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A Ring Expansion Approach to Pyranosylated Indolocarbazoles

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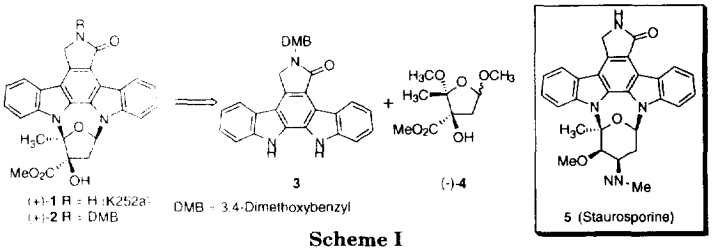
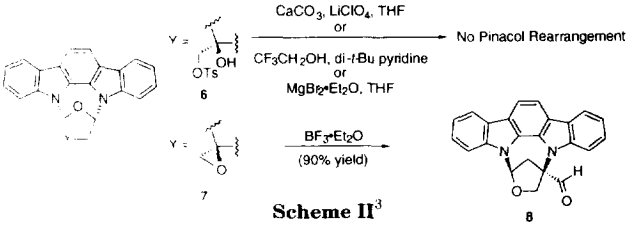
Abstract: A ring expansion protocol has been developed that allows efficient access to pyranosylated indolocarbazoles that are suited for further elaboration to staurosporine and its congeners.

Recently, we reported the first enantioselective synthesis of (+)- K252a (**1**), a naturally occurring and very potent protein kinase C inhibitor.[1] As part of this investigation we developed a highly stereoselective and moderately regioselective cycloglycosidation protocol that furnishes the protected natural product (**2**) from its constituent fragments, indolocarbazole (**3**) and furanose (**4**) (Scheme I). Herein we report results of a model investigation that demonstrate the feasibility of extending our cycloglycosidation approach, via ring expansion, to the synthesis of pyranosylated indolocarbazoles that are suited for conversion to staurosporine (**5**) and its many congeners.[2]



Scheme I

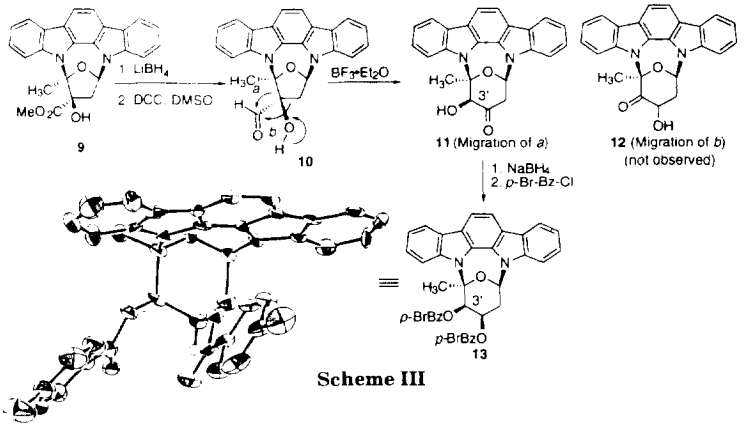
The potential of ring expanding furanosylated indolocarbazoles as a means of accessing the higher homologs was recognized several years ago by a group at Schering-Plough. However, the only productive result from attempts to ring expand **6** or **7** was the undesired skeletal rearrangement of **7** to **8** (Scheme II).[3] Our ability to access stereoselectively multigram quantities of **9**,[4] coupled with our recent successes using $BF_3 \cdot Et_2O$ to promote α-ketol rearrangements,[1] led us to explore an alternative strategy wherein aldehyde **10** would serve as a ring expansion substrate and precursor to either **11** (via migration of bond *a*) or **12** (via migration of bond *b*). From Hanessian's work in the spectinomycin system and our own experiences with α-ketol rearrangements, we expected the ring expansion to occur via the migration of bond *a*[5] through a transition state that would furnish the illustrated C(3') stereochemistry in the derived product (i.e., **11**).



Scheme II[3]

These hypotheses were tested by first preparing the ring expansion substrate **10**[6] via a two step sequence involving $LiBH_4$ reduction of **9** and then Moffatt oxidation of the derived diol (63% yield overall, Scheme III). Guided by our previous experiences with α-ketol rearrangements,[1] **10** was exposed to $BF_3 \cdot Et_2O$ and the reaction allowed to stir at room temperature for 3 h.

Standard work-up and isolation procedures provided a new compound (60% yield) that possessed proton NMR data consistent with that expected for **11**[6]. Given the precedented tendency for skeletal rearrangement (*vide supra*), we sought further confirmation of structure and thus subjected **11** to $NaBH_4$ reduction and derivatization with *p*-bromobenzoyl chloride.



Scheme III

Crystallization of the derived bisester (**13**[6]) from $CHCl_3$/MeOH furnished crystals suitable for single crystal X-ray analysis (see ORTEP in Scheme III). The latter, coupled with ^1H NMR data for **11**, unambiguously established that the ring expansion had proceeded with the anticipated regio- and stereochemistry. In addition, the crystal structure established that the diastereoface selectivity in the reduction of **11** was suited to a synthesis of staurosporine wherein reductive amination would give rise to the requisite methyl amine moiety.

In summary, an efficient three step procedure has been developed for expanding the K252a furanose to a pyranose suited for further elaboration to the staurosporine carbohydrate moiety. Currently, we are focusing our efforts on substrates possessing the fully functionalized aglycone. The results of these investigations will be reported in due course.

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Notes and References

1. Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J. *J. Am. Chem. Soc.* In Press.
2. For a review, see: Gribble, G.; Berthel, S. *Studies in Natural Products Chemistry, Vol. 12*; Elsevier Science Publishers: New York, 1993; pp 365-409 and references therein.
3. Shankar, B. B.; McCombie, S. W.; Kirkup, M. P.; Viet, A. Q.; Puar, M. S.; Ganguly, A. K. *Tetrahedron Lett.* **1993**, *34*, 5685.
4. Compound **9** is prepared by coupling furanose **4** with indolo[2,3-a]carbazole (camphorsulfonic acid (0.1 equiv)/ 1,2-dichloroethane at reflux, 48 h, 85% yield).
5. Hanessian, S.; Roy, R. *Tetrahedron Lett.* **1981**, *22*, 1005.
6. The structure assigned to each new compound is in accord with its infrared and high-field ^1H (500 MHz) and ^{13}C (125 MHz) NMR spectra, as well as appropriate parent ion identification by high-resolution mass spectrometry.

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