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THE CONVERSION OF NATURAL (+)-AROMADENDRENE INTO CHIRAL SYNTHONS-I

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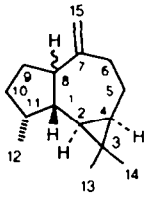
Abstract: (-)-Apoaromadendrone (**3**) can be obtained easily in large quantities from (+)-aromadendrene which is the main constituent in a commercially available distillation tail of the oil of *Eucalyptus globulus*. Acid catalyzed selective cleavage of the C3-C4 bond of the cyclopropane ring in **3** gave (-)-isoapoaromadendrone (**9**) in high yield. The regioselectivity of the cyclopropane ring opening was proved by NMR spectroscopy in combination with chemical transformations. Ozonolysis of **9** afforded the keto alcohol **14** which is a suitable chiral intermediate for the syntheses of guaianes and guaianolides.

(+)-Aromadendrene (**1**) is structurally characterized by a dimethyl cyclopropane ring fused to a hydroazulene skeleton and its relative and absolute stereochemistry is as indicated.[1] (+)-Aromadendrene is a constituent of numerous *Eucalyptus* oils[2] and one of the distillation tails of the oil of *Eucalyptus globulus*, which is commercially available[3], contains about 60% of this compound together with 15% of alloaromadendrene (**2**) and minor quantities of other sesquiterpenes.

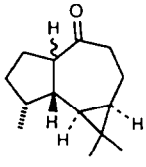
Although (+)-aromadendrene seems to be an attractive starting material for the synthesis of chiral intermediates, especially in the total synthesis of guaianes and guaianolides, little work has been done in this direction.[4,5] The use of (+)-aromadendrene as chiral starting material requires a commodious isolation and purification procedure. For (+)-aromadendrene itself this

process was troublesome, but after ozonolysis of the abovementioned distillation tail pure (-)-apoaromadendrone (**3**) was easily obtained in large quantities simply by crystallization from methanol[5]. The easiest way to obtain pure (+)-aromadendrene is a Wittig condensation of **3** with methylenetriphenylphosphorane in dimethyl sulfoxide.

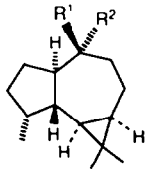
A direct route to guaiane sesquiterpenes requires a selective cleavage of the C2-C3 bond of the aromadendrane skeleton. The unclear data in the literature[6-8] prompted us to start a renewed investigation of this ring cleavage. Treatment of **1** with concentrated aqueous HCl in refluxing ethanol invariably led to unattractive mixtures. (-)-Epiglobulol (**5**) and (-)-globulol (**6**), both prepared from **1**[9], gave similar results. Probably, the presence of acid sensitive groups (an exocyclic double bond or a tertiary hydroxyl group) in these compounds is responsible for this behaviour. To avoid acid-catalyzed side-reactions 7-noraromadendrane (**7**) was prepared via reduction of **3** with $NaBH_4$, mesylation of the hydroxyl function, and finally reduction of the mesyloxy group with lithium triethylborohydride (Super-Hydride^R).[10] In this way **7** was obtained in an overall yield of 35%; a direct Wolff-Kishner reduction of **3** gave a mixture of C8 epimers of **7**.



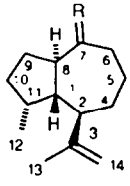
1 : αH
2 : βH



3 : αH
4 : βH



5 : R^1 = OH, R^2 = CH_3
6 : R^1 = CH_3; R^2 = OH
7 : R^1 = R^2 = H



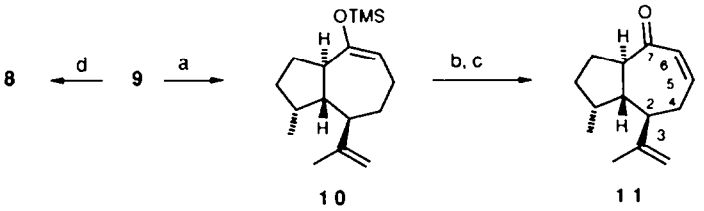
8 : R = H_2
9 : R = O

A short treatment (15 min) of **7** with concentrated aqueous HCl in refluxing ethanol gave a 4:1 mixture of **8** and a double bond isomer of **8**, respectively. Shorter reaction time led to partial recovery of the starting material, longer reaction times gave complex mixtures.

In contrast, treatment of **3** with concentrated aqueous HCl in refluxing ethanol for 1,5 h afforded (-)-isoapoaromadendrone (**9**)[6,7] in 75% yield. Probably, a competitive protonation of the carbonyl group of **3** strongly retards the double bond migration. Furthermore, we found that mixtures of **3** and alloaromadendrone (**4**)[11] also gave **9** as the sole product upon treatment with concentrated aqueous HCl in refluxing ethanol. This means that **4** undergoes epimerization at C8 before or after ring opening. This opened up the possibility to use the mother liquor of the ozonolysis reaction as starting material in the preparation of an additional portion of **9** (see Experimental).

The structure of **9** was elucidated by NMR spectroscopy in combination with some chemical transformations. Treatment of **9** with lithium diisopropylamide (LDA) and trimethylchlorosilane at -78°C gave the silyl enol ether **10** in quantitative yield. Bromination of **10** with N-bromosuccinimide (NBS) followed by dehydrobromination afforded the enone **11** in 38% yield (Scheme I).

Scheme I[a]



10 **11**

[a] (a) LDA, $(CH_3)_3$ SiCl, -78°C; (b) NBS, THF; (c) Li_2CO_3, LiBr, DMF, 120°C; (d) N_2H_4, diethylene glycol, 140→200°C.

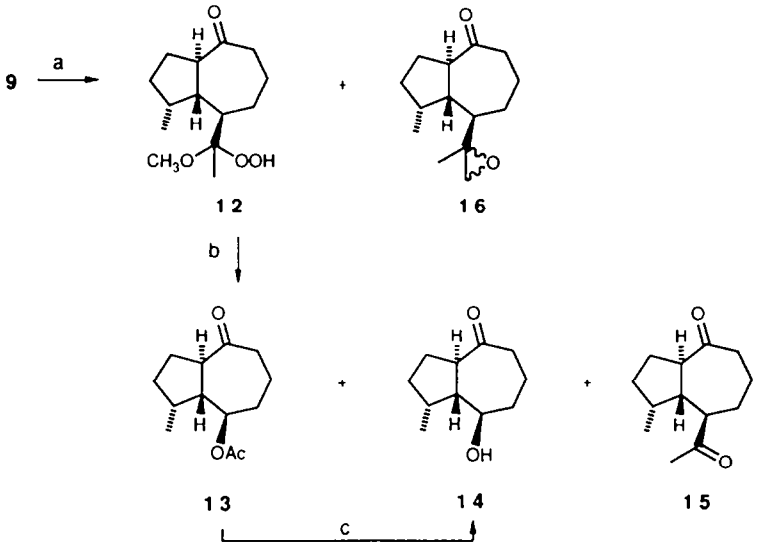
The ^{1}H NMR spectrum of **11** shows a signal (ddd) of the olefinic proton at C5 as a result of coupling with one proton at C6 (J = 11.8 Hz) and two protons at C4 (J = 5.5, 8.5 Hz). These data indicate that the isopropenyl group is located at C2. However, the question whether the ring junction is *cis* or *trans* could not be answered. 2D-NOE measurements on **9** yielded no information on the stereochemistry of this compound , due to the severe overlap of the signals in its ^{1}H NMR spectrum and the large amount of T_1 noise present in its 2D-NOE spectrum. By application of the lanthanide shift reagent Eu(fod)$_3$ both problems could be resolved simultaneously. Using a molar ratio **9**:Eu(fod)$_3$ = 1:0.765 in $CDCl_3$ an optimum was obtained between the demands of shift effect and retaining a reasonable line shape. In the 2D-NOE spectrum of the **9**/Eu(fod)$_3$ mixture both the diagonal peak and the corresponding cross peaks of the multiplet showing the largest down-field shift (a signal at δ 5.66) could not be observed. However, this was to be expected, as the T_1 values of protons spatially close to the Eu(fod)$_3$ moiety should be considerably smaller than those of most other protons in the **9**/Eu(fod)$_3$ mixture, and smaller than the mixing time used in the 2D-NOE experiments. Indeed, Inversion Recovery measurement of the T_1 values in the **9**/Eu(fod)$_3$ mixture yielded for the multiplet at δ 5.66 a T_1 of about 0.3 sec, while the T_1 values of the other protons in the molecule were found to vary between 0.9 and 1.4 sec. By recording a 2D-NOE spectrum using a much shorter mixing time, the signals belonging to the δ 5.66 resonance (both the diagonal and the cross peaks) could be made to appear. On the basis of its 2D-NOE spectrum, a series of double resonance experiments, and of all information gathered previously (*vide supra*), it proved possible to assign the ^{1}H NMR spectrum of the **9**/Eu(fod)$_3$ mixture completely, including a *trans* relationship between the two bridging protons at C1 and C8, witnessing the complete absence of NOE between

these protons. Having established the structure of **9** a Wolff-Kishner reduction of **9** also confirmed the structure of **8**.

The observed regioselectivity of the cyclopropane ring opening is not fully understood. The formation of a more favourable equatorial isopropenyl group could be an explanation for the selective cleavage of the C3-C4 bond. A similar argumentation has been used for the regioselective opening of the cyclopropane ring of maaliane.[12]

Although the selective cleavage of the C3-C4 bond does not lead directly to compounds with a guaiane skeleton, ketone **9** remains an attractive starting material for the preparation of several chiral synthons, especially because of its simple preparation in large quantities. Its use in the synthesis of guaianes and guaianolides requires the conversion of the isopropenyl group at C2 into a hydroxyl group. The easiest way to do this is given by Schreiber et al.[13] Thus, ozonolysis of **9** in the presence of methanol and subsequent treatment of the intermediate methoxyhydroperoxide **12** with acetic anhydride should result in Criegee rearrangement and dealkylation to afford the acetate **13**. Saponification of **13** then would provide the desired alcohol **14**. However, under standard conditions[13] the main product was the diketone **15**.

Scheme II[a]



[a] (a) O_3, 5:1 CCl_4/CH_3OH, -30°C; (b) Ac_2O, Et_3N, DMAP, -30°C; (c) $NaOCH_3$, CH_3OH

A much better result was obtained when the methoxyhydroperoxide **12** was treated with acetic anhydride immediately after ozonolysis at -30°C. The workup afforded, according to GC-MS analysis, a mixture of the acetate **13**, the alcohol **14**, the diketone **15**, and a 2:1 mixture of two diastereomeric epoxides **16** in a ratio of 6:1:1.5:3, respectively. The amount of epoxide formed,

could be diminished using carbon tetrachloride (μ = 0.0D) instead of dichloromethane (μ = 1.60D).[14] According to GC-MS analysis, a mixture of **13**, **14**, **15** and **16** was obtained in a ratio of 4.5:1:1:1.25, respectively. Upon treatment of this mixture with sodium methoxide in methanol the acetate **13** was converted into its alcohol **14**, and now the components could be separated easily. In this manner the ketone **9** could be converted into pure alcohol **14** on a large scale in 56% overall yield.

Starting from the commercially available distillation tail of *Eucalyptus* oil large quantities of the chiral alcohol **14** can be obtained via the procedure described. In this alcohol two different functionalities are properly located for the construction of the guaiane skeleton.

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 B-S Model A polarimeter. ^1H NMR spectra were recorded at 90 MHz on a Varian EM-390, at 200 MHz on a Bruker AC-E 200, or at 300 MHz on a Bruker CXP-300 spectrometer. ^{13}C NMR spectra were recorded at 50 MHz on a Bruker AC-E200 or at 75 MHz on a Bruker CXP-300 spectrometer. Chemicals shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0) as an internal standard. Mass spectra were recorded on a HP 5970 GC/MSD system. Accurate mass measurements were performed on an AEI MS 902 spectrometer equipped with a VG ZAB console. 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. Column chromatography was performed using Merck silica gel 60 (70-230 or 230-400 mesh). 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 sodium sulfate prior to evaporation of the solvent under reduced pressure by using a rotary evaporator.

(–)-Apoaromadendrone (3). Through a stirred solution of 60.0 g of the commercially available distillation tail of the oil of *Eucalyptus globulus*[3] in 300 mL of ethanol, cooled to -78°C, was passed an oxygen-ozone mixture. Progress of the reaction was monitored by TLC. When the starting material had disappeared (8 h) the solution was purged with nitrogen for 15 min. The reaction mixture was allowed to warm to -30°C and then a solution of 10.0 g of thiourea in 100 mL of a 9:1 mixture of ethanol/water was added. Stirring was continued at room temperature for 16 h. The white precipitate was removed by suction filtration and washed with 25 mL of ethanol. The solvent was evaporated under reduced pressure and the remaining residue was crystallized from methanol to afford 26.0 g of pure **3**. After concentration under reduced pressure and subsequent crystallization from a 5:1 mixture of methanol/water the mother liquor gave another 2.0 g of pure **3**: mp 81-82°C (lit.[15]: 82-83°C); $[\alpha]_D$ -2.4° (c 2.54) [lit.[1]: -3.5° (c 2.70)]; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.64-0.83 (m, 2H), 0.89 (d, J = 7.0 Hz, 3H), 0.91 (s, 3H), 1.02 (s, 3H), 1.19-1.81 (m, 5H), 1.89-2.13 (m, 3H), 2.26-2.45 (m, 2H), 2.73 (dt, J = 7.9, 11.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.25 (q), 15.77 (q), 18.38 (s), 20.03 (t), 23.40 (t), 26.31 (d), 27.06 (d), 28.53 (q), 34.29 (t), 36.22 (d), 42.37 (d), 44.13 (t), 58.58 (d), 212.60 (s); mass spectrum, *m/e* (relative intensity) 206 (M^+, 83), 193 (9), 163 (22), 111 (40), 109

(37), 95 (45), 83 (35), 82 (38), 81 (37), 69 (100); calcd for $C_{14}H_{22}O$ (M^+) *m/e* 206.1671, found *m/e* 206.1671. Anal. Calcd for $C_{14}H_{22}O$: C, 81.49; H, 10.74. Found: C, 81.24; H, 10.74.

The remaining mother liquor (33.6 g), according to GC-MS analysis a mixture of mainly **3** and **4** in a ratio of 2:3, respectively, was used for the synthesis of an additional portion of **9**.

(+)-Aromadendrene (1). To a stirred solution of 100 mL of 0.55 M dimethylsulfinylsodium in dry dimethyl sulfoxide was added 19.60 g (55.0 mmol) of methyltriphenylphosphonium bromide. The mixture was stirred at room temperature for 30 min, and then a solution of 5.65 g (25.0 mmol) of **3** in 25 mL of dry ether was added dropwise. The reaction mixture was stirred at room temperature for 2 h, and then poured into 250 mL of water. The aqueous solution was extracted with five 50-mL portions of petroleum ether (bp 40-60°C). The combined organic layers were washed with 75 mL of brine, dried, and then evaporated under reduced pressure. The remaining residue was chromatographed on silica gel (230-400 mesh) [5:1 petroleum ether (bp 40-60°C)/EtOAc] to give pure **1** as a colourless oil in quantitative yield: $[\alpha]_D$ +6.9° (c 2.62) [lit.[8]: +9° (ethanol)]; the ^1H NMR, ^{13}C NMR, and mass spectrum were consistent with those reported in the literature.[16,17] Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.83. Found: C, 88.10; H, 11.96.

(–)-Epiglobulol (5) and (–)-Globulol (6). A mixture of **5** and **6** was prepared from **1** as described.[9] Flash chromatography on silica gel [40:1 petroleum ether (bp 40-60°C)/EtOAc] gave pure **5** and **6**.

5: $[\alpha]_D$ -37.1° (c 1.40); ^1H NMR ($CDCl_3$, 90 MHz) δ 0.33-0.72 (m, 2H), 0.80-2.30 (m, 12H), 0.92 (d, J = 7 Hz, 3H), 0.99 (s, 3H), 1.03 (s, 3H), 1.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.83 (q), 16.57 (q), 19.13 (t), 20.55 (s), 26.57 (t), 27.12 (d), 28.74 (q), 28.87 (d), 31.30 (q), 34.59 (t), 35.76 (d), 37.54 (d), 42.91 (t), 55.91 (d), 72.25 (s); the mass spectrum was consistent with that reported in the literature[9]; calcd for $C_{15}H_{26}O$ (M^+) *m/e* 222.1984, found *m/e* 222.1982.

6: physical and spectroscopic data were consistent with those reported in the literature.[16,18]

(–)-Noraromadendrane (7). To a solution of 2.02 g (9.8 mmol) of **3** in 75 mL of ethanol, cooled to 0°C, was added 0.37 g (9.8 mmol) of $NaBH_4$. The reaction mixture was allowed to stir for 3 h at 0°C, and then poured into 150 mL of water. The aqueous solution was extracted with three 50-mL portions of EtOAc. The combined organic layers were washed with 50 mL of brine, dried, and then evaporated under reduced pressure. The remaining product, according to GC analysis a 3:2 mixture, was taken up in 50 mL of pyridine and 1.3 mL (20.0 mmol) of mesyl chloride was added. The mixture was stirred at 40°C for 18 h and then concentrated under reduced pressure. The resulting residue was taken up in 100 mL of CH_2Cl_2 and washed successively with one 50-mL portion of a 10% aqueous HCl solution, two 25-mL portions of a saturated aqueous $NaHCO_3$ solution, and one 50-mL portion of brine. The organic layer was dried and the solvent was removed under reduced pressure. The crude product was flash chromatographed on silica gel [15:1 petroleum ether (bp 40-60°C)/EtOAc] to give 1.91 g of an inseparable 3:2 mixture of two isomeric mesylates: ^1H NMR (main peaks, $CDCl_3$, 90 MHz) δ 3.01 (s, 3H), 4,40 (m, 0.6H), 5.15 (br d, J = 4.5 Hz, 0.4H). To a solution of this mixture of mesylates in 10 mL of dry THF, cooled to 0°C, was added 15 mL (15 mmol) of Super-Hydride® (1M in THF). The reaction mixture was allowed to stir at room temperature for 2 d. The excess Super-Hydride® was then destroyed by the careful addition of a minimum amount of a saturated aqueous Na_2SO_4 solution. After filtration through celite the solution was dried. The solvent was evaporated under reduced pressure and the remaining residue was chromatographed on silica gel (70-230 mesh) [petroleum ether (bp 40-60°C)] to give 0.87 g of crude **7** which, according to GC and ^1H NMR analysis was contaminated with an unsaturated impurity. The purification of **7** was accomplished after treatment of a solution of crude **7** in 75 mL of a 2:1 mixture of ether/water with 1.00 g (2.02 mmol) of

magnesium monoperoxyphtalate[19] at room temperature for 18 h. The workup and column chromatography on silica gel (70-230 mesh) [petroleum ether (bp 40-60°C)] gave 0.66 g (35%) of pure **7** as a colourless oil: $[\alpha]_D$ -29.3° (c 0.55); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.42-0.67 (m, 2H), 0.70-2.30 (m, 13H), 0.89 (d, J = 6 Hz, 3H), 1.00 (s, 6H); mass spectrum, *m/e* (relative intensity) 192 (M^+, 24), 149 (70), 108 (68), 82 (100); calcd for $C_{14}H_{24}$ (M^+) *m/e* 192.1878, found *m/e* 192.1872. Anal. Calcd for $C_{14}H_{24}$: C, 87.42; H, 12.57. Found: C, 87.20; H, 12.58.

Wolff-Kishner Reduction of 3. A solution of 4.95 g (24.0 mmol) of **3** and 30.0 g (600 mmol) of hydrazine hydrate in 100 mL of diethylene glycol was stirred at 140°C for 1 h. Water and hydrazine were then distilled off and 8.4 g (150 mmol) of KOH was added to the remaining solution. The mixture was stirred at 200°C for 2 h. After cooling, 100 mL of ice-water was added and the aqueous mixture extracted with three 75-mL portions of ether. The combined organic layers were washed with two 25-mL portions of brine, dried, and then evaporated under reduced pressure. The resulting product was chromatographed on silica gel (230-400 mesh) [petroleum ether (bp 40-60°C)] to give 1.90 g (41%) of a colourless oil. According to GC-MS analysis, the product consisted of a mixture of **7** and an isomer [mass spectrum, *m/e* (relative intensity) 192 (M^+, 11), 149 (44), 108 (34), 82 (100)] in a ratio of 9:1, respectively.

(-)-Isoapoaromadendrone (9). To a solution of 20.0 g (97.1 mmol) of **3** in 300 mL of ethanol was added 100 mL of concentrated aqueous HCl solution. The mixture was heated at reflux for 1.5 h, allowed to come to room temperature, and then diluted with 300 mL of water. The aqueous solution was extracted with four 125-mL portions of CH_2Cl_2. The combined organic layers were washed with 100 mL of saturated aqueous $NaHCO_3$ solution followed by 100 mL of brine, dried, and then evaporated under reduced pressure. The resulting product was crystallized from methanol to give 15.0 g (75%) of pure **9**: mp 60-61°C (lit.[7]: 61-62°C); $[\alpha]_D$ -53.0° (c 1.55) (lit.[6]: -48.6°); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.77 (d, J = 7.0 Hz, 3H), 1.10-1.41 (m, 2H), 1.49-1.93 (m, 6H), 1.62 (br s, 3H), 2.00-2.56 (m, 5H), 3.10 (dt, J = 4.8, 10.4 Hz, 1H), 4.68 (br s, 2H). In the ^{1}H NMR ($CDCl_3$, 300 MHz) of the 1:0.765 mixture of **9** and Eu(fod)$_3$ twelve signal groups were observed. The following assignments were made: δ 1.38 (C12 methyl protons), 2.02 [βH (C4) and C13 methyl protons], 2.40 [αH (C10)], 2.58 [βH (C10)], 2.80 [αH (C4) and αH (C5)], 2.90 [βH (C11)], 3.12 [αH (C2), βH (H5), and αH (C9)], 3.78 [βH (C1)], 5.02 [H (C14)], 5.18 [H' (C14)], 5.36 [αH (C8)], 5.66 [αH (C6), βH (C6), and βH (C9)]. In the 2D-NOE spectrum of the 1:0.765 mixture of **9** and Eu (fod)$_3$ the following cross peaks could be observed: strong signals from the geminal protons at C4, C5, C10, and C14; weaker non-geminal NOEs from βH (C1)-βH (C11), αH (C8) - αH (C9), βH (C1) - H' (C14), and βH (C5) - H' (C14). In the NOE spectrum using a shorter mixing time the following cross peaks appeared: strong signals from the geminal protons at C9; non-geminal NOEs from βH (C5) - βH (C6) and αH (C5) - αH (C6). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.70 (q) 19.23 (q), 22.31 (t), 23.11 (t), 32.42 (t), 35.17 (t), 37.82 (d), 43.51 (t), 50.64 (d), 50.77 (d), 51.37 (d), 110.72 (t), 148.65 (s), 214.43 (s); mass spectrum, *m/e* (relative intensity) 206 (M^+, 70), 191 (7), 165 (15), 164 (12), 163 (16), 137 (64), 125 (27), 109 (53), 73 (100), 72 (30); calcd for $C_{14}H_{22}O$ (M^+) *m/e* 206.1671, found *m/e* 206.1670. Anal. Calcd for $C_{14}H_{22}O$: C, 81.49; H, 10.74. Found: C, 81.26; H, 10.80.

In a similar experiment starting from 33.6 g of the mother liquor obtained after ozonolysis of the distillation tail of *Eucalyptus* oil an additional portion of **9** was prepared. After the workup the dark-brown oil (30.0 g) was submitted to steam-distillation[20] to give 17.0 g of a yellow oil. Repeated crystallization from methanol afforded 7.3 g of pure **9**.

Wolff-Kishner Reduction of 9. A sample of 2.50 g (12.0 mmol) of **9** was treated with hydrazine hydrate and KOH as described for the Wolff-Kishner reduction of **3**. The workup and chromatography on silica gel (230-400 mesh) [petroleum ether (bp 40-60°C)] afforded 0.20 g (9%)[21]

of pure **8** as a colourless oil: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.75 (d, J = 7.5 Hz, 3H), 1.10-2.20 (m, 16H), 1.70 (br s, 3H), 4.70 (br s, 2H); mass spectrum, *m/e* (relative intensity) 192 (M^+, 7), 177 (5), 149 (38), 135 (52), 107 (68), 94 (89), 81 (87), 67 (71), 55 (54), 41 (100). Anal. Calcd for $C_{14}H_{24}$: C, 87.42; H, 12.57. Found: C, 87.48; H, 12.73.

Acid Treatment of 7. A mixture of 3 mL of ethanol in which 0.095 g (0.5 mmol) of **7** was dissolved, and 0.5 mL of concentrated aqueous HCl solution was heated at reflux for 15 min. According to GC-MS analysis the reaction mixture consisted of mainly two compounds, **8** and a double bond isomer [^{1}H NMR (major peaks, $CDCl_3$, 90 MHz) δ 1.63 (br s, 3H), 1.69 (br s, 3H); mass spectrum, *m/e* (relative intensity) 192 (M^+, 39), 177 (6), 149 (89), 107 (81), 94 (72), 93 (71), 81 (68), 79 (58), 67 (54), 41 (100)] in a ratio of 4:1, respectively.

Trimethylsilyl Enol Ether 10. To a stirred mixture of 4.1 mL (6.5 mmol) of *n*-butyllithium (1.6 M in hexane) in 6.5 mL of dry THF, cooled at 0°C, was added dropwise 0.91 mL (6.5 mmol) of diisopropylamine. After 15 min the mixture was cooled to -78°C and then a solution of 1.03 g (5.0 mmol) of **9** in 6 mL of dry THF was added dropwise. When the addition was complete, the reaction mixture was allowed to stir for 40 min at -78°C after which time 0.88 mL (6.9 mmol) of chlorotrimethylsilane was added. The reaction mixture was allowed to come to room temperature and stirring was continued for an additional 2.5 h. After dilution with 15 mL of dry ether and subsequent filtration through a short column of basic alumina the solvents were evaporated under reduced pressure. The resulting crude **10** (1.34 g, 96%) [^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.21 (s, 9H), 0.78 (d, J = 7 Hz, 3H), 1.08-2.33 (m, 11H), 1.67 (br s, 3H), 2.76 (m, 1H), 4.67 (br s, 2H), 4.95 (dt, J = 2, 6.5 Hz, 1 H)] was used immediately for the next reaction.

Dehydroisoapoaromadendrone (11). To a stirred solution of 0.872 g (4.90 mmol) of N-bromosuccinimide in 13 mL of dry THF, cooled at 0°C, was added dropwise a solution of 1.34 g (4.87 mmol) of **10** in 7 mL of dry THF. The reaction mixture was allowed to stir for 20 min at 0°C, diluted with 30 mL of water, and then extracted with three 30-mL portions of carbon tetrachloride. The combined organic layers were washed with 50 mL of brine, dried, and then evaporated under reduced pressure to give 1.35 g (98%) of a solid bromo compound. To a solution of 1.21 g (4.24 mmol) of this bromo compound in 20 mL of dry DMF was added 0.762 g (8.76 mmol) of lithium bromide and 0.969 g (13.12 mmol) of lithium carbonate. The mixture was stirred at 120°C for 19 h, allowed to come to room temperature, and then filtered. The filtrate was diluted with 25 mL of brine and extracted with two 25-mL portions of ether. The combined organic layers were dried and evaporated under reduced pressure. The remaining residue was flash chromatographed on silica gel [30:1 petroleum ether (bp 40-60°C)/EtOAc] to give 0.379 g (38%) of pure **11**: 53-54°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (d, J = 6.9 Hz, 3H), 1.44 (m, 1H), 1.65 (m, 1H), 1.69 (br s, 3H), 1.82 (m, 1H), 2.04 (m, 1H), 2.15 (m, 1H), 2.35-2.44 (m, 2H), 2.64-2.76 (m, 3H), 4.74 (br s, 1H) 4.76 (br s, 1H), 6.07 (dd, J = 2.2, 11.8 Hz, 1H), 6.58 (ddd, J = 5.5, 8.5, 11.8 Hz, 1H); mass spectrum, *m/e* (relative intensity) 204 (M^+, 38), 189 (23), 176 (46), 161 (50), 136 (81), 133 (63), 121 (100), 107 (58), 105 (60), 93 (94); calcd for $C_{14}H_{20}O$ (M^+) *m/e* 204.1514, found *m/e* 204.1509.

Ozonolysis of 9. Through a stirred solution of 1.03 g (5.0 mmol) of **9** in 12 mL of a 5:1 mixture of carbon tetrachloride/methanol, cooled to -30°C, was passed an oxygen-ozone mixture. Progress of the reaction was monitored by GC. When the starting material had disappeared (45 min) the solution was purged with nitrogen for 10 min at -30°C. Sequentially acetic anhydride (5 mL), triethylamine (5 mL), and 0.02 g of 4-dimethylaminopyridine were added. Stirring was continued at -30°C for 10 min and then at 0°C for 1 h. The reaction mixture was poured into 30 mL of 10%

aqueous HCl solution and extracted with four 25-mL portions of CH_2Cl_2. The combined organic layers were washed with 25 mL of saturated aqueous $NaHCO_3$ solution followed by 25 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue (1.15 g) was according to GC-MS and ^1H NMR analysis a mixture of the acetate **13** (54%), the alcohol **14** (12%), the ketone **15** (12%), and the epoxide **16** (15%), the latter compound as a 2:1 mixture of two diastereomers. This residue was dissolved in 15 mL of 1M sodium methoxide in methanol. The reaction mixture was allowed to stir at room temperature for 16 h, and then poured into 75 mL of water. The aqueous solution was extracted with five 30-mL portions of CH_2Cl_2. The combined organic layers were washed with 50 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was flash chromatographed on silica gel (CH_2Cl_2) to give 0.56 g (61%) of pure **14**: mp 87-88°C (from methanol); $[\alpha]_D$ -84.7° (c 1.51); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.89 (d, J = 7.0 Hz, 3H), 1.20-1.88 (m, 8H), 2.09-2.52 (m, 5H), 2.91 (ddd, J = 4.5, 9.5, 11.0 Hz, 1H), 3.86 (dt, J = 4.2, 10.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.87 (q), 19.19 (t), 22.67 (t), 32.19 (t), 36.78 (d), 38.15 (t), 42.95 (t), 48.05 (d), 54.77 (d), 73.42 (d), 213.24 (s); mass spectrum, *m/e* relative intensity) 182 (M^+, 23), 167 (3), 164 (9), 154 (7), 149 (7), 125 (17), 111 (52), 109 (100), 95 (27), 81 (56); calcd for $C_{11}H_{18}O_2$ (M^+) *m/e*, found *m/e* 182.1309. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.20; H, 9.68.

In a similar experiment starting from 25.75 g (125 mmol) of **9**, bulb-to-bulb distillation (140°C, 1 mmHg) and subsequent crystallization from a 7:1 mixture of petroleum ether (bp 40-60°C)/EtOAc of the crude reaction product afforded 10.91 g (48%) of pure **14**. Flash chromatography of the mother liquor on silica gel [10:1 to 2:1 petroleum ether (bp 40-60°C)/EtOAc] gave another 1.82 g (8%) of pure **14** and fractions with pure ketone **15** and epoxides **16** as a 2:1 mixture of two diastereomers.

15: mp 100-102°C (from methanol); $[\alpha]_D$ -51.5° (c 1.54); ^{1} NMR ($CDCl_3$, 200 MHz), δ 0.74 (d, J = 7.0 Hz, 3H), 1.13-1.46 (m, 2H), 1.52-2.52 (m, 10H), 2.15 (s, 3H), 2.62 (dt, J = 3.1, 11.3 Hz, 1H), 3.02 (dt, J = 4.7, 10.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.42 (q), 22.14 (t), 22.66 (t), 28.17 (q), 31.89 (t), 32.48 (t), 37.12 (d), 43.03 (t), 49.12 (d), 51.07 (d), 56.52 (d), 210.90 (s), 212.78 (s); mass spectrum, *m/e* (relative intensity) 208 (M^+, 100), 165 (39), 147 (84), 127 (27), 125 (37), 109 (39), 95 (34), 84 (53), 81 (94), 41 (84); calcd for $C_{13}H_{20}O_2$ (M^+) *m/e* 208.1463, found *m/e* 208.1461. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.71; H, 9.80.

Diastereomeric epoxides **16**: ^1H NMR (main peaks, $CDCl_3$, 90 MHz) (major compound) δ 0.84 (d, J = 7 Hz, 3H), 1.15 (s, 3H); ^1H NMR (main peaks, $CDCl_3$, 90 MHz) (minor compound) δ 0.89 (d, J = 7. Hz, 3H), 1.16 (s, 3H); mass spectrum (major compound), *m/e* (relative intensity) 222 (M^+, 0.1), 204 (8), 165 (49), 147 (16), 135 (22), 123 (18), 109 (35), 93 (19), 81 (100), 67 (26); mass spectrum (minor compound), *m/e* (relative intensity) 222 (M^+, 3) 207 (6), 204 (3), 196 (6), 165 (38), 147 (13), 135 (14), 123 (14), 109 (39), 81 (100).

A pure sample of the acetate **13** was prepared by treating **14** with a 2:1 mixture of pyridine and acetic anhydride.

13: mp 51-52°C (from methanol); $[\alpha]_D$ -88.9° (c 0.99); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.74 (d, J = 7.0 Hz, 3H), 1.18-1.91 (m, 7H), 1.99 (s, 3H), 2.19-2.59 (m, 5H), 2.94 (ddd, J = 4.6, 9.6, 11.2 Hz, 1H), 4.80 (dt, J = 4.3, 10.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.85 (q), 18.99 (t), 21.18 (q), 22.63 (t), 32.06 (t), 34.15 (t), 36.83 (d), 42.89 (t), 48.14 (d), 51.72 (d), 75.56 (d), 170.27 (s), 212.46 (s); mass spectrum, *m/e* (relative intensity) 164 (M^+ -60, 100), 135 (28), 126 (22), 111 (14), 109 (30), 108 (4), 93 (17), 81 (41), 55 (17), 43 (57). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.98. Found: C, 69.56; H, 9.11.

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20. Instead of steam-distillation bulb-to-bulb distillation (120° C, 0.3 mmHg) could be used.
21. The high volatility of **8** made an efficient isolation of the pure compound extremely difficult.