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Annulation Routes to *trans*-Decalins

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1. Overview

The *trans*-decalin ring system is found in a wide variety of polyterpenoid and steroid natural products with interesting biological activity. Its ubiquity in natural products has led to the development of a wide variety of methods for its preparation. Most *trans*-decalin-containing polyterpenoids (e.g., drimanes, labdanes, abietanes, kauranes, atisiranes, clerodanes, and polycyclic triterpenoids too numerous to catalog) feature quaternary centers at C4 and C10 (or occasionally C5 and C9) (Figure 1). In steroids, the two C4 substituents have been removed enzymatically.

The importance of *trans*-decalins in natural products has led to the development of a multitude of methods for their preparation. As might be expected for a skeleton containing eleven C—C bonds, many different bond disconnections of the decalin can be made, and most if not all of these disconnections have

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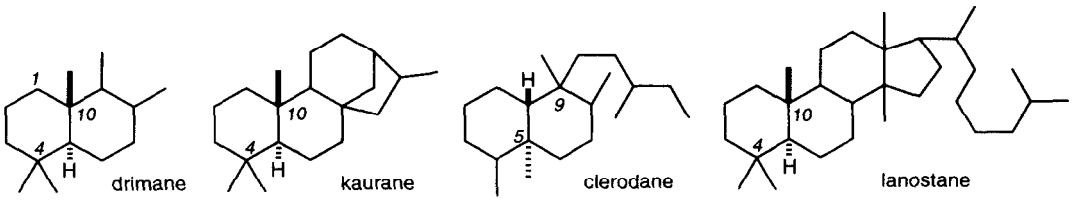


Figure 1. Some typical *trans*-decalin-containing polyterpenoid skeletons

appeared in various synthetic strategies over the years. The most important and interesting routes to *trans*-decalins, however, are *annulation* approaches, i.e., approaches in which two or three C—C bonds are made in a tandem or cascade process,[1-5] or at least in sequential steps.

This review covers methods for preparing *trans*-decalins with angular methyl groups in which two or more C—C bonds of the decalin are formed in one step or in sequential steps. Particular emphasis is placed on methods that provide *trans*-decalins with oxygenated methyl substituents at the ring junction, which are especially difficult to prepare and are present in many biologically active natural products. Surprisingly, no review comparing the different methods for preparing the *trans*-decalin ring system has been published, although many methods applicable to *trans*-decalin synthesis have been reviewed separately (and are referenced below in the appropriate sections). Many of the methods described in this review can also be found in Ho's much more general monograph, *Carbocycle Construction in Terpene Synthesis*.[6] A review on the preparation of the less common (and less easily prepared) *trans*-hydrindanes appeared in 1998.[7]

2. Sequences based on an intermolecular Michael reaction

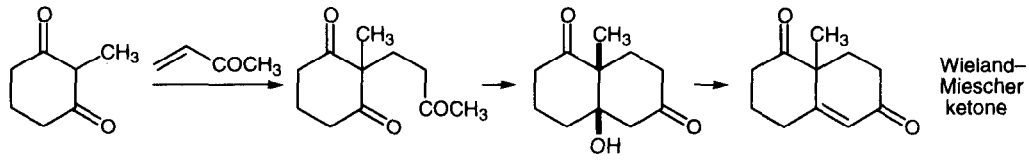
The Michael reaction,[8-10] the addition of a stabilized carbon nucleophile to an electrophilic C=C bond, is a classical reaction for very good reasons. It is a C—C σ bond-forming reaction, it is catalyzed by a large number of bases, acids, and transition metals, it is completely atom-economical, most of the functionality of the starting materials is preserved in the products, and the starting materials are readily available or are easily prepared. For these and other reasons, both the intermolecular and intramolecular variants of the Michael reaction are very prominent among methods used for preparing *trans*-decalins.

2.1 The Robinson annulation

The Robinson annulation is probably the most well-known classical method for constructing fused ring systems.[11,12] The first step in the Robinson annulation is a nucleophilic attack of a ketone or β-ketoester enolate onto an alkenone, or a Michael reaction (Scheme 1). The Michael adduct subsequently undergoes ring closure to afford a cis bicyclic ketol, which is dehydrated to give an unsaturated decalin (i.e., octalin). A subsequent reduction step is required to introduce a trans ring fusion.

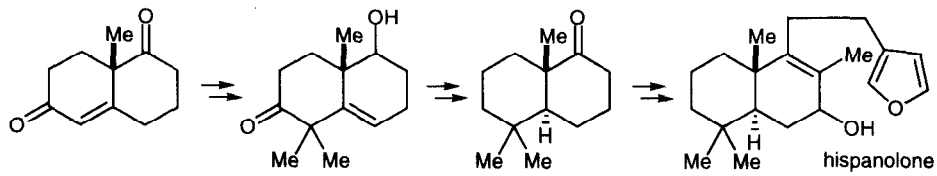
2.1.1 The Wieland–Miescher ketone

The Robinson annulation of 2-methyl-1,3-cyclohexanedione and methyl vinyl ketone (MVK) gives the Wieland–Miescher (W–M) ketone (Scheme 1). The W–M ketone is a venerable starting material for the synthesis of *trans*-decalin-containing natural products such as steroids and diterpenoids. However, the W–M

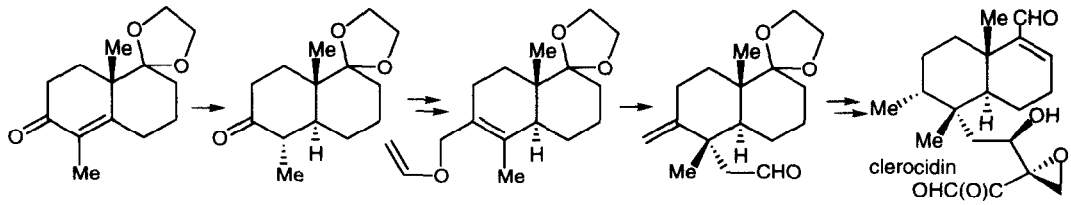


Scheme 1. The Robinson annulation and the Wieland–Miescher ketone

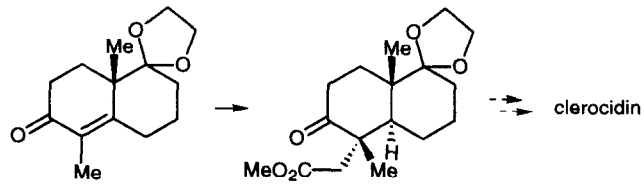
ketone is an octalin, not a decalin, so if it is to be used in terpenoid synthesis, it must be converted into a *trans*-decalin by reduction of the C=C π bond. A quaternary center must also usually be created at the α-carbon of the α,β-unsaturated ketone either before or after the reduction step. For example, in a synthesis of the labdane diterpenoid (±)-hispanolone, exhaustive alkylation of a simple derivative of the W–M ketone establishes the quaternary center with concomitant transposition of the double bond, which is subsequently hydrogenated to give the trans ring junction (Scheme 2).[13,14] By contrast, in a synthesis of the clerodane diterpenoid clerocidin, the trans ring junction stereochemistry is established first by dissolving metal reduction of a W–M ketone homolog, and the quaternary center is formed subsequently by a Claisen rearrangement (Scheme 3).[15,16] Another approach to clerocidin creates the quaternary center by dissolving metal reduction of the same W–M ketone homolog and alkylation of the nascent enolate with methyl bromoacetate (Scheme 4).[17]



Scheme 2. Wong's synthesis of (±)-hispanolone



Scheme 3. Theodorakis' synthesis of clerocidin

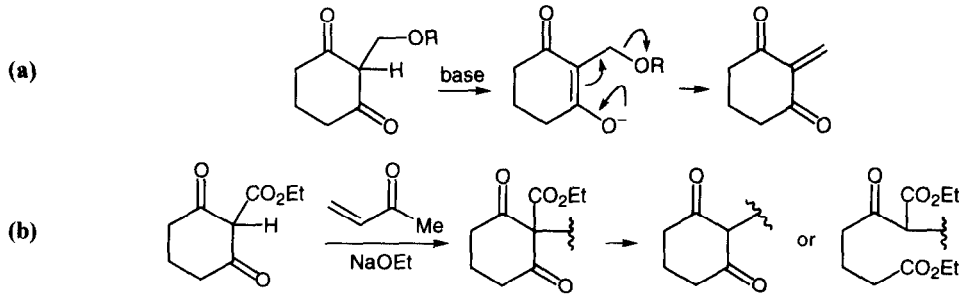


Scheme 4. Markó's approach to clerocidin

There are several methods for preparing enantiopure Wieland–Miescher ketone: enantioselective microbial reductions,[18] classical resolution of a hemiphthalate derivative,[19] and asymmetric synthesis.[20,21] The most efficient asymmetric preparation is to carry out the Robinson annulation in the presence of enantiopure proline.[22] The desired enantiomer is obtained in 50% yield and 100% ee after three recrystallizations.

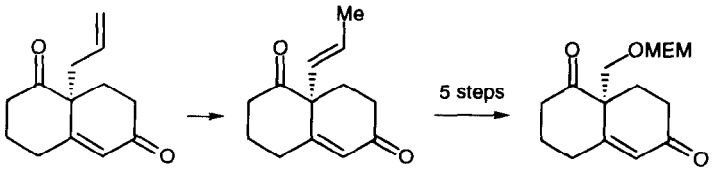
2.1.2 Angular oxygenated methyl group

Many polyterpenoid natural products of biological interest sport an angular oxygenated methyl group. The most obvious means of introducing this group into a Robinson annulation product is to have it already present on the methyl substituent in the starting cyclohexanone (Scheme 5). However, if the oxygenated methyl group is present as an alkoxymethyl group, then β-elimination occurs. Alternatively, if it is present as a CO_2R or CHO group, then the Michael product (if it can be obtained at all) is extremely susceptible to C—C bond cleavage adjacent to the newly formed quaternary center by retro-Claisen or retro-Dieckmann reaction.



Scheme 5. Difficulties with introducing an angular oxygenated methyl group into the Robinson annulation, (a) as an alkoxymethyl group, (b) as a carbonyl group

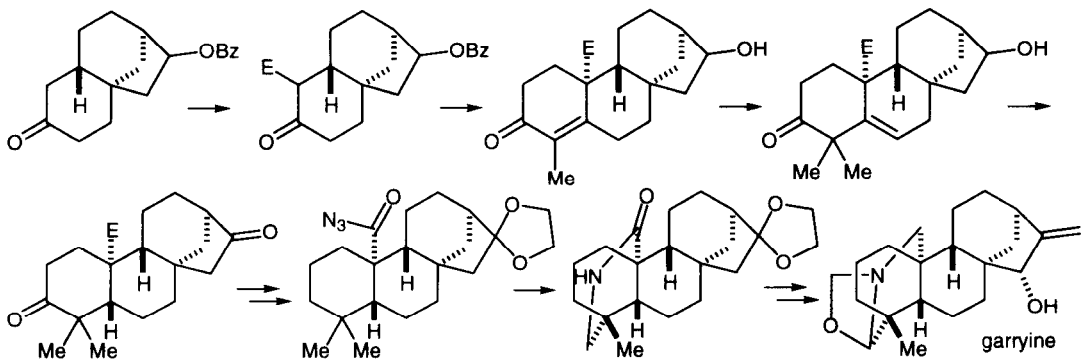
A masked hydroxymethyl group that is incapable of β-elimination can be used to circumvent these problems. Hanselmann and Benn used an allyl group for this purpose (Scheme 6). The terminal double bond of the Robinson annulation product was isomerized with $RhCl_3$ and conc. HCl to give the internal alkene. Protection of the ketones, ozonolysis of the more electron-rich C=C bond and $NaBH_4$ reduction, protection of the alcohol as the MEM ether, and ketone deprotection gave the desired compound in overall 25% yield.



Scheme 6. Synthesis of Wieland–Miescher ketone bearing an angular hydroxymethyl group

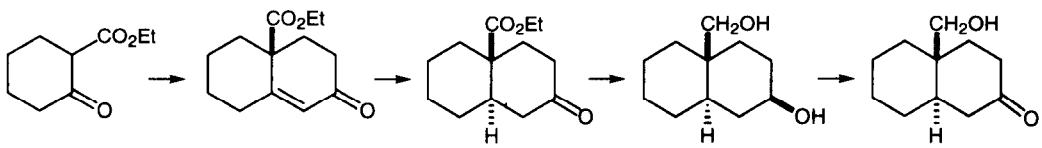
The other way to circumvent these problems is to use a 2-cyclohexanonecarboxylate as the nucleophile instead of a 1,3-cyclohexanedione. Masamune's early and very clever synthesis of the diterpenoid alkaloid garryine employs this strategy (Scheme 7).[23,24] Carbomethoxylation of the tricyclic ketone proceeds selectively on the more congested side of the ketone. Robinson annulation with ethyl vinyl ketone affords the

tetracyclic compound. After alkylation and concomitant double bond transposition, the trans ring junction is introduced by catalytic hydrogenation. Functionalization of the axial methyl of the *gem*-dimethyl group is then accomplished by converting the angular CO_2Me group to an acyl azide. Photolysis produces an acyl nitrene, which undergoes transannular C—H insertion to afford the lactam in very poor yield.



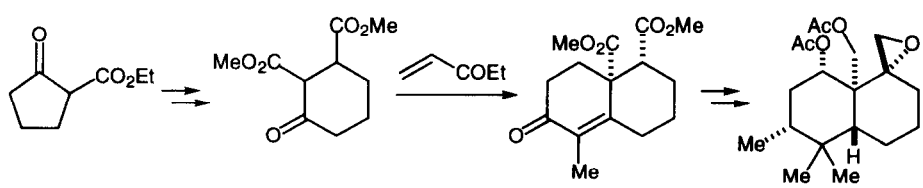
Scheme 7. Masamune's synthesis of garryine

In a simpler system, Mukharji showed that a Robinson annulation between ethyl cyclohexanone-2-carboxylate and MVK followed by hydrogenation gave a *trans*-decalin with an angular ester group (Scheme 8).[25] The ester and ketone functionalities were reduced with $LiAlH_4$, and the secondary alcohol was selectively reoxidized to the ketone. Mukharji's *trans*-decalin synthesis was later used to prepare a model of the *trans*-decalin portion of azadirachtin.[26]



Scheme 8. Mukharji's synthesis of a *trans*-decalin with an angular hydroxymethyl group

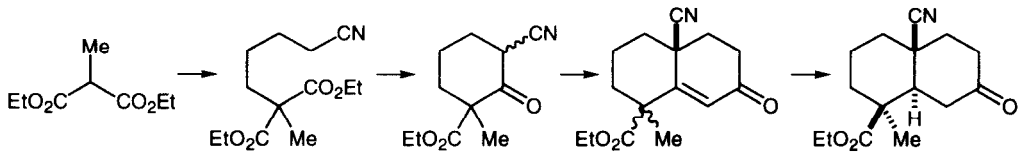
In Mukharji's method, no functionality is present on the A ring. In de Groot's model study of an approach to the clerodane diterpenoids (Scheme 9), functionality is introduced into the A ring before the Robinson annulation is carried out.[27] The starting material for the Robinson annulation, diethyl 3-cyclohexanone-1,2-dicarboxylate, is prepared from ethyl cyclopentanone-2-carboxylate and ethyl bromoacetate in three steps. After Robinson annulation with ethyl vinyl ketone, the trans stereochemistry at the ring junction



Scheme 9. de Groot's approach to a clerodane model

and the adjacent quaternary center are established by dissolving metal reduction of the C=C bond and alkylation of the nascent enolate with MeI.[28]

Meyer's route to the abietic acids also employs the Robinson annulation (Scheme 10).[29] The A ring is assembled by alkylation of diethyl methylmalonate with 5-bromovaleronitrile and a subsequent Dieckmann reaction. A Robinson annulation with MVK proceeds in nearly 1:1 dr, and hydrogenation of one of the isomers from the less hindered face selectively produces the trans ring junction.

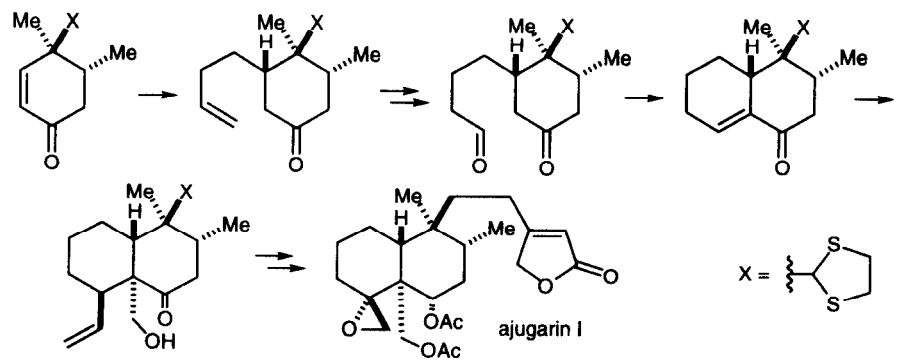


Scheme 10. Meyer's route to abietic acid analogs

2.2 *Inverted "Robinson annulation"*

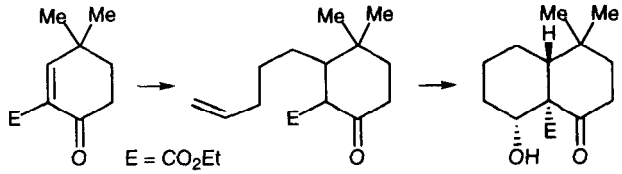
Both the cyclic compound and the alkenone used in the Robinson annulation have ambiphilic reactivity: the cyclic compound acts as a nucleophile in the first step and an electrophile in the second step, and the alkenone reacts in complementary fashion. It is also possible to carry out a Michael–intramolecular aldol sequence in which the six-membered ring is electrophilic in the first step and the acyclic reacting partner is nucleophilic. The second cyclization step, the aldol reaction, normally gives a *cis*-decalin for stereoelectronic reasons. However, either of two subsequent procedures — dehydration of the aldol and then addition across the newly formed C=C bond (as in the Robinson annulation route to *trans*-decalins), or thermodynamic equilibration — can ultimately provide a *trans*-decalin.

The first total synthesis of the clerodane diterpenoid insect antifeedant ajugarin I was achieved by the Ley group (Scheme 11).[30] Conjugate addition of lithium bis(3-butenyl)cuprate to the Diels–Alder-derived cyclohexenone was followed by hydroboration and two oxidations to afford a ketoaldehyde. The annulation was then completed by an intramolecular aldol condensation and dehydration, conjugate addition of a vinyl cuprate to the resulting enone, and enolate trapping with formaldehyde.



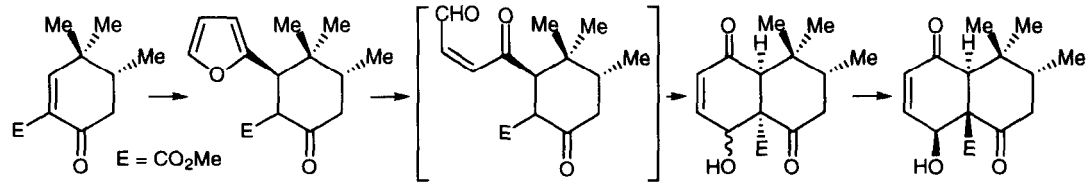
Scheme 11. Ley's synthesis of ajugarin I

In Lallemand's approach to a model of clerodin, another clerodane insect antifeedant, the starting material is prepared by copper-catalyzed conjugate addition of 4-pentenylmagnesium bromide to a highly activated cyclohexenone. Oxidation of the terminal alkene to the aldehyde is followed by in situ by an intramolecular aldol reaction, undoubtedly under thermodynamic control, to give the *trans*-decalin (Scheme 12).[31]



Scheme 12. Lallemand's approach to a model for clerodin

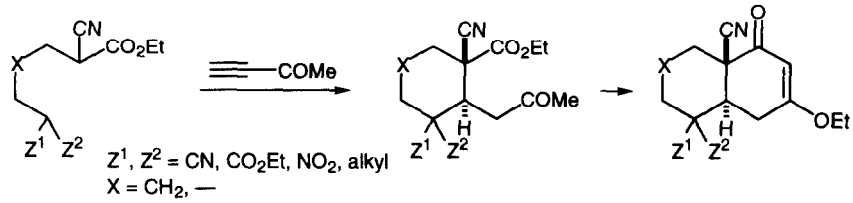
Lallemand has modified this route to prepare even more highly oxygenated *trans*-decalins (Scheme 13).[32] Acid-mediated conjugate addition of furan to a highly activated cyclohexenone, oxidative ring opening of furan, and intramolecular aldol condensation gives a *cis*-decalin as a mixture of alcohol epimers. Epimerization via a retro-aldol–aldol reaction occurs upon purification on silica gel to give the lowest energy isomer, a *trans*-decalin, out of four possible isomers.



Scheme 13. Lallemand's approach to polyfunctionalized *trans*-decalins

2.3 Double Michael reaction–Dieckmann condensation

Grossman has recently reported a two-step "double annulation" method for the preparation of highly substituted and functionalized *trans*-decalins and -hydrindanes (Scheme 14).[33,34] A compound consisting of an α-cyanoester tethered to another carbon acid is allowed to undergo two sequential Michael reactions to 3-butyn-2-one to give a five- or six-membered ring with good to excellent stereoselectivity. 1,3-Diaxial interactions in the TS leading to the double Michael adduct ensure the trans disposition of the acetonyl group and the CO_2Et group. These groups then combine in a Dieckmann condensation to afford a *trans*-decalin or a *trans*-

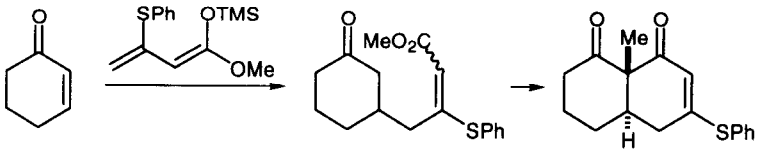


Scheme 14. Grossman's double annulation

hydrindane. Three new C—C σ bonds, two or three new stereocenters, and two new quaternary centers are formed between two separate starting materials with high selectivity. All three substituents at the two quaternary centers are in a high oxidation state, allowing further transformations of these groups. The tethered carbon acids are easily varied to provide a series of analogs.

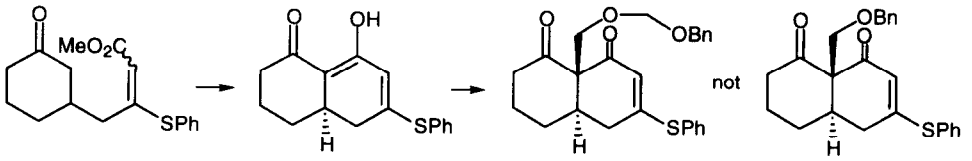
2.4 Michael reaction–Dieckmann condensation

Chan has developed a formal [4 + 2] annulation based on a sequential Michael–Dieckmann reaction (Scheme 15).[35-37] A very electron rich diene containing a masked ketene acetal undergoes a Michael addition to cyclohexenone, and the adduct is allowed to undergo a Dieckmann reaction; methylation of the nascent 1,3-diketone enolate then affords the *trans*-decalin. The undoubtedly cis stereochemistry of the decalin initially formed in the Dieckmann reaction is abolished upon deprotonation, and the trans stereochemistry of the final product is then established by the stereoelectronically controlled methylation. The final product has three differentiated carbonyl groups that can be individually manipulated in principle.



Scheme 15. Chan's sequential Michael–Dieckmann condensation

Chan later carried out a study to functionalize the decalin moiety with an angular hydroxymethyl group instead of a methyl group (Scheme 16). When the Dieckmann product was treated with diisopropylethylamine and excess benzyl chloromethyl ether, a *C*-alkylated product with an extra —CH_2O— group, and none of the expected product, was obtained in 45% yield. The authors attributed this result to the presence of formaldehyde in the benzyl chloromethyl ether. When the benzyl chloromethyl ether was distilled, the yield decreased significantly. However, when paraformaldehyde was added to the reaction mixture, the yield improved to 75%.



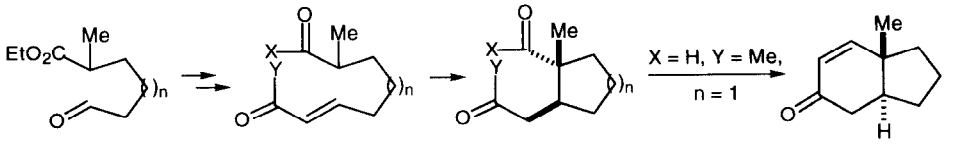
Scheme 16. Chan's angular hydroxymethylation

3. Sequences based on an intramolecular Michael reaction

The intramolecular Michael reaction has the virtue of creating a new ring, making it especially valuable for the preparation of bicyclic compounds from acyclic ones.[9] However, this approach has not seen nearly as wide application to the synthesis of diterpenoids as the intermolecular variant, perhaps because of its nonconvergency and the difficulty of preparing appropriately functionalized substrates.

3.1 Intramolecular Michael reaction–intramolecular aldol condensation

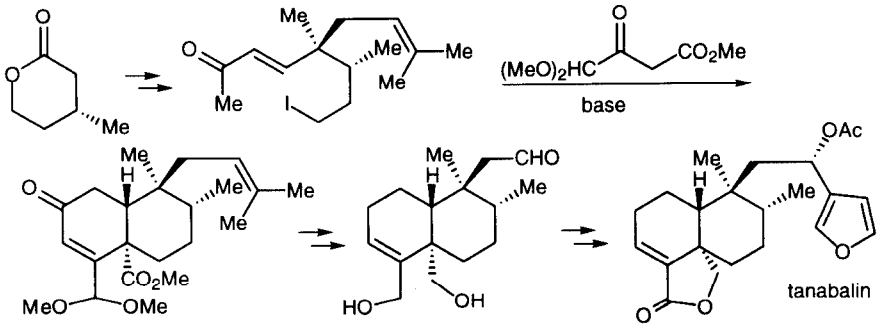
Stork has shown that the intramolecular Michael reaction of monounsaturated dicarbonyl compounds affords 1,2-disubstituted cyclopentanes or cyclohexanes with high trans selectivity and in high yields (Scheme 17).[38,39] The selectivity is explained by repulsion between the π bonds in the TS leading to the cis isomer. When an aldehyde–alkenone with a three-carbon tether is used as the substrate for the reaction, a subsequent intramolecular aldol reaction affords a *trans*-hydrindane; presumably a *trans*-decalin could be formed similarly.



Scheme 17. Stork's *trans*-hydrindane and -decalin syntheses

3.2 Alkylation–intramolecular Michael reaction–intramolecular aldol reaction

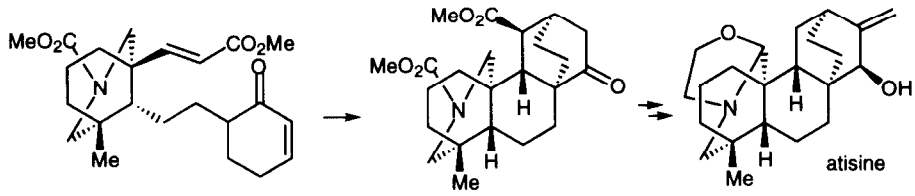
Kitahara has developed a variant of Stork's intramolecular Michael reaction–intramolecular aldol condensation route to *trans*-decalins that is initiated by alkylation of an ornately functionalized β-ketoester with an ω-iodoalkenone.[40] The utility of the method, which stereoselectively creates three new C—C σ bonds, is illustrated with an asymmetric synthesis of the clerodane diterpenoid (–)-tanabalin (Scheme 18).[40] The one stereocenter in (*R*)-3-methyl-δ-valerolactone is selectively parlayed into four of the five stereocenters of the natural product.



Scheme 18. Kitahara's synthesis of (–)-tanabalin

3.3 Intramolecular double Michael reaction

The double Michael reaction of an alkenone and another electrophilic alkene, a formal [4 + 2] annulation, has been studied extensively and has been reviewed.[41] When the alkenone is a cyclohexenone, the double Michael reaction affords a bicyclo[2.2.2]octanone. The Ihara group has used an intramolecular double Michael reaction to complete the first asymmetric synthesis of atisine (Scheme 19).[41] The AB ring system is made trans because of the trans disposition of the two reactive substituents on the A ring in the starting material, but the creation of a trans BC ring junction is inherent to the nature of the intramolecular Michael reaction.[38]



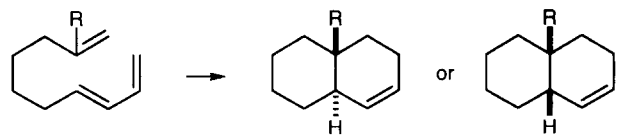
Scheme 19. Ihara's synthesis of atisine

4. Diels–Alder reactions

The Diels–Alder reaction is very widely used to create *trans*-decalins. Two variations can be used: the intramolecular Diels–Alder reaction, which provides *cis*- or *trans*-decalins, or the intermolecular Diels–Alder reaction, which provides only *cis*-decalins. The *cis*-decalins produced in the intermolecular Diels–Alder reaction can usually be isomerized to *trans*-decalins (if the latter are lower in energy) in a subsequent step.

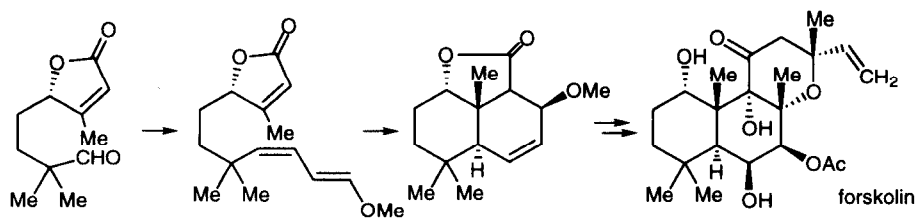
4.1 Intramolecular Diels–Alder reaction

In the intramolecular Diels–Alder (IMDA) reaction, the diene and the dienophile are connected by a tether. Initially reported in 1928, this [4 + 2] cycloaddition forms two new C—C bonds and up to four new stereocenters. The first example of an IMDA reaction was reported in 1953 by Alder and Shumaker. The next example was not published until the 1960s, and approximately 15 years later, use of the IMDA reaction became common in synthetic organic chemistry.[42-44] The IMDA reaction is usually very reliable, but lengthy, nonconvergent procedures are often required to prepare the tethered diene–dienophile. Furthermore, the IMDA reaction of dienes attached to a dienophile by a four-carbon tether can proceed to give either *cis*- and *trans*-decalins, with trans products being slightly more common (Scheme 20).



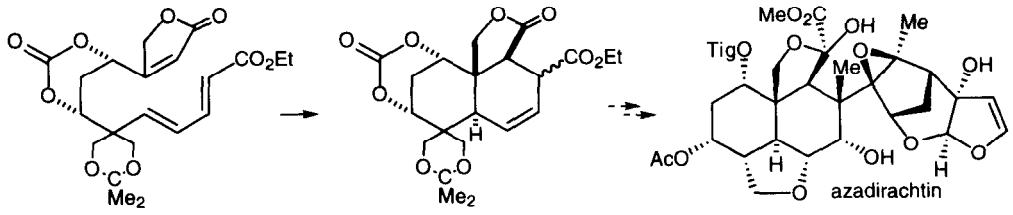
Scheme 20. Stereoselectivity in the intramolecular Diels–Alder reaction

The Ikegami group used an IMDA reaction as the key step in their preparation of the labdane diterpene, (±)-forskolin (Scheme 21).[45] Wittig extension of the aldehyde gave the diene as the undesired (*Z,E*)-isomer, but isomerization proceeded under the conditions of the IMDA reaction to give the *trans*-decalin.

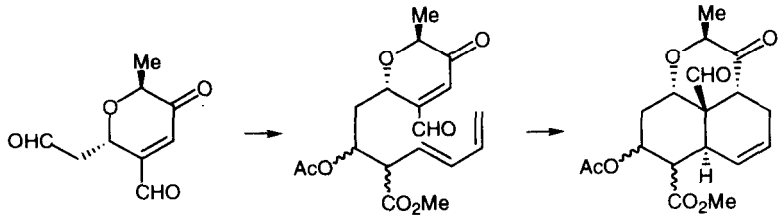


Scheme 21. Ikegami's approach to (±)-forskolin

The IMDA reaction has twice been used to prepare the *trans*-decalin portion of azadirachtin, a potent insect antifeedant. In Murai's approach (Scheme 22), the IMDA reaction of the rather easily prepared substrate creates two new stereocenters at the ring fusion of the decalin with very high trans selectivity.[46] When the carbonate ring is absent, both *cis*- and *trans*-decalins are obtained.[47] Fraser–Reid has prepared and separated all four stereoisomers of an IMDA reaction substrate by a stereorandom aldol reaction of a sugar-derived aldehyde and methyl sorbate (Scheme 23).[48] Each isomer proceeds stereoselectively to the corresponding *trans*-decalin upon heating.

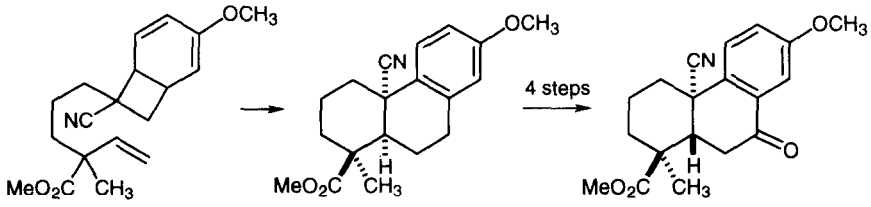


Scheme 22. Murai's approach to the *trans*-decalin portion of azadirachtin



Scheme 23. Fraser–Reid's approach to the *trans*-decalin portion of azadirachtin

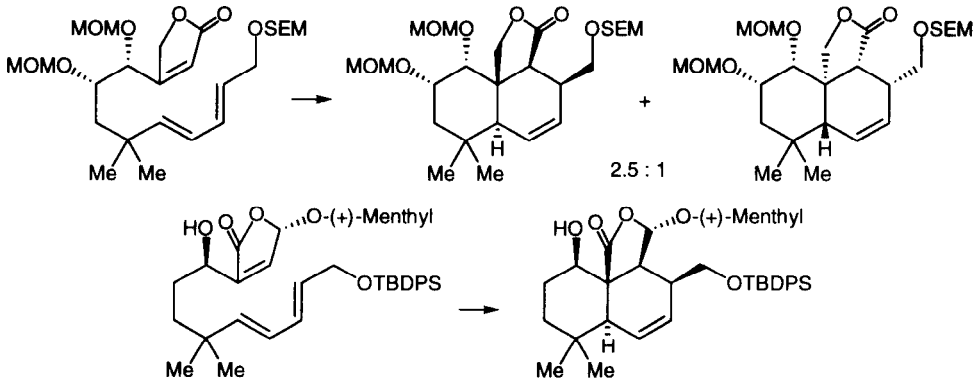
Kametani has reported the synthesis of a tetracyclic compound that has been used in the total synthesis of atisine, veatchine, garryine, and gibberellin A_{15} (Scheme 24).[49] Upon heating, the benzocyclobutane is converted to the *o*-quinodimethane, which then undergoes an IMDA reaction to give the benzo-fused decalin moiety as a single isomer. However, the reaction gives the *cis*-decalin instead of the desired trans isomer, and direct epimerization is unsuccessful. The *trans*-decalin is obtained by benzylic oxidation, α-bromination, dehydrobromination, and hydrogenation.



Scheme 24. Kametani's approach to diterpenes and diterpene alkaloids

Both the strengths and drawbacks of the IMDA reaction are illustrated by two very similar approaches to the mniopetal sesquiterpenoids (Scheme 25).[50,51] Both approaches use an IMDA reaction between a

butenolide and a 1,4-substituted 1,3-diene as the key step, but in one substrate the butenolide is tethered through C3, whereas in the other it is tethered through C2. The C3-tethered butenolide is transformed into two diastereomeric *trans*-decalins (out of four possible decalins) in a 2.5:1 ratio, whereas the C2-tethered butenolide is transformed into a single isomer. Such outcomes would have been difficult to predict *a priori*.



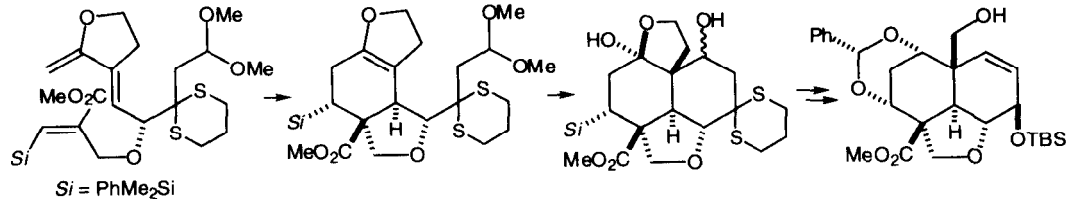
Scheme 25. Two approaches to the mniopetal sesquiterpenoids

The IMDA reaction is usually carried out late in a synthesis, so it is very important to be able to predict the stereochemical outcome. The nature of the diene and dienophile, the substituents and length of the tether, and the catalyst all play a role in the stereochemical outcome of the IMDA reaction. These issues are addressed in the numerous reviews of the IMDA reaction.[42-44]

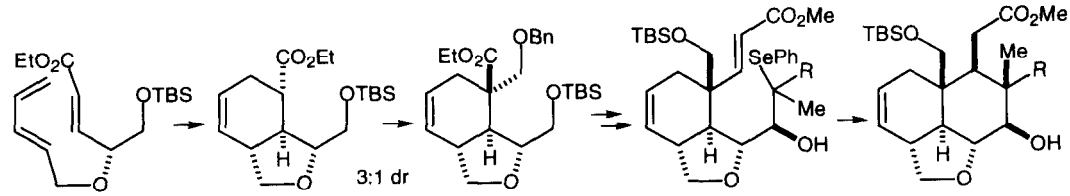
4.2 Intramolecular Diels–Alder reaction–cyclization

The IMDA reaction has twice been used to construct the *trans*-perhydroisobenzofuran portion of azadirachtin, with the second six-membered ring of the *trans*-decalin portion then being introduced by a cyclization reaction. As mentioned earlier, such cyclizations normally give the *cis*-decalin for stereoelectronic reasons, but thermodynamic control or an elimination–addition sequence can alter the usual selectivity.

For example, Ley creates the *trans*-perhydroisobenzofuran portion of azadirachtin by an IMDA reaction of a very highly functionalized substrate (Scheme 26).[52] An intramolecular aldol reaction of the enol ether and the acetal then installs the second six-membered ring of the *trans*-decalin portion. Ley suggests that the aldol reaction is selective for the *trans*-decalin because of the constraints imposed by the furan ring.[53] The angular 2-hydroxyethyl substituent is later degraded to a hydroxymethyl substituent by an arduous five-step sequence. By contrast, Mori uses a radical cyclization to install the second six-membered ring after the IMDA reaction (Scheme 27).[54] The trans relationship of the side chains in the radical cyclization is established by sterically controlled alkylation of the IMDA product. After a series of manipulations, the substrate for the radical cyclization is obtained, but the cyclization proceeds in poor yield, perhaps because of the severe steric repulsion between the Me and CH_2OTBS groups. The number of steps intervening between the two ring-forming steps makes this method not strictly an annulation, but it is included so that it may be compared to the other routes to the *trans*-decalin portion of azadirachtin.



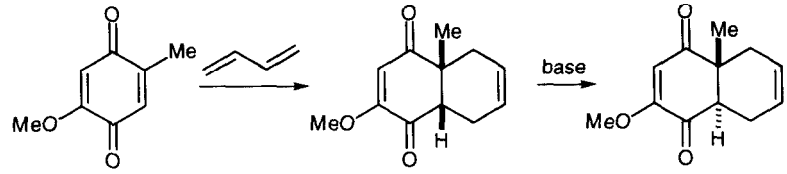
Scheme 26. Ley's approach to azadirachtin



Scheme 27. Mori's approach to azadirachtin

4.3 Intermolecular Diels–Alder reaction–epimerization

Woodward discovered that the *cis*-decalin formed in an intermolecular Diels–Alder reaction of a benzoquinone could be epimerized to the more thermodynamically stable trans isomer.[55] For example, 4-methoxy-2,5-toluquinone reacted with butadiene to give the *cis*-decalin (Scheme 28). Treatment with base afforded nearly equal amounts of the *trans*- and *cis*-decalins, but the isomerization could be driven to completion under acidic conditions by selective crystallization of the desired trans isomer from the reaction mixture.

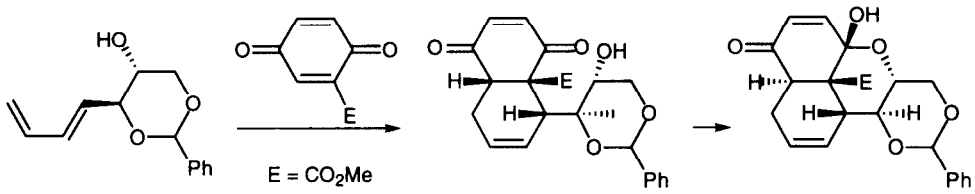


Scheme 28. Woodward's *trans*-decalin synthesis

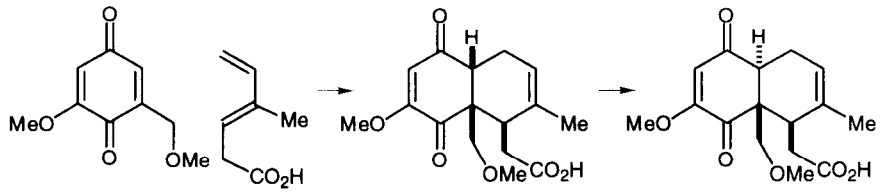
A similar strategy was used in another approach to forskolin. Again, a benzoquinone was used as the dienophile, and the diene was derived from D-glucose (Scheme 29).[56] The epimerization was carried out in the presence of basic alumina to afford the trans isomer in nearly quantitative yield. This strategy was also employed in Stevens' synthesis of the core of the quassinoid bruceantin (Scheme 30).[57] The Diels–Alder reaction proceeded under remarkably mild conditions (room temperature, 5–10 days). The epimerization to the trans adduct was catalyzed by aqueous $NaHCO_3$ and proceeded in excellent yield.

5. Cascade cyclizations of polyenes

Another method that has been commonly employed for synthesizing fused ring systems is the cascade cyclization of polyenes mediated by carbocations, free radicals, or transition metals.[58] The primary drawback of such cyclizations is that the polyene can be difficult to prepare, especially in diastereopure form. Cascade



Scheme 29. Suryawanshi and Bhakuni's approach to forskolin

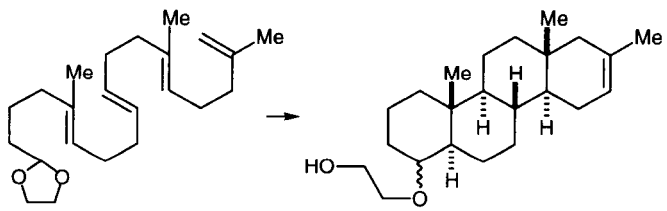


Scheme 30. Stevens' synthesis of the core of bruceantin

cyclizations have also suffered in the past from poor chemo- and regioselectivity and early termination of the cascade, although more and more successful examples are appearing in the literature, as highlighted below.

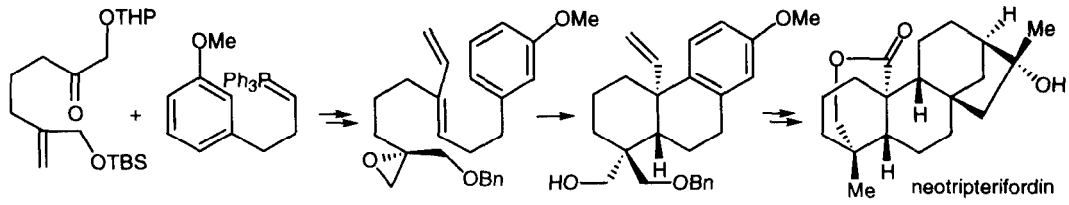
5.1 Carbocation-mediated cyclizations

Carbocation-mediated cyclizations of polyunsaturated acyclic compounds have been carried out by living organisms for billions of years, but the academic study of these reactions was begun only about fifty years ago, with the most important initial contributions coming from the laboratory of W. S. Johnson.[59,60] Extensive experimentation has now revealed conditions under which multiple C—C bonds are formed stereoselectively in a single step and in good yield (Scheme 31). These almost fantastic reactions generally provide polycyclic compounds with trans stereochemistries at the ring junctions.



Scheme 31. Johnson's cation–π tetracyclization

Corey's masterful synthesis of neotripterifordin, a potent inhibitor of HIV replication, uses a carbocation-mediated cascade cyclization as the key step in the preparation of an oxygenated *trans*-decalin (Scheme 32).[61] The stereochemistry of the Wittig reaction that creates the trisubstituted double bond of the cyclization substrate is controlled by the α-alkoxy substituent of the ketone. The alkoxymethyl group of the Wittig product is then converted to a vinyl group for the $TiCl_4$-mediated cyclization, which proceeds cleanly and stereoselectively to afford the tricyclic product with an axial vinyl group in very good yield. The vinyl group is later oxidized back to a carboxy group in the final product.

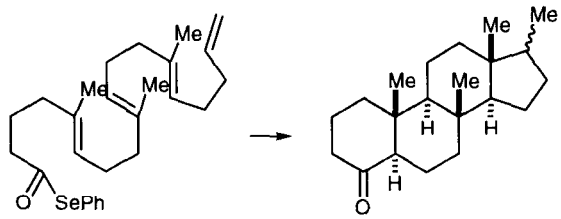


Scheme 32. Corey's synthesis of neotripterifordin

5.2 Radical-mediated cyclizations

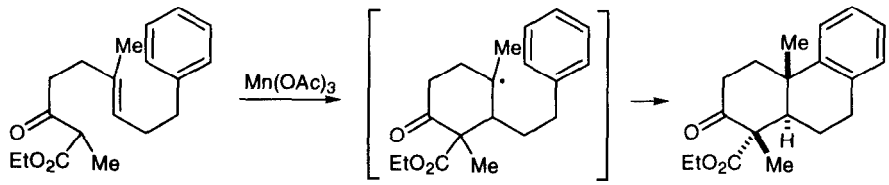
The free-radical cyclization of polyolefins has become an increasingly popular method for the synthesis of polycyclic compounds. The spectacular ability of these reactions to rapidly stitch together multiple rings from an acyclic substrate in one step is one reason why they are so appealing; another is their high functional-group tolerance. However, free-radical cyclizations have mostly been applied to the synthesis of cyclopentane-containing compounds, not *trans*-decalins, probably because the 5-*exo*-*trig* cyclization of radicals is so much faster than other cyclization modes.

The Pattenden group has utilized a tin-mediated reductive cyclization of a polyunsaturated acyl selenide to prepare a steroid nucleus (Scheme 33).[62] In this system, both the relatively low energy of the acyl radical and steric bias may contribute to the partitioning of the radical cyclizations through the 6-*endo* modes.

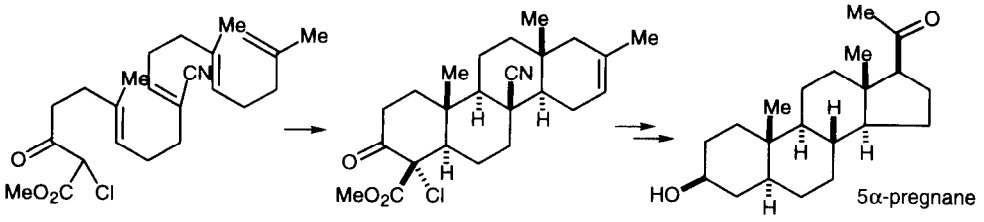


Scheme 33. Pattenden's steroid synthesis

Manganese (III) acetate can be used to promote oxidative free radical cyclizations of olefinic β-ketoesters to *trans*-decalins (Scheme 34).[63] The reagent oxidizes the β-ketoester to the corresponding radical, which then cyclizes in the 6-*endo* mode through a chair transition state, with the ester moiety assuming an axial position. The tertiary radical reacts further either by 6-*endo* radical cyclization followed by oxidation, or by oxidation to the cation followed by Friedel–Crafts cyclization. Zoretic has expanded this methodology to include triple and quadruple cyclizations, applying it to the synthesis of 5α-pregnane (Scheme 35).[64]



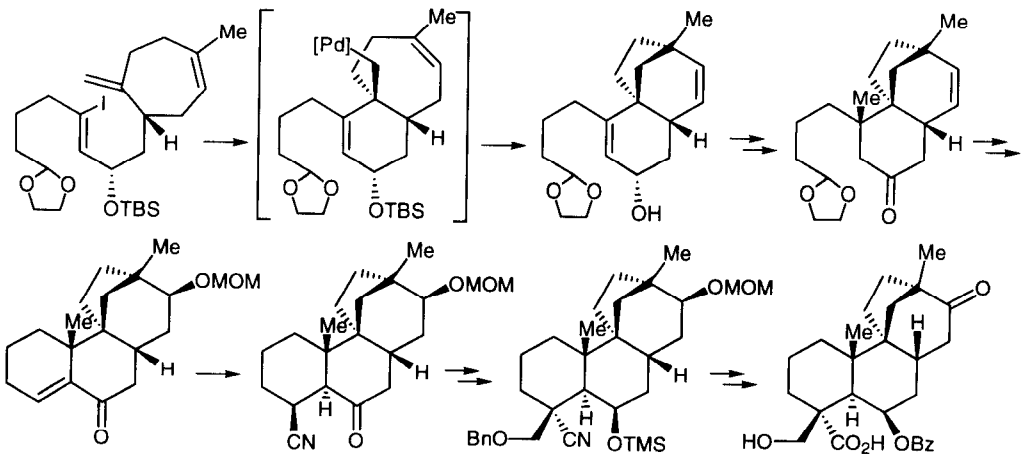
Scheme 34. Mn(III)-mediated oxidative free radical cyclization



Scheme 35. Zoretic's synthesis of 5α-pregnane

5.3 Transition-metal-mediated cyclizations

Metal-mediated and metal-catalyzed cascade cyclizations have seen increasing use in synthetic organic chemistry since the 1970s.[65] Applications to *trans*-decalin syntheses, however, have been slow in coming, perhaps because of the cis selectivity normally seen in cyclization reactions, as discussed earlier. In one particularly noteworthy example, however, a bis-Heck cyclization is used as the key step in Overman's synthesis of (–)-scopadulcic acid A (Scheme 36).[66] The bis-Heck reaction of the monocyclic precursor provides a tricyclic, ethano-bridged *trans*-decalin. The decalin is trans because the first Heck reaction, an intramolecular cyclization of the type discussed earlier, gives a *cis*-bicyclo[5.4.0]undecane, and the decalin portion of the tricyclic product is constructed only in the second Heck reaction. The other *trans*-decalin moiety in scopadulcic acid is assembled by intramolecular aldol condensation and elimination, conjugate addition of HCN, and alkylation with $BnOCH_2Cl$. (Cf. Ley's synthesis of ajugarin I above.)



Scheme 36. Overman's synthesis of (–)-scopadulcic acid

6. Conclusion

The importance of the *trans*-decalin moiety is manifested by the number of methods that have been developed for its preparation. In fact, this review has only scratched the surface of the area, as nonannulative approaches (cyclizations) have not been discussed,[67] nor have those approaches which provide *trans*-decalins

with only H substituents at the ring junction. Still, the synthesis of *trans*-decalins with specific substitution patterns in good yield, with high stereoselectivity, and in only a few steps is far from a solved problem, and the community can only expect to see further developments in this field.

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Biographical sketch

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Melissa A. Varner received her B. S. degree in chemistry from West Virginia University in 1994, where she worked on the synthesis of neocarzinostatin chromophore under the direction of Plato Magriotis. She enrolled at the University of Kentucky in the Fall of 1994, and she joined the research group of Robert B. Grossman in the Spring of 1995, where she discovered an efficient method for preparing monosubstituted α-cyanoesters and malononitrile derivatives, enabling her to develop the double Michael reaction of tethered carbon acids and alkynones. Since graduating with her Ph.D. in the Summer of 1999, Dr. Varner has worked at Affinity Labelling Technologies in Lexington, KY.

Robert B. Grossman earned his A.B. at Princeton University, where he carried out research under the direction of Robert A. Pascal. After graduating in 1987, he moved to MIT and worked under the direction of Stephen L. Buchwald to develop zirconium- and titanium-mediated and -catalyzed organic synthetic methodology. He earned his Ph.D. in 1992 and moved from Steve's lab in Cambridge to Steve's lab in Cambridge, England, where he worked in the Ley group on various aspects of the chemistry of azadirachtin. In 1994 he left the UK to join the faculty at UK. His research interests are currently focused on the preparation of highly substituted and functionalized trans-fused bicyclic compounds. He is also the author of a new intermediate-level textbook, *The Art of Writing Reasonable Organic Reaction Mechanisms* (Springer, 1999).