Cannabis. Part 27.[1] Synthesis of 8-, 10-, and 11-Oxygenated Cannabinols

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Two metabolites of cannabinol (1-hydroxy-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran) in man, 11-hydroxycannabinol (8) and 1-hydroxy-6,6-dimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-9-carboxylic acid (7), have been totally synthesized together with three possible metabolites, 11-oxocannabinol (9), 8-hydroxycannabinol (15), and 10-hydroxycannabinol (21). This is the first total synthesis of the novel compound (21) and the previously isolated acid (7) and occurs in high yield; compounds (8), (9), and (15) were obtained in substantially higher yields than had been achieved by partial synthesis only. The key step in these syntheses was the regiospecific formation of the aryl–aryl bond *via* nucleophilic aromatic substitution of the methoxy group in the *o*-methoxyaryldihydro-oxazoles (2), (11), and (17) by the Grignard reagent, 2,6-dimethoxy-4-pentylphenylmagnesium bromide. The acid (7) was prepared from the new and possibly psychoactive 9-bromo-9-norcannabinol (6), which was obtained from 4-bromo-2-methoxybenzoic acid. Reduction of the acid (7) with lithium aluminium hydride gave 11-hydroxycannabinol, which was oxidized by Jones reagent to 11-oxocannabinol. 8- and 10-Hydroxycannabinol were synthesized in several steps from 2,5-dimethoxy-*p*-toluic acid and 2,3-dimethoxy-*p*-toluic acid, respectively.

Cannabinol (1-hydroxy-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo-[*b*,*d*]pyran) is a minor constituent of *Cannabis sativa L.* and is considered to be an oxidative degradation product of the principal psychoactive component, Δ^9-tetrahydrocannabinol. Psychotomimetically, cannabinol is *ca.* 1/10 as active in man as Δ^9-tetrahydrocannabinol. The main metabolic reaction of cannabinol in man [2] is hydroxylation of the 9-methyl group to give 11-hydroxycannabinol (8), followed by further oxidation to give the carboxylic acid (7). The corresponding aldehyde, 11-oxocannabinol (9), which is one of the *in vivo* metabolites [3] in rats, is probably an intermediate in this metabolic scheme. The pharmacology of cannabinol has been extensively investigated.[4] Much less is known about the effects of its metabolites. however, undoubtedly because of the lack of synthetic material, as there are few preparative methods available. 11-Hydroxycannabinol has been synthesized [5] in 18% yield by SeO_2 oxidation of Δ^9-tetrahydrocannabinol acetate. The same reaction was later reported [6] to yield only 2% of 11-hydroxycannabinol, 4% of 11-oxocannabinol, and 6% of 8-hydroxycannabinol, together with other products. A synthesis of the acid (7) has not yet been published. We now report a new and efficient synthesis of the metabolites 11-hydroxycannabinol and the carboxylic acid (7), as well as a synthesis of the possible metabolites 11-oxo-, 8-hydroxy-, and 10-hydroxycannabinol.

The key step in our approach to the synthesis of each of these cannabinols was the regiospecific formation of the aryl–aryl bond. The nucleophilic aromatic substitution of *o*-methoxyaryldihydro-oxazoles by organometallics, developed by Meyers *et al.*,[7] seemed well suited for this. Application of their general reaction conditions [tetrahydrofuran (THF), 20 °C] to our more sterically hindered starting compounds resulted, however, in an almost complete failure. To our surprise, as noted in a preliminary communication,[8] performing the reaction under reflux led to a considerable improvement; the yields of this key step were 75% or higher.

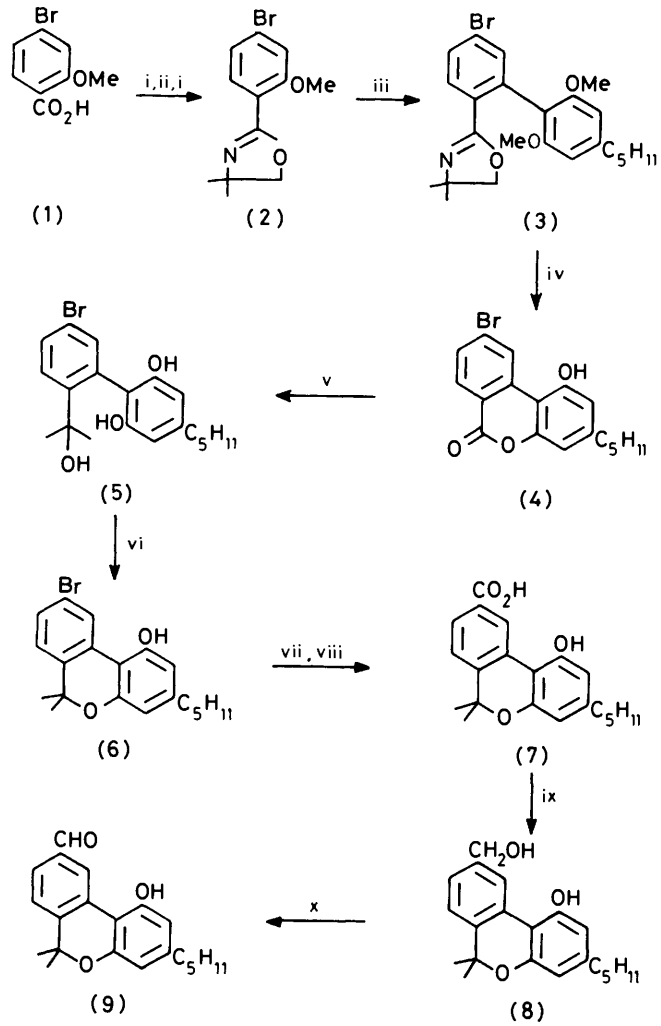
The synthesis of the three 11-oxygenated cannabinols was planned to proceed *via* a common intermediate, the end-products to be obtained *via* an appropriate oxidative or reductive manipulation. The bromo derivative was chosen as a precursor of the C-9 substituent. Thus, as outlined in Scheme 1, the reaction of 4-bromo-2-methoxyphenyldihydro-oxazole (2), prepared from the known [9] acid † (1) in 76.5% overall yield in a standard fashion,[7] with the Grignard reagent from 2-bromo-1,3-dimethoxy-5-pentylbenzene [8] in boiling THF for 22 h, afforded the biphenylyldihydro-oxazole (3) in 95% yield. Hydrolysis of the dihydro-oxazole moiety followed by cleavage of both methoxy groups and acid-catalyzed cyclization to the lactone (4) (84%) was performed as a one-pot reaction using HI–Ac_2O [8] with reflux for 5 h. The lactone (4) was converted into the bromocannabinol (6) in 94% overall yield by treatment with an excess of methylmagnesium iodide followed by dehydration and cyclization by trifluoroacetic acid. Bromocannabinol (6) was transformed into the carboxylic acid (7) *via* lithiation with butyl-lithium in diethyl ether–hexane (−78 ⟶ 5 °C) followed by carbonation (70%). This reaction proved to be solvent (diethyl ether > THF > toluene) and temperature dependent. For example, starting the lithiation at 0 °C instead of −78 °C gave the corresponding debromo compound as the main product; reduction of the acid (7) with lithium aluminium hydride in diethyl ether gave 11-hydroxycannabinol (8) in 92% yield, while oxidation of the alcohol (8) by Jones reagent in acetone afforded 11-oxocannabinol (9) in 89% yield, protection of the phenolic group being unnecessary.

The 8- and 10-hydroxycannabinols (15) and (21), the latter being a new compound, were synthesized using a principle similar to the approach described above (Schemes 2 and 3). The starting compound in the sequence leading to 8-hydroxycannabinol was the known [10] 2,5-dimethoxy-*p*-toluic acid, while the synthesis of 10-hydroxycannabinol commenced with 2,3-dimethoxy-*p*-toluic acid.[11] The first two steps in the latter sequence have been mentioned in a previous publication.[1] The ease and the high yields with which both these syntheses proceeded demonstrate further the utility of the approach presented here.

Experimental

M.p.s were determined in capillaries. ^{1}H N.m.r. spectra were recorded on a Varian EM-390 spectrometer, and ^{13}C n.m.r.

† A new, high yielding synthesis of this acid is given in the Experimental section.

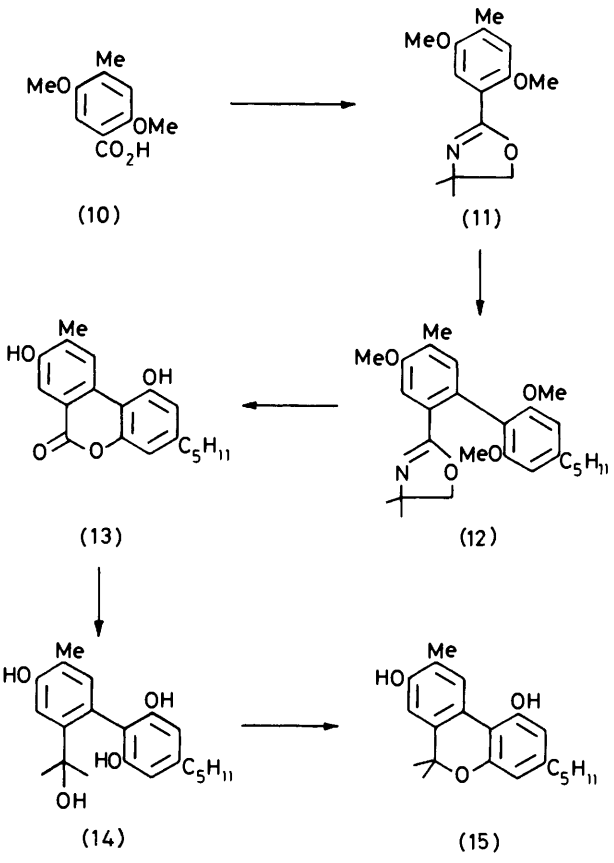


Scheme 1. *Reagents:* i, $SOCl_2$; ii, $Me_2C(NH_2)CH_2OH$; iii, 2,6-$(MeO)_2$-4-(C_5H_{11})-C_6H_2MgBr, THF; iv, 57% HI, Ac_2O; v, MeMgI, THF; vi, TFA, $CHCl_3$; vii, BuLi, Et_2O, hexane; viii, CO_2; ix, $LiAlH_4$, Et_2O; x, CrO_3, H_2SO_4, H_2O, acetone

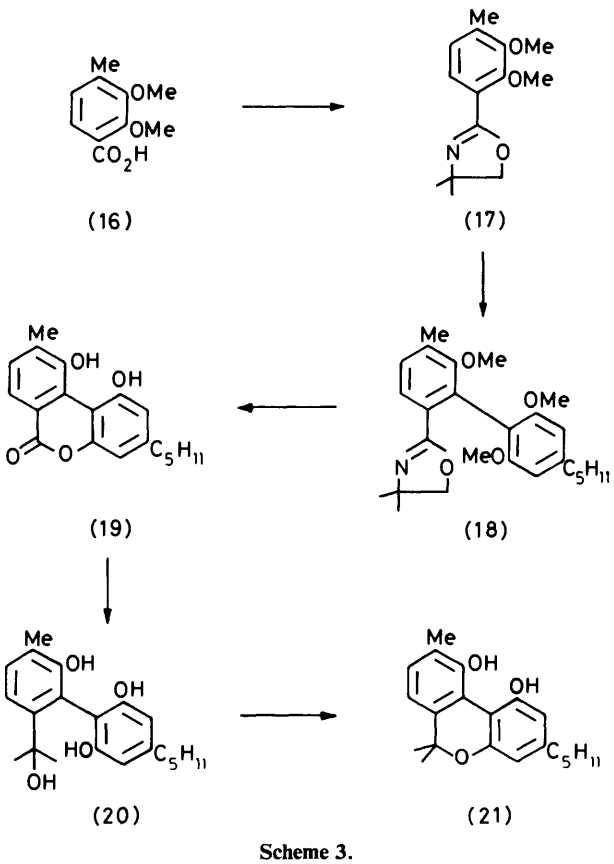
spectra on a Varian CFT-20 or a Bruker WP 200 spectrometer. Magnesium sulphate was used for drying. All reactions were carried out under dry nitrogen.

4-*Bromo*-2-*methoxyacetophenone*.—Methyl iodide (14 ml) was added dropwise to a stirred mixture of 4-bromo-2-hydroxyacetophenone [12] (36.8 g), potassium carbonate (62 g), and *N*,*N*-dimethylformamide (80 ml). The mixture was stirred at room temperature for 20 h, water (160 ml) was added and the mixture was extracted with diethyl ether (4 × 100 ml). The organic extracts were washed twice with water, dried, and concentrated under reduced pressure to give the product as pale yellow crystals (38.5 g, 98%). Crystallization of a small sample from ethanol gave analytically pure material, m.p. 63—64 °C; δ_H ($CDCl_3$) 2.6 (3 H, s, MeCO), 3.9 (3 H, s, OMe), 7.1 (2 H, m, 3- and 5-H), and 7.6 (1 H, d, *J* 9 Hz, 6-H).

4-*Bromo*-2-*methoxybenzoic Acid* (1).—The oxidation was carried out as described [13] for 2,5-bis(methoxymethoxy)-4-methoxyacetophenone. A NaOBr solution, prepared by adding bromine (22.4 ml) to 20% aqueous NaOH (400 ml) (<10 °C), was added dropwise to an ice-cold, stirred solution of 4-bromo-2-methoxyacetophenone (33.65 g) in dioxane (560 ml). After being stirred for 20 min with cooling, the



Scheme 2.



Scheme 3.

mixture was stirred at room temperature for 30 min and then refluxed for 2.5 h. To the cooled mixture was added a solution of $NaHSO_3$ (11 g) and NaOH (11 g) in H_2O (340 ml). The resulting mixture was shaken for 5 min and washed twice with diethyl ether. The aqueous layer was acidified with dilute HCl and extracted with ethyl acetate. The extracts were washed twice with water, dried, and evaporated to dryness to yield crystals (29.6 g, 87%), identical with an authentic sample; [9] δ_H ($CDCl_3$) 4.1 (3 H, s, OMe), 7.2—7.3 (2 H, m, 3- and 5-H), and 8.05 (1 H, d, *J* 9 Hz, 6-H).

2-(4-*Bromo*-2-*methoxyphenyl*)-4,4-*dimethyl*-4,5-*dihydro-oxazole* (2).—This compound was prepared from the acid (1) according to the method of Meyers *et al.*[7] in 76.5% overall yield as a pale yellow, viscous, hygroscopic oil; b.p. 122—127 °C/0.16 mmHg; δ_H ($CDCl_3$) 1.4 (6 H, s, 2 × Me), 3.9 (3 H, s, OMe), 4.05 (2 H, s, CH_2), 7.1 (2 H, m, 2 × ArH), and 7.6 (1 H, d, *J* 9 Hz, ArH); δ_C ($CDCl_3$) 28.1 (q, 2 C), 56.2 (q), 67.3 (s), 78.6 (t), 115.1 (d), 116.6 (s), 123.2 (d), 125.6 (s), 132.2 (d), 158.6 (s), and 160.2 p.p.m. (s).

2-[4-*Bromo*-2-(2,6-*dimethoxy*-4-*pentylphenyl*)*phenyl*]-4,4-*dimethyl*-4,5-*dihydro-oxazole* (3).—The Grignard reagent, prepared from 2-bromo-1,3-dimethoxy-5-pentylbenzene [8] (28.7 g) and magnesium (3 g) in THF (70 ml) which were refluxed for 1 h, was added to a solution of the dihydro-oxazole (2) (14.2 g) in THF (90 ml). The mixture was stirred and refluxed for 22 h, cooled, diluted with water (160 ml), and extracted with diethyl ether (3 × 200 ml). Work-up yielded an oil, from which any by-products were distilled off up to 170 °C (0.12 mmHg). The distillation residue was a very viscous oil (21.9 g, 95%), pure by ^1H n.m.r. analysis; δ_H ($CDCl_3$) 0.9 (3 H, t, ω-Me), 1.2 (6 H, s, 2 × Me), 1.2—1.9 (6 H, m, 3 × CH_2), 2.65 (2 H, t, *J* 8 Hz, benzylic CH_2), 3.7 (8 H, s, 2 × OMe and CH_2O), 6.4 (2 H, s, 2 × ArH), 7.4 (2 H, m, 2 × ArH), and 7.75 (1 H, d, *J* 9 Hz, ArH); δ_C ($CDCl_3$) 13.9 (q), 22 4 (t), 28.0 (q, 2 C), 30.9 (t), 31.4 (t), 36.5 (t), 55.6 (q, 2 C), 66.7 (s), 79.2 (t), 103.7 (d, 2 C), 114.9 (s), 123.9 (s), 128.4 (s), 129.5 (d), 130.8 (d), 135.0 (d), 136.3 (s), 144.3 (s), 156.8 (s, 2 C), and 163.0 p.p.m. (s).

9-*Bromo*-1-*hydroxy*-3-*pentyl*-6H-*dibenzo*[b,d]*pyran*-6-*one* (4).—Aqueous 57% HI (100 ml) was added dropwise, with cooling to 20 °C, to a stirred solution of the dihydro-oxazole (3) (10.6 g) in acetic anhydride (100 ml). The red-brown mixture was stirred and refluxed for 5 h, cooled, diluted with water (400 ml), and extracted with ethyl acetate (2 × 200 ml). Work-up yielded orange crystals (9.0 g) which were purified by crystallization from ethanol to give the product as white crystals (7.0 g, 84%), m.p. 220—221 °C; δ_H [$(CD_3)_2SO$] 0.85 (3 H, t, ω-Me), 1.1—1.8 (6 H, m, 3 × CH_2), 2.6 (2 H, t, benzylic CH_2), 6.70 (1 H, s, ArH), 6.71 (1 H, s, ArH), 7.7 (1 H, dd, *J* 9 and 1.5 Hz, ArH), 8.1 (1 H, d, *J* 9 Hz, ArH), and 9.25 (1 H, d, *J* 1.5 Hz, ArH); δ_C [$(CD_3)_2SO$] 13.9 (q), 22.0 (t), 29.8 (t), 30.8 (t), 34.8 (t), 102.8 (s), 107.6 (d), 111.9 (d), 118.8 (s), 129.0 (d), 129.3 (s), 130 3 (d), 131.3 (d), 136.3 (s), 146.2 (s), 152.3 (s), 156.3 (s), and 160.0 p.p.m. (s).

5′-*Bromo*-2′-(1-*hydroxy*-1-*methylethyl*)-4-*pentylbiphenyl*-2,6-*diol* (5).—To a stirred solution of the pyrone (4) (0.36 g) in THF (10 ml) was added dropwise a solution of methylmagnesium iodide prepared from methyl iodide (0.65 ml) and magnesium (0.24 g) in diethyl ether (5 ml). The mixture was stirred and refluxed for 70 min, then cooled and poured onto saturated aqueous ammonium chloride (15 ml). The mixture was extracted with diethyl ether (2 × 20 ml); the extracts were washed with water, dried, and concentrated under reduced pressure at room temperature to yield the biphenyl (5) as a viscous oil that slowly crystallized (0.37 g, 94%); δ_H ($CDCl_3$) 0.9 (3 H, t, ω-Me), 1.2—1.8 (6 H, m, 3 × CH_2), 1.45 (6 H, s, 2 × Me), 2.5 (2 H, t, *J* 7.5 Hz, benzylic CH_2), 6.35 (2 H, s, 2 × ArH), 7.3 (1 H, s, ArH), and 7.5 (2 H, s, 2 × ArH); δ_C ($CDCl_3$) 14.0 (q), 22.5 (t), 30.4 (q, 2 C), 30.6 (t), 31.5 (t), 35.7 (t), 73.4 (s), 108.6 (d, 2 C), 114.6 (s), 121.9 (s), 128.4 (d), 131.8 (d), 132.2 (s), 136.5 (d), 145.5 (s), 146.9 (s), and 153.0 p.p.m. (s, 2 C). The unstable product was used directly in the next step.

9-*Bromo*-6,6-*dimethyl*-3-*pentyl*-6H-*dibenzo*[b,d]*pyran*-1-*ol* (6).—Trifluoroacetic acid (0.1 ml) was added to a stirred solution of the alcohol (5) (0.5 g) in chloroform (7 ml). After 30 min at room temperature the red solution was washed with water. The pale yellow organic layer was evaporated to dryness to give the pyranol (6) (0.477 g, 100%); m.p. 95—96 °C (cyclohexane); b.p. 200—205 °C/0.2 mmHg; δ_H ($CDCl_3$) 0.9 (3 H, t, ω-Me), 1.1—1.8 (6 H, m, 3 × CH_2), 1.6 (6 H, s, 2 × Me), 2.5 (2 H, t, *J* 7.5 Hz, benzylic CH_2), 6.2 (1 H, finely split, ArH), 6.4 (1 H, finely split, ArH), 7.05 (1 H, d, *J* 8 Hz, ArH), 7.35 (1 H, dd, *J* 8 and 2 Hz, ArH), and 8.55 (1 H, d, *J* 2 Hz, ArH); δ_C ($CDCl_3$) 14.0 (q), 22.5 (t), 26.9 (q, 2 C), 30.4 (t), 31.4 (t), 35.6 (t), 77.1 (s), 107.5 (s), 109.9 (d), 110.3 (d), 121.4 (s), 124.1 (d), 129.1 (d), 129.4 (d), 130.0 (s), 138.0 (s), 145.4 (s), 153.8 (s), and 154.4 p.p.m. (s).

1-*Hydroxy*-6,6-*dimethyl*-3-*pentyl*-6H-*dibenzo*[b,d]*pyran*-9-*carboxylic Acid* (7).—To a stirred, cooled (−78 °C) solution of 1.5M-butyl-lithium in hexane (6.4 ml) was added slowly a solution of bromocannabinol (6) (1.6 g) in diethyl ether (20 ml). The temperature was allowed to rise to 5 °C during *ca.* 4 h. The reaction mixture was carbonated by slowly pouring it onto a slurry of powdered solid carbon dioxide in diethyl ether with stirring. The mixture was allowed to stand until it reached room temperature, after which it was extracted with 10% aqueous KOH solution (100 ml). The basic extract was acidified (HCl) and extracted with diethyl ether (2 × 80 ml). Usual work-up of the ethereal extracts afforded the crystalline acid (7) (70%), m.p. 156—157 °C (chloroform); δ_H ($CDCl_3$) 0.85 (3 H, t, ω-Me), 1.1—1.8 (6 H, m, 3 × CH_2), 1.6 (6 H, s, 2 × Me), 2.45 (2 H, t, *J* 7.5 Hz, benzylic CH_2), 6.3 (1 H, s, ArH), 6.4 (1 H, s, ArH), 7.3 (1 H, d, *J* 8 Hz, ArH), 8.0 (1 H, dd, *J* 8 and 1.5 Hz, ArH), and 9.3 (1 H, d, *J* 1.5 Hz, ArH); δ_C ($CDCl_3$) 13.9 (q), 22.4 (t), 26.7 (q, 2 C), 30.3 (t), 31.4 (t), 35.5 (t), 77.3 (s), 107.7 (s), 110.0 (d), 110.4 (d), 122.8 (d), 128.1 (s), 128.28 (d), 128.30 (s), 128.5 (d), 144.7 (s), 145.3 (s), 153.5 (s), 154.2 (s), and 172.2 p.p.m. (s).

1-*Hydroxy*-9-*hydroxymethyl*-6,6-*dimethyl*-3-*pentyl*-6H-*dibenzo*[b,d]*pyran* (8).—To a stirred mixture of lithium aluminium hydride (0.3 g) and diethyl ether (25 ml), a solution of the acid (7) (0.5 g) in diethyl ether (25 ml) was added dropwise causing gentle reflux. The mixture was refluxed for 1 h more, then cooled and water was added cautiously. After acidification (HCl) the ether layer was washed with water, dried, and concentrated under reduced pressure to yield the crystalline alcohol (8) (0.44 g, 92%), m.p. 167 °C (from ethanol) (lit.,[5] m.p. 163 °C); ^1H n.m.r. data were identical with the published values; [5,6] δ_C [$(CD_3)_2CO$] 13.7 (q), 22.5 (t), 26.9 (q, 2 C), 30.7 (t), 31.6 (t), 35.6 (t), 64.5 (t), 77.0 (s), 108.7 (s), 109.7 (d), 109.9 (d), 122.6 (d), 125.3 (d, 2 C), 128.4 (s), 138.3 (s), 141.3 (s), 144.4 (s), 154.9 (s), and 155.4 p.p.m. (s).

1-*Hydroxy*-6,6-*dimethyl*-3-*pentyl*-6H-*dibenzo*[b,d]*pyran*-9-*carbaldehyde* (9).—Jones reagent [14] was prepared by dissolving chromium trioxide (1 g) in water (8 ml), adding concentrated sulphuric acid (0.84 ml) and diluting the solution with water to a volume of 10 ml. A portion (1.8 ml) of this was then added

dropwise to a stirred solution of the alcohol (8) (0.6 g) in acetone (10 ml) with cooling (20 °C). After completion of the addition, the mixture was diluted with diethyl ether (100 ml), washed with saturated aqueous $NaHCO_3$ (2 × 10 ml) and water, dried and evaporated to dryness at room temperature to give the crystalline aldehyde (9) (0.53 g, 89%), m.p. 104—105 °C (from cyclohexane); ^1H n.m.r. data were identical with the published values; [6] δ_C ($CDCl_3$) 13.8 (q), 22.4 (t), 26.7 (q, 2 C), 30.2 (t), 31.3 (t), 35.5 (t), 77.2 (s), 107.3 (s), 110.0 (d), 110.2 (d), 123.2 (d), 128.0 (d), 128.4 (d), 129.1 (s), 135.3 (d, C-9), 145.6 (s, 2 C), 154.0 (s), 154.2 (s), and 193.3 p.p.m. (d).

2-(2,5-*Dimethoxy*-4-*methylphenyl*)-4,4-*dimethyl*-4,5-*dihydro-oxazole* (11).—This compound was prepared from the known [10] acid (10), by the same method as for the dihydro-oxazole (2) from the acid (1), in 75% overall yield, m.p. 86—87 °C (cyclohexane); δ_H ($CDCl_3$) 1.4 (6 H, s, 2 × Me), 2.25 (3 H, s, ArMe), 3.85 (6 H, s, 2 × OMe), 4.1 (2 H, s, CH_2), 6.8 (1 H, s, ArH), and 7.2 (1 H, s, ArH); δ_C ($CDCl_3$) 16.3 (q), 28.1 (q, 2 C), 55.6 (q), 56.8 (q), 67.0 (s), 78.6 (t), 112.3 (d), 115.0 (s), 115.5 (d), 130.8 (s), 151.2 (s), 152.1 (s), and 161.1 p.p.m. (s).

2-[2-(2,6-*Dimethoxy*-4-*pentylphenyl*)-5-*methoxy*-4-*methylphenyl*]-4,4-*dimethyl*-4,5-*dihydro-oxazole* (12)—The Grignard reagent, prepared from 2-bromo-1,3-dimethoxy-5-pentylbenzene [8] (11.5 g) and magnesium (1.2 g) in THF (30 ml) with reflux for 1 h, was added to a solution of the dihydro-oxazole (11) (5 g) in THF (35 ml). The mixture was stirred and refluxed for 22 h and worked up as for compound (3) to give the viscous dihydro-oxazole (12) (75%); δ_H ($CDCl_3$) 0.9 (3 H, t, ω-Me), 1.2 (6 H, s, 2 × Me), 1.2—1.85 (6 H, m, 3 × CH_2), 2.2 (3 H, s, ArMe), 2.6 (2 H, t, *J* 7.5 Hz, benzylic CH_2), 3.7 (8 H, s, 2 × OMe and CH_2O), 3.9 (3 H, s, OMe), 6.4 (2 H, s, 2 × ArH), 7.0 (1 H, s, ArH), and 7.3 (1 H, s, ArH); δ_C ($CDCl_3$) 13.9 (q), 16.1 (q), 22.4 (t), 28.0 (q, 2 C), 30.9 (t), 31.4 (t), 36.4 (t), 55.2 (q), 55.6 (q, 2 C), 66.5 (s), 79.0 (t), 103.8 (d, 2 C), 110.6 (d), 116.4 (s), 126.0 (s), 127.5 (s), 128.5 (s), 134.2 (d), 143.2 (s), 156.1 (s), 157.1 (s, 2 C), and 163.9 p.p.m. (s).

1,8-*Dihydroxy*-9-*methyl*-3-*pentyl*-6H-*dibenzo*[b,d]*pyran*-6-*one* (13).—Aqueous 57% HI (40 ml) was added dropwise with cooling (20 °C) to a stirred solution of the dihydro-oxazole (12) (5 g) in acetic anhydride (40 ml). The mixture was stirred and refluxed for 2 h, cooled, diluted with water (150 ml), and extracted with ethyl acetate (200 and 100 ml). Work-up yielded red crystals which were purified by crystallization from ethanol to give the product (70%) as pale yellow crystals, m.p. 187—188 °C; δ_H [$(CD_3)_2CO$] 0.9 (3 H, t, ω-Me), 1.1—1.8 (6 H, m, 3 × CH_2), 2.4 (3 H, s, Me), 2.6 (2 H, t, *J* 7.5 Hz, benzylic CH_2), 6.7 (1 H, d, *J* 2 Hz, ArH), 6.75 (1 H, d, *J* 2 Hz, ArH), 7.75 (1 H, s, ArH), and 8.95 (1 H, s, ArH); δ_C [$(CD_3)_2SO$] 14.0 (q), 17.1 (q), 22.1 (t), 30.1 (t), 31.0 (t), 34.9 (t), 104.4 (s), 107.6 (d), 111.8 (d), 113.0 (d), 119.1 (s), 126.8 (s), 129.3 (d), 133.3 (s), 143.5 (s), 151.4 (s), 155.1 (s), 155.3 (s), and 160.7 p.p.m. (s).

2′-(1-*Hydroxy*-1-*methylethyl*)-5′-*methyl*-4-*pentylbiphenyl*-2,4′,6-*triol* (14).—To a stirred solution of the lactone (13) (0.6 g) in THF (20 ml) was added dropwise a solution of methylmagnesium iodide prepared from magnesium (0.5 g) and methyl iodide (1.3 ml) in diethyl ether (10 ml). The mixture was stirred and refluxed for 70 min and then worked up as for compound (5) to give the crystalline carbinol (14) (0.63 g, 95%); δ_H ($CDCl_3$) 0.9 (3 H, t, ω-Me), 1.15—1.8 (6 H, m, 3 × CH_2), 1.4 (6 H, s, 2 × Me), 2.1 (3 H, s, ArMe), 2.5 (2 H, t, *J* 7 Hz, benzylic CH_2), 6.4 (2 H, s, 2 × ArH), 6.85 (1 H, s, ArH), and 7.1 (1 H, s, ArH); δ_C ($CDCl_3$) 13.9 (q), 15.0 (q), 22.4 (t), 30.0 (q, 2 C), 30.5 (t), 31.4 (t), 35.6 (t), 73.7 (s), 107.8 (d, 2 C), 114.0 (d), 114.4 (s), 118.8 (s), 124.5 (s), 136.4 (d), 145.0 (s), 147.5 (s), 153.3 (s, 2 C), and 154.5 p.p.m. (s). The unstable product was used directly in the next step.

6,6,9-*Trimethyl*-3-*pentyl*-6H-*dibenzo*[b,d]*pyran*-1,8-*diol* (15)—Trifluoroacetic acid (0.1 ml) was added to a stirred solution of the alcohol (14) (0.5 g) in chloroform (10 ml). After 30 min at room temperature the dark red solution was washed with water. The pale yellow organic layer was evaporated to dryness to give the diol (15) (0.47 g, 100%), m.p. 123 °C (benzene); ^1H n.m.r. data were identical with the published values; [6] δ_C ($CDCl_3$) 13.8 (q), 15.6 (q), 22.3 (t), 26.7 (q, 2 C), 30.3 (t), 31.3 (t), 35.4 (t), 77.0 (s), 108.5 (s), 109.5 (d), 109.9 (d), 110.4 (d), 120.3 (s), 122.4 (s), 128.8 (d), 139.0 (s), 143.3 (s), 152.3 (s), 152.5 (s), and 153.3 p.p.m. (s).

2-(2,3-*Dimethoxy*-4-*methylphenyl*)-4,4-*dimethyl*-4,5-*dihydro-oxazole* (17).—The synthesis of this compound was published previously; [1] δ_H ($CDCl_3$) 1.4 (6 H, s, 2 × Me), 2.25 (3 H, s, ArMe), 3.9 (6 H, s, 2 × OMe), 4.05 (2 H, s, CH_2), 6.9 (1 H, d, *J* 8 Hz, ArH), and 7.4 (1 H, d, *J* 8 Hz, ArH); δ_C ($CDCl_3$) 15.8 (q), 28.0 (q, 2 C), 60.1 (q), 60.9 (q), 67.2 (s), 78.6 (t), 120.9 (s), 125.1 (d), 125.3 (d), 135.4 (s), 151.8 (s), 152.3 (s), and 160.4 p.p.m. (s).

2-[2-(2,6-*Dimethoxy*-4-*pentylphenyl*)-3-*methoxy*-4-*methylphenyl*]-4,4-*dimethyl*-4,5-*dihydro-oxazole* (18).—This compound was described earlier; [1] δ_H ($CDCl_3$) 0.9 (3 H, t, ω-Me), 1.1 (6 H, s, 2 × Me), 1.2—1.85 (6 H, m, 3 × CH_2), 2.3 (3 H, s, ArMe), 2.65 (2 H, t, *J* 7.5 Hz, benzylic CH_2), 3.4 (3 H, s, OMe), 3.65 (2 H, s, CH_2O), 3.7 (6 H, s, 2 × OMe), 6.4 (2 H, s, 2 × ArH), 7.15 (1 H, d, *J* 8 Hz, ArH), and 7.45 (1 H, d, *J* 8 Hz, ArH); δ_C ($CDCl_3$) 13.8, 16.3, 22.3, 27.8 (2 C), 30.9, 31.2, 36.4, 55.6 (2 C), 59.6, 66.5, 78.8, 103.8 (2 C), 112.5, 124.5, 125.0, 128.7, 129.6, 133.1, 143.6, 156.9, 157.8 (2 C), and 163.1 p.p.m.

1,10-*Dihydroxy*-9-*methyl*-3-*pentyl*-6H-*dibenzo*[b,d]*pyran*-6-*one* (19).—The conversion of the dihydro-oxazole (18) into the pyranone (19) was carried out exactly as for the synthesis of the pyranone (13) from the dihydro-oxazole (12), in 80% yield, m.p. 220—221 °C (ethanol); δ_H [$(CD_3)_2SO$] 0.85 (3 H, t, ω-Me), 1.1—1.8 (6 H, m, 3 × CH_2), 2.35 (3 H, s, ArMe), 2.6 (2 H, t, benzylic CH_2), 6.8 (2 H, s, 2 × ArH), 7.45 (1 H, d, *J* 8 Hz, ArH), and 7.8 (1 H, d, *J* 8 Hz, ArH); δ_C [$(CD_3)_2SO$] 13.9 (q), 17.8 (q), 22.0 (t), 29.8 (t), 30.8 (t), 34.4 (t), 104.7 (s), 109.3 (d), 112.4 (d), 120.37 (s), 120.40 (s), 121.3 (d), 130.7 (d), 134.4 (s), 145.1 (s), 151.16 (s), 151.22 (s), 151.28 (s), and 160.5 p.p.m. (s).

6′-(1-*Hydroxy*-1-*methylethyl*)-3′-*methyl*-4-*pentylbiphenyl*-2,2′,6-*triol* (20).—This compound was prepared in 88% yield from the pyranone (19) by the same method as for compound (14) from the lactone (13), described above; δ_H ($CDCl_3$) 0.9 (3 H, t, ω-Me), 1.1—1.8 (6 H, m, 3 × CH_2), 1.45 (6 H, s, 2 × Me), 2.25 (3 H, s, ArMe), 2.55 (2 H, t, *J* 7.5 Hz, benzylic CH_2), 6.5 (2 H, s, 2 × ArH), 7.05 (1 H, d, *J* 8 Hz, ArH), and 7.2 (1 H, d, *J* 8 Hz, ArH); δ_C ($CDCl_3$) 13.9, 16.0, 22.4, 30.3, 30.5 (2 C), 31.4, 35.7, 73.4, 106.8, 108.9 (2 C), 113.0, 117.5, 117.8, 124.3, 131.6, 146.4, 147.0, 153.2, and 154.2 p.p.m. (2 C). The unstable crystalline product was used directly in the next step.

6,6,9-*Trimethyl*-3-*pentyl*-6H-*dibenzo*[b,d]*pyran*-1,10-*diol* (21).—This compound was synthesized, like its isomer (15) described above, from the biphenyl (20) in 100% yield, m.p.

84—85 °C (cyclohexane); δ_H ($CDCl_3$) 0.85 (3 H, t, ω-Me), 1.1—1.75 (6 H, m, 3 × CH_2), 1.5 (6 H, s, 2 × Me), 2.3 (3 H, s, ArMe), 2.5 (2 H, t, *J* 7.5 Hz, benzylic CH_2), 6.4 (1 H, d, *J* 1.5 Hz, ArH), 6.5 (1 H, d, *J* 1.5 Hz, ArH), 6.85 (1 H, d, *J* 8 Hz, ArH), and 7.15 (1 H, d, *J* 8 Hz, ArH); δ_C ($CDCl_3$) 13.9 (q), 16.8 (q), 22.3 (t), 26.4 (q, 2 C), 30.1 (t), 31.3 (t), 35.2 (t), 77.7 (s), 108.8 (s), 110.4 (d), 111.7 (d), 115.2 (d), 115.8 (s), 126.3 (s), 129.7 (d), 140.8 (s), 144.8 (s), 149.4 (s), 149.9 (s), and 154.5 p.p.m. (s).

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