Regiospecifically deuterated (−)-Δ^9-tetrahydrocannabivarins

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Deuterated (−)-Δ^9-tetrahydrocannabivarins† (Δ^9-THCVs) can be used as markers for confirming the illicit use of marijuana. Here, we first describe an efficient synthesis of side chain deuterated Δ^9-THCVs from the respective 5-propylresorcinols specifically deuterated at the side chain. Our approach involved the development of optimal, high yield methods for the introduction of deuterium at the C-3′ and C-2′ position of the side chain.

Introduction

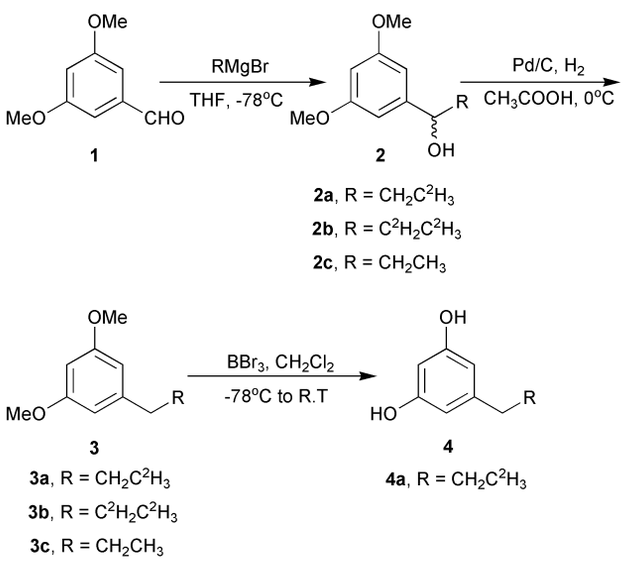
Cannabis (marijuana), obtained from *Cannabis Sativa* contains a mixture of natural cannabinoids and is one of the most commonly used drugs among recreational substance abusers. (−)-Δ^9-Tetrahydrocannabinol (Δ^9-THC), the major ingredient and most active constituent of marijuana, is quickly metabolized principally to 11-hydroxy-Δ^9-THC, 9-carboxy-11-nor-Δ^9-THC, and 8β, 11-dihydroxy-Δ^9-THC and their glucuronide conjugates. Deuteration and tritiation of these cannabinoids either at the alkyl side chain[1–3] or at the tricyclic ring[4] allows them to be used as mass spectral internal standards[1–4] and also as probes for studying the cannabinergic system.

Marinol, the trade name for synthetic (−)-Δ^9-THC, is a recommended drug for the treatment of refractory nausea and vomiting associated with cancer chemotherapy[5] and for anorexia[6] associated with weight loss in patients with AIDS. The assays for Δ^9-THCs presently available do not allow the differentiation between Marinol and marijuana users. Recently,[7] studies involving incubation of Δ^9-THCV with human hepatocytes, demonstrated that the presence of Δ^9-THCV metabolites could be related to the use or ingestion of cannabis-related product(s). However, the development of proper assays using Δ^9-THCV, as a marker for cannabis use and abuse, requires specifically deuterated cannabivarins in high isotopic purity. This goal is the subject of this publication.

Generally, Δ^9-THC analogs can be synthesized by the condensation of a chiral monoterpene with an appropriately substituted resorcinol. However, the synthesis of regiospecifically side chain deuterated 5-propylresorcinols without significant deuterium loss or scrambling represents a special challenge. The present work describes the methodologies we have developed for the preparative scale synthesis of specifically side chain deuterated 5-propylresorcinols and the corresponding (−)-Δ^9-tetrahydrocannabivarins in high deuterium purity. Synthesis of such deuterated compounds had not been reported previously and suitable procedures were required for their synthesis.

Results and discussion

Our initial approach to the synthesis of deuterated propylresorcinols involved a model Grignard reaction between 3,5-dimethoxybenzaldehyde **1** and undeuterated ethylmagnesium bromide to obtain the corresponding alcohol **2c** (Scheme 1). This could, in turn, be deoxygenated to **3c** following an earlier approach[8,9] we developed for the preparation of specifically deuterated 5-pentylresorcinols. This methodology was based on mesylate formation followed by triethylborohydride reduction.



Scheme 1

However, mesylation or tosylation of **2c** led to multiple by-products, probably due to the instability of the respective benzylic mesylates[10] or tosylates. Alternatively, direct benzylic deoxygenation of alcohol **2c** under catalytic hydrogenation conditions[11] gave **3c** in 77% yield.

Synthesis of the trideuterated compounds **2a** and **3a** was achieved following the same reaction sequence. The ^{1}H-NMR spectrum of **3a** showed no deuterium loss at the C-3′ position and no scrambling at the C-2′ and C-3′ positions. Additionally, the percentage of deuterium incorporation was determined by mass spectrometry using a field ionization technique and was found to be identical to that of the deuterated reagent ethyl bromide. Deprotection of dimethyl ether groups with BBr_3 at −78 °C gave **4a** in 96% yield.

Our efforts to synthesize the corresponding pentadeuterated compound **3b** by following the same sequence were less successful. Catalytic hydrogenolysis of compound **2b** gave the resorcinol dimethyl ether **3b** with approximately 20–24% deuterium loss and/or scrambling between the C-1′ and C-2′ positions as observed by ^{1}H-NMR (Fig. 1, *a*). Furthermore, the

† (−)-Δ^9-Tetrahydrocannabivarin is a common name used for (6a*R*,10a*R*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-propyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol. This name was first proposed by Frans W. H. M. Merkus (*Nature*, 1971, **232**, 579) to describe a (−)-Δ^9-tetrahydrocannabinol homologue, in which the side chain is C_3H_7 instead of C_5H_{11}.

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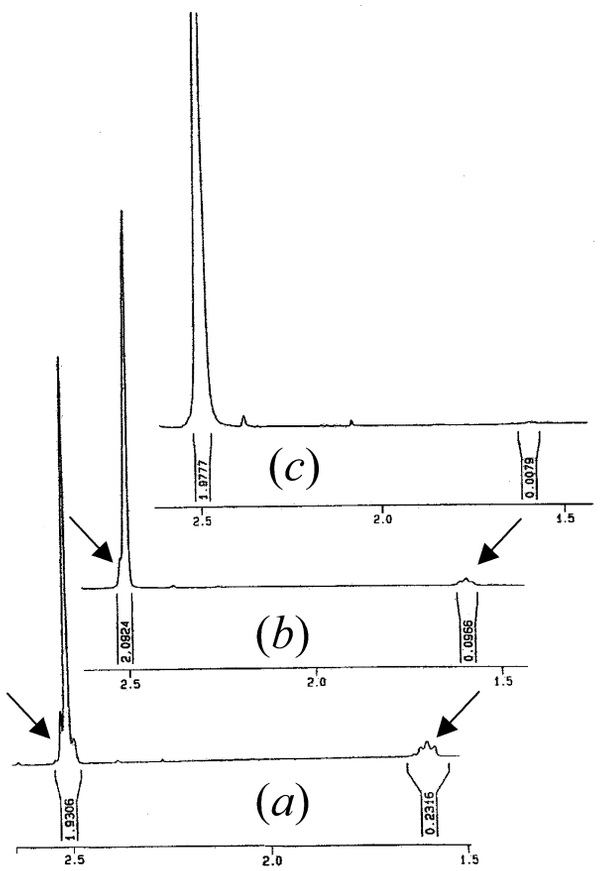


Fig. 1 Expansion of ^{1}H-NMR (500 MHz) spectra of **3b** obtained from a. catalytic hydrogenolysis, b. hydrogenolysis using TMSCl–NaI, c. copper(I)-catalyzed Grignard cross-coupling. The arrows indicate signals due to the deuterium loss and or scrambling at the C-1′ position (δ ~2.5) and at the C-2′ position (δ ~1.6).

isotope ratio analysis on the molecular ion cluster showed 21% deuterium loss (sum of ions containing $^2H_4$ and $^2H_3$). These results suggests deuterium loss occurs in this reaction that can be accounted for by an earlier reported mechanism[11a] for the catalytic hydrogenolysis of benzylic alcohols. Additionally, the percentage of loss was found to be dependent on the reaction time and scale. A subsequent attempt using TMSCl–NaI based deoxygenation[12] of **2b** led to products exhibiting 9–10% deuterium loss based on ^{1}H-NMR (Fig. 1, *b*) and isotopic ratio analysis (10% from the sum of ions containing $^2H_4$ and $^2H_3$). The reaction leading to the desired product **3b** is believed to involve formation of a benzylic iodide[13,14] (Chart 1), followed by reductive dehalogenation using *in situ* generated TMSH.[12b] The observed deuterium loss may be explained by invoking DI elimination of the benzylic iodide to the intermediate alkene,[15] which readily undergoes HI addition followed by TMSH reductive dehalogenation (Chart 1).

We also explored the ionic hydrogenation of **2b** using triethylsilane.[16] This reaction was promising as both ^{1}H-NMR and isotopic ratio analysis indicated the absence of deuterium scrambling or loss. However, the poor yields (19–21%) of this reaction prompted us to search for alternative options.

We thus turned to an approach involving C–C bond formation through a Li_2CuCl_4 based Grignard cross-coupling.[17] A survey of the literature led to two references[1,3] related to the coupling between 3,5-dimethoxybenzyl bromide with either but-3-enylmagnesium bromide or *n*-butylmagnesium bromide under Li_2CuCl_4 catalyzed conditions. The drawback of these approaches was the formation of substantial amounts (28–42%) of homocoupled and reduction by-products, whereas the desired cross-coupled product was

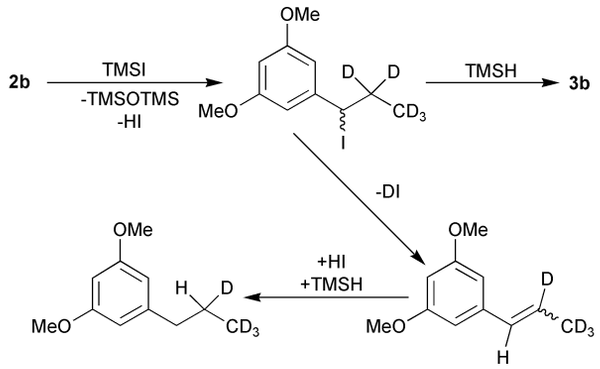
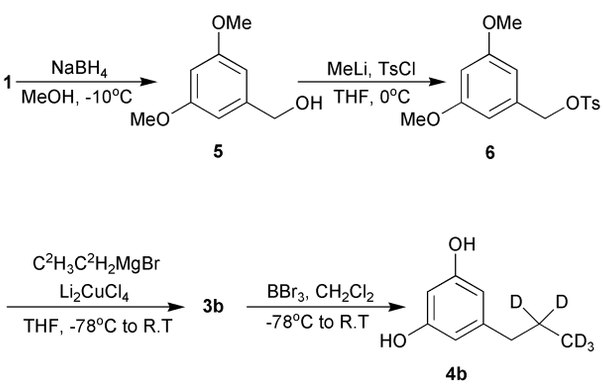


Chart 1

isolated in only 50–64% yields. Literature reports[17,18] of a modified version of this type of coupling reaction outlined the use of the tosyl functionality as a better leaving group. However, if the reaction is carried out using copper(I) iodide as a catalyst, a substantial amount of homocoupled by-product is still formed.[18]

We overcame these difficulties by employing a cross-coupling approach between 3,5-dimethoxybenzyl toluene-*p*-sulfonate **6** and $C^2H_3C^2H_2MgBr$ in the presence of Li_2CuCl_4 which led to the desired product **3b** in 81% yield (Scheme 2).

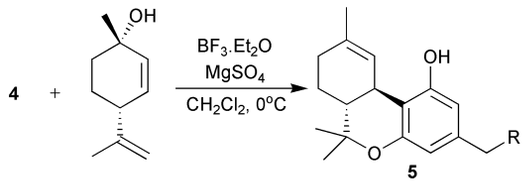


Scheme 2

The reaction was clean, high yielding with only small amounts of by-products (7–10%) and was scaled up to 30.0 g. The ^{1}H-NMR spectrum of the resulting *O*,*O*-dimethylpropylresorcinol (Fig. 1, *c*) showed no deuterium loss or isotopic scrambling. Also, isotope ratio analysis of the molecular ion cluster showed that the percentage of deuterium incorporation was identical to that of the reagent. Subsequently, deprotection of the methoxy groups to provide **4b** (96% yield) was achieved using BBr_3 at −78 °C.

The only previously reported[19] synthesis of unlabelled Δ^9-THCV had been carried out by a three step sequence involving first coupling of 5-propylresorcinol with (−)-*cis*-verbenol to give the thermodynamically more stable Δ^8-THCV isomer, which was further transformed to the Δ^9-isomer by HCl addition–elimination reactions[20] in a 21% overall yield. We obtained significantly improved results through a single step procedure used earlier[21] for the synthesis of (−)-Δ^9-THC. Thus, condensation of resorcinols **4a** and **4b** with (+)-*trans*-*p*-mentha-2,8-dien-1-ol in the presence of $BF_3{\cdot}Et_2O$ and anhydrous magnesium sulfate afforded **5a** and **5b** in 28 and 29% isolated yield respectively (Scheme 3).

The ^{1}H-NMR spectrum of specifically labeled (−)-Δ^9-THCVs showed no deuterium loss or isotopic scrambling. These results clearly indicate that the BBr_3 mediated demethylation followed by $BF_3{\cdot}Et_2O$ induced terpenylation is not associated with any carbon–deuterium bond cleavage in these molecules.



4a, R = $CH_2C^2H_3$ **5a**, R = $CH_2C^2H_3$

4b, R = $C^2H_2C^2H_3$ **5b**, R = $C^2H_2C^2H_3$

Scheme 3

Conclusions

In summary, the first synthesis of side chain specifically deuterated (−)-Δ^9-tetrahydrocannabivarins has been achieved in high isotopic purity without any deuterium scrambling or loss. An approach based on the catalytic hydrogenolysis of a benzylic alcohol was satisfactory only for the synthesis of (−)-Δ^9-THCV deuterated at the terminal methyl group of the side chain. However, Li_2CuCl_4 catalyzed Grignard cross-coupling was found to be the most suitable route for the synthesis of both side chain tri- and penta-deuterated (−)-Δ^9-THCVs.

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 (^1H at 500.13 MHz, ^{13}C at 125.77 MHz). Chemical shifts are in δ (ppm) relative to internal TMS and J values are given in Hz. Low,high-resolution mass spectra and isotopic ratio analysis 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-(1′-hydroxy[3′,3′,3′-$^2H_3$]propyl)benzene 2a

[2,2,2-$^2H_3$]Ethylmagnesium bromide. To a stirred mixture of magnesium turnings (3.31 g, 136.16 mmol) and anhydrous Et_2O (14 mL), under an argon atmosphere was added a solution of $C^2H_3CH_2Br$ (15.25 g, 136.16 mmol) in anhydrous Et_2O (122 mL) over a period of 1 h. Subsequently the reaction mixture was refluxed for an additional 10 min and then cooled to 0 °C.

Reaction of 3,5-dimethoxybenzaldehyde with organomagnesium reagent. To a stirred solution of aldehyde **1** (13.3 g, 80.1 mmol) in anhydrous THF (267 mL) at −78 °C, under an argon atmosphere was added the above Grignard reagent over a period of 30 min. The reaction temperature was then gradually raised (30 min) to rt and stirring continued for 1 h. The reaction was quenched by dropwise addition of sat. aqueous NH_4Cl, the crude suspension was diluted with AcOEt and brine, and stirred vigorously. The organic layer was separated and the aqueous phase extracted with AcOEt. The combined organic layer was washed with brine, dried ($MgSO_4$) and solvent evaporated under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel (AcOEt–petroleum ether; 30 : 70) afforded 15.6 g of **2a** (98% yield) as a viscous oil; δ_H ($CDCl_3$) 1.70 (1H, dd, J 13.6 and J 5.9, 2′-H), 1.77 (1H, dd, J 13.6 and J 7.1, 2′-H), 1.94 (1H, br s, OH), 3.79 (6H, s, OMe), 4.51 (1H, t, J 6.5, 1′-H), 6.36 (1H, t, J 2.1, 2-H), 6.50 (2H, d, J 2.1, 4-H, 6-H); δ_C 9.5 (septet, J 18.7, C-3′), 31.7 (C-2′), 55.5 (OMe), 76.2 (C-1′), 99.5 (C-2), 104.0 (C-4, C-6), 147.5 (C-5), 161.0 (C-1, C-3); m/z (EI) 199.1281 (M^+, $C_{11}H_{13}D_3O_3$ requires 199.1288, 43%), 182 (2), 167 (69), 139 (100), 124 (19), 77 (9).

1,3-Dimethoxy-5-(1′-hydroxy[2′,2′,3′,3′,3′-$^2H_5$]propyl)benzene 2b

The synthesis was carried out as for **2a** starting from 3,5-dimethoxybenzaldehyde **1** (3.5 g, 21.1 mmol) and $C^2H_3C^2H_2Br$ (4.1 g, 35.9 mmol), Mg (0.87 g, 35.8 mmol) in anhydrous Et_2O (36 mL) and anhydrous THF (70 mL) to yield 97% (5.9 g) **2b** as a viscous oil; δ_H ($CDCl_3$) 1.86 (1H, br s, OH), 3.78 (6H, s, OMe), 4.51 (1H, s, 1′-H), 6.36 (1H, t, J 2.1, 2-H), 6.50 (2H, d, J 2.1, 4-H, 6-H); δ_C 9.3 (septet, J 19.1, C-3′), 30.9 (qt, J 19.1, C-2′), 55.5 (OMe), 76.1 (C-1′), 99.5 (C-2), 104.0 (C-4, C-6), 147.5 (C-5), 161.0 (C-1, C-3), 147.5 (C-5); m/z (EI) 201.1418 (M^+, $C_{11}H_{11}D_5O_3$ requires 201.1413, 44%), 184 (2), 167 (68), 139 (100), 124 (20), 77 (9).

1,3-Dimethoxy-5-[3′,3′,3′-$^2H_3$]propylbenzene 3a

To a solution of alcohol **2a** (8.8 g, 44.2 mmol) in glacial acetic acid (147 mL) was added 10% Pd/C (613 mg) and the resulting suspension was stirred vigorously under a hydrogen atmosphere for 13 h at rt. Upon completion the reaction mixture was diluted with Et_2O, brine and water and the catalyst removed by filtration through Celite. The organic phase was separated, diluted with water and neutralized by portionwise addition of solid $NaHCO_3$. The organic layer was separated and the aqueous phase was extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$ and the solvent evaporated under reduced pressure. Purification by flash column chromatography (Et_2O–petroleum ether; 6 : 94) on silica gel afforded **3a** as a colorless liquid in 77% yield (6.2 g); δ_H ($CDCl_3$) 1.61 (2H, t, J 7.5, 2′-H), 2.53 (2H, t, J 7.6, 1′-H), 3.78 (6H, s, OMe), 6.30 (1H, t, J 2.1, 2-H), 6.35 (2H, d, J 2.1, 4-H, 6-H); δ_C 13.2 (septet, J 19.1, C-3′), 24.3 (C-2′), 38.5 (C-1′), 55.4 (OMe), 97.8 (C-2), 106.7 (C-4, C-6), 145.4 (C-5), 160.9 (C-1, C-3); m/z (EI) 183.1336 (M^+, $C_{11}H_{13}D_3O_2$ requires 183.1339, 60%), 165 (15), 153 (100), 138 (8), 122 (10), 91 (20), 77 (26); m/z (FI) 183 (M^+, 98.7% incorporation of $^2H_3$), 182 (1.1% $^2H_2$), 181 (0.1% $^2H_1$) and 180 (0.1% $^2H_0$).

1,3-Dihydroxy-5-[3′,3′,3′-$^2H_3$]propylbenzene 4a

To a solution of **3a** (6.0 g, 32.8 mmol) in anhydrous CH_2Cl_2 (328 mL) at −78 °C under an argon atmosphere was added BBr_3 (82 mL, 1.0 M solution in CH_2Cl_2) over a period of 15 min. Following the addition the reaction temperature was gradually raised (35 min) to rt and stirring was continued for 4 h. The reaction was quenched by the addition of MeOH and crushed ice at 0 °C, the resulting mixture was warmed to rt, stirred for 40 min and the volatiles removed under reduced pressure. The residual oil was diluted with AcOEt 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 **4a** (4.9 g) in 97% yield as a white solid; mp 85–86 °C; δ_H ($CDCl_3$) 1.59 (2H, t, J 7.5, 2′-H), 2.47 (2H, t, J 7.6, 1′-H), 4.72 (2H, br s, OH), 6.17 (1H, t, J 2.1, 2-H), 6.24 (2H, d, J 2.1, 4-H, 6-H); δ_C ($CDCl_3$ + DMSO-d_6) 13.0 (septet, J 19.0, C-3′), 24.0 (C-2′), 37.9 (C-1′), 100.4 (C-2), 107.3 (C-4, C-6), 145.2 (C-5), 157.7 (C-1, C-3); m/z (EI) 155.1032 (M^+, $C_9H_9D_3O_2$ requires 155.1026, 75%), 137 (25), 125 (100), 77 (10), 69 (21).

3,5-Dimethoxybenzyl alcohol 5

To a solution of **1** (34.5 g, 207.8 mmol) in methanol (1.38 L) at −10 °C was added sodium borohydride (15.8 g, 416 mmol) gradually over a period of 30 min. The reaction was stirred for 1 h and then quenched by the addition of sat. aqueous NH_4Cl, the volatiles were removed *in vacuo* and the residue was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$ and the solvent removed under

reduced pressure. The product was purified through a short column of silica gel (AcOEt–petroleum ether; 30 : 70) to give the title compound as a white solid in 95% yield (33.1 g); mp 47–49 °C (lit.,[18] mp 48 °C).

3,5-Dimethoxybenzyl toluene-*p*-sulfonate 6

The title compound was prepared according to the reported procedure[18] using alcohol **5** (31.7 g, 188.7 mmol), CH_3Li (203 mL, 1.4 M solution in Et_2O) and toluene-*p*-sulfonyl chloride (34.2 g, 227.2 mmol) in anhydrous THF (1.0 L); yield: 76% (46.3 g); white solid; mp 63–64 °C (lit.,[18] mp 64 °C).

1,3-Dimethoxy-5-[2′,2′,3′,3′,3′-$^2H_5$]propylbenzene 3b

Dilithium tetrachlorocuprate solution (0.1 M). The solution was prepared by reacting anhydrous LiCl (1.26 g, 30 mmol) and $CuCl_2$ (2.01 g, 15 mmol) in anhydrous THF (150 mL).

Preparation of [1,1,2,2,2-$^2H_5$]Ethylmagnesium bromide. The title compound was prepared by the method described for **2a** using $C^2H_3C^2H_2Br$ (33.0 g, 289.5 mmol) and Mg turnings (6.96 g, 286.4 mmol) in anhydrous Et_2O (580 mL).

Coupling reaction. The solution of Grignard reagent was diluted with anhydrous THF (700 mL) cooled to −78 °C, and Li_2CuCl_4 (138 mL, 0.1 M solution in THF) was added under an argon atmosphere. The mixture was stirred for 5 min and a solution of 3,5-dimethoxybenzyl toluene-*p*-sulfonate **6** (44.4 g, 137.9 mmol) in anhydrous THF (600 mL) was added over a period of 15 min. The reaction was warmed to rt, stirred for 1.5 h and quenched by adding sat. aqueous NH_4Cl. Workup of the reaction was performed in the usual manner as described for **2a**. Purification by flash column chromatography on silica gel (Et_2O–petroleum ether; 6 : 94) afforded **3b** as a colorless liquid in 81% yield (20.6 g); δ_H ($CDCl_3$) 2.51 (2H, s, 1′-H), 3.78 (6H, s, OMe), 6.30 (1H, t, *J* 2.1, 2-H), 6.34 (2H, d, *J* 2.1, 4-H, 6-H); δ_C 13.1 (septet, *J* 19.1, C-3′), 23.5 (qt, *J* 19.0, C-2′), 38.3 (C-1′), 55.4 (OMe), 97.8 (C-2), 106.7 (C-4, C-6), 145.4 (C-5), 160.9 (C-1, C-3); *m*/*z* (EI) 185.1466 (M^+, $C_{11}H_{11}D_5O_2$ requires 185.1464, 60%), 167 (12), 153 (100), 138 (8), 122 (10), 91 (18), 77 (23); *m*/*z* (FI) 185 (M^+, 98.7% incorporation of $^2H_5$), 184 (1.3% $^2H_4$), 183 (0% $^2H_3$), 182 (0% $^2H_2$).

1,3-Dihydroxy-5-[2′,2′,3′,3′,3′-$^2H_5$]propylbenzene 4b

The synthesis was carried out analogous to the preparation of **4a** starting from **3b** (18.2 g, 98.4 mmol) and BBr_3 (246 mL, 1.0 M solution in CH_2Cl_2) in anhydrous CH_2Cl_2 (984 mL); yield: 96% (14.8 g); white solid; mp 85–86 °C; δ_H ($CDCl_3$) 2.45 (2H, s, 1′-H), 4.95 (2H, s, OH), 6.17 (1H, t, *J* 2.1, 2-H), 6.24 (2H, d, *J* 2.1, 4-H, 6-H); δ_C ($CDCl_3$ + DMSO-d_6) 12.8 (septet, *J* 18.9, C-3′), 23.2 (qt, *J* 18.9, C-2′), 37.8 (C-1′), 100.5 (C-2), 108.3 (C-4, C-6), 146.2 (C-5), 156.6 (C-1, C-3); *m*/*z* (EI) 157.1154 (M^+, $C_9H_7D_5O_2$ requires 157.1151, 73%), 139 (22), 125 (100), 77 (7), 69 (17).

Δ^9-[3′,3′,3′-$^2H_3$]Tetrahydrocannabivarin 5a

To a stirred suspension of resorcinol **4a** (1.0 g, 6.5 mmol), (+)-*trans*-*p*-mentha-2,8-dien-1-ol (1.1 g, 7.1 mmol) and $MgSO_4$ (0.8 g) in anhydrous CH_2Cl_2 (41 mL) at −3 °C under an argon atmosphere was added $BF_3{\cdot}Et_2O$ (0.4 mL). Stirring was continued for 2.5 h at 0 °C and anhydrous sodium bicarbonate (2.1 g) was added. The mixture was warmed to rt,stirred vigorously for 30 min and filtered through Florisil. The filtrate was evaporated under reduced pressure to give a pale yellow gum. Purification by repeated flash column chromatography (three times) on silica gel using 10% Et_2O in hexane as eluent afforded 0.52 g (28% yield) of the title compound in 98–99% purity as confirmed by ^{1}H-NMR; δ_H ($CDCl_3$) 1.09 (3H, s, 6α-Me), 1.44–1.38 (4H, m, 7-H, 6β-Me, especially 1.40, s, 6β-Me), 1.56 (2H, t, *J* 7.6, 2′-H), 1.72–1.66 (4H, m, 6a-H, 11-H, especially 1.68, br s, 11-H), 1.95–1.89 (1H, m, 7-H), 2.17–2.15 (2H, m, 8-H), 2.41 (2H, td, *J* 7.6 and *J* 2.7, 1′-H), 3.19 (1H, br d, *J* 11.0, 10a-H), 4.79 (1H, s, OH), 6.14 (1H, d, *J* 1.4, 2-H), 6.26 (1H, d, *J* 1.4, 4-H), 6.30 (1H, m, 10-H); *m*/*z* (EI) 289.2116 (M^+, $C_{19}H_{23}D_3O_2$ requires 289.2121, 88%), 274 (100), 246 (55), 206 (92), 168 (19), 115 (11), 91 (10), 77 (14); *m*/*z* (FI) 289 (M^+, 98.3% incorporation of $^2H_3$), 288 (1.5% $^2H_2$), 287 (0.1% $^2H_1$) and 286 (0.1% $^2H_0$).

Δ^9-[2′,2′,3′,3′,3′-$^2H_5$]Tetrahydrocannabivarin 5b

The synthesis was carried out analogous to the preparation of **5a** starting from **4b** (5.0 g, 31.8 mmol), (+)-*trans*-*p*-mentha-2,8-dien-1-ol (5.32 g, 35.03 mmol), $MgSO_4$ (4.2 g) and $BF_3{\cdot}Et_2O$ (2.0 mL) in anhydrous CH_2Cl_2 (200 mL). Yield: 2.70 g (29%); pale yellow gum; δ_H ($CDCl_3$) 1.09 (3H, s, 6α-Me), 1.44–1.37 (4H, m, 7-H, 6β-Me, especially 1.41, s, 6β-Me), 1.72–1.63 (4H, m, 6a-H, 11-H, especially 1.68, br s, 11-H), 1.93–1.88 (1H, m, 7-H), 2.18–2.16 (2H, m, 8-H), 2.40 (2H, s, 1′-H), 3.19 (1H, br d, *J* 11.0, 10a-H), 4.83 (1H, s, OH), 6.13 (1H, d, *J* 1.4, 2-H), 6.27 (1H, d, *J* 1.4, 4-H), 6.30 (1H, m, 10-H); δ_C 12.9 (septet, *J* 19.1, C-3′), 19.4 (6α-Me), 23.1 (qt, *J* 19.3, C-2′), 23.5 (9-Me), 25.2 (C-7), 27.7 (6β-Me), 31.3 (C-8), 33.8 (C-10a), 37.5 (C-1′), 46.0 (C-6a), 77.5 (C-6), 107.9 (C-2), 109.3 (C-10b), 110.1 (C-4), 124.0 (C-10), 134.3 (C-9), 142.7 (C-3), 154.7 and 154.4 (C-1, C-4a); *m*/*z* (EI) 291.2247 (M^+, $C_{19}H_{21}D_5O_2$ requires 291.2247, 86%), 276 (96), 248 (54), 208 (100), 170 (15); *m*/*z* (FI) 291 (M^+, 98.6% incorporation of $^2H_5$), 290 (1.4% $^2H_4$), 289 (0% $^2H_3$), 288 (0% $^2H_2$).

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References and notes

1 H. Hoellinger, N. H. Nam, J. F. Decauchereux and L. Pichat, *J. Labelled Compd. Radiopharm.*, 1977, **13**, 401.
2 (*a*) M. A. Tius and G. S. K. Kannangara, *Tetrahedron*, 1992, **48**, 9173; (*b*) B. Schmidt, I. Franke, F. J. Witteler and M. Binder, *Helv. Chim. Acta*, 1983, **66**, 2564; (*c*) E. Pop, B. Rachwal, S. Rachwal, J. Vlasak, M. E. Brewster and L. Prokai, *J. Labelled Compd. Radiopharm.*, 1998, **41**, 885.
3 H. H. Seltzman, M. K. Begum and C. D. Wyrick, *J. Labelled Compd. Radiopharm.*, 1991, **29**, 1009.
4 (*a*) A. R. Banijamali, N. Abou-Taleb, C. J. Van der Schyf, A. Charalambous and A. Makriyannis, *J. Labelled Compd. Radiopharm.*, 1987, **25**, 73; (*b*) M. Szirmai, M. M. Halldin and A. Ohlsson, *J. Labelled Compd. Radiopharm.*, 1991, **31**, 131; (*c*) S. Feng and M. A. ElSohly, *J. Labelled Compd. Radiopharm.*, 2000, **43**, 655; (*d*) R. Mechoulam, P. Braun and Y. Gaoni, *J. Am. Chem. Soc.*, 1972, **94**, 6159; (*e*) R. A. Driessen and C. A. Salemink, *Recl: J. R. Neth. Chem. Soc.*, 1981, **100**, 342.
5 M. Lane, C. L. Vogel, J. Ferguson, S. Krasnow, J. L. Saiers, J. Hamm, K. Salva, P.H. Wiernik, C. P. Holroyde and S. Hammill, *J. Pain Symptom Manage.*, 1991, **6**, 352.
6 J. E. Bill, R. Olson, L. Lefkowitz, L. Laubenstein, P. Bellman, B. Yangco, J. O. Morales, R. Murphy, W. Powderly, T. F. Plasse, K. W. Mosdell and K. V. Shepard, *J. Pain Symptom Manage.*, 1997, **14**, 7.
7 (*a*) M. A. ElSohly, H. DeWit, S. R. Wachtel, S. Feng and T. P. Murphy, *J. Anal. Toxicol.*, 2001, **25**, 565; (*b*) M. A. ElSohly, S. Feng, T. P. Murphy, S. A. Ross, A. Nimrod, Z. Mehmedic and N. Fortner, *J. Anal. Toxicol.*, 1999, **23**, 222.
8 S. P. Nikas, G. A. Thakur and A. Makriyannis, *Synth. Commun.*, 2002, **32**, 1751.
9 S. P. Nikas, G. A. Thakur and A. Makriyannis, *J. Labelled Compd. Radiopharm.*, 2002, **45**, 1065.

10 K. Kobayashi, P. K. Jadhav, T. M. Zydowsky and H. G. Floss, *J. Org. Chem.*, 1983, **48**, 3510.
11 (*a*) E. W. Garbisch, Jr., L. Schreader and J. J. Frankel, *J. Am. Chem. Soc.*, 1967, **89**, 4233; (*b*) K. Ofosu-Asante and L. M. Stock, *J. Org. Chem.*, 1986, **51**, 5452; (*c*) K. Ofosu-Asante and L. M. Stock, *J. Org. Chem.*, 1987, **52**, 2938.
12 (*a*) T. Sakai, K. Miyata, M. Utaka and A. Takeda, *Tetrahedron Lett.*, 1987, **28**, 3817; (*b*) E. Ghera, R. Maurya and A. Hassner, *Tetrahedron Lett.*, 1989, **30**, 4741.
13 M. E. Jung and P. L. Ornstein, *Tetrahedron Lett.*, 1977, **31**, 2659.
14 G. A. Olah, S. C. Narang, B. G. B. Gupta and R. Malhotra, *J. Org. Chem.*, 1979, **44**, 1247.
15 Formation of alkenes during deoxygenation of closely related benzylic alcohols using TMSCl–NaI has been reported (see ref. 12*b*).
16 D. N. Kursanov, Z. N. Parnes and N. M. Loim, *Synthesis*, 1974, 633.
17 (*a*) M. Tamura and J. Kochi, *Synthesis*, 1971, 303; (*b*) G. Fouquet and M. Schlosser, *Angew. Chem., Int. Ed. Engl.*, 1974, **13**, 82.
18 S. Combes and J.-P. Finet, *Synth. Commun.*, 1997, **27**, 3769.
19 E. W. Gill, *J. Chem. Soc.*, 1971, 579.
20 A. R. Banijamali, C. J. Van der Schyf and A. Makriyannis, *J. Labelled Compd. Radiopharm.*, 1998, **41**, 121.
21 R. K. Razdan, H. C. Dalzell and G. R. Handrick, *J. Am. Chem. Soc.*, 1974, **96**, 5860.