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The Stereoselective Ring Contraction of a Pyranosylated Indolocarbazole. A Biosynthetic Link Between K252a and Staurosporine?

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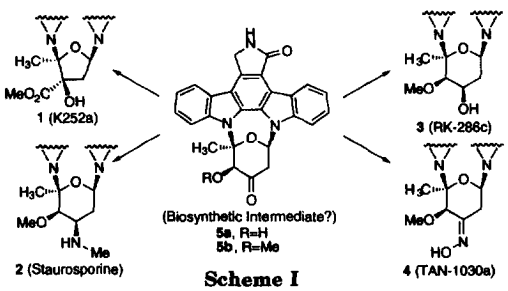
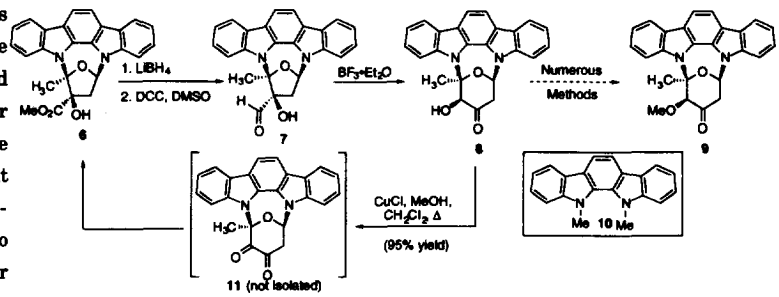
Abstract: Observation that oxidation and ring contractive benzilic acid rearrangement of **8** leads to the stereoselective production of the K252a carbohydrate moiety suggests a possible biosynthetic link between the furanosylated and pyranosylated indolocarbazoles. Copyright © 1996 Elsevier Science Ltd

Recent investigations in our laboratories have culminated in the first enantioselective synthesis of (+)-K252a (**1**) and the development of a ring expansion protocol for the stereoselective preparation of pyranosylated indolocarbazoles [e.g., staurosporine, (**2**)].[1,2] Our initial model investigations of the ring expansion (i.e., **6**→**7**→**8**, Scheme II) established that α-ketol rearrangement of aldehyde **7** proceeds in a highly regio- and stereoselective fashion to produce **8** as the only isolable product (60% yield).[3] Interestingly, attempts to further elaborate the model to methyl ether **9** resulted in the discovery of an oxidation/ring contractive benzilic acid rearrangement that stereoselectively produces the K252a carbohydrate moiety in a single step (i.e., **8**→ **6**). The facility and stereoselectivity of this rearrangement leads us to speculate that a similar α-hydroxy ketone may play a central role in indolocarbazole biosynthesis (e.g., **5a**→**1-4**, Scheme I). Indeed, a recent report by Fredenhagen describing the production of both K252a and staurosporine (i.e., furanosylated and pyranosylated indolocarbazoles) by a single microorganism, supports this notion of a common biosynthetic intermediate and has prompted us to herein report the results of our preliminary investigations leading to the discovery of the oxidation/ring contraction sequence.[4]



Scheme I

As part of a plan to produce the entire family of glycosylated indolocarbazoles from a common synthetic precursor, we began exploring the feasibility of converting the K252a carbohydrate to an α-methoxy ketone (e.g. **1**→**5b**, Scheme I) that contains the structural elements necessary for ready conversion to staurosporine (**2**), RK-286c (**3**),[5] and TAN-1030a (**4**).[6] While model investigations established the feasibility of a regio and stereoselective ring expansion,[2] subsequent attempts to alkylate the derived α-hydroxy ketone proved problematic. Of note is the propensity of **8** to undergo loss of the indolocarbazole nucleus as evidenced by isolation of **10** as the major product in many of our alkylation attempts. In an effort to avoid this deleterious event we turned our attention to methylation procedures that appeared to proceed under essentially neutral conditions. While these efforts failed to produce any of the desired α-methoxy ketone **9**, the conditions of Vowinkel (CuCl/DCC/MeOH)[7] were observed to cleanly convert **8** to **6**, the functionalized K252a sugar moiety.



Scheme II

Apparently these conditions induced either ring contractive α-ketol rearrangement and oxidation (i.e., **8**→**7**→**6**) or oxidation and ring contractive "benzilic" acid rearrangement (i.e., **8**→**11**→**6**). Since α-hydroxy aldehyde **7** failed to undergo conversion to **6** under the Vowinkel conditions, the latter of these two mechanistic possibilities appears most likely. In addition, subsequent investigations have revealed CuCl in MeOH without added DCC to be the optimal conditions for converting **8** to **6** (95% yield).[8]

In summary, an efficient single step procedure has been discovered for the stereoselective conversion of a pyranosylated indolocarbazole to the K252a carbohydrate moiety. Currently, we are focusing on the preparation of isotopically labeled α-hydroxy ketone **5a** in an effort directed toward establishing the centrality of this compound in indolocarbazole biosynthesis.

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Notes and References

1. Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1995**, *117*, 10413.

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. Stoltz, B. M.; Wood, J. L. *Tetrahedron Lett.* **1995**, *36*, 8543. This ring expansion protocol has been successfully extended to systems containing the fully elaborated aglycon (Stoltz, B. M.; Goodman, S. N.; Wood, J. L. unpublished results).

4. Fredenhagen, A.; Peter, H. H. *Tetrahedron* **1996**, *52*, 1235. In addition, these authors report a ring contractive Beckmann rearrangement that stereoselectively produces an amino analog of K252a.

5. Takahashi, H.; Osada, H.; Uramoto, M.; Isono, K. *J. Antibiotics* **1990**, *43*, 168.

6. (a) Tanida, S.; Takizawa, M.; Takahashi, T.; Tsubotani, S.; Harada, S. *J. Antibiotics* **1989**, *42*, 1619. (b) Tsubotani, S.; Tanida, S.; Harada, S. *Tetrahedron* **1991**, *47*, 3565. (c) Cai, Y.; Fredenhagen, A.; Hug, P.; Peter, H. H. *J. Antibiotics* **1995**, *48*, 143.

7. Vowinkel, E. *Chem. Ber.* **1966**, *99*, 1479. Although this method was reported for the preparation of aryl ethers and failure was anticipated, the thought of what appeared a trivial alkylation thwarting the elegant ring expansion approach led us to explore the remotest of possibilities.

8. In a typical experiment, Copper (I) chloride (700 mg, 7.1 mmol) was added to a solution of **8** (100 mg, 0.26 mmol) in 1:1 MeOH/CH_2Cl_2 (14 mL), and the mixture warmed to reflux for 6 h. Solvent was removed *in vacuo* and the resulting residue subjected to silica gel chromatography (2:1, hexane:ethyl acetate) to afford **6** (102 mg, 0.25 mmol, 95%) as a colorless solid (mp 235-239 °C).

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