Synthesis of 11-Nor-Δ^8-tetrahydrocannabinol-9-carboxylic Acid Methyl Ester

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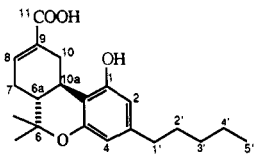
A short stereospecific synthesis of optically active Δ^8-THC carboxylic acid methyl ester proceeding from (+)-apoverbenone has been accomplished. The key steps are the addition of the cuprate derived from a lithiated olivetol ether to apoverbenone and the cationic cyclization of a vinyl trifluoromethanesulfonate. The methodology for this synthesis is general enough to be applied to other cannabinoids.

In spite of the determined efforts of two generations of chemists, enantioselective and stereospecific total syntheses of the oxidized metabolites of the cannabinoids have been lacking.[1] The problem of cannabinoid synthesis can be broken down into two operations: the conjunction of olivetol, or of an olivetol derivative with an appropriate monoterpene, and the subsequent cationic cyclization to the cannabinoid skeleton. The difficulty arises from the cyclization step which is typically nonregiospecific and leads to a mixture of the cannabinoid and its isomer in which hydroxyl and *n*-pentyl groups are formally transposed.[1,2] A very ingenious method for overcoming this problem has been described by Chan, wherein 4-carbomethoxyolivetol was used in place of olivetol.[3] The aromatic carbomethoxy group blocked the undesired cyclization; however, the introduction and subsequent removal of this blocking group from the product detracts somewhat from the overall efficiency. Another factor which has conspired to delay progress in this area is the recognized fact that cannabinoid chemistry is more complex than the simplicity of the structures would suggest.[4] Furthermore, the products are more often than not difficult to crystallize and are sensitive to oxidation, particularly in basic media.

The synthesis of cannabinoids has ramifications beyond those of an intellectual exercise. Extensive pharmacological studies have established useful activities for cannabinoids and for their analogues.[5] The most promising activities are associated with the antiemetic, antiglaucoma, and analgesic effects.[5,6] For example, the antinauseant effect of Δ^9-THC has long been recognized and has had a role in ameliorating one of the most distressing side effects of cancer chemotherapy.[7] Synthetic cannabinoid analogues are in clinical study as antiemetics and analgesics.[5,8] The major metabolic pathway for Δ^9-THC administered in smoke to humans involves the oxidation of the 9-methyl group to the corresponding carboxylic acid, which is subsequently converted to a mixture of glucuronides, which are excreted in urine.[9] 11-Nor-Δ^8-THC-carboxylic acid (1) is used in a rapid immunoassay for the detection of THC metabolites in human urine.[10] The trideuterio Δ^9 isomer **2** is used as an internal standard for the unambiguous confirmation, by gas chromatography/mass spectrometry, of positive results from the immunoassay screen.[11]

Earlier work from our laboratories has resulted in an improved synthesis of protio-**2**, via diol **3**.[12] This synthesis suffered both from the lack of regiocontrol during the cyclization step, which has been discussed, and from the difficulty in obtaining the optically active starting material, (+)-perillaldehyde, from a commercial source.[13] A synthesis which overcomes both of these problems and which provides a highly efficient entry into the optically pure Δ^8-THC skeleton will be described.



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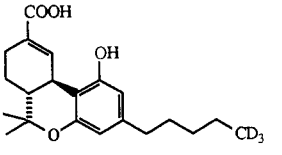

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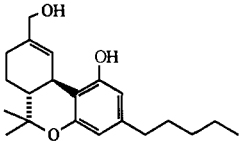

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The starting material for the synthesis was (+)-apoverbenone **4** (Scheme I), which was prepared from cheap and readily available (−)-β-pinene by Grimshaw's method.[14] Olivetol was converted to its bis(ethoxyethyl) ether in 77% yield by treatment in diethyl ether with a small excess of ethyl vinyl ether in the presence of *p*-toluenesulfonic acid. Metalation of this olivetol derivative took place with *n*-butyllithium in tetrahydrofuran (THF) at 25 °C. The lithiated olivetol derivative was transferred to 1 equiv of lithium 2-thienylcyanocuprate in THF, and the mixed, higher order cuprate[15] was treated with a THF solution of apoverbenone and boron trifluoride etherate (1/1). The

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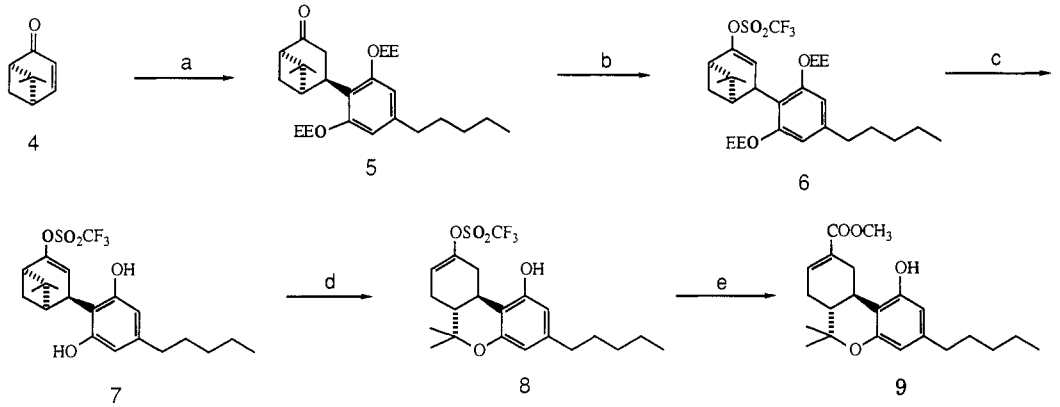
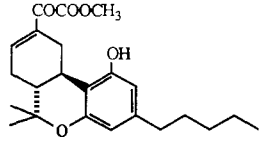
0022-3263/90/1955-5711$02.50/0

Scheme I[a]



[a] (a) See text; 66%; (b) $(Me_3Si)_2NK$, THF, 0 °C; $PhN(SO_2CF_3)_2$; (c) PPTS, CH_3OH; 65% over two steps; (d) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 25 °C; 87%; (e) $PdCl_2(PPh_3)_2$, 10 mol %, K_2CO_3, CO, CH_3OH, THF, 25 °C; 72%.

yield of the cuprate adduct **5** was 66%. Attack of the cuprate took place trans to the geminal dimethyl bearing bridge. The stereochemistry was not proven at this stage; the successful conversion of **5** to **9** conclusively proves the structure. The stereochemistry of the cuprate addition determines the ring junction stereochemistry of the final product. Ketone **5** was converted to enol triflate **6** by consecutive treatment in THF with potassium hexamethyldisilyl amide followed by bis(((trifluoromethyl)sulfonyl)oxy)aniline.[16] The enol triflate was robust, as expected, and exposure to pyridinium tosylate in methanol gave the dihydroxy compound **7** in 65% overall yield from **5**. A solution of **7** in anhydrous dichloromethane was treated at 25 °C with an excess of boron trifluoride etherate.[17] After 8 h the reaction mixture was worked up to produce cyclic vinyl triflate **8** in 87% yield following flash column chromatography on silica gel. Transposition of the double bond during cyclization leads *specifically* to the Δ^8 series. The cyclization reaction undoubtedly is a stepwise process and is facilitated by the relief of ring strain attending the cleavage of the four-membered ring. Upon treatment of a solution of **8** in methanolic THF with 10 mol % $PdCl_2(PPh_3)_2$, potassium carbonate and a static atmosphere of CO at 25 °C,[18] methyl ester **9** was obtained in 72% yield as a crystalline solid (mp 142 °C) following flash column chromatography. In preliminary experiments to optimize the carbonylation reaction, a strongly UV-absorbing byproduct was obtained when the ratio of THF–methanol was 6:1. This byproduct was assigned oxalate structure **10** based on spectroscopic evidence. No



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attempt to optimize the formation of **10** was made, and when the proportion of methanol in the solvent mixture was reduced, **9** was the only product observed. The spectroscopic data for **9** matched the data reported by Schwartz and Madan.[19] Through the use of ammonium formate in the palladium catalyzed reaction, acid **2** can be prepared from **8**.[20]

Several features of this synthesis are noteworthy and recommend it for the preparation of cannabinoids. It is brief: **9** was prepared in five steps from apoverbenone **4** (eight steps from β-pinene) in 27% overall yield. The starting material is cheap and readily available. The synthesis is enantiospecific, and the regiospecificity problem is completely avoided by using the cuprate reaction to join the olivetol derivative to the monoterpene fragment. Recently a very clever synthesis of the racemate of protio-**2** has been accomplished which also makes use of the carbonylation of an enol triflate for the introduction of the 9-carboxy group.[1b] A rather different problem which was encountered in this work was the formation of a mixture of ring-junction isomers which could not be separated by careful column chromatography.[21] Our work does not suffer from this drawback. It should, of course, be emphasized that this conjugate addition strategy has been used very successfully by others in the past, for both the synthesis of natural,[22] as well as nonclassical cannabinoids.[23] The conjunction of substituted resorcinols with apoverbenone under acidic conditions has also been used for cannabinoid synthesis.[24]

In summary, a very short and enantiospecific synthesis of 11-nor-Δ^8-THC-9-carboxylic acid methyl ester has been described. The methodology should prove to be general and will provide access to a number of THC structural variants. Triflate **8** is an ideal precursor for radiolabeled cannabinoids.

Experimental Section

All reactions were performed in flame-dried glass apparatus equipped with rubber septa under a static nitrogen or argon atmosphere. Thin-layer chromatography was performed on EM Reagents precoated silica gel 60 F-254 analytical plates (0.25 mm). Flash chromatography was performed on Brinkmann silica gel

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(0.040–0.063 mm). Melting points were reported for all crystalline products. All other products were isolated as clear, pale yellow oils.

Proton nuclear magnetic resonance spectra were recorded at 300 MHz on a GE QE300 spectrometer (Oxford magnet). NMR data are reported in ppm from $CHCl_3$ (7.26 ppm) or from C_6H_6 (7.15 ppm). Infrared spectra were recorded on a Perkin-Elmer IR 1430 spectrometer. Electron impact mass spectra were performed on a VG-70SE mass spectrometer.

(+)-4-[4-*n*-Pentyl-2,6-bis(2-ethoxyethyl)phenyl]-6,6-dimethyl-2-norpinanone (5). To a solution of 311 mg (0.956 mmol) of the bis(ethoxyethyl) ether of olivetol[25] in 15 mL of anhydrous THF was added at 0 °C 0.84 mL (1.150 mmol) of an *n*-butyllithium solution in hexane during 20 min. The mixture was stirred at 0 °C for 10 min and then at 25 °C for 2.5 h. In a separate flask 3.84 mL (0.956 mmol) of a solution of lithium 2-thienylcyanocuprate in THF was cooled to −78 °C. The lithiated olivetol was transferred by cannula to the cuprate solution over a 30-min period. Following addition, the reaction mixture was placed in an ice bath for 10 min, cooled to −78 °C, and stirred for 1.5 h. To the pale yellow cuprate solution was slowly added a mixture of 100 mg (0.735 mmol) of (+)-apoverbenone (**4**) and 0.10 mL (0.735 mmol) of $BF_3{\cdot}Et_2O$ in 1.5 mL of THF at −78 °C. The mixture was stirred at −78 °C until TLC showed the dissappearance of the starting material (1–2 h). The reaction was diluted with ether, washed with concentrated NH_4OH/saturated NH_4Cl (1/9) solution, extracted with ether (3 × 40 mL), and dried ($MgSO_4$). Evaporation of the solvent followed by flash column chromatography on silica gel eluting with 5% ethyl acetate in hexane produced 225 mg (66% yield; this material is a mixture of diastereomers due to the asymmetric center on each of the two ethoxyethyl protecting groups) of **5** as an oil: ^1H NMR ($CDCl_3$, 300 MHz) 6.59 (s, 1 H), 6.55 (s, 1 H), 5.39–5.46 (m, 2 H), 4.09–4.16 (m, 1 H), 3.74–3.64 (m, 2 H), 3.57–3.46 (m, 2 H), 3.38–3.29 (m, 1 H), 2.56–2.45 (m, 5 H), 2.22 (br s, 1 H), 1.48 (d, J = 5.1 Hz, 6 H), 1.35 (s, 3 H), 1.22–1.16 (m, 6 H), 0.98 (s, 3 H), 0.89 (t, J = 6.7 Hz, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) 215.73, 156.07, 155.95, 142.38, 118.69, 108.72, 108.61, 108.56, 108.41, 98.96, 98.84, 61.02, 60.92, 60.59, 57.71, 46.86, 42.28, 38.34, 36.01, 31.37, 30.92, 29.14, 26.25, 24.70, 22.43, 22.04, 20.09, 15.15, 13.93 ppm; IR (neat) 2975, 2925, 2860, 1710, 1605, 1570, 1430, 1380, 1071, 1050 cm^{-1}. In order to more fully characterize this material, the two ethoxyethyl groups were removed hydrolytically by treatment with pyridinium tosylate in methanol to produce the corresponding resorcinol as a single isomer: $[\alpha]^{24}_D$ +69.1° (*c* 0.4, ethanol); ^1H NMR ($CDCl_3$, 300 MHz) 6.17 (s, 2 H), 5.13 (s, 2 H, exchangeable with D_2O), 3.95 (t, J = 8.1 Hz, 1 H), 3.47 (dd, J = 18.9, 7.8 Hz, 1 H), 2.68–2.39 (m, 5 H), 2.30 (t, J = 5.4 Hz, 1 H), 1.36 (s, 3 H), 1.31–1.26 (m, 4 H), 0.99 (s, 3 H), 0.89 (t, J = 6.9 Hz, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) 171.66, 155.26, 142.58, 113.65, 108.59, 57.99, 46.84, 42.26, 37.91, 35.24, 31.51, 30.64, 29.48, 26.15, 24.42, 22.48, 22.13, 13.97 ppm; IR (CCl_4) 3350, 2950, 2920, 2850, 1680, 1620, 1590, 1430, 1265, 1020 cm^{-1}; mass spectrum, m/e 316 (M^+, 69), 301 ($M^+ - CH_3$, 25), 273 (55), 247 (25), 233 (100), 219 (40), 206 (33), 193 (70), 150 (66), 83 (65), 69 (35), 57 (50); mass calcd for $C_{20}H_{28}O_3$ 316.2038, found 316.2036.

Enol Triflate 6. To a solution of 1.302 mmol of potassium hexamethyldisilylamide in 8 mL of THF at 0 °C was added a solution of 200 mg (0.434 mmol) of **5** in 2 mL of THF. The solution was stirred for 1 h at 0 °C, and 465 mg (1.303 mmol) of solid $PhN(SO_2CF_3)_2$ was added to the reaction mixture. The progress of the reaction was monitored by thin-layer chromatography. The reaction mixture was diluted with ether, washed with brine, and dried ($MgSO_4$). Evaporation of the solvent produced the crude vinyl triflate. Separation of the product from the excess reagent was difficult as both had nearly identical chromatographic mobilities. The mixture of reagent and product which was obtained from flash column chromatography, eluting with 5% ethyl acetate in hexane was used for the next reaction: ^1H NMR ($CDCl_3$, 300 MHz) 6.63–6.58 (m, 2 H), 5.82–5.75 (br m, 1 H), 5.42–5.37 (m, 2 H), 4.15 (t, J = 2.6 Hz, 1 H), 3.73–3.64 (m, 2 H), 3.57–3.49 (m, 2 H), 2.51 (t, J = 7.6 Hz, 2 H), 2.41–2.33 (br m, 2 H), 2.09–2.05 (m, 1 H), 1.97–1.94 (m, 1 H), 1.47 (d, J = 5.4 Hz, 3 H), 1.33 (s, 3 H), 1.19 (t, J = 8.2 Hz, 3 H), 1.07 (s, 3 H), 0.89 (t, J = 6.9 Hz, 3 H) ppm; IR ($CHCl_3$) 2990, 2920, 1610, 1585, 1425, 1210, 1150, 1080, 1050, 1040, 930, 865 cm^{-1}; mass spectrum, m/e 592 (M^+, weak), 448 (64), 405 (38), 315 (30), 234 (55), 193 (34), 109 (32), 73 (100); mass calcd for $C_{29}H_{43}SO_7F_3$ 592.2682, found 592.2730.

Resorcinol 7. To the product from the preceding reaction in 15 mL of methanol was added ca. 15 mg of pyridinium tosylate. The reaction mixture was stirred vigorously at 25 °C until thin-layer chromatography indicated that all the starting material had been consumed (ca. 6 h). The reaction mixture was diluted with ether, washed with brine, and dried ($MgSO_4$). Solvent evaporation gave the crude diol, which was purified by flash column chromatography on silica gel, eluting with 5% ethyl acetate in hexane. The overall yield from **5** was 125 mg (65%): $[\alpha]^{24}_D$ −79.7° (*c* 0.38, ethanol); ^1H NMR ($CDCl_3$, 300 MHz) 6.21 (s, 2 H), 5.94 (s, 1 H), 5.20 (s, 2 H, exchangeable with D_2O), 4.12 (s, 1 H), 2.54–2.41 (m, 4 H), 2.28 (t, J = 5.6 Hz, 1 H), 1.76 (d, J = 9.3 Hz, 1 H), 1.38 (s, 3 H), 1.32–1.26 (m, 4 H), 1.08 (s, 3 H), 0.89 (t, J = 6.9 Hz, 3 H) ppm; ^1H NMR (C_6D_6, 300 MHz) 5.84 (s, 2 H), 5.56 (s, 1 H), 4.71 (s, 2 H, exchangeable with D_2O), 4.05 (br s, 1 H), 2.34 (t, J = 7.2 Hz, 2 H), 2.22–2.16 (m, 2 H), 2.11–2.04 (m, 1 H), 1.86 (d, J = 9.6 Hz, 1 H), 1.51 (br t, J = 7.2 Hz, 2 H), 1.28–1.24 (m, 5 H), 0.98 (s, 3 H), 0.89 (s, 3 H), 0.87 (t, J = 6.9 Hz, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) 156.51, 154.84, 143.72, 120.59, 113.78, 111.03, 108.77, 47.01, 42.37, 35.47, 35.35, 31.47, 30.57, 28.58, 25.34, 22.49, 20.69, 13.96 ppm; ^{13}C NMR (C_6D_6, 75 MHz) 155.56, 155.43, 143.29, 127.40, 114.79, 111.72, 108.89, 47.38, 47.24, 42.21, 35.84, 35.68, 31.74, 31.06, 28.66, 25.19, 22.93, 20.63, 14.19 ppm; IR ($CHCl_3$) 3005, 2960, 2860, 1630, 1580, 1420, 1250, 1220, 1140, 1060, 1025, 860 cm^{-1}; mass spectrum, m/e 448 (M^+, 46), 405 (35), 315 (22), 233 (100), 193 (41), 109 (46), 83 (22); mass calcd for $C_{21}H_{27}SO_5F_3$ 448.1531, found 448.1523.

Cationic Cyclization to (−)-(*trans*)-6a,7,10,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-9-yl Trifluoromethanesulfonate (8). To a solution of 125 mg (0.279 mmol) of diol **7** in 8 mL of anhydrous dichloromethane was added 0.32 mL (2.601 mmol) of boron trifluoride etherate at 25 °C. The reaction mixture was stirred at 25 °C for 8 h, at which time thin-layer chromatography indicated the complete consumption of starting material. The reaction mixture was diluted with ether, washed with brine, and dried ($MgSO_4$). Solvent evaporation produced the crude product, which was purified by flash column chromatography on silica gel, eluting with 10% ethyl acetate in hexane, to produce 106 mg (87% yield) of cyclic **8**: $[\alpha]^{24}_D$ −206.1° (*c* 0.31, ethanol); ^1H NMR ($CDCl_3$, 300 MHz) 6.28 (s, 1 H), 6.10 (s, 1 H), 5.81 (br s, 1 H), 4.76 (s, 1 H, exchangeable with D_2O), 3.67 (dd, J = 8.2, 4.5 Hz, 1 H), 2.86 (dt, J = 11.1, 4.8 Hz, 1 H), 2.44 (t, J = 7.8 Hz, 2 H), 2.39–2.18 (br m, 3 H), 2.05–1.93 (br m, 1 H), 1.86 (dt, J = 9.9, 3.6 Hz, 1 H), 1.41 (s, 3 H), 1.32–1.28 (m, 2 H), 1.12 (s, 3 H), 0.89 (t, J = 6.9 Hz, 3 H) ppm; ^1H NMR (C_6D_6, 300 MHz) 6.54 (s, 1 H), 5.62 (s, 1 H), 5.36 (t, J = 2.4 Hz, 1 H), 4.39 (s, 1 H, exchangeable with D_2O), 3.81 (dd, J = 8.7, 3.3 Hz, 1 H), 2.62 (dt, J = 11.1, 5.1 Hz, 1 H), 2.37 (t, J = 7.5 Hz, 2 H), 2.18–2.07 (m, 1 H), 1.54–1.45 (m, 4 H), 1.24–1.21 (m, 5 H), 1.08 (s, 3 H), 0.84 (t, J = 6.3 Hz, 3 H), 0.78 (s, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) 154.53, 149.35, 143.60, 120.64, 116.53, 110.07, 108.29, 107.74, 76.25, 43.61, 35.43, 33.15, 31.64, 31.49, 30.54, 27.49, 25.79, 22.49, 18.32, 13.95 ppm; ^{13}C NMR (C_6D_6, 75 MHz) 155.28, 155.18, 149.35, 143.47, 121.55, 116.98, 110.49, 108.59, 107.79, 75.85, 43.51, 35.85, 33.41, 31.87, 31.75, 31.12, 27.47, 25.54, 22.90, 18.26, 14.17 ppm; IR ($CHCl_3$) 3400, 2960, 2925, 2850, 1625, 1585, 1420, 1250, 1210, 1140, 1050, 950 cm^{-1}; mass spectrum, m/e 448 (M^+, 89), 392 (98), 231 (73), 193 (34), 109 (37), 69 (100); mass calcd for $C_{21}H_{27}SO_5F_3$ 448.1531, found 448.1514.

11-Nor-Δ^8-tetrahydrocannabinol-9-carboxylic Acid Methyl Ester (9). A solution of 7 mg (0.01 mmol) of $PdCl_2(PPh_3)_2$ in 2.00 mL of THF and 0.12 mL of methanol, containing 42 mg (0.304 mmol) of potassium carbonate, was purged with carbon monoxide at 25 °C for 5 min. A solution of 45 mg (0.100 mmol) of vinyl

(25) To a solution of olivetol in diethyl ether was added 2.5 equiv of ethyl vinyl ether at 0 °C, followed by a catalytic amount of *p*-toluenesulfonic acid in ether. The reaction mixture was stirred at 0 °C, and the progress of the reaction was monitored by TLC. After 7 h the reaction mixture was diluted with ether, washed with saturated aqueous sodium bicarbonate, followed by brine, and dried ($MgSO_4$). Solvent evaporation gave the crude bis(ethoxyethyl) ether of olivetol, which was purified by flash column chromatography on silica gel, eluting with 5% ethyl acetate in hexanes. The yield of the reaction was 77%.

triflate 8 in 2 mL of THF was added, and purging was continued for an additional 10 min. The reaction mixture was stirred at 25 °C under an atmosphere of carbon monoxide until thin-layer chromatography indicated the complete dissappearance of starting material (ca. 8 h). The reaction mixture was diluted with water and extracted with ether, and the ether layers were dried ($MgSO_4$). Solvent evaporation gave the crude product, which was purified by flash column chromatography on silica gel, eluting with 10% ethyl acetate in hexane. The yield of **9** (mp 142 °C, recrystallized from ether–hexane) was 26 mg (72% yield): $[\alpha]^{23}_D$ -219° (*c* 1.5, ethanol) [lit.[10] $[\alpha]_D$ -302° (ethanol)]; ^{1}H NMR (300 MHz, $CDCl_3$) 7.02 (br s, 1 H), 6.25 (s, 1 H), 6.14 (s, 1 H), 5.49 (s, 1 H, exchangeable with D_2O), 3.85 (dd, J = 8.7, 3.3 Hz, 1 H), 3.76 (s, 3 H), 2.67 (dt, J = 16.2, 4.5 Hz, 1 H), 2.43 (t, J = 7.8 Hz, 2 H), 2.06–1.92 (br m, 3 H), 1.82 (dt, J = 11.7, 4.2 Hz, 1 H), 1.39 (s, 3 H), 1.32–1.26 (br m, 4 H), 1.12 (s, 3 H), 0.88 (t, J = 6.9 Hz, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 168.15, 155.28, 154.58, 142.97, 138.05, 130.95, 109.63, 109.43, 107.72, 76.03, 51.79, 44.16, 35.47, 31.53, 31.22, 30.55, 30.08, 28.53, 27.51, 22.52, 18.28, 13.99 ppm; IR ($CHCl_3$) 3405, 2960, 2940, 2860, 1715, 1695, 1630, 1580, 1440, 1270, 1190, 1075 cm^{-1}; mass spectrum, m/e 358 (M^+, 100), 302 (49), 283 (23), 231 (66), 193 (29), 69 (18); mass calcd for $C_{22}H_{30}O_4$ 358.2144, found 358.2165. As a further check of the optical purity of **9**, the Mosher ester was prepared from (*R*)-(+)-MTPA: ^{19}F NMR (CD_3COCD_3, 283 MHz, $CFCl_3$ used as reference) -71.236 (s, CF_3) ppm; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.61–7.58 (m, 2 H), 7.34–7.29 (m, 3 H), 6.86 (br s, 1 H), 6.59 (s, 1 H), 6.49 (s, 1 H), 3.82 (s, 3 H), 3.64 (s, 3 H), 2.69 (br d, J = 8.4 Hz, 1 H), 2.52 (t, J = 7.5 Hz, 2 H), 2.35–2.25 (m, 1 H), 2.12 (dt, J = 9.6, 4.2 Hz, 1 H), 1.37 (s, 3 H), 1.33–1.24 (m, 6 H), 1.09 (s, 3 H), 0.88 (t, J = 5.4 Hz, 3 H) ppm.

Oxalate 10: ^{1}H NMR ($CDCl_3$, 300 MHz) 7.04 (br t, J = 2.7 Hz, 1 H), 6.27 (s, 1 H), 6.12 (s, 1 H), 4.94 (s, 1 H, exchangeable with D_2O), 3.89 (s, 3 H), 2.67 (dt, J = 11.1, 4.2 Hz, 1 H), 2.45 (t, J = 6.3 Hz, 2 H), 2.19–2.05 (m, 2 H), 1.98–1.82 (m, 2 H), 1.40 (s, 3 H), 1.35–1.21 (m, 6 H), 1.13 (s, 3 H), 0.88 (t, J = 6.6 Hz, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) 187.44, 164.79, 154.79, 154.59, 147.01, 143.29, 136.77, 110.03, 109.02, 107.82, 75.86, 52.50, 44.11, 35.44, 31.52, 30.76, 30.57, 29.37, 28.21, 27.47, 22.52, 18.27, 14.00 ppm; IR ($CHCl_3$) 3480, 2960, 2940, 2860, 1745, 1675, 1635, 1590, 1440, 1265, 1190, 1170, 1020 cm^{-1}; mass spectrum, m/e 386 (M^+, 7), 330 (8), 231 (6), 205 (10), 85 (33), 71 (53), 57 (100); mass calcd for $C_{23}H_{30}O_5$ 386.2093, found 386.2092.

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Registry No. 4, 35408-03-8; **5**, 128660-91-3; **6**, 128660-92-4; **7**, 128660-93-5; 8, 128660-94-6; **9**, 51263-84-4; **10**, 128660-95-7; CH_2=CHOEt, 109-92-2; olivetol, 500-66-3; olivetol bis(ethoxyethyl) ether, 125265-27-2.

Supplementary Material Available: Spectra for **5** and **7–9** (11 pages). Ordering information is given on any current masthead page.

1,3,5-Tri[2,6]pyridacyclohexaphane-2,4,6-trione Ketals: Synthesis, Structural Analysis, and Complexation[1a]

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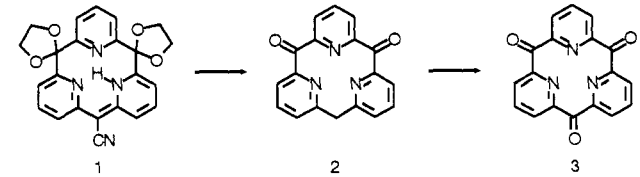
The synthesis, molecular distortions, and chemical behavior of 1,3,5-tri[2,6]pyridacyclohexaphane-2,4,6-trione ketals are described. The electron-deficient nature of the carbonyl bridges was confirmed by the facile addition of protic solvent to generate a stable hemiketal. The bridging methylene moiety of the carbonyl precursor exhibited novel chemical behavior, which results in a facile dimerization of a radical intermediate. X-ray structural analyses of the ketals and dimers afforded insight into the molecular deviations caused by changing the bond angles of the bridging carbon atoms.

Introduction

We have previously reported[2,3] the synthesis of tri- and tetraketo[2,6]pyridinophanes, which have N-electron-rich, highly rigid cavities comprised of only sp^2 ring atoms. Even though trione **3** should be essentially flat, deformations from planarity were observed, predominantly due to N,N,N-electron pair repulsions. The higher homologue, pyridinocalix[4]arene,[3,4] which is severly distorted from planarity, possesses a saddle shape with N-lone pairs pointing alternately above and below the best plane of the macrocycle. The contiguous electron-poor substituents instill a novel chemical behavior analogous to that experienced by the central carbonyl group in ninhydrin. We herein describe the preparation and reactivity these trione derivatives.

Scheme I



Results and Discussion

Trione 3. The initial C-bridged 2,6-pyridino macrocycle **1** was prepared (50%) in two steps from 2,6-bis(6-bromo-

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