Design and Implementation of an Efficient Synthetic Approach to Pyranosylated Indolocarbazoles: Total Synthesis of (+)-RK286c, (+)-MLR-52, (+)-Staurosporine, and (−)-TAN-1030a

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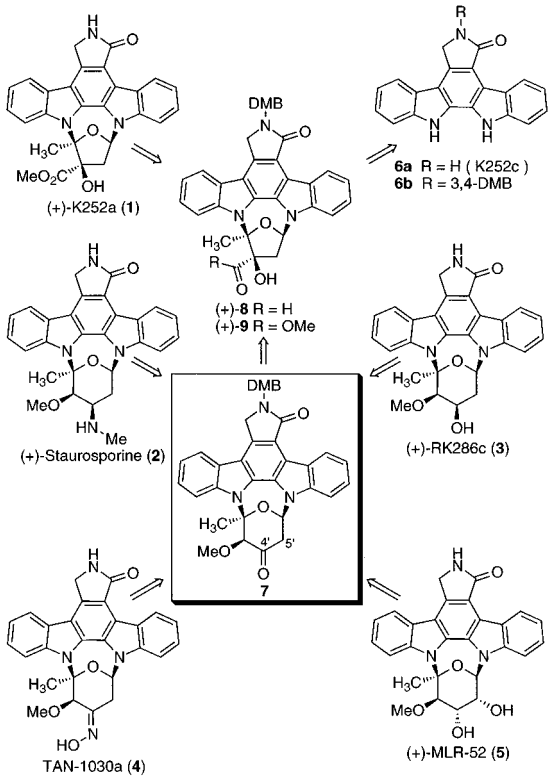
Abstract: A total synthesis of the natural products (+)-staurosporine (**2**), (+)-RK286c (**3**), (−)-TAN-1030a (**4**), and (+)-MLR-52 (**5**) has been achieved. The synthetic strategy involves the stereoselective ring expansion of a furanosylated indolocarbazole [(+)-**8**] to a pyranosylated congener [(+)-**12**] that serves as a common intermediate in the production of **2**−**5**.

The indolocarbazole alkaloids are an emerging class of natural products that possess diverse structures and biological activities.[1] As part of a program in the area of indolocarbazole total synthesis we initiated an effort toward K252a (**1**), a furanosylated member of this family.[2] The efficiency with which the synthesis of the latter compound was achieved led us to consider extending our efforts to the pyranosylated congeners illustrated in Scheme 1 (i.e., **2**−**5**).[3] Herein we describe the evolution and successful implementation of this synthetic approach.

Perhaps the most notable pyranosylated indolocarbazole, staurosporine (**2**), was isolated from *Streptomyces* sp. AM-2282 and subsequently found to affect a wide variety of biological functions.[4] In 1990, (+)-RK286c (**3**) was isolated and found to be a weak inhibitor of protein kinase C compared to **2** but comparable in its platelet aggregation inhibitory activity.[5] One year prior to this, TAN-1030a (**4**) was identified and shown to activate macrophage functions in mice.[6] Finally, in 1994 researchers at Abbott disclosed their isolation of the micromolar PKC inhibitor (+)-MLR-52 (**5**) and reported that it possessed potent *in vitro* immunosuppressive activity ($IC_{50} = 1.9 \pm 0.2$ nM) similar to FK-506 ($IC_{50} = 0.39 \pm 0.12$ nM), cyclosporine ($IC_{50} = 2.5 \pm 0.8$ nM), and staurosporine ($IC_{50} = 1.3 \pm 0.2$ nM).[7]

Retrosynthetic Analysis: Development of a Ring Expansion Approach to the Pyranosylated Indolocarbazoles. Given that cycloglycosidations akin to that employed in our synthesis of **1** had failed in the pyranosylated series,[2] we began by considering approaches that involved the ring expansion of a furanosylated intermediate. Noting the striking structural homology of **2**−**5**, we envisioned a strategy that would allow access to these congeners via a common intermediate. Specifically, α-methoxy ketone **7** was viewed as ideal since the stereogenic centers common among **2**−**5** are in place and flexibility for stereocontrolled functionalization at C(4′) and C(5′) is maintained (Scheme 1). Thus, reduction of **7** at C(4′) from the convex face would provide RK286c (**3**), reductive amination would produce staurosporine (**2**), and β-elimination of either a C(4′)-amine (via Cope elimination) or -hydroxyl (via Martin's sulfurane or Burgess dehydration) followed by dihydroxylation would produce MLR-52 (**5**). Furthermore, conver-

Scheme 1



[⊗] Abstract published in *Advance ACS Abstracts,* September 15, 1997.

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

(2) See the preceding paper in this issue.

(3) For a preliminary communication of our efforts in this area, see: Wood, J. L.; Stoltz, B. M.; Goodman, S. N. *J. Am. Chem. Soc.* **1996**, *118*, 10656.

(4) (a) Ōmura, S.; Iwai, Y.; Hirano, A.; Nakagawa, A.; Awaya, J.; Tsuchiya, H.; Takahashi, Y.; Masuma, R. *J. Antibiot.* **1977**, *30*, 275. (b) Tamaoki, T.; Nomoto, H.; Takahashi, I.; Kato, Y.; Morimoto, M.; Tomita, *F. Biochem. Biophys. Res. Commun.* **1986**, *135*, 397.

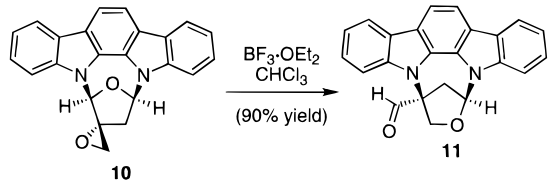
(5) Takahashi, H.; Osada, H.; Uramoto, M.; Isono, K. *J. Antibiot.* **1990**, *43*, 168.

(6) For the isolation and structure determination of TAN-1030a, see: (a) Tanida, S.; Takizawa, M.; Takahashi, T.; Tsubotani, S.; Harada, S. *J. Antibiot.* **1989**, *42*, 1619. (b) Tsubotani, S.; Tanida, S.; Harada, S. *Tetrahedron* **1991**, *47*, 3565.

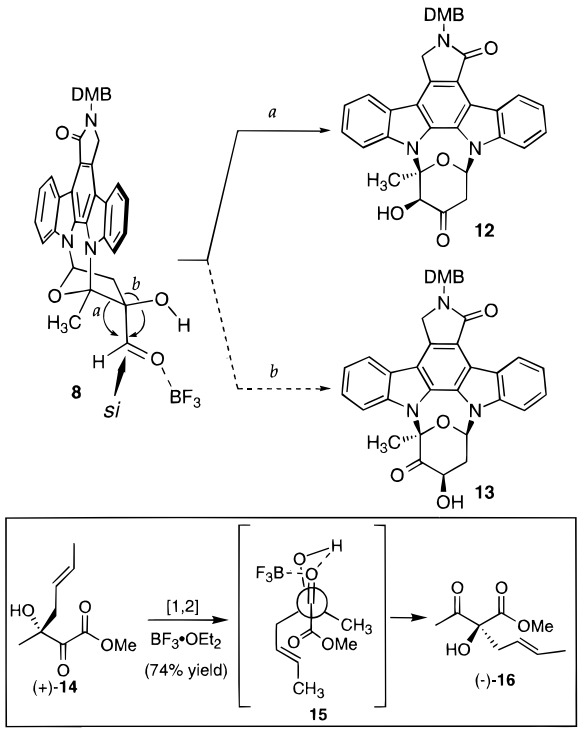
(7) McAlpine, J. B.; Karwowski, J. P.; Jackson, M.; Mullally, M. M.; Hochlowski, J. E.; Premachandran, U.; Burres, N. S. *J. Antibiot.* **1994**, *47*, 281.

S0002-7863(97)01304-8 CCC: $14.00

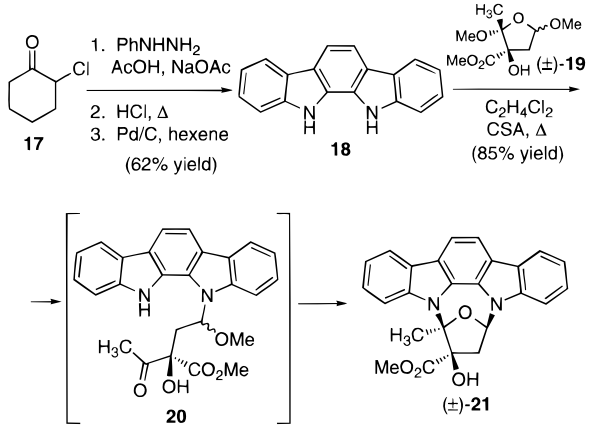
Scheme 2



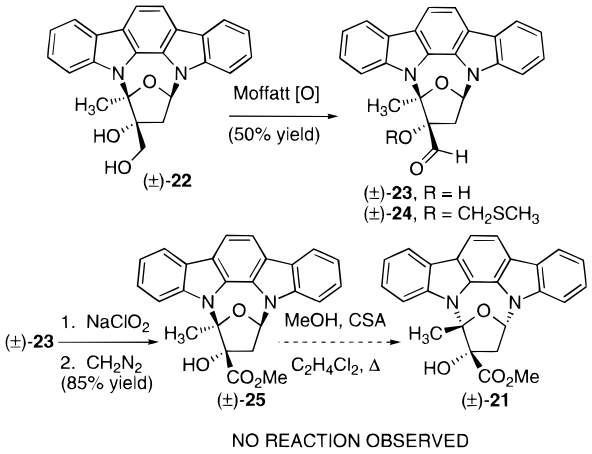
Scheme 3



Scheme 4



Scheme 5



sion of ketone **7** to the corresponding oxime would lead to TAN-1030a (**4**). The inspiration for developing this approach derived from our recognition that ketone **7** might be accessed from aldehyde **8** via a Tiffaneu−Demyanov-like ring expansion (Schemes 1 and 3). Aldehyde **8** was in turn envisioned to be readily available via reduction of (+)-**9**, the penultimate intermediate in our K252a synthesis.[2]

In designing this ring expansion approach, we considered the issues of regio- and stereochemical outcome and the known propensity of similar systems to undergo skeletal rearrangement upon attempted ring expansion (i.e., **10** → **11**, Scheme 2).[8] As shown in Scheme 3, the planned rearrangement could occur with migration of either bond a or bond b of aldehyde **8**, to produce regioisomeric hydroxy ketones **12** or **13**, respectively. Reasoning that bond a, being the more substituted linkage, would have a higher migratory aptitude, we anticipated production of **12**. In addition, we postulated that the stereochemical outcome, that is migration of bond a to either the *re* or *si* face of the aldehyde, would be in accord with that observed in the α-ketol rearrangement of **14** wherein a syn-periplanar orientation of the hydroxyl and carbonyl oxygens was shown to be operative (e.g., **14** → **15** → **16**).[2] Thus, we expected bond a would migrate to the *si* face of the aldehyde, producing a product (**12**), which possesses both the regio- and stereochemistry needed for further advancement to staurosporine.

Ring Expansion Model Studies. Since at the time these studies were initiated we were still in the process of optimizing our production of the protected aglycon **6b** we initiated our ring expansion efforts in a model system wherein indolo[2,3-*a*]-carbazole (**18**) replaces **6b**.[9] This indolocarbazole core was readily prepared on large scale (10 g of **18** produced in a single run) by slight modification of the known procedures (Scheme 4).[10] Importantly, bis-cycloglycosidative coupling of **18** with (±)-**19** (CSA, $C_2H_4Cl_2$, 86 °C)[11] proved highly stereoselective, producing (±)-**21** as the only isolable product in 85% yield. As in previous studies using aglycon **6b** as substrate, the reaction proceeds through an inseparable mixture of diastereomeric monoamino acetals **20**, and the product **21** proved stable upon reexposure to glycosylation conditions wherein MeOH is added in place of (±)-**19**. Although the irreversibility of this reaction suggested that the observed stereoselectivity results from a kinetic preference, definitive proof of this required independent preparation of the unobserved diastereomer [(±)-**25**].

The latter was readily accessed with aid from the McCombie group at Shering-Plough, who provided us with diol (±)-**22**, a precursor to **25** (Scheme 5). Exposure of (±)-**22** to Moffatt oxidation[12] produced (±)-**23** (50% yield) and the corresponding MTM-ether (±)-**24** (13% yield). The former was converted to (±)-**25** via chlorite oxidation and methylation (CH_2N_2).[13] As

(8) Shankar, B. B.; McCombie, S. W.; Kirkup, M. P.; Viet, A. Q.; Puar, M. S.; Ganguly, A. K. *Tetrahedron Lett.* **1993**, *34*, 5685.

(9) For preliminary communication of our efforts in this model system, see: (a) Stoltz, B. M.; Wood, J. L. *Tetrahedron Lett.* **1995**, *36*, 8543. (b) Stoltz, B. M.; Wood, J. L. *Tetrahedron Lett.* **1996**, *37*, 3929. (c) Wood, J. L.; Stoltz, B. M.; Onwueme, K.; Goodman, S. N. *Tetrahedron Lett.* **1996**, *37*, 7335.

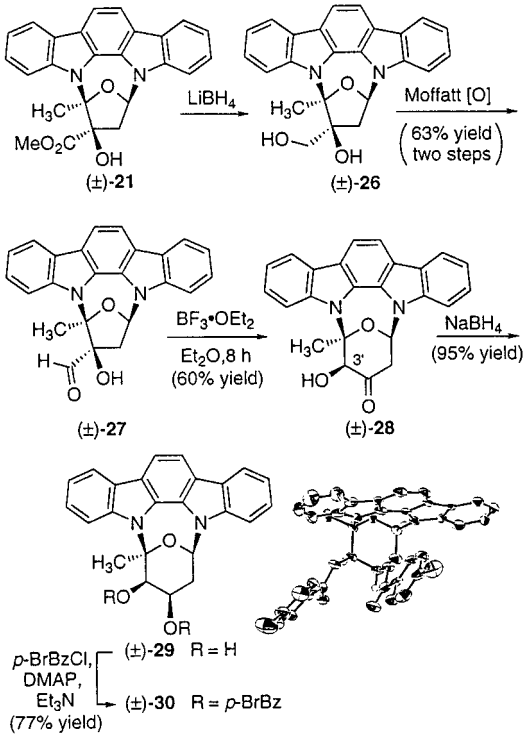
(10) (a) Bhide, G. V.; Tikotkar, N. L.; Tilak, B. D. *Chem. Ind.* **1957**, 363. (b) Mann, F. G.; Willcox, T. J. *J. Chem. Soc.* **1958**, 1525. (c) Moldenhauer, W.; Simon, H. *Chem. Ber.* **1969**, *102*, 1198.

(11) Furanose (±)-**19** can be prepared as described in the previous paper in this issue.

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

(13) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567.

Scheme 6

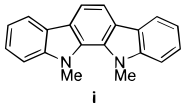


with (±)-**21**, isomeric ester (±)-**25** proved stable to the conditions of glycosidation in the presence of added (±)-**19** or MeOH, thus, confirming that an appreciable amount of **25** had not been formed in the coupling of **18** with **19**, otherwise it would have been observed.

Having explored the preparation of (±)-**21** in some detail, we turned to the ring expansion and converted (±)-**21** to aldehyde (±)-**27** via a two-step protocol (Scheme 6) involving $LiBH_4$ reduction and Moffatt oxidation (63% yield, two steps). Upon exposure to $BF_3{\cdot}OEt_2$ in Et_2O, the derived aldehyde (±)-**27** underwent slow conversion to a single new product that was found to be spectroscopically accordant with ketone (±)-**28**. The structure was unambiguously secured by single-crystal X-ray analysis of (±)-**30**, the product of bis-*p*-bromo benzoylation of diol (±)-**29**. Importantly, this X-ray structure, coupled with information obtained from the ^1H NMR of (±)-**28**, established that ring expansion furnishes the regio- and stereochemistry needed for the preparation of **2**−**5** and reduction reactions en route to these compounds could be expected to occur from the exposed convex face.

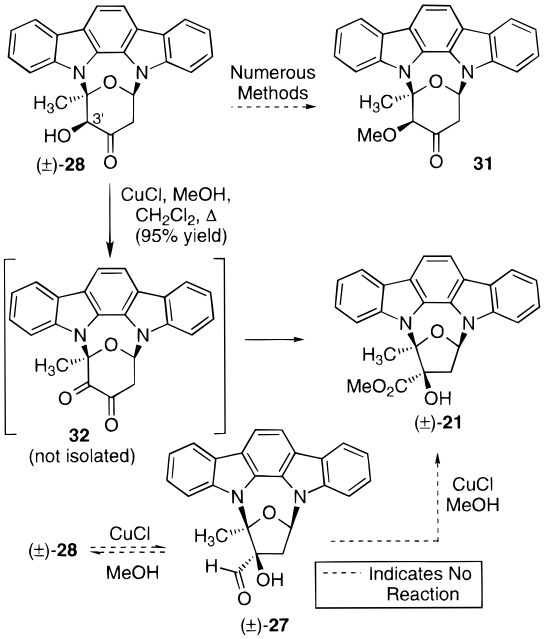
Completion of the Model Investigation. To complete our model investigation, we attempted accessing key intermediate **31** by methylating the C(3′) hydroxyl in (±)-**28**. Surprisingly, under numerous methylation conditions, this seemingly simple transformation failed.[14] However, in the course of these efforts we inadvertently discovered that CuCl in MeOH promotes the very facile and stereoselective oxidative ring contraction of (±)-**28** to (±)-**21** (95% yield). In an attempt to discern the mechanism, it was found that aldehyde (±)-**27** remains unchanged upon exposure to the CuCl reaction conditions; thus,

(14) Attempted methylation using, for example, MeI/AgO, Me_3OBF_4, MeOTf, $CH_2N_2/BF_3{\cdot}OEt_2$ or SiO_2, or MeI/KOH/*n*-Bu_4NBr resulted in either no reaction or the production of **i**

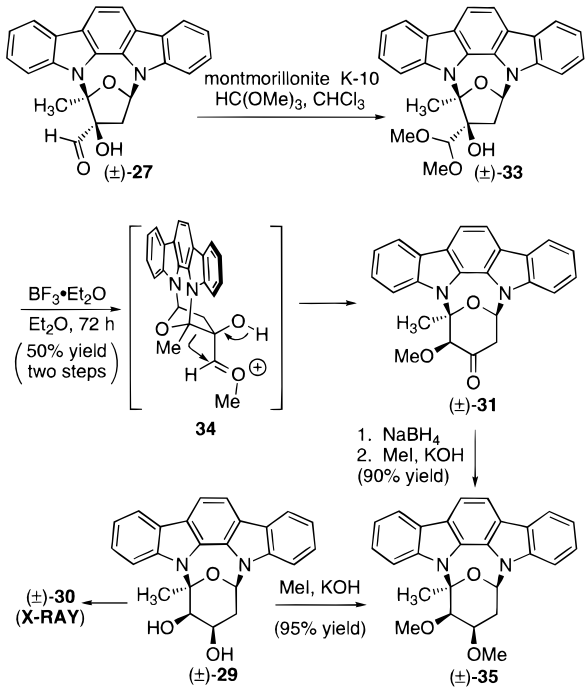


i

Scheme 7



Scheme 8



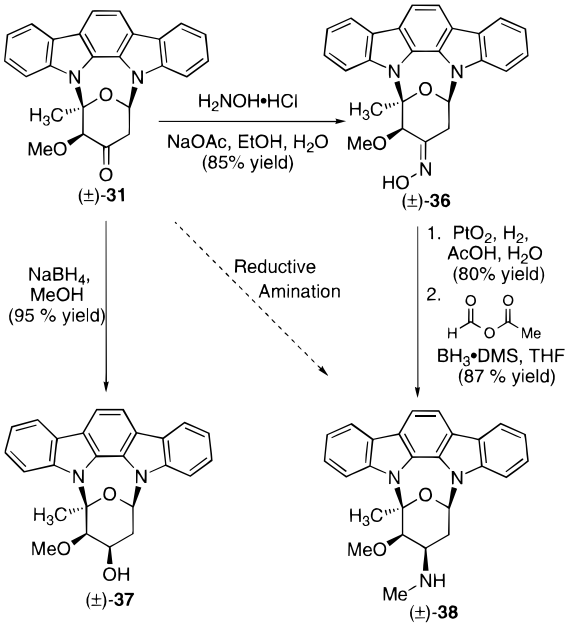
this reaction likely proceeds by oxidation of keto alcohol (±)-**28** to diketone **32** followed by stereoselective benzylic acid rearrangement to furanose (±)-**21** (Scheme 7).[15]

To circumvent the troublesome alkylation, an alternative method was envisioned wherein the methyl ether would arise directly from ring expansion through oxocarbenium ion **34** (Scheme 8). To orchestrate this event, aldehyde (±)-**27** was converted to the corresponding dimethyl acetal **33** with $CH(OMe)_3$ and montmorillonite clay K-10. Removal of the clay by filtration followed by solvent exchange with Et_2O and exposure of the crude product[16] to $BF_3{\cdot}OEt_2$ led to the slow formation

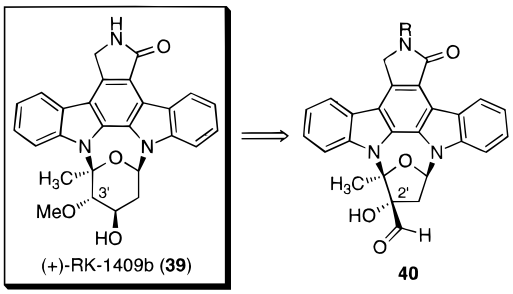
(15) Attempts to prepare diketone **32** by oxidation of hydroxyketone (±)-**28** using the conditions of Moffatt, Dess-Martin, or Swern were unsuccessful.

(16) Dimethyl acetal **33** proved difficult to isolate and was subject to rapid hydrolysis upon attempted purification.

Scheme 9



Scheme 10



of a new compound.[17] After 24 h at ambient temperature, the product was isolated and found to be spectroscopically accordant with the elusive α-methoxy ketone (±)-**31**. To provide unambiguous proof of structure, a chemical correlation to the X-ray structure obtained on (±)-**30** was implemented. As shown in Scheme 8, reduction of (±)-**31** with $NaBH_4$ followed by methylation produced (±)-**35**, a compound identical to that prepared by methylation of diol (±)-**29**, the benzoylation substrate that produced (±)-**30**.

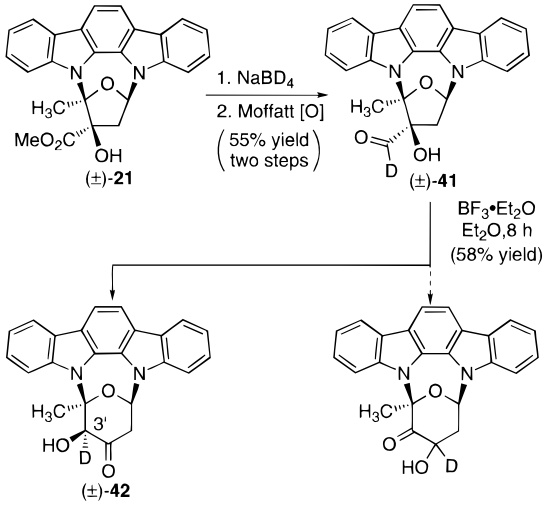
Having accessed common intermediate **31**, a synthesis of the desamido analogs of **2**−**5** was at hand. Thus, desamido TAN-1030a [(±)-**36**] and RK286c [(±)-**37**] were prepared by reaction of (±)-**31** with hydroxylamine hydrochloride in the presence of NaOAc and reduction with $NaBH_4$, respectively (Scheme 9). Attempts to prepare desamidostaurosporine [(±)-**38**] by direct reductive amination of (±)-**31** failed; however, a three-step protocol beginning with oxime formation, followed by reduction and monomethylation, proved quite effective in delivering (±)-**38** (59% yield, three steps).

In the final stages of our model investigation we directed our efforts toward RK-1409b (**39**), the C(3′) isomer of RK286c (Scheme 10).[18] On the basis of previous experiences in the synthesis of (±)-**28** and (±)-**31**, we reasoned that **39** would be available from **40**, the C(2′) epimer of **8**, via ring expansion through a transition state possessing a syn-periplanar relationship

(17) In addition to the new product, a small amount of (±)-**28** was also observed. The latter is likely the result of partial hydrolysis and rearrangement.

(18) Koshino, H.; Osada, H.; Amano, S.; Onose, R.; Isono, K. *J. Antibiot.* **1992**, *45*, 1428.

Scheme 11



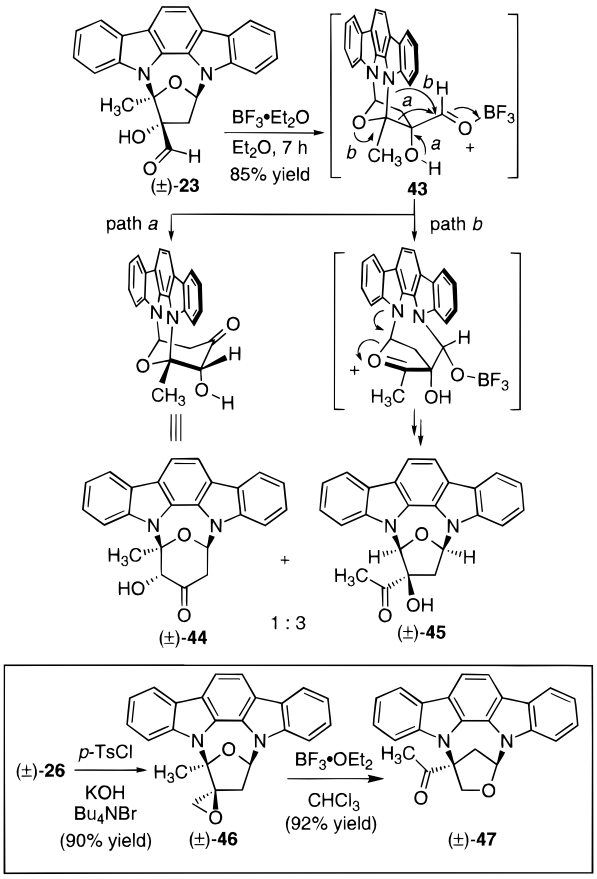
between the hydroxyl and carbonyl moieties (e.g., **43**, Scheme 12). Recognizing that this hypothesis was based on the assumption that the product in our model ring expansion [(±)-**28**] was not a thermodynamic trap but had been produced directly from (±)-**27**, we decided to probe the latter's rearrangement chemistry by employing deuterated aldehyde **41** as the substrate (Scheme 11). Thus, reduction of (±)-**21** with $NaBD_4$ followed by Moffatt oxidation afforded aldehyde (±)-**41** (92% deuterium incorporation) which, when exposed to our standard ring expansion conditions, formed (±)-**42** with over 90% D incorporation at C(3′). This observation provides evidence that (±)-**42** is the direct product from ring expansion and does not arise via epimerization of C(3′) or tautomerization of the corresponding regioisomer (Scheme 11).

Turning to the synthesis of desamido **39**, we exposed aldehyde (±)-**23** (*vide supra*) to $BF_3{\cdot}OEt_2$ and were surprised to discover the formation of two products (1:3 mixture) wherein the minor component was identified as the desired hydroxy ketone (±)-**44** (path a, Scheme 12). The major component possessed spectral properties in accord with (±)-**45**, the product of an acetal exchange (path b, Scheme 12) that is reminiscent of that seen by McCombie in an attempted ring expansion of epoxide **10** (Scheme 2, **10**→**11**) and experiences in our own laboratories wherein epoxide **46**, prepared from diol (±)-**26**, was found to undergo smooth conversion to **47** when exposed to $BF_3{\cdot}OEt_2$ (Scheme 12).

Ring Expansion Studies in the Natural System. With the rather extensive preliminary investigation complete, we advanced to the synthesis of **2**−**5** by preparing multigram quantities of (+)-**9** via our previously developed 11-step sequence.[2] To set the stage for ring expansion, (+)-**9** was subjected to the $LiBH_4$ reduction/Moffatt oxidation protocol developed in the model study. In the event, ring expansion substrate (+)-**8** was produced in good yield (Scheme 13). In accord with our previous studies, the ring expansion was attempted on both aldehyde (+)-**8** and the corresponding dimethyl acetal **49**; the latter was prepared by treatment of (+)-**8** with $CH(OMe)_3$ in the presence of montmorillonite clay K-10. To our delight, exposing an ether suspension of (+)-**8** to $BF_3{\cdot}OEt_2$,[19] followed by filtration was found to provide (+)-**12** as a pure white powder in 85% isolated yield! In contrast, ring expansion of **49** was much slower and, after 1 week, produced only a trace amount (5% yield) of a compound spectroscopically consistent with methoxy ketone **7**.[20]

(19) The reaction proceeded sluggishly and required stirring at 25−30 °C for 24 h, noticeably longer than in the model system.

Scheme 12



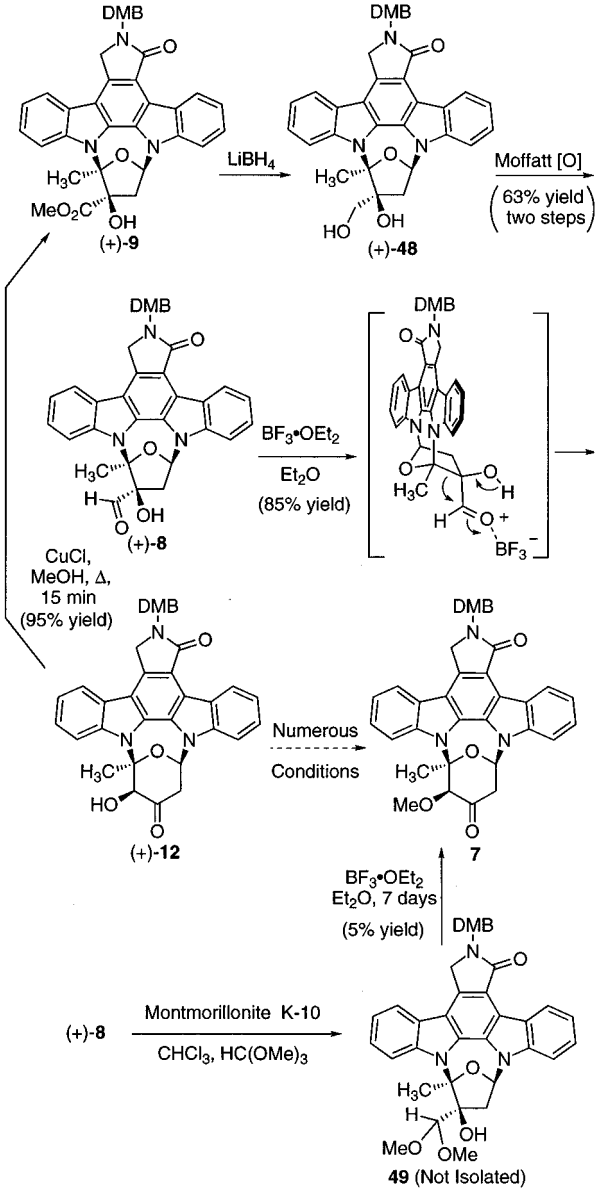
Regioselective Monomethylation: Completion of RK-286c and MLR-52. Our inability to effectively advance **49** led us to re-address the problematic C(3′) methylation identified in our model study (Scheme 13). In the event, (+)-**12** was found to be identical to the model α-hydroxy ketone (+)-**28** in both its resistance toward methylation and the interesting oxidation/ring contraction reactivity [e.g., (+)-**12**→(+)-**9**]. At this stage it became clear that successful alkylation of the C(3′) hydroxyl would require altering the substrate. Rather than expending (+)-**12** for these studies, we returned to the model and soon discovered that diol (±)-**29** could be advanced via complementary alkylation reactions promoted by either NaH/MeI, which produced the desired C(3′) ether (±)-**37** or [$Bu_2Sn(OMe)_2$]/MeI, which furnished the C(4′) ether (±)-**50** via the corresponding stannylene (Scheme 14). The excellent selectivity observed in the conversion of (±)-**29** to (±)-**37** is attributed to the propinquous aglycon which, as evidenced by the X-ray structure illustrated in Scheme 6, creates vastly different steric environments for the equitorial [C(3′)] and axial [C(4′)] hydroxyls.

As illustrated in Scheme 15, application of the reduction/selective alkylation sequence also proved effective in the natural series to furnish (+)-**52** from (+)-**12**. Cleavage of the DMB protecting group by treatment of (+)-**52** with TFA in anisole afforded synthetic (+)-RK286c (**3**) in 75% yield. Dehydration of alcohol (+)-**52** with Martin's sulfurane cleanly furnished olefin (+)-**53**, which was stereoselectively dihydroxylated in the presence of OsO_4/NMO to give (+)-**54**. Deprotection of (+)-**54** produced (+)-MLR-52 (**5**) in 77% yield.

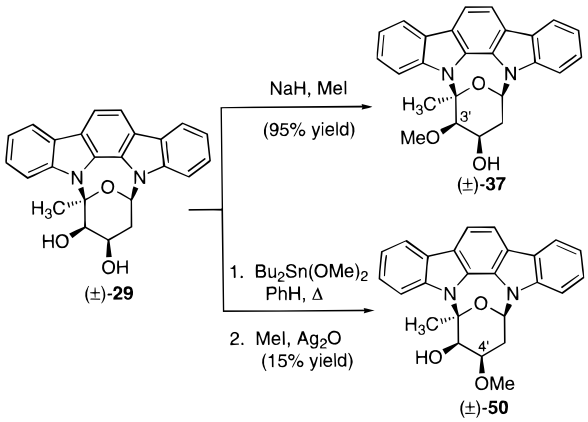
Completion of Staurosporine and TAN-1030a. Attempts to access the staurosporine and TAN-1030a systems via oxidation of (+)-**52** failed and prompted our return to ketone

(20) With this substrate, decomposition of the starting material to intractable materials competes with product formation.

Scheme 13

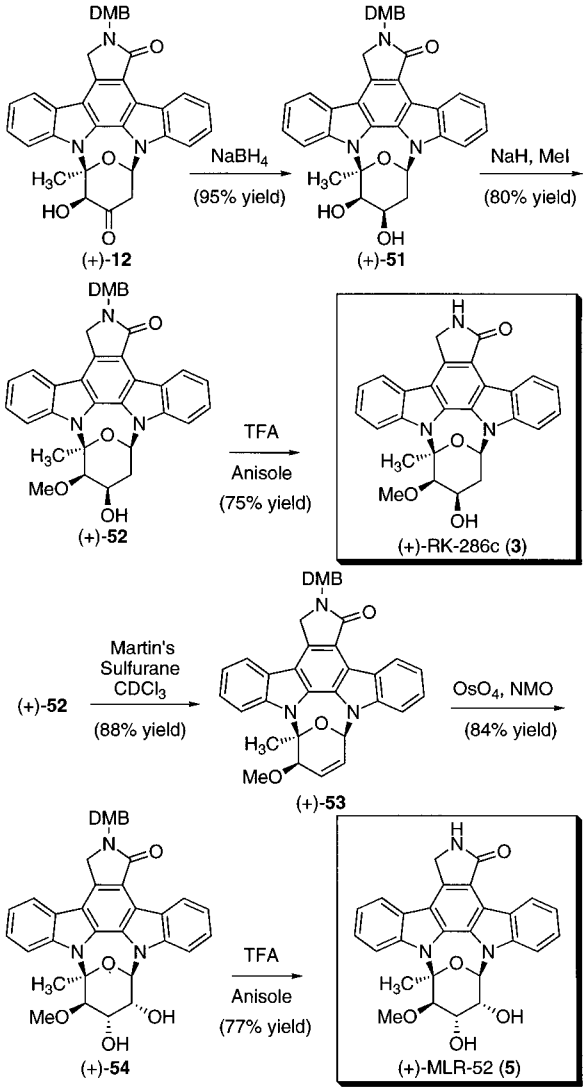


Scheme 14



(+)-**12** (Scheme 16). Thus, treatment of (+)-**12** with hydroxylamine hydrochloride produced oxime (−)-**55** in 95% yield. In contrast to ketone (+)-**12**, bis-methylation of (−)-**55** under phase transfer conditions (MeI, KOH, and *n*-Bu_4NBr in THF) occurred cleanly to afford (−)-**56** and set the stage for a stereoselective reduction (H_2/PtO_2) that furnished amine (+)-**57a**. Mono-

Scheme 15



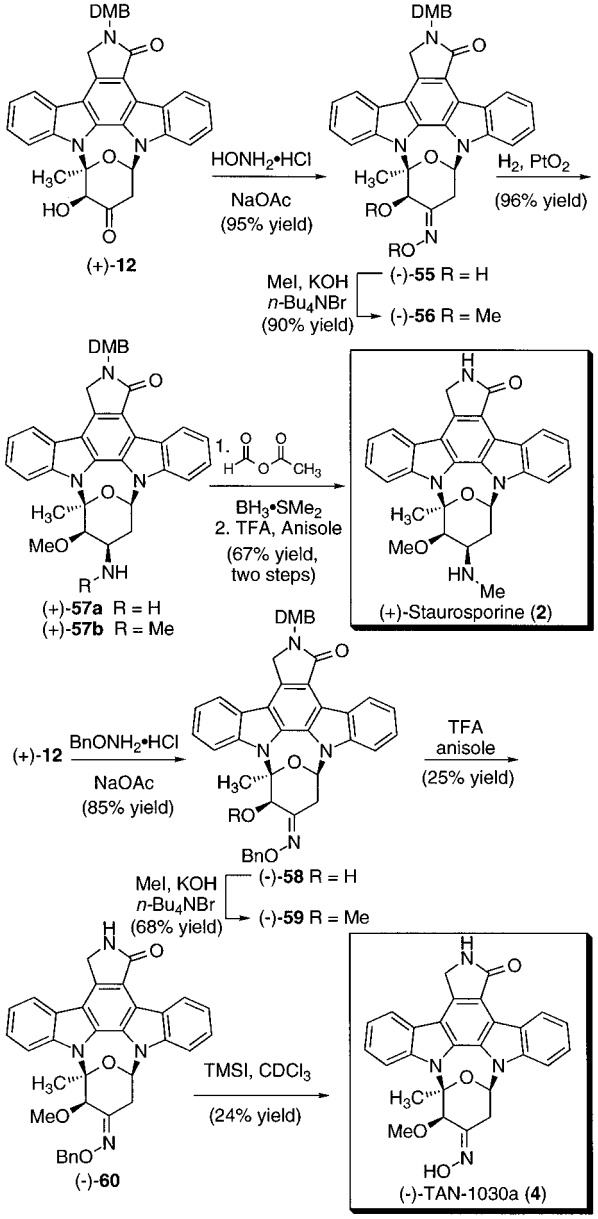
methylation and deprotection then afforded (+)-staurosporine (**2**) in 67% yield (two steps).

Our final target, TAN-1030a (**4**), required the introduction of a selectively protected oxime ether due to the instability of the free oxime to strong acid.[21] Thus, treatment of ketone (+)-**12** with *O*-benzylhydroxylamine hydrochloride followed by MeI, KOH, and *n*-Bu_4NBr produced (−)-**59**. Removal of the DMB group from (−)-**59** (TFA/anisole) followed by treatment of the derived amide (−)-**60** with iodotrimethylsilane afforded synthetic TAN-1030a (**4**) in 24% yield.

Conclusion. We have developed a ring expansion protocol which allows the transformation of a furanosylated indolocarbazole to a pyranosylated derivative suited for advancement to numerous natural products. Specifically, ring expansion of aldehyde (+)-**8** proceeds in a stereo- and regioselective manner to produce (+)-**12** (85% yield), a common intermediate in the synthesis of (+)-RK286c (**3**, 17 steps from ethyl glycinate), TAN-1030a (**4**, 18 steps), (+)-MLR-52 (**5**, 19 steps), and (+)-staurosporine (**2**, 19 steps). In addition, the unique oxidative benzylic acid rearrangement of (+)-**12** to (+)-**9** may have important biosynthetic implications. In more recent investigations, the preparation of novel indolocarbazole derivatives for biological testing and biosynthetic studies have been initiated. Results from these investigations will be reported in due course.

(21) Recently, Fredenhagen reported the effect of H_2SO_4 on TAN-1030a; see: Fredenhagen, A.; Peter, H. H. *Tetrahedron* **1996**, *52*, 1235.

Scheme 16



Experimental Section[22,23]

Diol (+)-48. To a stirred room-temperature solution of ester (+)-**9** (150 mg, 0.243 mmol, 1.0 equiv) in THF (2.5 mL) was added $LiBH_4$ (12 mg, 0.535 mmol, 2.3 equiv). After 20 min, the solvent was removed *in vacuo*, and the derived white residue was cooled to 0 °C and treated with 1.0 N HCl (10.0 mL). The aqueous solution was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic phases were dried over Na_2SO_4 and chromatographed (1:1 hexanes/EtOAc eluent) to afford diol (+)-**48** (127 mg, 89% yield) as a white solid: mp >225 °C (dec); $[\alpha]^{20}_D$ +112 (*c* 0.1, MeOH); IR (thin film/NaCl) 3343.8 (br m), 3001.5 (w), 2950.7 (m), 2926.1 (m), 1647.4 (s), 1588.0 (m), 1514.4 (m), 1459.7 (s), 1422.2 (m), 1399.6 (m), 1312.4 (m), 1138.0 (s), 744.7 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.25 (d, J = 7.9 Hz, 1H), 7.97 (d, J = 7.2 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.78 (d, J = 8.3 Hz, 1H), 7.48 (app t, J = 7.6 Hz, 1H), 7.43 (app t, J = 7.8 Hz, 1H), 7.29 (app t, J = 7.1 Hz, 1H), 7.28 (app t, J = 7.2 Hz, 1H), 7.02 (s, 1H), 7.96 (dd, J = 5.2, 7.2 Hz, 1H), 6.94 (s, 2H), 5.33 (s, 1H), 5.06 (t, J = 5.6

(22) The materials and methods used in these experiments were identical to those reported in the preceding article.

(23) Due to space limitations, experimental details pertaining to reactions performed on substrates lacking the fully functionalized aglycon have been included as Supporting Information.

Hz, 1H), 5.02 (d, J = 17.7 Hz, 1H), 4.95 (d, J = 17.6 Hz, 1H), 4.85 (d, J = 15.9 Hz, 1H), 4.85 (d, J = 15.7 Hz, 1H), 3.85−3.81 (comp m, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 3.14 (dd, J = 7.6, 13.7 Hz, 1H), 2.15 (s, 3H), 1.94 (dd, J = 4.8, 13.7 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.9, 148.9, 148.1, 140.0, 136.7, 130.5, 130.2, 128.7, 125.4, 125.3, 124.6, 124.3, 123.8, 122.4, 120.9, 120.0, 119.8, 119.2, 118.5, 115.2, 114.9, 114.0, 112.1, 111.8, 108.7, 100.2, 83.5, 64.7, 55.5, 55.5, 49.6, 45.4, 40.2, 40.1, 21.3; high-resolution mass spectrum (FAB) *m/z* 590.2289 [calcd for $C_{35}H_{32}N_3O_6$ (M + H) 590.2291].

Aldehyde (+)-8. To a stirred solution of diol (+)-**48** (395 mg, 0.67 mmol, 1.0 equiv) in 1:1 benzene/DMSO (4.6 mL) was added pyridinium trifluoroacetate (130 mg, 0.67 mmol, 1.0 equiv) followed by 1,3-dicyclohexylcarbodiimide (415 mg, 2.01 mmol, 3.0 equiv). The flask was quickly sealed with a septum, evacuated, and flushed with N_2 (3×). The heterogeneous mixture was stirred for 9 h at room temperature until reaction was complete as indicated by TLC. Benzene (5.0 mL) was added to the mixture, and the 1,3-dicyclohexylurea (DCU) precipitate was filtered. The filtrate was washed with H_2O (3 × 5.0 mL), and the combined aqueous layers were back-extracted with CH_2Cl_2 (3 × 10.0 mL). All organic layers were combined, dried over Na_2SO_4, and evaporated to give an oily residue. A minimum amount of acetone (2 mL) was added to precipitate the remaining DCU. Filtration and evaporation afforded a yellow oil, which was chromatographed (2:1 → 1:1 hexanes/EtOAc eluent) to furnish aldehyde (+)-**8** (280 mg, 71% yield, 63% yield 2 steps) as a yellow powder: mp >205 °C (dec); $[\alpha]^{20}_D$ +48 (*c* 0.1, MeOH); IR (thin film/NaCl) 3253.9 (br m), 3010.7 (m), 2953.6 (m), 2934.0 (m), 2833.9 (s), 1734.0 (s), 1646.2 (s), 1614.7 (w), 1589.9 (m), 1514.1 (m), 1399.1 (s), 1275.7 (m), 1138.4 (s), 1024.8 (m), 745.1 (s) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.07 (s, 1H), 9.31 (d, J = 7.9 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 7.7 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.50 (app t, J = 8.1 Hz, 1H), 7.47 (app t, J = 8.2 Hz, 1H), 7.32 (app t, J = 8.1 Hz, 2H), 7.17 (dd, J = 7.2, 4.8 Hz, 1H), 7.04 (s, 1H), 6.94 (d, J = 9.6 Hz, 1H), 6.93 (d, J = 8.1 Hz, 1H), 6.57 (br s, 1H), 5.02 (d, J = 17.6 Hz, 1H), 4.98 (d, J = 17.7 Hz, 1H), 4.87 (d, J = 15.2 Hz, 1H), 4.83 (d, J = 15.2 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.24 (dd, J = 7.6, 14.0 Hz, 1H), 2.22 (s, 3H), 2.00 (dd, J = 4.5, 14.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 202.2, 168.7, 148.9, 148.1, 139.9, 136.9, 130.4, 130.2, 128.2, 125.5, 125.1, 123.9, 123.9, 122.5, 121.1, 120.4, 119.9, 119.6, 119.1, 115.8, 114.6, 114.4, 112.1, 111.8, 109.0, 98.7, 86.8, 84.3, 55.5, 55.5, 49.6, 45.5, 39.4, 22.7; high-resolution mass spectrum (FAB) *m/z* 588.2135 [calcd for $C_{35}H_{30}N_3O_6$ (M + H) 588.2135].

Ketone (+)-12. To a suspension of aldehyde (+)-**8** (100 mg, 0.170 mmol, 1.0 equiv) in Et_2O (17.0 mL) was added BF_3·OEt_2 (23 μL, 0.187 mmol, 1.1 equiv). The mixture was stirred vigorously for 12 h at 25−30 °C and then treated with additional BF_3·OEt_2 (23 μL, 0.187 mmol, 1.1 equiv). After 12 h at the same temperature, the reaction mixture was filtered to provide ketone (+)-**12** (85 mg, 85% yield) as a white powder: mp >220 °C (dec); $[\alpha]^{20}_D$ +83 (*c* 0.1, DMSO); IR (thin film/NaCl) 3300.0 (br s), 2999.5 (br m), 2848.6 (m), 1728.9 (m), 1665.5 (s), 1503.3 (m), 1451.2 (s), 1406.8 (m), 1132.8 (s), 1021.9 (m), 750.6 (s) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6, 310 K) δ 9.35 (d, J = 7.9 Hz, 1H), 8.06 (d, J = 8.6 Hz, 1H), 7.92 (d, J = 7.7 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.53 (app t, J = 7.6 Hz, 1H), 7.43 (app t, J = 8.1 Hz, 1H), 7.40 (d, J = 6.6 Hz, 1H), 7.35 (app t, J = 7.5 Hz, 1H), 7.29 (app t, J = 7.4 Hz, 1H), 7.02 (s, 1H), 6.93 (s, 2H), 6.12 (d, J = 5.1 Hz, 1H), 5.23 (d, J = 4.5 Hz, 1H), 4.96 (s, 2H), 4.85 (d, J = 15.1 Hz, 1H), 4.81 (d, J = 15.1 Hz, 1H), 3.97 (dd, J = 6.7, 14.1 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 2.66 (d, J = 14.1 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (500 MHz, DMSO-d_6) δ 201.1, 168.6, 148.9, 148.1, 140.3, 136.0, 130.4, 129.8, 126.9, 125.6, 125.5, 124.9, 124.0, 123.6, 122.8, 120.7, 120.4, 119.9, 119.9, 118.8, 115.9, 115.1, 114.3, 112.1, 111.8, 109.2, 100.5, 84.4, 80.0, 55.5, 55.5, 49.6, 45.4, 44.9, 29.4; high-resolution mass spectrum (FAB) *m/z* 588.2135 [calcd for $C_{35}H_{30}N_3O_6$ (M + H) 588.2135].

Ester (+)-9. To a solution of ketone (+)-**12** (10 mg, 0.017 mmol, 1.0 equiv) in 1:1 MeOH/CH_2Cl_2 (1.0 mL) was added copper(I) chloride (30 mg, 0.30 mmol, 17.8 equiv), and the mixture warmed to reflux for 15 min. Solvent was removed *in vacuo* and the resulting residue subjected to flash chromatography (1:1 hexanes/EtOAc) to afford (+)-**9** (10 mg, 95% yield) as a colorless solid that possessed spectral properties identical to material prepared previously in these laboratories.[2]

Methoxy Ketone 7. Montmorillonite clay K-10 (160 mg) was mixed with trimethyl orthoformate (0.25 mL, 2.25 mmol, 15.0 equiv) and immediately transferred to a stirred solution of aldehyde (+)-**8** (90 mg, 0.15 mmol, 1.0 equiv) in $CHCl_3$ (0.6 mL). After 0.5 h, the reaction mixture was filtered and the filtrate evaporated *in vacuo*. The residue was dissolved in Et_2O (15 mL) under an inert atmosphere, treated with BF_3·OEt_2 (0.39 mL, 3.15 mmol, 21.0 equiv), and stirred for 7 days at 25 °C. The reaction was diluted with CH_2Cl_2 (10 mL), adsorbed onto silica gel *in vacuo*, and chromatographed (1:1 hexanes/ethyl acetate eluent) to provide methoxy ketone **7** (6 mg, 5% yield) as a yellow residue: ^{1}H NMR (500 MHz, DMSO-d_6, 320 K) δ 9.35 (d, J = 7.9 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 7.6 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.53 (app t, J = 7.6 Hz, 1H), 7.44 (app t, J = 7.6 Hz, 1H), 7.41 (d, J = 6.7 Hz, 1H), 7.35 (app t, J = 7.5 Hz, 1H), 7.30 (app t, J = 7.4 Hz, 1H), 7.02 (s, 1H), 6.93 (s, 2H), 5.04 (s, 1H), 4.96 (s, 2H), 4.85 (d, J = 15.3 Hz, 1H), 4.81 (d, J = 14.7 Hz, 1H), 3.98 (dd, J = 6.8, 14.1 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.42 (s, 3H), 2.66 (d, J = 14.2 Hz, 1H), 2.55 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6, 315 K) δ 200.0, 168.6, 148.9, 148.1, 139.9, 136.0, 130.4, 129.8, 126.8, 125.6, 125.5, 125.0, 124.9, 123.9, 123.6, 122.8, 120.8, 120.5, 120.0, 119.9, 118.9, 115.5, 115.2, 114.3, 112.2, 111.8, 109.1, 99.3, 88.0, 84.5, 58.9, 55.5, 49.5, 45.4, 29.4.

Diol (+)-51. To a stirred room-temperature solution of ketone (+)-**12** (85 mg, 0.15 mmol, 1.0 equiv) in 1:1:2 MeOH/CH_2Cl_2/$CHCl_3$ (20.0 mL) was added $NaBH_4$ (20 mg, 0.53 mmol, 3.5 equiv). After 5 min, solvent was removed *in vacuo* and the residual white solid was cooled to 0 °C and treated with 1.0 N HCl (10 mL) at 0 °C. The mixture was stirred for 15 min at 25 °C and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried with Na_2SO_4 and chromatographed (1:1 hexanes/EtOAc eluent) to afford alcohol (+)-**51** (81 mg, 95% yield) as a white solid: mp 174−176 °C (dec); $[\alpha]^{20}_D$ +37 (*c* 0.1, MeOH); IR (thin film/NaCl) 3355.5 (br m), 2922.9 (m), 2847.8 (m), 1654.5 (s), 1501.5 (w), 1449.3 (s), 1254.5 (s), 1136.8 (s), 1025.7 (m), 747.1 (s) cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 9.53 (d, J = 7.9 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 7.7 Hz, 1H), 7.51 (d, J = 8.2 Hz, 1H), 7.46 (app t, J = 7.2 Hz, 1H), 7.36 (app t, J = 7.9 Hz, 1H), 7.29 (app t, J = 7.4 Hz, 1H), 7.22 (app t, J = 7.4 Hz, 1H), 7.08 (s, 1H), 6.98 (d, J = 8.3 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 6.76 (d, J = 5.1 Hz, 1H), 4.95 (d, J = 17.1 Hz, 1H), 4.90 (d, J = 17.1 Hz, 1H), 4.89 (d, J = 15.2 Hz, 1H), 4.85 (d, J = 15.2 Hz, 1H), 4.24 (d, J = 8.5 Hz, 1H), 4.23 (br s, 1H), 4.14 (d, J = 8.6 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.64 (br s, 1H), 2.76 (d, J = 15.1 Hz, 1H), 2.65 (d, J = 15.1 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 170.4, 150.6, 149.7, 141.2, 137.7, 132.0, 130.7, 130.4, 127.6, 127.1, 125.8, 125.3, 125.0, 124.3, 121.5, 121.0, 120.6, 120.0, 119.8, 116.6, 116.0, 115.0, 112.8, 108.9, 93.3, 80.6, 74.7, 65.4, 56.1, 50.4, 46.6, 35.4, 30.4; high-resolution mass spectrum (FAB) *m/z* 590.2289 [calcd for $C_{35}H_{32}N_3O_6$ (M + H) 590.2291].

Alcohol (+)-52. To a stirred suspension of NaH (14 mg, 0.58 mmol, 4.2 equiv) in THF (1.0 mL) was added a solution of alcohol (+)-**51** (81 mg, 0.138 mmol, 1.0 equiv) in THF (7 mL). The resulting mixture was stirred for 10 min with the visible evolution of gas and for an additional 15 min thereafter. Addition of MeI (9.5 μL, 0.15 mmol, 1.1 equiv) produced a single product by TLC (2.5:1 hexanes/acetone). After approximately 50 min the reaction was quenched by addition of 1.0 N HCl (1.0 mL) followed by 2.0 mL of H_2O. Extraction of the solution with CH_2Cl_2 (3 × 10 mL), drying over Na_2SO_4, and evaporation furnished a residue which was purified by flash chromatography (2.5:1 hexanes/acetone eluent) to provide methyl ether (+)-**52** (67 mg, 80% yield) as a yellow foam: mp >235 °C (dec); $[\alpha]^{20}_D$ +48 (*c* 0.1, MeOH); IR (thin film/NaCl) 3423.7 (br m), 2923.2 (s), 2848.1 (m), 2636.2 (m), 1647.2 (s), 1514.3 (m), 1462.9 (s), 1258.0 (m), 1235.3 (m), 1136.9 (m), 1026.9 (w), 743.3 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.54 (d, J = 7.9 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.48 (app t, J = 7.6 Hz, 1H), 7.41 (app t, J = 7.2 Hz, 1H), 7.38 (app t, J = 7.2 Hz, 1H), 7.28 (m, 2H), 6.97 (d, J = 8.2 Hz, 1H), 6.95 (s, 1H), 6.86 (d, J = 8.1 Hz, 1H), 6.60 (d, J = 5.8 Hz, 1H), 4.96 (d, J = 15.0 Hz, 1H), 4.89 (d, J = 15.0 Hz, 1H), 4.84 (d, J = 16.7 Hz, 1H), 4.79 (d, J = 16.6 Hz, 1H), 4.38 (d, J = 2.6 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.71 (d, J = 2.6 Hz, 1H), 3.57 (s, 3H), 2.76 (dd, J = 3.1, 15.1 Hz, 1H), 2.50 (br d, J = 14.7 Hz, 1H), 2.3 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 315 K) δ 170.3, 149.6,

148.7, 140.1, 136.8, 130.8, 129.4, 127.0, 126.4, 125.3, 124.8, 124.3, 123.7, 120.7, 120.4, 120.2, 120.0, 119.6, 116.0, 115.5, 114.5, 111.6, 111.5, 107.1, 90.7, 83.2, 79.5, 60.6, 57.4, 56.1, 56.0, 49.9, 46.5, 33.6, 30.1; high-resolution mass spectrum (FAB) *m/z* 604.2449 [calcd for $C_{36}H_{34}N_3O_6$ (M + H) 604.2448].

(+)-RK286c (3). To a stirred solution of ether (+)-**52** (10 mg, 0.017 mmol, 1.0 equiv) in anisole or thioanisole (80 μL) was added TFA (0.5 mL). After the reaction had proceeded to completion as evidenced by TLC (ca. 24 h), H_2O (1.0 mL) was added and the derived mixture extracted with CH_2Cl_2 (3 × 5mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL), dried over Na_2SO_4, and evaporated to a residue which was purified by preparative TLC (5% MeOH/CH_2Cl_2) to provide (+)-RK-286c (**3**, 6 mg, 75% yield) as a pale white powder: mp >255 °C (dec); $[\alpha]^{20}_D$ +41 (*c* 0.18, EtOAc); IR (thin film/NaCl) 3354.0 (br m), 2920.4 (s), 2851.6 (m), 1677.2 (s), 1636.0 (m), 1585.3 (m), 1456.2 (s), 1352.8 (s), 1318.7 (s), 1231.7 (m), 1117.3 (m), 743.8 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.27 (d, J = 7.9 Hz, 1H), 8.47 (br s, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.94 (d, J = 7.7 Hz, 1H), 7.59 (d, J = 8.2 Hz, 1H), 7.45 (app t, J = 7.4 Hz, 1H), 7.40 (app t, J = 7.5 Hz, 1H), 7.26 (app t, J = 7.5 Hz, 2H), 6.78 (d, J = 5.3 Hz, 1H), 4.95 (d, J = 17.6 Hz, 1H), 4.89 (d, J = 17.7 Hz, 1H), 4.25 (br s, 1H), 4.17 (br s, 1H), 3.83 (d, J = 2.7 Hz, 1H), 3.41 (s, 3H), 2.60 (ddd, J = 3.2, 5.6, 14.8 Hz, 1H), 2.41 (dd, J = 3.3, 14.8 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 139.7, 136.1, 129.5, 125.5, 124.7, 124.1, 123.9, 122.6, 120.6, 119.5, 118.9, 118.6, 115.7, 108.6, 90.9, 82.3, 79.5, 58.8, 56.4, 45.3, 33.9, 29.9; high-resolution mass spectrum (FAB) *m/z* 454.1766 [calcd for $C_{27}H_{24}N_3O_4$ (M + H) 454.1767].

Olefin (+)-53. To a stirred solution of ether (+)-**52** (112 mg, 0.186 mmol, 1.0 equiv) in $CDCl_3$ (2.0 mL) was added Martin's sulfurane (187 mg, 0.28 mmol, 1.5 equiv). The reaction rapidly proceeded to a less polar product as evidenced by TLC and after 20 min was complete. Solvent was evaporated and the residue subjected to flash chromatography (2:1 hexanes/EtOAc eluent) to provide olefin (+)-**53** (96 mg, 88% yield) as a white solid: mp 185−187 °C; $[\alpha]^{20}_D$ +36 (*c* 0.1, MeOH); IR (thin film/NaCl) 2920.5 (s), 2851.5 (s), 1709.8 (m), 1674.3 (s), 1589.0 (m), 1513.7 (m), 1457.5 (s), 1222.9 (m), 1026.6 (m), 745.3 (m) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, 315 K) δ 9.31 (d, J = 7.9 Hz, 1H), 8.11 (d, J = 8.6 Hz, 1H), 7.91 (d, J = 7.7 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.50 (td, J = 1.0, 7.34 Hz, 1H), 7.43 (app t, J = 7.8 Hz, 1H), 7.31 (app t, J = 7.0 Hz, 1H), 7.28 (app t, J = 7.1 Hz, 1H), 7.13 (d, J = 1.9 Hz, 1H), 7.02 (s, 1H), 6.93 (d, J = 8.6 Hz, 1H), 6.92 (d, J = 8.6 Hz, 1H), 6.09 (d, J = 10.4 Hz, 1H), 5.77 (dt, J = 2.3, 10.4 Hz, 1H), 4.95 (s, 2H), 4.85 (d, J = 15.1 Hz, 1H), 4.81 (d, J = 15.1 Hz, 1H), 4.48 (d, J = 1.4 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.57 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 169.9, 150.5, 149.7, 141.3, 137.4, 131.8, 131.2, 130.5, 127.7, 127.1, 126.4, 126.2, 125.5, 125.3, 124.3, 121.5, 121.2, 121.1, 120.5, 120.4, 118.0, 117.1, 115.9, 112.8, 112.8, 109.1, 91.5, 80.8, 78.8, 57.7, 56.0, 56.0, 50.5, 46.5, 28.0; high-resolution mass spectrum (FAB) *m/z* 586.2343 [calcd for $C_{36}H_{32}N_3O_5$ (M + H) 586.2342].

Diol (+)-54. To a stirred solution of 4-methylmorpholine-*N*-oxide (6 mg, 0.05 mmol, 1.2 equiv) and OsO_4 (0.6 mL of a 2.5% solution in *t*-BuOH, 0.05 mmol, 1.2 equiv) in 4:1 acetone:H_2O (2 mL) was added a solution of olefin (+)-**53** (25 mg, 0.043 mmol, 1.0 equiv) in acetone (1 mL). The reaction was monitored by TLC and after 16 h had proceeded to completion. At this time, $NaHSO_3$ (100 mg) in H_2O (1.0 mL) was added, and the resulting black solution was stirred for 20 min, filtered, and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, evaporated to a residue, and purified by flash chromatography (1:1 hexanes/EtOAc eluent) to provide diol (+)-**54** (23 mg, 84% yield) as a white powder: mp 227−230 °C; $[\alpha]^{20}_D$ +17 (*c* 0.1, MeOH); IR (thin film/NaCl) 3411.2 (br m), 2929.3 (m), 2849.4 (w), 2656.3 (m), 1590.0 (m), 1514.0 (m), 1461.2 (s), 1350.9 (m), 1273.6 (s), 1127.1 (s), 1025.0 (m), 743.3 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.36 (d, J = 7.9 Hz, 1H), 7.95 (d, J = 8.6 Hz, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.55 (app t, J = 7.6 Hz, 1H), 7.45 (app t, J = 7.7 Hz, 1H), 7.35 (app t, J = 7.5 Hz, 1H), 7.29 (app t, J = 7.5 Hz, 1H), 7.02 (s, 1H), 6.94 (s, 2H), 6.59 (d, J = 1.6 Hz, 1H), 6.13 (d, J = 3.8 Hz, 1H), 5.07 (d, J = 6.0 Hz, 1H), 4.99 (d, J = 17.8 Hz, 1H), 4.95 (d, J = 17.8 Hz, 1H), 4.83 (s, 2H), 4.12 (d, J = 10.1 Hz, 1H), 4.12 (dd, J = 2.3, 3.8 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.62 (s, 3H), 3.55 (ddd, J = 2.3, 6.1, 10.1 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.8, 148.9, 148.1, 140.3, 136.5, 130.4, 129.9, 127.8, 125.7, 125.0, 124.7, 123.5, 122.7, 120.8, 120.2, 119.9, 119.9, 118.7, 115.5, 114.8, 114.1, 112.0, 111.7, 108.8, 95.6, 87.3, 83.1, 71.7, 65.6, 61.6, 55.5, 55.5, 49.6, 45.5, 29.0; high-resolution mass spectrum (FAB) *m/z* 620.2390 [calcd for $C_{36}H_{34}N_3O_7$ (M + H) 620.2397].

(+)-MLR-52 (5). To a stirred solution of diol (+)-**54** (10 mg, 0.016 mmol, 1.0 equiv) in anisole or thioanisole (80 μL) was added TFA (0.5 mL). The reaction was monitored by TLC and after 16 h had proceeded to completion. The reaction mixture was treated with H_2O (1.0 mL) and then extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL), dried over Na_2SO_4, and evaporated to a residue. Purification by preparative TLC (5% MeOH/CH_2Cl_2) provided (+)-MLR-52 (**5**, 6 mg, 77% yield) as a white solid: mp >260 °C (dec); $[\alpha]^{20}_D$ +65 (*c* 0.1, MeOH); IR (thin film/NaCl) 3348.5 (br m), 2922.9 (s), 2851.9 (m), 1638.2 (s), 1586.6 (m), 1455.5 (s), 1373.5 (m), 1336.6 (m), 1320.8 (m), 1275.0 (m), 1224.7 (m), 1200.3 (w), 1119.5 (s), 740.8 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.31 (d, J = 7.9 Hz, 1H), 8.61 (br s, 1H), 7.99 (d, J = 7.7 Hz, 1H), 7.96 (d, J = 8.7 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.53 (app t, J = 7.5 Hz, 1H), 7.45 (td, J = 0.8, 7.7 Hz, 1H), 7.32 (app t, J = 7.4 Hz, 1H), 7.32 (app t, J = 7.4 Hz, 1H), 6.58 (d, J = 1.6 Hz, 1H), 6.12 (d, J = 4.0 Hz, 1H), 5.06 (d, J = 5.9 Hz, 1H), 4.99 (d, J = 17.6 Hz, 1H), 4.95 (d, J = 17.5 Hz, 1H), 4.13 (d, J = 10.3 Hz, 1H), 4.12 (dd, J = 1.6, 2.6 Hz, 1H), 3.62 (s, 3H), 3.56 (ddd, J = 2.6, 6.2, 10.3 Hz, 1H), 3.28 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.8, 140.2, 136.4, 132.6, 127.8, 125.8, 125.5, 124.8, 124.6, 123.6, 122.7, 120.9, 120.1, 119.7, 119.3, 115.4, 114.9, 114.3, 108.7, 95.6, 87.2, 83.1, 71.7, 65.6, 61.6, 45.4, 29.0; high-resolution mass spectrum (FAB) *m/z* 470.1717 [calcd for $C_{27}H_{24}N_3O_5$ (M + H) 470.1716].

Oxime (−)-55. A suspension of ketone (+)-**12** (100 mg, 0.17 mmol, 1.0 equiv), hydroxylamine hydrochloride (165 mg, 2.38 mmol, 14.0 equiv), and NaOAc (167 mg, 2.04 mmol, 12 equiv) in 80% aqueous EtOH (35.0 mL) was heated gently to reflux for 30 min. Following cooling to room temperature, the sovent was removed *in vacuo* and the residue purified by flash chromatography (1:1 hexanes/EtOAc eluent) to provide oxime (−)-**55** (98 mg, 95% yield) as a yellow powder: mp >270 °C (dec); $[\alpha]^{20}_D$ −18 (*c* 0.1, CH_2Cl_2); IR (thin film/NaCl) 3324.0 (br m), 2995.0 (w), 2911.3 (m), 1660.0 (s), 1589.7 (m), 1513.5 (s), 1461.1 (s), 1417.9 (m), 1399.0 (m), 1349.2 (s), 1315.5 (m), 1260.0 (s), 1234.6 (m), 1124.4 (m), 1027.2 (m), 741.7 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 10.30 (s, 1H), 9.34 (d, J = 7.9 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.71 (d, J = 8.3 Hz, 1H), 7.51 (app t, J = 7.6 Hz, 1H), 7.42 (app t, J = 7.9 Hz, 1H), 7.32 (app t, J = 7.7 Hz, 1H), 7.28 (app t, J = 7.4 Hz, 1H), 7.04 (d, J = 6.3 Hz, 1H), 7.03 (s, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 5.56 (m, 2H), 4.97 (d, J = 18.1 Hz, 1H), 4.93 (d, J = 16.9 Hz, 1H), 4.85 (d, J = 15.0 Hz, 1H), 4.45 (d, J = 15.0 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.61 (d, J = 13.9 Hz, 1H), 3.01 (dd, J = 5.8, 14.3 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.8, 148.9, 148.1, 147.4, 140.2, 136.1, 130.5, 129.6, 128.1, 125.4, 125.3, 124.7, 124.6, 123.6, 122.8, 120.5, 120.1, 119.9, 119.6, 118.5, 116.0, 114.8, 113.9, 112.1, 111.9, 108.9, 97.4, 82.0, 74.9, 55.5, 55.5, 49.5, 45.5, 29.6, 28.6; high-resolution mass spectrum (FAB) *m/z* 603.2238 [calcd for $C_{35}H_{31}N_4O_6$ (M + H) 603.2244].

Methyl Ether (−)-56. To a mixture of oxime (−)-**55** (90 mg, 0.15 mmol, 1.0 equiv), MeI (88 μL, 1.42 mmol, 9.5 equiv), and powdered KOH (88 mg, 1.58 mmol, 10.5 equiv) in THF (15 mL) was added *n*-Bu_4NBr (10 mg, 0.03 mmol, 0.2 equiv). The mixture was stirred under N_2 for 30 min, solvent was removed *in vacuo*, and the residue was subjected to flash chromatography (1:1 hexanes/EtOAc eluent) to provide methyl ether (−)-**56** (85 mg, 90% yield) as a yellow powder: mp >270 °C (dec); $[\alpha]^{20}_D$ −22 (*c* 0.1, CH_2Cl_2); IR (thin film/NaCl) 2998.0 (w), 2926.3 (m), 1674.1 (s), 1590.0 (m), 1513.7 (s), 1460.9 (s), 1418.2 (m), 1397.9 (s), 1349.4 (s), 1316.2 (s), 1262.1 (m), 1225.6 (m), 1044.3 (m), 743.5 (m) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, 345 K) δ 9.36 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.6 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.51 (app t, J = 7.6 Hz, 1H), 7.44 (app t, J = 7.8 Hz, 1H), 7.33 (app t, J = 7.2 Hz, 1H), 7.30 (app t, J = 7.1 Hz, 1H), 7.04 (s, 1H), 7.02 (d, J = 5.6 Hz, 1H), 6.97 (d, J = 9.4

Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 4.97 (s, 2H), 4.86 (d, J = 15.5 Hz, 1H), 4.85 (d, J = 15.7 Hz, 1H), 4.76 (s, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.54 (d, J = 14.4 Hz, 1H), 3.45 (s, 3H), 3.16 (dd, J = 5.9, 14.4 Hz, 1H), 3.14 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.7, 148.9, 148.1, 147.3, 139.8, 136.1, 130.4, 129.5, 128.0, 125.4, 125.3, 124.7, 124.6, 123.6, 122.7, 120.6, 120.2, 119.9, 119.6, 118.6, 115.5, 114.9, 113.8, 112.2, 112.0, 108.9, 96.1, 83.3, 82.0, 60.8, 58.4, 55.5, 55.5, 49.5, 45.4, 30.4, 28.5; high-resolution mass spectrum (FAB) *m/z* 631.2564 [calcd for $C_{37}H_{35}N_4O_6$ (M + H) 631.2557].

Amine (+)-57a. A mixture of methyl ether (−)-**56** (85 mg, 0.13 mmol, 1.0 equiv) and PtO_2 (28 mg) in a 60% aqueous acetic acid (15.0 mL) was placed in a flask capped with a H_2-filled balloon. The reaction was monitored by TLC (1:1 hexanes/EtOAc) and upon completion was filtered through Celite. The filtrate was evaporated and the residue dissolved in CH_2Cl_2 (40 mL) and washed with 1.0 N NaOH (8.0 mL). The aqueous layer was backextracted with CH_2Cl_2 (2 × 15 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated to a residue (79 mg) that was typically used in the next step without further purification.

An analytically pure sample of primary amine (+)-**57a** could be obtained by preparative TLC (5% MeOH/CH_2Cl_2 eluent) of the above residue to afford (+)-**57a** as a yellow powder: mp >275 °C (dec); $[\alpha]^{20}_D$ +14 (*c* 0.14, $CHCl_3$); IR (thin film/NaCl) 3414.7 (br w), 2920.8 (s), 2851.7 (s), 1733.7 (w), 1672.8 (s), 1636.0 (w), 1588.1 (m), 1513.5 (s), 1352.7 (s), 1259.3 (s), 1136.7 (m), 744.2 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 310 K) δ 9.55 (d, J = 7.9 Hz, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.51 (app t, J = 7.6 Hz, 1H), 7.42 (app t, J = 8.2 Hz, 1H), 7.40 (app t, J = 7.5 Hz, 1H), 7.30 (app t, J = 7.8 Hz, 2H), 6.99 (d, J = 9.4 Hz, 2H), 6.87 (d, J = 8.0 Hz, 1H), 6.59 (d, J = 4.9 Hz, 1H), 4.98 (d, J = 14.9 Hz, 1H), 4.92 (d, J = 14.9 Hz, 1H), 4.87 (d, J = 16.7 Hz, 1H), 4.82 (d, J = 16.7 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.75 (m, 2H), 3.46 (s, 3H), 2.63 (m, 2H), 2.32 (s, 3H), 1.27 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 315 K) δ 170.2, 149.6, 148.7, 140.1, 137.0, 130.8, 129.6, 129.5, 127.0, 126.2, 125.4, 124.7, 124.5, 123.8, 120.8, 120.5, 120.2, 120.2, 119.6, 116.0, 115.4, 114.6, 111.6, 111.6, 107.4, 91.3, 84.2, 80.2, 57.5, 56.1, 56.1, 49.9, 46.5, 42.6, 34.6, 30.0; high-resolution mass spectrum (FAB) *m/z* 603.2229 [calcd for $C_{36}H_{35}N_4O_5$ (M + H) 603.2610].

Methylamine (+)-57b. A solution of amine (+)-**57a** (79 mg) in THF (2.0 mL) was treated with formic acetic anhydride in THF (1.3 μL of a 1.3 M solution in THF, 0.17 mmol, 1.3 equiv, prepared by treatment of 1.0 equiv of acetic anhydride with 1.2 equiv of formic acid followed by reflux for 2 h). After TLC analysis showed complete formation of a less polar substance, a stream of N_2 followed by high vacuum (ca. 1 torr for 15 min) was used to evaporate the solvent. The resultant residue was dissolved in THF (1.3 mL), cooled to 0 °C, and treated with BH_3·DMS (193 μL of a 2.0 N solution in toluene, 0.39 mmol, 3.0 equiv). The solution was heated to reflux for 2 h, cooled to 0 °C, and treated with methanolic HCl (1.0 mL) in excess MeOH (1.3 mL). The derived solution was then heated to reflux for an additional hour. After cooling, the volatiles were removed *in vacuo*, and residual boron was removed by repetative dissolution of the solids in MeOH followed by evaporation *in vacuo* (5 × 5.0 mL). The remaining residue was treated with CH_2Cl_2 (7.0 mL) and 1.0 N NaOH (5.0 mL). The biphasic mixture was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 7.0 mL). The combined organic layers were dried over Na_2SO_4, evaporated, and purified by flash chromatography (5% MeOH/CH_2Cl_2 eluent) to furnish **57b** [80 mg, 91% yield, two steps from (−)-**56**] as a yellow foam: mp 225−230 °C (dec); $[\alpha]^{20}_D$ +22 (*c* 0.1, MeOH); IR (thin film/NaCl) 2954.1 (m), 2915.1 (m), 1673.2 (s), 1635.8 (m), 1462.7 (s), 1399.0 (s), 1352.6 (s), 1258.7 (m), 1136.5 (m), 1026.9 (m), 745.2 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 320 K) δ 9.55 (d, J = 7.9 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 7.3 Hz, 1H), 7.48 (td, J = 1.0, 7.5 Hz, 1H), 7.39 (td, J = 1.0, 7.4 Hz, 1H), 7.38 (app t, J = 7.3 Hz, 1H), 7.27 (m, 2H), 7.01 (m, 2H), 6.88 (d, J = 8.7 Hz, 1H), 6.57 (dd, J = 1.4, 6.0 Hz, 1H), 4.98 (d, J = 14.9 Hz, 1H), 4.91 (d, J = 14.9 Hz, 1H), 4.84 (s, 2H), 3.92 (d, J = 3.0 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.37 (dd, J = 3.8, 7.7 Hz, 1H), 3.33 (br s, 3H), 2.72 (ddd, J = 1.3, 4.6, 14.5 Hz, 1H), 2.46 (m, 1H), 2.35 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 149.3, 148.4, 139.6, 136.7, 130.6, 130.4, 129.3, 127.1, 126.6, 125.1, 124.5, 124.3, 123.5, 120.7, 120.4, 120.0, 119.8, 119.1, 115.5, 114.9, 114.0, 111.2, 111.2, 107.0, 91.2, 83.9, 80.2, 57.5, 56.0, 55.9, 50.7, 49.9, 46.4, 33.2, 30.1, 29.9; high-resolution mass spectrum (FAB) *m/z* 617.2764 [calcd for $C_{37}H_{37}N_4O_5$ (M + H) 617.2764].

(+)-Staurosporine (2). To a stirred solution of methylamine **57b** (10 mg, 0.016 mmol, 1 equiv) in anisole or thioanisole (80 μL) was added TFA (0.5 mL). The sluggish reaction was monitored by TLC and after 48 h had proceeded to completion. The reaction mixture was diluted with H_2O (1.0 mL), adjusted to pH 10 with 5.0 N NaOH, and extracted with CH_2Cl_2 (3 × 5mL). The combined organic layers were dried over Na_2SO_4 and evaporated to a pale yellow residue which was purified by preparative TLC (5% MeOH/CH_2Cl_2 eluent) to provide (+)-staurosporine (**2**, 6 mg, 70% yield) as a yellow powder: mp 273−280 °C (dec); $[\alpha]^{20}_D$ +35 (*c* 0.1, MeOH); IR (thin film/NaCl) 3316.6 (m), 2925.0 (m), 2850.8 (m), 1678.7 (s), 1636.2 (m), 1584.2 (m), 1457.5 (s), 1352.2 (s), 1316.7 (s), 1281.3 (m), 1115.5 (m), 744.8 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.43 (d, J = 7.9 Hz, 1H), 7.94 (d, J = 8.5 Hz, 1H), 7.90 (d, J = 7.7 Hz, 1H), 7.49 (app t, J = 7.6 Hz, 1H), 7.43 (app t, J = 7.7 Hz, 1H), 7.37 (app t, J = 7.5 Hz, 1H), 7.33 (app t, J = 7.4 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 6.57 (d, J = 5.6 Hz, 1H), 6.33 (br s, 1H), 5.05 (d, J = 15.8 Hz, 1H), 5.01 (d, J = 15.8 Hz, 1H), 3.89 (br s, 1H), 3.42 (s, 3H), 3.37 (d, J = 3.2, 1H), 2.76 (dd, J = 3.9, 14.7 Hz, 1H), 2.41 (br d, J = 15.4 Hz, 1H), 2.37 (s, 3H), 1.59 (br s, 1H), 1.57 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 139.8, 136.7, 132.2, 130.8, 126.6, 125.0, 124.6, 124.2, 123.4, 120.6, 120.0, 119.8, 115.3, 114.1, 106.9, 91.1, 84.2, 80.1, 57.2, 50.4, 45.9, 33.3, 30.3, 30.1; high-resolution mass spectrum (FAB) *m/z* 467.2085 [calcd for $C_{28}H_{27}N_4O_3$ (M + H) 467.2083].

Alcohol (−)-58. A suspension of ketone (+)-**12** (75 mg, 0.128 mmol, 1.0 equiv), *O*-benzylhydroxylamine hydrochloride (290 mg, 1.8 mmol, 14.0 equiv), and NaOAc (126 mg, 1.5 mmol, 12 equiv) in 80% aqueous EtOH (15.0 mL) was heated gently to reflux for 30 min. After cooling to room temperature, sovent was removed *in vacuo* and the residue purified by flash chromatography (2:1 → 1:1 hexanes/EtOAc eluent) to provide oxime ether (−)-**58** (75 mg, 85% yield) as a yellow foam: $[\alpha]^{20}_D$ −20 (*c* 0.1, CH_2Cl_2); IR (thin film/NaCl) 3486.2 (br m), 3005.6 (br m), 1671.4 (s), 1513.9 (s), 1349.8 (m), 1317.2 (m), 1225.0 (m), 1026.8 (s), 745.3 (s) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.41 (d, J = 7.9 Hz, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.51 (app t, J = 7.6 Hz, 1H), 7.40 (app t, J = 7.8 Hz, 1H), 7.34 (app t, J = 7.6 Hz, 1H), 7.26 (app t, J = 7.4 Hz, 1H), 7.10 (d, J = 5.3 Hz, 1H), 7.06 (s, 1H), 6.93−6.98 (comp m, 2H), 6.80 (app t, J = 7.3 Hz, 1H), 6.75 (app t, J = 7.4 Hz, 2H), 6.13 (d, J = 7.4 Hz, 2H), 5.99 (br s, 1H), 4.88−5.03 (m, 4H), 4.75 (d, J = 14.9 Hz, 1H), 4.56 (d, J = 13.7 Hz, 1H), 4.33 (d, J = 13.7 Hz, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.68 (m, 1H), 3.12 (dd, J = 5.5, 14.1 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.9, 150.1, 148.9, 148.1, 140.3, 137.5, 136.1, 130.6, 129.6, 128.0, 127.5, 126.5, 125.7, 125.6, 125.5, 124.7, 123.6, 123.0, 120.7, 120.2, 120.0, 119.8, 118.7, 115.9, 115.1, 113.9, 112.0, 111.8, 109.1, 97.7, 82.3, 74.8, 74.0, 55.5, 55.4, 49.6, 45.5, 30.8, 28.8; high-resolution mass spectrum (EI) *m/z* 692.2633 [calcd for $C_{42}H_{36}N_4O_6$ (M^+) 692.2635]

Ether (−)-59. To a mixture of oxime ether (−)-**58** (67 mg, 0.10 mmol, 1.0 equiv), MeI (30 μL, 0.48 mmol, 4.8 equiv), and powdered KOH (33 mg, 0.59 mmol, 5.9 equiv) in THF (10 mL) was added *n*-Bu_4NBr (6 mg, 0.02 mmol, 0.2 equiv). The mixture was stirred under N_2 for 30 min, solvent was removed *in vacuo*, and the residue was subjected to flash chromatography (2:1 → 1:1 hexanes/EtOAc eluent) to provide methoxy oxime ether (−)-**59** (53 mg, 68% yield) as a yellow powder: mp >230 °C (dec); $[\alpha]^{20}_D$ −36° (*c* 0.1, CH_2Cl_2); IR (thin film/NaCl) 3002.9 (br m), 2931.6 (m), 2835.8 (m), 1672.1 (s), 1591.0 (m), 1514.2 (s), 1460.9 (s), 1398.9 (m), 1350.5 (s), 1317.2 (s), 1027.4 (s), 746.1 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (d, J = 7.8 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.39−7.51 (m, 3H), 7.25−7.29 (m, 2H), 6.94−7.07 (m, 5H), 6.85 (d, J = 8.1 Hz, 1H), 6.71 (d, J = 5.4 Hz, 1H), 6.51 (d, J = 7.4 Hz, 2H), 4.97 (d, J = 15.0 Hz, 1H), 4.89 (d, J = 14.9 Hz, 1H), 4.78 (s, 2H), 4.58 (d, J = 11.7 Hz, 1H), 4.39 (s, 1H), 4.29 (d, J = 11.7 Hz, 1H), 3.90 (d, J = 14.1 Hz, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.47 (s, 3H), 2.88 (dd, J = 5.6, 14.0 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 149.3, 148.4, 146.7, 140.3, 136.5, 136.3, 130.4, 129.7, 128.8, 128.0, 127.6, 127.4, 126.9, 125.5, 125.4, 124.8, 124.6, 124.0, 120.9, 120.4, 120.2, 119.4, 116.3, 115.2, 114.8, 111.2, 111.0, 107.5, 96.4, 84.9, 82.6,

75.8, 59.0, 55.9, 55.8, 49.7, 46.3, 31.1, 29.4; high-resolution mass spectrum (EI) *m/z* 706.2783 [calcd for $C_{43}H_{38}N_4O_6$ (M^+) 706.2791].

Amide (−)-60. To a stirred solution of ether (−)-**59** (50 mg, 0.071 mmol, 1.0 equiv) in anisole (385 μL, 50 equiv) was added TFA (0.71 mL). The reaction was monitored by TLC and after 24 h had proceeded to completion. The reaction mixture was diluted with H_2O (1.0 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL), dried over Na_2SO_4, and evaporated to a residue, which was purified by preparative TLC (5% MeOH/CH_2Cl_2) to provide amide (−)-**60** (10 mg, 25% yield) as a white solid: $[\alpha]^{20}_D$ −8 (*c* 0.1, $CHCl_3$); IR (thin film/NaCl) 3241.0 (br m), 3059.8 (m), 2848.9 (m), 1679.7 (s), 1455.7 (s), 1395.3 (m), 1316.1 (s), 1226.1 (m), 1125.0 (m), 742.2 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.48 (d, J = 7.8 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 7.5 Hz, 1H), 7.28−7.82 (comp m, 5H), 7.09 (app t, J = 7.4 Hz, 1H), 7.00 (app t, J = 7.5 Hz, 2H), 6.73 (dd, J = 1.4, 5.5 Hz, 1H), 6.62 (br s, 1H), 6.50 (d, J = 7.2 Hz, 2H), 4.94 (d, J = 10.5 Hz, 1H), 4.92 (d, J = 10.5 Hz, 1H), 4.58 (d, J = 11.7 Hz, 1H), 4.41 (s, 1H), 4.28 (d, J = 11.7 Hz, 1H), 3.92 (dd, J = 1.6, 14.0 Hz, 1H), 3.49 (s, 3H), 2.89 (dd, J = 5.6, 14.0 Hz, 1H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 146.6, 140.3, 136.5, 136.4, 132.7, 129.3, 128.0, 127.6, 127.5, 126.8, 125.6, 125.4, 124.9, 124.7, 123.9, 120.8, 120.6, 120.5, 116.4, 115.3, 114.8, 107.5, 96.5, 85.0, 82.7, 75.9, 59.0, 46.1, 31.1, 29.7, 29.4; high-resolution mass spectrum (EI) *m/z* 556.2105 [calcd for $C_{34}H_{28}N_4O_4$ (M^+) 556.2111].

TAN-1030a (4). A solution of amide (−)-**60** (9 mg, 0.02 mmol, 1.0 equiv) in $CDCl_3$ (3.0 mL) was treated with iodotrimethylsilane (0.3 mL) and stirred for 48 h at room temperature. Following addition of MeOH (3.0 mL) and stirring for 30 min, the solvent was removed *in vacuo* leaving a deep red residue which was dissolved in CH_2Cl_2 (3 mL) and washed with an aqueous 10% $Na_2S_2O_7$ solution (3 × 2 mL). The pale yellow organic layer was dried over Na_2SO_4 and purified by preparative TLC (5% MeOH/CH_2Cl_2 eluent) to provide TAN-1030a (**4**, 2 mg, 24% yield) as a white foam: $[\alpha]^{20}_D$ −4 (*c* 0.1, $CHCl_3$); IR (thin film/NaCl) 3410.2 (br m), 3059.8 (m), 2848.9 (m), 1680.0 (s), 1456.1 (s), 1419.4 (m), 1348.4 (s), 1316.1 (s), 1124.9 (m), 742.2 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 10.43 (br s, 1H), 9.28 (d, J = 7.9 Hz, 1H), 8.57 (br s, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.49 (app t, J = 7.6 Hz, 1H), 7.43 (app t, J = 7.7 Hz, 1H), 7.28−7.32 (comp m, 2H), 7.05 (d, J = 5.4 Hz, 1H), 4.95 (s, 2H), 4.75 (s, 1H), 3.62 (d, J = 14.2 Hz, 1H), 3.42 (s, 3H), 3.01 (dd, J = 5.7, 14.3 Hz, 1H), 2.47 (s, 3H); .

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Supporting Information Available: Spectral and experimental data pertaining to **21**, **23**−**31**, **35**−**38**, **44**−**47**, and **50** and crystallographic information pertaining to **30** (22 pages). Ordering information is given on any current masthead page.

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