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# A short synthesis of staurosporinone (K-252c)

Susana P. Gaudêncio, Maria M. M. Santos, Ana M. Lobo* and Sundaresan Prabhakar*

*Secção de Química Orgânica Aplicada, Departamento de Química, CQFB-REQUIMTE and SINTOR-UNINOVA, campus Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, Quinta da Torre, 2829 Monte de Caparica, Portugal*

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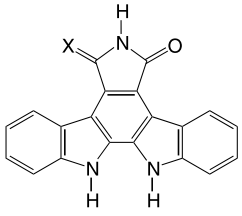
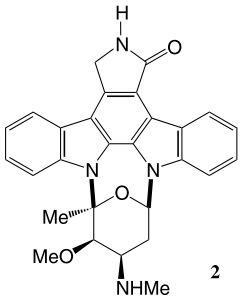
**Abstract**—A new, simple, high-yield synthesis of the indolo[2,3-*a*]carbazole alkaloid staurosporinone is described. 

Staurosporinone (**1a**), the aglycone of the biologically important alkaloid staurosporine (**2**),[1] is itself a natural product.[2] As the heterochromatic part is a common sub-unit in other structurally related indolocarbazole alkaloids, many syntheses[3] have been described for this substance since its structure determination.[4]

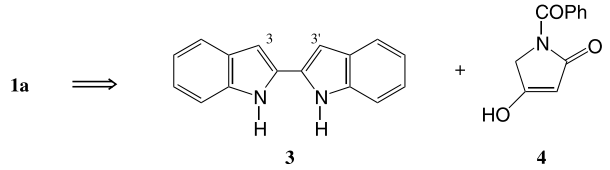


**1a** X= H, H
**1b** X= O



**2**

We describe herein a relatively short synthesis of staurosporinone (**1a**) which employs, as starting materials, the bis-indole (**3**) and the keto lactam (**4**) arising from a simple disconnection process shown in Scheme 1.



**3** **4**

**Scheme 1.**

The aforementioned retrosynthetic operation reduced the problem to the preparation of two simple molecules, namely, 2,2′-biindolyl (**3**) and the tetramic acid (**4**). Although a number of procedures for **3** are reported, the method of Madelung, as modified by Bergman, was selected because of its simplicity and good yield (73%).[5] The other required starting material **4** was also readily accessed from the commercially available hippuric acid and Meldrum acid in 82% overall yield in two steps.[6]

With respect to the electrophilic substitution of indoles at the 3 position, which is the key step in the contemplated synthesis, it is known that 1,2-dialkyl indoles and 2-methylindole participate efficiently in the coupling with a variety of 1,3-dicarbonyl compounds, in acid medium, to afford α,β-unsaturated compounds.[7] Although it was not obvious at the outset of the study as to how serious the problem of dialkylation[8] (i.e. at the 3,3′-positions) would be in 2,2′-biindolyl, it was anticipated that such undesired over-alkylation was controllable on steric grounds. In the event, heating a mixture of **3** and **4** in dry $CH_2Cl_2$ under reflux, in an inert atmosphere, in the presence of freshly distilled $BF_3{\cdot}Et_2O$, **5b** could be isolated from the complex reaction mixture (42% yield) along with the dilactam derivative (3%). However, the presence of activated molecular sieves (4 Å) in the reaction mixture[9] not only suppressed the formation of the latter but also afforded an improved yield of **5b**[10] (57%), along with its immediate precursor, the imide **5a** (15%), and unreacted **3** (28%) (Scheme 2).[11]

Photocyclisation of **5b** (ca. $5\times10^{-3}$ M) in MeOH–DMSO mixture (5:1) led directly to staurosporinone in high yield (**1a**; 81%; mp >300°C, lit.[4] mp >300°C) presumably via the dihydrobenzene intermediate under-

* Corresponding authors. Fax: +351-21-294-8550; e-mail: aml@fct.unl.pt; sp@dq.fct.unl.pt

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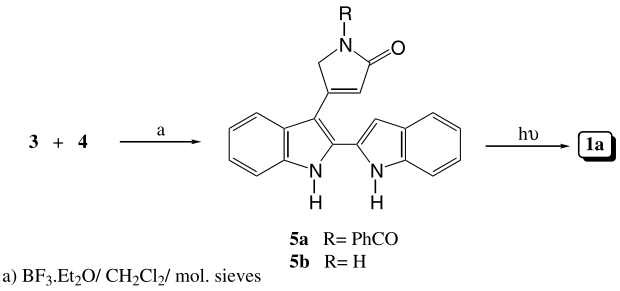


**Scheme 2.**

going in situ aromatisation (Scheme 2). Its spectral data ($^1$H NMR and IR spectra) were coincident with those reported for the natural product.[4] A by-product formed (< 7.5%), probably by aerial oxidation, was identified as arcyriaflavin A (**1b**), on the basis of its $^1$H NMR spectrum and TLC properties, both of which were identical with those of an authentic material.[12]

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9. A suspension of 2,2′-biindolyl (**3**; 505.4 mg), the lactam **4** (224 mg), $BF_3{\cdot}Et_2O$ (0.14 ml) and 4 Å molecular sieves (2.6 g; activated at 300°C for 3 days) in dry $CH_2Cl_2$ (20 ml) was heated under reflux in an atmosphere of argon for a total of 192 h. Further quantities of lactam (2×224 mg) were added at the end of 88 and 113 h, respectively, as were two additional portions of $BF_3{\cdot}Et_2O$ (0.14 ml each) after 18 and 95 h. The work-up consisted of decanting the dark brown solution from the precipitate, and washing it with aq. $NaHCO_3$. The residue that remained undissolved in $CH_2Cl_2$ was taken up in EtOAc and washed with a bicarbonate solution. The solid obtained (1.14 g) on evaporation of the combined organic solutions was chromatographed (silica; EtOAc–MeOH, 40:1) to furnish, in increasing order of polarity the unreacted **3** (146.6 mg, 28%), the imide **5a** (133 mg, 15%) and the lactam **5b** (390 mg; 57%). Based on recovered **3** and the conversion of **5a** into **5b** (see below) the overall yield of the latter compound is >95%.
10. Compound **5b**: mp >220°C (dec); selected spectroscopical data: IR (KBr): 3400, 3205, 3056, 1691, 1649, 1611 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.98 (1H, s, NH, exchangeable with $D_2O$), 11.56 (1H, s, NH, exchangeable with $D_2O$), 7.83 (1H, s, NH, exchangeable with $D_2O$), 6.77 (1H, C(3)-H), 6.14 (1H, CH-C=O), 4.15 (2H, $CH_2$); HRMS $m/z$ calcd for $C_{20}H_{15}N_3O$: 313.12150. Found: 313.12143.
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