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The preparation of [*pentane*-5,5,5-$^3H_3$]-*abnormal*-cannabidiol

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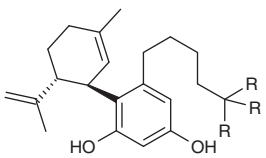
A bromoalkane precursor was synthesized in six steps, and its copper catalysed coupling with methylmagnesium chloride to provide unlabelled *abnormal*-cannabidiol (1a) was optimized. The methodology was used for an analogous coupling using [$^3H_3$]-methylmagnesium iodide to provide [*pentane*-$^2H_3$]-*abnormal*-cannabidiol (1b).

Keywords: *abnormal*-cannabidiol; copper-catalysed coupling; [$^3H_3$]-methylmagnesium iodide

Introduction

A number of reports have appeared in the last decade concerning the biological activity of *abnormal*-cannabidiol (**1a**).[1,2] This synthetic isomer of cannabidiol fails to elicit a response from either CB_1 or CB_2 receptors and lacks psychotropic activity. However, **1a** induces endothelium-dependent vasodilation via a CB_1/CB_2/NO-independent mechanism, and shows hypotensive activity that is not antagonized by cannabidiol or SR141716A.[2] Given the potential importance of this ligand as a research tool, and in order to facilitate the further investigation of the putative CB_3 receptor with which it is associated, a requirement for a tritiated form of **1** containing at least two tritium nuclei per molecule was identified. Work towards the tritiation of **1**, and the preparation of the labelled ligand **1b** are described in this publication.



1a (R = H), **1b** (R = ^{3}H)

Experimental

GC-MS data were obtained using an Agilent 6890 gas chromatograph fitted with a mass-selective detector (5970MSD) operating in CI mode, with methane as the ionisation gas. The injector temperature was 250°C and the oven temperature was increased, after an initial 2 min delay, from 70 to 230°C at 10°C per minute. LC-MS data were obtained using an Agilent 1200 HPLC system connected to a Bruker micro-TOF Focus mass spectrometer operating in esi mode and with sodium formate as internal calibrant. ^{1}H NMR spectra were recorded using a Bruker DRX-500 instrument. Reagents were obtained commercially; in particular, (4*R*)-1-methyl-4-(1-methylvinyl)cyclohex-2-en-1-ol (**2**) was obtained from Sai Life Sciences Limited, and [$^3H_3$]iodomethane was produced by Perkin-Elmer. Column chromatography was carried out using silica gel (Merck silica 60). Autoradiography was performed at 0°C after spraying with PPO and exposing plates to X-ray film. TLC plates were also scanned for applied radioactivity. Preparative and analytical HPLC were performed on a PerkinElmer instrument and peak detection was done simultaneously by UV and an IN/US Systems Beta RAM Model 3 radioactivity detector. Solution assays were performed with a Perkin Elmer Tri-Carb 3100TR instrument. Mass spectra for tritiated product were obtained on a Kratos Model MS25 RF instrument with direct injection.

4-(3,5-Dimethoxyphenyl)-1-butene (**5**).[3] A solution of 3,5-dimethoxybenzyl bromide (3.0 g, 13 mmol) in diethyl ether (17 mL) was added dropwise during 10 min under a nitrogen atmosphere to allylmagnesium bromide in diethyl ether (1 M; 25 mL) with ice cooling. The cooling bath was removed, and the reaction was stirred at RT for 23 h. After this time, the mixture was cooled to 0°C and quenched with saturated aqueous ammonium chloride (20 mL). Additional water (15 mL) was added, the phases were separated, and the aqueous layer was re-extracted with diethyl ether (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and solvent was removed under reduced pressure. The residue was purified by chromatography in ethyl acetate–hexane (1:9) to give 4-(3,5-dimethoxyphenyl)-1-butene (2.313 g, 84%). δ_H($CDCl_3$) 2.32–2.44 (2H, m),

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2.66 (2H, dd, *J* 8.3, 7.5 Hz), 3.79 (6H, s), 4.99 (1H, dm, J_{cis} 10.3 Hz), 5.07 (1H, dm, J_{trans} 16.7 Hz), 5.83–5.91 (1H, m), 6.32 (1H, t, *J* 2.3 Hz), 6.37 (2H, d, *J* 2.3 Hz); *m/z* 193 (100%, MH^+), 151.

4-(3,5-Dimethoxyphenyl)-1-butanol (**6**).[4] 9-Borabicyclo[3.3.1]-nonane (0.4 M in hexanes; 19.2 mL; 7.7 mmol) was added slowly at room temperature to a stirred solution of 4-(3,5-dimethoxyphenyl)-1-butene in toluene (19 mL). The mixture was warmed to 40°C for 4.5 h, after which time all starting material had been consumed (GC-FID). Aqueous sodium hydroxide (2 M, 4.2 mL) was added, followed by hydrogen peroxide (30 wt%, 2.0 mL) and the mixture was stirred overnight. The mixture was diluted with ethyl acetate (24 mL) and brine (25 mL), the phases were separated, and the aqueous phase was re-extracted with ethyl acetate (3 × 25 mL). The combined organic phases were dried (Na_2SO_4) and solvent was removed under reduced pressure. The residue was purified by chromatography in ethyl acetate–hexane (2:3, followed by 1:1) to give 4-(3,5-dimethoxyphenyl)-1-butanol (983 mg, 74%). $\delta_H(CDCl_3)$ 1.30 (br s, 1H, OH), 1.59–1.65 (2H, m), 1.66–1.73 (2H, m), 2.60 (2H, t, *J* 7.5 Hz), 3.67 (2H, t, *J* 5.4 Hz), 3.79 (6H, s), 6.31 (1H, t, *J* 2.2 Hz), 6.36 (2H, d, *J* 2.2 Hz); *m/z* 211 (100%, MH^+), 193.

4-(3,5-Dimethoxyphenyl)-1-bromobutane (**7**). Triphenylphosphine (2.086 g, 7.9 mmol) was added in one portion to a stirred, ice-cooled solution of 4-(3,5-dimethoxyphenyl)-1-butanol (972 mg, 4.6 mmol) and carbon tetrabromide (3.094 g, 9.2 mmol) in acetonitrile. A bright yellow colour formed, which faded after 10 min, at which stage the ice bath was removed and the reaction was stirred at room temperature for 1 h. Triethylamine (1.3 mL) and methanol (1.3 mL) were added, and the resulting precipitate was removed by filtration. The filtrate was evaporated and the residue was purified by column chromatography in ethyl acetate–hexane (5:95 followed by 8:92) to give 4-(3,5-dimethoxyphenyl)-1-bromobutane (1.206 g, 96%). $\delta_H(CDCl_3)$ 1.74–1.81 (2H, m), 1.86–1.93 (2H, m), 2.59 (2H, t, *J* 7.4 Hz), 3.42 (2H, t, *J* 6.7 Hz), 3.78 (6H, s), 6.31 (1H, t, *J* 2.2 Hz), 6.34 (2H, d, *J* 2.2 Hz); *m/z* 273, 275 (1:1, MH^+), 193 (100%).

4-(3,5-Dihydroxyphenyl)-1-bromobutane (**8**).[5] A solution of 4-(3,5-dimethoxyphenyl)-1-bromobutane (500 mg, 1.8 mmol) and boron tribromide (1.0 M in dichloromethane; 4.4 mL) in 1,2-dichloroethane (60 mL) was stirred at reflux for 1.5 h. After this time, TLC indicated complete reaction, and the mixture was cooled to room temperature. Water (60 mL) was added, the phases were separated, and the aqueous phase was re-extracted with ethyl acetate (2 × 50 mL). The combined organic phases were washed with brine (50 mL), dried (Na_2SO_4) and evaporated to give 4-(3,5-dihydroxyphenyl)-1-bromobutane (719 mg, 98% allowing for 39% ethyl acetate present by NMR).[3] $\delta_H(CDCl_3)$ 1.70–1.77 (2H, m), 1.84–1.91 (2H, m), 2.53 (2H, t, *J* 7.5 Hz), 3.41 (2H, t, *J* 6.7 Hz), 4.95 (2H, br s, OH), 6.19 (1H, t, *J* 2.1 Hz), 6.24 (2H, d, *J* 2.1 Hz); *m/z* 245, 247 (1:1, MH^+), 165 ($[MH\text{-}HBr]^+$, 100%).

5-(4-Bromobutyl)-4-[(1R,6R)-3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-1,3-benzenediol (**9**).[6] Boron trifluoride diethyl etherate (40 μL, 0.32 mmol) was added all at once under nitrogen at −40°C to a vigorously stirred suspension of anhydrous magnesium sulfate (780 mg 6.4 mmol) in dichloromethane (39 mL) containing (*4R*)-1-methyl-4-(1-methylvinyl)cyclohex-2-en-1-ol (949 mg; 6.2 mmol) and 4-(3,5-dihydroxyphenyl)-1-bromobutane (1.507 g, 3.1 mmol). After 1 h, the reaction was complete (TLC) and sodium hydrogencarbonate (203 mg, 2.4 mmol) was added. The mixture was stirred for a further 30 min, and then filtered. The filtrate was evaporated and the residue was purified by column chromatography in ethyl acetate–hexane, using a gradient from 1:9 to 1:1, to give:

(i) 5-(4-bromobutyl)-2-[(1*R*,6*R*)-3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-1,3-benzenediol (**B**; 199 mg, 17%) $\delta_H(CDCl_3)$ 1.48 (3H, s), 1.57–1.68 (2H, m), 1.70 (3H, br s), 1.74–1.83 (4H, m), 2.04–2.12 (1H, m), 2.18–2.27 (2H, m), 2.38–2.48 (1H, m), 2.61 (1H, ddd, *J* 14.5, 9.1, 5.4 Hz), 3.41 (2H, t, *J* 6.8 Hz), 3.48 (1H, br d, J_{app} 9.4 Hz), 4.50 (1H, s), 4.61 (1H, t, *J* 1.8 Hz), 5.48 (1H, s), 5.82 (1H, br s, OH), 6.19 (2H, s); *m/z* 379 (MH^+, 100%).

(ii) 5-(4-bromobutyl)-4-[(1*S*,6*R*)-3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-1,3-benzenediol (**A**; 389 mg, 33%)$\delta_H(CDCl_3)$ 1.66 (3H, s), 1.67–1.74 (2H, m), 1.79 (3H, br s), 1.77–1.88 (4H, m), 2.06–2.13 (1H, m), 2.19–2.28 (1H, m), 2.39 (1H, ddd, *J* 11.7, 10.7, 3.5 Hz), 2.48 (2H, t, *J* 7.5 Hz), 3.40 (2H, t, *J* 6.7 Hz), 3.85 (1H, br d, J_{app} 9.2 Hz), 4.55 (1H, s), 4.66 (1H, t, *J* 1.8 Hz), 5.56 (1H, s), 6.00 (1H, br s, OH), 6.17 (1H, br s), 6.26 (1H, br s); *m/z* 379 (MH^+, 100%).

(iii) 5-(4-bromobutyl)-4-[(1*R*,6*R*)-3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-1,3-benzenediol (**9**; 592 mg, 50%). $\delta_H(CDCl_3)$ 1.52 (3H, s, 3-C**H**$_3$), 1.57–1.68 (2H, m, 5-H), 1.80 (3H, br s, H_2C=C–C**H**$_3$), 1.76–1.91 (4H, m), 2.06–2.13 (1H, m), 2.18–2.25 (1H, m), 2.28 (1H, ddd, *J* 7.2, 4.9, 3.6 Hz, 4-$H_{equatorial}$), 2.47 (1H, ddd, *J* 12.2, 10.5, 3.6 Hz, 6-H), 2.66 (1H, ddd, *J* 14.7, 10.5, 5.8 Hz, 4-H_{axial}), 3.41 (2H, t, *J* 6.7 Hz, CH_2Br), 3.51 (1H, br d, J_{app} 9.4 Hz, 1-H), 4.47 (1H, s, HC(**H**)=C–CH_3), 4.66 (1H, t, *J* 1.8 Hz, **H**C(H)=C–CH_3), *ca.* 4.67 (1H, br s, OH), 5.52 (1H, s, 2-H), 6.06 (1H, br s, OH), 6.18 (1H, d, *J* 2.6 Hz), 6.22 (1H, d, *J* 2.6 Hz); *m/z* 379 (MH^+, 100%).

5-(4-Bromobutyl)-3,5-bis(tert-butyldimethylsilyloxy)-2-(6-isopropenyl-3-methyl-2-cyclohexenyl)benzene (**10**). *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.90 mL; 3.8 mmol) and 2,6-lutidine (452 μL; 3.8 mmol) were added to a solution of **9** (583 mg, 1.54 mmol) in dichloromethane (5 mL) at room temperature. The resulting pale yellow solution was stirred overnight after which time the reaction was complete. Water (5 mL) was added, the phases were separated, and the aqueous phase was re-extracted with ethyl acetate (2 × 5 mL). The combined organic layers were dried (Na_2SO_4) and evaporated, and the crude product was purified by chromatography on silica gel in hexane to give 5-(4-bromobutyl)-3,5-bis(*tert*-butyldimethylsilyloxy)-2-(6-isopropenyl-3-methyl-2-cyclohexenyl)benzene (829 mg, 89%). $\delta_H(CDCl_3)$ 0.16 (12H, s), 0.96 (9H, s), 0.98 (9H, s), 1.41 and 1.55 (3H, 2s), 1.57–1.75 (1H, m), 1.63 and 1.70 (3H, 2s), 1.76–1.83 (2H, m), 1.84–1.90 (2H, m), 1.97–2.08 (1H, m), 2.10–2.21 (1H, m), 2.30 (1H, ddd, *J* 8.1, 6.5, 2.7 Hz), 2.42 (1H, ddd, *J* 12.0, 12.0, 4.2 Hz), 2.55 (1H, ddd, *J* 11.8, 8.2, 5.4 Hz), 2.68–2.85 (2H, m), 2.97 (1H, ddd, J 15.0, 10.8, 4.8 Hz), 3.37–3.43 (2H, m), 4.11 (1H, br d, *J* 9.4 Hz), 4.40 and 4.47 (1H, 2s), 4.53 and 4.56 (1H, 2s), 5.24 and 5.29 (1H, 2s), 6.13 and 6.16 (1H, 2d, both *J* 2.8 Hz), 6.18 and 6.28 (1H, 2d, both *J* 2.8 Hz); *m/z* 607, 607 (*ca.* 1:1, MH^+), 527 ($[MH\text{-}HBr]^+$, 100%).

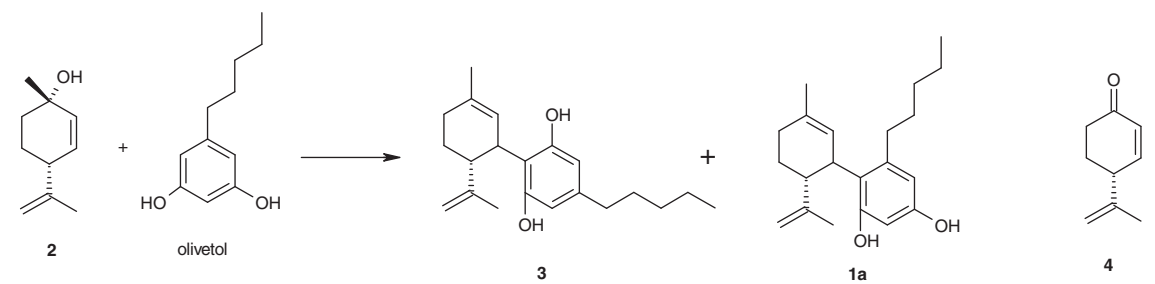
*4-[(1R,6R)-3-Methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol (abnormal-Cannabidiol,*1a*)*. Lithium tetrachlorocuprate(II) (0.1 M in THF; 25 μL) and methylmagnesium iodide (3.0 M in THF; 100 μL, 0.3 mmol) were added sequentially to a solution of 5-(4-bromobutyl)-3,5-bis(*tert*-butyldimethylsilyloxy)-2-(6-isopropenyl-3-methyl-2-cyclohexenyl)benzene (20 mg; 33 μmol) in THF (1.0 mL), forming a fine suspension, which was stirred at room temperature. Additional methylmagnesium iodide solution (150 μL, 0.45 mmol) was added after 1 h, and the mixture was stirred for a further 2 h, after which time the reaction was complete (TLC). Water (5 mL) and ethyl acetate (5 mL) were added, the phases were separated, and the aqueous layer was re-extracted with ethyl

acetate (3 × 5 mL). The combined organic phases were dried (Na_2SO_4) and solvent was removed under reduced pressure to leave crude 1,5-bis(*tert*-butyldimethylsilyloxy)-2-(6-isopropenyl-3-methyl-2-cyclohexenyl)-3-pentylbenzene. $\delta_H(CDCl_3)$ 0.17 (12H, s), 0.90 and 0.91 (3H, 2t, *J* 6.8 Hz), 0.97 (9H, s), 0.99 (9H, s), 1.26–1.36 (2H, m), 1.56 (3H, br s), 1.50–1.57 (1H, m), 1.63 and 1.68 (3H, 2s), 1.74–1.88 (2H, m), 1.99–2.09 (1H, m), 2.10–2.22 (1H, m), 2.24–2.32 (1H, m), 2.43–2.55 (2H, m), 2.63–2.82 (2H, m), 2.97 (1H, ddd, J 15.1, 11.1, 3.8 Hz), 3.40–3.46 (1H, m), 4.09–4.14 (1H, m), 4.42 and 4.47 (1H, 2s), 4.53 and 4.55 (1H, 2s), 5.27 and 5.30 (1H, 2s), 6.12 and 6.15 (1H, 2d, both *J* 2.2 Hz), 6.21 and 6.29 (1H, 2d, both *J* 2.2 Hz); *m/z* 543 (100%, MH^+), 527, 485. This material was redissolved in THF (2 mL) and tetrabutylammonium fluoride (1.0 M in THF; 110 μL) was added. The resulting dark yellow solution was stirred for a further 30 min and, the reaction being complete by TLC, saturated aqueous sodium hydrogencarbonate (5 mL) and ethyl acetate (5 mL) were added. The phases were separated, the aqueous phase was re-extracted with ethyl acetate (2 × 5 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure to leave 2-(6-isopropenyl-3-methyl-2-cyclohexenyl)-3-pentylresorcinol (*abnormal*-Cannabidiol, **1a**) (8.8 mg, 85%). $\delta_H(CDCl_3)$ 0.90 (3H, t, *J* 7.1 Hz), 1.28–1.35 (2H, m), 1.43–1.51 (2H, m), 1.54 (3H, s), 1.72–1.87 (2H, m), 1.79 (3H, br s), 2.06–2.09 (1H, m), 2.10–2.13 (1H, m), 2.18–2.30 (2H, m), 2.48 (1H, ddd, *J* 12.9, 9.5, 3.2 Hz), 2.59 (1H, ddd, *J* 14.2, 9.1, 7.6 Hz), 3.53 (1H, br d, *J* 9.5 Hz), 4.46 (1H, d), 4.64 (1H, t, *J* 1.5 Hz), *ca.* 4.80 (1H, br s, OH), 5.52 (1H, s), 6.04 (1H, s, OH), 6.20 (1H, d, *J* 2.8 Hz), 6.21 (1H, d, *J* 2.82 Hz); *m/z* 315 (100%, MH^+), 181. HPLC was carried out using a Waters XTerra Phenyl; 3.5 μm; 4.6 × 150 mm with eluant A as acetonitrile–water (19:1) and eluant B as acetonitrile–water (1:1) using a flow rate of 1 mL/min and a gradient from 100% B at 1 min to 100% A at 36 min and UV detection at 240 and 254 nm. In this system, **1a** had a RT of 13.97 min.

[pentane-5,5,5-$^3H_3$]-2-(6-Isopropenyl-3-methyl-2-cyclohexenyl)-3-pentylresorcinol (abnormal-Cannabidiol, **1b***).* All the following manipulations were conducted on a vacuum line. A solution of [$^3H_3$]-methylmagnesium iodide (1 mmol at 74.3 Ci/mmol) in diethyl ether (2 mL) was prepared using the procedure of Prasad and Franklin[7]; to this solution at ambient temperature, a solution of **9** (20 mg, 0.033 mmol) in anhydrous THF (1 mL) was added with stirring. The reaction was allowed to stir at ambient temperature for another 10 min and then lithium tetrachlorocuprate in THF (0.1 M; 0.025 mL) was added. The reaction was stirred for an additional 4 h at ambient temperature and then quenched by addition of water (2 mL), followed by ethyl acetate (5 mL). The phases were separated and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The organic phases were combined and labile tritium was removed by evaporation with several portions of methanol under vacuum. The mixture was then dissolved in ethyl acetate–ethanol (9:1, 10 mL), affording 495 mCi of crude tritiated intermediate that contained approximately 25% of the desired intermediate by TLC analysis (hexane on silica gel). This intermediate was initially purified by passing through a silica gel Sep-Pak eluted with hexane, providing 95 mCi of crude intermediate. Approximately 40 mCi of this intermediate was then evaporated to dryness and dissolved in anhydrous THF (1 mL). Tetrabutylammonium fluoride in THF (1 M; 0.05 mL) was added to this solution under argon and the mixture was stirred at ambient temperature for 30 min. Silica gel TLC analysis (9:1 hexane–ethyl acetate on silica gel) of the mixture showed good conversion to desired product and so saturated aqueous sodium hydrogencarbonate (5 mL) was added. The aqueous phase was extracted with ethyl acetate (3 × 5 mL) and the combined organic phases were dried ($MgSO_4$). Purification of the final product was accomplished by reverse phase HPLC eluted with a gradient of water–acetonitrile (1:1) to pure acetonitrile over the course of 50 min with fraction collection. Pooling of appropriate fractions, solvent evaporation under reduced pressure and reconstitution in ethanol afforded **1b** (9 mCi), with better than 99% radiochemical purity by reverse phase HPLC (Waters XTerra MS column eluted with the same gradient as above). The specific activity of the final product was measured as 74.3 Ci/mmol by mass spectrometry. *m/z* 321 (100%, MH^+ for **1b**), 319 (20.7%, [$^3H_2$]-**1**), 317 (9.16%, [^3H]-**1**), 315 (6.05%, **1a**).

Results and discussion

The coupling of *trans*-(+)-menthadienol (**2**) and olivetol (Scheme 1) in the presence of a protic or Lewis acid to give cannabidiol (**3**) commonly gives **1a**, along with isomeric tetrahydrocannabinols as side-products (Scheme 1).[6,8] The yield and the product ratio are dependent on the reaction conditions, and particularly on the acid used, the best-quoted yield of **1a** being 47%.[6] For our purposes, tritiation of the final product by exchange was not expected to be viable, since the presence of two double bonds precludes the use of hydrogen, and tritium exchanged into the arene from tritiated water is likely to be labile. Either precursor in Scheme 1 could be prepared in tritiated form but, with the preparation of a suitable enone (**4**) precursor to **2** requiring several steps,[9] the possibility that 1,4-addition of C^3H_3MgI to **4** could compete with the desired 1,2-addition and the certainty that **4** prepared in this way would be racemic, labelling in the olivetol unit would be preferred. Indeed, one approach to the preparation of [^3H_n]-**1** would be to prepare an unsaturated form of olivetol and to carry out tritiation prior to the coupling; the corresponding reaction using deuterium has been reported by previous workers.[10] Nevertheless, given the complex nature of mixtures expected from the coupling step, we preferred to modify the synthetic approach to



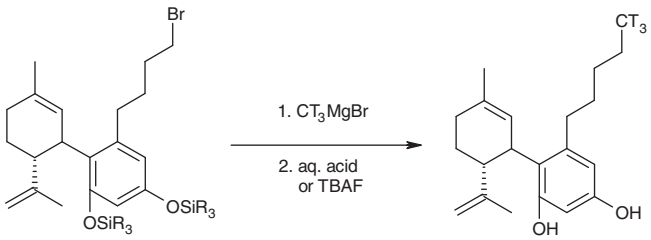
Scheme 1.

permit the introduction of tritium labels following the coupling step.

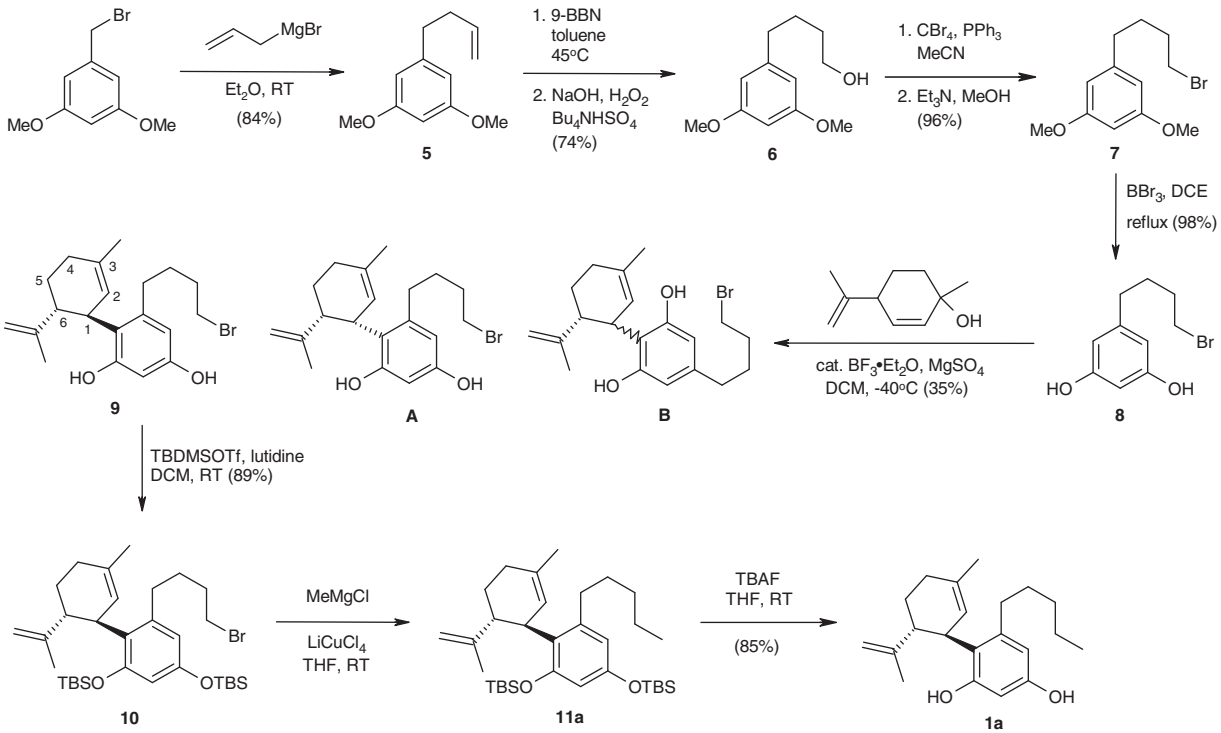
The preparation of olivetol, deuterated at the terminus of the pentyl chain, and its coupling with **2** to form deuterated tetrahydrocannabinol has also been reported.[11] A modification of this approach, in which the labelled methyl group was introduced after the coupling step, rather than before, would permit the number of labelled steps to be minimized (Scheme 2). Owing to the presence of phenolic groups in the final product, protection of the substrate for this last C–C coupling would be essential in order to avoid the generation of excessive quantities of radioactive waste, and so a single-step labelling method was unlikely to be feasible.

The sequence therefore used for the preparation of **1a** and **1b** is shown in Scheme 3. Grignard allylation of 3,5-dimethoxybenzyl bromide, as described by previous workers,[3] provided the terminal alkene **5**. Hydroboration of this intermediate has been reported previously using borane–dimethyl sulfide complex.[3] Nevertheless, we were disappointed that, despite an overall yield of approximately 95%, the product from this method was a mixture of primary and secondary alcohol products, the separation of which was difficult. Better selectivity was observed upon hydroboration of **5** with 9-BBN,[4] and oxidation of the intermediate borane with alkaline hydrogen peroxide, although the overall yield was actually poorer. Bromination of the alcohol thus obtained proceeded efficiently using triphenylphosphine–carbon tetrabromide to give the primary alkyl bromide **7**, which underwent O-demethylation in excellent yield upon treatment with boron tribromide, as described previously for the preparation of labelled olivetol.[11] These latter conditions were found to be very much superior to iodotrimethylsilane, as used by earlier workers.[3] Attempts were also made to convert the alcohol **6** directly into **8** using hydrobromic acid, either alone or in combination with boron tribromide. Indeed, treatment of **6** with hydrogen bromide in acetic acid did provide an 81% yield of **8** in a single step. However, purification of the product proved to be difficult, and the process was not improved by microwave heating at 150°C. In addition, the yield using the two-step process was better than that obtained in a single step.

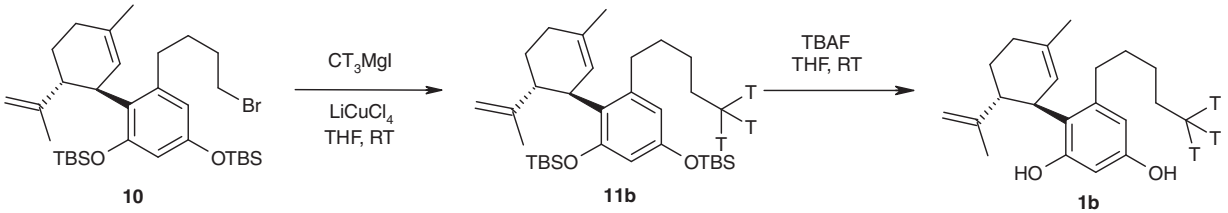
The olivetol synthon **8** was coupled with commercially obtained *trans*-(+)-menthadienol, in the presence of a catalytic amount of boron trifluoride etherate, and keeping the temperature at −40°C to minimize cyclodehydration of the initial adducts. Reducing the temperature below −40°C did not result in any advantage and, at −70°C the reaction was sluggish at best. Separation of the mixture of regioisomers and diastereoisomers produced required extensive chromatography but did provide pure *trans*-diastereomer **9** in an acceptable yield. The *cis* diastereomer **A** and the regioisomeric product **B** were isolated and identified also, the identity of the last being immediately clear from the single aromatic resonance observed in its ^{1}H NMR spectrum. The NMR spectra of the *cis* diastereomer **A** and the desired product **9** are similar, although the aromatic resonances in the spectrum of **A** are significantly broadened; this is likely to be the result of restricted rotation, due in turn to steric interactions between the aromatic and isopropenyl



Scheme 2.



Scheme 3.



Scheme 4.

groups. ^{1}H NMR resonances in the terpenoid unit are shifted downfield also in the spectrum of **A**, with the resonance due to CH_3 of the isopropenyl group in particular appearing at δ1.66, compared with δ1.52 in the spectrum of **9**. Simultaneously, that due to H1 (*geminal* to the aromatic ring) is shifted from δ3.51 in **9** to δ3.85 in **A**. The assignment of the individual ^{1}H NMR signals in the spectrum of **9** was established from 2D-COSY spectra with, in particular, both H1 and H6 correlating to the CH_3 of the isopropenyl group, and key assignments are given in the experimental section. An unequivocal assignment of the stereochemistry of **9** was made on the basis of the coupling between H1 and H6, ($J_{1,6}$ 10.5 Hz), which clearly shows that these protons are *trans* to each other. This assignment was further supported by nOe data. As expected, irradiation at the frequency corresponding to H1 of the terpene unit (δ3.51) results in enhancement of the signals due to the upfield proton of the isopropenyl group (δ4.47), to the olefinic H2 (δ5.52) and to H6 (δ2.66). However, irradiation at the frequency corresponding to H6 results in enhancements of the signals corresponding to the upfield proton of the isopropenyl group, to H1 and to the two protons H5, and also in a diminution of the signal due to $H4_{axial}$. The conclusion from these experiments is that both H1 and H6 are axial, and that the substituents at these centres must be equatorial and therefore trans.

Completion of the synthesis in unlabelled form required protection of the phenolic groups of **9**, with *tert*-butyldimethylsilyl proving to be a suitable choice of protecting group. The protected form **10** underwent copper-catalysed Grignard coupling with methylmagnesium chloride, providing protected unlabelled *abnormal*-cannabidiol (**11a**), which was not purified, but rather was desilylated directly to give **1a** in an 85% yield over two steps. The copper-catalysed coupling reaction described above proved to be general for methylmagnesium halides, and the procedure using [$^{3}H_3$]-methylmagnesium iodide was used to prepare high specific activity **1b** (Scheme 4). Following deprotection as above and purification by HPLC, **1b** was obtained with radiochemical purity above 99%, and a specific activity of 74.3 Ci/mmol.

Conclusion

The preparation of cannabidiol analogue **9** has been effectively optimized, and the coupling of protected form **10** with [$^{3}H_3$]-methylmagnesium iodide followed by deprotection provides an effective means for the preparation of **1b**, high-specific tritiated forms of *abnormal*-cannabidiol **1** being accessed only with considerable difficulty by other means.

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References

[1] a) E. Stern, D. M. Lambert, *Chem. Biodiversity* **2006**, *4*, 1707; b) L. Walter, A. Franklin, A. Witting, C. Wade, Y. Xie, G. Kunos, K. Mackie, N. Stella, *J. Neurosci.* **2003**, *23*, 1398.
[2] Z. Járai, J. A. Wagner, K. Varga, K. D. Lake, D. R. Compton, B. R. Martin, A. M. Zimmer, T. I. Bonner, N. E. Buckley, E. Mezey, R. K. Razdan, A. Zimmer, G. Kunos, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 14136.
[3] M. Girard, D. B. Moir, J. W. ApSimon, *Can. J. Chem.* **1987**, *65*, 189.
[4] E. R. Beerkhardt, K. Matos, *Chem. Rev.* **2006**, *106*, 2617–2650
[5] E. Alonso, D. J. Ramon, M. Yus, *J. Org. Chem.*,**1997**, *62*, 417.
[6] R. K. Razdan, H.C. Dalzell, G. R. Handrick, *J. Am. Chem. Soc.* **1974**, *96*, 5860.
[7] V. V. K. Prasad, S. O. Franklin, *J. Label. Compd. Radiopharm.* **1985**, *22*, 353.
[8] a) T. Petrzilka, W. Haefliger, C. Sikemeier, *Helv. Chim. Acta* **1969**, *52*, 1102; b) B. Cardillo, L. Merlini, S. Servi, *Tetrahedron Lett.* **1972**, 945; c) S.-H. Baek, M. Srebnik, R. Mechoulam, *Tetrahedron Lett.* **1985**, *26*, 1083; d) N. Lander, Z. Ben-Zvi, R. Mechoulam, B. Martin, M. Nordqvist, S. Agureli, *J. Chem. Soc. Perkin* **1976**, *1*, 8.
[9] a) R. V. Stevens, K. F. Albizati, *J. Org. Chem.* **1985**, *50*, 632; b) M. Kato, M. Watanabe, Y. Tooyama, B. Vogler, A. Yoshikoshi, *Synthesis* **1992**, 1055.
[10] E. W. Gill, G. Jones, *J. Label. Compd. Radiopharm.* **1972**, *8*, 237.
[11] S. P. Nikas, G. A. Thakur, A. Makriyannis, *J. Label. Compd. Radiopharm.* **2002**, *45*, 1065.