Solutions to the Problems

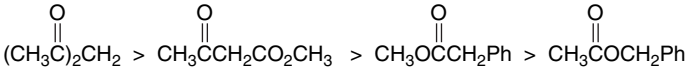
Chapter 1

1.1. These questions can be answered by comparing the electron-accepting capacity and relative location of the substituents groups. The most acidic compounds are those with the most stabilized anions.

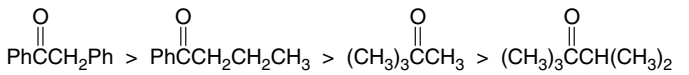
a. In (a) the most difficult choice is between nitroethane and dicyanomethane. Table 1.1 indicates that nitroethane ($pK = 8.6$) is more acidic in hydroxylic solvents, but that the order might be reversed in DMSO, judging from the high pK_{DMSO} (17.2) for nitromethane. For hydroxylic solvents, the order should be $CH_3CH_2NO_2 > CH_2(CN)_2 > (CH_3)_2CHC{=}O(Ph) > CH_3CH_2CN$.

b. The comparison in (b) is between N−H, O−H, and C−H bonds. This order is dominated by the electronegativity difference, which is O > N > C. Of the two hydrocarbons, the aryl conjugation available to the carbanion of 2-phenylpropane makes it more acidic than propane. $(CH_3)_2CHOH > [(CH_3)_2CH]_2NH > (CH_3)_2CHPh > CH_3CH_2CH_3$.

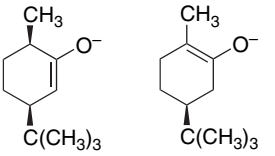
c. In (c) the two β-dicarbonyl compounds are more acidic, with the diketone being a bit more acidic than the β-ketoester. Of the two monoesters, the phenyl conjugation will enhance the acidity of methyl phenylacetate, whereas the nonconjugated phenyl group in benzyl acetate has little effect on the pK.



d. In (d) the extra stabilization provided by the phenyl ring makes benzyl phenyl ketone the most acidic compound of the group. The cross-conjugation in 1-phenylbutanone has a smaller effect, but makes it more acidic than the aliphatic ketones. 3,3-Dimethyl-2-butanone (methyl *t*-butyl ketone) is more acidic than 2,2,4-trimethyl-3-pentanone because of the steric destabilization of the enolate of the latter.

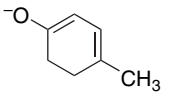


1.2. a. This is a monosubstituted cyclohexanone where the less-substituted enolate is the kinetic enolate and the more-substituted enolate is the thermodynamic enolate.



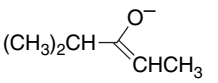
kinetic thermodynamic

b. The conjugated dienolate should be preferred under both kinetic and thermodynamic conditions.



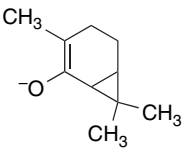
kinetic and thermodynamic

c. This presents a comparison between a trisubstituted and disubstituted enolate. The steric destabilization in the former makes the disubstituted enolate preferred under both kinetic and thermodynamic conditions. The *E*:*Z* ratio for the kinetic enolate depends on the base that is used, ranging from 60:40 favoring *Z* with LDA to 2:98 favoring *Z* with LiHMDS or Li 2,4,6-trichloroanilide (see Section 1.1.2 for a discussion).



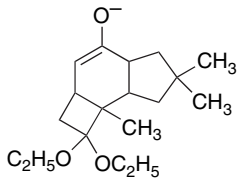
kinetic and thermodynamic; *E*:*Z* ratio depends on conditions

d. Although the deprotonation of the cyclopropane ring might have a favorable electronic factor, the strain introduced leads to the preferred enolate formation occurring at C(3). It would be expected that the strain present in the alternate enolate would also make this the more stable.



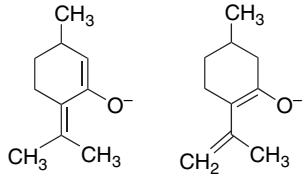
kinetic and thermodynamic

e. The kinetic enolate is the less-substituted one. No information is available on the thermodynamic enolate.



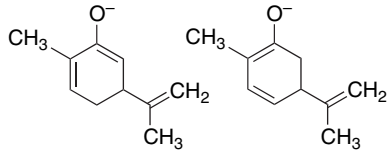
kinetic, no information on thermodynamic

f. The kinetic enolate is the cross-conjugated enolate arising from α′-rather than γ-deprotonation. No information was found on the conjugated α,γ-isomer, which, while conjugated, may suffer from steric destabilization.



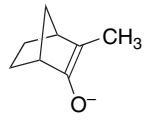
kinetic α,γ-isomer

g. The kinetic enolate is the cross-conjugated enolate arising from α′-rather than γ-deprotonation. The conjugated γ-isomer would be expected to be the more stable enolate.



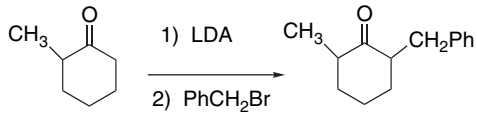
kinetic γ-isomer

h. Only a single enolate is possible under either thermodynamic or kinetic conditions because the bridgehead enolate suffers from strain. This was demonstrated by base-catalyzed deuterium exchange, which occurs exclusively at C(3) and with 715:1 *exo* stereoselectivity.

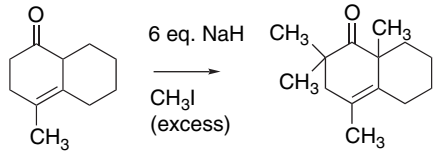


kinetic and thermodynamic

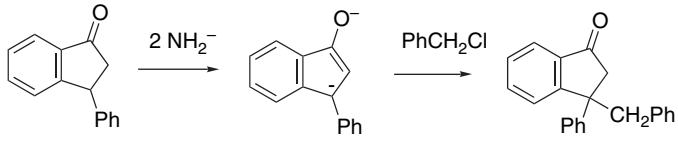
1.3. a. This synthesis can be achieved by kinetic enolate formation, followed by alkylation.



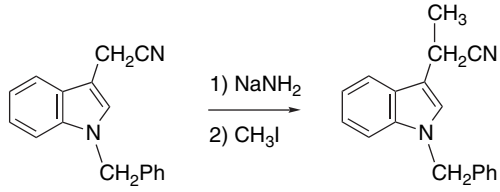
b. This transformation involves methylation at all enolizable positions. The alkylation was effected using a sixfold excess of NaH and excess methyl iodide. Evidently there is not a significant amount of methylation at C(4), which could occur through γ-alkylation of the C(8a)-enolate.



c. This alkylation was accomplished using two equivalents of $NaNH_2$ in liquid NH_3. The more basic site in the dianion is selectively alkylated. Note that the dianion is an indenyl anion, and this may contribute to its accessibility by di-deprotonation.

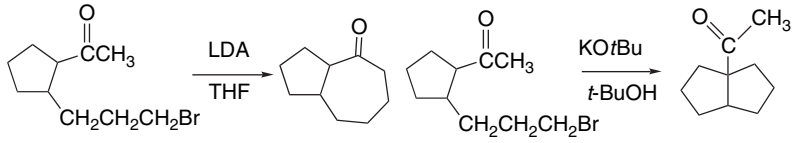


d. This is a nitrile alkylation involving an anion that is somewhat stabilized by conjugation with the indole ring. The anion was formed using $NaNH_2$ in liquid NH_3.



e. This silylation was done using TMS-Cl and triethylamine in DMF. Since no isomeric silyl enol ethers can be formed, other conditions should also be suitable.

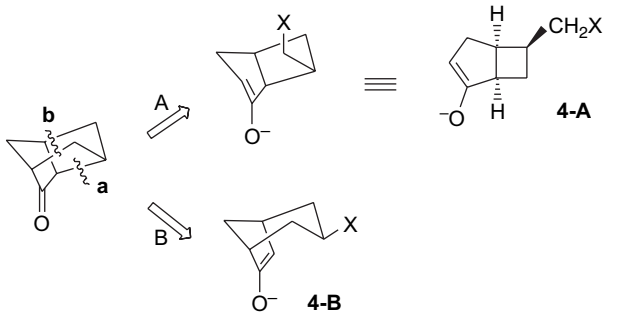
f, g. These two reactions involve selective enolate formation and competition between formation of five- and seven-membered rings. The product of kinetic enolate formation with LDA cyclizes to the seven-membered ring product. The five-membered ring product was obtained using *t*-BuO^- in *t*-BuOH. The latter reaction prevails because of the 5 > 7 reactivity order and the ability of the enolates to equilibrate under these conditions.



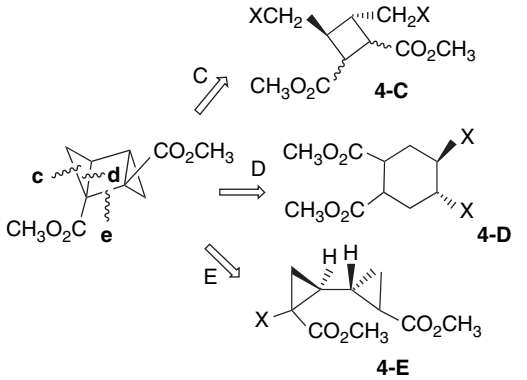
77–84%

86–94%

1.4. a. There are two conceivable dissections. The synthesis has been done from **4-B** with X = OTs using KO-*t*-Bu in benzene. Enolate **4-A** also appears to be a suitable precursor.

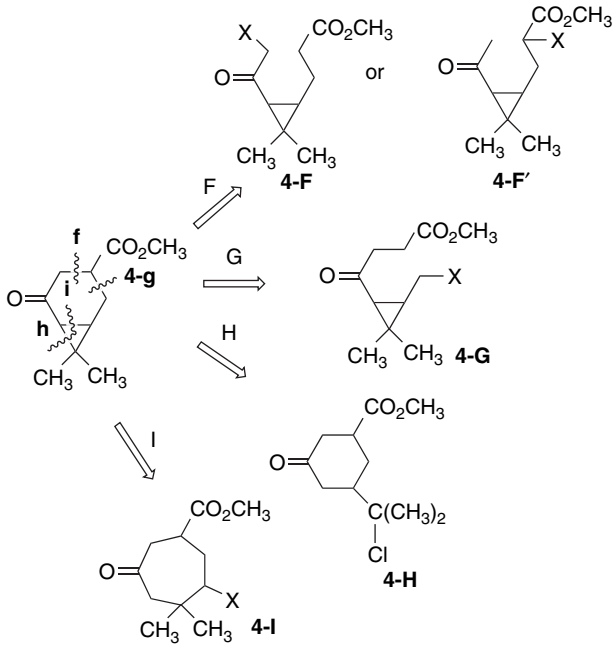


b. There are two symmetrical disconnections. Disconnection **c** identifies a cyclobutane reactant. Disconnection **d** leads to a cyclohexane derivative, with the stereochemistry controlled by a requirement for inversion at the alkylation center. Disconnection **e** leads to a considerably more complex reactant without the symmetry characteristic of **4-C** and **4-D**. The *trans*-3,4-*bis*-(dichloromethyl)cyclobutane-1,2-dicarboxylate ester was successfully cyclized in 59% yield using 2.3 eq of NaH in THF.

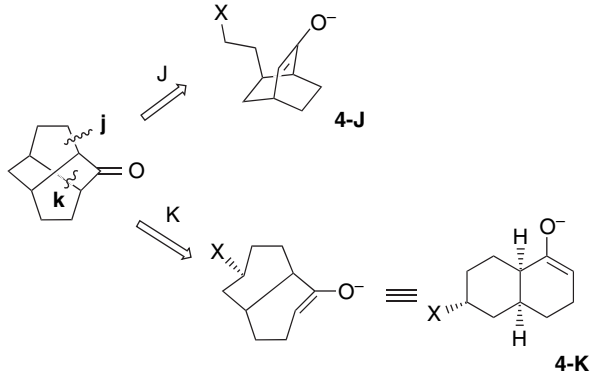


c. There are four possible dissections involving the ketone or ester enolates. Disconnection **f** leads to **4-F** or **4-F′**. Both potentially suffer from competing base-mediated reactions of α-haloketones and esters (see Section 10.1.4.1). Potential intermediate **4-G** suffers from the need to distinguish between the ketone enolate (five-membered ring formation) and the ester enolate (six-membered ring formation). Disconnection **h** leads to a tertiary halide, which is normally not suitable for enolate alkylation. However, the cyclization has been successfully accomplished with KO-*t*-Bu in *t*-BuOH in 70% yield as a 3:2 mixture of the *cis* and *trans* isomers. This successful application of a tertiary halide must be the result of the favorable geometry for cyclization as opposed to elimination. The required starting material is fairly readily prepared from 5-hydroxy-cyclohexane-1,3-dicarboxylic acid. The disconnection **i** leads to a cycloheptanone derivative. Successful use of this route would require a specific

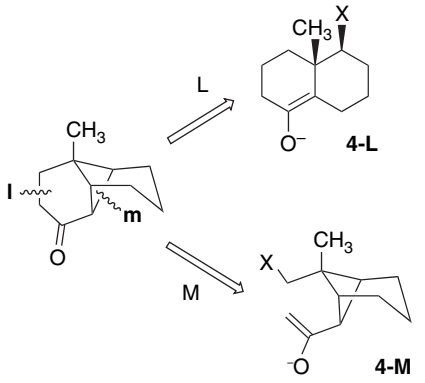
deprotonation of the more hindered and less acidic of the two methylene groups, and thus seems problematic.



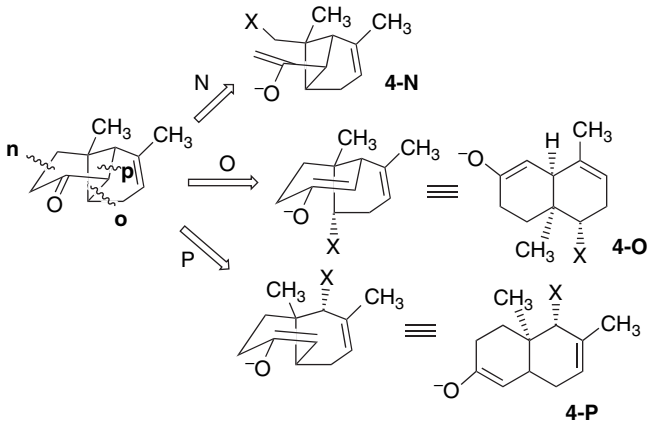
d. There are two possible dissections. Route **J** has been accomplished using excess NaH in DMF (90%) yield with OTs as the leaving group. Enolate **4-K** does not appear to be structurally precluded as an intermediate, as long as the leaving group has the correct stereochemistry.



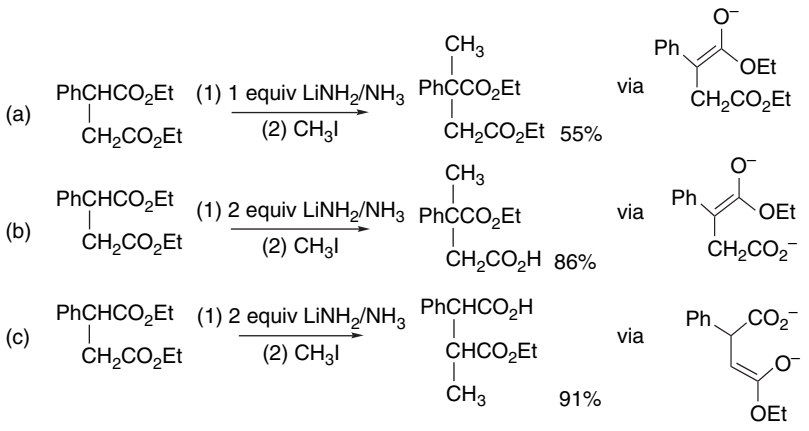
e. There are two disconnections in this compound, which has a plane of symmetry. A synthesis using route **L** has been reported using the dimsyl anion in DMSO. This route has an advantage over route **M** in the relatively large number of decalone derivatives that are available as potential starting materials.



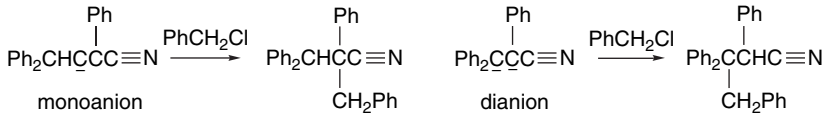
f. There are three possible disconnections. Route **N** leads to a rather complex tricyclic structure. Routes **O** and **P** identify potential decalone intermediates. There is no evident advantage of one over the other. Route **O** has been utilized. The level of success was marginal with 10–38% yield, the best results being with dimsyl anion or NaHMDS as base. KO-*t*-Bu, NaOMe, and Ph_3CNa failed to give any product. Elimination of the tosylate was a major competing reaction. No information is available on route **P**.



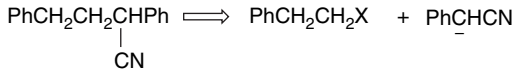
1.5. This question can be approached by determining the identity of the anionic species and the most reactive site in that species. In (a) CH(2) will be deprotonated because of the phenyl stabilization at that site. In (b) a dianion will be formed by deprotonation of both the carboxy and CH(2) sites. The CH(2) site will be a much more reactive nucleophile than the carboxylate. In (c) the carboxy group and CH_2(3) will be deprotonated because of the poor anion-stabilizing capacity of the deprotonated carboxy group. Methylation will occur at the much more basic and reactive CH(3) anionic site.



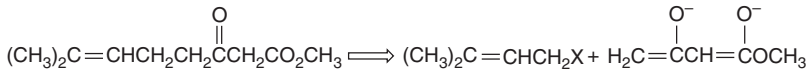
1.6. These differing outcomes are the result of formation of the monoanion at C(2) in the case of one equivalent of KNH_2 and the C(2),C(3) dianion with two equivalents. The less stabilized C(3) cite is more reactive in the dianion.



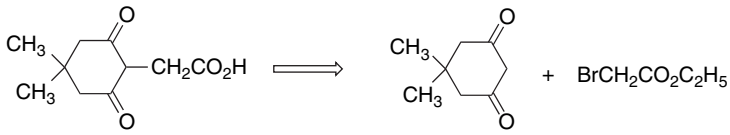
1.7. a. This compound can be made by alkylation of the phenylacetonitrile anion with a phenylethyl halide.



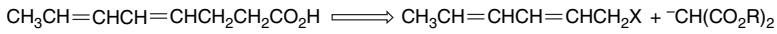
b. This alkylation can be done with an allylic halide and the dianion of an acetoacetate ester. The dianion can be formed both by sequential treatment with NaH and *n*-BuLi or by use of two equivalents of LDA.



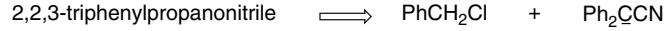
c. The readily available ketone 5,5-dimethylcyclohexane-1,3-dione (dimedone) is a suitable starting material. It can be alkylated by ethyl bromoacetate to introduce the substituent, then hydrolyzed to the desired carboxylic acid.



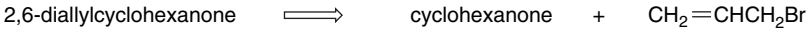
d. This preparation has been done by alkylation of a malonate ester anion, followed by LiI/DMF dealkoxycarboxylation. Direct alkylation of an acetate ester might also be feasible.



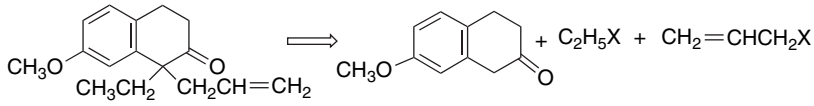
e. This reaction can be done by benzylation of the anion of diphenylacetonitrile.



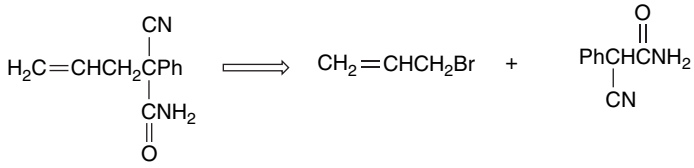
f. This 2,6-dialkylation was done as a "one-pot" process by alkylation of the pyrrolidine enamine using two equivalents of allyl bromide and *N*-ethyldicyclohexylamine as a base to promote dialkylation.



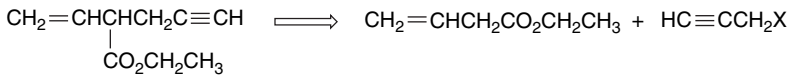
g. This reaction can be done by sequential alkylations. There should be no serious regiochemical complications because of the stabilizing influence of the aryl ring. One sequence employed the pyrrolidine enamine to introduce the ethyl group (C_2H_5I) followed by deprotonation with NaH and alkylation with allyl bromide.



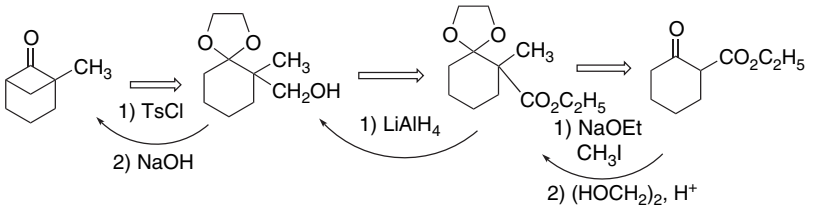
h. A potential stabilized nucleophile can be recognized in the form of α-cyanophenylacetamide, which could be alkylated with an allyl halide. In the cited reference, the alkylation was done in liquid ammonia without an added base, but various other bases would be expected to work as well.



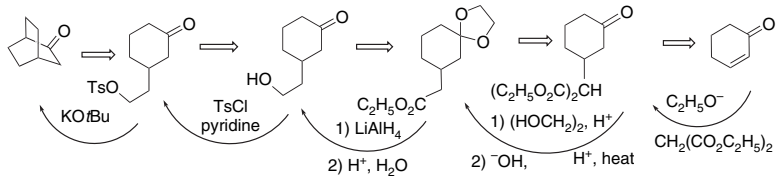
j. The desired product can be obtained by taking advantage of the preference for α-alkylation in enolates of α,β-unsaturated esters. The reaction has been done using LDA/HMPA for deprotonation and propargyl bromide for alkylation.



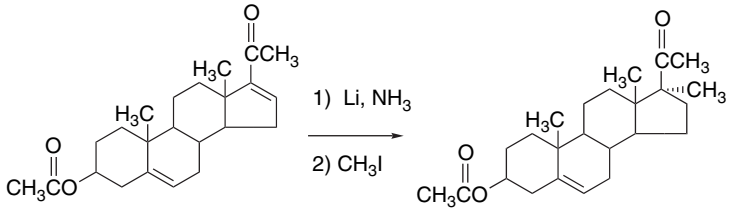
1.8. a. The required transformation involves an intramolecular alkylation. In principle, the additional methylene unit could initially be introduced at either the distabilized or monostabilized cite adjacent to the ketone. In the cited reference, the starting material was methylated at the distabilized position. The ketone was protected as a dioxolane and the ester was then reduced to the primary alcohol, which was converted to a tosylate. The dioxolane ring was hydrolyzed in the course of product isolation. Sodium hydroxide was used successfully as the base for the intramolecular alkylation.



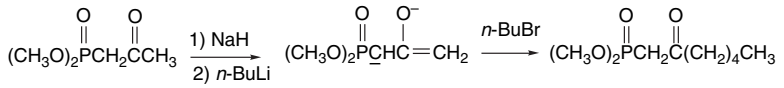
b. This ring system can be constructed from cyclohexenone by conjugate addition of a malonate ester enolate, decarboxylation, reduction, conversion to an alkylating agent, and cyclization. The synthetic sequence was conducted with a ketal protecting group in place for the decarboxylation and reduction



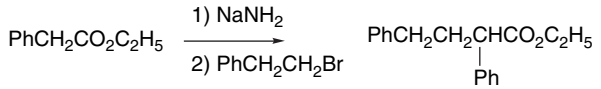
c. This reaction can be effected by reductive enolate formation followed by methylation. The stereochemistry is controlled by the adjacent angular methyl group.



d. The phosphonate ester group is an EWG of strength comparable to an ester group. The dianion undergoes alkylation at the monostabilized position.

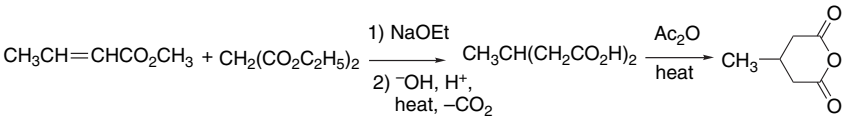


e. This reaction was originally done by forming the enolate with $NaNH_2$ and then alkylating with 2-phenylethyl bromide. Other enolate-forming conditions should also be acceptable.

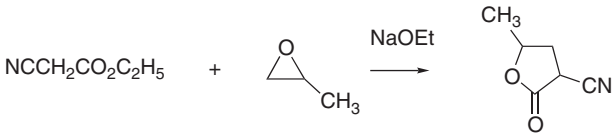


f. The use of methyl 2-butenoate as a starting material identifies the other carbon fragment as an acetate ester enolate. Conjugate addition was done using

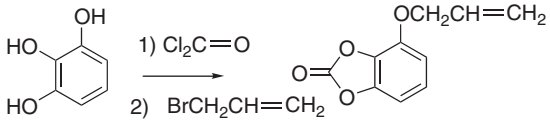
the malonate anion equivalent. The anhydride can be formed after complete hydrolysis and decarboxylation.



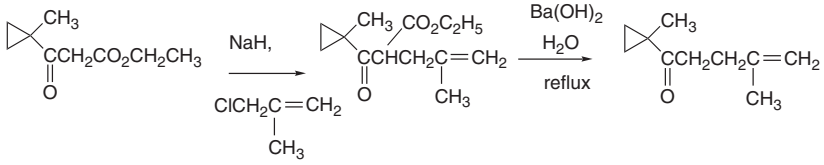
g. This transformation can be done in a single step by a base-mediated ring-opening reaction between the anion of ethyl cyanoacetate and 2-methyloxirane, which is followed by lactonization.



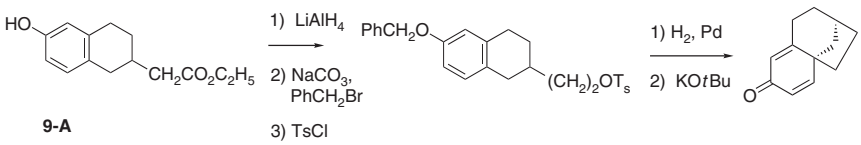
h. This reaction was done by forming the cyclic carbonate using phosgene, then alkylating the remaining hydroxy group.



i. This synthesis can be done by alkylation of the suggested β-ketoester starting material. In the cited reference, the decarboxylation was done by heating with $Ba(OH)_2$.

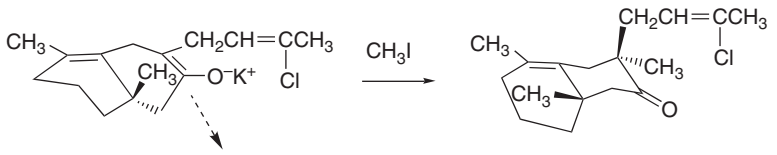


1.9. Conversion of the carboxy group in **9-A** to a primary halide or tosylate would permit an intramolecular C-alkylation of the phenolate and create the target structure. This was done by a sequence of reactions involving reduction of the ester to alcohol, tosylate formation, and phenolate C-alkylation using KO-*t*-Bu. A benzyl protecting group was in place during the tosylation.

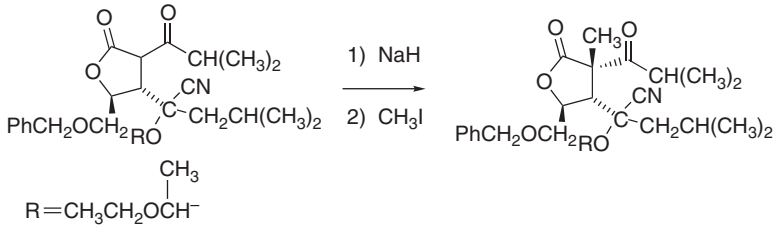


1.10. a. This alkylation was done both by initial introduction of the 3-chlorobutenyl group and by initial introduction of the methyl group. In both cases, the second group is introduced from the lower (α) face, opposite the methyl group at the

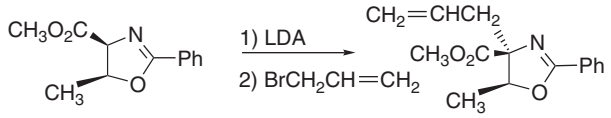
ring junction. Models suggest that the methyl group is tilted toward the upper face of the enolate leading to steric shielding.



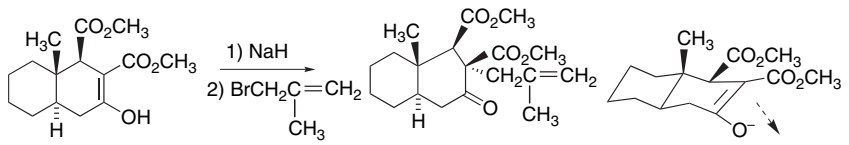
b. The branched substituent adjacent to the enolate site would be expected to exerts steric approach control leading to alkylation from the upper (β) face.



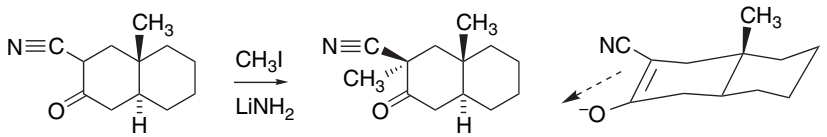
c. Deprotonation occurs adjacent to the ester substituent. The methyl group exerts steric approach control.



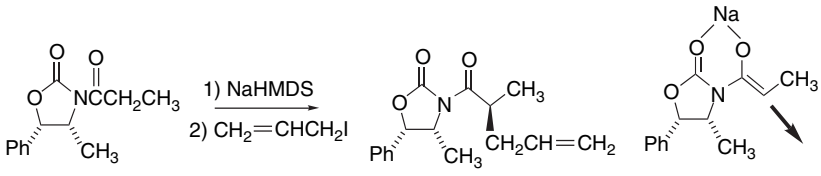
d. The angular methyl group exerts steric approach control. Alkylation occurs from the lower (α) face.



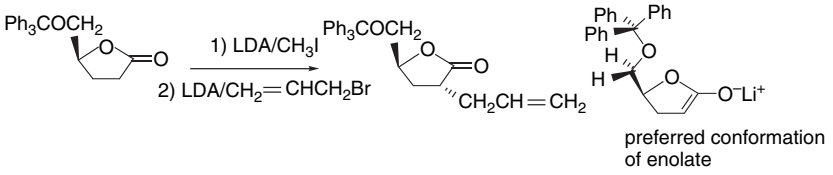
e. The angular methyl group exerts steric approach control. Alkylation occurs from the lower (α) face.



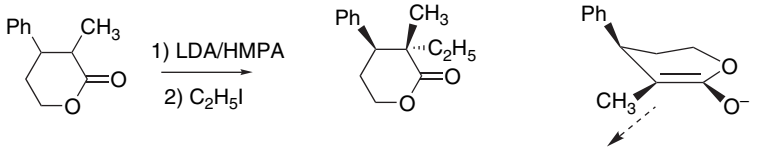
f. This is an example of use of a oxazolidinone chiral auxiliary. The methyl group in the oxazolidinone ring directs the alkylation to the opposite face of the chelated *Z*-enolate.



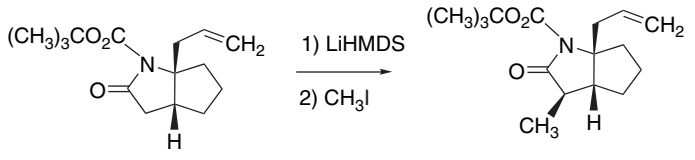
g. The trityl protecting group exerts steric control. NMR studies indicate that the oxygen of the trityloxymethyl group is positioned over the enolate double bond. It been suggested that there may be a stereoelectronic component involving σ-σ* donation from the ether oxygen to lactone group. Alternatively, there might be a chelation favoring this conformation.



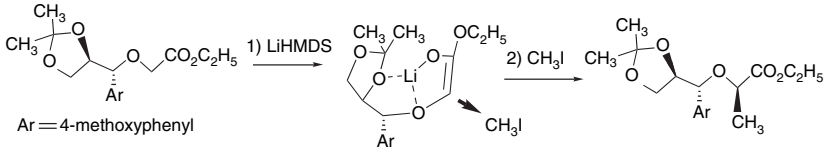
h. The phenyl substituent exerts steric approach control, leading to alkylation from the lower (α) face.



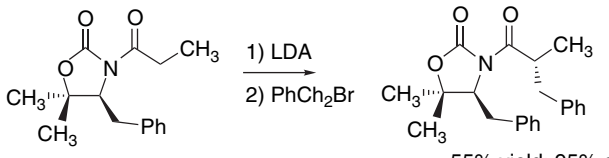
i. The convex face of the lactam enolate is more accessible and favors methylation *cis* to the allyl substituent.



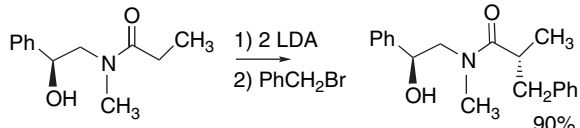
j. The lithium enolate can adopt a chelated structure that favors approach of the alkyl group from the enolate face remote from the chelate structure.



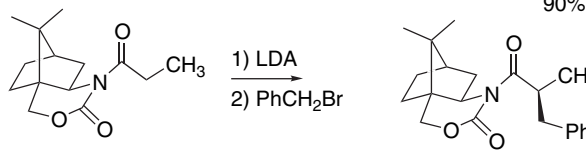
1.11. a. This alkylation can be carried out using several chiral auxiliaries.



55% yield; 95% de

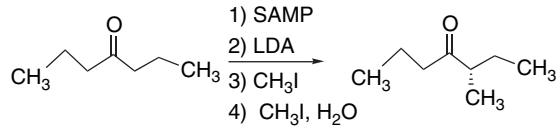


90% yield; 94% de



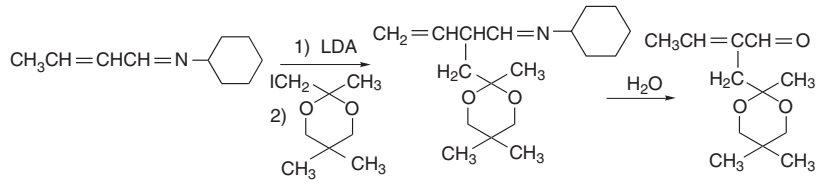
60% yield; 90% de

b. This alkylation was done using the SAMP hydrazone. The alkylated hydrazone was then *N*-methylated and hydrolyzed.

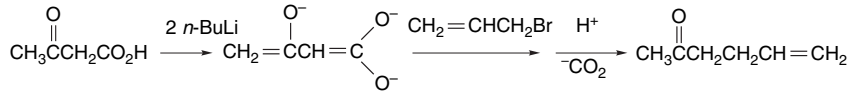


61%, 94% ee

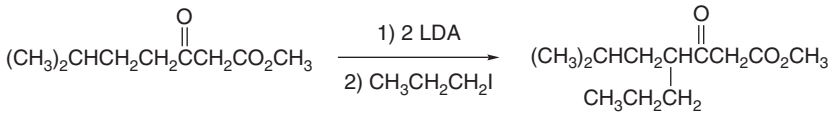
1.12. a. This transformation corresponds to the α-alkylation of an α,β-unsaturated aldehyde by a relatively hindered alkyl halide. The reaction can be done by alkylation of an enolate equivalent, followed by isomerization to the conjugated isomer. The reaction was done successfully using the lithiated *N*-cyclohexylimine. The conjugated isomer is formed during hydrolysis.



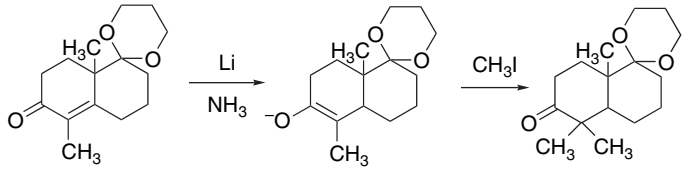
b. This transformation is well suited to an alkylation of the dianion of acetoacetic acid. The deprotonation was done using two equivalents of *n*-butyllithium to form the dianion. The β-keto acid was decarboxylated after the alkylation.



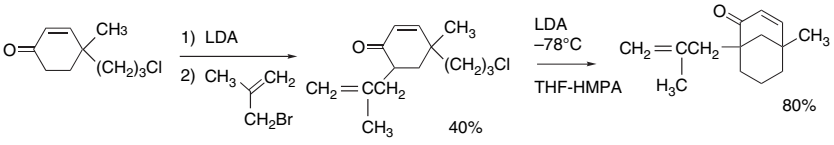
c. This reaction corresponds to the alkylation of the most reactive site in the *dianion* of the appropriate β-ketoester.



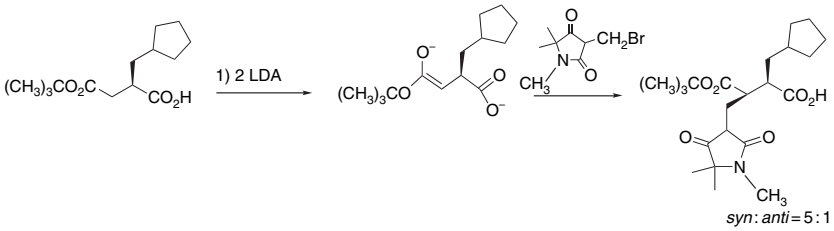
d. This α-alkylation of an enone can be done by reductive generation of the enolate using Li/NH_3, followed by alkylation. The reaction has been reported both by direct methylation of the enolate (80% yield) or by isolating the silyl enol ether and regenerating the enolate using CH_3Li (92% yield).



e. This transformation requires an intramolecular alkylation and an alkylation by a methallyl (2-methyl-2-propenyl) group. The latter reaction must be done first, since the bicyclic ketone would be resistant to enolate formation.



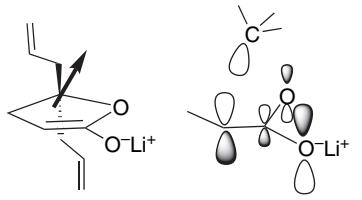
1.13. a. The reaction shows *syn* selectivity (5–6:1) and is relatively insensitive to cosolvents that would be expected to disrupt a chelate. An extended open TS would favor the observed stereoisomer.



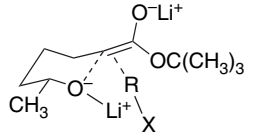
b. This reaction involves an enantioselective deprotonation. Although this base is often highly enantioselective, it appears that there is no consensus concerning the TS structure.

c. This reaction involves an enantioselective deprotonation of a symmetric reactant. The optimum results were obtained when one equivalent of LiCl was present. This led to the suggestion that a mixed lithium amide:lithium chloride species is involved, but a detailed TS does not seem to have been proposed.

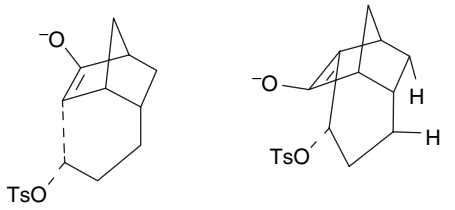
d. This reaction involves a *spiro* lactone enolate. There is some steric differentiation by the vinyl substituents, but it was judged that steric factors alone could not account for the observed selectivity. It was proposed that secondary orbital interactions between the enolate HOMO and the σ^* orbital of the electrophile favor a trajectory with an acute angle that favors the observed stereoisomer.



e. It is proposed that a cyclic TS is favored, but it is not clear why this should be more favored in the presence of HMPA.



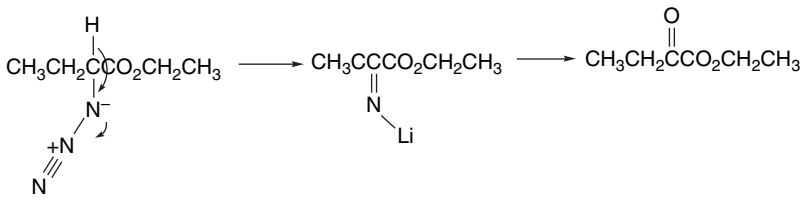
1.14. Models suggest that cyclization TS **14-A** is relatively free of steric interference, whereas TS **14-B** engenders close approaches to the endo C(6) hydrogen.



14-A **14-B**

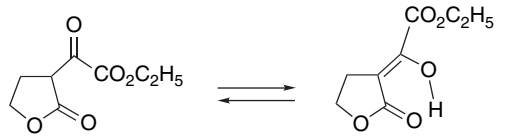
1.15. The results suggest that the main enolate is formed by deprotonation of the exocyclic methyl group, although the case of $n = 2$ indicates that the enolate from C(4) deprotonation is also present. The products found in each case are consistent with initial α-alkylation characteristic of enone enolates (see Section 1). For $n = 2$, cyclopropane formation (C-alkylation) is preferable to five-membered ring formation by O-alkylation. For $n = 3$, six-membered ring formation by O-alkylation is favored to four-membered ring formation by C-alkylation. For $n = 4$, five-membered C-alkylation is favored to seven-membered O-alkylation. This is consistent with the general order for ring formation $3 > 5 > 6 > 7 > 4$.

1.16. This reaction involves elimination of nitrogen to the lithio imine, which would hydrolyze on exposure to water.

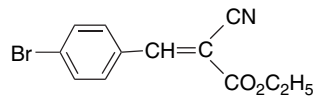


Chapter 2

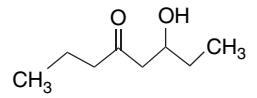
2.1. a. This mixed ester-type acylation proceeded in 90% yield. The product exists in enolic form.



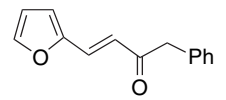
b. The reaction conditions gives a Knoevenagel condensation product.



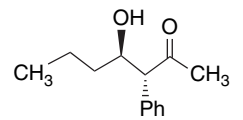
c. These reaction conditions result in a kinetically controlled aldol addition.



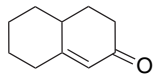
d. These conditions led to formation of the most stable condensation product. Condensation at the benzyl group would introduce steric repulsions.



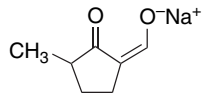
e. This is a mixed aldol addition reaction carried out by generation of the lithium enolate from an enol acetate. The inclusion of $ZnCl_2$ leads to stereoequilibration and favors the isomer with an *anti* relationship between the phenyl and hydroxy groups.



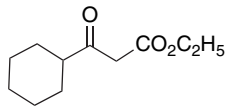
f. This reaction is analogous to a Robinson annulation, but with the α-methylenecyclohexanone as the electrophilic reactant. The final product is the result of dealkoxycarbonylation, which occurs by a reverse ester condensation.



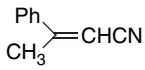
g. These conditions led to formation of the hydroxymethylene derivative at the unsubstituted methylene group.



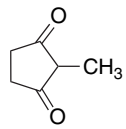
h. This mixed ester condensation gives the enolizable β-ketoester.



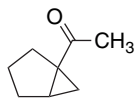
i. These are the conditions for a Wadsworth-Emmons olefination.



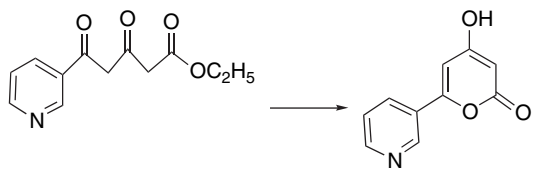
j. These conditions led to an intramolecular acylation to form the enolate of 2-methyl-1,3-cyclopentane-1,3-dione. The reported yield after workup is 70–71%



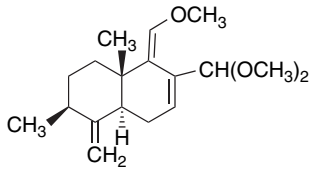
k. Reaction with dimethylsulfoxonium ylide with an enone results in cyclopropanation (see p. 178). A 74% yield was obtained.



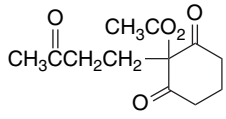
l. The reaction begins by acylation of the more basic C(4) enolate and then forms a pyrone ring by cyclization.



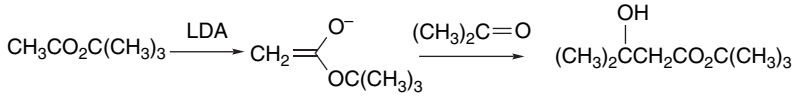
m. These conditions led to formation of a vinyl ether by a Peterson olefination.



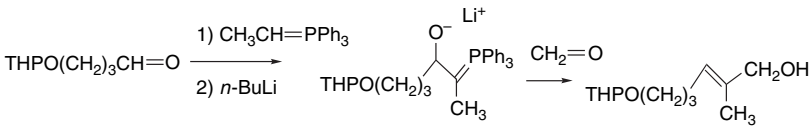
n. These conditions led to conjugate addition without cyclization.



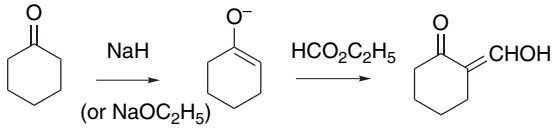
2.2. a. This transformation was accomplished by ester enolate formation and addition to acetone.



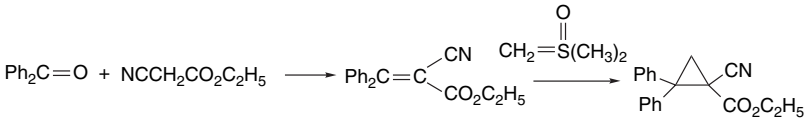
b. This synthesis was accomplished by using the Schlosser protocol to form the β-oxido ylide, followed by reaction with formaldehyde.



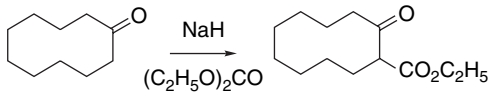
c. This hydroxymethylenation was accomplished in 95% yield with NaH and ethyl formate.



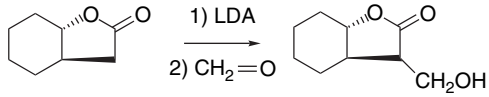
d. This transformation was accomplished in two steps by Knoevenagel reaction and cyclopropanation with dimethylsulfoxonium methylide.



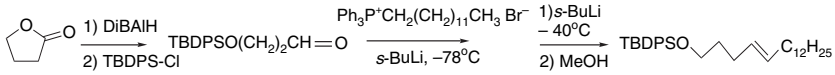
e. This ethoxycarbonylation was done in 99% yield using NaH and diethyl carbonate.



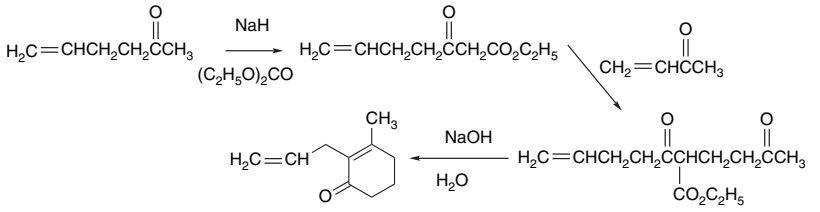
f. There are a number of ways of effecting this transformation but the direct formation of the enolate (using LDA) followed by reaction with formaldehyde is reported to proceed in more than 95% yield.



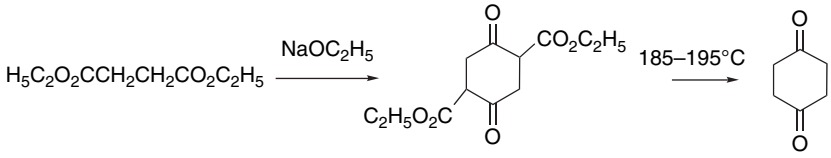
g. This transformation can be done by reducing the lactone to the lactol stage, silylating, and then doing a Wittig reaction. The reaction was selective for the *E*-isomer when done using *s*-BuLi for ylide formation at −78° C followed by equilibration of the betaine intermediate under the Schlosser conditions (see p. 162).



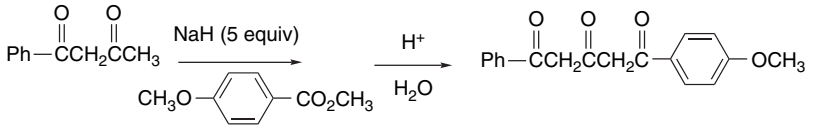
h. This transformation was accomplished in three steps: ketone acylation; conjugate addition to methyl vinyl ketone; intramolecular (Robinson) aldol condensation, with accompanying hydrolysis and decarboxylation.



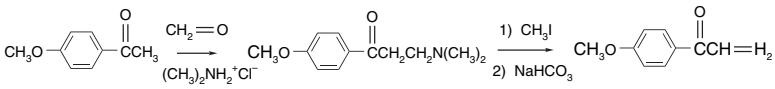
i. This transformation was effected by dimerization through ester condensation and decarboxylation. The dimerization was done in 64–68% yield using $NaOC_2H_5$ and the decarboxylation was done thermally (185°–195° C, 15 min) in 81–89% yield.



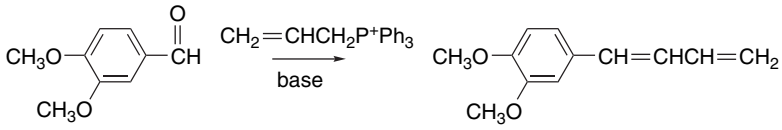
j. This acylation occurs at the less acidic methyl position, which is the thermodynamically favored position, because of the minimal substitution at the conjugated double bond. The reaction was done using five equivalents of NaH in 77–86% yield. It is probably thermodynamically controlled, although a kinetically controlled process through a dianion might also be possible under appropriate circumstances.



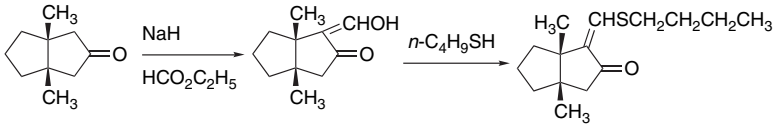
k. This methylenation of a substituted acetophenone was done by a Mannich reaction, followed by elimination from the quaternary salt.



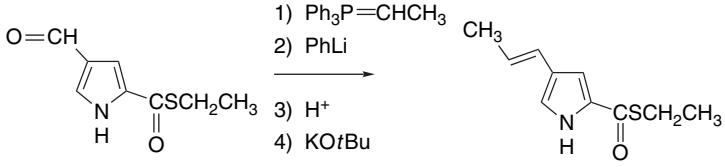
l. This conversion was done by a Wittig reaction using allyl triphenylphosphonium bromide.



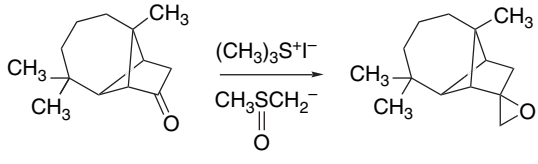
m. Thiomethylenation derivatives of this type have a number of synthetic applications. They can be prepared from hydroxymethylene derivatives by nucleophilic exchange with thiols.



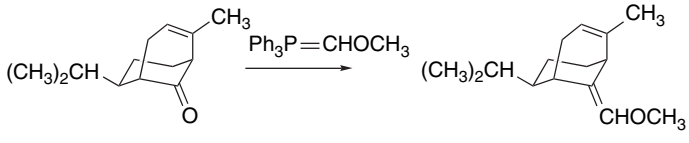
n. This olefination was done using a Wittig reaction. The *E*-stereoselectivity was achieved by lithiation of the adduct at low temperature prior to elimination (see p. 162).



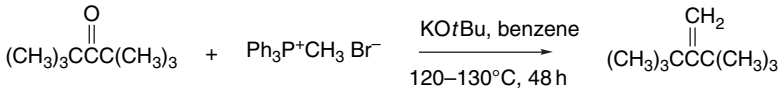
o. This was done by reaction of the ketone with dimethylsulfonium methylide in DMSO. A single epoxide is formed as a result of a kinetically controlled approach from the less hindered face (see p. 177).



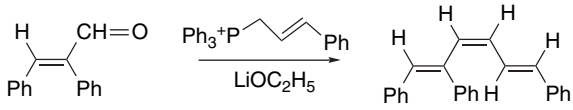
p. This reaction was done by a Wittig reaction using methoxymethylenetriphenylphosphorane.



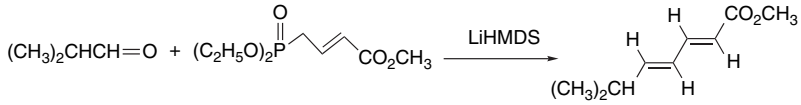
q. This Wittig olefination of a hindered ketone was done using the KO-*t*-Bu procedure with extended heating in benzene. The yield was 96%.



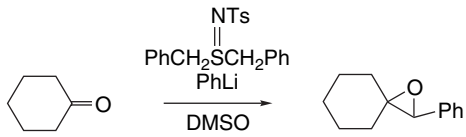
r. This *Z*-selective olefination was done in 77% yield with $LiOC_2H_5$ as the base. The steric effect of the 2-phenyl group is evidently the basis of the stereoselectivity, since the corresponding reaction of cinnamaldehyde gives a 2:3 mixture of the *E*- and *Z*-isomers. This steric effect must operate in the formation of the oxaphosphetane intermediate, since the *E*-product would be less congested.



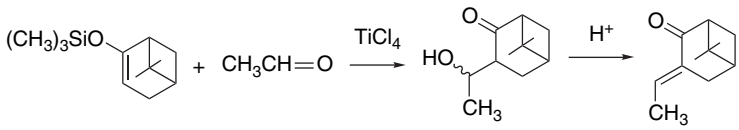
s. This *E*-selective reaction was done with a conjugated phosphonate.



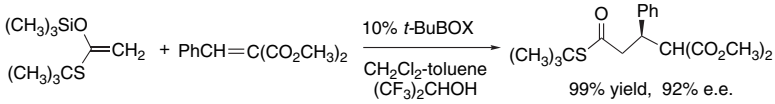
t. This benzylidene transfer reaction was accomplished using *N*-tosyl dibenzylsulfilimine.



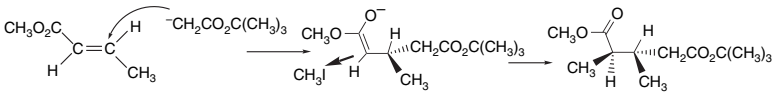
u. This transformation was accomplished by a $TiCl_4$-mediated Mukaiyama reaction, followed by acidic dehydration.



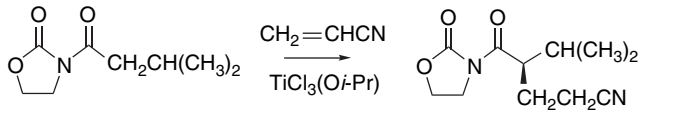
v. This transformation can be carried out in high enantioselectivity by addition of the trimethylsilyl enol ether of *t*-butylthio acetate, using a *t*-butyl BOX catalyst.



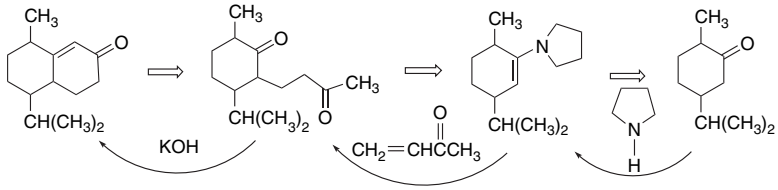
w. The transformation suggests a conjugate addition of an ester enolate with tandem alkylation. The reaction has been found to favor the *syn* isomer in the presence of HMPA, which is also used along with KO-*t*-Bu to enhance the reactivity of the enolate. The *syn* stereochemistry of the methyl groups arises from approach opposite to the ester substituent in an H-eclipsed conformation of the enolate.



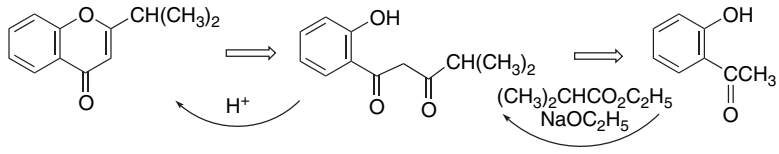
x. This transformation was accomplished by Lewis acid–mediated conjugate addition of the 4-benzyloxazolidinone derivative.



2.3. a. This transformation, which corresponds to a Robinson annulation that is regioselective for the less-substituted α-position, was done in three steps: enamine formation, conjugate addition to methyl vinyl ketone, and cyclizative condensation with base.

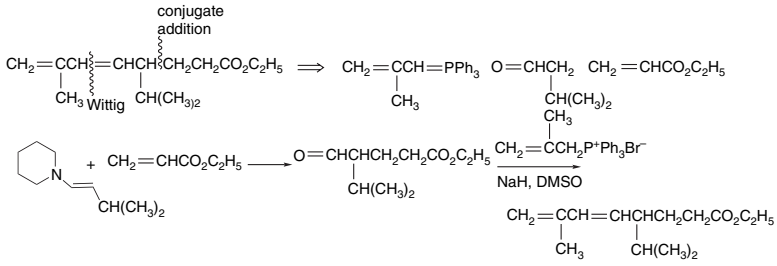


b. This transformation requires acylation of the ketone methyl group by an isobutyroyl group, which can then cyclize to the pyrone ring. The acylation was done using an ester.

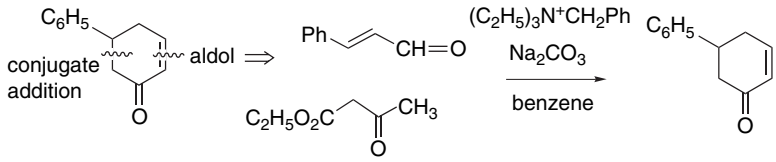


c. Retrosynthetic transforms suggest that the C(5)−C(6) bond could be formed by a Wittig-type reaction. The C(3)−C(4) bond could be formed by a conjugate addition. This route was accomplished synthetically by using

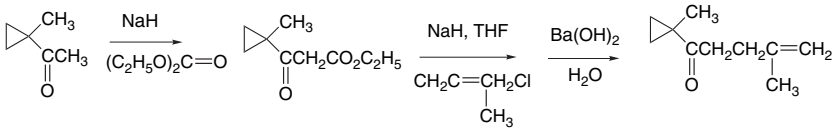
the enamine of 2-methylpropanal for conjugate addition to ethyl acrylate, followed by a Wittig reaction.



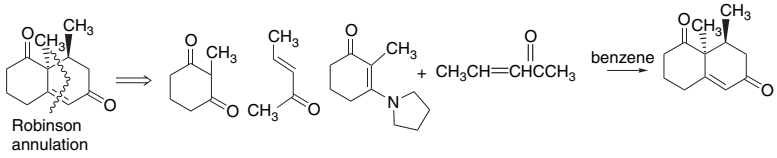
d. This ring could be formed by conjugate addition of an acetone enolate equivalent and intramolecular aldol condensation. The synthesis was achieved using ethyl acetoacetate and cinnamaldehyde under phase transfer conditions in the presence of sodium carbonate. The hydrolysis and decarboxylation of the ester group occurred under these conditions.



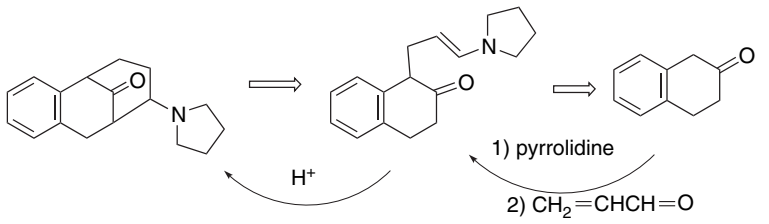
e. The disconnection to cyclopropyl methyl ketone suggests an enolate alkylation. In the referenced procedure the ketone was first activated by ethoxycarbonylation using diethyl carbonate and NaH. After alkylation, the ketoester was hydrolyzed and decarboxylated using $Ba(OH)_2$.



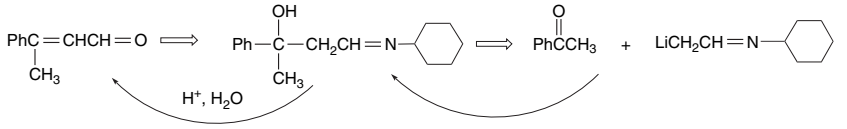
f. The desired product can be obtained by Robinson annulation of 2-methylcyclohexane-1,3-dione. The direct base-catalyzed reaction of pent-3-en-2-one gave poor results, but use of the enamine was successful.



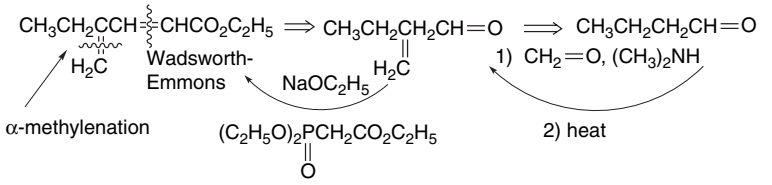
g. This transformation occurred on reaction of the pyrrolidine enamine of β-tetralone with acrolein. The reaction involves tandem conjugate addition, exchange of the pyrrolidine to the aldehyde group, and Mannich cyclization.



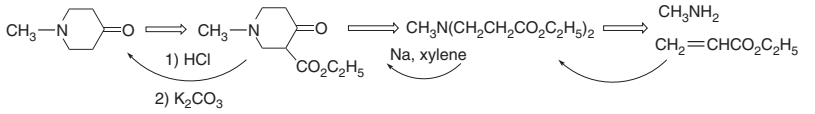
h. This transformation requires a mixed aldol condensation in which the less reactive carbonyl component, acetophenone, acts as the electrophile. In the cited reference this was done using the lithioimine of the *N*-cyclohexyl imine of acetaldehyde as the nucleophile.



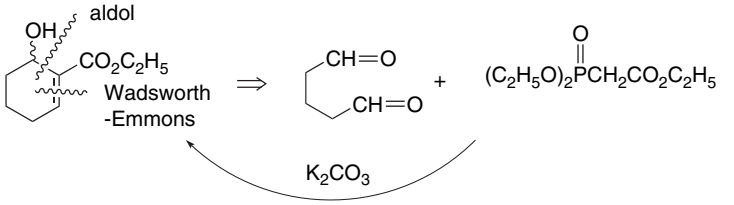
i. This transformation was done by methylenation of butanal via a Mannich reaction, followed by a Wadsworth-Emmons reaction.



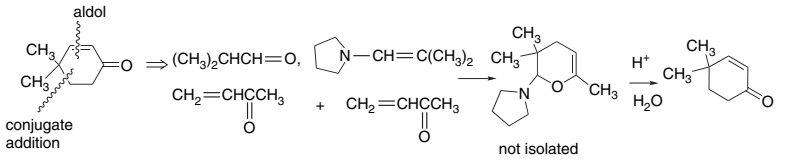
j. This transformation can be accomplished by conjugate addition of methyl amine to ethyl acrylate. The diester can then be cyclized under Dieckman conditions. Hydrolysis and decarboxylation under acidic conditions gives the desired product.



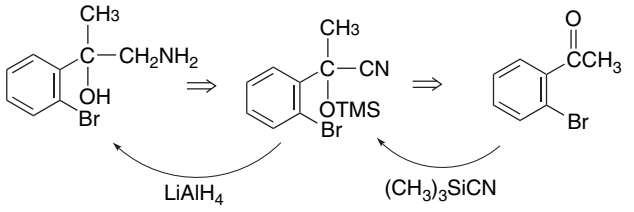
k. The retrosynthetic dissection to pentandial identifies a two-carbon fragment as the required complement. The required bonds could be formed from triethyl phosphonoacetate by combination of an aldol addition and a Wadsworth-Emmons reaction. The cyclization was effected using K_2CO_3.



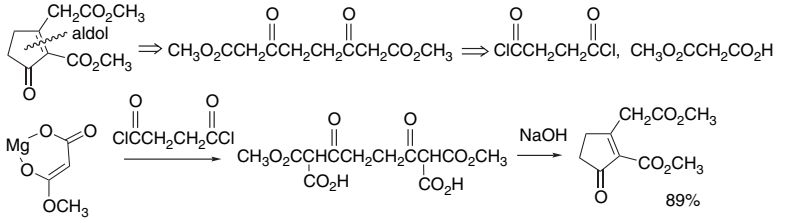
l. This reaction corresponds to the Robinson annulation of 2-methylpropanal. The reaction was done using the enamine and probably proceeds through a cyclic intermediate of a type observed in other conjugate additions of enamines to enones.



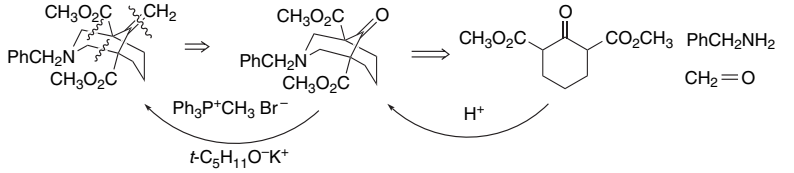
m. This transformation was accomplished by cyanohydrin formation and reduction. The reported procedure used TMSCN for cyanohydrin formation and $LiAlH_4$ for reduction.



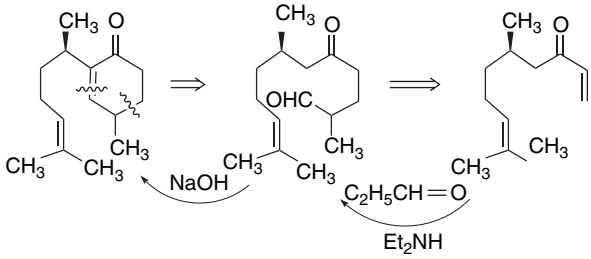
n. This compound can be dissected to succinoyl chloride by a reverse intramolecular aldol condensation to a *bis*-β-ketoester that can be obtained by acylation of an acetate equivalent at each terminus. In practice, the synthesis was done by acylation of the magnesium enolate of dimethyl malonate, followed by cyclization and hydrolytic decarboxylation.



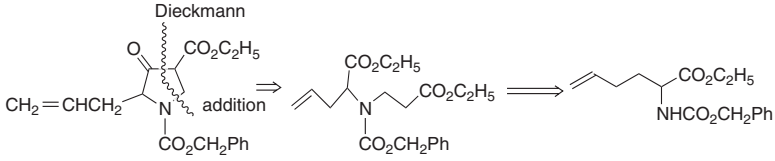
o. The nitrogen-containing ring can be installed by a Mannich reaction and the methylene group can be added by a Wittig reaction.



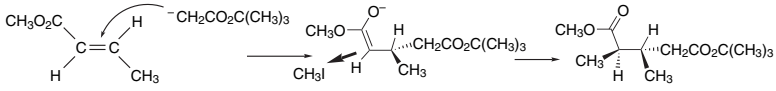
p. This transformation corresponds to a Robinson annulation of propanal. It was successfully accomplished by heating the enone with propanal and diethyl amine, followed by cyclization in basic solution.



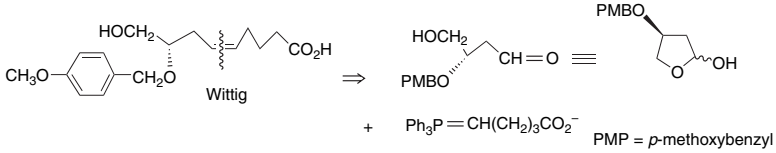
q. This reaction was conducted as a "one-pot" process that combines a conjugate addition to ethyl acrylate with a cyclic ester condensation (Dieckmann reaction). The reaction was done using NaH in benzene, which effects both the deprotonation and conjugate addition of the carbamate anion and the ester cyclization. The yield was 68%.



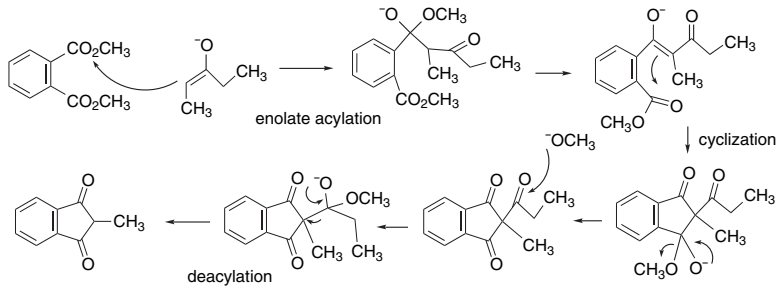
r. The transformation suggests a conjugate addition of an ester enolate with tandem alkylation. The reaction has been found to favor the *syn* isomer in the presence of HMPA, which is also used along with KO-*t*-Bu to enhance the reactivity of the enolate. The *syn* stereochemistry of the methyl groups arises from an approach opposite to the ester substituent in an H-eclipsed conformation of the enolate



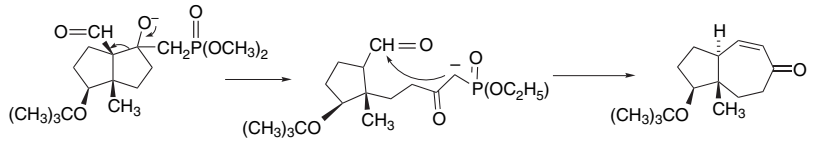
s. This transformation can be accomplished by a *Z*-selective Wittig reaction. The lactol was deprotonated with one equivalent of NaHDMS prior to the reaction with the ylide, which was formed using two equivalents of NaHDMS to account for the deprotonation of the carboxy group.



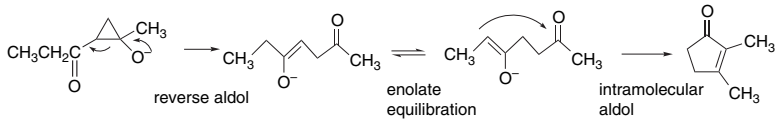
2.4. a. This reaction proceeds by ketone acylation, cyclization, and deacylation of the resulting triketone.



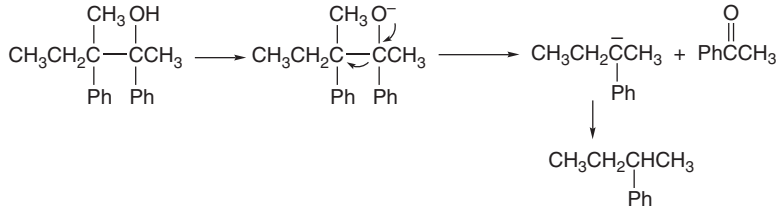
b. This reaction occurs by a reverse aldol addition followed by an intramolecular Wadsworth-Emmons reaction.



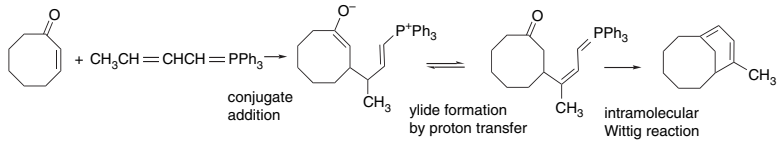
c. This transformation involves an opening of the cyclopropanol by a reverse aldol reaction, followed by intramolecular aldol condensation.



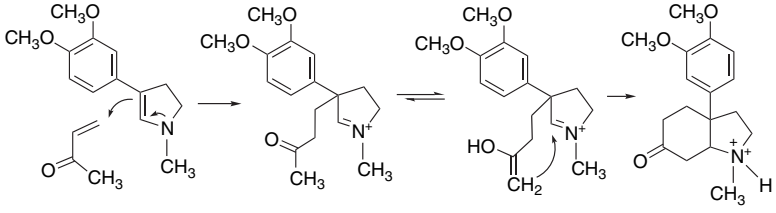
d. This cleavage occurs by carbanion elimination, which is irreversible because of the low acidity of the hydrocarbon product. (See p. 585 of Part A for additional information on this reaction.)



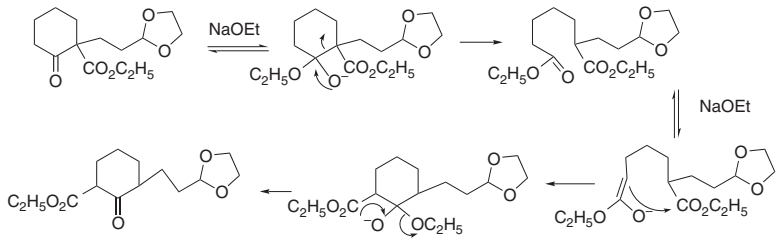
e. This reaction occurs by conjugate addition, proton transfer, and an intramolecular Wittig reaction. Note the formation of a bridgehead double bond, which probably involves some strain, but is driven by the irreversible elimination step of the Wittig reaction.



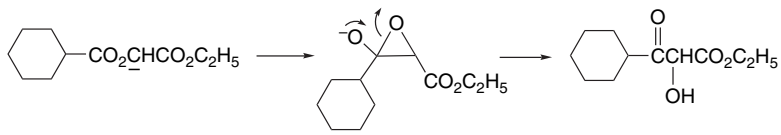
f. This reaction is an imine version of the Robinson annulation reaction, combining a conjugate addition with an intramolecular iminium addition (Mannich) reaction. An 85% yield was achieved using the hydrochloride salt in acetonitrile, but a much lower yield was observed in water.



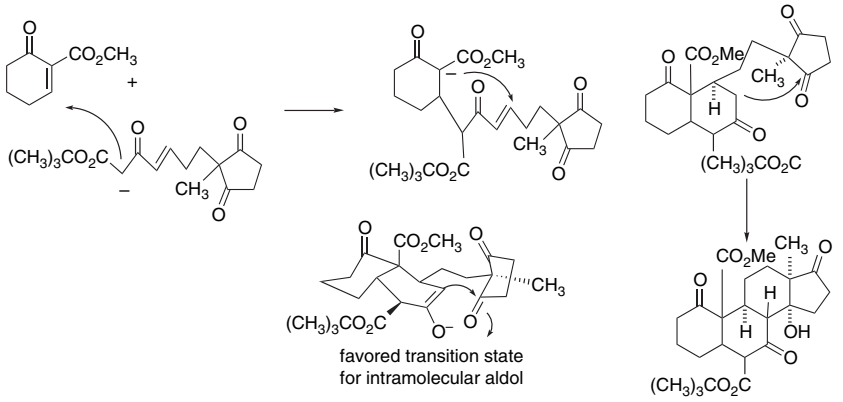
g. This transformation is the result of a reversible Dieckmann reaction, analogous to that described on p. 150.



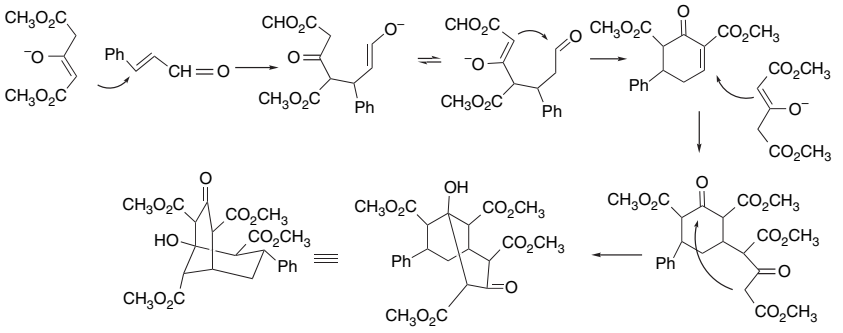
h. This reaction occurs by an intramolecular addition of the ester enolate to the adjacent carbonyl, with elimination of the oxygen leaving group. A number of similar examples were reported, suggesting that the reaction is general.



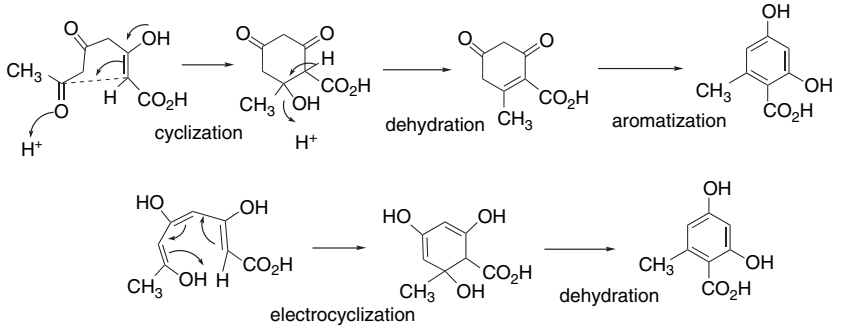
i. This is a base-catalyzed cascade that involves two conjugate additions. The *t*-butoxycarbonyl group is removed under acidic conditions after the base-mediated cyclizations. It is interesting that the reaction provides a single stereoisomer, despite the formation of two ring junctions and the creation of several new stereocenters. The first cyclization step can be formulated as a Diels-Alder reaction of the dienolate and the 2-carbomethoxycyclohexenone.



j. This reaction involves base-initiated addition of dimethyl acetonedicarboxylate to cinnamaldehyde, followed by an intramolecular aldol condensation. The resulting 2-carbomethoxycyclohex-2-ene can add a second molecule of dimethyl acetonedicarboxylate, and then cyclize by intramolecular aldol addition to the observed product.

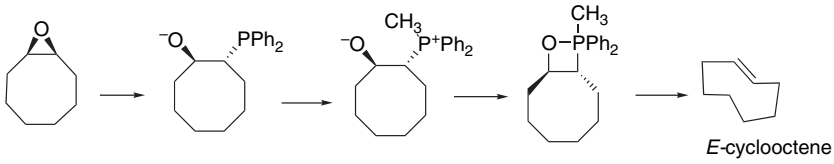


2.5. Under these mildly acidic conditions the reaction is likely to proceed through a concerted acid-catalyzed aldol reaction. The structure shows that addition must involve C(2) adding to C(6). It is conceivable that the reaction might be an electrocyclization of a trienolic form.

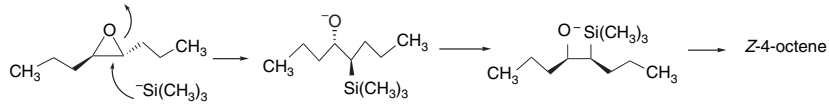


2.6. a. Inversion of configuration at the site of attack on the epoxide, followed by *syn* elimination accounts for the stereospecificity. The stereospecificity

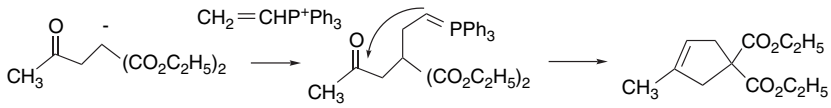
also precludes facile reversal dissociation-reformation of the betaine intermediate by a reverse Wittig reaction under these conditions. The betaine and oxaphosphetane structures are analogous to those involved in the Wittig reaction.



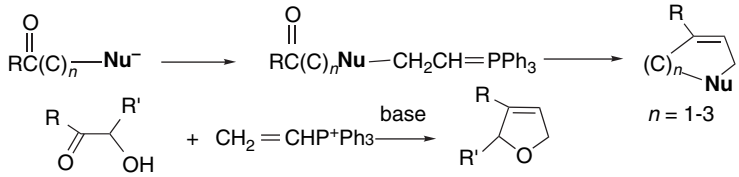
b. This reaction provides access to the β-oxysilane intermediate formed in the Peterson reaction. The *syn* elimination that occurs under basic conditions then gives rise to the *Z*-alkene.



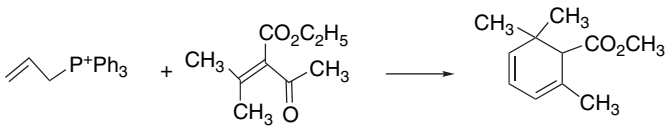
2.7. a. These reactions can proceed by conjugate addition to the vinyl group, generating a phosphorus ylide that can undergo an intramolecular Wittig reaction.



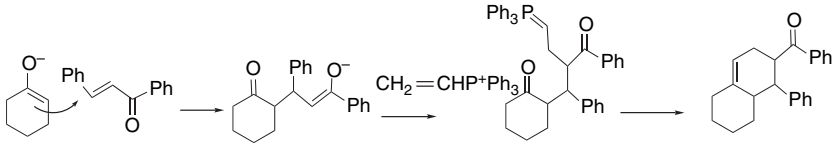
The reaction should be applicable to any molecule incorporating an anionic nucleophilic site β or γ to a carbonyl group, leading to formation of five- or six-membered rings, respectively. Conceivably, larger rings, e.g., seven-membered, could also be formed.



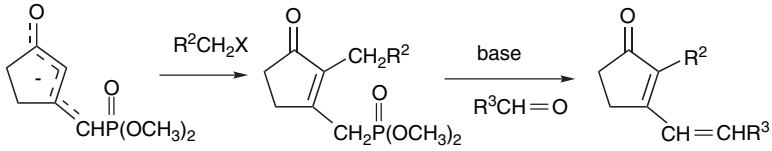
b. Generation of the ylide using CH_3Li and reaction with an alkylidene acetoacetate ester gave a cyclohexadiene by conjugate addition followed by an intramolecular Wittig reaction.



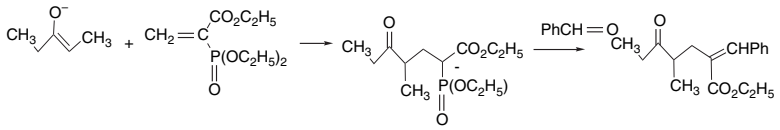
c. The reaction occurs by conjugate addition of the enolate to the enone, generating an enolate that undergoes conjugate addition to the vinyltriphenylphosphonium salt, which can then undergo cyclization with the carbonyl group.



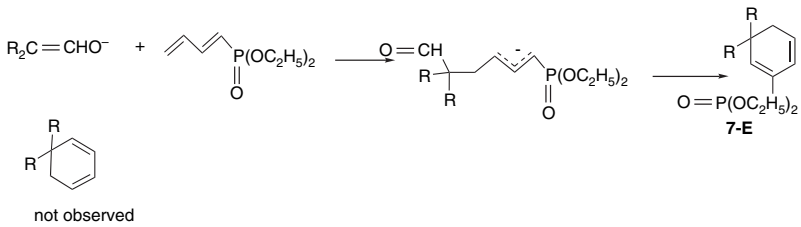
d. The enolate, which has a delocalized negative charge, must be selectively alkylated at C(2).



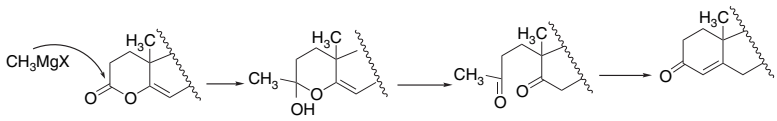
e. Conjugate addition of the enolate to the reagent sets the stage for a Wadsworth-Emmons reaction with benzaldehyde.



f. This product results from an aldol condensation rather than an Wadsworth-Emmons reaction after the conjugate addition step. Under other conditions, simple conjugate addition was observed.

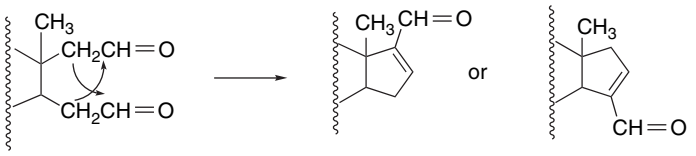


2.8. The first transformation involves a Grignard addition to the lactone carbonyl, generating a lactol that can open to a diketone. The two carbonyl groups are positioned for an intramolecular aldol condensation corresponding to the final stage of the Robinson annulation.

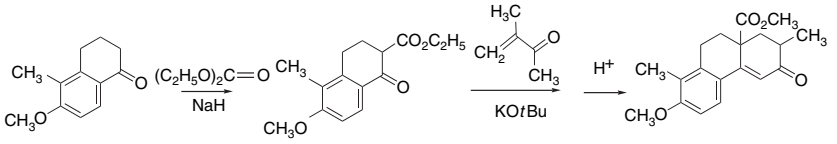


The second reaction involves an intramolecular aldol reaction in which there is an alternative regioisomeric possibility. The desired mode is favored (65% yield)

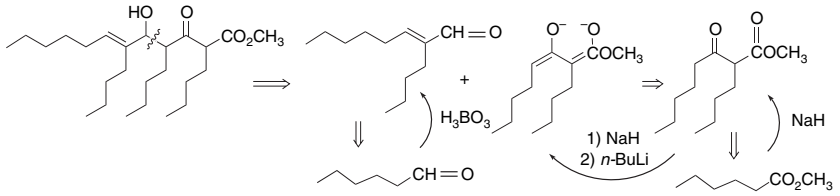
and the authors suggest that is this is due to a less hindered environment around the "upper" methylene group.



2.9. This transformation corresponds to methoxycarbonylation α to the carbonyl and a Robinson annulation with 3-methylbut-3-en-2-one.

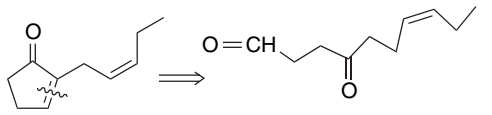


2.10. A retrosynthetic analysis suggests addition of the dianion of methyl 2-hexanoyl hexanoate to an aldehyde. These two compounds, respectively, are the Claisen condensation product of methyl hexanonate and the aldol condensation product of hexanal. The aldol product was effectively formed using boric acid as a catalyst. The dianion was formed using NaH followed by *n*-BuLi. The addition occurred at 0° C.



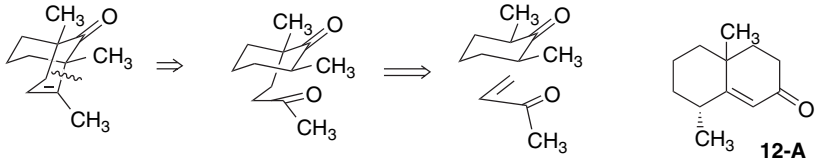
2.11. These results indicate that there is kinetically controlled formation of product **11-B** but that **11-C** is thermodynamically more stable. The reaction is reversible at 0° C, resulting in the formation of **11-C**. Although both **11-B** and **11-C** have the same collection of bond types, the following factors would contribute to the greater stability of **11-C**: (1) more-substituted and conjugated double bond; (2) steric destabilization of **11-C** owing to adjacent tetrasubstituted carbons; (3) weaker C–C bond in **11-B** due to the capto-dative nature of the exocyclic carbon (see Part A, p. 988).

2.12. a. This substance is an intermediate in the synthesis of methyl jasmonate. The C(2)–C(3) bond can be formed by an aldol condensation from *Z*-4-oxodec-7-enal.

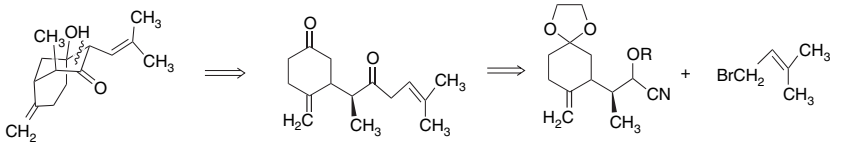


b. The marked bond can be obtained by an intramolecular aldol reaction. The double bond is located in the nonconjugated position because of the prohibition against a bridgehead double bond in this system. The required reactant can

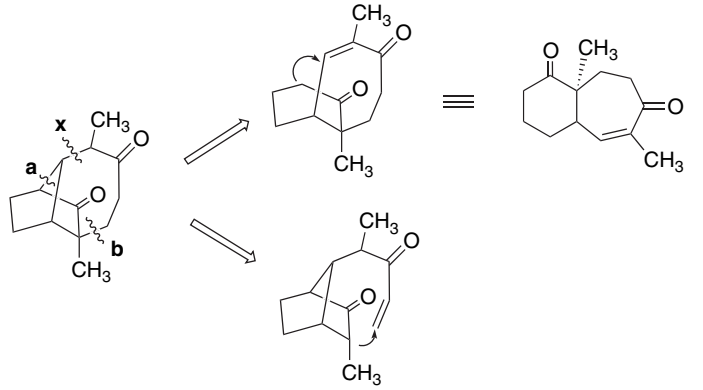
be obtained from 2,6-dimethylcyclohexanone and methyl vinyl ketone. The cyclization was done under acidic conditions. Under basic conditions the Robinson annulation product **12-A** is formed.



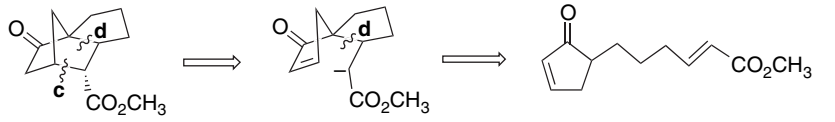
c. The marked bond identifies an intramolecular aldol disconnection. The side chain was added by using a cyanohydrin as an acyl anion equivalent.



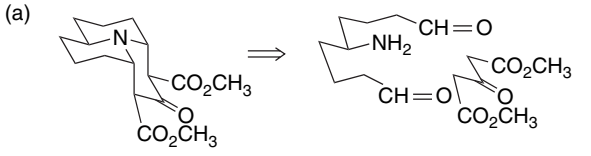
d. The bonds corresponding to possible intramolecular conjugate additions are marked **a** and **b**. The third bond marked **x** could formally be formed by a conjugate addition, but the double bond is at a bridgehead and would not be a practical intermediate. Disconnection **a** corresponds to the reported synthesis, which required heating with triethylamine in ethylene glycol at 225° C for 24 h.

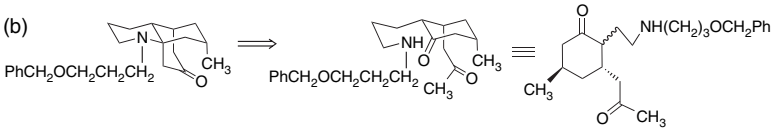


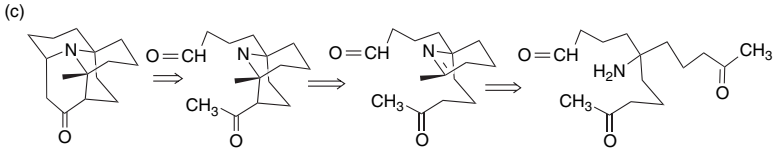
e. This molecule can be dissected to a monocyclic compound by a sequence of two anti-Michael disconnections. The cyclization occurred when the reactant was treated with LiHMDS.



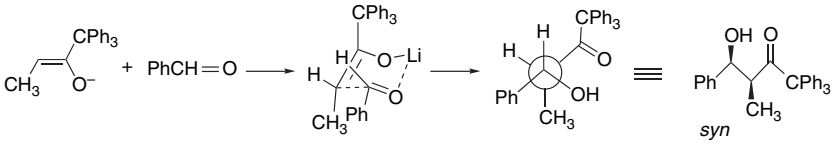
2.13.



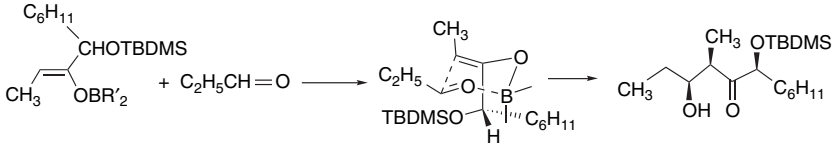




2.14. a. This ketone having one bulky substituent will form the *Z*-enolate and give primarily the *syn* product.



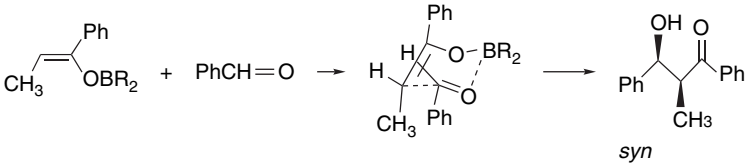
b. This ketone with one bulky substituent will form a *Z*-enolate and give 2,3-*syn* product. As the boron enolate does not accommodate further donors, there should be no chelation involving the silyloxy oxygen. There is a stereogenic center in the ketone and it controls the facial approach resulting in a 2, 2′-*syn* relationship between the methyl and siloxy substituents.



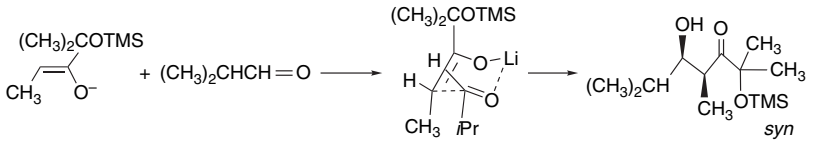
c. This unhindered ketone is expected to give a mixture of *E*- and *Z*-enolates and therefore not to be very stereoselective. The reported *E*:*Z* ratio is 70:30 and the observed *syn*:*anti* product ratio is 64:36.

d. This F^- mediated reaction would be expected to go through an open chain TS without high stereoselectivity. Experimentally, it is observed that the initial product ratio is 65:35 favoring the *syn* product and that this changes to 54:46 on standing. This suggests that equilibration occurs, as would be expected, but that there is no strong difference in stability of the *syn* and *anti* products.

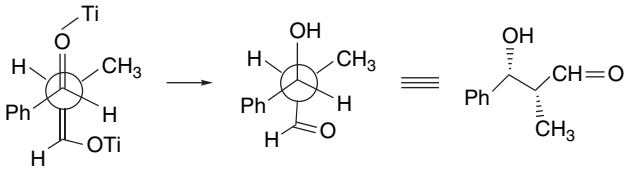
e. The *Z*-boron enolate is formed favoring *syn* product. The experimental ratio for these particular conditions is higher than 97:3 *syn*.



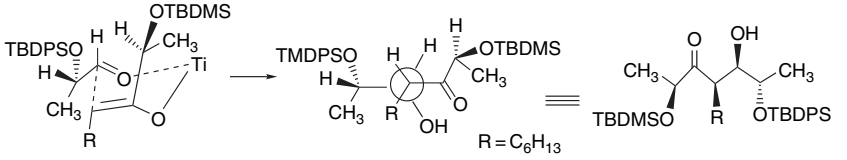
f. This ketone with one bulky substituent gives the *Z*-enolate and the *syn* product.



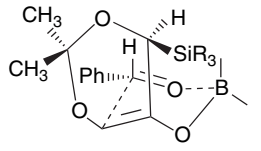
g. This reaction was carried out with excess Lewis acid. Under these conditions, it seems likely that an open TS would be involved (see p. 82). The observed 97:3 *syn* stereoselectivity is consistent with an open TS involving complexed aldehyde.



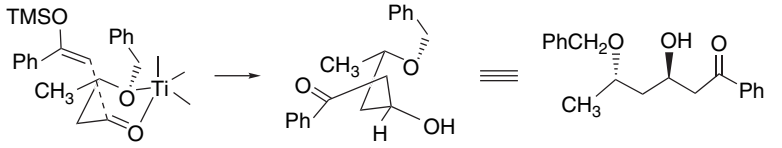
h. This reaction is highly stereoselective as a result of a Felkin-type approach governed by the siloxy substituents in both the aldehyde and enolate (see p. 113).



2.15. a.

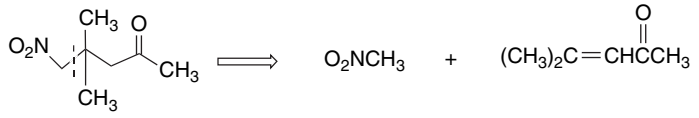


b. The predominance of the 1,3-*anti* product is consistent with a transition structure involving the chelated aldehyde.

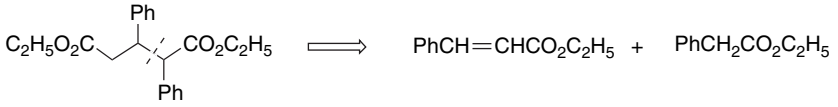


2.16. Conjugate additions reactions can always be dissected in two ways. Under equilibrium conditions, the more favorable dissection is to the stronger EWG(s) in the nucleophile and the weaker EWG(s) in the acceptor. This ensures that the adduct will be more extensively protonated than the nucleophilic reactant. All conjugate additions are usually thermodynamically favorable, however, since a new σ bond replaces a π bond, so the alternate combinations may both be feasible, especially under kinetic conditions.

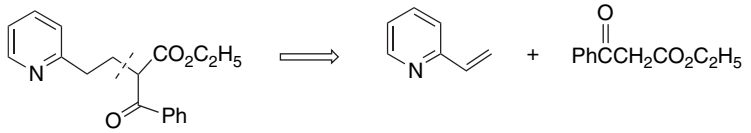
a. The nitro group is the strongest EWG, suggesting that nitromethane and the corresponding enone are the preferred reactants. The reaction has been carried out using triethylamine as the solvent.



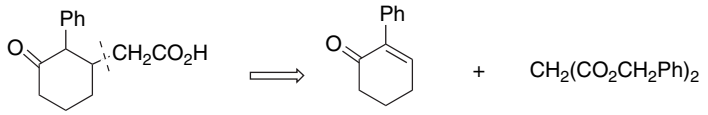
b. A retrosynthetic dissection suggests the readily available ethyl cinnamate and ethyl phenyl acetate as reactants. The reaction has been effected in quantitative yield by sodium ethoxide.



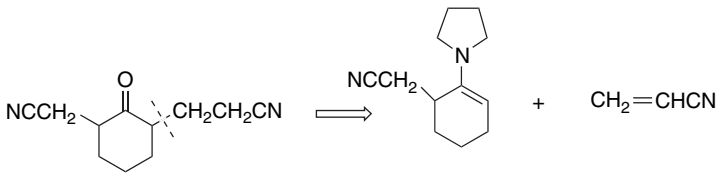
c. The EWG character of the pyridine ring makes vinylpyridine a suitable acceptor and indicates ethyl 3-oxo-3-phenylpropanoate as the potential nucleophilic component. The reaction has been done using sodium metal to generate the enolate.



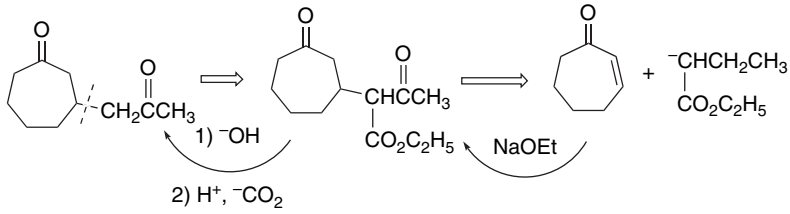
d. A direct reaction between 2-phenylcyclohexenone and the enolate of ethyl acetate is problematic because of the potential competition from 1,2-addition. The reaction has been done using dibenzyl malonate as the nucleophile, with debenzylation and decarboxylation to the desired product. The benzyl ester was used to permit catalytic debenzylation (see Section 3.5.1), which was followed by thermal decarboxylation.



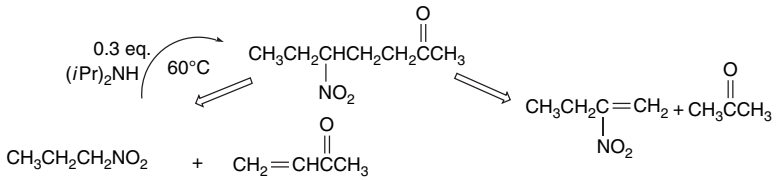
e. A retrosynthetic dissection identifies acrylonitrile as the most accessible acceptor. The reaction has been achieved in 38% yield via the pyrrolidine enamine, followed by hydrolysis of the adduct.



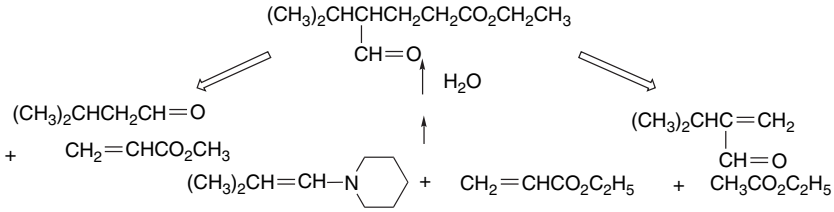
f. Ethyl acetoacetate can be used as the synthon for ethyl acetate in an addition to cycloheptenone. A 52% yield was obtained after hydrolysis and decarboxylation.



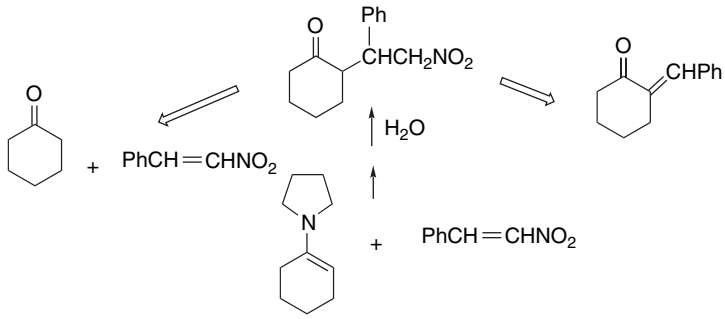
g. The retrosynthetic analysis identifies nitropropane and methyl vinyl ketone or a nitroalkene and acetone equivalent. The former combination takes advantage of the higher acidity of the nitroalkane and the reaction has been reported to proceed in 61% yield with amine catalysis.



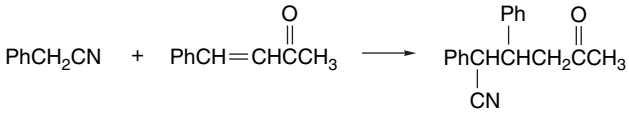
h. A formal retrosynthesis identifies 3-methylbutanal and ethyl acrylate or α-(isopropyl)acrolein and ethyl acetate as possible combinations. Because of the low acidity of each potential nucleophile, direct base-catalyzed addition is unlikely to be effective. The reaction was conducted successfully using an enamine as the equivalent of the aldehyde enolate.



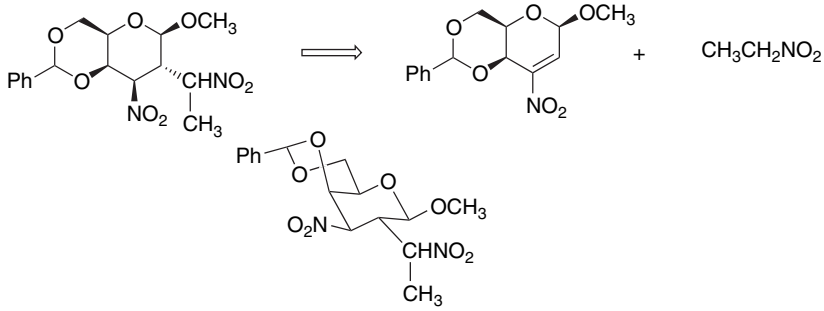
i. Retrosynthetic analysis identifies cyclohexanone and β-nitrostyrene or nitromethane and benzylidenecyclohexanone as the components. The reaction has been reported to occur in 84% yield using the enamine of cyclohexanone. The alternate combination also seems feasible, but does not appear to have been studied.



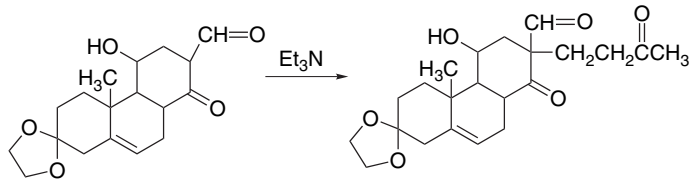
j. Phenylacetonitrile and 4-phenylbut-2-en-3-one gave a 65:35 *erythro*:*threo* mixture.



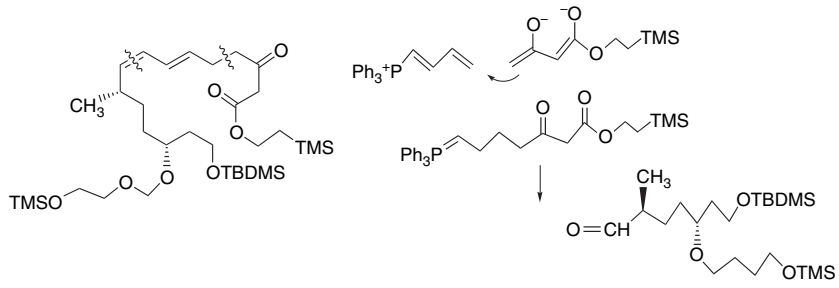
k. This compound can be made by addition of nitroethane to a bicyclic carbohydrate-derived nitroalkene. The reaction was done using triethylamine as the base. The stereoselectivity of the addition may reflect thermodynamic control through reversible elimination and addition, as well as equilibration at the nitro-substituted C(3) position.



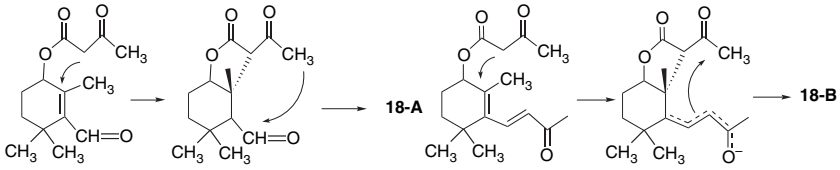
l. The 3-oxobutyl substituent was introduced by conjugate addition to but-3-en-2-one.



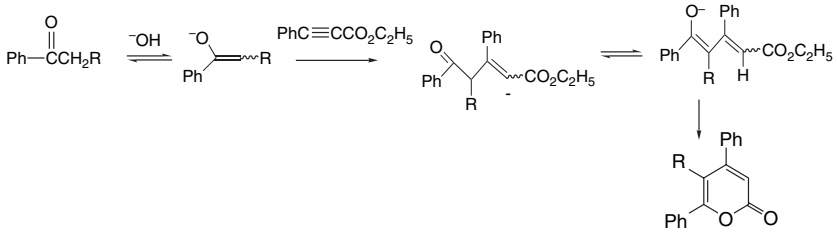
2.17. The 1,4-dibromo-2-butene (**17D**) can be converted to a butadienyl phosphonium salt. This can react as an electrophile toward addition of the *dianion* of the trimethylsilylethyl ester of acetoacetic acid to generate a phosphorus ylide. The ylide can react with the aldehyde **17E** to give the desired intermediate. The dianion was generated using two equivalents of LDA at 0° C and added to the butadienylphosphonium salt. The aldehyde was then added completing the synthesis.



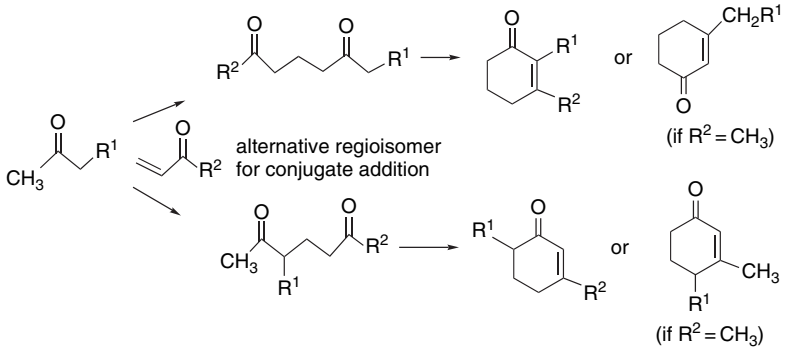
2.18. The formation of **18-A** involves conjugate addition of the acetoacetate group to the enal moiety, followed by intramolecular aldol cyclization to form the cyclohexenone ring. The reaction was effected using K_2CO_3. The formation of **18-B** occurs by a 1,6-conjugate addition, followed by addition of the resulting enolate to the ketone carbonyl of the acetoacetyl group. The cyclization was best done using Cs_2CO_3 as the base.



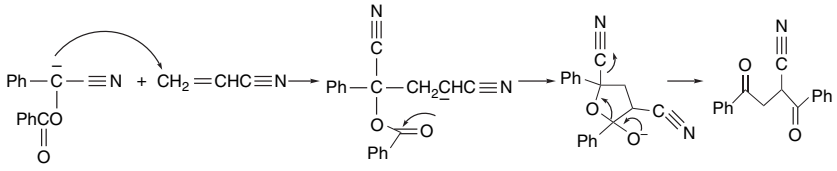
2.19. a. The pyrones can form by conjugate addition followed by formation of a new enolate and cyclization.



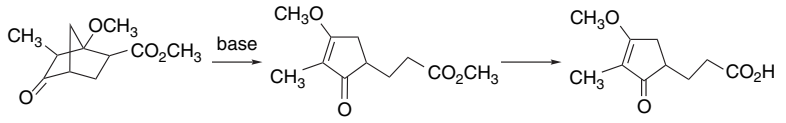
b. These reactions are analogous to Robinson annulation reactions. For unsymmetrical ketones, two enolates are possible. Also, for methyl ketones at least, there may be two alternative routes of cyclization. In most cases, it should be possible to distinguish between the isomers on the basis of NMR spectra.



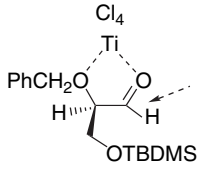
c. This transformation can occur by conjugate addition, followed by an intramolecular transfer of the benzoyl group.



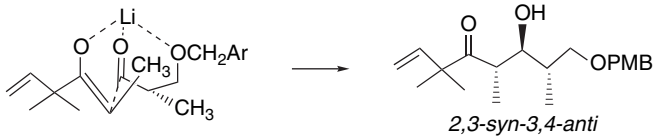
d. The minor product is the result of an intramolecular Michael addition involving the ester enolate. This reaction can be reversed during the basic hydrolysis, but hydrolysis to the carboxylate would make the process irreversible because the carboxylate would not provide an enolate suitable for addition.



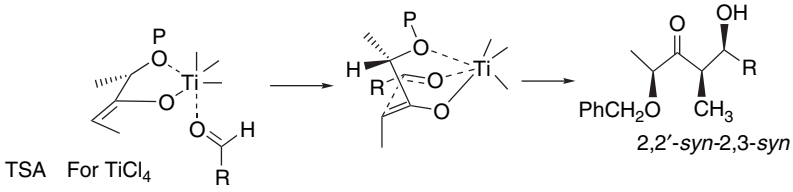
2.20. a. This reaction gives the *anti*,*anti*-stereoisomer as the result of a chelated reactant.

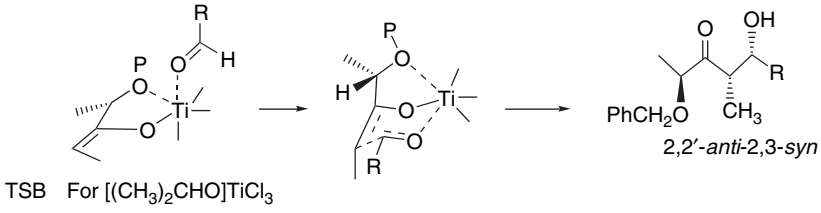


b. This reaction gives a 4:1 predominance of *syn*,*anti* product as the result of reaction through a chelate of the β-*p*-methoxybenzyl group.

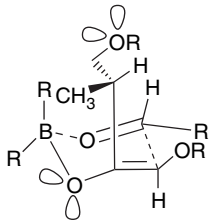


c. At a superficial level, this result could be explained by a chelated TS leading to the *anti*,*syn* product and an open TS leading to the *syn*,*syn* product. However, this requires that the $[(CH_3)_2CHO]TiCl_3$ Lewis acid be chelating and $TiCl_4$ be nonchelating. This does not accord with the known properties of $TiCl_4$ in such reactions. The authors suggested that the difference might be the result of stereoelectronic effects having their origin in the difference caused by the isopropxy versus Cl ligand and proposed TS **A** and **B**.



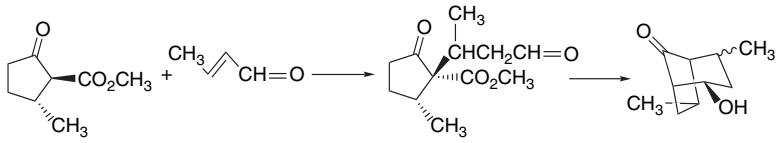


d. The transition structure has been suggested on the basis that it minimizes 1,3-allylic strain and repulsions between unshared electron pairs.

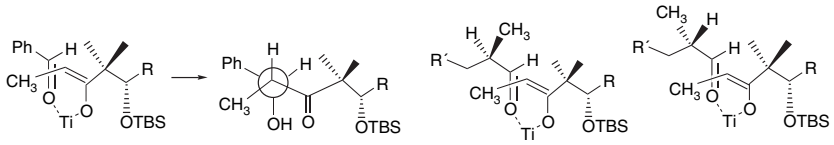


e. The stereoelectronic preference for an axial approach in combination with the steric shielding of the TBDMS group favors approach from the upper (β) face.

f. The Michael addition is followed by an aldol cyclization. The addition takes place exclusively *trans* to the methyl substituent, but is not entirely stereoselective with respect to the methyl substituent.

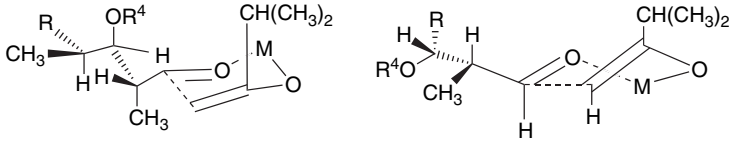


2.21. Although this reactant carries a chiral auxiliary, it is remote from the reaction site and unlikely to strongly influence the diastereoselectivity. Rather, this is a case of a hindered ketone that will form a *Z*-enolate. It also appears unlikely that there will be chelation with the siloxy substituent. The case of benzaldehyde indicates that the inherent stereoselectivity arising from the *Z*-enolate configuration is about 3:1. In the case of the aldehyde having the *R*-configuration, the C(2)-methyl substituent is mismatched. In the case of the *S*-aldehyde, the configuration is matched.



mismatched matched

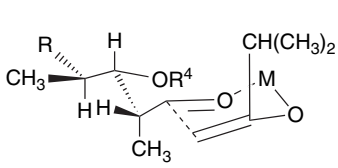
2.22. The 3,4-*syn* products are the Felkin approach products, whereas the 3,4-*anti* products result from an anti-Felkin approach. It has been suggested that the results reflect competition between chair and nonchair transition structures. For **22A**, interactions between the metal ligands and the enolate isopropyl group will destabilize the chair-Felkin TS.



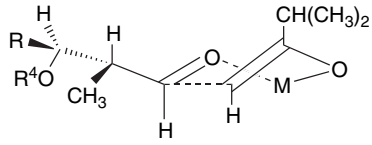
chair-Felkin TS for **22A**

nonchair anti-Felkin TS for **22A**

For **22B**, the chair-Felkin TS has an unfavorable alignment of the β-oxy substituent. However, this TS is destabilized by interactions between the metal ligands and the enolate isopropyl group, leading to diminished selectivity with increased bulk at the enolate metal.

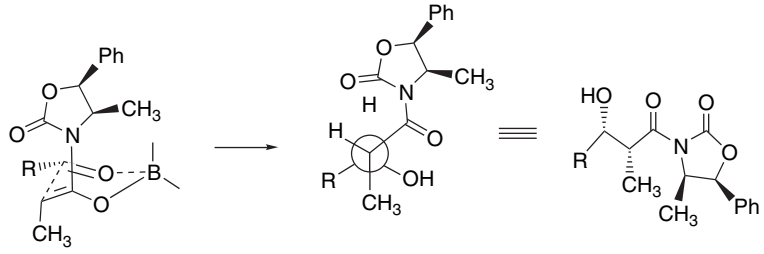


chair-Felkin TS for **22B**

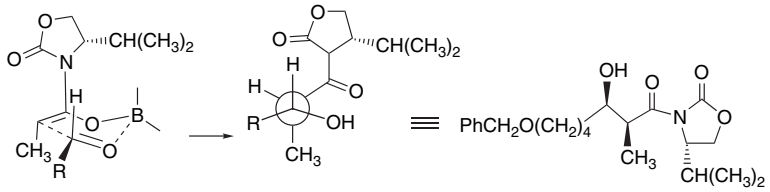


nonchair anti-Felkin TS for **22B**

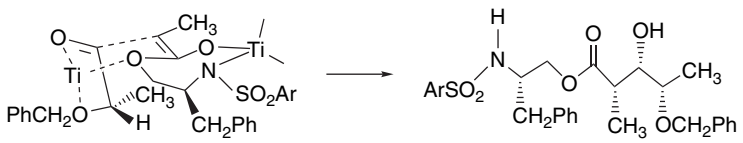
2.23. a. This reaction proceeds through the *Z*-boron enolate with approach controlled by the chiral auxiliary and gives the 2-(*R*)-3-(*S*) product. The aldehyde is achiral and presents no issue of facial selectivity.



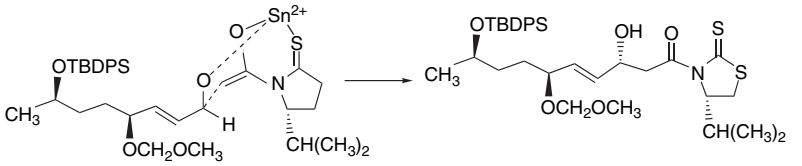
b. This reaction occurs through the *Z*-enol boronate with the facial selectivity determined by the chiral auxiliary. The aldehyde is achiral.



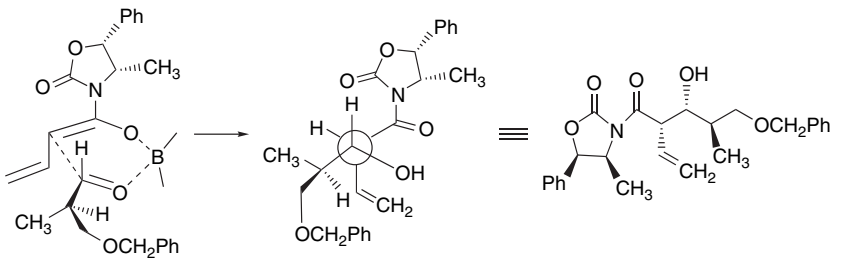
c. A transition structure with chelation of both aldehyde benzyloxy group and the enolate sulfonamide has been suggested and is consistent with the observed stereoselectivity.



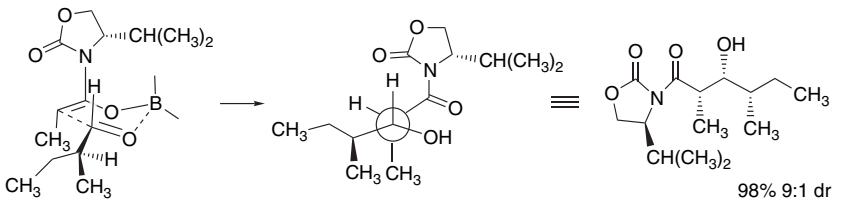
d. The observed 3,6-*anti* stereochemistry is consistent with approach to the chelated enolate *anti* to the methoxymethyl substituent.



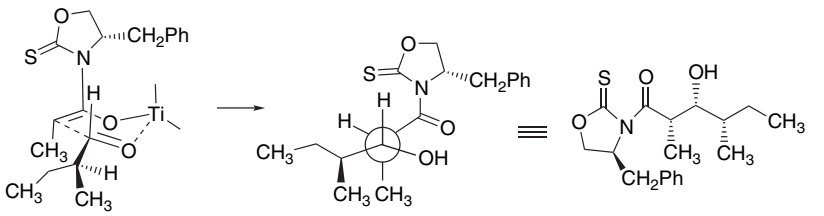
e. Deprotonation occurs at the γ-carbon and leads to a 2,3-*syn* aldol. The facial approach in the aldehyde control results from the β-benzyloxy group.



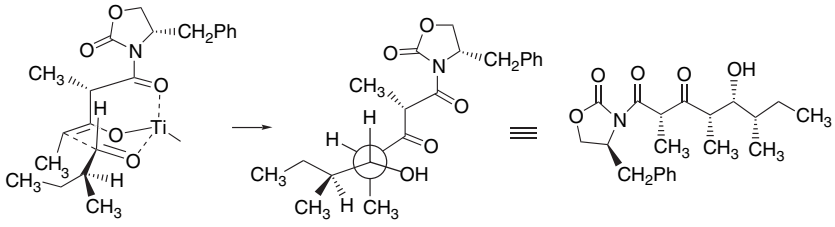
f. The reaction proceeds in 98% yield with 9:1 facial selectivity with respect to the aldehyde.



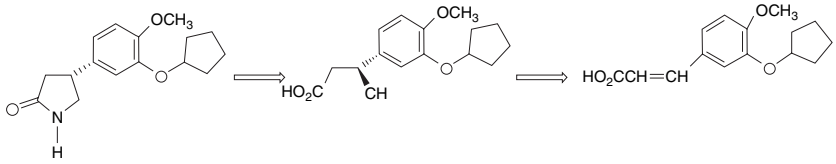
g. These conditions should result in reaction through a nonchelated transition structure, with respect to the oxazolidinethione ring. The stereoselectivity was higher than 98:2.



h. As described on p. 119, deprotonation occurs at the γ-carbon and there is a stereocenter at the α-carbon. The product is obtained in 65% yield and the *syn*:*anti* selectivity is 4:1.



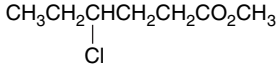
2.24. The retrosynthetic analysis shows that enantioselective introduction of cyanide followed by a reductive cyclization would accomplish the synthesis. The enantioselectivity was achieved by converting the carboxy group to a 4-phenyloxazoline derivative, which served as a chiral auxiliary in the introduction of cyanide.



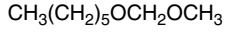
2.25. 1. All the structures show a hydrogen bond interaction between the carboxy group and the benzaldehyde carbonyl.
2. The (*S*,*R*), (*R*,*S*) and (*S*,*S*) structures have a relatively short N–H—O hydrogen bond.
3. The phenyl and cyclohexyl groups are staggered in the favored (*S*,*R*) TS.
4. The methyl group has an unfavorable interaction with the cyclohexyl group in the (*R*,*S*) TS.

Chapter 3

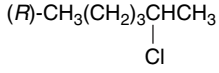
3.1. a. Methanolysis of the lactone and conversion of the alcohol group to the chloride occurs.



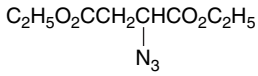
b. These conditions install the methoxymethyl (MOM) group.



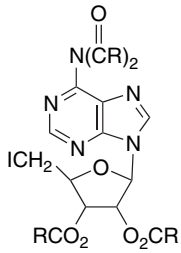
c. This reagent effects conversion of the secondary alcohol to a chloride with inversion of configuration.



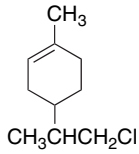
d. These conditions effect conversion to the azide by the Mitsunobu process. Inversion of configuration is expected.



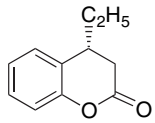
e. These conditions convert the unprotected primary alcohol to the iodide.



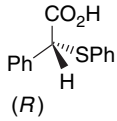
f. These conditions lead to the formation of the primary chloride.



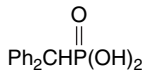
g. The ether group is cleaved and lactonization occurs.



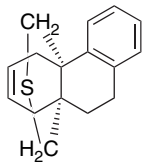
h. Conversion to the tosylate is followed by substitution with inversion of configuration in the second step.



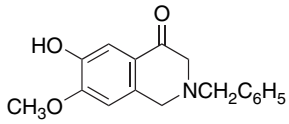
i. A Michaelis-Arbuzov reaction occurs. The product was isolated as the phosphonic acid after alkaline hydrolysis.



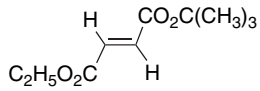
j. These conditions lead to formation of the cyclic sulfide by displacement of both mesylate groups.



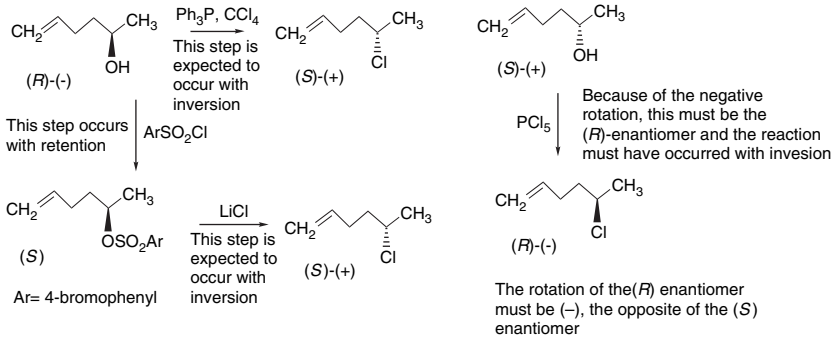
k. A selective monodemethylation occurs. The selectivity is attributed to the reduced basicity of the 7-methoxy groups as a result of its conjugation with the carbonyl group.



l. These reagents form the *t*-butyl ester at the free carboxy group.

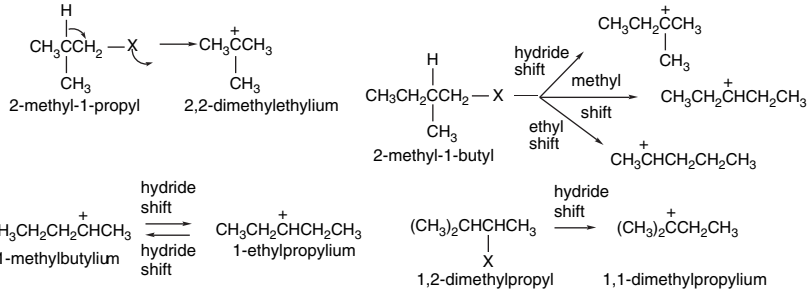


3.2. The following is a set of self-consistent stereochemical assignments. Precedent for the inversion in the two reactions leading to (+)-5-chloro-1-hexene leads to the assignment of the (*S*)-configuration. The (−) enantiomer must then have the (*R*)-configuration, and the reaction with PCl_5 must also involve inversion.

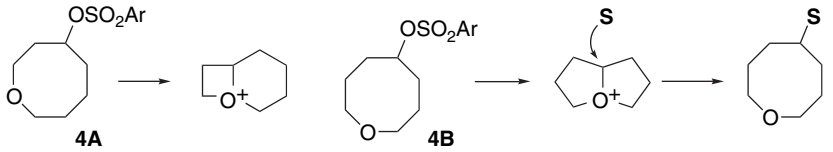


3.3. Steric hindrance at the reaction site is the most important factor leading to rearrangement. The extent of rearrangement also increases with the stability of the rearranged cationic intermediate. The unhindered 1-butanol gives no rearrangement product. A trace amount of rearrangement occurs in 2-methyl-1-propanol. Significant (22%) rearrangement occurs with the somewhat more hindered 2-methyl-1-butanol. The product mixture shows that both hydride and methyl migration occur to a similar extent, although the former leads to a more stable tertiary cation. The minor (1%) product can be accounted for by an ethyl shift or by successive methyl and hydride shifts. Nearly complete (98%) rearrangement occurs with 2,2-dimethyl-1-propanol (neopentyl alcohol). This case involves both a hindered substitution site and a favorable primary to tertiary rearrangement. The secondary alcohols, 2-pentanol and 3-pentanol show 2 and 10% rearrangement, respectively, consistent with modest hindrance and the existence of only secondary to secondary rearrangement. The more hindered 3-methyl-2-butanol, which can rearrange to a tertiary system, gives 95% rearrangement. The rearrangements are consistent with formation of carbocations under conditions of relatively short lifetime (see Section 4.4.3). The mechanism for formation of chlorides using thionyl chlorides suggests that chlorosulfite esters are involved as intermediates. The rearrangements may occur in tight ion

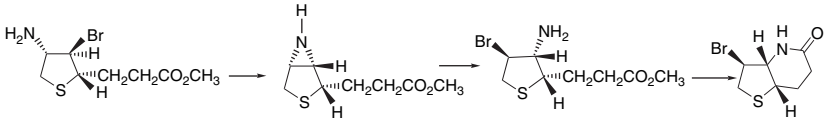
pairs formed by SO_2 elimination. The rearrangements that are observed are the following:



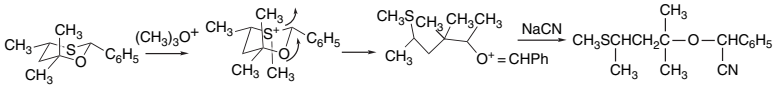
3.4. a. The solvolysis can be assisted by the ether oxygen. The 1-oxabicyclo [3.3.0]octane ring available from **4B** is less strained and more stable than the 1-oxabicyclo[4.2.0]octane isomer from **4A**.



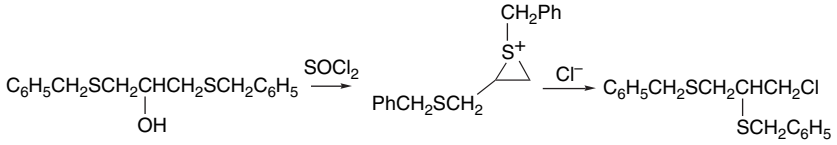
b. The rearrangement of bromine can be accounted for by reversible aziridine formation, with intramolecular acylation providing a stable cyclization product that leads to complete conversion.



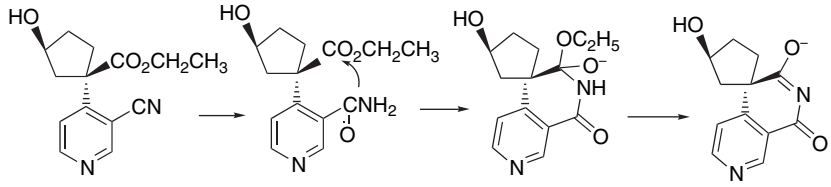
c. *S*-Methylation can lead to ring opening, followed by capture of the oxonium ion by cyanide.



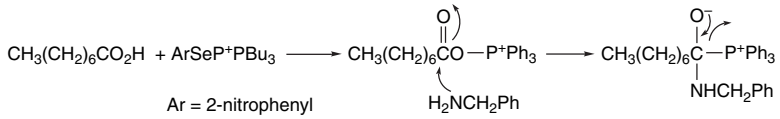
d. The rearrangement can occur by sulfur participation and formation of a thiiranium ion.



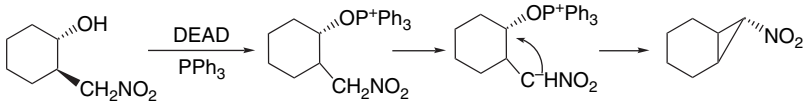
e. Addition of hydroxide to the cyano group can form an amide that undergoes cyclization. The reaction may also be favored by formation of the anion of the imide.



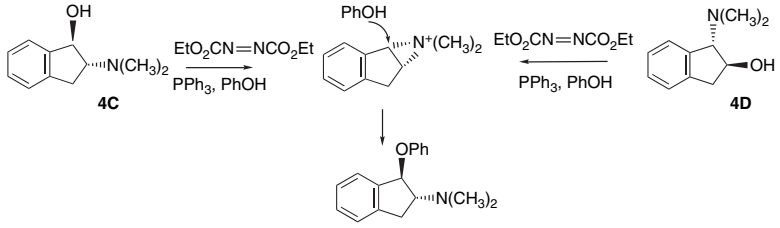
f. The selenenyl cyanide, which provides an electrophilic selenium, activates the phosphine in a manner similar to the halogen-phosphine combinations. An acyloxyphosphonium ion is the active acylating agent.



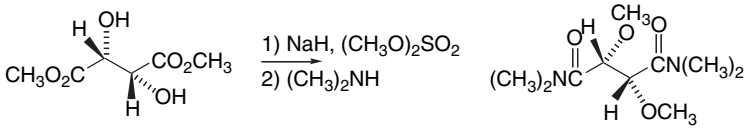
g. The hydroxy group is activated as a leaving group by a Mitsunobu reaction. The nitromethyl group is sufficiently acidic to provide a nucleophile anion that cyclizes.



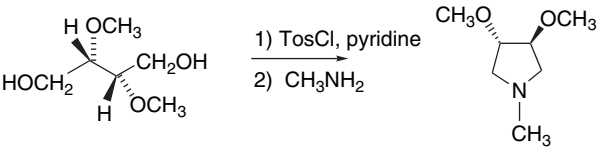
h. The Mitsunobu conditions convert both compounds to the same aziridinium ion, which is opened preferentially at the secondary benzylic position by phenol.



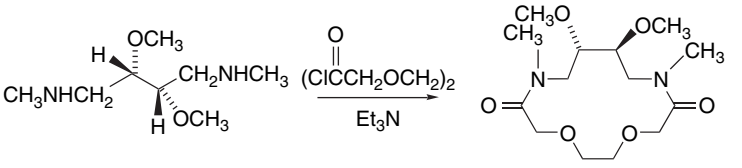
3.5. a. Starting with dimethyl tartrate, the hydroxy groups were methylated. The amide was formed by aminolysis of the ester. Neither of these reactions affects the stereocenters, so configuration is maintained.



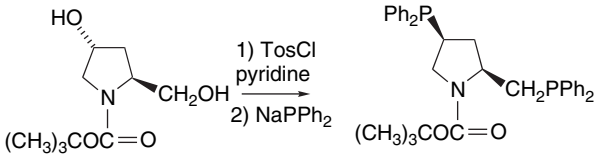
b. The methylated tartrate ester was reduced to give the diol, which was converted to a ditosylate. Reaction with methylamine led to cyclization. None of these reactions involves the stereocenters and configuration is maintained.



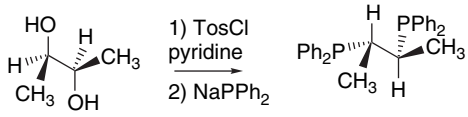
c. The dimethoxy-*N*,*N*′-dimethylamine was allowed to react with a diacid chloride. The macrocyclic dilactam formed in acceptable yield. The reaction does not involve the stereocenters.



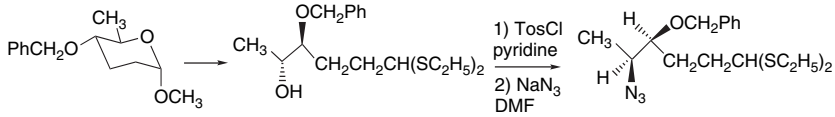
d. The diol, which is derived from the amino acid proline, was converted to a ditosylate. Displacement by $NaPPh_2$ gives the desired product, including inversion at C(4) of the pyrrolidine ring.



e. The diol was converted to the corresponding ditosylate, then subjected to displacement with $NaPPh_2$, with inversion of configuration.

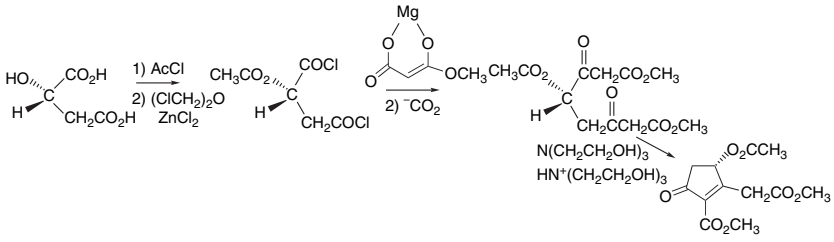


f. The ring was opened by conversion to a dithioacetal. The hydroxy group was then converted to a tosylate and subjected to displacement with NaN_3, with inversion of configuration.

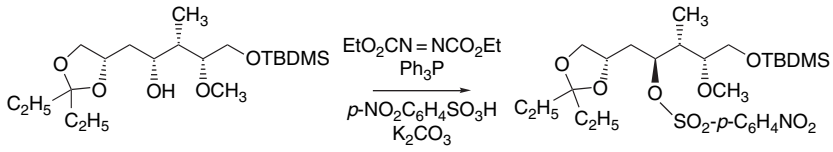


g. The starting compound, malic acid, was acetylated and then converted to the diacid chloride. The diacid chloride was used to acylate two equivalents of the magnesium salt of the monomethyl ester of malonic acid (see p. 152). The product was decarboxylated. On treatment with triethanolamine–triethanolamine hydrochloride, intramolecular aldol condensation occurred.

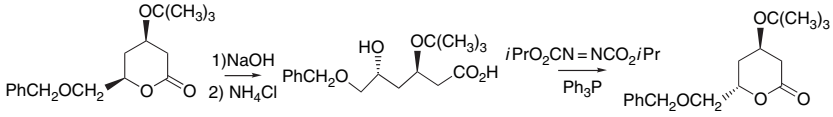
The configuration of the acetoxy-substituted carbon is unaffected by the other transformations.



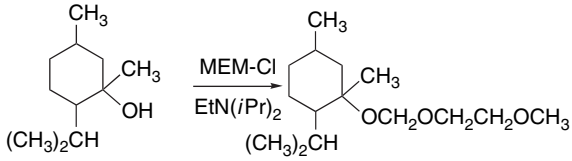
h. The hydroxy group was converted to the 4-nitrobenzenesulfonate with inversion via the Mitsunobu reaction.



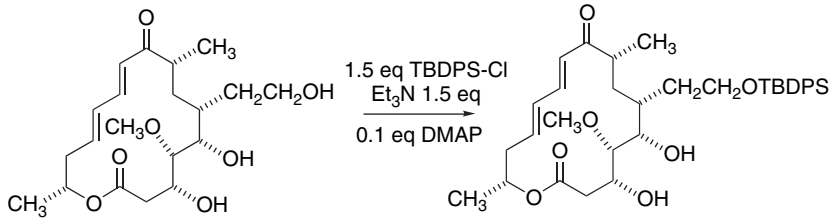
i. The lactone was hydrolyzed. Then, using the Mitsunobu reaction, the lactone was reformed with inversion of configuration at the oxygen-substituted carbon.



3.6. a. The methoxyethoxymethyl (MEM) group can be introduced at a tertiary alcohol by treatment with methoxyethoxymethyl chloride and a tertiary amine.



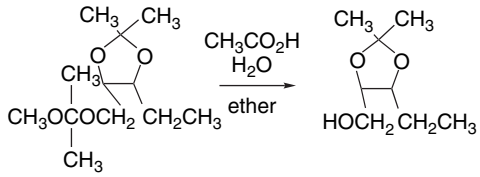
b. A TBDPS group can be selectively introduced on the primary hydroxy group using 1.5 equivalent of the silyl chloride and Et_3N and 0.1 equivalent of DMAP.



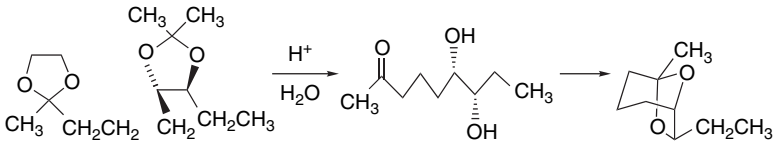
c. The TBDMS group can be introduced using 1.1 equivalent of the silyl chloride and 2.5 equivalent of imidazole in DMF.

d. This protection of an aldehyde group as a dithiane can be done by reaction with 1,3-propanedithiol in the presence of BF_3.

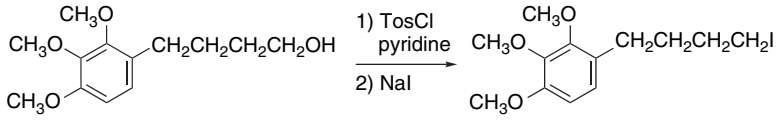
e. This removal of a 2-methoxypropyl group without hydrolysis of the dioxolane ring can be done by reaction with a mixture of acetic acid, water, and ether as the solvent.



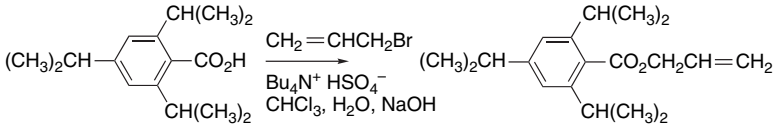
f. This transformation occurs in aqueous methanol in the presence of a catalytic amount of *p*-toluenesulfonic acid. The product is the internal acetal of the fully deprotected compound that is generated by removal of the two protecting moieties.



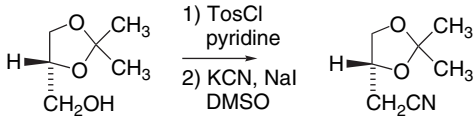
3.7. a. This transformation was done by conversion to the tosylate, followed by displacement with iodide. Other methods for preparation of iodides, such as the imidazole-Ph_3P-I_2 system should also be applicable. The potential for intramolecular participation of the electron-rich aromatic ring exists for very reactive leaving groups.



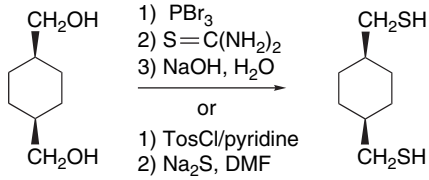
b. This hindered ester was prepared by carboxylate alkylation with allyl bromide under phase transfer conditions, but closely related structures were also obtained by forming the acyl chloride using $SOCl_2$.



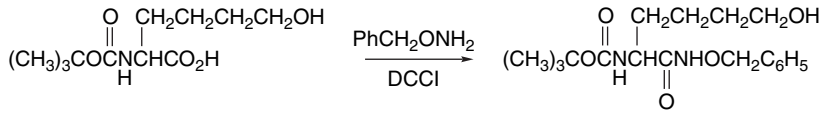
c. Because of the dioxolane protecting group, acidic conditions must be avoided. The reaction was done by tosylation, followed by iodide-catalyzed displacement by cyanide in DMSO.



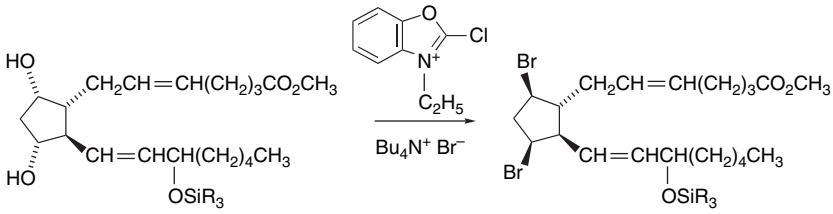
d. This reactant offers some potential for an intramolecular cyclization (see Problem 3.1j). The reaction was done by two sequences: (a) conversion to the dibromide with PBr_3, reaction with thiourea, and hydrolysis, or (b) conversion to the tosylate and reaction with Na_2S in DMF.



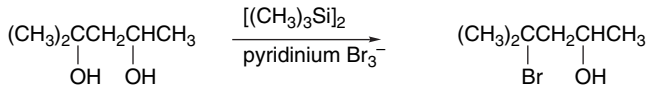
e. This amide formation was done using DCCI as a coupling agent. The *t*-butoxycarbonyl protecting group requires avoidance of acidic conditions.



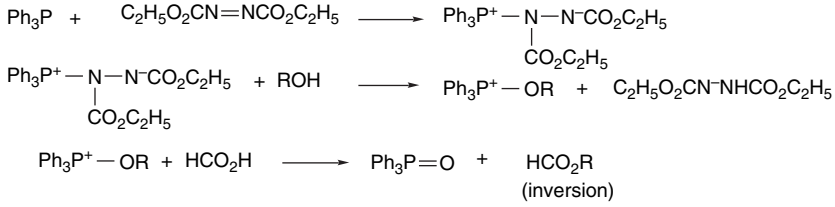
f. This replacement of two hydroxy groups in a prostaglandin skeleton by bromide with inversion of configuration was done using 2-chloro-3-ethylbenzoxazolium chloride and a bromide source. Preparation of the ditosylate, followed by bromide displacement was found to give a mixture of stereoisomers, presumably formed as the result of competing bromide on bromide displacement, leading to stereoisomers.



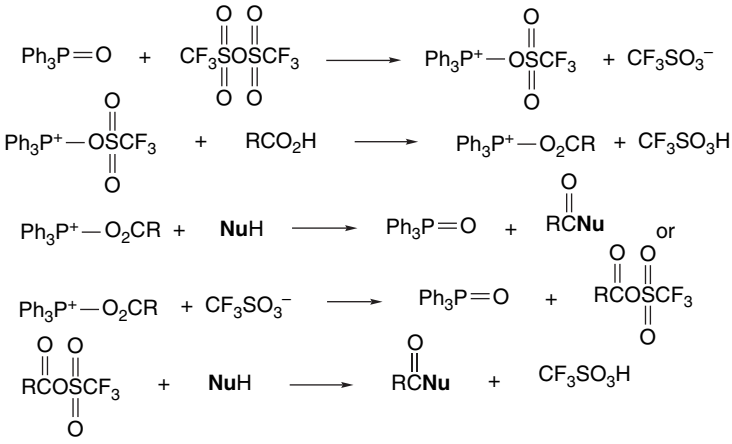
g. This preferential substitution of a tertiary alcohol in a diol can take advantage of reaction conditions that favor an S_N1 mechanism. Avoidance of pinacol rearrangement (see Section 10.1.3.1) has to be taken into account. The reaction was done successfully using trimethylsilyl bromide, generated in situ from hexamethyldisilane and pyridinium bromide perbromide.



3.8. a. The mechanism of the Mitsunobu reaction commences with activation of Ph_3P by DEAD, followed by formation of an alkoxyphosphonium salt and displacement.



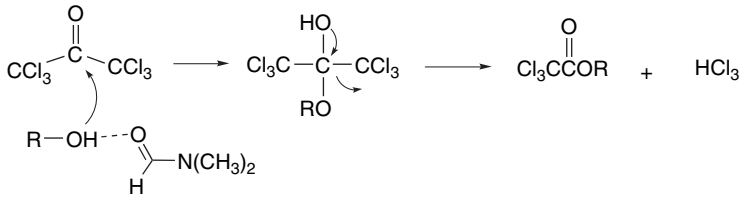
b. Nucleophilic displacement by Ph_3P would generate a highly reactive phosphonium triflate, analogous to the reaction of Ph_3P with the halogens. On reaction with a carboxylic acid, an acyloxy phosphonium ion would be formed. These are known to act as acylating agents. Conceivably, acyl triflate intermediates are formed, since they would also act as acylating agents.



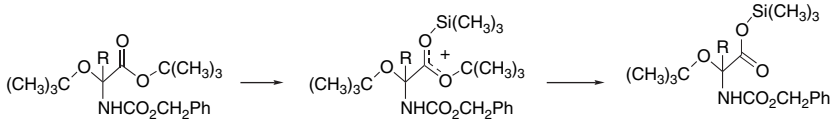
c. The positively charged nitrogen exerts an inductive EWG effect that will enhance the leaving-group ability of the substituted sulfonate. There is also a favorable electrostatic component in reactions with anionic nucleophiles. The enhanced reactivity in two-phase solvent systems suggests that they may also act as internal phase transfer agents by drawing desolvated anionic nucleophiles into the organic phase.

d. The formation of trichloroacetates indicates that the mechanism involves a nucleophilic addition at the carbonyl group of hexachloroacetone, followed

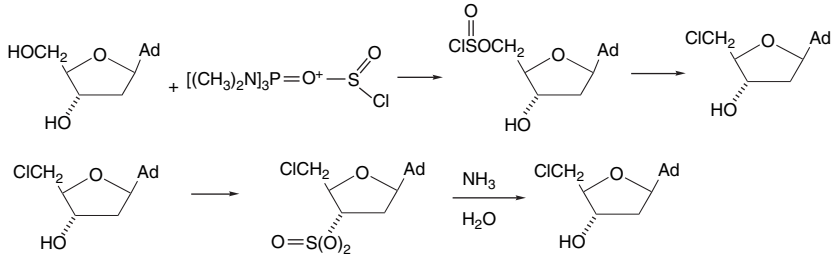
by cleavage with expulsion of the trichloromethyl anion, as in the haloform reaction. In this mechanism, the primary > secondary ≫ tertiary order is due to steric factors at the adduct formation stage. The role of the DMF is not entirely clear. It may assist in the formation of the tetrahedral adduct by hydrogen bonding. It may also play a role in facilitating the release of the trichloromethyl anion at the breakdown of the tetrahedral intermediate.



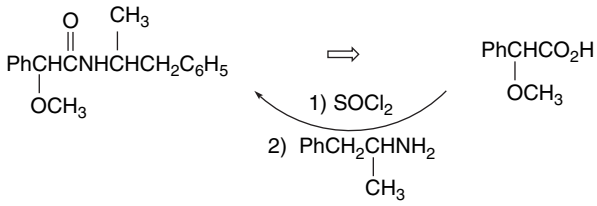
e. The preferential cleavage of the ester must be due to its greater basicity, resulting from the resonance stabilization available to the ester. The basicity of the carbamate carbonyl oxygen should be even higher, but evidently the primary benzylic bond does not cleave under these conditions.



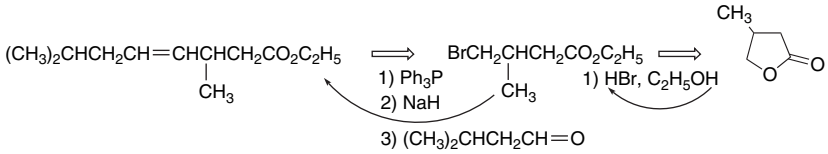
f. The $SOCl_2$-HMPA reagent combination is thought to involve an adduct of HMPA with $SOCl_2$. The composition of the intermediate shows that it is a sulfite ester at the 3′-hydroxy. In the absence of excess $SOCl_2$, this intermediate does not undergo a reaction with chloride. It is not clear how stringent the 1.5 equivalent stoichiometry is, but it does correspond exactly to that required for formation of a sulfite intermediate.



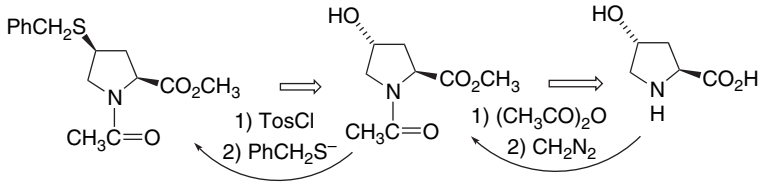
3.9. a. This transformation requires amide formation and probably could be done by nearly all of the amide-forming methods described in Section 3.4.3. Both reactants are chiral and two diastereomeric products are formed. In the cited reference, the reaction was done by converting the acid to the acyl chloride with $SOCl_2$, followed by reaction with the amine. Little stereoselectivity was observed, and the product was a 1:1 mixture of diastereomers.



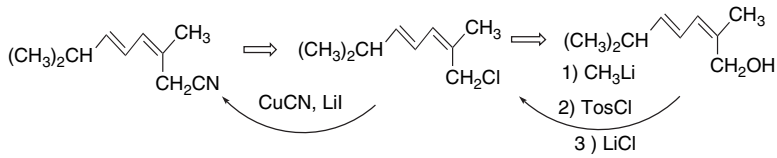
b. The lactone ring was opened in ethanolic HBr. The resulting bromo ester was converted to a phosphonium ylide and used in a Wittig reaction to obtain the desired product.



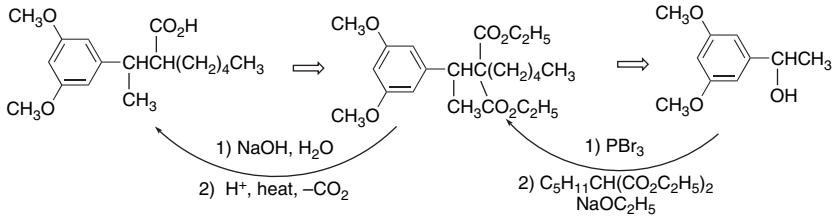
c. Three transformations are involved: (a) amine acetylation; (b) carboxy esterification, and (c) replacement of hydroxy by benzyl sulfide with inversion of configuration. These transformations were accomplished in that order using the standard methods in the cited reference.



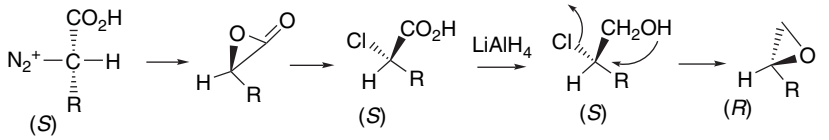
d. This reaction requires replacement of a primary allylic hydroxy by cyanide with preservation of alkene geometry. An S_N2 process meets these requirements. In the cited reference, the allylic alcohol was converted to the tosylate via its lithium salt and then to the allylic chloride. The introduction of cyanide was done using CuCN in the presence of LiI.



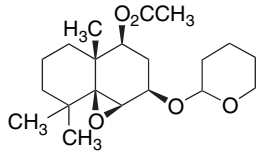
e. This transformation involves formation of a C−C bond at a secondary benzylic center. The *meta* placement of the two methoxy groups will have only a small electronic effect. The placement of the carboxy group in the product suggests a malonate synthesis and this method is reported in the cited reference. Since there is no stereochemical control in this route, the product is a mixture of diastereomers.



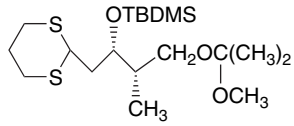
3.10. The key step in this sequence is the first one, in which the amino group is replaced by chloride with *retention of configuration.* This is believed to occur by participation of the carboxy group with formation of an α-lactone, which is then opened by chloride with two inversions leading to overall retention. The $LiAlH_4$ reduction does not involve the stereogenic center. The epoxide formation then occurs with inversion, leading to the (*R*)-epoxide.



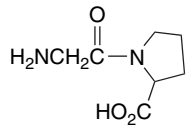
3.11. a. These conditions install a THP protective group without affecting any other group.



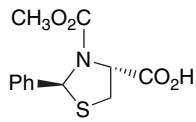
b. These conditions install a methoxypropyl protecting group at the primary alcohol.



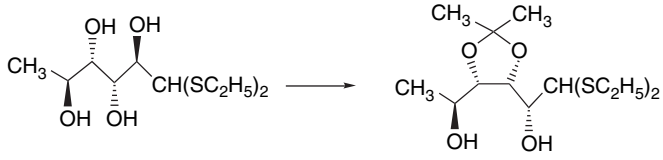
c. These are transfer hydrogenolysis conditions for removal of the carbobenzyloxycarbonyl group.



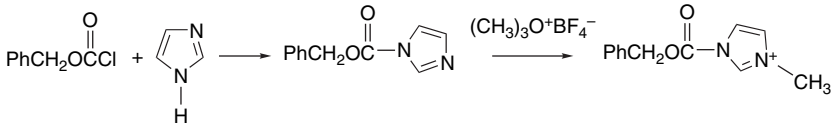
d. The reaction with benzaldehyde installs a thiazoline ring, and the methyl chloroformate acylates the nitrogen.



e. The composition shows that a monoacetonide is formed. The preferred reaction site is the 3,4-*syn* diol.



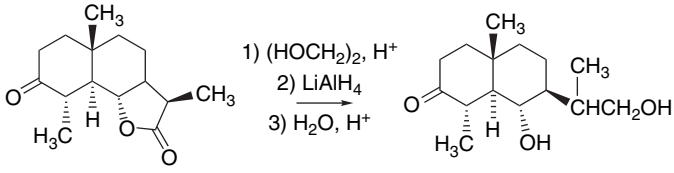
3.12. The imidazole is first acylated and then methylated at the other nitrogen by this sequence of reagents. The resulting imidazolium salt is highly reactive because the moderate reactivity of imidazolides is enhanced by the positive charge introduced by alkylation.



3.13. The first reaction suggests that an acyloxyphosphonium ion can react with a carboxylate to form an acid anhydride. The second reaction shows that neutral ethanol is not a strong enough nucleophile to compete with a carboxylate for an acyloxyphosphonium ion. This result implies that acyloxyphosphonium ions are not so reactive as to be unselective toward nucleophiles. The third reaction shows that the phosphorus can attack either oxygen of a peroxide bond with equal facility and that an alkoxyphosphonium ion that cannot undergo substitution reacts by elimination.

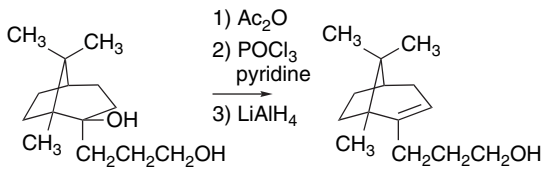
3.14. In order to avoid rearrangement, the reaction must involve an S_N2 mechanism. The major structural factor appears to be steric access. The relatively unhindered alcohols give clean reactions without rearrangement. The reaction presumably occurs via chlorophosphonium ion and alkoxyphosphonium ion intermediates. The critical step in the mechanism is the ability of Cl^- to displace $Ph_3P{=}O$ at the reaction site. If the attack is hindered, ionization takes place and a mixture of allylic rearrangement products and elimination products is formed.

3.15. a. This transformation can be accomplished by first protecting the ketone carbonyl with a dioxolane protective group.

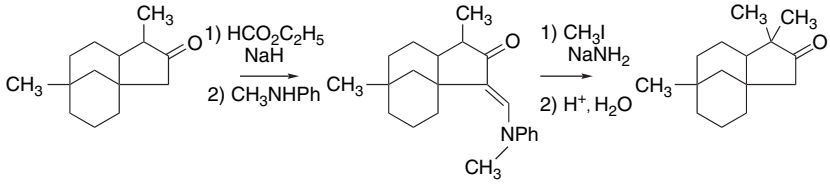


b. The primary hydroxy group requires protection with an acid-stable group. In the cited reference, the primary hydroxy was acetylated prior to the

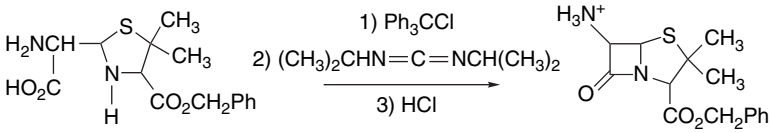
$POCl_3$ dehydration. It was removed by $LiAlH_4$ reduction, although alkaline hydrolysis would also seem possible.



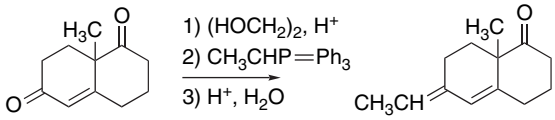
c. These alkylation conditions would not be expected to give high regioselectivity. The desired product was obtained by formylation, formation of the *N*-methylanilinomethylene derivative, methylation, and hydrolytic removal of the protecting group.



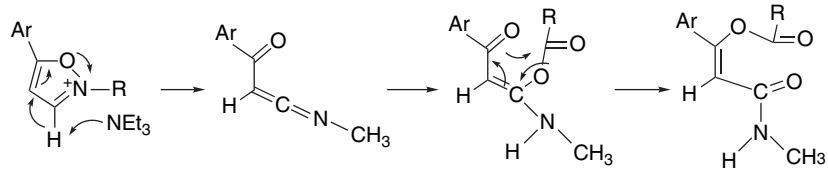
d. This reaction, which was part of the early methodology for the synthesis of penicillin, required protection of the primary amino group. In the cited reference, this was done with a trityl group.



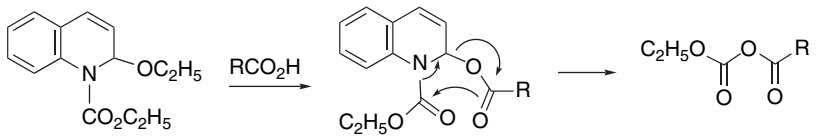
e. It is necessary to differentiate between the two carbonyl groups in order for this reaction to succeed. The unconjugated carbonyl group was selectively protected as the dioxolane.



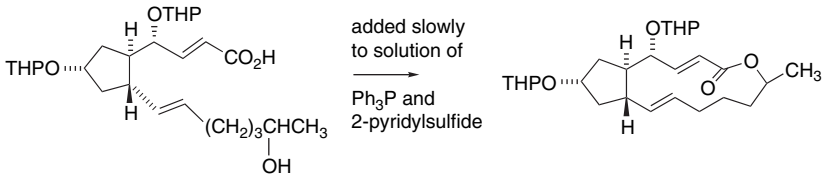
3.16. a. The isoxazolium salt is believed to undergo a ring cleavage to an acyl ketenimine. Addition of the carboxylic acid then generates a mixed imidic acid anhydride that can rearrange to an enol acetate, which is believed to be the active acylation reagent.



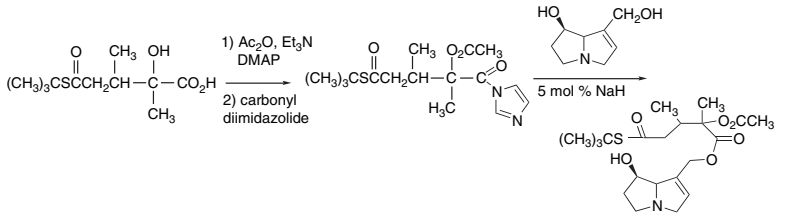
b. This reagent functions by exchange of the ethoxy group with the carboxylic acid. An intramolecular rearrangement then generates a mixed carbonic anhydride that is believed to be the active coupling reagent.



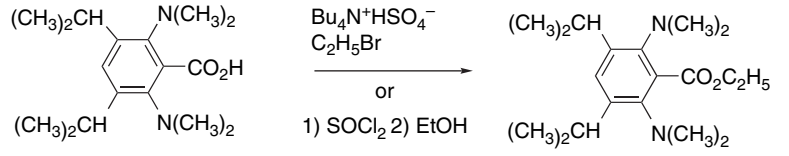
3.17. a. This transformation requires a macrocyclization. The problem is to avoid intermolecular reactions that can lead to dimers, trimers, etc. The approach taken is to run the reaction under conditions in which the active reagent is dilute. In the cited reference, the hydroxy acid was added very slowly to a Ph_3P–2-pyridylsulfide mixture. Under these conditions, the activated ester is kept at low concentration, favoring the desired intramolecular reaction.



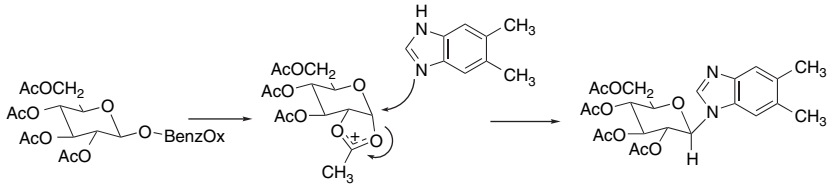
b. This reaction involves selective acylation of the primary alcohol group. It was found necessary to protect the hydroxy group in the carboxylic acid, and this was done by acetylation catalyzed by DMAP. The carboxy group was then converted to the acylimidazolide. The acylation required a base catalysis, which was accomplished by converting a fraction of the alcohol to its conjugate basic using NaH.



c. This reaction, which requires conversion of a hindered aromatic acid to an ester, and several others involving other alkyl groups were done successfully either by carboxylate alkylation under phase transfer conditions or by conversion to the acyl chloride with SO_2Cl.

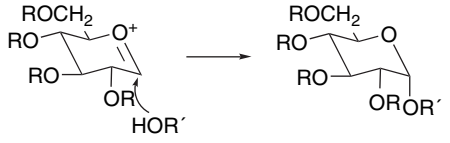


3.18. This reaction probably proceeds by participation of the 2-acetoxy group.

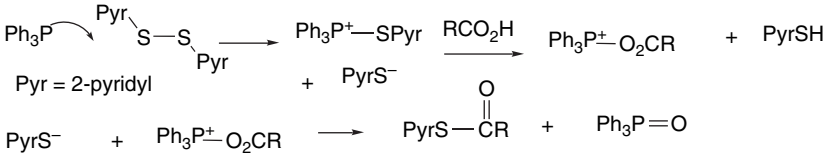


BenzOx = benzooxazolium

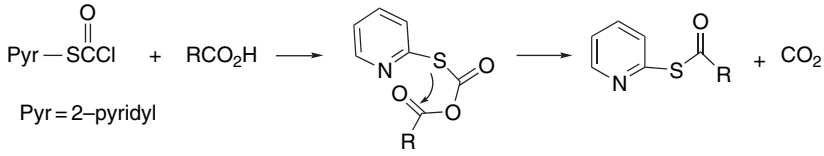
3.19. This is an example of the anomeric effect. The reaction occurs through a cation stabilized by the involvement of the pyran oxygen, and there is a preference for axial attack.



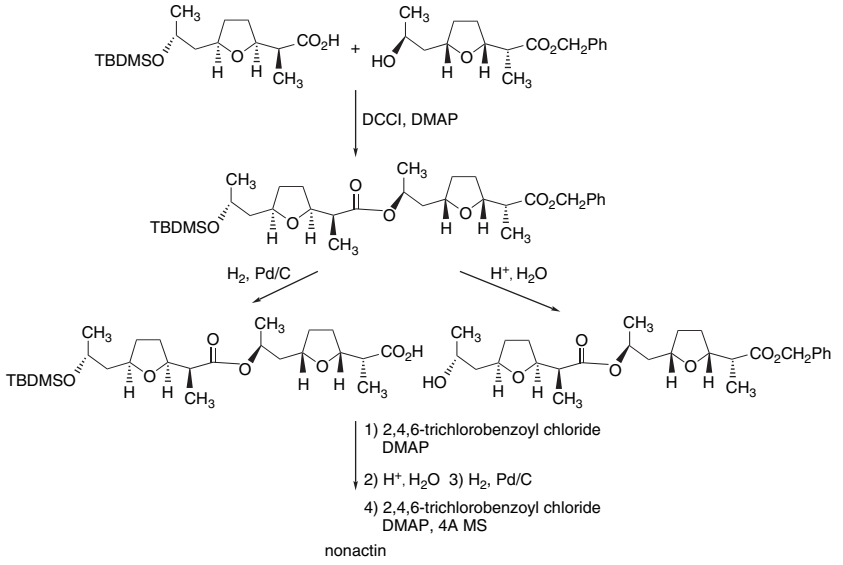
3.20. a. This reaction is similar to a the activation of Ph_3P by halogens.



b. Although the reaction does not seem to have been studied in detail, it presumably involves a collapse of the mixed anhydride formed in the first step.

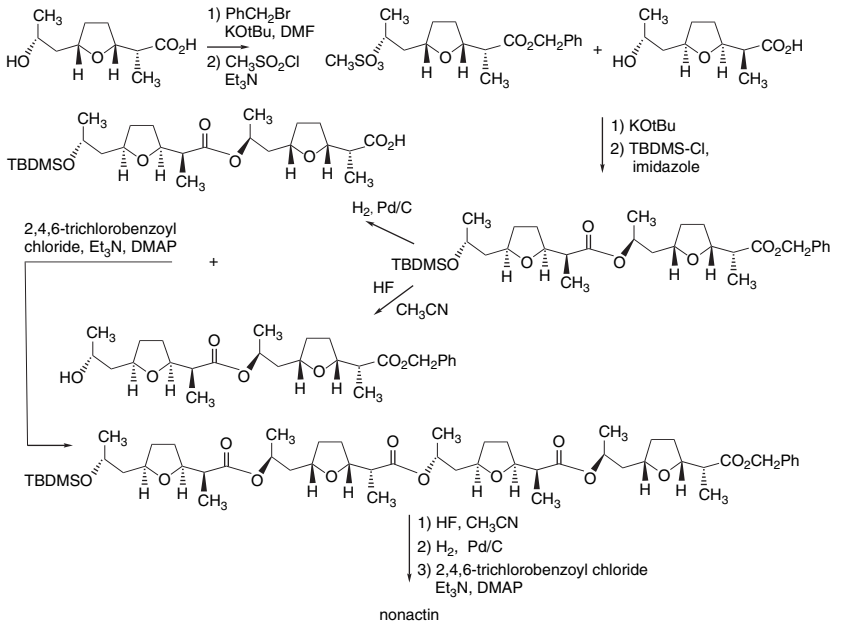


3.21. a. There are two broad strategies that could be followed. All four nonactic acids could be assembled in a linear sequence and a final lactonization done. An alternative strategy is to assemble the dimer and couple two dimers to obtain the tetramer. In the first approach the following sequence was used. Starting with the two enantiomers the hydroxy group of one was protected by silylation and the carboxy group of the other by benzylation. The two subunits were then coupled and finally the macrocyclization was done.

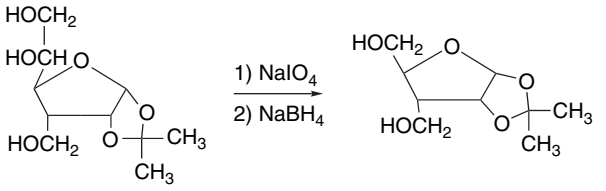


The coupling was also accomplished at the dimer stage by deproprotecting both groups. This method gave a somewhat lower yield because both the lactone of the dimer and possibly also higher oligomers were formed.

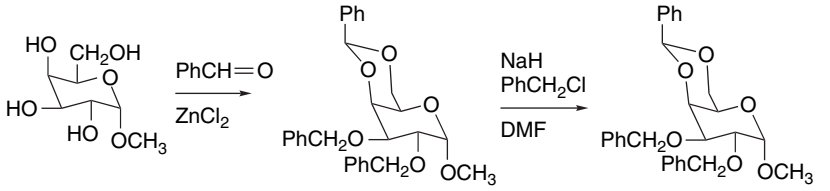
b. (+)-Nonactic acid and the C(8) epimer of (−)-nonactic acid can be used by coupling the two by a process that inverted the configuration at C(8). The single dimeric intermediate can then be selectively deprotected to afford monoprotected dimers that can be coupled to give the linear tetramer. Such a synthesis is described in the references cited in (b).



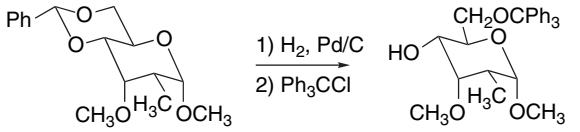
3.22. a. The acetonide protection at C(1)−C(2) permits $NaIO_4$ cleavage of the terminal diol to an aldehyde that can be reduced to the desired compound with $NaBH_4$.



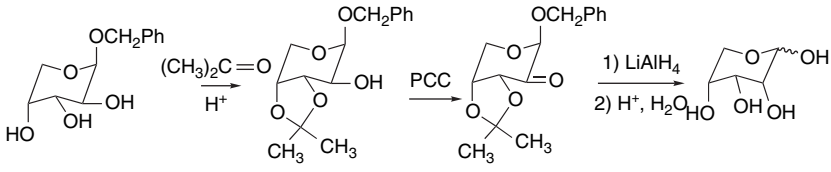
b. Treatment of the methyl glycoside with excess benzaldehyde and $ZnCl_2$ selectively gives the 4,6-benzylidene derivative. This intermediate was then 2,3-dibenzylated using NaH and excess benzyl chloride in DMF.



c. The benzylidene group was removed by hydrogenolysis over Pd-C. The trityl group was installed by reaction with Ph_3CCl.

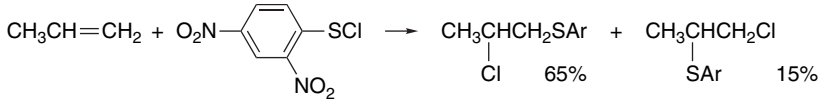


d. The configuration at C(2) was inverted by protecting C(3) and C(4) as the isopropylidene derivative. The C(2) hydroxy group was oxidized to the ketone using pyridinium chlorochromate. Reduction gave the inverted hydroxyl group.

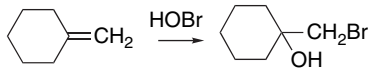


Chapter 4

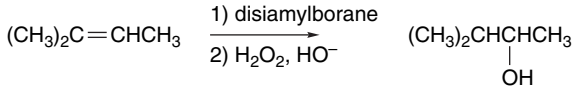
4.1. a. This addition reaction was observed to proceed with a moderate level of Markovnikov regioselectivity.



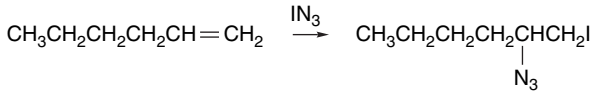
b. The bromohydrin is formed with the expected Markovnikov orientation.



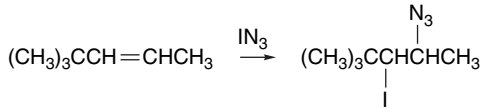
c. This hydroboration-oxidation is, as expected, selective for the less-substituted alcohol.



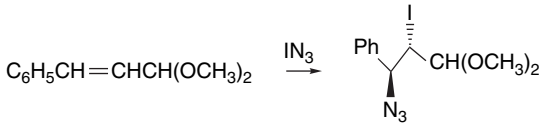
d. The regiochemistry is in accord with expectation for an iodonium ion intermediate with nucleophilic addition at the more highly substituted position.



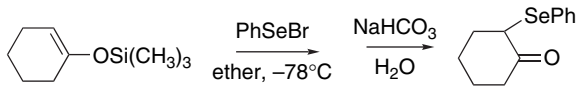
e. This reaction proceeds through an iodonium ion. There is no strong electronic influence on regioselectivity and the azide ion enters at the more sterically open carbon.



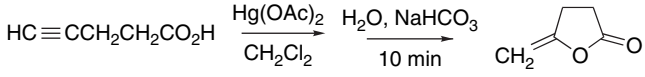
f. The regiochemistry is directed by the cation-stabilizing phenyl group and the stereochemistry is *anti*.



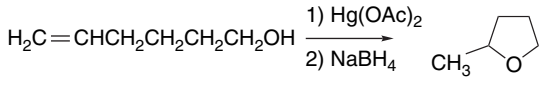
g. Selenenylation of the silyl enol ether, followed by hydrolysis, gives an α-selenyl ketone.



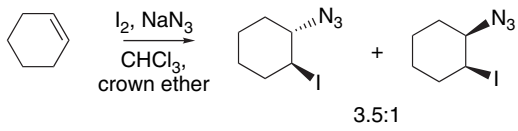
h. An 5-*exo* cyclization, followed by hydrolytic demercuration, generates a γ-methylenelactone.



i. An 5-*exo* cyclization, followed by reductive demercuration, generates a tetrahydrofuran.

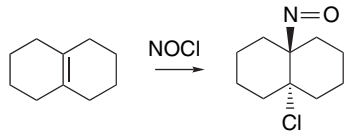


j. Somewhat unexpectedly, some *cis* as well as the expected *trans* product is formed.

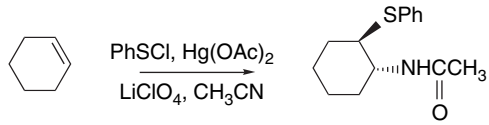


3.5:1

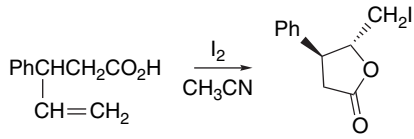
k. The reaction occurs with *anti* stereochemistry.



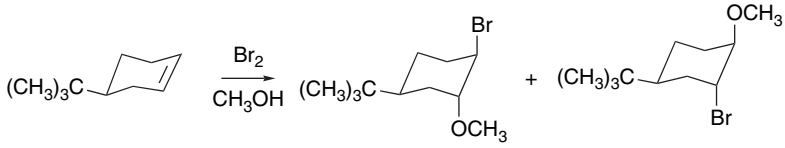
l. The reaction conditions lead to the precipitation of $HgCl_2$ and the formation of a reactive sulfenylation reagent. The product composition shows that capture of acetonitrile and hydration of the resulting nitrilium ion has occurred.



m. These conditions for thermodynamically controlled iodolactonization generate the more stable *trans* lactone.

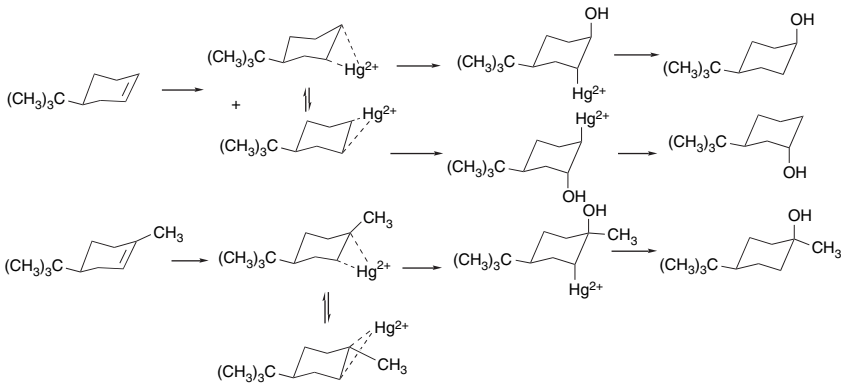


4.2. The addition is expected to be *trans* diaxial, as observed for reaction involving bridged intermediates in cyclohexane rings. There is little facial selectivity, leading to both regioisomers in nearly equal amounts. The *trans* stereochemistry could be confirmed by NMR coupling constants. The regiochemistry might be established by elimination in basic solution and characterization of the isomeric enol ethers.

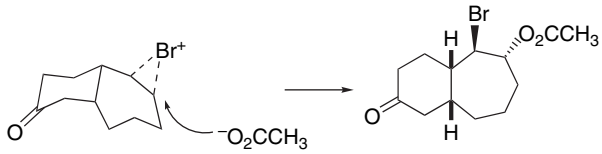


4.3. The reaction of 4-*t*-butylcyclohexene has no strong electronic influence nor facial selectivity. The dominant constraint is the preference for diaxial opening of the mercurinium ion intermediate. In the case of 1-methyl-4-*t*-butylcyclohexanol,

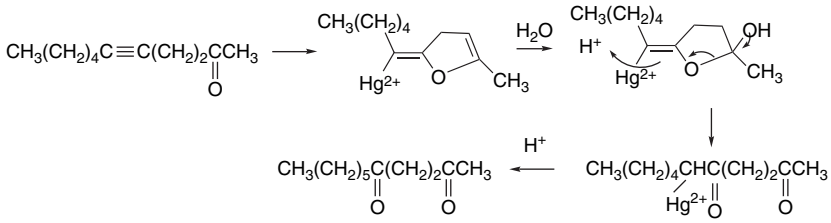
there is an electronic preference for nucleophilic addition at the more-substituted carbon (Markovnikov's rule) and the reaction becomes regioselective.



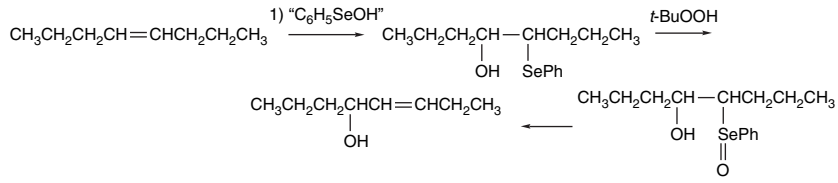
4.4. The composition of the product indicates that it has incorporated acetate as the nucleophile. Examination of the shape of the *cis*-fused ring system suggests that Br^+ would be added from the upper (β) face. *Anti* attack by acetate would lead to the observed product.



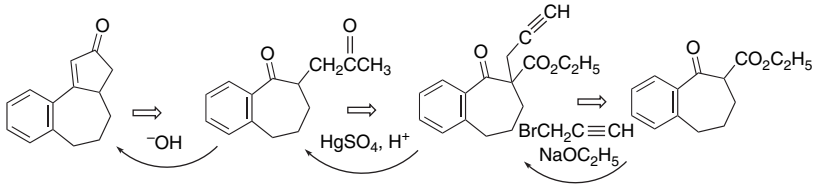
4.5. The carbonyl oxygen can participate, forming a five-membered ring that would then open to the observed dione. This is an example of the preference for *exo*-5-*dig* over *endo*-6-*dig* cyclization.



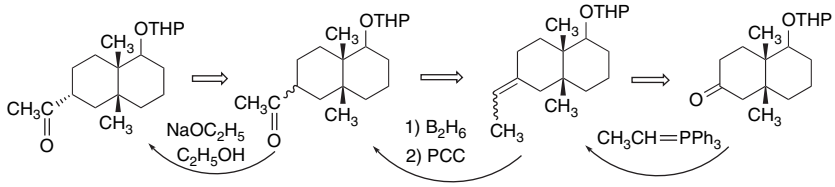
4.6. The addition generates a β-hydroxy selenide. The oxidation generates a selenoxide that undergoes regioselective elimination.



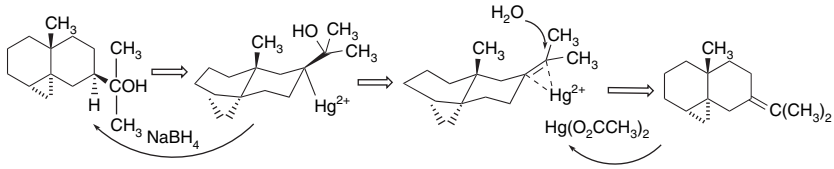
4.7. a. A propargyl group was introduced by enolate alkylation. The alkyne was then converted to the methyl ketone and the β-ketoester hydrolyzed and decarboxylated. The cyclopentenone ring was formed by intramolecular aldol condensation.



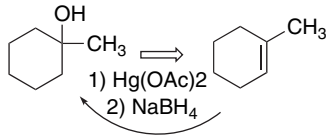
b. Formation of a double bond by a Wittig reaction with ethylidenetriphenylphosphorane and hydroboration and oxidation can introduce the acetyl group. A mixture of stereoisomers was formed but $NaOC_2H_5$ equilibration gives a 97.4:2.6 favoring the desired stereoisomer. This synthesis could also be addressed using an acetyl anion synthetic equivalent (see Section 13.1.2).



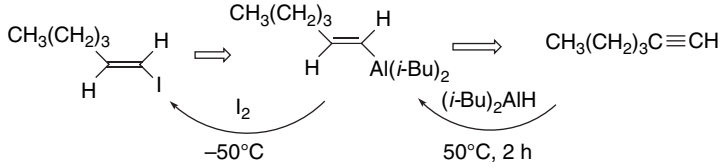
c. This transformation can be done by oxymercuration-demercuration. The stereoselectivity arises at the radical reduction, with a steric preference for approach from the lower (α) face. Steric factors (axial methyl blocks approach) are probably also responsible for the regioselectivity of the addition at the tetrasubstituted double bond.



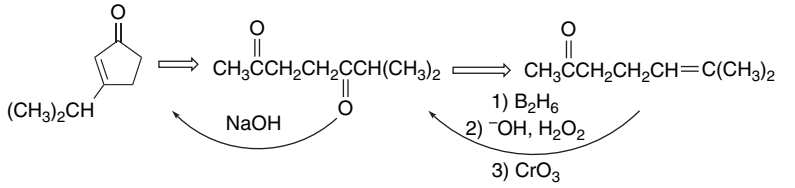
d. This transformation can be done by oxymercuration and reductive demercuration.



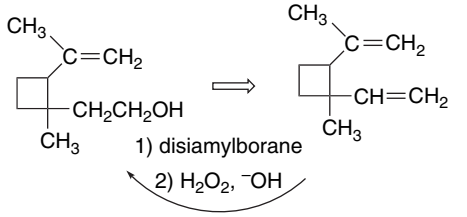
e. This transformation can be done by hydroalumination with DiBAlH followed by iodinolysis.



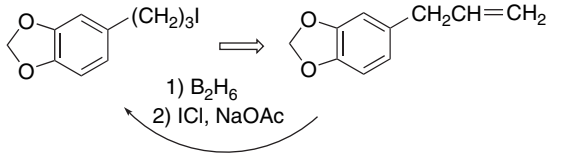
f. The ring can be closed by an intramolecular aldol condensation. Hydroboration can introduce the necessary oxygen. The existing carbonyl group is reduced during hydroboration, but oxidation with chromic acid provides the desired diketone.



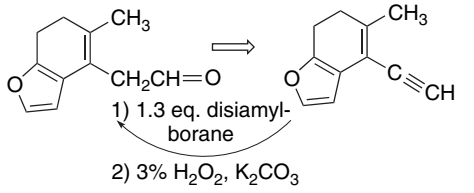
g. This transformation requires selective anti-Markovnikov hydration of the less-substituted double bond. This can be done using hydroboration with disiamylborane.



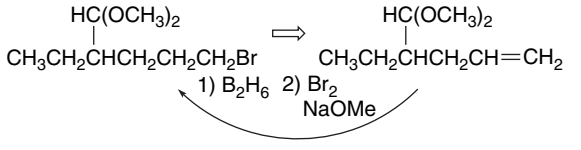
h. This anti-Markovnikov hydroiodination can be done by hydroboration and iodinolysis. A procedure using ICl and NaO_2CCH_3 was used in the cited reference.



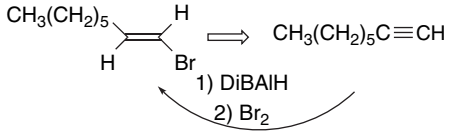
i. This conversion of a terminal alkyne to an aldehyde was done by hydroboration with a limited amount (1.3 equiv.) of disiamylborane, followed by oxidation with 3% H_2O_2. The relatively mild oxidation conditions generate the enol of the aldehyde.



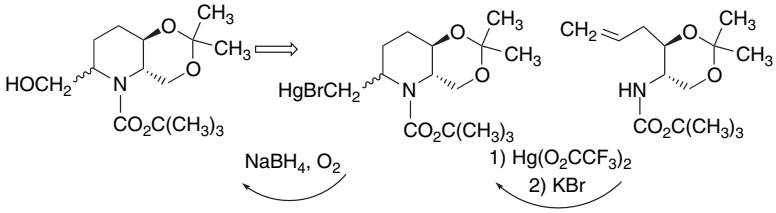
j. This transformation was accomplished by hydroboration and brominolysis.



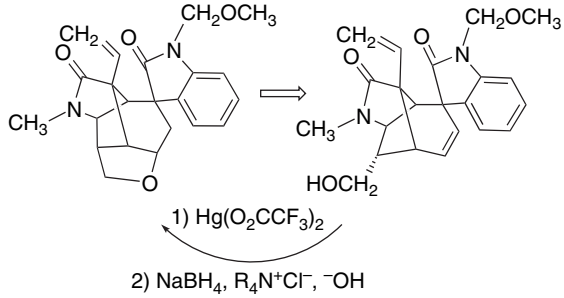
k. This conversion of a terminal alkyne to an *E*-vinyl bromide was done by hydroalumination and brominolysis.



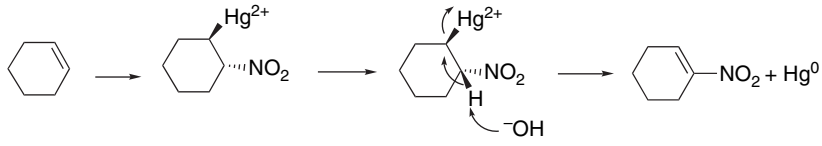
l. This transformation involves an *exo*-6 cyclization with the nitrogen of the carbamate acting as the nucleophile with oxidation at the unsubstituted carbon of the double bond. This can be accomplished by cyclization induced with mercuric ion and an oxidative workup. In the cited reference the cyclized mercuric intermediate was isolated as a bromide, then converted to the primary alcohol using $NaBH_4$ and O_2.



m. This reaction involves an *exo*-5 cyclization. It was done with $Hg(O_2CCF_3)_2$, followed by reductive demercuration. Note that a second double bond, which lacks an internal nucleophile, does not react under these conditions.

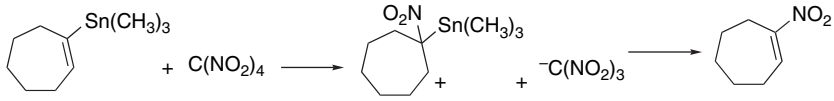


4.8. a. This reaction can proceed by an electrophilic mercurio-nitration. The base then takes advantage of the acidity of the nitro-substituted carbon to induce *elimination* of Hg^0.

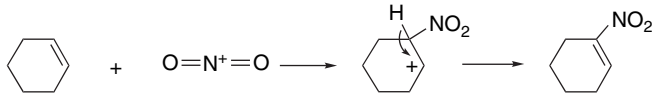


b. Tetranitromethane is an electrophilic reagent capable of formal generation of NO_2^+ and $^-C(NO_2)_3$. Electrophilic attack on the vinyl stannane can be followed by destannylation. The regiochemistry of the electrophilic attack is

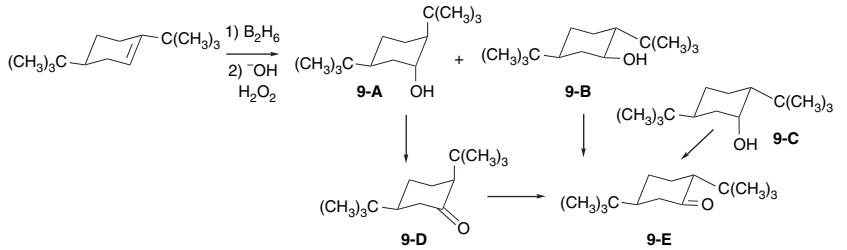
typical of vinyl stannanes and is due to the β-cation stabilization provided by the stannyl group (see Section 9.3). It is possible that the electrophilic attack occurs in two steps by an electron transfer mechanism.



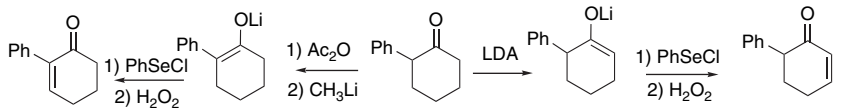
c. This transformation can occur by electrophilic attack by the nitronium ion. In the absence of a nucleophile, deprotonation occurs.



4.9. The hydroboration-oxidation should proceed with the usual anti-Markovnikov regiochemistry and *syn* stereochemistry. There is no strong facial preference so that alcohols **9-A** and **9-B** would be expected to be the two *syn* products. The fact that ketone **9-D** from **9-A** is converted to **9-E** indicates that **9-D** is the less stable *cis*-2,5-di-*t*-butylcyclohexanone and that **9-E** is *trans*-2,5-di-*t*-butylcyclohexanone. The fact that the minor product **9-C** also gives **9-E** must mean that it is a rare example of an *anti* hydroboration product.

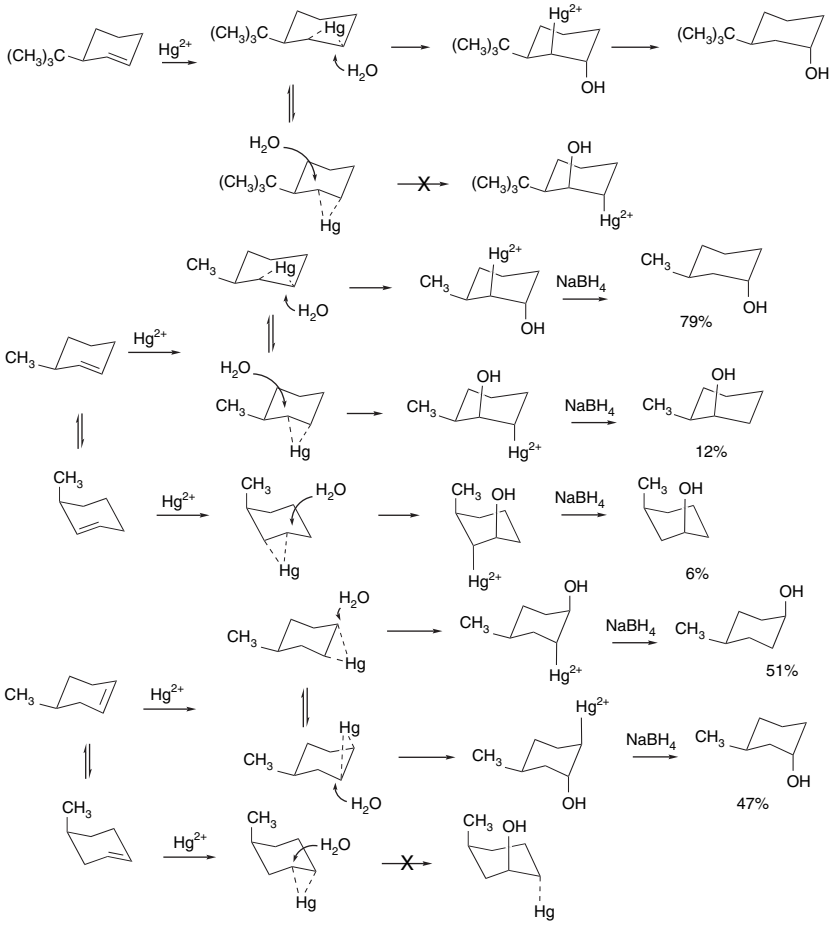


4.10. The isomeric enolates would be expected to undergo selective selenenylation. Oxidative elimination would then generate the corresponding enones. In the cited reference, the 2-phenyl enolate was generated from the enol acetate, whereas kinetic deprotonation was used to generate the 6-phenyl enolate.

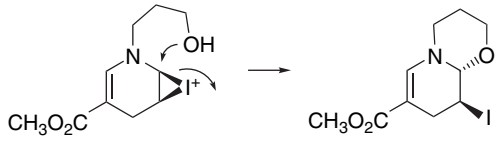


4.11. a. The *t*-butyl group will strongly bias the conformational equilibrium. Although no strong facial selectivity is expected, only the *cis*-mercurinium can open in a *trans* diaxial fashion and the main product (95%) is *trans*-3-*t*-butylcyclohexanol. The steric bulk of the *t*-butyl group also blocks nucleophilic attack by water at C(2). For 3-methylcyclohexene, the conformational equilibrium is not so strongly biased and steric hindrance of C(2) is reduced. As a result, significant amounts of both *cis*-2-methylcyclohexanol and *cis*-3-methylcyclohexanol are formed. In 4-methylcylohexene, both the *cis*- and *trans*-mercurinium ion can open in a *trans* diaxial mode and the two

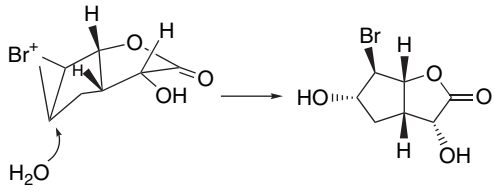
diaxial products are formed in nearly equal amounts. The absence of *cis*-3-methylcyclohexanol indicates that the conformer with an axial methyl is not productive, probably because of steric hindrance to approach by water.



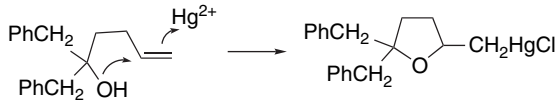
4.12. a. This iodocyclization proceeds with *anti* stereochemistry. The reaction involves the more nucleophilic of the two double bonds.



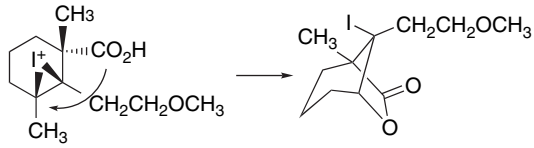
b. The composition of the product corresponds to addition of HOBr. The bromine attacks from the more accessible convex (β) face. Evidently the hydroxy group is not in a position to capture the bromonium ion internally. The regioselectivity may be due to a polar or steric effect of the adjacent oxygen of the lactone ring.



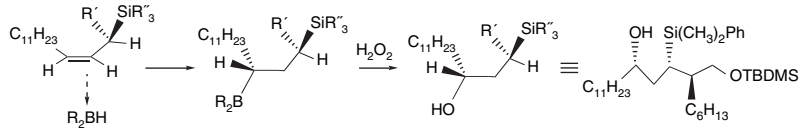
c. This reaction proceeds by the expected *exo*-5 cyclization with isolation of the mercuric compound as the chloride.



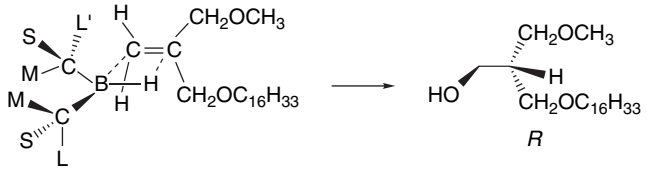
d. A five-membered lactone is formed by *anti* addition. The alternate regiochemistry would require formation of a four-membered lactone.



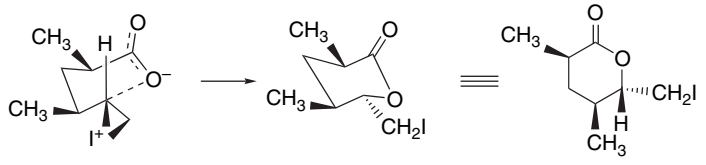
e. The steric effect of the silyl substituent leads to an attack on the *anti* face. The same steric factors are also probably responsible for the regioselectivity.



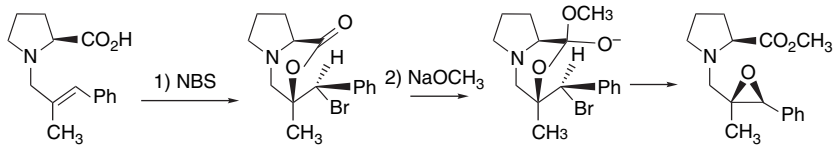
f. This disubstituted terminal alkene exhibited substantial stereoselectivity on hydroboration by (+)-di-isopinocampheylborane. Application of the conformational model for diisopinocampheylborane suggests that the larger group will be oriented away from the C(2) methyl group (L′) in the model. This leads to the observed *R* configuration.



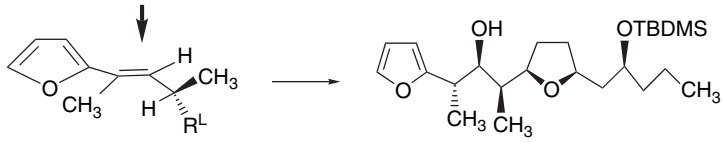
g. The major product results from *anti* opening of an iodonium ion derived from the dominant conformation of the unsaturated acid.



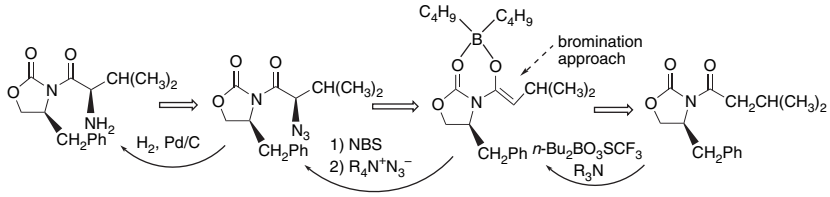
h. A stereoselective bromolactonization occurs. Treatment with methoxide leads to epoxide formation.



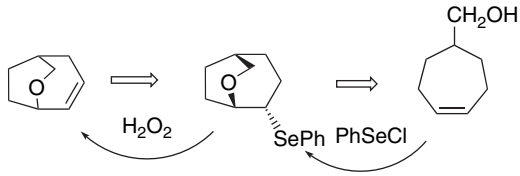
i. The alkene should adopt a conformation that minimizes $A^{1,3}$ strain. Preferred approach then occurs *syn* to the smaller methyl group and *anti* to the larger branched allylic substituent.



4.13. a. This transformation can take advantage of the oxazolidinone chiral auxiliary. The configuration at the amino group is opposite from the preferred face of approach for a chelated enolate. The transformation can be effected by formation of the boron enolate, bromination with NBS, introduction of azide with inversion of configuration, and reduction to the amino group.

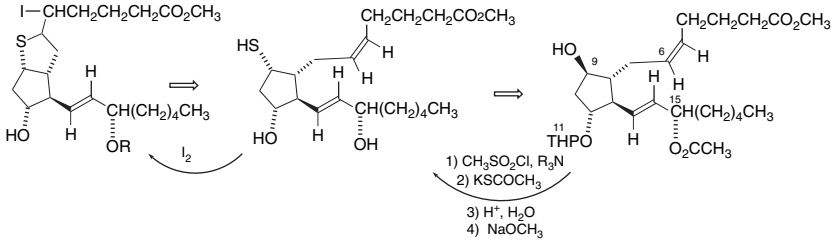


b. This transformation can be effected by a selenenylcyclization and oxidative elimination.

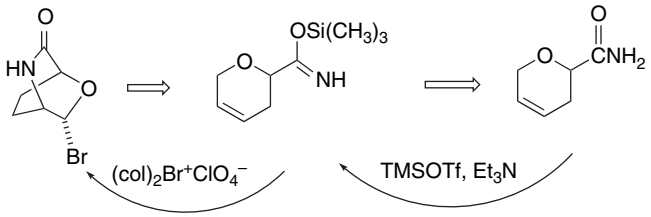


c. This transformation requires introduction of a sulfur substituent with inversion of configuration at the C(9) center of the prostaglandin ring, *exo*-5 iodocyclization, and deprotection of the C(11) and C(15) oxygens. These transformations were accomplished by: (a) sulfonation of the C(9) hydroxy, displacement

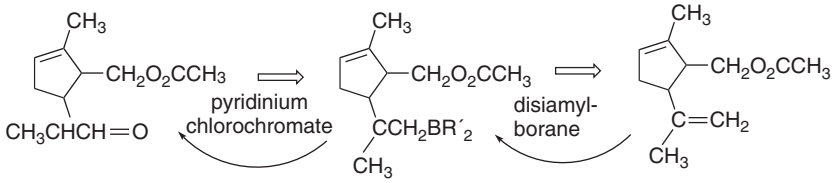
by potassium thioacetate, (b) deprotection of the C(11) hydroxy, (c) deacylation, and (d) iodocyclization.



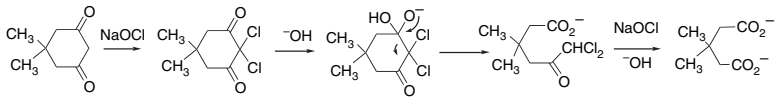
d. This transformation requires a bromocyclization with the amide nitrogen functioning as the nucleophile. This was accomplished by conversion of the amide to the *O*-TMS imidate and the bromocyclization was done using *bis*-collidine-bromonium perchlorate as the positive bromine source.



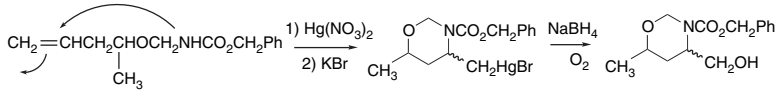
e. This transformation requires selective oxidation of a terminal disubstituted alkene in the presence of a cyclic trisubstituted alkene. This was done by hydroboration with disiamylborane and oxidation with pyridinium chlorochromate.



4.14. a. This reaction is a variation of the haloform cleavage of methyl ketones. In this case the dichloro derivative undergoes alkaline cleavage assisted by the adjacent carbonyl group. The dichloromethyl ketone can then be further chlorinated and cleaved.

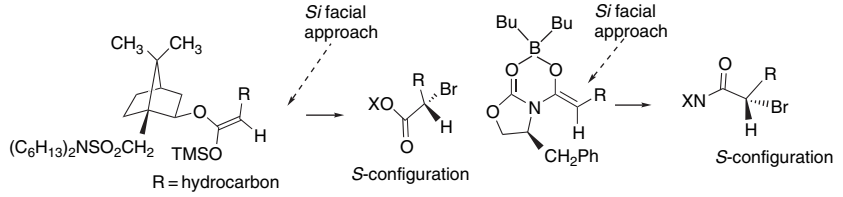


b. This reaction involves mercuriocyclization with the carbamate nitrogen acting as the internal nucleophile. The cyclization product is isolated as the bromide and then subjected to demercuration in the presence of oxygen, introducing the primary hydroxyl group.

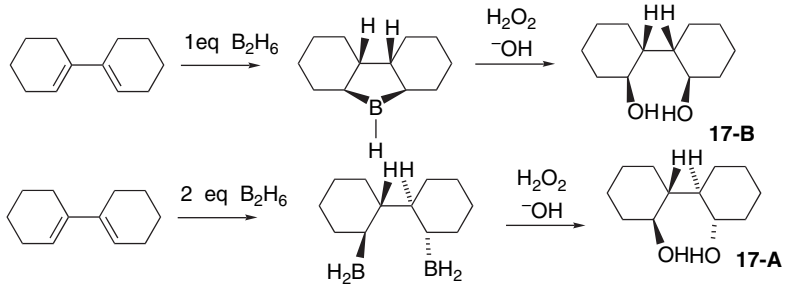


4.15. The dichotomy in N-versus O-cyclization can be explained in terms of ring-size and *exo*,*endo* preferences. For compound **15-A**, N-cyclization leads to a five-membered ring, which is preferred to the seven-membered ring resulting from O-cyclization. For compound **15-C**, N-cyclization would require either an *endo*-5 or *exo*-4-cyclization. Both of these are unfavorable relative to the observed *exo*-6 O-cyclization.

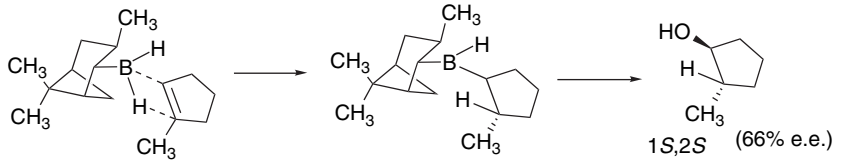
4.16. The configuration of the products can be predicted from the facial selectivity of the enolate derivatives, as discussed in Section 2.1.5.4.



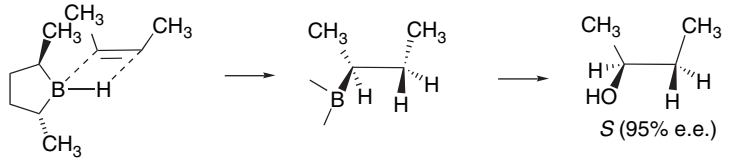
4.17. When only one equivalent of borane is used, some of the hydroboration must involve an intramolecular addition. This would generate a *cis*,*cis*,*cis*,*cis* relationship among the four newly formed bonds and lead to **17-B** as the major product. When two equivalents of borane are available, an intermolecular addition can occur at each double bond. In this case, there will be a preference for a *cis*,*cis-trans*,*trans* relationship among the newly formed bonds.



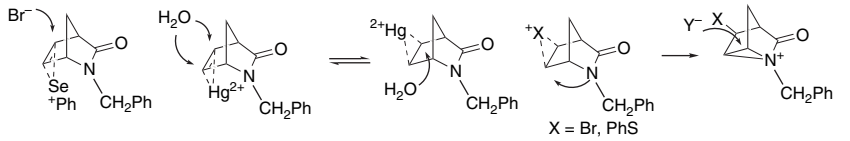
4.18. a. Avoidance of the *gem*-dimethyl bridge and the methyl substituent on the borane suggest a TS that leads to the (1*S*, 2*S*)-enantiomer.



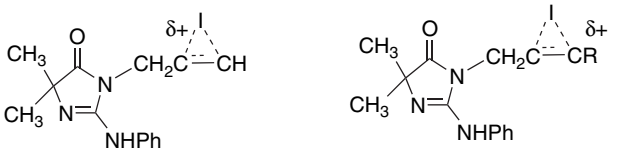
b. The alkene approaches the borane to avoid methyl-methyl interaction, leading to *S*-configuration at the new chiral center.



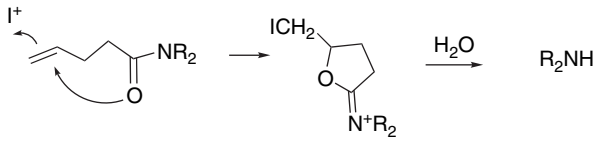
4.19. Examination of the product mixture shows that only selenenylation gives a regio- and stereospecific (*anti*) addition. Bromination and sulfenylation involve rearrangement with participation of the amide nitrogen. Oxymercuration gives both *exo* and *endo* products, but no rearrangement. This indicates that the selenenium ion is more stable than the corresponding bromonium and thiiranium ions. Since oxymercuration involves rate-determining capture of the mercurinium ion, the mixture of products indicates that both mercurinium ions are formed and are of comparable reactivity. The absence of rearrangement indicates that the mercurinium ion is not sufficiently electrophilic to induce amide participation. The more electrophilic bromonium and thiiranium ions react by rearrangement.



4.20. a. These results are compatible with the cation-stabilizing effect of the methyl and phenyl groups. In the substituted iodonium ion intermediates, more of the cationic character resides at the substituted carbon. In the unsubstituted alkyne, the internal carbon bears the greater positive charge.



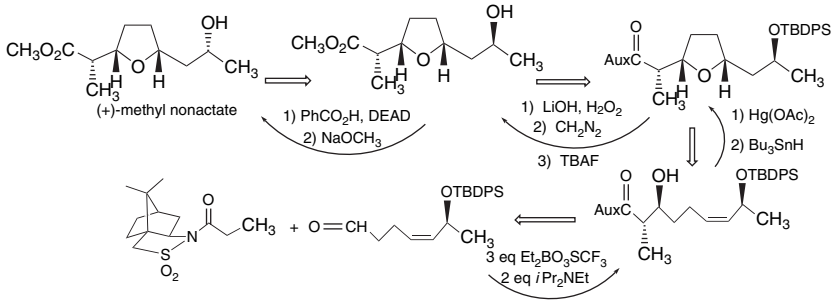
b. The amide carbonyl can participate as the nucleophile, forming an imino lactone that can hydrolyze readily.



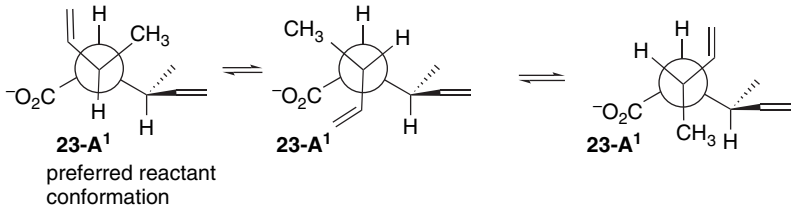
4.21. By examining the results from each reactant we see that **21-A** gives exclusively the expected anti-Markovnikov product. There are no stereochemical issues. **21-B** shows no evidence of stereoselectivity, but there seems to be a bias ($\sim 2:1$) toward C(3) as the position of oxidation, suggesting a directive effect by the homoallylic benzyloxy group. The results from **21-C** confirm a regiochemical influence by the homoallylic benzyloxy group because a substantial amount of the anti-Markovnikov product is formed, in contrast to **21-A**. The reaction is also now stereoselective at C(2), indicating that the combination of allylic and homoallylic substitution influences not only regioselectivity but also stereoselectivity. The *syn* stereoisomer **21-D** gives very similar results. Compound **21-E** is consistent with the previous pattern, showing a regiochemical preference for oxidation at C(3) with stereochemical control. The same pattern holds in **21-F** with a significant amount of anti-Markovnikov product and stereocontrol at C(2). The cited authors suggest a TS in which the allylic oxygen is eclipsed with the double

bond to minimize electron withdrawal by the polar oxygen. This suggests that the hydroxy group will be introduced *anti* to the allylic oxygen, as is observed. The regiochemical effect, which is independent of the configuration of the benzyloxy group (comparison of **21-C** and **21-D**) must result from some electronic relative enhancement of nucleophilicity of the proximal end of the double bond.

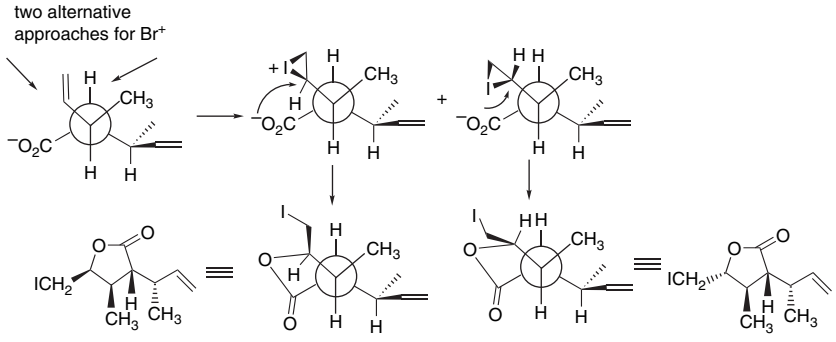
4.22. The suggested starting material in an allylic silyloxy ether and the stereochemistry of mercury-induced cyclization can be predicted on the basis of the relationships discussed on p. 325. The aldehyde also has to be extended by addition of a propanoate unit with *anti* stereoselectivity. The desired *anti* selectivity was achieved, as discussed on p. 123, by use of excess Lewis acid to control stereoselectivity. The oxymercuration reaction generates the required *cis* configuration of tetrahydrofuran ring, but requires inversion of configuration in the side chain. This was done by a Mitsunobu reaction (see p. 228).



4.23. In compound **23-A** there are three possible conformations. Two of these place the carboxy *gauche* to the allyl group, which is required for cyclization. Of these, **23-A^1** is preferred since it minimizes other *gauche* interactions.



There are two alternative approaches of the iodine.



As shown in Figure 4.P23A, the reaction can proceed from the most stable conformer, with the 30:1 mixture of stereoisomers arising from alternative facial

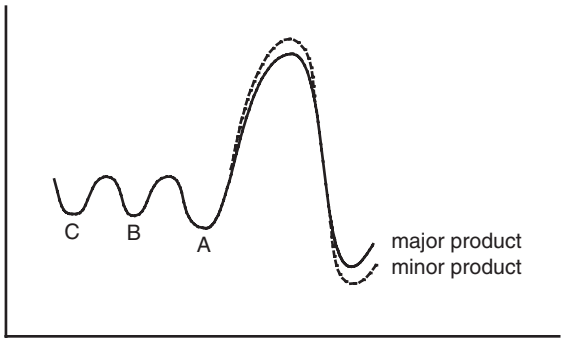


Fig. 4.P23A. Representation of energy profile for iodolactonization of **23-A.** In compound, the additional substituent makes the disubstituted double bond more reactive. This cyclization occurs from a conformation (**A**[1]), which is not the most stable but proceeds through a lower-energy intermediate because of the activation by the methyl group.

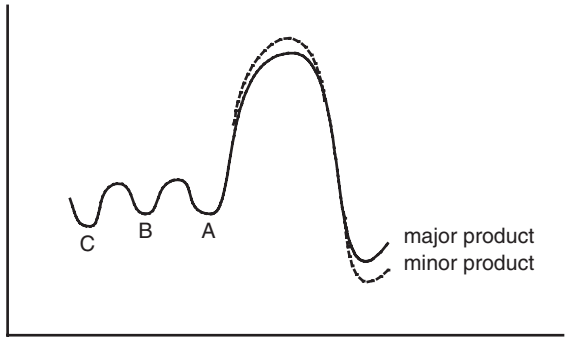
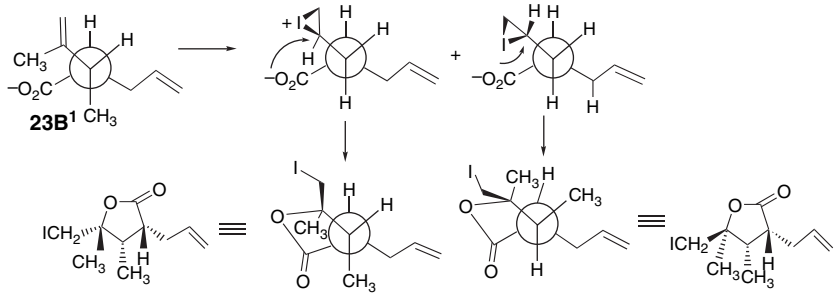
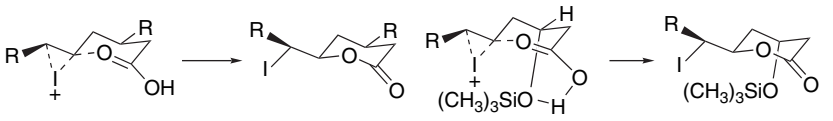


Fig. 4.P23B. Representation of energy profile for iodolactonization of **23-B.**

approaches to this conformer. In compound **23-B**, the additional substituent makes the disubstituted double bond more reactive. This cyclization occurs from a conformation (**23-B**[1]), which is not the most stable but proceeds through a lower energy intermediate because of the activation by the methyl group.

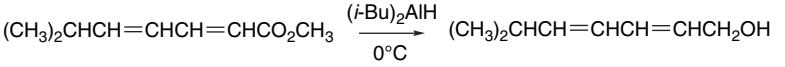


4.24. The alkyl substituent prefers an equatorial orientation and directs stereochemistry through a cyclic TS. The reversal is attributed to an axial preference for the siloxy substituent, resulting from hydrogen bonding.

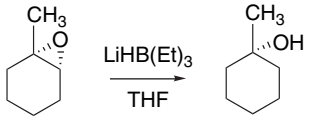


Chapter 5

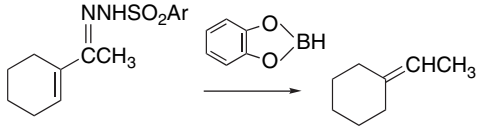
5.1. a. Because of the temperature at which this reaction is conducted, (0° C), the product is the alcohol.



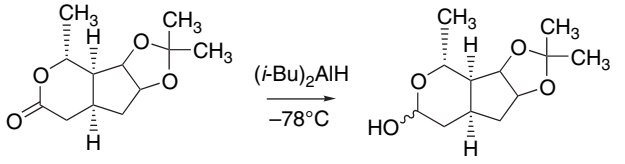
b. These reaction conditions lead to reductive epoxide ring opening by hydride delivery at the least-substituted position.



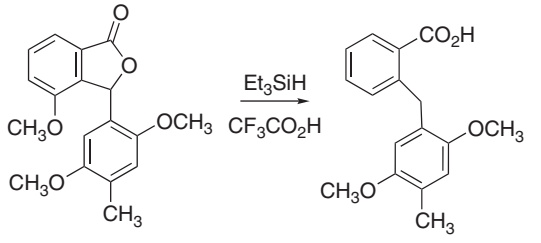
c. This reduction of an α,β-unsaturated tosylhydrazone gives an alkene.



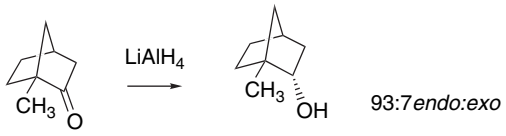
d. This low-temperature reduction gives the lactol.



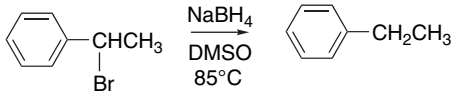
e. These conditions generate a carbocation that is reduced by the silane.



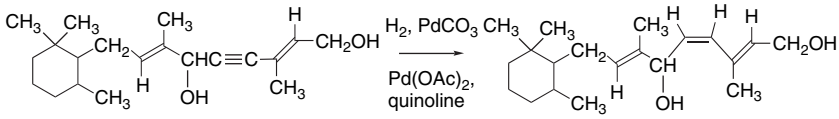
f. This reduction occurs with 93% stereoselectivity for the *endo* isomer.



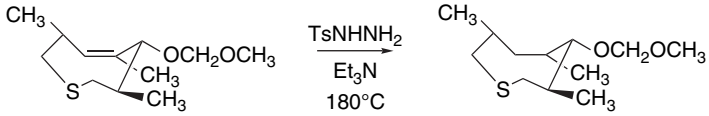
g. These conditions effect reductive dehalogenation.



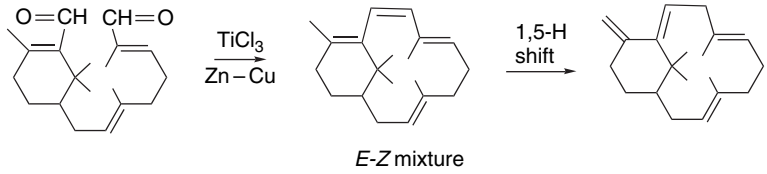
h. This hydrogenation over the Lindlar catalyst leads to the selective reduction of the triple bond to the *Z*-alkene.



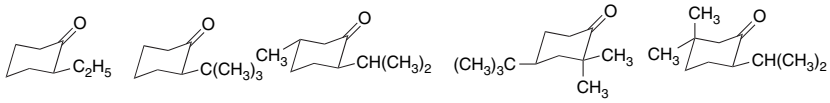
i. These conditions reduce the double bond via generation of diimide.



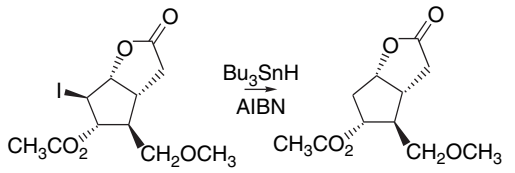
j. These reagents lead to reductive coupling. In practice the reaction gave a mixture of alkenes including, as the major product, the more stable product of 1,5-sigmatropic hydrogen shift.



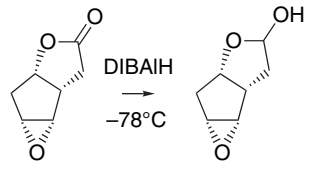
5.2. The dominant conformation for each ketone is shown below. Comparison of 2-ethylcyclohexanone with 4-*t*-butylcyclohexanone shows that the equatorial ethyl group has a modest effect in reducing the ratio of equatorial alcohol. The effect is slightly larger for the 2-(*t*-butyl) substituent. These results indicate a small steric effect for equatorial 2-substituents. For *trans*-2-(isopropyl)-5-methylcyclohexanone, this trend continues. The 5-methyl substituent would not be expected to have a significant effect and the 2-(isopropyl) group shows an effect similar to the 2-ethyl substituent. In the 2,2-dimethyl derivative, an axial 2-methyl group leads to a higher ratio of equatorial alcohol. Finally, in 2-(isopropyl)-5,5-dimethylcyclohexanone, the steric effect of the axial methyl group results in a modest increase in the amount of axial alcohol.



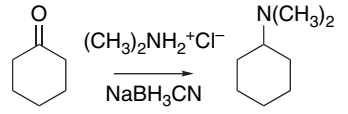
5.3. a. This dehalogenation can be done under radical chain conditions using Bu_3SnH as the hydrogen atom donor.



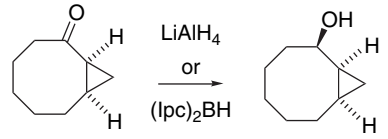
b. Low-temperature DiBAlH reduction can accomplish this transformation.



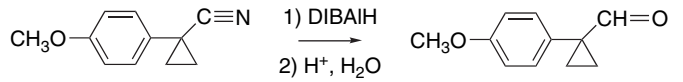
c. This reductive amination can be done using dimethylamine hydrochloride and $NaBH_3CN$.



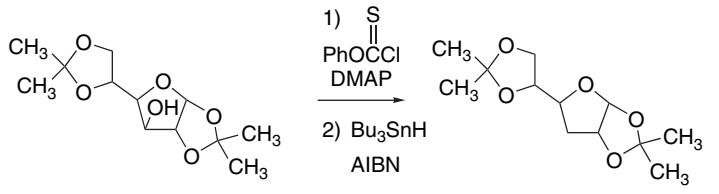
d. This reduction requires hydride delivery *anti* to the cyclopropane ring. Both $LiAlH_4$ and diisopinocampheylborane exhibited the required stereoselectivity. Presumably alkylborohydrides would show the same stereoselectivity.



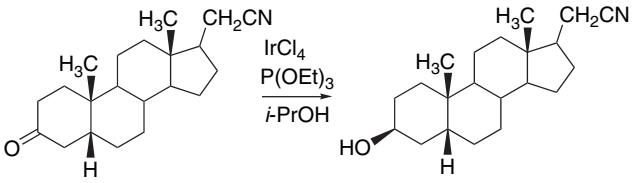
e. Partial reduction of nitriles to aldehydes can be done with DIBAlH and the cited reference reports an 86% yield.



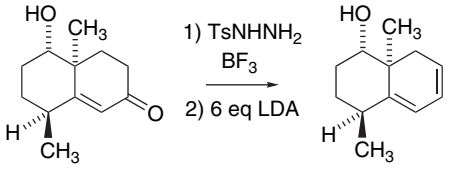
f. This deoxygenation can be done by conversion to the phenyl thiono carbonate followed by Bu_3SnH reaction. The other thiono esters such as the imidazolyl thio ester would presumably react in a similar way.



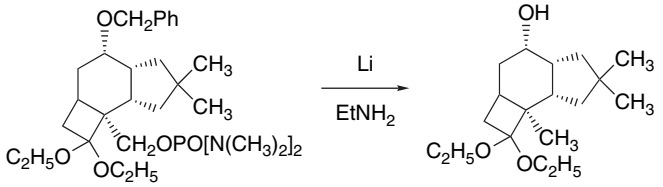
g. This reduction requires formation of the axial alcohol in an environment without any nearby steric control elements, so a bulky reductant is required. In the cited reference, $IrCl_4$, $(EtO)_3P$, and *i*-PrOH, a reduction system known to favor axial alcohols, was used. A sterically hindered alkylborohydrides would be expected to give the same result.



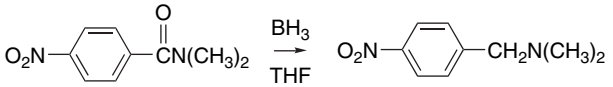
h. This transformation can be done by a Shapiro reaction.



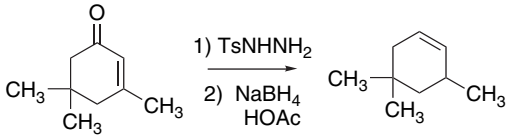
i. This transformation can be done by dissolving-metal reduction, which will effect both removal of the phoshorodiamidate group and debenzylation.



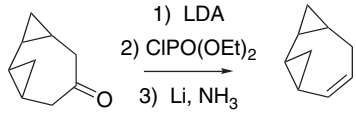
j. The selective reduction of amides in the presence of a nitro group can be done with borane-THF.



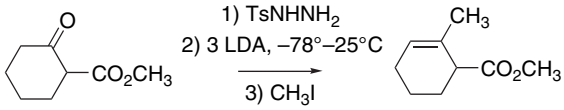
k. This transformation can be done by reduction of the tosylhydrazone. The reported yield for reduction by $NaBH_4$ in acetic acid was only 18%, although a number of other cases gave better yields. The other reductants used for this reaction would be expected to work.



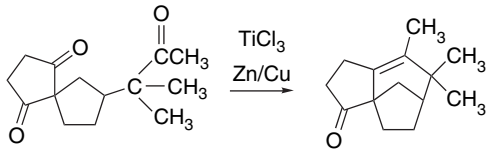
l. This transformation can be done by formation and dissolving-metal reduction of the enol phosphate. The Shapiro reaction should also work.



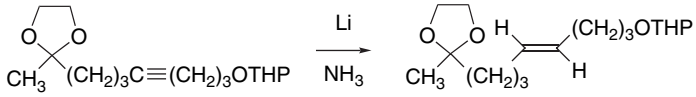
m. This transformation was done by a Shapiro reaction with a tandem methylation of the intermediate vinyllithium.



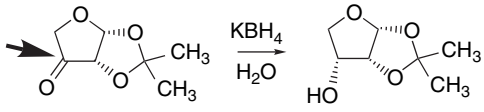
n. This reductive coupling was done in 57% yield using the $TiCl_3$-Zn-Cu system. A minor product was the alcohol formed at the unreacted carbonyl group.



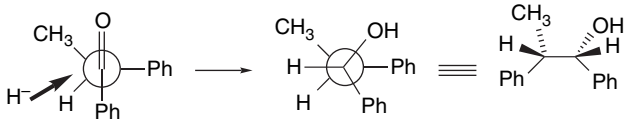
o. The formation of the *E*-double bond requires a dissolving-metal reduction. The reaction was done using Li-NH_3 in 97% yield.



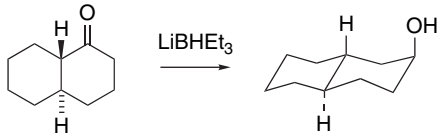
5.4. a. The reduction is governed by steric approach control to give the *cis*-hydroxy group.



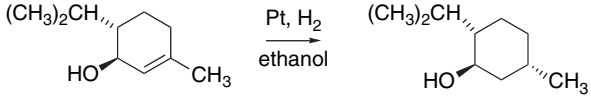
b. The stereochemistry is predictable by Cram's rule as formulated in the Felkin-Ahn TS model.



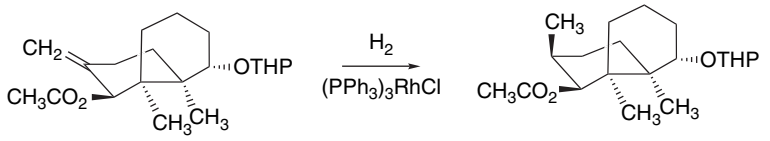
c. The use of the trialkylborohydride results in steric approach control and formation of the axial alcohol.



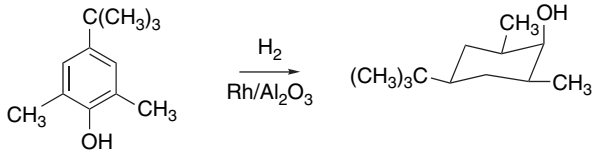
d. The steric effect of the isopropyl group and the *syn*-directive effect of the hydroxy group favor formation of *trans*,*trans*-2-(1-methylethyl)-5-methylcyclohexanol.



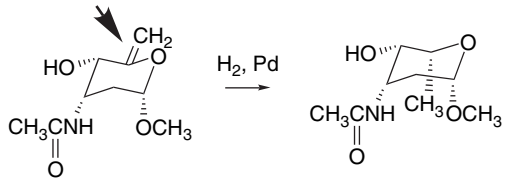
e. The product is the *cis* isomer formed by steric approach control. Wilkinson's catalyst has not been observed to exhibit a directing effect for oxygenated functional groups.



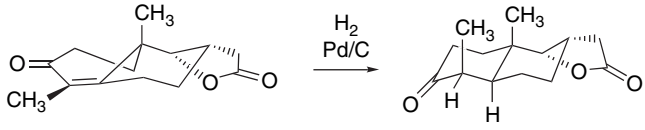
f. This hydrogenation of an aromatic ring was found to give all-*cis* product. This suggests that, as expected, the first step is rate determining and that the hydroxy group has no directing effect.



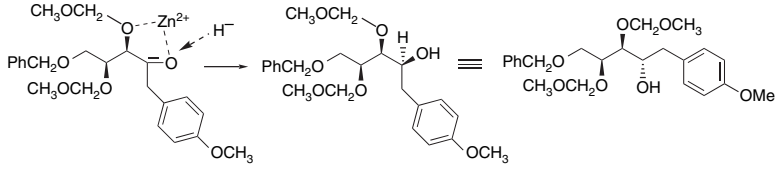
g. Under these conditions none of the substituents exerted a directive effect, the stereochemistry is governed by steric approach control, and the all-*cis* product is formed.



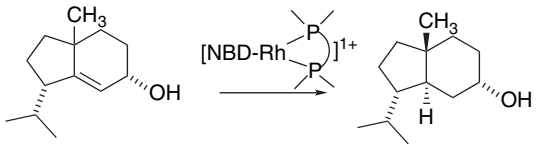
h. The axial β-methyl group at the ring juncture has the dominant influence on this hydrogenation, leading to delivery of hydrogen from the α-face.



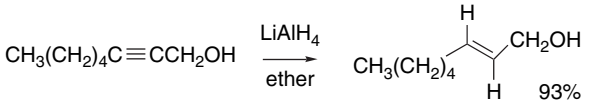
i. This reaction occurs through a chelation-controlled TS and generates an *anti* relationship to the chelating substituent.



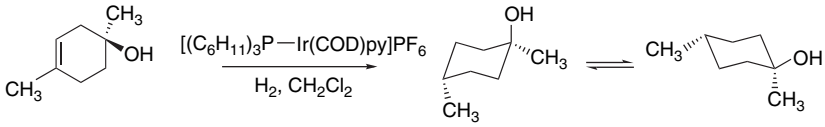
j. Both the steric effect of the methyl group and the hydroxy directing effect favor hydrogen delivery from the α-face. The isopropyl group is in a quasi-equatorial position and does not strongly shield the α-face.



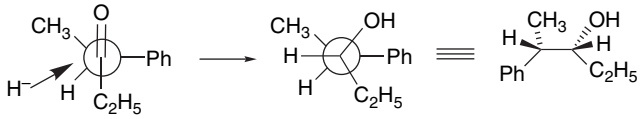
k. This hydroxy-assisted $LiAlH_4$ reduction gives the *E*-reduction product.



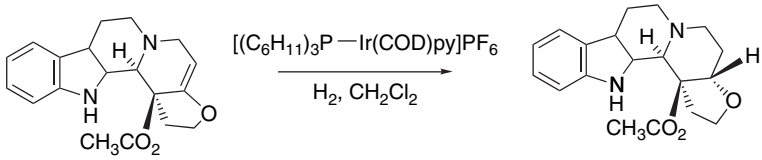
l. The hydroxy *cis*-directing effect with the iridium catalyst leads to the delivery of hydrogen *syn* to the hydroxy group. The observed selectivity was 33:1.



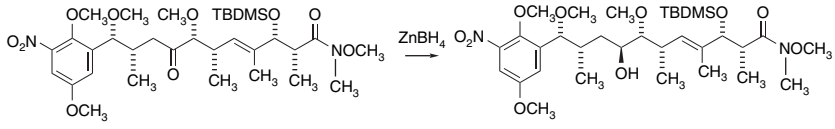
m. This reduction gives strong steric control through the Felkin-Ahn TS. The observed stereoselectivity was more than 99:1.



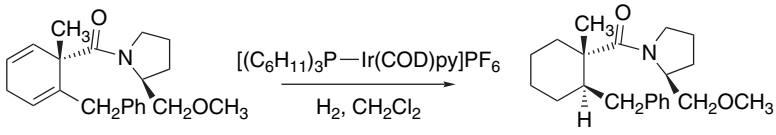
n. The directive effect of the acetoxy substituent leads to delivery of hydrogen from the β-face.



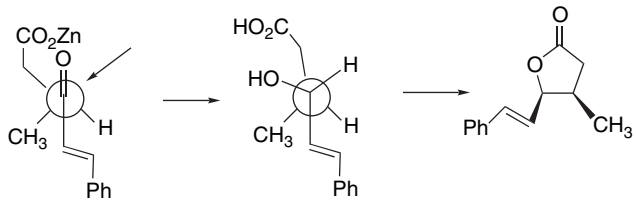
o. This reaction is chelation controlled, leading to an *anti* relationship between the hydroxy and the chelating methoxy group.



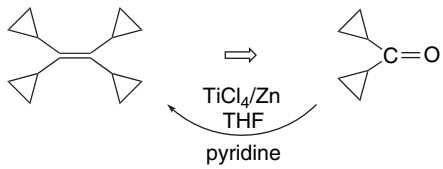
p. The amide carbonyl exerts the dominant directing effect with the iridium catalyst, leading to hydrogen delivery from the α-face.



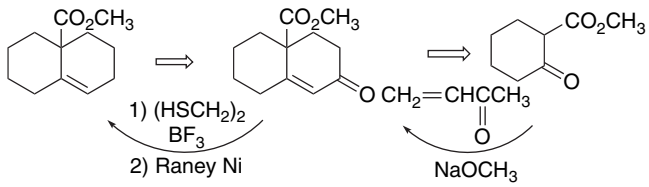
q. The reduction proceeds by chelation control and the product undergoes spontaneous lactonization.



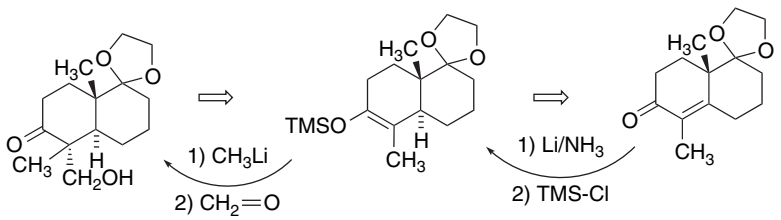
5.5. a. This reductive dimerization was accomplished in 25% yield using $TiCl_4$-Zn in THF containing pyridine.



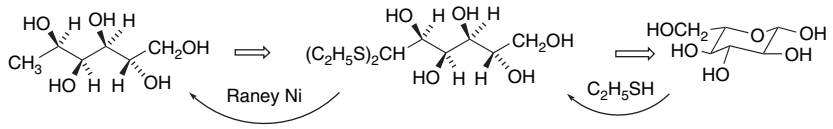
b. This transformation was done by a Robinson annulation, followed by removal of the carbonyl by formation of the dithiolane and desulfurization.



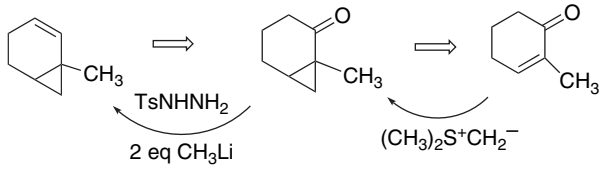
c. This transformation was done by reductive formation of the enolate, which was isolated as the silyl enol ether. The specific enolate was then regenerated with CH_3Li and allowed to react with $CH_2{=}O$.



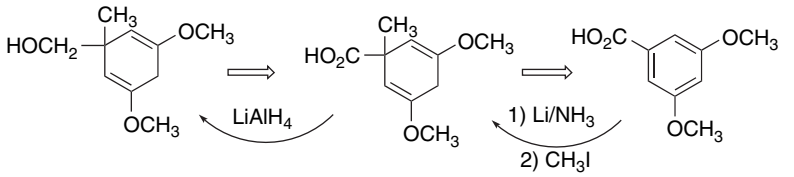
d. This transformation corresponds to conversion of the anomeric (acetal) carbon to methyl and was done by formation of the dithioacetal derivative, followed by Raney nickel desulfurization.



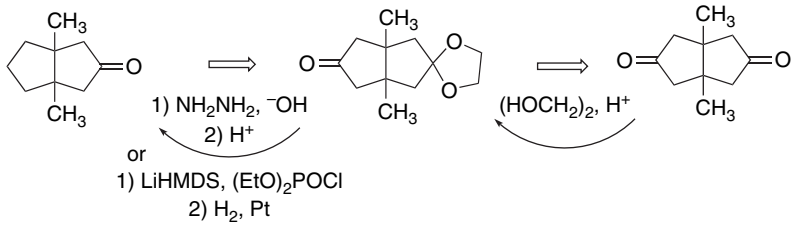
e. The cyclopropane ring was introduced using dimethylsulfoxonium methylide and the carbonyl was converted to an alkene by the Shapiro reaction.



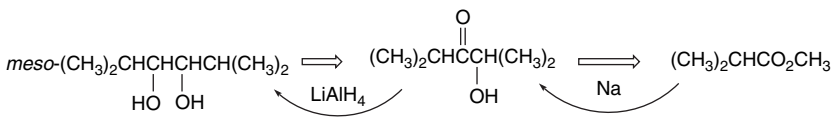
f. This sequence was accomplished by Birch reduction with tandem alkylation. The carboxy group was then reduced using $LiAlH_4$.



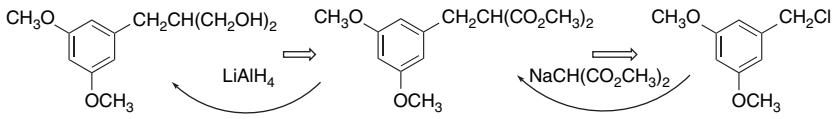
g. Selective monoketalization protected one carbonyl. The other was then converted to an alkene using either the Wolff-Kishner reduction or reduction of the enol phosphate. The resulting double bond was then hydrogenated.



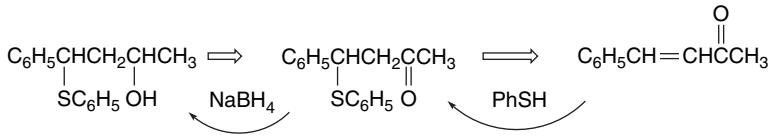
h. In the cited reference, the compound was prepared as a mixture of the stereoisomers by $LiAlH_4$ reduction of the corresponding acyloin, which was obtained from the ester. The ratio of the desired *meso* product could presumably be enhanced by use of strongly chelating reduction conditions.



i. The benzylic chloride was used to alkylate diethyl malonate and the product was reduced to the diol with $LiAlH_4$.



j. After conjugate addition of phenylthiol, the ketone was reduced using $NaBH_4$.

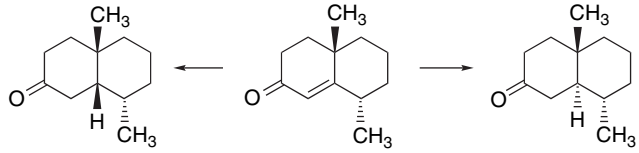


5.6. a. The greater reactivity of $LiAlH_4$ is due to the stronger Lewis acid character of Li^+ and the increased activation of the carbonyl group.

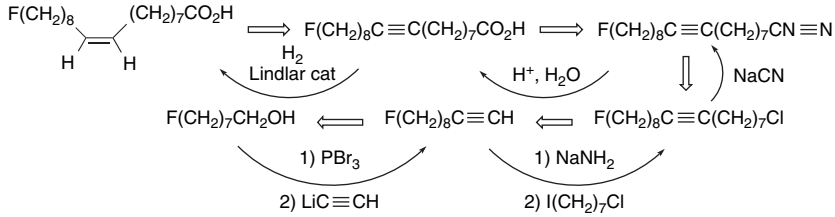
b. The crown ether can complex with the Li^+ ion, reducing its Lewis acid character.

c. Equatorial methyl groups as added in 3-methylcyclohexanone or 3,3,5-trimethylcyclohexanone have little steric influence on the rate of reaction. The introduction of the axial methyl group in 3,3-dimethylcyclohexanone blocks axial approach and reduces the rate. The addition of a second axial group at C(5) has little effect because the axial approach is already blocked by the axial methyl at C(3).

5.7. The C(8) methyl group provides steric encumbrance on the α-face, so catalytic hydrogenation gives mainly the *cis* ring junction. The stereochemistry of Li-NH_3 reduction is predicted to result from axial protonation, providing the *trans* ring junction.

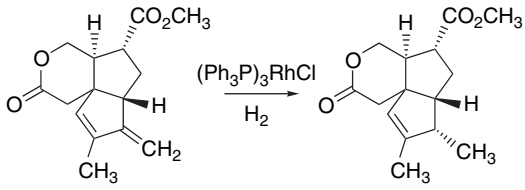


5.8.

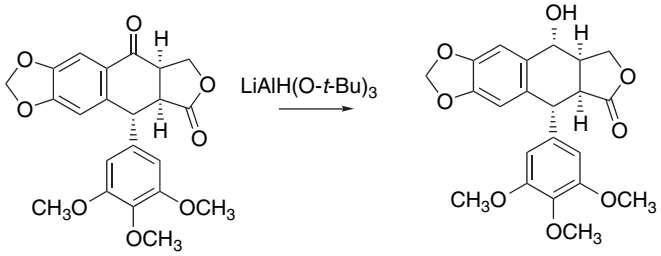


5.9. a. This transformation requires chemo- and stereoselective reduction of the exocyclic double bond, but there are no adjacent functional groups to exert stereochemical control. It was found that although Pd-C hydrogenation gave the endocyclic double bond (formal 1,4 reduction), Wilkinson's catalyst gave the desired product. This success probably results from the better steric access

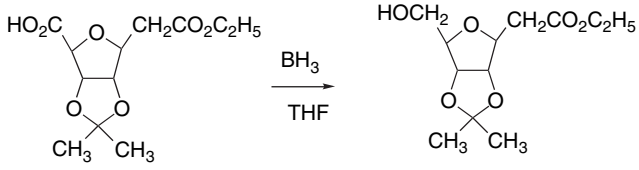
to the exocyclic double bond and the reduced tendency for isomerization of the Wilkinson catalyst.



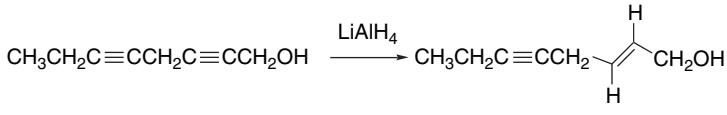
b. This transformation requires a stereoselective reduction of the ketone carbonyl without reaction with the lactone. The reaction was successfully carried out using four equivalents of $LiAlH(O\text{-}t\text{-}Bu)_3$. This success is based on steric approach control and diminished reactivity of the lactone carbonyl.



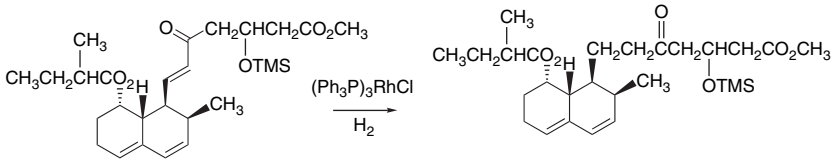
c. The selective reduction of a carboxylic acid in the presence of an ester can be done with borane in THF.



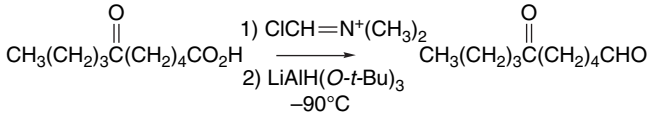
d. The hydroxy-assisted $LiAlH_4$ reduction shows the desired chemo- and stereoselectivity.



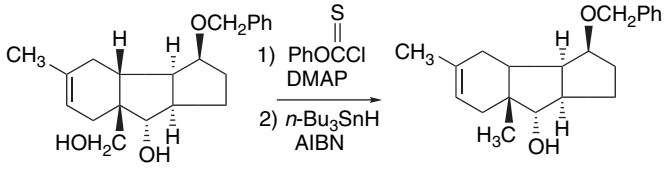
e. The reduction of the enone double bond in the presence of the conjugated diene was done with Et_3SiH and $(Ph_3P)_3RhCl$.



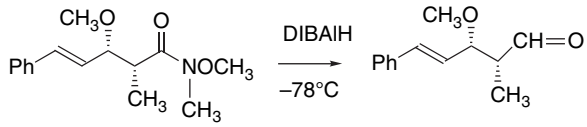
f. This transformation requires selectivity for the carboxylic acid and partial reduction to the aldehyde stage. The carboxylic acid was allowed to react with *N*,*N*-dimethylformidinium chloride and was then treated with 1.15 equivalents of $LiAlH(O\text{-}tBu)_3$ at −90° C. The reaction presumably proceeds through a mixed imino anhydride.



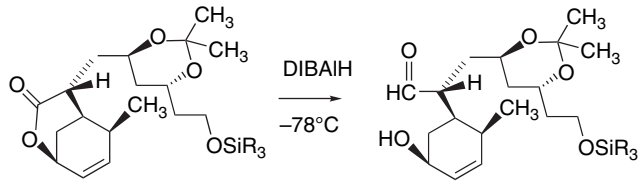
g. This transformation requires selective removal of a primary hydroxyl in the presence of a secondary hydroxyl. This was accomplished by selective formation of the phenyl thiono carbonate on the basis of steric access, followed by $n\text{-}Bu_3SnH$ reduction.



h. The *N*-methoxyamide can be reduced to the aldehyde using DiBAlH at −78° C.

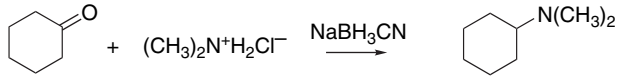


i. This partial reduction to a lactol, shown in open form, can be done by DiBAlH at low temperature.

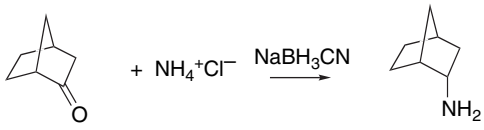


5.10. a. The use of a hindered hydride reducing agent leads to equatorial approach.
b. The hydrogen is delivered from the sterically least hindered side of the radical intermediate.
c. The stereochemistry at the β-carbon in dissolving-metal reduction of enones is governed by an axial protonation.

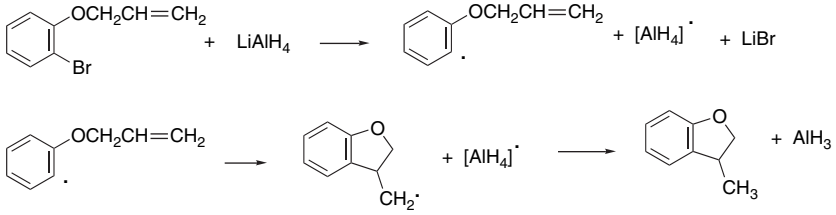
5.11. a. The most accessible combination is cyclohexanone and dimethylamine.



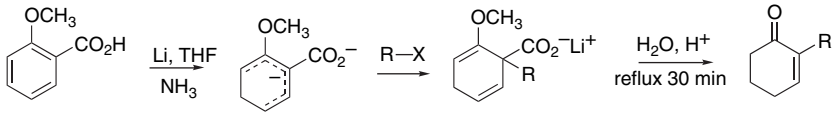
b. The combination is norbornan-2-one and ammonia.



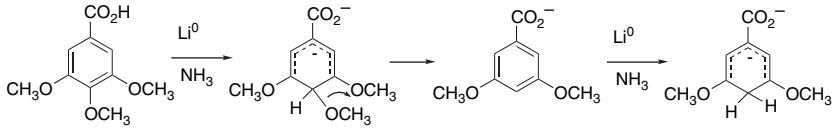
5.12. The formation of the cyclic product indicates that reaction occurs at least in part through an electron transfer mechanism generating an aryl radical. Increasing the $LiAlH_4$ concentration favors reduction of the first intermediate prior to cyclization. According to this mechanism, the deuterium would be located in the methyl group. The lack of complete deuteration suggests that there must be a competing source of hydrogen for the methyl group. This could involve hydrogen atom abstraction from solvent.



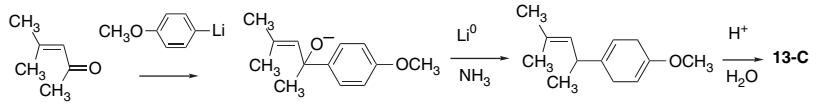
5.13. a. The first step is a Birch reduction that generates a dianion intermediate in the absence of any proton source. This dianion is alkylated in the second step of the sequence. The acidic hydrolysis generates a β-keto acid that can undergo decarboxylation to give the final product.



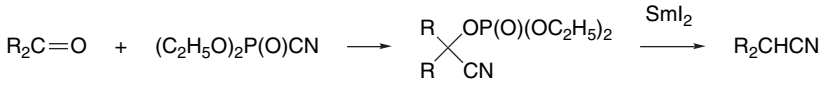
b. The intermediate dianion can eliminate the 4-methoxy group generating 3,5-dimethoxybenzoate, which could undergo a second Birch reduction. This mechanism predicts the product will be 3,5-dimethoxy-1,4-dihydrobenzoic acid.



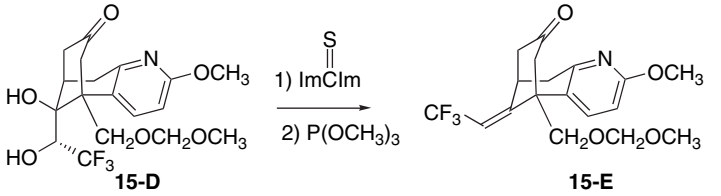
c. The first intermediate is the 1,2-addition product of reaction with 4-methoxyphenyllithium. The dissolving-metal conditions lead to both reduction of the methoxyphenyl ring and benzylic-allylic deoxygenation. Hydrolysis of the dihydromethoxyphenyl ring generates the cyclohex-3-enone ring.



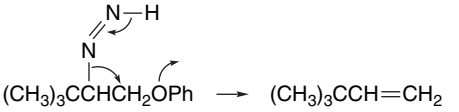
5.14. The combination of LiCN and $(C_2H_5O)_2P(O)CN$ generates a phophorylated cyanohydrin. The SmI_2 reductively removes the phosphoryl group with anion stabilization provided by the CN group.



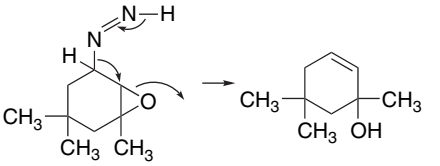
5.15. The transformation was done via the cyclic thiono carbonate, formed using thiocarbonyldiimidazole, followed by trimethyl phosphite reduction. Methods based on dissolving-metal reduction, e.g., deoxygenation of the cyclic sulfate, would be likely to reduce the pyridine ring and carbonyl group.



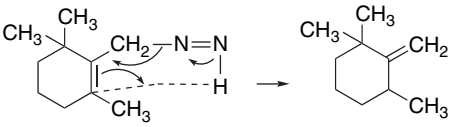
5.16. a. The phenoxy group is placed to undergo elimination in concert with decomposition of the diimide intermediate.



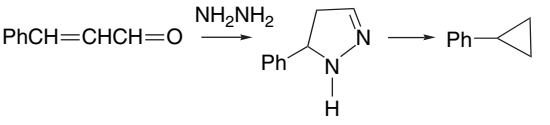
b. The epoxide ring is opened by the carbanionic character generated by diimide decomposition.



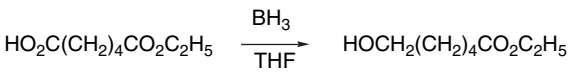
c. This product must be formed by alternative γ-protonation of the incipient allylic anion. A concerted mechanism may be involved.



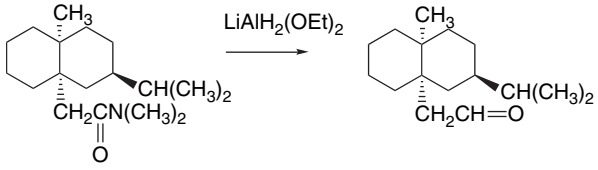
d. The reaction is diverted to the pyrazoline, which can give rise to the cyclopropane (see Section 6.6.2).



5.17. a. The reduction of a carboxylic acid in the presence of an ester can be done using borane in THF.

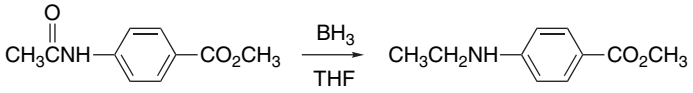


b. This transformation requires partial reduction of an amide. As with partial reduction of esters, this requires that the reaction be run under conditions in which the initial adduct is stable against further reduction. The reported transformation was done with $LiAlH_2(OEt)_2$. DIBAlH would probably be an alternative.

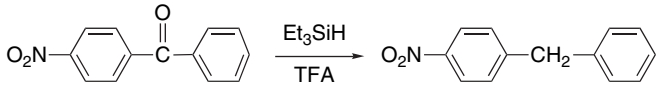


c. This transformation was done by reducing the tosylhydrazone with $NaBH_3CN$.

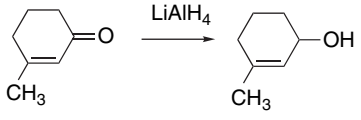
d. The reduction of an amide can be done in the presence of an ester using borane in THF.



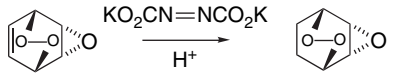
e. The reduction of a carbonyl group in the presence of a nitro group is unlikely to be successful under Clemmensen conditions. Wolff-Kischner reduction might be a possibility. The reaction was done in the cited reference using triethylsilane and TFA.



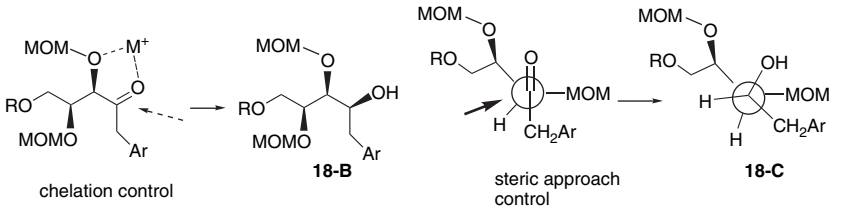
f. Any of the reductants that selectively reduce α,β-unsaturated ketones to allylic alcohol should work (see Section 5.3.1.3). The reaction has been done using $LiAlH_4$.



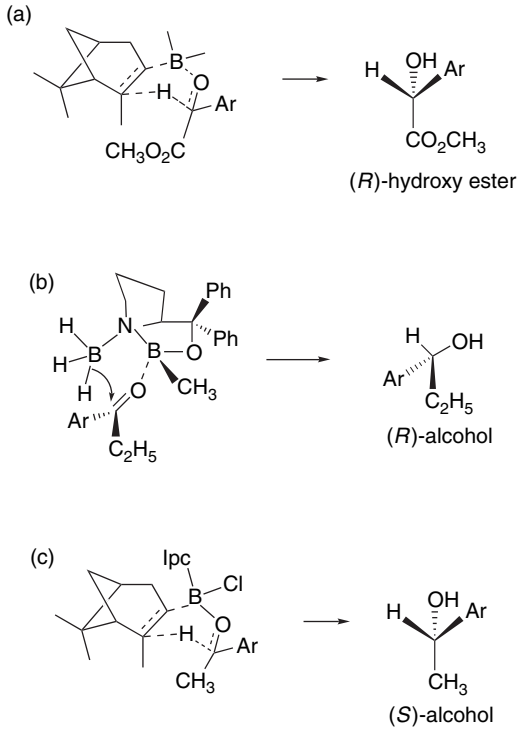
g. The reduction of a double bond was done in the presence of the very sensitive peroxide group using diimide generated from $KO_2CN{=}NCO_2K$.



5.18. Product **18-B** results from chelation control and the order $NaBH_4 < LiAlH_2(OCH_2CH_2OCH_3)_2 < Zn(BH_4)_2$ reflects increasing stereoselectivity for the chelation-controlled product, based on the chelating strength of the metal cation. With L-Selectride, the reaction is under steric approach control and occurs through a Felkin-Ahn TS with the α-methoxymethyl substituent in the perpendicular position.

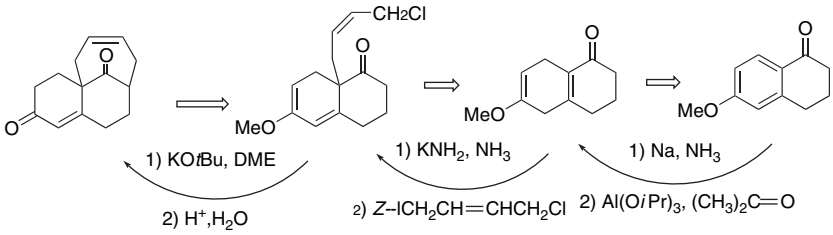


5.19.

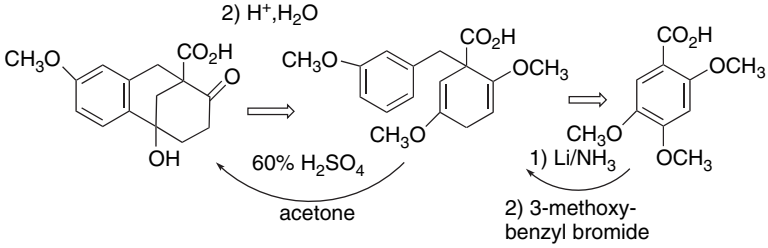


5.20. a. The location of the enone carbonyl suggests a Birch reduction for the conversion of the aromatic ring to the cyclohexenone. The double bond might suggest a reductive coupling, but in the cited reference it was derived from *Z*-1,4-dichloro-2-butene. The first step in the reported sequence was Birch reduction. The reduction also reduced the ketone to an alcohol and it was reoxidized using the Oppenauer conditions. A vinylogous enolate was then formed under thermodynamic conditions and resulted in alkylation of the bridgehead

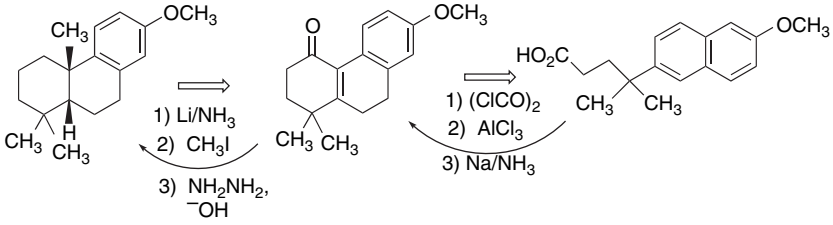
position. The cyclization was effected with a second enolate alkylation, after which the enol ether was hydrolyzed to the enone.



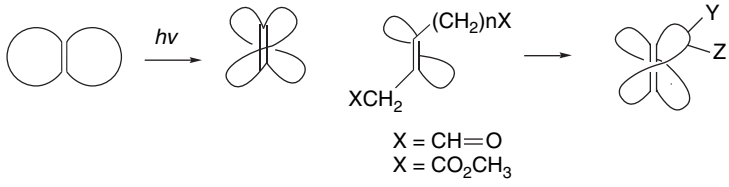
b. Birch reduction followed by tandem alkylation with 3-methoxybenzyl bromide gave the first intermediate. This was treated with sulfuric acid, which hydrolyzed both enol ethers and resulted in cyclization to a six-membered ring.



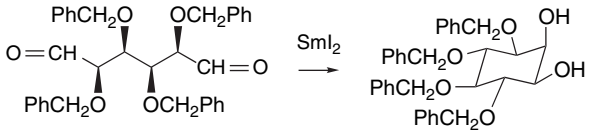
c. After an intramolecular Friedel-Crafts reaction, the naphthalene ring was subjected to Birch reduction. The enone obtained by Birch reduction was subjected to dissolving-metal reduction and tandem methylation. The final step was removal of the carbonyl group by Wolff-Kishner reduction.



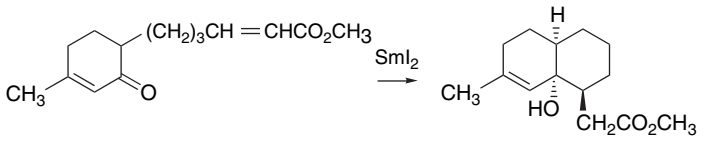
5.21. The topology of the "betweenanenes" requires a *trans* orientation of the chains that link the two opposite ends of the double bonds. One successful route involves photoisomerization of the corresponding *cis* isomers. Another approach involves synthesis of large-ring *E*-cycloalkenes having substituents that can be coupled. Both titanium-mediated reductive coupling and acyloin condensation have been used in the latter approach.



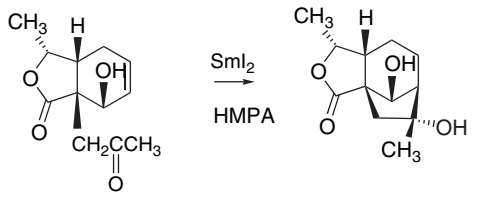
5.22. a. The reaction results in reductive coupling of the two aldehydes with the β,β-stereoisomer shown being the major (56%) product.



b. The radical generated at the carbonyl site undergoes an *exo*-6 cyclization.

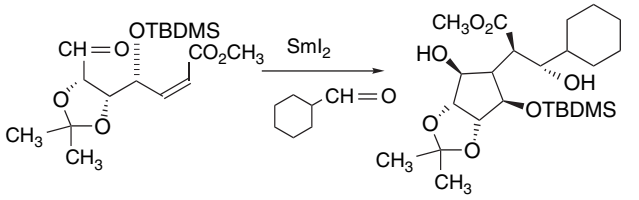


c. The radical generated by carbonyl reduction adds to the carbon-carbon double bond.

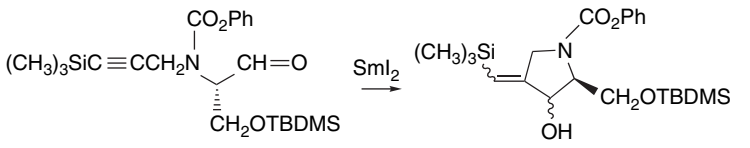


d. The radical generated by carbonyl reduction undergoes an *exo*-5 cyclization.

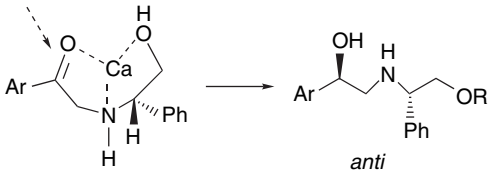
e. A tandem sequence involving *exo*-5 cyclization followed by intermolecular trapping by cyclohexanecarboxaldehyde occurs.



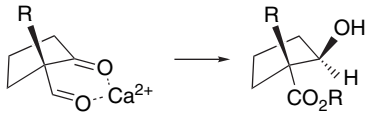
f. An *exo*-5 cyclization occurs by addition to the alkynyl bond.



5.23. a. The data indicate a reversal and enhancement of the stereoselectivity in the presence of $CaCl_2$. The methoxy substituent is not as effective as the hydroxy in promoting *anti* stereoselectivity. These data are consistent with the $NaBH_4$-$CaCl_2$ reaction conditions being under chelation control. Chelation by both the oxygen and nitrogen substituents would generate a bicyclic chelate having a concave and convex face. Selective approach from the convex face gives the observed preference for the *anti* isomer.

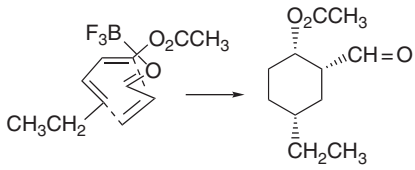


b. The reaction can proceed through a chelated TS in the presence of Ca^{2+}. The dependence on the alkyl group is somewhat puzzling since it is not obvious why the propyl group should be more sterically directive than a benzyl group.

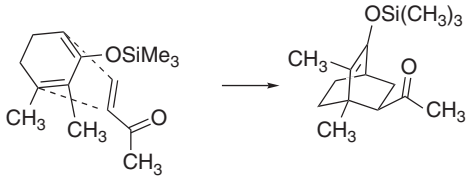


Chapter 6

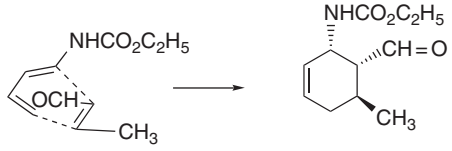
6.1. a. The regiochemistry is directed by the acetoxy substituent on the diene and the *cis-cis* stereoisomer is formed through an *endo* transition structure.



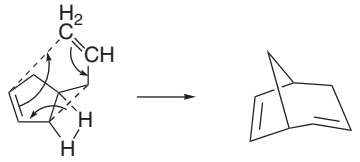
b. The regiochemistry is determined by the donor siloxy group and the stereochemistry by the *endo* transition structure.



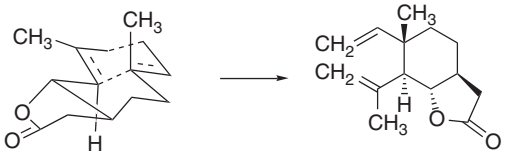
c. The regiochemistry is determined by the donor carbamate group and the stereochemistry results from an *endo* transition structure.



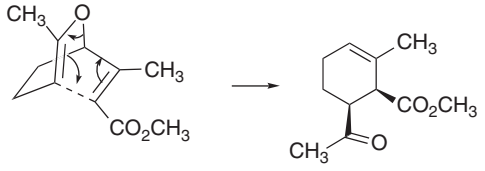
d. The favored reaction is a Cope rearrangement of the divinylcyclopropane.



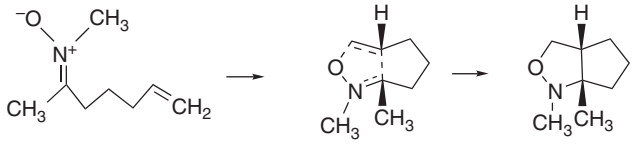
e. The 1,5-diene is subject to Cope rearrangement. The equilibrium favors the six-membered ring by about 2:1. The *anti* stereochemistry at the ring junction arises from a chairlike TS.



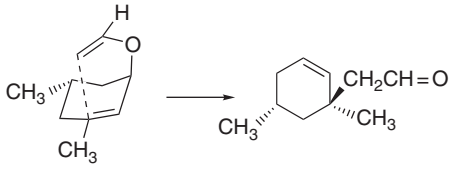
f. The compound would be expected to undergo a Cope reaction through a bicyclic TS. The observed product ratio is 95:5 *cis*:*trans*, which suggests a small amount of epimerization via enolization at one of the carbonyl centers.



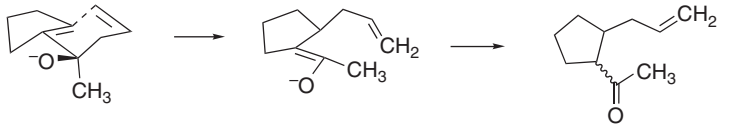
g. These conditions lead to an intramolecular 1,3-dipolar cycloaddition via a nitrone intermediate. The reduced strain associated with the *cis* ring juncture favors the observed stereochemistry.



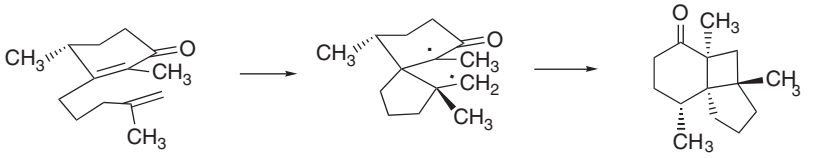
h. These conditions lead to a Claisen rearrangement. The suprafacial nature of the reaction establishes the stereochemistry.



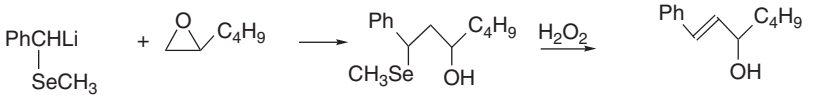
i. These conditions lead to an anionic oxy-Cope rearrangement. A chairlike TS is accessible and presumably operative. However, the stereochemistry is determined by the protonation of the enolate intermediate and a mixture of stereoisomers was obtained.



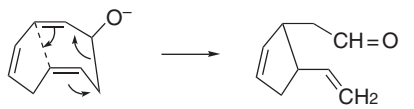
j. The expectation for this intramolecular enone photocyclization would be for initial formation of a five-membered ring. The *cis* closure of this diradical is less strained than the *trans* closure.



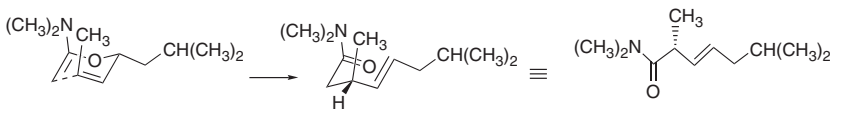
k. An α-selenenyl carbanion is generated by the lithiation and opens the epoxide. Oxidation to the selenoxide results in elimination.



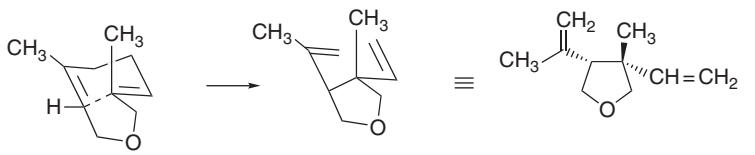
l. These conditions lead to an anionic oxy-Cope reaction. The all-*cis* stereochemistry of the cyclononatrienol appears to dictate a boatlike TS that predicts the observed *cis* stereochemistry.



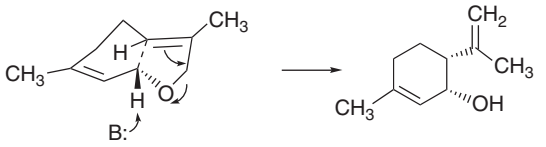
m. These conditions lead to an ortho amide Claisen rearrangement. The *Z*-double bond and a chairlike TS lead to formation of the *R*-configuration at the new chiral center.



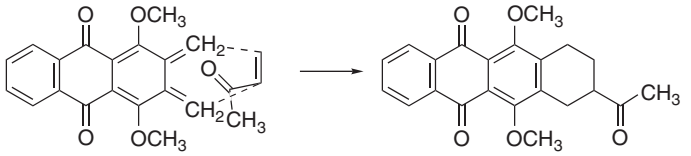
n. The compound can readily undergo a Cope rearrangement through a chairlike TS, generating a *cis* relationship between the two alkenyl substituents.



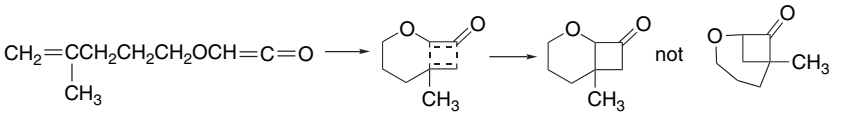
o. Under basic conditions this compound can undergo an anionic [2,3]-sigmatropic rearrangement.



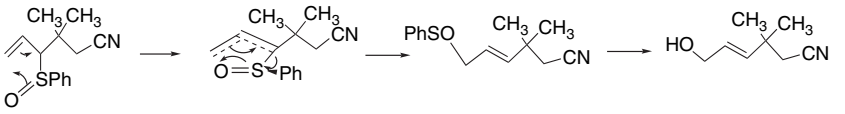
p. The conditions lead to the reductive generation of a quinodimethane intermediate, which gives a Diels-Alder adduct in 62% yield. Presumably the TS is *endo* but there are no regiochemical or stereochemical issues The usual reagent for reductive elimination, metallic zinc, gave rather poor yields.



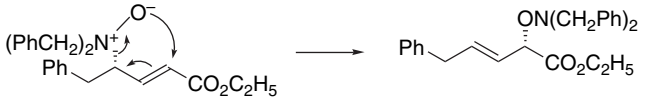
q. These conditions lead to an intramolecular [2 + 2] ketene cycloaddition. The observed product is consistent with initial bond formation at the more nucleophilic end of the double bond and corresponds to a less strained TS.



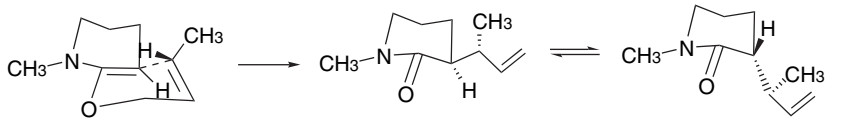
r. Generation of the sulfoxide by oxidation leads to [2,3]-sigmatropic rearrangement and solvolysis of the sulfenate.



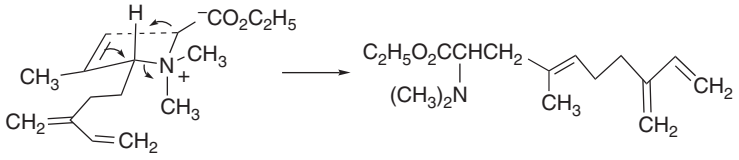
s. Oxidation of the amine to the amine oxide leads to [2,3]-sigmatropic rearrangement to the corresponding allylic hydroxylamine. The suprafacial reaction occurs with complete chirality transfer.



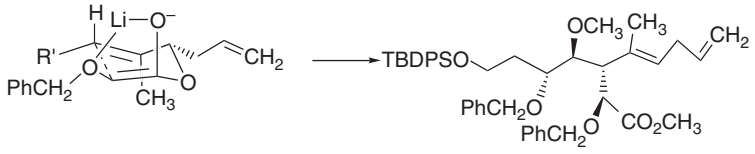
t. Reaction occurs by exchange of the 2-butenyloxy group at the imino ether followed by [3,3]-sigmatropic rearrangement. Although a chairlike TS predicts stereoselectivity, the product was found to be a 1:1 mixture of diastereomers. This result was attributed to epimerization α to the lactam carbonyl.



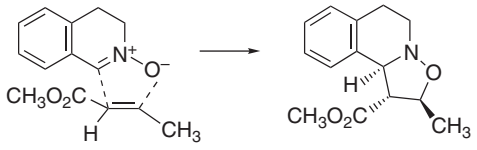
u. These conditions result in generation and [2,3]-sigmatropic rearrangement of the ammonium ylide. The new double bond is *E*, which is consistent with a pseudoequatorial conformation of the alkyl substituent.



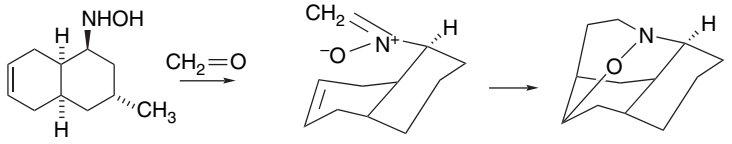
v. The stereochemistry of this Ireland-Claisen rearrangement is governed by a chelated TS involving the α-benzyloxy group.



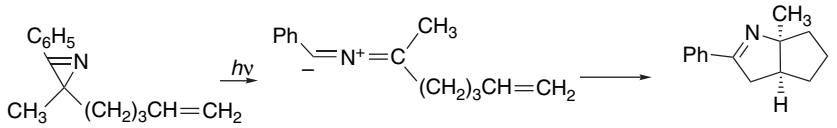
w. This 1,3-dipolar cycloaddition retains the configuration of the dipolarophile and proceeds through an *endo* TS. The regiochemistry is consistent with a HOMO-nitrone/LUMO-acrylate interaction.



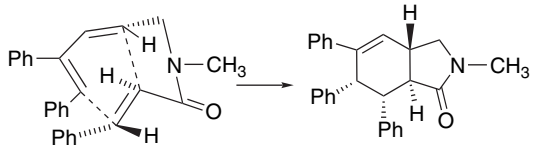
6.2. a. The reaction proceeds through a nitrone that is generated in situ. Total regioselectivity was observed although neither electronic nor steric reasons for the selectivity are apparent.



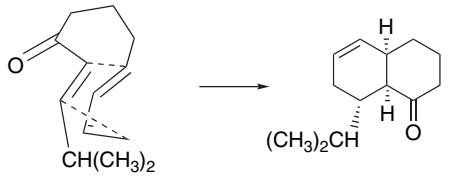
b. Photolysis of the azirine generates a nitrile ylide that can undergo cycloaddition. Owing to relative strain, the *cis* ring junction is preferred.



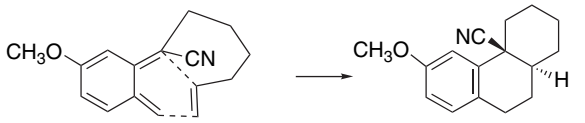
c. This compound can undergo an intramolecular Diels-Alder reaction. There is an 8:1 preference for the product of the *trans* ring juncture.



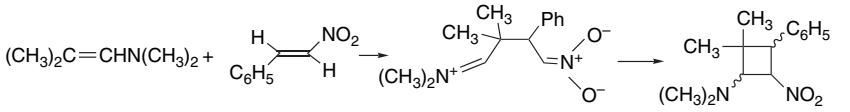
d. The intramolecular Diels-Alder reaction proceeds via an *endo* TS, leading to a *cis* ring juncture.



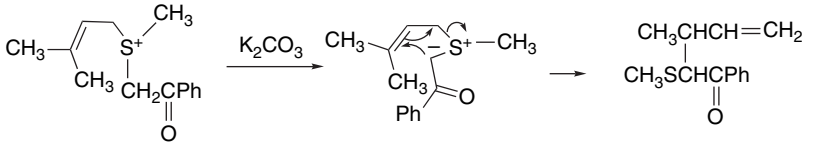
e. This reaction proceeds by thermal ring opening to a quinodimethane. There is a preference for outward rotation of the bulkier alkyl chain (perhaps reinforced by electronic factors) and this leads to a *trans* ring junction.



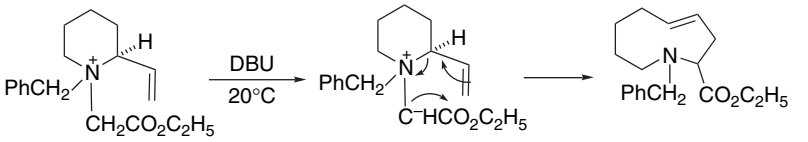
6.3. a. This reaction is a [2 + 2] cycloaddition that probably proceeds through a zwitterionic intermediate, which would account for the lack of stereospecificity.



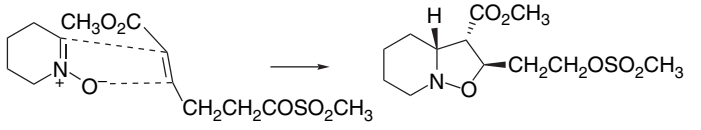
b. This reaction involves formation and [2,3]-sigmatropic rearrangement of a sulfonium ylide.



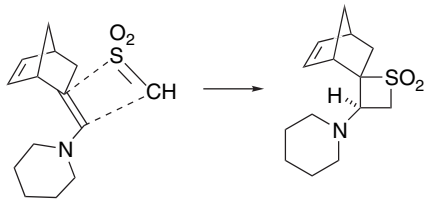
c. This ring expansion is a [2,3]-sigmatropic rearrangement of an ammonium ylide.



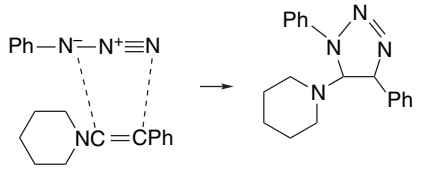
d. This is a 1,3-dipolar cycloaddition. The *trans* stereochemistry of the dipolarophile is maintained in the adduct.



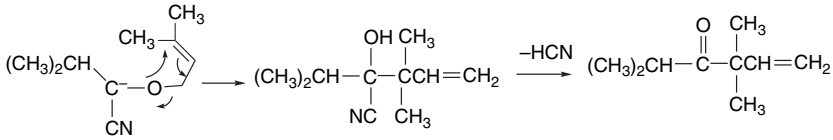
e. This reaction can occur by a "sultene" addition, analogous to a ketene addition.



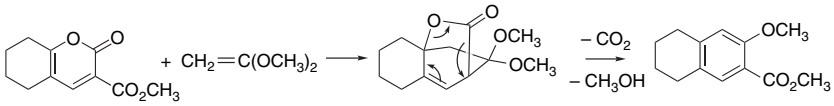
f. This is a 1,3-dipolar cycloaddition with the frontier orbitals being dipolarophile-HOMO/dipole-LUMO.



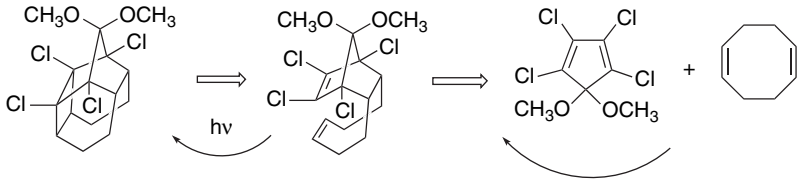
g. This is an anionic [2,3]-sigmatropic shift, with the cyano group providing anion stabilization. Subsequent elimination of HCN generates the carbonyl group.



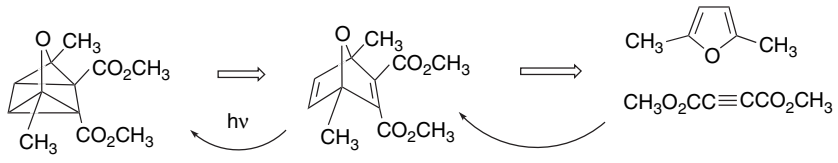
h. This reaction can occur by a $[2+4]$ cycloaddition to the pyrone, followed by a $[2+4]$ cycloreversion with loss of CO_2 and aromatization by loss of methanol.



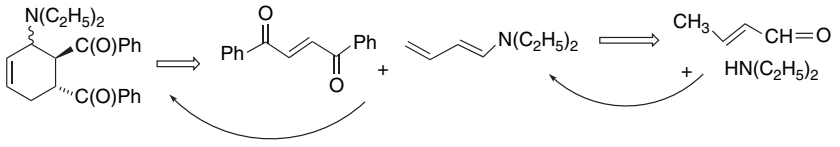
6.4. a. This transformation can be done in two steps. The first is a Diels-Alder addition that is *endo* selective, followed by $[2+2]$ photocycloaddition.



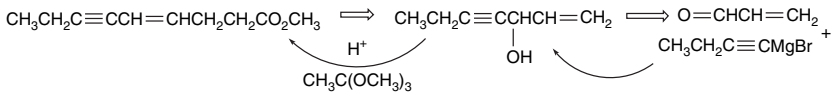
b. This synthesis can been done by a Diels-Alder reaction and photocyclization.



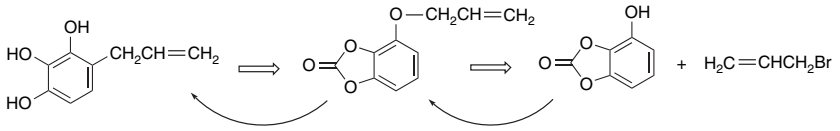
c. Formation of the enamine from 2-butenal and diethylamine gives a reactive diene that can form the desired product by Diels-Alder cycloaddition. The final reaction product was converted to a 1,3-diarylisobenzofuran by acid-catalyzed cyclization and aromatization.



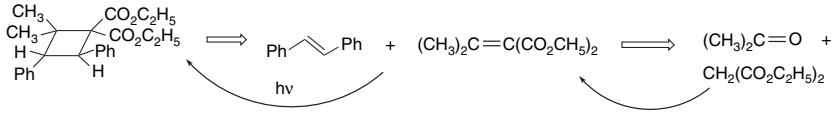
d. After 1,2-addition of the alkyne to propenal to generate an allylic alcohol, orthoester Claisen rearrangement gives the desired product.



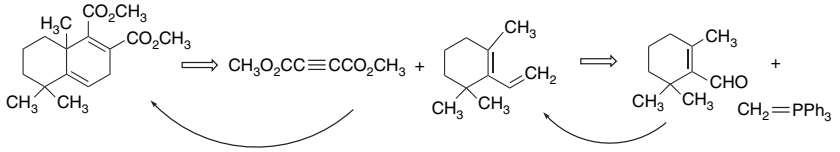
e. This transformation can be done by [3,3]-sigmatropic Claisen rearrangement of the allyl ether, followed by hydrolysis.



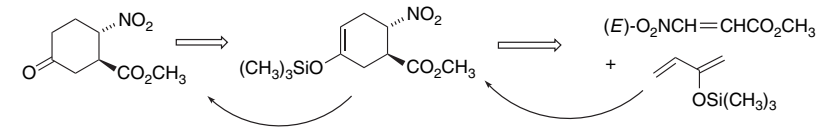
f. Photocycloaddition of *trans*-stilbene with diethyl 2-(2-methylethylidene) malonate can generate the desired compound. The latter reactant can be made by condensation of acetone and diethyl malonate.



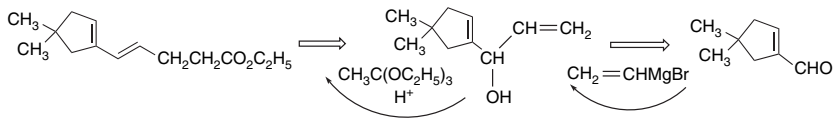
g. Conversion of the aldehyde reactant to a diene by a Wittig reaction followed by a Diels-Alder reaction with dimethyl acetylenedicarboxylate gives the desired product.



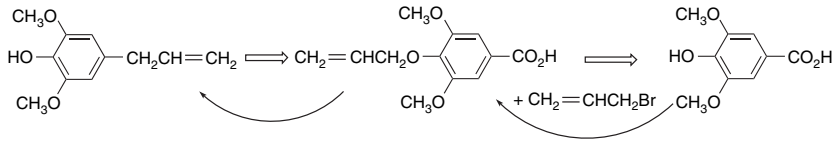
h. A Diels-Alder reaction with 2-(trimethylsilyloxy)-1,3-butadiene followed by hydrolysis of the silyl enol ether gives the desired product.



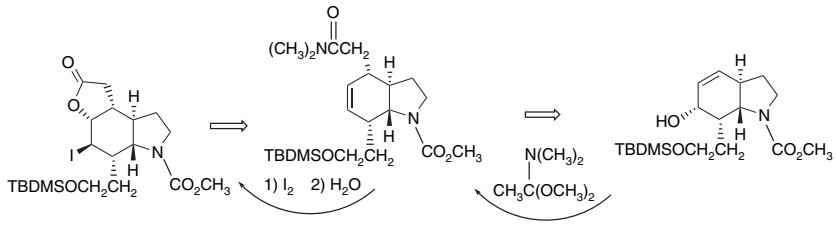
i. Addition of vinylmagnesium bromide to the starting aldehyde followed by a Claisen orthoester or silyl ketene acetal rearrangement generates the desired product.



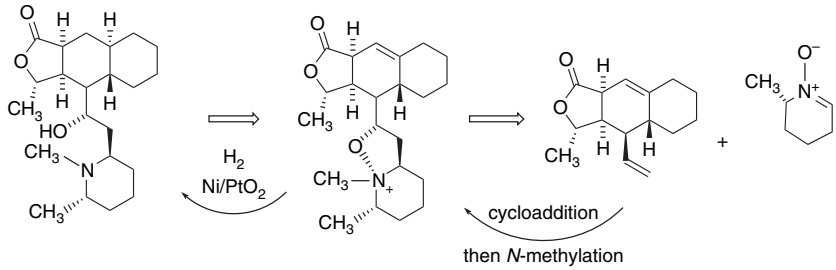
j. This transformation corresponds to a double aromatic Claisen rearrangement (see p. 564). Aromatization takes place by decarboxylation.



k. An orthoamide Claisen rearrangement was used to install the side chain, which was then cyclized to the lactone by iodination. Analogous transformation via the orthoester Claisen or silyl ketene acetal Claisen should be feasible.

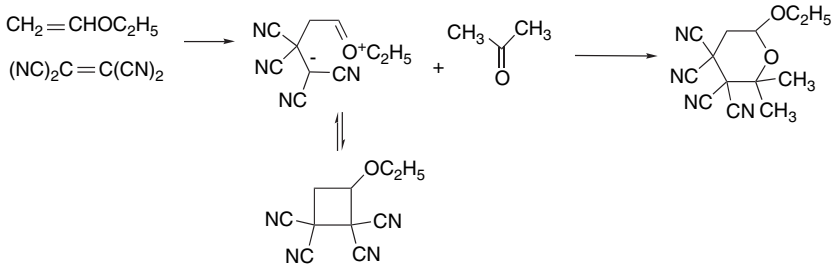


l. This transformation can be done with a nitrone cycloaddition, followed by reductive cleavage of the oxazolidine ring.

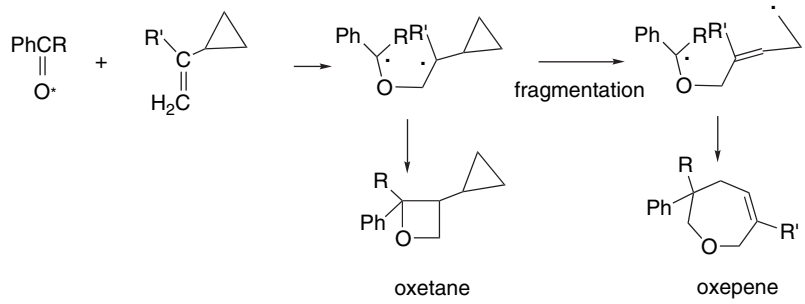


6.5. a. These results suggest the involvement of a zwitterionic intermediate that is inefficiently trapped in acetone. Reversible formation of the intermediate

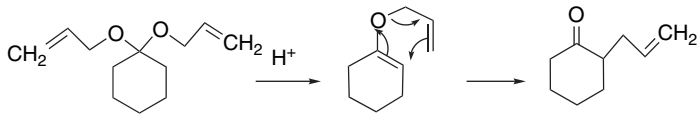
in acetone would lead to complete conversion, assuming that the acetone-containing adduct is stable.



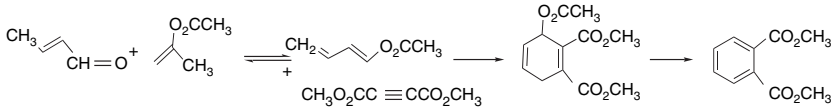
b. The formation of the oxepenes can be rationalized by competition between oxetane ring closure and cyclopropylcarbinyl radical fragmentation. The fragmented radical would lead to the observed oxepenes.



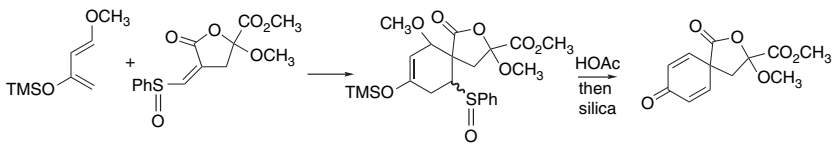
c. This reaction can occur by acid-catalyzed elimination of allyl alcohol from the acetal, followed by Claisen rearrangement of the resulting allyl vinyl ether.



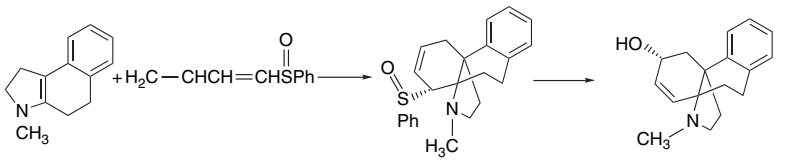
d. Acid-catalyzed enol acetate exchange will generate 1-acetoxy-1,3-butadiene from 2-butenal and 2-acetoxypropene. Diels-Alder cycloaddition followed by aromatization by elimination of acetic acid generates dimethyl phthalate.



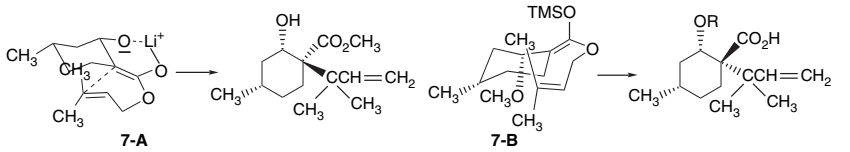
6.6. a. Use of the Danishefsky diene and the sulfoxide substituent in the dienophile permits generation of the cyclohexadienone moiety by sulfoxide elimination and hydrolysis of the silyl enol ether.



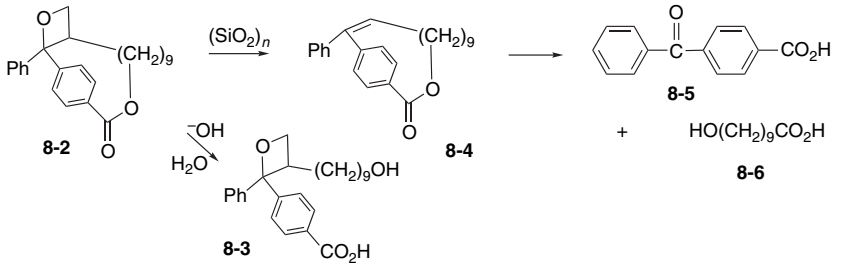
b. This inverse electron demand Diels-Alder reaction generates an adduct that can undergo [2,3]-sigmatropic shift to introduce the allylic alcohol functionality.



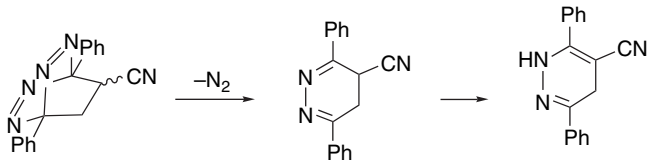
6.7. The hydroxy group would be expected to participate in chelation with the ester enolate leading to conformation **7-A** for the TS. In the silyl ketene acetal, this conformation would suffer from $A^{1,3}$ interaction between the methoxy and silyoxy substituent, resulting in **7-B** being the preferred TS.



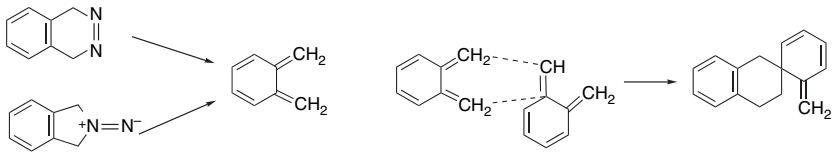
6.8. Photocycloaddition between the C=O and remote C=C generates oxetane **8-2**. Alkaline hydrolysis of the ester group gives **8-3**. Silica-promoted opening of the oxetane ring at the benzylic position, followed by loss of CH_2=O gives **8-4**. Oxidative cleavage at the double bond and alkaline hydrolysis of the ester group give **8-5** and **8-6**.



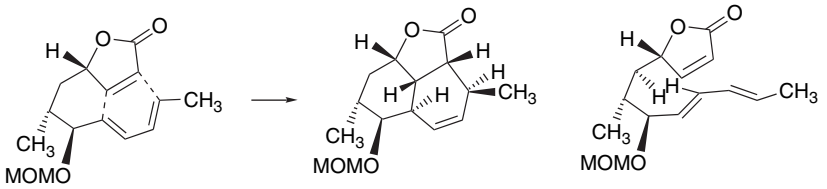
6.9. a. This transformation can occur by a Diels-Alder addition and cycloreversion, followed to tautomerism to the more stable hydrazone form.



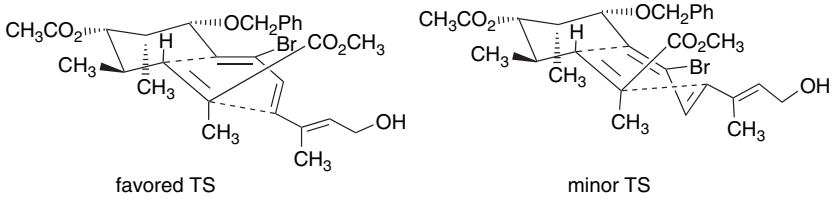
b. Both of these azo compounds can undergo concerted loss of nitrogen to generate *o*-quinodimethane. Product **9-3** results from Diels-Alder dimerization of *o*-quinodimethane.



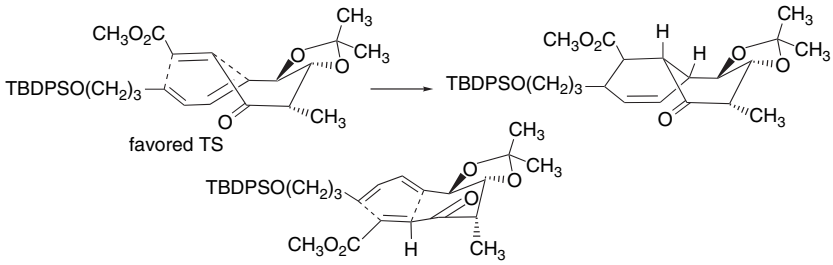
6.10. a. This intramolecular Diels-Alder reaction occurs through and an *exo* transition structure. The corresponding *endo* transition structure has steric interference.



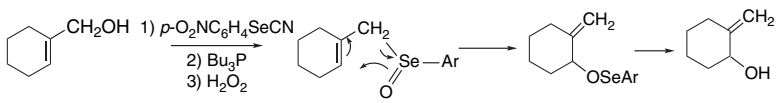
b. The major product results from an *endo* transition structure. A minor product (10%) arises from an alternate *endo* transition structure.



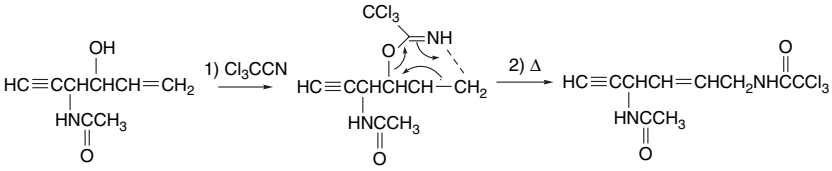
c. The product stereochemistry corresponds to a boat transition structure with an *endo* placement of the ketone carbonyl. The corresponding *endo* chair transition structure is destabilized by the axially oriented methyl group.



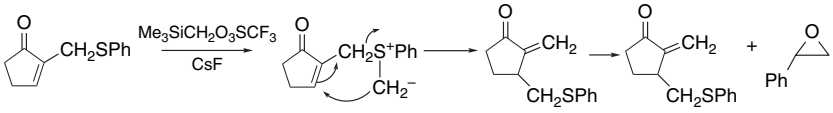
6.11. a. This reaction occurs by formation of the selenide, oxidation to the selenoxide, [2,3]-sigmatropic shift, and solvolysis of the aryl selenenate.



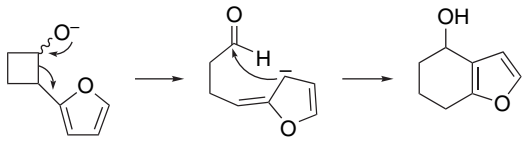
b. This reaction involves formation and [3,3]-sigmatropic rearrangement of an imidate.



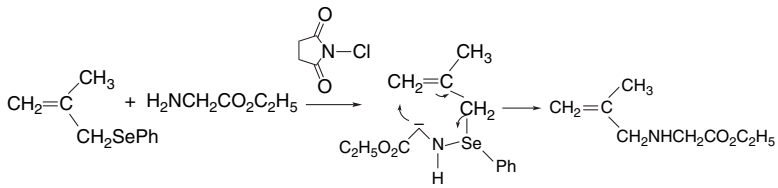
c. A sulfonium ylide is generated by S-alkylation and disilylation. This ylide undergoes [2,3]-sigmatropic shift. The rearrangement is evidently followed by generation of a second sulfonium ylide that acts as a methylene transfer reagent toward benzaldehyde.



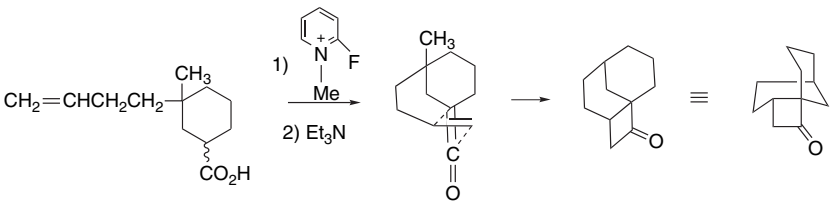
d. This reaction is an example of a vinylcyclobutanol rearrangement. These reactions appear to proceed by nonconcerted fragmentation and recombination with the vinyl substituent, in this case a furan ring, serving to stabilize the carbanion.



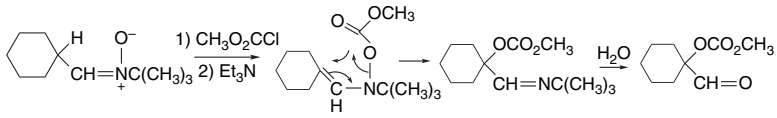
e. These conditions result in formation of amino selenide that undergoes a [2,3]-sigmatropic shift.



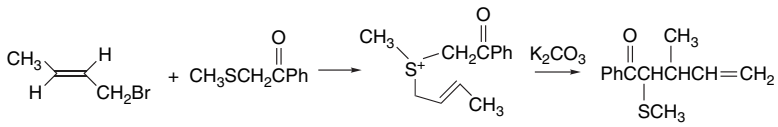
f. This reaction occurs by generation of a ketene that undergoes intramolecular [2 + 2] cycloaddition.



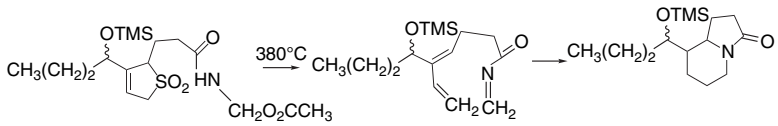
g. Acylation of the nitrone generates an acyloxy iminium ion that can be deprotonated to an *N*-acyloxy enamine. This intermediate undergoes a [3,3]-sigmatropic rearrangement to an imine. The imine is hydrolyzed to the aldehyde.



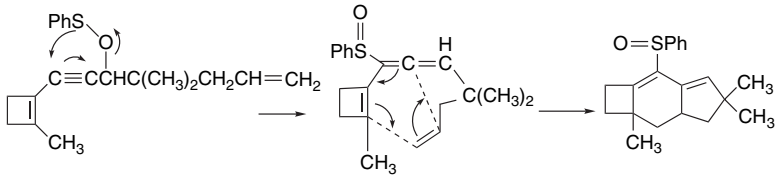
h. This reaction involves formation and [2,3]-sigmatropic rearrangement of a sulfonium ylide.



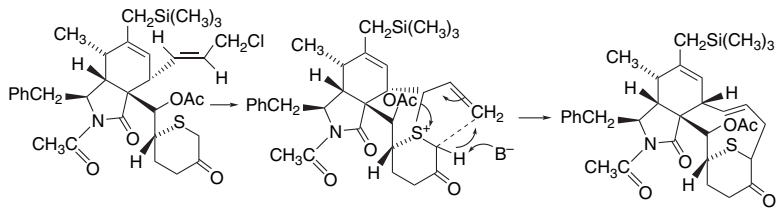
i. Thermolysis of the sulfolene oxide generates a diene and also an *N*-acylimine that can undergo intramolecular hetero-Diels-Alder cycloaddition.



j. The reagents result in the formation of a sulfenate that can lead through a [2,3]-sigmatropic shift to an allenyl sulfoxide, which, in turn, can undergo an intramolecular Diels-Alder reaction.

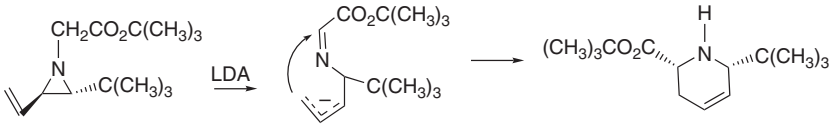


k. This ring expansion occurs via a sulfonium ylide rearrangement. Note that the alkylation step involves an S_N2' substitution

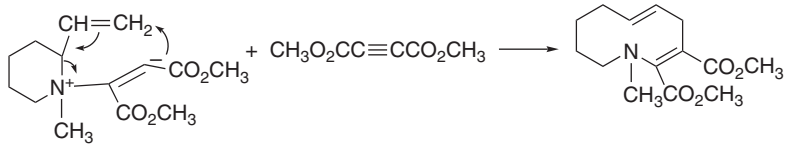


l. This reaction can be formulated in several ways. The experimental evidence suggests a nonconcerted fragmentation to an allylic anion, involving aziridine

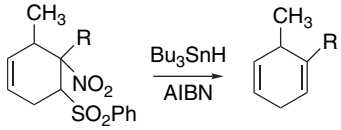
ring opening, followed by cyclization by addition of the allylic anion to the imine.



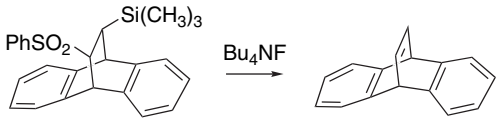
m. Addition of the amine to dimethyl acetylenedicarboxylate generates an ylide that can rearrange to the observed product.



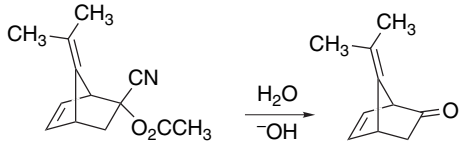
6.12. a. Reduction by Bu_3SnH was used to remove the nitro and phenylsulfonyl groups.



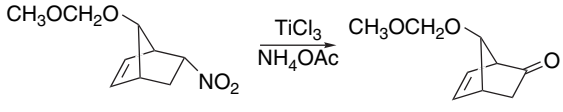
b. Fluoride ion was used to effect reductive elimination from the adduct.



c. Basic hydrolysis and elimination of cyanide generated the carbonyl group.

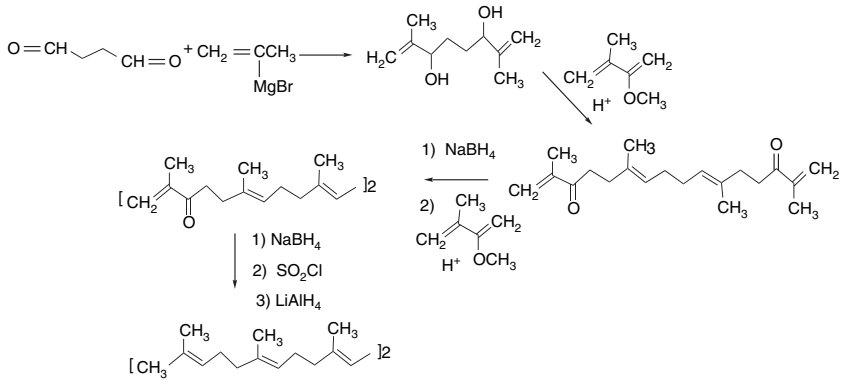


d. Reduction by $TiCl_3$ and ammonium acetate gave the ketone.

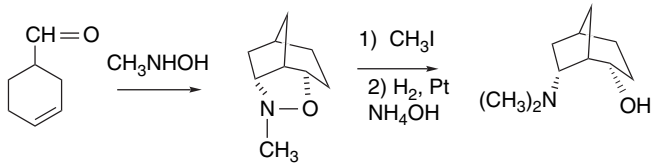


6.13. a. This synthesis used two cycles of the 3-methoxy-3-methyl-1,3-butadiene (3-methoxyisoprene) method to successively introduce isoprene units by Claisen rearrangements. After each rearrangement step, the product enone was reduced

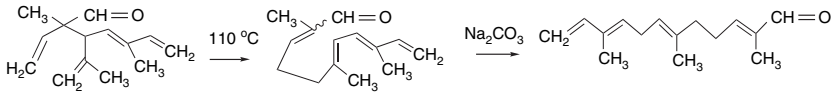
with $NaBH_4$. The final steps involved an S_N2' substitution by chloride and $LiAlH_4$ reduction.



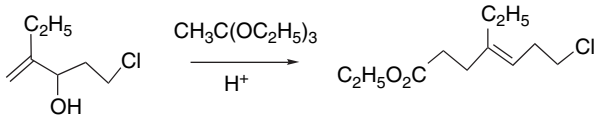
b. An intramolecular nitrone cycloaddition generates an oxazoline that is then methylated. Reductive cleavage of the N−O bond generates the product.



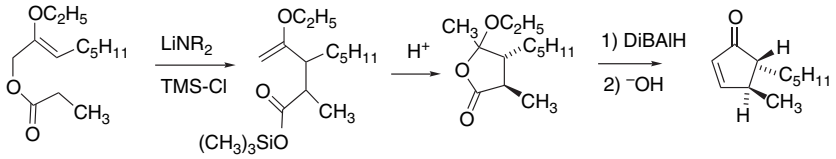
c. The reactant was converted to the product by a Cope rearrangement. The reactant was a mixture of stereoisomers and gave a 4:6 mixture of *E*- and *Z*-isomers. This mixture was isomerized to the more stable *E*-isomer by heating in the presence of Na_2CO_3 and methanol-xylene.



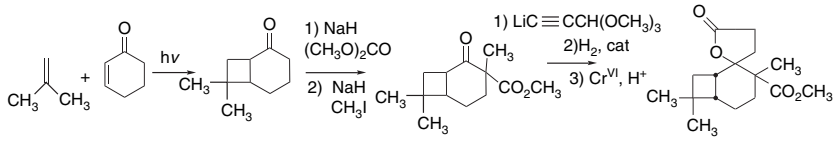
d. This transformation was done by an orthoester Claisen rearrangement.



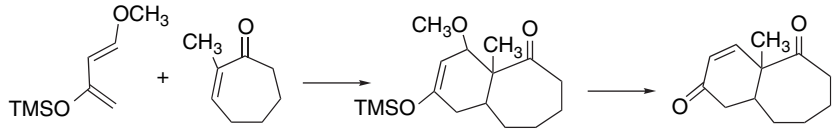
e. This transformation can be accomplished by a silyl ketene acetal rearrangement, followed by acid-catalyzed cyclization to an ethoxy lactone intermediate. Reduction then generated a keto aldehyde that can undergo intramolecular aldol condensation to the product.



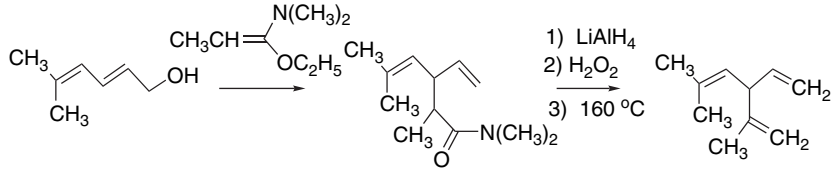
f. The dimethylcyclobutane ring was generated by photocycloaddition of isobutene with cyclohexenone. The carbomethoxy and methyl groups were then installed via the enolate. The spiro lactone ring was constructed by addition of lithio 3,3-dimethoxypropyne, followed by reduction, hydrolysis, cyclization, and oxidation to the lactone.



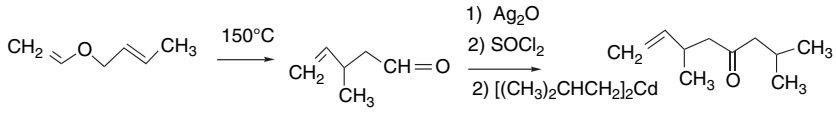
g. This transformation was done by a Diels-Alder cycloaddition with Danishefsky's diene, followed by hydrolysis.



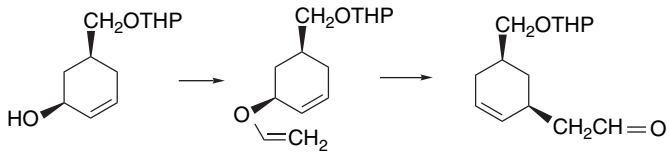
h. This transformation was done by an ortho amide Claisen rearrangement using *N*,*N*-dimethyl-1-ethoxypropen-1-amine as the reagent. After rearrangement, $LiAlH_4$ reduction to the tertiary amine and an amine oxide pyrolysis introduced the terminal double bond.



i. The starting material was converted into 3-methylpent-4-enal by Claisen rearrangement. The aldehyde was than converted to the desired ketone. In the cited reference, this was done by use of an organocadmium reagent, but there would be a number of alternative possibilities.

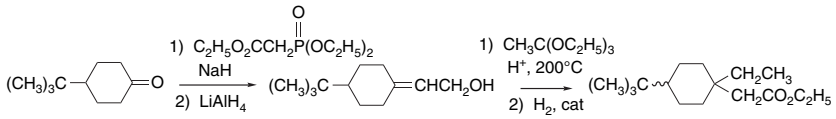


j. This transformation can be done by O-vinylation and Claisen rearrangement.

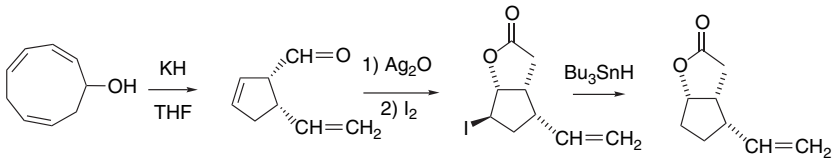


k. An allylic alcohol group was introduced by a Wadsworth-Emmons reaction, followed by $LiAlH_4$ reduction. An orthoester Claisen rearrangement was then

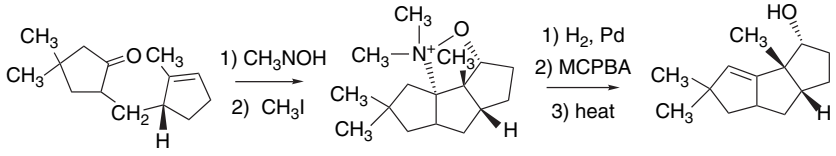
done at 200°C. Little stereoselectivity was observed with respect to axial or equatorial approach in the rearrangement. The vinyl group was then reduced to ethyl.



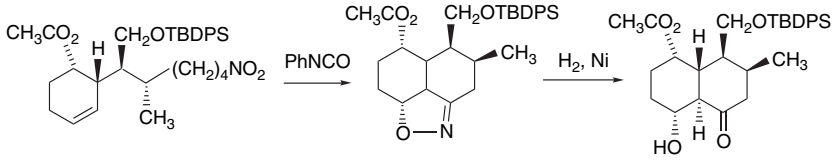
l. An anionic oxy-Cope rearrangement was used to generate 5-vinylcyclopentenecarboxaldehyde. This was oxidized to the carboxylic acid and subjected to iodolactonization. The iodide was removed by reduction with Bu_3SnH.



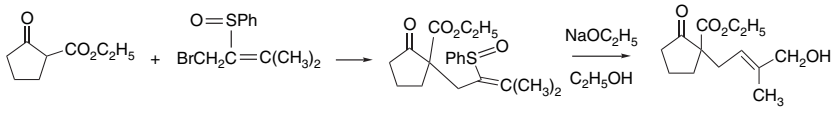
m. An intramolecular nitrone cycloaddition occurs in the first step. Alkylation and reduction generates a tertiary amine, which was subjected to elimination via the amine oxide.



n. A nitrile oxide is generated by dehydration of the primary nitro group. Intramolecular cycloaddition then forms the new C−C bond, giving an oxazoline. Reduction occurs with hydrolysis of the imine, generating the ketone.

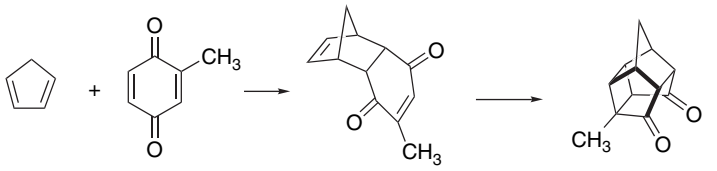


o. The β-ketoester was alkylated via the enolate. The sulfoxide was isomerized to the allylic isomer, which undergoes [2,3]-sigmatropic rearrangement to the sulfenate and is hydrolyzed under the reaction conditions ($NaOC_2H_5$ in ethanol).

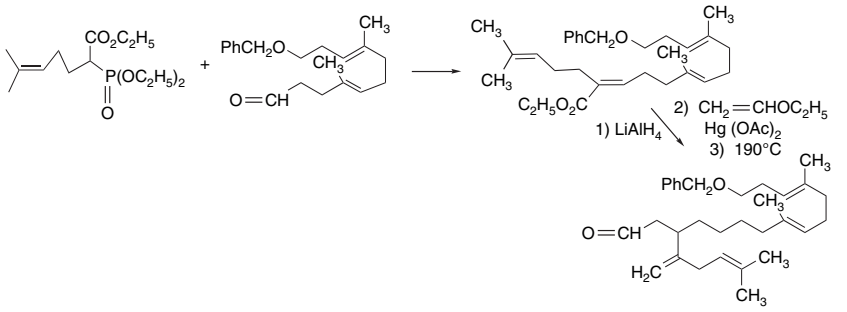


p. This transformation was done by Diels-Alder reaction between 2-methylbenzoquinone and cyclopentadiene, followed by photocyclization of the

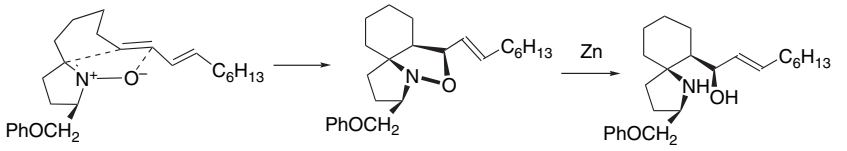
adduct. Note that the position of the methyl group shows that the Diels-Alder reaction occurred at the unsubstituted double bond of the quinone.



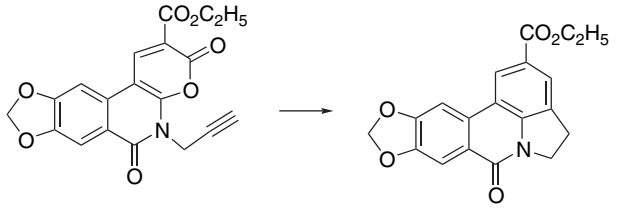
q. A phosphonate was prepared from the halide and trimethyl phosphonoacetate and used in a Wadsworth-Emmons reaction. The resulting ester was reduced to the allylic alcohol and subjected to Claisen rearrangement by exchange with ethyl vinyl ether and heating.



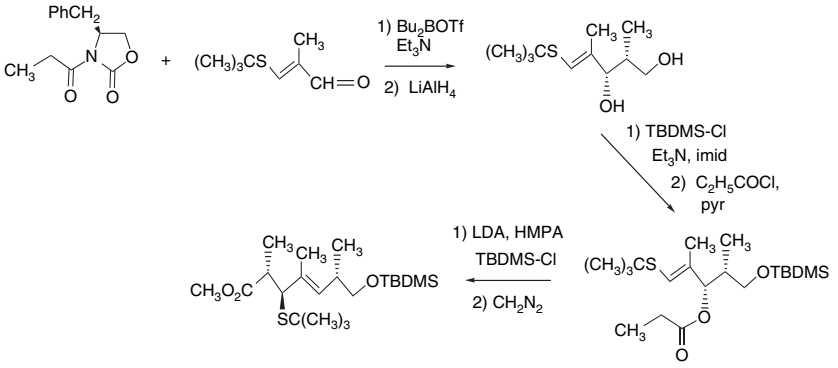
r. Deprotection of the carbonyl group led to formation of a cyclic nitrone that can then undergo an intramolecular cycloaddition. Reduction of the oxazolidine ring by zinc generates the desired product.



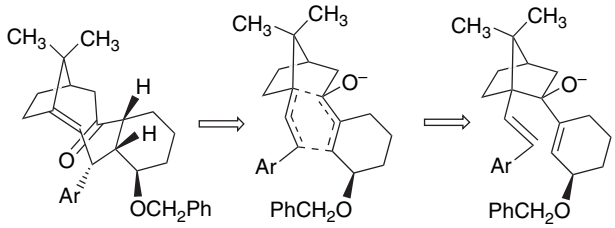
s. Alkylation of the amide nitrogen with propargyl bromide was followed by intramolecular pyrone cycloaddition, with aromatization via decarboxylation.



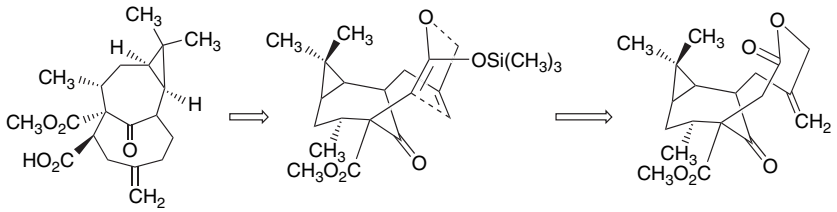
t. The oxazolidinone chiral auxiliary was used to establish *syn*-C(2)−C(3) stereochemistry. This was in turn used to establish the *E*-double bond and C(5)−C(6) stereochemistry by an Ireland-Claisen rearrangement.



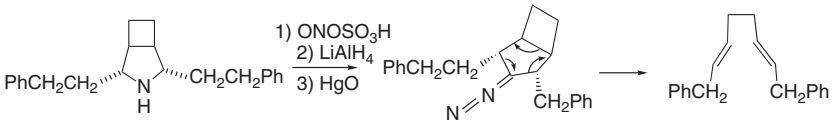
6.14. a. The δ, ϵ-enone structure can be formed by an anionic oxy-Cope rearrangement. The precursor is the corresponding carbinol, which is a bornanone derivative.



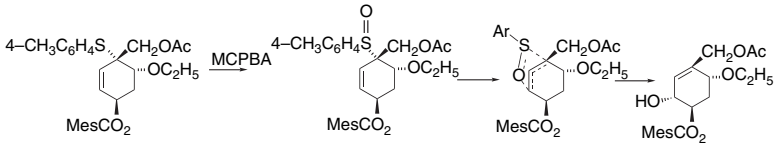
b. The γ, δ-unsaturated acid can be generated by Ireland-Claisen rearrangement of a silyl ketene acetal.



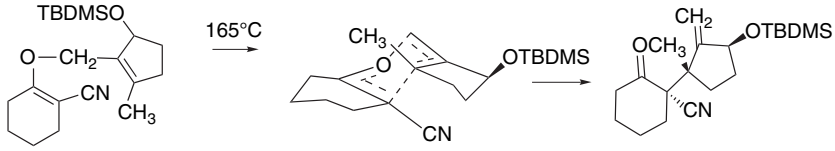
6.15. a. These reaction conditions will lead to formation of a diazene that will decompose by stereospecific disrotatory cheletropic elimination to the *E*,*E*-diene.



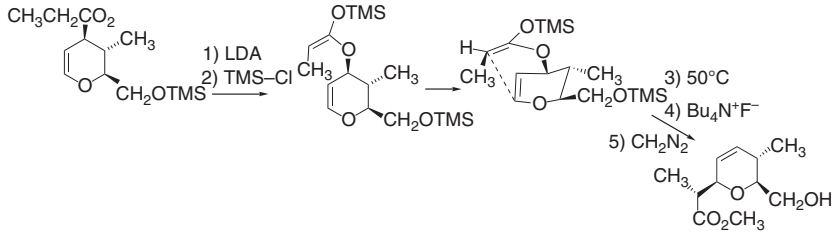
b. This reaction results in a suprafacial [2,3]-sigmatropic rearrangement of the sulfoxide generated by oxidation.



c. This reaction can occur by a thermal Claisen rearrangement. The product was a 16:1 mixture of stereoisomers at the cyano center. The major stereoisomer results from a chairlike TS.

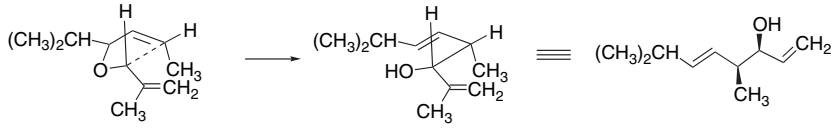


d. These reaction conditions will lead to formation of the *E*-silyl ketene acetal. A boatlike transition structure is expected for the rearrangement. This results in (*R*)-configuration at the new stereocenter in the major (5:1) stereoisomer.

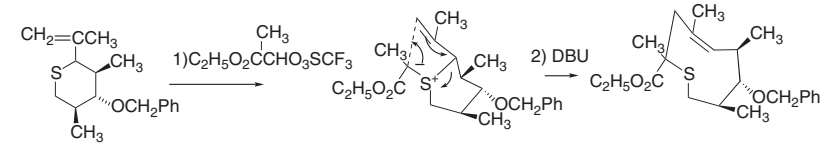


e. These conditions should lead to the *Z*-enolate. The silyl ketene acetal rearrangement gives a 6:1 preference for the axial approach via a chairlike TS.

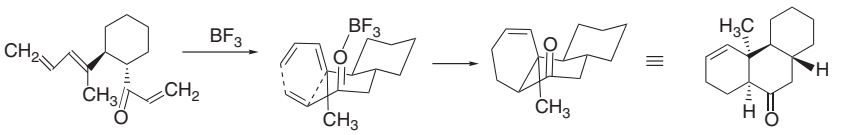
f. This anionic [2,3]-sigmatropic rearrangement proceeds with 97:3 stereoselectivity through the anticipated TS, leading to *E*-stereochemistry at the double bond and a *syn* relationship between the methyl and hydroxy groups at the new C−C bond.



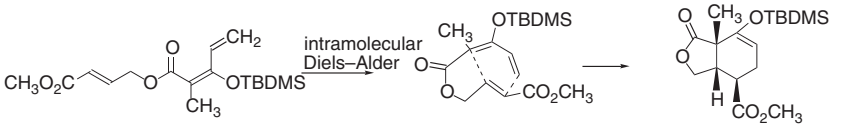
g. This reaction involves formation and rearrangement of a sulfonium ylide. The bicyclic TS leads to formation of an *E*-double bond in the nine-membered ring.



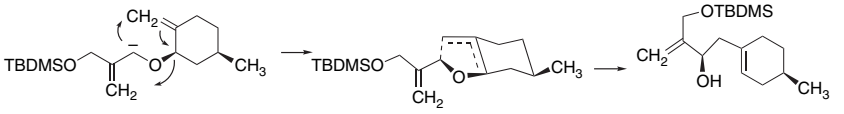
h. The reaction proceeds through an *endo* transition structure for the intramolecular Diels-Alder reaction and results in a *cis* ring junction.



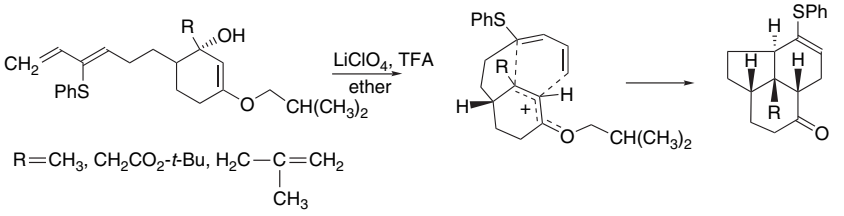
i. This intramolecular Diels-Alder reaction proceeds through an *endo* TS in which the exocyclic dienophile ester group is oriented toward the diene unit, leading to formation of a *cis* ring junction.



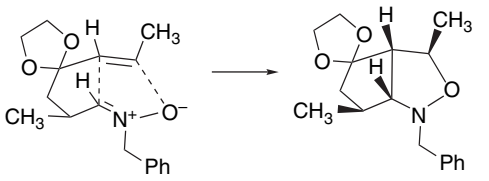
j. This reaction is an anionic [2,3]-sigmatropic shift. The TS involves an equatorial approach to the cyclohexane ring with the methyl group in an equatorial position.



k. This reaction involves an intramolecular Diels-Alder reaction involving an oxonium ion.

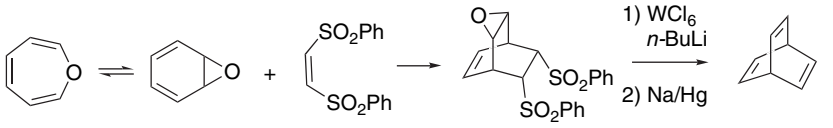


l. The reaction occurs by an intramolecular 1,3-dipolar cycloaddition. The methyl group occupies a pseudoequatorial position and only the *cis* ring juncture is formed.

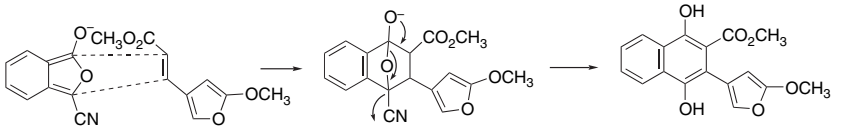


6.16. Capture of the benzene oxide form by a dienophile that could serve as an acetylene equivalent would generate the epoxide of a barrelene precursor. In the cited reference, *Z-bis*-benzenesulfonylethylene was used. The epoxide was

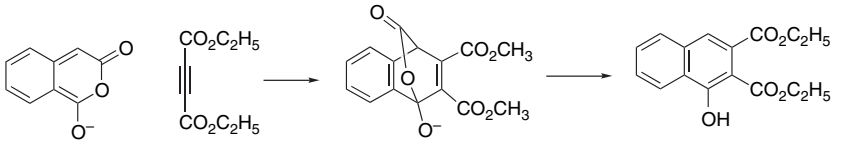
deoxygenated using WCl_6 and C_4H_9Li. The sulfonyl groups were then reductively eliminated, generating barrelene.



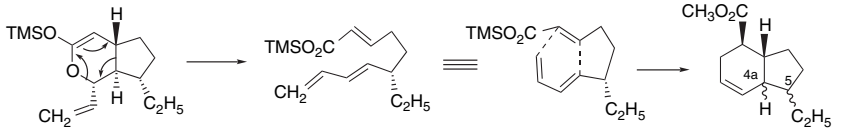
6.17. a. The base generates a phthalide anion that has quinodimethane character. The adduct can break down by elimination of cyanide to form the diketo tautomer of the observed product.



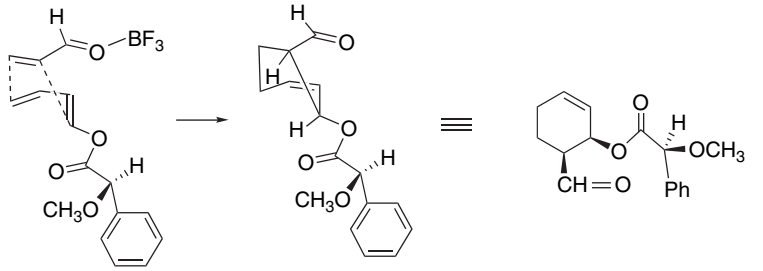
b. The anion of homophthalide has quinodimethane character. The adduct can aromatize by loss of CO_2.



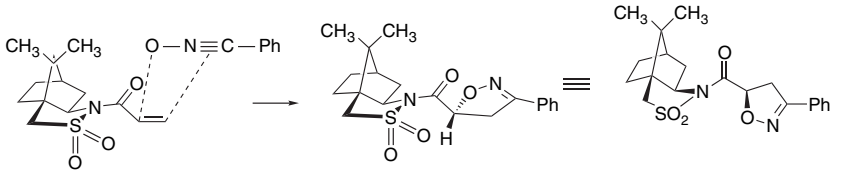
6.18. The reactant can give a triene ester by retro hetero-Diels-Alder reaction. Recyclization of the triene ester by intramolecular Diels-Alder reaction generates the same bicyclic skeleton but with competing conformations that result in loss of stereospecificity.



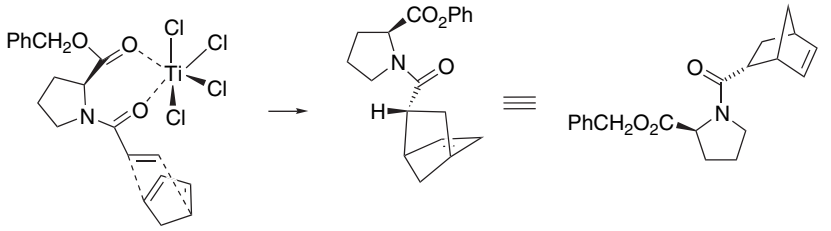
6.19. a. The diastereoselectivity is consistent with dominant reaction through an *endo* approach that is *anti* to the phenyl substituent.



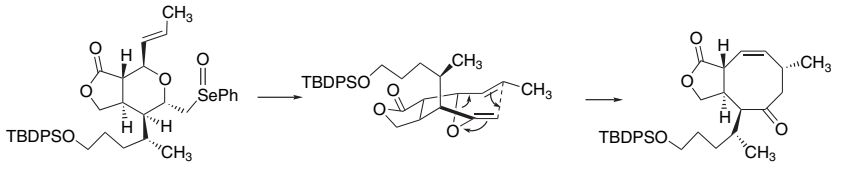
b. The diastereoselectivity of this uncatalyzed 1,3-dipolar cycloaddition is governed by the preferred conformation of the dipolarophile with approach *anti* to the sulfonyl goup.



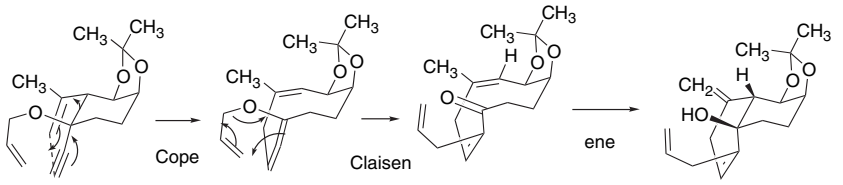
c. A chelated TS with shielding by the $TiCl_4$ group leads to approach *anti* to the Ti chelate.



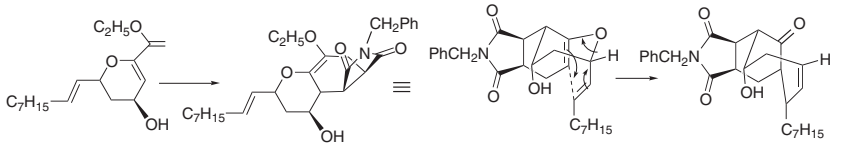
6.20. a. The oxidation forms a selenoxide that can undergo elimination, generating an allyl vinyl ether that can undergo Claisen rearrangement. The reaction was quite sensitive to solvent and other conditions, and *N*,*N*-dimethylacetamide was found to be the best solvent. Excess ethyl vinyl ether was added to trap acidic by-products resulting from the selenoxide elimination.



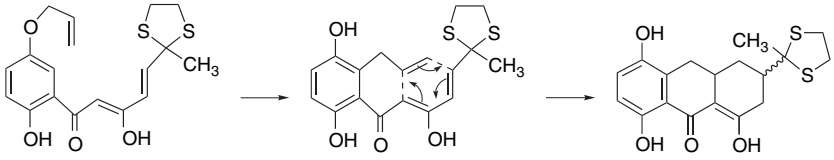
b. This transformation can occur by a Cope rearrangement of the 1,5-eneyne system, generating an allene that includes an allyl vinyl ether structure. This structure can undergo a Claisen rearrangement, generating a 10-membered ring that is well disposed for an intramolecular ene reaction.



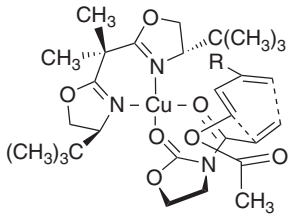
c. The initial Diels-Alder reaction places a double bond adjacent to the ether oxygen, permitting a Claisen rearrangement that generates the observed product.



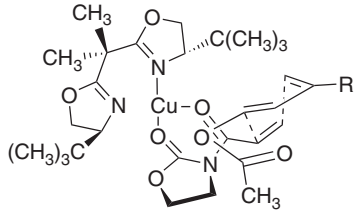
d. An aromatic Claisen rearrangement permits an intramolecular Diels-Alder reaction. Note that the conjugation in enolic β-dicarbonyl unit is reestablished.



6.21. The *endo* TS orients the methyl group of the diene toward the catalyst. This evidently gives rise to steric interferences that favor the *exo* TS.



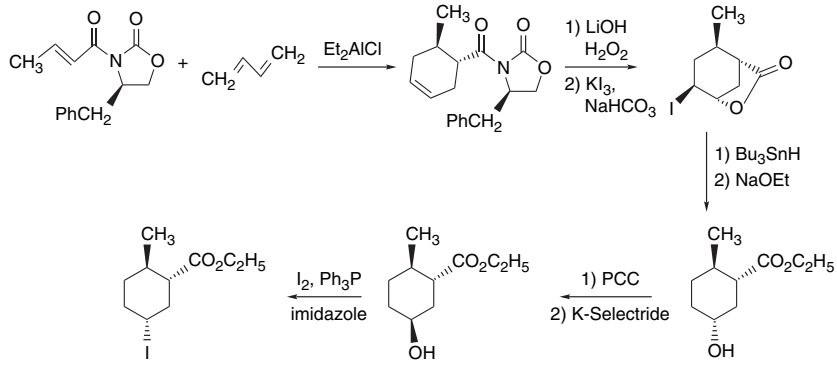
endo TS favored for R = H



exo TS favored for R = CH_3

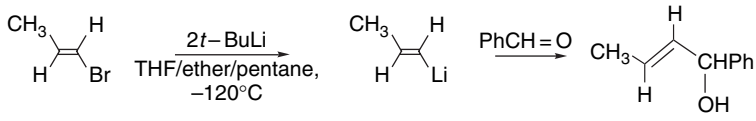
6.22. The two cases with $n =$ odd are in agreement with the hypothesis, and the major product is correctly predicted for $n = 2$.

6.24. A combination of diastereoselective Diels-Alder reaction, iodolactonization, stereoselective reduction, and conversion to the iodide with inversion at C(5) leads to the desired stereoisomer.

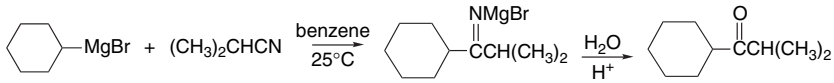


Chapter 7

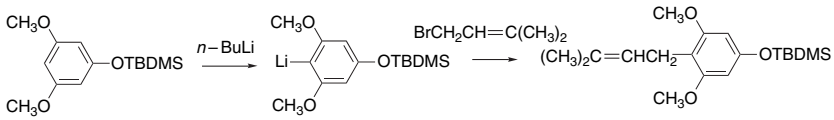
7.1. a. This reaction generates a vinyllithium reagent with *retention of configuration* that then adds to benzaldehyde to give the *E*-allylic alcohol.



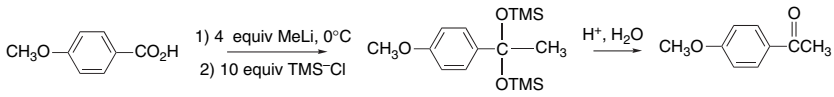
b. Ketone formation occurs under these conditions. An 86% yield was reported.



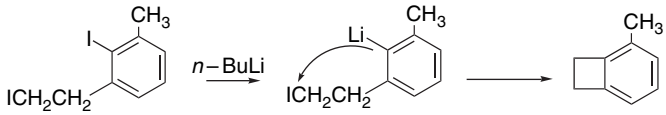
c. The directive effect of methoxy is greater than the hindered silyloxy substituent. Also relevant is the issue of whether the allyl group undergoes transposition. In this case the less hindered allylic product is formed, which may reflect either a steric factor or a direct displacement mechanism.



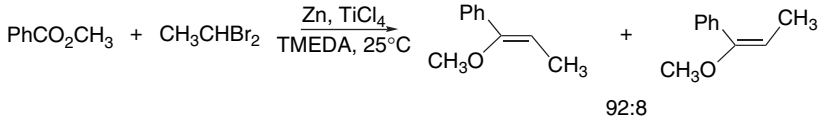
d. The isolated product is the ketone resulting from addition to the carboxylic acid group. One might also have considered lithiation *ortho* to either the methoxy or the carboxy group, but evidently this does not compete with addition to the carboxylate group.



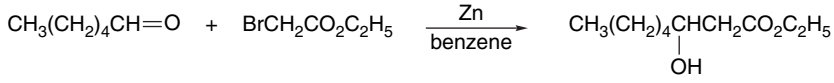
e. Diiodides of this sort give good yields of bicyclobenzocyclobutene on treatment with *n*-BuLi.



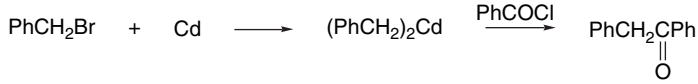
f. This is an adaptation of the use of the Lombardo reagent for conversion of esters to enol ethers (see p. 661). The *Z*:*E* ratio is reported to be 92:8.



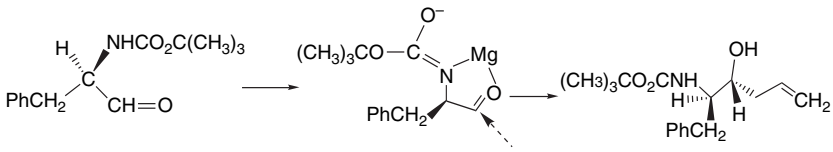
g. This is an example of a Reformatsky reaction. Under the specified conditions, nine runs averaged 74% yield.



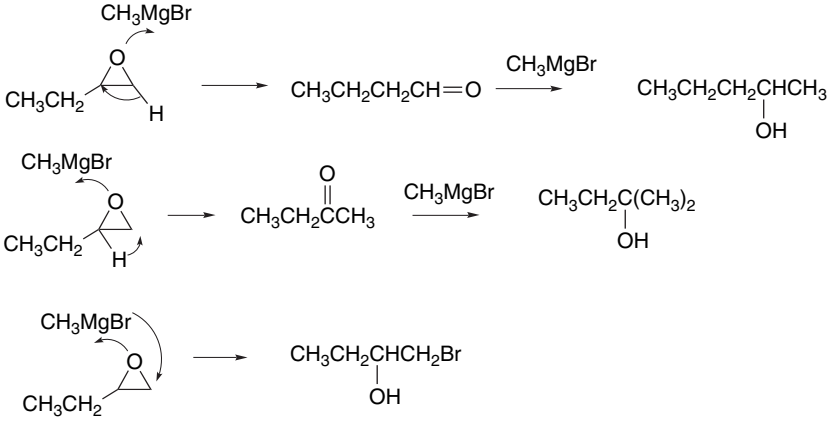
h. These conditions give benzyl phenyl ketone via an organocadmium reagent.



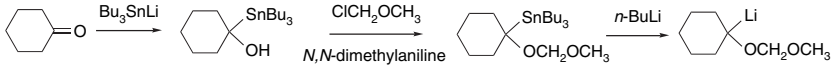
i. This reaction proceeds by stereoselective chelation-controlled addition to the deprotonated reactant, resulting in the *syn* (*threo*) stereoisomer.



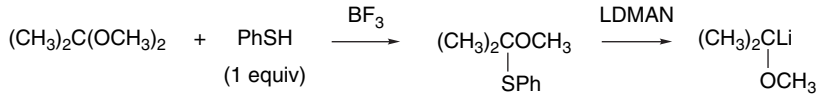
7.2. The high yield of 3-pentanol with CH_3Li is consistent with a dominant nucleophilic opening (see Section 12.2.3). The product mixture with CH_3MgBr is consistent with a Lewis acid–catalyzed ring opening, with subsequent reaction with CH_3MgBr. This indicates that the nucleophilicity is $CH_3Li > CH_3MgBr$, whereas the Lewis acid character is $CH_3MgBr > CH_3Li$.



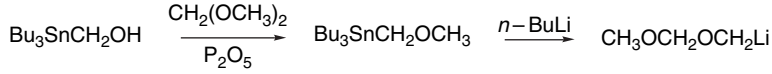
7.3. a. This transformation can be done by a stannyl anion addition, protection of the hydroxy group, and metal-metal exchange (see p. 634).



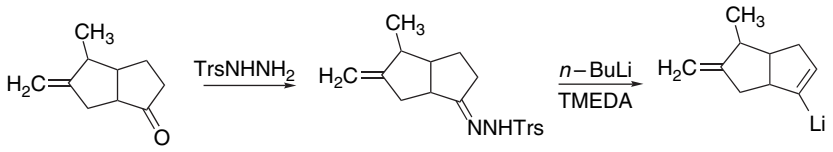
b. This transformation can be done by partial exchange to the monophenylthio acetal, followed by the sulfide reduction route to the lithium compound (see p. 625).



c. This transformation requires protection of the hydroxy and metal-metal exchange (see p. 633). In this particular case, an acid-catalyzed exchange was used to introduce the MOM group, in preference to the use of base-mediated alkylation by chloromethyl methyl ether.

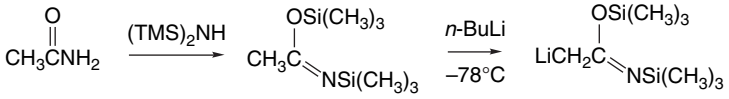


d. The transformation from a ketone to vinyllithium reagent can be done by the Shapiro reaction (see p. 454).

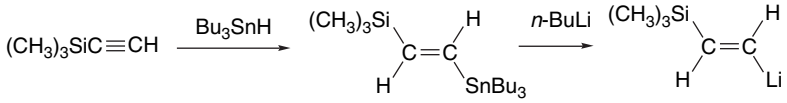


Trs = 2,4,6-tri-isopropylphenylsulfonyl

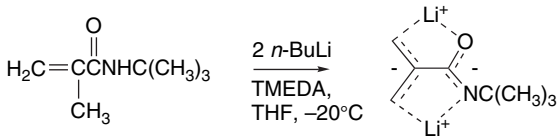
e. This reaction generates a lithiated equivalent of acetamide. The amide is *bis*-trimethylsilated by heating with hexamethyldisilazane. This masks both the acidity of the acetamide NH_2 group and the electrophilicity of the C=O group, and provides steric protection of the C=N bond. Under these circumstances, deprotonation occurs.



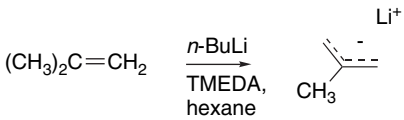
f. This transformation can be done by stereoselective *syn* hydrostannylation of the alkyne, followed by metal-metal exchange (see p. 633).



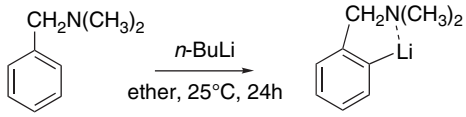
7.4. a. The amide is deprotonated and the second equivalent removes an allylic hydrogen. The dilithio derivative probably has a chelated structure.



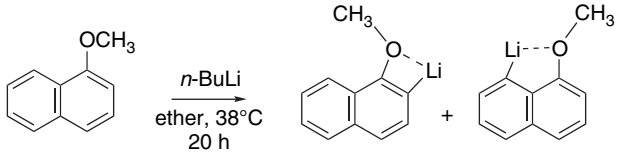
b. These conditions give an allylic lithio compound.



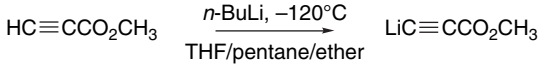
c. The dimethylamino group promotes *ortho* lithiation and the product has a chelated structure.



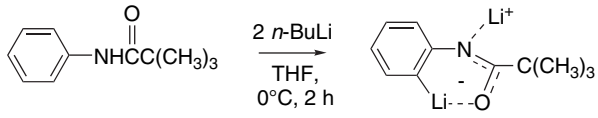
d. The methoxy group can promote lithiation at both the 2- and 8-positions. There is a somewhat stronger polar stabilization at the 2-position. The ratio of product favors the 2-position by from 2:1 to 5:1, depending on conditions.



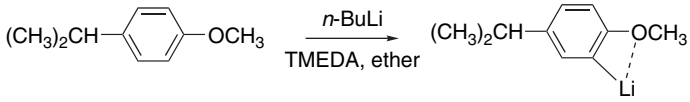
e. This reaction leads to deprotonation of the *sp* carbon. Geometry precludes an intramolecular interaction with the ester group.



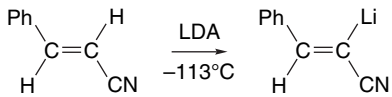
f. These conditions result in amide deprotonation and *ortho* lithiation. Chelation is possible.



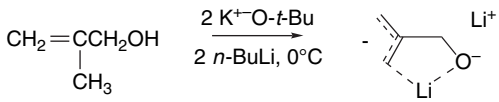
g. The methoxy group promotes *ortho* lithiation.



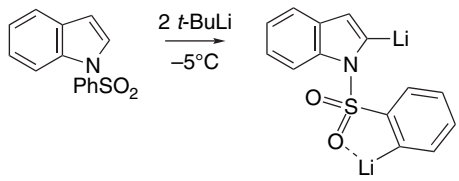
h. The product is the α-lithio derivative. This indicates that the polar effect of the cyano group is stronger than any delocalization by the phenyl group.



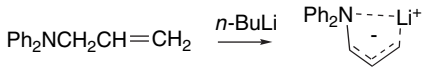
i. The hydroxy group is deprotonated, as is an allylic position. A chelated structure is likely.



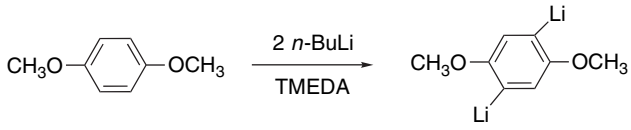
j. Both the 2-position of the indole ring (heteroaromatic) and the *ortho* position of the phenylsulfonyl group are lithiated.



k. The product results from allylic deprotonation and can be stabilized by the amino substituent.

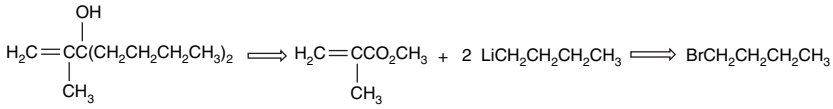


l. The product was found to result from dilithiation, with each methoxy group supporting lithiation.

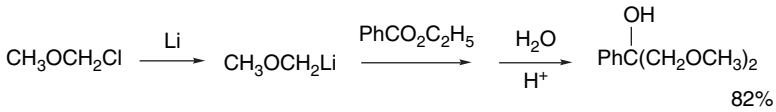


7.5. a. In the cited reference, this compound was prepared from allyl chloride and ethylene oxide. The reaction was done under Barbier-type conditions by simultaneous addition of the two reactants to magnesium. There would be many other possible ways of making this compound.

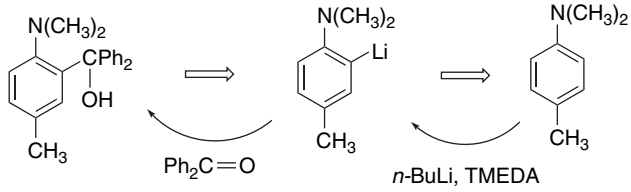
b. This tertiary alcohol can be prepared from an ester. A preparation using *n*-butyllithium is described in the cited reference (80–86% yield). The organolithium reagent can be made from bromobutane, but is also commercially available.



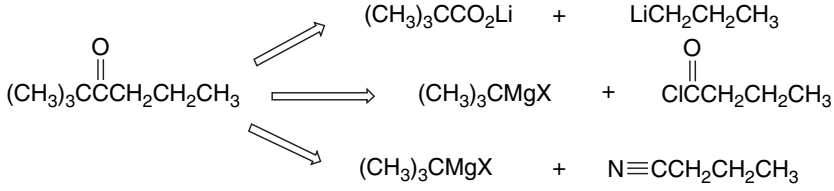
c. In this early example of the use of a functionalized organolithium reagent, methoxymethyllithium was prepared from chloromethyl methyl ether. Reaction with ethyl benzoate then gave the product. More recently, the organolithium reagent has been prepared by metal-metal exchange from the corresponding tin reagent.



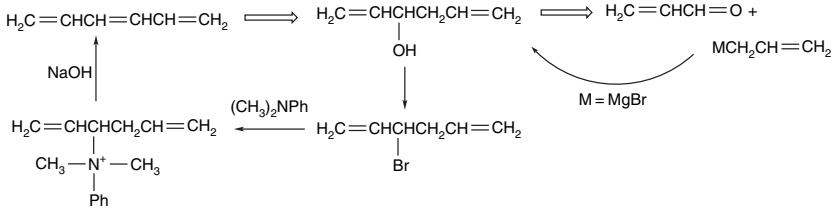
d. This compound can be prepared by *ortho* lithiation, followed by reaction with benzophenone. In the cited reference this reaction gave a 49–57% yield.



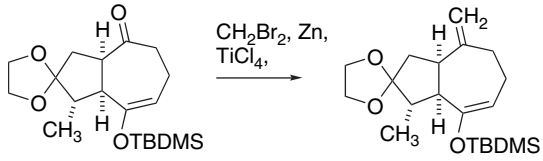
e. This ketone can be prepared by any of several organometallic approaches, e.g., carboxylate with organolithium, nitrile with organomagnesium halide, or acid chloride and organomagnesium halide. The latter method gave an 88% yield, which is slightly better than the yield (82%) obtained with the alternative combination of $(CH_3)_3CCOCl$ and $CH_3CH_2CH_2MgBr$. One of the less reactive organometallics, such as an organocadmium or organozinc, reagent might also be used.



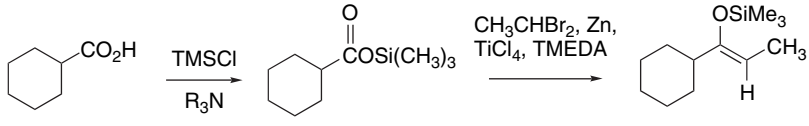
f. 1,3,5-Hexatriene can be prepared by dehydration of an appropriate secondary alcohol. The reported method begins with the synthesis of the alcohol by addition of allylmagnesium bromide to acrolein. Because of the sensitivity of the triene, a three-step sequence including conversion of the alcohol to a bromide, conversion to a quaternary ammonium salt, and Hoffmann elimination was carried out. This reaction sequence permits formation of the triene under basic conditions.



7.6. a. The modified Lombardo reagent combination can effect this transformation.

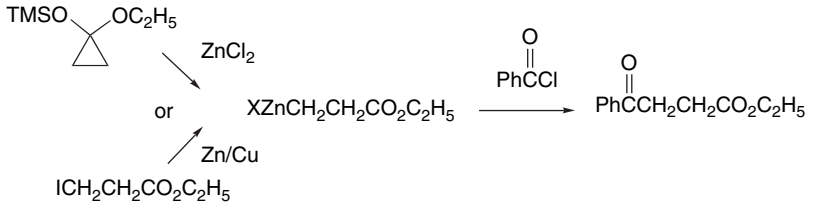


b. Conversion of the carboxylic acid to its TMS ester, followed by reaction of the reagent derived from CH_3CHBr_2, $TiCl_4$, Zn, and TMEDA is effective.

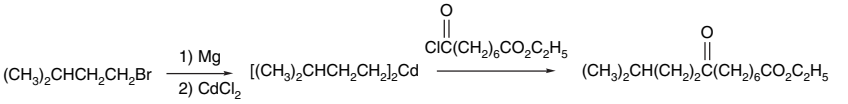


c. This transformation requires an organometallic reagent compatible with the ester functionality. The corresponding zinc reagent has been prepared from either $ICH_2CH_2CO_2C_2H_5$ or 1-trimethylsiloxy-1-ethoxy cyclopropane. More

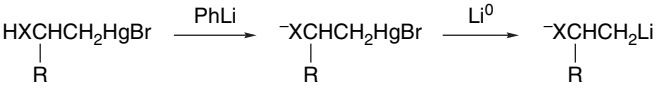
recent protocols for preparation of functionalized organozinc might also be appropriate.



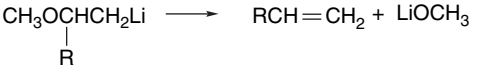
d. An organometalllic reagent that reacts selectively with the acyl chloride is required. An organocadmium reagent was used in the original work, but a zinc reagent would also be suitable.



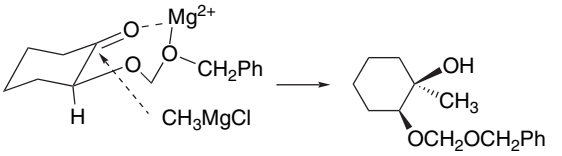
7.7. Organomercury reagents **7-1** and **7-2** have been converted successfully to **7-3** and **7-4**, respectively, by treatment with one equivalent of phenyllithium and then lithium metal (powder). The phenyllithium deprotonates the functional group rendering it a poor leaving group. The lithium metal then replaces the mercury.



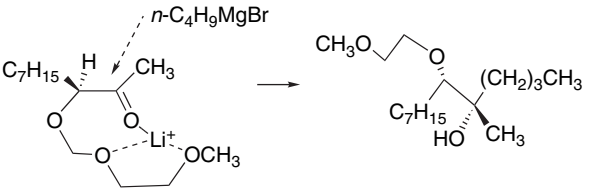
Since the methoxy group in the third reagent cannot be deprotonated, it is likely to undergo β-elimination when the mercury is replaced by lithium.



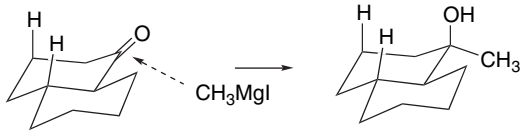
7.8. a. This reaction proceeds stereoselectively by equatorial addition to generate the axial (*cis*) alcohol. This result is consistent with a chelation-controlled addition mechanism.



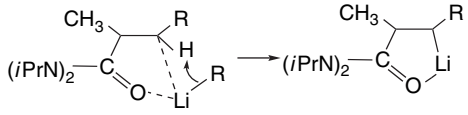
b. This is a case of addition to a ketone with an adjacent stereogenic center and is consistent with a chelation-controlled addition mechanism.



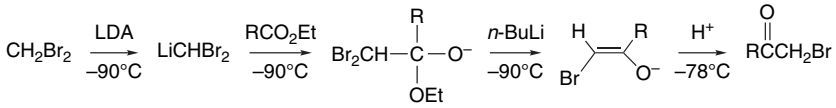
c. This ketone give dominant equatorial attack. Although the steric resistance to axial attack is no greater than in cyclohexanone, the rigid *trans* ring juncture favors the axial attack.



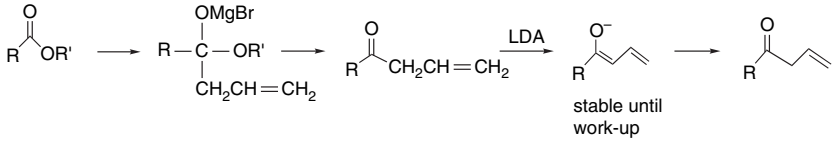
7.9. The amide carbonyl is closer to the β-hydrogen, permitting a coordinated organolithium reagent to more closely approach the β-hydrogen.



7.10.

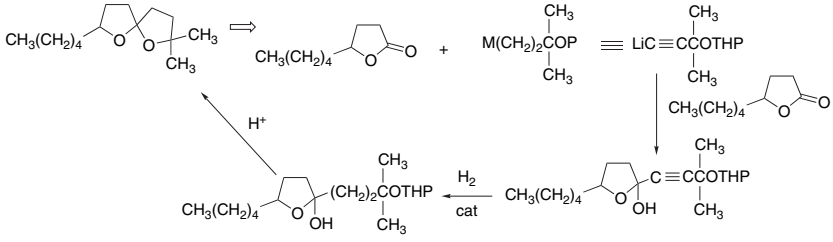


7.11. The LDA must react with some intermediate so that the normal addition-elimination-addition sequence is diverted. Because allylic Grignards are more effective than alkyl Grignards, it may be that the allylic position of the ketone is deprotonated fast enough to prevent the second addition step.

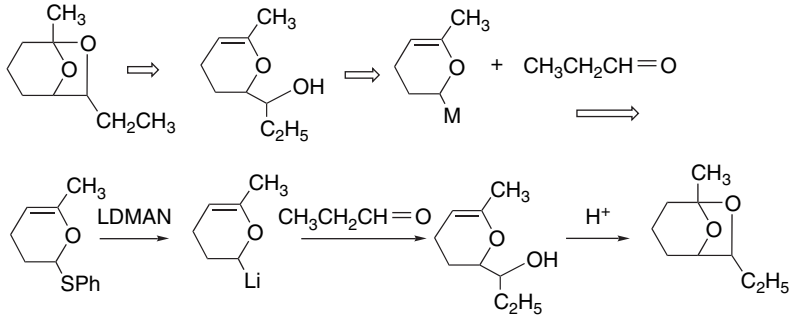


7.12. In order for cyclizations of this type to succeed, the halogen-metal exchange must be considerably faster than the addition of the organolithium reagent to the carbonyl, which is a fast reaction in its own right. The data for the system in (a) suggest that increasing the steric bulk of R facilitates cyclization, perhaps by slowing the direct addition at the carbonyl group.

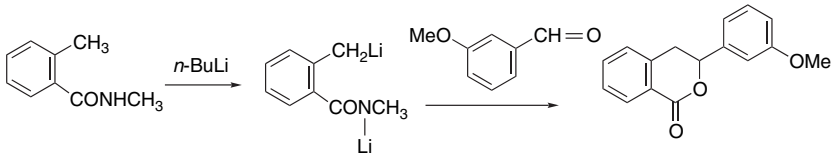
7.13. a. The crucial dissection identifies a 3,3-dimethyl-3-hydroxypropyl organometallic as the necessary fragment. The hydroxy group would need to be protected for strongly basic organometallics. In the reference cited, an alkynyl lithium reagent with the hydroxy protected as the THP ether was used. The triple bond was removed by catalytic hydrogenation. There is no fundamental reason that precludes the use of a saturated reagent. After the removal of the protecting group, the cyclic acetal is formed.



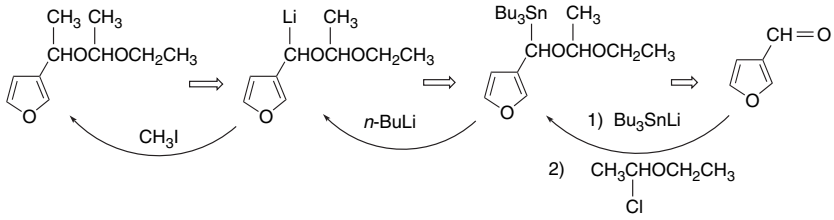
b. The product contains a cyclic acetal that can be formed by cyclization of 6,7-dihydroxynonan-2-one. The retrosynthetic dissection identifies 6-lithiodihydropyran as an appropriate organometallic reagent. It can be prepared from the corresponding thiophenyl derivative.



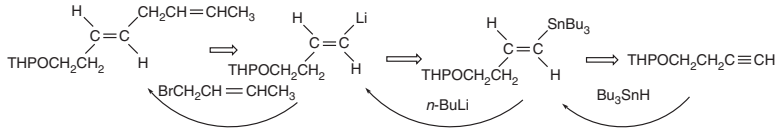
c. The dilithio derivative of *N*-methyltoluamide was prepared by reaction with excess *n*-butyllithium. Reaction with *m*-methoxybenzaldehyde gave the desired product.



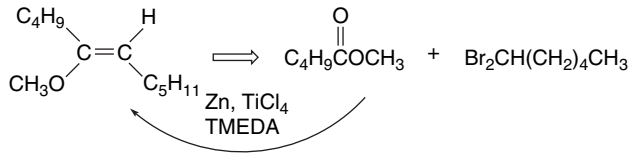
d. This transformation can be effected by methylation of a α-lithiomethylfuran derivative that can be prepared from the aldehyde by stannide addition, O-protection, and metal-metal exchange.



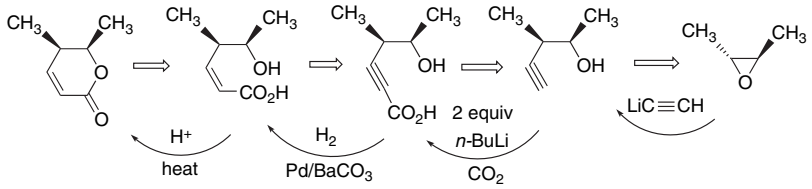
e. This transformation can be effected by synthesis of a vinyllithium reagent from the corresponding stannane, followed by alkylation with 2-butenyl bromide.



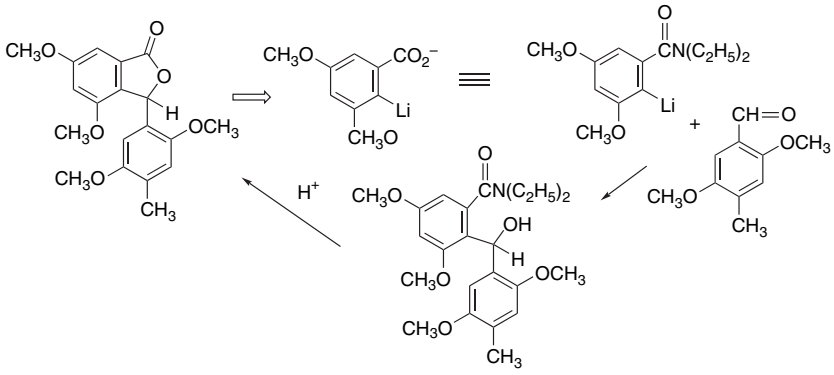
f. This transformation can be effected by a modified Lombardo-type reagent.



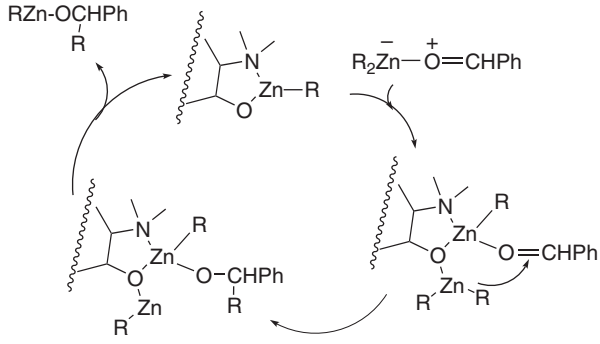
g. A critical aspect of this transformation is the inversion of configuration that must be effected at one of the chiral centers. This can be accomplished by nucleophilic ring opening of the epoxide. In the referenced procedure, the ring opening was done with lithioacetylene. The resulting alkynol was then dilithiated and carbonated. The *cis* double bond was established by partial hydrogenation, and the resulting hydroxy acid cyclized on heating.



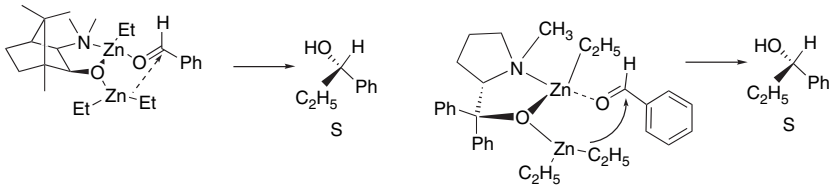
h. The retrosynthesis identifies an *ortho*-lithiated benzoic acid equivalent as the necessary reagent. This requires that lithiation occur *ortho* to a carboxyl equivalent, rather than at the C(4) between the two methoxy groups. The *N*, *N*-diethylamide was used successfully, followed by acid-catalyzed cyclization to the lactone (phthalide).



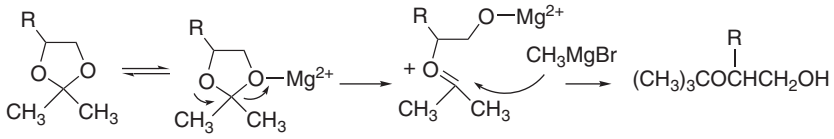
7.14. As discussed on p. 653, the mechanism involves reaction of the aldehyde with a complex containing two zinc ions.



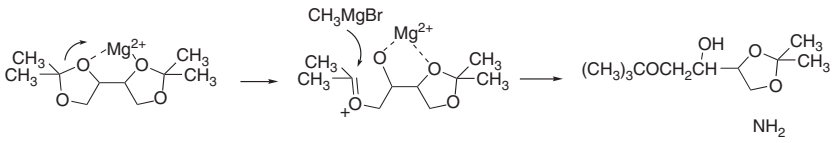
The preferred orientation of the benzaldehyde with respect to the amino alcohol ligand is *anti-trans.* In both cases this leads to *S*-product.



7.15. In the simpler dioxolanes, the controlling factor is likely the steric effect of the substituent. The reactions are promoted by the Lewis acid character of the magnesium and complexation will be more favorable at the more sterically accessible site, leading to addition to the more-substituted oxonium intermediate.

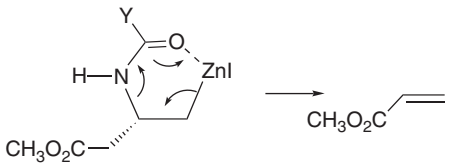


Reactants **15-A** and **15-B** can chelate at only one of the two dioxolane oxygens and this will favor breaking of the corresponding C–O bond that is capable of chelation.



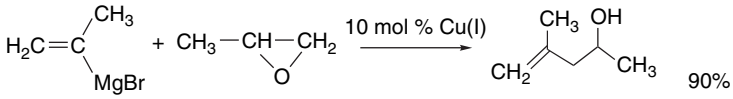
7.16. (1) Reduced sensitivity to steric effects; (2) reduced tendency to enolate formation; (3) increased reactivity toward certain functional groups such as amides; (4) tendency toward strong chelation effects. (See Section 7.4 for specific examples.)

7.17. a. The trifluoroacetamido group should be the better leaving group but it is a poorer Lewis base than the *t*-butoxycarbonylamino group. This suggests that a chelated structure may be involved in which the more favorable coordination capacity of the *t*-butoxycarbonylamino group is more favorable to elimination.

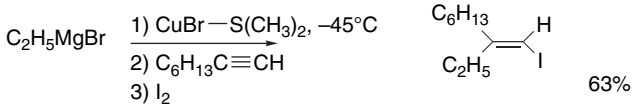


b. Elimination from these structures constitutes the reverse of *endo* cyclizations, which are generally unfavorable in small and normal rings because of stereoelectronic factors. This suggests that the same structural features retard the reverse elimination reaction.

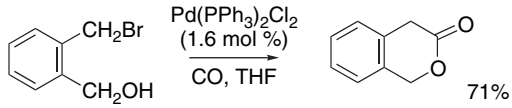
8.1. a. The epoxide is opened at the less-substituted carbon.



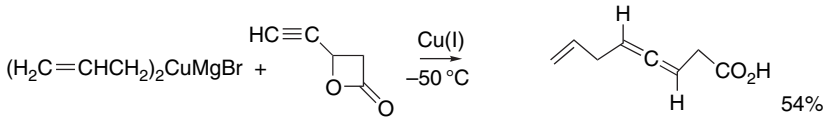
b. The mixed cuprate reagent adds to the substituted end of the alkyne by *syn* addition. The configuration of the double bond is retained during the iodinolysis.



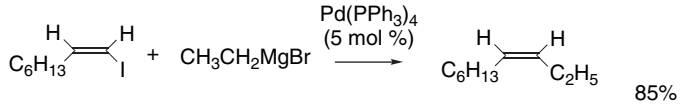
c. These conditions lead to carbonylation at the bromomethyl group followed by intramolecular lactone formation by nucleophilic attack by the hydroxy group.



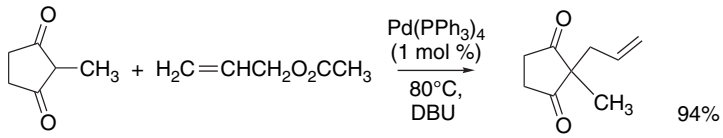
d. The reaction occurs by S_N2' substitution at the alkyne group with opening of the lactone ring.



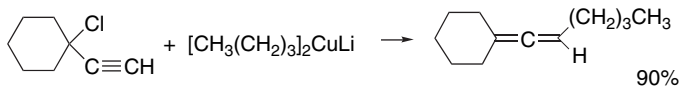
e. Palladium-catalyzed cross coupling occurs with retention of alkene configuration.



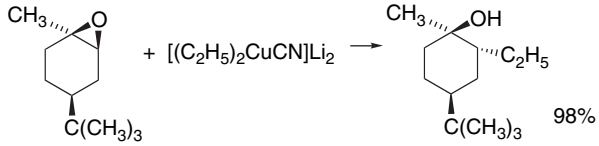
f. This diketone affords a highly stabilized enolate that can undergo allylation under these conditions.



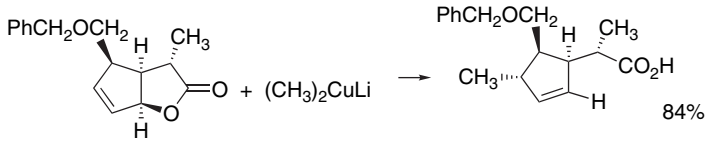
g. This system reacts by S_N2' substitution to give an alkene.



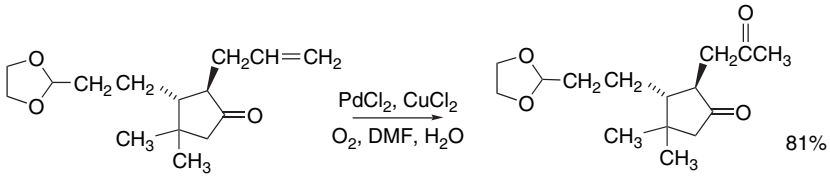
h. This reaction occurs by *anti* epoxide ring opening at the less-substituted carbon.



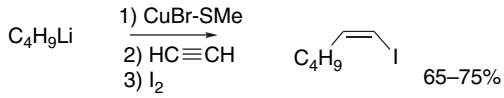
i. This reaction occurs by *anti* S_N2' substitution, opening the lactone ring.



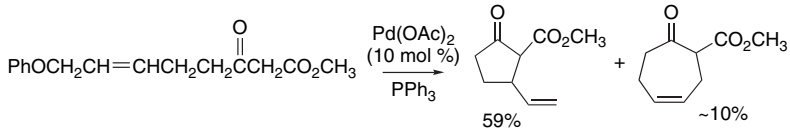
j. These are the conditions of the Wacker oxidation and result in the conversion of the terminal double bond into a methyl ketone.



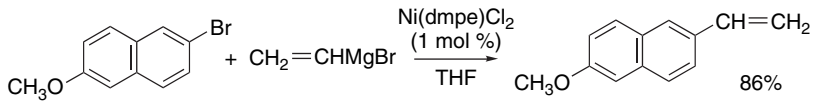
k. The mixed organometallic reagent adds *syn* to the triple bond and undergoes iodinolysis with retention of double-bond configuration.



l. The stabilized β-ketoester reacts primarily by intramolecular S_N2' substitution. There is a by-product resulting from S_N2 substitution. The primary factor in the regioselectivity is presumably the more favorable nature of the five-membered *exo* transition structure.

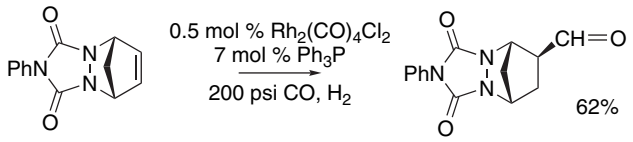


m. Reaction occurs by nickel-mediated cross coupling.

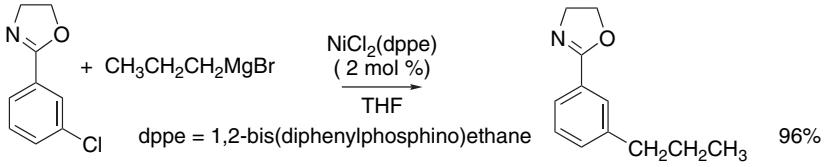


dmpe = 1,2-bis(dimethylphosphino)ethane

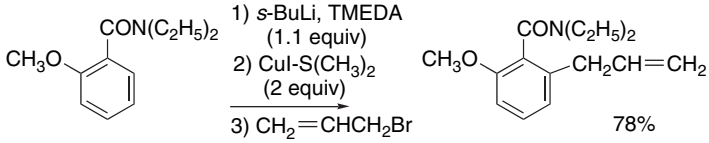
n. These conditions lead to hydroformylation. The reaction is stereoselective for the *exo* isomer.



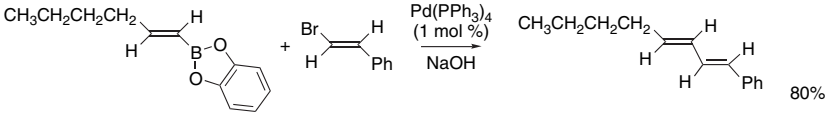
o. This reaction results in nickel-mediated cross coupling.



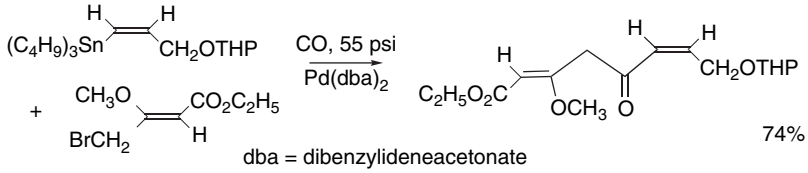
p. The lithiation is directed by the tertiary amide group. The lithio intermediate is converted to the cuprate reagent, which is then allylated.



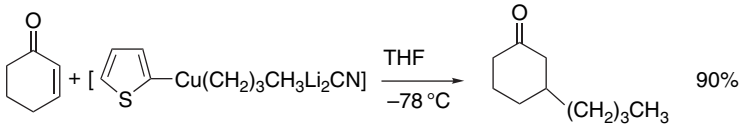
q. These conditions lead to a Suzuki-type cross coupling with retention of configuration at both double bonds.



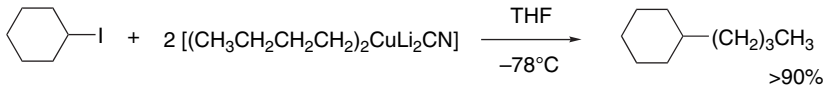
r. These are conditions for carbonylative coupling with retention of double-bond configuration.



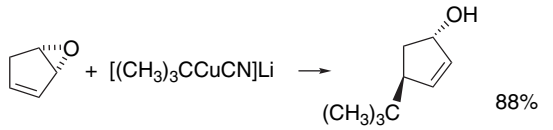
8.2. a. Conjugate addition of the butyl group from the mixed cuprate occurs.



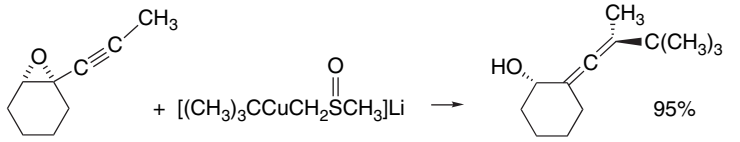
b. This reaction gives a good yield of the substitution product.



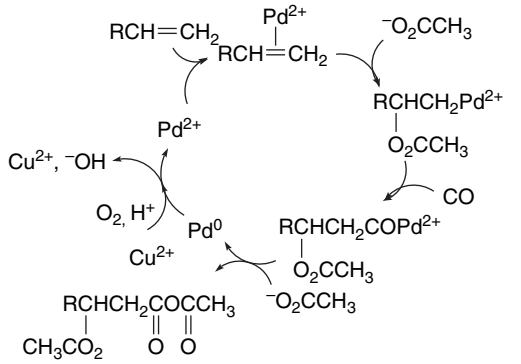
c. This reaction occurs by S_N2' substitution with *anti* stereochemistry.



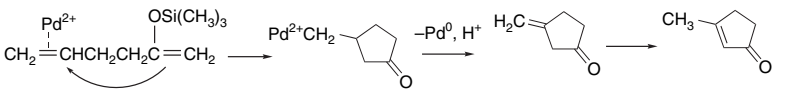
d. This reaction occurs by S_N2' substitution. There is also expected to be a preference for *anti* stereochemistry.



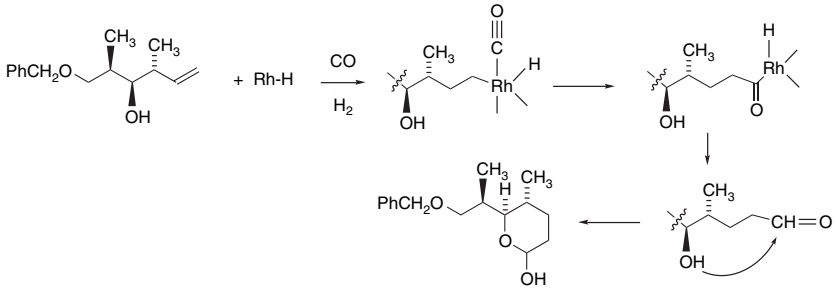
8.3. a. This is a solvocarbonylation with acetate acting as the nucleophile toward both the acylpalladium intermediate and the double bond. The $CuCl_2$ and O_2 function to reoxidize the Pd(0). The reaction shows a preference for carbonylation of the unsubstituted carbon of the alkene.



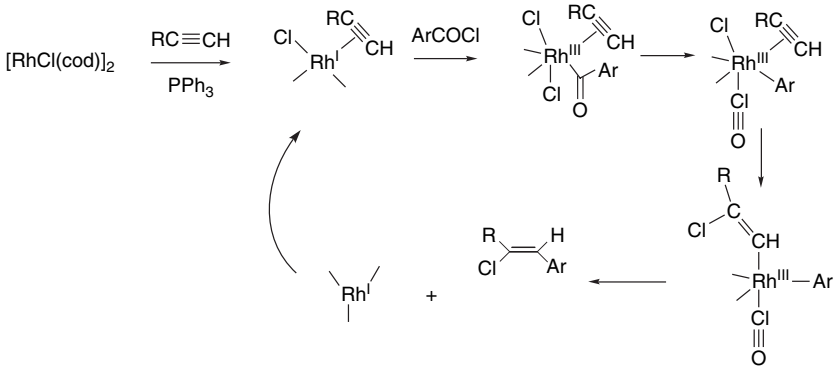
b. This transformation results from an intramolecular attack of the silyl enol ether group on a π complex. It was done with a stoichiometric amount of Pd^{2+}, although use of *p*-benzoquinone as an oxidant reduced the amount of Pd^{2+} needed. The regioselectivity presumably reflects a preference both to form the primary C–Pd bond and for a *exo*-5 transition structure.



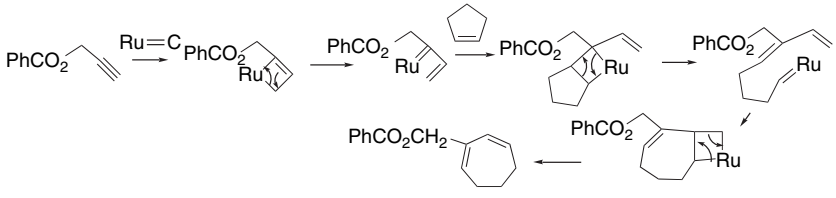
c. This transformation involves hydroformylation, followed by formation of the cyclic hemiacetal.



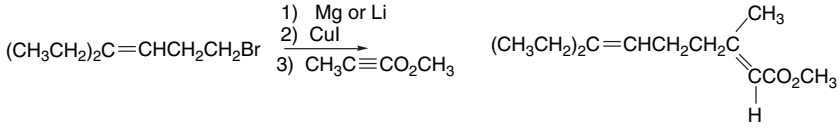
d. This reaction involves addition of Rh–Cl to the alkyne, decarbonylation of the aroylrhodium intermediate, and reductive elimination with the formation of the vinyl chloride.



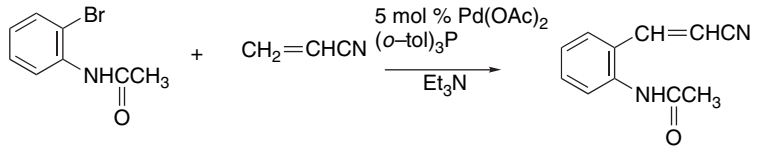
e. This reaction is an alkene-alkyne metathesis using a cyclic alkene, which results in a ring closure.



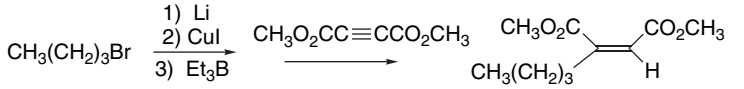
8.4. a. This conversion can be done by the regio- and stereospecific addition of an organocopper reagent to methyl butynoate.



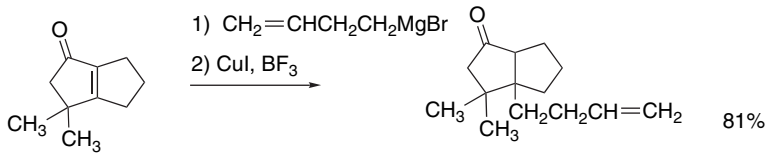
b. This is an example of a Heck reaction and was done under typical conditions.



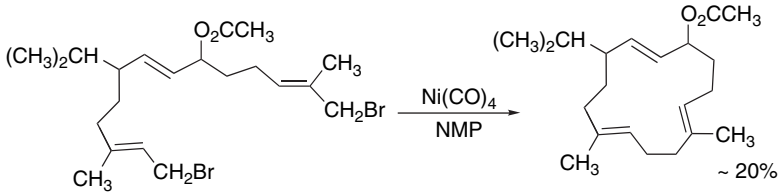
c. This reaction could presumably be done with any of the various cuprate-type reagents. In the referenced article, a mixed cuprate-triethylboron reagent was used. Under these conditions, the alkyl group transfer is exclusively from the copper.



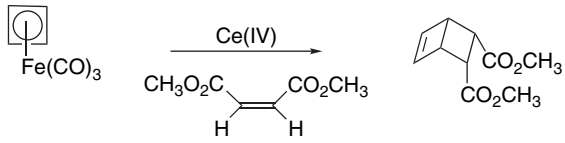
d. This conjugate addition to a rather hindered position was carried out using the BF_3-promoted reaction with a magnesium cuprate reagent.



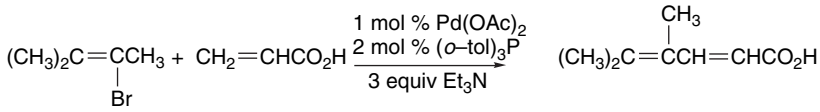
e. This reaction involves a macrocyclization by coupling of two allylic bromides. A zero-valent nickel species would be appropriate and the original transformation was done in modest yield using $Ni(CO)_4$.



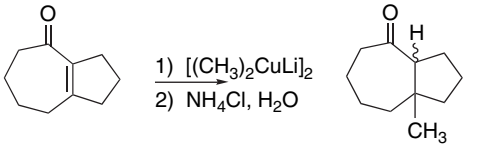
f. This transformation can be accomplished by release of cyclobutadiene from its $Fe(CO)_3$ complex and trapping with dimethyl *Z*-butendioate.



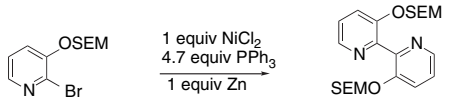
g. This reaction involves a Heck-type vinylation using a vinyl bromide and was carried out under standard conditions.



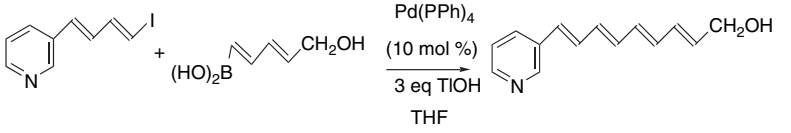
h. This reaction involves addition by dimethylcuprate. The protonation of the enolate is not stereoselective and leads to a 60:40 mixture of the *trans* and *cis* isomers.



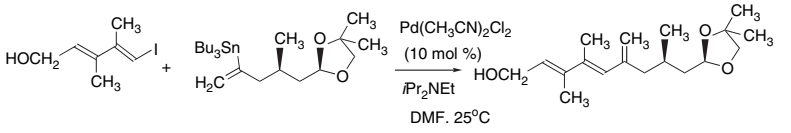
i. This homodimerization of an aromatic halide was done by in situ generation of an arylzinc reagent in the presence of a stoichiometric amount of $NiCl_2$. Various other methods of diaryl coupling presumably could also be applied.



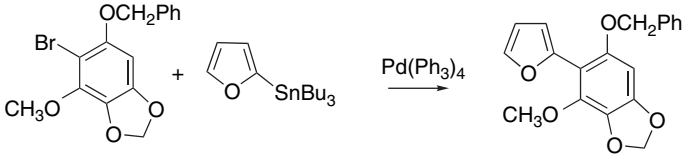
j. This reaction was done by a Suzuki-type coupling using TlOH as the base.



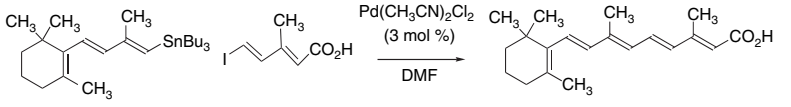
k. This conversion was accomplished using a Stille coupling.



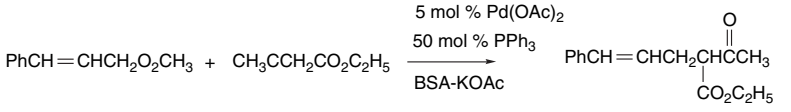
l. This reaction was done using 2-furyl-tri-*n*-butylstannane. Several closely related couplings were done under Suzuki conditions using the corresponding boronic acid.



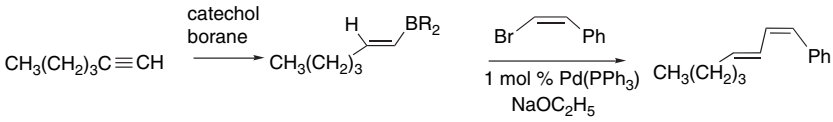
m. This synthesis of retinoic acid was done by a Stille coupling.



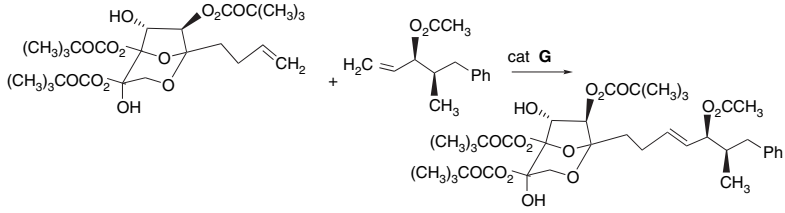
n. This is a typical allylation of a highly stabilized enolate system. The cited reference applies mildly basic conditions consisting of *N,O-bis*-trimethylsilylacetamide (BSA) and KOAc.



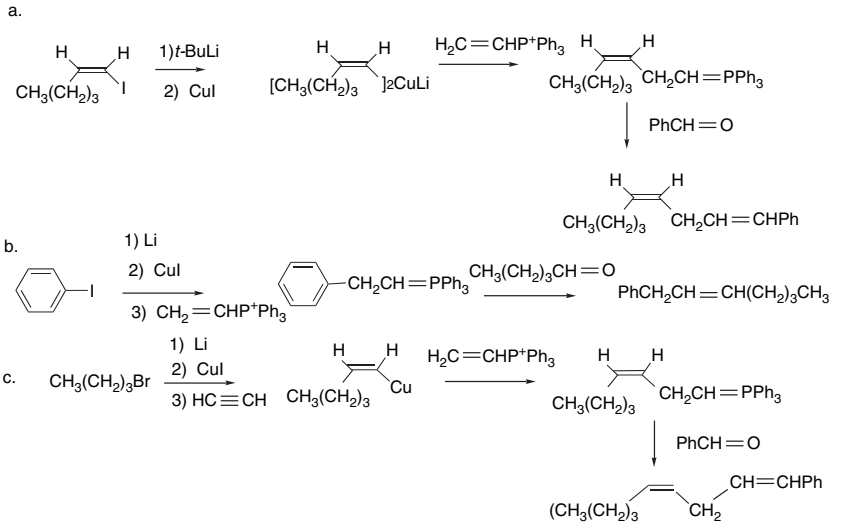
o. This transformation can be accomplished using an *E*-borane and $Z-\beta$-bromostyrene in a Suzuki-type coupling. The reaction has been done with catecholborane as the hydroboration reagent and $Pd(PPh_3)_4$ as the catalyst.



p. This reaction corresponds to an intermolecular olefin metathesis and was done using the second-generation catalyst **H** (see p. 762).

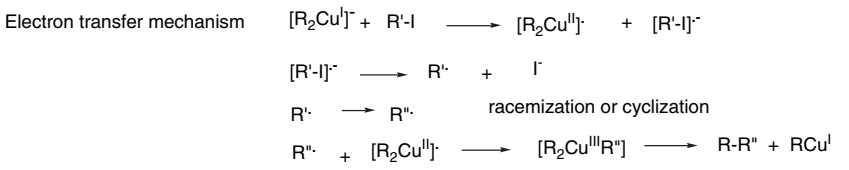


8.5. The various halides can be converted to cuprates. They then undergo addition to the vinylphosphonium cation, generating ylides. In examples (a) and (b) the ylides then react with the appropriate aldehyde to complete the synthesis. In example (c), the initial cuprate is added to acetylene, generating a vinyl cuprate before the addition to vinyltriphenylphosphonium ion, incorporating an additional double bond into the final products.

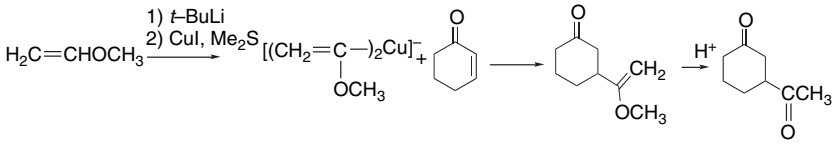


8.6. The behavior of the iodides strongly suggests radical intermediates, with the cyclization of the δ,ϵ-unsaturated system being characteristic of radicals (see Section 10.3.3). Involvement of radical intermediates implies that an electron-transfer occurs as a distinct step with the iodides. Since the iodides should be more reactive to either the oxidative addition or direct substitution mechanisms,

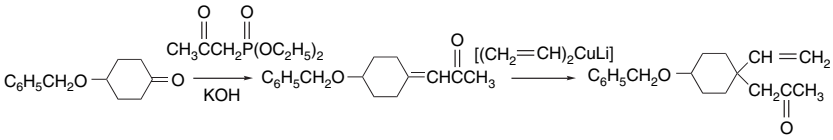
the change in mechanism must result from the greater ease of reduction of the iodides.



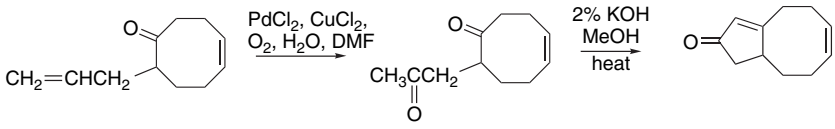
8.7. a. This conversion can be accomplished by using a vinyl ether moiety as the synthetic equivalent of a nucleophilic acyl group. The reaction was done by lithiation of methyl vinyl ether, conversion to the cuprate, conjugate addition, and hydrolysis.



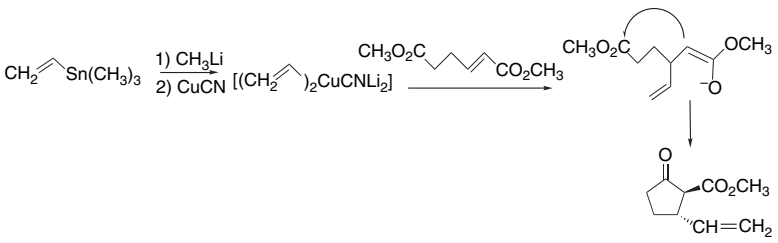
b. This transformation was done by a Wadsworth-Emmons phosphonate reaction followed by conjugate addition with divinylcuprate.



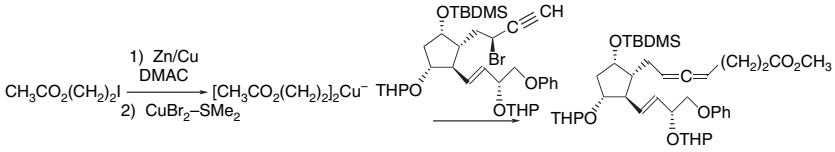
c. This transformation was accomplished by a Wacker oxidation of the terminal alkene followed by an intramolecular aldol condensation. The reaction also demonstrates the selectivity for the Wacker oxidation for terminal over internal or cyclic alkenes.



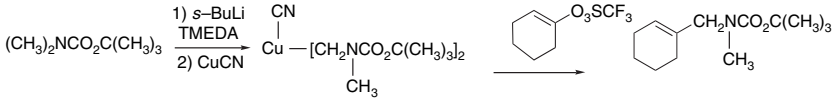
d. This transformation was done by a tandem conjugate addition and Dieckmann condensation. The vinyllithium reagent was generated by transmetallation from trimethylvinylstannane and converted to the cyanocuprate using CuCN.



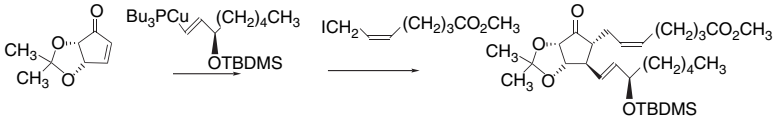
e. This transformation was accomplished by an S_N2' substitution using a functionalized organocuprate reagent, which was prepared from an organozinc compound. Any of the routes available for functionalized organocuprate reagents should be applicable.



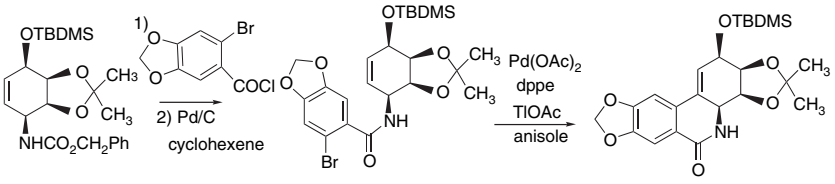
f. This transformation requires a functionalized cuprate that can couple with the enol triflate. The required reagent was prepared by lithiation of an *N*-methyl group of *N*, *N*-dimethylamino *t*-butyl carbamate (see p. 630), followed by conversion to the mixed cyanocuprate.



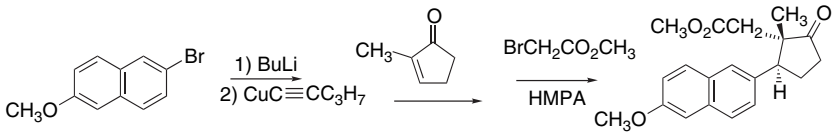
g. The pattern of this transformation corresponds to conjugate addition followed by tandem alkylation. The conjugate addition was done with a phosphine-stabilized cuprate and the alkylation with an allylic iodide. The initial reaction gave a 9:1 *trans:cis* mixture that was equilibrated to the pure *trans* product.



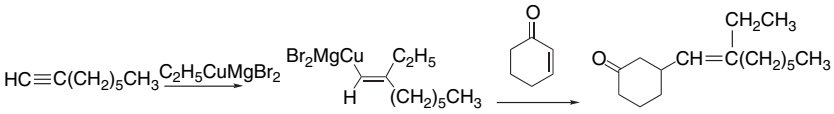
h. This transformation was accomplished by *N*-acylation and deprotection, followed by an intramolecular Heck reaction.



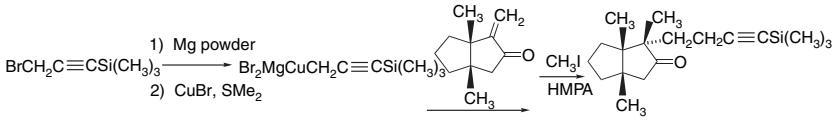
8.8. a. This transformation was achieved by a conjugate addition-alkylation sequence. The cuprate was prepared as a mixed alkynylcuprate. The alkylation was done with methyl bromoacetate in the presence of HMPA.



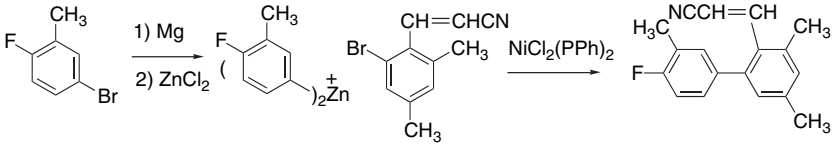
b. The side chain was added by conjugate addition. The cuprate was prepared by addition of $(C_2H_5)_2CuMgBr$ to 1-heptyne.



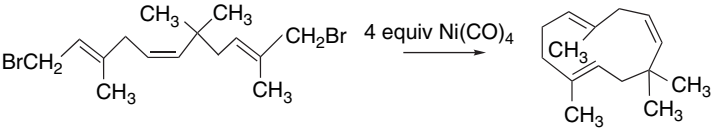
c. This reaction was done by addition of the silylpropargyl copper reagent to the exocyclic methylene group, followed by methylation. The stereochemistry of the methylation is under steric approach control.



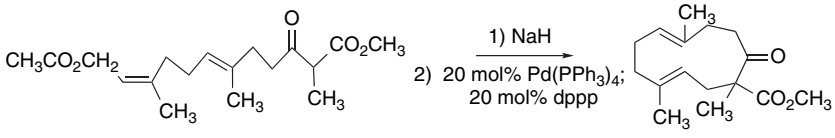
d. This synthesis requires an unsymmetrical biaryl coupling. The 4-bromo-2-methylfluorobenzene was converted to a diarylzinc reagent and then coupled using $NiCl_2(PPh_3)_2$.



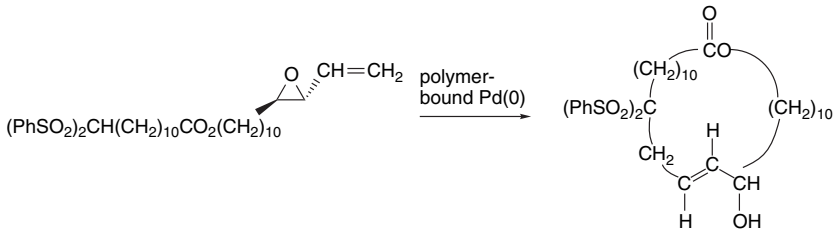
8.9. a. This transformation corresponds to coupling of a *bis*-allylic bromide. It was done using four equivalents of $Ni(CO)_4$. Presumably other Ni(0) reagents would also be effective.



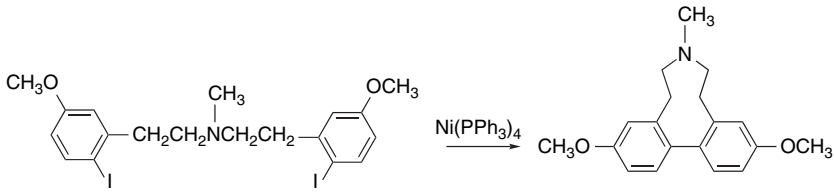
b. This macrocyclization through allylic substitution by a stabilized enolate was done using a fairly high concentration of a catalyst from $Pd(PPh_3)_4$ and dppp.



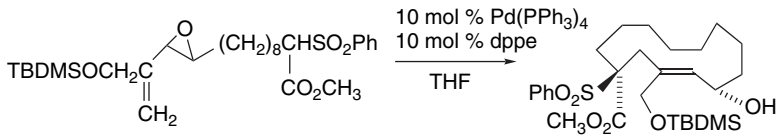
c. This transformation accomplishes macrocyclization through an S_N2' type of opening of a vinyl epoxide by a disulfonyl carbanion. A polymer-bound Pd catalyst was used.



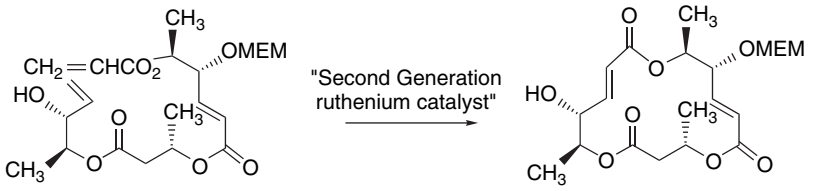
d. This reaction requires a biaryl coupling. It was done using $Ni(PPh_3)_4$ in DMF. Note that a stoichiometric amount of the reagent is required and in practice three equivalents were used.



e. This reaction involves S_N2' opening of a vinyl epoxide by a stabilized carbanion. A combination of $Pd(PPh_3)_4$ and dppe was used.

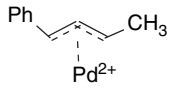


f. This cyclization can be accomplished by an olefin metathesis ring closure. Perhaps because it involves an acrylate group, the reaction was found to be sluggish and a full equivalent of the Ru-carbene catalyst **H** (see p. 762) was required.

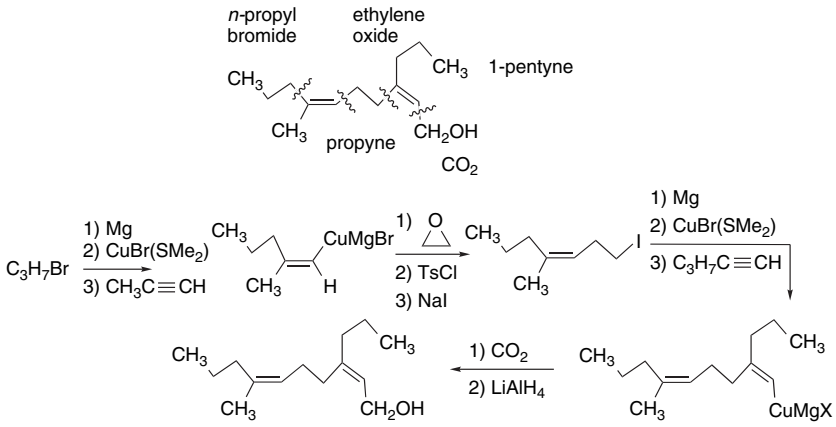


8.10. The results indicate that the cyclobutadiene derivative must become "free" of the $Fe(CO)_3$ in the sense that the latter has no influence on the approach to the trapping reagent. This implies that the cyclobutadiene has a sufficiently long lifetime to diffuse away from the oxidized iron.

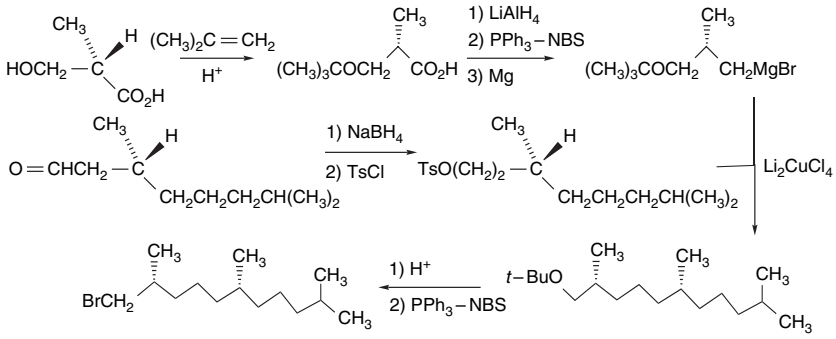
8.11. These results indicate that a common intermediate is formed from the two reactants, which is consistent with formulation of the intermediate as a π-allyl complex.



8.12. The following retrosynthesis was applied and resulted in the synthesis shown below.

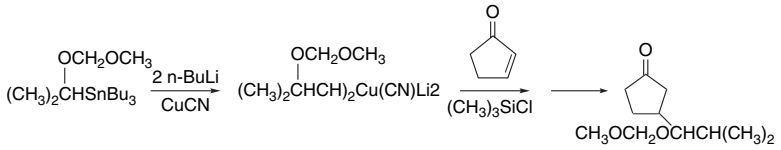


8.13. The two starting materials contain the necessary stereogenic centers in the correct configuration. All that is required is to effect the C(3)–C(4) coupling with the correct stereochemistry. Note that the carboxy group, not the primary alcohol group, must be the source of C(3) to obtain the correct stereochemistry. Although there are many conceivable sequences, the cited reference used a copper-mediated coupling of a Grignard reagent with a tosylate.

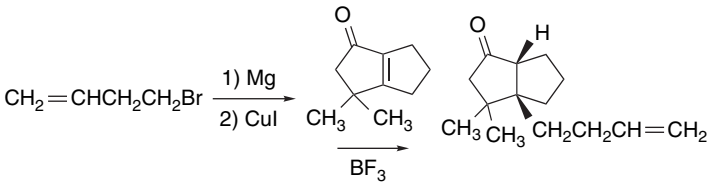


8.14. a. This reaction corresponds to a conjugate addition. The special factor is the presence of the methoxymethyl group, which makes the molecule acid sensitive. The transformation was done using a cuprate prepared from the

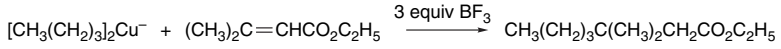
lithio derivative, which in turn was prepared from a stannane. The addition was carried out in the presence of TMSCl.



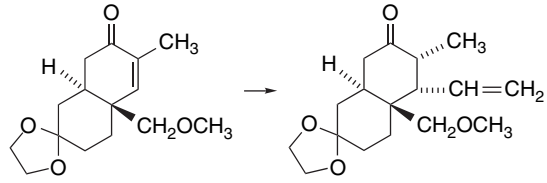
b. This represents a hindered case for conjugate addition. A cuprate was prepared from the corresponding Grignard reagent, and the reaction was carried out in the presence of BF_3. The stereoselectivity is determined by the enolate protonation and presumably arises from the greater stability of the *cis* ring juncture.



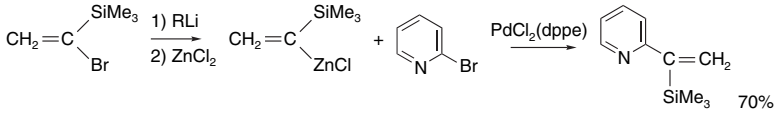
c. This reaction requires conjugate addition to a β, β-disubstituted position of a relatively unreactive unsaturated ester. The reaction was effected using three equivalents of BF_3.



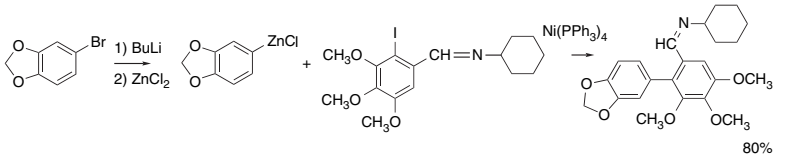
d. This is a conjugate addition to a relatively hindered position and was effected using a Bu_3P-modified cuprate.



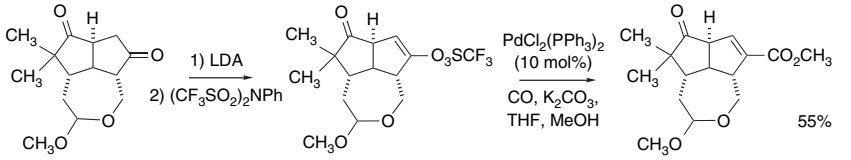
8.15. a. This transformation requires a vinyl-aryl coupling. A nickel-mediated coupling was accomplished by conversion of the vinylsilane to a zinc reagent, followed by coupling with $PdCl_2$(dppe).



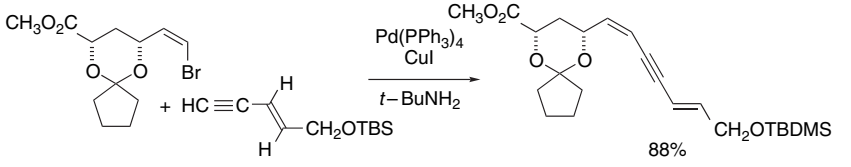
b. This aryl-aryl coupling was accomplished using the zinc reagent derived from the bromobenzodioxole and $Ni(PPh_3)_4$.



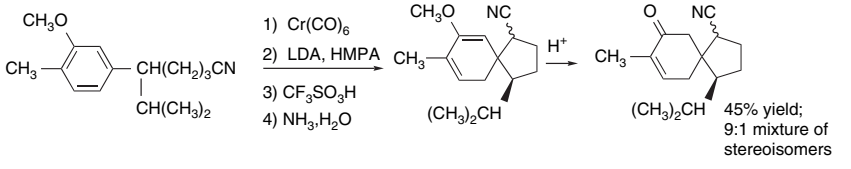
c. This transformation was done by converting the ketone to an enol triflate and then carbonylating in the presence of methanol, using $PdCl_2(PPh_3)_2$ as the catalyst.



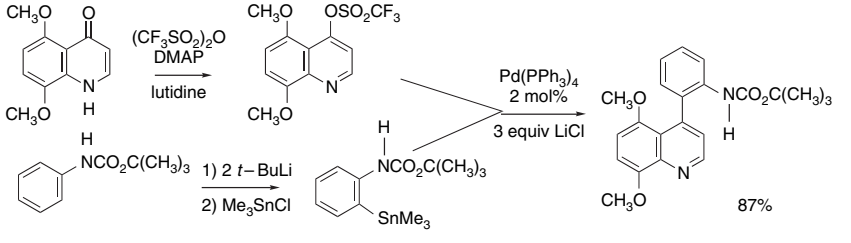
d. This alkenyl-alkynyl coupling was done using Sonogashira conditions.



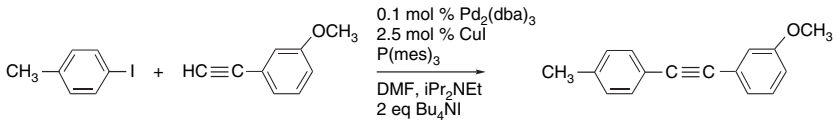
e. This intramolecular nucleophilic addition to the aromatic ring was done by forming the $Cr(CO)_3$ complex. The enolate was then formed with LDA. The enol ether intermediate was hydrolyzed to the product.



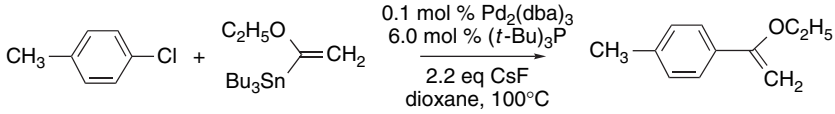
f. The quinolone was converted to the corresponding triflate. The *t*-butyl carbamate was lithiated in the *ortho* position and converted to the trimethylstannyl derivative. Coupling was accomplished using $Pd(PPh_3)_4$ as a catalyst in the presence of LiCl.



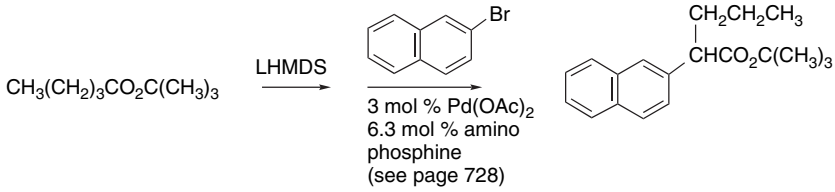
g. This arylation of an alkyne was accomplished using the Sonogashira reaction conditions.



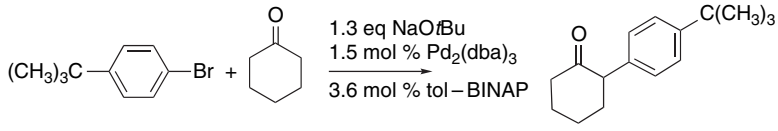
h. The Stille coupling of aryl chlorides require special conditions. A hindered trialkylphosphine and CsF were used in this reaction.



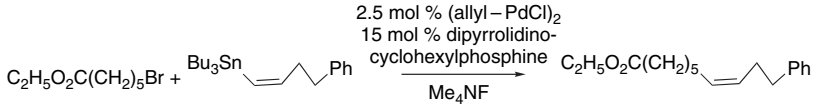
i. This reaction involves an enolate arylation. The enolate was prepared using LHMDS and used in 2.5 *M* excess. An aminophosphine ligand was used.



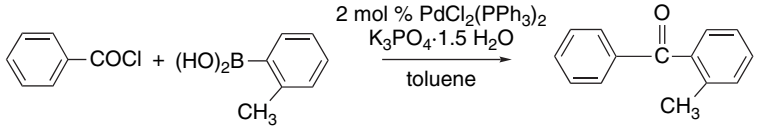
j. This enolate arylation was done using NaO*t*Bu for enolate formation and $Pd_2(dba)_3$ as the catalyst. The preferred phosphine ligand was tol-BINAP.



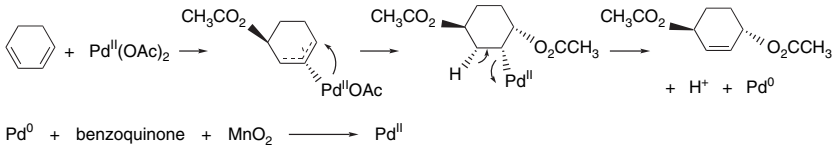
k. This is a Stille coupling with an alkyl bromide and requires special conditions to avoid β-elimination. Use of dipyrrolidinocyclohexylphosphine and tetrabutylammonium fluoride resulted in good yields.



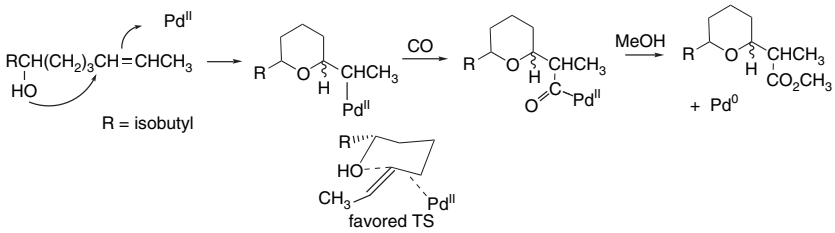
l. The synthesis of diaryl ketones from aroyl chlorides and arylboronic acids has been found to proceed well with $PdCl_2(PPh_3)_2$ using K_3PO_4 as a base.



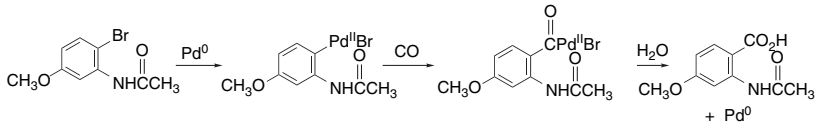
8.16. a. This reaction involves Pd-initiated nucleophilic addition of acetate to form a π-allyl palladium intermediate. The second acetate is then transferred internally, resulting in the *trans* stereochemistry. The Pd^0 is released by reductive elimination. The benzoquinone and MnO_2 serve to reoxidize the Pd^0. In the presence of LiCl the reaction gives the isomeric *cis* product by *anti* attack.



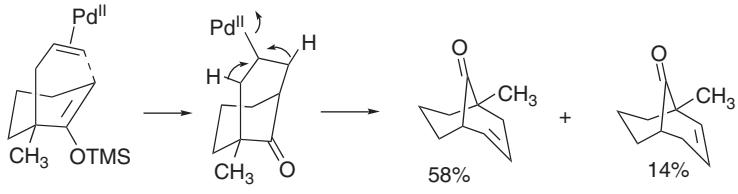
b. This reaction involves carbonylation accompanied by intramolecular nucleophilic attack. The selectivity for the six-membered ring presumably derives from the preference for an *exo*-6 over an *endo*-7 transition structure. The acylpalladium intermediate is cleaved by methanolysis. The $CuCl_2$ is used as a stoichiometric oxidant to regenerate the reactive Pd^{2+} oxidation state.



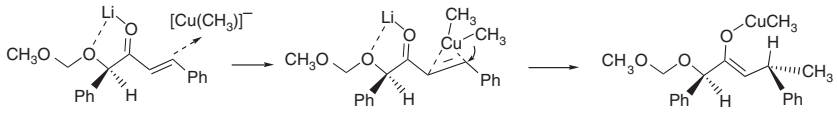
c. This is a palladium-catalyzed carbonylation of an aryl halide. The initiation phase must involve generation of an active Pd^0 species. It has been suggested that the amine serves as the reductant to generate the active catalyst. This is followed by oxidative addition, carbonylation, and reductive elimination, which regenerates the Pd in the active oxidation state.



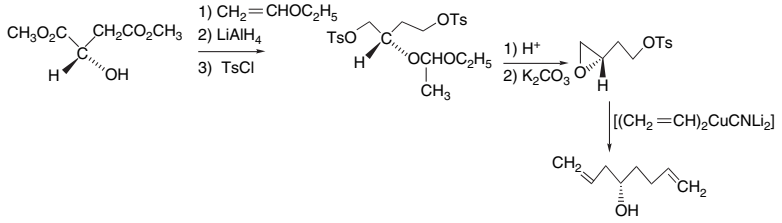
d. This reaction involves nucleophilic attack by the silyl enol ether group on the Pd^{2+}-alkene complex. The ring stereochemistry and geometry direct the course of the reaction. The cyclization was carried out with a stoichiometric amount of Pd^{2+}, which is converted to Pd^0 in the β-elimination step.



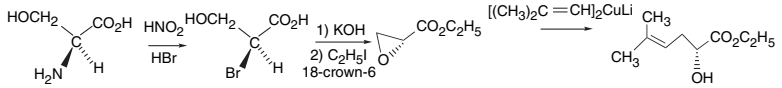
8.17. The observed stereoselectivity is in accord with a chelated structure with formation of the π complex *anti* to the phenyl group. According to the general mechanism for conjugate addition (see p. 687), this dominant conformation can give rise to the observed product through rate-determining reductive elimination.



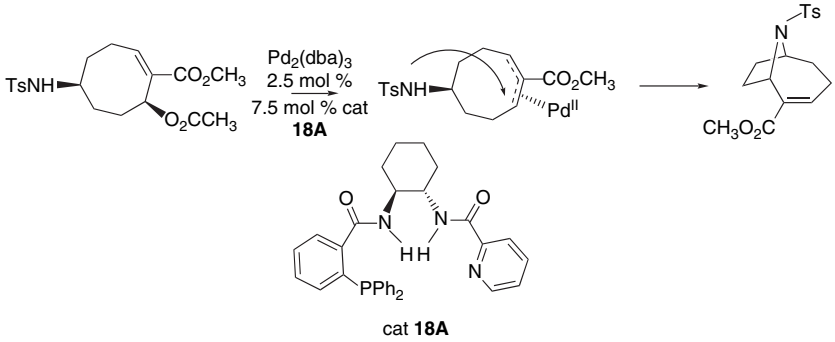
8.18. a. The chiral center is of the desired configuration so the goal is to selectively convert the two different carbomethoxy groups to the allyl and 3-butenyl substituents. In the referenced sequence, the diester was reduced to a diol and converted to a ditosylate. Advantage was then taken of the higher rate of formation of three-membered rings to form an epoxide intermediate. Reaction of the epoxy tosylate with divinylcyanocuprate installed *both* of the terminal double bonds in a single sequence, completing the synthesis.



b. This transformation involves elaboration of the serine hydroxymethyl group to the isoprenyl side chain and *inversion* of configuration at the chiral center. The sequence of reactions used involved conversion of the amino group to hydroxy *with retention* by nitrosation, a reaction that may proceed via an α-lactone intermediate. The hydroxy acid was then converted to an epoxide, which serves as the point of introduction of the side chain using a cuprate reagent.



c. This transformation requires an enantioselective reagent or catalyst. The reaction pattern corresponds to an substitution on the allylic acetate by the sulfonamide acting as a nucleophile. The reaction presumably proceeds through a π-allyl intermediate that would be *achiral*. A chiral ligand was used to induce enantioselectivity and achieved 88% e.e.



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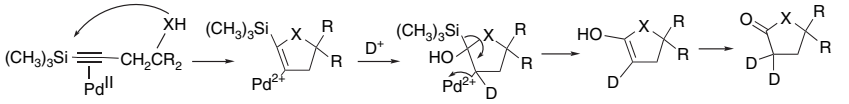
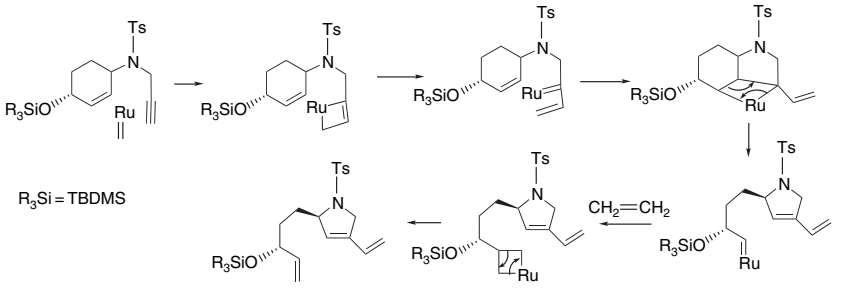
8.19. The incorporation of two deuteriums at C(3) requires that both of the protons be derived from solvent. The lack of deuteration at C(4) requires that the elimination of Pd be regiospecifically 2,3-, not 3,4. The following mechanism meets those criteria.

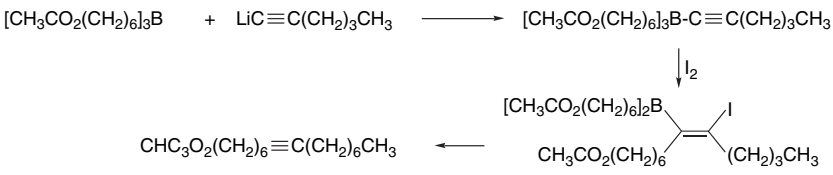


8.20.

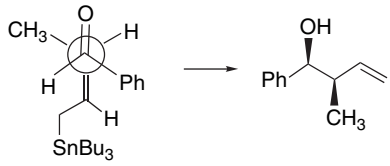


Chapter 9

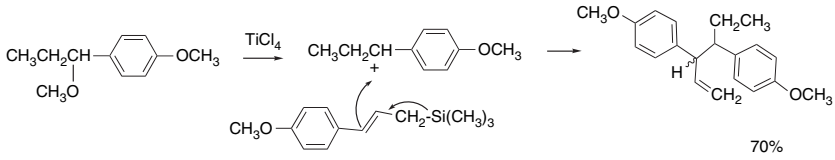
9.1. a. These conditions correspond to the synthesis of disubstituted alkynes by iodine- initiated migration followed by elimination (see p. 795).



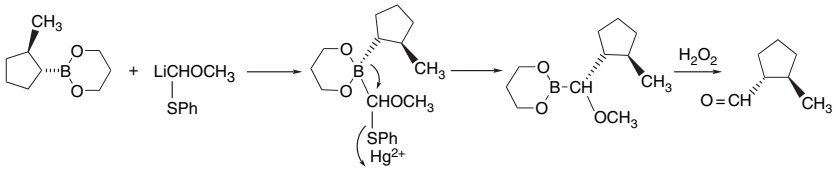
b. These conditions for Lewis acid–initiated allylstannane addition lead to the *syn* isomer through an open transition structure (see p. 836).



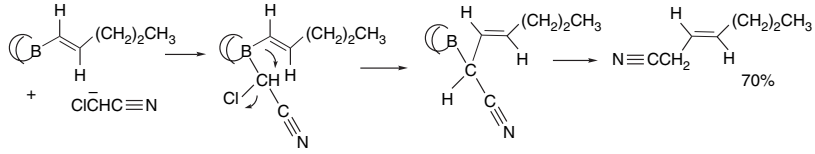
c. This is a somewhat specialized reactant combination in which the Lewis acid generates a benzylic carbocation by ether cleavage, assisted by the 4-methoxy substituent. The yield is 70% when the $TiCl_4$ is added to the precooled reagents. The product is a 1:1 mixture of stereoisomers.



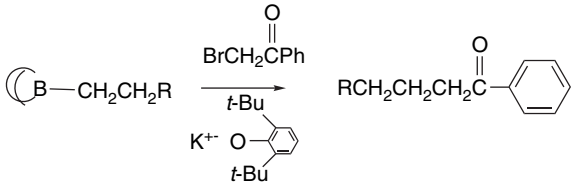
d. These conditions lead to a 66% yield of the aldehyde resulting from migration of a boron alkyl substituent with retention of configuration.



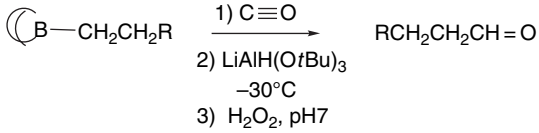
e. These conditions result in formation of the β, γ-unsaturated nitrile resulting from migration of the boron substituent.



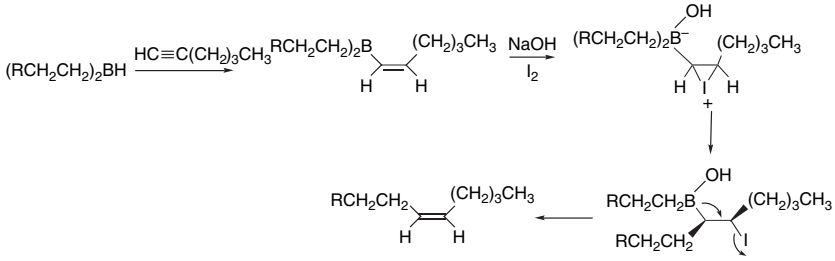
9.2. a. This transformation can be accomplished by a base-catalyzed reaction with α-bromoacetophenone. The most efficient conditions involve hydroboration with 9-BBN and induction of migration by 2,6-di-*t*-butylphenoxide.



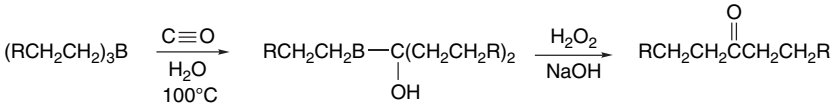
b. This conversion requires the reductive interception of the monomigration intermediate. The cited reference describes conditions involving hydroboration by 9-BBN and use of $LiAlH(O\text{-}t\text{-}Bu)_3$ that are suitable for alkenes having ester and nitrile substituents.



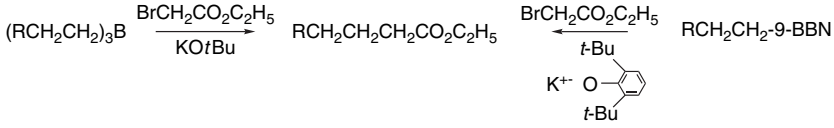
c. The synthesis of *Z*-alkenes can be achieved by *syn* hydroboration of an alkyne, followed by treatment with NaOH and I_2 (see p. 795).



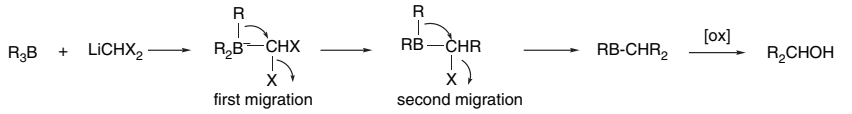
d. The inclusion of water in the carbonylation reaction, followed by oxidation leads to a symmetrical ketone.



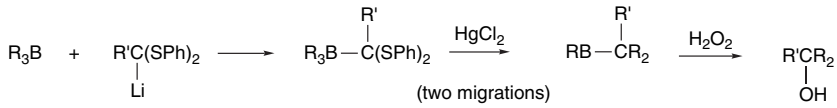
e. This homologation can be done using the trialkylborane or alternatively by hydroboration with 9-BBN. KO-*t*-Bu was used as the base in the original procedure, but potassium 2,6-di-*t*-butylphenoxide can also be used.



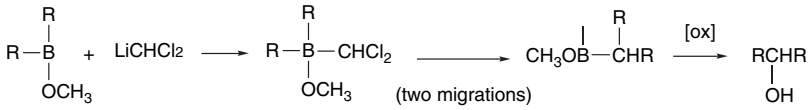
9.3. Each of these lithiated reagents can add to a trialkylborane to generate an anionic adduct. One structural requirement of the homologation reagents is that they be able to support deprotonation (lithiation). Each also contains one or two potential leaving groups that can be involved in a migration step. Thus, for a case with two potential leaving groups, two migrations can occur.



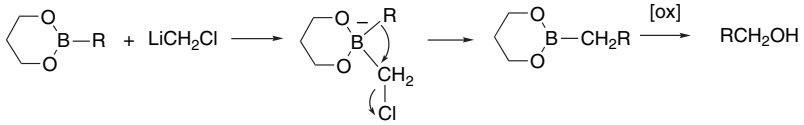
In the case of Entry 3, the reagent is a diphenylthioacetal and the H is replaced by an alkyl group. Migration induced by metastic chloride leads to the formation of an unsymmetrical tertiary alcohol.



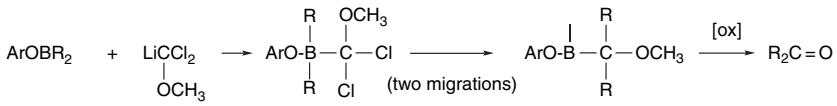
In Entry 4 use of lithiated dichloromethane and a borinate ester results in two migrations. Oxidation leads to a secondary alcohol.



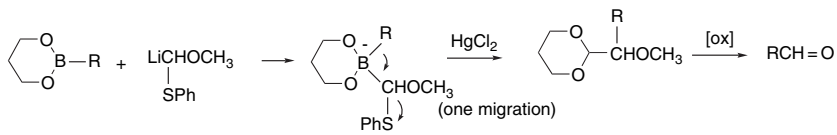
In Entry 5, the use of lithio monochloromethane and a cyclic boronate reagent limits the number of potential migrations to one and the product is a primary alcohol.



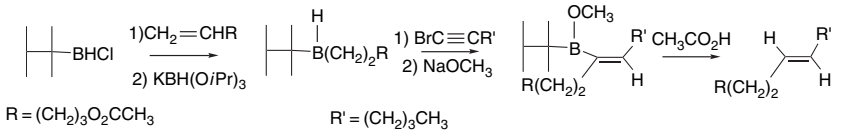
In Entry 11, an aryloxy borane is generated after the hydroboration of 1,5-cyclooctadiene with monochloroborane. The homologation reagent is dichloromethyl methyl ether, which permits two migrations. In this case, the deprotonation is accomplished by a tertiary alkoxide.



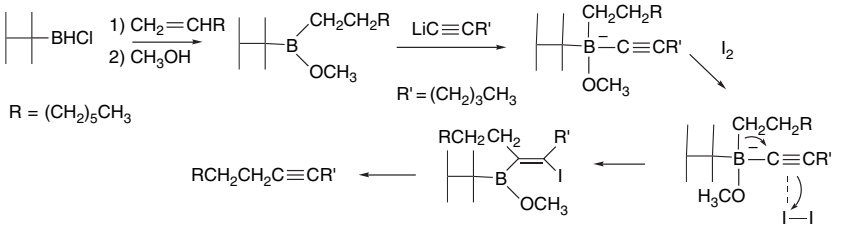
In Entry 14, lithio phenylthiomethyl methyl ether leads to a single migration and formation of an aldehyde.



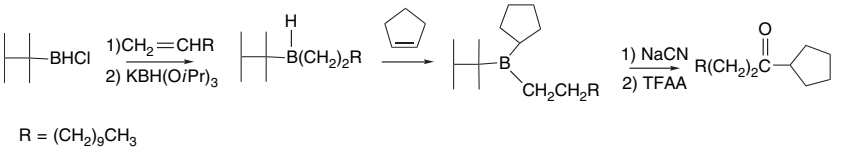
9.4. a. This is an example of a stereoselective synthesis of an *E*-alkene from a borane and a haloalkyne. The alkene is hydroborated using *B*-chlorothexylborane followed by reduction to the mixed dialkylborane. The haloalkyne is then hydroborated. Migration is effected by $NaOCH_3$ and the resulting alkenylborane is protonolyzed.



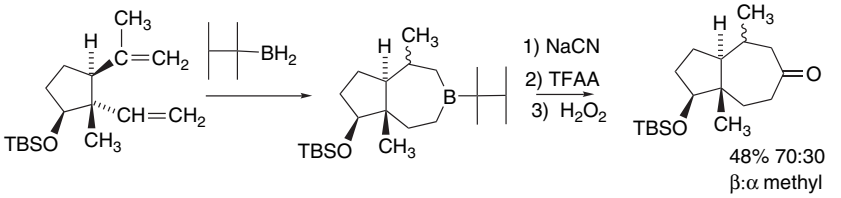
b. The alkylation of a terminal alkyne can be accomplished by formation of an "ate" complex using a mixed alkyl thexylborinate prepared by hydroboration with *B*-chlorothexylborane and converted to the borinate by methanolysis. The migration and elimination is done with I_2.



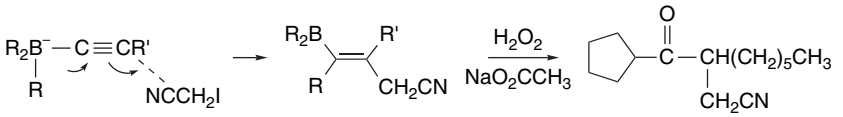
c. The formation of an unsymmetrical ketone can be done by sequential hydroboration with *B*-chlorothexylborane, reduction, and a second hydroboration. In the referenced case the cyanide-TFAA procedure was used for the migration step.



d. This transformation can be done by hydroboration with thexylborane, which results in formation of a cyclic borane. The migration was step was done using cyanide-TFAA. The product is a 70:30 mixture of β- and α-stereoisomers, indicating little stereoselectivity in the hydroboration of the isopropenyl group.

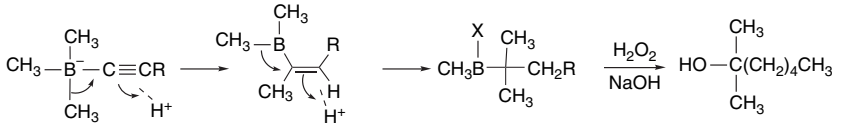


9.5. a. This transformation involves electrophilic attack on the triple bond of the alkynyl trialkylborate, resulting in migration of one alkyl group. Oxidation gives a ketone. Although irrelevant to the outcome of this particular reaction, it was shown that the alkylation-migration proceeds with *syn* stereoselectivity.



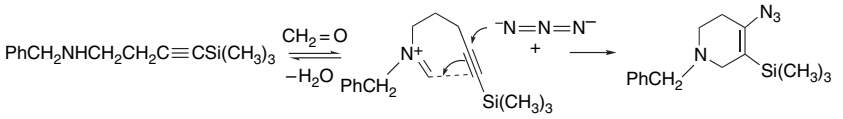
R = *c*–C_5H_9
R' = $(CH_2)_5CH_3$

b. This transformation results from two proton-induced migrations from an alkynyl trialkylborate.

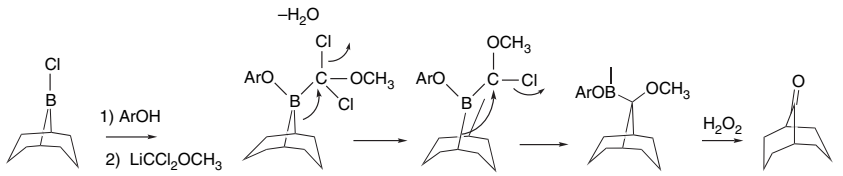


R = $(CH_2)_3CH_3$

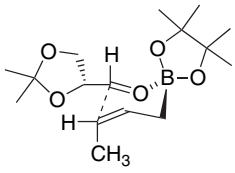
c. This is an iminium ion cyclization of an alkynyl silane. The azido group acts as the nucleophile to capture the developing cationic intermediate.



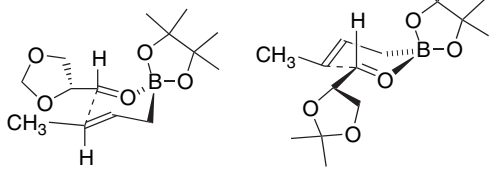
d. This facile synthesis of bicyclo[3.3.1]nonan-9-one involves two B → C migrations.



9.6. a. The starting point for analysis of this problem is the cyclic transition structure expected for the allylboration reaction (see pp. 797). The stereochemistry is *reactant controlled* in the sense that the facial approach of the borane to the aldehyde is governed by the dioxolanyl substituent on the aldehyde. This analysis reveals that there is one strongly favored TS conformation for the *Z*-allylic borane, but two of comparable energy for the *E*-borane. The difference is that *Z*-allylic borane avoids any destabilizing interaction with the aldehyde substituent, whereas with the *E*-allylic borane there is a destabilizing *gauche* interaction.

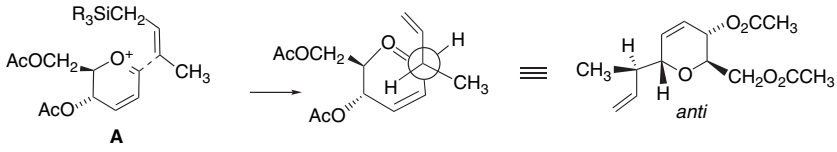


strongly favored for *Z*-boronate



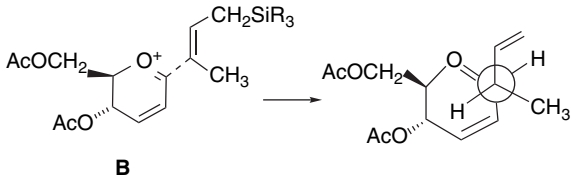
two competing transition structures for *E*-boronate

b. A starting point for analysis of the observed stereochemistry is the synclinal transition structure **A** for the *E*-isomer in which the methyl group is oriented away from the ring. This correctly predicts the observed *anti* stereoselectivity.

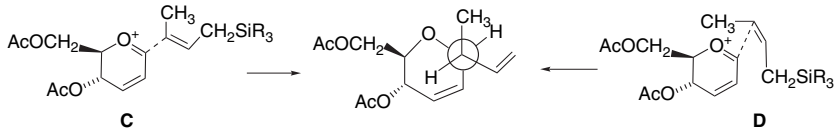


A *anti*

The corresponding synclinal transition structure **B** for the *Z*-silane does not predict a *syn* product. An antiperiplanar structure **C** or the more sterically congested synclinal structure **D** is predictive of the observed *syn* product. The steric effect of the silyl group would be difficult to reconcile with **D**, since it should become progressively less favorable as R_3Si increases in size, suggesting that reaction occurs through transition structure **C**.



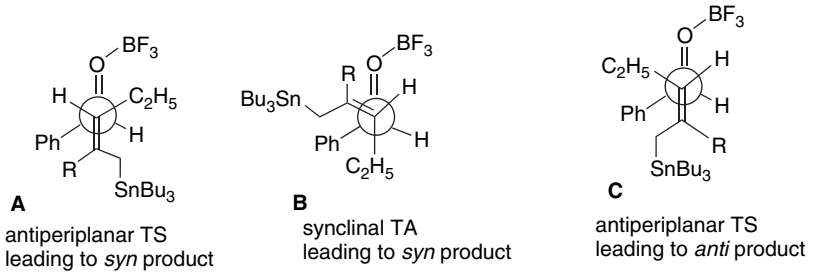
B



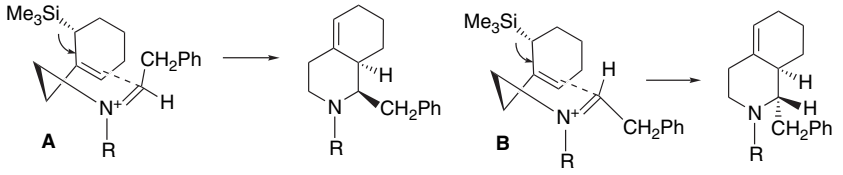
C **D**

c. In the absence of overriding steric influences, this reaction is expected to proceed through an open transition structure. Either an antiperiplanar (**A**) or synclinal structure (**B**) can be considered. When the substituent R becomes large it will interact with the aldehyde group in the antiperiplanar-*syn* TS or with the carbonyl-BF_3 complex in the synclinal-*syn* TS. The most likely TS

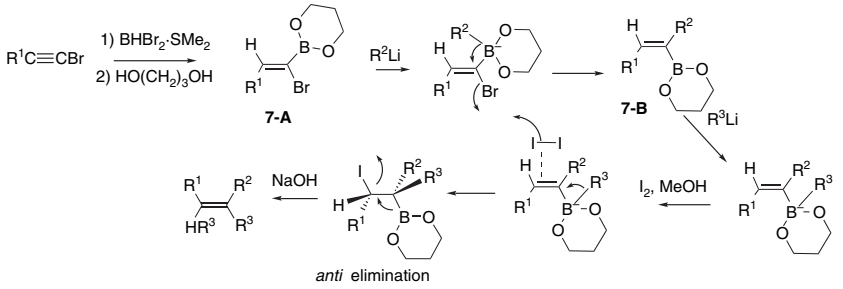
when R becomes large is the antiperiplanar TS **C**, which directs R toward the aldehyde hydrogen.



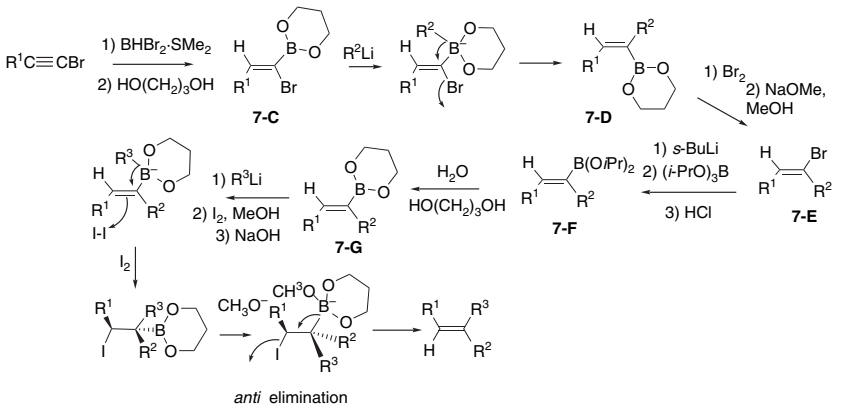
d. This result is consistent with competition between *E*- and *Z*-iminium transition structures. A large nitrogen substituent would favor **A**, which leads to the *trans* isomer. When the substituent is small, structure **B**, which avoids the interaction of the benzyl group with the ring structure, is preferred.



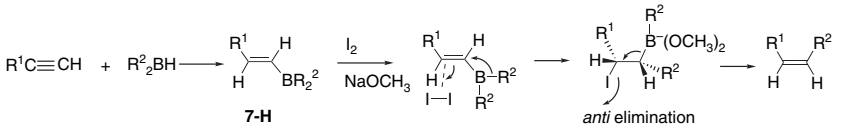
9.7. a. The first intermediate **7-A** results from *syn* hydroboration and conversion to the cyclic boronate ester. The alkyllithium reagent R^2Li then induces rearrangement via an "ate" adduct, giving intermediate **7-B**. The alkyllithium reagent R^3Li then forms a second "ate" adduct that is rearranged with I_2 and undergoes *anti* elimination.



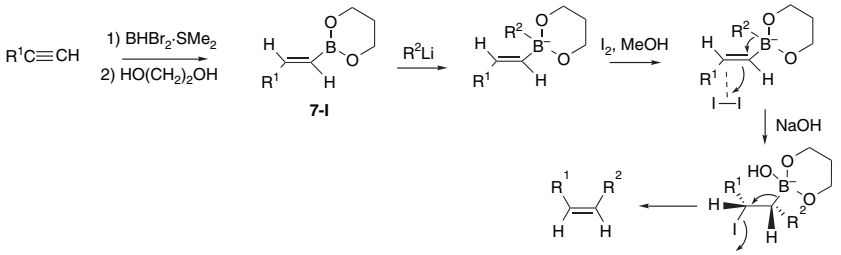
b. The first intermediate **7-C** would result from *syn* hydroboration and formation of the cyclic boronate ester. Intermediate **7-D** is the borane resulting from displacement of the alkenylbromide. This reaction occurs through formation of an "ate" adduct at boron. Intermediate **7-E** results from bromination followed by methoxide-induced elimination. Intermediate **7-F** results from a halogen-metal exchange to form an alkenyllithium intermediate, which is converted to an alkenyl di-*i*-propoxyborane. After reconversion to a cyclic boronate **7-G**, and formation of an "ate" adduct by addition, iodination and methoxide-induced rearrangement and gives the final product. In the overall process, two new R groups, both derived from an organolithium reagent, are installed.



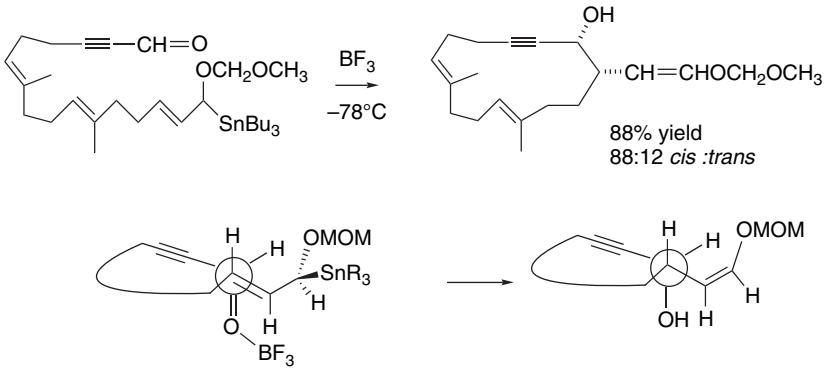
c. The reaction begins by *syn* hydroboration of the alkyne by a dialkylborane generated in situ. The I_2-$NaOCH_3$ reagent combination then triggers migration and elimination.



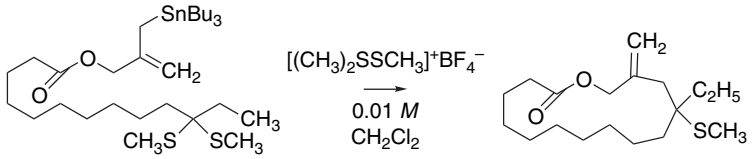
d. This sequence employs hydroboration by dibromoborane and conversion to the cyclic boronate to generate the first intermediate. An "ate" complex is formed by the alkyllithium reagent and migration-elimination is effected by I_2, followed by NaOH.



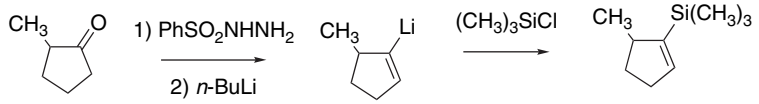
9.8. a. This cyclization of an α-oxy allylic stannane can be done with a Lewis acid. In the cited reference BF_3 was used at −78°C. The reactant was added slowly to the catalyst in solution, which favors the cyclization by keeping the concentration of the reactant low. The ring closure is stereoselective for the *cis* isomer. The reaction was also carried out using the enantiomerically pure reactant. The observed stereochemistry is consistent with a synclinal transition structure.



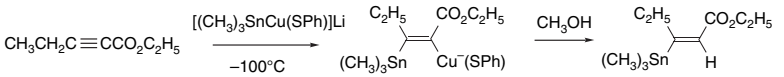
b. This cyclization depends on development of electrophilic character at the dithioketal. In the cited reference dimethy(methylthio)sulfonium tetrafluoroborate (DMTSF) was used. The reaction was run at 0.01 *M* concentration to favor the intramolecular reaction.



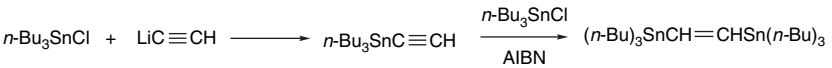
9.9. a. This transformation was effected by silylation of the alkenyllithium reagent generated from the ketone via the Shapiro reaction (see p. 454).



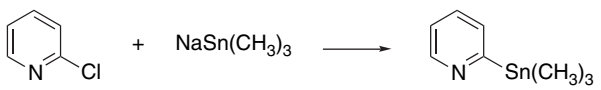
b. This electrophilic alkyne readily undergoes cuprostannylation, followed by protonolysis. The *syn* stereoselectivity is 97:3.



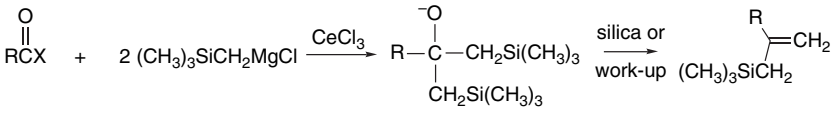
c. A two-step sequence involving stannylation of lithium acetylide, followed by radical addition of tri-*n*-butylstannane was successfully used to achieve this conversion.



d. Although lithiation of the chloropyridine might provide one approach, in the cited reference the chloride was displaced by $NaSn(CH_3)_3$, taking advantage of the susceptibility of the pyridine ring to nucleophilic substitution.

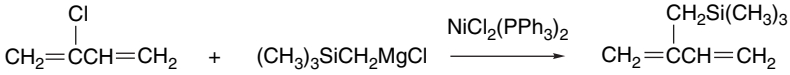


e. The cited references describe two related procedures. The key reactant is the Grignard reagent derived from chloromethyltrimethylsilane. Both methods use $CeCl_3$ for enhanced nucleophilicity (see p. 664). Addition of *two equivalents* generates a carbinol that can undergo a Peterson-type elimination (see p. 171). When esters are used as the reactant, this elimination is effected with silica. In the procedure using acyl chlorides, the elimination evidently occurs during the reaction or workup.

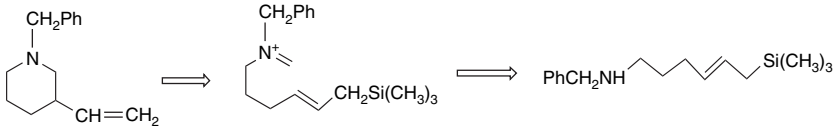


X = Cl or OR'

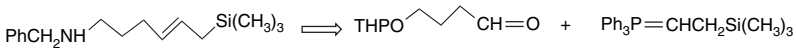
f. This transformation requires replacement of a *alkenyl* chloride by a nucleophilic derivative of tetramethylsilane. The Grignard reagent derived from chloromethylmethylsilane was used with a $NiCl_2(PPh_3)_2$ catalyst in a cross-coupling reaction.



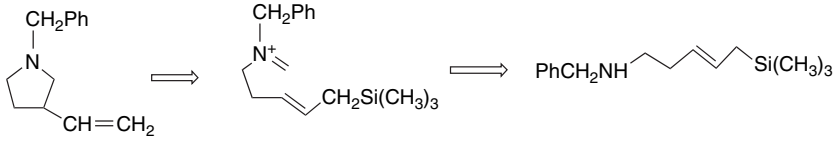
9.10. a.



There would be a number of ways to synthesize the starting aminoalkyl silane. In the cited reference, a THP-protected 4-hydroxypentanal was converted to an allylic silane by a Wittig reaction, and then converted to the amine.

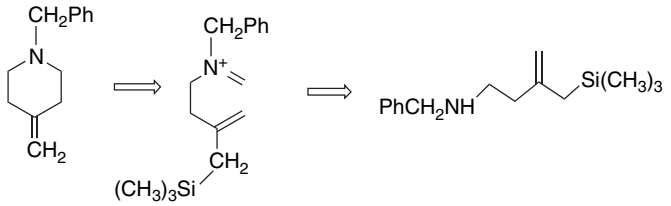


b.

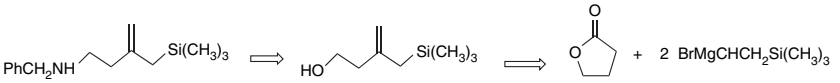


A pattern similar to that in (a) was used for synthesis of the required aminoalkyl silane.

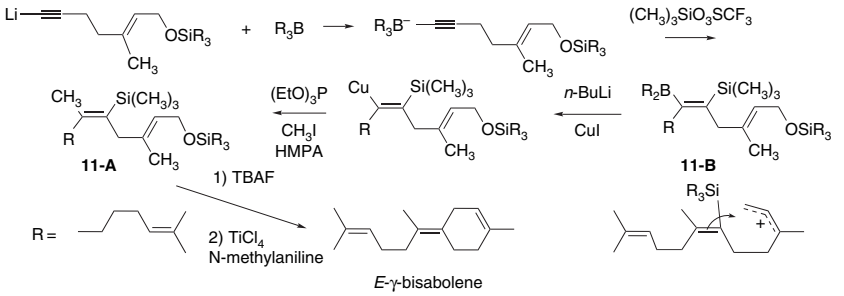
c.



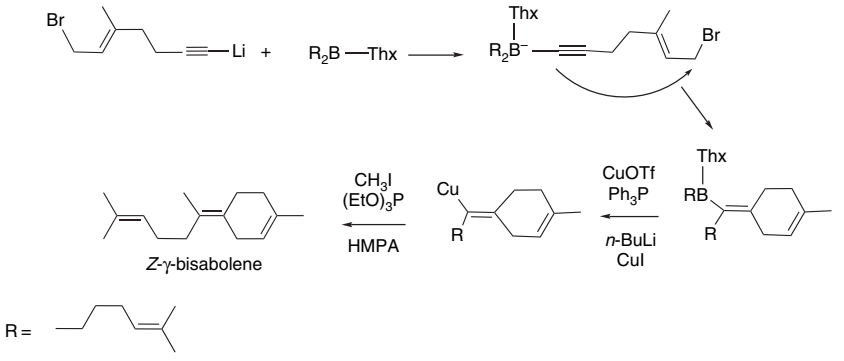
The amine was synthesized by addition of two equivalents of $(CH_3)_3SiCH_2MgBr$ to butyrolactone. One of the trimethylsilyl groups undergoes a Peterson-type elimination with the carbonyl group to generate the double bond.



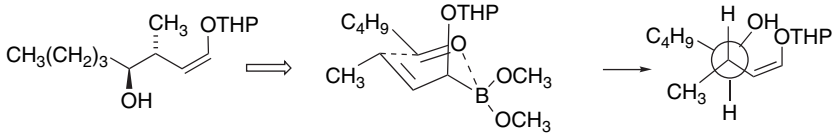
9.11. The intermediate **11-A** is synthesized by a variation of the method for alkene synthesis from terminal alkynes. The key elements in the synthesis of the *E*-isomer is the stereospecific migration induced by TMSOTf. As with other electrophilically induced migrations, the migrating group R and the electrophile are *anti*. The alkenylborane **11-B** is converted to an organocopper reagent and then methylated giving **11-A**. The allylic alcohol then serves as an electrophile in the cyclization of a vinyl silane intermediate.



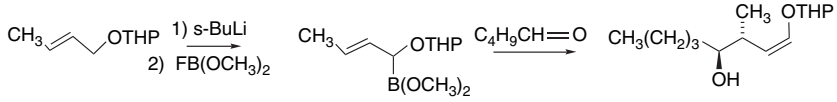
In the synthesis of the *Z*-isomer, an "ate" adduct is formed between the alkyne and a monothexylborane derivative. The allylic bromide **11-D** reacts with the adduct, inducing cyclization and migration. The cyclized borane is then converted to an organocopper reagent and methylated.



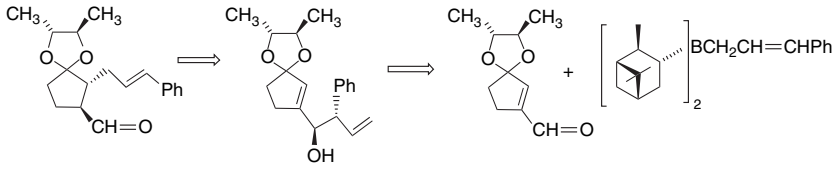
9.12. a. Retrosynthetic analysis identifies the potential for an allylic addition to the aldehyde by an α-tetrahydropyranyloxyborane reagent. The required *anti* stereochemistry corresponds to a cyclic transition structure with an *E*-allylic reagent. In the cited reference, a dimethoxyboronate ester was used as the reactant, but other boron derivatives would also be expected to give the same stereoisomer.



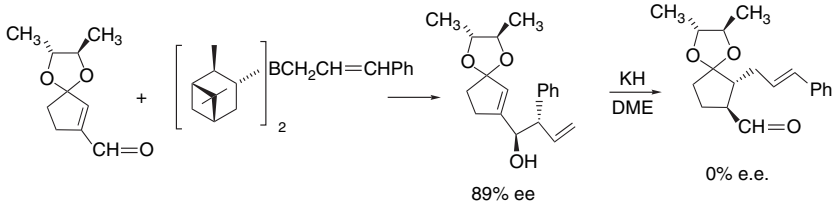
The THP-protected 2-butenol can be converted to an allylic borate by lithiation and reaction with dimethoxyfluoroborane.



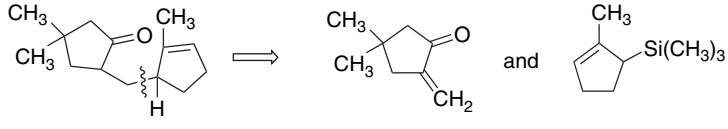
b. Although a retrosynthesis would identify conjugate addition as a possible disconnection, use of allylic boranes as nucleophiles for conjugate addition is not well developed. An alternative sequence would be addition to the aldehyde followed by oxy-Cope rearrangement.



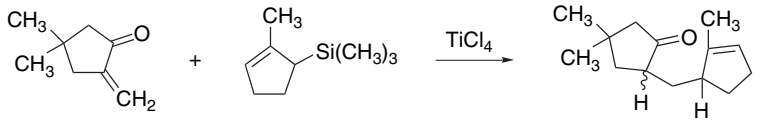
The allylboration proceeded with good stereoselectivity, consistent with a chair transition structure. Curiously, the oxy-Cope rearrangement led to racemization.



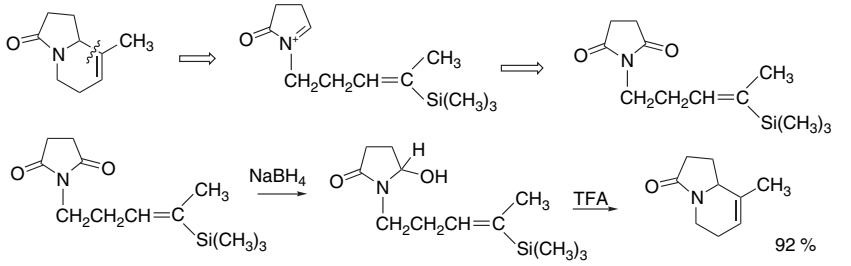
c. This transformation corresponds to a conjugate addition of the allylic silane to the exocyclic enone.



Use of $TiCl_4$ as the Lewis acid gave a 2:1 mixture of stereoisomers.

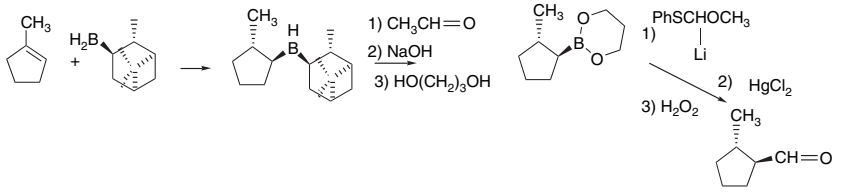


d. This transformation can be effected by intramolecular iminium ion cyclization of the vinyl silane group. The partial reduction of the imide by $NaBH_4$ provided the iminium ion precursor.

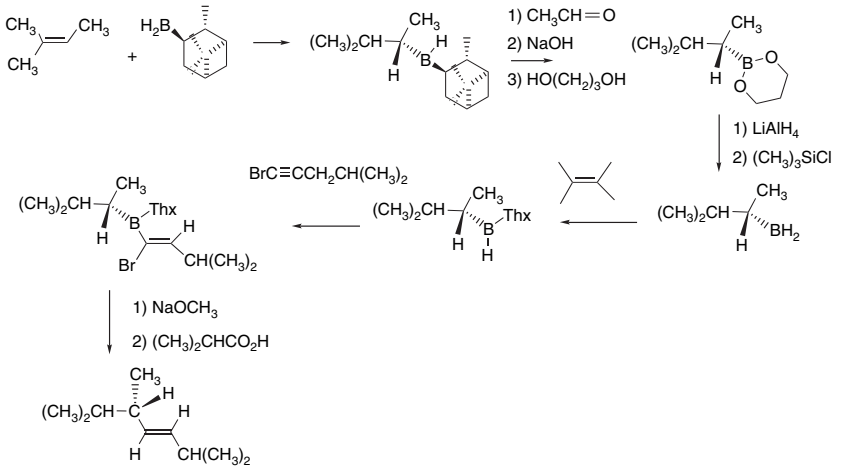


9.13. Each of these enantioselective syntheses can be done using the highly enantiomerically pure isopinocampheylborane reagents for enantioselective hydroboration (see p. 347). In each case the conditions for carbonylation or alkene synthesis can then be applied.

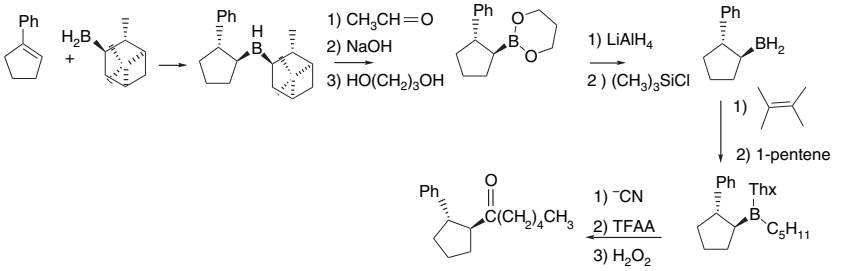
a. The product of hydroboration of 1-methylcyclopentene was converted to the corresponding cyclic boronate ester. The carbonylation was done using lithiated phenylthiomethyl methyl ether, with migration effected by mercuric chloride.



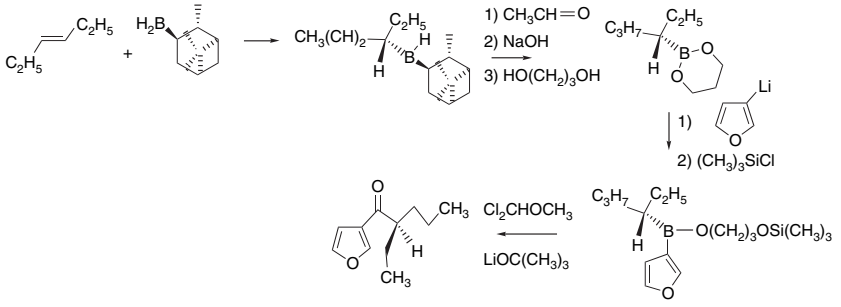
b. Synthesis of this alkene was done by generating an enantiopure monoalkylthexylborane, which was then used in stereospecific synthesis of the *E*-alkene by hydroboration of a bromoalkyne and protonolysis (p. 797).



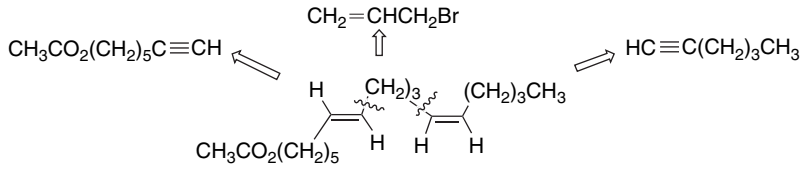
c. This transformation was accomplished by preparation of a dialkylthexylborane by use of 1-phenylcyclopentene and pentene following the sequence outlined in (b). The ketone was then obtained by carbonylation using either CO or the cyanide-TFAA method. In the specific case cited, the CN-TFAA method gave a 75% yield of product with 99% e.e..



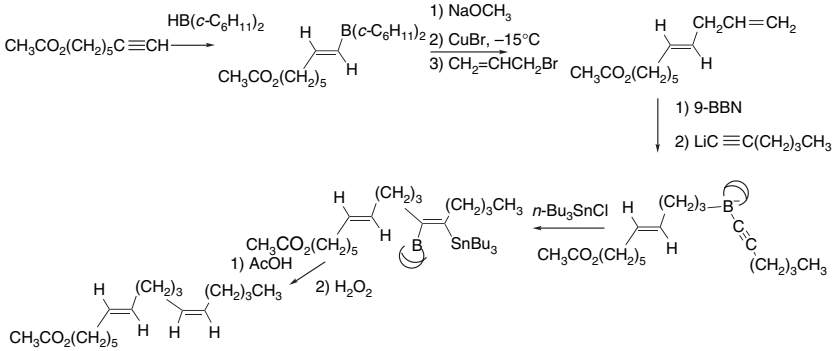
d. This synthesis involves the introduction of a group that cannot form organoboranes by hydroboration. The method also relies on an enantioselective hydroboration and conversion to enantiomerically pure 1,3,2-dioxaborinanes. An adduct was then formed with an organolithium reagent. The adduct reacts with $(CH_3)_3SiCl$ to give opening of the oxaborinane ring. The resulting borinate ester was carbonylated using dichloromethyl methyl ether and LiO-*t*-Bu.



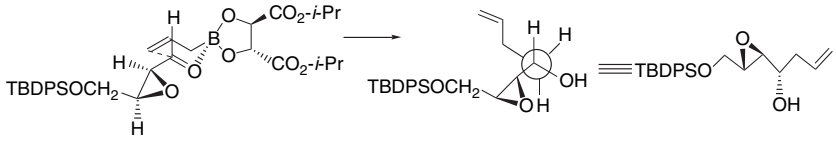
9.14. Retrosynthetic analysis relates three segments of the synthetic target to the potential starting materials.



The required *E*-stereochemistry at the 5,6-double bond was achieved by hydroboration followed by allylation through a cuprate intermediate. The terminal double bond was then selectively hydroborated by 9-BBN. The hexyne segment was introduced via an "ate" adduct. A stereospecific migration was induced by tri-*n*-butylstannyl chloride. Chemoselectivity in the migration was achieved by heating, which results in migration of the acyclic group. Both the stannyl and the boron substituent were removed by protonolysis with retention of the *Z*-double-bond configuration.

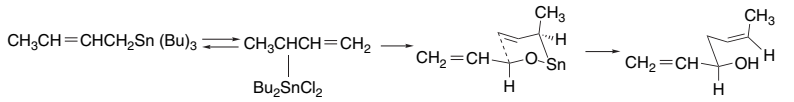


9.15. a. This is an example of use of a tartrate-derived boronate. The reaction would be expected to proceed through a chair transition structure. The observed diastereoselectivity is 96:4, with the major product exhibiting greater than 96% e.e.

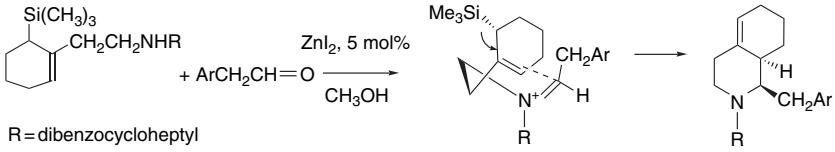


b. The use of a mixture of the isomeric stannanes and a relative long reaction time at room temperature suggests that the most likely product might be that derived from the most stable adduct. The use of a relatively stable aldehyde, acrolein, also suggests that equilibration might be favorable. Furthermore the use of 1.5 equivalents of the dihalostannane reagent suggests that exchange and a cyclic transition structure would be feasible. Note also that there is no net allylic inversion, which is consistent with allylic shift during both the transmetallation and the cyclization. The observed product is nearly exclusively (> 99%) *Z*. This would be the product if the butenyl methyl group occupied an *axial*

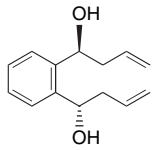
position in the cyclic transition structure and would indicate that steric effects with the stannyl substituents control the stereoselectivity.



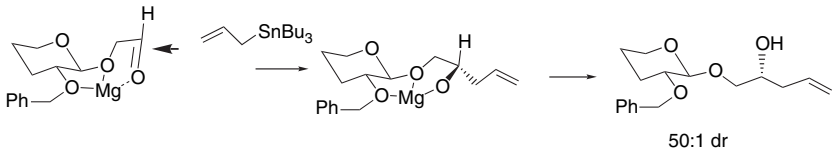
c. This reaction was used as part of an enantioselective synthesis of morphine. The stereoselectivity depends on the steric bulk of the dibenzocycloheptyl group, which promotes cyclization through the *anti* iminium ion (see Problem 9.6d).



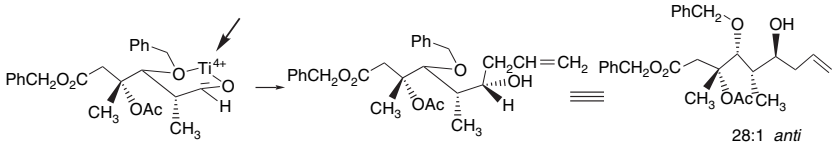
d. The enantioselectivity of this *bis*-allylation is determined by the isopinocampheyl group. The product is the *s*,*s*-enantiomer.



e. The use of four equivalents of $MgBr_2$ suggests that the aldehyde would be chelated. A tridentate chelate involving the aldehyde oxygen, the α-oxygen, and the benzyloxy oxygen exposes a convex face that should lead to high facial selectivity, as is observed.

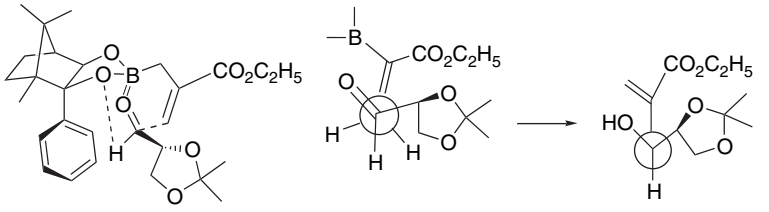


f. The β -benzyloxy group would be expected to lead to chelation control with $TiCl_4$. This is consistent with the observed 28:1 diastereoselectivity for the *anti* isomer.

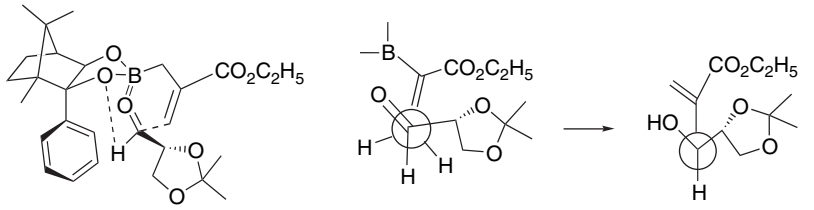


9.16. An organizing feature with this boronate is proposed to be the orientation of the formyl hydrogen toward a boronate oxygen. Within this framework, the

orientation of the dioxolane ring is more favorable when directed away from, rather than toward, the phenyl substituent.

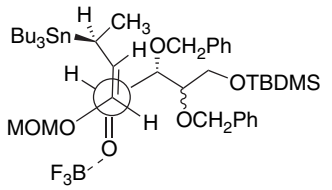


transition structure for *anti* product from *S*-aldehyde

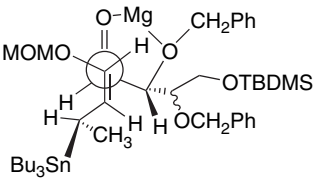


transition structure for *syn* product from *R*-aldehyde

9.17. The $MgBr_2$-promoted reactions would be expected to proceed through chelated transition structures. The BF_3-promoted reactions would be expected to react through an open transition structure, with a preferred Felkin approach. These transition structures are consistent with the observed stereoselectivity. Both of these transition structures lead to the *syn* configuration at the new bond, but they show opposite facial selectivity with respect to the aldehyde. The facial selectivity with respect to the aldehyde is governed by the configuration of the stannane and the requirement for *anti* orientation of the stannyl group with respect to the newly forming bond.



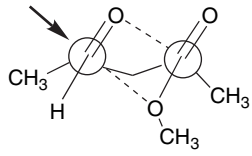
S-enatiomer
Open transition structures for BF_3-promoted reactions.



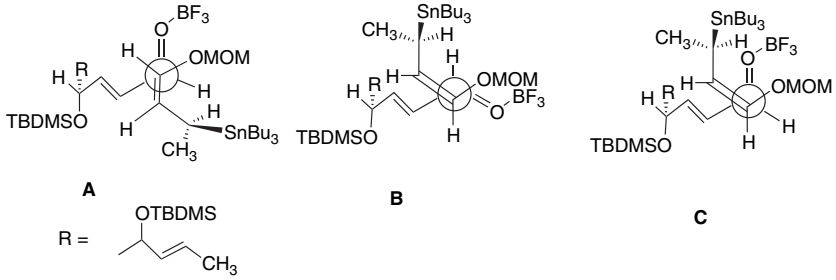
R-enantiomer
Chelated transition structures for $MgBr_2$-promoted reactions

9.18. The proposed chelate is contrary to considerable evidence that BF_3 reacts only through tetracoordinate species and cannot accommodate a second ligand from the reactant. Subsequently it was shown that this ω-formyl ester has a strong conformational preference, attributed to polar interactions between the two carbonyl groups. Evidently neither one nor two equivalents of BF_3 disrupts this

conformation, whereas three do. The compound shows the same stereoselectivity to allylic boron reagents.

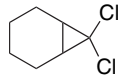


9.19. The transition states **A, B**, and **C** account for the three products. TS **A** has the enal in the *s-cis* conformation and involves approach *anti* to the group R. The TS is of the antiperiplanar type and shows the stereoelectronic preference for the C–Sn bond to be *anti* to the forming bond. In TS **B**, the enal is in the *s-trans* conformation. The approach is *anti* to R and the TS is antiperiplanar. In TS **C**, the enal is in the *s-cis* conformation and attack is *anti* to R. The TS is of the synclinal type. The results suggest that the most important feature, which is present in all three TSs, is the *anti* relationship between the C–Sn bond and the forming bond. The secondary factors are *s-cis*>*s-trans* and antiperiplanar>synclinal.

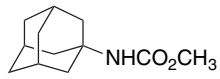


Chapter 10

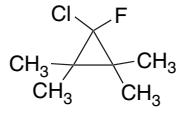
10.1. a. These are phase transfer conditions for generation and addition of dichlorocarbene to cyclohexene. A 77% yield was obtained.



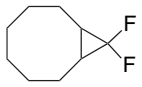
b. These conditions lead to the C–H insertion products. The reactivity ratio is about 7:1 in favor of the bridgehead C–H group relative to the CH_2 groups. The conversion and total yield were not reported.



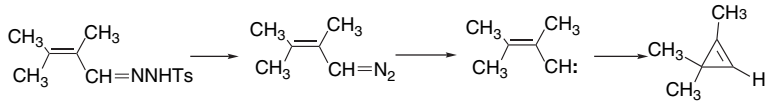
c. These conditions generate chlorofluorocarbene by lithiation–α-elimination. The addition product was obtained in 49% yield.



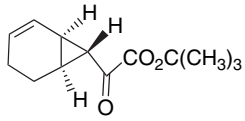
d. Decomposition of this organomercury compound leads to formation of difluorocarbene. The addition product with cyclooctene was obtained in 83% yield.



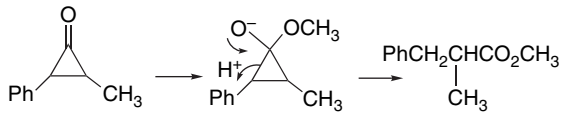
e. These conditions led to formation of the corresponding diazo compound and alkenylcarbene. The isolated product was 1,2,3-trimethylcyclopropene (72%), formed by cyclization of the carbene.



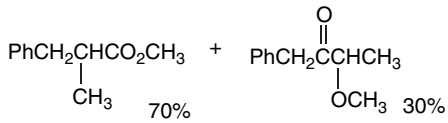
f. The isolated product results from a single carbenoid addition. The precise conditions are not specified but presumably the amount of reagent was limited to avoid addition at both double bonds.



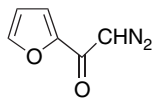
g. These conditions led to Favorskii rearrangement. The rearrangement product results from formation of the more stable enolate from the presumed cyclopropanone intermediate.



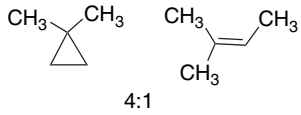
A by-product formed by solvolysis was isolated.



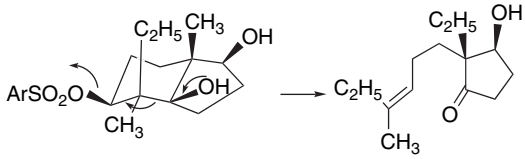
h. These are conditions for formation of a diazomethyl ketone from an acyl chloride.



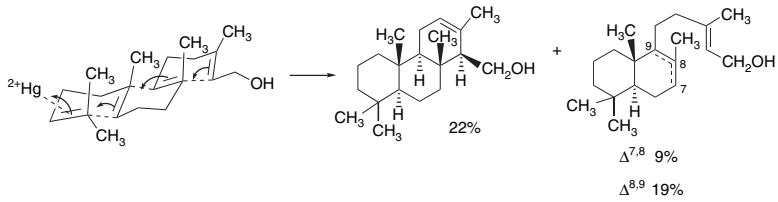
i. The photolysis of this diazirine generates 2,2-dimethylpropylidene, which undergoes intramolecular insertion or rearrangement. A 4:1 mixture of 1,1-dimethylcyclopropane (insertion) and 2-methyl-2-butene (rearrangement) was isolated.



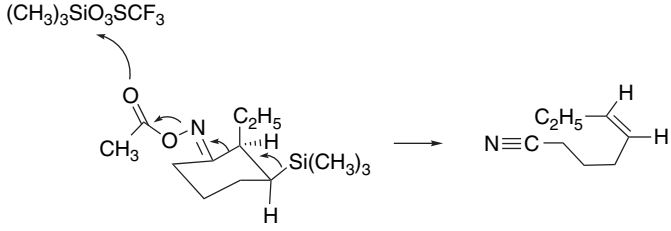
j. These conditions result in stereospecific fragmentation with formation of the *Z*-double bond.



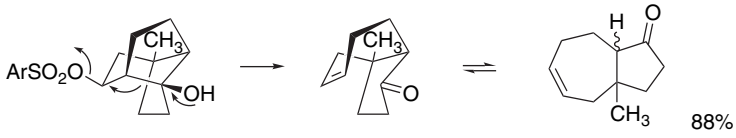
k. These conditions led to mercuric ion-mediated cyclization. The tricyclic product was obtained in 22% yield and two isomeric bicyclic products were also isolated. The cyclic mercurio intermediates were reduced by $NaBH_4$.



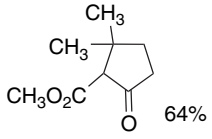
l. The trimethylsilyl substituent promotes fragmentation. The reaction is stereospecific, forming the *Z*-double bond from the *cis* isomer and the *E*-double bond from the *trans* isomer. As the trimethylsilyl group is regenerated in the fragmentation, a catalytic amount of the reagent suffices.



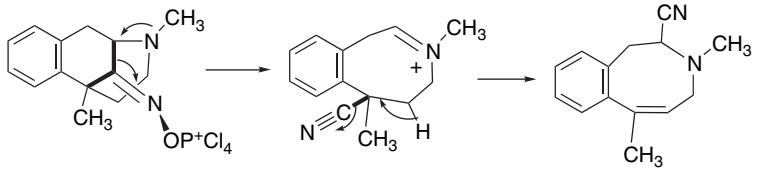
m. These conditions led to fragmentation of the γ-hydroxy sulfonate. The bicyclic ketone was isolated as a 3:2 mixture of stereoisomers, presumably because of subsequent isomerization via an enolate.



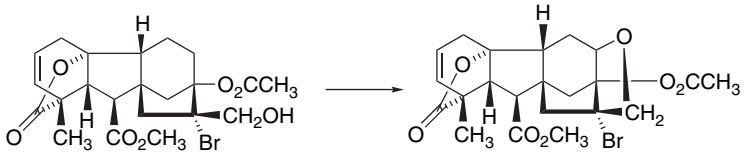
n. These conditions led to a five-membered product by carbene insertion.



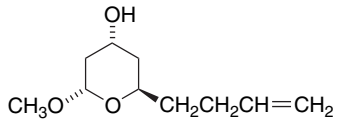
o. The overall change corresponds to dehydration. The amino nitrogen can assist in fragmentation of the oxime. The tertiary benzylic cyanide was evidently ionized under the acidic condition and captured by the iminium ion to form an α-cyano amine, which was isolated in 59% yield.



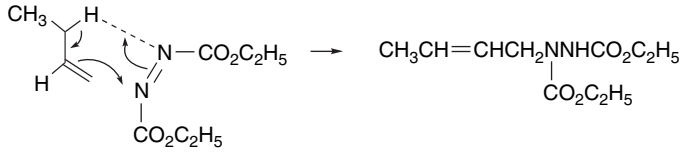
p. These conditions led to a tetrahydrofuran ring by hydrogen abstraction and cyclization. Only one position is in a feasible steric relationship. The product was isolated in 70% yield.



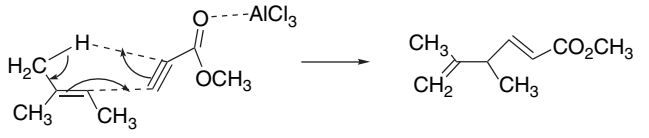
q. These conditions led to allylation at the thionocarbonate site. The product was isolated in 82% yield.



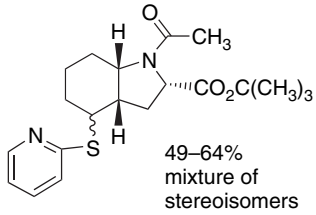
r. This is an ene reaction.



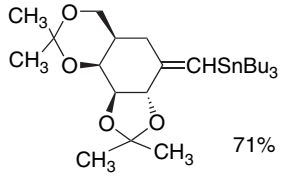
s. This is a Lewis acid–catalyzed ene reaction.



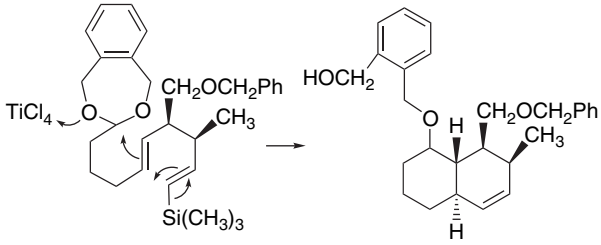
t. The radical generated by photolysis of the thiopyridyl ester undergoes a 5-*exo* cyclization with a *cis* ring fusion. The chain transfer step is not stereospecific.



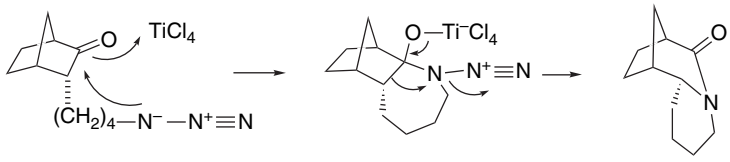
u. The reaction is initiated by attack on the alkyne by the stannyl radical. The substitution pattern favors a 6-*exo* cyclization. The hydrogen transfer step is stereoselective and leads to the *cis* ring fusion.



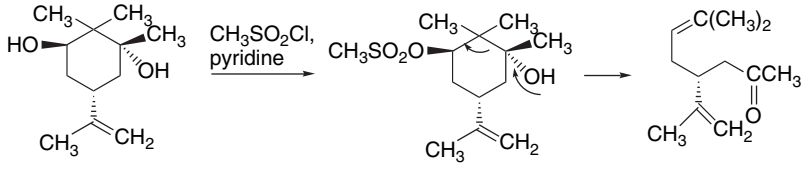
v. The dioxepane acetal reacts with $TiCl_4$, generating a stabilized carbocation that initiates a polyene cyclization, which is terminated by desilylation of the vinyl silane. The ring junction is *trans.*



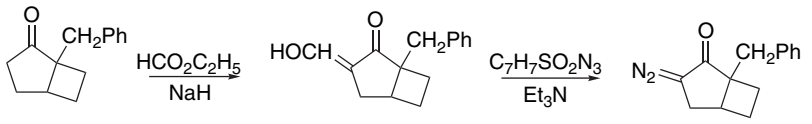
w. An intramolecular Schmidt-type reaction occurs in 97% yield.



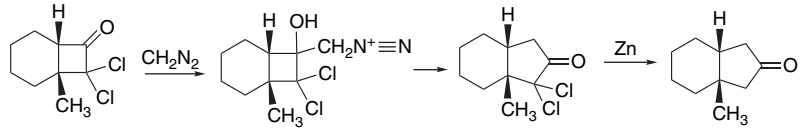
x. Selective mesylation occurs at the less hindered secondary alcohol group. Base causes a fragmentation.



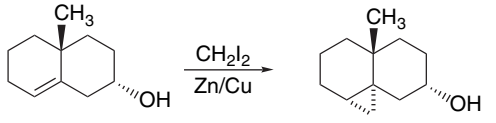
10.2. a. This transformation requires a diazo transfer. Various methods would be feasible, but the cited reference used a two-step sequence of formylation, then reaction with tosyl azide.



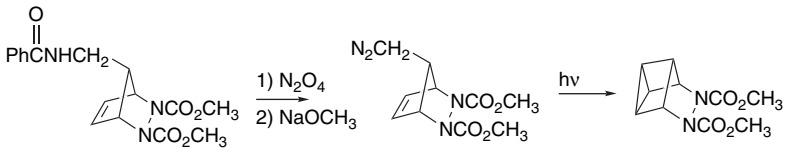
b. This ring expansion was done using diazomethane, followed by zinc reduction to remove the chlorines. The inductive effect of the chlorines presumably disfavors migration and leads to the observed regioselectivity. The inductive effect of the chlorines also enhances the reactivity of the carbonyl group in the addition step.



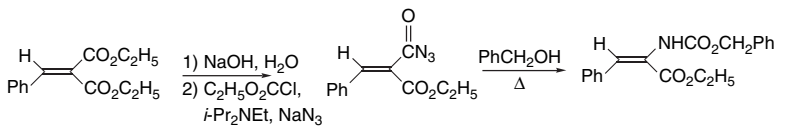
c. This transformation corresponds to a hydroxy-directed cyclopropanation. It was done under standard Simmons-Smith conditions, but other conditions (see p. 918) should be applicable.



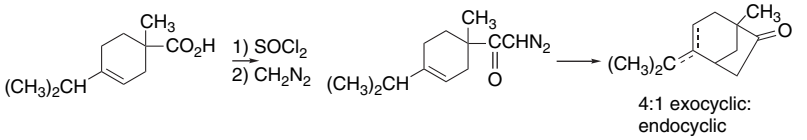
d. This transformation requires an intramolecular cyclopropanation. The amido group was nitrosated and converted to a diazo compound by base. The cyclopropanation was done by photolysis in 44% yield.



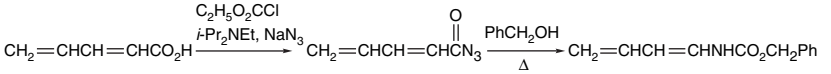
e. This transformation requires selective hydrolysis at one of the ester groups followed by a Curtius or similar C→N rearrangement. The differential steric environment facilitates selective hydrolysis, and the ethyl chloroformate activation procedure (see p. 948) was used to form the acyl azide, which was then thermolyzed in benzyl alcohol.



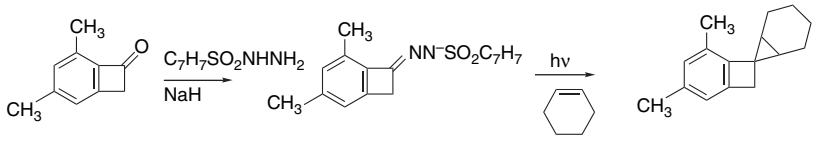
f. This transformation requires a cyclization with addition of a methylene group and was accomplished via a diazomethyl ketone, which gave rise to a mixture of the exocyclic and endocyclic isomers on treatment with BF_3. The kinetic preference is for the exocyclic isomer, but equilibration with the endocyclic isomer gives a 1:1, mixture.



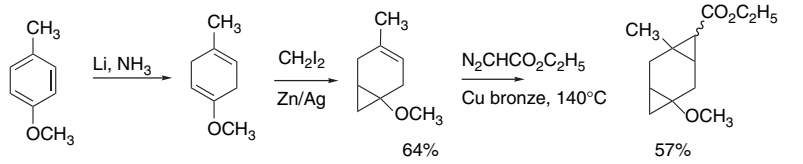
g. This requires a carboxylic acid to carbamate transformation and was done using a Curtius rearrangement. The acyl azide was prepared by the ethyl chloroformate activation procedure.



h. The transformation requires generation of a carbene from the carbonyl group and addition to cyclohexene. The reaction was done in 55% yield via photolysis of the tosylhydrazone salt. The transformation was also done in 22% yield by treatment of the dichlorobenzocyclobutane with *n*-BuLi.

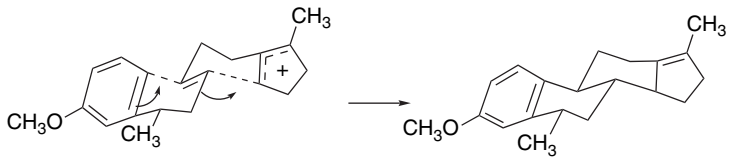


i. Several steps are required for this transformation. The two cyclopropane rings suggest carbenoid addition to a cyclohexadiene derivative, which could be obtained by Birch reduction from the starting material. The required regioselectivity can be achieved by taking advantage of the enhanced reactivity of the vinyl ether double bond. The transformation was accomplished by successive cyclopropanations using a modified Simmons-Smith reaction, followed by a copper-catalyzed carbenoid addition of ethyl diazoacetate. The yield could probably be improved by using more recently developed catalysts.

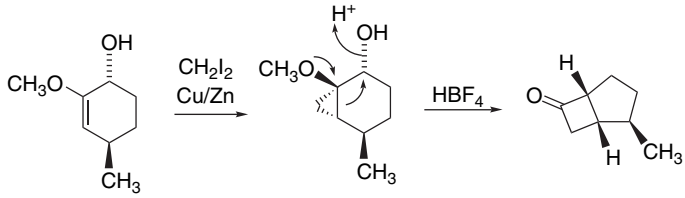


j. This transformation corresponds to a polyene cyclization. The initiation was done by ionization in the prospective D ring and was terminated by an electrophilic aromatic substitution. In the cited reference, use of three to five equivalents of $SnCl_4$ gave a 58% yield of the product shown, along with 10% of the *ortho* substitution product. The product is a 9:1 mixture

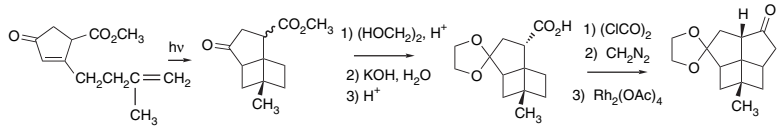
of β:α stereoisomers at C(6) methyl group. Note that the initiating allylic carbocation, which is unsymmetrical, evidently reacts at its less-substituted carbon.



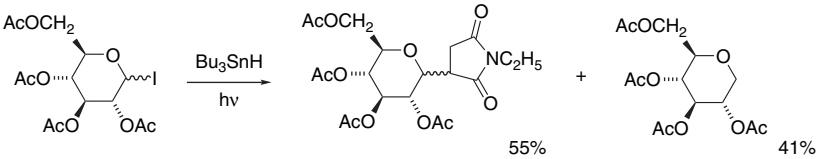
k. This transformation was accomplished by cyclopropanation followed by a specialized pinacol-type rearrangement. The rearrangement takes advantage of the high reactivity of the cyclopropyl carbinol structure present in the intermediate.



l. Several steps are required for this transformation. The key steps were a carbenoid insertion and a photochemical (2 + 2) photocycloaddition. The carbenoid insertion was done using a $Rh_2(O_2CCH_3)_4$ catalyst and conforms to the favorable five-membered ring formation.

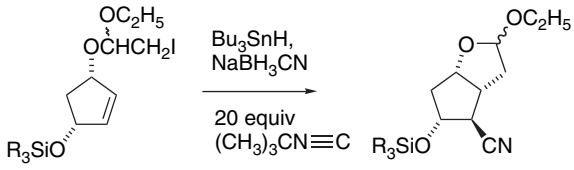


m. This transformation requires addition to a maleimide group at the anomeric position of a protected iodo pyranose. *N*-Ethylmaleimide is a suitable acceptor for radical addition and the reaction was done by photolytic initiation of reaction with tri-*n*-butylstannane. The reaction is not very stereoselective and the reduction product is also formed to a significant extent.

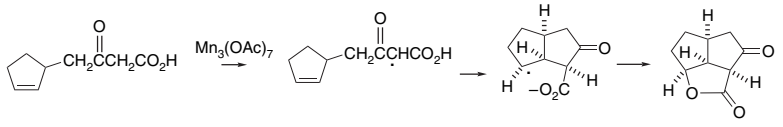


n. This is an example of the use of an iodoacetaldehyde acetal for ring formation. In this particular case, the chain transfer was done using a 20-fold excess of *t*-butyl isocyanide, which introduces a cyano substituent.

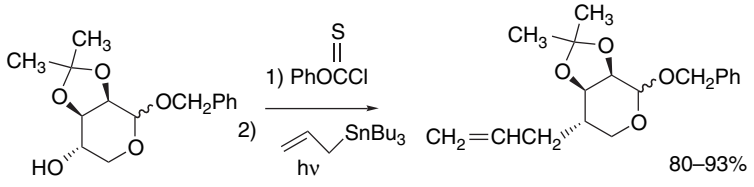
The overall transformation establishes a prostaglandin-type substitution pattern.



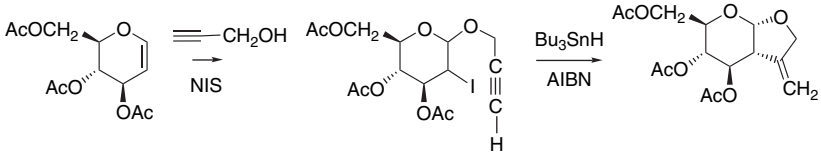
o. This transformation was accomplished in a single step by a $Mn_3(O_2CCH_3)_7$ oxidation. The radical generated at the enolic β-ketoacid site undergoes a 5-*exo* cyclization. The product radical is oxidized to a carbocation, which results in formation of a lactone by capture by the acetate group.



p. This transformation requires replacement of a hydroxy group by an allyl group and was done via allylation of the corresponding phenyl thiocarbonate using allyl-tri-(*n*-butyl)stannane. The stereochemistry is determined by ring shape.

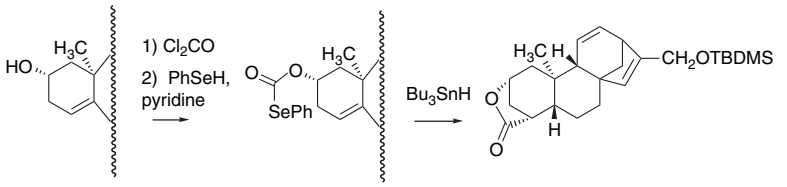


q. This annulation was done by forming a mixed acetal with propargyl alcohol. This iodosolvation step utilized *N*-iodosuccinimide and propargyl alcohol in acetonitrile. This sets up the possibility of a 5-*exo* cyclization, which was accomplished using Bu_3SnH as the hydrogen atom donor.

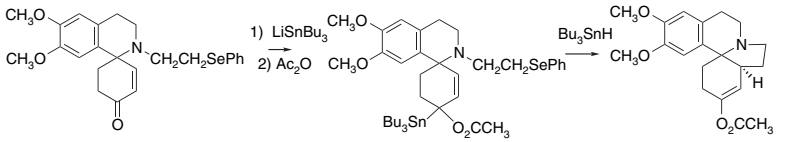


r. This transformation corresponds to the introduction and cyclization of a carbonyl group. It was effected by conversion of the alcohol to

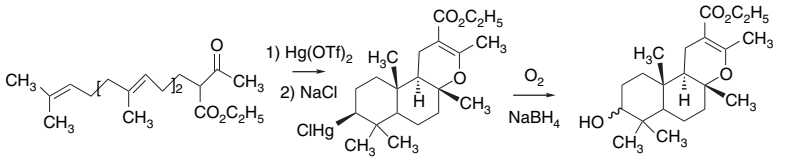
a phenylselenenyl carbonate, followed by Bu_3SnH-induced cyclization through an alkoxyacyl radical.



s. This transformation was accomplished by converting the ketone to an α-acetoxy stannane by addition of lithio tri-*n*-butylstannane, followed by acetylation. The 5-*exo* radical cyclization was then accomplished using Bu_3SnH as the chain carrier.

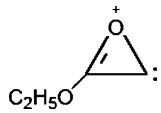


t. This reaction is a polyene cyclization that is terminated by capture of the oxygen of an enolized β-ketoester system. There might be several ways of effecting this transformation, e.g., by epoxidation and epoxide ring opening. In the cited reference, the cyclization was done with mercuric triflate, and the chloromercurio derivative was oxidized with O_2 in the presence of $NaBH_4$. (See p. 295 for this method of oxidative demercuration). The radical character of the oxidative demercuration accounts for the lack of stereospecificity at the hydroxy group.

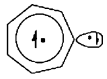


10.3. a. Application of simple Hückel MO theory suggests aromatic character for cyclopropenylidene, with the occupied sp^2 orbital in the plane of the ring. The most recent computations on this species indicate that this is the correct structure for the lowest energy form of C_3H_2.

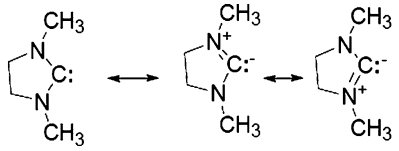
b. A very early MNDO computation on this carbene suggested that it would exist as a three-membered ring compound. There do not seem to be any more recent studies of this compound.



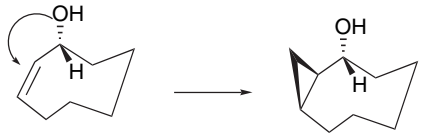
c. Like cyclopropenylidene, cycloheptatrienylidene can be formulated as an aromatic Hückel system. The most recent computations, while confirming that the singlet is the lowest-energy structure, assign an electronic configuration in which one of the nonbonded "carbene" electrons is delocalized in the π system.



d. The π-donor character of the nitrogen substituents strongly stabilizes the singlet state, making this a rather stable and nucleophilic carbene.

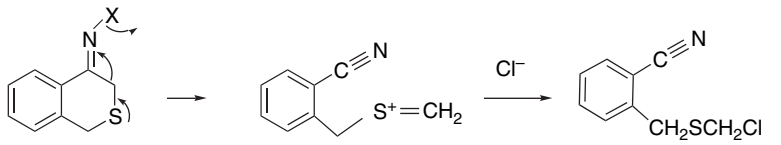


10.4. Of the several conformations available to *Z*-cyclooct-3-enol, the one shown below seems likely to be the most stable. In this conformation the hydroxy group is closer to the *anti* face of the double bond than to the *syn* face, which may account for the experimental observation that *Z*-cyclooct-3-enol gives the *trans* cyclopropane derivative. There does not seem to have been an experimental study on the conformation of *Z*-cyclooct-3-enol.

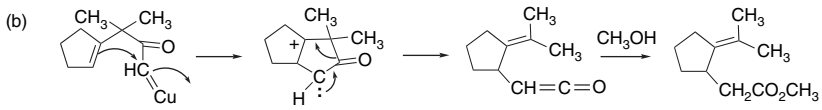


10.5. The reactions in question are pinacol rearrangements. The *t*-butyl group in these compounds imposes a strong conformational bias. It can be assumed that ionization takes place at the more reactive benzylic hydroxy group. The results indicate that an equatorial hydroxy group leads to a high preference for hydrogen migration, whereas an axial hydroxy leads to competition between ring contraction and hydrogen shift. Comparison of the two stereoisomeric benzylic carbocations indicates that an axial hydrogen is well aligned for interaction with the empty *p* orbital, facilitating a hydride shift. In the carbocation with an axial hydroxy, both the ring C–C bond and the C–H bond are approximately perpendicular to the *p* orbital and neither has a strong preference for migration.

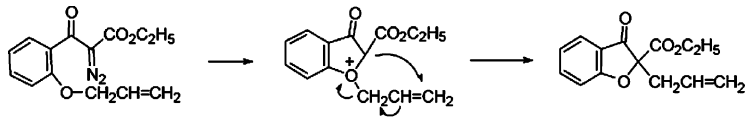
10.6. a. The product results from fragmentation, which is assisted by the sulfur substituent. A normal product would be formed by rearrangement of either the phenyl ring or thiomethylene group, leading eventually to a seven-membered lactam.



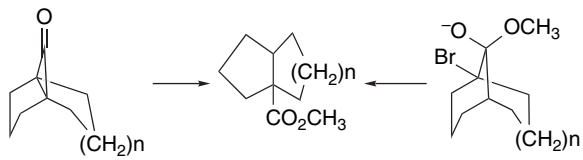
b. The observed product can be accounted for by a cyclic mechanism by which the electron-deficient carbene (or carbenoid) triggers a double-bond shift. This reaction is consistent with an electrophilic attack on the double bond by the metal carbene. The conditions suggest a carbenoid decomposition, which would most likely lead to insertion at C(5) in the cyclopentene ring; an addition at the double bond leads to a strained-ring system and is less likely.



c. The observed product can be accounted for by formation of an oxonium ylide that undergoes a [2,3]-sigmatropic shift. A normal product for the carbene might be insertion at the methylene group (six-membered ring) or cyclopropanation at the double bond (seven-membered ring).



10.7. The distinction between the two mechanisms lies in the symmetry of the cyclopropanone intermediate. It should lead to equivalence of the bridgehead protons and the matching pairs of methylene groups in the bridges. The semibenzilic mechanism would not lead to this equivalence.

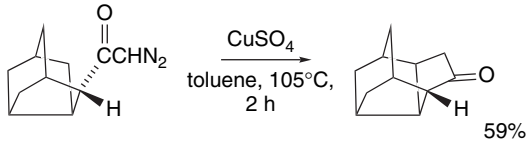


cyclopropanone intermediate is symmetrical — product — nonsymmetrical intermediate in semibenzylic mechanism

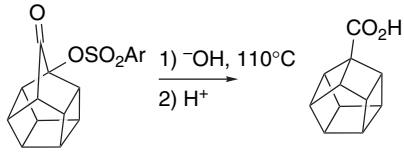
There would be several ways to test for the involvement of a symmetrical intermediate. The bromoketone can be prepared in enantiomerically enriched form. The product should be racemic if the cyclopropanone mechanism operates,

but not if the semibenzilic mechanism operates. Any of the potentially equivalent methylene groups could be isotopically labeled, and the distribution of label examined for evidence of scrambling via a symmetrical intermediate. The cyclopropanone mechanism requires proton exchange with the solvent at the bridge juncture, whereas the semibenzilic mechanism does not. In the cited reference, both the racemization and solvent (deuterium) incorporation studies were performed. NaOD in EtOD lead to both racemization and deuterium incorporation for $n = 3$, consistent with a cyclopropanone mechanism. For similar ketones with smaller bridges ($n = 1, 2$) only the semibenzilic mechanism was observed under these conditions, presumably because of the greater strain of the cyclopropanone intermediate in these cases.

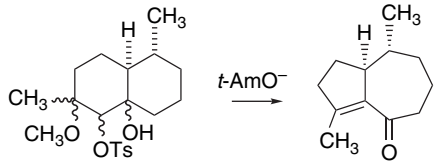
10.8. a. This reaction led to carbenoid insertion at C(4). Under the cited conditions a 59% yield was obtained, but this could probably be increased with one of the more recently developed catalysts.



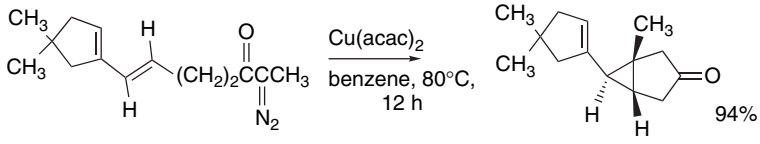
b. This reaction led to a Favorskii-type rearrangement.



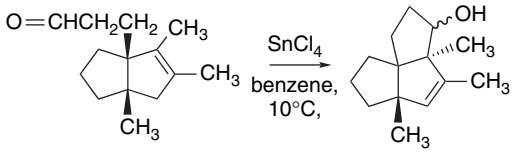
c. The β-hydroxy tosylate undergoes a directed pinacol rearrangement. In this case, β-elimination of the methoxy group also occurs.



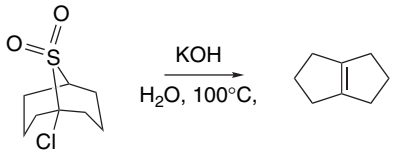
d. Cyclopropanation of the more proximate double bond occurs. The product was obtained in 94% yield.



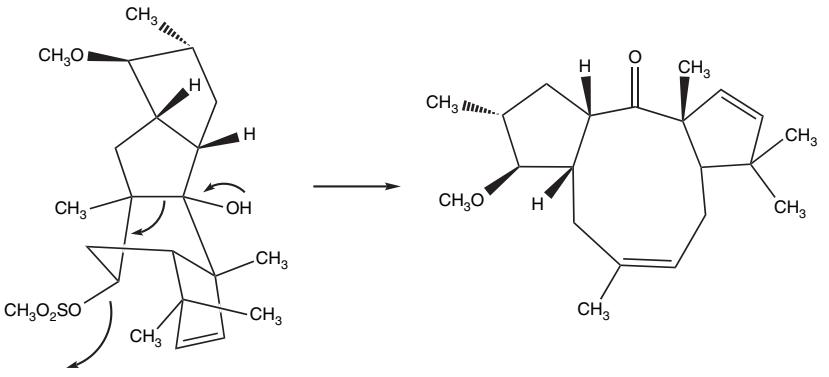
e. These conditions led to the carbonyl-ene cyclization product in 95% yield.



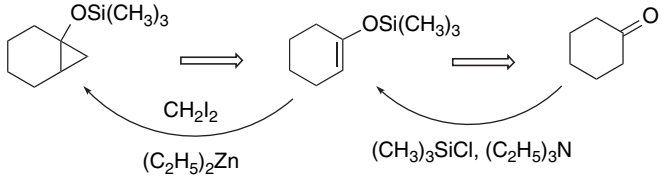
f. These conditions led to a Ramberg-Backlund reaction.



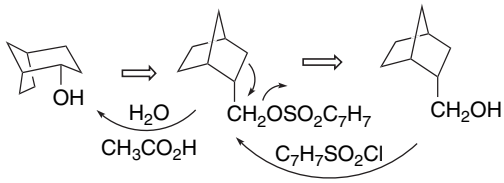
g. The stereochemistry of this system is such that monotosylation of the less hindered hydroxy group is followed by fragmentation to form a nine-membered ring.



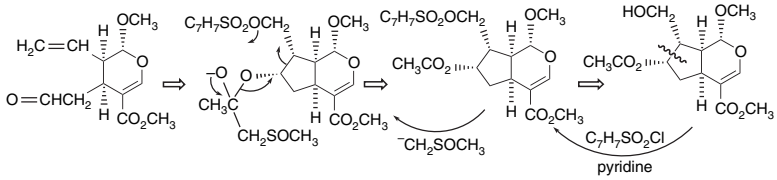
10.9. a. The desired product can be recognized as the product of methylenation of the trimethylsilyl enol ether of cyclohexanone. The reported synthesis used CH_2I_2 and $(C_2H_5)_2Zn$ for the methylenation.



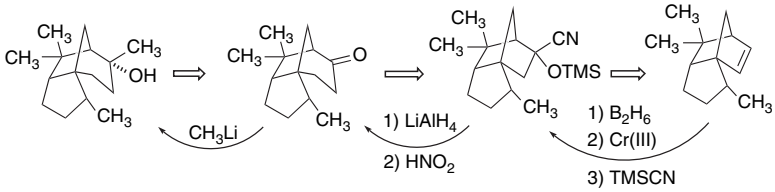
b. This system is stereoelectronically aligned to favor a ring expansion. The transformation was done by tosylation and hydrolysis.



c. The reaction involves a fragmentation at the marked bond. Tosylation of the primary alcohol followed by base treatment effected the desired transformation. Of several bases tried, the anion of dimethyl sulfoxide was best. The fragmentation presumably occurs from the tetrahedral intermediate formed at the acetoxy group.

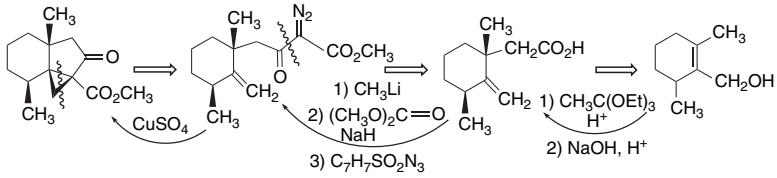


d. This transformation requires that the double bond serve to introduce the methyl and hydroxy groups and to add a carbon to the ring. The sequence shown corresponds to the last several steps in a synthesis of a sesquiterpene, cedrol. A carbonyl center was established by hydroboration and oxidation. This ketone was then ring expanded through the cyanohydrin, which was made using trimethylsilyl cyanide. The ring expansion was done by nitrosation after reduction of the cyano group to a primary amine. The methyl group was then added by reaction with methyllithium. This sequence does present an issue of regioselectivity in the ring expansion. The alternate ketone resulting from rearrangement of the bridgehead carbon was observed as a by-product.

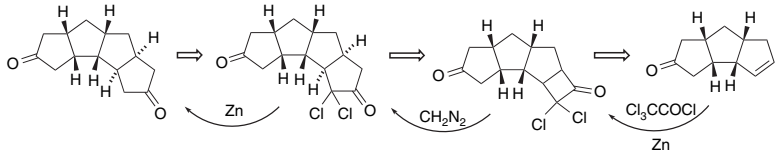


e. The first retrosynthetic step identifies an intramolecular carbenoid addition of a α-diazo-β-ketoester. The corresponding ester is the product of [3,3]-sigmatropic rearrangement of the identified starting material. The synthetic transformation was accomplished by an orthoester Claisen rearrangement,

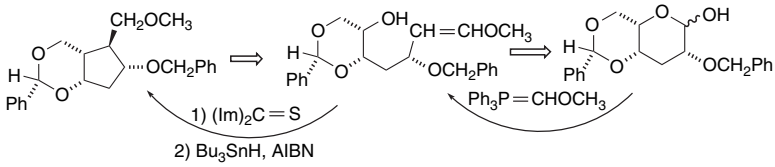
hydrolysis, conversion to the methyl ketone with methyllithium, methoxycarbonylation, diazo transfer, and copper-catalyzed cyclopropanation.



f. This transformation requires a cyclopentene to cyclopentanone annulation. One protocol for this transformation involves dichloroketene cycloaddition, ring expansion with diazomethane, and reduction of the dichloroketone with zinc. The dichloroketene cycloaddition is not regioselective, giving a 1:1 mixture of isomers, but this is not a problem, because the subsequent migration and reduction gives the desired product from both isomers. The reaction is stereoselective because of approach of the dichloroketene from the less hindered convex face.

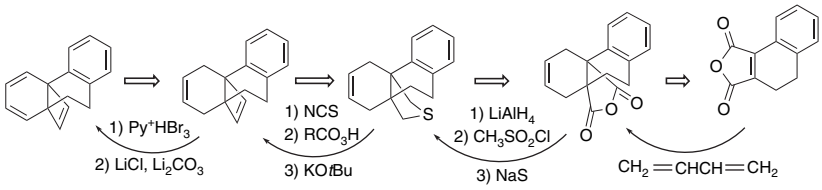


g. This transformation involves extrusion of the oxygen of the pyran ring and formation of a C–C bond. The reaction sequence was accomplished by a Wittig reaction of the hemiacetal with methoxymethylenetriphenylphosphorane, followed by a stannane-mediated 5-*exo* radical cyclization. Note that the overall sequence converts a 3-deoxypyranoside to the substitution pattern of the prostaglandins.

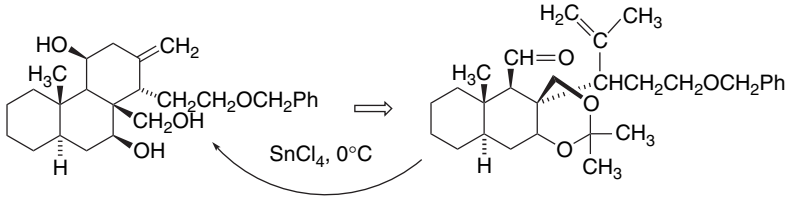


h. This conversion requires formation of a relatively strained cyclobutene. An efficient transformation depends on recognizing that the maleic anhydride unit has the potential for introduction of both the cyclohexadiene ring (by a Diels-Alder reaction) and conversion to a cyclobutene (via a Ramberg-Backlund reaction on the corresponding thiolane dioxide). In the reported sequence, the Diels-Alder reaction was done first. The anhydride moiety was then converted via a sulfide to the thiolane dioxide and the cyclobutene ring

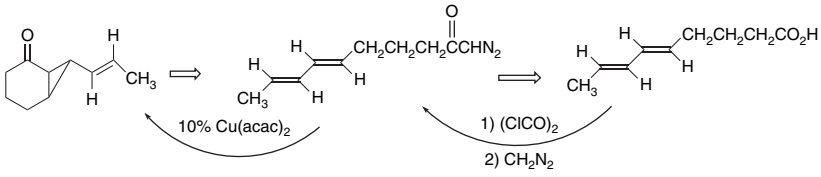
introduced. The cyclohexene ring was then converted to a cyclohexadiene by bromination–double dehydrobromination.



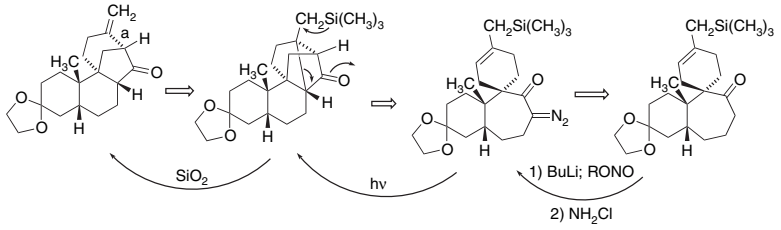
i. This transformation corresponds to a carbonyl-ene reaction and was effected with $SnCl_4$. These conditions also lead to removal of the acetonide protecting group.



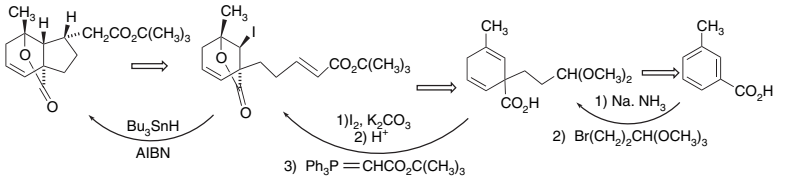
j. This transformation corresponds to an intramolecular carbenoid addition. The carboxylic acid was converted to the diazomethyl ketone by a standard method. The cyclopropanation was done using $Cu(acac)_2$ as the catalyst.



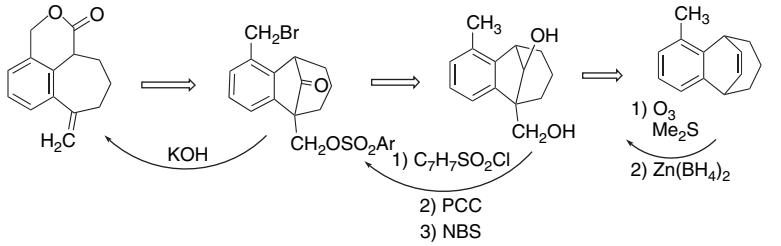
k. This transformation requires ring contraction, formation of a new bond (marked a) and disilylation. The reaction is believed to proceed through a cyclobutanone formed by intramolecular cycloaddition of a ketene intermediate. The sequence began with α-oximation and conversion to the α-diazoketone. The diazoketone was then photolyzed. Rupture of the extraneous ring was done by exposure to silica and is promoted by desilylation.



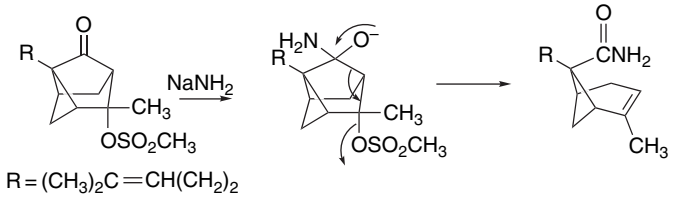
l. This reaction sequence used a Birch reduction-alkylation (see Section 5.5.1.2) to convert the starting material to the first intermediate. Iodolactonization then provides the second intermediate. The side chain was then modified by a Wittig reaction to provide an intermediate that can be converted to the desired product by a radical cyclization.



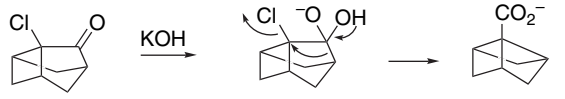
m. The double bond was ozonized. The resulting dialdehyde undergoes intramolecular aldol addition. The aldol was reduced to a diol, which was then treated with *p*-toluenesulfonyl chloride, which leads to selective sulfonylation of the primary alcohol. The secondary alcohol was then oxidized to a ketone. Benzylic bromination, followed by treatment with base, leads to fragmentation. The carboxylate group formed by fragmentation cyclizes at the benzylic position.



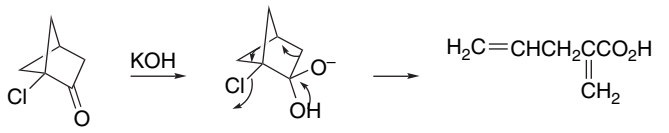
10.10. a. This reaction occurs by fragmentation of the intermediate resulting from addition of amide ion at the carbonyl center.



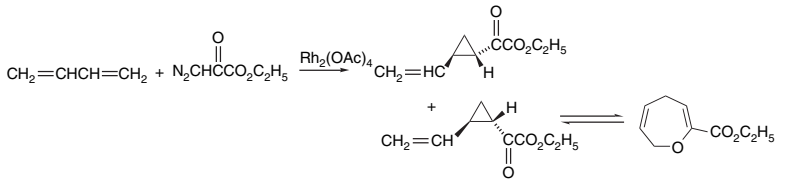
b. This ring contraction occurs by the semibenzilic version of the Favorskii rearrangement.



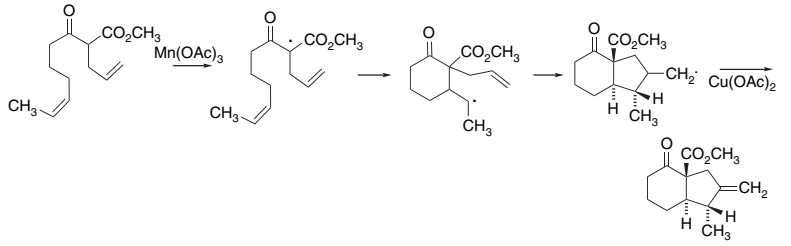
c. This is a fragmentation reaction proceeding through the hydroxide adduct of the carbonyl group.



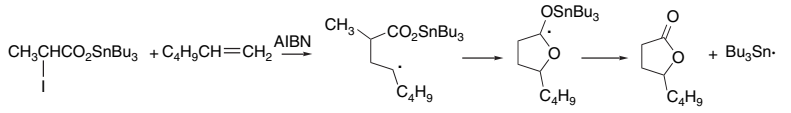
d. This reaction involves carbenoid addition, but in the case of the *cis*-vinyl derivative the electrocyclic equilibrium favors the dihydrooxepin ring.



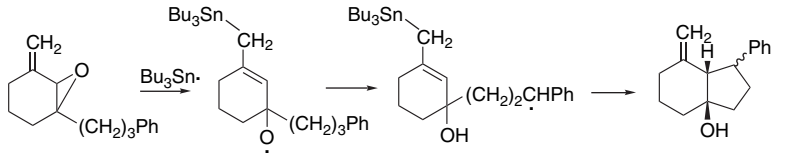
e. This transformation can occur by a tandem 6-*endo*–5-*exo* cyclization of the radical oxidatively generated at the reactive enolic site. The reaction sequence is terminated by Cu(II) oxidation. The stereoselectivity of the 5-*exo* cyclization results from avoidance of a *cis*-diaxial interaction between the methyl and carbomethoxy groups.



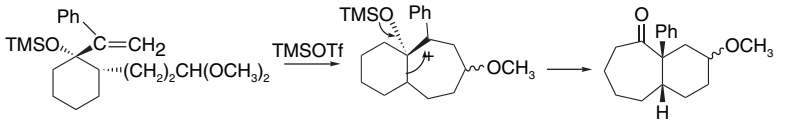
f. This reaction involves addition and cyclization at the carbonyl group of the stannyl ester.



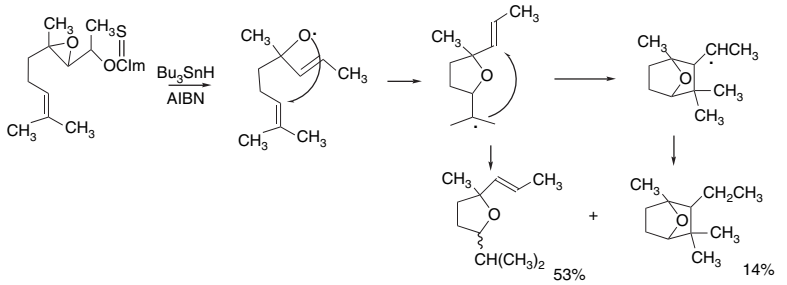
g. Stannyl radical addition leads to formation of an oxy radical by epoxide cleavage. Hydrogen atom transfer then gives a benzylic radical that cyclizes to the observed product.



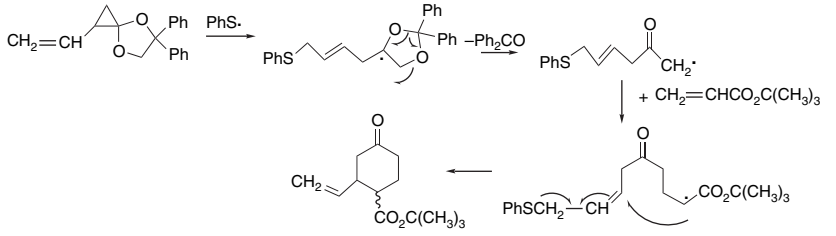
h. This transformation involves two main steps: a cationic cyclization initiated by ionization at the acetal center, followed by a pinacol-type rearrangement that leads to the ring expansion.



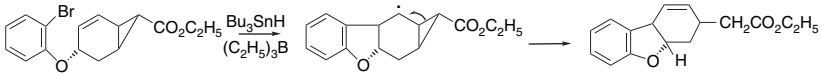
i. The reaction occurs via a radical intermediate and involves fragmentation of the epoxide ring. The alkoxyl radical undergoes intramolecular 5-*exo* addition and most of it is reduced at that stage to form the major product. The minor product arises from a second 5-*exo* cyclization.



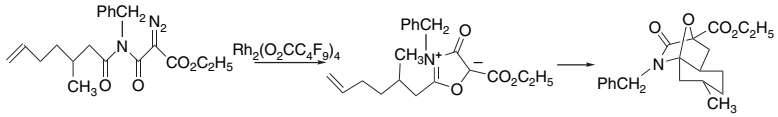
j. This reaction occurs by initial attack of the phenylthiyl radical at the terminal double bond, resulting in fragmentation of the cyclopropane ring and generation of a dioxanyl radical. This radical fragments with loss of benzophenone prior to capture by the acrylate. 6-*Exo* cyclization then occurs and the sequence is terminated by elimination of the phenylthiyl radical, which can initiate a new chain.



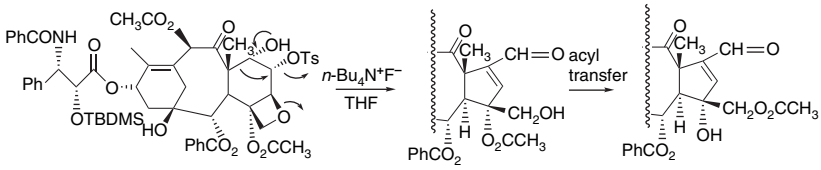
k. This reaction involves a 5-*exo* cyclization, followed by fragmentation of the cyclopropane ring. The sequence is completed by hydrogen atom transfer.



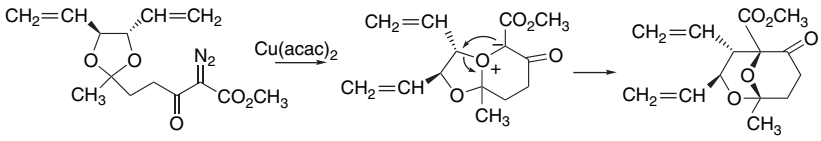
l. This reaction proceeds by formation of a cyclic oxazolium ylide, which undergoes cycloaddition.



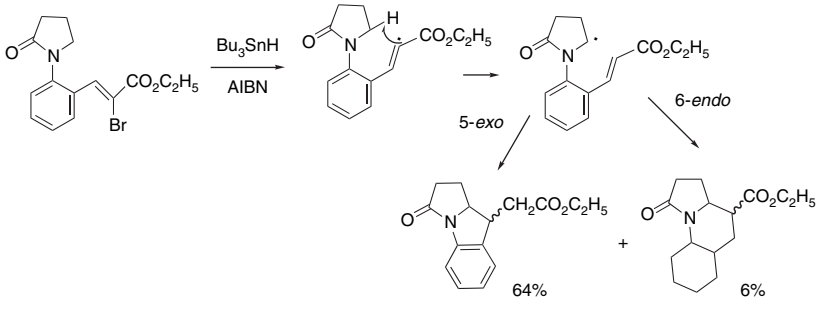
m. This reaction occurs by pinacol rearrangement, followed by opening of the oxetane ring by β-elimination. An acyl transfer then occurs from the tertiary to the primary hydroxy group.



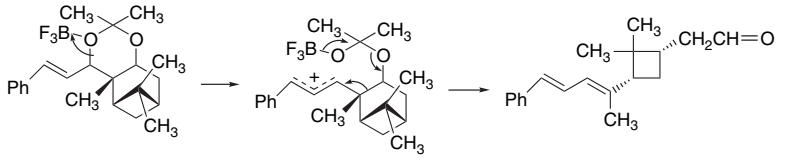
n. This reaction can be accounted for by formation of an oxonium ylide intermediate that then rearranges.



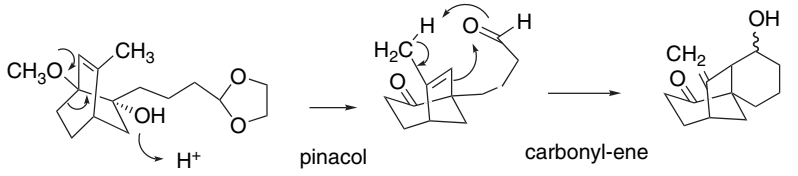
o. The products are 5-*exo* (major) and 6-*endo* (minor) cyclization products of a radical resulting from a 1,6-hydrogen atom transfer reaction of the radical formed by debromination.



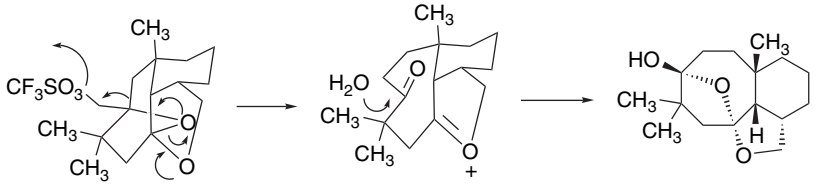
p. Lewis acid–catalyzed opening of the dioxane ring gives an allylic carbocation that can undergo fragmentation to the observed product.



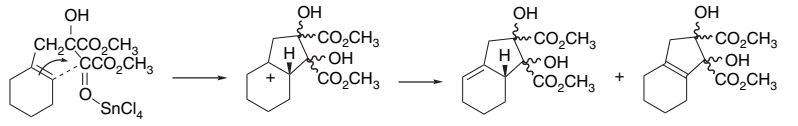
q. This transformation involves a pinacol rearrangement followed by an carbonyl-ene reaction.



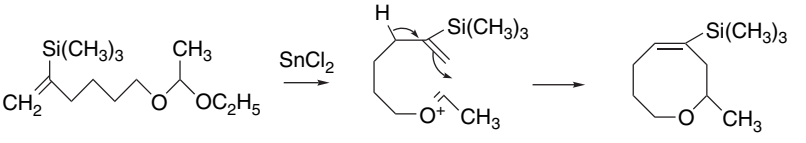
r. The oxygen atoms can participate in a tandem pinacol rearrangement-fragmentation. Addition of water to the carbonyl group results in cyclization to an acetal.



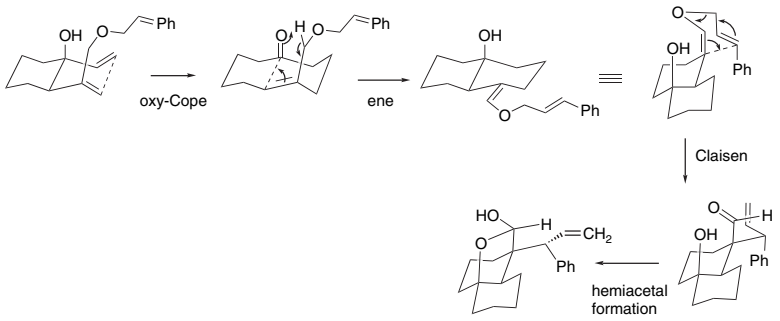
s. The transformation is an ene reaction.



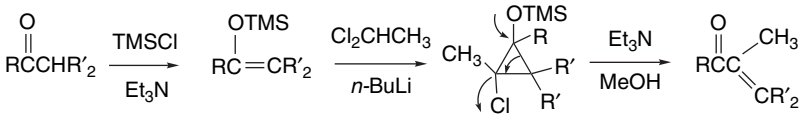
t. This cyclization can occur via an intramolecular ene reaction of an oxonium ion generated from the acetal.



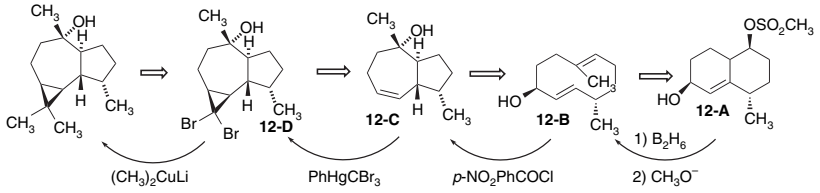
u. The initial reactant is a allyl vinyl carbinol and can undergo an oxy-Cope rearrangement. The product can form the decalin ring by an intramolecular ene reaction. This results in formation of an allyl vinyl ether that can undergo a Claisen rearrangement. The final product is the hemiacetal resulting from cyclization of the γ-hydroxy aldehyde.



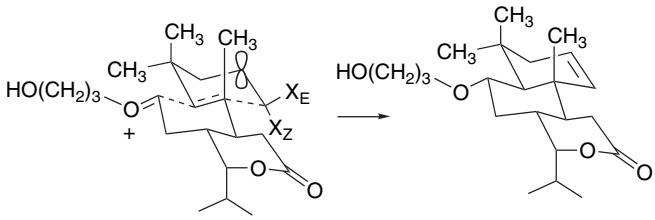
10.11. The transformation can be accomplished by carbenoid addition to the corresponding trimethylsilyl enol ether. The resulting chlorotrimethylsiloxy cyclopropane can then undergo fragmentation to the desired product. Probably because the reaction, at least in a formal sense, involves ionization of a cyclopropyl halide, it is rather slow.



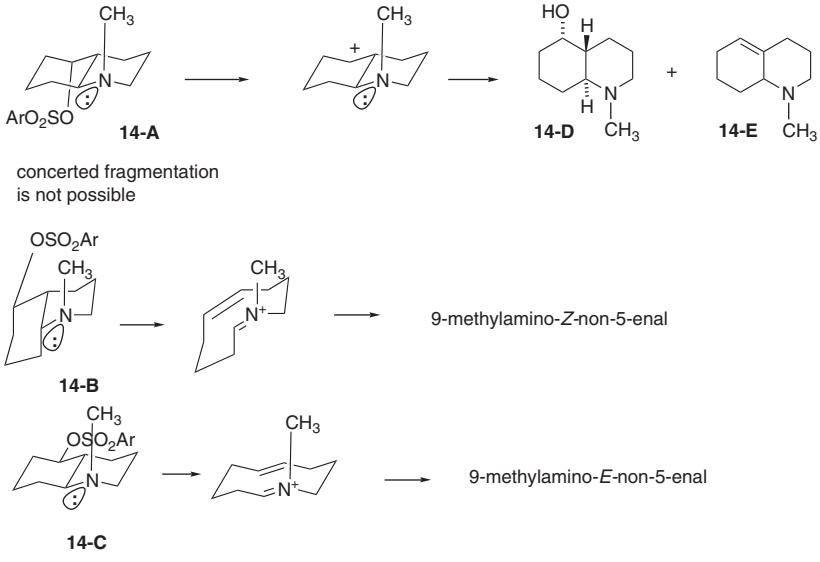
10.12. The penultimate dibromocyclopropane **12-D** can be obtained by cyclopropanation of the double bond in intermediate **12-C**. The cyclopropanation was done by decomposition of phenyltribromomethylmercury. Note that there does not appear to be a hydroxy directing effect on this reaction. Intermediate **12-C** was formed by a transannular cationic cyclization of **12-B**. In the cited synthesis, this cyclization was accomplished by solvolysis of the *p*-nitrobenzoate. The formation of **12-B** was done by a borane fragmentation.



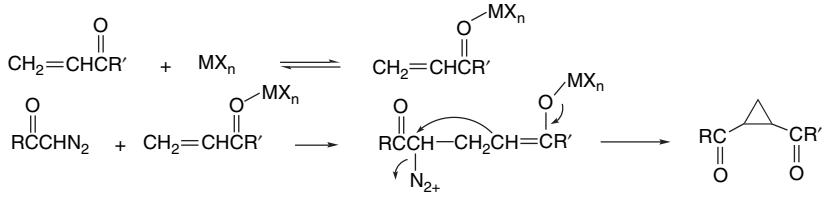
10.13. The *Z*-isomer places the trimethylsilyl group in the stereoelectronically preferred relationship for stabilization of the developing cationic center, whereas the *E*-isomer does not have optimum placement of the silyl group.



10.14. Conformational representation shows that **14-B** and **14-C** can undergo concerted fragmentation to 10-membered ring iminium ions that would hydrolyze to the *Z*- and *E*-isomers of 9-(methylamino)-non-5-enal, respectively. Compound **14-A** cannot achieve a conformation appropriate for concerted fragmentation and would be expected to generate a secondary carbocation that can give the observed mixture of **14-D** and **14-E**.

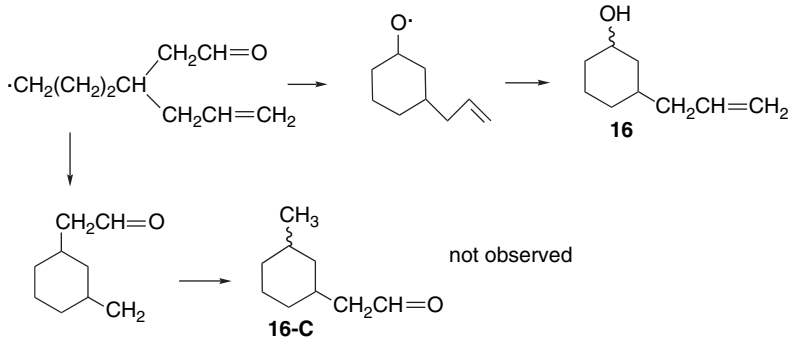


10.15. The reaction can be formulated as a conjugate addition of the diazo compound to the Lewis acid complex of the enone. Decomposition of the diazonio enolate can then generate the cyclopropane.

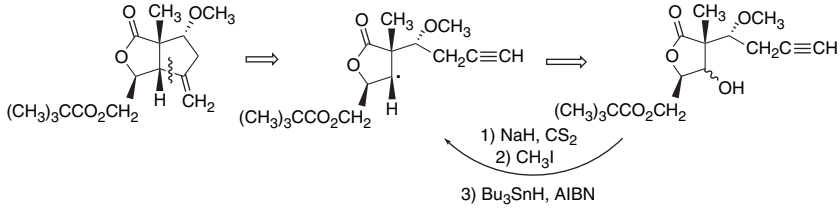


10.16. The outcome of the reaction indicates that a 6-*exo* cyclization on an aldehyde is preferred to a 6-*exo* cyclization on an alkene in geometrical equivalent positions. This is contrary to thermodynamic expectations but might be kinetically reasonable given the relatively nucleophilic character of alkyl radicals.

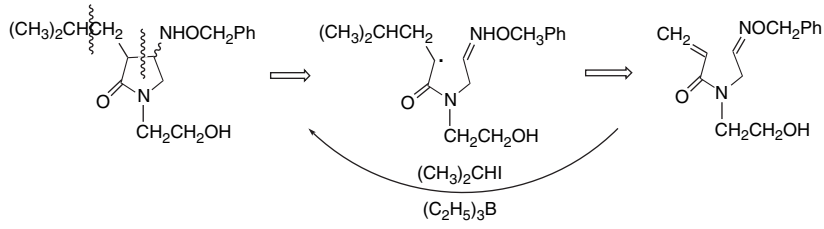
Reference to the data on p. 986 suggests that, at least in the case of 1,2-rearrangement, that addition to C=C > C=O by a factor of about 10^2.



10.17. a. The exocyclic methylene group suggests cyclization of a terminal alkyne. The compound was synthesized using a xanthate ester as the radical source and Bu_3SnH for initiation and chain transfer.

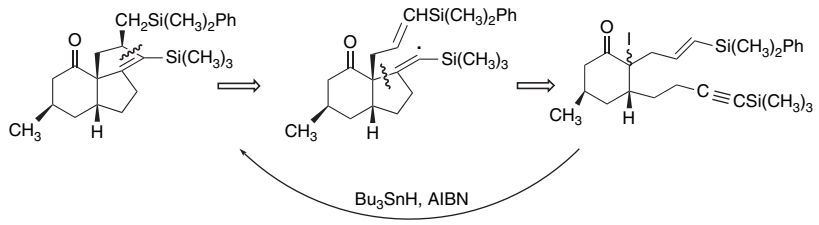


b. The *N*-benzyloxyamine function suggests cyclization of an oxime ether. The *i*-propyl group can be introduced by addition to the acrylamide moiety. The alkylation-cyclization was successfully carried out as a tandem sequence using the alkyl iodide and triethyl boron for radical initiation.

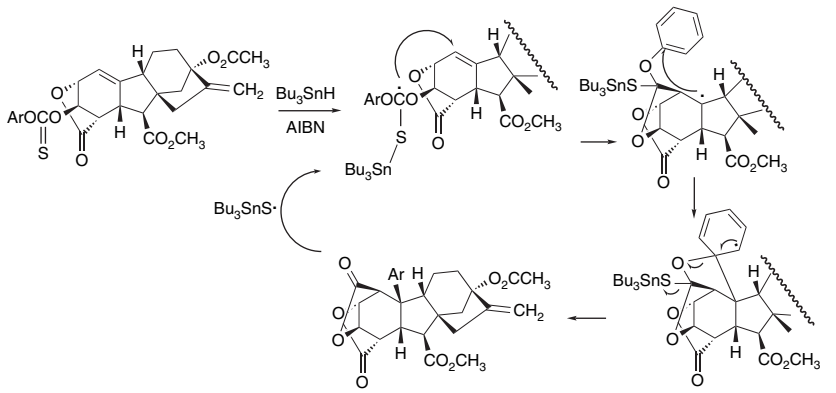


c. The tricyclic ring can be formed by tandem radical cyclization of a α-oxocyclohexyl radical by initial cyclization at an alkynyl group, followed by addition to the vinyl silane. The radical was generated from the corresponding iodo ketone, using Bu_3SnH-AIBN. The starting material was generated by cuprate conjugate addition to a cyclohexenone, with TMS-Cl

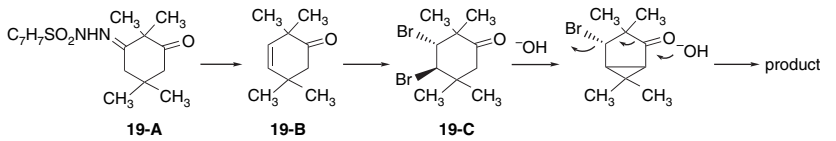
trapping. The resulting trimethylsilyl enol ether was converted to the α-iodo ketone using a peroxy acid and NaI.



10.18. The β-isomer places the thiono ester group in proximity to the C(4)–C(5) double bond and probably leads to a cyclization of the initial α-thiostannyl radical. Subsequent involvement of the aryl ring can account for the observed arylation. The α-stereoisomer does not have access to the double bond.



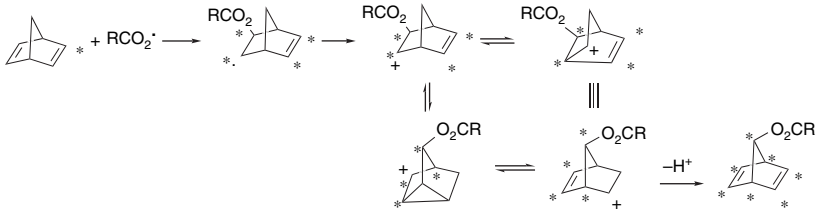
10.19. The first step results in the formation of the mono-*p*-toluenesulfonylhydrazone; the second results in formation of an enone by the carbenoid Bamford-Stevens reaction; the third involves an *anti* bromination of the double bond; and the final step involves two reactions: an intramolecular enolate alkylation, forming the cyclopropane ring, and a fragmentation reaction.



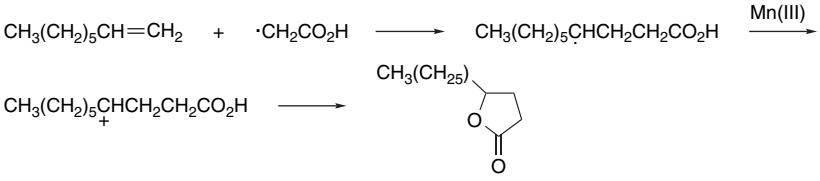
10.20. The computational results suggest that the fragmentation reaction will be fast, even for formation of the bicyclo[2.2.1]heptylium ion. The very low barriers for the other two systems suggest that trapping of the carbene will be difficult. The experimental results show that the amount of carbene trapped is greatest for the bicyclo[2.2.1]heptyl system, which is consistent with the computation. The bicyclo[2.2.2]octyl and adamantyl systems show little dependence on the methanol concentration or the amount of carbene that is trapped.

10.21. a. The formation of the 7-oxy products indicates a skeletal rearrangement. This is most likely to occur by a carbocation mechanism, with the carbocation being formed by oxidation of a radical intermediate by Cu(II). As all four

alkene positions are chemically identical, positions 2, 3, 5, and 6 are equivalent in the initial radical intermediate. Carbocation rearrangement involving C(3)–C(5) bonding introduces label into the C(7) and bridgehead C(1) and C(4) positions.

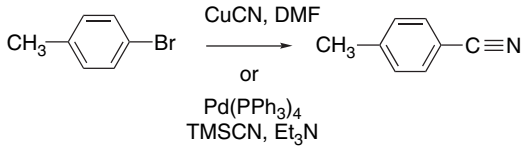


b. The Mn(III) ion can oxidize carboxylic acids to the corresponding radicals, which then add to the alkene. The intermediate radical is oxidized to a carbocation and this leads to cyclization to the lactone.

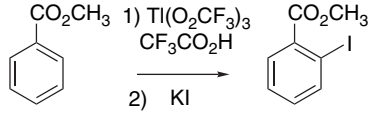


Chapter 11

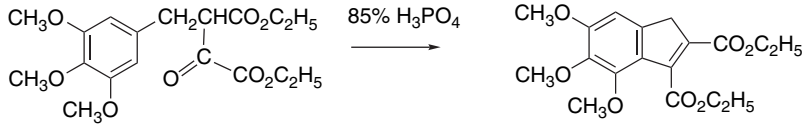
11.1. a. This transformation can be done using CuCN in an aprotic dipolar solvent. The reaction can also be done using a $Pd(PPh_3)_4$ catalyzed reaction.



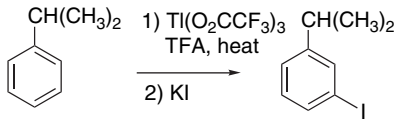
b. This *ortho*-selective iodination can be done by chelation-controlled thallation, followed by reaction with KI.



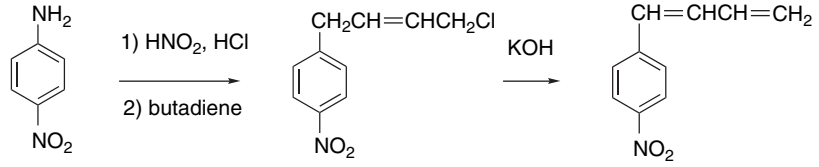
c. This transformation involves an intramolecular Friedel-Crafts alkylation and dehydration. It was accomplished in 77% yield using 85% H_3PO_4.



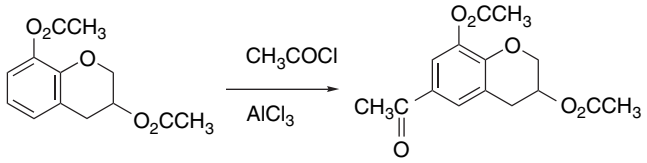
d. This transformation requires a *meta* iodination. The only direct means for accomplishing this reaction is by thermodynamically controlled thallation, followed by reaction with KI. The reported product distribution is 85% *meta*, 12% *ortho*, and 3% *para.*



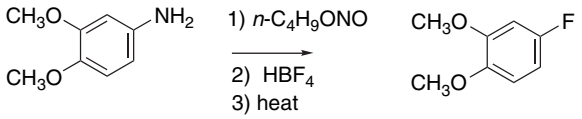
e. This transformation can be accomplished by a Meerwein arylation reaction. 4-Chloro-1-(4-nitrophenyl)-2-butene was isolated as an intermediate and subjected to dehydrohalogenation.



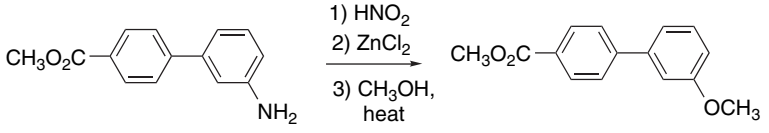
f. This transformation can be accomplished by a Friedel-Crafts acylation. The greater activating effect of the ether oxygen, complemented by steric factors, favors the desired position selectivity.



g. This replacement of an amino group by a fluoro substituent can be done by the Schiemann reaction. In the cited reference, the diazotization was done with butyl nitrite.



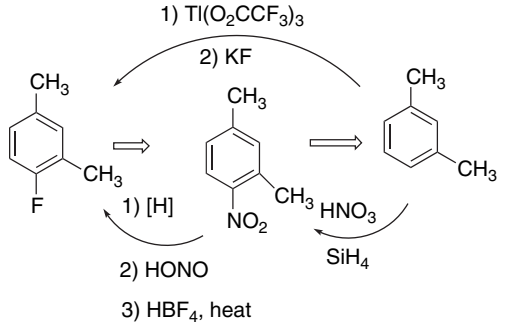
h. This transformation requires replacement of an amino group by methoxy. This can be done by diazotization, followed by solvolysis in methanol. In the cited reference, the diazonium salt was isolated as a $ZnCl_2$ complex.



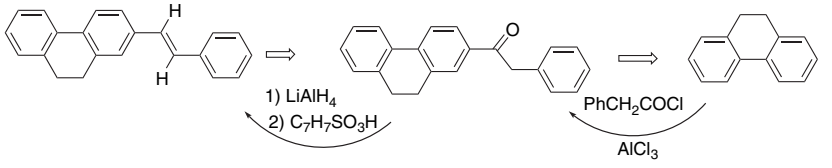
i. This transformation corresponds to a Fries rearrangement. Since there are two acetoxy substituents, an issue of position selectivity arises. The reaction is reported to give exclusively the desired product with BF_3 at 120°C. It is

not clear if this is due to the directing effect by the methyl substituent, or if other factors, such as the steric effect of the methyl group, are operating.

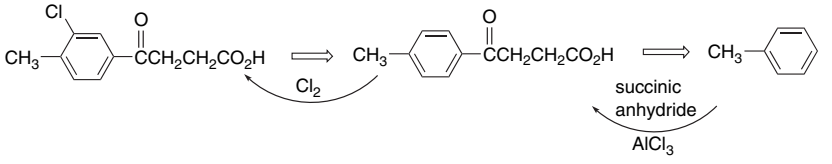
11.2. a. The cited reference used thallation and reaction with KF. Other routes that would be feasible include nitration, reduction, diazotization, and application of the Schiemann reaction, or use of one of the controlled fluorination agents.



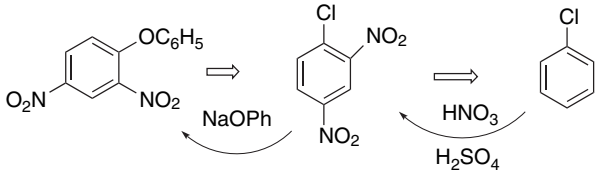
b. This transformation of 9,10-dihydrophenanthrene is done by a Friedel-Crafts acylation followed by $LiAlH_4$ reduction and acid-catalyzed dehydration.



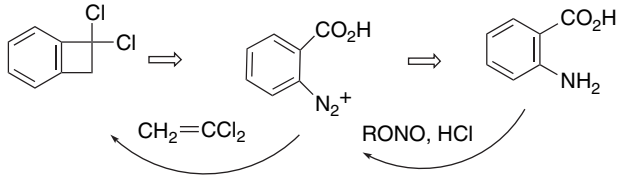
c. Acylation with succinic anhydride and chlorination was done as a one-pot process.



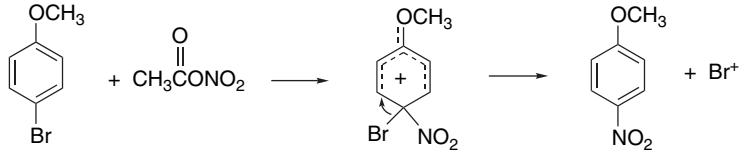
d. This transformation was accomplished by dinitration of chlorobenzene to 2,4-dinitrochlorobenzene, followed by displacement by phenoxide.



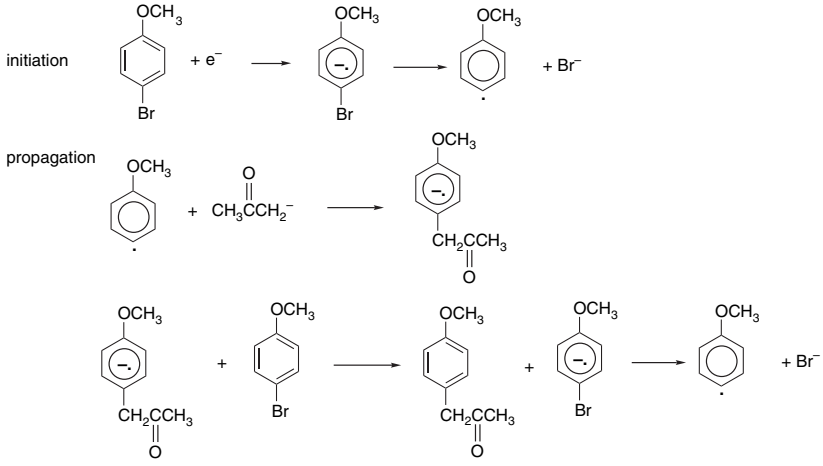
e. This transformation was accomplished by benzyne generation and trapping by 1,1-dichloroethene.



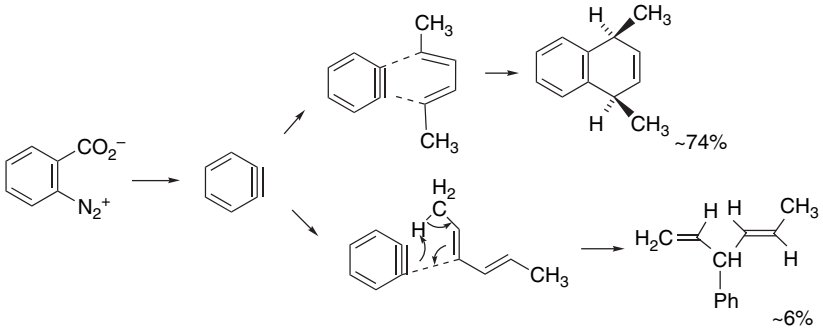
11.3. a. The formation of 4-nitromethoxybenzene in addition to the expected product 4-bromo-2-nitromethoxybenzene is the result of *ipso* substitution and the loss of Br^+. The strong *para*-directing effect of the methoxy group is responsible.



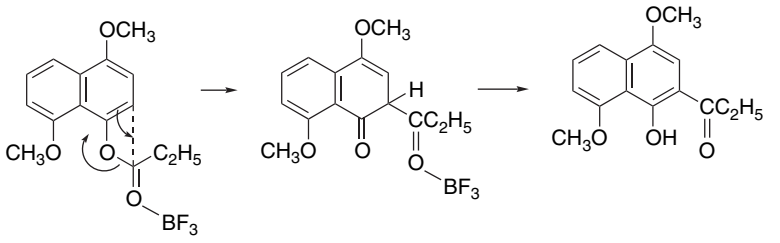
b. These conditions lead to substitution by the $S_{RN}1$ mechanism.



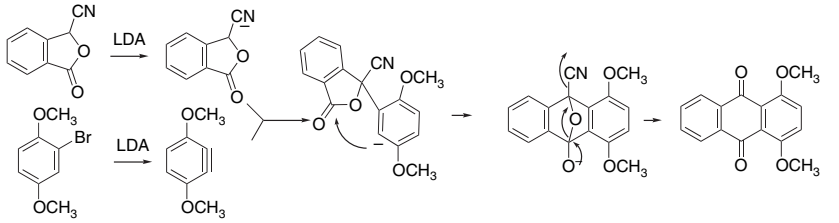
c. The diazonium salt will generate benzyne. The major product is the [4 + 2] cycloaddition product, whereas the minor product results from an ene reaction.



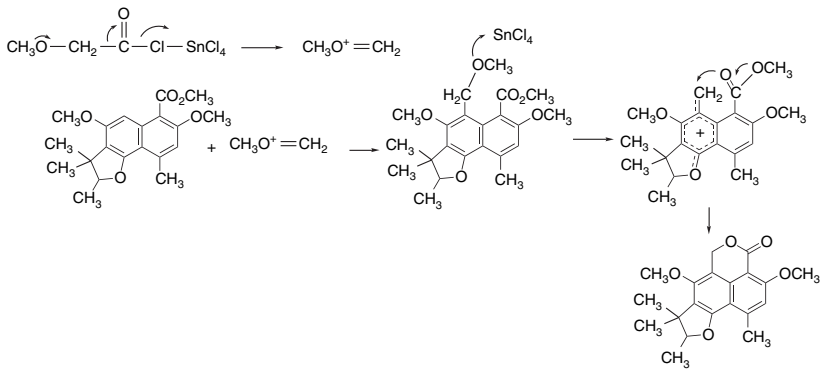
d. This transformation is a Fries rearrangement. In the cited reference, BF_3 was used as the Lewis acid.



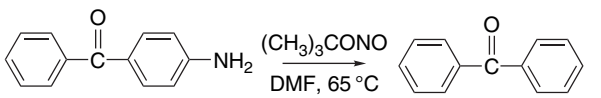
e. This product can be accounted for by formation of the anion of the cyano lactone and 3,6-dimethoxybenzyne. Addition of the carbanion to the benzyne then leads to an intermediate that can give the observed product.



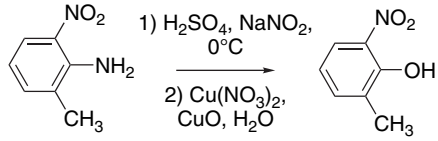
f. The introduction of a new $-CH_2-O-$ unit suggests decarbonylation of the acid chloride to the methoxymethylium ion, which alkylates the ring at the 8-position. Cleavage of the resulting benzylic ether leads to the observed lactone. Use of $TiCl_4$ in place of $SnCl_4$ leads to normal acylation at C(8).



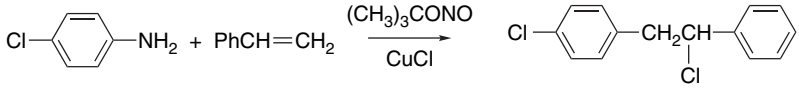
11.4. a. These conditions led to diazotization and reduction by hydrogen atom transfer from solvent.



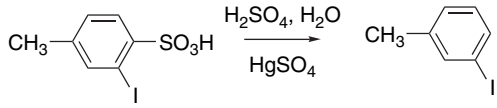
b. These conditions led to the diazonium ion followed by copper-catalyzed conversion to the phenol.



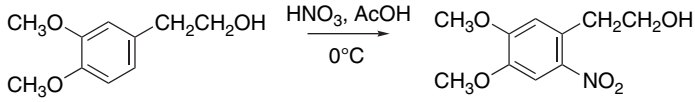
c. These conditions led to in situ diazotization and Meerwein arylation with capture of chloride.



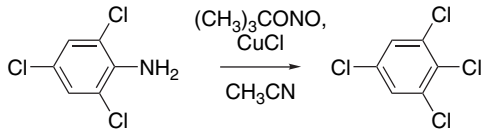
d. These conditions led to loss of the sulfonic acid substituent by reversal of the electrophilic substitution.



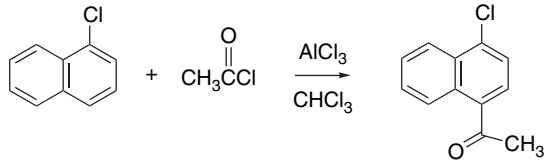
e. This reaction led to nitration at the position activated by both a methoxy and the hydroxyethyl substituent.



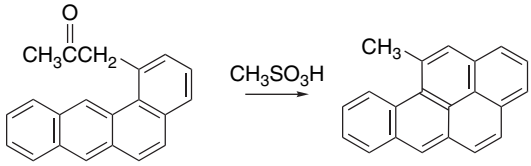
f. These conditions led to in situ diazotization and replacement of the diazonium group by chloride.



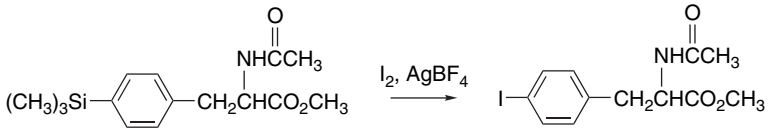
g. These conditions led to Friedel-Crafts acylation. The chloro substituent enhances the selectivity for the 4-position and this product accounted for 80% of the mixture. Each of the other isomers except the 8-isomer was formed in about 4% yield.



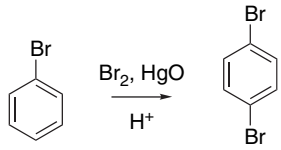
h. These conditions led to an intramolecular Friedel-Crafts alkylation and dehydration.



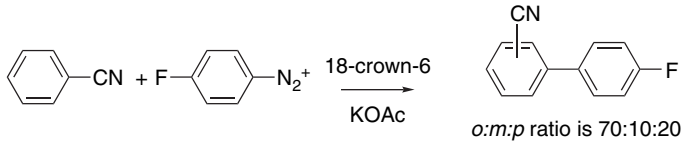
i. The trimethylsilyl group was replaced by an *ipso* substitution.



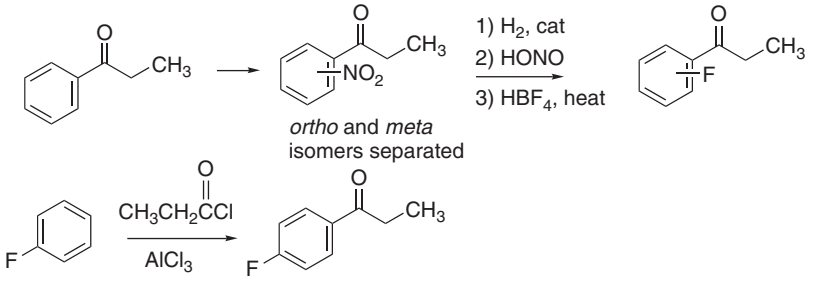
j. These conditions led to bromination with high *para* selectivity.



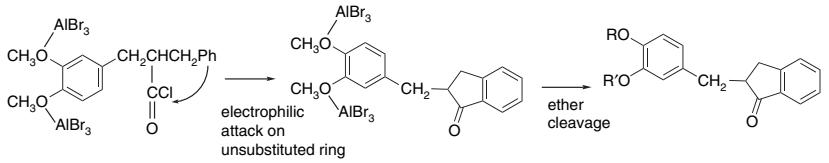
k. These conditions led to radical substitution. As noted on p. 1053, there is a relatively high ratio of *ortho* product.



11.5. A preparation of the *ortho* and *meta* isomers takes advantage of the fact that nitration of propiophenone gives substantial amounts of the *ortho* isomer, probably as a result of participation of the acyl group. After separation of the isomers, the nitro compounds were reduced to amines, diazotized, and converted to the fluoride by a modified Schiemann reaction. The *para* isomer can be made from fluorobenzene by a Friedel-Crafts acylation.

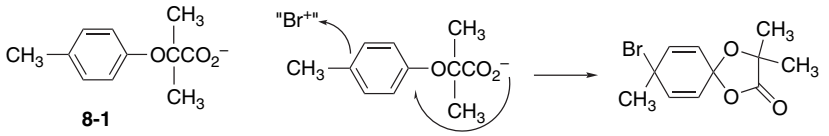


11.6. Use of a single equivalent of $AlBr_3$ led to the expected product resulting from acylation of the more activated of the two aromatic rings. Use of excess $AlBr_3$ led to coordination at one (or possibly both) of the methoxy groups, deactivating that ring, resulting in acylation of the unsubstituted ring. This mechanism is supported by the observation that demethylation occurs at one of the two methoxy groups.



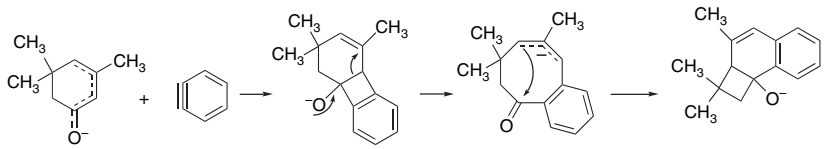
11.7. The product ratio favors the 2-acylation product in CS_2 and the ratio increases slightly with time. The product ratio favors the 1-alkylation product in CH_3NO_2 and this ratio decreases with time. These data indicate an interplay between kinetic and thermodynamic factors. In nitromethane, the 1-alkylation appears to be kinetically controlled, with a tendency to an increase of the thermodynamically favored product with time. The data in CS_2 are more difficult to interpret. Either there is a kinetic preference for the 2-acylation product, or, as is more likely the case, the equilibration is fast.

11.8. The product is formed by intramolecular trapping of the intermediate for electrophilic substitution. Several mechanistic points are relevant. The position of bromine attack appears to be governed by the electronic effect of the oxygen substituent. The *para* position is attacked, even though it is substituted by the methyl group. The cyclization to the lactone may be favored by the *gem*-dimethyl substitution, which tends to favor cyclization. The stereochemistry of the product is not known. If the attacking oxygen were *anti* to the bromine, it would suggest concerted attack, perhaps on the initial complex of the electrophile with the aromatic ring.



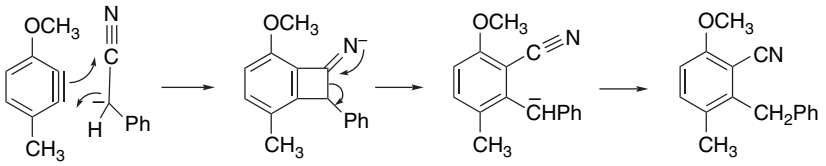
11.9. This reflects the chelation control of the thallation reaction, which is a very attractive synthetic feature. Unfortunately, the toxicity associated with the thallium compounds limits their application.

11.10. The excess of strong base generates benzyne from the bromobenzene. Reaction of benzyne with the enolate is followed by cyclization, fragmentation to an allylic anion, and a recyclization.

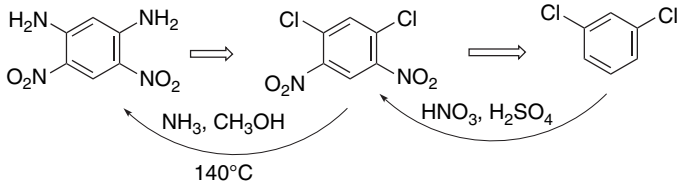


11.11. These reaction conditions generate both the anion of phenylacetonitrile and a benzyne intermediate. Cyclization of the anion formed by addition to the

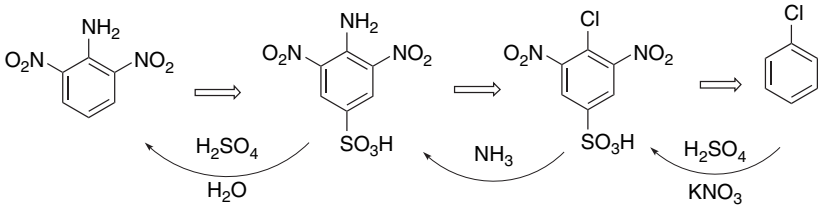
benzyne can generate a four-membered ring that can provide the observed product.



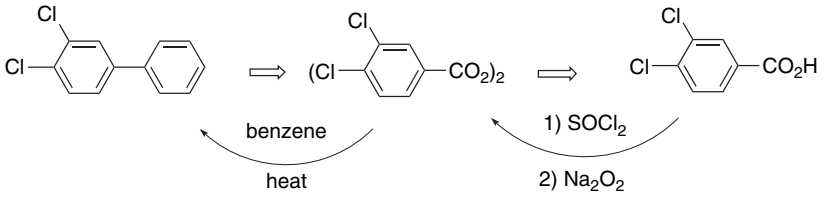
11.12. a. The chloro substituents direct nitration to the desired positions. Displacement of the chloro groups by ammonia then provides the desired product. The only question about this route might be the facility of the second displacement, but evidently the first amino group does not prevent the second substitution. The amination was done at 140°C in methanolic ammonia.



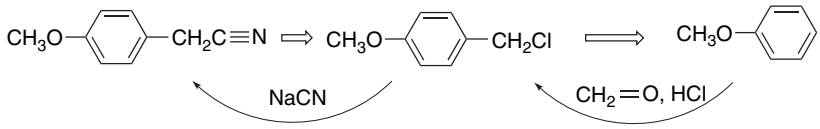
b. This transformation was accomplished by blocking the *para* position by sulfonation. In fact, there is a procedure that permits the sulfonation and dinitration to be carried out in a single reaction. The chloride was then displaced by ammonia and the sulfonate group removed by reversal with strong acid.



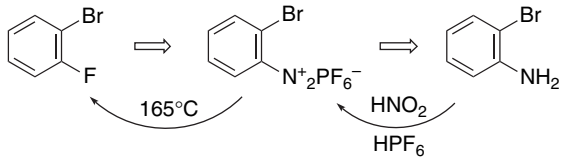
c. This reaction was done by conversion of the 3,4-dichlorobenzoic acid to a phenyl radical source. In the cited reference, it was converted to the peroxide. Thermolysis in benzene gave the desired product.



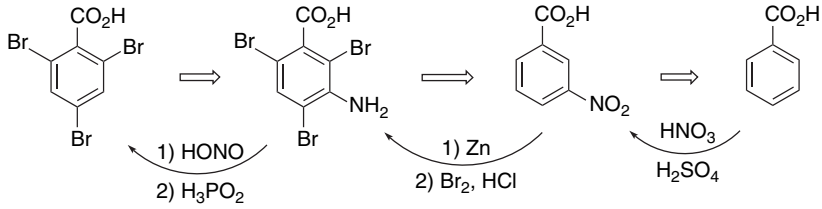
d. There might be a number of ways of doing this synthesis. The cited reference made the chloromethyl compound and used nucleophilic substitution to introduce the cyanide.



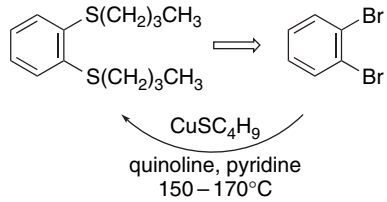
e. This transformation was done by diazotization and application of the Schiemann reaction. The cited reference used the diazonium hexafluorophosphate.



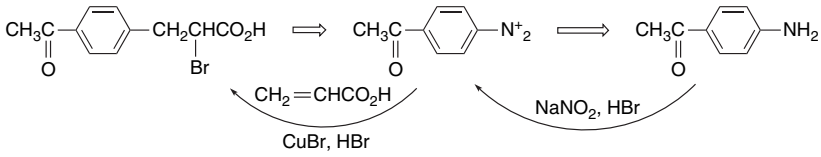
f. The transformation requires a reversal of the directive effect of the carboxy groups and must achieve polybromination. This was accomplished by *meta* nitration and reduction to the amine. Bromination then proceeded as desired. The amino group was removed by diazotization and reduction with hypophosphorous acid.



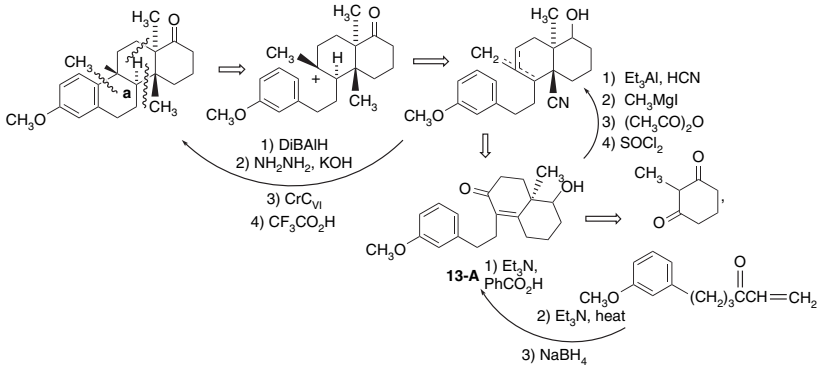
g. This unactivated substitution by butanethiolate was done using the copper salt in a pyridine-quinoline mixture at 150°–170°C.



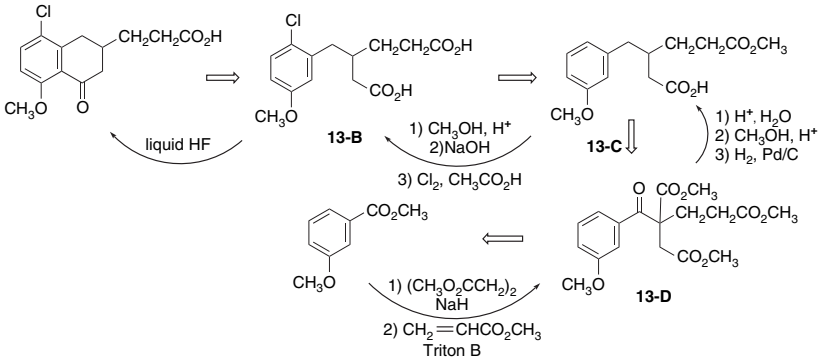
h. This transformation was accomplished by the Meerwein arylation protocol.



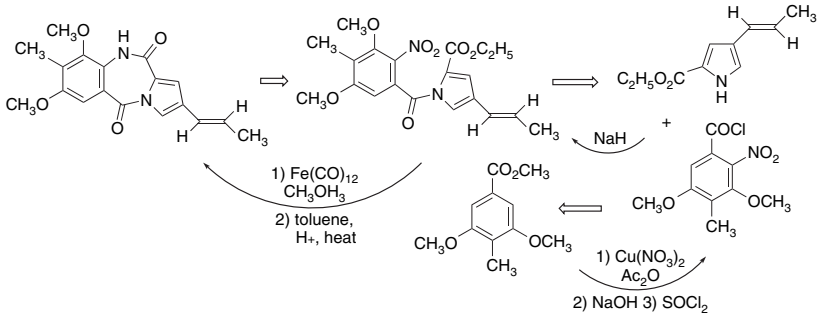
11.13. a. The tetracyclic ring system can be completed by an intramolecular electrophilic substitution, taking advantage of the directive effect of the methoxy group. Comparison of the target structure with the starting materials identifies the potential disconnections that are marked and also shows that two of the three methyl groups are not present in the starting materials. One of the disconnections (a) corresponds to the electrophilic cyclization, but the other two are related to the starting materials as a Robinson annulation, identifying **13-A** as a possible key intermediate. The transformation of the starting materials was done by Robinson annulation and selective reduction of the nonconjugated carbonyl. A cyano substituent was then introduced by conjugate addition, which subsequently served to introduce one of the methyl groups. The second methyl group was introduced by addition of methylmagnesium iodide, followed by selective acetylation of the secondary alcohol. The tertiary alcohol was then dehydrated to an alkene mixture. Finally, prior to cyclization, the cyano group was converted to a methyl group by partial reduction with DiBAlH and Wolff-Kishner reduction. The cyclization was done in trifluoroacetic acid.



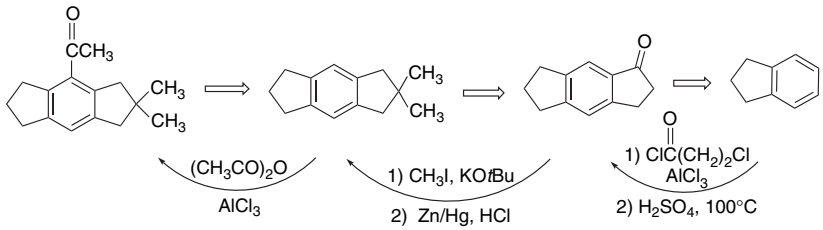
b. Two aromatic substitution reactions are involved in the late stages of this synthesis. The tetralone ring was closed by an intramolecular Friedel-Crafts acylation. The intermediate **13-D** was obtained by a series of enolate reactions. Condensation of methyl 3-methoxybenzoate gave a diester that reacted by conjugate addition to give triester **13-D**. This was decarboxylated and esterified. When the resulting diester was subjected to hydrogenolysis, the monoester **13-C** was obtained as a result of a lactone intermediate formed at the alcohol stage of the reduction. The monoester was esterified and then saponified to diacid **13-B.** The chlorination was done in acetic acid and the Friedel-Crafts acylation was done in liquid hydrogen fluoride.



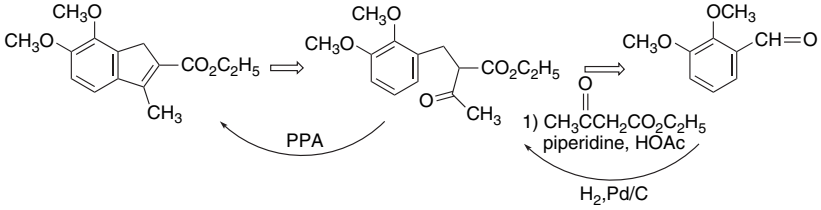
c. This synthesis of a member of the pyrrolo[1,4]benzodiazepine group of antibiotics requires introduction of a nitrogen substituent on the benzene ring and closure of the diazepine ring. The nitrogen substituent was introduced by nitration. The nitrobenzoate ester was converted to its acid chloride for coupling with the sodium salt of the pyrrole. The nitro group was then reduced and the cyclization conducted in refluxing toluene with a trace of acid catalyst. The nitro to amino transformation required special conditions to prevent reduction of the propenyl side chain and/or cleavage of the pyrrole amide.



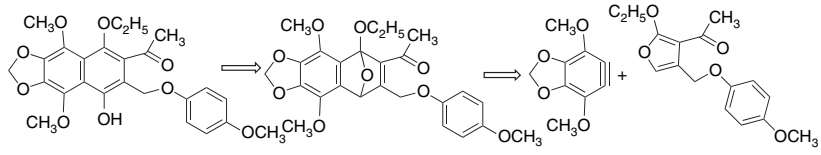
d. The synthesis requires an annulation with a 2,2-dimethylcyclopentane ring. A cyclopentanone ring was introduced by Friedel-Crafts acylation with 3-chloropropanoyl chloride, followed by intramolecular alkylation. The alkylation gave both the linear and angular isomers. The cyclization is interesting in that it both proceeds on a deactivated ring and forms a five-membered ring. The reaction may be a Nazarov-type cyclization proceeding through the protonated form of the enone formed by loss of HCl. The methyl groups were introduced by enolate alkylation; the carbonyl group was removed by Clemmensen reduction; and the acetyl group was introduced by Friedel-Crafts acylation. The linear and angular isomers were separated after this final reaction.



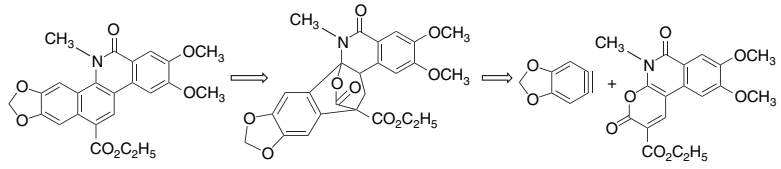
e. This transformation requires a cyclization and elaboration of the formyl group to provide a cyclization substrate. The cyclization was conducted using polyphosphoric acid. The required intermediate was prepared from the starting material by a Knoevenagel condensation, followed by hydrogenation.



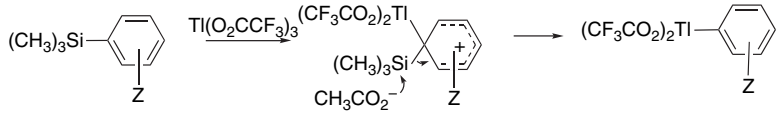
11.14. a. A furan acting as a diene can install the necessary substituents and provide for aromatization of the new carbocyclic ring by hydrolysis of the oxido bridge.



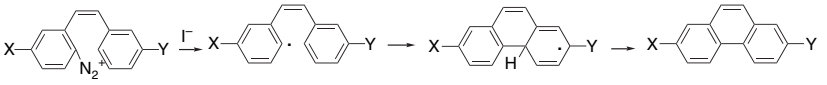
b. A pyrano[c]isoquinolone provides a pyrone ring that can form the center ring and aromatize by decarboxylation.



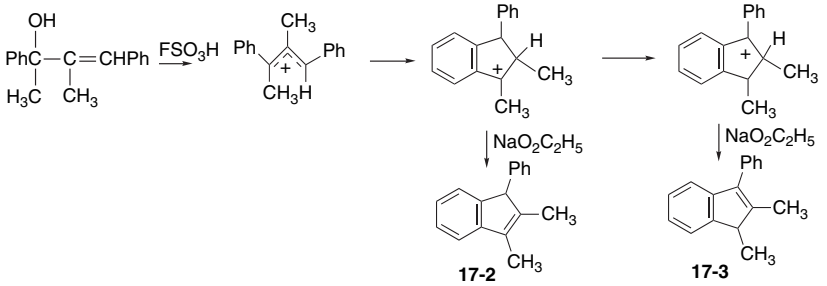
11.15. The silyl group can act as an *ipso*-directing and activating substituent by virtue of its electron donation to the ring and its facile removal by silyl transfer to a nucleophile.



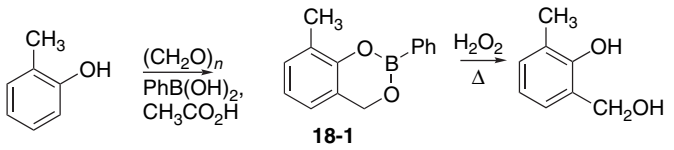
11.16. As is indicated on p. 1031, the decomposition of diazonium ions by iodide involves a reduction and formation of an aryl radical. The radical can evidently attack the adjacent phenyl ring, leading to cyclization, at a rate that exceeds further reaction with iodide.



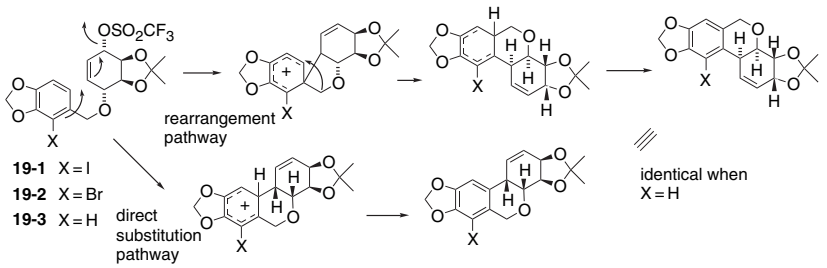
11.17. The ionization of the protonated alcohol can generate an allylic cation that can undergo a Nazarov cyclization. The initial cyclization will form a tertiary benzylic ion. A series of two hydride shifts can give a more stable ion. Removal of a 2-hydrogen from the two ions generates **17-2** and **17-3**, respectively.



11.18. The phenylboronic acid can facilitate the reaction and direct *ortho* substitution by forming a cyclic boronate ester.

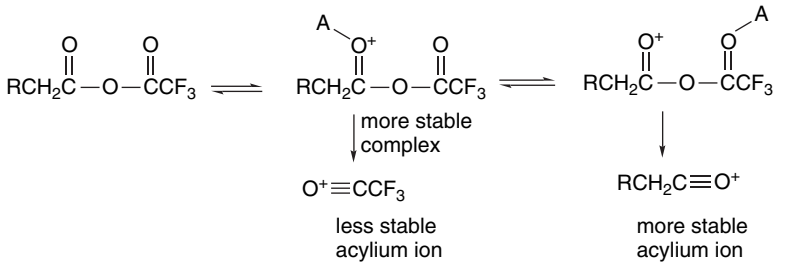


11.19. The formation of the isomeric product requires a rearrangement resulting from an *ipso* substitution. In the case of the unsubstituted compound, the product of direct substitution and *ipso* substitution with migration are identical.



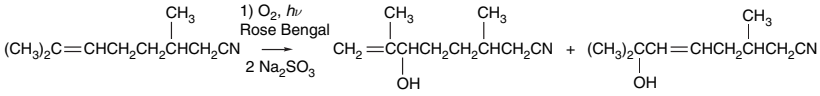
11.20. This is a characteristic feature of acylations with mixed trifluoroacetic acid. Two factors may contribute. The carbonyl oxygen of the trifluoroacetyl group is a poorer donor toward protic or Lewis acids because of the electron-withdrawing effect of the trifluoromethyl group. If reaction occurs through this complex, attack should be at the nonfluorinated acyl group. Furthermore, the trifluoroacetylium ion is less stable than an ion without the fluorine substituents. If

the reaction occurs through prior cleavage to an acylium ion, the nonfluorinated acylium ion would be expected.

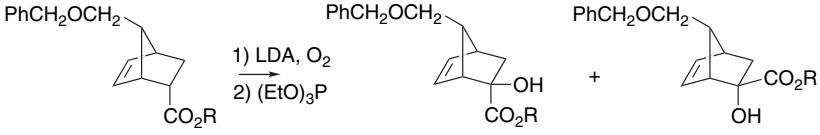


Chapter 12

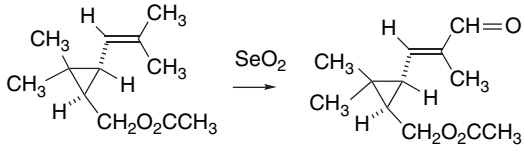
12.1. a. This transformation can be done by photosensitized $^1O_2$ oxidation. In the cited reference, the product was obtained as 1:1 mixture with the isomeric allylic alcohol after reductive workup with Na_2SO_3.



b. This transformation corresponds to an enolate oxidation. In the cited reference, the enolate was formed using LDA and a 2:1 mixture of *exo* and *endo* product was obtained after oxygenation in the presence of triethyl phosphite.

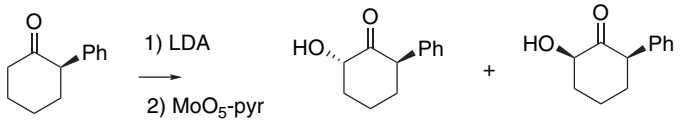


c. This transformation corresponds in both regio- and stereoselectivity with SeO_2 oxidation. A 49% yield was obtained.

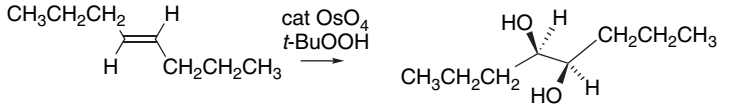


d. This transformation was accomplished by kinetically controlled enolate formation followed by MoO_5-pyridine-HMPA oxidation. The product was obtained as a 62:8 mixture of *trans: cis* isomers. Other enolate or silyl enol

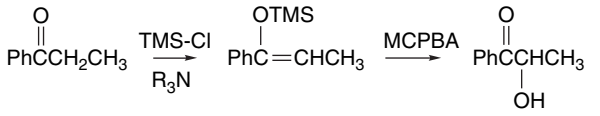
ether oxidations presumably would also be possible, as long as the enolate regiochemistry is controlled.



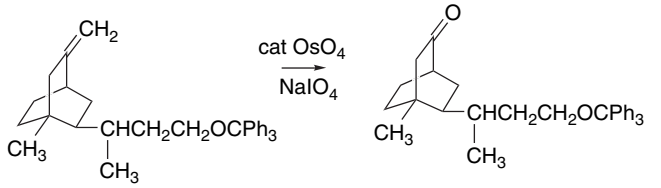
e. The stereochemistry of this transformation corresponds to formation of a diol by *syn* addition. A catalytic OsO_4 dihydroxylation was carried out in 81% yield.



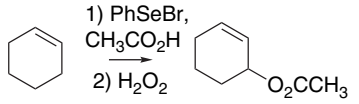
f. This transformation corresponds to a ketone hydroxylation and could presumably be carried out by several of the available methods. The cited reference used MCPBA oxidation of the silyl enol ether.



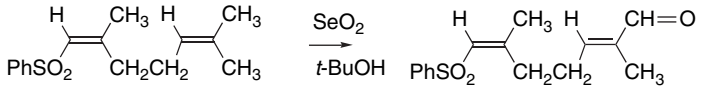
g. This oxidative cleavage was accomplished by the OsO_4-$NaIO_4$ (Lemieux-Johnson) procedure. Ozonolysis also would appear to be a possibility.



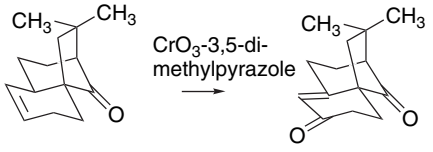
h. This is an allylic oxidation. Either Cr(VI)- or SeO_2-based allylic oxidation might provide the ketone and/or alcohol that could be converted to the allylic acetate. A one-pot transformation was effected in 78% yield by use of PhSeBr, followed by solvolysis and H_2O_2 oxidation in acetic acid. The cited reference also mentions direct conversion using phenylselenenic acid (see p. 1126).



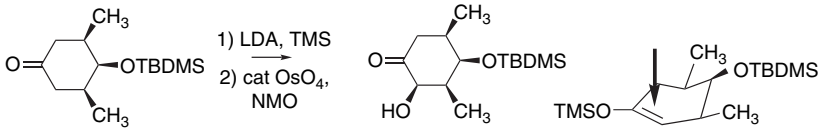
i. This transformation was accomplished using SeO_2. The product was isolated as the alcohol after $NaBH_4$ reduction.



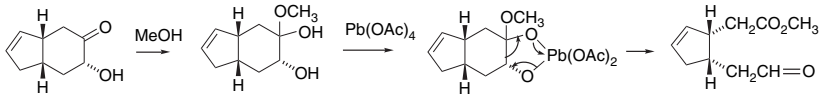
j. This allylic oxidation (with a double-bond shift) was done with the CrO_3-3,5-dimethypyrazole reagent.



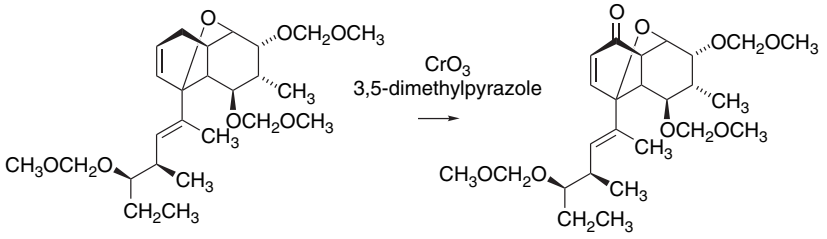
k. This transformation corresponds to an enolate oxidation and was accomplished using OsO_4 oxidation of the silyl enol ether. The stereoselectivity is reported to be high, although its origin is a bit puzzling, assuming that the two methyl groups lead to an axial orientation for the TBDMSO group.



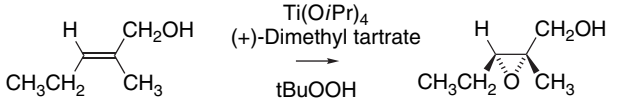
l. This oxidation was done using $Pb(OAc)_4$ in methanol. The reaction presumably proceeds through the hemiacetal.



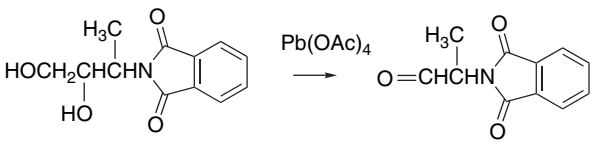
m. This reaction was accomplished in 39% yield using the CrO_3-3,5-dimethylpyrazole reagent. Steric effects presumably govern the selectivity for the cyclic as opposed to the more hindered acyclic double bond. The origin of the regiochemistry is not entirely clear.



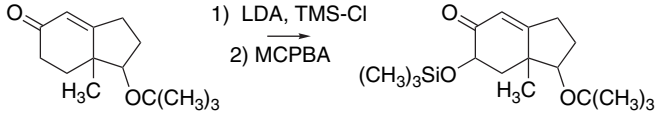
n. This transformation is an enantioselective epoxidation of an allylic alcohol that was done using the Ti(O-*i*-Pr)$_4$-(+)-dimethyl tartrate, *t*-BuOOH reactant system.



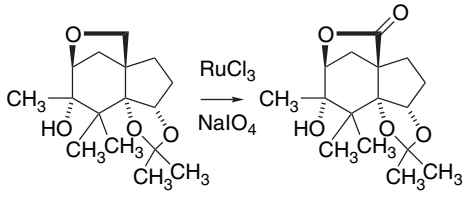
o. This glycol cleavage was done with $Pb(OAc)_4$ but presumably could also be done with $NaIO_4$.



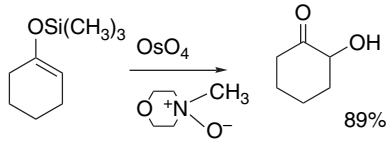
p. This transformation was accomplished via oxidation of the silyl enol ether using MCPBA.



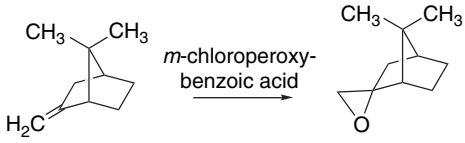
q. This oxidation was done with $RuCl_3$ and $NaIO_4$, with RuO_4 presumably being the active oxidant.



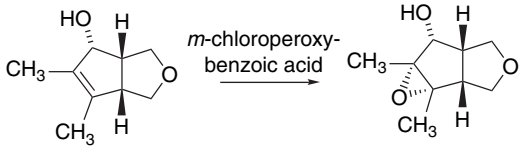
12.2. a. These conditions give the α-hydroxyketone.



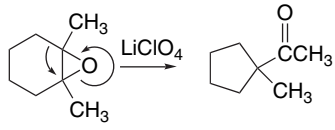
b. The epoxidation occurs primarily from the *endo* face, owing to the steric shielding of the 7-methyl group.



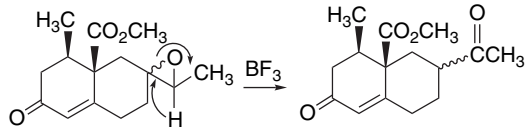
c. The directive effect of the hydroxy group controls the stereoselectivity and epoxidation occurs from the concave side of the molecule.



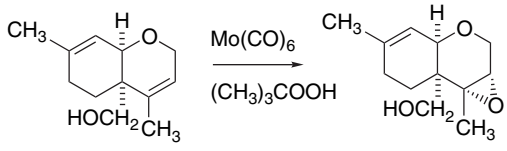
d. These conditions led to opening of the epoxide ring and ring contraction.



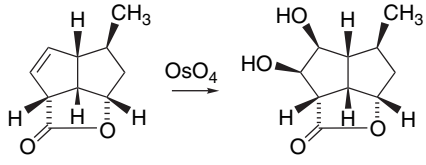
e. These conditions led to epoxide opening with hydride shift.



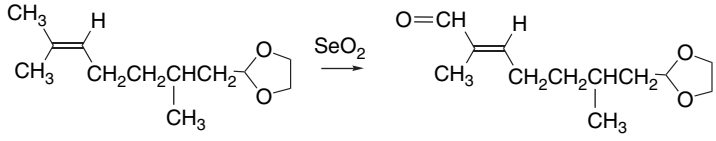
f. This oxidation is subject to the hydroxy-directing effect, similarly to vanadium and titanium-catalyzed epoxidation of allylic alcohols.



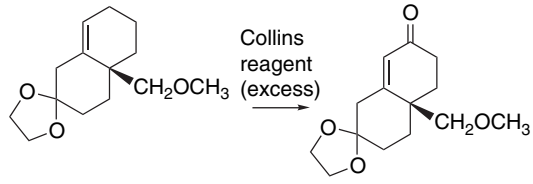
g. These conditions led to *syn* dihydroxylation from the less hindered convex face of the molecule.



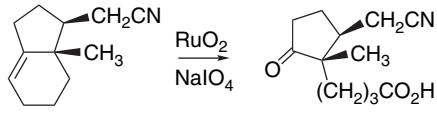
h. These conditions led to preferential oxidation of the *E*-methyl group.



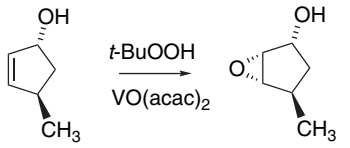
i. Allylic oxidation to the α, β-enone occurred under these conditions.



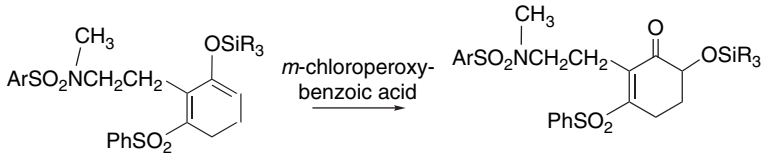
j. These conditions led to oxidative cleavage of the double bond to a ketone and carboxylic acid.



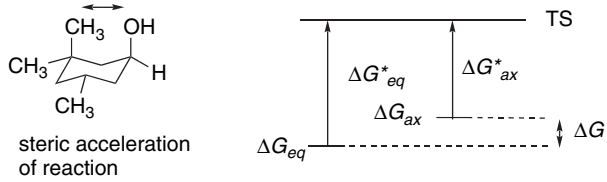
k. These conditions led to hydroxy-directed epoxidation.



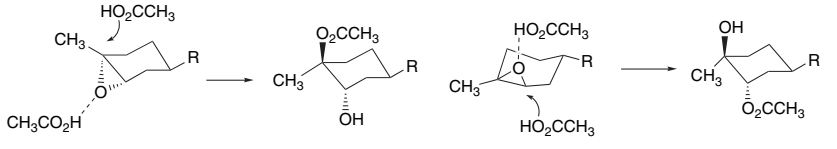
l. Epoxidation and rearrangement to the α-siloxy ketone occurs. The sulfonyl-substituted double bond is much less reactive.



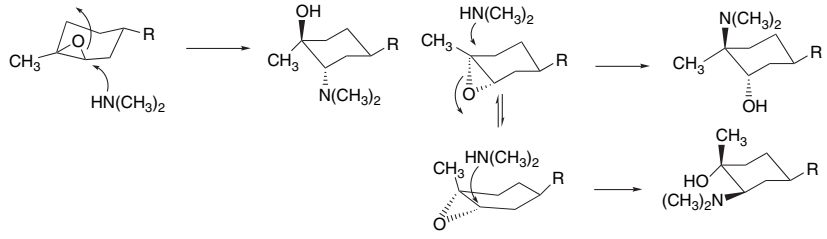
12.3. The observation that the more hindered axial alcohols react more rapidly than the equatorial epimers is consistent with the second step in the mechanism on p. 1064 being rate limiting, that is, it is not complexation with chromium that is rate limiting. The acceleration in *trans*-3,3,5-trimethylcyclohexanol suggests a steric *acceleration* of the rate-determining step. This can be interpreted in terms of the rate reflecting the *energy difference in the reactants*. The correlation of the relative rates with the equilibrium constant is consistent with the ΔG^* being dependent primarily on differences in the energies of the reactants.



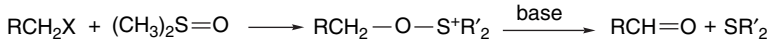
12.4. The cyclohexene-derived epoxides should be subject to preferential diaxial ring opening and also to preferred attack at the less-substituted carbon. The opening in acetic acid should have more electrophilic character because of partial protonation in the ring opening. The preference for diaxial ring opening is the dominant factor in the case of acetic acid, leading to nucleophilic attack at C(1) for the *cis* isomer and dominant nucleophilic attack at C(2) for the *trans* isomer. In the case of the *trans* isomer, about 10% of the product had the alternate regiochemistry.



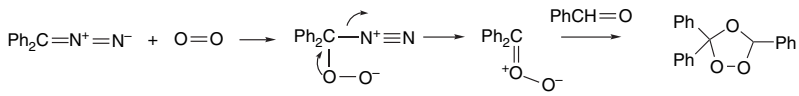
For dimethylamine, the regiochemistry is again dominated by the preference for diaxial ring opening, although the *cis*-epoxide also gives some of the alternate regioisomer, which may arise from a twist conformation.



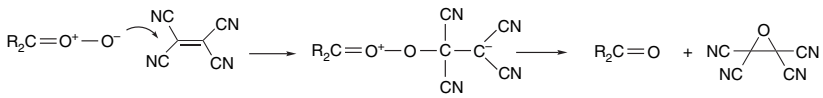
12.5. The nucleophilicity of DMSO permits formation of an alkoxy sulfonium ion, the same intermediate that is generated in electrophile-activated DMSO oxidations of alcohols. (see p. 1070).



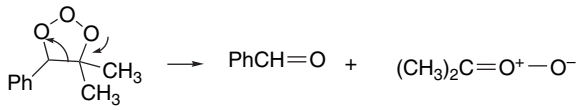
12.6. a. Singlet oxygen oxidation of the diazo compound followed by loss of nitrogen can generate the same carbonyl oxide intermediate as is generated in ozonolysis. Combination with the added aldehyde gives the ozonide.



b. The inclusion of the tetracyanoethylene appears to trap the carbonyl oxide and convert it to the carbonyl derivative. This is consistent with the strong electrophilicity of tetracyanoethylene, which should be particularly effective at trapping the carbonyl oxide.

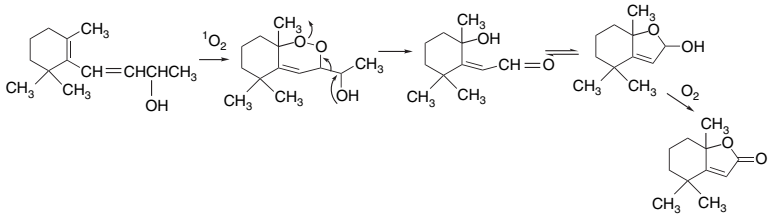


c. The breakdown of the ozonide is a reverse cycloaddition and occurs with a very small barrier. The polarization of the C–C bond in the initial ozonide may be sufficient to cause the observed selectivity.

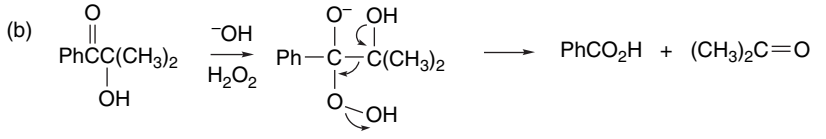


12.7. a. This product can be accounted for by a [4 + 2] addition of $^1O_2$ followed by a fragmentation that generates an aldehyde that would be in equilibrium

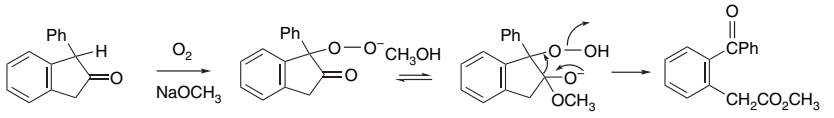
with the cyclic hemiacetal. Further oxidation of the aldehyde or hemiacetal would generate the observed product.



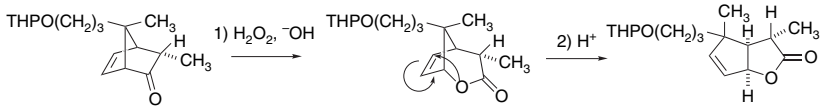
b. This reaction can occur by addition of the hydroperoxide at the carbonyl group followed by fragmentation.



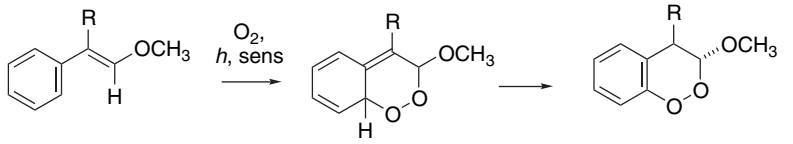
c. The hydroperoxide formed by enolate oxidation can undergo ring cleavage by a fragmentation reaction.



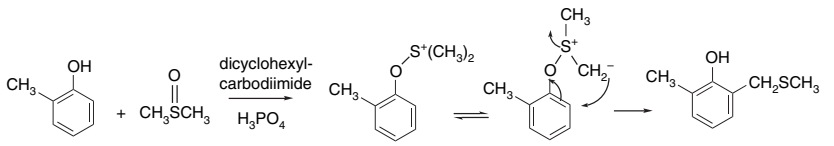
d. This transformation can occur by an alkaline Baeyer-Villiger reaction, followed by an acid-catalyzed allylic rearrangement.



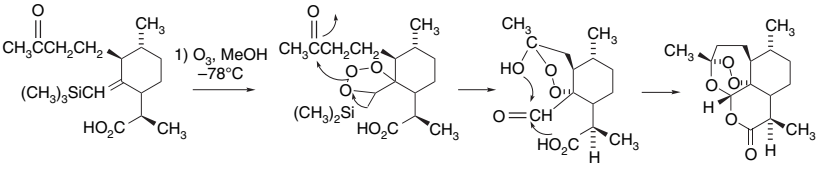
e. A simple formulation of this reaction is as a [4 + 2] cycloaddition of $^1O_2$, followed by aromatization. The presence of the electron-rich vinyl ether might suggest alternative zwitterionic intermediates.



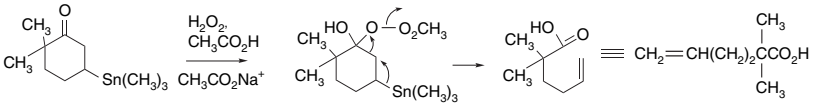
f. This reaction can occur by a mechanism that incorporates an aryloxysulfonium ion and [2,3]-sigmatropic rearrangement of the corresponding ylide and rearomatization (see p. 585). This explains the selective *ortho* substitution.



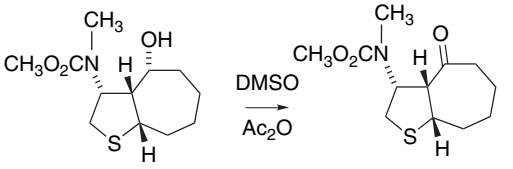
g. Comparison of the product and reactant show that no carbons have been lost. This suggests that some process diverts the initial ozonide from fragmentation. Silyl-assisted fragmentation would generate a hydroperoxide and aldehyde group. The former can cyclize with the nearby acetyl group. Comparison of the structure of this intermediate with the final product shows that the latter is the mixed bicyclic acetal derived by intramolecular addition of the hydroxy and carboxy groups to the aldehyde.



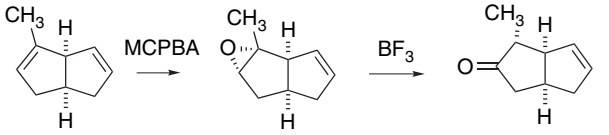
h. This transformation can occur by a Baeyer-Villiger oxidation with preferential engagement of the stannyl-substituted group. The migration-elimination could occur as a concerted process.



12.8. a. The most likely interference would be oxidation of the sulfide group. The oxidation was done successfully with DMSO and acetic anhydride. Other modifications of the DMSO oxidation would also likely succeed.

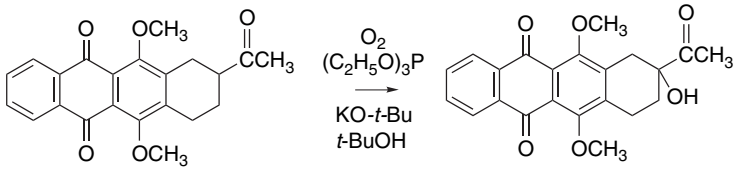


b. This transformation requires selective oxidation at the more-substituted double bond. The reaction was done by MCPBA epoxidation, followed by BF_3-mediated rearrangement.

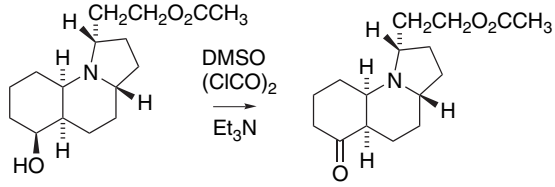


c. This transformation requires selective oxidation of the more-substituted enol or enolate derived from the starting ketone. The oxidation was done in *t*-butanol with KO-*t*-Bu as base using O_2 in the presence of triethyl phosphite.

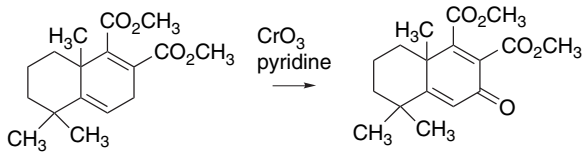
Under these conditions enolate composition is under thermodynamic control. The more substituted enolate is also probably more reactive.



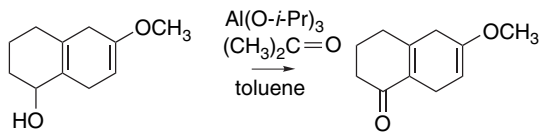
d. The most likely site for competitive oxidation would be at the tertiary amino group. Swern conditions gave the desired product in 89% yield.



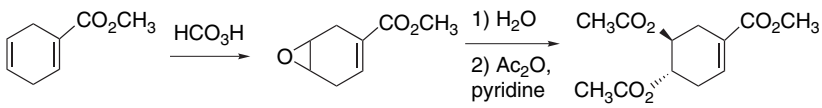
e. The doubly allylic position was successfully oxidized with CrO_3-pyridine.



f. This reaction requires a selective oxidation of the alcohol, while avoiding the potential from aromatization of the cyclohexadiene ring or hydrolysis of the enol ether. Oppenauer oxidation using $Al(O\text{-}i\text{-}Pr)_3$ and acetone in toluene gave a 97% yield.

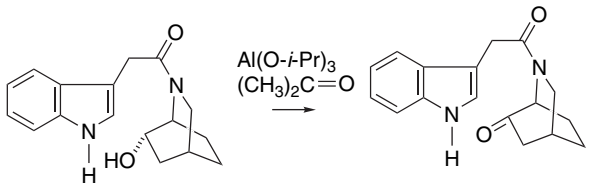


g. This transformation was done in 67% overall yield and good stereoselectivity by epoxidation with performic acid, followed by hydrolysis and acetylation.

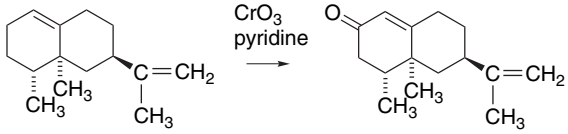


h. This reaction requires oxidation of a secondary alcohol without interference from the electron-rich indole ring. An Oppenauer oxidation was used. Based

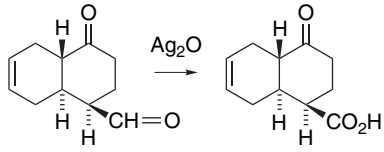
on Entry 3 in Scheme 12.3, it also seems likely that DMSO-based oxidations would also be successful.



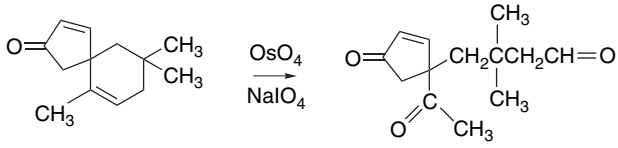
i. This transformation requires selective oxidation at the cyclic double bond. The CrO_3-pyridine allylic oxidation was highly selective. Several related structures were oxidized and it was found that allylic methyl groups are not normally very susceptible to oxidation with this reagent.



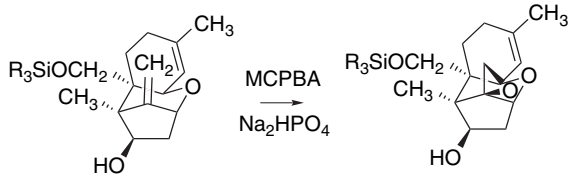
j. This oxidation of an aldehyde to a carboxylic acid in the presence of a double bond and ketone was done with silver oxide.



k. This oxidative cleavage was done using OsO_4 and $NaIO_4$. The less reactive conjugated double bond does not interfere.

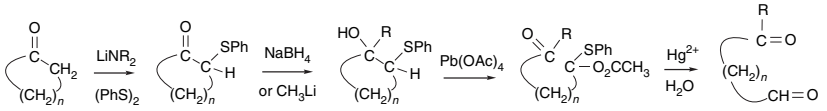


l. The reaction was done successfully using MCPBA with a Na_2HPO_4 buffer. The silyl protection of the hydroxy group is important since the trisubstituted double bond, which is subject to hydroxy-promoted epoxidation, reacts preferentially in the unprotected alcohol.

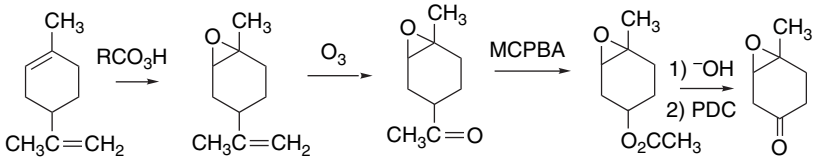


12.9. The key step in this sequence of reactions is the oxidative cleavage by $Pb(OAc)_4$. This probably is formulated best as a thio-assisted oxidative

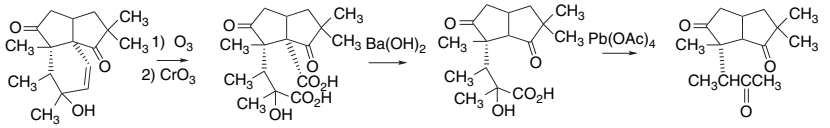
fragmentation, followed by capture by acetate. The mercury-catalyzed hydrolysis then provides the second carbonyl group. In some cases, intramolecular trapping to cyclic mixed acetals was observed.



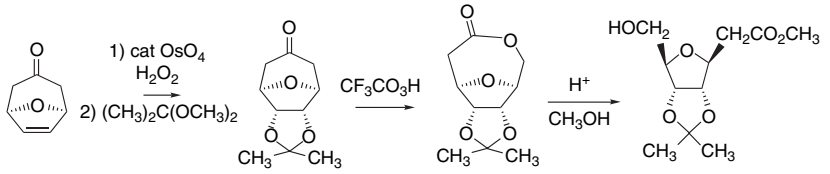
12.10. a. This transformation was accomplished by epoxidation and ozonolysis, followed by Baeyer-Villiger oxidation. After hydrolysis of the acetate ester the final oxidation was done with PDC.



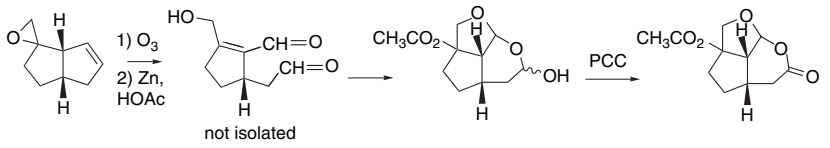
b. This transformation was begun by ozonolysis, followed by CrO_3 oxidation. The β-ketoacid was then thermally decarboxylated. The remaining α-hydroxy acid was then oxidatively decarboxylated with $Pb(OAc)_4$.



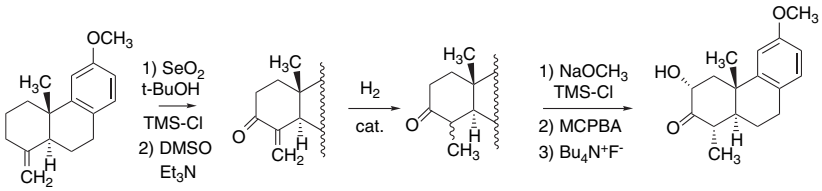
c. This transformation, which was used to generate carbohydrate and nucleoside structures, involves an initial oxidation with OsO_4 and H_2O_2 that was stereoselective. The diol was then protected as the acetonide and the ketone was converted to a lactone by a Baeyer-Villiger reaction. Methanolysis in the presence of acid generated the product.



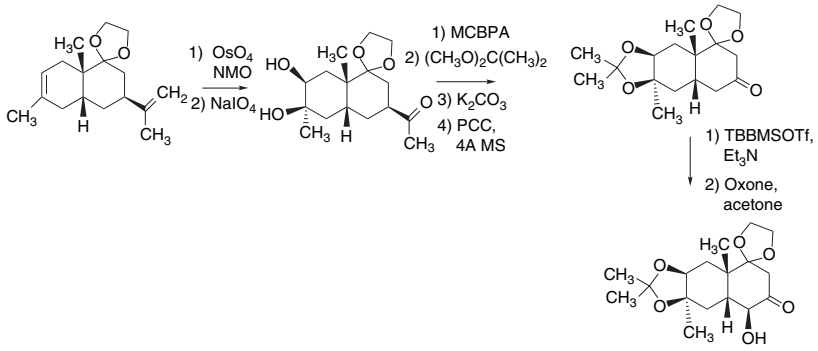
d. Ozonolysis followed by reduction with Zn in acetic acid, with concomitant opening of the epoxide, resulted in formation of a dialdehyde that was not isolated. Conjugate addition of acetic acid, followed by cyclization gave a tricyclic lactol, which was oxidized to the final product with pyridinium chlorochromate.



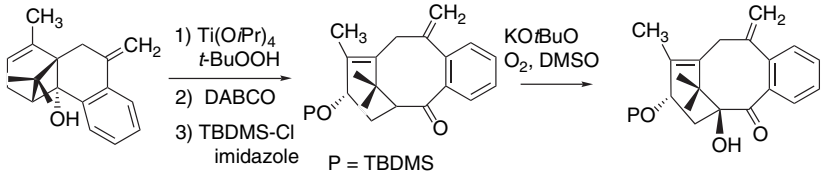
e. The oxygen was installed by a SeO_2 allylic oxidation and then converted to the enone by a Swern oxidation. The exocyclic methylene group was then reduced to methyl by catalytic hydrogenation. The α-hydroxy group was introduced by oxidation of the silyl enol ether with MCPBA.



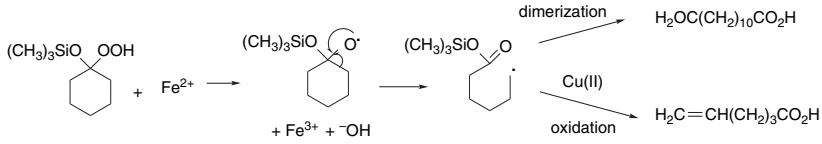
f. The first step was osmium-catalyzed dihydroxylation of both the endocyclic and exocyclic double bonds. This was followed by selective cleavage of the exocyclic diol by periodate and Baeyer-Villiger oxidation of the resulting methyl ketone. After protection of the diol as the acetonide and hydrolysis of the ester group, the hydroxy group was oxidized with PCC. The final oxygen substituent was introduced by oxidation of the silyl enol ether with Oxone.



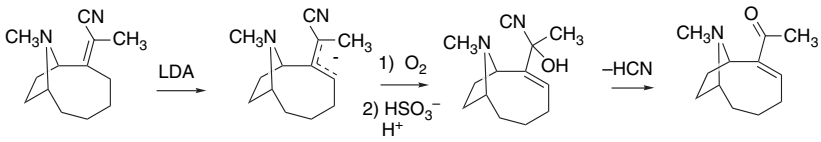
g. The first step was a hydroxy-directed epoxidation using $Ti(O\text{-}i\text{-}Pr)_4$ and *t*-BuOOH. The resulting epoxide was then opened by DABCO and the hydroxy group protected as the TBDMS ether. The bridgehead hydroxy was then introduced by enolate oxidation.



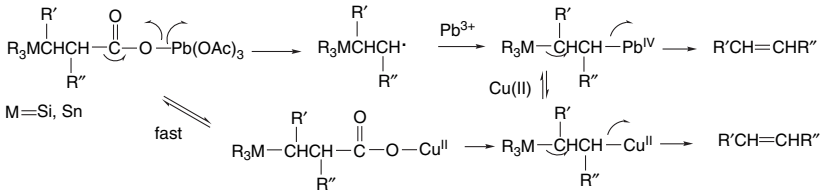
12.11. a. The main product in the absence of Cu^{2+} is a dimer, presumably formed by a radical coupling. The radical is diverted by Cu^{2+} by oxidation (see Section 12.6.2).



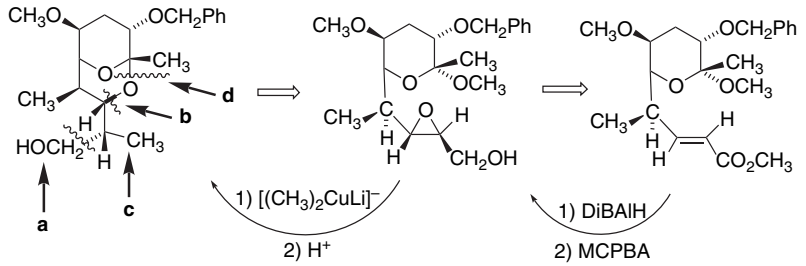
b. This transformation can be accounted for by reaction of the cyanide carbanion with oxygen, followed, after reduction of the hydroperoxide, by elimination of HCN.



c. The acceleration by Cu^{2+} suggests interception of an intermediate, presumably an alkyl lead species, that normally undergoes elimination more slowly.

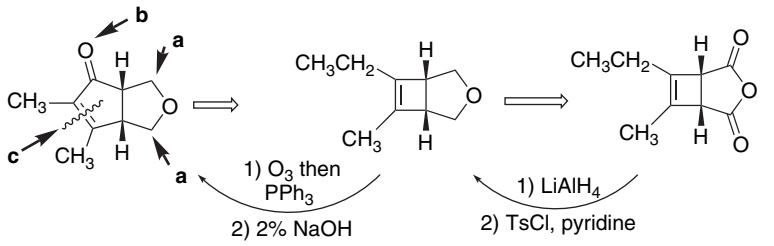


12.12. a. Comparison of the target compound with the starting material indicates four necessary changes: (a) reduction of the ester to a primary alcohol; (b) introduction of an oxygen at the β-carbon; (c) introduction of a methyl at the α-carbon; and (d) cyclization to the bicyclic acetal structure. The reduction of the ester was done with DiBAlH, giving an allylic alcohol. The allylic alcohol then permits a stereoselective epoxidation. The methyl group was added by a cuprate reagent and was regioselective, perhaps with assistance from the hydroxy group. The compound was then of the correct functionalization and stereochemistry to undergo acid-catalyzed cyclization to the bicyclic acetal.

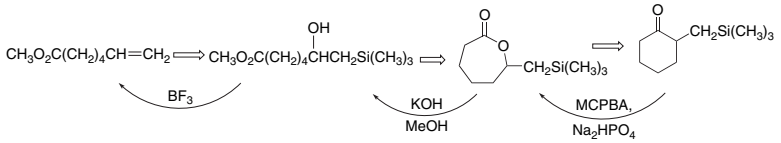


b. Comparison of the target and starting structures identifies the following changes: (a) reduction of the anhydride to a cyclic ether; (b) oxidation and cleavage of the four-membered ring; (c) formation of a double bond involving the methylene carbon of the ethyl group. The first transformation can be done reductive ring opening to a diol with $LiAlH_4$, followed by cyclization via the monotosylate. Transformations **b** and **c** are closely interrelated. Recognition of the enone character of the new five-membered ring suggests its formation by an aldol condensation. The required diketone is available from the cyclobutene structure by ozonolysis and reductive

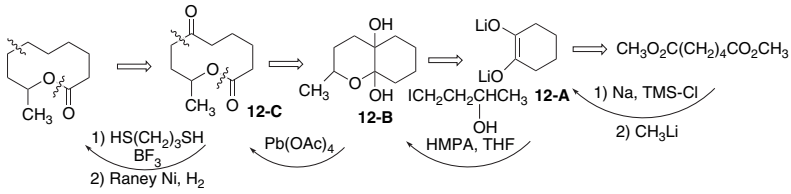
workup. The starting material was prepared by photocycloaddition of 2-pentyne to maleic anhydride.



c. This transformation requires an oxidation at the ketone and a fragmentation with desilylation. The reaction was accomplished by a Baeyer-Villiger oxidation using buffered MCPBA. The silyl group promotes migration, leading to regioselectivity. The lactone was then hydrolyzed with base and the elimination of the β-silylalcohol was achieved with BF_3.

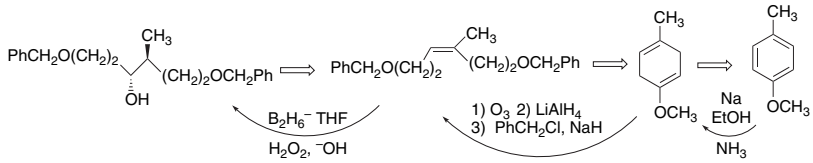


d. The key aspect of this synthesis is recognition of the potential role that the bicyclic diol (**12-B**) and enediolate (**12-A**) intermediates can play. The enediolate can be obtained by acyloin condensation in the presence of TMS-Cl, followed by cleavage with CH_3Li. The additional carbons can then be introduced by alkylation, which provides the correct oxidation state for cyclization to intermediate diol. This diol was oxidized to the macrocyclic ketolactone **12-C** by $Pb(OAc)_4$. The final step was removal of the ketone carbonyl by formation and hydrogenolysis of the dithiolane derivative. This route achieves formation of the macrocycle by application of the oxidative cleavage.

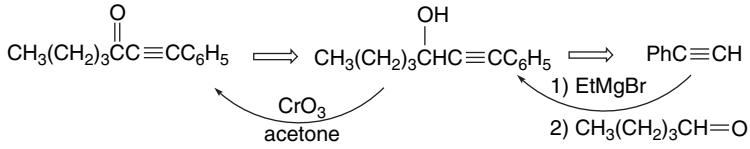


e. Recognition that the branched six-carbon chain corresponds to the one in the starting material suggests an oxidative cleavage, which can be done by Birch reduction, followed by selective ozonolysis of the vinyl ether group. Reduction of the ozonolysis product and benzylation introduces the

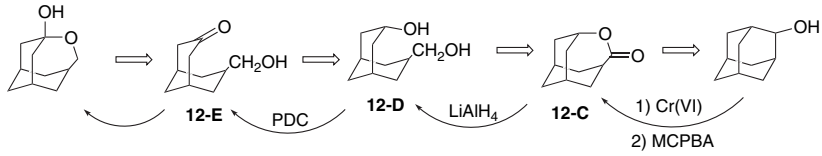
benzyloxy groups. The methyl group then controls the stereoselectivity of the hydroboration to provide the desired *anti* stereochemistry.



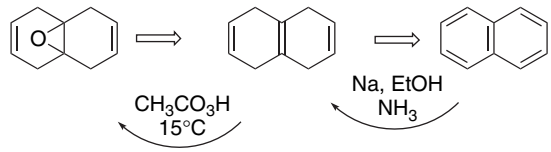
f. This is a straightforward construction of an alcohol by addition of an alkyne anion to an aldehyde, followed by oxidation to the desired ketone.



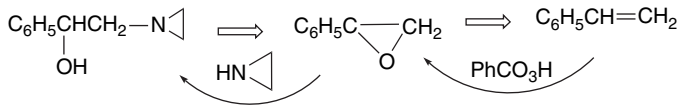
g. The desired product is the cyclic form of the keto alcohol intermediate **12-E**. It was obtained from **12-D** by taking advantage of the steric acceleration of Cr(III) oxidations. The diol **12-D** can be obtained from lactone **12-C** by $LiAlH_4$ reduction. The lactone can be obtained from admantanone by a Baeyer-Villiger oxidation.



h. This synthesis can be done by taking advantage of the greater reactivity of the tetrasubstituted double bond in 1,4,5,8-tetrahydronaphthalene, which can be obtained by Birch reduction of naphthalene.

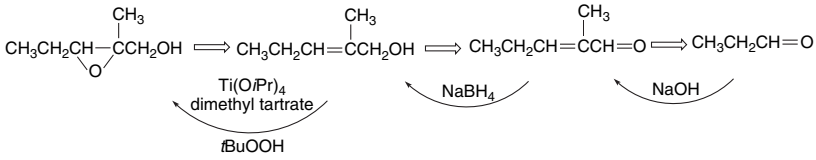


i. This transformation can be done by epoxidation, followed by nucleophilic ring opening using aziridine.

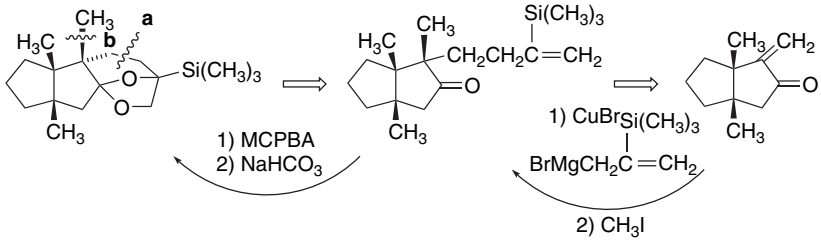


j. This α, β-epoxy alcohol can be made by allylic epoxidation using the $Ti(OR)_4$-*t*-BuOOH oxidation conditions. The reaction was carried out enantioselectively in the cited reference using a tartrate ester ligand. The

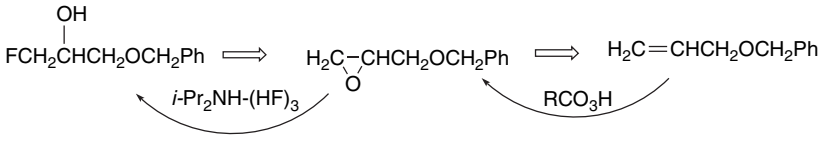
intermediate allylic alcohol can be obtained from the aldol condensation product of propanal.



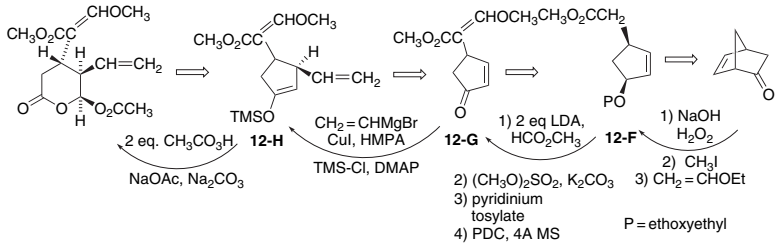
k. The disconnections **a** and **b** correspond to a tandem conjugate addition-alkylation, with respect to the enone unit present in the starting material. The β-silylallyl group was introduced using a mixed copper-magnesium reagent, followed by alkylation with methyl iodide. The terminal double bond was then converted to a diol by epoxidation and hydrolysis. The final product is the intramolecular cyclic acetal of this diol with the existing carbonyl.



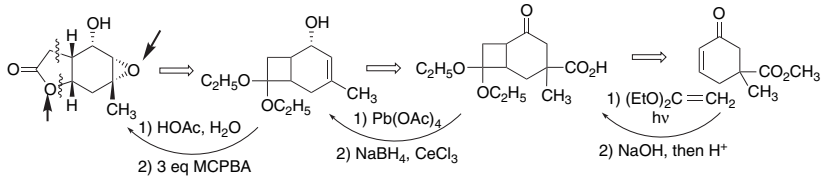
l. This transformation can be accomplished by nucleophilic ring opening of an epoxide intermediate with fluoride as the nucleophile. The transformation was accomplished with 6:1 regioselectivity using diisopropylammonium trihydrofluoride.



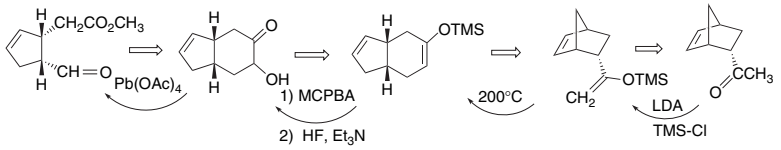
m. This synthetic sequence begins and ends with Baeyer-Villiger reactions. An alkaline Baeyer-Villiger reaction gave a lactone, which was hydrolyzed in situ. Methylation of the acid and protection of the hydroxy group by an EE group gave the first intermediate **12-F**. The methoxy methylene group was introduced by formylation and, after removal of the protecting group, the hydroxy group was oxidized to enone **12-G**. Copper-catalyzed conjugate addition of a vinyl group with trapping of the enolate with TMS-Cl generated intermediate **12-H**, setting the stage for the final oxidative cleavage. This step occurred in two stages: (a) transformation to the α-acetoxy ketone via the epoxide of the silyl enol ether and Baeyer-Villiger oxidation of this ketone.



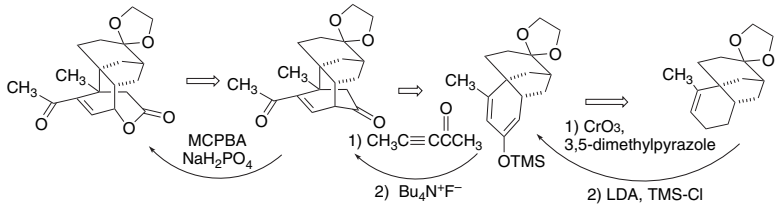
n. Comparison of the target molecule and the starting material identifies addition of the lactone ring, introduction of the epoxide and decarboxylation as the major changes required. The annulation was begun by a [2 + 2] photocycloaddition. The product was converted to an enone by oxidative decarboxylation using $Pb(OAc)_4$. This was followed by reduction of the ketone, the stereochemistry of which is controlled by the ring geometry. The hydroxy group then directed the epoxidation, and Baeyer-Villiger oxidation of the cyclobutanone ring was carried out at the same time.



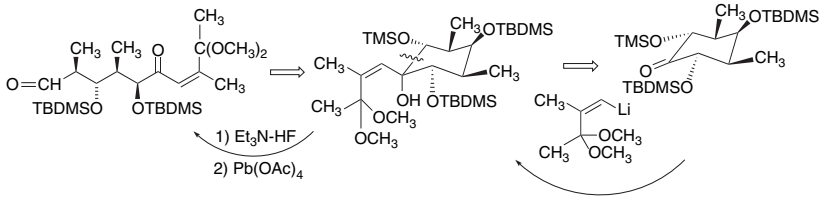
o. The first retrosynthetic transformation identifies an α-hydroxy ketone that can be oxidatively cleaved to the desired functionality. The α-hydroxy ketone can be obtained from a TMS enol ether. The required TMS ether is the product of Cope rearrangement of the TMS enol ether of the starting material.



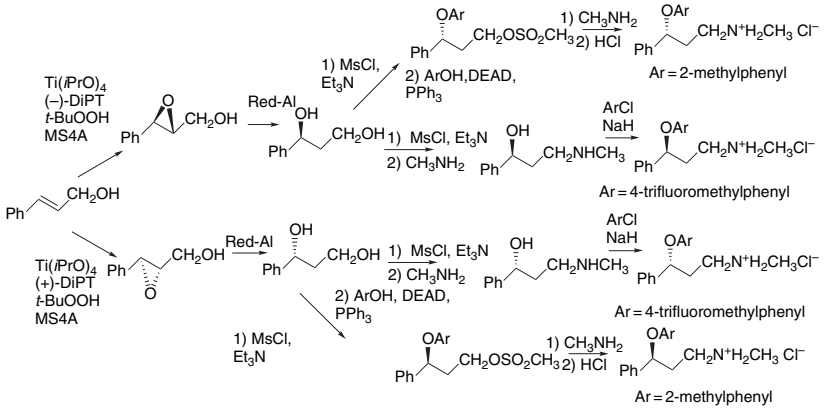
p. The bicyclic lactone can arise from the analogous bicyclo[2.2.2]ring by a Baeyer-Villiger oxidation. This compound can be formed from a Diels-Alder reaction. The required diene can be formed from the starting material by allylic oxidation, followed by conversion to the TMS enol ether.



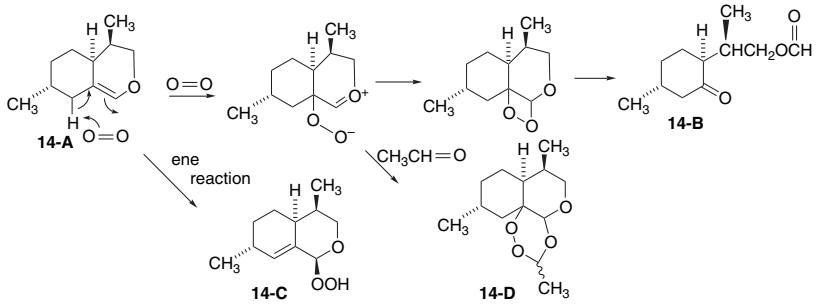
q. This transformation uses the stereochemistry present in the starting material to establish the configuration of the acyclic product. Indeed, all the stereocenters are present in the differentially protected starting material. The substituted vinyl group was introduced by an organometallic addition. The TMS group was then selectively removed, permitting oxidative fragmentation by $Pb(OAc)_4$.



12.13. These compounds can be prepared from cinnamyl alcohol by epoxidation and reductive ring opening of the epoxide. By choosing the correct tartrate ligand, the enantioselectivity of the epoxidation can be determined. Slightly different sequences were used for the stereospecific introduction of the aryloxy substituent. The 2-methylphenyl group in tomoxetine was introduced with *inversion* of configuration by a Mitsunobu reaction prior to amination. The amino substituent was introduced by nucleophilic displacement on the mesylate of the primary alcohol. The 4-trifluoromethylphenyl group in fluoxetine was introduced after the amination and was done with *retention* of configuration, taking advantage of the activating effect of the trifluoromethyl group toward nucleophilic aromatic substitution.

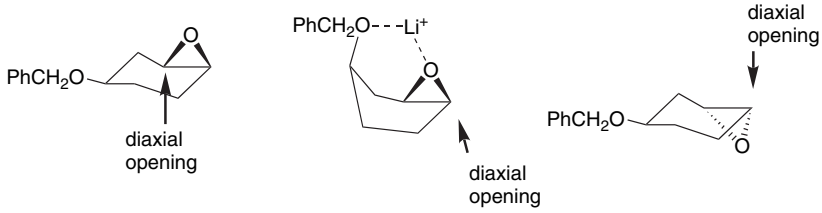


12.14. Product **14-B** can be formed by fragmentation of a the normal dioxetane product. Product **14-C** is the result of an ene reaction. The incursion of this process may reflect the change in solvent polarity. Product **14-D** results from trapping of the zwitterionic precursor of the dioxetane. Its formation provides evidence for the formation of this intermediate.

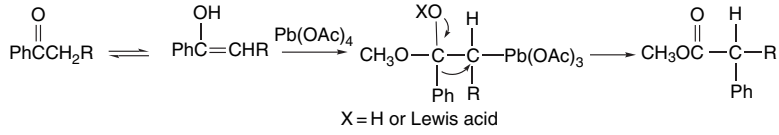


12.15. Only two substituents give preferential *cis* addition, namely hydroxy and amido. This suggests that a hydrogen-bonding effect is operating. In the case of the hydroxy substituent, the stereoselectivity is reversed in the presence of methanol, which provides competing hydrogen bonding. The hydrocarbon groups presumably operate primarily by steric effects. A correlation with a steric parameter is observed. The polar nonhydrogen bonding substituents are all *trans* directive, but the substituents that have a polar bond *directly* attached to the ring (CH_3O, Cl, CF_3) are more strongly directing than the others, which suggests that a dipolar effect may also be operating.

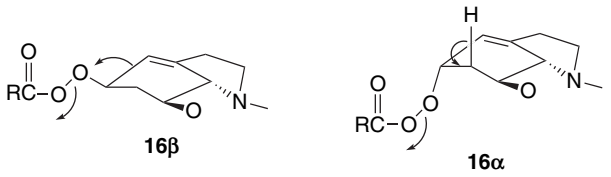
12.16. a. The *cis* isomer is evidently susceptible to chelation with Li^+ that causes a conformational shift. This chelation does not occur when Li^+ is complexed by 12-crown-4. No chelation is possible in the *trans* isomer and the usual diaxial opening is observed.



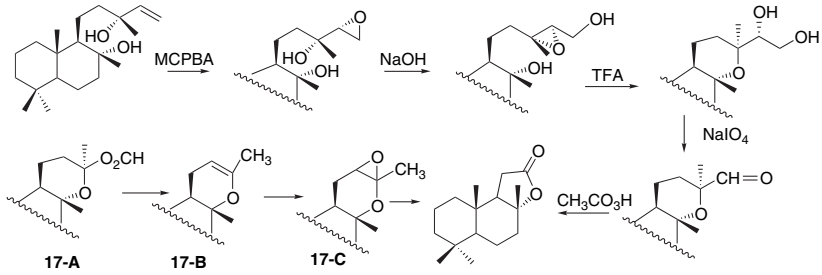
b. These reactions can be formulated as oxidation of an enol or enol ether, with migration of the aryl substituent.



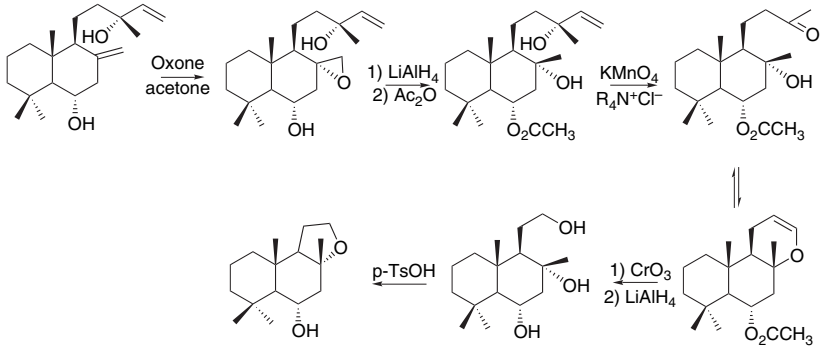
c. These results seem to reflect the preference for migration from an antiperiplanar arrangement. Such a conformation is accessible for vinyl group migration in **16β** but for **16α** the preferred reaction involves the loss of the proton.



12.17. a. The fist step is a hydroxy-directed epoxidation. This is followed by a reaction, known as the Payne rearrangement, in which an intramolecular opening of the epoxide occurs. The rearranged epoxide is then opened by a second, acid-catalyzed intramolecular reaction forming the six-membered ring. The diol is then cleaved by periodate. The final step in the sequence involves several reactions. The first step is a Baeyer-Villiger oxidation of the aldehyde to the formate ester **17-A**, which can undergo elimination to the dihydropyran **17-B**. This can undergo epoxidation to **17-C**, which is subject to ring opening to an α-hydroxyketone, that can undergo fragmentation to the carboxylic acid precursor of the lactone.



b. The first step is a selective epoxidation by Oxone involving in situ generation of dimethyldioxirane. Both double bonds are subject to a hydroxy-directing/activating step but the disubstituted double bond reacts preferentially. Perhaps *both* hydroxy groups can interact with dimethyldioxirane at this site. The epoxide is then opened by $LiAlH_4$ reduction. The allylic alcohol is cleaved with $KMnO_4$ in the presence of a phase transfer catalyst. The Cr(VI) cleavage of the dihydropyran ring proceeds to a mixture of aldehyde and acid that is reduced by $LiAlH_4$, which also removes the acetyl group from the 6-OH. The resulting diol is cyclized by acid.



12.18. The mechanisms follow a parallel route until diverging after step (d). This cation opens in the case of **18-B** but not for **18-A**. This result is attributed to the greater flexibility of the seven-membered ring in **18-B**, which allows for better stabilization of its carbocation. These results were supported by PM3 and B3LYP/6-31G* computations on the various intermediates, as shown in Figure 10.P18.

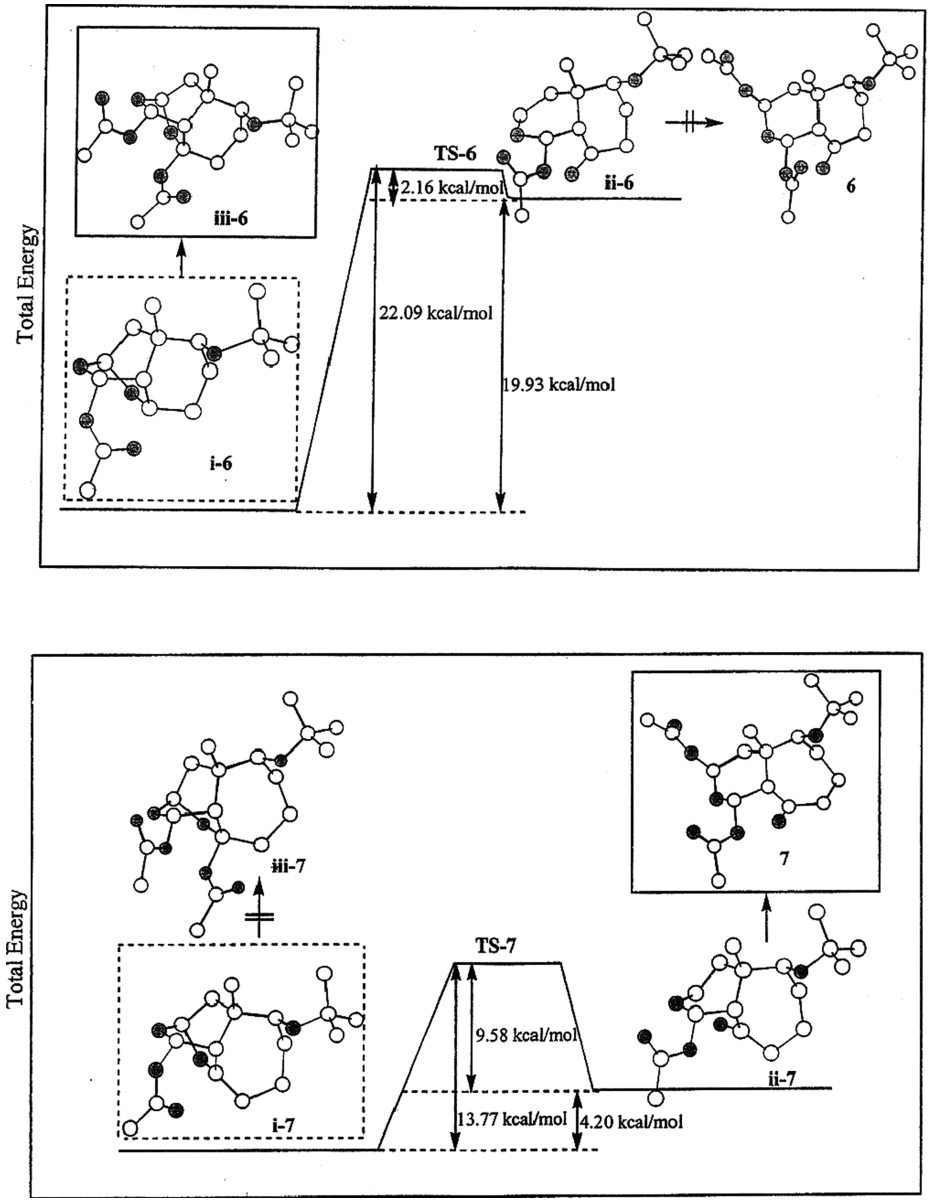
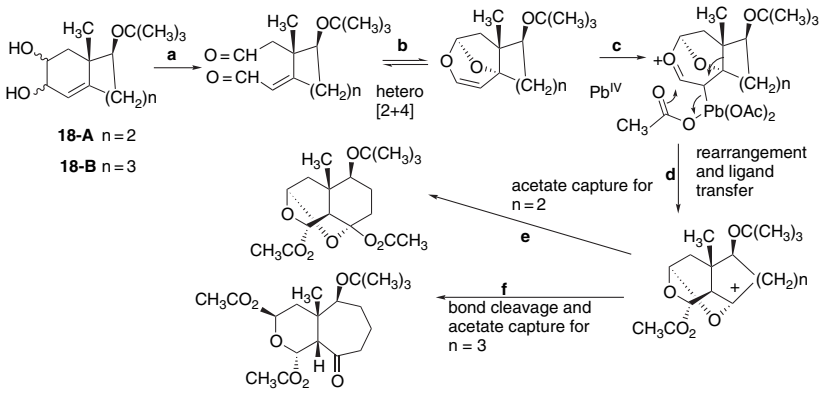
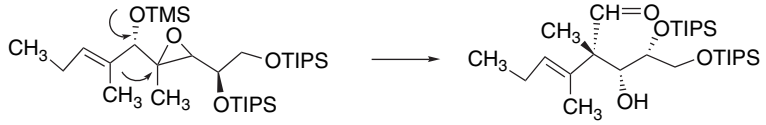


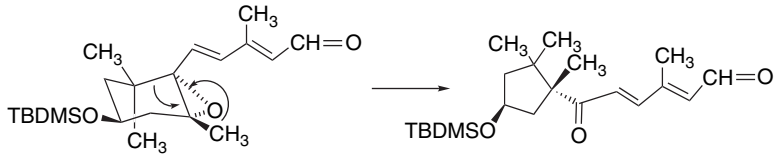
Fig. 12.P18. Comparison of the computed energy profiles for **18-A** and **18-B**. Reproduced from *J. Org. Chem.*, **67**, 2447 (2002), by permission of the American Chemical Society.



12.19. a. The trimethylsiloxy group promotes migration of the alkenyl substituent with inversion of configuration at the migration terminus.

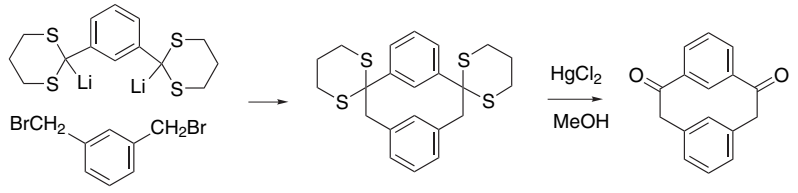


b. Ring contraction occurs by migration of the quaternary carbon center.

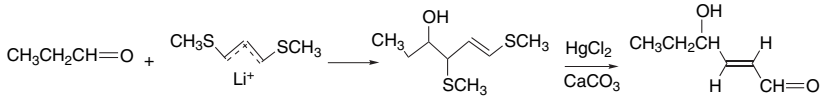


Chapter 13

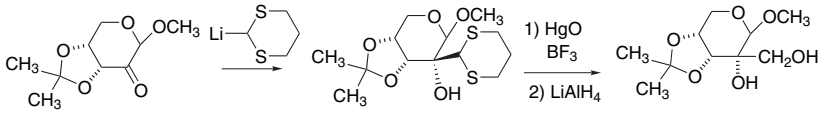
13.1. a. This transformation was done using the *bis*-dithiane derivative of 1,3-benzenedicarboxaldehyde. The *bis*-dithiane was lithiated and alkylated with the dibromide. The intermediate was hydrolyzed using $HgCl_2$ in methanol.



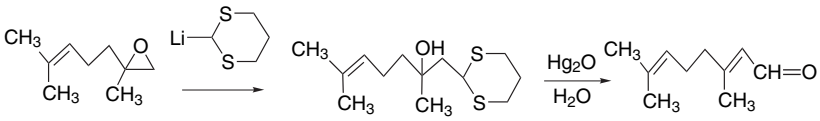
b. This synthesis was done by addition of the lithium derivative of 1,3-(methylthio)propene to propanal followed by hydrolysis. The reagent was generated from 2-methoxy-1,3-(dimethylthio)propane by treatment with LDA.



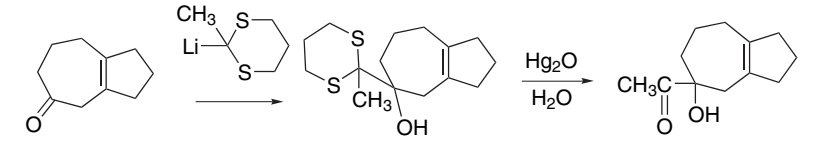
c. The carbon was added using 2-lithio-1,3-dithiane. The stereochemistry is the result of steric shielding by the dioxolane ring. The dithiane derivative was hydrolyzed to the aldehyde and reduced to the alcohol with $LiAlH_4$.



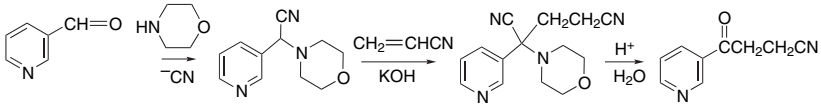
d. 2-Lithiodithiane was used to introduce the additional carbon. The hydrolysis conditions resulted in dehydration to the conjugated aldehyde.



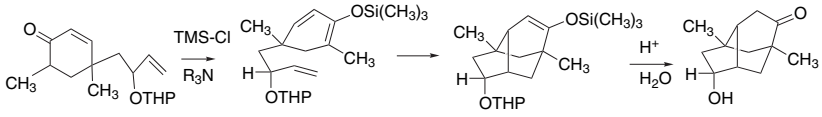
e. 2-Lithio-2-methyl-1,3-dithiane was used to introduce the two-carbon fragment as an acyl anion equivalent.



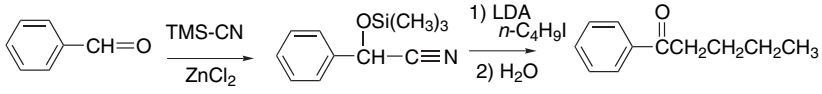
f. The amino nitrile derived from morpholine was lithiated and then alkylated by base-catalyzed conjugate addition to acrylonitrile. The amino nitrile was then hydrolyzed. This is a variant of the use of cyanohydrin ethers as acyl anion equivalents.



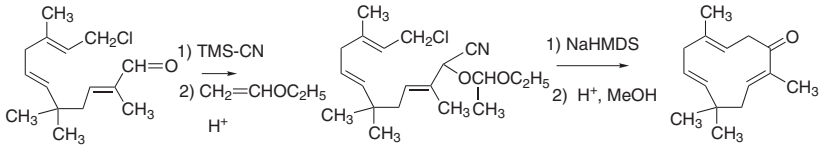
g. The conversion of the enone moiety to a trimethylsiloxy diene led to an intramolecular Diels-Alder reaction. Hydrolysis of the adduct generated the desired product.



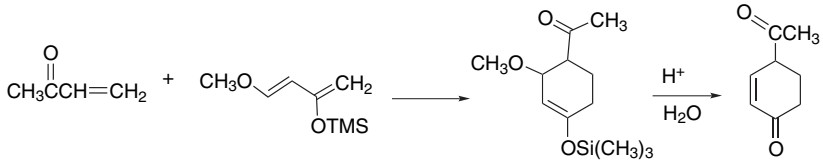
h. The aldehyde was converted to the TMS-protected cyanohydrin and then alkylated using LDA. Hydrolysis provided the ketone.



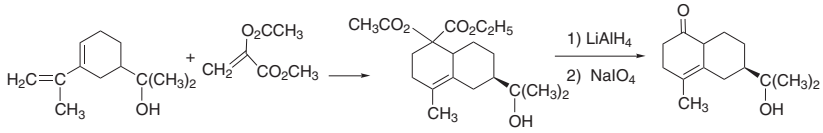
i. The aldehyde was converted to the ethoxyethyl-protected cyanohydrin. Intramolecular alkylation of the anion formed the ring and hydrolysis of the protected cyanohydrin provided the carbonyl group.



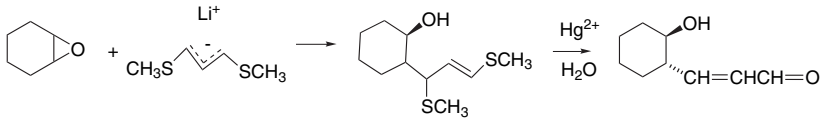
13.2. a. This transformation was accomplished by use of the Danishefsky diene, followed by hydrolysis.



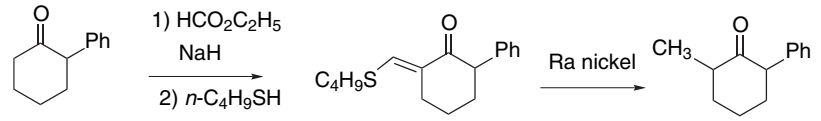
b. The transformation requires a "ketene equivalent" as a dienophile. The cited reference used ethyl α-acetoxyacrylate. The adduct was reduced to a diol and then cleaved by $NaIO_4$ to provide the desired product. Presumably other "ketene equivalent" dienophiles such as α-chloroacrylonitrile or nitroethene (see Section 6.1.4.1) would also be applicable.



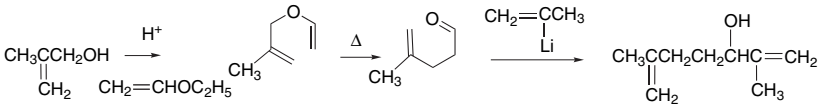
c. This transformation requires a nucleophilic equivalent of propenal. In the cited reference the anion of 1,3-di(methylthio)propene was used. Other examples of nucleophilic propenal equivalents are given on p. 1170.



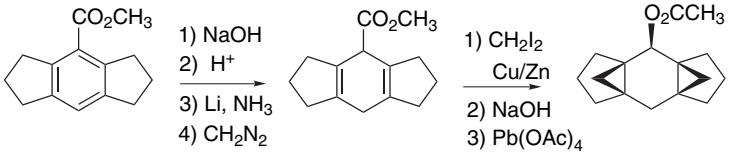
d. In the cited reference, this selective methylation was done by forming the *n*-butylthiomethylene derivative, which was then reduced and desulfurized with Raney nickel. The direct methylation of the less-substituted kinetic enolate does not seem to have been reported, but should be feasible.



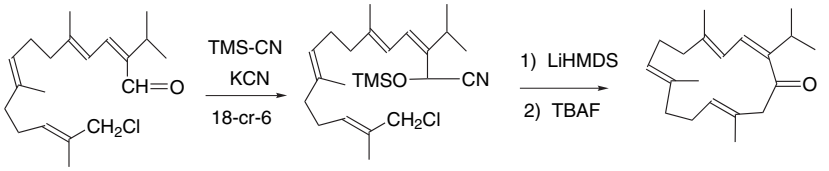
e. This transformation was effected in two major stages. An exchange-Claisen rearrangement with ethyl vinyl ether provided the intermediate aldehyde, which gave the product on reaction with 2-lithio propene.



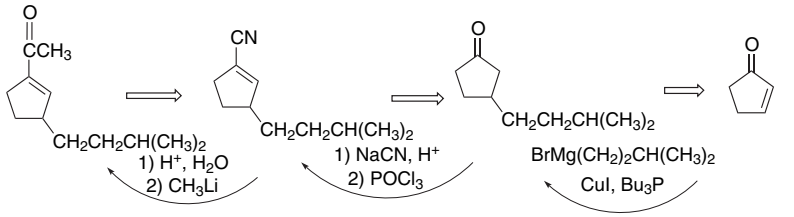
f. The ester was hydrolyzed and reduced to the 1,4-dihydro derivative by Birch reduction. After esterification with diazomethane, the *bis*-cyclopropanation was done with Simmons-Smith reagent. The *syn* stereochemistry suggests a directing effect by the ester group. After the cyclopropanation, the ester group was hydrolyzed and subjected to oxidative decarboxylation.



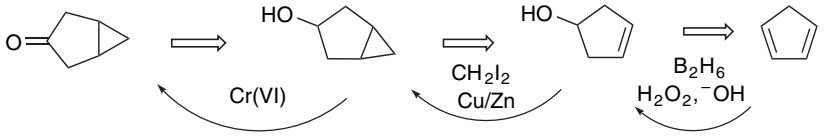
g. This intramolecular alkylation of an "aldehyde anion" equivalent was done by formation of the TMS-protected cyanohydrin anion by LiHMDS, intramolecular alkylation, and cleavage of the protected cyanohydrin using TBAF.



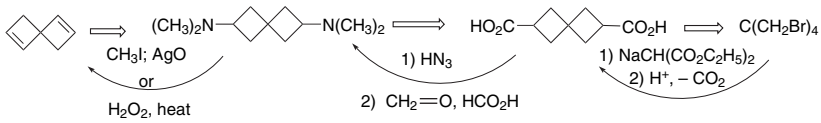
13.3. a. The sequence shown used copper-catalyzed conjugate addition to install the *i*-pentyl substituent. The C=O to acetyl transformation was then accomplished via a nitrile intermediate, which was hydrolyzed to the carboxylic acid and then converted to the methyl ketone by methyllithium. Addition of an acetyl anion equivalent, followed by dehydration would be an alternative approach.



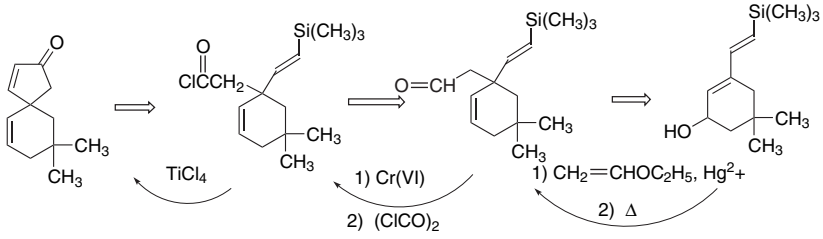
b. This transformation was done by selective hydroboration-oxidation, followed by Simmons-Smith cyclopropanation and oxidation to the ketone.



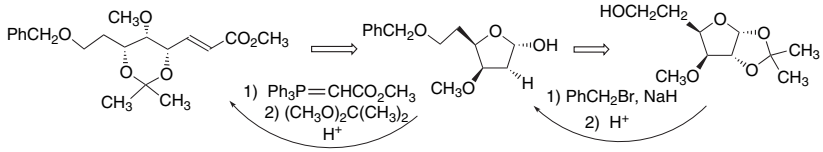
c. The cited reference reports several methods for preparation of this spiro diene, including both Hoffman and Cope eliminations. All proceed through a dicarboxylic acid precursor that is formed by a malonate alkylation and decarboxylation from the tetrabromide starting material. The amine intermediate was formed by a Schmidt reaction, followed by reductive methylation.



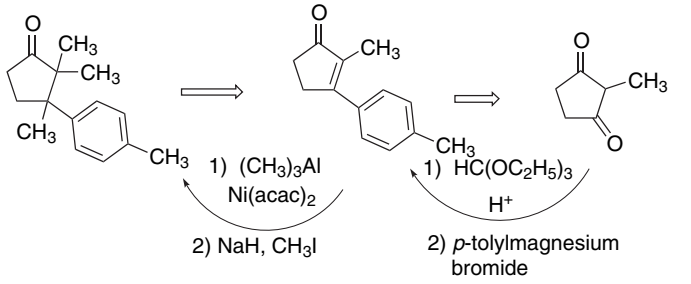
d. The allylic alcohol function was used to introduce a 2-carbon fragment by a Claisen rearrangement. After oxidation to the carboxylic acid level, the acid was converted to an acyl chloride, which was used in an intramolecular acylation of the vinyl silane.



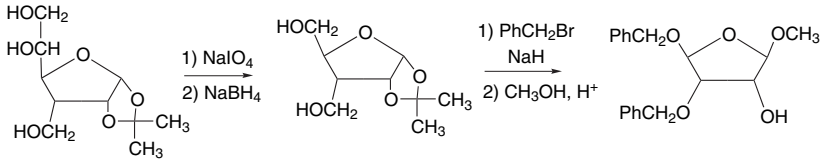
e. After protection of the primary alcohol by a benzyl group, the acetonide protecting group was removed, exposing a lactol. The α, β-unsaturated ester was introduced by a Wittig reaction. An acetonide protecting group was then installed at the 4,6-diol by exchange with 2,2-dimethoxypropane.



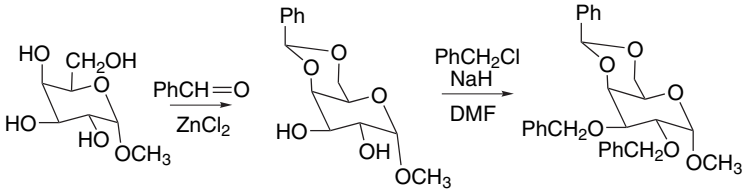
f. The starting material was converted to the enol ether and then subjected to conjugate addition, with elimination of the ethoxy group. The β-methyl group was introduced by a $Ni(acac)_2$-catalyzed addition reaction with trimethylaluminum. The α-methyl group was introduced by enolate alkylation under thermodynamic conditions.



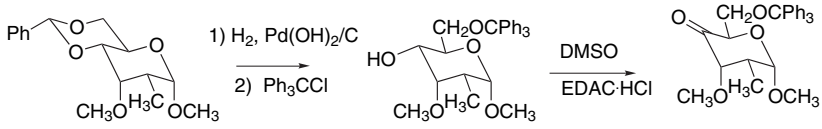
13.4. a. This chain-shortening sequence was carried out by periodate oxidation, followed by $NaBH_4$ reduction. Benzylation of the two unprotected primary hydroxy groups and removal of the acetonide and methanolysis at the anomeric center gave the product.



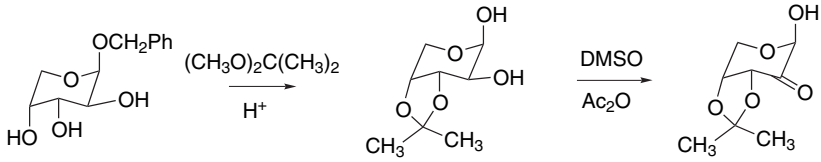
b. A benzylidene group selectively protected the 4- and 5-hydroxy groups. The remaining hydroxy groups were then benzylated.



c. The benzylidene protecting group was removed by benzylic hydrogenolysis. The primary hydroxy was protected as the trityl derivative and the unprotected secondary hydroxy was then oxidized.

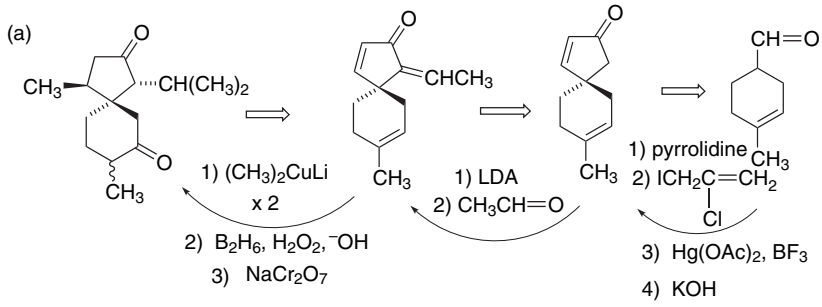


d. Selective protection of the 3,4-hydroxy groups was accomplished using 2,2-dimethoxypropane. The unprotected 2-hydroxy was then oxidized using DMSO, Ac_2O.

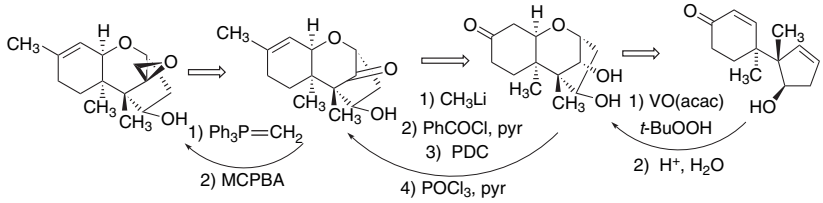


13.5. a. The first synthetic sequence formed the cyclopentenone ring using an enamine alkylation with 2-chloro-3-iodopropene, followed by hydrolysis of the vinyl chloride and an intramolecular aldol condensation. In the second synthetic sequence, an ethylidene group was introduced by enolate formation and aldol condensation. The two methyl groups were installed by two sequential one-pot reactions with lithium dimethyl cuprate. The addition to the endocyclic double was stereoselective, occurring *syn* to the cyclohexene

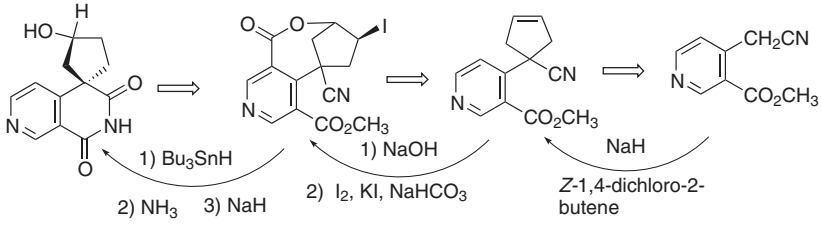
double bond. The remaining carbon-carbon double bond was then converted to the ketone by hydroboration followed by Cr(VI) oxidation.



b. The unconjugated double bond was epoxidized by a hydroxy-assisted reaction with VO(acac) and *t*-butyl hydroperoxide. Acid-catalyzed opening of the epoxide occurred with inversion and was followed by intramolecular conjugate addition to the enone to give the first intermediate. In the next sequence of reactions, a methyl group was added using CH_3Li, followed by selective benzoylation of the less hindered secondary alcohol, oxidation, and dehydration of the tertiary alcohol with $POCl_3$. Finally, the spiro epoxide was introduced by a Wittig reaction and epoxidation.

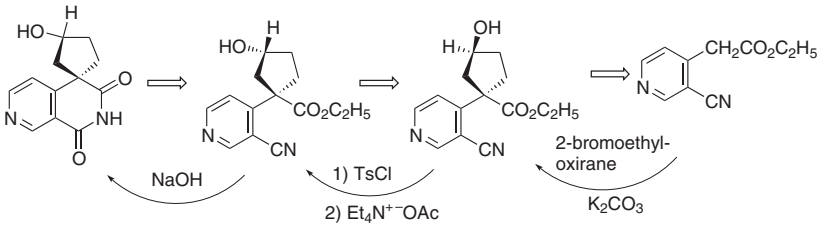


c. The hydroxycyclopentene ring was constructed by an cyclizative dialkylation using *Z*-1,4-dichlorobutene. The ester group was then hydrolyzed and subjected to iodolactonization. After reductive deiodination using Bu_3SnH, the lactone ring was cleaved by aminolysis and the amide cyclized with NaH. Hydrolytic workup gave the imide.

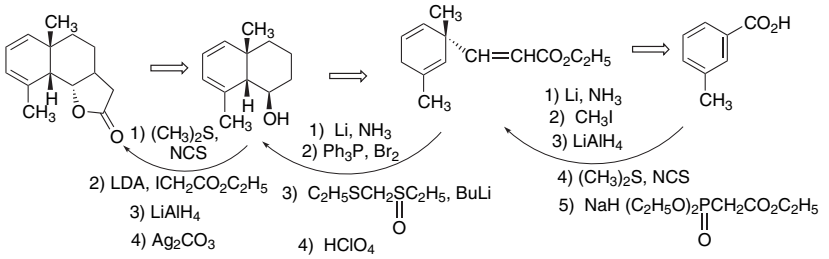


d. The hydroxycyclopentane ring was created by a dialkylation using 2-bromoethyloxirane. The opening of the epoxide ring gave a configuration

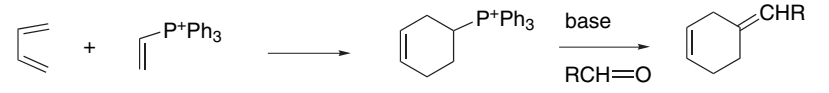
opposite to that required. The inversion was done via the tosylate by acetate displacement. The cyclization of the imide ring was then effected with NaOH.



e. The retrosynthetic diagram identifies the three major components of the synthesis: (a) Birch reduction of the aromatic ring and extension of the carboxy group by two carbons. (b) cyclization of the four-carbon side chain; and (c) construction of a lactone ring starting from the secondary alcohol group. In the cited reference, the Birch reduction was followed by methylation at C(1). Extension of the side chain was effected by conversion to the aldehyde, followed by a Wadsworth-Emmons reaction. In the second phase of the synthesis, the unsaturated ester side chain was converted to the primary alcohol by Li-NH_3, and then to the corresponding bromide. The additional carbon was introduced using ethylthiomethyl ethyl sulfoxide as a nucleophilic equivalent of a formyl group, and this derivative was cyclized by a carbonyl-ene reaction using $HClO_4$. In the third stage, the secondary alcohol was oxidized to the ketone and alkylated with ethyl iodoacetate. After $LiAlH_4$ reduction to the diol, the lactone ring was formed oxidatively using Ag_2CO_3.

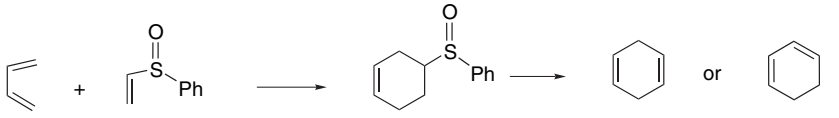


13.6. a. Diels-Alder reactions with vinylphosphonium salts generate adducts that be converted to ylides, which can react with carbonyl compounds to give alkenes. In this sequence, the vinylphosphonium salt serves as an equivalent of an allene dienophile.



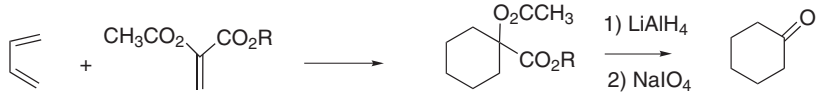
equivalent structure: $H_2C{=}C{=}CHR$

b. Diels-Alder reactions of vinyl sulfoxides generate sulfoxides that can undergo subsequent thermal elimination. In this sequence of reactions, the vinyl sulfoxide serves as an ethyne equivalent.



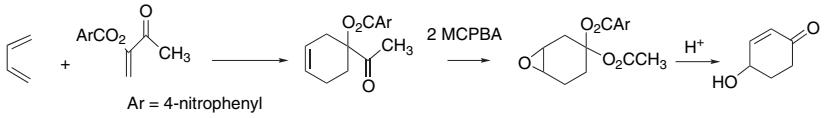
equivalent structure: HC≡CH if elimination gives the 1,4-diene

c. α-Acetoxyacrylate esters can serve as ketene equivalents. The adducts can be reduced to diols by $LiAlH_4$ and then oxidized by $NaIO_4$. This reaction sequence is equivalent to a ketene [4+2] cycloaddition.



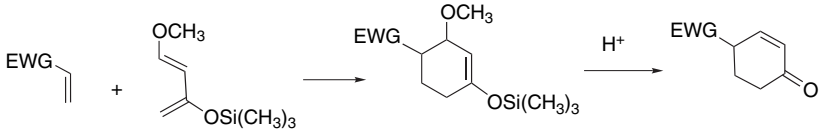
equivalent structure: $H_2C{=}C{=}O$

d. This compound can act as a ketene equivalent and also effects a formal allylic oxidation in the diene portion to give 4-hydroxycyclohexenone. The reaction sequence involves both epoxidation and a Baeyer-Villager oxidation. Hydrolysis and epoxide ring opening give the product without additional reagents, presumably under acid catalysis from the *m*-chlorobenzoic acid generated by the oxidation.



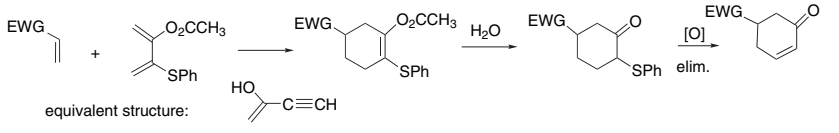
Ar = 4-nitrophenyl

e. This is the Danishefsky diene. Acidic hydrolysis and dehydration of the adducts give enones. The formal equivalent structure is 2-hydroxybuten-3-yne.



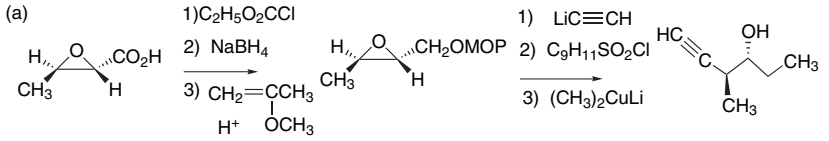
equivalent structure: $HC{\equiv}CC(OH){=}CH_2$

f. The Diels-Alder adducts are the enol acetates of α-phenylthio ketones. These can be oxidized to sulfoxides that can undergo elimination reactions. The formal equivalent is a hydroxyenyne structure. Because the regiochemistry is determined by the phenylthio substituent, the overall transformation is regioisomeric with respect to the Danishefsky diene (see (e) of this question).

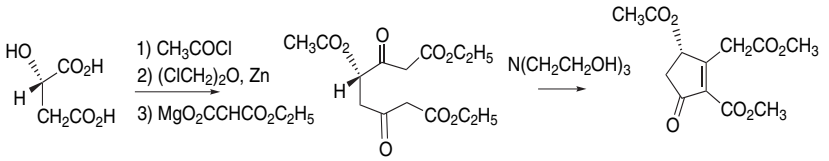


equivalent structure:

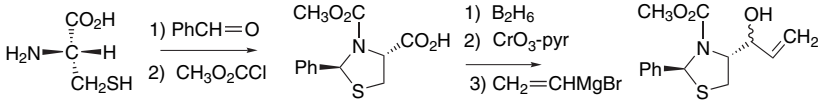
13.7. a. This transformation requires introduction of the alkyne moiety with inversion of configuration at C(3), which suggests opening of the epoxide by an acetylide anion. The carboxy group must be converted to ethyl with retention of configuration at C(2). The reported sequence involved reduction of the carboxy group to a primary alcohol via a mixed carbonic anhydride. After protection as the MOP derivative, the epoxide ring was opened with lithioethyne. The primary alcohol was then deprotected and converted to ethyl via the mesitylenesulfonate by reaction with lithium dimethylcuprate.



b. A key to an efficient route for this transformation is the identification of the potential of an intramolecular aldol condensation to form the five-membered ring. This requires conversion of both carboxy groups in the starting material to β-ketoesters. In the reported sequence, the hydroxy group was first acetylated and the two carboxy groups were converted to acyl chlorides using *bis*-chloromethyl ether–$ZnCl_2$. The β-ketoester groups were then introduced using the magnesio monoethyl malonate reagent, which permits facile decarboxylation (see p. 152). The aldol cyclization was done using triethanolamine.

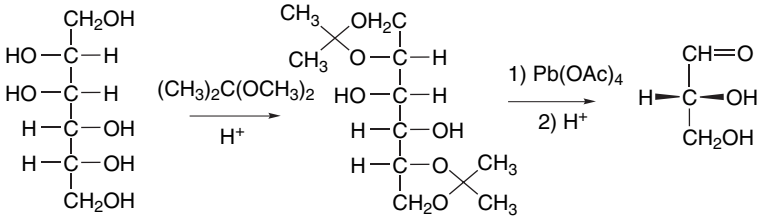


c. This transformation requires cyclization and *N*-protection of the NH_2 and SH groups in cysteine and introduction of an allylic alcohol moiety at the carboxy group. The former two conversions were effected by cyclization with benzaldehyde, followed by acylation with methyl chloroformate. The side-chain transformation was accomplished by reduction with B_2H_6, followed by oxidation to the aldehyde with CrO_3-pyridine. Addition of vinylmagnesium bromide completed the synthesis.

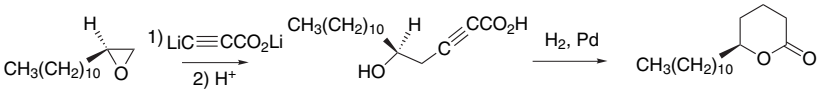


d. The configurations at C(2) and C(5) of mannitol, the starting material, correspond to that required for C(2) in the desired product. Thus oxidative cleavage of the C(3)–C(4) bond to the aldehyde level would provide the required product. Mannitol can be converted to the 1,2–5,6-diacetonide,

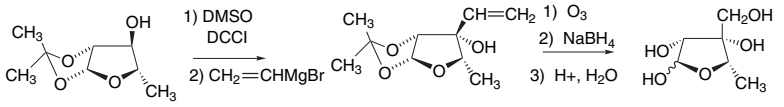
providing the required protection of the other hydroxy groups. The oxidation was carried out with $Pb(OAc)_4$, although $NaIO_4$ should also be suitable.



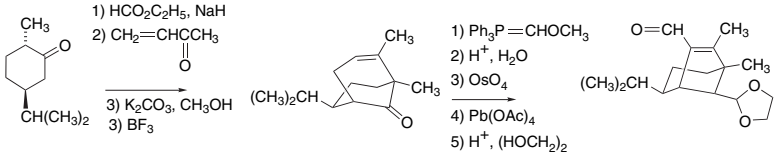
e. Opening of the epoxide ring with a synthon corresponding to C(1)–C(3) of the lactone followed by cyclization could accomplish this transformation. In the cited reference, the dilithium derivative of propynoic acid was used. After the ring opening, reduction of the triple bond led to spontaneous lactonization.



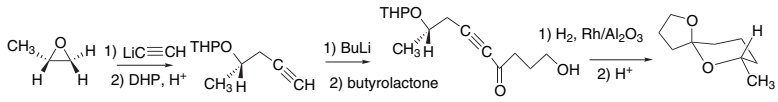
f. This transformation requires introduction of a hydroxymethyl group at C(3) of 5-deoxy-L-arabinose [protected as the C(1)–C(2) acetonide]. This was accomplished by oxidation of the unprotected C(3) hydroxy using DMSO-DCCI, followed by addition of vinylmagnesium bromide. The stereoselectivity is presumably the result of the steric shielding of the α-face of the molecule by the acetonide. The vinyl group was then ozonized, followed by reduction with $NaBH_4$. Removal of the protecting group led to the equilibrium mixture of the C(1) stereoisomers.



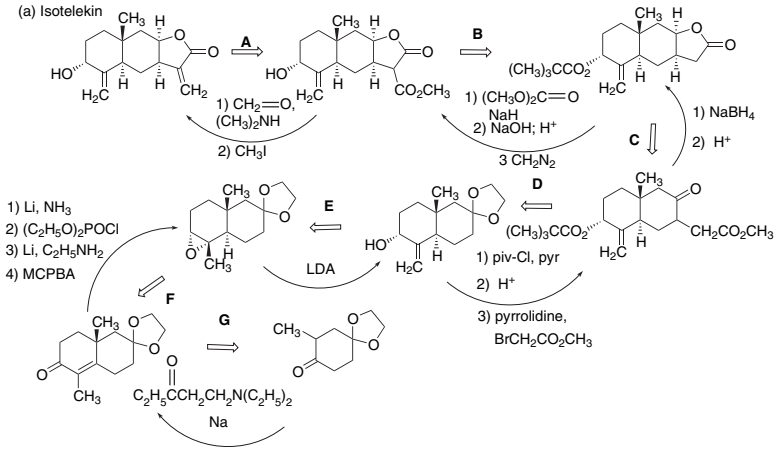
g. The starting material is carvomenthone. The first stage of the synthesis involved introduction of a 3-oxobutyl substituent by conjugate addition to methyl vinyl ketone. The unsubstituted methylene group was selectively activated by conversion to the hydroxymethylene derivative. After deformylation, intramolecular aldol reaction was effected with BF_3. The fully substituted bridgehead carbon results in a β, γ-elimination. In the next stage, the exocyclic aldehyde group was introduced by a Wittig reaction using methoxymethylene triphenylphosphorane, followed by hydrolysis. In the final step, the ring was contracted with introduction of the formyl group by oxidative cleavage, followed by an intramolecular aldol reaction.



h. This transformation was effected by first opening the epoxide at the less-substituted carbon with lithioethyne. The alcohol was then protected as the THP derivative, and the anion of the alkyne was added to butyrolactone. Reduction of the triple bond and exposure to acid led to cyclization to the internal acetal.

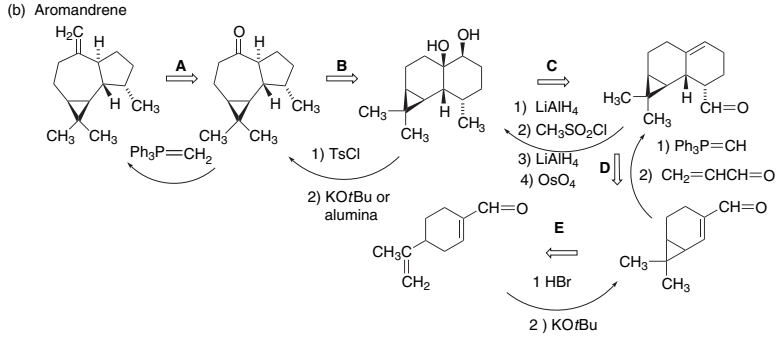


13.8. a. The first step in the forward synthetic direction was a Robinson annulation. In the cited reference this reaction was done by in situ generation of methyl vinyl ketone from 1-dimethylamino-3-pentanone. The conditions used are somewhat unusual. (See Section 2.1.4 for more typical Robinson annulation conditions.) Sodium metal was added to the pure ketone. Presumably this resulted in enolate formation. The amino ketone was then added. Enolate equilibration presumably leads to elimination of diethylamine. In the next stage of the synthesis, an enolate was formed by conjugate reduction, trapped as the enol phosphate, and reduced to the 1,2-ene. The final step in this sequence was epoxidation. In the next stage, the epoxide was opened to give the allylic alcohol. The hydroxy was then protected as the pivalate ester. After removal of the dioxolane protecting group, the ketone was alkylated via the pyrrolidine intermediate. Reduction was followed by lactonization in Step **C**. The last two reaction sequences installed the conjugated exocyclic methylene group. The lactone was then carboxymethylated, and this was accompanied by transesterification at the pivaloyloxy group. Both the ester and carbonate groups were hydrolyzed and the carboxy group re-esterified using diazomethane. A Mannich reaction followed by elimination promoted by quaternization completed the synthesis.

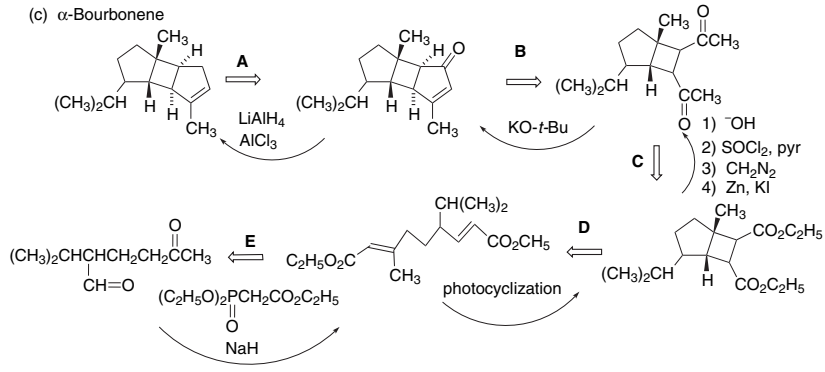


b. The synthesis started with the terpenoid perillaldehyde. Addition of HBr provided a tertiary bromide that underwent an intramolecular γ-alkylation to form the dimethylcyclopropane moiety on treatment with KO-*t*-Bu. The aldehyde reacted with methylenetriphenylphosphorane to give a diene, which on Diels-Alder reaction with acrolein formed the fused cyclohexene

ring. The aldehyde group was then converted to methyl by a three-step sequence and the remaining double bond was dihydroxylated using OsO_4. The diol was then monotosylated, setting the stage for the crucial pinacol-type rearrangement that converted the [4.4.0]-skeleton to a [5.3.0] skeleton. The synthesis was completed by Wittig methylenation.

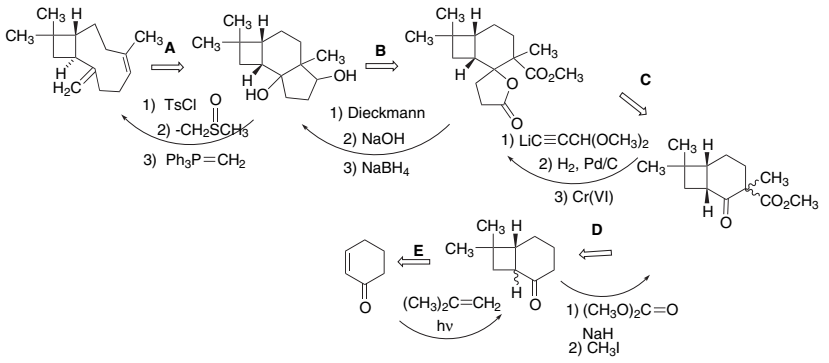


c. The first step was a Wadsworth-Emmons reaction that converted both the aldehyde and ketone carbonyls to α,β-unsaturated esters. The 1,6-diene system was photocyclized to give the [3.2.0] bicyclic core. The two ester groups were then converted to methyl ketones via the acid chloride and α-diazo ketone, followed by reduction with zinc These were then cyclized by an intramolecular aldol reaction. In the final step in the synthesis, the carbonyl group was removed using $LiAlH_4$-$AlCl_3$.



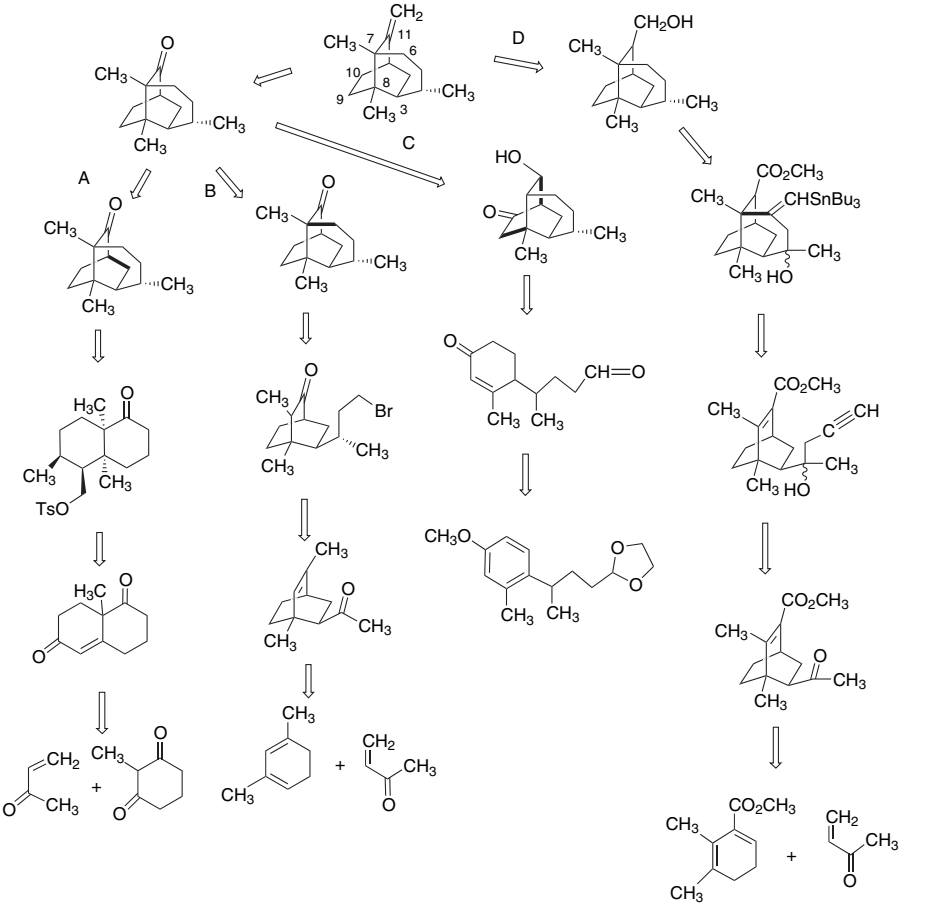
d. The synthesis started with regioselective photocycloaddition of 2-methylpropene to cyclohexenone (see Section 6.3.2.1). The carbonyl group was then carbomethoxylated and methylated. The spiro lactone ring was installed in the third phase of the synthesis by adding lithio-3,3-dimethoxypropyne, which serves as a propanal homoenolate equivalent. After hydrogenation, cyclization to a lactol occurred followed by conversion to the lactone by oxidation. The next stage effected an intramolecular Dieckmann reaction. The ketoester was hydrolyzed and decarboxylated prior to reduction to the secondary alcohol. The last phase of the synthesis was

a fragmentation of the γ-hydroxy tosylate to form the nine-membered ring and methylenation of the ketone by a Wittig methylenation.



13.9. a. About 15 syntheses of seychellene have been completed. A few of the retrosynthetic pathways are outlined below. Most of the syntheses proceed

Scheme 13.P9a. Retrosynthetic Schemes for Seychellene

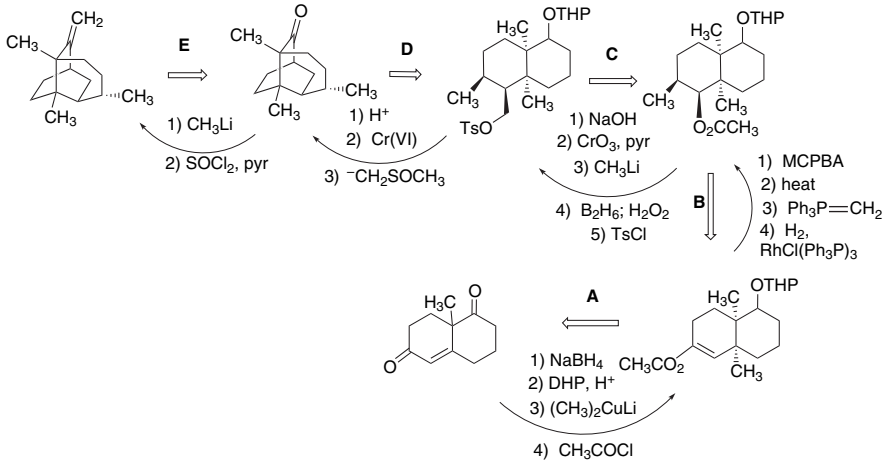


through the C(11) ketone, with final conversion to seychellene by addition of methyllithium to give the tertiary alcohol, followed by dehydration. Corresponding synthetic schemes are shown in Schemes 13.P9a1–a4. Key bond disconnections are shown in bold. Retrosynthetic path A is based on an enolate alkylation to form the C(1)–C(2) bond and leads back to the Wieland-Miescher ketone, which can be synthesized by a Robinson annulation, as the starting material. Route B also uses an intramolecular enolate alkylation to form the tricyclic ring system, but in this case the C(6)–C(7) bond is formed. The starting material in this case is a Diels-Alder adduct of 1,3-dimethyl-1,3-cyclohexadiene and methyl vinyl ketone. Note that the synthesis requires translocation of one of the methyl groups, suggesting that 2,3-dimethyl-1,3-cyclohexadiene may be an alternative starting material. In route C, a tandem Michael-aldol sequence forms both the C(1)–C(11) and C(8)–C(9) bonds, In this scheme, the C(7) methyl substituent is added by a subsequent alkylation. Route D uses a radical cyclization to form the C(6)–C(7) bond. This route also incorporates a Diels-Alder reaction for the preparation of the bicyclic starting material.

Scheme 13.P9a-1 shows the synthesis corresponding to retrosynthetic route A. This synthesis is stereocontrolled on the basis of the facial selectivity built into the Wieland-Miescher ketone. For example, the cuprate addition in Step **A**-3 led to a *cis* ring junction and the hydrogenation in Step **B**-4 led to the β-configuration of the methyl group. Another noteworthy feature of this synthesis is the thermal rearrangement of the acetoxy epoxide in Step **B**-2, which led to a 1-acetoxy-2-oxo intermediate. The key intramolecular enolate alkylation in Step **D**-3 was done using the anion of DMSO as the base.

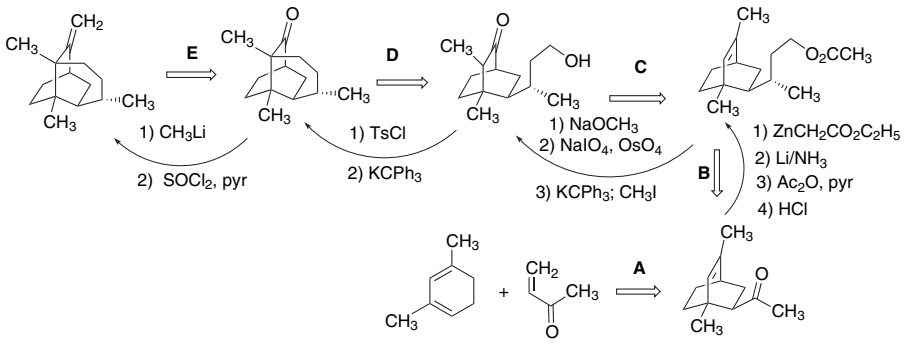
Scheme 13.P9a-2 shows the synthesis following retrosynthetic route B. This synthesis involved separation of isomers at two points. The Li-NH_3 reduction in Step **B**-2 generated a 4:1 mixture of stereoisomers at the methyl group. The dehydrochlorination at Step **C**-1 generated some of the endocyclic alkene as well as the desired exocyclic isomer. The intramolecular

Scheme 13.P9a-1. Seychellene Synthesis: E. Piers, R. W. Britton, and W. de Waal[a]



a. E. Piers, R. W. Britton, and W. de Waal, *J. Am. Chem. Soc*., **93**, 5113 (1971).

Scheme 13.P9a-2. Seychellene Synthesis: K. J. Schmalzl and R. N. Mirrington[a]



a. K. J. Schmalzl and R. N. Mirrington, *Tetrahedron Lett*., 3219 (1970).

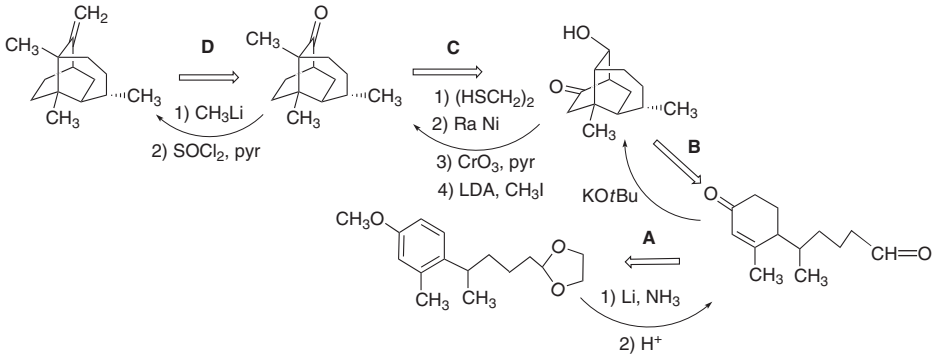
enolate alkylation in Step **D**-2 was done using potassium triphenylmethide as the base.

Scheme 13.P9a-3 shows the synthesis corresponding to retrosynthetic route C. The key intermediate was generated by a Birch reduction. The key step in this synthesis was the cyclization at Step **B**, which involves tandem conjugate addition to the enone and an aldol cyclization. The reactant was a mixture of stereoisomers at the methyl group in the side chain, but the major product has the correct stereochemistry.

Scheme 13.P9a-4 shows the synthesis corresponding to retrosynthetic route D. The key step in this synthesis was the radical cyclization at Step **B**. The hydrogenation at Step **D**-1 was completely stereoselective, as would be expected from the shape of the ring. In Step **E**-1, the lactone ring is methanolized and the alcohol that formed is dehydrated, followed by hydrogenation. In contrast to the prior three syntheses, the final step in this synthesis is the dehydration of a primary alcohol via the mesylate (Steps **E**-4 and **E**-5).

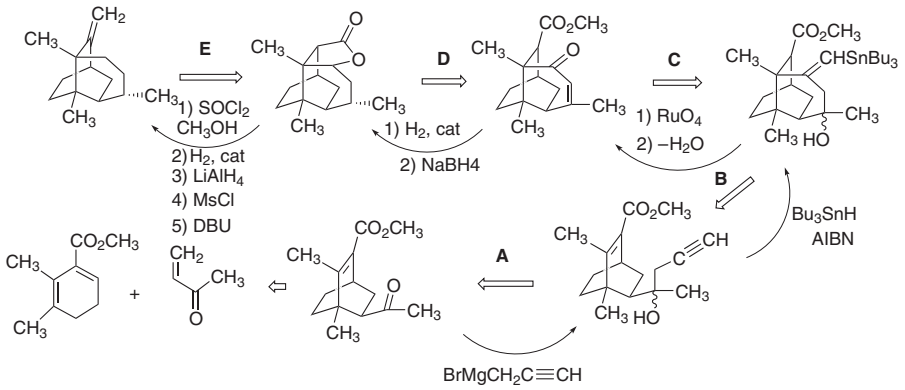
b. Approximately 30 syntheses of brefeldin A have been reported. Most use a macrolactonization as the final step. Several of the syntheses are outlined

Scheme 13.P9a-3. Seychellene Synthesis: K. Yamada, Y. Kyotani, S. Manabe, and M. Suzuki[a]



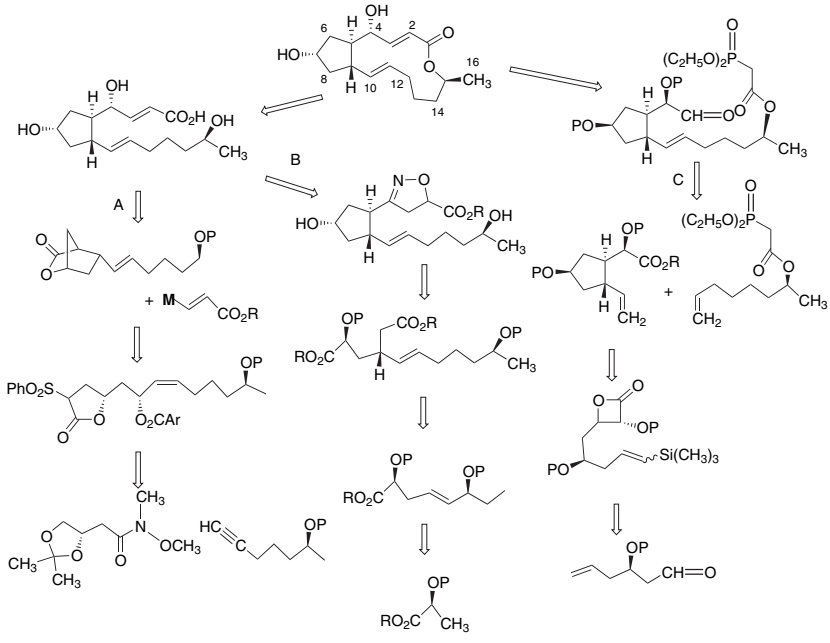
a. K. Yamada, Y. Kyotani, S. Manabe, and M. Suzuki, *Tetrahedron*, **35**, 293 (1979).

Scheme 13.P9a-4. Seychellene Synthesis: K. V. Bhaskar and G. S. R. S. Rao[a]

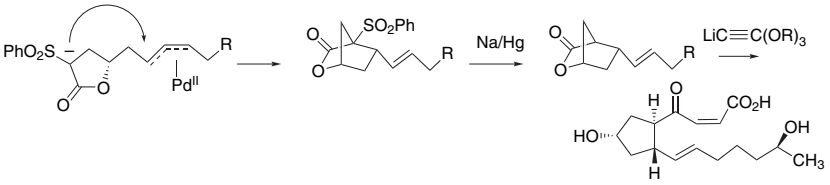


a. K. V. Bashkar and G. S. R. S. Rao, *Tetrahedron Lett*., **30**, 225 (1989).

in retrosynthetic format in the scheme below. Route A used a vinylogous acyl anion equivalent to add C(1)–C(3). The bicyclic lactone was formed by a Pd-catalyzed allylic substitution. Another major part of this synthesis involves coupling the C(10)–C(16) and C(6)–C(9) fragments via an acetylide and Weinreb amide. Route B used a nitrile oxide cycloaddition to add the carboxy terminus. The remainder of the molecule was built up from methyl 2-hydroxypropanoate by a series of [3.3]-sigmatropic (Claisen-type) rearrangements. Route C uses olefin metathesis reactions at two stages and a Wadsworth-Emmons reaction for the macrocyclization. The initial stage of this synthesis uses a variation of Mukaiyama reactivity in which the five-membered ring is formed by intramolecular reaction of a vinyl silane with a β-lactone.

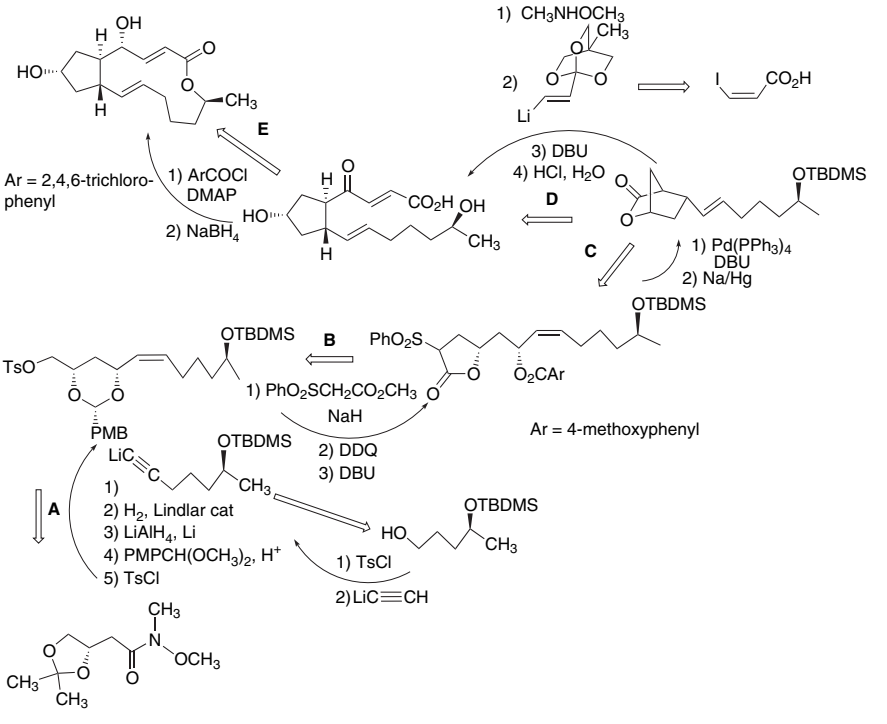


Scheme 13.P9b-1 shows the synthesis corresponding to retrosynthetic path A. A key feature of this synthesis is Step **C**, where an intramolecular, Pd-catalyzed allylic acetate displacement formed the five-membered ring. (See Section 8.2.1.2 to review Pd-catalyzed allylic displacement.) The sulfonyl substituent was then removed by reduction. The C(1)–C(3) terminus was introduced as a vinylogous acyl anion equivalent in the form of a propenoate homoenolate using a bicyclic orthoester protecting group. This reaction gave the *cis* isomer, but the thermodynamically favored *trans* stereochemistry was obtained by equilibration with DBU at Step **D**-3.



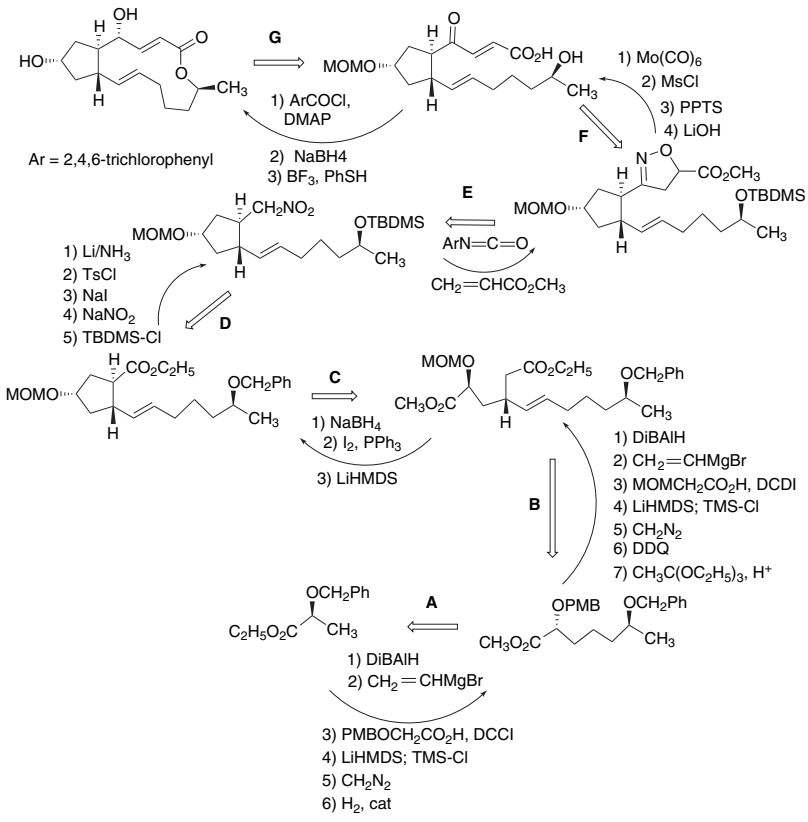
Scheme 13.P9b-2 shows a synthesis corresponding to retrosynthetic path B. The early stages of this synthesis built up the carbocyclic chain by a series of Ireland-Claisen rearrangements (**A**-4 and **B**-4), followed by an orthoester Claisen rearrangement (Step **B**-7). The cyclopentane ring was closed by an intramolecular enolate alkylation in Step **C**-3. The carbomethoxy group was

Scheme 13.P9b-1. Synthesis of Brefeldin A: Y.-G. Suh, J.-K. Jung, and Co-Workers[a]



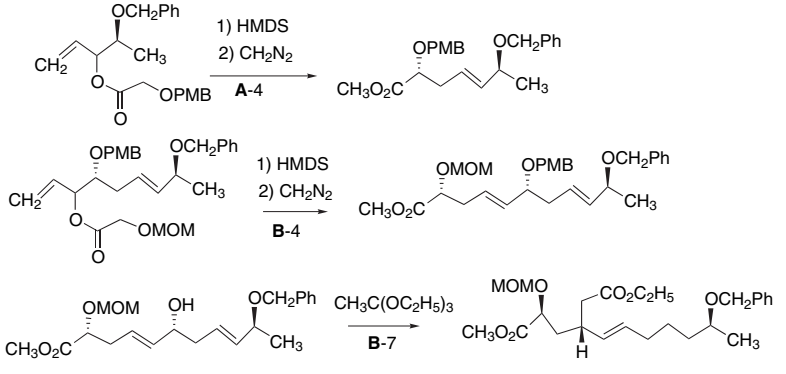
a. Y.-G. Suh, J.-K. Jung, S.-Y. Seo, K.-H. Min, D.-Y. Shin, Y.-S. Lee, S.-H. Kim, and H.-J. Park, *J. Org. Chem.*, **67**, 4127 (2002).

Scheme 13.P9b-2. Synthesis of Brefeldin A: D. Kim, J. Lee, and Co-Workers[a]



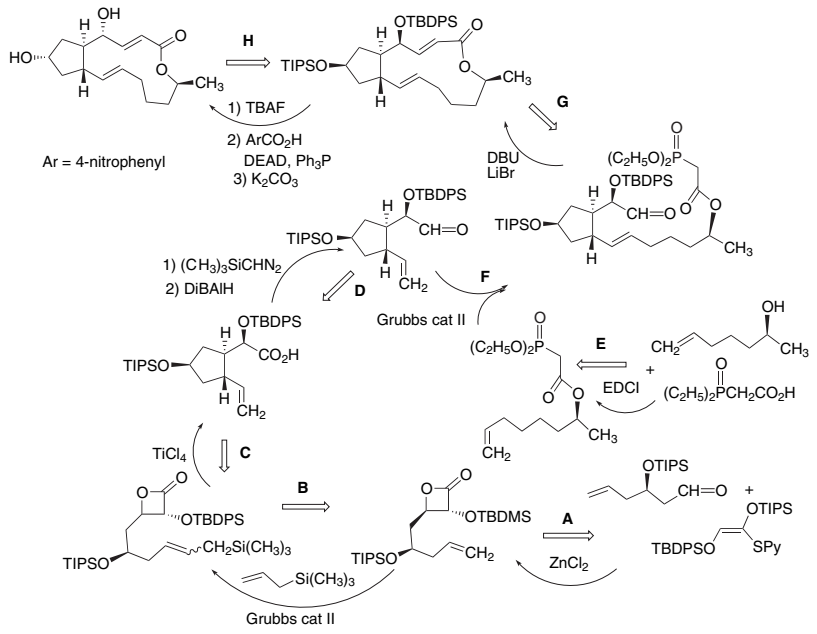
a. D. Kim, J. Lee, P.-J. Shim, J.-I. Lim, and H. Jo, and S. Kim, *J. Org. Chem.*, **67**, 764 (2002).

converted to a nitromethyl group by the sequence of reactions **D**-1**to D**-4, setting the stage for the nitrile oxide cycloaddition in Step **E**.



Scheme 13.P9b-3 shows a synthesis corresponding to retrosynthetic path C. A key step in this synthesis was the formation of the cyclopentane ring, which was based on a intramolecular allylic silane reaction with the β-lactone

Scheme 13.P9b-3. Brefeldin A Synthesis: Y. Wang and D. Romo[a]



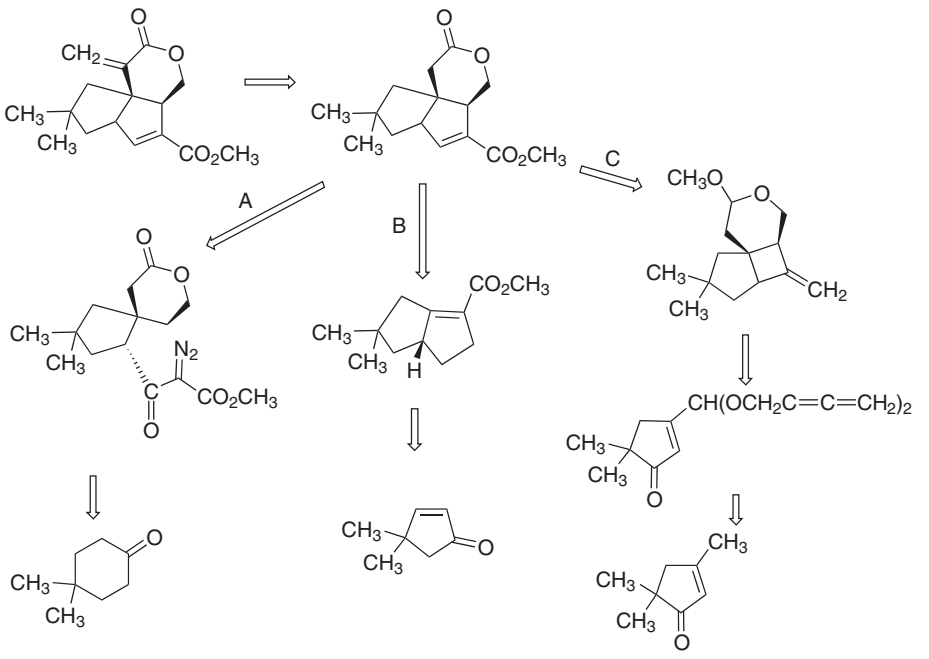
a. Y. Wang and D. Romo, *Org. Lett.* **4**, 3231 (2002).

intermediate in Step **C**. Olefin metathesis reactions were used at Steps **B** and **F**. The macrocycle was closed by a Wadsworth-Emmons reaction. The final stage of the synthesis inverts the configuration of the two hydroxy groups using the Mitsunobu method. This was necessary because of the stereoselectivity of the original cyclocondensation in Step **A**.

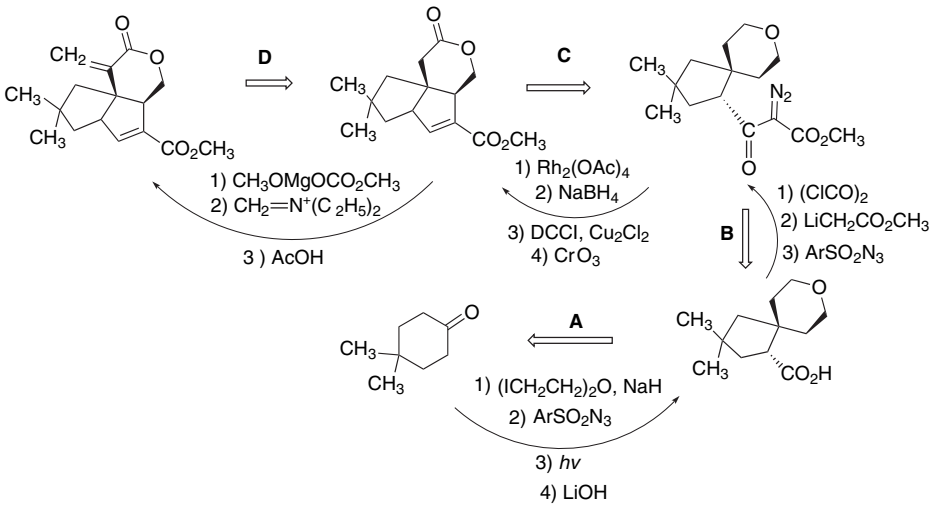
c. This compound is known as pentalenolactone E. There are several closely related structures. The molecule features two five-membered rings and one six-membered ring connected through a quaternary carbon. Pentalenolactone E also contains a geminal dimethyl quaternary carbon. Most of the syntheses have featured intramolecular reactions and cycloadditions designed to construct the carbon skeleton. Nearly all of the syntheses proceed through a lactone precursor that can be converted to pentalenolactone E by methylenation. Scheme 13.P9c shows retrosyntheses corresponding to several of the syntheses. Note that each uses a starting material with the geminal dimethyl groups in place. Retrosynthesis A features an intramolecular carbenoid insertion for closure of one of the five-membered rings. Retrosynthesis B proceeds through an intermediate having the two five-membered rings in place. This skeleton is created by an intramolecular aldol condensation. Retrosynthesis C is based on an enone photocycloaddition with an allene and also involves expansion of the four-membered ring.

Scheme 13.P9c-1 corresponds to retrosynthesis A, which is built around the intramolecular carbene insertion reaction at Step **C**-1. Another interesting feature is the use of a completely symmetrical starting material, which was dialkylated to install the spiro tetrahydropyran ring in Step **A**-1. This ring

Scheme 13.P9c. Retrosynthetic Schemes for Pentalenolactone E



Scheme 13.P9c-1. Pentalenolactone E Synthesis: D. F. Taber and J. L. Schuchardt[a]



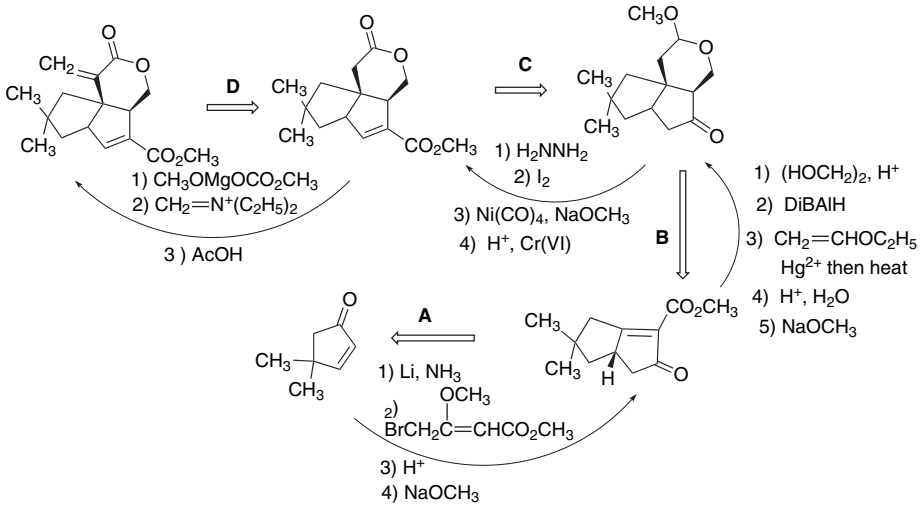
a. D. F. Taber and J. L. Schuchardt, *J. Am. Chem. Soc*., **107**, 5289 (1985); *Tetrahedron*, **43**, 5677 (1987).

was eventually converted to the lactone by an oxidation in Step **C**-4. The six-membered ring was contracted by a photolytic reaction of the corresponding diazo ketone in Step **A**-3. The final stage was a methylenation procedure that was used in several of the other syntheses of pentalenolactone E.

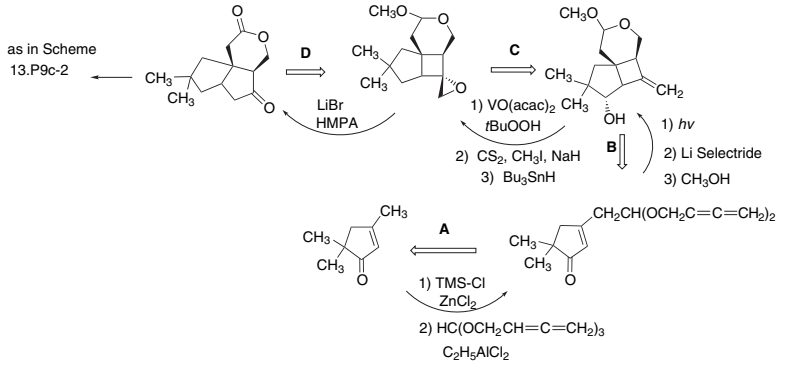
Scheme 13.P9c-2 corresponds to retrosynthesis B. The construction of the fused cyclopentane rings was done by an enolate alkylation and intramolecular aldol reaction. The ester substituent was converted to a primary alcohol and used to install a two-carbon chain by a Claisen rearrangement. After deprotection of the carbonyl group, acid-catalyzed conjugate addition and ketalization formed the six-membered acetal. The ketone was then converted to a vinyl iodide via the hydrazone. The carbonyl function was then used to add a carboxy group by a carbonylation reaction. The addition of the methylene substituent was done by carboxylation followed by a Mannich-type methylenation.

Scheme 13.P9c-3 corresponds to retrosynthesis C. In Step **A**-1 the enone was converted to a siloxydiene. A Mukaiyama-type reaction with 2,3-butadienyl orthoformate generated the first key intermediate (Step **A**-2). Photocyclization of one of the 2,3-butadienyloxy units with the enone formed the four-membered ring. The carbonyl group was reduced and the remaining 2,3-butadienyloxy group exchanged by methanol. The hydroxy group assists in a VO(acac)-mediated epoxidation (Step **C**-1), and was then removed by a radical deoxygenation (Steps **C**-2 and **C**-3). The next stage of the reaction was a rearrangement of the epoxide facilitated by a Lewis acid. The conversion to pentalenolactone E was then completed as in Scheme 13.P9c-2.

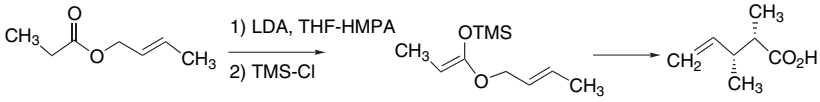
Scheme 13.P9c-2. Pentalenolactone E Synthesis: L. A. Paquette, G. D. Annis, and H. Schostarez[a]



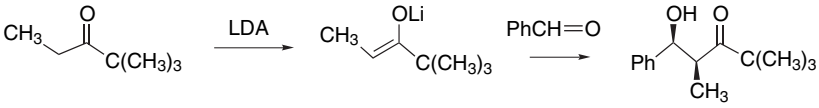
a. L. A. Paquette, G. D. Annis, and H. Schostarez, *J. Am. Chem. Soc*., **104**, 6646 (1982).



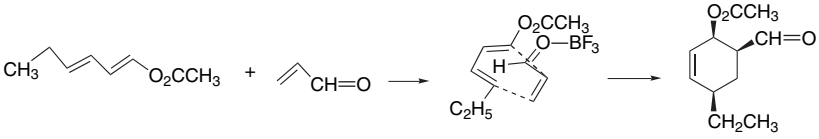
13.10. a. This compound was prepared with the required *syn* stereoselectively from *E*-butenyl propanoate by formation of the *Z*-silyl ketene acetal by using the HMPA-THF conditions for enolate formation.



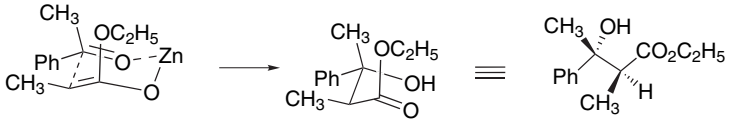
b. This *syn* aldol was formed with good stereoselectivity through the lithium enolate, which was formed primarily in the *Z*-configuration because of the bulky *t*-butyl substituent.



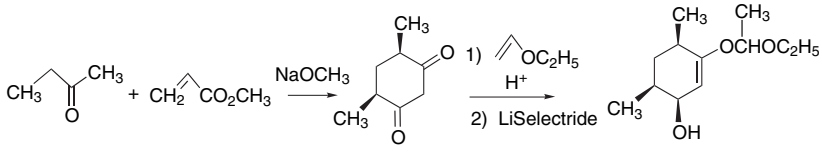
c. The regio- and stereoselectivity of the Diels-Alder reaction are suitable for preparation of this compound. The reaction occurred with high stereoselectivity through the *endo* TS using BF_3 catalysis.



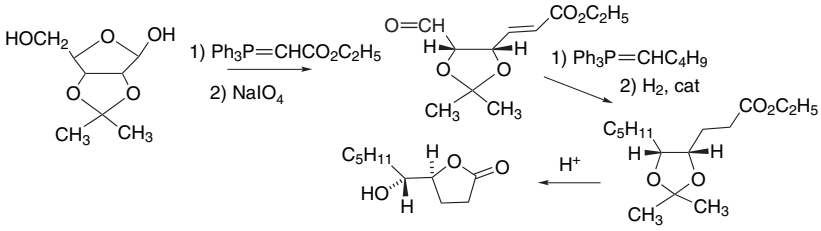
d. The desired product corresponds to an aldol addition of ethyl propanoate to acetophenone. The stereochemistry was initially investigated under Reformatsky conditions, which gave a 70:30 mixture favoring the *anti* (2-methyl-3-hydroxy) diastereomer. More recently, the reaction has been done using ultrasound promotion and with indium powder. The latter conditions gave a similar diastereomeric ratio. This stereochemical preference is consistent with a six-membered cyclic TS.



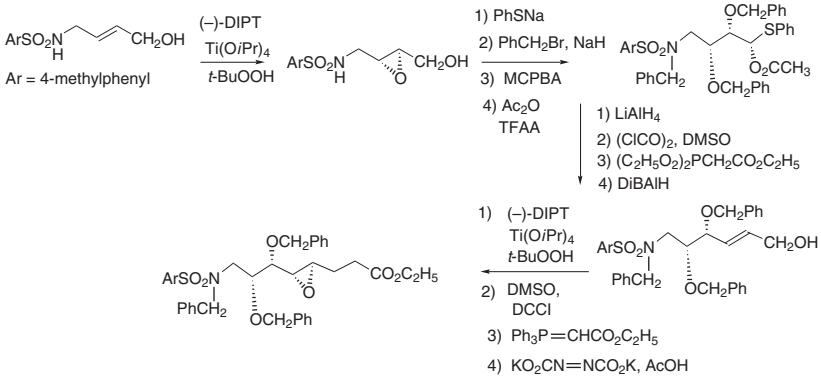
e. Condensation of 2-butanone and methyl acrylate gave 3,5-dimethylcyclohexane-1,3-dione via conjugate addition and intramolecular condensation. The thermodynamically favored *cis* isomer was formed. The ethoxyethyl protecting group was installed by acid-catalyzed addition with ethyl vinyl ether. A bulky hydride reagent led to equatorial approach in the reduction step.



13.11. a. The retention of the configuration at C(2) and C(3) during the synthetic sequence is required to obtain the desired compound. The sequence below was reported in the cited reference.

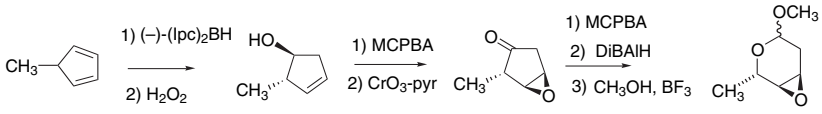


b. Use of (–)-DIPT with $Ti(O\text{-}i\text{-}Pr)_4$ and *t*-BuOOH led to enantioselective epoxidation with 95% e.e. The epoxide ring was then opened with phenylthiol, and a Pummerer rearrangement provided an acetoxy sulfide. This was converted to the aldehyde by $LiAlH_4$ reduction, followed by Swern oxidation. The chain was then extended by a Wadsworth-Emmons reaction. A second asymmetric epoxidation and another chain extension via a Wittig reaction and diimide reduction completed the synthesis.

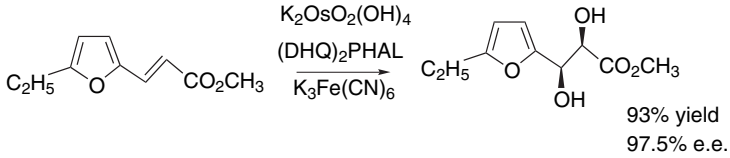


c. An enantioselective hydroboration-oxidation using $(–)\text{-}(Ipc)_2BH$ created two stereogenic centers in greater than 95% e.e. A hydroxy-directed epoxidation

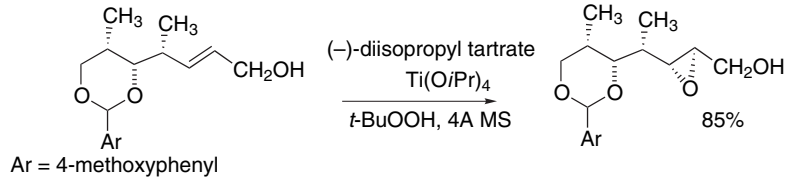
then established the chirality of two additional centers. The synthesis was completed by a Baeyer-Villager oxidation (retention) and partial reduction.



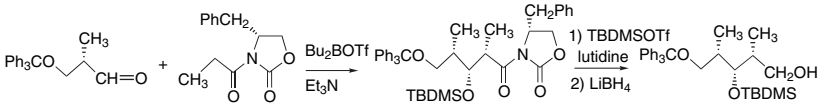
13.12. a. This product can be obtained with one of the DHQ-based Os(VIII) catalytic systems. A 93% yield with 97.5% e.e. was obtained using $K_2OsO_2(OH)_4$ and $(DHQ)_2PHAL$ with $K_3Fe(CN)_6$ as the stoichiometric oxidant.



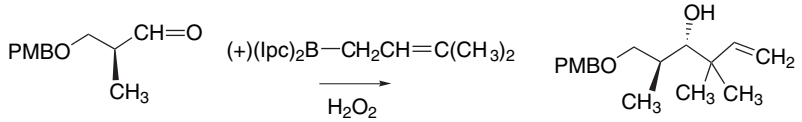
b. The required enantioselectivity corresponds to that provided by the (−)-tartrate ligands with $Ti(O\text{-}i\text{-}Pr)_4$ and *t*-BuOOH. An 85% yield was obtained.



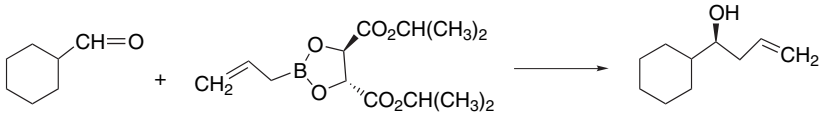
c. The boron enolate prepared from (*R*)-*N*-propanoyl-4-benzyloxazolidinone provided the desired stereoisomer. Protection and reductive removal of the chiral auxiliary provided the product.



d. The *B*-(4-methyl-2-butenyl) borane derived from (+)-diisopino campheylborane achieved this transformation with greater than 92% de.

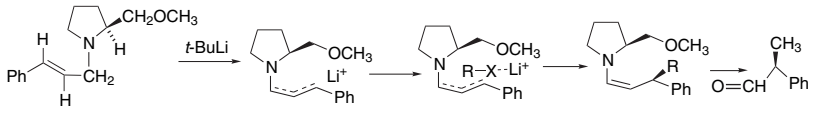


e. This reaction was done with good enantioselectivity using the allyl boronate reagent derived from *R,R*-diisopropyl tartrate.



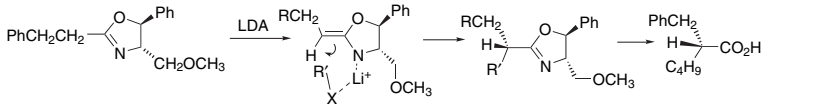
(*R,R*)-di-isopropyl tartrate boronate

13.13. a. This alkylation reaction proceeds through a lithio allylic anion. In this and related cases with alkoxy substituents, the alkoxy group exerts a *syn*-directive effect. This effect presumably operates on the basis of a tight coordination with the lithium cation and coordination of the Li^+ ion with the halide leaving group.



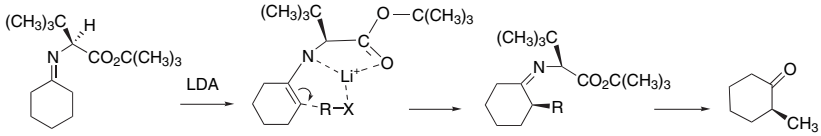
S for CH=O >Ph > CH_3

b. The methoxymethyl group in this oxazoline has a *syn*-directive effect.



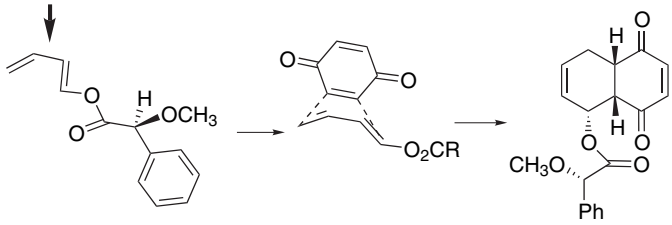
R for CO_2H > $PhCH_2$ > *n*-C_4H_9

c. The alkylation occurs through a chelated TS in which the Li^+ is coordinated to the leaving group.

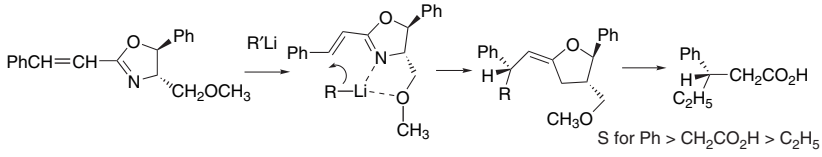


S for C=O > CH_2C > CH_3

d. The diene in this reaction contains a chiral auxiliary and exhibits good stereoselectivity toward a number of dienophiles. Although originally attributed to a π-stacking interaction, subsequent experimental and computational studies indicate that the facial selectivity is controlled by the conformation of the diene. The phenyl ring is oriented approximately perpendicular to the diene and provides steric shielding.

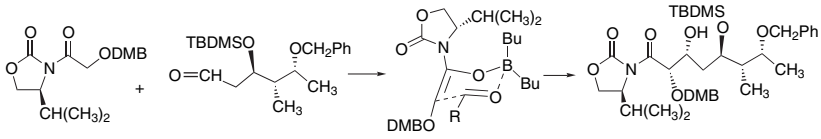


e. A chelated TS leads to delivery of the alkyl group *syn* to the methoxymethyl group.

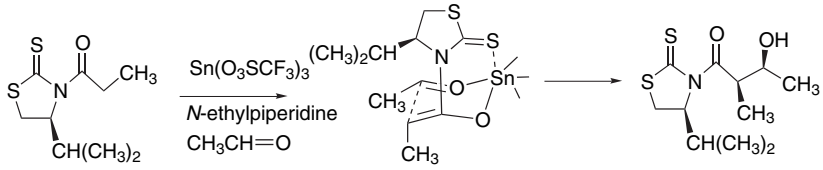


S for Ph > CH_2CO_2H > C_2H_5

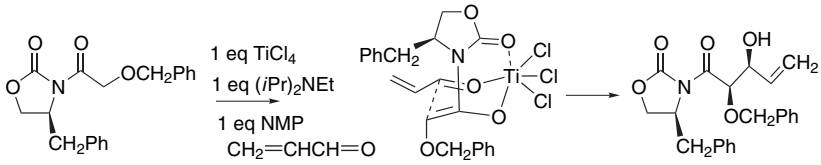
f. This diastereoselectivity is consistent with the nonchelated boron oxazolidinone transition structure.



g. The stereoselectivity is consistent with a chelated TS.



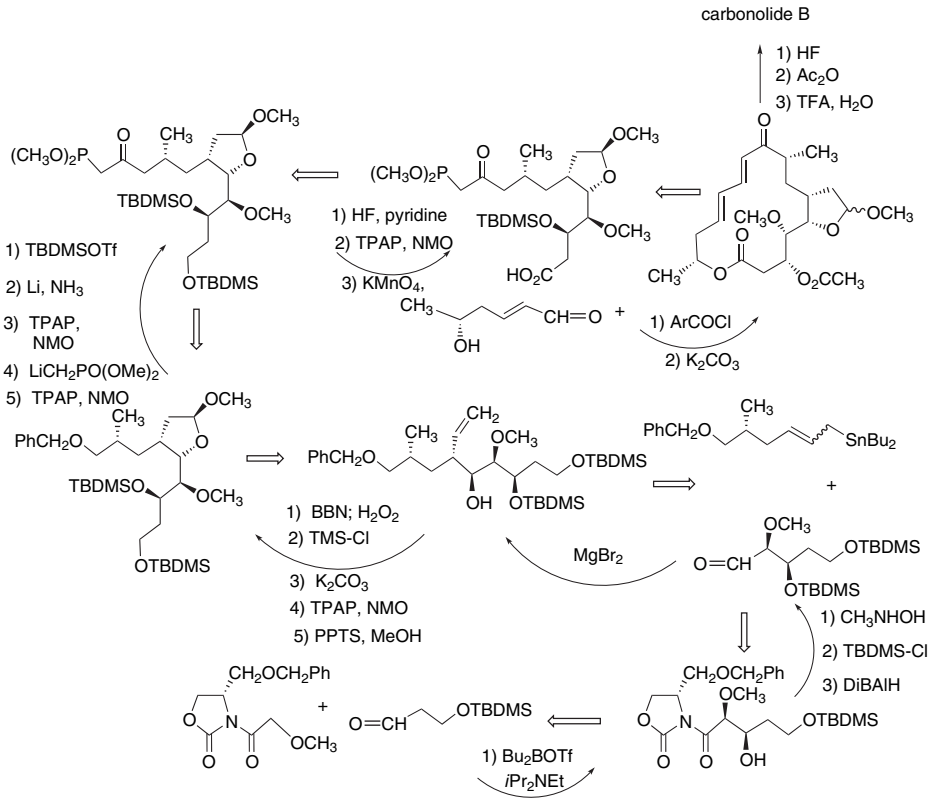
h. These conditions resulted in a chelated TS and led to the observed *syn* stereoselectivity.



13.14. The synthesis shown in Scheme 13.P14-1 used an oxazolidinone chiral auxiliary to establish the configuration at C(4) and C(5) on the basis of an aldol addition carried out through an enol borinate. The chiral auxiliary was then transformed to an aldehyde via reduction of the Weinreb amide. The configuration at C(6) was then established by allylic stannane addition to the aldehyde, which occurs under chelation control of the methoxy group. The stannane, which was synthesized from methyl (*S*)-3-hydroxy-2-methylpropanoate, incorporated the center at C(8). The vinyl group was then converted to an alcohol by hydroboration and oxidized to the aldehyde. Acidic methanol caused cyclization to the methoxy lactol, and a phosphonate side chain was installed by reductive deprotection, oxidation, and addition of lithio dimethyl methylphosphonate. The C(1) hydroxy group was then deprotected and oxidized to the carboxylate level.
The C(11)–C(16) segment was synthesized from ethyl (*R*)-3-hydroxybutanoate. The subunits were coupled by use of 2,4,6-trichlorobenzoyl chloride and the macrocyclization was done by a Wadsworth-Emmons procedure.

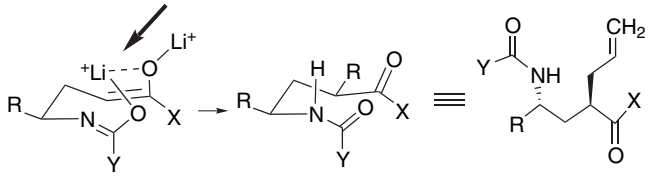
Other strategies are based on using carbohydrates as starting materials. An example is given is Scheme 13.P14-2. The starting material was readily obtained from D-glucose. A Wittig reaction was used to extend the chain by two carbons. A 2-methyl-2-propenyl substituent was added by conjugate addition, and the ester group was reduced and protected prior to hydroboration. The hydroboration led to a mixture of stereoisomers at C(8), which was carried through the synthesis, requiring a late purification. A dimethoxyphosphonyl methyl group was then added and oxidized to the β-keto phosphonate. The carboxy group was esterified with the C(11)–C(16) subunit. The macrocyclization was done by

Scheme 13.P14-1. Retrosynthesis and Synthesis of Carbonolide B: G. E. Keck, A Palani, and S. F. McHurdy



a Wadsworth-Emmons reaction under high dilution. Deprotection, oxidation, lactonization, and acetylation then set the stage for the final reduction to the lactol found in carbonolide B.

13.15. Formation of a dianion by deprotonation of the acylamino group and the ester (amide) can give rise to a chelated structure with the R substituent in an equatorial position. This TS is consistent with the observed 2,4-*anti* stereoselectivity.

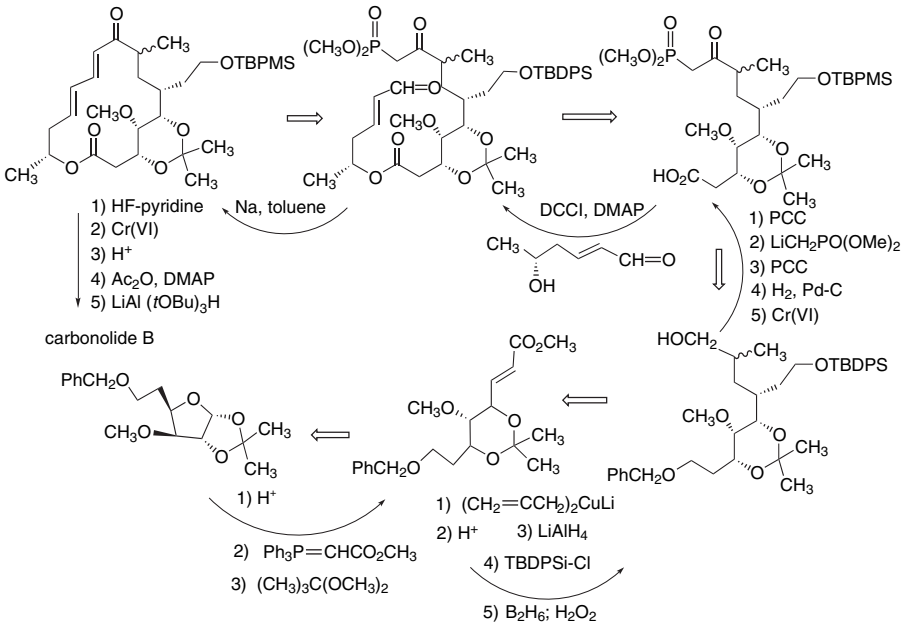


13.16. a. Scheme 13.53: R. A. Holton and co-workers.

A(1-3) ⟶ **B**(1-3) ⟶ **C**(1-6) ⟶ **D** ⟶ **E**(1-5) ⟶ **F**(1-7) ⟶ **G**(1-4) ⟶ **H**(1-10)

39 linear steps

Scheme 13.P14-2. Retrosynthesis and Synthesis of Carbonolide: K. C. Nicolaou, M. R. Pavia, and S. P. Seitz



b. Scheme 13.54: K. C. Nicolaou and co-workers.

A ⟶ **B** ⟶ **C**(1-3) ⟶ **F**(1-5)

D ⟶ **E**(1-3) ⟶ **G** ⟶ **H**(1-5) ⟶ **I**(1-3) ⟶ **J**(1-6) ⟶ **K**(1-3) ⟶ **L**(1-4)

35 total steps; 31 steps in longest linear sequence

c. Scheme 13.55; S. J. Danishefsky and co-workers

A(1-4) ⟶ **B**(1-5) ⟶ **C**(1-3) ⟶ **D**(1-4) ⟶ **E** ⟶ **F**(1-4) ⟶ **G**(1-4) ⟶ **H**(1-5) ⟶ **I**(1-6) ⟶ **J**(1-3)

39 total steps; 39 steps in longest linear sequence

d. Scheme 13.56; P. A. Wender and co-workers

A(1-4) ⟶ **B** ⟶ **C**(1-3) ⟶ **D**(1-5) ⟶ **E**(1-3) ⟶ **F**(1-6) ⟶ **G**(1-5) ⟶ **H**(1-6) ⟶ **I**(1-8) ⟶ **J**(1-4)

43 linear steps

e. Scheme 13.57: T. Mukaiyama and co-workers

A ⟶ **B**(1-4) ⟶ **C** ⟶ **D**(1-7) ⟶ **E**(1-5) ⟶ **F**(1-4) ⟶ **G**(1-6) ⟶ **H**(1-6) ⟶ **I**(1-10) ⟶ **J**(1-7)

51 steps; 51 steps in longest linear sequence

f. Scheme 13.58: H. Kusama, I. Kawajima, and co-workers.

A ⟶ **B**(1-5) ⟶ **C**(1-6) ⟶ **D**(1-8) ⟶ **E**(1-5) ⟶ **F**(1-7) ⟶ **G**(1-9)

41 steps; 41 steps in longest linear sequence

One reason for the high degree of linearity is that are no reactions that could be reasonably expected to close the central eight-membered ring. The inability to make a disconnection into two roughly equal segments at the center ring leads to a tendency for linearity. A second contributing structural feature is the high extent of closely related functionalization (eight oxygen substituent groups). This creates a need for a number of protecting groups and related manipulations to avoid interferences among these substituents.