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A new Synthesis of Furostifoline

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Abstract

Starting from 3-ethoxycarbonylmethyl-indole-1-carboxylic acid ethyl ester **1**, a new synthesis of the furo[3,2-*a*]carbazole furostifoline is reported.

Keywords: alkaloids, indoles, coupling reactions, electrocyclic reactions.

In the past twenty years, new highly substituted carbazole alkaloids have been isolated from different natural sources. The carbazole alkaloid furostifoline, a furo[3,2-*a*]carbazole derivative, was isolated in 1990 from *Murraya euchrestifolia.*[2] The first furostifoline synthesis, using a convergent iron-mediated construction of the carbazole nucleus, has been reported recently by Knölker.[3]

We have already reported new entries to 3-[(2-aryl-2-ethoxycarbonyloxy)ethenyl]-2-(ethoxycarbonyloxy)indole-1-carboxylates[4] and to 3-[(2-aryl-1-ethoxycarbonyloxy)ethenyl]-2-(ethoxycarbonyloxy)indole-1-carboxylates[5] and the results of their photocyclization to [a]annulated carbazoles. Following these studies, we report here a new synthesis of furostifoline starting from 3-ethoxycarbonylmethyl-indole-1-carboxylic acid ethyl ester **1**. From compound **1**, the 3-(1-ethoxycarbonyl-2-hydroxy-propenyl)-indole-1-carboxylic acid ethyl ester

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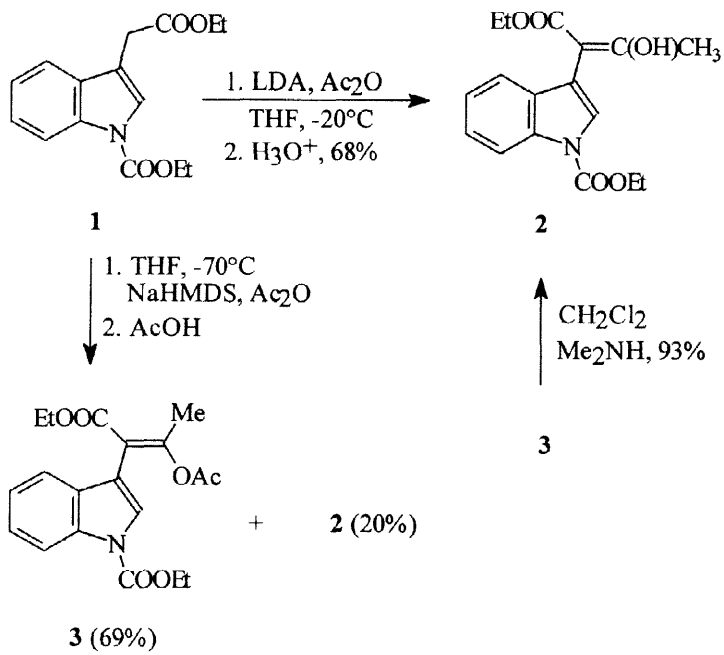
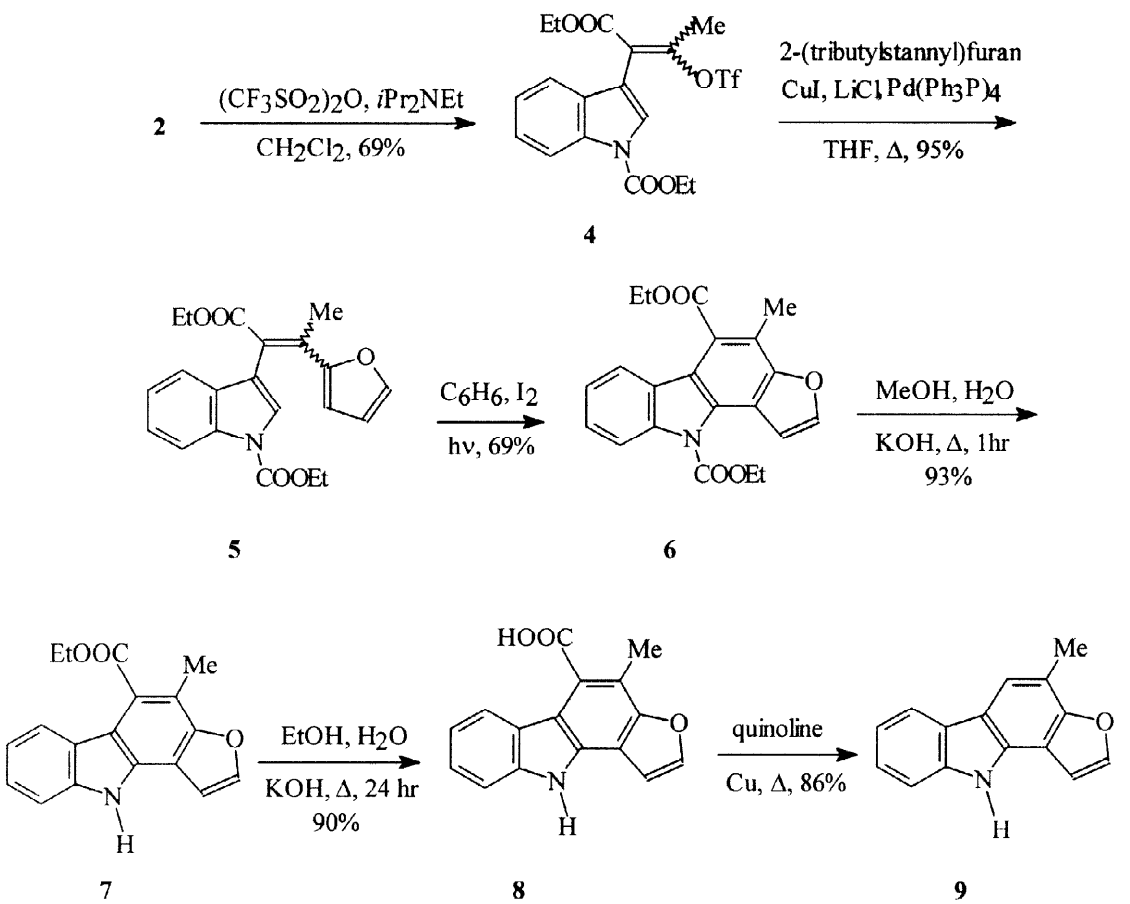
2 was prepared (68% yield) by reaction of the corresponding anion (-20°C, THF, LDA) with acetic anhydride. When the anion is formed at –70°C with sodium *bis*(trimethylsilyl)amide as a base, the reaction with acetic anhydride gave a mixture of compound **2** (20%) and 3-(2-acetoxy-1-ethoxycarbonyl-propenyl)-indole-1-carboxylic acid ethyl ester **3** (69%), as an 8 : 1 mixture of isomers, from which the pure *E* isomer could be isolated by crystallization. Since treatment of compound **3** with Me_2NH, in CH_2Cl_2 solution, gave compound **2** in nearly quantitative yield (Scheme 1), compound **2** may be obtained from **1**, without isolation of pure compound **3**, in 84% yield over two steps.

SCHEME 1



Reaction of compound **2** with trifluoromethanesulfonic anhydride gave the corresponding triflate **4** as an inseparable 1 : 1 mixture of isomers (Scheme 2). The coupling between triflate **4** and 2-(tributylstannyl)furan was carried out in THF solution with *tetrakis*(triphenylphosphine)palladium, LiCl and CuI[6] and afforded the coupled product **5** in excellent yield as a 1 : 1 mixture of isomers. Photocyclization of compound **5** (benzene, I_2, high-pressure Hg lamp, pyrex) gave the corresponding furo[3,2-a]carbazole **6** in 69% yield. Subsequent hydrolysis gave acid **8** *via* the N-deprotected ester **7** (Scheme 2).

SCHEME 2



Decarboxylation of compound **8** (quinoline, Cu, Δ) gave furostifoline **9** in 86% yield, whith spectral data in agreement with those described in the literature.[3]

Experimental

Melting points were determined on a Büchi 510 apparatus and are uncorrected. IR spectra were recorded on a JASCO IR Report 100 instrument, in Nujol mull for solids and as liquid films for oils. ^{1}H-NMR spectra were recorded on a Varian Gemini 200 or a Bruker AVANCE DRX 300 spectrometer in $CDCl_3$ solution unless otherwise stated; chemical shifts are expressed

in ppm (δ) relative to TMS, coupling constants (J) in Hz. Column chromatography was performed on Kieselgel Merck 60, 0.063-0.2 mm. Evaporation was carried out under vacuum on a rotary evaporator. Irradiation was carried out with a HPK-125 W Philips, high-pressure mercury vapour lamp in a preparative photochemical reactor equipped with a pyrex double-walled immersion well for water cooling of lamp.

3-Ethoxycarbonylmethyl-indole-1-carboxylic acid ethyl ester **1**.

Indole-3-acetic acid (20 mmol, 5.50 g) was dissolved in dry MeCN (40 mL) and then diethyl pyrocarbonate (25 mmol, 6.62 mL) and 4-dimethylaminopyridine (50 mg) were added. After 24 h at room temperature, the solvent was evaporated and the residue purified by silica gel column chromatography (hexane-CH_2Cl_2, 1 : 1.5) to give pure compound **1** (5.24 g, 95%); oil; IR 1720br, 1597 cm^{-1}; ^{1}H-NMR δ 1.27 (3H, t, 7.2), 1.47 (3H, t, 7.2), 3.70 (2H, s), 4.19 (2H, q, 7.2), 4.48 (2H, q, 7.2), 7.30 (2H, m), 7.55 (1H, m), 7.63 (1H, s), 8.19 (1H, d, 7.7); Anal. Calcd. for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.38; H, 6.30; N, 5.01.

3-(1-Ethoxycarbonyl-2-hydroxy-propenyl)-indole-1-carboxylic acid ethyl ester **2**.

To a solution of compound **1** (12 mmol, 3.30 g) in anhydrous THF (40 mL), at –20°C under nitrogen, 2M LDA (24 mmol, 12 mL) was added. After 5 min at –20°C, acetic anhydride (14 mmol, 1.32 mL) was added. After being warmed at room temperature, the reaction mixture was evaporated, diluted with 4.5% HCl (40 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was purified by silica gel column chromatography (hexane-Et_2O, 3 : 1) to give pure compound **2** (2.60 g, 68%); mp 84°C (hexane-Et_2O); IR 1725, 1640 cm^{-1}; ^{1}H-NMR δ 1.14 (3H, t, 7.1), 1.49 (3H, t, 7.2), 1.93 (3H, s), 4.16 (2H, m), 4.51 (2H, q, 7.2), 7.32 (3H, m), 7.46 (1H, s), 8.19 (1H, d, 8.6), 13.37 (1H, s, D_2O); Anal. Calcd. for: $C_{17}H_{19}NO_5$: C, 64.34; H, 6.04; N, 4.41. Found: C, 64.29; H, 5.98; N, 4.38.

3-(2-Acetoxy-1-ethoxycarbonyl-propenyl)-indole-1-carboxylic acid ethyl ester **3**.

To a solution of compound **1** (10 mmol, 2.75 g) in anhydrous THF (30 mL), at –70°C under nitrogen, 1M sodium bis(trimethylsilyl)amide (25 mmol, 25 mL) was added. When the

temperature increased to –50°C, acetic anhydride (20 mmol, 1.90 mL) was added. After being warmed at room temperature, the reaction mixture was evaporated, diluted with 4.5% HCl (45 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated. Silica gel column chromatography of the residue (hexane-Et_2O, 1 : 1) gave compound **2** (0.66 g, 20%) and compound **3** (2.48 g, 69%); mp 69°C (hexane-Et_2O) (pure isomer *E*); IR 1742, 1718, 1680, 1623 cm^{-1}; ^{1}H-NMR δ 1.18 (3H, t, 7.2), 1.48 (3H, t, 7.2), 1.96 (1.82 in the *Z* isomer) (3H, s), 2.28 (2.47 in the *Z* isomer) (3H, s), 4.14 (2H, q, 7.2), 4.51 (2H, q, 7.2), 7.30 (2H, m), 7.47 (1H, m), 7.65 (1H, s), 8.20 (1H, d, 8.0); Anal. Calcd. for: $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.46; H, 5.84; N, 3.85.

3-(1-Ethoxycarbonyl-2-hydroxy-propenyl)-indole-1-carboxylic acid ethyl ester **2**, *from* **3**.

Compound **3** (4 mmol, 1.44 g) was dissolved in CH_2Cl_2 (40 mL) and then a 33% ethanolic dimethylamine solution (10 mmol, 1.8 mL) was added. The reaction mixture was stirred at room temperature for 10 min and then washed with 4.5% HCl (40 mL). The organic layer was dried, filtered and evaporated. The residue was purified by silica gel column chromatography (hexane-Et_2O) to give pure compound **2** (1.19 g, 93%).

3-[1-Ethoxycarbonyl-2-(trifluoromethanesulfonyloxy)-propenyl]-indole-1-carboxylic acid ethyl ester **4**.

Compound **2** (7 mmol, 2.22 g) was dissolved in CH_2Cl_2 (40 mL) and then *N,N*-diisopropylethylamine (10 mmol, 1.72 mL) was added. The stirred reaction mixture was cooled to 0°C and a solution of trifluoromethanesulfonic anhydride (10 mmol, 1.64 mL) in CH_2Cl_2 (5 mL) was added. After 10 min at 0°C, the reaction mixture was washed with H_2O (2 x 30 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was purified by silica gel column chromatography (hexane-CH_2Cl_2, 2 : 1) to give pure compound **4** (2.17 g, 69%); oil; IR 1730br, 1600 cm^{-1}; ^{1}H-NMR δ 1.29 (3H, m), 1.49 (3H, m), 2.13 (1.5H, s), 2.59 (1.5H, s), 4.29 (2H, m), 4.55 (2H, m), 7.25-7.48 (3.5H, m), 7.73 (0.5H, s), 8.21 (1H, m); Anal. Calcd. for $C_{18}H_{18}F_3NO_7S$: C, 48.11; H, 4.04; N, 3.12. Found: C, 48.28; H, 3.99; N. 3.02.

3-(1-Ethoxycarbonyl-2-furan-2-yl-propenyl)-indole-1-carboxylic acid ethyl ester **5**.

Compound **4** (5 mmol, 2.25 g) was dissolved in anhydrous THF (40 mL). To this solution, LiCl (15 mmol, 636 mg), CuI (2.5 mmol, 476 mg), $Pd[(Ph)_3P]_4$ (116 mg, 0.1 mmol) and 2-(tributystannyl)furan (10 mmol, 3.15 mL) were added. The reaction mixture was heated under reflux for 45 min, evaporated and the residue purified by silica gel column chromatography (hexane-Et_2O, 6 : 1) to give: *E*-**5** (881 mg, 48%); oil; IR 1730br, 1600 cm^{-1}; ^{1}H-NMR δ 1.24 (3H, t, 7.2), 1.48 (3H, t, 7.2), 2.46 (3H, s), 4.22 (2H, q, 7.2), 4.48 (2H, q, 7.2), 5.94 (1H, d, 3.4), 6.16 (1H, dd, 1.8, 3.5), 7.10-7.36 (4H, m), 7.55 (1H, s), 8.19 (1H, d, 8.1); Anal. Calcd. for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.53; H, 5.71; N, 3.77. And *Z*-**5** (858 mg, 47%); oil; IR 1730br, 1600 cm^{-1}; ^{1}H-NMR δ 1.28 (3H, t, 7.2), 1.48 (3H, t, 7.2), 2.06 (3H, s), 4.25 (2H, q, 7.2), 4.51 (2H, q, 7.2), 6.46 (1H, dd, 1.8, 3.5), 6.53 (1H, d, 3.3), 7.24-7.40 (2H, m), 7.44 (1H, m), 7.56 (1H, m), 7.68 (1H, s), 8.20 (1H, d, 8.1); Anal. Calcd. for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.51; H, 5.73; N, 3.78.

3-Methyl-furo[3,2-a]carbazole-4,9-dicarboxylic acid diethyl ester **6**.

Compound **5** (6 mmol, 2.20 g) was dissolved in benzene (200 mL), a catalytic amount of iodine was added and the solution was irradiated for 16 h. The residue from the solvent evaporation was purified by silica gel column chromatography (hexane-CH_2Cl_2, 2 : 1) to give pure compound **6** (1.52 g, 69%); mp 95°C (hexane-Et_2O); IR 1738, 1710 cm^{-1}; ^{1}H-NMR δ 1.48 (3H, t, 7.1), 1.59 (3H, t, 7.2), 2.64 (3H, s), 4.64 (4H, m), 7.40 (2H, m), 7.58 (1H, d, 2.2), 7.75 (1H, d, 2.2), 7.82 (1H, m), 8.27 (1H, m); Anal. Calcd. for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83: Found: C, 68.97; H, 5.22; N, 3.79.

3-Methyl-furo[3,2-a]carbazole-4-carboxylic acid ethyl ester **7**.

Compound **6** (4 mmol, 1.46 g) was dissolved in MeOH (40 mL) and a solution of KOH (25 mmol, 1.4 g) in H_2O (5 mL) was then added. The reaction mixture was heated under reflux for 1 h. The residue from the solvent evaporation was diluted with H_2O (50 mL) and extracted with Et_2O (2 x 40 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to give compound **7** (1.10 g, 93%); mp 129°C (hexane-Et_2O); IR 3300, 1680 cm^{-1}; ^{1}H-NMR δ 1.58 (3H, t, 7.2), 2.68 (3H, s), 4.65 (2H, q, 7.2), 6.99 (1H, d, 2.2), 7.22 (1H, m), 7.40 (2H, m), 7.70

(1H, d, 2.2), 7.98 (1H, d, 8.0), 8.40 (1H, bs, exchange with D_2O); Anal. Calcd. for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15; N, 4.78. Found: C, 73.65; H, 5.12; N, 4.73.

3-Methyl-furo[3,2-a]carbazole-4-carboxylic acid **8**.

Compound **7** (3 mmol, 880 mg) was dissolved in EtOH (35 mL) and a solution of KOH (36 mmol, 2.02 g) in H_2O (5 mL) was then added. The reaction mixture was heated under reflux for 24 h. The residue from the solvent evaporation was diluted with 4.5% HCl (40 mL) and filtered to give compound **8** (716 mg, 90%); mp 206-208°C dec (acetone-Et_2O); IR 3400, 1682 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 2.60 (3H, s), 7.18 (1H, t, 7.0), 7.28 (1H, d, 2.2), 7.38 (1H, t, 7.0), 7.58 (1H, d, 8.1), 8.01 (1H, d, 8.1), 8.17 (1H, d, 2.2), 11.93 (1H, bs, exchange with D_2O); Anal Calcd. for $C_{16}H_{11}NO_3$: C, 72.44; H, 4.18; N, 5.28: Found: C, 72.53; H, 4.28; N, 5.36.

Furostifoline **9**.

Compound **8** (1 mmol, 265 mg) was dissolved in quinoline (3 mL), Cu (100 mg) was added and the mixture heated under reflux for 1h. After cooling, the reaction mixture was diluted with 9% HCl (30 mL) and extracted with Et_2O (2 x 30 mL). The residue from the solvent evaporation was purified by silica gel column chromatography (hexane-CH_2Cl_2, 3 : 1) to give furostifoline **9** (190 mg, 86%); mp 175°C (hexane-Et_2O); IR 3360, 1440 cm^{-1}; ^{1}H-NMR δ 2.68 (3H, d, 0.8), 7.00 (1H, d, 2.2), 7.26 (1H, dt, 1.1, 8.0), 7.38 (1H, dt, 1.3, 8.0), 7.49 (1H, bd, 7.9), 7.74 (1H, d, 2.2), 7.79 (1H, bs), 8.06 (1H, bd, 7.7), 8.26 (1H, bs, exchange with D_2O); Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.39; H, 5.03; N, 6.33.

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