
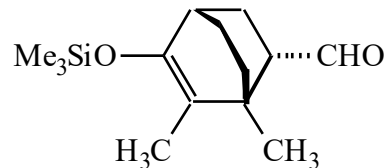

(e) Dienophile adds to less hindered face of diene. $C(sp^3)$ of five-membered ring is in, NO_2 is endo, so they are trans in product.
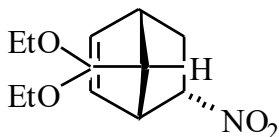

(f) Regio: Nucleophilic O adds to electrophilic β-C of unsaturated ester. Stereo: alkyl and CO_2Me groups remain trans; H is in, CO_2Me is endo, so they are trans in product.
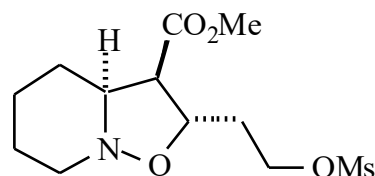

(g) Stereo: CO_2Me groups remain trans. Ar group is probably out for steric reasons, both CO_2Me are endo, so the three substituents are cis in the product.
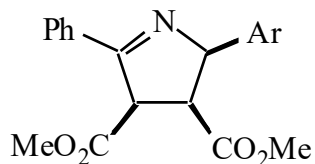
(h) The $[14 + 2]$ cycloaddition must be antarafacial with respect to one component. The two in groups of the 14-atom component become trans in the product.
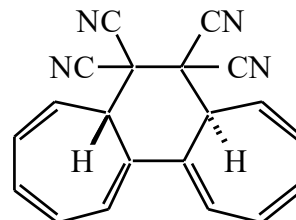
3. 1,3,5,7-Cyclononatetraene can theoretically undergo four different electrocyclic ring closures.
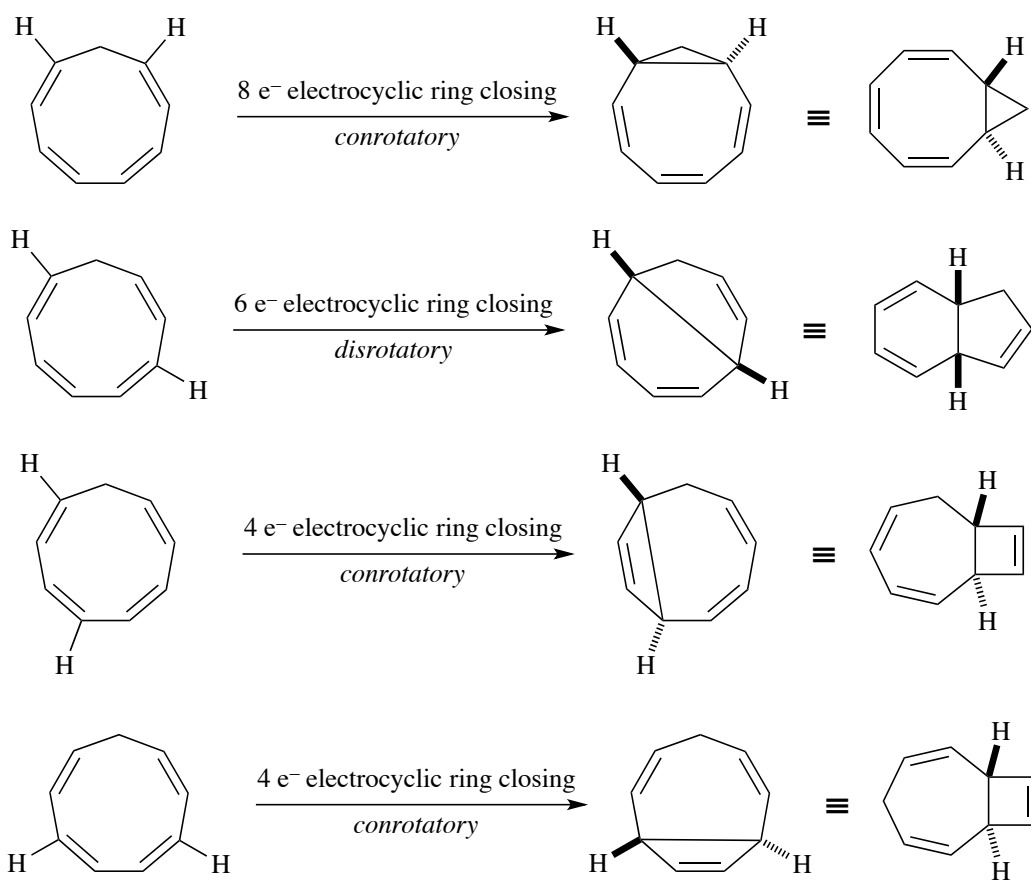

When small rings are fused to other rings, the *cis* ring fusion is almost always much more stable than the *trans* ring fusion. The opposite is true only for saturated 6–6 or larger ring systems. (Make models to confirm this.) The order of energy of the four possible products shown above is: *cis*-6–5 < both *trans*-7–4 < *trans*-8–3.
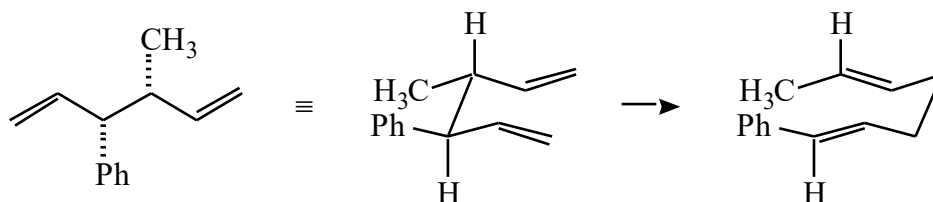
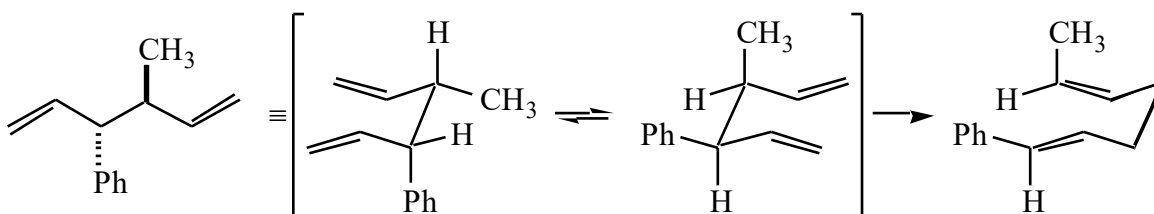4. (a) Chair TS, with the Ph equatorial.
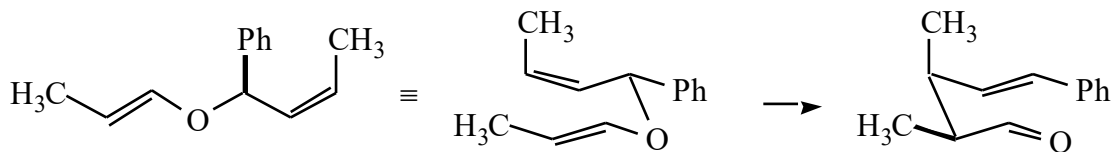
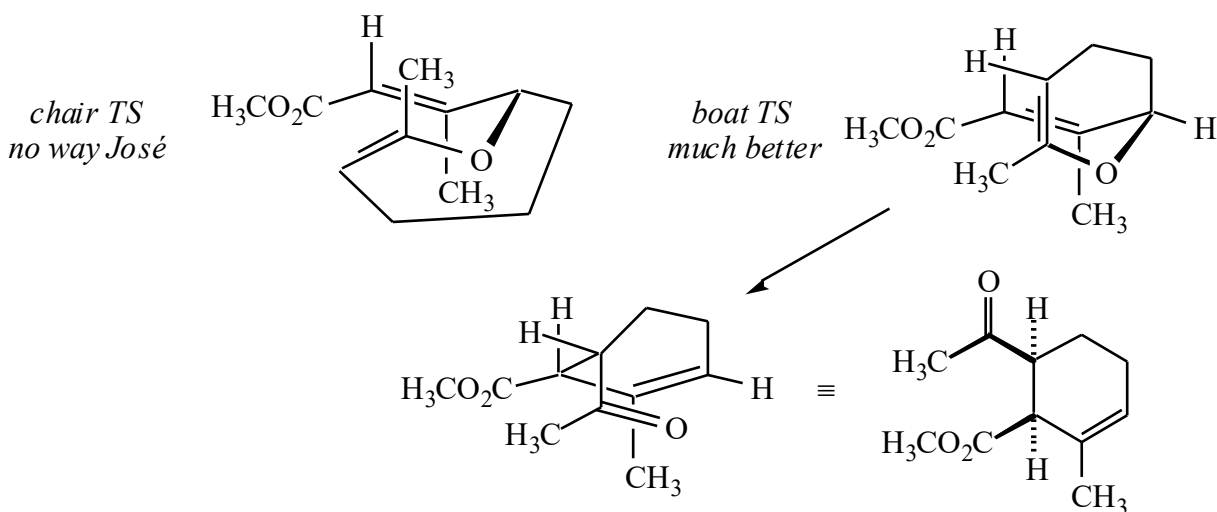(b) Chair TS, with the Ph equatorial.
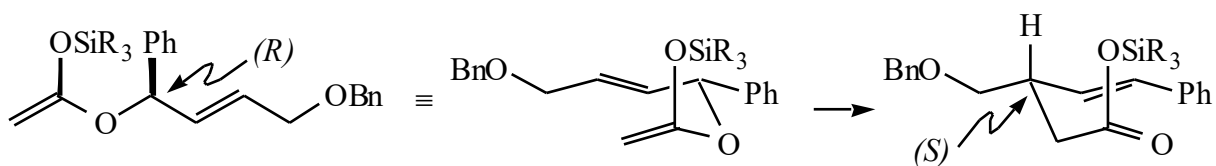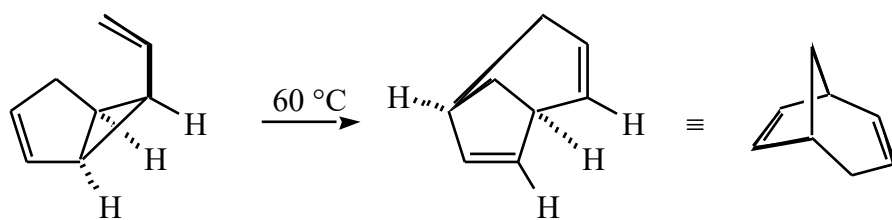
(c) Chair TS, with both substituents equatorial.

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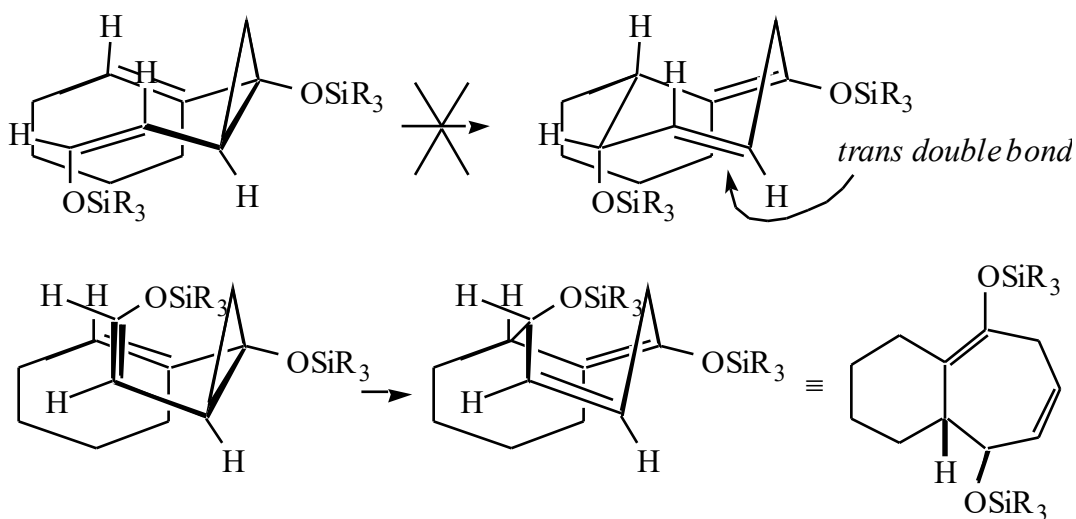

(e) A chair TS is not possible, so it goes through a boat TS.

chair TS
no way José
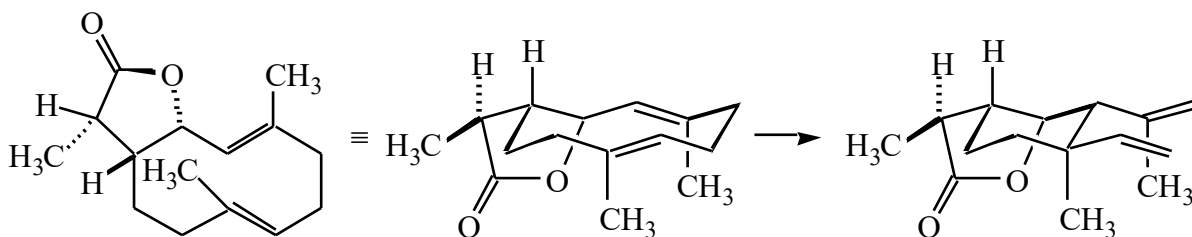
boat TS
much better

(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 OSiR$_3$ 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: $H_2C=C=\ddot{O} \leftrightarrow H_2\bar{C}-C\equiv\overset{+}{O}$. 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.
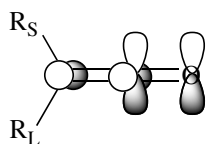
Because of the ketene's geometry, in the TS of the hetero-Diels–Alder reaction, either R_S or R_L must point directly at the diene. The lower energy approach towards R_S is chosen, and the product in which R_S points back toward the former diene portion of the compound is obtained.
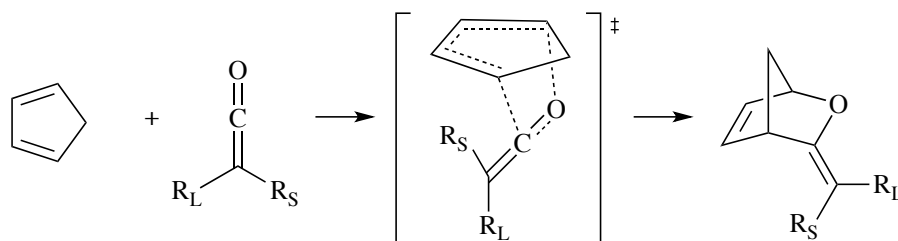
Second step: The new σ bond forms between the bottom face of the double bond on the left and the bottom face of the double bond on the right, giving the observed, less thermodynamically stable product.
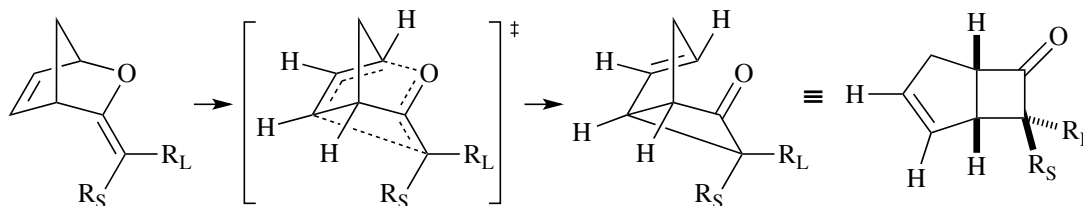
6. (a) Number the C atoms. C1, C2, C5 and C6 are clear in both starting material and product. The rest follow.
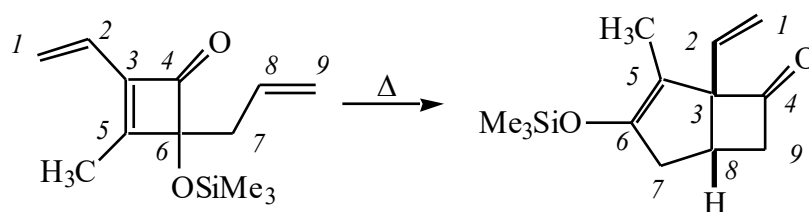
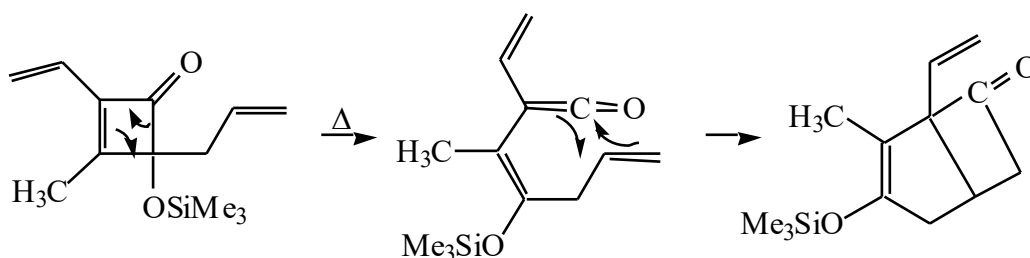We break the C4–C6 bond, and we form C3–C8 and C4–C9. The formation of the latter two bonds and the fact that we're forming a cyclobutanone suggests a [2 + 2] cycloaddition between a ketene at C3=C4=O and the C8=C9 π bond. We can generate the requisite C3=C4 π bond by electrocyclic ring opening of the cyclobutene ring in the starting material.

(b) Electrocyclic ring closing followed by base-catalyzed tautomerization (both starting material and product are bases) gives the product.
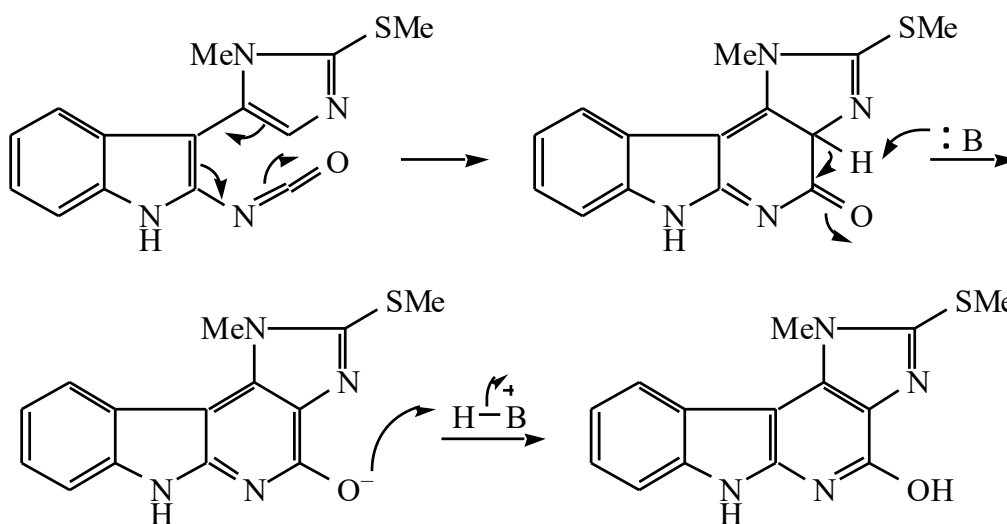
(c) Diels–Alder reaction followed by spontaneous elimination of Me₃SiO⁻ and aromatization gives the product. Loss of Me_3SiO^- occurs so readily because the Me_3Si group is a π electron withdrawer like a carbonyl group.

OSiMe₃ ... rendered as reaction schemes (structures)
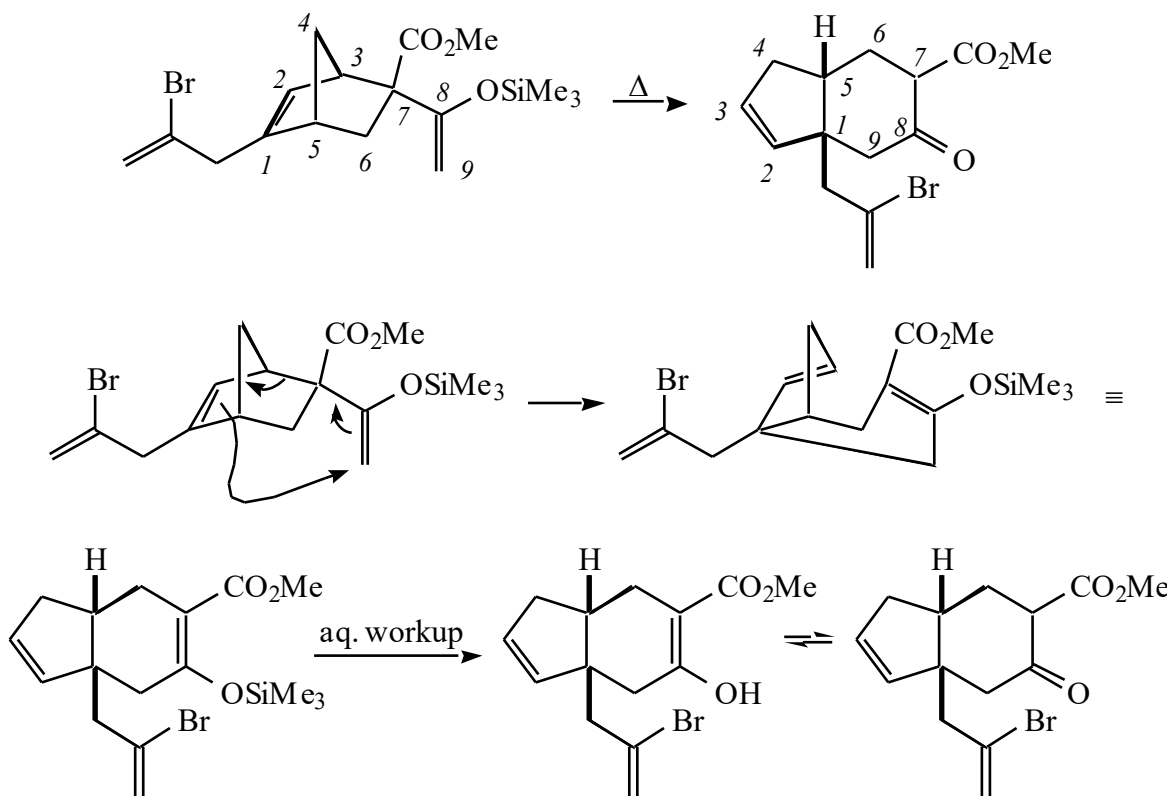
ArO, OSiMe₃, CO₂Me, Me₃SiO → ArO, OSiMe₃, CO₂Me, Me₃SiO →

ArO, CO₂Me, Me₃SiO, H H, ⁻OSiMe₃ → ArO, CO₂Me, Me₃SiO → **work-up** → ArO, CO₂Me, HO
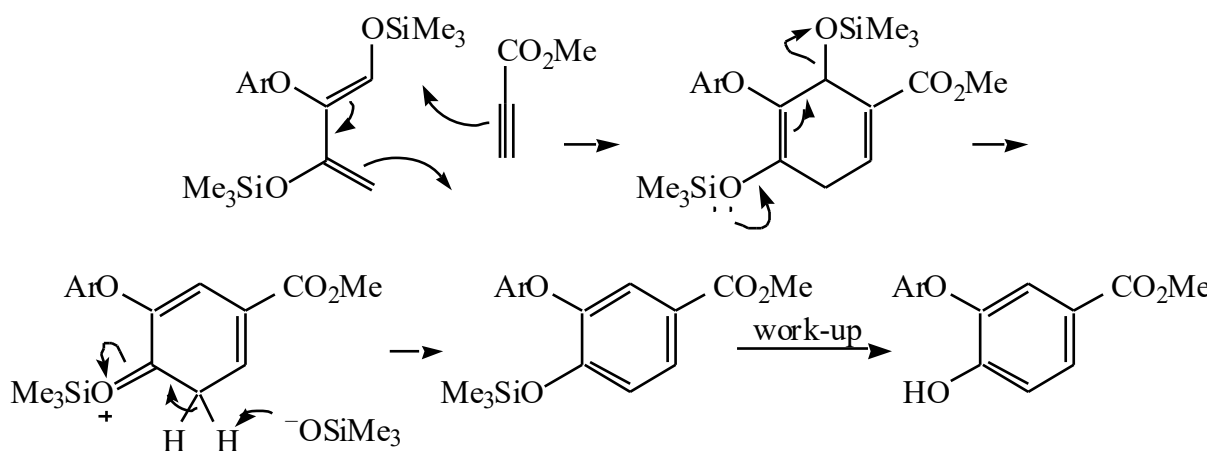
(d) The key atoms for numbering the C atoms are C1 (with the 2-bromoallyl group attached), C7 (ester group attached), and C8 (O attached). We form bond C1–C9 and break bond C3–C7. Since C3–C7 is the central bond of a 1,5-diene system terminating in C1 and C9, i.e. C1=C2–C3–C7–C8=C9, this must be a Cope rearrangement.

Br, CO₂Me, OSiMe₃ $\xrightarrow{\Delta}$ H, CO₂Me, O, Br

Br, CO₂Me, OSiMe₃ → Br, CO₂Me, OSiMe₃ ≡

H, CO₂Me, OSiMe₃, Br $\xrightarrow{\text{aq. workup}}$ H, CO₂Me, OH, Br ⇌ H, CO₂Me, O, Br

(e) Numbering the C atoms 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 atoms, 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.
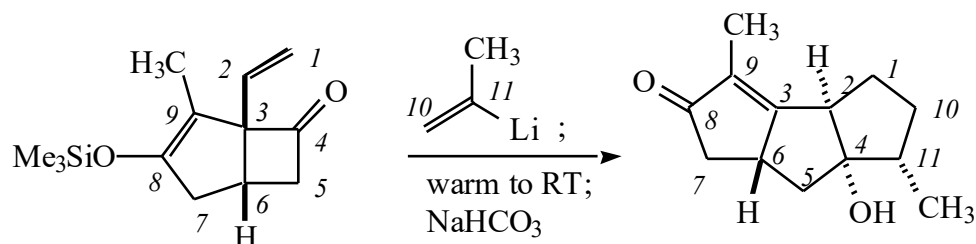

The first step is addition of C11 to C4. We still need to form C10–C1 and break C4–C3. Since we have a 1,5-diene (C11=C10–C4–C3–C2=C1), we can do an oxy-Cope rearrangement. This gives a 5-8 system in which we only have to form the C4–C2 bond. C4 is neither nucleophilic nor electrophilic, while C11 is nucleophilic (conjugation from OSiMe$_3$). Upon quenching with water, however, C4 becomes an electrophilic carbonyl C, whereupon C11 attacks with concomitant desilylation of O to give the product.
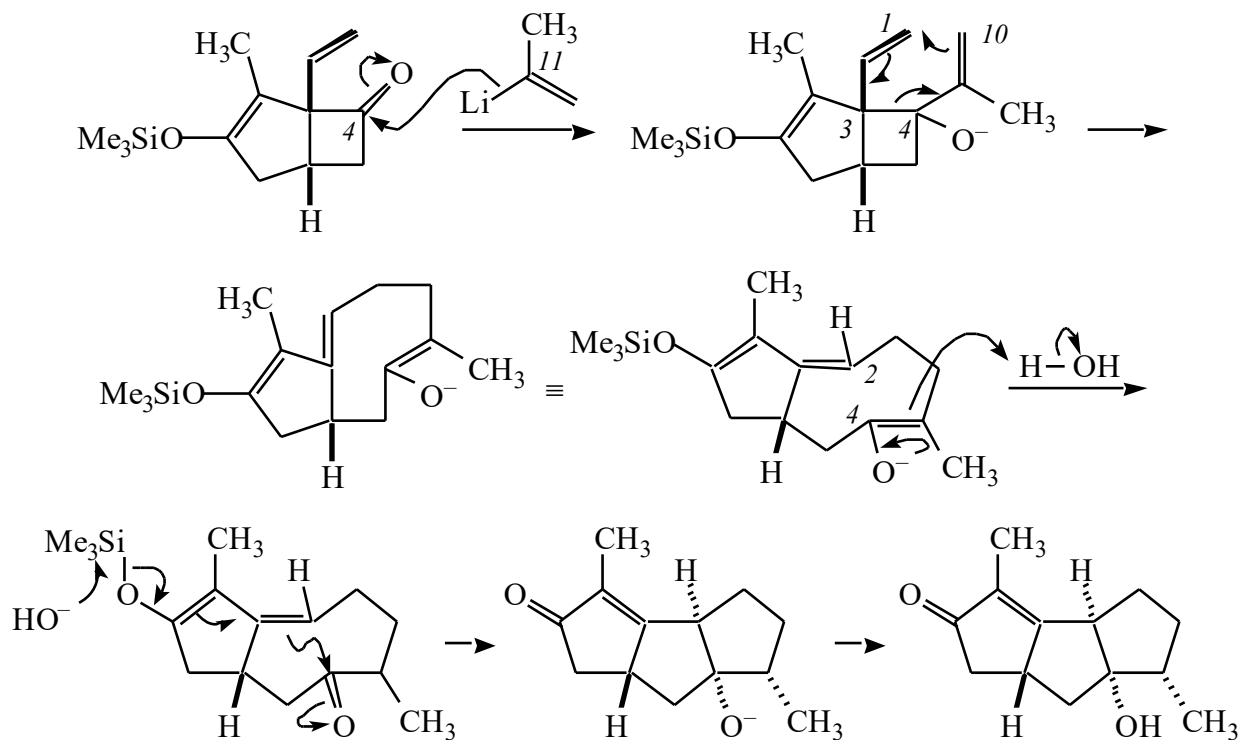
(f) It's clear that we form C4–C5 and C1–C6 bonds, and we break C1–C4. The strained C1–C4 bond can be opened by an electrocyclic ring opening to give an *o*-xylylene, which undergoes a [4 + 2] cycloaddition (can also be drawn as an [8 + 2] cycloaddition) to give the observed product.
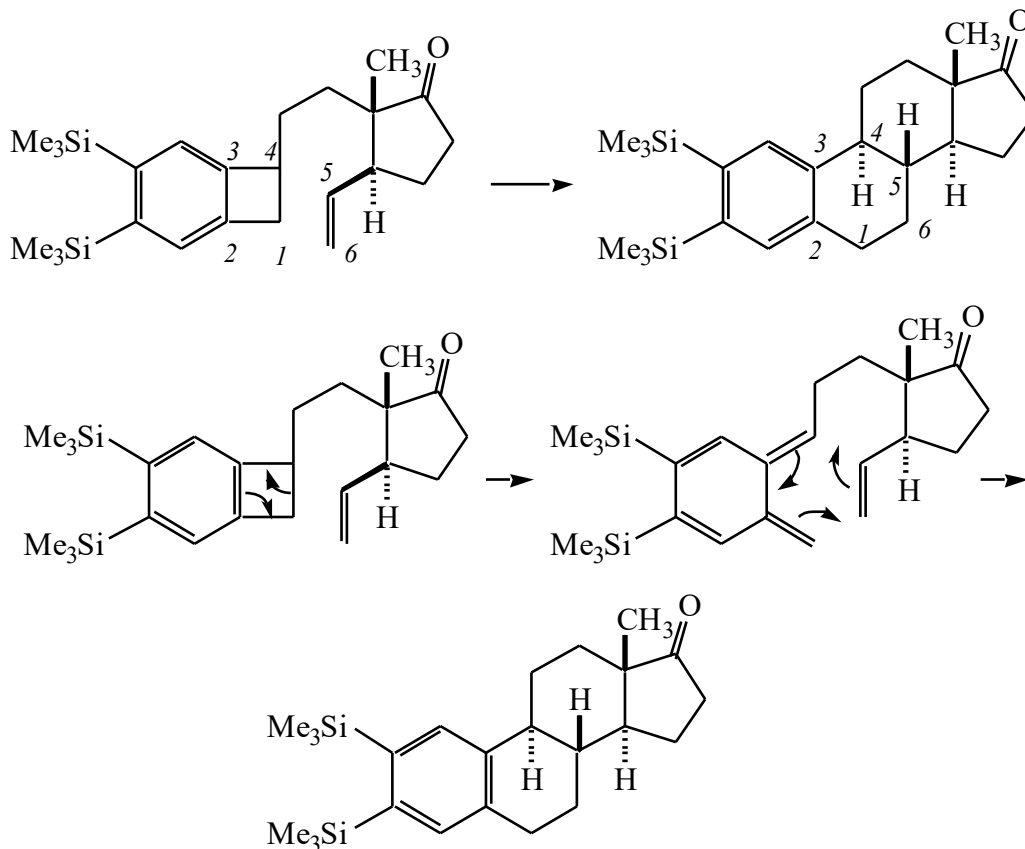

(g) We form C2–C11 and C5–C9 bonds, and we eliminate the elements of $Me_3SiO_2CCF_3$. The $ZnCl_2$ is a Lewis acid, so it coordinates to the carbonyl O and causes the cleavage of the carboxylate–C11 bond to give the nice stable allylic cation C9–C10–C11. This cation can undergo a six-electron, [4 + 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.
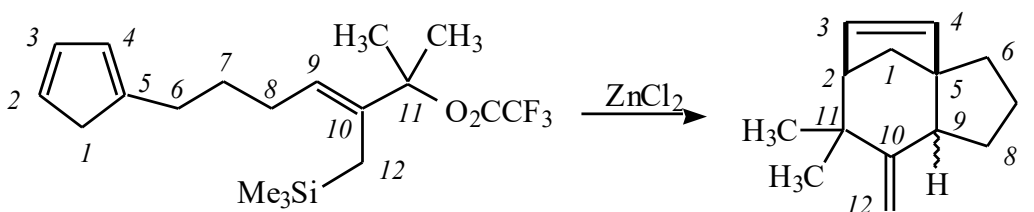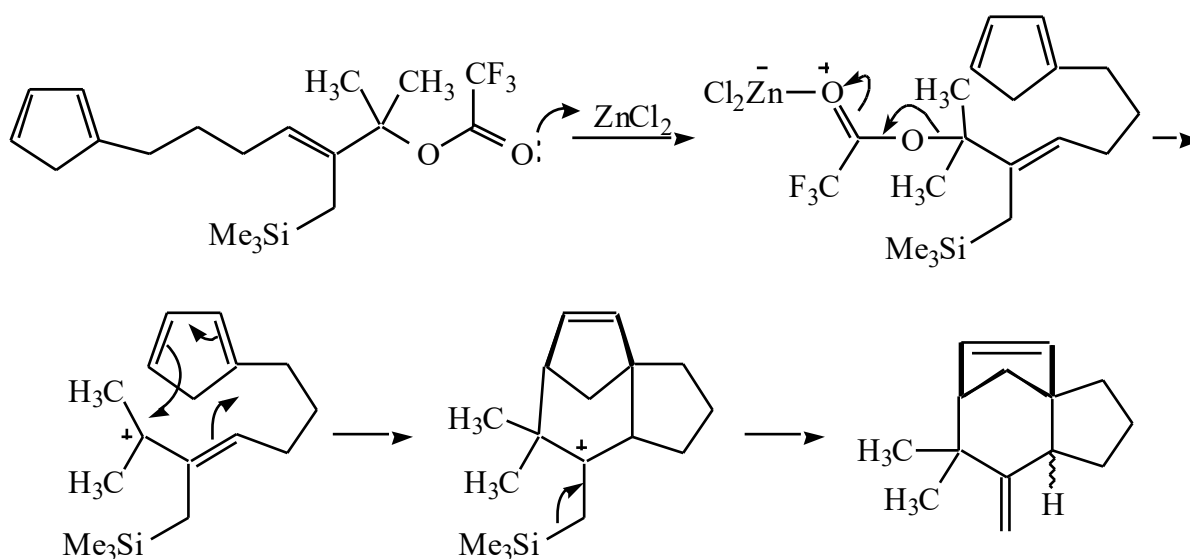
(h) The first product is formed by a hetero-ene reaction, with transfer of the H attached to S to the terminal C of styrene.
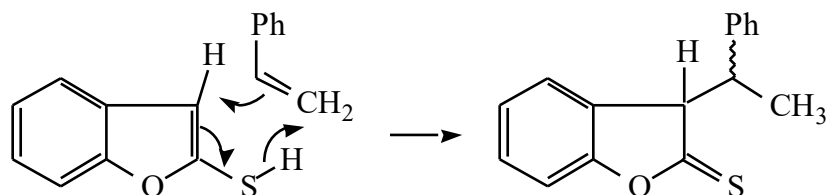

The second product must incorporate two equivalents of the enol ether. We form C3–C5, C5–C4´, and C5´–S1 bonds, and we transfer an H from S1 to C4. A hetero-ene reaction forms the C3–C5 bond and transfers the H. As for the other two bonds, since S1 and C5 are at the ends of a four-atom unit, we might 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.
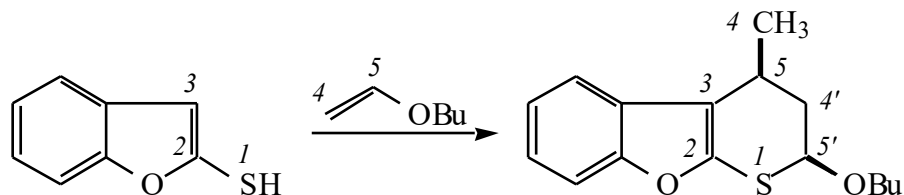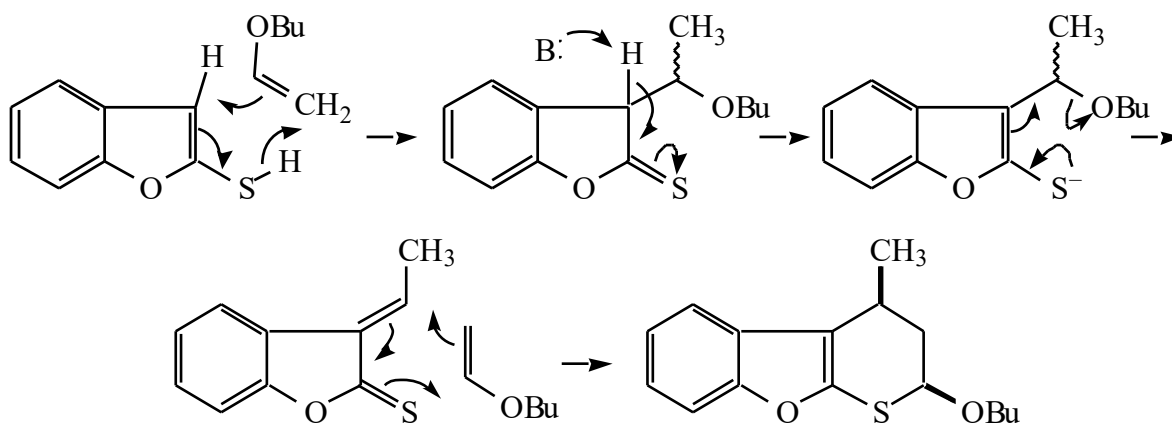
(i) We form C9–C1 and C4–C8 bonds, and we break C1–S and C4–S bonds. Since C1 and C4 are the ends of a four-carbon unit, we can expect a Diels–Alder reaction. The cyclohexene in the product should also tip you off. We can obtain the requisite diene by doing a [4 + 1] retrocycloaddition, eliminating SO_2 to give the C1=C2–C3=C4 diene. A stereospecific and endo-selective Diels–Alder reaction then gives the product.
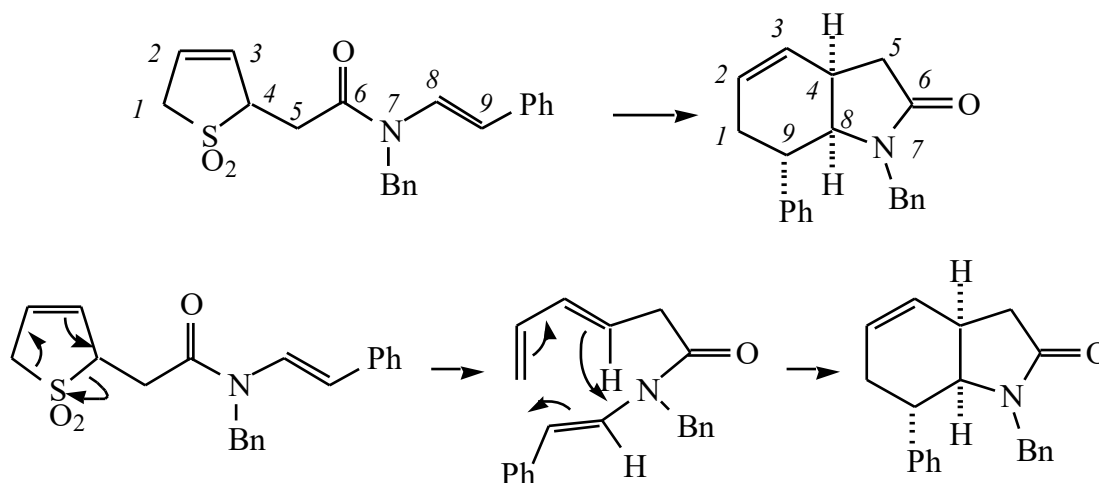

(j) When an acyl chloride is treated with Et_3N, β-elimination takes place to give a ketene. When a sulfonyl chloride is treated with Et_3N, β-elimination takes place in the same way. The intermediate undergoes [2 + 2] cycloadditions, just like ketenes do, to give the saturated four-membered ring.


analogous to ketene
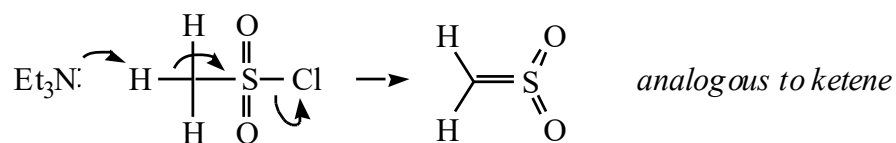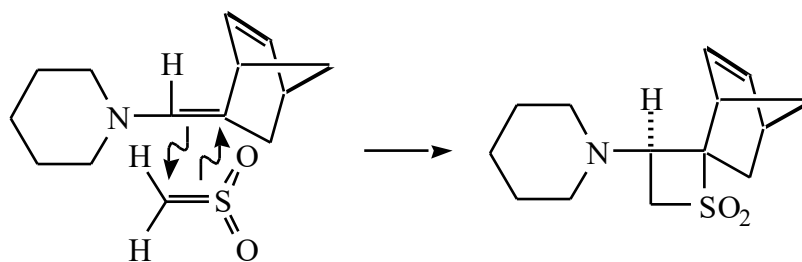
(k) The second product provides the key. It is a six-membered ring with a single double bond, probably the product of a hetero-Diels–Alder reaction. The requisite diene can be made from the starting material by a vinylogous β-elimination, with NPhth as the leaving group. The same diene intermediate can 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 C=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.
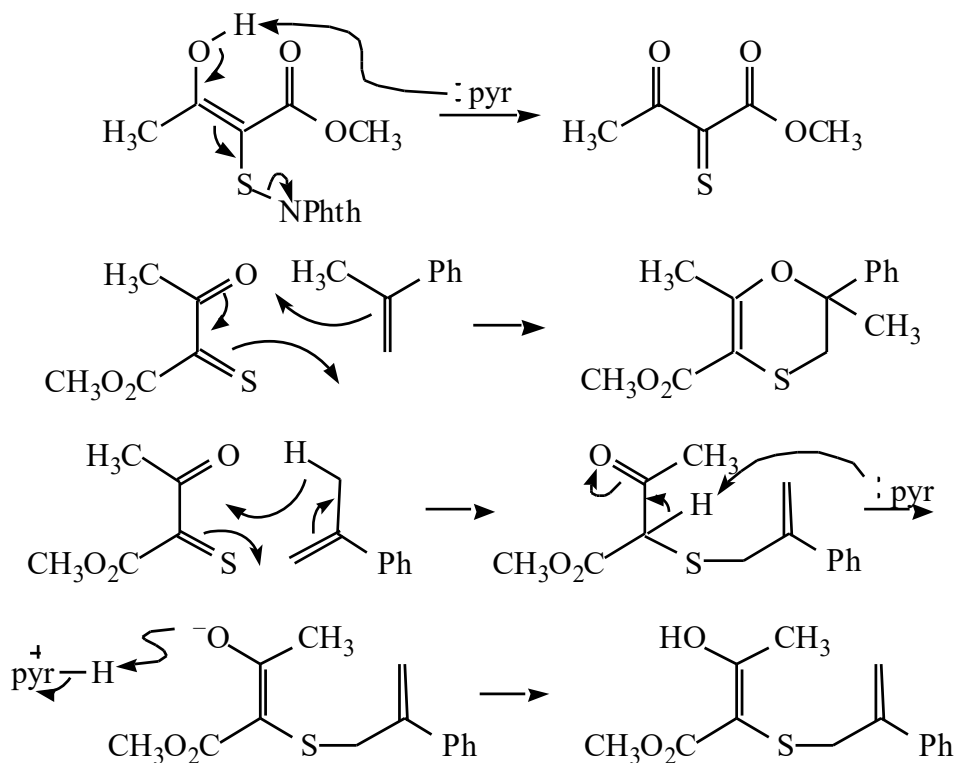
(ℓ) Whenever you see a five-membered heterocycle, think 1,3-dipolar cycloaddition. The heterocyclic rings shown can be made from an intramolecular cycloaddition of a nitrone and the alkene. The nitrone must be made from the hydroxylamine and formaldehyde.
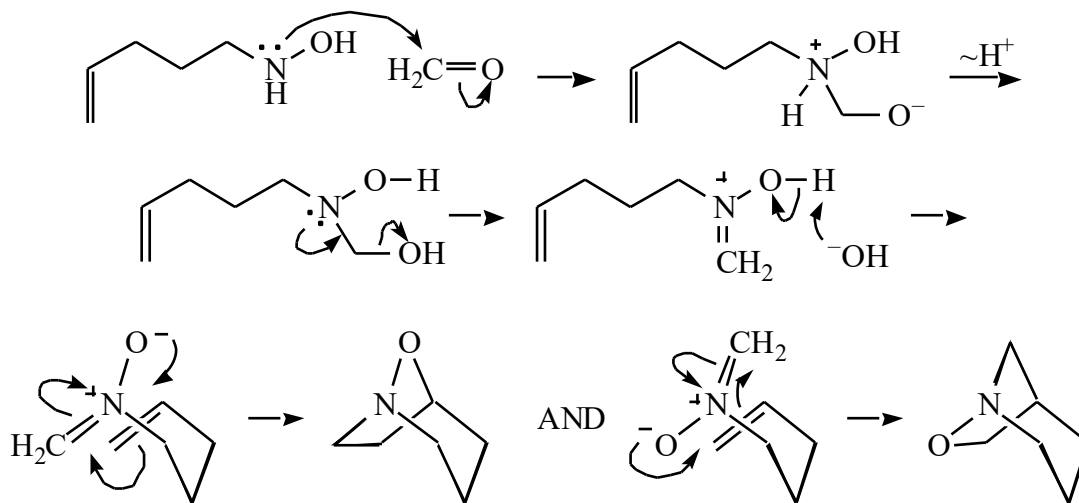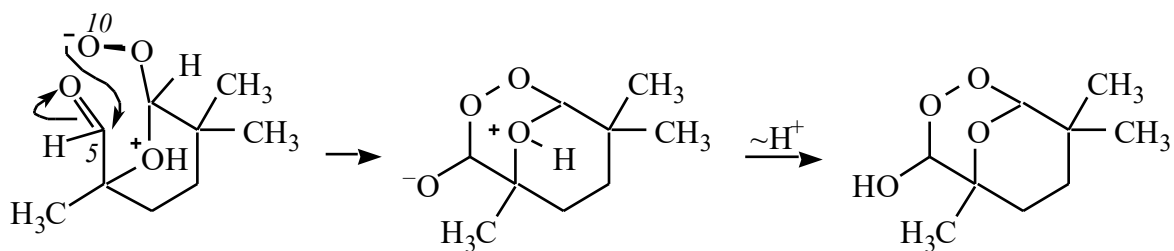
(m) Make: C5–O10, C5–O9, C6–O8, C6–O11. Break: C5–C6, C9–O10.
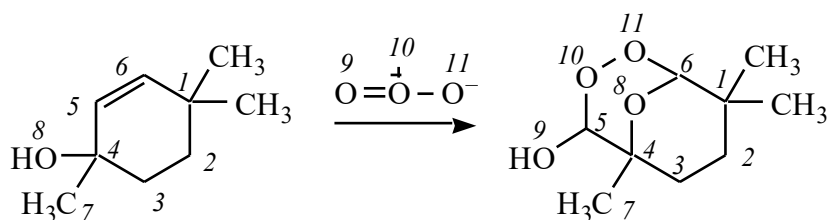
Ozone lives to do 1,3-dipolar cycloadditions. After the cycloaddition to give the C6–O11 and C5–O9 bonds, retro 1,3-dipolar cycloaddition occurs to break the C9–O10 and C5–C6 bonds. Then O8 can attack C6 and O10 can attack C5 to give the observed intermediate (after proton transfer).
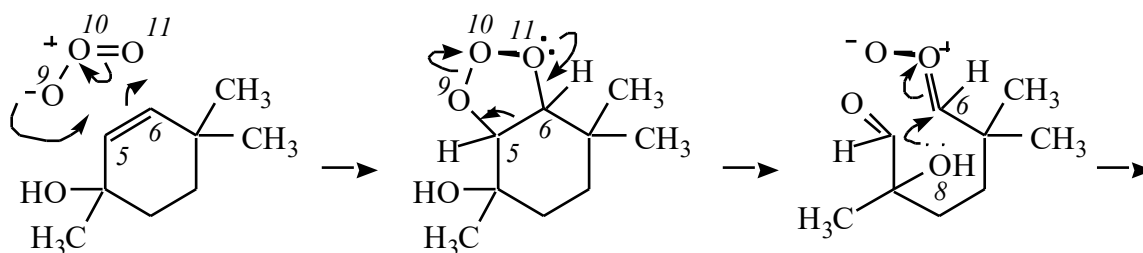
Second step. The elements of CH_4O_3 are eliminated. The most likely coproducts are H_2O and HCOOH. Make: None. Break: C4–C5, C6–O8, O10–O11. The base can deprotonate the OH on C5, and the lone pair on O can then push down to form a π bond with C5, causing the C4–C5 bond to break. The electrons keep 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.
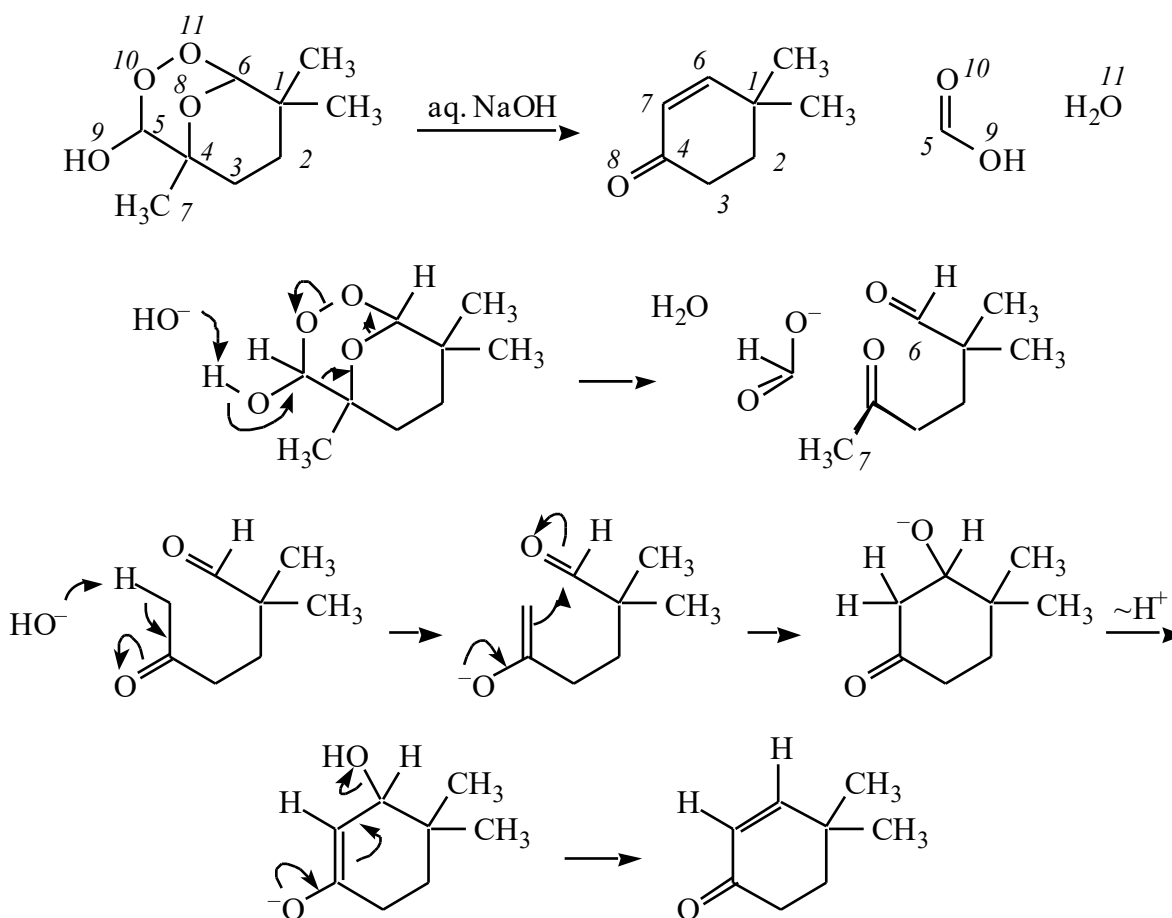
(n) Make: O9–C3. Break: C1–C3. Since O9 is nucleophilic, we must turn C3 into an electrophilic center.
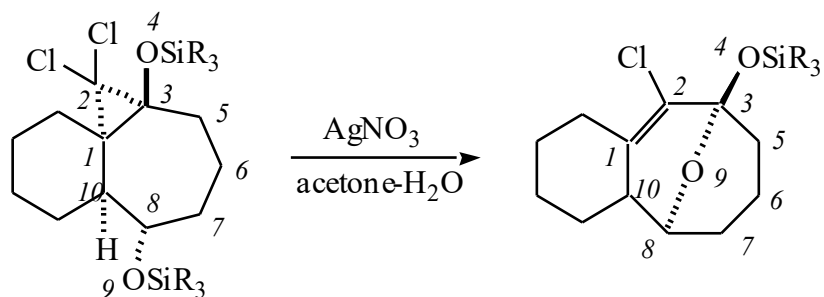
In the first step, Ag^+ promotes the departure of Cl^- to give a cyclopropyl carbocation. This undergoes two-electron disrotatory electrocyclic ring opening to give the chloroallylic cation, in which the empty orbital is localized on C1 and C3. Then O9 can add to C3; desilylation then gives the product.
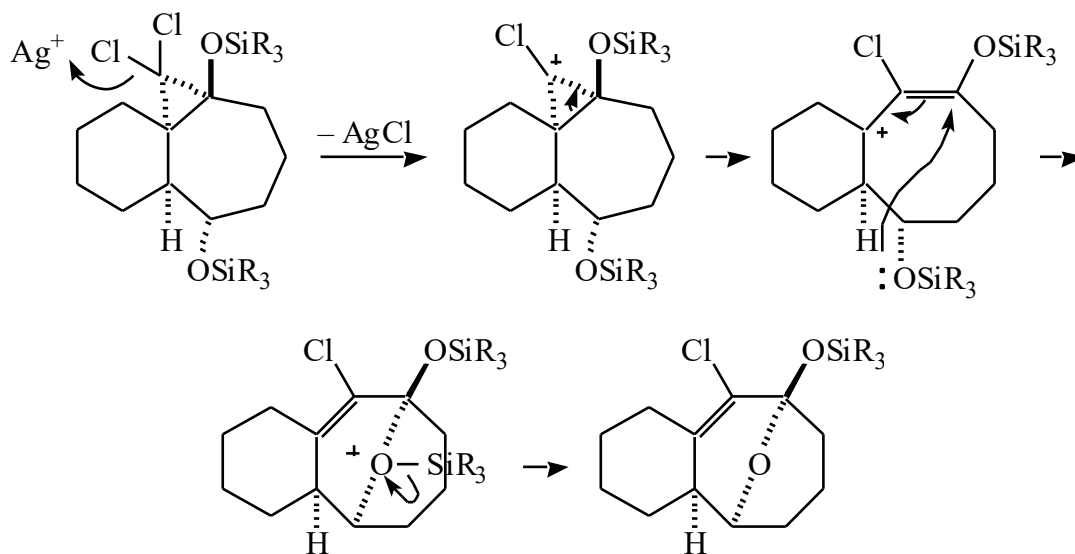

(o) The product is a 1,5-diene, specifically a γ,δ-unsaturated carbonyl, suggesting a Claisen rearrangement. Work backwards one step from the product.
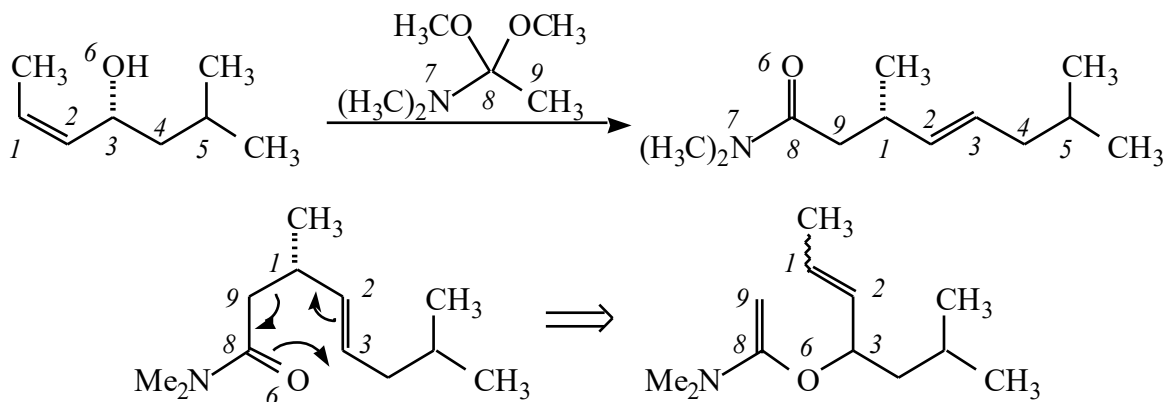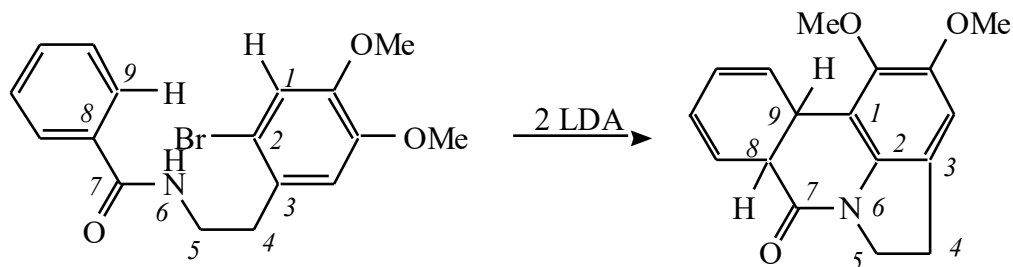
The immediate precursor retains the O6–C3 bond and would have a C8–O6 bond and a C8=C9 π bond. This calls for an S_N1 substitution at C8 to replace the C8–OMe bond with a C8–O6 bond and an E1 elimination to make the C8=C9 π bond. The overall reaction is an orthoamide Claisen rearrangement.
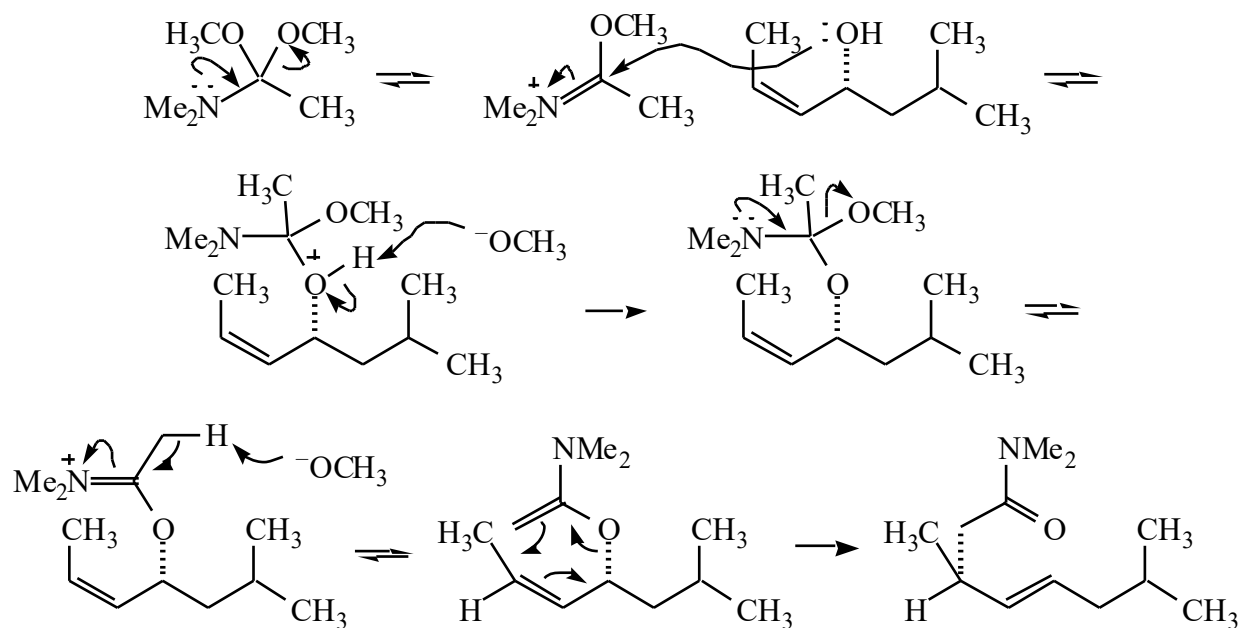
(p) Make: C1–C9, C2–N6.

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.
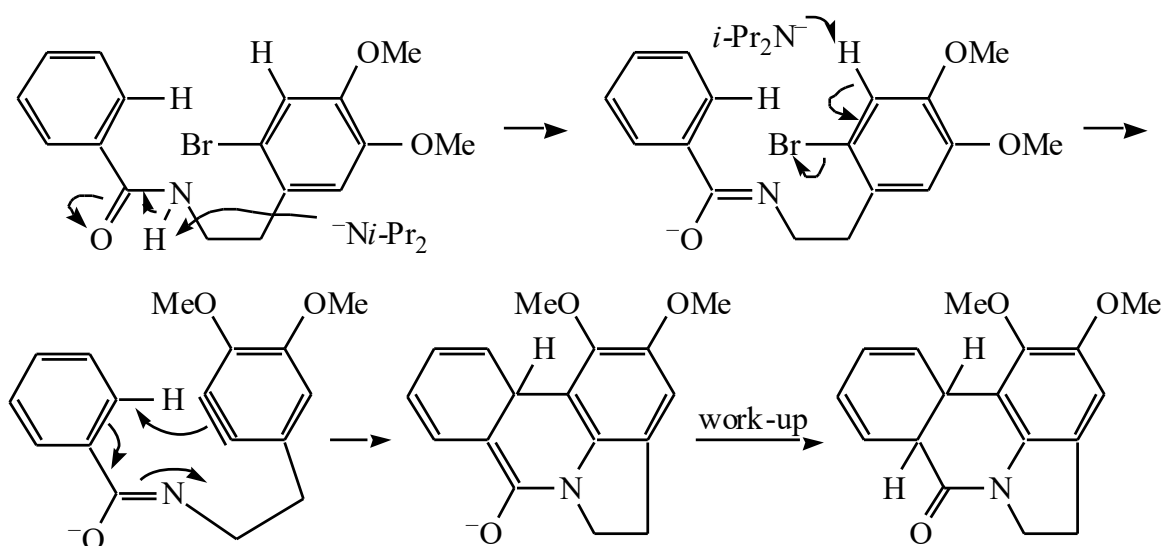

(q) We lose the elements of NH$_3$. Break: N3–N4, N4–C5. Make: C1–C6, N3–C5.
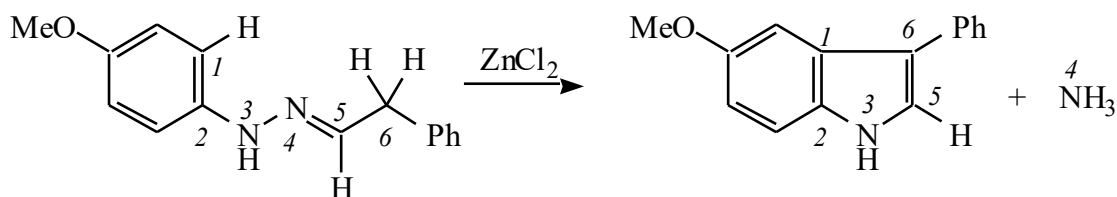

Since we are forming a σ bond at the end of a six-atom chain and breaking the σ bond in the middle, we might expect a Cope rearrangement. To do this, we must make a C5=C6 π bond. We can do this by transposing the N4=C5 π bond. This transposition converts an imine to an enamine, which is exactly analogous 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 NH$_3$ gives the indole.
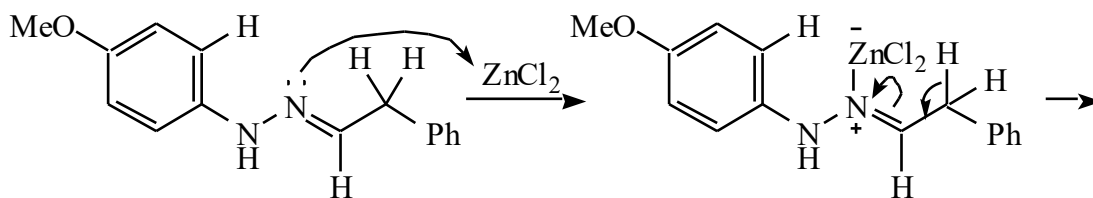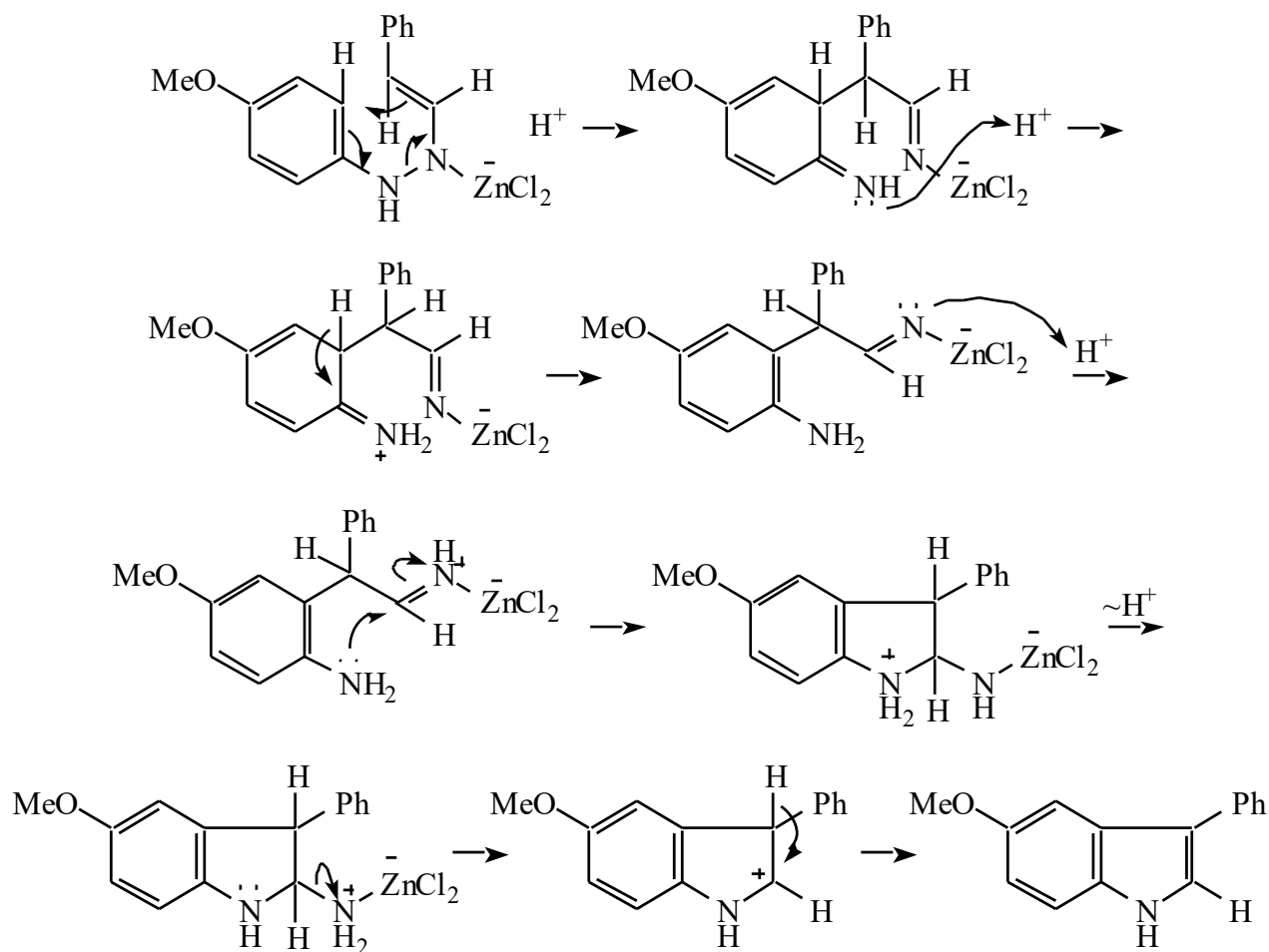
(r) Make: C2–C4, C1–C3. Break: C1–C2. Since only one equivalent of malonate is incorporated into the molecule, the other equivalent must act as a base. The migration of C1 from C2 to C3 is a 1,2-alkyl shift. Under these basic conditions, it is likely to proceed by a Favorskii mechanism. Deprotonation 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.
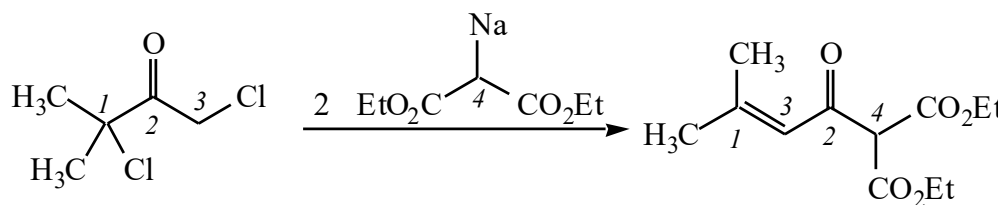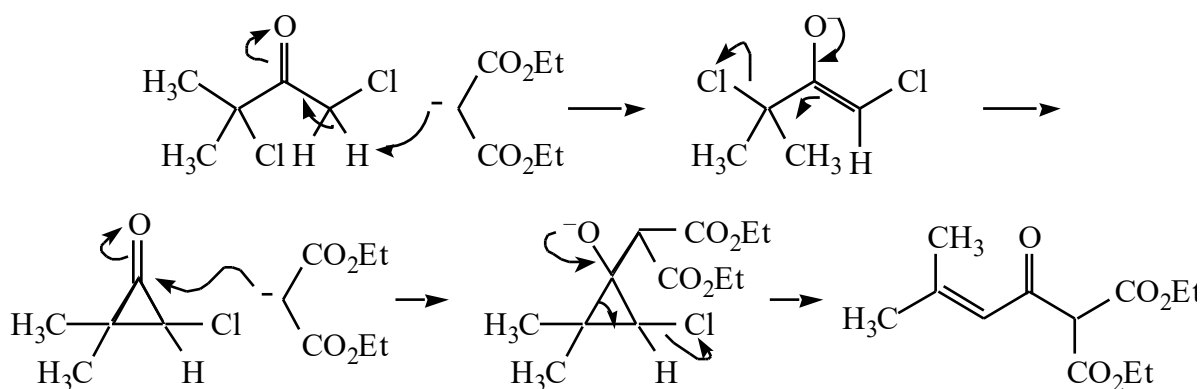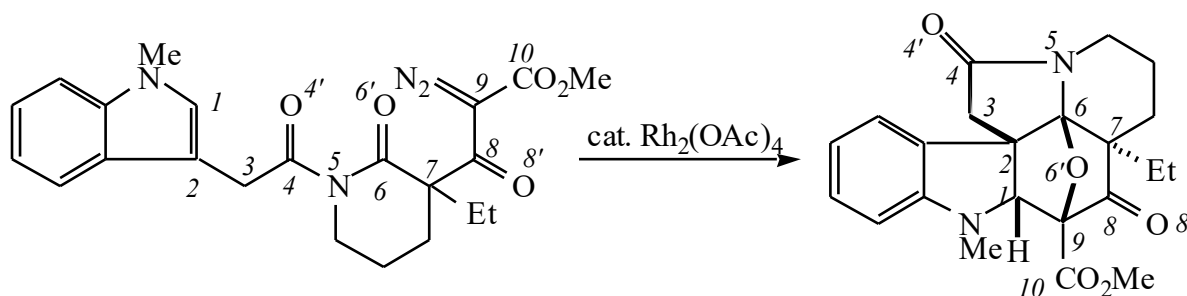
(s) The five-membered heterocycle should alert you to a 1,3-dipolar cycloaddition.
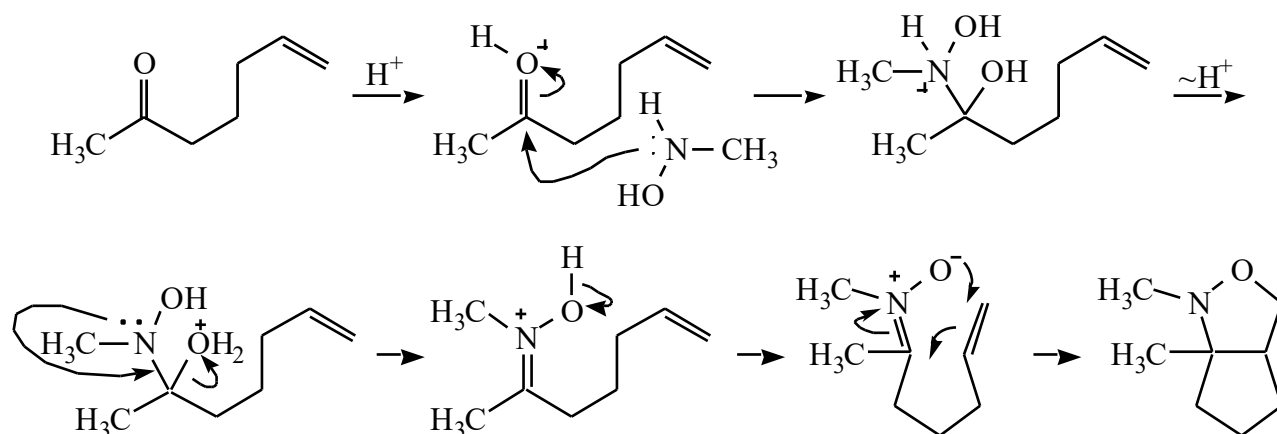
(t) Make: C1–C9, C2–C6, O6´–C9. Break: C9–N$_2$.

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, gener-

ating 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!
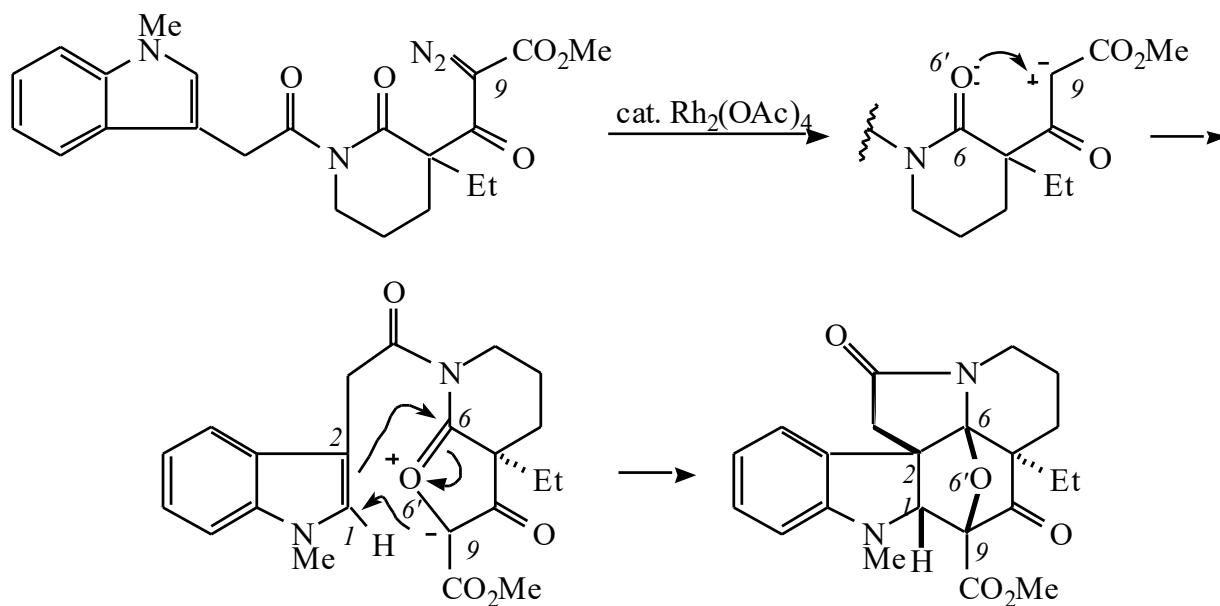

(u) The cyclobutanone should tip you off to a ketene–alkene cycloaddition. Ketenes are generally made by Et₃N-catalyzed elimination of HCl from acyl chlorides. Oxalyl chloride ClCOCOCl serves to convert the acid into an acid chloride.
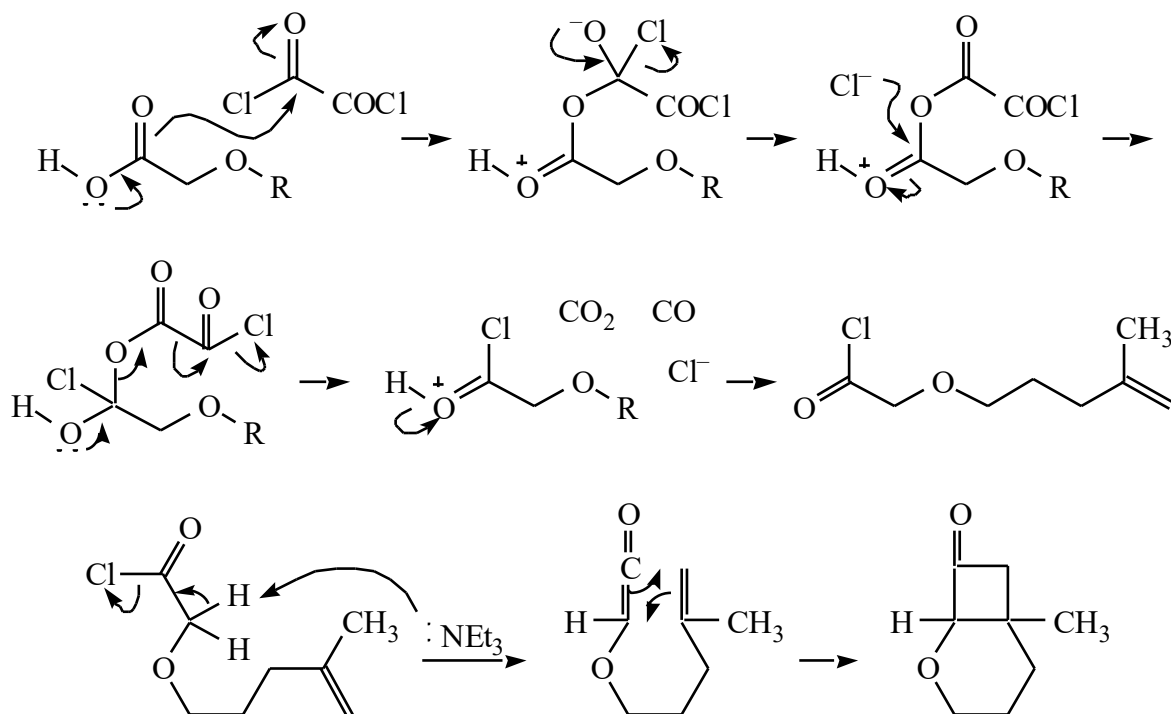
(v) Another five-membered heterocycle, another 1,3-dipolar cycloaddition. The first step is formation of the requisite 1,3-dipole, a nitrile ylide, by a two-electron electrocyclic ring opening. Then dipolar cycloaddition occurs.
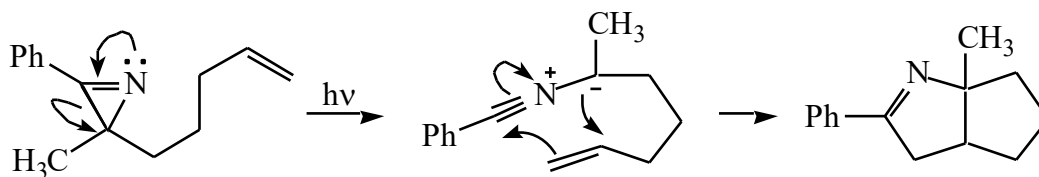

(w) *Formally* this reaction is a [2 + 2] cycloaddition. In practice, concerted [2 + 2] cycloadditions occur under thermal conditions *only* when one of the components is a ketene or has a π bond to a heavy element like P or a metal. Neither of the alkenes in this reaction fits the bill. However, one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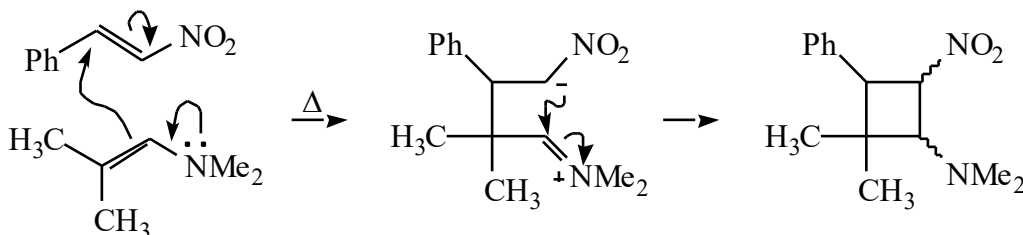

(x) The extra six C atoms must come from benzene. A photochemically allowed [2 + 2] cycloaddition between the alkyne and benzene gives an intermediate that can undergo disrotatory electrocyclic ring opening to give the observed product (after bond alternation). (Either two or three arrows can be drawn 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.
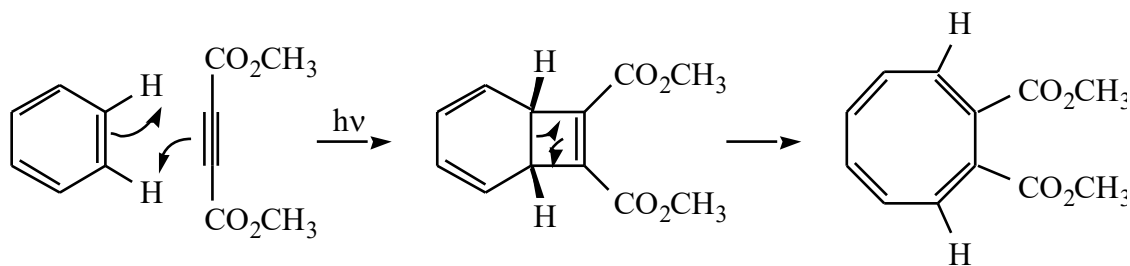
(y) The second product is clearly obtained by a hetero-Diels–Alder reaction between acrolein and isobutylene. The first product is less obvious. Two new C–C bonds are formed, and H atoms are transferred from C7 and C8 to C2 and O4. This suggests two ene reactions.
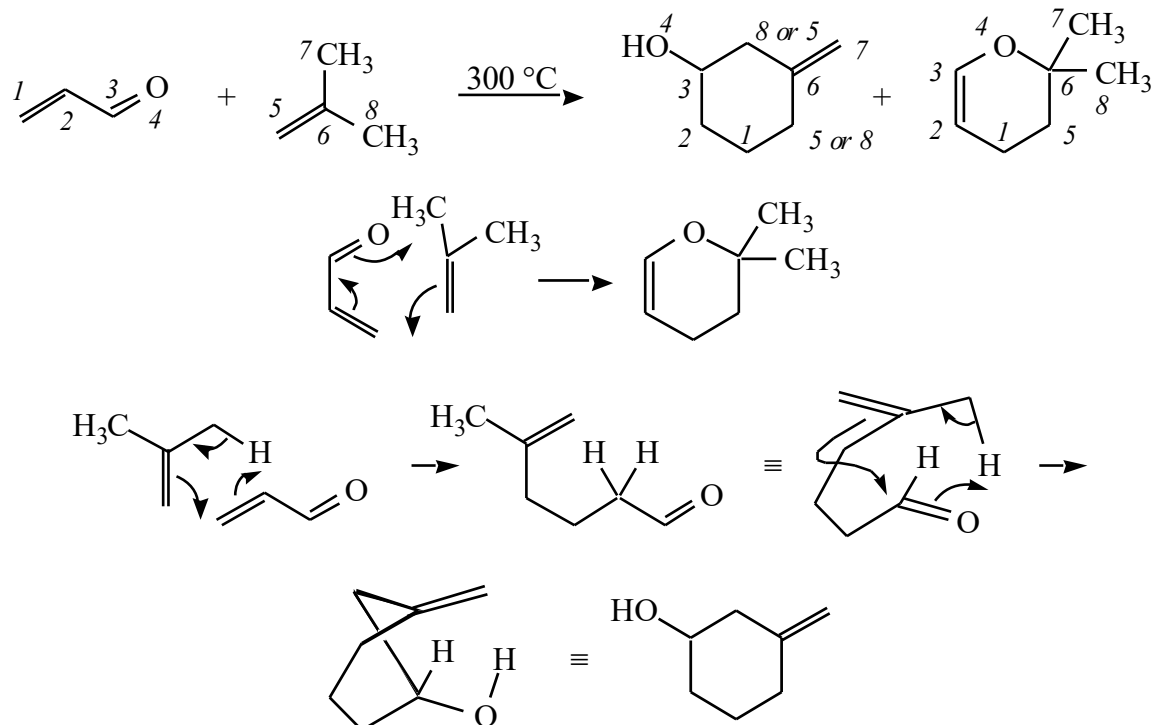

(z) Elimination of allyl alcohol occurs by an E1 mechanism. Then a Claisen rearrangement gives the product.
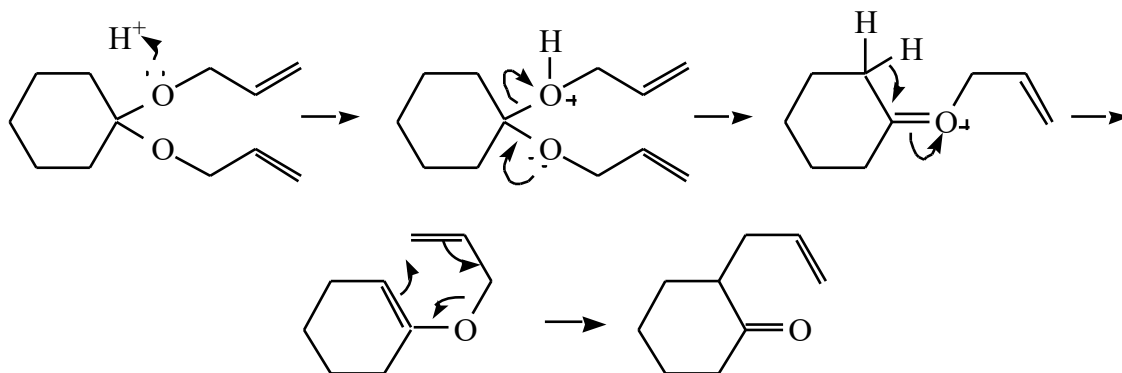

(aa) The C6 to C9 unit in the product is numbered by virtue of the two H atoms on C6. Make: C2–C9, C3–C6, C7–O11. Break: C9–S10, S10–O11.
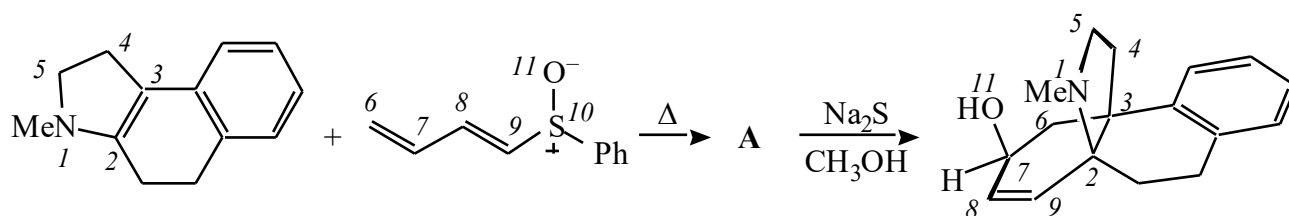
Formation of C2–C9 and C3–C6 suggests a Diels–Alder reaction, this one of the inverse electron demand flavor. The regioselectivity follows the *ortho-para* rule and the stereoselectivity is *endo*. The C7–O11 bond can now be formed and the C9–S10 bond cleaved by a [2, 3] sigmatropic rearrangement to give compound **A**. All that is left is to cleave the S10–O11 bond. Na$_2$S attacks S, with RO$^-$ acting as the leaving group, and protonation gives the final product.
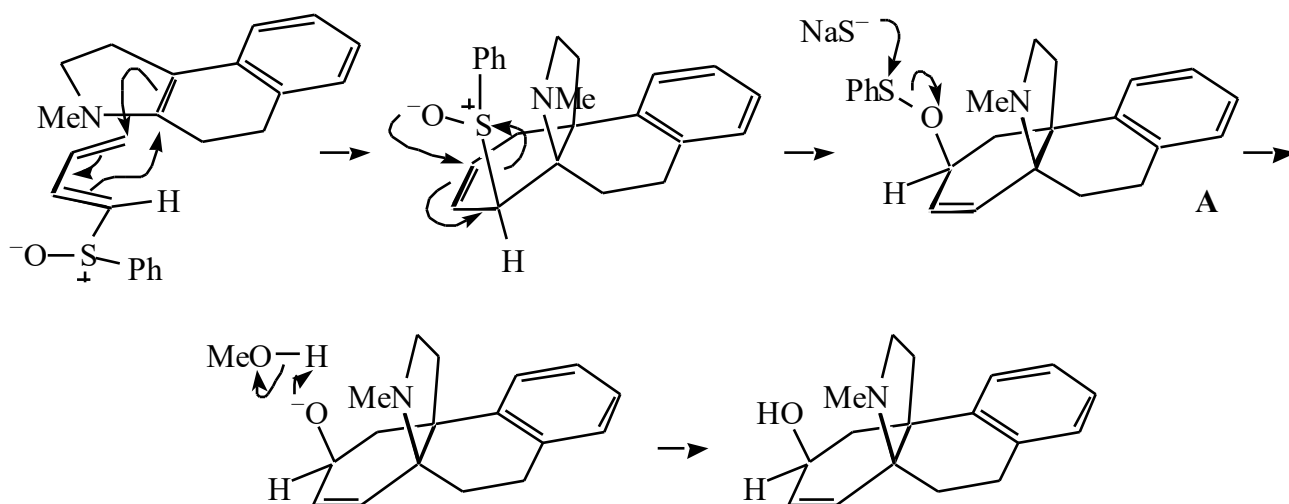

(bb) Retro Diels–Alder reaction gives off N$_2$ and an *ortho*-xylylene. With no other substrates available, this extremely reactive substance dimerizes in another Diels–Alder reaction to give the product.
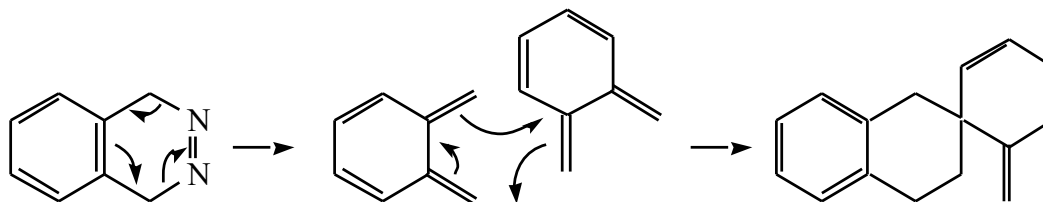

(cc) The product is formally the result of a [1, 3] sigmatropic rearrangement. ***STOP!*** [1, 3] sigmatroopic rearrangements are very rare, and they should be viewed with suspicion. They are thermally allowed only when one of the components is antarafacial. Sometimes an apparent [1, 3] shift is actually 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.
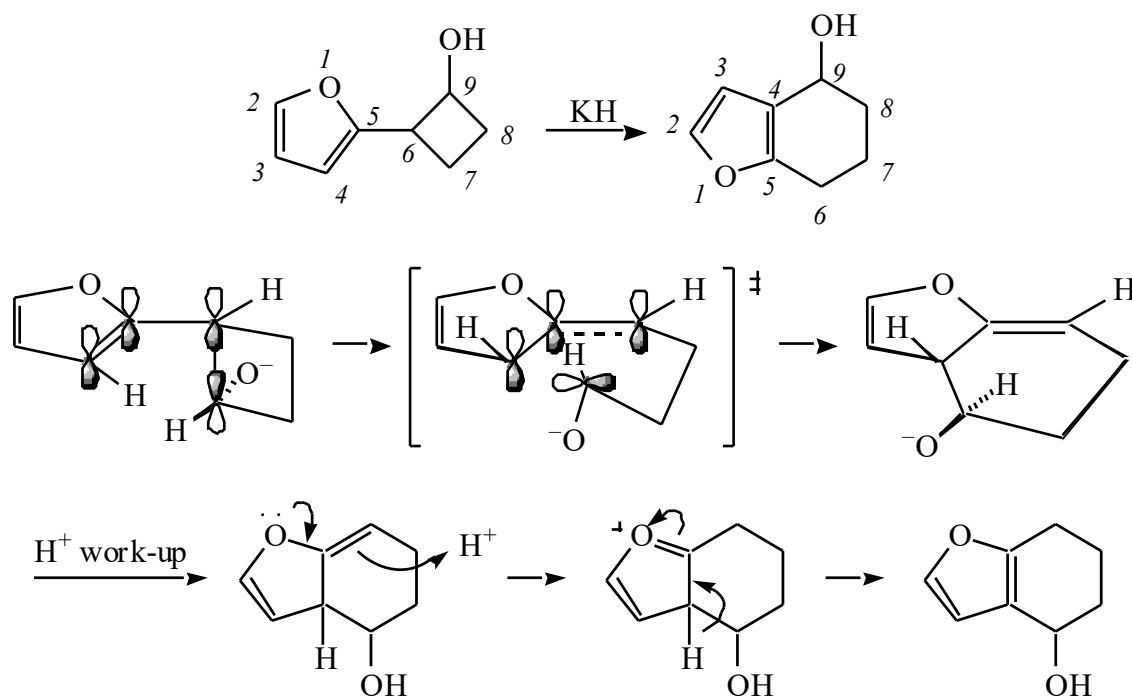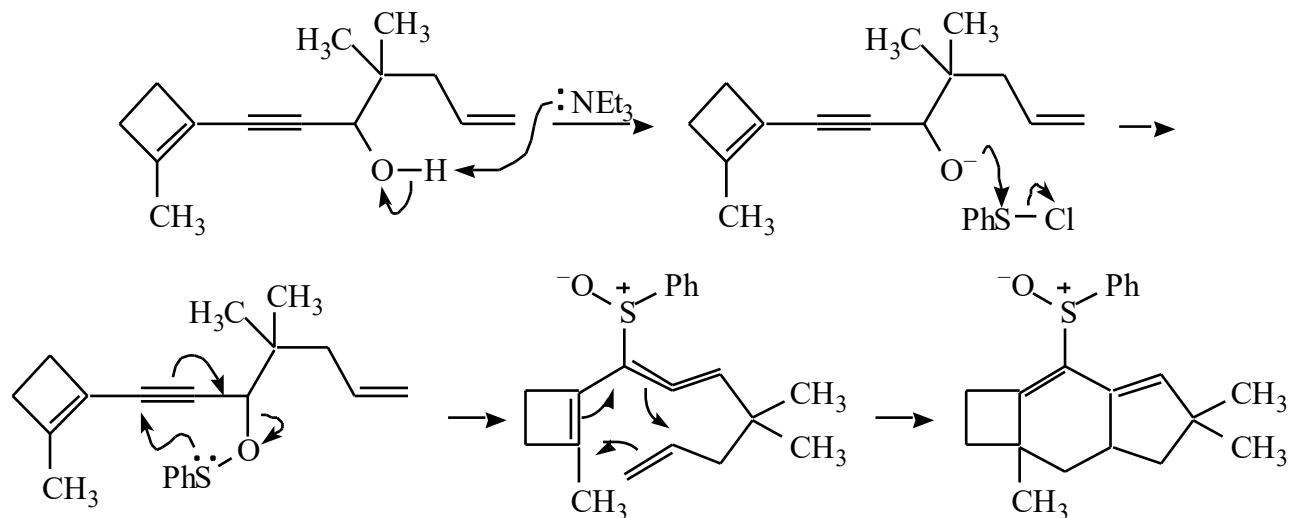

(dd) Make: C1–C11, C5–S13, C6–C10, O12–S13. Break: C7–O12, S13–Cl.
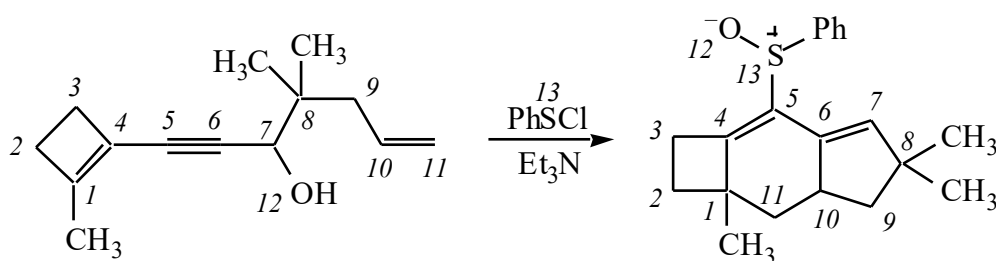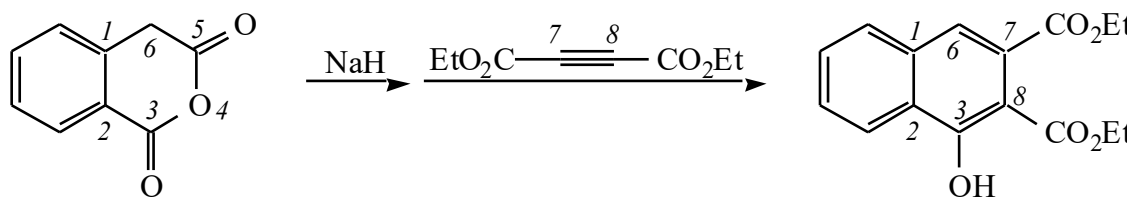

The product looks very much like the result of a Diels–Alder reaction that forms the C1–C11 and C6–C10 bonds. Work backwards one step from the product.
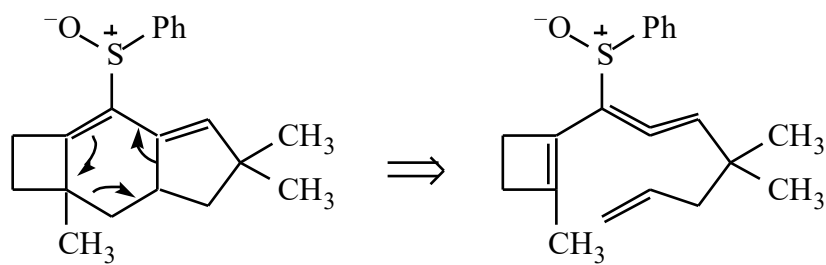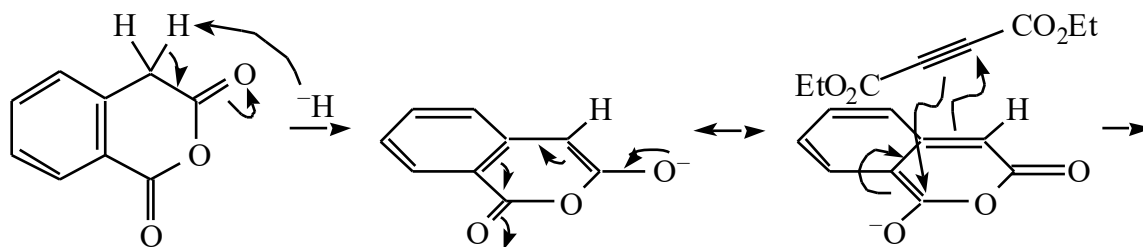
The intermediate might be made by a [2, 3] sigmatropic rearrangement of an RO–SPh compound.
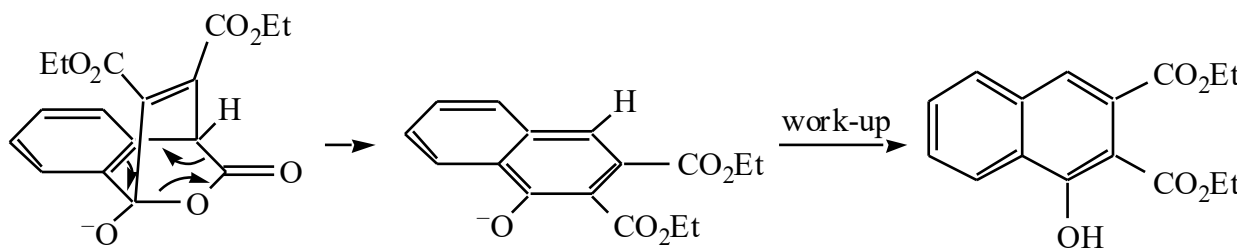


(ee) Make: C6–C7, C3–C8. Break: C5–C6, C3–O4.

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.)
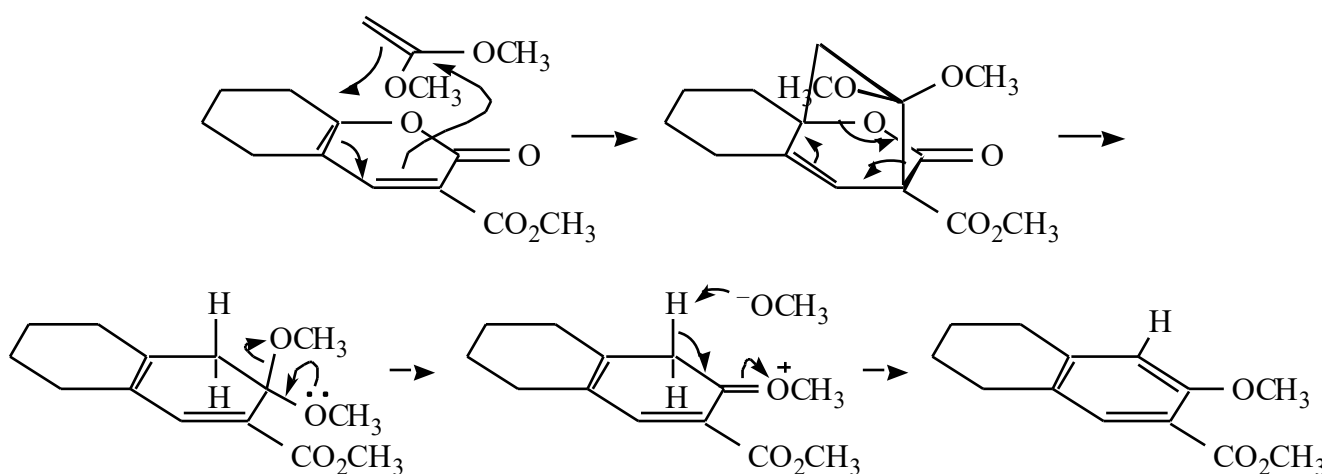

(gg) The D atoms give major clues to the numbering. Break: C5–C6, C9–C10, C11–C12. Make: C5–C11, C10–C12.
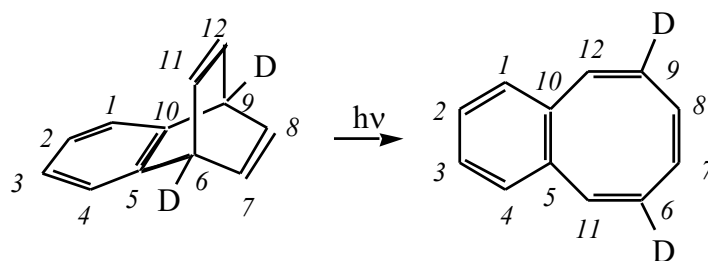
If we break the C5–C6 and C9–C10 bonds by a retro-Diels–Alder reaction first, we get two molecules of benzene. But irradiation of benzene doesn't give the observed product, so this can't be right. Instead, let's form the C5–C11 and C10–C12 bonds first by a (photochemically allowed) [2 + 2] cycloaddition. This gives the strained polycyclic compound shown. Now the C5–C6 and C10–C9 bonds can be broken

by a [4 + 2] retrocycloaddition (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.
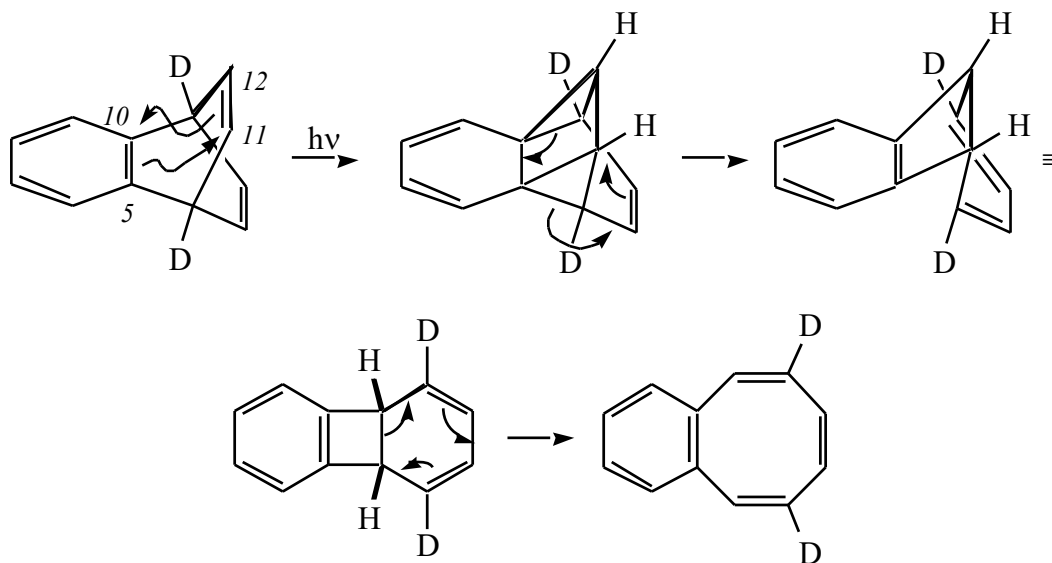
(hh) In this particular question, numbering is unnecessary. The mechanism begins with a [2 + 1] cycloaddition of the C atom to a π bond. The resulting bicyclic cyclopropylidene compound undergoes a four-electron electrocyclic ring opening to give a 9-membered cyclic allene, which then undergoes a six-electron electrocyclic ring closing to give the fused 5–6 ring system. Finally, a [1, 5] sigmatropic rearrangement occurs to give indene.
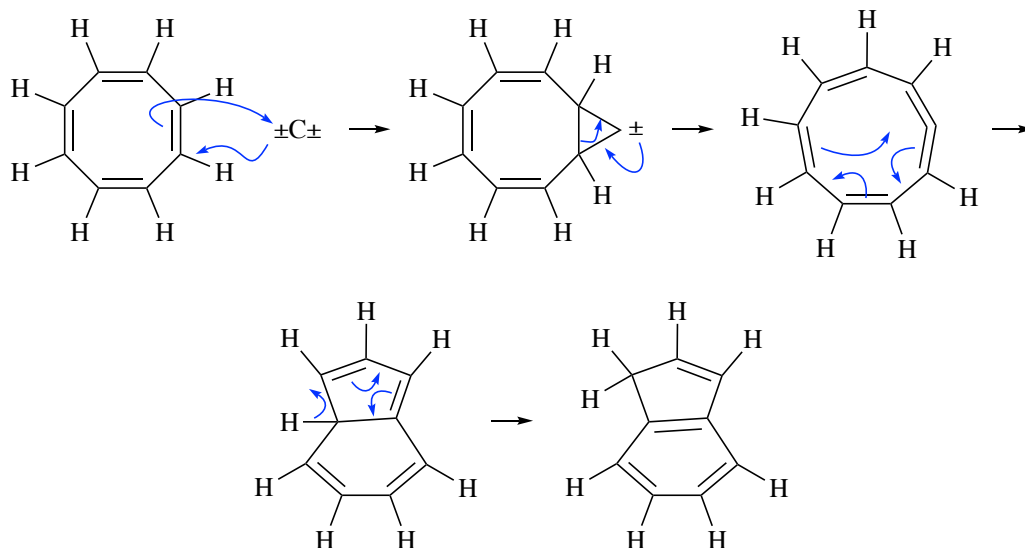
(ii) Make: C2–O3, C4–N9, N6–N9. Break: C2–C4, C2–N9, N6–N7, N9–N10.
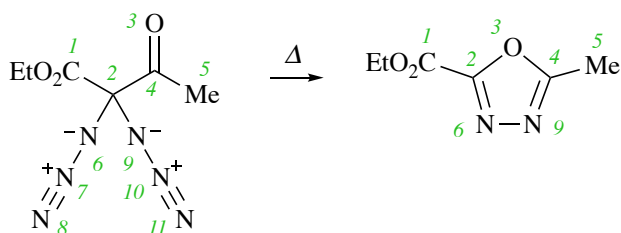
It seems pretty clear that the first step must involve cleavage of one of the N–N$_2$ bonds, but we can't leave N electron-deficient, so loss of N$_2$ can be accompanied by 1,2-shift of the acetyl group to break the C2–C4 bond and form the C4–N9 bond. Next, the N6–N9 bond can form by four-electron electrocyclic ring closing with expulsion of a second equivalent of N$_2$ to give a diazirine. Four-electron electrocyclic ring opening breaks the C2–N9 bond, and six-electron electrocyclic ring closing forms the C2–O3 bond and gives the product.
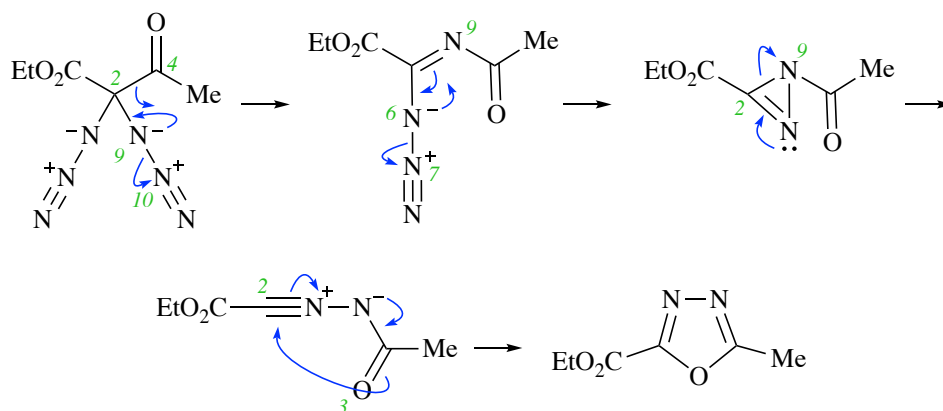
(jj) The diene and dienophile are electronically mismatched. The mechanism is not pericyclic, but stepwise. After the base deprotonates the indole, the resulting enamide undergoes a conjugate addition to the dienal. The resulting enolate then adds to the imine to close the ring. Base-promoted tautomerization then brings the new ring's double bond into conjugation.
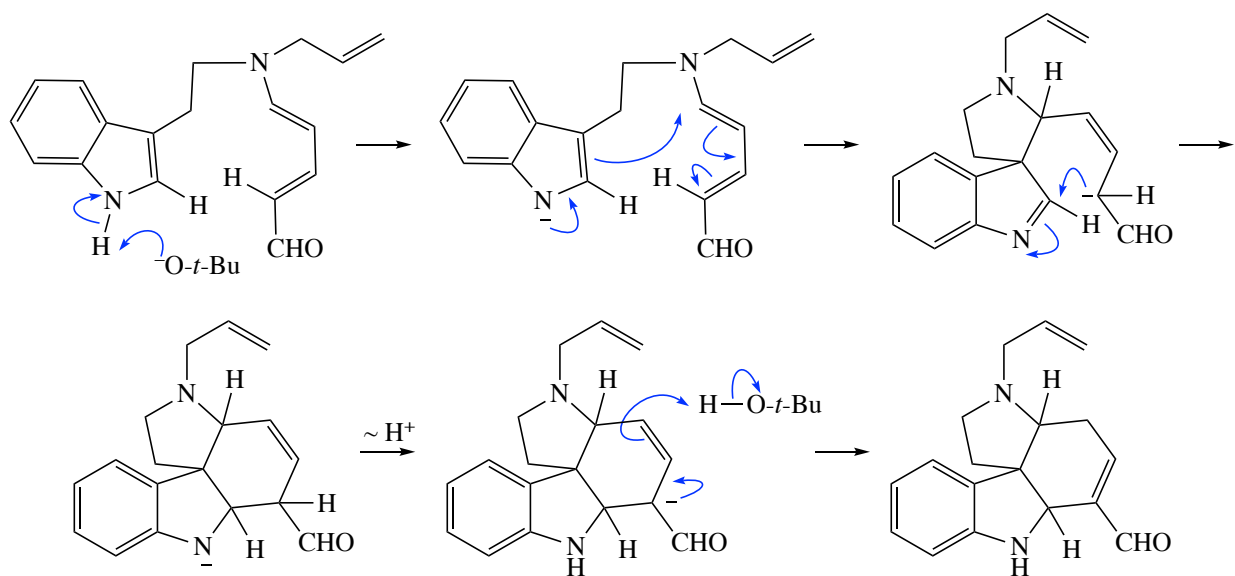
One subtlety to this mechanism: The C=C double bond must be cis for the second C–C bond-forming step to occur. Either both the aldehyde O and the indole N coordinate to K after the initial deprotonation, or the first C–C bond-forming step is reversible, allowing the cis and trans forms of the double bond to equilibrate.