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The synthesis of some 11-substituted tetrahydrocannabinol metabolites^{1,2}

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9-Bromo-11-oxo-hexahydrocannabinol (**5**) was prepared from the ketocannabinoid **3b** via the epoxysulfone **4**. The dehydrobromination of the bromoaldehyde **5** could be controlled to give either the thermodynamically more stable Δ^8 -aldehyde **2c**, or the Δ^9 -aldehyde **1c** by an intramolecularly assisted elimination. Reduction of the unsaturated aldehydes gave the allylic alcohol metabolites **2a** and **1a**, respectively.

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On a séparé le bromo-9 oxo-11 hexahydrocannabinol (**5**) à partir du céto-cannabinol **3b** via l'époxysulfone **4**. On peut contrôler la déhydrobromation du bromaldéhyde **5** pour obtenir soit le Δ^8 -aldéhyde (**2c**) thermodynamiquement le plus stable, soit le Δ^9 -aldéhyde (**1c**) par une élimination intramoléculaire assistée. La réduction des aldéhydes insaturés a conduit à l'alcool allylique des métabolites **2a** et **1a** respectivement.

[Traduit par le journal]

Introduction

The potential importance of tetrahydrocannabinol (THC) metabolites in biological investigations has resulted in considerable effort directed towards their synthesis (1). In this paper, we report two synthetic routes to both 11-hydroxy- Δ^9 -THC (**1a**)⁴ and 11-hydroxy- Δ^8 -THC (**2a**), the major psychotomimetically active metabolites of Δ^9 -THC (**1b**) and Δ^8 -THC (**2b**), respectively.

Most of the previous syntheses of **1a** have involved transformations of Δ^9 -THC (**1b**) or Δ^9 (11)-THC (**3a**), or condensations of olivetol (**9**) with suitable terpenoid synthons. One attempted synthesis of particular interest relating to our strategy and starting from benzylated 11-nor-9-keto-HHC⁵ (**3b**) failed to provide **1a** by phenoxide-assisted intramolecular elimination of chloride ion in **3c**, but instead led to the thermodynamically more stable Δ^8 -isomer **2a** (2). Despite many efforts, a simple efficient synthesis of the metabolite **1a** has not been

accomplished; the highest yielding synthesis at present is 20% of the metabolite from **1b** reported by Pitt *et al.* (3). Many of the syntheses have so far produced low overall yields, lack of regioselectivity in the introduction of the Δ^9 -unsaturation and the oxygen function, and often involve difficult separations. In addition, reactions involving olivetol condensations frequently give rise to abnormal THC by-products (incorrect orientation of the pentyl sidechain).

The problems stem in part from the lability of the Δ^9 -unsaturation, traditionally attributed to the steric interactions between H-10 and the phenolic oxygen, and H-10a and the 6 α -methyl group. Under acid-catalysis the double bond at Δ^9 rapidly equilibrates to the Δ^8 position, relieving the steric strain of these non-bonded interactions (4). More

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⁴Two numbering systems for cannabinoids are extensively in use today. One is based on the formal chemical rules for numbering of benzopyran. The second nomenclature has a biogenetic basis, regarding cannabinoids as substituted mono-terpenoids. The former system is used in this paper.

⁵Hexahydrocannabinol.

FIG. 1. Synthesis of 1c and 2c. Reagents: (a), TsCH_2Cl , phase transfer; (b), MgBr_2 in Et_2O or THF; (c) intramolecular elimination, collidine; thermodynamic elimination, Li_2CO_3 , LiBr , DMF.

recently, an alternative explanation has been put forward by Dalzell *et al.* based on torsional strain in the THC ring system (5).

In contrast to the above, the synthesis of 2a has been beset by fewer problems, since this is the thermodynamically preferred isomer. Two high yield syntheses have been reported up to the present time, both from the same laboratory (6, 7). In the first synthesis, however, a difficult separation is involved.

Our synthetic strategy, outlined in Fig. 1, is based on the dehydrobromination of 5, obtained from ketone 3b via an intermediate epoxysulfone 4.⁶ Under normal dehydrobrominating conditions, the thermodynamically more stable Δ^8 isomer 2c is formed. However, under carefully controlled conditions and the judicious choice of base, the Δ^9 -unsaturation may be generated by H-10 α proton abstraction initiated by the phenoxide anion, giving rise to isomer 1c as outlined in structure 6. Phen-

oxide-assisted intramolecular eliminations of a similar nature have already been successfully demonstrated in the contrathermodynamic conversion of Δ^8 -THC (2b) to Δ^9 -THC (1b) (8). However, Pitt and co-workers were unable to synthesise the metabolite 1a by a similar strategy (2).

Results and discussion

The starting material, 11-nor-9-keto-6a,10a-*trans*-HHC (3b) was prepared using a method developed by Archer and co-workers by condensing olivetol (9) with 2-(4-methoxy-1,4-cyclohexadienyl)-2-propanol (10) in the presence of stannic

⁶All compounds whose syntheses are described in this work are racemic mixtures; the naturally occurring THC ring junction (—)-(6aR,10aR) is shown only for convenience.

chloride and one molar equivalent of water to give 11-nor-9-keto-6a,10a-*cis*-HHC (3d) in 24% yield (9). The acid-catalyzed isomerisation of the *cis*-ketone to the required starting material 3b with the *trans*-ring junction was accomplished in 58% yield using AlCl_3 .

The synthesis of the bromoaldehydes 5 is based on the novel one-carbon homologation developed by Durst and co-workers in which a ketone is converted to an epoxysulfone and then cleaved with MgBr_2 in ether or THF to give an α -bromoaldehyde (10). Epoxysulfones may be prepared directly from ketones in high yields by using the phase transfer conditions of Makosza, obviating the isolation of an intermediate chlorohydrin (11). The overall transformation involves nucleophilic attack of the base-generated α -chloro- α -sulfonyl carbanion on the carbonyl group followed by intramolecular displacement of the chloride, to give a Darzens type condensation. Working with simple epoxysulfones, Durst and co-workers obtained bromoaldehydes cleanly and in high yield, demonstrating the value of this mild homologation method.

In this work an isomeric mixture of the unstable epoxides 4 was prepared in high yield under

phase-transfer conditions from the ketone **3b**, chloromethyl-*p*-tolyl sulfone (prepared by a method based on ref. 12)⁷ and 50% aqueous NaOH solution using benzyltriethylammonium chloride as the catalyst. The high sensitivity of these epoxides to acid-catalyzed decomposition necessitated using water adjusted to slightly basic pH during the work-up of the reaction.

Analysis of the crude products by thin layer chromatography indicated two major components with similar characteristics. The more polar of the two compounds could be isolated by crystallization and its nmr spectrum was compared with that of the mixture. Only two signals were significantly different between the two isomers in these spectra; the epoxide protons at δ 3.95 (**4b**) and δ 3.90 (**4a**) and the aromatic H-2 protons at δ 6.13 (**4a**) and δ 6.06 (**4b**). The ratio of the two isomers as determined by the relative integration of the H-2 protons was 43 (**4a**):57 (**4b**). The stereochemistry of the epoxides was assumed to be α and β , respectively, based on the ratio and stereochemical inversion about C-9 of the bromoaldehydes **5a** and **b** formed in the next step of the synthetic sequence.

The Lewis acid cleavage of the epoxysulfones **4** with MgBr_2 in ether or THF gave a good yield of bromoaldehydes. The nature of the products formed was determined by the solvent used. In the case of THF, only isomeric bromoaldehydes **5a** and **5b** were obtained. In ether, where the reaction occurred more rapidly, one epimer **5b** as well as unsaturated aldehydes **1c** and **2c** were formed. The stereochemistry of the bromoaldehydes was determined by comparison of the nmr spectra of the isomeric mixture **5a** and **5b** and the single isomer **5b**; the latter displays a large difference in the upfield chemical shift of the 6 α -methyl group (13).⁸ Molecular models demonstrate that in epimer **5b**, the 6 α -methyl group is within the shielding region of the carbonyl group, whereas H-10a lies within the deshielding region. Thus, H-10a is shifted 29 Hz downfield (δ 3.97, broadened doublet, $J_{\text{vic}} = 13$ Hz) and the 6 α -methyl group is shifted 18 Hz upfield (δ 0.99) with respect to **5a**. The ratio of the bromoaldehyde epimers arising from the epoxide cleavage in THF was also 43 (**5b**):57 (**5a**) as determined by integration of the aldehyde signals in the proton spectrum. The overall data suggests an $\text{S}_{\text{N}}2$ type reaction on epoxide cleavage by bromide ion where inversion about C-9 occurs (i.e. **4a** $\rightarrow$ **5b**, **4b** $\rightarrow$ **5a**).

⁷The use of the bromo-analogue was found to be unsuitable, when methyl-*p*-tolylsulfone was formed as a by-product.

⁸In 6a,10a-*trans* THC's, the 6 α -methyl group appears upfield with respect to the 6 β -methyl substituent. See ref. 13 for a detailed nmr study.

As mentioned above only the β -bromoaldehyde isomer **5b** was isolated where ether was used. We originally assumed that the α -bromo isomer, **5a**, in which there is a 1,2-diaxial arrangement of hydrogen and bromine, spontaneously dehydrobrominates in ether, forming **1c** and **2c** while leaving the less-reactive **5b** unchanged. This does not appear to be the case, however, since epoxide cleavage in THF, followed by replacement of solvent by ether, showed no evidence for unsaturated aldehydes **1c** and **2c** after hydrolysis of the complexes. It is therefore suggested that the dehydrobromination process observed during epoxide cleavage in ether proceeds by means of an intermediate such as **7** in which the three fates indicated lead to the observed products. Neutralisation of this carbocationic species from the least hindered β face leads to **5b**. On the other hand, in the reaction using THF as a solvent, $\text{S}_{\text{N}}2$ cleavage of epoxides **4a** and **4b** by bromide ion would lead directly to the products observed.

The unstable Δ^9 -aldehyde **1c** (5%) and the Δ^8 -aldehyde **2c** (18%) were separated by careful column chromatography and crystallized. The olefinic proton of **1c** (δ 7.88) displays an unusually large downfield chemical shift with respect to the olefinic proton of **2c** (δ 6.88) in the nmr spectrum (3)⁹ due to the highly deshielded region in which it resides. In the mass spectrum of **2c**, which has been studied by Inayama and co-workers (14), the enhanced abundance of the common cannabinoid fragment ion m/e 231, **8**, is diagnostic for the Δ^8 -unsaturation and arises from a retro-Diels-Alder (RDA) reaction in the isoprenoid ring of the molecule. In contrast, the Δ^9 -aldehyde **1c** displays a very low abundance of this ion. The Δ^9 -aldehyde **1c** has been identified as a metabolite from the incubation products of **1b** with rat liver microsomes (15). In this case, however, the investigators observed an abundant fragment ion at m/e 231 of the derivatised product.

Attempts to synthesise **1c** by intramolecular displacement of bromide in **5b** (see **6**) using potassium *t*-amylate or sodium hydride under various conditions led to indefinite results despite their successful use in the synthesis of Δ^9 -THC (**1b**) (8). No evidence of either **1c** or **2c** in the reaction products was observed. It is clear from projection **6** that no ideal geometry for elimination exists for **5a** or **5b** by an intramolecular pathway. However, use of pyridine as a weak base to remove only the most

⁹Nuclear magnetic resonance and ir spectra of the authentic materials were kindly supplied by Dr. Colin G. Pitt of the Research Triangle Institute, North Carolina, and Dr. Raj K. Razdan of the Sisa Institute for Research, Inc., Massachusetts.

acidic phenolic proton provided evidence for this process when aldehydes **1c** and **2c** were cleanly obtained in the ratio of 15:85 (based on integrating the olefinic proton signals in the nmr spectrum of the mixture). By using the more hindered base, collidine, this ratio was increased to 52:48 and the unsaturated aldehydes were easily separated by column chromatography. Other bases such as 2,6-di-*t*-butyl pyridine and quinoline gave respectively no reaction and predominantly **2c**.

Heating **5b** with Li_2CO_3 and LiBr in DMF (16) (conditions which presumably exclude phenoxide participation), the 1,2-elimination of HBr proceeded smoothly to provide the Δ^8 -aldehyde **2c** in 90% isolated yield together with a 3% yield of the Δ^9 -aldehyde **1c**.

The aldehydes **1c** and **2c** were reduced to the metabolites **1a** and **2a** with LiAlH_4 in THF. In a preliminary communication from another laboratory, the reduction of **1c** with LiAlH_4 was reported to proceed smoothly, but no conditions were specified (17). In our laboratories, however, various amounts of aromatic impurities in **1a** were observed in the samples that were reduced under our conditions.

This route represents a facile synthesis of 11-hydroxy- Δ^8 -THC (**2a**) from 11-*nor*-9-keto-HHC (**3b**) via **5b** with an overall yield of 64%. This compares favourably in terms of yield to the method reported by Pitt *et al.* (33%) (2) for the preparation of **2a** from benzylated **3b**. The overall yield of 11-oxo- Δ^9 -THC (**1a**) via **5b** was 36.5% based on recovered starting material. This synthetic route has the advantage that THC metabolite aldehydes and acids can also be made available if required. Our continuing work in this area is directed to the efficient regioselective formation of the thermodynamically less stable Δ^9 isomers of various THC metabolites.

Experimental

Melting points were determined on a Fisher-Johns melting point block and are uncorrected, and the infrared spectra were determined on a Perkin-Elmer 237B grating spectrophotometer. Nuclear magnetic resonance spectra were obtained on Varian Associates Model HA-100 instruments with deuteriochloroform as the solvent and tetramethylsilane as internal standard. Chemical shifts are expressed in the δ scale and the following abbreviations are used in describing the nmr signals: singlet (s), doublet (d), triplet (t), multiplet (m), and broadened (br). Combustion analyses were performed by Spang Microanalytical Laboratories, Eagle Harbour, Michigan and Guelph Chemical Laboratories Ltd., Guelph, Ontario. The mass spectra were determined with an H.P. 5985 G.C.-M.S. Quadrupole instrument at the Health and Welfare Canada operated at an ionising potential of 70 eV.

Pre-coated plates from E. Merck Reagents (silica gel F-254, 0.25 mm layer thickness) were used for thick layer; bands were

observed by viewing under a uv source or by heating the plate sprayed with a 1% solution of ceric ammonium nitrate in 50% aqueous sulphuric acid.

Tetrahydrofuran was distilled from LiAlH_4 and benzene was distilled from, and stored over, sodium metal. Mallikrodt anhydrous ether was used in the preparation of MgBr_2 . All other solvents were glass distilled prior to use. The term "work-up" refers to: extraction of the reaction mixture with solvent ($\times 3$), washing the combined extracts with water ($\times 3$) and saturated aqueous sodium chloride, drying of the organic phase with magnesium sulphate, and removal of solvent under reduced pressure. Water used in the work-up of reactions was adjusted to pH 7.2 by the addition of aqueous sodium bicarbonate and monitoring the change with a pH meter.

11-*nor*-9-Keto-6a,10a-cis-HHC (**3d**)

The *cis*-ketocannabinoid **3d** was prepared following mainly the procedure of Archer *et al.* (9). To a stirred solution of olivetol **9** (18.025 g, 100 mmol) and **10** (20.188 g, 120 mmol) in dichloromethane (400 mL) and under nitrogen at -15°C was added water (1.8 mL, 100 mmol), followed by the dropwise addition of SnCl_4 (26 mL, 222 mmol) over a 2 h period. The mixture was stirred at 0°C for 7 h after which time it was poured into water (500 mL) and extracted several times with ether. The ethereal extracts were washed three times with aqueous NaOH (1 M), three times with water, and then dried over MgSO_4 . After filtering off the solids and removing the solvent, the material was crystallized from hexanes to yield the *cis*-ketocannabinoid **3d** (7.58 g, 24%) as the major product (ref. 9 reports a 12% yield). Traces of the less polar *trans* **3b** isomer were observed by tlc analysis (20% EtOAc in benzene). Analytically pure *cis*-ketocannabinoid **3d** was obtained by H.P.L.C. (Waters Prep System - 500, 40% EtOAc in hexanes) and had the following characteristics: mp $149.5\text{--}150.5^\circ\text{C}$ (lit. $149.5\text{--}150.5^\circ\text{C}$ (8a)); ir (KBr pellet), 3255 cm^{-1} (OH), 1690 cm^{-1} (C=O); nmr δ 0.87 (3H, t, $J = 6\text{ Hz}$, C-5' CH_3), 1.34 (3H, s, C-6 α CH_3), 1.40 (3H, s, C-6 β CH_3), 2.42 (2H, m, Ar- CH_2), 6.22 (2H, s, H-2 and H-4), 7.38 (1H, s, Ar-OH D_2O exchangeable).

11-*nor*-9-Keto-6a,10a-trans-HHC (**3b**)

The *trans*-ketocannabinoid **3b** was prepared mainly by the procedure of Archer *et al.* (9). Aluminum chloride (13.5 g, 100 mmol) was added to a solution of *cis*-ketocannabinoid (9.00 g, 28.4 mmol) in dichloromethane (450 mL). The mixture was stirred for 3 h at room temperature under nitrogen and then additional AlCl_3 (7.5 g, 562 mmol) was added and the stirring continued for a further 2 h. After work-up with dichloromethane, the solid was crystallized (CH_2Cl_2 /hexanes) to give **3b** as the major product by tlc analysis (20% EtOAc in benzene), with only a trace of the *cis*-isomer (**3d**) remaining. Selective recrystallization (methanol/water) afforded pure **3b** (5.22 g, 58%) obtained as the higher melting polymorph: mp $160\text{--}163^\circ\text{C}$ (lit. $163\text{--}165^\circ\text{C}$ (8a)); ir (KBr pellet), 3285 cm^{-1} (OH), 1695 cm^{-1} (C=O); nmr, δ 0.89 (3H, br t, $J = 6\text{ Hz}$, C-5' CH_3), 1.13 (3H, s, C-6 α CH_3), 1.48 (3H, s, C-6 β CH_3), 2.46 (2H, br t, $J = 8\text{ Hz}$, Ar- CH_2), 4.19 (1H, br d, $J = 15\text{ Hz}$, H-10a), 6.23 (1H, d, $J = 2\text{ Hz}$, H-2), 6.31 (1H, d, $J = 2\text{ Hz}$, H-4), 7.93 (1H, s, Ar-OH D_2O exchangeable).

9, 11-Epoxy-11-tosyl-6a,10a-trans-HHC (**4a,b**)

Employing the phase transfer conditions of Makosza *et al.* (11), ketocannabinoid **3b** (316.4 mg, 1.0 mmol), chloromethyl-*p*-tolylsulfone (204.6 mg, 1.0 mmol), and benzytriethylammonium chloride (50 mg, 0.22 mmol) were dissolved in 8 mL of acetonitrile. 20 mL of aqueous sodium hydroxide (50%) was added and the mixture stirred vigorously under nitrogen in a stoppered flask. After 2 h, the yellow slurry was poured into water (200 mL) and worked up with ether to yield **4** (464.5 mg,

96%), sufficiently pure (tlc 10% EtOAc in benzene) to use for the next step. The more polar isomer **4a** was crystallized from ether or hexane and had the following characteristics: mp 124.5–128°C (dec); ir (KBr pellet), 2950 cm^{-1} (OH), 820 cm^{-1} (epoxide); nmr δ 0.88 (3H, br t, $J = 6$ Hz, C-5' CH_3), 1.09 (3H, s, C-6 α CH_3), 1.39 (3H, s, C-6 β CH_3), 2.45 (3H, s, Ts— CH_3), 3.90 (1H, s, epoxide-H), 4.09 (1H, br d, $J = 14$ Hz, H-10a), 5.44 (1H, br s, Ar—OH D_2O exchangeable), 6.13 (1H, br s, H-2), 6.22 (1H, br s, H-4), 7.36 (2H, d, $J_{AB} = 8$ Hz, Ts), 7.87 (2H, d, $J_{AB} = 8$ Hz, Ts); ms, m/e (rel. intensity) 484 (2), 329 (29), 328 (37), 286 (12), 285 (12), 272 (38), 231 (34), 193 (55), 91 (100). Anal. calcd. for $\text{C}_{28}\text{H}_{36}\text{O}_5\text{S}$: S 6.62; found: S 6.44.

9-Bromo-11-oxo-6a,10a-trans-HHC (5a,b)

Magnesium bromide was prepared by stirring together magnesium (243 mg, 10 mmol) and 1,2-dibromoethane (0.86 mL, 10 mmol) in dry THF (20 mL) under nitrogen until the reaction was completed. A solution of **4a**, **b** (370 mg, 0.76 mmol) in THF (20 mL) was added via syringe, and the mixture was stirred for 2 days at room temperature. The mixture was poured into water and worked up with ether. The material was purified by eluting from a thin column of Florisil (15 g, 100–200 mesh, 7% ether in light petroleum ether) to yield **5a**, **b** (228.5 mg, 73%): ir (CCl_4), 3600 cm^{-1} (sharp, free OH), 3475 cm^{-1} (broad, H-bonded OH), 1727 cm^{-1} ($\text{C}=\text{O}$); nmr δ 0.88 (3H, t, $J = 6$ Hz, C-5' CH_3), 0.99 and 1.17 (3H, s, C-6 α CH_3), 1.36 and 1.41 (3H, s, C-6 β CH_3), 2.43 (2H, br t, $J = 6$ Hz, Ar— CH_2), 3.68 and 3.97 (1H, br d, $J = 14$ Hz and $J = 13$ Hz, H-10a), 4.85 and 4.98 (1H, br s, Ar—OH D_2O exchangeable), 6.07 and 6.10 (1H, s, H-2), 6.24 (1H, br s, H-4), 9.37 and 9.47 (1H, s, CHO); ms, m/e (rel. intensity), 410 (28), 408 (28), 354 (30), 352 (33), 330 (21), 329 (76), 328 (11), 311 (14), 285 (12), 245 (15), 231 (15), 193 (100).

Reaction of 9,11-epoxy-11-tosyl-6a,10a-trans-HHC (4a,b) with MgBr_2 in ether

Magnesium bromide was prepared by stirring together magnesium (243 mg, 10 mmol) and 1,2-dibromoethane (0.86 mL, 10 mmol) in anhydrous ether (40 mL) under nitrogen until the reaction was completed. A solution of **4a**, **b** (484 mg, 1.0 mmol) in anhydrous ether (40 mL) was added dropwise to the cooled reagent (0°C) and the stirring was continued for 2 h, after which time the reaction mixture was poured into chilled water (200 mL). After work-up with ether, TLC analysis (10% EtOAc in benzene) indicated three major products: **5b**, **1c**, and **2c**. The less polar compound **5b** was easily isolated (65%) by elution from a thin column of Florisil (15 g, 100–200 mesh, 7% ether in light petroleum ether). Compounds **1c** and **2c** were separated by further careful elution from the column (12% ether in light petroleum ether) in 5% and 18% yields respectively (**1c** isomerizes to **2c** when left on the column for a period of 12 h or more). Analytical samples of **1c** and **2c** were obtained by crystallization (ether/*n*-heptane and hexane respectively).

9 β -Bromo-11-oxo-6a,10a-trans-HHC (5b): ir (CCl_4), 3600 cm^{-1} (sharp, free OH), 3475 cm^{-1} (broad, bonded OH), 1725 cm^{-1} ($\text{C}=\text{O}$); nmr δ 0.88 (3H, br t, $J = 6$ Hz, C-5' CH_3), 0.99 (3H, s, C-6 α CH_3), 1.36 (3H, s, C-6 β CH_3), 2.43 (2H, br t, $J = 7$ Hz, Ar— CH_2), 3.97 (1H, br d, $J = 13$ Hz, H-10a), 5.10 (1H, br s, Ar—OH D_2O exchangeable), 6.10 (1H, br s, H-2), 6.24 (1H, br s, H-4), 9.37 (1H, s, CHO); ms, m/e (rel. intensity), 410 (13), 408 (13), 354 (17), 352 (16), 330 (28), 329 (91), 328 (12), 311 (21), 285 (13), 245 (22), 231 (17), 193 (100). Anal. calcd. for $\text{C}_{21}\text{H}_{29}\text{O}_3\text{Br}$: C 61.62, H 7.14, Br 19.52; found: C 61.87, H 7.34, Br 19.34.

11-Oxo-6a,10a-trans- Δ^9 -THC (1c): mp 77–79.5°C; ir (CCl_4), 3600 cm^{-1} (sharp, free OH), 3350 cm^{-1} (broad, bonded OH), 1690 cm^{-1} ($\text{C}=\text{O}$); nmr δ 0.88 (3H, br t, $J = 6$ Hz, C-5' CH_3), 1.15 (3H, s, C-6 α CH_3), 1.45 (3H, s, C-6 β CH_3), 2.48 (2H, m, Ar— CH_2), 3.51 (1H, br d, $J = 15$ Hz, H-10a), 5.24 (1H, br s, Ar—OH D_2O exchangeable), 6.16 (1H, br s, H-2), 6.30 (1H, br s,

H-4), 7.88 (1H, br s, H-10), 9.45 (1H, s, CHO); ms, m/e (rel. intensity), 328 (100), 313 (8), 299 (34), 285 (18), 243 (10), 231 (6), 217 (8), 193 (12). Anal. calcd. for $\text{C}_{21}\text{H}_{28}\text{O}_3$: C 76.79, H 8.59; found: C 76.66, H 8.95.

11-Oxo-6a,10a-trans- Δ^8 -THC (2c): mp 119–120.5°C; ir (CCl_4), 3610 cm^{-1} (sharp, free OH), 3425 (broad, bonded OH), 1680 cm^{-1} ($\text{C}=\text{O}$); nmr δ 0.87 (3H, br t, $J = 6$ Hz, C-5' CH_3), 1.13 (3H, s, C-6 α CH_3), 1.41 (3H, s, C-6 β CH_3), 2.42 (2H, br t, $J = 7$ Hz, Ar— CH_2), 3.92 (1H, br d, $J = 18$ Hz, H-10 α), 6.16 (1H, br s, H-2), 6.22 (1H, br s, H-4), 6.51 (1H, s, Ar—OH D_2O exchangeable), 6.88 (1H, m, H-8), 9.46 (1H, s, CHO); ms (14), m/e (rel. intensity), 328 (82), 286 (28), 285 (19), 273 (20), 272 (100), 245 (8), 231 (74), 193 (100). Anal. calcd. for $\text{C}_{21}\text{H}_{28}\text{O}_3$: C 76.79, H 8.59; found: C 76.56, H 8.52.

11-Oxo-6a,10a-trans- Δ^8 -THC (2c)

To a solution of the bromoaldehyde **5b** (204.5 mg, 0.50 mmol) in dimethylformamide (50 mL) was added lithium carbonate (74 mg, 1.0 mmol) and lithium bromide (16) (44 mg, 0.50 mmol). The reaction was heated at 100°C under nitrogen for 6 h, then cooled and poured into 100 mL of water. After work-up with ether and careful chromatography (Florisil 12% ether in light petroleum ether) two products were isolated: Δ^9 -aldehyde **1c** (5.0 mg 3%) and Δ^8 -aldehyde **2c** (148.7 mg, 90%). An analytical sample of **2c** obtained by recrystallization from hexanes had identical spectral characteristics compared with the previously isolated compound: Anal. calcd. for $\text{C}_{21}\text{H}_{28}\text{O}_3$: C 76.79, H 8.59; found: C 76.53, H 8.94.

11-Oxo- Δ^9 -THC (1c) (impure sample): ms, m/e (rel. intensity), 346 (28), 328 (100), 313 (10), 311 (27), 309 (24), 299 (59), 290 (19), 285 (27), 257 (22), 243 (18), 231 (13), 217 (18), 193 (36).

Synthesis of 11-oxo-6a,10a-trans- Δ^9 -THC (1c) from 9 β -bromo-11-oxo-6a,10a-trans-HHC (5b)

Collidine¹⁰ (10 mL) was added to a stirred solution of bromoaldehyde (**5b**) (79.0 mg, 0.19 mmol) in refluxing benzene (25 mL) under argon, in the presence of 4A molecular sieves. The mixture was refluxed for 72 h. Chromatography on Florisil after work-up (elution with 7% ether in light petroleum) provided **5b** (38.4 mg, 48.6%), **2c** (15.4 mg, 24.3%), and **1c** (16.7 mg, 26.3%).

11-Hydroxy-6a,10a-trans- Δ^9 -THC (1a)

Lithium aluminum hydride (3 mg, 0.08 mmol) was added to a solution of the Δ^9 -aldehyde **1c** (36 mg, 0.11 mmol) in THF (10 mL), and the mixture was stirred under nitrogen at room temperature for 4 h. Saturated ammonium chloride solution was added to the reaction until no more aluminum salts precipitated out, and the supernatant layer was poured off. Repeated washings of the precipitate with ether followed by work-up of the combined organics furnished the impure allylic alcohol **1a** (36 mg, 99%); the material was partially purified by precipitation from carbon tetrachloride which was difficult to remove entirely: ir (CCl_4), 3600 cm^{-1} (sharp, free OH), 3340 cm^{-1} (broad, bonded OH); nmr δ 0.89 (3H, br t, $J = 6$ Hz, C-5' CH_3), 1.10 (3H, s, C-6 α CH_3), 1.43 (3H, s, C-6 β CH_3), 2.43 (2H, br t, $J = 7$ Hz, Ar— CH_2), 3.26 (1H, br d, $J = 11$ Hz, H-10a), 4.03 (2H, br s, H-11), 6.13 (1H, br s, H-2), 6.25 (1H, br s, H-4), 6.72 (1H, br s, H-10); ms (14), m/e (rel. intensity), 330 (19), 312 (8), 300 (22), 299 (100), 297 (18), 269 (7), 231 (13), 217 (11), 193 (13). The spectroscopic data were identical to those of the authentic material.⁹

11-Hydroxy-6a,10a-trans- Δ^8 -THC (2a)

To a solution containing the Δ^8 -aldehyde **2c** (220 mg, 0.67 mmol) in 30 mL of THF was added lithium aluminum hydride

¹⁰Collidine was distilled from and stored over NaOH. Benzene was degassed prior to use.

(13 mg, 0.34 mmol). The mixture was stirred under nitrogen for 3 h at room temperature until no more starting material remained. Saturated ammonium chloride was added dropwise until the solution lost its yellow colour and no more aluminum hydrates precipitated out. After the organic layer was poured off, the precipitate was washed repeatedly with ether and the combined extracts were worked-up. Precipitation from carbon tetrachloride (7 mL) afforded the metabolite **2a** (196 mg, 88%) as a white amorphous solid: ir (CCl₄), 3600 cm⁻¹ (sharp, free OH), 3340 cm⁻¹ (broad, bonded OH); nmr δ = 0.87 (3H, br t, J = 6 Hz, C-5' CH₃), 1.05 (3H, s, C-6 α CH₃), 1.35 (3H, s, C-6 β CH₃), 2.41 (2H, br t, J = 7 Hz, Ar—CH₂), 3.48 (1H, br d, J = 17 Hz, H-10 α), 4.04 (2H, br s, H-11), 5.69 (1H, m, H-8), 6.10 (1H, d, J = 1.5 Hz, H-2), 6.23 (1H, d, J = 1.5 Hz, H-4); ms (14), m/e (rel. intensity), 330 (55), 312 (13), 297 (15), 274 (26), 270 (13), 269 (29), 257 (18), 256 (18), 246 (11), 245 (11), 231 (100), 214 (18), 193 (59), 174 (30), 173 (12). *Anal.* calcd. for C₂₁H₃₀O₃: C 76.32, H 9.15; found: C 76.19, H 9.43 (recrystallization from 10% ether in light petroleum ether is preferable since carbon tetrachloride is difficult to remove completely from purified samples of **2a**).

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