Chemical Reviews

Volume 88, Number 5 July/August 1988

Synthesis of Cembranes and Cembranolides†

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Received February 9, 1988 (Revised Manuscript Received April 11, 1988)

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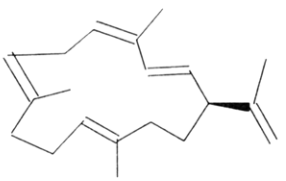
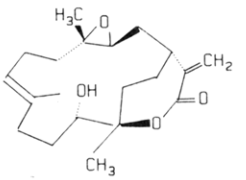
I. Introduction

A number of diterpenoid natural products containing a 14-membered ring have been isolated from terrestrial and especially from marine sources in recent years.[1] The challenge that these compounds pose is a result of the large ring as well as the array of stereocenters on the periphery of the ring. There is a wide range of structural complexity within the series. Cembrene, the

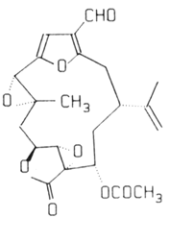


Cembrene

first naturally occurring 14-membered cyclic diterpene to be characterized, is found in pine oleoresins and is an example of a simple hydrocarbon member of this class.[2] Cembrane-A has been found in the gum exudate of a tree[3] and has been isolated from termites of the species *Nasutitermes exitiosus*.[4] Many of the most fascinating and complex structures have been isolated from marine sources. Typically these are oxygenated in several positions and often include lactone functionality. The soft corals have been a particularly rich source of cembrane and cembranolide lactone natural products. For example, sinulariolide was isolated from

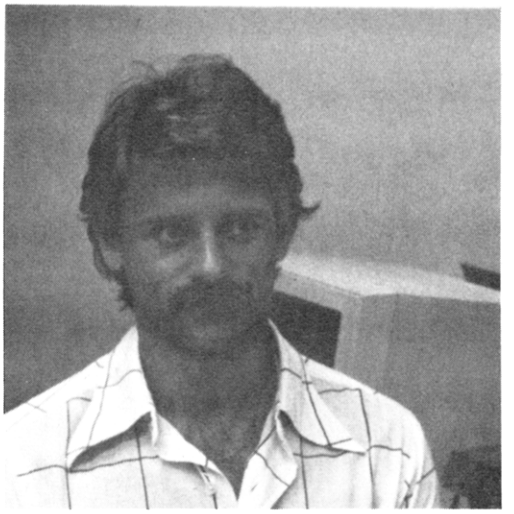


Sinulariolide



Lophotoxin

the alcyonarian *Sinularia flexibilis*[5] and has been found to have antineoplastic activity in the National Cancer Institute's (NCI) in vitro PS and KB tests.[6] Lophotoxin, a densely functionalized furanoditerpene, which has been found in several Pacific species of *Lophogorgia*



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† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

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by Fenical and coworkers,[7] is a potent (LD_{50} in mice 8.0 μg/g) neurotoxin that promises to be of some use as a biochemical probe for elucidating the mechanisms of nerve transmission.[8] Several other furanocembranes have been isolated from marine sources.[9]

The range of biological activity that has been recorded for 14-membered-ring diterpenoids is remarkably wide: insect trail pheromones, termite allomones, neurotoxins, cytotoxins, and antiinflammatory and antimitotic agents.[1,2,5,8] The intriguing range of activities, the often dense array of functional groups and stereocenters, and a lack of a general method for the preparation of 14-membered rings have made the cembranes an interesting problem for total synthesis. The synthetic problem is compounded by the conformational mobility of many of these natural products, some of which may exist as mixtures of stable conformers at ambient temperature.[10] A clear understanding of the conformational equilibria is helpful if one is to plan a synthesis. The conformational isomerism of 14-membered rings is, however, less of a problem for the synthetic chemist than might at first appear: transannular van der Waals repulsions or even intramolecular hydrogen bonding often biases the conformational preferences in a predictable way. Furthermore, the widespread availability of user-friendly molecular mechanics software packages has put a powerful tool in the hands of the chemist. Since software exists even for minicomputers, virtually everyone can easily perform calculations to predict structures and to determine the relative stability of conformers. Parameter sets for these programs have also evolved sufficiently that useful stereochemical predictions can be made with some confidence.

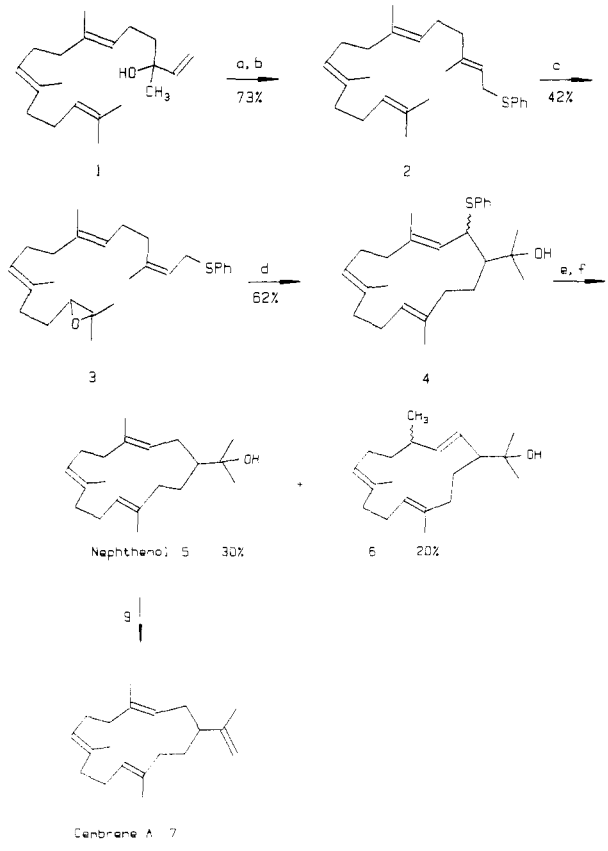
There are several distinct strategies that can be applied to the synthesis of cembrane natural products. Since the cyclization reaction is often the key step in the total synthesis, each of these strategies will be discussed in the sections that follow.

II. Sulfur-Stabilized Carbanion Alkylations

Closure of the macrocyclic ring by means of an intramolecular S_N2 reaction is a straightforward approach to the problem and one that has seen success for the synthesis of 10-membered rings of germacrone natural products.[11] The synthesis of nephthenol and cembrene-A is an example of this methodology (Scheme 1).[12] *trans,trans*-Geranyllinalool (**1**) is converted to phenyl thioether **2** in 73% yield. The selective epoxidation of the terminal trisubstituted alkene is accomplished in moderate yield with van Tamelen's procedure.[13] Carbanion formation takes place upon treatment of **3** as a dilute solution in tetrahydrofuran at −78 °C with an excess of *n*-butyllithium and DBU. Reductive cleavage of sulfur produces nephthenol **5** in 30% yield, along with 20% of isomer **6**. The reductive cleavage of allylic sulfur functionality is often complicated by double-bond migration and/or isomerization. Dehydration of the tertiary alcohol of **5** produces cembrene-A (**7**), a trail pheromone of *Nasutitermes exitiosus*.

This compound has also been prepared through the use of an alternative strategy (Scheme 2).[14] The key step here is the regiospecific coupling of two functionalized geranyl units. The advantage to this convergent approach is that it allows the regioselective introduction

SCHEME 1[a]

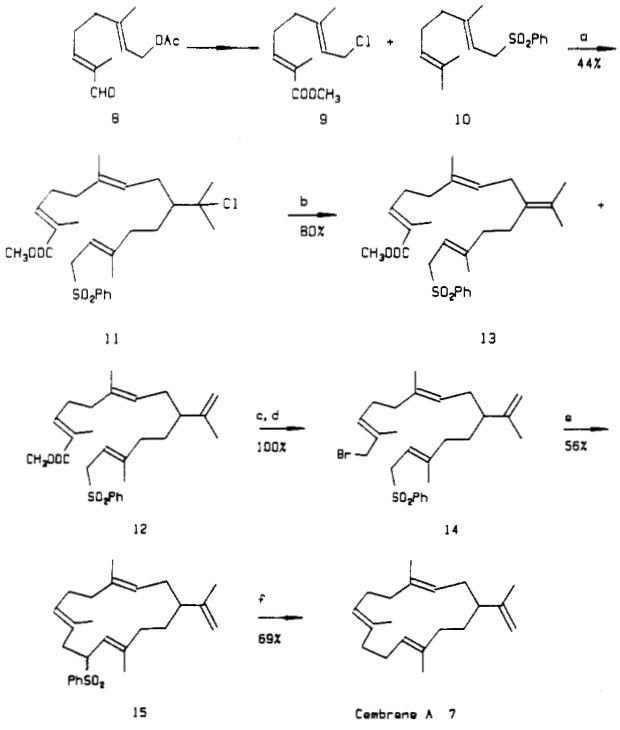


[a] (a) PBr_3; (b) NaSPh; (c) NBS, aqueous THF; K_2CO_3, MeOH; (d) excess *n*-BuLi, THF, DBU, −78 °C; (e) Li, $EtNH_2$; (f) preparative TLC, $AgNO_3$; (g) $SOCl_2$, pyr.

of functionality prior to cyclization. Acetate–aldehyde **8**, which is available from geranyl acetate, is readily converted to allylic chloride **9**. Treatment of **9** at −94 °C with geranyl phenyl sulfone (**10**) in dichloromethane in the presence of Lewis acid produces tertiary chloride **11** in 44% yield. The elimination of hydrochloric acid from **11** is found to depend markedly upon the reaction conditions. The usual conditions for performing this type of reaction, lithium bromide/lithium carbonate in hot DMF, produces an equimolar mixture of **12** and the isopropylidene isomer **13**. When the reaction mixture containing **11** is sprayed onto a Kieselgel plate that is kept at room temperature for 4 days, **12** is the exclusive product. Conversion of the carbomethoxy group of **12** to an allylic bromide by treatment with lithium aluminum hydride, followed by triphenylphosphine/carbon tetrabromide, gives a quantitative yield of **14**. The macrocyclization reaction of **14** takes place by treatment in THF at −78 °C with 1 equiv of lithium diisopropylamide. Desulfurization with lithium in ethylamine produces **7** in 69% yield. It is worthy of note that the allylic chloride corresponding to **14** undergoes no reaction under the conditions for the cyclization. The advantage of the phenyl sulfone as a removable carbanion-stabilizing group is its ease of reductive cleavage with sodium amalgam. Trost's very mild procedure is particularly effective.[15] The attenuation of the reactivity of the sulfone anions relative to the corresponding thiophenyl ether (cf. **3**) can be corrected by using the easily generated sulfone dianions.[16]

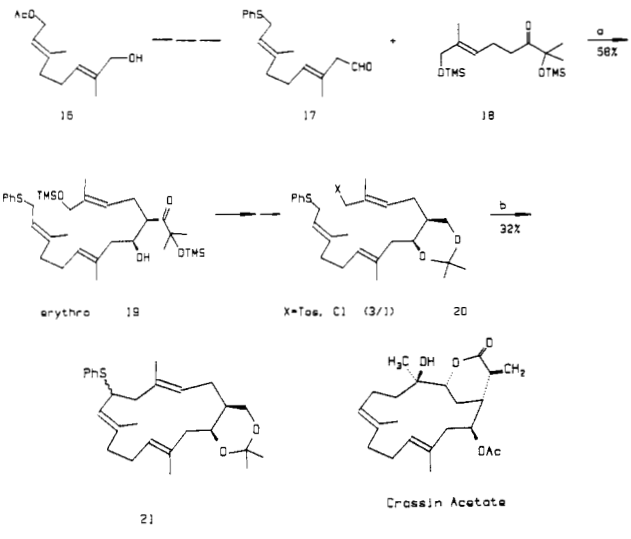
Dauben's approach to crassin acetate[17a] also makes use of a convergent strategy (Scheme 3). Crassin

SCHEME 2[a]



[a] (a) $SnCl_4$, CH_2Cl_2, −94 °C, 3 h; (b) LiBr, Li_2CO_3, DMF, 100 °C; (c) LAH, −20 °C; (d) PPh_3, CBr_4, CH_3CN, room temperature; (e) LDA, THF, −78 °C; (f) Li, $EtNH_2$, −78 °C.

SCHEME 3[a]

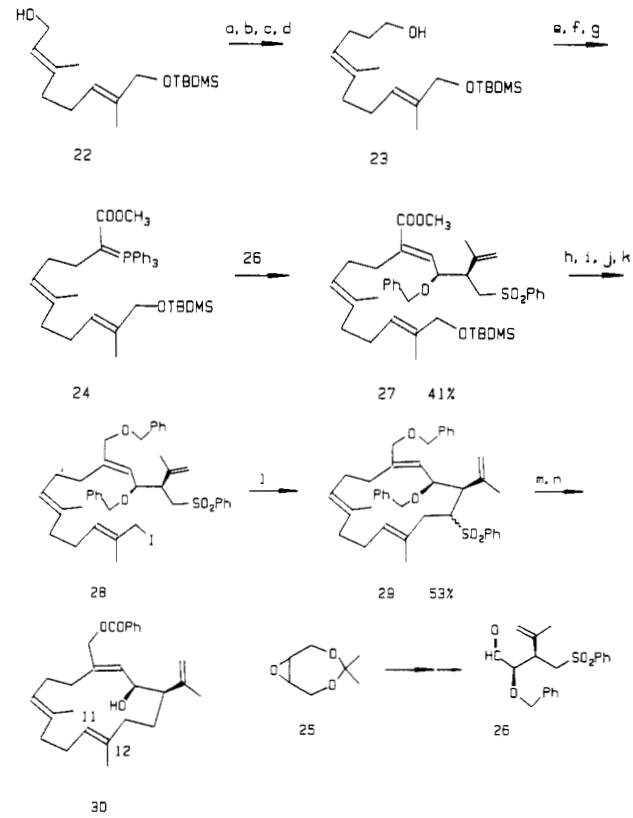


[a] (a) LDA, THF, hexane, −78 °C; (b) LDA, THF, −78 °C.

acetate has significant (1 mg/mL) in vitro activity against the KB cell line.[17b] Alcohol **16** is derived from geranyl acetate and is converted to phenyl thioether **17**. In an application of Heathcock's[18] aldol methodology, the enolate of ketone **18** provides erythro product **19** in 58% yield. A straightforward series of steps converts **19** to **20** as a 3/1 mixture of the allylic tosylate and the corresponding allylic chloride. Deprotonation of the allylic phenyl thioether with lithium diisopropylamide at −78 °C in THF produces the cyclized compound **21** in modest yield.

Another example of a convergent cembranoid synthesis that makes use of a sulfone-stabilized carbanion is provided by Marshall's preparation of *dl*-7(8)-

SCHEME 4[a]

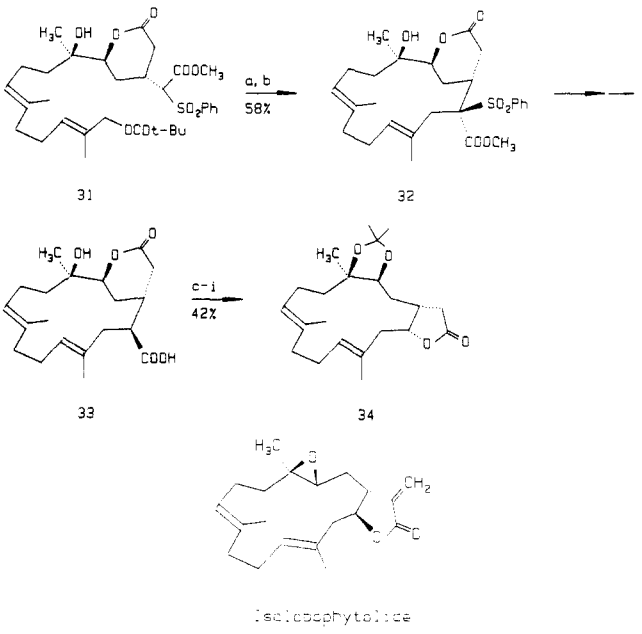


[a] (a) MsCl, LiCl, DMF, 2,6-lutidine, 0 °C; (b) CH_2=$CHLi$, CuI, THF, −23 °C; (c) $(Siam)_2BH$, THF, −10 °C; (d) H_2O_2, NaOH; (e) I_2, PPh_3, imidazole, CH_3CN, Et_2O, 0 °C; (f) PPh_3, PhH; (g) $(TMS)_2NK$, THF, MeOCOCl, −78 to +25 °C; (h) DIBAL, CH_2Cl_2, −78 °C; (i) *t*-BuLi, THF, HMPA, $PhCH_2Br$, −78 to +25 °C; (j) *n*-Bu_4NF, THF, 25 °C; (k) I_2, PPh_3, imidazole, CH_3CN, Et_2O, 0 °C; (l) $(TMS)_2NK$, THF, 18-crown-6; (m) Na, NH_3, THF, −33 °C; (n) PhCOCl, TEA, DMAP.

deoxyasperdiol (Scheme 4).[19] The two-carbon atom homologation of **22** produces **23**, which is converted to **24** by treatment of the unstabilized ylide with methyl chloroformate. The Wittig reaction between **24** and aldehyde **26** produces **27** in 41% yield as a single geometrical isomer. The phosphorane **24** is used for the coupling because in a bimolecular reaction, which was studied as a model, extensive decomposition of the aldehyde is seen with the more reactive phosphonic ester. Since **27** contains all of the carbon atoms of the final product, a series of functional group transformations are all that is needed to complete the synthesis. It is necessary to reduce the methyl ester group and to protect the resultant allylic alcohol as a benzyl ether prior to cyclization. Sulfone iodide **28** is cyclized in 53% yield by treatment with potassium hexamethyldisilylamide in THF in the presence of 18-crown-6. Sodium in ammonia serves both to reduce benzyl ethers and to cleave the sulfone to produce deoxyasperdiol in 71% yield. The selective benzoylation of the primary alcohol produces **30**, an intermediate in Kato's synthesis of asperdiol (vide infra). The strategic placement of the phenyl sulfone group at a nonallylic position in the final product ensures the stereochemical integrity of the C-11 alkene during the reductive cleavage.

Marshall has used a conceptually similar approach for his synthesis of *dl*-isolobophytolide (Scheme 5).[20] Palladium-mediated macrocyclizations of sulfone–esters and disulfones have been explored in detail by Trost.[21]

SCHEME 5[a]



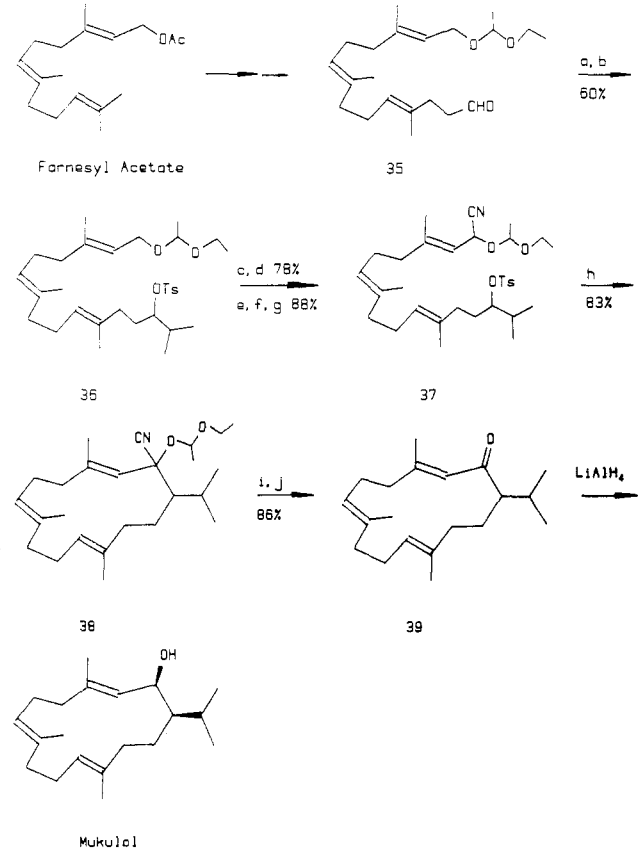
[a] (a) *O,N*-Bis(trimethylsilyl)acetamide (BSA); (b) $Pd(PPh_3)_4$, Diphos, THF; (c) EtOCOCl, TEA, THF, CH_2Cl_2, −78 °C; (d) *m*-CPBA Na salt, −78 °C; (e) NH_4Cl, CH_2Cl_2, THF, H_2O; (f) EtOAc, Et_2O, 25 °C, 2 days; (g) NaOH, THF, H_2O; (h) H_2O, HCl, 0–25 °C; (i) 2-methoxypropene, PPTS.

It is somewhat surprising that this methodology has only been applied to cembranoid synthesis in this one instance, particularly since the method is tolerant of a variety of functional groups and proceeds in high yield. Polymer-bound catalysts could probably improve cyclization yields in difficult cases by suppressing bimolecular reaction pathways.[22] The cyclization of pivalate **31** is accomplished in 58% yield by treating the trimethylsilyl enol ether derivative with $Pd(PPh_3)_4$ in refluxing THF with diphos. The advantage of this strategy over the conventional sulfone-stabilized carbanion route is due to the mildness and specificity of the generation of the (π-allyl)palladium complex from the allylic pivalate ester: no protecting groups are necessary. A disadvantage for the synthesis of this particular molecule is the presence of the carboxylate in **33**, which is obtained after reductive removal of the sulfone and equilibration with base. In order to exchange the carboxylate for an oxygen, a modified Baeyer–Villiger type of reaction was performed on **33**. Treatment with ethyl chloroformate and triethylamine gives a mixed carbonic anhydride which upon subsequent exposure to sodium *m*-chloroperoxybenzoate leads to the mixed acyl peroxide. Carboxy inversion takes place with retention of stereochemistry during 2 days at 25 °C. Treatment with base hydrolyzes the chlorobenzoate ester intermediate and causes a translactonization to take place. Protection of the vicinal diol as an acetonide leads to **34** in 42% overall yield. This intermediate is converted to *dl*-isolobophytolide through a conventional series of reactions.

III. Cyanohydrin Alkylations

In addition to sulfone- and thioether-stabilized carbanionic cyclizations, ethoxyethyl-protected cyanohydrin-derived anions have seen use in cembrane synthesis. A synthesis of the cembrane alcohol mukulol

SCHEME 6[a]



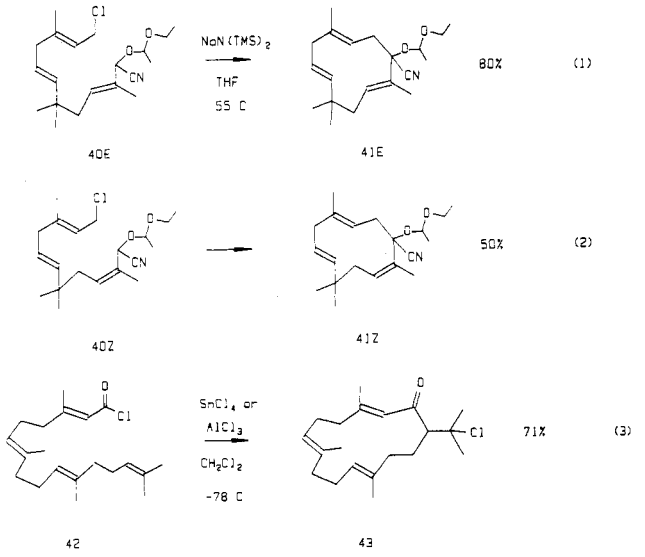
[a] (a) Isopropylmagnesium bromide; (b) TsCl; (c) H_3O^+; (d) MnO_2; (e) TMSCN, KCN-18-crown-6, 0 °C, 15 min; (f) F^-, THF, H_2O, 0 °C, 20 min; (g) ethyl vinyl ether (EVE), H^+; (h) $(TMS)_2NNa$, THF; (i) PPTS, MeOH, 40 °C, 1 h; (j) 1% aqueous NaOH, 0 °C, 1 min.

has been described that proceeds from farnesyl acetate (Scheme 6).[23] This is an attractive starting material for cembrane synthesis because it contains two of the trisubstituted alkenes of the final product. Furthermore, the selective functionalization of the terminal alkene can be accomplished in good yield, allowing for the introduction of the remaining carbon atoms. Farnesyl acetate is converted to aldehyde **35**, which is alkylated with isopropylmagnesium bromide. The tosylate derivative **36** is converted to cyanohydrin acetal **37**. Sodium hexamethyldisilylamide in refluxing THF produces the cyclized product **38** in 83% yield. This reaction is remarkable for proceeding in such high yield, particularly since the electrophile is secondary with β branching. Cyanohydrin hydrolysis produces ketone **39**, which is converted to *dl*-mukulol by treatment with lithium aluminum hydride.

The allylic carbanion derived from cyanohydrin ether **37** maintains its geometric integrity. This useful property has been demonstrated in a particularly convincing way during a humulene synthesis.[24] The *E* and *Z* cyanohydrin ether isomers **40E** and **40Z** (eq 1 and 2) are cyclized with complete specificity by treatment with an excess of sodium hexamethyldisilylamide in THF at 55 °C.

IV. Friedel–Crafts Acylation

A truly effective method for forming 14-membered rings is through the intramolecular Friedel–Crafts



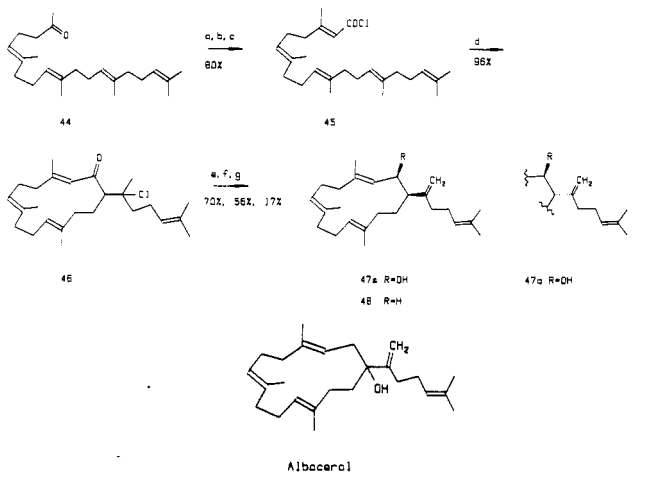
acylation of *trans*-geranylgeranoyl chloride **42** (eq 3).[25] It is surprising that this reaction proceeds in such high yield (71%) and that chloro ketone **43** is formed as the exclusive cyclization product when formation of a 10-membered ring might have taken place. It has been shown in fact that the 14-membered-ring products are formed from any geranylgeranoyl chloride having a 2,3-*E* geometry.[26] The geometry of the C-6 and the C-10 double bonds has no influence on the outcome of the cyclization. Cyclohexenones are formed from the Friedel–Crafts reaction of the 2,3-*Z* isomers.[26]

The high selectivity for 14-membered-ring formation has been demonstrated during a model study for the synthesis of albocerol (Scheme 7).[27] Geranylgeranyl acetone (**44**) is converted in three steps to acid chloride **45**. Treatment of **45** with 0.5 equiv of $SnCl_4$ at −78 °C in dichloromethane produces the 14-membered-ring chloro ketone **46** in 96% yield. Dehydrochlorination with lithium bromide/lithium carbonate, followed by alane reduction in ether, produces a 10/1 ratio of syn and anti alcohols **47**. Reductive cleavage of the hydroxyl forms **48**, a hydrocarbon having the albocerol skeleton.

Chloro ketone **43** has been used as a starting material for a number of cembrane natural products. The sequential treatment of **43** with tri-*n*-butyltin hydride followed by LAH produces mukulol,[28] which is converted, inter alia, to incensole (Scheme 8).[29] Mukulol is converted to bromo ether **49** in 54% yield by exposure to tetrabromocyclohexadienone (TBCO)[30] in dichloromethane. Treatment at −15 °C with boron trifluoride etherate leads to rearranged product **50**. This reaction presumably takes place through the intermediacy of the C-1,C-3 diene. It is interesting that the geometry of the trisubstituted alkene is preserved during the rearrangement. In all likelihood this represents an example of thermodynamic control. Silver ion assisted solvolysis followed by LAH reduction produces incensole. The secondary alcohol in incensole can be induced to undergo a second bromoetherification reaction with TBCO. Silver ion assisted solvolysis once again gives rise to a mixture of diastereomeric acetates **52** and **53**. The major diastereomer **52** is converted in 80% yield to isoincensole oxide.[31]

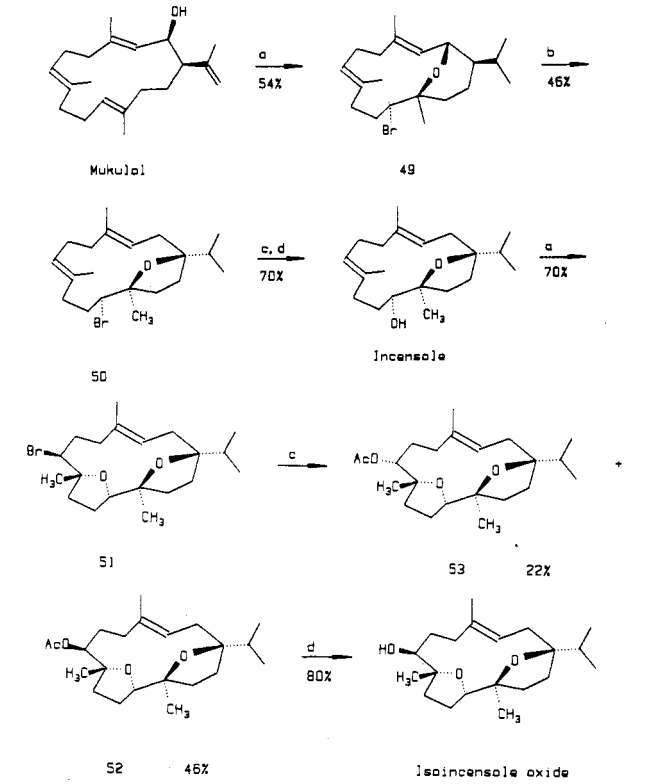
Epimukulol, which is also available from chloro ketone **43**, has been converted to thunbergol, a constituent

SCHEME 7[a]



[a] (a) $(EtO)_2POCH_2COOMe$, NaH; (b) KOH, dioxane, 90 °C, 12 h; (c) $SOCl_2$, PhH, pyr, 0 °C, 1 h; (d) 0.5 mol equiv of $SnCl_4$, −78 °C, CH_2Cl_2; (e) LiBr, Li_2CO_3, DMF, 105 °C, 8 h; (f) AlH_3, Et_2O; (g) Ac_2O, pyr; $EtNH_2$, Li, −78 °C, 1 h.

SCHEME 8[a]

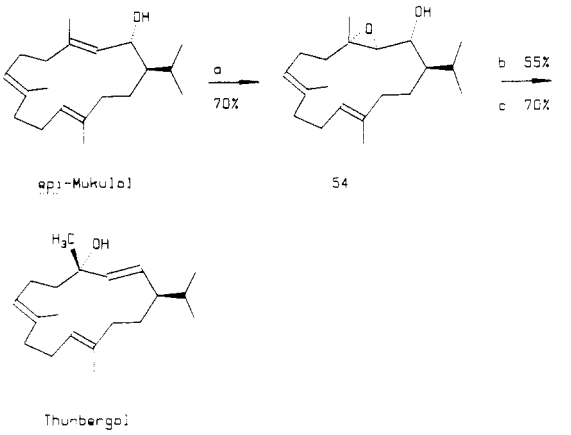


[a] (a) TBCO, CH_2Cl_2; (b) $BF_3{\cdot}Et_2O$, −15 °C, 1 h; (c) AgOAc, HOAc, 55 °C, 2 h; (d) LAH.

of the resin of the Douglas fir, *Pseudotsuga menziensii* (Scheme 9).[32] In this work the allylic alcohol is used to direct epoxidation of the C-3,C-4 alkene. Mesylation of the alcohol followed by reduction with sodium in liquid ammonia produces thunbergol.

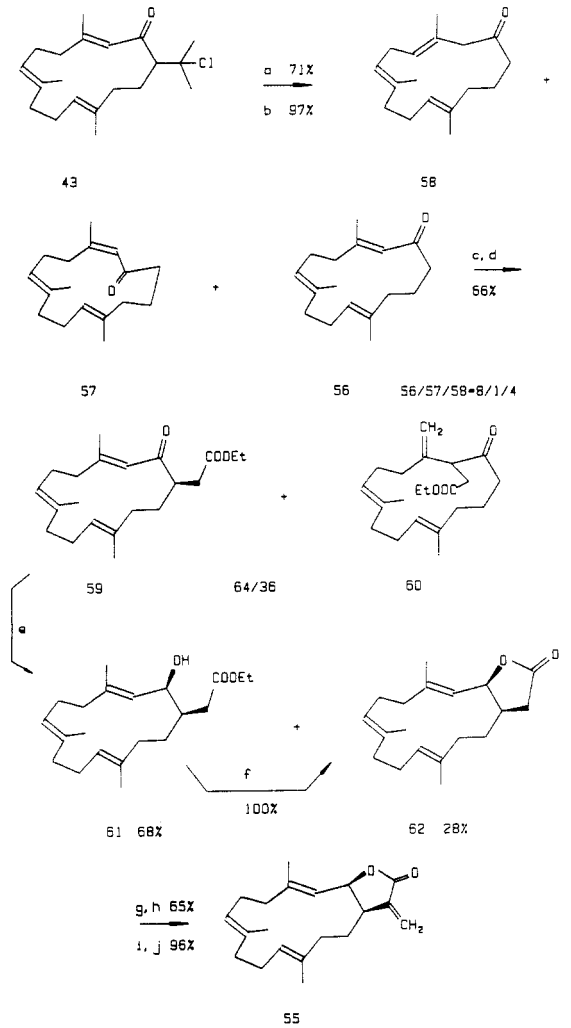
An unnamed cembranolide lactone (**55**) that has been isolated from the soft coral *Lobophytum michaelae*[33] has been prepared from **43** (Scheme 10).[34] The base-catalyzed retro-aldol reaction of the tertiary alcohol derived from **43** produces a mixture of ketones **56**, **57**, and **58**. The two undesired isomers **57** and **58** are reequilibrated with base to produce additional quantities of **56** through recycling. The alkylation of **56** with ethyl

SCHEME 9[a]



[a] (a) *t*-BuOOH, $VO(acac)_2$, PhH; (b) MsCl, TEA, CH_2Cl_2; (c) Na, NH_3.

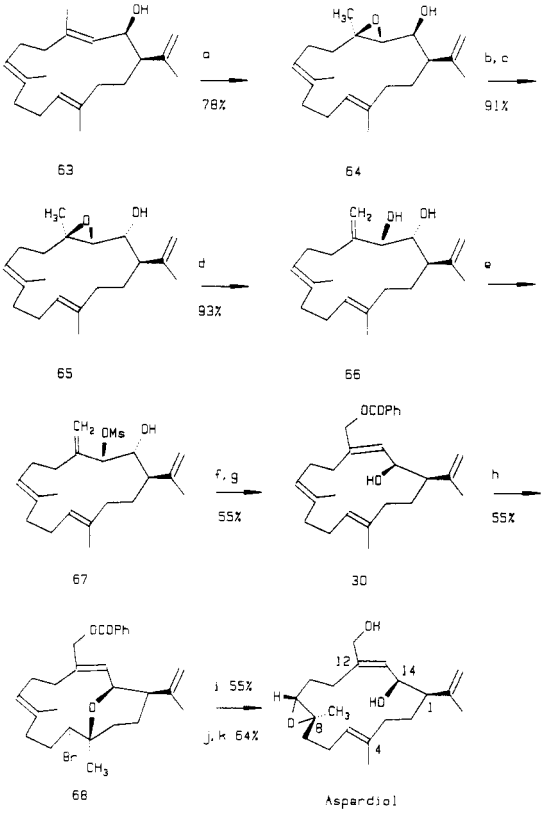
SCHEME 10[a]



[a] (a) ZnO, AcOH, 45 °C, 3 h; (b) LiOH, aqueous dioxane, 75 °C, 5 h; (c) LDA, THF, HMPA, −78 °C; (d) ICH_2COOEt; (e) $NaBH_4$; (f) PPTS, PhH, 10 min; (g) LDA; (h) CH_2=O gas, −20 °C; (i) MsCl, pyr, CH_2Cl_2, DMAP, room temperature; (j) DBU, PhH, room temperature.

iodoacetate produces a mixture of **59** and **60**. The major isomer **59** is reduced with sodium borohydride to produce a mixture of hydroxy ester **61** and lactone **62**. Brief treatment with acid results in the complete lactonization of the product. Introduction of the *exo*-methylene group completes the synthesis of **55**.

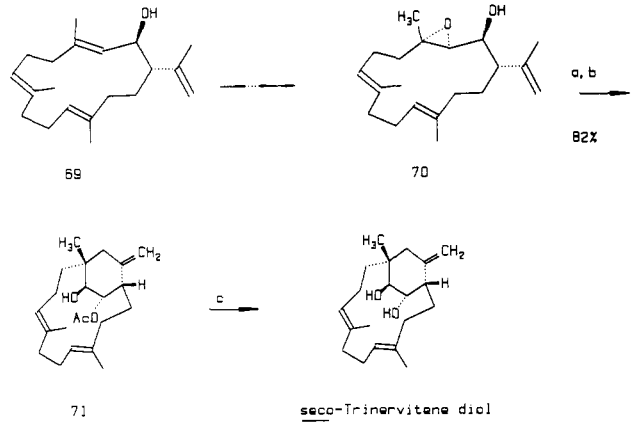
SCHEME 11[a]



[a] (a) *t*-BuOOH, $VO(acac)_2$; (b) Collins, room temperature; (c) $LiAlH(O\text{-}t\text{-}Bu)_3$; (d) $Ti(O\text{-}i\text{-}Pr)_4$, PhH, 90 °C; (e) MsCl, TEA; (f) TMSCl, TEA, DMAP, −20 °C; (g) PhCOOH, DBU, cat. NaI, DMF, 70 °C; (h) TBCO; (i) *m*-CPBA, −20 °C, 2 days; (j) Zn, EtOH, reflux; (k) KOH, dioxane, reflux.

The most ambitious work to date that uses **43** as a starting material is Kato's synthesis of *dl*-asperdiol.[35] A very clever synthesis results from the deft manipulation of alcohol groups to direct the stereospecific introduction of oxygen functionality (Scheme 11). Asperdiol has been isolated from two species of Caribbean gorgonians, *Eunicea asperula* and *E. tournefortii*, and has been found to be active against several of the NCI's tumor cell lines at the μg/mL level.[36] As a consequence of the interesting level of activity, several total syntheses have been described to date.[37,38] The selective epoxidation of the allylic alcohol double bond in dehydromukulol (**63**) is accomplished with vanadyl acetylacetonate and *tert*-butyl hydroperoxide. The next step involves an oxidation–reduction sequence in order to adjust the stereochemistry at C-14. Titanium tetraisopropoxide catalyzes the rearrangement of epoxy alcohol **65** to the allylic diol **66** in 93% yield. The excellent yield of this reaction strongly suggests that **65** exists preponderantly as a single conformer. The allylic alcohol group of **66** allows oxygen to be introduced at C-20 through a [1,3] transposition. Mesylation is selective for the C-13 allylic alcohol. The alcohol at C-14 is sterically encumbered by the C-1 isopropenyl group. The C-14 alcohol is converted to the trimethylsilyl ether, which is treated in a subsequent step with benzoic acid and DBU in warm DMF with a catalytic amount of sodium iodide. The rearranged benzoate **30** is isolated in 55% yield. The solvolysis of the free hydroxyl compound leads to poorer yields of product, possibly

SCHEME 12[a]



[a] (a) Ac_2O, pyr; (b) $BF_3{\cdot}Et_2O$, −40 °C; (c) LAH.

due to the intramolecular participation of the hydroxyl group.

The next step in the synthesis, the introduction of the C-8,C-9 epoxide, necessitates the protection of the C-4,C-5 double bond. This is accomplished with a bromoetherification reaction that is mediated by TBCO. Bromo ether **68** is subjected to *m*-chloroperoxybenzoic acid at −20 °C to produce in 55% yield a 3/1 mixture of isomeric epoxides. The regiochemistry of the epoxidation reaction follows from the faster rate of electrophilic epoxidation of trisubstituted versus 1,1-disubstituted alkenes.[39] The stereochemical requirement for peripheral attack on the major conformer of **68** determines the stereochemistry at C-8 and C-9. Finally, reductive cleavage of the bromo ether and benzoate hydrolysis produces *dl*-asperdiol.

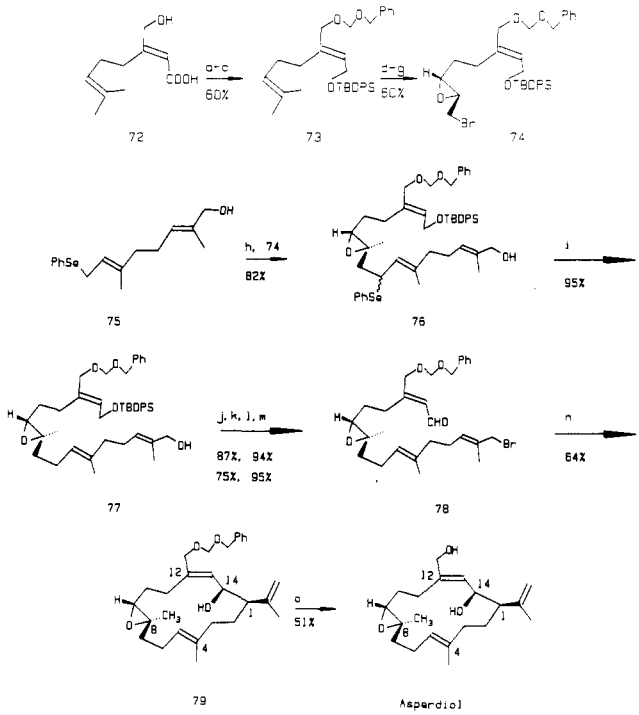
The technique of exploiting the proximity of functional groups, typically alcohols, to double bonds on the periphery of the 14-membered ring to induce transannular reactions has also been used for the synthesis of *seco*-trinervitenediol, a termite defense secretion, starting from *trans*-dehydromukulol (**69**) (Scheme 12).[40] Epoxy alcohol **70**, derived from **69**, is first acetylated and then treated with boron trifluoride etherate at −40 °C in ether. Cyclization to the cyclohexane takes place in 82% yield. Reductive cleavage of the acetate with LAH produces *seco*-trinervitenediol.

Because of the ease and the efficiency of the synthesis of chloro ketone **43** and the control over product double-bond geometry, **43** is an attractive starting material for a large number of cembrane natural products. This is particularly true for the simpler members of this class. For the more complex and more highly oxygenated compounds a tradeoff is established between the efficiency of the preparation of the starting material and the number of steps required for the sequential introduction of multiple oxygen atoms. The advantages of a convergent strategy cannot be realized in these syntheses.

V. Allylmetal Addition to Aldehydes

Many cembranoid syntheses, particularly of multiply functionalized natural products, use one or more monoterpene-derived fragments as starting materials. Since the methodology for the regiospecific functionalization of these smaller molecules is known, this approach can often be implemented very effectively. Still

SCHEME 13[a]

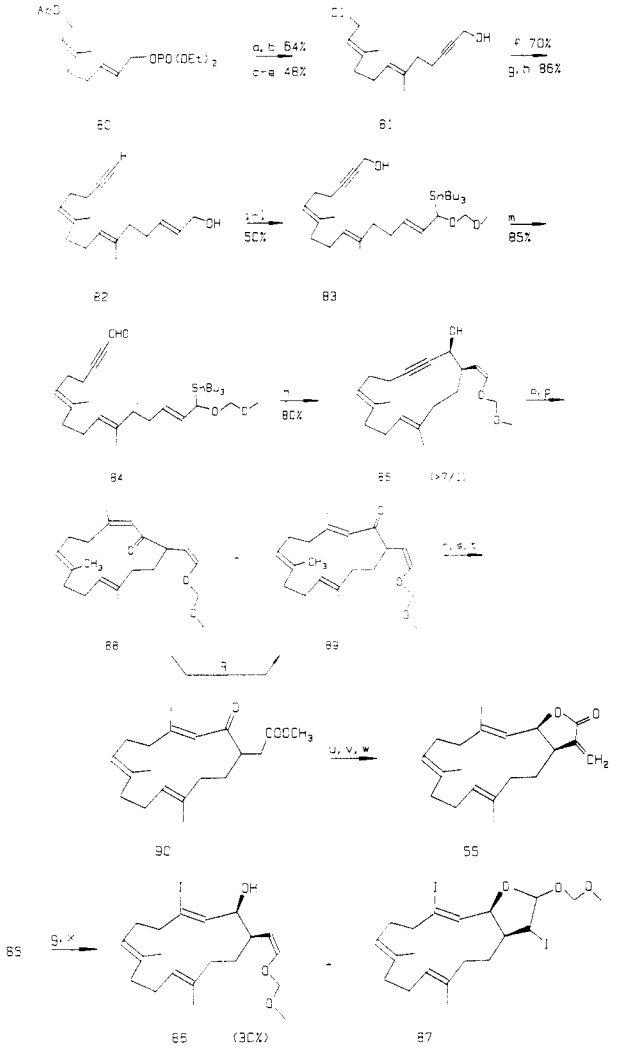


[a] (a) $PhCH_2OCH_2Cl$, *i*-Pr_2NEt; (b) LAH; (c) TBDPSiCl, DMF, imidazole; (d) *t*-BuOOH, cat. SeO_2; (e) *t*-BuOOH, $VO(acac)_2$; (f) MsCl, TEA; (g) LiBr, acetone; (h) LDA, −55 °C; (i) W-2 Ra/Ni; (j) $(Me_2N)_3P$, CCl_4; (k) *n*-Bu_4NF; (l) MnO_2, CH_2Cl_2; (m) LiBr; (n) $CrCl_2$; (o) Na, NH_3, −78 °C, <1 min.

and Mobilio's synthesis of *dl*-asperdiol (Scheme 13) provides a particularly apt example of this chemistry.[37] Copper-catalyzed Grignard addition to hydroxytetrolic acid provides hydroxy acid **72** in good yield. Orthogonal protecting groups are used to mask the diol from **72**. Allylic oxidation of the *E* methyl group of **73** is followed by vanadyl acetonylacetonate catalyzed epoxidation of the resulting allylic alcohol and conversion to the bromide **74**. Seleno ether **75**, which is derived from geranyl acetate, is deprotonated with 2 equiv of lithium diisopropylamide (LDA) and is treated with bromide **74** to produce coupled product **76** in 82% yield. The reductive cleavage of the allylic phenylselenyl group is accomplished in 95% yield with W-2 Raney nickel. The product is isolated as a 2/1 mixture of trisubstituted and disubstituted alkenes. Some positional scrambling of the double bond is unavoidable during the removal of allylic sulfur and selenium anion stabilizing groups. The primary allylic alcohol of **77** is converted to the chloride, C-14 is oxidized to the aldehyde, and the chloride is converted to the highly labile allylic bromide **78**. The macrocyclization reaction is accomplished by applying the Hiyama–Heathcock protocol[41] with chromous chloride in THF. This provides **79** in 64% yield as a 4/1 mixture of diastereomers at C-1 and C-14. Reductive removal of the protecting group provides *dl*-asperdiol in 51% yield.

Unlike Kato's asperdiol synthesis,[35] Still uses no temporary rings to protect the alkenes or to restrict the conformational mobility of the cembrane. An attempt to use the calculated conformational energies of **79** and its α-C-1,α-C-14 diastereomer to rationalize the observed selectivity failed to produce persuasive evidence for a thermodynamic preference for the formation of **79**. Strategies that take advantage of remote stereo-

SCHEME 14[a]

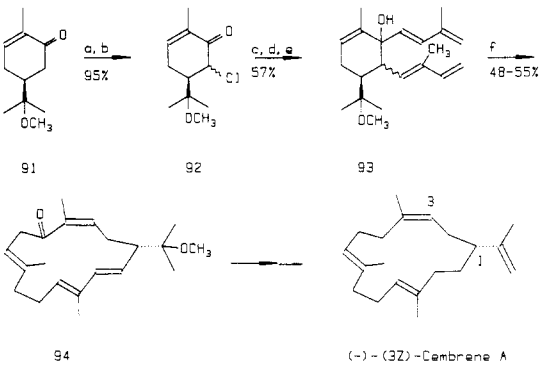


[a] (a) TIPSCCCH$_2$MgCl, CuI, THF, Me$_2$S; (b) n-Bu$_4$NF, THF; (c) K$_2$CO$_3$, MeOH, 0 °C; (d) LiCl, MsCl, 2,6-lutidine, DMF, 0 °C; (e) LDA, THF, -78 °C; (CH$_2$=O)$_n$; (f) TIPSCCCH$_2$MgCl, 0.5 equiv of CuI, THF; (g) Red-Al, THF, 25 °C; (h) n-BuN$_4$F, THF; (i) (COCl)$_2$, DMSO, TEA, CH$_2$Cl$_2$; (j) LiSnBu$_3$, THF; (k) MeOCH$_2$Cl, i-Pr$_2$NEt, CH$_2$Cl$_2$, 0 °C; (l) LDA, THF, -78 °C; (CH$_2$=O)$_n$; (m) ref 43; (n) BF$_3$·Et$_2$O, CH$_2$Cl$_2$, -78 °C; (o) PCC, NaOAc; (p) LiCuMe$_2$; (q) lithium isopropyl mercaptide, THF; (r) HCl, aqueous THF; (s) PDC, DMF; (t) CH$_2$N$_2$; (u) NaBH$_4$; (v) LDA; (CH$_2$=O)$_n$; (w) -H$_2$O; (x) NIS.

selection are inherently efficient, since the stereochemistry of one or two centers is allowed to control the stereochemistry of all other asymmetric centers. This type of approach is very well suited for enantioselective synthesis as well.

Marshall has also used an intramolecular addition of an allylic organometallic to an aldehyde for his synthesis of cembrane lactone **55** (Scheme 14).[42] Allylic phosphate ester **80**, which is derived from geranyl acetate, is homologated by treatment with a copper-catalyzed propargyl Grignard reagent. Exchange of acetoxy for chloride, deprotonation, and trapping with formaldehyde produce propargyl alcohol **81**. Three-carbon homologation of the allylic chloride portion of **81** is accomplished with the same Grignard method. The selective reduction of the propargyl alcohol and protecting group removal furnish **82**. Swern oxidation, treatment of the enal with tributyltin lithium, and quenching with methoxymethyl chloride are followed

SCHEME 15[a]



[a] (a) LDA; (b) F$_3$CSO$_2$Cl; (c) (*E*)-1-lithio-2-methyl-1,3-butadiene; (d) lithium isopropenyl acetylide; (e) LAH; (f) KH, 18-crown-6, THF, room temperature.

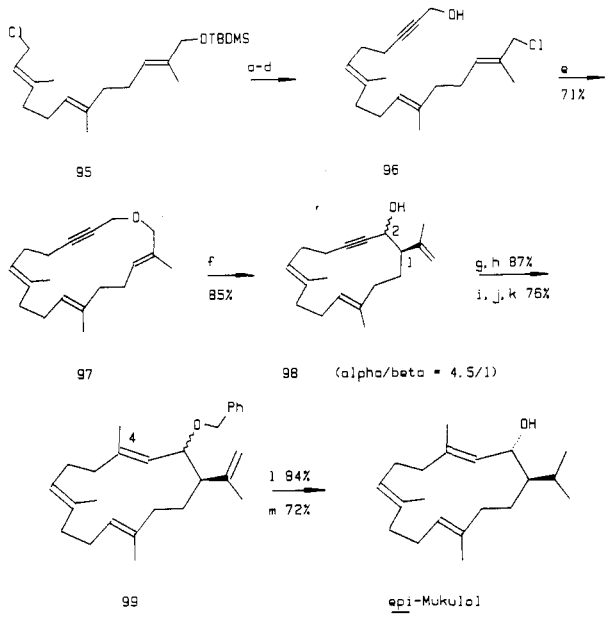
by alkyne homologation to propargyl alcohol **83** in 50% overall yield from **82**. The oxidation of **83** to acid-labile aldehyde **84** is accomplished in 85% yield through the use of Mukaiyama's excellent method.[43] It is worth mentioning that this method is very well suited for the oxidation of sensitive tin-containing substrates.[44] The intramolecular cyclization reaction is accomplished at -78 °C with boron trifluoride etherate. The cyclic product **85** is isolated in 80% yield as a >7/1 mixture of syn and anti diastereomers. The stereoselectivity in this case is notable, because an acyclic model closely resembling **84** produces a 2.5/1 mixture of syn and anti diastereomers in which the enol ether double bond is formed as a 1/1 mixture of *E* and *Z* geometrical isomers. It appears that in the case of **84**, the conformation of the developing ring is controlling the stereochemistry of the product. Marshall's suggestion that high levels of asymmetric induction can be anticipated by using chiral, nonracemic alkoxy groups in **84** is likely to be borne out.

Some difficulties were encountered during the conversion of **85** to the natural product **55**.[42b] The reduction of **85** with Red-Al followed by trapping of the organoaluminum intermediate with *N*-iodosuccinimide produces iodide **86** along with **87**, the product of an iodoetherification reaction. Neither **86** nor **87** shows promising reactivity with lithium dimethylcuprate. An ingenious alternative was devised. Oxidation of **85** with PCC followed by lithium dimethylcuprate produces an *E,Z* mixture of enones **88** and **89**. The undesired isomer is converted to **89** by exposure to lithium isopropyl mercaptide. Conventional methodology is used to convert **89** to **55**.

VI. Macroexpansion

A classical method for preparing rings of sizes larger than six is by a ring expansion. This technique has been elegantly applied to the preparation of cembranes by Wender. His synthesis of (-)-3(*Z*)-cembrene-A (Scheme 15), a substance found in the frontal gland secretion of *Cubitermes umbratus*, demonstrates the potential of this method very convincingly.[45] The acid-catalyzed addition of methanol to *d*-carvone produces enone **91**. Chlorination of the kinetic enolate of **91** with trifluoromethanesulfonyl chloride produces an epimeric mixture of chloro ketones **92** in 95% yield. Remarkably, the attachment of both isoprenyl units to **92** is accom-

SCHEME 16[a]



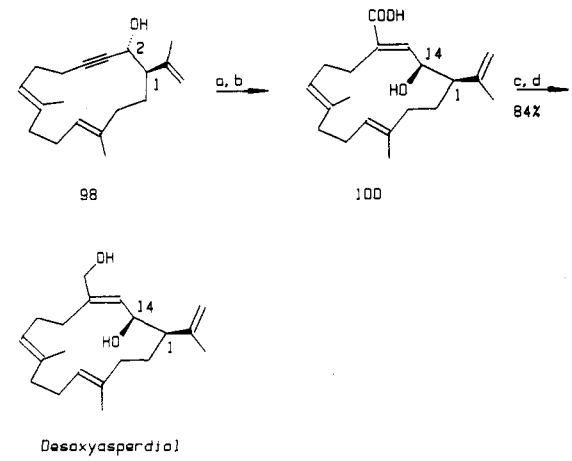
[a] (a) TIPSCCCH$_2$MgBr, CuI; (b) *n*-Bu$_4$NF, THF; (c) MsCl, LiCl, 2,6-lutidine; (d) *n*-BuLi; CH_2=O; (e) EtMgBr, THF, HMPA; (f) *n*-BuLi, THF, hexane, −78 °C; (g) Red-Al, THF; (h) I_2; (i) BnOCH$_2$Cl; *i*-Pr$_2$NEt, CH_2Cl_2; (j) *t*-BuLi, THF; (k) MeOSO$_2$F, −78 to 0 °C; (l) RhCl(PPh$_3$)$_3$, H_2, EtOH; (m) Na, NH_3, THF.

plished in a single operation. Treatment of **92** with (*E*)-1-lithio-2-methyl-1,3-butadiene at −78 °C leads to an intermediate 1,2-adduct that is not isolated. Subsequent addition of lithium isopropenylacetylide to the reaction mixture and warming to 0 °C induce a pinacol rearrangement with expulsion of chloride.[46] The acetylide adds to the carbonyl group of the intermediate. Reduction of the alkyne with LAH leads to **93** as a mixture of diastereomers. In a single operation all carbon atoms of the final product are added to **92**. Each diastereomer of **93** is independently rearranged to **94** upon treatment with potassium hydride and 18-crown-6 ether in THF at room temperature for 2 h. Macrocyclic ketone **94** is converted to (−)-3(*Z*)-cembrene-A. Studies of the mechanism of this reaction suggest that the predominant pathway for the rearrangement is through a [5,5] process and that two consecutive [3,3] rearrangements account for a small fraction of the product.[47]

VII. Ring Contraction

Another general method for preparing rings of a difficultly accessible size is through a ring contraction. Marshall has exploited this approach to the synthesis of cembranoids with great ingenuity. His synthesis of epimukulol nicely illustrates this concept (Scheme 16).[48] Chloride **95** is easily available from *trans,trans*-farnesol. Homologation of the allylic chloride with a protected propargyl Grignard reagent and conversion of the allylic silyl ether to the chloride is followed by acetylide anion generation and trapping with formaldehyde to produce **96**. The treatment of a 0.02 M solution of **96** in THF/HMPA with ethylmagnesium bromide, first at 0 °C followed by warming to reflux over 4.5 h, leads to 17-membered-ring ether **97** in 71% yield. The deprotonation of **97** with *n*-butyllithium in THF/hexane at −78 °C for 1 h results in a stereoselective Wittig rearrangement.[49] Fourteen-membered-ring compound **98** is isolated in 85% yield. The ease of this reaction is probably a consequence of the enforced proximity of the two reacting centers due to the constraints imposed by the 17-membered ring. The introduction of the isopropenyl group at C-1 in **98** by the Wittig rearrangement is a consequence of careful planning. The final task remaining in order to complete this total synthesis is to introduce the C-4 methyl. Hydroalumination–iodination of **98** followed by (benzyloxy)methyl ether formation produces the *Z* C-3 iodide. Metal–halogen exchange with *tert*-butyllithium and quenching of the intermediate vinyllithium species with methyl fluorosulfate furnish **99**. The selective saturation of the isopropenyl double bond is accomplished by homogeneous hydrogenation with Wilkinson's catalyst. Reductive removal of the oxygen protecting group with sodium in THF/liquid ammonia produces epimukulol.

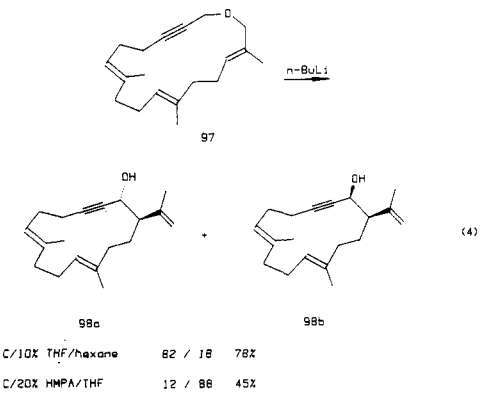
SCHEME 17[a]



[a] (a) *i*-PrMgBr, Cp_2TiCl_2; (b) CO_2; (c) CH_2N_2; (d) Dibal.

Propargyl alcohol **98** has also been used for a synthesis of *dl*-deoxyasperdiol (Scheme 17).[50] Titanocene-promoted hydromagnesiation of **98** and trapping of the intermediate vinyl magnesium species lead to carboxylic acid **100**. Reduction of the derived methyl ester produces *dl*-deoxyasperdiol in 84% yield. This is a formal total synthesis of *dl*-asperdiol as well.[35]

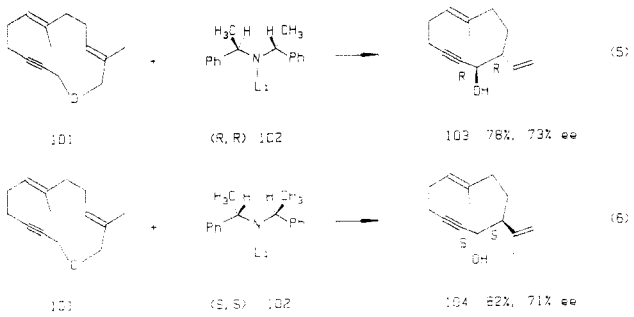
The full potential of the Wittig rearrangement–ring contraction strategy for cembranoid total synthesis has yet to be realized. The method is made even more powerful by the ability to control the stereochemical outcome of the cyclization by simple choice of the reaction medium (eq 4).[50] Whereas in THF/hexane the



(4)

ratio of α to β alcohols is 82/18, in HMPA/THF the

ratio of diastereomers is unexpectedly inverted. Another development that may increase the appeal of this approach is Marshall's recent demonstration that very significant asymmetric induction can be seen in the [2,3] Wittig rearrangement leading to a 10-membered ring (eq 5 and 6).[51] Treatment of the 13-membered-ring



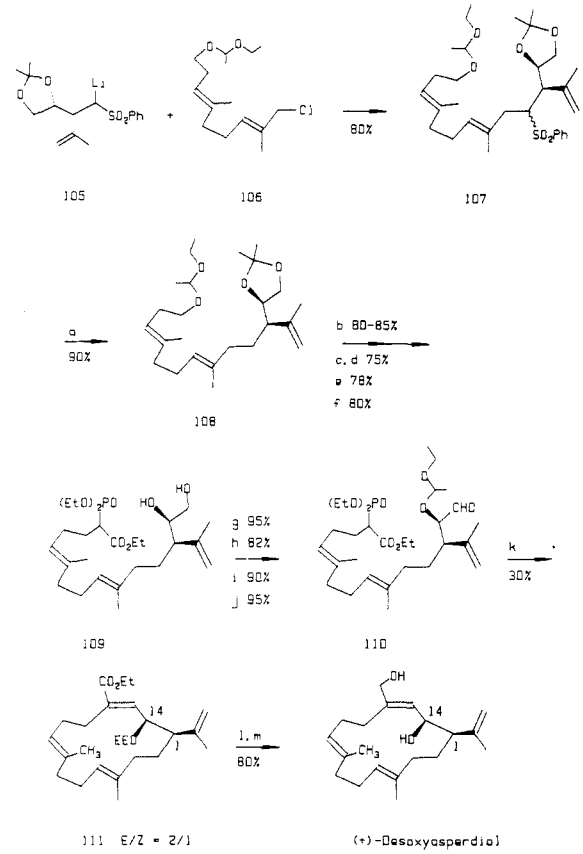
ether **101** with lithio (*R,R*)-bis(1-phenylethyl)amide (**102**) affords rearranged carbocycle **103** in 78% chemical yield and of 73% enantiomeric excess. Use of the (*S,S*)-lithio amide produces the enantiomer **104** in 82% chemical yield and of 71% enantiomeric excess. This is an important development, regardless of whether it will ultimately be applicable to cembranoid synthesis. The carbanion that is initially formed from the deprotonation of **101** apparently retains its configuration, either because of the restriction of conformational mobility due to the ring or because of early carbon–carbon bond formation along the reaction coordinate. If the very useful levels of asymmetric induction are a result of the rigidity of the 13-membered ring, somewhat poorer enantioselectivity may be anticipated for the cembranoid case. These questions will undoubtedly receive close scrutiny in the near future.

VIII. Intramolecular Horner–Emmons Reaction

For the construction of more densely functionalized cembranes, it is useful to have a method for ring closure that will tolerate oxygen functionality. It is also advantageous to use a cyclization strategy that is compatible with a convergent approach and that might be used to control the geometry of one of the trisubstituted bonds in the product. The effectiveness of the Horner–Emmons reaction in this regard has been demonstrated in several total syntheses.

A total synthesis of (+)-deoxyasperdiol (Scheme 18) has been described in which the C-2,C-3 double bond is formed by a Horner–Emmons reaction during the ring-closure step.[52] Allylic chloride **106**, which is derived from geraniol, is coupled with chiral, nonracemic sulfone anion **105**. Reductive removal of the sulfone functionality is accomplished with sodium amalgam. Removal of the ethoxyethyl protecting group from **108** and conversion to the primary iodide is followed by displacement with the sodium salt of triethyl phosphonoacetate and acetonide cleavage to produce **109**. The conversion of **109** to aldehyde **110** is accomplished in four steps. A number of methods for the Horner–Emmons reaction were examined; however, all had failed to produce useful quantities of **111**.[53] The conditions that were developed by Masamune and Roush and Rathke,[54] DBU and lithium chloride in acetonitrile, produce **111** as a 2/1 *E/Z* mixture in 30% yield. The two geometrical isomers are separated chromatographically, and

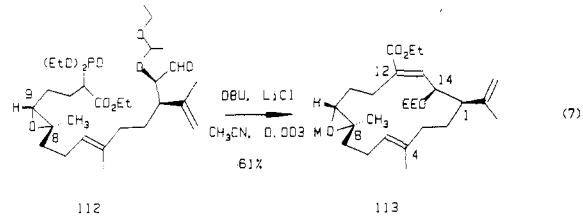
SCHEME 18[a]



[a] (a) Na/Hg, MeOH; (b) PPTS, *n*-PrOH; (c) MsCl, TEA, CH_2Cl_2; (d) NaI, acetone; (e) $(EtO)_2POCHNaCOOEt$, 18-crown-6, DMF; (f) Amberlyst IR-120, $HOCH_2CH_2OH$; (g) TBDMSiCl, DMF, imidazole; (h) ethyl vinyl ether, PPTS; (i) *n*-Bu_4NF, THF; (j) $(ClCO)_2$, DMSO, TEA; (k) see text; (l) LAH; (m) PPTS, MeOH.

the *E* isomer is converted to (+)-deoxyasperdiol.

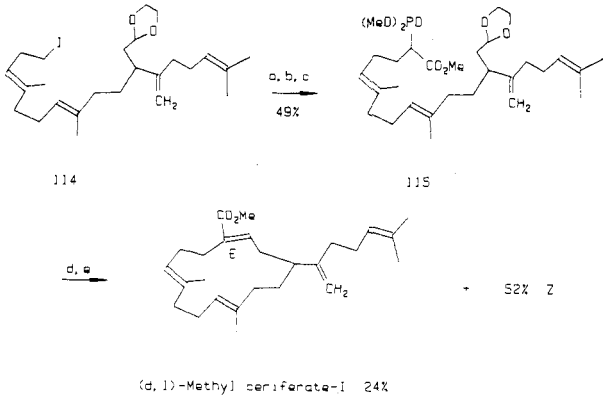
Although this synthesis is successful in arriving at the optically active target compound, the yield for the cyclization step and the stereoselectivity are clearly disappointing. Nevertheless, two structural features distinguish **110** from all other substrates that had been reported for this reaction: branching on the carbon atom adjacent to the aldehyde and a tertiary carbon nucleophile. That the poor yield for the conversion of **110** to **111** cannot be attributed to these two factors alone is demonstrated by the reaction of eq 7.[38] Al-



dehyde phosphonate **112** is the C-6,C-7 epoxide corresponding to **110**. Treatment of **112** under the Masamune–Roush[54] conditions leads to Horner–Emmons product **113** in 61% yield as a single geometrical isomer. Ester **113** is subsequently converted to (−)-asperdiol. The divergence in reactivity between **110** and **112** is puzzling and is not easily rationalized by molecular mechanics calculations.

Related examples of 14-membered-ring synthesis can be found in the recent literature. Methyl ceriferate-I,

SCHEME 19[a]

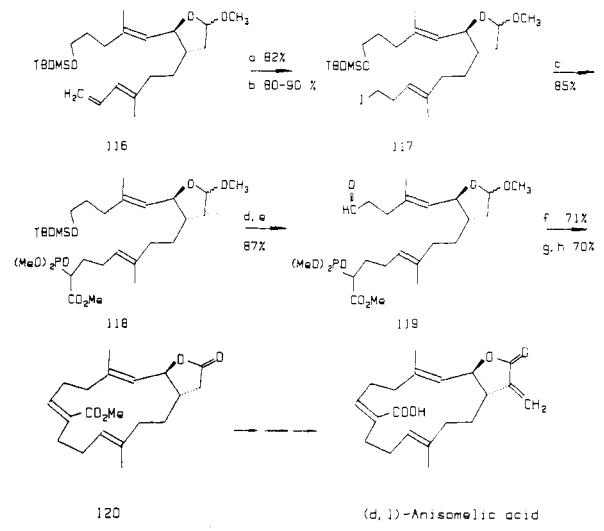


[a] (a) $(MeO)_2POCH_2Li$, −78 °C; (b) *n*-BuLi; (c) MeOCOCl, −78 °C; (d) TsOH; (e) NaH, DME.

a sesterterpene that has been isolated from scale insect wax, has been prepared by a route in which the macrocycle is formed by an intramolecular Horner–Emmons reaction (Scheme 19).[55] Iodide **114** is treated with the lithium salt of dimethyl methylphosphonate. Subsequent exposure to *n*-butyllithium followed by methyl chloroformate produces phosphonic ester **115** in 49% yield. This same transformation can be accomplished more efficiently in a single step by displacing the iodide with sodium methyl(dimethylphosphono)acetate or sodium ethyl(diethylphosphono)acetate.[52,56] Ethylene acetal hydrolysis with tosic acid is followed by sodium hydride in 1,2-dimethoxyethane in a subsequent step to produce methyl ceriferate in 24% yield along with 52% of the *Z* isomer. It is interesting that the ratio of geometric isomers for this Horner–Emmons reaction shows the same preference as the reaction of **110**.

Marshall's synthesis of *dl*-anisomelic acid, a cembrane lactone isolated from the Indian medicinal plant *Anisomeles malabarica*, makes use of a *Z*-selective Horner–Emmons condensation in the key cyclization step (Scheme 20).[56] The selective hydroboration of the terminal alkene linkage in **116** with disiamylborane, followed by basic peroxide, provides an alcohol that is converted to the corresponding iodide with iodine and triphenylphosphine in the presence of imidazole. Displacement of the iodide with the sodium salt of methyl (dimethylphosphono)acetate produces **118** in 85% yield. Cleavage of the silyl ether of **118** is accomplished with methanolic pyridinium tosylate at reflux. Swern oxidation furnishes aldehyde **119**. Initially, the intramolecular Horner–Emmons reaction was accomplished with sodium hydride in DME in the presence of 18-crown-6 ether. As in the cases discussed earlier in this section, the success of this reaction is found to be highly dependent upon the conditions. A yield of 71% (Z/E = 95/5) is achieved through the use of the Masamune–Roush[54] conditions. Cyclic acetal hydrolysis with aqueous pyridinium tosylate (PPTS) followed by oxidation with PCC furnishes lactone ester **120** in 70% yield. This compound is converted to *dl*-anisomelic acid. It is interesting that **120** is obtained as the *Z* geometrical isomer. The reason for the selectivity, which is opposite of what has been observed for **115**, **112**, and **110**, has not been discussed. It is worth noting that solvent effects have been found to have a strong influence on the E/Z ratios of products from the reaction of stabilized Wittig reagents with aldehydes.[57]

SCHEME 20[a]

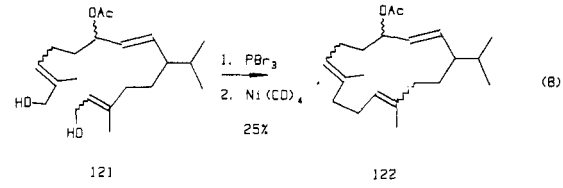


[a] (a) $(Siam)_2BH$; H_2O_2, NaOH; (b) PPh_3, I_2, imidazole, −10 °C; (c) $(MeO)_2POCHNaCOOMe$, DMSO; (d) PPTS, MeOH; (e) $(ClCO)_2$, DMSO, TEA; (f) DBU, LiCl, CH_3CN; (g) PPTS, H_2O; (h) PCC, NaOAc, Celite, CH_2Cl_2.

IX. Miscellaneous Approaches

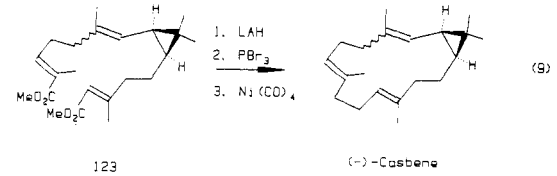
Many approaches to cembrane synthesis that do not fit into the classification scheme that has been used to organize this Review have been examined during recent years. These methods will now be reviewed.

Nickel tetracarbonyl mediated intramolecular coupling of a bis-allylic bromide has been used by Dauben in his synthesis of cembrene (eq 8). A mixture of



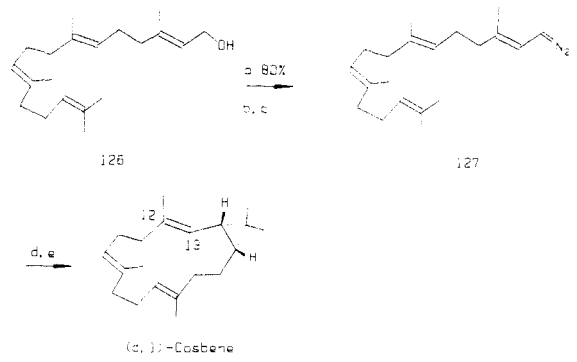
geometric isomers of **121** is converted to the bis-allylic dibromide, which is treated with nickel tetracarbonyl in *N*-methylpyrrolidone. The yield for the isomeric mixture of products that is obtained from this two-reaction sequence is 25%. Acetate mixture **122** is converted to cembrene; however, vapor phase chromatography is needed to isolate the natural product from the mixture.

A synthesis of (−)-casbene has also made use of the nickel tetracarbonyl cyclization reaction.[59] *cis*-Chrysanthemic acid methyl ester is converted to diester **123** (eq 9). Reduction with LAH followed by phosphorus



tribromide furnishes the substrate for the nickel tetracarbonyl reaction. The yield for the cyclization reaction is disappointing once again. The nonstereoselective nature of the reaction, the modest yields, and the hazards of handling nickel tetracarbonyl detract

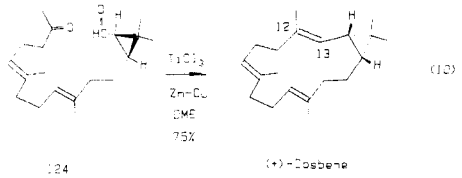
SCHEME 21[a]



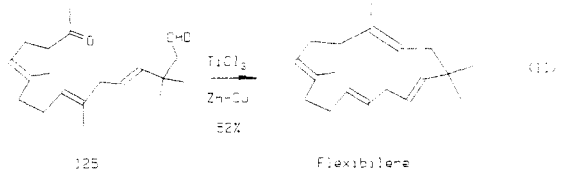
[a] (a) MnO_2, hexane, 0 °C; (b) H_2NNH_2, TEA, EtOH; (c) MnO_2, CH_2Cl_2, 0 °C; (d) CuI, THF; (e) $AgNO_3/SiO_2$ chromatography.

from the utility of this method.

A synthesis of (+)-casbene is due to McMurry.[60] (+)-2-Carene is the starting material for keto aldehyde **124** (eq 10). The slow addition of **124** to a refluxing



mixture of zinc–copper couple and titanous chloride produces (+)-casbene and the C-12 *Z* isomer in a 2/1 ratio in 75% yield. The high yield for the coupling reaction of **124**, and for many other systems,[61] highly recommends this method for macrocycle synthesis. McMurry has used a conceptually related approach for the synthesis of flexibilene,[61] a 15-membered-ring natural product (eq 11). Keto aldehyde **125** is cyclized

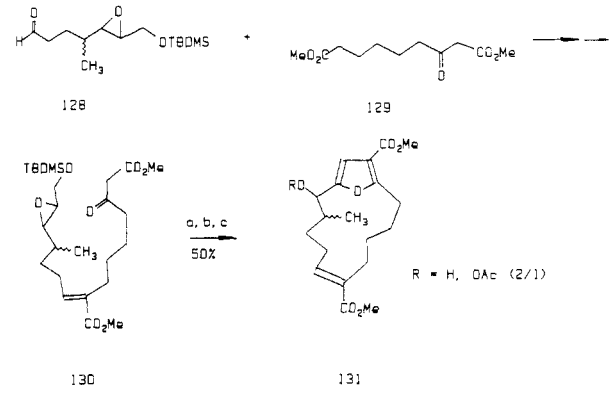


reductively to produce flexibilene in 52% yield. The spectrum of reactivity of the low-valent titanium reagent suggests that highly oxygenated precursors may be unsuitable for the cyclization reaction. Notwithstanding, this is an excellent method for the preparation of nonoxygenated cembrenes.

A short, biomimetic route to *dl*-casbene has been disclosed (Scheme 21).[62] *all-trans*-Geranylgeraniol (**126**) is oxidized with active manganese dioxide to the corresponding enal. Treatment with excess anhydrous hydrazine in ethanol at room temperature produces a hydrazone, which is oxidized with manganese dioxide in dichloromethane. Diazo compound **127** is added slowly in THF to a suspension of cuprous iodide. The resulting mixture is separated on silver nitrate impregnated silica gel to produce *dl*-casbene in 14% overall yield. The elegance of this opportunistic approach is not diminished by the modest yield for the last step. The selectivity for the cyclization reaction is interpreted as being the result of carbenoid addition to a folded conformation of the precursor.

Although it is useful to have general methods for cembrane synthesis, it is often the case that the most

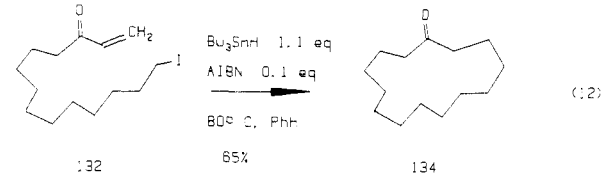
SCHEME 22[a]



[a] (a) F^-; (b) PCC; (c) HOAc, *cat. piperidine*.

efficient and interesting methods will be opportunistic, in the sense that they exploit a unique structural feature of one specific target molecule. Such an approach to the related furanocembranoids pukalide and lophotoxin has been described in a model study (Scheme 22).[63] An aldol reaction between aldehyde **128** and keto diester **129** produces **130**. Removal of the silyl ether protecting group from **130** followed by oxidation with PCC furnishes an epoxy aldehyde. Treatment of a dilute solution of the epoxy aldehyde with catalytic piperidine in acetic acid leads to furan ester **131**. An aldol reaction between the protected keto ester and the activated aldehyde presumably initiates the cyclization to the furan.

The resurgence in interest in radical chemistry that has been witnessed in recent years suggests some interesting possibilities for yet another ring-closure strategy. Iodo enone **132** is cyclized in 65% yield to cyclotetradecanone by treatment in refluxing benzene with tributyltin hydride and catalytic AIBN (eq 12).[64]

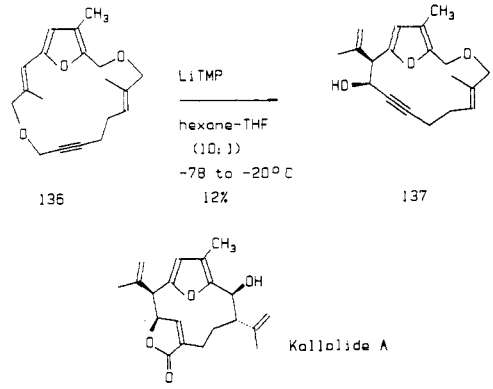


The success of this reaction depends upon the presence of an active, electrophilic radical acceptor with a minimum of steric encumbrance at the reation site. This should not pose an impediment for cembrane synthesis, and one can anticipate that applications of this radical ring closure will be forthcoming, particularly since this method should be largely tolerant of other functional groups.

X. Conclusion

This Review has attempted to summarize progress in the development of strategies for the total synthesis of 14-membered-ring-containing natural products. The attraction of this area of organic synthesis stems from the structural diversity and complexity of the cembranoids as well as their often marked biological activity. The shortcomings of available synthetic methods for the stereoselective assembly of such complex macrocyclic compounds are being addressed. Several strategies that promise to be quite general have been developed. The

SCHEME 23



widespread availability of user-friendly molecular mechanics software is making it possible to rationalize the high levels of stereochemical induction that often characterize these systems. Calculations of molecular structure are also being performed with increasing frequency during the planning stages of a total synthesis. It is likely that the synthesis of cembranoids will continue to be used to demonstrate the utility of new synthetic methods. One can also anticipate the development of opportunistic or goal-oriented total syntheses because of the useful spectrum of pharmacological activity that has been noted for many of the natural products and the difficulties in obtaining sufficient quantities for testing from natural sources. Organic chemists will hone their skills with this family of molecules for some years to come.

XI. Addendum

Marshall has recently disclosed an approach to kallolide A (**135**)[65] that makes use of a [2,3] Wittig ring contraction.[66] Macrocyclic diether **136** is treated with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in hexane–THF (10:1) at −78 to −20 °C to give a single product **137** in 12% (unoptimized) yield (Scheme 23).

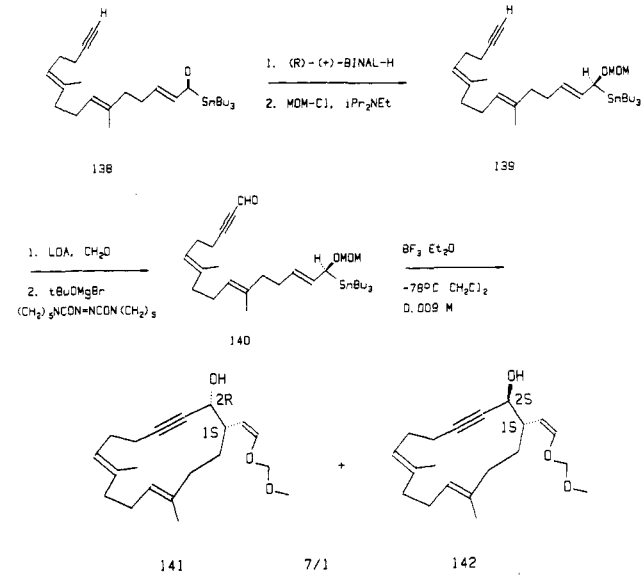
The identity of syn compound **137** is proven by spectroscopic comparison with kallolide A and is surprising given that (*E*)-crotyl propargylic ethers usually provide anti products. This appears to be another example in which the stereochemistry that is enforced by the macrocycle causes the reaction to follow a course that is different from the acyclic case.

In unrelated work, Marshall[67] has shown that the boron trifluoride etherate catalyzed cyclization of chiral α-alkoxystannane **140** produces 1*S*,2*R* alcohol **141** enantiospecifically (Scheme 24). Anti alcohol **142** is formed as the minor product. The preparation of **140** involves interesting new methodology that promises to be generally applicable. The reduction of acylsilane **138** with Noyori's (*R*)-(+)-BINAL-H reagent[68] takes place with complete enantioface control. Protection of the hydroxyl group as the methoxymethyl ether produces **139**. Treatment of the lithium acetylide anion from **139** with formaldehyde furnishes a propargylic alcohol that is oxidized to **140** with Mukaiyama's reagent[43] as in the racemic series (Scheme 14).

XII. Acknowledgments

I thank the NIH (Grants CA 45288 and GM 38598) for their continuing support of my research program.

SCHEME 24



Financial support from the Alfred P. Sloan Foundation is also gratefully acknowledged. I thank Professor James A. Marshall for providing me with preprints of his manuscripts and for many helpful suggestions.

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