Total Synthesis of the Spirans of *Cannabis*: Cannabispiradienone, Cannabispirenone-A and -B, Cannabispirone, α- and β-Cannabispiranols and the Dihydrophenanthrene Cannithrene-1

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O-Methylcannabispirenone has been synthesised (57% overall from 3,5-dimethoxycinnamic acid) *via* 5,7-dimethoxyindanone, *p*-tolylsulphonylmethyl isocyanide conversion into the 1-nitrile, alkylation with 1-iodo-3,3-ethylenedioxybutane, deacetalisation, and spirocyclisation. 5,7-Dimethoxyindanone is 7-deprotected by boron trichloride with high selectivity, and re-protected as the methoxyethoxymethyl ether: following the above route, finally deprotecting by boron trichloride, gives cannabispirenone-A (2) in 21% overall yield. *O*-Methylcannabispirenone can be demethylated to give (2) by lithium 1,1-dimethylethanethiolate: demethylation with boron tribromide gives cannabispirenone-B (3).

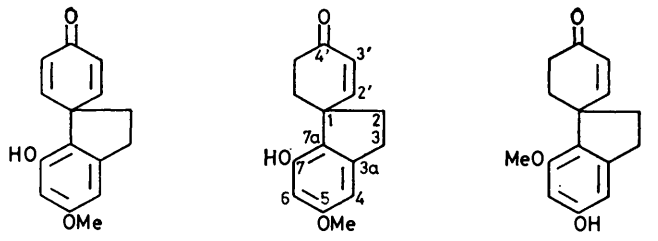
Hydrogenation of synthetic cannabispirenone-A gives cannabispirone (4), reduced by borohydride to the epimeric α-(6) and β-(5) cannabispiranols, separated by h.p.l.c. Dehydrogenation of *O*-methylcannabispirenone with dichlorodicyanobenzoquinone, followed by lithium 1,1-dimethylethanethiolate demethylation, gives cannabispiradienone (1). Under acidic conditions, the latter undergoes dienone–phenol rearrangement to give cannithrene-1 (8), thus completing the total synthesis of the spiro-cannabinoid group of natural products discussed in the preceding paper. The unsubstituted cannabispirenone parent has also been synthesised.

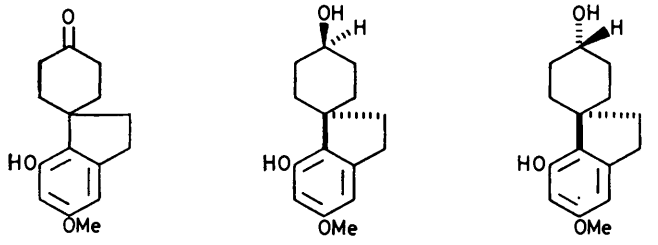
RECENT studies on *Cannabis sativa* have led to the isolation of six spirans, cannabispiradienone (1),[1,2] cannabispirenone-A (2),[3-5] cannabispirenone-B (3),[6] cannabispirone (4),[3,4,7] β-cannabispiranol (5),[5,8] and α-cannabispiranol (6).[1] They have been shown to co-occur in a single variety of Thailand *Cannabis* (drug type).[1,2] Five of the spirans can be derived by *o*-*p*-coupling of the diradical arising from the dihydrostilbene (7) (which occurs in *Cannabis*) the sixth through *p*-*p*-coupling, presumably *via* a dienone isomeric with (1) which has not been isolated from the plant. Also co-occurring is the trioxygenated dihydrophenanthrene (8) [1,2] which is related to (1) *via* a dienone–phenol rearrangement, and dihydrophenanthrene (9). Structurally, the spiro-compounds (1)—(6) bear resemblance to certain synthetic spirans known to potentiate the action of stilbestrol,[9] adding to their pharmacological interest. There is considerable current interest in non-cannabinoid components of *Cannabis* which may influence the action of whole-leaf drug and this has led us to undertake a synthesis of the family of spirans (1)—(6) and the associated dihydrophenanthrene (8).

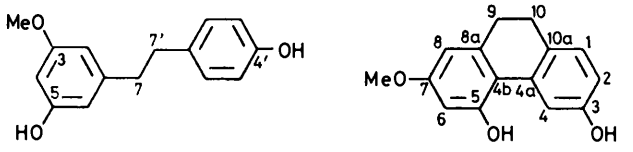
The enone (2) is a chiral molecule unlike (1) and (4)—(7). From *Cannabis* leaf it has been isolated in both (−)- and (±)-forms [2] and the latter, and its *O*-methyl ether, were selected as the first objectives. The retrosynthetic plan was (2) ⟶ (15) ⟶ (19) ⟶ (11) ⟶ (10). For preliminary work, the indancarbonitrile (12a) was made by refluxing 1-chloroindan with sodium cyanide in dimethylformamide (DMF) and it was found to be converted into the aldehyde (20) in good yield by di-isobutylaluminium hydride (DIBAL) [10] reduction. However, a better method of forming the nitrile was required. Reaction of indanone with *p*-tolylsulphonylmethyl isocyanide (TOSMIC) [11] has been reported to proceed in 55% yield.[12] In our laboratory yields of *ca.* 40% were obtained, but when these conditions were extended to 5,7-dimethoxyindanone yields were poor even when solvent variations were tried [*hexamethylphosphoric triamide* (HMPA) and *dimethyl sulphoxide* (DMSO)]. However, when the dimethoxyindanone (11b) was treated in dimethoxyethane (DME) with 10 equiv. of potassium t-butoxide, and the TOSMIC added slowly as recommended by Bull and Tuinman,[13] a high yield of nitrile (12b) (84%) could be obtained: this was converted into the aldehyde (21) by DIBAL reduction in almost quantitative yield.

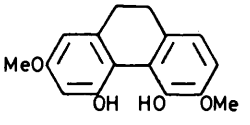
Spiroannulation by treating compound (21) with methyl vinyl ketone led to the required spirenone (16b) but we were dissatisfied by the yields, and under some conditions, *e.g.* 2 mol methyl vinyl ketone with Triton B catalyst, (22) and (23) were isolated along with the spirenone. The latter is derived by a second Michael step involving methyl vinyl ketone, leading to (24), followed by aldol cyclisation. An alternative approach was suggested by the observation that 4-methoxycarbonylindan-1-carbonitrile can be satisfactorily methylated using sodium hydride in DMSO.[14] Generating the anion from indan-1-carbonitrile in the same way, we were able to alkylate it with 3-iodobutanone ethylene acetal (25), a reagent which has been used as an electrophile in other alkylations,[15] to give compound (13a) in 81% yield. DIBAL reduction then proceeded smoothly at temperatures below 0 °C to give the γ-keto-aldehyde (94%) protected as its acetal (14a); use of DIBAL at higher temperatures produced some evidence of cleavage at the carbon–oxygen bond of the acetal, as has been noted by others.[10] Deprotection gave the keto-aldehyde (15a) (70%), which was cyclised by base in good yield (80%) to the spirenone (16a).

Extension of the alkylation procedure to the dimethoxynitrile (12b) was rather disappointing as (13b) formed in much reduced yield (40%). Since *o*,*p*-OMe groups might have adverse influences on the formation of the benzylic anion, a stronger base, lithium diethylamide in





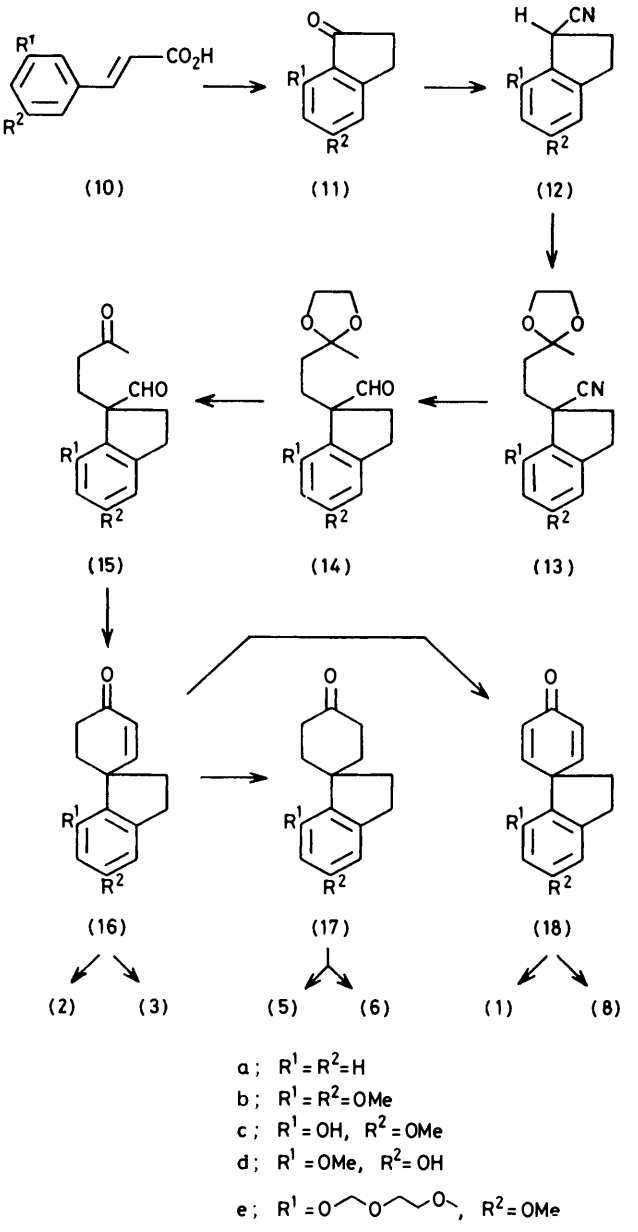




HMPA–THF at −78 °C,[16] was tried. Using the unmethoxylated nitrile (12a) as a model, a coloured anion formed, but addition of the iodoacetal (25) did not discharge this until the mixture was warmed to −50 °C: the acetal-nitrile (13a) was then isolated in yields of >90%. In the case of the dimethoxynitrile (12b), the red–brown anion was decolourised almost immediately at −75 °C and the acetal-nitrile (13b) was isolated in 91% yield. With this preliminary work completed the full synthesis of *O*-methylcannabispirenone was as follows.

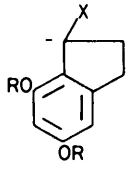
3,5-Dimethoxycinnamic acid (10b) was hydrogenated (Pd–C) to 3,5-dimethoxyphenylpropionic acid in almost theoretical yield and cyclised to give the dimethoxyindanone (11b) (91%) with polyphosphoric acid. Conversion into the nitrile (12b) using TOSMIC proceeded in 84% yield, and the alkylation with (25), to give (13b), in 84% yield. Reduction with DIBAL at −78 °C gave the aldehyde (99%), deacetalised by M-hydrochloric in tetrahydrofuran (98%) and cyclised by aqueous potassium hydroxide to (±)-*O*-methylcannabispirenone (16b) (92%). Spectral and other comparisons showed this to be the same as the *O*-methyl ether of natural cannabispirenone-A. The overall yield was 57% from the 3,5-dimethoxycinnamic acid or 63% from 3,5-dimethoxyindanone.

In order to prepare the half-methylated phenol cannabispirenone-A, the dimethoxyindanone was selectively



demethylated in high yield (96%) using boron trichloride at 0 °C to give (11c). The high regioselectivity is doubtless due to boron complexation involving the 1-carbonyl group (aluminium chloride was less selective).[17] The half methyl ether was then 7-*O*-protected as the methoxyethoxymethyl (MEM) [18] ether (11e) (88%) using potassium carbonate–18-crown-6 as the base. Yields in the TOSMIC reaction were poorer (51%) than for (12b), and this resulted largely from greater difficulty in getting clean separation during the chromatographic purifi-

cation. The nitrile (12e) was alkylated as before to give (13e) (87%), reduced with DIBAL at low temperature to the aldehyde (98%), deacetalised with toluene-*p*-sulphonic acid in acetone–water at 20 °C (96%), and cyclised with base to give (16e) (87%). The MEM protecting group was removed selectively by boron trichloride at −78 °C to give, after chromatography, (±)-cannabispirenone-A (69%), m.p. 172.5—173.5 °C, identical in all respects with the (±)-compound isolated from *Cannabis*.[2] The overall yield from 5,7-dimethoxycinnamic acid was 19%.



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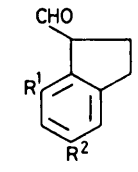
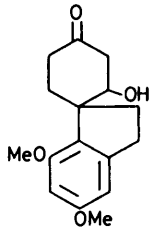


(20) $R^1 = R^2 = H$
(21) $R^1 = R^2 = OMe$



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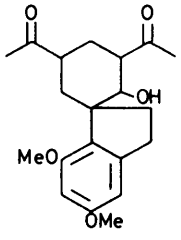

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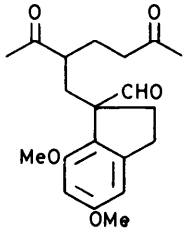

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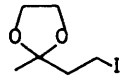

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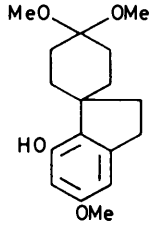

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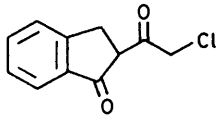

(27)

(±)-Cannabispirenone-B (3) was obtained from low-temperature partial demethylation of the *O*-methyl ether (16b), with boron tribromide in dichloromethane, 32% after chromatographic separation. No m.p. has been recorded for the natural compound, nor apparently is it known if it is optically active, but mass-spectral data and ^{13}C n.m.r. data recorded by Kettenes-van den Bosch and Salemink [6] leave little doubt that their identification of the natural substance is correct. Data agree well with those for our synthetic enone-ether-B, which is very clearly distinguishable from cannabispirenone-A. Other demethylating agents were tried for the partial demethylation of (16b), among them lithium 1,1-dimethylethanethiolate.[19] Using this we were able to monodemethylate (16b) regioselectively to give (±)-cannabispirenone-A (2) in 85% yield. This provides an attractive alternative to the MEM-protection approach given above.

Starting from synthetic (±)-cannabispirenone-A and its *O*-methyl ether, the remaining four naturally occurring spirans, and the natural phenanthrene (8) have been synthesised. (±)-Cannabispirenone-A was catalytically hydrogenated (Pd–C, ethyl acetate) to cannabispirone (4) in theoretical yield: with the same catalyst in methanol the dimethyl acetal (26) was also formed and characterised. Reduction of cannabispirone with sodium borohydride gave a mixture of α-(6) and β-(5) cannabispiranols (4 : 1) which were separated by h.p.l.c. on a C_{18}-reversed phase column. All three reduction products of (2) were identical with natural specimens isolated from Thailand *Cannabis*: these reactions have earlier been effected on natural (2).[2-5]

O-Methylcannabispirenone (16b) could be dehydrogenated in dioxan under nitrogen with DDQ at 100 °C in excellent yield (91%) and the dienone was isolated as pale yellow crystals. Demethylation by lithium 1,1-dimethylethanethiolate in HMPA under argon allowed the isolation of cannabispiradienone (1) (82%) identical in all respects with the natural product isolated in our previous paper.[2] Finally, a spiro-dienone rearrangement of compound (1) was carried out to give the natural dihydrophenanthrene, cannithrene-1 (8), again identical with material isolated from *Cannabis*.[2] In the previous paper [1,2] the rearrangement of (1)→(8) was observed as a thermal reaction using natural cannabispiradienone: this time the rearrangement was carried out under acid conditions and gave (8) in 56% yield.

In early experiments Darzen's condensation,[20] dimethyl sulphoxonium methylide,[21] ethoxymethylene Grignard reagents,[22] and the Wittig reaction [23] were examined briefly in connexion with the conversion (11a) or (11b) into (20) or (21). These all gave poorer preliminary results than our nitrile route. In the Darzens condensation, using either the usual conditions,[20] or those employed by Borch (lithium bistrimethylsilylamide),[24] enolate formation by the indanone is frustrating and (27) becomes a major product as found by Barnes *et al.*[25] After publication of the preliminary account of our work [26] an alkoxymethylene-Wittig approach to the aldehyde (21) was reported, and the latter was converted into the dimethoxy-compound (16b) by methyl vinyl ketone annulation.[27]

EXPERIMENTAL

All evaporations were under reduced pressure. Visualisation of t.l.c. plates was by Fast Blue Salt B in 0.1M-sodium hydroxide or iodine vapour.

5,7-Dimethoxyindan-1-one (11b).—3,5-Dimethoxycinnamic acid (25.5 g) was hydrogenated in ethyl acetate (500 ml) over 5% Pd–C to give 3-(3,5-dimethoxyphenyl)propionic acid (25.6 g) in almost theoretical yield. Crystallised from light petroleum (b.p. 40—60 °C) it had m.p. 60—62 °C

(lit.,[28] m.p. 61—62 °C), $\nu_{max.}$ (KBr) 1 705 cm^{-1}. The acid (25.0 g) was heated with polyphosphoric acid (250 g) at 70 °C for 2 h. Work-up by pouring into 2M-sodium hydroxide and extraction with benzene gave 5,7-dimethoxyindan-1-one (11b) (21.0 g, 91%), m.p. 98—99 °C from ether–dimethoxyethane (lit.,[28] m.p. 98.5—99.5 °C), $\nu_{max.}$ (KBr) 1 690 cm^{-1}; δ ($CDCl_3$), 2.57—2.73 (m, 2 H, 2-CH_2), 2.98—3.12 (m, 2 H, 3-CH_2), 3.94 (s, 3 H, 5-OMe), 4.0 (s, 3 H, 7-OMe), 6.40 (d, 1 H, 6-H), and 6.58 (d, 1 H, 4-H).

7-Hydroxy-5-methoxyindan-1-one (11c).—Boron trichloride (25 g, 0.21 mol) was added to 5,7-dimethoxyindanone (21 g, 0.11 mol) in dichloromethane (1 l, refluxed over and distilled from P_2O_5) at 0 °C; the mixture was stirred for 2 h, and then poured into ice–water. Work-up gave *7-hydroxy-5-methoxyindanone* (11c) (18.7 g, 96%), m.p. 103—103.5 °C from ether (Found: C, 67.2; H, 5.65%; M^+, 178.0640. $C_{10}H_{10}O_3$ requires C, 67.4; H, 5.65%; *M*, 178.0630), $\nu_{max.}$ (KBr) 1 665 cm^{-1}; δ ($CDCl_3$) 2.67 (t, 2 H, *J* 6 Hz, 2-CH_2), 3.05 (t, 2 H, *J* 6 Hz, 3-CH_2), 3.85 (s, 3 H, OMe), 6.28 (d, 1 H, *J* 1.5 Hz, 6-H), 6.47 (d, 1 H, *J* 1.5 Hz, 4-H), and 9.17 (br s, 1 H, D_2O exch., OH).

5-Methoxy-7-methoxyethoxymethyloxyindan-1-one (11e).—β-Methoxyethoxymethyl chloride (10.5 g, 0.084 mol) was added dropwise to a mixture of 7-hydroxy-5-methoxyindanone (10 g, 0.056 mol), anhydrous potassium carbonate (11.7 g, 0.084 mol), and a catalytic quantity of 18-crown-6 in dry acetone (1 l; refluxed over, and distilled from K_2CO_3). The mixture was stirred at 20 °C for 24 h and then filtered and the filtrate evaporated. The residual oil was dissolved in ethyl acetate, and the solution was washed, dried, and evaporated to give the *title compound* (11e) (13.1 g, 88%), m.p. 48—49.5 °C (M^+, 266.1151. $C_{14}H_{18}O_5$ requires *M*, 226.1154), $\nu_{max.}$ (KBr) 1 687 cm^{-1}; δ ($CDCl_3$) 2.48—2.77 (m, 2 H, 2-CH_2), 2.84—3.05 (m, 2 H, 3-CH_2), 3.36 (s, 3 H, Me of MEM), 3.4—3.6 (m, 2 H, MeOCH_2CH_2O), 3.87 (s, 3 H, OMe), 3.7—3.9 (m, 2 H, MeOCH$_2CH_2$O), 5.37 (s, 2 H; CH_2CH_2O-CH_2O). 6.51 (d, 1 H, *J* 1 Hz, 6-H), and 6.58 (d, 1 H, *J* 1 Hz, 4-H). The use of Corey's sodium hydride–dimethoxyethane base system [18] led to mixtures of products.

5,7-Dimethoxyindan-1-carbonitrile (12b).—5,7-Dimethoxyindan-1-one (8 g, 0.0417 mol) in dimethoxyethane (400 ml) was added slowly, with stirring at 0 °C under nitrogen, to potassium t-butoxide [from potassium (16.25 g, 0.417 mol) and t-butyl alcohol (420 ml, freshly distilled from calcium hydride)]. The solution was allowed to warm to 20 °C and *p*-tolylsulphonylmethyl isocyanide (TOSMIC) (16.32 g, 0.0836 mol) added during 2 h. The red-brown solution was stirred (48 h) and then cooled to 0 °C; saturated aqueous sodium chloride (100 ml) was then added with vigorous stirring. The mixture was poured into saturated aqueous sodium chloride (800 ml) and extracted with ether (4 × 250 ml). The extracts were pooled and washed (saturated sodium chloride), dried, and evaporated to give a semi-solid product. Chromatography on neutral alumina (activity 1), with hexane and ether as eluant gave *5,7-dimethoxyindan-1-carbonitrile* (7.1 g, 84%), needles from cyclohexane, m.p. 94—95 °C (Found: C, 70.75; H, 6.5; N, 6.7%; M^+, 203.0951. $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.4; N, 6.9%; *M*, 203.0946), $\nu_{max.}$ (KBr) 2 260 cm^{-1} (CN); δ ($CDCl_3$) 6.32 (m, 1 H, 4-H), 6.26 (d, 1 H, *J* 2 Hz, 6-H), 3.92 (t, 1 H, *J* 7.5 Hz, 1-H), 3.76 (s, 3 H, 5-OMe), 3.68 (s, 3 H, 7-OMe), 2.96 (dd, 2 H, *J* 16, 7.5 Hz, 3-CH_2), and 2.24—2.52 (m, 2 H, 2-CH_2).

5-Methoxy-7-methoxyethoxymethyloxyindan-1-carbonitrile (12e).—The MEM-protected indanone (11e) (4 g, 0.015 mol) was converted into the nitrile by the procedure above using TOSMIC (5.86 g, 0.03 mol) added in dry dimethoxyethane (25 ml) added during 2 h. Work-up using flash-chromatography on Kieselgel 60 (230—240 mesh), with ether–hexane (1 : 1) as eluant gave the *nitrile* (12e) as a yellow oil (2.13 g, 51%) (M^+, 277.1322. $C_{15}H_{19}NO_4$ requires *M*, 277.1314), $\nu_{max.}$ 2 265 cm^{-1} (CN); δ ($CDCl_3$), 2.28—2.36 (m, 2 H, 2-CH_2), 2.99 (m, 2 H, 3-CH_2), 3.36 (s, 3 H, Me of MEM), 3.44—3.6 and 3.78—3.92 (m's, 2 × 2 H, OCH_2CH_2O), 3.76 (s, 3 H, ArOMe), 4.04 (t, 1 H, *J* 7 Hz, CHCN), 5.29 (d, 2 H, OCH_2O), 6.39 (d, 1 H, *J* 1 Hz, 6-H), and 6.53 (d, 1 H, *J*1 Hz, 4-H).

5-Methoxy-7-methoxyethoxymethyloxy-1-(3,3-ethylenedioxybutyl)indan-1-carbonitrile (13e).—n-Butyl-lithium (1.5M in hexane; 8 ml, 0.012 mol) was added dropwise to diethylamine (0.88 g, 0.012 mol) in dry tetrahydrofuran (20 ml; refluxed and distilled from lithium aluminium hydride) at 0 °C under nitrogen. The clear yellow solution was stirred at 0—5 °C for 15 min and then hexamethylphosphoric amide (HMPA) (10 ml, distilled from calcium hydride) was added (syringe); the solution was then cooled to −78 °C and stirred (30 min). 7-Methoxyethoxymethyloxy-5-methoxyindan-1-carbonitrile (12e) (3 g, 0.011 mol) in dry tetrahydrofuran (5 ml) and HMPA (5 ml) were added dropwise *via* a syringe: the solution became deep red-brown. After addition, the lithionitrile solution was stirred for 2 h at −78 °C. 1-Iodo-3,3-ethylenedioxybutane (7.98 g, 0.033 mol) in dry THF (6 ml) and HMPA (2 ml) was added dropwise to give a pale yellow solution. The reaction mixture was stirred at −78 °C for 30 min and then for 1 h at room temperature. Ammonium chloride solution was added to the mixture which was then extracted with ethyl acetate, washed with brine, dried (K_2CO_3), and evaporated to give a brown oil. This was chromatographed on alumina, with ether as eluant, to give the nitrile (13e) (3.68 g, 87%) as a colourless oil (M^+, 391.1998, $C_{21}H_{29}NO_6$ requires *M*, 391.1995); n.m.r.: δ 1.29 (s, 3 H, Me attached to ethylenedioxy ring), 1.5—2.7 (m, 6 H, 3-CH_2's), 2.93 (t, 2 H, *J* 7.5 Hz, ArCH_2), 3.37 (s, 3 H, $CH_3OCH_2CH_2O$) 3.46—3.6 and 3.78—3.92 (m, 4 H, methylenes of MEM), 3.86 (s, 4 H, acetal protons), 3.76 (s, 3 H, ArOMe), 5.3 (d, 2 H, OCH_2O), 6.35 (d, 1 H, *J* 2 Hz, 6-H), and 6.54 (d, 1 H, *J* 2 Hz, 4-H).

5,7-Dimethoxy-1-(3,3-ethylenedioxybutyl)indan-1-carbonitrile (13b).—Similarly prepared from the dimethoxynitrile (12b) (0.92 g) the *title compound* (13b) (1.2 g, 84%) was isolated, after chromatography, as needles from cyclohexane, m.p. 60—61 °C (Found: C, 68.1; H, 7.4; N, 4.2%; M^+, 317.1641. $C_{18}H_{23}NO_4$ requires C, 68.1; H, 7.30, N, 4.4%; *M*, 317.1627, $\nu_{max.}$ 2 260 cm^{-1} (CN); n.m.r.: δ 6.20 (m, 2 H, 4- and 6-ArH), 3.85 (s, 4 H, acetal protons), 3.82 (s, 3 H, 5-OMe), 3.75 (s, 3 H, 7-OMe), 2.90 (t, 2 H, *J* 7.5 Hz, ArCH_2), 1.5—2.7 (m, 6 H, 3 × CH_2), and 1.30 (s, 3 H, Me attached to ethylenedioxy-ring).

5,7-Dimethoxy-1-(3,3-ethylenedioxybutyl)indan-1-carbaldehyde (14b).—The above nitrile (13b) (2.5 g, 7.9 mmol) in dry toluene (50 ml) was stirred under nitrogen at − 78 °C and di-isobutylaluminium hydride (DIBAL) (7.5 ml of a 25% solution in toluene, 13.2 mmol) was added slowly *via* a syringe. The mixture was stirred at −78 °C for 2.5 h (the reaction being monitored by g.l.c. on 2% OV-17 on Chromosorb W at 250 °C). Saturated aqueous ammonium chloride was added and the solution was allowed to warm to room temperature when aqueous acetic acid (10%, 50 ml) was added and the solution stirred vigorously for 30 min. The organic layer was separated and the aqueous phase extracted

with ether (3 × 100 ml). The extracts were pooled and washed successively with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride and then dried (K_2CO_3). Evaporation of the solvent left a clear viscous oil (2.5 g, 99%), virtually pure by g.l.c. (2% OV-17/250 °C). The *acetal-aldehyde* (14b) was analysed as the *semicarbazone*, m.p. 219—220 °C (Found: C, 60.65; H, 7.45; N, 11.1. $C_{19}H_{27}N_3O_5$ requires C, 60.5; H, 7.2; N, 11.15%). For (14b): $\nu_{max.}$ (film) 1 725 cm^{-1} (C=O); ^1H n.m.r.: δ ($CDCl_3$) 1.28 (s, 3 H, Me adjacent to acetal), 1.36—2.64 (m, 6 H), 2.90 (t, 2 H, *J* 7 Hz, $ArCH_2$), 3.76 and 3.80 (each s, 3 H, 5- and 7-OMe), 3.90 (s, 4 H, acetal protons), 6.24 (d, 1 H, *J* 2 Hz, 6-H), 6.36 (d, 1 H, *J* 2 Hz, 4-H), and 9.60 (1 H, CHO).

5-*Methoxy*-7-*methoxyethoxymethyloxy*-1-(3,3-*ethylenedioxybutyl*)*indan*-1-*carbaldehyde* (14e).—Reduced with DIBAL (8.5 ml of 25% solution in toluene) by the method above, the methoxy MEM-nitrile (13e) (3.55 g) gave the *aldehyde* (14e) (3.51 g, 98%) as a pale yellow oil, $\nu_{max.}$ (film) 1 725 cm^{-1} (M^+, 394.1979. $C_{21}H_{30}O_7$ requires *M*, 394.1991), ^1H n.m.r. ($CDCl_3$): 1.28 (s, 3 H, Me adjacent to acetal), 1.37—2.70 (m, 6 H), 2.90 (t, 2 H, *J* 7 Hz, $ArCH_2$), 3.36 (s, 3 H, Me of MEM), 3.44—3.6 and 3.78—3.92 (m, 4 H, OCH_2CH_2O), 3.75 (s, 3 H, ArOMe), 3.86 (s, 4 H, acetal protons), 5.19 (s, 2 H, OCH_2O), 6.36 (d, 1 H, *J* 2 Hz, 6-H), 6.51 (d, 1 H, *J* 2 Hz, 4-H), and 9.54 (s, 1 H, CHO).

5,7-*Dimethoxy*-1-(3-*oxobutyl*)*indan*-1-*carbaldehyde* (15b).—The acetal (14b) (6 g) in tetrahydrofuran (100 ml) and M-hydrochloric acid (50 ml) was kept under nitrogen for 12 h when g.l.c. analysis (2% OV17/250 °C) showed completion of the reaction. The mixture was poured into saturated aqueous sodium chloride (100 ml) and extracted with ether; the combined extracts were then washed with saturated brine and dried ($MgSO_4$). Evaporation of the solvent gave the title δ-*keto-aldehyde* as a viscous oil (5.1 g, 98%), pure by g.l.c. (M^+, 276.1348. $C_{16}H_{20}O_4$ requires *M*, 276.1361), $\nu_{max.}$ (film) 1 725 (aldehyde) and 1 710 cm^{-1} (ketone); ^1H n.m.r. ($CDCl_3$): δ 9.48 (s, 1 H, CHO), 6.34 (m, 1 H, 4-H), 6.22 (d, 1 H, *J* 2 Hz, 6 H), 3.78 (s, 3 H, 5-OMe), 3.74 (s, 3 H, 7-OMe), 2.90 (t, 2 H, *J* 7.5 Hz, $ArCH_2$), 2.10—2.52 (m, 4 H, methylenes), 2.08 (s, 3 H, MeCO), and 1.64—2.0 (m, 2 H, 2-CH_2).

5-*Methoxy*-7-*methoxyethoxymethyloxy*-1-(3-*oxobutyl*)*indan*-1-*carbaldehyde* (15e).—The methoxy-MEM-acetal (14e) (3.4 g) was stirred for 20 h at 20 °C with toluene-*p*-sulphonic acid (1 g) in acetone (45 ml) and water (22 ml). The acetone was removed under reduced pressure, ether was added, and the reaction mixture was extracted with ethyl acetate to give the MEM-protected δ-*keto-aldehyde* (15e) (2.9 g, 96%), a pale yellow oil (M^+, 350.1738. $C_{19}H_{26}O_6$ requires *M*, 350.1729), $\nu_{max.}$ 1 725 (aldehyde), 1 710 cm^{-1} (ketone); ^1H n.m.r.: δ ($CDCl_3$) 1.61—2.01 (m, 2 H, 2-CH_2), 2.04 (s, 3 H, CH_3CO) 2.06—2.52 (m, 4 H, methylenes), 2.89 (t, 2 H, *J* 7 Hz, $ArCH_2$), 3.30 (s, 3 H, $CH_3OCH_2CH_2$), 3.42—3.59 and 3.58—3.83 (m's, 4 H, OCH_2CH_2O), 3.71 (s, 3 H, ArOMe), 5.14 (s, 2 H, OCH_2O), 6.33 (d, 1 H, *J* 2 Hz, 6-H), 6.46 (d, 1 H, *J* 2 Hz, 4-H), and 9.44 (s, 1 H, CHO).

O-*Methylcannabispirenone* (16b).—The ketoaldehyde (15b) (4.8 g) in methanol (75 ml) was cooled to O °C with stirring under nitrogen. Aqueous potassium hydroxide (10%; 50 ml) was added and the solution was stirred at 20 °C for 24 h. The methanol was evaporated off and the mixture was extracted with ether (4 × 50 ml). The pooled extracts were washed (brine), dried, and evaporated to give (±)-O-*methylcannabispirenone* (15b) (4.1 g, 92%), m.p. 107—108.5 °C (Found: C, 74.1; H, 6.75. $C_{16}H_{18}O_3$ requires C, 74.4; H, 7.0%), $\nu_{max.}$ (KBr) 1 640 cm^{-1} (C=O). The ^1H n.m.r. spectrum ($CDCl_3$) showed identity with that of the naturally derived methyl ether of cannabispirenone-A (which was partially optically active), m.p. 110—112 °C.[2] On admixture no clear m.p. depression was observed. ^{13}C N.m.r. ($CDCl_3$): δ 31.05 (t, C-5′), 31.17 (t, C-3), 35.38 (t, C-6′), 35.50 (t, C-2), 48.42 (s, quaternary C-1), 54.97 and 55.38 (each q, two OMe), 97.07 (d, C-6), 100.99 (d, C-4), 126.25 (d, C-3′), 127.42 (s, C-7a), 145.84 (s, C-3a), 156.90 (s, C-7), 158.42 (d, C-2′), 161.22 (s, C-5), and 199.52 p.p.m. (s, C-4′).

5-*Methoxy*-7-*methoxyethoxymethyloxy*-1-*spiro*-1′-*cyclohex*-2′-*en*-4′-*one* (16e).—Similarly cyclised, the keto-aldehyde (15e) (2.85 g) gave an oil (2.60 g) which was purified by flash-chromatography on Kieselgel 60 (230—240 mesh) with ethyl acetate–hexane (3 : 7) as eluant to give the MEM-protected *spirenone* (16e) (2.34 g, 87%) as a pale yellow oil, $\nu_{max.}$ (film) 1 673 cm^{-1} (α-unsat. ketone) (M^+, 332.1637. $C_{19}H_{24}O_5$ requires *M*, 332.1624), ^1H n.m.r.: δ ($CDCl_3$) 1.8—2.7 (m, 6 H, 3 alicyclic methylenes), 2.7—3.12 (m, 2 H, $ArCH_2$), 3.37 (s, 3 H, $CH_3O{\cdot}CH_2CH_2$), 3.44—3.6 and 3.64—3.84 (m's, 4 H, OCH_2CH_2O), 3.78 (s, 3 H, ArOMe), 5.19 (s, 2 H, OCH_2O), 5.94 (d, 1 H, *J* 10 Hz, CH=C*H*CO), 6.43 (d, 1 H, *J* 2 Hz, 6-H), 6.55 (d, 1 H, *J* 2 Hz, 4-H), and 6.91 (d, 1 H, *J* 10 Hz, C*H*=CHCO).

(±)-*Cannabispirenone-A* (2).—Boron trichloride (706 mg) was added dropwise *via* a syringe to a solution of the MEM-protected compond (16e) (1.00 g) in dry dichloromethane (100 ml; refluxed over and distilled from P_2O_5) at −78 °C. The mixture was then stirred for 1 h after which dry methanol (20 ml) was added at −78 °C; stirring of the mixture was continued in the acetone–solid CO_2 bath until room temperature was attained. The solvents were evaporated to give a brown oil which crystallised. It was purified by flash-column chromatography on Kieselgel 60 with ethyl acetate–hexane (3 : 7) as eluant. (±)-*Cannabispirenone-A* (505 mg, 69%) had m.p. 172—173 °C and its m.p. was undepressed on admixture with authentic (±)-cannabispirenone-A of natural derivation (m.p. 172.5—173.5 °C) [2] (Found: *M*, 244.1087. $C_{15}H_{16}O_3$ requires *M*, 244.1099). It had $\nu_{max.}$ (KBr) 1 640 (C=O), 1 610, 1 597, and 1 497 cm^{-1}; $\lambda_{max.}$ (EtOH) 205 (40 800), 228 (20 600), and 284 nm (2 520). The ^1H n.m.r. spectrum was identical with that of the natural material,[2] as was the mass spectrum. ^{13}C N.m.r. ($CDCl_3$): δ 31.26 (t, C-5′), 31.43 (t, C-3), 35.5 (t, C-6′), 35.96 (t, C-2), 48.34 (s, C-1), 55.54 (q, OMe), 100.86 (d, C-6), 102.74 (d, C-4), 125.70 (s, C-7a), 127.91 (d, C-3′), 146.61 (s, C-3a), 153.17 (s, C-7), 157.55 (s, C-2′), 161.19 (s, C-5), and 199.80 (s, C-4′). Zinc bromide [18] proved ineffective for the deprotection whilst titanium tetrachloride or boron tribromide gave poor yields.

(±)-*Cannabispirenone-A by Demethylation of Compound* (16b).—The dimethyl ether (16b) (100 mg) in HMPA (5 ml) was stirred and heated to 70 °C under an argon atmosphere. Lithium 1,1-dimethylethanethiolate (1 ml of a 2M-solution in HMPA) was added *via* a syringe and the product was stirred 2 h at 70 °C. After the mixture had been cooled to 0 °C, saturated aqueous ammonium chloride was added and the product was extracted with ethyl acetate. Washing, drying, and evaporation of the extract gave a product which was purified by flash chromatography on Kieselgel 60 with hexane containing 30% of ethyl acetate as eluant. (±)-Cannabispirenone-A (2) (80 mg, 85%) crystallised from ethyl acetate–hexane, m.p. and mixed m.p. 173—174 °C. It was

identical with naturally derived (±)-cannabispirenone-A [2] as judged by i.r., n.m.r., and mass spectral and t.l.c. evidence.

(±)-*Cannabispirenone-B by Demethylation of Compound* (16b).—The dimethyl ether (16b) (1.0 g) in dry dichloromethane (50 ml) was stirred and cooled to −78 °C under nitrogen and boron tribromide (15.6 ml; 0.5 M-solution in dichloromethane) was added *via* a syringe. The solution was stirred for 30 min at −78 °C and then 2—3 h at −10 to 0 °C, after which dry methanol (20 ml) was added to it. Following this, the solution was stirred (15 min) and poured into brine and extracted with chloroform. Washing, drying, and evaporation of the extract gave a brown solid which was chromatographed on silica gel with hexane–ethyl acetate as eluant. This gave (±)-*cannabispirenone-B* (3) (0.30 g, 32%), m.p. 238—242 °C (decomp.) from ethyl acetate–hexane (Found: C, 73.65; H, 6.4%; M^+, 244.1125, $C_{15}H_{16}O_3$ requires C, 73.75; H, 6.60%; *M*, 244.1100), *m/e* 244, 216 (base peak), and 173; $\nu_{max.}$ (KBr) 3 300 (OH) and 1 645 cm^{-1} (C=O); ^1H n.m.r. (CD_3COCD_3): δ 6.87 (dd, 1 H, *J* 10.1 and 1.9 Hz, 2′-H), 6.33 (dt, 1 H, *J* 2 Hz and 1 Hz, 4-H), 6.30 (d, 1 H, *J* 2 Hz, 6-H), 5.81 (d, 1 H, *J* 10.1 Hz, 3′-H), 3.70 (s, 3 H, OMe), 2.9 (m, 2 H, 3-CH_2), 2.3—2.6 (m, 4 H), and 2.03—1.93 (m, 2 H); ^{13}C n.m.r.: δ [$(CD_3)_2SO$] 30.46 (t, C-5′), 30.82 (t, C-3), 34.82 (t, C-6′), 35.17 (t, C-2), 47.84 (s, C-1, quaternary), 55.02 (q, OMe), 97.53 (d, C-6), 103.47 (d, C-4), 125.38 (s, C-7a), 125.56 (d, C-3′), 145.55 (s, C-3a), 156.55 and 158.67 (each s, C-7 and C-5), 158.93 (d, C-2′), and 198.48 (s, C-4′).

Although no m.p. is given for natural cannabispirenone-B,[6] nor is it clear if the compound is optically active or not, comparison of spectral data (i.r., ^1H n.m.r., mass spectral and ^{13}C n.m.r.) clearly indicate identity of the two compounds.

Cannabispirone (4).—Cannabispirenone-A (2) (50 mg) was hydrogenated over 5% Pd–C (25 mg) in ethyl acetate (25 ml): the theoretical amount of hydrogen was absorbed. The catalyst was filtered off and the solvent evaporated to give cannabispirone (51 mg), m.p. 181—182 °C from ethyl acetate (lit.,[2] m.p. 179—180 °C) and mixed m.p. (M^+, 246.1263. $C_{15}H_{18}O_3$ requires *M*, 246.1256), $\nu_{max.}$ (KBr) 1 687 (C=O) cm^{-1}; $\lambda_{max.}$ (EtOH) 207 (32 500), 224 (9 290), 276 (1 830), and 284 nm (1 940). The ^1H n.m.r. spectrum ($CDCl_3$) was identical with that of the natural product. ^{13}C N.m.r. ($CDCl_3$): δ 30.96 (t, C-3), 34.4 (t, C-2′),* 34.4 (t, C-6′),* 35.64 (t, C-2), 38.96 (t, C-3′),* 38.96 (t, C-5′),* 47.66 (s, C-1), 55.46 (q, OMe), 101.00 (d, C-6), 102.12 (d, C-4), 126.91 (s, C-7a), 146.34 (s, C-3a), 153.31 (s, C-7), 160.34 (s, C-5), and 213.74 p.p.m. (s, C-4′). The mass spectrum was also in agreement with that for the natural material.

When cannabispirenone-A was hydrogenated in methanol, the *dimethyl acetal* (26), m.p. 155—157 °C was also formed (M^+, 292.1697. $C_{17}H_{24}O_4$ requires *M*, 292.1674). No carbonyl absorption was present, $\nu_{max.}$ (KBr) 1 616 and 1 590 cm^{-1}. The n.m.r. spectrum ($CDCl_3$) contained two new OMe groups appearing as a 6 H singlet at δ 3.32.

O-*Methylcannabispiradienone* (18b).—*O*-Methylcannabispirenone (1 g) in freshly distilled dioxan (70 ml) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (2.65 g) were stirred and heated at 100 °C under nitrogen for 48 h. After being cooled to 20 °C, the solution was filtered and the precipitate well washed with ether. The combined organic extracts were washed successively with 1 M-sodium hydroxide and water, and dried (K_2CO_3). Evaporation gave the *dienone* (18b) as a pale yellow solid (0.9 g, 91%), m.p. 118—120 °C from ether (Found: C, 74.8; H, 6.1. $C_{16}H_{16}O_3$ requires C, 75.0; H, 6.25%), $\nu_{max.}$ 1 655 cm^{-1} (cyclohexadienone carbonyl); ^1H n.m.r. ($CDCl_3$): δ 6.80 and 6.16 (A_2B_2 quartet, 4 H, *J* 10 Hz, olefinics of dienone), 6.36 (m, 1 H, 4-H), 6.18 (d, 1 H, *J* 2 Hz, 6-H), 3.80 (s, 3 H, 5-OMe), 3.60 (s, 3 H, 7-OMe), 3.05 (t, 2 H, *J* 7.5 Hz, 3-CH_2), and 2.22 (t, 2 H, *J* 7.5 Hz, 2-CH_2); ^{13}C n.m.r. ($CDCl_3$): δ 31.87 (t, C-3), 38.08 (t, C-2), 52.13 (s, C-1 quaternary) 55.19 (q, OMe), 55.52 (q, OMe), 97.4 (d, C-6), 101.56 (d, C-4), 121.4 (s, C-7a), 127.09 (d, C-3′ and C-5′), 146.90 (s, C-3a), 153.05 (d, C-2′ and C-6′), 157.58 (s, C-7), 162.05 (s, C-5), and 186.48 (s, C-4′).

Cannabispiradienone (1).—*O*-Methylcannabispiradienone (255 mg) in hexamethylphosphoric amide (10 ml) was stirred and heated to 70 °C in an argon atmosphere. Lithium 1,1-dimethylethanethiolate (4 ml of 2 M-solution in HMPA: this was prepared from 1,1-dimethylethanethiol and lithium hydride in HMPA for 5 h at 50 °C and stored under argon) was added slowly *via* a syringe and the red-brown solution was stirred for 2 h at 70 °C. The mixture was cooled to 0 °C and aqueous ammonium chloride was added to it; it was then extracted with ethyl acetate. The combined extracts were washed thoroughly with water to remove HMPA, dried ($MgSO_4$), and evaporated. The solid product was purified by chromatography on silica gel 60 (230—400 mesh) with hexane containing 30% ethyl acetate as eluant. *Cannabispiradienone* (1) (198 mg, 82%)formed pale yellow crystals from ethyl acetate–hexane, m.p. 174—176 °C (decomp.) (Found: C, 74.3; H, 6.0%; M^+, 242.0959. $C_{15}H_{14}O_3$ requires C, 74.4; H, 5.8%; *M*, 242.0943). It had $\lambda_{max.}$ (EtOH), 212, 239.5, 277, 284, and 306sh nm; $\nu_{max.}$ (KBr) 1 655 cm^{-1}. On admixture with a natural specimen,[1,2] m.p. 172—174 °C (decomp.) there was no depression. ^1H n.m.r. data for natural and synthetic specimens were identical. ^{13}C N.m.r.: δ [$(CD_3)_2SO$] 31.23 (t, C-3), 37.49 (t, C-2), 51.52 (s, C-1 quaternary), 55.05 (q, OMe), 100.00 (d, C-6), 101.21 (d, C-4), 119.41 (s, C-7a), 126.35 (d, C-3′, C-5′), 147.08 (s, C-3a), 153.61 (d, C-2′, C-6′), 154.99 (s, C-7), 160.90 (s, C-5), and 185.48 p.p.m. (s, C-4′).

Cannabispiradienone (10 mg) was hydrogenated over 5% Pd–C in ethyl acetate at atmospheric pressure and room temperature with absorption of 2 mol equiv. of hydrogen to give cannabispirone (8.5 mg, 85%), m.p. and mixed m.p. 181—182 °C.

α- *and* β-*Cannabispiranols* (6) *and* (5).—Sodium borohydride (50 mg) was added to a solution of synthetic cannabispirone (50 mg) in methanol (3 ml). After the mixture had been stirred for 3 h, the methanol was evaporated off and the colourless solid residue was treated with water and extracted with ethyl acetate. The pooled extracts were evaporated and purified by h.p.l.c. using a C_{18}-reversed phase column and with methanol-water (9 : 1) as eluant to give β-*cannabispiranol* (5) (3.5 mg, 7%), m.p. 190—192 °C from ethyl acetate: mixed m.p. with naturally derived material [2] m.p. 190—192 °C showed no depression. The synthetic specimen had M^+, 248.1427 ($C_{15}H_{20}O_3$ requires *M*, 248.1412). The ^1H n.m.r. spectrum in CD_3COCD_3 was identical with that of β-cannabispiranol of natural origin, as was the mass spectrum.

Also eluted was α-*cannabispiranol* (6) (16.7 mg, 33%), m.p. 176—177 °C from ethyl acetate (and mixed m.p. with natural material [2] m.p. 176 °C). It had M^+, 248.1422 ($C_{15}H_{20}O_3$ requires *M*, 248.1412). The ^1H n.m.r. spectrum

* Assignments for the 2′/6′ and 3′/5′ pairs may be interchanged.

(CD_3COCD_3) and mass spectrum confirmed identity with the specimen of natural origin.[2]

Cannithrene-1 (8).—Cannabispiradienone (1) (50 mg) in glacial acetic acid (5 ml) was treated, with cooling, with 2 drops of concentrated hydrochloric acid and the mixture was kept at 20 °C (48 h). Dilution with water, neutralisation with sodium hydrogen carbonate and extraction with ethyl acetate gave a gum. This was chromatographed on Kieselgel 60 (230—400 mesh) with ethyl acetate–hexane (2 : 3) as eluant to give *cannithrene*-1 (28 mg, 56%), m.p. 189—191 °C: the compound darkened on prolonged exposure to the atmosphere (Found: C, 74.25; H, 5.65. $C_{15}H_{14}O_3$ requires C, 74.4; H, 5.8%), $\lambda_{max.}$ (EtOH) 220, 265sh, 274, 301, and 310 nm. The synthetic specimen did not depress the m.p. of cannithrene-1 extracted from *Cannabis*,[1,2] m.p. 189 °C. The ^1H n.m.r. spectrum (CD_3COCD_3) was identical with that of the natural specimen. ^{13}C n.m.r.: δ [$(CD_3)_2SO$] 28.3 (t, C-10), 30.7 (t, C-9), 100.5 (d, C-6), 112.1 (d, C-2 or C-4), 104.9 (d, C-8), 114.2 (s, C-4b), 114.7 (d, C-4 or C-2), 127.2 (s, C-10a), 127.4 (d, C-1), 133.6 (s, C-4a), 141.1 (s, C-8a), 155.8 (s, C-5 or C-3), 155.2 (s, C-3 or C-5), 158.5 (s, C-7), and 54.8 p.p.m. (q, OMe).

Indan-1-*carbonitrile* (12a).—Indan-1-one was reduced with sodium borohydride to give indan-1-ol (89.5%), m.p. 52.5—53.5 °C (lit.,[29] m.p. 49—50 °C) and converted into the 1-chloro-compound [30] (96%), b.p. 88—92 °C/5 mmHg by thionyl chloride treatment. 1-Chloroindan (6.1 g) was stirred under nitrogen for 6 h at 50 °C with sodium cyanide (3 g) in dry DMF (400 ml).

Dilution with water and extraction with benzene gave, after chromatography on silica and elution with chloroform, indan-1-carbonitrile (5 g, 87%), b.p. 84—86 °C/0.3 mmHg, n_D^{24} 1.5415 (Found: C, 84.0; H, 6.1; N, 9.5. Calc. for $C_{10}H_9N$: C, 83.9; H, 6.3; N, 9.8%), $\nu_{max.}$ (film) 2 250 (CN) cm^{-1}; ^1H n.m.r.: δ 7.10—7.50 (m, 4 H, aromatics), 4.04 (t, 1 H, *J* 8 Hz, 1-H), 2.80—3.10 (m, 2 H, $ArCH_2$), and 2.10—2.60 (m, 2 H, 2-CH_2).

Indan-1-*carbaldehyde* (20).—Indan-1-carbonitrile (5.8 g) in dry ether (200 ml) was stirred under nitrogen at 0 °C and DIBAL (60 ml; 1M-in hexane) was added and the solution stirred (2 h) at 20 °C.

Treatment with 5% sulphuric acid (cooling) and extraction with ether gave, after hydrogen carbonate and water washing, the aldehyde (20) (4.1 g, 70%), a clear oil which was analysed as its *semicarbazone*, m.p. 168—169 °C (Found: C, 64.95; H, 6.35; N, 20.45. $C_{11}H_{13}N_3O$ requires C, 65.0; H, 6.4; N, 20.7%). The aldehyde had $\nu_{max.}$ (film) 1 710 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ 9.68 (d, 1 H, *J* 4 Hz, CHO), and 3.90 (m, 1 H, 1-H).

1-(3,3-*Ethylenedioxybutyl*)*indan*-1-*carbonitrile* (13a).—Sodium hydride (3.2 g, 50% dispersion in mineral oil) was washed several times with dry, light petroleum (b.p. 40—60 °C) under nitrogen. Dimethyl sulphoxide (100 ml; distilled *in vacuo* from calcium hydride) was added and the mixture was stirred (45 min). Indan-1-carbonitrile (3.8 g) in DMSO (60 ml) was added slowly and the resulting solution stirred for 1.5 h. The flask was cooled in ice and 1-iodo-3,3-ethylenedioxybutane (8 g) in DMSO (10 ml) was added with stirring under nitrogen and stirred for a further 3 h. The mixture was poured onto crushed ice and the products were extracted with ether; the extract was washed with brine and dried (K_2CO_3). Evaporation of solvent and distillation of the residue gave the *nitrile* (13a) (5.6 g, 81%), b.p. 138—142 °C/0.1 mmHg (Found: C, 74.5; H, 7.2, N, 5.3%. $C_{16}H_{19}NO_2$ requires C, 74.7; H, 7.4; N, 5.45%), $\nu_{max.}$ 2 250 cm^{-1} (CN); ^1H n.m.r. ($CDCl_3$): δ 7.0—7.4 (m, 4 H, ArH), 3.88 (s, 4 H, ethyleneacetal) 2.96 (t, 2 H, *J* 7 Hz, 3-H), 1.60—2.72 (complex m, 6 H), and 1.32 (s, 3 H, Me adjacent to acetal).

1-(3,3-*Ethylenedioxybutyl*)*indan*-1-*carbaldehyde* (14a).—The nitrile (13a) (4 g) in ether (200 ml) was treated slowly at −20 °C with DIBAL (15 ml; 25% solution in toluene) under nitrogen and stirred for 5 h at 0 °C (monitored by g.l.c. on 2% OV 17 at 200 °C after working up aliquots at intervals). Work-up with aqueous ammonium chloride and then 10% aqueous acetic acid gave the aldehyde (14a) (3.8 g, 94%) which was pure as judged by g.l.c.; $\nu_{max.}$ 1 710 cm^{-1} (aldehyde); ^1H n.m.r. ($CDCl_3$): δ 9.48 (s, 1 H, CHO), 7.02—7.36 (m, 4 H, aromatics), 3.90 (s, 4 H, acetal protons), 2.96 (t, 2 H, *J* 7.5 Hz, 3-CH_2), 1.50—2.70 (complex m, 6 H), and 1.30 (s, 3 H, Me adjacent to acetal).

1-(3-*Oxobutyl*)*indan*-1-*carbaldehyde* (15a).—The acetal aldehyde (14a) (3.8 g) in tetrahydrofuran (100 ml) and M-aqueous hydrochloric acid (50 ml) were kept under nitrogen at 20 °C overnight (g.l.c., 2% OV 17, 200 °C, showed reaction complete). The reaction mixture was poured into brine, and the product was extracted with ether. Washing (brine), drying ($MgSO_4$), and evaporation of the extract gave the aldehyde (2.2 g, 70%), pure as adjudged by g.l.c., $\nu_{max.}$ 1 720 (aldehyde) and 1 710 cm^{-1} (ketone); ^1H n.m.r. ($CDCl_3$): δ 9.38 (s, 1 H, CHO), 7.0—7.3 (m, 4 H, aromatics), 2.96 (t, 2 H, *J* 7 Hz, 3-CH_2), 2.12 (s, 3 H, MeCO), 2.24—2.60 (m, 4 H), and 1.80—2.20 (m, 2 H, 2-CH_2). It was used directly for cyclisation.

Indan-1-*spirocyclohex*-2′-*en*-4′-*one* (16a).—The keto-aldehyde (15a) (1.5 g) in methanol (30 ml) was treated with 10% aqueous potassium hydroxide (20 ml) and the mixture was kept overnight at 20 °C. Methanol was removed under reduced pressure and water added; the product was then extracted with ether. Washing (brine), drying ($MgSO_4$), and evaporation of the extract gave the spirocyclohexenone (16a) (1.10 g, 80%), m.p. 47—48 °C (lit.,[31] m.p. 41 °C) (Found: M^+, 198.1053. Calc. for $C_{14}H_{14}O$: *M*, 198.1045), $\nu_{max.}$ (KBr) 1 678 cm^{-1} (unsatd. C=O); $\lambda_{max.}$ (EtOH), 214 (12 000), 225 (11 100), 263 (2 120), and 271 nm (1 390); ^1H n.m.r. ($CDCl_3$): δ 2.0—2.3 (m, 4 H, two alicyclic methylenes) 2.53 (t, 2 H, *J* 6 Hz, CH_2COCH=CH), 2.95—3.15 (m, 2 H, $ArCH_2$), 6.04 (d, 1 H, *J* 10 Hz, COCH=CH), 6.76 (d, 1 H, *J* 10 Hz, COCH=CH), and 7.04—7.32 (m, 4 H, 4 × Ar*H*); ^{13}C n.m.r. ($CDCl_3$): δ 30.43, 33.90, 34.93, 37.81 (all t, 4 × 1C, four methylenes), 49.66 (s, 1-C quaternary) 123.53, 125.11, 126.70, 127.64 (all d, 4 × 1C, four unsubstituted aromatic carbons), 128.47 (d, C-3′), 143.08, 147.26 (s, two substituted aromatic carbons), 156.22 (d, C-2′), 199.27 p.p.m. (s, C=O); *m/e* 198 (100) M^+, 170 (57), 156 (41), 155 (7), 142 (19), 141 (39), 128 (11), and 115 (30).

5,7-*Dimethoxyindan*-1-*carbaldehyde* (21).—The nitrile (12b) (2 g) was reduced with DIBAL (6 ml; 25% solution in toluene) by the procedure given previously to give 5,7-dimethoxyindan-1-carbaldehyde (2 g, 98%), $\nu_{max.}$ 1 710 cm^{-1} (aldehyde); ^1H n.m.r. ($CDCl_3$): δ 9.72 (d, 1 H, aldehyde), 6.52 (m, 1 H, 4-H), 6.40 (d, 1 H, *J* 2 Hz, 6-H), 4.06 (m, 1 H, 1-H), 3.92 (s, 3 H, 5-OMe), 3.90 (s, 3 H, 7-OMe), 3.04 (t, 2 H, *J* 7.5 Hz, 3-H), and 2.20—2.60 (m, 2 H, 2-CH_2). It was used directly in the next experiments.

Spiro-annulation of 5,7-*Dimethoxyindan*-1-*carbaldehyde*.—The aldehyde (21) (0.8 g, 3.9 mmol) and freshly distilled methyl vinyl ketone (0.5 g, 7.1 mmol) in dry t-butyl alcohol (10 ml) and dimethoxyethane (10 ml) was cooled to −40 °C with stirring under nitrogen. Triton B (1.6 ml; 40%

solution in methanol) was added to the mixture which was then stirred for 1 h at −40 °C, 1 h at 0 °C, and 3 h at 20 °C. It was poured into saturated ammonium chloride (100 ml) and extracted with ethyl acetate. After drying ($MgSO_4$) and evaporation the mixture was separated by p.l.c. on silica gel HF 254 with ether–hexane (3 : 1) as eluant. After removal of the least polar band which crystallised from ether–hexane, m.p. 107.5—108.5 °C and mixed m.p. with *O*-methylcannabispirenone, the next polar band crystallised from ether to give the *spirohydroxycyclohexanone* (22), m.p. 125—127 °C (60 mg) (Found: C, 69.4; H, 7.1%; M^+, 276.1370. $C_{16}H_{20}O_4$ requires C, 69.55; H, 7.30%; *M*, 276.1361), $\nu_{max.}$ (KBr) 3 350—3 500 (OH), 1 700 cm^{-1} (C=O); ^1H n.m.r. ($CDCl_3$): δ 6.40 (d, 1 H, *J* 2.3 Hz, 4-H), 6.30 (d, 1 H, *J* 2.3 Hz, 6-H), 4.65 (dd, 1 H, $J_{ax.ax}$ 12.3 Hz, $J_{ax.-eq.}$ 5.3 Hz, 2′-H), 3.80 (s, 3 H, 5-OMe), 3.76 (s, 3 H, 7-OMe), 3.00 (m, 2 H, 3-H), 2.70 (dd, 1 H, J_{gem} 14.8 Hz, $J_{ax,eq}$ 5.3 Hz, 3′-H_{eq}), 2.30—2.60 (m, 5 H), 2.00 (m, 2H, 2-CH_2), and 1.63 (s, 1 H, OH, D_2O exchg.); ^{13}C n.m.r. ($CDCl_3$): δ 28.42 (t, C-3), 30.47 (t, C-5′), 31.75 (t, C-2), 38.30 (t, C-6′), 46.84 (t, C-3′), 54.68 (s, C-1, quaternary), 55.03 (q, OMe), 55.44 (q, OMe), 71.23 (d, C-2′), 97.365 (d, C-6), 101.34 (d, C-4), 124.15 (s, C-7a), 147.60 (s, C-3a), 157.31 (s, C-7), 161.28 (s, C-5), and 209.53 (s, C-4′).

The third product isolated was the *diacetyl-spiran* (23) (15 mg), m.p. 165—166 °C, from ether (Found: C, 69.4; H, 7.65%; M^+, 346.1796. $C_{20}H_{26}O_5$ requires C, 69.35; H, 7.5%; *M*, 346.1780), $\nu_{max.}$ (KBr) 3 350—3 550 (OH) and 1 710 cm^{-1} (C=O); ^1H n.m.r. ($CDCl_3$): δ 6.35 (d, 1 H, *J* 2 Hz, 4-H), 6.29 (d, 1 H, *J* 2 Hz, 6-H), 4.55 (dd, 1 H, $J_{ax.ax}$ 12.3 Hz, $J_{ax.eq}$ 2.8 Hz, 2′-H), 3.78 (s, 6 H, 2 × OMe), 2.93 (m, 2 H, 3-H), 2.25 (s, 3 H, CH_3CO), 2.14 (s, 3 H, CH_3CO), and 1.63 (s, 1 H, OH).

1-*Iodo*-3,3-*ethylenedioxybutane* (25).—1-Chlorobutan-3-one (75% yield), b.p. 60—62 °C/15 mmHg (lit.,[15] b.p. 39—44 °C/12 mmHg), 1-iodobutan-3-one (96% yield), and 1-iodo-3,3-ethylenedioxybutane, b.p. 60—62 °C/0.05 mmHg (62% after distillation) (lit.,[15] b.p. 60—62 °C/0.05 mmHg) were prepared according to Trost and Kunz.[15]

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