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Asymmetric [C + NC + CC] Coupling Entry to the Naphthyridinomycin Natural Product Family: Formal Total Synthesis of Cyanocycline A and Bioxalomycin β2

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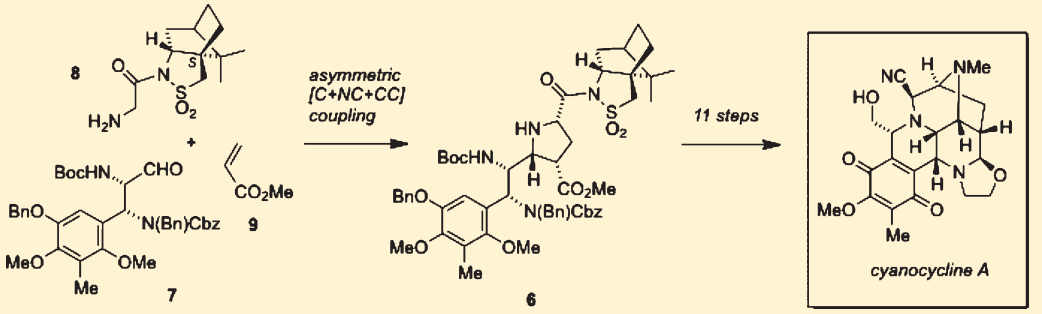
Supporting Information

ABSTRACT:



A full account of our [C + NC + CC] coupling approach to the naphthyridinomycin family of natural products is presented, culminating in formal total syntheses of cyanocycline A and bioxalomycin β2. The key complexity-building reaction in the synthesis involves the Ag^{I}-catalyzed *endo*-selective [C + NC + CC] coupling of aldehyde **7**, (*S*)-glycyl sultam **8**, and methyl acrylate (**9**) to provide the highly functionalized pyrrolidine **6**, which was carried forward to an advanced intermediate (compound **33**) in Fukuyama's synthesis of cyanocycline A. Since cyanocycline A has been converted to bioxalomycin β2, this constitutes a formal synthesis of the latter natural product as well. The multicomponent reaction-based strategy reduces the number of steps previously needed to assemble these complex molecular targets by one-third. This work highlights the utility of the asymmetric [C + NC + CC] coupling reaction in the context of a complex pyrrolidine-containing target and provides an illustrative guide for its application to other synthesis problems. The synthesis also fueled collaborative biological and biochemical research that identified a unique small molecule inhibitor of cell migration (compound **30**).

INTRODUCTION

The cyanocyclines,[1−3] SF-1739HP,[4] dnacins (*Actinosynnema pretiosum* C-14482),[5−7] bioxalomycins (*Streptomyces viridostaticus* and *S. lusitanus*),[8,9] and aclidinomycins (*Streptomyces halstedi* KB012)[10] comprise the naphthyridinomycin family of tetrahydroisoquinoline antibiotics.[11] As a group, these natural products share a number of structural features (principally, their ABCD ring skeleta) with the simpler quinocarcin family of tetrahydroisoquinolines.[11] Although naphthyridinomycin was the first member of this family to be characterized (by X-ray crystallography),[12,13] Ellestad and co-workers subsequently showed that this compound is actually an artifact formed by hydrolysis of the bioxalomycin G-ring.[9] The structure of bioxalomycin β2 was established by its chemical conversion to cyanocycline A (treatment with KCN, pH 8.0), whose structure had been unambiguously assigned by X-ray crystallography[4] and total synthesis (see below). The conversion of cyanocycline A to bioxalomycin β2 (by treatment with $AgNO_3$) was also reported in this paper. The structures of the dnacins and aclidinomycins are less secure, being based on NMR studies alone. Considering the history of naphthyridinomycin, dnacin B_1 may actually possess a bioxalomycin-like oxazolidine G-ring ($M^+ - H_2O$ parent in MS).

Members of the naphthyridinomycin family of tetrahydroisoquinoline natural products exhibit varying degrees of antibacterial and anticancer activities.[11] The cytotoxic biological activities of these compounds have long been attributed to their interaction with DNA (based on *in vitro* experiments and computational modeling), but there is growing evidence that proteins may be biological targets as well. For example, the dnacins have been found to inhibit the dual specificity phosphatase cdc25B,[14] a protein involved in regulation of the cell division cycle and whose overexpression is connected with cancer cell proliferation. DX-52-1, a derivative of quinocarcin, binds strongly to the ERM protein radixin and inhibits cell migration, a process essential to cancer metastasis and tumor progression.[15] As a result of its potency for a specific

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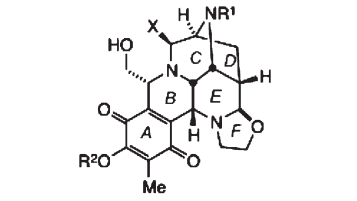
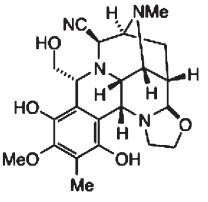
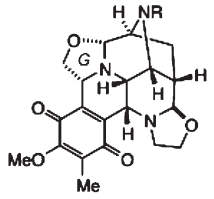
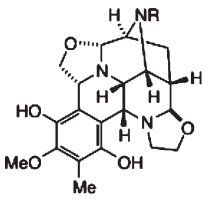

naphthyridinomycin (X = OH, $R^1 = R^2 = Me$)
SF-1739 HP (X = OH, $R^1 = Me$, $R^2 = H$)
cyanocycline A (X = CN, $R^1 = R^2 = Me$)
cyanocycline B (X = CN, $R^1 = H$, $R^2 = Me$)


cyanocycline C


bioxalomycin β1 (R = H)
bioxalomycin β2 (R = Me)


bioxalomycin α1 (R = H)
bioxalomycin α2 (R = Me)

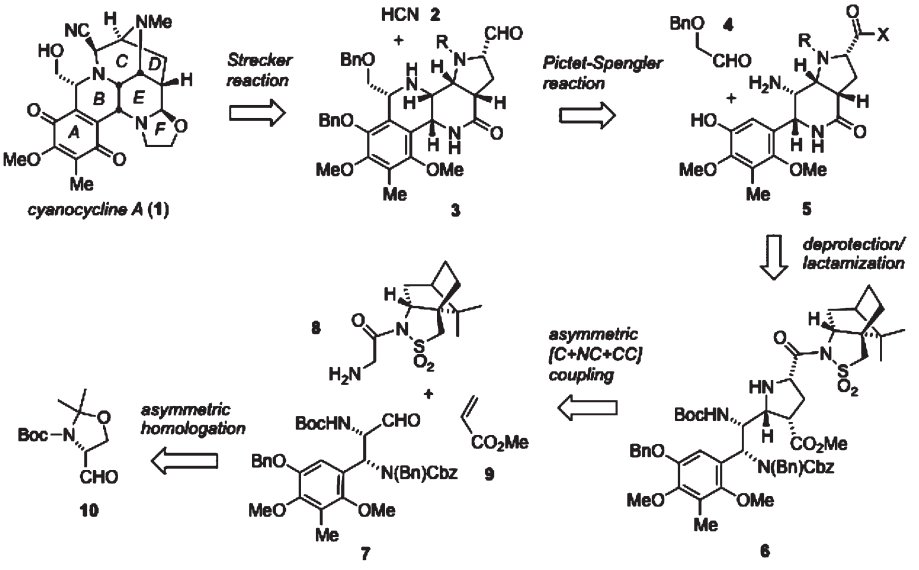
protein target, the antimigratory effect of DX-52-1 is observed at subtoxic doses. These observations support the notion that other members of the naphthyridinomycin and quinocarcin families may also inhibit therapeutically relevant proteins and could therefore be used to develop small molecule drugs. However, the limited availability of these complex natural products and, consequently, analogues thereof has severely hindered biological studies on the naphthyridinomycin family. It was in this context that set out to devise an efficient synthetic strategy that could be applied to both natural and unnatural members of the naphthyridinomycin family.

The densely functionalized polycyclic structures associated with the naphthyridinomycin family present a significant synthetic challenge. Cyanocycline A and bioxalomycin $\beta 2$ are the only members of the naphthyridinomycin family to be synthesized to date.[11,16] In 1986, Evans reported the first total synthesis of racemic cyanocycline A (30 steps from cyclopentadiene),[17] and an asymmetric synthesis of (+)-cyanocycline A was subsequently described in a dissertation (35 steps from 2,6-dimethoxytoluene).[18] Fukuyama disclosed his group's synthesis of racemic cyanocycline A in 1987 (32 steps from *tert*-butyl azidoformate).[19] In 1992, he reported the asymmetric synthesis of (+)-naphthyridinomycin (29 steps from L-glutamic acid 5-methyl ester).[20] While these total syntheses were ground breaking in their own right, they do not represent especially efficient and general synthetic routes to the naphthyridinomycin family. In addition to these successful efforts, notable synthetic excursions targeting the naphthyridinomycin family have also been made by the groups of Danishefsky,[21] Williams,[22] Myers,[23] Fukuyama,[24] as well as our own.[25] In this Article, we detail our asymmetric [C + NC + CC] coupling approach to the naphthyridinomycin family, culminating in an efficient formal total synthesis of cyanocycline A and bioxalomycin $\beta 2$.[26] The approach described herein provides a viable framework for synthesis of the entire naphthyridinomycin family as well as structurally related analogues.

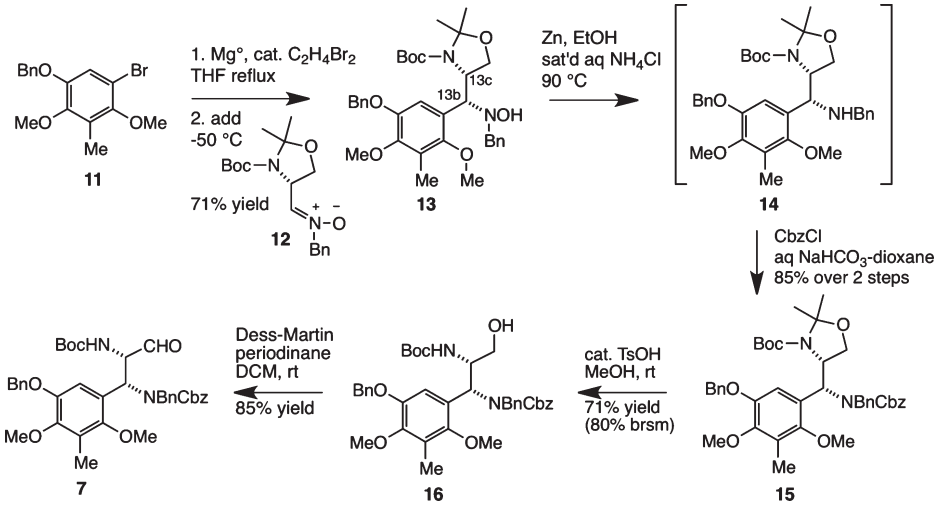
RESULTS AND DISCUSSION

Retrosynthetic Analysis. Our retrosynthetic logic is shown in Scheme 1. The first disconnection (ring C) involves the application of a Strecker transform to cyanocycline A (**1**) to give HCN (**2**) and the amino aldehyde **3**. Drawing from Fukuyama's racemic synthesis of **1**,[19a] we fully expected that trapping of the intermediate iminium species by cyanide would proceed from the less-hindered convex face. Fukuyama's synthesis also provided good precedent for the second disconnection (ring B) via a Pictet–Spengler transform on **3** to give the aldehyde **4** and aminophenol **5**. We reasoned that this reaction would be tolerant of changes in substituents R (urethane to methyl) and X (methoxy to sulfamoyl). Disconnection of the E-ring lactam leads to the highly functionalized pyrrolidine **6**. With the end game in place, access to this key intermediate would essentially solve the cyanocycline A synthesis problem. On paper it appears that such a pyrrolidine might be readily prepared using existing [3 + 2] cycloaddition protocols. However, it soon became apparent that the existing dipolar cycloaddition methodology[27] was wholly inadequate for our purposes.[28] This state of affairs led us on a methodological journey that resulted in our development of the asymmetric [C + NC + CC] coupling reaction,[29] the *endo* version of which[30] was perfectly suited to ours needs. Application of this [C + NC + CC] transform effectively deconstructs the target's D-ring to give the [C + NC + CC] coupling

Scheme 1. Retrosynthetic Analysis



Scheme 2. Synthesis of Aldehyde 7



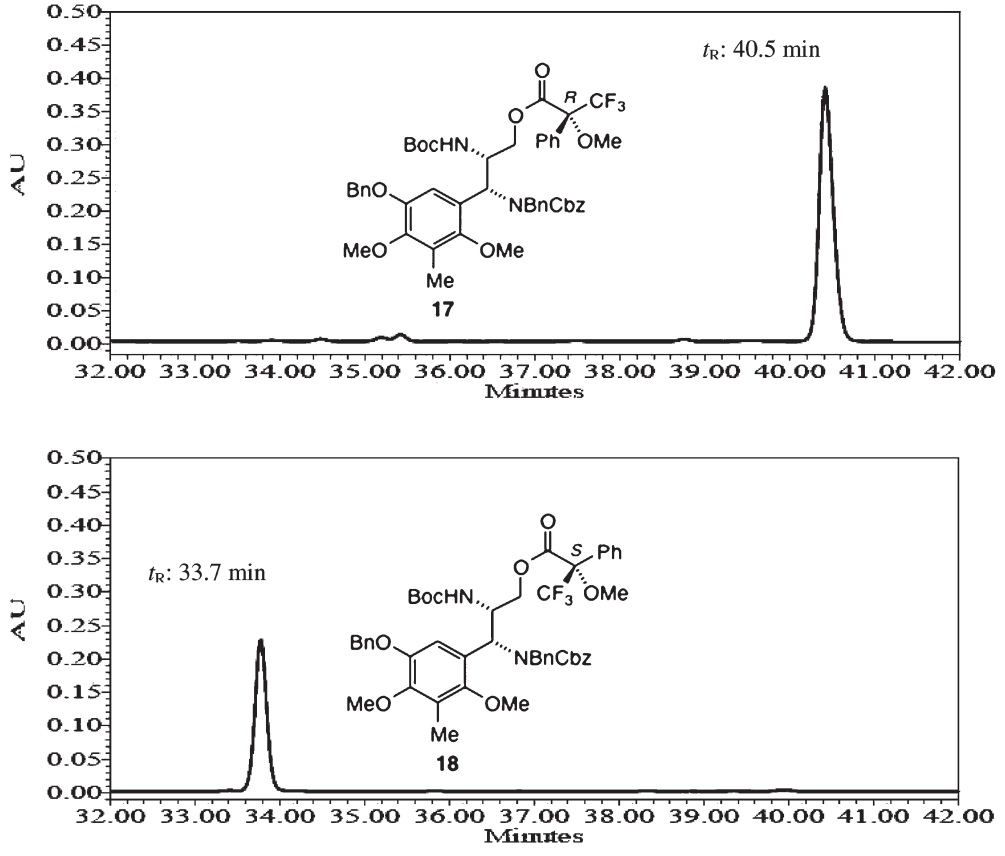


Figure 1. HPLC analysis of the crude Mosher esters prepared from alcohol **16**.

components, α,β-diaminoaldehyde **7**, 1(*S*)-glycylsultam **8**,[31] and methyl acrylate (**9**). Based on our earlier work, we were confident that the required pyrrolidine stereochemistry would predominate in this multicomponent reaction. Aldehyde **7** was to be prepared via asymmetric homologation[32] of the readily available serinal derivative **10**.[33]

Synthesis of Aldehyde 7. Asymmetric synthesis of the starting aldehyde **7**, a compound that incorporates the target's C13b and C13c stereocenters[34] along with a precursor to the target's A-ring, is depicted in Scheme 2. The sequence began with the stereoselective addition of a Grignard reagent, prepared from bromide **11**,[35] to the known serinal-derived nitrone **12** at −50 °C to yield a single crystalline hydroxylamine **13** in 71% yield. The outcome of this Grignard addition was expected on the basis of the work of Merino,[32] who had performed an analogous addition of phenylmagnesium bromide to **12** and established the product

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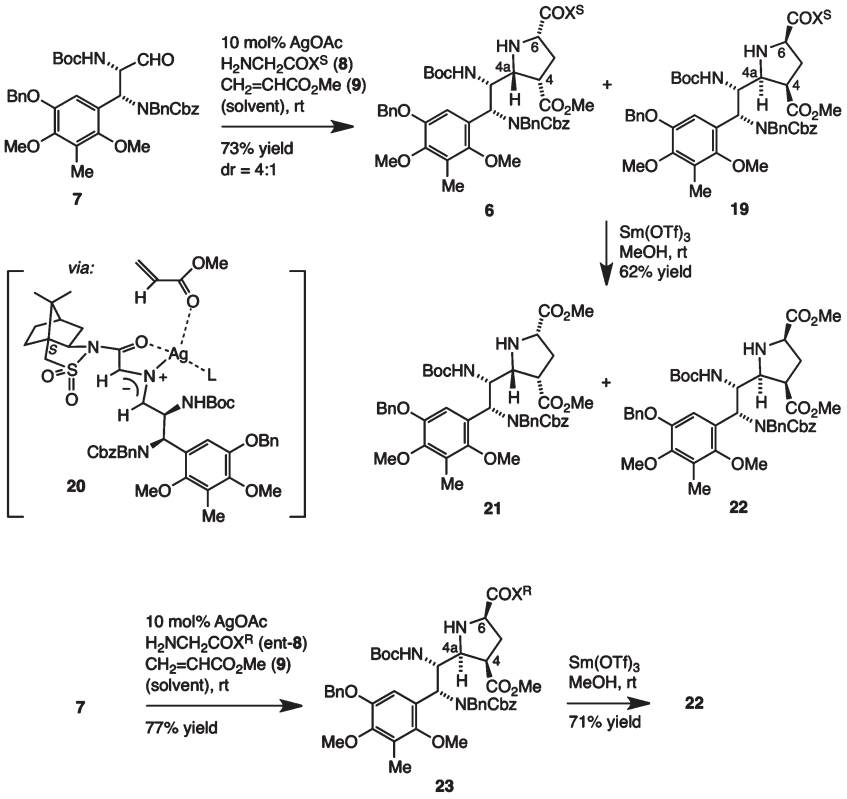
Scheme 3. Cornerstone [C + NC + CC] Coupling Reaction



stereochemistry by a combination of chiroptical and chemical methods. The high *syn*-selectivity can be rationalized by a substrate-controlled addition of the Grignard reagent to nitrone **12** via an A-strain-induced pre-TS conformation. Our stereochemical assignment would be corroborated by correlation of **13** with cyanocycline A. Interestingly, while compounds that contain the *N*-Boc 2,2-dimethyl-1,3-oxazolidine moiety generally exist as dynamic mixtures of conformers in solution, **13** appears to be locked in a very stable conformation (its ^{1}H NMR spectrum shows a single set of well-resolved signals at rt). Zinc-mediated reduction of hydroxylamine **13** proceeded cleanly to give the secondary amine **14**, which was immediately treated with benzyl chloroformate to provide the urethane **15** in 85% overall yield. Mildly acidic methanolysis of the acetonide afforded the alcohol **16** in 71% isolated yield. This compound was shown to be >98% enantiomerically pure through a separate Mosher ester study (Figure 1). Finally, Dess−Martin oxidation of **16** gave the desired aldehyde **7** in 85% yield.

Asymmetric [C + NC + CC] Coupling Reaction. With the aldehyde **7** in hand, we were ready for the cornerstone asymmetric [C + NC + CC] coupling reaction. When the standard *endo*-selective asymmetric [C + NC + CC] coupling reaction conditions were applied to **7** (1 equiv aldehyde, 1.1 equiv glycylsultam, 3 equiv dipolarophile, and 5 mol % AgOAc), a mixture of pyrrolidines was produced in 38% yield along with what appeared to be a mixture of imidazolines and oxazolidines.[36] Formation of these byproducts is indicative of ineffective trapping of the sterically congested azomethine ylide by a relatively poor dipolarophile. This problem was solved by employing methyl acrylate (**9**) as the solvent and increasing the amount of catalyst to 10 mol %. The optimized reaction conditions involved combining aldehyde **7** and (1*S*)-glycylsultam **8** in methyl acrylate with 10 mol % AgOAc at room temperature to give a white solid, mp 79−81 °C, isolated in 73% yield after flash chromatography (Scheme 3). On the basis of our understanding of the asymmetric [C + NC + CC] coupling process,[29] we anticipated that the [3 + 2] cycloaddition would proceed via a pre-TS ensemble such as **20**. The diastereofacial selectivity in this model would be determined by a ylide conformation that places the *N*-acyl sultam CO and SO_2 dipoles *anti* to each other while still maintaining the usual imine-carbonyl chelation by Ag(I). In this model, the coordinated acrylate dipolarophile approaches the ylide from the least hindered *endo-si* face opposite the pro-*R* sulfoxide moiety. The high-resolution mass spectrum of this solid was consistent with the molecular formula of **6**. Although this material was homogeneous by normal phase TLC and had a relatively sharp melting point, its ^{1}H NMR spectrum could not be satisfactorily resolved into a single set of signals, even when the sample was heated to 110 °C in DMSO-d_6. We initially attributed this anomalous NMR behavior to the presence of one or more bonds with relatively high rotation barriers. (This, in fact, turns out to be the case for other compounds that were encountered downstream in the synthesis.) However, subsequent analysis of this material by careful reverse-phase HPLC revealed it to consist of a 4:1 mixture of diastereoisomeric cycloadducts **6** and **19**.

The major cycloadduct diastereomer **6** was initially assigned as the desired product of *endo-si* addition on the basis of our chiral sultam-directed [3 + 2] cycloaddition pre-TS model (see ensemble **20**). This stereochemical assignment was ultimately confirmed by the successful correlation of **6** with the natural product cyanocycline A, whose structure had been unambiguously determined by X-ray crystallography. We hypothesized

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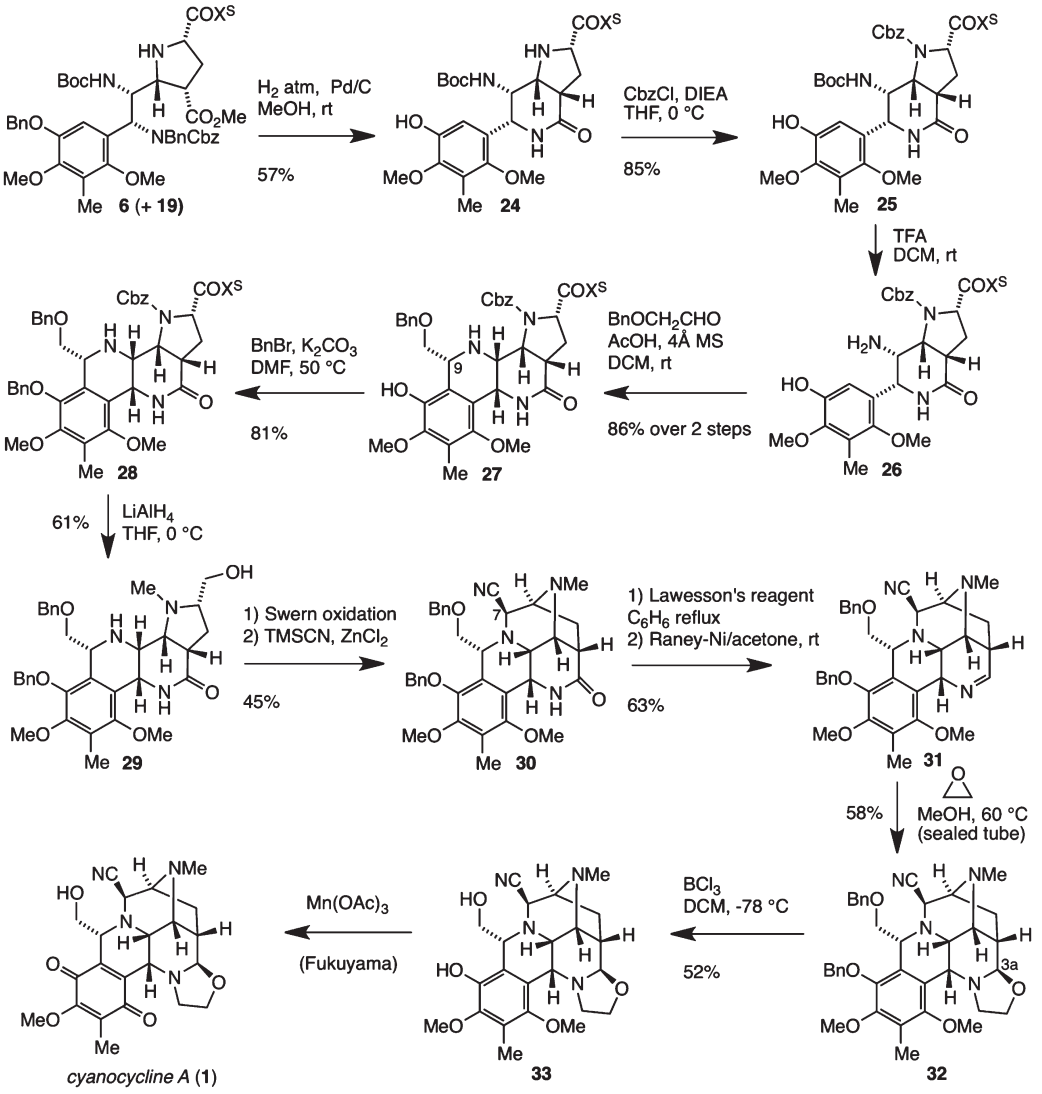
Scheme 4. Completion of the Cyanocycline A Synthesis



that the minor diastereomer was most likely the result of (1) *endo-re* addition of **9** to the (*E*,*E*)-azomethine ylide, (2) the *exo-si* addition product, or (3) the product of *endo-si* addition to the α-epimerized azomethine ylide. This issue was clarified in the following manner. The cycloadduct mixture (**6** + **19**) was subjected to $Sm(OTf)_3$-mediated methanolysis,[37] removing the chiral sultam moiety and producing a pair of diastereomeric diesters **21** and **22** in good yield. To determine the structure of **22** unambiguously, it was decided to prepare an authentic sample of the *endo-Re* product for comparison. Accordingly, an asymmetric [C + NC + CC] coupling reaction was performed with aldehyde **7**, the antipodal 1(*R*)-glycylsultam *ent*-**8** and methyl acrylate (**9**). We have previously shown that absolute stereocontrol in the asymmetric [C + NC + CC] reaction is governed by the camphorsultam auxiliary.[30] This reaction produced a cycloadduct **23** in good yield, which was diastereomeric to **6**. Methanolysis of **23** produced a compound that was shown to be identical to the diester **22** in the previously prepared (**21** + **22**) mixture by careful HPLC and NMR analyses (see Supporting Information). These experiments unambiguously established the structure of the minor cycloadduct **19**. Thus, it appears that we have a stereochemically mismatched [3 + 2] cycloaddition between ylide **20** (derived from **7** and **8**) and methyl acrylate (**9**) versus a matched [3 + 2] cycloaddition (via the diastereomeric ylide derived from **7** and *ent*-**8**). In the former case, the ability of the chiral sultam to dominate the stereochemical outcome of this reaction (auxiliary control) was opposed by the inherent directing effect of the CHNHBoc stereocenter (substrate control). Fortunately, the unresolved mixture of **6** and **19** could be used directly in the next reaction, obviating the need for their separation at this stage. The stereocontrolled assembly of cycloadduct **6**, which possesses the target's A and D rings as well as 5 of its 8 stereocenters, essentially solves the cyanocycline A synthesis problem in line with the strategy outlined in Scheme 1.

The synthetic end game (Scheme 4) began with Pd-catalyzed hydrogenolysis of the **6** + **19** mixture to give the pure δ-lactam **24** in an isolated yield of 57% (71% based on **6**). In contrast to its precursor **6**, compound **24** was readily purified by flash chromatography. This multistep transformation involves removal of the *O*-benzyl, *N*-benzyl, and *N*-Cbz protecting groups, followed by intramolecular acylation of the free amine by the methyl ester to install the target's E-ring.[38] The spontaneous lactamization also confirmed the *endo*-cycloadduct stereochemistry at this

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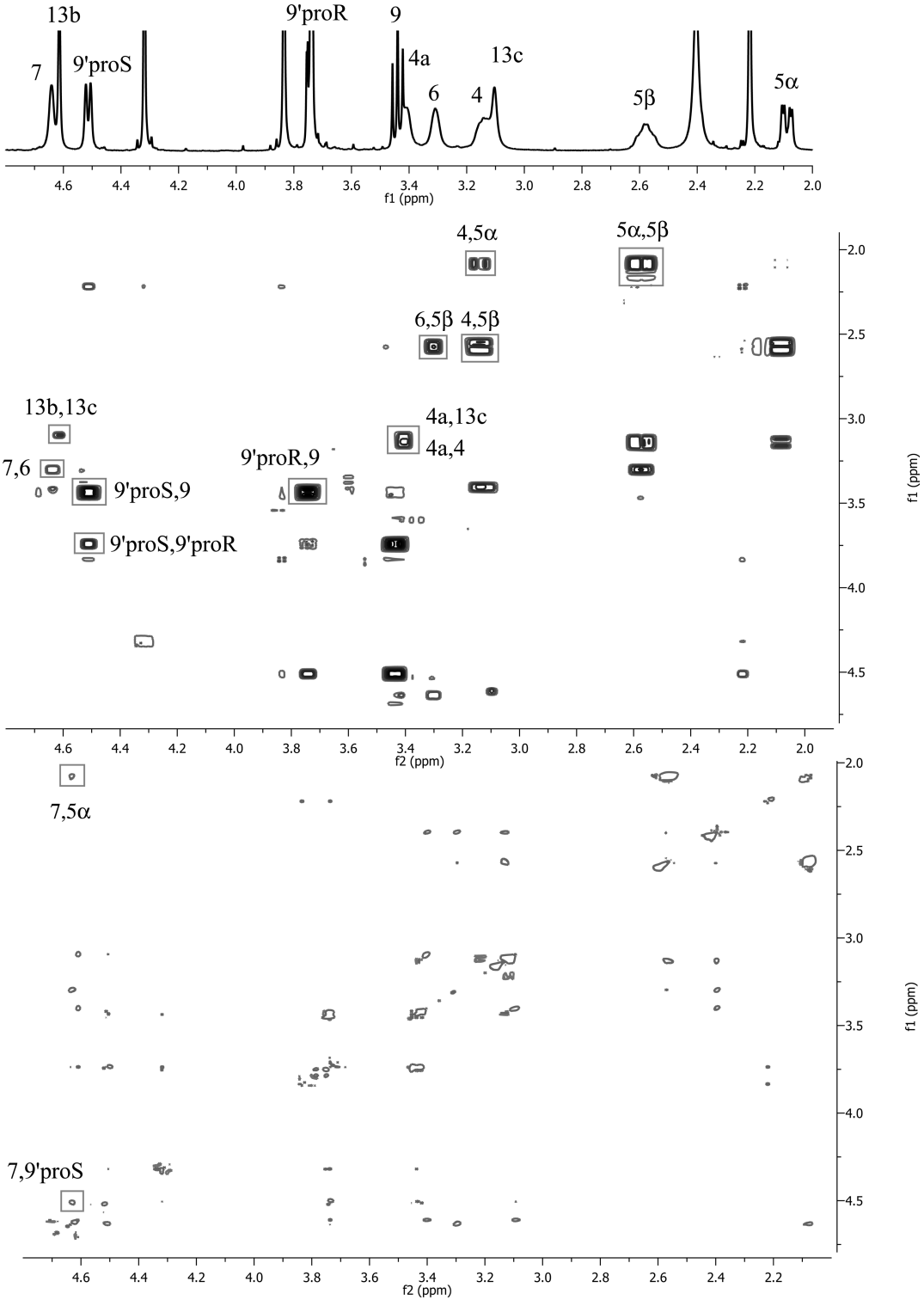

Figure 2. Expanded 600 MHz COSY (top) and NOESY (bottom) spectra of compound **30** showing key correlations.

stage since an *exo*-cycloadduct would resist formation of the corresponding trans-fused bicycle. To preclude potential interference with the upcoming Pictet−Spengler process, the pyrrolidine amine was converted to its *N*-Cbz derivative **25** in 85% yield. The urethane moiety also served as a convenient precursor to the target's *N*-Me group (vide infra). Removal of the *N*-Boc group released the phenolic amine **26**, providing the necessary synthon for the Pictet−Spengler reaction that would install ring B. In the event, the reaction of **26** with benzyloxyacetaldehyde in the presence of acetic acid plus molecular sieves produced the tetrahydroisoquinoline **27** in 86% overall yield. The 9(*R*) stereochemistry in **27** was tentatively assigned on the basis of Fukuyama's precedent[19] and eventually confirmed by correlation with cyanocycline A. Reprotection of the free phenol produced

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compound **28** in 81% yield.[39] The reduction of **28** with $LiAlH_4$ not only released the chiral auxiliary but also converted the urethane moiety to the required *N*-methyl group,[40] producing the primary alcohol **29** in 61% yield. In this way, two desired functional group transformations were achieved in a single step. Following the strategy of Fukuyama,[19] the C-ring was assembled using a two-step sequence. First, Swern oxidation of **29** produced a mixture of hemiaminals that was immediately subjected to the action of TMSCN in the presence of anhydrous $ZnCl_2$ to deliver aminonitrile **30** in 45% yield. The latter reaction presumably involves the stereoselective addition of cyanide to the less hindered convex face of an intermediate iminium ion. Due to its rigid structure, compound **30** exhibited a particularly well-resolved ^{1}H NMR spectrum that allowed extensive structural analysis via COSY and NOESY experiments (Figure 2). In particular, the observation of NOESY cross-peaks between H7 and H5α as well as H7 and H9′*pro-S* supported our configuration assignments for C9 and C7. The oxazolidine ring was then introduced using methodology developed by Pelletier as follows.[41] The lactam moiety of **30** was converted to the corresponding thiolactam with Lawesson's reagent, and this compound was reduced with Raney Ni to give the stable imine **31** in 63% yield.[42] This imine reacted smoothly with hot ethylene oxide in MeOH to afford the desired 3a(*R*) oxazolidine **32** in 58% yield. Finally, **32** was treated with BCl_3 to remove the benzyl ether protecting groups and give diol **33**. This compound corresponded to an advanced intermediate that Fukuyama had converted to cyanocycline A,[19] thus completing a formal synthesis of the natural product. Since cyanocycline A is convertible to bioxalomycin β2 through the agency of Ag(I),[9] the attainment of **33** also constitutes a formal synthesis of this natural product as well.

CONCLUSION

Our formal synthesis of cyanocycline A was accomplished in 22 linear steps from 2,6-dimethoxytoluene (19 steps from the readily available serinal **10**). This represents the most efficient synthesis of cyanocycline A to date and illustrates the value of the asymmetric [C + NC + CC] coupling reaction in the context of a complex synthetic problem. With appropriate modification, this same [C + NC + CC] coupling-based synthetic strategy may be used to access both natural and unnatural members of the naphthyridinomycin family. This [C + NC + CC] synthesis of cyanocycline A also enabled biological and biochemical studies on the naphthyridinomycin family that led to some significant discoveries. As part of our collaboration with Gabriel Fenteany's group at the University of Connecticut, advanced intermediate **30** (which we have designated as HUK-921) was found to inhibit cell migration, a process involved in cancer metastasis and tumor progression.[43] Although HUK-921 turned out to be a less potent inhibitor of cell migration than DX-52-1,[15] it exerted its inhibitory effect in a different manner via selective binding to galectin-3, revealing a potential therapeutic target that had not previously been implicated in cell migration. This was the first example of a non-carbohydrate small molecule inhibitor of this protein, illustrating the untapped potential of the naphthyridinomycin family as a source of small molecule probes of protein-mediated transduction as well as novel drug leads for the treatment of cancer.

EXPERIMENTAL SECTION

General Experimental Methods. All moisture-sensitive reactions were performed in flame-dried glassware under an inert, dry atmosphere of argon. Air-sensitive liquids were transferred via syringe or cannula through rubber septa. Reagent grade solvents were used for extraction and flash chromatography. Anhydrous solvents were prepared as follows: THF was distilled from Na/benzophenone under argon; dichloromethane (CH_2Cl_2) and benzene were distilled from CaH_2 under argon. Diisopropylethylamine (DIEA) and triethylamine (TEA) were distilled from CaH_2 under argon. All other reagents and solvents were purchased from commercial sources were used directly without further purification. The progress of reactions was monitored by analytical thin layer chromatography (TLC, silica gel F-254 plates). TLC plates were visualized first with UV illumination (254 nm) followed by charring using either ninhydrin stain (0.3% ninhydrin (w/v) in 97:3 EtOH/AcOH) or a modification of Hanessian's stain (10 g ammonium molybdate ($(NH_4)_6Mo_7O_{24}\cdot 4H_2O$) and 5 g cerium sulfate ($Ce(SO_4)_2$) in 1 L 10% aq H_2SO_4). Flash column chromatography was performed on flash grade (230−400 mesh) silica gel. The solvent compositions reported for all chromatographic separations are on a volume/volume (v/v) basis. High performance liquid chromatography (HPLC) was carried out using an X-Bridge C18 (3 × 250 mm column) for analytical separations and X-Bridge prep C18 (19 × 150 mm) column for semipreparative separations. Melting points are uncorrected. Optical rotations were recorded at room temperature at the sodium D line (589 nm). ^{1}H NMR spectra were recorded at 300, 400, 500, or 600 MHz and are reported in parts per million (ppm) on the δ scale relative to tetramethylsilane (TMS) as an internal standard (δ 0.00). ^{13}C NMR spectra were recorded at 75.5, 125.7, 150.8, or 100 MHz and are reported in parts per million (ppm) on the δ scale relative to $CDCl_3$ as an internal standard (δ 77.00). Unless indicated otherwise, NMR spectra were acquired at ambient temperature. High resolution mass spectrometry (HRMS) was performed using either FAB or ESI techniques.

Aromatic Bromide 11. To a suspension of NaH (3.1 g, 78 mmol, 60% dispersion in mineral oil) in DMF (70 mL) was added a solution of 5-bromo-2,4-dimethoxy-3-methylphenol[35] (16.0 g, 64.8 mmol) in DMF (70 mL) at 0 °C under argon via a dropping funnel over 15 min. After 1 h of stirring at this temperature, benzyl bromide (9.24 mL, 13.3 g, 77.8 mmol) was added, and the reaction was stirred for 3 h, when TLC analysis showed the reaction to be complete. The mixture was diluted with water (150 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (25:1 then 15:1 hexanes/EtOAc) gave **11** as a yellow oil (20.5 g, 94%). Compound **11** is a yellow oil that forms clear colorless crystals on standing at rt. R_f 0.51 (9:1 hexanes/EtOAc); mp 45−47 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 7.2 Hz, 2H), 7.39 (t, J = 7.4 Hz, 2H), 7.33 (t, J = 7.1 Hz, 1H), 7.00 (s, 1H), 5.04 (s, 2H), 3.82 (s, 3H), 3.75 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 149.8, 148.8, 147.9, 136.6, 128.6, 128.0, 127.3, 127.2, 115.5, 110.6, 71.2, 60.4, 60.4, 10.1; HRMS (FAB) m/z calcd for $C_{16}H_{17}BrO_3$ [M^+] 336.0361, found 336.0369.

Nitrone 12. To a well-stirred solution of *N*-Boc-D-serinal acetonide **10**[33] (12.5 g, 54.5 mmol) in CH_2Cl_2 (500 mL) were added anhydrous magnesium sulfate (9.84 g, 81.8 mmol) and *N*-benzylhydroxylamine (6.71 g, 54.5 mmol) sequentially, and the resulting mixture was stirred at rt for 4 h. The reaction was filtered, and the filtrate concentrated to give the crude product. Purification by flash chromatography on silica gel (3:1 EtOAc/hexanes) gave the pure nitrone **12** as a colorless oil (12.95 g, 71%). $[\alpha]_D$ +48.8 (*c* 1.8, $CHCl_3$), [lit.[32] for *ent*-**12**. $[\alpha]_D$ −46.6 (*c* 1.8, $CHCl_3$)]; ^{1}H NMR (500 MHz, $CDCl_3$, 55 °C) δ 7.43−7.35 (m 5H), 6.74 (br s, 1H), 4.93 (br s, 1H), 4.87 (s, 2H), 4.18 (dd, J = 9.2, 6.8 Hz, 1H), 4.06 (dd, J = 9.4, 2.4 Hz, 1H), 1.56 (s, 3H), 1.50 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (125.7 MHz, $CDCl_3$, 55 °C) δ 139.8, 132.7, 129.1, 128.9, 94.3, 80.4, 69.1, 66.4, 55.2, 28.3, 26.5, 23.4.

Hydroxylamine 13. A solution of aromatic bromide **11** (17.9 g, 53.1 mmol) in 30 mL of dry THF was added to a stirred suspension of

Mg turnings (1.29 g, 53.1 mmol) in 30 mL THF. A crystal of I_2 was added, and the mixture was heated to reflux. Grignard formation was slow, so 1,2-dibromoethane (100 μL) was added, and the mixture was heated under reflux for ~1 h at which point almost all of the Mg had reacted. The cooled Grignard mixture was then transferred via a cannula to a stirred solution of nitrone **12** (11.8 g, 35.4 mmol) in 30 mL of dry THF at −50 °C. The reaction was stirred at this temperature for 5 h when TLC showed that almost all of the nitrone was consumed. The mixture was partitioned between saturated NH_4Cl solution (80 mL) and Et_2O (2 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (9:1 hexanes/EtOAc) to yield hydroxylamine **13** as a white foam (14.9 g, 71%). R_f 0.39 (9:1 hexanes/EtOAc); $[\alpha]_D$ −35.0 (*c* 0.84, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.07 (11H), 5.10 (d, *J* = 11.6 Hz, 1H), 4.98 (d, *J* = 11.6 Hz, 1H), 4.54 (dd, *J* = 10.8, 5.0 Hz, 1H), 4.23 (d, *J* = 10.8 Hz, 1H), 3.87 (s, 3H), 3.85 (d, *J* = 10.8 Hz, 1H), 3.83 (d, *J* = 9.1 Hz, 1H), 3.76 (dd, *J* = 9.1, 5.2 Hz, 1H), 3.65 (s, 3H), 3.49 (d, *J* = 10.9 Hz, 1H), 3.45 (d, *J* = 5.3 Hz, 1H), 2.27 (s, 3H), 1.64 (s, 3H), 1.59 (s, 9H), 1.56 (s, 3H); ^{13}C NMR (150.8 MHz, $CDCl_3$) δ 154.8, 152.5, 148.2, 148.1, 139.9, 137.5, 128.7, 128.5, 127.9, 127.8, 126.6, 125.0, 124.3, 113.1, 94.4, 81.3, 70.9, 65.9, 63.6, 61.0, 60.5, 60.1, 58.7, 28.8, 28.1, 25.1, 10.3; HRMS (FAB) *m*/*z* calcd for $C_{34}H_{45}N_2O_7$ [MH^+] 593.3221, found 593.3234.

Acetonide 15. To a solution of hydroxylamine **13** (14.8 g, 25.0 mmol) in EtOH (270 mL) were added saturated aq NH_4Cl (270 mL) and zinc dust (32.6 g, 500 mmol). The mixture was heated under reflux overnight (bath temperature ~90 °C), when TLC analysis showed the reaction to be complete. The reaction mixture was cooled to room temperature and extracted with EtOAc (3 × 100 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give crude **14**. The resulting white foam was dissolved in dioxane (450 mL) and cooled to 0 °C. To this solution were added CbzCl (4.9 mL, 27 mmol) and 7% aq $NaHCO_3$ (80 mL), and the mixture was stirred for 4 h, when TLC showed the reaction to be complete. The mixture was partitioned between water (450 mL) and EtOAc (3 × 300 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (17:3 hexanes/EtOAc) to give **15** as a yellow oil (15.1 g, 85%). R_f 0.23 (85:15 hexanes/EtOAc); $[\alpha]_D$ +48.8 (*c* 1.8, $CHCl_3$); ^{1}H NMR (600 MHz, DMSO-d_6, 90 °C) δ 7.45−7.16 (10H), 7.00−6.87 (3H), 6.75 (br s, 1H), 6.66 (s, 2H), 5.75 (d, *J* = 10.2 Hz, 1H), 5.10 (br s, 1H), 5.00 (d, *J* = 12.4 Hz, 2H), 4.91−4.81 (m, 2H), 4.69 (d, *J* = 17.0 Hz, 1H), 4.27 (d, *J* = 16.9 Hz, 1H), 3.84 (dd, *J* = 9.4, 5.6 Hz, 1H), 3.55 (s, 3H), 3.50 (s, 3H), 3.32 (d, *J* = 9.4 Hz, 1H), 1.99 (s, 3H), 1.57 (s, 3H), 1.47 (s, 12H); ^{13}C NMR (150.8 MHz, DMSO-d_6, 90 °C) δ 156.8, 153.0, 153.0, 148.9, 148.1, 139.7, 138.2, 137.6, 128.9, 128.7, 128.3, 128.1, 128.0, 127.6, 127.0, 126.2, 125.8, 125.5, 113.7, 94.9, 80.1, 71.7, 67.2, 66.1, 60.9, 60.2, 56.8, 55.5, 48.5, 28.8, 27.6, 25.0 10.0; HRMS (FAB) *m*/*z* calcd for $C_{42}H_{50}N_2O_8$ [M^+] 710.3567, found 710.3557.

Alcohol 16. To a solution of acetonide **15** (15.9 g, 22.4 mmol) in MeOH (580 mL) was added catalytic amount of p-TsOH·H_2O (318 mg, 1.84 mmol). The reaction was stirred at room temperature for 48 h but was still incomplete according to TLC. The MeOH was evaporated under reduced pressure, and the residue was partitioned between saturated aq $NaHCO_3$ (300 mL) and CH_2Cl_2 (2 × 200 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to a yellow oil. The crude product was purified by flash chromatography to give **16** as a white foam (8.8 g, 71%, 80% based on recovered starting material). Mp 48−49 °C; R_f 0.33 (3:2 hexanes/EtOAc); $[\alpha]_D$ −38.1 (*c* 0.1 $CHCl_3$); ^{1}H NMR (600 MHz, DMSO-d_6, 90 °C) δ 7.42−7.20 (m, 10H), 7.20−6.94 (br s, 2H), 6.94−6.88 (br s, 2H), 6.76−6.68 (br s, 2H), 5.78 (d, *J* = 10.3 Hz, 1H), 5.55 (br s, 1H), 5.11 (br s, 2H), 4.97 (d, *J* = 12.1 Hz, 1H), 4.90 (d, *J* = 12.1 Hz, 1H), 4.53 (d, *J* = 16.9 Hz,1H), 4.32 (br s, 2H), 4.19 (d, *J* = 16.9 Hz,1H), 3.62 (s, 3H), 3.52 (s, 3H), 3.53 (br s, 1H), 3.24 (br s, 1H), 2.01 (s, 2H), 1.40 (s, 9H); ^{13}C NMR (125.7 MHz, DMSO-d_6, 90 °C) δ 161.4, 157.2, 155.9, 152.9, 148.8, 148.0, 139.5, 138.1, 129.0, 128.8, 128.3, 128.2, 128.1, 128.0, 127.8, 127.2, 126.4, 125.5, 125.3, 113.5, 78.7, 71.6, 67.3, 61.9, 61.0, 60.4, 53.9, 48.3, 45.3, 28.9, 9.8; HRMS (ESI) *m*/*z* (%) for $C_{39}H_{47}N_2O_8$ [MH^+] calcd 671.3327, found 671.3343.

(*R*)-Mosher Ester 17. A solution of (*R*)-(+)-Mosher acid (14 mg, 0.060 mmol) in dry CH_2Cl_2 (1 mL) was combined with amino alcohol **16** (13 mg, 0.020 mmol), DCC (12 mg, 0.060 mmol), and DMAP (13 mg, 0.060 mmol). This mixture was stirred at room temperature for 18−20 h when the reaction was judged to be complete by TLC. The reaction mixture was filtered through a cotton plug to remove *N*,*N*′-dicyclohexylurea and roughly purified by flash chromatography (7:3 hexanes/EtOAc) to give **17** as a yellow oil (24 mg, 122%). Care was taken to combine all fractions that contained Mosher ester. R_f 0.56 (7:3 hexanes/EtOAc); HPLC: C18 (3 × 250 mm) XBridge column, gradient: 95% to 5% H_2O in CH_3CN over 30 min, flow rate 0.5 mL/min, UV detection at 254 nm, t_R: 40.5 min, identified by coinjection with **18**; ^{1}H NMR (600 MHz, DMSO-d_6, 90 °C) δ 7.6−7.2 (15H), 7.1−6.9 (4H), 6.7 (s, 2H), 6.0−6.05 (br s, 1H), 5.6 (d, *J*= 10.8 Hz, 1H), 5.1−5.09 (2H), 5.0 (d, *J* = 12.6 Hz, 1H), 4.92 (d, *J* = 12.6 Hz, 1H), 4.69 (m, 1H), 4.52 (d, *J* = 17 Hz, 1H), 4.32 (dd, *J* = 11.4, 3.6 Hz, 1H), 4.2 (d, *J* = 17 Hz, 1H), 4.12 (dd, *J* = 11.4, 4.0 Hz, 1H), 3.65 (s, 3H), 3.42 (s, 3H), 3.48 (s, 3H), 2.0 (s, 3H), 1.4 (s, 9H); ^{13}C NMR (150.8 MHz, DMSO-d_6, 90 °C) δ 166.5, 152.8, 149.3, 148.3, 139.2, 137.4, 132.3, 130.3, 129.04, 128.8, 128.3, 127.9, 127.2, 126.6, 124.4, 113.5, 71.7, 67.5, 66.9, 66.8, 61.1, 60.4, 55.8, 55.5, 54.8, 48.5, 48.3, 35.1, 33.9, 28.8, 24.5, 10.1; ^{19}F NMR (300 MHz, DMSO-d_6, 22 °C) δ 3.95 (br s), 3.93 (br s); HRMS (ESI) *m*/*z* calcd for $C_{49}H_{53}F_3N_2O_{10}Na$ [MNa^+] 909.3545, found 909.3537.

(*S*)-Mosher Ester 18. A solution of (*S*)-(+)-Mosher acid (14 mg, 0.060 mmol) in dry CH_2Cl_2 (1 mL) was combined with amino alcohol **16** (13 mg, 0.020 mmol), DCC (12 mg, 0.060 mmol), and DMAP (13 mg, 0.060 mmol). The mixture was stirred at room temperature for 18−20 h when the reaction was judged to be complete by TLC. The reaction mixture was filtered through a cotton plug to remove *N*,*N*′-dicyclohexylurea and roughly purified by flash chromatography (7:3 hexanes/EtOAc) to give **18** as a yellow oil (25 mg, 125%). Care was taken to combine all fractions that contained Mosher ester. R_f 0.58 (7:3 hexanes/EtOAc); HPLC: C18 (3 × 250 mm) XBridge column, gradient: 95% to 5% H_2O in CH_3CN over 45 min, flow rate 0.5 mL/min, UV detection at 214 nm, t_R: 33.7 min, identified by coinjection with **17**; ^{1}H NMR (600 MHz, DMSO-d_6, 90 °C) δ 7.50 − 7.19 (15H), 7.04 (br s, 1H), 7.02 − 6.96 (m, 3H), 6.73 (m, 2H), 5.62 (d, *J* = 10.9 Hz, 1H), 5.12 (d, *J* = 11.8 Hz, 1H), 5.08 (d, *J* = 12.5 Hz, 1H), 4.98 (d, *J* = 12.1 Hz, 1H), 4.91 (d, *J* = 12.0 Hz, 1H), 4.70 (s, 1H), 4.51 (d, *J* = 16.6 Hz, 1H), 4.33 − 4.16 (m, 3H), 3.65 (s, 3H), 3.48 (s, 3H), 3.45 (s, 3H), 2.02 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (150.8 MHz, DMSO-d_6, 90 °C) δ 166.5, 152.8, 149.3, 148.4, 137.4, 132.4, 129.0, 128.8, 128.2, 127.9, 127.2, 126.6, 113.4, 66.8, 61.1, 60.4, 54.8, 48.4, 33.9, 28.8, 25.0, 10.1; ^{19}F NMR (300 MHz, DMSO-d_6, 22 °C) δ 3.80 (br s), 3.72 (br s); HRMS (ESI) *m*/*z* calcd for $C_{49}H_{53}F_3N_2O_{10}Na$ [MNa^+] 909.3545, found 909.3537.

Aldehyde 7. To a stirred mixture of alcohol **16** (8.80 g, 13.1 mmol) in CH_2Cl_2 (70 mL) at room temperature was added Dess−Martin periodinane (8.35 g, 19.7 mmol). The reaction mixture was stirred at room temperature for 1 h, when TLC analysis showed the reaction to be complete. The reaction mixture was washed with a 1:1 mixture (v/v) of 1 N $Na_2S_2O_3$ and saturated aq $NaHCO_3$ (250 mL), water (100 mL), and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (7:3 hexanes/EtOAc) gave **7** as a yellow oil (7.42 g, 85%). R_f 0.48 (7:3 hexanes/EtOAc); $[\alpha]_D$ −28.8 (*c* 1.82, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, complex mixture of rotomers, ONLY diagnostic signals are identified) δ 9.41 (br s, CHO),

7.52−6.74 (16H), 5.91 (NH), 5.53 (d, J = 8.7 Hz), 4.48 (d, J = 16.1 Hz), 4.09 (d, J = 15.6 Hz), 3.79 (s, OMe), 3.58 (s, OMe), 2.14 (s, Me), 1.33 (s, *t*-Bu); ^{13}C NMR (150.8 MHz, $CDCl_3$) δ 198.7, 170.9, 155.5, 148.2, 136.3, 128.8, 128.7, 128.3, 128.2, 128.0, 127.6, 127.3, 112.3, 79.8, 71.3, 67.9, 64.9, 55.5, 50.3, 30.9, 28.7, 21.4, 19.3, 14.5, 13.9, 10.2; HRMS (FAB) m/z calcd for $C_{39}H_{45}N_2O_8$ [MH^+] 669.3170, found 669.3189.

Cycloadducts 6 + 19. Aldehyde **7** (7.40 g, 11.1 mmol), (1*S*)-glycylsultam **8** (6.03 g, 22.1 mmol), and AgOAc (190 mg, 1.1 mmol) were combined in methyl acrylate (40.0 mL, 444 mmol), and the reaction mixture was stirred at room temperature for 2.5 h when TLC analysis showed the reaction to be complete. The mixture was partitioned between saturated aq NH_4Cl (100 mL) and CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield a yellow oil. The crude product was purified by flash chromatography (3:2 EtOAc/hexanes) to yield an inseparable 4:1 mixture of **6** + **19** as a white solid (8.14 g, 73%). Mp 79−81 °C; R_f 0.35 (2:1 hexanes/EtOAc); $[\alpha]_D$ −62.6 (*c* 1.73, $CHCl_3$); HPLC: C18 (3 × 250 mm) XBridge column, gradient: 80% to 20% H_2O in CH_3CN over 32 min, flow rate 0.5 mL/min, UV detection at 254 nm, t_R: 18.8 min (**19**) and 20.7 min (**6**) in a ratio of 1:4; ^{1}H NMR (500 MHz, C_6D_6, 70 °C, complex mixture of diastereomers and rotamers, diagnostic signals are identified) δ 7.48 (d, J = 7.2 Hz, 2H), 7.31 (s, 1H), 7.24 (t, J = 7.4 Hz, 2H), 7.18−6.88 (aromatic protons, 11H), 6.27 (br s), 5.99 (d, J = 8.1 Hz), 5.14 (d, J = 12.1 Hz), 5.07 (d, J = 12.1 Hz), 4.94 (br s, 1H), 4.67 (br s), 4.45−4.41 (m), 4.46 (br t, J = 3.0 Hz, 1H), 4.37 (d, J = 16.0 Hz, 1H), 4.34 (d, J = 16.0 Hz, 1H), 3.72 (br s, 3H), 3.69 (s, 3H), 3.62 (br s, 3H), 3.49 (s, 1H), 3.18 (1H), 2.80 (m + d, J = 13.3 Hz, 2H), 2.71 (d, J = 13.9 Hz, 1H), 2.42 (br s, 1H), 2.16 (m, 1H), 2.12 (s, 3H), 1.96 (d, J = 14.2 Hz, 1H), 1.76 (dd, J = 13.8, 7.8 Hz, 1H), 1.41 (s, 9H), 1.35−1.28 (m, 2H), 1.14 (br t, J = 12.0 Hz, 1H), 0.94 (s, 3H), 0.76 (br t, J = 11.5 Hz, 1H), 0.65 (br t, J = 11.3 Hz, 1H), 0.43 (s, 3H); ^{13}C NMR (125.7 MHz, C_6D_6, 70 °C) δ 174.8, 171.3, 157.8, 155.9, 151.8, 147.6, 138.0, 137.2, 136.4, 128.4, 128.3, 127.8, 127.6, 127.5, 127.4, 127.0, 126.2, 125.3, 111.6, 78.9, 70.6, 67.3, 64.6, 61.0, 60.3, 60.1, 52.9, 52.1, 48.6, 48.5, 47.8, 44.5, 44.4, 38.1, 36.6, 32.6, 28.3, 26.5, 20.8, 20.6, 19.8, 9.8 HRMS (ESI) m/z (%) for $C_{55}H_{68}N_4O_{12}S$ [MH^+] calcd 1009.4627, found 1009.4601.

Methyl Esters 21 + 22. To a solution of **6** + **19** (200 mg, 0.198 mmol) in dry MeOH (2.0 mL) was added $Sm(OTf)_3$ (118 mg, 0.198 mmol). The turbid yellow reaction mixture was purged with argon and stirred for 1 h at room temperature. The mixture was partitioned between saturated NH_4Cl (30 mL) and EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (7:3 hexanes/EtOAc) to afford an inseparable mixture of **21** + **22** as a yellow oil (97 mg, 62%). R_f 0.41 (1:1 EtOAc/hexanes); HPLC: C18 (3 × 250 mm) XBridge column, gradient, 95% to 5% H_2O in CH_3CN over 45 min, flow rate 0.5 mL/min, UV detection at 214 nm, t_R: 31.5 min (**22**) and 32.3 min (**21**) in a ratio of 1:3); ^{1}H NMR (600 MHz, $CDCl_3$, complex mixture of rotomers, ONLY diagnostic signals are identified) δ 3.80 (s, minor OMe), 3.77 (s, minor OMe), 3.76 (s, major OMe), 3.72 (s, major OMe), 3.70 (s, major OMe), 3.69 (s, minor OMe), 3.67 (s, major OMe), 3.63 (s, major OMe), 3.60 (s, major OMe), 3.59 (s, minor OMe), 2.12 (s, major Me), 2.08 (s, minor Me), 2.05 (s, major Me), 2.01 (s, minor Me), 1.46 (s, minor Boc), 1.41 (s, minor Boc), 1.32 (s, major Boc); ^{13}C NMR (150.8 MHz, DMSO-d_6, 90 °C) δ 175.7, 172.3, 155.9, 153.8, 149.4, 148.4, 139.9, 129.4, 129.2, 128.4, 128.7, 128.6, 127.9, 127.6, 126.6, 126.1, 125.4, 113.8, 78.8, 71.9, 61.4, 60.7, 59.9, 59.3, 55.6, 52.5, 48.4, 32.9, 29.3, 10.4; HRMS (ESI) m/z calcd for $C_{46}H_{55}N_3O_{11}$ [MH^+] 826. 3915, found 826.3916.

Cycloadduct 23. Aldehyde **7** (0.30 g, 0.35 mmol), (1*R*)-glycylsultam *ent*-**8** (0.19 g, 0.69 mmol) and AgOAc (9 mg, 10 mol %) were combined in methyl acrylate (**9**, 2.1 mL, 240 mmol), and the reaction mixture was stirred at room temperature for 4 h when TLC analysis showed the reaction to be complete. The mixture was partitioned between saturated NH_4Cl solution (20 mL) and CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (3:2 hexanes/EtOAc) to give **23** as a white solid (0.27 g, 77% yield). Mp 79−81 °C; R_f 0.35 (2:1 hexanes/EtOAc); $[\alpha]_D$ +60.6 (*c* 1.8, $CHCl_3$); HPLC: C18 (3 × 250 mm) XBridge column, gradient, 80% to 20% H_2O in CH_3CN over 32 min, flow rate 0.5 mL/min, UV detection at 254 nm, t_R: 17.7 min; ^{1}H NMR (600 MHz, DMSO-d_6, 90 °C, mixture of rotamers, diagnostic signals are identified) δ 7.44 (m, 2H), 7.33 (m, 7H), 6.97−6.87 (4H), 6.62 (s, 2H), 5.78 (d, J = 10.7 Hz, 1H), 5.12 (d, J = 10.9 Hz, 1H), 5.02 (dd, J = 12.0 Hz, 2H), 4.48 (m, 1H), 4.37 (t, J = 8.6 Hz, 1H), 4.06−3.78 (m, 1H), 3.78−3.68 (m, 4H), 3.67−3.60 (m, 6H), 3.53 (d, 2H), 3.50−3.40 (m, 1H), 3.23 (m, 1H), 2.39 (d, J = 6.9 Hz, 1H), 2.26−2.15 (m, 1H), 2.10−1.94 (5H), 1.94−1.76 (3H), 1.42 (s, 9H), 1.14 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (150.7 MHz, DMSO-d_6, 90 °C) δ 171.8, 157.2, 153.5, 148.1, 138.0, 129.2, 128.9, 128.7, 128.3, 128.1, 127.6, 71.6, 67.1, 65.5, 60.4, 53.3, 52.3, 48.7, 48.1, 45.2, 41.3, 41.2, 40.9, 40.7, 40.5, 40.3, 38.6, 32.8, 29.1, 28.9, 26.7, 21.1, 20.2, 10.0; HRMS (ESI) m/z for $C_{55}H_{68}N_4O_{12}S$ [MH^+] calcd 1009.4627, found 1009.4601.

Methyl Ester 22. To a stirring solution of **23** (65 mg, 0.06 mmol) in dry MeOH (0.5 mL) was added $Sm(OTf)_3$ (40 mg, 0.069 mmol). The reaction mixture was purged with argon and stirred at room temperature for 1 h when TLC analysis showed the reaction to be complete. The reaction mixture was concentrated, diluted with 15 mL of EtOAc, and washed with saturated NaCl solution (15 mL) and saturated $NaHCO_3$ solution (15 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (7:3 hexanes/EtOAc) afforded **22** as a colorless oil (0.176 g, 71%). R_f 0.35 (1:1 EtOAc/hexanes); HPLC: C18 (3 × 250 mm) XBridge column, gradient: 95% to 5% H_2O in CH_3CN over 45 min, flow rate 0.5 mL/min, UV detection at 214 nm, t_R: 31.5 min, identified by coinjection with (**21** + **22**); ^{1}H NMR (600 MHz, $CDCl_3$, complex mixture of rotamers, ONLY diagnostic signals are identified) δ 7.55 - 6.59 (16H), 5.91 (d, J = 10.8 Hz), 5.82 (d, J = 10.3 Hz, 1H), 5.40 (d, J = 12.6 Hz,), 5.20 (dd, J = 12.3, 23.0 Hz 1H), 5.06 (d, J = 13.9 Hz), 5.01 (d, J = 13.9 Hz), 4.88 (d, J = 11.9 Hz), 4.80 (d, J = 16.2 Hz), 4.61 (d, J = 17.0 Hz), 4.59 − 4.50 (m, 1H), 4.16 (d, J = 16.1 Hz), 4.03 (d, J = 16.3 Hz), 3.84 (t, J = 8.9 Hz 1H), 3.80 (s, OMe), 3.77 (s, OMe), 3.69 (s, OMe), 3.59 (s, OMe), 3.47 (dd, J = 8.3, 5.7 Hz, 1H), 3.01 (m, 1H), 2.39 (m, 1H), 2.25 (m, 1H), 2.08 (s, aromatic Me), 2.01 (s, aromatic Me), 1.48 (s, Boc), 1.42 (s, Boc); ^{13}C NMR (150.8 MHz, $CDCl_3$) δ 174.8, 174.6, 171.9, 171.7, 157.5, 157.0, 156.0, 155.9, 148.7, 148.2, 139.1, 138.9, 137.3, 136.8, 128.8, 128.7, 128.6, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 126.9, 79.3, 78.4, 71.1, 67.5, 61.0, 60.5, 59.5, 59.4, 52.6, 51.2, 47.3, 47.0, 32.4, 32.3, 29.9, 28.7, 28.6, 9.9, 9.8; HRMS (ESI) m/z calcd for $C_{46}H_{55}N_3O_{11}$ [MH^+] 826. 3915, found 826.3916.

Bicyclic Lactam 24. To a stirred solution of cycloadducts **6** +**19** (5.30 g, 5.25 mmol) in MeOH (500 mL) was added Pd−C (1.3 g) portion-wise under argon. The reaction flask was then purged with H_2 gas and stirred at rt under hydrogen (balloon) for 60 h when TLC analysis showed the reaction to be complete. The mixture was filtered through a pad of Celite 545 and concentrated. Purification of this residue by flash chromatography yielded **24** as a white solid (2.0 g, 57%). Mp 180−182 °C; R_f 0.37 (19:1 CH_2Cl_2/MeOH); $[\alpha]_D$ −78.1 (*c* 1.56, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers, diagnostic signals are identified) δ 6.81 (s, 1H), 5.85 (s, 1H), 5.74 (d, J = 10.0 Hz, 1H), 4.98 (s, 1H), 4.41 (t, J = 6.8 Hz, 2H), 4.10 (t, J = 8.3 Hz 1H), 3.89 (dd, J = 7.0, 5.1 Hz, 1H), 3.79−3.68 (m, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.53−3.42 (m, 2H), 3.06−2.95 (m, 1H), 2.66−2.56 (m, 1H), 2.40 (dt, J = 13.0, 6.3 Hz, 1H), 2.23 (s, 3H), 2.05 (dd, J = 13.8, 7.9 Hz, 1H), 1.91 (br s, 3H), 1.43 (t, J = 9.8 Hz, 1H), 1.33 (s, 9H), 1.23 (s, 3H), 1.10 (s, 2H), 0.98 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 173.4, 155.9, 149.50, 145.9, 145.6, 125.7, 124.6, 111.2, 79.5, 65.1, 61.3, 60.6, 60.4, 58.5,

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53.8, 52.9, 51.6, 51.2, 48.7, 47.8, 44.5, 43.4, 37.9, 33.9, 32.6, 29.2, 28.1, 27.9, 26.5, 20.7, 19.9, 9.9; HRMS (ESI) m/z for $C_{32}H_{47}N_4O_9S$ $[MH^+]$ calcd 663.3058, found 663.3088.

A small amount of byproduct **iv** was also isolated as a white solid (8%). R_f 0.31 (19:1 CH_2Cl_2/MeOH); mp 140−143 °C; $[\alpha]_D$ −9.6 (c 0.9, $CHCl_3$); ^{1}H NMR (600 MHz, DMSO-d_6, 90 °C) δ 8.36 (s, 1H), 6.68 (s, 1H), 5.63 (br s, 1H), 4.78 (s, 1H), 3.76 (s, 4H), 3.67 (s, 3H), 3.63 (s, 1H), 3.58 (s, 3H), 3.41 (br s, 1H), 3.35 (m, 1H), 2.36 (br t, J = 11.7 Hz, 1H), 2.10 (s, 3H), 1.22 (br s, 9H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 178.7, 171.2, 154.6, 149.1, 145.6, 145.3, 127.7, 124.6, 111.5, 110.3, 79.2, 77.2, 77.0, 76.7, 64.0, 62.3, 61.2, 60.4, 53.4, 52.4, 50.8, 50.6, 48.2, 29.0, 28.1, 27.7, 10.1; HRMS (ESI) m/z for $C_{23}H_{34}N_3O_8$ $[MH]^+$ calcd 480.2340, found 480.2382.

Cbz-Protected Pyrrolidine 25. To a stirred solution of the bicyclic lactam **24** (2.00 g, 3.02 mmol) in dry THF (250 mL) at 0 °C was added diisopropylethylamine (0.69 mL, 3.9 mmol) followed by CbzCl (0.45 mL, 3.2 mmol). The mixture was stirred for 2 h at 0 °C when TLC analysis showed the reaction to be complete. Saturated NH_4Cl solution (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield a white solid. Purification by flash chromatography gave **25** as a white solid (2.04 g, 85%). Mp 203−205 °C; R_f 0.59 (19:1 CH_2CL_2/MeOH); $[\alpha]_D$ −74.6 (c 1.54, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, complex mixture of conformers, ONLY diagnostic signals are reported) δ 7.45−7.00 (6H), 6.85 (s, NH), 6.83 (s, NH), 3.80 (s, minor OMe), 3.78 (s, minor OMe), 3.76 (s, major OMe), 3.71 (s, major OMe), 2.24 (s, major aromatic Me), 2.17 (s, minor aromatic Me), 1.33 (s, major Boc Me), 1.29 (s, minor Boc Me), 1.11 (s, major auxiliary Me), 0.99 (s, major auxiliary Me), 0.98 (s, minor auxiliary Me), 0.96 (s, minor auxiliary Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 170.9, 155.6, 154.0, 149.4, 145.7, 136.2, 129.0, 128.3, 128.2, 128.1, 127.8, 127.7, 126.0, 124.3, 111.5, 110.7, 78.6, 70.6, 67.7, 65.0, 61.3, 60.8, 60.6, 58.8, 58.6, 57.0, 53.4, 52.9, 52.1, 50.8, 50.6, 49.1, 47.8, 44.5, 42.4, 41.2, 37.6, 32.8, 32.7, 29.5, 28.2, 28.1, 27.8, 26.5, 20.8, 20.6, 20.0, 10.1, 9.8; HRMS (FAB) m/z for $C_{40}H_{53}N_4O_{11}S$ $[MH^+]$ calcd 797.3426, found 797.3433.

Pictet−Spengler Product 27. To a stirred mixture of the bicyclic lactam **25** (2.0 g, 2.5 mmol) in CH_2Cl_2 (68 mL) was added TFA (3.87 mL, 50.2 mmol) at 0 °C. The reaction was allowed to warm to room temperature over 5 h when TLC analysis showed the reaction to be complete. The solvent was removed under reduced pressure, and diethyl ether was added to the residue to precipitate the TFA salt of **26**. The salt was collected and dissolved in CH_2Cl_2 (12 mL). Acetic acid (158 μL) and 4 Å MS were added sequentially, and the resulting mixture was degassed via three freeze−pump−thaw cycles with argon. A solution of benzyloxyacetaldehyde (415 mg, 2.51 mmol, freshly prepared by Dess−Martin oxidation of 2-benzyloxyethanol) in CH_2Cl_2 (6 mL) was added in portions over 2 h at room temperature when TLC analysis showed the reaction to be complete. The mixture was filtered to remove the molecular sieves and then partitioned between saturated aq $NaHCO_3$ (100 mL) and CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a yellow oil. The residue was purified by flash chromatography (3:1 EtOAc/hexanes) to afford compound **27** (1.76 g, 86%) as a yellow solid. R_f 0.22 (3:1 EtOAc/hexanes); $[\alpha]_D$ −17.5 (c 0.96, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, complex mixture of conformers, ONLY diagnostic signals are reported) δ 8.23 (s, NH), 8.01 (s, NH), 5.43 (br s), 5.26 (d, J = 12.5 Hz), 5.13 (d, J = 12.1 Hz), 5.08 (d, J = 12.2 Hz), 5.05 (d, J = 12.1 Hz), 3.79 (s, OMe), 3.70 (s, OMe), 3.44 (d, J = 13.9 Hz,), 3.32 (d, J = 13.7 Hz), 2.20 (s, aromatic Me), 1.07 (s, minor auxiliary Me), 1.01 (s, minor auxiliary Me), 0.96 (s, major auxiliary Me), 0.93 (s, major auxiliary Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 170.9, 154.4, 154.0, 149.5, 144.3, 136.1, 136.0, 128.8, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 123.5, 122.7, 122.6, 73.4, 67.7, 65.0, 61.7, 61.6, 60.0, 59.8, 59.3, 59.2, 52.8, 52.7, 52.4, 52.2, 50.4, 49.5, 48.7, 48.6, 47.7, 47.6, 47.3 47.2, 44.5, 44.4, 41.1, 40.2, 37.8, 36.6, 32.6, 26.8, 21.0, 20.8, 19.8, 9.8; HRMS (FAB) m/z for $C_{44}H_{53}N_4O_{10}S$ $[MH^+]$ calcd 829.3482, found 829.3480.

Compound 28. To a stirred solution of the phenol **27** (1.80 g, 2.17 mmol) and K_2CO_3 (0.90 g, 3.3 mmol) in DMF (38 mL) was added BnBr (0.39 mL, 3.3 mmol), and the resulting mixture was stirred at 50 °C for 3 h. The reaction mixture was partitioned between water (100 mL) and EtOAc (3 × 100 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography of this residue yielded pure **28** (1.62 g, 81%, 92% based on recovered starting material). R_f 0.32 (3:1 EtOAc/hexanes); $[\alpha]_D$ −32.4 (c 2.30, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, complex mixture of conformers, ONLY diagnostic signals are reported) δ 7.46−7.15 (15H), 5.29 (s, NH), 5.27 (s, NH), 5.03 (d, J = 11.3 Hz), 4.81 (d, J = 11.6 Hz), 3.79 (s, major OMe), 3.75 (s, minor OMe), 3.74 (s, major OMe), 2.54 (q, J = 11.8 Hz), 2.20 (s, aromatic Me), 1.02 (s, minor auxiliary Me), 0.96 (s, major auxiliary Me), 0.90 (s, minor auxiliary Me), 0.87 (s, major auxiliary Me); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.9, 170.6, 170.2, 154.5, 154.3, 152.8, 152.7, 152.5, 145.8, 145.8, 139.3, 139.2, 137.5, 137.4, 136.3, 136.2, 128.8, 128.5, 128.4, 128.4, 128.2, 128.1, 127.9, 127.9, 126.8, 126.8, 124.0, 123.9, 123.9, 77.2, 76.1, 75.9, 74.4, 72.5, 67.6, 67.5, 65.1, 64.9, 61.5, 61.4, 60.4, 60.1, 60.0, 59.5, 59.4, 53.4, 52.8, 52.7, 50.8, 49.9, 48.7, 48.6, 47.9, 47.9, 47.6, 47.5, 44.4, 44.3, 41.3, 40.3, 37.8, 37.7, 34.8, 33.8, 32.6, 32.5, 29.7, 26.2, 20.9, 20.7, 19.8, 19.7, 9.8; HRMS (FAB) m/z for $C_{51}H_{59}N_4O_{10}S$ $[MH^+]$ calcd 919.3946, found 919.3964.

Tetracyclic Alcohol 29. To a stirred mixture of $LiAlH_4$ (159 mg, 4.20 mmol) in dry THF (7 mL) was added a solution of **28** (1.54 g, 1.68 mmol) in dry THF (10 mL) at 0 °C, and the reaction mixture was allowed to stir for 1 h. The mixture was diluted with aq saturated NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a yellowish residue. Flash chromatography (95:5 CH_2Cl_2/MeOH) furnished pure **29** as yellow solid (619 mg, 61%). Mp 69−71 °C; R_f = 0.31 (9:1 CH_2Cl_2/MeOH + 1% AcOH); $[\alpha]_D$ +35.6 (c 1.47, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.22 (m, 10H), 5.21 (s, 1H), 5.05 (d, J = 10.9 Hz, 1H), 4.84 (d, J = 10.9 Hz, 1H), 4.52 (s, 1H), 4.49 (d, J = 11.9 Hz, 1H), 4.45 (d, J = 11.9 Hz, 1H), 4.43 (d, J = 5.8 Hz, 1H), 4.23 (dd, J = 8.3, 2.2 Hz, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.70 (dd, J = 11.3, 4.0 Hz, 1H), 3.62 (dd, J = 11.3, 2.7 Hz, 1H), 3.32 (t, J = 8.4 Hz, 1H), 3.15 (dd, J = 10.7, 4.1 Hz, 1H), 3.11−3.12 (m, 1H), 2.96−2.88 (m, 1H), 2.75−2.66 (m, 1H), 2.40 (s, 3H), 2.31−2.24 (m, 2H), 2.22 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 174, 152.8, 152.4, 145.9, 138.7, 137.4, 128.4, 128.3, 127.9, 127.6, 127.3, 124.9, 124.1, 75.3, 74.4, 73.3, 66.6, 66.2, 62.1, 61.7, 60.4, 53.8, 49.9, 48.2, 39.6, 39.5, 31.8, 9.7; HRMS (FAB) m/z for $C_{34}H_{42}N_3O_6$ $[MH^+]$ calcd 588.3074, found 588. 3089.

Pentacyclic Nitrile 30. To a cooled solution (−60 °C) of oxalyl chloride (77 μL, 0.88 mmol) in dry CH_2Cl_2 (2 mL) was added dry DMSO (85 μL, 1.20 mmol) via a syringe, and the resulting mixture was stirred for about 5 min. The alcohol **29** (235 mg, 0.407 mmol) in CH_2Cl_2 (3 mL) was added slowly over 2 min and stirred for 1 h at this temperature. Triethylamine (281 μL, 2.00 mmol) was added slowly, and the reaction was stirred at −60 °C for an additional 15 min at which point it was allowed to warm to room temperature. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in 4 mL of CH_2Cl_2, and to this solution was added a 0.5 N solution of $ZnCl_2$ in THF (1.0 mL, 0.5 mmol) and TMSCN (100 μL, 0.8 mmol) sequentially. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was partitioned between water (20 mL) and CH_2Cl_2 (3 × 40 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (95:5 CH_2Cl_2/MeOH) gave pure **30** (107 mg, 45%). R_f = 0.4

(95:52 CH_2Cl_2/MeOH); $[\alpha]_D$ = +48.5 (*c* 0.69, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.1 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.36−7.23 (4H), 7.17 (d, *J* = 6.8 Hz, 2H), 5.18 (s, 1H), 5.11 (d, *J* = 10.7 Hz, 1H), 4.94 (d, *J* = 10.7 Hz, 1H), 4.63 (br s, 1H), 4.61 (br s, 1H), 4.51 (d, *J* = 7.6 Hz, 1H), 4.32 (s, 2H), 3.84 (s, 3H), 3.76−3.72 (m, 1H), 3.74 (s, 3H), 3.44 (t, *J* = 8.9 Hz, 1H), 3.39 (m, 1H), 3.29 (br s, 1H), 3.19− 3.10 (m, 2H), 2.65−2.52 (m, 1H), 2.39 (br s, 3H), 2.22 (s, 3H), 2.08 (dd, *J* = 13.2, 4.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.2, 152.6, 152.1, 145.3, 137.9, 136.9, 128.5, 128.3, 128.2, 128.2, 127.4, 127.4, 126.0, 124.9, 123.1, 118.0, 78.2, 74.9, 72.8, 63.9, 62.4, 61.9, 60.2, 57.9, 55.8, 53.3, 47.8, 41.4, 39.3, 30.5, 9.7; HRMS (FAB) *m*/*z* for $C_{35}H_{39}N_4O_5$ (MH^+) calcd 595.2915, found 595.2921.

Pentacyclic Imine 31. To a flask charged with Lawesson's reagent (0.11 g, 0.26 mmol) was added **30** (0.11 g, 0.18 mmol) in benzene (5 mL). This mixture was heated under reflux for 1 h. After cooling to room temperature, the mixture was partitioned between EtOAc and a dilute aq solution of $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated to a yellow residue. The residue was dissolved in acetone (4 mL) and Raney nickel (washed three times with acetone) was added. After stirring for 30 min, the reaction mixture was filtered through a short plug of Celite and concentrated. Flash chromatography (3:1 EtOAc/hexanes) yielded pure **31** as a yellow solid (63%). Mp 86−89 °C; R_f 0.36 (3:1 EtOAc/hexanes); $[\alpha]_D$ +27.5 (*c* 0.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (t, *J* = 2.6 Hz, 1H), 7.54−7.50 (2H), 7.4−7.27 (5H), 7.20−7.15 (3H), 5.13 (d, *J* = 10.9 Hz, 1H), 4.95 (d, *J* = 10.7 Hz, 1H), 4.64−4.62 (m, 1H), 4.56 (d, *J* = 3.5 Hz, 1H), 4.47 (d, *J* = 8.6 Hz, 1H), 4.35 (d, *J* = 11.4 Hz, 1H), 4.18 (d, *J* = 11.9 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.70 (dd, *J* = 9.5, 1.7 Hz, 1H), 3.37 (dd, *J* = 9.5, 8.0 Hz, 1H), 3.34−3.28 (m, 1H), 3.19−3.13 (m, 1H), 3.02 (t, *J* = 2.1 Hz, 1H), 2.84−2.77 (m, 1H), 2.38 (s, 3H), 2.37−2.32 (m, 1H), 2.24 (s, 3H), 1.66 (dd, *J* = 12.8, 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 151.9, 151.6, 145.1, 138.1, 137.3, 128.5, 128.4, 128.3, 128.0, 127.5, 127.4, 125.7, 124.8, 118.3, 78.7, 74.8, 72.6, 62.8, 62.4, 61.8, 60.3, 57.8, 56.0, 55.6, 51.8, 41.3, 37.1, 29.7, 28.8, 9.4; HRMS (ESI) *m*/*z* for $C_{35}H_{39}N_4O_4$ $[MH]^+$ calcd 579.2971, found 579. 2959.

Oxazolidine 32. A mixture of **31** (21 mg, 0.036 mmol) and AcOH (100 μL) in a 1:1 mixture of ethylene oxide/methanol (2 mL) was heated at 60 °C in a sealed tube for 6 h. After cooling, the tube was opened, and the solvent was evaporated. The residue was purified by flash chromatography (3:1 EtOAc/hexanes) to give **32** (13 mg, 58%). R_f 0.28 (3:1 EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.57−7.55 (m, 1H), 7.41−7.12 (7H), 7.16−7.13 (m, 2H), 5.14 (d, *J* = 10.5 Hz, 1H), 4.91 (d, *J* = 10.5 Hz, 1H), 4.71 (s, 1H), 4.58 (d, *J* = 3.7 Hz, 1H), 4.56 (dd, *J* = 8.6, 1.58 Hz, 1H), 4.37 (d, *J* = 11.9 Hz, 1H), 4.21 (d, *J* = 11.9 Hz, 1H), 4.03 (t, *J* = 8.9 Hz, 1H), 3.85 (s, 3H), 3.84−3.79 (m, 1H), 3.61 (s, 3H), 3.63−3.56 (3H), 3.35−3.30 (m, 1H), 3.23−3.21 (m, 1H), 3.16−3.13 (m, 1H), 2.92 (d, *J* = 2.7 Hz, 1H), 2.91−2.78 (2H), 2.37 (s, 3H), 2.26 (dt, *J* = 12.7, 6.5 Hz, 1H), 2.21 (s, 3H), 1.85 (dd, *J* = 12.6, 6.5 Hz, 1H); ^{13}C NMR (100 MHz) δ 151.6, 151.5, 145.5, 138.4, 137.4, 128.6, 128.5, 128.2, 128.1, 127.6, 127.4, 127.2, 127.1, 123.7, 119.0, 94.2, 78.2, 74.9, 72.4, 62.8, 61.9, 61.6, 60.9, 60.2, 58.2, 55.3, 55.2, 50.7, 50.6, 41.4, 35.6, 29.7, 9.7; HRMS (FAB) *m*/*z* (%) for $C_{37}H_{43}N_4O_5$ $[MH^+]$ calcd 623.3228, found 623.3215.

Fukuyama's Alcohol 33. To a −78 °C solution of **32** (13 mg, 0.021 mmol) in dry CH_2Cl_2 (1 mL) was slowly added BCl_3 (140 μL, 0.13 mmol, 1.0 M solution in CH_2Cl_2). The resulting mixture was allowed to stir at this temperature for 2 h. The mixture was diluted with CH_2Cl_2 (10 mL) and poured into a dilute solution of $NaHCO_3$ (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative TLC (4:1 EtOAc/hexanes) to yield **33** (4.8 mg, 52%). R_f 0.16 (4:1 EtOAc/hexanes); $[\alpha]_D$ −9.0 (*c* 0.48, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.34 (br s, 1H), 5.74 (s, 1H), 4.80 (s, 1H), 4.39 (s, 1H), 3.97 (d, *J* = 3.32 Hz, 1H), 3.96−3.90 (m, 1H), 3.88−3.87 (m, 2H), 3.81 (s, 3H), 3.75−3.71 (m, 2H), 3.62 (s, 3H), 3.45−3.42 (m, 1H), 3.40−3.38 (m, 1H), 3.24−3.22 (m, 1H), 3.04 (d, *J* = 2.92, Hz, 1H), 2.99−2.87 (m, 2H), 2.34 (s, 3H), 2.26 (dt, *J* = 12.5, 6.63 Hz, 1H), 2.24 (s, 3H), 1.80 (dd, *J* = 12.8, 6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 145.7, 142.5, 126.1, 122.3, 119.9, 117.8, 93.1, 62.6, 61.8, 61.7, 61.2, 60.8, 60.1, 57.3, 54.7, 54.0, 49.7, 49.5, 41.4, 35.3, 29.0, 9.9; HRMS (FAB) *m*/*z* (%) for $C_{23}H_{31}N_4O_5$ $[MH^+]$ calcd 443.2289, found 443.2299. (A tabulated comparison of our ^1H NMR data with that reported by Fukuyama and Li[19] is provided in the Supporting Information.)

■ ASSOCIATED CONTENT

Supporting Information. ^1H and ^{13}C NMR data for compounds **11**, **12**, **13**, **14**, **15**, **16**, **7**, **17**, **18**, (**6** + **19**), (**21** + **22**), **22**, **23**, **24**, **25**, **26**, **27**, **28**, **29**, **30**, **31**, **32**, and **33**; HPLC data for (**6** + **19**), (**21** + **22**), **22**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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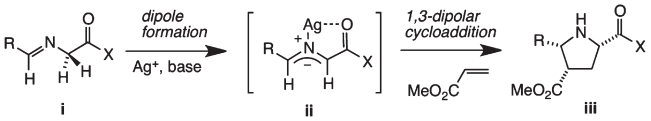
(28) The obvious choice for constructing a pyrrolidine such as **iii** would involve the [3 + 2] cycloaddition of an azomethine ylide **ii** as exemplified below for the prototypical Grigg reaction (or its asymmetric catalytic variants). However, prior to our methodological work in this area, it was not generally possible to apply this chemistry to azomethine ylides such as **ii** derived from aliphatic aldimines **i** capable of tautomerization (R = C(sp^3)-H). Only when this problem was solved could the critical issue of controlling the pyrrolidine stereochemistry in the presence of the chiral R group (see structure **6**) be dealt with.



(29) For an account describing our group's development of the asymmetric [C + NC + CC] coupling reaction, see: Garner, P.; Kaniskan, H. Ü. *Curr. Org. Synth.* **2010**, *7*, 348. The *N*-acyl camphorsultam plays a critical role in this embodiment of an *in situ* azomethine ylide generation/cycloaddition by both facilitating the underlying multicomponent reaction cascade and influencing the stereochemical outcome of the [3 + 2] cycloaddition in a predictable manner.

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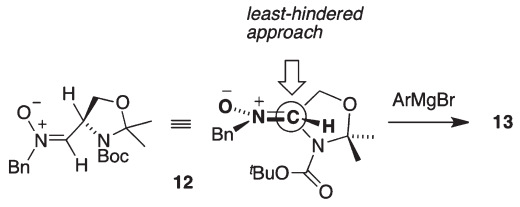
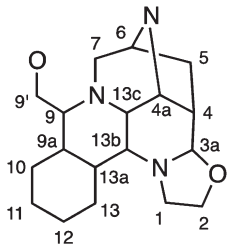


(33) Serinal **10** was conveniently prepared using a modification of Dondoni's procedure: Dondoni, A.; Perrone, D. *Org. Synth.* **2000**, *77*, 64. In our procedure the final oxidation was performed with the Dess–Martin reagent: Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(34) The following numbering system for the cyanocyclines is used throughout this paper.



(35) Bromide **11** was prepared starting from commercially available 2,6-dimethoxytoluene in 5 steps (68% overall yield) via (1) Friedel–Crafts acylation with propionyl chloride, (2) pTsOH-catalyzed Bayer–Villiger oxidation with mCPBA, (3) aromatic bromination with NBS, (4) saponification of the propionate with KOH, and (5) benzylation of the phenol with benzyl bromide. For detailed descriptions of the first four steps, see: Marques, M. M.; Pichlmair, M. M. B.; Martin, H. J.; Mulzer, J. *Synthesis* **2002**, 2766.

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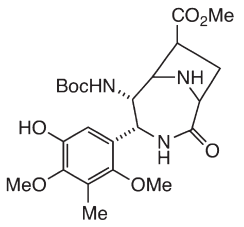
(38) When this reaction was performed on a larger scale, a small amount of the product **iv** resulting from cyclization onto the *N*-acyl sultam was also isolated. The absolute stereochemistry about the pyrrolidine ring was not established.



(39) Conducting this reaction at 50 °C (rather than the originally reported 60 °C) minimized the formation of a byproduct resulting from *N*-benzylation of the tetrahydroisoquinoline ring of **28**.

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