THE SYNTHESIS OF DEUTERIUM, CARBON–14, AND CARRIER-FREE TRITIUM LABELED CANNABINOIDS

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SUMMARY

1',2'-Dehydroolivetol and its monomethyl ether, 5'-bromoolivetol, and olivetol-5'-$^{2}H_{3}$, have been synthesized. Acid catalyzed condensation of the latter three compounds with p-mentha-2,8-dien-1-ol gave 1',2'-dehydro-Δ^{8}-THC methyl ether, 5'-bromo-Δ^{8}-THC, and Δ^{9}-THC-5'-$^{2}H_{3}$, respectively. 5'-Bromo-Δ^{8}-THC served as a precursor of 4',5'-dehydro-Δ^{8}- and Δ^{9}-THC, 4'- and 5'-hydroxy-Δ^{8}-THC, 5'-dimethylamino-Δ^{8}-THC and 5'-carboxy-Δ^{8}-THC. Reduction of 4',5'-dehydro-Δ^{8}- and Δ^{9}-THC in the presence of homogeneous catalysts afforded tritium labeled Δ^{8}-THC (50 Ci/mmole) and Δ^{9}-THC (58 Ci/mmole), respectively. Syntheses of Δ^{9}-THC-11-$^{2}H_{3}$, Δ^{9}-THC-11-^{14}C, cannabinol-5'-$^{2}H_{3}$, and other labeled cannabinoids are described.

INTRODUCTION

The determination of drugs and their metabolites in vivo requires analytical methods capable of detecting amounts in the nanogram to picogram range. Both radioimmunoassay[1] and mass spectrometric AVA techniques[2] provide this sensitivity if appropriate isotopically labeled standards are available. As part of a program to utilize these techniques for the analysis of marihuana, we have developed methods of synthesis of isotopically pure deuterium and tritium labeled Δ^{8}- and Δ^{9}-tetrahydrocannabinol (THC, 3a, 5a). This work has also provided access to other labeled cannabinoids and metabolites, and a novel hapten.

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SYNTHETIC METHODS AND RESULTS

Tritium Labeled Δ^8- and Δ^9-THC

Since the sensitivity of the radioimmunoassay technique is proportional to the specific activity of the radiolabeled drug, a synthesis of carrier-free tritium labeled Δ^8- and Δ^9-THC was desirable. None of the published methods[3] of tritium labeling cannabinoids is suitable for this purpose, involving either exchange procedures or carrying a labeled precursor through a number of chemical transformations and difficult chromatographic purifications. Ideally, carrier-free labeling requires a method of introducing tritium (as T_2) quantitatively and specifically at a non-labile site in the last step of a chemical synthesis. To this end, the synthesis and selective reduction of 4',5'-dehydro derivatives of Δ^8- and Δ^9-THC (3b, 5b) have been studied, taking advantage of the fact that the trisubstituted double bonds of Δ^8- and Δ^9-THC are relatively inert to catalytic hydrogenation.

The synthetic route to 3b and 5b is summarized in Scheme 1. The Wittig reaction of 3,5-dimethoxybenzaldehyde and 4-phenoxybutylidenetriphenylphosphorane afforded 2a as a mixture of cis and trans isomers in 60-80% yield. Hydrogenation of the side chain double bond of 2a in the presence of palladium on charcoal was quantitative. Treatment of 2b with an excess of boron tribromide served to cleave all three ether groups and gave 5'-bromoolivetol (2c) in 98% yield. Utilizing a standard method of constructing the THC skeleton[4], condensation of 2c with p-mentha-2,8-dien-1-ol in the presence of p-toluenesulfonic acid gave 5'-bromo-Δ^8-THC (3c) in 35% yield. Conversion of 3c to its hydrogen chloride adduct 4, and treatment with an excess of potassium triethylcarbinolate effected introduction of both the 4',5' and 9,10 double bonds, the latter being formed more rapidly by an intramolecular process.[5] The product, 4',5'-dehydro-Δ^9-THC (5b), was obtained in 54% yield after chromatographic purification.

The synthesis of 4',5'-dehydro-Δ^8-THC (3b) proved somewhat more difficult. Treatment of 5'-bromo-Δ^8-THC (3c) with an excess of potassium

triethylcarbinolate in benzene gave 3b (61%) contaminated with two difficultly separable isomers (25 and 14%). The major isomeric impurity was identified as 6 after the elimination reaction was repeated using one equivalent of alkoxide. In this case 6 was the major product (6/3b=6) and must be formed by intramolecular C-alkylation[6] of the phenolate ion of 3c. Several other dehydrohalogenating agents were examined in an attempt to minimize the formation of 6. Trimethylstannyldimethylamine[7] gave only 5'-dimethylamino-Δ^8-THC (3d) via a metathetical reaction, and 1,5-diazobicyclo-[5.4.0]-undec-5-ene[8] also failed to give 3b. Potassium tert-butoxide in dimethylsulfoxide gave a 4:1 mixture of 3b and 5'-tert-butoxy-Δ^8-THC (3e), from which 3b was isolated in 27% yield. 3b was best obtained indirectly by isomerization of 5b using 1% $BF_3.Et_2O$ in benzene (25°, 3 hr, 100% yield).

As a prelude to tritiation, 4',5'-dehydro-Δ^9-THC in benzene was reduced with deuterium in the presence of tris(triphenylphosphine)rhodium (I) chloride.[9] Regiospecific incorporation of deuterium in the product, Δ^9-THC-4',5'-$^2H_2$, was confirmed by mass spectroscopic (2.7% d_3, 96.9% d_2, 0.3% d_1, 0.2% d_o) and nmr spectroscopic analysis, the 5'-methyl group appearing as a broad two proton singlet at 0.86 ppm. There was no evidence of reduction of the trisubstituted 9,10-double bond. Repetition of the catalytic reduction using carrier-free tritium gas gave pure Δ^9-THC-$^3H_2$, specific activity 58 Ci/mmole.

Surprisingly, the tris(triphenylphosphine)rhodium (I) chloride catalyzed reduction of the vinyl group of 4',5'-dehydro-Δ^8-THC (3b) could not be accomplished without concomitant reduction of the trisubstituted 8,9-double bond. The reactivity of the 8,9-double bond was confirmed by establishing that Δ^8-THC was partially reduced to hexahydrocannabinol under the same conditions. However, complete saturation of the 8,9-double bond did not occur, the reduction generally stopping after 30-50% completion. It was then established that quantitative reduction could be accomplished by the introduction of catalytic amounts of air. This suggested that oxygen activation of the catalyst[10] was responsible for the reduction of

the 8,9-double bond, although rigorous degassing of benzene solutions of 4',5'-dehydro-Δ^8-THC failed to eliminate this unwanted reaction entirely. Interestingly, the hexahydrocannabinol produced by reduction of the 8,9-double bond proved to be the 11-equatorial isomer. Heterogeneously catalyzed hydrogenation of Δ^8- and Δ^9-THC is known to give a difficultly separable mixture of equatorial and axial isomers.[11,12]

Regiospecific reduction of the 4',5'-double bond of 4',5'-dehydro-Δ^8-THC was accomplished by utilizing the more selective homogeneous catalyst, hydridochlorotris(triphenylphosphine)ruthenium(II),[13] although at the expense of some scrambling of the label in the side chain (see experimental). Reduction with carrier-free tritium under the same conditions gave Δ^8-THC-^3H with a specific activity of 50 Ci/mmole.

The possibility of labeling Δ^8-THC by reduction of 1',2'-dehydro derivatives was also explored. Although condensation of 1',2'-dehydroolivetol monomethyl ether with p-mentha-2,8-dien-1-ol gave 1',2'-dehydro-Δ^8-THC methyl ether, which could be selectively reduced to Δ^8-THC methyl ether, the analogous synthesis of 1',2'-dehydro-Δ^8-THC from 1',2'-dehydroolivetol proved impractical.[14]

Deuterium Labeled Cannabinoids

The synthesis of Δ^9-THC-4',5'-$^2H_2$ by catalytic deuteration of 4',5'-dehydro-Δ^9-THC has already been described in the preceding section. Trideuteration of Δ^8- and Δ^9-THC at C-11 was accomplished by oxidation of $\Delta^{9(11)}$-THC acetate (7a) to the ketone 7b,[15] followed by treatment with methyl-$^2H_3$-magnesium iodide. Conversion of the resulting tertiary carbinol 7c to the corresponding chloride 7d and intramolecularly assisted dehydrohalogenation[5] then gave Δ^9-THC-11-$^2H_3$. Acid catalyzed isomerization of Δ^9-THC-11-$^2H_3$ gave Δ^8-THC-11-$^2H_3$. While treatment of Δ^9-THC-11-$^2H_3$ with sulfur[4a] at 200°C afforded cannabinol-$^2H_3$ (8), extensive hydrogen-deuterium scrambling was observed.

Two other deuterated standards required for AVA analysis of marihuana are 11-hydroxy-Δ^9-THC (9a)[16] and the corresponding carboxylic acid (9b),[17]

these compounds being important metabolites of Δ^9-THC in man. Various considerations, including the need to introduce three or more deuterium atoms,[18] ruled out labeling C-11. A method of multiple labeling of the pentyl side chain was therefore developed.

The reaction of 3,5-dimethoxybenzaldehyde with the Wittig reagent from methyl γ-bromocrotonate gave 10a in 53% yield. Catalytic hydrogenation gave 10b. Reduction of the ester with $LiAlD_4$ gave 10c, which was converted to the bromide 10d and again treated with $LiAlD_4$. The product 10e was converted to olivetol-5'-$^2H_3$ with boron tribromide. Other sites in the side chain could be labeled by varying this sequence of reactions.

Using established syntheses,[4,5,19] olivetol-5'-$^2H_3$ was converted to Δ^9-THC-5'-$^2H_3$, cannabinol-5'-$^2H_3$, and 11-hydroxy-Δ^9-THC-5'-$^2H_3$.

Carbon-14 Labeled Δ^8- and Δ^9-THC

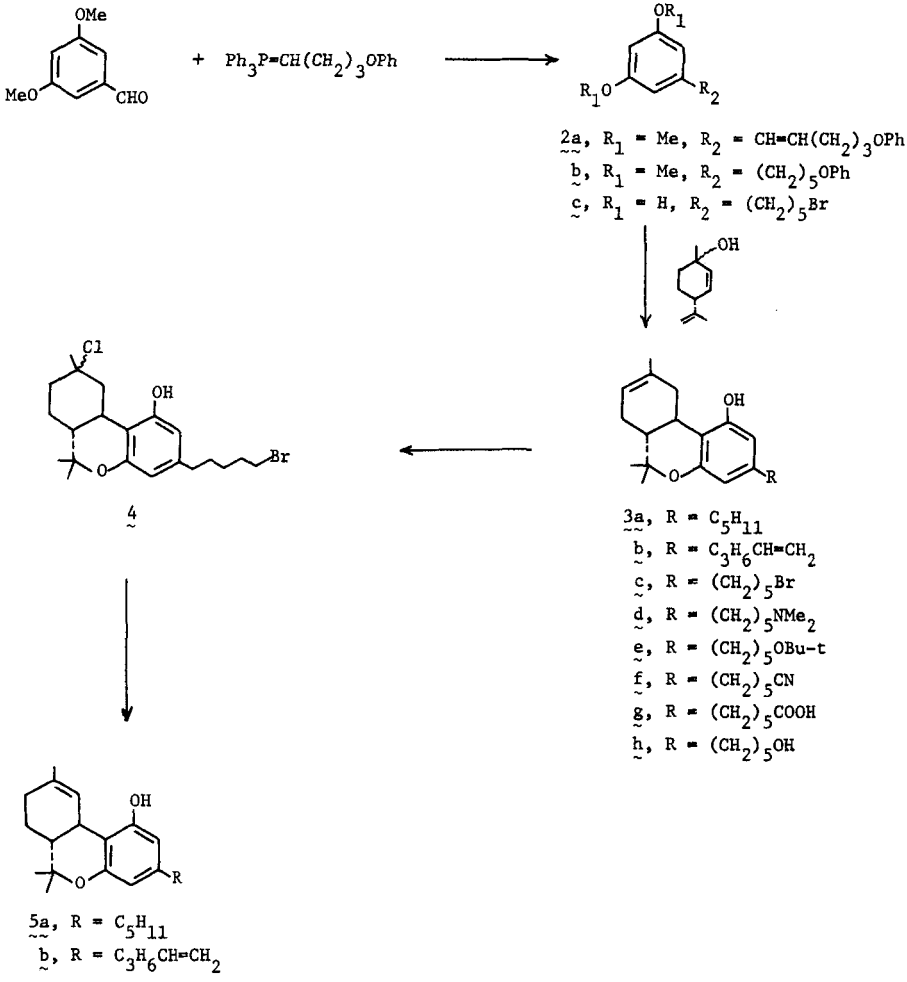
Carbon-14 labeled cannabinoids have been synthesized previously by several different methods,[16b,20-22] including the reaction of methyl-^{14}C-magnesium iodide with 9-keto-11-norhexahydrocannabinol.[22] The latter method alone has the advantage of introducing the label at a late stage in the synthesis, although labeled Grignard reagent is not easily handled on a small scale and an excess is required to neutralize the phenolic hydroxyl group. We have independently adopted the same approach, but utilized the Wittig reaction of methylene-^{14}C-triphenylphosphorane with 7b because of the experimental simplicity and the more efficient utilization of label. The product, 7a-11-^{14}C, was then converted to Δ^9-THC-11-^{14}C by treatment of the hydrogen chloride adduct with potassium triethylcarbinolate.[5a] Acid catalyzed isomerization gave Δ^8-THC-11-^{14}C.

Other Cannabinoid Derivatives from 5'-Bromo-Δ^8-THC

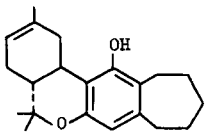
5'-Carboxy-Δ^8-THC-5'-^{14}C. This compound was prepared for use as a hapten for the radioimmunoassay of cannabinoids by treatment of 5'-bromo-Δ^8-THC with sodium cyanide-^{14}C in dimethylsulfoxide, followed by hydrolysis of the resulting 5'-nitrile.

4'- and 5'-Hydroxy-Δ^8-THC. These compounds were synthesized as standards for the spectroscopic identification[23] of cannabinoid metabolites derived

from hydroxylation of the pentyl side chain. 5'-Hydroxy-Δ^8-THC was prepared for the 5'-bromide 3c by acetolysis with tetramethylammonium acetate in acetone followed by deacetylation with $LiAlH_4$. 4'-Hydroxy-Δ^8-THC was obtained by conversion of 4',5'-dehydro-Δ^9-THC acetate to its bis-epoxide 11, reduction to the triol 12 with $LiAlH_4$, and selective dehydration of the tertiary hydroxyl group.



Scheme 1. Synthesis of 4',5'-Dehydro-Δ^8- and Δ^9-THC



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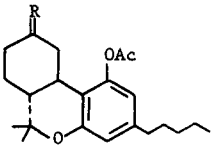
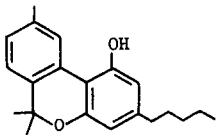


7a, R = CH_2
b, R = O
c, R = CD_3, OH
d, R = CD_3, Cl



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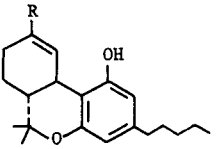
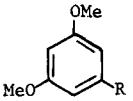
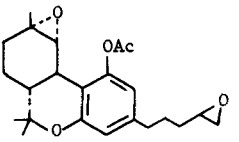


9a, R = CH_2OH
b, R = COOH



10a, R = CH=CH·CH=CH·COOMe
b, R = $(CH_2)_4COOMe$
c, R = $(CH_2)_4CD_2OH$
d, R = $(CH_2)_4CD_2Br$
e, R = $(CH_2)_4CD_3$



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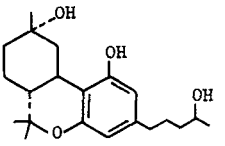

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EXPERIMENTAL SECTION

Infrared spectra were measured using Perkin Elmer Model 267 and 467 spectrophotometers. Nmr spectra were obtained using a Varian HA-100 spectrometer with samples dissolved in deuteriochloroform or deuterio-

acetone (internal standard tetramethylsilane). Mass spectroscopic analyses were carried out using either an AEI MS-9A spectrometer or a Varian CH-7 combined glc mass spectrometer. Gas-liquid chromatographic analyses were performed using a Varian Model 1400 instrument, with columns (5' x 1/16") containing 1.4% OV-17 on Chromosorb W-HP. Precoated silica gel 60 F-254 (Merck) plates were employed for tlc analysis. High pressure liquid-solid chromatography was carried out using Chromatronix equipment. Radio-purity was detemined using a radio-scanner (Autochrom LB2722). Silver nitrate impregnated silica gel was prepared by mixing silica gel (450 g., Mallinckrodt, 100 mesh) with silver nitrate (125 g) in water (200 ml) and methanol (550 ml), the majority of solvent then being removed at ca. 30 Torr using a Buchler rotary evaporator. Further drying was carried out at <1 Torr.

Solvents were dried over 3A molecular sieve before use, and the majority of reactions were carried out under an atmosphere of dry nitrogen. Unlabeled Δ^8- and Δ^9-THC and p-mentha-2,8-dien-1-ol (cis, trans mixture) were kindly supplied by the National Institute on Drug Abuse.

1-(3',5'-Dimethoxyphenyl)-5-phenoxypent-1-ene (2a).... A solution of 4-phenoxybutyl bromide (7.90 g, 34.5 mmoles) and triphenylphosphine (9.50 g, 36.3 mmoles) in benzene (25 ml) were stirred and refluxed for 36 hr. The precipitate was filtered, washed with benzene, and dried, to give 16.1 g (92%) of 4-phenoxybutyltriphenylphosphonium bromide, m.p. 180-181° (capill.).

To a stirred slurry of 4-phenoxybutyltriphenylphosphonium bromide (11.0 g, 22.4 mmoles) in dry ether (25 ml) at 0°C was slowly added 12.5 ml (22.5 mmoles) of a 1.85M solution of n-butyl lithium in hexane. The deep red suspension was stirred for 30 min at 0°C, when 3,5-dimethoxybenzaldehyde (3.74 g, 22.5 mmoles) in ether (25 ml) was added. The nearly colorless solution was allowed to warm to room temperature, and then refluxed for 2 hr. The ether was removed in vacuo and the residual solid was extracted with three 50 ml portions of refluxing benzene. The combined benzene extracts was concentrated and distilled, to give 4.07 g (61%) of 2a as

a colorless oil, bp 135-140°C (0.025 mm), pure by tlc, but a 2:1 mixture of cis, trans isomers by glc. NMR ($CDCl_3$) 1.94 (q, J=7Hz, 2H, 4-CH_2), 2.3-2.7 (m, 2H, 3-CH_2), 3.75 (s, 6H, OMe), 3.99 (t, J=7Hz, 2H, 5-CH_2), 6.2-7.4 (m, 10H, ArH, CH=CH); $\nu_{max}^{CCl_4}$ 2830 (OMe), 1590 (Ar) cm^{-1}. Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43, m/e 298.1568; Found: C, 76.35; H, 7.24; m/e 298.1565.

1-(3',5'-Dimethoxyphenyl)-5-phenoxypentane (2b).... A solution of 2a (3.75 g) in ethanol (60 ml) was shaken overnight with 10% palladium on carbon (500 mg) under a hydrogen atmosphere (40 psi). After filtration of the catalyst and concentration in vacuo, 2b (3.56 g) was obtained as a colorless oil, homogeneous by tlc and glc. Nmr ($CDCl_3$): 1.4-1.9 (m, 6H, $(CH_2)_3$), 2.58 (t, J=7Hz, 2H, 1-CH_2), 3.72 (s, 6H, OMe), 3.93 (t, J=7Hz, 2H, 5-CH_2), 6.2-7.5 (m, 8H, ArH); $\nu_{max}^{CCl_4}$ 2835 (OMe), 1600 (Ar) cm^{-1}; Calcd. for $C_{19}H_{24}O_3$: C, 76.00; H, 8.10; m/e 300.1725; Found: C, 76.17; H, 8.14; m/e 300.1718.

1-(3',5'-Dihydroxyphenyl)-5-bromopentane (2c).... Boron tribromide (3 g, 12 mmoles) in benzene (30 ml) was added to a solution of 2b (3.46 g, 11.5 mmoles) in benzene (80 ml) at 5-10°C. The mixture was stirred at room temperature, the extent of reaction being followed by glc. Selective loss of the phenoxy group was observed after 1 hr. Loss of the two methoxy groups was complete at 80 hr, after adding a further 2 g (20 hr) and 1 g (40 hr) of boron tribromide. Unchanged boron tribromide was destroyed by addition of iced water, and the benzene phase was washed with 5% aqueous sodium sulfite, water, and brine. Phenol was removed by addition of water (100 ml) to a solution of the concentrate in acetone (10 ml), and extraction with benzene. After drying (Na_2SO_4) and concentrating the solution, 2c (3.05 g, 102%) remained as a brown oil, pure by tlc and glc. NMR ($CDCl_3$): 1.2-1.9 (m, 6H, $(CH_2)_3$), 2.38 (t, J=7Hz, 2H, 1-CH_2), 3.31 (t, J=7Hz, 2H, 5-CH_2), 6.22 (s, 3H, ArH); $\nu_{max}^{CHCl_3}$ 3600, 3350 (br) cm^{-1} (OH). Calcd. m/e for $C_{11}H_{15}BrO_2$: 258.0256, 260.0236. Found: 258.0262, 260.0228. An attempt to distill this product in a bulb to bulb still at 170° (0.05 mm) led to decomposition.

The use of hydrogen bromide in refluxing glacial acetic acid, in place

of boron tribromide, resulted in dehydrohalogenation as well as cleavage of the methoxy and phenoxy groups of 2b.

5'-Bromo-Δ^8-THC (3c).... A stirred mixture of p-mentha-2-dien-1-ol (3.867 g, 25.27 mmoles), 2c (5.234 g, 20.22 mmoles), and p-toluenesulfonic acid monohydrate (0.645 g, 3.39 mmoles) in benzene (150 ml) was refluxed for 4 hr, when tlc and glc showed the reaction was complete. The mixture was extracted with aq. sodium bicarbonate, water, and dried (Na_2SO_4). The solvent was removed in vacuo and the residual oil (7.533 g) was eluted from florisil (700 g) using a hexane/benzene gradient. The desired product (2.627 g, 33%), was eluted with 50% hexane in benzene as a colorless oil, pure by tlc and glc; nmr ($CDCl_3$): 1.07, 1.35 (ss, 6H, CMe_2), 1.67 (br.s, 11-Me), 2.41 (t, J=7Hz, 1'-CH_2), 3.35 (t, J=7Hz, 2H, 5'-CH_2), 5.27 (s, 1H, OH), 5.41 (br.s, 1H, CH=C), 6.05, 6.25 (ss, 2H, ArH); $\nu_{max}^{CCl_4}$ 3600 (OH), 1550, 1625 (Ar) cm^{-1}; λ_{max}^{hexane} 275 (1090), 282 (1150) nm; Calcd. m/e for $C_{21}H_{29}BrO_2$: 394.1331, 392.1351. Found: 394.1327, 392.1347.

4',5'-Dehydro-Δ^9-THC (5b).... Dry hydrogen chloride was passed through a stirred solution of 3c (530 mg, 1.35 mmoles) in methylene chloride (40 ml) containing freshly fused zinc chloride (200 mg) for 30 min. The mixture was stirred at room temperature for 6 hr before diluting with methylene chloride (30 ml) and washing with iced-water, aq. sodium bicarbonate, and brine. The solution was dried (Na_2SO_4) and concentrated in vacuo, to leave 570 mg (100%) of 4; nmr ($CDCl_3$) 1.10, 1.36 (ss, 6H, CMe_2), 1.64 (s, 3H, 11-CH_3), 2.43 (t, J=7Hz, 1'-CH_2), 3.06 (t, J=10Hz, 1H, 10α-H), 3.36 (t, J=7Hz, 2H, 5'-CH_2), 6.05, 6.22 (ss, 2H, ArH). A solution of 4 (560 mg) in benzene (5 ml) was stirred with 0.15M potassium triethylcarbinolate in toluene (60 ml, 4.0 mmoles) at 35-40°C for 15 hr, and then at 55-60°C for 4 hrs. The reaction mixture was diluted with benzene (30 ml), and reduced to pH 8 by addition of water (40 ml) and dry ice. The organic phase was washed with iced water, dried (Na_2SO_4), and concentrated in vacuo. The residual oil, containing triethylcarbinol and 5b, was purified by elution from silver nitrate on silica gel (50 g) with a benzene/acetone gradient,

affording 230 mg (54% of the latter as a colorless oil; nmr ($CDCl_3$): 1.05, 1.38 (ss, 6H, CMe_2), 1.64 (s, 3H, 11-CH_3), 2.42 (t, J=7Hz, 1'-CH_2), 3.20 (d, J=10Hz, 1H, 10a-H), 4.87-6.0 (m, 3H, CH=CH_2), 6.11, 6.24 (ss, 2H, Ar-H), 6.34 (s, 1H, C=CH); $\nu_{max}^{CCl_4}$ 3605 (OH) cm^{-1}; Calcd. m/e for $C_{21}H_{28}O_2$: 312.2089. Found: 312.2083.

Catalytic Deuteration and Tritiation of 4',5'-Dehydro-Δ^9-THC (5b)

Deuteration.... A solution of 5b (9.9 mg) and tris(triphenylphosphine)-rhodium chloride (4.6 mg) in benzene (0.5 ml) was stirred under a deuterium atmosphere at room temperature for 15 hr, when tlc showed the absence of 5b. The solution was placed on a silica gel (10 g) column, and eluted with hexane-benzene mixtures to separate the catalyst. Δ^9-THC-4', 5'-$^2H_2$ (10 mg) was eluted with 60-100% benzene in hexane. The deuterium content was determined by mass spectral analysis: d_0 0.2%, d_1 0.3%, d_2 96.9%, d_3 2.6%. The nmr spectrum was identical to that of Δ^9-THC, with the exception that the 5'-CH_3 absorption was a broad singlet at 0.86 δ (CHD-CH_2D).

Tritiation.... A solution of 5b (14.7 mg, 0.047 mmole) and tris(triphenyl-phosphine)rhodium chloride (6.6 mg) in benzene (1 ml) was stirred under an atmosphere of carrier-free tritium (1.9 ml, 5 Ci). After 15 hr, 1.43 ml (0.058 mmole) of tritium was absorbed and tlc showed the absence of 5b. The catalyst was removed by elution from silica gel (*vide supra*), to give pure Δ^9-THC-4',5'-$^3H_2$ with a specific activity of 58 Ci/mmole. The specific activity was confirmed by dilution with a known weight of Δ^9-THC, and conversion to 11-hydroxy-Δ^9-THC-4',5'-$^3H_2$. The latter is a solid and so may be weighed accurately.

Dehydrohalogenation of 3c with Potassium Triethylcarbinolate.... A mixture of 3c (91 mg, 0.24 mmole) in benzene (2 ml) and 0.15 molar potassium triethylcarbinolate in toluene (5 ml, 0.75 mmole) was stirred at 70° for 18 hr, when glc showed the absence of 3c. The cooled mixture was reduced to pH 8 by addition of water (10 ml) and solid carbon dioxide. The organic phase was washed with water, dried (Na_2SO_4), and concentrated *in vacuo*. The residual oil was distilled bulb to bulb at 160° (0.05 mm), to give

52 mg (70%) of a colorless oil which was homogeneous by tlc but a mixture of 3b (60%) and 6 (25%) by glc.

Repetition of the experiment using 3c (80 mg, 0.20 mmole), 0.25M potassium triethycarbinolate in toluene (0.8 ml, 0.20 mmole) and benzene (20 ml) gave a crude product (70 mg) which was shown by glc to contain 60% of 6 and 10% of 3b. Elution from silica gel (5 g) with hexane-benzene and with hexane-benzene-diethylamine[23] failed to separate this mixture. Dry column silica gel chromatography (50 x 2.5 cm nylon column, benzene eluent)[24] afforded 18 mg of pure 6; nmr ($CDCl_3$) 1.07, 1.34 (ss, 6H, CMe_2), 1.69 (s, 3H, 11-Me), 2.68 (m, 4H, 1'-CH_2, 5'-CH_2), 3.15 (br.d, J=16Hz, 1H, 10α-H), 5.43 (br.s, 1H, C=CH), 6.23 (s, 1H, ArH); $\nu_{max}^{CCl_4}$ 3610 (OH) cm^{-1}. Calcd. m/e for $C_{21}H_{28}O_2$: 312.2089. Found: 312.2096.

Dehydrohalogenation of 3c with Potassium tert-Butoxide/Dimethyl Sulfoxide.... 3c (115 mg, 0.290 mmole) and sublimed potassium tert-butoxide (120 mg, 1.05 mmoles) in dry dimethyl sulfoxide (3 ml) was stirred at room temperature for 24 hr, when glc showed the absence of 3c. The pH of the mixture was reduced to 8 by addition of iced water and solid carbon dioxide. The mixture was extracted with ether and the combined organic extracts were washed with water, dried (Na_2SO_4), and concentrated in vacuo. Glc-mass spectral analysis of the crude residual oil showed the presence of 3b (80%) and a component (18%) with the empirical formula of 5'-tert-butoxy-Δ^8-THC. Elution from silica gel with a benzene-hexane gradient gave 25 mg (27.5%) of pure 4',5'-dehydro-Δ^8-THC; nmr ($CDCl_3$) 1.07, 1.35 (ss, 6H, CMe_2); 1.68 (br.s, 3H, 11-Me), 2.44 (t, J=7Hz, 1'-CH_2), 3.21 (br.d, J=18Hz, 1H, 10α-H), 4.9-5.9 (m, 3H, $CH{=}CH_2$), 5.42 (br.s, 1H, C=CH), 6.08, 6.22 (ss, 2H, ArH); $\nu_{max}^{CCl_4}$ 3605 (OH) cm^{-1}. Calcd. m/e for $C_{21}H_{28}O_2$: 312.2089. Found 312.2080.

5'-Dimethylamino-Δ^8-THC.... A mixture of 3c (187 mg, 0.476 mmole) and trimethylstannyldimethylamine (435 mg, 2.09 mmoles) was heated at 37° for 1 hr and then allowed to stand at room temperature overnight, when glc and tlc showed the absence of 3c and the formation of a single product. The mixture was diluted with water and extracted with benzene. The combined ben-

zene extracts were washed with water, dried (Na_2SO_4), and concentrated, to give 170 mg of 3d as a light orange oil. An analytical sample was obtained by elution from silica gel (8 g) with methanol; nmr ($CDCl_3$) 1.08, 1.35 (ss, 6H, CMe_2), 1.68 (br.s, 3H, 11-Me), 2.23 (s, 6H, NMe_2), 3.31 (br.d, J=18Hz, 10α-H), 5.40 (br.s, 1H, C=CH), 6.00, 6.16 (ss, 2H, ArH); $\nu_{max}^{CCl_4}$, 3605 (OH) cm^{-1}. Calcd. m/e for $C_{23}H_{35}NO_2$: 357.2668. Found: 357.2663.

Catalytic Reduction of 4',5'-Dehydro-Δ^8-THC (3b)

Deuteration.... A solution of 3b (10 mg), tris(triphenylphosphine)ruthenium dichloride (2.8 mg), and triethylamine (0.5 µl), in benzene (0.5 ml) was stirred under a deuterium atmosphere for 24 hr. The catalyst was removed by passing the violet solution through a column of neutral grade III alumina (1.5 g), eluting with 25% methylene chloride in hexane, and then florisil (1.5 g), eluting with benzene. The product was identified as Δ^8-THC-4',5'-$^2H_2$ by tlc, glc, and nmr spectroscopy. Mass spectrometry established the following deuterium content: 9.3% d_0, 27.0% d_1, 47.9% d_2, 11.2% d_3, 3.9% d_4, 0.2% d_5; Σd=1.76. The major site of deuteration was shown to be C-4' and 5' by nmr, the 5'-CH_2D group appearing as a broad doublet (2.0 H). In an experiment where 3b was incompletely reduced, its glc-ms showed incorporation of 1.36 deuterium atoms (35.9% d_0, 26.4% d_1, 22.6% d_2, 6.5% d_3, 6.6% d_4, 2.1% d_5).

Tritiation.... Reduction of 3b (10 mg) under a carrier-free tritium atmosphere, and purification of the product as described above, gave Δ^8-THC-^3H (10 mg). The specific activity was calculated to be 50 Ci/mmole after determination of the concentration by glc using an internal standard. The product could be stored in benzene/ethanol (1:1), 250 ng/ml, at 0°C with no significant decomposition over several months.

eq-Hexahydrocannabinol.... A solution of Δ^8-THC (62 mg) and tris(triphenylphosphine)rhodium chloride (15.5 mg) in benzene (3.1 ml) was stirred under a hydrogen atmosphere. After 18 hr, glc showed 71% unchanged Δ^8-THC and 29% of a single new product. This composition remained constant. Air (50 µl) was then introduced and the % product was monitored by glc: 37%, 3 hr; 60%, 21 hr; 97% 94 hr. The catalyst was removed by eluting the re-

action mixture from neutral grade III alumina (1.5 g) with 25% methylene chloride in hexane, then from florisil (1.5 g) with benzene. The pure product (62 mg) was identified as eq-hexahydrocannabinol by its mass spectrum with (m/e 316) and by comparison of its nmr spectrum with literature values.[12]

1',2'-Dehydroolivetol Dimethyl Ether.... n-Butyl lithium in hexane (6.40 ml, 16.5 mmoles) was added to a stirred slurry of n-butyltriphenylphosphonium bromide (6.60 g, 16.5 mmoles) in dry ether (50 ml) at 0°C. After 30 min, 3,5-dimethoxybenzaldehyde (2.75 g, 16.5 mmoles) in ether (15 ml) was added to the deep red suspension. The resulting colorless mixture was stirred at room temperature for 2 hr, when the solvent was removed in vacuo. The residual solid was extracted with refluxing benzene (3 x 50 ml), and the combined extracts were filtered and concentrated. Distillation of the residue gave the desired product (2.4 g, 70%) as a colorless liquid, bp 101-102° (0.05 mm), pure by tlc but a 1:1 mixture of cis and trans isomers by glc; $\nu_{max}^{CCl_4}$ 2835 cm^{-1} (OMe); λ_{max}^{EtOH} 290 (3.2), 255 (4.0) nm; nmr ($CDCl_3$) 0.94 (t, J=7Hz, 3H, 5'-Me), 1.50 (m, 2H, 4'-CH_2), 2.25 (m, 2H, 3'-CH_2), 3.75 (s, 6H, OMe), 6.35 (m, 5H, ArH, CH=CH). Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.43; H, 8.72.

1',2'-Dehydroolivetol Monomethyl Ether.... Ethanethiol (2.5 g, 40 mmoles) in dry DMF (40 ml) was added to a suspension of sodium hydride (1.5 g, 57% dispersion, 36 mmoles) in DMF (20 ml). The mixture was stirred until hydrogen evolution ceased. 1',2'-Dehydroolivetol dimethyl ether (2.0 g, 9.7 mmoles) in DMF (20 ml) was added, and the mixture was heated at 130°C for 5 hr, when tlc showed the absence of starting material. The mixture was diluted with water, acidified with 10% hydrochloric acid, and extracted with benzene. The benzene extracts were washed with aqueous sodium bicarbonate and water, dried (Na_2SO_4), and concentrated. Distillation gave the product (1.5 g, 80%) as a colorless liquid, bp 130° (0.025 mm); $\nu_{max}^{CCl_4}$ 3610, 3420 (OH), 2840 (OMe)cm^{-1}; λ_{max}^{EtOH} 295 (3.2), 258 (4.0) nm; nmr ($CDCl_3$): 0.92 (t, J=7Hz, 3H, 5'-CH_3), 1.45 (s, J=7Hz, 2H, 4'-CH_2), 2.16 (q, J=7Hz,

2H, 3'-CH_2), 3.75 (s, 3H, OMe), 6.27, 6.48 (mm, 5H, ArH, CH=CH). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39; m/e 192.1155. Found: C, 74.74; H, 8.37; m/e 192.1150.

1',2'-Dehydroolivetol.... Following the procedure used above, the reaction of 3,5-diacetoxybenzaldehyde (4.3 g) with n-butylidenetriphenylphosphorane gave 1.2 g (22%) of 1',2'-dehydroolivetol diacetate as a 3:1 mixture of cis-trans isomers, bp 135° (0.05 mm); $\nu_{max}^{CCl_4}$ 1775 (OAc) cm^{-1}; λ_{max}^{EtOH} 285 (2.81), 246 (4.13) nm; nmr ($CDCl_3$): 0.92 (t, J=7Hz, 3H, 5'-Me), 1.47 (s, J=7Hz, 2H, 4'-CH_2), 2.24 (s, 6H, OAc), 2.25 (m, 2H, 3'-CH_2), 5.5-6.5 (m, 2H, CH=CH), 6.8 (m, 3H, ArH). Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92, m/e 262.1210. Found: C, 68.53; H, 6.80; m/e 262.1205.

Saponification of this product (660 mg, 2.52 mmoles) with potassium hydroxide (1 g) in water (1 ml) and ethanol (18 ml) for 3 hr at 25°C gave 1',2'-dehydroolivetol (420 mg, 93%), as a 3:1 mixture of cis-trans isomers; bp 130° (0.02 mm); $\nu_{max}^{CHCl_3}$ 3600, 3330 (OH) cm^{-1}; λ_{max}^{EtOH} 295 (3.21), 254 (3.99) nm; nmr ($CDCl_3$), 0.80 (t, J=7Hz, 3H, 5'-Me), 1.35 (s, J=7Hz, 2H, 4'-CH_2), 2.16 (q, J=7Hz, 2H, 3'-CH_2), 5.3-6.3 (m, 5H, ArH, CH=CH). Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; m/e 178.0993. Found: C, 74.03; H, 8.00; m/e 178.0997.

The reaction of 1',2'-dehydroolivetol with p-mentha-2,8-dien-1-ol in the presence of p-toluenesulfonic acid gave a complex mixture of products. Elution from silica gel failed to provide pure 1',2'-hydro-Δ^8-THC. An impure sample exhibited the following nmr spectrum: 0.90 (t, J-7Hz, 5'-Me), 1.07, 1.35 (ss, CMe_2), 1.68 (br.s, 11-Me), 2.27 (t, J-7Hz, 2H, 1'-CH_2), 3.21 (br.d, J=18Hz, 1H, 10α-CH), 5.43 (br.s, 1H, 8-CH), 5.60-6.40 (m, 4H, ArH, CH=CH).

1',2'-Dehydro-Δ^8-THC Methyl Ether.... p-Mentha-2,8-dien-1-ol (472 mg, 3.10 mmoles), 1',2'-dehydroolivetol monomethyl ether (620 mg, 3.23 mmoles), and p-toluenesulfonic acid monohydrate (84 mg, 0.48 mmole) in benzene (35 ml) was refluxed for 4 hr. The solution was cooled, washed with aqueous sodium bicarbonate and water, dried (Na_2SO_4), and concentrated. The residual oil (0.992 mg) was eluted from silica gel (50 g) with hexane-benzene mixtures.

The desired product (112 mg, 11%) was eluted with 1:1 benzene-hexane, as a colorless oil, pure by tlc but a 4:1 mixture of cis,trans isomers; $\nu_{max}^{CCl_4}$ 2840 (OMe) cm^{-1}; nmr ($CDCl_3$): 0.93 (t, J=7Hz, 3H, 5'-Me), 1.08, 1.37 (ss, CMe_2), 1.71 (s, 11-Me), 3.15 (d, J=16Hz, 1H, 10α-CH), 3.82 (s, 3H, OMe), 5.42 (br.s, 1H, 8-CH), 6.0-6.3 (m, 4H, ArH, CH=CH). An isomer (436 mg, 43%), also a 4:1 mixture of cis,trans isomers, was eluted with 4:1 benzene-hexane; $\nu_{max}^{CCl_4}$ 2840 (OMe) cm^{-1}; nmr ($CDCl_3$) 0.95 (t, J=7Hz, 3H, 5'-Me), 1.10, 1.37 (ss, CMe_2), 1.65 (s, 11-Me), 2.77 (d, J=18Hz, 1H, 10α-CH), 3.74 (s, 3H, OMe), 5.42 (br.s, 1H, 8-CH), 5.9-6.6 (m, 4H, ArH, CH=CH).

The first eluted product (100 mg) in dioxane (7 ml) was stirred under a hydrogen atmosphere in the presence of prehydrogenated 10% palladium on carbon (20 mg). One mole equiv. of hydrogen was absorbed in 15 min; further gas uptake was very slow. Filtration and concentration in vacuo gave 100 mg of an oil, identified as Δ^8-THC methyl ether by comparison (tlc, glc, nmr) with an authentic sample. Nmr ($CDCl_3$): 0.89 (t, J=7Hz, 3H, 5'-Me), 1.08, 1.36 (ss, 6H, CMe_2), 1.71 (s, 3H, 11-Me), 2.52 (t, J=7Hz, 2H, 1'-CH_2), 3.18 (br.d, J=16Hz, 1H, 10α-CH), 3.79 (s, 3H, OMe), 5.42 (br.s, 1H, 8-CH), 6.24, 6.30 (ss, 2H, ArH).

Hydrogenation of the second eluted product (90 mg) under identical conditions resulted in uptake of 1 mole equiv. of hydrogen after 15 min. Tlc and nmr showed that the reduction product was an isomer of Δ^8-THC methyl ether. Nmr ($CDCl_3$): 0.90 (t, J=7Hz, 3H, 3'-Me), 1.06, 1.36 (ss, 6H, CMe_2), 1.70 (s, 3H, 11-Me), 2.52 (d, J=4Hz, 10α-H), 2.60 (t, J=7Hz, 1'-CH_2), 3.73 (s, 3H, OMe), 5.46 (br.s, 1H, C=CH), 6.22 (d, J=2Hz, 1H, ArH), 6.37 (d, J=2Hz, 1H, ArH).

9-Keto-11-norhexahydrocannabinol Acetate (10a).... This compound was prepared in 80% yield by oxidation of $\Delta^{9(11)}$-THC acetate using a previously described procedure.[15]

Δ^9-THC-11-$^2H_3$.... A solution of 10a (1.978 g, 5.552 mmoles) in ether (10 ml) was added to methyl-$^2H_3$-magnesium iodide [from methyl-$^2H_3$ iodide (2.53 g, 17.4 mmoles) and magnesium turning (429 mg, 17.6 mg atoms)] in ether

(15 ml) at 0°C. The mixture was stirred at room temperature for 72 hr before hydrolyzing with saturated ammonium chloride (20 ml). The aqueous phase was extracted with ether and the combined ether phases were washed with water, dried (Na_2SO_4), and concentrated.

The residual oil (1.817 g, 98%), which showed no carbonyl absorption in its infrared spectrum, was dissolved in methylene chloride (50 ml) and freshly fused zinc chloride (516 mg) added. Hydrogen chloride was bubbled into the solution at 0°C for 30 min. After 90 min at room temperature, the solution was washed with water, dried (Na_2SO_4), and concentrated. The residual oil (1.952 g) was dissolved in toluene (50 ml) containing potassium triethylcarbinolate (7.5 mmoles), and heated at 50-60°C for 15 hr. Water (50 ml) was added to the cooled solution, and the pH was reduced to 8 by addition of Dry Ice. The aqueous phase was extracted with benzene, and the combined organic phases were washed with water, dried (Na_2SO_4), and concentrated. Elution of the residual oil from silica gel (150 g) with a benzene-hexane gradient gave 724 mg (41%) of pure Δ^9-THC-11-$^2H_3$ and 343 mg (19%) of a fraction containing 37% of the Δ^8-isomer. The structure was confirmed by glc, tlc, and nmr spectroscopy. The isotopic purity was determined by mass spectrometry: m/e 317, 95.9%; 316, 2.6%; 315, 1.5%.

Methyl 5-(3',5'-Dimethoxyphenyl)penta-2,4-dien-1-oate (10a).... A solution of methyl γ-bromocrotonate (85%, 6.25 g, 35.0 mmoles) and triphenylphosphine (9.80 g, 37.5 mmoles) in benzene (30 ml) was stirred at room temperature for several days. The precipitated phosphonium salt (14.8 g, 95%) was filtered and dried *in vacuo*, mp 184-5° dec.

The phosphonium salt (29.5 g, 66.9 mmoles) was added batchwise to sodium (1.54 g, 66.9 mgatoms) in ethanol (150 ml) at 0°C. After stirring for 30 min, 3,5-dimethoxybenzaldehyde (11.0 g, 66.9 mmoles) in ethanol (100 ml) was added to the yellow slurry. The mixture was stirred at 25°C for several hours (pH=7), before diluting with water (166 ml). The yellow precipitate was filtered, dissolved in ether, filtered, and the filtrate washed with water, dried, and concentrated. Crystallization from ether gave 4.95 g of 10a, mp 114.5-115.5°; $\nu_{max}^{CCl_4}$ 2840 (OMe), 1720 (C=O), 1625 (C=C) cm^{-1}; nmr

($CDCl_3$) 3.76 (s, 3H, COOMe), 3.78 (s, 6H, OMe), 5.98 (d, J=15Hz, 1H, CH-COOMe), 6.42 (t, J=3Hz, 1H, 4'-CH), 6.60 (d, J=2Hz, 2H, 2',5'-CH), 6.79, 6.84 (ss, 2H, ArCH=CH), 7.40 (m, 1H, CH=CH-CO) Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.43; H, 6.50. Found: C, 67.59; H, 6.48.

The remainder of the reaction mixture was concentrated, diluted with water, and extracted with ether. The ether phase was dried, concentrated, and precipitated triphenylphosphine oxide was filtered repetitively. Distillation gave 3.84 g of 10a, bp 130-150°C (0.05 mm), a mixture of cis-trans isomers (glc). Yield 50%.

Methyl 5-(3',5'-Dimethoxyphenyl)pentan-1-oate (10b).... A mixture of 10% Pd/C (785 mg) and 10a (7.85 g) in ethanol (250 ml) at 50°C was shaken under a hydrogen atmosphere (40 psi) for 48 hr, when glc indicated reduction was complete. The mixture was filtered, and the filtrate concentrated and distilled to give 4.86 g (61%) of 10b, bp 124-7° (0.05 mm); $\nu_{max}^{CCl_4}$ 2840 (OMe), 1745 (COOMe) cm^{-1}; nmr ($CDCl_3$) 1.65 (q, J=4Hz, 4H, Ar-C-CH_2-CH_2), 2.36, 2.57 (m, 4H, ArCH_2, CH_2CO), 3.64 (s, 3H, COOMe), 3.74 (s, 6H, ArOMe), 6.32 (br.s, 3H, ArH). Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.79; H, 7.95.

5-(3',5'-Dimethoxyphenyl)pentan-1-ol-1-$^2H_2$ (10c).... To a stirred slurry of $LiAlD_4$ (411 mg, 9.78 mmoles) in dry ether (200 ml) was added 10b (4.86 g, 19.3 mmoles in dry ether (50 ml). The mixture was stirred overnight, then refluxed. Further amounts of $LiAlD_4$ were added until tlc indicated the reduction was complete. The mixture was diluted with 10% aqueous tartaric acid, and the ether phase washed with 1N hydrochloric acid. After extraction of the aqueous phases with ether, the combined organic phase was washed with hydrochloric acid, aq. sodium bicarbonate, and water, dried, and concentrated, to give 4.38 g (100%) of 10c: bp 132-6° (0.15 mm); $\nu_{max}^{CCl_4}$ 3640 (OH), 2840 (OMe), 2200, 2095 (CD) cm^{-1}; nmr ($CDCl_3$) 1.60 (m, 7H, OH, CH_2), 2.57 (t, J=8Hz, 2H, ArCH_2), 3.74 (s, 6H, OMe), 6.32 (br.s, 3H, ArH).

The nmr of the perhydro analog of 10c showed an additional absorption

at 3.63 δ (t, J=7Hz, 2H, CH_2OH). Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.77; H, 8.91.

Olivetol-5'-$^2H_3$ Dimethyl Ether (10e).... Phosphorus tribromide (0.91 ml, 2.6 mmoles) in benzene (3 ml) was added dropwise to 10c (4.33 g, 19.2 mmoles) in benzene (7 ml) at 0°C. After stirring for 1 hr at 0°C, the mixture was refluxed for 3 hr, then poured onto ice. The oily product was extracted with benzene, washed with 5% aq. sodium hydroxide, 5% hydrochloric acid, water, and dried. Concentration in vacuo gave 5.00 g of the bromide 10d, pure by tlc and glc; nmr ($CDCl_3$) 1.55 (m, 4H, 2',3'-CH_2), 1.87 (t, J=7Hz, 2H, 4'-CH_2), 2.57 (t, J=7Hz, 2H, 1'-CH_2); 3.74 (s, 3H, OMe), 6.33 (s, 3H, ArH).

A solution of 10d (4.97 g, 17.2 mmoles) in thf (5 ml) was added to $LiAlD_4$ (578 mg, 13.8 mmoles) in thf (20 ml). The mixture was stirred and refluxed for 1 hr, when glc showed the reduction was complete. Water, then aqueous tartaric acid, was added to the reaction mixture. The aqueous phase was extracted with ether, and the combined organic phases were washed with 1N hydrochloric acid and water. After drying and concentrating, distillation gave 3.12 g (77%) of 10e, bp 73-6° (0.025 mm); $\nu_{max}^{CCl_4}$ 2840 (OMe), 2220, 2090 (CD) cm^{-1}; nmr ($CDCl_3$) 1.31 (m, 4H), 1.60 (br.t, J=7Hz, 2H), 2.55 (t, J=7Hz, 2H, 1'-CH_2), 3.74 (s, 6H, OMe), 6.33 (br.s, 3H, ArH); m/e 211; 0.2% d_0, 0.8% d_1; 4.6% d_2; 94.4% d_3. The identity of the product was confirmed by comparison of its tlc, glc, and spectroscopic properties with olivetol dimethyl ether.

Olivetol-5'-$^2H_3$.... Boron tribromide (7.35 g, 29.4 mmoles) in methylene chloride (15 ml) was added to 10e (3.10 g, 14.7 mmoles) in methylene chloride (50 ml) at -70°C. The mixture was stirred at this temperature for 1 hr, and at 0°C for 2.5 hr. The mixture was poured into 10% aq sodium sulfite and ice. The organic phase was washed with aq. sodium bicarbonate, dried, and concentrated, to give 2.59 g (96%) of the desired product, mp 39-40°C. The structure was confirmed by nmr and mixed mp.

Methyl-^{14}C-triphenylphosphonium Iodide.... A solution of triphenylphosphine (1.20 g, 4.58 mmoles) and methyl-^{14}C iodide (ca. 430 mg) in benzene (6 ml) was sealed in a glass ampule and allowed to stand at room temperature

for 5 days. The precipitated product was filtered and washed with benzene. Yield 1.361 g; specific activity 21.4 mCi/mmole.

Δ^9-THC-11-^{14}C.... To a stirred slurry of methyl-^{14}C-triphenylphosphonium iodide (447 mg, 1.11 mmoles) and triphenylmethane (6 mg) in dry tetrahydrofuran (20 ml) was added 0.60 ml (1.44 mmoles) of butyl lithium in hexane. The solution turned dark red at the end of the addition due to the formation of anion of triphenylmethane. The clear solution was stirred for 15 min, when 9-keto-11-norhexahydrocannabinol acetate (625 mg, 1.74 mmoles) in dry tetrahydrofuran (4 ml) was added. The mixture was refluxed for 4 hr, and stirred overnight at room temperature. The solvent was removed in vacuo, and the residue was diluted with hexane and water. The aqueous phase was extracted with hexane and the combined organic phases were dried (Na_2SO_4) and concentrated. The residual oil was eluted from silica gel with a benzene-hexane mixture, to give 187.5 mg of a 1:2 mixture of $\Delta^{9(11)}$-THC-11-^{14}C and its acetate.

Freshly fused zinc chloride (58 mg) was added to this product in methylene chloride (5 ml), and hydrogen chloride was bubbled through the solution at 0-5° for 45 min. The mixture was then stirred overnight at room temperature, and washed with aq. sodium bicarbonate, water, and brine. The organic phase was dried (Na_2SO_4) and concentrated in vacuo.

The residual hydrochloride adduct (204 mg) in benzene (5 ml) was added to 12.2 ml of 0.15 molar potassium triethylcarbinolate in benzene and the solution was heated at 50° for 18 hr. The mixture was reduced to pH 8 by addition of water and solid carbon dioxide, and the organic phase was separated, washed with water, dried (Na_2SO_4), and concentrated. The residual oil (130 mg) was shown by glc to be a 9:1 mixture of Δ^9-THC and $\Delta^{9(11)}$-THC. Elution from silver nitrate on silica gel with a hexane-benzene gradient gave 62 mg of pure Δ^9-THC-11-^{14}C, specific activity 21.4 mCi/mmole, and 25 mg of a fraction contaminated with 10% of $\Delta^{9(11)}$-THC-11-^{14}C.

Δ^8-THC-5'-carboxylic-^{14}C Acid (3g).... A solution of 5'-bromo-Δ^8-THC (407 mg, 1.04 mmoles) and sodium cyanide (137 mg, 2.79 mmoles, 695 μC/mmole) in

dimethylsulfoxide (8 ml) was stirred at 50° for 3 hr, when glc showed that the reaction was complete. The mixture was diluted with water (10 ml) and extracted with ether. The combined ether extracts were washed with water, dried (Na_2SO_4), and concentrated, to leave 5'-cyano-Δ^8-THC (341 mg, 97%) as a frothy solid, pure by glc and tlc; $\nu_{max}^{CCl_4}$ 3610, 3420 (OH), 2250 (CN) cm^{-1}; nmr ($CDCl_3$) 1.08, 1.37 (ss, 6H, CMe_2), 1.69 (br.s, 3H, 11-Me), 2.33 (t, J=7Hz, 2H, CH_2CN), 2.46 (t, J=8Hz, 2H, 1'-CH_2), 3.18 (d, J=17Hz, 1H, 10α-H), 5.42 (br.s, 1H, C=CH), 6.08, 6.23 (ss, 2H, ArH). Calcd. m/e for $C_{22}H_{29}NO_2$: 339.2198. Found: 339.2192.

A degassed solution of 5'-cyano-Δ^8-THC (341 mg, 1.01 mmole) in ethanol (50 ml), water (4 ml), and potassium hydroxide (4 g), was stirred and refluxed for 20 hr. The solvent was removed *in vacuo*, and water was added to the residue. The aqueous solution was extracted with ether, before acidification with 1.2N hydrochloric acid. The aqueous phase was again extracted with ether, and ether extracts were washed with water, dried (Na_2SO_4) and concentrated, to give 3g (298 mg, 83%) as a frothy solid, pure by tlc and glc; $\nu_{max}^{CCl_4}$ 3610, 3400 (br), 3300-2500 (br), 1710 cm^{-1}; nmr ($CDCl_3$) 1.06, 1.36 (ss, 6H, CMe_2), 1.66 (br.s, 3H, 11-Me), 2.3 (m, 4H, 1'-CH_2, 5'-CH_2), 3.19 (d, J=19Hz, 1H, 10α-H), 5.40 (br.s, 1H, C=CH), 6.06, 6.22 (ss, 2H, ArH). Calcd. m/e for $C_{22}H_{30}O_4$: 358.2144. Found: 358.2139. Specific activity 695 μC/mmole.

4'-Hydroxy-Δ^8-THC.... A solution of 4',5'-dehydro-Δ^9-THC acetate (75 mg, 0.21 mmole) and m-chloroperbenzoic acid (97 mg, 0.48 mmole) in chloroform (3 ml) was stirred at room temperature for 24 hr. The solution was diluted with chloroform, washed with aqueous sodium sulfite, sodium bicarbonate, and water, dried and concentrated, to give 11 (82 mg, 100%) as an oil, pure by tlc and glc; $\nu_{max}^{CCl_4}$ 1770 (OAc) cm^{-1}; nmr ($CDCl_3$) 0.92, 1.20, 1.28 (sss, CMe_2, 11-Me), 2.26 (s, 3H, OAc), 2.3-2.7 (m, 1'-CH_2, 5'-CH_2), 2.73 (m, 4'-CH), 6.40, 6.47 (ss, 2H, ArH). Calcd. m/e for $C_{23}H_{30}O_5$: 386.2093. Found: 386.2089.

A solution of 11 (75 mg, 0.19 mmole) in ether (5 ml) was added to a stirred slurry of lithium aluminum hydride (32 mg, 0.85 mmole) in ether

(5 ml) at 0°. The mixture was stirred and refluxed for 3 hr, and then hydrolyzed by addition of water followed by satd. aqueous ammonium chloride. The aqueous phase was extracted with ether and the combined ether phases were washed with water, dried (Na_2SO_4), and concentrated, to give 12 as a gum (75 mg, 100%), pure by tlc; $\nu_{max}^{CHCl_3}$ 3600, 3350 br. (OH) cm^{-1}; nmr ($CDCl_3$), 0.96, 1.27 (ss, CMe_2), 1.09 (d, J=7Hz, 5'-Me), 1.40 (br.s, 11-Me), 3.01 (d, J=13Hz, 1H, 10α-H), 3.70 (m, 1H, 4'-CH), 6.12 (s, 2H, ArH). Calcd. m/e for $C_{21}H_{32}O_4$: 348.2300. Found: 348.2307.

A solution of 12 (70 mg) and p-toluenesulfonic acid (10 mg) in benzene (10 ml) was stirred at room temperature for 15 hr. The mixture was washed with aqueous sodium bicarbonate and water, dried (Na_2SO_4) and concentrated. The crude product was eluted from silica gel (5 g) with a benzene-acetone gradient, to give 11.6 mg (17%) of 4'-hydroxy-Δ^8-THC, pure by tlc and glc; $\nu_{max}^{CCl_4}$ 3605, 3350 br. (OH) cm^{-1}; nmr ($CDCl_3$) 1.09, 1.39 (ss, CMe_2), 1.18 (d, J=7Hz, 5'-Me), 1.70 (br.s, 11-Me), 2.48 (t, J=7Hz, 2H, 1'-CH_2), 3.21 (d, J=18Hz, 1H, 10α-H), 3.8 (m, 1H, CHOH), 5.42 (br.s, 1H, C=CH), 6.10, 6.25 (ss, 2H, ArH). Calcd. m/e for $C_{21}H_{30}O_3$: 330.2195. Found: 330.2191.

5'-Hydroxy-Δ^8-THC.... A solution of 5'-bromo-Δ^8-THC (41 mg, 0.10 mmole) and tetramethylammonium acetate (56 mg, 0.42 mmole) in acetone (5 ml) was refluxed for 15 hr, when tlc showed the absence of starting material. The acetone was removed in vacuo and the residue was dissolved in benzene (3 ml) and water (3 ml). The aqueous phase was extracted with benzene, and the combined benzene phases were washed with water, dried (Na_2SO_4) and concentrated.

The residual oil (37 mg) in dry tetrahydrofuran (0.5 ml) was added to a stirred slurry of lithium aluminum hydride (5 mg) in tetrahydrofuran (1 ml), and the mixture was refluxed for 2 hr. The mixture was hydrolyzed by addition of water followed by 1.2N hydrochloric acid, and extracted with benzene. The benzene extracts were washed with aqueous sodium bicarbonate and water, dried (Na_2SO_4) and concentrated, to leave 30 mg of 5'-hydroxy-Δ^8-THC as a colorless oil, pure by tlc. The product was crystallized from chloroform, m.p. 162-3° (capill.): $\nu_{max}^{CHCl_3}$ 3620, 3610, 3380 br., (OH) cm^{-1};

nmr ($CDCl_3$) 1.08, 1.35 (ss, 6H, CMe_2), 1.69 (br.s, 3H, 11-Me), 2.46 (t, J= 7Hz, 2H, 1'-CH_2), 3.19 (d, J=18Hz, 1H, 10α-H), 3.64 (t, J=7Hz, 2H, CH_2OH), 5.42 (br.s, 1H, C=CH), 6.08, 6.24 (ss, 2H, ArH). Calcd. m/e for $C_{21}H_{30}O_3$: 330.2195. Found: 330.2201.

The mass spectra (70 eV) of the bis(trimethylsilyl) ethers of 4'- and 5'-hydroxy-Δ^8-THC showed the following characteristic fragment ions (intensity 4', intensity 5'): M (100, 100), M-15 (9, 7), M-68 (7, 10), M-83 (56, 69), M-90 (10, 3), M-121 (6, 12), M131 (11, 12), M-132 (19, 8), M-133 (15, 17), M-137 (11, 15), M-144 (35, 64), M-145 (9, 0), M-173 (9, 7), M-189 (11, 12), M-215 (16, 0), m/e 117 (18, 0).

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