Synthesis of the Vancomycin CD and DE Ring Systems

Dale L. Boger,* Robert M. Borzilleri, Seiji Nukui, and Richard T. Beresis

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

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Full details of the synthesis of the fully substituted vancomycin CD and DE ring systems are described and a potential solution to the control of the atropisomer stereochemistry is defined.

Vancomycin (**1**)[1] was isolated in 1956 from *Streptomyces orientalis* and its structure and stereochemistry were ultimately secured over 25 years later through a combination of chemical degradation,[1b] NMR,[1d,e] and X-ray crystallography studies (Figure 1).[1f] It represents the prototypic member of a large class of clinically effective glycopeptide antibiotics,[2−7] which now includes teicoplanin,[2a] ristocetin,[2b] β-avoparcin,[2c] actaplanin (A4696),[2d] and A33512B,[2e] characterized by a polycyclic heptapeptide backbone composed of two 16-membered biaryl ether ring systems (CD and DE). In addition, it possesses a challenging 12-membered biaryl AB ring system which imposes the cis secondary amide structure in the 16-membered CD ring system, two sensitive β-hydroxy 3-chlorophenylalanines susceptible to retro-Aldol cleavage in the corners of central CDE ring system, three substituted phenylglycines prone to epimerization including a pivotal 3,4,5-trihydroxyphenylglycine central to the CDE ring system, and a defined atropisomer stereochemistry resulting from the monochloro substitution of the aryl C and E rings, as well as an unusual phenol glycosidic linkage capping off its structure. Teicoplanin and ristocetin possess an additional 14-membered FG ring system and the former lacks the DE ring benzylic hydroxyl group while the latter agent lacks the aromatic chlorine substituents. Several congeners of vancomycin have been disclosed and differ in the number and location of its chlorine substituents and in the number, structure, and position of the linked carbohydrates.[3] Two especially interesting variants on the vancomycin structure are orienticin C,[3c,d] which lacks both aromatic chlorine substituents, thus simplifying the synthetic target, and complestatin and the chloropeptins which incorporate an aryl−indole linkage into the DE ring system in place of the characteristic biaryl ether.[4]

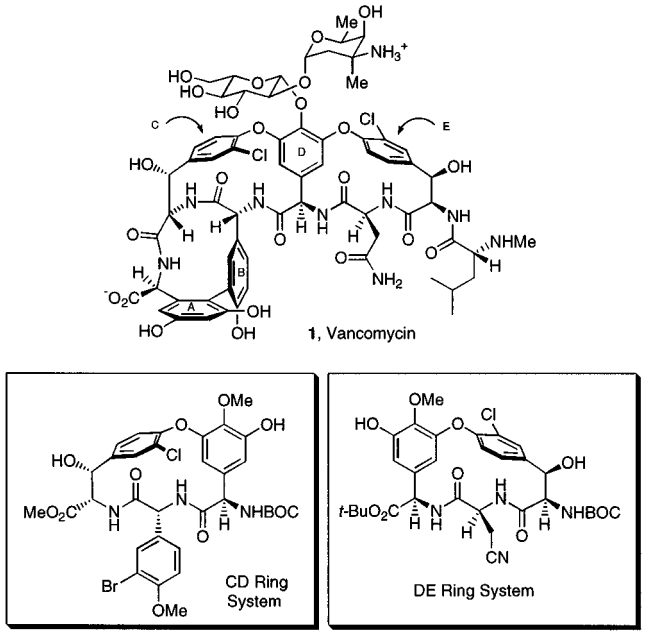

Figure 1.

Vancomycin has been in clinical use for over 35 years and its use has increased steadily over the past 20 years. Currently, it is the therapeutic agent of choice for the treatment of Gram-positive bacterial infections caused by methicillin-resistant *Staphylococcus aureus*, and is routinely used against enterococci and bacterial infections in patients allergic to β-lactam antibiotics. It inhibits bacterial cell wall biosynthesis by selectively binding to mucopeptides terminating in the sequence D-Ala-D-Ala.[5,8] Consequently, the binding affinity and selectivity of

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vancomycin with the C-terminal D-Ala-D-Ala sequence and related cell wall mimics have been the subject of numerous investigations.[5] As its use has increased, the emergence of resistant bacteria insensitive to vancomycin has also increased. This has serious clinical implications and has been shown to be derived from transposition of the normal D-Ala-D-Ala peptidoglycan termini of the bacterial cell wall into a depsipeptide D-Ala-D-lactate sequence which binds 1000 times less effectively with **1**.[9]

As a result of the structural complexity of the vancomycin family of antibiotics, the interest in defining the fundamental principles underlying the structural basis for its dipeptide binding affinity and selectivity, and the importance surrounding the emergence of vancomycin resistance in the clinic, a number of synthetic efforts[7] directed toward this family of natural products have been detailed. Efforts from the laboratories of Hamilton,[10] Williams,[11] Yamamura,[12] Evans,[13] Pearson,[14] Brown,[15] Rao,[16] Reddy,[17] Beugelmans,[18] Gallagher,[19] Danishefsky,[20] Still,[21] and Nicolaou[21] as well as our own[22−25] have addressed aspects of this challenging problem. With one exception,[19] previous efforts to prepare model 16-membered CD or DE macrocyclic rings through conventional macrolactamization techniques have been unsuccessful[11,14,16] or were found to proceed in low yields.[10,14,15,22] In the pioneering efforts of Yamamura[12] and Evans,[13] a two-step biomimetic thallium(III)-promoted intramolecular oxidative phenol coupling procedure was used initially to access a highly functionalized bicyclic species embodying the CDE biaryl ether subunits of vancomycin as symmetrical tetrahalogenated products. More recently, this has been reported with unsymmetrical 2-bromo-6-chlorophenol coupling partners providing access to the biaryl ethers possessing a single chlorine substituent. In complementary efforts, we disclosed the unusually successful implementation of an Ullmann macrocyclization reaction for the preparation of related and more refractory 14-membered biaryl ethers[23] and its surprisingly effective extension to the core 16-membered CD and DE ring systems of vancomycin.[22] Subsequent to this demonstration, both Beugelmans and Rao have expanded on the scope of such cyclization strategies through use of aromatic nucleophilic substitution reactions of *o*-halonitro aromatics. Initially examined in the intermolecular preparation of vancomycin related biaryl ethers[16,18] as first described by Hamilton,[10] the studies have been extended to the key intramolecular macrocyclization reaction for formation of 16-membered biaryl ethers

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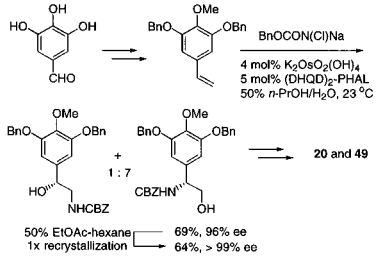
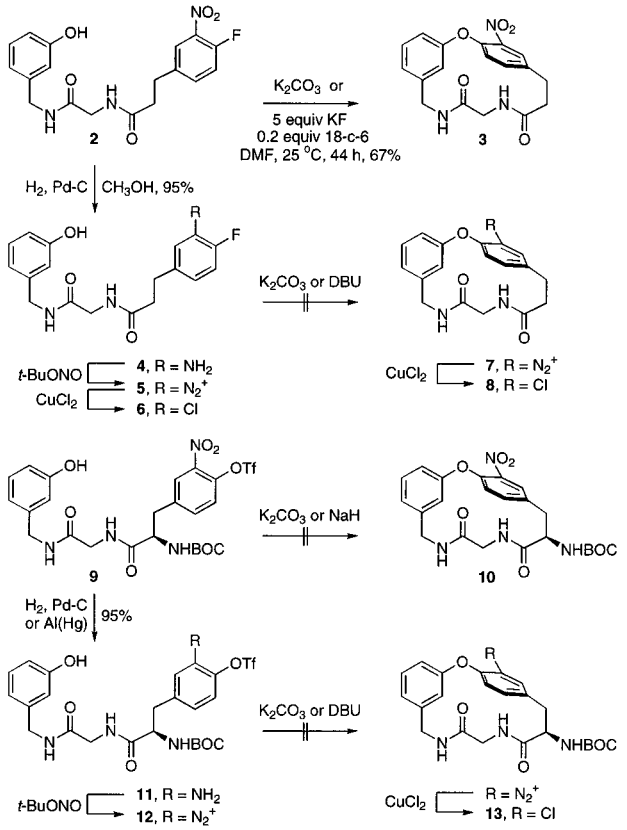


based on our Ullmann strategy. Complementary with these later studies, we disclosed the effective synthesis of the cycloisodityrosine 14-membered biaryl ether ring system adopting the intramolecular nucleophilic substitution reaction of an *o*-fluoronitro aromatic and its extension to the vancomycin CD and DE ring systems.[24] In addition to providing smooth access to the 16-membered biaryl ethers, the activating nitro group serves as useful functionality for the introduction of the single aromatic chlorine substituents required of vancomycin. In our efforts, which are complemented by the recent studies of Evans,[13] we also elected to pursue the preparation of the fully functionalized vancomycin CD and DE ring systems complete with their sensitive β-hydroxy 3-chlorophenylalanines, assuring the applicability of the approach to all members of this class of glycopeptide antibiotics. In these studies, we anticipated determining if there is any tactical advantage to the order of the introduction of the 16-membered rings and whether the atropisomer diastereoselectivity might be subject to substrate control. Herein, we report full details of our efforts,[24] including a significant technical improvement in the methodology, their extensions culminating in the preparation of the fully functionalized 16-membered CD and DE ring systems of vancomycin, and a potential solution to the control of the atropisomer stereochemistry (Figure 1).

Model Biaryl Ether Cyclization Substrates. In the course of our investigations, we have examined a range of systems reported to activate aromatic nucleophilic substitution reactions. The three most promising options included the *o*-fluoronitro aromatics[16,18,24] and the *o*-[[(trifluoromethyl)sulfonyl]oxy]nitro aromatics[26−28] bearing a nitro activating group as well aryldiazonium salts[29] in which the diazonium salt serves as a powerful electron-withdrawing substituent for activation of the aromatic nucleophilic substitution reaction and as the immediate *in situ* precursor to the vancomyin aromatic chlorine substituent. For comparison purposes, the intramolecular variant of these reactions for the preparation of the simplified vancomycin DE skeleton have been examined (Scheme 1). Of these, the closure employing the *o*-fluoronitro aromatic acceptor **2** proved most successful,[24] and such observations were first disclosed by Beugelmans[18] and Rao[16] and more recently by Evans.[13] In contrast, the corresponding diazonium salt **5** prepared *in situ* by diazotization (1.6 equiv of *t*-BuONO, 1.6 equiv of HBF_4, THF or CH_3CN, 0 °C, 1 h) of the amine **4** failed to provide evidence of ring closure upon exposure to base (DBU or K_2CO_3, THF or CH_3CN, 0−25 °C, 14 h), affording modest conversions to the corresponding acyclic aryl chloride **6** upon Sandmeyer quench of the reaction

Scheme 1



mixture. Although this was not investigated in detail due to the success with **2**, the powerful electron-withdrawing nature of the diazonium salt, which exceeds that of a nitro group, along with its documented activation properties for aromatic nucleophilic substitution suggested the stepwise sequence required for the conversion of **2** to **8** ultimately may be combined into a single step. Similarly, the aromatic triflate activated for displacement by the *o*-nitro group in **9** or by the *o*-diazonium salt in **12** failed to undergo the intramolecular closure to the biaryl ether when subjected to similar reaction conditions (K_2CO_3, DMF, 85−100 °C, 4−18 h; NaH, DMF, 0−25 °C, 1−3 h, THF, 45 °C, 15 h). With these observations in hand, we proceeded with efforts directed at the vancomycin CD and DE ring systems recognizing that the opportunity to further explore closures related to those of **5**, **9**, and **12** could be conducted in these efforts.

The Vancomycin CD Ring System. Protection of methyl (2*S*,3*R*)-β-hydroxy-β-(4-fluoro-3-nitrophenyl)alaninate (**14**)[24,30] as its TBDMS ether **15** (4 equiv of TBDMSOTf, 4.5 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 4 h, 85%), which was isolated as the free amine upon chromatography purification followed by coupling (3 equiv of EDCI, 3.3 equiv of HOBt, DMF, 0 °C, 5 h) with (*R*)-*N*-BOC-(3-bromo-4-methoxyphenyl)glycine (**17**), provided **18** (80%), $[\alpha]^{25}_D$ −55 (*c* 0.7, $CHCl_3$), and a small amount of a

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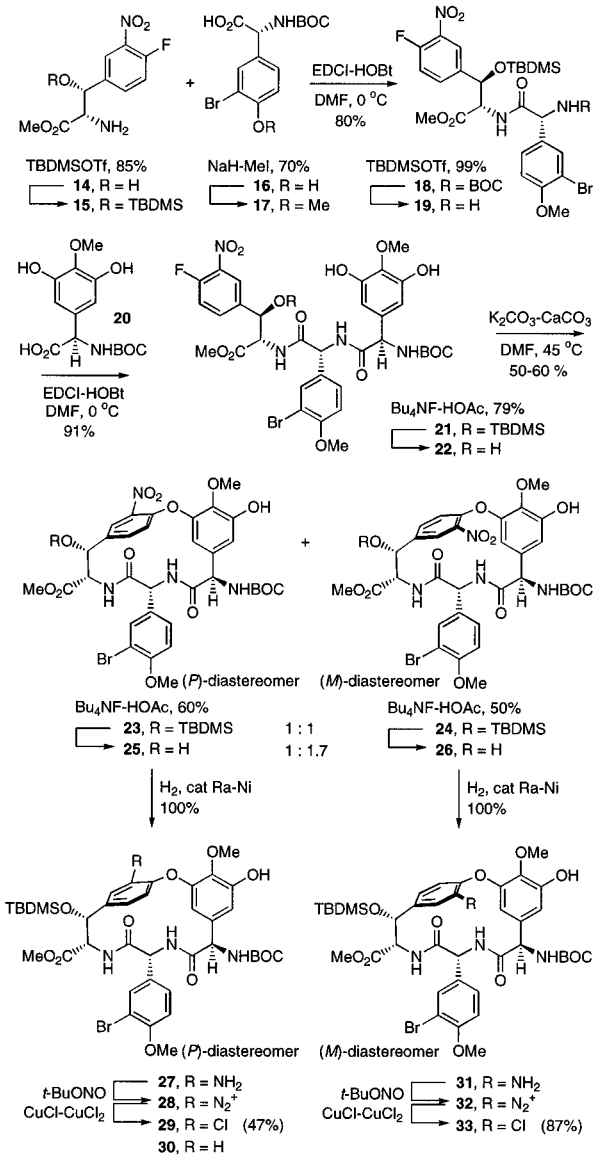
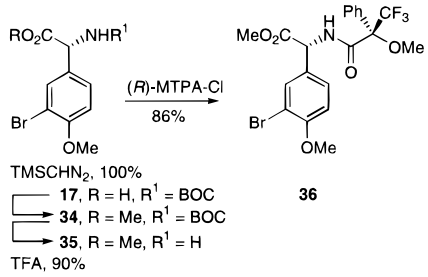
Scheme 2



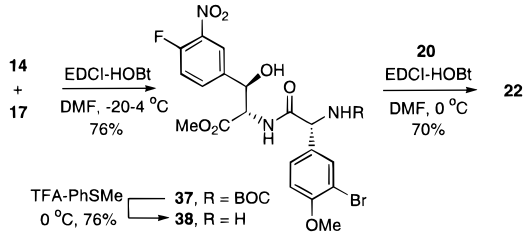
separable diastereomer (9%) derived from epimerization at the phenylglycine center (Scheme 2). The preparation of **17** was most conveniently conducted by direct *O*-methylation (1.9 equiv of NaH, 1 equiv of CH_3I, 1:1 THF−DMF, 0 °C, 3.5 h, 70%) of the free acid **16**[15,31] and attempts to prepare **17** from the corresponding methyl ester of **16** suffered substantial racemization upon *O*-methylation and ester hydrolysis (48% ee).

The optical purity of **17** and related intermediates was assessed by methyl ester formation (6.7 equiv of $TMSCHN_2$, 80% C_6H_6−CH_3OH, 25 °C, 30 min), *N*-BOC deprotection (30% TFA−CH_2Cl_2, 0−25 °C, 1.3 h), and subsequent formation of the Mosher amide **36** (1.0 equiv of (*R*)-MTPA-Cl, 1.0 equiv of pyridine, CH_2Cl_2, 0 °C, 1 h, 77% for three steps), (Scheme 3).[32] ^1H NMR analysis[32] ($CDCl_3$, 400 MHz) established that minimal racemization

Scheme 3



Scheme 4



(18:1 diastereomeric mixture, 90% ee) occurred in route to **17** as well as **36**. Moreover, the 9% of the undesired diastereomer of **18** obtained upon coupling (*R*)-**17** with **15** may, in fact, be derived principally from the small amount of contaminant (*S*)-**17**.[31]

N-BOC deprotection by a method that precludes *O*-desilylation was effected by treatment of **18** with TBDMSOTf (2.7 equiv, CH_2Cl_2, 0 °C, 1.5 h, 99%) and cleanly provided **19**, $[\alpha]^{26}_D$ −25 (*c* 0.4, $CHCl_3$), with no evidence of racemization of the sensitive phenylglycine.[33] Subsequent coupling (3 equiv of EDCI, 3.3 equiv of HOBt, DMF, 0 °C, 12 h) of the free amine **19** with (*R*)-*N*-BOC-(3,5-dihydroxy-4-methoxyphenyl)glycine (**20**, ≥94% ee)[25] provided **21** (91%) accompanied by less than 5−7% of a separable diastereomer (≥10.5−11:1) derived from epimerization of the intermediate activated carboxylate or contaminant (*S*)-**20**. TBDMS ether deprotection of **21** (13 equiv of Bu_4NF, 3 equiv of HOAc, THF, 25 °C, 12 h, 79%) cleanly provided the alcohol **22**. Comparable deprotections (5 equiv of Bu_4NF, THF, 25 °C, 3 h) conducted in the absence of added HOAc led to competitive macrocyclization providing both **22** (15%) and **25/26** (38%, 1:1.7 respectively). Alternatively, the free alcohol **22** could be prepared by direct coupling of **38** (3 equiv of EDCI, 3.5 equiv of HOBt, DMF, −20 to 0 °C, 14 h, 70%) with (*R*)-**20** (≥94% ee). In turn, **38** was derived from the direct coupling of **14** with **17** (3 equiv of EDCI, 3.3 equiv of HOBt, DMF, −20 to 4 °C, 18 h, 76%) followed by acid-catalyzed *N*-BOC deprotection (Scheme 4).[32]

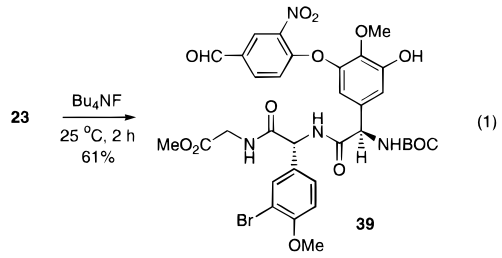
Both the alcohol **22** and the TBDMS ether **21** underwent smooth macrocyclization upon treatment with K_2CO_3−$CaCO_3$ (5 equiv of, 0.005 M DMF, 45 °C, 12.5 h for **21**, 6 h for **22**) in the presence of 4 Å molecular sieves to provide **25** and **26** (1:1.7, 38%) or **23** and **24** (50−60%, 1:1), respectively, as separable mixtures of diastereomers. Although this was not examined in extensive detail,

(31) The preparation of **16** from (*R*)-4-hydroxyphenylglycine was more convenient and provided higher yields if the order of steps was reversed: 1 equiv of BOC_2O, 1.5 equiv of $NaHCO_3$, 50% THF−H_2O, 25 °C, 14 h, 88%; 1 equiv of Br_2-py·HBr, THF, 0 °C, 2 h, 70%)[32] versus (Br_2, HBr−HOAc, 49%; BOC_2O, 100%).[15] This reversed order of steps permitted the chromatographic separation of the dibrominated byproduct and unreacted starting material that was only possible after *N*-BOC protection.[32] To date we have not been successful in enriching the optical purity of **17** by recrystallization as it has only been isolated as a foam.

(32) Full experimental details are provided in the Supporting Information.

(33) Interestingly, when this reaction was worked up with a saturated aqueous $NaHCO_3$ wash rather than direct chromatographic purification, additional undesired and unidentified reaction products were isolated.

macrocyclizations conducted in the presence of 18-crown-6 or in the absence of $CaCO_3$ led to much lower conversions and consumption of the desired cyclization products. Similarly, conducting the reaction in the absence of 4 Å molecular sieves proved less satisfactory. Presumably $CaCO_3$ serves as an effective scavenger of the liberated fluoride, which is sufficiently basic to promote product decomposition, and the molecular sieves serve to remove adventitious moisture. Consistent with this expectation and in contrast to reactions run in its absence, little or no TBDMS ether deprotection of **21** was observed to accompany macrocyclization to **23** and **24** in the presence of the added $CaCO_3$ under the prescribed reaction conditions. Moreover, under these conditions, 10−15% of the starting material is routinely recovered and its examination revealed no evidence of substrate epimerization under the reaction conditions. Anticipating appending the DE ring system onto the preformed CD ring system and recognizing the inherent sensitivity of the free alcohol, this development permitted us to devote our efforts to conducting the cyclization of **21** to provide **24** and to carrying this stable, protected material forward. The sensitivity of the free β-hydroxyphenylalanine subunit within the CD ring system became apparent upon deprotection of **23** and **24** to provide the corresponding free alcohols **25** and **26**, respectively, which were conducted to complete our structural correlations and stereochemical assignments. Deprotection of **24** promoted by Bu_4NF treatment (20 equiv of, THF, 25 °C, 3 h, 50%) conducted in the presence of HOAc (5 equiv) cleanly provided **26**, whereas conducting a similar reaction on **23** proved more sensitive to the precise reaction conditions. Treatment of **23** (5 equiv of Bu_4NF, 6 equiv of HOAc, 25 °C, 1 h, 60%) cleanly provided **25**, whereas conditions employing more Bu_4NF and less HOAc (13 equiv of Bu_4NF, 2 equiv of HOAc, 25 °C, 2 h, 61%) cleanly provided the retro-Aldol product **39**[34] (eq 1). This selected



(1)

sensitivity of the undesired atropisomer **25** to retro-Aldol ring cleavage is surprising and suggests that caution should be used in interpreting the origin of apparent atropisomer diastereoselectivity observed in macrocyclization reactions conducted with such substrates. This same retro-Aldol product **39** was observed in small amounts in the macrocyclization closure of **21**, which provided **25** and **26** (40%, 1:1.7) directly along with **22** (15%). Thus, the ratio of **25** to **26** may well reflect a diastereomeric sensitivity to the subsequent retro-Aldol cleavage rather than a macrocyclization diastereoselectivity. This same byproduct **39** derived from the desired cyclization products was not observed with **21** unless the reaction was conducted for prolonged reaction times leading to contaminant TBDMS ether deprotection and subsequent retro-Aldol cleavage.

Both **23** and **24** were independently converted to the corresponding chlorides **29** and **33**, respectively. Reduction of the nitro group to the aryl amines **27** and **31** without competitive removal of the aryl bromide was effectively accomplished by H_2/cat. Raney Ni (CH_3OH, −20 °C, 1.5 h, 100%). Alternative attempts employing 10% Pd−C (CH_3OH, >90%) or a large excess of Raney Ni (10 equiv) led to effective removal of the aryl bromide as well as nitro reduction. Similarly, H_2/cat. PtO_2 and Al(Hg) reduction ($EtOH-Et_2O-H_2O$ 2:10:1, 25 °C, 1 h) gave additional unidentified products, $SnCl_2$ (EtOH, 40 °C) led to competitive *N*-BOC deprotection, Zn−HOAc promoted decomposition of the substrate, and no reaction was observed upon exposure to $Na_2S_2O_4$ ($THF-H_2O$, 25−60 °C). Diazotization of **27** or **31** (1.3 equiv of *t*-BuONO, 1.3 equiv of HBF_4, CH_3CN, 0 °C, 1 h) followed by Sandmeyer substitution of the corresponding diazonium salts **28** and **32** with chloride (50 equiv of CuCl, 60 equiv of $CuCl_2$, CH_3CN, 0 °C, 50−87%) cleanly provided **29** and **33** with virtually no competitive production of the reduction product **30**. However, the success of the conversions depended on the prescribed reaction conditions. The use of larger amounts of HBF_4 in the diazotization reaction led to diminished conversions, presumably due to competitive *N*-BOC deprotection. Similarly, the elimination of the reduction product **30** required the use of large excesses of both CuCl (50 equiv) and $CuCl_2$ (60 equiv), the use of CH_3CN as a cosolvent, a minimal diazotization reaction time with subsequent manipulation at 0 °C, and the reverse addition of the diazonium salt to the aqueous solution of $CuCl-CuCl_2$ at 0 °C. Under these conditions, **33** (87%) could be generated in superb yield with no competitive reduction to **30**. In the course of optimizing this reaction, the reduced byproduct **30** was obtained from the sequences leading to both **29** and **33**, confirming that **23** and **24** and their subsequent products were atropisomers and not diastereomers derived from epimerization. More importantly, both **29** and **33** were prepared free of the contaminant atropisomer indicating that the isomerization of intermediates, particularly the diazonium salts **28** or **32** and related Sandmeyer reaction intermediates, was not observed through this sequence.

The assignment of the atropisomer stereochemistry was accomplished by 2D $^1H-^1H$ ROESY NMR conducted first on **23** (DMSO-d_6, 600 MHz) and **24** (acetone-d_6, 600 MHz) and later with the amines of **29** and **33**. The desired atropisomer **24** exhibited strong and diagnostic NOE crosspeaks between H-15/H-17 (s) and H-14/H-17 (s) that were not observed with its diastereomer **23** (Figure 2). Instead, **23** exhibited diagnostic H-20/H-15 (s) and H-20/H-14 NOE (s) crosspeaks which in turn were not observed with **24**. Several additional strong (s) and medium (m) NOE crosspeaks along with an unusually small H-14/H-15 coupling constant (J = 0 Hz) for both **23** and **24** established the rigid 16-membered ring conformation which, unlike **1**, adopts the more stable

(34) For **39**: ^1H NMR (acetone-d_6, 400 MHz) δ 10.05 (s, 1H), 8.52 (d, 1H, J = 2.0 Hz), 8.20−8.15 (m, 1H), 8.12 (dd, 1H, J = 2.0, 8.6 Hz), 7.98−7.90 (m, 1H), 7.65 (d, 1H, J = 2.3 Hz), 7.44 (dd, 1H, J = 2.3, 8.6 Hz), 7.13 (d, 1H, J = 8.6 Hz), 7.08 (d, 1H, J = 2.2 Hz), 7.01 (d, 1H, J = 8.6 Hz), 6.92 (d, 1H, J = 2.2 Hz), 6.60−6.53 (m, 1H), 5.52 (d, 1H, J = 7.2 Hz), 5.35−5.30 (m, 2H), 3.93−3.90 (m, 2H), 3.86 (s, 3H), 3.74 (s, 3H), 3.61 (s, 3H), 1.28 (s, 9H); IR (neat) ν_{max} 3327, 2955, 2924, 2853, 1726, 1658, 1571, 1494, 1462, 1377, 1260, 1163 cm^{-1}; FABHRMS (NBA-CsI) m/z 907.0449 (M^+ + Cs, $C_{33}H_{35}N_4O_{13}Br$ requires 907.0438). For **42**: $[\alpha]^{25}_D$ −14 (c 0.028, $CHCl_3$); ^1H NMR (acetone-d_6, 400 MHz) δ 7.59 (s, 1H), 7.42−7.35 (m, 2H), 7.30−7.25 (m, 3H), 7.02−6.95 (m, 1H), 7.01 (d, 1H, J = 8.7 Hz), 6.71 (s, 1H), 6.59 (s, 1H), 6.25−6.17 (m, 1H), 5.85 (d, 1H, J = 8.7 Hz), 5.50−5.40 (m, 2H), 4.58−4.50 (m, 1H), 3.96 (s, 3H), 3.83 (s, 3H), 3.74 (s, 3H), 1.39 (s, 9H), 0.79 (s, 9H), −0.01 (s, 3H), −0.13 (s, 3H); IR (neat) ν_{max} 3309, 2958, 2925, 2855, 1731, 1716, 1682, 1651, 1584, 1504, 1463, 1261, 1121, 1073, 1038, 800 cm^{-1}; FABHRMS (NBA-CsI) m/z 932.1978 (M^+ + Cs, $C_{39}H_{50}N_3O_{11}ClSi$ requires 932.1957).

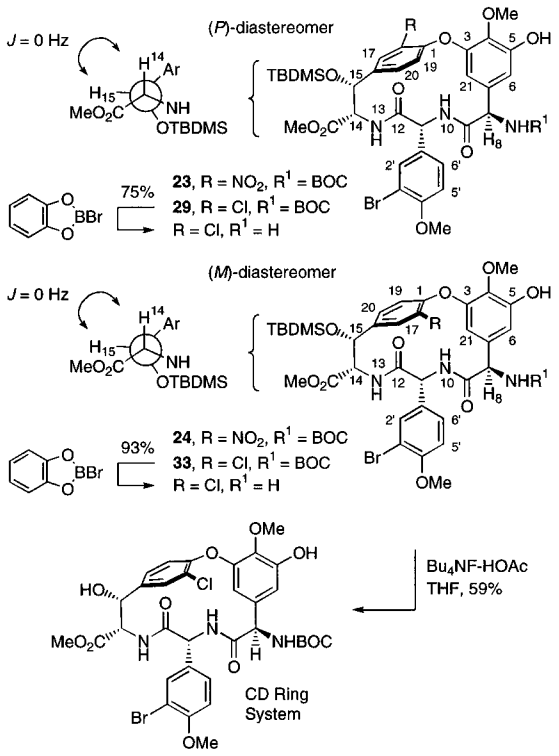
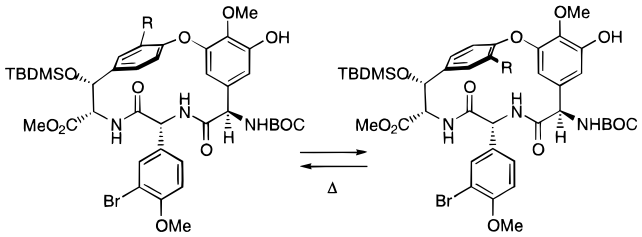


Figure 2.

trans $N^{13}-C^{12}$ secondary amide stereochemistry. The additional diagnostic $^1H-^1H$ NOEs for **24** include H-17/H-13 (w), H-15/H-14 (s), H-13/H-20 (m), H-11/H-10 (m), H-10/H-8 (s), H-10/H-21 (m), H-8/H-6 (s), H-8/H-21 (m), and H-6/C5-OH (w). Notably, **24** failed to exhibit a strong and diagnostic H-14/H-11 NOE crosspeak required of the cis N^{13}-C^{12} amide conformation. For **23**, additional NOE crosspeaks were observed for H-15/H-14 (s), H-14/H-13 (m), H-13/H-11 (m), H-11/H-10 (w), H-10/H-8 (s), H-10/H-21 (w), H-6 and H-21/H-8 (m,s), H-8/NHBOC (m), H-6/NHBOC (m), H-6/C5-OH (m), H-21/H-19 (w), and H-20/H-19 (m). Similar observations were made with the amines of **29** and **33**. For the free amine of the desired (*M*)-atropisomer **33** (CD_3CN, 600 MHz), strong diagnostic H-15/H-17 (s) and H-17/H-14 (s) NOE crosspeaks were observed and those of H-15/H-20 and H-14/H-20 were absent. Additional clear crosspeaks were observed for H-15/H-14 (s), H-11/H-10 (m), H-10/H-21 (w), and H-20/H-19 (s). In contrast, the HBr salt of the amine of the undesired (*P*)-atropisomer **29** exhibited diagnostic H-15/H-20 (s), and H-14/H-20 (m) NOE crosspeaks.

In contrast to past studies, the thermal interconversion of the atropisomers **23** and **24** or **29** and **33** was examined and found to proceed rapidly at temperatures of ≥155 °C and more slowly at 140 °C (Table 1). This productive observation allows the undesired atropisomer **23** or **29** to be thermally equilibrated with **24** or **33**, chromatographically reisolated, and recycled to provide the desired atropisomers. More importantly, the nitro-substituted agents **23** or **24** equilibrated more rapidly than the corresponding chloro atropisomers **29** or **33**, and the rate of atropisomerism could be controlled not only by the choice of temperature but also by the choice of solvent. These observations, in conjunction with similar observations on the atropisomer equilibration of the DE ring system, provide the basis for the strategic plan to conduct the synthesis in a manner that provides the fully installed CD aryl chloride and DE aryl nitro intermediate. As disclosed in the following section, the DE atropisomer equilibration occurs more readily and the aryl nitro intermediate similarly isomerizes more rapidly than the corresponding aryl chloride. This suggests that it may be possible to preferentially equilibrate the DE versus CD atropisomers and that this may be best conducted with a DE aryl nitro intermediate containing the fully installed CD aryl chloride. Importantly, this also implies that, once the CD atropisomer stereochemistry is set through equilibration of the aryl nitro derivative **24**, its subsequent conversion to the aryl chloride **33** may be utilized to ultimately control the atropisomer stereochemistry of a subsequently introduced DE ring system.

Table 1. Atropisomer Isomerization



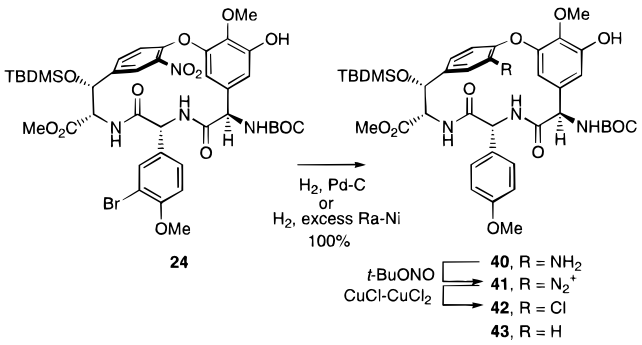
23, R = NO_2 **24**, R = NO_2
29, R = Cl **33**, R = Cl

agent	conditions	**23**:**24** or **29**:**33**
23	DMSO, 120 °C, 1 h	100:0
23	DMSO, 155 °C, 1.3 h	2:1
23	DMSO, 155 °C, 4 h	1.7:1 (72%)
23	DMSO, 140 °C, 5 min	>20:1
23	DMSO, 140 °C, 0.5 h	10:1
23	DMSO, 140 °C, 1 h	5:1
23	DMSO, 140 °C, 1.5 h	3.5:1
23	DMSO, 140 °C, 3.5 h	2:1
23	DMSO, 140 °C, 7 h	1.2:1
23	DMF, 120 °C, 1 h	100:0
23	DMF, 155 °C, 0.5 h	1.7:1
23	DMF, 155 °C, 1.1 h	1.2:1 (57%)
23	*o*-$C_6H_4Cl_2$, 140 °C, 20 min	>20:1
23	*o*-$C_6H_4Cl_2$, 140 °C, 2 h	11:1
23	*o*-$C_6H_4Cl_2$, 140 °C, 3 h	8:1
23	*o*-$C_6H_4Cl_2$, 140 °C, 16 h	1.6:1
23	*o*-$C_6H_4Cl_2$, 140 °C, 56 h	1.1:1
29	DMSO, 120 °C, 0.25 h	100:0
29	DMSO, 140 °C, 1 h	16:1
29	DMSO, 140 °C, 1.5 h	11:1
29	DMSO, 140 °C, 3.5 h	4:1
29	DMSO, 140 °C, 4.5 h	3:1
29	DMSO, 140 °C, 6 h	2:1
29	DMSO, 140 °C, 7 h	1.5:1
29	DMSO, 155 °C, 1.5 h	3:1
33	*o*-$C_6H_4Cl_2$, 140 °C, 9.5 h	1:13
33	*o*-$C_6H_4Cl_2$, 140 °C, 19.5 h	1:6
33	*o*-$C_6H_4Cl_2$, 140 °C, 32 h	1:4
33	*o*-$C_6H_4Cl_2$, 140 °C, 53 h	1:3
33	*o*-$C_6H_4Cl_2$, 140 °C, 96 h	1:2

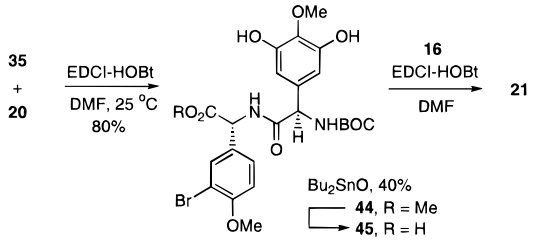
Given the clean debromination of **24** that accompanied reduction to the aryl amine upon hydrogenation using a 10% Pd−C catalyst or excess Raney Ni (10 equiv of, conditions, 25 °C, 3 h, 100%), the conversion of **40** to the corresponding aryl chloride **42** was also accomplished (Scheme 5).[34] The sample of **42** prepared through this sequence was identical to that obtained by debromination of **33** (H_2, Pd-black, 2 equiv of NaOAc, CH_3OH, 25 °C, 4 h, 74%).[12]

Finally, in conjunction with projected efforts on the synthesis of vancomycin itself, we also examined an alternative order of amide coupling reactions for the preparation of **21**. That which was detailed in Scheme

Scheme 5

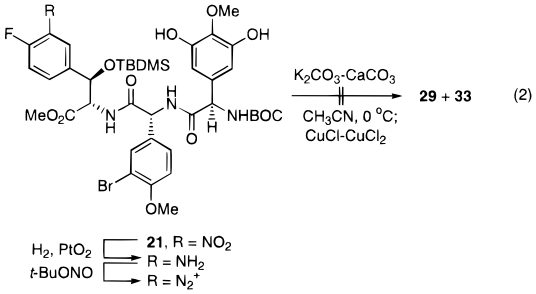


Scheme 6



2 uses progressive couplings requiring carboxylate activation of the sensitive phenylglycine derivatives at an early stage and on intermediates that do not require a preceding phenylglycine ester deprotection minimizing the opportunity for adventious epimerization. In efforts to establish whether this might not prove problematic, the alternative coupling order for the preparation of **21** was examined (Scheme 6).[32] Although coupling of **35** with **20** proceeded smoothly without problematic racemization of the sensitive phenylglycine center, conventional efforts to hydrolyze the resulting methyl ester (LiOH, THF−CH_3OH−H_2O, 25 °C) met with significant racemization. This could be avoided by employing Bu_2-SnO, which cleanly provided **45** as a single diastereomer, albeit in a low but unoptimized conversion. However, its coupling with **16** to provide **21** also proved problematic and was not further pursued.

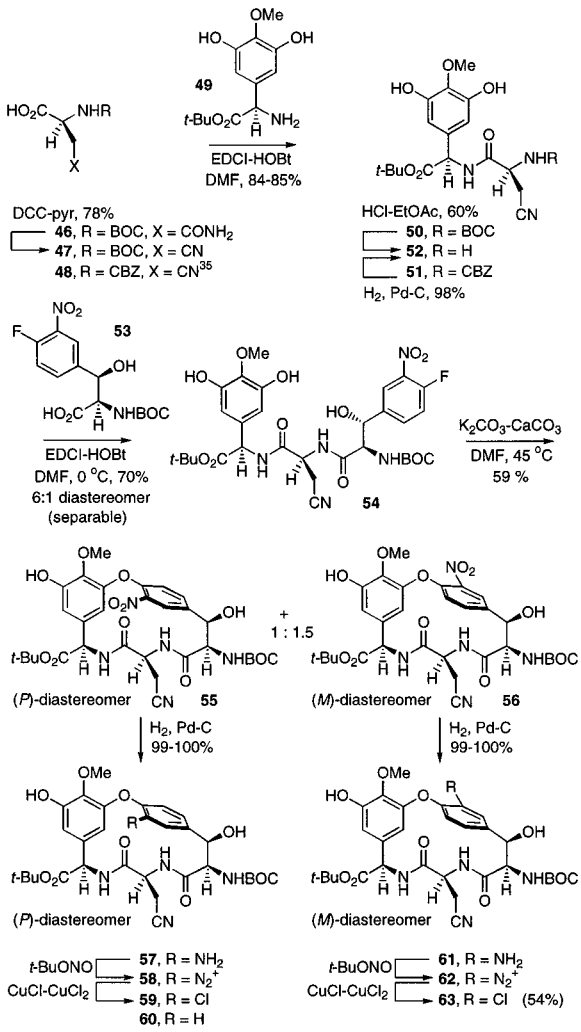
We also examined the potential of effecting the macrocyclization reaction directly on the diazonium salt derived from **21** (eq 2). Thus, reduction of **21** to the



corresponding amine (H_2, cat. PtO_2, CH_3OH, 25 °C, 91%), diazotization (1.3 equiv of *t*-BuONO, 1.3 equiv of HBF_4, CH_3CN, 0 °C, 1 h) followed by K_2CO_3−$CaCO_3$ treatment (7 equiv of each, 4 wt equiv of 4 Å MS, CH_3CN, 0 °C, 48 h), and final Sandmeyer reaction (50 equiv of CuCl, 60 equiv of $CuCl_2$, H_2O, 1.5 h) failed to provide **29** or **33** or evidence of macrocyclization (*i.e.* **30**).

The Vancomycin DE Ring System. Coupling (2.2 equiv of EDCI or 1.3 equiv of DCC, 1.1 equiv of HOBt, DMF, 0−25 °C, 16 h, 84%) of *N*-BOC or *N*-CBZ-L-*β*-

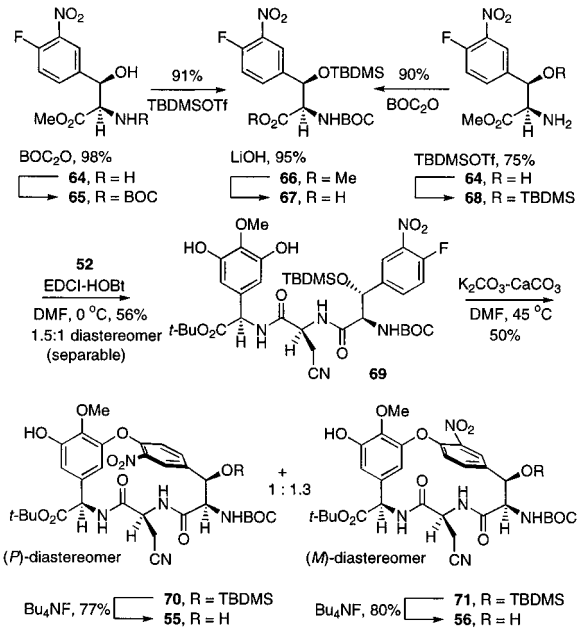
Scheme 7



cyanoalanine (**47**[32] and **48**[35]) with *tert*-butyl (*R*)-(3,5-dihydroxy-4-methoxyphenyl)glycine (**49**, ≥94% ee)[25] cleanly provided **50** and **51** as single detectable diastereomers (Scheme 7). Acid-catalyzed *N*-BOC deprotection of **50** (1 N HCl−EtOAc, 25 °C, 5 h, 60%) followed by $NaHCO_3$ workup or hydrogenolysis of **51** (H_2, Pd−C, CH_3OH, 25 °C, 4 h, 98%) provided **52** as the free base. Hydrolysis (2 equiv of LiOH, 2:1 *t*-BuOH−H_2O, 25 °C, 0.5 h, 96%) of methyl (2*R*,3*R*)-*N*-BOC-*β*-hydroxy-*β*-(4-fluoro-3-nitrophenyl)alaninate,[24,30] $[\alpha]^{23}_D$ +21 (*c* 0.35, $CHCl_3$), followed by coupling (3 equiv of EDCI, 1.1 equiv of HOBt, DMF, 0−25 °C, 14 h, 70%) of **53**, $[\alpha]^{23}_D$ +6.9 (*c* 0.85, CH_3OH), with **52** provided **54**. To date, the best conditions examined for effecting this coupling has provided a 6:1 mixture of separable diastereomers, presumably derived from partial epimerization of the intermediate activated carboxylate. Alternative methods including the use of DPPA or BOPCl (0−25 °C, DMF, 12−36 h) were less successful. Exposure of **54** to K_2CO_3−$CaCO_3$ (5/7.5 equiv of, 0.005 M DMF, 45 °C, 6 h) cleanly provided **55** and **56** (59%) as a separable 1:1.5 mixture of diastereomers with the (*M*)-atropisomer possessing the natural stereochemistry being preferentially formed. Thus, in sharp contrast to the macrocyclization model studies of Zhu,[18] which provide only the unnatural atropisomer, the cyclization of **54**

(35) Badet, B.; Vermoote, P.; Le Goffic, F. *Biochemistry* **1988**, *27*, 2282. For the dehydration procedure: Liberek, B.; Buczel, Cz.; Grzunka, Z. *Tetrahedron* **1966**, *22*, 2303; Ressler, C.; Ratzkin, H. *J. Org. Chem.* **1961**, *26*, 3356.

Scheme 8



provided preferentially the natural atropisomer, and analogous observations have been disclosed by Evans and co-workers.[13] In the absence of $CaCO_3$, exposure of **54** to K_2CO_3 (4 equiv of, 0.008 M DMF) provided recovered starting material (25 °C , 14 h) or lower conversions to **55** and **56** (55−60 °C, 3 h) with extensive decomposition. In the presence of 18-crown-6, treatment with only K_2CO_3 (10 equiv) in THF (25 °C, 0.008 M) provided recovered starting material, while reactions in DMF (25 °C) or CH_3CN (55 °C) underwent conversion to multiple products. Na_2CO_3−$CaCO_3$ (5/8 equiv), but not Li_2CO_3−$CaCO_3$ (9/6 equiv), was also effective at promoting the cyclization reaction but required substantially longer reaction times (DMF, 45 °C, 72−96 h), and $CaCO_3$ alone failed to provide evidence of ring closure. In a potentially useful alternative, the use of DMSO versus DMF as the reaction solvent provided a slightly faster cyclization reaction. Thus, treatment with K_2CO_3−$CaCO_3$ (7/10 equiv of, DMSO, 40 °C, 5 h) provided comparable cyclization results and when conducted in the presence of 18-crown-6 (1 equiv of, DMSO, 25 °C, 8 h) led to cyclization at room temperature with comparable results. However, unlike the studies conducted in DMF, additional potentially epimeric products were also detected. To date, CsF (5 equiv of, DMF, 25 °C, 48 h) has failed to provide cyclization, affording only recovered starting material, although two independent studies[13,18] have experienced the best conversions with such conditions.

The TBDMS ether **69** was similarly examined (Scheme 8). However, the coupling of **67** with **52** proved more problematic than that observed with **53**. Although this was not examined in detail, coupling of **67** with **52** under the same conditions (3 equiv of EDCI, 1.1 equiv of HOBt, DMF, 25 °C, 14 h, 56%) proceeded more slowly and suffered more substantial racemization (1.5:1 mixture of diastereomers). The TBDMS ether **69** underwent clean closure to **70** and **71** upon treatment with K_2CO_3−$CaCO_3$ (5/7.5 equiv of, 0.005 M DMF, 25 °C, 5 h). With this substrate, the closure occurred under even milder conditions (25 °C versus 45 °C) and the major diastereomer was isolated in yields as high as 40%. Treatment of this substrate with $CaCO_3$ alone (5 equiv of, DMF, 70 °C, 6.5 h) led to only recovered starting material. Deprotection

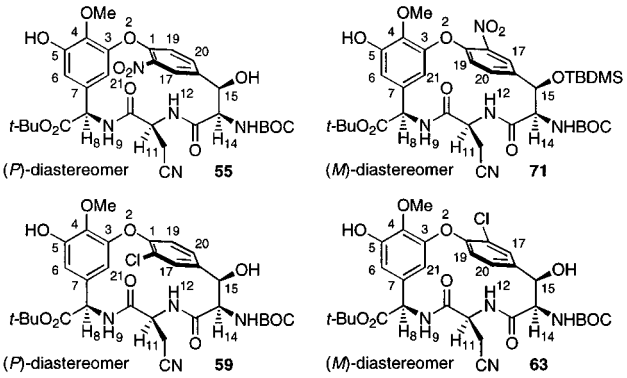


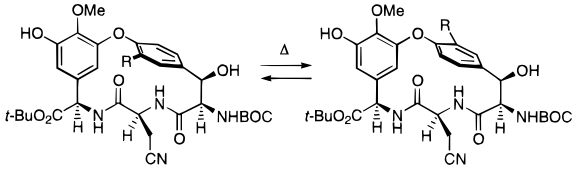
Figure 3.

of both **70** and **71** provided **55** and **56**, respectively, establishing the correlation of atropisomers between the two approaches.

Both **55** and **56** were independently converted to the corresponding chlorides **59** and **63**, respectively, without atropisomer interconversion. Reduction of the nitro group to the aryl amines **57** and **61** (H_2, 10% Pd−C, CH_3OH, 25 °C, 2 h, 99%), diazotization (1.3 equiv of *t*-BuONO, 1.3 equiv of HBF_4, CH_3CN, 0 °C, 1 h), and Sandmeyer substitution of chloride for the diazonium salt (50 equiv of CuCl, 60 equiv of $CuCl_2$, CH_3CN-H_2O, 0−25 °C, 1.5 h) provided the chlorides **59** and **63**. When the Sandmeyer substitution was conducted in H_2O (25 °C, 1.5 h) with more modest amounts of CuCl/$CuCl_2$ (50/20 equiv) or with just CuCl (6 equiv) following diazotization in THF (0 °C, 1 h) and low temperature removal of the solvent (0−10 °C), significant or exclusive conversion to the reduced product **60** was observed. In fact, conducting the reaction with only 6 equiv of CuCl led to superb conversion to **60** (76%). In these latter preliminary studies, the isolation of the same reduction product **60** from the reactions of both **57** and **61** confirmed that the diastereomers **55** and **56** and their corresponding derivative products were atropisomers and not isomeric at alternative, epimerized sites.

The stereochemical assignments of the atropisomers was accomplished by 2D ^1H−^1H ROESY NMR conducted on nitro compounds **55** and **71** (acetone-d_6, 500 MHz) and subsequently with the corresponding chlorides **59** and **63** (acetone-d_6, 600 MHz) (Figure 3). The desired TBDMS-protected atropisomer **71** exhibited diagnostic NOE crosspeaks between C15-H/C17-H (s) and C14-H/C17-H (m) which were clearly not observed with **55**. Instead, **55** exhibited C14-H/C20-H (s) and C15-H/C20-H (m) NOE crosspeaks which in turn were not evident with **71**. Several additional strong (s) and medium (m) NOE crosspeaks for both **55** and **71** established the rigid 16-membered ring conformation which possesses two secondary *trans*-amides and confirmed the required C14 stereochemistry (the relative C14-C15 stereochemistry). The additional diagnostic ^1H−^1H NOEs for **55** and **71** included C8-H/N9-H (m), N9-H/C21-H (m), N9-H/C11-H (s), N12-H/C14-H (m), N12−H/C15-H (m), C14-H/NHBOC (s), C15-H/NHBOC (s), and C14-H/C15-H (s). For **55**, additional strong NOE crosspeaks were observed for C8-H/C21-H and C8-H/C6-H. Similar observations were made with chloride atropisomers **59** and **63**. For the desired (*M*)-atropisomer **63**, diagnostic NOEs were observed between C15-H/C17-H (s) and C14-H/C17-H (m), as well as C20-H/C15-OH (w). As expected for the undesired (*P*)-atropisomer **59**, strong diagnostic NOEs were

Table 2. Atropisomer Isomerization



55, R = NO_2
59, R = Cl

56, R = NO_2
63, R = Cl

compound	conditions	**55**:**56** or **59**:**63**
55	DMSO, 115 °C, 20 min	100:0
55	DMSO, 130 °C, 5 min	5.6:1
55	DMSO, 130 °C, 10 min	4.6:1
55	DMSO, 130 °C, 15 min	3.0:1
55	DMSO, 130 °C, 30 min	1.7:1
55	DMSO, 130 °C, 50 min	1.2:1
55	DMSO, 140 °C, 3 min	6.1:1
55	DMSO, 140 °C, 7 min	2.6:1
55	DMSO, 140 °C, 11 min	2.0:1
55	DMSO, 140 °C, 15 min	1.6:1
55	DMSO, 140 °C, 20 min	1.3:1
55	DMSO, 140 °C, 30 min	1.1:1
55	DMSO, 140 °C, 60 min	1:1
55	*o*-$C_6H_4Cl_2$, 140 °C, 10 min	55:45
59	DMSO, 115 °C, 20 min	100:0
59	DMSO, 140 °C, 20 min	2.4:1
59	DMSO, 140 °C, 40 min	1.5:1
59	DMSO, 140 °C, 60 min	1:1
59	*o*-$C_6H_4Cl_2$, 140 °C, <2 h	1:1

observed for C15−H/C20-H, C14-H/C20-H, and C17-H/C15-OH; however, one additional weak NOE crosspeak was also observed for C15-H/C17-H (w). This observation along with the lack of the C15-H/C14-H crosspeaks would indicate that the C15 proton is bisecting and orthogonal to the E aromatic ring. Additional clear crosspeaks for both **59** and **63** were observed for C8-H/C6-H (m), C8-H/N9-H (m), N9-H/C21-H (m), N9-H/C11-H (s), and N12-H/C14-H (s), while C11-H/C20-H (s) and C11-H/C21−H (w) were observed only with **59**, suggesting that the C11 proton may be positioned underneath the E aromatic ring.

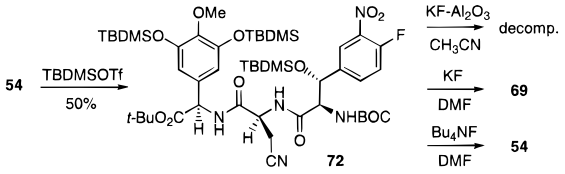
Analogous to studies with the CD ring system, the thermal interconversion of the atropisomers **55** and **56** or **59** and **63** was examined and found to proceed rapidly at 140 °C (Table 2). Consistent with analogous observations with the CD ring system, the isomerization of the chloride atropisomers **59** and **63** was slower than that of the corresponding nitro atropisomers **55** and **56**. More importantly, the DE ring system atropisomers equilibrated much more rapidly than the CD ring system atropisomers (DMSO or *o*-$Cl_2C_6H_4$, 140 °C) under conditions where little or no equilibration of the CD ring system was observed. This distinction is especially true in the comparisons of the more readily equilibrated DE ring system nitro atropisomers (10 min, 140 °C, *o*-$Cl_2C_6H_4$) versus the more stable CD ring system chloride atropisomers (30 min, 140 °C, DMSO, >16:1 or 140 °C, *o*-$Cl_2C_6H_4$, >20:1) (Table 3). Thus, it may be possible to control the atropisomer stereochemistry of a newly appended DE ring system via thermal equilibration while the appropriate CD atropisomer stereochemistry is maintained during the assemblage of the CDE substructure of vancomycin. Significantly, this may be accomplished by employing DE substrates bearing an L-*β*-cyanoalanine side chain versus the L-asparagine carboxamide side chain, which can be expected to suffer competitive backbone rearrangement under comparable thermal treatment.

Table 3. Atropisomer Equilibration Rates

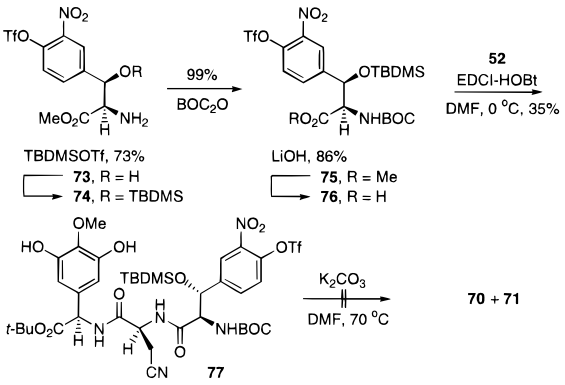
compound	conditions	k (h^{-1})	$t_{1/2}$ (h)
	CD ring system		
23[a]	155 °C, DMSO	0.27	1.06
23[a]	140 °C, DMSO	0.082	3.52
23	140 °C, *o*-$Cl_2C_6H_4$	0.029	9.77
29	140 °C, DMSO	0.071	4.03
29	140 °C, *o*-$Cl_2C_6H_4$	0.0054	53.0
	DE ring system		
55[b]	130 °C, DMSO	0.66	0.23
55[b]	140 °C, DMSO	1.05	0.17
55	140 °C, *o*-$Cl_2C_6H_4$	nd	<0.16
59	140 °C, DMSO	0.67	0.35

[a] E_a = 26.6 kcal/mol, $\Delta H^{\ddagger}$ = 27.0 kcal/mol, $\Delta S^{\ddagger}$ = −1.7 eu. [b] E_a = 15.3 kcal/mol, $\Delta H^{\ddagger}$ = 14.5 kcal/mol, $\Delta S^{\ddagger}$ = −24.0 eu.

Scheme 9



Scheme 10

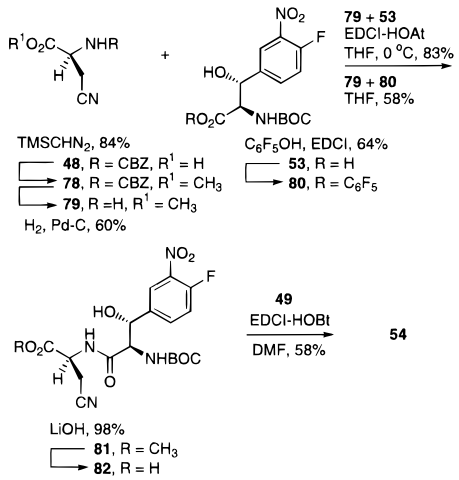


In an additional but concurrent study, exhaustive treatment of **54** with TBDMSOTf (3 equiv of, 4 equiv of Et_3N, CH_2Cl_2, 0 °C, 3 h, 50%) provided **72** (Scheme 9).[32] The intention with **72** was to determine whether it was possible to selectively deprotect the phenol TBDMS ethers and promote the *in situ* cyclization of the resulting phenoxide potentially with and without deprotection of the secondary alcohol. Although cyclization was not observed, selective or exhaustive deprotection of **72** was observed upon treatment with KF or Bu_4NF, respectively. Thus, although the conversion of **72** to either **55**/**56** or **70**/**71** was not realized, the selective deprotection of **72** to provide **69** offers alternatives to the key intermediate syntheses as we address the natural product itself.

Similarly, the corresponding *o*-nitroaryl triflate **77** was prepared[32] and its potential closure to **70**/**71** examined (Scheme 10). Treatment of **77** with K_2CO_3 (5−10 equiv of, DMF, 70 °C, 5 h) resulted in epimerization of the starting material and at temperatures below 70 °C resulted only in recovered starting materials.

Finally, a more convergent assembly of the key cyclization precursor **54** was examined (Scheme 11). Conversion of *N*-CBZ-*β*-cyano-L-alanine (**48**)[35] to the corresponding methyl ester **78** (1.3 equiv of $TMSCHN_2$, 20% $CH_3OH-C_6H_6$, 25 °C, 1 h, 84%) and subsequent CBZ

Scheme 11



hydrogenolysis (H_2, 10% Pd−C, CH_3OH, 25 °C, 5 h, 60%) provided *β*-cyano-L-alanine methyl ester (**79**). Although the direct coupling of **79** with the free acid **53** under a variety of conditions (1.1−1.6 equiv of EDCI, DCC, or HATU; 1.1 equiv of HOAt or HOBt; with or without 1.1 equiv of collidine, 64−82%) provided the desired dipeptide **81**, it was typically accompanied by substantial epimerization when this reaction was conducted at 25 °C (*ca.* 2:1). This could be minimized by first converting **53** to the diastereomerically pure activated pentafluorophenol ester **80** (64%), followed by room temperature coupling with **79** in THF (3 h) in the absence of additional reagents, providing **81** (58%) accompanied by a smaller amount of the separable epimerized diastereomer (18%).[36] However, the best conversions were ultimately obtained by conducting the direct reaction of **79** with **53** at 0−5 °C (3 equiv of EDCI, 3.3 equiv of HOAt, 14 h), providing **81** (98%) as a 14:1 mixture of diastereomers. A single recrystallization (30% *i*-PrOH/hexane) provided **81** as a 34:1 mixture of diastereomers suitable for direct use and avoided an otherwise tedious chromatographic separation. Both the reaction temperature (0−5 °C) and the use of HOAt proved critical to the success of this coupling and suggests that the preceding results for the preparation of **54**, **69**, and **74** may be further improved by adopting this reaction protocol. Although unappreciated in the discussion of studies disclosed to date, epimerization of this substituted phenylalanine α-center has proven much more facile than could be predicted and constitutes a stereocenter that should be closely monitored.[14,18,24] Methyl ester hydrolysis (2 equiv of LiOH, 2:1 *t*-BuOH-H_2O, 0 °C, 45 min, 98%) and subsequent coupling of **82** with **49** (2.2 equiv of EDCI, 1.1 equiv of HOBt, DMF, 0 °C, 15 h, 58%) provided **54** identical in all respects with our prior sample (*cf.* Scheme 7).

Conclusions. The fully functionalized vancomycin CD and DE ring systems were prepared by employing an aromatic nucleophilic substitution reaction for formation of the biaryl ether linkage and key macrocyclization of the 16-membered rings. Closure to form the CD ring system provided a 1:1 mixture of atropisomers, while closure of the DE ring system exhibited a slight preference for the natural atropisomer (1.5:1). This contrasts the preferential closure of related simplified models to provide predominantly or exclusively the unnatural atropisomers.[18] The first disclosure of the thermal equilibration of the stable atropisomers was also detailed. Important substituent effects on the rate of thermal equilibration were defined (C1 more stable than NO_2). Significantly, thermal equilibration of the DE ring system proved substantially faster than the CD ring system, suggesting a potential solution to the control of the vancomycin CDE atropisomer stereochemistry. Extensions of these efforts to the total synthesis of the vancomycin CDE ring system and vancomycin itself are in progress and will be disclosed in due course.

(36) Both the *β*-cyano-L-alanine methyl ester (**79**) and the pentafluorophenyl ester **80** were enantiomerically and diastereomerically pure going into the reaction.

Experimental Section

Methyl (2*S*,3*R*)-2-Amino-3-[(*tert*-butyldimethylsilyl)-oxy]-3-(4-fluoro-3−nitrophenyl)propionate (15). A solution of **14**[25] (104 mg, 0.40 mmol) in CH_2Cl_2 (4 mL) was treated with 2,6-lutidine (194 mg, 1.81 mmol, 4.5 equiv), TBDMSOTf (0.37 mL, 1.6 mmol, 4 equiv) at 0 °C and the mixture was stirred at 0 °C (4 h) before saturated aqueous $NaHCO_3$ (2 mL) was added. The resulting mixture was extracted with EtOAc (2 × 9 mL), and the combined EtOAc extracts were washed with saturated aqueous NaCl (2 × 3 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (SiO_2, 1.5 × 12 cm, EtOAc) afforded **15** (127 mg, 150 mg theoretical, 85%) as a yellow film: $[\alpha]^{26}_D$ −6.1 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) *δ* 8.07 (dd, 1H, *J* = 2.1, 7.1 Hz), 7.64 (ddd, 1H, *J* = 2.1, 4.1, 8.6 Hz), 7.26 (dd, 1H, *J* = 8.6, 10.5 Hz), 5.27 (s, 1H), 3.75 (s, 3H), 3.48 (br s, 1H), 0.86 (s, 9H), −0.01 (s, 3H), −0.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 173.5, 154.8 (d, *J* = 264 Hz), 139.1, 136.9, 133.2 (d, *J* = 10 Hz), 124.0, 118.1 (d, *J* = 21 Hz), 74.3, 61.4, 52.2, 25.5 (3C), 18.0, −4.7, −5.5; IR (neat) ν_{max} 2954, 2950, 2857, 1743, 1619, 1595, 1598, 1538, 1499, 1350, 1255, 1083, 835 cm^{-1}; FABHRMS (NBA) *m*/*z* 373.1607 (M^+ + H, $C_{16}H_{25}N_2O_5FSi$ requires 373.1595).

(*R*)-(3-Bromo-4-methoxyphenyl)-*N*-[(*tert*-butyloxy)carbonyl]glycine (17). A suspension of **16**[15,31] (2.0 g, 5.8 mmol) in DMF−THF (1:5, 35 mL) was treated with a suspension of NaH (80% in oil, 330 mg, 1.1 mmol, 1.9 equiv) in DMF (23 mL) at −40 °C and the temperature was raised to 0 °C. The reaction mixture was stirred for 15 min before CH_3I (0.38 mL, 6.1 mmol, 1 equiv) was added and the mixture was stirred at 0 °C (3.5 h). Aqueous citric acid (pH 3, 5 mL) was added and the resulting mixture was extracted with EtOAc (2 × 50 mL). The combined EtOAc extracts were washed with saturated aqueous NaCl (2 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (SiO_2, 2 × 20 cm, CH_2Cl_2−CH_3OH−HOAc, 90:2:1) afforded **17** (1.5 g, 2.1 g theoretical, 70%) as a white film: $[\alpha]^{26}_D$ −127 (*c* 0.5, CH_3OH); ^1H NMR (CD_3OD, 400 MHz) *δ* 7.56 (d, 1H, *J* = 1.9 Hz), 7.34 (dd, 1H, *J* = 8.5, 1.9 Hz), 7.01 (d, 1H, *J* = 8.5 Hz), 5.07 (s, 1H), 3.86 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (CD_3OD, 100 MHz) *δ* 173.8, 157.4, 157.3, 133.3, 132.4, 129.0, 113.1, 112.5, 80.8, 58.1, 56.7, 28.7 (3C); IR (neat) ν_{max} 3333, 2974, 2929, 1713, 1602, 1496, 1359, 1257, 1163, 1054, 1019 cm^{-1}; FABHRMS (NBA-CsI) *m*/*z* 491.9435 (M^+ + Cs, $C_{14}H_{18}NO_5Br$ requires 491.9423).

Methyl (2*S*,3*R*)-2-[(*R*)-*N*-[(3-Bromo-4-methoxyphenyl)-*N*-[(*tert*-butyloxy)carbonyl]glycyl]amino]-3-[(*tert*-butyldimethylsilyl)oxy]-3-(4-fluoro-3-nitrophenyl)propionate (18). A solution of **15** (140 mg, 0.37 mmol), HOBt (160 mg, 1.2 mmol, 3.3 equiv), and **17** (140 mg, 0.39 mmol, 1.1 equiv) in DMF (7.4 mL) was treated with EDCI·HCl (210 mg, 1.1 mmol, 3 equiv) at −20 °C, and the mixture was stirred at −20 °C (15 min) and at 0 °C (15 h). The reaction mixture was quenched with the addition of saturated aqueous citric acid (pH 3) and extracted with EtOAc (2 × 12 mL). The combined organic layers were washed with H_2O (3 mL) and saturated aqueous NaCl (2 × 5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (SiO_2, 2 × 17 cm, 67% EtOAc−hexane) afforded **18** (210 mg, 260 mg theoretical, 80%) as a white film and its separable diastereomer (6.7 mg, 74 mg theoretical, 9%). For **18**: $[\alpha]^{26}_D$ −55 (*c* 0.7, $CHCl_3$); ^1H NMR (acetone-d_6, 250 MHz) *δ* 8.09 (d, 1H, *J* = 5.9 Hz), 7.76 (d, 1H,

J = 9.5 Hz), 7.60−7.55 (m, 1H), 7.50 (d, 1H, J = 2.2 Hz), 7.22−7.05 (m, 2H), 6.92 (d, 1H, J = 8.5 Hz), 6.42−6.36 (m, 1H), 5.57 (d, 1H, J = 1.9 Hz), 5.21 (d, 1H, J = 7.9 Hz), 4.87 (dd, 1H, J = 1.9, 9.5 Hz), 3.91 (s, 3H), 3.79 (s, 3H), 1.35 (s, 9H), 0.89 (s, 9H), 0.26 (s, 3H), −0.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.29, 169.26, 156.0, 154.8, 154.76 (d, J = 264 Hz), 137.1, 136.7, 136.6, 132.6 (d, J = 8 Hz), 131.8, 127.2, 123.3, 118.3 (d, J = 21.0 Hz), 112.2, 112.0, 80.2, 77.2, 72.6, 58.3, 56.2, 52.9, 28.2 (3C), 25.4 (3C), 17.8, −4.8, −5.7; IR (neat) ν_{max} 2951, 2926, 1714, 1693, 1682, 1538, 1495, 1349, 1259, 1166, 1094, 837 cm^{-1}; FABHRMS (NBA-CsI) m/z 846.0862 (M^+ + Cs, $C_{30}H_{41}N_3O_9BrFSi$ requires 846.0834).

Methyl (2*S*,3*R*)-2-[*N*-[(*R*)-3-Bromo-4-methoxyphenyl)-glycyl]amino]-3-[(*tert*-butyldimethylsilyl)oxy]-3-(4-fluoro-3-nitrophenyl)propionate (19). A solution of **18** (130 mg, 0.18 mmol) in CH_2Cl_2 (32 mL) was treated with TBDMSOTf (110 μL, 0.50 mmol, 2.7 equiv) at 0 °C and the mixture was stirred at 0 °C (1.5 h). The reaction mixture was directly passed through a short column (SiO_2, EtOAc). The combined eluant was washed with saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous NaCl (2 × 5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (SiO_2, 1.5 × 10 cm, EtOAc) afforded **19** (110 mg, 111 mg theoretical, 99%) as a white film: $[\alpha]^{26}_D$ −25 (*c* 0.4, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.44 (d, 1H, J = 10.2 Hz), 8.15 (dd, 1H, J = 2.1, 7.2 Hz), 7.86 (ddd, 1H, J = 2.1, 4.4, 8.6 Hz), 7.58 (d, 1H, J = 2.1 Hz), 7.47 (dd, 1H, J = 8.6, 11.1 Hz), 7.32 (dd, 1H, J = 2.1, 8.5 Hz), 6.99 (d, 1H, J = 8.5 Hz), 5.63 (d, 1H, J = 1.7 Hz), 4.73−4.66 (m, 2H), 3.85 (s, 3H), 3.77 (s, 3H), 0.99 (s, 9H), 0.092 (s, 3H), −0.13 (s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 171.2, 170.6, 156.1, 155.5 (d, J = 260 Hz), 154.2, 139.6, 139.5, 134.7 (d, J = 9.0 Hz), 133.0, 128.9, 124.9, 118.9 (d, J = 21 Hz), 112.8, 111.6, 73.7, 67.0, 58.7, 56.5, 52.9, 26.0 (3C), 18.5, −4.5, −5.5; IR (neat) ν_{max} 3580, 2925, 2856, 1738, 1687, 1618, 1598, 1537, 1494, 1346, 1259, 1092 cm^{-1}; FABHRMS (NBA-CsI) m/z 746.0337 (M^+ + Cs, $C_{25}H_{33}N_3O_7BrFSi$ requires 746.0310).

Methyl (2*S*,3*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-[*N*-[(*R*)-*N*-[(*R*)-*N*-[(*tert*-butyloxy)carbonyl](3,5-dihydroxy-4-methoxyphenyl)glycyl](3-bromo-4-methoxypheny)glycyl]-amino]-3-(4-fluoro-3-nitrophenyl)propionate (21). A solution of **19** (520 mg, 0.846 mmol), HOBt (385 mg, 2.79 mmol, 3.3 equiv), and **20**[25] (265 mg, 0.846 mmol, 1 equiv) in DMF (25 mL) was treated with EDCI·HCl (488 mg, 2.54 mmol, 3 equiv) at −20 °C and the mixture was stirred at −20 °C (15 min) and at 0 °C (15 h). The reaction mixture was quenched with the addition of saturated aqueous citric acid (pH 3) and extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with H_2O (25 mL) and saturated aqueous NaCl (2 × 20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (SiO_2, 4 × 25 cm, 67% EtOAc−hexane) afforded **21** (700 mg, 770 mg theoretical, 91%) as a white film: $[\alpha]^{25}_D$ −63 (*c* 1.0, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.07 (dd, 1H, J = 2.0, 7.2 Hz), 7.97 (s, 2H, OH), 7.91 (d, 1H, J = 7.3 Hz), 7.81 (d, 1H, J = 7.3 Hz), 7.55−7.49 (m, 1H), 7.50 (d, 1H, J = 2.0 Hz), 7.17 (dd, 1H, J = 2.0, 8.6 Hz), 7.04 (dd, 1H, J = 8.7, 11 Hz), 6.89 (d, 1H, J = 8.6 Hz), 6.46 (s, 2H), 6.27 (d, 1H, J = 7.3 Hz), 5.53 (d, 1H, J = 2.4 Hz), 5.49 (d, 1H, J = 7.3 Hz), 5.11 (d, 1H, J = 7.3 Hz), 4.45 (dd, 1H, J = 9.5, 2.4 Hz), 3.91 (s, 3H), 3.74 (s, 3H), 3.73 (s, 3H), 1.34 (s, 9H), 0.87 (s, 9H), 0.001 (s, 3H), −0.19 (s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 170.41, 170.4, 170.1, 156.4, 155.51 (d, J = 260 Hz), 155.5, 151.2 (2C), 138.8, 137.2, 135.8, 135.5 (d, J = 8 Hz), 134.4, 133.4, 132.7, 128.3, 124.8, 118.4 (d, J = 22 Hz), 112.5, 111.7, 107.4 (2C), 79.4, 73.7, 60.5, 58.9, 58.4, 56.4, 55.9, 52.8, 28.6 (3C), 25.9 (3C), 18.5, −4.6, −5.5; IR (neat) ν_{max} 3331, 2954, 2857, 1742, 1703, 1693, 1678, 1659, 1651, 1599, 1537, 1497, 1350, 1260, 1164, 1055 cm^{-1}; FABHRMS (NBA-CsI) m/z 1041.1396 (M^+ + Cs, $C_{39}H_{50}N_4O_{13}BrFSi$ requires 1041.1365).

Methyl (2*S*,3*R*)-2-[*N*-[(*R*)-*N*-[(*R*)-*N*-[(*tert*-Butyloxy)carbonyl](3,5-dihydroxy-4-methoxyphenyl)glycyl](3-bromo-4-methoxyphenyl)glycyl]amino]-3-hydroxy-3-(4-fluoro-3-nitrophenyl)propionate (22). From 21. A solution of **21** (2.0 mg, 2.2 μmol) in THF (0.2 mL) was treated with HOAc (38 μL, 6.6 μmol, 3 equiv) and Bu_4NF (1.0 M in THF, 29 μL, 13 equiv), and the mixture was stirred at 25 °C (10 h). The reaction mixture was quenched with the addition of saturated aqueous NH_4Cl (1 mL) and extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with saturated aqueous NH_4Cl (2 × 2 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (SiO_2, 0.5 × 5 cm, 75% EtOAc−hexane) afforded **22** (1.4 mg, 1.8 mg theoretical, 79%) as a white film: R_f = 0.20 (75% EtOAc−hexane); ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.03 (d, 1H, J = 6.4 Hz), 8.00−7.93 (br s, 2H), 7.88−7.80 (m, 2H), 7.60−7.52 (m, 1H), 7.48 (s, 1H), 7.14 (d, 1H, J = 8.6 Hz), 7.14−7.04 (m, 1H), 6.83 (d, 1H, J = 8.6 Hz), 6.48 (s, 2H), 6.34−6.26 (m, 1H), 5.50−5.38 (m, 3H), 5.12 (d, 1H, J = 7.4 Hz), 4.96 (dd, 1H, J = 2.2, 9.4 Hz), 3.88 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 1.35 (s, 9H); IR (neat) ν_{max} 3300, 2924, 2854, 1738, 1709, 1698, 1694, 1657, 1651, 1644, 1538, 1501, 1462, 1440 cm^{-1}; FABHRMS (NBA-CsI) m/z 927.0501 (M^+ + Cs, $C_{33}H_{36}N_4O_{13}BrF$ requires 927.0537).

From 38.[32] A solution of **38** (5.2 mg, 10 μmol), HOBt (4.6 mg, 34 μmol, 3.3 equiv), and **20** (3.3 mg, 10 μmol, 1 equiv) in DMF (0.3 mL) was treated with EDCI·HCl (6.0 mg, 31 μmol, 3 equiv) at −20 °C and the mixture was stirred at −20 °C (15 min) and at 0 °C (15 h). The reaction mixture was quenched with the addition of saturated aqueous citric acid (pH 3) and extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with H_2O (2 mL) and saturated aqueous NaCl (2 × 2 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (SiO_2, 0.5 × 4 cm, 75% EtOAc−hexane) afforded **22** (5.8 mg, 8.3 mg theoretical, 70%) as a white film.

Methyl (*P*)- and (*M*)-(8*R*,11*R*,14*S*,15*R*)-11-(3-Bromo-4-methoxyphenyl)-15-[(*tert*-butyldimethylsilyl)oxy]-8-[*N*-[(*tert*-butyloxy)carbonyl]amino]-5-hydroxy-4-methoxy-18-nitro-10,13-diaza-2-oxatricyclo[14.2.2.1^{3,7}]heneicosa-1(18),3(21),4,6,16,19-hexaene-14-carboxylate (23 and 24). A solution of **21** (350 mg, 0.385 mmol) in DMF (80 mL) was treated with K_2CO_3 (267 mg, 1.93 mmol, 5 equiv), $CaCO_3$ (193 mg, 1.93 mmol, 5 equiv), and 4 Å molecular sieves (700 mg), and the mixture was stirred at 45 °C (14 h). The reaction mixture was filtered through Celite (EtOAc wash) and concentrated *in vacuo*. Flash chromatography (SiO_2, 2 × 14 cm, 67% EtOAc−hexane then 44% acetone−hexane) afforded **23** (95 mg, 347 mg theoretical, 27%, typically 21−29%) as a white solid, **24** (84 mg, 347 mg theoretical, 24%, typically 20−26%) as a white solid, and recovered **21** (53 mg, 15%, typically 10−15%).

For 23 (more polar isomer): R_f = 0.25 (67% EtOAc−hexane); $[\alpha]^{25}_D$ −180 (*c* 0.5, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.24 (s, 1H, OH), 8.15 (d, 1H, J = 2.1 Hz), 7.93−7.87 (m, 1H), 7.84−7.80 (m, 1H), 7.55−7.45 (m, 2H), 7.41 (d, 1H, J = 8.5 Hz), 7.15 (d, 1H, J = 8.3 Hz), 6.69 (d, 1H, J = 2.0 Hz), 6.42 (d, 1H, J = 2.0 Hz), 6.20−6.10 (m, 2H), 5.62 (s, 1H), 5.48 (d, 1H, J = 7.7 Hz), 5.37−5.30 (m, 1H), 4.68−4.63 (m, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 3.77 (s, 3H), 1.39 (s, 9H), 0.86 (s, 9H), 0.04 (s, 3H), −0.03 (s, 3H); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.97 (s, 1H), 8.51 (d, 1H, J = 8.4 Hz), 8.25 (s, 1H), 7.70−7.60 (m, 1H), 7.58 (d, 1H, J = 2.0 Hz), 7.29 (dd, 1H, J = 8.4, 2.0 Hz), 7.22 (d, 1H, J = 8.4 Hz), 7.06 (d, 1H, J = 8.4 Hz), 6.99 (d, 1H, J = 8.4 Hz), 6.42−6.33 (m, 1H), 5.79 (br s, 1H), 5.56 (s, 1H), 5.40−5.33 (m, 1H), 5.12−5.04 (m, 1H), 4.80−4.75 (m, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.70 (s, 3H), 1.39 (s, 9H), 0.92 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 168.9, 168.8, 155.3, 155.2, 152.1, 151.3, 148.3, 141.7, 138.5, 135.6, 134.3, 133.1, 131.2, 130.8, 128.0, 125.5, 123.5, 112.5, 110.7, 108.4, 103.0, 78.6, 71.5, 60.2, 59.0, 56.7, 56.3, 55.9, 55.8, 52.1, 29.6 (3C), 25.6 (3C), 17.7, −4.7, −5.5; IR (film) ν_{max} 3328, 2926, 2854, 1723, 1703, 1677, 1584, 1535, 1498, 1463, 1344, 1260, 1165, 1094, 838, 779 cm^{-1}; FABHRMS (NBA-CsI) m/z 1021.1331 (M^+ + Cs, $C_{39}H_{49}N_4O_{13}BrSi$ requires 1021.1303).

The 2D ^{1}H−^{1}H ROESY NMR spectrum (DMSO-d_6, 600 MHz) of **23** displayed the following diagnostic NOE cross-peaks: C20-H/C15-H (s), C20-H/C14-H (s), C15-H/C14-H (s), C14-H/C13-H (m), C13-H/C11-H (m), C11-H/C10-H (w), C10-H/C8-H (s), C10-H/C21-H (w), C6-H/C8-H (m), C21-H/C8-H (s), C8-H/NHBOC (m), C6-H/NHBOC (m), C6-H/C5-OH (m), C21-H/C19-H (w), C20-H/C19-H (m).

For 24 (less polar isomer): R_f = 0.70 (67% EtOAc−hexane); $[\alpha]^{25}_D$ −34 (*c* 0.2, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.32 (s, 1H, OH), 8.16 (d, 1H, J = 2.1 Hz), 7.68−7.62

(m, 1H), 7.58−7.48 (m, 2H), 7.37 (d, 1H, J = 8.6 Hz), 7.37−7.32 (m, 1H), 7.18 (d, 1H, J = 8.4 Hz), 6.76 (d, 1H, J = 2.2 Hz), 6.68 (d, 1H, J = 2.2 Hz), 6.35−6.25 (m, 1H), 5.90 (d, 1H, J = 8.5 Hz), 5.62 (s, 1H), 5.49 (d, 1H, J = 7.4 Hz), 5.19−5.10 (m, 1H), 4.56 (d, 1H, J = 8.5 Hz), 3.944 (s, 3H), 3.936 (s, 3H), 3.78 (s, 3H), 1.39 (s, 9H), 0.79 (s, 9H), 0.02 (s, 3H), −0.11 (s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 169.8, 169.1, 168.5, 157.1, 152.8, 151.7, 151.4, 143.5, 138.7, 138.6, 133.6, 132.4, 130.3, 129.8, 124.60, 124.57, 122.9, 113.3, 113.2, 112.6, 109.9, 79.4, 74.2, 61.5, 61.3, 60.9, 58.2, 57.6, 56.7, 53.0, 28.5 (3C), 25.9 (3C), 18.3, −4.3, −5.7; IR (film) ν_{max} 3408, 2956, 1742, 1709, 1677, 1582, 1530, 1495, 1343, 1252, 1166, 1101 cm^{-1}; FABHRMS (NBA-CsI) m/z 1021.1332 (M^+ + Cs, $C_{39}H_{49}N_4O_{13}$-BrSi requires 1021.1303).

The 2D ^{1}H−^{1}H ROESY NMR spectrum (acetone-d_6, 400 MHz) of **24** displayed the following diagnostic NOE cross-peaks: C15-H/C17-H (s), C14-H/C17-H (s), C17-H/C13-H (w), C15-H/C14-H (s), C13-H/C20-H (m), C11-H/C10-H (m), C10-H/C8-H (s), C10-H/C21-H (m), C8-H/C6-H (s), C8−H/C21-H (m), C6-H/C5-OH (w).

Methyl (*P*)- and (*M*)-(8*R*,11*R*,14*S*,15*R*)-11-(3-Bromo-4-methoxyphenyl)-8-[*N*-[(*tert*-butyloxy)carbonyl]amino]-5,15-dihydroxy-4-methoxy-18-nitro-10,13-diaza- 2-oxatricyclo[14.2.2.1^{3,7}]heneicosa-1(18),3(21),4,6,16,19-hexaene-14-carboxylate (25 and 26). From 21. A solution of **21** (3.8 mg, 4.2 μmol) in THF (0.2 mL) was treated with Bu_4NF (1.0 M in THF, 21 μL, 5 equiv), and the mixture was stirred at 25 °C (3 h). The reaction mixture was quenched with the addition of saturated aqueous NH_4Cl and extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with saturated aqueous NH_4Cl (2 × 2 mL), dried (Na_2SO_4), and concentrated *in vacuo*. PTLC (SiO_2, 75% EtOAc−hexane, then 56% acetone−hexane) afforded **22** (0.5 mg, 3.4 mg theoretical, 15%) as a white film, **25** (0.46 mg, 3.3 mg theoretical, 14%) as a white film, and **26** (0.79 mg, 3.3 mg theoretical, 24%) as a white film.

For 25 (more polar isomer): R_f = 0.50 (56% acetone−hexane); $[\alpha]^{25}_D$ −113 (*c* 0.09, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.39 (s, 1H), 8.30−8.20 (m, 2H), 7.90−7.75 (m, 2H), 7.68 (d, 1H, J = 2.2 Hz), 7.44 (dd, 1H, J = 8.7, 2.2 Hz), 7.28 (d, 1H, J = 8.4 Hz), 7.03 (d, 1H, J = 8.7 Hz), 6.67 (s, 1H), 6.20−6.12 (m, 1H), 5.98−5.88 (m, 1H), 5.72 (s, 1H), 5.60−5.50 (m, 1H), 5.54 (d, 1H, J = 9.0 Hz), 5.31 (d, 1H, J = 9.1 Hz), 5.12−5.06 (m, 1H), 3.96 (s, 3H), 3.88 (s, 3H), 3.75 (s, 3H), 1.39 (s, 9H); IR (neat) ν_{max} 3312, 2916, 2846, 1715, 1698, 1650, 1538, 1504, 1455, 1350, 1259, 1161, 1090, 1040 cm^{-1}; FABHRMS (NBA-CsI) m/z 907.0464 (M^+ + Cs, $C_{33}H_{35}N_4O_{13}Br$ requires 907.0438).

For 26 (less polar isomer): R_f = 0.55 (56% acetone−hexane); $[\alpha]^{25}_D$ −25 (*c* 0.03, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.29 (s, 1H, OH), 8.12 (s, 1H), 8.05−7.90 (m, 1H), 7.93 (d, 1H, J = 8.5 Hz), 7.78−7.60 (m, 2H), 7.48 (d, 1H, J = 8.5 Hz), 7.36 (d, 1H, J = 8.5 Hz), 7.06 (d, 1H, J = 8.5 Hz), 6.68 (s, 1H), 6.22−6.13 (m, 1H), 5.93−5.80 (m, 2H), 5.63−5.56 (m, 1H), 5.57 (d, 1H, J = 8.7 Hz), 5.30 (d, 1H, J = 8.6 Hz), 5.03−4.98 (m, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 3.74 (s, 3H), 1.36 (s, 9H); IR (neat) ν_{max} 3300, 2914, 2851, 1694, 1658, 1586, 1532, 1497, 1348, 1286, 1259, 1164, 1084, 1037 cm^{-1}; FABHRMS (NBA-CsI) m/z 907.0414 (M^+ + Cs, $C_{33}H_{35}N_4O_{13}Br$ requires 907.0438).

From 23 and 24, Correlation of Isomers. A solution of **23** (2.0 mg, 2.0 μmol) in THF (0.25 mL) was treated with HOAc (1/100 v/v in THF, 63 μL, 11 μmol, 6 equiv) followed by Bu_4NF (1.0 M in THF, 13 μL, 5 equiv). The solution was stirred at 25 °C (1 h) and then quenched with the addition of saturated aqueous NH_4Cl (1.0 mL) and extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with saturated aqueous NaCl (4 mL), dried ($MgSO_4$) and concentrated *in vacuo*. PTLC (SiO_2, 75% EtOAc−hexane) afforded **25** (1.1 mg, 1.7 mg theoretical, 60%) as a white film.

A solution of **24** (1.5 mg, 1.7 μmol) in THF at 0 °C was treated dropwise with a 0.17 M solution of HOAc in THF (49 μL, 8.4 μmol, 5 equiv) and a 1.0 M solution of Bu_4NF in THF (22 μL, 22 μmol, 13 equiv) under Ar. The resulting reaction mixture was gradually warmed to 25 °C, stirred for 2 h, and concentrated *in vacuo*. PTLC (SiO_2, 75% EtOAc−hexane) afforded **26** (0.65 mg, 1.3 mg theoretical, 50%) as a white film identical in all respects with authentic material.

Methyl (*P*)-(8*R*,11*R*,14*S*,15*R*)-11-(3-Bromo-4-methoxyphenyl)-15-[(*tert*-butyldimethylsilyl)oxy]-8-[*N*-[(*tert*-butyloxy)carbonyl]amino]-18-chloro-5-hydroxy-4-methoxy-10,13-diaza-2-oxatricyclo[14.2.2.1^{3,7}]heneicosa-1(18),3(21),4,6,16,19-hexaene-14-carboxylate (29). Following the procedure detailed below for **33**, **27** afforded **29** (47%) as a white film: $[\alpha]^{25}_D$ −66 (*c* 0.4, $CHCl_3$); ^{1}H NMR (CD_3CN, 500 MHz) mixture of two rotamers (rotamer A:B = 4.8:1) δ (for rotamer A) 7.61 (d, 1H, J = 2.0 Hz), 7.40 (dd, 1H, J = 8.5, 2.0 Hz), 7.31 (d, 1H, J = 8.5 Hz), 7.30 (d, 1H, J = 2.0 Hz), 7.17 (br s, 1H), 7.12 (d, 1H, J = 8.5 Hz), 7.11 (br s, 1H), 6.93−6.70 (m, 1H), 6.64 (d, 1H, J = 2.0 Hz), 6.33 (br s, 1H), 5.82 (br s, 1H), 5.71 (d, 1H, J = 9 Hz), 5.47 (s, 1H), 5.19 (d, 1H, J = 5.5 Hz), 5.03 (br s, 1H), 4.69 (d, 1H, J = 5.5 Hz), 4.01 (s, 3H), 3.91 (s, 3H), 3.73 (s, 3H), 1.40 (s, 9H), 0.78 (s, 9H), −0.01 (s, 3H), −0.11 (s, 3H); IR (neat) ν_{max} 3419, 2930, 2857, 1709, 1674, 1588, 1499, 1434, 1341, 1259, 1168, 1094, 1058, 836, 779 cm^{-1}; FABHRMS (NBA-CsI) m/z 1010.1083 (M^+ + Cs, $C_{39}H_{49}N_3O_{11}BrClSi$ requires 1010.1063).

Methyl (8*R*,11*R*,14*S*,15*R*)-11-(3-Bromo-4-methoxyphenyl)-15-[(*tert*-butyldimethylsilyl)oxy]-8-[*N*-[(*tert*-butyloxy)carbonyl]amino]-5-hydroxy-4-methoxy-10,13−diaza-2-oxatricyclo[14.2.2.1^{3,7}]heneicosa-1(18),3(21),4,6,16,19-hexaene-14-carboxylate (30): ^{1}H NMR (CD_3CN, 400 MHz) mixture of two rotamers A:B = 5:1) δ (for rotamer A) 7.36 (d, 1H, J = 8.4 Hz), 7.20−7.17 (m, 3H), 7.11−7.06 (m, 4H), 6.84 (d, 1H, J = 3.7 Hz), 6.60 (d, 1H, J = 2.2 Hz), 5.72 (d, 1H, J = 9.2 Hz), 5.43 (d, 1H, J = 2.0 Hz), 5.09 (d, 1H, J = 4.8 Hz), 4.70−4.78 (m, 1H), 4.68 (d, 1H, J = 9.6 Hz), 3.98 (s, 3H), 3.88 (s, 3H), 3.71 (s, 3H), 1.37 (s, 9H), 0.73 (s, 9H), −0.06 (s, 3H), −0.20 (s, 3H); IR (neat) ν_{max} 3304, 2929, 2855, 1699, 1651, 1588, 1504, 1259, 1164, 1087, 836 cm^{-1}; FABHRMS (NBA-NaI) m/z 844.2476 (M^+ + H, $C_{39}H_{50}O_{11}N_3BrSi$ requires 844.2470).

Methyl (*M*)-(8*R*,11*R*,14*S*,15*R*)-11-(3-Bromo-4-methoxyphenyl)-15-[(*tert*-butyldimethylsilyl)oxy]-8-[*N*-[(*tert*-butyloxy)carbonyl]amino]-18-chloro-5-hydroxy-4-methoxy-10,13-diaza-2-oxatricyclo[14.2.2.1^{3,7}]heneicosa-1(18),3(21),4,6,16,19-hexaene-14-carboxylate (33). A solution of **24** (50 mg, 0.055 mmol) in CH_3OH (9 mL) was treated with cat. Raney Ni at −20 °C and the mixture was stirred under 1 atm of H_2 at −20 °C for 1 h. The reaction mixture was filtered through a pad of Celite (CH_3OH, 20 mL), the solvent was removed under a stream of N_2, and the product was dried under vacuum to afford **31** (100%) as a crude residue which was used directly.

A solution of crude **31** in anhydrous CH_3CN (1.0 mL) was treated with HBF_4 (48% aqueous solution, 9.16 μL, 71.5 μmol, 1.3 equiv) at 0 °C under Ar, and the resulting solution was stirred at 0 °C for 10 min before being warmed to 25 °C for 30 min. The reaction mixture was recooled to 0 °C and treated dropwise with *tert*-butyl nitrite (9.0 μL, 71.5 μmol, 1.3 equiv), and the resulting reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was cooled to −20 °C and added to the aqueous suspension of CuCl (272 mg, 2.75 mmol, 50 equiv) and $CuCl_2$ (443 mg, 3.3 mmol, 60 equiv) in H_2O (1.8 mL) at 0 °C. Additional CH_3CN (2.0 mL) was used for transfer washing the diazonium salt. The heterogeneous mixture was warmed to 25 °C and stirred for 45 min. The reaction mixture was quenched with the addition of 5% aqueous $NaHCO_3$ (4 mL) and extracted with EtOAc (3 × 10 mL). The combined EtOAc extracts were washed with saturated aqueous NaCl (5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Chromatography (SiO_2, 3% CH_3OH−$CHCl_3$) afforded **33** (42 mg, 47 mg theoretical, 87%) as a white film: $[\alpha]^{25}_D$ −22 (*c* 0.27, $CHCl_3$); ^{1}H NMR (CD_3CN, 500 MHz) mixture of two rotamers (rotamer A:B = 7:1) δ (for rotamer A) 7.54 (d, 1H, J = 2.0 Hz), 7.32 (s, 1H), 7.26 (dd, 1H, J = 8.5, 2.0 Hz), 7.20 (d, 1H, J = 8.5 Hz), 7.10 (d, 1H, J = 8.5 Hz), 7.06 (dd, 1H, J = 8.5, 2.0 Hz), 6.83 (d, 1H, J = 5.5 Hz), 6.66 (d, 1H, J = 2.0 Hz), 6.33 (br s, 1H), 5.87 (br s, 1H), 5.74 (d, 1H, J = 9 Hz), 5.41 (s, 1H), 5.21 (d, 1H, J = 5.5 Hz), 4.90 (br s, 1H), 4.67 (d, 1H, J = 5.5 Hz), 4.01 (s, 3H), 3.90 (s, 3H), 3.73 (s, 3H), 1.40 (s, 9H), 0.76 (s, 9H), −0.03 (s, 3H), −0.17 (s, 3H); IR (neat) ν_{max} 2956, 2928, 1709, 1692, 1659,

Table 4. Representative Results of the Conversion of 31 to 33

solvent	*t*-BuONO/HBF_4 (equiv)	CuCl/$CuCl_2$ (equiv)	result
THF	1.6/1.6	50/20	27% **33**, 30% **30**
CH_3CN	1.3/1.3	50/20	36% **33**, 12% **30**
CH_3CN	1.3/1.3	50/60	61−64% **33**
CH_3CN	1.3/1.3	50/60	87% **33**[a]

[a] Large scale.

1588, 1498, 1340, 1259, 1165, 1099, 1059, 835 cm^{-1}; FAB-HRMS (NBA-NaI) *m/z* 878.2069 ($M^+ + H$, $C_{39}H_{49}N_3O_{11}BrClSi$ requires 878.2087).

Representative results of a study of the conversion of **31** to **33** are summarized in Table 4.

Methyl (*M*)-(8*R*,11*R*,14*S*,15*R*)-8-Amino-11-(3-bromo-4-methoxyphenyl)-15-[(*tert*-butyldimethylsilyl)oxy]-18-chloro-5-hydroxy-4-methoxy-10,13-diaza-2-oxatricyclo-[14.2.2.1^{3,7}]heneicosa-1(18),3(21),4,6,16,19-hexaene-14-carboxylate. A solution of **33** (9.0 mg, 10 μmol) in CH_2Cl_2 (0.7 mL) was treated with a solution of *B*-bromocatecholborane in CH_2Cl_2 (0.28 mL) at 0 °C, and the mixture was stirred at 0 °C for 2 h. The reaction mixture was directly passed through a short column (SiO_2, 0.5 × 2 cm, 20% CH_3OH−$CHCl_3$). The combined eluant was washed with saturated aqueous $NaHCO_3$ (3 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (SiO_2, 0.8 × 4 cm, EtOAc then 8% CH_3OH−$CHCl_3$) afforded the title amine (7.3 mg, 93%) as a pale yellow film: $[\alpha]^{25}_D$ +78 (*c* 0.32, $CHCl_3$); ^1H NMR (CD_3CN, 400 MHz) δ 8.00 (s, 1H), 7.53 (d, 1H, *J* = 2.0 Hz), 7.21 (d, 1H, *J* = 8.4 Hz), 7.20 (d, 1H, *J* = 8.4 Hz), 7.05 (s, 2H), 6.80 (dd, 1H, *J* = 8.4, 1.6 Hz), 6.77 (s, 1H), 6.62 (s, 1H), 6.28 (s, 1H), 5.74 (d, 1H, *J* = 9.8 Hz), 5.42 (d, 1H, *J* = 2.0 Hz), 4.91 (dd, 1H, *J* = 9.8, 2.0 Hz), 4.89 (s, 1H), 4.22 (s, 1H), 4.02 (s, 3H), 3.87 (s, 3H), 3.75 (s, 3H), 0.72 (s, 9H), −0.04 (s, 3H), −0.23 (s, 3H); ^{13}C NMR (CD_3CN, 100 MHz) δ 171.8, 169.9, 169.7, 156.9, 154.1, 153.9, 151.2, 138.9, 138.3, 138.0, 133.1, 129.5, 128.9, 128.6, 128.3, 127.2, 123.9, 112.9, 112.3, 111.9, 108.5, 73.5, 62.3, 62.0, 60.1, 58.1, 56.9, 53.3, 25.8 (3C), 18.3, −4.5, −5.6; IR (neat) ν_{max} 3423, 2958, 2928, 2857, 1732, 1694, 1667, 1601, 1498, 1463, 1262, 1123, 1060, 833 cm^{-1}; FABHRMS (NBA-CsI) *m/z* 912.0596 ($M^+ + Cs$, $C_{34}H_{41}N_3O_9BrClSi$ requires 912.0637).

The 2D ^1H−^1H ROESY NMR spectrum (CD_3CN, 600 MHz) displayed the following diagnostic NOE crosspeaks: C15-H/C17-H (s), C17-H/C14-H (s), C15-H/C14-H (s), C11-H/C10-H (m), C10-H/C21-H (w), C20-H/C19-H (s).

Methyl (*P*)-(8*R*,11*R*,14*S*,15*R*)-8-Amino-11-(3-bromo-4-methoxyphenyl)-15-[(*tert*-butyldimethylsilyl)oxy]-18-chloro-5-hydroxy-4-methoxy-10,13-diaza-2-oxatricyclo-[14.2.2.1^{3,7}]heneicosa-1(18),3(21),4,6,16,19-hexaene-14-carboxylate. A solution of **29** (6.1 mg, 6.9 μmol) in CH_2Cl_2 (0.68 mL) was treated with a solution of *B*-bromocatecholborane (0.19 mL, 38 μmol, 0.2 M solution in CH_2Cl_2) in CH_2Cl_2 (2.7 mL) at 0 °C and the mixture was stirred at 0 °C for 2 h. The reaction mixture was directly passed through a short column (SiO_2, 0.8 × 6 cm, EtOAc then 20% CH_3OH−$CHCl_3$ to provide the title amine·HBr (4.6 mg, 75%) as a yellow film: $[\alpha]^{25}_D$ +18 (*c* 0.2, $CHCl_3$) for free amine; ^1H NMR (CD_3CN, 500 MHz) δ 7.59 (s, 1H), 7.39 (d, 1H, *J* = 7.3 Hz), 7.28 (d, 1H, *J* = 7.3 Hz), 7.27−7.17 (m, 2H), 7.13−7.11 (m, 1H), 7.10 (d, 1H, *J* = 8.4 Hz), 7.00 (s, 1H), 6.43 (s, 1H), 5.71 (d, 1H, *J* = 8.4 Hz), 5.43 (s, 1H), 5.36 (br s, 1H), 4.87 (br s, 1H), 4.59 (d, 1H, *J* = 8.4 Hz), 4.02 (s, 3H), 3.90 (s, 3H), 3.73 (s, 3H), 0.85 (s, 9H), 0.04 (s, 3H), −0.15 (s, 3H); ^{13}C NMR (CD_3CN, 100 MHz) δ 170.0 (2C), 168.7, 157.5, 153.4, 151.8, 151.7, 142.9, 140.5, 137.9, 133.5, 131.5, 130.3, 129.6, 128.5, 128.0, 126.5, 125.6, 113.5, 112.8, 107.8, 74.1, 61.3, 60.9, 58.4, 58.1, 57.1, 53.4, 25.9 (3C), 18.4, −4.3, −5.6; IR (neat) ν_{max} 3329, 2929, 2852, 1730, 1673, 1592, 1496, 1434, 1339, 1258, 1086, 1058, 838 cm^{-1}; FABHRMS (NBA-CsI) *m/z* 910.0510 ($M^+ + Cs$, $C_{34}H_{41}N_3O_9BrClSi$ requires 910.0538).

The 2D ^1H−^1H ROESY NMR spectrum (CD_3CN, 600 MHz) displayed the following diagnostic NOE crosspeaks: C15-H/C20-H (s), C14-H/C20-H (s), C14-H/C15-H (s).

Methyl (*M*)-(8*R*,11*R*,14*S*,15*R*)-8-[(*tert*-butyloxycarbonyl)amino]-11-(3-bromo-4-methoxyphenyl)-18-chloro-5,15-dihydroxy-4-methoxy-10,13-diaza-2-oxatricyclo[14.2.2.1^{3,7}]-heneicosa-1(18),3(21),4,6,16,19-hexaene-14-carboxylate. A solution of **33** (3.0 mg, 0.0034 mmol) in THF (0.25 mL) was first treated with HOAc (1/100 v/v in THF, 97 μL, 0.017 mmol, 5 equiv) followed by Bu_4NF (1.0 M in THF, 20 μL, 0.02 mmol, 5 equiv). The solution was stirred at 25 °C (1 h) and then quenched with the addition of saturated aqueous NH_4Cl (1.0 mL) and extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. PTLC (SiO_2, 75% EtOAc−hexane) afforded the free alcohol (1.5 mg, 2.5 mg theoretical, 59%) as a white film: ^1H NMR (CD_3CN, 400 MHz) mixture of two rotamers (rotamer A:B = 10:1) δ (for rotamer A) 7.54−7.49 (m, 2H), 7.44 (dd, 1H, *J* = 2.0, 0.7 Hz), 7.32−7.26 (m, 2H), 7.25 (d, 1H, *J* = 8.4 Hz), 7.05 (m, 1H), 7.01 (d, 1H, *J* = 8.4 Hz), 6.92 (d, 1H, *J* = 7.0 Hz), 6.53 (s, 1H), 5.81 (s, 1H), 5.66 (d, 1H, *J* = 1.4 Hz), 5.32 (d, 1H, *J* = 8.0 Hz), 5.13 (d, 1H, *J* = 9.6 Hz), 5.04 (d, 1H, *J* = 6.7 Hz), 4.76 (dd, 1H, *J* = 7.5, 4.4 Hz), 3.98 (s, 3H), 3.86 (s, 3H), 3.71 (s, 3H), 1.39 (s, 9H); IR (film) ν_{max} 3311, 2917, 1651, 1495, 1260, 1089 cm^{-1}; FABHRMS (NBA-CsI) *m/z* 898.0212 ($M^+ + Cs$, $C_{33}H_{35}O_{11}N_3ClBr$ requires 898.0177).

The Thermal Interconversion of Atropisomers (Tables 1 and 2). A solution of **23**, **29**, **33**, **55**, or **59** (2.0 mg, 2.3 μmol) in DMSO-d_6, DMF-d_7, or *o*-$Cl_2C_6D_4$ (0.63 mL) was warmed at the indicated temperature in an NMR tube under Ar for the indicated time and cooled to 25 °C. The ratio of **23** and **24** was determined by ^1H NMR analysis (at 25 °C) by integration.

A solution of **23** (45 mg, 0.049 mmol) in dried and degassed 1,2-dichlorobenzene (30 mL) under Ar was warmed at 140 °C. After 43 h, ^1H NMR (400 MHz) analysis of a reaction aliquot indicated the presence of **23** and **24** in a ratio of 1.5:1. The solution was cooled and directly subjected to chromatography (SiO_2, 75% EtOAc−hexane) to afford **24** (less polar isomer, 14 mg, 31%; typically 25−35%) and recovered **23** (22 mg, 49%; typically 68−49%).

***tert*-Butyl (*R*)-*N*-[*tert*-(Butyloxy)carbonyl]-*N*-[(*S*)-β-cyanoalanyl](3,5-dihydroxy-4-methoxyphenyl)glycine (50).** A solution of **49**[25] (58 mg, 0.22 mmol) in anhydrous DMF (1.5 mL at 0 °C was treated sequentially with HOBt (32 mg, 0.24 mmol, 1.1 equiv), **47**[32] (69 mg, 0.32 mmol, 1.5 equiv) dissolved in DMF (0.7 mL), and DCC (58 mg, 0.28 mmol, 1.3 equiv) under Ar. The reaction mixture was warmed to 25 °C and stirred under Ar for 14 h. After removal of the solvent *in vacuo*, the crude residue was dissolved in $CHCl_3$ (0.5 mL), and Et_2O (1.0 mL) was added. The insoluble salts which formed were filtered and washed with Et_2O (2 × 0.5 mL), and the filtrate was concentrated *in vacuo*. Flash chromatography (SiO_2, 3.5 × 10 cm, 2−10% CH_3OH−$CHCl_3$ gradient elution) afforded **50** (85 mg, 100 mg theoretical, 85%) as a foam: $[\alpha]^{25}_D$ −53 (*c* 0.16, CH_3OH); ^1H NMR (acetone-d_6, 400 MHz) δ 8.13 (br s, 2H, OH), 7.80 (d, 1H, NH, *J* = 7.1 Hz), 6.67 (d, 1H, NHBOC, *J* = 8.5 Hz), 6.45 (s, 2H), 5.12 (d, 1H, *J* = 7.1 Hz), 4.58 (ddd, 1H, *J* = 5.1, 8.5, 17.0 Hz), 3.77 (s, 3H), 3.00 (dd, 1H, *J* = 5.1, 17.0 Hz), 2.86 (dd, 1H, *J* = 8.8, 17.0 Hz), 1.43 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 170.0, 169.4, 156.3, 151.5 (2C), 136.1, 133.2, 118.1, 107.4 (2C), 82.4, 80.4, 60.6, 57.9, 51.5, 28.5 (3C), 28.1 (3C), 20.9; IR (film) ν_{max} 3328, 2979, 2935, 1666, 1600, 1524, 1455, 1392, 1369, 1254, 1158, 1058 cm^{-1}; FABHRMS (NBA-CsI) *m/z* 598.1140 ($M^+ + Cs$, $C_{22}H_{31}N_3O_8$ requires 598.1165).

***tert*-Butyl (*R*)-*N*-[(Benzyloxy)carbonyl]-*N*-[(*S*)-β-cyanoalanyl](3,5-dihydroxy-4-methoxyphenyl)glycine (51).** A solution of **49**[25] (0.11 g, 0.41 mmol) in anhydrous DMF (4.1 mL) at 0 °C was treated sequentially with **48**[35] (0.11 g, 0.45 mmol, 1.1 equiv), HOBt (61 mg, 0.45 mmol, 1.1 equiv), and EDCI·HCl (0.17 g, 0.90 mmol, 2.2 equiv). The reaction mixture was gradually warmed to 25 °C and stirred under Ar for 14 h. H_2O (10 mL) and EtOAc (10 mL) were added, the two layers were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with H_2O (10 mL) and saturated aqueous NaCl (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (SiO_2, 3.0 × 1.5 cm, 2−5% CH_3OH−$CHCl_3$ gradi-

ent elution) afforded **51** (0.17 g, 0.20 g theoretical, 84%) as a foam: $[\alpha]^{25}_D$ −46 (*c* 1.7, CH_3OH); ^1H NMR (acetone-d_6, 400 MHz) δ 8.14 (br s, 2H, phenol OH), 7.87 (d, 1H, NH, J = 7.11 Hz), 7.41−7.28 (m, 5H), 7.03 (d, 1H, NHCBZ, J = 8.5 Hz), 6.46 (s, 2H), 5.15 (s, 1H), 5.14 (s, 2H), 4.70 (ddd, 1H, J = 5.1, 8.5, 8.6 Hz), 3.77 (s, 3H), 3.03 (dd, 1H, J = 5.1, 17.0 Hz), 2.89 (dd, 1H, J = 8.6, 17.0 Hz), 1.39 (s, 9H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 170.0, 169.1, 156.9, 151.5 (2C), 137.7, 136.2, 133.1, 129.2 (2C), 128.7 (2C), 128.6, 117.9, 107.6 (2C), 82.3, 67.2, 60.5, 58.0, 52.0, 27.9 (3C), 21.2; IR (film) ν_{max} 3326, 2978, 2938, 1706, 1670, 1600, 1526, 1456, 1369, 1259, 1155 cm^{-1}; FABHRMS (NBA-CsI) *m*/*z* 632.1011 (M^+ + Cs, $C_{25}H_{29}N_3O_8$ requires 632.1009).

***tert*-Butyl (*R*)-*N*-[(*S*)-*β*-Cyanoalanyl](3,5-dihydroxy-4-methoxyphenyl)glycine (52). From 50.** The dipeptide **50** (82 mg, 0.18 mmol) was treated with 1 N HCl−EtOAc (1.8 mL) and the resulting mixture was stirred under Ar at 25 °C for 5 h. The volatiles were removed *in vacuo*, and the oily solid was dissolved in saturated aqueous $NaHCO_3$ (1.0 mL). The aqueous phase was extracted with EtOAc (4 × 5 mL), and the combined organic extracts were washed with saturated aqueous NaCl (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was triturated with $CHCl_3$ (2 mL) to afford **52** (35 mg, 64 mg theoretical, 55%) as a colorless oil: ^1H NMR (CD_3OD, 400 MHz) δ 6.33 (s, 2H), 5.00 (s, 2H), 3.70 (s, 3H), 3.63 (dd, 1H, J = 5.4, 7.1 Hz), 2.75 (dd, 1H, J = 5.4, 16.8 Hz), 2.64 (dd, 1H, J = 7.1, 16.8 Hz), 1.35 (s, 9H); FABHRMS (NBA-NaI) *m*/*z* 310.1027 (M^+ − *tert*-Bu, $C_{13}H_{15}N_3O_6$ requires 310.1039).

From 51. A solution of **51** (90 mg, 0.18 mmol) in CH_3OH (2.0 mL) at 25 °C was treated with 10% Pd−C (9.0 mg, 0.10 wt equiv) and was stirred under H_2 (1 atm) for 4 h. The reaction mixture was filtered through a pad of Celite (5% CH_3OH−$CHCl_3$, 3 × 10 mL) and the solvent was removed *in vacuo*. The crude amine **52** (65 mg, 66 mg theoretical, 98%) was sufficiently pure to use in the subsequent step.

(2*R*,3*R*)-2-[*N*-[(*tert*-Butyloxy)carbonyl]amino]-3-[(4-fluoro-3-nitro)phenyl]-3-hydroxypropionic Acid (53). A solution of **65**[25,32] (18 mg, 0.050 mmol) in *t*-BuOH-H_2O (2:1, 1.5 mL) was treated with LiOH·H_2O (4.2 mg, 0.10 mmol, 2.0 equiv) at 25 °C for 0.5 h. The volatiles were removed *in vacuo* before H_2O (5 mL) and EtOAc (8 mL) were added to the residue. The pH of the solution was adjusted to 5 by the dropwise addition of 15% aqueous citric acid at 0 °C. The two layers were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with H_2O (8 mL) and saturated aqueous NaCl (8 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude solid was triturated with anhydrous Et_2O (2 × 1 mL) and dried thoroughly to afford **53** (16.5 mg, 17.1 mg theoretical, 96%) as a yellow film: $[\alpha]^{25}_D$ +6.9 (*c* 0.85, CH_3OH); ^1H NMR (acetone-d_6, 400 MHz) δ 8.19 (dd, 1H, J = 1.7, 7.2 Hz), 7.89−7.85 (m, 1H), 7.46 (dd, 1H, J = 8.8, 11.0 Hz), 6.20 (d, 1H, NH, J = 8.6 Hz), 5.19 (d, 1H, J = 6.2 Hz), 4.46 (dd, 1H, J = 6.2, 8.6 Hz), 1.32 (s, 9H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 171.6, 156.1, 155.3 (d, J = 260 Hz), 140.1, 138.0, 135.0 (d, J = 9.0 Hz), 125.0, 118.6, (d, J = 21 Hz), 79.7, 73.4, 60.4, 28.3 (3C); IR (film) ν_{max} 3423, 1670, 1636, 1540, 1349, 1251, 1159, 1052 cm^{-1}; FABHRMS (NBA-NaI) *m*/*z* 367.0934 (M^+ + Na, $C_{14}H_{17}N_2O_7F$ requires 367.0917).

***tert*-Butyl (*R*)-*N*-[(2*R*,3*R*)-2-[*N*-[(*tert*-Butyloxy)carbonyl]amino]-*N*-[(*S*)-*β*-cyanoalanyl]-3-(4-fluoro-3-nitrophenyl)-3-hydroxypropionamido]-*β*-cyano-L-alanyl-*N*-(3,5-dihydroxy-4-methoxyphenyl)glycine (54). From 52.** A solution of **52** (29 mg, 0.079 mmol) in anhydrous DMF (1.0 mL) at 0 °C was treated sequentially with HOBt (12 mg, 0.087 mmol, 1.1 equiv), **53** (30 mg, 0.087 mmol, 1.1 equiv), and EDCI·HCl (40 mg, 0.21 mmol, 2.6 equiv) under Ar. The reaction mixture was slowly warmed to 25 °C, stirred for 14 h, and concentrated *in vacuo*. EtOAc (5 mL) and H_2O (5 mL) were added to the residue, the two layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 5 mL), H_2O (2 × 5 mL), and saturated aqueous NaCl (5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. PTLC (SiO_2, eluted twice with 5% CH_3OH−$CHCl_3$) afforded **54** (36 mg, 55 mg theoretical, 65%) and a second separable minor diastereomer. For **54**: white film (less polar isomer, R_f = 0.40, 5% CH_3OH−$CHCl_3$); $[\alpha]^{25}_D$ −13 (*c* 0.3, CH_3OH); ^1H NMR (acetone-d_6, 400 MHz) δ 8.26−8.21 (m, 2H, two NH), 8.13−8.10 (m, 3H), 7.91−7.88 (m, 1H), 7.45 (dd, 1H, J = 8.8, 11.0 Hz), 6.45 (s, 2H), 6.28 (d, 1H, NHBOC, J = 9.4 Hz), 5.49 (s, 1H, OH), 5.18 (d, 1H, J = 7.3 Hz), 4.99 (d, 1H, J = 7.6 Hz), 4.94 (ddd, 1H, J = 5.0, 6.4, 7.9 Hz), 4.44 (dd, 1H, J = 7.6, 9.4 Hz), 3.76 (s, 3H), 3.08 (dd, 1H, J = 5.0, 17.0 Hz), 2.96 (dd, 1H, J = 7.9, 17.0 Hz), 1.40 (s, 9H), 1.24 (s, 9H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 171.7, 170.0, 168.8, 155.6, 155.4, (d, J = 260 Hz), 151.4 (2C), 140.0, 137.8, 135.5 (d, J = 9.0 Hz), 135.0, 133.0, 125.5, 118.5 (d, J = 21 Hz), 117.8, 107.5 (2C), 82.4, 79.6, 74.1, 60.5, 60.3, 58.1, 50.4, 28.2 (3C), 28.0 (3C), 20.9; IR (film) ν_{max} 3300, 2919, 2854, 2241, 1657, 1531, 1452, 1350, 1248, 1155 cm^{-1}; FABHRMS (NBA) *m*/*z* 692.2556 (M^+ + H, $C_{31}H_{38}N_5O_{12}F$ requires 692.2579).

For the minor diastereomer: white film (more polar isomer, R_f = 0.35, 5% CH_3OH−$CHCl_3$); $[\alpha]^{25}_D$ −58 (*c* 0.8, CH_3OH); ^1H NMR (acetone-d_6, 400 MHz) δ 8.20−8.16 (m, 4H, phenol OH and NH), 7.98 (d, 1H, J = 7.2 Hz), 7.85−7.82 (m, 1H), 7.42 (dd, 1H, J = 8.6, 11.1 Hz), 6.47 (s, 2H), 6.31 (d, 1H, NHBOC, J = 8.7 Hz), 5.54 (s, 1H), 5.15 (d, 1H, J = 7.3 Hz), 5.09 (d, 1H, J = 7.5 Hz), 4.87 (ddd, 1H, J = 5.4, 6.5, 7.4 Hz), 4.22 (dd, 1H, J = 7.5, 8.7 Hz), 3.77 (s, 3H), 3.03 (dd, 1H, J = 5.4, 17.0 Hz), 2.96 (dd, 1H, J = 7.4, 17.0 Hz), 1.40 (s, 9H), 1.26 (s, 9H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 171.6, 170.0, 168.6, 155.7, 155.5 (d, J = 260 Hz), 151.5 (2C), 140.1, 137.7, 135.6 (2C), 133.0, 125.6, 118.7 (d, J = 21 Hz), 117.8, 107.6 (2C), 82.4, 79.8, 73.7, 60.6, 60.4, 58.0, 50.4, 28.3 (3C), 28.0 (3C), 20.9; IR (film) ν_{max} 3337, 2921, 2930, 2249, 1652, 1646, 1540, 1352, 1165, 1053 cm^{-1}; FABHRMS (NBA) *m*/*z* 824.1573 (M^+ + Cs, $C_{31}H_{38}N_5O_{12}F$ requires 824.1555).

From 82.[32] A solution of **49** (1.0 mg, 3.4 μmol) in anhydrous DMF (0.10 mL) at 0 °C was treated sequentially with **82** (1.6 mg, 3.4 μmol, 1.0 equiv), HOBt (0.6 mg, 4.1 μmol, 1.1 equiv), and EDCI·HCl (1.6 mg, 8.2 μmol, 2.2 equiv) under Ar. The reaction mixture was stirred at 0 °C for 15 h before being diluted with H_2O (0.5 mL). The solution was extracted with EtOAc (5 × 0.5 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 1 mL), H_2O (2 × 1 mL), and saturated aqueous NaCl (1 mL), dried (Na_2SO_4), and concentrated *in vacuo*. PTLC (SiO_2, eluted twice with 5% CH_3OH−$CHCl_3$) afforded **54** (1.5 mg, 2.6 mg theoretical, 58%) as a white film.

***tert*-Butyl (*P*)- and (*M*)-(8*R*,11*S*,14*R*,15*R*)-14-[*N*-[(*tert*-Butyloxy)carbonyl]amino]-11−(cyanomethyl)-5,15-dihydroxy-10,13-dioxo-4-methoxy-18-nitro-9,12-diaza-2−oxatricyclo[14.2.2.1^{3,7}]heneicosa-3,4,7(21),16,18,19-hexaene-8-carboxylate (55 and 56).** A solution of **54** (49 mg, 71 μmol) in anhydrous degassed DMF (9 mL) was treated with a predried (180 °C, 0.1 mmHg, 2 h) mixture of K_2CO_3 (50 mg, 0.37 mmol, 5.0 equiv), $CaCO_3$ (55 mg, 0.55 mmol, 7.5 equiv), 4 Å molecular sieve powder (100 mg, 2 wt equiv) at 25 °C under Ar. The reaction mixture was warmed at 48 °C for 24 h. The resulting mixture was cooled to 25 °C, filtered through Celite (EtOAc, 4 × 5 mL) and the solvent was removed *in vacuo*. Flash chromatography (SiO_2, 1.5 × 10 cm, 2−5% CH_3OH−$CHCl_3$, gradient elution) afforded **55** and **56** (28 mg, 47 mg theoretical, 59%) as a separable 1:1.5 mixture of diastereomers. For the major diastereomer **56**: white film (17 mg, 36%); (more polar isomer, R_f = 0.31, 5% CH_3OH−$CHCl_3$); $[\alpha]^{25}_D$ +85 (*c* 0.33, CH_3OH); ^1H NMR (acetone-d_6, 500 MHz) δ 8.43 (br s, 1H, phenol OH), 8.21 (d, 1H, NH, J = 8.5 Hz), 8.16 (s, 1H), 7.84 (dd, 1H, J = 1.5, 8.5 Hz), 7.54 (d, 1H, NH, J = 6.7 Hz), 7.32 (d, 1H, J = 8.5 Hz), 6.67 (dd, 1H, J = 1.1, 1.2 Hz), 6.24 (d, 1H, NHBOC, J = 6.0 Hz), 5.70 (d, 1H, J = 1.1 Hz), 5.41 (dt, 1H, J = 1.0, 8.9 Hz), 5.32−5.26 (m, 1H), 5.06−4.98 (m, 1H), 4.73 (dd, 1H, J = 6.6, 13 Hz), 4.71−4.67 (m, 1H), 3.92 (s, 3H), 2.95−2.75 (m, 2H), 1.50 (s, 9H), 1.44 (s, 9H); ^1H NMR (DMSO-d_6, 400 MHz) δ 9.74 (br s, 1H, phenol OH), 8.97 (d, 1H, NH, J = 9.0 Hz), 8.06 (d, 1H, NH, J = 6.8 Hz), 7.99 (d, 1H, J = 2.0 Hz), 7.69 (dd, 1H, J = 1.8, 8.5 Hz), 7.25 (d, 1H, J = 8.5 Hz), 5.53 (s, 1H), 6.41 (d, 1H, NHBOC, J = 8.2 Hz), 5.74−5.69 (m, 1H), 5.49 (s, 1H), 5.27 (d, 1H, J = 8.8 Hz), 5.07 (s, 1H), 4.53 (dd, 1H, J = 6.5, 13 Hz), 4.48−4.40 (m, 1H), 3.79 (s, 3H), 2.77−

2.62 (m, 2H), 1.47 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 170.2, 168.1, 167.6, 155.3, 153.3, 151.5, 147.4, 142.6, 140.0, 136.3, 131.8, 131.3, 126.4, 124.4, 116.2, 107.5, 104.4, 82.9, 72.6, 60.6, 58.6, 55.2, 54.8, 49.7, 27.8 (3C), 27.4 (3C), 20.7; IR (film) ν_{max} 3323, 2974, 2923, 2256, 1692, 1656, 1533, 1513, 1364, 1236, 1154 cm^{-1}; FABHRMS (NBA-CsI) m/z 804.1465 (M^+ + Cs, $C_{31}H_{37}N_5O_{12}$ requires 804.1493).

For the minor diastereomer **55**: white film (11.0 mg, 23%); (less polar isomer, R_f = 0.34, 5% $CH_3OH-CHCl_3$); $[\alpha]^{25}_D$ +57 (*c* 0.30, CH_3OH); ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.43 (br s, 1H, phenol, OH), 8.24−8.21 (m, 2H, NH), 7.86 (dd, 1H, *J* = 1.8, 8.5 Hz), 7.46 (d, 1H, NH, *J* = 7.1 Hz), 7.10 (d, 1H, *J* = 8.2 Hz), 6.81 (dd, 1H, *J* = 0.9, 2.2 Hz), 6.21 (d, 1H, NHBOC, *J* = 7.6 Hz), 5.60 (d, 1H, *J* = 0.9 Hz), 5.40 (d, 1H, *J* = 7.6 Hz), 5.24−5.22 (m, 1H), 4.94 (d, 1H, *J* = 8.5 Hz), 4.80−4.75 (m, 2H), 3.96 (s, 3H), 2.81−2.70 (m, 2H), 1.45 (s, 9H), 1.43 (s, 9H); ^{1}H NMR (DMSO-d_6, 400 MHz) 11:1 mixture of conformational isomers at 25 °C (signals coalesce at 55 °C), δ 9.74 (s, 1H, phenol OH), 9.38 and 8.95 (two d, 1H, *J* = 8.6 Hz), 8.13 and 8.12 (two d, 1H, *J* = 1.4 Hz), 7.91 (d, 1H, *J* = 7.2 Hz), 7.75 and 7.73 (two dd, 1H, *J* = 1.8, 8.5 Hz), 7.20 and 7.15 (two d, 1H, *J* = 8.5 Hz), 6.61 (d, 1H, *J* = 1.2 Hz), 6.38 (d, 1H, *J* = 8.2 Hz), 5.83−5.78 (m, 1H), 5.50 and 5.31 (two s, 1H), 5.21 and 5.19 (two d, 1H, *J* = 8.1 Hz), 5.05 (s, 1H), 4.70−4.64 (m, 1H), 4.55 and 4.51 (two dd, 1H, *J* = 7.4, 13 Hz), 3.91 and 3.83 (two s, 3H), 2.74−2.68 (m, 2H), 1.44 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 170.5, 168.7, 168.4, 156.1, 153.6, 152.2, 148.8, 144.0, 140.8, 134.2 (2C), 132.1, 126.3, 123.0, 116.8, 108.9, 104.8, 83.5, 72.5, 61.3, 58.5, 56.3, 55.4, 49.7, 28.5 (3C), 27.9 (3C), 21.7; IR (film) ν_{max} 3364, 2974, 2933, 2246, 1703, 1646, 1533, 1503, 1364, 1229, 1157 cm^{-1}; FABHRMS (NBA-CsI) m/z 804.1471 (M^+ + Cs, $C_{31}H_{37}N_5O_{12}$ requires 804.1493).

The 2D ^{1}H−^{1}H ROESY NMR spectrum (acetone-d_6, 500 MHz) of **55** displayed the following diagnostic NOE cross-peaks: C14-H/C15-H (s), C14-H/N12-H (m), C14-H/C20-H (s), C11-H/C21-H (w), C11-H/N9-H (s), C15-H/C20-H (w), C8-H/C21-H (s), C8-H/C6-H (s), C8-H/N9-H (m), C21−H/N9-H (m), C20-H/C19-H (s), C11-H/CH_2CN (w).

***tert*-Butyl (*P*)- and (*M*)-(8*R*,11*S*,14*R*,15*R*)-15-[(*tert*-Butyldimethylsilyl)oxy]-14-[*N*-[(*tert*-butyloxy)carbonyl]amino]-11-(cyanomethyl)-10,13-dioxo-5-hydroxy-4-methoxy-18-nitro-9,12-diaza-2-oxatricyclo[14.2.2.1^{3,7}]heneicosa-3,4,7(21),16,18,19-hexaene-8-carboxylate (70 and 71).** A solution of **69**[32] (9.0 mg, 11 μmol) in anhydrous degassed DMF (2.2 mL) was treated with a predried (180 °C, 0.1 mmHg, 2 h) mixture of K_2CO_3 (7.7 mg, 55 μmol, 5.0 equiv), $CaCO_3$ (8.4 mg, 84 μmol, 7.5 equiv), 4 Å molecular sieve powder (18 mg, 2 wt equiv) at 25 °C under Ar. The reaction mixture was warmed at 48 °C for 25 h. The resulting mixture was cooled to 25 °C and filtered through Celite (EtOAc, 4 × 5 mL), and the solvent was removed *in vacuo*. PTLC (SiO_2, 30% EtOAc−hexane) afforded **70** and **71** (3.6 mg, 50%; 7.0 mg theoretical based on 1.8 mg recovered **69**, 62%) as a separable 1:1.3 mixture of diastereomers. For major product **71**: white film (2.0 mg, 28%); (less polar isomer, R_f = 0.75, 30% EtOAc−hexane); $[\alpha]^{25}_D$ +75 (*c* 0.085, CH_3OH); ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.45 (br s, 1H, C5-OH), 8.19 (d, 1H, *J* = 9.0 Hz, N9-H), 8.13 (s, 1H, C17−H), 7.78 (dd, 1H, *J* = 1.8, 8.5 Hz, C20-H), 7.31 (d, 1H, *J* = 8.5 Hz, C19-H), 7.22 (d, 1H, *J* = 6.4 Hz, N12-H), 6.67 (dd, 1H, *J* = 1.0, 2.2 Hz, C6-H), 5.82 (d, 1H, *J* = 1.0 Hz, C21-H), 5.55 (d, 1H, *J* = 8.7 Hz, NHBOC), 5.44 (dt, 1H, *J* = 1.0, 9.0 Hz, C8-H), 5.35 (d, 1H, *J* = 3.0 Hz, C15-H), 4.74 (dd, 1H, *J* = 3.0, 8.7 Hz, C14-H), 4.61 (ddd, 1H, *J* = 4.7, 6.4, 10.0 Hz, C11-H), 3.92 (s, 3H, OCH_3), 2.91−2.74 (m, 2H, partially obscured by H_2O, CH_2CN), 1.51 (s, 9H, *t*-BuO_2C), 1.46 (s, 9H, NBOC), 1.00 (s, 9H, *t*-*Bu*Me_2Si), 0.20 (s, 3H, *t*-Bu*Me*$_2$Si), −0.05 (s, 3H, *t*-Bu*Me*$_2$Si); FABHRMS (NBA-CsI) m/z 918.2319 (M^+ + Cs, $C_{37}H_{51}N_5O_{12}Si$ requires 918.2358).

The 2D ^{1}H−^{1}H ROESY NMR spectrum (acetone-d_6, 500 MHz) of **71** displayed the following diagnostic NOE cross-peaks: C19-H/C20-H (m), C11-H/N12-H (w), C11-H/N9-H (s), C14-H/C15-H (s), C14-H/NHBOC (s), C14-H/N12-H (m), C14-H/C17-H (m), C15-H/NHBOC (s), C15-H/N12-H (m), C15-H/C17-H (s), C8-H/C6-H (w), C8-H/N9-H (m), C21-H/C19-H (m), C21-H/N9-H (m).

For the minor diastereomer **70**: colorless oil (1.6 mg, 22%); (more polar product, R_f = 0.40, 30% EtOAc−hexane).

Conversion of 71 to 56 (Correlation of Major Isomers). A solution of **71** (1.8 mg, 2.2 μmol) in THF (0.2 mL) at 0 °C was treated dropwise with a 1.0 M solution of Bu_4NF in THF (4.5 μL, 4.5 μmol, 2.0 equiv) under Ar. The resulting reaction mixture was gradually warmed to 25 °C, stirred for 1 h, and concentrated *in vacuo*. PTLC (SiO_2, 5% $CH_3OH-CHCl_3$) afforded **56** (1.2 mg, 1.5 mg theoretical, 80%) as a white film identical in all respects with authentic material.

Conversion of 70 to 55 (Correlation of Minor Isomers). A solution of **70** (0.9 mg, 1.2 μmol) in THF (0.1 mL) at 0 °C was treated dropwise with a 1.0 M solution of Bu_4NF in THF (2.3 μL, 2.3 μmol, 2.0 equiv) under Ar. The resulting reaction mixture was gradually warmed to 25 °C, stirred for 1 h, and concentrated *in vacuo*. PTLC (SiO_2, 5% $CH_3OH-CHCl_3$) afforded **55** (0.6 mg, 0.77 mg theoretical, 77%) as a white film identical in all respects with authentic material.

***tert*-Butyl (*P*)- and (*M*)-8*R*,11*S*,14*R*,15*R*)-18-Amino-14-[*N*-[(*tert*-butyloxy)carbonyl]amino]-11-(cyanomethyl)-5,-15-dihydroxy-10,13-dioxo-4-methoxy-9,12-diaza-2-oxatricyclo[14.2.2.1^{3,7}]heneicosa-3,4,7(21),16,18,19-hexaene-8-carboxylate (57 and 61).** A solution of either **55** or **56** (6.0 mg, 9.3 μmol) in anhydrous CH_3OH (1 mL) was treated with 10% Pd−C (1.2 mg, 0.2 wt equiv) at 25 °C and stirred under one atmosphere of H_2 for 4 h. The reaction mixture was filtered through a pad of Celite (CH_3OH wash), concentrated *in vacuo*, and dried thoroughly under vacuum to afford **57** and **61** (5.9 mg, 5.9 mg theoretical, 100%) as colorless oils. Both **57** and **61** were somewhat unstable to storage and handling but sufficiently pure to use immediately in the subsequent reactions.

***tert*-Butyl (*P*)-(8*R*,11*S*,14*R*,15*R*)-14-[*N*-[(*tert*-Butyloxy)-carbonyl]amino]-18-chloro-11-(cyanomethyl)-5,15-dihydroxy-10,13-dioxo-4-methoxy-9,12-diaza-2-oxatricyclo-[14.2.2.1^{3,7}]heneicosa-3,4,7(21)16,18,19-hexaene-8-carboxylate (59).** Following the procedure detailed below for **63**, **57** provided **59**: $[\alpha]^{25}_D$ +52 (*c* 0.1, CH_3OH); ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.33 (s, 1H, phenol OH), 8.25 (d, 1H, *J* = 8.2 Hz), 7.63 (s, 1H), 7.50 (d, 1H, *J* = 7.1 Hz), 7.30−7.26 (m, 1H), 7.14 (d, 1H, *J* = 8.3 Hz), 6.72 (s, 1H), 6.16 (d, 1H, NHBOC, *J* = 7.0 Hz), 5.52 (s, 1H), 5.34 (d, 1H, *J* = 8.1 Hz), 5.16−5.10 (m, 1H), 5.86−5.74 (m, 2H), 4.69−4.61 (m, 1H), 3.96 (s, 3H), 2.77−2.69 (m, 2H), 1.48 (s, 9H), 1.44 (s, 9H); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.67 (s, 1H, phenol OH), 8.98 (d, 1H, *J* = 8.4 Hz), 7.77 (d, 1H, *J* = 7.7 Hz), 7.54 (s, 1H), 7.39 (d, 1H, *J* = 8.6 Hz), 7.09 (d, 1H, *J* = 8.6 Hz), 6.58 (s, 1H), 6.34 (d, 1H, *J* = 8.7 Hz), 5.64−5.61 (m, 1H), 5.31 (s, 1H), 5.20 (d, 1H, *J* = 8.4 Hz), 4.99 (dd, 1H, *J* = 4.4, 8.7 Hz), 4.72−4.64 (m, 2H), 3.86 (s, 3H), 2.74−2.61 (m, 2H), 1.48 (s, 9H), 1.44 (s, 9H); IR (film) ν_{max} 3292, 2923, 2851, 2236, 1708, 1646, 1503, 1369, 1236, 1154 cm^{-1}; FABHRMS (NBA-CsI) m/z 793.1278 (M^+ + Cs, $C_{31}H_{37}N_4O_{10}Cl$ requires 793.1253).

The 2D ^{1}H−^{1}H ROESY NMR spectrum (acetone-d_6, 600 MHz) of **59** displayed the following diagnostic NOE cross-peaks: C14-H/N12-H (s), C14-H/C20-H (s), C11-H/N12-H (s), C11-H/C20-H (s), C17-H/C15-OH (s), C11-H/N9-H (s), C11-H/C21-H (w), C15-H/C20-H (s), C15-H/C17-H (w), C8-H/C6-H (m), C8-H/N9-H (m), C21-H/N9-H (w), C20-H/C19-H (s), C11-H/CH_2CN (s).

Representative results of a study of the conversion of **57** to **59** is summarized in Table 5.

***tert*-Butyl (8*R*,11*S*,14*R*,15*R*)-14-[*N*-[(*tert*-butyloxy)carbonyl]amino]-11-(cyanomethyl)-5,15-dihydroxy-10,13-dioxo-4-methoxy-9,12-diaza-2-oxatricyclo[14.2.2.1^{3,7}]-heneicosa-3,4,7(21),16,18,19-hexaene-8-carboxylate (60):** white film; $[\alpha]^{25}_D$ +67 (*c* 0.14, CH_3OH); ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.26 (s, 1H, phenol OH), 8.14 (d, 1H, *J* = 8.3 Hz), 7.53 (d, 1H, *J* = 8.6 Hz), 7.49 (d, 1H, *J* = 8.1 Hz), 7.22 (d, 1H, *J* = 7.2 Hz), 7.09 (dd, 1H, *J* = 2.4, 8.4 Hz), 7.00 (dd, 1H, *J* = 2.4, 8.4 Hz), 6.65 (dd, 1H, *J* = 1.0, 2.2 Hz), 6.24 (d, 1H, NHBOC, *J* = 6.2 Hz), 5.65 (dd, 1H, *J* = 1.0, 2.2 Hz), 5.34 (dt, 1H, *J* = 1.0, 8.4 Hz), 5.14−5.07 (m, 1H), 4.78−4.70 (m, 1H), 4.63 (d, 1H, *J* = 9.4 Hz), 4.59−4.57 (m, 1H), 3.94 (s, 3H), 2.78−2.66 (m, 2H), 1.47 (s, 9H), 1.44 (s, 9H); ^{1}H NMR (CD_3OD, 400 MHz) δ 7.47 (dd, 1H, *J* = 1.8, 8.4 Hz), 7.25 (dd, 1H, *J* = 1.8,

Table 5. Representative Results of the Conversions of 57 and 61 to 59 and 63

compound	solvent	*t*-BuONO/HBF_4 (equiv)	CuCl/$CuCl_2$ (equiv)	result
57	THF	1.6/1.6	6/0	76% **60**
57	THF	1.6/1.6	50/20	23% **59**, 25% **60**
57	CH_3CN	1.6/1.6	50/60	30% **59**, 0% **60**
61	THF	1.3/1.3	50/25	47% **63**, 23% **60**
61	CH_3CN	1.3/1.3	50/60	54% **63**, 0% **60**

8.4 Hz), 7.00 (dd, 1H, J = 2.5, 8.4 Hz), 6.84 (dd, 1H, J = 1.8, 8.4 Hz), 6.51 (dd, 1H, J = 1.0, 2.2 Hz), 5.48 (dd, 1H, J = 1.0, 2.2 Hz), 5.22 (s, 1H), 4.96 (d, 1H, J = 3.9 Hz), 5.54 (dd, 1H, J = 6.3, 7.0 Hz), 4.37 (d, 1H, J = 3.9 Hz), 3.85 (s, 3H), 2.64−2.61 (m, 2H), 1.41 (s, 9H), 1.38 (s, 9H); IR (film) ν_{max} 3288, 2974, 2925, 2247, 1702, 1648, 1587, 1506, 1368, 1330, 1212, 1160 cm^{-1}; FABHRMS (NBA-CsI) m/z 759.1664 (M^+ + Cs, $C_{31}H_{38}N_4O_{10}$ requires 759.1642).

***tert*-Butyl (*M*)-(8*R*,11*S*,14*R*,15*R*)-14-[*N*-[(*tert*-butyloxy)-carbonyl]amino]-18-chloro-11-(cyanomethyl)-5,15-dihydroxy-10,13-dioxo-4-methoxy-9,12-diaza-2-oxatricyclo-[14.2.2.1^{3,7}]heneicosa-3,4,7(21),16,18,19-hexaene-8(*R*)-carboxylate (63).** A solution of **61** (6.2 mg, 9.7 μmol) in anhydrous CH_3CN (0.2 mL) was treated with HBF_4 (48% aqueous solution, 2.3 mg, 1.6 μmol, 12.6 μmol, 1.3 equiv) at 0 °C under Ar, and the resulting solution was stirred at 0 °C for 10 min before being warmed to 25 °C for 30 min. The reaction mixture was recooled to 0 °C and treated dropwise with *tert*-butyl nitrite (1.3 mg, 1.5 μL, 12.6 μmol, 1.3 equiv) and the resulting reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was cooled to −20 °C and immediately added to an aqueous solution (0.4 mL) containing CuCl (48 mg, 0.48 mmol, 50 equiv) and $CuCl_2$ (78 mg, 0.24 mmol, 60 equiv) at 0 °C, and the heterogeneous mixture was warmed to 25 °C and stirred for 1.5 h. The reaction mixture was poured into saturated aqueous NH_4Cl (1 mL) and extracted with EtOAc (4 × 1 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (2 mL), H_2O (2 mL), and saturated aqueous NaCl (2 mL), dried (Na_2SO_4), and concentrated *in vacuo*. PTLC (SiO_2, eluted twice with 5% CH_3OH−$CHCl_3$) afforded **63** (3.5 mg, 6.4 mg theoretical, 54%) as a white film: $[\alpha]^{25}_D$ +49 (*c* 0.1, CH_3OH); ^1H NMR (acetone-d_6, 400 MHz) δ 8.35 (s, 1H, phenol, OH), 8.17 (d, 1H, J = 8.6 Hz), 7.63 (s, 1H), 7.50 (dd, 1H, J = 0.8, 8.4 Hz), 7.49 (dd, 1H, J = 2.0, 8.4 Hz), 7.22 (d, 1H, J = 8.4 Hz), 6.69 (dd, 1H, J = 1.0, 2.2 Hz), 6.16 (d, 1H, NHBOC, J = 7.0 Hz), 5.60 (s, 1H), 5.38 (d, 1H, J = 8.6 Hz), 5.14−5.09 (m, 1H), 4.78 (d, 1H, J = 8.4 Hz), 4.73 (dd, 1H, J = 7.0, 7.4 Hz), 4.68−4.61 (m, 1H), 3.96 (s, 3H), 2.80−2.71 (m, 2H), 1.48 (s, 9H), 1.44 (s, 9H); ^1H NMR (DMSO-d_6, 400 MHz) δ 9.67 (s, 1H, phenol OH), 8.94 (d, 1H, J = 8.8 Hz), 7.99 (d, 1H, J = 7.8 Hz), 7.51 (s, 1H), 7.40 (d, 1H, J = 8.4 Hz), 7.19 (d, 1H, J = 8.4 Hz), 6.56 (s, 1H), 6.33 (d, 1H, J = 8.6 Hz), 5.59−5.53 (m, 1H), 5.43 (s, 1H), 5.25 (d, 1H, J = 8.8 Hz), 4.96 (dd, 1H, J = 4.4, 8.6 Hz), 4.64−4.56 (m, 2H), 3.87 (s, 3H), 2.72−2.59 (m, 2H), 1.49 (s, 9H), 1.44 (s, 9H); IR (film) ν_{max} 3286, 2971, 2920, 2849, 2240, 1699, 1648, 1506, 1363, 1231, 1155 cm^{-1}; FABHRMS (NBA-CsI) m/z 793.1284 (M^+ + Cs, $C_{31}H_{37}N_4O_{10}Cl$ requires 793.1253).

The 2D ^1H−^1H ROESY NMR spectrum (acetone-d_6, 600 MHz) of **63** displayed the following diagnostic NOE cross-peaks: C14-H/N12-H (m), C14-H/C17-H (m), C11-H/N9-H (s), C8-H/N9-H (m), C21-H/N9-H (m), C20-H/C15-OH (w), C17-H/C15-H (s), C6-H/C8-H (w), C20-H/C19-H (s), C11-H/CH_2CN (s).

Representative results of a study of the conversion of **61** to **63** are summarized in Table 5.

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Supporting Information Available: Full experimental details and characterization for **16**, **34**, **36**, improvements in the preparation of **20**/**49**, **37**, **38**, **44**−**47**, **65**−**69**, and **72**−**82**, and ^1H NMR spectra of all intermediates detailed herein (83 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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