Pergamon

Tetrahedron Letters, Vol. 37, No. 41, pp. 7335-7338, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01639-5

The Synthesis of Desamido Analogs of Staurosporine, RK-286c, and TAN-1030a.

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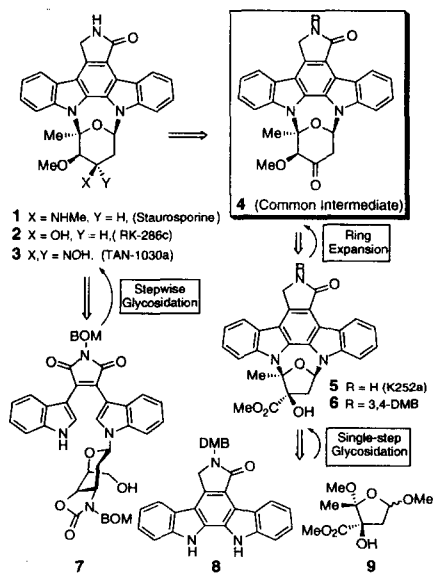
Abstract. Ring expansion of dimethyl acetal **16** proceeds stereo- and regioselectively to **15** which is in turn converted to the desamido analogs of staurosporine, RK-286c, and TAN-1030a.

The nanomolar kinase inhibitory activity of staurosporine (**1**) and K252a (**5**) has prompted a continuing effort to isolate and/or synthesize novel pyranosylated and furanosylated indolocarbazoles.[1,2,3,4] Recently, we reported the enantioselective synthesis of (+)-K252a via an approach involving the late-stage coupling of aglycon **8** and furanose **9** (Scheme 1). Although this approach proved efficient for the preparation of furanosylated indolocarbazoles (e.g., **5**), attempts to access the corresponding pyranosylated structures (e.g., **1-3**) via a similar single-step glycosidation strategy have met with limited success.[5] In fact, the stepwise procedures developed in Danishefsky's landmark synthesis of staurosporine have stood as the only successful means of accessing the fully functionalized pyranosylated indolocarbazoles (Scheme 1, e.g. **7** → **1**).[2] Herein we report results from a model investigation that demonstrate the feasibility of an alternative approach wherein a ring expansion reaction is utilized to access a single pyranosylated intermediate that can be readily transformed into desamido analogs of staurosporine, RK-

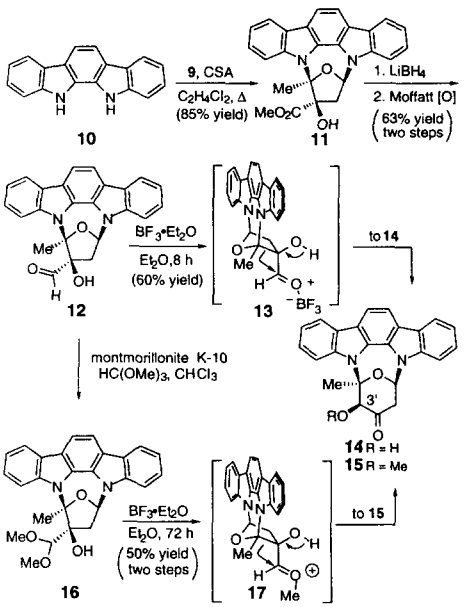
Scheme 1



286c, and TAN-1030a (cf., **1**→**3** in Scheme 1 and **23**, **19**, **18** in Scheme 3, respectively).[6]

At the outset of our investigations we had yet to develop a protocol for the large-scale separation of **6** from its regioisomer and thus to simplify our study we turned to a substrate possessing a symmetrical aglycon (i.e., **11**).[7] This model system was readily prepared by coupling indolo[2,3-a]carbazole (**10**) with **9** in a manner similar to that employed in our synthesis of K252a. This coupling again proved highly stereoselective and produced **11** as the only isolable product in 85% yield.

Scheme 2

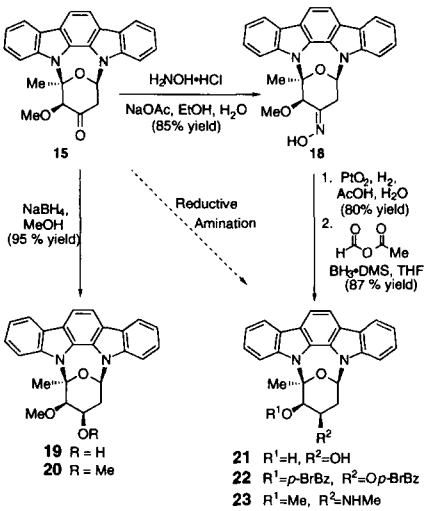


Turning to the ring expansion, we soon discovered that transformation of **11** into aldehyde **12** followed by treatment with $BF_3 \bullet Et_2O$ results in a regio- and stereoselective rearrangement to the pyranosylated indolocarbazole **14**.[8] At this stage all that remained for the preparation of **15** was what appeared to be a trivial alkylation of the C(3') hydroxyl. Much to our surprise, ketone **14** proved quite resistant to methylation under numerous alkylation conditions. In addition, attempts to incorporate directly the methyl substituent by promoting the rearrangement with a source of Me^+ (e.g., Meerwein's reagent,[9] TMSOTf/TMSOMe,[10] and MeOTf) also failed. Eventually, these difficulties led to the development of an alternative strategy that targeted dimethyl acetal **16** as the substrate for a ring expansion that was envisioned to proceed via oxocarbenium ion **17** (Scheme 2). Although **16** was readily produced under a variety of conditions, its instability to chromatographic purification required our employing montmorillonite clay K-10 to promote acetal formation.[11] Removal of the clay via filtration, solvent exchange with Et_2O, and subsequent treatment with $BF_3 \bullet Et_2O$ resulted in the slow (72 h, 25 °C) conversion of **16** to **15**[12] (50% yield). Chemical correlation of **15** to **20**[12] (Scheme 3) unambiguously established structure and confirmed that the sense of asymmetric induction was analogous to that observed in the rearrangement of **12** (cf. **13** and **17** in Scheme 2).[13,14]

Having rapidly assembled α-methoxy ketone **15**, we investigated its conversion to the desamido pyranosylated indolocarbazoles. To this end, the analogs of RK-286c (**19**[12]) and TAN-1030a (**18**[12]) were readily prepared from **15** under standard conditions using $NaBH_4$ and $H_2NOH \bullet HCl$, respectively (Scheme 3). Attempts to access desamido staurosporine (**23**) via the direct reductive amination of **15** failed. However, an alternative two-step procedure involving stereoselective Pt-catalyzed hydrogenation of **18**,[15] followed by monomethylation (HCO_2COCH_3, $BH_3 \bullet SMe_2$) readily furnished **23**[12] in excellent overall yield.[16]

In summary, Lewis acid-promoted ring expansion of dimethyl acetal **16** has been found to proceed regio- and stereoselectively to produce an α-methoxy ketone (**15**) that can be readily transformed into desamido analogs of RK-286c, TAN-1030a, and staurosporine. Efforts to extend this model to the natural products will be reported in due course.

Scheme 3



Acknowledgment. We are pleased to acknowledge the support of this investigation by Yale University, Bayer Corporation, and the Elsa U. Pardee Foundation. The Camille and Henry Dreyfus Foundation (NF-93-0) and the American Cancer Society (JFRA-523) provided additional support through their Junior Faculty Awards Programs. BMS thanks W.R. Grace and Bayer for graduate student fellowships. In addition, we acknowledge Susan DeGala and Dr. Ben Bangerter for their assistance in securing the X-Ray crystal structure and NMR spectra respectively. Finally, we thank Dr. Steve Coats for helpful discussions.

Notes and References

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2. For the first total synthesis of staurosporine, see: Link, J. T.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 552.

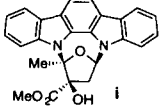
3. Recently a review on the biological activity of staurosporine appeared, see: Omura, S.; Sasaki, Y.; Iwai, Y.; Takeshima, H. *J. Antibiotics* **1995**, *48*, 535.

4. For the enantioselective total synthesis of K252a, see: Wood, J.L.; Stoltz, B.M.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1995**, *117*, 10413.

5. For efforts at cyclo-pyranosylation, see: Shankar, B.B.; McCombie, S.W. *Bioorganic. Med. Chem. Lett.* **1994**, *4*, 3005.

6. For a previous attempt at a ring expansion approach, see: Shankar, B.B.; McCombie, S.W.; Kirkup, M.P.; Viet, A.Q.; Puar, M.S.; Ganguly, A.K. *Tetrahedron Lett.* **1993**, *34*, 5685.

7 Cycloglycosidative coupling of **8** and **9** produces a 2:1 mixture of **6** and **i**, respectively, in 80% yield.[4] Recent efforts have revealed that **6** and **i** can be separated via normal-phase flash column chromatography using CH_2Cl_2:EtOAc:MeOH (190:10:1) as eluant.



i

8. For details of the ring expansion of **12** and proof of structure via X-ray analysis, see: Stoltz, B.M.; Wood, J.L. *Tetrahedron Lett.* **1995**, *36*, 8543.

9 Meerwein, H. *Org. Syn. Collective Vol. V*, 1096.

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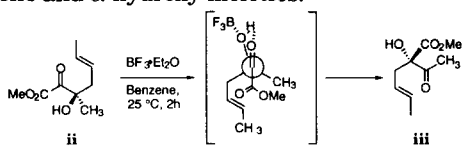
12. The structure assigned to each new compound is in accord with its infrared and high field ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra, as well as appropriate parent ion identification by high-resolution mass spectrometry.

13. Conversion of **15** to **20** was effected with $NaBH_4$ followed by methylation (MeI/NaOH in DMSO). Structure proof followed from the independent synthesis of **20** from **21** and single crystal X-ray analysis of the bis-*p*-bromobenzoate corresponding to latter (i.e., **22**).

14 It is interesting to note that the stereochemical outcome in the α-ketol rearrangement of **ii**, an intermediate in our K252a synthesis, is also consistent with a syn-periplanar relationship of the ketone and α-hydroxy moieties.[4]



ii iii

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(*Received in USA* 8 *August* 1996; *accepted* 16 *August* 1996)