Articles

Stereochemical Requirements for Cannabinoid Activity

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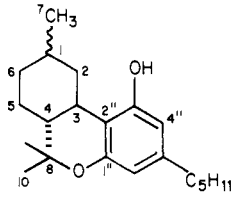
Several pairs of cannabinoid isomers were synthesized and tested for pyschotropic activity in rhesus monkeys. Two regularities were observed: (a) In the absence of the other substituents, the equatorial stereochemistry of the substituent at C-1 determines activity. (b) Two groups of THC-type cannabinoids which differ only in that the chemical groupings in one of them at C-1, C-2 are situated at C-1, C-6 in the other (but retain their stereochemistry) have almost equivalent pyschotropic activity.

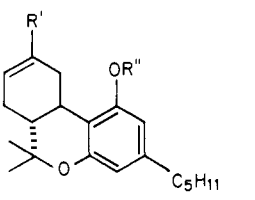
Several years ago we reported[1] that while the hexahydrocannabinol **1a** (C-7 methyl group equatorial) was as psychoactive in the rhesus monkey as Δ^6-THC (**2a**),[2] the hexahydrocannabinol **1b** (C-7 methyl group axial) was nearly 20 times less active. Other stereochemical correlations are also known. Thus, 3,4-*trans*-(−)-Δ^1-tetrahydrocannabinol (Δ^1-THC; **3a**),[2,3] the main natural active cannabinoid, exhibits activity in rhesus monkeys at 50 μg/kg, while the cis-(±)-Δ^1 isomer (**4**)[1] is not active at 1 mg/kg. The Δ^1-THC metabolites 6α-hydroxy-Δ^1-THC (**5**) and 6β-hydroxy-Δ^1-THC (**6**) are essentially equipotent in psychotropic activity (rhesus monkey).[4] However, the Δ^6-THC metabolites 5α-hydroxy-Δ^6-THC (**7**) and 5β-hydroxy-Δ^6-THC (**8**) are considerably different, the former being six to eight times less potent (rhesus monkeys) than the latter.[5] More recently, compound **10**, in which the C-1 hydroxyl group is equatorial, was found to be a potent analgetic in rodents, while **9**, in which the C-1 hydroxyl group is axial, was found to be inactive.[6]

It seemed of interest to generate additional data on the stereochemical requirements for psychotropic cannabinoid activity with the aim of formulating tentative rules.[7]

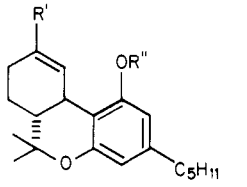
Chemistry. Synthesis of 14b and 15b (Scheme I). Catalytic reduction of Δ^6-THC-7-oic acid methyl ester acetate (**11**)[8] led to a mixture of the hexahydrocannabinol-7-oic acid methyl ester acetates **12** and **13**. These were separated by chromatography and were further reduced by lithium aluminum hydride to the respective alcohols **14a** and **15a** which on acetylation gave the 7-



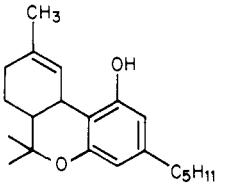
1a, C-7 methyl group β, equatorial
b, C-7 methyl group α, axial



2a, R' = CH_3; R'' = H
b, R' = CH_3; R'' = Ac
c, R' = CH_2OH; R'' = H



3a, R' = CH_3; R'' = H
b, R' = CH_3; R'' = Ac
c, R' = CH_2OH; R'' = H



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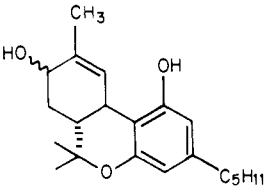
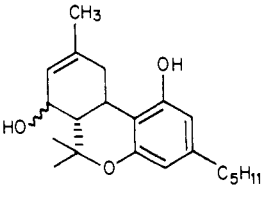
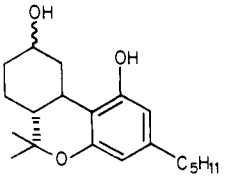


5, hydroxyl group α, pseudoequatorial
6, hydroxyl group β, pseudoaxial



7, hydroxyl group α, pseudoaxial
8, hydroxyl group β, pseudoequatorial



9, hydroxyl group α, axial
10, hydroxyl group β, equatorial

(1) Edery, H.; Grunfeld, Y.; Ben-Zvi, Z.; Mechoulam, R. *Ann. N.Y. Acad. Sci.* **1971**, *191*, 40.
(2) By the pyran nomenclature, generally employed in the U.S., Δ^1-THC and Δ^6-THC are named Δ^9-THC and Δ^8-THC, respectively.
(3) Gaoni, Y.; Mechoulam, R. *J. Am. Chem. Soc.* **1964**, *86*, 1646. Gaoni, Y.; Mechoulam, R. *Ibid.* **1971**, *93*, 217.
(4) Ben-Zvi, Z.; Mechoulam, R.; Edery, H.; Porath, G. *Science* **1971**, *174*, 951.
(5) Mechoulam, R.; Varconi, H.; Ben-Zvi, Z.; Edery, H.; Grunfeld, Y. *J. Am. Chem. Soc.* **1972**, *94*, 7930.
(6) Wilson, R. S.; May, E. L. *J. Med. Chem.* **1975**, *18*, 700; Wilson, R. S.; May, E. L.; Martin, B. R.; Dewey, W. L. *J. Med. Chem.* **1976**, *19*, 1165.
(7) For reviews of cannabinoid SAR, see: (a) Mechoulam, R.; Edery, H. "Marijuana. Chemistry, Pharmacology, Metabolism, and Clinical Effects"; Mechoulam, R., Ed.; Academic Press: New York, 1973; p 101. (b) Mechoulam, R.; McCallum, N.; Burstein, S. *Chem. Rev.* **1976**, *76*, 75. Pars, H. G.; Razdan, R. K.; Howes, J. F. *Adv. Drug Res.* **1977**, *11*, 97.
(8) Mechoulam, R.; Ben-Zvi, Z.; Agurell, S.; Nilsson, I. M.; Nilsson, J. L. G.; Edery, H.; Grunfeld, Y. *Experientia* **1973**, *29*, 1193. Nilsson, J. L. G.; Nilsson, I. M.; Agurell, S.; Ben-Zvi, Z.; Mechoulam, R. *Acta Pharm. Suec.* **1972**, *9*, 215.

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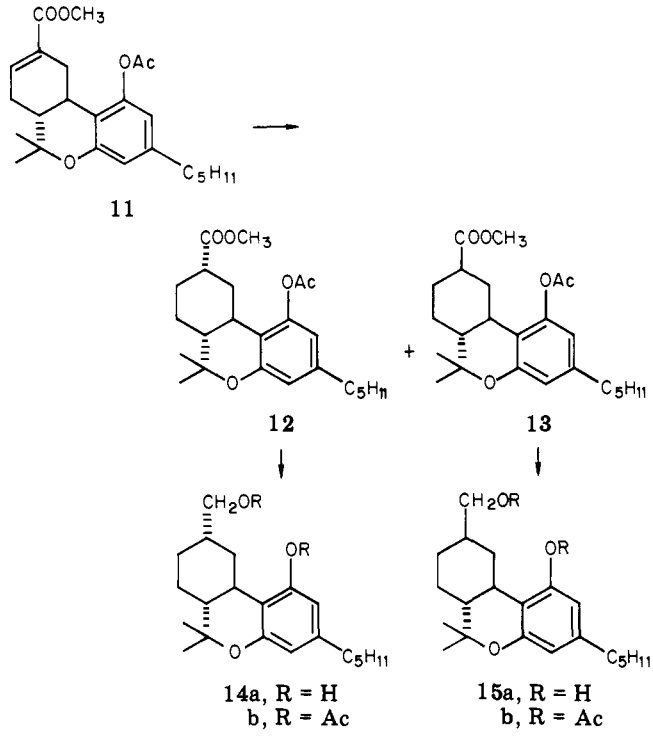
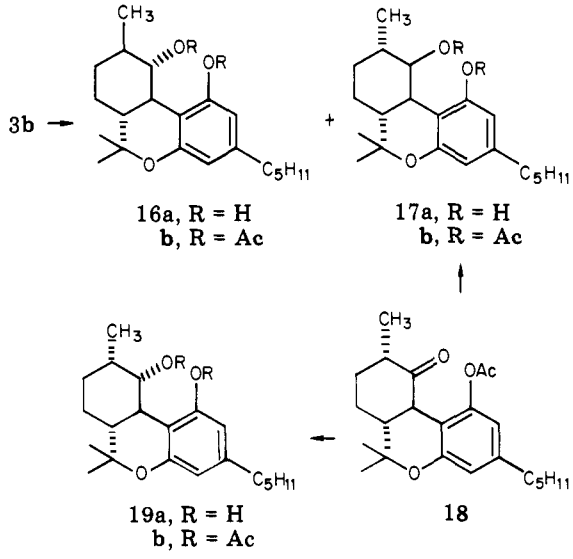
Scheme I

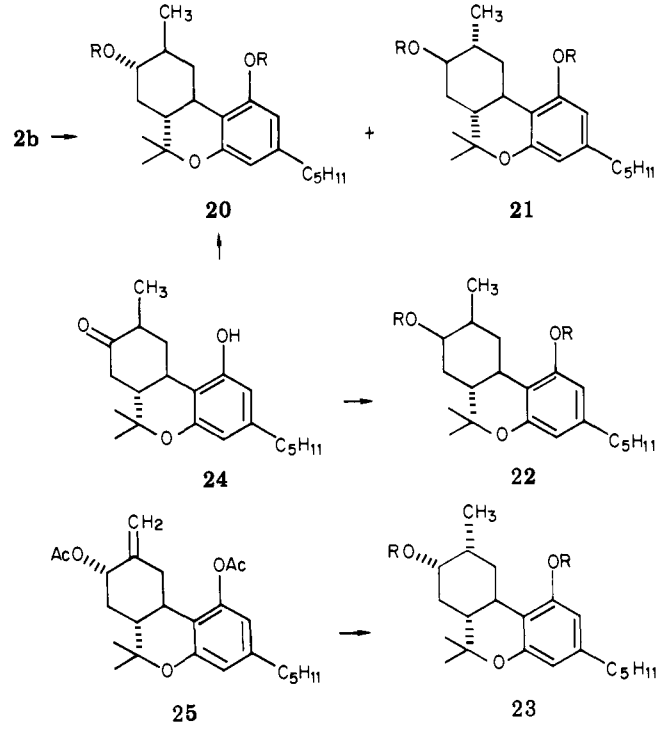


Scheme II



hydroxyhexahydrocannabinol diacetates **14b** and **15b**.[9,10] Harvey et al.[9] have shown that the carbomethoxyl group in **12** is axial. This was deduced mainly on the basis of the shielding of the C-10 axial methyl group (as compared to the corresponding group in **13**) and on mass spectral data. This assignment is now confirmed by the following observations: The ^{13}C NMR signal (at 15.08 MHz) for the axial 7-carbinyl carbon in **14b** is observed at δ 65.535, while the corresponding equatorial carbon in **15b** is at δ 68.385. The shielding of the axial carbon is in accord with precedence.[11] The ^{1}H NMR signal for the C-7 methylene protons of the axial isomer **14b** at 4.17 ppm is deshielded by 0.25 ppm compared to that of the equatorial isomer **15b**. These results are in excellent agreement for related pairs of isomers.[11]

Scheme III[a]



[a] In all formulas, a, R = H; b, R = Ac

Synthesis of 16, 17, and 19 (Scheme II). Hydroboration of Δ^1-THC acetate (**3b**) gave a mixture of two diols (**16a** and **17a**).[12] In these compounds the hydroxyl group on C-2 and the C-7 methyl group have to be trans, following the generally accepted hydroboration pathway. The acetates **16b** and **17b** were easily differentiated on the basis of the deshielding effect of the aromatic ring. In **17b** the proton on C-2 (δ 5.71) is in the plane of the ring (i.e., equatorial), whereas in **16b** the corresponding proton appears at δ 4.6 and is assumed to be above the aromatic ring (i.e., axial).

2-Oxohexahydrocannabinol acetate (**18**)[5] was reduced with lithium aluminum hydride to give two diols (**17a** and **19a**). Diol **17a** was shown to be identical with one of the compounds obtained on hydroboration. The structure of the second diol, **19a**, was deduced from the observation that the C-2 proton of its acetate (**19b**) resonates at δ 4.88 which is at a considerably higher field than the corresponding equatorial proton in **17b** (δ 5.71) and is, hence, axial. Diol **19a** differs from **16a**, which also has a C-2 axial proton, and is, hence, its C-1 epimer.

Synthesis of 20–23 (Scheme III). The diols **20a** and **21a** were obtained by hydroboration of Δ^6-THC acetate

(9) Compounds **12**, **13**, **14a**, and **15a** were independently prepared in small amounts for drug metabolic studies by Harvey, D. J.; Martin, B. R.; Paton, W. D. M. *J. Pharm. Pharmacol.* **1977**, *29*, 495, from compound 11 supplied by us.

(10) Recently **14a** and **15a** were obtained as a mixture. This *mixture* was found to cause cannabinoid-type effects in mice (Skinner, W. A.; Rackur, G.; Uyeno, E. *J. Pharm. Sci.* **1979**, *68*, 330).

(11) Buchanan, G. W.; Stothers, J. B. *Chem. Commun.* **1967**, 1250. Buchanan, G. W.; Stothers, J. B.; Wu, S. T. *Can. J. Chem.* **1969**, *47*, 3113.

(12) This reaction was first described by the senior author in a monograph (ref 13, p 79). Due to typographical errors in some formulas, the stereochemistry drawn there is obviously wrong. Compounds **17a** and **17b** were later synthesized by Petrzilka et al. by a different route (ref 14).

(13) Mechoulam, R., Ed. "Marijuana. Chemistry, Pharmacology, Metabolism, and Clinical Effects"; Academic Press: New York, 1973.

(14) Petrzilka, T.; Prasad K. K.; Schmid, G. *Helv. Chim. Acta* **1976**, *59*, 1963.

Table I. Psychotropic Activity of Cannabinoids Differing in Stereochemistry at C-1 Only

compd	C-1 stereochem	act. in rhesus monkey,[a] mg/kg	
7-acetoxyhexahydrocannabinol acetate (14b)	acetoxymethyl group axial	1.0 (2)[c]	–
		5.0 (3)	–
7-acetoxyhexahydrocannabinol acetate (15b)	acetoxymethyl group equatorial	0.5 (3)	+
		1.0 (3)	++
		2.0 (3)	+++
hexahydrocannabinol (1b)[b]	methyl group axial	1.0 (2)	–
		2.0 (4)	+
hexahydrocannabinol (1a)	methyl group equatorial	0.1 (2)	±
		0.5 (3)	++
		1.0 (3)	+++

[a] For test method and notation, see text and Experimental Section. [b] The separation between 1a and 1b is very difficult; hence, 1b may contain 1a as minor impurity (2-3%). [c] Numbers in parentheses indicate number of animals used.

(**2b**).[15] The diol **22** was obtained by reduction of 6-oxohexahydrocannabinol (C-7 methyl equatorial; **24**).[15] This reaction produced also **20a**. The fourth isomer in this series, diol **23**, was obtained by reduction of the known[16] 6α-hydroxy-$\Delta^{1(7)}$-THC diacetate (**25**) over palladium on charcoal, followed by reduction by lithium aluminum hydride. Diol **23** is different from the other three diols in this series (in particular diol **21**) and, by elimination, is assigned the structure indicated.

Pyschotropic Test in Rhesus Monkeys. The pyschotropic activity of cannabinoids has been tested in a number of laboratory animals, including dogs, mice, rats, and gerbils, but it has been found that the rhesus monkey represents the most suitable model.[17] A comparison of the major somatic and behavioral effects elicited by Δ^1-THC in man and in rhesus monkey shows a reasonable similarity: close threshold effective doses (ca. 50 μg/kg), dose-dependent effects, impairment of motor coordination, redness of conjunctivae, pseudoptosis, loss of muscle strength, heart rate increase, decline of aggression, sleep state, impairment of performance, etc. Some of these symptoms seem to be specific for primates.

The estimation of the pyschotropic effects is semiquantitative. These effects were monitored by the use of Norton's sheet.[18] Ratings were as follows: (–) no change; (±) tranquility; (+) drowsiness, decreased motor activity, occasional partial ptosis, occasional head drop; (++) stupor, ataxia, suppression of motor activity, full ptosis, typical crouched posture (thinker position) kept for up to 3 h (the animal can, however, regain normal behavior for short periods of time if external sensorial stimuli are applied); (+++) severe stupor and ataxia full ptosis, immobility, crouched posture lasting for more than 3 h, and absence of reaction to external stimuli.[7a] We consider a compound "nonpyschotropic" if at 5 mg/kg it fails to induce the above or any other abnormal behavioral sign.

Results and Discussion

The results are tabulated in Tables I and II using the above notation. The most striking result (Table I) is that 7-acetoxyhexahydrocannabinol acetate (**15b**), in which the C-1 substituent is equatorial, is active at 0.5 mg/kg, while the stereoisomer **14b**, in which the corresponding substituent is axial, is inactive up to 5 mg/kg. These results parallel the observations made with the corresponding hexahydrocannabinol stereoisomers **1a** and **1b**.

What is the biological significance of these results? We can only speculate that the receptor site has a stereochemical requirement, at least for the top part of the cannabinoid molecule. Archer et al.[19] have shown that the dihedral angle between the aromatic ring and cyclohexenyl ring (C-1′, C-2′, C-3, C-4 angle) in Δ^1-THC (**3a**) is 19°. It can be assumed that this angle is not significantly different in compounds **1a**, **1b**, **14a**, and **15a**. The C-1 methyl in **1a**, the C-1 acetoxymethyl in **15b**, as well as the corresponding C-1 moieties in Δ^1-THC (**2a**) and in the metabolites 7-hydroxy-Δ^1-THC (**3c**) and 7-hydroxy-Δ^6-THC (**2c**) are essentially in this near plane. All these compounds, as reported now or previously,[7] are psychotropically active. Compounds **1b** and **14b** which are psychotropically less active or inactive, respectively, differ stereochemically from **1a** and **15b** by the presence of a methyl or an acetoxymethyl group on C-1 which protrudes out of this near plane, thus possibly inhibiting the approach to a presumed receptor.[20] However, the presence of additional groups in the vicinity of the C-1 substituent changes this regularity (see below).

There is also a certain regularity in the activity of the hexahydrocannabinols hydroxylated on the cyclohexane ring (Table II). This table is arranged in a manner which facilitates a comparison between isomers which differ only in the *position* of the alicyclic hydroxyl groups (being on either C-2 or C-6) but not in the *stereochemistry* of the methyl group on C-1 nor of that of the hydroxyl group. The activity of such pairs was found to be essentially identical. Thus, the pair **16a** and **20a** (in which both the alicyclic hydroxyl group and the C-7 methyl group are equatorial) are inactive up to at least 2 mg/kg. Neither isomer in the pair **17a** and **21a** (in which both the hydroxyl group and the methyl group are axial) shows any activity up to 5 mg/kg. However, both **19a** and **23a**, in which the methyl groups are axial while the hydroxyl groups are equatorial, are active at 0.5 mg/kg.

The present results, together with those previously reported,[7] indicate that two groups of THC-type cannabinoids, which differ only in that the chemical groupings in one of them at C-1, C-2 are situated at C-1, C-6 in the other (but retain their stereochemistry), have almost equivalent psychotropic activity. Thus, Δ^1-THC (**3a**) and 7-hydroxy-Δ^1-THC (**3c**) parallel Δ^6-THC (**2a**) and 7-hydroxy-Δ^6-THC (**2c**); as shown now, **16a** and **20a**, **17a** and **21a**, and **19a** and **23** also parallel each other in psychotropic activity. A biochemical rationalization of this is not obvious at present.

Experimental Section

Pharmacology. The compounds were administered to rhesus monkeys as described previously.[17] To minimize any subjective influence in the assessment of drug effects, the observers were unaware of the nature of the compounds being tested. Two to six different animals were used for testing each compound. In some cases the same cannabinoid was tested in the same animal, but at least 1 week separated the trials. Magnitude of psychotropic

(15) Mechoulam, R.; Ben-Zvi, Z.; Varconi, H.; Samuelov, Y. *Tetrahedron* **1973**, *29*, 1615.
(16) Ben-Zvi, Z.; Mechoulam, R.; Burstein, S. *J. Am. Chem. Soc.* **1970**, *92*, 3468.
(17) Grunfeld, Y.; Edery, H. *Psychopharmacol.* **1969**, *14*, 200.
(18) Norton, S. "Psychotropic Drugs", Garatini, S.; Ghetti, V., Eds.; Elsevier: Amsterdam, 1957; p 73.
(19) Archer, R. A.; Boyd, D. B.; Demarco, P. V.; Tyminski, I. J.; Allinger, N. L. *J. Am. Chem. Soc.* **1970**, *92*, 5200.
(20) For a discussion of the inactivity of $\Delta^{1(7)}$-THC, see Binder, M.; Edery, H.; Porath, G. "Marihuana: Biological Effects"; Nahas, G. G.; Paton, W. D. M., Eds.; Pergamon Press: Oxford, 1979; p 71.

Table II. Psychotropic Activity of Stereochemical Pairs of Hydroxyhexahydrocannabinols (OH-HHC)

compd	stereochem of OH and CH_3 groups	act., mg/kg		act., mg/kg		stereochem of OH and CH_3 groups	compd
2-OH-HHC (16a)	2α-OH (equat) 1β-CH_3 (equat)	1.0 (2)[a]	–	1.0 (3)[a]	–	6α-OH (equat) 1β-CH_3 (equat)	6-OH-HHC (20a)
		2.0 (3)	–	2.0 (3)	–		
		5.0 (3)	+	5.0 (3)	–		
2-OH-HHC (17a)	2β-OH (ax) 1α-CH_3 (ax)	1.0 (3)	–	1.0 (2)	–	6β-OH (ax) 1α-CH_3 (ax)	6-OH-HHC (21a)
		5.0 (4)	–	5.0 (3)	–		
				0.25 (2)	–		
2-OH-HHC (19a)	2α-OH (equat) 1α-CH_3 (ax)	0.5 (3)	+	0.5 (3)	+	6α-OH (equat) 1α-CH_3 (ax)	6-OH-HHC (23a)
		1.0 (3)	++	1.0 (4)	++		
		2.0 (4)	++				
Δ^1-THC (3a)[b]		0.05 (4)	+	0.1 (3)	±		Δ^6-THC (2a)[b]
		0.1 (3)	++	0.25 (4)	+		
		0.25 (3)	++	0.5 (4)	++		

[a] Numbers in parentheses indicate number of animals used. [b] Tabulated for comparison purposes.

activity was compared with that of the reference compounds Δ^1-THC (**3a**) and Δ^6-THC (**2a**) and rated as described above. The solvent used was propylene glycol, except for compound **17** which was dissolved in dimethyl sulfoxide. Injections were made into one of the saphenous veins at a maximum volume of 0.1 mL/kg. This amount of solvent did not cause any noticeable changes in control animals. The results are presented in Tables I and II.

Chemistry. The IR spectra were recorded on Perkin-Elmer instruments, Models 137 and 577; the NMR spectra were measured on JEOL-60H, Brucker 90-MHz, JEOL miNiMaR-100, and Brucker 270-MHz instruments; UV spectra were measured on a Unicam S.P. 800 or a Varian Techtron Model 635 spectrometer; mass spectra (MS) were determined on a Varian Mat-CH-5/DF instrument. Gas chromatography was conducted on a Packard Model 803 with a flame-ionization detector on glass columns. Thin-layer chromatography (TLC) was performed on silica gel chromatoplates. Microanalyses were made on the crystalline compounds only, as most oily cannabinoids described herein retain solvents tenaciously and cannot be distilled for analysis at high vacuum due to partial degradation.

Hydrogenation of Δ^6-THC-7-oic Acid Methyl Ester Acetate (11). A mixture of **11** (907 mg, 2.3 mmol) and 10% palladium on carbon in ethyl acetate (30 mL) was shaken under hydrogen at 3 atmospheric pressures for 5 days. After the catalyst and the solvent were removed, the residue was chromatographed on silica gel (170 g). Elution with 10% ether in light petroleum ether gave two products. The more polar one was shown to be the oily hexahydrocannabinol-7-oic acid methyl ester (equatorial) acetate (**13**; 309 mg, 34%): MS, m/e 402 (M^+); $[\alpha]_D$ -208.3° (EtOH); UV λ_{max} 277 nm (ϵ 1651), 284 (1773); IR ($CHCl_3$) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3, ω-CH_3), 1.07 (s, 3, CH_3) 1.38 (s, 3, CH_3), 1.94 (br d, 1, C-3), 2.30 (s, 3, OAc), 2.50 (t, 2, benzylic), 2.97 (br d, 1, C-2), 3.69 (s, 3, OCH_3), 6.40 (d, 1, J = 2 Hz) (aromatic protons). The less polar one was shown to be hexahydrocannabinol-7-oic acid methyl ester (axial) acetate (**12**; 493 mg, 54.2%): MS, m/e 402 (M^+); $[\alpha]_D$ -190° (EtOH); UV (EtOH) λ_{max} 277 nm (ϵ 1569), 284 (1727); IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3, ω-CH_3), 1.04 (s, 3, CH_3), 1.35 (s, 3, CH_3), 1.77 (br, d, 1, C-3), 2.36 (s, 3, OAc), 2.48 (t, 2, benzylic), 3.18 (br d, 1, C-2), 3.73 (s, 3, OCH_3), 6.38 (d, 1, J = 2 Hz), 6.53 (d, 1, J = 2 Hz) (aromatic protons).

7-Hydroxyhexahydrocannabinol (15a). Compound **13** (214 mg, 0.5 mmol) in dry ether (10 mL) was slowly added to a suspension of lithium aluminum hydride (1 g, 26 mmol) in dry ether (30 mL). The mixture was boiled under reflux for 2 h under nitrogen. Ethyl acetate (3 mL), water, and ether (50 mL) were added. The organic layer was dried and evaporated to give 169 mg (96%) of 7-hydroxyhexahydrocannabinol (hydroxymethyl group equatorial) (**15a**): MS, m/e 332 (M^+); $[\alpha]_D$ -87.5° (EtOH); UV (EtOH) λ_{max} 275 nm (ϵ 1212), 282 (1185); IR ($CHCl_3$) 3600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82, 1.02, 1.22, 1.33 (s, CH_3 groups), 2.35 (br d, C-3 H), 3.48 (d, 2, J = 6 Hz, C-7 H), 6.06 (d, 1, J = 2 Hz), 6.21 (d, 1, J = 2 Hz) (aromatic protons).

Acetylation of **15a** with acetic anhydride in pyridine gave the acetate **15b**: MS, m/e 416 (M^+); $[\alpha]_D$ -83.6° (EtOH); UV (EtOH) λ_{max} 276 nm (ϵ 471), 282 (498); IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3, ω-CH_3), 1.07, 1.25, 1.37 (methyl groups), 2.07 (s, 3, OAc), 2.28 (s, 3, OAc), 2.49 (t, 2, benzylic), 2.76 (br d, 1, C-2), 3.92 (octet, 2, C-7 H), 6.28 (d, J = 2 Hz), 6.54 (d, J = 2 Hz); ^{13}C NMR δ 68.385 (C-7 H).

7-Hydroxyhexahydrocannabinol (14a). Compound **12** was reduced with lithium aluminum hydride and worked up as described above to give 7-hydroxyhexahydrocannabinol (hydroxymethyl group axial) (**14a**): MS, m/e 332 (M^+); $[\alpha]_D$ -95.8° (EtOH); UV (EtOH) λ_{max} 276 nm (ϵ 1940), 282 (1790); IR ($CHCl_3$) 3600 (OH) cm^{-1}; ^1H NMR δ ($CDCl_3$) 0.83, 0.95, 1.20, 1.35 (methyl groups), 2.29 (br d, J = 7 Hz, C-3 H), 3.70 (m, 2, C-7 H), 6.04, 6.14 (d, J = 2 Hz aromatic).

Acetylation of **14a** gave **14b**: MS, m/e 416 (M^+); $[\alpha]_D$ -98.7° (EtOH); UV (EtOH) λ_{max} 276 nm (ϵ 583), 281 (613); IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87, 1.05, 1.37 (methyl groups), 2.08, 2.31 (OAc groups), 2.48 (t, 2, benzylic H), 2.65 (br, d, C-2 H), 4.17 (double quartet, 2, C-7 H), 6.37, 6.53 (d, J = 2 Hz) (aromatic); ^{13}C NMR δ 65.535 (C-7).

Reduction of 18 with Lithium Aluminum Hydride. Compound **18** (120 mg, 0.32 mmol) was dissolved in dry ether (25 mL). Lithium aluminum hydride (50 mg) was slowly added. The mixture was boiled under reflux for 3 h. Ethyl acetate (2 mL), water, and ether (50 mL) were added. The organic layer was dried and evaporated. The residue obtained was purified on preparative TLC to give two products. The less polar one was shown to be 2α-hydroxyhexahydrocannabinol (C-1 methyl group α, axial) (**19a**; 36 mg, 34%): MS, m/e 332 (M^+); $[\alpha]_D$ -94.1° (EtOH); UV (EtOH) λ_{max} 282 (ϵ 1470), 286 (1545); IR ($CHCl_3$) 3210, 1630, 1570, 1590, 1390 cm^{-1}; ^1H NMR δ ($CDCl_3$) 0.88, 1.03, 1.14, 1.34 (methyl groups), 3.90 (dd, $J_{1,2}$ = 4 Hz, $J_{2,3}$ = 10 Hz, C-2), 6.22, 6.30 (d, J = 2 Hz) (aromatic). The more polar one is 2β-hydroxyhexahydrocannabinol (C-1 methyl group α, axial) (**17a**; 46 mg, 43%): mp 218 °C; NMR, MS, TLC, and mp identical with those of **17a** obtained previously by Petrzilka et al.[14]

Acetylation of **19a** gave the acetate **19b** an oil: MS m/e 416 (M^+); $[\alpha]_D$ -122.7° (EtOH); IR ($CHCl_3$) 2920, 1725, 1625, 1560, 1370, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) 0.88, 1.00, 1.05, 1.22, 1.37 (methyl groups), 2.10, 2.29 (OAc groups), 4.88 (dd, 1, $J_{1,2}$ = 4.4 Hz, $J_{2,3}$ = 9 Hz, C-2 H), 6.35, 6.53 (d, J = 2 Hz) (aromatic). Acetylation of **17a** gave **17b**. Acetate **17b** thus obtained had NMR, MS, and TLC identical with those of **17b** obtained previously by Petrzilka et al.[14]

Hydroboration of Δ^1-THC Acetate (3b). Δ^1-THC acetate (**3b**; 3.5 g, 9.8 mmol) was dissolved in dry THF (40 mL). The solution was cooled in an ice bath. A solution (2.5 mL, 2 M) of diborane was injected and the mixture was stirred for 1 h under nitrogen. Then it was brought to room temperature, stirred for an additional hour, and water (15 mL) was added, followed by a solution of 3 N NaOH (7 mL) and then a solution of 30% H_2O_2 (7 mL). The solution was stirred for 15 min, extracted with ether, dried and evaporated. The oil obtained was chromatographed on silica gel (320 g). Elution with ether–light petroleum ether (1:1) gave 2α-hydroxyhexahydrocannabinol (C-1 methyl group β, equatorial) (**16a**): mp 86 °C; MS, m/e 332 (M^+); $[\alpha]_D$ -143.9° (EtOH); UV (EtOH) λ_{max} 279 nm (ϵ 1100), 285 (1130); IR (CCl_4) 3500, 3030, 1640, 1580 cm^{-1}; ^1H NMR δ ($CDCl_3$) 0.87, 0.98, 1.09, 1.34 (methyl groups), 3.3 (t, 1, $J_{1,2}$ = 9 Hz, $J_{2,3}$ = 9 Hz, C-2 H), 6.23, 6.28 (aromatic). Anal. ($C_{21}H_{32}O_3$) C, H. A second compound eluted was shown to be **17a**, described above (mp, NMR, IR).

Acetylation of **16a** gave **16b**, an oil: MS, m/e 416 (M^+); $[\alpha]_D$ -169° (EtOH); UV (EtOH) λ_{max} 278 nm (sh, ϵ 2180), 284 (2390); IR (CCl_4) 1730 cm^{-1}; ^1H NMR δ ($CDCl_3$) 0.88, 0.95, 1.01, 1.38 (methyl groups), 2.14, 2.28 (OAc groups), 4.6 (t, $J_{1,2}$ = 9 Hz, $J_{2,3}$ = 9 Hz, C-2 H), 6.31, 6.53 (d, J = 2 Hz) (aromatic).

6α-Hydroxyhexahydrocannabinol (23a). Compound **25**[16] (100 mg) in ethyl acetate (5 mL) was reduced with hydrogen at 3 atmospheric pressures over Adam's catalyst (20 mg). The solution was filtered and evaporated to dryness. The oil obtained (**23b**) showed one spot on TLC. It was reduced without prior purification with lithium aluminum hydride, following the procedure and workup described above. 6α-Hydroxyhexahydrocannabinol (C-1 methyl group α, axial) (**23a**) was obtained as an oil: MS, m/e 332 (M^+); $[\alpha]_D$ -85.4° (EtOH); ^1H NMR δ ($CDCl_3$) 0.87, 1.09, 1.27, 1.36 (methyl groups), 3.92 (br s, 1, C-6 H), 6.05, 6.23 (d, J = 2 Hz) (aromatic).

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Fluoroprostaglandins: Synthesis and Biological Evaluation of the Methyl Esters of (+)-12-Fluoro-, (-)-*ent*-12-Fluoro-, (+)-15-*epi*-Fluoro-, and (-)-*ent*-15-*epi*-12-Fluoroprostaglandin $F_{2\alpha}$

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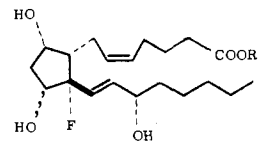
The synthesis and biological activity of the methyl esters of (+)-12-fluoroPGF$_{2\alpha}$, (+)-15-*epi*-12-fluoroPGF$_{2\alpha}$, (-)-*ent*-12-fluoroPGF$_{2\alpha}$, and (-)-*ent*-15-*epi*-12-fluoroPGF$_{2\alpha}$ are described. Each fluoroprostaglandin has been evaluated from pregnancy interruption in the hamster and smooth-muscle stimulating effects on gerbil colon and hamster uterine strips. All fluoroprostaglandins synthesized were shown to be neither substrates for the 15-hydroxyprostaglandin dehydrogenase nor inhibitors of the enzyme.

Our interest in developing luteolytic prostaglandins devoid of smooth-muscle stimulating activity led us some years ago to undertake the synthesis of ring-fluorinated derivatives of natural PGF$_{2\alpha}$.[1] The rationale behind incorporating fluorine atoms into the prostaglandin nucleus was, in part, based on the early observation by Fried and Sabo[2] who demonstrated that substantial enhancement of biological activity can be realized by substituting fluorine atoms for protons in biologically active substances. We were also cognizant of the possibility that analogues of natural PGF$_{2\alpha}$ possessing strategically placed fluorine atoms might not only exhibit prostaglandin-like activity but, more importantly, be more resistant to metabolic deactivation.

In order to probe the effect on biological activity of introducing a fluorine atom into the C(12) position of natural PGF$_{2\alpha}$, we set out to prepare and evaluate the methyl esters of 12-fluoroPGF$_{2\alpha}$ (**1a**), 15-*epi*-12-fluoroPGF$_{2\alpha}$ (**2a**), *ent*-12-fluoroPGF$_{2\alpha}$ (**3a**), and *ent*-15-*epi*-12-fluoroPGF$_{2\alpha}$ (**4a**). Despite numerous published reports during the last decade describing syntheses of prostaglandin analogues,[3] accounts detailing work relating to fluorinated prostaglandins have been few.[4] We detail below the synthetic routes to the four ring-fluorinated prostaglandins **1b**–**4b** and present the biological results which have primarily been concerned with pregnancy interruption in the hamster and smooth-muscle stimulating effect on gerbil colon and hamster uterine strips.



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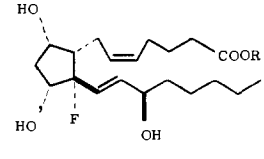

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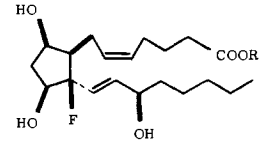

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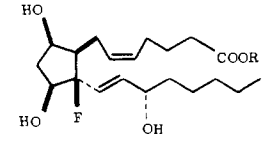
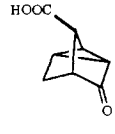


4a R = H; 4b R = Me

Chemistry. Fluoro analogues **1b** and **2b** were synthesized from (+)-*anti*-5-carboxytricyclo[2.2.1.0^{2,6}]heptan-3-one (**2**),[5] $[\alpha]_D$ +81.8° (dioxane), which was obtained in optically pure form by resolution of racemic **2** with



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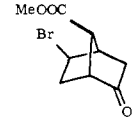

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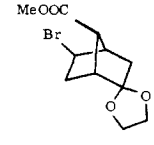

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(-)-α-methylbenzylamine. Addition of hydrobromic acid

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