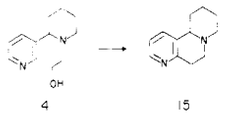

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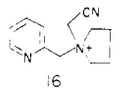
(6) F. Haglid, *Acta Chem. Scand.*, **21**, 580 (1967).
(7) E. Leete, M. R. Chedekel, and G. B. Bodem, *J. Org. Chem.*, **37**, 4465 (1972).
(8) This keto nitrile has been obtained independently by E. B. Sanders, H. V. Secor, and J. I, Seeman, *J. Org. Chem.*, **41**, 2658 (1976), **43** 324 (1978), via the Sommelet–Hauser rearrangement product of compound **16.**



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(9) Two equivalents of butyllithium are required since one is consumed by reaction with the NH group of the pyrrolidine ring.
(10) J. C. Sheehan, P. A. Cruickshank, and G. L. Boshart, *J. Org. Chem.*, **26**, 2525 (1961).
(11) (a) S. V. Kessar, *Experientia*, **18**, 56 (1962); (b) H. S. Aaron, *Chem. Ind. (London)*, 1338 (1965); (c) A. E. Theobald and R. G. Lingard, *Spectrochim. Acta, Part A*, **24a**, 1245 (1968); (d) H. S. Aaron and C. P. Ferguson, *Tetrahedron Lett.*, 6191 (1968); (e) R. Cahill, T. A. Crabb, and R. F. Newton, *Org. Magn. Reson.*, **3**, 263 (1971).
(12) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).
(13) J. F. Whidby and J. I. Seeman, *J. Org. Chem.*, **41**, 1585 (1976).
(14) N. K. Hart, S. R. Johns, and J. A. Lamberton *J. Chem. Soc., Chem. Commun.*, 460 (1971).
(15) Melting points are uncorrected. Elemental analyses were determined by MHW Laboratories, Garden City, Mich. Mass Spectra were determined by Dr. Roger Upham and his assistants at the University of Minnesota on an AEI-MS-30 instrument. The Fourier transform ^{13}C-NMR spectra were determined by Dr. Robert M. Riddle at the University of Minnesota on a Varian XL-100 spectrometer (25.2 MHz). ^1H-NMR spectra were determined on a Varian HFT-80 spectrometer. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrometer. Ultraviolet spectra were determined on a Cary 11 spectrometer.
(16) The 2-methylpyridine-3-aldehyde was obtained from methyl 2-methylnicotinate[17] via 3-hydroxymethyl-2-methylpyridine, using the method whereby J. M. Bobbit and D. A. Scola, *J. Org. Chem.*, **25**, 560 (1960), obtained 4-methylpyridine-3-aldehyde from methyl 4-methylnicotinate.
(17) Prepared in 66% yield from propynal and methyl 3-aminocrotonate according to the method used by F. Bohlmann and D. Rahtz, *Chem. Ber.*, **90**, 2265 (1957), for the synthesis of the corresponding ethyl ester.

Cembranoid Diterpenes from a South Pacific Soft Coral

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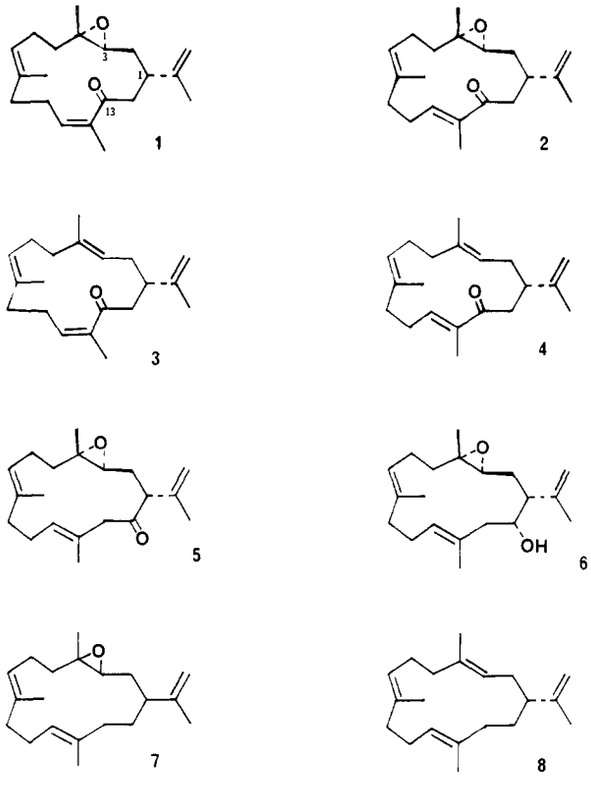
Eight cembranoid diterpenes have been isolated from an unidentified soft coral. The structures were elucidated from spectral data and chemical degradation sequences. The compounds were identified as (1*S**,3*S**,4*S**,7*E*,11*Z*)-3,4-epoxy-13-oxo-7,11,15-cembratriene, (1*S**,3*S**,4*S**,7*E*,11*E*)-3,4-epoxy-13-oxo-7,11,15-cembratriene, (3*E*,7*E*,11*Z*)-13-oxo-3,7,11,15-cembratetraene, (3*E*,7*E*,11*E*)-13-oxo-3,7,11,15-cembratetraene, (1*S**,3*S**,4*S**,7*E*,11*E*)-3,4-epoxy-14-oxo-7,11,15-cembratriene, (1*S**,3*S**,4*S**,14*R**,7*E*,11*E*)-3,4-epoxy-14-hydroxy-7,11,15-cembratriene, (7*E*,11*E*)-3,4-epoxy-7,11,15-cembratriene, and (−)-cembrene-A. The application of ^{13}C NMR spectroscopy to the determination of stereochemistry is discussed.

The soft corals or alcyonaceans are known to be a source of interesting marine natural products[1] which include sesquiterpenes,[2] cembranoid diterpenes,[3] polyhydroxylated sterols,[4] and pregnanes.[5] Some cembranoid diterpenes from soft corals are known to be toxic and have been cast in the role of deterrents to predation by reef fishes.[1] We wish to report the isolation and identification of eight cembranoid diterpenes from an unidentified soft coral[6] which was collected at Canton Island in the South Pacific.

Silica gel chromatography of the chloroform-soluble material from the combined acetone and 15% methanol in chloroform extracts of the soft coral gave a series of fractions from which the ketones 1 and 2 and the hydrocarbon 8 were obtained in high purity. Chromatography of one of the mixed fractions on silver nitrate impregnated silica gel gave two pure compounds, the ketones 3 and 5, and a mixture of the ketone 4 and the epoxide 7 which could only be separated after reduction of the ketone 4. The alcohol 6 was isolated from a mixture with the ketone 2 as the corresponding acetate. The molecular formulas, optical rotations, and yields of the compounds isolated are summarized in Table I.



1 2 3 4 5 6 7 8

The ketone 1 was shown to have the molecular formula $C_{20}H_{30}O_2$ by high-resolution mass measurement. The infrared band at 1690 cm^{-1} and the UV absorption at 236 nm (ϵ 3000) both suggested the presence of an α,β-unsaturated ketone. The ^1H NMR spectrum contained signals at δ 5.68 (1 H, t, J = 6.5 Hz) due to the β proton on an α,β-unsaturated ketone, 5.08 (1 H, t, J = 7 Hz) assigned to the vinyl proton on a trisubstituted olefinic bond, 4.85 (1 H, bs) and 4.74 (1 H, bs) for the terminal methylene protons and four methyl signals at 1.84, 1.80, 1.67, and 1.21 ppm. When recorded in $CDCl_3$ solution, the ^1H-NMR spectrum contained an unresolved proton multiplet at δ 2.84 and a signal at 2.64 (1 H, t, J = 6.5 Hz) which could be assigned to an α-epoxy proton. When recorded in C_6D_6 solution, the ^1H-NMR spectrum of 1 contained three mutually coupled signals at δ 3.06 (1 H, m, J = 7 Hz, H_c), 2.77 (1 H, dd, J = 17, 7 Hz, H_a), and 2.58 (1 H, dd, J = 17, 7 Hz, H_b)

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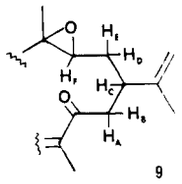
Table I. The Molecular Formulas, Percent Dry Weight, and Optical Rotations of Compounds 1–8

Compd No.	Molecular formula	% dry weight	$[\alpha]^{20}_D$, deg
1	$C_{20}H_{30}O_2$	0.76	+8.8
2	$C_{20}H_{30}O_2$	1.1	+12.8
3	$C_{20}H_{30}O$	0.09	−20.6
4	$C_{20}H_{30}O$	<0.01	
5	$C_{20}H_{30}O_2$	0.15	+38.7
6	$C_{20}H_{32}O_2$	0.51	
7	$C_{20}H_{32}O$	0.09	−19.3
8	$C_{20}H_{32}$	0.02	−3.5

and the α-epoxy proton signal at 2.64 (1 H, t, J = 6.5 Hz, H_f). Irradiation of a two-proton triplet at δ 1.67 (H_d, H_e) caused the α-epoxy proton signal to become a singlet and the signal at 3.06 (H_c) to become a triplet. Thus the ketone **1** must contain the partial structure **9**. Decoupling studies showed that the methyl signals at δ 1.84 and 1.61 were coupled to the vinyl protons at 5.68 and 5.08, respectively, while the methyl signal at 1.80 was coupled to the methylene protons at 4.85 and 4.75 ppm, forming an isopropenyl group. The ^{13}C-NMR spectrum contained signals for one carbonyl carbon, six olefinic carbons, the two carbons of the trisubstituted epoxide, and four methyl carbons. Since the ketone must be monocyclic, it was assigned the cembranoid structure **1**.[7]

The presence of the trisubstituted epoxide was confirmed by periodic acid oxidation of the ketone **1** to obtain a ketoaldehyde **10** in low yield. Ozonolysis of the ketone **1**, followed by oxidation and methylation, gave methyl levulinate, indicating the presence of a 1,5-diene system. Reduction of the



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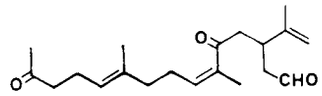

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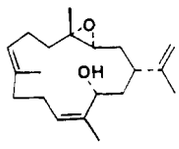

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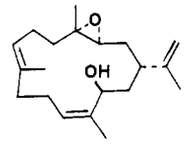

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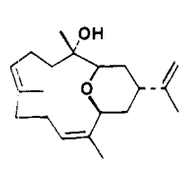


13

ketone **1** with lithium aluminum hydride in refluxing ether resulted in the formation of two epimeric alcohols **11** and **12** in a ratio of 3:2.[8] The alcohols **11** and **12** were both treated with p-toluenesulfonic acid in refluxing chloroform. The alcohol **12** underwent a smooth isomerization to the ether **13**, while alcohol **11** gave a complex mixture of products. The ^{1}H-NMR spectrum of the cyclic ether **13** clearly indicated the regiochemical and stereochemical relationships between the epoxide, the isopropenyl side chain, and the allylic alcohol in **12**. The signals at δ 3.88 (1 H, dd, J = 12, 2 Hz, C-13) and δ 3.22 (1 H, dd, J = 12, 2 Hz, C-3) were assigned to axial protons on the α carbons in a six-membered cyclic ether, while the signal at 2.59 (1 H, bs, $w_{1/2}$ = 13 Hz, C-1) was due to an equatorial proton on the carbon bearing the isopropenyl group. Examination of molecular models revealed that the 13α-alcohol **11** could not attain a suitable conformation for ether formation.

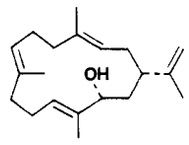
The stereochemistry of the Δ^{11} double bond was established by comparing spectral data with those of the isomeric ketone **2**. On catalytic hydrogenation over 10% palladium on charcoal, both ketones **1** and **2** gave the identical hexahydro derivative which could be purified by sublimation. This indicated that both molecules contained epoxide and ketone functionalities in the same positions on the same carbon skeleton. Since ozonolysis of **2** also gave methyl levulinate, the positions of the olefinic bonds must be the same. Thus the ketones **1** and **2** must be geometrical isomers.

The major differences in spectral data for the ketones **1** and **2** were all associated with the α,β-unsaturated ketone system. Whereas the ketone **2** was rapidly reduced with lithium tri-*tert*-butoxyaluminum hydride in ether at room temperature, the ketone **1** did not undergo a similar reduction. In the ^{1}H-NMR spectra, the signal for the proton at C-11 appeared at 5.68 ppm in ketone **1** and 6.64 ppm in ketone **2**, suggesting that the C-11 proton was trans to the carbonyl group in **1** and cis in **2**. The ^{13}C-NMR spectra also supported this assignment, with signals at δ 20.5 (C-20) and 134.5 (C-11) obtained from ketone **1** and δ 11.4 (C-20) and 143.4 (C-11) from ketone **2**. In addition, the extinction coefficients in the UV spectra can be correlated with cisoid and transoid enone systems.[9] Ketone **1**, λ_{max} 236 (ϵ 3000), has a cisoid configuration, while ketone **2**, λ_{max} 234 (ϵ 9500), has a transoid configuration. The stereochemistry about all remaining trisubstituted olefinic bonds and epoxide rings is E (see discussion on ^{13}C-NMR correlations).

Among the minor metabolites of the soft coral, there were two α,β-unsaturated ketones **3** and **4** which lacked an epoxide functionality. The ketone **4** was obtained from an inseparable mixture with the epoxide **7** by reduction of the mixture with lithium aluminum hydride in dry ether to obtain a mixture of two alcohols **14** and **15**, which were separated from the unreacted epoxide **7**. The alcohol mixture was reoxidized with Jones' reagent to obtain the ketone **4** in low yield. Although there was insufficient material to perform chemical transformations on either compound, the spectral data indicated that the ketones **3** and **4** were 3,4-deoxy derivatives of ketones **1** and **2**, respectively. In particular, each compound had the molecular formulation $C_{20}H_{30}O$ and contained two E-trisubstituted olefinic groups and an isopropenyl group. We propose that the ketone **3**, UV 234 nm (ϵ 3200), ^{1}H NMR δ 5.61 (1 H, t, J = 7 Hz, C-11), has the 11Z stereochemistry, while ketone **4**, UV 231 (ϵ 8100), ^{1}H NMR δ 6.62 (1 H, t, J = 7 Hz, C-11), is the 11E geometrical isomer.

The ketone **5** had the molecular formula $C_{20}H_{30}O_2$ and was therefore an isomer of ketones **1** and **2**. The infrared band at 1705 cm^{-1} indicated an unconjugated carbonyl group, while the UV absorption at 217 nm (ϵ 1070) suggested that **5** was a β,γ-unsaturated ketone. On equilibration with deuterium oxide, three protons were exchanged to obtain a trideuterio derivative **16**. The ^{1}H-NMR spectrum of **16** lacked the three-proton multiplet at δ 2.61. Since the spectral data of ketone **5** indicated the presence of two trisubstituted olefinic bonds, an isopropenyl group, and a trisubstituted epoxide ring, and ozonolysis of **5** gave methyl levulinate, the carbonyl group must be at C-14 in a cembrane containing a 3,4-epoxide.

Reduction of ketone **5** with sodium borohydride gave a 3:1 mixture of two alcohols, both of which still contained the epoxide ring. The major alcohol was shown to be identical to the



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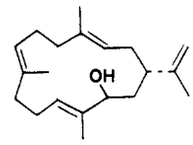

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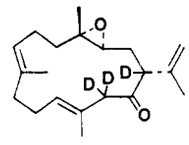

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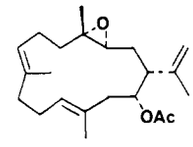

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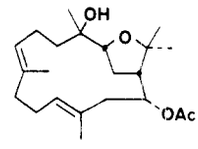

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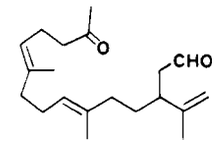

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alcohol **6**, which had been isolated from the soft coral as the acetate **17**. The acetate **17** was converted into the alcohol **6** by treatment with lithium aluminum hydride in ether. Moffatt oxidation of the alcohol **6** gave the ketone **5**. Examination of a molecular model of the ketone **5** suggested that the hydride attack occurred from the face of the ring opposite the isopropenyl ring to give the stereochemistry shown for the alcohol **6**. The relative stereochemistry of the isopropenyl group and the epoxide was determined when it was found that treatment of the acetate **17** with *p*-toluenesulfonic acid in benzene caused formation of an ether **18** which could not be acetylated. The most likely mechanism for this reaction required formation of a carbonium ion at C-15, which rearranged, with participation of the epoxide oxygen, to an ether with a new carbonium ion at C-4, which was subsequently hydrated. Since this reaction did not occur in simpler systems, it is possible that the carbonium ion was stabilized by transannular interaction with the acetate carbonyl. If this mechanism is correct, the epoxide oxygen and the isopropenyl group must be on the same face of the large ring. The geometry of the trisubstituted olefinic bonds was again deduced from ^{13}C-NMR spectra.

The two remaining minor metabolites were identified as (−)-cembrene-A (**8**)[10] and a monoepoxide **7** related to cembrene-A. Since the monoepoxide **7** gave methyl levulinate on ozonolysis and contained an isopropenyl group, the epoxide ring must be at C-3 or C-11. Oxidation of the epoxide **7** with periodic acid in ether gave a ketoaldehyde **19**. The ^{1}H-NMR spectrum of the ketoaldehyde **19** contained an aldehyde signal at δ 9.75 (t, 1 H, J = 2 Hz) which was coupled to a two-proton signal at 2.50 (dd, 2 H, J = 7.5, 2 Hz) which was in turn coupled to part of a three-proton multiplet at 2.34, which was assigned to protons on the carbon bearing the isopropenyl group and the methylene group adjacent to the ketone group. The epoxide must therefore be situated at C-3. We were unable to define the relative stereochemistry of the epoxide and isopropenyl groups.

The ^{13}C-NMR spectra have been particularly helpful in the assignment of the stereochemistry about the trisubstituted olefinic bonds. It appears that the 14-membered ring of the cembrane skeleton is large enough that transannular effects are small and that the chemical shift criteria for establishing the stereochemistry of trisubstituted double bonds in acyclic polyisoprenoids can be applied to cembranolides. In acyclic polyisoprenoids, the chemical shift of a methyl carbon on an *E*-trisubstituted olefinic bond is 15–16 ppm, while that of methyl on a *Z*-trisubstituted olefin is 23–24 ppm.[11] The methyl of the isopropenyl group should give rise to a signal at 19–21 ppm. The methyl signal in an *E*-trisubstituted epoxide should be at ~17 ppm and that in a *Z*-trisubstituted epoxide at ~25 ppm. The differences between methyl signals in *E*- and *Z*-trisubstituted olefins are more easily observed in ^{13}C-NMR spectra than in the corresponding ^{1}H-NMR spectra.[12] On the basis of these correlations, we have assigned the *E* stereochemistry for all trisubstituted olefins and epoxides, with the exception of the C-11 olefinic bonds in **1** and **3**. The *Z*-trisubstituted olefinic bonds in ketones **1** and **3** are unique among cembranes from marine organisms.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Ultraviolet spectra were recorded on a Perkin-Elmer Model 124 double beam spectrophotometer. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter, using a 10-cm microcell. ^{1}H-NMR spectra were recorded on a Varian HR-220 NMR spectrometer, and ^{13}C spectra were recorded on a Varian CFT-20 NMR spectrometer; all chemical shifts are reported with respect to Me_4Si (δ 0). Low-resolution mass spectra were recorded on a Hewlett-Packard 5930A mass spectrometer. High-resolution mass spectra were recorded on a Varian MAT 311 spectrometer and were also supplied by the Analytical Facility at California Institute of Technology. Melting points were determined on a Fisher-Johns apparatus and are reported uncorrected. All solvents used were either spectral grade or distilled from glass prior to use.

Collection and Extraction of Soft Coral. The unidentified soft coral was collected by hand, using scuba at a depth of 15 m on the leeward side of Canton Island (2°50′S, 171°42′W) in October 1976. The soft coral was stored and shipped in acetone. The soft coral (195 g dry weight) was homogenized in acetone and filtered and the solid material was extracted with 15% methanol in chloroform in a Soxhlet extractor for 48 h. Evaporation of the combined extracts gave a brown gum (21 g, 10.8% dry weight).

Isolation of Cembranes 1–8. The crude extract (20 g) was applied to a column (100 × 5 cm diameter) of silica gel (50–200 mesh) and material was eluted with solvents of gradually increasing polarity from hexane through ether. Fraction 1, eluted with hexane, contained (−)-cembrene-A (**8**) (40 mg, 0.02% dry weight). Fraction 2, eluted with 10% ether in hexane, contained a mixture of compounds **3**, **4**, **5**, and **7**. Fraction 2 was rechromatographed on silica gel impregnated with 10% silver nitrate using 5% ether in hexane as eluant to obtain the ketone **3** (175 mg, 0.09% dry weight), the ketone **5** (275 mg, 0.15% dry weight), and a mixture of ketone **4** and epoxide **7**. Fraction 3, eluted with 25% ether in hexane, contained the ketone **1** (1.65 g, 0.89% dry weight). Fraction 4, eluted with 50% ether in hexane, contained the ketone **2** (1.55 g, 0.76% dry weight). Fraction 5, eluted with ether, contained a mixture of the ketone **2** and the alcohol **6**.

(1*S,3*S**,4*S**,7*E*,11*Z*)-3,4-Epoxy-13-oxo-7,11,15-cembratriene (1):** $[\alpha]^{20}_D$ +8.8° (*c* 1.6, $CHCl_3$); UV (hexane) 236 nm (ϵ 3000); IR ($CHCl_3$) 1690, 1642, 918 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.68 (1 H, t, J = 6.5 Hz), 5.08 (1 H, t, J = 7 Hz), 4.85 (1 H, s), 4.74 (1 H, s), 2.84 (3 H, m), 2.64 (1 H, t, J = 6.5 Hz), 1.84 (3 H, s), 1.80 (3 H, s), 1.61 (3 H, s), 1.21 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 186.66 (s), 147.25 (s), 137.30 (s), 135.40 (s), 134.46 (d), 124.06 (d), 110.49 (t), 60.36 (d), 59.49 (s), 44.89 (t), 38.99 (t), 38.19 (d), 31.09 (t), 29.24 (t), 23.54 (t), 21.72 (q), 20.54 (q), 16.71 (q), 16.71 (q); high resolution mass measurement 302.2245, $C_{20}H_{30}O_2$ requires 302.2245.

(1*S,3*S**,4*S**,7*E*,11*E*)-3,4-Epoxy-13-oxo-7,11,15-cembratriene (2):** $[\alpha]^{20}_D$ +12.78° (*c* 1.65, $CHCl_3$); UV (hexane) 234 nm (ϵ 9000); IR ($CHCl_3$) 1690, 1650, 910 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.64 (1 H, t, J = 7 Hz), 5.18 (1 H, t, J = 7 Hz), 4.74 (1 H, s), 4.64 (1 H, s), 3.09 (1 H, dd, J = 7, 14 Hz), 2.76 (1 H, dd, J = 5, 7 Hz), 2.64 (1 H, broad q), 1.75 (3 H, s), 1.73 (3 H, s), 1.64 (3 H, s), 1.22 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 189.01 (s), 147.36 (s), 143.39 (d), 137.25 (s), 134.18 (s), 125.46 (d), 110.78 (t), 61.74 (d), 59.85 (s), 43.68 (d), 40.88 (t), 38.61 (t), 38.22 (t), 32.49 (t), 25.46 (t), 24.06 (t), 19.41 (q), 16.58 (q), 15.69 (q), 11.41 (q); high resolution mass measurement 302.2286, $C_{20}H_{30}O_2$ requires 302.2245.

(3*E*,7*E*,11*Z*)-13-Oxo-3,7,11,15-cembratetraene (3): $[\alpha]^{20}_D$ −20.56° (*c* 5.3, CCl_4); IR ($CHCl_3$) 1692, 1650, 921 cm^{-1}; UV (hexane)

234 nm (ε 3200); ^{1}H NMR ($CDCl_3$) δ 5.61 (1 H, t, J = 5 Hz), 5.02 (2 H, m), 4.71 (1 H, s), 4.69 (1 H, s), 2.71 (3 H, m), 1.83 (3 H, s), 1.78 (3 H, s), 1.62 (3 H, s), 1.55 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 181.5 (s), 148.2 (s), 136.4 (s), 135.39 (s), 134.52 (d), 134.38 (s), 124.30 (d), 123.19 (d), 109.13 (t), 45.27 (t), 40.48 (d), 38.96 (t), 38.71 (t), 32.17 (t), 29.17 (t), 23.98 (t), 21.00 (q), 20.11 (q), 16.73 (q), 15.13 (q); high resolution mass measurement 286.2295, $C_{20}H_{30}O$ requires 286.2296.

(1*S,3*S**,4*S**,7*E*,11*E*)-3,4-Epoxy-14-oxo-7,11,15-cembratriene (5):** mp 66 °C (ether); $[\alpha]^{20}_D$ +38.65° (*c* 4.16, $CHCl_3$); UV (hexane) 217 nm (ε 1070); IR ($CHCl_3$) 1706, 1650, 915 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.02 (1 H, t, J = 7 Hz), 4.88 (1 H, t, J = 7 Hz), 4.73 (1 H, s), 4.66 (1 H, s), 2.86 (1 H, t, J = 6.5 Hz), 2.61 (3 H, m), 1.71 (3 H, s), 1.60 (3 H, s), 1.40 (3 H, s), 1.35 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 209.56 (s), 148.36 (s), 136.21 (s), 132.13 (s), 127.74 (d), 122.29 (d), 110.20 (t), 63.57 (s), 58.50 (d), 39.43 (t), 38.99 (d), 37.04 (t), 36.61 (t), 30.71 (t), 25.37 (t), 24.68 (t), 21.69 (q), 15.45 (q), 14.98 (q), 12.37 (q); high resolution mass measurement 302.2244, $C_{20}H_{30}O_2$ requires 302.2245.

(−)-Cembrene-A (8) $[\alpha]^{20}_D$ −3.5° (*c* 3, $CHCl_3$); IR ($CHCl_3$) 1640, 1462, 1441, 1393, 1382, 904 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.19 (1 H, t, J = 7 Hz), 5.07 (1 H, t, J = 7 Hz), 4.98 (1 H, t, J = 7 Hz), 4.72 (1 H, s), 4.66 (1 H, s), 1.66 (3 H, s), 1.59 (3 H, s), 1.55 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 149.16 (s), 134.65 (s), 133.8 (s), 133.2 (s), 125.81 (d), 124.01 (d), 121.84 (d), 110.0 (t), 45.94 (d), 39.33 (t), 38.89 (t), 33.93 (t), 32.36 (t), 28.21 (t), 24.81 (t), 23.69 (t), 19.20 (q), 17.88 (q), 15.40 (q), 15.21 (q); mass spectrum *m/e* 272 ($M^{+\cdot}$).

Separation of Ketone 4 from Epoxide 7. Lithium aluminum hydride (~50 mg) was added to a solution of the mixture (175 mg) in dry ether (10 mL), and the reaction mixture was stirred at room temperature for 30 min. Ethyl acetate was added dropwise to destroy excess reagent, and the product was partitioned between ether and 3 N hydrochloric acid. The ether extracts were dried over anhydrous sodium sulfate and filtered and the solvent was evaporated to yield an oil. The oil was chromatographed on silica gel to obtain the epoxide **7** (140 mg, equivalent to 0.09% dry weight) and a mixture of alcohols **14** and **15** (18 mg combined).

Jones' reagent (3 drops) was added to a solution of the alcohol mixture (18 mg) in acetone (5 mL), and the reaction mixture was stirred at room temperature for 10 min. Excess reagent was destroyed by addition of isopropyl alcohol. The reaction mixture was filtered and the filtrate was evaporated. The residue was purified by preparative TLC in silica gel to obtain the ketone **4** (1.7 mg).

(7*E*,11*E*)-3,4-Epoxy-7,11,15-cembratriene (7): $[\alpha]^{20}_D$ −19.3° (*c* 3.9, CCl_4); IR ($CHCl_3$) 932 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.07 (2 H, m), 4.77 (1 H, s), 4.64 (1 H, s), 2.64 (1 H, dd, J = 5, 7 Hz), 1.71 (3 H, s), 1.64 (3 H, s), 1.53 (3 H, s), 1.21 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 147.55 (s), 135.00 (s), 132.56 (s), 126.22 (d), 124.44 (d), 110.00 (t), 61.03 (s), 61.03 (d), 45.03 (d), 38.72 (t), 36.30 (t), 32.61 (t), 29.84 (t), 24.72 (t), 24.44 (t), 24.24 (t), 21.04 (q), 17.25 (q), 14.94 (q), 14.94 (q); high resolution mass measurement 288.2450, $C_{20}H_{32}O$ requires 288.2453.

(3*E*,7*E*,11*E*)-13-Oxo-3,7,11,15-cembratetraene (4): UV (hexane) 231 nm (ε 8100); ^{1}H NMR ($CDCl_3$) δ 6.62 (1 H, t, J = 7 Hz), 5.16 (2 H, m), 4.73 (1 H, s), 4.68 (1 H, s), 3.29 (1 H, dd, J = 15, 5 Hz), 2.82 (1 H, m), 1.71 (3 H, s), 1.66 (3 H, s), 1.61 (3 H, s), 1.56 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 191.1 (s), 148.0 (s), 141.25 (d), 135.9 (s), 134.5 (s), 132.5 (s), 126.5 (d), 122.0 (d), 110.0 (t), 45.6, 37.5, 34.5, 31.7, 28.0, 26.0, 22.25 (q), 18.85 (q), 15.75 (q), 10.75 (q); mass spectrum, *m/e* 286 ($M^{+\cdot}$).

Separation of Alcohol 6 from a Mixture with Ketone 2. Acetic anhydride (1 mL) and pyridine (1 mL) were added to a solution of a mixture of alcohol **6** and ketone **2** (1.7 g) in benzene (5 mL), and the reaction mixture was stirred at room temperature overnight. The solvent and reagents were removed in vacuo. The residue was chromatographed on silica gel to obtain the ketone **2** (0.5 g) and the acetate **17** (1.2 g). Lithium aluminum hydride (~100 mg) was added to a solution of the acetate **17** (500 mg) in dry ether (25 mL), and the reaction mixture was stirred for 1 h at room temperature. Ethyl acetate was added dropwise to destroy excess reagent, and the product was partitioned between ether and 3N hydrochloric acid. The ether extracts were dried over anhydrous sodium sulfate and the ether was evaporated to yield an oil which was chromatographed on silica gel to obtain the alcohol **6** (397 mg).

(1*R,3*S**,4*S**,14*R**,7*E*,11*E*)-3,4-Epoxy-14-hydroxy-7,11,15-cembratriene (6):** IR ($CHCl_3$) 3200, 1642, 910 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.14 (1 H, t, J = 8 Hz), 5.08 (1 H, t, J = 7 Hz), 4.82 (1 H, bs), 4.77 (1 H, bs), 3.58 (1 H, bs), 2.98 (1 H, t, J = 7 Hz), 1.74 (3 H, s), 1.63 (3 H, s), 1.55 (3 H, s), 1.30 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 148.3 (s), 135.9 (s), 133.0 (s), 126.3 (d), 123.6 (d), 110.9 (t), 70.6 (d), 60.8 (s), 59.5 (d), 45.4 (d), 38.7 (t), 36.5 (t), 36.1 (t), 33.8 (t), 33.2 (t), 24.8 (t), 24.8 (q), 19.4 (q), 16.6 (q), 15.8 (q).

Periodic Acid Oxidation of Ketone 1. A saturated solution of periodic acid in anhydrous ether (2 mL) was added to a solution of ketone **1** (30 mg, 0.1 mmol) in dry ether (10 mL). The mixture was stirred at room temperature for 1 h and washed with water. The ether layer was dried over anhydrous sodium sulfate and the solvent was evaporated to yield an oil, which was chromatographed on a silica gel plate to obtain starting material (12 mg) and a ketoaldehyde **10** (1 mg, 6% theoretical): ^{1}H NMR ($CDCl_3$) δ 9.69 (1 H, t, J = 6.5 Hz), 5.67 (1 H, t, J = 7 Hz), 5.10 (1 H, t, J = 6.5 Hz), 4.82 (2 H, bs), 2.13 (3 H, s), 1.91 (3 H, s), 1.73 (3 H, s).

Ozonolysis of Ketone 1 (and Other Cembranes). Ozone in oxygen was bubbled through a solution of the ketone **1** (10 mg) in ethyl acetate (10 mL) which had been cooled to −78 °C. After 5 min, the excess reagent was removed by flushing with dry nitrogen. The solvent was evaporated and the residue was dissolved in acetone (2 mL) and titrated with Jones' reagent (4 drops). After 30 min, the reaction mixture was filtered. The filtrate was evaporated to dryness and a solution of diazomethane in ether was added until a slight excess of reagent caused a yellow solution. Analysis of the product by GC–MS indicated the presence of methyl levulinate, identical with an authentic sample.

Reduction of Ketone 1 with Lithium Aluminum Hydride. Lithium aluminum hydride (~25 mg) was added to a solution of the ketone **1** (90 mg, 0.3 mmol) in dry ether (15 mL), and the reaction mixture was boiled under reflux for 2 h. Excess reagent was destroyed by addition of ethyl acetate and then water; the solution was filtered to remove salts. The ether solution was dried over anhydrous sodium sulfate and the solvent was evaporated to yield an oil. Chromatography of the product on a preparative TLC plate (silica gel, 1:1 cyclohexane/ether) gave alcohol **11** (32 mg, 35% theoretical) as an oil and alcohol **12** (22 mg, 24% theoretical) as a crystalline solid from hexane.

Alcohol 11: IR ($CHCl_3$) 3367, 1634, 911 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.17 (1 H, t, J = 7.5 Hz), 5.06 (1 H, t, J = 7.5 Hz), 4.81 (1 H, s), 4.76 (1 H, s), 4.53 (1 H, broad m), 2.93 (1 H, dd, J = 3, 10 Hz), 1.78 (3 H, s), 1.71 (3 H, s), 1.62 (3 H, s), 1.24 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 148.57 (s), 136.91 (s), 135.75 (s), 127.64 (d), 124.79 (d), 110.89 (t), 69.49 (d), 61.69 (d), 60.93 (s); 39.72, 38.82, 38.27, 37.79, 33.84, 26.91, 23.36, 20.80, 19.29, 17.86, 17.36; high resolution mass measurement 304.2391, $C_{20}H_{32}O_2$ requires 304.2402.

Alcohol 12: mp 111 °C; IR ($CHCl_3$) 3355, 1636, 908 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.06 (1 H, t, J = 7 Hz), 4.91 (1 H, t, J = 7.5 Hz), 4.70 (1 H, s), 4.60 (1 H, s), 4.45 (1 H, dd, J = 5, 7 Hz), 2.73 (1 H, t, J = 5 Hz), 2.41 (1 H, q, J = 7 Hz), 1.79 (3 H, s), 1.73 (3 H, s), 1.59 (3 H, s), 1.25 (3 H, s); high resolution mass measurement 304.2401, $C_{20}H_{32}O_2$ requires 304.2402.

Transannular Cyclization of Alcohol 12. The alcohol **12** (4 mg) and *p*-toluenesulfonic acid (1 mg) were dissolved in chloroform (5 mL), and the stirred solution was boiled under reflux for 1 h. The reaction mixture was partitioned between chloroform and 5% aqueous sodium bicarbonate solution, and the chloroform extract was dried over anhydrous sodium sulfate. The product was chromatographed on a silica gel plate to obtain the ether **13** (3.5 mg, 82% theoretical): ^{1}H NMR ($CDCl_3$) δ 5.26 (1 H, t, J = 8 Hz), 5.03 (1 H, bs), 4.91 (1 H, m), 4.87 (1 H, s), 3.88 (1 H, dd, J = 12, 2 Hz), 3.22 (1 H, dd, J = 12, 2 Hz), 2.59 (1 H, broad), 1.79 (3 H, s), 1.66 (3 H, s), 1.65 (3 H, s), 1.12 (3 H, s); mass spectrum 304 ($M^{+\cdot}$). The ether **13** did not form an acetate.

Hydrogenation of Ketones 1 and 2. A solution of ketone **1** or ketone **2** (80 mg) in anhydrous ether (25 mL) was hydrogenated over 10% palladium on charcoal catalyst for 18 h. The solution was filtered and the solvent was evaporated. The residue was chromatographed on a preparative TLC plate (silica gel, 10% ether in hexane) to obtain, among other products, a solid hexahydro derivative which sublimed at 96 °C. The same product was obtained from both ketones (25 mg, 31% theoretical from **1**; 6 mg, 7% theoretical from **2**): ^{1}H NMR ($CDCl_3$) δ 1.30 (3 H, s), 1.04 (3 H, d, J = 7 Hz), 0.89 (3 H, d, J = 7 Hz), 0.87 (3 H, d, J = 7 Hz), 0.85 (3 H, d, J = 7 Hz); mass spectrum, *m/e* 308 ($M^{+\cdot}$).

Reduction of Ketone 2 with Lithium Tri-*tert*-butoxyaluminum Hydride. Lithium tri-*tert*-butoxyaluminum hydride (25 mg) was added to a solution of ketone **2** (25 mg, 0.08 mmol) in 1:1 ether–tetrahydrofuran (10 mL), and the solution was stirred at room temperature for 100 min. Excess reagent was destroyed with water and the precipitate was removed by filtration. Evaporation of the solvent gave an inseparable mixture of alcohols. The corresponding acetates could be separated by preparative TLC on silica gel.

Equilibration of Ketone 5 with Deuterium Oxide. Potassium *tert*-butoxide (15 mg) was added to a solution of the ketone **5** (10 mg) in dry ether (2 mL). The reaction mixture was stirred for 1 h and deuterium oxide (100 μL) was added. After 15 min, the solution was neutralized with CO_2 and dried over anhydrous sodium sulfate. The

solvent was evaporated, the residue was taken up in hexane, and the solution was filtered. Evaporation of the solvent gave the trideuterio derivative **16**, in which three hydrogens had exchanged with deuterium. The ^{1}H-NMR spectrum of **16** did not contain the usual signals at 2.61 ppm but did contain a broad signal thought to be a contaminant (<1 H). The mass spectrum of **16** contained a group of four peaks at *m/e* 305 (M + 3), 304 (M + 2), 303 (M + 1), and 302 ($M^{+\cdot}$), indicating that three protons had been replaced by deuterium.

Reduction of Ketone 5 with Sodium Borohydride. Sodium brohydride (50 mg) was added to a solution of the ketone **5** (20 mg, 0.66 mmol) in methanol (10 mL) and the solution was stirred at room temperature for 3 h. The solvent was evaporated and the residue was partitioned between water (10 mL) and dichloromethane (3 × 10 mL). The dichloromethane extract was dried over anhydrous sodium sulfate and the solvent was evaporated to obtain a 3:1 mixture of two alcohols. The mixture was chromatographed on a preparative silica gel plate using ether as eluant to obtain the major alcohol, which was shown to be identical in all respects to a sample of the alcohol **6**.

Treatment of Acetate 17 with *p*-Toluenesulfonic Acid. A solution of the acetate **17** (46 mg, 0.13 mmol) and *p*-toluenesulfonic acid (2 mg) in benzene (10 mL) was boiled under reflux for 10 min. The cooled benzene solution was washed with aqueous sodium bicarbonate solution and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was chromatographed on silica gel to yield the ether **18** (22 mg, 45% theoretical) as the major product: IR (CCl_4) 3270, 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.23 (1 H, t, J = 7 Hz), 5.05 (1 H, bs), 4.76 (1 H, t, J = 6.5 Hz), 3.86 (1 H, dd, J = 11, 5 Hz), 2.11 (3 H, s), 1.61 (3 H, s), 1.55 (3 H, s), 1.28 (3 H, s), 1.11 (3 H, s), 1.06 (3 H, s); ^{13}C NMR (CCl_4) δ 169.2, 135.3, 134.8, 125.7, 124.4, 81.3, 81.0, 75.2, 74.4, 48.8, 39.1, 34.8, 32.8, 29.5, 27.3, 27.2, 25.2, 24.1, 20.6, 20.4, 16.5, 15.6; mass spectrum *m/e* 364 (M^+). The ether **18** did not form an acetate when treated with acetic anhydride in pyridine.

Moffatt Oxidation of the Alcohol 6. Dicyclohexylcarbodiimide (23 mg, 0.11 mmol), 100% phosphoric acid (1 drop), and dimethyl sulfoxide (1 mL) were added to a solution of the alcohol **6** (11 mg, 0.36 mmol) in benzene (10 mL). The reaction mixture was stirred overnight and then washed with water. The benzene solution was dried over sodium sulfate and the solvent evaporated to obtain a semisolid residue. The residue was purified to HPLC using a μ-porasil column and 5% ether in hexane as eluant to obtain the ketone **5** (3 mg, 27% theoretical), mp 65–66 °C.

Oxidation of Epoxide 7 with Periodic Acid. A saturated solution of periodic acid in dry ether (2 mL) was added to a solution of the epoxide **7** (20 mg, 0.07 mmol) in dry ether (5 mL) and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was washed with water and the ether layer was dried over anhydrous sodium sulfate. The product was purified by HPLC on μ-porasil using 20% ether in hexane to obtain the ketoaldehyde **19** (17 mg, 80% theoretical): IR (CCl_4) 2720, 1720, 1642 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.74 (1 H, t, J = 2 Hz), 5.13 (1 H, m), 5.04 (1 H, m), 4.77 (1 H, bs), 4.67 (1 H, bs), 2.50 (2 H, dd, J = 7.5, 2 Hz), 2.34 (3 H, m), 2.11 (3 H, s), 1.62 (3 H, s), 1.59 (6 H, s); mass spectrum, *m/e* 304 (M^+).

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Registry No.—**1**, 65622-45-9; 1 hexahydro derivative, 65622-46-0; **2**, 65634-83-5; **3**, 65622-47-1; **4**, 65622-49-3; **5**, 65622-48-2; **6**, 65622-50-6; **7**, 65622-51-7; **8**, 31570-39-5; **10**, 65622-52-8; **11**, 65622-53-9; **12**, 65634-84-6; **13**, 65622-54-0; **17**, 65622-55-1; **18**, 65622-56-2; **19**, 65622-57-3.

References and Notes

(1) B. Tursch, *Pure Appl. Chem.*, **48**, 1 (1976).
(2) (a) D. Daloze, J. C. Braekman, P. Georget, and B. Tursch, *Bull. Soc. Chim. Belg.*, **86**, 47 (1977), and references cited therein; (b) Y. M. Sheikh, C. Djerassi, J. C. Braekman, D. Daloze, M. Kaisin, B. Tursch, and R. Karlsson, *Tetrahedron*, **33**, 2115 (1977), and references cited therein; (c) J. C. Braekman, D. Daloze, R. Ottinger, and B. Tursch, *Experientia*, **33**, 993 (1977); (d) J. C. Coll, S. J. Mitchell, and G. J. Stokie, *Tetrahedron Lett.*, 1539 (1977); (e) C. M. Beechan, C. Djerassi, J. S. Finer, and J. Clardy, *Tetrahedron Lett.*, 2395 (1977).
(3) (a) F. J. Schmitz, D. J. Vanderah, and L. S. Ciereszko, *Chem. Commun.*, 407 (1974); (b) B. Tursch, J. C. Braekman, and D. Daloze, *Bull. Soc. Chim. Belg.*, **84**, 767 (1975); (c) B. Tursch, J. C. Braekman, D. Daloze, M. Herin, and R. Karlsson, *Tetrahedron Lett.*, 3769 (1974); (d) M. G. Missakian, B. J. Burreson, and P. J. Scheuer, *Tetrahedron*, **31**, 2513 (1975); (e) Y. Kashman and A. Groweiss, *Tetrahedron Lett.*, 1159 (1977), and references cited therein; (f) B. F. Bowden, J. A. Brittle, J. C. Coll, N. Liyanage, S. J. Mitchell, and G. J. Stokie, *Ibid.*, 3661 (1977), and references cited therein; (g) A. J. Weinheimer, J. A. Matson, M. B. Hossain, and D. van der Helm, *Ibid.*, 2923 (1977); (h) see also M. Herin, M. Colin, and B. Tursch, *Bull. Soc. Chim. Belg.*, **85**, 801 (1976), and references cited therein.
(4) J. C. Braekman in "Marine Natural Products Chemistry", D. J. Faulkner and W. H. Fenical, Ed., Plenum Press, London, 1977, pp 5–15, and references cited therein.
(5) M. D. Higgs and D. J. Faulkner, *Steroids*, **30**, 379 (1977).
(6) The soft coral was tentatively assigned to the genus *Sarcophytum*. A voucher sample (76-265) is available.
(7) The presence of the cembranoid skeleton can be rigorously established through a series of arguments which have been omitted for the sake of clarity and brevity. In essence, there is only one way in which fragment 9 can be joined to a five-carbon fragment in order that levulinic acid can be produced by ozonolysis of two trisubstituted olefinic bonds. The remaining three carbon atoms must be in the ring in order to obtain the observed multiplicities in the ^{13}C-NMR spectrum.
(8) The epoxide ring was not reduced by lithium aluminum hydride in refluxing ether in any of the cembranoids that we have studied.
(9) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products", Pergamon, Oxford, 1964, pp 55–62.
(10) V. D. Patil, U. R. Nayak, and S. Dev, *Tetrahedron*, **29**, 341 (1973).
(11) P. Crews and E. Kho-Wiseman, *J. Org. Chem.*, **42**, 2812 (1977), and references cited therein.
(12) D. J. Falkner, *Synthesis*, 175 (1971), and references cited therein.