mode. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6MG instrument.

For more spectroscopic data (IR, UV, and mass spectra) of the previously described compounds (**2–6**) see references[5-12,15] and notes.[18]

X-ray Structure Determination of Montanin C (5). $C_{24}H_{30}O_8$ crystallized in the space group $P2_1$ with $Z = 4$ and $a = 16.748$ (2) Å, $b = 11.777$ (1) Å, and $c = 12.634$ (1) Å and $\beta = 111.78$ (1)°. The molecular weight is 446.48, and the calculated density is 1.275 g cm^{-3}. The intensities of the 2929 independent Friedel pairs to $\Theta = 60°$ were alternately collected on an automated four-circle diffractometer. The single crystal used, of section ~0.2 mm, decomposed during the experiment, showing an intensity decay of 23% for graphite-monochromated Cu Kα radiation (1.5418 Å). Some experimental details are as follows: $\omega/2\Theta$ scan mode; 1.20° scan width; 0.040 s g^{-1} scan speed with the same measurement time for both backgrounds as for the peak. After the usual correction for Lorentz and polarization effects, 2368 Friedel pairs were considered as observed, when $I > 2\sigma(I)$, and were used for the structure determination and refinement. No absorption correction was applied ($\mu = 7.58$ cm^{-1}). The atomic scattering factors and the anomalous dispersion corrections were taken from the literature.[21] The structure was solved by MULTAN[22] and refined by full-matrix least-squares methods with anisotropic thermal parameters for the non-hydrogen atoms. The hydrogen atoms, except those of the three methyl groups, found in a Fourier difference map were included as fixed isotropic contributors in the refinement.

A weighting scheme was selected to prevent bias in $\langle\omega\Delta^2F\rangle$ vs. $\langle|F_o|\rangle$ and $\langle\sin\Theta/\lambda\rangle$. Several cycles of weighted anisotropic refinement, including both hkl and $\bar{h}\bar{k}\bar{l}$ reflections, gave the following unweighted and weighted discrepancy indices: $R = 0.066$ and $R_w = 0.069$.[23]

The absolute configuration of montanin C could not be determined, either, by comparing only the more relevant Bijvoet pairs. Figure 1 shows the X-ray molecular model of one (**5b**) of the two crystallographically independent molecules, assuming a neoclerodane[3a] absolute configuration, which, furthermore, is the one predicted when comparing the [α] values of compound **3** ([α]$_D$ +33.5, [α]$_{578}$ +35.3, [α]$_{546}$ +39.9, [α]$_{436}$ +66.2, [α]$_{365}$ +100.3 (*c* 0.97, $CHCl_3$)) with those of montanin C (**5**, [α]$_D$ +7.4, [α]$_{578}$ +8.1, [α]$_{546}$ +9.2, [α]$_{436}$ +13.1, [α]$_{365}$ +23.1 (*c* 0.89, $CHCl_3$)).

Isolation of 12-*epi*-Teucvin (7). Dried and finely powdered *Teucrium flavum* L. ssp. *glaucum* (Jordan and Fourr) Ronniger (aerial parts, 900 g), collected on the Gennargentu mountains, Sardinia (Italy), were extracted with acetone, as previously described.[14] The chromatographic fraction (450 mg) obtained before elution of teuflavin[14] was repeatedly chromatographed over silica gel columns eluted with petroleum ether–EtOAc (1:1), yielding pure 12-*epi*-teucvin (**7**): 290 mg; mp and [α]$^{17}_D$ see Table I; IR (KBr) 3160, 3140, 3120, 2980, 2940, 2920, 2880, 2870, 2860, 1760, 1740, 1690, 1610, 1508, 1470, 1440, 1385, 1360, 1350, 1330, 1315, 1280, 1220, 1200, 1175, 1155, 1050, 1030, 1025, 975, 945, 880, 805, 745 cm^{-1}; UV (EtOH) λ_{max} 224 nm (log ϵ 4.00); ^{1}H NMR see Table III; ^{13}C NMR see Table II; mass spectrum (75 eV, direct inlet), *m/z* (relative intensity) 328 (M^+, 20), 310 (45), 299 (25), 238 (15), 265 (5), 234 (15), 229 (20), 201 (10), 179 (25), 178 (22), 161 (17), 150 (32), 136 (30), 117 (15), 115 (15), 108 (16), 107 (20), 105 (35), 96 (48), 95 (100, base peak), 94 (50), 91 (47), 81 (50), 79 (58), 77 (55), 69 (25), 65 (27), 53 (30); CD nm ([Θ]) 281 (0), 231 (+65 000), 220 (0), 212 (−24 000), 210 (−20 000) (*c* 0.218, dioxane). [For the CD data of teucvin (**6**) see ref 15e.] Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.77; H, 6.25.

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Registry No. **4**, 72948-20-0; **5**, 67987-83-1; **7**, 89617-43-6.

Supplementary Material Available: A list of atomic parameters, bond distances, bond angles, torsion angles, and conformational analysis for the rings (17 pages). Ordering information is given on any current masthead page.

(21) "International Tables for X-Ray Crystallography"; Kynoch Press: Birmingham, 1974; Vol. IV.
(22) Main, P. "MULTAN-80"; Physics Department, University of York: York, England, 1980.
(23) Stewart, J. M.; Kundell, F. A.; Baldwin, J. C. "The X-Ray 76 System"; Computer Science Center, University of Maryland: College Park, MD, 1976.

Carbon-13 Nuclear Magnetic Resonance Spectra of Cannabichromene, Cannabicitran, and Cannabicyclol and Their Analogues

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Carbon-13 nuclear magnetic resonance spectra have been recorded for cannabichrome, cannabicitran, and cannabicyclol and their analogues. The absorptions have been assigned to specific carbons with the aid of off-resonance, selective proton decoupling, ^{13}C J_R vs. ^{1}H δ's, and chemical shift comparison with model compounds.

Despite the wide variety of ring systems isolated[1] from the plant *Canabis sativa* L, only three reports concerning ^{13}C NMR spectra of cannabinoids have been published.[2-4] These studies were largely limited to Δ^8-, Δ^9-tetrahydrocannabinols and related model compounds[2,3] and cannabidiol.[4] Apparently, ^{13}C NMR spectra of cannabichromene (**1**, R = H; $R_1 = C_5H_{11}$)[5-7] and other conforma-

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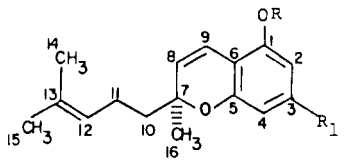
(1) For a recent review, see: Turner, C. E.; Elsohly, M. A.; Boeren, E. G. *J. Nat. Prod.* **1980**, *43*, 205.
(2) (a) Wenkert, E.; Cochran, D. W.; Schell, F. M.; Archer, R. A.; Matsumoto, K. *Experientia* **1972**, *28*, 250. (b) Archer, R. A.; Johnson, D. W.; Hagaman, E. W.; Moreno, L. N.; Wenkert, E. *J. Org. Chem.* **1977**, *42*, 490.

0022-3263/84/1949-1793$01.50/0

Chart I

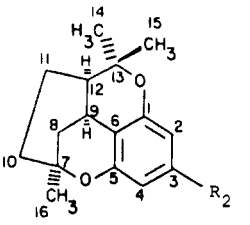


Chromenes

1 R=H,$COCH_3$ R_1=C_5H_{11}=

2 R=CH_3 R_1=OCH_3

3 R=H R_1=CH_3

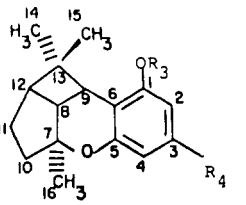


Tetracyclic Ethers

4 R_2=C_5H_{11}=

5 R_2=OH,-$OCOCH_3$

6 R_2=CH_3



Cyclols

7 R_3=H R_4=C_5H_{11}=

8 R_3=CH_3 R_4=OCH_3

9 R_3=H R_4=CH_3

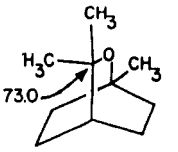


Table I. ^{13}C NMR Chemical Shifts of Compounds 1-9[a]

	chromenes			tetracyclic ethers			cyclols		
C no.	1	2	3	4	5	6	7	8	9
1	151.3[b]	156.2*	151.5	157.0*	157.5*	157.1*	154.3*	159.1*	154.1**
2	108.1[d]	91.3[d]	108.8[d]	108.9**	96.9**	109.7**	107.5	91.3[d]	108.0[d]
3	144.9	161.2	139.5	142.6	155.8[b]	137.2	142.6	159.5*	137.4
4	109.2[d]	94.0[d]	109.8[d]	109.7**	98.6**	110.5*	110.5	94.6	108.4[d]
5	154.0	155.1*	154.1	156.7*	157.1*	156.7**	154.1*	154.5*	154.2*
6	107.2	104.1	107.2	114.0	109.4	113.9	108.7	105.5	111.2
7	78.5	78.5	78.4	83.4	84.6	83.5	83.4	83.5	83.2
8	127.4	124.7[d]	127.1	35.4	35.3[c]	35.4	46.2	46.4[d]	46.3
9	117.2	117.4[d]	117.3	28.1	27.8[d]	28.1	36.2	36.1[d]	36.0
10	41.0	41.2[d]	41.2	37.3	37.3[c]	37.4	37.9	37.8[d]	37.8
11	22.8	22.8[d]	22.8	22.2	22.1[d]	22.2	25.7	25.7[d]	25.7
12	124.4	124.4[d]	124.4	46.8	46.7	46.8	37.9	37.8[d]	37.8
13	131.7	131.4	131.5	76.1	75.1	74.5	39.1	39.0	39.0
14	17.6	17.5[d]	17.6	29.7	29.6[d]	29.8	27.7	27.8[d]	27.6
15	25.7	25.7[d]	25.7	23.7	23.7	23.7	18.0	17.8[d]	17.9
16	26.2	26.3	26.2	29.1	29.0[d]	29.1	34.0	33.7[d]	33.9
1′	36.0			36.1			35.8		
2′	30.7			31.0			30.8		
3′	31.6			31.4			31.7		
4′	22.6			22.5			22.6		
5′	14.0			14.0			14.0		
17		55.3	21.5			21.5		55.1**	21.2
18		55.1						54.9**	

[a] *, ** = these signals in any vertical column may be reversed. [b] Confirmed by preparation of an acetate. [c] Confirmed by J_R analysis. [d] Confirmed by utilizing specific proton decoupling.

tionally rigid constituents of hashish, such as cannabicitran (4, R_2 = C_5H_{11}, citrylidenecannabis)[8,9] and cannabicyclol[10,11] (7, R_3 = H; R_4 = C_5H_{11}, previously known as cannabipinol), have not been studied. We have undertaken a ^{13}C NMR study of 1 (R = H; R_1 = C_5H_{11}), 4 (R_2 = C_5H_{11}), and 7 (R_3 = H; R_4 = C_5H_{11}) and report our findings at this time. Synthetic analogues 2 (R = CH_3; R_1 = OCH_3), 3 (R = H; R_1 = CH_3), 5 (R_2 = OH); 6 (R_2 = CH_3), 8 (R_3 = CH_3; R_4 = OCH_3), and 9 (R_3 = H; R_4 = CH_3) which lack the C_5H_{11} side chain were useful references because their ^{13}C NMR spectra were less complex. In addition to the normal ^{13}C NMR technique of single-frequency off-resonance decoupling (SFORD), extensive use was made of selective proton decoupling (SPD) and analysis of J_R vs. ^1H δ's. The ^1H NMR region from δ 2.3 to 6.5 is similar in appearance between most synthetic analogues and their corresponding natural products 1 (R = H; R^1 = C_5H_{11}), 4 (R_2 = C_5H_{11}),

(3) Hawkins, B. L.; Roberts, J. D. *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 1027.
(4) Wehrli, F. W.; Nishida, T. *Fortschr. Chem. Org. Naturst.* **1979**, *36*, 1.
(5) For isolation and structure elucidation, see: Gaoni, Y.; Mechoulam, R. *Chem. Commun.* **1966**, 20.
(6) For the synthesis of cannabichromene, see: (a) Crombie, L.; Ponsford, R. *Chem. Commun.* **1968**, 894. (b) Kane, V. V.; Razdan, R. K. *J. Am. Chem. Soc.* **1968**, *90*, 6551. (c) Mechoulam, R.; Yagnitinsky, B.; Gaoni, Y. *Ibid.* **1968**, *24*, 4825. (d) Elsohley, M. A.; Boeren, E. G.; Turner, C. E. *J. Heterocycl. Chem.* **1978**, *15*, 699.
(7) Recently, the ^{13}C NMR spectrum of chalcone chromene lespeol has been reported by: Miyase, T.; Ueno, A.; Noro, T.; Fukushima, S. *Chem. Pharm. Bull.* **1980**, *28*, 1172. But no carbon chemical shifts were assigned.
(8) For isolation of cannabicitran, see: Bercht, C. A. L.; Lousberg, R. J. J.; Kuppers, F. J. E. M.; Salemink, C. A. *Phytochemistry* **1974**, *13*, 619.
(9) For synthesis, see ref 6a,c.
(10) For isolation of cannabicyclol, see: Calussen, U.; Von Spulak, R.; Korte, F. *Tetrahedron* **1968**, *24*, 1021.
(11) (a) For synthesis, see ref 6a–c. (b) Crombie, L.; Ponsford, R.; Shani, A.; Yagnitinsky, B.; Mechoulam, R. *Tetrahedron Lett.* **1968**, 5771.

and **7** (R_3 = H; R_4 = C_5H_{11}). Specific ^1H NMR assignments in this region were known or could be unambiguously assigned, and this facilitated assignments of C's attached to these H's by ^{13}C NMR SPD experiments. The present results should be useful in biosynthetic studies[12] using ^{13}C-labeled precursors, which generally require unambiguous assignments of all carbons in molecules under study.

The numbering system for these cannabinoids are shown in the formulas (Chart I), and the spectral data obtained for the compounds are listed in Table I. The carbon assignments in the case of chromenes **1** (R = H; R_1 = C_5H_{11}), **2** (R = CH_3; R_1 = OCH_3), and **3** (R = H; R_1 = CH_3) were derived after reference to several models. The near identity of the C_6H_{11} (C_{10}–C_{15}) side chain in the chromenes vs. those in linalool[13,14] provided an assignment of C_{10} to C_{15}. SPD experiments with **2** (R = CH_3; R_1 = OCH_3) reinforced these same assignments. Likewise, the carbon shifts of the C_5H_{11} side chain in **1** (R = H; R_1 = C_5H_{11}), **4** (R_2 = C_5H_{11}), and **7** (R_3 = H; R_4 = C_5H_{11}) were identified by reference to the nearly identical shifts in Δ^9-tetrahydrocannabinol.[15] The C_8 and C_9 line assignments in **2** (R = CH_3; R_1 = OCH_3) [and by extrapolation, in **1** (R = H; R_1 = C_5H_{11}) and **3** (R = H; R_1 = CH_3)] come from SPD at the known ^1H shift positions of H_8 (δ 5.36) and H_9 (δ 6.60), which resulted in marked sharpening of the carbon resonances at δ 124.7 and 117.4, respectively. The aromatic carbon shifts in **1** (R = H; R_1 = C_5H_{11}) were assigned as follows: calculated[16] δ's for **1** (R = H; R_1 = C_5H_{11}) identified C_3 and C_6 (δ calcd: C_3 = 144.6; C_6 = 108.4), but they could not reliably distinguish between C_2 and C_4 or C_1 and C_5. Alternatively, SPD at the known H_2 and H_4 shift positions allowed identification of C_2 vs. C_4. Lastly, C_1 and C_5 were distinguished by comparison between **1** (R = H; R_1 = C_5H_{11}) and its acetate **1** [R = C(=O)CH_3; R_1 = C_5H_{11}]. When the former vs. the latter is compared, C_1 shifts upfield by 5 ppm [δ 151.3, **1** (R = H; R_1 = C_5H_{11}), to δ 146.3, **1** (R = C(=O)CH_3; R_1 = C_5H_{11})], while C_5 remains unchanged.

Synthetic compound **5** (R_2 = OH) was invaluable as a model for cannabicitran **4** (R_2 = C_5H_{11}). The aromatic ring in **5** (R_2 = OH) would have C_s symmetry if C_{11} were excluded. This approximate symmetry makes it impossible to exactly assign the sets C_2 and C_4 and C_1 and C_5, whereas calculated values nicely identify C_3 and C_6 (δ calcd: C_3 = 154.0, C_6 = 113.3). The nonaromatic tricyclic portion of **5** (R_2 = OH) is rigid, which is reflected in its richly detailed ^1H NMR spectra (see Experimental Section). Among these hydrogens, the C_{11}-H_β, which is directly over the aromatic ring, is the most shielded, while the benzylic C_9 H is the most deshielded. Significant anisochrony is apparent for each diastereotopic CH_2; $\Delta\delta$'s: C_8 = 0.37, C_{10} = 0.27, and C_{11} = 1.35.

A selective irradiation of C_{11} H_β proton signals in **5** (R_2 = OH) (at δ 0.6) transformed C_{11} to a doublet and both C_8 and C_{10} to doubled doublets. Using J_R values C_{10} = 70, 50 Hz and C_8 = 90, 74 Hz vs. ^1H shifts ($CDCl_3$) δ $H_{8\alpha}$ = 2.15, $H_{8\beta}$ = 1.78, $H_{10\beta}$ = 1.75 and $H_{10\alpha}$ = 1.38 enabled unambiguous assignments of C_8 and C_{10} carbons.[17] SPD at H_9 in **5** (R_2 = OH) resulted in a marked sharpening of the signal at δ 27.8, dictated its assignment as C_9, and enabled C_{12} to be assigned at δ 46.8. The C_7 vs. C_{13} assignment was made by reference to 1,8-cineol **10**.[4,14] The relative upfield shift of the *pseudo-axial* Me_{15}[18] easily differentiated it from the remaining two *equatorial* methyls, which were further distinguished by SPD. Interpretation of the rather complex spectra of cannabicitran **4** (R_2 = C_5H_{11}) was now greatly simplified by reference to the shift assignments for **1** (R = H; R_1 = C_5H_{11}) (C_5H_{11} part) and **5** (R_2 = OH).

Finally, the task of carbon chemical shift assignments for cannabicyclol **7** (R_3 = H; R_4 = C_5H_{11}) and synthetic analogues **8** (R_3 = CH_3; R_4 = OCH_3) and **9** (R_3 = H; R_4 = CH_3) were considered. We have previously analyzed the ^1H NMR of the analogue **8** (R_3 = CH_3; R_4 = OCH_3);[19] hence, SPD was used extensively to locate C_2, C_8, C_9, C_{10}, C_{11}, and C_{12} by irradiation of proton signals in **8** (R_3 = CH_3; R_4 = OCH_3) at δ 6.03, 3.02, 2.51, 2.35, 1.95 and 1.62, respectively. In the case of cannabicyclol **7** (R_3 = H; R_4 = C_5H_{11}) and analogue **9** (R_3 = H; R_4 = CH_3), it was found extremely difficult to assign C_{14} and C_{16} signals, since both of the methyl groups in the ^1H NMR are accidentally isochronous ($CDCl_3$), δ 1.37 in **7** (R_3 = H; R_4 = C_5H_{11}) and 1.38 in **9** (R_3 = H; R_4 = CH_3). By contrast, the C_{14} and C_{16} in **8** (R_3 = CH_3; R_4 = OCH_3) appear at δ 1.32 (s, 3 H, OCCH_3) and 1.38 (s, 3 H, cyclobutyl CH_3). SPD at these signals in **8** (R_3 = CH_3; R_4 = OCH_3) resulted in marked sharpening of the carbon resonances at δ 33.7 and 27.8, respectively. The C_{16} methyl is α and *equatorial* to the ring ether oxygen and would be expected to be more deshielded than C_{14}. Distinction between C_{14} and C_{15} is in accordance with the carbon chemical shift trends in pinane derivatives.[4] The chemical shift assignments of these three methyl groups were also verified by J_R values vs. ^1H shifts measured in SFORD at δ 1.95.

In summary, all ^{13}C signals of cannabichromene **1** (R = H; R^1 = C_5H_{11}), cannabicitran **4** (R_2 = C_5H_{11}), and cannabicyclol **7** (R_3 = H; R_4 = C_5H_{11}) and their corresponding analogues have been assigned.

Experimental Section

All melting points were taken with an electrothermal capillary melting point apparatus and are uncorrected. ^1H nuclear magnetic resonance spectra were recorded on Varian Associates EM-360 and Bruker WM-250 spectrometers and are reported in parts per million from internal tetramethylsilane on the δ scale. Data are reported as follows: chemical shifts multiplicity (s, singlet; d, doubled; t, triplet; q, quartet; m, multiplet), integration coupling constants (J, hertz) interpretation. The ^{13}C NMR spectra of approximately 1 M solutions of all compounds in $CDCl_3$ were obtained with Me_4Si as internal standard. Field-frequency stability was achieved by locking on the deuterium resonance of the solvent. The ambient probe temperature was about 30 °C. The spectrometer used was a Bruker WH-90 operating at 22.62 MHz. The specific proton–carbon decoupling experiments were carried out on a Bruker WM-250 NMR instrument operating at 62.9 MHz. Infrared spectra were taken with a Perkin-Elmer Infracored spectrometer. Mass spectra were recorded on a Varian MAT 311A. Samples on which exact masses were measured exhibited no significant peaks at m/e greater than that of the parent; ultraviolet measurements were carried out on a Cary 15 instrument. Solvents and reagents were dried and purified prior to use when deemed necessary; pyridine (distilled from potassium hydroxide). Ana-

(12) Mechoulam, R.; McCallum, N. K.; Burnstein, S. *Chem. Rev.* **1976**, *76*, 75. Despite the intense interest in the chemistry of cannabinoids, virtually nothing is known about the biogenesis of this important class of naturally occurring compounds.

(13) Linalool shifts[14] (numbered as in **1**): 42.2 (C_{10}), 22.6 (C_{11}), 124.6 (C_{12}), 130.3 (C_{13}), 17.2 (C_{14}), 25.3 (C_{15}).

(14) Breitmaier, E.; Voelter, W. "^{13}C NMR Spectroscopy"; Verlag Chemie: Dusseldorf, 1974; pp 199–200.

(15) Δ^9-THC C_5H_{11} shifts:[2b] 35.4 ($C_{1'}$), 30.5 ($C_{2'}$), 31.4 ($C_{3'}$), 22.5 ($C_{4'}$), 14.0 ($C_{5'}$), respectively.

(16) (a) Ewing, D. F. *Org. Magn. Res.* **1979**, *12*, 499. (b) Cooper, J. W. "Spectroscopic Techniques for Organic Chemistry"; Wiley: New York; 1980.

(17) We have previously pointed out the advantages of J_R analysis at superconducting fields: Selover, S.; Crews, P.; Tagle, B.; Clardy, J. *J. Org. Chem.* **1981**, *46*, 964.

(18) Crews, P.; Kho-Wiseman, E. *Tetrahedron Lett.* **1978**, 2483.

(19) Kane, V. V. *Tetrahedron Lett.* **1971**, 4101.

lytical thin-layer chromatography was performed with Analtech Inc. 250-μm silica gel GF plates. Column chromatography was performed with Merck (Darmstadt) silica gel (70–230 mesh). Reactions requiring an inert atmosphere were run under a blanket of nitrogen or argon.

Compounds 1 (R = H; $R_1 = C_5H_{11}$), 4 ($R_2 = C_5H_{11}$), and 7 (R_3 = H; $R_4 = C_5H_{11}$) were obtained according to the procedure previously described in the literature[6] and have the following physical constants.

Cannabichromene (1, R = H; $R_1 = C_5H_{11}$) was obtained as a colorless liquid in 20% yield: NMR (250 MHz, $CDCl_3$) δ 0.85 (t, 3 H, C_5 CH_3), 1.36 (s, 3 H, $OCCH_3$), 1.54 and 1.63 (6 H, 2 s, olefinic CH_3), 5.07 (br t, 1 H, olefinic H), 5.43 and 6.66 (2 H, AB quartet J_{AB} = 10 Hz, olefinic H), 6.10 and 6.26 (s, 2 H, aromatic H), 6.36 (s, 1 H, OH, D_2O exchangeable); UV λ_{max} (EtOH) 280 nm (ϵ 9700), 225 (27 500); mass spectrum, m/z 314, 299, 232, 231, 174.

Cannabicitran (4, $R_2 = C_5H_{11}$) was obtained as a colorless oil in 18% yield: homogeneous by TLC; NMR (60 MHz, $CDCl_3$) δ 0.87 (t, 3 H, CH_3), 0.94, 1.30, and 1.44 (3 s, 9 H, 3 CH_3), 6.16 (br s, 2 H, aromatic); mass spectrum, m/z 314, 299, 271, 258, 243, 232, 231, 193, 174.

Cannabicyclol (7, R_3 = H; $R_4 = C_5H_{11}$) was obtained as a crystalline compound in 3% yield: mp 145–146 °C; NMR (250 MHz, $CDCl_3$) δ 0.79 (s, 3 H, CH_3 on cyclobutyl), 0.87 (t, 3 H, C_5 CH_3), 1.37 (s, 6 H, 2 CH_3), 1.69 (m, 3 H, CH_2CH), 1.95 (m, 1 H), 2.39 (m, 1 H, CH_{12}), 2.57 (d of d, 1 H, CH_8), 3.06 (d, 1 H, J = 10 Hz, benzylic CH_9), 4.46 (br s, 1 H, OH, D_2O exchangeable), 6.17 and 6.32 (2 s, 2 H, aromatic H); mass spectrum calcd for $C_{21}H_{30}O_2$, M_r 314.2245; found, 314.2259.

Synthesis of Compound 5 (R_2 = OH). A solution of anhydrous phloroglucinol (4.87 g, 0.03 mol), citral (4.56 g, 0.03 mol), and pyridine (2.4 g, 0.03 mol) was refluxed for 8 h. The cooled solution was diluted with H_2O (100 mL) and Et_2O (500 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with saturated $CuSO_4$, saturated $NaHCO_3$, and saturated NaCl, dried ($MgSO_4$), and filtered, the filtrate was concentrated under reduced pressure, and the crude product (9.05 g) was chromatographed on silica gel (210 g) in hexane. Elution with 10% EtOAc/hexane gave a solid. Recrystallization from benzene/hexane gave **5** (R_2 = OH) as colorless prisms: mp 169–170 °C; IR 3360 (OH) cm^{-1}; mass spectrum calcd for $C_{16}H_{20}O_3$, M_r 260.1412; found, 260.1418.

^1H NMR (360 MHz) assignments of the nonaromatic resonances for **5** (R_2 = OH) were made from spectra in benzene-d_6: δ 0.62 (dddd, 1 H, J = 13.5, 11.5, 5.9, and 13.5 Hz, $H_{11\beta}$), 0.79 (dt, 1 H, J = 13.5, 5.4, and 5.4 Hz, $H_{11\alpha}$), 0.89 (s, 3 H, CH_3 at C_{15}), 0.96 (dt, 1 H, J = 13.5, 13.5, and 5.4 Hz, $H_{10\alpha}$), 1.22 (s, 3 H, CH_3 at C_{16}), 1.28 (dd, 1 H, J = 13.1, 1.8 Hz, $H_{8\beta}$), 1.30 (s, 3 H, CH_3 at C_{14}), 1.44 (ddd, 1 H, J = 11.5, 5.4, and 2.7 Hz, H_{12}), 1.57 (br ddd, 1 H, J = 13.5, 5.9, and 3.6 Hz, $H_{10\beta}$), 1.94 (ddd, 1 H, J = 13.1, 4.5, and 2.7 Hz, $H_{8\alpha}$), 2.61 (br m, 1 H, J = 4.5, 2.7, and 1.8 Hz, C_9 H). Spin decoupling (sd) was carried out at each multiplet, but the most definitive results included sd at δ 0.62 eliminated J = 13.5 Hz at δ 0.79, perturbed δ 0.96, eliminated J = 11.5 Hz at δ 1.44, eliminated J = 5.9 Hz at δ 1.57; sd at δ 0.96 perturbed δ 0.62, eliminated J = 5.4 Hz at δ 0.79, eliminated J = 13.5 Hz at δ 1.57; sd at 1.44 perturbed δ 0.62, eliminated J = 5.4 Hz at δ 0.79, eliminated J = 2.7 Hz at δ 2.61; sd at δ 2.61, eliminated J = 1.8 Hz at δ 1.28, eliminated J = 2.7 Hz at δ 1.44, eliminated J = 4.5 Hz at 1.94; and spectrum in $CDCl_3$ (360 MHz), δ 0.60 (dddd, 1 H, J = 13.5, 13.5, 11.5, and 5.9 Hz, $H_{11\beta}$), 1.00 (s, 3 H, CH_3 at C_{15}), 1.20 (dt, 1 H, J = 13.5, 5.4, and 5.4 Hz, $H_{11\alpha}$), 1.32 (s, 3 H, CH_3 at C_{16}), 1.38 (dt, 1 H, J = 13.5, 13.5, and 5.4 Hz, $H_{10\alpha}$), 1.49 (s, 3 H, CH_3 at C_{14}), 1.7 (br ddd, 1 H, J = 13.5, 5.9, and 3.6 Hz, $H_{10\beta}$), 1.78 (dd, 1 H, J = 13.1 and 1.8 Hz, $H_{8\beta}$), 1.95 (ddd, 1 H, J = 11.7, 5.4, and 2.7 Hz, H_{12}), 2.15 (ddd, 1 H, J = 13.1, 4.5, and 2.7 Hz, $H_{8\alpha}$), 2.80 (br multiplet, 1 H, J = 4.5, 2.2, and 1.8 Hz, C_9 H).

Condensation of Orcinol with Citral: Synthesis of Compounds 3, (R = H; $R_1 = CH_3$), 6 ($R_2 = CH_3$), and 9 (R_3 = H; $R_4 = CH_3$). A solution of anhydrous orcinol (4.26 g, 0.03 mol), citral (4.56 g, 0.03 mol), and pyridine (2.45 g, 0.03 mol) was refluxed for 10 h. The reaction was cooled and worked up as above. The crude product (8.63 g) was chromatographed on silica gel (200 g) in hexane. Elution with 3:97 EtOAc/hexane gave **6** ($R_2 = CH_3$) as a colorless oil (1.8 g, 23%): IR no OH bands, 1064, 1130 (ether bands) cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 1.00, 1.36, 1.56, and 2.20 (4 s, 12 H, 4-CH_3), 2.81 (br s, 1 H, benzylic CH), 6.22 (s, 2 H, aromatic H); mass spectrum calcd for $C_{17}H_{22}O_2$, M_r 258.1619; found, 258.1612. Further elution with 5:95 EtOAc/hexane gave **9** (R_3 = H; $R_4 = CH_3$) as a crystalline solid (0.32 g, 4%): mp 149–151 °C; IR (KBr) 3362 (OH) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 0.79 (s, 3 H, CH_3), 1.38 (s, 6 H 2 CH_3), 2.21 (s, 3 H, CH_3 on aromatic ring), 3.02 (d, 1 H, J = 9.5 Hz, benzylic CH), 4.5 (br s, 1 H, OH), 6.16 and 6.51 (2 s, 2 H, 2 aromatic H); mass spectrum calcd for $C_{17}H_{22}O_2$, M_r 258.1619; found, 258.1623. Further elution with 7:93 and 8:92 EtOAc/hexane gave **3** (R = H; $R_1 = CH_3$) as a slightly yellow oil, homogeneous on TLC: mass spectrum calcd for $C_{17}H_{22}O_2$, M_r 258.1619; found, 258.1633; NMR (250 MHz, $CDCl_3$), δ 1.35 (s, 3 H, $OCCH_3$), 1.57 and 1.65 (2 s, 6 H, olefinic CH_3), 2.20 (s, 3 H, aromatic CH_3), 5.08 [m, 1 H, $CH{=}C(CH_3)_2$], 5.44 and 6.45 (d, 2 H, J_{AB} = 10 Hz, 2 olefinic H), 6.16 and 6.24 (2 s, 2 H, aromatic H), 6.27 (s, 1 H, OH, D_2O exchangeable).

Condensation of 3,5-Dimethoxyphenol with Citral. Synthesis of Compound 2 (R = CH_3; $R_1 = OCH_3$). A solution of 3,5-dimethoxphenol (4.62 g, 0.03 mol), citral (4.56 g, 0.03 mol), and pyridine (2.45 g, 0.031 mol) was refluxed for 10 h. The reaction was cooled and worked up as indicated above. The crude product (8.4 g) was chromatographed on silica gel (200 g) in hexane. Elution with 3:97 EtOAc/hexane gave **2** as a slightly yellowish oil (3.45 g, 40%), homogeneous on TLC: NMR (250 MHz in $CDCl_3$) δ 1.36 (s, 3 H, $OCCH_3$), 1.57 and 1.66 (2 s, 6 H, 2 olefinic CH_3), 5.09 (t, 1 H, olefinic H), 5.36 and 6.61 (d, 2 H, AB quartet, J_{AB} = 10 Hz), 5.98 (d, 1 H, J = 2 Hz, aromatic H), 6.02 (d, 1 H, J = 2 Hz, aromatic H); mass spectrum showed principal ions at m/z 288, 273, 207, 206 (base peak); calcd for $C_{18}H_{24}O_3$, M_r 288.1725; found, 288.1711.

Synthesis of Compound 8 ($R_3 = CH_3$; OCH_3). The chromene **2** (1.00 g) in acetone (290 mL) and *tert*-butyl alcohol (290 mL) was irradiated with a 450-W medium-pressure mercury lamp using a pyrex filter for 18 h. The solution was evaporated, and the crude product was chromatographed on silica gel (40 g) in hexane. Elution with 2:98 EtOAc/hexane gave **8** (742 mg, 74%) as colorless crystals: mp 107–108 °C; UV λ_{max} (EtOH) 218 (ϵ 35 980) 232 (35 900); NMR (250 MHz, $CDCl_3$) δ 0.69 (s, 3 H, CH_3 on cyclobutane ring), 1.32 (s, 3 H, $OCCH_3$), 1.38 (s, 3 H, cyclobutane CH_3), 1.62 (m, 3 H, CH_2CH), 1.95 (m, 1 H), 2.35 (m, 1 H, CH_{12}), 2.51 (d of d, 1 H, CH_8), 3.02 (d, 1 H, CH_9), 3.72 and 3.75 (2 s, 6 H, 2-OCH_3), 6.03 (d, 1 H, J = 2 Hz, aromatic H), 6.07 (d, 1 H, J = 2 Hz, aromatic H), mass spectrum calcd for $C_{18}H_{24}O_3$, M_r 288.1725; found, 288.1729.

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Registry No. (±)-**1** (R = H), 18793-28-7; (±)-**2**, 89462-14-6; (±)-**3**, 81489-41-0; (±)-**4**, 62504-22-7; (±)-**5** (R_2 = OH), 89460-90-2; (±)-**6**, 89460-91-3; (±)-**7**, 67920-00-7; (±)-**8**, 35508-57-7; phloroglucinol, 108-73-6; citral, 5392-40-5; orcinol, 504-15-4; 3,5-dimethoxyphenol, 500-99-2.