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A new Synthesis of Staurosporinone

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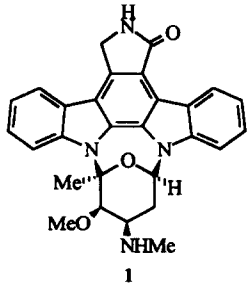
Abstract

A new six steps synthesis of staurosporinone **4**, starting from 3-cyano-3-(1*H*-indol-3-yl)-2-oxo-propionic acid ethyl ester **5**, is reported.

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

The alkaloids that incorporate the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole nucleus have been isolated from various soil organisms, blue-green algae and slime moulds. Representative examples are staurosporine **1** [1], K-252a **2**, initially isolated from *Actinomadura* [2], and rebeccamycin **3**, from *Nocardia aerocoligenes* [3].



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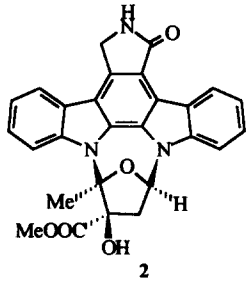

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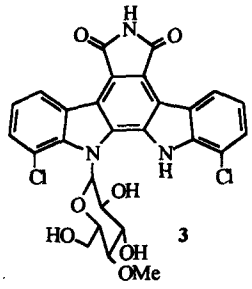

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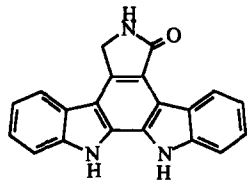


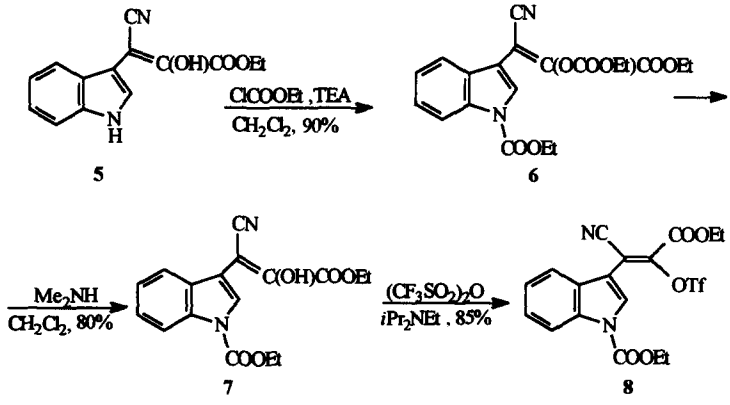
4

These indolocarbazoles are biologically active and display properties ranging from antifungal, antimicrobial, antitumor and antihypertensive activities as well as inhibition of various serine-threonine and tyrosine specific protein kinases [4]; K-252-a has been reported to possess neurotrophic-like properties [5]. The aglycone of staurosporine and K-252a, now commonly referred to as staurosporinone **4**, is itself a natural product [2,6]. Primary interest has been focused on the protein kinase C (PKC) activity of this class of compounds and in view of the therapeutic potential several synthetic analogues have been described in the patent literature [7] .

Several approaches to staurosporinone **4** have been developed [8].

In this paper we describe a new synthesis of the staurosporinone **4** starting from the readily accessible 3-cyano-2-hydroxy-3-(1*H*-indol-3-yl)-acrylic acid ethyl ester **5** [9].

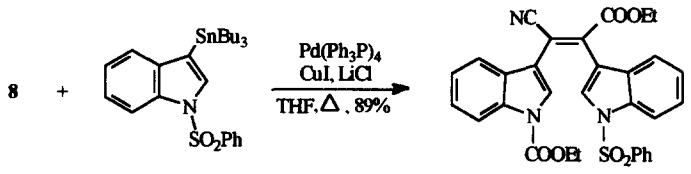
Scheme 1



The reaction of compound **5** with ethyl chlorocarbonate and triethylamine gave the derivative **6** from which compound **7** was obtained by reaction with dimethylamine. The triflate **8** was

prepared from **7** by reaction with trifluoromethanesulfonic anhydride in presence of ethyl diisopropylamine (Scheme 1). The coupling between the triflate **8** and 1-benzenesulfonyl-3-tributylstannylindole **9** [10] was carried out in THF with tetrakis(triphenylphosphine)palladium, LiCl and CuI [11] and afforded the coupling product **10** in good yield (Scheme 2).

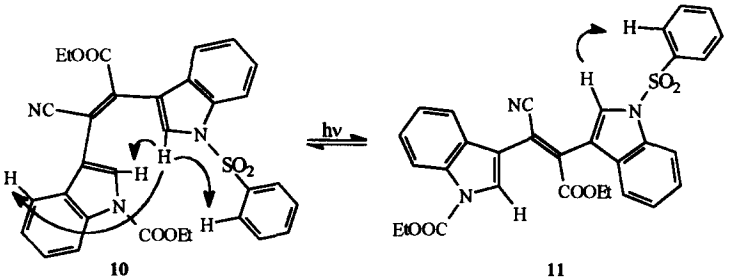
Scheme 2



9 **10**

Short time irradiation of an acetone solution of compound **10** afforded a photostationary mixture from which compound **11** was isolated. *Z*- and *E*-stereochemistry were respectively assigned to **10** and **11** on the basis of NOE experiments (Scheme 3).

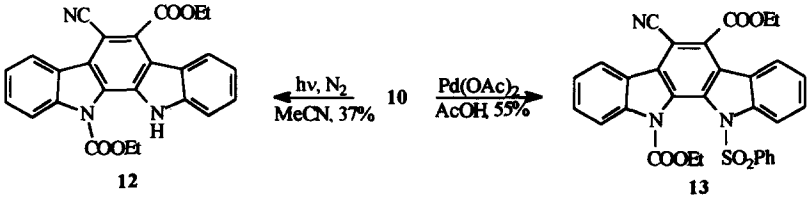
Scheme 3



10 **11**

Photocyclization of compound **10** in MeCN gave a poor yield of the corresponding indolocarbazole **12**, *via* phenylsulfinic acid elimination from the dihydroderivative intermediate. However, treatment of **10** with one equivalent of palladium acetate in acetic acid at reflux gave the cyclized product **13** in 55 % yield (Scheme 4).

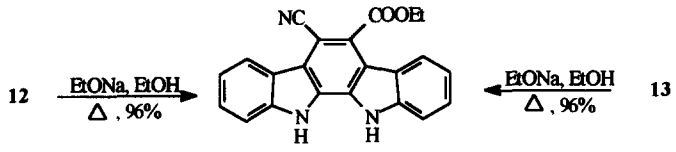
Scheme 4



12 **13**

From compounds **12** and **13**, the same indolocarbazole **14** was obtained in quantitative yield by reaction with sodium ethoxide in ethanol (Scheme 5).

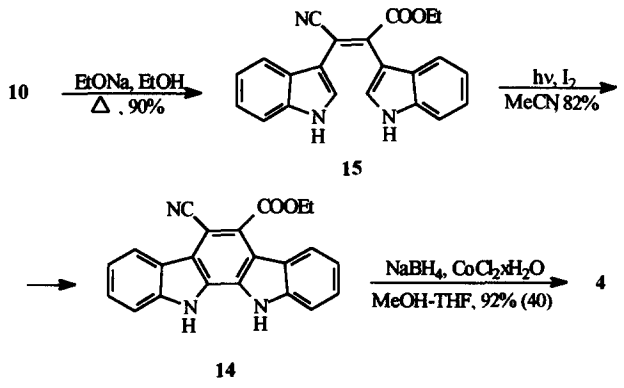
Scheme 5



14

Better results were obtained by deprotection of both nitrogen atoms of **10** with sodium ethoxide in ethanol to compound **15** (mixture of isomers) which was photocyclized (MeCN) to indolocarbazole **14** in 82 % yield (Scheme 6).

Scheme 6



14

Reduction of the cyano group was achieved with sodium borohydride-cobaltous chloride [12]. The staurosporinone **4**, whose spectroscopic properties closely matched those described in the literature, was directly formed in 92% yield, based on the reacted **14**.

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 film

for oils. ^{1}H-NMR were recorded on a Varian Gemini 200 and Bruker AVANCE DRX 300 spectrometers 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 in a rotary evaporator. Irradiations were carried out with a HPK-125 W Philips, high-pressure mercury vapor lamp in a preparative photochemical reactor equipped with a pyrex double-walled immersion well for water cooling of lamp.

3-(1-Cyano-2-ethoxycarbonyl-2-ethoxycarbonyloxy-vinyl)-indole-1-carboxylic acid ethyl ester **6**.

Compound **5** (20 mmol, 5.12 g) was dissolved in dichloromethane (100 mL) and then triethylamine (60 mmol, 8.36 mL) was added. The stirred reaction mixture was cooled at 0°C and ethyl chlorocarbonate (50 mmol, 4.78 mL) was added. After 10 min at 0°C, the reaction mixture was washed with water (2 x 60 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, 1.5:1) to give pure compound **6** (7.13 g, 88%); oil; IR 2210, 1770, 1735 br cm^{-1}; ^{1}H-NMR δ 1.31 (3H, t, 7.2), 1.44 (3H, t, 7.1), 1.50 (3H, t, 7.1), 4.28 (2H, q, 7.2), 4.46 (2H, q, 7.1), 4.54 (2H, q, 7.1), 7.38 (2H, m), 7.96 (1H, m), 8.09 (1H, s), 8.24 (1H, m); Anal. Calcd. for $C_{20}H_{20}N_2O_7$: C, 59.99; H, 5.04; N, 7.00. Found: C, 60.04; H, 4.99; N, 6.91.

3-(1-Cyano-2-ethoxycarbonyl-2-hydroxy-vinyl)-indole-1-carboxylic acid ethylester **7**.

Compound **6** (18 mmol, 7.21 g) was dissolved in dichloromethane (100 mL) and then a 33% ethanolic dimethylamine solution (20 mmol, 3.6 mL) was added. The reaction mixture was stirred at room temperature for 10 min and then washed with diluted HCl (120 mL, 4.5%). The organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was purified by silica gel column chromatography (CH_2Cl_2-Et_2O, 3:1) to give pure compound **7** (4.61 g, 78%); mp 130-131°C (Et_2O); IR 3100, 2220, 1721, 1702 cm^{-1}; ^{1}H-NMR δ 1.51 (6H, m), 4.55 (4H, m), 7.35 (2H, m), 7.53 (1H, s, D_2O), 8.24 (3H, m); Anal. Calcd. for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.11; H, 4.87; N, 8.60.

3-[1-Cyano-2-ethoxycarbonyl-2-(trifluoro-methanesulfonyloxy)-vinyl]-indole-1-carboxylic acid ethyl ester **8**.

Compound **7** (6 mmol, 1.97 g) was dissolved in dichloromethane (50 mL) and then *N,N'*-diisopropylethylamine (12 mmol, 2.13 mL) was added. The stirred reaction mixture was cooled at 0°C and a solution of trifluoromethanesulfonic anhydride (9 mmol, 1.52 mL) in dichloromethane (5 mL) was added. After 5 min at 0°C, the reaction mixture was washed with water (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, 1:1) to give pure compound **8** (2.35 g, 85%); mp 70-71°C (pentane); IR 1745 br, 1600 cm^{-1}; ^{1}H-NMR δ 1.49 (6H, m), 4.57 (4H, m), 7.43 (2H, m), 7.89 (1H, m), 8.17 (1H, s), 8.28 (1H, m); Anal. Calcd. for $C_{18}H_{15}F_3N_2O_7S$: C, 46.96; H, 3.28; N, 6.08. Found: C, 46.89; H, 3.26; N, 6.01.

3-[2-(1-Benzenesulfonyl-1H-indol-3-yl)-1-cyano-2-ethoxycarbonyl-vinyl]-indole-1-carboxylic acid ethyl ester **10**.

Compound **8** (4 mmol, 1.84 g) was dissolved in anhydrous THF (80 mL). To this solution, LiCl (12 mmol, 509 mg), CuI (2 mmol, 381 mg), $Pd[(Ph)_3P]_4$ (0.08 mmol, 92 mg) and 1-benzenesulfonyl-3-tributylstannylindole **9** (5 mmol, 2.73 mL) were added. The reaction mixture was heated under reflux for 3.5 h, evaporated and the residue purified by silica gel column chromatography (hexane-CH_2Cl_2, 2:1 to CH_2Cl_2) to give pure compound **10** (2.02 g, 89%); mp 147-148°C (Et_2O-hexane); IR 2200, 1737, 1708 cm^{-1}; ^{1}H-NMR (C_6D_6) δ 0.76 (3H, t, 7.1), 1.06 (3H, t, 7.1), 3.73 (2H, q, 7.1), 4.15 (2H, q, 7.1), 6.74 (3H, m), 6.84 (2H, m), 6.98 (1H, m), 7.07 (1H, m), 7.24 (1H, m), 7.44 (1H, s), 7.48 (3H, m), 7.81 (1H, s), 8.01 (1H, d, 8.3), 8.36 (1H, d, 8.1); Anal. Calcd. for $C_{31}H_{25}N_3O_6S$: C, 65.70; H, 4.44; N, 7.40. Found: C, 65.68; H, 4.39; N, 7.36.

Photochemical Isomerization of Compound **10**.

Compound **10** (284 mg, 0.5 mmol) was dissolved in acetone (40 mL) and the solution was irradiated (external lamp) for 20 min. The residue from the solvent evaporation was separated by silica gel column chromatography (hexane-CH_2Cl_2, 1:1) to give compound **10** (180 mg, 63 %)

and compound **11** (76 mg, 26 %); mp 136-137°C (hexane-Et_2O); IR 2200, 1738, 1718 cm^{-1}; ^1H-NMR (C_6D_6) δ 0.62 (3H, t, 7.1), 0.86 (3H, t, 7.1), 3.78 (2H, q, 7.1), 3.91 (2H, q, 7.1), 6.73 (3H, m), 6.99 (1H, t, 7.5), 7.22 (3H, m), 7.62 (1H, d, 8.0), 7.83 (1H, s), 7.90 (2H, m), 8.18 (2H, d, 8.1), 8.51 (1H, s), 8.41 (1H, d, 8.3). Anal. Calcd. for $C_{31}H_{25}N_3O_6S$: C, 65.70; H, 4.44; N, 7.40. Found: C, 65.66; H, 4.40; N, 7.37.

Photocyclization of Compound **10**.*Ethyl 5-cyano-indolo[2,3-a]carbazole-6,12-dicarboxylate* **12**.

Compound **10** (284 mg, 0.5 mmol) was dissolved in MeCN (60 mL), the solution placed in the photochemical reactor and N_2 bubbled through the solution for 2 min before irradiation. After irradiation for 1.5 h, the solution was evaporated and the residue purified by silica gel column chromatography (hexane-CH_2Cl_2, 0.5:1) to give pure compound **12** (79 mg, 37%); mp 203-204 °C (CH_2Cl_2-Et_2O); IR 3350, 2200, 1705 cm^{-1}; ^1H-NMR δ 1.61 (6H, m), 4.70 (4H, m), 7.38 (5H, m), 8.04 (2H, m), 8.68 (1H, d, 7.7), 11.16 (1H, s, D_2O); Anal. Calcd. for: $C_{25}H_{19}N_3O_4$: C, 70.58; H, 4.50; N, 9.88. Found: C, 70.49; H, 4.48; N, 9.91.

Thermal Cyclization of Compound **10**. *Ethyl 12(benzenesulfonyl)-6-cyano-indolo[2,3-a] carbazole-5,11-dicarboxylate* **13**.

Compound **10** (284 mg, 0.5 mmol) was dissolved in AcOH (25 mL), $Pd(OAc)_2$ (0.5 mmol, 114 mg) was added and the reaction mixture heated to reflux for 2 h. The residue from the solvent evaporation was purified by silica gel column chromatography (hexane-Et_2O, 2:1) to give pure compound **13** (156 mg, 55%); mp 207-209°C (hexane-Et_2O); IR 2202, 1741, 1707 cm^{-1}; ^1H-NMR δ 1.52 (6H, t, 7.1), 4.68 (4H, m), 7.02 (4H, m), 7.30 (2H, m), 7.55 (2H, m), 7.73 (1H, m), 7.83 (1H, d, 8.0), 8.27 (1H, d, 8.1), 8.53 (1H, d, 8.3), 8.84 (1H, d, 7.4); Anal. Calcd. for $C_{31}H_{23}N_3O_6S$: C, 65.83; H, 4.10; N, 7.43. Found: C, 65.78; H, 4.02; N, 7.39.

5-Carbethoxy-6-cyanoindolo[2,3-a]carbazole **14** *from compound* **13**.

Compound **13** (283 mg, 0.5 mmol) was dissolved, at 50 °C, in EtOH (30 mL) and a solution of Na (35 mg, 1.5 mmol) in EtOH (3 mL) was added. The reaction mixture was heated to reflux for 30 min. The solvent was then evaporated, the residue treated with diluted HCl (5 mL, 4.5%)

and extracted with CH_2Cl_2 (2 x 10 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated. Column cromatography of the residue (CH_2Cl_2-Et_2O, 20:1) gave pure compound **14** (175 mg, 99%); mp 286-288°C (CH_2Cl_2); IR 3350, 2200, 1680, 1638 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.50 (3H, t, 7.2), 4.66 (2H, q, 7.2), 7.37 (2H, m), 7.59 (2H, m), 7.87 (2H, m), 8.17 (1H, d, 8.1), 8.58 (1H, d, 8.1), 11.81 (1H, s, D_2O), 11.95 (1H, s, D_2O); Anal. Calcd. for $C_{22}H_{15}N_3O_2$: C, 74.78; H, 4.28; N, 11.89. Found : C, 74.70; H, 4.22; N, 11.91.

5-Carbethoxy-6-cyanoindolo[2,3-a]carbazole **14** *from compound* **12**.

To a suspension of compound **12** (212 mg, 0.5 mmol) in EtOH (30 mL) a solution of Na (35 mg, 1.5 mmol) was added. The reaction mixture was heated to reflux for 15 min. The solvent was then evaporated, the residue treated with diluted HCl (5 mL, 4.5%) and extracted with CH_2Cl_2 (2 x 10 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated. Column cromatography of the residue (CH_2Cl_2-Et_2O, 20:1) gave pure compound **14** (158 mg, 90%).

3-Cyano-2,3-bis-(1H-indol-3-yl)-acrylic acid ethyl ester **15** *from compound* **10**.

Compound **10** (2 mmol, 1.14 g) was dissolved, at 50°C, in EtOH (70 mL) and a solution of Na (6 mmol, 138 mg) in EtOH (10 mL) was added. The reaction mixture was heated under reflux for 15 min and then evaporated. The residue was treated with diluted HCl (25 mL, 4.5%) 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 (CH_2Cl_2-Et_2O, 20:1) gave pure compound **15** (1:1 mixture of isomers) (640 mg, 90%); mp 205-209°C; 3300 br, 3250, 2200, 1670 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 0.97 (1.5H, t, 7.1), 1.33 (1.5H, t, 7.1), 4.14 (1H, q, 7.1), 4.40 (1H, q, 7.1), 6.88-7.55 (9H, m), 7.70 (0.5H, d, 7.2), 8.11 (0.5H, d, 2.3), 11.60 (1.5H, bs, D_2O), 11.94 (0.5H, bs, D_2O); Anal. Calcd. for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82. Found: C, 74.30; H, 4.78; N, 11.80.

5-Carbethoxy-6-cyanoindolo[2,3-a]carbazole **14** *from compound* **15**.

Compound **15** (1.07 g, 3 mmol) was dissolved in MeCN (160 mL), a catalytic amount of iodine was added and the solution irradiated for 6 h. The residue from the solvent evaporation

was purified by silica gel column chromatography (Et_2O) to give pure compound **14** (870 mg, 82%).

Staurosporinone **4**.

Compound **14** (1.06 g, 3 mmol) and cobaltous chloride hexahydrate (1.43 g, 6 mmol) were dissolved in a mixture of MeOH (120 mL) and THF (50 mL). Sodium borohydride (1.14 g, 30 mmol) was then added in portions with stirring at room temperature (20 min). When the addition was complete, stirring was continued for 1h at room temperature. After evaporation of the solvents, water (100 mL) was added and the mixture filtered. The solid was suspended in acetone (100 mL) and the mixture, after 10 min at 45-50°C, filtered. The solid was washed with acetone (2 x 50 mL). The acetone solution was evaporated and the residue separated by silica gel column chromatography (CH_2Cl_2 to CH_2Cl_2-acetone, 1:1) to give: unreacted **14** (604 mg, 57%) and staurosporinone **4** (370 mg, 92% based on the reacted **14**); mp > 310°C; IR 3400, 3280, 1650 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 4.98 (2H, s), 7.25 (1H, t, 7.1), 7.32 (1H, t, 7.0), 7.45 (2H, m), 7.74 (1H, d, 8.0), 7.79 (1H, d, 8.1), 8.06 (1H, d, 7.7), 8.50 (1H, s), 9.24 (1H, d, 7.7), 11.35 (1H, bs, D_2O), 11.52 (1H, bs, D_2O); Anal. Calcd for $C_{20}H_{13}N_3O$: C, 77.15; H, 4.21; N, 13.50: Found: C, 76.98; H, 4.21; N, 13.37.

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