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# The Synthesis of Mono- and Dihydroxy Aromadendrane Sesquiterpenes, Starting from Natural (+)-Aromadendrene-III[1]

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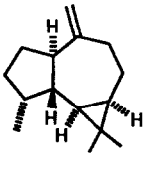
***Abstract:*** *The monoalcohols (−)-globulol (2), (−)-epiglobulol (3), (−)-ledol (4), and (+)-viridiflorol (5) were synthesized from (+)-aromadendrene (1). The cis-fused alloaromadendrone (14), the key intermediate used in the synthesis of 4 and 5, was obtained from the trans-fused apoaromadendrone (13) via a selective protonation of the thermodynamic enol trimethylsilylether 15. After hydroxylation of the tertiary C11 of 13 with $RuO_4$, (+)-spathulenol (6), (−)-allospathulenol (7), and the aromadendrane diols 8-11 could be prepared. Compounds 2-11 were tested for antifungal properties, but their activity was only moderate.*

(+)-Aromadendrene (1), the main constituent in a commercially available distillation tail of the oil of *Eucalyptus globulus*[2], is a representative of a group of tricyclic sesquiterpenes, structurally characterized by a dimethyl cyclopropane ring fused to a hydroazulene ringsystem. In previous papers, the large-scale conversion of 1 into a chiral synthon[3] and its conversion into (−)-kessane[4] were described. We now wish to report the outcome of our investigations on the usefulness of 1 in the synthesis of the hydroxylated aromadendrane derivatives 2 - 11. In addition, the results of testing these compounds for their antifungal properties are given.

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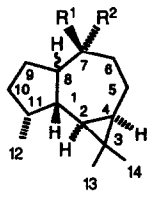
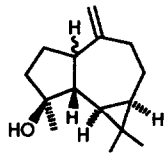
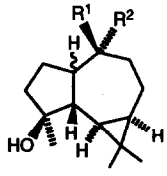


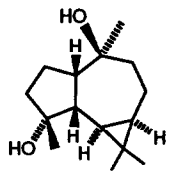
**2** : 8αH; $R^1$=$CH_3$; $R^2$=OH
**3** : 8αH; $R^1$=OH; $R^2$=$CH_3$
**4** : 8βH; $R^1$=$CH_3$; $R^2$=OH
**5** : 8βH; $R^1$=OH; $R^2$=$CH_3$



**6** : 8αH
**7** : 8βH



**8** : 8αH; $R^1$=$CH_3$; $R^2$=OH
**9** : 8αH; $R^1$=OH; $R^2$=$CH_3$
**10** : 8βH; $R^1$=$CH_3$; $R^2$=OH
**11** : 8βH; $R^1$=OH; $R^2$=$CH_3$



**12**

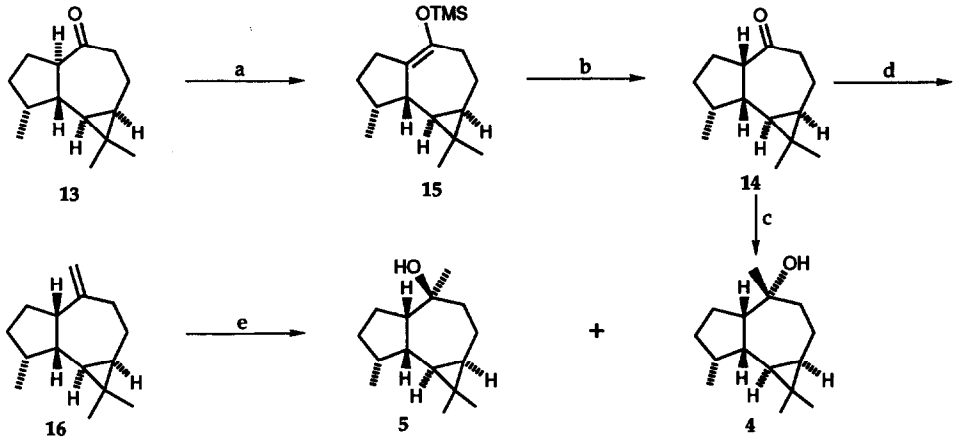
The aromadendrane C7 monoalcohols (–)-globulol (**2**), (–)-epiglobulol (**3**), (–)-ledol (**4**)[5], and (+)-viridiflorol (**5**) have been found in a broad spectrum of plant species. (+)-Spathulenol (**6**), a C11 monoalcohol, is also present in many plant genera. The dihydroxy aromadendrane sesquiterpenes are less commonly found in nature. (–)-Aromadendrane-7α,11β-diol (**8**) has been isolated from only four different plant species[6]. The structure of **8** has been determined through synthesis from **6**[6b]. From the soft coral *Sinularia mayi* (+)-**8**, (–)-aromadendrane-7α,11α-diol, and a related diol with unknown stereochemistry have been isolated[7]. An alloaromadendrane-7,11-diol, to which structure **12** was assigned, has been obtained from *Ambrosia peruviana*.[8] Direct comparison of the spectral data of **12** with those of the unknown metabolite from *S. mayi* showed that these compounds are identical in all respects except in their rotation.

Some of the compounds mentioned above show activity as an antifungal agent, e.g. ledol against *Coriolus renatus*[9] and diol **12** against *Cladosporium herbarium*.[8] The antifungal properties of spathulenol might be responsible for its repellency against leaf cutter ants[10].

Although **1** seems to be the obvious starting material for the synthesis of aromadendrane alcohols, no detailed study has been reported in this direction. As described previously, an easily separable mixture of **2** and **3** could be prepared via epoxidation of **1** with *m*-CPBA and subsequent reduction of the epoxides with $LiAlH_4$[3,11]. Treatment of (–)-apoaromadendrone (**13**), which was easily obtained in large quantities after ozonolysis of the abovementioned distillation tail[3,12], with MeLi at -78°C selectively produced **3** in 94% yield[11a].The use of the *trans*-fused ketone **13** as the starting material for the synthesis of the *cis*-fused alcohols **4** and **5** required epimerization at C8. Treatment of **13** with NaOMe led to an equilibrium mixture of **13** and (–)-alloaromadendrone (**14**) in a ratio of 4 : 1, respectively, which was very difficult to separate by column chromatography. It was discovered that pure **14** could be obtained from the thermodynamic enol trimethylsilylether **15**. The crystalline **15** was prepared in 97% yield upon treatment of **13** with TMSCl and triethylamine ($Et_3N$) in DMF at reflux temperature for 2 d. During the recrystallization of **15** from MeOH we noticed a partial conversion into **14**. This observation led to an experiment in which **15** was treated with MeOH in the presence of $Et_3N$[13] at -20°C for 4 h. In this way **14** was obtained in almost quantitative yield (Scheme I). This unexpected selectivity can be explained by an approach of the electrophile from the sterically

less hindered β side of the molecule. Another explanation for the selective formation of **14** might be a stereoelectronically controlled ketonization of **15**[14]. The reaction of **14** with MeMgI gave a mixture of **4** and **5** in a ratio of 2 : 1, respectively. On the other hand, treatment of **14** with MeLi at -78°C afforded **4** as the sole product in 91 % yield.

**Scheme I**[a]



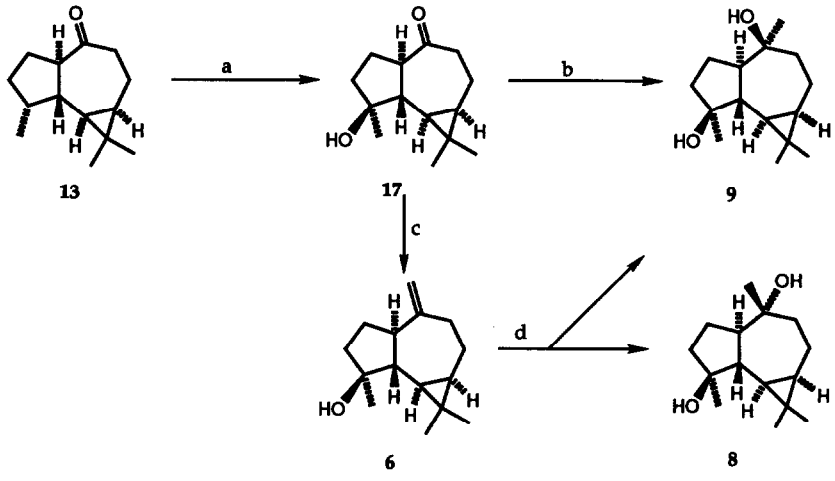

[a] (a) TMSCl, $Et_3N$, DMF, 130°C; (b) MeOH, $Et_3N$; (c) MeLi, -78°C→rt; (d) $TMSCH_2MgCl$; KH; (e) dimethyldioxirane; $LiAlH_4$.

The synthesis of **5** proceeded via (–)-alloaromadendrene (**16**). Using normal Wittig reaction conditions ($Ph_3P{=}CH_2$, DMSO) the *cis* ketone **14** only gave **1**. Evidently, **14** epimerizes at C8 under these reaction conditions and the resulting *trans* ketone **13** preferentially condenses with $Ph_3P{=}CH_2$. This epimerization could be prevented by using a Peterson olefination reaction[15]. Thus, reaction of **14** with trimethylsilylmethylmagnesium chloride ($TMSCH_2MgCl$) and subsequent treatment with KH in THF[16] afforded **16** in 91% yield. Epoxidation of **16** with *in situ* generated dimethyldioxirane[17] and reduction of the resulting mixture of epoxides with $LiAlH_4$ gave a 1 : 4 mixture of the alcohols **4** and **5** in 89% yield. Unfortunately, separation of the two isomers by column chromatography was not possible. However, preparative gas chromatography afforded pure **5** in an overall yield of 54% from **16**.

For the synthesis of the aromadendranediols **8** - **11** the five-membered ring of the aromadendrane skeleton had to be hydroxylated at C11. The ozonization of **13** was reported to give the hydroxy ketone **17** in 9% yield[12]. We found that the yield of **17** could be considerably improved using ruthenium(IV)oxide ($RuO_2$) and sodium periodate ($NaIO_4$) in a mixture of $CCl_4$, MeCN, and $H_2O$ at 50°C[18]. Optimum yields (35-40%) of **17** were obtained after 50% conversion of **13** (Scheme II). Completion of the reaction gave only poor yields of **17**, probably as the result of overoxidation. Higher reaction temperatures (> 60°C) also lowered the yield and led to polar, unidentified products.

Other substrates, such as **2** and **3** , which would lead directly to the *trans*-fused diols **8** and **9**, respectively, showed predominantly overoxidation with $RuO_2/NaIO_4$. Therefore, starting from the hydroxy ketone **17**, the methods outlined above for the synthesis of the monoalcohols **2-7** were employed in the synthesis of the diols **8-11**. Treatment of **17** with MeMgI afforded (–)-**9** in 91% yield. For the synthesis of its C7 epimer **8** the hydroxy ketone **17** was converted into (+)-spathulenol (**6**). A Peterson olefination reaction gave **6** in quantitative yield[19]. Epoxidation of **6** with dimethyldioxirane and subsequent reduction of the resulting mixture of epoxides led to a 1 : 1 mixture of the diols **8** and **9** in 88% yield. Careful column chromatography and crystallization from petroleum ether (bp. 80-100°C) gave a pure sample of **8**.

**Scheme II**[a]

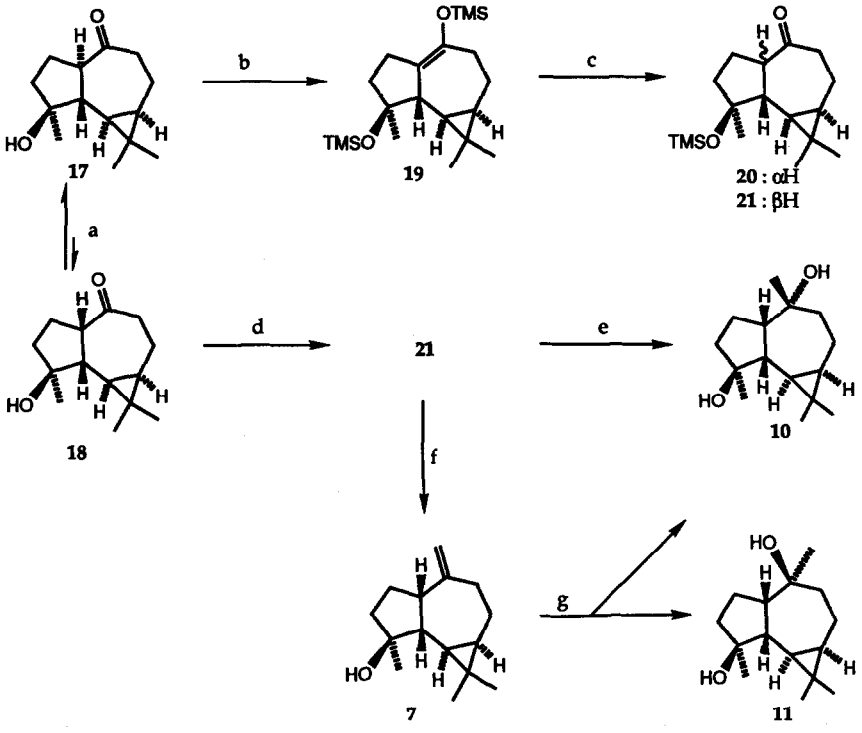



[a] (a) $RuO_2$, $NaIO_4$, 50°C; (b) MeMgI; (c) $TMSCH_2MgCl$; $H^+$, THF; (d) dimethyldioxirane; $LiAlH_4$.

For the synthesis of the alloaromadendrane-7,11-diols **10** and **11** the preparation of the *cis*-fused hydroxy ketone **18** was required. In an effort to synthesize **18** via the C11 hydroxylation of **14** with $RuO_2/NaIO_4$, predominantly overoxidation was observed. Therefore, it was tried to prepare **18** in a similar way as described above for the synthesis of **14**. Treatment of **17** with TMSCl and $Et_3N$ in DMF at reflux temperature for 22 h resulted in the formation of the enol trimethylsilylether **19** (Scheme III). Unfortunately, the ketonization of **19** with MeOH in the presence of $Et_3N$ did not proceed in a selective way. According to $^1H$ NMR, an inseparable 1 : 1 mixture of **20** and **21** was obtained. Probably, the β-silyloxy group at C4 of **19** sterically hinders the approach of the electrophile from the β side of the molecule. On the other hand, a short treatment of **17** with NaOMe in MeOH resulted in an equilibrium mixture of **17** and **18** in a ratio of 7 : 3, respectively. Since **17** and **18** could be easily separated by flash chromatography, this simple procedure was used to produce sufficient amounts of **18**. After three successive

treatments of **17** with NaOMe, **18** was obtained in 58% overall yield. Treatment of **18** with MeMgI did not give the expected diol **10**. Instead, considerable amounts of **17** were obtained. Probably, the alcohol function at C11 is deprotonated and stimulates intramolecularly the enolization of the carbonyl group towards C8 which will prevent the addition of the Grignard reagent. After protection of the hydroxyl group as its trimethylsilylether (**18** → **21**), the reaction with MeMgI proceeded smoothly. Cleavage of the trimethylsilylether resulted in a 79% yield of (+)-allo-aromadendrane-7α,11β-diol (**10**) starting from **18**.

**Scheme III**[a]




[a] (a) NaOMe, MeOH; (b) TMSCl, $Et_3N$, DMF, 130°C; (c) MeOH, $Et_3N$; (d) TMSCl, HMDS; (e) MeMgI; (f) $TMSCH_2MgCl$; $H^+$,THF; (g) dimethyldioxirane; $LiAlH_4$.

The diol **11** could be prepared from **21** in a similar reaction sequence as employed for the synthesis of **5**. A Peterson olefination reaction of **21** gave (–)-allospathulenol (**7**)[20] in 87% yield. Epoxidation of **7** followed by reduction afforded (+)-alloaromadendrane-7β,11β-diol (**11**) in 86% yield, together with 9% of **10**. Direct comparison of **11** with the aromadendranediol isolated from *A. peruviana* showed that these compounds are identical in all respects. As a

consequence, the structure assigned to the natural product from *A. peruviana* must be **11**, and not **12** as proposed in the literature[8].

The compounds **2 - 11** were tested for antifungal activity on the fungi *Cladosporium cucumerinum* and *Penicillium italicum* via the minimal inhibitory concentration (MIC) test[21] and a thin-layer bioautography test[22]. In MIC tests the toxicity of all compounds was higher for *C. cucumerinum* than for *P. Italicum*. MIC's of all compounds to *P. Italicum* were higher than 100 μg $ml^{-1}$. Therefore, only the results obtained with *C. cucumerinum* are presented (Table 1). The MIC test and the thin-layer bioautography test demonstrated fungitoxicity for the monoalcohols **2, 3, 5, 6,** and **7**. The compounds **8** and **11** were only active in the thin-layer bioautography test. However, the fungitoxicity of the active compounds should be regarded as moderate, since complete growth inhibition only takes place at high (≥100 μg $ml^{-1}$) concentrations of the test compounds[23].

**Table 1.** Fungitoxicity of test compounds to growth of *Cladosporium cucumerinum* in a Minimal Inhibitory Concentration (MIC) test and a Thin-layer Bioautography test.

| Compound | MIC test | | | | Bioautography test | | | |
|---|---|---|---|---|---|---|---|---|
| | Concentration (μg $mL^{-1}$) | | | | Concentration (μg $mL^{-1}$) | | | |
| | 0 | 1 | 10 | 100 | 0 | 10 | 100 | 1000 |
| **2** | 5[a] | 5 | 5 | 0 | 3[b] | 2 | 1 | 0 |
| **3** | 5 | 5 | 4 | 0 | 3 | 2 | 1 | 0 |
| **4** | 5 | 5 | 5 | 4 | 3 | 3 | 3 | 2 |
| **5** | 5 | 5 | 5 | 0 | 3 | 3 | 1 | 0 |
| **6** | 5 | 4 | 3 | 0 | 3 | 2 | 1 | 0 |
| **7** | 5 | 5 | 4 | 0 | 3 | 2 | 1 | 0 |
| **8** | 5 | 5 | 5 | 5 | 3 | 3 | 1 | 0 |
| **9** | 5 | 5 | 5 | 5 | 3 | 3 | 3 | 2 |
| **10** | 5 | 5 | 5 | 5 | 3 | 3 | 3 | 2 |
| **11** | 5 | 5 | 5 | 5 | 3 | 3 | 1 | 0 |

[a] Scores used for evaluation of fungal growth in MIC tests: 5 = dense mycelial growth and heavy sporulation, 4 = dense mycelial growth but slight sporulation, 3 = 100-1000 colonies per plate, 2 = idem 10-100, 1 = idem 1- 10, and 0 = no colonies present.

[b] Scores used for evaluation of fungal growth in bioautography test: 3 = normal dense growth, 2 = slight growth inhibition, 1 = strong growth inhibition, and 0 = no growth.

## EXPERIMENTAL SECTION

Melting points were determined on an Olympus HSA melting point apparatus and are uncorrected. Optical rotations were obtained from $CHCl_3$ solutions on a Perkin-Elmer 241 polarimeter. $^1H$ and $^{13}C$ NMR spectra were recorded at 200 MHz and 50 MHz, respectively, on a Bruker AC-E 200 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0) as an internal standard in $CDCl_3$ as the solvent. Mass spectral data were determined on either an AEI MS 902 spectrometer or a Hewlett Packard 5970 B series MSD

coupled with a Hewlett Packard 5890 A gas chromatograph with a DB-17 fused silica capillary column. Elemental analyses were determined on a Carlo Erba elemental analyzer 1106. GC analyses were carried out on a Varian Vista 6000 gaschromatograph with a flame ionization detector and a DB-17 fused silica capillary column, 30 m x 0.25 mm i.d., film thickness 0.25 μm. Peak areas were integrated electronically with a Spectra-Physics integrator SP 4290. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh). Solvents were dried and distilled fresh by common practice. For all dry reactions, flasks were dried at 150°C and flushed with dry nitrogen just before use, and reactions were carried out under an atmosphere of dry nitrogen. Product solutions were dried over anhydrous $MgSO_4$, unless otherwise noted, prior to evaporation of the solvent under reduced pressure by using a rotary evaporator.

**(−)-Epiglobulol (3).** To a solution of 2.04 g (10.0 mmol) of **13** in 40 mL of dry ether, cooled to -78°C, was added dropwise 10 mL (15 mmol) of MeLi (1.5 M in ether). The reaction mixture was stirred for 1 h at -78°C, allowed to come to room temperature, and then carefully quenched with 15 mL of saturated aqueous $NH_4Cl$. The two-phase mixture was separated, and the aqueous solution was extracted with four 25-mL portions of ether. The combined organic layers were washed with 25 mL of brine, dried, and evaporated under reduced pressure. The crude product was flash chromatographed [6:1 petroleum ether (bp 40-60°C)/EtOAc] to give 2.05 g (94%) of **3** as a colourless oil. Physical and spectroscopic data were consistent with those reported in the literature[3,11b].

**Enol trimethylsilylether 15.** To a stirred mixture of 32 mL of DMF, 16.8 mL (192 mmol) of $Et_3N$, and 13.0 mL (102 mmol) of TMSCl was added 14.42 g (70.0 mmol) of **13**. The reaction mixture was heated at reflux for 48 h, allowed to come to room temperature, and then 200 mL of petroleum ether (bp 40-60°C) was added. The resulting mixture was washed twice with 50 mL of saturated aqueous $NaHCO_3$, and the combined aqueous layers were back-extracted with two 100-mL portions of petroleum ether (bp 40-60°C). The combined organic layers were dried over $Na_2SO_4$ and evaporated under reduced pressure. According to GC-MS analysis, the solid residue (19.42 g) consisted for 97% of **15**. Recrystallization from 350 mL of dry $CH_3CN$ afforded 16.54 g (85%) of pure **15**: mp 57°C; $[\alpha]_D$ +76.5° (c 1.42); $^1H$ NMR ($CDCl_3$) δ 0.13 (s, 9H), 0.48 (ddd, J = 4.8, 9.5, 11.5 Hz, 1H), 0.67 (t, J = 9.5 Hz, 1H), 0.92 (d, J = 6.9 Hz, 3H), 0.95 (s, 3H), 1.02 (s, 3H), 1.04-2.54 (m, 10H); $^{13}C$ NMR ($CDCl_3$) δ 0.53 (3·q), 15.30 (q), 15.47 (q), 17.55 (s), 20.55 (t), 24.94 (d), 28.16 (q), 29.89 (t), 30.45 (d), 32.10 (t), 35.03 (t), 37.23 (d), 37.43 (d), 126.33 (s), 141.26 (s); mass spectrum, *m/e* (relative intensity) 278 ($M^+$, 17), 263 (10), 235 (40), 221 (8), 195 (10), 181 (15), 145 (19), 91 (21), 73 (100), 45 (30); calcd for $C_{17}H_{30}OSi$ ($M^+$) *m/e* 278.2066, found *m/e* 278.2066. Anal. Calcd for $C_{17}H_{30}OSi$: C, 73.31; H, 10.85. Found: C, 73.26; H, 11.10.

**(−)-Alloaromadendrone (14).** To a solution of 751 mg (2.7 mmol) of **15** in 60 mL of dry MeOH, cooled to -20°C, was added 2 mL of $Et_3N$, after which the mixture was stirred for 4 h at -20°C. Evaporation of the solvent under reduced pressure gave 552 mg (99%) of crude **14**. According to GC analysis, the purity of **14** was 97%. This crude **14** could be used without further purification for the next reaction. Recrystallization from petroleum ether (bp 80-100°C) gave pure **14**: mp 75-76°C; $[\alpha]_D$ -11.7° (c 3.54); $^1H$ NMR ($CDCl_3$) δ 0.31 (dd, J = 9.1, 11.1 Hz, 1H), 0.60 (ddd, J = 4.9, 9.1, 11.6 Hz, 1H), 0.89 (d, J = 6.8 Hz, 3H), 0.93 (s, 3H), 0.99 (s, 3H), 1.17-2.05 (m, 6H), 2.18-2.37 (m, 2H), 2.46 (ddd, J = 7.1, 11.6, 14.4 Hz, 1H), 2.62 (ddd, J = 2.5, 7.4, 14.4 Hz, 1H), 3.15 (dt, J = 5.1, 9.2 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 14.90 (q), 15.15 (q), 17.55 (s), 18.64 (t), 24.09 (d), 24.23 (t), 24.94 (d), 27.94 (q), 31.42 (t), 38.62 (d), 40.06 (d), 44.03 (t), 55.14 (d), 211.62 (s); mass spectrum, *m/e* (relative intensity) 206 ($M^+$, 32), 191 (7), 163 (16), 145 (13), 135 (20), 107 (25), 95 (33), 83 (56), 69 (100), 55 (56), 41 (85); calcd for $C_{14}H_{22}O$ ($M^+$) *m/e* 206.1671, found *m/e* 206.1667. Anal. Calcd for $C_{14}H_{22}O$: C, 81.49;H, 10.74. Found: C, 81.76; H, 10.95.

**(–)-Ledol (4).** This compound was prepared from crude **14** (155 mg, 0.75 mmol) as described for the synthesis of **3**. The workup and flash chromatography [15:1 petroleum ether (bp 40-60°C)/EtOAc] afforded 152 mg (91%) of **4**: mp 103-104°C [from petroleum ether (bp 80-100°C)] (lit.[24]: 103-104°C); $[\alpha]_D$ -5.8° (c 1.50) (lit.[5]: -5.6°); $^1$H NMR data were identical to those reported in the literature[24]; $^{13}$C NMR ($CDCl_3$) δ 15.17 (q), 15.74 (q), 19.20 (s), 20.05 (t), 23.14 (d), 24.36 (t), 24.73 (d), 28.41 (q), 30.26 (q), 30.56 (t), 38.18 (d), 38.96 (t), 40.53 (d), 53.47 (d), 74.65 (s); the mass spectrum was consistent with that reported in the literature[24]. Anal. Calcd for $C_{15}H_{26}O$: C, 81.01; H, 11.78. Found: C, 80.67; H, 11.75.

**(–)-Alloaromadendrene (16).** To 438 mg (18 mmol) of Mg turnings and a crystal of $I_2$ in 6 mL of dry ether was added dropwise a solution of 2.58 mL (18 mmol) of $(CH_3)_3SiCH_2Cl$ in 10 mL of dry ether. The mixture was heated at reflux for 1 h, allowed to come to room temperature, and then a solution of 618 mg (3.0 mmol) of pure **14** in 10 mL of dry ether was added dropwise. After stirring for 2.5 h at room temperature, the reaction mixture was cooled to 0°C and carefully quenched with 15 mL of saturated aqueous $NH_4Cl$. After dilution with 25 mL of $H_2O$, the two-phase mixture was separated, and the aqueous layer was extracted with four 25-mL portions of $CH_2Cl_2$. The combined organic layers were washed with 30 mL of brine, dried, and evaporated under reduced pressure. The remaining residue (890 mg) was dissolved in 20 mL of dry THF and added dropwise to 0.35 g of KH (8.7 mmol, freed from mineral oil) in 15 mL of dry THF. The reaction mixture was stirred at room temperature for 1 h, and then poured into 25 mL of cold saturated aqueous $NH_4Cl$. The resulting mixture was extracted with four 25-mL portions of ether. The combined organic layers were washed with 30 mL of brine, dried, and evaporated under reduced pressure. The crude product was flash chromatographed (pentane) to give 560 mg (91%) of pure **16** as a colourless oil: $[\alpha]_D$ -27.7° (c 1.62) (lit.[25]: -21.6°); $^1$H NMR ($CDCl_3$) δ 0.23 (dd, J = 9.3, 10.7 Hz, 1H), 0.53 (ddd, J = 6.1, 9.3, 10.8 Hz, 1H), 0.93 (d, J = 6.3 Hz, 3H), 0.95 (s, 3H), 0.99 (s, 3H), 1.12-1.42 (m, 2H), 1.63-2.14 (m, 6H), 2.23-2.37 (m, 2H), 2.66 (br q, J = 8.0 Hz, 1H), 4.72 (br s, 2H); $^{13}$C NMR ($CDCl_3$), δ 15.63 (q), 16.17 (q), 16.98 (s), 21.90 (t), 23.28 (d), 24.56 (d), 27.98 (t), 28.37 (q), 30.96 (t), 35.47 (t), 37.56 (d), 41.93 (d), 50.54 (d), 109.44 (t), 152.24 (s); mass spectrum, *m/e* (relative intensity) 204 ($M^+$, 18), 189 (10), 161 (32), 147 (21), 133 (30), 119 (31), 105 (48), 91 (63), 79 (46), 67 (34), 41 (100); calcd for $C_{15}H_{24}$ ($M^+$) *m/e* 204.1878, found *m/e* 204.1874.

**(+)-Viridiflorol (5).** To a solution of 430 mg (2.1 mmol) of **16** in 30 mL of $CH_2Cl_2$ were added 30 mL of acetone, 30 mL of water, 50 mg of 18-Crown-6, and 3.0 g of $NaHCO_3$. The mixture was vigorously stirred and 10 mL of 0.29 M Oxone (5.8 mmol of $KHSO_5$) in water was added dropwise at 0 °C. Stirring was continued for 1 hr, after which time 40 mL of saturated aqueous $NaHCO_3$ was added. The aqueous layer was extracted with four 40-mL portions of $CH_2Cl_2$. The combined organic layers were washed with 40 mL of 10% aqueous $Na_2S_2O_3$ and 40 mL of saturated aqueous $NaHCO_3$, and then dried. After evaporation of the solvent under reduced pressure, the residue was taken up in 40 mL of dry THF and an excess $LiAlH_4$ was added. The mixture was stirred at room temperature for 18 h, diluted with 100 mL of ether, and then carefully quenched with a few drops of saturated aqueous $Na_2SO_4$. The mixture was dried and concentrated under reduced pressure. Flash chromatography [50:1 petroleum ether (bp 40-60°C)/EtOAc] afforded 417 mg (89%) of a 1:4 mixture of the alcohols **4** and **5**, respectively. Separation of both isomers by preparative gas chromatography, using a 9.5% Carbowax HP on Chromosorb W-HP column, 3m x 1/8" o.d., gave pure **5** in 54% yield from **16**. Also a column with a larger capacity (2m x 3/8" o.d.) could be used. Physical data of **5**: mp 75°C (from $CH_3CN$) (lit[25]: 75°C); $[\alpha]_D$ +4.8° (c 0.86) (lit.[25]: +4.0°); $^1$H NMR[26], $^{13}$C NMR[26], and MS[11b] spectroscopic data were consistent with those reported in the literature. Anal. Calcd for $C_{15}H_{26}O$: C, 81.01; H, 11.78. Found: C, 81.01; H, 11.81.

**(+)-11β-Hydroxy-apoaromadendrone (17).** To a bottle containing 16 mL of $CCl_4$, 16 mL of $CH_3CN$, 24 mL of $H_2O$, and 3.42 g (16 mmol) of $NaIO_4$ was added 824 mg (4.0 mmol) of **13** and 35 mg of $RuO_2 \cdot xH_2O$. The bottle was closed air-tight and rotated around its axis in a waterbath of 50°C until the colour of the mixture had turned from yellow to black (48 h). The reaction mixture was filtered through celite, and the filter cake was washed with 25 mL of $H_2O$ and 40 mL of $CH_2Cl_2$. The combined filtrates were separated, and the aqueous layer was extracted with two 25-mL portions of $CH_2Cl_2$. The combined organic layers were washed with 30 mL of aqueous 10% $Na_2S_2O_3$ and 30 mL of saturated aqueous $NaHCO_3$, and then dried. Evaporation of the solvent under reduced pressure gave a crude mixture of mainly **13** and **17**. Flash chromatography [5:1 to 3:1 petroleum ether (bp 40-60°C)/EtOAc] afforded 240 mg (28%) of **13** and 318 mg (36%) of **17**[27]: mp 103-104°C [from petroleum ether (bp 80-100°C)]; $[\alpha]_D$ +21.4° (c 1.37); $^1H$ NMR ($CDCl_3$) δ 0.64 (dd, J = 9.3, 10.8 Hz, 1H), 0.85 (ddd, J = 5.8, 9.3, 11.1 Hz, 1H), 0.98 (s, 3H), 1.02-1.12 (m, 1H), 1.07 (s, 3H), 1.25 (s, 3H), 1.28-1.80 (m, 5H), 1.93-2.08 (m, 1H), 2.17-2.53 (m, 3H), 2.69 (dt, J = 7.9, 11.4 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 15.98 (q), 18.73 (s), 20.08 (t), 20.93 (t), 23.60 (q), 26.20 (d), 26.51 (d), 28.59 (q), 40.84 (t), 43.97 (t), 49.53 (d), 57.82 (d), 80.04 (s), 211.35 (s); mass spectrum *m/e* (relative intensity) 222 ($M^+$, 100), 207 (16), 204 (59), 179 (40), 164 (69), 161 (69), 146 (75), 121 (50), 95 (65), 81 (92); calcd for $C_{14}H_{22}O_2$ ($M^+$) *m/e* 222.1620, found *m/e* 222.1618. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.62; H, 9.97. Found: C, 75.47; H, 10.17.

**(−)-Aromadendrane-7β,11β-diol (9).** To a stirred solution of 10 mL (6 mmol) of 0.6 M MeMgI in ether was added dropwise at room temperature a solution of 113.5 mg (0.51 mmol) of **17** in 7.5 mL of dry ether. After stirring for 1 h at room temperature, the reaction mixture was cooled to 0°C, and the excess MeMgI was quenched by the careful addition of saturated aqueous $NH_4Cl$. After addition of 25 mL of $H_2O$, the two-phase mixture was separated, and the aqueous layer was extracted with four 20-mL portions of $CH_2Cl_2$. The combined organic layers were washed with 30 mL of brine, dried, and then evaporated under reduced pressure. The crude product was flash chromatographed [3:1 petroleum ether (bp 40-60°C)/EtOAc] to give 111 mg (91%) of **9**: mp 142°C [from petroleum ether (bp 40-60°C)] (lit.[7]: 142.5-142.7°C); $[\alpha]_D$ -11.2° (c 2.20) (lit.[7]: -12.6°); $^1H$ NMR, $^{13}C$ NMR, and MS spectroscopic data were consistent with those reported in the literature[6b,7]. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.34; H, 10.95. Found: C, 75.57; H, 10.99.

**(+)-Spathulenol (6).** The ketone **17** (222 mg, 1.0 mmol) was treated with $(CH_3)_3SiCH_2MgCl$ for 1.5 h as described for the synthesis of **16**. After workup, the remaining residue was dissolved in 10 mL of THF, and a solution of 3 drops of concd $H_2SO_4$ in 10 mL of THF was added. After stirring at room temperature for 2 h, 25 mL of saturated aqueous $NaHCO_3$ was added. The two-phase mixture was separated, and the aqueous layer was extracted with 25 mL of EtOAc. The combined organic layers were washed with 25 mL of brine, dried, and evaporated under reduced pressure. The crude product was flash chromatographed [15:1 petroleum ether (bp 40-60°C)/EtOAc] to give 220 mg (100%) of **6** as a colourless oil: $[\alpha]_D$ +9.8° (c 4.7) (lit.[6a]; +5.3°); $^1H$ NMR, $^{13}C$ NMR, and MS spectroscopic data were consistent with those reported in the literature[6a]. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.97. Found: C, 81.73; H, 10.95.

**(−)-Aromadendrane-7α,11β-diol (8).** The olefin **6** (220 mg, 1.0 mmol) was epoxidized and reduced as described for the synthesis of **5**. The workup gave a crude mixture of **8** and **9** in a ratio of 1:1, according to GC analysis. Flash chromatography [3:1 to 3:2 petroleum ether (bp 40-60°C)/EtOAc] afforded 209 mg (88%) of the diols **8** and **9**. Fractions containing predominantly **8** were recrystallized from petroleum ether (bp 80-100°C) to give pure **8**: mp 132-134°C (lit.[6a]: 133-134°C); $[\alpha]_D$ -21.7° (c 0.99) (lit.[6a]: -21.7°); $^1H$ NMR, $^{13}C$ NMR, and MS spectroscopic data were consistent with those reported in the literature[6,7]. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.57; H, 10.99. Found: C, 75.33; H, 10.93.

**(+)-11β-Hydroxy-alloaromadendrone (18).** A solution of 1.25 g (5.6 mmol) of **17** in 10 mL of 1 M MeONa in MeOH was stirred at room temperature for 1 h. After dilution with 40 mL of $H_2O$, the reaction mixture was extracted with three 25-mL portions of ether. The combined organic layers were washed with 25 mL of brine, dried, and evaporated under reduced pressure. The remaining residue (1.22 g), according to GC-analysis a 7:3 mixture of **17** and **18**, respectively, was flash chromatographed [5:1 petroleum ether (bp 40-60°C)/EtOAc] to give 300 mg of pure **18**. This procedure was repeated twice with the recovered starting material **17** to give in total 450 mg (36%) of **17** and 720 mg (58%) of **18**: mp 99-100°C (from diisopropylether); $[\alpha]_D$ +1.6° (c 1.06); $^1H$ NMR ($CDCl_3$) δ 0.20 (dd, J = 9.1, 11.4 Hz, 1H), 0.64 (ddd, J = 4.8, 9.1, 11.9 Hz, 1H), 0.95 (s, 3H), 1.07 (s, 3H), 1.27 (s, 3H), 1.36 (br s, 1H), 1.48-1.90 (m, 5H), 2.14 (br t, J = 10.2 Hz, 1H), 2.31-2.71 (m, 3H), 3.47 (m, J = 5.3, 8.9, 9.4 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 15.57 (q), 18.00 (s), 18.80 (t), 22.31 (t), 24.01 (q), 25.14 (d), 27.07 (d), 28.17 (q), 37.95 (t), 44.07 (t), 47.90 (d), 54.09 (d), 83.46 (s), 211.59 (s); mass spectrum, *m/e* (relative intensity) 222 (M+, 9), 204 (6), 194 (6), 179 (36), 161 (21), 146 (18), 131 (15), 121 (23), 91 (30), 79 (40), 43 (100); calcd for $C_{14}H_{22}O_2$ ($M^+$) *m/e* 222.1620, found *m/e* 222.1609. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.62; H, 9.97. Found: C, 75.54; H, 10.13.

**Trimethylsilylether 21.** To a stirred solution of 444 mg (2.0 mmol) of **18** in 10 mL of dry pyridine was added 2.0 mL of hexamethyldisilazane (HMDS) and 1.0 mL of TMSCl. The reaction mixture was stirred at room temperature for 0.5 h, and then concentrated under reduced pressure. The resulting residue was flash chromatographed [10:1 petroleum ether (bp 40-60°C)/EtOAc] to give 588 mg (100%) of **21** [ $^1H$ NMR ($CDCl_3$) δ 0.09 (s, 9H), 0.16 (dd, J = 9.1, 11.5 Hz, 1H), 0.62 (ddd, J = 4.9, 9.1, 11.8 Hz, 1H), 0.94 (s, 3H), 1.07 (s, 3H), 1.27 (s, 3H), 1.47-1.90 (m, 5H), 2.13 (dd, J = 8.8, 11.5 Hz, 1H), 2.25-2.72 (m, 3H), 3.39 (m, J = 5.4, 8.8, 9.7 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 2.17 (3·q), 15.57 (q), 17.78 (s), 18.60 (t), 22.27 (t), 23.31 (q), 24.79 (d), 26.90 (d), 28.04 (q), 37.65 (t), 43.76 (t), 48.98 (d), 54.20 (d), 85.86 (s), 212.04 (s)] as a colourless oil, which was used immediately for the next reactions.

Treatment of the enol trimethylsilylether **19** [$^1H$ NMR ($CDCl_3$) δ 0.07 (s, 9H), 0.13 (s, 9H), 0.37-0.65 (m, 2H), 0.96 (s, 3H), 1.06 (s, 3H), 1.22 (s, 3H), 1.34-1.79 (m, 4H), 2.18-2.40 (m, 5H); $^{13}C$ NMR ($CDCl_3$) δ 0.50 (3·q), 2.19 (3·q), 15.97 (q), 17.94 (s), 20.81 (t), 23.84 (q), 25.10 (d), 27.89 (t), 28.31 (q), 31.52 (d), 34.86 (t), 38.88 (t), 47.29 (d), 83.74 (s), 124.02 (s), 141.82 (s)], prepared from **17** as described for the synthesis of **15**, with MeOH and $Et_3N$ gave an unseparable 1:1 mixture of **20** [$^1H$ NMR (major peaks, $CDCl_3$) δ 0.05 (s, 9H), 0.94 (s, 3H), 1.05 (s, 3H), 1.21 (s, 3H)] and **21**, according to $^1H$ NMR analysis

**(+)-Alloaromadendrane-7α,11β-diol (10).** A sample of 294 mg (1.0 mmol) of **21** was treated with MeMgI as described for the synthesis of **9**. After workup, the remaining residue was dissolved in 10 mL of MeOH, and then 5.5 mL of 10% aqueous HOAc was added. The reaction mixture was stirred at room temperature for 18 h, after which 20 mL of saturated aqueous $NaHCO_3$ was added. Stirring was continued at room temperature for an additional 15 min. The mixture was then poured into 40 mL of $H_2O$ and extracted with four 25-mL portions of $CH_2Cl_2$. The combined organic layers were washed with 25 mL of brine, dried, and evaporated under reduced pressure. The remaining residue was crystallized from petroleum ether (bp 80-100°C) to give 189 mg (79%) of **10**: mp 155-156°C; $[\alpha]_D$ +14.0° (c 1.09); $^1H$ NMR ($CDCl_3$) δ 0.28 (dd, J = 8.8, 11.1 Hz, 1H), 0.75 (ddd, J = 5.0, 8.8, 11.6, 1H), 1.02 (s, 3H), 1.04 (s, 3H), 1.10 (s, 3H), 1.28 (s, 3H), 1.29 (m, 1H), 1.50-2.09 (m, 9H), 2.51 (br s, 1H), 2.52 (m, J = 7.8, 7.9, 9.8 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 15.28 (q), 20.12 (s), 20.43 (t), 23.83 (t), 24.22 (q), 24.59 (d), 26.38 (d), 28.64 (q), 30.62 (q), 38.20 (t), 39.51 (t), 48.46 (d), 49.58 (d), 74.48 (s), 83.12 (s); mass spectrum, *m/e* (relative intensity) 238 ($M^+$, 0.5), 220 (3), 205 (5), 187 (4), 162 (13), 147 (9), 121 (19), 107 (16), 93 (19), 79 (17), 43 (100); calcd for $C_{15}H_{26}O_2$ ($M^+$) *m/e* 238.1933, found *m/e* 238.1920. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.57; H, 10.99. Found: C, 75.33; H, 11.02.

**(−)-Allospathulenol (7).** The hydroxy olefin **7** was prepared from a sample of 294 mg (1.0 mmol) of **21** as described for the synthesis of **6**. The workup and flash chromatography [20:1 petroleum ether (bp 40-60°C)/EtOAc] afforded 192 mg (87%) of **7**: $[\alpha]_D$ −11.3° (c 1.16); $^1$H NMR ($CDCl_3$) δ 0.14 (dd, J = 9.3, 11.3 Hz, 1H), 0.52 (ddd, J = 5.7, 9.3, 11.4 Hz, 1H), 0.97 (s, 3H), 1.00 (s, 3H), 1.24 (m, 1H), 1.28 (s, 3H), 1.58-2.06 (m, 7H), 2.33-2.47 (m, 2H), 3.07 (br q, J = 8.1 Hz, 1H), 4.73 (t, J=1.9 Hz, 1H), 4.78 (br s, 1H); $^{13}$C NMR ($CDCl_3$) δ 15.81 (q), 16.94 (s), 20.87 (t), 23.91 (d), 25.07 (q), 25.94 (d), 26.42 (t), 28.34 (q), 35.86 (t), 38.66 (t), 47.02 (d), 49.59 (d), 82.62 (s), 109.66 (t), 150.97 (s); mass spectrum, *m/e* (relative intensity) 220 ($M^+$, 2), 205 (22), 202 (9), 187 (10), 177 (9), 159 (20), 147 (15), 131 (15), 119 (33), 105 (29), 91 (44), 79 (31), 43 (100); calcd for $C_{15}H_{24}O$ ($M^+$) *m/e* 220.1827, found *m/e* 220.1811. Anal Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.97. Found: C, 81.79; H, 11.10.

**(+)-Alloaromadendrane-7β,11β-diol (11).** The diol **11** was prepared from **7** (180 mg, 0.8 mmol) as described for the synthesis of **5**. The workup and flash chromatography [5:1 petroleum ether (bp 40-60°C)/EtOAc] gave 17.5 mg (9%) of **10** and 167.5 mg (86%) of **11**: mp 116°C [from petroleum ether (bp 80-100°C)] (lit.[8]: 112-113°C); $[\alpha]_D$ +10.6° (c 0.87) (lit.[8]: +7°); $^1$H NMR[7,8] ($CDCl_3$) δ -0.02 (t, J = 9.5 Hz, 1H), 0.60 (ddd, J = 5.6, 9.5, 11.3 Hz, 1H), 1.00 (s, 3H), 1.02 (s, 3H), 1.18 (s, 3H), 1.32 (s, 3H), 1.33-1.85 (m, 11H), 2.46 (m, 1H); $^{13}$C NMR[7,8] ($CDCl_3$) δ 16.00 (q), 18.50 (t), 18.50 (s), 24.93 (t), 25.08 (d), 25.41 (q), 28.33 (q), 28.56 (d), 31.93 (q), 37.20 (t), 37.75 (t), 47.58 (d), 53.83 (d), 74.08 (s), 81.90 (s); mass spectrum[7,8], *m/e* (relative intensity) 238 (M+, 0.5), 220 (4), 205 (5), 187 (5), 177 (5), 162 (22), 147 (12), 119 (14), 107 (17), 93 (20), 79 (17), 43 (100); calcd for $C_{15}H_{26}O_2$ ($M^+$) *m/e* 238.1933, found *m/e* 238.1963. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.57; H, 10.99. Found: C, 75.77; H, 11.30.

**Fungitoxicity tests.**

Minimal inhibitory concentration test. The MIC's of the compounds were determined in potato dextrose agar (PDA)[21]. Agar amended with the test compounds at various concentrations were inoculated with 10 μL of conidial suspension ($10^7$ conidia $mL^{-1}$) of both test fungi. Growth was assessed after 5 days of incubation at 25°C.

Thin-layer bioautography test. Various amounts of test compounds were applied on silicagel thin-layer plates (Merck) and sprayed with conidial suspensions ($10^7$ conidia $mL^{-1}$ nutrient solution) of *C. cucumerinum*[22]. Plates were incubated in humid chambers at 25°C for 3 days, and then assessed for growth inhibition at the site were the chemicals where spotted.

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