First Total Synthesis of Staurosporine and *ent*-Staurosporine

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Staurosporine was first isolated by Omura and colleagues from *Streptomyces staurosporeus*.[1] Its configuration was recently revealed to be that shown in structure **1**.[2] Previously, structure **2**, now known to be *ent*-staurosporine, had been assigned to staurosporine.[3] (See Chart 1.)

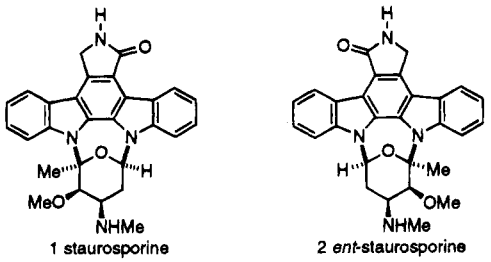
Interest in staurosporine at the biological level springs from its nanomolar inhibition of protein kinase C(PKC).[4] Given the central role of protein phosphorylation in orchestrating the cell cycle, powerful inhibitors of PKC might be useful as antiproliferative agents.[5] Needless to say, high levels of tissue specificity in the delivery of a PKC inhibitor would be critical for its development as a drug.

The most obvious chemical challenge posed by a total synthesis of **1**[6,7] is the fashioning of glycosidic bonds to each of the indolic nitrogens. Provision must also be made for the introduction of properly configured methoxy and methylamino groups. A further complication is the daunting issue of regioselectivity in the formation of a lactam from a nearly symmetric imide precursor (cf. **25**). Herein we report the first total synthesis of staurosporine (**1**) and *ent*-staurosporine (**2**).

Our strategy called for containment of the future *N*-methyl and *O*-methyl moieties in a cyclic framework which would provide chemical protection and offer stereochemical guidance for the intermolecular indole glycosylation. Specifically, we identified oxazolidinone glycal **10** to serve as the glycosyl donor and bis(indolyl) maleimide **5** to function as the aglycon acceptor. (See Scheme 1.)

Aglycon **5** was synthesized from benzyloxymethyl (BOM) dibromomaleimide **3** in the modular fashion shown. Triisopropylsilyl-L-glucal **6** (TIPS-L-glucal) was converted to its bis(trichloroacetimidate) and thence to oxazoline **7** by an apparent vinylogous Schmidt glycosylation.[8] The oxazolidinone, fashioned from the derived **8,** was protected as its BOM derivative **9**. The TIPS protecting group was cleaved, and a *p*-methoxybenzyl ether (PMB) was installed (see compound **10**).

Chart 1



1 staurosporine 2 *ent*-staurosporine

The stage was now set for the intermolecular indole glycosylation. Previous experience had demonstrated that the 1,2 anhydro-sugar coupling method represents, to date, the best available tactic for the glycosylation of complex indoles with complex donors.[9] Accordingly, glycal **10** was oxidized with 2,2-dimethyldioxirane. The mixture of epoxides (**11** and **12**) was treated with the sodium salt of **5**.[10] Indole glycoside **13** was obtained in 47% yield.[11] In the next step, the C_2' hydroxyl function was removed by Barton deoxygenation, yielding **14**.[12]

Deprotection of the C_6' PMB and the indolic SEM groups provided seco-system **15**. Photolytic oxidative cyclization led to **16**.[13] The *exo*-glycal, needed for the critical intramolecular glycosylation, was fashioned by iodination of **16** followed by elimination. Treatment of **17** with potassium *tert*-butoxide and iodine indeed yielded **18**, and after treatment with tri-*n*-butyltin hydride and deprotection of the BOM groups, compound **20** was in hand. (See Scheme 2.)

A BOC group was installed specifically on the oxazolidinone ring (see compound **21**). This group was to play a crucial role. Its presence would facilitate disconnection of the oxazolidinone.[14] When opening had been accomplished the BOC group would guard against dimethylation of the amine. To shield the imide sector during operations which would generate the *N*-methyl and *O*-methyl functions, compound **21** was converted into **22**. Treatment of **22** with cesium carbonate in methanol gave **23**.[15] It was here that the plan for introduction of the *O*-methyl and single *N*-methyl groups was implemented and **24** was secured. Subsequent deprotection was accomplished as shown to provide 7-oxostaurosporine (**25**), identical with an authentic sample.[16]

A protocol was developed to convert the 7-oxo compound **25** to staurosporine itself.[17] It started with a precedented reduction with sodium borohydride.[18] Not easily achieved or precedented was the capacity to deoxygenate the carbanolamide linkage. However, this was eventually smoothly accomplished via the action of benzeneselenol. When this two step sequence was carried out on **25**, there was obtained a 1:1 mixture of

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(9) Secoaglycons such as **5** are much more potent glycosyl acceptors than are compounds in which the indolocarbazole ring is in place. Gallant, M.; Link, J. T.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 343.
(10) The epoxidation yielded a 2.5:1 ratio of α-epoxide **11**:β-epoxide **12** as determined by ^{1}H-NMR and by the isolation of the methyl glycosides obtained from their methanolysis and acetylation.
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(16) Synthetic material was identical with a natural sample by TLC, ^{1}H-NMR, ^{13}C-NMR, IR, high-resolution mass spectrometry, and rotation.

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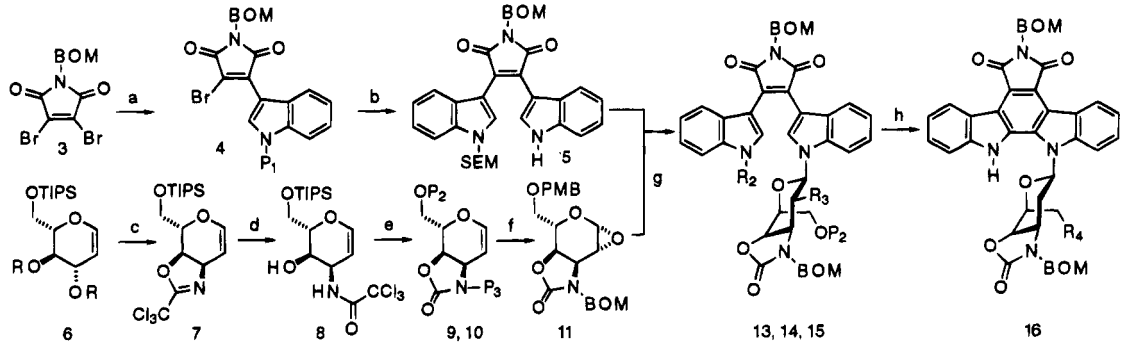
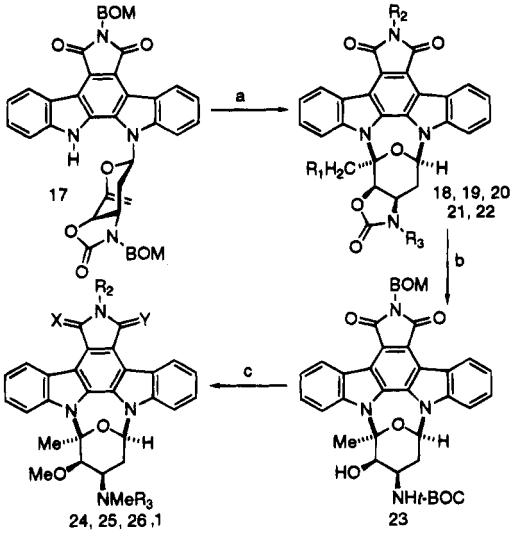
Scheme 1[a]



[a] (a) (i) Indole Grignard, PhH, 0 °C → room temperature, overnight, 82% (P_1 = H). (ii) NaH, THF, room temperature, then SEMCl, 91% (P_1 = SEM). (b) Indole Grignard, PhH, 0 °C → room temperature, overnight, 75%. (c) NaH, CH_2Cl_2, 0 °C, then Cl_3CCN, 0 °C → room temperature, (R = $CNHCCl_3$), then BF_3·OEt_2, -78 °C, 78%. (d) cat. TsOH, H_2O, pyr, 80 °C, 80%. (e) (i) NaH, CH_2Cl_2, 0 °C → room temperature, 92% of **9** (P_2 = TIPS, P_3 = H). (ii) NaH, DMF, then BOMCl, 40 °C, 65% (P_2 = TIPS, P_3 = BOM) and 22% of **9**. (iii) TBAF, THF, 0 °C, 95% (P_2 = H, P_3 = BOM). (iv) NaH, DMF, 0 °C → room temperature, then PMBCl, 0 °C → room temperature, 92% of **10** (P_2 = PMB, P_3 = BOM). (f) Dimethyldioxirane, CH_2Cl_2, 0 °C, 100% of α-epoxide **11** and β-epoxide **12**. (g) (i) **5**, NaH, THF, room temperature, then **11** and **12**, room temperature → reflux, 47% of **13** (P_2 = PMB, R_2 = SEM, R_3 = OH). (ii) Thiophosgene, DMAP, pyr, CH_2Cl_2, reflux, then C_6F_5OH, reflux, 79% (P_2 = PMB, R_2 = SEM, R_3 = $OCSOC_6F_5$). (iii) *n*-Bu_3SnH, AIBN, PhH, reflux, 74% **14** (P_2 = PMB, R_2 = SEM, R_3 = H). (iv) DDQ, CH_2Cl_2, H_2O, 0 °C → room temperature, 97% (P_2 = H, R_2 = SEM, R_3 = H). (v) TBAF, THF, reflux, 91% of **15** (P_2 = H, R_2 = H, R_3 = H). (h) (i) *hν*, cat. I_2, air, PhH, room temperature, 73% of **16** (R_4 = OH). (ii) I_2, $P(Ph)_3$, imidazole, CH_2Cl_2, 0 °C → room temperature, 84% (R_4 = I).

Scheme 2[a]



[a] **16** (R_4 = I), THF, DBU, room temperature, 89% of **17**. (a) (i) *t*-BuOK, I_2, THF, MeOH, room temperature, 65% of **18** (R_1 = I, R_2, R_3 = BOM) and 15% of recovered **17**. (ii) *n*-Bu_3SnH, AIBN, PhH, reflux, 99% of **19** (R_1 = H, R_2, R_3 = BOM). (iii) H_2, $Pd(OH)_2$, EtOAc, MeOH, room temperature, then NaOMe in MeOH, 92% of **20** (R_1, R_2, R_3 = H). (iv) $(BOC)_2O$, THF, cat. DMAP, room temperature, 81% of **21**(R_1, R_2 = H, R_3 = BOC). (v) NaH, DMF, room temperature, then BOMCl, 82% of **22** (R_1 = H, R_2 = BOM, R_3 = BOC). (b) Cs_2CO_3, MeOH, room temperature, 93%. (c) (i) NaH, $(CH_3)_2SO_4$, THF, DMF, room temperature, 86% of **24** (X, Y = O, R_2 = BOM, R_3 = BOC). (ii) H_2, $Pd(OH)_2$, EtOAc, MeOH, room temperature, then NaOMe in MeOH, 84% (X, Y = O, R_2 = H, R_3 = BOC). (iii) TFA, CH_2Cl_2, room temperature, 97% of **25** (X, Y = O, R_2, R_3 = H). (iv) $NaBH_4$, EtOH, room temperature, workup (X,Y = O, OH, R_2, R_3 = H), then PhSeH, cat. TsOH, CH_2Cl_2, room temperature, 39% of **1** (X = H_2, Y = O, R_2, R_3 = H), 39% of **26** (X = O, Y = H_2, R_2, R_3 = H), and 15% of **25**.

*iso*staurosporine (**26**) and staurosporine (**1**). After separation, homogeneous fully synthetic staurosporine (**1**) was isolated.[19] The total synthesis of staurosporine (**1**) has thus been completed.

During the late stages of the synthesis, the absolute configuration of natural staurosporine was revealed to be that shown in structure **1** rather than **2**. Operating under the prevailing misconception, we had initially carried out the same steps described herein with D-glucal as our starting material. This identical sequence led to *ent*-staurosporine (**2**) and to *ent iso* compound **27** (the enantiomer of **26**).[20] The biological evaluation of these compounds, which is currently underway, should provide unique insights into the interactive roles of the carbohydrate, indolocarbazole, and lactam (or imide) domains in this extraordinary class of PKC inhibitors.

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Supplementary Material Available: Selected analytical data for compounds **13**, **18**, **25**, **26**, and **1** (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(17) We have in fact achieved promising levels of selectivity when the imide reduction is carried out on substrates in which the staurosporine core has not been completed. However, those regioselectively produced lactams have not yet been interfaced with intermediates which have gone through to staurosporine. We note that the chemistry practiced here, where the protected imide is maintained until virtually the end of the synthesis, works much more smoothly than when it is applied to systems in which the lactam is in place early. See: Link, J. T.; Danishefsky, S. J. *Tetrahedron Lett.* **1994**, *49*, 9135.

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(19) *Iso*staurosporine (**26**) and staurosporine (**1**) were separated by preparative thin layer chromatography on silica gel (19:1 CH_2Cl_2/MeOH). Synthetic staurosporine (**1**) was identical with a natural sample by TLC, ^{1}H-NMR, IR, high-resolution mass spectrometry, and optical rotation.

(20) Synthetic *ent*-7-oxostaurosporine and *ent*-staurosporine were identical with natural samples by TLC, ^{1}H-NMR, ^{13}C-NMR, IR, high-resolution mass spectrometry, and magnitude (opposite in sign) of optical rotation.