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An Improved Synthesis of Cannabinol and Cannabiorcol[1]

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Cannabinol **(4a)**[2] was first synthesized[3] in 1940 in order to establish the basic skeleton of the tetrahydrocannabinol structure. Dihydroolivetol and 2-bromo-4-methylbenzoic acid were

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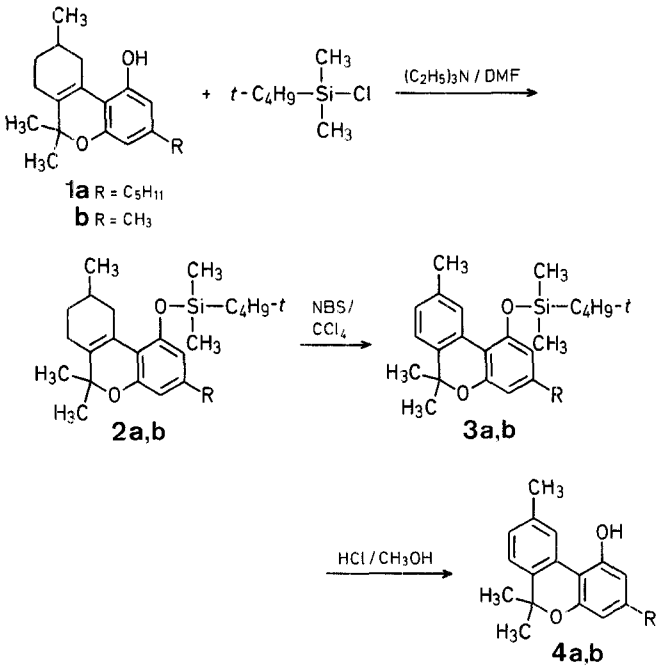
utilized in this synthesis and dehydrogenation (sulfur) of the resultant pyrone, followed by Grignard reaction, then gave the product **4a**.

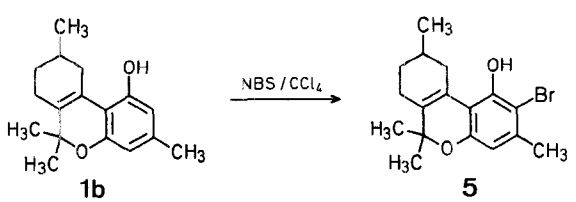
Since then, cannabinol **(4a)** has been obtained by sulfur dehydrogenation of both *iso*-tetrahydrocannabinols[6] and Δ^6-tetrahydrocannabinol[7], as well as by aerial oxidation of Δ^1-tetrahydrocannabinol[2,9]. Chloranil dehydrogenation[8] of Δ^1-tetrahydrocannabinol, but not of Δ^6-tetrahydrocannabinol or *cis*-Δ^1-tetrahydrocannabinol, has also led to **4a**. To date, the most practical procedure for the synthesis of **4a** and its analogs has proved to be via the dehydrogenation of various $\Delta^{3,4}$-tetrahydrocannabinols (for example, **1a**, with palladium on carbon or selenium)[4] or of their corresponding pyrones[5], followed by Grignard reaction.

The $\Delta^{3,4}$-tetrahydrocannabinols are readily available from the appropriate resorcinols, either directly by condensation with pulegone[10,11] or with the keto esters[4,12] (Pechmann condensation) followed by Grignard reaction. Dehydrogenation with sulfur has proved most effective, although yields are moderate and the crude cannabinol **(4a)** obtained is difficult to purify.

We describe here an efficient and simple procedure for the conversion of $\Delta^{3,4}$-tetrahydrocannabinol **(1a)** to cannabinol **(4a)** via treatment of the silyloxy derivative **(2a)** with *N*-bromosuccinimide in the presence of U.V. light. Deprotection of **3a** with methanolic hydrogen chloride then gave **4a** cleanly and in excellent yield. Similarly, the cannabinol analog cannabiorcol **(4b)**[14] was obtained in good yield.



When the free phenol **1b** was treated with *N*-bromosuccinimide, however, the brominated product **5** was formed. The position of the bromine was assigned on the basis of the shift of the aromatic protons in the ^{1}H-N.M.R. spectrum[13] measured in benzene-d_6.



2'-(Dimethyl-*t*-butylsilyloxy)-$\Delta^{3,4}$-tetrahydrocannabinol (2a):
A solution of $\Delta^{3,4}$-tetrahydrocannabinol (**1a**; 1.35 g, 4.28 mmol), *t*-butyldimethylchlorosilane (2.60, 17.20 mmol) and triethylamine (5.0 ml, 35.8 mmol) in dry dimethylformamide (20 ml) is stirred at 24 °C for 16 h. After extraction with ether (3 × 20 ml) and distillation, **2a** is obtained as a yellow oil; yield: 1.70 g (93%); b.p. 210–220 °C/1 torr.

^{1}H-N.M.R. ($CDCl_3$): δ = 0.23 [s, 6H, $Si(CH_3)_2$]; 0.98 [s, 9H, $SiC(CH_3)_3$]; 1.20 (s, 3H, CH_3); 1.40 (s, 3H, CH_3); 1.0–2.6 (m, 21H); 6.26 (d, 1H$_{arom}$); 6.35 ppm (d, 1H$_{arom}$).

Cannabinol (4a):
A mixture of the silyl-protected $\Delta^{3,4}$-tetrahydrocannabinol **2a** (0.795 g, 1.857 mmol), benzoyl peroxide (17 mg), and *N*-bromosuccinimide (0.72 g, 4.04 mmol) in carbon tetrachloride (10 ml) is stirred at 24 °C for 7 h under soft ultraviolet radiation. The suspension obtained is filtered, and the filtrate washed with brine and evaporated in vacuo. The oil obtained **(3a)** is dissolved in methanolic hydrogen chloride (15 ml) and stirred for 12 h. Column chromatography (silica gel 60; eluent: 10% ethyl acetate in hexane) yields cannabinol **(4a)** as an oil, which crystallizes on trituration with hexane; yield: 0.472 g (82%); m.p. 74.5–75.0 °C; mixture m.p. 74.0–74.5 °C. The product was identical to an authentic sample (R_f, N.M.R.).

Cannabiorcol (4b):
The cannabinol analog **4b** is similarly prepared. Analogous treatment of $\Delta^{3,4}$-tetrahydrocannabinol **1b** (1.08 g, 4.18 mmol) gives **2b** as a pale yellow oil; yield: 1.42 g (92%); b.p. 170–173 °C/0.1 torr.

^{1}H-N.M.R. ($CDCl_3$): δ = 0.23 [s, 6H, $Si(CH_3)_2$]; 0.98 [s, 9H, $Si\text{-}C(CH_3)_3$]; 1.00 (d, 3H, $CHCH_3$); 1.20 (s, 3H, CH_3); 1.40 (s, 3H, CH_3); 1.4–2.6 (m, 7H); 2.20 (s, 3H, $ArCH_3$); 6.20–6.38 ppm (dd, 2H$_{arom}$).

Treatment of **2b** (0.38 g, 1.02 mmol) with *N*-bromosuccinimide (0.25 g, 1.38 mmol) and benzoyl peroxide (5 mg) in carbon tetrachloride (5 ml) for 5 h (24 °C) gives an oil **3b** which, on stirring with concentrated hydrochloric acid (1 ml) in methanol (10 ml) for 12 h, gives **4b**; yield: 0.156 g (54%); viscous gum.
M.S. Accurate mass: found: m/e = 254.1316; calculated for $C_{17}H_{18}O_2$: 254.1307.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.57 (s, 6H, CH_3); 2.18 (s, 3H, $ArCH_3$); 2.33 (s, 3H, $ArCH_3$); 5.73 (bs, 1H, OH); 6.23–6.40 (dd, 2H$_{arom}$); 7.07 (s, 2H$_{arom}$); 8.18 ppm (s, 1H$_{arom}$).

3'-Bromotetrahydrocannabiorcol (5):
When **1b** (0.82 g, 3.19 mmol) is treated with *N*-bromosuccinimide (0.64 g, 3.60 mmol) in carbon tetrachloride (30 ml) and stirred for 6 h at 0 °C, the bromo derivative **5** is obtained as a colorless oil after column chromatography on silica gel 60, eluting with ethyl acetate; yield: 0.58 g (55%).

^{1}H-N.M.R. (CCl_4): δ = 0.98 (s, 3H, $CHCH_3$); 1.13 (s, 3H, CH_3); 1.33 (s, 3H, CH_3); 1.2–2.7 (m, 7H); 2.23 (s, 3H, $ArCH_3$); 6.28 ppm (s, 1H$_{arom}$).

^{1}H-N.M.R. (C_6D_6): δ = 1.00 (d, 3H, $CHCH_3$); 1.16 (s, 3H, CH_3); 1.35 (s, 3H, CH_3); 1.4–2.8 (m, 7H); 2.12 (s, 3H, $ArCH_3$); 6.43 ppm (s, 1H$_{arom}$).

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1 Hashish, Part 28: for Part 27, see R. P. Duffley, G. Lambert, H. C. Dalzell, R. K. Razdan *Experientia* in press (1981).

2 For a review, see (a) *Marijuana, Chemistry, Pharmacology, Metabolism and Clinical Effects*, R. Mechoulam Ed., Academic Press, New York, 1973.
(b) R. K. Razdan in *The Total Synthesis of Natural Products*, Vol. 4, J. Apsimon Ed., John Wiley & Sons, Inc., New York, 1981, p. 185.

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(b) Unpublished results from our laboratory. We are grateful to Dr. C. G. Pitt of Research Triangle Institute, N. C., for giving us experimental details.
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