A Convenient Synthesis of 11-Nor-Δ^8-tetrahydrocannabinol-9-carboxylic Acid

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The metabolism of Δ^9-tetrahydrocannabinol (Δ^9-THC, **1**) in humans has been shown to be highly dependent on the route of administration.[1] When cannabis is smoke, as is most common, the major metabolic pathway is microsomal oxidation, resulting in an appreciable urinary concentration of 11-nor-Δ^9-THC-9-carboxylic acid (**2a**) and its glucuronides **2b–d**.[2,3] The analysis of these metabolites has been the basis of accurate cannabinoid detection in urine. Compound **3a** provides the basis of both a radioimmunoassay and an enzyme immunoassay for detection of THC metabolites in urine.[4] (See Figure 1.)

The dearth of synthetically useful routes to **2a** and **3a**[4,5] encouraged us to look for an alternate, more efficient synthesis. Pioneering work by Fahrenholtz et al.[6] produced an efficient and convenient route to racemic 11-nor-9-ketohexahydrocannabinol (**4a**), which we felt to be a strategic intermediate en route to **2a** and **3a**. This feeling was shared by Pitt et al.,[5a] who employed the protected ketone **4b** to prepare **3a** as well as 11-OH-Δ^8-THC (**5**). Our goal was to accomplish the efficient transformation of **4a** into **3a** in gram quantities without the use of protecting groups. The simplicity of the method we have developed prompts us to report our success. (See Scheme I.)

Results and Discussion

Our approach involves the 1-carbon homologation of ketone **4a**. This was accomplished with excess NaCN and gave >95% yield of a mixture of the epimeric cyanohydrins **6**. Treatment with methanolic HCl produced imidate **7**, which was not isolated but directly hydrolyzed with 6 N HCl to provide a mixture of epimeric hydroxy esters **8** in 75% overall yield from **6**. Treatment of **8** with $POCl_3$ in pyridine gave only one product that after hydrolysis in either strong acid or base led to a 50% yield of the 1-phosphate **3b**, which could not be converted to the desired **3a**.[7] Burgess's reagent[8] in C_6H_6 gave only a 10% yield of **3a**.[9] However, $SOCl_2$ (2–3 equiv)[10] in pyridine gave 50–73% of the desired unsaturated ester **3c**.[11] Compound **3c** was readily converted to **3a** in >95% yield upon treatment with refluxing 10% aqueous methanolic NaOH that had first been sparged with Ar for 30 min at reflux.[12]

This synthesis should also be useful for the preparation of the optically active **3a** as the corresponding optically active ketone **4a** can be prepared from ozonolysis of olefin **9**[13] (available from the material (–)-Δ^8-THC, **1**, by photolysis[13,14]).

Experimental Section

All melting points were taken on a Thomas-Hoover capillary apparatus and are uncorrected. NMR spectra were recorded on a Varian XL-100. IR spectra were recorded on a Digilab FTS-15E spectrometer. Mass spectra were obtained by using a Varian-MAT CH5 spectrometer at 70 eV. All of the solvents and reagents were of ACS-certified grade purchased from Fisher Scientific and used without purification.

Preparation of (*trans-rac*)-6a,7,8,9,10,10a-Hexahydro-1,9-dihydroxy-6,6-dimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]-pyran-9-carbonitrile (6). To a suspension of 5 g (0.10 mol) of sodium cyanide in 20 mL of methanol was added a solution of 5 g (0.016 mol) of **4a** in 175 mL of methanol, and the resulting mixture was stirred at room temperature under nitrogen for 2 h.

To this mixture was added 5.75 mL of glacial acetic acid in 50 mL of methanol, and stirring was continued for 0.5 h. The pH of the mixture was adjusted to ~2 with anhydrous HCl(g), and the mixture was stirred overnight under nitrogen whereupon the solvent was removed by using a 40 °C water bath and an aspirator. The residue was dissolved into 75 mL of water and extracted with 2 × 100 mL of methylene chloride. The combined organic layers were dried (Na_2SO_4), and the solvent was concentrated to dryness, first on a rotary evaporator at 40 °C (20 mm) and finally for 0.5 h at 0.5 mm, to afford 5.5 g (100%) of **6** as a light yellow foam, which was used without further purification in the next step. An analytical sample was prepared by recrystallization from CH_2Cl_2/petroleum ether to give colorless needles: mp 131–133 °C; ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 6 Hz, 3 H, CH_3), 1.08 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 5.88 (s, 1 H, OH), 6.04 (s, 1 H, Ar), 6.24 (s, 1 H, Ar); IR (KBr) 3440 (OH), 2235 (C≡N), 1622, 1580 cm^{-1}. Anal. Calcd for $C_{21}H_{29}NO_3$: C, 73.43; H, 8.51; N, 4.07. Found: C, 73.41; H, 8.56; N, 4.24.

Preparation of (*trans-rac*)-6a,7,8,9,10,10a-Hexahydro-1,9-dihydroxy-6,6-dimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]-pyran-9-carboxylic Acid Methyl Ester (8). Anhydrous HCl(g) was bubbled into a stirred solution of 5.5 g (0.016 mol) of **6** in 150 mL of methanol at 3 °C (ice bath) over a period of 1.25 h to saturation. The flask was capped with a septum and kept in the freezer (–20 °C) for 72 h.

To this mixture was added 75 mL of 6 N aqueous HCl, and the solvent was concentrated to dryness, first on a rotary evaporator (35 °C (20 mm)) and finally at 0.5 mm to afford an oil that was suspended in 150 mL of 50% aqueous methanol. A copious white precipitate was formed on standing at room temperature overnight. The solids were collected by filtration and then dissolved in 250 mL of ethyl acetate. A small amount of water was separated and the organic layer dried (Na_2SO_4) and concentrated to dryness in vacuo (30 °C (20 mm)).

The residue was triturated with 50 mL of petroleum ether (bp 30–60 °C). The solids were collected by filtration, washed with

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(6) Fahrenholtz, K. E.; Lurie, M.; Kierstead, R. W. *J. Am. Chem. Soc.* **1966**, *88*, 2079; **1967**, *89*, 5934.

(7) The enzymatic hydrolysis of **3b** with alkaline phosphatase is under investigation.

(8) Burgess, E. M.; Penton, R. H.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.

(9) The low yield of the desired **3a** was probably also due to phenolic participation with the Burgess reagent.

(10) Excess $SOCl_2$ increased the yield of the byproduct.

(11) When the 1-phenol was protected as the acetate to eliminate participation with the dehydrating reagent, the overall yield for the protection, dehydration, deprotection sequence was actually lower (40%). The use of other protecting groups is under investigation.

(12) The phenoxide is extremely sensitive to oxidation. When oxygen is not removed by the process described, a dark color is imparted to the reaction mixture and a 20–30% loss of yield was obtained.

(13) This photolysis and ozonolysis sequence was performed on the 2′-dimethyheptyl side chain analogue of Δ^8-THC en route to nabilone (the 2′-dimethylheptyl side chain analogue of **4a**). See: Archer, R. A.; Blanchard, W. B.; Day, W. A.; Johnson, D. W.; Lavagnino, E. R.; Ryan, C. W.; Baldwin, J. E. *J. Org. Chem.* **1977**, *42*, 2277.

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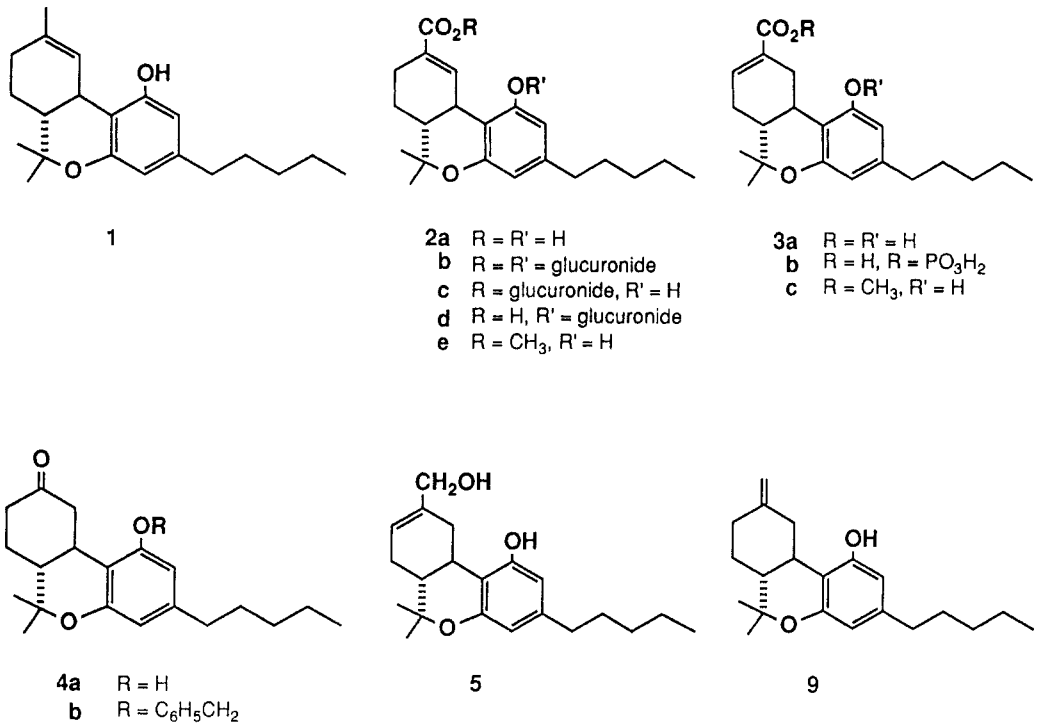
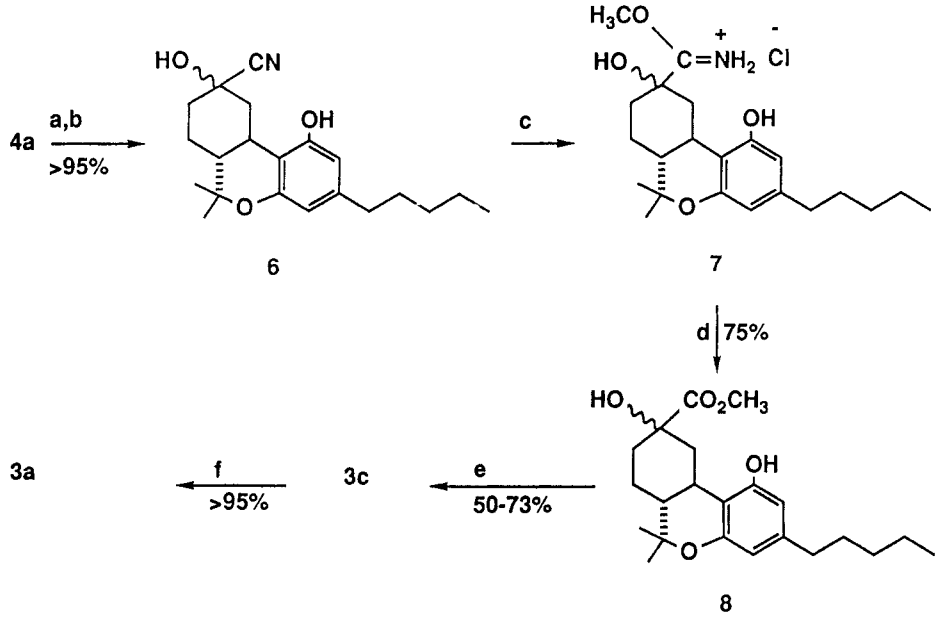


Figure 1.

Scheme I[a]



[a] (a) NaCN, CH_3OH, H_2O, 25 °C; (b) AcOH; (c) HCl(g), CH_3OH; (d) 6 N HCl; (e) $SOCl_2$, Pyr; (f) NaOH, CH_3OH, H_2O.

50 mL of petroleum ether, and then dried in vacuo (0.5 mm) for 2 h to afford 3.1 g (53%) of **8** as a colorless solid, mp 178–180 °C. The mother liquors were concentrated to give 1.3 g (22.5%) of a yellow oil, which was analyzed by NMR to the epimeric hydroxy ester of **8**. The total yield of hydroxy esters was 75%: ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 6 Hz, 3 H, CH_3), 1.08 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 3.77 (s, 3 H, $COOCH_3$), 4.80 (s, 1 H, OH), 6.05 (s, 1 H, Ar), 6.18 (s, 1 H, Ar); IR (KBr) 3330 (OH), 1748 (C=O) cm^{-1}; MS, m/e 376 (M^+). Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.56. Found: C, 70.24; H, 8.75.

Preparation of (*trans*-*rac*)-6a,7,10,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-9-carboxylic Acid Methyl Ester (3c). A 50-mL reaction flask equipped with a nitrogen bubbler and a magnetic stirrer was charged with 1.4 g (0.004 mol) of **8**, 10 mL of pyridine, and 20 mL of thionyl chloride, and then the reaction mixture was stirred at room temperature under nitrogen for 1 h. This mixture was quenched by pouring into 30 mL of ice water and extracted into 3 × 30 mL of ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated to dryness to afford 1.2 g as a solidified foam. This foam was triturated with 30 mL of petroleum ether (30–60 °C) to afford 975 mg (73%) of **3c** as a light yellow solid, mp 107–110 °C.

An analytical sample was recrystallized from ether–hexanes to give colorless crystals: mp 139–141 °C; ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 5 Hz, 3 H, CH_3), 1.13 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 3.78 (s, 3 H, $COOCH_3$), 5.63 (s, 1 H, OH), 6.16 (s, 1 H, Ar), 6.26 (s, 1 H, Ar), 7.05 (s, 1 H, vinyl); IR (KBr) 3405 (OH), 1712, 1691 (C=O) cm^{-1}; MS, m/e 358 (M^+). Anal. Calcd for $C_{22}H_{30}O_4 \cdot 0.2H_2O$: C, 72.96; H, 8.46. Found: C, 72.92; H, 8.29.

Preparation of (*trans*-*rac*)-6a,7,10,10a-Tetrahydro-6,6-dimethyl-1-hydroxy-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-9-carboxylic Acid (3a). A solution of 50 mL of MeOH and 15 mL of 1 N NaOH was placed in a 100-mL three-necked flask equipped

with magnetic stirrer and bubbler and heated to reflux while Ar gas was passed through the solution for 30 min via a gas dispersion tube. The tube was removed, 540 mg of **3c** was added in one portion to the refluxing solution, and the resultant mixture (now light green) was allowed to reflux for 2 h, after which TLC analysis on silica (EtOAc–hexanes, 1:1) indicated complete reaction. The reaction mixture was cooled to +5 °C (ice bath) and acidified with methanolic HCl to pH 1. The solvent was removed under vacuum, and the residue was dissolved in 25 mL of water, extracted into $CHCl_3$ (3 × 100 mL), and dried over Na_2SO_4. The solvent was removed under vacuum to give an oil, to which 25 mL of hexanes were added, and the solution was kept in a refrigerator (+10 °C) overnight. The resultant crystals were filtered to give 490 mg (95%) of **3a**: mp 173–175 °C; ^1H NMR ($CDCl_3$) δ 0.85 (t, J = 6 Hz, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 6.13 (s, 1 H, Ar), 6.25 (s, 1 H, Ar), 7.12 (s, 1 H, vinyl); IR (KBr) 3400 (br, OH), 1679 (C=O) cm^{-1}; MS m/e 344 (M^+). Anal. Calcd for $C_{21}H_{28}O_4 \cdot 0.3H_2O$: C, 72.08; H, 8.25. Found: C, 72.07; H, 8.18; H_2O (Karl Fischer), 1.42%. This material was identical spectroscopially with material prepared by Pitt et al.[5b,15] The melting point for this compound is different each time it is prepared.[16a] This may be explained by differing degrees of hydration.[16b]

Acknowledgment. We thank the Physical Chemistry staff for the spectral determinations and the Microchemistry staff for performing elemental analyses. We thank David Parrish for his intuitive input and helpful discussions concerning the homologation sequence. We also thank Laura Crowe for preparation of the manuscript.

(15) We thank Dr. C. G. Pitt of the Research Triangle Institute for graciously supplying reference NMR spectra for comparison.
(16) (a) Dr. C. G. Pitt, personal communications. (b) On a previous occasion, the monohydrate was prepared, mp 138–140 °C.

Synthesis and Properties of Cyclopropanone Hydrazones

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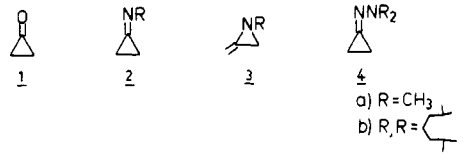
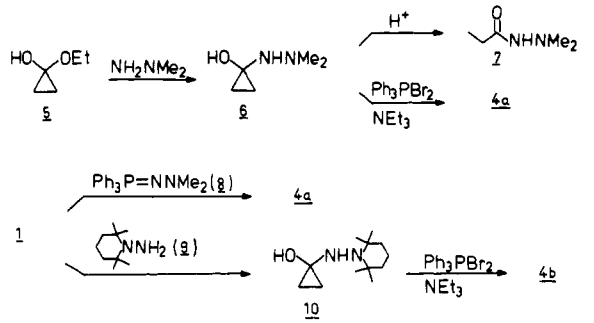
The chemistry of cyclopropanone **1** and its derivatives has been studied thoroughly.[1] Whereas **1** is extremely reactive and can only be handled in solution at low tempertures, the parent imines **2** are less sensitive.[2] Solutions



of the latter are best generated by thermal rearrangement (150–190 °C) of methyleneaziridines **3**, conditions under which partial cheletropic fragmentation to ethylene and isonitriles sets in.[2] Here we describe the synthesis, isolation, and reactivity of the novel hydrazones **4**.[3]

Upon reacting the hemiacetal **5** with *N,N*-dimethylhydrazine, the distillable but sensitive hemiaminal **6** was formed (64% yield). Unfortunately, it fails to undergo acid-catalyzed dehydration to **4a**, the hydrazide **7** being the main product. The desired transformation was finally accomplished by treatment with Ph_3PBr_2 in the presence of 2 equiv of triethylamine in dichloromethane (conversion ~40%). Alternatively, the reaction of cyclopropanone



1 with the phosphorus reagent **8**[4] also afforded **4a**. The crude product mixture was distilled rapidly to provide CH_2Cl_2 solutions of **4a** (~30% yield according to ^1H NMR spectroscopy). Pure **4a** was obtained by preparative gas chromatography. The bulky analogue **4b** is accessible by adding the hydrazine **9** to cyclopropanone and dehydrating the product **10** either by heating at 70 °C or preferably by treatment with Ph_3PBr_2/NEt_3 (64% yield).

Compound **4a** is a colorless, volatile material which is stable at −78 °C; at +4 °C decomposition sets in within 1 day. In solution at room temperature it is stable for longer periods of time. **4b** is even more stable, the pure form showing no signs of decomposition after several weeks in the refrigerator; the same applies to toluene solutions at 110 °C (4 h). Rearrangement to methyleneaziridine of the type **3** (R = amino) is not observed. All spectral and analytical data are in accord with the proposed structures. For example, the IR absorption of the C=N functionality in **4a** occurs at 1715 cm^{-1}, compared to 1680 and 1647 cm^{-1} for the *N,N*-dimethylhydrazones of cyclobutanone and cyclopentanone, respectively.[3] This is qualitatively the same trend that is observed in the ketone series itself.[1] The corresponding absorption of **4b** is shifted to 1765 cm^{-1}, probably due to steric reasons. The ^1H NMR ($DCCl_3$) spectrum shows a singlet at 2.85 ppm for the methyl groups and an AA′BB′-system for the ring protons (which was computer simulated). The ^{13}C NMR spectrum ($DCCl_3$) contains a singlet at 138 ppm (C=N) and two triplets for the other two ring C-atoms at 1.1 (J = 162 Hz) and 7.5 ppm (J = 165 Hz).

4a,b are surprisingly stable toward H_2O and CH_3OH. For example, treating a chloroform solution of **4a** with H_2O for 24 h results in only 40% loss of the compounds, i.e., more than half of it survives such conditions.

It was of synthetic interest to see if the cyclopropanone hydrazones can be alkylated via the deprotonated form without undergoing undesired polymerization. Indeed, compound **4b** can be converted into the anion **11** by treatment either with LDA (−78 °C/0.5 h) in THF or with *tert*-butyllithium (−78 °C/2 h) in ether followed by THF addition (to bring the precipitated **11** into solution). In the former case it is not certain whether deprotonation is complete or whether there is an equilibrium involving **4b**, LDA, **11**, and diisopropylamine. In any case, addition of Me_3SiCl or MeI afforded the derivatives **12a** (89%) and **12b** (56%), respectively, as distillable syn/anti mixtures.

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