Total Synthesis of (+)-RK-286c, (+)-MLR-52, (+)-Staurosporine, and (+)-K252a

John L. Wood,*,† Brian M. Stoltz, and Steven N. Goodman

Sterling Chemistry Laboratory
Department of Chemistry, Yale University
New Haven, Connecticut 06520-8107

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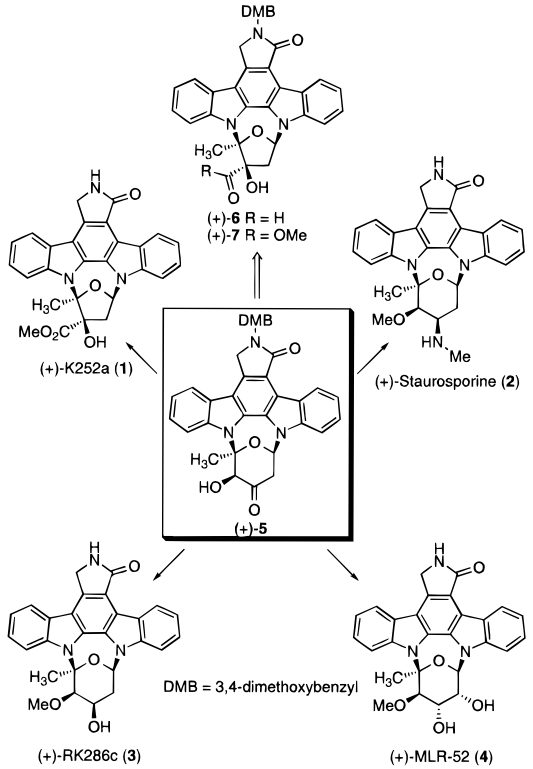
The observation that nanomolar concentrations of K252a (**1**) and staurosporine (**2**) inhibit a variety of protein kinases continues to spawn intense efforts in the isolation and synthesis of novel indolocarbazoles.[1] Our interest in these natural products has evolved over the past 10 months from the first total synthesis of (+)-K252a[2,3] to a general synthetic approach to staurosporine[4,5] and its congeners [e.g., RK-286c (**3**)[6] and MLR-52 (**4**)[7]].[8] These latest developments were inspired after considering the structural similarities of **1**−**4** and recognizing that a logical common intermediate (**5**) might be accessible via ring expansion of **6**, a derivative of the penultimate intermediate in our synthesis of (+)-**1** (i.e., (+)-**7**, Scheme 1). Herein we report the successful application of this ring expansion strategy to the preparation of (+)-**5** and its use in the total synthesis of (+)-**1**−**4**.

The initial challenge of preparing the quantities of (+)-**7** needed to initiate the synthesis was met by advancing glycine methyl ester through the 11-step sequence developed in our K252a synthesis.[2] With multigram quantities of material available, we set the stage for ring expansion by converting (+)-**7** to (+)-**6**[9] via a two-step sequence that involves $LiBH_4$ reduction and Moffatt oxidation[10] (63% yield overall, Scheme 2). Given that the proposed ring expansion of **6** to **5** could proceed to a mixture of regio- and stereoisomeric products, we were delighted to discover that treatment of (+)-**6** with BF_3·OEt_2 in Et_2O (2.2 equiv, 25−30 °C, 24 h) produces *a single product, (+)-***5**[9]*, in 85% yield!* The regio- and stereochemical outcomes of this reaction, which were confirmed by spectral comparison to a closely related model and the conversion of (+)-**5** to (+)-**1**−**4** (*vide infra*),[8a] are consistent with migration of the C−C bond engaged in the quaternary aminal linkage to the *si*-face of the aldehyde; thus suggesting the syn-periplanar alignment of the carbonyl and hydroxyl moieties illustrated in structure **8** (Scheme 2).

Scheme 1



In an effort to generate a more versatile intermediate, we initiated what proved to be a futile but interesting effort to convert (+)-**5** into the corresponding methyl ether **9**. Although unproductive in terms of preparing **9**, these methylation attempts led to the unexpected observation that exposure of (+)-**5** to CuCl in MeOH results in *a highly stereoselective oxidation/ring contraction sequence that produces (+)-***7** *in 95% yield!*[11,12]

Turning from our inadvertent discovery of a potentially biomimetic synthesis of (+)-K252a, to alternatives for the troublesome methylation, we recognized that reduction of **5** would likely proceed with a high degree of stereoselectivity to produce a diol (i.e., **10**) wherein the differing steric environments of the equatorial (C3′) and axial (C4′) hydroxyl groups might allow selective methylation. In practice, ketone (+)-**5** was indeed found to undergo selective conversion to (+)-**11**[9] upon sequential treatment with $NaBH_4$ and NaH/MeI.[13]

Having installed all of the functional groups common to (+)-**2**−**4**, our approach diverged into the synthesis of (+)-RK286c and (+)-MLR-52. The former was completed via deprotection of (+)-**11** (TFA/anisole) while the latter required a three-step sequence that was initiated by exposing (+)-**11** to the Martin Sulfurane.[14] Oxidation of the derived olefin with OsO_4 followed by deprotection of the resultant diol [(+)-**12**[9]] produced (+)-**4**.

The elusive nature of α-methoxy ketone **9** guided our approach to staurosporine along a route wherein the 4′ nitrogen is introduced via conversion of (+)-**5** to the corresponding oxime (−)-**13**[9,15] (H_2NOH·HCl, NaOAc, Scheme 3). Crucial for the

† 1996 Eli Lilly Grantee in Organic Chemistry.

(1) For reviews on the synthesis and biological activity of indolocarbazoles, see: (a) Bergman, J. *Stud. Nat. Prod. Chem., Part A* **1988**, *1*, 3. (b) Gribble, G. W.; Berthel, S. J. *Stud. Nat. Prod. Chem.* **1993**, *12*, 365. (c) Steglich, W. *Fortschr. Chem. Org. Naturst.* **1987**, *51*, 216. (d) Omura, S.; Sasaki, Y.; Iwai, Y.; Takeshima, H. *J. Antibiot.* **1995**, *48*, 535.

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

(3) For the isolation of (+)-K252a, see: Kase, H.; Iwahashi, K; Matsuda, Y. *J. Antibiot.* **1986**, *39*, 1059.

(4) For an excellent full account of the landmark Danishefsky−Link synthesis of staurosporine, see: Link, J. T.; Raghavan, S.; Gallant, M.; Danishefsky, S. J.; Chou, T. C.; Ballas, L. M. *J. Am. Chem. Soc.* **1996**, *118*, 2825.

(5) For the isolation of (+)-staurosporine, see: Omura, S.; Iwai, Y.; Hirano, A.; Nakagawa, A.; Awaya, J.; Tsuchiya, H.; Takahashi, Y.; Masuma, R. *J. Antibiot.* **1977**, *30*, 275.

(6) Takahashi, H.; Osada, H.; Uramoto, M.; Isono, K. *J. Antibiot.* **1990**, *43*, 168.

(7) McAlpine, J. B.; Karwowski, J. P.; Jackson, M.; Mullally, M. M.; Hochlowski, J. E.; Premachandran, U.; Burres, N. S. *J. Antibiot.* **1994**, *47*, 281.

(8) Our initial model system work in developing this approach has been disclosed in part, see: (a) Stoltz, B. M.; Wood, J. L. *Tetrahedron Lett.* **1995**, *36*, 8543. (b) Stoltz, B. M.; Wood, J. L. *Tetrahedron Lett.* **1996**, *37*, 3929.

(9) 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. Optical rotations were determined using methanol solutions with the following exceptions: **3** (EtOAc), **5** (DMSO), **13** and **14** (CH_2Cl_2), and **15** ($CHCl_3$).

(10) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5670.

(11) Model investigations of this reaction suggest that oxidation precedes a ring contractive "benzylic acid" rearrangement.[8b]

(12) This constitutes an alternative synthesis of (+)-K252a, hence its inclusion in the title.[2]

(13) Although Danishefsky reports that exposure of similar substrates to strong bases such as NaH results in benzylic oxidation to the corresponding maleimide, no such products were observed in the alkylation of (+)-**10**.[4]

(14) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003.

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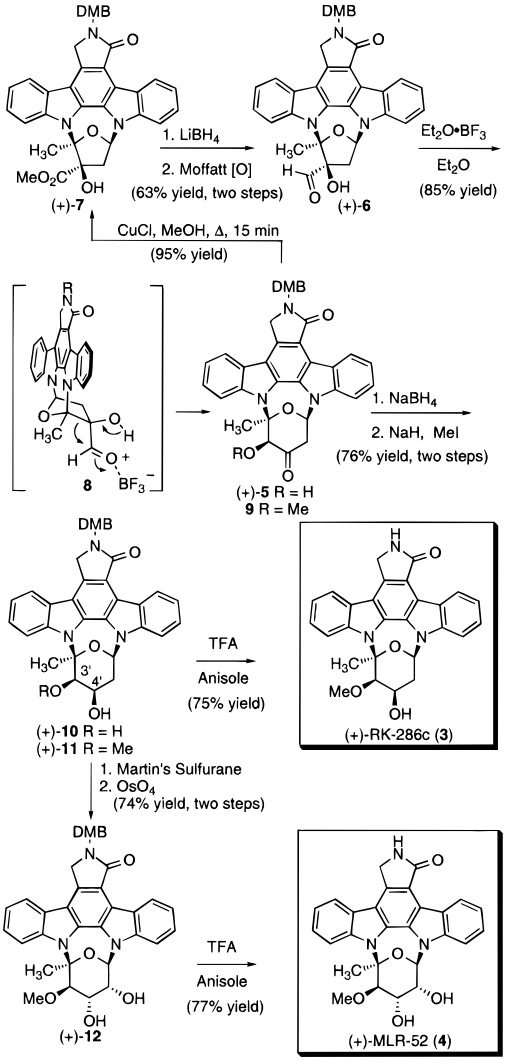
Scheme 2



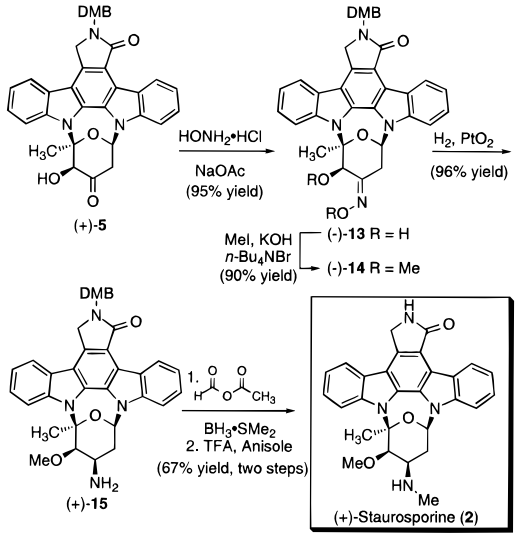
success of this approach is the fact that (−)-**13**, unlike ketone (+)-**5**, readily undergoes alkylation to the C3′ methyl ether (MeI, KOH, *n*-Bu_4NBr). Stereoselective reduction of the derived methoxy oxime (−)-**14**[9,16] (H_2, PtO_2) to the corresponding primary amine ((+)-**15**)[9] followed by monomethylation (HCO_2-$COCH_3$, BH_3·DMS)[17] and deprotection (TFA) produced (+)-staurosporine.[18]

In summary, our efforts to devise an efficient synthesis of the pyranosylated indolocarbazoles via a common intermediate

(15) This approach was adopted following failed attempts to oxidize (+)-**11** to the elusive **9**.

(16) Tanida, S.; Takizawa, M.; Takahashi, T.; Tsubotani, S.; Harada, S. *J. Antibiot.* **1989**, *42*, 1619.

Scheme 3



[i.e., (+)-**5**] have been successful in delivering (+)-**2** (19 steps), (+)-**3** (17 steps), and (+)-**4** (19 steps).[19] In addition, these investigations have revealed both ring expansion and contraction reactivity that may play a central role in the biogenesis of both the furanosylated and pyranosylated members of this important class of natural products.[20] Studies directed toward elucidating the relevance of these biosynthetic implications are underway and will be reported in due course.

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Supporting Information Available: Experimental procedures and compound characterization data for compounds **2**−**6**, and **10**−**15**, along with ^{1}H NMR (500 MHz) spectral comparison of our synthetic (+)-**2** with that prepared in the Danishefsky laboratories (17 pages). See any current masthead page for ordering and Internet access instructions.

JA9626143

(17) Krishnamurthy, S. *Tetrahedron Lett.* **1982**, *23*, 3315.

(18) Spectroscopic data for our synthetic staurosporine were identical to a sample kindly provided by Professor Danishefsky.

(19) The indicated number of steps refer to the total number of transformations required to convert *o*-toluidine, glycine ethyl ester, and methyl-2-diazo-3-oxobutyrate to the specified product.

(20) This notion is supported by the concomitant isolation of **2** with RK-286c[6] and MLR-52,[7] and the recent report that *Streptomyces longisporoflavus* R-19 produces both staurosporine and K252a, see: Fredenhagen, A.; Peter, H. H. *Tetrahedron* **1996**, *52*, 1235.