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Enantioselective synthesis of 11-hydroxy-(1′S,2′R)-dimethylheptyl-Δ^8-THC, a very potent CB_1 agonist

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Abstract—An enantioselective synthesis of the (1*S*,2*R*)-dimethylheptyl cannabinoid side chain has been developed and employed in the synthesis of 11-hydroxy-(1′*S*,2′*R*)-dimethylheptyl-Δ^8-THC, one of the most potent traditional cannabinoids known. The synthesis involves a highly stereoselective addition of dimethylcopperlithium to an enoyl sultam which incorporates Opplozer's auxiliary. © 2001 Elsevier Science Ltd. All rights reserved.

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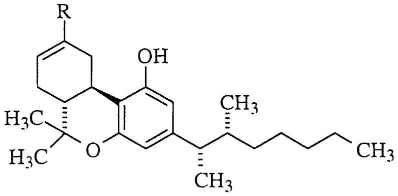
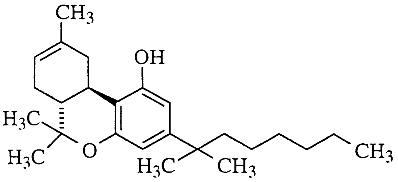
1. Introduction

In the thirty years since Gaoni and Mechoulam described the isolation and elucidation of the structure of Δ^9-THC (Δ^9-tetrahydrocannabinol),[1] a comprehensive set of structure–activity relationships (SAR) for cannabinoids has been developed.[2] For traditional cannabinoids structurally related to Δ^9-THC, these SAR have demonstrated that the cannabinoid side chain is an important pharmacophore. While the 1,2-dimethylheptyl (DMH) side chain is known to dramatically increase potency,[3] the 1,1-dimethylheptyl side chain is used almost exclusively in contemporary investigations. Not only are those cannabinoids which incorporate the 1,1-dimethylheptyl side chain very potent, but their precursor 1,3-dimethoxy-5-(1,1-dimethylheptyl)-benzene is readily available and this side chain substitution pattern does not introduce additional chiral centers.[4] Recent work has focused on the preparation of all four homochiral isomers of 1,2-DMH-Δ^8-THC via resolution methodology and (1′*S*,2′*R*)-DMH-Δ^8-THC (**1**) was shown to be significantly more potent than 1,1-DMH-Δ^8-THC (**2**) at the CB_1 receptor.[5] In view of the potency of **1**, an enantioselective synthesis of the (1′*S*,2′*R*)-dimethylheptyl cannabinoid side chain has been developed and employed in the synthesis of 11-hydroxy-(1′*S*,2′*R*)-dimethylheptyl-Δ^8-THC (**3**). We recently reported that **3** is one of the most potent traditional cannabinoids, both in vitro and in vivo at the CB_1 receptor,[6] and herein we report the asymmetric synthesis in detail.



1 R = CH_3

3 R = CH_2OH



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2. Results and discussion

The synthetic approach was based on a strategy reported by Mechoulam et al.[7] which employs 4-hydroxy-myrtenyl pivalate (**4**) as a source of the non-aromatic portion of an 11-hydroxy-cannabinoid. The cannabinoid skeleton is constructed via the Lewis acid catalyzed condensation of 4-hydroxy-myrtenyl pivalate with the corresponding homochiral resorcinol as shown in Scheme 1.

We reasoned that the two stereogenic centers of the resorcinol **5** could be developed via an asymmetric conjugate addition of dimethylcopperlithium to a cinnamic acid derivative which incorporated Opplozer's chiral auxiliary.

Keywords: cannabinoid; THC; cannabinoid receptor; Oppolzer's auxiliary.

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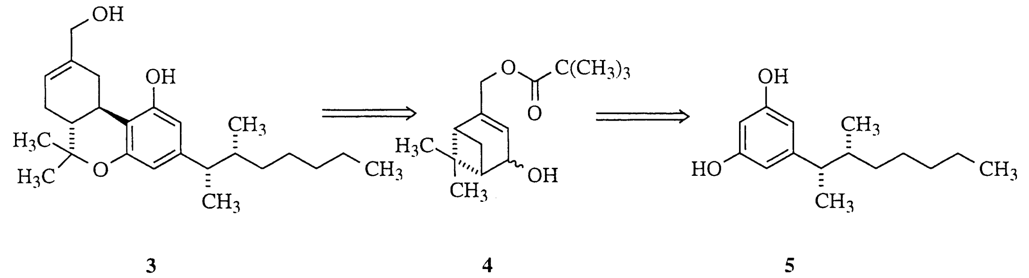
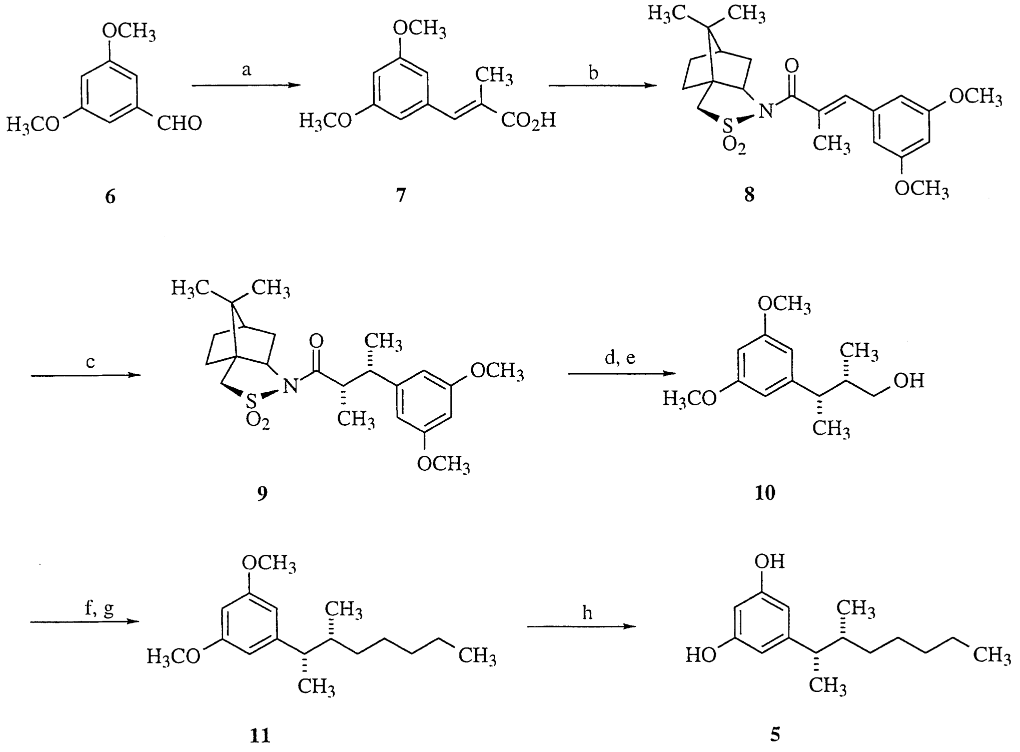
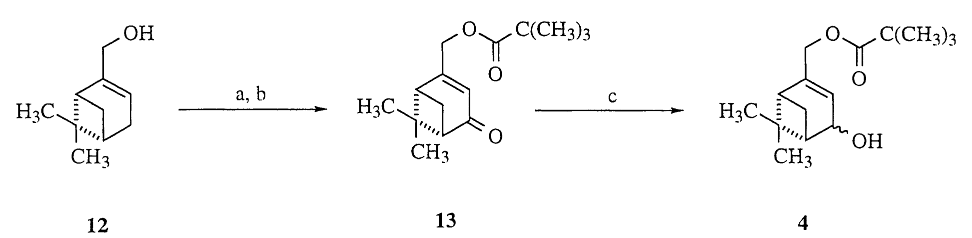


Scheme 1.

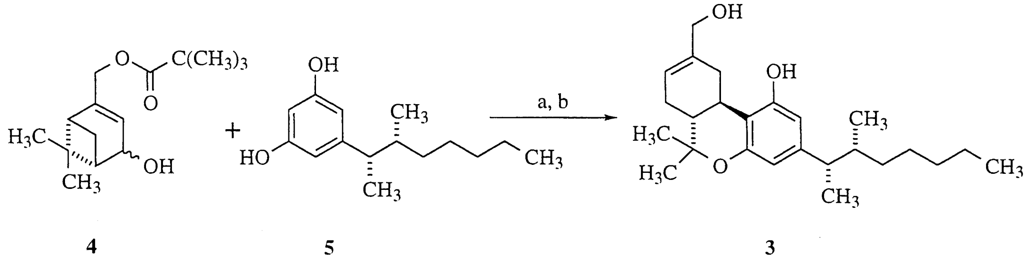
The synthesis of resorcinol **5** employed 3,5-dimethoxybenzaldehyde as starting material, which was subjected to a Horner–Emmons reaction with triethyl phosphonopropionate in the first step (Scheme 2).[8] The cinnamate ester underwent essentially complete hydrolysis during work up and was not isolated. The resulting cinnamic acid (**7**) was converted to the acid chloride using standard conditions and coupled to Oppolzer's auxiliary in 88% yield. Oppolzer's auxiliary was prepared from (+)-(1*S*)-camphor-10-sulfonic acid in four steps following the literature procedure.[9,10] The key step in the synthesis was the asymmetric addition of dimethylcopperlithium to enoyl sultam **8** and subsequent asymmetric protonation which established the stereochemistry at both chiral centers in a single step. Asymmetric conjugate addition of organocopper reagents to *N*-enoyl sultams and subsequent enolate protonation is well documented.[10] Oppolzer has reported that the addition of dimethylcopperlithium to *N*-[(*E*)-2-methyl-3-phenyl-2-propenoyl]-bornane-10,2-sultam, the phenyl derivative of **8**, gave the desired (*S*,*S*)-diastereoisomer in 80% diastereomeric excess and 60% yield.[10] In our hands the addition of dimethylcopperlithium to **8** proceeded well at −40°C to give a 94:2:2:2 mixture of diastereoisomers. The diastereoselectivity was determined by capillary GC–MS analysis of the crude reaction mixture and the major isomer (**9**) was isolated in 85% yield and >98% de following recrystallization. The acyl sultam (**9**) was homogeneous to capillary GC, ^1H- and ^{13}C NMR. Mild saponification using LiOH in THF/H_2O gave the corresponding butanoic acid in quantitative yield with no signs of epimerization and also served to recover the chiral auxiliary. Reduction of the acid with $LiAlH_4$ gave primary alcohol **10**. Comparison of the spectroscopic data and optical rotation of **10** to that of material prepared previously in these laboratories confirmed the absolute and relative stereochemistry.[5] Conversion of **10** to the resorcinol dimethyl ether (**11**) was effected by first formation of the tosylate, followed by a copper catalyzed reaction with butylmagnesium bromide using a modification of the procedure developed by Kochi.[8,11] Ether cleavage with boron tribromide gave resorcinol **5** and completed



Scheme 2. (a) Ref. 8; (b) $(COCl)_2$ then sodium salt of Oppolzer's auxiliary, Toluene, 3 h, 0–20°C, 90%; (c) Me_2CuLi, Toluene, 24 h then NH_4Cl, −40°C, 85%; (d) LiOH, H_2O, THF, 4 days, 60°C, 100%; (e) $LiAlH_4$, THF, 16 h, 0–20°C, 90%; (f) *p*-Toluenesulfonyl chloride, $CHCl_3$, Pyridine, 3 h, 0°C, 75%; (g) *n*-BuMgBr, Li_2CuCl_4, THF, 48 h, −78–0°C, 64%; (h) BBr_3, CH_2Cl_2, 16 h, 0–20°C, 94%.



Scheme 3. (a) $(CH_3)_3COCl$, CH_2Cl_2, Pyridine, 4 h, 0°C, 84%; (b) CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2, 4 h, −20°C, 53%; (c) $LiAlH(O{-}Bu)_3$, THF, 4 h, 0–20°C, 89%.



Scheme 4. (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 1 h, −20–20°C, 43%; (b) $LiAlH_4$, THF, 2 h, 0–20°C, 81%.

the synthesis of the aromatic portion of the target cannabinoid.

4-Hydroxy-myrtenyl pivalate (**4**) was employed to introduce the correct absolute stereochemistry in the synthesis of the carbocyclic portion of the cannabinoid ring structure. Pivalate **4** was prepared in three steps from (1*R*,5*S*)-myrtenol by a modification of the procedure reported by Mechoulam.[7] The hydroxyl group of **12** was first protected by esterification with trimethylacetyl chloride (Scheme 3), and allylic oxidation of the pivalate with the 3,5-dimethylpyrazole-chromium trioxide complex[12] gave 4-oxo-myrtenyl pivalate (**13**) in 53% yield. This method compares favorably to the 30% yield reported for the procedure using sodium chromate in acetic anhydride and acetic acid.[7] Finally, reduction of the ketone **13** with lithium tri-*tert*-butoxyaluminium hydride in THF led to 4-hydroxy-myrtenyl pivalate (**4**) as a single diastereoisomer.

Alcohol **4** was condensed with homochiral resorcinol **5** in dry dichloromethane at −20°C to give the resulting cannabinoid ester in 43% yield (Scheme 4). The ester was reduced with $LiAlH_4$ to afford cannabinoid **3** in 81% yield. Alcohol **10** and the (1*R*,5*S*)-myrtenol (**12**) employed in the synthesis of cannabinoid **3** are both of >98% ee and consequently the final cannabinoid **3** is of comparable optical purity.

In summary, we have developed a facile, and highly stereoselective synthesis of the (1′*S*,2′*R*)-dimethylheptyl side chain making it a viable alternative to the more commonly used 1′,1′-dimethylheptyl side chain. This methodology has been applied to the synthesis of 11-hydroxy-(1′*S*,2′*R*)-dimethylheptyl-Δ^8-THC (**3**), one of the most potent traditional cannabinoids known (K_i 0.49 nM). Cannabinoid (**3**) is approximately eighty times more potent than Δ^9-THC (K_i 41 nM) at the CB1 receptor. Second, an improved synthesis of the key intermediate, 4-hydroxy-myrtenyl pivalate, has been described.

3. Experimental

3.1. General

^1H and ^{13}C NMR spectra were recorded on a Bruker 300AC spectrometer. Mass spectral analyses were performed on a Hewlett–Packard 5890A gas chromatograph with a mass sensitive detector and HRMS data were obtained in the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois. THF was distilled from Na-benzophenone ketyl; toluene from sodium; dichloromethane from calcium hydride; other solvents were purified using standard procedures. Column chromatography was carried out on Universal silica gel (32–63 μ). All new compounds were homogeneous to TLC and NMR.

3.1.1. *N*-[(*E*)-2-Methyl-3-{3,5-dimethoxyphenyl}-2-propenoyl]-bornane-10,2-sultam (8). To a slurry of sodium hydride (600 mg, 80% dispersion in mineral oil, 20.0 mmol) in dry toluene (20 ml) at 0°C was added a solution of (2*R*)-bornane-10,2-sultam[9] (2.80 g, 13.0 mmol) in toluene (30 ml) and the mixture was allowed to warm to ambient temperature over 1 h. To a slurry of cinnamic acid **7**[8] (3.50 g, 15.77 mmol) in dry dichloromethane (10 ml) under argon was added a drop of DMF followed by the dropwise addition of oxalyl chloride (7.0 ml, 80 mmol). The mixture was stirred at ambient temperature for 1 h, evaporated to dryness, the residue was dissolved in dry toluene (30 ml) and added dropwise with stirring to the sultam solution at 0°C. The mixture was allowed to warm to ambient temperature over 3 h and poured into saturated aqueous ammonium chloride. The product was extracted with ethyl acetate, the combined extracts were washed with brine, dried ($MgSO_4$) and the solvent evaporated in vacuo. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 3:1) to give 4.9 g (90%) of enoyl sultam **8** as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (3H, s), 1.26 (3H, s), 1.32–1.46

(2H, m), 1.89–2.05 (5H, m), 2.08 (3H, d, *J*=1.4 Hz), 3.40 (1H, d, *J*=13.6 Hz), 3.50 (1H, d, *J*=13.6 Hz), 3.77 (6H, s), 4.06 (1H, dd, *J*=5.1, 7.2 Hz), 6.40 (1H, t, *J*=2.2 Hz), 6.51 (2H, d, *J*=2.2 Hz), 7.07 (1H, d, *J*=1.4 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.5, 19.5, 21.0, 26.2, 32.8, 37.9, 44.9, 47.4, 53.1, 55.0, 65.1, 100.0, 107.0, 131.6, 136.9, 138.1, 160.6, 172.1; IR (neat) 1653, 1463 cm^{-1}; MS (EI) *m/z* 419 (30), 420 (20); HRMS calcd for $C_{22}H_{29}NO_5S$: 419.1734, found 419.1733.

3.1.2. 3′*S*-(3,5-Dimethoxyphenyl)-2′*S*-methylbutanoic acid. To a stirred slurry of copper(I) iodide (5.60 g, 29.50 mmol) in anhydrous toluene (90 ml) at −40°C under argon was added dropwise methyllithium (42.0 ml, 1.4 M in ether, 58.8 mmol) and the mixture was stirred for 1 h at −40°C. The resulting complex was cooled to −78°C and a solution of enoyl sultam **8** (4.1 g, 9.97 mmol) in anhydrous toluene (50 ml) was added dropwise and the mixture was allowed to warm to −40°C and stirred overnight. The reaction mixture was quenched at −40°C with saturated aqueous ammonium chloride/THF and extracted with dichloromethane. The combined extracts were washed with brine, dried ($MgSO_4$), and the solvent evaporated to yield a crystalline solid. The crude product was purified by two recrystallizations from ethyl acetate/petroleum ether to give **9** (3.6 g, 85%) as a white solid, mp 212–215°C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.59 (3H, s), 0.85 (3H, s), 1.19–1.39 (9H, m), 1.59–1.86 (4H, m), 2.95 (1H, m), 3.22 (1H, m), 3.33 (1H, d, *J*=14.0 Hz), 3.39 (1H, d, *J*=14.0 Hz), 3.71 (1H, m), 3.75 (6H, s), 6.23 (1H, t, *J*=2.2 Hz), 6.40 (2H, d, *J*=2.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.1, 18.6, 19.8, 20.5, 26.4, 32.9, 38.3, 44.4, 44.6, 46.6, 47.8, 53.2, 55.2, 65.1, 99.4, 105.6, 146.8, 160.4, 175.1; IR (neat) 1671, 1620, 1593 cm^{-1}; MS (EI) *m/z* 435 (40); HRMS calcd for $C_{23}H_{33}NO_5S$: 435.2076, found 435.2079; Anal. calcd for $C_{23}H_{33}NO_5S$: C, 63.42; H, 7.64; N, 3.22, found: C, 63.41, H, 7.80, N, 3.25.

A mixture of sulphonamide **9** (2.3 g, 5.29 mmol) in THF (20 ml) and aqueous lithium hydroxide solution (7 M, 20 ml) was heated at 60°C for 4 days. The reaction mixture was evaporated to dryness and the residue was triturated with dichloromethane. The precipitate was filtered off and the filtrate was dried ($MgSO_4$) and the solvent was removed to give the recovered auxiliary (0.90 g, 79%) as a cream colored solid. The dichloromethane-insoluble residue was acidified with 2 M hydrochloric acid, extracted with dichloromethane, dried ($MgSO_4$) and the solvent evaporated to give the butanoic acid (1.26 g, 100%) as a colorless solid. The spectroscopic data were consistent with previously reported data:[5b] mp 108–111°C (lit. [13] mp 101–105°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (3H, d, *J*=7.0 Hz), 1.23 (3H, d, *J*=7.1 Hz), 2.68 (1H, quintet, *J*=7.0 Hz), 3.08 (1H, quintet, *J*=7.1 Hz), 3.74 (6H, s), 6.31 (1H, t, *J*=2.2 Hz), 6.53 (2H, d, *J*=2.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.2, 16.6, 41.7, 46.0, 55.1, 98.2, 105.5, 147.1, 160.5, 181.9.

3.1.3. 3′*S*-(3,5-Dimethoxyphenyl)-2′*S*-methyl-1-butanol (10). A solution of the butanoic acid (0.60 g, 2.52 mmol) in dry THF (5 ml) was added dropwise to a suspension of $LiAlH_4$ (0.20 g, 5.26 mmol) in THF (20 ml) at 0°C under argon. The reaction mixture was stirred for 16 h and allowed to warm to room temperature. The reaction was quenched with water, the THF was removed in vacuo and the residue was acidified with 10% aqueous hydrochloric acid and extracted with ether. The ethereal extracts were washed with brine, dried ($MgSO_4$) and the ether removed in vacuo to give alcohol **10** as a pale yellow oil (0.51 g, 90%) which was used without further purification. The spectroscopic data were consistent with previously reported data[5b]: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (3H, d, *J*=6.7 Hz), 1.21 (3H, d, *J*=7.1 Hz), 1.80 (2H, m), 2.60 (1H, quintet, *J*=7.1 Hz), 3.28 (1H, dd, *J*=6.7, 10.6 Hz), 3.45 (1H, dd, *J*=5.0, 10.6 Hz), 3.77 (6H, s), 6.31 (1H, t, *J*=2.2 Hz), 6.36 (2H, d, *J*=2.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 17.9, 41.9, 55.1, 66.5, 97.5, 105.5, 149.0, 160.6; IR (neat) 3329, 1496, 1454 cm^{-1}; $[\alpha]_D^{25}=+26.5°$ (*c*=1.0, $CHCl_3$) (lit.[5b] $[\alpha]_D^{25}=+20.5°$ (*c*=0.5, $CHCl_3$)); HRMS calcd for $C_{13}H_{20}O_3$: 224.1412, found 224.1416.

3.1.4. 2′*S*-(3,5-Dimethoxyphenyl)-3′*R*-methyloctane (11). To a stirred solution of the alcohol **10** (0.40 g, 1.78 mmol) in dry $CHCl_3$ (5 ml) at 0°C was added 0.3 ml of dry pyridine, followed by *p*-toluenesulfonyl chloride (0.34 g, 1.78 mmol). The reaction was stirred for 3 h at 0°C, diluted with water and extracted with ether. The ethereal extracts were washed successively with 10% aqueous hydrochloric acid, saturated aqueous sodium bicarbonate solution, brine, dried ($MgSO_4$) and the solvent removed in vacuo to give the crude tosylate as a yellow oil which was chromatographed (petroleum ether/ethyl acetate 4:1) to provide 0.51 g (75%) of pure material: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, d, *J*=6.7 Hz), 1.13 (3H, d, *J*=7.1 Hz), 1.92 (1H, m), 2.40 (3H, s), 2.55 (1H, d, *J*=7.6 Hz), 3.64 (1H, dd, *J*=6.3, 9.4 Hz), 3.73 (6H, s), 3.80 (1H, dd, *J*=4.6, 9.4 Hz), 6.21 (2H, d, *J*=2.2 Hz), 6.26 (1H, t, *J*=2.2 Hz), 7.26 (2H, d, *J*=8.2 Hz), 7.67 (2H, d, *J*=8.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 17.9, 21.5, 39.0, 41.4, 55.1, 73.8, 97.9, 105.3, 127.7, 129.6, 132.8, 144.5, 147.6, 160.6.

A solution of LiCl (0.084 g, 2.0 mmol) and $CuCl_2$ (0.1345 g, 1.0 mmol) in 10 ml of dry THF was stirred for 15 min under N_2 to produce the Li_2CuCl_4 complex. This Li_2CuCl_4 complex 1.2 ml (0.12 mmol) was added dropwise to a solution of the tosylate (0.45 g, 1.19 mmol) and butylmagnesium bromide (12 ml, 2 M in ether, 24 mmol) in dry THF (15 ml) at −78°C. The reaction mixture was allowed to warm to ambient temperature and was stirred for 48 h. The mixture was poured into saturated aqueous ammonium chloride and extracted with ether. The ethereal extracts were filtered through celite® to remove any copper salts, washed well with 10% aqueous hydrochloric acid, brine, dried ($MgSO_4$) and the solvent removed in vacuo to give 0.20 g (64%) of **11** as a colorless oil after chromatography (petroleum ether/ethyl acetate 19:1). The spectroscopic data were consistent with previously reported data:[5b] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85–1.03 (7H, m), 1.12–1.38 (10H, m), 1.66 (1H, m), 2.52 (1H, quintet, *J*=7.0 Hz), 3.80 (6H, s), 6.31 (1H, t, *J*=2.2 Hz), 6.35 (2H, d, *J*=2.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 16.1, 17.3, 22.7, 26.9, 32.1, 34.9, 30.9, 45.1, 55.2, 97.2, 105.9, 150.0, 160.5; IR 2957, 2872, 2836, 1596, 1457 cm^{-1}; $[\alpha]_D^{25}=+31.9°$ (*c*=1.0, $CHCl_3$) (Lit.[13] $[\alpha]_D^{25}=+36.9°$); HRMS calcd for $C_{17}H_{28}O_2$: 264.2089, found 264.2087.

3.1.5. 4-Oxomyrtenyl pivalate (13). To a solution of

(1*R*,5*S*)-myrtenol **12** (5.0 g, 32.8 mmol) in anhydrous dichloromethane (30 ml) and pyridine (30 ml) at 0°C under argon was added dropwise trimethylacetyl chloride (5 ml, 41.0 mmol). The reaction was stirred for 4 h at 0°C, ether (100 ml) was added and the mixture was washed well with 10% aqueous hydrochloric acid, saturated aqueous bicarbonate solution, brine, dried ($MgSO_4$) and evaporated to yield myrtenyl pivalate (6.5 g, 84%) as a colorless oil which was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75 (3H, s), 1.20 (9H, s), 1.29 (3H, s), 2.10 (2H, d, *J*=5.5 Hz), 2.21–2.43 (4H, m), 4.44 (2H, dd, *J*=12.4, 17.1 Hz), 5.55 (1H, brs).

To a suspension of chromium trioxide (15.3 g, 153.0 mmol) in dry dichloromethane (120 ml) at −20°C under argon was added 3,5-dimethylpyrazole (14.6 g, 152.0 mmol) in small portions. After stirring for 15 min a solution of myrtenyl pivalate (3.0 g, 12.7 mmol) in dichloromethane (30 ml) was added and the mixture was stirred at −20°C for 4 h. Aqueous sodium hydroxide solution (5 M, 10 ml) was added and the mixture stirred at 0°C for 1 h. The organic phase was separated, washed with 10% aqueous hydrochloric acid, brine, dried (MgSO4) and evaporated to give ketone **13** (1.7 g, 53%) as a yellow oil after chromatography (petroleum ether/ethyl acetate 7:3). The spectroscopic data were consistent with previously reported data[7]: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (3H, s), 1.22 (9H, s), 1.50 (3H, s), 2.12 (1H, d, *J*=9.3 Hz), 2.42 (1H, t, *J*=5.3 Hz), 2.68 (1H, dt, *J*=1.6, 5.9 Hz), 2.85 (1H, m), 4.65 (1H, d, *J*=16.8 Hz), 4.73 (1H, d, *J*=16.8 Hz), 5.84 (1H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.0, 26.4, 27.1, 38.3, 40.7, 45.3, 54.0, 58.0, 63.9, 119.1, 165.9, 177.5, 202.8; MS (EI) *m/z* 252 (10).

3.1.6. 4-Hydroxy-myrtenyl pivalate (4).

To a solution of ketone **13** (0.50 g, 2.0 mmol) in dry THF (2 ml) at 0°C under argon was added dropwise a solution of lithium tri-*tert*-butoxyaluminium hydride (2.0 ml, 1 M in ether, 2.0 mmol). The mixture was allowed to warm to room temperature and stirred for a further 4 h. The reaction was quenched with saturated aqueous ammonium chloride solution and extracted with ether. The combined ethereal extracts were dried ($MgSO_4$) and evaporated in vacuo to yield alcohol **4** (0.45 g, 89%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (3H, s), 1.21 (9H, s), 1.43 (3H, s), 1.78 (1H, m), 2.10 (1H, t, *J*=5.3 Hz), 2.33 (1H, m), 2.51 (1H, m), 4.50 (3H, m), 5.65 (1H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.8, 26.6, 27.1, 35.6, 38.7, 38.8, 44.0, 48.3, 65.7, 72.8, 122.1, 145.2, 178.1.

3.1.7. 11-Hydroxy-(1′*S*,2′*R*)-dimethylheptyl-Δ^8-THC (3).

A solution of the dimethyl ether **11** (0.18 g, 0.68 mmol) in 1.5 ml of boron tribromide (1.0 M in CH_2Cl_2) was stirred at 0°C under argon for 1 h. The reaction mixture was allowed to warm to ambient temperature, stirred for 16 h and carefully quenched with water. The mixture was extracted with ether, the combined ethereal extracts were washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo to give 0.15 g (94%) of resorcinol **5** as a brown oil which was used without purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74–1.37 (17H, m), 1.77 (1H, m), 2.45 (1H, quintet, *J*=6.8 Hz), 5.93 (2H br s), 6.22 (1H, s), 6.30 (2H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 15.8, 16.8, 22.7, 26.9, 32.0, 39.0, 44.5, 100.3, 107.6, 151.0, 156.0.

To a solution of resorcinol **5** (0.070 g, 0.30 mmol) and pivalate ester **4** (0.075 g, 0.30 mmol) in anhydrous dichloromethane (100 ml) at −20°C under argon was added boron trifluoride etherate (0.20 ml, 1.6 mmol). The mixture was allowed to warm up to room temperature and then stirred for a further 1 h. The mixture was carefully washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo. The product was purified by chromatography (petroleum ether/ethyl acetate 9:1) to give the cannabinoid ester (0.060 g, 43%) as a colorless oil: R_f 0.38 (petroleum ether/ethyl acetate 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (6H, m), 0.86–1.31 (20H, m), 1.37 (3H, s), 1.55 (2H, m), 1.88 (4H, m), 2.20 (1H, m), 2.42 (1H, quintet, *J*=6.8 Hz), 2.69 (1H, dt, *J*=6.3, 10.7 Hz), 3.35 (1H, dd, *J*=16.8, 4.1 Hz), 4.49, 2H s), 5.21 (1H, m), 5.73 (1H, d, *J*=4.6 Hz), 6.10 (1H, d, *J*=1.2 Hz), 6.24 (1H, d, *J*=1.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 15.8, 16.2, 18.4, 22.6, 27.0, 27.2, 27.5, 31.1, 31.7, 32.0, 34.9, 39.0, 43.9, 44.8, 68.1, 76.4, 107.0, 109.3, 109.9, 123.2, 133.9, 147.3, 154.5, 154.7, 178.7; MS (EI) *m/z* 470 (20); $[\alpha]_D^{25}=-235°$ (c=1.1, $CHCl_3$).

A solution of the cannabinoid ester (0.030 g, 0.064 mmol) in dry THF (1 ml) was added dropwise to a suspension of $LiAlH_4$ (0.010 g, 0.26 mmol) in THF (1 ml) at 0°C under argon. The reaction mixture was stirred for 2 h and allowed to warm to room temperature. The reaction was quenched with water and extracted with ether. The ethereal extracts were washed with brine, dried ($MgSO_4$) and the ether removed in vacuo. The product was purified by chromatography (petroleum ether/ethyl acetate 7:3) to give the cannabinoid (0.020 g, 81%) as a colorless oil which crystallizes slowly on standing: R_f 0.22 (petroleum ether/ethyl acetate 7:3), R_f 0.15 ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (3H, d, *J*=6.7 Hz), 0.83 (3H, t, *J*=6.5 Hz), 0.96–1.35 (8H, m), 1.04 (3H, s), 1.07 (3H, d, *J*=7.1 Hz), 1.35 (3H, s), 1.55 (1H, m), 1.82 (3H, m), 2.21 (2H, m), 2.38 (1H, quintet, *J*=6.7 Hz), 2.67 (1H, dt, *J*=4.4, 11.1 Hz), 3.48 (1H, dd, *J*=3.7, 15.7 Hz), 4.02 (1H, d, *J*=12.5 Hz), 4.08 (1H, d, *J*=12.5 Hz), 5.71 (1H, d, *J*=4.1 Hz), 6.10 (1H, d, *J*=1.1 Hz), 6.14 (1H, br s), 6.22 (1H, d, *J*=1.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 15.8, 16.3, 18.4, 22.7, 27.0, 27.5, 27.7, 31.4, 32.0, 34.9, 38.9, 43.9, 45.0, 67.1, 76.4, 107.1, 109.3, 110.1, 121.8, 138.2, 147.3, 154.4, 154.8; MS (EI) *m/z* 386 (60), 387 (40); $[\alpha]_D^{25}=-206°$ (c=0.9, $CHCl_3$); HRMS calcd for $C_{25}H_{38}O_3$: 386.2821, found 386.2827.

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