Total Synthesis of Sarcophytol A, an Anticarcinogenic Marine Cembranoid

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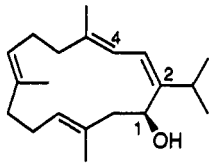
A highly stereo- and enantioselective total synthesis of sarcophytol A (1), a marine cembranoid promising as a cancer chemopreventive agent, is described. The nitrile **10** obtained *Z*-selectively (*Z*:*E* = >35:1) by the Horner–Emmons reaction of (*E*,*E*)-farnesal (**5**) with the phosphononitrile **9** in 91% yield was converted to the conjugated 2(*Z*),4(*E*)-dienal **3** in which the terminal (*E*)-methyl group was functionalized. Intramolecular alkylation of the cyanohydrin TMS ether of **3** provided the macrocyclic ketone **2** in 79% of overall yield from **3** without isolation of the cyclic cyanohydrin **20** as well as its TMS ether **19**. Reduction of **2** with several chiral $LiAlH_4$ reagents afforded **1** highly enantioselectively (87–93% ee) in 78–97% yield, from which enantiomerically pure **1** (>99% ee) was readily obtained upon a single recrystallization.

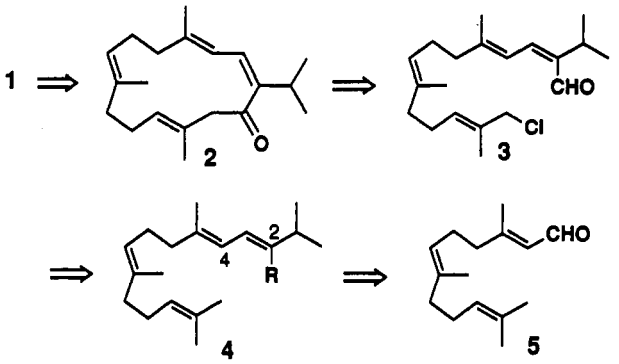
Cembranoids, a 14-membered cyclic diterpene family, have become of interest to synthetic chemists and biologists because of their unusual structures and wide range of biological activities.[1,2] Sarcophytol A (**1**),[3] a cembranoid isolated in 1979 from the Okinawan soft coral *Sarcophyton glaucum*, has been reported to have antitumor activity[4] and also potent inhibitory activities against the various classes of tumor promoters.[5,6] Moreover, it was demonstrated that **1** in diet inhibited the spontaneous tumor development in organs such as the mamma,[7] liver,[8] and thymus,[6] besides inhibiting chemical carcinogenesis in the colon.[9] In those experiments **1** did not show any toxic



sarcophytol-A (1)

effect on animals. Recently, inhibition of TNF-α[10] release from cells was proposed as a mechanism of the anticarcinogenesis of **1**.[11] Although human intervention trials with possible cancer chemopreventive agents are now being conducted in the U.S., further studies to find new inhibitory and nontoxic agents are required.[9,12] Cembranoid **1** has potential as a new cancer chemopreventive agent, and its production by chemical synthesis is thus strongly desired.

Scheme 1. Synthetic Strategy for Sarcophytol A



In 1988, the geometrical structure and absolute configuration of **1** were finally confirmed to be 2*Z*, 4*E*, 8*E*, 12*E*, and 1*S*, respectively,[13] and since then efforts to synthesize this cembranoid have used a variety of methodologies.[14–17] We have now achieved the first total synthesis of **1**[15] and here provide details of this accomplishment.

Our strategy started from (*E*,*E*)-farnesal (**5**)[18] as outlined in Scheme 1, and involved three key steps: (1) stereose-

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(1) For a review of cembranoid synthesis, see: Tius, M. A. *Chem. Rev.* **1988**, *88*, 719.

(2) Cox, N. J. G.; Mills, S. D.; Pattenden, G. *J. Chem. Soc. Perkin Trans. 1* **1992**, 1313 and references cited therein.

(3) Kobayashi, M.; Nakagawa, T.; Mitsuhashi, H. *Chem. Pharm. Bull.* **1979**, *27*, 2382.

(4) Japanese patent no. 8161318 to Mitsubishi Kasei Corp.

(5) Fujiki, H.; Sugimura, T. *Cancer Surveys* **1983**, *2*, 539. Fujiki, H.; Suganuma, M.; Suguri, H.; Takagi, K.; Kobayashi, M. *J. Cancer Res. Clin. Oncol.* **1989**, *115*, 25.

(6) Fujiki, H.; Suganuma, M.; Takagi, K.; Nishikawa, S.; Yoshizawa, S.; Okabe, S.; Yatsunami, J.; Frenkel, K.; Troll, W.; Marshall, J. A.; Tius, M. A. In *Phenolic Compounds in Food and Their Effects on Health II*; Huang, M.-T., Ho, C.-T., Lee, C. Y., Eds.; ACS Symposium Series 507; American Chemical Society: Washington, DC, 1992; p 380.

(7) Fujiki, H.; Suganuma, M.; Suguri, H.; Takagi, K.; Yoshizawa, S.; Ootsuyama, A.; Tanooka, H.; Okuda, T.; Kobayashi, M.; Sugimura, T. In *Antimutagenesis and Anticarcinogenesis Mechanism II*; Kuroda, K., Shankel, D. M., Waters, M. D., Eds.; Plenum Press, New York, London, 1990; p 205.

(8) Yamauchi, O.; Omori, M.; Ninomiya, M.; Okuno, M.; Moriwaki, H.; Suganuma, M.; Fujiki, H.; Muto, Y. *Jpn. J. Cancer Res.* **1991**, *82*, 1234.

(9) Narisawa, T.; Takahashi, M.; Niwa, M.; Fukaura, Y.; Fujiki, H. *Cancer Res.* **1989**, *49*, 3287.

(10) Abbreviations: TNF-α = tumor necrosis factor α; DIBAL = diisobutylaluminum hydride; TMS = trimethylsilyl; EE = 1-ethoxyethyl; THF = tetrahydrofuran.

(11) Komori, A.; Suganuma, M.; Okabe, S.; Zou, X.; Tius, M. A.; Fujiki, H. *Cancer Res.* **1993**, *53*, 3462.

(12) Kellof, G. J.; Boone, C. W.; Malone, W. F.; Steele, V. E. *Mutat. Res.* **1992**, *267*, 291.

(13) Kobayashi, M.; Kondo, K.; Osabe, K.; Mitsuhashi, H.; *Chem. Pharm. Bull.* **1988**, *36*, 2331.

(14) Kodama, M.; Fukuzumi, K.; Kumano, M. *Chem. Pharm. Bull.* **1989**, *37*, 1691.

(15) Takayanagi, H.; Kitanao, Y.; Morinaka, Y. *Tetrahedron Lett.* **1990**, *31*, 3317.

(16) Takahashi, T.; Yokoyama, H.; Haino, T.; Yamada, H. *J. Org. Chem.* **1992**, *57*, 3521.

(17) Kodama, M.; Yoshio, S.; Yamaguchi, S.; Fukuyama, Y.; Takayanagi, H.; Morinaka, Y.; Usui, S.; Fukazawa, Y. *Tetrahedron Lett.* **1993**, *34*, 8453.

(18) Prepared from commercially available (*E*,*E*)-farnesol by $BaMnO_4$ oxidation.

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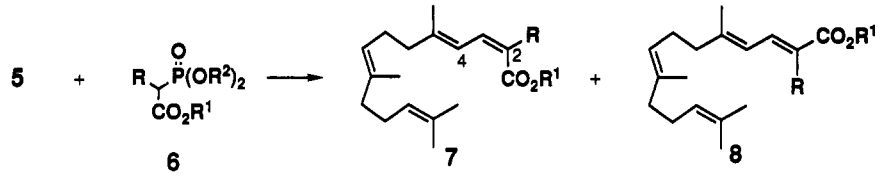
Table 1. Horner–Emmons Reactions of 5 with α-Phosphono Esters 6



entry		R	R^1	R^2	condns[a]	yield[b] (%)	2Z:2E (7:8)[d]
1	**6a**	i-Pr	Et	Et	A	59	2.3:1 (**7a:8a**)
2	**6a**	i-Pr	Et	Et	B	78	2.0:1 (**7a:8a**)
3	**6a**	i-Pr	Et	Et	C	none[c]	
4	**6b**	i-Pr	Me	CF_3CH_2	D	65	6.8:1 (**7b:8b**)
5	**6b**	i-Pr	Me	CF_3CH_2	E	none[c]	
6	**6c**	H	Me	CF_3CH_2	D	82	10.5:1 (**7c:8c**)

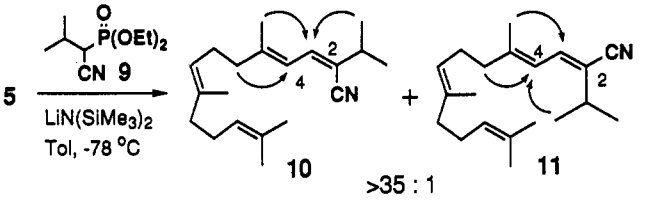
[a] A = n-BuLi, THF, −20 °C to rt, 5 h; B = n-BuLi, THF, 0 °C to rt, 5 h; C = n-BuLi, THF, −78 °C, 5 h; D = $KN(SiMe_3)_2$, THF, 18-crown-6 ether, −20 °C to rt, 5 h; E = $KN(SiMe_3)_2$, 18-crown-6 ether, −78 °C, 5 h. [b] Isolated yields. [c] See text. [d] Determined by GC analysis of crude products.

lective synthesis of the acyclic precursor for the macrocyclization, conjugated 2(*Z*),4(*E*)-dienal **3**, (2) macrocyclization of **3** using a modified protected cyanohydrin procedure, and (3) final enantioselective reduction of the resulting 14-membered ketone **2** to **1**.

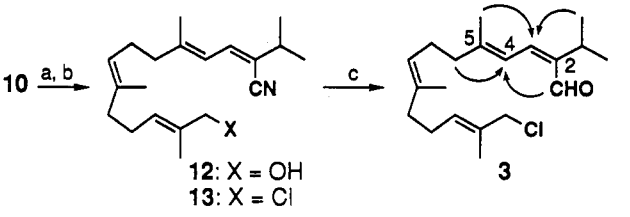
Results and Discussion

***Z*-Selective Formation of the 2(*Z*),4(*E*)-Diene Moiety.** In the first stage of the synthesis we constructed stereoselectively the conjugated 2(*Z*),(4*E*)-diene moiety which possesses a functional group convertible into an aldehyde. Predominant formation of *Z*-isomer **7a** (2*Z*:2*E* (**7a**:**8a**) = 2.7:1) was reported in the Horner–Emmons reaction of α-phosphono ester **6a** with (*E*,*E*)-farnesal (**5**)[19] and was reproduced in our experiment (2–2.3:1, by GC) as shown in Table 1. Although decreasing the reaction temperature tended to increase the *Z*-selectivity, the reaction did not take place below ca. −20 °C. Moreover, the resulting prolonged reaction time caused isomerization of the dienal moiety (by ^1H NMR and GC) and decomposition of **5**; this gave an unidentified byproduct difficult to separate from the desired adduct **7a** by usual SiO_2 flash column chromatography. To enhance the *Z*-selectivity,[20] the corresponding bis(trifluoroethyl) ester **6b**[21] was used. The reaction of **5** with **6b** in the presence of $KN(SiMe_3)_2$ (1 equiv) and 18-crown-6 ether (5 equiv)[20] gave a mixture of the methyl esters **7b** and **8b** in 65% yield with somewhat improved *Z*-selectivity (6.8:1) compared to that of **6a**. The reaction of **6b** at a low temperature resulted in decreased yield for the same reason as **6a**. Under the same reaction conditions, the reaction of **5** with bis(2,2,2-trifluoroethyl) [(methoxycarbonyl)methyl]phosphonate (**6c**) proceeded more smoothly than **6b** to give the condensation products **7c** and **8c** in a ratio of 10.5:1 in 82% yield, suggesting that the α-substituent of the phosphonate plays an important stereochemical role in Still's modification of the Horner–Emmons reaction.[20,22]

Scheme 2



Scheme 3[a]



[a] Key: (a) 2 mol % SeO_2, 80% t-BuO_2H, CH_2Cl_2; (b) PPh_3, CCl_4; (c) DIBAL, *n*-hexane, −78 °C; then 10% aqueous oxalic acid.

We found that the Horner–Emmons reaction of phosphonate nitrile **9**[23] with **5** under selected reaction conditions[24] gave fairly good results. When the anion generated from nitrile **9** in toluene by $LiN(SiMe_3)_2$ was reacted with **5** at −78 °C, the desired 2(*Z*),4(*E*)-diene nitrile **10** was almost exclusively obtained along with a small amount of the 2(*E*),4(*E*)-isomer **11** in a ratio of >35:1 (Scheme 2). The structures of **10** and **11** were confirmed by 2-D NMR experiments (NOESY) as shown in Scheme 2 (indicated by arrows), respectively. In contrast to the esters **6a** and **6b**, the reaction of the anion generated from the nitrile **9** with **5** proceeded smoothly even below ca. −20 °C. Isolated yield of **10** reached 91% by chromatography.

Transformation to the Key Intermediate 3. 2(*Z*),4(*E*)-Nitrile **10** was transformed into the key intermediate for our projected synthesis, dienal **3**, in which the terminal (*E*)-methyl group was functionalized (Scheme 3). Oxidation of **10** on treatment with 80% t-BuO_2H in the presence of a catalytic amount of SeO_2[25] in CH_2Cl_2 at 25 °C gave hydroxy nitrile **12** in 52% yield (based on the consumed **10**), which was then converted to the corresponding

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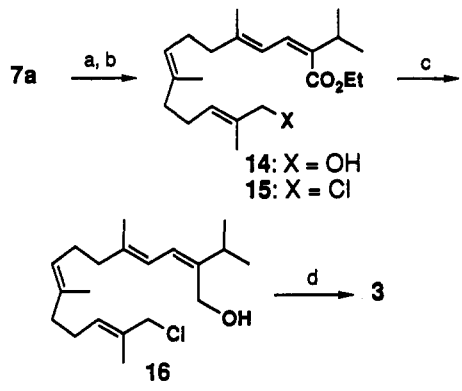
(20) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(21) Poss, M. A.; Reid, J. A. *Tetrahedron Lett.* **1992**, *33*, 1411.
(22) Although this modification has frequently been applied to natural product syntheses, the bis(trifluoroethyl)phosphono esters other than acetates or propionates did not always provide high *Z*-selectivity; see: Marshall, J. A.; DeHoff, B. S.; Cleary, D. G. *J. Org. Chem.* **1986**, *51*, 1735. Poss, M. A.; Reid, J. A. *Tetrahedron Lett.* **1992**, *33*, 1411. Xiao, X.; Prestwich, D. *Tetrahedron Lett.* **1991**, *32*, 6843. Medina, J. C.; Guajardo, R.; Kyler, K. S. *J. Am. Chem. Soc.* **1989**, *111*, 2310. Hammond, G. B.; Cox, M. B.; Wiemer, D. F. *J. Org. Chem.* **1990**, *55*, 128.
(23) Freerksen, R. W.; Selikson, S. J.; Wroble, R. R.; Kyler, K. S.; Watt, D. S. *J. Org. Chem.* **1983**, *48*, 4087.
(24) *Z*,*E* ratios were dependent on the bases and solvents used. The generality of this procedure and its application to a stereoselective synthesis of a natural product has been reported, see: Takayanagi, H. *Tetrahedron Lett.* **1994**, *35*, 1581.
(25) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.

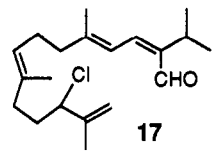
Scheme 4[a]



[a] Key: (a) 2 mol % SeO_2, 80% t-BuO_2H, CH_2Cl_2; (b) PPh_3, CCl_4; (c) DIBAL, *n*-hexane, −78 °C; (d) $BaMnO_4$, CH_2Cl_2.

chloride **13** in 93% yield with PPh_3 (1.3 equiv) in refluxing CCl_4 for 1 h. DIBAL reduction of the nitrile group in **8** at −78 °C and careful hydrolysis[26] of the resulting imine with aqueous acid (AcOH or oxalic acid) at 0 °C under an argon atmosphere gave the desired **3** accompanied by slight isomerization of the dienal moiety. By flash column chromatography on SiO_2, **3** was readily obtained as a single isomer in 87% yield in spite of its significant lability.[27] 2-D NOESY analysis (Scheme 3) showed a strong response between H-1 and H-4, H-4 and H-6, H-3 and the isopropyl group, and H-3 and Me-5, providing the 2(*Z*),4(*E*)-dienal structure in **3**; this indicated that the geometry of **10** was retained during the sequence of reactions.

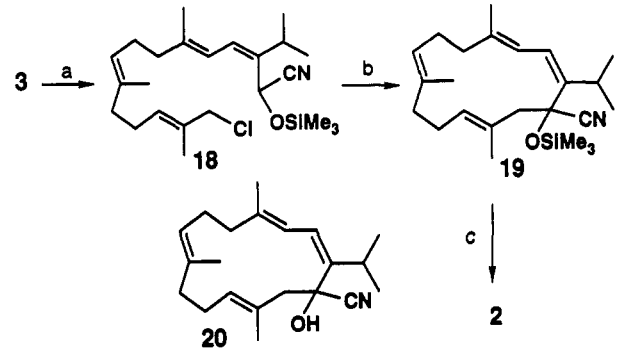
Alternatively, **3** could also be obtained starting from (2*Z*,4*E*)-ester **7a** (Scheme 4). Oxidation of the (*E*)-isopropylidene methyl group (35% yield, based on the consumed **7a**) and subsequent chlorination (96%) of the resulting allylic alcohol was carried out in a manner similar to that described for the conversion of **10** into **13**. DIBAL reduction of the chloro ester **15** thus obtained yielded the alcohol **16** in 79% yield. Oxidation of **16** with MnO_2 in n-hexane afforded the desired aldehyde **3** contaminated by nearly 15% of the rearranged chloride **17** according to



^1H NMR analysis of the characteristic exomethylene and secondary allylic chloride signals (4.96 and 4.86 ppm; 4.31 ppm (t, J = 7.2Hz), respectively); these isomers were inseparable by usual SiO_2 flash column chromatography. This difficulty was overcome by employing $BaMnO_4$ oxidation in CH_2Cl_2, and the aldehyde **3** was obtained without isomerization in 95% yield. Attempted direct reduction of **15** into **3** using 1 equiv of DIBAL was unsuccessful, leading to ca. a 1:1 mixture of alcohol **16** and recovered **15**.[28]

Macrocyclization. The unstable conjugated dienal **3** thus obtained could be cleanly converted to the cyanohydrin TMS ether **18** by addition of Me_3SiCN in the presence of a catalytic amount of KCN/18-crown-6 complex.[29] The macrocyclization reaction of **18** was immediately carried out without purification substantially according to the method of Takahashi et al.,[30] except for the use of a TMS ether[31] instead of an EE ether as a protecting group for the cyanohydrin (Scheme 5). Thus, a solution of **18** in THF was added over 50 min under argon atmosphere to a 55 °C THF solution of $LiN(SiMe_3)_2$ (3.5 equiv). The desired cyclized product **19** was obtained in 64% yield along with 10% of unexpected cyclic ketone **2** whose spectral data (^1H NMR, IR, MS) were identical with those reported[32] for **2** derived from naturally occurring **1**. On the basis of this result, direct formation of the ketone **2** was attempted without isolation of the TMS ether **19**. However, in a preliminary experiment, the isolated **18** was, surprisingly, recovered unchanged when it was dissolved in aqueous THF. We finally found that **2** could be simply obtained in 79% overall yield from **3** after chromatographic purification when the crude cyclization product was dissolved in 10% aqueous THF containing a catalytic amount of n-$Bu_4N^+F^-$ at 25 °C for 2 days under argon atmosphere. On the other hand, acid treatment of **18** (a catalytic amount of *p*-toluenesulfonic acid in methanol–ethyl ether (2:1)) furnished cyanohydrin **20**, which was stable in the acidic solution[33] but altered rapidly to **2** during workup and chromatographic purification. The proposed structure of **20** was supported by its chromatographic behavior as well as by ^1H NMR analysis[34] of a crude product containing **20**, although attempts to isolate **20** in pure form were unsuccessful.

Scheme 5[a]



[a] Key: (a) Me_3SiCN, cat. KCN/18-crown-6 ether complex; (b) $LiN(SiMe_3)_2$, THF, 55 °C; (c) n-$Bu_4N^+F^-$, 10% aqueous THF.

These results show that the intramolecular alkylation occurred regioselectively at the α-carbon without accompanying isomerization of the dienal moiety. This is

(26) The 2(*Z*),4(*E*)-dienal system of **3** was easily isomerized by prolonged exposure to even weak acid to afford a mixture of geometrical isomers.

(27) A solution of the dienal **3** is relatively stable. However, after complete evaporation of the solvent, **3** is rather labile upon storage even at −20 °C. Therefore, it is desirable that **3** be used in the next step immediately after column chromatographic purification.

(28) Baeckstrom, P.; Li, L.; Wickramaratne, M.; Norin, T. *Synth. Commun.* **1990**, *20*, 423.

(29) Tetra-*n*-butylammonium cyanide was also effective as the catalyst. However, use of zinc iodide resulted in isomerization of the conjugated-diene moiety to afford ca. a 1:3 mixture of **18** and its geometrical isomer, in which ^1H NMR spectra characteristic singlet signals due to C*H*(OTMS)-CN appeared at 4.93 and 5.33 ppm, respectively.

(30) Takahashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fukazawa, Y.; Okajima, T.; Fujise, Y. *Tetrahedron* **1987**, *43*, 5499 and references cited therein.

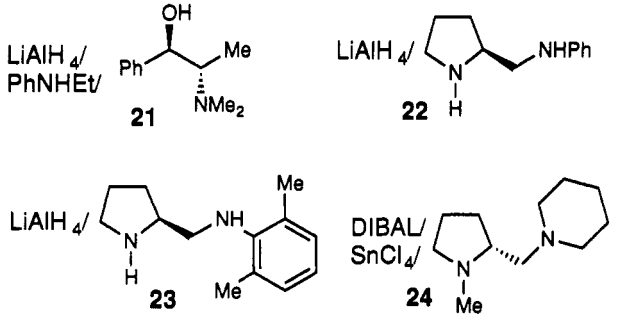
(31) Intermolecular alkylation of a cyanohydrin TMS ether of enal was reported; see: Bohlmann, F.; Steinmyer, A. *Tetrahedron Lett.* **1986**, *27*, 5359.

(32) Nakagawa, T.; Kobayashi, M.; Hayashi, K.; Mitsuhashi, H. *Chem. Pharm. Bull.* **1981**, *29*, 82.

(33) However, removal of solvent from the acidic solution resulted in prompt and complete decomposition of **20** accompanied by slight evolution of heat.

(34) ^1H NMR for **20**: δ 1.15 (d, J = 6.7 Hz), 1.19 (d, J = 6.7 Hz), 1.55 (s), 1.63 (s), 1.69 (s), 2.51 (sept, J = 6.7 Hz), 2.66 (d, J =14.1 Hz), 2.73 (d, J = 14.1 Hz), 6.22 (d, J = 11.1 Hz), 6.42 (d, J = 11.1 Hz).

Table 2. Enantioselective Reduction of Macrocyclic Ketone 2 to Sarcophytol A (1)



chiral reducing agent	yield[a] (%)	optical purity[c] (% ee)	confign
21[38]	97[b]	87	*S*
22[39,40]	78	92	*S*
23[41]	88	93	*S*
24[42]	79	42	*S*

[a] Isolated yield. [b] Yield based on 63% conversion. [c] Enantiomeric excess (ee) was determined by HPLC analysis using a chiral column.

the first example of macrocyclization from an α,β-conjugated dienal. To our surprise, the desired reaction proceeded successfully, employing a TMS ether in spite of the absence of the metal chelating effect[35] expected in an EE group. Since the previous macrocyclizations based on intramolecular alkylation of protected cyanohydrins had usually been carried out after conversion of the TMS ether into an EE ether,[30] the present direct procedure employing a TMS ether instead of an EE group considerably shortened the process.

Enantioselective Reduction of Macrocyclic Ketone 2. Reduction of the 14-membered ketone **2** with DIBAL gave racemic **1**, whose IR and ^{1}H NMR spectra agreed with those of natural **1**,[36] in 88% yield. The final remaining subject was an enantioselective reduction of **2**. Since few studies on asymmetric reduction of a macrocyclic ketone such as **2** have been reported,[37] we examined the reduction of **2** with several chiral reducing agents known to provide S-alcohols,[38-42] the same configuration as natural **1**, from acyclic ketones (Table 2). In all cases examined, $[\alpha]_D$ values obtained were positive, which indicated that the configurations of **1** formed were *S*[13] and enantioselectivity in reduction of macrocyclic ketone **2** was the same as that in acyclic ones. The chirally modified $LiAlH_4$ reagents **21–23** gave especially high enantioselectivities (87–93% ee), which were determined by chiral HPLC and high chemical yields (78–97%). In that regard, it is of great interest that higher optical yields were observed than were expected for acyclic ketones using the same reducing reagent. For example, the value of 92% ee obtained by reduction with **22** was extremely high in view of the results previously reported in which **22** provided an optical yield of only 13% ee for a simple acyclic ketone and 85% ee as the highest value for an aryl alkyl ketone.[40]

Upon a single recrystallization, the crude **1** of 93% ee obtained from **2** with 5 equiv of the asymmetric reducing reagent **23**[41] gave enantiomerically pure (>99% ee) **1**[36] as white crystals in 72% yield. The melting point and optical rotation of the synthetic **1** thus obtained showed good agreement with those of natural **1**[36] [synthetic: mp 56.5–57.5 °C, $[\alpha]_D$ +225° (c = 0.9, $CHCl_3$); natural: lit.[43] mp 55–57 °C, lit.[44] $[\alpha]_D$ +228° (c = 1.2, $CHCl_3$)]. In addition, the chromatographic (HPLC, chiral HPLC, TLC) and spectral (^{1}H and ^{13}C NMR, IR, MS) data of synthetic **1** were identical with those of the naturally occurring material.

Thus, we have succeeded in the total synthesis of **1**, a marine cembranoid which shows promise as a cancer chemopreventive agent, in a highly stereo- and enantioselective manner and were able to obtain enantiomerically pure **1**. Our current attention is focused on establishment of a more practical synthetic route toward **1**.

Experimental Section

General. All flash column chromatographies were performed on silica gel 60 (Merck) using a mixed solvent system of *n*-hexane/ethyl acetate as an eluent. ^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ solution with Me_4Si as an internal standard. TLC was performed on precoated TLC plates, silica gel $60F_{254}$ (Merck). All reactions were carried out under argon or nitrogen.

Ethyl (2*Z*,4*E*,8*E*,12*E*)- and Ethyl (2*E*,4*E*,8*E*,12*E*)-2-(1-Methylethyl)-5,9,13-trimethyl-2,4,8,12-tetradecatetraenoate (7a) and (8a), respectively. Although the synthesis of **7a** by the Horner–Emmons reaction was reported,[19] experimental details and spectral data were not described. To a stirred, cooled (−78 °C) solution of phosphono ester **6a** (4.4 g, 16.5 mmol) in THF (90 mL) was added 11 mL of 1.49 M n-BuLi in THF. The resulting solution was stirred at the same temperature for 30 min and then was warmed to 0 °C, and (*E*,*E*)-farnesal (**5**) (3.4 g, 15.5 mmol) was slowly added. The mixture was stirred for 5 h, allowed to gradually warm to room temperature, quenched with saturated NH_4Cl, and partitioned between ether and water. The organic layer was washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (*n*-hexane–ethyl acetate (100:1)) to afford 2*Z* ester **7a** (1.6 g, 31%), a 1:1 mixture (by ^{1}H NMR) of **7a** and 2*E* ester **8a** (2.3 g, 45%), and **8a** (135 mg, 3%). GC analysis of the crude product before chromatography indicated a 2.0:1 mixture of **7a** and **8a**. **7a**: oil; IR (film) 1710, 1635 cm^{-1}; ^{1}H NMR (250 MHz) δ 1.09 (d, J = 6.9 Hz, 6H), 1.31 (t, J = 7.0 Hz, 3H), 1.58 (s, 3H × 2), 1.66 (s, 3H), 1.85 (s, 3H), 1.9–2.1 (m, 4H), 2.11 (m, 4H), 2.78 (sept, J = 6.9 Hz, 1H), 4.23 (q, J = 7.0 Hz, 2H), 5.09 (m, 2H), 6.52 (d, J = 11.7 Hz, 1H), 6.55 (d, J = 11.7 Hz, 1H); MS m/z 332 (M^+), 287, 69 (bp). Anal. Calcd for $C_{22}H_{36}O_2$: C, 79.58; H, 10.93. Found: C, 79.38; H, 11.02.

8a: oil; IR (film) 1710, 1635 cm^{-1}; ^{1}H NMR (250 MHz) δ 1.17 (d, J = 7.0 Hz, 6H), 1.28 (t, J = 7.3 Hz, 3H), 1.57 (s, 3H), 1.58 (s, 3H), 1.65 (s, 3H), 1.85 (d, J = 7.0 Hz, 3H), 1.9–2.1 (m, 4H), 2.16 (bs, 4H), 3.03 (sept, J = 7.0 Hz, 1H), 4.17 (q, J = 7.3 Hz, 2H), 5.06 (m, 2H), 6.19 (d, J = 11.9 Hz, 1H), 7.30 (d, J = 11.9 Hz, 1H); MS m/z 366 (M^+), 332, 287, 69 (bp).

Methyl (2*Z*,4*E*,8*E*,12*E*)-2-(1-Methylethyl)-5,9,13-trimethyl-2,4,8,12-tetradecatetraenoate (7b). To a stirred, cooled (−78 °C) mixture of phosphonate **6b** (420 mg, 1.16 mmol) and 18-crown-6 (1.32g, 5 mmol) in THF (20 mL) was added 1.93 mL of 0.5 M $KN(SiMe_3)_2$ in toluene. The resulting solution was stirred at the same temperature for 30 min and then was warmed to −20 °C, and **5** (198 mg, 0.89 mmol) was added. The mixture was stirred for 5 h and allowed to gradually warm to room temperature. The similar workup as described above afforded a crude product of ester as a 6.8:1 mixture of 2*Z*,4*E* and 2*E*,4*E* isomers **7b** and

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(44) Specific rotation of +141° (c = 1.10, $CHCl_3$) had been recorded[3,36] for natural **1**.

8b according to GC analysis, from which **7b** (58 mg, 20%) and a mixture of **7b** and **8b** (a ratio of ca. 5:1 by 1H NMR, respectively; 129 mg, 45%) were obtained by flash column chromatography (100:1). **7b**: oil; IR (film) 1710, 1635 cm^{-1}; ^1H NMR (500 MHz) δ 1.10 (d, J = 6.8 Hz, 6H), 1.31 (t, J = 7.0 Hz, 3H), 1.60 (s, 3H × 2), 1.68 (s, 3H), 1.83 (s, 3H), 1.98 (m, 2H), 2.05 (m, 2H), 2.14 (m, 4H), 2.80 (sept, J = 6.8 Hz, 1H), 3.78 (s, 3H), 5.10 (m, 2H), 6.57 (s, 2H); ^{13}C NMR (125 MHz) δ 16.0, 16.7, 17.7, 22.1, 25.7, 26.2, 26.5, 26.7, 31.7, 39.7, 40.6, 51.2, 121.7, 123.7, 124.3, 130.0, 131.3, 133.5, 135.8, 145.0, 169.2; MS m/z 318 (M^+), 182, 69 (bp). Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.91; H, 10.87.

Methyl (2*Z*,4*E*,8*E*,12*E*)- and Methyl (2*E*,4*E*,8*E*,12*E*)-5,9,-13-Trimethyl-2,4,8,12-tetradecatetraenoate (7c) and (8c), Respectively. The procedure described above for ester **7b** was followed using 830 mg (2.6 mmol) of phosphonate **6c**, 4.8 mL of 0.5 M $KN(SiMe_3)_2$ in toluene, and 2.6 g of 18-crown-6 (10 mmol) in THF (48 mL) to which 440 mg (2.0 mmol) of **5** was added at −20 °C. The mixture was stirred for 5 h and allowed to gradually warm to room temperature. The similar workup as described above afforded a crude product of ester as a 10.5:1 mixture of 2*Z*,4*E* and 2*E*,4*E* isomers **7c** and **8c** according to GC analysis, from which **7c** (431 mg, 78%) and **8c** (23 mg, 4%) were obtained by flash column chromatography (100:1). **7c**: oil; IR (film) 1710, 1635 cm^{-1}; ^1H NMR (500 MHz) δ 1.60 (s, 3H), 1.61 (s, 3H), 1.68 (s, 3H), 1.86 (s, 3H), 1.98 (m, 2H), 2.05 (m, 2H), 2.20 (m, 4H), 3.72 (s, 3H), 5.09 (bt, J = 6.5 Hz, 1H), 5.12 (bt, J = 6.5 Hz, 1H), 5.58 (d, J = 11.4 Hz, 1H), 6.89 (t, J = 11.4 Hz, 1H), 7.20 (d, J = 11.4 Hz, 1H); ^{13}C NMR (125 MHz) δ 16.0, 16.7, 17.6, 25.7, 26.2, 26.4, 26.7, 39.7, 40.6, 50.9, 114.5, 121.5, 123.4, 124.3, 131.3, 135.7, 140.7, 150.4, 167.2; MS m/z 276 (M^+), 140, 69 (bp). Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.15; H, 10.34.

8c: oil; IR (film) 1710, 1635 cm^{-1}; ^1H NMR (500 MHz) δ 1.60 (s, 3H × 2), 1.68 (s, 3H), 1.89 (s, 3H), 1.97 (m, 2H), 2.05 (m, 2H), 2.16 (m, 4H), 3.74 (s, 3H), 5.08 (bm, 1H), 5.78 (d, J = 15.2 Hz, 1H), 5.99 (d, J = 11.6 Hz, 1H), 7.59 (dd, J = 11.6, 15.2 Hz, 1H); ^{13}C NMR (125 NHz) δ 16.0, 17.4, 17.7, 25.7, 26.2, 26.7, 39.7, 40.3, 51.4, 118.4, 123.2, 123.3, 124.2, 131.4, 135.9, 141.2, 150.0, 168.1; MS m/z 285 (M^+), 242, 69 (bp). Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.04; H, 10.34.

(2*Z*,4*E*,8*E*,12*E*)- and (2*E*,4*E*,8*E*,12*E*)-2-(1-Methylethyl)-5,9,13-trimethyl-2,4,8,12-tetradecatetraenenitrile (10) and (11), Respectively. To a solution of phosphononitrile **9** (710 mg, 3.25 mmol) in toluene (27 mL) was gradually added 3 mL of 1 M $LiN(SiMe_3)_2$ in *n*-hexane with stirring at −78 °C under argon atmosphere. After 30 min, (*E*,*E*)-farnesal (**5**) (550 mg, 2.0 mmol) was added, and the mixture was gradually warmed to room temperature overnight with continuous stirring. After addition of water, the organic layer was separated, washed with water and then brine, and dried over $MgSO_4$. The solvent was evaporated to give a crude product of nitrile as a >35:1 mixture of 2*Z*,4*E* and 2*E*,4*E* isomers **10** and **11** according to GC analysis, from which **10** (520 mg, 91%), **11** (12 mg, 2%), and ca. a 1:1 mixture of **10** and **11** (17 mg, 3%) were obtained by flash column chromatography (100:1). **10**: oil; IR (film) 2210, 1640, 1450 cm^{-1}; ^1H NMR (500 MHz) δ 1.17 (d, J = 6.8 Hz, 6H), 1.60 (s, 6H), 1.61 (s, 3H), 1.68 (s, 3H), 1.83 (d, J = 1.0 Hz, 3H), 1.98 (m, 2H), 2.08 (m, 2H), 2.17 (s, 4H), 2.52 (sept, J = 6.8 Hz, 1H), 5.08 (m, 2H), 6.28 (d, J = 12.0 Hz, 1H), 6.82 (d, J = 12.0 Hz, 1H); ^{13}C NMR (125 MHz) δ 16.0, 17.3, 17.6, 21.6, 25.7, 26.3, 26.7, 33.3, 39.6, 40.2, 117.5, 117.6, 121.8, 123.2, 124.3, 131.3, 135.9, 137.6, 147.83; MS m/z 285 (M^+), 242, 69 [base peak (bp)]; HRMS calcd for $C_{20}H_{31}N$ m/z 285.2456, found m/z 285.2454. Anal. Calcd for $C_{20}H_{31}N$: C, 84.15; H, 10.95; N, 4.91. Found: C, 84.19; H, 11.12; N, 4.89.

11: oil; IR (film) 2210, 1640, 1450 cm^{-1}; ^1H NMR (500 MHz) δ 1.14 (d, J = 6.9 Hz, 6H), 1.60 (s, 3H), 1.61 (s, 3H), 1.67 (s, 3H), 1.84 (s, 3H), 1.98 (m, 2H), 2.06 (m, 2H), 2.18 (s, 4H), 2.90 (sept, J = 6.9 Hz, 1H), 5.08 (bt, J = 6.5 Hz, 2H), 6.12 (d, J = 11.8 Hz, 1H), 6.88 (d, J = 11.8 Hz, 1H); ^{13}C NMR (125 NHz) δ 16.0, 17.2, 17.7, 21.3 × 2, 25.7, 26.2, 26.7, 27.0, 39.7, 40.5, 117.7, 118.8, 119.9, 123.1, 124.2, 131.4, 136.0, 137.8, 149.2; MS m/z 285 (M^+), 242, 69 (bp). Anal. Calcd for $C_{20}H_{31}N$: C, 84.15; H, 10.95; N, 4.91. Found: C, 83.85; H, 11.03; N, 4.52.

(2*Z*,4*E*,8*E*,12*E*)-14-Hydroxy-2-(1-methylethyl)-5,9,13-trimethyl-2,4,8,12-tetradecatetraenenitrile (12). The method of Umbreit and Sharpless[25] was employed. To a suspension of SeO_2 (58 mg), 2-hydroxybenzoic acid (365 mg), and 80% t-BuOOH (11.6 mL) in 10.5 mL of CH_2Cl_2 was added the nitrile **10** (7.65 g, 26.8 mmol) on a water bath. The resulting mixture was stirred at room temperature for 30 h and then diluted with ether. The organic layer was washed with saturated Na_2SO_3, water, and brine and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo to afford a crude oil, which was chromatographed on SiO_2 (6:1) to give the alcohol **12** (2.53 g, 52% based on the consumed **12**) as an oil: IR (film) 3450, 2210, 1635, 1445 cm^{-1}; ^1H NMR (500 MHz) δ 1.17 (d, J = 6.9 Hz, 6H), 1.62 (s, 3H), 1.67 (s, 3H), 1.84 (s, 3H), 2.03 (t, J = 7.5 Hz, 2H), 2.13 (t, J = 7.5 Hz, 2H), 2.18 (s, 4H), 2.53 (sept, J = 6.9 Hz, 1H), 3.99 (bs, 2H), 5.11 (bm, 1H), 5.39 (bt, J = 5.5 Hz, 1H), 6.28 (d, J = 11.5 Hz, 1H), 6.83 (d, J = 11.5 Hz, 1H); ^{13}C NMR (125 MHz) δ 13.7, 16.0, 17.3, 21.6 × 2, 26.1, 26.2, 33.3, 39.2, 40.2, 68.9, 117.5, 117.6, 121.8, 123.4, 125.9, 134.8, 135.5, 137.6, 147.7; MS m/z 301 (M^+), 284, 93 (bp). Anal. Calcd for $C_{20}H_{31}NO$: C, 79.68; H, 10.37; N, 4.65. Found: C, 79.84; H, 10.70; N, 4.59.

(2*Z*,4*E*,8*E*,12*E*)-14-Chloro-2-(1-methylethyl)-5,9,13-trimethyl-2,4,8,12-tetradecatetraenenitrile (13). A solution of the alcohol **12** (904 mg, 3.0 mmol) and triphenylphosphine (1.02 g, 3.9 mmol) in 2.0 mL of CCl_4 was stirred at reflux for 1 h. Most of the CCl_4 was removed in vacuo, and *n*-hexane was added to the residue. The resultant mixture was filtered and washed, and the filtrate was concentrated to give a residue, which was purified by flash column chromatography (10:1), affording 890 mg (93%) of chloride **13**: oil; IR (film) 2215, 1635, 1445 cm^{-1}; ^1H NMR (500 MHz) δ 1.17 (d, J = 6.8 Hz, 6H), 1.61 (s, 3H), 1.73 (s, 3H), 1.83 (s, 3H), 2.03 (bt, J = 7.1 Hz, 2H), 2.13 (bt, J = 7.1 Hz, 2H), 2.18 (s, 4H), 2.53 (sept, J = 6.8 Hz, 1H), 4.01 (s, 2H), 5.10 (bm, 1H), 5.50 (bt, J = 5.5 Hz, 1H), 6.28 (d, J = 11.5 Hz, 1H), 6.82 (d, J = 11.5 Hz, 1H); ^{13}C NMR (125 MHz) δ 14.1, 16.0, 17.4, 21.6 × 2, 26.3, 26.6, 33.3, 38.8, 40.1, 52.5, 117.5, 117.7, 121.8, 123.8, 130.6, 131.7, 135.2, 137.6, 147.7; MS m/z 319 (M^+), 284, 81 (bp); HRMS calcd for $C_{20}H_{30}NCl$ m/z 319.2066, found m/z 319.2026. Anal. Calcd for $C_{20}H_{30}NCl$: C, 75.09; H, 9.45; N, 4.38. Found: C, 75.28; H, 9.67, N, 4.39.

(2*Z*,4*E*,8*E*,12*E*)-14-Chloro-2-(1-methylethyl)-5,9,13-trimethyl-2,4,8,12-tetradecatetraenenal (3). To a solution of nitrile **13** (890 mg, 2.78 mmol) in 30 mL of *n*-hexane was added a 1 M solution (4.2 mL) of DIBAL in toluene at −78 °C under argon atmosphere, and the mixture was stirred at the same temperature for 1 h. Water (2 mL) was added to the mixture, and the cooling bath was removed. The mixture was vigorously stirred, and the resultant solid was filtered and washed with *n*-hexane. The filtrate was stirred with 10% oxalic acid at 0 °C for 2 h, washed with water, and dried over anhydrous $MgSO_4$. Removal of solvent left an oil, which was purified by flash column chromatography (20:1), affording 781 mg (87%) of aldehyde **3**: oil; IR (film) 1670, 1630, 1445 cm^{-1}; ^1H NMR (250 MHz) δ 1.04 (d, J = 7.0 Hz, 6H), 1.59 (bs, 3H), 1.70 (bs, 3H), 1.87 (d, J = 1.0 Hz, 3H), 1.9–2.2 (m, 8H), 2.89 (sept, J = 7.0 Hz, 1H), 3.98 (bs, 2H), 5.09 (m, 1H), 5.47 (bt, J = 6.5 Hz, 1H), 6.82 (d, J = 12.0 Hz, 1H), 7.11 (d, J = 12.0 Hz, 1H), 10.27 (s, 1H); ^{13}C NMR (125 MHz) δ 14.1, 16.0, 16.7, 22.0 × 2, 26.3, 26.6, 27.1, 38.2, 40.7, 52.5, 117.9, 123.8, 130.5, 131.7, 135.2 , 138.0, 142.2, 148.3, 190.5; MS m/z 322 (M^+), 307, 137 (bp). Anal. Calcd for $C_{20}H_{31}OCl$: C, 74.39; H, 9.68; Cl, 10.98. Found: C, 74.59; H, 9.90, Cl, 11.15.

Aldehyde 3 from 16. To a solution of alcohol **16** (492 mg, 1.5 mmol) in 22 mL of CH_2Cl_2 was added powdered $BaMnO_4$ (8.5 g). The mixture was stirred for 8 h at room temperature, filtered, and washed. The filtrate and washing were combined and concentrated to an oil which was purified by flash column chromatography (15:1) affording **3** (468 mg, 95%).

Ethyl (2*Z*,4*E*,8*E*,12*E*)-14-Hydroxy-2-(1-methylethyl)-5,9,-13-trimethyl-2,4,8,12-tetradecatetraenoate (14). The method of Umbreit and Sharpless[25] as detailed above for **10** was followed using SeO_2 (73 mg, 0.67 mmol), 2-hydroxybenzoic acid (456 mg, 3.3 mmol), and 80% t-BuOOH (14.5 mL) in 13 mL of CH_2Cl_2 to which was added the ester **7a** (11.3 g, 33.8 mmol). Following workup and flash column chromatography (5:1) as described above, alcohol **14** (2.8 g, 35% based on the consumed **7a**) was obtained as an oil: IR (film) 3440, 1710, 1635 cm^{-1}; ^1H NMR (250 MHz) δ 1.08 (d, J = 6.8 Hz, 6H), 1.30 (s, 3H), 1.58 (s, 3H), 1.63 (s, 3H), 1.79 (s, 3H), 1.98 (m, 2H), 2.0–2.2 (m, 6H), 2.77 (sept, J = 6.8 Hz, 1H), 3.95 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 5.10 (bm,

1H), 5.35 (bt, J = 7.3 Hz, 1H), 6.52 (d, J = 11.7 Hz, 1H), 6.55 (d, J = 11.7 Hz, 1H); MS m/z 348 (M^+), 331, 285, 43 (bp). Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 75.79; H, 10.58.

Ethyl (2*Z*,4*E*,8*E*,12*E*)-14-Chloro-2-(1-methylethyl)-5,9,13-trimethyl-2,4,8,12-tetradecatetraenoate (15). The procedure described for **13** was employed with 713 mg (2.03 mmol) of alcohol **14**. Flash column chromatography (20:1) of the residue afforded 720 mg (96%) of chloride **15** as an oil: IR (film) 1710, 1635, 1445 cm^{-1}; ^1H NMR (250 MHz) δ 1.09 (d, J = 6.9 Hz, 6H), 1.31 (t, J = 7.1 Hz, 3H), 1.57 (bs, 3H), 1.70 (bs, 3H), 1.80 (bs, 3H), 1.9–2.2 (m, 8H), 2.78 (sept, J = 6.9 Hz, 1H), 3.98 (bs, 2H), 4.23 (q, J = 7.1 Hz), 5.10 (m, 1H), 5.47 (bt, J = 6.5 Hz, 1H), 6.53 (d, J = 12.0 Hz, 1H), 6.54 (d, J = 12.0 Hz, 1H); MS m/z 366 (M^+), 331, 121 (bp). Anal. Calcd for $C_{22}H_{35}O_2$: C, 72.00; H, 9.61, Cl, 9.66. Found: C, 72.04; H, 9.75, Cl, 9.47.

(2*Z*,4*E*,8*E*,12*E*)-14-Chloro-2-(1-methylethyl)-5,9,13-trimethyl-2,4,8,12-tetradecatetraene-1-ol (16). To a stirred solution of 670 mg (1.81 mmol) of ester **14** in 20 mL of toluene was added 4 mL of 1 M DIBAL in toluene at −78 °C under argon atmosphere. The resulting mixture was stirred for 30 min at the same temperature and then added with 1.5 mL of water and, after removing the cooling bath, vigorously stirred. Anhydrous $MgSO_4$ was added, and the mixture was further stirred and filtered. The filtrate was concentrated in vacuo to afford a colorless oil, which was purified by flash column chromatography (12:1), yielding 492 mg (79%) of alcohol **16**: oil; IR (film) 3360 cm^{-1}; ^1H NMR (500 MHz) δ 1.06 (d, J = 6.8 Hz, 6H), 1.58 (bs, 3H), 1.70 (bs, 3H), 1.75 (bs, 3H), 1.9–2.2 (m, 8H), 2.47 (sept, J = 6.8 Hz, 1H), 3.98 (bs, 2H), 4.23 (bs, 2H), 5.09 (m, 1H), 5.47 (bt, J = 6.7 Hz, 1H), 6.13 (d, J = 12.0 Hz, 1H), 6.16 (d, J = 12.0 Hz, 1H); ^{13}C NMR (125 MHz) δ 14.1, 16.0, 16.5, 22.0 × 2, 26.55, 26.58, 33.9, 38.8, 40.3, 52.5, 59.6, 119.6, 122.2, 124.5, 130.6, 131.5, 134.6, 139.5, 144.5; MS m/z 324 (M^+), 287, 71 (bp). Anal. Calcd for $C_{20}H_{33}OCl$: C, 73.93; H, 10.24. Found: C, 73.37; H, 10.26.

(3*Z*,5*E*,9*E*,13*E*)-15-Chloro-3-(1-methylethyl)-6,10,14-trimethyl-2-[(trimethylsilyl)oxy]-3,5,9,13-pentadecatetraenenitrile (18). To a mixture of 468 mg (1.44 mmol) of aldehyde **3** and 0.25 mL (1.87 mmol) of trimethylsilyl cyanide was added a catalytic amount of KCN/18-crown-6 complex while stirring under nitrogen atmosphere at 0 °C. After 2 h, excess trimethylsilyl cyanide was removed in vacuo to give 610 mg (quantitative) of cyanohydrin TMS ether **18**, which was used in the next step without further purification. **18**: oil; IR (film) 2320, 1445 cm^{-1}; ^1H NMR (250 MHz) δ 0.19 (s, 9H), 1.11 (d, J = 6.9 Hz, 3H), 1.15 (d, J = 6.9 Hz, 3H), 1.60 (bs, 3H), 1.71 (bs, 3H), 1.77 (bs, 3H), 1.9–2.2 (m, 8H), 2.64 (sept, J = 6.9 Hz, 1H), 3.99 (bs, 2H), 5.11 (m, 1H), 5.33 (s, 1H), 5.48 (bt, J = 6.5 Hz, 1H), 6.04 (d, J = 11.3 Hz, 1H), 6.25 (d, J = 11.3 Hz, 1H); ^{13}C NMR (125 MHz) δ −0.3, 14.1, 16.0, 16.7, 23.1, 23.2, 26.5, 26.6, 30.8, 38.8, 40.4, 52.5, 59.7, 118.5, 119.4, 123.3, 124.2, 130.6, 131.7, 134.9, 139.1, 142.2; MS m/z 421 (M^+), 263, 224, 181, 137, 73 (bp).

(2*Z*,4*E*,8*E*,12*E*)-2-(1-Methylethyl)-5,9,13-trimethyl-1-[(trimethylsilyl)oxy]-2,4,8,12-cyclotetradecatetraene-1-carbonitrile (19) and (2*Z*,4*E*,8*E*,12*E*)-2-(1-Methylethyl)-5,9,13-trimethyl-2,4,8,12-cyclotetradecatetraen-1-one (2). The method of Takahashi et al.[30] was employed. A solution of 378 mg (0.895 mmmol) of the foregoing cyanohydrin TMS ether **18** in 15 mL of THF was added with stirring under an argon atmosphere over 50 min to a 55 °C solution of 5 mL of 1 M $LiN(SiMe_3)_2$ in 20 mL of THF. The resultant mixture was stirred at the same temperature for 20 min and poured into a mixture of brine (30 mL) and n-hexane (20 mL) containing 50 g of ice. The organic layer was separated and extracted with n-hexane and ether (5:1, 30 mL) and dried over anhydrous $MgSO_4$. Removal of the solvent left an oil that was purified by flash column chromatography (60:1), providing 267 mg (77%) of macrocyclic ketone cyanohydrin TMS ether **19** and 53 mg (15%) of macrocyclic ketone **2**. **19**: oil; IR (film) 2214, 1705, 1647 cm^{-1}; ^1H NMR (500 MHz) δ 0.25 (s, 9H), 1.11 (d, J = 6.7 Hz, 3H), 1.17 (d, J = 6.7 Hz, 3H), 1.52 (s, 3H), 1.64 (s, 3H), 1.72 (d, J = 1.3 Hz, 3H), 2.1–2.2 (m, 8H), 2.51 (sept, J = 6.7 Hz, 1H), 2.60 (d, J = 14.2 Hz, 1H), 2.67 (d, J = 14.2 Hz, 1H), 4.96 (bt, J = 6.1 Hz, 1H), 5.18 (bt, J = 5.6 Hz, 1H), 6.19 (d, J = 11.8 Hz, 1H), 6.47 (d, J = 11.8 Hz, 1H); ^{13}C NMR (125 MHz) δ 1.07, 16.4, 16.7, 18.3, 24.5, 24.7, 24.9, 25.2, 30.7, 37.8, 39.3, 52.2, 121.9, 122.6, 123.8, 127.8, 132.1, 134.0, 138.0, 140.6; MS m/z 385 (M^+), 342, 274, 249, 206 (bp); HRMS calcd for $C_{24}H_{39}NOSi$ m/z 385.2800, found m/z 385.2803.

2: oil; IR (film) 1680, 1650 cm^{-1}; ^1H NMR (250 MHz) δ 1.06 (d, J = 6.9 Hz, 6H), 1.45 (s, 3H), 1.70 (bs, 3H), 1.75 (d, J = 1.3 Hz, 3H), 2.05–2.15 (m, 8H), 2.66 (sept, J = 6.9 Hz, 1H), 3.13 (s, 2H), 4.92 (bt, J = 6.5 Hz, 1H), 4.99 (bt, J = 6.5 Hz, 1H), 5.87 (d, J = 11.9 Hz, 1H), 6.19 (dd, J = 11.9, 1.3 Hz, 1H); ^{13}C MNR (125 MHz) δ 15.3, 16.5, 18.1, 21.8 × 2, 24.8, 25.2, 30.8, 38.6, 39.7, 51.7, 122.6, 123.4, 124.7, 128.2, 128.4, 134.4, 140.5, 146.7, 206.9; MS m/z 286 (M^+), 271, 243, 203, 135 (bp); HRMS calcd for $C_{20}H_{30}O$ m/z 286.2296, found m/z 286.2320. [IR, ^1H NMR and MS data were identical with those[32] reported for **2** derived from natural **1**.]

Macrocyclic Ketone 2. A. From Cyanohydrin TMS Ether 19. To a solution of 657 mg (1.7 mmol) of TMS ether **19** in 10 mL of 10% aqueous THF was added 0.02 mL of 1 M n-$Bu_4N^+F^-$ in THF under an argon atmosphere. The mixture was stirred at room temperature for 2 days. Most of the THF was removed in vacuo, and the residue was dissolved in ethyl ether, which was dried over $MgSO_4$, filtered, concentrated, and subjected to flash column chromatography (30:1) to obtain the ketone **2** (411 mg, 85%).

B. Without Isolation of TMS Ether 19. A crude macrocyclization product obtained by employing the above procedures starting from 640 mg (2.0 mmol) of aldehyde **3** was dissolved in 12 mL of 10% aqueous THF, and 0.04 mL of 1 M n-$Bu_4N^+F^-$ in THF was added to the mixture. After the mixture was allowed to stand for 2 days at room temperature, following workup and chromatographic purification as described above, there was 451 mg (79%, overall yield from **3**) of **2**.

DIBAL Reduction of 2. To a solution of ketone **2** (137 mg, 0.48 mmol) in toluene (2.5 mL) was dropwise added at −78 °C with stirring 0.6 mL of 1 M DIBAL in toluene. After addition of water (0.25 mL) and stirring, followed by drying over $MgSO_4$, filtration, and concentration, the residue was purified by flash column chromatography (12:1) to obtain 125 mg (88%) of racemic **1** as an oil: IR (film) 3330, 1660, 1600 cm^{-1}; ^1H NMR (500 MHz) δ 1.05 (d, J = 6.5 Hz, 3H), 1.11 (d, J = 6.5 Hz, 3H), 1.47 (s, 3H), 1.60 (s, 3H), 1.74 (s, 3H), 2.58 (sept, J = 6.5 Hz, 1H), 4.98 (m, 3H), 5.99 (d, J = 11.5 Hz, 1H), 6.14 (d, J = 11.5 Hz, 1H); ^{13}C NMR (125 MHz) δ 15.5, 16.3, 18.2, 24.4, 24.5, 25.4, 25.5, 27.1, 38.8, 39.6, 44.5, 69.9, 120.5, 121.2, 124.5, 125.4, 131.3, 134.6, 136.0, 146.9; MS m/z 288 (M^+), 137 (bp), 109. [The spectra were identical with those of an authentic sample.]

Enantioselective Reduction of 2. A. With 21. The method of Terashima et al. was employed.[38] To a suspension of $LiAlH_4$ (80 mg, 2.11 mmol) in diethyl ether (5 mL) was added dropwise a solution of (1*R*,2*S*)-(−)-*N*-methylephedrine (**21**, 380 mg, 2.12 mmol) in diethyl ether (5 mL) at room temperature over 5 min under argon atmosphere. After refluxing with stirring for 1 h, *N*-ethylaniline (0.53 mL, 4.23 mmol) was dropwise added to the mixture over 5 min. The resulting mixture was refluxed for an additional 1 h and then cooled to −72 °C; thereto was dropwise added a solution of ketone **2** (136 mg, 0.475 mmol) in diethyl ether (3 mL), and the mixture was stirred at the same temperature for 6 h. After 1 N hydrochloric acid (9 mL) was added to the mixture, the organic layer was separated, washed with 3 N hydrochloric acid (5 mL × 2), and dried over anhydrous $MgSO_4$. Removal of solvent and flash column chromatography on SiO_2 (12:1) afforded 51 mg (37%) of unreacted ketone **2** and 80 mg (60%) of (+)-sarcophytol A (**1**) of 84% ee as an oil. Enantiomeric excess was determined by HPLC analysis using a chiral column (Chiralcell OD, Daicel Chemical Industry K.K.) using n-hexane/EtOAc (100:1) as an eluent.

B. With 22. To a solution of $LiAlH_4$ in diethyl ether (2.9 mL, 2.0 mmol, 0.68 M) (5 mL) was dropwise added a solution of (*S*)-2-(anilinomethyl)pyrrolidine (**22**, 296 mg, 1.68 mmol) in diethyl ether (3 mL) with stirring at rt over 10 min under an argon atmosphere. The mixture was stirred for an additional 1 h and then cooled to −72 °C. To the mixture was dropwise added a solution of **2** (162 mg, 0.56 mmol) in diethyl ether (5 mL). After stirring at −72 °C for 1 h, saturated aqueous $NaSO_4$ (1 mL) was added to the mixture, which was then stirred at room temperature for 10 min. After addition of 1 N aqueous HCl (15 mL) and diethyl ether (20 mL), the organic layer was separated, washed with a saturated brine (20 mL), and dried over $MgSO_4$. Removal

of solvent and flash column chromatography on SiO_2 (12:1) afforded optically active 1 (126 mg, 78%) of 92% ee (by the chiral HPLC), $[\alpha]_D$ +210° (c 0.37, $CHCl_3$), which crystallized on standing in a refrigerator for a day.

C. With 23. The method detailed above with **22** was followed using 2.9 mL of 0.62 M $LiAlH_4$ in ethyl ether, 490 mg (2.4 mmol) of (*S*)-2-(2,6-xylidinomethyl)pyrrolidine (**23**)[41] to which was added 69 mg (0.24 mmol) of the ketone **2**. Following workup and flash column chromatography there was obtained 61 mg (88%) of (+)-**1** as crystals: 93% ee; $[\alpha]_D$ +204° (*c* = 0.27, $CHCl_3$), of which recrystallization from aqueous ethanol gave 48 mg (72%) of **1** of >99% ee; $[\alpha]_D$ +225° (*c* = 0.9, $CHCl_3$); mp 56.5–57.5 °C. [The data with natural **1**[36] were >99% ee; $[\alpha]_D$ +228° (*c* = 1.2, $CHCl_3$); 55–57 °C,[43] respectively.]

D. With 24. To a cooled (−72 °C) suspension of $SnCl_4$ (382 mg, 2.0 mmol) and (*R*)-1-methyl-2-(piperidinomethyl)pyrrolidine[42] (**24**, 366 mg, 2.0 mmol) in CH_2Cl_2 (6 mL) was added 1 mL of 1 M DIBAL in toluene. After 10 min stirring, a solution of **2** (100 mg, 0.35 mmol) in CH_2Cl_2 (3 mL) was added to the mixture, which was stirred for 4 h, and then the stirring was continued at room temperature for 30 min with saturated aqueous NaCl (3 mL). Resultant precipitates were filtered through Celite, and the filtrate was dried over Na_2SO_4 and evaporated in vacuo to give a residue which was purified by flash column chromatography affording 79 mg (79%) of (+)-**1** as an oil: 42% ee; $[\alpha]_D$ +102° (*c* = 0.54, $CHCl_3$).

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Supplementary Material Available: 2-D NOESY spectra of **3**, **10**, and **11**, ^1H NMR spectra of **2**, **18**, and **19**, and a chiral HPLC chart of natural and synthetic **1** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.