Preparation of Racemic, (−)- and (+)-11-Nor-Δ^9-Tetrahydrocannabinol-9-carboxylic Acid

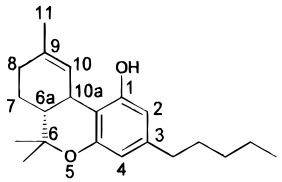
David F. Kachensky*,† and Raymond A. H. F. Hui*

Roche Research Center, Nutley, New Jersey 07110

Received June 2, 1997

Introduction

Assays designed for urinary detection of drug use rely heavily upon antibodies formed specifically to major metabolites. In the instance of cannabis intoxication, the primary metabolic pathway of the major active constituent, Δ^9-tetrahydrocannabinol (**1**), is C-11 oxidation resulting in the formation of 11-hydroxy tetrahydrocannabinol and ultimately to 11-nor-Δ^9-tetrahydrocannabinol-9-carboxylic acid (**2c**).[1] Moffat[2] and Halldin[3] have further demonstrated the major urinary excretion product, in at least a few urine samples, to be the carboxylate glucuronide[4] **2a**. The presence of the phenolic glucuronide **2b** has yet to be demonstrated unambiguously.[5] In our studies on the synthesis of cannabinoid metabolites, for assay development purposes, we found a convenient method for the preparation of racemic, (−)-, and (+)-Δ^9-tetrahydrocannabinol-9-carboxylic acid (**2c**) from the common and easily accessible (±)-11-nor-9-ketohexahydrocannabinol (**3a**).[6] This intermediate has also shown utility in the preparation of (±)-11-nor-Δ^8-tetrahydrocannabinol-9-carboxylic acid (**4**).[7]



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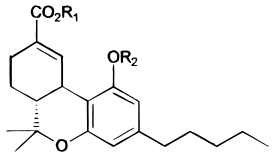
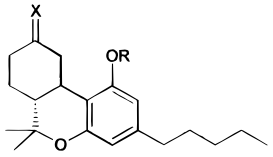
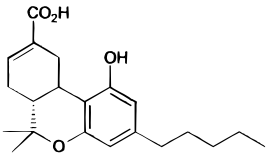


2a: R_1=Glucuronide, R_2=H
b: R_1=H, R_2=Glucuronide
c: R_1=H, R_2=H





3a: X=O, R=H
b: X=NNHSO$_2$-(2,4,6)-Triisopropylphenyl R=H
c: X=NNHSO$_2$-(2,4,6)-Triisopropylphenyl R=CH_3

4

Results and Discussion

In our synthetic strategy, ketone **3a** seemed amply suited for the classical Shapiro reaction[8] operating with the variant of intramolecular phenolic participation during the metalation process. Thus, base-effected decomposition of trisylhydrazone **3b** (4.2 eqiv of *n*-butyllithium solution, in hexanes, −78 °C, 10% TMEDA) according to the modifications of Bond[9] provided an intramolecularly assisted kinetic deprotonation occurring at C-10 of the cannabinoid nucleus, generating intermediate vinyllithium derivative **5** regioselectively. This was made evident *vide infra* after quenching this intermediate with CO_2 which provided the Δ^9-isomer **2c** without contamination by the Δ^8-isomer. Careful scrutiny of the crude reaction mixture indicated it to be isomerically homogeneous with respect to the placement of the vinylic group within the limits of detectability by 200 MHz ^{1}H NMR spectroscopy, and chromatographically distinguishable (HPLC)[10] when compared with an authentic sample of 11-nor-Δ^8-tetrahydrocannabinol-9-carboxylic acid.[11] Extractive isolation and chromatographic purification provided the crystalline acid which displayed identical spectral characteristics when compared with an authentic sample.[12] By comparison, base-effected decomposition of derivative **3c**, and subsequent quenching with CO_2, generated a ca. 9:1 mixture of the Δ^8:Δ^9-isomers, thus demonstrating the necessity for a free phenol to effect intramolecular deprotonation. Further, vinyllithium derivative **5**, generated by this procedure, is also reactive with a variety of other electrophiles (CH_3I, CH_2O, I_2, $ClCOCH_3$) and should also be amenable to isotopic labeling.

The synthesis of optically active **2c** by this procedure now required the corresponding optically active ketone **3a**. Racemic **3a** was resolved by way of formation of its (+)-diisopropyl-*l*-tartrate ketals.[13,14] Chromatographic separation of the diastereomeric ketals **6a** and **6b** followed by deprotection then provided enantiomerically pure (by NMR)[15] (−)-(6a*R*,10a*R*)-**3a** and (+)-(6a*S*,10a*S*)-**3a**. The absolute stereochemistry of the ketones were assigned by correlation with similar ketones of known stereochemistry[6b] differing only in the aliphatic chain attached to the aromatic ring at C-3, and in the case of (−)-**3a** by chemical conversion to (−)-**2c** and correlation

† Present address: Molecular Biosciences, Inc.; Boulder, Colorado. (303) 581-7722.

(1) Please note Agurell, S.; Halldin, M.; Lindgren, J. E.; Ohlsson, A.; Widman, M. *Pharmacol. Rev.* **1986**, *38*, 21−43 and references therein.

(2) Williams, P. L.; Moffat, A. C. *J. Pharm. Pharmacol.* **1980**, *32*, 445−448.

(3) Halldin, M. M.; widman, M. *Arzneim. Forsch. Drug Res.* **1983**, *33*, 177−178.

(4) The extent of carboxylic glucuronidation has been observed to vary from individual to individual and is dependent upon at least a few parameters which include the origin of the urine, the pH of the urine, and the length of time for which it has been stored.

(5) Several reports have speculated on the presence of 11-nor-Δ^9-tetrahydrocannabinol-9-carboxylic acid phenolic glucuronide, but its structure has never been authenticated. Please note Wall, M. E.; Perez-Reyes, M. *J. Clin. Pharmacol.* **1981**, *21*, 1785−1795; Kanter, S. L.; Hollister, L. G.; Williams, M. *J. Chromatogr.*, **1982**, *234*, 255−260 and reference 2.

(6) (a) Fahrenholtz, K. E.; Lurie, M.; Kierstead, R. W. *J. Am. Chem. Soc.*, **1966**, *88*, 2079; **1967**, *89*, 5934. (b) For optically pure (-)-11-nor-9-ketohexahydrocannabinol derivatives, please note Archer, R. A.; Blanchard, W. B.; Day, W. A.; Johnson, D. W., Lavaghino, E. R.; Baldwin, J. E. *J. Org. Chem.* **1977** *42*, 2277−2284.

(7) Schwartz, A.; Madan, P. *J. Org. Chem.*, **1986**, *51*, 5463−5465.

(8) Shapiro, R. H.; Heath, M. J. *J. Am. Chem. Soc.*, **1967**, *89*, 5734−5735.

(9) Chamberlin, R. A.; Stemke, J. G.; Bond, F. T. *J. Org. Chem.*, **1978**, *43*, 147−154.

(10) 11-Nor-Δ^8-tetrahydrocannabinol-9-carboxylic acid had t_R = 2.72 min on Zorbax ODS analytical column (4.6 mm × 15 cm) eluting with 45% acetonitrile−water (pH 3) whereas the corresponding Δ^9-isomer had t_R = 5.84 min.

(11) We thank the synthesis research department of Hoffmann-La Roche for a supply of this material.

(12) We thank Dr. Herbert Seltzman of Research Triangle Institute for providing us with an ^{1}H NMR spectrum of authentic 11-nor-Δ^9-tetrahydrocannabinol-9-carboxylic acid.

(13) We thank Professor George Whitesides for suggesting the use of this material for the resolution of this ketone.

(14) Resolution of **3a** is also achievable by chromatographic separation of the (2*R*,4*R*)-pentanediol ketals, but not of the (2*R*,3*R*)-butanediol ketals.

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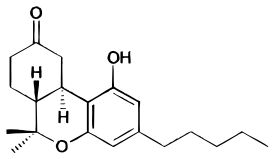
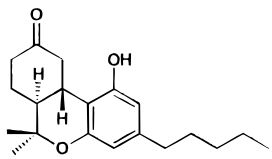
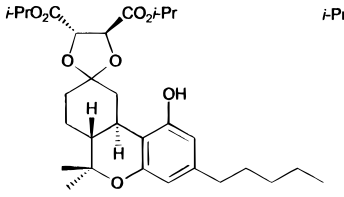


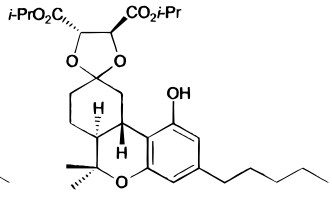
6a*R*,10a*R*, **3a**



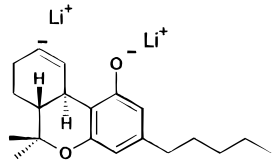
6a*S*,10a*S*, **3a**



6a



6b



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with an authentic sample[18a] of natural 6a*R*,10a*R* configuration. Additionally, ORD/CD spectroscopy showed a negative Cotton Effect curve for (−)-**3a** in accordance with the octant rule for a 6a*R*,10a*R* configuration, while a positive Cotton Effect curve for the mirror-image form was demonstrated for (+)-**3a** in keeping with a 6a*S*,10a*R* configuration (Table 1).

Application of the present procedure to (−)-(6a*R*,10a*R*)-**3a** then furnished the natural metabolite (−)-(6a*R*,10a*R*)-**2c**, spectroscopically identical to authentic material,[12,18a] while (+)-**3a** afforded (+)-(6a*S*,10a*S*)-**2c**. Both optical isomers of the metabolite **2c** are therefore now available in simple, one-pot syntheses.[19,20,21] Additionally, the availability of both (+)-**3a** and (−)-**3a** should provide an entry into Δ^9-11-nor-9-substituted or Δ^9-11-substituted THC derivatives of both unnatural (6a*S*,10a*S*) and natural (6a*R*,10a*R*) configuration.

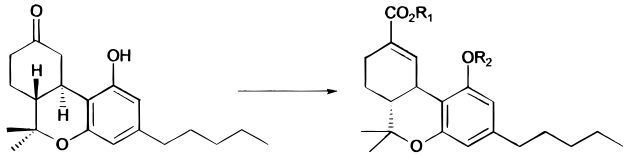
Experimental Section

^{1}H NMR spectra were obtained at 200 MHz or 400 MHz and ^{13}C NMR at 50 MHz all for $CDCl_3$ solutions. THF was distilled from sodium−benzophenone ketal under argon. Hexanes were distilled from sodium metal under argon. All other solvents were distilled from CaH_2 under argon. Medium pressure liquid chromatography (MPLC) was performed on E. M. Science silica gel 60 with automatic fraction collection. TLC were performed on E. M. Science silica gel 60 PF_{254}. Preparative thin-layer chromatography (PLC) was performed on Merck 5717 (2 mm) or Merck 5715 (0.25 mm) silica plates. Visualization of developed plates was by fluorescence quenching or staining with phosphomolybdic acid. Melting points are uncorrected.

Table 1. ORD and CD Data of (−)-3a and (+)-3a

	ORD[a]			CD[a]	
	mol Ampl[b]	Peak[c]	trough[e]	[θ]	λ^c
(−)-**3a**	−19.5	273	298	−3275	285
(+)-**3a**	+20.0	299	271	+3275	283

[a] In methanol. [b] Molecular amplitude, in hundreds of degrees. [c] Positions of extrema in nm. [e] Positions of minima in nm.



6a*R*,10a*R*, **3a** **2c**: R_1=H, R_2=H

(*trans-rac*)-6a,7,8,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-9-carboxylic Acid; (±)-11-Nor-Δ^9-carboxylic Acid, (±)-2c. To a 25 mL flask containing (±)-**3a**[11] (37.4 mg, 0.118 mmol) and trisylhydrazine[18c] (37.1 mg, 0.121 mmol) was added absolute ethanol (10 mL) at 27 °C. The reaction was stirred for 5 min and then evaporated in vacuo to provide trisylhydrazone (+)-**3b** as a foam in quantitative yield: mp 78−81 °C. The material was redissolved in 9:1 hexanes/TMEDA, cooled to −78 °C under argon, and treated with *n*-butyllithium (0.495 mmol, 2.5 M in *n*-hexane).[22] Intermediate vinyllithium formation was judged complete by the visual disappearance of nitrogen evolution after warming to 0 °C for 30 min. After this time, dry CO_2 was bubbled into the reaction for 30 s and the pH adjusted to 2 (HCl). Extractive isolation with diethyl ether then provided the crude acid which cospotted identically with authentic, optically pure material (different solvent systems, multiple elutions). TLC: R_f = 0.37 (silica, 20% ethyl acetate/hexanes). Purification by MPLC on silica gel (100−200 mesh), gradient elution with hexanes to 8:2 hexanes/ethyl acetate provided an oil which crystallized upon the addition of hexanes. Recrystallization from ether/hexanes afforded pure material (54%): mp 170−171 °C; IR (thin film) 1420 (s), 1580 (s), 1620 (s), 1670 (s), 1680 (s), 2860 (s), 3600 (m) cm^{-1}; ^{1}H NMR (200 MHz) δ 0.87 (t, 3H, J = 6.9 Hz), 1.11 (s, 3H), 1.17−1.60 (m, 10H; s at δ 1.43), 1.72 (t, 1H, J = 11.8 Hz), 2.00 (m, 1H), 2.30−2.66 (m, 4H), 3.37 (br d, 1H $J \sim$ 11 Hz), ca. 4.90 (v br, ca 2H), 6.12 (s, 1H), 6.27 (s, 1H), 8.09 (s, 1H); ^{13}C NMR δ 13.97 (q), 19.12 (q), 22.50 (t), 24.20 (t), 25.08 (t), 27.52 (d), 30.58 (t), 31.46 (t), 34.66 (d), 35.44 (t), 44.21 (d), 106.71 (s), 107.57 (d), 110.24 (d), 128.44 (s), 143.44 (s), 145.06 (d), 153.99 (s), 154.92 (s), 171.86 (s), C-6 not seen; MS *m*/*z* 344 [M$^+$], 329, 299, 288, 283; HRMS (+)-FAB calcd for $C_{21}H_{29}O_4$ [M·H]$^+$ 345.2066, found 345.2089.

(4′*R*,5′*R*,6a*R*,10a*R*)-6,6a,7,8,10,10a-Hexahydro-1-hydroxy-6,6-dimethyl-3-pentylspiro-9*H*-dibenzo[*b*,*d*]pyran-9,2′-[1,3]dioxolane-4′,5′-dicarboxylic Acid Bis-1-methylethyl Ester (6a) and (4′*R*,5′*R*,6a*S*,10a*S*) (6b).[23] To a solution of **3a** (2.00 g, 6.32 mmol) in dry toluene (50 mL) under argon was added (+)-diisopropyl-*l*-tartrate[18b] (1.554 g, 6.64 mmol, 1.05 mol equiv) and *p*-toluenesulfonic acid monohydrate (0.10 g, 0.53 mmol, 0.08 mol equiv). The solution was refluxed under a Dean−Stark trap for 26 h and cooled to rt, and the dark mixture

(15) (−)-**3a** and (+)-**3a** show diastereomeric solute−solute interactions[16] in $CDCl_3$ resulting in nonequivalence of the ^{1}H NMR spectrum of racemic **3a** and the spectra of the pure enantiomers, while nonracemic mixtures of (−)-**3a** and (+)-**3a** show two sets of signals[17] with relative intensities directly proportional to the ratio of each enantiomer present. The enantiomeric purity of the ketones is hence self-indicated by the ^{1}H NMR spectra.

(16) For a review, see: Pirkle, W. H.; Hoover, D. J. *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; Wiley-Interscience: New York, 1982; Vol. 13, pp 316−319.

(17) Details will be reported elsewhere.

(18) Obtained from (a) Research Triangle Institute; (b) Aldrich Chemical Co., (c) Fluka AG.

(19) Synthesis from Δ^9-THC: Pitt, C. G.; Fowler, M. S.; Sathe, S.; Srivastava, S. C.; Williams, D. L. *J. Am. Chem. Soc.* **1975**, *97*, 3798. No optical rotations were reported by the authors; it is not clear if the materials obtained were racemic or not.

(20) Racemic **2c** has also been previously synthesized: Mago', E.; Szirmai, M.; Ohlsson, A.; Agurell, S. *Marihuana, 1984 Proceedings of the Oxford Symposium on Cannabis*; Harvey, D. J., Ed.; IRL Press: Oxford, 1985; pp 191−195.

(21) Synthesis of (−)-**4**: Mechoulam, R.; Ben Zvi, Z.; Agurell, S.; Nilsson, I. M.; Nilsson, J. L. G.; Edery, H.; Grunfeld, Y. *Experientia* **1973**, *29*, 1193. The authors report $[a]^{25}_D = -278$ (EtOH).

(22) The quality of the *n*-butyllithium is crucial to the success of the synthesis. The use of "aged" reagent, even allowing for titrated strength of reagent, gave considerably lower yields (typically 25−40%) of eventual **2c**.

(23) See also: Schacht, E.; Desmarets, G.; Bogaert, Y. *Makromol. Chem.* **1978**, *179*, 837 for syntheses of tartrate acetals of an aromatic aldehyde.

filtered through silica gel (4.5 × 3 cm pad), followed by elution with diethyl ether (200 mL). The initial toluene filtrate was discarded. The combined ether washings containing the products was stripped of solvent to give a brownish, viscous syrup (3.51 g). This was subjected to MPLC on silica, gradient elution of CH_2Cl_2 to 15:85 ethyl acetate/CH_2Cl_2, with rechromatography of mixed fractions to provide **6a** (0.79 g, 23%) and **6b** (0.92 g, 27%), both as colorless foams, recovered starting ketone **3a** (0.18 g, 9%), and a final mixed **6a** and **6b** fraction (0.12 g, 3.5%). Separation of **6a** and **6b** could also be performed by gradient elution with 2:98 to 5:95 ethyl acetate/hexanes.

The (6a*S*,10a*S*)-ketal **6b**: TLC $R_f = 0.39$ (silica, 15:85 ethyl acetate/hexanes, three elutions); TLC $R_f = 0.33$ (silica, CH_2Cl_2); $[\alpha]^{25}_D = -52.9$ (*c* 0.22, $CHCl_3$); IR ($CHCl_3$) 1625 (m), 1732 (s), 3300−3650 (br) cm^{-1}; ^1H NMR (400 MHz) d 0.87 (t, 3H, $J = 7.1$ Hz), 1.10 (s, 3H), 1.25−1.37 (m, 16H), 1.39 (s, 3H), 1.37−1.50 (m, 2H), 1.52−1.63 (m, 3H), 1.85−1.94 (m, 2H), 2.04 (br d, 1H, $J \sim 13$ Hz), 2.38−2.50 (m, 2H), 2.91 (ddd, 1H, $J = 2.0$, 13.5, 13.5 Hz), 2.95 (ddd, 1H, $J = 2.4$, 2.4, 13.5 Hz), 4.73 (d, 1H , $J = 5.4$ Hz), 4.74 (d, 1H, $J = 5.4$ Hz), 5.15 (qq, 1H, $J = 6.3$, 6.3 Hz), 5.21 (qq, 1H, $J = 6.3$, 6.3 Hz), 6.20 (s, 1H, OH), 6.24 (d, 1H, $J = 1.8$ Hz), 6.28 (d, 1H, $J = 1.8$ Hz); ^{13}C NMR δ 14.01 (q), 18.94 (q), 21.73 (q × 4), 22.56 (t), 25.26 (t), 27.76 (q), 30.54 (t), 31.59 (t), 32.02 (d), 35.53 (t), 36.51 (t), 38.95 (t), 48.77 (d), 69.90 (d), 70.71 (d), 76.44 (s), 77.45 (d × 2), 108.33 (s), 108.93 (d), 109.65 (d), 114.48 (s), 143.32 (s), 154.47 (s), 154.98 (s), 168.72 (s), 171.67 (s); MS *m/z* 532 [M^+], 490, 489, 476, 445, 403, 315, 299, 298, 283, 273, 260, 245, 233, 231; HRMS calcd for $C_{30}H_{44}O_8$ 532.3036, found 532.3013.

The (6a*R*,10a*R*)-ketal **6a**: TLC $R_f = 0.32$ (silica, 15:85 ethyl acetate/hexanes, 3 elutions); TLC $R_f = 0.18$ (silica, CH_2Cl_2); $[\alpha]^{25}_D = -55.9$ (*c* 0.23, $CHCl_3$); IR ($CHCl_3$) 1624 (m), 1740 (s), 3300−3650 (br), 3590 (m, free OH) cm^{-1}; ^1H NMR (400 MHz) δ 0.88 (t, 3H, $J = 7.0$ Hz), 1.08 (s, 3H), 1.24−1.37 (m, 16H), 1.38 (s, 3H), 1.39−1.59 (m, 5H), 1.72 (ddd, 1H, $J = 4.8$, 13.7, 13.7 Hz), 1.83 (m, 1H), 2.07 (dddd, 1H, $J = 2.5$, 2.5, 2.5, 13.3 Hz), 2.35−2.48 (m, 2H), 2.81 (ddd, 1H, $J = 2.5$, 10.5, 11.6 Hz), 3.36 (ddd, 1H, $J = 2.5$, 2.5, 13.3 Hz), 4.73 (d, 1H, $J = 5.7$ Hz), 4.83 (d, 1H, $J = 5.7$ Hz), 5.04 (s, 1H, OH), 5.13 (qq, 1H, $J = 6.3$, 6.3 Hz), 5.14 (qq, 1H, $J = 6.3$, 6.3 Hz), 6.07 (d, 1H, $J = 1.5$ Hz), 6.23 (d, 1H, $J = 1.5$ Hz); ^{13}C NMR δ 14.01 (q), 19.14 (q), 21.73 (q × 4), 22.54 (t), 25.06 (t), 27.80 (q), 30.56 (t), 31.58 (t), 32.60 (d), 35.43 (t), 35.72 (t), 39.16 (t), 48.02 (d), 69.62 (d), 69.73 (d), 76.80 (s), 77.18 (d × 2), 107.72 (d), 109.02 (s), 109.83 (d), 114.35 (s), 142.79 (s), 154.62 (s), 154.92 (s), 169.44 (s), 169.59 (s); MS *m/z* 532 [M^+], 490, 489, 445, 403, 315, 299, 298, 283, 273, 271, 260, 258, 245, 242, 233, 231; HRMS calcd for $C_{30}H_{44}O_8$ 532.3036, found 532.3004.

(6a*R*,10a*R*)-6,6a,7,8,10,10a-Hexahydro-1-hydroxy-6,6-dimethyl-3-pentyl-9*H*-dibenzo[*b*,*d*]pyran-9-one; (6a*R*,10a*R*)-3a. To a solution of the (6a*R*,10a*R*)-ketal **6a** (0.69 g, 1.30 mmol) in THF (20 mL) under argon was added 3 N $HClO_4$ (10 mL) and the clear solution heated at 70 °C for 4 h. The clear, light yellow solution was cooled to rt, diluted with water (20 mL), cautiously treated with solid sodium bicarbonate to saturation, and extracted with four portions of ethyl acetate. The combined extracts were washed with water and saturated NaCl, dried (Na_2SO_4), and evaporated in vacuo to provide the crude product (0.232 g, 57%) as a slightly discolored foam. This material was dissolved in 35:65 THF/hexanes and passed through a short column of silica gel, eluting with the same solvent mixture. Evaporation in vacuo of the filtrates then provided pure (6a*R*,10a*R*)-**3a** (0.184 g, 45%) as a white crystalline foam: mp 114−117 °C; $[\alpha]^{25}_D = -91$ (*c* 0.12, $CHCl_3$); UV (MeOH) 207 (e 49750), 230 (sh, 10500), 275 (1420), 282 (1510) nm; IR (KBr) 1623 (s), 1691 (s), 3000−3650 (br) cm^{-1}; ^1H NMR (400 MHz) δ 0.88 (t, 3H, $J = 7.0$ Hz), 1.12 (s, 3), 1.25−1.38 (m, 4H), 1.47 (s, 3H), 1.48−1.52 (m, 3H), 1.97 (ddd, 1H, $J = 3.2$, 11.2, 12.2 Hz), 2.14 (dd, 1H, $J = 12.8$, 15.0 Hz), 2.18 (m, 1H), 2.44 (t, 2H, $J = 7.7$ Hz), ca. 2.48 (m, 1H), 2.62 (dddd, 1H, $J = 2.6$, 2.6, 5.2, 15.2 Hz), 2.89 (ddd, 1H, $J = 3.2$, 12.5, 13.4 Hz), 4.04 (ddd, 1H, $J = 2.1$, 3.5, 15.1 Hz), 6.20 (d, 1H, $J = 1.5$ Hz), 6.26 (d, 1H, $J = 1.5$ Hz), 6.50 (s, 1H, OH); ^{13}C NMR d 14.04 (q), 18.88 (q), 22.55 (t), 26.89 (t), 27.85 (q), 30.68 (t), 31.60 (t), 34.77 (d), 35.52 (t), 40.86 (t), 45.15 (t), 47.42 (d), 77.22 (s), 107.78 (d), 108.11 (s), 109.48 (d), 143.58 (s), 154.62 (s), 154.98 (s), 213.50 (s); MS *m/z* 316 [M^+], 301, 283, 273, 260, 245, 233, 231, 206, 193, 150; HRMS calcd for $C_{20}H_{28}O_3$ 316.2038, found 316.2032. Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.96; H, 8.81.

In another run with 0.23 g of **6a** in 10 mL of THF and 10 mL of 3 N $HClO_4$ for 2.4 h at 70 °C followed by workup and chromatography (PLC) on silica (3:7 ethyl acetate/hexanes) there was obtained 0.102 g, 74%, of (−)-**3a**.

The alternate use of 8:2 glacial acetic acid/water gave, after workup and PLC, 64% of (−)-**3a**, $[\alpha]^{25}_D = -93$ (*c* 0.12, $CHCl_3$).

(6a*S*,10a*S*)-6,6a,7,8,10,10a-Hexahydro-1-hydroxy-6,6-dimethyl-3-pentyl-9*H*-dibenzo[*b*,*d*]pyran-9-one; (6a*S*,10a*S*)-3a. The (6a*S*,10a*S*)-ketal **6b** (0.60 g, 1.13 mmol) was heated at 70 °C in THF (10 mL) and 3 N $HClO_4$ (10 mL) for 3 h. Workup as before followed by PLC on silica (3:7 ethyl acetate/hexanes) then gave (6a*S*,10a*S*)-**3a** (0.22 g, 62%) as a pale yellow crystallizing gum, elongated prisms from hexanes (at −20 °C): mp 115−117 °C; $[\alpha]^{25}_D = +92$ (*c* 0.09, $CHCl_3$); UV (MeOH) 207 (ϵ 44000), 230 (sh, 9300), 275 (1280), 282 (1370) nm; IR (KBr) 1620 (s), 1690 (s), 3000−3600 (br) cm^{-1}; ^1H NMR (400 MHz) δ 0.88 (t, 3H, $J = 6.8$ Hz), 1.12 (s, 3H), 1.25−1.38 (m, 4H), 1.47 (s, 3H), 1.48−1.53 (m, 3H), 1.96 (ddd, 1H, $J = 3.2$, 11.2, 11.2 Hz), 2.14 (dd, 1H, $J = 12.8$, 14.7 Hz), 2.17 (m, 1H), 2.44 (t, 2H, $J = 7.7$ Hz), ca. 2.48 (m, 1H), 2.62 (dddd, 1H, $J = 2.9$, 2.9, 5.8, 15.4 Hz), 2.89 (ddd, 1H, $J = 3.5$, 12.2, 13.4 Hz), 4.05 (ddd, 1H, $J = 2.2$, 3.5, 15.0 Hz), 6.20 (d, 1H, $J = 1.1$ Hz), 6.26 (s, 1H), 6.59 (s, 1H, OH); ^{13}C NMR δ 1405 (q), 18.88 (q), 22.55 (t), 26.92 (t), 27.86 (q), 30.69 (t), 31.62 (t), 34.81 (d), 35.54 (t), 40.88 (t), 45.09 (t), 47.43 (d), ca. 77 (s), 107.79 (d), 108.06 (s), 109.38 (d), 143.59 (s), 154.61 (s), 155.10 (s), 213.88 (s); MS *m/z* 316 [M^+], 301, 283, 273, 260, 245, 233, 231, 206, 193, 150; HRMS calcd for $C_{20}H_{28}O_3$ 316.2038, found 316.2034. Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.70; H, 9.09.

In some runs, especially on a larger scale, incomplete hydrolysis of the tartrate ketals accounted for lower yields of the ketones. A run with 6a*S*,10a*S*-**6b** (0.89 g) provided after workup and silica gel filtration 0.17 g of 6a*S*,10a*S*-**3a** (33%) from ethyl acetate extraction of the basic aqueous. Acidification (concd HCl) of the aqueous and ethyl acetate extraction then gave, after removal of solvent, a brownish foam (0.44 g, 58% crude). A sample was purified on florisil, eluting with 1:1 $CHCl_3$/MeOH, to give pale yellow flakes of the corresponding tartaric diacid ketal (4′*R*,5′*R*,6a*S*)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-3-pentylspiro-9*H*-dibenzo[*b*,*d*]pyran-9,2′-[1,3]dioxolane-4′,5′-dicarboxylic acid: ^1H NMR δ 0.85 (t, 3H, $J = 6.4$ Hz), 1.00 (s, 3H), 1.10−1.60 (m, 12H; s at δ 1.35), 1.85 (m, 2H), 1.99 (m, 1H), 2.37 (t, 2H, $J = 7.5$ Hz), 2.82 (dd, 1H, $J \sim 11$,11 Hz), 3.10 (d, 1H, $J \sim 12.5$ Hz), 4.96 (d, 1H, $J = 4.0$ Hz), 5.04 (d, 1H, $J = 4.0$ Hz), 6.15 (s, 1H), 6.23 (s, 1H), 6.89 (br, ca 3H, O*H* + 2 × CO_2H); δ (CD_3OD) 0.89 (t, 3H, $J = 6.4$ Hz), 1.06 (s, 3H), 1.20−1.65 (m, 12H; s at δ 1.34), 1.79 (m, 2H), 2.10 (m, 1H), 3.02 (dd, 1H, $J \sim 11$, 11 Hz), 3.14 (d, 1H, $J \sim 12.5$ Hz), 4.41 (m, 2H), 6.08 (s, 1H), 6.15 (s, 1H); HRMS (+)-FAB *m/z* 449.2137 [M·H]$^+$, calcd for $C_{24}H_{33}O_8$ 449.2175.

Other methods[24] that were tried for the deprotection of the tartrate ketals, and the yields of ketone obtained, included the following: (i) wet $MgSO_4$, benzene, rt; no reaction; (ii) silica gel, cat. 15% H_2SO_4, CH_2Cl_2, rt; no reaction; (iii) wet acetone, cat. PPTS or TsOH, reflux; no reaction or decomposition; (iv) 10% aqueous HCl, THF, reflux, 15 h, 24% ketone.

(6a*R*,10a*R*)-6a,7,8,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-9-carboxylic Acid, (6a*R*,10a*R*)-2c. In an analogous manner to that described above for the racemic ketone, the (6a*R*,10a*R*)-ketone (−)-**3a** (30 mg, 0.096 mmol) was converted to the trisyl hydrazone and then treated with *n*-butyllithium (4.2 mol equiv) at −78 °C to −10 °C to 0 °C (9:1 hexanes/TMEDA) followed by CO_2 gas (3 min). Workup up then gave a light yellow oil which was subjected to MPLC on silica ($CHCl_3$ gradient to 95:5 $CHCl_3$/MeOH) to give the crude acid (17 mg, 50%) as a light yellow oil. Rechromatography (silica, 98:2 $CHCl_3$/MeOH) provided (6a*R*,10a*R*)-**2c** as a white crystalline solid: mp 206−209 °C (subl ∼170 °C) (lit.[19] 205−207 °C); $[\alpha]^{25}_D = -169$ (*c* 0.15, $CHCl_3$)[25] (authentic material,[18a]

(24) For leading references, see: Greene, T. W. *Protective Groups in Organic Synthesis*; Wiley: New York, 1981; pp 124−128.

$[\alpha]^{25}_D = -164$ (*c* 0.15, $CHCl_3$); ^1H NMR identical[25] to those of (±) and of authentic material.[12,18a] IR[26] (KBr) 3700−2400 (br), 1681 (s), 1626 (s) cm^{-1}; ^{13}C NMR δ 14.03 (q), 19.15 (q), 22.54 (t), 24.21 (t), 25.15 (t), 27.55 (q), 30.65 (t), 31.48 (t), 34.64 (d), 35.48 (t), 44.20 (d), 77.19 (s), 106.70 (s), 107.56 (d), 110.30 (d), 128.31 (s), 143.50 (s), 144.95 (d), 153.95 (s), 154.96 (s), 170.89 (s); MS (+)-FAB *m*/*z* 345 $[M\cdot H]^+$, 343 [M − H], 329, 327, 299; HRMS (+)-FAB calcd for $C_{21}H_{29}O_4$ $[M\cdot H]^+$ 345.2066, found 345.2077.

(6a*S*,10a*S*)-6a,7,8,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-9-carboxylic Acid, (6a*S*, 10a*S*)-2c. In a similar manner, the use of (+)-(6a*S*,10a*S*)-**3a** (100 mg, 0.316 mmol) gave, after workup, a clear oil (220 mg). This was subjected to PLC on silica (5:4:1 ethyl; acetate/hexanes/MeOH) to give, in two overlapping bands (6a*S*,10a*S*)-**2c** (22 mg, 20%) followed by a 2:1 mixture (19 mg, 17%) of (6a*S*,10a*S*)-**2c** and (6a*S*,10a*S*)-**4** (=CH at δ 6.98, H_{10a} at δ 3.78) (lit.[21] for (−)-**4**, δ (CCl_4) 7.05, 3.65) as shown by ^1H NMR. Yield of the Δ^9-acid (6a*S*,10a*S*)-**2c**, 31%; of the Δ^8-acid (6a*S*,10a*S*)-**4**, 7%. Recrystallization ($CHCl_3$) of the material from the upper band then gave pure (6a*S*,10a*S*)-**2c** as a white crystalline solid: mp 210−213 °C (sublimes 150 °C) (lit.[19] 205−207 °C); $[\alpha]^{25}_D = +166$ (*c* 0.10, $CHCl_3$) (authentic natural (6a*R*,10a*R*) material,[18a] $[\alpha]^{25}_D = -164$); IR[26] ($CHCl_3$) 3590 (m), 1712 (m), 1682 (s), 1635 (m, sh), 1423 (s), 1260 (s) cm^{-1}; IR (KBr) 3400 (br), 1682 (vs), 1578 (m) cm^{-1}; ^1H and ^{13}C NMR identical to those of authentic natural[12,18a] and enantiomeric [(−)-**2c**] material; MS *m*/*z* 344 $[M]^+$, 329, 327, 299, 288, 283, 231; HRMS (+)-FAB calcd for $C_{21}H_{29}O_4$ $[M\cdot H]^+$ 345.2066, found 345.2056.

(25) The material so obtained contains a trace of the Δ^8-isomer **4** by ^1H NMR spectroscopy, presumably because of a somewhat longer exposure to silica than before, as an NMR of the crude material reveals no isomer contamination. The slightly larger negative value of the optical rotation, if significant, may then be due to the presence of a trace of (−)-**4**.[21]

(26) The IR spectra of (+)-**2c** and (−)-**2c** are identical to each other but nonsuperimposable on that of (±)-**2c**.

Acknowledgment. We gratefully acknowledge the Physical Chemistry staff of Hoffmann-La Roche for aid in characterization of compounds.

JO970969E