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A FACILE SYNTHESIS OF STAUROSPORINE AGLYCONE

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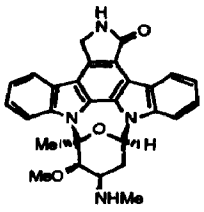
Abstract: **A highly efficient method is described for the synthesis of staurosporine aglycone 3 from the readily available dibromomaleic acid in six steps.**

The indolocarbazole alkaloids are a structurally rare, but biologically interesting, class of natural products.[1] Of this family staurosporine **1**[2] and K252a **2**[3] are the most well known members owing to their very interesting biological activities such as antimicrobial,[4] hypotensive,[5] cell cytotoxic,[2a] inhibition of protein kinase C,[2a] and platelet aggregation.[6] Since the common aglycone portion of these compounds is known to retain much of the activity of the parents and is essential for the total synthesis of the indolocarbazoles, increasing interest in the synthesis of the staurosporine aglycone **3** has developed in the last few years.[7]



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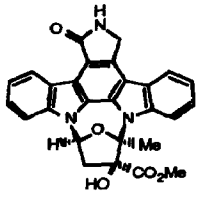

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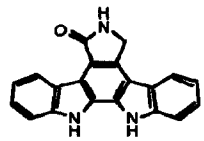

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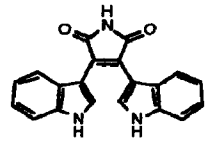

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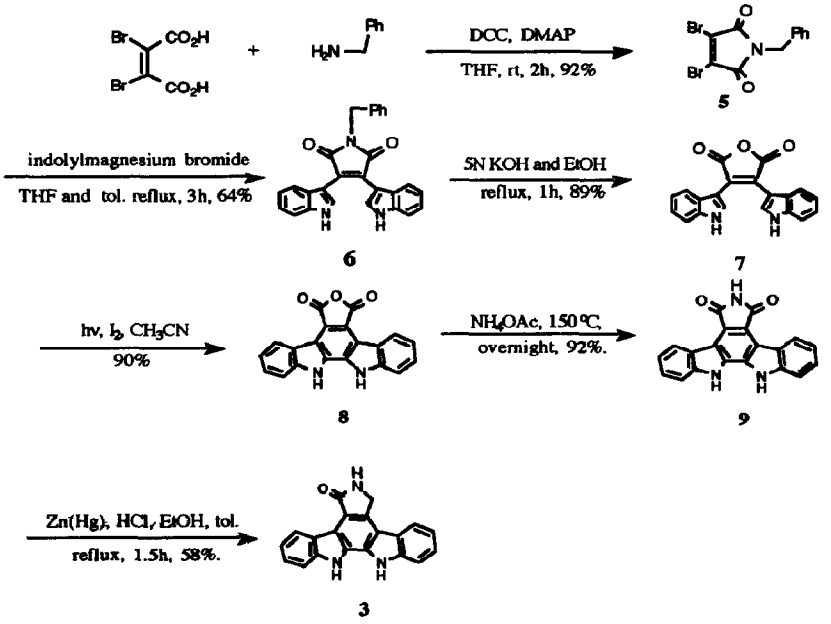
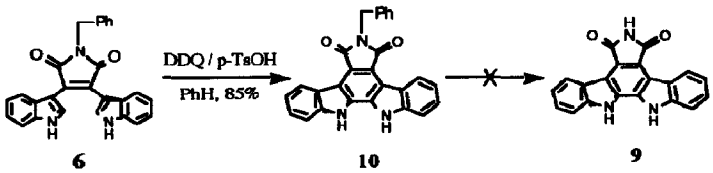
During the course of our work on indolocarbazole derivatives we required a high yielding, facile approach to the aglycone **3** that would allow the synthesis of a wide range of analogues. However, to our knowledge, the earlier syntheses either used some inconvenient reagents[7b,d-f] or afforded low yields of products.[7a-c] This prompted us to search for an alternative method for our purpose. In this communication, we report an efficient chemical route to synthesize the staurosporine aglycone **3**.

The approach to the aglycone **3** via bisindolylmaleimide, arcyriarubin A **4**[8] has been shown to be attractive. However, the preparation of **4** from dibromomaleimide and indolylmagnesium bromide was furnished in only 29% yield,[7f] and furthermore, dibromomaleimide, in our hands, is not an easily available starting material. Thereby, we designed a pathway in which N-benzyl protected bisindolylmaleimide **6** was used in place of **4**. To prepare **6**, we first developed a new coupling reaction which permitted the preparation of the precursor **5** in excellent yield: readily available dibromomaleic acid was treated with one equivalent of benzylamine in the presence of 1, 3-dicyclohexylcarbodiimide (DCC) and a trace of 4-dimethylaminopyridin (DMAP) to afford



compound **5** as a white solid in 92% yield. Subsequently, treatment of compound **5** with excess of indolylmagnesium bromide in a mixture of THF and toluene under refluxing for 3h gave the desired imide **6** in 64% yield. We further envisaged that the following suquence, in which cyclization of **6** to compound **10** was followed by deprotection of the imide nitrogen of **10**, should lead straightforward to the imide **9**. Thus, with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) as the oxidizing reagent, the cyclization of **6** proceeded smoothly to yield the corresponding indolocarbazole compound **10** in 85% yield.[9] However, it proved



impossible by any means to remove the N-benzyl protecting group to give the imide **9**. We, therefore, wished to seek alternative pathways.

The hydrolysis of N-methyl bisindolylmaleimide to the anhydride is known to proceed readily under alkaline conditions.[10] Thus, using the reaction conditions as in the case of N-benzyl bisindolylmaleimide **6**, slightly modified by adding ethanol as a co-solvent, the anhydride **7** was obtained in 89% yield. Then highly efficient photocyclization of **7** , using a medium pressure mercury lamp (400W),[11] gave the indolocarbazole anhydride **8** in 90% yield.[12] Conversion of the anhydride **8** to the corresponding imide **9** was achieved in excellent yield (92%) by heating with ammonium acetate[10] overnight.

The final reduction of the symmetric imide **9** to the lactam, staurosporine aglycone **3** proved to be crucial. Although this type of conversion has been carried out with the Clemmenson method by several groups,[7c,9,10,13] the yields and reaction conditions have not been clear in the literature. There is only one exception[7c] in which the yield of this reaction was reported to be 26%. After attempts with this method, we found that the results of this reaction depended on both reaction conditions and isolation procedure. Thus zinc amalgam was prepared from granular zinc which was purified by washing twice with dilute hydrochloric acid.[14] Then treatment of **9** with the zinc amalgam in mixed solvents of 5 N hydrochloric acid, ethanol[15] and toluene[16] under refluxing for 1.5 h afforded the staurosporine aglycone **3** in a much improved yield (58%) after purification by silica gel chromatography (eluent: Et_2O (50%), EtOAc (49%), MeOH (1%), v/v). Therefore, the staurosporine aglycone **3** was synthesized in 25% overall yield from dibromomaleic acid in six steps. Apparently, the present approach is shown to be not only particularly convenient but also the highest yielding chemical route toward the aglycone **3**.[17]

In summary, we have disclosed a highly efficient method for the synthesis of staurosporine aglycone **3**. Further work is underway to explore the scope of this methodology for development of a general synthesis of indolocarbazole analogues.

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17. For comparison, the overall yields in the citations in reference 7 are examined and listed as follows a) Sarstedt *et al.*: 2.2% yield over 7 steps; b) Hughes *et al.*: 10.9% yield over 10 steps; c) Toullec *et al.*: 8.2% yield based on the last 4 steps, the yield of the first coupling reaction was not reported; d) Fabre *et al.*: 20.8% yield from the degradation of natural rebeccamycin over 3 steps; e) Moody *et al.*: 22.6% yield over 5 steps, but one of the starting reagent required a three step-preparation; f) Harris *et al.*:14% yield over 4 steps, the starting material dibromomaleimide is not commercially available.

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