Total Synthesis of (+)- and (−)-K252a

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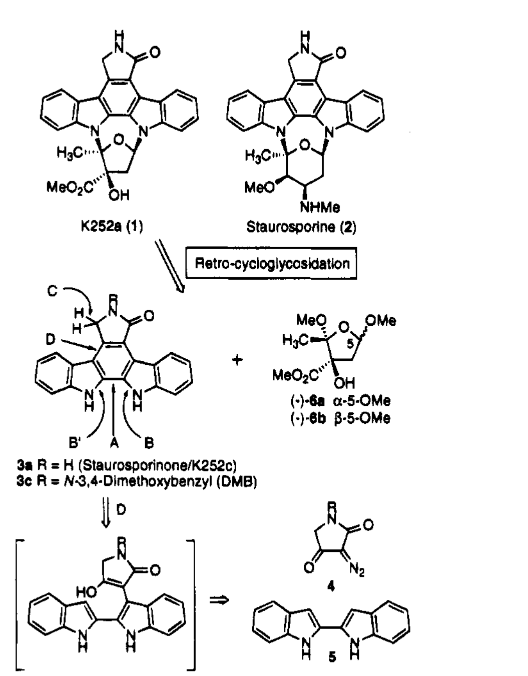
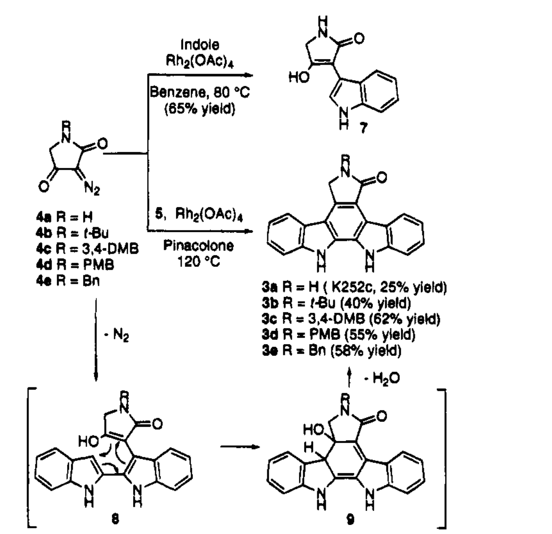
The isolation and structural characterization of architecturally novel and biologically important natural products is often followed by a flurry of synthetic activity. The indolo[2,3-*a*]-carbazoles K252a (**1**) and staurosporine (**2**)[1] have been no exception, and several papers describing possible synthetic routes and derivatizations of the natural material have appeared.[2,3] In addition, four approaches to the naturally occurring aglycon K252c (**3a**, also known as staurosporinone) have been developed.[4−6] Classified by the last covalent bond(s) formed, these approaches include cycloaromatization (A),[4a] double nitrene C−H insertion (B,B′),[4b] nitrene C−H insertion (B′),[4c,d] and maleimide reduction (C) (see Scheme 1).[4e−g] In this communication we report the development of a unique approach to **3** wherein coupling of diazolactam **4**[7] and 2,2′-biindole (**5**)[8] initiates cycloaromatization to form bond D.[9] Application of this strategy allows efficient access to both the parent aglycon (**3a**) and the selectively protected derivative (**3c**) employed in the total synthesis reported herein. Overall, preparation of the enantioenriched furanose **6** and aglycon unit **3c** and their conversion to **1** require only 11 synthetic operations with a longest linear sequence of seven steps.

The feasibility of our carbenoid approach to **3** was initially assessed by reaction of **4a** (1.0 equiv) with indole (3.0 equiv) in the presence of catalytic $Rh_2(OAc)_4$ (0.01 equiv, Scheme 2). After only 12 h, TLC analysis indicated complete consumption of **4**, and standard workup and isolation procedures furnished **7**[10] in 65% yield. Similar conditions proved ineffective for the coupling of **4a** with **5**, and it was only after considerable

Scheme 1



Scheme 2



experimentation that a procedure was developed which provided satisfactory yields of **3**. The use of degassed pinacolone proved critical as this solvent was found to be both compatible with the carbenoid chemistry and capable of solvating the biindole substrate. Under these conditions the coupling of **4a** and **5** proceeded directly to **3a** in 25% yield. Presumed intermediates **8** and **9** were not apparent by TLC or NMR analysis of the crude reaction mixture. In an attempt to complete the synthesis, the cycloglycosidation of **6** with **3a** revealed a tendency of the latter to alkylate at the amide nitrogen; thus, we turned to the selectively protected aglycons **3b−e**.[10] Preparation of the corresponding diazolactams **4b−e**[10,11] followed by reaction with **5** in the presence of $Rh_2(OAc)_4$ (0.1 equiv) established that several protecting groups can withstand the carbenoid conditions and that the best yields (50−62%) are obtained within the benzyl

(1) Illustrations in Schemes 1 and 4 reflect the absolute stereochemistry of natural K252a as determined by this investigation. All rotations on indolocarbazole-containing compounds were obtained on methanol solutions.

(2) Several relevant reviews have appeared; 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.

(3) Recently, Danishefsky reported the first total synthesis of staurosporine, see: Link, J. T.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 552.

(4) For approaches that deliver an intact and fully deprotected aglycon (i.e., **3a**), see: (a) Burkhard, S.; Winterfeldt, E. *Heterocycles* **1983**, *20*, 469. (b) Hughes, I.; Nolan, W. P.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2475. (c) Moody, C. J.; Rahimtoola, K. F. *J. Chem. Soc., Chem. Commun.* **1990**, 1667. (d) Moody, C. J.; Rahimtoola, K. F.; Porter, B.; Ross, B. C. *J. Org. Chem.* **1992**, *57*, 2105. (e) Toullec, D.; Pianetti, P.; Coste, H.; Bellevergue, P.; Grand-Perret, T.; Ajakane, M.; Baudet, V.; Boissin, P.; Boursier, E.; Loriolle, F.; Duhamel, L.; Charon, D.; Kirilovxky, J. *J. Biol. Chem.* **1991**, *266*, 15771. (f) Harris, W.; Hill, C. H.; Keech, E.; Malsher, P. *Tetrahedron Lett.* **1993**, *34*, 8361. (g) Xie, G.; Lown, J. W. *Tetrahedron Lett.* **1994**, *35*, 5555.

(5) For an approach to **3a** that involves the degradation of rebeccamycin, see: (a) Fabre, S.; Prudhomme, M.; Rapp, M. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 449. (b) Fabre, S.; Prudhomme, M.; Rapp, M. *Bioorg. Med. Chem.* **1993**, *1*, 193. (c) Fabre, S. Prudhomme, M.; Sancelme, M.; Rapp, M. *Bioorg. Med. Chem.* **1994**, *2*, 73.

(6) For approaches that deliver an intact and protected aglycon but do not demonstrate the feasibility of deprotection, see the following: (a) *N*-Protected indole: Magnus, P. D.; Sear, N. L. *Tetrahedron* **1984**, *40*, 2795. Brüning, J.; Hache, T.; Winterfeldt, E. *Synthesis* **1994**, 25. (b) *N*-Protected indole and amide: Link, J. T.; Danishefsky, S. J. *Tetrahedron Lett.* **1994**, *35*, 9135. Winterfeldt, E. In *Heterocycles in Bioorganic Chemistry*; Bergman, J., Ed.; The Royal Society of Chemistry: 1991. (c) *N*-Protected amide: Hughes, I.; Raphael, R. A. *Tetrahedron Lett.* **1983**, *24*, 1441. Joyce, R. P.; Gainor, J. A.; Weinreb, S. M. *J. Org. Chem.* **1987**, *52*, 1177.

(7) Lowe, G.; Yeung, H. W. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2907.

(8) Access to 2,2′-biindole is gained from *o*-toluidine in two steps and 80% overall yield; see: Bergman, J.; Koch, E.; Pelcman, B. *Tetrahedron* **1995**, *51*, 5631.

(9) For a leading reference to the addition of cyclic rhodium carbenoids to indole, see: Pirrung, M. C.; Zhang, J.; Lackey, K.; Sternbach, D. D.; Brown, F. *J. Org. Chem.* **1995**, *60*, 2112.

(10) The structure assigned to each new compound is in accord with its infrared and high-field ^1H (500 MHz) and ^{13}C (125 or 62.5 MHz) NMR spectra, as well as appropriate parent ion identification by high-resolution mass spectrometry.

(11) Protection of **4a** under standard conditions provided **4c−e**. Alternatively, we have demonstrated that **4b−e** can be prepared from the corresponding *N*-protected glycine ethyl ester.[7]

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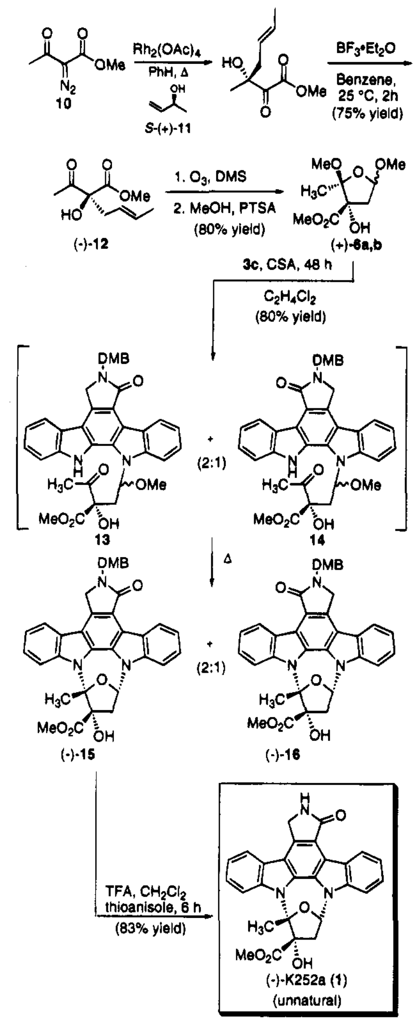
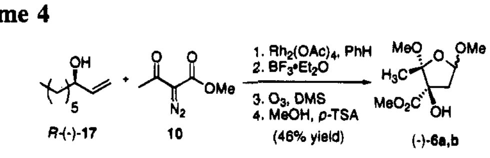
Scheme 3



class (e.g., **4c**–**e** → **3c**–**e**, Scheme 2). To provide the most flexibility in the eventual deprotection, we chose to proceed with the 3,4-dimethoxybenzyl protected aglycon **3c**.

Having gained efficient access to **3c**, we turned our attention to the preparation of the furanose component (**6**). To this end, a novel tandem rearrangement protocol was developed that combines methyl 2-diazo-3-oxobutyrate (**10**) and (*S*)-(+)-1-buten-3-ol (**11**) to furnish (−)-**12**[10] in a single pot (92% ee, 75% yield)[12] (Scheme 3). Reductive ozonolysis of (−)-**12** followed by acid-promoted cyclization in methanol produced (+)-**6a**[10] and (+)-**6b**[10] in good yield.[13] With both (+)-**6** and **3c** in hand we began exploring the cycloglycosidative coupling. Of several conditions reported by McCombie[14] for related transformations we found camphorsulfonic acid in 1,2-dichloroethane to be the catalyst and solvent of choice. In the event, **3c** and (+)-**6** combined rapidly to form two regioisomeric pairs of open chain monoamino acetal diastereomers (**13** and **14**).[15,16] Prolonged heating of the quaternary mixture induced cycloglycosidation to *only two* of the four possible diastereomers.[17] Preliminary assignment of structure was based on ^{1}H NMR analysis, which indicated that the reaction had produced the regioisomeric products (−)-**15** (55% yield) and (−)-**16** (25% yield).[18] The observed formation of (−)-**1** upon deprotection of (−)-**15** under standard conditions (TFA/CH_2Cl_2/thioanisole) established the cycloglycosidation as both regio- and stereoselective for the natural configuration.[19] Comparison of synthetic (−)-**1**[10] to material derived from natural sources established its identity as the unnatural enantiomer of K252a.

Scheme 4



Total synthesis of the natural enantiomer (i.e., (+)-**1**) was effected in an analogous fashion using **3c** and (−)-**6**[10,13] as coupling partners (Scheme 4). The latter compound was prepared via our tandem [3,3]/[1,2] rearrangement protocol using (*R*)-(−)-1-nonen-3-ol (**17**)[20] as the source of asymmetry.

In summary, application of a novel carbenoid-mediated synthesis of K252c coupled with a highly selective tandem [3,3]/[1,2] rearrangement protocol provides efficient access to both (+)- and (−)-K252a. Investigations into extending our synthetic approach to staurosporine and further understanding the diastereoselective coupling of **3** and **6** are in progress.

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Supporting Information Available: Complete spectral data for compounds **3b**–**d**, **4b**–**e**, **6**, **7**, **12**, **15**, **16**, experimental details for the preparation of **3c**, **12**, **15**, and **16**, and ^{1}H NMR (500 MHz) spectral comparison of natural and synthetic (+)-**1** (6 Pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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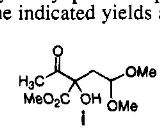
(12) (a) The absolute stereochemistry of (−)-**12** was determined to be as illustrated via chemical correlation studies. (b) These studies as well as further details regarding the tandem rearrangement protocol will be reported elsewhere.

(13) The relative stereochemical configurations of **6a** and **6b** were determined via single-crystal X-ray analyses of the corresponding acetates.[12b] The preparation of (+)- and (−)-**6** was accompanied by the formation of methyl ketone **i**, which was omitted from the schemes for clarity. Spectral data obtained on an analytically pure sample of **i** are included in the supporting information. The indicated yields are for the mixture of **6a**, **6b**, and **i**.

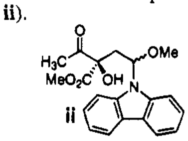


i

(14) McCombie, S. W.; Bishop, R. W.; Carr, D.; Dobek, E.; Kirkup, M. P.; Kirschmeier, P.; Lin, S.-I.; Petrin, J.; Rosinski, K.; Shankar, B. B.; Wilson, O. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1537.

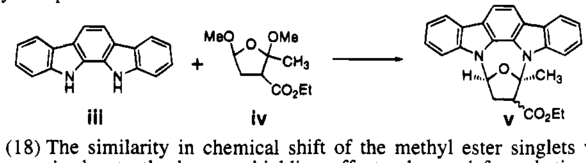
(15) In typical reactions a mixture of **6a**, **6b**, and **i** was employed.

(16) This observation was consistent with a model investigation wherein reaction of **6** with carbazole was found to produce a diastereomeric mixture of methyl ketones (i.e., **ii**).



ii

(17) Although it is tempting to invoke transannular participation of the C(3) carboxymethyl substituent as the stereocontrolling element in the coupling of **3** and **6**, our observations taken with those of a group at Schering-Plough (i.e., **iii** + **iv** → **v**) indicate that the C(3) hydroxyl is a key component.[14]



(18) The similarity in chemical shift of the methyl ester singlets was diagnostic due to the known shielding effects observed for substituents oriented syn to the aglycon unit.[14]

(19) The observed regiochemistry is in accord with the known differential reactivity of the indolyl nitrogens; see: Kleinschroth, J.; Hartenstein, J.; Rudolph, C.; Schächtele, C. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1959.

(20) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.