Hashish.[1] A Simple One-Step Synthesis of (−)-Δ^1-Tetrahydrocannabinol (THC) from *p*-Mentha-2,8-dien-1-ol and Olivetol

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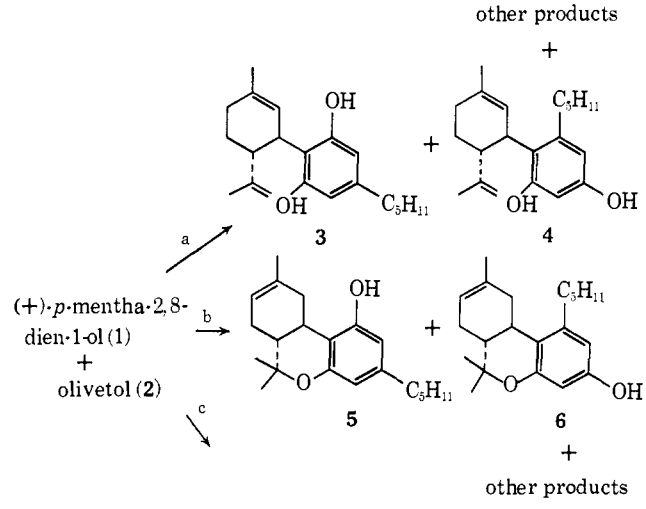
Abstract: Optically pure (−)-Δ^1-THC (**7**) was produced in 50% yield (glc; isolated yield 31%) in a single-step synthesis from *cis/trans*-(+)-*p*-mentha-2,8-dien-1-ol (**1**) and olivetol (**2**) in the presence of 1% boron trifluoride etherate and anhydrous magnesium sulfate in methylene chloride at 0°. The product was readily separated by column chromatography. The other major product formed was *trans*-Δ^8-iso-THC (**8**). By the same procedure (−)-cannabidiol (**3**) was obtained on a preparative scale when <0.5% boron trifluoride etherate or wet *p*-toluenesulfonic acid was used. A mechanistic scheme is presented for this reaction. It is shown that cannabidiols (**3** and **4**) are the key intermediates in this reaction and abnormal cannabidiol (**4**) undergoes a retro-Friedel–Crafts reaction followed by recombination to normal cannabidiol (**3**). This retroreaction of **4** is rationalized on steric arguments. The isolation and study of products from this reaction give a much clearer understanding of the factors which control the outcome of acid-catalyzed reactions of *p*-mentha-2,8-dien-1-ol and olivetol and have provided three new cannabinoids, **9**, **10**, and **12**.

In this paper we report a convenient single-step synthesis of (−)-Δ^1-THC (**7**) in 50% yield (glc) from (+)-*p*-mentha-2,8-dien-1-ol (**1**) and olivetol (**2**) under controlled conditions. The reaction mixture was readily separated by column chromatography to give (−)-Δ^1-THC (**7**) of very high optical purity in 31% isolated yield[2] (purity by glc > 96%). The same procedure also provides experimental conditions for stopping the isomerization of the thermodynamically less stable Δ^1-double bond to the more stable $\Delta^{1(6)}$ unsaturation, a problem which has hindered the synthesis of *trans*-Δ^1-THC derivatives.[3,4]

Other syntheses from (−)-verbenol[5] and (+)-*p*-mentha-2,8-dien-1-ol[6] do not avoid this double bond isomerization but give the more thermodynamically stable (−)-$\Delta^{1(6)}$-THC (**5**) isomer, which must be transformed to (−)-Δ^1-THC (**7**) by addition and elimination of hydrogen chloride. These processes thus require three steps and involve at least two very tedious and careful chromatographic separations. The one-step synthesis of (−)-Δ^1-THC that we described earlier[7] was achieved from *trans*-(+)-2-carene oxide, but it suffered from the difficult separation of *trans*-Δ^1- and *cis*-Δ^1-THC's, which were the major products. Of the three syntheses described above, the *p*-menthadienol process is presently being used for large-scale production of **7** because of the commercial availability of **1**.[6b]

Although the condensation of olivetol (**2**) with (+)-*p*-mentha-2,8-dien-1-ol (**1**) in the presence of weak or strong acids, including BF_3–Et_2O, has been reported to give (−)-cannabidiol (**3**) or (−)-$\Delta^{1(6)}$-THC (**5**), respectively[6] (Scheme I), we have found that treatment of equimolar quantities of these materials in the presence of 1% $BF_3 \cdot Et_2O$ and anhydrous magnesium sulfate in methylene chloride at 0° for 1.5 hr yielded Δ^1-THC as the major product and practically no $\Delta^{1(6)}$ isomer was formed. When the reaction was carried out either in the absence of magnesium sulfate or at room temperature, considerable amounts of $\Delta^{1(6)}$-THC (**5**) were formed.

Scheme I[a]



diadducts + *trans*-Δ^1-THC (**7**) + **8** + **9** + **10**

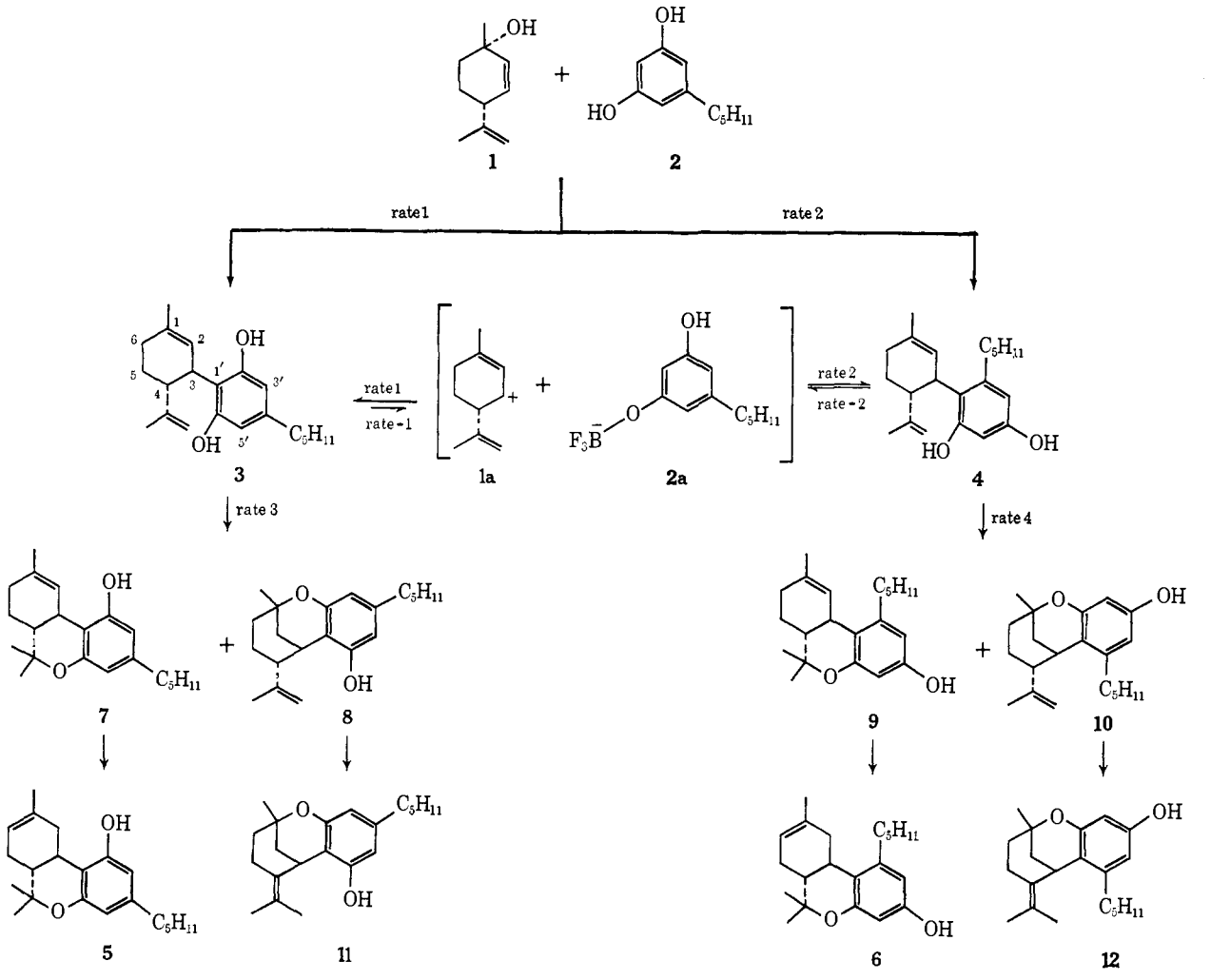
[a] Reagents: (a) weak acids,[6a] *e.g.*, $(CH_3)_2NCH(OCH_2C(CH_3)_3)_2$, $(COOH)_2 \cdot 2H_2O$; (b) strong acids,[6a] *e.g.*, *p*-TSA, CF_3COOH; (c) 1% $BF_3 \cdot Et_2O$ in CH_2Cl_2 + $MgSO_4$.

In order to study the nature of other materials formed in the reaction in the presence of $MgSO_4$, the crude mixture was carefully chromatographed on Florisil using ether–petroleum ether mixtures to give four fractions, each appearing to be homogeneous by tlc.

Fraction I (1:99 ether–petroleum ether) was shown

(1) Part X. For part IX, see R. K. Razdan, D. B. Uliss, and H. C. Dalzell, *J. Amer. Chem. Soc.*, **95**, 2361 (1973).
(2) The isolated yield has not been optimized.
(3) Review: R. K. Razdan in "Progress in Organic Chemistry," Vol. 8, W. Carruthers and J. K. Sutherland, Ed., Butterworths, London, 1973.
(4) (a) See, for example, ref 1; (b) it is interesting to note that in a study of the effect of various acids on cannabidiol (**3**) it was shown that $BF_3 \cdot Et_2O$ gave a mixture of Δ^1-THC (**7**) and **8**.[9]
(5) R. Mechoulam, P. Braun, and Y. Gaoni, *J. Amer. Chem. Soc.*, **94**, 6159 (1972).
(6) (a) T. Petrzilka, W. Haefliger, and C. Sikemeier, *Helv. Chim. Acta*, **52**, 1102 (1969); (+)-*p*-mentha-2,8-dien-1-ol refers to both cis and trans isomers; (b) the isolated overall yield in this process is 17–22% based on our experience on numerous large scale syntheses of **7** of purity >96%; see R. K. Razdan, A. J. Puttick, B. A. Zitko, and G. R. Handrick, *Experientia*, **28**, 121 (1972), and ref 16.
(7) R. K. Razdan and G. R. Handrick, *J. Amer. Chem. Soc.*, **92**, 6061 (1970).

Scheme II



by glc to be a mixture of diadducts[8] with one component comprising 50% of the mixture. Nmr showed no exchangeable protons; similarly hydroxyl bands were absent in the ir; mass spectrum *m/e* 448 ($M\cdot^+$), 433, 377, 365, 297 corresponded to a 2:1 adduct of **1** and **2**. No attempt was made to separate the mixture further.

Fraction II (1:99 and 2:98) was a single component by glc; nmr, ir, and mass spectra were in agreement with the compound being *trans*-Δ^8-iso-THC (**8**),[9] also obtained from cannabidiol (**3**) by treatment with $BF_3\cdot Et_2O$. This compound, heated with *p*-toluenesulfonic acid (*p*-TSA) in refluxing benzene, was converted to $\Delta^{4(8)}$-iso-THC, identical with an authentic sample, thus confirming structure **8**.

Fraction III (2:98) was identified as **7**. Fraction IV (10:90) gave an oil, which analysis by nmr and glc showed was a mixture of **9** and **10** (ratio of 30:70). It was rechromatographed twice on thick silica gel plates to give 87% pure **10** (glc). The nmr spectrum of **10** showed the presence of a methyl α to OR (at δ 1.28), one olefinic methyl group (at δ 1.88), and two olefinic protons as a broad singlet (at δ 4.92). The presence of a free hydroxyl group was confirmed by infrared spectrum, ν neat 3410 cm^{-1}. The mass spectrum[10] showed principal ions at *m/e* 314 ($M\cdot^+$), 299, 271, 258, 243, 231, which are consistent with structure **10**.

In our experience the isolation and purification of Δ^1-THC by the process reported here are so easy that it is recommended as the method of choice for the preparation of very pure $\Delta^{1(6)}$-THC, *i.e.*, by isomerization of Δ^1-THC with *p*-TSA in refluxing benzene. It is preferred to the direct preparation[6] of $\Delta^{1(6)}$-THC from **1** and **2** with *p*-TSA, inasmuch as the latter requires multiple chromatographies for purification.

Mechanism and Discussion

To get a clearer picture of the mode of formation of Δ^1-THC (**7**) and other products from **1** and **2**, we studied this reaction in greater detail.

We have found, by glc analysis during the course of the reaction, that normal cannabidiol (*n*-CBD, **3**) and abnormal cannabidiol (*abn*-CBD, **4**)[11] were formed first and in the ratio of 1:2. (The reaction stopped at this stage if <0.5% $BF_3\cdot Et_2O$ or wet *p*-TSA was used. See Experimental Section.) This was followed by con-

(8) (a) The formation of diadducts is not without precedent since similar products were formed from **1** and **2** with weak or strong acids;[6a] (b) B. Cardillo, L. Merlini and S. Servi, *Gazz. Chim. Ital.*, **103**, 127 (1973).

(9) Y. Gaoni and R. Mechoulam, *Tetrahedron*, **22**, 1481 (1966); *J. Amer. Chem. Soc.*, **93**, 217 (1971); see also *Isr. J. Chem.*, **6**, 679 (1968).

(10) The mass spectrum showed the presence of a minor impurity, *m/e* 466, 383, 365, which corresponds to an adduct of 2 mol of **1** to 1 mol of **2** with loss of only 1 mol of water. This impurity did not appear in the glc analysis.

(11) The terms "normal" and "abnormal" refer to the products in which the *n*-C_5H_{11} group occurs in the 4′ or 2′ positions, respectively. All the natural materials have the *n*-C_5H_{11} group in the 4′ position and for the purposes of this paper are considered "normal."

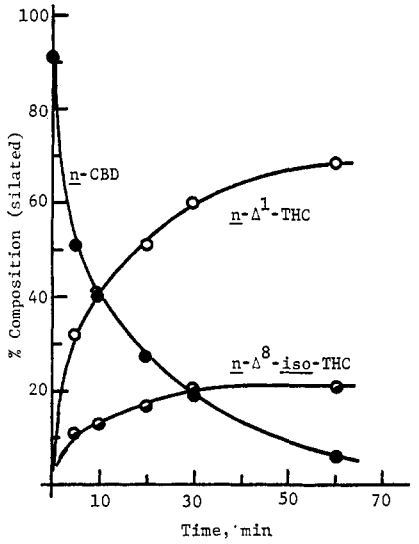


Figure 1. Composition changes in the reaction of *n*-cannabidiol catalyzed by boron trifluoride etherate. Dichloromethane solution at 0–5°. Experiment 2 of Tables I and II.

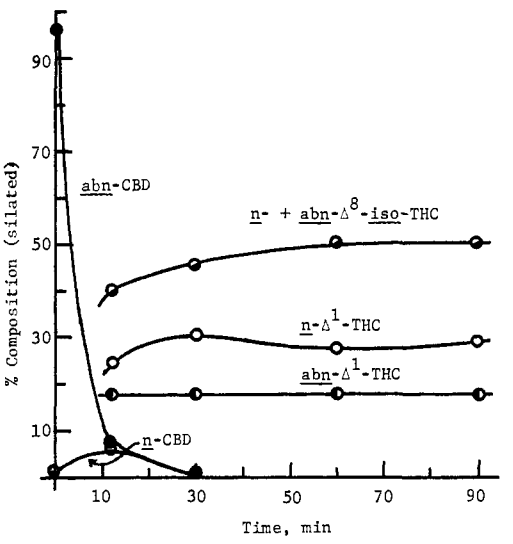


Figure 2. Composition changes in the reaction of *abn*-cannabidiol catalyzed by boron trifluoride etherate. Dichloromethane solution at 0–5°. Experiment 1 of Tables I and II.

version of cannabidiols **3** and **4** into normal and abnormal THC's (**7** and **9**) and iso-THC's (**8** and **10**). Significantly, the ratio of normal to abnormal products was now greater than 3:1. To elucidate the mechanism for the apparent transformation of *abn*-CBD (**4**) to normal products, a series of experiments was performed with both normal and abnormal compounds (see Scheme II).

n-CBD (**3**) treated under reaction conditions similar to those described above for the synthesis of Δ^1-THC (0.3% $BF_3 \cdot Et_2O$; experiment 2, Table I) yielded Δ^1-THC (**7**, 70%), iso-THC (**8**, 23%),[9] olivetol (**2**, 2%), and unreacted starting material (5%). Neither $\Delta^{1(6)}$-THC (**5**) nor abnormal products were observed (see Figure 1). *abn*-CBD (**4**), under similar conditions (experiment 1, Table I), formed **7** (34%), **8** (13%), **9** (15%), and **10** (30%). In addition, small quantities of **5**, **2**, and diadducts[8] were detected (see Figure 2). The ratio of normal to abnormal products formed was greater than 1 but varied somewhat with experimental conditions. Furthermore, normal compounds **7** and **8** were present in about the same ratio (70:30) as were formed from *n*-CBD (**3**), while the abnormal compounds **9** and **10** were formed in a ratio of 35:65. Thus the THC/iso-THC ratios were reversed in the abnormal series. After prolonged treatment (44 hr) of **3** the reaction mixture contained **5** and **11** in addition to **7** and **8**. Similarly **6** and **12** were formed from **4**.

Iso-THC's **8** and **10** did not revert to cannabidiols and were recovered unchanged after 1 hr under the experimental conditions (experiments 5 and 6, Table I). After prolonged treatment (20 hr) at 16° they were isomerized to **11** and **12**, respectively, as the major products. Considerable amounts of unidentified products were also formed.

The overall yield of products obtained from the *p*-menthadienol–olivetol reaction agreed with the results obtained from the individual cannabidiols.

Assuming that normal products can arise from abnormal ones by a retro-Friedel–Crafts reaction followed by recombination to *n*-CBD (**3**, Scheme II)[12] (similar retro-Friedel–Crafts reactions have been observed with other cannabinoids),[6a,8b,13] we interpret these results as follows: (a) reaction rate 2 = twice rate 1, since **3** and **4** are formed in a ratio of 1:2, with *p*-menthadienol (**1**) appearing to react statistically with the three available positions in olivetol (**2**); (b) rate $-2 \geq$ rate 4, because *abn*-CBD (**4**) is converted into more normal than abnormal products; (c) rate $-1 \ll$ rate -2, because **4** gives 50% normal products, whereas **3** gives no abnormal products and only a small amount of olivetol; and (d) rate 1 > rate 3 and rate 2 > rate 4, since the reaction can give cannabidiols **3** and **4** exclusively.

The different behavior of cannabidiols **3** and **4** can be explained on steric grounds. An examination of Dreiding models shows that in **4**, unlike **3**, ring closure to abnormal THC **9** results in a large steric interaction between the benzylic methylene of the C_5H_{11} group and the C-2 vinylic proton. This interaction retards the formation of compound **9** and also increases the propensity of **4** to undergo cleavage, probably by forcing a larger contribution of trans-diaxial conformation of the cyclohexene ring substituents. This conformation favors ring closure to compound **10** or cleavage to **1a** and **2a**.

The importance of the steric effect of the 5-alkylresorcinol side chain has been further illustrated by the observation that when the *n*-C_5H_{11} chain in **2** was substituted by a more sterically hindered $CH(CH_3)$-$CH(CH_3)C_5H_{11}$ group,[14] the reaction gave a 3:1 normal to abnormal cannabidiol ratio and subsequent ring closure gave only traces of abnormal products.

The above discussion provides an understanding of the formation of Δ^1-THC (**7**) as the main product from **1** and **2**. It is interesting to note that qualitatively similar results were obtained from a study in which *p*-toluenesulfonic acid was substituted for $BF_3 \cdot Et_2O$. Some rates were different, however, and in particular the conversion of Δ^1- to $\Delta^{1(6)}$-THC (**7** → **5**) was more

(12) The *p*-menthadienyl cation **1a** and olivetol–BF_3 complex **2a**, or similar species, are envisaged in the retroreaction.

(13) R. Adams, C. K. Cain, W. D. McPhee, and R. B. Wearn, *J. Amer. Chem. Soc.*, **63**, 2209 (1941).

(14) H. S. Aaron and C. P. Ferguson, *J. Org. Chem.*, **33**, 684 (1968).

difficult to avoid. The results are compared in Figures 1 and 3. Another point of difference appears to be that much less *n*-Δ^8-iso-THC (**8**) is formed with *p*-TSA than with $BF_3 \cdot Et_2O$.

As a result of this study three new THC's, **9**,[14a] **10** and **12**, all in the abnormal series, have been isolated and characterized. The nmr of *abn*-Δ^1-THC **9** shows the vinylic proton at a higher field compared to Δ^1-THC **7** (δ 5.69 instead of 6.3) probably due to the proximity of an alkyl group instead of a hydroxyl in **9**. Similar upfield shifts are observed for the C-3 benzylic proton in *abn*-iso-THC's **10** (δ 3.24 compared to 3.35 in **8**)[9] and **12** (δ 3.96 compared to 4.19 in **11**).[15] This is in agreement with similar findings in other abnormal THC's.[8b]

Experimental Section

General. The ir spectra were recorded on a Perkin-Elmer Model 700 instrument and the nmr spectra were measured on a Varian T-60 spectrometer. A Varian Aerograph Model 1440 equipped with a 6 ft × 1/8 in. stainless steel column packed with 2% OV-17 on 100–200 mesh Gas Chrom Q and a flame ionization detector was used for glc analysis. Carrier gas was helium and the column temperature was 210–270° as needed to elute the charge within 3 to 8 min. Samples analyzed by glc were both silylated and unsilylated. The compounds were identified on the basis of relative retention times of authentic samples (silylated and unsilylated) and by addition of authentic samples to the reaction mixture with subsequent glc. (−)-$\Delta^{1(6)}$-THC **5** was used as a reference standard for relative retention time. Tlc used silica gel (Adsorbosil-2) on microscope slides developed in 1:4 ethyl acetate–hexane or 1:9 ether–petroleum ether (30–40°) and visualized in iodine. Boron trifluorate etherate was distilled from calcium hydride and stored over Linde molecular seives; *p*-toluenesulfonic acid was the monohydrate, unless otherwise stated. Bis(trimethylsilyl)trifluoroacetamide was used as the silylating agent.

(−)-*trans*-Δ^1-THC (7) from (+)-*p*-Mentha-2,8-dien-1-ol (1) and Olivetol (2). A mixture of 2.88 g (16.0 mmol) of olivetol (**2**), 2.45 g (16.1 mmol) of (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol (**1**), and 2 g of anhydrous magnesium sulfate was stirred with 100 ml of methylene chloride under N_2 atmosphere. After cooling in an ice bath, 1 ml of freshly distilled $BF_3 \cdot Et_2O$ was added. The mixture was stirred for 1.5 hr at 0° and 5 g of anhydrous sodium bicarbonate was added; stirring continued until color faded, and the reaction mixture was filtered and evaporated to give a colorless gum (5 g). On the basis of glc it contained 50% Δ^1-THC (**7**). One-half of this material was chromatographed on 150 g of Florisil (100–200 mesh) packed in a 1 in. × 3 ft column in petroleum ether (30–40°). It was eluted with petroleum ether followed by graded mixtures up to 2:98 of ether–petroleum ether. Fractions containing pure **7** (tlc) were combined and evaporated to give 0.77 g (31%) of (−)-Δ^1-THC identical in all respects with the authentic material: $[\alpha]_D$ −176° ($CHCl_3$), glc purity >96%. An authentic sample of (−)-**7** has $[\alpha]_D$ −174° ($CHCl_3$).[16]

When the above reaction was carried out with magnesium sulfate omitted, the mixture showed Δ^1-THC (**7**, 27%) and $\Delta^{1(6)}$-THC (**5**, 25%) by glc. Similarly when the reaction was carried out at room temperature with magnesium sulfate the mixture contained only **5** (51% glc).

Chromatography of the Crude Mixture and Isolation of the Side Products. The glc of the crude mixture showed the presence of *abn*-Δ^8-iso-THC (**10**) 5%, Δ^8-iso-THC (**8**) 20%, *abn*-Δ^1-THC (**9**) 6%, $\Delta^{1(6)}$-THC (**5**) <6%, Δ^1-THC (**7**) 50%, and diadducts 13%.

The separation of the crude mixture (1.5 g of gum) was effected by chromatography on Florisil (90 g) and elution was carried out with petroleum ether and with increasing portions of ether in petroleum ether, a total of 3.15 l. of solvent being used. The eluent was collected in fractions which were monitored by tlc. Following this procedure four fractions were obtained which were homogeneous by tlc.

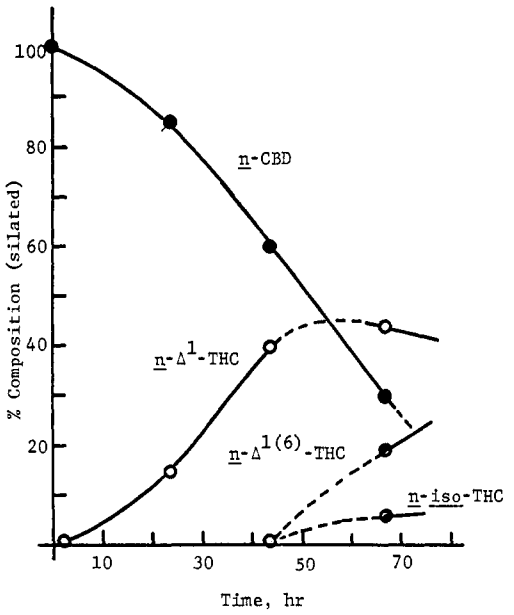


Figure 3. Composition changes in the reaction of *n*-cannabidiol catalyzed by *p*-toluenesulfonic acid. Benzene solution at 40–45°. Experiment 4 of Tables I and II.

Fraction I (1:99 ether–petroleum ether) was shown by glc to be a mixture of isomers with one component comprising 50% of the mixture. Spectral evidence indicates this to be a mixture of 2:1 adducts of **1** and **2**: mass spectrum *m/e* 448 (calcd for $C_{31}H_{44}O_2$, 448), 433, 377, 365, 297.

Fraction II (1:99 and 2:98) was a single component by glc and was identified as *trans*-Δ^8-iso-THC (**8**): nmr (CCl_4) δ 0.87 (3 H, t, ω-CH_3), 1.28 (3 H, s, α to OCH_3), 1.68 (6 H, broad, alicyclic), 1.86, (3 H, s, olefinic CH_3), 3.45 (1 H, broad, C_3–H), 4.90 (2 H, broad, olefinic), 5.95, 6.17 (2 H, 2d, J = 2 Hz, aromatic H), 5.4 (1 H, s, D_2O exchangeable); ν neat 3400 cm^{-1} (OH). The mass spectrum showed principal ions at *m/e* 314 ($M \cdot^+$), 299, 271, 258, 243, 231 (base peak) which are consistent with structure **8**. This material was found to be identical (tlc, nmr, ir) with *trans*-Δ^8-iso-THC prepared from cannabidiol (**3**) with $BF_3 \cdot Et_2O$.[9] As a further structural proof compound **8** (30 mg) was refluxed for 1 hr in 20 ml of benzene containing a crystal of *p*-TSA. After cooling, the benzene solution was washed with dilute sodium bicarbonate solution. It was dried and evaporated to leave a gum (~28 mg) which was identical in all respects with an authentic sample of $\Delta^{4(8)}$-iso-THC (**11**).[15]

Fraction III (2:98) was identified as **7** (see above for details).

Fraction IV (10:90) was obtained as an oil on evaporation of the solvent and was shown to be a mixture of **9** and **10**. An nmr examination of the mixture showed the ratio of vinylic to terminal methylene hydrogen was 3:14 and glc showed it to be a mixture of two components in the ratio of 3:7. Two preparative tlc separations on 2-mm thick silica gel (Merck, 50% ether–petroleum ether) gave 87% pure **10** (glc): nmr (CCl_4) δ 0.89 (3, H, t, ω-CH_3), 1.28 (3 H, s, α to OCH_3), 1.67 (6 H, broad, alicyclic), 1.88 (3 H, s, olefinic CH_3), 3.24 (1 H, broad, C_3–H), 4.92 (2 H, broad s, olefinic), 6.13 (2 H, m, aromatic); ir ν neat 3410 cm^{-1} (OH), mass spectrum[10] *m/e* 314 ($M \cdot^+$), 299, 271, 258, 243, 231.

The nmr (CCl_4) of the mixture of **9** and **10** (oil prior to preparative tlc) showed additional signals at δ 1.01, 1.33, and 5.69, which correspond to **9** (see below).

2- and 4-(*p*-Mentha-1,8-dien-3-yl)olivetol (*n*-CBD 3 and *abn*-CBD 4). (a) With Boron Trifluoride Etherate. Exactly the same experiment was carried out as in the preparation of Δ^1-THC (**7**) except that 0.1 ml of $BF_3 \cdot Et_2O$ was added. After work-up the reaction mixture showed mainly two compounds, (glc) **3** (28%) and **4** (47%).

(b) With *p*-TSA.[16] A solution of olivetol (**2**, 72 g, 0.4 mol) and (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol (**1**, 60.8 g, 0.4 mol) in 200 ml of benzene was added quickly to a stirred mixture of *p*-TSA (0.76 g) and 12 ml of water in 120 ml of benzene. The reactants were washed in with 123 ml of benzene. The solution was heated rapidly to reflux (5 min) and held there for 5 min longer. The reaction mixture was then cooled in ice and diluted with benzene. The benzene

(14a) NOTE ADDED IN PROOF. Compound **9** had $[\alpha]_D$ −160° ($CHCl_3$); >97% pure by glc. This compound (purity doubtful) was reported by K. Bailey and D. Verner, *Can. J. Pharm. Sci.*, 7, 51 (1972). We thank Professor R. Mechoulam for drawing our attention to this publication.

(15) E. C. Taylor, K. Lenard, and Y. Shvo, *J. Amer. Chem. Soc.*, **88**, 367 (1966); Y. Gaoni and R. Mechoulam, *ibid.*, **88**, 5673 (1966).

(16) Arthur D. Little, Inc., Technical Report 3, to National Institute of Mental Health, Contract PH-43-68-1339, January 1972. One of the present authors (G. R. H.) did the work originally.

Table I. Reaction Conditions

	Experiment no.					
	1	2	3	4	5	6
Charge	*abn*-CBD[a]	*n*-CBD[b]	*abn*-CBD[a]	*n*-CBD[b]	*abn*-Δ^8-iso-THC	*n*-Δ^8-iso-THC
mg	50	115	22	22	52	10
% concn, g/100 ml	5	1	1	2	5	1
Catalyst	BF_3	BF_3	*p*-TSA	*p*-TSA	BF_3	BF_3
μl[c]	10	30			9	9.5
% concn, ml/100 ml	1	0.3			0.9	0.95
mg[d]			2	2		
% concn, g/100 ml			0.1	0.2		
Solvent[e]	DCM	DCM	Bz[d]	Bz[d]	DCM	DCM
ml	1	10	2	1	1	1
$MgSO_4$, mg	22	0	20	24	21	
Time, hr						
At 0–5°	1.5	1			1.5	1
At 16–20°	18.5	0			20	44
At other temp, °C			93 35–40	138 40–45		

[a] 96% *abn*-CBD + 1% *n*-CBD. [b] 91% *n*-CBD + 9% unknown. [c] As the etherate. [d] Both catalyst and solvent anhydrous by azeotropic distillation. [e] DCM = dichloromethane; Bz = benzene.

Table II. Reaction Products

Relative retention time by glc				% composition[a]									
				Experiment no.									
				1		2	3		4	5		6	
Si-lylated	Not silylated	Tlc R_f	Products	1 hr	20 hr	1 hr	27 hr	92 hr	138 hr	0 hr	21 hr	0 hr	20 hr	45 hr
0.57	0.80	0.61	CBD, *n*-	0	0	5	4	0						
0.68	0.78	0.35	, *abn*-	0	0	0	7	0						
1.00	1.00	0.67	$\Delta^{1(6)}$-THC, *n*-	5	34	0	0	0	65			19	10	12
1.06	0.82	0.52	, *abn*-	0	0	0	0	64	0		22		0	0
1.09	1.09	0.65	Δ^1-THC, *n*-	34	2	70	4[b]	0	23					
1.20	0.93	0.51	, *abn*-	15	9	0	58	5	0	25	3			
0.95	0.82	0.66	Δ^8-iso-THC, *n*-	13	0	23	0	0				79	0	0
0.99	0.77	0.54	, *abn*-	30	0	0	22	0		75	0			
1.05	0.80	0.68	$\Delta^{4(8)}$-iso-THC, *n*-	0	18	0	0	0	12			0	67	48[c]
1.01	0.78	0.41	, *abn*-	0	28	0	0	30	0		60			
0.72	a 0.61		Unknown peaks								16			
0.80	b 0.66		a + b											
0.70	c 0.62													
0.74	d 0.65		c + d										15	18

[a] By glc analysis. [b] Or *abn*-$\Delta^{1(6)}$-THC. [c] Plus 19% of a compound appearing at *abn*-Δ^1-THC (silated) but absent for *abn*-Δ^1-THC not silated.

layer was separated, washed, dried, and evaporated to leave a gum of 101 g (80%) which showed the composition (glc): **2**, 17%, *n*-CBD 17%, *abn*-CBD 51%, diadducts[17] (late peaks) 11%. The material was separated by chromatography on Florisil (1200 g) in petroleum ether. The elution was carried out using graded mixtures of ether in petroleum ether, a total of 32 l. of solvent being used. The usual work-up yielded (−)-*n*-CBD (**3**, 20 g, isolated yield 16%), mp 66–67°, $[\alpha]D$ −126° (C_2H_5OH), identical in all respects with an authentic sample,[6a] and (−)-*abn*-CBD (**4**, 40 g, isolated yield 32%), $[\alpha]D$ −76° ($CHCl_3$), identical in all respects with an authentic sample.[6a]

Procedure for the Mechanistic Study. The quantities and conditions used for studies with the cannabidiols **3** and **4** and iso-THC's **8** and **10** are given in Table I. Dilute solutions of the compound to be studied were placed in a round-bottom flask with a magnetic stirrer, magnesium sulfate was added if employed, and the flask was either stoppered with a rubber septum or put under a reflux condenser with a drying tube. The appropriate amount of acid was added and the flask was maintained at the desired temperature. Aliquots were withdrawn at intervals and added to a mixture of a small amount of solid sodium carbonate, dichloromethane, and a drop of water to quench the reaction. The supernatant liquid was used directly for tlc and glc analyses. The products formed, with their tlc and glc characteristics, are given in Table II.

abn-trans-Δ^1-**THC (9).**[14a] A solution of 2.34 g of *abn*-CBD (**4**) and 0.10 ml of $BF_3 \cdot Et_2O$ in 100 ml of dry dichloromethane was stirred at 0° under nitrogen. After 18.5 hr the reaction was quenched with sodium carbonate as described above and worked up to yield 2.2 g of a resin. Further purification by column chromatography (Florisil, graded ether–petroleum ether mixture) afforded compound **9** as a resin: nmr (CCl_4) δ 0.89 (3 H, t, ω-CH_3), 1.01, 1.33 (6 H, 2s, geminal CH_3), 1.63 (3 H, broad s, olefinic CH_3), 3.03 (1 H, broad d, C_3–H), 5.69 (1 H, broad vinylic), 6.05, 6.22 (2 H, 2d, J = 2 Hz, aromatic); ν neat 3400 cm^{-1} (OH).

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.93; H, 10.09. On treatment with *p*-TSA in refluxing benzene, compound **9** was isomerized to the known compound **6**[6a] (see also experiment 3 in Tables I and II). A better procedure for the preparation of compound **9** is from **4** with *p*-TSA for 27 hr as described in experiment 3 (Tables I and II).

abn-$\Delta^{4(8)}$-*iso*-**THC (12).** A solution of 52 mg of *abn-trans*-Δ^8-iso-THC (**10**) and 9 μl of BF_3–Et_2O in 1 ml of dry dichloromethane was stirred at 20° for 21 hr. After quenching the reaction and usual work-up, compound **12** was obtained as a gum: nmr (CCl_4) δ 0.89 (3 H, t, ω-CH_3), 1.34 (3 H, s, α to OCH_3), 1.63, 1.87 (6 H, 2s, olefinic CH_3), 3.96 (1 H, broad m, C_3–H), 6.07 (2 H, s, aromatic), 4.40 (1 H, s, D_2O exchangeable).

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.89; H, 9.90.

3-(1,2-Dimethylheptyl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*c*,*d*]pyran-1-ol (Table III). A mixture of 74 mg of *threo*-5-(1,2-dimethylheptyl)resorcinol,[14] 54 mg of (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol (**1**), 1.8 μl of $BF_3 \cdot Et_2O$, and 100 mg of anhydrous magnesium sulfate in 2 ml of dichloromethane was stirred

(17) The main diadduct was isolated and identified as 2,4-bis(*p*-mentha-1,8-dien-3-yl)olivetol.[6a]

Table III. Products of Reaction between *p*-Menthadienol (1) and Dimethylheptylresorcinol at 0 and 40°

Reaction time, hr	% composition (glc), C_9-[c]					
	n-CBD	*abn*-CBD	*n*-Δ^8-iso-THC	*n*-Δ^1-THC	*n*-$\Delta^{1(6)}$-THC	*n*-$\Delta^{4(8)}$-iso-THC
3.5	69	31				
17.5[a]	71	22				
20.5	13	3	16	64		
41	3	0	22	72		
159[b]	0		22	61	17	
160					*ca.* 82	*ca.* 18

[a] Fresh $BF_3 \cdot Et_2O$ was added at this time. [b] Fresh $BF_3 \cdot Et_2O$ was added and the mixture was heated at reflux for 1 hr. [c] The *n*-C_5 side chain of the cannabinoids has been replaced by $CH(CH_3)CH(CH_3)C_5H_{11}$.

at 0°. After 20 min an aliquot showed (glc) the presence of only 2- and 4-*p*-mentha-2,8-dien-3-yl-5-(1,2-dimethylheptyl)resorcinols, in a ratio of 70:30, respectively. When no further change had occurred after 17.25 hr, 3 μl of $BF_3 \cdot Et_2O$ was added and the reaction mixture was allowed to stand for 118 hr more at 0°. Aliquots withdrawn during this time showed (glc) the formation of the dimethylheptyl homolog of Δ^1-THC. At this point 1 ml of dichloromethane and 30 μl of $BF_3 \cdot Et_2O$ were added and the reaction mixture was heated at reflux for 1 hr. After quenching and work-up, 51 mg of a cloudy amber resin was obtained which was shown to be 82% 3-(1,2-dimethylheptyl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*c*,*d*]pyran-1-ol (nmr, glc, tlc).[6a]

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Total Synthesis of 15-Methylprostaglandins

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Abstract: A total synthesis of 15-methyl-substituted prostaglandins starting from (−)-2β,4β-dihydroxy-3α-iodo-5α-(methoxymethyl)cyclopentane-1β-acetic acid γ-lactone (**1**) is described. A key synthetic intermediate, (−)-3α,5α-dihydroxy-2β-(3-oxo-*trans*-1-octenyl)cyclopentane-1α-acetic acid γ-lactone 3-benzoate, **6**, is also reported. The following 15-methylprostaglandin analogs as methyl esters are described: (15*S*)-15-methyl-$PGF_{2\alpha}$, -$PGF_{2\beta}$, -PGE_2, -PGA_2, -PGE_1, -$PGF_{1\alpha}$, -PGA_1; 13,14-dihydro-(15*S*)-15-methyl-$PGF_{1\alpha}$, -PGE_1; (15*R*)-15-methyl-$PGF_{2\alpha}$, -$PGF_{2\beta}$, -PGE_2, -PGE_1, -PGA_2. The PGE compounds were prepared from the PGF compounds by selective trimethylsilylation at C-11 followed by oxidation. Preparation of the 15-methylprostaglandins in the PG_1 series involved selective hydrogenation of the 5,6 bond without prior derivativization. The PGA compounds were prepared from the PGE structures by a novel procedure not involving acid treatment. Each 15 epimer of 15-methyl-$PGF_{2\alpha}$ methyl ester and 15-methyl-PGE_2 methyl ester was readily and cleanly epimerized to an equal mixture of both (15*R*) and (15*S*) epimers by treatment with acetic acid at 40°.

Prostaglandins are a family of 20-carbon fatty acids found in virtually all mammalian cells.[1] They are highly active biologically in many systems and have been implicated in mediation of many physiological responses.[2] Their general biology[2] and chemistry[3] have recently been reviewed.

The most rapid mode of metabolism (deactivation) of the natural prostaglandins in man has been shown to be oxidation of the allylic C-15 alcohol, followed by very rapid reduction of the 13,14 double bond.[4] The enzyme responsible for the oxidation, 15-hydroxyprostaglandin dehydrogenase, has been isolated from a variety of tissue preparations.[4,5] Syntheses reported in this and in a related manuscript[6] were initiated to determine whether compounds which were substituted at C-15 with methyl groups could still maintain biological activity. Several 15-methyl-substituted prostaglandins were first reported in 1970.[7] One of these reports included not only a synthetic outline for representative members of this family of prostaglandins but also some preliminary biological assay results.[7a] A communication[8a] outlining a synthetic method for preparation of the 15-methyl members of the PGE_2

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