TOTAL SYNTHESIS OF CANNABISPIRAN[1, 2] AND (±)-DEHYDROCANNABISPIRAN

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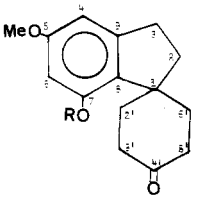
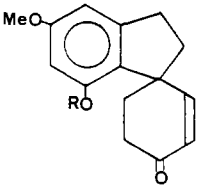
ABSTRACT.—Cannabispiran (**1**) and (+)-dehydrocannabispiran (**2**) were synthesized in moderate yields by homologation of the ketone **3** to the aldehyde **4**, followed by annelation and selective demethylation with lithium *tert*-butylmercaptide to provide **2**. Catalytic hydrogenation of the annelation product **6** then selective demethylation with the same reagent furnished **1**. Of the reactions described in this sequence, the homologation of **3** to **4** is of particular interest as it presents hitherto unreported chemistry.

Cannabispiran (Cannabispirone) (**1**) and dehydrocannabispiran (Cannabispirenone-A) (**2**) are among the major spiroindans reported (1) to occur in the leaves of *Cannabis sativa* (marihuana). Their presence in this source has sparked considerable interest as they are likely to contribute to the overall pharmacology of marihuana, notably its estrogenic activity in view of the fact that they are structurally similar to some synthetic estrogen-potentiating agents (2). As a part of an ongoing program devoted to the in-depth study of the biological effects of these unique compounds, an investigation was initiated to make them available by chemical synthesis. In a previous publication we reported (3) the synthesis of cannabispiran (**1**) by a biomimetic approach; in this publication we wish to report on the total synthesis of **1** and **2** using a purely chemical approach.



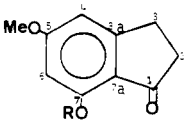
1, R=H

9, R=CH_3



2, R=H

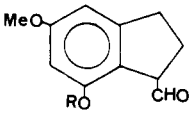
6, R=CH_3



3, R=CH_3

7, R=H

10, R=CH_2-O-CH_3



4, R=CH_3

8, R=H

[1]Taken in part from the PhD. dissertation of Y. -M. Chan.

[2]Presented before the MALTO Pharmacognosy-Medicinal Chemistry meeting held in Austin, Texas, May 25, 1980. After the submission of this work for publication Novak *et al.* reported a similar but not identical route for the synthesis of these compounds. See *Tetrahedron Letters*, **22**, 1063 (1981) and reference therein.

The starting material for this synthesis was the ketone **3** which was obtained (95%) by the cyclization of 3,5-dimethoxyphenylpropionic acid which, in turn, was obtained by the catalytic hydrogenation of the commercially available 3,5-dimethoxycinnamic acid. Conversion of **3** to the analogous aldehyde **4** by Wittig reaction (methoxymethyltriphenylphosphonium chloride/*n*-butyllithium then hydrolysis with aqueous perchloric acid) provided the desired material in a poor yield. This route was abandoned, and, instead, an attempt was made to form the epoxide **5** by treatment with trimethylsulfonium iodide and sodium hydride in the presence of dimethylsulfoxide. To our surprise, the aldehyde **4** was obtained directly in about 50% yield and was separated from the remaining unreacted starting material by chromatography.

The formation of **4** under the above conditions can be rationalized on the basis that the epoxide **5** might have been formed as would be expected but could have undergone ring opening triggered by electrons flowing from the two methoxy groups as shown in figure 1. The scope and limitations of these reactions are being pursued further in our laboratories.

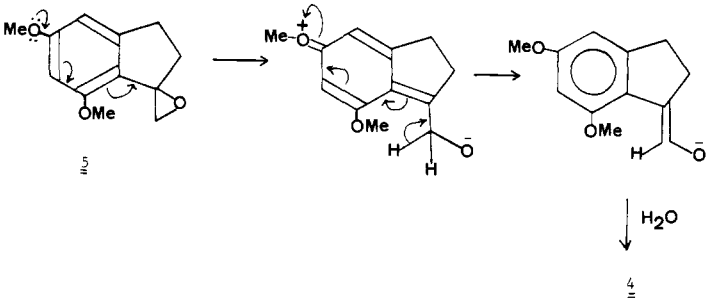


Figure 1.

Annelation of **4** was achieved by refluxing its benzene solution with methyl-vinyl ketone in the presence of potassium *tert*-butoxide to provide the spiran **6** in about 40–45% yield (5). Selective demethylation with lithium *t*-butyl-mercaptide (6) provided (+)-dehydrocannabispiran (**2**) (89% yield) which could be quantitatively converted to cannabispiran (**1**) by catalytic hydrogenation. Also, cannabispiran (**1**) could be obtained by catalytic hydrogenation of the annelated product **6** followed by regioselective demethylation[3,4] with the same reagent. An attempt was then made to modify the synthesis by selective demethylation of **3** to **7** by treatment with sodium cyanide in dimethylsulfoxide (7). The resulting phenol (90%), mp 104–105°, showed a relatively deshielded carbonyl signal in the ^{13}C nmr spectrum at δ 207.6 (the ketone **3** showed a corresponding signal at δ 202.7, see Experimental) thus confirming the presence of a hydrogen-bonded ketonic carbonyl group (8). Homologation of **7** to the corresponding aldehyde **8** by treatment with trimethylsulfonium iodide, as described above, resulted in the recovery of the starting material whether **7** was used as such or in the form of its methoxymethylmethyl ether. Therefore, selective demethylation after annelation remains the only route that would lead to **1** and **2**.

[3]The use of boron tribromide for demethylation provided a low yield of **1** (about 20%) along with the other monomethylated isomer.

[4]Regioselective demethylation with lithium *t*-butylmercaptide and sodium cyanide (in converting **3** to **7**) are being investigated further in our laboratories.

EXPERIMENTAL[5]

HYDROGENATION OF 3,5-DIMETHOXYCINNAMIC ACID TO 3,5-DIMETHOXYPHENYLPROPIONIC ACID.—The acid (10.0 g) was hydrogenated in absolute ethanol in the presence of 5.0 g of 5% paladium on carbon under 15 lb. of pressure for 10 h. The product was obtained in quantitative yield (10.0 g); when it was crystallized from ether-chloroform colorless needles were obtained: mp 56–60°; ir ($CHCl_3$): ν max at 3600–3000 (OH), 1720 (C=O), and 1600 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 9.33 (1H, *s*, carboxyl proton), δ 6.35 (3H, *s*, aromatic protons), δ 3.75 (6H, *s*, two OCH_3), and δ 2.76 (4H, *m*, two CH_2); ms: M^+ at *m/z* 210 (63%) with the base peak at *m/z* 165.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.99; H, 6.66.

CYCLODEHYDRATION OF 3,5-DIMETHOXYPHENYLPROPIONIC ACID TO THE KETONE **3**.—Polyphosphoric acid (60.0 g) was heated at 100° then 3,5-dimethoxyphenylpropionic acid (3.0 g) was added to it, and the mixture was stirred at 100° for 4 h. The mixture was then poured over crushed ice and extracted with three 300 ml portions of chloroform. The chloroform extract was washed with water, dried over anhydrous Na_2SO_4, and then filtered through a short column of silica gel 60 column. The eluate was evaporated *in vacuo*, and the residue was crystallized from ether-chloroform to provide 2.6 g of **3** (95% yield) as orange crystals: mp 98–99°; ir ($CHCl_3$): ν max at 1710 (C=O), and 1610 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 6.45 (1H, *br s*, aromatic proton), δ 6.26 (1H, *br s*, aromatic proton), δ 3.87 (3H, *s*, OCH_3), δ 3.83 (3H, *s*, OCH_3), δ 3.00 (2H, *m*, CH_2) and δ 2.63 (2H, *m*, CH_2); ^{13}C nmr ($CDCl_3$): δ 202.7 (*s*, C-1), δ 167.1 (*s*, C-7), δ 160.3 and 159.5 (both *s*, due to C-5 and C-3a without designation), δ 119.5 (*s*, C-7a), δ 101.9 (*d*, C-4), δ 97.5 (*d*, C-6), δ 55.7 (*q*, $-OCH_3$), δ 36.9 and δ 25.9 (*t*, C-2 and C-3); uv: λ max (MeOH) at 300 nm (shoulder, log ϵ 3.61), 272 nm (log ϵ 4.10) and 225 nm (log ϵ 4.08); ms: M^+ at *m/z* 192 (100%).

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 68.74; H, 6.29. Found: C, 68.81; H, 6.30.

HOMOLOGATION OF THE KETONE **3** TO THE ALDEHYDE **4** BY WITTIG REACTION.—(Methoxymethyl)triphenylphosphonium chloride (215 mg) was stirred in 5 ml of anhydrous benzene under nitrogen; 0.7 ml of *n*-Bu-Li was injected through a septum, and the resulting red solution was stirred at room temperature for 30 min. The ketone **4** (100 mg) was then added, and the mixture was stirred for 5 h. The resulting enol ether (17 mg) was isolated by plc (on silica gel G plates with benzene as solvent; R_f value=0.48); ir ($CHCl_3$): no carbonyl or hydroxyl absorption bands; the strongest absorption band was the aromatic absorption band at 1600 cm^{-1}; ^1H nmr ($CDCl_3$): δ 6.40 (1H, *br s*, aromatic proton), δ 6.33 (1H, *br s*, aromatic proton), δ 6.02 (1H, *s*, enolic proton), δ 3.85 (3H, *s*, OCH_3), δ 3.79 (3H, *s*, OCH_3) and δ 2.73 (4H, *m*, two CH_2); ms: M^+ at *m/z* 220 (100%).

This product was hydrolyzed with 0.5 ml of 70% aqueous perchloric acid in 2 ml of ether for 8 h at room temperature, then the reaction mixture was diluted with 15 ml of H_2O and extracted with ethyl acetate. After drying over anhydrous Na_2SO_4 the organic solvent was evaporated to give 15 mg of aldehyde **14** as a yellow oil, identical to the material prepared with trimethylsulfonium iodide (*vide infra*).

HOMOLOGATION OF THE KETONE **3** TO ALDEHYDE **4** WITH TRIMETHYLSULFONIUM IODIDE.—Sodium hydride (200 mg) in 13 ml of dimethylsulfoxide (DMSO) was stirred at 75° under nitrogen for 30 min; tetrahydrofuran (THF) (13 ml) was then added, and the mixture was cooled to −2° in an ice-salt bath. Trimethylsulfonium iodide (1.7 g) in DMSO (6 ml) was injected into the DMSO-NaH mixture, followed by the injection of the ketone **3** (1.0 g) in THF (6 ml). The resulting mixture was stirred in the ice bath for 15 min., then at 50–55° for one hour. The THF was removed under vacuum and the DMSO solution was diluted with an equal volume of water and extracted with three 200 ml portions of chloroform. When the chloroform extract was evaporated, and the residue was chromatographed on a silica gel G column with benzene as the eluting solvent, 506 mg of the aldehyde **4** (47% yield) was obtained, followed by 300 mg

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[5]Melting points were determined on a Thomas Hoover Uni-melt capillary apparatus and are uncorrected. Optical rotations were taken on a Perkin-Elmer 141 automatic polarimeter. The ultraviolet (uv) spectra were determined in methanol solution with a Beckman Acta III recording spectrophotometer. Infrared (ir) absorption spectra were recorded on potassium bromide pellets or chloroform solutions on a Beckman IR-33 spectrophotometer, a Perkin-Elmer 257 spectrophotometer or a Perkin-Elmer 281B spectrophotometer. ^1H nuclear magnet resonance (^1H nmr) spectra were recorded on a Jeol C-60 HL NMR spectrometer, or a Joel JNM FX-60 Fourier Transform NMR spectrometer. The latter was also used for the ^{13}C nmr determinations. Chemical shifts are reported in (ppm) values with tetramethylsilane (TMS) as the internal reference. Mass spectra were measured on a Finnigan GC-MS 3200 mass spectrometer.

Microanalyses were carried out by Scandinavian Microanalytical Laboratory in Herlev, Denmark, or Galbraith Laboratories, Inc., in Knoxville, Tennessee.

All reagents and starting compounds were obtained from Aldrich Chemical Company unless otherwise stated.

of unreacted ketone **3**. The aldehyde **4** was an optically inactive oily material: ir ($CHCl_3$): ν max at 1730 (C=O), and 1600 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ9.73 (1H, *d*, J=2.0 Hz, -CHO), δ 6.47 (1H, *br s*, aromatic proton), δ 6.37 (1H, *br s*, aromatic proton), δ 3.87 (6H, *s*, two OCH_3) and a multiplet between δ 2.20–3.13 (5H, aliphatic protons); ^{13}C nmr ($CDCl_3$): δ 200.5 (*d*, -CHO), δ 161.9 (*s*, C-7), δ 157.2 (*s*, C-5), δ 147.7 (*s*, C-3a), δ 119.2 (*s*, C-7a), δ 101.5 (*d*, C-4), δ 96.8 (*d*, C-6), δ 55.5 and δ 55.3 (*q*, $-OCH_3$), δ 32.5 and δ 25.5 (*t*, C-2 and C-3); uv: λ max (MeOH) at 272 nm (log ϵ 3.87) and 215 nm (log ϵ 4.29); ms: M^+ at m/z 206 (3.5%) with the base peak at m/z 177.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.11; H, 6.81.

SPIROANNELATION OF **4** WITH METHYLVINYL KETONE (MVK).—A solution of the aldehyde **4** (200 mg) and MVK (136 mg) in 2.5 ml of benzene was stirred at 5–10°, then a solution of potassium *t*-butoxide (130 mg) in one ml of *t*-butanol and one ml of benzene was added dropwise to this solution. The resulting mixture was stirred at room temperature for two h and refluxed for one h. A few drops of glacial acetic acid were added to the mixture, and the mixture was extracted with chloroform. After removal of the chloroform, the residue was chromatographed on a silica gel 60 column with benzene as the eluting solvent to give 86 mg of **6** (40% yield) as colorless prisms, mp 95–96°; ir ($CHCl_3$): ν max at 1600 (C=O) and 1595 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 6.77 (1H, *dd*, J=10.0 and 1.0 Hz, H-6'), δ 6.29 (1H, *br s*, aromatic proton), δ 6.19 (1H, *br s*, aromatic proton), δ 5.84 (1H, *d*, J=10.0 Hz, H-5'), δ 3.68 (3H, *s*, OCH_3), δ 3.74 (3H, *s*, OCH_3), and a multiplet between δ 1.94–3.28 (8H, aliphatic protons); ^{13}C nmr ($CDCl_3$): δ 199.6 (*s*, C-4'), δ 161.5 (*s*, C-5), δ 158.3 (*d*, C-6'), δ 157.1 (*s*, C-7), δ 140.1 (*s*, C-9), 127.1 (*s*, C-8), δ 126.5 (*d*, C-5'), δ 101.3 (*d*, C-4), δ 97.4 (*d*, C-6), δ 55.5 and δ 55.1 (*q*, C-10 and C-11), δ 48.6 (*s*, C-1), δ 35.8 (*t*, C-2), δ 35.6 (*t*, C-2'), and δ 31.3 (*t*, C-3 and C-3'); ms: M^+ at m/z 258 (57%) with the base peak at m/z at 230; uv: λ max (MeOH) at 225 nm (log ϵ 3.70).

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.14; H, 7.22.

HYDROGENATION OF **6** TO CANNABISPIRAN METHYL ETHER **9**.—Compound **6** (60 mg) in 15 ml of ethanol was hydrogenated with 30 mg of 5% paladium on carbon under atmospheric pressure to yield **9** in almost quantitative yield (59 mg): mp 123–124°: ir ($CHCl_3$): ν max at 1710 (C=O), and 1600 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 6.40 (1H, *br s*, aromatic proton), δ 6.33 (1H, *br s*, aromatic proton), δ 3.80 (3H, *s*, OCH_3), δ 3.78 (3H, *s*, OCH_3), and a multiplet between δ 1.20–3.20 (12H, aliphatic protons uv: λ max (MeOH) at 275 nm (log ϵ 3.50) and 225 (log ϵ 4.04); ms: M^+ at m/z 260 (54%) with the base peak at m/z 203.

Anal. Calcd. for $H_{16}H_{20}O_3$: C, 74.40; H, 7.02. Found: C, 74.14; H, 7.14.

SELECTIVE DEMETHYLATION OF **6** TO DEHYDROCANNABISPIRAN **2**.—2-Methyl-2-propanethiol (1.0 ml) was added to a suspension of lithium hydride (500 mg) in dry, oxygen-free hexamethylphosphoramide (HMPA) (8.0 ml) and stirred under a nitrogen atmosphere at 50° for 5 h. Compound **6** (50 mg) was dissolved in 2 ml of oxygen-free HMPA, and the solution was warmed to 70°, then 5 ml of the mercaptide solution were added to the solution. The resulting mixture was stirred for 2 h at 70° under nitrogen then treated at room temperature with 25 ml of saturated aqueous ammonium chloride solution followed by 10 ml of 2N HCl and extracted with two 50 ml portions of chloroform. The organic layer, washed twice with water and evaporated *in vacuo*, yielded a residue (130 mg). The residue, when chromarographed on a silica gel column, yielded 30 mg of an optically inactive crystalline product that was identical with the natural dehydrocannabispiran (**7**) except in optical activity: mp 160–161° (literature mp (2) 163–164°); ir (KBr): ν max at 3400–3200 (OH), 1650 (C=O), and 1600 (C=C) cm^{-1}; ^1H nmr (Acetone d_6): δ 6.80 (1H, *dd*, J=10.0 and 1.0 Hz, H-6'), δ 6.19 (2H, *s*, H-4 and H-6), δ 5.80 (1H, *d*, J=10.0 Hz, H-5'), δ 3.74 (3H, *s*, OCH_3) and a multiplet between δ 1.94–3.30 (8H, aliphatic protons).

SELECTIVE DEMETHYLATION OF **9** TO CANNABISPIRAN **1**.—Compound **9** (50 mg), when demethylated with lithium *t*-butylmercaptide in HMPA as described above, gave 29 mg of Cannabispiran **1**. The synthetic material was identical in all respects to the natural product.

SELECTIVE DEMETHYLATION OF THE KETONE **3** WITH SODIUM CYANIDE IN DMSO.—A solution of 1.0 g of the ketone **3** and 1.5 g of sodium cyanide in 15 ml of DMSO was stirred at 120–125° for 10 h. The mixture was then diluted with water; 50 ml of 10% HCl was added, then extracted with chloroform. The chloroform extract was evaporated, and the residue was redissolved in 10 ml of chloroform and filtered through a silica gel 60 column. The phenol **7** was obtained in 90% yield (890 mg) as light yellow crystals: mp 104–105°; ir ($CHCl_3$): ν max at 3420 (OH, unchanged upon dilution), and 1660 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 6.5 (1H, *br s*, aromatic proton), δ 6.33 (1H, *br s*, aromatic proton), δ 3.93 (3H, *s*, OCH_3), and two distorted 2-proton triplets at δ 3.10 and δ 2.67 for H-2 and H-3; ^{13}C nmr ($CDCl_3$); δ 207.6 (*s*, C-1), δ 168.2 (*s*, C-7), δ 159.2 (*s*, C-5), δ 157.1 (*s*, C-3a), δ 117.1 (*s*, C-7a), δ 103.6 (*d*, C-4), δ 99.3 (*d*, C-6), δ 55.7 (*q*, $-OCH_3$), δ 36.2 (*t*, C-2 and C-3); uv: λ max (MeOH) at 273 nm (log ϵ 3.90), 222 nm (log ϵ 3.87); ms: M^+ at m/z 178 (100%).

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.37; H, 5.55.

PREPARATION OF THE METHOXYMETHYL ETHER **10**.—The phenolic ketone **7** (800 mg) was stirred at room temperature for 20 min. with 15 ml of methylene chloride, 600 mg of NaOH, 8 ml of water and 600 mg of Adogen 464.[6] Chloromethylmethyl ether (1.0 ml) was then added and the mixture was stirred for 6 h. The reaction mixture was diluted with 200 ml of chloroform and washed with 50 ml of water. The chloroform phase, when dried over anhydrous Na_2SO_4 and evaporated, left a crystalline residue which was recrystallized from chloroform-ether to give 500 mg of **10** as colorless prisms: mp 265–267°; ir (KBr): ν max at 1660 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 6.25 (2H, *br s*, aromatic protons, δ 3.78 (6H, *s*, two OCH_3), δ 3.45 (2H, *s*, $-CH_2-O-CH$) and δ 2.71 (4H, m, H-2 and H-3), ms: at *m/z* 222 (2%) with the base peak at *m/z* 69.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.99; H, 6.60.

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[6]Adogen 464 is the phase-transfer catalyst methyltrialkyl (C_8–C_{10})-ammonium chloride available from Aldrich Chemical Company.