The First Synthesis of a Fully Functionalized Core Structure of Staurosporine: Sequential Indolyl Glycosidation by Endo and Exo Glycals

J. T. Link, Michel Gallant, and Samuel J. Danishefsky*

Department of Chemistry
Yale University
New Haven, Connecticut 06511-8118

Susan Huber

Center for Chemical Instrumentation
Yale University
New Haven, Connecticut 06511-8118

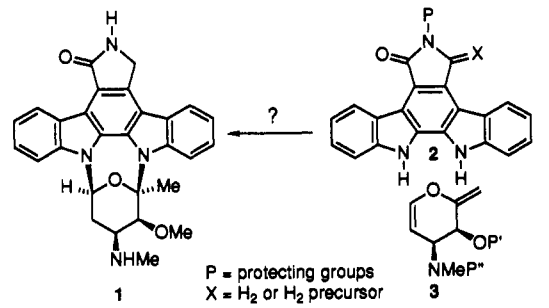
Received January 27, 1993

Staurosporine (**1**), isolated by Omura and co-workers from *Streptomyces staurosporeus*, is one of the most potent known inhibitors of protein kinase C.[1] It also inhibits other protein kinases in nanomolar concentrations by binding to their conserved catalytic regions.[2] Our interest in staurosporine arose from two considerations. First, its unusual structure invites interesting solutions for its total synthesis.[3,4] Furthermore, synthetic mastery of the system could provide specific inhibitors of protein phosphorylation. Such specificity is important for the application of protein kinase inhibitors as useful drugs for intervention at the level of signal transduction.

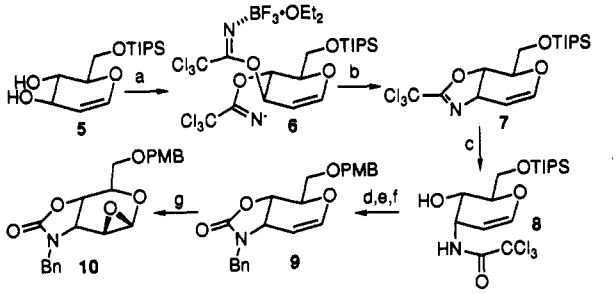
The chief structural challenge posed by staurosporine (**1**) is the construction of the two *N*-glycosidic linkages which anchor the amino sugar to the indolocarbazole matrix. Another synthetic consideration involves correlating the regiochemical dissymmetry between the remote carbohydrate and unsaturated lactam sectors. The strategy we envisioned contemplated twofold glycosidative coupling between indolocarbazole **2** and bis enol ether **3** en route to **1** (Scheme I). In its pristine sense, such an approach raises obvious questions of regiochemical control not to speak of gross feasibility. Herein we describe the realization of the overall logic of this scheme by a more methodical approach.

The components presented for the first encounter of the aglycone and carbohydrate sectors were the bis(indolyl) system **4** and the glycal **9**. Compound **4** was synthesized according to protocols developed in our recent total synthesis of rebeccamycin.[5]

Scheme I



Scheme II[a]



[a] (a) NaH, CH_2Cl_2, 0 °C, then Cl_3CCN, 0 °C → rt. (b) $BF_3{\cdot}OEt_2$, −78 °C, 78%. (c) Cat. TsOH, H_2O, pyr, 80 °C, 80%. (d) NaH, CH_2Cl_2, 0 °C → rt, then DMF, BnBr, 0 °C → rt, 94%. (e) TBAF, THF, 0 °C → rt, 96%. (f) NaH, DMF, 0 °C → rt, then PMBCl, 0 °C → rt, 97%. (g) Dimethyldioxirane, CH_2Cl_2, 0 °C, mixture of isomers, quantitative.

An interesting and concise route to **9** began with readily available glucal **5**.[6] Thus, treatment of **5** with sodium hydride and trichloroacetonitrile generated an intermediate which, upon treatment with $BF_3{\cdot}OEt_2$, gave rise to oxazoline **7**. We suspect the intermediate to be the 3,4-bis(acetimidate) **6**, which reacts by what can be viewed as a vinylogous intramolecular Schmidt glycosidation.[7] Conversion of **7** to **9** proceeded as shown in Scheme II.

Treatment of endo glycal **9** with 2,2-dimethyldioxirane generated the corresponding 1,2-anhydro sugars as a mixture of diastereomers.[8] This material, enriched in β-epoxide **10**, was treated with the sodium anion of **4** (Scheme III) to afford a 48% yield of **11** (as well as approximately 8% of the product arising from glycosidation of the α-epoxide).[5] Deoxygenation of **11** produced the 2-deoxy-β-indolocarbazolyl glycoside **12**.[9] It was at this stage that the 2,2′-bis(indolyl) bond was fashioned by photocyclization.[3a,4a,10] Unveiling the exo glycal equivalent of **2** was accomplished by oxidative cleavage of the *p*-methoxybenzyl group of **13**, conversion to iodide **15**, and treatment with DBU which, after indolocarbazole deprotection, yielded **16**.

^{1}H NMR analysis indicated that the bulky indolocarbazole moiety of **16** adopts an equatorial orientation which is not conducive to the required 7-exo cyclization. Indeed, a variety of attempts to accomplish an electrophilically triggered cyclization failed and served to identify the vulnerability of the glycosidic bond. However, success was eventually achieved by sequential treatment of **16** with potassium *tert*-butoxide at room temperature

(1) (a) Omura, S.; Iwai, Y.; Hirano, A.; Nakagawa, A.; Awaya, J.; Tsuchiya, H.; Takahashi, Y.; Masuma, R. *J. Antibiot.* **1977**, *30*, 275. (b) Furusaki, A.; Hashiba, N.; Matsumoto, T. *J. Chem. Soc., Chem. Commun.* **1978**, 800. (c) Furusaki, A.; Hashiba, N.; Matsumoto, T.; Hirano, A.; Iwai, Y.; Omura, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3681. (d) Tamaoki, T.; Nomoto, H.; Takahashi, I.; Kato, Y.; Morimoto, M.; Tomita, F. *Biochem. Biophys. Res. Commun.* **1986**, *135*, 397.

(2) (a) Tamaoki, T.; Nakano, H. *Biotechnology* **1990**, *8*, 732. (b) Nakano, H.; Kobayashi, E.; Takahashi, I.; Tamaoki, T.; Kuzuu, Y.; Iba, H. *J. Antibiot.* **1987**, *40*, 706. (c) Badwey, J. A.; Erickson, R. W.; Curnutte, J. T. *Biochem. Biophys. Res. Commun.* **1991**, *178*, 423. (d) Fujita-Yamaguchi, Y.; Kathuria, S. *Biochem. Biophys. Res. Commun.* **1988**, *157*, 955.

(3) Attempted total syntheses: (a) Winterfeldt, E. In *Heterocycles in Bio-Organic Chemistry*; Bergman, J., Ed.; The Royal Society of Chemistry: London, 1991; pp 18–27. (b) Weinreb, S. M. *Heterocycles* **1984**, *21*, 309. (c) Joyce, R.; Gainor, J.; Weinreb, S. M. *J. Org. Chem.* **1987**, *52*, 1177.

(4) Aglycone synthetic studies: (a) Sarstedt, B.; Winterfeldt, E. *Heterocycles* **1983**, *20*, 469. (b) Magnus, P. D.; Exon, C.; Sear, N. *Tetrahedron* **1983**, *39*, 3725. (c) Hughes, I.; Raphael, R. A. *Tetrahedron Lett.* **1983**, *24*, 1441. (d) Hughes, I.; Nolan, W. P.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2475. (e) Davis, P. D.; Bit, R. A.; Hurst, S. A. *Tetrahedron Lett.* **1990**, *31*, 2353. (f) Davis, P. D.; Bit, R. A. *Tetrahedron Lett.* **1990**, *31*, 5201. (g) Bergman, J. *Chem. Scr.* **1986**, *27*, 539. (h) Bergman, J.; Pelcman, B. *Tetrahedron Lett.* **1987**, *28*, 4441. (i) Bergman, J.; Pelcman, B. *J. Org. Chem.* **1989**, *54*, 824. (j) Moody, C. J.; Rahimtoola, K. F. *J. Chem. Soc., Chem. Commun.* **1990**, 1667. (k) Moody, C. J.; Rahimtoola, K. F. *J. Org. Chem.* **1992**, *57*, 2105. (l) Steglich, W. *Pure Appl. Chem.* **1989**, *61*, 281. (m) Gribble, G. W.; Berthel, S. J. *Tetrahedron* **1992**, *41*, 8869. (n) Somei, M.; Kodama, A. *Heterocycles* **1992**, *34*, 1285.

(5) Gallant, M.; Link, J. T.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 343.

(6) Gordon, D. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 659.

(7) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212.

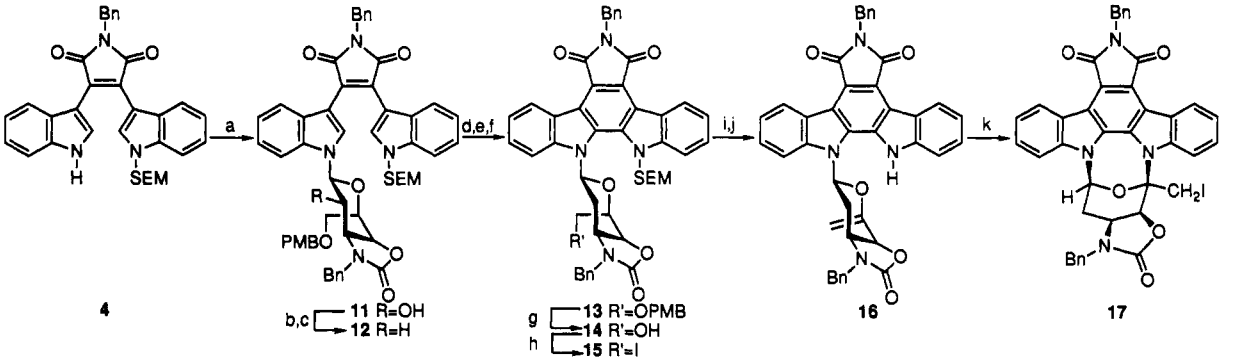
(8) (a) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661. (b) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656. (c) Gordon, D. M.; Danishefsky, S. J. *Carbohydr. Res.* **1990**, *206*, 361.

(9) (a) Gervay, J.; Danishefsky, S. *J. Org. Chem.* **1991**, *56*, 5448. (b) Barton, D. H. R.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1989**, *30*, 2619.

(10) (a) Tominaga, Y.; Lee, M.; Castle, R. *J. Heterocycl. Chem.* **1981**, *18*, 967. (b) Rawal, V. H.; Jones, R. J.; Cava, M. P. *J. Org. Chem.* **1987**, *52*, 19.

0002-7863/93/1515-3782$04.00/0

Scheme III[a]

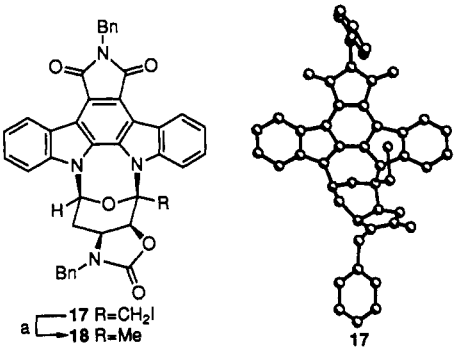


[a] (a) NaH, THF, 0 °C, then **10**, 0 °C → reflux, 48%. (b) Thiophosgene, DMAP, pyr, CH_2Cl_2, reflux, then pentafluorophenol, reflux, 95%. (c) n-Bu_3SnH, AIBN, PhH, reflux, 80%. (d) TBAF, THF, powdered 4-Å molecular sieves, reflux, 92%. (e) hν, cat. I_2, air, PhH, rt, 65%. (f) NaH, THF, 0 °C → rt, then SEMCl, rt, 97%. (g) DDQ, CH_2Cl_2, H_2O, rt, 87%. (h) I_2, $P(Ph)_3$, imidazole, CH_2Cl_2, 0 °C → rt, 87%. (i) DBU, THF, 0 °C → rt, 92%. (j) TBAF, THF, powdered 4-Å molecular sieves, reflux, 82%. (k) *t*-BuOK, THF, MeOH, rt, then I_2, −78 °C → 0 °C, 30%.

followed by iodine in THF–methanol at −78 °C → 0 °C.[11] Cyclized compound **17** (mp 228–229 °C), whose structure was corroborated by single crystal X-ray analysis, was obtained in 30% yield. The crystallographic data also revealed that the carbohydrate sector of **17** adopts a twist boat conformation in contrast to the chairlike disposition of staurosporine itself.[12] Deiodination of **17** occurred smoothly to give rise to **18** (Scheme IV).[13] We note that compound **18** contains, in principle, all of the functionality present in staurosporine.

We are now in the process of addressing the delicate matter of interfacing the regiochemical dissymmetries of the unsaturated lactam and carbohydrate sectors. Our continuing goals are the total synthesis of staurosporine as well as the delineation of the relationship between protein kinase inhibition and contour of the carbohydrate sector of the molecule. A broader investigation of the chemistry of exo glycals is also in progress.

Scheme IV[a]



[a] (a) *n*-Bu_3SnH, AIBN, PhH, reflux, 99%.

Acknowledgment. This work was supported by NIH Grant HL-25848. We gratefully acknowledge Yale University for a Kent Fellowship (J.T.L.) and the Natural Sciences and Engineering Research Council of Canada for a postdoctoral fellowship (M.G.).

Supplementary Material Available: A chart of reactions including yields and conditions for all transformations reported herein with selected analytical data for **7**, **9**, **16**, **17**, and **18** (25 pages). Ordering information is given on any current masthead page.

(11) (a) Barrett, A. G. M.; Bezuidenhoudt, B. C. B.; Gasiecki, A. F.; Howell, A. R.; Russell, M. A. *J. Am. Chem. Soc.* **1989**, *111*, 1392. (b) Haudrechy, A.; Sinay, P. *J. Org. Chem.* **1992**, *57*, 4142. For other reactions of exo glycals, see: (c) Rajanbabu, T. V.; Reddy, G. S. *J. Org. Chem.* **1986**, *51*, 5458. (d) Thiem, J.; Kleeburg, M. *Carbohydr. Res.* **1990**, *205*, 333. (e) Haudrechy, A.; Sinay, P. *Tetrahedron Lett.* **1990**, *31*, 4035. (f) Noort, D.; Veeneman, G. H.; Boons, G. J. P. H.; van der Marel, G. A.; Mulder, G. J.; van Boom, J. H. *Letters* **1990**, 205. (g) Francesco, F.; Panza, L.; Russo, G. *Tetrahedron Lett.* **1991**, *32*, 4035. (h) Maag, H.; Rydzewski, R. M.; McRoberts, M. J.; Crawford-Ruth, D.; Verheyden, J. P. H.; Prisbe, E. J. *J. Med. Chem.* **1992**, *35*, 1440.

(12) Davis, P. D.; Hill, C. H.; Thomas, W. A.; Whitcombe, I. W. A. *J. Chem. Soc., Chem. Commun.* **1991**, 182.

(13) Kuivila, H. G.; Menapace, L. W. *J. Org. Chem.* **1963**, *28*, 2165.