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Synthetic Studies on Biologically Active Natural Compounds. Part III. Stereospecific Transformation of Uvidin A into (-) - Cinnamosmolide.

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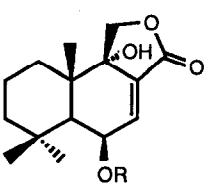
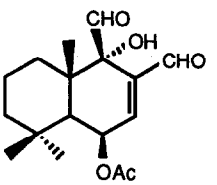
Abstract: The first synthesis of natural (-)-cinnamosmolide (**1a**) from the sesquiterpene uvidin A (**3**) is described. The important synthetic intermediates **12a-b** were also obtained from (-)-cinnamodial (**2**)

INTRODUCTION

Cinnamosmolide (**1a**),a sesquiterpene isolated from the bark of the Madagascar plant *Cinnamosma fragrans*[2] and from the leaf-twig extract of *Capsicodendron dinisii*[3] (Canellaceae) is structurally related to biologically active drimane derivatives, such as the cytotoxic pereniporin B (**1b**)[4] and the insect antifeedant, pepper-like tasting, cinnamodial (**2**).[2,3,5] Compound **1a** itself shows cytotoxic activity in the 9KB5 cell culture system.[3] Racemic cinnamosmolide has been synthesized by Naito *et al.*,[6] whereas the synthesis of the natural (-)-enantiomer has not been accomplished so far.



1a R = Ac
1b R = H



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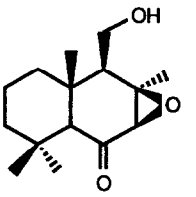

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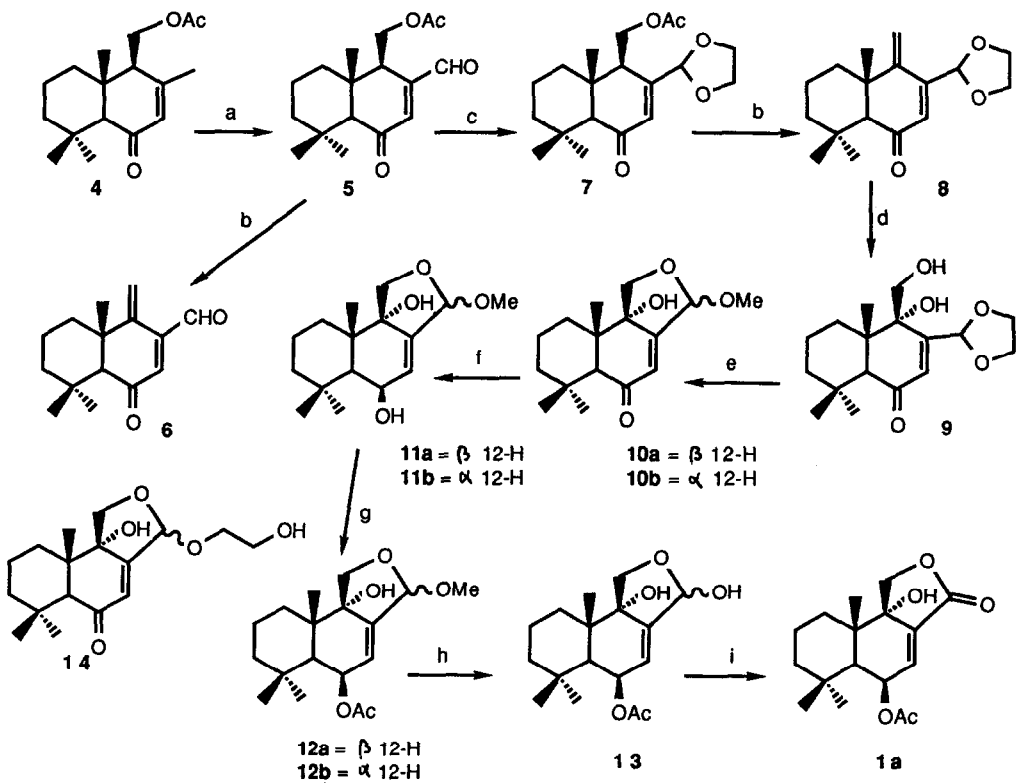
This paper is dedicated with pleasure to Professor Paolo Grünanger on the occasion of his 65th birthday.

In this paper we report the first synthesis of natural cinnamosmolide (**1a**) from (+) uvidin A (**3**), which is easily available as a major metabolite of *Lactarius uvidus* (Basidiomycetes).[7] The variety of functions with different level of oxidation makes uvidin A (**3**) an attractive chiral starting material for the synthesis of highly oxidized drimane type sesquiterpenes, as it has been shown with the synthesis[8] of natural (-)-cinnamodial (**2**). In particular, uvidin A already incorporates a carbonyl at C-6, a feature which gives obvious advantages over other syntheses[6,9] requiring a lengthy sequence for introducing an oxygen functionality at C-6 of the bicyclofarnesyl skeleton.

RESULTS AND DISCUSSION

The synthesis of (-)-cinnamosmolide (**1a**) is outlined in Scheme 1. By a well established procedure, including a new de-epoxidation reaction,[10] uvidin A (**3**) was smoothly converted into enone **4** (84% yield).[8] Allylic oxidation at C-12 was performed before introduction of the 6β,9α-diol system, for taking advantage of the activating effect of the unsaturated carbonyl group over SeO_2 oxidation.[11] As expected, oxidation of **4** with SeO_2 in anhydrous dioxane led directly to the desired aldehyde **5** (60-70%), accompanied only by minor quantities of other oxidized compounds at C-9 and C-12. At this stage we considered protection of the formyl group more convenient than further oxidation to a carboxylic acid derivative. In fact such a function, for example a carbomethoxy group, was expected to interfere in the following reduction of the highly hindered C-6 ketone. A mixed acetal (see formula **10**) involving the carbonyl at C-12 and the primary alcohol of 9,11-diol was therefore the next target of our synthesis. Towards this end, exposure of compound **5** to DBU

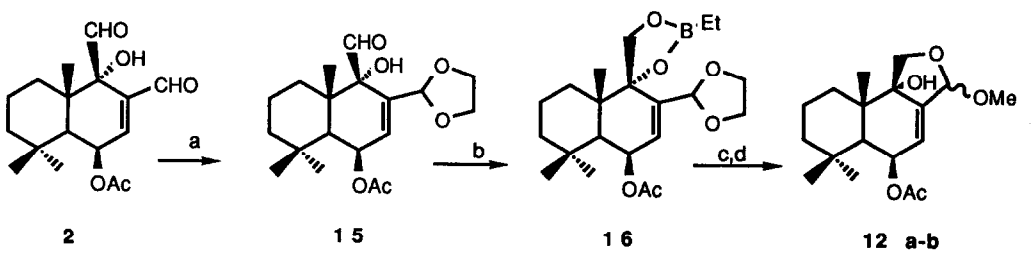


Scheme 1 - Reagents: a, SeO_2 ,dioxane; b, DBU; c, $HOCH_2CH_2OH$, *p*-TsOH ; d, OsO_4, Py ; e, MeOH, *p*-TsOH ; f , $NaBH_4$, EtOH ; g , Ac_2O, Py, DMAP ; h, aq. Me_2CO , Py.*p*-TsOH ; i , $BaMnO_4$, $CuSO_4$ - Al_2O_3

readily afforded the dienone **6**; however, selective osmylation of the 9,11-double bond of **6** with OsO_4 in pyridine met with no success, probably for the instability of the 9-OH ene-dicarbonyl system. The less hindered C-12 carbonyl in compound **5** was therefore first protected as acetal **7**, followed by vinylogous β-elimination with DBU to afford dienone **8** (77% for the two steps), which was immediately subjected to osmilation.

This reaction now proceeded smoothly, electrophilic addition occurring, as expected, at the more nucleophilic 9,11 double bond and from the less hindered α face of the π system. The stereochemistry at C-9 for compound **9** is in agreement with the subsequent conversion into cinnamosmolide (**1a**) and is supported by the shift of the proton 5-H (δ 2.91), in comparison with the corresponding signal for the enone **7** (δ 2.14). This downfield shift can be attributed to the *cis* 1,3-diaxial interaction of 5-H with the free C_9-OH group. By brief treatment with MeOH-*p*-TsOH, compound **9** was converted into mixed acetals **10** (73%), thus securing protection of both the aldehyde at C-12 and the primary alcohol. Protection of the latter was necessary before conversion of C-6 ketone to secondary acetate and for preventing formation of mixed acetals, such as **14**, by traces of acids.[12] **10** was obtained as a mixture (2.7:1) of epimers at C-12. The major isomer was assigned structure **10a**, on the basis of NOE experiments and the assumption that acetalyzation reaction is under thermodinamic control, thus favouring the intramolecularly H-bonded α-12-OMe. Each separated anomers **10a** and **10b** were converted into cinnamosmolide (**1a**), although in principle the entire mixture **10** could be used throughout the synthetic sequence. Reduction of **10a** with excess $NaBH_4$ slowly afforded the 6β-alcohol **11a** ($J_{5\text{-}6}$ = 4.2 Hz), arising from hydride delivery from the botton face of the carbonyl group. It is possible that the 9α-OH appendage serves to direct hydride attack by coordination with the reducing agent.[13] Acetylation of the sterically hindered axial alcohol of **11a** with Ac_2O-Py, in the presence of a catalytic quantity of 4-(dimethylammino)pyridine[14] provided the acetate **12a** (63% for the two steps). In the same way **10b** gave the epimeric acetate **12b** (56% yield).

In order to confirm the stereostructures of intermediates **12a-b** and to secure additional material for the last synthetic steps, cinnamodial (**2**) was partially reduced to acetals **12** (Scheme 2). In this conversion we took advantage of our previous experience in playing with the carbonyl groups of dialdehyde **2**.[15] Exposure of cinnamodial (**2**) to ethylene glycol and pyridinium *p*-toluenesulphonate[16] slowly afforded the acetal (**15**) of the less hindered and more reactive unsaturated C-12 formyl group. Selective reduction of the free aldehyde **15** with excess $LiEt_3BH$ led directly to the cyclic boronate **16** (66% from **2**).[15,17] Sequential treatment of compound **16** with 30% H_2O_2 in MeOH and then with dry MeOH, in the presence of a catalytic amount of pyridinium *p*-toluenesulphonate, allowed unmasking of the 9,11 glycol and exchange of the acetal group at C-12, affording a mixture (3.2:1) of the two acetals **12a** and **12b**.



Scheme 2 - Reagents: a , $HOCH_2CH_2OH$, Py . *p*-TsOH ; b , $LiEt_3BH$; c , H_2O_2 , MeOH - H_2O ; d , MeOH , Py . *p*-TsOH

Each of them was identical in all respects with the corresponding compound obtained from uvidin A (**3**). With **12a-b** in hand, the stage was now opened to the crucial hydrolysis of the cyclic acetal group. It was anticipated, from the presence of a labile allyl 9-OH moiety, that conversion of each O-methyl acetal **12a and**

12b into hemiacetal **13** should be conducted under very mild acidic conditions. After several attempts, this difficulty was overcome by use of Py-*p*-TsOH in aq Me_2CO. The desired hemiacetal **13** was obtained as a mixture of anomers at C-12. They were not separated but immediately submitted to oxidation of the lactol group. To this purpose neither various Cr^{VI} oxidants[18] nor Fetizon's reagent[19] gave satisfactory results. Finally we discovered that reaction of **13** with $BaMnO_4$-Al_2O_3-$CuSO_4.5H_2O$[20] readily provided the target lactone **1a** (58% yield from **12a** and 50% from **12b**), mp 191-3°C, $[\alpha]_D^{20}$ -340. [lit.: mp 204°C[2], 197-198°C[3]; $[\alpha]_D^{20}$-332.4 [2], -336 [3]]. The spectral data (IR, NMR, MS spectra) and TLC mobility were identical with those of an authentic sample of natural cinnamosmolide.[2,3]

In conclusion, the overall yield in the synthesis of (-)cinnamosmolide (**1a**) was 10-12%, starting from uvidin A. This approach compares favorably with previously reported synthesis[6] of racemic **1a** and illustrates, once more, the utility of uvidin A (**3**) for the synthesis of highly functionalized drimane type sesquiterpenes.

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 spectrophotometer. 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 AC300 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 argon. During work up of reactions organic solutions were eventually 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.

11-Acetoxy-6-oxo-7-drimen-12-al (**5**). A mixture of compound **4**[8] (80 mg, 0.288 mmol) and sublimed SeO_2 (192 mg, 1.72 mmol) in dry dioxane (8 mL) was kept refluxing for 16 h. CH_2CH_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 separated (hexane-AcOEt, 80:20) with radial centrifugal chromatography to afford aldehyde **5** (62 mg, 74%), mp 86-92°C, $[\alpha]_D^{20}$ + 54.1 (c=0.5); $\bar{\nu}_{max}$ 2920, 2865, 1740,1700, 1685, 1465, 1390, 1365, 1328, 1295, 1235, 1148, 1122, 1070, 1045, 972, 960, 930, 875, 810, 738, 700 cm^{-1}; δ (80 MHz) 0.96, 1.10 and 1.23 (3H each, 3 s's, 10-CH_3 and 4-$(CH_3)_2$), 1.95 (3H, s, CH_3COO), 2.16 (1H, s, 5α-H), 2.84 (1H, m, X part of an ABX system, 9α-H), 4.42 (1H, B part of an ABX system, J_{AB} = 12.0 Hz, J_{BX} = 2.0 Hz, 11-Ha), 4.70 (1H, A part of an ABX system, J_{AB} = 12.0 Hz, J_{AX} = 5.0 Hz, 11-Hb), 6.52 (1H, d, $J_{7,9}$ = 3.0 Hz, 7-H), 9.75 (1H, s, CHO, 12-H); m/z (%): 292 (M^+, 3), 277(3), 250(100), 232(12), 217(11), 204(11), 189(9), 161(8), 151(10), 149(20), 137(10), 126(23), 123(28), 109(34), 95(10), 81(12), 69(17), 57(17), 55(12), 43(51).

6-Oxo-7,9-drimadien-12-al (**6**). DBU (50 mg, 0.33 mmol) was added to compound **5** (27 mg, 0.092 mmol) dissolved in dry benzene (3 mL). The mixture was stirred overnight at room temperature. After evaporation of the solvent, the crude residue was chromatographed with hexane-AcOEt (85:15) to afford dienone **6** (17 mg, 80%), $\bar{\nu}_{max}$ 2920, 2860, 1708, 1675, 1460, 1380, 1320, 1285, 1235, 1180, 1143, 1075, 1040, 972, 925, 870, 805 cm^{-1}; δ (80 MHz) 1.12 and 1.25 (3H and 6H, respectively, 2 s's, 4-$(CH_3)_2$ and

10-CH_3), 2.0 (1H, s, 5α-H), 5.50 (1M, bs, 11-Ha), 6.10 (1H, s, 11-H_b), 6.28 (1H, bs, 7-H), 9.87 (1H, s, CHO, 12-H); m/z (%): 232 (M^+, 80), 217(36), 189(12), 149(100), 123(10).

11-Acetoxy-6-oxo-7-drimen-12-al 12-ethylene acetal (**7**). Ethylene glycol (220 mg, 3.5 mmol) and a catalytic amount of *p*-TsOH were added to a stirred solution of aldehyde **5** (115 mg, 0.394 mmol) in dry benzene (10 mL). The mixture was heated to reflux for 6 h, cooled to room temperature, diluted with Et_2O (10 mL) and washed with 5% $NaHCO_3$. After drying and removal of solvent, the residue was chromatographed (hexane-AcOEt, 70:30) to give the acetal **7** (115 mg, 87%), mp 75-78°C, $[\alpha]_D^{20}$ + 41.9 (c = 4.5); $\bar{\nu}_{max}$ 2920, 1740, 1677,1465, 1388, 1365, 1235, 1168, 1150, 1135, 1100, 1030, 945, 895 cm^{-1}; δ (80 MHz) 0.95, 1.12 and 1.20 (3H each, 3 s's, 4-$(CH_3)_2$ and 10-CH_3), 2.04 (3H, s, CH_3COO), 2.14 (1H, s, 5α-H), 2.69 (1H, m, X part of an ABX system, 9α-H), 3.97(4H, s,-OCH_2CH_2O-), 4.40 (2H, AB part of an ABX system, 11-Ha and 11-Hb), 5.62 (1H, s, 12-H), 6.25 (1H, d, $J_{7\text{-}9}$ = 3.0 Hz, 7-H); m/z (%): 336(M^+, 35), 276(70), 263(56), 261(28), 248(25), 233(26), 193(57), 184(70), 170(42), 152(30), 135(25), 125(55),109(52), 81(32), 73(100), 69(37), 55(40), 43(85), 41(62).

6-Oxo-7,9-drimadien-12-al 12-ethylene acetal (**8**). DBU (300 mg, 1.97 mmol) was added to compound **7** (90 mg, 0.27 mmol) dissolved in dry benzene (2 mL). The solution was stirred for 3 h at reflux temperature. After evaporation of the solvent, the crude residue was chromatographed with hexane-AcOEt (80:20) to give diene **8** (65 mg, 88%), $[\alpha]_D^{20}$ -174.1 (c = 3.2), λ_{max}^{hexane} nm (log ε) 268.8 (4.19); $\bar{\nu}_{max}$ 2929, 1670, 1466, 1384, 1353, 1329, 1288, 1238, 1184, 1124, 1065, 1056, 996, 974, 945 cm^{-1}; δ (80 MHz) 1.14 and 1.20 (6H and 3H respectively, 2s's, 4-$(CH_3)_2$ and 10-CH_3), 2.30 (1H, s, 5α-H), 4.02 (4H, s, -OCH_2CH_2O-), 5.37 (1H, bs, 11-Ha), 5.55 (1H, s, 11-H_b), 5.72 (1H, s, 12-H), 6.17 (1H, bs, 7-H); m/z (%): 276 (M^+, 21), 261(6), 248(2), 233(6), 193(31), 149(6), 135(21), 121(7), 105(7), 91(13), 73(100), 55(9), 45(17), 41(18).

9α-11-Dihydroxy-6-oxo-7-drimen-12-al 12-ethylene acetal (**9**). OsO_4 (72 mg, 0.28 mmol) dissolved in dry pyridine (2 mL) was added to dienone **8** (65 mg, 0.23 mmol) in dry pyridine (2 mL). The dark mixture was stirred for 6 h at room temperature, then 4M aq $NaHSO_3$ (1.5 mL) was added. After a further 90 min the mixture was diluted with H_2O (7 mL) and extracted with $CHCl_3$ (3 x 15 mL) and then with AcOEt (3 x 15 mL). Drying and evaporation of the solvent from the organic phase gave an oily residue which was chromatographed with hexane-AcOEt (1:1) to afford the diol **9** (70 mg. 98%), mp 100-103°C, $[\alpha]_D^{20}$ - 12.43 (CH_2Cl_2, c = 0.7); $\bar{\nu}_{max}$ 3422, 2928, 1676, 1462, 1384, 1361, 1147, 1094, 1032 cm^{-1}; δ (80 MHz) 1.02, 1.14 and 1.22 (3H ech, 3 s's, 4-$(CH_3)_2$ and 10-CH_3), 2.91 (1H, s, 5α-H), 3.85 (2H, ABq, 11-Ha and 11-H_b), 4.06 (4H, s, -OCH_2CH_2O-), 5.77 (1H, s, 12-H), 6.20 (1H, s, 7-H); m/z (%): 310(M^+, 5), 292(5), 280(36), 279(57), 248(9), 192(25), 189(11), 186(10), 175(10), 168(50), 161(12), 155(18), 147(15), 125(16), 124(15), 121(18), 110(14), 109(30), 105(11), 95(17), 91(16), 83(18), 81(23), 73(100), 69(32), 67(21), 57(32), 55(36), 45(41), 43(32), 41(52).

Conversion of diol **9** *into acetals* **10a** *and* **10b**. A solution of diol **9** (68,3 mg, 0.22 mmol)and *p*-TsOH (6 mg) in dry MeOH (10 mL) was stirred at room temperature for 48 h, then diluted with AcOEt (25 mL) and washed with 5% $NaHCO_3$ and brine. After drying and removal of solvent, the residue was chromatographed (hexane-AcOEt, 30:20) to give, in order of elution, the acetals **10b** (12.2 mg, 20%) and **10a** (33 mg, 53%), followed by an unidentified compound (8 mg). **10a** : mp 124-126°C, $[\alpha]_D^{20}$ -137.48 (c = 1.2), $\bar{\nu}_{max}$ 3473, 2943, 1665, 1455, 1388, 1359, 1292, 1218, 1190, 1157,1121, 1100, 1071, 1028, 994, 954, 884, 869, 808, 696, 669 cm^{-1}; δ (300 MHz) 1.08, 1.17 and 1.19 (3H each, 3s's, 4-$(CH_3)_2$ and 10-CH_3), 2.93 (1H, s, 5α-H), 3.45 (3H, s, OCH_3), 3.83 (1H, d, J_{AB} = 10.0 Hz, 11-Ha), 4.11 (1H, d, J_{AB} = 10.0 Hz, 11-H_b), 5.52 (1H, bs, 12-H), 5.91(1H, bs, 7-H); m/z (%): 280 (M^+, 6), 250(40), 249(14), 248(19), 156(15), 151(14), 125(10), 124(100), 123(13), 121(10), 109(24), 97(14), 91(10), 81(11), 69(11), 67(10), 55(13), 43(12), 41(25). **10b**: $[\alpha]_D^{20}$ + 21.67 (c = 0.4); $\bar{\nu}_{max}$ 3458, 1672, 1463, 1383, 1350, 1309, 1284, 1221, 1189, 1140, 1126, 1077, 1033, 1001, 962, 913, 889, 874 cm^{-1}; δ (300 MHz) 0.97, 1.15 and 1.18 (3H each, 3s's, 4-$(CH_3)_2$ and 10-CH_3), 3.04 (1H, s,

5α-H), 3.47 (3H, s, OCH_3), 3.97 (1H, d, J_{AB} = 10.0 Hz, 11-Ha), 4.26 (1H, d, J_{AB} = 10.0 Hz, 11-H_b), 5.3 (1H, s, 12-H), 5.85 (1H, s, 7-H); m/z (%): 280 (M^+, 5), 250(51), 249(12), 248(17), 156(17), 151(13), 125(10), 124(100), 121(11), 109(27), 97(17), 91(11), 81(13), 77(10), 69(13), 67(12), 55(15), 43(16), 41(31).

Separate reduction of Ketones **10a** *and* **10b**: **11a** *and* **11b**. Solid $NaBH_4$ (6.2 mg, 0.164 mmol) was added to a stirred solution of acetal **10a** (23 mg, 0.082 mmol) in EtOH (1 mL) at 0°C. After 1 h the reaction mixture was warmed to room temperature, stirred for an additional hour, then quenched with few drops of Me_2CO. The volatiles were evaporated under vacuum and the residue was taken up in CH_2Cl_2 and filtered on a $MgSO_4$ pad. After removal of solvent, column chromatography (hexane-AcOEt, 1:1) afforded **11a** (18.6 mg, 81%), $[\alpha]_D^{20}$ - 212.9 (c = 0.6); $\bar{\nu}_{max}$ 3444, 2919, 1457, 1381, 1218, 1190, 1097, 1022, 996, 957, 921, 884 cm^{-1}; δ (300 MHz) 1.05, 1.10 and 1.28 (3H each, 3 s's, 4-$(CH_3)_2$ and 10-CH_3), 3.39 (3H, s, OCH_3), 3.67 (1H, d, J_{AB} = 10.0 Hz, 11-Ha), 3.95 (1H, d, J_{AB} = 10.0 Hz, 11-H_b), 4.47 (1H, bt, $J_{5-6} \cong J_{6-7}$ = 4.2 Hz, 6α-H), 5.36 (1H, bs, 12-H), 5.92 (1H, dd, J_{6-7} = 4.2 Hz, J_{7-12} = 1.5 Hz, 7-H); m/z (%): 264(M-H_2O, 5), 252(23), 250(23), 237(11), 233(20), 217(16), 189(11), 158(83), 153(38), 151(23), 140(15), 135(17), 126(100), 123(20), 109(35), 107(15), 105(12), 97(18), 95(19), 91(24), 83(19), 81(24), 79(15), 69(49), 67(17), 55(29), 43(40), 41(53); CIMS (NH_3) m/z: 317 (M + NH_3 + NH_4^+), 300 (M + NH_4^+), 285, 268, 250.

In a similar way, $NaBH_4$ reduction of acetal **10b** (7 mg) gave the alcohol **11b** (5.6 mg, 80%); $\bar{\nu}_{max}$ 3464, 2925, 1461, 1379, 1214, 1077, 1045, 1026, 997, 963, 922, 865, 843, 775, 746 cm^{-1}; δ (80 MHz) 1.09 and 1.35 (6H and 3H respectively, 2 s's, 4-$(CH_3)_2$ and 10-CH_3), 1.96 (1H, d, J_{5-6} = 5.0 Hz, 5α-H), 3.45 (3H, s, OCH_3), 3.95 (1H, d, J_{AB} = 10.0 Hz, 11-Ha), 4.17 (1H, d, J_{AB} = 10.0 Hz, 11-H_b), 4.58 (1H, dd, J_{5-6} = 5.0 Hz, J_{6-7} = 4.4 Hz, 6α-H), 5.22 (1H, s, 12-H), 5.96 (1H, d, J_{6-7} = 4.4 Hz, 7-H).

Separate acetylation of diols **11a** *and* **11b**: *acetates* **12a** *and* **12b**. To a stirred solution of **11a** (15 mg, 0.053 mmol) in dry benzene (0.5 mL) was added NEt_3 (20 μL), acetic anhydride (22 μL), and a catalytic amount of 4-(N,N-dimethylamino)pyridine. After 24 h the volatiles were evaporated under vacuum and the residue was chromatographed (hexane-AcOEt, 60:40) to yield the acetate **12a** (13.5 mg, 78%), mp 119-121°C, $[\alpha]_D^{20}$ -281.5 (c = 0.7); $\bar{\nu}_{max}$ 3456, 2956, 1734, 1461, 1369, 1309, 1242, 1216, 1192, 1106, 1081, 1017, 997,981, 961, 910, 890, 799, 757, 698, 666 cm^{-1}; δ (80 MHz) 1.01 and 1.17 (3H and 6H respectively, 2 s's, 4-$(CH_3)_2$ and 10-CH_3), 2.07 (3H, s, CH_3COO), 3.46 (3H, s, OCH_3), 3.75 (1H, d, J_{AB} = 9,5 Hz, 11-Ha), 4.05 (1H, d, J_{AB} = 9.5 Hz, 11-H_b), 5.45 (1H, bs, 12-H), 5.70 (1H, bt, $J_{5-6} \cong J_{6-7}$ = 4.2 Hz, 6α-H), 5.92 (1H, bd, J_{6-7} = 4.2 Hz, 7-H); m/z (%): 324 (M^+, 1), 294(5), 264(21), 235(17), 234(15), 233(14), 232(23), 217(20), 200(41), 163(17), 158(56), 151(25), 135(15), 133(10), 126(31), 123(13), 121(12), 109(17), 105(27), 95(13), 91(24), 81(19), 79(15), 77(16), 69(33), 67(15), 57(16), 55(39), 43(100), 41(49).

In a similar way, acetylation of **11b** (5 mg, 0.018 mmol) yielded isomeric acetate **12b** (4.0 mg, 70%), $[\alpha]_D^{20}$ -159.1 (c = 0.2); $\bar{\nu}_{max}$ 3458, 2920, 1729, 1462, 1368, 1241, 1214, 1075, 1018, 954, 910 cm^{-1}; δ (80 MHz) 1.00, 1.11 and 1.16 (3H each, 3 s's, 4-$(CH_3)_2$ and 10-CH_3), 2.06 (3H, s, CH_3COO), 2.21 (1H, d, J_{5-6} = 5.0 Hz, 5α-H), 3.43 (3H, s, OCH_3), 3.95 (1H, d, J_{AB} = 10.0 Hz, 11-Ha), 4.18 (1H, d, J_{AB} = 10.0 Hz, 11-H_b), 5.20 (1H, s, 12-H), 5.67 (1H, bt, J_{5-6} = 5.0 Hz, J_{6-7} = 4.2 Hz, 6α-H), 5.90 (1H, d, J_{6-7} = 4.2 Hz, 7-H); m/z (%): 294 (M-CH_2O, 18), 293(15), 292(17), 264(33), 251(16), 235(17), 234(47), 233(22), 232(23), 219(16), 217(33), 200(47), 193(16), 176(12), 168(14), 163(33), 158(83), 152(32), 151(44), 135(20), 133(17), 126(60), 123(18), 121(15), 119(13), 109(25), 107(15), 105(23), 97(13), 95(19), 93(15), 91(23), 83(15), 81(21), 79(17), 77(16), 69(40), 67(16), 55(29), 43(100), 41(44).

Cinnamodial 12-Ethylene acetal (**15**). Ethylene glycol (220 mg, 3.55 mmol) and a catalytic amount of *p*-TsOH was added to a stirred solution of cinnamodial (**2**) (25,8 mg, 0.084 mmol) in dry benzene (3 mL) at reflux, using a Dean-Stark apparatus. After 5 h, benzene (10 mL) was added and the organic layer was washed with 5% $NaHCO_3$ and brine. After drying and removal of solvent, the residue was chromatographed (hexane-AcOEt, 80:20) to give the acetal **15** (27 mg, 92%), mp 168-171°C, $[\alpha]_D^{20}$ -100.83 (c = 0.1); $\bar{\nu}_{max}$ 3488, 2927, 2854, 1729, 1460, 1366, 1316, 1237, 1210, 1164, 1127, 1082, 1057, 1036, 1024, 971, 951, 920,

802 cm^{-1}; δ (300 MHz) 0.92, 1.15 and 1.47 (3H each, 3 s's, 4-$(CH_3)_2$ and 10-CH_3), 2.05 (1H, d, J_{5-6} = 4.6 Hz, 5α-H), 2.09 (3H, s, CH_3COO), 3.75-4.0 (4H, m, -OCH_2CH_2O-), 5.17 (1H, s, 12-H), 5.68 (1H, bt, J_{5-6} = 4.6 Hz, J_{6-7} = 4.9 Hz, 6α-H), 6.27 (1H, d, J_{6-7} = 4.9 Hz, 7-H); m/z (%): 323 (M-CHO, 31), 292 (M-CH_3COOH, 28), 281(23), 263(100), 235(13), 219(12), 201(13), 168(28), 157(17), 149(14), 135(9), 127(11), 123(13), 121(10), 109(21), 105(18), 95(12), 91(16), 87(24), 81(13), 79(9), 77(10), 73(88), 69(23), 55(16), 45(27), 43(56), 41(24), 29(7).

Ethylboronate **16**. 1.0 M solution of $LiEt_3BH$ in THF (200 μL) was added at 0°C, by syringe, to a magnetically stirred solution of acetal **15** (26 mg, 0.074 mmol) in dry THF (2 mL). After 10 min, the reaction mixture was quenched with H_2O and extracted with AcOEt (3 x 10 mL). After drying (Na_2SO_4) and removal of solvent, column chromatography of the residue (hexane-AcOEt, 80:20) afforded ethylboronate **16** (20.6 mg, 72%), $[\alpha]_D^{20}$ -191.7 (c = 1); $\bar{\nu}_{max}$ 3449, 2949, 1733, 1459, 1367, 1241, 1212, 1122, 1069, 1022, 949, 919, 880, 827, 795 cm^{-1}; δ (300 MHz) 0.8 (3H, q, J = 7.6 Hz, B-CH_2-$\underline{CH_3}$), 0.97 (2H, t, J = 7.6 Hz, B-$\underline{CH_2}$-CH_3), 1.0, 1.07 and 1.12 (3H each, 3 s's, 4-$(CH_3)_2$ and 10-CH_3), 1.97 (1H, d, J_{5-6} = 4.5 Hz, 5α-H), 2.05 (3H, s, CH_3COO), 3.8-4.1 (4H, m, -OCH_2CH_2O-), 4.06 (1H, d, J_{AB} = 10.0 Hz, 11-H_a), 4.42 (1H, d, J_{AB} = 10.0 Hz, 11-H_b), 5.34 (1H, s, 12-H), 5.67 (1H, t, J_{5-6} = J_{6-7} = 4.5 Hz, 6α-H), 6.24 (1H, d, J_{6-7} = 4.5 Hz, 7-H); m/z (%): 392 (M, 4), 349(17), 332(17), 268(65), 226(100), 164(17), 109(13), 105(10), 95(10), 91(13), 87(49), 83(12), 81(15), 73(95), 69(23), 67(12), 57(20), 55(28), 45(29), 43(51), 41(31).

Conversion of ethylboronate **16** *into acetals* **12a** *and* **12b**. 30% H_2O_2 (150 μL) was added to a solution of ethylboronate **16** (20 mg, 0.051 mmol) in MeOH (2 mL) at 0°C. After 10 min AcOEt (20 mL) was added and the organic layer was washed with 5% Na_2SO_3, then with brine. Drying and removal of solvent gave a residue which was dissolved in dry MeOH (5 mL) containing *p*-TsOH (2 mg). After stirring for 8 h at room temperature, the reaction mixture was diluted with AcOEt (15 mL), washed with 5% $NaHCO_3$ and brine. After removal of solvent, the residue was chromatographed (hexane-AcOEt, 3:2) to afford **12b** (3.1 mg, 19%) and **12a** (10.1 mg, 61%).

Hydrolysis of acetal **12a**, *followed by oxidation to cinnamosmolide* (**1a**). A solution of acetal **12a** (7 mg, 0.022 mmol) in Me_2CO-H_2O (2 mL, 1:3) containing pyridinium *p*-toluenesulphonate (1 mg) was stirred overnight at room temperature. The reaction mixture was then diluted with AcOEt (15 mL) and washed with brine. Drying (Na_2SO_4) and removal of solvent afforded a residue, no longer showing OMe signal in the ^{1}H-NMR spectrum, which was assigned structure **13** tentatively. A benzene solution (2 mL) of crude hemiacetal **13** (5.3 mg) was stirred at room temperature with a freshly prepared[20] solid mixture of $BaMnO_4$-Al_2O_3-$CuSO_4$. 5 H_2O (100 mg). After 7 h, the solid reagent was removed by filtration over a celite pad and evaporation of solvent gave a residue which was purified by column chromatography. Elution with hexane-AcOEt (70:30) afforded crystalline cinnamosmolide (**1a**) (3.9 mg, 58% from **12a**), mp 191-193°C, $[\alpha]_D^{20}$ -340 (c = 0.4). All spectral data matched those reported in the literature and are identical with an authentic sample of the natural compound.

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