Drugs derived from Cannabinoids. Part 8.[1] The Synthesis of Side-chain Analogues of $\Delta^{6a,10a}$-Tetrahydrocannabinol

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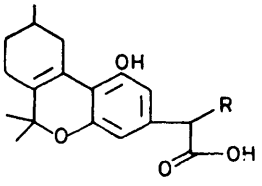
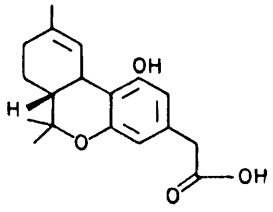
The continuation of studies on the synthesis of side-chain analogues of $\Delta^{6a,10a}$-tetrahydrocannabinol as potential therapeutic agents has led to the syntheses of a possible metabolite 1-hydroxy-6,6,9-trimethyl-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-3-ylacetic acid (1) and 2-(1-hydroxy-6,6,9-trimethyl-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-3-yl)pent-4-ynoic acid (17c). The Pechmann condensation of ethyl 4-methyl-2-oxocyclohexane-1-carboxylate with methyl 3,5-dihydroxyphenylacetate (11), followed by Grignard reaction, was utilized to produce the pyran (1). The key step in the synthesis of the propargylacetic acid (17c) was propargylation of the malonate (15) under phase-transfer catalysis.

THE recent availability of Δ^9-tetrahydrocannabinol (Δ^9-THC) as an anti-nauseant in patients undergoing cancer chemotherapy, has revived interest in the therapeutic potential of cannabinoids. Undoubtedly, the discovery of further useful therapeutic agents will come from synthetic analogues of Δ^9-THC.[2] With this in mind, we have maintained a programme designed to investigate the utility of certain $\Delta^{6a,10a}$-THCs for therapeutic use. Further, based upon structure–activity relationship studies, it is well documented that the 3-alkyl side-chain in THCs plays an important role in the biological activity of these compounds.[2] Our efforts have thus been directed towards a modification of this side-chain within the $\Delta^{6a,10a}$-THC series. This paper describes the first synthesis of 1-hydroxy-6,6,9-trimethyl-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-3-ylacetic acid, (1), and its α-propargyl analogue (17c).

Recently, the synthesis of the Δ^9-analogue, (2), *via* a



(1) R = H
(17c) R = $CH_2C{\equiv}CH$

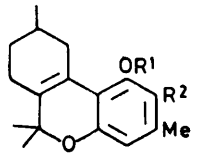


(2)

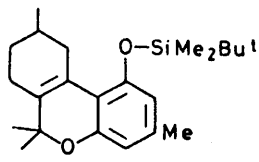
synthetic pathway completely different from the one presented here, has been reported.[3] Compound (2) is important since various carboxylic acid metabolites, including (2), of Δ^9-THC have been identified.[4] It is therefore considered very likely that compound (1) could be a similar metabolite in the $\Delta^{6a,10a}$-THC series. We therefore feel it timely to report our findings.

RESULTS AND DISCUSSION

Our initial investigation centred on substitution of the methyl group of the tetrahydrodibenzopyran (3a) obtained from the Pechmann condensation of ethyl 4-methyl-2-oxocyclohexane-1-carboxylate with orcinol. Treatment of (3a) with *N*-bromosuccinimide yielded the 2-bromo-derivative (3b). The position of bromination was established by n.m.r. spectroscopy. A study[5] of the n.m.r. spectral characteristics of cannabinoids has shown that the proton in the 4-position undergoes a downfield shift in deuteriobenzene. Similarly, for (3b) a downfield shift observed for the singlet in deuteriobenzene (δ 6.43), compared with that in carbon tetrachloride (δ 6.30), indicated a proton in the 4-position, and thus bromination at the 2-position. When (4), sterically hindered for attack at the 2-position, was treated with *N*-bromosuccinimide, none of the desired material was obtained.



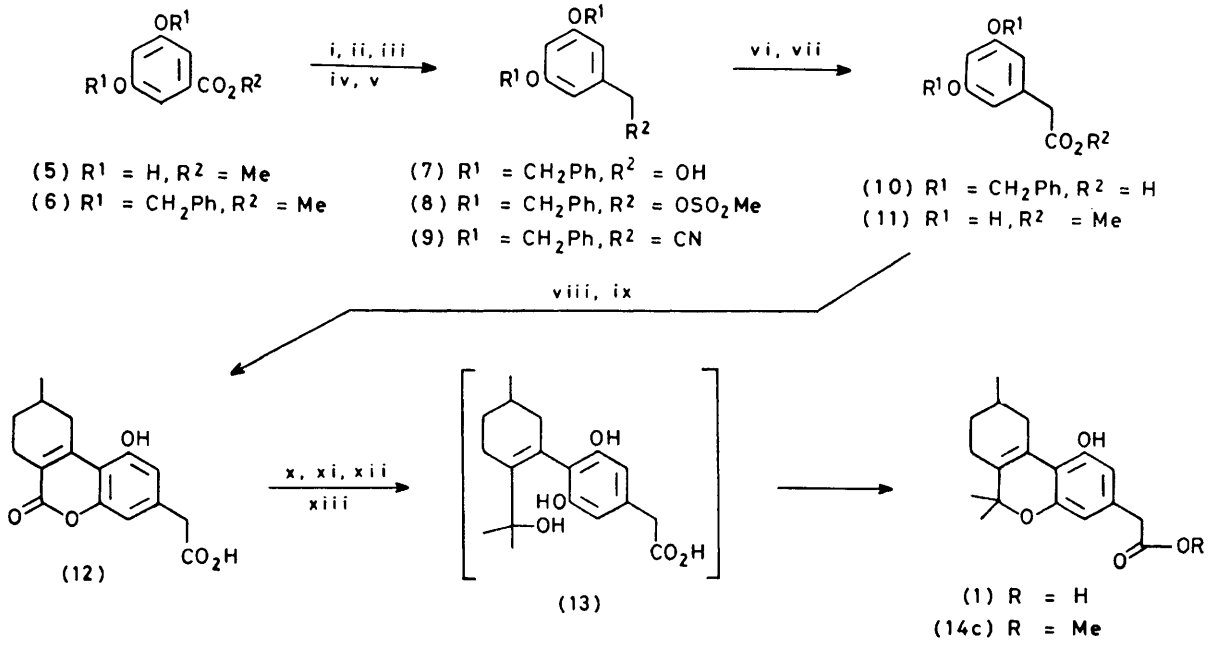
(3) a; $R^1 = R^2 = H$
b; $R^1 = H$, $R^2 = Br$



(4)

Proton abstraction (with either lithium di-isopropylamide or n-butyl-lithium) from the 3-methyl group of either (3a) or (4), and subsequent quenching with carbon dioxide, proved unsuccessful. As a result of these experiments, *ab initio* synthesis of (1) appeared to be most advantageous. The synthetic scheme is presented in Scheme 1.

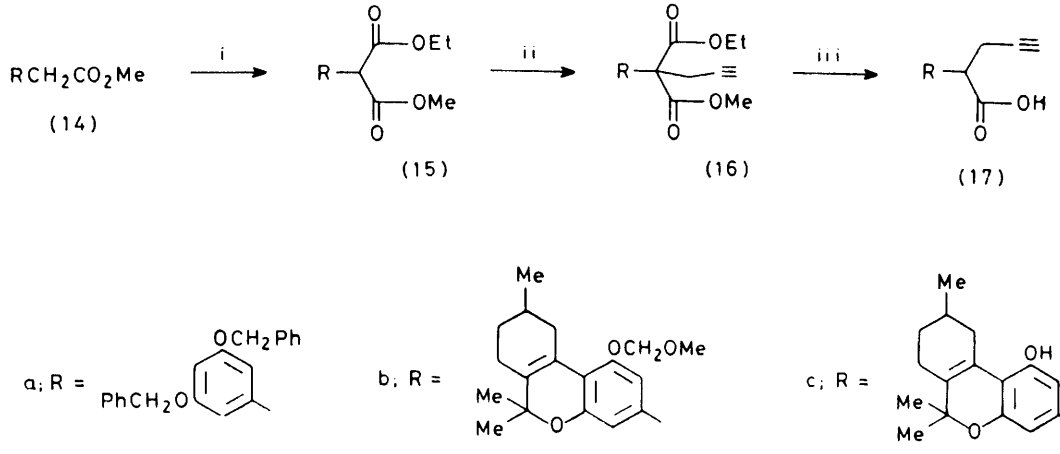
Etherification of the methyl ester (5) was achieved in 95% yield. Reduction of (6) then gave the benzyl alcohol (7) in 97% yield. Mesylation (97%) to yield (8), followed by reaction with sodium cyanide, yielded the nitrile (9) (93%).[6] Hydrolysis of (9) (97%) and subsequent concomitant debenzylation and esterification with methanolic hydrogen chloride, gave the methyl ester (11) (96%). Even with the ester, although a wide variety of condensing agents was investigated, conditions for the Pechmann condensation proved capricious. However, this reaction could be achieved best by prolonged stirring, at 22 °C, of ethyl 4-methyl-2-oxocyclohexane-1-carboxylate with the ester (11) in phosphorus oxychloride. The acid (12), required for subsequent Grignard reaction, was obtained in 88% yield after the ester was hydrolysed. This is, we think, the first example of a resorcinol acetic ester to be used in the Pechmann condensation.[7]



SCHEME 1 *Reagents:* i, HCl, MeOH; ii, $BrCH_2C_6H_5$, K_2CO_3, Me_2CO; ii, $LiAlH_4$, Et_2O, or Red-Al; iv, $MeSO_2Cl$, Et_3N, CH_2Cl_2; v, NaCN, $HOCH_2CH_2OMe$; vi, KOH, EtOH; vii, HCl, MeOH; viii, $POCl_3$, ethyl 4-methyl-2-oxocyclohexane-1-carboxylate; ix, H_2O; x, CH_3MgBr, tetrahydrofuran; xi, NH_4Cl (aq); xii, HCl, MeOH; xiii, KOH, H_2O

The Grignard reaction to produce the pyran (14c) is extremely sensitive to reaction conditions and reagents. Inverse addition of freshly prepared methylmagnesium bromide, at 23 °C, in tetrahydrofuran formed the ring-opened compound (13). Treatment with methanolic hydrogen chloride, yielded the pyran (14c). Hydrolysis of (14c) then gave the desired acid (1).

utilized for this purpose. Selective mono- or di-methylation of (14a) could be achieved with sodium hydride and methyl iodide. However, when these conditions were applied to compound (14b), mixtures of both mono- and di-methylated compounds were obtained. Further, selectivity with regard to mono-propargylation of (14a), with sodium hydride and propargyl bromide, was even



SCHEME 2 *Reagents:* i, $LiNPr^i_2$, tetrahydrofuran, $ClCO_2Et$; ii, $Bu^n_4N^+OH^-$, CH_2Cl_2, NaOH, $BrCH_2C{\equiv}CH$; iii, KOH, H_2O

The conditions required for the substitution of (1), (14b), or (14c) to produce the mono-propargyl compound (17c), proved sufficiently complex to warrant a model study of this reaction sequence. The protected methyl ester (14a), prepared from either (10) * or (11), was less satisfactory. In order to effect mono-substitution, the mixed ester malonate (15a) was prepared (Scheme 2). Compound (14a) was treated with lithium di-isopropylamide and ethyl chloroformate, selected in preference to methyl chloroformate for ease of n.m.r. interpretation, to yield the desired model compound (15a) quantitatively. Propargylation of (15a) was effected by a number of means (NaH–$BrCH_2C{\equiv}CH$; K_2CO_3–$BrCH_2C{\equiv}CH$), however, the highest yield was obtained with phase-transfer

* Compound (10) has also been synthesized in these laboratories in connection with another project. See also F-L. Hsu, K. C. Rice, and A. Brossi, *Helv. Chim. Acta*, 1980, **63**, 2042.

catalysis (100%) using tetra-n-butylammonium hydroxide in a two-phase system of methylene chloride and aqueous sodium hydroxide. The progress of this reaction could be monitored only by high-pressure liquid chromatography since separation by other means (thin-layer or gas chromatography) could not be obtained. The introduction of the propargyl group was confirmed by n.m.r. spectroscopy. The methine proton in (15a) appears as a sharp singlet (δ 4.58), while in (16a) a doublet (δ 3.15, *J* 3 Hz) and a triplet (δ 1.97, *J* 3 Hz) are apparent. Base hydrolysis and decarboxylation of malonate (16a) then provided the desired product (17a) in 62% yield. These results were then extended to the dibenzopyran (14c).

The hydroxy-moiety of compound (14c) had first to be protected. The methoxymethylated pyran (14b) was obtained on treatment of (14c) with chloromethylmethyl ether and potassium carbonate in acetonitrile (96%). The subsequent steps were similar to those described for the model. Lithium di-isopropylamide–ethyl chloroformate gave (15b) (56%) which on propargylation by phase-transfer catalysis ($Bu_4^nN^+OH^-$) afforded (16b) (95%). Compound (16c) was then obtained by refluxing (16b) over Dowex 50W-X4 cation exchange resin (66%). Both (16b) and (16c) proved to be unstable over long periods. Hydrolysis and concomitant mono-decarboxylation then gave the desired compound (17c) in 52% yield.

Pharmacological evaluation of this and other related compounds is currently in progress.

EXPERIMENTAL

N.m.r. spectra were obtained with a Varian T-60 spectrometer with tetramethylsilane as internal standard. Deuteriochloroform was used as solvent unless otherwise specified. I.r. spectra were recorded on a Perkin-Elmer model 700 spectrometer. Anhydrous sodium sulphate was used as drying agent for solutions in organic solvents. Pre-coated plates with silica gel 60F–254 (E. Merck) were used for t.l.c. and these were visualized with iodine. The solvent system used for t.l.c. was 50% (v/v) ethyl acetate–hexane unless otherwise specified.

Methyl 3,5-*Dihydroxybenzoate* (5).—Hydrogen chloride was bubbled through 3,5-dihydroxybenzoic acid (32.7 g, 0.212 mol) in methanol (250 ml) for 0.5 h followed by reflux for 5 h, to give a solid (36 g, 100%), m.p. 165—165.5 °C (from ethyl acetate–hexane); R_F 0.44; δ[$(CD_3)_2CO$] 3.82 (3 H, s, OCH_3), 6.55 (1 H, m, ArH), 6.95 (2 H, d, ArH), and 8.43br (2 H, s, OH).

Methyl 3,5-*Bisbenzyloxybenzoate* (6).—A mixture of benzyl bromide (156 ml, 1.31 mol), methyl 3,5-dihydroxybenzoate (5), (108.4 g, 0.645 mol), and powdered potassium carbonate (393 g, 2.84 mol) was refluxed (4.5 h) in acetone (1 l). The product was obtained as a white *solid* (213.4 g, 95%), m.p. 69—69.5 °C (from ethanol); R_F 0.82; δ 3.90 (3 H, s, OCH_3), 5.07 (4 H, s, CH_2Ar), 6.80 (1 H, t, ArH), and 7.40 (2 H, s, m, ArH) (Found: C, 75.7; H, 5.8. $C_{22}H_{20}O_4$ requires C, 75.85; H, 5.8%).

3,5-*Bisbenzyloxybenzyl Alcohol* (7).—Treatment of methyl 3,5-bisbenzyloxybenzoate (6) (38.3 g, 0.110 mol) with Red-al (52 ml, 0.182 mmol) in refluxing (4 h) toluene (65 ml) gave (7) as a *solid* (34.0 g, 97%), m.p. 80—80.5 °C (from ether; R_F 0.68; δ 2.23 (1 H, t, OH), 4.50 (2 H, d, CH_2OH), 4.95 (4 H, s, OCH_2Ph), 6.55br (3 H, s, ArH), 7.32 (10 H, s, Ph); $\nu_{max.}$ 1 600, 1 160, and 1 030 cm^{-1} (Found: C, 78.7; H, 6.3. $C_{21}H_{20}O_3$ requires C, 78.8; H, 6.3%).

3,5-*Bisbenzyloxybenzyl Methanesulphonate* (8).—This was prepared from the bisbenzyloxy alcohol (7) (17.75 g, 55.40 mmol), triethylamine (10.0 ml, 71.88 mmol), and methanesulphonyl chloride (5.0 ml, 65 mmol) in methylene chloride at 0 °C (1.75 h). The product (8) was obtained as a white *solid* (8) (21.21 g, 97%), R_F 0.58; δ 2.77 (3 H, s, CH_3), 4.97 (4 H, s, OCH_2Ph), 5.05 (2 H, s, $CH_2OSO_2CH_3$), 6.57 (3 H, s, ArH), and 7.30 (10 H, s, ArH).

3,5-*Bisbenzyloxyphenylacetonitrile* (9).—A mixture of the methanesulphonate (8) (15.75 g, 39.57 mmol) and sodium cyanide (2.9 g, 59 mmol) in 2-methoxyethanol (100 ml) was stirred at 24 °C for 17 h. Ether (250 ml) was added and the white precipitate was filtered off. The filtrate was washed, dried, and evaporated *in vacuo* to leave a *solid* (12.1 g, 93%), m.p. 85.0—85.5 °C (from carbon tetrachloride); R_F 0.73; $\nu_{max.}$ 2 280 (w), 1 600, 1 460, 1 170, and 1 150 cm^{-1}; δ 3.58 (2 H, s, CH_2CN), 5.02 (4 H, s, CH_2Ph), 6.57 (3 H, s, ArH), and 7.40 (10 H, s, ArH) (Found: C, 80.2; H, 5.9; N, 4.25. $C_{22}H_{19}NO_2$ requires C, 80.2; H, 5.8; N, 4.25%).

3,5-*Bisbenzyloxyphenylacetic Acid* (10).—The nitrile (9) (13.60 g, 41.28 mmol), ethanol (140 ml), and potassium hydroxide (25.2 g) were stirred under reflux for 18 h. After work-up an orange *solid* (13.93 g, 97%) was obtained, m.p. 113—114 °C (from carbon tetrachloride); R_F (10% MeOH–$CHCl_3$) 0.42; δ 3.53 (2 H, s, CH_2CO_2H), 4.97 (4 H, s, CH_2Ph), 6.48 (3 H, s, ArH), and 7.28 (10 H, s, ArH) (Found: C, 75.7; H, 5.8. $C_{22}H_{20}O_4$ requires C, 75.85; H, 5.8%).

Methyl 3,5-*Dihydroxyphenylacetate* (11).—The ester was prepared from the acid (10) (0.354 g, 1.01 mmol) [methanolic hydrogen chloride (20 ml) for 16.5 h]. Recrystallization from chloroform gave the *methyl ester* (11) (0.178 g, 96%), m.p. 106—107 °C; R_F 0.55; δ[$(CD_3)_2CO$] 3.42 (2 H, s, CH_2), 3.58 (3 H, s, OCH_3), and 6.23 (3 H, s, ArH) (Found: C, 59.2; H, 5.6. $C_9H_{10}O_4$ requires C, 59.3; H, 5.5%).

1-*Hydroxy*-9-*methyl*-6-*oxo*-7,8,9,10-*tetrahydro*-6H-*dibenzo*-[b,d]*pyran*-3-*ylacetic Acid* (12).—Ethyl 4-methyl-2-oxocyclohexane-1-carboxylate (7.36 g, 40.4 mmol), methyl 3,5-dihydroxyphenylacetate (11) (4.09 g, 22.2 mmol), and phosphorus oxychloride (47 ml) were stirred at 24 °C for 22 h. Ice (*ca.* 100 ml) was added and the mixture was brought to reflux for 1 h. The suspension was cooled to 24 °C and stirred overnight. The solid obtained was stirred with ether–hexane for 4 h, filtered off, and dried (5.71 g, 88%), m.p. 239.5—241 °C; R_F 0.47; δ($CDCl_3$–CF_3CO_2H), 1.10 (3 H, d, *J* 5 Hz, CH_3), 1.3—3.3 (8 H, m), 3.73br (2 H, s, OH), and 6.76 (2 H, dd, ArH); $\nu_{max.}$ 1 675 snd 1 600 cm^{-1}.

Methyl 1-*Hydroxy*-6,6,9-*trimethyl*-7,8,9,10-*tetrahydro*-6H-*dibenzo*[b,d]*pyran*-3-*ylacetate* (14c).—A solution of methylmagnesium bromide (0.41 mol) in tetrahydrofuran (440 ml) was led, by cannula, at 24 °C, onto a solution of the pyrone (12) (4.16 g, 14.4 mmol) in dry tetrahydrofuran (830 ml), over 30 min. The brick-red reaction mixture was stirred, at room temperature, for 5 h and then quenched by adding it to methanol (500 ml) containing concentrated hydrochloric acid (50 ml). The solution was stirred for 8 h at room temperature. The reaction mixture was diluted with water and extracted with methylene chloride to give a red solid. Purification on a silica gel column, using ethyl acetate–hexane as eluant gave (14c) as an oil (3.18 g, 70%). This could be triturated with hexane and recrystallized from

aqueous ethanol to give analytically pure white crystals (1.0 g, 22%). Additional product was obtained (0.86 g, 19%) after the oil recovered from the filtrate was brought to reflux with methanolic hydrogen chloride; m.p. 139—140 °C; R_F (25% ethyl acetate–hexane) 0.46; $\nu_{max.}$ 1 695 and 1 410 cm^{-1}; δ 0.98 (3 H, d, *J* 6 Hz, CHCH_3), 1.20 (3 H, s, CH_3), 1.40 (3 H, s, CH_4), 1.4—2.6 (7 H, m, aliphatic protons), 3.48 (2 H, s, C$H_2CO_2CH_3$), 3.70 (3 H, s, OCH_3), 5.58br (1 H, s, OH), 6.28 (1 H, d, *J* 2 Hz ArH), and 6.38 (1 H, d, *J* 2 Hz, ArH) (Found: C, 72.0; H, 7.7. $C_{19}H_{24}O_4$ requires C, 72.1; H, 7.6%).

1-*Hydroxy*-6,6,9-*trimethyl*-7,8,9,10-*tetrahydro*-6H-*dibenzo*-[b,d]*pyran*-3-*ylacetic Acid* (1).—The pyran (14c) (0.460 g, 1.455 mmol) was stirred with 5% aqueous potassium hydroxide (50 ml) for 2.5 h. The mixture was acidified with dilute hydrochloric acid, extracted with ethyl acetate, washed with brine, dried, filtered, and evaporated *in vacuo*. The material obtained was chromatographed on silica gel to yield the acid (0.371 g, 84% recovery) as a brown foam which could not be decolourised or crystallized.

Methyl 3,5-*Bisbenzyloxyphenylacetate* (14a).—(*a*) Treatment of 3,5-bisbenzyloxyphenylacetic acid (10) (7.74 g, 22.2 mmol) with methyl iodide (3.0 ml, 48 mmol) and freshly sieved anhydrous potassium carbonate (11 g, 80 mmol) in acetonitrile (300 ml) for 23 h (23 °C) furnished (14a) as a *solid* (6.64 g, 82.5%), m.p. 65.5—66.5 °C (from ether); R_F 0.86; δ 3.40 (2 H, s, CH_2), 3.50 (3 H, s, OCH_3), 4.83 (4 H, s, OCH_2), 6.47 (3 H, s, ArH), and 7.22 (10 H, s, ArH) (Found: C, 76.1; H, 6.1. $C_{23}H_{22}O_4$ requires C, 76.2; H, 6.1%).

(*b*) Similarly, treatment of 3,5-dihydroxyphenylacetate (11) (0.323 g, 1.77 mmol) with benzyl bromide (1.5 ml, 12 mmol) and potassium carbonate (1.1 g, 8 mmol) in acetonitrile (21 ml) for 21 h gave an oil which was chromatographed (silica gel; eluant hexane and finally ethyl acetate) to give (14a) in 92% yield (0.59 g).

Ethyl 2-(3,5-*Bisbenzyloxyphenyl*)-2-*methoxycarbonylacetate* (15a).—A solution of lithium di-isopropylamide [made at 0 °C by the addition of n-butyl-lithium (5 ml, 12 mmol) to distilled di-isopropylamine (5 ml, 36 mmol) in dry tetrahydrofuran] was cooled, under nitrogen, to −76 °C. Methyl 3,5-bisbenzyloxyphenyl acetate (14a) (2.07 g, 5.72 mmol) in dry tetrahydrofuran (40 ml) was cooled to 0 °C and led, *via* cannula, under nitrogen, onto the lithium di-isopropylamide solution. The reaction mixture was stirred for 0.5 h at −76 °C.

Ethyl chloroformate (1.1 ml, 11.5 mmol) was then added and stirring was continued for 3 h at −76 °C. The reaction was quenched with saturated aqueous ammonium chloride, warmed to room temperature, and extracted with ether. The extracts were washed with water and 1M-hydrochloric acid and dried. Evaporation of the solvent yielded the *product* (15a) (2.5 g, 100%) which was recrystallized from hexane (1.95 g, 78.6%), m.p. 92.5—93.5 °C; R_F (25% ethyl acetate–hexane) 0.39; $\nu_{max.}$ 1 730 cm^{-1}; δ 1.23 (3 H, t, *J* 7 Hz, CH_2CH_3), 3.75 (3 H, s, OCH_3), 4.22 (2 H, q, *J* 7 Hz, OCH_2CH_3), 4.58 [1 H, s, Ar CH($CO_2R)_2$], 5.05 (4 H, s, $ArOCH_2$), 6.72 (3 H, m, ArH), and 7.42 (10 H, s, ArH) (Found: C, 71.8; H, 6.1. $C_{26}H_{26}O_6$ requires C, 71.9; H, 6.0%).

Ethyl Methyl 3,5-*Bisdibenzyloxyphenyl*(*prop*-2-*ynyl*)*malonate* (16a).—A mixture of the phenyl malonate (15a) (1.24 g, 2.86 mmol) and tetra-n-butylammonium hydroxide (0.28 g, 1.0 mmol) in a two-phase system of methylene chloride (70 ml), water (55 ml), and 5% sodium hydroxide (15 ml), containing propargyl bromide (0.30 ml, 3.98 mmol), was stirred vigorously, under reflux, for 6 h. The mixture was then stirred at room temperature for a further 14 h. High pressure liquid chromatographic analysis (h.p.l.c.) showed the presence of some starting material and thus more propargyl bromide (0.15 ml, 2 mmol) was added and reflux was resumed for a further 5 h. The reaction was complete at this stage and the mixture was extracted with methylene chloride. The extracts were washed with brine, dried, filtered and evaporated *in vacuo* to yield (16a) as an oil, R_F (25% ethyl acetate–hexane) 0.36; $\nu_{max.}$ 1 740, 1 600, and 1 460 cm^{-1}; δ 1.20 (3 H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 1.97 (1 H, t, *J* 3 Hz, C≡CH), 3.15 (2 H, d, *J* 3 Hz, $CH_2C{\equiv}CH$), 3.77 (3 H, s, OCH_3), 4.23 (2 H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.02 (4 H, s, OCH_2Ar), 6.62 (1 H, t, ArH), 6.82 (2 H, d, ArH), and 7.40 (10 H, s, ArH).

2-(3,5-*Bisbenzyloxyphenyl*)*pent*-4-*ynoic Acid* (17a).—The propargyl acetate (16a) (1.35 g, 2.86 mmol) was brought to reflux in 5% potassium hydroxide (50 ml) for 10 h, then stirred at room temperature for a further 7 h. After acidification and extraction with ether, a solid was obtained (0.99 g, 90%) which was crystallized from hexane–ethyl acetate (0.68 g, 62%), m.p. 124.5—125.5 °C; R_F (5% methanol–chloroform) 0.40; $\nu_{max.}$ 1 715 and 1 600 cm^{-1}; δ 1.93 (1 H, t, C≡CH), 2.6—3.0 (2 H, m of 14 resonances, $CH_2C{\equiv}$CH), 3.57 (s, OH), 3.75 (1 H, t, ArCHCH_2), 5.02 (4 H, s, OCH_2Ar), 6.60 (3 H, s, ArH), and 7.37 (10 H, s, ArH).

Methyl 1-*Methoxymethoxy*-6,6,9-*trimethyl*-7,8,9,10-*tetrahydro*-6H-*dibenzo*[b,d]*pyran*-3-*ylacetate* (14b).—The phenolic pyran (14c) (1.98 g, 6.27 mmol) was dissolved in acetonitrile (100 ml) containing freshly sieved potassium carbonate (2.6 g, 19 mmol). Chloromethyl methyl ether (0.3 ml, 3.9 mmol) was added and the mixture was stirred, at room temperature, for 16 h. The suspension was filtered, the precipitate was washed with ether, and the combined organic extracts were washed consecutively with water (2 × 50 ml), 1M NaOH (2 × 50 ml), and brine (2 × 50 ml). The organic extract was then dried, filtered, and evaporated *in vacuo* to leave an oil (14b) (0.307 g, 96%); R_F (1% methanol–chloroform) 0.72; $\nu_{max.}$ 1 740 cm^{-1}; δ 0.98 (3 H, d, *J* 6 Hz, CH_3), 1.20 (3 H, s, CH_3), 1.38 (3 H, s, CH_3), 1.5—2.5(m), 3.47 (5 H, s, C$H_2CO_2CH_3$ and OCH_3), 3.65 (3 H, s, CO_2CH_3), 5.08 (2 H, s, OCH_2O), and 6.45 (2 H, dd, ArH).

Ethyl Methyl 1-*Methoxymethoxy*-6,6,9-*trimethyl*-7,8,9,10-*tetrahydro*-6H-*dibenzo*[b,d]*pyran*-3-*ylmalonate* (15b).—A solution of lithium di-isopropylamide, formed at 0 °C, from n-butyl-lithium (5.3 ml, 12 mmol) and distilled di-isopropylamine (5.4 ml, 39 mmol) in dry tetrahydrofuran (35 ml), was cooled to −76 °C. The methyl ester (14b) (2.11 g, 5.86 mmol) was dissolved in dry tetrahydrofuran (75 ml), cooled to 0 °C, and led, over 10 min, *via* cannula, onto the lithium di-isopropylamide solution. The yellow solution was stirred at −76 °C, for 1 h.

Ethyl chloroformate (2.0 ml, 21 mmol) was added and stirring was continued for 4 h. The reaction temperature was raised to −30 °C and additional ethyl chloroformate (1.0 ml, 10 mmol) was introduced. After a further 0.5 h, the reaction mixture was warmed to 0 °C and quenched with aqueous ammonium chloride. Ether was added and the organic fraction was washed consecutively with brine, saturated sodium hydrogen carbonate, and brine, and dried. After filtration and evaporation *in vacuo*, a red oil was obtained. This was separated on a silica gel column using a graded eluant (hexane→25% ethyl acetate–hexane) to yield the product, (15b), as a yellow *oil* (1.42 g, 56%), R_F (25% ethyl acetate–hexane) 0.38; $\nu_{max.}$ 1 760 and 1 740 cm^{-1}; δ

0.98 (3 H, d, *J* 6 Hz, CH_3), 1.20 (3 H, s, CH_3), 1.25 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.40 (3 H, s, CH_3) 1.8—2.5 (7 H, m, aliphatic protons), 3.50 (3 H, s, CH_2OCH_3), 3.73 (3 H, s, CO_2CH_3), 4.20 (2 H, q, *J* 7 Hz, CH_2CH_3), 4.50 [1 H, s, $ArCH(CO_2R)_2$], 5.13 (2 H, s, OCH_2OCH_3), and 6.63 (2 H, dd, ArH) (Found: C, 66.5; H, 7.5. $C_{24}H_{32}O_7$ requires C, 66.65; H, 7.45%).

Ethyl Methyl (1-*Methoxymethoxy*-6,6,9-*trimethyl*-7,8,9,10-*tetrahydro*-6H-*dibenzo*[b,d]*pyran*-3-*yl*)*prop*-2-*ynylmalonate* (16b).—A mixture of the malonate (15b) (1.41 g, 3.26 mmol), tetra-n-butylammonium hydroxide (0.30 g, 1.16 mmol), and propargyl bromide (0.75 ml, 9.95 mmol) in a two-phase system of water (44 ml), 1M-sodium hydroxide (16 ml), and methylene chloride (60 ml) was stirred under reflux for 8 h. This was cooled to room temperature and stirred for a further 8 h. The reaction mixture was then extracted with methylene chloride, and the organic extracts were washed with brine and dried. Evaporation *in vacuo* gave (16b) as an *oil* (1.45 g, 94.5%), b.p. 237—239 °C at 0.05 mmHg; R_F (25% ethyl acetate–hexane) 0.45; $\nu_{max.}$ 1 740 cm^{-1}; δ 1.02 (3 H, d, *J* 6 Hz, $ArCH_3$), 1.22 (3 H, s, CH_3), 1.27 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.40 (3 H, s, CH_3), 1.45—2.63 (m, aliphatic protons), 2.03 (t, *J* 3 Hz, $CH_2C{\equiv}CH$), 3.15 (2 H, d, *J* 3 Hz, $CH_2C{\equiv}CH$), 3.50 (3 H, s, CH_2OCH_3), 3.80 (3 H, s, CO_2CH_3), 4.22 (2 H, q, *J* 7 Hz, CH_2CH_3), 5.15 (2 H, s, OCH_2OCH_3), 6.63 (1 H, d, *J* 2 Hz, ArH), and 6.85 (1 H, d, *J* 2 Hz, ArH) (Found: M^+, 470.2315. $C_{27}H_{34}O_7$ requires *M*, 470.230).

Demethoxymethylation of (16b) *to yield* (16c).—The methoxymethyl-protected compound (16b) (1.39 g, 2.96 mmol) was dissolved in methanol (45 ml) and brought to reflux together with Dowex 50W-X4 cation exchange resin (50—100 mesh) (140 mg) for 15 h. After stirring for a further 15 h at room temperature, the suspension was filtered and washed with carbon tetrachloride. The combined organic extracts were evaporated *in vacuo* (1.3 g) and the residue was separated on a silica gel column (25% ethyl acetate–hexane as eluant) to yield (16c) as a *foam* (0.83 g, 66%). The product is unstable in air even at low temperature, as evidenced by t.l.c. In order to obtain satisfactory spectral analyses, a second column was run (yield 0.70 g, 56%), m.p. 41—42 °C; R_F (25% ethyl acetate–hexane) 0.43; $\nu_{max.}$ 1 720 cm^{-1}; δ 0.98 (3 H, d, *J* 7 Hz, CH_3), 1.20 (3 H, s, CH_3), 1.23 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.40 (3 H, s, CH_3), 1.5—2.6 (m, aliphatic protons), 2.01 (1 H, t, *J* 3 Hz, C≡CH), 3.12 (2 H, d, *J* 3 Hz, $CH_2C{\equiv}CH$), 3.77 (3 H, s, OCH_3), 4.25 (2 H, q, *J* 7 Hz, CH_2CH_3), 5.85 (1 H, s, OH), and 6.50 (2 H, s, ArH) (Found: M^+, 426.203. $C_{25}H_{30}O_6$ requires *M*, 426.204).

2-(1-*Hydroxy*-6,6,9-*trimethyl*-7,8,9,10-*tetrahydro*-6H-*dibenzo*[b,d]*pyran*-3-*yl*)*pent*-4-*ynoic Acid* (17c).—The malonate (16c) (0.35 g, 0.82 mmol) was refluxed gently with 5% aqueous potassium hydroxide (80 ml) for 1 h. The mixture was cooled to room temperature and stirred for a further 2 h and then filtered, acidified with 1M-hydrochloric acid, and extracted with ether. The extract was then washed with brine and dried over sodium sulphate, filtered, and evaporated *in vacuo* to leave a brown oil which was purified by column chromatography (silica gel; 50% ethyl acetate–hexane as eluant) to yield (17c) as a *foam* (144 mg, 52%), m.p. 73—78 °C (decomp.) (the product discoloured on prolonged standing); R_F 0.34; δ 1.00 (3 H, d, *J* 6 Hz, CH_3), 1.20 (3 H, s, CH_3), 1.40 (3 H, s, CH_3), 1.48—3.02 (10 H, m, aliphatic and acetylenic protons), 3.63 (1 H, t, *J* 8 Hz, $ArCHRCO_2H$), 6.23 (1 H, d, *J* 2 Hz, ArH), 6.37 (1 H, d, *J* 2 Hz, ArH), and 7.13br (2 H, s, OH) (Found: M^+, 340.167. $C_{21}H_{24}O_4$ requires *M*, 340.167).

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