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SYNTHESIS OF RACEMIC AND OPTICALLY ACTIVE Δ^1- AND Δ^6-3,4-*CIS*-TETRAHYDROCANNABINOLS[1]

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Abstract—Three syntheses of the hitherto unknown (±)-Δ^6-3,4-*cis*-THC **4a** and the first total synthesis of optically active Δ^1- and Δ^6-*cis*-THC's are described. These syntheses utilize a stereospecific intramolecular epoxide opening by phenolate anion; an acid catalyzed equilibration of Δ^1- and Δ^6-*cis*-THC acetates; and a kinetically controlled dehydration. The use of HPLC, GLC and NMR for the separation and identification of closely related THC's is discussed.

(−) - Δ^1 - 3,4 - *trans* - Tetrahydrocannabinol (THC) **1** and (−) - Δ^6 - 3,4 - *trans* - THC **2** are the physiologically most active constituents of marijuana and have been the object of intensive synthetic and pharmacological investigations for many years.[2] The Δ^1-isomer is commonly found in *Cannabis sativa* L., whereas the Δ^6-isomer occurs only in a few varieties. Relatively little is known, however, concerning their 3,4-*cis* - counterparts which have yet to be found in the plant.

A one-step synthesis of (±)-Δ^1-*cis*-THC **3a**, from citral and olivetol in the presence of 0.0005N hydrochloric acid, was first reported by Taylor *et al.*[3] in 1966. Taylor also claimed that the same reactants with BF_3·etherate gave (±)-Δ^6-*cis*-THC **4a**; Mechoulam[4] later showed it was actually $\Delta^{4,8}$-*iso*-THC **5**. A second synthesis of (±)-**3a** was published by Fahrenholtz *et al.*[5] in 1967.

In 1975, in a preliminary communication, we reported the synthesis of the elusive (±)-Δ^6-3,4-*cis*-THC **4a** by three unambiguous routes.[1b] In the present paper, we present the details of our syntheses, and describe the first total synthesis of optically active Δ^1- and Δ^6-*cis*-THC's.

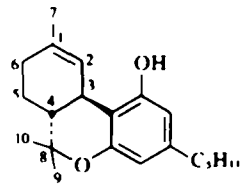
We previously reported[6] a novel, stereospecific, intramolecular epoxide cleavage by phenolate anion, which was discovered during our studies on cannabidiol derivatives. In this reaction, the epoxide of cannabidiol diacetate **6** on treatment with a base under mild conditions, afforded the dihydrofuran derivative cannabielsoin **7** in excellent yield. We therefore envisioned that a similar transformation of the epoxide **8** derived from (±)-Δ^1-*cis*-THC acetate **3b** would lead to the corresponding dihydrofuran derivative **9**. Dehydration of **9** and subsequent cleavate of the furan ring would provide the hitherto unknown (±)-Δ^6-*cis*-THC **4a**. (±)-Δ^1-*cis*-THC **3a** would be expected as well if equilibration of the anion between C2 and C6 occurs during the reductive cleavage.

Thus (±)-**3b**, upon oxidation with *m*-chloroperbenzoic acid in CH_2Cl_2 at 0°C, gave the epoxide **8** (80% yield), as indicated in the NMR by the absence of a vinylic proton signal and the presence of a multiplet (centered at δ 3.00) corresponding to two protons at C2 and C3. The assignment of the configuration for the epoxide ring as β (i.e. on the same side as the hydrogens at C3 and C4) is based on the assumption that the peracid attacks from the less hindered side. Under basic hydrolytic conditions, the epoxide was opened by an intramolecular attack of the phenolate anion at C2 (Scheme 1) to furnish the 2,3-*cis*-benzofuran **9** in 90% yield. The facility of this epoxide opening supports a β-orientation of the oxirane ring; an epoxide with the α-configuration is sterically unable to achieve the required geometry for a favorable *trans*-opening. The reaction probably proceeds by an *anti-periplanar* opening of the β-oxirane ring to give, initially, a boat C ring, which then assumes the more stable chair conformation with the oxygen functions equatorial. In addition, as a consequence of this opening, the stereochemistry at C2 and C3 is fixed as *cis*. The observed coupling constant of 9 Hz between the C2 and C3 protons is in accord with the values reported for the cannabielsoic acid series (5–6 Hz)[7] and for vicinal *cis*-protons in the dihydrobenzofurans (7 Hz).[8] Corresponding *trans*-dihydrofurans have smaller coupling constants (2–3 Hz).[8] The high field signal (δ 0.83) observed for the C1–CH_3 group is consistent with a methyl group being within the shielding cone of the benzene ring. This further supports its axial orientation.

Dehydration of **9** with $SOCl_2$ and pyridine gave the exocyclic allylic ether **10**. Dehydration with hexamethylphosphoramide (HMPA) at 240°C gave a mixture of *exo*-**10** and *endo*-**11** allylic ethers (ratio of 1:1 by NMR). In contrast, cannabielsoin **7**, which has an axial C1-hydroxyl group, gave upon dehydration ($SOCl_2$, pyridine), a product with an endocyclic double bond.[6] These results are consistent with the studies of Barton *et al.*[9] on the elimination of tertiary axial and equatorial hydroxyl groups. Shani and Mechoulam have reported similar findings in the cannabielsoic acid series.[7]

The mixture of **10** and **11** as isolated from the reaction with HMPA was treated with potassium and liquid ammonia for 1.5 h, which cleaved the allylic ether bond,[10] affording a mixture (7:3 by GLC after silylation) of (±)-Δ^1- and -Δ^6-*cis*-THC's (**3a** and **4a**, 90% from **9**). Because **3a** and **4a** were separated more easily as their acetates **3b** and **4b**, the mixture was acetylated and separated by high pressure liquid chromatography (HPLC). Hydrolysis of **4b** at room temperature with dilute methanolic sodium hydroxide furnished (±)-Δ^6-*cis*-THC.

Treatment of **4a** with *p*-toluenesulfonic acid in boiling benzene gave $\Delta^{4,8}$-*iso*-THC **5** as the major product. (±)-Δ^1-*cis*-THC undergoes the identical transformation on acid catalysis.[4,11] When the acetate **4b** was subjected to these conditions, the equilibrium mixture consisted of isomer **3b** (77%) and, unexpectedly, a substantial quan-



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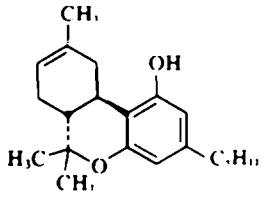

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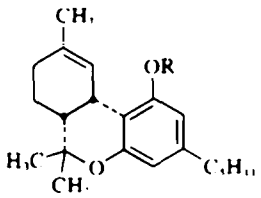
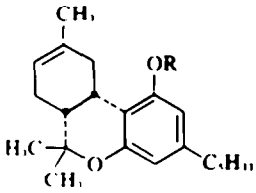


3a: R = H
3b: R = COCH$_3$



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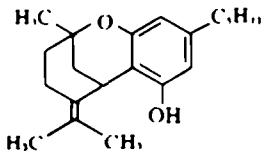

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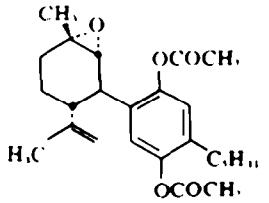

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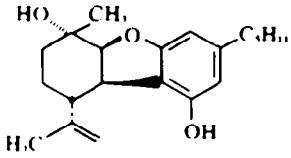

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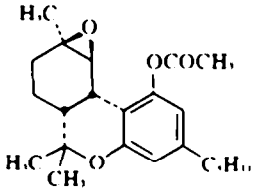

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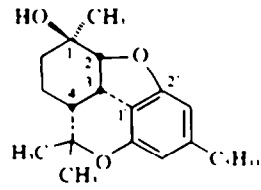

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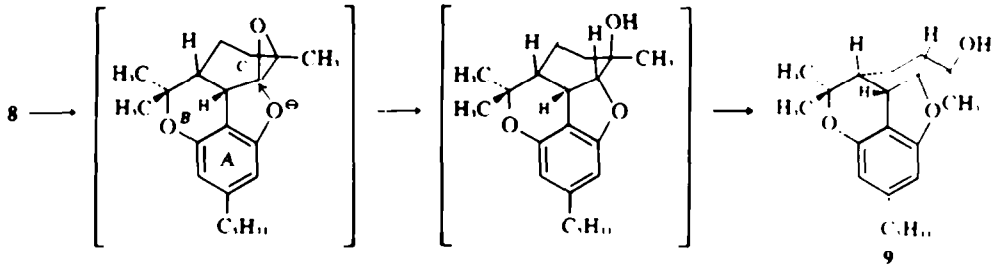
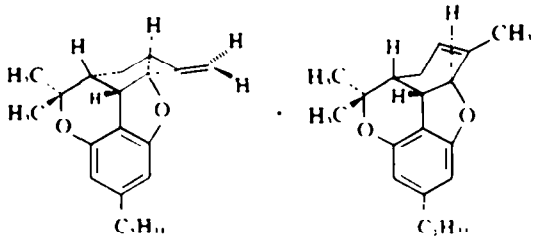
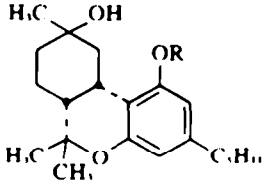




10 11



12a: R = H
12b: R = COCH$_3$

3a + 4a

Scheme 1.

tity of **4b** (23%). The same mixture was formed starting with **3b**; this is contrary to the result reported by Gaoni and Mechoulam.[4] The mixture was separated and the fraction containing **4b** was hydrolyzed as before. This thus constitutes a second synthesis of (±)-Δ^6-*cis*-THC **4a**.

In a third synthesis, the acetate **12b** (Scheme 1) obtained from the known *cis*-tertiary alcohol **12a**,[5] in the presence of thionyl chloride and pyridine at 0°C for 0.5 h furnished a mixture of **3b** and **4b** (3:2 by GLC after hydrolysis and silylation). (±)-Δ^6-*cis*-THC **4a** was obtained from the acetate as previously described.

The use of GLC alone for the identification of the four THC isomers (Table 1) can lead to misinterpretations because of the similarity of retention times. In our experience, these compounds are reliably differentiated by the NMR position (Table 1) of (a) the C8-α-CH_3, which is shielded to a greater extent in the *trans*-isomers (δ 1.05) than in the *cis*-isomers (δ 1.25 or 1.22), and (b) the vinylic proton which appears at δ 5.30 or 5.32 for the Δ^6-isomers and at δ 6.27 or 6.28 for the Δ^1-isomers. Acetylation causes a shift (upfield) of the vinyl signal in *cis*-Δ^1- and *trans*-Δ^1-THC's only (0.52 and 0.36 ppm respectively). The C8-α-CH_3 signals are unaffected by acetylation.

Synthesis of (+)-Δ^1- *and* -Δ^6-cis-*THC's*

We reported earlier[12] an entry into cannabinoids via carene derivatives, a one-step stereospecific synthesis of (−)-Δ^1-*trans*-THC **2**. In this reaction (Scheme 2) (+)-*trans*-2-carene oxide **13** and olivetol **14** in the presence of BF_3 etherate gave a complex mixture containing optically active Δ^1-*trans*-THC **1** and Δ^1-*cis*-THC **3a**.

We have restudied this reaction, and have separated the *cis*-THC from its isomers by the following sequence of reactions. The crude mixture was acetylated and allowed to react with *m*-chloroperbenzoic acid, to presumably give a mixture containing optically active epoxides **8** and **15**. Hydrolysis with dilute methanolic sodium hydroxide was accompanied by an intramolecular opening of the epoxide ring (as in the racemic case, Scheme 1) which occurred exclusively with the 3,4-*cis*-isomer **8**, resulting in the dihydrofuran derivative **9**. Conformational constraints introduced by the 3,4-*trans*-ring junction in **15** would prevent the formation of the corresponding dihydrofuran (**16**, Scheme 2). After alkali treatment the *cis*-furan **9** was easily isolated as a neutral fraction by extraction with hexane. The neutral component was then dehydrated, reductively cleaved, and purified to give pure (+)-Δ^1-*cis*-THC, 0.7%, $[\alpha]_D$ +121° (ethanol). A second component isolated in smaller amounts was identified as (+)-Δ^6-*cis*-THC, 0.06%, $[\alpha]_D$ +104° (ethanol), the thermodynamically less stable isomer.

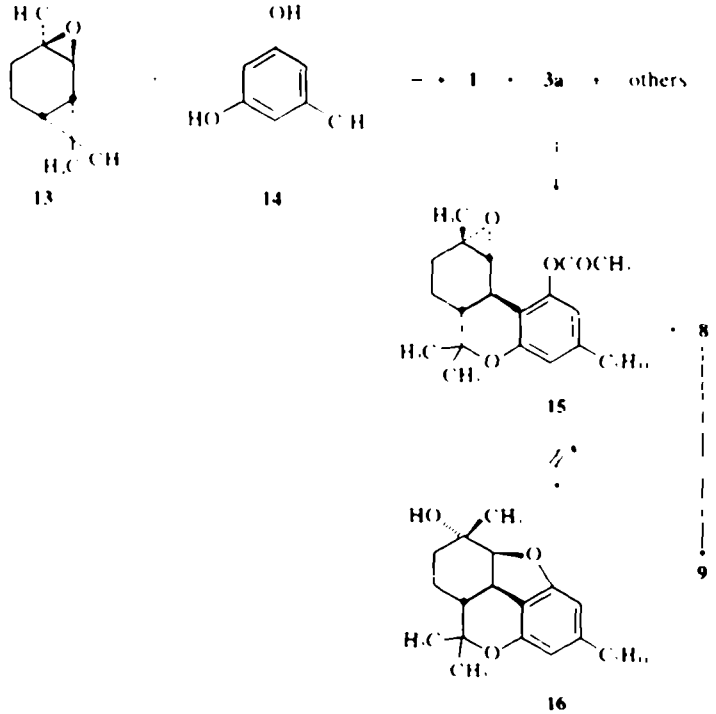
As expected,[11] (+)-Δ^1-*cis*-THC is much less biologically active than (−)-Δ^1*trans*-THC. The details of the pharmacological profile will be published elsewhere.

EXPERIMENTAL

NMR spectra were measured on a Varian T-60 spectrometer. A Varian Aerograph Model 1440 was used for GLC under conditions detailed in Table 1. IR spectra were recorded on a Perkin Elmer 700 instrument. High-pressure liquid chromatography was performed on a Waters Associates ALC-202 chromatograph equipped with a Model 6000 solvent delivery system.

Synthesis of (±)-Δ^6-cis-*THC* **4a**

2,2'-Epoxy-2,3,4-cis-hexahydro-1-hydroxy-2'-desoxycannabinol **9**. A solution of 285 mg (1.65 mmol) of *m*-chloroperbenzoic acid in 30 ml of CH_2Cl_2 was added dropwise to a solution of 500 mg (1.40 mmol) of (±)-Δ^1-*cis*-THC acetate **3b**[4] in 75 ml of CH_2Cl_2 held in an ice bath at 0–5°C. The solution was allowed to come to room temp. and was stirred overnight. The CH_2Cl_2 was replaced by ether and the solution was washed with



Scheme 2.

Table 1

Relative retention time by GLC[a]				NMR data[b]					
Unsilylated	Silylated	Acetylated	Compound	Aromatic (AB, 2, J = 2 Hz)	Olefinic (br, 1)	C3-H	C1-CH_3 (s, 3)	C8-$(CH_3)_2$ (s, 3)	ω-CH_3 (t, 3)
1.00	1.00	1.08	Δ^6-*cis*-THC **4a**	6.12, 5.93	5.30	3.13(br, 1)	1.63	1.33 1.25	0.88
1.00	1.00	1.00	Δ^6-*trans*-THC **2**	6.08, 5.88	5.32	2.65(m, 1)	1.65	1.30 1.05	0.88
1.00	1.09	1.08	Δ^1-*cis*-THC **3a**	6.13, 5.97	6.27	3.47(br, 1)	1.63	1.33 1.22	0.87
1.10	1.09	1.08	Δ^1-*trans*-THC **1**	6.13, 5.97	6.28	3.13(br, 1)	1.65	1.37 1.05	0.88

[a]Determined on a Varian Aerograph Model 1440 equipped with a 6 ft × 1/8 in. stainless steel column packed with 3% OV-17 on 80–100 mesh Supelcoport and a flame ionization detector. Carrier gas was helium and column temperature was 240–250° as needed to elute the charge within 4 to 6 min. Bis(trimethylsilyl)-trifluoroacetamide was used as silylating agent.

[b]Chemical shift values (δ) measured in CCl_4 solution on a Varian T-60 spectrometer.

1N NaOH, 1N HCl, and brine. The ether solution was dried over Na_2SO_4 and the solvent was removed under vacuum to give 418 mg (80%) of resinous 1β,2β - epoxy - 3,4 - *cis* - hexahydrocannabinol acetate **8**; NMR(CCl_4) δ: 6.40 (s, 2, aromatics), 3.00 (m, 2, C2-H, C3-H), 2.50 (m, 2, α-CH_2), 2.28 (s, 3, acetate), 1.30 (s, 3, C1-CH_3), 1.23, 1.20 (2s, 6, C8-$(CH_3)_2$), 0.90 (t, 3, ω-CH_3). The epoxide (250 mg, 0.67 mmol), without further purification, was dissolved in 15 ml of 4% aqueous NaOH and enough MeOH for homogeneity. The now purple solution was allowed to stir at room temp. for 2 h and then was neutralized with 2N HCl. Ether was added and the organic phase was washed with brine and dried over Na_2SO_4. The reaction products were separated by preparative TLC (silica gel, 1:1 ether/petroleum ether) to give 200 mg (90%) of **9** as colorless crystals, m.p. 102° (petroleum ether); NMR (CCl_4) δ: 6.00 (s, 2, aromatics), 4.73 (d, 1, J = 9 Hz, C2-H), 3.65 (dd, 1, $J_{2,3}$ = 9 Hz, $J_{3,4}$ = 6 Hz, C3-H), 2.45 (m, 2, α-CH_2), 1.34, 1.30 (2s, 6, C8-$(CH_3)_2$), 0.90 (t, 3, ω-CH_2), 0.83 (s, 3, C1-CH_3); IR (CCl_4) cm^{-1}: 3725 (O–H), 2950, 1610; mass spectrum (70 eV) *m/e* (%): 330 (M^+, 90), 315(9), 312(4), 297(11), 287(11), 274(16), 247(58), 231(9), 205(100), 204(53), 148(42), 147(30).

Anal. Calc. for $C_{21}H_{30}O_3$: C, 76.31; H, 9.16. Found: C, 76.26; H, 9.17%).

Dehydration of compound **9** *with hexamethylphosphoramide(HMPA).* Compound **9** (200 mg, 0.61 mmol) was dissolved in 20 ml of HMPA and heated to 240°C. Reaction was complete (TLC) within 20 min. The solution was allowed to cool to room temp. poured into 150 ml of ice-water, and neutralized with 2N HCl. Extraction with ether was followed by washing the organic phase with H_2O and brine. After drying over $MgSO_4$, the ether was removed under vacuum to give 170 mg (90%) of a mixture of **10** and **11** (1:1 by NMR); NMR(CCl_4) of **11** (as part of a mixture) δ: 5.98 (s, aromatics), 5.38 (br, C6-H), 5.02 (d, J = 9 Hz, C2-H), 3.62 (m, C3-H), 2.47 (m, 2, α-CH_2), 1.72 (s, C1-CH_3), 1.35 (s, C8-$(CH_3)_2$), 0.88 (t, ω-CH_3); mass spectrum (70 eV) *m/e* (%): 312 (M^+, 100), 297(50), 284(22), 270(11), 269(28), 257(44), 256(42), 244(44), 214(36). This mixture was used in the next step without purification.

Dehydration of compound **9** *with* $SOCl_2$*/pyridine.* Compound **9** (100 mg, 0.30 mmol) in 5 ml of pyridine at 0°C was treated with $SOCl_2$ (39 mg, 0.33 mmol). After 2 h the reaction was quenched with 2N HCl. After addition of 200 ml of ether the organic phase was separated and washed with 2N HCl and brine. The ether solution was dried over $MgSO_4$ and removed under vacuum to give 80 mg of dark oil. Purification by preparative TLC (silica gel, 1:1 ether/petroleum ether, rf 0.68) gave 25 mg (27%) of compound **10**; NMR (CCl_4) δ: 6.08, 5.98 (2s, 2, aromatics), 5.23–5.00 (m, 2, C2-H, and C7-H), 4.72 (br, 1, C7-H), 3.55 (dd, 1, $J_{2,3}$ = 8 Hz, $J_{3,4}$ = 6 Hz, C3-H), 2.47 (m, 2, α-CH_2), 1.33 (s, 6, C8-$(CH_3)_2$), 0.88 (t, 3, ω-CH_3).

(±)-Δ^1- and -Δ^6-cis-THC acetates **3b**[3] and **4b**. The mixture of furano compounds **10** and **11** (170 mg, 0.55 mmol) in 50 ml of liquid NH_3 in a dry-ice bath was treated with excess potassium metal. The initial blue color faded after 0.5 h. Solid NH_4Cl was added and the liquid NH_3 was allowed to evaporate.

Ether was added and the solution was washed with brine to give a mixture of the *cis*-THC's, **3a** and **4a** (7:3 by GLC, after silylation) in quantitative yield. A solution of 260 mg (0.84 mmol) of such a mixture (from several experiments) and 430 mg (4.21 mmol) of acetic anhydride in 10 ml of pyridine was stirred overnight at room temp. Ether was added and the solution was washed with 2N HCl, saturated $NaHCO_3$, and brine, and was dried over Na_2SO_4. Evaporation of solvent left 300 mg of a mixture of the acetates **3b** and **4b**, which was separated by high-pressure liquid chromatography. A 7-ft × 3/8-in. column packed with Porasil C and 3% ether-hexane as eluant were used for the preparative separation. The capacity factor (k') was 0.72 for the Δ^1-isomer and 0.88 for the Δ^6-isomer, giving a separation factor (α) of 1.22. After 5 recycles, baseline separation was achieved, and 100 mg of **4b** was isolated; NMR (CCl_4) δ: 6.48, 6.33 (AB, 2, J = 2 Hz), 5.38 (br, 1, C6-H), 3.05 (br, 1, C3-H), 2.47 (m, 2, α-CH_2), 2.23 (s, 3, acetate), 1.65 (s, 3, C1-CH_3), 1.35, 1.25 (2s, 6, C8-$(CH_3)_2$), 0.92 (t, 3, ω-CH_3); IR (CCl_4) cm^{-1}: 2950, 1760 (C=O), 1620, 1205.

(±)-Δ^6-cis-THC **4a**. A solution of 100 mg (0.28 mmol) of (±)-

Δ^6-*cis*-THC acetate **4b** in 10 ml of equal parts of 4% aqueous NaOH and MeOH was allowed to stand at room temp. for 2 h. It was then neutralized with 1N HCl and extracted with ether. The ether solution was dried over Na_2SO_4 and the solvent removed, leaving 80 mg of (+)-Δ^6-*cis*-THC **4a** as an orange oil; GLC and NMR (Table 1); mass spectrum (70 eV) *m/e*(%): 314 (M^+, 22), 299(7), 271(10), 258(6), 246(21), 231(100), 193(8); IR (CCl_4) cm^{-1}: 3700 (O–H), 2950, 1620, 1585.

Synthesis of **4a** *by equilibration of* **3b**. To 40 mg (0.11 mmol) of **3b**[1] in 10 ml of benzene at reflux was added 3 mg of *p*-toluenesulfonic acid monohydrate. After 90 min, when equilibration was judged complete (GLC; hydrolysis and silylation), saturated aqueous $NaHCO_3$ was added to the hot solution. The organic phase was separated and dried over Na_2SO_4. Removal of benzene gave in quantitative yield a mixture of Δ^1- and Δ^6-*cis*-THC acetates in a ratio of 77:23 (GLC, after hydrolysis and silylation). The mixture was separated by HPLC, and the fraction containing **4b** was hydrolyzed as described above, to yield (±)-**4a**, identical in all respects (NMR, GLC, TLC, mass spectrum) with an authentic sample.

Formation of **3b** *by equilibration of* **4b**. Equilibration was carried out as described above. The reaction was quenched after 60 min. Analysis of the mixture by GLC (after hydrolysis and silylation) and NMR indicated a Δ^1- to Δ^6-*cis*-THC ratio of 77:23.

Synthesis of **4a** *from* **12a**

(±) - 1 - *Hydroxy* - 3,4 - cis - *hexahydrocannabinol acetate* **12b**. After 2 h at 0°C, a solution of 320 mg (0.96 mmol) of **12a**[1] and 1.0 ml (10.6 mmol) of acetic anhydride in 10 ml of pyridine was diluted with ether. It was washed with 2N HCl, saturated $NaHCO_3$, and brine, and dried over Na_2SO_4. Removal of solvent gave 360 mg (100%) of the acetate **12b** as an orange oil; NMR (CCl_4) δ: 6.50, 6.30 (AB, 2, J = 2 Hz), 3.08 (m, 1, 2α-H), 2.25 (s, 3, CH_3CO), 1.35 (s, 3, C1-CH_3), 1.20 (s, 3, C8-CH_3), 1.10 (s, 3, C8-CH_3), 0.90 (t, 3, ω-CH_3). The acetate was used without further purification. Thionyl chloride (160 mg; 1.36 mmol) was added to a stirred solution of 360 mg (0.96 mmol) of **12b** in 10 ml of pyridine at 0°C. After 30 min, the reaction was quenched with saturated $NaHCO_3$. Ether was added and the solution was washed with brine. The organic layer was dried (Na_2SO_4) and removal of the solvent gave a quantitative yield of a mixture of **3b** and **4b** (3:2 by GLC), which was separated by HPLC as before. Alkaline hydrolysis of the Δ^6-isomer as described above yielded **4a**; identical in all respects (NMR, GLC, TLC, mass spectrum) to an authentic sample.

Synthesis of (+)-Δ^1- *and* -Δ^6-cis-*THC's from carene oxide.* (+) - *trans* - 2 - Carene oxide (**13**, 25.3 g, 0.14 mol), olivetol (**14**, 25.3 g, 0.17 mol), and 3.0 ml of BF_3·Et_2O were allowed to react in 350 ml of methylene chloride at 0°C for 2.4 h. The reaction was quenched with $NaHCO_3$ and the products were isolated by washing and drying in the usual fashion. The crude material, dissolved in 75 ml of pyridine and 86.7 g (0.85 mol) of acetic anhydride, was acetylated after standing overnight at room temp. Ether was added and the solution was washed with 2N HCl, saturated $NaHCO_3$ solution, and brine, and dried over Na_2SO_4. The ether was removed and replaced with 250 ml of CH_2Cl_2. A solution of 38.0 g (0.22 mol) of *m*-chloroperbenzoic acid in 300 ml of CH_2Cl_2 was added to the acetate solution at 0°C. After being stirred at room temp. overnight, the solution was evaporated *in vacuo* and 300 ml of a 1:1 mixture of 4% aqueous NaOH and MeOH was added. The solution became dark purple. After being stirred overnight, the solution was stripped of methanol *in vacuo* and the aqueous residue was extracted with hexane. After drying (Na_2SO_4), the solution was evaporated to give 12 g of a brown oil. It was chromatographed on Florisil (400 g) and eluted with graded mixtures of ether/petroleum ether to give 2.3 g (5% yield from carene oxide) of **9** as a gum. It was dehydrated and reductively cleaved as described for the racemic compounds, to give a mixture of optically active **3a** and **4a**. This mixture was separated by HPLC, and hydrolyzed as described above, to produce (+)-Δ^1-*cis*-THC ($[\alpha]_D$ + 108° (ethanol)) and (+)-Δ^6-*cis*-THC ($[\alpha]_D$ + 104° (ethanol)) in overall yields of 0.7% and 0.06%, respectively. The compounds were identical in all respects except optical rotation (NMR, GLC, TLC, mass spectrum) with authentic samples of (±)-**3a** and (±)-**4a**. The analytical sample of (+)-Δ^1-*cis*-THC was obtained after a further purification by HPLC (μ-Porasil, 2% ether/isooctane; k' = 3.3): $[\alpha]_D$ + 121° (ethanol). *Anal.* Calc. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.33, H, 9.65%).

Treatment of (±)-Δ^6-cis-*THC with* p-*toluenesulfonic acid* (p-*TSA*). A solution of 7 mg of (±)-**4a** and 10 mg of *p*-TSA·H_2O in 10 ml of benzene was refluxed for 2 h. Saturated aqueous $NaHCO_3$ was added to quench the reaction. The organic phase was separated, dried, and evaporated to leave a gum, which contained $\Delta^{4,8}$-*iso*-THC **5** as the major product (NMR, GLC).

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REFERENCES

[1a]Part XIX. For Part XVIII, see: R. K. Razdan, H. C. Dalzell and P. Herlihy, *J. Heterocyclic Chem.* **13**, 1101 (1976); [b]Preliminary Communication of racemic synthesis: D. B. Uliss, R. K. Razdan, H. C. Dalzell and G. R. Handrick, *Tetrahedron Letters* 4369 (1975); [c]Presented in part at the 170th National Meeting of the American Chemical Society, San Francisco, Calif., 30 Aug. 1976, ORGN 12.

[2]Reviews: R. K. Razdan, In *Progress in Organic Chemistry* (Edited by W. Carruthers and J. K. Sutherland), Vol. 8, Butterworths, London (1973); *Marihuana, Chemistry, Pharmacology, Metabolism and Clinical Effects* (Edited by R. Mechoulam), Academic Press, New York (1973); R. Mechoulam, N. K. McCallum and S. Burstein, *Chemical Rev.* **76**, 75 (1976).

[3]E. C. Taylor, K. Lenard and Y. Shvo, *J. Am. Chem. Soc.* **88**, 367 (1966).

[4]Y. Gaoni and R. Mechoulam, [a]*Ibid* **88**, 5673 (1966); [b]*Isr. J. Chem.* **6**, 679 (1968).

[5]K. E. Fahrenholtz, M. Lurie and R. W. Kierstead, *Ibid* **89**, 5934 (1967).

[6]D. B. Uliss, R. K. Razdan, H. C. Dalzell and G. R. Handrick, *J. Am. Chem. Soc.* **96**, 7372 (1974).

[7]A. Shani and R. Mechoulam, *Tetrahedron* **30**, 2437 (1974).

[8]E. C. Hayward, S. D. Tarbell and L. C. Colebrook *J. Org. Chem.* **33**, 399 (1968); M. Gheraldoni, V. Pestellini and C. Musante, *Gazz. Chim. Ital.* **99**, 1273 (1969); M. P. Mertes, L. J. Powers and E. Shefter, *J. Chem. Soc. Chem. Commun.* 620 (1970); M. P. Mertes, L. J. Powers and N. M. Hava, *J. Med. Chem.* **14**, 361 (1971).

[9]D. H. R. Barton, A. da S. Campos-Neves and R. C. Cookson, *J. Chem. Soc.* 3500 (1956).

[10]This transformation has been used in THC and other classes of compounds. See for example: R. K. Razdan, H. G. Pars, W. R. Thompson and F. E. Granchelli, *Tetrahedron Letters* 4315 (1974); K. W. Bentley, R. Robinson and A. E. Wain, *J. Chem. Soc.* 958 (1952); A. J. Birch and M. Maung, *Tetrahedron Letters* 3275 (1967); A. J. Birch, P. L. Macdonald and V. H. Powell, *J. Chem. Soc. (C)* 1469 (1970); C. W. Wilson, III and P. E. Shaw, *J. Org. Chem.* **38**, 1684 (1973).

[11]R. K. Razdan and B. A. Zitko, *Tetrahedron Letters* 4947 (1969).

[12]R. K. Razdan and G. R. Handrick, *J. Am. Chem. Soc.* **92**, 6061 (1970).

[13]D. B. Uliss, H. C. Dalzell, G. R. Handrick, J. F. Howes and R. K. Razdan, *J. Med. Chem.* **18**, 213 (1975).