of **19b** resulted in disproportionation to 1 equiv each of DNN and **21b.** In the ^1H NMR spectra of these solutions, a peak corresponding to 0.5 equiv of methanol was also observed. The elemental analysis is recorded in Table II.

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Synthesis of Metabolites of Δ^9-Tetrahydrocannabinol

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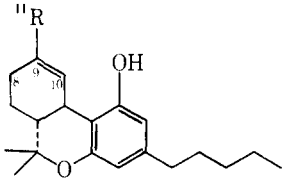
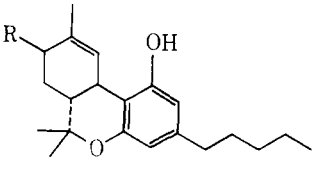
Abstract: New syntheses of the human metabolites, 11-hydroxy-, 8α-, and 8β-hydroxy-Δ^9-THC, and the first syntheses of the metabolites, 8α,11- and 8β,11-dihydroxy-Δ^9-THC, and 11-nor-Δ^9-THC-9-carboxylic acid, are described. The base-induced epoxide–allylic alcohol rearrangement, followed by S$_N$′ displacement, provides a new method of derivatizing the allylic 11-methyl group of Δ^9-THC.

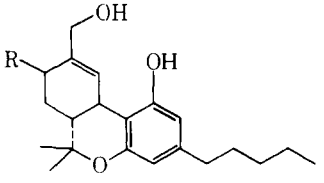
Δ^9-Tetrahydrocannabinol (Δ^9-THC, **1a**), the psychotomimetic principle of marihuana,[1] is metabolized via allylic hydroxylation.[2] Three monohydroxy (**1b, 2a, 2b**), two dihydroxy (**3a, 3b**), and one carboxy (**1c**) metabolites have already[3] been positively identified in man.[4] Of these, **1b, 2a,** and **2b** are bioactive and probably contribute in part to the activity profile of marihuana.[5] Synthetic sources of these metabolites, urgently sought to aid pharmacological studies, have been restricted by a paucity of regioselective methods of functionalizing the allylic 11-methyl group of Δ^9-THC.[6] Procedures which satisfactorily provide Δ^8-THC (**4**) metabolites[2,7] work poorly when applied to the metabolites of Δ^9-THC[8] because of the instability of the 9,10-double bond and the ease of oxidation and aromatization.[7f] As a result, no syntheses of **1c, 3a,** and **3b** have been reported, and syntheses of the key[5] metabolite **1b** have suffered from low yields and difficult separations.[8] Here we describe new regioselective routes to all six human metabolites of Δ^9-THC, starting with the synthesis of 11-hydroxy-Δ^9-THC (**1b**).



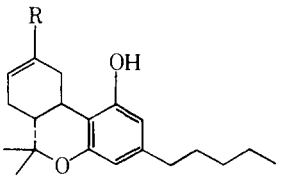
1a, R = CH_3
b, R = CH_2OH
c, R = COOH
d, R = CH_2Br



2a, R = α-OH
b, R = β-OH
c, R = O

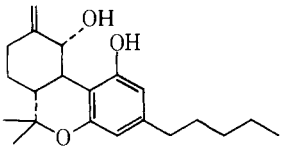


3a, R = α-OH
b, R = β-OH

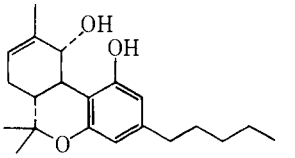


4a, R = CH_3
b, R = CH_2OH

Δ^9-THC acetate was quantitatively converted to its known α-epoxide,[10] which was isomerized to a mixture of the allylic alcohols **5** and **6** in >80% yield by treatment with



5



6

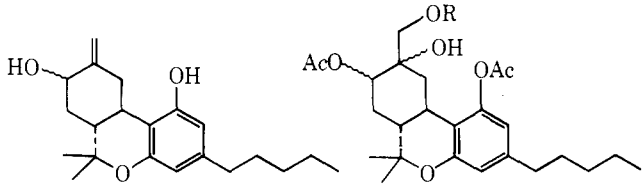
the lithium salt of an amine in ether.[11-13] The choice of amine determined the ratio **5/6** (e.g., C_6H_5NH-*i*-Pr or Et_2NH, 0.2; *i*-Pr_2NH, 2,2,6,6-tetramethylpiperidine, or $(Me_3Si)_2NH$, 1.0; Me_3SiNH-*t*-Bu, 4.0), the bulkier sub-

stituents favoring abstraction of the primary C-11 proton and formation of **5**. Hence this rearrangement served to functionalize either C-11 or C-8 selectively.[14] Without purification, **5** was converted to 11-bromo-Δ^9-THC (**1d**) acetate with 5% HBr in acetic acid, taking advantage of the thermodynamically controlled sN' isomerization of allylic bromides.[15] Acetolysis of the unpurified product with tetramethylammonium acetate in acetone,[16] followed by $LiAlH_4$ reduction, gave 11-hydroxy-Δ^9-THC (20% yield from Δ^9-THC).

In an alternative procedure, **5** was converted to 11-hydroxy-Δ^9-THC via a kinetically controlled SNi' rearrangement.[15b,c] Thus selective alkylation of the phenolic group of **5** with chloromethyl ethyl ether, followed by treatment with thionyl chloride and pyridine in ether,[15c] afforded 11-chloro-Δ^9-THC ethoxymethyl ether. Acetolysis with tetramethylammonium acetate, and acid-catalyzed removal of the acetyl and ethoxymethyl groups, then gave 11-hydroxy-Δ^9-THC in 12% overall yield (17% based on recovered **5**).

Although the metabolites **2a,b** are potentially accessible from the intermediate **6** by SN' solvolysis, **2b** was more directly prepared (30% yield) by bromination of Δ^9-THC acetate with *N*-bromisuccinimide, followed by acetolysis and saponification. **2a** was prepared in 66% yield from **2b** by selective acetylation of the phenolic group, manganese dioxide oxidation to the acetate of the known ketone **2c**,[17] and reduction with $LiAlH_4$.[19]

The two dihydroxy metabolites, **3a,b**, of Δ^9-THC could be synthesized from 11-hydroxy-Δ^8-THC (**4b**)[7a-e] or 8-hydroxy-$\Delta^{9(11)}$-THC (**7**), the latter being available as a 1:1 mixture of epimers at C-8 by epoxidation of Δ^8-THC acetate followed by isomerization with either *n*-butyllithium[7c,e] or lithium diisopropylamide. Diacetylation of **7** and dihydroxylation of the 9,11-double bond with osmium tetroxide gave **8** (R = H). Acetylation of the primary 11-hydroxyl group of **8**, dehydration ($SOCl_2$, pyridine, 0°) of the unchanged tertiary 9-hydroxyl group of the product **8** (R = Ac), and saponification gave pure **3b** in 11% yield, plus a lesser amount (3%) of **3a**, after elution from silica gel. The latter metabolite was better obtained by applying the identical hydroxylation-dehydration scheme[19a] to **4b**, the yield increasing to 17%.



7 **8**

The carboxy metabolite **1c** was prepared by selective acetylation of the phenolic hydroxyl group of **1b**, oxidation to the aldehyde (MnO_2, MeCN), and further oxidation with MnO_2 in methanol containing acetone cyanohydrin.[20]

The GLC-mass spectral and TLC properties of **1c** and **3b** verified the identities of these metabolites in man.[4b,c]

Experimental Section

Infrared spectra were measured using Perkin-Elmer Model 267 and 467 spectrophotometers. NMR spectra were obtained using a Varian HA-100 spectrophotometer with samples dissolved in deuteriochloroform or deuterioacetone (internal standard tetramethylsilane). Mass spectroscopic analyses were carried out using either an AEI MS902 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 ft × 1/16 in.) containing 1.4% OV-17 on Chromosorb W-HP. Precoated silica gel 60 F-254 (Merck) plates were employed for TLC analysis. The elemental composition of crystalline products was determined by combustion analysis (Micro-Tek Laboratories, Skokie, Ill.). The elemental composition of noncrystalline products was determined by high resolution spectroscopy after verifying the purity of samples by TLC and GLC analysis. Solvents were dried over 3A molecular sieves or distilled from $LiAlH_4$ before use, and reactions were carried out under an atmosphere of dry nitrogen. Δ^8- and Δ^9-THC were kindly supplied by the National Institute on Drug Abuse.

10α-Hydroxy-$\Delta^{9(11)}$- and -Δ^8-THC (5,6). 9α,10α-Oxidohexahydrocannabinol acetate was prepared from Δ^9-THC (95% purity) by a literature procedure;[19,21] the product was used without purification. Butyllithium in hexane (169 ml, 0.372 mol) was added to *tert*-butyltrimethylsilylamine (55.0 g, 0.372 mol) in ether (250 ml) at 0°, and the solution was stirred for 45 min before addition of the 9α,10α-epoxide (48.7 g, 0.131 mol) in ether (300 ml). The mixture was refluxed for 70 hr, when more lithium *tert*-butyltrimethylsilylamide (0.222 mol) was added. After a further 24 hr, the mixture was washed with 1 *N* hydrochloric acid, aqueous sodium bicarbonate, dried, and concentrated in vacuo. The residual oil was dissolved in methanol (250 ml) to cleave any trimethylsilyloxy groups; after 5 hr, the solvent was removed. The residue was eluted from silica gel (1 kg) with a benzene–acetone gradient, to give 36.8 g (89%) of a 4:1 mixture of **5** and **6**.

Pure samples were obtained by preparative TLC. **5**: ir (CCl_4) 3310 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, 7 Hz, 3 H, 5′-Me), 1.00, 1.33 (ss, CMe_2), 2.45 (t, 7 Hz, 2 H, 1′-CH_2), 2.69 (t, 8 Hz, 1 H, 10a-H), 4.24 (d, 8 Hz, 1 H, C*H*OH), 4.96 5.10 (ss, 2 H, C=CH_2), 6.21, 6.30 (ss, 2 H, ArH); *m/e* (Calcd for $C_{21}H_{30}O_3$, 330.219) 330.219. **6**: ir (CCl_4) 3260 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, 7 Hz, 3 H, 5′-Me), 1.04, 1.36 (ss, CMe_2), 1.77 (s, 3 H, 11-Me), 2.44 (t, 8 Hz, 2 H, 1′-CH_2), 2.80 (t, 8 Hz, 1 H, 10a-CH), 4.29 (d, 8 Hz, 1 H, C*H*OH), 5.69 (d, 4 Hz, 1 H, C=CH), 6.20, 6.31 (ss, 2 H, ArH); *m/e* (Calcd for $C_{21}H_{30}O_3$, 330.219) 330.219.

Both **5** and **6** were viscous oils which failed to crystallize.

11-Hydroxy-Δ^9-THC (1b). Method A. Chloromethyl ethyl ether (2.13 ml) in acetonitrile (10 ml) was added in portions during a 2-hr period to a stirred solution of a 4:1 mixture of **5** and **6** (8.80 g, 26.7 mmol) in acetonitrile (140 ml) stirred over anhydrous potassium carbonate (25 g) at 0°, until TLC showed the absence of starting materials. The mixture was filtered, concentrated, diluted with water, and extracted with benzene. The organic extract was dried and concentrated to leave 10.3 g of the phenolic ethoxymethyl ethers as a brown oil: ir (CCl_4) 3400 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 7 Hz, 3 H, 5′-Me), 1.00, 1.34 (ss, CMe_2), 1.24 (t, 7 Hz, OCH_2CH_3), 2.50 (t, 7 Hz, 2 H, 1′-CH_2), 3.77 (d, q, 2 Hz, 8 Hz, 2 H, OCH_2CH_3), 4.09 (d, 8 Hz, 1 H, C*H*OH), 4.88, 5.14 (ss, 2 H, C=CH_2), 5.24 (s, 2 H, OCH_2O), 6.38, 6.52 (ss, 2 H, ArH).

Redistilled thionyl chloride (1.92 ml, 26.7 mmol) was added dropwise to a stirred solution of the crude product (10.3 g) in pyridine (2.16 ml, 26.7 mmol) and ether (125 ml) at 0°. After 30 min, TLC showed the absence of starting material and the formation of a major product. The mixture was washed successively with 1 *N* hydrochloric acid, aqueous sodium bicarbonate, and water, dried, and concentrated, to give 10.8 g of impure 11-chloro-Δ^9-THC ethoxymethyl ether: ^1H NMR ($CDCl_3$) δ 0.88 (t, 7 Hz, 3 H, 5′-Me), 1.07, 1.40 (ss, CMe_2), 1.24 (t, 7 Hz, OCH_2CH_3), 2.49 (t, 7 Hz, 2 H, 1′-CH_2), 3.26 (brd, 11 Hz, 1 H, 10a-CH), 3.75 (q, 7 Hz, 2 H, OCH_2CH_3), 4.01 (s, 2 H, CH_2Cl), 5.24 (s, 2 H, OCH_2O), 6.33, 6.48 (ss, 2 H, ArH), 6.73 (s, 1 H, C=CH). This product (10.8 g) and tetramethylammonium acetate (10.6 g, 79.8 mmol) in acetone (125 ml) were stirred and refluxed for 21 hr, when TLC showed no starting material remained. The mixture was filtered, concentrated, diluted with water, and extracted with benzene. The organic extracts were washed with water, dried, and concentrated. The residual oil (9.9 g) and cation exchange resin (20 g, Biorad, AG-50 X-4, H^+ form) in methanol (150 ml) were stirred and refluxed for 5 hr. The mixture was filtered, washing the resin with benzene. The filtrate was concentrated, diluted with water, and extracted with benzene. The benzene extracts were washed with aqueous sodium bicarbonate and water, dried, and concentrated. The residual gum (9.9 g) was eluted from silica gel (500 g) with an acetone–benzene gradient to give 2.46 of unchanged **5** and then **1b**. The latter was obtained as a amorphous solid, mp 139–140° (cap-

illary), pure by TLC and GLC, after dissolution in a minimum volume of acetone and precipitation with carbon tetrachloride. Its structure was confirmed by comparison (GLC, TLC, ir, NMR, MS) with an authentic sample,[8] yield 1.09 g (12%; 17% based on recovered **5**).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found; C, 76.35; H, 9.27.

Method B. A 4:1 mixture of **5** and **6** (14.80 g) was dissolved in pyridine (42 ml) and acetic anhydride (42 ml). After 18 hr, the solution was poured onto iced water (200 g) and extracted with hexane. The combined organic extracts were washed successively with 1 *N* hydrochloric acid, water, aqueous sodium bicarbonate, and water, dried, and concentrated in vacuo, to leave 18.59 (100%) of the diacetates as an oil: ir (CCl_4) 1765, 1215 (OAc), 1745, 1235 (OAc) cm^{-1}. To this product in glacial acetic acid (154 ml) was added 30% hydrogen bromide in acetic acid (31 ml). The solution was stirred for 30 min at room temperature, when TLC of an aliquot showed absence of starting material. Water (100 ml) was added, and the mixture was extracted with benzene. The combined organic extracts were washed successively with water, aqueous sodium bicarbonate, and water, dried, and concentrated in vacuo, to a viscous brown oil (20.84 g): ^1H NMR ($CDCl_3$) δ 3.94 (s, $C{=}CHCH_2Br$). This oil was immediately dissolved in acetone (450 ml), tetramethylammonium acetate (16.41 g, 92.7 mmol) was added, and the mixture was stirred and refluxed for 2 hr. TLC showed no starting material. The acetone was removed in vacuo, and the residue was diluted with water (100 ml) and extracted with hexane. The combined hexane extracts were washed with aqueous sodium bicarbonate and water, dried, and concentrated. The residual oil (18.40 g) in ether (30 ml) was added dropwise to a stirred slurry of $LiAlH_4$ (4.22 g, 111 mmol) in ether (250 ml) at 0°. The mixture was stirred at room temperature for 1 hr and quenched with water, then aqueous tartaric acid. The aqueous phase was extracted with ether, and the combined organic phases were washed with water, aqueous sodium bicarbonate, and brine. After drying and concentrating, the residual solid (15.07 g) was eluted from silica gel (450 g) with benzene, 3% acetone in benzene, and 10% acetone in benzene. 11-Hydroxy-Δ^9-THC was eluted by the latter solvent and was purified by precipitation from acetone with carbon tetrachloride, yield 3.28 g (22%).

8β-Hydroxy-Δ^9-THC (2b). Δ^9-THC acetate (1.28 g, 3.60 mmol) and *N*-bromosuccinimide (832 mg, 1.3 mol equiv) in carbon tetrachloride (18 ml) were stirred at 50° for 2.5 hr. The mixture was cooled, filtered to remove succinimide, and the filtrate was concentrated. The residual oil (1.56 g) and silver acetate (1.00 g, 6.00 mmol) in acetic acid (50 ml) were stirred at room temperature for 60 hr. The mixture was filtered and diluted with water and benzene. The aqueous phase was extracted with benzene. The combined organic phases were washed with water and aqueous sodium bicarbonate, dried, and concentrated.

The residual oil (1.60 g) in ether (20 ml) was added slowly to lithium aluminum hydride (300 mg) in ether (10 ml). The mixture was stirred for 2 hr before addition of 10% aqueous tartaric acid. The separated aqueous phase was extracted with ether, and the combined organic phases were washed with 0.1 *N* hydrochloric acid and water, dried, and concentrated.

The residual oil (1.235 g) was eluted from silica gel (100 g) with a benzene–acetone gradient, to give 346 mg (30%) of 8β-hydroxy-Δ^9-THC, identical (GLC, TLC, NMR) with an authentic sample.[5d,8b,19] Crystallization from acetone gave the acetone solvate, mp 70–72° (capillary).

Anal. Calcd for $C_{21}H_{30}O_3 \cdot Me_2CO$: C, 74.19; H, 9.34. Found: C, 74.31; H, 9.20.

8α-Hydroxy-Δ^9-THC (2a). The acetone solvate of 8β-hydroxy-Δ^9-THC (500 mg, 1.29 mmol) in benzene (30 ml) was treated with 10.1 ml (1.51 mmol) of 0.15 *M* potassium triethylcarbinolate in benzene and, after 30 min, acetic anhydride (155 mg, 1.51 mmol) was added to the stirred solution. After 2 hr, a further 0.151 mmol of potassium triethylcarbinolate and acetic anhydride were added, and the solution was stirred overnight. The solution was washed successively with 0.1 *N* hydrochloric acid, aqueous sodium bicarbonate, and water, dried, and concentrated. The residue (520 mg), a 5:1 mixture of the mono- and diacetates (ν_{max} (CCl_4) 1775 (s), 1745 (w) cm^{-1}), was dissolved in acetonitrile (40 ml) and stirred with manganese dioxide (4.56 g) until TLC showed the absence of starting material (28 hr). The mixture was filtered, the filtrate concentrated, and the residue diluted with hexane. Precipitated acetamide was removed by filtration, and the filtrate was concentrated, giving 460 mg (82%) of 8-keto-Δ^9-THC acetate as a yellow oil, purity >90% (GLC, TLC). The ir and ^1H NMR spectra were in agreement with published data.[10,18]

Lithium aluminum hydride (328 mg, 8.75 mmol) was added to a stirred solution of the ketone (410 mg, 1.11 mmol) in ether (30 ml). After 1 hr, excess hydride was decomposed by addition of water, then 10% aqueous tartaric acid. The aqueous phase was extracted with ether, and the combined organic extracts were dried and concentrated. The residue was eluted from silica gel (65 g) with a benzene–acetone gradient, to give 8β-hydroxy-Δ^9-THC (48 mg) and then 8α-hydroxy-Δ^9-THC (251 mg). The structures of both alcohols were confirmed by comparison (GLC, TLC, NMR) with authentic samples.[5d,8b,19] Overall yield from 8β-hydroxy-THC was 66%.

8α- and 8β-Hydroxy-$\Delta^{9(11)}$-THC (7). To a stirred solution of diisopropylamine (5.36 g, 53.0 mmol) in dry ether (50 ml) at 0° was added 28.0 ml (50.4 mmol) of 1.8 *M* butyllithium in hexane. After 10 min, 8,9-oxidohexahydrocannabinol acetate[21] (5.00 g, 13.4 mmol) in ether (30 ml) was added, and the mixture was refluxed for 4 days, at which time analysis of an aliquot indicated the rearrangement was incomplete. A further 26 mmol of lithium diisopropylamide was then added and refluxing continued for 2 days. The reaction mixture was washed successively with water, 1 *N* hydrochloric acid, and saturated aqueous sodium bicarbonate and dried. Removal of solvent in vacuo left 4.69 g (105%) of an oil, shown by GLC analysis (after acetylation) to contain 81% of a 1:1 mixture of 8α- and 8β-hydroxy-$\Delta^{9(11)}$-THC and 19% of unrearranged 8,9-oxidohexahydrocannabinol. The structures of the epimeric alcohols were confirmed by separation using thick layer chromatography (silica gel, 5% ethyl acetate in chloroform) and spectroscopic analysis. 8α-Epimer: ir (CCl_4) 3605, 3380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, 7 Hz, 5′-Me), 1.04, 1.38 (ss, 6 H, CMe_2), 2.41 (t, 8 Hz, 2 H, 1′-CH_2), 3.87 (d, 10 Hz, 1 H, 10α-H), 4.24 (m, $W^{1/2}$ 20 Hz, 1 H, 8β-H), 4.97, 5.06 (ss, 2 H, $C{=}CH_2$), 6.10, 6.24 (ss, 2 H, ArH); *m/e* (calcd for $C_{21}H_{30}O_3$, 330.2194) 330.220. 8β-Epimer: ir (CCl_4) 3605, 3380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, 7 Hz, 5′-Me), 1.01, 1.35 (ss, 6 H, CMe_2), 2.42 (t, 7 Hz, 2 H, 1′-CH_2), 3.65 (d, 12 Hz, 1 H, 10α-H), 4.42 (brs, 1 H, 8α-H), 4.94 (s, 2 H, $C{=}CH_2$), 6.08, 6.22 (ss, 2 H, ArH); *m/e* (calcd for $C_{21}H_{30}O_3$, 330.2194) 330.219.

The same two epimers have been obtained by butyllithium-induced rearrangement of the 8,9-epoxide.[7c,e]

11-Hydroxy-Δ^8-THC (4b). A 1:1 mixture of 8α- and 8β-hydroxy-Δ^9-THC (80% purity, 2.00 g, 4.85 mmol), obtained from the preceding experiment, was dissolved in benzene (100 ml) and added to 44.4 ml (6.67 mmol) of 0.15 *M* potasssium triethylcarbinolate in benzene. After 30 min, acetic anhydride (0.680 g, 6.67 mmol) was added, and the solution was stirred overnight at room temperature. The solution was washed with 0.1 *N* hydrochloric acid, aqueous sodium bicarbonate, and water, dried, and concentrated in vacuo. TLC and ir analysis indicated the residual oil (2.30 g) was predominantly the phenolic monoacetate: ν_{max} (CCl_4) 3605, 1770 cm^{-1}. Redistilled thionyl chloride (0.46 ml, 6.4 mmol) was added to a stirred solution of the crude product (2.18 g, 5.80 mmol) in dry ether (20 ml) at 0°. The mixture was allowed to warm to room temperature and, after 1.5 hr when TLC showed the absence of starting material, it was diluted with benzene, washed with water, dried, and concentrated in vacuo. The residual oil (2.03 g) was identified as 11-chloro-Δ^8-THC acetate on the basis of its ^1H NMR ($CDCl_3$): δ 0.87 (t, 7 Hz, 3 H, 5′-Me), 1.10, 1.37 (ss, CMe_2), 2.31 (s, 3 H, ArO*Ac*), 2.51 (t, 8 Hz, 1′-CH_2), 4.03 (s, 2H, CH_2Cl), 5.86 (s, $W^{1/2}$ 8 Hz, 1 H, C=CH), 6.43, 6.56 (ss, 2 H, ArH). This product was dissolved in acetone (15 ml) containing tetramethylammonium acetate (1.39 g, 10.4 mmol), and the solution was refluxed until TLC showed solvolysis was complete (ca. 20 hr). The acetone was removed in vacuo and the residue diluted with benzene, washed with water, and dried. After removal of solvent, the residual oil was dissolved in ethanol (50 ml), degassed, and potassium hydroxide (3.05 g) in water (3 ml) was added. The solution was stirred overnight, concentrated in vacuo, diluted with benzene and water, and the pH was reduced to ca. 8 with solid carbon dioxide. The aqueous phase was extracted with benzene, and the combined organic extracts were washed with water, dried, and concentrated in vacuo. The residual oil (1.59 g) was eluted from

silica gel (70 g) with a benzene–acetone gradient, to give 565 mg of pure 11-hydroxy-Δ^8-THC. The structure was confirmed by comparison (NMR, TLC, GLC) with an authentic sample.[7] Yield from Δ^8-THC was 29%.

8α,11-Dihydroxy-Δ^9-THC (3a). A solution of 11-hydroxy-Δ^8-THC diacetate (1.60 g, 3.86 mmol) and osmium tetroxide (1.00 g, 3.94 mmol) in carbon tetrachloride (118 ml) and pyridine (4 ml) was stirred for 24 hr at room temperature. The solvent was removed in vacuo, and the residue was diluted with 10% aqueous sodium bisulfite (90 ml) and pyridine (90 ml). After stirring for a further 24 hr, the majority of the pyridine was removed in vacuo, and the residue was acidified with iced 1 *N* hydrochloric acid. The resulting solution was extracted with ether, and the organic extracts were washed with water, saturated aqueous bicarbonate, and dried. Concentration in vacuo and elution of the residual oil (1.48 g) from silica gel (100 g) with a benzene–acetone gradient gave 520 mg (30%) of **8** (R = H) as a viscous oil, plus 301 mg of an 80% pure fraction: ir (CCl_4) 3540 (OH), 1770, 1745 (OAc) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, 7 Hz, 3 H, 5′-Me), 1.08, 1.38 (ss, 6 H, CMe_2), 2.08, 2.30 (ss, 6 H, 20Ac), 3.88, 4.26 (dd, 11 Hz, 2 H, CH_2OH), 3.55 (m, 1 H, $CHOH$), 6.37, 6.52 (ss, 2 H, ArH); *m/e* (calcd for $C_{25}H_{36}O_7$, 448.246) 448.246.

A solution of **8** (520 mg) in pyridine (2 ml) and acetic anhydride (2 ml) was allowed to stand overnight at room temperature, stirred with iced water (30 ml) for 15 min, and extracted with ether. The organic extracts were washed with 1 *N* hydrochloric acid, water, and saturated aqueous sodium bicarbonate, and dried. The solvent was evaporated in vacuo, to leave 530 mg of a viscous yellow oil, pure by TLC: ir (CCl_4) 3590 (OH), 1770, 1750 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) 0.86 (t, 7 Hz, 3 H, 5′-Me), 1.08, 1.36 (ss, 6 H, CMe_2), 2.05, 2.10, 2.30 (sss, 9 H, 30Ac), 3.94 (s, 2 H, CH_2OAc), 4.88 (m, 1 H, $CHOAc$), 6.37, 6.52 (ss, 2 H, ArH); *m/e* 490.

A solution of this product (530 mg) in pyridine (5 ml) was cooled to −5°, and thionyl chloride (ca. 3 ml) was slowly and cautiously added, swirling to effect mixing. After 17 hr at −5°, the mixture was cautiously poured onto ice (30 g), allowed to stand for 15 min with occasional stirring, and then extracted with ether. The organic extracts were washed successively with 1 *N* hydrochloric acid, water, and saturated aqueous sodium bicarbonate, and dried. The solvent was evaporated in vacuo, leaving 488 mg of a yellow gum, homogeneous by TLC. Spectral data showed it to be predominantly 8α,11-dihydroxy-Δ^9-THC triacetate: ir (CCl_4) 1770, 1745 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.86 (t, 7 Hz, 3 H, 5′-Me), 4.37, 4.68 (dd, 12 Hz, 2 H, CH_2OAc), 5.60 (m, 1 H, $CHOAc$), 6.40, 6.53 (ss, 2 H, ArH), 6.60 (s, 1 H, C=CH); *m/e* 472.

A solution of this acetate (488 mg) in methanol (13 ml) was degassed and treated with potassium hydroxide (350 mg) in water (1.5 ml). After stirring overnight at room temperature, the solution was concentrated in vacuo and diluted with water (13 ml) and ether (13 ml). Solid carbon dioxide was added until the pH was ca. 8, and the organic products were extracted with ether. After drying and removing the solvent in vacuo, the residual gum (328 mg) was eluted from silica gel (30 g) with a benzene–acetone gradient, to give 180 mg (14% overall yield) of pure 8α,11-dihydroxy-Δ^9-THC as a clear gum. The yield increased to 17% if the chromatographic purification of the osmium tetroxide product was omitted. The identity of the 8α,11-dihydroxyΔ^9-THC was confirmed by comparison of its NMR and mass spectra with those of an authentic sample.[5b]

8β,11-Dihydroxy-Δ^9-THC was detected in fractions just preceding the elution of the 8α,11 isomer; the yield of this isomer was ca. 1%.

8β,11-Dihydroxy-Δ^9-THC (3b). A 1:1 mixture of 8α- and 8β-hydroxy-$\Delta^{9(11)}$-THC diacetate (80% purity, 1.412 g, 2.728 mmol) and osmium tetroxide (0.911 g, 3.59 mmoles) in carbon tetrachloride (145 ml) and pyridine (4 ml) was stirred at 25° for 24 hr. The solvent was removed in vacuo and the residue was diluted with 10% aqueous sodium bisulfite (80 ml) and pyridine (80 ml). After stirring for a further 24 hr, most of the pyridine was removed in vacuo, and the aqueous residue was acidified with iced 1 *N* hydrochloric acid and extracted with ether. The organic extracts were washed with water and saturated aqueous sodium bicarbonate and dried. The solvent was removed in vacuo, and the residual oil (1.57 g) was dissolved in pyridine (10 ml) and acetic anhydride (10 ml). After 24 hr at room temperature, the solution was concentrated in vacuo, diluted with 1 *N* hydrochloric acid, and extracted with ether. The ether extracts were washed with water and saturated aqueous sodium bicarbonate and dried. The solvent was removed in vacuo, and the residual brown gum [1.67 g, ir (CCl_4) 3595, 3490 (OH), 1770, 1750 (C=O) cm^{-1}] was dissolved in pyridine (16 ml), cooled to −5°, and thionyl chloride (9 ml) was added slowly and cautiously to the stirred solution. After 20 hr at −5°, the mixture was cautiously poured onto ice (150 g) and extracted with ether. The organic extracts were washed successively with 1 *N* hydrochloric acid, water, and saturated aqueous sodium bicarbonate and dried. The solvent was removed in vacuo, and the residual gum [1.38 g, ir (CCl_4) 1770, 1745 cm^{-1}] was dissolved in methanol (40 ml), degassed, and treated with potassium hydroxide (990 mg) in water (5 ml). After 20 hr, the methanol was removed in vacuo, the residue was diluted with water and ether, and the pH of the aqueous phase was reduced to ca. 8 by addition of solid carbon dioxide. Extraction with ether and concentration of the combined organic extracts gave 1.03 g of a crude mixture (1:3) of 8α,11- and 8β,11-dihydroxy-Δ^9-THC. Elution from silica gel (Brinkmann HF-254, 100 g) with a benzene–acetone gradient gave 110 mg (11%) of pure 8β,11-dihydroxy-Δ^9-THC: ir (CCl_4) 3340 (OH) cm^{-1}; ^1H NMR (perdeuterioacetone) δ 0.87 (t, 7 Hz, 3 H, 5′-Me), 1.05, 1.35 (ss, CMe_2), 2.41 (t, 7 Hz, 2 H, 1′-CH_2), 3.05 (d, 10 Hz, 1 H, 10a-H), 4.14 (s, 2 H, CH_2OH), 4.34 (brd, 2 Hz, 1 H, 8α-H), 6.13, 6.26 (ss, 2 H, ArH), 6.95 (s, 1 H, CH=C); *m/e* (calcd for $C_{21}H_{30}O_4$, 346.214) 346.215. Pure 8α,11-dihydroxy-Δ^9-THC (35 mg, 4%) was eluted after fractions (66 mg, 8%) containing both epimers.

11-Nor-Δ^9-THC-9-carboxylic Acid (1c). To 11-hydroxy-Δ^9-THC (961 mg, 2.91 mmol) in benzene (130 ml) was added 14.0 ml of 0.25 *M* potassium triethylcarbinolate (3.50 mmol) in benzene. The solution was stirred for 30 min, when acetic anhydride 0.30 ml, 3.2 mmol) was added. After 1.5 hr, when TLC showed the absence of starting material, the mixture was acidified with 0.1 *N* hydrochloric acid. The organic phase was washed with aqueous sodium bicarbonate and water, dried, and concentrated in vacuo, to give a 9:1 mixture of mono- and diacetates. The structure of the monoacetate was confirmed spectroscopically after chromatographic purification: ir (CCl_4) 3610 (OH), 1770 (ArOAc) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, 7 Hz, 3 H, 5′-Me), 1.08, 1.39 (ss, CMe_2), 2.23 (s, 3 H, OAc), 2.50 (t, 9 Hz, 1′-CH_2), 3.10 (d, 10 Hz, 1 H, 10a-H), 3.94 (s, 2 H, CH_2OH), 6.25 (s, 1 H, C=CH), 6.39, 6.54 (ss, 2 H, ArH).

The unpurified monoacetate in acetonitrile (120 ml) was stirred over manganese dioxide (5 g), the extent of reaction being followed by TLC. After 3 hr, more manganese dioxide (2.5 g) was added. After 5 hr, the mixture was filtered and the filtrate concentrated. The residue was diluted with hexane, filtered to remove acetamide, and again concentrated, to give 985 mg of the 9-aldehyde (80%, TLC): ir (CCl_4) 1770 (OAc), 1690 (-CHO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, 7 Hz, 5′-Me), 1.14, 1.44 (ss, CMe_2), 2.29 (s, 3 H, OAc), 2.54 (t, 8 Hz, 2 H, 1′-CH_2), 3.38 (brd, 12 Hz, 1 H, 10a-CH), 6.49, 6.61 (ss, 2 H, ArH), 7.39 (s, 1 H, C=CH), 9.44 (s, 1 H, CHO); *m/e* 372. This product and acetone cyanohydrin (9.4 ml) in ethanol (30 ml) was stirred for 1 hr before addition of manganese dioxide (4.7 g). After a further 3 hr, the mixture was filtered and the filtrate concentrated in vacuo. The residue was diluted with benzene, washed with water, dried, and again concentrated. This product in ethanol (41.4 ml), water (2.3 ml), and potassium hydroxide (2.3 g) was stirred overnight. The mixture was partially concentrated, diluted with water, and extracted with ether. The aqueous phase was acidified and extracted with ether. The latter extracts were dried, concentrated, and eluted from silica gel (35 g) with 0–10% acetone in benzene, to give 275 mg of **1c** as an oil, which precipitated from acetone with hexane and crystallized from carbon tetrachloride, wt 160 mg: mp 205–207° (Kofler); ir (KBr) 3600–2500 (br, OH), 1680 (C=O) cm^{-1}; NMR (perdeuterioacetone), 0.86 (t, 7 Hz, 3 H, 5′-Me), 1.08, 1.39 (ss, 6 H, CMe_2), 2.41 (t, 7 Hz, 1′-CH_2), 3.36 (d, 12 Hz, 1 H, 10a-H), 6.12, 6.29 (ss, 2 H, ArH), 8.10 (brs, 1 H, C=CH).

Anal. Calcd for $C_{21}H_{28}O_4$ (*m/e* 334.199): C, 73.22; H, 8.19. Found (*m/e* 334.198): C, 72.68; H, 8.29.

The use of Corey's conditions[20] failed to give **1c**.

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Use of ^{1}H Nuclear Magnetic Resonance Spectroscopy for Sequence and Configuration Analysis of Cyclic Tetrapeptides. The Structure of Tentoxin[1,2a-d]

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Abstract: Tentoxin, a metabolite of *Alternaria tenuis* Nees. which induces chlorosis in germinating seedlings of many dicotyledonous plant species, was previously shown to be a cyclic tetrapeptide containing one unit each of glycine, L-leucine, *N*-methylalanine, and *N*-methyldehydrophenylalanine. Detailed analysis of ^{1}H NMR data from tentoxin and its dihydro, *N,N*-dimethyl, and *N,N*-dimethyldihydro derivatives permits deduction of the full structure, sequence, and configuration of the natural product as cyclo(L-leucyl-*N*-methyl-(*Z*)-dehydrophenylalanyl-glycyl-*N*-methyl-L-alanyl), with the conformation depicted in structure **1**.

Tentoxin is a phytotoxic metabolite of the pathogenic fungus *Alternaria tenuis* Nees. [*A. alternata* (Fries) Keissler] (ATCC 24127) which causes the cotyledons of germinating cotton and many other dicotyledonous plants to develop severe variegated chlorosis.[3] Additional interest in tentoxin developed with its identification as a cyclic tetrapeptide containing one unit each of glycine, L-leucine, *N*-methylalanine, and *N*-methyldehydrophenylalanine,[1a,3e,f,4,5] for previously no cyclic tetrapeptide had been recognized in nature,[6] and the presence of an α,β-unsaturated α-amino acid unit in its structure placed tentoxin among a small but growing group of antibiotic and phyto-