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SYNTHETIC STUDIES ON BIOLOGICALLY ACTIVE NATURAL COMPOUNDS. PART I: STEREOSPECIFIC TRANSFORMATION OF UVIDIN A INTO (-)-CINNAMODIAL

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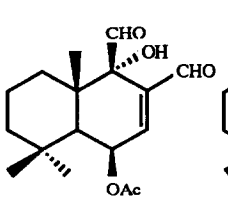
Abstract. A partial synthesis of (-)-cinnamodial (**1**) has been achieved, using (+)-uvidin A (**3**) as starting material. This also represents a formal synthesis of (-)-cinnamosmolide (**2a**) and pereniporin B (**2b**).

Introduction. Cinnamodial (**1**), also known with the name of ugandensidial, is a constituent of plants of the family Canellaceae,[1] and has a hot taste to the human tongue. It has been shown to possess remarkable insect antifeedant activity against the African army worm (Spodoptera species)[2] as well as cytotoxic activity in the P-388 test system in vitro.[1c] The correlation with confertifolin[1a] allowed the absolute stereochemistry of cinnamodial to be established as **1**. The total synthesis of (±)-**1** has been reported,[3-5] however the synthesis of the natural (-)enantiomer has not been accomplished so far. In this paper we report the first synthesis of natural cinnamodial starting from uvidin A (**3**), easily available as a major metabolite of Lactarius uvidus (Basidiomycetes).[6] The absolute configuration of uvidin A has been established on the firm grounds of spectroscopic and chemical evidences,[6] and corresponds to that of (-)-**1**. Moreover, since cinnamodial has been converted[1a] into (-)-cinnamosmolide (**2a**) and (-)-pereniporin B (**2b**)[7,8] this also represents a formal partial synthesis of the latter drimane sesquiterpenes, reconfirming the assigned stereostructures.



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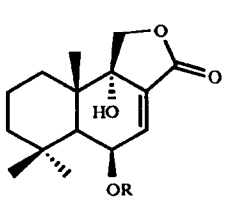
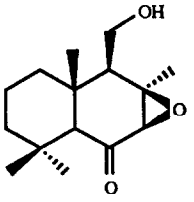


2a R = Ac
2b R = H



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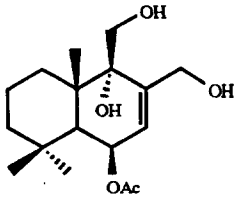

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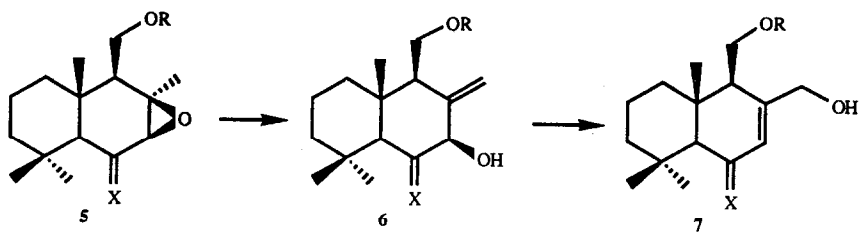
Pereniporin B (**2b**) isolated from liquid cultures of the basidiomycete Perenniporia medullaepanis,[7] showed potent cytotoxicity against Friend leukemia cells, F5-5.

Uvidin A was considered to be an attractive chiral synthon for the elaboration of other highly oxygenated drimane sesquiterpenes, such as compounds **1** and **2**, since in principle the different level of oxidation at carbons 6, 7, 8 and 11 of **3** could have appropriately been exploited for introducing either the sensitive hydroxy ene-dialdehyde or the ene-lactone function . More important uvidin A already incorporates a carbonyl at C-6, a feature that gives obvious advantages over other syntheses[3] requiring a lengthy sequence for introducing an oxygen functionality at C-6 of the bicyclofarnesyl skeleton.

Results and discussion

The triol **4** was selected as the logical immediate precursor of cinnamodial and other congener sesquiterpenes, such as **2a** and **2b**, since this substance could permit a number of variations in planning the oxidation level at C-11 and C-12.[9]

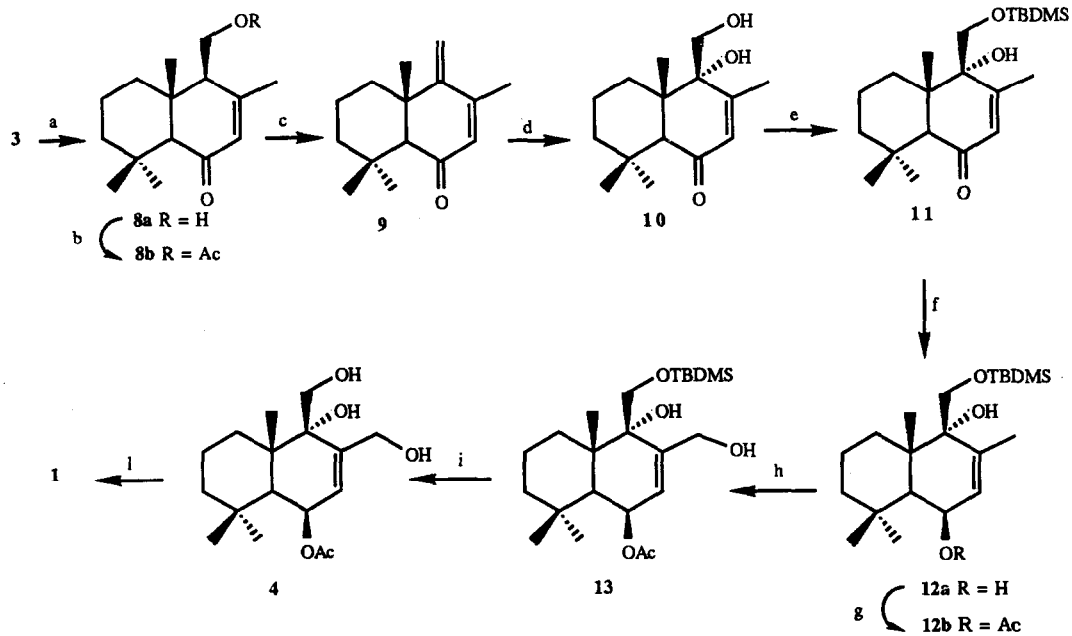
Our initial scheme for deploying an oxygen function at C-12 of a suitable uvidin A derivative **5** envisioned isomerization of the C-7,8 epoxide to the allylic alcohol **6**, followed by an acid-catalyzed rearrangement to the more stable trisubstituted olefin **7** (scheme I)



Scheme I

The reaction **5**→**6** was initially attempted on **3** itself and on two O-protected derivatives of uvidin A (**5**, X=O, R=THP or EEE), by using strong bases (LDA or $LiNEt_2$). In all cases substantial amounts of products arising from a Favorskii-like rearrangement of the α,β-epoxyketone were obtained.[10] In an attempt to suppress this rearrangement, the 6-ß-alcohol **5** (R=TBDMS, X=ß-OH, H) was readily prepared from uvidin A, by protection of the primary alcohol with tert-butyldimethylsilyl chloride in DMF/imidazole,[11] followed by a clean reduction of the C-6 carbonyl group with alcoholic $NaBH_4$. However, when this

substrate was exposed to $Ti(O\underline{i}\text{-}Pr)_4$ in CH_2Cl_2, under the Sharpless conditions for performing the hydroxyl-directed Lewis acid mediated epoxide rearrangement,[12] it could be recovered unchanged in more than 80% yield. This result was not completely unexpected in view of the severe steric hindrance encountered by the C-6 hydroxyl group toward complexation with the Ti(IV) reagent. When $Al(O\underline{i}\text{-}Pr)_3$ was substituted for $Ti(O\underline{i}\text{-}Pr)_4$ under the normal rearrangement conditions,[12] again no reaction was observed. More forcing conditions (excess of reagent, toluene, reflux temperature) rapidly converted 5 (R=TBDMS, X=β-OH, H) to several unidentified products. After these failures, we decided to manipulate the functional groups of uvidin A in a more conventional way and to introduce a primary OH at C-12 by SeO_2 allylic oxidation of the corresponding allylic methyl.[13]



a, $\Phi_3P\cdot I_2$, moist CH_3CN; b, Ac_2O, Py; c, DBU; d, OsO_4, Py; e, $\underline{t}$-$BuMe_2SiCl$, DMF, Im; f, DIBAL, THF, C_6H_6; g, Ac_2O, Py, DMAP; h, SeO_2, dioxane; i, $nBu_4N^+F^-$; l, DMSO, TFAA, NEt_3

Scheme II

To this end uvidin A (3) was smoothly converted, by a new de-epoxidation procedure (Φ_3P I_2/moist CH_3CN),[14] to the enone **8a** (98%), which was then acetylated in the usual way. Our plan at this juncture called for introduction of the 9-α-hydroxyl group prior to reduction

of the C-6 ketone to the corresponding 6-ß-OH. It is very well known, in fact, that the C-6 keto function of these bicyclofarnesane derivatives is extremely resistant to hydride reduction, unless a strategically placed 9-α-hydroxyl appendage directs hydride attack by coordination with the reducing reagent.[4] Compound **8b** was then submitted to a vinylogous ß-elimination with DBU and the resulting unstable dienone **9**, obtained in 88% yield, was immediately subjected to 1 equiv of OsO_4 in pyridine. It was anticipated that osmilation would occur preferentially at the more nucleophilic γ,δ-unsaturation and from the less hindered α face of the π system, as shown in Scheme II. In practice the reaction was completely diastereo- and site-selective, giving the diol **10** as the sole product in 96% isolated yield.

The stereochemistry at C-9 is in agreement with the subsequent conversion of **10** into cinnamodial (**1**) and is supported by the shift of the proton 5-H ($\tilde{\delta}$ 2.77), in comparison with the corresponding signal of the enone **8a** ($\tilde{\delta}$ 2.10). This downfield shift can be attributed to the cis 1,3-diaxial interaction of 5-H with the free C_9-OH group. Monoprotection of the diol **10** with the Corey's procedure[11] gave the O-tert-butyldimethylsilyl ether **11** (93%). Reduction of **11** with DIBAL in THF-C_6H_6 slowly afforded the expected 6-ß alcohol (J_{5-6} = 4.5 Hz), arising from hydride delivery from the bottom face of the carbonyl group. The sterically hindered, axial alcohol of **12a** was reluctant to undergo acetylation but, with Ac_2O-Py in the presence of a catalytic quantity of 4-(dimethylamino)pyridine,[15] the acetate **12b** was slowly produced (60% based on **11**). With **12b** in hand, the stage was now opened to the crucial functionalization of the olefinic methyl C-12. Allylic oxidation of the acetate **12b** was achieved in dioxane with an excess of SeO_2, at reflux temperature. Variable amounts (40-50%) of the desired diol **13**, accompanied by minor quantities (5-10%) of the corresponding 12-aldehyde, were formed. Compound **13** could be obtained in pure form only after deprotection of the primary OH group.This was achieved, in 85% yield, by stirring the mixture in THF with Bu_4NF supported on silica gel.[16] The key intermediate **4** was identical, by comparison of its IR and NMR spectra and optical rotation, with the compound obtained from enantiomerically pure, natural cinnamodial.[17] Oxidation of the triol **4**, m.p. 93-96°C, $[\alpha]_D^{20}$ - 140.4°, with DMSO-TFAA-NEt_3,[18] strictly following the Ley conditions,[9] afforded cinnamodial (**1**) in 35% yield. This product was identical on direct comparison with natural material.[19] Thus, despite the disappointing final oxidation steps, the route described above shows the feasibility of converting uvidin A into cinnamodial.[17]

EXPERIMENTAL

Melting points were determined on a Fisher-Johns hot-stage apparatus and are uncorrected. IR spectra were recorded as neat oils or as KBr pellets or nujol dispersion for solids on a Perkin-Elmer 197 spectrometer. Mass spectra were obtained on a Finnigan MAT 8222 instrument at 70 eV (0.5 mA). ^{1}H-NMR spectra were recorded on a Bruker WP80 SY or a Bruker CPX 300 instruments in $CDCl_3$. Chemical shifts are reported in δ units with Me_4Si as the internal standard; the abbreviations s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and b=broad are used throughout. UV absorptions were measured on a Perkin Elmer Hitachi 200 spectrophotometer. Optical rotations were determined in a $CHCl_3$ solution with a digital Perkin-Elmer 241 polarimeter. Column chromatography was performed on Kieselgel 60 (Merck), 0.04-0.06 mm, slurry packed, and run at atmospheric pressure. Analytical TLC plates (250 μm) were obtained from Merck. All solvents were purified and dried by standard techniques just before use. All reactions were routinely carried out under an inert atmosphere of dry nitrogen. All organic solutions were washed with brine, then dried over $MgSO_4$ and filtered prior to rotary evaporation at water aspirator pressure. Residual solvent was removed under vacuum, usually at less than 1 torr.
Uvidin A (**3**) was isolated from a Me_2CO extract of Lactarius uvidus Fr., as reported in reference 6.

6-Oxo-7-drimen-11-ol (**8a**). Uvidin A (**3**) (101 mg, 0.40 mmol) was added at once to a solution of I_2 (56 mg, 0.22 mmol) and PPh_3 (115 mg, 0.44 mmol) in CH_3CN (10 mL) containing ca 2% of H_2O. The solution became dark red-brown in a very short time, at room temperature. After stirring for 10 min the mixture was diluted with H_2O and extracted with $CHCl_3$ (3x25 mL). The organic layer was washed with 5% aq. $NaHSO_3$ solution and brine, dried and concentrated, yielding an oil which was chromatographed. Elution with hexane-AcOEt (70:30) afforded the crystalline enone **8a** (99 mg, 98%), m.p. 84-85°C (from hexane); $[\alpha]_D^{20}$ +25° (c 0.9), identical with the compound already prepared from uvidin A according to another procedure.[6] Spectral data of **8a** can be found in reference 6.

6-Oxo-7-drimen-11-ol acetate (**8b**). Compound **8a** (90 mg, 0.38 mmol) was acetylated with Ac_2O-pyridine in the usual way. After evaporation of the volatiles under high vacuum, the residue was chromatographed. Elution with hexane-AcOEt (80:20) afforded the crystalline acetate **8b**, (91 mg, 86%), m.p. 62-63°C (from hexane); ν_{max} 2920, 2860, 2840, 1740, 1670, 1460, 1440, 1380, 1360, 1225, 1150, 1130, 1110, 1045, 1035, 1000, 965, 920, 880, 865 cm^{-1}; δ (80 MHz) 0.92, 1.14 and 1.18 (3H each, 3s, 4-$(CH_3)_2$ and 10-CH_3), 1.93 (3H, t, J=1.5 Hz, 8-CH_3), 2.08 (3H, s, CH_3COO-), 2.37-2.62 (1H, m, 9-H), 4.05-4.50 (2H, AB part of an ABX system, 11-Ha and 11-Hb), 5.85 (1H, m, 7-H); m/z (%) 278 (M^+, 5), 218(40), 203(14), 148(19), 135(100), 112(33), 109(10), 95(13), 55(9), 43(18).

7,9-Drimadien-6-one (**9**). DBU (378 mg, 2.5 mmol) was added to compound **8b** (230 mg, 0.827 mmol) dissolved in dry benzene (3 mL). The mixture was stirred for 6 h at reflux temperature. After evaporation of the solvent, the crude residue was chromatographed with hexane-AcOEt (90:10) to afford (in order of elution): **9** (158 mg, 88%), an unidentified UV active compound (4 mg), starting material (3 mg). **9**, pale yellow oil, $[\alpha]_D^{20}$ - 160.8°(c 1.0); λ_{max}^{hexane} nm (Log ϵ) 271 (4.03); ν_{max} 2920, 2840, 1665, 1595, 1460, 1375, 1355, 1320, 1285, 1225, 1185, 1145, 985, 970, 955, 900, 860 cm^{-1}; δ (80 MHz) 1.14 and 1.21 (9H, 4-$(CH_3)_2$ and 10-CH_3), 2.02 (3H, d, J 1.0 Hz, 8-CH_3), 2.25 (1H, s, 5-H), 5.28 (1H, br s, 11-Ha), 5.32 (1H, br s, 11-Hb), 5.83 (1H, m, 7-H); m/z(%) 218 (M^+, 31), 203(15), 149(13), 148(13), 136(21), 135(100), 121(10), 91(11), 41(14).

6-Oxo-7-drimen-9α,11-diol (**10**). OsO_4 (240 mg, 0.944 mmol) dissolved in dry pyridine (5 ml)

was added to the dienone **9** (180 mg, 0.826 mmol) in pyridine (2 mL). The dark mixture was stirred overnight at room temperature, then $Na_2S_2O_5$ (304 mg, 1,6 mmol) in H_2O (5 mL) was added. After a further 90 min the mixture was diluted with brine (7 mL) and extracted with $CHCl_3$ (3x20 mL) and then with AcOEt (3x15 mL). Drying and evaporation of the solvent from the organic fraction gave a white solid, which was crystallized from hexane-AcOEt to give the diol **10** (200.6 mg, 96%), m.p. 139-141°C, $[\alpha]_D^{20}$ -43.96° (c 1.0); ν_{max} 3440, 3320, 2950, 2920, 2865, 2840, 1658, 1635, 1435, 1385, 1355, 1290, 1240, 1208, 1195, 1170, 1155, 1100, 1078, 1060, 1030, 970, 950, 925, 890, 882, 865, 805, 735, 680 cm^{-1}; δ (80 MHz) 0.96, 1.17 and 1.20 (3H each, 3s, 4-$(CH_3)_2$ and 10-CH_3), 2.01 (3H, d, J=1.8 Hz, 8-CH_3). 2.77 (1H, s, 5-H), 3.85 (2H, ABq, J=11 Hz, 11-Ha and 11-Hb), 5.75 (1H, br s, 7-H); m/z (%) 252 (M^+, 8), 234(3), 221(15), 189(6), 151(13), 128(100), 111(13), 110(97), 109(15), 95(6), 83(100), 69(12), 55(9), 43(11), 41(11).

11-O-tert-Butyldimethylsilyl ether of the diol **10**: **11**. Imidazole (135 mg, 1.98 mmol) and t-$BuMe_2SiCl$ (180 mg, 1.19 mmol) were added at once to a solution of the diol **10** (200 mg, 0.793 mmol) in dry DMF (3 mL). The mixture was stirred for 15 h at 40°C, then more t-$BuMe_2SiCl$ (100 mg, 0.66 mmol) was added to achieve complete conversion of the substrate (a further 5 h at 40°C). The mixture was cooled to room temperature, diluted with H_2O (10 mol) and extracted with hexane (5x10 mL). Drying and evaporation of the solvent gave a white solid which was chromatographed with hexane-AcOEt (90:10) to yield **11** (270 mg, 93%), m.p. 114-115°C (from hexane), $[\alpha]_D^{20}$ -44° (c 1.0); ν_{max} 3420, 2920, 2855, 1655, 1460, 1440, 1390, 1365, 1340, 1295, 1260, 1250, 1235, 1137, 1107, 1090, 1075, 1065, 1050, 1018, 988, 970, 960, 940, 870, 855, 840, 815, 780 cm^{-1}; δ (80 MHz) 0.08 (6H, s, $(CH_3)_2Si$), 0.90 (12 H, s, $(CH_3)_3C$-Si and 4-α-CH_3), 1.12 and 1.15 (3H each, 2s, 4-βCH_3 and 10-CH_3), 1.87 (3H, d, J=1.8 Hz, 8-CH_3), 2.80 (1H, s, 5-H), 3.71 (2H, br s, collapsed ABq, 11-Ha and 11-Hb), 5.70 (1H, br s, 7-H); m/z (%) 366(M^+, 7), 336(12), 309(48), 279(55), 242(11), 234(33), 221(23), 217(32), 209(23), 205(10), 203(10), 185(85), 177(13), 175(11), 161(13), 151(12), 135(16), 124(13), 119(12), 115(11), 111(33), 109(29), 105(31), 95(9), 89(53), 75(100), 73(68), 69(17), 57(13), 55(15), 43(15), 41(14).

11-O-tert-Butyldimethylsilyl ether of 7-drimen-6ß,9α,11-triol: (**12a**). To a magnetically stirred solution of **11** (77 mg, 0.210 mmol) in dry THF (2 mL), cooled in an ice bath, was added 0.5 mL of 1M DIBAL in toluene. After 5h at 0°C, TLC control showed, besides **12a**, traces of starting material and other unidentified compounds. The mixture was quenched with 25 ml of aq NH_4Cl and extracted with $CHCl_3$ (5x20 mL). The organic extract was washed with saturated aq $NaHCO_3$, dried, and concentrated to yield an oil which was chromatographed with hexane-AcOEt (90:10) to give 54 mg (70%) of **12a** as a colorless solid, m.p. 67-70°C, $[\alpha]_D^{20}$ - 50° (c 1.2); ν_{max} 3500, 2950, 2930, 2860, 1460, 1445, 1390, 1362, 1260, 1220, 1105, 1075, 1030, 1005, 985, 965, 942, 920, 900, 880, 870, 840, 815, 780, 740, 680 cm^{-1}; δ (80 MHz) 0.06 (6H, s, $(CH_3)_2Si$), 0.88 (9H, s, $(CH_3)_3C$-Si), 1.07 (6H, s, 4-αCH_3 and 10-CH_3), 1.29 (3H, s, 4-βCH_3), 1.77 (3H, br s, 8-CH_3), 3.62 (2H, collapsed ABq, 11-Ha and 11-Hb), 4.38 (1H, brt, 6-H), 5.60 (1H, dd, J_{6-7}=5.0 Hz, J_{7-Me}=1.5 Hz, 7-H); m/z(%) 368(M, 0.2), 335(5), 245(14), 244(50), 223(46), 219(8), 205(17), 201(13), 187(19), 177(13), 169(31), 163(11), 161(13), 159(13), 149(11), 145(21), 135(30), 123(16), 121(21), 119(22), 112(48), 111(21), 109(38), 107(16), 105(41), 97(16), 95(41), 89(30), 83(21), 81(17), 75(100), 73(70), 69(48), 57(24), 55(31), 43(42), 41(31).

11-O-tert-Butyldimethylsilyl ether of 6ß-acetoxy-7-drimen-9α,11-diol: (**12b**) To a stirred solution of **12a** (50 mg, 0.136 mmol) in dry pyridine (3 mL) was added Ac_2O (0.5 mL) and a catalytic amount of 4-(dimethylammino)pyridine. After 20 h, MeOH (10 mL) was added and the organic solution was taken to dryness. The residue was chromatographed with hexane-AcOEt (90:10) to yield **12b** (45 mg, 81%) as a colorless solid, m.p. 54-56°C, ν_{max} 3525, 2950,

2930, 2860, 1730, 1465, 1445, 1390, 1372, 1250, 1220, 1110, 1065, 1025, 960, 952, 910, 885, 840, 818, 780, 745, 678 cm^{-1}; δ (80 MHz) 0.11 (6H, s, $(CH_3)_2Si$), 0.94 (9H, s, $(CH_3)_3C$-Si), 1.00, 1.07 and 1.12 (3H each, 3s, 4-$(CH_3)_2$ and 10-CH_3), 1.78 (3H, br s, 8-CH_3), 2.00 (1H, d, J_{5-6}=4.5 Hz, 5-H), 2.05 (3H, s, CH_3COO), 3.67 (2H, s, collapsed ABq, 11-Ha and 11-Hb), 5.45-5.70 (2H, m, 6-H and 7-H); EIMS, m/z (%) 350 (M-AcOH, 22), 293 (19), 286(100), 265(54), 244(22), 223(19), 219(19), 205(41), 201(38), 187(24), 169(28), 161(13), 145(15), 135(17), 119(14), 105(24), 95(10), 75(22), 73(19); CIMS (isobutane)m/z 411 (MH^+), 393 ($MH-H_2O$), 351 (MH-AcOH), 333, 286, 201.

6-ß-Acetoxy-7-drimen-9α,11,12-triol (**4**). A mixture of compound **12b** (44 mg, 0.107 mmol) and SeO_2 (78 mg, 0.7 mmol) in dioxane (5 mL) was kept refluxing for 4 h. CH_2Cl_2 (5 mL) was added and the mixture was filtered through a pad of $MgSO_4$ and silica gel to remove the precipitated selenium. Evaporation of the solvent gave a yellow oil which was chromatographed (hexane-AcoEt, 90:10) to afford 21 mg of a mixture whose ^{1}H-NMR spectrum, consistent with the structure of the diol **13**, showed a signal at δ 9.40, attributed to the 8-CHO group of the corresponding aldehyde (~ 10%). As the two compounds could not be separated by column chromatography, a sample of the mixture (14 mg, ca 0.033 mmol), was vigorously stirred with Bu_4NF on silica gel (FLUKA) (70 mg, 0.064 mmol) in anhydrous THF (2 mL) for 5 h at room temperature. Filtration through a $MgSO_4$ pad and removal of solvent gave a residue which was chromatographed (hexane-AcOEt, gradient) to yield crystalline **4** (8.1 mg, 85%), m.p. 93-96°C, $[\alpha]_D^{20}$ -140.4° (c 0.4); ν_{max} 3400, 2940, 2910, 2850, 1725, 1460, 1365, 1240, 1210, 1070, 1050, 1020, 950, 908 cm^{-1}; δ (300 MHz) 0.99, 1.05 and 1.11 (3H each, 3s, 4-$(CH_3)_2$ and 10-CH_3), 1.96 (1H, d, J_{5-6}=4.5 Hz, 5-H), 2.04 (3H, s, CH_3COO), 3.78 (2H, collapsed ABq, 11-Ha and 11-Hb), 4.15 (1H, d, J_{AB}=12.5 Hz, 12-Ha), 4.38 (1H, d, J_{AB}=12.5 Hz, 12-Hb), 5.58 (1H, t, J ~ 5.0 Hz, 6-H), 5.89 (1H, d, J_{6-7}=5 Hz, 7-H); m/z(%) 281 ($M-CH_2OH$), 21), 252 (M-AcOH, 14), 221(95), 203(61), 188(47), 181(17), 175(14), 161(16), 149(13), 147(26), 135(29), 133(13), 128(67), 123(16), 121(17), 119(16), 110(74), 109(42), 107(14), 105(18), 97(30), 95(21), 91(15), 81(23), 71(29), 69(55), 57(35), 55(35), 43(100), 41(38).

(-)-Cinnamodial (**1**). A solution of the triol **4** (8 mg, 0.026 mmol) in DMSO-CH_2Cl_2 (1:1, 0.3 mL) was added to the Swern reagent (0.156 mmol, 6 equiv., prepared by the addition of trifluoroacetic anhydride (38 mg, 25 μl) in CH_2Cl_2 (0.3 mL) to DMSO (73 μL) in CH_2Cl_2 (1.4 ml) at -50°C under N_2) dropwise by syringe, at -50°C. After 30 min at - 50°C, dry NEt_3 (33 μL, 9 equiv.) was added, and the reaction worked up as usual. Chromatography of the product mixture (hexane-AcOEt, 80:20) gave cinnamodial (**1**) (2.8 mg, 35%), m.p. 135-138°C (lit.,[1a] 141-143°C), $[\alpha]_D^{20}$ - 415° (lit.,[1a] - 421.5°). IR and ^{1}HNMR (300 MHz) spectra were identical to an authentic sample.[19]

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