Synthesis of the Staurosporine Aglycone

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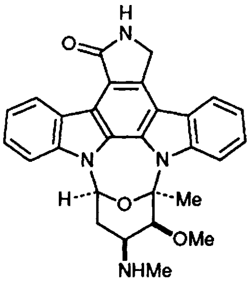
The staurosporine aglycone **3** has been synthesised in 22.6% overall yield from ethyl indole-2-acetate by a route which involves an intramolecular Diels–Alder reaction of the pyranoindolone **8** followed by nitrene mediated cyclisation.

The indolocarbazole alkaloids, exemplified by staurosporine **1** and rebeccamycin **2**, form a structurally rare class of natural products.[1] Interest in such compounds has been heightened by the discovery that staurosporine **1** and related natural products, together with their common aglycone **3**, are potent inhibitors of protein kinase C, and therefore, not surprisingly, several approaches to the indolocarbazole ring system have been developed.[1,2] However, in most cases the final product is *N*-protected, or, more commonly, is a derivative of the more symmetrical aglycone **4**, and so to date only one complete synthesis of the aglycone **3** has appeared.[3]§ In continuation of our interest in carbazole containing natural products,[4] we now report a short new synthesis of the staurosporine aglycone **3**.

The route to the indolocarbazole system is based on an intramolecular Diels–Alder reaction of a pyrano[4,3-*b*]indol-3-one[5,6] followed by nitrene mediated cyclisation.[7] The substrate **8** for the intramolecular Diels–Alder reaction was prepared in good yield in three steps from ethyl indole-2-acetate **5** (Scheme 1). Thus the ester **5** was converted into the disubstituted indole **6** (76%), m.p. 81–83 °C, by reaction with



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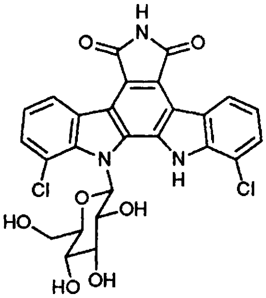

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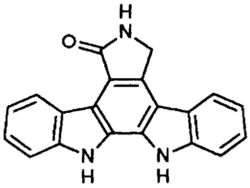

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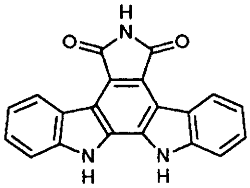

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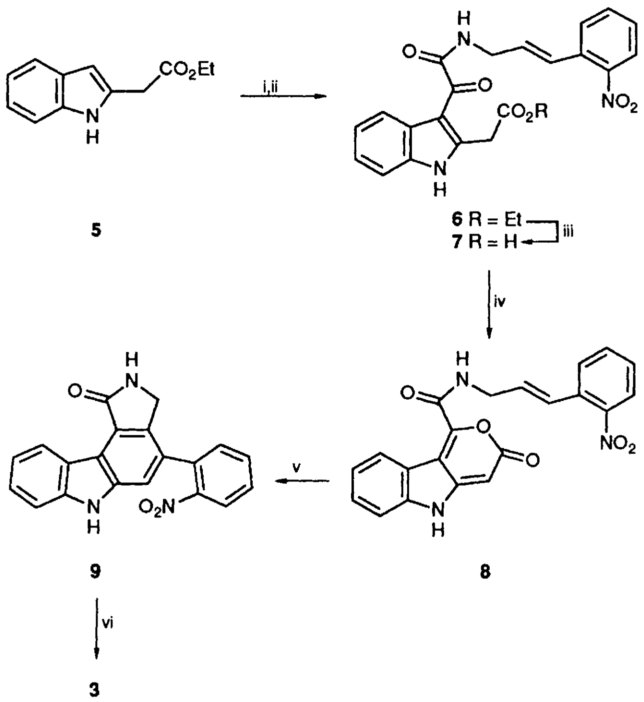
§ *Note added in proof*: Another synthesis of aglycone **3** has appeared recently (ref. 8).



Scheme 1 *Reagents and conditions*: i, $(COCl)_2$, diethyl ether; ii, 3-(2-nitrophenyl)prop-2-enylamine; iii, aq. 2 mmol dm^{-3} KOH, THF–MeOH (9:1); iv, Ac_2O, THF; v, PhBr, reflux; vi, $(EtO)_3P$, reflux (THF = tetrahydrofuran)

oxalyl chloride followed by quenching the indole-3-glyoxalyl chloride *in situ* with 3-(2-nitrophenyl)prop-2-enylamine (2 equiv.).‡ Hydrolysis of the ester (97%), followed by cyclodehydration of the keto acid **7**, m.p. 181–183 °C, with acetic anhydride in tetrahydrofuran (THF) gave the pyranoindolone **8**, m.p. 195 °C (decomp.), in 83% yield. On heating in bromobenzene, the pyranoindolone **8** underwent an intramolecular Diels–Alder reaction, followed by loss of carbon dioxide and aromatisation by aerial oxidation to give the polysubstituted carbazole **9**. Although the carbazole **9**, m.p. 168 °C (decomp.), could be purified (48% after chromatography), it was carried through to the final ring closure step, which was effected by heating the carbazole **9** in triethyl phosphite, and gave staurosporine aglycone **3**, the spectroscopic properties of which closely matched those described in the literature, in 37% yield from **8**.

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‡ The amine was prepared from commercially available 2-nitrocinnamaldehyde by reduction with sodium borohydride and cerium(III) chloride (99%), Mitsunobu reaction with phthalimide (71%), and removal of the phthaloyl group with hydrazine hydrate (83%).

References

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