Cembranolide Total Synthesis. Macrocyclization of (α-Alkoxyallyl)stannane–Acetylenic Aldehydes as a Route to Cembrane Lactones

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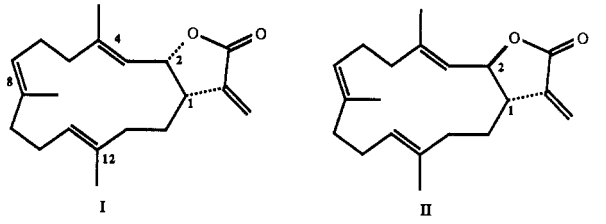
The synthesis of an unnamed cembranolide constituent of Pacific soft coral (I) was effected starting from the tetrahydropyranyl ether of geraniol (1). Selective allylic oxidation, conversion to the allylic bromide **3**, coupling with (cyanomethyl)copper(I), reduction of the nitrile **4**, and Wittig homologation led to the conjugated ester **6**. Further elaboration to allylic chloride **9** and coupling with triisopropylsilyl-protected propargylmagnesium bromide, deprotection, Swern oxidation of the allylic alcohol **11**, addition of (tri-*n*-butylstannyl)lithium to the derived aldehyde **12**, and in situ addition of MOMCl yielded the alkoxy stannane **13**. Lithiation (LDA) of the acetylene, addition of formaldehyde, and subsequent Swern oxidation afforded the cyclization substrate **15**. Cyclization of **15** with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −78 °C gave the cis and trans cembranoid alcohols **16** and **17** (88:12) in 88% yield. Conversion to the cembrane lactone I was best achieved via the related ketone **24** by addition of $LiMe_2Cu$, equilibration (LiS-*i*-Pr) of the resulting enone mixture, and hydrolysis of the exclusively formed *E* isomer **26** to the keto aldehyde **33** followed by oxidation to the acid **34** and esterification. The keto ester **35** was reduced directly to lactone **31** by $NaBH_4$. α-Methylenation of this lactone was achieved through addition of formaldehyde to the lactone lithio enolate and dehydration.

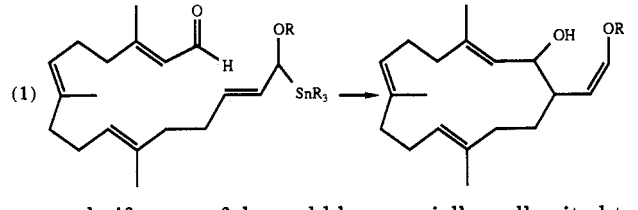
The cembranolide I, first elaborated by Coll and co-workers, is a constituent of the soft coral *Lobophytum michaelae* Texier–Durivault, a common inhabitant of the Great Barrier Reef.[1] Uchio et al. subsequently isolated I and its stereoisomer II from the soft coral *Sinularia mayi*



I II

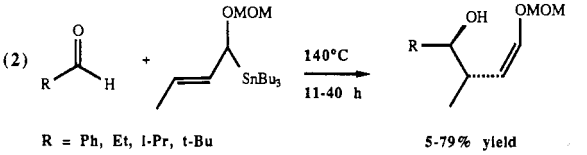
Lüttschw.[2] Although the absolute stereochemistry of these lactones was not determined, Pacific cembrenes generally possess an α-oriented substituent at C-1 and the structures are written accordingly.[3]

The foregoing pair of unnamed lactones represents an attractive set of target structures for the development of cembranolide synthesis methodology.[4] In that regard, we were interested in exploring the feasibility of an intramolecular (α-alkoxyallyl)stannane–aldehyde condensation as a method for cembranoid ring closure (eq 1). This



(1)

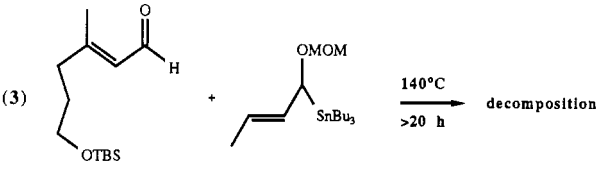
approach, if successful, would be especially well suited to cembranolides such as I and II because the acetic acid side chain at C-1 is produced in a partially oxidized state. (α-Alkoxyallyl)stannanes had not previously been examined as coupling partners in Lewis acid catalyzed additions, and no macrocyclizations involving allylstannanes of any sort had been recorded prior to our work. However, Thomas and co-workers had previously found that ((*E*)-α-alkoxycrotyl)stannanes add intermolecularly to aldehydes upon prolonged heating to afford the anti products (eq 2).[5,6] An associated six-membered chairlike transition



(2)

R = Ph, Et, i-Pr, t-Bu 5-79% yield

state was suggested to account for the high anti stereoselectivity of the process. We attempted an analogous addition to a prototype conjugated aldehyde but obtained none of the expected addition product (eq 3).[6] Prolonged



(3)

heating of the mixture led only to decomposition of the reactants. In some earlier work we found acetylenic aldehydes to be significantly more reactive than β,β-disubstituted α,β-unsaturated aldehydes in Lewis acid catalyzed additions of allylstannanes.[7] Heating such an acetylenic aldehyde with the foregoing (α-alkoxycrotyl)stannane caused complete reaction to occur within 5 min at 140 °C, affording a nearly 1:1 mixture of syn and anti products (eq 4).[6] The above addition reaction could also be effected by $BF_3{\cdot}Et_2O$ catalysis[8] at −78 °C to give four isomeric

(1) Coll, J. C.; Mitchell, S. J.; Stokie, G. J. *Aust. J. Chem.* **1977**, *30*, 1859.

(2) Uchio, Y.; Eguchi, S.; Nakayama, M.; Hase, T. *Chem. Lett.* **1982**, 277.

(3) Weinheimer, A. J.; Matson, J. A.; Hossain, M. B.; van der Helm, D. *Tetrahedron Lett.* **1977**, 2923.

(4) For a summary of synthetic approaches to this class of natural products, see: Marshall, J. A.; Jenson, T. M.; DeHoff, B. S. *J. Org. Chem.* **1986**, *51*, 4316. Marshall, J. A.; Andrews, R. C.; Lebioda, L. *J. Org. Chem.* **1987**, *52*, 2378. Wender, P. A.; Holt, D. A. *J. Am. Chem. Soc.* **1985**, *107*, 7771.

(5) Pratt, A. J.; Thomas, E. J. *J. Chem. Soc. D* **1982**, 1115. Jephcote, V. J.; Pratt, A. J.; Thomas, E. J. *J. Chem. Soc. D* **1984**, 800.

(6) Abbreviations: DIBAH = diisobutylaluminum hydride, DMF = *N*,*N*-dimethylformamide, LDA = lithium diisopropylamide, 2,6-lutidine = 2,6-dimethylpyridine, MCDI = 1-cyclohexyl-3-(2-morpholinoethyl)-carbodiimide metho-*p*-toluenesulfonate, MOM = methoxymethyl, NIS = *N*-iodosuccinimide, PCC = pyridinium chlorochromate, PDC = pyridinium dichromate, PPTS = pyridinium *p*-toluenesulfonate, Red-Al = bis(2-methoxyethoxy)aluminum hydride, TBAF = tetra-(*n*-butyl)ammonium fluoride, TBS = *tert*-butyldimethylsilyl, THP = 2-tetrahydropyranyl, THF = tetrahydrofuran, TLC = thin layer chromatography.

(7) Marshall, J. A.; DeHoff, B. S. *J. Org. Chem.* **1986**, *51*, 858.

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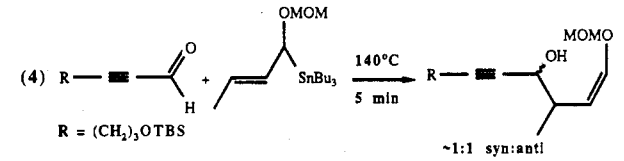
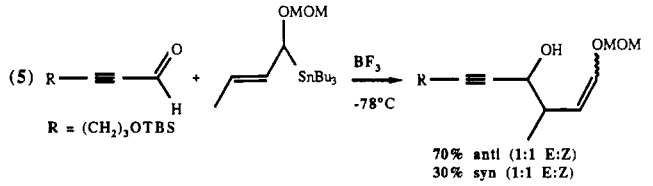
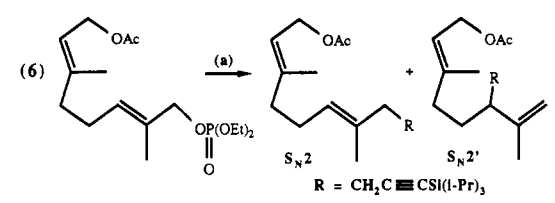


adducts, *E*-syn, *Z*-syn, *E*-anti, and *Z*-anti in the approximate ratio 35:35:15:15 according to capillary GC and high-field ^{1}H NMR analysis (eq 5). In contrast allylic stannanes without an α-alkoxy substituent have been found to give mainly syn adducts (~9:1) with acetylenic aldehydes.[7]



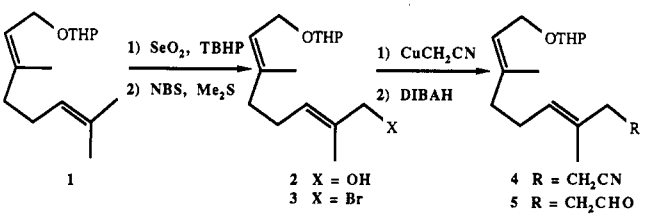
The high reactivity shown by the acetylenic aldehyde carbonyl toward (α-alkoxyallyl)stannanes in both thermal and Lewis acid reactions indicated that our intended intramolecular application might best be attempted on an acetylenic aldehyde such as **15**. We were not concerned about the low stereoselectivity of the intermolecular additions as we have found that conformational factors can play an overriding role in cyclization reactions leading to cembranoids.[9]

Our first route to the cyclization precursor **15** employed the phosphate of oxidized geranyl acetate[10] as a coupling partner for [3-[(triisopropyl)silyl]propynyl]magnesium bromide (eq 6).[6] Although initial trials were promising,

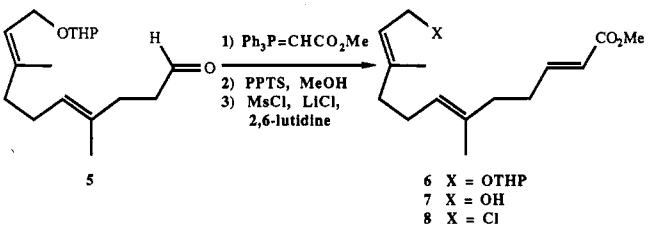


(a) TIPSC≡ CCH_2MgBr, CuI, DMS, THF, -78 to -20°C

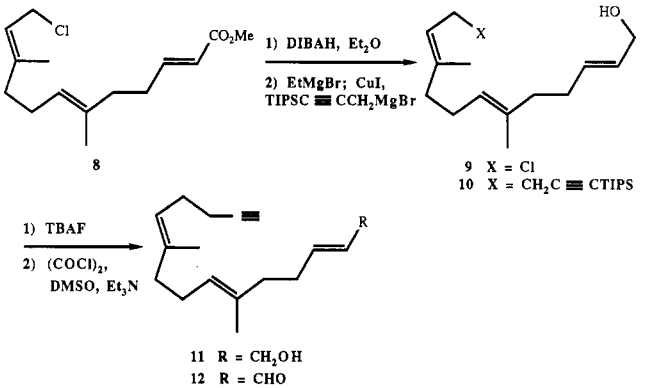
showing only traces of S_N2' and allenic byproducts, later attempts gave as much as 15% of the unwanted S_N2' product.[11] Accordingly, an alternative route was developed that employed the bromide **3**,[12] readily available from the tetrahydropyranyl ether of geraniol (**1**).[10] This bromide underwent smooth S_N2 coupling with Corey's (cyanomethyl)copper reagent[13] to afford the nitrile **4** in 84% yield, free of S_N2' byproduct. Reduction with DIBAH[6] in ether followed by hydrolysis afforded aldehyde **5** in 82% yield.



Addition of methyl (triphenylphosphorylidene)acetate to aldehyde **5** led to the *E*-conjugated ester **6** in 87% yield. Cleavage of the THP[6] ether with methanolic PPTS[6] yielded the allylic alcohol **7** which was converted to the chloride **8** by the Collington–Meyers procedure in 92% yield.[14]



Chloro ester **8** upon reduction with DIBAH[6] in ether at −78 °C afforded the alcohol **9**. This chloro alcohol was treated with 1 equiv of ethylmagnesium bromide at 0 °C to form the magnesium salt prior to coupling at −78 to −17 °C with [3-[(triisopropyl)silyl]propynyl]magnesium bromide–CuI.[15] The resulting alkyne **10** (76% yield) was free of S_N2' and allenic byproducts. The TIPS[6] directing–protecting group[15] was cleaved by TBAF[6] in THF and the derived acetylenic alcohol **11** was subjected to Swern oxidation,[16] giving aldehyde **12** in 87% yield.



Addition of (tri-*n*-butylstannyl)lithium to aldehyde **12** followed by protection with MOMCl[6] afforded the α-alkoxy stannane **13** in 78% yield.[17] Deprotonation of the acetylene with LDA[6] and then addition of formaldehyde gave the propargylic alcohol **14** in 76% yield. This alcohol could be oxidized to aldehyde **15** by the Swern protocol,[16] but the method of Mukaiyama[18] employing bromomagnesium *tert*-butoxide and 1,1′-(azodicarbonyl)dipiperidine gave the best results (81% yield).

We were now in a position to examine the critical unprecedented cyclization step. Thermolysis of aldehyde **15**,

(8) For leading references to Lewis acid catalyzed additions of allylstannanes to aldehydes, see: Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *Tetrahedron* **1984**, *40*, 2239. Yamamoto, Y. *Aldrichimica Acta* **1987**, *20*, 45. For a recent mechanistic study, see: Denmark, S. E.; Henke, B. R.; Weber, E. *J. Am. Chem. Soc.* **1987**, *109*, 2512. Lewis acid catalyzed additions of (α-alkoxyallyl)stannanes to aldehydes have not previously been examined. Recently additions of (γ-alkoxyallyl)stannanes to aldehydes have been studied. Keck, G. E.; Abbott, D. E.; Wiley, M. R. *Tetrahedron Lett.* **1987**, *28*, 139. Koreeda, M.; Tanaka, Y. *Tetrahedron Lett.* **1987**, *28*, 143.

(9) (a) Marshall, J. A.; DeHoff, B. S. *Tetrahedron Lett.* **1986**, *27*, 4873. (b) Marshall, J. A.; Jenson, T. M.; DeHoff, B. S. *J. Org. Chem.* **1987**, *52*, 3860.

(10) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 1742. Geranyl acetate was oxidized according to Umbriet, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526. See also: Marshall, J. A.; Andrews, R. C. *J. Org. Chem.* **1985**, *50*, 1602.

(11) For a preliminary account, see: Marshall, J. A.; DeHoff, B. S.; Crooks, S. L. *Tetrahedron Lett.* **1987**, *28*, 527.

(12) Knight, D. W.; Rustidge, D. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 679.

(13) Corey, E. J.; Kuwajima, I. *Tetrahedron Lett.* **1972**, 487.

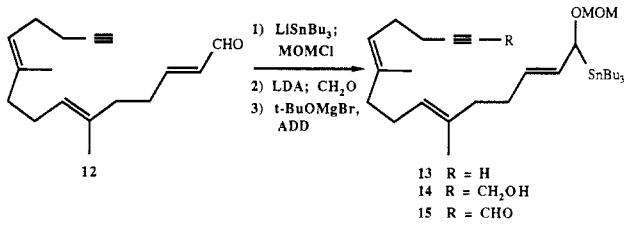
(14) Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044.

(15) Corey, E. J.; Rücker, C. *Tetrahedron Lett.* **1982**, *23*, 719.

(16) Omurka, K.; Swern, D. *Tetrahedron* **1978**, 1651.

(17) Cf. Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

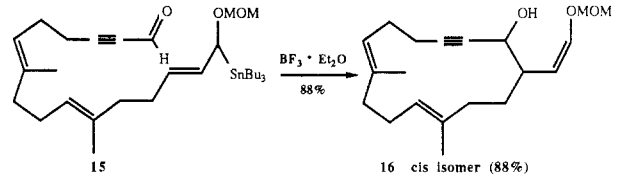
(18) Narasaka, K.; Morikawa, A.; Saigo, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2773. For a related application, see: Denmark, S. E.; Weber, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 7970.



12

13 R = H
14 R = CH_2OH
15 R = CHO

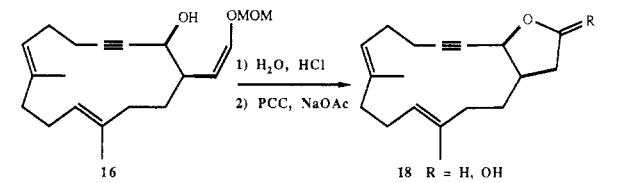
under conditions previously employed for the intermolecular coupling[5] (eq 4), led to decomposition of the starting material and afforded no identifiable product. Treatment with BF_3·Et_2O at −78 °C in CH_2Cl_2 at high dilution (0.009 M), on the other hand, afforded an 88:12 mixture of the separable cis and trans products **16** and **17** in 88% yield. The efficiency of this process is noteworthy and suggestive of additional applications with both (α-alkoxyallyl)stannanes and allylstannanes. The cis stereochemistry was



15

16 cis isomer (88%)
17 trans isomer (12%)

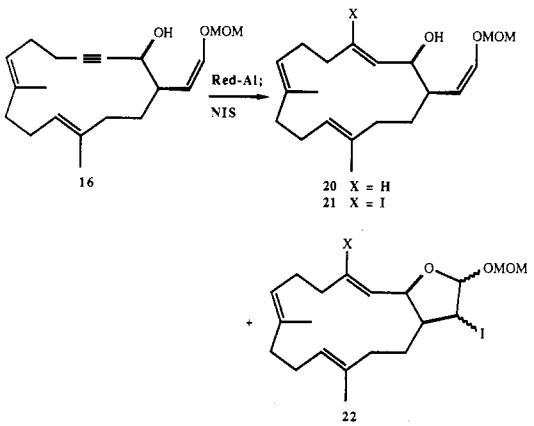
assigned to the major product after its conversion to the lactone **19** by hydrolysis of the enol ether and PCC[6] oxidation[19] of the resulting lactol **18**. The carbinyl proton of lactone **19** appeared as a doublet (J = 7.0 Hz) at 5.19 ppm in the ^1H NMR spectrum close to values reported for cis-fused cembranolides of an analogous structure.[20,21] A doublet (J = 2 Hz) of low intensity at 4.70 ppm in the above spectrum could be ascribed to the minor trans-fused isomer of lactone **19**.[20]



16

18 R = H, OH
19 R = O

The conversion of propargylic alcohol **16** to the cembranoid skeleton **23** was next examined. The methodology developed by Corey[22] and employed by us quite successfully in earlier studies[7] seemed ideally suited to this task. Accordingly, alcohol **16** was treated with Red-Al[6,23] followed by I_2 or NIS[6] as previously described.[7,9,24] The vinyl iodide **21** was obtained in only 15% yield along with a byproduct, presumably **22**, arising from iodoetherification of the enol ether double bond. The reduction itself, although slow in comparison to acyclic systems,[7] proceeded efficiently as evidenced by the formation of allylic alcohol **20** in high yield upon aqueous quench of the reaction.

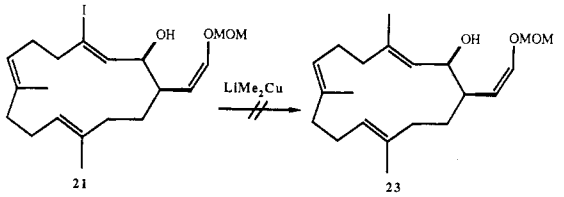


16

20 X = H
21 X = I

22

The vinyl iodide **21** was separated from the various byproducts and treated with lithium dimethylcuprate to effect coupling.[7,22] However, despite numerous trials with a large excess (tenfold) of cuprate, only starting material was recovered from these attempts. None of the desired methylated product **23** was formed. The reasons for the unreactivity of iodide **21** are unclear at this time, although steric factors are a prime suspect.



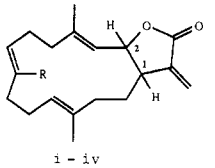
21

23

In a previous related example of an analogous cembranoid vinylic iodide that was unreactive toward $LiMe_2Cu$, we were able to achieve methylation by first protecting the alcohol and then metalating with *tert*-butyllithium and trapping the resulting vinyllithium with methyl fluorosulfonate.[9b] In the case at hand, we decided to explore an alternative option. Our plan was based on molecular mechanics calculations which showed the *E*-enone **26** to be of lower energy than the *Z* isomer **25**.[25] Accordingly, we hoped to add a methylcuprate reagent to ynone **24** under thermodynamically controlled conditions.[26] Ynone **24** was readily prepared by Swern oxidation[16] of alcohol **16**. Addition of lithium dimethylcuprate in THF–ether at 0 °C led to a 1:1 mixture of enones **25** and **26**. This reaction was not examined in detail as equilibration of these isomers could be easily effected with lithium isopropylthiolate in THF whereupon the *E* isomer **26** was formed quantitatively.

Reduction of ketone **26** with $NaBH_4$ or DIBAH[6] afforded a nearly 1:1 mixture of cis and trans alcohols. With L-Selectride,[6] however, only a single product was formed. This was shown to be the trans isomer **27** by conversion

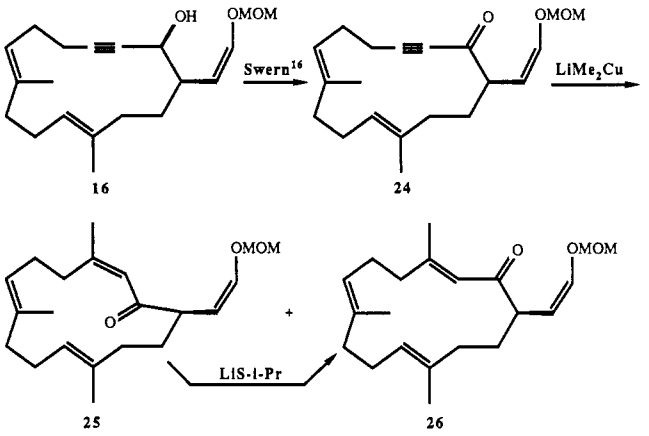
(19) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(20) The following are representative values



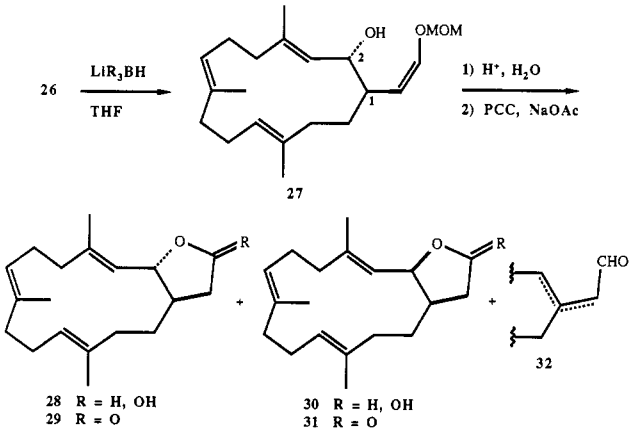
i - iv

	δ H2 (ppm)	$J_{2,1}$ (Hz)
i. R = Me, cis-fused lactone[1]	5.39	7.5
ii. R = CO_2H, cis-fused lactone[21]	5.44	7.5
iii. R = Me, trans-fused lactone[2]	4.86	3.5
iv. R = CO_2H, trans-fused lactone[9]	4.86	4.1

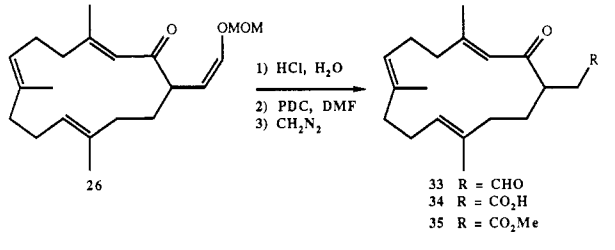
(21) Uchio, Y.; Toyota, J.; Nozaki, H.; Nakayama, M.; Nishizono, Y.; Hase, T. *Tetrahedron Lett.* **1981**, *22*, 4089.
(22) Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245. Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1968**, *90*, 5610.
(23) Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595.
(24) Marshall, J. A.; Lebreton, J.; DeHoff, B. S.; Jenson, T. M. *J. Org. Chem.* **1987**, *52*, 3883.
(25) The program MacroModel was employed for these calculations. Global minima were searched via the Multiconformer Submode. We are indebted to Professor W. C. Still and Dr. Wayne Guida for a prototype version and helpful advice on its use.
(26) Cf. Marino, P. J.; Linderman, R. J. *J. Org. Chem.* **1983**, *48*, 4621.



to the corresponding lactone **29** possessing a carbinyl signal at 4.80 ppm ($J_{2,1}$ = 6.6 Hz) in the ^{1}H NMR spectrum.[20] This spectrum also showed a signal at 5.32 ppm ($J_{2,1}$ = 6.2 Hz) attributable to the cis lactone **31**, even though the starting alcohol was homogeneous by TLC and ^{1}H NMR criteria. The amount of cis lactone **31** from a single source of alcohol **27** varied, depending upon the hydrolysis conditions, suggestive of acid-catalyzed (carbonyl-assisted) inversion. The hydrolysis also produced varying amounts of less polar products, possibly resulting from dehydration (**32**).

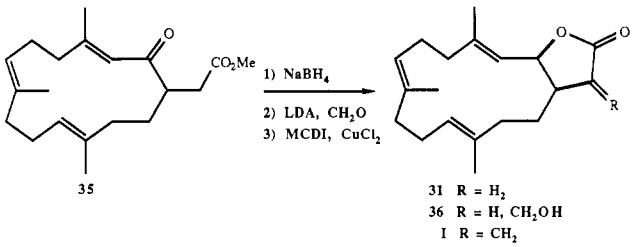


In view of these developments, we examined an alternative sequence in which enol ether hydrolysis preceded carbonyl reduction. Thus treatment of the keto enol ether **26** with aqueous HCl–THF readily afforded the keto aldehyde **33**. Oxidation with PDC[6,27] yielded the keto acid **34**, which was esterified with diazomethane.



Reduction of keto ester **35** with $NaBH_4$ in ethanol led to the cis lactone **31**, previously obtained as a minor product from enol ether **27**, and the trans lactone **29** as a 9:1 mixture. This result contrasts with the analogous reduction of the keto enol ether **26** which produced a 1:1 mixture of epimeric alcohols. Possibly the larger α-substituent of ketone **35** imposes greater steric shielding on the carbonyl center or provokes a conformational change causing the favored attack of hydride to afford the cis lactone **31** predominantly. Solvent effects (H-bonding) and metal cation (chelation) may also be important as $LiBH_4$, $LiAlH_4$, and $Li(O\text{-}t\text{-}Bu)_3AlH$ in THF all afforded predominantly trans-fused lactone and lactol products from keto ester **35**, reminiscent of the L-Selectride reduction of **26**.[28]

To complete the synthesis of the cembranolide I, we had only to introduce the α-methylene moiety for which numerous methods are available. We selected one that was recently developed in connection with our synthesis of isolobophytolide,[4] although other methods would have no doubt sufficed.[29] Accordingly, hydroxymethylation of lactone **31** with LDA[6] and formaldehyde followed by dehydration of the intermediate β-hydroxy lactone **31** with MCDI[6,29] gave the α-methylene lactone I, identical with an authentic specimen according to ^{1}H and ^{13}C NMR comparison.[1]



In summary, we have completed the first total synthesis of the cembranolide I by a route that could be used, with appropriate modification, for other related members of this family.[30] The key cyclization step proceeds in high yield with good stereoselectivity. Other applications of this cyclization can be forseen, although the process fails with alkyl β,β-disubstituted conjugated aldehydes.[7] The use of a methylcuprate 1,4-addition to introduce a vinyl methyl substituent to the cembrane nucleus also has the potential for other applications. Presumably, conditions (kinetic control) could be found to favor the cis double bond when desired. The present example suggests that trans double bonds will depend upon thermodynamics for their formation. Unfortunately, the methylation sequence does not efficiently utilize the favorable diastereoselectivity of the cyclization reaction. Furthermore, the cyclization affords racemic materials. Solutions to both of these problems are currently under development.

Experimental Section

The apparatus and methods described by Kramer, Midland, and Levy[31] were used to maintain an argon or nitrogen atmosphere in the reaction flask. Anhydrous solvents were obtained by distillation from sodium benzophenone ketyl (diethyl ether, tetrahydrofuran), calcium hydride (dichloromethane), or sodium (benzene). Infrared absorption maxima are reported in wavenumbers (cm^{-1}). Proton magnetic resonance samples were prepared as dilute solutions in deuteriochloroform ($CDCl_3$). Chemical shifts (δ) are reported downfield from tetramethylsilane (Me_4Si), in parts per million (ppm) of the applied field. Peak multiplicities are abbreviated as follows: singlet, s; doublet, d; triplet, t; quartet, q; pentuplet, p; envelope, e; multiplet, m. Coupling constants

(27) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(28) These experiments were conducted by Dr. Wei Yi Gung to whom we are grateful.

(29) Andrews, R. C.; Marshall, J. A.; DeHoff, B. S. *Synth. Commun.* **1986**, *16*, 1593.

(30) Cf. Bowden, B. F.; Coll, J. C.; Englehardt, L. M.; Meehan, G. V.; Pegg, G. G.; Tapiolas, D. M.; White, A. H.; Willis, R. H. *Aust. J. Chem.* **1986**, *39*, 123.

(31) Brown, H. C. *Organic Syntheses via Boranes*; Wiley: New York, 1975; pp 191–202.

(*J*) are reported in hertz (Hz). Glass capillary gas chromatography was performed on a Superox 425 M column. Combustion microanalyses were performed by Atlantic Laboratories, Atlanta, GA. Analytical thin-layer chromatography (TLC) was routinely used to monitor reactions. Plates precoated with E. Merck silica gel 60 F254 of 0.25 mm thickness, supplied by Brinkmann Instruments, were used. E. Merck silica gel 60 (230–400 ASTM mesh) was employed for column chromatography according to the procedure of Still.[32]

(*E*,*E*)-4,8-Dimethyl-10-(tetrahydropyranyloxy)-4,8-decadienenitrile (4). A mechanically stirred solution of 4.7 mL (90 mmol) of acetonitrile in 135 mL of THF was cooled to −78 °C and 31 mL of 2.3 M *n*-BuLi in hexanes was added dropwise over 0.5 h. The salmon-pink suspension was stirred an additional 0.5 h at −78 °C and then was brought to −25 °C. After 10 min, 17 g (90 mmol) of CuI was added, producing a dark reddish brown suspension.[13] After another 15 min, 5.78 g (18.2 mmol) of bromide **3**[12] in 30 mL of THF was added dropwise over 20 min. The suspension was stirred for another 1 h at −25 °C and then was quenched with saturated NH_4Cl and 10% NH_4OH. The mixture was extracted with ether and the combined ether layers were washed successively with 10% NH_4OH, water, and brine. The organic phase was dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was chromatographed on silica gel, eluting with 15% ethyl acetate–hexane to provide 4.26 g (84%) of the nitrile: IR (film) ν 2910, 2850, 2230, 1440, 1200, 1120, 1080, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.34 (1 H, t, J = 6.3 Hz, vinyl H), 5.22 (1 H, t, J = 6.8 Hz, vinyl H), 4.60 (1 H, t, J = 2.8 Hz, acetal H), 4.22 (1 H, A of ABX, J_{AB} = 11.9 Hz, J_{AX} = 6.4 Hz, allylic CH_2O), 3.99 (1 H, B of ABX, J_{BA} = 11.9 Hz, J_{BX} = 7.4 Hz, allylic CH_2O), 3.87 (1 H, m, THP OCH_2), 3.49 (1 H, m, THP OCH_2), 2.40 (2 H, dt, J = 2.0, 7.0 Hz, CH_2CH_2CN), 2.28 (2 H, t, J = 7.0 Hz, CH_2CN), 2.2–1.9 (4 H, m, allylic CH_2), 1.9–1.4 (6 H, m, THP CH_2), 1.65 (3 H, s, vinyl CH_3), 1.61 (3 H, s, vinyl CH_3); ^{13}C NMR (20 MHz, $CDCl_3$) δ 139.1, 131.2, 126.7, 120.8, 119.1, 97.5, 63.2, 61.9, 38.8, 34.6, 30.4, 25.8, 25.2, 19.3, 16.0, 15.3; MS, *m/e* 277 (M). Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.60; H, 9.81; N, 5.05. Found: C, 73.69; H, 9.84; N, 5.01.

(*E*,*E*)-4,8-Dimethyl-10-(tetrahydropyranyloxy)-4,8-decadienal (5). A solution of 6.59 g (23.8 mmol) of nitrile **4** in 20 mL of ether was cooled to −78 °C and treated dropwise with 35 mL of 1 M DIBAH[6] in hexane. After 30 min, the solution was brought to 0 °C and 15 min later the mixture was hydrolyzed with saturated Rochelle's salt solution. The mixture was extracted into ether and dried over $MgSO_4$ and solvent was removed under reduced pressure. The residue was chromatographed on silica gel, eluting with 15% ethyl acetate–hexane to give 5.5 g (82%) of aldehyde: IR (film) ν 2900, 2850, 2700, 1712, 1665, 1450, 1390 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (1 H, t, J = 1.9 Hz, CHO), 5.32 (1 H, t, J = 6.3 Hz, vinyl H), 5.12 (1 H, t, J = 6.3 Hz, vinyl H), 4.60 (1 H, t, J = 2.8 Hz, acetal H), 4.21 (1 H, A of ABX, J_{AB} = 11.9 Hz, J_{AX} = 6.4 Hz, allylic CH_2O), 3.99 (1 H, B of ABX, J_{BA} = 11.9 Hz, J_{BX} = 7.4 Hz, allylic CH_2O), 3.87 (1 H, m, THP OCH_2), 3.47 (1 H, m, THP OCH_2), 2.48 (2 H, dt, J = 1.9, 7.0 Hz, CH_2CHO), 2.29 (2 H, t, J = 7.3 Hz, CH_2CH_2CHO), 2.1–1.9 (4 H, m, allylic CH_2), 1.9–1.4 (6 H, m, THP CH_2), 1.64 (3 H, s, vinyl CH_3), 1.59 (3 H, s, vinyl CH_3); ^{13}C NMR (20 MHz, $CDCl_3$) δ 202.2, 139.5, 133.1, 124.9, 120.9, 97.7, 63.5, 62.1, 42.0, 39.3, 31.7, 30.6, 26.1, 25.4, 19.5, 16.2, 16.0; MS, *m/e* 280 (M). Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.90; H, 10.07.

Methyl (*E*,*E*,*E*)-6,10-Dimethyl-12-(tetrahydropyranyloxy)-2,6,10-dodecatrienoate (6). A solution of 7.01 g (25 mmol) of aldehyde **5** in 25 mL of CH_2Cl_2 was cooled to 0 °C and 12.5 g (37 mmol) of methyl (triphenylphosphoranylidene)acetate was added in portions. The solution was allowed to warm to room temperature and was stirred overnight. The mixture was concentrated and chromatographed on silica gel, eluting with 10% ethyl acetate–hexane, to provide 7.28 g (87%) of the ester: IR (film) ν 2925, 2850, 1725, 1660, 1440, 1280, 1205, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (1 H, dt, J = 15.7, 6.9 Hz, CH=$CHCO_2$), 5.79 (1 H, dt, J = 15.7, 1.5 Hz, $CHCO_2$), 5.33 (1 H, t, J = 6.9 Hz, vinyl H), 5.11 (1 H, t, J = 6.1 Hz, vinyl H), 4.60 (1 H, t, J = 3.5 Hz, acetal H), 4.21 (1 H, A of ABX, J_{AB} = 11.9 Hz, J_{AX} = 6.4 Hz, allylic CH_2O), 4.00 (1 H, B of ABX, J_{BA} = 11.9 Hz, J_{BX} = 7.4 Hz, allylic CH_2O), 3.87 (1 H, m, THP OCH_2), 3.70 (3 H, s, OCH_3), 3.49 (1 H, m, THP OCH_2), 2.30–2.24 and 2.11–2.02 (8 H, m, allylic CH_2), 1.9–1.45 (6 H, m, THP CH_2's), 1.65 (3 H, s, vinyl CH_3), 1.58 (3 H, s, vinyl CH_3); ^{13}C NMR (20 MHz, $CDCl_3$) δ 166.7, 148.8, 139.5, 133.4, 124.7, 120.6, 120.5, 97.5, 63.3, 61.9, 51.0, 39.1, 37.6, 30.4, 25.9, 25.2, 19.3, 16.1, 15.6; MS, *m/e* 336 (M), 305 (M − OCH_3). Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.49; H, 9.63.

Methyl (*E*,*E*,*E*)-6,10-Dimethyl-12-hydroxy-2,6,10-dodecatrienoate (7). A solution of 8.80 g (26 mmol) of THP ether **6** in 15 mL of MeOH was stirred at room temperature and 0.66 g (2.6 mmol) of PPTS[6] was added in one portion. The solution was stirred overnight and then was diluted with ether and washed with saturated aqueous $NaHCO_3$. The aqueous layer was back-extracted with ether and then the combined organic phases were washed with brine and dried over $MgSO_4$. Removal of solvent and chromatography on silica gel, eluting with 15% ethyl acetate–hexanes, afforded 6.01 g (91%) of the hydroxy ester: IR (film) ν 3400, 2910, 2850, 1725, 1660, 1445 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.92 (1 H, dt, J = 15.6, 6.9 Hz, CH=CHCO), 5.79 (1 H, dt, J = 15.6, 1.6 Hz, CH=CHCO), 5.37 (1 H, tq, J = 6.9, 1.3 Hz, vinyl H), 5.10 (1 H, tq, J = 6.8, 1.3 Hz, vinyl H), 4.12 (2 H, d, J = 6.7 Hz, CH_2OH), 3.70 (3 H, s, OCH_3), 2.25 (2 H, apparent q, J = 7.0 Hz, CH_2CH=CHCO), 2.15–1.95 (6 H, m, allylic CH_2), 1.64 (3 H, s, vinyl CH_3), 1.57 (3 H, s, vinyl CH_3); ^{13}C NMR (20 MHz, $CDCl_3$) δ 167.0, 149.2, 138.4, 133.4, 124.9, 123.8, 120.7, 59.0, 51.2, 39.1, 37.7, 30.4, 25.9, 16.0, 15.7; MS, *m/e* 252 (M)8 220 (M − CH_3OH). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found; C, 71.45; H, 9.64.

Methyl (*E*,*E*,*E*)-12-Chloro-6,10-dimethyl-2,6,10-dodecatrienoate (8). A solution of 2.46 g (9.7 mmol) of hydroxy ester **7** in 20 mL of DMF was cooled to 0 °C and 1.3 g (31 mmol) of LiCl was added, followed by 4.5 mL (39 mmol) of 2,6-lutidine.[6] After 15 min, the white suspension was treated dropwise with 2.2 mL (28 mmol) of methanesulfonyl chloride.[14] After a further 4 h at 0 °C, the mixture was diluted with ether and washed with water. The organic phase was dried over $MgSO_4$. Removal of solvent and chromatography on silica gel, eluting with 5% ethyl acetate–hexanes, gave 2.41 g (92%) of the chloro ester: IR (film) ν 2970, 2930, 2845, 1725, 1660, 1440, 1395, 1280, 1215, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.92 (1 H, dt, J = 15.6, 6.8 Hz, CH=CHCO), 5.80 (1 H, dt, J = 15.6, 1.6 Hz, CH=CHCO), 5.41 (1 H, qt, J = 1.3, 8.0 Hz, H-11), 5.09 (1 H, qt, J = 1.2, 6.8 Hz, H-7), 4.07 (2 H, d, J = 8.0 Hz, CH_2Cl), 3.70 (3 H, s, OCH_3), 2.32–2.25 (2 H, m, H-4), 2.12–2.02 (6 H, m, allylic CH_2's), 1.70 (3 H, d, J = 1.3 Hz, C-10 vinyl CH_3), 1.58 (3 H, d, J = 1.3 Hz, C-6 vinyl CH_3); ^{13}C NMR (20 MHz, $CDCl_3$) δ 166.9, 149.0, 142.3, 133.9, 124.5, 120.9, 120.4, 51.2, 40.9, 39.2, 37.8, 30.6, 25.9, 15.92, 15.86; MS, *m/e* 234 (M − HCl), 203 (M − HCl, CH_3OH). Anal. Calcd for $C_{15}H_{23}ClO_2$: C, 66.53; H, 8.56; Cl, 13.09. Found: C, 66.63; H, 8.61; Cl, 13.04.

(*E*,*E*,*E*)-12-Chloro-6,10-dimethyl-2,6,10-dodecatrien-1-ol (9). A solution of 2.41 g (8.9 mmol) of chloro ester **8** was cooled to −78 °C and 22 mL of 1 M DIBAH[6] in hexane was added dropwise. After 10 min, the reaction was quenched by the addition of saturated aqueous Rochelle's salt. The mixture was extracted with ether and the organic phase was dried over $MgSO_4$. Solvent removal followed by chromatography on silica gel, eluting with 15% ethyl acetate–hexanes, afforded 2.1 g (97%) of the chloro alcohol. Satisfactory combustion analysis could not be obtained on this marginally stable compound: IR (film) ν 3310, 2960, 2905, 2850, 1670, 1460, 1395 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.63 (2 H, m, H-2, H-3), 5.42 (1 H, qt, J = 1.3, 7.0 Hz, H-11), 5.08 (1 H, t, J = 6.8 Hz, H-7), 4.08 (2 H, d, J = 8.0 Hz, CH_2Cl), 4.06 (2 H, d, J = 4.3 Hz, CH_2OH), 2.16–2.00 (8 H, m, allylic CH_2), 1.70 (3 H, d, J = 1.3 Hz, C-10 vinyl CH_3), 1.57 (3 H, s, C-6 vinyl CH_3); ^{13}C NMR (20 MHz, $CDCl_3$) δ 142.3, 134.8, 132.4, 128.9, 123.6, 120.3, 63.3, 40.9, 39.2, 39.0, 30.6, 25.9, 15.8; MS, *m/e* 206 (M − HCl).

(*E*,*E*,*E*)-6,10-Dimethyl-15-(triisopropylsilyl)-2,6,10-pentadecatrien-14-yn-1-ol (10). A suspension of 1.3 g (6.8 mmol) of copper(I) iodide in 20 mL of THF was cooled to −78 °C and treated dropwise with 40 mL of 0.5 M TIPS-protected[6] propargylmagnesium bromide in THF.[15] The mixture was stirred at −78 °C for 30 min and then at −20 °C for 1 h. The olive-green suspension was recooled to −78 °C, and the bromomagnesium

(32) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

alkoxide, formed at −25 °C from 2.2 g (9.1 mmol) of chloro alcohol 9 in 3 mL of THF and 4.3 mL of 2.1 M EtMgBr in THF, was added via cannula. The mixture was stirred at −20 °C overnight, then quenched with saturated aqueous NH_4Cl. The mixture was extracted into ether and was washed with 10% NH_4OH until the washes were colorless. The combined washes were back-extracted with ether, and the combined organic phases were dried ($MgSO_4$). Removal of solvent and then chromatography on silica gel (15% ethyl acetate–hexane) gave 2.77 g (76%) of the silyl acetylene: IR (film) ν 3320, 2920, 2855, 2160, 1460, 1365 cm^{-1}; ^1H NMr (300 MHz, $CDCl_3$) δ 5.64 (2 H, m, H-2, H-3), 5.19 (1 H, t, J = 7.0 Hz, vinyl H), 5.10 (1 H, t, J = 6.9 Hz, vinyl H), 4.05 (2 H, d, J = 4 Hz, CH_2OH)8, 2.28–1.94 (12 H, m, allylic and propargylic CH_2's), 1.60 (3 H, s, vinyl CH_3), 1.57 (3 H, s, vinyl CH_3), 1.07–0.99 (21 H, m, $((CH_3)_2CH)_3Si$); ^{13}C NMR (20 MHz, $CDCl_3$) δ 136.2, 134.3, 133.0, 129.0, 124.6, 122.9, 109.0, 80.1, 63.7, 39.6, 39.2, 30.8, 27.6, 26.5, 20.3, 18.6, 16.2, 15.9, 11.3; MS, m/e 359 (M − $(CH_3)_2CH$). Anal. Calcd for $C_{26}H_{46}OSi$: C, 77.54; H, 11.51. Found: C, 77.55; H, 11.51.

(*E*,*E*,*E*)-6,10-Dimethyl-2,6,10-pentadecatrien-14-yn-1-ol (11). To a solution of 2.52 g (6.3 mmol) of silyl acetylene **10** in 5 mL of THF was added 20 mL of 1 M n-Bu_4NF in THF. The dark solution was stirred 3 h at room temperature and then diluted with water. The mixture was extracted with ether and the combined ether layers were dried over anhydrous $MgSO_4$. Removal of solvent left an oil that was chromatographed on silica gel, eluting with 15% ethyl acetate–hexanes, to provide 1.48 g (96%) of the acetylene: IR (film) ν 3300, 3270, 2900, 2840, 2120, 1665, 1455, 1090, 980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.67 (1 H, dd, J = 5.1, 15.5 Hz, CH=C*H*), 5.59 (1 H, dd, J = 4.9, 15.4 Hz, C*H*=CH), 5.15 (1 H, m, vinyl H), 5.09 (1 H, m, vinyl H), 4.05 (2 H, d, J = 4.3 Hz, CH_2OH), 2.24–1.95 (12 H, m, allylic and propargylic CH_2's), 1.92 (1 H, t, J = 2.3 Hz, acetylenic H), 1.59 (3 H, s, vinyl CH_3), 1.57 (3 H, s, vinyl CH_3); ^{13}C NMR (20 MHz, $CDCl_3$) δ 136.4, 134.3, 132.6, 128.9, 124.4, 122.4, 84.4, 68.1, 63.4, 39.4, 39.0, 30.7, 27.0, 26.3, 18.8, 16.0, 15.9; MS, m/e 231 (M − CH_3), 213 (M − CH_3, H_2O). Anal. Calcd for $C_{13}H_{20}O$: C, 82.87; H, 10.64. Found: C, 82.98; H, 10.66.

(*E*,*E*,*E*)-6,10-Dimethyl-2,6,10-pentadecatrien-14-ynal (12). To a −78 °C solution of 0.79 mL (9.0 mmol) of oxalyl chloride in 15 mL of CH_2Cl_2 was added 1.3 mL (18 mmol) of DMSO, and after 5 min a solution of 1.13 g (5.3 mmol) of alcohl **11** in 3 mL of CH_2Cl_2 was added dropwise.[16] The mixture was stirred a further 1 h at −78 °C and then 5 mL (36 mmol) of Et_3N was added. The suspension was warmed to 0 °C, then diluted with hexanes, and washed successively with water, aqueous 1% HCl, water, and saturated aqueous $NaHCO_3$. The organic phase was dried over $MgSO_4$ and solvent was removed. Chromatography of the residue on silica gel, eluting with 7.5% ethyl acetate–hexanes, afforded 1.13 g (87%) of the aldehyde: IR (film) ν 3280, 2910, 2840, 2730, 1690, 1640, 1460, 1140, 985 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.46 (1 H, d, J = 7.9 Hz, CHO), 6.80 (1 H, dt, J = 15.6, 6.7 Hz, H-3), 6.09 (1 H, ddt, J = 15.6, 7.9, 1.5 Hz, H-2), 5.20–5.10 (2 H, m, H-7 and H-11), 2.46–2.38 and 2.30–1.91 (12 H, m, allylic and propargylic CH_2's), 2.18 (1 H, t, J = 1.8 Hz, H-15), 1.59 (6 H, s, vinyl CH_3's); ^{13}C NMR (20 MHz, $CDCl_3$) δ 193.5, 158.0, 136.1, 132.9 (2-C), 125.4, 122.5, 84.2, 68.1, 39.3, 37.5, 30.9, 26.9, 26.2, 18.7, 15.9, 15.7; MS, m/e 243 (M − H). Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.40; H, 9.92.

(*E*,*E*,*E*)-6,10-Dimethyl-16-(tri-*n*-butylstannyl)-16-(methoxymethoxy)-6,10,14-pentadecatrien-1-yne (13). To 12.7 mL (4.7 mmol) of 0.37 M LDA[6] in THF at 0 °C was added 1.3 mL (4.7 mmol) of tri-n-butyltin hydride.[17] The solution was stirred for 15 min at 0 °C and then cooled to −78 °C, and 507 mg (2.1 mmol) of aldehyde **12** in 2 mL of THF was added. The solution was stirred at −78 °C for 0.5 h and then 5 mL of water was injected. The mixture was warmed to room temperature and extracted with ether. The combined organic layers were dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude hydroxy stannane was immediately taken up in 5 mL of CH_2Cl_2 and cooled to 0 °C. Addition of 1.5 mL (8.4 mmol) of diisopropylethylamine was followed by the addition of 0.48 mL (6.3 mmol) of chloromethyl methyl ether. The solution was stirred at 4 °C overnight and then water was added. The mixture was extracted with hexane and the combined extracts were dried over $MgSO_4$. Removal of solvent gave an oil that was purified by chromatography on silica gel, deactivated with 2% ethylamine–hexanes followed by hexane elution, to afford 930 mg (78%) of the stannane: IR (film) ν 3290, 2940, 2910, 1465, 1385, 1160, 1080, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.53 (1 H, dd, J = 7.3 Hz, 15.3 Hz, H-2), 5.36 (1 H, dt, J = 15.3 Hz, 7.9 Hz, H3)8 5.16 (1 H, br t, J = 7 Hz, vinyl H), 5.09 (1 H, br t, J = 6 Hz, vinyl H), 4.55 (2 H, AB q, J_{AB} = 6.4 Hz, $\Delta\nu$ = 56.5 Hz, OCH_2OCH_3), 4.54 (1 H, d, J = 7.2 Hz, H1), 3.31 (3 H, s, OCH_3), 2.22–1.9. (12 H, m, allylic and propargylic CH_2's), 1.92 (1 H, t, J = 2.5 Hz, C≡CH), 1.60 (3 H, s, vinyl CH_3), 1.57 (3 H, s, vinyl CH_3), 1.54–1.44 (6 H, m, CH_2), 1.35–1.22 (6 H, m, CH_2), 0.90 (6 H, t, J = 6.3 Hz, $SnCH_2$), 0.87 (9 H, t, J = 7.2 Hz, CH_2CH_3); ^{13}C NMR (20 MHz, $CDCl_3$) δ 136.5, 134.6, 131.2, 125.0, 124.1, 122.4, 95.0, 84.3, 72.3, 68.0, 55.2, 39.9, 39.5, 31.0, 30.6, 29.0, 27.3, 27.1, 26.5, 18.8, 16.0, 15.9, 13.6, 9.9, 9.0; MS, m/e 535 (M − CH_2OCH_3). Anal. Calcd for $C_{31}H_{56}O_2Sn$: C, 64.25; H, 9.74. Found: C, 64.14; H, 9.78.

(*E*,*E*,*E*)-7,11-Dimethyl-16-(tri-*n*-butylstannyl)-16-(methoxymethoxy)-6,10,14-hexadecatrien-2-yn-1-ol (14). A solution of 2.00 g (3.45 mmol) of acetylene **13** in 5 mL of THF at −78 °C was treated with 7.8 mL (5.2 mmol) of 0.67 M LDA in THF. The solution was stirred an additional 1 h at −78 °C and then 420 mg (14 mmol) of paraformaldehyde was added. The cold bath was removed and the mixture was allowed to warm to room temperature, with stirring for 1 h after the addition was complete. Water was added and the mixture was extracted with ether. The organic phase was dried over $MgSO_4$ and solvent was removed under reduced pressure. Chromatogrphy on silica gel, eluting with 15% ethyl acetate–hexanes, gave 1.64 g (78%) of the alcohol: IR (film) ν 3400, 2950, 2910, 2850, 1470, 1160, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.54 (1 H, dd, J = 7.3, 15.2 Hz, H-15), 5.36 (1 H, dt, J = 15.2, 6.1 Hz, H-14), 5.14–5.07 (2 H, m, H-6 and H-10), 4.56 (2 H, AB, q, J_{AB} = 6.4 Hz, $\Delta\nu$ = 56.6 Hz, OCH_2OCH_3), 4.54 (1 H, d, J = 7.2 Hz, H-16), 4.22 (2 H, d, J = 6.0 Hz, CH_2OH), 3.31 (3 H, s, OCH_3), 2.20, 2.08–2.00 (12 H, m, allylic and propargylic CH_2), 1.59 (3 H, s, vinyl CH_3), 1.57 (3 H, s, vinyl CH_3), 1.54–1.43 (6 H, m, CH_2), 1.35–1.21 (6 H, m, CH_2), 0.89 (6 H, t, J = 6.3 Hz, $SnCH_2$), 0.87 (9 H, t, J = 7.2 Hz, CH_2CH_3); ^{13}C NMR (20 MHz, $CDCl_3$) δ 136.5, 134.7. 131.1, 125.0, 124.1, 122.6, 94.9, 85.9, 78.4, 72.3, 65.7, 55.1, 51.0, 39.9, 39.5, 31.0, 29.0, 27.3, 26.5, 19.2, 16.0, 15.9, 15.1, 13.6, 9.0; MS, m/e 565 (M − CH_2OCH_3). Anal. Calcd for $C_{32}H_{58}O_3Sn$: C, 63.06; H, 9.59. Found: C, 63.05; H, 9.62.

(*E*,*E*,*E*)-7,11-Dimethyl-16-(tri-*n*-butylstannyl)-16-(methoxymethoxy)-6,10,14-hexadecatrien-2-ynal (15). A solution of 0.84 mL (8.9 mmol) of *tert*-butyl alcohol in 15 mL of THF was cooled to 0 °C and treated with 4.6 mL of 1.9 M ethylmagnesium bromide in THF. After 3 min a solution of 3.18 g (5.22 mmol) of alcohol **14** in 3 mL of THF was added. After a further 5 min, 2.24 g (8.9 mmol) of 1,1′-(azodicarbonyl)dipiperidine was added, producing a deep red solution.[18] The solution was stirred at 0 °C for 15 min, then quenched with brine, and extracted into ether. The organic layer was washed with saturated aqueous $NaHCO_3$ and then dried over $MgSO_4$. The solvent was removed in vacuo and then the residue was chromatographed on silica gel, eluting with 5% ethyl acetate–hexane, to provide 2.58 g (81%) of the aldehyde. A satisfactory combustion analysis of this compound could not be obtained: IR (film) ν 2945, 2915, 2850, 2270, 2200, 1670, 1465, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.14 (1 H, s, CHO), 5.53 (1 H, dd, J = 15.3, 7.3 Hz, H-15), 5.35 (1 H, dt, J = 15.3, 7.9 Hz, H-14), 5.13 (1 H, t, J = 7.1 Hz, vinyl H), 5.08 (1 H, t, J = 6.8 Hz, vinyl H), 4.55 (2 H, AB q, J_{AB} = 6.3 Hz, $\Delta\nu$ = 56 Hz, OCH_2OCH_3), 4.53 (1 H, d, J = 7.3 Hz, H-16), 3.30 (3 H, s, OCH_3), 2.42–1.98 (12 H, m, allylic and propargylic CH_2's), 1.61 (3 H, s, vinyl CH_3), 1.57 (3 H, s, vinyl CH_3), 1.54–1.40 (6 H, m, CH_2's), 1.34–1.22 (6 H, m, CH_2's), 0.89 (6 H, t, J = 8.1 Hz, $SnCH_2$), 0.86 (9 H, t, J = 7.2 Hz, CH_2CH_3); ^{13}C NMR (20 MHz, $CDCl_3$) δ 176.9, 137.8, 134.9, 131.2, 124.0, 121.4, 98.8, 95.0, 81.6, 72.3, 55.2, 39.9, 39.6, 31.1, 29.0 (4-C), 27.4 (4-C), 26.5, 26.2, 19.6, 16.1, 15.9, 13.6 (4-C), 9.1 (4-C); MS, m/e 608 (M + H).

***rel*-(1*S*,2*R*)-(5*E*,9*E*)-5,9-Dimethyl-2-[(*Z*)-2-(methoxymethoxy)-1-ethenyl]-5,9-cyclotetradecadien-13-yn-1-ol (16).** A solution of 3.36 g (5.5 mmol) of aldehyde **15** in 15 mL of CH_2Cl_2 was added with stirring over 1 h to a solution of 2.0 mL (17 mmol) of BF_3 etherate in 600 mL of CH_2Cl_2 at −78 °C. The solution was stirred for a further 15 min at −78 °C and then was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with ether and the organic phase was dried over $MgSO_4$. Removal of

solvent left an oil that was chromatographed on silica gel, eluting with 20% ethyl acetate–hexane, to provide 1.55 g (88%) of the macrocyclic alcohol as a 88:12 mixture of cis and trans isomers: IR (film) ν 3470, 3035, 2975, 2930, 2910, 2885, 2270, 2230, 1740, 1665, 1440, 1372, 1240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.25 (1 H, d, J = 6.4 Hz, C=C*H*OCH_2), 5.20–5.07 (2 H, m, vinyl H's), 4.76 (2 H, s, OCH_2O), 4.47 (1 H, m, H-1), 4.46 (1 H, dd, J = 9.6, 6.4 Hz, C*H*=$CHOCH_2$), 3.35 (3 H, s, OCH_3), 2.92–2.83 (1 H, m, H-2), 2.35–1.75 (10 H, m, allylic and propargylic CH_2's), 1.65–1.50 (2 H, m, CH_2), 1.56 (3 H, s, vinyl CH_3), 1.54 (3 H, s, vinyl CH_3); ^{13}C NMR (20 MHz, $CDCl_3$) δ 144.0, 134.9, 134.8, 124.5, 122.4, 108.6, 96.1, 85.5, 80.1, 65.6, 65.5, 55.4, 39.9, 38.9, 34.7, 28.6, 26.4, 23.7, 18.8, 17.4, 15.2, 15.0; MS, m/e 318 (M). Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.50; H, 9.52.

(5*E*,9*E*)-5,9-Dimethyl-2-[(*Z*)-2-(methoxymethoxy)-1-ethenyl]-5,9-cyclotetradecadien-13-ynone (24). To a solution of 0.10 mL (1.1 mmol) of oxalyl chloride in 2.5 mL of CH_2Cl_2 was added 0.13 mL (1.8 mmol) of DMSO at −78 °C.[16] After 5 min 100 mg (0.314 mmol) of alcohol **16** in 0.5 mL of CH_2Cl_2 was added. After a further 30 min 0.50 mL (3.6 mmol) of Et_3N was added, and the mixture was allowed to warm to 0 °C, then diluted with hexane, and washed with water. The organic phase was dried over $MgSO_4$, and solvent was removed in vacuo. The resulting oil was chromatographed on silica gel, eluting with 5% ethyl acetate–hexane, to provide 86 mg (87%) of the ynone: IR (film) ν 2930, 2855, 2210, 1670, 1440, 1150, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.21 (1 H, d, J = 6.2 Hz, CH=C*H*OCH_2), 5.14 (2 H, m, vinyl H's), 4.78 (2 H, AB q, J_{AB} = 6.4 Hz, $\Delta\nu$ = 6.4 Hz, OCH_2O), 4.44 (1 H, dd, J = 6.2, 9.5 Hz, C*H*=$CHOCH_2$), 3.84 (1 H, dt, J = 7.0, 14.0 Hz, H-2), 3.36 (3 H, s, OCH_3), 2.51–2.02 (10 H, m, allylic CH_2's and H-3), 1.95 (2 H, t, J = 6.4 Hz, H-12), 1.60 (3 H, s, vinyl CH_3), 1.57 (3 H, d, J = 1.3 Hz, vinyl CH_3); ^{13}C NMR (20 MHz, $CDCl_3$) δ 189.6, 144.1, 136.4, 133.8, 124.5, 123.4, 105, 4, 96.3, 95.2, 81.8, 55.6, 48.4, 38.8, 36.0, 30.3, 25.6, 24.1, 19.4, 16.0, 15.1; MS, m/e 316 (M). Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.74; H, 8.99.

(5*E*,9*E*,13*E*)-2-[(*Z*)-2-(Methoxymethoxy)-1-ethenyl]-5,9,13-trimethyl-5,9,13-cyclotetradecatrienone (26). To a suspension of 250 mg (1.3 mmol) of CuI in 5 mL of THF at 0 °C was added 1.6 mL (2.6 mmol) of 1.6 M MeLi·LiBr in ether. After 10 min a solution of 116 mg (370 μmol) of ynone **24** in 1 mL of THF was added dropwise.[26] The mixture was stirred for 15 min at 0 °C and then quenched with saturated aqueous NH_4Cl and 10% NH_4OH. The blue mixture was extracted with ether and the organic phase was dried over $MgSO_4$. Removal of solvent left an oil that was chromatographed on silica gel, eluting with 5% ethyl acetate–hexane, to provide 118 mg (97%) of the enone as a 1:1 mixture of **25** and **26** according to the ^1H NMR spectrum (13*E* vinyl methyl = 2.07 ppm; 13*Z* vinyl methyl = 1.91 ppm). The mixture of enones was dissolved in 1 mL of THF and cooled to 0 °C, and 0.10 mL (1.1 mmol) of 2-propanethiol was added, followed by 7 mg (1 mmol) of LiH. The mixture was stirred for 17 h at room temperature and then quenched with water and extracted into ether. The extract was dried over $MgSO_4$ and solvent was removed. The resulting oil was chromatographed on silica gel (5% ethyl acetate–hexane) to afford 110 mg (93%) of enone **26** (90% from **24**): IR (film) ν 2910, 2850, 1670, 1610, 1430, 1375 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.08 (1 H, dd, J = 0.8, 6.1 Hz, C=C*H*OCH_2), 5.98 (1 H, q, J = 1.1 Hz, H-14), 4.93 (1 H, m, vinyl H), 4.87 (1 H, m, vinyl H), 4.79 (2 H, AB q, J_{AB} = 6.4 Hz, $\Delta\nu$ = 6.0 Hz, OCH_2O), 4.40 (1 H, dd, J = 6.1, 9.8 Hz, C*H*=$CHOCH_2$), 3.66 (1 H, dt, J = 3.3, 9.9 Hz, H-2), 3.37 (3 H, s, OCH_3), 2.4–1.8 (12 H, m, allylic H's), 2.07 (3 H, d, J = 1.1 Hz, C-13 CH_3), 1.60 (3 H, s, vinyl CH_3), 1.55 (3 H, s, vinyl CH_3); ^{13}C NMR (20 MHz, $CDCl_3$) δ 201.9, 156.6, 143.2, 134.5, 133.8, 125.5, 125.4, 125.1, 107.9, 96.4, 55.6, 46.2, 39.4, 39.0, 36.8, 29.4, 24.4, 24.1, 19.5, 15.0, 14.9; MS, m/e 322 (M). Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.77; H, 9.78.

***rel*-(1*S*,14*R*)-(2*E*,6*E*,10*E*)-16-Oxo-3,7,11-trimethyl-17-oxabicyclo[12.3.0]heptadeca-2,6,10-triene (31).** To a solution of 22 mg (69 μmol) of keto ester **35** in 0.7 mL of methanol was added 40 mg (1.2 mmol) of $NaBH_4$ at 0 °C. After 45 min, ketone was no longer evident by TLC. The mixture was neutralized to pH 7 with 10% HCl, then extracted into ether, and dried over $MgSO_4$. Removal of solvent followed by chromatography on silica gel, eluting with 15% ethyl acetate–hexane, gave 14 mg (70%) of the lactone as a 9:1 mixture of cis:trans isomers according to ^1H NMR analysis (cis carbinyl = 5.32 ppm; trans carbinyl = 4.80 ppm): IR (CCl_4) ν 2920, 2850, 1775, 1430, 1310, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.32 (1 H, dd, J = 6.4, 10.0 Hz, H-1), 5.20 (1 H, d, J = 10.0 Hz, H-2), 4.90 (1 H, t, J = 7 Hz, vinyl H), 4.81 (1 H, d, J = 9.2 Hz, vinyl H), 2.55–1.60 (15 H, m, CH, CH_2's), 1.63 (3 H, s, C-3 CH_3), 1.55 (3 H, s, vinyl CH_3), 1.53 (3 H, s, vinyl CH_3); ^{13}C NMR (20 MHz, $CDCl_3$) δ 176.8, 142.0, 133.7, 133.6, 125.5, 123.3, 119.5, 80.2, 40.0, 39.7, 39.3, 34.7, 28.1, 24.7, 23.4, 16.2, 15.21, 15.16; MS, m/e 288 (M). Anal. Calcd for $C_{19}H_{20}O_2$: C, 79.12; H, 6.99. Found: C, 79.03; H, 9.85.

(5*E*,9*E*,13*E*)-2-(2-Oxoethyl)-5,9,13-trimethyl-5,9,13-cyclotetradecatrienone (33). A solution of 60 mg (180 μmol) of enol ether **26** in 1 mL of THF was stirred with 1 mL of aqueous 10% HCl at room temperature for 7 h. The biphasic mixture was extracted into ether and then washed with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and solvent was removed under reduced pressure. The resulting oil was chromatographed on silica gel, eluting with 10% ethyl acetate–hexane, to give 43 mg (83%) of the keto aldehyde: IR (CCl_4) ν 2920, 2840, 2700, 1724, 1670, 1610, 1440, 1380, 1095, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (1 H, s, CHO), 6.02 (1 H, s, H-14), 4.93 (2 H, m, vinyl H's), 2.97 (1 H, m, H-2), 2.76 (1 H, A of ABX, J_{AB} = 17.8 Hz, J_{AX} = 7.8 Hz, CH_2CHO), 2.38 (1 H, B of ABX, J_{BA} = 17.8 Hz, J_{BX} = 5.7 Hz, CH_2CHO), 2.30–1.75 (12 H, m, CH_2's), 2.07 (3 H, s, C-13, CH_3), 1.59 (3 H, s, vinyl CH_3), 1.54 (3 H, s, vinyl CH_3); ^{13}C NMR (20 MHz, $CDCl_3$) δ 202.7, 200.5, 158.1, 134.4, 133.3, 125.2 (2-C), 124.1, 46.1, 44.1, 39.4, 38.9, 35.8, 29.5, 24.3, 23.8, 19.6, 15.4, 15.2, 15.1; MS, m/e 288 (M). Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.00; H, 9.84.

Methyl [(3*E*,7*E*,11*E*)-4,8,12-Trimethyl-2-oxo-3,7,11-cyclotetradecatrieneacetate (35). A solution of 85 mg (290 μmol) of aldehyde **33** in 1.2 mL of DMF[6] was treated with 560 mg (1.5 mmol) of pyridinium dichromate.[27] The mixture was stirred at room temperature for 4 h and then water was added and the mixture was extracted with ether. The organic phase was dried over $MgSO_4$ and filtered through a short plug of silica gel. Removal of solvent left an oil that was chromatographed on silica gel, eluting with 50% ethyl acetate–hexane, to afford 70 mg (78%) of the acid **34**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (1 H, s, H-14), 4.94 (2 H, m, vinyl H's), 2.89 (1 H, m, H-2), 2.65 (1 H, A of ABX, dd, J_{AB} = 16.6 Hz, J_{AX} = 8.0 Hz, CH_2CO_2H), 2.35–1.75 (13 H, m, CH_2's), 2.07 (3 H, s, C-13 CH_3), 1.58 (3 H, s, vinyl CH_2), 1.53 (3 H, s, vinyl CH_3). A 36-mg (120 μmol) portion of of acid **34** was dissolved in 0.5 mL of ether and treated with excess ethereal diazomethane at 0 °C. Removal of solvent followed by chromatography on silica gel, eluting with 5% ethyl acetate–hexane, gave 36 mg (95%) of the keto ester: IR (CCl_4) ν 2920, 2850, 1730, 1678, 1610, 1435, 1190, 1150, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.01 (1 H, s, H-14), 4.92 (2 H, m, vinyl H), 3.62 (3 H, s, OCH_3), 2.90 (1 H, m, H-2), 2.61 (1 H, A of ABX, dd, J_{AB} = 16.3 Hz, J_{AX} = 8.1 Hz, CH_2CO_2), 2.40–1.70 (13 H, m, CH_2's), 2.08 (3 H, s, C-13 CH_3), 1.59 (3 H, s, vinyl CH_3), 1.54 (3 H, s, vinyl CH_3); ^{13}C NMR (20 MHz, $CDCl_3$) δ 203.1, 172.8, 157.9, 134.6, 133.5, 125.3 (2-C), 124.5, 51.5, 46.1, 39.6, 39.0, 36.6, 36.1, 36.0, 29.6, 24.4, 23.9, 19.7, 15.4, 15.2; MS, m/e 318 (M). Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.64; H, 9.56.

***rel*-(1*S*,14*R*)-(2*E*,6*E*,10*E*)-15-Methylene-16-oxo-3,7,11-trimethyl-17-oxabicyclo[12.3.0]heptadeca-2,6,10-triene (I).** To a solution of 42 mg (150 μmol) of lactone **32** in 1 mL of THF at −78 °C was added 0.9 mL of ~1 M LDA[6] in THF dropwise. The resulting solution was stirred at −78 °C for 40 min and then warmed to −20 °C whereupon gaseous formaldehyde generated in a stream of argon was introduced for 5 min. The mixture was stirred at −20 °C for 10 min and then quenched with 5% HCl. The solution was extracted with ether and the ether extract was dried over anhydrous $MgSO_4$. Removal of solvent left an oil that was purified by chromatography on silica gel, eluting with 25% ethyl acetate–hexanes, to provide 30.3 mg (66%) of the hydroxymethylated lactone: ^1H NMR (300 MHz, $CDCl_3$) δ 5.38–5.21 (m, carbinyl H), 5.10 (d, J = 10.6 Hz, H2), 4.85 (t, J = 7.6 Hz, vinyl H), 4.75 (d, J = 9.2 Hz, vinyl H), 4.03–3.86, 3.75–3.67 (m, CH_2OH), 2.92–1.28 (m, CH_2's and CH's), 1.65 (s, 3-CH_3), 1.54 (s, vinyl CH_3), 1.52 (s, vinyl CH_3).

A solution of 17 mg (53 μmol) of the foregoing hydroxymethyl lactone, 100 mg (230 μmol) of 1-cyclohexyl-3-(2-morpholino-

ethyl)carbodiimide metho-*p*-toluenesulfonate (MCDI) and a catalytic amount of copper(II) chloride in 1 mL of acetonitrile was heated at 60 °C for 2 h and then diluted with ether and filtered through a plug of silica gel.[29] Removal of solvent left 11 mg (69%) of α-methylene lactone: IR (CCl_3) ν 2975, 2925, 2850, 1765, 1650 (w), 1435, 1310, 1250, 1100, 955, 935 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.22 (1 H, d, J = 3.2 Hz, α-methylene), 5.49 (1 H, d, J = 2.9 Hz, α-methylene), 5.39 (1 H, dd, J = 7.7, 10.1 Hz, carbinyl H), 4.98 (1 H, d, J = 10.3 Hz, H-2), 4.90 (1 H, t, J = 7.8 Hz, vinyl H), 4.76 (1 H, d, J = 8.0 Hz, vinyl H), 3.03 (1 H, m, H-14), 2.39–1.32 (12 H, m, CH_2's), 1.64 (3 H, s, CH_3 on C-3), 1.56 (3 H, s, vinyl CH_3), 1.54 (3 H, s, vinyl CH_3); ^{13}C NMR (20 MHz, $CDCl_3$) δ 170.7, 142.4, 139.1, 133.6 (2-C), 125.5, 124.0, 120.3, 120.2, 78.2, 43.5, 40.0, 39.7, 36.4, 27.2, 24.6, 23.5, 15.8, 15.2 (2-C); MS, m/e 300 (M), 285 (M – CH_3). These spectra were identical with those of the natural cembranolide.[1]

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Supplementary Material Available: ^1H NMR spectra of key synthetic intermediates (23 pages). Ordering information is given on any current masthead page.

Stereoselective Total Synthesis of (±)-Subergorgic Acid, a New Type of Angular Triquinane Sesquiterpene

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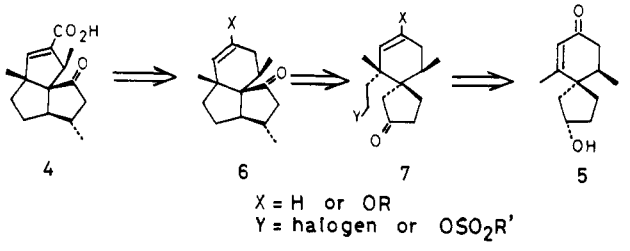
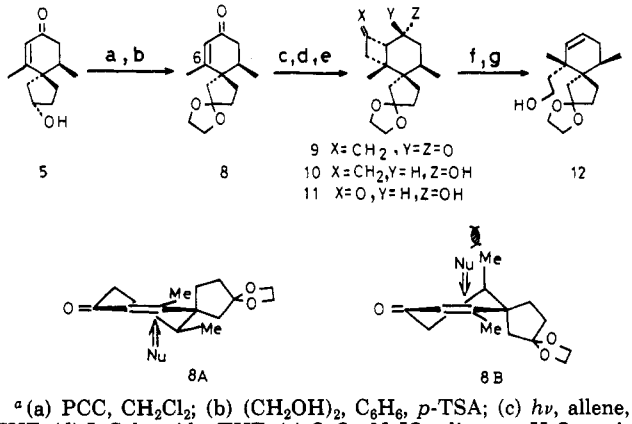
The first stereoselective total synthesis of (±)-subergorgic acid (**4**), a new angular triquinane sesquiterpene isolated from a gorgonian coral, has been achieved by beginning with *rel*-(2*R*,5*R*,10*S*)-2-hydroxy-6,10-dimethylspiro[4.5]dec-6-en-8-one (**5**). Transformation of **5** to **8** followed by a photochemical [2 + 2] cycloaddition reaction with allene afforded cyclobutanone **9** with a high stereoselectivity. Reductive β-fragmentation of **11** gave **12**, which was converted to the mesylate **19** by a six-step sequence. The cyclized product **20** was transformed to **22** and finally contraction of the cyclohexene ring of **22** to a cyclopentene carboxaldehyde followed by oxidation provided the target compound, (±)-subergorgic acid (**4**).

Angular triquinane sesquiterpenes, which have the tricyclo[6.3.0.0^{1,5}]undecane framework and are represented by isocomene[1,2] (**1**), silphinene[3,4] (**2**), and pentalenene[5,6] (**3**), have continued to attract the attention of synthetic organic chemists because of their unique carbon skeletons. In 1985, subergorgic acid was isolated from the Pacific gorgonian coral *Subergorgia suberosa* by Fenical et al. and assigned an angular triquinane structure **4** on the basis of

Scheme I



Scheme II[a]



[a] (a) PCC, CH_2Cl_2; (b) $(CH_2OH)_2$, C_6H_6, *p*-TSA; (c) *hν*, allene, THF; (d) L-Selectride, THF; (e) OsO_4, $NaIO_4$, dioxane, H_2O, pyridine; (f) MsCl, pyridine; (g) $NaBH_4$, MeOH.

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