Cannabis. Part 25.[1] Synthesis of Cannabispirenone-B and its 5,7-Difluoro-analogue

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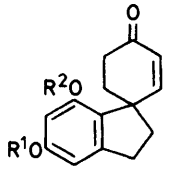
The naturally occurring cannabispirenone-B (1a) was synthesized by spiroannelation of the piperidine enamine of 5,7-dimethoxyindan-1-carbaldehyde to *O*-methylcannabispirenone (1b), followed by selective demethylation with lithium iodide in 2,4,6-collidine. Its 5,7-difluoro-analogue (10) was synthesized by spiroannelation of 5,7-difluoroindan-1-carbaldehyde obtained by homologation of 5,7-difluoroindan-1-one, which was synthesized from 1-bromo-3,5-difluorobenzene in three steps.

CANNABISPIRANOIDS represent a major group of the recently isolated new natural constituents [2] of *Cannabis sativa* L. Their remarkable structural resemblance to some synthetic estrogen-potentiating spiro-compounds,[3] coupled with the reported [4] estrogenic activity of *Cannabis*, stimulated synthetic efforts [5-8] to make these compounds, possessing a rather uncommon structure, available for pharmacological research.

As mentioned very briefly in our preliminary communication,[5] the spiroannelation of the aldehyde (2) *via* its enamine seemed possible. Thus, using a Michael-type addition of the piperidine enamine (3) to methyl vinyl ketone (MVK), followed by hydrolysis and aldol cyclization, we obtained the desired spirenone (1b), the key intermediate in the synthesis of the cannabispirans, in high overall yield. The use of asymmetric induction in the alkylation † of the enamine from compound (2) by means of an optically active amine offers, moreover, the possibility of an asymmetric synthesis of cannabispirenones.



(1) a; R^1 = H, R^2 = Me
b; R^1 = R^2 = Me
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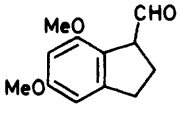
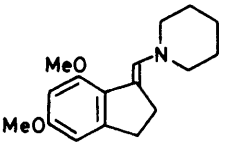


(2)



(3)

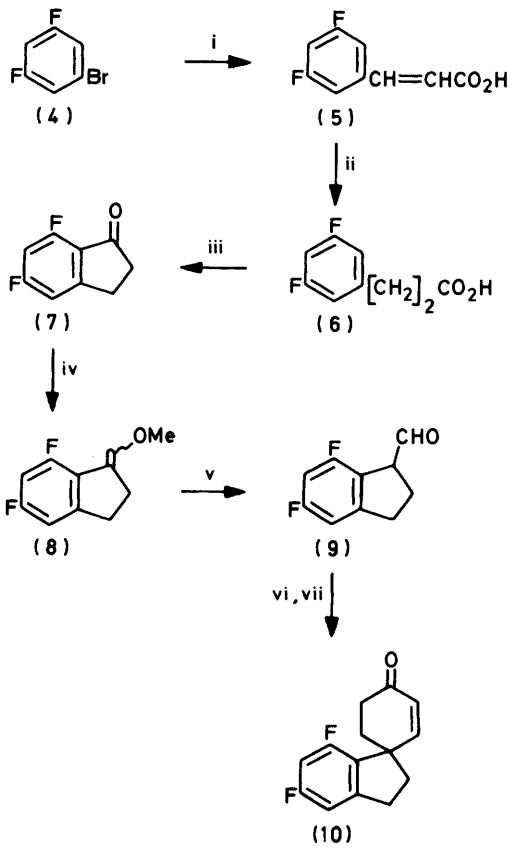
The published syntheses of cannabispirans make them readily available, except for cannabispirenone-B. The synthesis of this compound requires a selective ether cleavage of the sterically *less* hindered methoxy-group in *O*-methylcannabispirenone. The reported [6,7] yields for this step with BBr_3 as the reagent are 32 and 20%, respectively, the main problem being the formation of insoluble tars, as we have observed. This proved to be a difficult step, due to the presence of the sensitive enone function, and from the ten reagents tried, only lithium iodide [9] in 2,4,6-trimethylpyridine (2,4,6-collidine) was successful. The selectivity of the ether cleavage with this reagent was almost quantitative, the formation of tars was negligible, and the yield was 82% at 56% conversion. This represents a novel chemical methodology, exactly the opposite of the known cleavage of the *more* hindered ether group—as exemplified with other substrates—by thiolates [10] or trimethylsilyl iodide,[11] as well as by the conversion of *O*-methylcannabispirenone into cannabispirenone-A (1c) by lithium t-butyl sulphide.[6,7] The recently reported [12] new, ether-cleaving reagent, sodium *N*-methylanilide, was not compatible with the enone system of *O*-methylcannabispirenone.

As a result of our synthetic efforts towards the total synthesis of cannabispirans, we also report the synthesis of a selected fluoro-analogue ‡ of cannabispirenone-B, namely 5',7'-difluorospiro[cyclohex-2-ene-1,1'-indan]-4-one (10). The starting compound in our synthetic sequence (Scheme) was the known 1-bromo-3,5-difluorobenzene (4), prepared from 2,4-difluoroaniline by bromination and subsequent deamination according to the literature procedure.[13] Under the conditions of the Heck reaction [14] only the bromine atom in compound (4) was reactive, so the aryl bromide could be selectively transformed into the new 3,5-difluorocinnamic acid (5). This acid was reduced by the $NaBH_4$–$NiCl_2 \cdot 6H_2O$ reagent to the saturated acid (6). This reducing agent has previously been used for the reduction of αβ-unsaturated esters.[15] Our reduction method thus represents a new, convenient, and selective method of reduction of αβ-unsaturated acids to the corresponding saturated acids. The acid (6) was cyclized to 5,7-difluoroindan-1-one (7) by polyphosphoric acid (PPA) in high yield.

The fluorinated indanone was a useful starting compound for the spiroannelation approach developed by us earlier.[5] Thus, compound (7) was first converted by the Wittig reagent methoxymethylenetriphenylphosphorane (3 equiv.) into a mixture of the methoxymethylene isomers (8), *E* : *Z* 81 : 19 by ^{1}H n.m.r. analysis, from

† Asymmetric α-alkylation of various aldehydes has been reported: T. Sone, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.*, 1976, **24**, 1273.

‡ For a short, general review of fluoro-organic biochemistry, see T. B. Patrick, *J. Chem. Educ.*, 1979, **56**, 228.



SCHEME *Reagents*: i, acrylic acid, $Pd(OAc)_2$, Ph_3P, Bu_3N, xylene; ii, $NaBH_4$, $NiCl_2 \cdot 6H_2O$, MeOH; iii, PPA; iv, $Ph_3\overset{+}{P}CH_2OMe\ Cl^-$, $KOBu^t$, dioxan; v, *p*-$MeC_6H_4SO_3H$, H_2O, dioxan; vi, MVK, EtOH, H_2O, KOH, Et_2O; vii, KOH, H_2O, MeOH

which the (*E*)-isomer crystallized out. The enol-ether mixture was easily hydrolysed to the aldehyde (9) by toluene-*p*-sulphonic acid in aqueous dioxan. In the spiroannelation step, combining a Michael addition and an aldol condensation, the aldehyde was treated with MVK and KOH to afford the desired spiro-compound (10) in 67% yield. This synthesis thus further demonstrates the utility of our spiroannelation approach and enables research of the pharmacological properties of this interesting new fluorinated spiran to be pursued.

EXPERIMENTAL

M.p.s were measured on a Kofler hot-stage. ^1H N.m.r. spectra were recorded on a Varian EM-390 spectrometer, and ^{13}C n.m.r. spectra on a Varian CFT-20 spectrometer. Magnesium sulphate was used for drying.

5,7-Dimethoxyindan-1-carbaldehyde Piperidine Enamine (3).—This compound was prepared from the aldehyde (2),[5] according to the method of Zoretic *et al.*,[16] in 98% yield as yellow, moisture-sensitive crystals which were used directly in the next step; δ_H (CCl_4) 1.5br (6 H, s, 3 × CH_2), 2.85 (8 H, m, 4 × CH_2), 3.7 (3 H, s, OMe), 3.8 (3 H, s, OMe), 6.1 (1 H, s, *J* 2 Hz, ArH), 6.2 (1 H, s, *J* 2 Hz, ArH), and 6.45 (1 H, t, *J* 2 Hz, CH= *).

* Throughout the n.m.r. data, CH= refers to aliphatic olefinic protons.

O-Methylcannabispirenone (1b).—To a stirred solution of the enamine (3) (0.85 g) in benzene (2 ml) and methanol (12 ml) was added methyl vinyl ketone (MVK) (0.75 g) under nitrogen at 0 °C. The mixture was stirred at 20 °C for 60 h, then concentrated under reduced pressure. The residue was dissolved in benzene and the solution was washed in turn with 3N HCl and water then dried and concentrated under reduced pressure to give a yellow oil, the ^1H n.m.r. spectrum (CCl_4) of which showed peaks characteristic of the intermediate *geminal* formylbutanone derivative, δ_H 9.5 (1 H, s, CHO), and cyclic ketol, δ_H 4.5 (1 H, dd, C*H*OH, *J* 12 and 6 Hz) in a 58 : 42 ratio. A mixture of this oil, piperidine (1.65 ml), and acetic acid (3.3 ml) in methanol (50 ml) was refluxed for 16 h, then evaporated to dryness under reduced pressure. Dissolved in diethyl ether the solution was washed in turn with 6N HCl, saturated aqueous $NaHCO_3$ (32 ml), and water and was then dried and evaporated to dryness to yield a viscous oil. Crystallization from diethyl ether at low temperature gave the pure spiro-compound (1b) (0.595 g, 74%), identical with a sample synthesized by us earlier by a different method;[5] δ_H ($CDCl_3$) 1.8—3.1 (8 H, m, 4 × CH_2), 3.7 (3 H, s, OMe), 3.8 (3 H, s, OMe), 5.9 (1 H, d, *J* 10 Hz, 3-H), 6.3 (1 H, d, *J* 2 Hz, ArH), 6.4 (1 H, d, *J* 2 Hz, ArH), and 6.85 (1 H, dd, *J* 10 and 1.7 Hz, 2-H).

Cannabispirenone-B (1a).—*O*-Methylcannabispirenone (2 g) and anhydrous lithium iodide (7.5 g) were stirred and refluxed in 2,4,6-collidine (45 ml) under nitrogen for 5 h in the dark. After the solution had cooled, ethyl acetate (200 ml) was added and the mixture was acidified with 3N HCl. The organic layer was washed in turn with 6N HCl and water and was then dried and concentrated under reduced pressure to leave yellow crystals (1.75 g), the ^1H n.m.r. spectrum of which showed them to be a mixture of the starting compound and the product in a 1 : 1 ratio. Separation was most easily carried out using Claisen's alkali.[17] Thus, the crystals were dissolved in diethyl ether (200 ml) and were extracted with Claisen's alkali (2 × 70 ml). Work-up of the alkali-insoluble material gave pale yellow crystals (0.88 g) of the starting compound. The alkaline extracts were acidified, methanol was evaporated off under reduced pressure, and the residue was extracted with ethyl acetate. The combined extracts were washed with water, then were dried and concentrated under reduced pressure to yield crystals (0.87 g, 46%). The yield based on converted *O*-methylcannabispirenone was thus 82%. Crystallization from methanol afforded the pure phenol (1a), m.p. 237—240 °C (decomp.), identical with the natural product;[6,18] δ_H [$(CD_3)_2CO$] 1.8—3.1 (8 H, m, 4 × CH_2), 3.7 (3 H, s, OMe), 5.8 (1 H, d, *J* 10 Hz, 3-H), 6.3br (2 H, s, ArH), and 6.85 (1 H, dd, *J* 10 and 1.7 Hz, 2-H); δ_C [$CDCl_3$–$(CD_3)_2SO$] 30.5 (C-5 and C-3′), 34.7 (C-6), 35.1 (C-2′), 47.8 (C-1), 54.8 (OMe), 97.2 (C-6′), 103.3 (C-4′), 125.3 (C-7a′), 125.5 (C-3), 145.4 (C-3a′), 156.5 (C-7′), 158.7 (C-2 and C-5′), and 198.4 p.p.m. (C-4). Use of more lithium iodide failed to improve the conversion significantly. Application of a longer reaction time resulted in a higher conversion but not in a higher yield, due to the formation of insoluble tars.

3,5-Difluorocinnamic Acid (5).—A mixture of 1-bromo-3,5-difluorobenzene (4),[13] (19.3 g), freshly distilled acrylic acid (9 g), palladium(II) acetate (0.225 g), triphenylphosphine (0.53 g), and tributylamine (46.5 g) in xylene (20 ml) was stirred and heated at 105 °C for 5 h under nitrogen. The cooled mixture was extracted with 5% aqueous KOH

(3 × 100 ml), the extracts were washed with diethyl ether, acidified, and extracted with diethyl ether. Work-up of the ethereal extract afforded pale-yellow crystals of the crude acid (5) (17.1 g), the major impurity being acrylic acid (*ca.* 2.5 g). A small sample was crystallized from hexane–chloroform to give crystals of the pure acid (5), m.p. 202 °C; δ_H [$(CD_3)_2CO$] 6.6 (1 H, d, *J* 16 Hz, CH=), 6.9—7.5 (3 H, m, ArH), and 7.65 (1 H, d, *J* 16 Hz, CH=).

3-(3,5-*Difluorophenyl*)*propionic Acid* (6).—To a stirred solution of the impure acid (5) (17 g) and $NiCl_2 \cdot 6H_2O$ (6 g) in methanol (500 ml) was added portionwise sodium borohydride (16.5 g) at 20 °C during 40 min with evolution of hydrogen. The mixture was stirred for a further 1 h and was then filtered and evaporated under reduced pressure. The residue was dissolved in 5% aqueous KOH (250 ml) and the solution was washed with diethyl ether and was then acidified and extracted with diethyl ether. The extract was washed with water, dried, evaporated to dryness, and distilled, b.p. 123 °C/1.5 mmHg, to afford an oil which solidified in the receiver [11 g, 75% based on pure acid (5), 59% based on 1-bromo-3,5-difluorobenzene], m.p. 58—59 °C (from hexane); δ_H ($CDCl_3$) 2.5—3.1 (4 H, m, 2 × CH_2) and 6.5—6.9 (3 H, m, ArH).

5,7-*Difluoroindan*-1-*one* (7).—To stirred polyphosphoric acid (200 g) at 80 °C was added the acid (6) (20 g). After being stirred for 70 min at 80 °C, the mixture was poured into water (1 l) and extracted with diethyl ether. The extract was washed in turn with 5% KOH and water, then dried and evaporated to dryness to yield off-white crystals (17.4 g, 96%). Recrystallization from hexane–chloroform gave crystals of the ketone (7), m.p. 81—82 °C; δ_H ($CDCl_3$) 2.65—2.9 (2 H, m, CH_2), 3.1—3.3 (2 H, m, CH_2), 6.75 (1 H, dt, *J* 9 and 2 Hz, 6-H), and 7.0br (1 H, d, *J* 9 Hz, 4-H); δ_C ($CDCl_3$) 25.8 (C-3), 36.6 (C-2), 103.0 (dd, *J* 26.9 and 23.1 Hz, C-6), 109.3 (dd, *J* 22.2 and 4.2 Hz, C-4), 121.3 (dd, *J* 13.5 and 2.3 Hz, C-7a), 159.0 (dd, *J* 11.6 and 4.2 Hz, C-3a), 159.1 (dd, *J* 266.1 and 14.3 Hz, C-7), 167.1 (dd, *J* 258.4 and 11.0 Hz, C-5), and 201.0 p.p.m. (d, *J* 1.8 Hz, C-1).

5,7-*Difluoro*-1-*methoxymethyleneindan* (8).—To a stirred, cooled (water-bath at 20 °C) suspension of methoxymethyltriphenylphosphonium chloride (30.9 g) in dioxan (250 ml) was added potassium t-butoxide (10 g) in one portion. After 90 min, 5,7-difluoroindan-1-one (7) (5.1 g) was added in one portion to the red solution. The mixture was stirred for 1 h at 20 °C, then was heated under reflux for 3 h. The mixture was cooled, diluted with water (250 ml), and extracted with hexane. The extracts were washed twice with water, dried, and concentrated to dryness. The crude product was distilled, b.p. 125—135 °C/12 mmHg, to afford the enol ether (8) as an oil (4.5 g, 76%) which partially crystallized with time. The ^1H n.m.r. spectrum indicated the product to be a mixture of isomers, *E* : *Z* 81 : 19; the crystals were the pure (*E*)-isomer, m.p. 47—48 °C; δ_H (mixture) (CCl_4) 2.6—3.1 (4 H, m, 2 × CH_2), 3.65 [0.6 H, s, (*Z*)-OMe], 3.7 [2.4 H, s, (*E*)-OMe], 6.0 [0.2 H, m, (*Z*)-CH=], CH= and 6.4—6.75 [total 2.8 H, m, 2 × ArH and (*E*)-CH=].

5,7-*Difluoroindan*-1-*carbaldehyde* (9).—A mixture of toluene-*p*-sulphonic acid (5.7 g), water (60 ml), dioxan (280 ml), and the enol ether mixture (8) (5.7 g) was refluxed for 16 h. The cooled mixture was diluted with water (280 ml), then extracted with hexane; the extracts were washed with water, dried, concentrated to dryness and distilled, b.p. 112—115 °C/12 mmHg, to yield the aldehyde (9) as a fragrant oil (3.7 g, 70%), δ_H (CCl_4) 2.0—3.1 (4 H, m, 2 × CH_2), 4.1 (1 H, dd, *J* 8 and 4 Hz, 1-H), 6.5—6.85 (2 H, m, ArH), and 9.75 (1 H, finely split s, CHO).

5′,7′-*Difluorospiro*[*cyclohex*-2-*ene*-1,1′-*indan*]-4-*one* (10).—A stirred solution of the aldehyde (9) (3.0 g) and MVK (1.35 g) in diethyl ether (30 ml) was treated at 0 °C with a solution of KOH (0.41 g) in 95% ethanol (2.25 ml). The mixture was stirred at 0 °C for 2 h and at 20 °C for another 2 h, and was then evaporated to dryness. Methanol (20 ml) and 10% aqueous KOH (20 ml) were added to the residue and the mixture was refluxed for 3 h and evaporated to dryness. The residue was dissolved in diethyl ether and the solution was washed with water, then dried, evaporated to dryness and the residue was distilled, b.p. 115—118 °C/0.15 mmHg, to yield the spiro-ketone (10) as an oil which rapidly crystallized in the receiver (2.6 g, 67%), m.p. 86—87 °C (from cyclohexane); δ_H ($CDCl_3$) 1.9—3.2 (8 H, m, 4 × CH_2), 6.05 (1 H, d, *J* 10 Hz, 3-H), and 6.5—7.0 (total 3 H, m, 2 × ArH and 2-H); δ_C ($CDCl_3$) 31.0 (C-3′), 31.9 (C-5), 35.0 and 36.2 (C-2′ and C-6, not specifically assignable), 48.3 (d, *J* 2 Hz, C-1), 102.2 (t, *J* 25.6 Hz, C-6′), 107.8 (dd, *J* 22.0 and 3.6 Hz, C-4′), 127.7 (C-3), 129.4 (dd, *J* 15.0 and 3.5 Hz, C-7a′), 147.6 (dd, *J* 9.6 and 7.2 Hz, C-3a′), 154.7 (C-2), 159.0 (dd, *J* 250.9 and 12.9 Hz, C-7′), 162.8 (dd, *J* 247.9 and 11.1 Hz, C-5′), and 198.5 p.p.m. (C-4).

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