CRYSTAL AND MOLECULAR STRUCTURE OF CANNABISPIRAN AND ITS CORRELATION TO DEHYDROCANNABISPIRAN

TWO NOVEL CANNABIS CONSTITUENTS

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(Received in USA 12 January 1977; Received in UK for publication 19 April 1977)

Abstract—Full details are provided on the isolation, spectral data and X-ray crystallographic analysis of cannabispiran (1) [7' - hydroxy - 5' - methoxyspiro(cyclohexane - 1,1' - indan) - 4 - one] and its correlation to Δ^2 -cannabispiran (dehydrocannabispiran) (2); both of which are novel spiro-compounds isolated from the leaves of *Cannabis sativa* L. Cannabispiran (1) crystallizes in the space group *Pbca*, cell dimensions: a = 10.388(5) Å, b = 14.754(7) Å, c = 16.950(8) Å, with eight molecules in the unit cell. The structure model was refined, using 852 observed reflections collected by counter methods, to an *R*-factor of 0.074 and a weighted R_w of 0.054.

As a part of a large scale program for studying noncannabinoidal constituents of *Cannabis sativa* L. (marihuana), several alkaloids have been reported from our laboratories' and recently the crystal structure of cannabispiran, a new noncannabinoidal spiroindan compound was also reported.² Here, we wish to report the details for the isolation, spectroscopic properties and crystal structure of cannabispiran (1) and its correlation with another *Cannabis* constituent which was identified as dehydrocannabispiran (2).

When the alcohol extract of an Indian marihuana variant was subjected to gas chromatographic analysis, it showed a peak that had similar relative retention times to that of $(-) - \Delta^{*}$ - trans-tetrahydrocannabinol (Δ^{*} -THC) both before silulation (0.43) and after silulation (0.21). Combined gas chromatographic-mass spectrometric analysis revealed that Δ^8 -THC was absent and this peak was due to the presence of a novel compound with a molecular weight of 246. The marihuana extract was then chromatographed on silica gel and elution started with n-hexane to remove the waxes and hydrocarbons, then with increasing concentrations of benzene in n-hexane to remove most of the cannabinoids. Elution with 10% ether in benzene provided (-) - Δ^9 - trans-tetrahydrocannabinolic acid B⁴ which was followed by cannabispiran (1) when the eluent composition was changed to 20% ether in benzene. It should be noted at this stage that the similarity in retention times between cannabispiran (1) and Δ^{*} -THC makes it easy to confuse both compounds with each other and is a major source of error in the quantitation of Δ^* -THC in marihuana samples.

Cannabispiran (1), $C_{15}H_{18}O_3$, m.p. 178–179°C was found to be optically inactive. Its spectral features†

suggested that it was phenolic, having one methoxyl

While the Indian marihuana variant examined yielded



Cannabispiran (I)

Dehydrocannabispiran (2)



group, two aromatic protons and a cyclohexanone ring system. The amounts of available cannabispiran (1) did not permit its structure elucidation by degradation to easily identifiable fragments and consequently, it was decided to deduce its structure by X-ray crystallographic analysis (Experimental). Figure 1 shows the crystal packing in the cell unit while Fig. 2 is a computergenerated representation of the crystal structure of cannabispiran (1) as viewed down on the plane of the phenyl ring. Table 2 shows that all bond lengths are normal (within $2.5 \times \sigma$) and the distortion in the phenyl ring is as would be expected for this type of compound. Opening of C(6)-C(5)-O(15) and closing of C(4)-C(5)-O(15) are as found for phenylmethyl ethers. The bond angles around the indan and cyclohexanone rings are normal. The indan system however, except for C(8), which deviates by 0.2 Å, is planar, Table 3. This explains the optical inactivity of cannabispiran (1).

[†]See Experimental, and Ref. 2.



Fig. 1. The molecular packing of cannabispiran (1) with 25% probability ellipsoids. The hydrogen atoms are drawn artificially small. The b and c axes are in the plane of the paper.

only cannabispiran (1), a South African variant yielded both cannabispiran (1) and the related compound dehydrocannabispiran (2) upon extraction with alcohol 95% followed by repeated chromatography on silica gel. Dehydrocannabispiran (2), C15H16O3, was obtained as needle crystals, m.p. 163–164° and $[\alpha]_D^{\alpha 2}$ +34° (c 0.28, MaOII). The ID MeOH). The IR spectrum of 2 resembled that of cannabispiran (1) but it showed a carbonyl absorption at $\nu_{\rm max}^{\rm KBr}$ 1650 cm⁻¹ suggesting the presence of an α,β -unsaturated ketone group. Likewise the ¹H NMR spectra of the two compounds were similar; however, that of dehydrocannabispiran showed signals for two olefinic protons forming an AB pair of doublets at δ 6.16 and δ 6.85 (J = 10 Hz); the doublet for the lower olefinic proton, however, showed further splitting (J = about 1 Hz)presumably due to allylic coupling. Catalytic hydrogenation of dehydrocannabispiran (2) using 5% palladium on charcoal as a catalyst yielded cannabispiran (1), thus establishing its structure as (2). In contrast to cannabispiran (1) the molecule of dehydrocannabispiran (2) does not have a plane of symmetry and this explains its optical activity. Nevertheless, the chirality of the spiro-C atom is yet to be established. Cannabispiran (1), dehydrocannabispiran (2) and dihydrocannabispirant represent a new family of Cannabis constituents and they all bear structural resemblance to the synthetic compound 3 which was found to potentiate the estrogenic activity of Stilbestrol.5 In view of the reported estrogenic activity of marihuana⁶ further biological evaluation of

⁺This is the secondary alcohol analog of cannabispiran which was also isolated from the South African marihuana variant. Its structure and stereochemistry will be the subject of a forthcoming publication.

Fig. 2. Computer-generated representation of the crystal structure of cannabispiran (1) as viewed down on the plane of the phenyl ring. The thermal ellipsoids are shown with 25% probability. The hydrogen atoms are drawn artificially small.

Table 1. Fractional atomic coordinates and thermal parameters with estimated standard deviations. The temperature factor for nonhydrogen atoms is given by $\exp(-2\pi^2(U_{11}(a^*h)^2 + U_{22}(b^*k)^2 + U_{33}(c^*1)^2 + 2U_{12}((a^*b^*)hk + 2U_{13}(a^*c^*)hl + 2U_{23}(b^*c^*)kl))$

Atom	<u>×</u>	¥	<u>z</u>	$\underline{\mathbf{U}}_{11}$	<u>U</u> ,,	<u>U</u> 33	<u>U</u> 12	U_1 3	<u>U</u> 2 3
C(1) C(2) C(3) C(4) C(5) C(6) C(7) C(8) C(10) C(11) C(12) C(12) C(14) O(15) C(16) O(17) O(18)	. 2856(7) . 34 33(7) . 4345(7) . 4538(7) . 4021(7) . 3122(7) . 1953(7) . 1781(8) . 3001(7) . 2684(8) . 2226(7) . 3208(7) . 3671(8) . 4057(8) . 4391(5) . 3739(8) . 4948(5) . 3563(5)	.3859(5) .4010(5) .3382(5) .2627(5) .2517(5) .3127(5) .4630(5) .5101(5) .4903(5) .5746(5) .6462(5) .6462(5) .5746(5) .5622(5) .1758(3) .1584(5) .3516(3) .6970(3)	.0108(4) .0841(4) .1088(4) .0031(4) .0030(5) .0360(4) .0022(4) .0722(5) .1218(4) .2087(4) .2288(5) .1451(4) .1118(4) .0498(3) .1234(5) .1299(3) .2804(3)	.0406(56) .0312(51) .0540(63) .0509(53) .0573(65) .0742(68) .0426(58) .0426(58) .0923(68) .0577(66) .0501(57) .0726(65) .0593(61) .0556(41) .0968(73) .0719(37) 0917(46)	. 0382(48) .0426(48) .0539(57) .0460(54) .0298(44) .0402(52) .0478(50) .0513(57) .0396(51) .0396(51) .041(47) .0688(56) .0499(55) .0588(59) .0568(59) .0520(38) .0379(54) .0736(38) .0812(44)	.0325(49) .0352(50) .0216(47) .0179(41) .0468(58) .0367(51) .0559(56) .1000(72) .0451(51) .0381(49) .0434(51) .0514(66) .0417(53) .0451(50) .0591(37) .0743(65) .0458(31) .0506(38)	0008(44) 0030(47) 0061(50) .0044(48) .00079(49) .0137(53) .0128(57) .0000(48) 0184(50) 0213(53) 0088(50) 0130(53) 0130(53) 0104(51) 0022(32) 0075(52) .0233(35) 0278(36)	0120(43) 0074(45) 0164(45) .0101(48) 0042(43) 0273(51) 0380(59) 0123(44) .0166(49) .0156(47) 0018(50) 0018(50) 0023(32) 0241(57) 0268(32) .0041(36)	.0103(42) .0019(42) .0062(45) .0030(41) 0088(43) 0191(47) 0055(57) 0002(47) .0039(43) 0041(51) 0030(45) .0030(45) .0030(45) 0094(32) 0078(50) 0058(31) 0291(34)
Atom	×	<u>ک</u>	<u>z</u>	B	Atom	<u>×</u>	<u>۲</u>	<u>Z</u>	<u>B</u>
H4 H71 H82 H102 H112 H141 H163 H81 H142	.529(6) .118(7) .160(10) .217(9) .135(7) .485(7) .285(7) .107(9) .422(6)	.222(4) .442(5) .566(6) .433(5) .595(4) .531(5) .140(4) .467(6) .570(4)	.081(3) 030(4) .071(6) .226(5) .218(4) .143(4) 120(3) .093(5) .059(3)	3.0(20) 9.0(31) 3.6(47) 4.2(34) 5.9(25) 4.3(28) 3.6(21) 4.0 a 4.0 a	H6 H72 H101 H111 H131 H161 H171 H132 H162	.265(6) .245(7) .369(8) .219(7) .445(7) .405(9) .543(6) .292(8) .379(7)	.301(4) .513(5) .563(4) .691(4) .107(5) .309(3) .681(5) .216(4)	087(4) 046(4) .246(5) .292(4) .151(4) 126(5) .191(3) .117(5) 168(4)	6.9(21) 5.6(27) 7.7(28) 2.9(26) 5.5(25) 5.9(38) 4.7(16) 5.5 a 4.5 a



Bond Length (A)

Table 2. Molecular parameters with estimated standard deviations. The numbering of atoms is given in Fig. 2

Bond Angle (0)

C1-C2	1.400(8)	C6-C1-C2	123.7(7)
C1-C6	1.368(8)	C1-C2-C3	117.0(7)
C2-C3	1.391(8)	C2-C3-C4	121.0(7)
C3-C4	1.391(8)	C3-C4-C5	118.9(7)
C4-C5	1.389(8)	C4-C5-C6	122.0(7)
C5-C6	1.376(9)	C5-C6-C1	117.4(7)
C1-C7	1.508(9)	C2-C1-C7	109.7(7)
C2-C9	1.531(9)	C6-C1-C7	126.7(7)
C7-C8	1.541(9)	C1-C2-C9	112.5(7)
C8-C9	1.549(9)	C3-C2-C9	130.4(7)
C9-C10	1.516(8)	C2-C3-017	118.6(7)
C9-C14	1.536(9)	C4-C3-017	120.4(7)
C10-C11	1.553(8)	C4-C5-015	114.2(7)
C11-C12	1.486(9)	C6-C5-015	123.8(7)
C12-C13	1,505(9)	C1-C7-C8	102.9(6)
C13-C14	1.538(9)	C7-C8-C9	107.5(6)
C5-015	1.373(8)	C2-C9-C8	100.2(6)
015-C16	1.443(8)	C2-C9-C10	113.5(6)
C3-017	1.373(7)	C2-C9-C14	109.8(6)
C12-018	1.209(7)	C8-C9-C10	111.5(7)
Hydrogen bond		C8-C9-C14	113.2(6)
017-018(1- <u>x</u> ,-½+	<u>v,¦s+z</u>)2.838(10)	C10-C9-C14	108.6(6)
		C9-C10-C11	110.4(6)
		C10-C11-C12	111.2(6)
		C11-C12-C13	115.2(6)
		C12-C13-C14	110.5(6)
		C13-C14-C9	113.0(6)
		C11-C12-018	122.7(7)
		C13-C12-018	122.1(7)
		C5-015-C16	116.8(6)
Selected dihedr	al angles (⁰). The	e angles are posítive i	n a right-hand screw.
C4-C5-015-C16	177.1(6)	C2-C1-C7-C8	-15.6(8)
C1-C2-C9-C8	16.8(8)	C1-C7-C8-C9	26.2(8)
C7-C8-C9-C2	-26.0(7)	C7-C8-C9-C10	-146.4(6)
C7-C8-C9-C14	90.9(7)	C1-C2-C9-C10	1 35, 7(7)
C1-C2-C9 - C14	-102.6(7)	C2-C9-C10-C11	-178.8(6)
C14-C9-C10-C11	58.8(8)	C2-C9-C14-C13	177.6(Ø)
C10-C9-C14-C13	-57.8(8)	C9-C10-C11-C12	-56.8(9)
<u>C10-C11-C12-C13</u>	52.3(9)	C10-C11-C12-018	-131.4(8)
C11-C12-C13-C14	-49.6(9)	C12-C13-C14-C9	52.1(9)

		Plane I	Pla	Plane II		
Atom		Atom		Atom		
C1	<u>4</u>	C10	-902	C11	<u>6</u>	
C2	- <u>7</u>	C11	-790	C12	- <u>21</u>	
C3	<u>7</u>	C12	601	C1 3	<u>6</u>	
C4	- <u>3</u>	C1 3	1660	018	<u>6</u>	
C5	<u>0</u>	C14	1490	C10	-1105	
C6	- <u>1</u>	015	8	C14	-1055	
C7	62	C16	-53	C9	-962	
C8	-320	017	19	C2	-2006	
C9	66	018	863	C8	336	

Table 3.	Deviations from least-squares plane ($\dot{A} \times 10^3$).	The deviations for	or those atoms use	d to define the p	lanes are
	given in its	alicized numbers			

these compounds is in order, so as to determine their contribution, if any, to the overall pharmacology of marihuana.

EXPERIMENTAL

M.ps were determined on a Thomas-Hoover Uni-Melt m.p. apparatus and are uncorrected. IR spectra were measured in KBr disc or as 8% solution in chloroform on a Perkin-Elmer 257 or Beckman IR-33 spectrophotometer. UV spectra were obtained in MeOH on a Beckman Acta III spectrophotometer. ³H NMR spectra were recorded on a Jeolco C-60 HL spectrometer or a Varian HA-100 spectrometer using chloroform-d or acetone-d₆ as solvents and TMS as the internal standard; chemical shifts are reported in δ (ppm) units. Optical rotations were determined on a Perkin-Elmer 141 automatic polarimeter. Mass spectral data were obtained on a Dupont-CEC 492 spectrometer. Gas chromatographic analysis was performed on a Beckman GC 72-5 instrument as previously reported.³

Isolation of cannabispiran (1). The powdered leaves of an Indian variant of marihuana grown in Mississippi (5.0 kg) were extracted by percolation with n-hexane (501.). The percolate was evaporated in vacuo at 40° to yield a dark semisolid residue (218 g). This residue (154 g) was chromatographed on 2.25 kg of silica gel packed in a column 110×6.6 cm using n-hexane as eluent (91.). The column was then eluted with 20% benzene in n-hexane (61.), 60% benzene in n-hexane (61.), benzene (81.) then 10% ether in benzene (41.). This last solvent system eluted Δ° -THC acid B (6 g). Elution was then continued with 20% ether in benzene (41.) which upon evaporation left 0.76 g of an oily residue that crystallized from n-hexane ether to give colorless plates of I (109 mg), m.p. 178-179°, which was optically inactive. Low resolution MS gave the parent ion peak at m/e 246; high resolution MS, on the other hand, established that the molecular formula was C₁₅H₁₈O₃ (calculated 246.1256; found 246.1265). Other significant peaks in the MS were found at m/e (relative intensity) 189 (100), 176 (59), 229 (5) and 216 (2). The IR spectrum showed major absorption bands at $\nu_{nat}^{CHC1_3}$ 3600, 3390, 1715, 1602, 1145 and 877 cm⁻¹. The 100 MHz ¹H NMR spectrum taken in chloroform-d showed peaks at δ 3.75 (s, 3H), δ 2.22 and δ 2.95 (a pair of 2-hydrogen triplets, J = 7.0 Hz due to the homobenzylic and the benzylic methylene groups of the indan ring, respectively), δ 5.24 (s, 1H, exchangable; phenolic OH), δ 6.20 and 6.36 (a pair of spin-coupled doublets, J = 1.8 Hz; aromatic protons). The remaining protons absorbed as 8H multiplet centered at δ 2.56.

X-ray crystallography of cannabispiran (1). Oscillation and Weissenberg diagrams of the plate crystals indicated twinning for most of the crystal sample. A small crystal of approximate dimensions $0.13 \times 0.08 \times 0.04$ mm was, therefore, selected for the

crystallographic work. Film diagrams indicated orthorhombic symmetry and the systematic absences uniquely defined the space group as *Pbca*.

An automatic Picker 4-circle diffractometer with graphitemonochromatized MoK_{α} radiation was utilized for preliminary experiments and for the recording of intensity data. Unit cell parameters were determined by a least-squares treatment of the angular coordinates of 19 reflections with 20-values from 11 to 32°. The computer program used, as well as programs subsequently employed, is part of a local (Oslo) assembly of computer programs for CYBER-74, and is previously described.⁷

3-Dimensional intensity data were recorded using the $\omega - 2\theta$ scanning mode with scan speed 2° min⁻¹, and the scan area was from 2θ ($K\alpha_1$) - 0.9° to 2θ ($K\alpha_2$) + 0.9°. Background counting time was 30 sec on each side of the scan area. The temperature was kept constant within 1° at 18°. The variations in the intensities of three standard reflections which were remeasured after every hundred reflections were random and less than three times their estimated standard deviations. Accordingly, no corrections were applied for these variations.

The estimated standard deviations were taken as the square root of the total counts with an addition of 2% of the net intensity for experimental uncertainties. Of the 1570 symmetryindependent reflections measured $(2\theta_{max} = 45^\circ)$, 852 had intensities larger than twice their standard deviations. These were regarded as "observed" reflections and the remaining were excluded from further calculations. The intensities were corrected for Lorentz and polarization effects.

The atomic scattering factors used were those of Doyle and Turner⁸ for carbon and oxygen, and of Stewart *et al.*⁹ for hydrogen.

The phase problem was solved by direct methods utilizing the MULTAN program assembly.¹⁰ The structure model was refined to an $R = \Sigma |F_0 - |F_c|| / \Sigma F_0$ of 0.15. Introduction of anisotropic thermal parameters for all nonhydrogen atoms and least-squares refinement yielded an agreement residual R of 0.126 and an $R_w = [\Sigma w (\Delta F)^2 / \Sigma w (F_0)^2]$ of 0.10. The weights used are: w = $1/\sigma^2(F_0)$. The hydrogen atoms were placed in calculated positions. In order to test the structure model of this unknown compound, the H atoms were included in the least-squares refinement. Full-matrix least-squares refinement of all positional parameters, anisotropic thermal parameters for nonhydrogen atoms and isotropic thermal parameters for H atoms lowered Rto 0.075 and R_w to 0.054. The results for the hydrogen thermal parameters were reasonable (Table 1), except for H81 (B = 14.4 Å²), H132 (14.8 Å²), H142 (0.3 Å²) and H162 (10.6 Å²). The thermal parameters for these atoms were reset in accordance with the values obtained for the other H atoms bonded to the same C atoms (Table 1).

The final full-matrix least-squares refinement of all parameters involving nonhydrogen atoms converged to an R_w of 0.054 and an R of 0.074. The weights used are $w = 1\hbar\sigma^2(F_0)$. Atomic parameters for all atoms are listed in Table 1. A listing of calculated and observed reflections with estimated standard deviations is available from Department of Chemistry (Div. C), University of Oslo, Oslo 3, Norway. (Also available from the authors upon request.)

Standard deviations in molecular parameters were calculated from the correlation matrix ignoring standard deviations in cell parameters.

Crystal data. Cannabispiran (1) [7' - hydroxy - 5 - methoxyspiro(cyclohexane - 1,1' - indan) - 4 - one], $C_{15}H_{18}O_3$, orthorhombic, space group: *Pbca*. Cell dimensions: A = 10.388(5) Å, b = 14.754(7) Å, c = 16.950(8) Å, V = 2597.7(9) Å³. M =246.13 amu, D_{obs} (floatation) = 1.26 g cm⁻³, $Z \approx 8$, $D_{calc} =$ 1.259 g cm⁻³, F(000) = 1056. Absent reflection: 0kl for k odd, k0lfor l odd, hk0 for k odd.

Isolation of dehydrocannabispiran (2). Dry leaves and small stems (4.5 kg) of a South African variant of Cannabis grown in Mississippi were defatted by percolation with n-hexane at room temp. (361.), dried and then extracted with alcohol 95% (601.) again, by percolation at room temp. The alcohol extract was evaporated in vacuo at 40° and the residue was partitioned between 2% HCl (1500 ml) and chloroform (21.) in order to remove any bases. The chloroform phase was washed with water, dried over Na₂SO₄ and evaporated. The chloroform solubles were partitioned between 10% aqueous MeOH (500 ml) and n-hexane (1500 ml); the methanolic phase yielded upon evaporation a brown semi-solid residue (85 g). This residue was chromatographed on 1.25 kg of silica gel in a column 5.7 × 150 cm using chloroform as a solvent. The polarity of the eluent was increased gradually by adding increasing concentrations of MeOH. Evaporation of the fraction eluted with 20% MeOH in CHCl₃ left 18.1 g of a residue (fraction A). Fraction A obtained above (10 g) was chromatographed on a column 4.4 × 50 cm of tlc grade silica gel packed in CHCl3-EtOAc (2:1) and 15-ml fractions were collected. Fractions 47-56 of this column were found to contain 1 $(R_f 0.35)$ and 2 $(R_f 0.23)$ when examined by the using silica gel G plates and ether-hexane (6:4) as the solvent system. Thus, these fractions were combined and evaporated to yield 2.4 g of an oily residue which was rechromatographed on 300 g of tlc grade silica gel packed in a column 50 × 4.4 cm using n-hexane-ether mixture (4:6) as eluent. Fractions of 9-ml each were collected. Evaporation of the combined fractions 57-65 from this column yielded 120 mg of 1, identical to the material isolated from the Indian variant.

The more polar 2 was obtained in fractions 80-93. These fractions were combined, evaporated and the residue chromatographed on a column (40×2.8 cm) of tlc grade silica gel (100 g) using 30% EtOAc in CHCl₃ as eluent. Fractions of 9-ml each

were collected. Fractions 24-29 were combined, evaporated and the residue yielded upon crystallization, from aceton-n-hexane mixture, 90 mg of 2, $C_{15}H_{16}O_3$, m.p. 163-164°, $(\alpha)_D^{20}$ +34° (c 0.28, MeOH); UV λ_{MeO}^{MEOH} 212 (shoulder; log ϵ 2.96), 229 (3.74) and 282 (2.96) nm; IR μ_{max}^{MEB} 3400-3100 (broad OH absorption), 1650 (α , β unsaturated ketone) and 1605 cm⁻¹ (aromatic absorption). The ¹H NMR spectrum taken in acetone-d₆ showed signals at δ 3.7 (s, 3H, OCH₃) δ 5.8 (d, 1H, J = 10 Hz), δ 6.16 (s, 2H, Ar'), δ 6.85 (dd, 1H, J = 10, 1 Hz) and δ 7.77 (s, 1H, exchangeable). Low resolution mass spectrometry gave the parent ion peak at m/e244 (73%) and high resolution MS showed that 2 has the molecular formula $C_{15}H_{16}O_3$ (Calc. 244.1100; obs. 244.1106). Other major ions were observed at m/e (% relative intensity) 216 (10), 202 (5), 201 (10), 194 (12), 189 (100), 187 (74), 176 (5), 174 (11) and 173 (12).

Catalytic hydrogenation of dehydrocannabispiran (2). 2 (20 mg) was dissolved in MeOH (10 ml) and reduced with H_2 using 10 mg of 5% Pd/C as a catalyst. The hydrogenation took place under atmospheric pressure and was allowed to proceed for an overnight. The mixture was then filtered and the filtrate yielded upon evaporation 20 mg of 1 identical in all regards to the natural compound (m.p., m.m.p., IR, ¹H NMR, MS and UV spectra).

Acknowledgements—This work was supported by Contract HSM-42-70-109 from the National Institute on Drug Abuse and by the Research Institute of Pharmaceutical Sciences of the University of Mississippi. The authors are indebted to Dr. S. Billets for measuring the mass spectra and for Dr. S. Burstein for obtaining the 100 MHZ ¹H NMR spectrum of cannabispiran.

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