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CANNABINOID REARRANGEMENTS
SYNTHESIS OF Δ^5-TETRAHYDROCANNABINOL

R. MECHOULAM, Z. BEN-ZVI, H. VARCONI and Y. SAMUELOV
Department of Natural Products, Hebrew University, Pharmacy School, Jerusalem – Israel

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Abstract– 1β,6β-Epoxy-hexahydrocannabinol acetate (**1**) in the presence of borontrifluoride rearranged to 6-oxo-hexahydrocannabinol acetate (**3b**) and to the aldehyde (**4**). Hydroboration of Δ^6-THC gave the 6-hydroxy hexahydrocannabinols **5a** and **8a**. The latter was converted into Δ^5-THC (**11**). This THC isomer shows no cannabis-type activity in rhesus monkeys.

Terpenoids are known to undergo numerous rearrangements. Although the cannabinoids can be viewed upon as mono-terpenoids (substituted with an olivetol moiety on the C_3 position) few rearrangements have been published so far in this series.[1] We report now that the epoxy-hexahydrocannabinol acetate (**1**) undergoes two rearrangements under acid catalysis.

1β,6β-Epoxy-hexahydrocannabinol acetate (**1**) was prepared as previously described[2] from Δ^6-tetrahydrocannabinol acetate (Δ^6-THC) (**2b**). Treatment with boron-trifluoride etherate in benzene gave two products, which were identified as 6-oxo-hexahydrocannabinol acetate (**3b**) m.p. 57° and the aldehyde (**4**) m.p. 63°.

The structure and stereochemistry of **1** and **3b** were determined as follows. Treatment of **3b** with base gave 6-oxo-hexahydrocannabinol (C_1 Me equatorial) (**3a**), m.p. 128°, which on acetylation gave back unchanged starting material (**3b**). This reaction shows that the C_1 Me group in **3** is pseudo equatorial (β). If the C_1 Me group were pseudo axial (α) it would have become equatorial by equilibration on basic treatment.[1] This reaction gives support to the suggested [2] β configuration of the epoxy ring in **1**. Epoxy-ketone rearrangements of the above described type are well known[3] to proceed with retention of configuration of the migrating hydride ion. As the C_1 hydrogen in **3** is α, the C-6 hydrogen in **1** is also α, hence the epoxy group is β.

LAH reduction of **3b** gave a mixture of 6$_\alpha$-hydroxy-hexahydrocannabinol (**5a**) and its C_6 epimer (**6a**) which were separated and characterized. On individual tosylation the ditosylates **5b** and **6b** were obtained. Further LAH reduction of either **5b** or **6b** produced the known[4] hexahydrocannabinol (**7**) in which the C_1 methyl group has been shown to be equatorial.

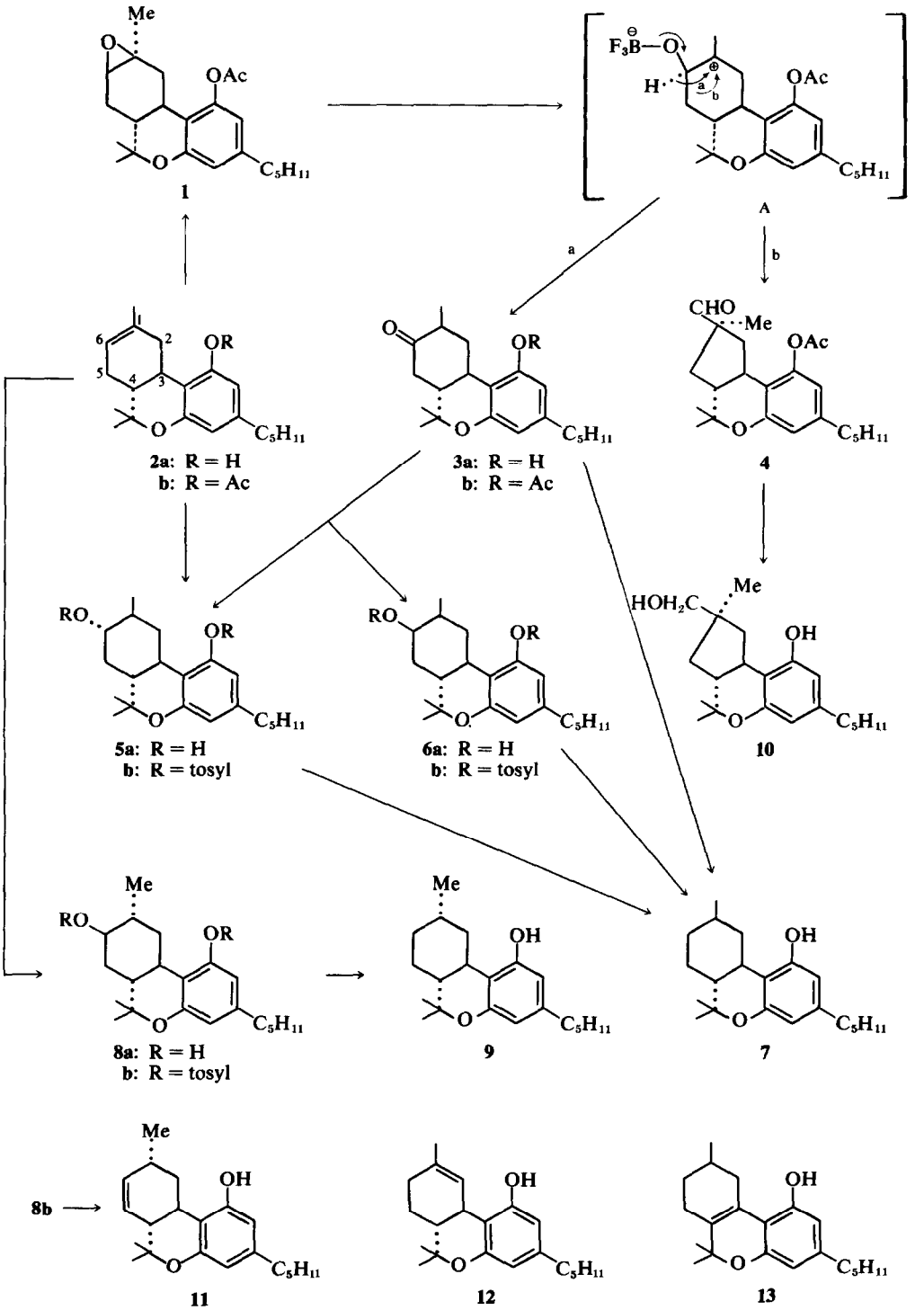
Further correlations were established. Δ^6-Tetrahydrocannabinol (**2a**) was hydroborated to give 6β-hydroxy-hexahydrocannabinol (C_1 Me α) (**8a**) and 6α-hydroxy-hexahydrocannabinol (C_1 Me β) (**5a**) identical to the material described above. It is known[5] that in the hydroboration reaction the OH group and the hydrogen are introduced on the same side of the molecule. Therefore the above hydroboration reaction, establishes the configuration of the OH group in **5a** as α on the basis of the α configuration of the C_1 hydrogen which is firmly based on its correlation with **7**. The relative configurations at C_1 and C_6 in **8a** were also determined by conversion *via* tosylation and LAH reduction to the known hexahydrocannabinol **9**.[4] The above correlations provide an independent proof of the stereochemistry of the epoxy-ketone rearrangement.

The stereochemical assignments at C_6 (and hence also at C_1) of the three isomers of 6-hydroxy-hexahydrocannabinol (**5a**, **6a** and **8a**) are also supported by the chemical shifts and coupling constants of the C_6 protons. Thus the axial C_6 proton in **5a** resonates at a considerably higher field than the corresponding equatorial protons in **6a** and **8a**. Due to two diaxial couplings and an axial-equatorial one, the axial C_6 proton in **5a** appears as a very wide broad multiplet, while the corresponding equatorial protons in **6a** and **8a** appear as a narrow quartet and a broad singlet respectively.

Wolf-Kischner reduction of **3b** gave **7**. This reduction which takes place in a strongly basic medium produces, as expected, the isomer in which the C_1 Me group retains its equatorial conformation.

The second compound (**4**) formed by the opening of the epoxide **1b** with BF_3 etherate is the product of the less known epoxy-aldehyde rearrangement in which a C—C bond breaks leading to ring contraction. Several related rearrangements have been described.[3b,6]

The structure **4** put forward is based on the following considerations: *a*, the presence of a signal, in the NMR, at δ 9·37 (singlet) attributable to an



aldehydic proton; *b*, the presence of the two CO bands in the IR spectrum, one at 1780 cm^{-1}, due to the acetate group, and the other at 1740 cm^{-1} attributable to the aldehyde group; *c*, reduction of **4** with LAH to give **10**, whose NMR spectrum shows the presence of *two* equivalent protons α to the newly formed OH group; *d*, on attempted deuteration, no change was observed in the NMR spec-

trum, except for partial exchange of the aromatic protons, and *e*, the mass spectrum in which all major peaks can be rationalized in terms of structure **4**. The molecular ion peak **a** *m/e* 372 (90%) through loss of ketene gives the ion peak **b** of *m/e* 330 (100%). Loss of 29 (H· and CO) leads to the tertiary ion **c** (*m/e* 301, 90%). Initial loss of mass 29 from the molecular ion gives ion **d** (*m/e* 343, 50%). Cleavage of isobutylene (mol. weight 56) from either ion **c** or ion **d** and rearrangements within the formed ions will lead to the hypothetical ions **e** (*m/e* 245, 60%) and **f** (*m/e* 287, 68%) respectively. The rest of the peaks are unexceptional. Peak *m/e* 315 is formed by loss of a Me group from peak *m/e* 330; peak *m/e* 231 (50%) is the standard cannabinoid peak **g**; peak *m/e* 357 (47%) is formed from the molecular peak by loss of a Me group.

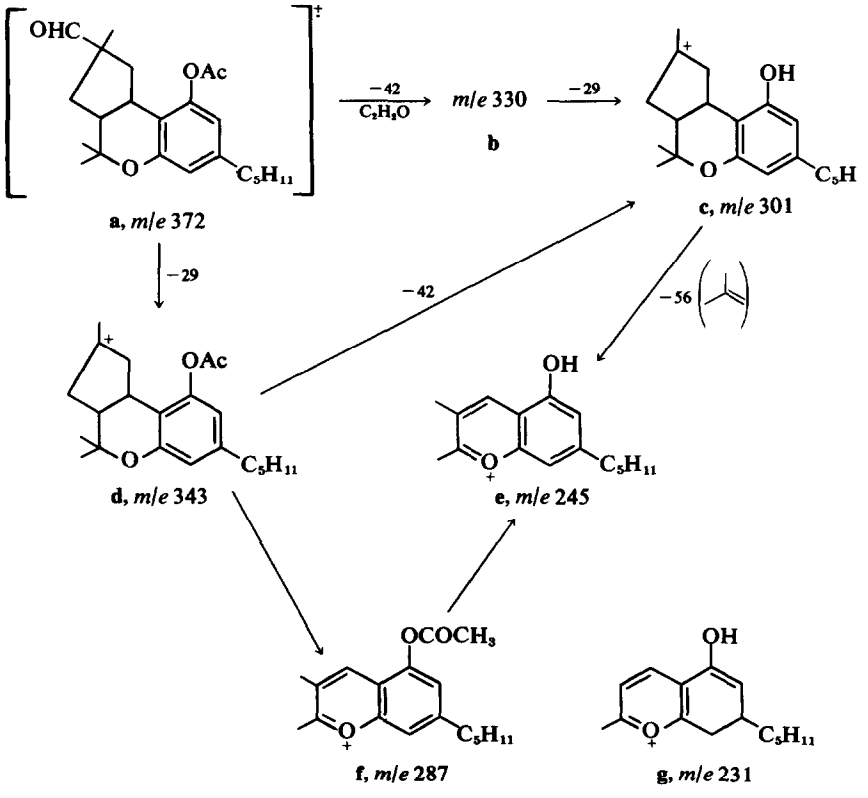
We have no chemical proof for the stereochemistry at C_1 in **4**. The suggested configuration is based on mechanistic considerations only. In the intermediate ion A one can expect a σ-overlap of the orbital of the oxygen (of the *axial* oxygen-BF_3 group) with the "vacant" p-orbital of the sp^2 hybridised C atom. This overlap will then be gradually replaced by the rear-side overlap with the orbital of the migrating group. From consideration of molecular models one can assume that the rear side attach will lead to the stereochemistry indicated in **4**. However a chemical correlation is needed before the above stereochemical assignment is considered final.

The availability of **8a** led us to prepare the hitherto unknown Δ^5-THC (**11**). The tosylate **8b** was prepared in the usual fashion. Boiling of **8b** with sodium hydroxide in ethanol lead to Δ^6-THC; however, reaction with a bulky nucleophile, potassium t-amylate in amyl alcohol, led to a mixture of Δ^5-THC (C_1 Me axial) (**11**) and Δ^6-THC. Apparently for steric reasons (bulkiness of the nucleophile and the equatorial position of the C_1 hydrogen) the nucleophile partially initiates the elimination reaction by attack at the C_5 position. By contrast, reaction of **5b**, (in which the C_1 hydrogen is axial), with potassium t-amylate in amyl alcohol gives Δ^6-THC (**2a**) and the reduced product **7**. Reductions of this type with strong bases are not unusual.

Δ^5-THC (**10**) is inactive when tested in monkeys by the method previously described,[7] in doses up to 10 mg/kg. By comparison[7] Δ^1-THC (**12**) is active at 0·05 mg/kg; Δ^6-THC (**2a**) at 0·25 mg/kg and Δ^3-THC (**13**)—at 1·0 mg/kg. Δ^5-THC (**11**) is hence the first THC, with an endocyclic double bond and the natural absolute configuration at C_3 and C_4 which is inactive in the monkey test.

EXPERIMENTAL

The instruments, materials and methods for the determination of IR, UV and mass spectra, as well as condi-



tions for GLC and TLC have been described.[8] The NMR spectra were measured on a Jeol 60-H spectrometer.

1β,6β-Epoxy-hexahydrocannabinol acetate (**1**) *from Δ⁶-THC acetate* (**2b**). Δ⁶-THC acetate **2b** (7·0 g) was dissolved in chloroform (100 ml). The soln was cooled to 0° and *meta*-chloroperbenzoic acid (3·15 g) was added in small portions. The soln was left overnight in the dark. The ppt formed was then filtered off, twice washed with chloroform and the filtrates were washed with 10% NaOHaq. The chloroform soln was dried and evaporated to give an oil (7·1 g), which was chromatographed on silica gel (Merck, 0·05–0·2 mm) (710 g). Elution with 10% ether in light petroleum gave **1** (6·0 g, 84%), molecular weight (mass spectrum) 372, $[\alpha]_D^{EtOH}$ −185°; λ_{max}^{EtOH} 274 (shoulder), 279 mμ (ε, 1959, 2022); IR, ν (CCl_4) 1770 cm^{-1}; NMR, δ (CCl_4), 0·9 (t, terminal Me), 1·00, 1·26 (s, Me groups), 2·21 (s, $OCOCH_3$), 2·3–2·65 (m, benzylic protons), 2·87 (br d, J=4·5 Hz, C_6—H), 6·25, 6·37 (d, aromatic protons) (Found: C, 74·02; H, 8·61. $C_{23}H_{32}O_4$ requires: C, 74·16; H, 8·66%).

Treatment of **1b** *with* BF_3 *to give* **3b** *and* **4**. Compound **1b** (2·6 g) was dissolved in dry benzene (140 ml) under N_2. BF_3 etherate (3 ml) was added over a period of 5 min. After an additional 5 min during which the soln turned gradually dark red, a sat. $NaHCO_3$ aq (25 ml) was added. The aqueous layer was extracted with ether. The combined organic layers were washed with water, dried and evaporated The oil obtained (2·5 g) was chromatographed on 250 g silica gel Elution with 10% ether in light petroleum yielded first the aldehyde **4** (0·54 g) followed by 6-oxo-hexahydrocannabinol acetate (C_1 Me β) **3b** (1·78 g). Pure **4** has m.p. 63°; $[\alpha]_D^{EtOH}$ −44·5°; λ_{max}^{EtOH} 273, 280 mμ (ε 1918, 2153); ν (CCl_4) 1780 cm^{-1}, 1740 cm^{-1}; δ (CCl_4) 0·91 (t. terminal Me), 1·16, 1·21, 1·35 (s, Me groups), 2·20 (s, Ac) 6·20, 6·38 (d, aromatic H), 9·37 (s, aldehydic); mol. weight (mass spectrum) 372. The mass spectrum is discussed in the text. (Found: C, 73·86; H, 8·72. $C_{23}H_{32}O_4$ requires: C, 74·16; H, 8·66%). Pure **3b** has m.p. 57°, $[\alpha]_D^{EtOH}$ −195°, molecular weight (mass spectrum) 372, λ_{max}^{EtOH} 223 (shoulder), 275, 281 mμ (ε, 9000, 1735, 1954); ν (CCl_4) 1770, 1720 cm^{-1}; δ (CCl_4) 0·90, 0·98, 1·12, 1·32 (Me groups), 2·21 ($OCO\underline{CH_3}$), 2·2–2·6 (protons benzylic and α to ketone) 6·25, 6·60 (aromatic H). (Found: C, 74·19; H, 8·66. $C_{23}H_{32}O_4$ requires: C, 74·16; H, 8·66%).

Treatment of **3b** *with base* Compound **3b** (300 mg) was dissolved in 10 ml MeOH. 10% NaOH aq was added till cloudiness formed. The soln was boiled for 6 hr, cooled, neutralized with dil HCl extracted with ether, dried and evaporated. The residue was crystallized from light petroleum to give pure 6-oxo-hexahydrocannabinol (C_1 Me group β) **3a** (212 mg), m.p. 128°; molecular weight (mass spectrum) 330; λ_{max}^{EtOH} 276, 283 mμ (ε, 1300, 1400); ν (CCl_4) 1710 cm^{-1}; δ (CCl_4) 0·9, 1·02, 1·1, 1·3 (Me groups), 2·2–2·5 (benzylic and α to keto group H), 3·5 (br d, $C_{2\alpha}$—H), 6·10, 6·45 (aromatic H) (Found: C, 75·50; H, 9·03. $C_{21}H_{30}O_3$ requires: C, 76·33; H 9·15%).

Acetylation of **3a** with Ac_2O in pyridine gave **3b** (comparison by mixed m.p., IR and NMR).

Reduction of **3b** *with LAH*. Compound **3b** (300 mg) was dissolved in dry ether (50 ml). LAH (100 mg) was slowly added. The mixture was stirred for 4 hr. EtOAc (2 ml), water and ether (50 ml) were added. The organic layer was dried and evaporated. The residue was purified by preparative TLC to give two products. One was shown to be 6α-hydroxy-hexahydrocannabinol (C_1 Me group β) **5a**, (98 mg) an oil, $[\alpha]_D^{EtOH}$ −110°; λ_{max}^{EtOH} 228 (shoulder), 275, 283 (ε, 10850, 1234, 1290); δ ($CDCl_3$) 0·89, 1·08, 1·35 (Me groups), 2·92–3·53 (C_6—H) (br, mult), 6·0, 6·15 (aromatic protons) molecular weight (mass spectrum) 332. The second product was 6β-hydroxy-hexahydrocannabinol (C_1 Me β) **6a**, (92 mg), an oil, $[\alpha]_D^{EtOH}$ −138°; λ_{max}^{EtOH} 230 (shoulder), 276, 282 mμ (ε, 6435, 1240, 1240); δ ($CDCl_3$) 0·88, 0·95, 1·05, 1·36 (Me groups), 2·35 (benzylic H), 2·82 ($C_{2\alpha}$—H), 3·90 (d) (C_6H) (dd J=4·5 Hz, J=6·0 Hz), 6·01, 6·15 (2 aromatic H); molecular weight (mass spectrum) 332.

Conversion of **5a** *and* **6a** *into hexahydrocannabinol* **7**. Compound **5a** (340 mg) was dissolved in pyridine (7 ml). *p*-Toluene sulfonyl chloride (3·5 g) was added and left overnight. Pyridine (20 ml) and ice were added and left for ½ hr. The mixture was extracted with ether (100 ml) and the etheral soln was washed with $NaHCO_3$ aq, then with 5% HCl aq and again with $NaHCO_3$ aq. After a further washing with NaCl aq the organic layer was dried and evaporated. The ditosylate **5b** was obtained as an oil (662 mg), pure by TLC, δ ($CDCl_3$) 0·8, 0·85, 1·25 (Me groups), 2·8 (C_2—H), 4·2 (C_6—H), 6·3, 6·45 (aromatic H). Without further purification **5b** (155 mg) were dissolved in THF (20 ml) (distilled over LAH). LAH (200 mg) was added to the soln. The reaction was boiled under N_2 for 4 hr. Then it was worked up as described above. Hexahydrocannabinol (**7**) (115 mg) was obtained, which was purified on preparative TLC giving 38 mg **7**, identical with the same material described previously.[4] The comparisons were made with authentic material by IR, NMR, R_f of TLC and retention time on GLC.

Compound **6a** was converted into **7** by the same procedure via **6b**. The hexahydrocannabinol (**7**) obtained was identical to **7** from the preceding reaction.

Hydroboration of Δ⁶-THC (**2a**). Δ⁶-Tetrahydrocannabinol (2 g) was dissolved in THF (40 ml) dried by distillation over LAH. The soln was cooled in an ice bath. A soln (3·2 ml) of 2 M diborane was injected and the mixture was stirred for 1 hr under N_2, when it was brought to room temp and stirred for an additional hr. Water (15 ml) was added, then 3N NaOH (7 ml) and then a soln of 30% H_2O_2 (7 ml). The soln was stirred for 15 min, extracted with ether, dried and evaporated. The oil obtained was chromatographed over Florisil (250 gr). Elution with ether-light petroleum (1:1) gave a mixture of **5a** and **8a**, which were separated by preparative TLC (elution with ether-light petroleum, 1:1). Compound **5a**, an oil (410 mg) was shown to be identical to the product obtained by reduction of **3b**. The second material obtained was **8a**, an oil (470 mg), $[\alpha]_D^{EtOH}$ −130°; λ_{max}^{EtOH} 225 (shoulder), 275, 283 (ε 10380, 1211, 1292); δ ($CDCl_3$) 0·86, 1·05, 1·15, 1·31, (Me groups), 2·82 ($C_{2\alpha}$–H), 3·86 (C_6–H) (W/½h = 6Hz) 6·0, 6·27 (asomatic H).

Δ⁵-THC (**11**). Potassium (0·8g) was dropped into t-amyl alcohol (20 ml) under N_2. Compound **8b** (prepared as described for **5b**) (540 mg) in the same solvent (5 ml) was added. The soln was boiled for 7 hr. The dark brown soln was cooled to 5°, water was added and twice extr with ether (50 ml). The etheral soln was washed with 5% HCl aq, then 5% $NaHCO_3$ aq and finally 5% NaCl aq. The dried soln was evaporated to give an oil (300 mg) which was chromatographed on preparative TLC. Elution with ether: light petroleum (5:95) gave pure Δ⁵-THC (C_1 Me axial) (**11**) (50 mg) an oil, $[\alpha]_D^{EtOH}$ −37°; λ_{max}^{EtOH} 230 (shoulder), 276, 283 mμ (ε, 8572, 1192, 1170); δ (CCl_4) 0·85, 1·02, 1·18 (Me groups), 1·38 (d, C_1—Me), 2·95 ($C_{2\alpha}$—H), 5·52 (s) (2H, C_5—H, C_6—H), 5·32, 6·08 (aromatic H). A further fraction (40 mg) was identified as Δ⁶-THC (**2a**). When the same reaction was performed on the ditosylate

of 6α-hydroxy-hexahydrocannabinol (C_1-Me equatorial) (**5b**) only Δ^6-THC (**2a**) (25%) and the hexahydrocannabinol **7** (15%) were obtained.

Conversion of **8b** *into hexahydrocannabinol* **9**. This reaction was performed exactly as the one described for the conversion of **5b** into **7** (see above). Compound **9** **thus obtained was identical with the same material described previously.**

Reduction of **4** *to* **10** *with LAH*. The aldehyde **4** (200 mg) was reduced and worked up as described above. The mixture was boiled under reflux for 12 hr. The material obtained was purified by preparative TLC (silica gel, Merck; elution with ether-light petroleum 3 : 10) to give **10** (55 mg), an oil, $[\alpha]_D^{EtOH}$ −47°; λ_{max}^{EtOH} 225 (shoulder), 274, 282, (ε, 5700, 1170, 1170); δ (CCl_4), 0·88, 1·11, 1·36 (Me groups), 3·45 (s, 2H, —$\underline{CH_2}$OH), 6·08, 6·18 (aromatic H).

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