Synthesis of Bibenzyl Cannabinoids, Hybrids of Two Biogenetic Series Found in *Cannabis sativa*

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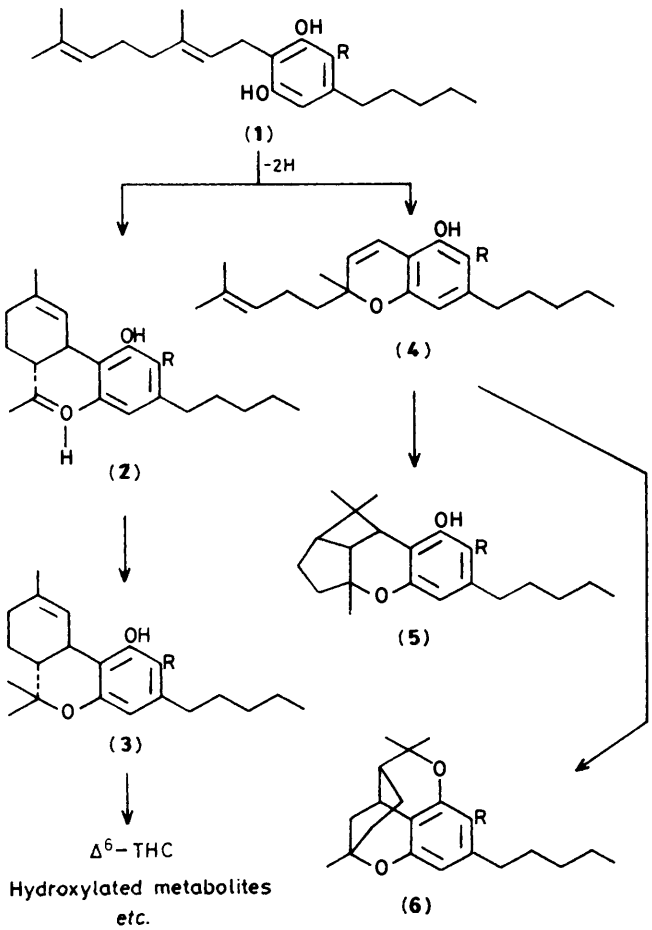
Syntheses of a series of compounds which merge a *m*-dihydroxybibenzyl with a terpenoid structure, giving a series of hybrid cannabinoids in which products of two major biogenetic routes of *Cannabis* are united, are described. The compounds made are the bibenzyl/*o*- and *p*-cannabigerols (**19**) and (**18**)/*o*- and *p*-cannabidiols (**21**) and (**20**),/Δ^1-THC (**22**),/Δ^6-THC (**23**),/*o*- and *p*-cannabichromenes (**25**) and (**24**),/*o*- and *p*-cannabicyclols (**28**) and (**27**) and/cannabicitran (**26**). Chromatographic and spectral data are listed in order to facilitate search for such 'crossed' types since only the bibenzyl cannabigerols and a chromene have as yet been found in natural sources.

The bibenzyl/*p*-cannabigerol (**18**) has been reported in *Helichrysum umbraculigerum* (Compositae) and the liverwort *Radula variabilis*. Our synthetic work confirms the former observation, but the liverwort compound appears to be its *o*-isomer.

The so-called cannabinoid class of natural products found in *Cannabis sativa* is generally considered to be a biogenetically related group, though actual experimental information is sparse.[1] Scheme 1 shows the core of the relationships, dealing only with major structural types. Good laboratory analogies are available, though in the plant the chemistry appears to take place on carboxylated forms[2] under much milder conditions. A second important group of related metabolites from *C. sativa* has lately come to light,[3] and, omitting less significant members, the main biogenetic relationships are in Scheme 2. This group originates from *m*-hydroxylated bibenzyls and includes a spirodienone and its reduction products, and dihydrophenanthrenes. Two flavonoids, canniflavone-1 and -2 (**13a**) and (**13b**)* also occur in the plant and have some biogenetic connections with the bibenzyl group.[3] Early processes in the biogenesis of all three classes of natural product involve tris-malonate acylation and decarboxylations, using either hexanoic acid or *p*-hydroxycinnamic acid as starters. Condensation is followed by oxidation, methylation *etc.* and, importantly for the present work, terpenylation (Scheme 3).



a; R = H

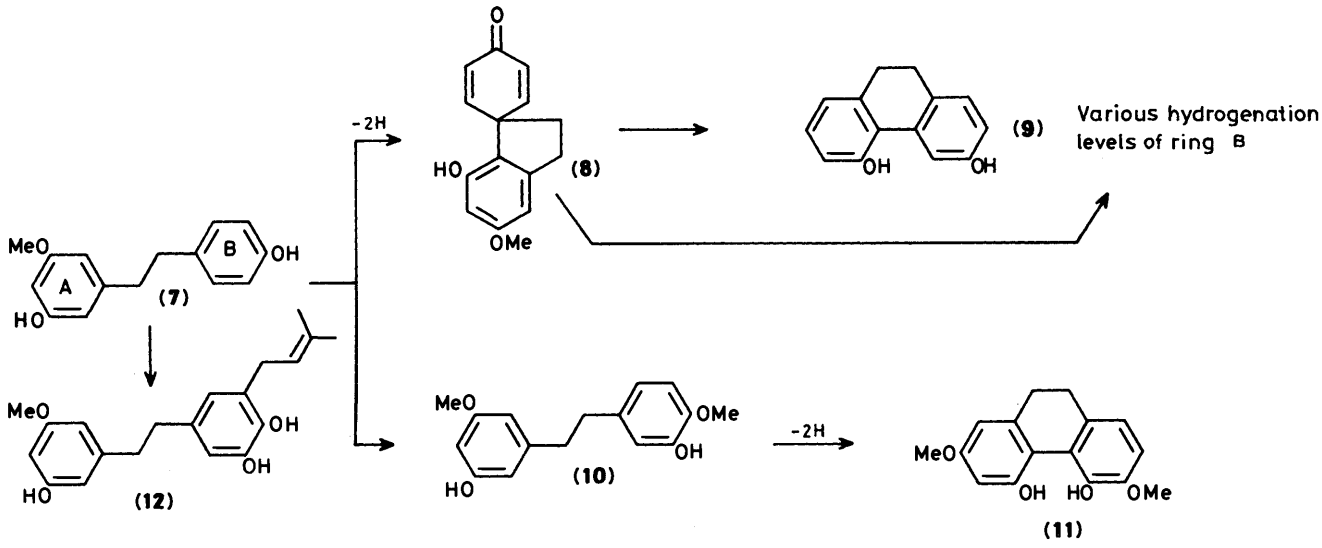
b; R = CO_2H

Scheme 1. Biogenic connections for the cannabinoids

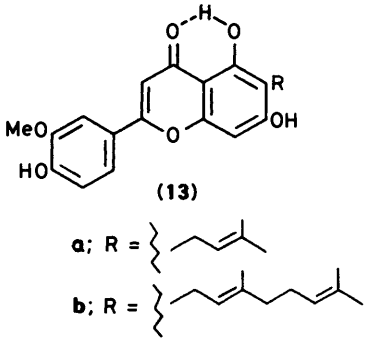
This paper presents the synthetic part of an investigation designed to find whether the plant terpenylation systems which are effective for olivetol are also effective in plants on other resorcinol types such as bibenzyls. There is some circumstantial evidence that this is so. Thus Bohlmann and Hoffmann[5] report that the S. African plant *Helichrysum umbraculigerum* (Compositae) contains cannabigerol (**1a**) and its acid (**1b**) alongside the geranylated bibenzyl (**18**) and its acid. Other members of the group (**1**)—(**6**) of Scheme 1 were not reported and presumably, although possessing the necessary geranylating enzyme, the converting enzymes for modification of the geranyl unit were not present. *Cannabis* contains enzymic equipment both for geranylation of resorcinols and the terpenic modification steps of Scheme 1: it also contains bibenzyls having a resorcinol type ring. It has therefore become of interest to see if *Cannabis* (or other plants) contain 'crossed' bibenzyl/cannabinoids which have hitherto been overlooked.

Such searches among the many natural substances a plant contains (around 500 natural products have been recognised in *Cannabis*)[6] would be aided by synthetic specimens, or at least close synthetic analogues of the natural product. Since it is not possible to predict what other substitutions the bibenzyl might have in Nature, we have chosen the simple case (**17**) and have grafted on to this the set of terpenic modifications shown in Scheme 1. In view of the pharmacological interest of cannabi-

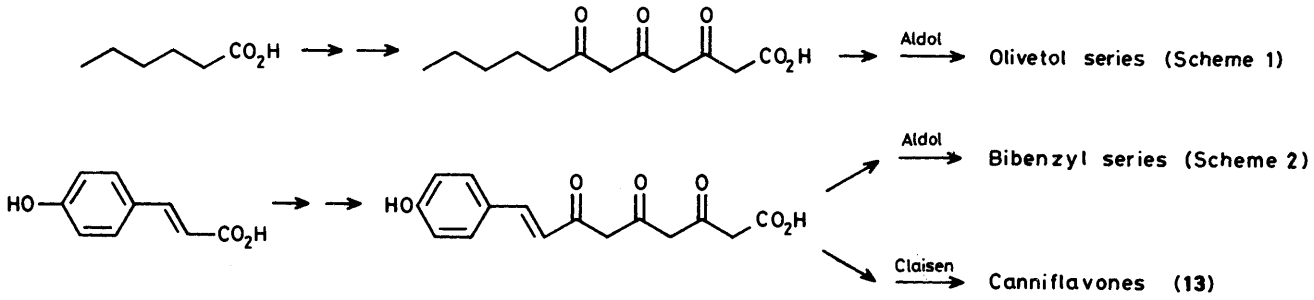
* Unaware of our earlier work, these compounds have very recently been rediscovered and named canniflavins-A and -B.[4]



Scheme 2. Biogenetic connections for the *Cannabis* bibenzyl group



with separation and purification using C_{18}-reversed phase h.p.l.c. gave the two geranylated bibenzyls: bibenzyl/*p*-cannabigerol hybrid (**18**) (BB/pCBG) and bibenzyl/*o*-cannabigerol hybrid (**19**) (BB/oCBG). Each could be obtained in 15% yield. Each compound has *meta*-related hydrogens in the A-ring but the two isomers are readily distinguished since, because of the symmetry of (**18**), the C-3′ and -5′ signals in the carbon spectrum (Table 2) resonate at the same field: the same applies to C-2′ and -6′. Isolation of (**18**) from natural sources has been claimed by two groups. Asakawa and colleagues[9] report its occurrence in the liverwort *Radula variabilis*, and as mentioned above Bohlmann found it in *H. umbraculigerum*.[5] Close comparison of the ^{1}H n.m.r. data recorded by these two groups

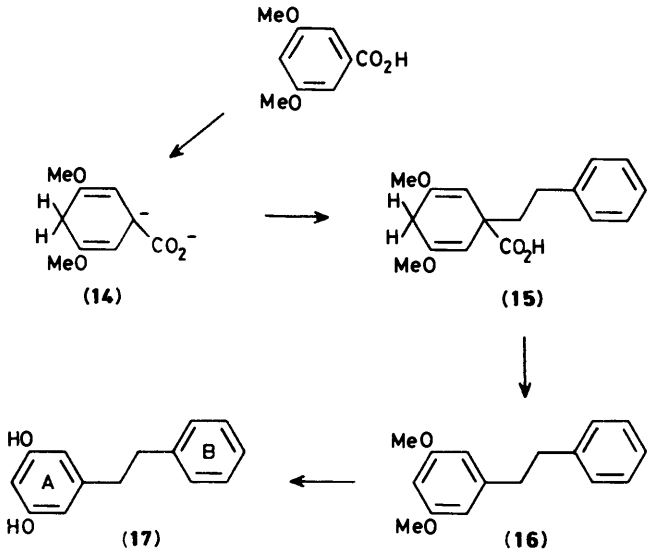


Scheme 3. Connections at the polyketide level

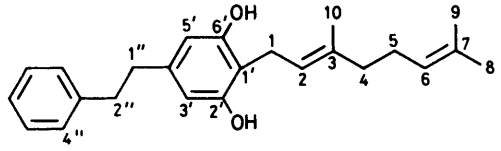
noids, the biological activities of the new set of compounds are also of interest.

Supplies of 3,5-dihydroxybibenzyl (**17**) were made in 40% overall yield by the Birch reduction method[7,8] of Scheme 4. 3,5-Dimethoxybenzoic acid was treated with sodium–liquid ammonia at −70 °C and the bis-anion (**14**) was then alkylated with phenethyl bromide to give crystalline compound (**15**) (74%). Decarboxylative dehydrogenation with lead tetra-acetate in the presence of copper acetate led to the dimethyl ether (**16**) (78%) which was readily demethylated to give (**17**) using boron tribromide in dichloromethane at −78 °C rising to 20 °C (71%).

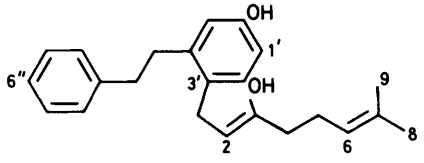
Geranylation of 3,5-dihydroxybibenzyl using geraniol under acid conditions [toluene-*p*-sulphonic acid (PTSA) in benzene] indicates small but significant discrepancies. Thus Asakawa reports[9] the *meta*-oriented hydrogens of ring A as resonating at δ 6.28 as a 'broad singlet' whereas Bohlmann reports 'singlet'. The latter agrees with our data for (**18**) (Table 1) but in (**19**) the hydrogens have a small coupling (*J* 2 Hz). Our value for the benzylic 1-methylene of (**18**) is 3.40 d, *J* 7 Hz: Bohlmann[5] gives 3.40 broad d, Asakawa[9] 3.27 d, *J* 8 Hz. The latter agrees better with our data for isomer (**19**) (3.29 d, *J* 7 Hz). Most telling are the 1″-and 2″-signals which in (**18**) resonate as two 2 H multiplets (2.88, 2.76) whereas in (**19**) they form a singlet (2.82). Bohlman[5] records AA′BB′ signals, not first order[1], 2.84, whilst Asakawa[9] gives 2.80, singlet. Whilst Asakawa's data do not agree with ours for the *p*-compound (**18**), they do agree very well with those for our *o*-compound (**19**). We, therefore, believe that



Scheme 4. Route to 3,5-dihydroxybibenzyl



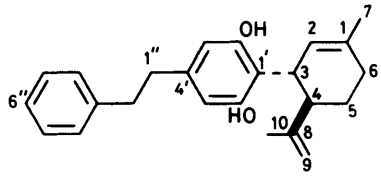
(18)



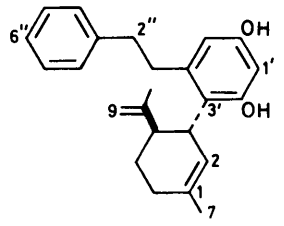
(19)

Bohlmann's natural material was authentic BB/pCBG whilst Asakawa's was BB/oCBG*.

Terpenylation of bibenzyl (**17**) with (1*S*,4*R*)-(+)-*trans*-*p*-mentha-2,8-dien-1-ol[10] using PTSA catalyst at room temperature allowed isolation of the (3*R*,4*R*)-bibenzyl/*p*-cannabidiol hybrid (**20**) (BB/pCBD) in 27% yield together with its *ortho*-isomer (**21**) (BB/oCBD) (13%). In the case of the cannabidiols themselves it is known that the *p*-compound shows evidence of slow exchange involving rotation of the *p*-methadienyl residue[11] which is not evident in the *o*-isomer. As might be expected compounds (**20**) and (**21**) show analogous behaviour. In the proton spectrum of (**20**) the hydrogens at 3′ and 5′ have very broadened signals and the carbon signals at the same positions are likewise much broadened and diminished in height. The more hindered *ortho* isomer does not display such slow exchange characteristics. Fast Blue Salt B (FBSB) colours and chromatographic retention orders follow those for the cannabidiols and this type of relationship was found throughout the hybrid series. A useful ^{13}C n.m.r. criterion for orienting compounds in the bibenzyl series has also emerged in the present work (Table 2). In the *p*-series, *e.g.* (**18**) and (**20**), the resonances of the C-1″ and -2″ benzylic methylenes of the bridge are nearly coincident at δ 37.5. In the *ortho* isomers (**19**) and (**21**)



(20)



(21)

one methylene occurs at about the same position but the other is shifted upfield by shielding of some 2—3 p.p.m. This applies in the bibenzyl/cannabichromene and cannabicyclol series as well as the cannabidiols and cannabigerols.

Under more vigorous conditions[10] (refluxing acid solution in benzene) *o*- ⟶ *p*-cannabidiol conversion occurred as expected (the formation reaction is reversible, and the *p*- is thermodynamically the more stable): this was accompanied by cyclisation and isomerisation of the Δ^1-double bond of the bibenzyl/Δ^1-THC hybrid (**22**) to the Δ^6-position. Thus the product isolated under these conditions was the (3*R*,4*R*)-bibenzyl/Δ^6-THC hybrid (**23**) (BB/Δ^6THC) (44%). By careful adjustment of reaction conditions it was possible to isolate the acid-unstable (3*R*,4*R*)-bibenzyl/Δ^1-THC hybrid (**22**) (BB/Δ^1THC) intermediate though in low yield—*ca.* 10%. Spectral data in the Tables and Experimental verify the structures proposed.

Base-catalysed chromenylation of 3,5-dihydroxybibenzyl by heating with citral[12] gave (±)-bibenzyl/*p*-cannabichromene (**24**) and /*o*-cannabichromene (**25**) hybrids (BB/pCBC and /oCBC) along with lesser amounts of (±)-bibenzyl/cannabicitran (BB/Cit) (**26**) and the cyclols (**27**) and (**28**). Pyridine at 160 °C gave a predominance of *o*- and *p*-chromenes (**25**) and (**24**) in 52% g.l.c. yield (see Experimental section). Investigated by g.l.c., 2,6-di-t-butylpyridine gave a higher proportion of cyclols (**27**) and (**28**) (12%) and citran (**26**) (17%), together with 47% of chromenes. 2,4,6-Trimethylpyridine also gave increased amounts of cyclols and citran along with 35% of chromenes. Employing 2,6-di-t-butylpyridine at 160 °C and isolating the products by h.p.l.c., using normal and then reversed phase methods, BB/pCBC (**24**) was isolated in 15% yield as well as the *o*-isomer (9%) and some of BB/Cit. Despite the final poor yields after rigorous purification, this chromenylation procedure is quick and direct.

The two (±)-bibenzyl/cannabicyclols, *p*-(**27**) and *o*-(**28**) were prepared by irradiating the chromenes (**24**) and (**25**) in acetone solution,[12,13] Both cyclols were obtained crystalline, a reflection of their compact and rigid structures, and spectral data are recorded in the Tables.

3,4′-Dihydroxy-5-methoxybibenzyl (**7**) occurs naturally in *Cannabis*[3,14] and terpenylation with (1*S*,4*R*)-(+)-*trans*-*p*-mentha-2,8-dien-1-ol was attempted. Only one product was isolated pure and this proved to be the *o*-terpenylation product (**29**). N.m.r. data showed that substitution had taken place on ring A. The placing of the methoxy group at C-6 rather than C-2 follows from a comparison of the observed ^{13}C signals of ring A with those calculated (see Experimental section) for the two *o*-

* Professor Y. Asakawa (personal communication) has recently found both (**19**) and the corresponding chromene (**25**) in the liverwort *Radula kojana*: we thank him for this information.

Table 1. ^{1}H N.m.r. data for bibenzyl/cannabinoid hybrids

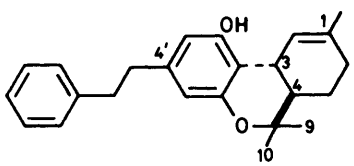
		1	2	3	4	5	6	7	8	9	10	1′	5′	3′	2′	6′	1″ 2″	4″—8″
BB/*p*CBG	(**18**)	3.40 (d, 2 H, *J* 7.0)	5.27 (t, 1 H, *J* 6.2)		← 2.10 (*m*, 4 H) →		5.05 (dt, 1 H, *J* 1.3, 5.7)		1.68 (s, 3 H)	1.59 (s, 3 H)	1.81 (s, 3 H)		← 6.26 (s, 2 H) →		←→ 5.20 (br s, 2 H, D_2O exchg.)	←→ 2.88, 2.76 (each 2 H, m) (4 H)	→7.31—7.17 (m, 5 H)
BB/*o*CBG	(**19**)	3.29 (d, 2 H, *J* 6.7)	5.10 (dt, 1 H, *J* 0.9, 6.3)		← 2.08 (m, 4 H) →		5.04 (dt, 1 H, *J* 1.7, 6.4)		1.65 (s, 3 H)	1.57 (s, 3 H)	1.78 (s, 3 H)	← 6.27 (d, 2 H) *J* 2.1→ ← 6.26 (d, 2 H) → (*J* 2.1)		←	5.40 (br s, 2 H, D_2O exchg.)	→← 2.82 (s, 4 H)	→ 7.32—7.14 (m, 5 H)
BB/*p*CBD	(**20**)		5.57 (s, 1 H)	3.87 (d, 1 H, *J* 10.2)	2.41 (dt, 1 H, *J* 4.4, 10.5)	1.25 (m, 2 H)	1.7—1.9 (m, 2 H)	1.80 (s, 3 H)		4.67 (t, 1 H) 4.56 (s, 1 H) (2 H, *J* 1.7)	1.66 (s, 3 H)		← 6.30, 6.15 (each br s, 2 H)	→←	6.00, 4.75 (each br s, 2 H, D_2O exchg.)	←→ 2.85, 2.75 (each 2 H, m) (4 H)	→ 7.30—7.14 (m, 5 H)
BB/*o*CBD	(**21**)		5.41 (s, 1 H)	3.55 (d, 1 H, *J* 9.5)	2.48 (dt, 1 H, *J* 3.7, 10.6)	1.25 (m, 2 H)	1.7—1.9 (m, 2 H)	1.77 (s, 3 H)		4.66 (t, 1 H, *J* 1.6) 4.67 (s, 1 H)	1.52 (s, 3 H) ←	6.23, 6.21 each (d, 2 H, *J* 2.7)	→	←	6.08, 4.70 (each br s, 2 H, D_2O exchg.)	→← 2.78(t, 2 H, *J* 7.6) 2.91, 2.64 (each 1 H, m), (2 H)	→ 7.35—7.10 (m, 5 H)
BB/Δ^1THC	(**22**)		6.31 (s, 1 H)	3.21 (d, 1 H, *J* 10.2)	1.76 (m, 1 H)	← 2.15 (m, 2 H) → ← 1.92 (m, 1 H) → ← 1.43 (m, 1 H) →		1.68 (s, 3 H)		← 1.42 (s, 3 H) → ← 1.09 (s, 3 H) →			← 6.33, 6.14 (each d, *J* 1.3) (2 H) →		5.10 (br s, 1 H, D_2O exchg.)	← 2.86, 2.73 (each 2 H, m) (4 H)	→ 7.31—7.15 (m, 5 H)
BB/Δ^6THC	(**23**)		1.76 (m, 2 H)	3.23 (dd, 1 H, *J* 4.9, 16.2)	2.06 (m, 1 H)	1.70 (m, 2 H)	5.35 (d, 1 H, *J* 3.9)	1.70 (s, 3 H)		← 1.38 (s, 3 H) → ← 1.11 (s, 3 H) →			← 6.35, 6.14 (each d, *J* 1.3) (2 H) →		4.87 (s, 1 H, D_2O exchg.)	← 2.79, 2.65 (each 2 H, m) (4 H)	→ 7.24—7.09 (m, 5 H)
BB/*p*CBC	(**24**)	6.65 (d, 1 H, *J* 10.0)	5.49 (d, 1 H, *J* 10.0)		1.65 (m, 2 H)	2.10 (m, 2 H)	5.09 (m, 1 H)		1.65 (s, 3 H)	1.57 (s, 3 H)	1.37 (s, 3 H)		← 6.28, 6.09 (each d, *J* 1.5) (2 H) →		5.40 (br s, 1 H, D_2O exchg.)	← 2.86, 2.73 (each 2 H, m) (4 H)	→ 7.33—7.14 (m, 5 H)
BB/*o*CBC	(**25**)	6.47 (d, 1 H, *J* 10.0)	5.45 (d, 1 H, *J* 10.0)		1.65 (m, 2 H)	2.10 (m, 2 H)	5.10 (m, 1 H)		1.66 (s, 3 H)	1.58 (s, 3 H)	1.36 (s, 3 H) ←	6.19, 6.17 (each d, *J* 2.3) (2 H) →			5.30 (br s, 1 H, D_2O exchg.)	← 2.82 (s, 4 H) →	7.31—7.15 (m, 5 H)
BB/Cit	(**26**)		1.23 (m, 2 H)	2.21 (m, 1 H)	2.03 (dm, 1 H, *J* 2.8, 11.6)	1.83 (dd, 1 H, *J* 1.7, 13.4 0.61 (m, 1 H, *J* 5.9, 12.7)	1.45 (m, 2 H, *J* 6.0, 12.9)	1.38 (s, 3 H)		← 1.52 (s, 3 H) → ← 1.00 (s, 3 H) →			← 6.36, 6.26 (each d, *J* 1.0) (2 H) →			← 2.83 (m, 4 H) →	7.33—7.13 (m, 5 H)
BB/*p*CCY	(**27**)		2.59 (t, 1 H, *J* 8.4)	3.07 (d, 1 H, *J* 9.6)	2.40 (br t, 1 H, *J* 7.0)	← 1.64 (m, 4 H) →		1.38 (s, 3 H)		0.80 (s, 3 H)	1.38 (s, 3 H)		← 6.38, 6.18 (each d, *J* 2.0) (2 H) →		4.40 (s, 1 H, D_2O exchg.)	← 2.89, 2.78 (each 2 H, m) (4 H)	→7.31—7.16 (m, 5 H)
BB/*o*CCY	(**28**)		2.51 (t, 1 H, *J* 8.8)	3.09 (d, 1 H, *J* 9.5)	2.42 (dt, 1 H, *J* 3.4, 8.0)	← 1.68 (m, 4 H) →		1.36[a] (s, 3 H)		0.62 (s, 3 H)	1.25[a] (s, 3 H) ←	6.35, 6.27 (each d, *J* 2.5) (2 H) →			4.75 (br s, 1 H, D_2O exchg.)	← 2.76 (s, 4 H) →	7.33—7.13 (m, 5 H)
(HO)BB/*o*CBD	(**29**)		5.43 (s, 1 H)	3.54 (d, 1 H, *J* 10.0)	2.48 (dt, 1 H, *J* 3.5, 10.5)	1.30 (m, 2 H)	1.80 (m, 2 H)	1.78 (s, 3 H)		4.65 (t, 1 H, *J* 1.5) 4.47 (s, 1 H)	1.52 (s, 3 H) ←	6.30, 6.27 (each d, *J* 1.7) (2 H) →		6.08 (s, 1 H, D_2O ex.)	3.73 (s, 3 H, OMe)	← 2.85 (m, 1 H) → ←2.72 t, 2 H, *J* 7.0)→ ← 2.59 (m, 1 H) → (4 H)	*b*

[a] May be interchanged. [b] 7.01 (dd, 2 H, *J* 1.9, 6.5), 6.75 (dd, 2 H, *J* 1.9, 6.5 Hz), and 4.00 (1 H, D_2O exchg., OH)

Table 2. ^{13}C N.m.r. data for bibenzyl/cannabinoid hybrids[a]

		C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	C-1″	C-2″	C-3″	C-4″	C-5″	C-6″	C-7″	C-8″	OMe
BB/*p*CBG	**(18)**	22.3 CH_2	123.9 CH	138.7 C	39.7 CH_2	26.5 CH_2	121.6 CH	132.0 C	25.6 CH_3	17.7 CH_3	16.2 CH_3	111.2 C	154.9 C	108.3 CH	141.8 C	108.3 CH	154.9 C	37.4 CH_2	37.4 CH_2	141.4 C	128.3 CH	128.4 CH	125.9 CH	128.4 CH	128.3 CH	
BB/*o*CBG	**(19)**	24.8 CH_2	123.9 CH	137.7 C	39.6 CH_2	26.5 CH_2	122.7 CH	131.9 C	25.6 CH_3	17.7 CH_3	16.2 CH_3	101.6 CH	155.7 C	117.8 C	142.2 C	109.0 CH	154.5 C	35.6 CH_2	37.5 CH_2	141.8 C	128.4 CH	128.4 CH	126.0 CH	128.4 CH	128.4 CH	
BB/*p*CBD	**(20)**	139.9 C	124.2 CH	46.3 CH	37.1 CH	28.4 CH_2	30.5 CH_2	20.3 CH_3	149.0 C	110.9 CH_2	23.6 CH_3	114.3 C	154— 156 (br) C	108— 110 (br)OH	141.8 C	108— 100 (br)OH	154— 156 (br)C	37.4 CH_2	37.5 CH_2	141.8 C	128.3 CH	128.4 CH	125.9 CH	128.4 CH	128.3 CH	
BB/*o*CBD	**(21)**	139.7 C	124.6 CH	45.1 CH	40.4 CH	28.2 CH_2	30.3 CH_2	21.5 CH_3	147.8 C	111.5 CH_2	23.6 CH_3	102.6 CH	156.5 C	120.1 C	142.8 C	108.8 CH	154.9 C	35.8 CH_2	37.8 CH_2	141.8 C	128.4 CH	128.4 CH	125.9 CH	128.4 CH	128.4 CH	
BB/Δ^1THC	**(22)**	134.3 C	123.8 CH	33.7 CH	45.8 CH	25.1 CH_2	29.7 CH_2	23.3 CH_3	77.3 C	19.3 CH_3	27.6 CH_3	109.5 C	154.9 C	110.0 CH	142.0 C	107.6 CH	154.4 C	37.4 CH_2	37.4 CH_2	141.7 C	128.3 CH	128.3 CH	125.9 CH	128.3 CH	128.3 CH	
BB/Δ^6-THC	**(23)**	134.7 C	36.0 CH_2	31.6 CH	44.9 CH	27.9 CH_2	119.3 CH	23.4 CH_3	76.9 C	18.4 CH_3	27.5 CH_3	111.1 C	155.0 C	109.9 CH	141.9 C	107.8 CH	154.8 C	37.2 CH_2	37.3 CH_2	141.5 C	128.3 CH	128.3 CH	125.8 CH	128.3 CH	128.3 CH	
BB/*p*CBC	**(24)**	116.9 CH	127.3 CH	78.3 C	41.1 CH_2	22.7 CH_2	124.3 CH	131.6 C	25.6 CH_3	17.6 CH_3	26.2 CH_3	107.4 C	154.2 C	109.1 CH	143.3 C	107.9 CH	151.3 C	37.4 CH_2	37.8 CH_2	141.8 C	128.3 CH	128.4 CH	125.9 CH	128.4 CH	128.3 CH	
BB/*o*CBC	**(25)**	119.2 CH	126.8 CH	78.0 C	41.0 CH_2	22.7 CH_2	124.3 CH	131.5 C	25.6 CH_3	17.6 CH_3	26.1 CH_3	102.0 CH	156.1 C	112.7 C	139.4 C	108.7 CH	154.8 C	34.3 CH_2	37.4 CH_2	141.6 C	128.4 CH	128.4 CH	126.0 CH	128.4 CH	128.4 CH	
BB/Cit	**(26)**	83.6 C	35.4 CH_2	28.2 CH	46.9 CH	22.2 CH_2	38.1 CH_2	29.1 CH_3	74.5 C	23.7 CH_3	29.7 CH_3	114.5 C	156.8 C	109.0 CH	142.0 C	109.9 CH	157.1 C	37.8 CH_2	37.4 CH_2	141.4 C	128.4 CH	128.5 CH	125.8 CH	128.5 CH	128.4 CH	
BB/*p*CCY	**(27)**	83.3 C	46.4 CH	36.1 CH	37.6 CH	25.7 CH_2	37.7 CH_2	34.0 CH_3	39.1 C	17.9 CH_3	27.6 CH_3	109.0 C	154.2 C	110.5 CH	142.1 C	107.3 CH	154.2 C	38.0 CH_2	37.8 CH_2	141.5 C	128.3 CH	128.4 CH	125.9 CH	128.4 CH	128.3 CH	
BB/*o*CCY	**(28)**	83.5 C	46.6 CH	40.0 H	37.3 CH	26.0 CH_2	40.0 CH_2	34.1 CH_3	40.0 C	18.9 CH_3	25.3 CH_3	103.4 CH	154.5 C	126.6 C	141.9 C	108.8 CH	155.0 C	34.9 CH_2	37.2 CH_2	142.1 C	128.4 CH	128.4 CH	126.0 CH	128.4 CH	128.4 CH	
(OH)BB/*o*CBD	**(29)**	139.7 C	124.7 CH	45.0 CH	40.4 CH	28.2 CH_2	30.3 CH_2	21.5 CH_3	147.8 C	11.5 CH_2	23.6 CH_3	100.7 CH	158.9 C	120.0 C	142.5 C	107.9 CH	156.6 C	36.3 CH_2	37.0 CH_2	139.1 C	129.4 CH	115.2 CH	153.8 C	115.2 CH	129.4 CH	55.1 CH_3

[a] Close assignments may be interchanged.



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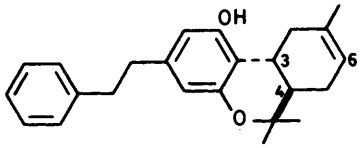

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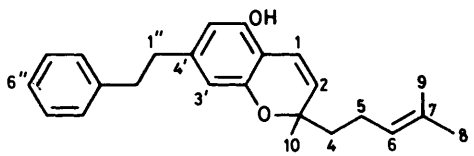

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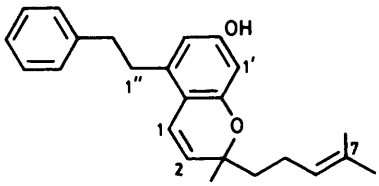

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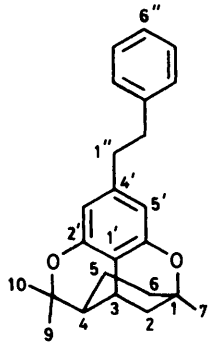

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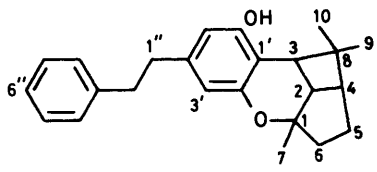

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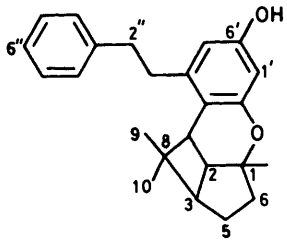

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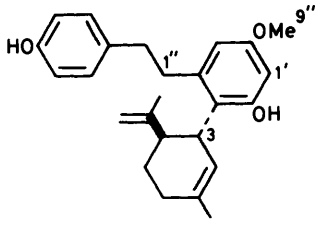

(29)

cannabidiol structures: on this basis, structure (**29**) is proposed.

With the objective of making the hybrid data set (**18**)—(**28**) complete, and the availability of ^1H and ^{13}C n.m.r. data (Tables 1 and 2) and chromatographic characteristics (Table 3) to hand, search for these 'crossed' types in *Cannabis* and other plants will be facilitated. It is hoped to describe such searches, along with g.l.c./m.s. data, in a later paper.

Experimental

Fast Blue Salt B Spray was freshly made up in dilute sodium hydroxide solution before use. Unless stated otherwise, n.m.r. data are reported in $CDCl_3$ solutions.

3,5-*Dimethoxybibenzyl* (**16**).—Sodium (1.61 g) was added to a stirred solution of 3,5-dimethoxybenzoic acid (5.07 g) in liquid ammonia (100 ml) under nitrogen at −70 °C. After 2.5 h the blue colour had disappeared and was replaced by a yellow precipitate: phenethyl bromide (10.38 g) was added with stirring and the mixture was allowed to attain room temperature overnight. The sodium salt was dissolved in water (300 ml), washed with ethyl acetate (3 × 50 ml), and then acidified to pH 4 (meter) with 2M-hydrochloric acid. The creamy precipitate was extracted into ethyl acetate. Drying and evaporation under reduced pressure gave 3,5-dimethoxy-1-phenethylcyclohexa-2,5-dienecarboxylic acid (**15**) (5.92 g, 74%), m.p. 81—82 °C, *m/z* 288.1350 and 244.1464 ($M^+ - CO_2$) ($C_{17}H_{20}O_4$ requires *M*, 288.1361), $\nu_{max.}(CHCl_3)$ 1 700 and 1 615 cm^{-1}; $\delta(CD_3COCD_3)$ 10.3 (1 H, br s, CO_2H, D_2O exchg.), 7.22 (3 H, d, *J* 2.0 Hz, ArH), 6.73 (2 H, t, *J* 2.0 Hz, ArH), 4.88 (2 H, m, =CH), 3.65 (6 H, s, 2 × OMe), and 2.75 and 2.69 (each 2 H, s, CH_2CH_2).

The above dihydro compound (5.92 g) with cupric acetate (0.1 g) was stirred in dry benzene (100 ml) and lead tetra-acetate (9.11 g) was added: CO_2 was evolved and the mixture was stirred overnight. The solution was decanted from gummy material, washed with 2M hydrochloric acid and water, dried, and evaporated. After chromatography on silica (eluting with chloroform) the 3,5-dimethoxybibenzyl (**16**)[15] was distilled (3.89 g, 78%), b.p. 86—88 °C/0.1 mmHg (Found: C, 79.0; H, 7.65%; M^+, 242.1293. Calc. for $C_{16}H_{18}O_2$: C, 79.3, H, 7.5%; *M*, 242.1307).

3,5-*Dihydroxybibenzyl* (**17**).—Boron tribromide (20.11 g) in dry dichloromethane (75 ml) was added to a stirred solution of the above dimethoxy compound (3.89 g) in dichloromethane (75 ml) under nitrogen at −70 °C. The mixture was allowed to attain room temperature and then stirred for 2 h. Water (50 ml) was added carefully and the product was extracted with ether. The ether extracts were themselves extracted with 2M aqueous sodium hydroxide. The alkaline extractives were acidified (2M hydrochloric acid) and re-extracted into ether. Evaporation and chromatography on silica (eluant 2% methanol in chloroform), followed by distillation, b.p. 167—169 °C/1 mmHg gave 3,5-dihydroxybibenzyl (2.44 g, 71%)[15] (Found: C, 78.8; H, 6.8%; M^+, 214.0983. Calc. for $C_{14}H_{14}O_2$: C, 78.5; H, 6.6%; *M*,

Table 3. Chromatographic data for bibenzyl/cannabinoid hybrids

		Visualisation	R_F for t.l.c. systems		R_t (min) for h.p.l.c. and g.l.c.	
		Fast-Blue Salt-B Colour[a]	Ether–hexane (1:3) (silica)[b]	Chloroform (silica)[b]	H.p.l.c. (%) Methanol in water (C_{18} reversed phase)[c]	G.l.c. on OV 17 (sample silylated)[d]
BB/*p*CBG	(**18**)	Orange-red	0.40	0.52	2.8 (85%)	45.0
BB/*o*CBG	(**19**)	Purple	0.10	0.14	3.6 (85%)	41.6
BB/*p*CBD	(**20**)	Orange-red	0.47	0.73	3.8 (85%)	21.5
BB/*o*CBD	(**21**)	Orange-pink	0.18	0.25	5.9 (85%)	26.5
BB/Δ^1THC	(**22**)	Purple	0.45	0.66	10.1 (85%)	48.6
BB/Δ^6THC	(**23**)	Crimson	0.58	0.70	9.3 (85%)	47.0
BB/*p*CBC	(**24**)	Purple	0.45	0.50	5.8 (85%)	45.0
BB/*o*CBC	(**25**)	Blue-purple	0.32	0.20	4.4 (85%)	31.5
BB/Cit	(**26**)	*e*	0.61	0.75	5.7 (95%)	55.0
BB/*p*CCY	(**27**)	Pink	0.55	0.66	6.2 (85%)	26.9
BB/*o*CCY	(**28**)	Brown-purple	0.27	0.20	5.5 (90%)	24.2

[a] FBSB in 5% aqueous KOH. [b] Thickness 0.25 mm: fluorescent indicator ($\lambda_{max.}$ 254 mm) present. [c] Run on 8 mm 10μ C_{18}-reversed phase Rad. Pak with solvent flow 2.0 ml min^{-1}. [d] Samples silylated with *N,O*-bistrimethylsilyltrifluoroacetamide and 1% trimethylchlorosilane at 60 °C for 15 min. Column OV 17 open tube capillary (50 M) at 220 °C, flow rate 5 ml/min. Injection ≯ 0.5 μl. Standard 3,5-dihydroxybibenzyl (R_t 6.2 min). [e] Detection u.v. or brown with iodine vapour.

214.0994); δ(CD_3COCD_3) 8.09 (2 H, s, OH, D_2O exchg.), 7.28 (5 H, m, ArH), 6.31 (3 H, m, ArH), and 2.84 (4 H, m, $ArCH_2CH_2Ar$).

o- *and* p-*Bibenzyl/Cannabigerol Hybrids* (**19**) *and* (**18**).—Geraniol (277.5 mg, 315 μl), was stirred at 20 °C for 20 min with a solution of 3,5-dihydroxybibenzyl (343.1 mg) and PTSA (144 mg) in dry benzene (10 ml). Aqueous sodium hydrogen carbonate was added and the mixture was worked up to afford a product which was chromatographed on a dry silica column [eluting with 100% light petroleum (b.p. 60—80 °C) ⟶ 100% ether]. Fractions containing the *p*-compound and those containing the *o*-compound were united. {Monitoring was by t.l.c. [silica, eluant light petroleum (b.p. 60—80 °C)—ether (2:1)] and visualisation was by Fast Blue Salt B Spray (the *o*-compound gave a purple colour and the *p*-a pink-purple) and g.l.c. (SCOT OV 17 column at 220 °C)}. Both compounds were further purified by reverse-phase C_{18} h.p.l.c. eluting with methanol–water (85:15). The *p*-isomer (**18**) had *m/z* 350.2228 ($C_{24}H_{30}O_2$ requires *M*, 350.2246): yield 86.1 mg (15%), $\lambda_{max.}$(EtOH) 267 (ε 1 010) and 280 nm (890). The *o*-isomer (**19**) had *m/z* 350.2234: yield 48.7 mg (9%), $\lambda_{max.}$(EtOH) 269i (1 540) and 282 nm (2 930).

A second experiment using bibenzyl (72.2 mg) and similar conditions gave the *p*-isomer (13% yield) and the *o*-isomer (15% yield).

(3R,4R)-o- *and* p-*Bibenzyl/Cannabidiol Hybrids* (**21**) *and* (**20**).—3,5-Dihydroxybibenzyl (92.2 mg) and PTSA (79.3 mg) were dissolved in dry benzene (10 ml) and (1*S*,4*R*)-*p*-menthadienol (100 μl) was added at 17 °C; the mixture was then stirred for 4 h. Aqueous sodium hydrogen carbonate was added and the organic layer was separated, washed, dried, and evaporated. The product was chromatographed on a dry silica column (1.2 × 7 cm) eluting with light petroleum (b.p. 60—80 °C)–ether (1:4) in steps. Fractions containing the *o*-compound and the *p*- compound were united [monitoring by t.l.c. as above *p*- (**20**) gives orange FBSB colour, *o*- (**21**) purple; and g.l.c. (OV 17/220 °C) after silylation by heating for 15 min at 60 °C with BSTFA—1% TMCS solution]. The yield of *p*-compound (**20**) was 27%, and *o*-(**21**) 13%. The two samples were further purified by C_{18}-reversed phase h.p.l.c. as above. A second run, using bibenzyl (453 mg) gave, after reversed phase C_{18} h.p.l.c. purifications, 152 mg (21%) of *p*-(**20**) and 63 mg (9%) of *o*-(**21**). The *p*-isomer (**20**) had *m/z* 348.2095 ($C_{24}H_{28}O_2$ requires *M*, 348.2089); $\lambda_{max.}$(EtOH) 273 (ε 1 400) and 282 (1 300) nm. The *o*-isomer (**21**) had *m/z* 348.2079, $\lambda_{max.}$(EtOH) 267infl (ε 1 240) and 283 nm (2 590).

(3R,4R)-*Bibenzyl/*Δ^6*-THC Hybrid* (**23**).—(1*S*,4*R*)-*p*-menthadienol (90 μl), 3,5-dihydroxybibenzyl (83.3 mg), and dry PTSA (49.7 mg) were refluxed together in dry benzene (5 ml) for 2.5 h. Sodium carbonate and water were added and the mixture was worked up to afford a product which was chromatographed on a dry silica column. It was applied to the column in light petroleum (b.p. 60—80 °C) containing 2 drops of ether and the column was developed with light petroleum–ether mixtures varying in proportions from 6:1 to 1:1. 22 Fractions were taken and examined by g.l.c. (after silylation) and t.l.c. (FBSB colours). Early fractions gave dull purple FBSB, and later ones purple colours, but the Δ^6-THC hybrid was in fractions 6—8 giving a crimson colour; the yield was 58.9 mg (43.5%). A second experiment using bibenzyl (592 mg) with purification by a dry column procedure similar to the above followed by preparative reversed phase C_{18}-h.p.l.c. (Prep Pak 500, elution methanol–water, 85/15) gave the (3R,4R)-*bibenzyl/*Δ^6*-THC* (247 mg, 26%) hybrid (Found: M^+, 348.2094. $C_{24}H_{28}O_2$ requires *M*, 348.2089); $\lambda_{max.}$(EtOH) 268i (ε 1 000), 275 (1 160), and 281 nm (1 220).

(3R,4R)-*Bibenzyl/*Δ^1*-THC Hybrid* (**22**).—Bibenzyl (**17**) (131.7 mg) and PTSA (101.9 mg) in dry benzene (10 ml) were equilibrated at 45 °C and (1*S*,4*R*)-*p*-menthadienol (130 μl) was added; the mixture was then stirred for 2 h with t.l.c. monitoring (t.l.c., FBSB) at intervals. The reaction was stopped by addition of aqueous sodium carbonate when small amounts of Δ^6-THC hybrid began to be formed. Work-up gave a product which when examined by g.l.c. (samples silanised) showed that almost all the bibenzyl had reacted, that *p*- and *o*-cannabidiol hybrids were present along with the Δ^1THC hybrid, but that little Δ^6THC hybrid had formed. Chromatography on a dry silica column eluting with light petroleum (b.p. 60—80 °C)–ether concentrations varying from 10:1 to 100% ether gave 24 fractions. Fractions 8—10 (52.8 mg) contained a mixture of Δ^1-THC and *p*-cannabidiol hybrids along with a little Δ^6-THC hybrid. Fractions 19—22 contained *o*- cannabidiol hybrid.

Fractions 8—10 were purified by reverse-phase C_{18} h.p.l.c. (eluting with methanol–water, 85:15) to give the *p*-cannabidiol hybrid (14.0 mg, 7%) and (3R,4R)-*bibenzyl/*Δ^1*-THC hybrid* (**22**)

(14.1 mg, 7%) (Found: M^+, 348.2071. $C_{24}H_{28}O_2$ requires M, 348.2089). A second experiment on about twice the above scale gave a yield of 9%.

The compound had $\lambda_{max.}$(EtOH) 268infl. (1 390), 274 (1 550), and 283 nm (1 600).

(±)-*Bibenzyl*/o- *and* p-*Cannibichromene Hybrids* (**25**) *and* (**24**).—3,5-Dihydroxybibenzyl (304.4 mg) was heated with citral (300 mg) and freshly distilled 2,6-di-t-butylpyridine (294 mg) at 160 °C for 5.5 h. The products were dissolved in ether and washed with 2M hydrochloric acid and water, dried, and evaporated. Silica gel chromatography gave a series of fractions monitored by g.l.c. (after silylation, on OV 17/220 °C) and t.l.c. (FBSB and iodine colours). Four products were located in order of elution (1) bibenzyl/cannabicitran hybrid—no colour with FBSB but brown with iodine; (2) bibenzyl/cannabicyclol–FBSB pink red; (3) bibenzyl/*p*-cannabichromen–FBSB purple; (4) bibenzyl/*o*-cannabichromen–FBSB blue-purple. Finally eluted was a little unchanged 3,5-dihydroxybibenzyl (FBSB purple). Fractions (1), (3), and (4) were further purified first by h.p.l.c. on μPorasil (eluant 1.5% ether in light petroleum (b.p. 60—80 °C), then by C_{18}-reversed phase h.p.l.c. [eluant methanol–water (85:15)]. This gave *bibenzyl*/p-*cannabichromene* (**24**) (75 mg, 15%), m/z 348.2061 ($C_{24}H_{28}O_2$ requires M, 348.2089), $\lambda_{max.}$(EtOH) 280 (ε 10 240) and 289 nm (9 670); *bibenzyl*/o-*cannabichromene* (**25**) (37 mg, 8%), m/z 348.2096, $\lambda_{max.}$(EtOH) 279 (ε 6 700), 287 (6 770), and 315 nm (4 640); and *bibenzyl*/*cannabicitran* (**26**) (6.3 mg), m/z 348.2106, $\lambda_{max.}$(EtOH) 280 nm (1 250).

3,5-Dihydroxybibenzyl (18.6 mg), citral (21.9 mg), and 2,4,6-trimethylpyridine (10.5 mg) were heated at 160 °C for 5.5 h. The mixture was then silylated (BSTFA + 1% TMCS, 60 °C, 15 min) and examined by g.l.c. (SCOT OV 17/220 °C, injection 250 °C). This gave the following proportions: recovered bibenzyl (**17**) (31%); BB/CCY's (**27**) and (**28**) 20%; BB/CBC's (**24**) and (**25**) 35%; BB/Cit (**26**) 14%.

Bibenzyl (**17**) (19.9 mg), citral (27.7 mg), and 2,6-di-t-butylpyridine (17.8 mg) heated and analysed as above gave the following proportions: recovered (**17**) 24%; BB/CCY's (**27**) and (**28**) 12%; BB/CBC's (**24**) and (**25**) 47%; BB/Cit (**26**) 17%.

Bibenzyl (**17**) (17.4 mg), citral (20.9 mg), and pyridine (6.5 mg) heated and analysed as above gave the following proportions: recovered (**17**) 40%; BB/CCY's (**27**) and (**28**) 5%; BB/CBC's (**24**) and (**25**) 52%; BB/Cit 3%.

(±)-*Bibenzyl*/o- *and* p-*Cannabicyclol Hybrids* (**28**) *and* (**27**).—*p*-Chromene (**24**) (42.5 mg) in dry acetone (10 ml) was irradiated under nitrogen overnight (Hanovia 450 W, Hg discharge lamp). Work-up and chromatography of the residue on silica (dry column), followed by reversed phase C_{18} h.p.l.c. [eluant methanol–water (85:15)] gave the p-*cyclol* (**27**) (8 mg, 18%), m.p. 60—61 °C, m/z 348.2103 ($C_{24}H_{28}O_2$ requires M 348.2089); $\lambda_{max.}$(EtOH) 276 (ε 1 320) and 280 nm (2 200).

In a similar way the *o*-chromene (**25**) (29.5 mg) gave the o-*cyclol* (**28**) (5 mg, 7%), m.p. 105—106 °C; m/z 348.2103; $\lambda_{max.}$(EtOH), 280 (ε 2 150), 284 (2 630), and 291 nm (2 390).

p-*Hydroxybibenzyl*/o-*Cannabidiol Monomethyl Ether Hybrid* (**29**).—3,4′-Dihydroxy-5-methoxybibenzyl (dihydrostilbene) (**7**) was prepared according to our earlier procedure.[14] The bibenzyl (**30**) (125 mg) was stirred with PTSA (106 mg) in dry benzene (10 ml) at 45 °C and *p*-menthadienol (120 μl) was added. Stirring was continued for 90 min. Addition of sodium hydrogen carbonate and work-up followed by chromatography of the residue on silica gel gave the p-*hydroxybibenzyl hybrid* (**29**) (11 mg, 6%), m/z 378.2208. ($C_{25}H_{30}O_3$ requires M, 378.2195); $\lambda_{max.}$(EtOH) 282 nm (ε 3 670); ^{13}C spectral data for ring A follows.

	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
Calc. for 2-OH, 6-OMe (**29**)[a]	101.5	156.8	119.9	143.2	107.2	159.6
Found	100.7	158.9	120.0	142.5	107.9	156.6
Calc. for 2-OMe, 6-OH[a]	101.5	155.2	108.4	143.2	118.7	161.2

[a] Data from this paper.

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