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Synthetic Studies on Indolocarbazoles: Total Synthesis of Staurosporine Aglycon

Ganesan Gobi Rajeshwaran and Arasambattu K Mohanakrishnan*

Department of Organic Chemistry, School of Chemistry, University of Madras, Guindy Campus Chennai 600 025, Tamil Nadu, India

mohanakrishnan@unom.ac.in

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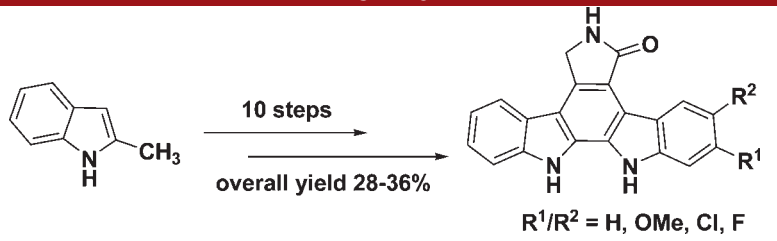
ABSTRACT



A synthesis of staurosporine aglycon and its analogs was achieved in a 28−36% overall yield starting from 2-methylindole. The prominent key steps for the synthesis of the indolocarbazole alkaloids involved electrocyclization and nitrene insertion reactions.

Indolocarbazole alkaloids, which are obtained from either soil organisms or marine sources, contain an indolo-[2,3-*a*]carbazole core.[1] Of these, staurosporine **1**, a metabolite from *Streptomyces*, is an ATP competitive inhibitor which is highly potent against protein kinase C (PKC) (IC_{50} = 1 nM)[2] as well as an inhibitor of cyclin B/CDK1.[3] Thus, Staurosporine has become an important lead structure for the development of novel PKC inhibitors such as compounds **2** and **3**, which have shown higher selectivity for PKC. These compounds also have antitumor properties against various human cancer cell lines.[4] Another compound, in this important class is rebeccamycin **4**, which exhibits topoisomerase I inhibitory activity (Figure 1).[5]

A structure−activity relationship profile of related molecules demonstrated that edotecarin **5** and its analogs are more potent and specific topoisomerase I inhibitors than rebeccamycin.[6] Recently, 6-substituted indolocarbazole aglycons **6** and their simplified analogs were characterized as a new class of D1/CDK4 as well as JAK3 inhibitors.[7] In addition to the biological activities, the indolocarbazole analogs are also being explored for their optical applications such as FET and OTFT and also for solar cells.[8]

Prompted by the PKC and cyclin-dependent kinase activity of indolocarbazoles, several approaches for the synthesis of these alkaloids have been developed.[1,6]

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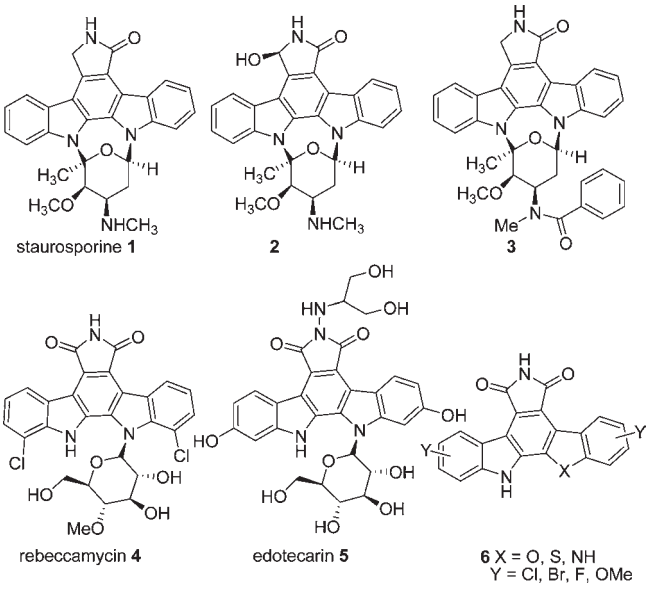
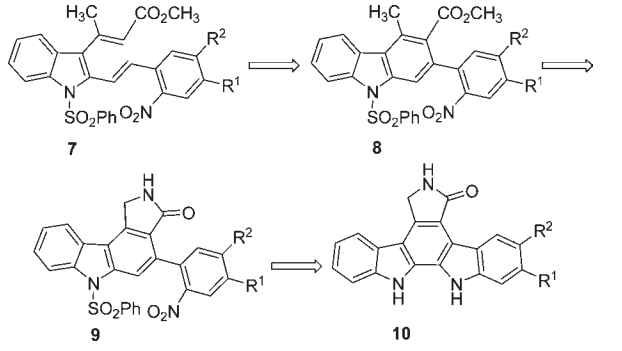


Figure 1. Structures of biologically important indolocarbazoles.

Recently, Knölker and Reddy extensively reviewed the synthesis and biological activity of carbazole alkaloids, wherein different synthetic strategies for indolocarbazole alkaloids were discussed.[9] The synthesis protocols outlined to date for indolocarbazoles are based on readily available bisindolylmaleimides and involve electrocyclization under photochemical conditions,[10] cyclization using Pd-catalysts,[11] and acid-catalyzed cyclization followed by aromatization.[12] The synthesis of indolocarbazoles has also been achieved through nitrene[13] and carbene[14] insertion reactions and through ring-closing metathesis.[15] Recently, Orito and co-workers achieved the staurosporinone framework by the reduction of a 5-cyano indolo[2,3-*a*]carbazole followed by a Pd-mediated carbonylation reaction.[16] Howard-Jones and Walls established a biosynthetic route to staurosporine and rebeccamycin aglycons from chromopyrrolic acid.[17]

It is important to bear in mind that most of the indolocarbazoles, which exhibit potent biological activities, have substituents on the benzene portion of the core. Despite the synthetic efforts for indolocarbazoles mentioned above, there remains a need for a flexible and efficient route. Previously, we reported the synthesis of quino[4,3-*b*]carbazole analogs,[18] a precursor of calothrixin[19] which involved a thermal electrocyclization in the key step. In a continuation of these synthetic studies on carbazole analogs,[20] we report herein our results on the assembly of an unsymmetrical indolocarbazole framework from 2-methylindole. This methodology involves thermal electrocyclization of 2,3-divinylindole **7** followed by allylic bromination and amidation to give **9**. The carbazole **9** was subjected to a nitrene insertion reaction followed by hydrolysis to afford the target compound **10** (Scheme 1).

Scheme 1. Schematic Pathway for Staurosporine Aglycon



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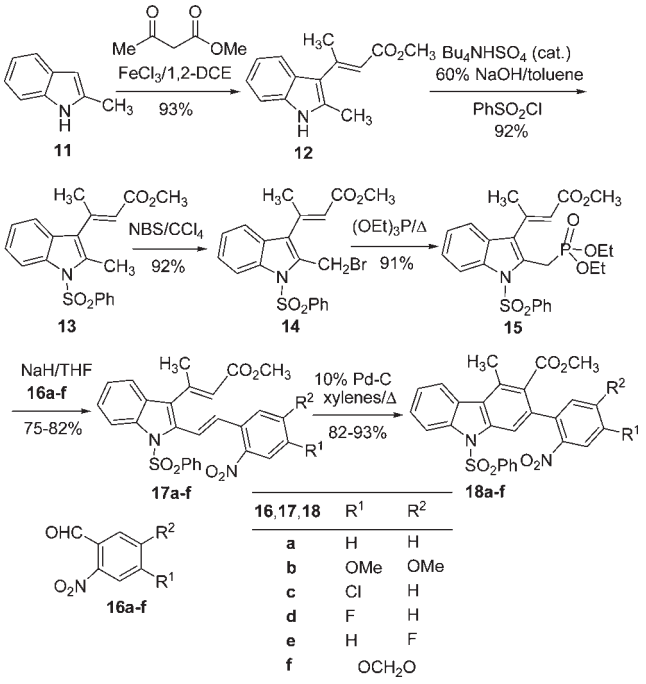
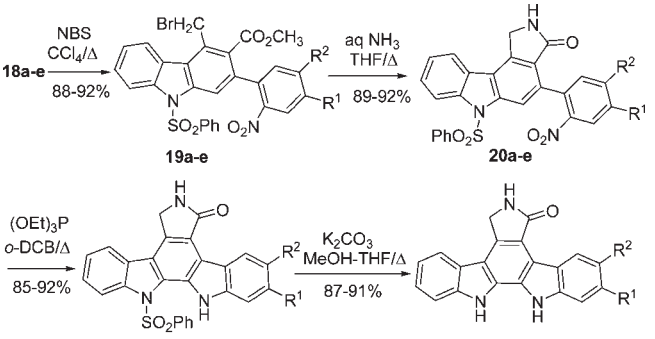
Our synthesis of the desired 2-nitroarylcarbazole is illustrated in Scheme 2. Reaction of 2-methylindole **11** with ethylacetoacetate in the presence of 20 mol % $FeCl_3$ furnished vinylindole **12** in 93% yield.[21] Phenylsulfonylation of **12** under PTC conditions[22] gave compound **13**, which could be preferentially brominated at the allylic position using 1.1 equiv of NBS in the presence of catalytic amounts of AIBN in CCl_4 at reflux. Bromo compound **14**, which was isolated as a thick brown liquid, underwent a Michaelis−Arbuzov reaction with triethylphosphite at 170 °C for 2 h followed by workup to give phosphonate ester **15**, which was elaborated using a Wittig−Horner reaction with 2-nitroarylaldehydes **16a**−**f**. This was accomplished using NaH as a base in dry THF and furnished 2,3-divinylindoles **17a**−**f** as yellow solids, which, upon refluxing in xylene in the presence of 10% Pd−C, underwent smooth electrocyclization followed by aromatization to afford 2-nitroarylcarbazoles **18a**−**f**. The structures of carbazoles **18c**, **18e**, and **18f** were confirmed by single crystal X-ray analyses.[23]

Scheme 2. Synthesis of 2-Nitroarylcarbazoles



16,17,18	R^1	R^2
a	H	H
b	OMe	OMe
c	Cl	H
d	F	H
e	H	F
f	OCH_2O	

Scheme 3. Synthesis of Stauorsporine Aglycon



19, 20, 21, 22	R^1	R^2
a	H	H
b	OMe	OMe
c	Cl	H
d	F	H
e	H	F

With the 2-nitroarylcarbazoles in hand, further synthetic elaboration was accomplished according to Scheme 3. This began by boiling a dilute solution of each 4-methylcarbazole **18a**−**e** with 2−3 equiv of NBS in the presence of AIBN to obtain the bromomethylcarbazoles **19a**−**e** in good yields. It should be noted that the allylic bromination of 4-methyl carbazole **18f** was complicated by the preferential bromination at the methylenedioxy unit. Reaction of bromomethylcarbazoles **19a**−**e** with aq. NH_3 in dry THF under reflux conditions underwent amination followed by intramolecular cyclization to give amides **20a**−**e**. The reaction of 2-nitroarylcarbazoles **20a**−**e** with triethylphosphite using *o*-DCB as a solvent under reflux for 12 h effected final ring closure and thus afforded indolocarbazoles **21a**−**e** in excellent yields.

It should be noted that during the triethylphosphite-mediated nitrene insertion of the 2-nitroarylcarbazoles **20a**−**e**, we did not observe any *N*-ethylation as reported by Moody and co-workers.[13g] Moreover, the ring closure proceeded in quantitative yields compared to Moody's work wherein a low yield (37%) was reported. The excellent yield obtained in the present case might be due to the nitrene insertion taking place *meta*- to the amide carbonyl unlike Moody's work wherein a similar reaction proceeded at the *para*-position to the amide. Finally, the cleavage of the phenylsulfonyl in **21a**−**e** using K_2CO_3 in MeOH−THF under reflux led to the formation of staurosporine aglycons **22a**−**e** as brown solids. The structures

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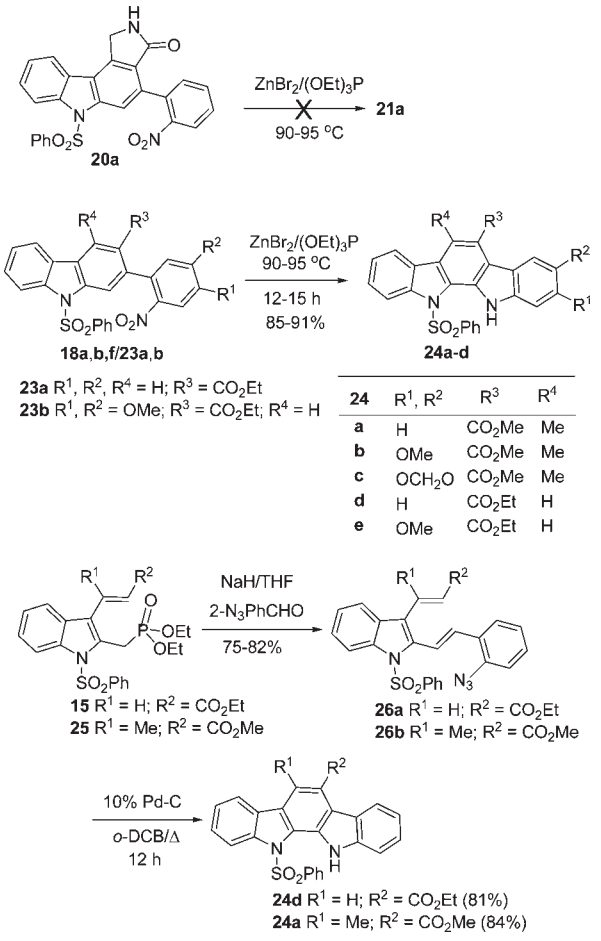
(23) Structures of carbazoles were confirmed by single-crystal X-ray data. CCDC numbers for **18c**, **18e**, and **18f** are 804433, 805205, and 805204, respectively (see the Supporting Information).

Scheme 4. Synthesis of Indolocarbazoles



of the indolocarbazoles **22a**−**e** were confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS analyses.

Having assembled an indolocarbazole framework, our results on triethylphosphite-mediated nitrene insertion in the presence of a Lewis acid are outlined in Scheme 4. Attempts to perform triethylphosphite-mediated nitrene insertion of 2-nitroarylcarbazole **20a** at 90−95 °C in the presence of $ZnBr_2$ led to a complex mixture. However, the interaction of carbazoles **18a**,**b** and **23a**,**b** with triethylphosphite in the presence of 1 equiv of $ZnBr_2$ at 90−95 °C for 12−15 h led to the formation of the respective indolocarbazoles **24a**−**d** in 85−91% yields. Next, the Wittig−Horner reaction of 2-indolylmethylphosphonate ester **15**/**25** with 2-azidobenzaldehyde[24] led to the formation of the corresponding 2-azidophenylvinylindole **26a**/**26b** as a yellow solid. Upon refluxing a solution of 2-azidophenylvinylindole **26a**/**26b** in *o*-DCB in the presence of 10% Pd−C, indolocarbazole **24c**/**24a** were formed through consecutive electrocyclization and nitrene insertion.

In conclusion, a facile synthesis of staurosporine aglycon and related indolocarbazole analogs was achieved through thermal electrocyclization and nitrene insertion reactions. For the first time, triethylphosphite-mediated nitrene insertion of 2-nitroarylcarbazole was performed at a moderate temperature using anhydrous $ZnBr_2$ as a catalyst. An alternative protocol for the synthesis of indolocarbazoles involving concurrent electrocyclization followed by nitrene insertion was also achieved.

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Supporting Information Available. Experimental procedure along with characterization data, ^{1}H and ^{13}C NMR spectra of all new compounds and HRMS spectra of **22a**−**e**, CIF files, and ORTEP diagrams. This material is available free of charge via the Internet at http://pubs.acs.org.

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