Synthesis of 2'- and 3'-Acetoxyolivetols [5-(2- and 3-Acetoxypentyl)-1,3-benzenediols]: Key Intermediates in the Synthesis of Tetrahydrocannabinol Derivatives[1]

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Extensive literature[2-5] has appeared in recent years describing the various metabolites of tetrahydrocannabinols (THC's) isolated from *in vivo* and *in vitro* studies. In the case of Δ^1-THC, the active constituent of marihuana, the most important sites of metabolic attack are the alicyclic ring at C-7 and the pentyl side chain of the aromatic ring. Thus, Δ^1-THC and other THC's (like Δ^6-THC, cannabidiol, and cannabinol) give microsomal hydroxylations at carbons 1''–5''[5]. Generally, the synthesis of side-chain derivatives of THC's has been achieved by condensation of the appropriately substituted olivetol with a monoterpene[6], e.g., the biologically potent metabolite 3''-hydroxy-Δ^1-THC was synthesized[7] from 3'-acetoxyolivetol and *p*-2-menthene-1,8-diol.

We describe here a practical route to two of these key intermediates, i.e., 2'- and 3'-acetoxyolivetol [5-(2-acetoxypentyl)-1,3-benzenediol, **1**; 5-(3-acetoxypentyl)-1,3-benzenediol, **2**], from the readily available methyl 3,5-dihydroxybenzoate in overall yields of 34% and 35%, respectively.

Alternative routes to these olivetols were tried, including other protecting groups for the phenol function, but the results were usually poorer yields. Indeed, even with the methoxymethoxy ethers the isolation and identification of desired compounds were complicated by the presence of mono ethers as by-products, which could not be cleaved (or reacted) without adverse effect on the yield of the main product.

Methyl 3,5-dihydroxybenzoate was treated with excess chloromethyl methyl ether in the presence of finely divided anhydrous potassium carbonate in dry acetonitrile to give the *O*-protected derivative **3** which was reduced with lithium alanate in ether to the benzyl alcohol **4**. Oxidation to 3,5-bis[methoxymethoxy]-benzaldehyde (**5**) proceeded smoothly, without affecting the acid-sensitive methoxyme-

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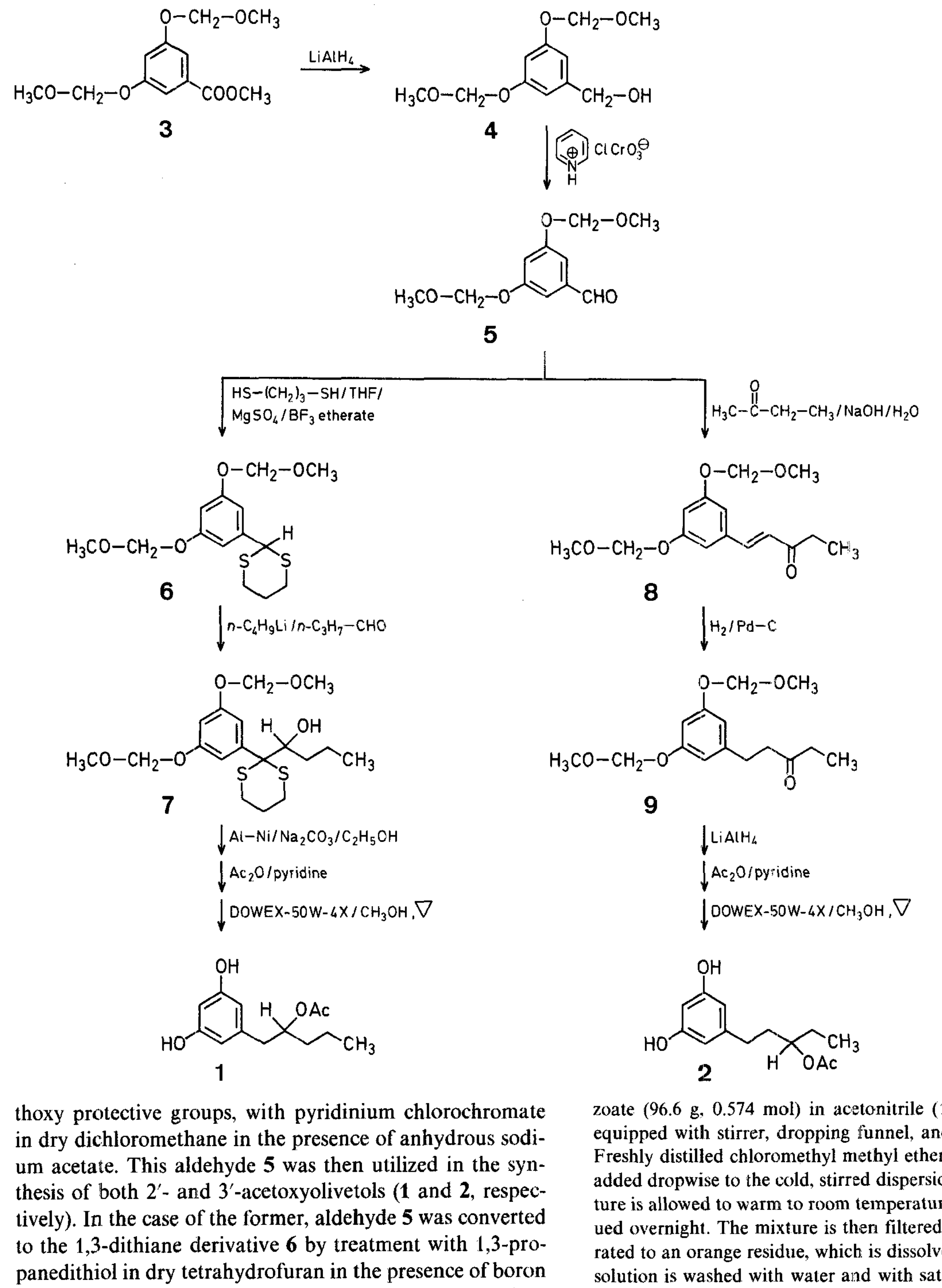

thoxy protective groups, with pyridinium chlorochromate in dry dichloromethane in the presence of anhydrous sodium acetate. This aldehyde **5** was then utilized in the synthesis of both 2′- and 3′-acetoxyolivetols (**1** and **2**, respectively). In the case of the former, aldehyde **5** was converted to the 1,3-dithiane derivative **6** by treatment with 1,3-propanedithiol in dry tetrahydrofuran in the presence of boron trifluoride etherate. The addition of anhydrous magnesium sulfate to the reaction mixture prevented some removal of the *O*-methoxymethyl groups, which otherwise was observed. Condensation of the anion of **6** with butanal to give **7**, followed by removal of the dithiane group, acetylation of the 2′-hydroxy group, and deprotection of the phenolic groups proceeded smoothly to give **1** as colorless crystals.

Compound **2** was prepared from **5** as follows. Aldol condensation with butanone formed **8**, which on catalytic reduction gave the ketone **9**. Lithium aluminum hydride reduction of **9** followed by acetylation and removal of the *O*-methoxymethyl groups gave **2** as viscous oil.

Methyl 3,5-Bis[methoxymethoxy]-benzoate (3):

Sieved (200 mesh) anhydrous potassium carbonate (302.5 g, 2.189 mol) is added to an ice-cold solution of methyl 3,5-dihydroxybenzoate (96.6 g, 0.574 mol) in acetonitrile (1368 ml) in a 5-l flask equipped with stirrer, dropping funnel, and nitrogen atmosphere. Freshly distilled chloromethyl methyl ether (186.6 g, 2.317 mol) is added dropwise to the cold, stirred dispersion during 1 h. The mixture is allowed to warm to room temperature and stirring is continued overnight. The mixture is then filtered and the filtrate evaporated to an orange residue, which is dissolved in ether. The ethereal solution is washed with water and with saturated sodium chloride solution, dried with magnesium sulfate, and evaporated. The residual yellow oil is distilled in vacuo to give a clear liquid; yield: 143.2 g (91%); b.p. 123–133 °C/0.2 torr.

$C_{12}H_{16}O_6$	calc.	C 56.25	H 6.29
(256.3)	found	56.34	6.31

^{1}H-N.M.R. (CCl_4): $\delta = 7.23$ (d, 2H, Ar-2-H, 6-H); 6.78 (t, 1H, Ar-4-H); 5.07 (s, 4H, O—CH_2—O); 3.83 (s, 3H, ester OCH_3); 3.42 ppm (s, 6H, ether OCH_3).

3,5-Bis[methoxymethoxy]-benzaldehyde (5):

3,5-Bis[methoxymethoxy]-benzyl Alcohol (**4**): A solution of methyl 3,5-bis[methoxymethoxy]benzoate (**3**; 133.8 g, 0.522 mol) in anhydrous ether (455 ml) is added during 1.5 h to a stirred slurry of lithium aluminum hydride (20.0 g, 0.527 mol) in anhydrous ether (455 ml) under nitrogen. After the addition is completed the mixture is refluxed for 45 min, cooled, and then decomposed by the addition of ethyl acetate (60 ml) followed by saturated ammonium chloride solution (150 ml).Vigorous stirring is continued for 1 h at reflux. The mixture is then filtered, the filtrate washed with saturated ammonium chloride solution and with saturated sodium chloride solution, dried with sodium sulfate, and concentrated to give **4** as colorless oil; yield: 114 g (95%). The product shows a single spot on T.L.C. (silica, ether), R_F: 0.44. It is used in the next step without further purification. An analytical sample may be obtained by distillation; b.p. 172 °C/1 torr.

$C_{11}H_{16}O_5$	calc.	C 57.88	H 7.06
(218.2)	found	57.61	7.12

3,5-Bis[methoxymethoxy]-benzaldehyde (**5**): A solution of alcohol **4** (114 g, 0.500 mol) in dry dichloromethane (330 ml) is added dropwise, under nitrogen, to a stirred dispersion of pyridinium chlorochromate (163 g, 0.756 mol) and anhydrous (fused) sodium acetate (13 g, 0.158 mol) in dry dichloromethane (650 ml). The temperature of the mixture is maintained at 24–25 °C by cooling in a cold water bath. Stirring is continued for 2 h, ether (2.5 l) is added, the mixture is filtered, and the solids on the filter are washed with ether. The ether solutions are washed with water (3 x 100 ml) and with saturated sodium chloride solution (150 ml), dried with magnesium sulfate, and slurried with Florisil® to remove color. After filtration of the solution, the ether is evaporated to leave the aldehyde **5** as a yellow oil; yield: 100 g (88%). An analytical sample may be obtained by preparative T.L.C. (silica, 20% ethyl acetate in hexane).

$C_{11}H_{14}O_5$	calc.	C 58.40	H 6.24
(216.2)	found	58.57	6.29

^{1}H-N.M.R. (CCl_4): δ=9.77 (s, 1H, $C\underline{H}O$); 7.07 (d, J=2 Hz, 2H, Ar-2-$\underline{H}$, 6-$\underline{H}$); 6.83 (t, 1H, Ar-4-$\underline{H}$); 5.12 (s, 4H, $O—C\underline{H}_2—O$); 3.42 ppm (s, 6H, $OC\underline{H}_3$).

2-(3,5-Bis[methoxymethoxyl]-phenyl)-1,3-dithiane (6):

1,3-Propanedithiol (24 ml, 0.21 mol) is added to a stirred mixture of 3,5-bis[methoxymethoxy]-benzaldehyde (**5**; 42.0 g, 0.19 mol) and anhydrous magnesium sulfate (80.0 g) in dry tetrahydrofuran (400 ml) at ice-bath temperature. Stirring is continued for 1 h at 0 °C. Then, a solution of boron trifluoride etherate (8 ml) in dry tetrahydrofuran (150 ml) is added during 40 min. The mixture is allowed to warm to room temperature and is stirred overnight. It is then filtered, the filtrate is concentrated to ~300 ml, washed with 10% aqueous potassium hydroxide (2 x 100 ml) and with saturated sodium chloride solution (100 ml). The solution is dried with magnesium sulfate, filtered through a pad of Florisil®, and evaporated to an oil. The oil is triturated with hexane and the resultant crystalline product **6** isolated by suction; yield: 41.4 g (71%); colorless prisms, m.p. 62–63 °C.

$C_{14}H_{20}O_4S_2$	calc.	C 53.14	H 6.37
(316.3)	found	53.19	6.41

^{1}H-N.M.R. (CCl_4): δ=6.72 (d, J=2 Hz, 2H, Ar-2-$\underline{H}$, 6-$\underline{H}$), 6.58 (t, J=2 Hz, 1H, Ar-4-$\underline{H}$); 5.08 (s, 4H, $ArO—C\underline{H}_2—O$); 4.97 (s, 1H, $S—C\underline{H}—S$); 3.42 (s, 6H, $OC\underline{H}_3$); 2.52–2.98 (m, 4H, $S—C\underline{H}_2$); 1.78–2.15 ppm (m, 2H, $S—CH_2—C\underline{H}_2—CH_2—S$).

2-(3,5-Bis[methoxymethoxy]-phenyl)-2-(1-hydroxy-1-butyl)-1,3-dithiane (7):

A 2.2 molar solution of butyllithium in hexane (7 ml, 15.4 mmol) is added to a stirred solution of compound **6** (4.38 g, 0.014 mol) in dry tetrahydrofuran (100 ml) in a Dry Ice/acetone bath under a nitrogen atmosphere. Stirring is continued for 1 h whereafter a solution of butanal (1.10 g, 0.015 mol) in dry tetrahydrofuran (5 ml) is added. The mixture is stirred for a further 30 min, allowed to warm to room temperature, and the reaction then quenched with saturated ammonium chloride solution (~50 ml). The organic layer is separated and the aqueous layer extracted with ether (50 ml). The combined organic layers are washed with saturated sodium chloride solution (150 ml), dried with magnesium sulfate, and evaporated to give **7** as an oil; yield: 5.3 g (98%). This product is used in the next step without further purification.

^{1}H-N.M.R. (CCl_4): δ=7.22 (d, J=2 Hz, 2H, Ar-2-$\underline{H}$, 6-$\underline{H}$); 6.60 (t, J=2 Hz, 1H, Ar-4-$\underline{H}$); 5.03 (s, 4H, $Ar—O—C\underline{H}_2—O$); 3.63 (m, 1H, $C\underline{H}—OH$); 3.42 (s, 6H, $OC\underline{H}_3$); 2.60–2.78 (m, 4H, $S—C\underline{H}_2$); 1.73–2.17 (m, 2H, $S—CH_2—C\underline{H}_2—CH_2—S$); 1.33 (m, 4H, alkane); 0.87 ppm (t, 3H, ω-$C\underline{H}_3$).

5-(2-Acetoxypentyl)-1,3-benzenediol (2′-Acetoxyolivetol, 1):

1-(3,5-Bis[methoxymethoxy]-phenyl)-2-pentanol:

Sodium carbonate (1.5 g) and freshly prepared Raney nickel (60 g) are added to a stirred solution of compound **7** (5.34 g, 0.014 mol) in ethanol (150 ml). The mixture is stirred and heated under reflux for 19 h, cooled, and filtered through Celite®. The filter cake is washed with acetone (3 x 50 ml); the filtrate is concentrated and dissolved in ether (150 ml). This solution is washed with water (2 x 75 ml) and saturated sodium chloride solution (100 ml), dried with magnesium sulfate, and evaporated to give 1-(3,5-bis[methoxymethoxy]-phenyl)-2-pentanol as an oil; yield: 3.2 g (82%). The compound is used in the next step without purification.

1-(2-Acetoxypentyl)-3,5-bis[methoxymethoxy]-benzene: The crude 1-(3,5-bis[methoxymethoxy]-phenyl)-2-pentanol (3.2 g) is dissolved in acetic anhydride/pyridine mixture (1/3; 50 ml), the solution stirred at room temperature overnight, and then poured into ice/water (200 ml). The mixture is extracted with ether (3 x 25 ml), the extract washed with water (75 ml), 10% aqueous hydrochloric acid (2 x 50 ml), and again with water (50 ml), and dried with magnesium sulfate. The solvent is evaporated and the residue column-chromatographed on Florisil® using ethyl acetate/hexane (1/4) as eluent to give 1-(2-acetoxypentyl)-3,5-bis[methoxymethoxy]-benzene as an oil; yield: 3.32 g (91%). The product is used in the next step without purification.

^{1}H-N.M.R. (CCl_4): δ=1.93 ppm (s, 3H, $O—CO—C\underline{H}_3$).

5-(2-Acetoxypentyl)-1,3-benzenediol (**1**): The crude 1-(2-acetoxypentyl)-3,5-bis[methoxymethoxy]-benzene (3.0 g, 0.009 mol) is dissolved in methanol (75 ml), DOWEX-50W-4X (0.6 g) is added, the mixture is refluxed for 3 h, and then allowed to stand at room temperature overnight. It is then filtered and the precipitate washed with methanol (2 x 25 ml). The combined filtrate is evaporated to give **1** as an oil; yield: 1.7 g (77%). Trituration of the oil with dichloromethane/hexane affords **1** as colorless crystals; m.p. 138–139 °C.

$C_{13}H_{18}O_4$	calc.	C 65.53	H 7.61
(238.3)	found	65.68	7.67

^{1}H-N.M.R. (acetone-d_6): δ=6.23 (s, 3H, $Ar—\underline{H}$); 5.00 (m, 1H, $C\underline{H}—OAc$); 3.03 (br s, 2H, exchangeable with D_2O); 2.67 (d, J=6 Hz, 2$H_{benzylic}$); 1.95 (s, 3H, $—O—CO—C\underline{H}_3$); 1.28–1.42 (m, 4H, $2CH_2$); 0.95 ppm (t, 3H, ω-CH_3).

1-(3,5-Bis[methoxymethoxy]-phenyl)-3-oxo-1-pentene (8):

Under a nitrogen atmosphere, a mixture of 3,5-bis[methoxymethoxy]-benzaldehyde (**5**; 100.3 g, 0.443 mol), butanone (120.8 g, 1.675 mol), and a solution of sodium hydroxide (13.6 g, 0.34 mol) in water (1360 ml) is stirred and heated at 65–70 °C (pot temperature) for 3 h and then allowed to stand overnight at 25 °C. The dark bottom layer is separated and the upper aqueous layer is neutralized with 1:1 hydrochloric acid (~60 ml). The aqueous solution is extracted with ether (2 x 50 ml) and discarded. The organic extract is washed with water (2 x 250 ml), dilute sodium hydrogen carbonate solution (5 x 200 ml), then with water to neutrality, and finally with saturated sodium chloride solution (200 ml). It is dried with sodium sulfate and concentrated in a rotary evaporator to give the crude ketone **8** as a yellow oil; yield: 119.0 g (95%). The product is used in the next step without purification. It may be purified by column chromatography (silica gel, 1:1 ether/petroleum ether).

$C_{15}H_{20}O_5$	calc.	C 64.27	H 7.19
(280.3)	found	64.07	7.27

^{1}H-N.M.R. (CCl_4): δ=7.35 (d, J=16 Hz, 1H, $Ar—C\underline{H}{=}CH$); 6.76 (d, J=2 Hz, 2H, Ar-2-$\underline{H}$, 6-$\underline{H}$); 6.66 (t, 1H, Ar-4-$\underline{H}$); 6.53 (d, J=16 Hz, 1H, $Ar—CH{=}C\underline{H}$); 5.10 (s, 4H, $O—C\underline{H}_2—O$); 3.41 (s, 6H, $OC\underline{H}_3$); 2.56 (q, 2H, 4-$\underline{H}$); 1.08 ppm (t, 3H, ω-$C\underline{H}_3$).

1-(3,5-Bis[methoxymethoxy]-phenyl)-3-pentanone (9):

A solution of compound **8** (119 g, 0.424 mol) in absolute ethanol (890 ml) is hydrogenated in a Parr apparatus in the presence of 10% palladium-on-charcoal (3 g). After the reaction is complete (1 h) the mixture is filtered through Celite® and concentrated to give **9** as a colorless oil; yield: 115 g (96%). The product shows a single spot on T.L.C. (silica); R_F=0.4 (ether/petroleum ether 1/1). It is used in the next step without further purification. An analytical sample may be obtained by column chromatography (silica gel, 1:1 ether/petroleum ether).

$C_{15}H_{22}O_5$	calc.	C 63.81	H 7.85
(282.3)	found	63.73	7.80

^{1}H-N.M.R. (CCl_4): $\delta = 6.41$ (s, 3H_{arom}); 5.03 (s, 4H, O—$C\underline{H}_2$—O); 3.38 (s, 6H, 2$OC\underline{H}_3$); 2.67, 2.30 (2m, 6H, side-chain CH_2); 0.97 ppm (3H, ω-$C\underline{H}_3$).

5-(3-Acetoxypentyl)-1,3-benzenediol (3′-Acetoxyolivetol, 2):

1-(3,5-Bis[methoxymethoxy]-phenyl-3-pentanol: A solution of compound **9** (115.2 g, 0.408 mol) in anhydrous ether (460 ml) is reduced with lithium aluminum hydride (11.5 g, 0.303 mol) in anhydrous ether (460 ml) in a similar manner as described for the reduction of **4**; yield: 114.5 g (98%); G.L.C. (3% OV-17, column 230 °C) retention time: 3.20 min.

1-(3-Acetoxypentyl)-3,5-bis[methoxymethoxy]-benzene: The above crude alcohol (114.5 g) is acetylated with acetic anhydride (93 ml, 0.98 mol) in pyridine (545 ml) for 65 h at room temperature as described above and then distilled; yield: 116 g (88%); b.p. 153–155 °C/0.1 torr; G.L.C. (3% OV-17, column 230 °C) retention time: 3.98 min.

I.R. ($CDCl_3$): $\nu = 1725$ cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.0$ ppm (s, 3H, O—CO—$C\underline{H}_3$).

5-(3-Acetoxypentyl)-1,3-benzenediol (**2**): The crude 1-(3-acetoxypentyl)-3,5-bis[methoxymethoxy]-benzene (20.0 g, 0.061 mol) is dissolved in methanol (250 ml), DOWEX-50W-4X (10.0 g) is added, the mixture is stirred for 1 h at room temperature and then at gentle reflux for 1.25 h, and allowed to stand at room temperature overnight. It is then filtered through a bed of Celite® and the solid washed well with methanol. The filtrate is evaporated and purified by column chromatography on silica gel using ethyl acetate/hexane (1/2) as eluent; yield of **2** as viscous oil: 8.5 g (59%).

$C_{13}H_{18}O_4 \cdot 0.2H_2O$	calc.	C 64.55	H 7.67
	found	64.56	7.71

I.R. ($CDCl_3$): $\nu = 1725$ (C=O), 3350 (OH) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 6.23$ (s, 3H_{arom}); 6.86 (br, 2H, Ar—O$\underline{H}$); 4.81 (t, 1H, C$\underline{H}$—OAc); 2.45 (m, 2H, Ar—$C\underline{H}_2$); 2.00 (s, 3H, O—CO—$C\underline{H}_3$); 1.9–1.2 (m, 4H, 2CH_2); 0.83 ppm (t, 3H, —$C\underline{H}_3$).

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