Staurosporine and *ent*-Staurosporine: The First Total Syntheses, Prospects for a Regioselective Approach, and Activity Profiles[1]

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Abstract: The total syntheses of staurosporine and *ent*-staurosporine have been achieved. Both glycosidic bonds were built from glycal precursors. The first was constructed by intermolecular coupling of an indole anion with a 1,2-anhydrosugar derived from an endo-glycal by direct epoxidation. The second bond was assembled from an exo-glycal by intramolecular iodoglycosylation.

Background

In 1977 an unusual natural product was isolated from *Streptomyces staurosporeus* by Omura and co-workers during a search for new alkaloids present in actinomycetes and was given the name AM-2282.[2] Later, the structure of AM-2282 was established by X-ray crystallography of its methanol solvate. The indolocarbazole alkaloid was renamed staurosporine (**1**) (Figure 1).[3] The absolute configuration of the alkaloid was initially assigned from circular dichroism measurements.[4] We began our synthetic studies with the perception that structure **2** represented the absolute configuration of staurosporine (**1**). While our work was in progress, the assignment of absolute configuration of staurosporine was revised to that shown in structure **1**. This assessment arose from anomalous dispersion measurements performed on crystalline 4′-*N*-methylstaurosporine methiodide.[5] Chemical proof in support of structure **1** as properly depicting the absolute stereochemistry of staurosporine (**1**) arose from our synthesis (*vide infra*).[6]

Since 1977, the number of isolated and recognized indolocarbazole alkaloids has grown considerably.[7] The collection has attracted the interest of organic chemists due to the novel structures and wide range of activity (*vide infra*) of its members. Rebeccamycin (**3**) and K-252a (**4**) are two representatives of the class which serve to illustrate both bioactivity and structural diversity (Figure 2). Rebeccamycin (**3**), which is currently in late stage clinical evaluation as an anticancer agent, induces topoisomerase I mediated DNA cleavage.[8] Staurosporine (**1**) and K-252a (**4**) are also potential antitumor agents. They act by potent inhibition of protein kinase C (PKC) which is an enzyme of much current interest (*vide infra*).[9] Reports that staurosporine (**1**) possesses immunosuppressive activity[10] and reverses multidrug resistance have also appeared.[11] It has also been noted that indolocarbazole alkaloids have diverse effects on cell cycle progression.[12] However, it is through its

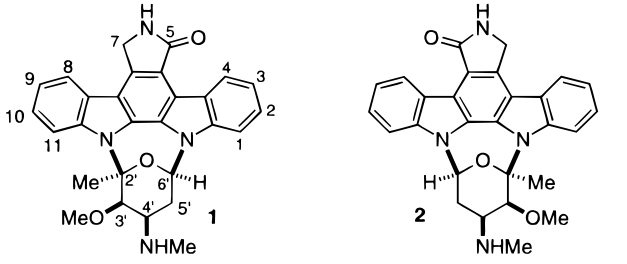

Figure 1. Structures of staurosporine (**1**) and *ent*-staurosporine (**2**).

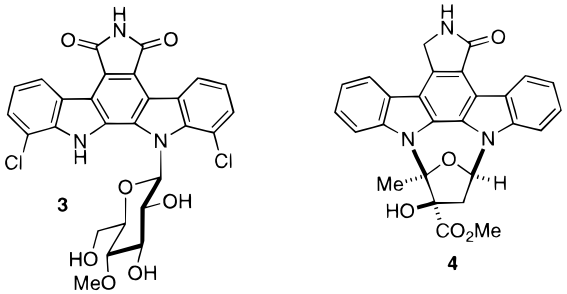

Figure 2. Structures of rebeccamycin (**3**) and K-252a (**4**).

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nanomolar inhibition of PKC that staurosporine has gained its current acclaim.[13]

Protein kinase C is a family of cytosolic serine/threonine phosphorylating isoenzymes which plays a key role in several crucial cellular processes such as signal transduction, cell differentiation, and cell growth.[14] A particular isoenzyme is apt to show distinct patterns of tissue expression and presumably has different functions. Interest in the kinases is due to their central role in mediating cell cycle progression. The curiosity of chemists was further heightened by the discovery that tumor-promoting phorbol esters function by activating PKC.[15] Correspondingly, inhibitors of PKC upregulation might serve as anticancer agents and could be of value in studying the mechanism of action of the kinases.

Staurosporine (**1**) is one of the most potent inhibitors of PKC known with an IC_{50} value of 2.7 nM.[16] The natural product interacts with PKC at the ATP binding site which is in the catalytic domain.[17] Since the catalytic domain is highly conserved among all types of protein kinases, it is not surprising that staurosporine (**1**) is a rather unselective kinase inhibitor.[18] Interestingly, related compounds have displayed selectivity for PKC, although isoenzyme specificity has remained elusive.[19]

Not surprisingly, synthetic chemists have also been drawn to this class of natural products. Early efforts centered on aglycon construction, and many syntheses of the hexacyclic aglycon have appeared.[20] The first publication in this area was due to Steglich and co-workers who described the addition of indole Grignard reagents to dibromomaleimide.[21] This is still the most efficient and widely utilized method for obtaining bis-indolyl maleimides which commonly serve as aglycon precursors. Magnus has detailed an approach which featured an indole-2,3-quinodimethane Diels−Alder reaction and provided the first synthesis of regioselectively protected aglycon intermediates.[22] Raphael and Moody have both described routes which rely upon a Diels−Alder reaction and nitrene insertions to provide staurosporinone.[23] Syntheses which rely upon the Fischer indole synthesis have been published by both Bergman and Gribble.[24] Winterfeldt and co-workers have described a proposed biomimetic route which, with subsequent modification, provides regioselectively protected intermediates.[25] Weinreb also had made strides toward a total synthesis of **1** and has assembled both the aglycon and the monosaccharide.[26] Recently, Wood and co-workers have completed an imaginative synthesis which relies upon the reaction of a rhodium carbenoid with an indole.[27]

The construction of the glycosidic bonds is one of the chief synthetic challenges posed by these natural products. Prior to our efforts, there were a few scattered reports of indole or carbazole *N*-glycosylations.[28] We began our efforts in this area with model studies which indicated that the coupling of indole anions with 1,2-anhydrosugars constituted a powerful route to indole glycosides. These studies culminated in a recently documented total synthesis of rebeccamycin (**3**).[29]

As we began to confront the challenge of staurosporine (**1**), there were few examples of interpolating a carbohydrate, either as a pyranose (e.g. **1**) or as a furanose (e.g. **4**), between two indolic nitrogens.[30] The methods that were known did not seem to have the promise of actually reaching staurosporine or K-252a. We expected that the pyranose case would be more challenging. Presumably, once the first indole glycoside bond was established, the aglycon would occupy an equatorial position with respect to the pyranose. Formation of the second bond requires the aglycon to assume an axial disposition relative to the pyranose. This could be particularly difficult in the case of staurosporine (**1**) where the methylamino group would be 1,3 diaxial to the aglycon. Such a conformational change could be energetically quite costly in the pyranose case. In the furanose series, McCombie and co-workers have demonstrated that "cycloglycosylations" can be effected by mild acid treatment of indolocarbazoles and 2,5-dimethoxyfurans.[31] However, similar efforts to glycosylate 2,6-dimethoxypyrans were only marginally successful.[32a] Wood and co-workers have recently completed the only total synthesis of the furanose K-252a, utilizing a variant of the McCombie methodology.[32b] They have also ring expanded the furanose sugar of K-252a to a pyranose sugar.[32c]

Synthetic Planning

As noted above, a central challenge in a total synthesis of staurosporine (**1**) is that of constructing two glycosidic bonds to weakly nucleophilic indolic nitrogens. Another challenge

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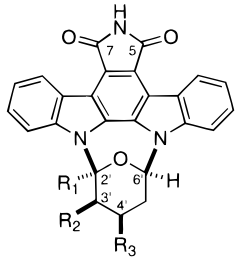
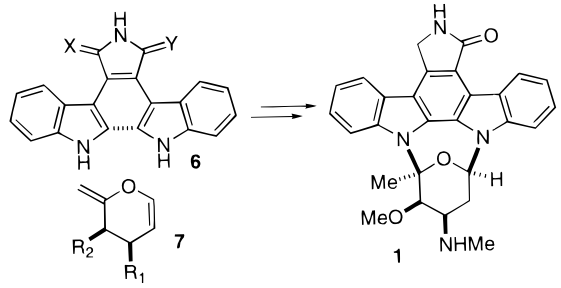
Scheme 1



5a R_1, R_2=H: C5 and C7 are "enantiotopic"
5b R_1, $R_2 \neq$H: C5 and C7 are regiodifferentiated

Scheme 2



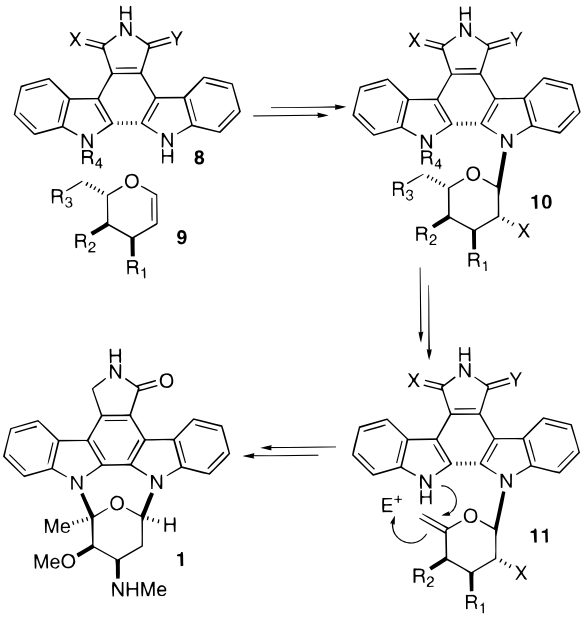
becomes apparent upon examination of structures **5a** and **5b** (Scheme 1). The 4′-(methylamino)pyranose is endowed with desymmetrizing methoxy and methyl groups at $C_{3'}$ and $C_{2'}$, respectively (staurosporine numbering). We note that in the hypothetical 7-oxo-system **5a**, lacking such substituents, the remote imide carbonyl centers at C_5 and C_7 are enantiotopic. In hypothetical precursor **5b** which bears relevant $C_{2'}$ and $C_{3'}$ substituents the two carbonyl centers are regiochemically differentiated. Hence another issue in a total synthesis involves the question as to how the dissymmetries of the lactam and pyranose rings can be interrelated in a controlled manner. Our attempts to deal with the problem of indole glycoslation, functional group management in the pyranose ring, and regiochemical harmonization are described in the course of the first total synthesis of staurosporine (**1**) detailed herein.

The central plan can be expressed through the paradigm which envisioned coupling of bis-glycal **7** with the indolic nitrogens of structure **6** (Scheme 2). We have, for the moment, left unspecified several crucial questions regarding these structures. First we avoid commitment as to the precise nature of X, Y, R_1, and R_2 at the various phases of the two-fold indole glycosylation. We also leave unspecified the status of the 2,2′ bis-indole bond. In other words this bond might or might not exist at either the first or second stage of the indole glycosidation.

We emphasize that the bis-glycal **7** served at the conceptual level rather than as a specific compound which would function as a two-stage two-fold glycosyl donor. Given the weakly nucleophilic character of indolic nitrogens, it seemed unlikely that the intermolecular step leading to the first attachment could be efficiently conducted directly on a glycal. Rather we favored creation of a precedented type of glycosyl donor, perhaps derived from a glycal, to furnish the first glycosidic bond. The intramolecular glycosylation would then be accomplished *via* a glycal or another type of donor derived from a glycal.

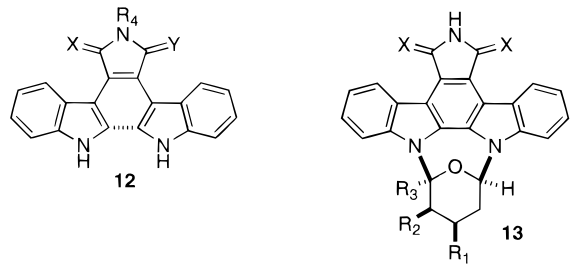
Neglecting for the moment the regiochemical issue, the preferred order for the two indole glycosylations was apparent. The first glycosylation (intermolecular) would join the secondary pyranosyl donor carbon to the first of the indole nitrogens. The formation of the second and perhaps less accessible of the two indole glycosidic bonds (this time involving a tertiary donor carbon) would be reserved for the cyclization step where intramolecularity might be employed to advantage.

Scheme 3



From this reasoning a more detailed prospectus emerged. Thus, consider aglycon acceptor **8** and donor **9** (Scheme 3). Again we leave unspecified the status of the 2,2′ bis-indole bond in the aglycon or the state of the C_5 and C_7 carbons (X = Y or X ≠ Y). Joining of **8** and **9** would lead to **10**. After further development, a system such as **11** would be fashioned. Again several protection states and the precise status of C_5 and C_7 (X = Y or X ≠ Y) are left unspecified. *The key step, however, emerges clearly. It is an electrophilically induced cyclization of the second indolic nitrogen onto a novel exo-glycal to establish the staurosporine core skeleton.* Ultimately, the success of the synthesis would depend critically on the feasibility of this reaction.

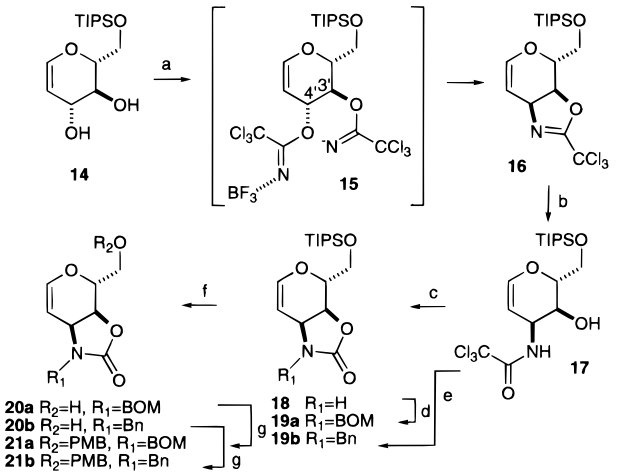
Scheme 4



Two types of solutions were entertained to confront the issue of regiochemistry. First we consider structure **12** (X ≠ Y) (Scheme 4). In this case, the two indole glycosylations are achieved in an ordered way by finding a feature through which the nonequivalence of X and Y is communicated and exploited for sequential glycosylation. We note here that control could be sought via direct glycosylation exploiting the "X-Y nonequivalence". Alternatively the nonequivalence might be used to direct a blocking maneuver which, in turn, governs the sequencing of the glycosylation.

Another potential solution is seen upon consideration of structure **13** wherein C_5 and C_7 bear identical X functions. This is the bolder approach in that it would call for distinguishing the chemically equivalent X functions on the basis of their nonequivalent relationship to the nonsymmetrical and remote

Scheme 5[a]



[a] NaH, CH_2Cl_2, 0 °C, then Cl_3CCN, 0 °C → rt, then $BF_3{\cdot}OEt_2$, −78 °C, 78%. (b) Cat. TsOH, H_2O, pyr, 80 °C, 80%. (c) NaH, CH_2Cl_2, 0 °C → rt, 92%. (d) NaH, TBAI, DMF, then BOMCl, 40 °C, 65% and 22% of recovered **18**. (e) NaH, TBAI, DMF, then BnBr, 0 °C → rt, 94%. (f) TBAF, THF, 0 °C, 95%. (g) NaH, DMF, 0 °C → rt, then PMBCl, 0 °C → rt, 92%.

carbohydrate domain. We hoped to build intermediates whereby these formalisms could be evaluated.

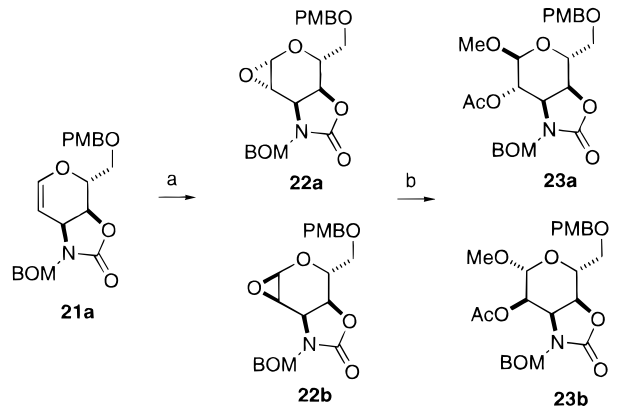
Results and Discussion

Monosaccharide Synthesis. In accord with the discussion above, we formulated our donor to be a glucal of the type **21a**. We set for ourselves the task of assembling the required glycosyl donor. We envisioned that the end game of the synthesis could potentially involve some sensitive compounds. Hence, our donor should be equipped with maximal relevant functionality to avoid the need for extensive transformations following establishment of the ring system. We hoped the future $C_{3'}$ methoxy and $C_{4'}$ methylamino vestiges would be contained in an oxazolidinone ring. The nitrogen would be further protected with a benzyloxymethyl group. A $C_{1'}$-*p*-methoxybenzyl ether would protect a primary alcohol which, at a strategic point, could be exposed and utilized in fashioning the exo-glycal critical for the crucial intramolecular indole glycosylation. We note that the role of the oxazolidinone transcended that of a protecting device to contain otherwise troublesome hydroxyl and amino functions. It was envisioned that the oxazolidinone would provide stereochemical guidance in activating the endo-glycal *en route* to the first indole glycosylation.

Again we point out that at the time we undertook this work, the structure of staurosporine (**1**) had been thought to be that which we now recognize to correspond to *ent*-staurosporine (**2**). Accordingly, our efforts started with tri-*O*-acetyl-D-glucal (Scheme 5). Deacetylation followed by selective protection of the primary alcohol with a triisopropylsilyl (TIPS) protecting group provided glycal **14** in good yield.[33] Formation of putative bis-trichloroacetimidate **15** occurred under standard conditions and treatment with $BF_3{\cdot}OEt_2$ *in situ*, at low temperature, provided glycal **16** in 78% yield. This reaction can be considered to be a type of Schmidt reaction with the novel twist that the imidate at $C_{4'}$ serves as a vinylogous glycosyl donor to an imidate acceptor stationed at $C_{3'}$.[34]

Hydrolysis of the resultant oxazoline yielded (trichloroacetyl)-amino glycal **17**. We initially considered the possibility of achieving both *O* and *N* methylation at this stage, thereby effecting early emplacement of the monomethylamino and methyl ether functions in the pyranosyl domain of staurosporine. However, treatment of **17** with base provided the corresponding oxazolidinone even in the presence of methyl iodide. We thus took advantage of this reaction to protect the amino-sugar as an oxazolidinone. Accordingly, **17** was treated with NaH and then BOMCl to provide protected oxazolidinone **19a**. The epoxide derived from oxazolidinone **19a** turned out to be a poor glycosyl donor for glycosylating sterically demanding bis-indolyl maleimides. It was reasoned that this sluggishness might be due to the large silyl protecting group at $C_{1'}$. Hence the silyl protecting group was removed and replaced with a *p*-methoxybenzyl ether (**19a** → **21a**). This sequence provided oxazolidinone glycal **21a** which proved to be a competent glycosyl donor upon suitable activation.

Scheme 6[a]



[a] 3,3-Dimethyldioxirane, CH_2Cl_2, 0 °C, 100%, 2.5:1 **22a**:**22b**. (b) MeOH, 0 °C; Ac_2O, DMAP, pyr, 0 °C, 100%, 2.5:1 **23a**:**23b**.

Oxidation of glycal **21a** with 3,3-dimethyldioxirane provided a 2.5:1 mixture of desired α-epoxide **22a** and *β*-epoxide **22b** (Scheme 6). It was hoped that 1,2-anhydrosugar **22a** would function as a glycosyl donor with respect to an indolic NH group in the aglycon acceptor. Before proceeding to this possibility we sought validation of our stereochemical assignment of **22a** and **22b**. For this purpose, the mixture was subjected to methanolysis and acetylation, thereby affording methyl glycosides **23a** and **23b**.

In the spirit of our orienting paradigm, we synthesized pyranosyl dienes closely related to **7** and probed their utility. In so doing we discovered their derived epoxides to be unusually stable (Scheme 7).[35] Pyranosyl diene **25**, obtained by elimination of mesylate **24**, was epoxidized with 3,3-dimethyldioxirane to yield a 2.3:1 mixture of α-endo monoepoxide **26a** and α-exo monoepoxide **26b**. Direct methanolysis and acetylation of the mixture of monoepoxides provided methyl glycoside **27**.[36] Further epoxidation provided bis-epoxides **28a** and **28b**. The structure of **28a** was confirmed crystallographically. Methanolysis in the presence of zinc chloride followed by acetylation provided **29a** and **29b** in a 4:1 ratio. That **26a** could serve as a glycosyl donor is shown by its successful glycosylation of diisopropylidene galactose. However, we were unable to couple **26a** with indole anions and we returned to a circumscribed but more implementable version of the original plan.

In this connection, attempts were also made to construct an endo glycal containing the full functionality required for the monosaccharide domain (Scheme 8). Accordingly, **21b** was

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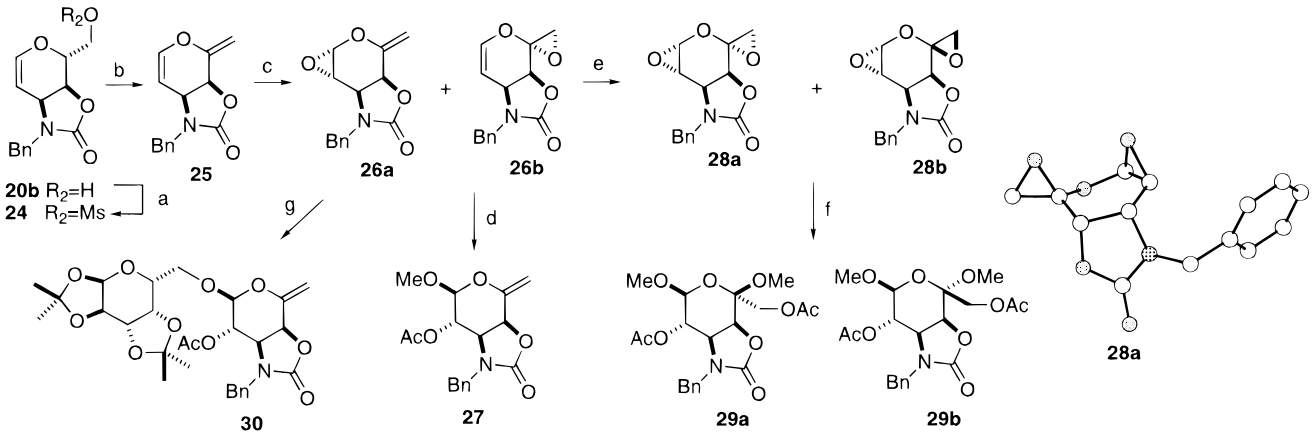
(34) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212.

(35) Link, J. T.; Danishefsky, S. J.; Schulte, G. *Tetrahedron Lett.* **1994**, *35*, 9131.

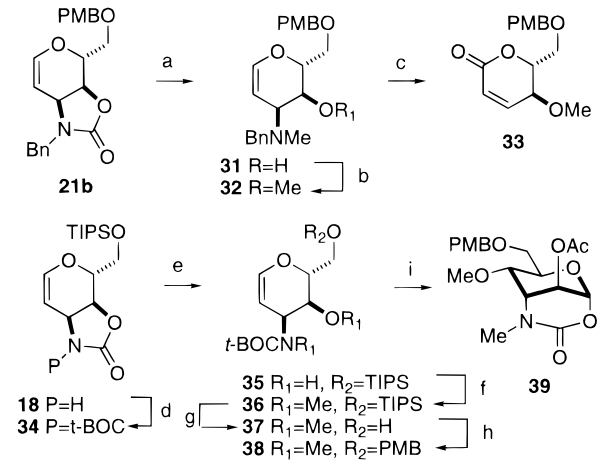
(36) Epoxide **26b** slowly decomposed during the reaction and did not yield a methyl glycoside.

Scheme 7[a]



[a] (a) MsCl, pyr, 0 °C → rt, 95%. (b) KO*t*-Bu, THF, −78 °C, 90%. (c) 3,3-Dimethyldioxirane, CH_2Cl_2, 0 °C, 100%. (d) MeOH, 0 °C → rt, then pyr, Ac_2O, 0 °C → rt, 65% (from **25**). (e) 3,3-Dimethyldioxirane, CH_2Cl_2, rt, 100%. (f) MeOH, THF, $ZnCl_2$, −78 °C → rt, 98%. (g) 1,2:3,4-*di*-*O*-isopropylidenegalactose, $ZnCl_2$, THF, −78 °C → rt, 65% (from **25**).

Scheme 8[a]



[a] (a) $LiAlH_4$, Et_2O, 0 °C, 73%. (b) NaH, THF, DMF, MeI, 53%. (c) 3,3-Dimethyldioxirane, CH_2Cl_2, 0 °C, 37%. (d) BOC_2O, Et_3N, DMAP, THF, 90%. (e) $Cs_2(CO)_3$, MeOH, 80%. (f) NaH, MeI, THF, DMF, 0 °C → rt, 92%. (g) TBAF, THF, 0 °C, 85%. (h) NaH, DMF, 0 °C → rt, then PMBCl, 0 °C → rt, 96%. (i) i. 3,3-Dimethyldioxirane, CH_2Cl_2, 0 °C; ii. MeOH, 0 °C → rt; iii. Ac_2O, pyr, DMAP, 96%.

treated with LAH which cleaved the oxazolidinone to provide **31**, and the alcohol was methylated to provide **32**. Oxidation of the glycal with 3,3-dimethyldioxirane oxidized the amine to the *N*-oxide prior to oxidizing the glycal ultimately giving rise to enone **33**. Possible use of a carbamate protection device for the amine to prevent *N*-oxide formation was also surveyed. Toward this end, glycal **34**, obtained from **18**, was treated with Cs_2CO_3 in methanol thereby accomplishing oxazolidinone cleavage under mild conditions.[37] Methylation followed by protecting group exchange at $C_{1'}$ then provided **38**. Attempts to couple the 1,2-anhydrosugar derived from epoxidation of **38** with indoles were unsuccessful. Even methanolysis failed to provide the expected methyl glycoside. The expected methanolysis was interdicted by opening of the epoxide with the carbamate oxygen with loss of the *tert*-butyl group providing **39**. Although neither **32** nor **38** served their intended roles of useful glycosyl donors for the total synthesis of staurosporine, their syntheses from the corresponding oxazolidinones provided precedents and protocols which found application in the late stages of the total synthesis.

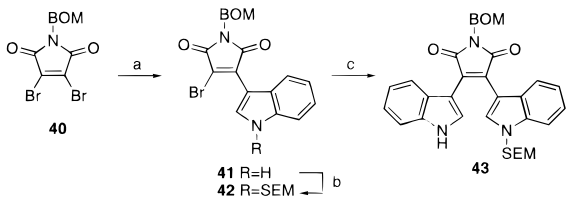
(37) Kuneida, T.; Ishizuka, T. *Tetrahedron Lett.* **1987**, *28*, 4185.

Glycosylation and Elaboration. These and related experiments had resulted in the identification of oxazolidinone glycal **21a** and its derived epoxide **22a** as functional versions of our hypothetical glycals **7** and **9**. We turned to the formation of the first glycosidic bond (Scheme 9). The attachment of the aglycon precursor **43**[38] to the monosaccharide **22a** was accomplished following the protocols developed in our total synthesis of rebeccamycin wherein it had been established that bis-indolyl maleimides were competent glycosyl acceptors for 1,2-anhydrosugar donors.[39] Accordingly, the sodium anion of the bis-indolyl maleimide **43** was prepared and treated with a solution of 1,2-anhydrosugars **22a** and **22b** obtained from the epoxidation of glycal **21a** with 3,3-dimethyldioxirane. Upon heating the reaction, a mixture of desired indole glycoside **44** (47% yield) and indole glycoside **45** (10% yield) was obtained. We note that this ratio reflects not only the ratio of the predecessor epoxides **22a** and **22b** but the effectiveness of each in serving as a glycosyl donor with respect to the sodium salt of **43**. Apparently the desired epoxide isomer **22a** had outperformed **22b** under the conditions of our experiment.

In order to pave the way for construction of the second glycosidic bond, some functional group modification was necessary. Deoxygenation of the newly created alcohol at $C_{5'}$, deprotection of the indole, formation of the 2,2′ indole bond, and exo-glycal formation must precede testing the critical reaction. Fortunately the required progression could be accomplished (Scheme 10).

Deoxygenation of indole glycoside **44** was accomplished by its conversion to pentafluorophenyl thiocarbonate **46** via the chloroformate.[40] These types of thiocarbonates have been shown to undergo Barton deoxygenation more readily than more

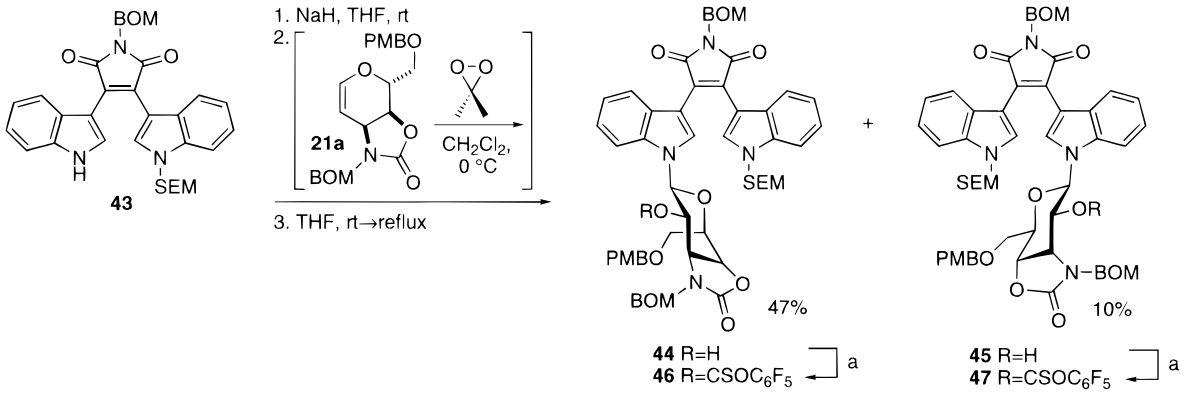
(38) Compound **43** was prepared from protected dibromomaleimide **40** via the shown three-step sequence.



(a) Indole Grignard, PhH, 0 °C → rt, overnight, 82%. (b) NaH, THF, rt, then SEMCl, 91%. (c) Indole Grignard, PhH, 0 °C → rt, overnight, 75%.

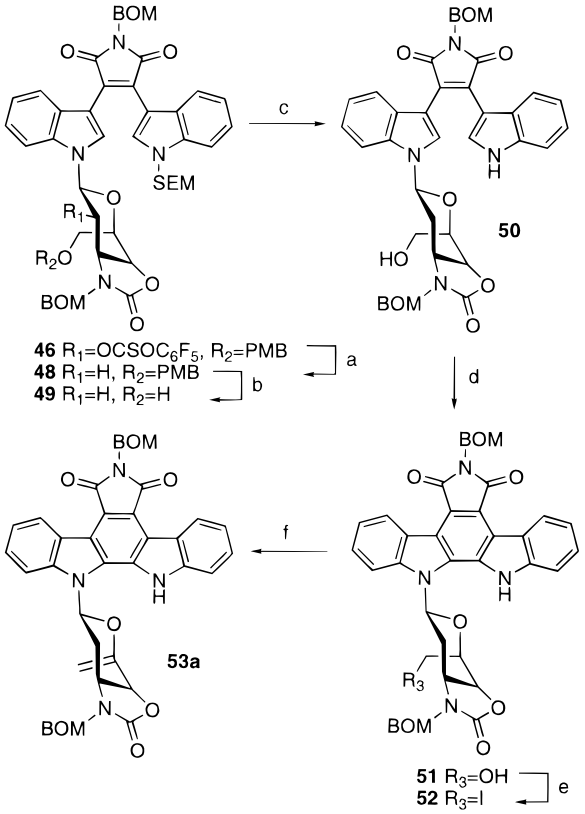
(39) For a similar coupling which ultimately provided our first access to the core structure of *ent*-staurosporine (**2**) see Link, J. T.; Gallant, M.; Danishefsky, S. J.; Huber, S. *J. Am. Chem Soc.* **1993**, *115*, 3782.

Scheme 9[a]



[a] (a) Thiophosgene, DMAP, pyr, CH_2Cl_2, reflux, then C_6F_5OH, reflux, 79%.

Scheme 10[a]



[a] (a) *n*-Bu_3SnH, AIBN, PhH, reflux, 74%. (b) DDQ, CH_2Cl_2, H_2O, 0 °C → rt, 97%. (c) TBAF, THF, reflux, 91%. (d) *hν*, cat. I_2, air, PhH, rt, 73%. (e) I_2, $P(Ph)_3$, imidazole, CH_2Cl_2, 0 °C → rt, 84%. (f) DBU, THF, 0 °C, 89%.

commonly used thiocarbonates and have been utilized in our group to make 2-deoxy-*β*-glycosides.[41] Treatment of the thiocarbonate under standard Barton conditions provided the 2-deoxy indole glycoside **48** in 74% yield. The *p*-methoxybenzyl group was then cleaved to reveal the primary alcohol ($C_{1'}$ of the pyranose). This was followed by removal of the SEM protecting group, thus exposing the indolic NH function (see compound **50**). Photocyclization of **50** with a medium pressure mercury lamp provided indolocarbazole glycoside **51** in 73% yield. The time was at hand to reveal the exo-glycal. This subgoal was attained by conversion of primary alcohol **51** to the corresponding iodide **52**. Treatment of **52** with DBU furnished **53a** which bears all of the chemical implements required to address the central skeleton building reaction.

The Key Cyclization. Early screening of the reaction of indolocarbazole glycoside **53** with an array of electrophiles failed to uncover conditions to effect the desired cyclization leading to the fully functionalized core of staurosporine (**1**).[42] While unsuccessful, these attempts tended to identify a process which was interdicting the desired cyclization (Scheme 11). In order for cyclization to occur, indolocarbazole glycoside **53** must have its exo-glycal activated and must undergo a conformational change. The sterically demanding aglycon must adopt an axial conformation as in **54** rather than the preferred equatorial conformation as in **53**. Cyclization to **55** could then ensue as the nucleophillic nitrogen attacks the activated exo-glycal. Instead of cyclized product **55**, we often obtained mixtures of aglycon and a product consistent with the structure **58**.[43] We believe that the exo-glycal was successully activated but that opening of the sugar provided **57**, on the way to **58**, faster than the desired cyclization. Trapping of the vinylogous acyliminium intermediate **57** with adventitious water presumably leads to the recovered aglycon.

At this point in our studies, we noticed a report by Barrett and co-workers detailing the construction of disaccharides via alcohol−enol ether cyclizations (e.g. **59** → **60**). Clearly, in this reaction, the enol ether was activated and trapped prior to the unraveling of the ketal at the anomeric position. Hoping that in our related system the aminal at the anomeric position would not unravel, we applied conditions similar to Barrett's to **53b** (Scheme 12).[44] These reaction conditions provided cyclized iodide **55b**. Though initial yields were low, we were pleased to have gained admission to the staurosporine ring system. The structure of **55b** was verified crystallographically.

A variable temperature ^{1}H-NMR study revealed an interesting

(40) In practice **44** and **45** were not separated and were converted to **46** and **47** which were readily separated. Coupling constant analysis of **46** and **47** indicated the stereochemistry of the materials. Indole glycoside **46** shows an H1′−H2′ coupling constant of J = 6.6 Hz and a H2′−H3′ coupling constant of J = 5.6 Hz consistant with the axial−axial−axial proton arrangement in the conformation shown for **46**. Indole glycoside **47** shows an H1′−H2′ coupling constant of J = 5.2 Hz and a H2′−H3′ coupling constant of J = 3.2 Hz consistant with the axial−axial−equatorial proton arrangement in the conformation shown for **47**.

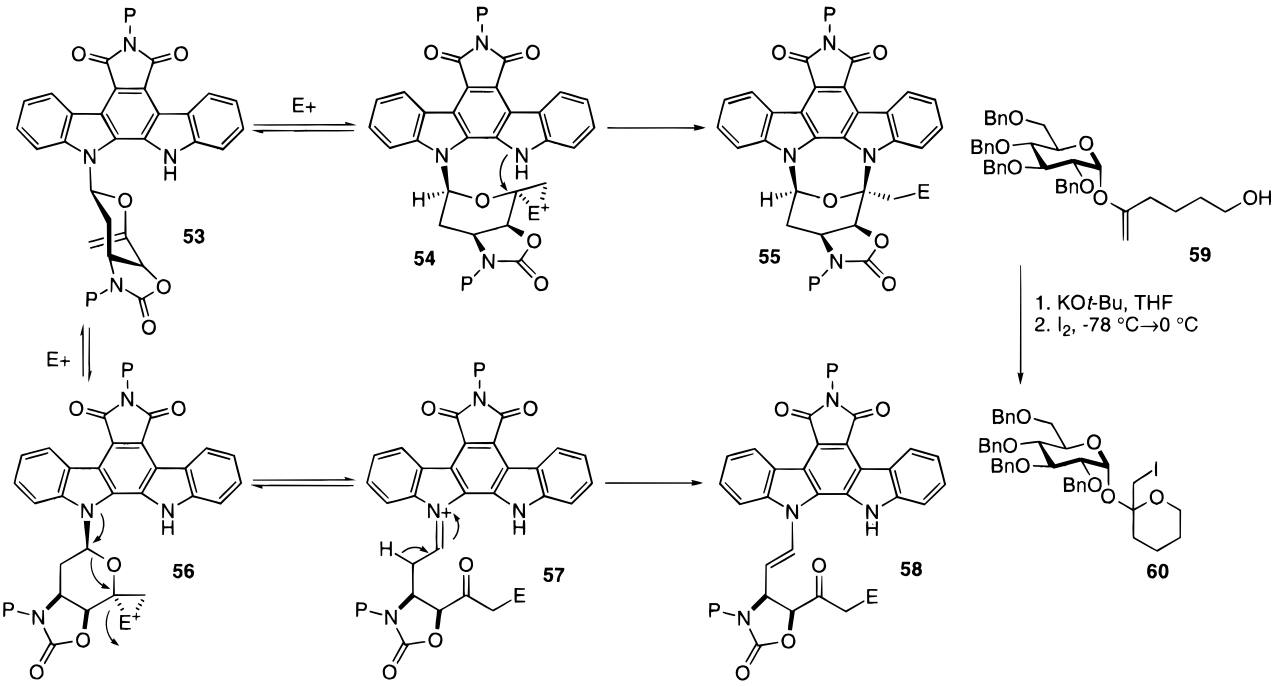
(41) (a) Barton, D. H. R.; Jazberenyi, J. C. *Tetrahedron Lett.* **1989**, *30*, 2619. (b) Gervay, J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5448.

(42) Electrophilic reagents surveyed included PhSeCl, NBS, NIS, I(*sym*-collidine)ClO_4, triphenylphosphine hydrobromide, *N*-(phenylseleno)phthalimide, iodine, 3,3-dimethyldioxirane, $PdCl_2(CH_3CN)_2$, and $Hg(COCF_3)_2$. All failed to mediate the desired cyclization and in some cases failed even when attempts were made to make the more nucleophilic stannylated indole. Attempts to trap the activated intermediates with methanol and thiophenol also failed as did attempts to generate a nitrogen centered radical.

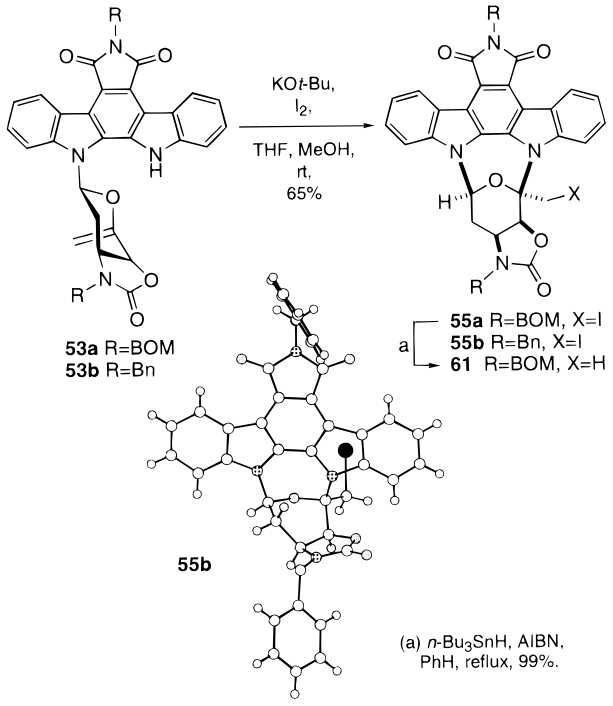
(43) **58** was not fully characterized and was assigned on the basis of ^{1}H-NMR spectroscopy.

(44) Barrett, A. G. M.; Bezuidenhoudt, B. C. B.; Gasieki, A. F.; Howell, A. R.; Russell, M. A. *J. Am. Chem. Soc.* **1989**, *111*, 1392.

Scheme 11



Scheme 12

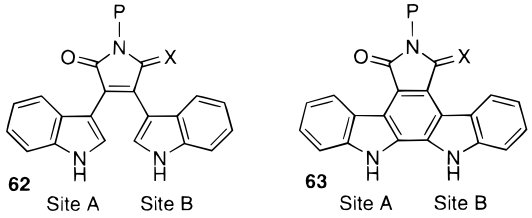


conformational facet which helped to identify reaction conditions for optimization of the cyclization reaction. The ^{1}H-NMR spectrum of exo-glycal **53b** in a variety of solvents revealed that the aglycon is disposed equatorially as shown.[45] However, when base was added to the solution the aglycon of the anion of **53b** was completely axial at ambient temperature![46] Surprisingly, as the temperature was lowered to −78 °C, the signals broadened and other conformations became accessible on the

(45) For instance in $CDCl_3$ at ambient temperature the coupling constants for the dd (6.17 ppm) observed for the anomeric proton of **53b** were J = 11.8 Hz and J = 2.5 Hz.

(46) A solution of **53b** in a 10:1 solution of THF-d_8 and CD_3OD was treated with 2 equiv of potassium *tert*-butoxide. The signal for the anomeric proton moved downfield to 6.94 ppm and appeared as an apparent triplet with J = 4.3 Hz.

Scheme 13

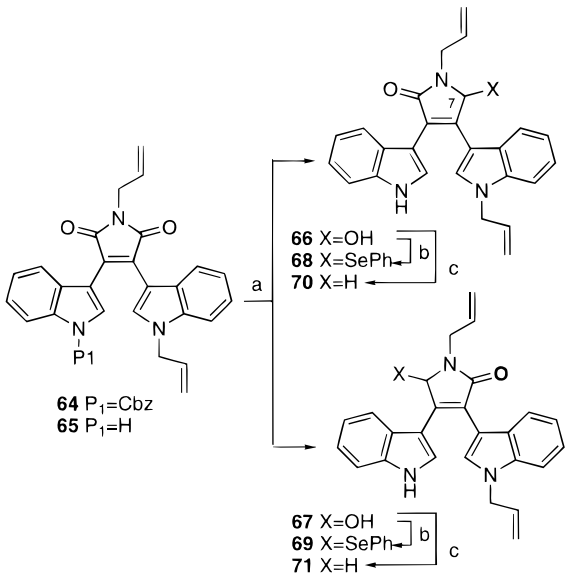


NMR timescale. This finding suggested that the reaction may potentially be more successful at ambient temperature. Indeed, treatment of **53a** with potassium *tert*-butoxide and iodine at ambient temperature in THF and MeOH provided cyclized **55a** in 65% isolated yield. Deiodination under radical conditions then provided **61** in nearly quantitative yield.

It was during this time frame that we learned about the revision of assignment of the absolute configuration of staurosporine (**1**) discussed above. We therefore began a program starting with tri-*O*-acetyl-L-glucal, to execute the steps shown here which, in retrospect, had been conducted in the *ent*-series. We shall describe this work at the end of the acccount.

Evaluation of Strategies for a Regioselective Synthesis. We continued our work in the D-glucal derived *ent* series, both for purposes of modeling the issues remaining to be addressed and for purposes of reaching *ent*-staurosporine. An interesting challenge raised by any potential total synthesis of staurosporine (**1**) is the daunting matter of fostering communication between the widely separated "northern" and "southern" districts. We have evaluated several strategies, albeit in a somewhat cursory manner, for overcoming this obstacle. Our attempts (conducted in the *ent*-series) have focused on regioselective alkylation or glycosylation and regioselective reduction of maleimides. Inspection of structure **62** invites several speculative but interesting ideas concerning regioselective glycosylation or, correspondingly selective protection sequences (Scheme 13). Conceivably, addition of 1 equiv of base to **62** or **63** (X = H_2) might predominantly abstract a particular indolic proton. Although both indole nitrogens are formally in conjugation with the lactam carbonyl in **63** (X = H_2), the circuitry of conjugation is such that the more acidic proton should still be the one at

Scheme 14[a]



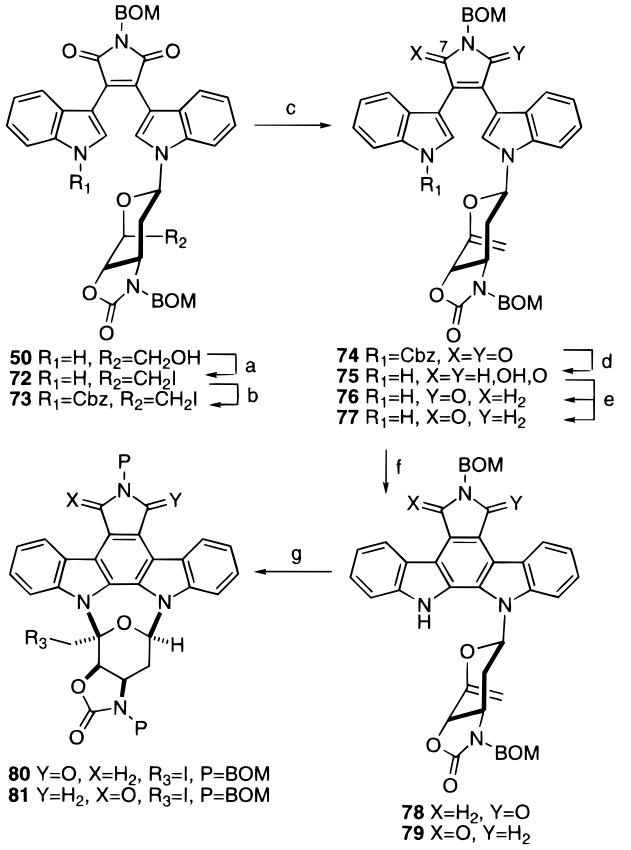
[a] (a) P_1 = Cbz, L-Selectride, THF, −78 °C → rt, 93% (3:1 **67**:**66**) or P_1 = H, NaH, THF, then DIBAL, L-Selectride, −78 °C → rt, 98% (4:1 **66**:**67**). (b) PhSeH (1 equiv), TsOH, CH_2Cl_2. (c) PhSeH (2 equiv), TsOH, CH_2Cl_2, 100%.

site B in both **62** and **63** (X = H_2). Thus, in the presence of an alkylating agent (or glycosyl donor) this site should be the first point of attack. However, if the pK_a difference between site A and site B is not large, a percentage of the aglycon might be singly deprotonated at site A. Thus, alkylation could occur at site A even though its "NH proton" is less acidic. Treatment of **62** or **63** (X = H_2) with 2 equiv of strong base should yield the dianion which should alkylate at site A. In the event, we were able to alkylate **63** (P = Bn, X = H_2) in the presence of 1 equiv of base predominantly at site B. However, we were unable to pursue this route due to the difficulties we have had in glycosylating indolocarbazoles.[47] This also defeated our plan to directly glycosylate the dianion of **63**.

We then turned to the seco-aglycon **62**. This decision stemmed from our previous finding in the rebeccamycin (**3**) synthesis in which bis-indolyl maleimides emerged as more reactive glycosyl acceptors than indolocarbazoles. Unfortunately, our experiments to glycosylate the monoanion and dianion of **62** (P = allyl) were compromised due to the instability of **62** (P = allyl) under our glycosylation conditions.[48]

More compatible with our synthetic scheme was the possibility of selectively reducing the imide at either the seco (pentacyclic) or hexacyclic stage. Moreover, opportunities to test reduction strategies upon unglycosylated, monoglycosylated, and cyclized maleimides could be explored. Our early findings on the matter were the subject of a recent report.[49] We wondered whether indole substituents of differing electron-donating potentials would cause a difference in the rate of reduction of the two imide carbonyl groups. In practice, reduction of bis-indolyl maleimide **64** (P_1 = electron-withdrawing Cbz group) at low temperature gave a 3:1 ratio of hydroxy lactams **67** and **66** in 93% yield (Scheme 14). Reversing the electronic bias, by reducing the sodium salt of **65** (P_1 = electron-donating anion), reversed the reduction selectivity delivering a 4:1 ratio of **66** and **67** in 98% yield. The observed sense of regioselectivity implied that the more electron rich imide carbonyl function was reduced. The finding suggested that complexation of the reducing agent was the determining factor in the reduction. Further reduction of the hydroxy lactams **66** and **67** was accomplished with 2 equiv of phenylselenol in the presence of a catalytic amount of acid. This protocol gave quantitative yields of regioselectively protected lactams **70** and **71** via phenyl selenides **68** and **69**, respectively. Both lactams were successfully photocyclized to give the hexacyclic aglycon structures. During the course of successful glycosylation studies of seco-lactams **70** and **71** with **22a** and **22b**, we learned that the lactam (C_7 position by staurosporine numbering) was vulnerable to oxidation to the imide under basic conditions. Furthermore the seco-lactams were sensitive materials which caused us to delay the reduction step until later in the synthesis.

Scheme 15[a]



[a] (a) Ph_3P, imidazole, I_2, 0 °C → rt, 88%. (b) CbzCl, TEA, DMAP, CH_2Cl_2, rt, 98%. (c) DBU, THF, 0 °C → rt, 98%. (d) L-Selectride, THF, −78 °C → rt, 98%. (e) SmI_2, THF, *tert*-butyl alcohol, rt, 78%. (f) *hν*, air, acetone, 44%. (g) KO*t*-Bu, I_2, THF, MeOH, 10% (and 10% of **55a**—see text).

Toward that end, **50** was converted to iodide **72** which was further protected by placement of a Cbz group on the indolic nitrogen to give **73** (Scheme 15). According to the model studies this should guide the reductant to the more electron rich C_7 carbonyl. After fashioning the exo-glycal (**73** → **74**), treatment of the seco-imide **74** with L-Selectride produced a mixture of hydroxy lactams **75**. Though treatment with phenylselenol in the presence of acid decomposed these sensitive compounds, they were efficiently reduced with samarium diiodide to provide a 2:1 ratio lactams **76** and **77**.[50] Photocyclization under modified conditions provided moderate yields of hexacyclic lactam exo-glycals **78** and **79**. After separation

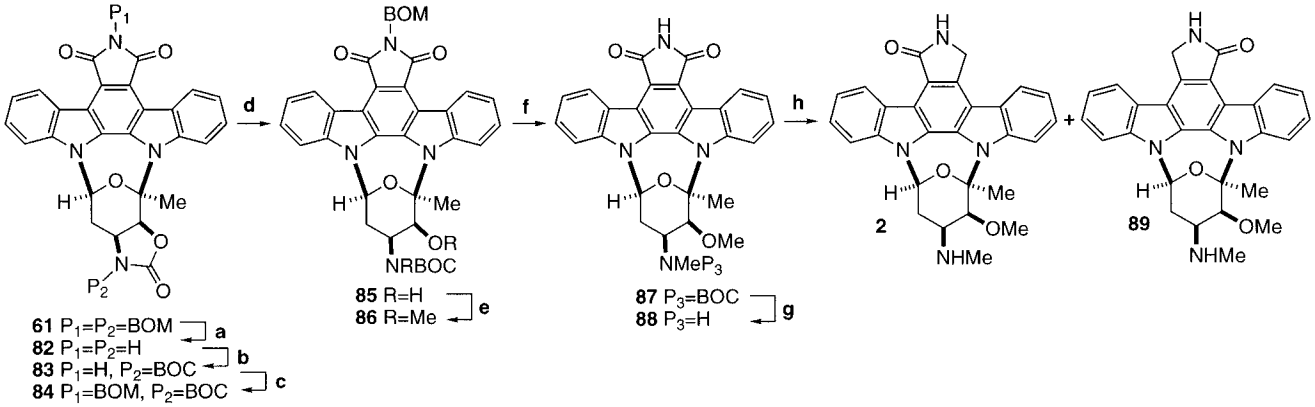
(47) Our attempts have been plagued by mixtures of anomers, low yields, and competitive C-glycosylation.

(48) We also had considered converting the imides **62** and **63** (X = O) to mono-thioimides **62** and **63** (X = S) which could be reduced at a late stage of the synthesis. Unfortunately, in our hands attempts to thiate our intermediates with Lawesson's reagent were unsuccessful.

(49) Link, J. T.; Danishefsky, S. J. *Tetrahedron Lett.* **1994**, *35*, 9135.

(50) For a review of the application of lanthanide reagents in organic synthesis see Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.

Scheme 16[a]



[a] (a) H_2, $Pd(OH)_2$, ETOAc, MeOH, rt, then NaOMe in MeOH, 92%. (b) BOC_2O, THF, cat. DMAP, rt, 81%. (c) NaH, DMF, rt, then BOMCl, 82%. (d) Cs_2CO_3, MeOH, rt, 93%. (e) NaH, $(CH_3)_2SO_4$, THF, DMF, rt, 86%. (f) H_2, $Pd(OH)_2$, ETOAc, MeOH, rt, then NaOMe in MeOH, 84%. (g) TFA, CH_2Cl_2, rt, 97%. (h) $NaBH_4$, ETOH, rt, workup, then, PhSeH, cat. TsOH, CH_2Cl_2, rt, 39% of **2**, 39% of **89**, and 15% of **88**.

the crucial cyclizations could be attempted.[51] Attempted cyclization of the minor isomer **79** led mostly to decompositon. A small amount of cyclized and oxidized maleimide-produced **55a** (<10%) was isolated.[52] Identical treatment of major isomer **78** provided a low yield (<10%) of a compound which was assumed by ^{1}H NMR analysis and mass spectroscopic criteria (FAB HRMS *m/e* calcd for $C_{43}H_{35}N_4O_6I$ 830.1601, found 830.1638) to be a cyclized lactam. On the basis of analogy with the reduction of imide **70** one would be tempted to formulate the major cyclization precursor as **78** though the point has not been proven and the cyclization product could be either **80** or **81**.

In a theoretical sense, the desired "communication" between the indolic nitrogens and imide carbonyls has been established, and the approach may have yielded greater margins of selectivity upon optimization. Most damaging to the success of this route were experiments which indicated that the hexacyclic lactams were vulnerable to oxidation. These probes virtually dictated that the reduction of the imide to the lactam must be delayed until late in the synthesis. Thus selective reduction of 7-oxostaurosporine derivatives or the compound itself became our last hope for control.

We next considered the possibility that a Lewis acid might be chelated between the hydroxyl and amino residues of the sugar in a 7-oxostaurosporine derivative. Such a chelate might then interact electronically with the aglycon potentially altering the reduction potential of one imide carbonyl. However, addition of Lewis acids to the reducing medium did not lead to selectivity.[53]

The possibility of directly attaching the metal to one of the aryl rings by making arene−chromium tricarbonyl complexes was also briefly examined.[54] Treatment of hexacyclic benzyl protected imide **63** (X = O, P = Bn) with Kundig's naphthalene chromium tricarbonyl complex provided a mono-tricarbonyl complex at the external aryl ring as the major product.[55] We then hoped to form complexes of *ent*-7-oxostaurosporine (**88**). On the basis of a steric argument, complexation of the face opposite the sugar on the $C_{6'}$ side (the least hindered face) should occur preferentially. In fact, there resulted a mixture of inseparable complexes (both 1:1 and 2:1 complexes by mass spectroscopy). Reduction of the mixture, followed by decomplexation provided a 1:1 mixture of *ent*-staurosporine (**2**) and *ent*-isostaurosporine (**89**).[56] With misgivings we set aside the regiochemical dissymmetry problem.

Completion of the Synthesis. Returning to the total synthesis of *ent*-staurosporine (**2**), a two-step deprotection sequence (hydrogenation followed by aminal hydrolysis) delivered **82** from **61** in high yield (Scheme 16). We chose to elaborate the monosaccharide domain prior to reducing the maleimide function. This decision reflected our concerns that attempted methylation under basic conditions might result in alkylation or oxidation of the lactam. In our early experiments, carbamate formation had placed a *t*-BOC group on both the imide and the oxazolidinone. Treatment of that compound with cesium carbonate opened the oxazolidinone without affecting the maleimide. However, attempted methylation of the urethane nitrogen compromised the imide. This foray indicated that the imide would have to be reprotected for this sequence. Accordingly, the oxazolidinone was selectively protected (**82** → **83**). The imide was then reprotected with a BOM protecting group providing **84**. The oxazolidinone was then opened with cesium carbonate in methanol to provide hydroxy amine **85**. Methylation yielded **86** which was ready for deprotection and reduction. Removal of the BOM protecting group and deprotection provided *ent*-7-oxostaurosporine (**88**) in excellent yield. Synthetic material matched published data[57] for the natural product by ^{1}H-NMR, ^{13}C-NMR, IR, mass spectroscopy, and TLC characteristics. The rotation was also nearly equal in magnitude but was opposite in sign. These experiments constituted independent chemical proof as to the absolute configuration of staurosporine.

Several methods were then surveyed for reducing *ent*-7-oxostaurosporine (**88**) to *ent*-staurosporine (**2**). The most efficient method in our hands involved reduction of the imide group with sodium borohydride[58] to provide a 1:1:1:1 mixture of hydroxy lactams. Further reduction to *ent*-staurosporine (**2**)

(51) It should be noted that the structures of **78** and **79** were assigned in analogy with the reduction results of model imide **64**.

(52) All cyclization studies were performed only in the *ent*-series. However, the natural series is shown throughout Scheme 15 since characterization was performed in that series.

(53) Lewis acids such as $CeCl_3$ and $AlCl_3$ were tried with sodium borohydride and Red-Al respectively on both *ent*-7-oxostaurosporine and *ent*-7-oxo-4′-*N*-(*tert*-butyloxycarbonyl)staurosporine.

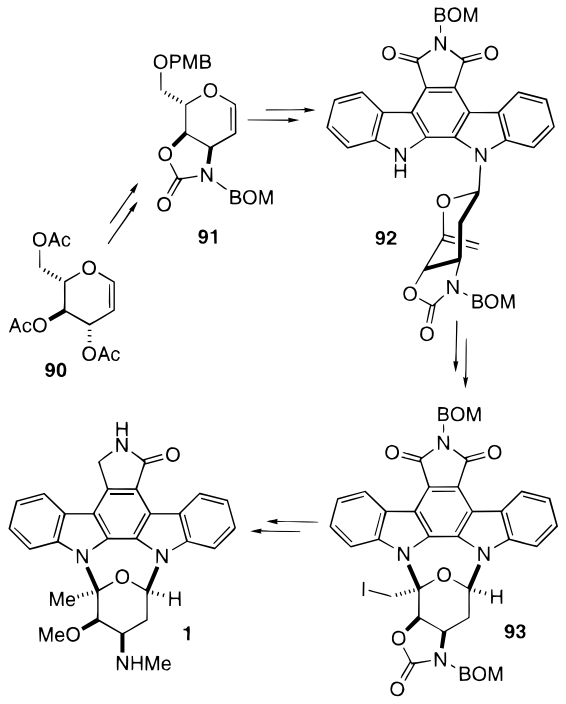
(54) For a review see Semmelhack, M. F. Nucleophilic Addition to Arene-Metal Complexes. In *Comprehensive Organic Synthesis*; Pergamon Press: New York, 1991; pp 517−549.

(55) (a) Kundig, E. P.; Perret, C.; Spichiger, S.; Bernardinelli, G. J. *J. Organomet. Chem.* **1985**, *286*, 183. (b) Kundig, E. P.; Leresche, J. *Tetrahedron* **1993**, *49*, 5599.

(56) The reduction to the hydroxy lactams was performed with sodium borohydride and was followed by decomplexation with iodine. Further reduction to **2** and **89** was accomplished with phenylselenol.

(57) (a) Schroeder, D.; Lam, K. S.; Mattel, J.; Hesler, G. A. Eur. Pat. 0,388,962, Mar 22, 1990. (b) Koshino, H.; Osada, H.; Isono, K. *J. Antibiot.* **1992**, *45*, 195.

Scheme 17



and *ent*-isostaurosporine (**89**) was then accomplished with phenylselenol and *p*-toluenesulfonic acid. Compounds **2** and **89** were each isolated in a homogeneous state from the 1:1 mixture generated from this two-step sequence. This completed the total synthesis of *ent*-staurosporine (**2**). The synthetic material was identical to a natural sample of **1** by ^{1}H-NMR, ^{13}C-NMR, IR, mass spectroscopy, and TLC characteristics. The rotation was also nearly equal in magnitude and was opposite in sign.

With this chemistry worked out in the *ent*-series, the path to a total synthesis of staurosporine (**1**) was clear (Scheme 17). We started with tri-*O*-acetyl-L-glucal **90** and converted it to oxazolidinone **91**. Coupling to the aglycon, deoxygenation, photocyclization, and exposure of the exo-glycal provided **92**. The key cyclization then gave **93**. Opening the oxazolidinone, methylation, deprotection, and reduction provided staurosporine (**1**) and isostaurosporine (**94**). The synthetic material was identical to a natural sample by ^{1}H-NMR, ^{13}C-NMR, IR, mass spectroscopy, optical rotation, and TLC characteristics. The first total synthesis of staurosporine (**1**) had thus been accomplished.

Biological Results: Protein Kinase C Modulating Activity of Staurosporine and *ent*-Staurosporine and Implications for the Binding Site. We have evaluated *ent*-staurosporine (**2**), *ent*-isostaurosporine (**89**), a related imide **82**, and their corresponding enantiomers for their *in vitro* antitumor activity, their capacity to inhibit PKC (Table 1), and their ability to inhibit topoisomerase I. Two cell lines and three human PKC isoenzymes were targeted for this study. The results provide an interesting insight into the finer structural features effects upon the potency of PKC inhibition, antitumor activity, and topoisomerase I inhibition.

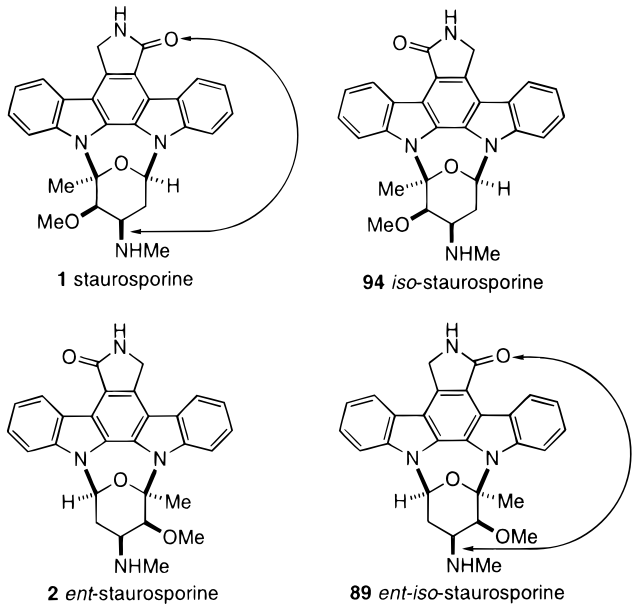
The inhibition data for PKC isoenzyme α are illustrative of the trend observed among these compounds. Staurosporine (**1**) is a much more potent inhibitor than isostaurosporine (**94**). The activity is somewhat recovered by *ent*-staurosporine (**2**) and nearly fully recovered by *ent*-isostaurosporine (**89**). We take this trend to indicate that the spatial arrangement of the lactam carbonyl and pyranosyl methylamino group is important for activity. This sense of arrangement is the same in staurosporine (**1**) as it is in *ent*-isostaurosporine (**89**).

Table 1. PKC Inhibition and *in Vitro* Cytotoxicity

compound	PKC inhibition: IC_{50} (μM)		cytotoxicity[a] HL-60	833K
staurosporine (**1**)	α	0.02		
	β1	<0.005	0.014	0.0065
	β2	<0.005		
ent-staurosporine (**2**)	α	0.29		
	β1	0.19	3.84	0.312
	β2	0.15		
isostaurosporine (**94**)	α	0.98		
	β1	0.08	2.39	0.55
	β2	0.05		
ent-isostaurosporine (**89**)	α	0.03		
	β1	0.02	6.55	0.272
	β2	0.01		
imide **95** (*ent*-**82**)	α	1.25		
	β1	0.25	1.68	0.74
	β2	0.10		
imide **82**	α	0.24		
	β1	0.02	593	454
	β2	0.03		

[a] Cytotoxicities are given as IC_{50}'s in μM units.

Scheme 18



By this reasoning the data also suggests that the $C_{3'}$ methoxy and $C_{1'}$ methyl group do not seriously contribute to this proposed secondary "pitch factor" (see arrows in Scheme 18). Otherwise, *ent*-isostaurosporine (**89**) and staurosporine (**1**) would not exhibit similar potencies.

The drop in activity of isostaurosporine (**94**) relative to staurosporine and the drop in activity observed in both enantiomers of imides **82** and **95** indicates that a carbonyl group at C_7 of the aglycon weakens PKC inhibition as well as cytotoxicity. It is also interesting that the *in vitro* cytotoxicity experiments in the 833K tumor cell line mirror the PKC inhibitory potency. However in the HL-60 cell line, the compounds are less potent, and the trend is not necessarily reliable.

The cytotoxicity of indolocarbazole alkaloids can also be effected by a different mechanism than inhibition of PKC, i.e. inhibition of topoisomerase I (Table 2). We have measured the topoisomerase I inhibition induced by these compounds in

(58) Caravatti, G.; Meyer, T.; Fredenhagen, A.; Trinks, U.; Mett, H.; Fabbro, D. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 399.

Table 2. Topo I Inhibition

	topo I inhibition[a]	
compound	DNA cleavage	inhibition of supercoiled DNA relaxation
staurosporine (**1**)	++	+
ent-staurosporine (**2**)	++	+
isostaurosporine (**94**)	++	+
ent-isostaurosporine (**89**)	+++	+
imide **95** (*ent*-**82**)	++	++++
imide **82**	+	+
camptothecin	++++	++++

[a] Relative potencies are compared with camptothecin (++++) at 100 μM.

two assays. In one assay the relative DNA cleavage relative to the known topoisomerase inhibitor camptothecin (cytotoxicities in the HL-60 cell line IC_{50} of 0.005 μM and in the 833K cell line IC_{50} of 0.017 μM) was determined. In the second assay the inhibition of the relaxation of supercoiled DNA again relative to camptothecin was measured. All of the compounds showed activity; however, *ent*-isostaurosporine (**89**) showed the greatest capacity to mediate DNA cleavage. Surprisingly this did not lead to a corresponding leap in cytotoxicity. It is also interesting to note that imide **95** showed the capacity to inhibit the relaxation of supercoiled DNA roughly as well as camptothecin itself.

Conclusions

The first total synthesis of the indolocarbazole alkaloid staurosporine (**1**) has been completed. Glycosylation protocols were developed to construct both glycosidic bonds from glycal precursors. *En route*, the total synthesis of *ent*-staurosporine (**2**) was also completed. This work provided compounds with which to compare PKC inhibition capacity and *in vitro* antitumor activity in the *ent*-series with those related to the natural enantiomer. These studies revealed that the spatial disposition of the lactam C_5 carbonyl and pyranosyl $C_{4'}$ methylamino group are stronger determinants for activity than the corresponding disposition of the $C_{3'}$ methoxy and $C_{1'}$ methyl groups.

Experimental Section

General Methods. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 400, Varian 300, or Bruker WM-250. Infrared spectra were recorded on a Perkin Elmer Model 1420 spectrometer or Perkin Elmer 1600 Series FTIR. Optical rotations were measured on a Jasco DIP-370 polarimeter. Combustion analyses were performed by Robertson Microlit Laboratories, Inc. (Madison, NJ). Mass spectra were obtained on a JEOL JMS-DX-303 HF or Kratos Model MS-80 RFA spectrometer. Analytical chromatography was performed on E. Merck silical gel 60 F_{254} plates (0.25 mm). Flash chromatography was performed on Selecto Scientific silica gel (particle size 32−63). Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2), acetonitrile, benzene (PhH), triethylamine, and pyridine were distilled from calcium hydride. *N*,*N*-Dimethylformamide (DMF) was purchased from Aldrich in sure-seal containers. Methanol was distilled from $Mg(OMe)_2$. All other commercially obtained reagents were used as received. Analytical data has been recorded for compounds derived from tri-*O*-acetyl-D-glucal and leading to *ent*-staurosporine and are reported herein. ^{1}H NMR spectra for all compounds derived from tri-*O*-acetyl-L-glucal, which provided staurosporine, matched and the optical rotations were nearly equal in magnitude and opposite in sign.

Protein kinase C isoenzymes were partially purified from baculovirus infected Sf9 cells expressing the recombinant human PKC α, βI, or βII enzymes and the activity was measured *in vitro* as previously described.[59]

Staurosporine, its analogs, and camptothecin (as a positive control) were evaluated for their cytotoxic effects on the growth of HL-60 (human promyelocytic leukemic) and 833K (human teratocarcinoma) cells. The cells were cultured in an initial density of 5×10^4 cell/mL. The cells were maintained in a 5% CO_2 humidified atmosphere at 37 °C in RPMI-1640 media (GIBCO-BRL, Grand Island, NY) containing penicillin (100 μg/mL)/streptomycin (100 μg/mL) (GIBCO-BRL) and 10% heat inactivated fetal bovine serum. The assay was done in duplicate in 96 well microplates. The cytotoxicity of the compounds toward HL-60 cells following 72 h incubation was determined by XTT-microculture tetrazolium assay.[60] 2′,3′-Bis(methoxy-4-nitro-5-sulfophenyl)-5-[(phenylamino)carbonyl]-2*H*-tetrazolium hydroxide (XTT) was prepared at 1 mg/mL in prewarmed (37 °C) medium without serum. Phenazine methosulfate (PMS) and fresh XTT were mixed together to obtain 0.075 mM PMS-XTT solution (25 μL of the stock 5 mM PMS was added per 5 mL of 1 mg/mL XTT). Fifty microliters of this mixture was added to each well of the cell culture at the end of 72 h of incubation. After incubation at 37 °C for 4 h, absorbance at 450 and 630 nm was measured with a microplate reader (EL 340, Bio-Tek Instruments, Inc., Winooski, VT).

The cytotoxicity of the staurosporine analogs toward 833K teratocarcinoma solid tumor cells was determined in 96-well microplates by a method described by Skehan for measuring the cellular protein content.[61] Cultures were fixed with trichloroacetic acid and then stained for 30 min with 0.4% sulforhodamine B dissolved in 1% acetic acid. Unbound dye was removed by acetic acid washes, and the protein bound dye was extracted with an unbuffered Tris base [tris(hydroxymethyl)-aminomethane] for determination of optical density at 570 nm in a 96 well microplate reader. The experiments were carried out in duplicate each using five to six concentrations of the drugs tested. Data were analyzed utilizing computer software.[62]

Topo I Mediated DNA Cleavage Assay. For DNA cleavage assay the reaction mixture consisted of Tris-HCE buffer 10 mM, pH 7.5; PBR_{322} supercoiled double stranded circular DNA (4363 base pairs, from Boehringer Mannheim Biochemicals) 0.125 μg/mL, drug (staurosporine analog or camptothecin) concentration at 1, 10, and 100 μM, in the presence of nuclear extract partially purified for DNA topoisomerase I as described previously (20 μg protein) with final volume of 20 μL.[63] Incubation was carried out at 37 °C for 60 min. The reaction was stopped by adding the loading buffer dye (2% sodium dodecyl sulfate, 0.05% bromophenol blue and 6% glycerol). Electrophoresis was carried out on 1% agarose gel + ethidium bromide (1 μg/mL) in TBE buffer (Tris−base−boric acid−EDTA) and ran at 25 V for 18 h. Photographs were taken under UV light using Polaroid film type 55/N and developed as indicated by the manufacturer.

Inhibition of Topo I Mediated Relaxation of Supercoiled DNA. The method described by Liu and Miller was used to study the inhibiting effect on topo I mediated relaxation of DNA.[64] For this assay, 0.18 mg of PBR_{322} DNA, 0.5 units of Topo I (GIBCO-BRL, Grand Island, NY), and various concentrations of staurosporine analog or camptothecin in a reaction buffer were used. The reaction mixture (20 μL) was incubated at 37 °C for 30 min, and stopped with 5% SDS and 150 μg/mL proteinase K. The samples were loaded on to 1% agarose in TAE running buffer, electrophoresed overnight at 39 V, stained with EtBr, and photographed under UV light.

3-Amino-1,5-anhydro-2,3-dideoxy-3-*O*,4-*N*-[(trichloromethyl)-oxazolino]-6-*O*-(triisopropylsilyl)-D-*ribo*-hex-1-enopyranose (16). To a clear, colorless solution of 53.55 g (177.0 mmol) of diol **14** in 1.0 L

(59) Toker, A.; Meyer, M.; Reddy, K. K.; Falck, J. R.; Aneja, R.; Aneja, S.; Parra, A.; Burns, D. J.; Ballas, L. M.; Cantley, L. C. *J. Biol. Chem.* **1994**, *269*, 32358.

(60) Scudiero, D. A.; Showmaker, R. H.; Paull, K. D.; Monks, A.; Tieney, S.; Hafziget, T. H.; Currens, J. J.; Sheriff, D.; Boyd, M. R. *Cancer Res.* **1988**, *48*, 4827.

(61) Skehan, P.; Storeng, R.; Scudiero, D. *J. Natl. Cancer Inst.* **1990**, *82*, 1107.

(62) Chou, J.; Chou, T. C. Dose−effect analysis with microcomputers: Quantitation of ED_{50}, LD_{50}, synergism, antagonism, low-dose risk, receptor−ligand binding and enzyme kinetics, 2nd ed.; Biosoft: Cambridge, U.K., 1987.

(63) Hsian, Y. H.; Hertzberg, S. H.; Liu, L. F. *J. Biol. Chem.* **1985**, *260*, 14873.

(64) Liu, L. F.; Miller, K. G. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *260*, 14873.

of CH_2Cl_2 at 0 °C was added 15.93 g (398.4 mmol, 60% dispersion) of NaH. The reaction bubbled and was stirred at 0 °C for 30 min. Following the addition of 175.0 mL (1770 mmol) of trichloroacetonitrile, the reaction was slowly warmed to ambient temperature and stirred overnight. The resulting brown solution was cooled to −78 °C and 23.9 mL (194.4 mmol) of $BF_3{\cdot}OEt_2$ was added. After stirring for 5 h at −78 °C the reaction was quenched at −78 °C with 300 mL of saturated $NaHCO_3$. The reaction was then slowly warmed to ambient temperature. The crude products were diluted with EtOAc and extracted with H_2O and brine. The aqueous layers were then extracted with EtOAc, and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (98:2 → 6:4 → 9:1 hexane:EtOAc) to yield 59.23 g (78%) of **16** as a clear, colorless oil: R_f 0.38 (9:1 hexane:EtOAc); $[\alpha]^{20}_D$ +87.3° (*c* 2.28, CH_2Cl_2); IR (film) 2920, 1660, 1460, 1240, 1125, 980, 800 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.57 (dd, J = 6.0, 1.9 Hz, 1H), 5.17 (dd, J = 6.0, 4.2 Hz, 1H), 5.08 (app t, J = 9.1, 8.7 Hz, 1H), 4.61 (ddd, J = 8.7, 4.2, 1.9 Hz, 1H), 3.99 (dd, J = 11.4, 2.4 Hz, 1H), 3.88 (dd, J = 11.4, 3.8 Hz, 1H), 3.45 (ddd, J = 9.1, 3.8, 2.4 Hz, 1H), 1.01 (app s, 21H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 161.9, 147.0, 99.8, 86.6, 77.3, 73.6, 62.2, 60.9, 17.8, 11.9.

1,5-Anhydro-2,3-dideoxy-3-(trichloroacetamido)-6-*O*-(triisopropylsilyl)-D-*ribo*-hex-1-enopyranose (17). To a clear, colorless solution of 50.88 g (118.7 mmol) of **16** in 1 L of pyridine and 200 mL of water was added 0.4515 g (2.373 mmol) of *p*-toluenesulfonic acid monohydrate. The reaction was heated to 80 °C until the disappearance of starting material was complete (ca. 14 h). The resulting brown solution was cooled, and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (6:1 hexane:EtOAc) on silica gel to provide 42.42 g (80%) of **17** as a clear, colorless oil: R_f 0.41 (4:1 hexane:EtOAc); $[\alpha]^{20}_D$ +121° (*c* 2.02, CH_2Cl_2); IR (CH_2Cl_2) 3345, 2875, 2800, 1745, 1615, 1510, 1210, 1095, 795 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.97 (br d, J = 6.3 Hz, 1H), 6.35 (dd, J = 6.0, 1.2 Hz, 1H), 4.79 (dd, J = 6.0, 4.5 Hz, 1H), 4.37 (m, 1H), 4.07 (m, 1H), 3.73−3.98 (m, 3H), 3.30 (d, J = 4.1 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 162.3, 145.7, 97.3, 92.6, 75.0, 66.7, 63.3, 45.8, 17.8, 11.8; HRMS *m*/*e* calcd for EI (M + H) $C_{17}H_{31}N_1O_4Cl_3Si_1$ 446.1087, found 446.1081. Anal. Calcd for $C_{17}H_{30}N_1O_4Cl_3Si_1$: C, 45.69; H, 6.77; N, 3.13; Cl, 23.80. Found: C, 45.67; H, 6.47; N, 2.99; Cl, 23.49.

3-Amino-1,5-anhydro-3-*N*,4-*O*-carbonyl-2,3-dideoxy-6-*O*-(triisopropylsilyl)-D-*ribo*-hex-1-enopyranose (18). To a clear, colorless solution of 42.42 g (101.9 mmol) of glycal **17** in 575 mL of CH_2Cl_2 at 0 °C was added 4.56 g (113.9 mmol, 60% dispersion) of NaH. The reaction bubbled, was warmed slowly to ambient temperature, and was stirred overnight. The reaction was quenched with H_2O, diluted with EtOAc, extracted with H_2O, rinsed with brine, and dried over Na_2SO_4. After filtration and concentration *in vacuo*, purification by flash chromatography (2:3 hexane:EtOAc) on silica gel provided 28.79 g (97%) of glycal **18** as a white solid: mp 136−137 °C; R_f 0.38 (1:1 hexane:EtOAc); $[\alpha]^{20}_D$ +108.1° (*c* 3.075, CH_2Cl_2); IR (film) 3300, 2920, 2850, 1770, 1730, 1630, 1240 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.70 (s, 1H), 6.55 (d, J = 5.9 Hz, 1H), 4.83 (m, 2H), 4.30 (dd, J = 7.5, 3.9 Hz, 1H), 3.95 (m, 2H), 3.78 (m, 1H), 1.02 (s, 21H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.1, 146.7, 98.9, 74.0, 71.1, 61.8, 46.1, 17.8, 11.9; FAB HRMS *m*/*e* calcd for (M + H) $C_{16}H_{30}N_1O_4Si_1$ 328.1944, found 328.1933.

1,5-Anhydro-3-[[(benzyloxy)methyl]amino]-3-*N*,4-*O*-carbonyl-2,3-dideoxy-6-*O*-(triisopropylsilyl)-D-*ribo*-hex-1-enopyranose (19a). To a clear, colorless solution of 28.79 g (92.43 mmol) of glycal **18** in 225 mL of DMF was added 2.49 g (101.7 mmol, 60% dispersion) of NaH. After stirring for 30 min, 15.4 mL (110.9 mmol) of BOMCl and 1.7071 g (4.62 mmol) of tetrabutylammonium iodide were added and the reaction was heated to 40 °C for 10 h. The reaction was cooled to rt, quenched with 100 mL of H_2O, diluted with ether, and extracted with H_2O (3×). After a brine rinse, the crude products were dried with Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (5:1 → 4:1 → 1:1 hexane:EtOAc) on silica gel yielded 27.13 g (65%) of **19a** as a clear, colorless oil along with 6.42 g (22%) of recovered glycal **18** as a white solid: R_f 0.68 (1:1 hexane:EtOAc); $[\alpha]^{20}_D$ +98.8° (*c* 6.52, CH_2Cl_2); IR (film) 2940, 2860, 1770, 1650, 1260, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H), 6.67 (d, J = 5.9 Hz, 1H), 5.02 (d, J = 11.0 Hz, 1H), 5.00 (app t, J = 5.9, 4.2 Hz, 1H), 4.72 (d, J = 11.0 Hz, 1H), 4.78 (app t, J = 9.1, 7.6 Hz, 1H), 4.57 (s, 2H), 4.28 (dd, J = 7.6, 4.2 Hz, 1H), 4.03 (m, 2H), 3.56 (dt, 9.1, 2.7, 1H), 1.07 (m, 21H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 156.9, 148.2, 137.3, 128.4, 127.8, 127.7, 96.1, 74.2, 72.5, 70.7, 68.1, 61.5, 47.8, 17.8, 11.8; FAB HRMS *m*/*e* calcd for (M + Na) $C_{24}H_{37}N_1O_5Na_1Si_1$ 470.2332, found 470.2332.

1,5-Anhydro-3-[[(benzyloxy)methyl]amino]-3-*N*,4-*O*-carbonyl-2,3-dideoxy-D-*ribo*-hex-1-enopyranose (20a). To a clear, colorless solution of 27.13 g (57.2 mmol) of glycal **19a** in 500 mL of THF at 0 °C was added 60.2 mL of tetrabutylammonium fluoride (60.2 mmol, 1.0 M solution in THF). Over 15 min the reaction turned from clear to yellow to light brown and was complete. The crude reaction mixture was diluted with EtOAc and extracted with H_2O (3×). The combined aqueous layers were extracted with EtOAc (2×), and the combined organic layers were rinsed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (2:1 → 3:1 EtOAc:hexane) on silica gel provided 16.67 g (95%) of glycal **20a** as a clear, colorless oil: R_f 0.30 (1:2 hexane:EtOAc); $[\alpha]^{20}_D$ +92.2° (*c* 1.275, CH_2Cl_2); IR (film) 3430, 2880, 1750, 1640, 1250, 1070 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.31 (app s, 5H), 6.63 (d, J = 6.1 Hz, 1H), 5.01 (dd, J = 6.1, 4.3 Hz, 1H), 4.96 (d, J = 11.0 Hz, 1H), 4.66 (d, J = 11.0 Hz, 1H), 4.62 (app t, J = 7.7 Hz, 1H), 4.53 (s, 2H), 4.25 (m, 1H), 3.95 (m, 1H), 3.82 (m, 1H), 3.55 (m, 1H), 2.47 (br s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 156.8, 147.9, 137.3, 128.4, 127.9, 127.8, 96.8, 74.0, 72.6, 70.8, 68.1, 60.8, 47.9; FAB HRMS *m*/*e* calcd for (M + Na) $C_{15}H_{17}N_1O_5Na_1$ 314.1005, found 314.1018.

1,5-Anhydro-3-[[(benzyloxy)methyl]amino]-3-*N*,4-*O*-carbonyl-2,3-dideoxy-6-*O*-(4-methoxybenzyl)-D-*ribo*-hex-1-enopyranose (21a). To a clear, colorless solution of 16.67 g (57.2 mmol) of **20a** in 400 mL of DMF at 0 °C was added 2.40 g (60.0 mmol, 60% dispersion) of NaH. The reaction darkened and was stirred at 0 °C for 10 min and at ambient temperature for 10 min before being cooled back to 0 °C and treated with 10.9 mL (80.1 mmol) of PMBCl. The reaction was slowly warmed to ambient temperature and stirred for 4 h. The crude reaction mixture was diluted with Et_2O, extracted with H_2O (3×), rinsed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (1:1 hexane:EtOAc) on silica gel yielded 21.66 g (92%) of **21a** as a clear, colorless oil: R_f 0.42 (1:1 hexane:EtOAc); $[\alpha]^{20}_D$ +100.13° (*c* 0.76, CH_2Cl_2); IR (film) 2860, 1760, 1650, 1510, 1250, 1040 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.339 (app s, 5H), 7.25 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.65 (dd, J = 6.0, 0.71 Hz, 1H), 5.02 (app t, J = 6.0, 4.2 Hz, 1H), 4.98 (d, J = 11.1 Hz, 1H), 4.95 (app t, J = 9.0, 7.8 Hz, 1H), 4.69 (d, J = 11.1 Hz, 1H), 4.56 (s, 2H), 4.52 (m, 2H), 4.25 (m, 1H), 3.80 (s, 3H), 3.63−3.83 (m, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 159.4, 156.8, 148.1, 137.4, 129.7, 129.4, 128.5, 127.9, 127.8, 113.9, 96.6, 73.4, 73.2, 72.6, 70.9, 68.6, 67.7, 55.2, 48.0; FAB HRMS *m*/*e* calcd for (M + Na) $C_{23}H_{25}N_1O_6Na_1$ 434.1580, found 434.1578.

Methyl 2-*O*-Acetyl-3-[[(benzyloxy)methyl]amino]-3-*N*,4-*O*-carbonyl-6-*O*-(4-methoxybenzyl)-α-D-altropyranoside (23a). A 10 mL (ca. 1.0 M in acetone) solution of 3,3-dimethyldioxirane was added dropwise to a clear, colorless solution of 0.1305 g (0.3172 mmol) of **21a** in CH_2Cl_2 at 0 °C and was stirred until **21a** was consumed by TLC. The reaction was then concentrated *in vacuo* and left on a high vacuum pump for 30 min. The flask was then cooled to 0 °C, and 8.0 mL of MeOH was added. The reaction was slowly warmed to ambient temperature and stirred for 2 h. The reaction was concentrated *in vacuo* and left on a high vacuum pump for 30 min. After dissolving in 6.0 mL of pyridine and cooling to 0 °C, a crystal of DMAP and 0.15 mL (1.59 mmol) of Ac_2O were added. The resulting mixture was slowly warmed to ambient temperature and stirred for 2 h. The reaction was then concentrated *in vacuo*, and the products were purified by flash chromatography (1:1 hex:EtOAc) on silica gel (3× to completely separate) to provide 0.1119 g (70%) of **23a** and 0.0457 g (29%) of **23b** both as clear, colorless oils: R_f 0.47 (1:1 hexane:EtOAc); $[\alpha]^{20}_D$ +1.166° (*c* 2.405, CH_2Cl_2); IR (film) 2940, 1730, 1610, 1515, 1375, 1230, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (app s, 5H), 7.28 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.13 (t, J = 4.2, 3.3 Hz, 1H), 4.92 (d, J = 11.0 Hz, 1H), 4.83 (d, J = 3.3 Hz, 1H), 4.65 (d, J = 11.0 Hz, 1H), 4.51 (s, 2H), 4.48−4.55 (m, 3H), 4.30 (dd, J = 8.7, 4.2 Hz, 1H), 4.02 (m, 1H), 3.79 (s, 3H), 3.65 (dd, J = 10.7, 3.0 Hz, 1H), 3.56 (dd, J = 10.7, 5.3 Hz, 1H), 3.42 (s, 3H), 2.02 (s, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.3, 159.4, 157.3, 137.5, 129.8, 129.3, 128.4, 127.8, 127.6, 113.8, 99.0, 73.8, 73.4, 71.0, 68.7, 67.8, 67.4, 66.8, 55.5, 55.3, 54.8, 20.8; FAB HRMS *m*/*e* calcd for (M + H) $C_{26}H_{30}N_1O_9$ 500.1921, found 500.1935.

Methyl 2-*O*-Acetyl-3-[[(benzyloxy)methyl]amino]-3-*N*,4-*O*-carbonyl-6-*O*-(4-methoxybenzyl)-*β*-D-allopyranoside (23b): R_f 0.40 (1:1 hexane:EtOAc); $[\alpha]^{20}_D$ +10.4° (*c* 5.5, CH_2Cl_2); IR (film) 2930, 1760, 1600, 1520, 1370, 1230, 1075 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.18 (t, *J* = 4.2, 2.4 Hz, 1H), 4.94 (d, *J* = 11.4 Hz, 1H), 4.77 (d, *J* = 11.4 Hz, 1H), 4.68 (d, *J* = 2.4 Hz, 1H), 4.59 (m, 1H), 4.58 (d, *J* = 11.8 Hz, 1H), 4.57 (d, *J* = 11.7 Hz, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 3.93 (m, 2H), 3.79 (s, 3H), 3.67 (m, 2H), 3.32 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 171.1, 158.9, 158.2, 147.3, 129.3, 128.5, 129.9, 127.8, 113.9, 98.4, 76.6, 73.7, 73.3, 72.1, 71.1, 69.6, 69.5, 66.9, 56.1, 55.3, 51.1, 20.8; FAB HRMS *m*/*e* calcd for (M + H) $C_{26}H_{30}N_1O_9$ 500.1921, found 500.1931.

1,5-Anhydro-3-(benzylamino)-3-*N*,4-*O*-carbonyl-2,3-dideoxy-6-(methanesulfonyl)-D-*ribo*-hex-1-enopyranose (24). To a clear, colorless solution of 1.66 g (0.636 mmol) of glycal **20b** in 70 mL of pyridine at 0 °C was added 0.54 mL (0.70 mmol) of mesyl chloride. The resulting mixture was slowly warmed to ambient temperature and stirred overnight. The solvent was removed azeotropically with toluene *in vacuo*. The crude product was purified by flash chromatography (20:1 → 10:1 CH_2Cl_2:EtOAc) on silica gel giving 2.04 g (95%) of mesylate **24** as a clear, colorless oil: R_f 0.32 (67:33 hexane:EtOAc); $[\alpha]^{20}_D$ 67.2° (*c* 1.105, CH_2Cl_2); IR (film) 3020, 1755, 1645, 1405, 1355, 1255, 1175, 1045, 945 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.24−7.33 (m, 5H), 6.59 (d, *J* = 6.1 Hz, 1H), 4.88 (dd, *J* = 6.1, 4.4 Hz, 1H), 4.71 (d, *J* = 15.1 Hz, 1H), 4.42−4.58 (m, 3H), 4.09 (d, *J* = 15.1 Hz, 1H), 3.99 (dd, *J* = 7.4, 4.4 Hz, 1H), 3.78−3.84 (m, 1H), 3.02 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 156.4, 147.6, 135.1, 128.8, 128.1, 97.2, 77.2, 71.6, 67.5, 67.3, 48.4, 46.2, 37.5. Anal. Calcd for $C_{15}H_{17}N_1O_6S_1$: C, 53.09; H, 5.05; N, 4.13. Found: C, 52.98; H, 4.83; N, 4.02.

1,5-Anhydro-3-(benzylamino)-3-*N*,4-*O*-carbonyl-2,3,6-trideoxy-D-*ribo*-hexa-1,5-dienopyranose (25). To a clear, colorless solution of 1.324 g (3.9 mmol) of mesylate **24** in 150 mL of THF at −78 °C was added a precooled (−78 °C) solution of 0.5262 g (4.68 mmol) of potassium *tert*-butoxide in 50 mL of THF. The reaction was stirred at −78 °C for 1 h and at −40 °C for 2 h. The reaction was quenched with saturated NH_4Cl. The crude products were diluted with Et_2O, extracted with saturated $NaHCO_3$, rinsed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (1:1 hexane:EtOAc) gave 0.8539 g (90%) of diene **25** as a clear, colorless oil: R_f 0.40 (1:1 hexane:EtOAc); $[\alpha]^{20}_D$ 20.3° (*c* 1.965, CH_2Cl_2); IR (film) 3030, 2920, 1760, 1670, 1420, 1300, 1270, 1235, 1100, 995, 700 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.24−7.36 (m, 5H), 6.47 (d, *J* = 6.3 Hz, 1H), 4.91−4.93 (m, 2H), 4.78−4.82 (m, 2H), 4.75 (d, *J* = 14.9 Hz, 1H), 4.01−4.08 (m, 1H), 4.04 (d, *J* = 14.9 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 156.6, 148.9, 144.1, 135.5, 128.8, 128.1, 99.4, 95.6, 70.1, 49.3, 46.0; HRMS *m*/*e* calcd for $C_{14}H_{13}N_1O_3$ 243.0895, found (EI) 243.0868. Anal. Calcd for $C_{14}H_{13}N_1O_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.94; H, 5.39; N, 5.61.

Methyl Glycoside 27. To a clear, colorless solution of 0.085 g (0.3494 mmol) of diene **25** in 3.0 mL of CH_2Cl_2 at 0 °C was added 8 mL (ca. 1.0 M in acetone) of 3,3-dimethyldioxirane. After stirring for 30 min at 0 °C the starting material was consumed and the reaction was concentrated *in vacuo*. After 15 min on a high vacuum pump, the flask was cooled to 0 °C and 5.0 mL of methanol was added. The reaction was slowly warmed to ambient temperature and stirred overnight. The resulting yellow solution was concentracted *in vacuo*, dissolved in 5.0 mL of pyridine, cooled to 0 °C, and treated with a crystal of DMAP and 0.165 mL (1.747 mmol) of acetic anhydride. The reaction turned red and was slowly warmed to ambient temperature and stirred for 4 h. The reaction was concentrated *in vacuo*, and the product was purified by flash chromatography (1:1 → 1:2 hexane: EtOAc) on silica gel to provide 0.0750 g (65%) of methyl glycoside **27** as a clear, colorless oil: R_f 0.45 (1:1 hexane:EtOAc); $[\alpha]^{20}_D$ 90.0° (*c* 1.525, CH_2Cl_2); IR (film) 2935, 1765, 1660, 1420, 1230, 1075, 1005, 705 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.30 (app s, 5H), 4.99 (br s, 1H), 4.93 (app t, *J* = 1.8 Hz, 1H), 4.86 (d, *J* = 9.0 Hz, 1H), 4.83 (d, *J* = 15.1 Hz, 1H), 4.74 (d, *J* = 1.4 Hz, 1H), 4.50 (d, *J* = 1.4 Hz, 1H), 4.11 (d, *J* = 15.1 Hz, 1H), 3.66 (d, *J* = 9.0 Hz, 1H), 3.41 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.4, 156.9, 148.6, 135.7, 128.7, 128.4, 128.0, 98.2, 98.1, 69.7, 64.0, 55.8, 53.7, 45.7, 20.6; HRMS *m*/*e* calcd for $C_{17}H_{20}N_1O_6$ (M + H) 334.1291, found (FAB) 334.1292. Anal. Calcd for $C_{17}H_{19}N_1O_6$: C, 61.24; H, 5.75; N, 4.20. Found: C, 60.14; H, 5.52; N, 3.95.

Diacetate 29a. To a clear, colorless solution of 0.0309 g (0.1122 mmol) of diene **25** at 0 °C in 3.0 mL of CH_2Cl_2 was added excess 3,3-dimethyldioxirane (ca. 1.0 M in acetone). The reaction was allowed to stir for 20 min at 0 °C and all of the starting material was converted into mono-epoxides by TLC. The reaction was then warmed to ambient temperature, and excess 3,3-dimethyldioxirane (ca. 1.0 M in acetone) was added in two portions. After stirring for 30 min the mono-epoxides had been converted to bis-epoxides by TLC. The reaction was then concentrated *in vacuo* and placed under high vacuum for 30 min. The bis-epoxides were dissolved in 1.0 mL of THF, cooled to −78 °C, and treated with 1.0 mL of methanol and a solution of 0.22 mL (0.22 mmol, 1.0 M in Et_2O) of $ZnCl_2$. The reaction was slowly warmed to ambient temperature and stirred for 12 h. The crude products were concentrated and flash chromatographed (4:1 to 6:1 EtOAc:hexane) on silica gel. This yielded two products which were acetylated separately in 0.5 mL of pyridine, DMAP (one crystal), and excess acetic anhydride for 1 h. Each acetylation was concentrated *in vacuo*, and the products were each purified by flash chromatography (15:1 EtOAc:hexane) on silica gel to give 0.0086 g (18%) of methyl glycoside **29b** as a clear, colorless oil and 0.0375 g (80%) of methyl glycoside **29a** as a clear, colorless oil: mp 112−113 °C; R_f 0.22 (1:1 hexane:EtOAc); $[\alpha]^{20}_D$ +52.7° (*c* 0.74, CH_2Cl_2); IR (neat) 2950, 1740, 1420, 1370, 1290, 1070, 915, 705 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.26−7.32 (m, 3H), 7.12−7.15 (m, 2H), 5.64 (app t, *J* = 7.5, 7.6 Hz, 1H), 4.94 (d, *J* = 15.7 Hz, 1H), 4.67 (d, *J* = 10.4 Hz, 1H), 4.50 (d, *J* = 11.9 Hz, 1H), 4.44 (d, *J* = 7.5 Hz, 1H), 4.05 (d, *J* = 11.9 Hz, 1H), 3.89 (d, *J* = 15.7 Hz, 1H), 3.88 (app t, *J* = 10.4, 7.6 Hz, 1H), 3.4 (s, 6H), 2.1 (s, 3H), 2.0 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.1, 169.0, 157.3, 135.1, 128.8, 127.9, 127.5, 99.0, 97.2, 71.9, 70.6, 61.6, 56.2, 53.5, 49.8, 46.2, 21.1, 20.8; FAB HRMS *m*/*e* calcd for (M + Na) $C_{20}H_{25}N_1O_9Na_1$ 446.1427, found 446.1469.

Diacetate 29b: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.96 (t, *J* = 3.8, 3.3 Hz, 1H), 4.87 (d, *J* = 15.3 Hz, 1H), 4.72 (dd, *J* = 4.0, 0.5 Hz, 1H), 4.65 (d, *J* = 12.1 Hz, 1H), 4.47 (d, *J* = 8.0 Hz, 1H), 4.08 (d, *J* = 15.3 Hz, 1H), 3.95 (d, *J* = 12.1 Hz, 1H), 3.73 (dd, *J* = 8.1, 3.0 Hz, 1H), 3.39 (s, 3H), 3.21 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H); FAB HRMS *m*/*e* calcd for $C_{20}H_{25}N_1O_9$ 446.1458, found 446.1458.

Dissaccharide 30. To a solution of 0.0393 g (0.1615 mmol) of diene **25** in 3 mL of CH_2Cl_2 at 0 °C was added 5 mL of 3,3-dimethyldioxirane (ca. 1.0 M in acetone). The resulting mixture was stirred at 0 °C for 30 min and was concentrated *in vacuo* and dried on a high vacuum pump for 1 h. The resulting white solid was dissoved in 0.15 mL of THF, was cooled to −78 °C, and was cannulated into a solution of 0.1261 g (0.4846 mmol) of 1,2:3,4 di-*O*-isopropylidene-galactopyranose in 0.15 mL of THF at −78 °C. A solution of 0.32 mL (0.32 mmol, 1.0 M in Et_2O) of $ZnCl_2$ was then added. The reaction was warmed slowly to ambient temperature and stirred for 24 h. THF was added intermittantly to keep the reaction from going dry. The crude products were concentrated *in vacuo*, dissolved in pyridine, and treated with a crystal of DMAP and acetic anhydride. After 1 h the solution was concentrated *in vacuo* and flash chromatography (2:1 → 1:1 hexane:EtOAc) on silica gel yielded 0.0590 g (65%) of disacharride **30** as a clear, colorless oil: R_f 0.53 (1:1 hexane:EtOAc); $[\alpha]^{20}_D$ +23.7° (*c* 0.46, CH_2Cl_2); IR (film) 2985, 2935, 1760, 1657, 1375, 1230, 1070, 1005, 705 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.47 (d, *J* = 5.0 Hz, 1H), 5.09 (app t, *J* = 2.0, 1.7 Hz, 1H), 5.04 (app t, *J* = 1.2, 0.9 Hz, 1H), 4.85 (d, *J* = 9.3 Hz, 1H), 4.80 (d, *J* = 15.1 Hz, 1H), 4.74 (d, *J* = 1.4 Hz, 1H), 4.62 (dd, *J* = 8.0, 2.4 Hz, 1H), 4.51 (d, *J* = 1.4 Hz, 1H), 4.30 (dd, *J* = 5.0, 2.5 Hz, 1H), 4.20 (dd, *J* = 7.9, 1.8 Hz, 1H), 4.16 (d, *J* = 15.1 Hz, 1H), 4.03 (ddd, *J* = 9.2, 5.3, 1.7 Hz, 1H), 3.86 (dd, *J* = 9.0, 5.3 Hz, 1H), 3.68 (m, 2H), 2.03 (s, 3H), 1.59 (s, 3H), 1.42 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.4, 156.7, 148.6, 135.9, 128.8, 128.5, 128.0, 109.1, 108.9, 98.5, 97.3, 96.3, 70.8, 70.6, 70.4, 69.7, 66.2, 65.1, 64.2, 53.9, 45.9, 26.0, 25.9, 25.0, 24.5, 20.7; FAB HRMS *m*/*e* calcd for (M + Na) $C_{28}H_{35}N_1O_{11}Na_1$ 584.2109, found 584.2075.

1-[(Benzyloxy)methyl]-4-bromo-3,4-dihydro-3-[1*H*-indol-3-yl]-1*H*-pyrrole-2,5-dione (41). A solution of indole Grignard was prepared by treating a clear, colorless solution of 11.89 g (31.7 mmol) of indole in 200 mL of PhH dropwise with 11.1 mL (33.3 mmol, 3 M in Et_2O) of MeMgI. The reaction bubbled vigorously and after 1 h was cannulated (dropwise) into a clear, colorless vigorously stirred solution of 11.89 g (31.70 mmol) of dibromomaleimide **40** in 200 mL of PhH which had just been placed in an ice bath. The reaction turned blue initially and, as the entire solution was transferred, turned black. The resulting mixture was slowly warmed to ambient temperature and vigorously stirred overnight. The resulting red solution was diluted with acetone, preabsorbed onto silica gel, and purified by flash chromatography (2:1 hexane:EtOAc) on silica gel to yield 10.61 g (82%) of monoindole maleimide **41** as a red solid: mp 138−139 °C; R_f 0.30 (2:1 hexane:EtOAc); IR (film) 3350, 1720, 1700, 1600, 1420, 1345, 1070, 745 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 11.31 (s, 1H), 8.15 (d, J = 6.8 Hz, 1H), 7.98 (m, 2H), 7.55 (m, 1H), 7.16−7.36 (m, 7H), 5.15 (s, 2H), 4.66 (s, 2H).

1-[(Benzyloxy)methyl]-4-bromo-3,4-dihydro-3-(1-[2-(trimethylsilyl)ethoxy]-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (42). To a red solution of 10.61 g (25.8 mmol) of **41** in 400 mL of THF was added 1.08 g (27.1 mmol, 60% dispersion) of NaH. The reaction bubbled and turned purple. After 20 min, 5.7 mL (32.2 mmol) of SEMCl was added. The reaction turned back to red and was stirred for 1 h. The reaction was diluted with EtOAc, extracted with H_2O, and rinsed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (4:1 hexane:EtOAc) on silica gel gave 12.71 g (91%) of **42** as a red solid: IR (film) 2940, 1770, 1720, 1600, 1340, 1075 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 8.17 (s, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.22−7.36 (m, 7H), 5.74 (s, 2H), 5.14 (s, 2H), 4.66 (s, 2H), 3.62 (t, J = 8.1 Hz, 2H), 0.91 (t, J = 8.1 Hz, 2H), −0.07 (s, 9H); ^{13}C NMR (74.5 MHz, acetone-d_6) δ 169.9, 168.5, 139.1, 137.7, 134.7, 134.0, 129.0, 128.2, 124.1, 123.9, 122.1, 121.9, 111.9, 111.8, 78.8, 71.9, 68.8, 66.7, 18.2, −1.4; MS *m/e* calcd for FAB (M^+) $C_{26}H_{29}N_2O_4Si_1Br_1$ 540.1089, found 540.1080.

1-[(Benzyloxy)methyl]-3,4-dihydro-4-(1*H*-indol-3-yl)-3-(1-[2-(trimethylsilyl)ethoxy]-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (43). To a vigorously stirred, red solution of 12.71 g (23.5 mmol) of monoindole **42** in 200 mL of PhH which had just been placed in an ice bath was cannulated (dropwise over 20 min) a solution of 150 mL (0.16 M in PhH) of indole Grignard. The reaction turned from red to purple to black, the ice bath was removed, and the reaction was vigorously stirred overnight. The products were diluted with acetone, preabsorbed on silica gel, and purified by flash chromatography (4:1 → 2:1 hexane:EtOAc) to yield 10.2 g (75%) of bis-indolyl maleimide **43** as a red solid: mp 74−75 °C; R_f 0.60 (1:1 hexane:EtOAc); IR (film) 3350, 2925, 1750, 1690, 1600, 1525, 1350, 1075, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (br s, 1H), 7.83 (s, 1H), 7.78 (s, 1H), 7.48 (d, J = 8.2 Hz, 1H), 7.43 (d, J = 8.3 Hz, 2H), 7.27−7.37 (m, 4H), 7.14 (m, 2H), 7.00 (d, J = 8.1 Hz, 1H), 6.89 (d, J = 8.1 Hz, 1H), 6.78 (m, 2H), 5.55 (s, 2H), 5.26 (s, 2H), 4.75 (s, 2H), 3.55 (t, J = 8.1 Hz, 2H), 0.94 (t, J = 8.1 Hz, 2H), 0.01 (s, 9H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 171.8 (2), 136.3, 135.7, 131.9, 128.3, 128.1, 127.8, 127.7, 126.7, 125.5, 122.7, 122.6, 122.1, 121.9, 120.7, 120.4, 111.2, 110.2, 76.1, 71.6, 67.2, 66.1, 17.8, −1.4; MS *m/e* calcd for FAB (M^+) $C_{34}H_{35}N_3O_4Si_1$ 577.2397, found 577.2365.

1-[(Benzyloxy)methyl]-3,4-dihydro-4-([3-[[(benzyloxy)methyl]-amino]-3-*N*,4-*O*-carbonyl-6-*O*-(4-methoxybenzyl)-α-D-altropyranosyl]-1*H*-indol-3-yl)-3-(1-[2-(trimethylsilyl)ethoxy]-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (44). To a clear, colorless solution of 0.9217 g (2.24 mmol) of **21a** in 5.0 mL of CH_2Cl_2 at 0 °C was added 40 mL of 3,3-dimethyldioxirane (ca. 0.1 M in acetone) until the glycal was consumed by TLC. The resulting solution of 1,2-anhydrosugars was concentrated *in vacuo* and dried on a high vacuum pump for 1 h yielding a slightly yellow foam. The mixture of 1,2-anhydrosugars was then dissolved in 10 mL of THF to yield a slightly yellow, clear solution. In a separate flask, a red solution of 0.8628 g (1.493 mmol) of **43** in 10 mL of THF at ambient temperature was treated with 0.0627 g (1.57 mmol, 60% dispersion) of NaH. The vigorously stirred solution turned purple and after 30 min was chilled to 0 °C, and the solution of 1,2-anhydrosugars in THF was added dropwise via a cannula. The purple reaction was then stirred at 0 °C for 15 min and ambient temperature for 15 min and then was slowly heated to reflux for 1 h. The resulting red solution was cooled, diluted with EtOAc, extracted with $NaHCO_3$, rinsed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (9:1 CH_2Cl_2:Et_2O) on silica gel to yield 0.7055 g (47%) of **44** as a red solid: mp 88−90 °C (sublimes); R_f 0.4 (1:1 hexane:EtOAc); $[\alpha]^{20}_D$ −1.2° (*c* 1.66, CH_2Cl_2); IR (film) 3360, 2900, 1735, 1680, 1585, 1330, 1055, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.73 (s, 1H′), 7.22−7.47 (m, 14H), 7.12 (t, J = 8.8 Hz, 4H), 6.89 (t, J = 8.6 Hz, 3H), 6.83 (t, J = 7.3 Hz, 1H), 6.72 (t, J = 7.3 Hz, 1H), 5.95 (d, J = 9.1 Hz, 1H), 5.48 (s, 2H), 5.23 (s, 2H), 5.17 (d, J = 11.2 Hz, 1H), 4.71 (s, 2H), 4.70 (m, 4H), 4.52 (s, 2H), 4.12 (m, 2H), 3.96 (m, 2H), 3.80 (s, 3H), 3.63 (dd, J = 11.0, 3.8 Hz, 1H), 3.51 (t, J = 8.1 Hz, 2H), 0.91 (t, J = 8.1 Hz, 2H), −0.02 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 171.5, 159.5, 156.6, 137.7, 136.5, 136.3, 132.3, 129.4, 129.1, 128.7, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.1, 126.6, 126.2, 122.8, 122.7, 122.3, 120.9, 120.8, 120.6, 114.0, 110.5, 110.3, 107.7, 106.5, 82.1, 76.0, 74.0, 73.5, 72.4, 72.1, 71.8, 71.5, 70.8, 70.3, 67.1, 66.1, 60.6, 55.2, 17.6, −1.4; FAB HRMS *m/e* calcd for (M^+) $C_{57}H_{60}N_4O_{11}Si_1$ 1004.4030, found 1004.4060.

1-[(Benzyloxy)methyl]-3,4-dihydro-4-([3-[[(benzyloxy)methyl]-amino]-3-*N*,4-*O*-carbonyl-6-*O*-(4-methoxybenzyl)-2-*O*-[(pentafluorophenoxy)thiocarbonyl]-α-D-altropyranosyl]-1*H*-indol-3-yl)-3-(1-[2-(trimethylsilyl)ethoxy]-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (46). To a red solution of 3.0 g (2.98 mmol) of **44** plus some of anomer **45** in 140 mL of CH_2Cl_2 were added 0.0364 g (0.298 mmol) of DMAP, 6.03 mL (74.6 mmol) of pyridine, and 1.14 mL (14.9 mmol) of thiophosgene. The reaction darkened, and a solid formed which dissolved upon refluxing for 4 h. The reaction was cooled to ambient temperature, and a solution of 5.49 g (29.8 mmol) of pentafluorophenol in 40 mL of CH_2Cl_2 was added dropwise. The reaction turned orange and was refluxed for 4 h. The reaction was cooled, diluted with $CHCl_3$, extracted with $NaHCO_3$, rinsed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The products were then purified by flash chromatography (1.5:1 hexane:EtOAc) on silica gel to provide 2.3901 g (65−79% from pure **44**) of **46** and 0.5087 g (14%) of **47** both as red solids: R_f 0.46 (1:1 hexane:EtOAc); $[\alpha]^{20}_D$ +55.5° (*c* 1.26, CH_2Cl_2); IR (film) 2940, 1760, 1700, 1520, 1350, 1170, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.61 (s, 1H), 7.20−7.46 (m, 14H), 7.05−7.14 (m, 3H), 6.93 (d, J = 7.5, 2H), 6.63−6.70 (m, 3H), 6.29 (d, J = 6.6 Hz, 1H), 6.02 (dd, J = 6.6, 5.6 Hz, 1H), 5.46 (d, J = 10.5 Hz, 1H), 5.40 (d, J = 10.5 Hz, 1H), 5.20 (s, 2H), 5.03 (d, J = 11.4 Hz, 1H), 4.65−4.72 (m, 4H), 4.58 (s, 2H), 4.54 (m, 2H), 4.46 (m, 3H), 3.96 (d, J = 9.7 Hz, 1H), 3.81 (s, 3H), 3.74 (m, 1H), 3.42−3.48 (m, 2H), 0.89 (app t, J = 8.1 Hz, 2H), −0.21 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 189.7, 171.3, 159.6, 156.0, 142.0, 137.6, 137.5, 136.0, 135.7, 131.8, 129.4, 129.0, 128.6, 128.4, 128.1, 127.7, 127.6, 127.5, 126.9, (126.8), 126.2, 122.8, 122.5, 122.3, 122.0, 120.8, 120.7, 114.0, 110.1, 109.8, 108.0, 106.6, 84.0, 80.1, 77.1, 75.9, 73.8, 73.6, 73.3, 72.5, 71.3, 71.2, 67.1, 65.9, 56.6, 55.1, 17.5, −1.6; FAB HRMS *m/e* calcd for (M^+) $C_{64}H_{59}N_4O_{12}S_1F_5Si_1$ 1230.3540, found 1230.3530.

1-[(Benzyloxy)methyl]-3,4-dihydro-4-(1-[3-[[(benzyloxy)methyl]-amino]-3-*N*,4-*O*-carbonyl-6-*O*-(4-methoxybenzyl)-β-D-allopyranoside]-1*H*-indol-3-yl)-3-(1-[2-(trimethylsilyl)ethoxy]-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (47): R_f 0.78 (1:1 hexane:EtOAc); $[\alpha]^{20}_D$ +2.6° (*c* 1.48, CH_2Cl_2); IR (film) 2950, 1770, 1715, 1610, 1535, 1350, 1075, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.70 (s, 1H′), 7.21−7.46 (m, 13H), 7.05 (m, 3H), 6.98 (d, J = 8.1 Hz, 1H), 6.90 (m, 3H), 6.77 (app t, J = 8.5 Hz, 1H), 6.73 (app t, J = 8.1, 1H), 6.24 (d, J = 5.2 Hz, 1H), 5.93 (t, J = 4.1, 3.2 Hz, 1H), 5.52 (d, J = 11.1 Hz, 1H), 5.47 (d, J = 11.1 Hz, 1H), 5.25 (d, J = 10.9 Hz, 1H), 5.21 (d, J = 10.9 Hz, 1H), 4.89 (s, 2H), 4.71 (s, 2H), 4.50−4.65 (m, 5H), 4.38 (dd, J = 8.1, 3.6 Hz, 1H), 4.10 (m, 1H), 3.85 (m, 2H), 3.82 (s, 3H), 3.52 (t, J = 7.1 Hz, 2H), 0.93 (t, J = 7.1 Hz, 2H), 0.02 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 190.0, 171.4, 171.3, 159.4, 157.2, 139.5, 137.7, 137.0, 136.3, 135.3, 132.1, 129.4, 129.3, 128.5, 128.3, 128.0, 127.9, 127.8, 127.6, 126.8, 126.7, 126.5, 123.2, 122.7, 122.4, 121.9, 121.2, 120.8, 113.9, 110.3, 110.1, 108.2, 106.4, 81.0, 78.8, 76.1, 75.4, 74.4, 73.6, 71.5, 71.3, 68.7, 68.5, 67.2, 66.1, 55.2, 52.8, 17.6, −1.4; FAB HRMS *m/e* calcd for (M^+) $C_{64}H_{59}N_4O_{12}Si_1S_1F_5$ 1230.3540, found 1230.3525.

1-[(Benzyloxy)methyl]-3,4-dihydro-4-([3-[[(benzyloxy)methyl]amino]-3-*N*,4-*O*-carbonyl-6-*O*-(4-methoxybenzyl)-2-deoxy-α-D-allopyranosyl]-1*H*-indol-3-yl)-3-(1-[2-(trimethylsilyl)ethoxy]-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (48). To an orange, clear degassed solution of 3.045 g (2.47 mmol) of **47** in 200 mL of PhH was added 6.7 mL (24.7 mmol) of tri-*n*-butyltin hydride and 0.0406 g (0.247 mmol) of AIBN. The resulting mixture was heated to reflux for 2 h. Additional AIBN (0.0203 g) was added every 20 min until the reaction was complete. The reaction was then cooled and was concentrated *in vacuo*. The residue was purified by flash chromatography (5:4 EtOAc:hexane) to yield 1.81 g (74%) of **48** as a red solid: mp 58−60 °C (sublimes); R_f 0.45 (1:1 hexane:EtOAc); $[\alpha]^{20}_D$ +12.8° (*c* 2.31, CH_2Cl_2); IR (film) 2940, 1755, 1700, 1610, 1540, 1300, 1240, 1075, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.63 (s, 1H), 7.05−7.45 (m, 17H), 6.88 (m, 3H), 6.73 (m, 2H), 6.09 (dd, J = 10.5, 4.2 Hz, 1H), 5.46 (s, 2H), 5.20 (s, 2H), 4.96 (d, J = 11.2 Hz, 1H), 4.71 (d, J = 11.2 Hz, 1H), 4.69 (s, 2H), 4.61 (d, 12.0 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.51 (t, J = 8.1 Hz, 1H), 4.45 (s, 2H), 4.15 (m, 1H), 3.87 (m, 1H), 3.76 (s, 3H), 3.67 (dd, J = 10.1, 2.0 Hz, 1H), 3.56 (dd, J = 10.1, 4.0 Hz, 1H), 3.51 (t, J = 8.1 Hz, 2H), 2.56 (m, 1H), 2.10 (m, 1H), 0.91 (t, J = 8.4, 2H), 0.05 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.3, 159.3, 156.5, 137.7, 137.2, 136.3, 135.5, 132.2, 129.3, 129.2, 128.5, 128.4, 129.3, 128.2, 127.9, 127.7, 127.5, 127.4, 127.0, 126.6, 125.9, 122.7, 122.6, 122.3, 122.1, 120.9, 120.5, 113.8, 110.3, 110.0, 107.2, 106.3, 78.2, 75.9, 73.3, 73.1, 71.4, 71.2, 70.9, 69.8, 69.5, 67.1, 66.0, 55.1, 50.6, 29.9, 17.5, −1.5; FAB HRMS *m*/*e* calcd for (M^+) $C_{57}H_{60}N_4O_{10}Si_1$ 988.4078, found 988.4074.

1-[(Benzyloxy)methyl]-3,4-dihydro-4-([3-[[(benzyloxy)methyl]amino]-3-*N*,4-*O*-carbonyl-2-deoxy-α-D-allopyranosyl]-1*H*-indol-3-yl)-3-(1-[2-(trimethylsilyl)ethoxy]-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (49). A red solution of 2.13 g (2.15 mmol) of indole glycoside **48** in 180 mL of CH_2Cl_2 and 10 mL of H_2O at 0 °C was treated with 0.7316 g (3.22 mmol) of DDQ. The reaction was slowly warmed to ambient temperature and stirred vigorously overnight. The crude products were diluted with EtOAc, extracted with saturated $NaHSO_3$, rinsed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (3:1 EtOAc:hexane) on silica gel yielded 1.8110 g (97%) of **49** as a red solid: R_f 0.31 (1:2 hexane:EtOAc); $[\alpha]^{20}_D$ +18.25° (*c* 1.09, CH_2Cl_2); IR (film) 3450, 2950, 1760, 1700, 1610, 1545, 1350, 1075, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.52 (s, 1H), 7.05−7.42 (m, 15H), 6.97 (m, 1H), 6.65 (m, 2H), 5.98 (dd, J = 10.9, 4.8 Hz, 1H), 5.56 (d, J = 10.6 Hz, 1H), 5.48 (d, J = 10.6 Hz, 1H), 5.19 (s, 2H), 4.82 (d, J = 11.2 Hz, 1H), 4.71 (d, J = 11.2 Hz, 1H), 4.68 (s, 2H), 4.59 (d, J = 11.9 Hz, 1H), 4.52 (d, J = 11.9 Hz, 1H), 4.31 (t, J = 9.1 Hz, 1H), 4.04 (m, 1H), 3.48−3.55 (m, 4H), 3.22 (m, 1H), 2.63 (m, 1H), 1.97 (m, 1H), 0.89 (t, J = 8.2 Hz, 2H), −0.05 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 171.4, 156.5, 137.6, 137.1, 136.5, 135.1, 132.3, 128.5, 128.4, 128.3, 128.0, 127.8, 127.6, 127.4, 126.8, 125.5, 125.4, 122.9, 122.8, 122.6, 122.3, 121.1, 120.5, 110.4, 109.9, 107.0, 106.4, 78.6, 75.9, 73.2, 71.8, 71.5, 71.0, 69.4, 67.1, 66.3, 61.8, 50.2, 29.8, 17.7, −1.5; HRMS (FAB) *m*/*e* calcd for (M^+) $C_{49}H_{52}N_4O_9Si_1$ 868.3503, found 686.3534.

1-[(Benzyloxy)methyl]-3,4-dihydro-4-([3-[[(benzyloxy)methyl]amino]-3-*N*,4-*O*-carbonyl-2-deoxy-α-D-allopyranosyl]-1*H*-indol-3-yl)-3-(1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (50). A red solution of 1.7674 g (1.786 mmol) of indole glycoside **49** in 125 mL of THF was treated with 1.77 g of 4 Å molecular sieves and 2.7 mL (2.7 mmol, 1.0 M in THF) of TBAF. The reaction was heated to reflux and every 30 min for 2.5 h 1.4 mL of TBAF was added. The reaction turned purple and was cooled to ambient temperature. After quenching with brine the crude products were diluted with EtOAc. The organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide 1.2011 g (91%) of **50** as a red solid: mp 76−78 °C (sublimes); R_f 0.60 (EtOAc); $[\alpha]^{20}_D$ +38.7° (*c* 0.76, CH_2Cl_2); IR (film) 3386, 2930, 1760, 1705, 1610, 1530, 1420, 1350, 1075, 750 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 10.92 (s, 1H), 7.93 (s, 2H), 7.55 (d, J = 10.1 Hz, 1H), 7.15−7.43 (m, 10H), 7.07−7.12 (m, 2H), 6.92−7.02 (m, 1H), 6.83 (m, 1H), 6.74 (m, 1H), 6.64 (m, 2H), 6.32 (dd, J = 11.3, 4.1 Hz, 1H), 5.18 (s, 2H), 4.90 (d, J = 11.0 Hz, 1H), 4.81 (d, J = 11.0 Hz, 1H), 4.69 (s, 2H), 4.68 (m, 1H), 4.60 (d, J = 12.1 Hz, 1H), 4.56 (d, J = 12.1 Hz, 1H), 4.43 (m, 1H), 4.01 (m, 1H), 3.74 (m, 1H), 3.64 (m, 1H), 2.71 (m, 1H), 2.53 (m, 1H); ^{13}C NMR (75.4 MHz, acetone-d_6) δ 157.4, 156.6, 130.7, 130.5, 130.4, 129.1, 128.9, 128.8, 128.9, 128.6, 128.4, 128.3, 128.2, 127.8, 123.2, 122.9, 122.8, 122.7, 122.6, 122.5, 122.4, 121.7, 121.2, 120.6, 117.3, 112.5, 112.4, 111.3, 79.2, 74.1, 73.3, 71.8, 70.9, 70.5, 88.0, 62.6, 62.4, 51.7, 30.8; CI HRMS (NH_3) *m*/*e* calcd for (M^+) $C_{43}H_{38}N_4O_8$ 738.2690, found 738.2686.

6-[[(Benzyloxy)methyl]-12-(3-[[(benzyloxy)methyl]amino]-3-*N*,4-*O*-carbonyl-2-deoxy-α-D-allopyranosyl]indolo[2,3-*a*]pyrrolo[3,4-*c*]-carbazole-5,7-dione (51). A red solution of 1.1492 g (1.56 mmol) of **50** in 800 mL of PhH was treated with 0.0395 g (0.156 mmol) of iodine. Air was continuously bubbled through the reaction which was irradiated with a medium pressure mercury lamp equipped with a Vycor filter for 8 h. PhH was added to the reaction each hour to keep the solvent volume constant. The crude products were diluted with EtOAc, extracted with saturated $Na_2S_2O_4$, rinsed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (EtOAc → 20:1 EtOAc:MeOH) yielded 0.8366 g (73%) of **51** as a yellow solid: R_f 0.3 (EtOAc); $[\alpha]^{20}_D$ +112° (*c* 0.89, CH_2Cl_2); IR (film) 3350, 2915, 1750, 1700, 1565, 1325, 1065, 750 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 10.57 (s, 1H), 9.26 (d, J = 7.8 Hz, 1H), 9.13 (d, J = 8.1 Hz, 1H), 7.75 (m, 2H), 7.58 (m, 2H), 7.27−7.44 (m, 5H), 7.04 (m, 4H), 6.93 (m, 2H), 5.26 (d, J = 11.0 Hz, 1H), 5.22 (d, J = 11.0 Hz, 1H), 5.01 (m, 1H), 4.86 (dd, J = 6.6, 2.1 Hz, 1H), 4.61 (m, 5H), 4.35 (m, 4H), 2.55 (m, 1H), 2.42 (m, 1H); ^{13}C NMR (75.4 MHz, acetone-d_6) δ 169.9, 169.8, 157.1, 141.1, 140.6, 139.2, 138.5, 128.8, 128.6, 128.2, 128.0, 127.9, 126.2, 125.6, 123.0, 122.1, 121.5, 119.5, 112.9, 112.8, 110.9, 78.6, 76.6, 74.0, 72.1, 71.7, 70.8, 67.5, 63.9, 63.7, 52.9, 33.8; FAB HRMS *m*/*e* calcd for (M^+) $C_{43}H_{36}N_4O_8$ 736.2533, found 736.2540.

6-[(Benzyloxy)methyl]-12-(3-[[(benzyloxy)methyl]amino]-3-*N*,4-*O*-carbonyl-2,6-dideoxy-6-iodo-α-D-allopyranosyl)indolo[2,3-*a*]-pyrrolo[3,4-*c*]carbazole-5,7-dione (52). To a solution of 0.9785 g (3.73 mmol) of triphenylphosphine and 0.5079 g (7.461 mmol) of imidazole in 38 mL of CH_2Cl_2 at 0 °C was added 0.9784 g (7.46 mmol) of iodine. The reaction turned from clear and colorless to bright yellow over 30 min. A green solution of 0.9162 g (1.244 mmol) of indolocarbazole glycoside **51** in 65 mL of CH_2Cl_2 was added dropwise via cannula. The reaction was slowly warmed to ambient temperature and stirred for 6 h. The crude products were diluted with CH_2Cl_2, extracted with H_2O, rinsed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography (3:1 EtOAc:hexane) on silica gel yielded 0.9445 g (84%) of **52** as a yellow solid: R_f 0.7 (EtOAc); $[\alpha]^{20}_D$ +43.3° (*c* 0.85, CH_2Cl_2); IR (film) 3375, 2915, 1755, 1700, 1570, 1325, 1075, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 9.11 (d, J = 8.1 Hz, 1H), 9.01 (d, J = 8.1 Hz, 1H), 7.06−7.59 (m, 16H), 6.20 (dd, J = 11.7, 3.2 Hz, 1H), 5.08 (d, J = 10.9 Hz, 1H), 5.01 (d, J = 10.9 Hz, 1H), 4.81 (d, J = 11.5 Hz, 1H), 4.74 (m, 1H), 4.70 (s, 2H), 4.63 (d, J = 11.5 Hz, 1H), 4.38 (m, 3H), 4.24 (m, 1H), 3.62 (m, 2H), 2.41 (m, 1H), 2.35 (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 168.8, 168.7, 155.6, 140.6, 139.8, 137.7, 137.1, 129.3, 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 127.4, 127.2, 126.0, 125.1, 122.6, 121.9, 121.3, 120.6, 119.0, 118.7, 118.5, 111.7, 109.2, 76.3, 73.4, 71.5, 71.3, 66.7, 50.5, 32.1, 29.3, 1.4; FAB HRMS *m*/*e* calcd for (M^+) $C_{43}H_{35}N_4O_7I_1$ 846.1556, found 846.1600.

6-[(Benzyloxy)methyl]-12-(3-[[(benzyloxy)methyl]amino]-3-*N*,4-*O*-carbonyl-2,6-dideoxy-5,6-anhydro-α-D-allopyranosyl)indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-dione (53a). To a green solution of 1.092 g (1.29 mmol) of indolocarbazole glycoside **52** in 100 mL of THF at 0 °C was added 0.58 mL (3.869 mmol) of DBU. The reaction turned from green to red and after 10 min was diluted with EtOAc and extracted with H_2O (2×). The organic layer was rinsed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (3:1 EtOAc:hexane) provided 0.8250 g (89%) of **53a** as a yellow solid: mp 98−99 °C (sublimes); R_f 0.40 (3:1 Et_2O:EtOAc); $[\alpha]^{20}_D$ +2.74° (*c* 0.84, CH_2Cl_2); IR (film) 3400, 2910, 1750, 1700, 1570, 1325, 1065, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H, N12*H*), 9.22 (d, J = 8.0 Hz, 1H, *H*8), 9.07 (d, J = 8.0 Hz, 1H, *H*4), 7.58 (d, J = 8.1 Hz, 1H, *H*11), 7.51 (m, 2H, Ar*H*), 7.21−7.42 (m, 8H, Ar*H*), 7.12 (m, 3H, Ar*H*), 7.01 (m, 2H, Ar*H*), 6.17 (dd, J = 11.8, 2.5 Hz, 1H, *H*1), 5.46 (d, J = 2.0 Hz, 1H, *H*6), 5.27 (d, J = 2.0 Hz, 1H, *H*6′), 5.19 (d, J = 10.9 Hz, 1H, CH_2OBn), 5.13 (d, J = 10.9 Hz, 1H, CH_2OBn), 4.82 (d, J = 11.4 Hz, 1H, CH_2OBn), 4.78 (d, J = 6.8 Hz, 1H, *H*4), 4.72 (s, 2H, CH_2Ph), 4.62 (d, J = 11.4 Hz, 1H,

CH_2OBn), 4.38 (s, 2H, CH_2Ph), 4.27 (m, 1H, *H*3), 2.51 (m, 1H, *H*2), 2.32 (m, 1H, *H*2′); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.1, 169.0, 155.9, 151.2, 140.6, 139.8, 137.8, 137.0, 129.3, 128.3, 128.0, 127.7, 127.8, 127.7, 127.6, 127.4, 126.2, 125.3, 122.6, 122.1, 121.9, 121.5, 119.5, 119.1, 118.8, 111.6, 108.7, 105.9, 81.8, 73.4, 71.5, 71.2, 70.5, 66.8, 51.7, 33.6; FAB HRMS *m*/*e* calcd for (M^+) $C_{43}H_{34}N_4O_7$ 718.2427, found 718.2439.

3′-*O*,4′-*N*-Carbonyl-3′-*O*-desmethyl-4′-*N*-desmethyl-6-*N*,4′-*N*-bis-[(benzyloxy)methyl]-*ent*-1′-iodo-7-oxostaurosporine (55a). To a green solution of 0.4268 g (0.5938 mmol) of indolocarbazole glycoside **53a** in 70 mL of THF and 7 mL of MeOH was added 0.2532 g (2.256 mmol) of potassium *tert*-butoxide. The reaction turned red and was treated with 0.4823 g (1.90 mmol) of iodine. After 3 h the reaction was diluted with EtOAc, extracted with saturated $Na_2S_2O_4$, rinsed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography (3:1 Et_2O:EtOAc) on silica gel afforded 0.0640 g (15%) of recovered **53a** and 0.3260 g (65%) of **55a** as a yellow solid: R_f 0.30 (3:1 Et_2O:EtOAc); $[\alpha]^{20}_D$ −91.7° (*c* 1.14, CH_2Cl_2); IR (film) 2915, 1760, 1700, 1570, 1340, 1070, 745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (d, J = 8.1 Hz, 1H, *H*8), 9.21 (d, J = 8.0 Hz, 1H, *H*4), 8.00 (d, J = 8.5 Hz, 1H, *H*11), 7.61 (app t, J = 8.2, 7.3 Hz, 2H, Ar*H*), 7.36−7.57 (m, 4H, Ar*H*), 7.14−7.32 (m, 9H, Ar*H*), 6.56 (dd, J = 10.5, 6.3 Hz, 1H, *H*6′), 5.33 (d, J = 10.9 Hz, 1H, CH_2OBn), 5.29 (d, J = 10.9 Hz, 1H, CH_2OBn), 5.03 (d, J = 8.9 Hz, 1H, *H*3′), 4.87 (d, J = 11.4 Hz, 1H, CH_2OBn), 4.77 (s, 2H, CH_2Ph), 4.70 (d, J = 11.4 Hz, 1H, CH_2OBn), 4.47 (m, 3H, *H*1′, CH_2Ph), 4.33 (m, 1H, *H*4′), 3.92 (d, J = 11.63 Hz, 1H, *H*1′), 2.84 (m, 1H, *H*5′), 2.36 (m, 1H, *H*5′); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.3, 169.1, 155.0, 141.5, 137.8, 137.1, 131.6, 128.6, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.5, 126.5, 126.1, 125.1, 122.9, 122.2, 121.6, 121.3, 119.6, 117.5, 114.8, 107.6, 91.9, 79.4, 73.8, 73.4, 71.6, 71.5, 67.0, 50.9, 30.5, 12.2; FAB HRMS *m*/*e* calcd for (M^+) $C_{43}H_{33}N_4O_7I_1$ 844.1394, found 844.1384.

3′-*O*,4′-*N*-Carbonyl-3′-*O*-desmethyl-4′-*N*-desmethyl-6-*N*,4′-*N*-bis-[(benzyloxy)methyl]-*ent*-7-oxostaurosporine (61). To a degassed green solution of 0.5523 g (0.654 mmol) of indolocarbazole glycoside **55a** in 150 mL of PhH were added 0.7 mL of *n*-Bu_3SnH and 0.0107 g (0.0654 mmol) of AIBN. The reaction was then heated to reflux for 30 min. After cooling, the reaction was concentrated *in vacuo*. Flash chromatography (1:1 → 4:1 EtOAc:hexane) provided 0.4652 g (99%) of **61** as a yellow solid: R_f 0.50 (1:4 hexane:EtOAc); $[\alpha]^{20}_D$ −61.4° (*c* 0.85, CH_2Cl_2); IR (film) 2910, 1760, 1700, 1340, 1035, 745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (d, J = 7.1 Hz, 1H, *H*8), 9.29 (d, J = 8.1 Hz, 1H, *H*4), 8.12 (d, J = 8.6 Hz, 1H, *H*11), 7.68 (app t, J = 8.1, 7.3 Hz, 2H, Ar*H*), 7.20−7.55 (m, 13H, Ar*H*), 6.59 (dd, J = 10.4, 6.3 Hz, 1H, *H*6′), 5.26 (d, J = 10.9 Hz, 1H, CH_2OBn), 5.18 (d, J = 10.9 Hz, 1H, CH_2OBn), 4.94 (d, J = 9.03 Hz, 1H, *H*3′), 4.91 (d, J = 11.6 Hz, 1H, CH_2OBn), 4.84 (s, 2H, CH_2Ph), 4.73 (d, J = 11.6 Hz, 1H, CH_2OBn), 4.52 (s, 2H, CH_2Ph), 4.41 (m, 1H, *H*4′), 2.85 (m, 1H, *H*5′), 2.41 (m, 1H, *H*5′), 2.11 (s, 3H, C*H*1′); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.2, 169.0, 155.4, 155.3, 142.0, 137.7, 137.1, 130.5, 128.6, 128.3, 128.2, 128.0, 127.8, 127.6, 127.3, 126.2, 125.6, 124.5, 122.1, 122.0, 121.4, 120.7, 119.4, 119.2, 117.1, 116.2, 107.5, 93.0, 78.9, 76.5, 73.2, 71.5, 71.2, 66.8, 50.5, 30.4, 30.2, 29.8; HRMS (FAB) *m*/*e* calcd for FAB (M^+) $C_{43}H_{34}N_4O_7$ 718.2427, found 718.2405.

3,4-Dihydro-2-hydroxy-4-(1*H*-indol-3-yl)-1-(2-propenyl)-3-(1-[2-propenyl]-1*H*-indol-3-yl)-1*H*-pyrrol-5-one (66). To a red solution of 1.1789 g (2.893 mmol) of aglycon **65** in 240 mL of THF was added 0.1215 g (3.038 mmol, 60% dispersion) of NaH. The reaction turned purple and was cooled to −78 °C. A 7.2 mL (7.23 mmol, 1.0 M in toluene) solution of DIBAL was added dropwise, and the reaction turned red. After stirring at −78 °C for 1 h, 4.9 mL (4.9182 mmol, 1.0 M in THF) of L-Selectride was added. The reaction was warmed slowly to room temperature over 6 h and was then cooled to 0 °C and quenched by slowly adding a saturated solution of sodium potassium tartrate (50 mL). The crude products were diluted with EtOAc and extracted with saturated sodium potassium tartrate (3×) and brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (1:1 → 1:2 hexane: EtOAc) on silica gel to yield 0.2269 g (20%) of hydroxy lactam **67** as a yellow solid and 0.8886 g (78%) of hydroxy lactam **66** as a yellow solid: mp 118−119 °C; R_f 0.18 (1:1 hexane:EtOAc); IR (film) 3270, 3010, 2920, 1670, 1540, 1410, 1100, 750 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.12 (s, 1H), 7.56−7.65 (m, 2H), 7.16−7.43 (m, 4H), 6.92−7.11 (m, 3H), 6.78 (m, 1H), 6.03 (d, J = 8.62 Hz, 1H), 5.73−5.95 (m, 2H), 5.34 (d, J = 19.4 Hz, 1H), 5.27 (d, J = 12.1 Hz, 1H), 5.17 (d, J = 8.6 Hz, 1H), 5.03 (d, J = 20.7 Hz, 1H), 4.41−4.62 (m, 3H), 3.92−4.07 (m, 1H), 3.45−3.64 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.5, 142.5, 136.3, 136.1, 133.6, 132.4, 130.8, 127.2, 126.5, 124.9, 122.1, 121.9, 121.7, 121.6, 120.4, 119.3, 117.7, 117.3, 111.4, 109.9, 108.8, 107.3, 82.7, 48.8, 42.4; FAB HRMS *m*/*e* calcd for $C_{26}H_{23}N_3O_2$ 409.1790, found 409.1770.

3,4-Dihydro-5-hydroxy-4-(1*H*-indol-3-yl)-1-(2-propenyl)-3-(1-[2-propenyl]-1*H*-indol-3-yl)-1*H*-pyrrol-2-one (67). To a red solution of 0.5276 g (0.9741 mmol) of aglycon **64** in 50 mL of THF at −78 °C was added 2.2 mL (2.14 mmol, 1.0 M in THF) of L-Selectride. The reaction was slowly warmed to ambient temperature over 6 h. Then the light purple reaction mixture was cooled to 0 °C and quenched with 10 mL of H_2O. The crude products were diluted with EtOAc and extracted with H_2O and brine. The combined aqueous layers were extracted with EtOAc (2×), and the combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography of the residue on silica gel (1:1 → 1:2 hexane:EtOAc) provided 0.2786 g (70%) of hydroxy lactam **67** as a yellow solid and 0.0927 g (23%) of hydroxy lactam **66** as a yellow solid: mp 105−106 °C; R_f 0.26 (1:1 hexane:EtOAc); IR (film) 3280, 1670, 1540, 1439, 740 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.57 (s, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.01−7.25 (m, 4H), 6.85−6.91 (m, 2H), 6.68−6.74 (m, 1H), 5.84−5.97 (m, 3H), 5.03−5.29 (m, 4H), 4.63 (d, J = 5.4 Hz, 2H), 4.39 (dd, J = 15.5, 4.7 Hz, 1H), 3.92 (dd, J = 15.5, 7.1 Hz, 1H), 2.71 (d, J = 10.3 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.5, 142.9, 136.2, 136.0, 133.5, 133.1, 130.2, 127.2, 126.2, 125.4, 122.2, 121.9, 121.5, 121.3, 120.2, 119.4, 117.3, 111.5, 109.6, 109.5, 106.7, 82.7, 48.8, 42.4; FAB HRMS *m*/*e* calcd for $C_{26}H_{23}N_3O_2$ 409.1790, found 409.1787.

3,4-Dihydro-4-(1*H*-indol-3-yl)-2-(phenylseleno)-1-(2-propenyl)-3-(1-[2-propenyl]-1*H*-indol-3-yl)-1*H*-pyrrol-5-one (68). To a light brown, clear solution of 0.2949 g (0.72 mmol) of hydroxy lactam **66** in 30 mL of CH_2Cl_2 was added 0.075 mL (0.72 mmol) of benzeneselenol. The reaction turned yellow, and 0.0066 g (0.036 mmol) of *p*-toluenesulfonic acid monohydrate was added. The reaction was stirred at ambient temperature for 1 h and was concentrated *in vacuo*. Flash chromatography (1:1 hexane:EtOAc) of the residue yielded 0.3328 g (84%) of phenylselenide **68** as a brown solid: mp 110−111 °C; IR (film) 3250, 1670, 1540, 1440, 1180, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.09−7.31 (m, 10H), 6.94−7.09 (m, 3H), 6.77 (m, 2H), 6.17 (s, 1H), 5.96 (m, 1H), 5.83 (m, 1H), 5.38 (d, J = 17.0 Hz, 1H), 5.31 (d, J = 12.3 Hz, 1H), 5.30 (s, 1H), 5.15 (d, J = 10.3 Hz, 1H), 4.98 (d, J = 18.1 Hz, 1H), 4.85 (dd, J = 15.3 Hz, 4.1H), 4.61 (d, J = 5.1 Hz, 2H), 4.18 (dd, J = 15.3, 8.0 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.7, 142.7, 137.1, 136.2, 136.0, 133.4, 132.6, 131.5, 129.7, 129.1, 129.0, 128.9, 128.6, 127.7, 126.2, 126.0, 125.1, 124.8, 121.9, 121.2, 120.1, 119.1, 118.2, 117.5, 111.0, 109.9, 109.4, 107.7, 63.9, 48.8, 43.2; FAB HRMS *m*/*e* calcd for (M + H) $C_{32}H_{28}N_3OSe$ 550.1400, found 550.1385.

3,4-Dihydro-4-(1*H*-indol-3-yl)-5-(phenylseleno)-1-(2-propenyl)-3-(1-[2-propenyl]-1*H*-indol-3-yl)-1*H*-pyrrol-2-one (69). To a light brown, clear solution of 0.0983 g (0.24 mmol) of hydroxy lactam **67** in 10 mL of CH_2Cl_2 was added 0.025 mL (0.24 mmol) of benzeneselenol. The reaction turned yellow, and 0.0022 g (0.012 mmol) of *p*-toluenesulfonic acid monohydrate was added. The reaction was stirred at ambient temperature for 1 h and was concentrated *in vacuo*. Flash chromatography (1:1 hexane:EtOAc) of the residue yielded 0.1068 g (82%) of phenyl selenide **69** as a gold solid: mp 119−120 °C; IR (film) 3220, 1660, 1540, 1440, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H, NH), 7.17−7.28 (m, 5H), 7.02−7.13 (m, 5H), 6.92 (m, 3H), 6.82 (m, 2H), 5.98 (s, 1H), 5.95 (m, 1H), 5.79 (m, 1H), 5.40 (d, J = 17.4 Hz, 1H), 5.33 (d, J = 10.3 Hz, 1H), 5.09 (d, J = 10.3 Hz, 1H), 4.96 (d, J = 16.8 Hz, 1H), 4.83 (d, J = 11.6 Hz, 1H), 4.51 (d, J = 5.1 Hz, 1H), 4.20 (dd, J = 15.7, 8.0 Hz, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 169.9, 143.1, 137.3, 136.1, 133.3, 133.1, 131.5, 129.2, 129.1, 128.6, 127.7, 126.3, 126.0, 125.1, 124.6, 123.1, 122.0, 121.9, 121.5, 119.8, 119.2, 118.1, 117.1, 111.6, 110.0, 109.6, 109.4, 107.0, 64.1, 48.7, 43.2; FAB HRMS *m*/*e* calcd for (M + H) $C_{32}H_{28}N_3O_1Se_1$ 550.1400, found 550.1416.

3,4-Dihydro-4-(1*H*-indol-3-yl)-1-(2-propenyl)-3-(1-[2-propenyl]-1*H*-indol-3-yl)-1*H*-pyrrol-5-one (70). To a light brown, clear solution of 0.8886 g (2.17 mmol) hydroxy lactam **66** in 40 mL of CH_2Cl_2 was added 0.48 mL (4.56 mmol) of benzeneselenol. The reaction turned yellow and 0.0206 g (0.11 mmol) of *p*-toluenesulfonic acid monohydrate was added. The reaction was stirred at ambient temperature for 1 h and was concentrated *in vacuo*. Flash chromatography (1:1 hexane:EtOAc) of the residue yielded 0.8538 g (100%) of lactam **70** as a beige crystalline solid: mp 94−95 °C (sublimes); R_f 0.20 (1:2 hexane:EtOAc); IR (film) 3240, 1670, 1615, 1535, 1460, 1330, 1285, 1190, 740 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 1.9 Hz, 1H), 7.00−7.33 (m, 7H), 6.79−6.85 (m, 1H), 5.91−6.07 (m, 1H), 5.58−5.73 (m, 1H), 5.26−5.38 (m, 2H), 5.01 (dd, J = 10, 2, 1.1 Hz, 1H), 4.85 (dd, J = 17.1, 1.0 Hz, 1H), 4.66 (s, 2H), 4.40 (d, J = 5.4 Hz, 1H), 4.32 (d, J = 5.8 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.3, 141.6, 136.5, 136.0, 133.9, 133.6, 132.3, 131.8, 130.4, 130.3, 126.6, 126.5, 126.2, 124.5, 122.0, 121.6, 121.3, 120.5, 119.0, 117.7, 117.5, 111.7, 110.2, 110.0, 109.2, 107.6, 52.8, 48.7, 45.3; FAB HRMS *m/e* calcd for $C_{26}H_{23}N_3O_1$ 393.1841, found 393.1848.

3,4-Dihydro-4-(1*H*-indol-3-yl)-1-(2-propenyl)-3-(1-[2-propenyl]-1*H*-indol-3-yl)-1*H*-pyrrol-2-one (71). To a light brown, clear solution of 0.2269 g (0.55 mmol) of hydroxy lactam **67** in 10 mL of CH_2Cl_2 was added 0.12 mL (1.16 mmol) of benzeneselenol. The reaction turned yellow, and 0.0053 g (0.0277 mmol) of *p*-toluenesulfonic acid monohydrate was added. The reaction was stirred at ambient temperature for 1 h and was concentrated *in vacuo*. Flash chromatography (1:1 hexane:EtOAc) of the residue yielded 0.2180 g (100%) of lactam **71** as a yellow crystalline solid: mp 88−89 °C (sublimes); R_f 0.32 (1:2 hexane:EtOAc); IR (film) 3230, 1650, 1540, 1455, 1440, 1240, 1180, 740 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.44 (s, 1H), 7.41 (d, J = 7.7 Hz, 1H), 6.96−7.26 (m, 6H), 6.79−6.88 (m, 2H), 5.79−5.96 (m, 2H), 5.02−5.31 (m, 4H), 4.55 (d, J = 5.4 Hz, 2H), 4.51 (s, 2H), 4.21 (d, J = 5.8 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.2, 142.1, 136.4, 136.2, 133.6, 133.2, 129.2, 126.4, 126.0, 125.2, 122.0, 121.8, 121.4, 121.2, 120.3, 119.2, 117.3, 111.9, 110.2, 109.6, 107.6, 52.9, 48.8, 45.2; FAB HRMS *m/e* calcd for $C_{26}H_{23}N_3O_1$ 393.1841, found 393.1868.

3′-*O*,4′-*N*-Carbonyl-3′-*O*-desmethyl-4′-*N*-desmethyl-*ent*-7-oxo-staurosporine (82). To a green solution of 0.4652 g (0.647 mmol) of indolocarbazole **61** in 18 mL of EtOAc and 18 mL of MeOH was added 0.0454 g of $Pd(OH)_2$ (20% on carbon). The reaction was then placed under a H_2 atmosphere by several evacuation/refill with H_2 cycles. The reaction was then sonicated for 20 min and stirred vigorously overnight. The reaction was then placed under an argon atmosphere and was filtered through a pad of Celite and silica gel with EtOAc, acetone and then 19:1 CH_2Cl_2:MeOH. The crude products were concentrated *in vacuo*, dissolved in 36 mL of MeOH, and treated with 0.9 mL of 25 wt % NaOMe in MeOH. After stirring for 30 min the reaction was diluted with EtOAc, extracted with saturated NH_4Cl, rinsed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography (19:1 CH_2Cl_2:MeOH) provided 0.2848 g (92%) of **82** as a yellow solid: mp > 230 °C; R_f 0.20 (19:1 CH_2Cl_2:MeOH); $[\alpha]^{20}_D$ −176.7° (*c* 0.49, acetone); ^1H NMR (400 MHz, acetone-d_6) δ 9.84 (s, 1H), 9.21 (d, J = 8.1 Hz, 1H), 9.04 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 8.7 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.53 (m, 2H), 7.32 (m, 2H), 7.16 (s, 1H), 6.94 (dd, J = 10.1, 6.4 Hz, 1H), 5.39 (d, J = 8.2 Hz, 1H), 4.47 (m, 1H), 2.82 (m, 1H), 2.41 (m, 1H), 2.02 (s, 3H); ^{13}C NMR (75.4 MHz, acetone-d_6) δ 170.8, 170.5, 156.9, 141.3, 137.7, 129.8, 128.2, 127.1, 126.3, 124.7, 124.5, 123.4, 121.3, 121.1, 120.7, 116.7, 115.6, 109.3, 92.7, 78.9, 77.4, 47.4, 31.1, 29.8, 29.6; CI HRMS (M + NH_4) *m/e* calcd for $C_{27}H_{22}N_5O_5$ 496.1621, found 496.1631.

3′-*O*,4′-*N*-Carbonyl-3′-*O*-desmethyl-4′-*N*-desmethyl-*ent*-7-oxo-4′-*N*-(*tert*-butyloxycarbonyl)staurosporine (83). To a green solution of 0.2831 g (0.592 mmol) of indolocarbazole **82** in 30 mL of THF was added 0.0072 g (0.0788 mmol) of DMAP and 0.41 mL (2.96 mmol) of triethylamine. A 0.4 mL portion of a 0.39 M solution of BOC_2O in THF was added dropwise every 30 min until the starting material was nearly consumed. The reaction mixture was diluted with EtOAc, extracted with H_2O, rinsed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography (19:1 CH_2Cl_2:MeOH) on silica gel provided 0.2781 g (81%) of **83** as a yellow solid: R_f 0.44 (19:1 CH_2Cl_2:MeOH); $[\alpha]^{20}_D$ −55.7° (*c* 3.19, acetone); IR (film) 3280, 1800, 1740, 1710, 1560, 1450, 1300, 740 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 9.92 (s, 1H), 9.32 (d, J = 7.3 Hz, 1H), 9.13 (d, J = 8.6 Hz, 1H), 8.10 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 8.3 Hz, 1H), 7.59 (m, 2H), 7.39 (m, 2H), 7.11 (dd, J = 10.2, 6.3 Hz, 1H), 5.46 (d, J = 8.4 Hz, 1H), 4.99 (m, 1H), 3.19 (m, 1H), 2.61 (m, 1H), 2.14 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (75.4 MHz, acetone-d_6) δ 171.1, 170.8, 150.3, 149.6, 142.8, 139.1, 131.4, 129.5, 128.1, 127.4, 126.5, 126.1, 125.3, 122.8, 122.1, 121.7, 121.3, 119.3, 117.4, 109.5, 94.1, 84.2, 80.3, 75.5, 54.2, 28.0; HRMS (FAB) *m/e* calcd for FAB (M^+) $C_{32}H_{26}N_4O_7$ 578.1802, found 578.1824; 578, 479, 391, 309, 289, 167, 149, 136.

6-*N*-[(Benzyloxy)methyl]-3′-*O*,4′-*N*-carbonyl-3′-*O*-desmethyl-4′-*N*-desmethyl-*ent*-7-oxo-4′-*N*-(*tert*-butyloxycarbonyl)staurosporine (84). To a green solution of 0.2470 g (0.427 mmol) of indolocarbazole **83** in mL of DMF was added 0.0119 g (0.4695 mmol, 95%) of NaH. After 15 min, 0.077 mL (0.555 mmol) of BOMCl was added dropwise and the reaction was allowed to stir at ambient temperature for 30 min. The reaction was then quenched by the addition of 5.0 mL of saturated NH_4Cl and was diluted with EtOAc. The resulting solution was extracted with H_2O (3×), rinsed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography (4:1 EtOAc:hexane) provided 0.2446 g (82%) of **84** as a yellow solid: R_f 0.54 (1:4 hexane:EtOAc); $[\alpha]^{20}_D$ −56.4° (*c* 0.67, CH_2Cl_2); IR (film) 2950, 1815, 1750, 1710, 1565, 1340, 1165, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.38 (d, J = 7.9 Hz, 1H), 9.21 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 8.7 Hz, 1H), 7.60 (m, 2H), 7.42 (m, 4H), 7.17−7.36 (m, 5H), 6.59 (dd, J = 10.6, 6.5 Hz, 1H), 5.35 (s, 2H), 5.11 (d, J = 8.7 Hz, 1H), 4.79 (m, 1H), 4.75 (s, 2H), 3.12 (m, 1H), 2.49 (m, 1H), 2.06 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.0, 168.8, 149.3, 148.9, 141.8, 137.7, 130.4, 128.4, 128.2, 127.7, 127.5, 127.3, 127.2, 126.8, 126.1, 125.6, 124.4, 122.1, 121.8, 121.2, 120.6, 119.2, 119.1, 117.0, 116.1, 107.5, 93.0, 84.9, 79.0, 75.5, 71.4, 56.7, 51.1, 29.8, 29.7, 28.0, 27.7; FAB HRMS *m/e* calcd for (M^+) $C_{40}H_{34}N_4O_8$ 698.2377, found 698.2375.

6-*N*-[(Benzyloxy)methyl]-3′-*O*-desmethyl-4′-*N*-desmethyl-*ent*-7-oxo-4′-*N*-(*tert*-butyloxycarbonyl)staurosporine (85). To a green solution of 0.2446 g (0.350 mmol) of indolocarbazole **84** in 80 mL of MeOH was added 0.0171 g (0.0525 mmol) of Cs_2CO_3. After 15 and 30 min an additional 0.0171 g (0.0525 mmol) of Cs_2CO_3 was added. The reaction was complete after 45 min and had turned yellow. The reaction mixture was diluted with EtOAc, extracted with 10% citric acid, rinsed with brine (2×), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography (5:1 EtOAc:hexane) on silica gel provided 0.2189 g (93%) of **85** as a yellow solid: R_f 0.50 (1:4 hexane:EtOAc); $[\alpha]^{20}_D$ −72.9° (*c* 1.43, CH_2Cl_2); IR (film) 3420, 1750, 1700, 1565, 1500, 1340 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.34 (d, J = 8.1 Hz, 1H), 9.24 (d, J = 7.8 Hz, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.23−7.59 (m, 10H), 6.55 (d, J = 4.6 Hz, 1H), 5.41 (d, J = 5.3 Hz, 1H), 5.25 (d, J = 11.0 Hz, 1H), 5.18 (d, J = 11.0 Hz, 1H), 4.70 (s, 2H), 4.30 (m, 3H), 4.21 (m, 1H), 2.84 (m, 1H), 2.51 (m, 1H), 2.35 (s, 3H), 0.70 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.4, 169.2, 166.9, 141.2, 137.8, 137.6, 129.0, 128.5, 128.3, 127.8, 127.6, 127.3, 126.9, 126.3, 125.4, 123.6, 122.5, 121.6, 121.3, 119.0, 118.0, 116.4, 115.3, 107.9, 93.6, 80.8, 79.5, 75.4, 71.3, 66.7, 46.2, 32.8, 28.9, 28.1, 27.3; FAB HRMS *m/e* calcd for (M^+) $C_{39}H_{36}N_4O_7$ 672.2584, found 672.2583.

6-*N*-[(Benzyloxy)methyl]-*ent*-7-oxo-4′-*N*-(*tert*-butyloxycarbonyl)-staurosporine (86). A green solution of 0.2073 g (0.308 mmol) of indolocarbazole **85** in 15 mL of THF and 5 mL of DMF was treated with 0.30 mL (3.08 mmol) of dimethyl sulfate and 0.0296 g (1.26 mmol) of NaH. After 1 h an additional 0.15 mL (1.58 mmol) of dimethyl sulfate and 0.0148 g (0.63 mmol) of NaH were added. After 2 h the reaction was diluted with EtOAc, extracted with H_2O (3×), extracted with saturated $NaHCO_3$, rinsed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography (1:1 to 4:1 EtOAc:hexane) on silica gel provided 0.1837 g (86%) of **86** as a yellow solid: R_f 0.60 (1:4 hexane:EtOAc); $[\alpha]^{20}_D$ −104.6° (*c* 1.43, CH_2Cl_2); IR (film) 2850, 1750, 1700, 1570, 1350, 1145 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.36 (d, J = 7.7 Hz, 1H), 9.19 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.51 (m, 2H), 7.39 (m, 4H), 7.17−7.22 (m, 4H), 6.55 (m, 1H), 5.20 (s, 2H), 4.63−4.82 (br m, 1H), 4.72 (s, 2H), 3.83 (br m, 1H), 2.69 (br s, 3H), 2.61 (br m, 1H), 2.45 (br m, 1H), 2.41 (br s, 3H), 2.33 (br s, 3H), 1.48 (br s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.2, 168.9, 139.1, 137.9, 137.5, 131.2, 129.6, 128.2, 127.6, 127.4, 126.6,

126.3, 126.0, 123.6, 122.2, 120.8, 119.6, 118.2, 116.9, 115.9, 111.2, 108.0, 94.4, 85.2, 82.2, 80.3, 71.3, 66.7, 60.0, 49.8, 49.7, 29.9, 28.8, 28.4, 28.2; FAB HRMS *m*/*e* calcd for (M^+) $C_{41}H_{40}N_4O_7$ 700.2897, found 700.2942.

***ent*-7-Oxo-4′-*N*-(*tert*-butyloxycarbonyl)staurosporine (87).** To a green solution of 0.1634 g (0.2331 mmol) of indolocarbazole **86** in 7 mL of EtOAc and 7 mL of MeOH was added 0.0163 g of $Pd(OH)_2$ (20% on carbon). The reaction was then placed under a H_2 atmosphere by several evacuation/refill with H_2 cycles. The reaction was then sonicated for 15 min and was stirred vigorously overnight. The reaction was then placed under an argon atmosphere and filtered through a pad of Celite and silica gel with EtOAc, acetone, and then 19:1 CH_2Cl_2:MeOH. The crude products were concentrated *in vacuo*, dissolved in 28 mL of MeOH, and treated with 0.5 mL of 25 wt % NaOMe in MeOH. After stirring for 30 min the reaction was diluted with EtOAc, extracted with saturated NH_4Cl, rinsed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography (1:1 hexane:EtOAc) provided 0.1138 g (84%) of **87** as a yellow solid: R_f 0.41 (1:1 hexane:EtOAc); $[\alpha]^{20}_D$ −121.4° (*c* 0.72, CH_2Cl_2); IR (film) 3215, 2960, 1750, 1720, 1570, 1310, 1140, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.33 (d, J = 8.1 Hz, 1H), 9.18 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.64 (s, 1H), 7.52 (m, 2H), 7.39 (m, 2H), 7.24 (m, 1H), 6.64 (br m, 1H), 4.55−4.83 (br m, 1H), 3.81−3.96 (br m, 1H), 2.69 (s, 3H), 2.67 (br m, 1H), 2.55 (br m, 1H), 2.42 (s, 3H), 2.41 (s, 3H), 1.49 (br m, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.9, 169.6, 139.6, 137.9, 131.5, 129.9, 127.0, 126.9, 126.8, 126.6, 126.4, 126.3, 123.9, 122.6, 121.2, 121.1, 120.9, 119.6, 117.3, 116.4, 111.6, 108.2, 94.8, 85.4, 82.6, 80.6, 60.5, 50.3, 30.1, 29.9, 28.8, 28.6; FAB HRMS *m*/*e* calcd for (M^+) $C_{33}H_{32}N_4O_6$ 580.2322, found 580.2340.

***ent*-7-Oxostaurosporine (88).** To a green solution of 0.0618 g (0.1064 mmol) of indolocarbazole **87** in 8.5 mL of CH_2Cl_2 was added 1.5 mL of TFA. The reaction turned red and was complete after 15 min. The crude products were diluted with EtOAc, extracted with saturated $NaHCO_3$ (3×), rinsed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography (19:1 CH_2Cl_2:MeOH) on silica gel yielded 0.0495 g (97%) of *ent*-7-oxostaurosporine (**88**) as a yellow solid: mp > 220 °C; R_f 0.42 (9:1 $CHCl_3$:MeOH); $[\alpha]^{20}_D$ −40.0° (*c* 0.065, $CHCl_3$); 7-oxostaurosporine $[\alpha]^{20}_D$ +39.2° (*c* 0.05, $CHCl_3$); natural 7-oxostaurosporine $[\alpha]^{20}_D$ +38.3° (*c* 0.06, $CHCl_3$); IR (film) 3215, 2940, 1755, 1700, 1570, 1460, 1320, 750 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 9.78 (s, 1H, N6*H*), 9.31 (d, J = 8.0 Hz, 1H, *H*8), 9.19 (d, J = 7.9 Hz, 1H, *H*4), 8.01 (d, J = 8.7 Hz, 1H, *H*11), 7.54 (m, 2H, Ar*H*), 7.43 (m, 1H, Ar*H*), 7.35 (m, 1H, Ar*H*), 7.27 (m, 1H, Ar*H*), 6.66 (br d, J = 4.2 Hz, 1H, *H*6′), 4.08 (br s, 1H, *H*3′), 3.45 (s, 3H, OCH_3), 3.39 (br m, 1H, *H*4′), 2.77 (m, 1H, *H*5′), 2.53 (m, 1H, *H*5′), 2.33 (s, 3H, NCH_3), 2.04 (s, 1H, N4′*H*), 1.44 (s, 3H, C$H_3$1′); ^{13}C NMR (75.4 MHz, acetone-d_6) δ 171.5, 171.3, 142.0, 139.0, 132.5, 131.6, 127.4, 126.6, 126.2, 125.7, 124.3, 122.9, 121.3, 121.1, 120.7, 120.2, 117.2, 116.3, 115.9, 109.2, 92.1, 84.5, 81.1, 57.4, 51.1, 33.7, 30.5, 30.1; CI(CH_4) HRMS *m*/*e* calcd for $C_{28}H_{25}N_4O_4$ 481.1867, found 481.1876.

***ent*-Staurosporine (2).** To a green solution of 0.0257 g (0.0534 mmol) of 7-oxostaurosporine (**88**) in 4.0 mL of EtOH was added 0.0060 g (0.16 mmol) of $NaBH_4$. Every hour an additional (0.0060 g) portion of $NaBH_4$ was added. Over 4.0 h the reaction had turned slowly clear and then light brown and was complete by TLC. The crude products were diluted with EtOAc, extracted with saturated NH_4Cl, extracted with $NaHCO_3$, rinsed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude products were dissolved in 2.0 mL of CH_2Cl_2 and were treated with 0.04 mL (0.3745 mmol) of phenylselenol and 0.0020 g (0.0107 mmol) of *p*-toluenesulfonic acid monohydrate. After stirring for 1 h the reaction was concentrated *in vacuo*. Flash chromatography (19:1 → 10:1 CH_2Cl_2:MeOH) on silica gel provided a 1:1 mixture of *ent*-staurosporine (**2**) and *ent*-isostaurosporine (**89**) and 0.0038 g (15%) of recovered **88**. Preparative TLC (19:1 CH_2Cl_2:MeOH) provided 0.0097 g (39%) of *ent*-isostaurosporine (**89**) and 0.0097 g (39%) of *ent*-staurosporine (**2**) as light yellow solids: mp > 230 °C; R_f 0.55 ($CHCl_3$:MeOH); $[\alpha]^{20}_D$ −33.5° (*c* 1.02, MeOH); staurosporine $[\alpha]^{20}_D$ +30.0° (*c* 0.22, MeOH); natural staurosporine $[\alpha]^{20}_D$ +35.0° (*c* 1.0, MeOH); IR (film) 3200, 2890, 1650, 1440, 1325, 1290, 1100, 725 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 9.46 (d, J = 8.0 Hz, 1H, *H*4), 8.04 (d, J = 8.6 Hz, 1H, *H*11), 7.97 (d, J = 7.7 Hz, 1H, *H*4), 7.53 (d, J = 8.1 Hz, 1H, *H*1), 7.47 (br s, 1H, N6*H*), 7.45 (app t, J = 8.1, 7.1 Hz, 1H, Ar*H*), 7.40 (app t, J = 7.2 Hz, 1H, Ar*H*), 7.27 (m, 2H, Ar*H*), 6.71 (dd, J = 5.6, 1.3 Hz, 1H, *H*6′), 5.03 (s, 2H, *H*7), 4.12 (d, J = 3.7 Hz, 1H, H3′), 3.49 (s, 3H, OCH_3), 3.40 (dd, J = 3.7, 1.4 Hz, 1H, *H*4′), 2.74 (ddd, J = 15.0, 3.8, 1.5 Hz, 1H, *H*5′), 2.40 (ddd, J = 15.0, 5.5, 3.7 Hz, 1H, *H*5′), 2.36 (s, 3H, C$H_3$1′), 1.50 (s, 3H, 4′NCH_3); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 173.6, 139.8, 136.7, 132.2, 130.8, 128.8, 127.1, 125.0, 124.7, 124.2, 123.5, 120.6, 119.9, 119.7, 118.5, 115.5, 115.2, 114.1, 106.8, 91.2, 84.2, 80.2, 57.3, 50.5, 45.9, 33.3, 30.3, 30.0; FAB HRMS *m*/*e* calcd for (M + H) $C_{28}H_{27}N_4O_3$ 467.2083, found 467.2090.

***ent*-Isostaurosporine (89):** mp > 230 °C; R_f 0.51 ($CHCl_3$:MeOH); $[\alpha]^{20}_D$ +17.1° (*c* 1.04, CH_2Cl_2); IR (film) 3218, 2923, 1675, 1258, 1350, 1314, 1235, 1108, 743 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 9.66 (d, J = 8.0 Hz, 1H, *H*8), 8.06 (d, J = 7.8 Hz, 1H, *H*4), 7.97 (d, J = 8.6 Hz, 1H, *H*11), 7.62 (d, J = 8.1 Hz, 1H, *H*1), 7.50 (dt, J = 8.1, 1.1 Hz, 1H, Ar*H*), 7.45 (br s, 1H, Ar*H*), 7.35 (m, 2H, Ar*H*), 7.19 (dt, J = 7.8, 1.0 Hz, 1H, Ar*H*), 6.71 (dd, J = 5.6, 1.3 Hz, 1H, *H*6′), 5.04 (s, 2H, *H*5), 4.12 (d, J = 3.6 Hz, 1H, *H*3′), 3.43 (s, 3H, OCH_3), 3.41 (dd, J = 7.7, 3.9 Hz, 1H, *H*4′), 2.75 (ddd, J = 10.9, 4.1, 1.6 Hz, 1H, *H*5′), 2.62 (m, 1H, *H*5′), 2.36 (s, 3H, 1′CH_3), 1.60 (s, 3H, 4′NCH_3), 1.29 (s, 1H, 4′N*H*); ^{13}C NMR (74.5 MHz, acetone-d_6) δ 173.7, 140.6, 138.1, 134.2, 130.6, 129.2, 127.9, 125.7, 125.1, 124.1, 122.3, 120.9, 119.9, 119.7, 119.5, 116.4, 115.3, 114.1, 109.4, 92.1, 84.8, 81.4, 58.3, 57.7, 51.8, 46.1, 34.0, 30.9; FAB HRMS *m*/*e* calcd for (M + H) $C_{28}H_{27}N_4O_3$ 467.2083, found 467.2080.

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Supporting Information Available: Experimental data for selected compounds and crystallographic data for **28a** (23 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 ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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