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Synthesis of Novel Carbocyclic Analogues of Indolocarbazole Natural Products

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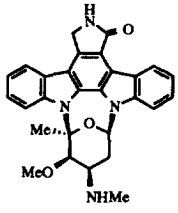
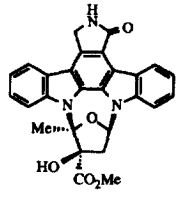
Abstract: The synthesis of some cyclopentane-bridged indolocarbazoles, representing carbocyclic analogues of the natural product K-252a, has been achieved by a concise, convergent route, and the ring expansion of one compound to a Staurosporine-type derivative demonstrated. The products are potent inhibitors of protein kinase C (PKC).

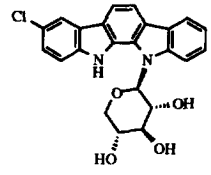
Since the initial isolation of staurosporine **1** in 1977, over 50 alkaloids of the indolocarbazole family have been characterised, including K252a **2**, tjippanazole F1 **3**, and rebeccamycin **4**.[1] Synthetic activity in this area has been spurred on by the finding of diverse biological activities associated with members of this class. Most notably, rebeccamycin is in late stage clinical evaluation as an anticancer agent whose mode of action involves topoisomerase I mediated DNA cleavage.[2] Staurosporine and K252a are also antitumour agents whose activity involves inhibition of protein kinase C (PKC).[3] Along with reports of immunosuppression,[4] reversal of drug resistance,[5] etc., such diverse and important potential applications promise much for the future of these compounds.



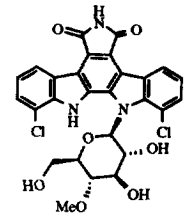
(1)



(2)



(3)



(4)

Although several of these targets have succumbed to total synthesis, perhaps most notably through the efforts of the groups of Wood and Danishefsky,[6,7] there remains a strong interest in the synthesis of this family of compounds and also in biologically active analogues. Our interest in asymmetric synthesis involving symmetry-breaking reactions (especially deprotonations) prompted us to explore the possibility of assembling a prochiral indolocarbazole of general structure **5**, which might then be transformed into various

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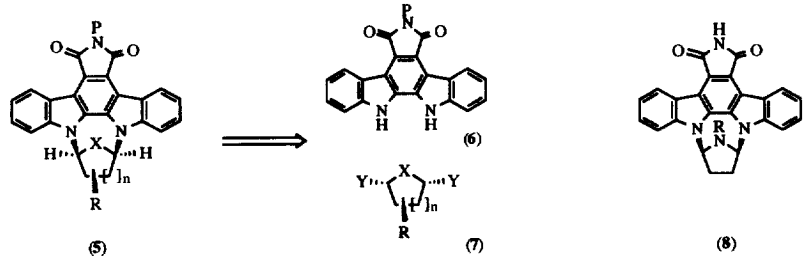
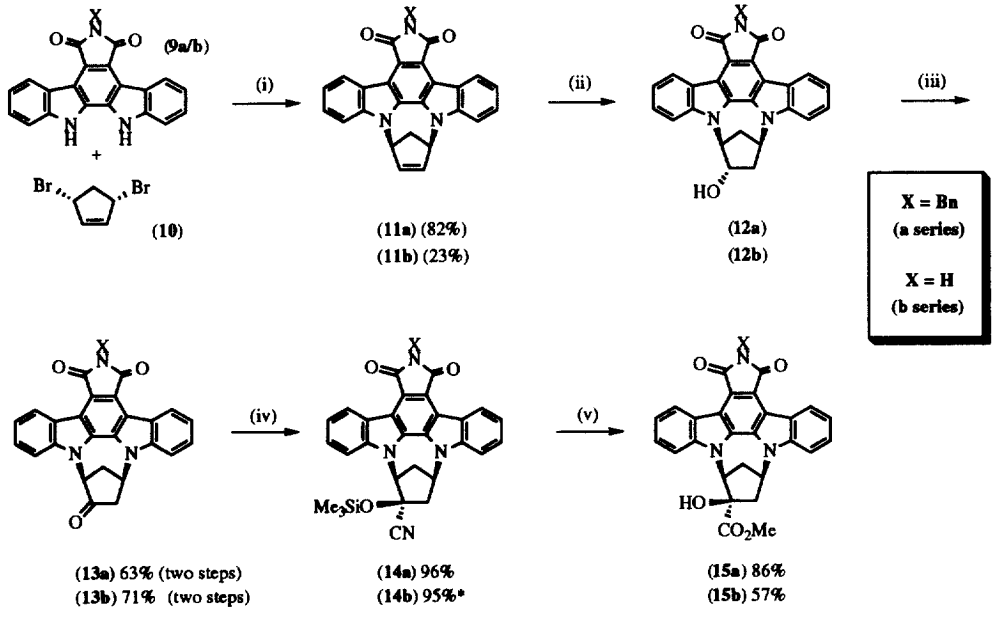
non-racemic derivatives. It was hoped that such key intermediates might be prepared very rapidly by reaction of a simple indolocarbazole, such as **6**, with a doubly electrophilic partner **7**. Since we encountered difficulties in preparing appropriate intermediates in the natural series (i.e. X = O), and nitrogen analogues (X = NR), including **8**, had been explored previously,[8] we focused on the corresponding carbocyclic derivatives having X = CH_2. Here we describe our preliminary work in this area, which has furnished a novel family of potent PKC inhibitors (see later).



(5) (6) (7) (8)

Following preliminary work, we were delighted to find that the condensation of indolocarbazole **9a**, bearing a benzyl group on the imide nitrogen,[9] with dibromide **10** (available in one step from cyclopentadiene) proceeded extremely well, to give **11a** in high yield, Scheme 1.[10]



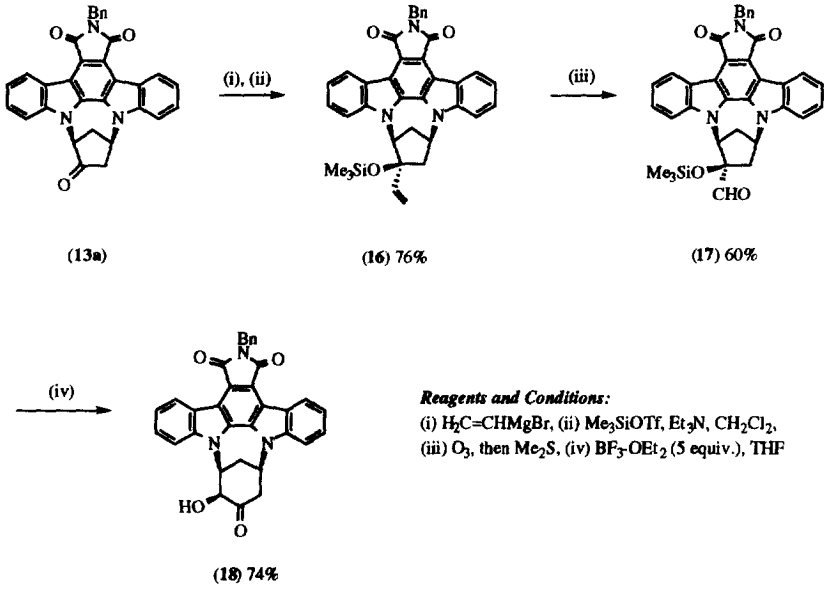
Reagents and Conditions:
(i) NaH, DMF, RT (ii) BH_3-THF (5equiv.); NaOH, H_2O_2 (15 equiv.), RT (iii) Dess-Martin periodinane (2 equiv.), CH_2Cl_2
(iv) Me_3SiCN, cat. KCN, cat. 18-crown-6 (v) THF, MeOH, conc. HCl, reflux
(* for **14b** X = $SiMe_3$ at this stage)

Scheme 1

Although we have not yet applied asymmetric methodology to this compound, we have transformed it into a series of more highly functionalised derivatives, as shown in Scheme 1. Hydroboration occurred with complete stereoselectivity to give **12a**, which could be oxidised to give ketone **13a**, which in turn gave protected cyanohydrin **14a** on exposure to Me_3SiCN under conditions described by Danishefsky.[11] Subsequent hydrolysis then gave the hydroxy-ester derivative **15a**, which can be regarded as a carbocyclic analogue of K252a.[12]

The presence of an unsubstituted N–H bond in a lactam or imide function is known to be a prerequisite for PKC inhibition by this type of compound, and so debenzylation of **15a** to give **15b** was regarded as a key objective. Unfortunately, despite extensive efforts, we were unable to effect this reaction,[13] and whilst several other nitrogen protecting groups present themselves as more labile candidates, we decided to try and apply the chemistry to intermediates with a free N–H. As can be seen from Scheme 1 this approach works reasonably well, apart from the initial coupling reaction to give **11b**, which at present proceeds in a much reduced yield.

We were also interested in access to carbocyclic analogues of staurosporine, but we were unable to find a direct route to such systems according to the disconnection shown above. Instead we focused on the type of ring expansion which has been described by Wood's group for the K252a type structures.[6] We were very pleased to find that this methodology can be transposed to the carbocyclic series, as shown in Scheme 2.



Scheme 2

Conversion of ketone **13a** into the protected α-hydroxyaldehyde **17** was straightforward, via the intermediate *O*-silylated vinyl Grignard adduct **16**. As in the previous work the reactions proceed with very high diastereoselectivity due to the facial bias created by the indolocarbazole bridge. To our delight, **17** was

transformed cleanly into a single ring-expanded product **18** on exposure to excess boron trifluoride etherate, along the lines described by Wood. We initially assigned the structure of this product as **18** primarily on the precedent set by Wood, but the structure shown is also supported by evidence from high field NMR studies.[14]

A number of the above compounds have been submitted to preliminary biological screening, with the N–H series of compounds showing nanomolar inhibition of PKC.[15] Not surprisingly, the compounds shown in Scheme 1 having an N-Bn group were effectively inactive in these screens.

Further exploration of this very facile entry to novel PKC inhibitors is underway, including asymmetric synthesis aspects and the design of more potent and selective enzyme inhibitors.

Acknowledgements

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10. Compound **11a** was obtained as yellow needles, m.p. 310–311 °C. Found: C, 79.75; H, 4.47; N, 9.14. $C_{32}H_{21}N_3O_2$ requires C, 80.14; H, 4.42; N, 8.77%.
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12. Compound **15a** was obtained as a yellow solid, m.p. 329–330 °C. *m/z* (FAB) Found: $M+H^+$, 466.1359. $C_{27}H_{20}N_3O_5$ requires $M+H$, 466.1403); ν_{max}/cm^{-1} ($CHCl_3$) 3437, 2930, 2867, 1754, 1720, 1572 and 1462.
13. Attempted hydrolysis under the conditions used by Faul (ref. 1b) was not successful.
14. The 400 MHz ^1H NMR spectrum (D_6-DMSO) shows a signal at δ 5.17 which is assigned as the new C*H*OH methine. ^1H COSY experiments show this signal to be coupled to both the CHO*H* (δ 5.35) and to the proximal C*H*N (δ 6.05) signal, but not to any other signals. This arrangement is not compatible with the alternative regiochemical outcome for the ring expansion (see reference 6).
15. For example compound **15b** inhibits PKC with an IC_{50} value of 53 nM (*cf.* IC_{50} of 9 nM for staurosporine). Inhibitor activity was determined using PKC obtained from Sigma Chemical Company (Poole UK) and employing an assay system available from Amersham International PLC (Little Chalfont, UK). More detailed screening results will be disclosed elsewhere.