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TETRAHEDRON

Synthesis of Wiedendiol-A and Wiedendiol-B from Labdane Diterpenes

Alejandro F. Barrero,[*] Enrique J. Alvarez-Manzaneda and Rachid Chahboun

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Granada, 18071 Granada (Spain).

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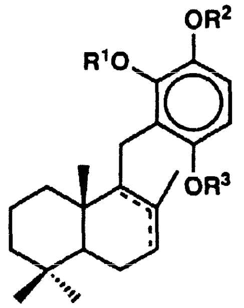
Abstract: Two efficient enantiospecific syntheses of wiedendiol-A (**1**) from (-)-sclareol (**7**), via 11-bromo-8-drimene (**11**) and 8-drimen-11-al (**3**), are reported. The first enantiospecific synthesis of wiedendiol-B (**2**), via 8*S*,9*S*-driman-11-al (**26**), by two alternative routes starting from **7** and (+)-*cis*-abienol (**8**) is also described. **21** prepared from protocatechualdehyde (**17**) was used as aromatic synthon for preparing **1** and **2**. © 1998 Published by Elsevier Science Ltd. All rights reserved.

INTRODUCTION

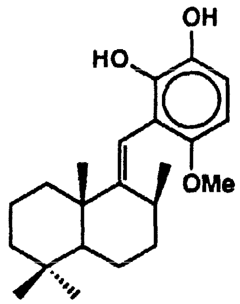
Over the last few years the isolation of marine metabolites showing a considerable biological activity, has been reported.[1] Compounds of mixed biosynthesis which are constructed of drimane and polyphenolic moieties, among them wiedendiol-A (**1**) and wiedendiol-B (**2**), have become of great interest because they inhibit the cholesteryl ester transfer protein (CETP),[2-4] and may find utility in reducing the risk of coronary artery disease.[5,6]

Chackalamannil et al have recently reported the synthesis of **1** from (+)-sclareolide (**6**) and 1,3,4-trimethoxybenzene in a nine-step sequence. Wiedendiol-A (**1**) was obtained, along with a high proportion of its isomer **4**, in an overall yield of 8.8% from **6**.[7]

Two efficient syntheses of wiedendiol-A (**1**) from (-)-sclareol (**7**) are described herein. The preparation of wiedendiol-B (**2**), starting from **7** and (+)-*cis*-abienol (**8**), is also reported for the first time.[8]



1 R^1, R^2 : H ; R^3 : Me; Δ^8
4 R^2, R^3 : H ; R^1 : Me; Δ^8
5 R^1, R^2 : H ; R^3 : Me; Δ^7



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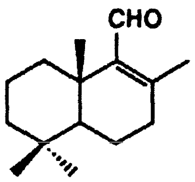

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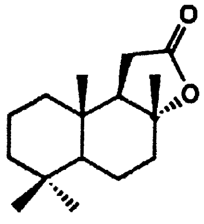

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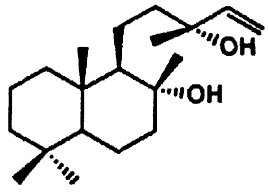

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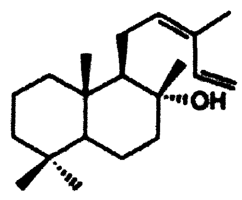

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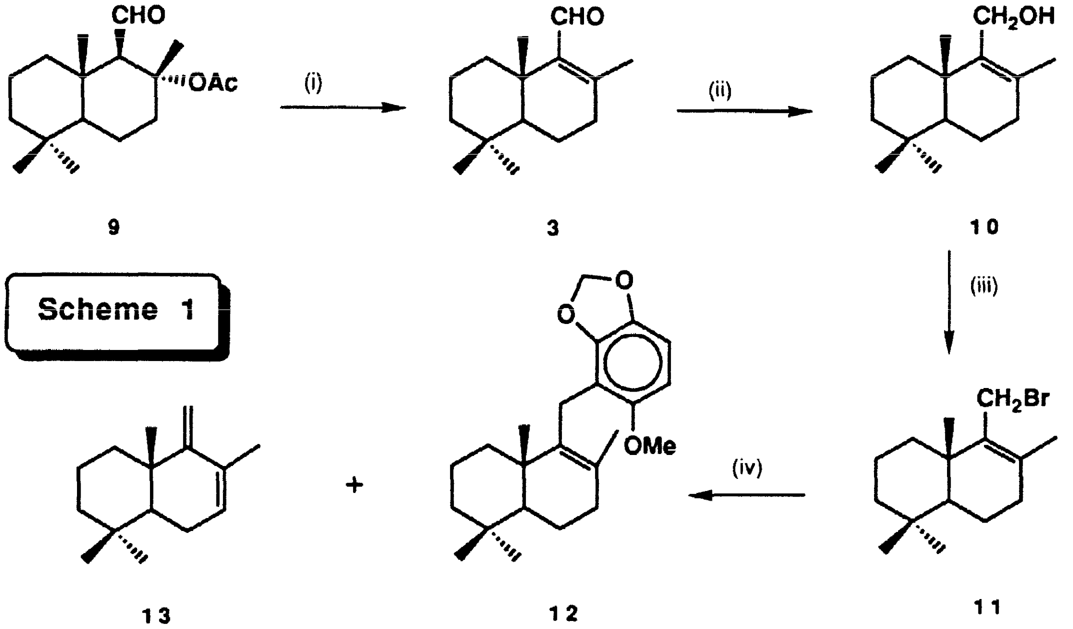
RESULTS AND DISCUSSION

The allylic bromide **11** and the *O*-methylderivative from sesamol **14** were used in a first approach to synthesize **1**, on the basis of the synthesis of (±)-puupehenone, as previously reported by Trammell. This author described the easy cleavage of the methylenedioxy group of sesamol by halogenation with PCl_5 and further hydrolysis.[9]

The acetoxyaldehyde **9**, efficiently prepared from (-)-sclareol (**7**),[10] undergoes regioselective elimination to give **3** by heating with collidine. The treatment of **3** with $NaBH_4$ affords the alcohol **10**,[11,12] which was converted into the bromide **11** by treating it with PBr_3. Prior accomplishing the condensation of the drimane synthon with the aromatic portion, the suitable regiochemistry of the lithiation of sesamol was confirmed. The deuteroderivative **15** was obtained by treating **14** with *n*-BuLi and subsequently D_2O. The condensation of **11** with the aryllithium derived from **14** gave **12** in 55% yield, along with the diene **13** (30%) (Scheme 1). When **12** was treated with PCl_5, under different experimental conditions, an unresolvable mixture of compounds was obtained. In order to clarify this result **14** was treated with PCl_5 in dichloromethane. A complex mixture of compounds was obtained at room temperature, whilst the monochloroderivative **16** was formed when the reaction was carried out at 0°C.

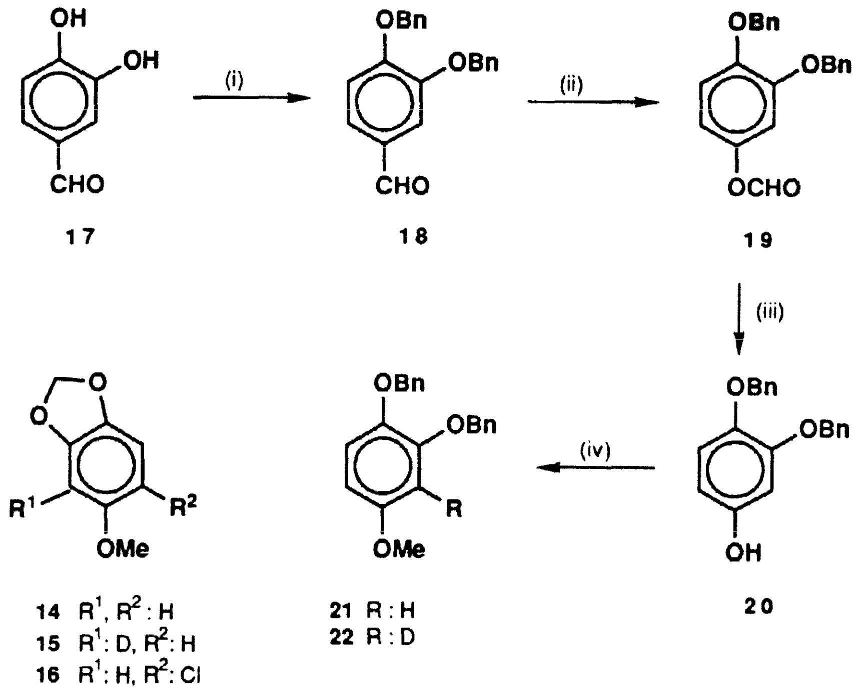


Scheme 1

(i) Collidine, 200°C, 3h, 78%. (ii) $NaBH_4$, EtOH, -8°C, 30 min, 92%. (iii) PBr_3, Et_2O, 0°C, 30 min, 97%. (iv) 14, *n*-BuLi, hexane, TMEDA, 0°C--rt, 16h.

Taking into account the above results the aromatic synthon **21** was used, since it has easily removable groups. The benzylation of protocatechualdehyde (**17**) yielded **21**, which was converted into the formate **19** by treatment with m-chloroperbenzoic acid. The dibenzyloxyphenol **20**[13] was obtained after saponification and then transformed into **21** when it was treated with MeI (Scheme 2). In order to establish the influence of the benzyl groups in the lithiation of the tri-*O*-substituted benzene **21**, the latter was treated with *n*-BuLi and then D_2O to afford the deuteroderivative **22**.

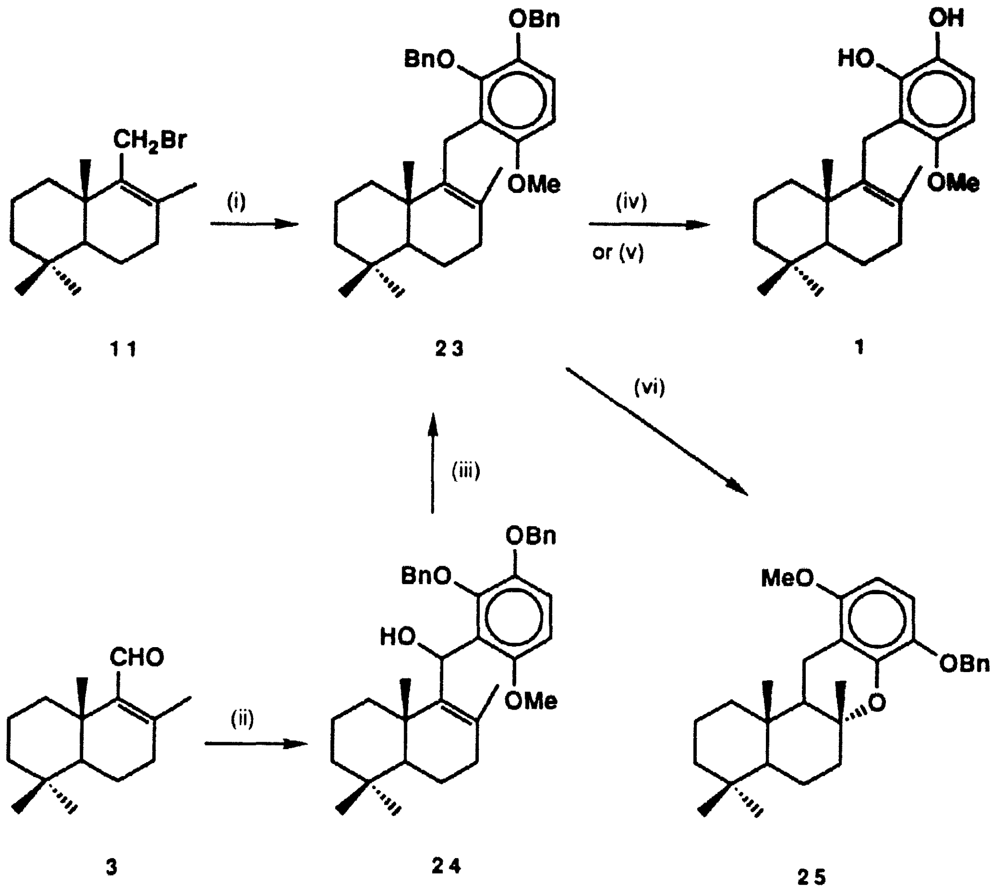
Scheme 2



(i) BnBr, K_2CO_3, acetone, reflux, 15h, 92%. (ii) MCPBA, CH_2Cl_2, rt, 12h, 95%. (iii) 6N NaOH-MeOH, rt, 5min, 96%. (iv) NaH, THF, MeI, reflux, 4h, 97%.

The condensation of the bromide **11** with the lithium diarylcuprate[14] derived from **21** afforded **23** in a high yield (Scheme 3). In an alternative route, **23** was prepared from **3**. The nucleophilic addition of the organolithium compound derived from **21** to the aldehyde **3** yielded the alcohol **24**, which was reduced to **23** by treatment with ZnI_2 and $NaBH_3CN$.[15] Debenzylation of **23** was achieved to give wiedendiol-A (**1**) in two alternative ways, using Raney Ni[13] or $LiAlH_4/NiCl_2$.[16] In order to try to isomerize the di-*O*-benzylderivative **23** to the corresponding derivative of wiedendiol-B (**2**), **23** was treated with p-toluenesulphonic acid at room temperature for 3 days, affording the cyclic ether **25** and the Δ^7 isomer **5**, in 60% and 30% yield,respectively. The configuration at C-8 of **25** was established on the basis of nOe experiments.

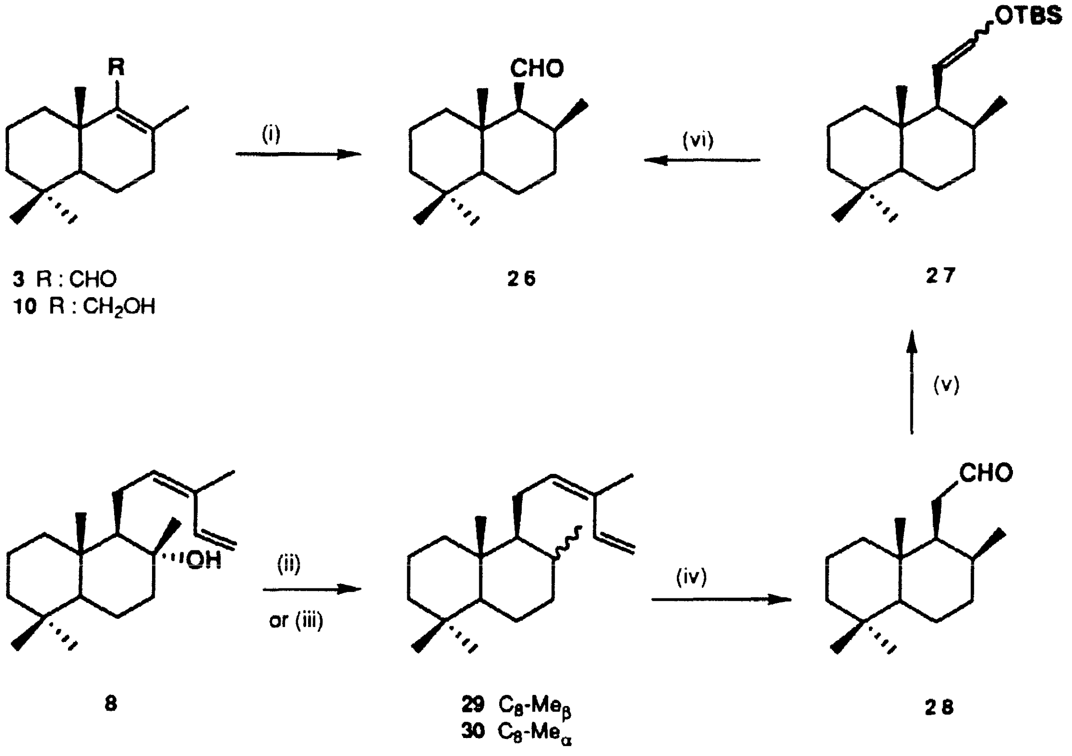
Scheme 3



(i) **21**, *n*-BuLi, Et_2O, TMEDA, -78°C--0°C, CuCN, 15°C, 15min; **11**, rt, 2h, 80%. (ii) **21**, *n*-BuLi, Et_2O, TMEDA, -78°C--0°C; **3**, 0°C, 1h, 65%. (iii) ZnI_2-$NaBH_3CN$ (1.5:10 equiv.), CH_2Cl_2, rt, 50 min, 71%. (iv) Raney Ni, H_2O-THF, rt, 20h, 81%. (v) $LiAlH_4$-$NiCl_2$ (3:1 equiv.), THF, reflux, 8h, 80%. (vi) TsOH, $CHCl_3$, rt, 3 days.

Wiedendiol-B (**2**) has been synthesized from (-)-sclareol (**7**) and (+)-*cis*-abienol (**8**) following a similar methodology to that described above for preparing **1** . The aldehyde **26** was used as drimanic synthon and **21** as the aromatic one. **26** was obtained from (-)-sclareol (**7**), via the enal **3**, which underwent chemo- and diastereoselective catalytic hydrogenation at 0°C to give the saturated aldehyde **26** and the allylic alcohol **10** in 70 and 10% yield, respectively. The configuration at C-8 of **26** was determined by an nOe enhancement observed between the methyl protons H-12 and H-15 and by comparison of ^1H NMR and ^{13}C NMR data of this compound with those of its C-8 epimer, which had previously been obtained as a racemate by electrophilic cyclization.[17] In an alternative route, **26** was synthesized from (+)-*cis*-abienol (**8**). Treatment of **8** with Et_3SiH-CF_3COOH yields a 1:1 mixture of epimers **29** and **30**. Diastereoselective cationic reduction of **8** took place by treating it with ZnI_2-$NaBH_3CN$, affording **29** as the main product (ratio **29/30** 4:1). The ^1H NMR spectrum of this mixture allows some representative signals to be assigned. Thus, three doublets at δ 0.91 (J = 7.6 Hz, 3H), 5.08 (J = 10.7 Hz, 1H) and 5.19 (J = 17.2 Hz, 1H) and a double doublet at 6.83 ppm (J = 17.2 and 10.7 Hz) may be assigned to Me-16, H-15, H-15' and H-14, respectively in compound **29**, whereas the same protons appear at δ 0.82 (d, J = 10.8 Hz, 1H), 5.15 (d, J = 17.2 Hz, 1H) and 6.82 (dd, J = 17.2 and 10.8 Hz) in **27**. The ozonolysis of **29** and **30**, with Me_2S as the reducing agent, gave a resolvable mixture of epimeric aldehydes. The treatment of **28** with TBSCl yields the corresponding silyl enol ethers **27** (*E/Z* 3:1), which after ozonolysis afforded the aldehyde **26** (Scheme 4).

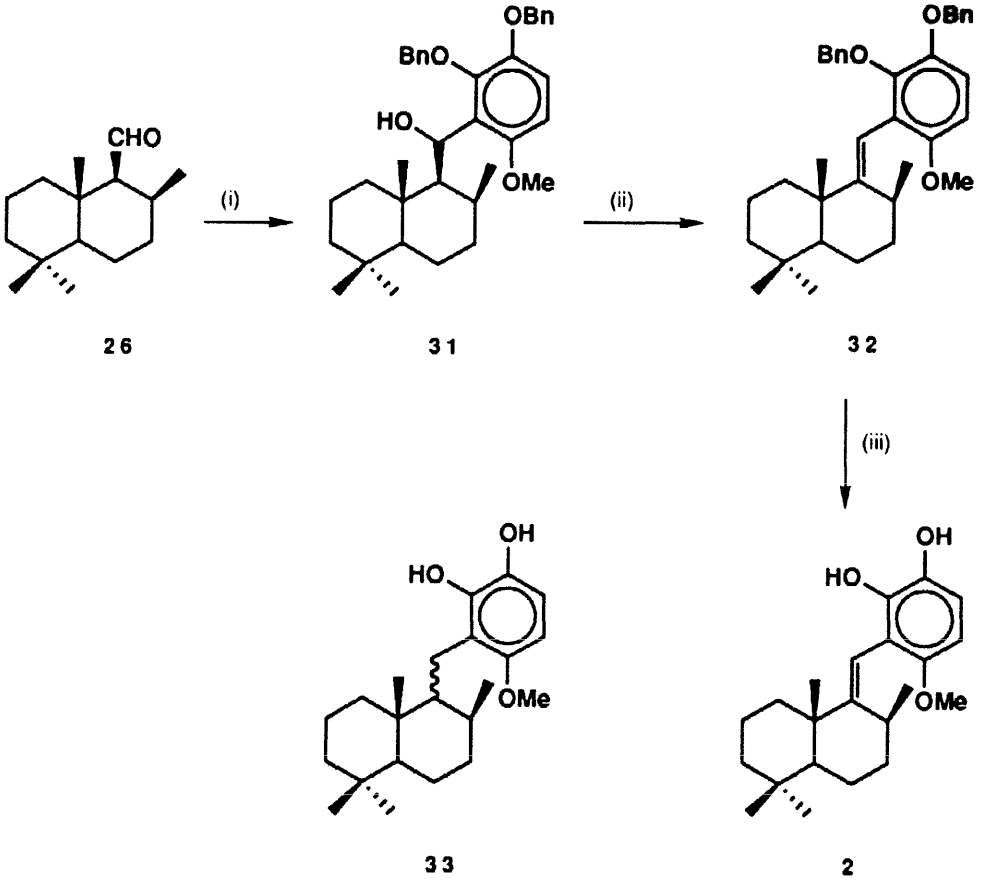
Scheme 4



(i) H_2, Pd-C, MeOH-EtOAc (1:1), 0°C, 1h, 70%. (ii) Et_3SiH-CF_3COOH, -78°C--15°C, 2h 30 min, 80%. (iii) ZnI_2-$NaBH_3CN$ (1.8:3 equiv.), 0°C--rt, 2h 15 min, 96%. (iv)) O_3, CH_2Cl_2, -78°C, 1h 15 min; Me_2S, rt, 18h, 83%. (v) NaH, THF, TBSCl, rt, 4h, 92%. (vi) O_3, CH_2Cl_2, -78°C, 45 min; Me_2S, rt, 4h, 95%.

The alcohol **31** was obtained as a mixture of two diastereomers by adding the anion derived from **21** to the aldehyde **26**. p-Toluenesulphonic acid-mediated dehydration lead to **32** in 82% yield. The configuration of the double bond was shown to be *Z* by an nOe enhancement observed between H-14 and the methylene protons on CH_2-1. It should be pointed out that when the dehydration temperature was increased, the debenzylation products underwent cationic cyclization reactions involving the olefinic system leading to the formation of cyclic ethers. In order to prepare 2 different debenzylation methods were tried. Thus the treatment of 32 with Raney Ni[10] caused simultaneous debenzylation and double bond reduction to give 33, whereas the catalytic hydrogenation of 32 at 0°C gave wiedendiol-B (2) in 93% yield. This compound had physical properties which are identical to those of the natural product.

Scheme 5



(i) **21**, *n*-BuLi, Et_2O-TMEDA (4:1), -40°C--0°C, 1h 30 min, 55%. (ii) TsOH, Benzene, 35°C, 13h, 82%. (iii) H_2, Pd-C, MeOH-EtOAc (1:1), 0°C, 2h, 93%.

EXPERIMENTAL

Melting points were determined with a Kofler hot stage melting point apparatus and are uncorrected. IR spectra were obtained on Perkin-Elmer Models 782 and 983G spectrometers with samples between sodium chloride plates or as potassium bromide pellets. Proton nuclear magnetic resonance spectra were taken on a Bruker AM 300 (300 MHz) and Bruker ARX 400 (400 MHz) spectrometers using $CDCl_3$, and CD_3COCD_3 as solvent and TMS or residual protic solvent $CHCl_3$ (δ_H= 7.25 ppm) as internal reference, and the multiplicity of a signal is a singlet unless otherwise stated, when the following abbreviations are used: s, singlet; bs, broad singlet; d, doublet; bd, broad doublet; dd, double doublet; t, triplet; m, multiplet. ^{13}C NMR spectra were run at 75 MHz on Bruker AM 300 instruments. Chemical shifts are in ppm (δ scale) and the coupling constants are in Hertz. Carbon substitution degrees were established by DEPT pulse sequence. MS were recorded on a Hewlett-Packard 5988A spectrometer using an ionizing voltage of 70 eV. HRMS were obtained on a trisector WG AutoSpecQ spectrometer. For analytical TLC Merck silica gel 60G in 0.25 mm thick layers was used. Chromatographic separations were carried out by conventional column on Merck silica gel 60 (70-230 mesh) and by flash column on Merck silica gel 60 (230-400 mesh) using hexane-MeO^{t}Bu (H-E) mixtures of increasing polarity. Ozonization reactions were carried out with a mixture of ozone-oxygen provided by an oxygen-feed Fischer apparatus (8.3 mmol of O_3 in 10 litres of O_2/h). Routinely, dry organic solvents were stored under argon, over freshly activated molecular sieves. Ether, benzene, and THF, were dried over sodium-benzophenone ketyl, TMEDA from Na, dichloromethane over calcium hydride, and methanol from magnesium methoxide. Where necessary reactions were carried out under a nitrogen or argon atmosphere.

8-Drimen-11-al (3)

A stirred solution of the aldehyde **9** (1.5 g, 5.4 mmol) in collidine (10 ml) was refluxed at 200°C for 3h.Then it was diluted with ether (50 ml) and washed with 2N HCl solution (3 x 20 ml), brine (3 x 10 ml), dried (Na_2SO_4) and concentrated to afford after cromatography of the crude on silica gel (Hexane - ether, 95:5) 926 mg (78%) of the aldehyde **3**. IR (film): 2924, 1724, 1673, 1458, 1374, 1281, 1133, 805. cm^{-1} MS *m/z* (rel. int.) : 220 (M^+, 55), 205 (34), 191 (100), 163 (34), 147 (73), 135 (73), 123 (81),121 (96), 109 (82), 107 (59), 95 (98), 91 (69). ^1H NMR ($CDCl_3$, 300 MHz): δ 10.1 (1H, s, H-11), 2.53 (1H, d, J=12.8 Hz, H-7), 2.25 (1H, d, J=4.0 Hz, H-7), 2.23 (1H, d, J=4.5 Hz), 2.01 (3H, s, Me-8), 1.15 (3H, s, Me-15), 1.08 (dd, J=12.8 y 2.1 Hz, H-5), 0.87 (3H, s, Me-14), 0.83 (3H, s, Me-13) ^{13}C NMR ($CDCl_3$, 75 MHz) 36.8 (C-1), 18.4 (C-2), 41.7 (C-3), 33.4 (C-4), 51.6 (C-5), 18.8 (C-6), 36.3 (C-7), 153.5 (C-8), 143.8 (C-9), 37.6 (C-10), 192.7 (C-11), 21.7 (C-12), 33.3 (C-13), 20.2 (C-14), 18.9 (C-15).

8-Drimen-11-ol (10)

Solid $NaBH_4$ (60 mg, 1.6 mmol) was added to a solution of the aldehyde 3 (200 mg, 0.909 mmol) in ethanol (8 ml) at -8°C. After 15 min the reaction was warmed to room temperature and stirred for an additional 15 min , Then it was diluted with ether (30 ml) and washed with water, brine, dried (Na_2SO_4) and concentrated to give 187 mg (92 %) of **10**. IR (KBr): 3805, 1652, 1541, 1490, 1261, 1203, 1016, 998 cm^{-1}. MS *m/z* (rel. int.): 222 (M^+, 10), 204 (11), 191 (100), 133 (35), 121 (55), 105 (45), 95 (68), 91 (69).^1H NMR ($CDCl_3$, 300 MHz): δ 4.18 (1H, d, J = 11.5 Hz, H_A-11), 4.02 (1H, d, J=11.5, H_B-11), 2.04 (2H, m, H-7), 1.70 (3H, s, Me-12), 0.94 (3H, s, Me-13), 0.87 (3H, s, Me-14), 0.82 (3H, s, Me-15). ^{13}C NMR ($CDCl_3$, 75 MHz) 36.8 (C-1), 18.9 (C-2), 41.7 (C-3), 33.35 (C-4), 51.7 (C-5), 19.0 (C-6), 33.7 (C-7), 132.5 (C-8), 141.0 (C-9), 38.1 (C-10), 58.3 (C-11), 21.6 (C-12), 33.3 (C-13), 20.7 (C-14), 19.3 (C-15).

11-Bromo-8-drimene (11)

To a solution of the allylic alcohol **10** (440 mg, 1.98 mmol) in ether (20 ml) was added dropwise over 3 min freshly distilled phosphorus tribromide (0.1 ml). After 30 min, the reaction mixture was carefully treated with methanol (0.25 ml) and then diluted with ether (30 ml) and poured into ice-water. The organic layer was separated and successively washed with 5% aqueous $NaHCO_3$, water, and brine. The organic solution was dried (Na_2SO_4) and concentrated to afford 550 mg of bromide **11** (97%) as a colorless oil IR (film): 2925, 1777, 1638, 1440, 1388, 1375, 1254, 1239, 1203, 1039 cm^{-1}. MS *m/z* (rel. int.): 284 (M^+, 0), 204 (84), 189 (42), 161 (66), 148 (30), 133 (72), 119 (93), 105 (100).^1H NMR ($CDCl_3$, 300 MHz): δ 4.17 (1H, d, J = 11.6 Hz, H_A-11), 4.03 (1H, d, J=11.6 Hz, H_B-11), 2.14 (2H, m, H-7), 1.73 (3H, s, Me-12), 1.01 (3H, s, Me-13), 0.90 (3H, s, Me-14), 0.85 (3H, s, Me-15). ^{13}C NMR ($CDCl_3$, 75 MHz) 36.6 (C-1), 18.7 (C-2), 41.5 (C-3), 33.2 (C-4), 51.4 (C-5), 18.9 (C-6), 34.0 (C-7), 136.6 (C-8), 137.3 (C-9), 38.7 (C-10), 30.2 (C-11), 21.6 (C-12), 33.3 (C-13), 20.8 (C-14), 19.7 (C-15).

O-Methylsesamol (14)

Sesamol (100 mg, 0.72 mmol) and K_2CO_3 (100 mg) were dissolved in acetone (10 ml). MeI (0.5 ml) was added to this solution and the mixture stirred under reflux for 18 h. Then it was diluted with H_2O (20 ml) and extracted with ether (3 x 25 ml). The organic solution was dried over Na_2SO_4 and concentrated to give 105 mg (96%) of **14** as a colorless oil. MS *m/z* (rel. int.): 152 (M^+, 100), 137 (80), 107 (40), 79 (50), 51 (30). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.73 (1H, d, J=8.5 Hz, H-6), 6.70 (1H, dd, J=8.5 y 2.5 Hz, H-5), 6.51 (1H, d, J=2.5 Hz, H-3), 5.92 (2H, s, OCH_2O), 3.76 (3H, s, OMe).

Deuteration of 14

To a cold (-78°C) solution of **14** (200 mg, 1.3 mmol) in THF (10 ml), a 2M solution of *n*-butyllithium (0.7 ml) in hexane was added under argon atmosphere. The reaction mixture was warmed to 0°C, stirred for 30 min and then treated with D_2O (0.5 ml). After this, the mixture was diluted with ether (40 ml) and washed with brine. The organic solution was dried (Na_2SO_4) and concentrated to afford **15**. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.72 (1H, d, J=8.5 Hz, H-6), 6.67 (1H, d, J= 8.5 Hz, H-5), 5.88 (2H, s, OCH_2O), 3.73 (3H, s, OMe).

2-(8'-Drimen-11'-yl)-3,4-methylendioxy-1-methoxybenzene (12)

Dry tetramethylenediamine (0.7 ml) was added dropwise over 5 min to a 2M solution of *n*-butyllithium (1.5 ml) in hexane under argon atmosphere. The resulting mixture was stirred for 5 min at 0°C and then a solution of **14** (450 mg, 3 mmol) in hexane (10 ml) was added. After this, the mixture was stirred for 1h at 25 °C and a solution of **11** (0.5g, 1.76 mmol) in 10 ml of hexane was added. The reaction mixture was warmed to room temperature and stirred for 16h. The mixture was diluted with ether (50 ml) and washed with 2N HCl and brine. The organic phase was dried (Na_2SO_4) and concentrated to a crude mixture, which after chromatography silica gel (5% ether- hexane) afforded 345 mg (55%) of **12** and 107 mg (30%) of 7,9-drimadiene (**13**). **12**: IR (film) 2938, 1736, 1631, 1457, 1242, 1085, 894, 786, 758 cm^{-1}. MS *m/z* (rel. int) : 355 [$(M-H)^+$, 36], 326 (61), 311 (24), 279 (10), 251 (12), 205 (8), 148 (22), 127 (100). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.56 (1H, d, J=8.4 Hz, H-3), 6.24 (1H, d, J=8.4 Hz, H-6), 5.89 (1H, s, OCH_2O), 5.85 (1H, s, OCH_2O), 3.75 (3H, s, OMe), 3.34 (1H, d, J=16.8 Hz, H-11'), 3.30 (1H, d, J=16.8 Hz, H-11'), 2.03 (2H, m, H-7), 1.52 (3H, s, Me-12'), 0.92 (3H, s, Me-14'), 0.88 (3H, s, Me-13'), 0.82 (3H, s, Me-15').^{13}C NMR ($CDCl_3$, 75 MHz). 36.3 (C-1'), 19.1 (C-2'), 41.9 (C-3'), 33.4 (C-4'), 51.5 (C-5'), 23.6 (C-6'), 33.9 (C-7'), 127.7 (C-8'), 136.3 (C-9'), 39.0 (C-10'), 23.6 (C-11'), 20.4 (C-12'), 33.5 (C-13'), 21.8 (C-14'), 20.3 (C-15'), 114.7 (C-1), 153.3 (C-2), 102.0 (C-3), 104.3 (C-4), 141.6 (C-5), 146.5 (C-6), 56.3 (C-OCH_3), 100.5 (C-OCH_2O).

13: . IR (film): 2927, 1457, 1385, 1360, 1257, 1203 cm^{-1}. MS *m/z* (rel. int.): 204 (84), 189 (42), 161 (66), 148 (30), 133 (72), 119 (93), 105 (100). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.65 (bs, 1H), 4.83 (s, 1H), 4.78 (s, 1H), 1.78 (s, 3H), 0.95 (s, 3H), 0.91 (s, 3H), 0.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) 37.8 (C-1), 19.1 (C-2), 42.3 (C-3), 33.4 (C-4), 48.7 (C-5), 24.4 (C-6), 126.6 (C-7), 131.3 (C-8), 158.3 (C-9), 37.9 (C-10), 101.8 (C-11), 21.2 (C-12). 33.0 (C-13), 22.2 (C-14), 20.6 (C-15).

Treatment of 14 with PCl_5

PCl_5 (146 mg, 0.7 mmol) was added to a cold (0°C) solution of **14** (100 mg, 0.657 mmol) in CH_2Cl_2 (8 ml) and the mixture stirred for 5 min. Then it was diluted with ether (20 ml) and washed with brine. The organic solution was dried (Na_2SO_4) and concentrated to afford 99 mg (81%) of **16** as a colorless oil. MS *m/z* (int. rel.): 188 [$(M+2)^+$, 20], 186 (M^+, 65), 173 (30), 171 (100), 143 (22), 113 (19). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.82 (1H, s, H-3), 6.55 (1H, s, H-6), 5.91 (2H, s, OCH_2O), 3.79 (3H, s, OMe).

3,4-Dibenzyloxybenzaldehyde (18)

Protocatechualdehyde (**17**) (6.9 g, 50 mmol) and K_2CO_3 (14.5 g) was dissolved in 150 ml of acetone. and then benzyl bromide (17.2 g, 101 mmol) was added. After stirring under reflux for 15h the mixture was concentrated in vacuo, diluted with ether and washed with H_2O. The ether solution was dried over Na_2SO_4 and evaporated to give 14.6 g of the aldehyde **18** (92%). IR (KBr): 3026, 2934, 2856, 2819, 1676, 1595, 1580, 1508, 1433, 1245, 1135, 1080, 1023 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) : δ 9.81 (1H, s), 7.01 (1H, d, J=8.3 Hz), 7.39 (12H, m), 5.24 (2H, s), 5.20 (2H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): 70.7 (CH_2, Bn), 70.8 (CH_2, Bn), 112.4 (CH, C-2), 113.0 (CH, C-5), 126.5 (CH, C-6), 127.0 and 128.5 (10CH, 2Bn) 130.2 (C, C-1), 136.2 (C, C-Bn), 136.5 (C, C-Bn), 149.1 (C, C-3), 154.2 (C, C-4), 190.6 (CH, CHO).

1,2-Di-*O*-benzyl-4-*O*-formylbenzenetriol (19)

m- Chloroperbenzoic acid (85%) (1.2 g, 6.9 mmol) was added to a solution of the aldehyde **18** (2.0 g, 6.3 mmol) in dry dichloromethane (75 ml), and the mixture stirred at room temperature for 12h and then diluted with ether (150 ml). The organic solution was successively washed with saturated aqueous Na_2CO_3 solution (3 x 50 ml), brine (3 x 25 ml) and dried. The solvent was evaporated in vacuo to give 1.98 g of **19** (96%) as a crystalline solid (m.p. 49°C). IR (film) 3063, 3032, 1759, 1736, 1602, 1500, 1452, 1264, 1161, 1013 cm^{-1}. MS *m/z* (rel. int.): 334 (M^+, 6), 215 (5), 91 (100).^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.25 (1H, s, OCHO), 7.38 (10H, m, Bn), 6.92 (1H, d, J=8.7 Hz, H-6), 6.75 (1H, d, J=2.6 Hz, H-3), 6.67 (1H, dd, J=8.7, 2.6 Hz, H-5), 5.10 (4H, s, 4H-Bn).^{13}C NMR ($CDCl_3$, 75 MHz): 71.2 (CH_2, Bn), 71.7 (CH_2, Bn), 108.3 (CH, C-3), 113.2 (CH, C-5), 115.4 (CH, C-6), 127.2-128.5 (10CH, 2Bn), 136.5 (C, C-Bn), 137.0 (C, C-Bn), 144.0 (C, C-1), 147.0 (C, C-4), 149.6 (C, C-2), 159 (CH, OCHO).

3,4-Dibenzyloxyphenol (20)

6N NaOH (2 ml) was added to a stirred solution of **18** (2.0g, 5.99 mmol) in MeOH (15 ml).After stirring at room temperature for 5 min, the reaction mixture was diluted with ether (50 ml), washed with H_2O (2 x 10 ml), brine (2 x 10 ml) and dried over anhydrous Na_2SO_4. Filtration and concentration gave 1.75 g (96%) of the phenol **20** as a brown solid (m.p. 110°C). IR (KBr) : 3320, 1607, 1505, 1452, 1378, 1311, 1283, 915 cm^{-1}. MS *m/z* (rel. int.): 306 (M^+, 6), 215 (5), 91 (100). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38-7.30 (10H, m, Bn), 6.7 (1H, d, J=8.0 Hz, H-6), 6.4 (1H, d, J=2.9 Hz, H-3), 6.23 (1H, dd, J=8.0 , 2.9 Hz, H-5), 5.44 (1H, s, OH), 5.01 (2H, s, 2H-Bn), 4.99 (2H, s, 2H-Bn). ^{13}C NMR (CDCl$_3$, 75 MHz) : 71.0 (CH$_2$, Bn), 72.9 (CH$_2$, Bn), 103.3 (CH, C-3), 107.1 (CH, C-6), 117.8 (CH, C-5), 127.4-128.7 (10CH, 2Bn), 136.9 (C, C-Bn), 137.5 (C, C-Bn), 142.5 (C, C-4), 150.3 (C, C-3), 151.0 (C, C-1).

1,2-Dibenzyloxy-4-methoxybenzene (21)

NaH (60% dispersion in mineral oil) (100 mg, 2.5 mmol) was carefully added to a cold (0°C) solution of **20** (0.5 g. 1.63 mmol) in dry THF (20 ml) under argon and the mixture was stirred at room temperature for 15 min. MeI (0.4 ml) was added and the resulting mixture heated at 80°C for an additional 4h, and then MeOH (2 ml) was added. After this, the mixture was filtered through silica gel (3 g) to give a crude wich was purified by flash chromatography (6 g of SiO$_2$; 5% ether in hexane) to yield 510 mg of **21** IR (film) : 1609, 1595, 1506, 1452, 1379, 1260, 1218, 1080 cm^{-1}. MS *m/z* (rel. int.): 320 (M$^+$, 7), 229 (14), 91 (100), 65 (8). ^{1}H NMR (CDCl$_3$, 300 MHz) : δ 7.44-7.31 (10H, m, OBn), 6.86 (1H, d, J=8.8 Hz, H-6), 6.56 (1H, d, J=2.9 Hz, H-3), 6.37 (1H, dd, J=8.8, 2.9 Hz, H-5), 5.13 (1H, s, 2H-OBn), 5.08 (2H, s, 2H-OBn), 3.72 (3H, s, OMe). ^{13}C NMR (CDCl$_3$, 75 MHz) 55.6 (CH$_3$, OCH$_3$), 71.2 (CH$_2$, Bn), 72.7 (CH$_2$, Bn), 103.0 (CH, C-3), 104.5 (CH, C-6), 117.2 (CH, C-6), 127.4-128.5 (10CH, 2Bn), 137.2 (C, C-Bn), 137.7 (C, C-Bn), 143.1 (C, C-1), 150.3 (C, C-2), 155.0 (C, C-4).

Deuteration of 21

A 2M solution of *n*-butyllithium (0.7 ml) in hexane was added under argon atmosphere to a cold (-78°C) solution of **21** (140 mg, 0.43 mmol) in Et$_2$O (5 ml), and the mixture was warmed to 0°C and stirred for 30 min. Compound **22** (135 mg, 97%) was obtained following the same work-up as for **15**. MS *m/z* (rel. int): 321 (M$^+$, 64), 231 (100), 230 (100), 91 (100), 65 (100).^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.44-7.31 (m, 10H, CH-OBn), 6.86 (1H, d, J=8.8 Hz, H-6), 6.37 (1H, d, J=8.8 Hz, H-5), 5.13 (2H, s, 2H-OBn), 5.08 (2H, s, 2H-OBn), 3.72 (3H, s, OMe).^{13}C NMR (CDCl$_3$, 75 MHz) : 55.6 (CH$_3$, OCH$_3$), 71.2 (CH$_2$, Bn), 72.7 (CH$_2$, Bn), 103.0 (C, C-3), 104.5 (CH, C-6), 117.2 (CH, C-6), 127.4-128.5 (10CH, 2Bn), 137.2 (C, C-Bn), 137.7 (C, C-Bn), 143.1 (C, C-1), 150.3 (C, C-2), 155.0 (C, C-4).

1,2-Di-*O*-benzyl-3-(11'-hydroxy-8'-drimen-11'-yl)-4-*O*-methylbenzenetriol (24)

Dry tetramethylendiamine (10 ml) was added dropwise to a solution of **21** (2g, 6.25 mmol) in Et$_2$O (45 ml). The mixture was cooled to -78°C and *n*-butyllitium (3.1 ml, 2M solution in hexane) was added . The resulting yellow solution was slowly warmed to 0°C, stirred for 30 min and then a solution of **3** (0.8 g, 3.6 mmol) in Et$_2$O (25 ml) was added. The mixture was stirred for an additional 1h, diluted with ether (40 ml) and the solution washed with 2N HCl and brine. The organic phase was dried (Na$_2$SO$_4$) and concentrated under reduced pressure to give a residue, which was chromatographed on silica gel (hexane-ether, 7:3) affording 1,2 g (65%) of **24** as a colorless oil IR (film): 3544, 2938, 1736, 1589, 1475, 1369, 1257, 1159, 1090, 1015, 790, 784 cm^{-1}. MS *m/z* (rel. int.): 540 (M$^+$, 6), 307 (82), 277 (48), 230 (83) 217 (55), 139(89), 91 (100). ^{1}H NMR(CDCl$_3$, 300 MHz): δ 7.42-7.29 (10H, m, Bn), 6.86 (1H, d, J=8.9 Hz, H-6), 6.55 (1H, d, J=8.9 Hz, H-5), 5.69 (1H, d, J=9.0 Hz), 5.28 (1H, d, J=10.0 Hz), 5.08 (1H, s), 5.06 (1H, s), 5.03 (1H, d, J=10.0 Hz), 4.91 (1H, d, J=9.0 Hz), 3.75 (3H, s, OMe), 2.03 (2H, m, H-7'), 1.33 (3H, s, Me-12'), 1.13 (3H, s, Me-13'), 0.88 (3H, s, Me-14'), 0.86 (3H, s, Me-15'). ^{13}C NMR (CDCl$_3$, 75 MHz) 37.1 (C-1'), 19.2 (C-2'), 41.7 (C-3'), 33.5 (C-4'), 51.7 (C-5'), 19.3 (C-6'), 36.1 (C-7'), 129.1 (C-8'), 143.4 (C-9'), 39.8 (C-10'), 68.9 (C-11'), 20.6 (C-12'), 33.6 (C-13'), 22.0 (C-14'), 69.1 (C-15'), 127.5 (C-1), 151.9 (C-2), 106.0 (C-3), 113.0 (C-4), 146.3 (C-5), 147.6 (C-6), 55.5 (C-OCH_3).

Reduction of 24: Synthesis of 1,2-di-*O*-benzyl-3-(8'-drimen-11'-yl)-4-*O*-methylbenzenetriol (23)

ZnI_2 (76.5 mg, 0.24 mmol) was added at 0°C to a solution of **24** (90 mg, 0.16) and $NaBH_3CN$ (93 mg, 1.5 mmol) in CH_2Cl_2 (5 ml). The mixture was stirred for 50 min and allowed to warm to room temperature. It was then filtered through celite and washed with ether (15 ml). The combined filtrate was evaporated to afford 62.5 mg (71%) of **23** as a colorless oil IR (film): 3060, 1946, 1802, 1742, 1599, 1370, 1257, 1093, 1028, 844, 786, 694, 753,733 cm^{-1}. MS *m/z* (rel. int.) 524 (M^+, 14), 433 (11), 295 (9), 243 (25), 153 (22), 91 (100). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.42-7.29 (10H, m, Bn), 6.76 (1H, d, J=8.9 Hz, H-6), 6.44 (1H, d, J=8.9 Hz, H-5), 5.01 (4H, m, Bn), 3.69 (3H, s, OMe), 3.49 (1H, d, J=15.8 Hz, H-11'), 3.41 (1H, d, J=15.8 Hz, H-11'), 1.45 (3H, s, Me-12'), 0.88 (3H, s, Me-15'), 0.83 (3H, s, Me-14'), 0.80 (3H, s, Me-13').^{13}C NMR ($CDCl_3$, 75 MHz) 36.9 (C-1'), 19.3 (C-2'), 41.8 (C-3'), 33.4 (C-4'), 51.8 (C-5'), 23.9 (C-6'), 34.8 (C-7'), 126.9 (C-8'), 137.4 (C-9'), 39.5 (C-10'), 23.9 (C-11'), 20.7 (C-12'), 33.3 (C-13'), 21.9 (C-14'), 20.3 (C-15'), 126.1 (C-1), 153.5 (C-2), 105.9 (C-3), 112.2 (C-4), 146.4 (C-5), 147.6 (C-6), 55.9 (C-OCH_3).

Synthesis of 23 from the bromide 11

n- Buthyllithium (1.6 ml, 2M solution in hexane) was added dropwise to a cooled (-78°C) solution of **21** (1 g, 3.1 mmol) in tetramethylenediamine (5 ml) and dry Et_2O (30 ml) and the resulting yellow solution was slowly warmed to 0°C and stirred for 20 min. Then copper (I) cyanide (280 mg) was added in one portion and the mixture was warmed to 15°C for 15 min. A solution of the allylic bromide **11** (350 mg, 1.23 mmol) in dry Et_2O (15 ml) was added and the resulting mixture stirred for 2h at room temperature. Then it was poured into water and extracted with ether. The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated to a yellow oil, which after column chromatography on silica gel (20% ether-hexane) gave 510 mg (80%) of **23**.

Reduction of 23 with Raney Ni: Synthesis of Wiedendiol-A (1)

A solution of **23** (100 mg, 0.2 mmol) in THF (3 ml) was added to a suspension of Raney Ni in water (0.8 g) and the mixture was stirred at 25°C for 15h. The solid was removed by filtration through a Celite filter bed and washed several times with ether. Concentration of the combined filtrate afforded 53 mg (81%) of **1** as a yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.48 (1H, s, OH), 6.69 (1H, d, J=8.8 Hz, H-6), 6.44 (1H, d, J=8.8 Hz, H-5), 5.14 (1H, s, OH), 3.77 (3H, s, H-OMe), 3.50 (1H, d, J=17.6 Hz, H-11'), 3.41 (1H, d, J=17.6 Hz, H-11'), 2.17 (2H, m, H-7'), 1.72 (3H, s, Me-12'), 1.03 (3H, s, Me-15'), 0.93 (3H, s, Me-14'), 0.86 (3H, s, Me-13') .^{13}C NMR ($CDCl_3$, 100 MHz) 35.8 (C-1'), 18.8 (C-2'), 41.5 (C-3'), 33.4 (C-4'), 51.7 (C-5'), 18.8 (C-6'), 33.6 (C-7'), 133.2 (C-8'), 140.3 (C-9'), 39.6 (C-10'), 24.8 (C-11'), 20.6 (C-12'), 33.3 (C-13'), 21.8 (C-14'), 18.7 (C-15'), 113.5 (C-1), 150.7 (C-2), 101.5 (C-3), 110.7 (C-4), 139.1 (C-5), 143.7 (C-6), 55.9 (C-OCH_3).

Reduction of 23 with $LiAlH_4/NiCl_2$: Wiedendiol-A (1).

Solid $LiAlH_4$ (298 mg, 0.57 mmol) and $NiCl_2$ (26 mg, 0.2 mmol) were added to a solution of **23** (100 mg, 0.19 mmol) in THF (10 ml), and the mixture was refluxed for 8h. Then it was cooled, the excess lithium aluminium hydride was decomposed with moist ether and 2N HCl (20 ml) was added. The organic phase was separated and the aqueous layer extracted with ether (2 x 20 ml). The combined organic phases were washed with water, brine, dried over anh Na_2SO_4 and evaporated in vacuo to yield a residue which was chromatographed on silica gel (30% ether - hexane) to give 49 mg (75%) of **1**.

Reaction of 23 with TsOH: Synthesis of 1,2-di-*O*-benzyl-3-(7'-drimen-11'-yl)-4-*O*-methylbenzenetriol (5) and (4a*S*,6a*S*,12a*R*,12b*S*)-8-benzyloxy-1,2,3,4,4a,5,6,6a,12a,12b-decahydro-11-methoxy-4,4,6a,12b-tetramethyl-9H-benzo[a]xanthene (25)

p-Toluenesulphonic acid (20 mg) was added to a solution of **23** (100 mg, 0.19 mmol) in $CHCl_3$ (5 ml) and the mixture was stirred at room temperature for 3 days. Then it was diluted with ether (30 ml), washed with sat. aqueous $NaHCO_3$ (2 x 10 ml), dried over anhydrous Na_2SO_4 and concentrated to give after chromatography (hexane-ether 8:2) 48 mg (59%) of **5** and 19 mg (30%) of **25**. **5**: IR (film) 3062, 1717, 1598, 1456, 1327, 1285, 1195, 1155, 1044, 946, 897, 789 cm^{-1}. MS *m/z* (rel. int.) 435 [$(M+H)^+$, 15], 419 (3), 243 (2), 91(100). ^1H NMR (CD_3COCD_3, 300 MHz): δ 7.91 (1H, s, OH), 7.05 (1H, s, OH), 6.61 (1H, d, J=8.8 Hz, H-6), 6.24 (1H, d, J=8.7 Hz, H-5), 5.34 (1H, bs, OH), 3.71 (3H, s, OMe), 2.89 (1H, bs), 2.70 (2H, d, J=5.3 Hz, H-11'), 1.56 (3H, bs, Me-12'), 0.94 (3H, s, Me-15'), 0.90 (3H, s, Me-14'), 0.85 (3H, s, Me-13'). ^{13}C NMR (CD_3COCD_3, 75 MHz) 39.6 (C-1'), 19.7 (C-2'), 40.0 (C-3'), 33.6 (C-4'), 51.3 (C-5'), 22.7 (C-6'), 122.3 (C-7'), 137.4 (C-8'), 53.7 (C-9'), 38.2 (C-10'), 24.4 (C-11'), 22.4 (C-12' ó C-14'), 33.8 (C-13'), 22.5 (C-14' ó C-12'), 14.0 (C-15'), 119.7 (C-1), 153.0 (C-2), 102.0 (C-3), 112.4 (C-4), 139.3 (C-5), 145.1 (C-6), 55.7 (C-OCH_3). HRMS: Calcd for $C_{29}H_{38}O_3$ 434.2710, found 434.2718. **25**: IR (film) 3406, 1488, 1088 cm^{-1}. MS *m/z* (rel. int.) 435 [$(M+H)^+$, 3], 191 (2), 153 (19). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.43 (2H, d, J= 6.6 Hz), 7.36-7.23 (3H, m), 6.68 (1H, d, J=8.7 Hz, H-6), 6.20 (1H, d, J= 8.7 Hz, H-5), 5.03 (2H, s), 3.75 (3H, s, OMe), 2.67 (1H, dd, J= 5.1,17.2 Hz, H-15), 2.30 (1H, dd, J=17.2, 13.1 Hz, H-15), 2.16 (1H, bd, J= 12.4 Hz), 1.60 (1H, dd, J= 13.1, 5,1 Hz), 1.21 (3H, s), 1.05 (1H, dd, J= 12.4, 1.8 Hz), 0.91 (6H, s), 0.85 (3H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) 39.3 (C-1), 17.6 (C-2), 41.9 (C-3), 33.3 (C-4), 51.5 (C-5), 18.6 (C-6), 41.1 (C-7), 76.9 (C-8), 56.3 (C-9), 36.9 (C-10), 33.5 (C-11), 20.7 (C-12), 21.7 (C-13), 14.9 (C-14), 19.9 (C-15), 112.8 (C-1), 145.2 (C-2), 142.1 (C-3), 114.8 (C-4), 99.7 (C-5), 152.9 (C-6), 55.4 (C-OCH_3), 138.3 (C-Bn), 128.3-127.5 (5 CH, Bn), 73.1 (CH_2, Bn). HRMS: Calcd for $C_{22}H_{32}O_3$ 344.2248, found 344.2249.

Reduction of 8 with Et_3SiH-CF_3COOH: Synthesis of 8*S*-labda-12*Z*,13-diene (29) and 8*R*-labda-12*Z*,13-diene (30)

CF_3COOH (0.3 ml) was slowly added to a solution of *cis-* abienol (**8**) (0.5 g,1.72 mmol) and Et_3SiH (0.5ml) in CH_2Cl_2 (15 ml) at -78°C. After being allowed to warm to -15°C over 2h 30min, a saturated aqueous $NaHCO_3$ solution (2 ml) was introduced, and the cooling bath removed to allow the solution to warm to room temperature with vigorous stirring. The mixture was diluted with ether (50 ml) and the organic phase separated and washed with 10% $NaHCO_3$ (2 x 10 ml), brine (2 x 10 ml) and dried over anhydrous Na_2SO_4. Concentration under reduced pressure afforded a 1:1 mixture of **29** and **30** (452 mg, 96%).

Reduction of 8 with ZnI_2-$NaBH_3CN$: Synthesis of 29 and 30

ZnI_2 (988 mg, 3.1 mmol) was slowly added to a solution of *cis*- abienol (**8**) (500 mg, 1.72 mmol) and $NaCNBH_3$ (325 mg, 5.16 mmol) in CH_2Cl_2 (10 ml) at 0°C and the mixture allowed to warm to room temperature and stirred for 2h 15 min. It was then filtered through a plug of celite, eluting with ether (30 ml). The combined filtrate was evaporated to afford 452 mg (96%) of a 4:1 mixture of **29** and **30**. **29**:IR (film) : 3089, 1680, 1640, 1457, 1441, 1383, 1037, 900 cm^{-1}. MS *m/z* (rel. int.): 274 (M^+, 20), 259 (10), 191 (90), 177 (23), 137 (60), 123 (100). ^1H NMR ($CDCl_3$, 300 MHz) : δ 6.81 (1H, dd, J=17.2, 10.7 Hz, H-14), 5.35 (1H, t, J=7.4 Hz, H-12), 5.17 (1H, d, J=17.2 Hz, H-15), 5.06 (1H, d, J=10.7 Hz, H-15), 1.80 (3H, bs, Me-16), 0.89 (3H, d, J=7,6 Hz, Me-17), 0.87 (3H, s, Me-19), 0.85 (3H, s, Me-18), 0.81 (3H, s, Me-20). ^{13}C NMR ($CDCl_3$, 75 MHz) 39.8 (C-1), 17.7 (C-2), 42.4 (C-3), 33.4 (C-4), 54.8 (C-5), 18.6 (C-6), 35.0 (C-7), 30.1 (C-8), 56.8 (C-9), 42.3 (C-10), 24.0 (C-11), 134.1 (C-12), 132.3 (C-13), 131.8 (C-14), 113.0 (C-15).

8*S*-13,14,15,16-tetranorlabdan-12-al (28)

An O_3/O_2 mixture was slowly bubbled through a stirred solution of **29** (350 mg, 1.48 mmol) in CH_2Cl_2 (20 ml) at -78°C for 1h 15 min and the ozone excess in the solution removed by bubbling with argon. After addition of Me_2S (5 ml) at -78°C, the mixture was kept at room temperature for 18h. The mixture was concentrated in vacuo and purified by flash chromatography (4 g of SiO_2; 10% ether in hexane) to yield **28** (290 mg, 83%). IR (film): 2929, 1724. cm^{-1} MS *m/z* (rel. int): 236 (M^+, 2), 221 (16), 192 (62), 177 (45), 123 (100). ^1H NMR ($CDCl_3$, 300 MHz): δ 9.86 (1H, d, J= 1.7 Hz, H-11), 2.37(1H, m), 1.94 (1H, m), 1.16 (3H, s, Me-15), 1.08 (3H, d, J=7.4 Hz, Me-8), 0.85 (3H, s, Me-14), 0.83 (3H, s, Me-13). ^{13}C NMR ($CDCl_3$, 75 MHz) 39.9 C-1), 17.5 (C-2), 42.7 (C-3), 33.5 (C-4), 56.5 (C-5), 18.4 (C-6), 34.6 (C-7), 32.6 (C-8), 48.2 (C-9), 39.4 (C-10), 39.8 (C-11), 203.7 (C-12), 16.6 (C-13), 33.4 (C-14), 21.6 (C-15), 15.8 (C-16).

8*S*-12*t*-Butyldimethylsilyloxy-13,14,15,16-tetranorlabd-11*E*/*Z*-ene (27)

TBDMSCl (121 mg, 0.98 mmol) and NaH (250 mg of 60% reagent in oil, 6.25 mmol) were added to a stirred and ice-cooled solution of aldehyde **28** (190 mg, 0.8 mmol) in THF (5 ml) and the mixture was allowed to warm to room temperature for 4h. It was then filtered through silica gel to afford 359 mg (92%) of **27**. IR (film) : 2929, 1653, 1460, 1386, 1298, 1255, 926 cm^{-1}. MS *m/z* (rel. int): 350 (M^+,12), 293 (100), 211 (55), 169 (21), 137 (14). ^1H NMR ($CDCl_3$, 300 MHz) : δ 6.18 (1H, d, J=11.7 Hz, H-12), 5.20 (1H, dd, J=11.7, 10.4 Hz, H-11), 1.68 (1H, dd, J=10.4, 4.9 Hz, H-9), 0.98 (3H, d, J=7.4 Hz, Me-13), 0.93 (9H, s, Si-^{t}Bu), 0.88 (3H, s, Me-15), 0.86 (3H, s, Me-14), 0.83 (3H, s, Me-16), 0.15 (6H, s, Si-Me_2).

8*S*-Driman-11-al (26)

A solution of crude silyl enol ether **27** (359 mg, 0.74 mmol) in dry CH_2Cl_2 - MeOH, 3:2 (25 ml) was slowly bubbled with a O_3/O_2 mixture at -78°C for 45 min. Then Me_2S (10 ml) was added and the mixture stirred for 4h. The solvent was evaporated, affording a crude mixture that after chromatography (hexane-ether 9:1) yielded 156 mg (95%) of **26**. IR (film): 2930, 1715, 1366, 1112. cm^{-1} MS *m/z* (rel. int): 222 (M^+, 16), 207 (14), 138 (59), 123 (98), 109 (68), 84 (100). ^1H NMR ($CDCl_3$, 400 MHz): δ 9.86 (1H, d, J= 1.7 Hz, H-

11), 2.37(1H, m), 1.94 (1H, m), 1.16 (3H, s, Me-15), 1.08 (3H, d, J=7.4 Hz, Me-12), 0.85 (3H, s, Me-14), 0.83 (3H, s, Me-13). ^{13}C NMR ($CDCl_3$, 100 MHz) 39.7 C-1), 17.3 (C-2), 42.0 (C-3), 33.2 (C-4), 55.7 (C-5), 18.1 (C-6), 34.2 (C-7), 29.9 (C-8), 65.6 (C-9), 37.1 (C-10), 206.7 (C-11), 18.0 (C-12), 33.5 (C-13), 21.6 (C-14), 17.2 (C-15).

8*S*-Driman-11-al (26) from 3

A solution of **3** (500 mg, 0.23 mmol) in MeOH-AcOEt, (1:1; 10 ml) was hydrogenated over 10% Pd-C (60 mg) under an atmosphere of hydrogen at 0°C for 1h. Filtration and concentration gave a crude which after chromatography (5% ether -hexane) yielded 307 mg (61%) of **26** as a colorless oil and 130 mg (26%) of **10**.

Synthesis of 8*S*-1,2-di-*O*-benzyl-3-(11'-hydroxydriman-11'-yl)-4-*O*-methylbenzenetriol (31)

A 1.7 M solution of *t*- butyllithium in hexane (1.9 ml) was added dropwise to a cold (-40°C) solution of **21** (1 g, 3.125 mmol) in Et_2O (25 ml), over 5 min . After 45 min at this temperature, the aldehyde **26** (0.4 g, 1.8 mmol) in Et_2O (10 ml) was added and the mixture stirred for 1h 30 min and allowed to warm to 0°C. Saturated NH_4Cl solution (10 ml) was added to the mixture and the organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane - ether 3:1) to give 0.53 g (55%) of **31**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.47-7.38 (20H, m, Bn), 6.88 (1H, d, J=8.9 Hz, H-6), 6.87 (1H, d, J=8.9 Hz, H-6), 6.59 (2H, d, J=8.9 Hz, H-5), 5.37-4.97 (10H, m), 3.86 (3H, s, OMe), 3.85 (3H, s, OMe), 3.40 (1H, bd, J=10.7 Hz, H-9'), 2.90 (1H, d, J=11.1 Hz, H-9'), 2.28 (1H, m), 2.08 (1H, m), 1.90 (1H, m), 1.79 (m, 1H), 1.18 (3H, d, J= 7,3 Hz, Me-12'), 1.13 (3H, s), 1.03 (3H, s, 0.90 (3H, s), 0.87 (3H, s), 0.83 (3H, s), 0.82 (3H, s), 0.69 (3H, d, J= 7,3 Hz, Me-12'). ^{13}C NMR ($CDCl_3$, 75 MHz) 16.5 (CH_3), 17.1 (CH_3), 17.2 (CH_3), 17.4 (CH_3), 17.5 (CH_2), 17.7 (CH_2), 18.5 ($2CH_2$), 21.6 ($2CH_3$), 29.4 (CH), 31.4 (CH), 33.4 (C), 33.5 (C), 33.7 (CH_3), 33.8 (CH_3), 35.4 (CH_2), 35.7 (CH_2), 39.2 (CH_2), 39.8 (2C), 41.2 (CH_2), 42.0 (CH_2), 42.3 (CH_2), 55.6 (CH_3), 55.7 (CH_3), 56.8 (CH), 56.9 (CH), 57.3 (CH), 60.1 (CH), 68.2 (CH), 68.9 (CH), 71.7 (CH_2), 71.9 (CH_2), 75.5 ($2CH_2$), 105.7 (CH), 106.0 (CH), 113.3 (CH), 113.9 (CH), 126.9-129.0 (24C), 137.1 (C), 137.2 (C), 137.4 (C), 137.6 (C), 146.4 (C), 146.5 (C), 152.4 (2C).

Reaction of 31 with TsOH: Synthesis of 8*S*-1,2-di-*O*-benzyl-3-(9'-drimen-11'-yl)-4-*O*-methylbenzenetriol (32)

A solution of the alcohol **31** (60 mg, 0.11 mmol), in dry benzene (3 ml) was stirred at 35°C in the presence of *p*- toluenesulphonic acid (20 mg) for 13h. The mixture was diluted with ether (20ml), washed with saturated aq. sodium hydrogen carbonate (2 x 5 ml), dried and evaporated to give 49 mg (82%) of **32**. IR (film) : 3055, 1598, 1230, 1020, 782 cm^{-1}. MS *m/z* (rel. int): 524 (M^+, 0), 433 (M^+-Bn-H_2O, 44), 386 (12), 279 (21), 191(37), 165 (39), 147 (95), 91 (100). ^{1}H NMR ($CDCl_3$, 400 MHz) : δ 7.28-7.45 (10H, m, Bn), 6.83 (1H, d, J=8.9 Hz, H-6), 6.55 (1H, d, J=8.9 Hz, H-5), 5.89 (1H, s, H-14'), 5.08 (2H, s, 2H-Bn), 4.95 (1H, d, J=10.6 Hz, H-Bn), 3.72 (3H, s, OMe), 2.66 (1H, m, H-8'), 1.84 (1H, d, J= 11.9 Hz), 1.70 (1H, dt, J= 13.7, 3.5 Hz), 1.20 (3H, s, Me-13'), 1.05 (3H, d, J= 7.5 Hz, Me-12'), 0.89 (3H, s, Me-15'), 0.86 (3H, s, Me-14'). ^{13}C NMR ($CDCl_3$, 100 MHz) 38.7 (C-1'), 19.0 (C-2'), 42.3 (C-3'), 34.0 (C-4'), 54.6 (C-5'), 17.9 (C-6'), 33.9 (C-7'), 32.3 (C-8'), 158.0 (C-9'), 40.9 (C-10'), 113.1 (C-11'), 21.5 (C-12'), 33.5 (C-

15'), 22.5 (C-13'), 21.9 (C-14'), 124.5 (C-1), 152.2 (C-2), 106.1 (C-3), 110.9 (C-4), 146.5 (C-5), 147.4 (C-6), 56.0 (C-OCH_3), 137.6 (C-Bn), 138.2 (C-Bn), 127.6-128.5 (10 CH, Bn), 71.9 (CH_2, Bn), 74.5 (CH_2, Bn).

Reaction of 31 with Raney Ni: Synthesis of 8*S*-3-(driman-11'-yl)-4-*O*-methylbenzenetriol (33)

Deprotection of benzyl groups of **31** (50 mg, 0.095 mmol) with Raney Ni under the same reaction conditions as for **2** yielded 30 mg (93%) of **33**. IR (film) 3674, 2671, 1654, 1603, 1382, 1315, 1285, 1088, 947 , 786 cm^{-1}. MS *m/z* (rel. int) 346 (M^+, 30), 358 (15), 228 (17), 206 (20) ^1H NMR (CD_3COCD_3, 300 MHz): δ 7.95 (2H, s, OH), 6.95 (2H, s, OH), 6.12 (2H, d, J=8.7 Hz, H-6), 6.08 (2H, d, J=8.7 Hz, H-5), 3.71 (3H, s, H-OMe), 3.70 (3H, s, H-OMe), 2.70 (4H, m), 1.12 (6H, s), 1.04 (3H, d, J= 7.5 Hz), 0.83 (12H, s), 0.78 (3H, d, J=7.5 Hz). HRMS: Calcd for $C_{22}H_{34}O_3$ 346.2470, found 346.2507.

Wiedendiol B (2)

A solution of **32** (120 mg, 0.23 mmol) in 1:1 MeOH-AcOEt (3 ml) was hydrogenated over 10% Pd-C (10 mg) under an atmosphere of hydrogen at 0°C for 2h. Filtration and concentration gave 73 mg (93%) of **2**. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.76 (1H, d, J=8.8 Hz, H-6), 6.35 (1H, d, J=8.8 Hz, H-5), 5.78 (1H, s, H-11'), 3.71 (3H, s, H-OMe), 2.60 (1H, m), 1.25 (3H, s, Me-15'), 1.04 (3H, d, J= 7.5 Hz, Me-12'), 0.91 (3H, s, Me-14'), 0.91 (6H, s, Me-13'). ^{13}C NMR ($CDCl_3$, 100 MHz) 38.9 (C-1'), 18.9 (C-2'), 42.1 (C-3'), 34.1 (C-4'), 55.3 (C-5'), 17.9 (C-6'), 34.3 (C-7'), 32.1 (C-8'), 164.3 (C-9'), 41.3 (C-10'), 112.7 (C-11'), 21.9 (C-12'), 33.4 (C-13'), 22.9 (C-14'), 22.0 (C-15'), 137.9 (C-1), 139.8 (C-2), 114.9 (C-3), 151.1 (C-4), 102.9 (C-5), 109.2 (C-6), 56.1 (C-OCH_3). HRMS: Calcd for $C_{22}H_{32}O_3$ 344.2335, found 344.2351.

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