Synthesis of Cannabinoids Carrying ω-Carboxy Substituents: The Cannabidiols, Cannabinol and Δ^1- and Δ^6-Tetrahydrocannabinols of this Series

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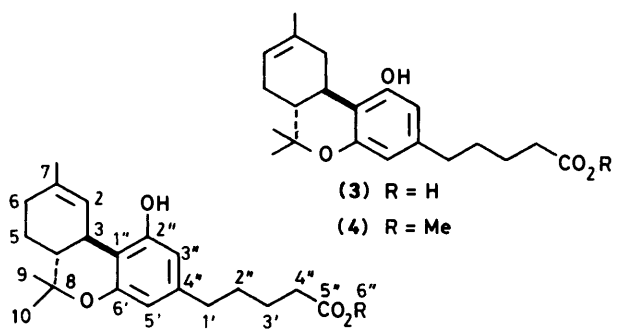
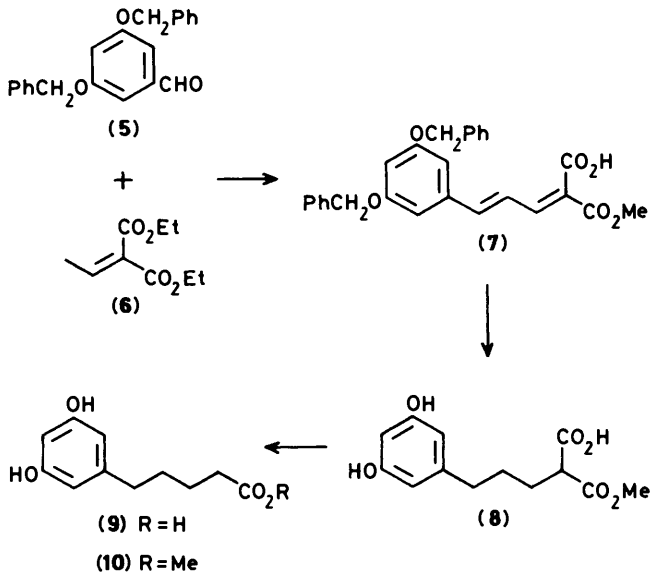
A convenient synthesis of methyl 5-(3,5-dihydroxyphenyl)pentanoate adaptable for isotopic side-chain labelling is reported. Using acid-catalysed terpenylations involving (1*S*,4*R*)-(+)-*trans*-*p*-menthadienol, conditions for making (3*R*,4*R*)-*o*-and *p*-cannabidiols, (3*R*,4*R*)-Δ^1-THC's, (3*R*,4*R*)-Δ^6-THC's and cannabinol in ω-carboxylated or methoxycarbonylated formats are described. Multigram amounts of the thermodynamically labile (3*R*,4*R*)-Δ^1-THC-ω-ester, readily convertible to the ω-acid, were made: the acid is a mammalian and microbial metabolite of Δ^1-THC and is of interest for membrane studies as well as for spin-labelling and radioimmunoassay purposes. A convenient synthesis of (2*E*,4*E*)-5-(3,5-dihydroxyphenyl)penta-2,4-dienoate allows its conversion into the crystalline Δ^6-THC analogue having a conjugated dienoic ester side chain. Chromatographic information is tabulated for esters of the ω-carboxy cannabinoid series along with data for esters of the naturally occurring Ar-carboxylated cannabinoid series made synthetically in earlier work.

4″- or ω-Carboxylated cannabinoids [*e.g.* (**1**)] are of interest in connection with spin-labelling and radio-immunoassay work.[1] Their enhanced polarities also make them of interest for study of the separation of peripheral and central nervous effects through modification of distribution across membrane barriers. Furthermore, enzymic terminal oxidation of the aromatic side-chain is one of the processes involved in both mammalian[2] and microbial[3] metabolism of the cannabinoids. Along with others,[4–6] our preliminary communication[7] reported the synthesis of the Δ^6-acid (**3**) but apart from our own work there appears to be no synthesis to date of the more important, but thermodynamically more labile, Δ^1-acid (**1**) corresponding to natural Δ^1-tetrahydrocannabinol (Δ^1-THC). We have therefore sought syntheses of (**1**) and (**3**) which permit their preparation in multigram quantities for adequate biological work, and which also permit easy side-chain deuteriation or tritiation through olefinic hydrogenation.

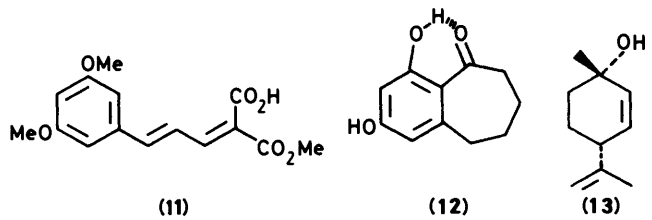


3,5-Dibenzyloxybenzaldehyde (**5**) was condensed with diethyl ethylidenemalonate (**6**) in the presence of methanolic benzyltrimethylammonium hydroxide (Triton B)[8] to give, with accompanying ester exchange, the half methyl ester (**7**)[7] in 68% yield (Scheme). The olefinic side-chain was reduced over palladium on charcoal catalyst (deuterium or tritium can be introduced in this step), with concomitant debenzylation giving the half-ester (**8**) (95%). The latter could then be decarboxylated



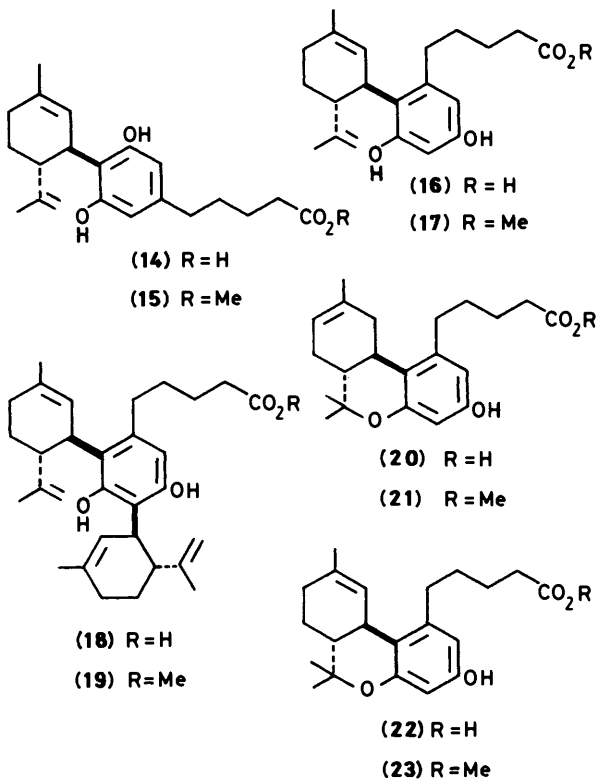
Scheme. Route to methyl 5-(3,5-dihydroxyphenyl)pentanoate

by refluxing in pyridine to produce (94%) the methyl 5-(3′,5′-dihydroxyphenyl)pentanoate (**10**) required for terpenylation work. Overall, the yield from (**5**) was 61%. Use of the dimethoxy unsaturated half-ester (**11**) proved less satisfactory since although hydrogenation proceeded smoothly, demethylation with hydriodic acid gave low yields of (**9**) along with some 7,9-dihydroxybenzsuberone (**12**). Boron tribromide also induced cyclisation: thiolate anion methods may prove satisfactory but



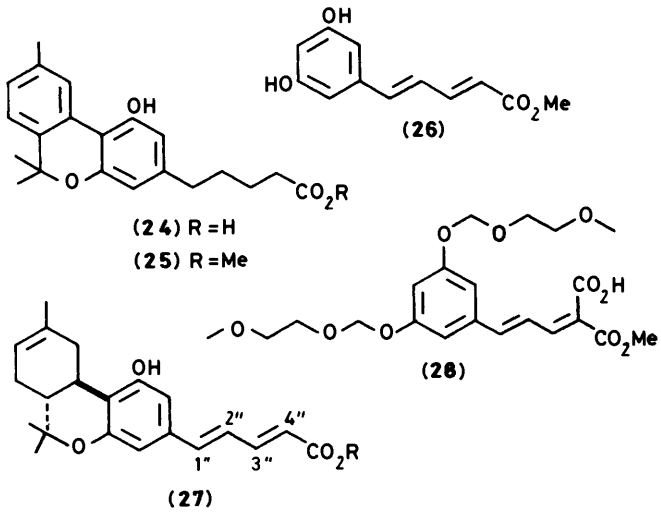
they have not been pursued in view of the success of the benzyloxy protection.

Condensed with (1*S*,4*R*)-(+)-*trans*-*p*-menthadienol[9] (PMD) (**13**) (0.36 mol) in the presence of toluene-*p*-sulphonic acid (PTSA) (0.06 mol) in benzene–ether for 2.5 h at 24 °C, the ester (**10**) (0.31 mol) gave the two ω-methoxycarbonylcannabidiol analogues (**17**) and (**15**), readily separated by preparative layer chromatography (p.l.c.) in 34 and 27% yields respectively: small amounts of diterpenylated material (**19**) were also formed. The (3*R*,4*R*)-cannabidiol analogue (**15**) of the 'natural' *p*-cannabinoid series had $[\alpha]_D^{25}(CHCl_3)$ −75.5° and that of the *o*-series (**17**) had $[\alpha]_D^{25}(CHCl_3)$ −75.4°. These esters could be hydrolysed to the corresponding acids (**14**) and (**16**) or, alternatively, the acid (**9**) could be terpenylated directly giving the acid (**14**) of the 'natural' *p*-series, $[\alpha]_D^{23}(CHCl_3)$ −58.2° in 27% yield after separation from the product (**16**) of *o*-orientation.



Increasing the stringency of the acid conditions allowed isolation of the (3*R*,4*R*)-Δ⁶-THC-ester relative (**4**). Thus PMD (0.10 mol) and the ω-ester (**10**) (0.08 mol) when heated with PTSA (0.028 mol) in benzene for 3 h at 60—70 °C gave (**4**) along with minor amounts of (**21**). The *p*-isomer in the natural series (**4**) was isolated in 35% yield, $[\alpha]_D^{23}(CHCl_3)$ −156°.

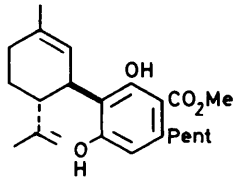
Conditions for the formation and separation of the Δ¹-THC analogues (**2**) and (**23**) proved critical and exacting[10,11] and considerable experimentation was carried out. The following procedure is typical. The ester (**10**) was stirred in dichloromethane with PMD and PTSA at 19 °C for 6 h. The reaction was followed by t.l.c. which showed that at the end of the period, it had proceeded mainly to the cannabidiol stage. Further PTSA was then added and the mixture heated to 40 °C (2 h), the reaction being monitored and stopped whilst cannabidiol still remained. Using large-plate t.l.c., ω-methoxycarbonylated Δ¹-THC (**2**) (10%) could be isolated as an almost pure band. The adjacent mixed band (22%) contained (**4**) and (**15**) as well as (**2**) and by using h.p.l.c. [C_{18} reversed phase] a further 5% of (**2**) could be obtained. The (3*R*,4*R*)-Δ¹-THC analogue (**2**) had $[\alpha]_D^{25}(CDCl_3)$ −125° and could be hydrolysed to the corresponding acid (**1**) $[\alpha]_D^{25}(CHCl_3)$ −97.8°. Only traces of the *o*-series (**23**) were encountered. As described in the Experimental section, large-scale work using 12.35 g of methyl 5-(3,5-dihydroxyphenyl)pentanoate (**10**) provided the (3*R*,4*R*)-(−)-Δ¹-THC ω-ester (**2**) 2.78 g (14.1%) of 98% purity, together with the (3*R*,4*R*)-(−)-Δ⁶-THC ω-ester (**4**) 3.81 g (19.3%) of 98% purity, along with less pure material from which further useful cannabinoid ω-esters could be extracted or used for other purposes. Part, for example, was diverted to make the cannabinol ω-ester (**25**) and its crystalline acid (**24**) *via* sulphur-induced dehydrogenation.



Using similar terpenylation methods and the diene ester (**26**), crystalline (3*R*,4*R*)-Δ⁶-THC ω-ester (**27**) having a conjugated diene side chain has also been prepared in the present work. Attempts to debenzylate (**7**) under acid conditions were unsuccessful, but ethylidene malonate condensation with the methoxyethoxymethyl (MEM) protected analogue of (**5**) gave compound (**28**) which was decarboxylated by heating in pyridine and then deprotected by treatment with methanolic hydrochloric acid to give crystalline (**26**). Data for the synthetic ω-methoxycarbonylated cannabinoids are collected in Table 1 and are compared with synthetic Ar-methoxycarboxylated cannabinoids (**29**)—(**35**) prepared in our earlier work.[12] Similar data are given for the acids in Table 2. Spectral measurements (u.v., ^{13}C n.m.r. and ^{1}H n.m.r.) are collected in Tables 3—5. Whilst the ω-carboxylated series are metabolites of natural cannabinoids, the Ar-carboxylic acids are found as the major natural cannabinoids of fresh *Cannabis sativa* plants though they decarboxylate rather readily on handling.[12] Cannabinols are artefacts resulting from dehydrogenation on ageing or heating of the natural materials.[13]

Experimental

(2E,4E)-*Methyl 2-Carboxy*-5-(3,5-*dibenzyloxyphenyl*)*penta*-2,4-*dienoate* (**7**).—3,5-Dibenzyloxybenzaldehyde (3.18 g, 10 mmol) and diethyl ethylidenemalonate (2.05 g, 11 mmol) in methanol (40 ml) were stirred at 20 °C in the presence of Triton B (40% in methanol, 14 ml) for 48 h. After addition of ice, the mixture was neutralised with dilute hydrochloric acid and stirred (2 h). The yellow product was filtered off and crystallised from ethanol to give the *half-methyl ester* (**7**) (3.02 g, 68%), m.p. 180—181 °C (Found: C, 72.65; H, 5.5%; M^+, 444.1597 $C_{27}H_{24}O_6$ requires C, 72.95; H, 5.4%; *M*, 444.1573); $\nu_{max.}$(KBr) 1 720 (conj. ester), 1 680 (conj. acid), and 1 595 cm^{-1}; $\lambda_{max.}$-



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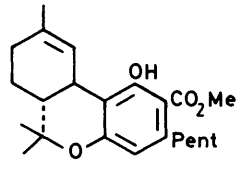

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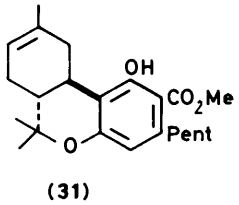

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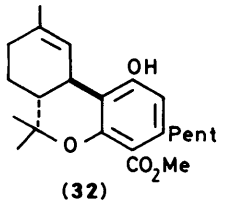

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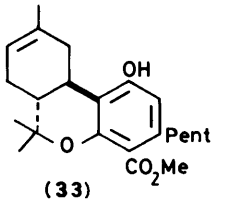

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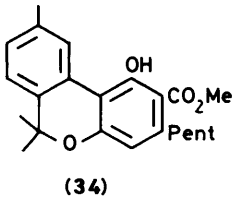

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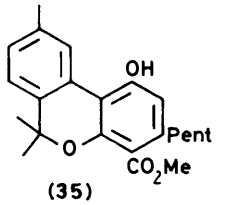

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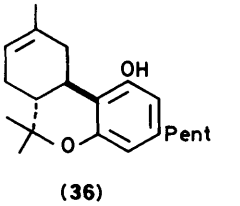

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(EtOH) 211 (ε 42 700), 248 (94 600), and 329 nm (25 200); $\delta_H(CDCl_3)$ 3.9 (3 H, s, CO_2Me), 5.16 (4 H, s, OCH_2Ph), 6.66 (1 H, *J* 2 Hz, *p*-ArH), 6.86 (2 H, d, *J* 2 Hz, *o*-ArH), and 7.2—7.8 (13 H, contains 10 Ar*H* and olefinicH).

Methyl 5-(3,5-*Dihydroxyphenyl*)*pentanoate* (**10**).—The above half ester (**7**) (3.02 g, 6.8 mmol) was shaken in ethyl acetate (120 ml) and glacial acetic acid (120 ml) with hydrogen over 5% palladium on carbon catalyst (300 mg); the theoretical quantity of hydrogen was absorbed. Work-up gave methyl 2-carboxy-5-(3,5-dihydroxyphenyl)pentanoate (1.73 g, 95%), an oil, *m/z* M^+, 268.0974 ($C_{13}H_{16}O_6$ requires *M*, 268.0947); $\nu_{max.}$(film) 1 720 (ester) and 1 705 cm^{-1} (acid). The latter (1.73 g, 6.5 mmol) was refluxed in pyridine (25 ml) (24 h). Work-up gave, after chromatography on silica eluting with ethyl acetate, the saturated ester (**10**) (1.35 g, 94%), m.p. 67—68 °C (from ethyl acetate–carbon tetrachloride) (lit.,[6] m.p. 63—68 °C); *m/z* 224; $\nu_{max.}$(film) 1 750 cm^{-1} (ester); $\delta_H(CDCl_3)$ 1.38—1.72 (4 H, m, 3- and 4-CH_2) 2.1—2.5 (4 H, m, 2- and 5-CH_2), 3.68 (3 H, s, CO_2Me), 6.23 (3 H, s, 3 × ArH), and 6.5—6.9 (2 H, br s., 2 OH exchangeable with D_2O).

HI-*Demethylation of Methyl* 2-*Carboxy*-5-(3-,5-*dimethoxyphenyl*)*pentanoate*.—The title ester (3.5 g, 12 mmol), made by hydrogenation of the diene half-ester, itself made from Triton-B-catalysed ethylidenemalonate condensation, was refluxed with hydriodic acid (distilled from red phosphorus; 35 ml) and red phosphorus (3.5 g) for 20 h. Work-up gave 5-(3,5-dihydroxyphenyl)pentanoic acid (**9**) (420 mg, 17%), m.p. 110—113 °C, *m/z* 210.0880 ($C_{11}H_{14}O_4$ requires *M*, 210.0892) and 7,9-dihydroxybenzsuberone (**12**) (198 mg, 9%), m.p. 93—95 °C.

(3R,4R)-ω-*Methoxycarbonyl*-p-*cannabidiol* (**15**), -o-*cannabidiol* (**17**) *and Diterpenylated* (**19**) *Analogues*.—Methyl 5-(3,5-dihydroxyphenyl)pentanoate ('olivetol ω-methyl ester') (**10**) (69 mg, 0.31 mmol) in dry benzene (1 ml) and ether (0.5 ml) was stirred with (1*S*,4*R*)-(+)-*trans*-*p*-menthadienol (60 μl, 0.36 mmol) and toluene-*p*-sulphonic acid (11.8 mg, 0.06 mmol) for 2.5

Table 1. Chromatographic data for synthesized cannabinoids having carboxymethyl addenda

Compound		Fast Blue salt-B[a] colour	R_F for t.l.c. systems: CH_2Cl_2 plus[b] (silica)	Ether–hexane (2:1) (silica)	Korte type[c] (silica)	C_{18} Reversed phase[d]	R_t (min) for g.l.c. systems: OV225[e]	OV17[f]
p-CBD-C_5-ω-CO_2Me[g]	(**15**)	Orange	0.28	0.69	0.10	0.34	8.8	9.0
o-CBD-C_5-ω-CO_2Me	(**17**)	Blue–purple	0.05	0.43	0.08	0.29	10.4	10.3
Disubs-CBD-C_5-ω-CO_2Me	(**19**)	Pink–orange	0.60	0.81	0.76	0.03	—	63.2
Δ^1-THC-C_5-ω-CO_2Me	(**2**)	Crimson	0.21	0.68	0.42	0.16	21.4	17.7
Δ^6-THC-C_5-ω-CO_2Me	(**4**)	Crimson	0.21	0.70	0.47	0.14	19.0	15.9
CBN-C_5-ω-CO_2Me	(**25**)	Purple	0.26	0.62	0.24	0.23	34.0	21.6
p-CBD-C_5-Ar-CO_2Me	(**29**)	Orange	0.97	0.93	0.84	0.03	4.9	6.3
Δ^1-THC-C_5-Ar-CO_2Me-A	(**30**)	Deep red	0.95	0.97	0.94	0.01	13.8	12.2
Δ^1-THC-C_5-Ar-CO_2Me-B	(**32**)	Purple–red	0.46	0.79	0.58	0.15	15.2	—
Δ^6-THC-C_5-Ar-CO_2Me-A	(**31**)	Deep red	0.95	0.95	0.94	0.03	12.6	11.9
Δ^6-THC-C_5-Ar-CO_2Me-B	(**33**)	Orange–red	0.45	0.82	0.60	0.16	13.5	11.2
CBN-C_5-Ar-CO_2Me-A	(**34**)	Purple	0.95	0.95	0.95	0.02	19.4	16.4
CBN-C_5-Ar-CO_2Me-B	(**35**)	Brown–purple	0.48	0.79	0.45	0.19	22.4	16.1
Δ^6-THC-C_5 (standard)	(**36**)	Crimson	0.83	0.92	0.75	0.05	4.0	5.0

[a] Zinc double salt of bis-diazotized *o*-dianisidine. [b] Solvent: CH_2Cl_2–(hexane–MeOH, 95 : 5) (97:3). [c] Nanoplates (5 × 5 cm) impregnated with dimethylformamide–CCl_4 (2:3), dried 1 h at 20 °C and then run using cyclohexane–ether (3:1) as eluant. [d] Reversed-phase C_{18}-h.p.l.c. plates (5 × 20 cm) run in MeOH–H_2O (4:1). [e] SCOT column 50 ft × 0.02 in i.d. at 220 °C with injection port and detector at 250 °C, N_2 flow 7 ml/min. Samples were silylated with BSTFA + 1% TMCS by heating for 20 min. at 85 °C. [f] SCOT column 50 ft × 0.02 in i.d. at 240 °C with injection port and detector at 250 °C, N_2 flow 10 ml/min. Samples silylated as above. [g] CBD = cannabidiol, THC = tetrahydrocannabinol, CBN = cannabinol, C_5 = the number of carbons in the aromatic side chain and ω = CO_2Me indicates that the terminus of this chain is oxidised and esterified. Ar-CO_2Me indicates carboxymethyl attachment is on the resorcinol unit.

Table 2. Chromatographic data for synthesized cannabinoids having carboxylic acid addenda

Compound		R_F for t.l.c. systems: Fast-Blue salt-B[a] colour	Ether–hexane–HCO_2H (2:1:0.02) (silica)	Korte type[a] (silica)	C_{18} Reversed phase[a]	R_t(min) g.l.c. OV17[a]
p-CBD-C_5-ω-CO_2H	(**14**)	Orange	0.32	0.03	0.70	10.4
Δ^1-THC-C_5-ω-CO_2H	(**1**)	Crimson	0.31	0.05	0.68	18.6
Δ^6-THC-C_5-ω-CO_2H	(**3**)	Crimson	0.31	0.05	0.61	17.0
CBN-C_5-ω-CO_2H	(**24**)	Purple	0.27	0.03	0.75	25.2
p-CBD-C_5-Ar-CO_2H	*cf.* (**29**)	Orange	0.68	0.15	0.61	6.5
Δ^1-THC-C_5-Ar-CO_2H-A	*cf.* (**30**)	Red	0.73	0.50	0.52	12.1
Δ^1-THC-C_5-Ar-CO_2H-B	*cf.* (**32**)	Red	0.44	0.05	0.80	
Δ^6-THC-C_5-Ar-CO_2H-A	*cf.* (**31**)	Red	0.72	0.60	0.44	11.9
Δ^6-THC-C_5-Ar-CO_2H-B	*cf.* (**33**)	Red	0.39	0.02	0.77	12.1
CBN-C_5-Ar-CO_2H-A	*cf.* (**34**)	Purple	0.35	0.02	0.64	
Δ^6-THC-C_5 (standard)	(**36**)	Crimson	0.82	0.95	0.06	5.2

[a] For further details see Table 1.

Table 3. U.v. data [$\lambda_{max.}$/nm($\varepsilon_{max.}$) ethanol] for synthesized cannabinoids having ω-carboxy or carboxymethyl addenda

Compound		$\lambda_{max.}$/nm($\varepsilon_{max.}$) in EtOH					
p-CBD-C_5-ω-CO_2Me	(**15**)	208.5 (29 500)	227 i (9 000)	278 i (1 000)	281 (1 100)		
p-CBD-C_5-ω-CO_2H	(**14**)	209 (29 100)	227 i (10 100)	275 i (2 500)	281 (2 400)		
p-CBD-C_5			232 i (14 100)	274 (1 300)	282 (1 300)		
o-CBD-C_5-ω-CO_2Me	(**17**)		227 i (11 000)		282 (2 400)	287 (2 400)	
o-CBD-C_5-ω-CO_2H	(**16**)	206 (35 000)	225 i (9 500)		282.5 (2 400)	285.5 (2 400)	
o-CBD-C_5			221 (8 300)		283—287 (2 000)		
Δ^1-THC-C_5-ω-CO_2Me	(**2**)	210 (30 400)	230 i (9 700)	278.5 (2 000)	283 (2 000)		
Δ^1-THC-C_5-ω-CO_2H	(**1**)		233 i (5 600)	277 i (1 600)	284 (2 200)		
Δ^1-THC-C_5			230 i (10 700)	276 (1 600)	283 (1 600)		
Δ^6-THC-C_5-ω-CO_2Me	(**4**)	209 (27 200)	227 i (7 400)	276 (1 200)	283 (1 200)		
Δ^6-THC-C_5-ω-CO_2H	(**3**)		231 i (10 300)	277 i (1 400)	283 (1 400)		
Δ^6-THC-C_5	(**36**)		230 (11 800)	275 (1 700)	282 (1 700)		
Cannabinol-C_5-ω-CO_2Me	(**25**)		234 i (29 700)		286 (26 800)		301 i (16 800)
Cannabinol-C_5-ω-CO_2H	(**24**)		235 i (22 700)		285 (21 000)		301.5 (11 800)
Cannabinol-C_5			223 (33 900)		285 (16 600)		299 i (11 500)

h at 24 °C. The reaction was quenched by addition of aqueous sodium hydrogen carbonate. After re-acidification (HCl) the products were extracted into ether, washed, dried ($MgSO_4$), and separated by preparative layer chromatography (p.l.c.) on three 20 × 20 cm silica G HF 254 plates eluting with ether–hexane (2:1). Four main bands were collected. Band 1, unchanged 'olivetol ω-methyl ester' (8.7 mg); band 2, ω-*methoxycarbonyl*-o-*cannabidiol* (**17**) (35.8 mg, 34%), an oil, *m/z* 358.2136 ($C_{22}H_{30}O_4$ requires *M*, 358.2144), $[\alpha]_D^{23.5}$ −75.4° (*c*, 0.206, $CHCl_3$); band 3: ω-*methoxycarbonyl*-p-*cannabidiol* (**15**) (27.7 mg, 27%), oil, *m/z* 358.2160 ($C_{22}H_{30}O_4$ requires *M*, 358.2144); $\nu_{max.}$(film) 1 725 cm^{-1} (ester); $[\alpha]_D^{25}$ −75.5° (*c*, 0.194, $CHCl_3$); M^+ of bis-trimethylsilyl derivative 502 (requires *M*, 502); band 4, the *diterpenylated* ω-*methoxycarbonyl compound* (**19**) (7.9 mg), oil, *m/z* 492.3266 ($C_{32}H_{44}O_4$ requires *M*, 492.3239). See Tables for further data.

(3R,4R)-ω-*Carboxy*-p-*cannabidiol* (**14**), -o-*cannabidiol* (**16**), *and Diterpenylated* (**18**) *Analogues*.—Pentanoic acid (**9**) (25.1 mg, 0.12 mmol) in dry benzene (0.75 ml) and ether (0.25 ml) was stirred with (1*S*,4*R*)-(+)-*trans*-*p*-menthadienol (16 μl, 0.10 mmol) and toluene-*p*-sulphonic acid (7.0 mg) at 25 °C for 30 min; the mixture was then warmed to 50 °C for 5 min, when t.l.c. monitoring indicated optimum reaction had occurred. Products were worked up and separated as above except that elution was with ether–hexane–formic acid (1:1:0.02): bands were extracted

Table 4 ^{13}C N.m.r. data for ω-carboxymethylated esters in $CDCl_3$

Carbon no.	Δ^1-THC-C_5-ω-CO_2Me (**2**)	Δ^6-THC-C_5 ω-CO_2Me (**4**)	Δ^6-THC-C_5 (diene)-ω-CO_2Me (**27**)
1	133.1 (s)	134.8 (s)	134.6 (s)
2	124.9 (d)	36.0 (t)	35.8 (t)
3	33.7 (d)	31.7 (d)	32.0 (d)
4	45.8 (d)	45.0 (d)	44.8 (d)
5	25.0 (t)	27.9 (t)	27.9 (t)
6	31.2 (t)†	119.3 (d)	119.4 (d)
7	23.3 (q)	23.5 (q)	23.4 (q)
8	77.2 (s)	76.7 (s)	77.3 (s)
9	19.2 (q)	18.5 (q)	18.5 (q)
10	27.5 (q)	27.6 (q)	27.5 (q)
1′	109.4 (s)	110.9 (s)	115.0 (s)
2′	155.0 (s)*	155.4 (s)*	155.5 (s)
3′	109.4 (d)	109.6 (d)	109.3 (d)
4′	141.5 (s)	141.6 (s)	135.4 (s)
5′	107.7 (d)	107.7 (d)	106.1 (d)
6′	154.6 (s)*	154.6 (s)*	155.4 (s)
1″	35.0 (t)	35.1 (t)	145.0 (d)
2″	30.3 (t)†	30.3 (t)	126.0 (d)
3″	25.0 (t)	24.6 (t)	120.5 (d)
4″	33.9 (t)	34.0 (t)	140.3 (d)
5″	174.8 (s)	174.7 (s)	167.7 (s)
6″	51.6 (q)	51.6 (q)	51.6 (q)

[a] Values * or †, possibly interchanged. [b] The numbering employed is illustrated for the Δ^1-compound in formula (**1**).

with ether–methanol. Band 1, unchanged acid (**9**) (10 mg); band 2, ω-*carboxy*-o-*cannabidiol* (**16**) (9.3 mg, 22%), an oil, *m/z* 344.1972 ($C_{21}H_{28}O_4$ requires *M*, 344.1987), $\nu_{max.}$(film) 1 701 cm^{-1} (acid); band 3, ω-*carboxy*-p-*cannabidiol* (**14**) (10.9 mg, 27%), oil *m/z* 344.1972 ($C_{21}H_{28}O_4$ requires *M*, 344.1987), $\nu_{max.}$(film) 1 705 cm^{-1} (acid), $[\alpha]_D^{23}$ −58.2° (*c* 0.064, $CHCl_3$); band 4, *diterpenylated* ω-*carboxy compound* (**18**) (6.6 mg), glassy solid, *m/z* 478.3074 ($C_{31}H_{42}O_4$ requires *M*, 478.3083).

An identical specimen of ω-carboxy-*p*-cannabidiol (**14**) was made by hydrolysing the methyl ester (**15**) (25 mg) in 10% aqueous potassium hydroxide (2 ml) for 1 h under reflux. M^+ of tris-trimethylsilyl derivative 560 (requires *M*, 560).

(3R,4R)-ω-*Methoxycarbonyl*-Δ^6-*tetrahydrocannabinol* (**4**).—The pentanoate (**10**) (18.0 mg, 0.08 mmol) was heated with (+)-*trans*-*p*-menthadienol (16 μl, 0.10 mmol) in benzene (0.8 ml) containing toluene-*p*-sulphonic acid (4.8 mg, 0.028 mmol) for 3 h at 60—70 °C in a sealed vessel. Work-up as for the methyl ester above gave minor compounds together with the ω-*methoxycarbonyl*-Δ^6-*tetrahydrocannabinol* (**4**) (9.2 mg, 35%), an oil, *m/z* 358.2121 ($C_{22}H_{30}O_4$ requires *M* 358.2144), $\nu_{max.}$(film) 1 725 cm^{-1} (ester), $[\alpha]_D^{23}$ −156° (*c* 0.135, $CHCl_3$); M^+ of trimethylsilyl derivative 430 (requires *M*, 430).

(3R,4R)-ω-*Carboxy*-Δ^6-*tetrahydrocannabinol* (**3**).—The methyl ester (**4**) (30 mg) was hydrolysed by refluxing with 10% aqueous potassium hydroxide (3 ml) for 2 h. Customary work-up gave the *acid* (**3**) (17 mg, 60%), an oil, *m/z* 344.1991 ($C_{21}H_{28}O_4$ requires *M*, 344.1987), $\nu_{max.}$(film) 1 700 (acid) cm^{-1}; $[\alpha]_D^{21}$ −134.5° (*c*, 0.083, $CHCl_3$); M^+ of bistrimethylsilyl derivative 488 (requires *M*, 488).

(3R,4R)-ω-*Methoxycarbonyl*-Δ^1-*tetrahydrocannabinol* (**2**).—The pentanoate (**10**) (0.9 g, 3.7 mmol) was stirred with *p*-menthadienol (0.75 ml, 4.5 mmol) and toluene-*p*-sulphonic acid (0.34 g, 1.8 mmol) in dichloromethane (21 ml) at 19 °C for 6 h. T.l.c. indicated that the reaction had progressed only to the cannabidiol stage. The temperature was raised to 40 °C for 2 h and t.l.c. monitoring showed that much of the cannabidiol-type material had formed THC compounds. Neutralisation (Na_2CO_3) and work-up followed by p.l.c. on 40 × 40 cm silica G HF 254 plates, eluting with dichloromethane–(hexane–methanol, 95:5) (97:3), gave the following main cannabinoid bands: band 2 (0.10 g, 7.5%) mainly mixed *o*-compounds; band 3 (0.13 g, 10%), oil, almost pure ω-*methoxycarbonyl*-Δ^1-THC (**2**); band 4 (0.29 g, 22%), oil, a mixture of ω-methoxycarbonyl-Δ^1-, and -Δ^6-THC's plus a little of the corresponding *p*-cannabidiol compound; band 5 (0.16 g) oil, mainly diterpenylated compounds (from m.s.). In a series of runs of a similar type the yields of almost pure ω-methylcarbonyl-Δ^1-THC varied between 6 and 15% whilst the mixed band 4 was 14—22%. This mixed band could be further separated by h.p.l.c. using a C_{18} reversed-phase bonded Corasil column (50 cm × 3 mm i.d.) using 35 μl injections of a solution of 130 mg in 0.36 ml methanol–water (2:1) and eluting with this solvent (450—500 p.s.i., flow rate 0.8 ml/min, detection u.v. at 280 nm). It gave: fraction 2 (elution time 30—35 min) ω-methoxycarbonyl-C_5-*p*-cannabidiol (9.7 mg); fractions 3 and 4 (E_t 56—63 min) ω-methoxycarbonyl-Δ^1-THC (25.2 mg); fraction 5 (E_t 63—71 min) mixture of Δ^1-and Δ^6-esters (18.9 mg); fraction 6 ω-methoxycarbonyl-Δ^6-THC (13.5 mg).

(3*R*,4*R*)-ω-Methoxycarbonyl-Δ^1-THC (**2**) was an oil, *m/z* 358.2163 ($C_{22}H_{30}O_4$ requires *M*, 358.2144), $\nu_{max.}$(film) 1 725 cm^{-1} (ester), $[\alpha]_D^{25}$ −125° (c, 0.146, $CHCl_3$); M^+ of trimethylsilyl derivative 430 (requires *M*, 430).

(3R,4R)-ω-*Carboxy*-Δ^1-*tetrahydrocannabinol* (**1**).—This was obtained by hydrolysis of the methyl ester (as above) as a *gum*, *m/z* 344.2000 ($C_{21}H_{28}O_4$ requires *M*, 344.1987), $\nu_{max.}$ 1 700 cm^{-1} (acid), $[\alpha]^{25}$ −97.8° (*c* 0.084, $CHCl_3$); M^+ of bistrimethylsilyl derivative 488 (requires *M*, 488).

ω-*Methoxycarbonylcannabinol* (**25**).—A crude fraction (81.6 mg) from a synthetic run, containing the ω-methoxycarbonyl-C_5 derivatives of *p*-cannabidiol, Δ^1-THC and Δ^6-THC was heated with sulphur (15.1 mg) at 185—190 °C for 45 min. Work-up and p.l.c. (silica, eluant ether–hexane, 2:1) gave the *title compound* (**25**) (16.6 mg, 21%), *m/z* 354.1829 ($C_{22}H_{26}O_4$ requires M^+, 354.1831).

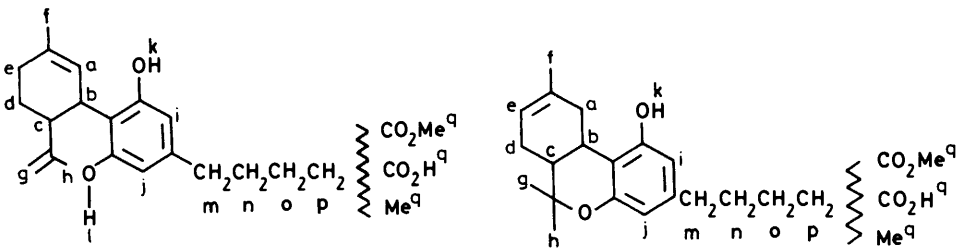
ω-*Carboxy-cannabinol* (**24**).—Hydrolysis of the above methyl ester gave the *acid* (**24**) as colourless crystals from ether–hexane, m.p. 165—167 °C, *m/z* 340.1677 ($C_{21}H_{24}O_4$ requires *M*, 340.1674); M^+ of bistrimethylsilyl derivative 484 (requires *M*, 484).

Preparation of (3R,4R)-(−)-ω-*Methoxycarbonyl*-Δ^1- *and* Δ^6-*tetrahydrocannabinols on a Multigram Scale*.—The pentanoate (**10**) (5.86 g), (+)-*trans*-*p*-menthadienol (5.08 g), and toluene-*p*-sulphonic acid (1.20 g) in dichloromethane (700 ml) were mechanically stirred for 1 h 5 min. During this time, the reaction was repeatedly monitored by t.l.c. using two systems (the CH_2Cl_2 plus, and the Korte systems of Table 1). Plates were sprayed with Fast-Blue Salt B and the reaction was stopped when the orange colour of the cannabidiol analogue spot had considerably diminished. At the end of 1 h 5 min, water and sodium hydrogen carbonate were added and the products isolated in dichloromethane after suitable washings. Drying and evaporation of the extracts gave a product which when analysed by g.l.c. was shown to contain starting pentanoate (13%) and the ω-methoxycarbonyl analogues of Δ^6-THC (17%), Δ^1THC 52%, and other peaks (2 + 5 + 12%). The mixture was chromatographed on a dry silica column (nylon tube, 2 ft × 2 in) eluting with ether–light petroleum (1:1). The developed column was cut into sections and each section examined by g.l.c. on an OV 17 column at 250 °C. Fractions 1—3 were discarded. Fractions 4—8 (6.93 g) were united and contained Δ^1-(56%) and

Table 5. ^{1}H N.m.r. data for ω-carboxylated acids and esters in $CDCl_3$

Compound		δ_H for protons† a	b	e	f	g	h	i	j	k	l	m	q
p-CBD-C_5-ω-CO_2Me	(15)	5.56 (brs, 1 H)	3.86 (brd, 1 H)		1.79 (s, 3 H)	4.65(s) 4.53 (s) (2 H)	1.66 (s, 3 H)	← 6.19 → (s, 2 H)		← 5.90, ~5.55 → (D_2O ex., 2 H)		~2.4 (m, 2 H)	3.65 (s, 3 H)
p-CBD-C_5-ω-CO_2H	(14)	5.56 (brs, 1 H)	3.85 (brd, 1 H)		1.78 (s, 3 H)	4.63 (brs) 4.53 (brs) (2 H)	1.66 (s, 3 H)	← 6.20 → (s, 2 H)		← ~6.2 → (D_2O ex., 2 H)			~6.2 (br, D_2O ex.)
p-CBD-C_5		5.57 (brs, 1 H)	3.85 (brd, 1 H)		1.79 (s, 3 H)	4.66 (s) 4.58 (s) (2 H)	1.65 (s, 3 H)	← 6.22 → (s, 2 H)		← 4.0—6.4 → (D_2O ex., 2 H)		2.45 (t, 2 H)	0.88 (t, 3 H)
o-CBD-C_5-ω-CO_2Me	(17)	5.48 (brs, 1 H)	3.48 (br, 1 H)		1.78 (s, 3 H)	4.63 (s) 4.45 (s) (2 H)	1.52 (s, 3 H)	← 6.21 → (s, 2 H)		← 6.04 → (D_2O ex., 2 H)		2.48 (m, 2 H)	3.68 (s, 3 H)
o-CBD-C_5-ω-CO_2H	(16)	5.48 (brs, 1 H)	3.55 (br, 1 H)		1.77 (brs, 3 H)	4.63 (s) 4.45 (s) (2 H)	1.52 (s, 3 H)	← 6.20 → (s, 2 H)		← ~6.20 → (D_2O ex., 2 H)		—	~6.2 (br, D_2O ex.)
o-CBD-C_5		5.54 (brs, 1 H)	3.35—3.75 (br, 1 H)		1.80 (3 H)	4.67 (s) 4.50 (s) (2 H)	1.54 (s, 3 H)	← 6.22 → (s, 2 H)		← 4.82, 6.06 → (D_2O ex., 2 H)		2.53 (t, 2 H)	0.90 (t, 3 H)
o-*p*-bis-CBD-C_5-ω-CO_2Me	(19)	5.56 (br, 1 H) 5.46 (br, 1 H)	3.98 (br, 1 H) 3.53 (br, 1 H)		1.81 (brs, 6 H)	4.62 (s) 4.46 (4 H)	1.72 (s, 3 H) 1.52 (s, 3 H)		6.28 (s, 1 H)	← 5.99s, 5.66br → (D_2O ex., 2 H)		2.36 (t, 2 H)	3.68 (s, 3 H)
o-*p*-bis-CBD-C_5-ω-CO_2H	(18)	5.55 (br, 1 H) 5.48 (br, 1 H)	4.00 (br, 1 H) 3.52 (br, 1 H)		1.82 (brs, 6 H)	4.65 (br) 4.49 (br) (4 H)	1.73 (s, 3 H) 1.51 (s, 3 H)		6.17 (s, 1 H)	← 5.95br, 5.88s → (D_2O ex., 2 H)		2.36 (t, 2 H)	
o-*p*-bis-CBD		5.57 (brs, 2 H)	3.2—4.2 (2 H)			4.64 (br) 4.51 (br) (4 H)			6.23 (s, 1 H)	← 5.74, 5.93 → (D_2O ex., 2 H)			
Δ^1-THC-C_5-ω-CO_2Me	(2)	6.28 (br, 1 H)	3.07 (br, 1 H)		1.69 (s, 3 H)	1.41 (s, 3 H)	1.10 (s, 3 H)	6.22 (d, *J*2, H)	6.11 (d, *J*2, 1 H)	4.89 (br, D_2O ex., 1 H)		~2.45	3.68 (s, 3 H)
Δ^1-THC-C_5-ω-CO_2H	(1)	6.27 (br, 1 H)	3.13 (br, 1 H)		1.67 (brs, 3 H)	1.41 (s, 3 H)	1.10 (s, 3 H)	6.19 (d, 1 H)	6.05 (br, 1 H)	~7.4 (vbr)		—	~7.41 (v. br)
Δ^1-THC-C_5		6.35 (1 H)	2.90—3.35 (m, 1 H)		1.69 (brs, 3 H)	1.40 (s, 3 H)	1.09 (s, 3 H)	6.29 (d, *J*1.5, 1 H)	6.14d (*J*1.5, 1 H)			2.45 (t, 2 H)	0.89 (t, 3 H)
Δ^6-THC-C_5-ω-CO_2Me	(4)		3.22 (1 H)	5.41 (brs, 1 H)	1.68 (3 H)	1.38 (s, 3 H)	1.10 (s, 3 H)	6.25 (d, 1 H)	6.11 (d, 1 H)	~5.05			3.67 (s, 3 H)
Δ^6-THC-C_5-ω-CO_2H	(3)		3.19 (1 H)	5.41 (brs, 1 H)	1.69 (br, 3 H)	1.36 (s, 3 H)	1.10 (s, 3 H)	6.24 (d, 1 H)	6.09 (d, 1 H)	6.0—7.2 (br, D_2O ex.)			6.0—7.2
Δ^6-THC-C_5	(36)		3.0—3.5 (m, 1 H)	5.43 (brs, 1 H)	1.71 (s, 3 H)	1.38 (s, 3 H)	1.11 (s, 3 H)	6.27 (d, 1 H)	6.10 (d, 1 H)	4.73 (s, D_2O ex.)		2.46 (t, 2 H)	0.88 (t, 3 H)
CBN-C_5-ω-CO_2Me	(25)	8.27 (d, 1 H)		7.17 (m, 2 H)*	2.41 (s, 3 H)	← 1.62 → (s, 6 H)		6.34 (d, 1 H)	6.47 (d, 1 H)	5.85 (s, D_2O ex.)		~2.55 (m, 2 H)	3.74 (s, 3 H)
CBN-C_5-ω-CO_2H	(24)]	8.22 (d, 1 H)		7.13 (m, 2 H)*	2.39 (s, 3 H)	← 1.60 → (s, 6 H)		6.30 (d, 1 H)	6.44 (d, 1 H)	~5.55 (br, D_2O ex.)		2.52 (m, 2 H)	~5.55
CBN-C_5		8.20 (s, 1 H)		7.10 (m, 2 H)*	2.39 (s, 3 H)	← 1.61 → (s, 6 H)		6.24 (d, 1 H)	6.45 (d, 1 H)	5.44 (s, D_2O ex.)		2.49 (t, 2 H)	0.89 (t, 3 H)

* Includes both aromatic protons d and e. † Examples for lettering code:



Δ^6-(18%) analogues along with other peaks (1 + 21 + 4%). Fractions 9 and 10 contained mainly *ortho*-compounds and fraction 11 mainly pentanoate (**10**).

Fractions 4—8 were combined with similar fractions (*ca.* 50% Δ^1-THC ester) from a second experiment to give 8.5 g material which was chromatographed on a Waters 'Prep Pak 500' silica column (5.7 × 30 cm) eluting with ether–light petroleum (b.p. 60—80 °C) (1:5) at 150 ml/min using a refractive index detector. Fractions were collected and analysed by g.l.c. as follows:

Fraction no.	Early peaks	Δ^6-THC ω-ester	Δ^1-THC ω-ester	Late peaks	Wt. (g)
6	← very impure →				0.37
7	35	43	14	8	1.59
8	5	32	59	4	1.57
9	Trace	15	85	Trace	1.06
10	—	5	95	Trace	0.53
11	—	2	98	—	0.28
12	—	—	100	—	0.12
13	5 + 4	12	79	Trace	0.06
Original mixture	1 + 21	27	51	—	8.5

Fractions 8—13 (3.62 g) were now further purified by reversed-phase chromatography using a Waters Prep. Pak 500-C_{18} column (5.7 × 30 cm) eluting with 73% methanol in water at 250 ml/min. This gave 1.52 g of Δ^1-THC ω-ester (**2**) of >96% purity. From a total of 12.35 g of methyl 5-(3,5-dihydroxyphenyl)pentanoate (**10**) 2.78 g of Δ^1-THC ω-ester (14.1%) analysing for 98% purity (2% Δ^6-THC ω-ester impurity) was obtained.

Residues from the above work (8.87 g) (a mixture of Δ^1-THC ω-ester, Δ^6-THC ω-ester, and some starting materials) in benzene (700 ml) were refluxed with toluene-*p*-sulphonic acid (1.82 g) and (+)-*trans*-*p*-methadienol (2.5 g). Cooling, neutralisation with aqueous sodium hydrogen carbonate, and extraction was followed by chromatography on dry silica (nylon tube 2 in × 18 in) eluting to the column base with ether–light petroleum (b.p. 60—80 °C) (1:1). The column was sectioned and fractions rich in Δ^6-THC ω-ester (t.l.c.) were collected (7.5 g crude). These were chromatographed on a 'Prep Pak 500' silica column (5.7 × 30 cm) eluting with ether–light petroleum (1:5) at 150 ml/min. Fractions were collected and analysed by g.l.c. Those containing >93% Δ^6-THC ω-ester (**4**) (3.81 g) were combined and could be further purified by reversed phase h.p.l.c. as required.

The original 12.35 g of methyl 5-(3,5-dihydroxyphenyl)-pentanoate provided 3.81 g (19.3%) of 93% pure Δ^6-ester along with the 2.78 g (14.1%) of Δ^1-ester, together with 1.79 g (9.1%) of the Δ^6-ester of *ca.* 70% purity.

(2E,4E)-*Methyl* 5-(3,5-*Dihydroxyphenyl*)*penta*-2,4-*dienoate* (**26**).—Methyl 3,5-dihydroxybenzoate was converted into its bis-MEM ether (65%) using MEM chloride[14] in acetone and potassium carbonate containing a little 18-crown-6, and the protected ester was then reduced by lithium aluminium hydride in ether (86%) to the phenol-protected benzyl alcohol. The latter was converted (88%) into the corresponding aldehyde by oxidation with pyridinium chlorochromate in dichloromethane. The aldehyde (2.3 g, 10 mmol) in methanol (50 ml) was stirred with diethyl ethylidenemalonate (**6**) (2.05 g, 11 mmol) and Triton B solution in methanol (14 ml) at 20 °C for 18 h. Work-up gave the half ester (**28**) (3.5 g, 98%) as an oil. The M^+ at 352 was weak ($C_{17}H_{20}O_8$ requires 352) and measurement 334.1044 was made on the $M^+ - 18$ ion ($C_{17}H_{18}O_7$ requires 334.1052). The half-ester (1 g) was refluxed in pyridine (10 ml) for 6 h, and worked up to give the mono-ester (600 mg, 69%) (M^+, 308.1268. $C_{16}H_{20}O_6$ requires *M*, 308.1260). Refluxing (6 h) the latter (600 mg) in methanol (6 ml) containing a drop of conc. hydrochloric acid brought about deprotection. Chromatographic purification then gave the *title ester* (**26**) (130 mg, 30%), m.p. 197—199 °C from ethyl acetate–chloroform (Found: C, 65.3; H, 5.6%; M^+, 220.0735. $C_{12}H_{12}O_4$ requires C, 65.45; H, 5.5%; M^+, 220.0736); $\lambda_{max.}$(EtOH) 212 (ε 15 000), 245 (8 000), and 321 nm (27 000); $\nu_{max.}$ 1 675, 1 625, and 1 585 cm^{-1}; δ($CHCl_3$) 8.56 (2 H, br s, D_2O exchg., 2 × OH), 7.20—6.14 (7 H, m, olefinic and aromatic H), 3.85 (3 H, s, CO_2Me).

(3R,4R)-ω-*Methoxycarbonyl*-1″,2″,3″,4″-*tetradehydro*-Δ^6-*tetrahydrocannabinol* (**27**) (2*E*,4*E*)-Methyl 5-(3,5-dihydroxyphenyl)penta-2,4-dienoate (0.215 g, 0.97 mmol) in dry dichloromethane (36 ml) was refluxed with (+)-*trans*-*p*-menthadienol (0.20 ml) and toluene-*p*-sulphonic acid (60 mg) for 2 h 45 min. Water (20 ml) and saturated aqueous sodium hydrogen carbonate (20 ml) were added: unchanged starting pentadienoate (96 mg) was precipitated and this was filtered off. The filtrate was acidified and the product was extracted into dichloromethane. The extract was washed and evaporated and the residue chromatographed on silica (dry column, 1.5 × 20 cm) eluting with a gradient of pure chloroform ⟶ 2% methanol in chloroform, 25-ml fractions being collected. The product ester (170 mg) was found in fractions 10—12 [monitoring: t.l.c. on HF 254 silica, eluting with 5% methanol in chloroform: spray reagent Fast Blue salt B (pink–purple spot)]. It was further purified by C_{18}-reversed phase h.p.l.c./elution with 85% methanol/15% water, 100 ml/min) carried out twice. The pure *tetradehydro*-Δ^6-*THC ester* (**27**) (44.7 mg, 13%) formed powdery crystals from aqueous methanol, m.p. 84—87 °C; *m/z* 354.1820 ($C_{22}H_{26}O_4$ requires *M*, 354.1831); $\nu_{max.}$(KBr) 1 700 (unsatd. ester), 1 635 (C=C), and 1 580 cm^{-1} (Ar); $\lambda_{max.}$(EtOH) 215 (ε 17 300), 254 (10 400), and 328 nm (25 000); δ_H($CDCl_3$) 7.42 (1 H, ddd, *J* 15.3, 7.9, 2.4 Hz, 3″-H), 6.76 (2 H, m, 1″ and 2″-H), 6.57 (1 H, d, *J* 1.5 Hz) and 6.40 (1 H, d, *J* 1.5 Hz) (3′- and 5′-H's), 5.95 (1 H, d, *J* 15.3 H, 5″-H), 5.43 (1 H, br m, 6-H), 5.05 (1 H, br s, OH, D_2O ex.), 3.77 (3 H, s, 6″-CO_2Me), 3.20 (1 H, br dd, 3-H), 1.71 (3 H, s, 9-Me), and 1.39 (3 H, s) and 1.10 (3 H, s) (9- and 10-Me).

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