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TERPENOIDS—LXXIV[1]

THE SESQUITERPENES FROM THE SOFT CORAL *SINULARIA MAYI*[a]

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Abstract—Eleven sesquiterpene hydrocarbons, one [sinularene **11**] with a new non-farnesolic skeleton, and two new sesquiterpene diols from *S. mayi* were identified or structurally elucidated. Four 4,7-aromadendranediols were synthesized for reference purposes from spathulenol **23** and the stereochemistry assigned by ^{13}C spectroscopy.

The Alcyonaria[b] (Octocorallia) are an exclusively marine subclass of the Coelenterata and comprise six orders, two of the orders being the closely related Gorgonacea (horny corals) and Alcyonacea (soft corals).[2] The Gorgonacea, which are plentiful in the Caribbean area, were the first to be investigated and have yielded an abundance of natural products.[3] The Alcyonacea, which are plentiful in Indo-Pacific waters, have also proved to be a rich source of natural products yielding interesting sesquiterpenes,[4–8] diterpenes,[4,8–14] sterols,[4,8] and other compounds. We wish to report here the identification or structure elucidation of 13 sesquiterpenes from the alcyonacean *Sinularia mayi*.

S. mayi was found to contain eight major and a number of minor sesquiterpene hydrocarbons. The eight major sesquiterpene hydrocarbons were isolated by preparative GC; seven of these were identified as (+)-α-muurolene **1**, (+)-γ-muurolene **2**, (−)-δ-cadinene **3**, (+)-β-copaene **4**, (−)-aromadendrene **5**, (−)-bicyclogermacrene **6** and (+)-germacrene D **7**. These seven compounds are the optical antipodes of the more common or only enantiomeric forms found in terrestrial sources and hence support the generalization made by other workers that sesquiterpenes from the Coelenterata tend to have structures antipodal to those from terrestrial sources.[c] Several of the minor sesquiterpene hydrocarbons were tentatively identified[d] by combined GC-MS as α-copaene **8**, β-bourbonene **9** and calamenene **10**. Some of the above-mentioned sesquiterpenes could possibly be artifacts from the somewhat unstable germacrenes (**6** and **7**).[15,16] GC analysis of a crude hexane extract of *S. mayi* indicated that all of the major and the obvious minor sesquiterpene hydrocarbons were probably present before silica gel column chromatography; however, the amount of aromadendrene increased greatly upon silica gel chromatography or heating. (−)-Bicyclogermacrene **6** and (+)-germacrene D **7** are possibly the biosynthetic precursors of the other sesquiterpenes in *S. mayi*, and their presence emphasizes the importance of careful work that does not lead to artifacts when isolating natural compounds.

(−)-Sinularene **11**, the most abundant sesquiterpene hydrocarbon, proved to be a new terpenoid based on a hitherto unknown structure that cannot be derived by direct cyclization of a farnesol precursor. Derivatives **12**, **13** and **14** were prepared in an effort to determine the structure by chemical and spectral means. The structure **11**, which has recently been reported by us in a preliminary communication and is consistent with the spectral data, was established via an X-ray crystal structure determination of the *p*-bromobenzoate derivative **15**; a biogenetic scheme for **11** was also presented in that communication.[1] Experimental details for the earlier mentioned chemical transformations are now recorded in the experimental section.

Three sesquiterpene diols—(+)-4α,7β-aromadendranediol[e] **17**, (−)-4α,7α-aromadendranediol **18** and **19** (structure not determined)—were isolated from *S. mayi*. The structures of **17** and **18** were determined through synthesis (Fig. 2) of the four diols **18**, **20**, **21** and **22** from (+)-spathulenol **23**.[19] Interestingly, the two

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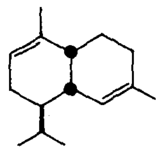
[a] Taken from the Ph.D. Dissertation (1977) of Curtis M. Beechan.

[b] Many researchers use the name "Alcyonaria" for a subclass of the Anthozoa as used here; others use the name "Alcyonaria" for just one order of this subclass—namely the order Alcyonacea.

[c] Sources of sesquiterpenes that are antipodal to those usually found are uncommon and thus worthy of note. Two such terrestrial sources are the liverworts[17] and the African tree *Brachylaena hutchinsii*;[18] from the latter source five of the reported sesquiterpene hydrocarbons have been found in the Alcyonaria and the remaining four are closely related compounds.

[d] β-Bourbonene and calamenene were identified by Dr. I. Wahlberg (Swedish Tobacco Company).

[e] In this paper the name "aromadendrane" is restricted to the most common aromadendrane skeleton—having the same relative stereochemistry for all three rings as aromadendrene **5**, the numbering system being that employed by *Chemical Abstracts*.



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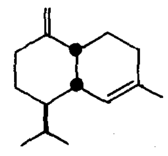

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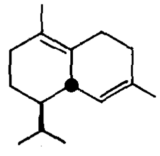

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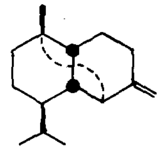

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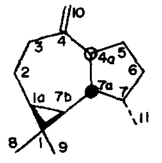

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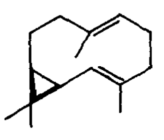

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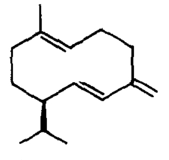

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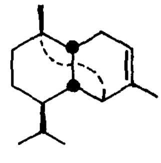

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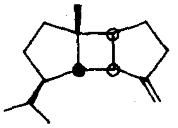

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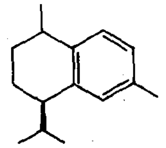

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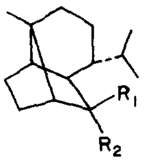
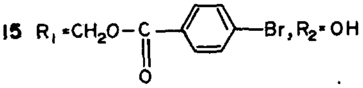


11 $R_1R_2{=}CH_2$

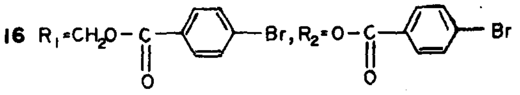
12 $R_1R_2{=}O$

13 $R_1{=}CH_2OH, R_2{=}H$

14 $R_1{=}CH_2OH, R_2{=}OH$



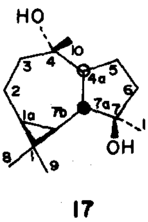
15 $R_1{=}CH_2O{-}C(=O){-}C_6H_4{-}Br, R_2{=}OH$



16 $R_1{=}CH_2O{-}C(=O){-}C_6H_4{-}Br, R_2{=}O{-}C(=O){-}C_6H_4{-}Br$

synthetic routes in Fig. 2 gave all four isomeric diols with no overlap of products. Synthetic diol **22** is the enantiomer of the major diol **17** from *S. mayi* whereas synthetic diol **18** is identical to **18** isolated from *S. mayi*. That **17** and **18** from *S. mayi* have frameworks that are antipodal to each other is interesting but not without precedent—a similar finding has recently been reported for sesquiterpene alcohols with the allo-aromadendrane skeleton isolated from another alcyonacean.[7] Based on spectral data, diol **19** from *S. mayi* probably has structure **28** which differs from the other two sesquiterpene diols (**17** and **18**) from *S. mayi* by having a *cis* as opposed to a *trans* ring juncture between the two larger rings.

The relative stereochemistry at C-7 of synthetic diols **21** and **22** is the same as for (+)-spathulenol **23** since the chemical transformations (Fig. 2) did not alter this part of the molecule; therefore, the relative stereochemistry at C-7 must be the opposite for the remaining two synthetic diols, **18** and **20**. The stereochemistry at C-4 for the four synthetic diols, and thus also for the diols **17** and **18** from *S. mayi*, was determined from ^{13}C NMR data (Table 1). For the compounds **18**, **20**, **21** and **22** comparison of proton noise decoupled spectra with off resonance spectra, obtained at two different decoupling frequencies, allowed the separation of all signals into those corresponding to C, CH, CH_2 and CH_3 carbon atoms. The assignment of the methyl group signals to their respective carbon atoms C-8, C-9, C-10 and C-11 was accomplished by comparison of the shifts of the compounds in Table 1 with each other and with the methyl chemical shifts of model compounds **29**, **30** and **31**.[20] Thus, in the diols **18** and **22** C-10 has an "axial" orientation with two more 1–4 steric γ-gauche interactions (with C-2 and C-7a) than in the diols **20** and **21**. Consequently, the "axial" C-10 signals are expected to occur at about 10 ppm higher field than the "equatorial" C-10 signals. Based on the environments, the respective chemical shifts of methyl carbons C-8, C-9 and C-11 would not be expected to vary appreciably for the four synthetic diols (**18**, **20**, **21**, **22**). All four synthetic diols have three resonances from methyl groups around 16, 25 and 29 ppm. Within each pair of diols, **18**, **20** and **21**, **22**, one have the fourth (C-10) methyl group signal around 20 ppm while in the other it is found around 31 ppm. Thus, the compounds with the high field C-10 signals are



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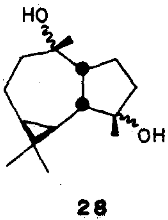

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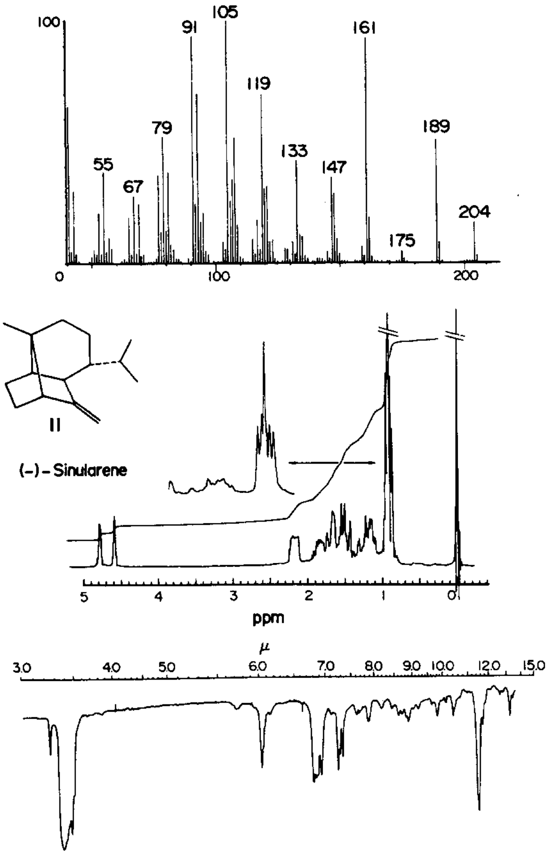
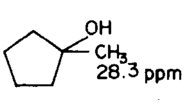


Fig. 1. NMR (100 MHz, $CDCl_3$, +TMS), IR and mass spectra of sinularene **11**.

assigned the structures **18** and **22**; and the diols with the low field C-10 signals, the structures **20** and **21**. In the same way, the signals for the remaining carbon atoms are assigned by comparison with known chemical shift data and shift parameters[21] and by correlating the systematic shifts due to differences in the structures of the six related compounds of Table 1, and are seen to confirm the assigned stereochemistry.



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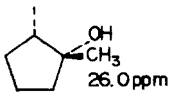

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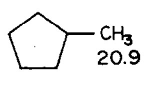

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Other sesqui- and diterpenes were encountered in *S. mayi* but were not thoroughly investigated. The present report demonstrates how rich a source of terpenes a single soft coral species can be and that care must be taken in the choice of separation methods so as to avoid artifact formation (e.g. acid-catalyzed cyclization of germacrenes). A detailed examination of terpenic constituents is also useful in order to determine whether radiolabel incorporation experiments are justified for eventual biosynthetic studies.

EXPERIMENTAL

The ^1H NMR spectra were run on a Varian T-60, Varian XL-100, or a Bruker 360 HXS spectrometer, and the ^{13}C NMR spectra were run on a Varian XL-100 spectrometer; all chemical shifts are relative to TMS. IR spectra were run on a Perkin–Elmer 421 spectrophotometer using thin films or KBr pellets. Conventional mass spectrometry was carried out on an A.E.I. MS-9 or an Atlas CH-4 spectrometer. GCMS analyses were performed on a Varian MAT 711 spectrometer interfaced with a Hewlett Packard 7610A gas chromatograph or a Varian MAT CH-7 mass spectrometer interfaced with a Hewlett Packard 402 gas chromatograph or an LKB 2091 instrument. Optical rotations were measured on a Perkin–Elmer 141 polarimeter using spectroscopy grade chloroform (without EtOH as a stabilizer) unless mentioned otherwise. The ORD and CD measurements were obtained on a JASCO model ORD/UV-5 instrument. M.ps were determined on a Thomas Hoover capillary m.p. apparatus or a Kofler hot stage m.p. apparatus and are uncorrected. All GC work was performed on Hewlett Packard 402 gas chromatographs using glass columns (4 mm i.d. × 1.5 m for analytical work and 8 mm i.d. × 1.5 m for preparative work). All TLC plates were prepared from aqueous slurries of silica gel (usually Silica Gel HF-254+366, Type 60, EM Reagents), and were dried at ~30° exposed to the atmosphere. All solvent ratios are for volumes. The percentage yields for compounds isolated from *S. mayi* are based on the mass of thoroughly dried colonies of this marine animal.

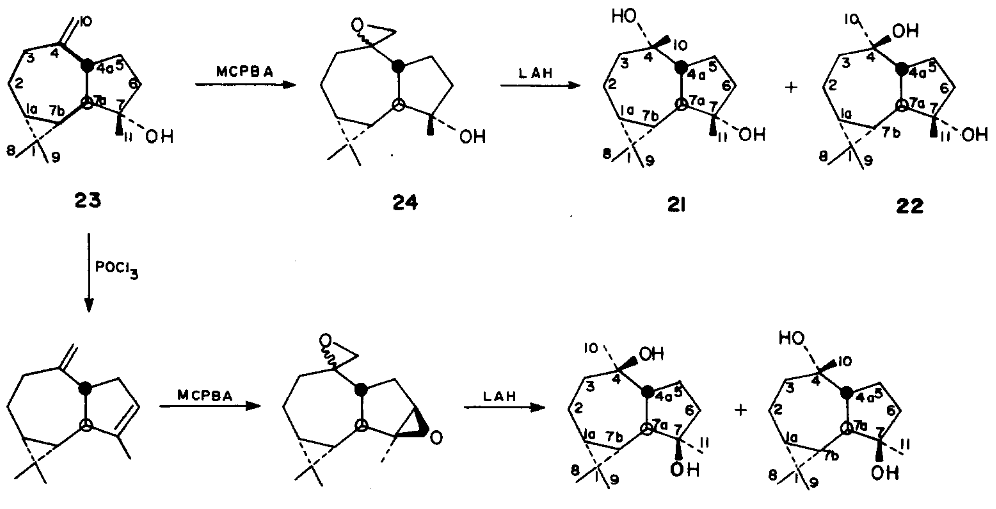


Fig. 2. Synthetic schemes for diols **18**, **20**, **21** and **22**.

Table 1. Chemical shifts[a] in ppm relative to TMS of compounds **5**, **18**, **20**, **21**, **22** and **23**

Carbon atom	Diol **18**	Diol **20**	Diol **21**	Diol **22**[b]	Spathulenol **23**[c]	Aromadendrene **5**[d]
1	18.9	20.1	20.9	19.4	20.3	20.0
1a	26.2	27.0	26.9	26.5	27.6	27.5
2	20.3	19.1	19.2	20.0	24.9	24.8
3	44.2	42.4	42.8	44.3	39.0	39.1
4	75.3	72.8	71.8	74.8	153.4	154.5
4a	54.5	52.5	56.4	56.2	53.6#	53.7
5	23.7	23.7	24.3	23.7	26.8*	29.2*
6	40.3	39.6	41.4	41.0	41.9	35.1
7	80.1	80.5	80.3	80.1	81.0	35.3
7a	47.5	45.8	47.2	48.2	54.4#	43.8
7b	25.0	24.9	30.1	28.3	30.1	29.5*
8	16.4	16.4	16.4	16.3	16.4	15.8
9	28.8	29.0	28.7	28.5	28.7	28.7
10	19.7	31.2	30.5	20.0	106.4	105.2
11	25.6	25.8	25.1	24.3	26.1*	17.1

[a] Entries marked with a * or # may be reversed. The spectra were run in $CDCl_3$ at ~35°.

[b] The above data presented for **22** were actually obtained for the enantiomer **17**.

[c] The chemical shift values of spathulenol **23** are from Ref. 22, but are reassigned in light of the data for the closely related compounds presented in this paper.

[d] Comparison of the chemical shifts of aromadendrene **5** with those of spathulenol **23** allowed the assignment of the spectrum of the former even though no off resonance data were available.

Colonies of *S. mayi* were collected in 1970 by Professor B. Tursch (University of Brussels) in shallow water at the outer edge of the Eastern reef of Telukdalam, Nias Island, Indonesia. The partially sun-dried animals were stored in a cold room. After tearing into small pieces and thoroughly drying at ~30°, a total of 2.5 kg of the resulting animal material was ground in hexane in a Waring blender and then allowed to soak in hexane to yield 44 grams of extract. Column chromatography through silica gel afforded the terpene hydrocarbons with partial resolution in the hexane fractions. Individual sesquiterpene hydrocarbons were isolated by preparative GC—utilizing 12% OV-17 on Chrom W A/W at 120–155° or 15% Carbowax 20 M on Chrom P A/W at 105–135°.

(+)-*α-Muurolene* **1** was isolated in approx. 0.008% yield and was identified via IR,[23,24] (GC) mass,[23,25] and NMR[23,26] spectra. The NMR shifts are slightly different from those in the literature which could be due to different solvents. For **1**: NMR (100 MHz, $CDCl_3$) δ 0.84 and δ 0.90 (doublets, J 6 Hz, isopropyl methyls), δ 1.69 (olefinic methyls), δ 5.44 (m, olefinic protons); $[\alpha]_D^{20^\circ} = +73^\circ$ (c 3.7, $CHCl_3$) (lit.[27,28] $[\alpha]_D^{23^\circ} = -85^\circ$ (c 1.5, $CHCl_3$)).

(+)-*γ-Muurolene* **2** was isolated in approximately 0.004% yield and was identified via IR,[23,24] (GC) mass,[23,25] and NMR[23,26] spectra. The NMR shifts are slightly different from those in the literature which could be due to different solvents. For **2**: NMR (100 MHz, $CDCl_3$) δ 0.78 and 0.91 (doublets, J 7 Hz, isopropyl methyls), δ 1.67 (olefinic methyl), δ 4.62 (broad d, vinylidene), δ 5.55 (m, olefinic proton); $[\alpha]_D^{20^\circ} = +9.7^\circ$ (c 1.6, $CHCl_3$) (lit.[28,29,30] $[\alpha]_D^{20^\circ} = -5^\circ$ to $+5^\circ$).

(−)-*δ-Cadinene* **3** was isolated in approx. 0.007% yield and was identified via IR,[23,31] (GC) mass[23,25,32] and NMR[23,33] spectra. $[\alpha]_D^{20^\circ} = -68^\circ$ (c 3.3, $CHCl_3$) (lit.[27,28] $[\alpha]_D^{23^\circ} = +93^\circ$ (c 0.8, $CHCl_3$)).

(+)-*β-Copaene* **4** was isolated in approx. 0.004% yield and was identified via IR,[23,34,35] mass[23,36,37] and NMR[23,34] spectra. For **4**: ^{13}C NMR ($CDCl_3$) 151.2 ppm, 116.0(?), 105.9, 59.7, 43.9, 42.7, 40.9, 36.6, 32.4, 32.2(?), 24.3, 22.4, 21.8, 19.9, 19.5; $[\alpha]_D^{20^\circ} = +9.8^\circ$ (0.6, CCl_4) (lit.[28,34] $[\alpha]_D^{22^\circ} = -7.5^\circ$ (c 0.9, $CHCl_3$)).

(−)-*Aromadendrene* **5** was isolated in approx. 0.004% yield and was identified via IR,[23,24] (GC) MS[23] and NMR[23,38] spectra; MS and NMR spectra of authentic aromadendrene for comparison were obtained from Prof. G. Büchi of the Massachusetts Institute of Technology. ^{13}C NMR data for **5** are in Table 1; $[\alpha]_D^{22^\circ} = -26^\circ$ (c 0.36, $CHCl_3$) (lit.[28,39] $[\alpha]_D^{20^\circ} = +24.5^\circ$).

(−)-*Bicyclogermacrene* **6** of about 87% purity (based solely on GC peak areas) was isolated in about 0.003% yield and was identified via its NMR spectrum.[23,40] The sample used for the mass spectrum apparently underwent the Cope rearrangement prior to ionization since the mass spectrum[23] agrees with that of bicycloelemene according to Dr. I. Wahlberg (Swedish Tobacco Company). For **6**: IR[23] 3026 cm^{-1}, 2930, 2864, 1657, 1453, 1412, 1392, 1378, 1239, 1202, 1179, 1150, 1122, 1066, 1042, 1030, 996, 981, 928, 882, 879, 868, 851, 831, 789; MS[23] M^+ 204 (17%), 121 (100%); $[\alpha]_D^{21^\circ} = -83^\circ$ (c 1.4, $CHCl_3$) (lit.[16] $[\alpha]_D = +61^\circ$ (acetone)).

(+)-*Germacrene D* **7** of about 80% purity (based solely on GC peak areas) was isolated in about 0.003% yield and was identified via IR,[23] MS[23] and NMR[15,23] spectra; spectra of authentic germacrene D for comparison were obtained from Prof. R. E. Kepner of the University of California (Davis). $[\alpha]_D^{22^\circ} = +190^\circ$ (c 1.0, $CHCl_3$) (lit.[41] $[\alpha]_D^{15^\circ} = -225^\circ$ (c, 1, *n*-hexane)).

(−)-*Sinularene* **11** was isolated in approx. 0.010% yield: IR[23] (see Fig. 1) (3072 cm^{-1}, 1660, 870) vinylidene, (1382 and 1365) isopropyl, 2957, 2879, 1471, 1460, 1441, 1374, 1312, 1303, 1269, 1160, 1148, 1131, 1124, 1019, 962, 855, 757; MS[23] (see Fig. 1) M^+ 204 ($C_{15}H_{24}$, 17%), 189 ($M-CH_3$, 51%), 161 (M-isopropyl, 93%), 105 (100%); NMR[23] (Fig. 1) (100 MHz, $CDCl_3$), δ 0.90 and 0.92 (doublets, J 6.4 Hz, isopropyl methyls), 0.915 (s, tertiary methyl), δ 2.1–2.25 allylic protons, δ 4.59 and 4.79 (vinylidene); ^{13}C NMR ($CDCl_3$) three CH_3 (20.7, 20.7, 21.4 ppm), five CH_2 (22.4, 26.0, 30.2, 31.7, 101.1 vinylidene), five CH (29.1, 42.9, 49.2, 50.2, 53.3), and two C (46.9, 162.9 vinylidene); $[\alpha]_D^{20^\circ} = -142^\circ$ (c 0.55, CCl_4).

Ketone **12**. Typically, ozonolysis[42] of 5.5 mg of sinularene **11** in CH_2Cl_2 at −78° gave 1.5 mg of **12** after treatment with saturated (aq) $FeSO_4$ and preparative GC [3% OV-25 on Chrom W, 130°]. Ketone **12** was also prepared via periodate cleavage of diol **14**. For **12**: IR[23] 1745 cm^{-1} (characteristic of cyclopentanones); MS[23] M^+ 206 ($C_{14}H_{22}O$, 100%), 135 (99%); NMR[23] (100 MHz, CCl_4) δ 0.90 and 0.93 (doublets, J 6.5 Hz, isopropyl methyls), δ 0.99 (s, tertiary methyl); ORD (methanol) $[\phi]_{589} - 96^\circ$, $[\phi]_{303} - 2700^\circ$, $[\phi]_{272} + 750^\circ$; CD (methanol) $[\theta]_{317.5} + 220$, $[\theta]_{287} - 2500$.

Alcohol **13**. Hydroboration-oxidation[43,44] of 12 mg of sinularene **11** gave 7.5 mg of alcohol **13** after preparative GC [3% OV-25 on Chrom W, 151°]. For **13**: IR (crude product) 3340 cm^{-1} (OH); MS[23] M^+ 222 ($C_{15}H_{26}O$, 28%), 204 ($M-H_2O$, 25%), 95 (100%); NMR[23] (60 MHz, $CDCl_3$) δ 0.83–0.92 (isopropyl methyls δ 0.92 (s, tertiary methyl), δ 3.77 (CH_2–O); $[\alpha]_D^{22^\circ} = -61^\circ$ (c 0.74, $CHCl_3$).

Diol **14**. To a soln of 74 mg of sinularene **11** in 0.5 ml of pyridine-dioxane (7 : 1) in a two dram vial was added 146 mg of OsO_4 dissolved in 3 ml of pyridine-dioxane (7 : 1).[45] The void volume was flushed briefly with N_2, and a Teflon-lined cap was screwed on tightly. After standing in the dark for three months with occasional agitation, 2.5 ml of pyridine and 12 ml of 95% EtOH were added and H_2S was bubbled through the mixture for 4 h. After remaining in a stoppered container for 10 h, H_2S was bubbled through for 2 more hours. The mixture was filtered and the solid was washed with95% EtOH. The residue from the filtrate and washings was subjected to preparative TLC [C_6H_6–EtOAc (4:1), double development, R_f 0.45] to yield 38 mg of **14**. For **14**: m.p. 96.5–97° (crystallized from CCl_4-isooctane); IR 3380 cm^{-1} (OH); MS[23] M^+ 238 ($C_{15}H_{26}O_2$, 12%), 41 (100%); NMR[23] (100 MHz, $CDCl_3$) δ 0.86 and 0.90 (doublets, J 6 Hz, isopropyl methyls), δ 1.01 (s, tertiary methyl), δ 3.68 and 3.91 (doublets, J 11 Hz, CH_2–O).

p-Bromobenzoate **15** *and* bis-(p-*bromobenzoate)* **16** *of* **14**. To a one dram vial were added 27 mg of diol **14**, 1.3 ml of pyridine and 123 mg of *p*-bromobenzoyl chloride. A Teflon-lined cap was screwed on tightly. The mixture was stirred at 61° for 7.5 h and then partitioned between ether and H_2O. Repetitive preparative TLC [C_6H_6, triple development, **15** R_f 0.40, **16** R_f 0.88] gave 35 mg of **15** and 9 mg of **16**. For **15**: m.p. 48–49° (crystallized from acetone-H_2O); the NMR[23] and IR spectra are consistent with the assigned structure; (Anal. Calc. for $C_{22}H_{29}O_3Br$: MW 420.1300/422.1280. Found: MW (MS), 420.1269/422.1281). For **16**: m.p. 160.0–160.3° (crystallized from hexane); MS M^+ 604 ($C_{29}H_{32}O_4Br_2$); the NMR spectrum[23] is consistent with the assigned structure.

Isolation of (+) - *4α,7β - aromadendranediol* **17**, (–) - *4α,7α - aromadendranediol* **18** *and sesquiterpene diol* **19** *from* S. mayi. The crude hexane extract of *S. mayi* was subjected to silica gel column chromatography using gradient elution with hexane-$CHCl_3$-MeOH. Silica gel column chromatography of appropriate resulting fractions using gradient elution with hexane-acetone afforded **17** and then a mixture of **18** and **19** in the 20% and 25% acetone fractions respectively. Diol **17** and the mixture of diols **18** and **19** were separately rechromatographed through silica gel columns using gradient elution with hexane-ether. Diol **17**, obtained in about 0.02% yield, was further purified by crystallization: Diol **17** was dissolved in a very small amount of $CHCl_3$ or $CHCl_3$-hexane. Hexane was layered on top of this solution, and the mixture was left undisturbed in a sealed container for the solvents to slowly diffuse into each other. Sometimes slow evaporation and/or seeding of the resulting solution were necessary. The NMR,[23] IR[23] and mass[23] spectra and other physical data (except for the sign of the optical rotation) of **17** match those of synthetic diol **22** (see below). For **17**: m.p. 134.8–135.5°; ^{13}C NMR (see Table 1); $[\alpha]_D^{20°} = +22.4°$ (c 1.4, $CHCl_3$); (Found: C, 75.49; H, 10.84. Calc. for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99%). Diols **18** and **19** were separated from each other by HPLC [two Waters Associates μBondapak C_{18} columns (each 4 mm i.d. × 30 cm) in series, MeOH–H_2O (2:1), 2500 psi, ~1 ml/min flow, **18** r.t. 20 min, **19** r.t. 40 min]. Diol **18**, obtained in about 0.001% yield, was further purified by preparative TLC [$CHCl_3$-acetone (7:2), double development, R_f 0.45] and then crystallized from $CHCl_3$-hexane (as described for diol **17**) whereas diol **19**, isolated in about 0.001% yield, was just crystallized from $CHCl_3$-hexane (as described for diol **17**). The NMR[23] and IR[23] spectra and other physical data of **18** from *S. mayi* matched those of synthetic **18** (see below). For **18** from *S. mayi*: m.p. 137.3–138.0°; $[\alpha]_D^{20°} = -41.6°$ (c 0.6, $CHCl_3$). For **19**: m.p. 114.8–114.9°; MS[23] M^+ 238 ($C_{15}H_{26}O_2$, 2%), 220 (M–H_2O, 13%), 205 (M-H_2O–CH_3, 12%), 202 (M-2H_2O, 13%), 187 (M-2H_2O–CH_3, 10%), 177 (M-H_2O–C_3H_7, 10%), 159 (M-2H_2O–C_3H_7, 24%), 43 (100%); NMR[23] (100 MHz, $CDCl_3$) δ 0.02 (dd, J_1 10 Hz, J_2 10 Hz, cyclopropyl proton), δ 0.63 (m, cyclopropyl proton), δ 1.06 (geminal methyls), δ 1.22 and 1.36 (singlets, methyls); ^{13}C NMR ($CDCl_3$) 81.9 (s) ppm, 74.1 (s), 53.8 (d), 47.5 (d), 38.0, 37.6, 32.0 (q), 28.8, 28.5, 25.4, 25.1, 18.7, 18.6, 16.1 (q), the signal of the remaining carbon was not obvious; $[\alpha]_D^{20°} = -10°$ (c 0.9, $CHCl_3$, soln somewhat turbid); (Found: C, 73.65; H, 10.96. Calc. for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99%).

Isolation of (+)-*spathulenol* **23** *from* Eucalyptus spathulata.[19] (+)-Spathulenol **23** was isolated from the essential oil of *Eucalyptus spathulata* (kindly provided by Prof. P. R. Jefferies of the University of Western Australia) via vacuum distillation followed by column chromatography on silica gel impregnated with $AgNO_3$ using gradient elution with $CHCl_3$-acetone. The IR and NMR spectra of the isolated **23** agree with published spectra.[19,22]

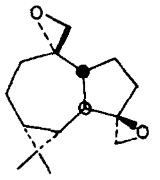
Spathulenol epoxides **24**. The reaction of spathulenol **23** with 85% *m*-chloroperbenzoic acid was performed essentially as described below for the epoxidation of *β*-spathulene **25** and gave epoxides **24** which were not separated due to separation problems. For the mixture of epoxides **24**: IR 3450 cm^{-1} (OH); MS[23] M^+ 236 ($C_{15}H_{24}O_2$, 0.5%, not unambiguously M^+), 218 (M-H_2O, 31%), 41 (100%); NMR (100 MHz, CCl_4) δ 1.05 (methyls), δ 1.12 (s, methyl), δ 1.16 (s, methyl), δ 1.20 (s, methyl), δ 2.25–2.71 (epoxy protons).

(–)-4β,7β-Aromadendranediol **21** *and (–)-4α,7β-aromadendranediol* **22**. A mixture of 12 ml of ether, 184 mg of the mixture of epoxides **24**, and 355 mg of $LiAlH_4$ was stirred for 5.5 h. Excess $LiAlH_4$ was destroyed with saturated (aq) Na_2SO_4. Preparative TLC [$CHCl_3$-acetone (9:1), triple development, **21** R_f 0.35, **22** R_f 0.45] yielded 84 mg of **21** and 50 mg of **22**, which were purified further by crystallizing from $CHCl_3$-hexane (as described for diol **17**). For **21**: m.p. 142.5–142.7°; IR[23] 3345 cm^{-1} (OH); MS[23] M^+ 238 ($C_{15}H_{26}O_2$, 4%), 220 (M-H_2O, 11%), 205 (M-H_2O–CH_3, 11%), 202 (M-2H_2O, 32%), 187 (M-2H_2O–CH_3, 21%), 177 (M-H_2O–C_3H_7, 12%), 159 (M-2H_2O–C_3H_7, 36%), 43 (100%); NMR[23] (100 MHz, $CDCl_3$) δ 0.23–0.74 (cyclopropyl protons), δ 1.03 and 1.11 (singlets, tertiary methyls), δ 1.20 and 1.25 (singlets, methyls); ^{13}C NMR (see Table 1); $[\alpha]_D^{20°} = -12.6°$ (c 1.2, $CHCl_3$); (Found: C, 75.44; H, 10.99. Calc. for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99%). For **22**: m.p. 134.8–135.3°; IR[23] 3384 cm^{-1} (OH); MS[23] M^+ 238 ($C_{15}H_{26}O_2$, 5%), 220 (M-H_2O, 19%), 205 (M-H_2O–CH_3, 23%), 202 (M-2H_2O, 16%), 187 (M-2H_2O–CH_3, 12%), 177 (M-H_2O–C_3H_7, 17%), 159 (M-2H_2O–C_3H_7, 22%), 43 (100%); NMR[23] (100 MHz, $CDCl_3$) δ 0.30–1.0 (cyclopropyl protons), δ 1.04 (s, geminal methyls), δ 1.17 and 1.25 (singlets, methyls); ^{13}C NMR (see Table 1); $[\alpha]_D^{20°} = -22.9°$ (c 1.9, $CHCl_3$).

β-Spathulene **25**. To a stirred soln of 170 mg of (+)-spathulenol **23** in 1.5 ml of dry pyridine in an ice-water-salt bath was slowly added 0.3 ml of phosphorus oxychloride $POCl_3$.[46] After being stirred for 2 days at room temp. the mixture was slowly added to crushed ice. Partitioning between H_2O and hexane followed by preparative TLC (silica gel containing 15% $AgNO_3$, C_6H_6, double development, R_f 0.40) yielded 109 mg of *β*-spathulene **25** which was identified by IR,[22,23] mass[23,47] and NMR[23,47] spectra. The published description of the NMR spectrum differs slightly.[47] For **25**: MS[23] M^+ 202 ($C_{15}H_{22}$, 33%), 159 (100%), 105 (99%); NMR[23] (100 MHz, $CDCl_3$) δ 1.04 and 1.08 (singlets, tertiary methyls), δ 1.67 (olefinic methyl), δ 4.70 (broad s, vinylidene), δ 5.37 (m, olefinic proton); $[\alpha]_D^{20°} = +77°$ (c 0.48, CCl_4).

Diepoxides **26**, **27** *and* **32**. A mixture of 113 mg of *β*-spathulene **25**, 1.5 g of 85% *m*-chloroperbenzoic acid, and 12 ml of $CHCl_3$ was stirred in the dark for 5.25 h and was then partitioned between ether and 10% (aq) Na_2SO_3. The organic phase was washed with 5% (aq) $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated to give a residue consisting of essentially the three diepoxides. Preparative TLC [hexane–ether (4:1), four developments, **26** R_f 0.38, **27** R_f 0.53, **32** R_f 0.65] gave 25 mg of **26**, 73 mg of **27**, and 4 mg of **32**. For **26**: MS[23] M^+ 234 ($C_{15}H_{22}O_2$, 37%), 43 (100%); NMR (100 MHz, C_6D_6) δ 0.90 and 0.96 (singlets, tertiary methyls), δ 1.23 (s, epoxy methyl), δ 2.94 (broad s, epoxy proton)—the other epoxy protons are not obvious; $[\alpha]_D^{20°} = -2°$ (c 0.5, CCl_4). For **27**: MS[23] M^+ 234 ($C_{15}H_{22}O_2$, 29%), 43 (100%); NMR (100 MHz, C_6D_6) δ 0.97 and 0.99 (singlets, tertiary methyls), δ 1.22 (s, epoxy methyl), δ 2.10 and 2.26 (doublets, J 5 Hz, epoxy protons), δ 2.97 (broad s, epoxy proton); $[\alpha]_D^{20°} = -13°$ (c 0.27, CCl_4). For **32**: NMR (100 MHz, CCl_4) δ 1.00 (s, tertiary methyls), δ 2.36, 2.50, 2.61 and 2.65 (four doublets, J 5 Hz for each, epoxy protons), no epoxy methyls.

Synthetic (–)-4α,7α-aromadendranediol **18**. $LiAlH_4$ reduction of **26** to diol **18** was accomplished in excellent yield using essentially the procedure given for the reduction of spathulenol epoxides **24**. The product was crystallized from $CHCl_3$-hexane (as described for **17**). For **18**: m.p. 137.5–138.5°; IR[23] 3410 cm^{-1} (OH); MS[23] M^+ 238 ($C_{15}H_{26}O_2$, 1%), 220 (M-H_2O, 11%), 205



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(M-H_2O-CH_3, 14%), 202 (M-2H_2O, 21%), 187 (M-2H_2O-CH_3, 15%), 177 (M-H_2O-C_3H_7, 10%), 159 (M-2H_2O-C_3H_7, 30%), 43 (100%); NMR[23] (100 MHz, $CDCl_3$) δ 0.58–0.90 (cyclopropyl protons), δ 0.98 and 1.06 (singlets, geminal methyls), δ 1.10 and 1.24 (singlets, methyls); ^{13}C NMR (see Table 1); $[\alpha]_D^{20°} = -39.3°$ (c 0.6, $CHCl_3$); (Found: C, 76.42; H, 11.06. Calc. for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99%).

(−)-4*β*,7*α*-*Aromadendranediol* **20**. $LiAlH_4$ reduction of **27** or **32** gave diol **20** in good yield using essentially the same procedure given for the reduction of spathulenol epoxides **24**. That the product from both **27** and **32** is the same is based on analytical TLC and NMR spectra. Diol **20** from **27** was purified by slow precipitation as beads or clumps of solid from supersaturated hexane solutions. For **20**: m.p. 86.7–87.7°; IR[23] 3430 cm^{-1} (OH); MS[23] M^+ 238 ($C_{15}H_{26}O_2$, 7%), 220 (M-H_2O, 10%), 205 (M-H_2O-CH_3, 8%), 202 (M-2H_2O, 20%), 187 (M-2H_2O-CH_3, 16%), 177 (M-H_2O-C_3H_7, 9%), 159 (M-2H_2O-C_3H_7, 20%), 43 (100%); NMR[23] (100 MHz, $CDCl_3$) δ 0.54–0.72 (cyclopropyl protons), δ 1.05 (s, geminal methyls), δ 1.21 and 1.25 (singlets, methyls); ^{13}C NMR (see Table 1); $[\alpha]_D^{20°} = -35.8°$ (c 1.1, $CHCl_3$); (Found: C, 75.42; H, 10.96. Calc. for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99%).

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