Synthesis of (*R*)- and (*S*)-4′-Acetoxyolivetol [(*R*)- and (*S*)-5-(4′-Acetoxypentyl)-1,3-benzenediol]: Key Intermediates in the Synthesis of Tetrahydrocannabinol Derivatives

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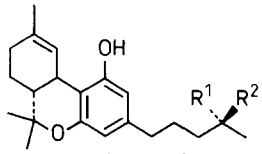
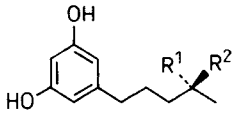
The synthesis of (*R*)- and (*S*)-4′-acetoxyolivetols, key intermediates in the synthesis of tetrahydrocannabinol derivatives from 3,5-dihydroxybenzoic acid **(4)** is described. The 3,5-dihydroxy groups were protected as their *tert*-butyldimethylsilyl derivatives, and the benzoic acid group was transformed into the benzyl-1,3-dithiane derivative **8**. Treatment of the anion of **8** with the chiral 1,2-epoxypropane gave the dithianyl alcohol **9**, which after acetylation followed by desulfurization and deprotection of the phenolic hydroxyl groups, furnished the desired 4′-acetoxyolivetols **(2a,b)** in an overall yield of 13%.

In the last few years there has been a resurgence of interest in the cannabinoid field. The psychoactive constituent of cannabis, Δ^9-tetrahydrocannabinol (Δ^9-THC), has been shown to bind to a specific G-protein-coupled receptor in the brain and very recently the endogenous ligand which binds to this receptor has been identified.[1] It is well established that various hydroxy metabolites of Δ^9-THC contribute to the full spectrum of pharmacological effects displayed by the parent compound.[2-9] We had previously synthesized the (*R*)- and (*S*)-3′-hydroxy-Δ^9-THCs and showed, on the basis of behavioral tests,[10] that the main cannabinoid activity resides in the (*S*)- rather than the (*R*)-isomer. This observed stereospecificity in the 3′-hydroxy-THCs is important in terms of pharmacological activity and is regarded as a reflection of the processes involved in drug-receptor interactions. In order to examine if similar specificity resides in the (*R*)- and (*S*)-isomers of 4′-hydroxy-Δ^9-THC **(1)**, a known metabolite of Δ^9-THC,[2] we embarked on their synthesis. We describe here an efficient route to (*R*)- and (*S*)-4′-acetoxyolivetol **(2a,b)**. These compounds are key intermediates in the synthesis of various THCs.



1a R¹ = OH, R² = H
b R¹ = H, R² = OH



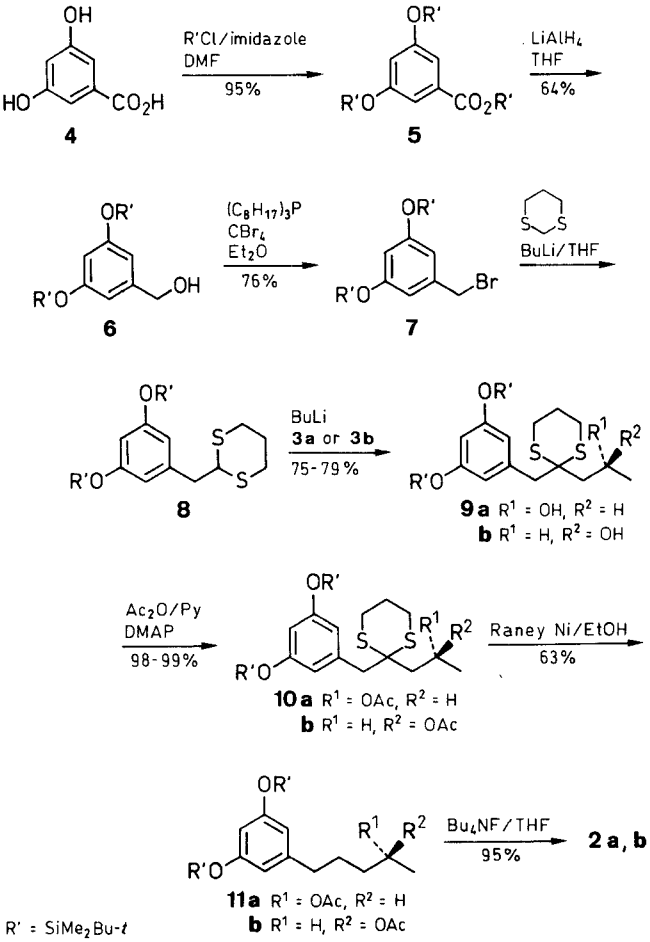
2a R¹ = OAc, R² = H
b R¹ = H, R² = OAc

3a

3b

Generally, the synthesis of side-chain derivatives of THCs has been achieved by the condensation of a monoterpene with an appropriately substituted olivetol.[11,12] The synthesis of **2a** and **2b** was achieved from the readily available 3,5-dihydroxybenzoic acid **(4)** in an overall yield of 13%. The route which we now report (Scheme) has proved most efficient since the use of other protecting groups such as methoxymethoxy ethers and benzyl resulted in inferior yields.

Treatment of 3,5-dihydroxybenzoic acid **(4)** with *tert*-butyldimethylsilyl chloride (TBDMS) in the presence of imidazole in dimethylformamide formed the protected ester **5** (95% yield). Reduction with lithium aluminum hydride gave the alcohol **6** which was purified by chromatography (64%). Treatment of **6** with carbon tetrabromide in the presence of trioctylphosphine[13] in diethyl ether formed the bromide **7** in 76% yield. Compound **8** was obtained in 60% yield by displacement of the bromine in **7** by the lithium anion of 1,3-dithiane.[11,12] Chirality was introduced in the *n*-pentyl side chain of **2** by reaction of the known (*R*)-(+)-1,2-epoxypropane **(3a)**[14] with the lithium anion of **8** at −78 °C to form the dithianyl alcohol **9a** in 79% yield. Acetylation to give **10** followed by desulfurization with Raney nickel[11,12] to yield **11** and deprotection with tetrabutylammonium fluoride gave **2a** in 61% overall yield from **9a**. Compound **2b** was synthesized in an analogous fashion from **8** using the known (*S*)-(−)-1,2-epoxypropane **(3b)**.[15]



Scheme

All reagents were of commercial quality from freshly opened containers. Anhydrous reagent quality solvents were used without further purification. Analytical TLC plates and silica gel (40 μm particle size) were purchased from J.T. Baker. Melting points were taken using a Gallenkamp melting point apparatus and are uncorrected.

Elemental analyses were performed by Atlantic Microlab, Inc (Norcross, GA). Observed rotations were obtained at the Na-D line at the indicated temperature on a Perkin-Elmer 241 polarimeter. ^{1}H NMR spectra were obtained using a Varian XL-400 MHz spectrometer. For new compounds satisfactory microanalyses were obtained: C ± 0.17, H ± 0.04.

(R)-1,2-Epoxypropane **(3a)** *and (S)-1,2-Epoxypropane* **(3b)**: Both compounds were prepared from the commercially available (*S*)-(−)-ethyl lactate. Compound **3a** was prepared in an overall yield of 15%; bp 33–34°C/760 Torr; $[\alpha]_D^{15}$ + 11.15° (neat); (Lit.[14] bp 33–34°C/730 Torr; $[\alpha]_D^{22}$ + 13.0° (neat)). Compound **3b** was obtained in an overall yield of 35%; bp 34°C/760 Torr; $[\alpha]_D^{15}$ − 11.04° (neat); (Lit.[15] bp 34°C/760 Torr; $[\alpha]_D$ − 12.5° (neat)).

3,5-Bis(*tert*-butyldimethylsilyloxy)benzoic Acid *tert*-Butyldimethylsilyl Ester (5):
To a solution of 3,5-dihydroxybenzoic acid (**4**; 45 g, 292 mmol) in DMF (250 mL) was added a solution of imidazole (119.2 g, 1753 mmol) in DMF (250 mL) followed by the addition of a solution of *tert*-butyldimethylsilyl chloride (134.3 g, 891 mmol) in DMF (250 mL). The mixture was stirred at 60°C for 16 h, poured over ice water and the aqueous phase extracted several times with Et_2O (1000 mL total). The combined Et_2O extracts were then washed with H_2O (200 mL), brine (200 mL) and dried (Na_2SO_4). The solvent was removed in vacuo to give **5** as an oil; yield: 143 g (95%) which was used without further purification.

^{1}H NMR ($CDCl_3$): δ = 7.0 (d, *J* = 2 Hz, 2 H_{arom}), 6.4 (m, 1 H_{arom}), 0.99 [s, 18 H, $SiC(CH_3)_3$], 0.19 (s, 12 H, $SiCH_3$).

3,5-Bis(*tert*-butyldimethylsilyloxy)benzyl Alcohol (6):
$LiAlH_4$ (22.05 g, 580 mmol) was suspended in THF (300 mL) and cooled to 0°C. A solution of **5** (143 g, 276 mmol) in THF (250 mL) was added dropwise over 45 min. After a further 30 min the reaction is quenched by the dropwise addition of H_2O (22 mL), NaOH (22 mL) and H_2O (66 mL). The mixture was filtered through Celite 454 and washed with Et_2O (1200 mL). The Et_2O phase was dried (Na_2SO_4) and evaporated to yield a viscous oil. This was purified by chromatography on silica gel (500 g) eluting with 2.5% followed by 20% and 50% Et_2O/petroleum ether (bp 35–60°C) and finally with Et_2O to give **6** as an oil; yield: 71.7 g (64%).

^{1}H NMR ($CDCl_3$): δ = 6.47 (d, *J* = 2, 2 H_{arom}), 6.26 (br s, 1 H_{arom}), 4.56 (s, 2 H, $ArCH_2OH$), 0.98 [s, 18 H, $SiC(CH_3)_3$], 0.19 (s, 12 H, $SiCH_3$).

3,5-Bis(*tert*-butyldimethylsilyloxy)benzyl Bromide (7):
To a stirred solution of **6** (68.6 g, 86 mmol) and CBr_4 (137 g, 413 mmol) in anhydr. Et_2O (1000 mL) at 0°C was added dropwise a solution of trioctyl phosphine (153 g, 418 mmol) in anhydr. Et_2O (200 mL) over 5 min. After 15 min the mixture was filtered through neutral alumina and washed with copious amounts of Et_2O (1000 mL). The solvent was removed in vacuo and the residue purified by column chromatograpy on silica gel (600 g) with hexanes followed by 10% Et_2O/hexanes as eluent to give an oil. Crystallization from cold MeOH afforded **7** as a white crystalline solid; yield: 61 g (76%); mp 42–45°C.

^{1}H NMR ($CDCl_3$): δ = 6.50 (d, *J* = 2, 2 H_{arom}), 6.27 (d, *J* = 2, 1 H_{arom}), 4.37 (s, 2 H, $ArCH_2Br$), 0.98 [s, 18 H, $SiC(CH_3)_3$], 0.20 (s, 12 H, $SiCH_3$).

2-[3,5-Bis(*tert*-butyldimethylsilyloxy)benzyl]-1,3-dithiane (8):
To a solution of 1,3-dithiane (20.88 g, 174 mmol) in THF (250 mL) was added dropwise a 2.5 M solution of BuLi in hexane (77.4 mL, 116 mmol) at − 78°C. The mixture was stirred between − 40 and − 20°C for 3 h, and a solution of **7** in THF (25 mL) was added rapidly. The reaction was quenched after 10 min with sat. NH_4Cl (50 mL). The THF was removed in vacuo and the aqueous layer was extracted several times with Et_2O (1400 mL), and the combined Et_2O extracts were washed with H_2O (200 mL), brine (200 mL), dried (Na_2SO_4), and concentrated. The residue obtained was chromatographed on silica gel (700 g) with 1% Et_2O/hexanes as eluent to give **8** as an oil; yield: 28.5 g (60%).

^{1}H NMR ($CDCl_3$): δ = 6.55 (d, *J* = 2, 2 H_{arom}), 6.45 (br s, 1 H_{arom}), 4.30 (s, 1 H, CH), 2.95 (m, 6 H, $ArCH_2$, SCH_2), 1.95 (m, 2 H, $CH_2CH_2CH_2$) 0.98 [s, 18 H, $SiC(CH_3)_3$], 0.19 (s, 12 H, $SiCH_3$).

2-[3,5-Bis(*tert*-butyldimethylsilyloxy)benzyl]-2-[2-(*R*)-hydroxypropyl]-1,3-dithiane (9a):
To a solution of **8** (28.5 g, 60.6 mmol) in THF (500 mL) was added dropwise a 2.5 M solution of BuLi in hexane (31.5 mL, 78.8 mmol) at − 78°C. The resulting dark red-brown solution was stirred between − 40 and − 20°C for 3 h, and a chilled solution of *R*-(+)-1,2-epoxypropane (**3a**; 5.8 mL, 72.7 mmol) in THF (2 mL) was added rapidly. The mixture was stirred at − 20°C for 30 min, placed in the freezer (− 5°C) overnight and stirred at r.t. for 30 min. The reaction was quenched with sat. NH_4Cl (50 mL), the volatiles were removed in vacuo and the aqueous layer was extracted several times with Et_2O (400 mL). The combined Et_2O extracts were washed with H_2O (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated to yield an oil. This was purified by chromatography on silica gel (650 g) by eluting with 5% followed by 10% Et_2O/hexanes to give **9a** as an oil; yield: 25.4 g (79%).

^{1}H NMR ($CDCl_3$): δ = 6.55 (d, *J* = 2, 2 H_{arom}), 6.45 (br, s, 1 H_{arom}), 3.50 (s, 1 H, CH), 3.10 (m, 2 H, $ArCH_2$), 3.0 (m, 4 H, SCH_2), 1.95 (m, 4 H, $CH_2CH_2CH_2$, CH_2CHOH), 1.1 (d, 3 H, CH_3), 0.98 [s, 18 H, $SiC(CH_3)_3$], 0.19 (s, 12 H, $SiCH_3$).

Similarly **8** (30.0 g, 63.8 mmol) and *S*-(−)-1,2-epoxypropane (**3b**; 7.6 mL, 82 mmol) gave **9b**; yield: 25.43 g (75%).

2-[3,5-Bis(*tert*-butyldimethylsilyloxy)benzyl]-2-[2-(*R*)-acetoxypropyl]-1,3-dithiane (10a):
To a solution of **9a** (23.6 g, 44.7 mmol) in CH_2Cl_2 (40 mL) was added pyridine (16 mL), Ac_2O (16 mL) and 4-dimethylaminopyridine (DMAP) (15 mg). The mixture was stirred at r.t. overnight and quenched with 1 N HCl (25 mL). The aqueous layer was extracted several times with Et_2O (200 mL) and the combined Et_2O extracts are washed with 1 N HCl (50 mL), H_2O (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated to give **10a** as an oil; yield: 23.43 g (98%). The product was used in the next step without any further purification.

^{1}H NMR ($CDCl_3$): δ = 6.55 (d, *J* = 2, 2 H_{arom}), 6.35 (br s, 1 H_{arom}), 3.50 (s, 1 H, CH), 3.10 (m, 2 H, $ArCH_2$), 2.95 (m, 4 H, SCH_2), 2.1 (s, 3 H, $COCH_3$), 1.95 (m, 4 H, $CH_2CH_2CH_2$, CH_2CHOH), 1.3 (d, 3 H, CH_3), 0.98 [s, 18 H, $SiC(CH_3)_3$], 0.19 (s, 12 H, $SiCH_3$).

Similarly **9b** (25.34 g, 47.8 mmol) gave **10b**; yield: 26.99 g (99%).

1-[4′-(*R*)-Acetoxypentyl]-3,5-bis[*tert*-butyldimethylsilyloxy]benzene (11a):
To a suspension of freshly prepared Raney Ni (58 g) in absolute EtOH (250 mL) was added rapidly a solution of **10a** (5.6 g, 9.8 mmol) in absolute EtOH (250 mL). The suspension was stirred at reflux for 1 h and filtered through Celite 454 washing with EtOH (1000 mL). The solvent was removed in vacuo and the residue chromatographed on silica gel (250 g) using 5% Et_2O/hexanes as eluent to give **11a** as an oil; yield: 2.9 g (63%).

^{1}H NMR ($CDCl_3$): δ = 6.26 (d, *J* = 2, 2 H_{arom}), 6.15 (t, *J* = 2, 1 H_{arom}), 4.88 (m, 1 H, CHOAc), 2.46 (t, *J* = 7, 2 H, $ArCH_2$), 2.00 (s, 3 H, $OCOCH_3$), 1.53–1.58 (m, 4 H, CH_2), 1.17 (d, *J* = 7, 3 H, CH_3), 0.95 [s, 18 H, $SiC(CH_3)_3$], 0.16 (s, 12 H, $SiCH_3$).

Similarly **10b** (26.9 g, 47.1 mmol) gave **11b**; yield: 14.0 g (63%).

5-[4′-(*R*)-Acetoxypentyl]-1,3-benzenediol (2a), [4′-(*R*)-Acetoxyolivetol]:
To a solution of **11a** (2.9 g, 6.17 mmol) in THF (20 mL) was added a 1 M solution of Bu_4NF in THF (32 mL, 32 mmol) and stirred at r.t for 1 h. The THF was removed in vacuo and the residue partitioned between EtOAc and H_2O. The aqueous layer was extracted 3 times with EtOAc (200 mL). The combined EtOAc extracts were washed with 1 M HCl (50 mL), H_2O (50 mL), brine (50 mL), dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (100 g) eluting with 20% followed by 50% EtOAc/hexanes to afford **2a** as an oil, yield: 1.39 g (95%); $[\alpha]_D^{15}$ + 2.30° (*c* = 12.8, EtOH).

^{1}H NMR ($CDCl_3$): δ = 6.61 (br s, 2H, ArOH), 6.22 (s, 3 H_{arom}), 4.89 (m, 1H, CHOAc), 2.41 (t, J = 7, 2H, $ArCH_2$), 2.02 (s, 3H, $COCH_3$), 1.59–1.42 (m, 4H, CH_2), 1.15 (d, 3H, J = 6, CH_3).

Similarly **11b** (12.3 g, 21.5 mmol) gave **2b**; yield: 5.92 g (95%); $[\alpha]_D^{15}$ −2.57° (c = 14.0, EtOH).

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