**p-Tolyl Ketone (6f).** Again, no extraction step was employed. Ninety milligrams of small white crystals was collected as a crude product (46%) which gave the same $R_f$ on silica-gel TLC plates as **2f**. This was recrystallized with difficulty from about 30 mL of 95% ethanol. After a number of recrystallizations, a small amount of product, mp 205–210 °C, was obtained. This was identified as a mixture of **2f** and an isomer of **6f**: NMR of mixture δ 2.00 (s, OH), 2.21 (s, $CH_3$), 2.26 (s, $CH_3$), 2.36 (s, $CH_3$), 2.40 (s, $CH_3$), 2.52, 2.70, 4.22, 4.41 (AB, $CH_2$ (open chain), $J_{AB}$ = 18.5 Hz), 3.01, 3.17, 3.29, 3.44 [AB, $CH_2$ (cyclized), $J_{AB}$ = 15.5], 4.26 (s, OH), 5.27, (s, CH), 5.33, (s, OH), 6.03 (s, OH), 6.83–7.32, 7.50–7.92 (m, arom). The singlets at δ 2.00, 4.26, 5.33, and 6.03 disappear on addition of $D_2O$.

**Reduction of 1,3,4,6-Tetraphenyl-2,4-hexadiene-1,6-dione (4a).** A white precipitate was collected and was recrystallized from benzene, giving two crops of white crystals: mp 210 and 225 °C, respectively; TLC, NMR, and IR indicated these two crops were identical. A second recrystallization from benzene yielded colorless needles of 1,3,4,6-tetraphenyl-3-hexene-1,6-dione: mp 232 °C; IR 3065, 2912, 1680, 1591, 1568, 1478, 1421, 1318, 1200, 748, 703 $cm^{-1}$; NMR (saturated) δ 3.98 (s, $CH_2$) 7.06–7.76 (m, arom). Anal. Calcd for $C_{30}H_{24}O_2$: C, 86.50; H, 5.82. Found: C, 86.56; H, 5.78.

**Acknowledgment.** The authors thank David F. Hillenbrand for his assistance with the high-field NMR experiments.

**Registry No.**—**1a,** 1704-15-0; **1b,** 62375-96-6; **1c,** 62375-97-7; **1d,** 6909-81-5; **1f,** 62375-98-8; *meso*-**2a,** 62375-99-9; **2b,** 62376-00-5; **2c,** 62376-01-6; **2d,** 62376-02-7; **2f,** 62376-03-8; **3a,** 62376-04-9; **3b,** 62376-05-0; **4a,** 10562-16-0; **4b,** 62376-06-1; **4c,** 62376-07-2; **4d,** 62376-08-3; **4f,** 62376-09-4; **5a,** 62376-10-7; **6a,** 62376-11-8; **6ai,** 62445-07-2; **6aii,** 62445-08-3; **6f,** 62376-12-9; 1,3,4,6-tetraphenyl-3-hexene-1,6-dione, 62376-10-7.

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# Hashish.[1] Synthesis of (±)-$\Delta^1$- and $\Delta^6$-3,4-*cis*-Cannabidiols and Their Isomerization by Acid Catalysis

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The total synthesis of (±)-$\Delta^1$- and $\Delta^6$-3,4-*cis*-cannabidiols (CBD, **5a** and **5b**) by two independent routes is described. The starting materials for these new cannabinoids were the lactones **1a** and **7**. High-pressure liquid chromatography was used to separate the mixture of $\Delta^1$- and $\Delta^6$-CBD diacetates obtained in the final step of each route. The acid-catalyzed (*p*-TSA) transformation products of *cis*-CBDs (**5a** and **5b**) were isolated and identified as the ring closed *cis*-cannabinoids **12–15**. The rate of the reaction and the relative proportions of products were found to be dependent on the acid concentration.

(−)-Cannabidiol (CBD), which occurs naturally in marijuana (*Cannabis sativa*) and is the precursor in some of the syntheses of $\Delta^1$- and $\Delta^6$-tetrahydrocannabinols (THC),[2] has a 3,4-trans ring junction and a double bond in the $\Delta^1$ position. The $\Delta^6$-trans isomer and the corresponding $\Delta^1$- and $\Delta^6$-CBDs with a 3,4-cis junction are not known in the literature.[3-5] This article describes the first syntheses of (±)-$\Delta^6$- and $\Delta^1$-3,4-*cis*-CBDs and the transformations they undergo under the influence of an acid catalyst.

In an earlier article[6] Razdan and Zitko described the acid-catalyzed (*p*-toluenesulfonic acid, *p*-TSA) interconversion of $\Delta^1$-3,4-*cis*-tetrahydrocannabinol (THC) and the isotetrahydrocannabinols (iso-THCs) by way of citrylidene-cannabis as a short-lived intermediate. We have found that both $\Delta^1$- and $\Delta^6$-*cis*-CBD undergo a similar conversion, the extent of which is strongly dependent on the concentration of the acid catalyst.

A total synthesis of (±)-$\Delta^6$-*cis*-cannabidiol (**5a**) was achieved by two different routes from the lactones **1a** and **7** (Schemes I and II). (±)-$\Delta^1$-*cis*-CBD (**5b**) was obtained from a mixture of lactones (**1a** and **1b**), produced by acid-catalyzed equilibration, with subsequent separation of the mixed CBDs.

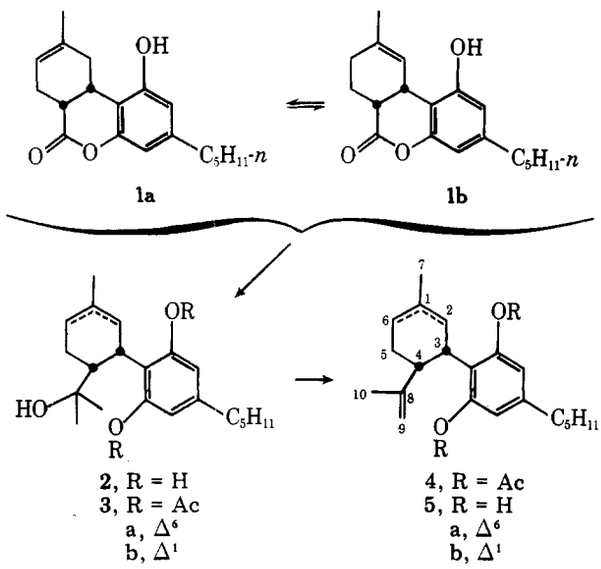
Lactone **1a** was prepared from isoprene and 3-carboxy-5-hydroxy-7-*n*-pentylcoumarin by a Diels–Alder reaction accompanied by decarboxylation. Taylor and Strojny[7] developed this procedure to prepare similar lactones, demonstrating that isoprene adds to the coumarin to give a cis ring fusion and a methyl substituent at C-1, as shown in **1a**. The NMR of **1a** (Table I) is in complete agreement with the assigned structure. The benzylic proton at C-3 appears as two triplets with coupling constants of 6, 6, and 11 Hz, which is consistent with 3,4-cis ring fusion and the double bond at C-6. Hively[8] also prepared **1a** and arrived at similar conclusions

**Table I. NMR of (±)-*cis*-Cannabidiols and Precursors[a]**

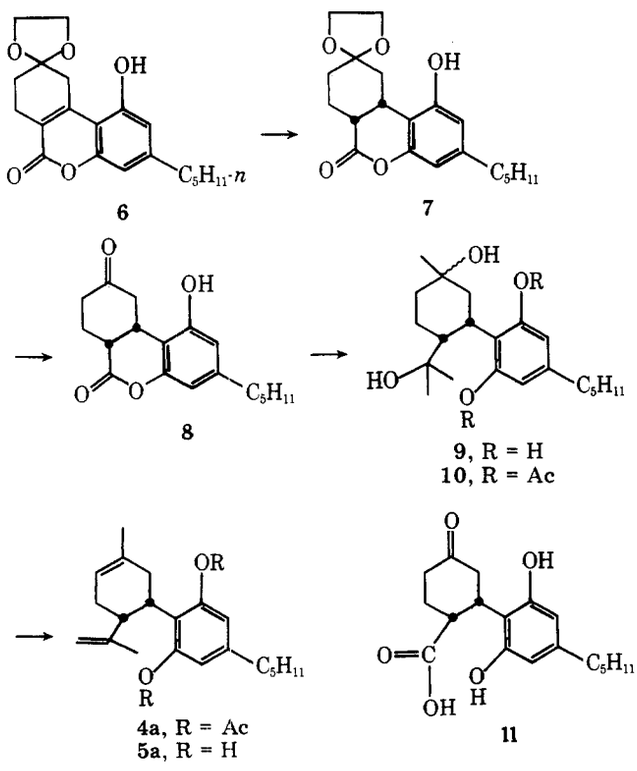
| Type of proton | 1a | 1b | 4a | 4b | 5a | 5b |
|---|---|---|---|---|---|---|
| ω-$CH_3$ | 0.88 (t) | 0.88 (t) | 0.88 (t) | 0.87 (t) | 0.87 (t) | 0.88 (t) |
| C-8 $CH_3$ | | | 1.40 (s) | 1.27 (s) | 1.73 (s) | 1.87 (s) |
| C-1 $CH_3$ | 1.63 (s)[b] | 1.63 (s)[b] | 1.67 (s) | 1.70 (s) | 1.63 (s) | 1.45 (s) |
| Acetyl $CH_3$ | | | 2.18 (s) | 2.10 (s) | | |
| C-3 benzylic | 3.50 (dt) | 3.92 (br m) | 3.33 (m) | 3.80 (m) | 3.87 (br m) | 4.02 (br m) |
| C-8 $=CH_2$ | | | 4.60 (br d) | 4.52 (s) | 4.77 (br m) | 4.75 (s) |
| Vinylic | 5.47 | 5.32 | 5.40 (br) | 5.32 (br d) | 5.77 (br) | 5.87 (br d) |
| OH | 5.83 (s) | | | | 5.60 (s) | 5.70 (br) |
| Aromatic | 6.48 (s) | 6.48 (s) | 6.65 (s) | 6.62 (s) | 6.13 (s) | 6.17 (s) |

[a] All spectra were determined on a Varian A-60 spectrometer; δ values are given in $CDCl_3$ for **1a** and **1b** and in $CCl_4$ for **4a,b** and **5a,b**, relative to $Me_4Si$ as internal standard. [b] C-9 $CH_3$, in the numbering system used for the dibenzopyranones.

Scheme I




Scheme II




on the basis of degradation and NMR studies. Reaction of **1a** with $CH_3MgI$ gave the triol **2a**; its diacetate **3a** was dehydrated with thionyl chloride in pyridine to give Δ⁶-3,4-*cis*-CBD diacetate (**4a**).

When the lactone **1a** was heated in solution with *p*-toluenesulfonic acid (*p*-TSA), a 1:1 equilibrium mixture with its isomer **1b** was formed after about 1 h. This mixture was carried through the same transformations as for the pure Δ⁶-cis isomer to give a mixture of the Δ⁶- and Δ¹-*cis*-CBD diacetates (**4a** and **4b**). These were quite different in both their GLC and NMR characteristics, and they were easily separated by high-pressure liquid chromatography (HPLC).

The corresponding diols (**5a** and **5b**) were obtained by hydrolysis in $CH_3OH$ with 5% KOH at ambient temperature. When the hydrolysis of **4b** was interrupted after 20 min, its monoacetate was isolated, indicating that the rate of removal of the second acetate was considerably slower than the first. A difference in rates of silylation was also observed in gas chromatographic studies with both CBDs **5a** and **5b**.

Differences in the NMR ($CCl_4$) of **5a** and **5b** are noteworthy (Table I): (a) C-1 and C-8 methyl protons in **5a** appear at δ 1.63 and 1.73, whereas in **5b** the corresponding signals are at δ 1.45 and 1.87; (b) the vinylic proton is a broad single peak at δ 5.77 in Δ⁶-*cis*-CBD (**5a**), but is a broad doublet at 5.87 in Δ¹-*cis*-CBD (**5b**); (c) the terminal methylene protons appear as a broad multiplet at δ 4.77 for **5a**, but as a singlet at δ 4.75 for

Scheme III

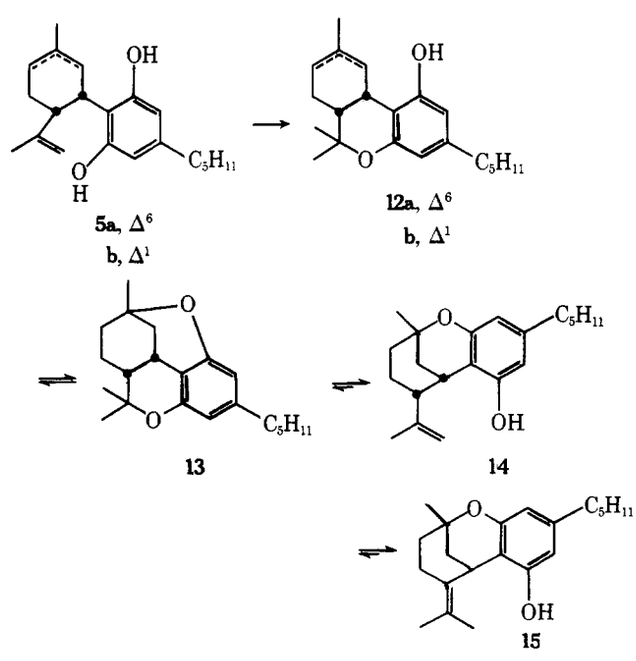


**Table II. Effect of Acid on *cis*-Cannabinoids**

| Reactants | Expt 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Vol benzene, mL | 22 | 25 | 25 | 1.5 | 1.7 | 1.5 |
| Wt cannabinoid, mg | 26.2[a] | 13.6[b] | 16[c] | 1.06[d] | 1.08[e] | 1.27[d] |
| Concn, g/100 mL | 0.12 | 0.05 | 0.06 | 0.07 | 0.06 | 0.08 |
| Wt *p*-TSA·$H_2O$, mg | 1.4 | 10.2 | 50 | 2.87 | 2.5 | 0.05 |
| Concn, g/100 mL | 0.006 | 0.04 | 0.20 | 0.19 | 0.15 | 0.003 |
| Products[f] | %, by GLC | | | | | |
| $\Delta^6$-*cis*-CBD | 12 | 0 | 0 | 0 | 0 | 10 |
| $\Delta^1$-*cis*-CBD | 7 | 0 | 0 | 0 | 0 | 0 |
| $\Delta^6$-*cis*-THC | 50 | 28 | 8 | 22 | 17 | 51 |
| $\Delta^1$-*cis*-THC | 4 | 67 | 31 | 16 | 40 | 12 |
| $\Delta^8$-*cis*-Iso-THC | 24 | 1 | 15 | 10 | 7 | 17 |
| $\Delta^{4(8)}$-Iso-THC | 0 | 4 | 44 | 52 | 36 | 10 |
| Cannabicitran[g] | 2 | Tr | 2 | | | |

[a] Synthesis; $\Delta^6$-*cis*-CBD, >95% assay by GLC. [b] Fraction by high-pressure liquid chromatography of product from expt 1; $\Delta^6$-*cis*-THC (84%), $\Delta^1$-*cis*-THC (5%), $\Delta^1$- + $\Delta^6$-*cis*-CBD (11%), by GLC. [c] Product from expt 2; $\Delta^6$-*cis*-THC (28%), $\Delta^1$-*cis*-THC (67%), $\Delta^8$-*cis*-iso-THC (1%), $\Delta^{4(8)}$-iso-THC (4%) by GLC. [d] Synthesis; $\Delta^6$-*cis*-CBD (88%), $\Delta^8$-*cis*-iso-THC (12%). [e] Synthesis; $\Delta^1$-*cis*-CBD (>95%). [f] At 30 min for expt 1; all others at 60 min. [g] Also called tetracyclic ether (TCE) and citrylidene-cannabis.[6]

**Table III. Products from Experiment 1 (Table II) Separated by High-Pressure Liquid Chromatography[a]**

| | Analysis by GLC | | |
|---|---|---|---|
| | | Rel retention time[b] | |
| | % | Silylated (230 °C) | Not silylated (260 °C) |
| Fraction 1 ($k'$ = 1.1; 0.9 mg) | | | |
| cannabicitran[c] | 88 | 0.96 | 0.52 |
| Fraction 2 ($k'$ = 2.6; 2.8 mg) | | | |
| $\Delta^8$-*cis*-iso-THC[d] | 95 | 0.74 | 0.63 |
| $\Delta^{4(8)}$-iso-THC | 4 | 1.06 | 0.82 |
| Fraction 3 ($k'$ = 3.6; 0.9 mg) | | | |
| $\Delta^1$-*cis*-CBD | 63 | 0.66 | 0.85 |
| $\Delta^8$-*cis*-iso-THC | 10 | 0.74 | 0.63 |
| $\Delta^{4(8)}$-iso-THC | 25 | 1.06 | 0.81 |
| Fraction 4 ($k'$ = 4.4; 17.4 mg) | | | |
| $\Delta^1$-*cis*- + $\Delta^6$-*cis*-CBD | 11 | 0.69 | |
| $\Delta^6$-*cis*-THC[e] | 84 | 0.98 | 1.0 |
| $\Delta^1$-*cis*-THC | 5 | 1.08 | |

[a] μPorasil, eluent 2% $Et_2O$/isooctane. [b] 3% OV-17, $\Delta^6$-*trans*-THC as reference = 1.00, time silylated (230 °C) 5.50 min, not silylated (260 °C) 3.84 min. [c] Not affected by silylation. [d] NMR ($CCl_4$) δ 6.08, 6.18 (2, 2 d, aromatic), 4.88, 4.67 (2, 2 m, C8 $CH_2$), 3.30 (1, m, C3 H), 1.82 (s, C8 $CH_3$), 1.37 (s, C1 $CH_3$), 0.95 (3, t, ω-$CH_3$), 4.47 (1, exchangeable OH). [e] NMR ($CCl_4$) δ 6.15, 5.95 (2, 2 d, aromatic), 5.37 (1, br, C6 olefinic), 3.17 (1, m, C2α), 1.65 (s, C1 $CH_3$), 1.36, 1.25 (2 s, *gem*-diMe), 0.89 (t, ω-$CH_3$).

**5b.** In comparison, signals for the equivalent protons in $\Delta^1$-*trans*-CBD, the natural isomer, are δ 1.63 and 1.80 for the methyl protons, δ 5.57 (br, s) for the vinylic proton, and δ 4.53 (m) for the terminal methylene protons.

The second synthesis of $\Delta^6$-*cis*-CBD (Scheme II) started with the lactone (**6**).[9] Reduction with Raney nickel at high pressure gave the lactone **7**, which Fahrenholtz et al.[9] have shown to be cis at C-3–C-4. Homogeneous acid hydrolysis of ketal **7** in dioxane produced the keto lactone **8**, along with a significant amount of the acid **11**. The latter was readily recyclized to lactone **8**.

Reaction of methyl Grignard with this keto lactone gave two major products, which were separated by high-pressure liquid chromatography. One of them was identified as the desired tetrol **9**. Its acetate (**10**) was dehydrated ($SOCl_2$/pyridine), to give $\Delta^6$-*cis*-CBD diacetate (**4a**) exclusively. Hydrolysis of the diacetate gave $\Delta^6$-*cis*-CBD (**5a**), which was identical in all respects (NMR, GLC, TLC) with the compound synthesized by Scheme I. As a practical matter, the mixture of polyols after Grignard reaction was carried through the acetylation and dehydration steps, and the CBD diacetate **4a** was separated from the mixture by HPLC.

**Treatment of *cis*-CBDs with Acids.** The *cis*-CBDs under the influence of a strong acid catalyst (*p*-TSA) were readily converted to ring closed compounds (Scheme III); the extent of reaction was strongly dependent on the concentration of catalyst.

With low acid concentration, as previously used in the interconversion of $\Delta^1$-*cis*-THC and iso-THCs[6] (0.006 g of *p*-TSA/100 mL of solution, expt 1, Table II), solutions of $\Delta^6$-*cis*-CBD in benzene at reflux for 30 min produced a mixture containing mainly $\Delta^6$-*cis*-THC (**5a**, 50%) and $\Delta^8$-*cis*-iso-THC (**14**, 24%), with lesser amounts of $\Delta^1$-*cis*-CBD (**5b**), $\Delta^1$-*cis*-THC (**12b**), cannabicitran (**13**),[6] and unchanged $\Delta^6$-*cis*-CBD (Table II). These products were separated by HPLC and identified by NMR and GLC analyses (Table III), as well as by comparison with authentic samples from other sources.

When the reaction at low acid concentration (0.003 g/100

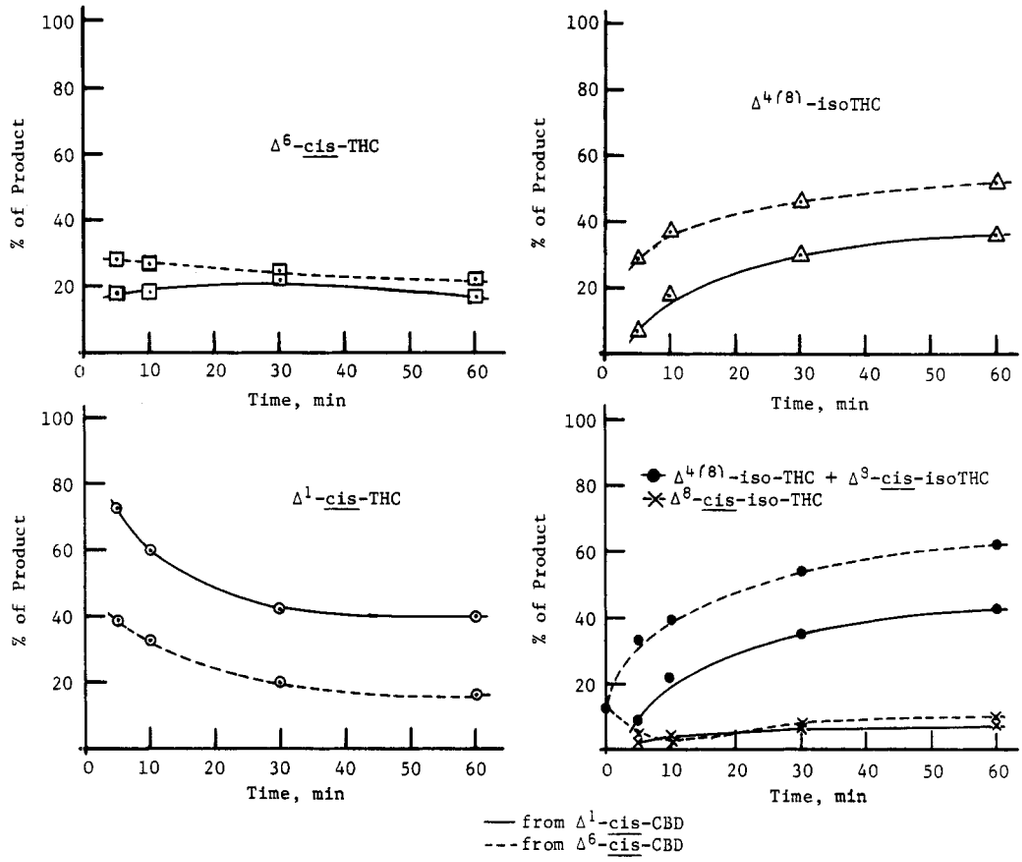



**Figure 1.** Rate of product formation in strong acid catalyzed ring closure of *cis*-cannabidiols.

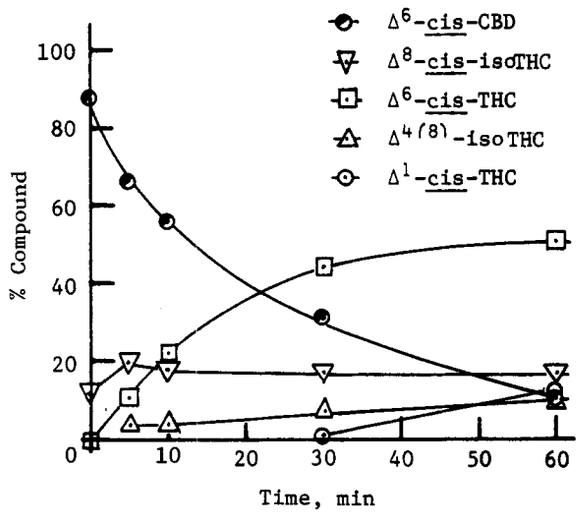



**Figure 2.** Reaction products from Δ6-*cis*-CBD with low acid concentration.

mL; expt 6, Table II) was followed by sampling at regular intervals, a steady state appeared to be reached in about 60 min, with Δ6-*cis*-THC (**12a**) being the major component (Figure 1).

Similarly, at high acid concentration (0.15–0.19 g of *p*-TSA/100 mL of solution; expt 4 and 5, Table II) a steady state was approached after 60 min for both Δ1- and Δ6-*cis*-CBD (Figure 2). Interestingly, Δ6-*cis*-CBD (**5a**) gave more iso-THCs (**7** and **8**) than did Δ1-*cis*-CBD (**5b**). The THC/iso-THC ratio after 5 min was 2:1 from the Δ6 isomer and 10:1 from the Δ1 isomer, and 0.6:1 and 1.3:1, respectively, at the end of 1 h.

The ratio of the THCs to iso-THCs in the products from the *cis*-CBDs (**5a** and **5b**) depends on the relative rates of cyclization at the Δ8 and Δ6 (or Δ1) double bonds, respectively. Because Δ1-CBD gave less iso-THC than did Δ6-CBD (Figure 1), and because the rate of reaction at the Δ8 double bond should be similar for both CBDs, it is likely that steric hindrance by the proximal hydroxy group deactivates the Δ1 double bond of **5b** relative to the Δ6 double bond of **5a**.

The fact that acid concentration has a pronounced effect on the rate of reaction but not necessarily on the distribution of products is demonstrated by a comparison of two similar experiments. The total products formed after 17 h at low acid concentration (continuation of expt 6, Table II) were the same as after 15 min with high acid concentration (expt 4, Table II) (% from expt 6 vs. from expt 4: Δ6-*cis*-CBD, 3, 0; Δ6-*cis*-THC, 29, 26; Δ1-*cis*-THC, 26, 28; Δ8-*cis*-iso-THC, 3, 3; Δ4(8)-iso-THC, 39, 39).

These results prompted a reinvestigation of the reaction of Δ1- and Δ6-*cis*-THCs (**12a,b**) with higher concentrations of *p*-TSA (expt 2 and 3, Table II).[6] The composition of the resulting mixture as shown by GLC was confirmed by NMR. As with the *cis*-CBDs, the major products were *cis*-THCs[10,11] at low acid concentrations (expt 2) and iso-THCs at higher acid concentrations (expt 3).

The present results are in agreement with our previous studies on acid transformations of cis compounds.[6,11] Furthermore, a comparison of the acid-catalyzed reactions of *cis*- and *trans*-CBDs shows that Δ1-*cis*-CBD gives much more iso-THC than does Δ1-*trans*-CBD.[12]

## Experimental Section

All compounds are (±) racemic mixtures. Melting points were determined in a Thomas-Hoover melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer Model 700 instrument and the NMR spectra were measured on a Varian T-60

spectrometer. The high-pressure liquid chromatographic separations were made with a Waters Associates ALC-202 chromatograph equipped with a Model 6000 solvent delivery system. Preparative separations were made on a 7 ft × 0.375 in. i.d. column packed with Porasil C. Analytical separations were made on a 1 ft × 0.25 in. o.d. column packed with μ Porasil. The analyses by gas chromatography were made on a Varian Aerograph Model 1440, equipped with a 6 ft × 0.125 in. i.d. stainless steel column packed with 2% OV-17 on 100/200 mesh Supelcoport, and a flame ionization detector.

***cis*-6a,10a-1-Hydroxy-9-methyl-3-pentyl-6a,7,10,10a-tetrahydro-6*H*-dibenzo[*b,d*]pyrone (1a).**[8a] 2,6-Dimethoxy-4-pentylbenzaldehyde[13a,b] was demethylated with $AlBr_3$ in $CS_2$, according to a procedure[13c] used for 2-resorcylaldehyde. 2,6-Dihydroxy-4-pentylbenzaldehyde was obtained in 38% yield as a solid melting at 69–71 °C: NMR ($CDCl_3$) δ 10.35 (1, s, CHO), 9.25 (2, br, OH), 6.18 (2, s, aromatics), 2.52 (2, t, $J$ = 8 Hz, benzylic), 0.88 (3, t, ω-$CH_3$). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: C, 69.18; H, 7.82. Further evidence for the structure of this aldehyde was provided by the subsequent reactions that led to a cannabidiol (**5a**) identical with that prepared by another route (see below) and whose structure was unequivocal.[14] The aldehyde was allowed to react with malonic acid in the presence of aniline and pyridine by a literature procedure[13c] to give an 81% yield of the known 3-carboxy-5-hydroxy-7-pentylcoumarin as a solid melting at 192–193 °C (lit.[8a] 198–199 °C). A Diels–Alder reaction of this coumarin with isoprene gave pyrone **1a**. The reaction was carried out in an autoclave at 180 °C for 18 h, according to the literature procedure.[8a,13c] The product was a solid melting at 115–117 °C (lit.[8a] 123–125 °C): NMR ($CDCl_3$) δ 6.48 (2, s, aromatics), 5.83 (1, s, OH), exchangeable), 5.47 (1, br, C8 H, vinylic), 3.50 (1, dt, $J$ = 11, 6, 6 Hz, C10a H), 1.63 (3, s, C9 $CH_3$), 0.88 (3, t, ω-$CH_3$).

**2-[3,4-*cis*-1-Methyl-3-(5-pentyl-2-resorcinyl)cyclohex-6-en-4-yl]-2-propanol (2a).** A solution of 0.30 g (0.001 mol) of **1a** in 10 mL of dry benzene was added to the Grignard reagent prepared from 0.24 g (0.010 mol) of Mg turnings and 0.65 mL of $CH_3I$ in 6 mL of anhydrous ether. The reaction mixture was then heated at reflux for 1.5 h under $N_2$. It was decomposed by the addition of saturated $NH_4Cl$ solution. The organic layer was separated, washed once with saturated $NH_4Cl$ solution followed by brine, and dried. Solvent was removed in vacuo to give 0.32 g (98%) of **2a** as a sticky semisolid. It showed a single spot on TLC (1:4 ethyl acetate/hexane).

On treatment with 0.5 mL of $Ac_2O$ in 5 mL of pyridine (3.5 h at ambient temperature) it formed the diacetate **3a** in 89% yield: IR (neat) 3550 (OH), 1765 $cm^{-1}$ (ester C=O). It was used in the subsequent step without further purification.

**$\Delta^6$-*cis*-Cannabidiol Diacetate (4a).** A solution of 45 mg (0.11 mmol) of **3a** in 1 mL of dry pyridine was cooled in ice and 2 drops of $SOCl_2$ was added. After 30 min at 24 °C the dark yellow solution was diluted with brine and extracted with ether. The ether extract was washed several times with water and once with very dilute HCl followed by water until neutral, dried, and concentrated in a rotary evaporator. The residue was 28 mg (65%) of **4a** as a colorless gum: NMR (see Table I); IR ($CCl_4$) 1770 (ester C=O), 900 $cm^{-1}$ (=$CH_2$); mass spectrum $m/e$ 398.2454 ($M^{+\cdot}$) (calcd for $C_{25}H_{34}O_4$, 398.2457). Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 74.98; H, 9.0.

**(±)-$\Delta^6$-3,4-*cis*-Cannabidiol (5a).** A solution of 144 mg (0.36 mmol) of **4a** in 3 mL of MeOH and 1.0 mL of 5% KOH in MeOH was allowed to stand in ice for 20 min under $N_2$. An additional 2.0 mL of 5% KOH in MeOH was added and the reaction mixture was allowed to stand at 22 °C for 1.5 h. The resultant dark solution was poured into a water/ether mixture and made acidic with 1:1 dilute HCl and the organic layer was separated. It was washed with saturated brine until neutral, dried, and evaporated to leave 105 mg (93%) of crude **5a**. It was easily purified by chromatography on 5 g of Florisil and eluted with 40:60 benzene/petroleum ether mixture to give 54 mg of **5a** as a colorless gum: NMR (see Table I); IR ($CCl_4$) 3450 (OH), 1615, 1570, 1450, 1220, 1165, 1010, 905 $cm^{-1}$ (=$CH_2$); mass spectrum $m/e$ 314 ($M^{+\cdot}$), 231 (base).

**$\Delta^1$-*cis*-Cannabidiol Diacetate (4b).** A solution of 0.709 g (2.36 mmol) of **1a** and 0.133 g (0.7 mmol) of $p$-TSA·$H_2O$ in 50 mL of dry $C_6H_6$ was heated at reflux for 1.5 h under $N_2$. The cooled solution was stirred well with 3 g of $Na_2CO_3·H_2O$ and filtered. The filtrate was concentrated in vacuo to give a 1:1 mixture of **1a** and **1b** (based on NMR integration of vinylic proton) as a glassy gum.

This mixture of lactones **1a** and **1b** was converted to a mixture of the diacetates **4a** and **4b** following the same sequence of reactions as in the preparation of **4a**. The two *cis*-CBD diacetates **4a** and **4b** were readily distinguished by GLC; the retention times (column 260 °C) were 3.30 min for **4a** and 3.56 min for **4b**.

The two diacetates were separated by high-pressure liquid chromatography with 5:95 ether/isooctane as solvent. The capacity factor ($k'$) was 0.68 for **4a** and 1.32 for **4b**, giving a separation factor (α) of 1.94. In a typical run a 100-mg charge was separated in a single pass. Thus 0.24 g of **4a** and 0.15 g of **4b** were collected in an overall yield of 26 and 16%, respectively, from the starting lactones **1**.

The $\Delta^1$-diacetate **4b** was obtained as a colorless gum: NMR (see Table I); IR ($CCl_4$) 1770 (ester C=O), 900 $cm^{-1}$ (=$CH_2$), indistinguishable from that of **4a**; mass spectrum $m/e$ 398.2465 ($M^{+\cdot}$) (calcd for $C_{25}H_{34}O_4$, 398.2457). Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.08; H, 9.03.

**(±)-$\Delta^1$-3,4-*cis*-Cannabidiol (5b).** Compound **4b** was hydrolyzed as with **4a** to give **5b** as a colorless gum: NMR (see Table I); IR ($CCl_4$) was the same as for **5a** except for a weak absorption peak at 1070 $cm^{-1}$; mass spectrum $m/e$ 314 ($M^{+\cdot}$), 231 (base). Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.20; H, 9.62. Found: C, 80.44; H, 9.65.

When the hydrolysis of **4b** was stopped after 20 min, the product obtained was mostly the monoacetate, which showed hydroxyl and acetyl groups by IR ($CCl_4$) 3330 (OH), 1760 $cm^{-1}$ (ester C=O), and by NMR ($CCl_4$) δ 6.35, 6.47 (2, aromatic), 6.47 (1, s, OH, exchangeable), 5.75 (m, olefinic, C2 H), 4.60 (br, C8 $CH_2$), 2.15 (3, s, $OCOCH_3$), 1.38 (s, C1 $CH_3$), 0.92 (t, ω-$CH_3$).

**6aβ,7,8,9,10,10aβ-Hexahydro-1-hydroxy-3-pentylspiro[6*H*-dibenzo[*b,d*]pyran-9,2′-[1′,3′]dioxolan]-6-one (7).** By a published procedure,[9] 5.00 g (0.0145 mol) of 1-hydroxy-3-pentyl-7,8,9,10-tetrahydrospiro[6*H*-dibenzo[*b,d*]pyran-9,2′-[1′,3′]dioxolan]-6-one (**6**)[9] was hydrogenated with W-2 Raney nickel as a catalyst to give 4 g of **7** as a colorless solid: mp 142–144 °C (81%) (lit. 142.5–143.5 °C);[9] NMR ($CDCl_3$) δ 6.50 (2, s, aromatic), 4.02 (4, s, methylene of ketal), 3.61 (1, dt, C10a H), 0.88 (3, t, ω-$CH_3$), 6.27 (OH, exchangeable); IR ($CDCl_3$) ν 3350 (OH), 1750 $cm^{-1}$ (C=O); TLC, $R_f$ (silica, 80:20 $Et_2O$/petroleum ether) 0.61.

**6aβ,7,8,9,10,10aβ-Hexahydro-1-hydroxy-3-pentyl-6*H*-dibenzo[*b,d*]pyran-6,9-dione (8).** The ketal **7** (3.5 g, 0.01 mol) was hydrolyzed in dioxane (50 mL) by the slow addition of 40 mL of 3 N HCl. After being stirred at room temperature for nearly 4 h, the yellowing solution was drowned in water and stirred until crystallization was complete. The colorless solid, collected by filtration, washing, and drying, amounted to 2.25 g (75%) of the dione **8**, mp 194–198 °C. The analytical sample, mp 197–198 °C, was obtained by recrystallization from diethyl ether/petroleum ether. Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.48; H, 7.35. NMR ($CDCl_3$) δ 6.52 (2, s, aromatic), 3.75 (1, dt, C10a H), 0.88 (ω-$CH_3$), 7.25 (OH, exchangeable); IR ($CDCl_3$) ν 3280 (OH), 1750 (C=O, ester), 1700 $cm^{-1}$ (C=O, keto); TLC, $R_f$ (silica, 80:20 $Et_2O$/petroleum ether) 0.68.

Another product of the hydrolysis, extracted from mother liquors by benzene as a yellow solid of broad melting point, soluble in $NaHCO_3$ (purple solution), was the acid **11** ($R_f$, silica, 80:20 $Et_2O$/petroleum ether, 0.14): NMR ($CDCl_3$) δ 6.28 (2, aromatic), 6.93 (3, exchangeable OH); IR ($CDCl_3$) ν 3350 (OH), 1700 (C=O, keto), 1690 $cm^{-1}$ (C=O, acid). It was converted to the lactone **8** by heating in benzene at reflux for 2 h with $p$-TSA as catalyst, and a Dean-Stark trap to remove water. The product isolated was identical (melting point, TLC) with authentic dione **8**. The overall yield of **8** was thus raised to 91% of theory.

Heating at reflux or a longer reaction time at room temperature increased the proportion of acid during the hydrolysis.

**2-[3,4-*cis*-1-Hydroxy-1-methyl-3-(5-pentyl-2-resorcinyl)-4-cyclohexyl]-2-propanol (9).** A solution of 2.0 g (0.0066 mol) of **8** in 120 mL of anhydrous diethyl ether (a saturated solution) was added rapidly to a refluxing solution of the Grignard reagent made from 2.57 g (0.105 mol) of magnesium turnings and 7.0 mL (16.0 g, 0.112 mol) of methyl iodide in 40 mL of anhydrous ether. The dione was rinsed in with 50 mL of anhydrous tetrahydrofuran. After 1 h of refluxing the excess Grignard reagent was destroyed by addition of ethyl acetate, followed by saturated aqueous $NH_4Cl$. The layers were separated, the aqueous layer was extracted with $Et_2O$, and the combined organic layers were washed with saturated $NH_4Cl$, dried, and concentrated. After all solvents had been removed, the crude tetrol **9** was obtained (2.47 g) as a light-colored foam. This product melted over a wide range (56–113 °C), was very soluble in $Et_2O$ and insoluble in $CCl_4$, and showed two spots on TLC in a variety of solvents ($R_f$, silica, 0.65 and 0.53 in 2:1 EtOAc/benzene; 0.57 and 0.41 in $Et_2O$). Elemental analysis and NMR indicated that it was a mixture of nonisomeric compounds. Without further purification it was used for the subsequent steps to cannabidiol diacetate.

In a small experiment the products from the Grignard reaction were separated by high-pressure liquid chromatography (μPorasil, 80:20 $Et_2O$/isooctane as eluent); the $k'$ for the compound moving faster on TLC was 1.6, and for the slower moving compound it was 5.1. The latter compound, a foamy solid, could not be made to crystallize from solution, but it gave an acceptable analysis for the tetrol **9**. Anal. Calcd

for $C_{21}H_{34}O_4$: C, 71.96; H, 9.77. Found: C, 71.68; H, 9.73.

**2-(4,5-*cis*-*p*-Mentha-1,8-dien-5-yl)-5-pentylresorcinol Acetate (4a).** A solution of 1.46 g (0.0041 mol) of the crude tetrol **9**, from the preceding experiment, 8 mL of dry pyridine, and 1.6 mL of $Ac_2O$ in 20 mL of anhydrous ether was allowed to stand at 20 °C for 4.75 h. Then, 3.3 mL of a solution made from 0.9 mL of $SOCl_2$ and 3.0 mL of anhydrous ether was added during 15 min to the ice-cooled acetate solution. The nearly colorless solution and white precipitate were stirred for 10 min longer. Saturated NaCl solution (8 mL) and 20 mL of petroleum ether were added, and the layers were separated. The aqueous layer was extracted with 1:1 $Et_2O$/petroleum ether, the pyridine was removed from the organic layer by washing with water and dilute HCl, and the acid was removed by washing with water and $NaHCO_3$. The organic solution was dried and concentrated, leaving 1.44 g of a pale amber resin. NMR indicated that this product was about 50% CBD diacetate (**4a**).

Column chromatography of the diacetate (Florisil, 2:1 benzene/hexane, then 100% benzene) separated impure (about 70% by NMR) *cis*-CBD diacetate (0.27 g).

The final purification was accomplished with HPLC (Porasil, 5% diethyl ether/isooctane). At this point, the *cis*-CBD diacetate (144 mg) showed a single spot on TLC in both 1:4 EtOAc/hexane ($R_f$ 0.58) and 2:1 benzene/hexane, and by GLC it had >90% purity.

**$\Delta^6$-*cis*-CBD (5a).** The $\Delta^6$-*cis*-CBD diacetate (**4a**) obtained above was hydrolyzed to **5a** with dilute alcoholic KOH as described above in the alternative synthesis, and finally purified by HPLC on μPorasil with eluent 3% $Et_2O$/isooctane ($k'$ = 3.1) or 2% $Et_2O$/isooctane ($k'$ = 5.6). The material (60 mg) was identical in all respects (NMR, GLC, TLC) with **5a** prepared earlier. There was no evidence by either GLC or NMR for the presence of $\Delta^1$-*cis*-CBD (**5b**).

**Reaction of *cis*-CBDs and *cis*-THCs with *p*-TSA (Table II). General Procedure.** The solution of the cannabinoid in dry benzene was mixed with a solution of *p*-toluenesulfonic acid in benzene, made anhydrous from the acid monohydrate by azeotropic distillation of the water, and heated at reflux (oil bath) under nitrogen, with gentle magnetic stirring. Samples for GLC were taken at regular intervals in expt 4, 5, and 6, and added to a slurry of $Na_2CO_3 \cdot H_2O$ and $CH_2Cl_2$ in order to quench the reaction. At the end of the time period, the catalyst was neutralized by the addition of solid $Na_2CO_3 \cdot H_2O$ and the solution was filtered. Samples were taken from the filtrate for analysis by GLC, and for the NMR spectra. The cannabinoid products were identified by comparison with authentic specimens from other sources, both unsilylated and silylated analyses being required in the GLC because of overlapping retention times.

Products from expt 1 were separated by high-pressure liquid chromatography and their identities were confirmed by NMR spectra (Table III). The first fraction from HPLC was cannabicitran (**13**) (also called citrylidene-cannabis),[6] identified by its retention time on GLC compared to an authentic sample, and by the fact that this retention time was unchanged by attempted silylation. $\Delta^8$-*cis*-Iso-THC constituted the next fraction eluted from the column; although the compound was identified earlier,[17] its NMR spectrum (Table III) has not been reported. (±)-$\Delta^6$-*cis*-THC was eluted last from the column, and had an NMR spectrum identical with that given by Uliss et al.[11]

$\Delta^6$-*cis*-THC, upon treatment with 0.04 g of *p*-TSA/100 mL (expt 2 of Table II), reached an equilibrium with $\Delta^1$-*cis*-THC (30:70, respectively, GLC) after 60 min. This ratio is similar to that observed by Uliss et al.[11] The NMR spectrum ($CCl_4$) supported the composition shown by GLC. Olefinic protons for both a $\Delta^6$-THC (**12a**) (δ 5.35, C6 H) and a $\Delta^1$-THC (**12b**) (δ 6.27, C2 H) were evident, and the *gem*-dimethyl protons (δ 1.37, 1.27) were typical for a cis configuration at the C3–C4 ring junction. The absorption at δ 3.17 (m) attributed to the 2α proton of $\Delta^6$-*cis*-THC was partially replaced by a multiplet at δ 3.50, corresponding to the C-3 proton of $\Delta^1$-*cis*-THC.[9]

At a still higher acid concentration (0.2 g/100 mL; expt 3, Table II) this mixture gave a product containing a large proportion (44% by GLC) of $\Delta^{4(8)}$-iso-THC [characteristic NMR absorption peaks ($CDCl_3$) at δ 4.18 and 1.93 corresponding to the protons at C-3 and C-9, respectively[18]]. The olefinic protons for $\Delta^1$- and $\Delta^6$-*cis*-THCs (31% by GLC) were still visible (δ 6.30 and 5.27, respectively). The composition was confirmed by GLC analysis (Table II).

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**Registry No.**—**1a,** 62461-63-6; **1b,** 62461-64-7; **2a,** 62461-65-8; **3a,** 62461-66-9; **4a,** 62461-67-0; **4b,** 62504-25-0; **4b** monoacetate, 62461-68-1; **5a,** 62461-69-2; **5b,** 7663-52-7; **6,** 6469-57-4; **7,** 27279-31-8; **8,** 62461-70-5; **9,** 62461-71-6; **11,** 62461-72-7; **12a,** 6216-87-1; **12b,** 6087-73-6; **13,** 62504-22-7; **14,** 62504-23-8; **15,** 62504-24-9; 2,6-dimethoxy-4-pentylbenzaldehyde, 3410-84-2; 2,6-dihydroxy-4-pentylbenzaldehyde, 24237-04-5.

## References and Notes

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(3) Petrzilka has noted[4] that the compound he called "*cis*-cannabidiol" in a preliminary communication[5] was in fact the trans position isomer 4-(*p*-mentha-1,8-dien-3-yl)olivetol. For this reason, a reaction ascribed to *cis*-CBD[6] has been amended (ref 2a, footnote, p 93).
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(10) In our earlier equilibrium studies of $\Delta^1$-*cis*-THC with *p*-TSA,[6] the presence of $\Delta^6$-*cis*-THC was not noted, probably because its GLC retention time and those of $\Delta^1$-*cis*- and $\Delta^6$-*trans*-THCs are the same. Silylated samples of the same materials, however, have appreciably different retention times relative to 1.00 for $\Delta^6$-*trans*-THC (0.98 for $\Delta^6$-*cis*-THC and 1.08 for $\Delta^1$-*cis*-THC).
(11) D. B. Uliss, R. K. Razdan, H. C. Dalzell, and G. R. Handrick, *Tetrahedron Lett.*, 4369 (1975).
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(14) Hively[8a] reported the use of 2,6-dihydroxy-4-pentylbenzaldehyde as his starting material for synthesizing lactone **1a**, but he did not describe its synthesis, source, or physical properties. Jen et al.[15] claimed the preparation of 2,6-dihydroxy-4-pentylbenzaldehyde, mp 53–56 °C from olivetol, $Zn(CN)_2$, and HCl. Upon repeating Jen's synthesis, we obtained an aldehyde [mp 58–60 °C; NMR ($CDCl_3$) δ 10.83 (1, s, –OH, exchangeable), 10.07 (1, s, –CHO), 7.40 (1, br, –OH, exchangeable), 6.30 (2, s, aromatics), 2.82 (2, t, $J$ = 8 Hz, benzylic), 0.88 (3, t, ω-$CH_3$)], which we believe to be the 2,4-dihydroxy-6-pentyl isomer.[16]
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