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Research Article

Synthesis of side chain specifically deuterated (−)-Δ^9-tetrahydrocannabinols

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Summary

(−)-Δ^9-Tetrahydrocannabinols specifically deuterated at the *n*-pentyl side chain were prepared using the corresponding resorcinols as key intermediates. To obtain the deuterated resorcinols we developed conditions under which no deuterium scrambling or loss was observed. The methodology allows for the preparative scale synthesis of deuterated resorcinols and corresponding (−)-Δ^9-tetrahydrocannabinols. Copyright © 2002 John Wiley & Sons, Ltd.

Key Words: (−)-Δ^9-tetrahydrocannabinols; deuterated 5-pentylresorcinols; cerium(III) chloride; deoxygenation

Introduction

For centuries marijuana has been a popular recreational drug of abuse because of its psychoactive properties. (−)-Δ^9-Tetrahydrocannabinol

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(Δ^9-THC), the major ingredient of marijuana, quickly metabolizes to several cannabinoids—mainly 11-hydroxy-Δ^9-THC, 11-nor-9-carboxy-Δ^9-THC, and 8β, 11-dihydroxy-Δ^9THC and their glucuronide conjugates. Deuteration and tritiation of these cannabinoids in the alkyl side chain[1–3] and various other positions[4] makes them eligible as mass spectral internal standards[4] for studying their biochemical properties and for confirming illicit use of marijuana. Moreover, deuterated cannabinoids serve as important probes for solid-state NMR experiments aimed at studying the interactions of cannabinoids with membranes[5] and other sites of action. Such information can be used for the development of novel cannabinergic medications.

Our interest in the synthesis of various deuterated cannabinoids for all the above-mentioned purposes required the availability of specifically deuterated pentylresorcinols of high isotopic purity with no significant deuterium scrambling or loss. The present work describes the methodology we developed for the efficient preparative scale synthesis of such specifically deuterated resorcinols and their corresponding Δ^9-tetrahydrocannabinols.

Results and discussion

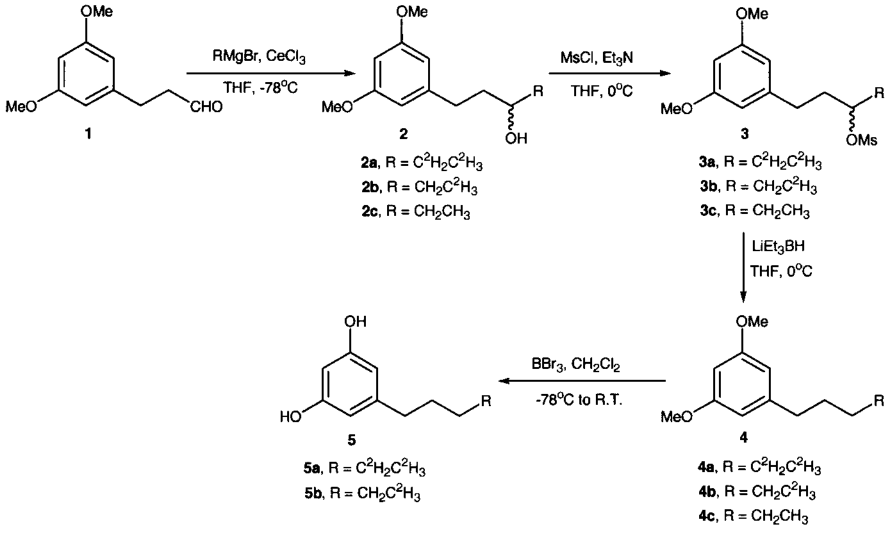
Although the existing literature reports a number of methods[6–12] for the preparation of unlabeled alkylresorcinols, only a relatively small number of these can be adapted for the synthesis of their deuterium labeled analogs,[2c,3,13] since most of the methods are expected to be accompanied by deuterium loss or isotopic scrambling. Our choice of synthetic approaches was also restricted by the availability of suitable deuterated starting materials. The available procedures for the synthesis of (−)-tetrahydrocannabinol analogs generally involve the condensation of a suitable chiral terpene with a 5-alkyl resorcinol. Synthesis of the specifically ^{2}H-labeled Δ^9-THC to be used in our biochemical and biophysical experiments would require 5-pentylresorcinols specifically deuterated at either the terminal ethyl group of the side chain **5a** or the terminal methyl group **5b**. Of these, no synthetic procedure for the pentadeuterated product **5a** had been carried out while synthesis of the trideuterated compound **5b** has been reported using two different procedures. In the first of these, reported by Pitt and co-workers,[14] compound **5b** was obtained from 3,5-dimethoxybenzaldehyde through a six-step sequence involving first a Wittig reaction to give methyl 5-(3′,5′-

dimethoxyphenyl)penta-2,4-dien-1-oate and then introduction of two deuterium atoms at the terminal carbon of the chain using $LiAl^2H_4$ reduction. This was followed by bromination and subsequent substitution of the bromo functionality, again using $LiAl^2H_4$. The second approach, by Girard *et al.*,[13] involved conversion of 3-5-dimethoxybenzoic acid to 4-(3,5-dimethoxyphenyl)-1-bromobutane in five steps followed by its coupling with C^2H_3MgI under Li_2CuCl_4 conditions.

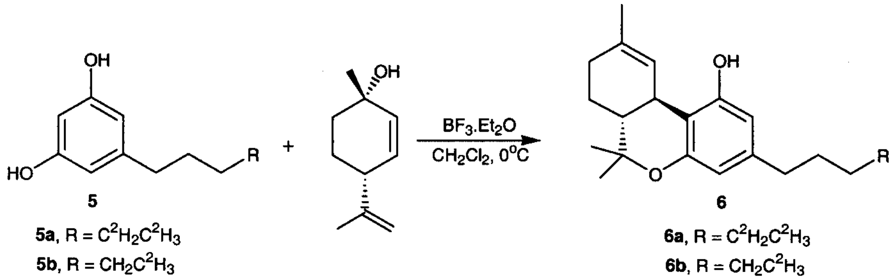
Our interest in developing a convergent and efficient approach for the synthesis of pentylresorcinols led us to a versatile starting material, 3-(3,5-dimethoxyphenyl)-propanal **1**, previously utilized for synthesis of various functionalized cannabinoids.[15] This intermediate was synthesized on a large scale using an efficient route developed in our laboratory.[16]

The reaction sequence carried out for the synthesis of **5a** and **5b** is outlined in Scheme 1.

The first step involves a Grignard reaction between **1** and ethylmagnesium bromide. In our hands this coupling gave nearly 25% of the corresponding alcohol with several by-products under both normal and reverse addition of the Grignard reagent. To improve these low yields we utilized the $CeCl_3$-based Grignard reaction reported by Imamoto and co-workers.[17] Indeed, reaction of **1** with ethylmagnesium bromide in the presence of anhydrous $CeCl_3$ at −78°C gave the hitherto unknown alcohol **2c** in 87% isolated yield. This alcohol was



Scheme 1. Synthesis of deuterated 5-pentylresorcinols



Scheme 2. Synthesis of (–)-Δ^9-tetrahydrocannabinols

subsequently deoxygenated following standard methodology,[18] involving mesylate formation and lithium triethylborohydride (superhydride) reduction. These two reactions were carried out without purification of the unstable mesylate intermediate **3c** leading to **4c** in an overall 95% yield. The same reaction sequence was used for the preparation of the penta- and tri-deuterated products **2a**, **2b**, **3a**, **3b**, **4a** and **4b** by using $C^2_2H_5Br$ and $C^2H_3CH_2Br$, respectively. The ^{1}H-NMR (500 MHz) spectrum showed no deuterium loss or scrambling. The percentage of deuterium incorporation was also determined by mass spectrometry using field ionization techniques and was found to be $^2H_5$: 98.4%, $^2H_4$: 1.4%, $^2H_3$: 0.1% and $^2H_2$: 0.1% for **4a** and $^2H_3$: 98.8%, $^2H_2$: 1.0%, $^2H_1$: 0.1% and $^2H_0$: 0.1% for **4b**. Indeed, the deuterium content in all the above resorcinols was almost identical to that of the deuterated ethyl bromides used as starting materials. Demethylation of **4a** and **4b** under boron tribromide conditions gave **5a** and **5b**, respectively, in nearly quantitative yields. These two labeled resorcinols were condensed[19] with (+)-*trans*-*p*-mentha-2,8-dien-1-ol to afford the corresponding (–)-Δ^9-tetrahydrocannabinols **6a** and **6b** (Scheme 2).

Experimental

All reagents and solvents were purchased from Aldrich Chemical Company unless specified otherwise and used without further purification. $C^2H_3CH_2Br$ and $C^2H_3C^2H_2Br$ were obtained in 99% isotopic purity from Aldrich. Melting points were determined on a micro-melting point apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$, unless otherwise stated, on a Bruker DMX-500 instrument (^{1}H at 500.13 MHz, ^{13}C at 125.77 MHz), and chemical shifts are in δ (ppm) relative to internal TMS. GC/MS data were recorded on a HP6890 GC/MS instrument operating at 70 eV. Low-, high-resolution mass spectra and isotopic ratio analyses were performed on a Micromass 70-VSE instrument at the School of Chemical Sciences, University of Illinois at Urbana-Champaign. Flash column chromatography employed silica gel 60 (230–400 mesh).

*1,3-Dimethoxy-5-[3′-(hydroxy)-4′-($^2H_2$)-5′-($^2H_3$)-pentyl]benzene (**2a**)*

(A) Preparation of 1-($^2H_2$)-2-($^2H_3$)-ethyl magnesium bromide. To a stirred mixture of magnesium turnings (11.0 g, 454.0 mmol) and anhydrous Et_2O (40 ml), under an argon atmosphere was added a solution of $C^2H_3C^2H_2Br$ (52.0 g, 454.0 mmol) in anhydrous Et_2O (400 ml) over a period of 1 h. Subsequently, the reaction mixture was refluxed for an additional 10 min and then cooled to 0°C.

(B) Reaction of 3-(3,5-dimethoxyphenyl)propanal with organomagnesium reagent. To a solution of aldehyde **1** (42.0 g, 216.5 mmol) in anhydrous THF (720 ml) under an argon atmosphere was added anhydrous $CeCl_3$ (112.0 g, 454.4 mmol). The resulting suspension was stirred at r.t. for 1 h, cooled to −78°C and the Grignard reagent was added gradually over a period of 30 min. Subsequently, the reaction mixture was warmed to r.t. and stirring was continued for additional 1 h. The reaction was quenched by dropwise addition of 3% aq AcOH solution at 0°C, the crude suspension warmed to r.t., diluted with EtOAc and brine, and stirred vigorously. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The residue obtained was purified by flash column chromatography (EtOAc/petroleum ether 30:70) on silica gel to afford **2a** (43.1 g) as a white crystalline solid in 87% yield; mp = 50–51°C.

^1H NMR: $\delta = 6.37$ (d, 2H, $J = 2.1$, H-4, H-6), 6.30 (t, 1 H, $J = 2.1$, H-2), 3.78 (s, 6 H, OMe), 3.56 (dd, 1 H, $J = 8.0$, $J = 3.7$, H-3′), 2.74 (m, 1 H, H-1′), 2.61 (m, 1 H, H-1′), 1.82–1.76 (m, 1 H, H-2′), 1.75–1.67 (m, 1 H, H-2′), 1.62 (brs, 1 H, OH). ^{13}C NMR: $\delta = 160.8$ (C-1, C-3), 144.7 (C-5), 106.5 (C-4, C-6), 97.8 (C-2), 72.5 (C-3′), 55.3 (OMe), 38.3 (C-1′), 32.4 (C-2′), 29.3 (qt, $J = 19.5$, C-4′), 8.8 (septet, $J = 19.5$, C-5′). MS: *m/e* (relative intensity) = 229 (M^+, 7), 165 (4), 152 (100), 139 (10), 121 (4), 77 (5). HRMS calculated for $C_{13}H_{15}D_5O_3$: 229.1726; found: 229.1725.

*1,3-Dimethoxy-5-[3′-hydroxy)-5′-($^2H_3$)-pentyl]benzene (**2b**)*

The synthesis was carried out as with **2a** using **1** (14.0 g, 72.2 mmol), anhydrous $CeCl_3$ (37.2 g, 150.9 mmol), $C^2H_3CH_2Br$ (16.9 g, 150.9 mmol), Mg (3.6 g, 150.0 mmol), in anhydrous Et_2O (151 ml), and anhydrous THF (240 ml); yield: 88% (14.4 g); white solid; mp = 50–51°C.

^1H NMR: $\delta = 6.37$ (d, 2 H, $J = 2.1$, H-4, H-6), 6.30 (t, 1 H, $J = 2.1$, H-2), 3.78 (s, 6 H, OMe), 3.56 (tt, 1 H, $J = 7.8$, $J = 4.3$, H-3′), 2.74 (m, 1 H, H-1′), 2.61 (m, 1 H, H-1′), 1.82–1.75 (m, 1 H, H-2′), 1.74–1.67 (m, 1 H, H-2′), 1.53 (dd, 1 H, $J = 13.6$, $J = 4.2$, H-4′), 1.50 (brs, 1 H, OH), 1.45 (dd, 1 H, $J = 13.6$, $J = 7.1$, H-4′). ^{13}C NMR: $\delta = 160.9$ (C-1, C-3), 144.9 (C-5), 106.6 (C-4, C-6), 97.9 (C-2), 72.7 (C-3′), 55.4 (OMe), 38.5 (C-1′), 32.6 (C-2′), 30.2 (C-4′), 9.1 (septet, $J = 19.1$, C-5′). MS: *m/e* (relative intensity) = 227 (M^+, 8), 165 (4), 152 (100), 139 (12), 121 (5), 77 (4). HRMS calculated for $C_{13}H_{17}D_3O_3$: 227.1601; found: 227.1602.

*1,3-Dimethoxy-5-(3′-hydroxy-pentyl)benzene (**2c**)*

The synthesis was carried out analogous to the preparation of **2a** using **1** (2.00 g, 10.3 mmol), anhydrous $CeCl_3$ (5.30 g, 21.5 mmol), CH_3CH_2Br (2.35 g, 21.6 mmol), Mg (0.52 g, 21.6 mmol), in anhydrous Et_2O (22 ml), and anhydrous THF (35 ml); yield: 88% (2.03 g); white solid; mp = 50–51°C.

^1H NMR: $\delta = 6.37$ (d, 2 H, $J = 2.1$, H-4, H-6), 6.30 (t, 1 H, $J = 2.1$, H-2), 3.78 (s, 6 H, OMe), 3.57 (m, 1 H, H-3′), 2.68 (m, 2 H, H-1′), 1.83–1.66 (m, 2 H, H-2′), 1.61 (brs, 1 H, OH), 1.58–1.45 (m, 2 H, H-4′), 0.95 (t, 3 H, $J = 7.5$, H-5′). ^{13}C NMR: $\delta = 160.8$ (C-1, C-3), 144.7 (C-5), 106.5 (C-4, C-6), 97.8 (C-2), 72.7 (C-3′), 55.3 (OMe), 38.4 (C-1′), 32.4 (C-2′), 30.3 (C-4′), 9.8 (C-5′). MS: *m/e* (relative intensity) = 224 (M^+, 9), 165 (5), 152 (100), 139 (12), 121 (5), 77 (8). HRMS calculated for $C_{13}H_{20}O_3$: 224.1412; found: 224.1411.

*1,3-Dimethoxy-5-[3′-(methanesulfonyloxy)-4′-($^2H_2$)-5′-($^2H_3$)-pentyl]benzene (**3a**)*

To a solution of alcohol **2a** (42.0 g, 183.0 mmol) and Et_3N (32 ml, 238.0 mmol) in anhydrous THF (1.3 L) at 0°C under an argon atmosphere was added methanesulfonyl chloride (17 ml, 220 mmol) dropwise over a period of 10 min. After stirring for 10 min the reaction was treated with water and diluted with Et_2O. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The pale yellow residue **3a** was sufficiently pure (^{1}H-NMR) and used for the next reaction without further purification.

^{1}H NMR: $\delta = 6.37$ (d, 2 H, $J = 2.1$, H-4, H-6), 6.32 (t, 1 H, $J = 2.1$, H-2), 4.71 (t, 1 H, $J = 5.9$, H-3′), 3.79 (s, 6 H, OMe), 3.02 (s, 3 H, OSO_2Me), 2.79–2.55 (m, 2 H, H-1′), 2.11–1.90 (m, 2 H, H-2′). MS: *m/e* (relative intensity) = 307 (M^+, 23), 228 (63), 211 (27), 193 (18), 177 (27), 165 (17), 151 (100), 121 (11). HRMS calculated for $C_{14}H_{17}D_5O_5S$: 307.1502; found: 307.1507.

1,3-Dimethoxy-5-[3′-(methanesulfonyloxy)-5′-($^2H_3$)-pentyl] benzene (3b)

The synthesis was carried out as with **3a** starting from **2b** (13.5 g, 59.5 mmol), and Et_3N (10.8 ml, 77.3 mmol), CH_3SO_2Cl (5.5 ml, 71.4 mmol) in anhydrous THF (400 ml). The corresponding mesylate **3b** was used for the next step without further purification.

^{1}H NMR: $\delta = 6.37$ (d, 2 H, $J = 2.1$, H-4, H-6), 6.32 (t, 1 H, $J = 2.1$, H-2), 4.71 (qt, 1 H, $J = 6.0$, H-3′), 3.79 (s, 6 H, OMe), 3.02 (s, 3 H, OSO_2Me), 2.80–2.55 (m, 2 H, H-1′), 2.11–1.72 (m, 4 H, H-2′, H-4′). MS: *m/e* (relative intensity) = 305 (M^+, 20), 226 (55), 209 (23), 193 (15), 177 (25), 165 (15), 151 (100), 121 (10). HRMS calculated for $C_{14}H_{19}D_3O_5S$: 305.1373; found: 305.1379.

1,3-Dimethoxy-5-[3′-(methanesulfonyloxy)-pentyl]benzene (3c)

The synthesis was carried out anologous to the preparation of **3a** starting from **2c** (1.5 g, 6.7 mmol), and Et_3N (1.21 ml, 8.71 mmol), CH_3SO_2Cl (0.62 ml, 8.04 mmol) in anhydrous THF (45 ml). The corresponding mesylate **3c** was used for the next step.

^{1}H NMR: $\delta = 6.37$ (d, 2 H, $J = 2.1$, H-4, H-6), 6.32 (t, 1 H, $J = 2.1$, H-2), 4.71 (qt, 1 H, $J = 6.0$, H-3′), 3.79 (s, 6 H, OMe), 3.02 (s, 3 H, OSO_2Me), 2.80–2.56 (m, 2 H, H-1′), 2.10–1.92 (m, 2 H, H-2′), 1.79 (qt, 2 H, $J = 6.8$, H-4′), 0.99 (t, 3 H, $J = 7.4$, H-5′). MS: *m/e* (relative intensity) = 302 (M^+, 18), 223 (50), 206 (21), 191 (13), 177 (23), 165 (15), 151 (1 0 0), 121 (9). HRMS calculated for $C_{14}H_{22}O_5S$: 302.1188; found: 302.1180.

*1,3-Dimethoxy-5-[4′-($^2H_2$)-5′-($^2H_3$)-pentyl]benzene (**4a**)*

To a stirred solution of mesylate **3a** (56.3 g, 183.4 mmol) in anhydrous THF (1.4 L) at 0°C under an argon atmosphere was added lithium triethylborohydride (790 ml, 1 M solution in THF) over a period of 30 min. Following the addition, the mixture was warmed to r.t. and stirring was continued until the reaction was complete (2 h). Excess hydride was decomposed by drop wise addition of water at 0°C, subsequently the pH was adjusted to approximately 8 using 10% aq NaOH solution. The mixture was diluted with Et_2O, warmed to r.t. and stirred vigorously for 30 min. Insoluble materials were filtered off through celite, the organic phase was separated and the aqueous phase was extracted with Et_2O. The combined organic layer was washed with water, brine, dried over $MgSO_4$ and solvent evaporated under reduced pressure to give an oil. The crude product was purified by flash column chromatography (Et_2O/petroleum ether 6:94) on silica gel to give **4a** as a colorless liquid (36.7 g) in 94% yield (2 steps).

^{1}H NMR: $\delta = 6.34$ (d, 2 H, $J = 2.1$, H-4, H-6), 6.29 (t, 1 H, $J = 2.1$, H-2), 3.78 (s, 6 H, OMe), 2.54 (t, 2 H, $J = 7.8$, H-1′), 1.60 (qt, 2 H, $J = 7.7$, H-2′), 1.30 (t, 2 H, $J = 7.6$, H-3′), ^{13}C NMR: $\delta = 160.9$ (C-1, C-3), 145.6 (C-5), 106.7 (C-4, C-6), 97.7 (C-2), 55.4 (OMe), 36.5 (C-1′), 31.5, 31.1, 21.7 (qt, $J = 19.0$, C-4′), 13.1 (septet, $J = 19.0$, C-5′). MS: *m/e* (relative intensity) = 213 (M^+, 21), 166 (8), 152 (100), 137 (6), 121 (10), 91 (20), 77 (24). HRMS calculated for $C_{13}H_{15}D_5O_2$: 213.1777; found: 213.1777. The deuterium incorporation on the molecular ion cluster was $^2H_5$: 98.4%, $^2H_4$: 1.4%, $^2H_3$: 0.1% and $^2H_2$: 0.1%.

*1,3-Dimethoxy-5-[5′-($^2H_3$)-pentyl]benzene (**4b**)*

The synthesis was carried out analogous to the preparation of **4a** starting from **3b** (18.13 g, 59.44 mmol), $LiEt_3BH$ (256 ml, 1 M solution in THF) in anhydrous THF (457 ml) to give **4b** as a colorless liquid[13,14] in overall 95% yield from **2b** (11.92 g). ^{1}H NMR: $\delta = 6.34$ (d, 2 H, $J = 2.1$, H-4, H-6), 6.29 (t, 1 H, $J = 2.1$, H-2), 3.78 (s, 6 H, OMe), 2.54 (t, 2 H, $J = 7.7$, H-1′), 1.60 (qt, 2 H, $J = 7.5$, H-2′), 1.30 (m, 4 H, H-3′, H-4′), ^{13}C NMR: $\delta = 160.7$ (C-1, C-3), 145.4 (C-5), 106.5 (C-4, C-6), 97.5 (C-2), 55.2 (OMe), 36.3 (C-1′), 31.5, 31.0, 22.3 (C-4′), 13.1 (septet, $J = 19.0$, C-5′). MS: *m/e* (relative intensity) = 211 (M^+, 15), 152 (100), 137 (6), 121 (8), 91 (17), 77 (19). HRMS calculated for $C_{13}H_{17}D_3O_2$: 211.1652; found: 211.1654. The deuterium incorporation on the molecular ion cluster was ${}^2H_3$: 98.8%, ${}^2H_2$: 1.0%, ${}^2H_1$: 0.1%, and ${}^2H_0$: 0.1%.

*1,3-Dihydroxy-5-[4′-(${}^2H_2$)-5′-(${}^2H_3$)-pentyl]benzene (**5a**)*

To a solution of olivetol dimethyl ether (**4a**) (33.5 g, 157.3 mmol) in anhydrous CH_2Cl_2 (1.57 L) at −78°C under an argon atmosphere was added BBr_3 (393 ml, 1.0 M solution in CH_2Cl_2) over a period of 15 min. Following the addition the reaction was warmed to r.t. over a period of 30 min and stirring continued at r.t. for 4 h. The reaction was quenched by the addition of MeOH and crushed ice at 0°C, the resulting mixture was warmed to r.t., stirred for 40 min and the solvent removed under reduced pressure. The residual oil was diluted with EtOAc and the solution was washed with sat. $NaHCO_3$, water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel using Et_2O/petroleum ether 50:50 as eluent afforded **5a** (27.9 g) in 96% yield as a white solid; mp = 50–51°C.

^{1}HNMR: $\delta = 6.25$ (d, 2 H, $J = 1.9$, H-4, H-6), 6.17 (t, 1 H, $J = 1.9$, H-2), 4.89 (brs, 2 H, OH), 2.48 (t, 2 H, $J = 7.7$, H-1′), 1.57 (qt, 2 H, $J = 7.7$, H-2′), 1.27 (t, 2 H, $J = 7.5$, H-3′). ^{13}C NMR: $\delta = 156.4$ (C-1, C-3), 146.6 (C-5), 108.5 (C-4, C-6), 100.5 (C-2), 36.0 (C-1′), 31.4, 30.9, 21.6 (qt, $J = 19.3$, C-4′), 13.1 (septet, $J = 19.0$, C-5′). MS: *m/e* (relative intensity) = 185 (M^+, 29), 138 (7), 124 (100), 77 (4), 69 (8). HRMS calculated for $C_{11}H_{11}D_5O_2$: 185.1464; found: 185.1472.

*1,3-Dihydroxy-5-[5′-(${}^2H_3$)-pentyl]benzene (**5b**)*

The synthesis was carried out analogous to the preparation of **5a** starting from **4b** (11.0 g, 52.1 mmol) and BBr_3 (130 ml, 1.0 M solution in CH_2Cl_2) in anhydrous CH_2Cl_2 (521 ml); yield: 97% (9.3 g); white solid; mp = 50–51°C (lit., [13]mp = 38–39°C, lit., [14]mp = 39–40°C).

^{1}HNMR: $\delta = 6.25$ (d, 2 H, $J = 1.9$, H-4, H-6), 6.17 (t, 1 H, $J = 1.9$, H-2), 5.18 (brs, 2 H, OH), 2.48 (t, 2 H, $J = 7.7$, H-1′), 1.57 (qt, 2 H, $J = 7.5$, H-2′), 1.29 (m, 4 H, H-3′, H-4′). ^{13}C NMR: $\delta = 156.2$ (C-1, C-3), 146.7 (C-5), 108.6 (C-4, C-6), 100.6 (C-2), 36.0 (C-1′), 31.6, 30.9, 22.4 (C-4′), 13.3 (septet, $J = 19.0$, C-5′). MS: *m/e* (relative intensity) = 183 (M^+, 22), 137 (7), 124 (100), 77 (4), 69 (7). HRMS calculated for $C_{11}H_{13}D_3O_2$: 183.1339; found: 183.1332.

$4'$-($^2H_2$)-$5'$-($^2H_3$)-Δ^9-Tetrahydrocannabinol (**6a**)

To a stirred suspension of olivetol (**5a**) (13.0 g, 70.3 mmol), (+)-*trans*-*p*-mentha-2,8-dienl-ol (11.7 g, 77.3 mmol) and $MgSO_4$ (8.8 g) in anhydrous CH_2Cl_2 (440 ml) at -3°C, under an argon atmosphere was added $BF_3.Et_2O$ (4.4 ml). Stirring was continued for 2.5 h at 0°C and anhydrous sodium bicarbonate (23 g) was added. The mixture was warmed to r.t. stirred vigorously for 30 min and filtered through florisil. The filtrate was evaporated under reduced pressure to give pale yellow gum. Purification by repeated flash column chromatography (three times) on silica gel using 10% Et_2O: Hexane as eluent afforded 6.5 g (29% yield) of the title compound in 98–99% purity, as confirmed by ^{1}H NMR.

^{1}H NMR: $\delta = 6.30$ (m, 1 H, H-10), 6.27 (d, 1 H, $J = 1.2$, H-4), 6.14 (d, 1 H, $J = 1.2$, H-2), 4.76 (s, 1 H, OH), 3.20 (brd, 1 H, $J = 11.0$, H-10a), 2.43 (td, 2 H, $J = 7.5$, $J = 2.4$, H-1′) 2.17–2.15 (m, 2 H, H-8), 1.93–1.89 (m, 1 H, H-7), 1.72-1.67 (m, 4 H, H-6a, H-11, especially 1.68, brs, H-11), 1.55 (qt, 2 H, $J = 7.7$, H-2′), 1.44–1.36 (m, 4 H, H-7, 6β-Me, especially 1.40, s, 6β-Me), 1.27 (t, 2 H, $J = 7.4$, H-3′), 1.09 (s, 3 H, 6α-Me). GC/MS: m/e (relative intensity) = 319 (M^+, 22), 304 (41), 276 (32), 252 (13), 236 (90), 219 (19), 187 (25), 174 (32), 128 (41), 115 (60), 91 (100), 77 (94). HRMS calculated for $C_{21}H_{25}D_5O_2$: 319.2560; found: 319.2557. The deuterium incorporation on the molecular ion cluster was $^2H_5$: 98.3%, $^2H_4$: 1.5%, $^2H_3$: 0.1% and $^2H_2$: 0.1%.

$5'$-($^2H_3$)-Δ^9-Tetrahydrocannabinol (**6b**)

The synthesis was carried out analogous to the preparation of **6a** starting from **5b** (2.0 g, 10.9 mmol), (+)-*trans*-*p*-mentha-2,8-dien-l-ol (1.8 g, 12.0 mmol) and $MgSO_4$ (1.5 g) in anhydrous CH_2Cl_2 (70 ml); yield: 30% (1.0 g); pale yellow gum.[14]

^{1}H NMR: $\delta = 6.30$ (m, 1 H, H-10), 6.27 (d, 1 H, $J = 1.2$, H-4), 6.14 (d, 1 H, $J = 1.2$, H-2), 4.80 (s, 1 H, OH), 3.19 (brd, 1 H, $J = 11.0$, H-10a), 2.43 (td, 2 H, $J = 7.5$, $J = 2.4$, H-1′) 2.17–2.15 (m, 2 H, H-8), 1.93–1.88 (m, 1 H, H-7), 1.72–1.67 (m, 4 H, H-6a, H-11, especially 1.68, brs, H-11), 1.55 (qt, 2 H, $J = 7.7$, H-2′), 1.44–1.36 (m, 4 H, H-7, 6β-Me, especially 1.40, s, 6β-Me), 1.28 (t, 2 H, $J = 7.4$, H-3′), 1.09 (s, 3 H, 6α-Me). GC/MS: m/e (relative intensity) = 317 (M^+, 29), 302 (23), 274 (19), 252 (46), 234 (82), 219 (58), 187 (19), 174 (26), 128 (37), 115 (42), 91 (81), 77 (100). HRMS calculated for $C_{21}H_{27}D_3O_2$: 317.2434; found: 317.2440. The deuterium incorporation on the molecular ion cluster was $^2H_3$: 98.7%, $^2H_2$: 1.1%, $^2H_1$: 0.1% and $^2H_0$: 0.1%.

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