Terpenylations Using (*R*)-(−)-α-Phellandrene. Synthesis of the (3*S*,4*R*)-8,9-Dihydro-*o*- and -*p*-cannabidiols, their iso-THC's, and the Natural Dihydrochalcone (3*S*,4*R*)-(+)-Linderatin

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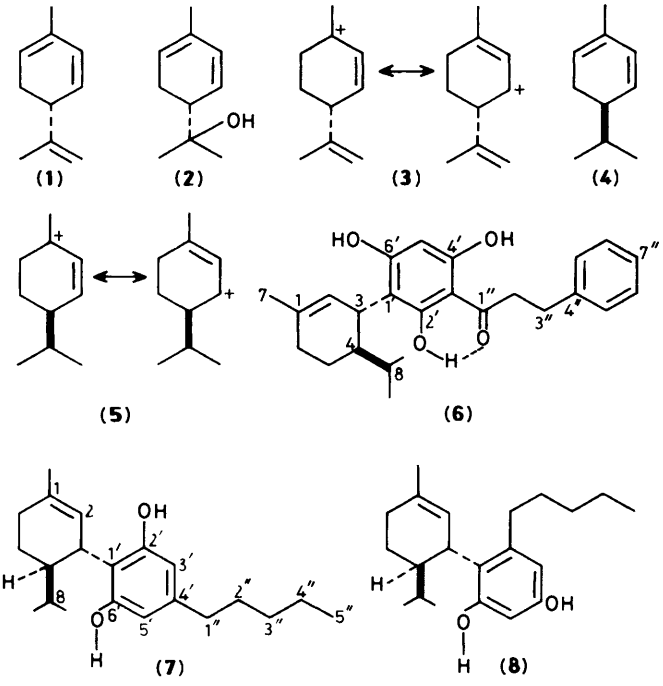
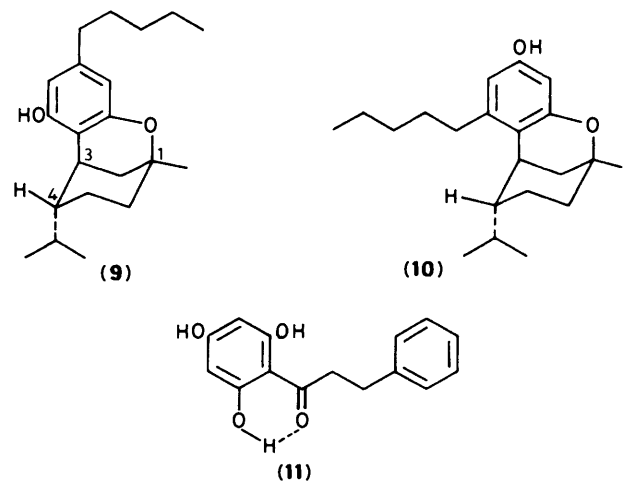
Catalysed by toluene-*p*-sulphonic acid at 5 °C,(*R*)-(−)-α-phellandrene reacts with olivetol to give (3*S*,4*R*)-8,9-dihydro-*p*- and -*o*-cannabidiols. At 80 °C under the acid conditions the latter retrogresses substantially to the former and both cyclise giving 51% of (1*S*,3*S*,4*R*)-8,9-dihydro-*p*-iso-tetrahydrocannabinol and only 3% of the corresponding *o*-isomer. ^{1}H N.m.r. and ^{13}C N.m.r. data show that (3*S*,4*R*)-8,9-dihydro-*p*-cannabidiol (but not *o*-) is undergoing restricted rotation near room temperature. By terpenylation of a suitably substituted dihydrochalcone using (*R*)-(−)-α-phellandrene the natural meroterpene linderatin was synthesized in 46% yield and shown to be the (3*S*,4*R*)-(+)-stereoisomer.

Entries into cannabinoid synthesis frequently involve carbonium ions generated from suitable chiral terpenic alcohols. In the preceding paper[1] it was shown that the likely route to cannabidiol and Δ^1- and Δ^6-THC's from the toluene-*p*-sulphonic acid (PTSA) catalysed condensation of car-3-ene epoxide with olivetol involves generation of the 2,6,8-triene (**1**), which can be trapped as α-phellandren-8-ol (**2**). Proton addition to (**1**) gives the allylic cation (**3**) which is the effective terpenylating agent for olivetol in this and certain other methods. α-Phellandren-8-ol itself may be used, and gives Δ^6-THC in *ca.* 40% yield. In this paper the terpenylation of olivetol using the cation (**5**) derived by PTSA treatment from (*R*)-(−)-α-phellandrene (**4**) itself, is examined. The reaction is then extended to a synthesis of the recently discovered terpenylated dihydrochalcone (+)-linderatin (**6**)[2] thereby establishing its absolute configuration.



Treatment of olivetol with (*R*)-(−)-α-phellandrene at 5 °C for 5 min, catalysed by PTSA in benzene, produced a mixture of (3*S*,4*R*)-8,9-dihydro-*p*-cannabidiol (**7**) (24% by g.l.c.) and (3*S*,4*R*)-8,9-dihydro-*o*-cannabidiol (**8**) (17% by g.l.c.), stereoisomers of compounds reported from terpenylation with piperitol.[2] Chromatographic isolation gave the two compounds in yields of 26 and 19% and n.m.r. data verify that each is a *trans*- compound ($J_{3,4}$ for *p*- = 9.8 Hz, for *o*- = 9.9 Hz). R_F Characteristics and Fast Blue Salt B colours parallel those of *p*- and *o*-cannabidiols themselves, and the *p*-compound (**7**) has $\lambda_{max.}$ 274 and 282 nm characteristic for the *p*- (or 'normal') series.[3] As had been observed for natural cannabidiol,[4,5] the *p*-dihydrocannabidiol (**7**) shows evidence for restricted rotation near room temperature. In the ^{1}H n.m.r. spectrum the 3'- and 5'-protons of the aromatic ring appear as a broadened singlet δ 6.20 at 313 K, which splits into two sharp signals as the temperature is lowered (δ 6.39 and 6.31 measured at 210 K). Similar evidence appears in the ^{13}C n.m.r. spectrum (293 K) where the resonances for C-3' and -5' and C-2' and -6' stand out as broad peaks (δ 108.9 and 155.5 respectively) among the sharp lines of the proton decoupled spectrum. The *o*-compound, where the energy barrier to rotation is heightened, has four distinct signals for the ^{13}C resonances of these atoms.

At higher temperature (80 °C) the α-phellandrene/olivetol reaction, sampled at 20 min, showed 28% of (3*S*,4*R*)-dihydro-*p*-cannabidiol (**7**) and only 0.3% of the *o*-isomer (**8**). Also formed was 25% of the (1*S*,3*S*,4*R*)-8,9-dihydro-iso-THC (**9**) derived from the *p*-series with only 2% of the (1*S*,3*S*,4*R*)-*o*-series isomer (**10**). This provides clear evidence of the reversibility of the terpenylation giving dihydrocannabidiol with the *o*- being a kinetic product, but the *p*- being thermodynamically favoured.



After 2 h no *p*- or *o*-dihydrocannabidiol remained and the product was a mixture of 51% of (**9**) and 3% of (**10**) as estimated by g.l.c. Isolation and separation by chromatography gave a 47% yield of (**9**) with 4% (**10**). The *p*- isomer had $\lambda_{max.}$ 274 and 282 nm as expected. Attention was then turned to linderatin.

Linderatin occurs in the hexane extract of fresh leaves of *Lindera umbellata* Thunb. (var. lancea Momiyama), a small deciduous tree which grows in the mountains of Japan. Its structure has recently been shown to be the *p*-menth-1-enylated dihydrochalcone (**6**) by Tanaka and his colleagues[2] though information on its absolute configuration has been lacking. The dihydrochalcone (**11**) required for synthesis occurs in *L. umbellata* and has been made earlier:[6,7] our supply was obtained by acylation of phloroglucinol and also by the Hoesch procedure. Treatment of compound (**11**) with (*R*)-(−)-α-phellandrene in the presence of PTSA in benzene at 25 °C for 45 min gave linderatin in 46% yield after purification by reversed phase C_{18} h.p.l.c. The synthetic structure was compared spectrally (^{1}H and ^{13}C n.m.r., u.v., and i.r.) with natural linderatin using data given in the literature,[2] and left little doubt as to the structural identity of the two samples. Both samples had (+)-rotations demonstrating the (3*S*,4*R*)-configuration (*i.e.* opposite to natural cannabidiol) shown in (**6**). However, the magnitude given for the rotation of natural linderatin $[\alpha]_D$ +19.1° (*c* 0.45, $CHCl_3$)[2] was distinctly lower than the value of $[\alpha]_D^{24}$ +30.3 (*c* 0.33, $CHCl_3$) for our synthetic material. Through the kindness of Professor Kazuo Ito we have been able to repurify a specimen of crude linderatin and this had $[\alpha]_D^{21}$ +28.8° (*c* 0.11, $CHCl_3$). Direct chromatographic comparisons also fully confirmed the identity of the synthetic and natural specimens.

Experimental

^{1}H N.m.r. and ^{13}C n.m.r. data are reported for $CDCl_3$ solutions unless stated otherwise.

Reaction of (R)-(−)-α-*Phellandrene* (**4**) *with Olivetol in the Presence of Toluene*-p-*sulphonic Acid at* 5 °C.—α-Phellandrene (70 μl) was added to a pre-cooled (5 °C) mixture of olivetol (97.1 mg), toluene-*p*-sulphonic acid (19.7 mg), and docosane (14.2 mg; g.l.c. quantitation standard) in benzene (4 ml) and stirred (5 min). The reaction was quenched by shaking with aqueous sodium hydrogen carbonate. After being washed and dried a small portion of the benzene solution was removed, silylated (BSTFA with 1% TMCS at 50 °C), and examined by g.l.c. (SCOT OV 225 at 210 °C). (3*S*,4*R*)-8.9-Dihydro-*p*-cannabidiol (**7**) (24.4%) and dihydro-*o*-cannabidiol (**8**) (17.3%) had formed with only traces of other cannabidoid materials. Work-up of the main product by chromatography on dry silica (1 × 7 cm) gave compound (**7**) in 26% yield, eluted in light petroleum (b.p. 40—60 °C)–ether (1:2). (3S,4R)-8,9-*Dihydro*-p-*cannabidiol* (**7**), a gum, *m/z* 316.2391 ($C_{21}H_{32}O_2$ requires *M*, 316.2402); $\lambda_{max.}$(EtOH) 232sh (ε 6 300), 274 (800), and 282 nm (800); $\nu_{max.}$(film) 3 400br, 2 930, 2 850, 1 612, 1 580, 1 502, and 1 460 cm^{-1}. Mass spectral fragments for $C_{18}H_{25}O_2$, $C_{17}H_{24}O_2$, $C_{16}H_{22}O_2$, $C_{15}H_{19}O_2$, $C_{12}H_{17}O_2$, and $C_{11}H_{10}O_2$ were accurately mass-measured; δ_H($CHCl_3$ at 297 K) 6.4—6.0 (3 H, v br, D_2O removes one OH: remaining two resonances due to 3′-H and 5′-H v br indicating slow exchange), 5.51 (1 H, br s, 2-H), 5.22 (1 H, br s, OH, D_2O exch.), 3.83 (1 H, br d, *J* 9.8 Hz, 3-H), 2.43 (2 H, t, 1″-CH_2), *ca.* 1.1 (2 H, br m), *ca.* 1.85—1.2 (13 H, m, includes 7-Me at 1.76), 0.88 (3 H, t, 5″-Me), 0.83 and 0.86 (2 × 3H, each d *J* 5.2 Hz, 9- and 10-Me). Exchange was confirmed by a series of spectra in the range 210—313 K; δ_C 14.0 (q, C-5″), 16.5 (q, C-9), 21.7 (t, C-5), 22.3 (d, C-8), 22.6 (t, C-4″), 27.9 (q, C-10), 23.6 (q, C-7), 30.7 (t, C-6), 30.7 (t, C-3″), 31.6 (t, C-2″), 35.6 (t, C-1″), 35.6 (d, C-4), 43.8 (d, C-3), *ca.* 108.9 (broad due to restricted rotation, C-3′ and C-5′), 114.1 (s, C-1′), 125.0 (d, C-2), 139.9 (s, C-1), 143.0 (s, C-4′), and 155.5 (broad due to restricted rotation (C-2′ and C-6′).

(3*R*,4*S*)-8,9-Dihydro-*p*-cannabidiol has been reported as being formed by catalytic hydrogenation of natural cannabidiol using Adams catalyst: it has been isomerised to its iso-THC.[8] (3S,4R)-8,9-*Dihydro*-o-*cannabidiol* (**8**), gum, *m/z* 316.2383 ($C_{21}H_{32}O_2$ requires *M*, 316.2402); $\nu_{max.}$ 3 420br, 2 960, 2 890, 1 626, and 1 606 cm^{-1}; δ_H 6.24 (1 H, d, *J* 2.7 Hz, 3′-H), 6.21 (1 H, d, *J* 2.7 Hz, 5′-H), 6.09 (1 H, s, OH, D_2O exch.), 5.47 (1 H, br s, 2-H), *ca.* 4.95 (1 H, br, OH, D_2O exch.), 3.43 (1 H, br d, *J* 9.9 Hz, 3-H), 2.65 and 2.33 (each 1 H, m, 1″-H), *ca.* 2.15 (2 H, m), 1.65—1.9 (5 H, m, including 1.77 methyl), 1.23—1.65 (8 H, m), 0.89 (3 H, t, 5″-Me), 0.84 (3 H, d, *J* 4.3, 9-Me), and 0.82 (3 H, d, *J* 4.2, 10-Me). Mass spectral fragments for $C_{16}H_{22}O_2$, $C_{15}H_{19}O_2$, $C_{13}H_{15}O_2$, $C_{12}H_{13}O_2$, and $C_{11}H_{11}O_2$ were accurately mass-measured; δ_C 14.0 (q, C-5″), 16.8 (q, C-9), 21.9 (t, C-5), 22.3 (d, C-8), 22.6 (t, C-4″), 23.6 (q, C-7), 27.4 (q, C-10), 30.7 (t, C-6), 31.3 (t, C-3″), 31.9 (t, C-2″), 34.2 (t, C-1″), 38.5 (d, C-4), 43.1 (d, C-3), 108.7 and 102.5 (d, C-3′ and C-5′), 120.3 (s, C-1′), 125.3 (d, C-2), 139.8 (s, C-1), 144.1 (s, C-6′), and 154.7 and 156.7 (s, C-2′ and C-4′).

On t.l.c. on silica [eluant light petroleum (b.p. 40—60 °C)–ether (3:1)] (**7**) had the higher R_F value and gave an orange–red colour with Fast Blue Salt B spray: *o*-(**8**) gave a purple colour.

Reaction of (R)-(−)-α-*Phellandrene* (**4**) *with Olivetol in the Presence of PTSA at* 80 °C.—α-Phellandrene (72 μl) was added to olivetol (102.3 mg), PTSA (40.4 mg), and docosane (13.8 mg) in benzene (4 ml) and heated at 80 °C. Sampling after 20 min showed the *p*-diol (**7**) (28%), the *o*-diol (**8**) (0.3%), 8,9-dihydro-iso-THC (**9**) (24.5%), and the isomer (**10**) (2%). After 2 h no *p*- or *o*-diol was present but there was 50.6% of 8,9-dihydro-*p*-iso-THC (**9**) with 2.7% of the isomer (**10**). Chromatography on dry silica [eluant light petroleum (b.p. 40—60 °C)–ether (4:1)] gave 8,9-dihydro-*p*-iso-THC (**9**) (50.2 mg, 47%). A small amount of the isomer (**10**) (which has lower polarity (7.3 mg, 4%) was also isolated but g.l.c. indicated contamination (16%) with a compound of longer R_t.

(1S,3S,4R)-8,9-*Dihydro*-p-iso-*THC* (**9**) *m/z* 316.2373. ($C_{21}H_{32}O_2$ requires *M*, 316.2402); $\lambda_{max.}$(EtOH) 274 (ε 630) and 282 nm (630); $\nu_{max.}$ 3 350br, 3 040, 2 900, 1 615, 1 590, 1 570, and 1 500 cm^{-1}; δ_H 6.27 and 6.11 (each 1 H, d, *J* 1.3 Hz, 3′-H and 5′.H), 4.86 (1 H, s, OH, D_2O exch.), 3.33 (1 H, br dd, *J* 2.8 Hz, 3-H), 2.44 (2 H, t, *J* 7.8 Hz, 1″-H), 1.95—0.88 (15 H including 1.33 s, 7-Me), 1.08 and 0.94 (each 3 H, d, *J* 6.5 Hz, 9- and 10-Me), and 0.88 (3 H, t, 5″-Me). The C-2 methylene hydrogens (δ 1.88 dd, *J* 2.6 and 13.2 Hz) were shown to be coupled to the benzylic resonance at δ 3.33; δ_C 14.0 (q, C-5″), 21.1 (q) and 22.1 (q) (C-9 and C-10), 29.3 (q, C-7), 20.6 (t), 22.6 (t), 30.6 (t), 30.8 (t), 31.6 (t), 35.7 (t) (methylene at 1″ to 4″ and C-2, C-5, and C-6), 26.3 (d) and 27.9 (d) (C-4 and C-8), 44.4 (d, C-3), 74.5 (s, C-1), 106.0 (d) and 107.9 (d) (C-3′ and C-5′), 111.8 (s, C-1′), 142.4 (s, C-4′), and 152.1 (s) and 157.5 (s) (C-2′ and C-6′). Mass spectral fragments for $C_{18}H_{25}O_2$, $C_{17}H_{24}O_2$, $C_{16}H_{24}O_2$, $C_{16}H_{22}O_2$, $C_{15}H_{21}O_2$, $C_{15}H_{19}O_2$, and $C_{12}H_{17}O_2$ were mass measured.

Data for 8,9-dihydro-*o*-iso-THC (**10**) was obtained on material of 85% purity; *m/z* 316.2390 ($C_{21}H_{32}O_2$ requires *M*, 316.2402); δ_H 6.20 and 6.15 (each d, *J* 2.5 Hz, 3′-H and 5′-H), 4.5 (1 H, br s, OH, D_2O exch.), 3.17 (1 H, br m, 3-H), 2.3—2.6 (4 H, m), 0.8—1.95 multiplet which includes 1.32 (s, 7-Me), 1.08 and 0.94 (each d, *J* 6.5, 9- and 10-Me), and 0.90 (t, 5″-Me). Mass spectral fragments for $C_{20}H_{29}O_2$, $C_{18}H_{23}O_2$, $C_{15}H_{19}O_2$, $C_{16}H_{24}O_2$, and $C_{12}H_{17}O_2$ were mass measured.

Synthesis of Linderatin (**6**).—3-Phenyl-1-(2,4,6-trihydroxyphenyl)propan-1-one (**11**) was made both by the Hoesch procedure[6] and by Friedel-Crafts acylation.[7] It had m.p. 138—

139 °C (from water) (lit.,[9] m.p. 138—139 °C) (Found: C, 69.6; H, 5.55%; M^+, 258.0898. Calc. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.45%; *M*, 258.0892); $\nu_{max.}$($CHCl_3$) 3 400—3 480 (OH), 1 640 (chelated C=O), and 1 605 cm^{-1} (Ar); δ(CD_3COCD_3) 12.2—10.0 (3 H, 3 × OH, D_2O exch.), 7.29 (5 H, m, ArH), 5.98 (2 H, s, ArH of oxygenated ring), and 3.39 and 2.97 (4 H, both in CH_2CH_2 bridge).

The above ketone (**11**) (50.7 mg, 0.196 mmol) and toluene-*p*-sulphonic acid (41.6 mg, 0.242 mmol) in dry benzene (5 ml) were stirred with (*R*)-(−)-α-phellandrene (**4**) (40.9 mg, 0.30 mmol), $[\alpha]_D^{20}$ −225° (*c* 10 in ether) at 20 °C for 45 min. The mixture was washed with aqueous sodium hydrogen carbonate and water, dried, and evaporated to afford a residue (78.2 mg) which was purified by column chromatography on silica (eluant hexane–chloroform) and then reversed phase C_{18} h.p.l.c. (eluant methanol–water: 85:15). *Linderatin* (**6**) *m/z* 394.2156 ($C_{25}H_{30}O_4$ requires M^+, 394.2144); $\lambda_{max.}$(EtOH) 224 (ε 13 300) and 292 (14 000) nm; $\nu_{max.}$($CHCl_3$) 3 575, 3 350, 1 620, and 1 605 cm^{-1}; $[\alpha]_D^{24}$ +30.3° (*c* 0.33, $CHCl_3$); δ_H(CD_3COCD_3) 0.79 (7 H, 9- and 10-Me and 8-H), 1.32 (1 H, m, 4-H), 1.52 (2 H, dt, 5-CH_2), 1.61 (3 H, s, 7-Me), 1.72 (2 H, dt, 6-CH_2), 2.93 (2 H, t, *J* 7.8 Hz, 3″-CH_2), 3.35 (2 H, t, *J* 7.8 Hz, 2″-CH_2), 3.81 (1 H, d, *J* 8.9, 3-CH), 5.19 (1 H, s, 2-CH), 5.97 (1 H, s, 5′-CH), 7.23 (5 H, m, 5″—9″-ArH), 8.60 and 9.90 (each 1 H, br s, OH, D_2O exch.), and 13.70 (1 H, br s chelated OH, D_2O exch.); δ_C(CD_3COCD_3) 16.8 (9-CH_3), 21.9 (10-CH_3), 23.6 (5-CH_2), 23.7 (7-CH_3), 29.1 (8-CH), 31.5 (6-CH_2), 31.6 (3″-CH_2), 36.0 (3-CH), 42.7 (4-CH), 46.6 (2″-CH_2), 95.5 (5′-CH), 105.0 (3′-C tert.), 110.0 (1′-C tert.), 126.5 (2-CH), 127.0 (7″-CH), 129.1 (5″- and 9″-CH), 129.3 (6″- and 8″-CH), 134.3 (1-C tert.), 143.0 (4″-C tert.), 161.1 (2′-C tert.), 163.7 (4′-C tert), 165.1 (6′-C tert.), and 207.1 (1-C=O). Close ^{13}C assignments may be interchanged. Literature data for natural Linderatin are:[2] $\lambda_{max.}$(EtOH) 225 (ε 12 800) and 290 (14 130) nm; $\nu_{max.}$ 3 530, 3 350, 1 620, 1 605, and 1 495 cm^{-1}; $[\alpha]_D$ +19.1 (*c* 0.45, $CHCl_3$); δ_H(CD_3COCD_3) 0.82 (6 H, d, *J* 7 Hz), 1.64 (3 H, s), 2.92 (2 H, t, *J* 8 Hz), 3.37 (2 H, t, *J* 8 Hz), 3.84 (1 H, br d, *J* 12 Hz), 5.23 (1 H, s), 5.96 (1 H, s), 7.20 (5 H, br s), and 13.88 (1 H, s); δ_C(CD_3COCD_3) 16.9, 22.0, 23.7, 23.7, 29.1, 31.5, 36.0, 43.0, 46.6, 95.8, 105.4, 110.5, 126.9, 127.1, 129.4, 129.6, 135.4, 143.2, 143.2, 161.4, 163.9, 165.9, and 205.9. An impure specimen of natural linderatin was chromatographed on silica (eluting with chloroform). The fraction containing linderatin was further purified by C_{18}-reversed phase chromatography (eluant methanol–water, 85:15) and had $[\alpha]_D^{21}$ +29.8° (*c* 0.11, $CHCl_3$). It was chromatographically identical with our synthetic specimen.

Acknowledgements

We thank Professor Kazuo Ito for a sample of crude linderatin. One of us (D. F. F.) thanks the S.E.R.C. for a studentship.

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Received 14*th April* 1987; *Paper* 7/671