Synthesis of Modified Carboxyl Binding Pockets of Vancomycin and Teicoplanin†

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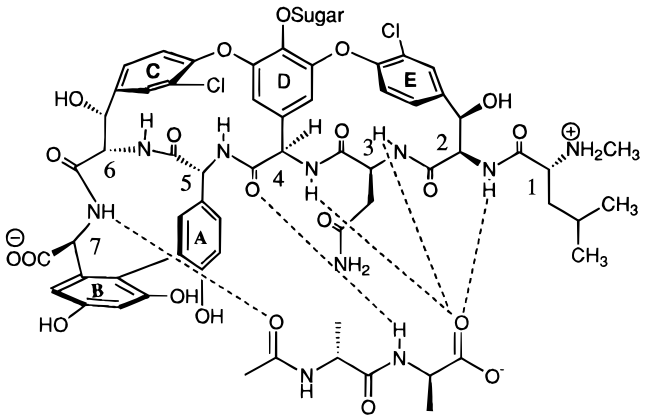
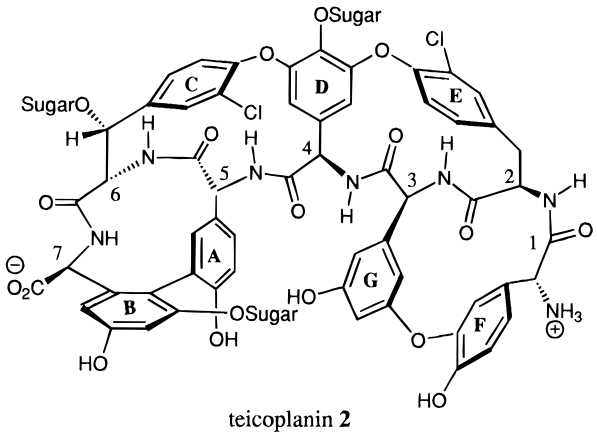
Sixteen-membered macrocycle **3** and 16+14 bicyclic compound **4**, incorporating a terminal primary hydroxyl group in the peptide sequence, have been designed and synthesized. The syntheses feature the use of an efficient cycloetherification based on an intramolecular S_NAr reaction for the formation of biaryl ether bonds. Cyclization of linear tetrapeptide **30**, prepared via a convergent [2+2] segment coupling between **26** and **29**, gave macrocycle **31** (P configuration) as a single isolable atropisomer. Removal of the Boc protecting group afforded the modified carboxyl binding pocket of vancomycin **3**. A sequential 2-fold intramolecular S_NAr reaction has been used to construct the model bicyclic system (i.e. **4**) of the **D**-O-**E**-**F**-O-**G** ring of teicoplanin. Cyclization conditions (CsF, DMF, room temperature) are sufficiently mild that the configuration of the racemization-prone arylglycine residue was not affected. Chiral building blocks such as D-(1*R*)-[2-[(*tert*-butyldimethylsilyl)oxy]-1-[3-(allyloxy)phenyl]ethyl]amine **16**, and L-(*S*)-*N*-Boc-[3-(isopropyloxy)phenyl]glycine (**32**) were synthesized employing Evans' asymmetric azidation method, while L-(*S*)-4-fluoro-3-nitrophenylalanine methyl ester **23** was prepared using Schöllkopf's bislactim ether as chiral glycine template. Compound **3** showed interesting conformational properties compared to vancomycin and its binding with Ac-D-Ala was studied by NMR titration experiments. A dissociation constant ($K_d = 5 \times 10^{-4}$) was calculated by a curve fitting method. Compound **4** is currently the most advanced synthetic intermediate toward the total synthesis of teicoplanin.

Introduction

The glycopeptide group of antibiotics,[1] exemplified by vancomycin (**1**) and teicoplanin (**2**) (Figure 1), is important in the treatment of infections caused by Gram-positive organisms, especially those which are β-lactam resistant. The antibacterial activity of this family of antibiotics arises from specific binding of the glycopeptide to bacterial cell wall precursors terminating in the sequence D-Ala-D-Ala.[2] After more than 30 years of clinic use, resistance to drugs of vancomycin family has been recognized since the late 1980s. Biosynthesis of a D-Ala-D-lactate depsipeptide and its incorporation as the terminal peptidoglycan of resistant bacteria has been proposed as the principal mechanism of resistance.[3] Since vancomycin-resistant enterococci (VRE) also carry resistance to virtually all other known antibiotics, the prognosis for patients with such refractory infections is grim.



vancomycin **1** Ac- D-Ala-D-Ala Complex



teicoplanin **2**

Figure 1.

This growing problem of resistance has recently rekindled interest in this field.[4]

The complex structure of vancomycin makes it a challenging synthetic target.[5] Since the first successful

† Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday.

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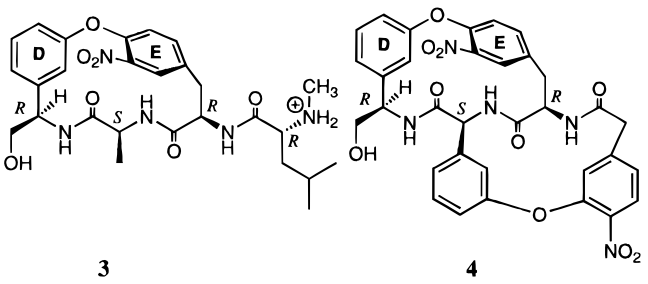
synthesis of a model **C**-O-**D** ring of vancomycin by Hamilton's group in 1986,[6] remarkable achievements have been registered in recent years. Biomimetic synthesis of bicyclic **C**-O-**D**-O-**E** ring by Evans' [7] and Yamamura's group[8] as well as Evans' brilliant, and until now, only synthesis of the 12-membered **AB** fragment[9] illustrate the notable progress made toward the long awaited total synthesis of vancomycin.

Recent work in our laboratory has demonstrated that the intramolecular nucleophilic aromatic substitution (S_NAr)[10] reaction offers an exceptionally efficient method of synthesizing macrocycles containing a biaryl ether bridge. Biaryl ether formation with concomitant ring closure under extremely mild conditions (K_2CO_3 or CsF, DMF, rt) constitutes the basic strategy of our approach.[11] This method has been successfully applied to the synthesis of the naturally occurring 17-membered cyclic tripeptide K-13,[12] 16-membered vancomycin models,[13] 14-membered teicoplanin,[14] and bouvardin models.[15] Shortly after the disclosure of our work, other groups, notably, those of Rama Rao,[16] Boger,[17] Rich,[18a] Pearson,[18b] and very recently Evans,[19] have employed this methodology in the realization of their synthetic strategies.



3 **4**

Figure 2.

In the search for synthetic analogs having enhanced affinity toward the D-Ala-D-lactate, we have designed molecules **3** and **4** (Figure 2) as modified carboxyl binding pockets of antibiotics.[20] We hypothesized that the primary hydroxy group of compounds **3** and **4** could, *a priori*, lead to increased affinity toward N-Ac-D-Ala-D-lactate. This polar function may be considered as a hydrogen-bond donor which, if the solution conformation permitted, could form a hydrogen bond with the ester function (hydrogen acceptor) of D-Ala-D-lactate, thus restoring the four hydrogen bonds required for inhibiting cell wall biosynthesis of modified peptidoglycan in vancomycin-resistant bacteria. Hamilton *et al.*[21] have recently reported a new family of neutral, multidentate receptors for carboxylate recognition and have demonstrated a dramatic increase in binding affinity when a hydroxyl group was incorporated in their receptor. The present paper details the successful synthesis of compounds **3** and **4** and presents additional peripheral observations recorded along the way.

Results and Discussion

Synthesis of D-O-E Ring 3. Our strategy for the synthesis of **3**, illustrated in Scheme 1, features an intramolecular S_NAr reaction as the key ring closure step. D-(*R*)-[3-(allyloxy)phenyl]glycine methyl ester was prepared using Evans' asymmetric electrophilic azidation method[22] as depicted in Scheme 2. Allyl protection of (3-hydroxyphenyl)acetic acid (**8**) followed by incorporation of chiral auxiliary *R*-**10** via the mixed anhydride method afforded imide **11**. Azidation employing a modified work-up procedure afforded **12**. The de of this reaction was higher than 85% and two diastereoisomers were readily separated by careful flash chromatography. Treatment of **12** with LiOOH gave the α-azido acid **13** which was immediately transformed into methyl ester **14**. Reduction of **14** with $SnCl_2$ in methanol[23] afforded α-amino ester **15** whose optical purity (95%) was determined by transformation into its (*S*)-lactamide derivative **17**. We noted that transesterification of **12** using magnesium methoxide led to significant racemization. Conversion

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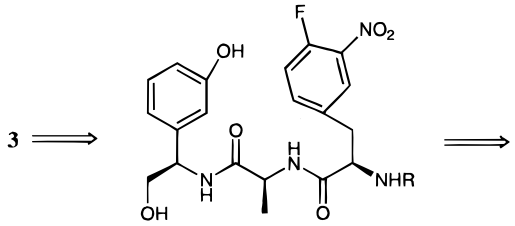
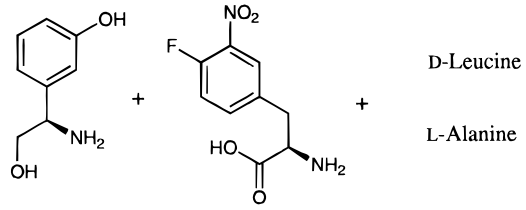
Scheme 1

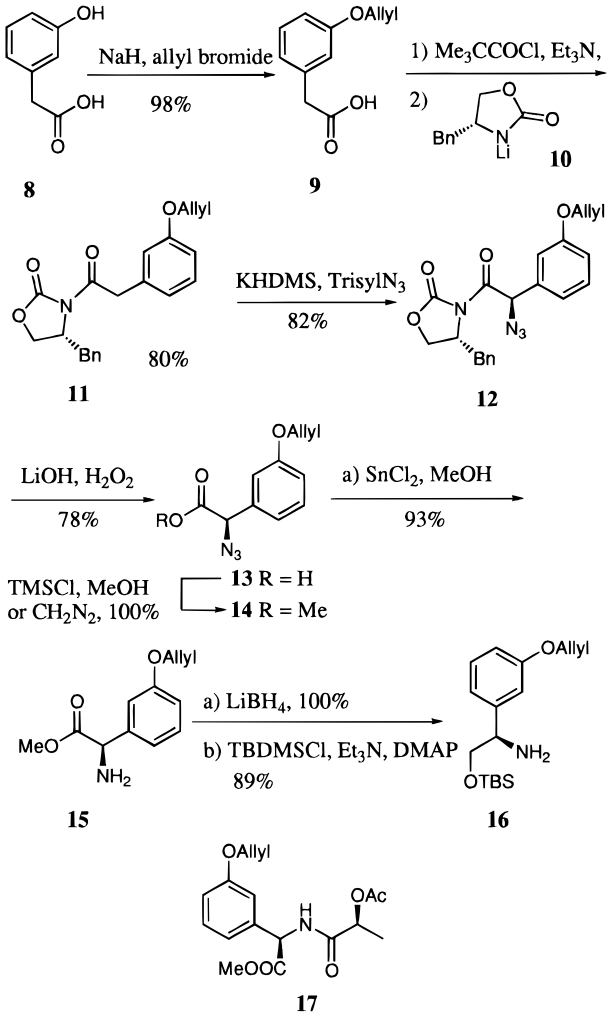


5 R = Boc or D-*N*-Boc-*N*-methyl Leu



6 **7**

Scheme 2

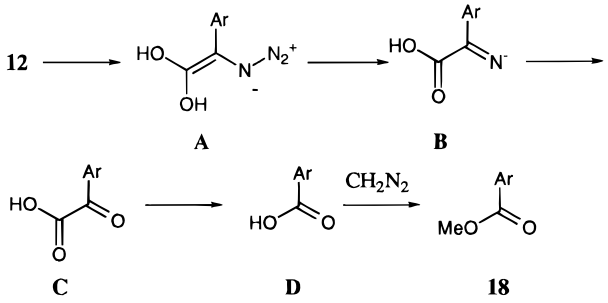


8 **9** **10** **11** **12** **15** **16** **17**

of **15** into TBS-protected amino alcohol **16** was realized uneventfully via a two-step sequence.

3-(Allyloxy)benzoic acid, isolated as the methyl ester **18** after CH_2N_2 treatment, was also formed in the hydrolysis of **12**. A control experiment showed that **18** resulted from the decomposition of the corresponding α-azido acid **13**. Thus, pure **13** obtained by flash chromatography was decomposed under hydrolytic conditions

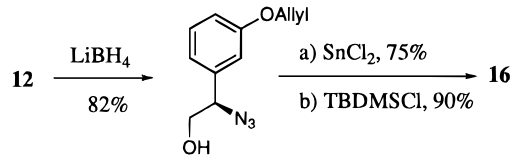
Scheme 3



A **B** **C** **D** **18**

Ar: *m*-CH_2=$CHCH_2O$-C_6H_4

Scheme 4



19 **16**

(LiOH, H_2O_2) to give benzoic acid which was also isolated as the methyl ester **18**.[24] While no detailed mechanistic studies have been carried out, a reaction scenario was proposed as shown in Scheme 3. Enol **A** is formed followed by nitrogen extrusion to give the imino ketone **B** which was then hydrolyzed to α-keto acid **C** and ultimately, to the benzoic acid **D**. This mechanism was reminiscent of that of *N*-haloamino acid whose decomposition mechanism has been investigated in detail.[25] To the best of our knowledge, such a decomposition pathway has not yet been reported though α-azido acids are common synthetic intermediates. While the above-mentioned instability of α-azido acid may not be general, degradation of several other α-aryl-α-azido acids has indeed been observed in our laboratory.[26]

A more direct route for converting **12** into **16** is shown in Scheme 4. Reductive removal of chiral oxazolidinone with $LiBH_4$[27] gave the corresponding alcohol **19**, which was transformed into **16** by way of straightforward reduction−protection steps.

(*R*)-4-Fluoro-3-nitrophenylalanine (**23**) was synthesized using Schöllkopf's bislactim ether[28] as chiral glycine template under conditions that we have developed in related studies[15] (Scheme 5). Thus the higher order (H.O.) organocuprate of **21** reacted with 4-fluoro-3-nitrobenzyl bromide at −78 °C to afford the coupling product **22** in 90% yield. At 0 °C, some dialkylated product was observed. Mixed H.O. organocuprate R(2-Th)$CuCNLi_2$[29] could also be used to afford compound **22**, albeit in moderate yield. Mild acidic hydrolysis of **22** (TFA in CH_3CN) afforded the desired (*R*)-amino ester (**23**, 87%)

(24) While this control experiment did show the instability of α-azido acid under hydrolytic conditions (LiOH and H_2O_2 in THF−H_2O), it is also possible, as suggested by a referee that byproduct **18** could directly result from compound **12** before hydrolysis.

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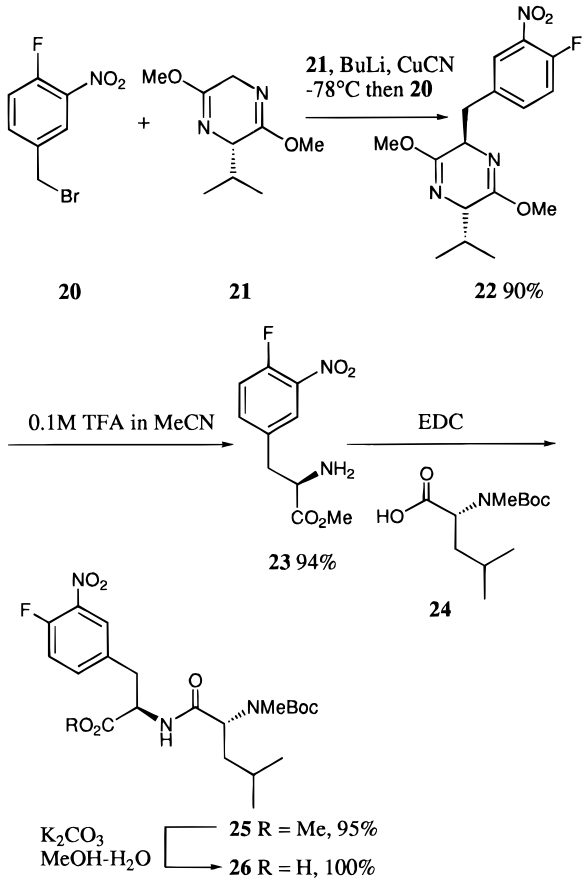
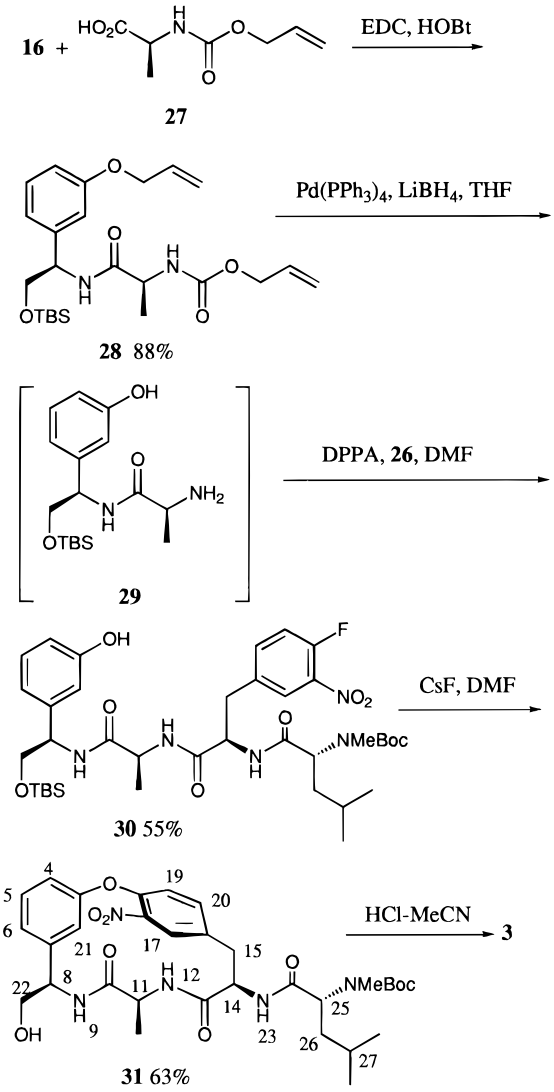
Scheme 5



Scheme 6



which was coupled with D-(*R*)-*N*-Boc-*N*-methylleucine to provide the dipeptide **25** in 93% yield. Hydrolysis of the methyl ester gave the acid **26** in quantitative yield.

With the desired amino acids in hand, the synthesis of the 16-membered macrocycle **3** was accomplished as shown in Scheme 6. Coupling of **16** with L-(*S*)-*N*-alloc-alanine **27** produced dipeptide **28** in 84% yield. Simultaneous reductive deprotection of *O*-allyl and *N*-alloc groups using the reagent combination $LiBH_4-Pd(PPh_3)_4$ (catalytic) recently developed in our laboratory[30] furnished the corresponding amino alcohol **29**. The use of $LiBH_4$ was essential as other nucleophilic reagents such as $NaBH_4$ and amines led to a significant amount of *N*-allylated product. The crude amino alcohol **29** thus obtained was directly coupled with the dipeptide **26** (DPPA,[31] DMF, Et_3N)[32] to give tetrapeptide **30** in 55% overall yield. Little, if any, epimerization occurred in this reaction. However, if EDC or DCC was employed as coupling agent instead of DPPA, racemization at the chiral center of amino ester **23** was observed, leading to two separable diastereoisomers in a 2/1 ratio.

Treatment of a DMF solution of **30** with 6 equiv of K_2CO_3 at room temperature did furnish the cyclized product **31** but the conversion was low and longer reaction time led to degradation, indicating that **30** was not fully stable. To our satisfaction, macrocyclization of **30** proceeded smoothly using anhydrous CsF in dry DMF (0.01 M) at rt.[14] Under these conditions, deprotection of the primary alcohol and cyclization occurred in one pot to afford the 16-membered macrocycle **31** as a single isolable atropisomer in 63% yield. The newly created chirality resulting from the restricted rotation of the biaryl ether bond was determined by NOE techniques (*vide infra*) to have a P configuration (helix nomenclature)[33] as shown in Scheme 6.

A major concern at the outset of these cyclization studies was participation of the primary hydroxy group as a potential nucleophile. In principle, two side reactions were possible: (i) an intramolecular acyl transfer reaction leading to a depsipeptide; (ii) nucleophilic attack of the fluoro nitro aromatic system by the hydroxy group leading to a 14-membered macrocycle via formation of an aryl−alkyl ether bond. A carefully controlled experiment showed that, under the above mentioned cyclization conditions, deprotection of the TBS ether proceeds before

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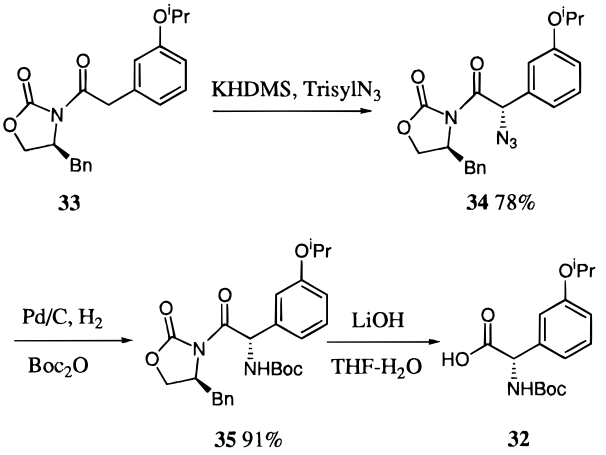
(31) Abbreviations used: DPPA, diphenylphosporyl azide; TFA, trifluoroacetic acid; DCC, 1,3-dicyclohexylcarbodiimide; EDC, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride; HOBt, 1-hydroxybenzotriazole hydrate.

(32) Shioiri, T.; Ninomiya, K.; Yamada, S.-I. *J. Am. Chem. Soc.* **1972**, *94*, 6203−6205.

(33) The configuration (P or M) of the atropisomer was determined by viewing the atropisomer as helix: "For this designation, only the ligands of highest priority in front and in the back of the framework are considered. If the turn from the priority front ligand to the priority rear ligand is clockwise, the configuration is P, if counterclockwise it is M". See: Eliel, E. L.; Willen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons Inc.: New York, 1994; Chapter 14.

Scheme 7



the cyclization. However, neither of these two side reactions was observed.

Finally, removal of the Boc protective group of **31** was carried out with 0.1 N HCl in CH_3CN and after the usual acid−base extraction, an analytically pure compound was obtained whose physical data were in complete agreement with those of the target structure. However, an interesting phenomenon was observed during the course of NMR studies. Well-resolved ^1H NMR spectra of this compound (named **3′**) could be obtained both in $CDCl_3$ and in freshly prepared Me_2CO-d_6 solution at room temperature. Curiously, in Me_2CO-d_6, the intensity of the initial set of resonances (**3′**) decreased and a second set of resonances (named **3**) appeared over a period of several hours. After 12 h at room temperature, the ratio of **3/3′** became 1/1. Pure **3** could be produced by heating an acetone solution of **3′** at 60 °C for 30 min or even at 0 °C over a period of 1 week.

The sufficient stability of **3′** in $CDCl_3$ allowed detailed NMR studies. Both **3** and **3′** had an intense NOE crosspeak in NOESY spectra between H-20 and H-14 indicative of P configuration at the atropstereocenter; hence they are not atropisomers. As epimerization of the peptide backbone in acetone solution seems improbable, this observation could be tentatively explained in terms of conformational changes or different aggregation states. It is worth noting that compound **3′** had negative NOE effects at 268 K, unusual for such a small molecular weight compound (MW = 541) and in such a nonviscous solvent as $CHCl_3$. This is indicative of aggregates.[34] In addition, several NOE cross peaks could only be explained by means of self-association of the molecule, e.g. the NOEs between H-22 and NH-23, NH-9 and N-*Me*H, which may be diagnostic of head-to-tail dimer of **3**. The ^1H NMR and IR spectra of **3′** are concentration dependent which is also consistent with the suggested aggregation. No further efforts have been devoted to defining the exact conformational properties of **3′** and in the following discussion, compound **3** refers to the conformer produced after acetone treatment.

Synthesis of the Bicyclic D-O-E-F-O-G Ring of Teicoplanin 4. To proceed to the synthesis of **4**, another nonproteinogenic amino acid, L-(*S*)-*N*-Boc-[3-(isopropyloxy)phenyl]glycine (**32**), was required. Evans' asymmetric azidation method once again proved to be very efficient (Scheme 7). Azidation of **33** under standard conditions afforded a 78% yield of diastereomerically pure **34** which, in the presence of Boc anhydride, was treated with hydrogen over 10% palladium on carbon to give **35**.[35] Hydrolysis of the latter with LiOH furnished the desired amino acid (*S*)-**32** in quantitative yield.

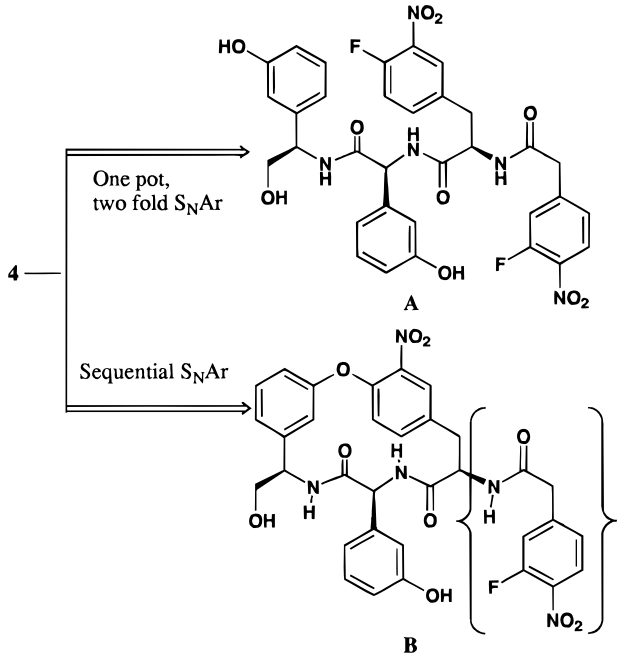


Figure 3.

For the synthesis of **4**, two strategies could be envisaged (Figure 3). The first one, involving a one-pot double intramolecular S_NAr reaction of a linear tetrapeptide **A**, has been successful in the synthesis of the bicyclic **C**-O-**D**-O-**E** ring of vancomycin;[36] the second one involves sequential S_NAr reactions via the monocyclic intermediate **B**. Although it would be interesting to see the outcome of the cyclization of substrate **A** (whether bicyclic 16+14 or 17+13 pathway), the second strategy was preferred for the purpose of differentiating the two nitro groups. Synthesis of the linear tripeptide **40** was achieved as follows (Scheme 8). Coupling of the amino alcohol **16** with the racemization-prone L-(*S*)-*N*-Boc-[3-(isopropyloxy)phenyl]glycine (**32**) (EDC, HOBt) provided the dipeptide **36** in 92% yield. The presence of HOBt is essential to minimize racemization and other coupling conditions, including EDC−$CuCl_2$[37] or DPPA, did not give superior results in terms of diastereomeric purity. Palladium-catalyzed reductive removal of the allyl protecting group[30] afforded compound **37** in 85% yield with less than 5% racemization as determined by NMR analysis. Application of the TBDMSOTf-mediated one step deprotection−protection procedure[38] to **37** provided **38**. This amine was coupled with D-(*R*)-*N*-Boc-4-fluoro-3-nitrophenylalanine (**39**), in turn obtained from **23** via amine protection (Boc) and ester hydrolysis, to furnish the tripeptide **40** in excellent yield. The small amount of undesired diastereoisomer was readily removed by flash chromatography.

Macrocyclization of diastereomerically pure **40** using dry CsF as promotor in DMF (0.01M) gave an 84% yield

(34) For a brief discussion concerning negative NOE effects, see ref 1a.

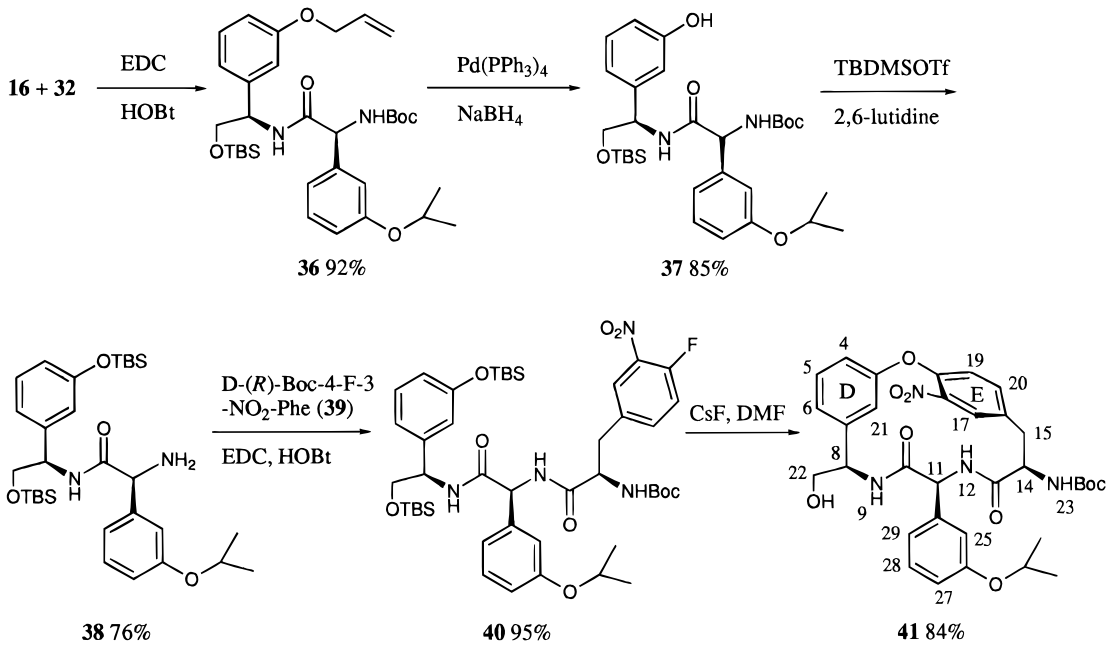
(35) Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 837−838.

(36) Beugelmans, R.; Bois-Choussy, M.; Vergne, C.; Bouillon, J. P.; Zhu, J. *J. Chem. Soc., Chem. Commun.* **1996**, 1029−1030.

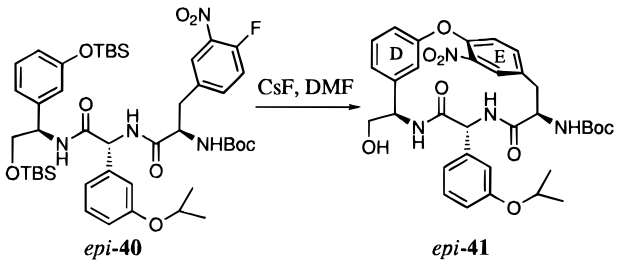
(37) Miyazawa, T.; Otomatsu, T.; Fukui, Y.; Yamada, T.; Kuwata, S. *Int. J. Peptide Protein Res.* **1992**, *39*, 237−244.

(38) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870−876.

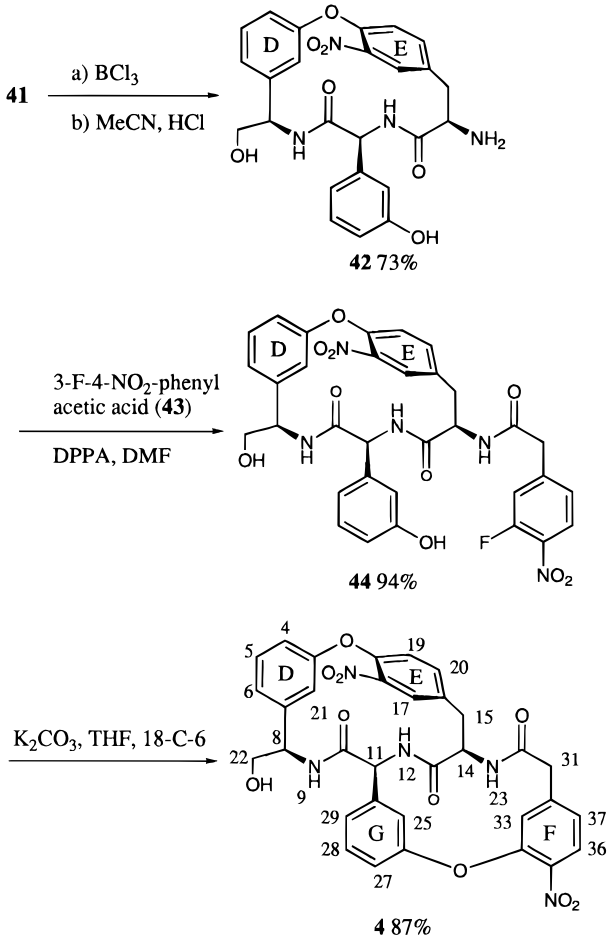
Scheme 8



Scheme 9



Scheme 10



of the desired macrocyclic **D**-O-**E** ring (**41**) as a single atropisomer with the "nonnatural" (P) configuration. To ascertain the absence of racemization in this key ring closure step, racemic amino acid (±)-**32** was prepared via a Strecker synthesis[39] and incorporated into the tripeptide **40** following the previously described synthetic scheme. Flash chromatographic separation then gave the diastereomerically pure compounds **40** (*R*,*S*,*R*) and *epi*-**40** (*R*,*R*,*R*). Cyclization of the latter under conditions identical to that used for **40** afforded the *epi*-**41** macrocycle (Scheme 9) which had an R_f value and physical data completely different from those of **41**. This result convincingly showed that no racemization had occurred under our macrocyclization conditions. Similar observations have recently been disclosed in related cyclization studies carried out by Boger's[17b] and Evans'[19] groups. It is interesting to note that CsF[40] played a dual role in this cyclization reaction: it removed the TBS protecting group and promoted the cyclization in a one-pot fashion.

The completion of the synthesis of the bicyclic **D**-O-**E**-**F**-O-**G** ring model **4** is shown in Scheme 10. Cleavage of the Boc group and the isopropyl ether was realized in a single step by treatment of **41** with BCl_3 followed by acidic workup and simple acid−base extraction, providing pure amino compound **42** in 73% yield. DPPA-promoted coupling between **42** and the known (3-fluoro-4-nitrophenyl)acetic acid (**43**)[14] gave the desired macrocyclization precursor **44** in 94% yield. This reaction is noteworthy in that the two hydroxy groups do not need to be protected. After studying different reaction parameters, the optimized conditions for the cyclization of **44**, leading to the bicyclic **D**-O-**E**-**F**-O-**G** ring compound **4** in 87% yield, were found to be 10 equiv of K_2CO_3 in THF in the presence of crown ether (18-C-6).[41] Given the obvious strain in this bicyclic system, the high yield and mild

(39) (a) Mai, K.; Patil, G. *Org. Prep. Proced. Int.* **1985**, *17*, 183−186. (b) Zhu, J.; Beugelmans, R.; Bigot, R.; Singh, G. P.; Bois-Choussy, M. *Tetrahedron Lett.* **1993**, *34*, 7401−7404.

(40) Clark J. H. *Chem. Rev.* **1980**, *80*, 429−452.

Table 1. ^{1}H NMR Assignment of 3 and NOE Observed (CD_3CN, 300 K)

proton	chemical shift	NOE
H17	7.90, d	H15
H20	7.75, dd	H15′, **H14**, H21, H19
NH9	7.31, d	H22, H11, H8, H21, NH12
H5	7.29, t	H4, H6
H6	7.10, dd	H5
H19	6.99, d	H20
NH12	6.95, d	NH9, H8, H11, H14, MeAla
H4	6.91, DD	H5
H21	6.18, t	H22, H8, NH9
H8	4.76, td	H21, H22, NH9, NH12
H11	4.45, qd	NH9, NH12, MeAla
H14	4.33, dd	**H20**, NH12, N15′, H15
H15′	3.59, dd	H20, H14, H15
H22	3.46, d	NH9, H21, H8
H15	3.27, dd	H17, H14, H15′
H25	3.18, dd	
N-Me	2.40 s	
H26′	1.65 m	
H26	1.35 m	
CH_3(Ala)	1.25, d	H11, NH12
H27	0.95 m	
CH_3(Leu)	0.88, d	
CH_3(Leu)	0.86, d	

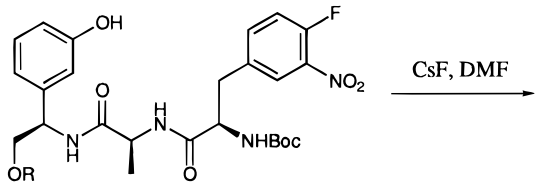
conditions of this second macrocyclization are remarkable. The bicyclic **D**-O-**E**-**F**-O-**G** ring model, obtained in 28% overall yield from the first peptide coupling reaction, is the most advanced synthetic intermediate to date for the total synthesis of teicoplanin and related antibiotics.

Stereochemistry of Atropdiastereoisomers and Conformational Studies. Due to restricted rotation of the biaryl ether bond across the 16-membered macrocycle and on the basis of our previous synthesis of model **C**-O-**D** rings,[13] formation of two atropisomers may be anticipated in the cyclization of compounds **30** and **40**. Much to our surprise, cyclization of **30** or **40** gave the corresponding cyclic compounds **31** or **41**, respectively, as single isolable atropisomers. The configuration of the newly formed chiral atropstereocenter was determined from detailed NMR analysis of the final compound **3**. Initial studies were carried out in Me_2CO-d_6 solution, and although the resolution was good, the overlap of H-14 and H-11 proton signals made the stereochemical assignment difficult. After screening of conventional deuterated solvents, we found that MeCN-d_3 was the best choice for our purpose. In this solvent, both **3** and **41** adopt a single conformation and the ^{1}H NMR signals could be fully assigned from 2D ^{1}H−^{1}H COSY 90, NOEDIFF, and 2D NOESY experiments. The ^{1}H NMR assignments and NOE effects observed for compound **3** are listed in Table 1.

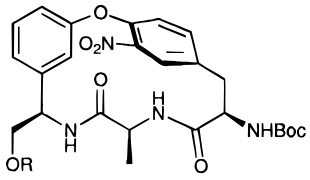
The easy identification of H-17 (downfield) *ortho* to the nitro function allowed assignment of H-20, and subsequently of H-19; while the proton H-21, whose shift to high field is characteristic of a cyclic structure, led to the localization of H-4, H-5, and H-6. The methyl protons of alanine, which showed a distinct doublet at $\delta = 1.25$ ppm (d, $J = 7.2$ Hz), served to assign H-11, and hence NH-12. The NH-9 resonance was established from its coupling with H-8 which, in turn is coupled to the two H-22 protons. Through these iterative COSY and NOESY studies, all the protons were thus unambiguously located. An intense NOE, characteristic of a P configuration for the atropstereocenter, was observed between

(41) The following conditions have also been tested for closing the 14-membered ring: CsF−DMF, K_2CO_3−DMF, K_2CO_3−THF, K_2CO_3−MeCN, K_2CO_3−DMSO. None of these gave satisfactory results.

Scheme 11



45a R = H
45b R = Me

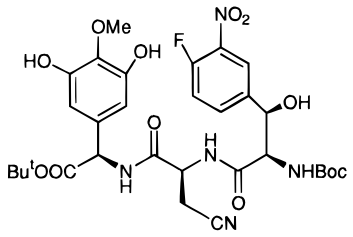


46a R = H
46b R = Me

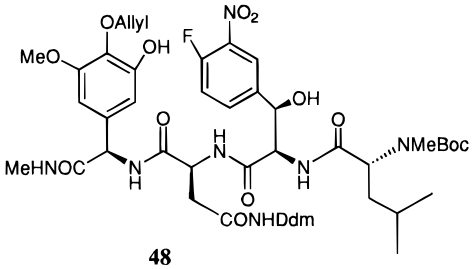
H-20 and H-15′, and more importantly between H-20 and H-14. No NOE was observed between H-17 and H-14, thus eliminating the possibility of an M configuration for the atropstereocenter. Full assignments of the spectra of **41** and **4** were made in an entirely analogous way. The atropstereoisomerism of compound **41** was determined by spectra recorded in MeCN-d_3 at 313 K. Once again, the NOE crosspeak between H-20 and H-14 was highly indicative of a P configuration for the atropstereocenter. A conformational search of compound **3** revealed that for the atropisomer with P configuration, the distance between H-14 and H-20 is 2.71 Å, while that between H-14 and H-17 is 4.39 Å. Similarly, for the M configuration, the distances between H-14 and H-20, and between H-14 and H-17 were found to be 4.38 and 2.72 Å, respectively. These computational results are in full agreement with our NOE observations.

In the course of these studies, we observed an interesting conformational property of compounds **3** and **41**. From Williams' classic studies of the vancomycin structure, it is known that the carboxylate binding pocket of the antibiotic is formed only in the presence of the cell wall peptide. In its absence, three amide protons, NH-9, NH-12, and NH-23, were oriented alternately up−down−up, a usual arrangement found in the normal β-pleated sheet form. Significantly, NOE crosspeaks between NH-12 and NH-9 for compound **3** and between NH-12, NH-9, NHBoc, and H-17 for compound **41** were found in both acetone and acetonitrile solution. These observations established that NH-12 of Ala had rotated from its "normal" position at the "back" of the molecule to the "front" face of the structure and that the conformer needed to bind the same carboxylate function was significantly populated in both solvents. The low energy requirement for pocket formation in compound **3** and **41** could derive from the fact that the amino acids have the *R*, *R*, *S*, and *R* configuration at positions 1, 2, 3, and 4 from the *N*-terminus.

The high atropdiastereoselectivity observed in the formation of **3** and **41** is unique. To determine if the presence of the primary hydroxy function may play a role (e.g. via hydrogen bonding with the nitro group) in the stereoselective ring formation, compounds **45a** and **45b** were prepared. Cyclization of **45a** and **45b** under the standard conditions (CsF, DMF) again gave single atropisomers **46a** and **46b**, respectively, in 75% yield (Scheme 11). This control experiment shows that the primary



47



48

Figure 4.

hydroxy group is not responsible for the observed atropstereoselectivity in the cyclization of **30** and **40**.

Boger *et al.*[17b] and Evans *et al.*[19] have very recently carried out the cyclization of **47** and **48** (Figure 4) and have reported the formation of the two possible atropisomers with a slight preference for the nonnatural one (P configuration). Intrigued by these subtle differences in terms of atropdiastereoselectivity, we carried out a detailed computational study of compounds **30** and **47**. While the result is indeed in agreement with the preferential formation of the P configuration,[42] we found that the difference in conformational properties between **30** and **47** is not significant enough to account for the higher atropdiastereoselectivity of **30** *vs* **47**. Further studies are in progress to understand the intrinsic atropdiastereoselectivity observed in the above-mentioned cyclization.

Binding Studies. The initial motivation in synthesizing compounds **3** and **4** was to enhance the affinity with Ac-D-Ala-D-lactate by means of the primary hydroxy group. The binding properties of **3** with Ac-D-Lact were studied by ^{1}H NMR titration experiments. Because there is a rapid exchange between the free and bound species, the observed chemical shifts are weighted averages of the free (δ_f) and bound (δ_b) species under conditions of fast exchange on the NMR time scale. As the amount of AcLact is increased, the signals of **3** shift progressively toward those of the complexed form. The molar fraction (X) of free substrate **3** in the equilibrium mixture can be expressed as shown in eq 1 where $\Delta\delta_{max} = \delta_b - \delta_f$, $\Delta\delta_{obs} = \delta_{obs} - \delta_f$

$$X = 1 - (\Delta\delta_{obs}/\Delta\delta_{max}) \quad (1)$$

The dissociation constant K_d can be expressed by eq 2 where $[S]_0$ is the initial concentration of **3** and $[R]_0$ is the initial concentration of AcLact:

$$K_d = X\,[[R]_0 - (1 - X)\,[S]_0]/1 - X \quad (2)$$

The chemical shift change of NH-12 was subjected to a curve fitting method.[43] In connection with the above relationship (eq 2), a dissociation constant (K_d) of 5×10^{-4} between **3** and Ac-D-lactate has been determined. About 83% of **3** was present in the bound form when 1.05 equiv of Ac-D-lactate was added. This value compares favorably to the binding between vancomycin and Ac-D-Ala where only 69% of the antibiotic was in the complexed form at the highest concentration of Ac-D-Ala.[44]

The proton assignment of bound **3** was made by a ^{1}H−^{1}H COSY technique. It was seen that almost all the protons of compound **3** were influenced by the binding. A surprising observation was that the chemical shift of NH-9 was almost unchanged upon addition of AcLact. One possible explanation for this is a relatively strong internal hydrogen bonding between the primary hydroxyl group and NH-9 which may have some inhibitory effect on its binding with AcLact.[45] Besides the amide protons, large opposing shielding effects were observed for H-15 methylene protons. Thus, one was shifted to low field ($\Delta\delta = +103$ Hz) and the other to high field ($\Delta\delta = -83$ Hz). Another major perturbation after addition of Ac-D-lactic acid involved the H-20 proton (from 7.78 to 7.71 ppm) which was shifted downfield relative to H-17 (from 7.67 to 7.75 ppm). Similar opposed shielding effects of H-17 (upfield) and H-20 (downfield) have been observed upon complex formation between vancomycin and Ac-D-Ala-D-Ala.[44] The slight modification of the relative position of the two aromatic rings **D** and **E** may account for such changes. It is also clear from the values of $J_{\alpha,NH}$ (9.0 Hz for free substrate and 9.62 Hz for the bound form) that no major conformational change such as peptide bond rotation or *cis*−*trans* isomerization takes place on binding. The conformation of **3** in its bound state might be essentially the same as in its free state. Unfortunately, the failure to identify the NH-23 amide proton in the NMR despite the use of different solvents has thus far hampered the definition of the exact structure of the complex.

Interesting biological properties of compounds **3′**, **3**, and **4** were observed and will be detailed elsewhere.

Conclusion

We have described an efficient synthesis of modified binding pockets of vancomycin and teicoplanin (**3** and **4**), employing a unique S_NAr-based macrocyclization technique under conditions sufficiently mild that the configuration of the racemization-prone arylglycine is not

(42) Five thousand conformations of the precursor **45a** and macrocyclic product **46a** were generated by a random search Monte Carlo method and optimized by molecular mechanics minimization using the Macromodel (Version 3.5) program with the AMBER hydrocarbon force field. From these 5000 conformations, only the conformations with energy values within 3.0 kcal/mol compared to the most stable conformation were analyzed. AMBER generated geometries served as starting points for calculating heats of formation with the help of the MOPAC program (Version 5.0) using semiempirical AM1/RHF parameters (Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902−3909). The AM1 calculated heats of formation of the two lowest energy conformers **45a-P** (P configuration)- and **45a-M** (M configuration) which have very similar geometrical features to those of the two atropisomers **46a-P** (P configuration) and **46a-M** (M configuration) were found to be −244.04 and −241.42 kcal/mol, respectively. The torsional angles around the C14−C15 and C15−C16 bonds of **45a-P** are −73°52 and −76°35 while those of **45a-M** are −49°17 and −62°27, respectively. The reduced torsional angles found in the latter create severe steric interactions in the **E** ring between the methyl hydrogen of the Ala moiety and C19 and between NH12 and C17. These unfavorable interactions may explain the greater heat of formation of **45a-M** compared to **45a-P** and suggest the predominant formation of **46a-P**.

(43) Wilcox, C. S.; Cowart, M. D. *Tetrahedron Lett.* **1986**, *27*, 5563−5566.

(44) Convert, O.; Bongini, A.; Feeney, J. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1262−1270.

(45) Adrian, J. C.; Wilcox, C. S. *J. Am. Chem. Soc.* **1992**, *114*, 1398−1403.

affected. The synthesis of **4** represents the most advanced synthetic intermediate toward the total synthesis of teicoplanin. The facile cyclization observed in the synthesis of this highly constrained 16+14 bicyclic compound is remarkable and illustrates the power of the intramolecular S_NAr reaction for the construction of complex molecular frameworks. Further studies toward designing more elaborate models of modified vancomycin binding pocket as well as toward the total synthesis of natural products are being actively pursued.

Experimental Procedure

General procedures and methods for characterization have been described previously.[13b] Melting points are uncorrected.

[3-(Allyloxy)phenyl]acetic Acid (9). To a solution of (3-hydroxyphenyl)acetic acid (**8**, 5.0 g, 32.9 mmol) in THF (500 mL) was added NaH (3.95 g, 98.7 mmol). After 1 h of stirring allyl bromide (11.4 mL, 131.6 mmol) was added, and the resulting reaction mixture was heated to reflux for 15 h. The reaction was cooled to 0 °C, quenched by addition of water, and stirred for 2 h at room temperature. The volatile was evaporated, and the residue was extracted with ether to remove the neutral species. The aqueous phase was then acidified and extracted with dichloromethane. The combined organic phases were washed with brine, dried over Na_2SO_4, and evaporated to give a white solid. Recrystallization from ether−heptane gave **9** as white needles (6.2 g, 98%): mp 78 °C; IR ($CHCl_3$) 3300, 1716, 1580 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.61 (s, 2H), 4.52 (dt, J = 1.5, 5.3 Hz, 2H), 5.23 (qd, J = 1.5, 10.6 Hz, 1H), 5.39 (qd, J = 1.5, 17.3 Hz, 1H), 6.03 (tdd, J = 5.3, 10.6, 17.3 Hz, 1H), 6.80 (m, 2H), 7.20 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 41.9, 69.6, 114.5, 116.8, 118.5, 122.7, 130.4, 134.0, 135.5, 159.6, 178.8; MS m/z 192. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.71; H, 6.24.

(4*R*)-3-[2-[3-(Allyloxy)phenyl]-1-oxoethyl]-4-(phenylmethyl)-2-oxazolidinone (11). A solution of [3-(allyloxy)-phenyl]acetic acid (**9**,1.92 g, 10 mmol) in dry THF (40 mL) was cooled to −78 °C, and Et_3N (1.68 mL, 12 mmol) and redistilled pivaloyl chloride (1.29 mL, 10.5 mmol) were added successively via syringe with stirring. The resulting slurry was stirred at −78 °C for 15 min and at 0 °C for 45 min and then cooled again to −78 °C. In a separate flask, (4*R*)-4-(phenylmethyl)-2-oxazolidinone (2.12 g, 12 mmol) was dissolved in dry THF (40 mL) and cooled to −78 °C, a solution of butyllithium in hexane (7.5 mL, 1.6 M) was added slowly and stirred at −78 °C for another 5 min after completion of the addition. The so-formed metalated oxazolidinone (yellow colored) was transfered via cannula to the flask containing the mixed anhydride. The resulting slurry was stirred for 15 min at −78 °C and then warmed up to room temperature over 90 min. The reaction was quenched by addition of aqueous NH_4Cl, the volatile was removed *in vacuo*, and the aqueous solution was extracted with EtOAc. The combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, EtOAc/heptane = 1/6 then 1/3) to afford compound **11** as a colorless oil (2.81 g, 80%): $[\alpha]_D$ −104° (*c* 2, $CHCl_3$); IR ($CHCl_3$) 1780, 1700, 1386, 1367 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.78 (dd, J = 8.4, 13.4 Hz, 1H), 3.25 (dd, J = 3.3, 13.4 Hz, 1H), 4.12−4.18 (m, 2H), 4.20 (d, J = 15.4 Hz, 1H), 4.30 (d, J = 15.4 Hz, 1H), 4.52 (td, J = 1.5, 5.3 Hz, 2H), 4.66 (tdd, J = 3.3, 7.1 and 13.4 Hz, 1H), 5.28 (qd, J = 1.5, 10.5 Hz, 1H), 5.42 (qd, J = 1.5, 17.3 Hz, 1H), 6.05 (tdd, J = 5.3, 10.5 and 17.3 Hz, 1H), 6.8−7.3 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 37.2, 41.1, 54.8, 65.7, 68.3, 113.2, 116.0, 117.1, 122.0, 126.9, 128.5, 129.2, 133.1, 134.9, 153.1, 158.5, 170.5; MS m/z 351, 174. Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.57; H, 6.07; N, 3.94.

(4*S*)-3-[2-[3-(Isopropyloxy)phenyl]-1-oxoethyl]-4-(phenylmethyl)-2-oxazolidinone (33). Following the procedure detailed for **11**, compound **33** was isolated in 95% yield: $[\alpha]_D$ +51.3° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 1780, 1695, 1595, 1460 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.32 (d, J = 6.0 Hz, 6H), 2.78 (dd, J = 9.4, 13.4 Hz, 1H), 3.27 (dd, J = 3.3, 13.4 Hz, 1H), 4.20 (m, 4H), 4.51 (septet, J = 6.0 Hz, 1H), 4.65 (m, 1H), 6.8−7.3 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 22.0, 37.6, 41.5, 55.2, 66.0, 69.7, 114.6, 117.3, 121.8, 127.2, 128.9, 129.4, 129.5, 135.0, 135.1, 153.3, 158.0, 171.0; MS m/z 354 ($M + H^+$). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 70.88; H, 6.67; N, 3.97.

(2*R*,4*R*)-3-[2-Azido-2-[3-(allyloxy)phenyl]-1-oxoethyl]-4-(phenylmethyl)-2-oxazolidinone (12). To the solution of KHMDS (37 mL, 0.5 M, 18.5 mmol) in dry THF (40 mL), stirred at −78 °C under argon, was added via syringe a precooled (−78 °C) solution of imide **11** (5.4 g, 15.4 mmol) in dry THF (90 mL). The resulting yellow solution was stirred at −78 °C for 30 min, and then a precooled (−78 °C) solution of trisyl azide (5.71 g, 18.5 mmol) in dry THF (50 mL) was introduced via syringe. The reaction was stirred for 4 min at −78 °C (the solution became slightly red) and was then quenched by addition of HOAc (4.4 mL, 76.9 mmol). The cooling bath was removed, and the reaction mixture was stirred at rt for 90 min. Saturated aqueous NH_4Cl (50 mL) was added, and the aqueous layer was extracted with EtOAc. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated. To the above-obtained reaction mixture in acetone (250 mL), NaI (11.5 g, 77.0 mmol) and $NaOAc{\cdot}3H_2O$ (6.3 g, 46.1 mmol) were added and stirring was continued for 3 h at room temperature. Inorganic salt was removed by filtration. The filtrate was evaporated and then partitioned between CH_2Cl_2 and H_2O. The aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, EtOAc/heptane = 1/6) to give the major diastereoisomer **12** (4.95 g, 82%) as colorless oil: $[\alpha]_D$ −201.5° (*c* 4.1, $CHCl_3$); IR ($CHCl_3$) 2110, 1785, 1706, 1387, 1368 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.86 (dd, J = 9.6, 13.3 Hz, 1H), 3.40 (dd, J = 3.2, 13.3 Hz, 1H), 4.08−4.20 (m, 2H), 4.52 (td, J = 1.5, 5.3 Hz, 2H), 4.65 (tdd, J = 3.2, 7.4 and 9.6 Hz, 1H), 5.28 (qd, J = 1.5, 10.4 Hz, 1H), 5.42 (qd, J = 1.5, 17.3 Hz, 1H), 6.05 (tdd, J = 5.3, 10.4 and 17.3 Hz, 1H), 6.30 (s, 1H), 6.9−7.4 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 37.8, 55.8, 63.7, 66.6, 69.1, 115.0, 116.2, 117.9, 121.0, 123.7, 127.7, 129.1, 129.5, 130.2, 133.1, 134.4, 134.9, 152.5, 159.2, 169.4; MS m/z 392, 364, 351. Anal. Calcd for $C_{21}H_{20}N_4O_4$: C, 64.28; H, 5.14; N, 14.28. Found: C, 63.63; H, 5.15; N, 13.83. Minor diastereoisomer: mp 110−112 °C; $[\alpha]_D$ +83.3° (*c* 0.72, $CHCl_3$); IR ($CHCl_3$) 2110, 1784, 1707, 1387, 1368 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.63 (dd, J = 9.1, 13.4 Hz, 1H), 3.40 (dd, J = 3.4, 13.4 Hz, 1H), 4.12 (dd, J = 3.3, 9.1 Hz, 1H), 4.25 (t, J = 9.1 Hz, 1H), 4.56 (td, J = 1.4, 5.2 Hz, 2H), 4.78 (tt, J = 3.4, 9.3 Hz, 1H), 5.27 (qd, J = 1.4, 10.5 Hz, 1H), 5.41 (qd, J = 1.4, 17.2 Hz, 1H), 6.05 (tdd, J = 5.2, 10.4 and 17.2 Hz, 1H), 6.11 (s, 1H), 6.9−7.4 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 37.5, 55.1, 63.5, 66.6, 69.1, 115.1, 116.5, 117.9, 121.2, 127.6, 129.2, 129.5, 130.3, 133.1, 134.5, 134.6, 152.7, 159.4, 169.3; MS m/z 392, 364, 351. Anal. Calcd for $C_{21}H_{20}N_4O_4$: C, 64.28; H, 5.14; N, 14.28. Found: C, 63.93; H, 5.17; N, 13.96.

(2*S*,4*S*)-3-[2-Azido-2-[3-(isopropyloxy)phenyl]-1-oxoethyl]-4-(phenylmethyl)-2-oxazolidinone (34). Following the procedure detailed for **12**, compound **34** was isolated in 95% yield: mp 87 °C; $[\alpha]_D$ +210° (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) 2987, 2106, 1781, 1712, 1600, 1387, 1368 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.33 (d, J = 6.1 Hz, 6H), 2.85 (dd, J = 9.7, 13.4 Hz, 1H), 3.41 (dd, J = 3.2, 13.4 Hz, 1H), 4.1−4.2 (m, 2H), 4.55 (septet, J = 6.1 Hz, 1H), 4.62 (m, 1H), 6.09 (s, 1H), 6.9−7.4 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 21.9, 37.4, 55.5, 63.4, 66.3, 69.9, 115.7, 116.9, 120.3, 127.4, 128.9, 129.3, 130.0, 134.1, 134.8, 152.3, 158.3, 169.2; MS m/z 366 ($M - N_2$), 351. Anal. Calcd for $C_{21}H_{22}N_4O_4$: C, 63.95; H, 5.62. Found: C, 64.13; H, 6.03.

(2*R*)-2-Azido-2-[3-(allyloxy)phenyl][Acetic Acid Methyl Ester (14). To a solution of **12** (3.2 g, 8.1 mmol) in THF (120 mL) and H_2O (40 mL) was added $LiOH{\cdot}H_2O$ (685 mg, 16. 32 mmol) and H_2O_2 (4.6 mL, 40.8 mmol) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C and the volatile was evaporated. The residue was diluted with 20 mL of 0.5 N aqueous $NaHCO_3$ and extracted with ether. The combined organic phase was washed with brine, dried (Na_2SO_4), and evaporated to afford the recovered chiral auxiliary **10** (1.34 g, 93%). The aqueous phase was acidified to pH 1−2 with 3 N

aqueous HCl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried, and evaporated to give the α-azido acid **13** (1.62 g, 85.2%) which was directly esterified with diazomethane to afford the methyl α-azido ester **14** in quantitative yield: IR ($CHCl_3$) 2112, 1742 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.78 (s, 3H), 4.55 (td, J = 1.5, 5.3 Hz, 2H), 4.97 (s, 1H), 5.29 (qd, J = 1.5, 10.5 Hz, 1H), 5.43 (qd, J = 1.5, 17.3 Hz, 1H), 6.05 (tdd, J = 5.3, 10.5, 17.3 Hz, 1H), 6.9−7.4 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 52.9, 65.4, 69.1, 114.2, 115.8, 117.9, 120.2, 130.2, 133.1, 135.4, 159.3, 169.5; MS m/z 247, 205, 188; HRMS m/z 247.0953 ($C_{12}H_{13}N_3O_3$ requires 247.0957).

D-2-Hydroxy-1-[3-(allyloxy)phenyl]ethyl Azide (19). To a solution of compound **12** (1.58g, 4.04 mmol) in Et_2O (50 mL) were added distilled water (218 μL, 12.10 mmol) and $LiBH_4$ (267 mg, 12.10 mmol) at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was quenched by addition of HCl (1 N). The aqueous phases (pH = 4) were extracted with EtOAc. The combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, EtOAc/heptane = 1/1) to afford compound **19** (725 mg, 82%) as a colorless oil: $[\alpha]_D$ −158.6° (*c* 0.76, $CHCl_3$); IR ($CHCl_3$) 3480, 2933, 2115, 1611, 1580 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.70 (m, 2H), 4.55 (td, J = 1.4, 5.3 Hz, 2H), 4.65 (m, 1H), 5.30 (qd, J = 1.4, 10.5 Hz, 1H), 5.42 (qd, J = 1.4, 17.2 Hz, 1H), 6.10 (m, 1H), 6.90 (m, 3H), 7.3 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 66.4, 67.7, 68.9, 113.7, 114.8, 117.9, 119.6, 130.0, 133.0, 137.9, 159.0; MS m/z 219, 202, 187. Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98. Found: C, 60.42; H, 6.26.

D-[3-(Allyloxy)phenyl]glycine Methyl Ester 15. A solution of compound **14** (1.3 g, 5.26 mmol) and $SnCl_2{\cdot}2H_2O$ (2.37 g, 10.52 mmol) in methanol (50 mL) was stirred for 14 h at room temperature. The volatile was evaporated *in vacuo*, and the residue was partitioned between Et_2O and H_2O. The aqueous phase was extracted with Et_2O to remove the neutral species. The aqueous solution was then neutralized with phosphate buffer (pH 7) and extracted with CH_2Cl_2. The combined CH_2Cl_2 phases were washed with brine, dried (Na_2SO_4), and evaporated *in vacuo* to afford pure compound **15** (1.08 g, 93%): $[\alpha]_D$ −98° (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 3400, 1739, 1689, 1583, 1497 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H), 4.52 (td, J = 1.5, 5.3 Hz, 2H), 4.60 (s, 1H), 5.28 (qd, J = 1.5, 10.5 Hz, 1H), 5.42 (qd, J = 5.3, 17.2 Hz, 1H), 6.03 (tdd, J = 5.3, 10.5, 17.2 Hz, 1H), 6.82 (td, J = 1.7, 7.5 Hz, 1H), 6.96 (m, 2H), 7.23 (t, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 52.4, 58.7, 68.9, 113.4, 114.3, 117.6, 119.3, 129.0, 129.8, 133.2, 141.9, 159.0, 174.3; MS m/z 221, 162; HRMS m/z 221.1052 ($C_{12}H_{15}NO_3$ requires 221.1051).

D-[2-[(*tert*-Butyldimethylsilyl)oxy]-1-[3-(allyloxy)-phenyl]ethyl]amine (16). A solution of compound **19** (190 mg, 0.86 mmol) and $SnCl_2{\cdot}2H_2O$ (582 mg, 2.58 mmol) in methanol (15 mL) was stirred for 20 h at room temperature. The volatile was evaporated *in vacuo*, and the residue was partitioned between Et_2O and H_2O. The aqueous phase was extracted with Et_2O to remove the neutral species. The aqueous solution was then basified with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined CH_2Cl_2 phases were washed with brine, dried (Na_2SO_4), and evaporated *in vacuo* to afford pure compound 3-hydroxyphenylglycine methyl ester as a colorless oil (124 mg, 74%) which was used without further purification: $[\alpha]_D$ −14.4° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3300−3500, 2950, 1610, 1490 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.10 (brs, 3H), 3.55 (dd, J = 8.2, 10.7 Hz, 1H), 3.75 (dd, J = 4.2, 10.7 Hz, 1H), 4.01 (dd, J = 4.2, 8.2 Hz, 1H), 4.55 (td, J = 1.3, 5.2 Hz, 2H), 5.30 (qd, J = 1.3, 10.4 Hz, 1H), 5.42 (qd, J = 1.3, 17.3 Hz, 1H), 6.08 (tdd, J = 5.2, 10.4 and 17.3 Hz, 1H), 6.78−6.88 (m, 3H), 7.26 (t, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 57.5, 68.2, 69.0, 113.4, 113.7, 117.1, 119.1, 129.8, 133.5, 144.8, 159.2; MS m/z 162 (M^+ − 31). To a solution of [3-(allyloxy)phenyl]-glycine methyl ester (220 mg, 1.14 mmol) in dry CH_2Cl_2 were added Et_3N (639 μL, 4.56 mmol), DMAP (139.3 mg, 1.14 mmol), and TBDMSCl (515.5 mg, 3.42 mmol) at room temperature. The reaction mixture was stirred for 5 h at room temperature and diluted with aqueous NH_4Cl. The aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, EtOAc:heptane = 1/3 then 1/2) to give compound **16** (311 mg, 89%) as a colorless oil: $[\alpha]_D$ −10.7° (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) 3300−3500, 2990, 1610, 1500 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ −0.1 (s, 6H), 0.85 (s, 9H), 3.58 (dd, J = 8.0, 10.1 Hz, 1H), 3.78 (dd, J = 4.0, 10.1 Hz, 1H), 4.03 (dd, J = 4.0, 8.0 Hz, 1H), 4.50 (td, J = 1.5, 5.3 Hz, 2H), 5.24 (qd, J = 1.5, 10.5 Hz, 1H), 5.39 (qd, J = 1.5, 17.3 Hz, 1H), 6.01 (tdd, J = 5.3, 10.5 and 17.3 Hz, 1H), 6.8−6.9 (m, 3H), 7.18 (t, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −5.4, 18.4, 26.0, 57.6, 68.1, 69.0, 113.5, 114.5, 117.7, 119.6, 129.7, 133.4, 141.7, 159.0; MS m/z 307, 250, 162. Anal. Calcd for $C_{17}H_{29}NO_2Si$: C, 66.40; H, 9.51; N, 4.55. Found: C, 66.25; H, 9.37; N, 4.56.

***N*-(L-2-Acetoxypropionyl)-D-[3-(allyloxy)phenyl]glycine Methyl Ester (17).** A solution of **15** (72.0 mg, 0.33 mmol), (*S*)-2-(acetyloxy)propionyl chloride (118.5 μL, 1.02 mmol), DMAP (42 mg, 0.34 mmol) and Et_3N (173 μL, 1.23 mmol) in CH_2Cl_2 was stirred at 0 °C for 1 h. The reaction mixture was diluted with aqueous NH_4Cl, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography (SiO_2, EtOAc/heptane = 1/2) afforded amide **17** (106.0 mg, 96%): mp 84−85; $[\alpha]_D$ −104.9° (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 3431, 3025, 1738, 1694, 1606, 1513, 1431 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.48 (d, J = 6.8 Hz, 3H), 2.15 (s, 3H), 3.74 (s, 3H), 4.52 (dt, J = 1.5, 5.3 Hz, 2H), 5.23 (q, J = 6.8 Hz, 1H), 5.29 (qd, J = 1.5, 10.4 Hz, 1H), 5.42 (qd, J = 1.5, 17.2 Hz, 1H), 5.51 (d, J = 7.1 Hz, 1H), 6.04 (tdd, J = 5.3, 10.4, 17.2 Hz, 1H), 6.90 (m, 3H), 7.08 (d, J = 7.1 Hz, 1H), 7.28 (t, J = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.6, 21.0, 52.9, 56.1, 69.0, 70.5, 114.0, 115.0, 117.8, 119.5, 130.1, 133.1, 137.6, 159.2, 169.8, 171.1; MS m/z 335, 276. Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31. Found: C, 60.78; H, 6.34.

(3*R*,6*S*)-2,5-Dimethoxy-6-isopropyl-3-(4-fluoro-3-nitrophenyl)-3,6-dihydro-1,4-pyrazine (22). Cuprous cyanide (89.6 mg, 1.0 mmol) was placed in a 25 mL, two-necked round bottomed flask, evacuated with a vacuum pump and purged with argon. The procedure was repeated three times and dry THF (3 mL) was injected. In another 25 mL two-necked flask was introduced the (2*S*)-(+)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (**21**, 358 mL, 2.0 mmol) and dry THF (2 mL). The solution was cooled to −78 °C and *n*-butyllithium (1.6 M, 2 mmol) was added dropwise. After being stirred for 10 min, it was transferred via cannula to the flask containing the cuprous cyanide slurry, precooled to 0 °C. The reaction mixture was further stirred for 5 min after addition, the resulting tan colored solution was then cooled again to −78 °C and a solution of 4-fluoro-3-nitrobenzyl bromide (**20**, 234 mg, 1.0 mmol) in THF (3 mL) was introduced dropwise via syringe. The reaction was stirred at this temperature for 10 min and quenched by addition of 10 mL of aqueous NH_4Cl/NH_4OH (9/1). The aqueous layer was extracted with EtOAc. The combined organic phases were washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, heptane/ether = 10/3) afforded compound **22** as a colorless oil (305 mg, 90%): $[\alpha]_D$ −28° (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) 2980, 1700, 1535, 1350 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.63 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H), 2.16 (m, 1H), 3.16 (d, J = 3.9 Hz, 1H), 3.18 (d, J = 3.9 Hz, 1H), 3.53 (dd, J = 3.4, 3.6 Hz, 1H), 3.70 (s, 3H), 3.73 (s, 3H), 4.30 (ddd, J = 3.4, 3.9, 4.8 Hz, 1H), 7.16 (dd, J = 8.6, 10.7 Hz, 1H), 7.36 (m, 1H), 7.90 (dd, J = 2.2, 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.6, 19.0, 31.8, 38.7, 52.4, 52.5, 55.9, 60.8, 117.7 (d, J = 21 Hz), 127.5, 134.9, 136.9, 154.4 (d, J = 262 Hz), 161.8, 164.5; MS m/z 338 (M + 1), 336 (M − 1), 295, 184. Anal. Calcd for $C_{16}H_{20}FN_3O_4$: C, 56.97; H, 5.98. Found: C, 57.26; H, 6.06.

D-(4-Fluoro-3-nitrophenyl)glycine Methyl Ester (23). A solution of **22** (337 mg, 1 mmol) in acetonitrile (5 mL) and TFA (3 mmol, 0.1 N in water) was stirred at room temperature for 3 h. The volatile was evaporated and the residue was basified to pH = 8 with aqueous $NaHCO_3$. The aqueous solution was extracted with EtOAc. The combined organic phase was washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. Purification by flash chromatography (SiO_2, Et_2O/

MeOH = 10/1) afforded compound **23** as a colorless oil (227.5 mg, 94%): $[\alpha]_D$ −14° (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) 1735, 1537, 1356 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.60 (br s, 2H), 2.90 (dd, *J* = 13.8, 7.8 Hz, 1H), 3.13 (dd, *J* = 13.8, 5.1 Hz, 1H), 3.70 (m, 1H), 3.73 (s, 3H), 7.23 (dd, *J* = 10.6, 8.5 Hz, 1H), 7.50 (m, 1H), 7.93 (dd, *J* = 7.1, 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 39.7, 52.3, 55.4, 118.5 (d, *J* = 21 Hz), 126.0, 134.0, 136.0, 154.5 (d, *J* = 262 Hz), 174; MS *m*/*z* (CI) 243 ($M^+ + 1$). Anal. Calcd for $C_{10}H_{11}FN_2O_4$: C, 49.59; H, 4.58. Found: C, 49.36; H, 4.64.

Compound 25. To a solution of amino ester **23** (300 mg, 1.24 mmol) in CH_2Cl_2 (10 mL) was added EDC (260 mg, 1.36 mmol) and *N*-Boc-*N*-methyl-D-leucine (340 mg, 1.40 mmol). After being stirred at room temperature for 5 h, the reaction mixture was diluted with H_2O and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH = 100/1) to afford dipeptide **25** (550 mg, 95%): mp 66−68 °C; $[\alpha]_D$ +50° (*c* 0.15, $CHCl_3$); IR ($CHCl_3$) 2950, 1743, 1680, 1550, 1350 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 1.43 (s, 9H), 1.63 (m, 3H), 2.66 (s, 3H), 3.06 (dd, *J* = 6.0, 14.0 Hz, 1H), 3.26 (dd, *J* = 5.5, 14.0 Hz, 1H), 3.76 (s, 3H), 4.60 (t, *J* = 7.6 Hz, 1H), 4.83 (m, 1H), 6.76 (br s, 1H), 7.20 (t, *J* = 8.5 Hz, 1H), 7.37 (m, 1H), 7.80 (dd, *J* = 2.0, 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.8, 23.1, 24.7, 28.2, 31.4, 36.3, 37.0, 52.9, 56.5, 57.0, 81.0, 118.6 (d, *J* = 21 Hz), 126.5, 133.5, 136.4, 137.5, 154.6 (d, *J* = 262 Hz), 171.0, 171.5; MS *m*/*z* (CI) 470 ($M^+ + 1$), 414, 370. Anal. Calcd for $C_{22}H_{32}FN_3O_7$: C, 56.28; H, 6.87. Found: C, 56.65; H, 6.67.

Compound 26. A solution of **25** (469 mg, 1 mmol) in methanol (6 mL) and water (2 mL) was stirred for 5 h in the presence of K_2CO_3 (207 mg, 1.5 mmol). The volatile was removed and the residue was acidified. The aqueous solution was extracted with EtOAc, and the combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated to give **26** as a yellowish solid in quantitative yield: mp 140−145 °C; $[\alpha]_D$ +28° (*c* 0.1, MeOH); IR ($CHCl_3$) 3400−3500, 1730, 1680, 1630, 1540, 1400, 1340 cm^{-1}; ^1H NMR (300 MHz, CD_3COCD_3) δ 0.87 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 1.43 (s, 9H), 1.4−1.6 (m, 3H), 2.60 (s, 3H), 3.15 (dd, J = 6.2, 13.8 Hz, 1H), 3.38 (dd, *J* = 5.0, 14.0 Hz, 1H), 4.63 (m, 1H), 4.80 (m, 1H), 7.25 (m, 1H), 7.37 (dd, *J* = 8.6, 11.2 Hz, 1H), 7.70 (m, 1H), 7.79 (dd, *J* = 1.8, 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.9, 23.6, 25.5, 28.6, 31.4, 36.9, 37.8, 54.2, 57.1, 80.4, 119.0 (d, *J* = 20.8 Hz), 127.6 (d, *J* = 3.8 Hz), 136.5 (d, *J* = 3.8 Hz), 138.0 (d, *J* = 9.4 Hz), 150.7, 154.8 (d, *J* = 258.4 Hz), 171.8, 173.4; MS *m*/*z* (CI) 456 ($M^+ + 1$), 400, 356.

Compound 28. A solution of **16** (75 mg, 0.25 mmol), *N*-alloc-L-alanine **27** (43 mg, 0.25 mmol) and EDC (53 mg, 0.27 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature under argon for 2 h. The reaction mixture was then diluted with water and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, CH_2Cl_2) to afford compound **28** (101 mg, 88%) as a colorless oil: $[\alpha]_D$ −19.5° (*c* 0.35, $CHCl_3$); IR ($CHCl_3$) 3430, 1720, 1680, 1500 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ −0.1 (s, 3H, SiMe), −0.05 (s, 3H, SiMe), 0.85 (s, 9H, SiBu^t), 1.40 (d, *J* = 6 Hz, 3H, CH*Me*), 3.75 (dd, *J* = 4.4, 10.3 Hz, 1H, C*H*$_2$OTBDMS), 3.90 (dd, *J* = 4.3, 10.3 Hz, 1H, C*H*$_2$-OTBDMS), 4.29 (m, 1H, C*H*Me), 4.52 (td, *J* = 1.5, 5.2 Hz, 2H, OC*H*$_2$CHCH$_2$), 4.58 (br d, *J* = 5.5 Hz, 2H, OC*H*$_2$CHCH$_2$), 4.95 (dt, *J* = 4.3, 7.5 Hz, 1H, ArC*H*), 5.21 (qd, *J* = 1.3, 10.5 Hz, 1H, OCH$_2$CHC*H*$_2$), 5.27 (qd, *J* = 1.5, 10.5 Hz, 1H, OCH$_2$-CHC*H*$_2$), 5.35 (qd, *J* = 1.3, 17.3 Hz, 1H, OCH$_2$CHC*H*$_2$), 5.40 (qd, *J* = 1.5, 17.2 Hz, 1H, OCH$_2$CHC*H*$_2$), 5.9 (m, 1H, OCH$_2$C*H*CH$_2$), 6.05 (tdd, *J* = 5.2, 10.5 and 17.2 Hz, 1H, OCH$_2$C*H*CH$_2$), 6.72 (d, *J* = 7.3 Hz, 1H, NH), 6.78−6.88 (m, 3H − aromatic + NH), 7.2 (t, *J* = 8.4 Hz, 1H, H − aromatic); ^{13}C NMR ($CDCl_3$) δ −6.0, 18.3, 19.0, 25.9, 50.7, 54.7, 66.0, 66.2, 66.9, 113.8, 117.6, 118.0, 119.3, 123.4, 132.7, 133.4, 141.6, 155.0, 158.8, 171.7; MS *m*/*z* 462, 447, 405. Anal. Calcd for $C_{24}H_{38}N_2O_5Si$: C, 62.31; H, 8.28. Found: C, 62.34; H, 8.51.

Compound 30. To the solution of **28** (101 mg, 0.22 mmol) in dry THF (3 mL) were added $Pd(PPh_3)_4$ (11 mg, 0.01 mmol) and $LiBH_4$ (28 mg, 1.32 mmol). Stirring was continued at room temperature for 1 h. The reaction was quenched by addition of 2 N HCl and then ajusted to pH = 7. The aqueous solution was extracted with EtOAc. The combined organic phase was washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was passed through a short pad of Sephadex LH 20 (CH_2Cl_2, then EtOAc). The so-obtained amino alcohol was dissolved in dry DMF, dipeptide **26** (100 mg, 0.22 mmol), DPPA (56 μL, 0.26 mmol), and Et_3N (34 μl, 0.24 mmol) were added successively. After being stirred for 3 h at room temperature under argon, the reaction mixture was diluted with water. The aqueous solution was extracted with EtOAc. The combined organic phase was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. Purification by preparative TLC (EtOAc/ether = 1/2) afforded tetrapeptide **30** in 55% yield (94 mg); mp 85−90°; $[\alpha]_D$ +12.0° (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) 3200−3400, 1700, 1680, 1550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ −0.05 (s, 3H, SiMe), −0.03 (s, 3H, SiMe), 0.87 (s, 9H, SiBu^t), 0.89 (d, *J* = 5.7 Hz, 3H, CH*Me*$_2$), 0.92 (d, *J* = 6.5 Hz, 3H, CH*Me*$_2$), 1.21 (d, *J* = 6.9 Hz, 3H, CH*Me*), 1.43 (m, 1H, C*H*$_2$CHMe$_2$), 1.47 (s, 9H, Bu^t), 1.46−1.48 (m, 1H, CH$_2$C*H*Me$_2$), 2.70 (s, 3H, NMe), 2.92 (dd, *J* = 7.0, 13.9 Hz, 1H, H15), 3.05 (dd, *J* = 6.3, 13.9 Hz, 1H, H15′), 3.80 (dd, *J* = 5.4, 10.2 Hz, 1H, C*H*$_2$OTBDMS), 3.88 (dd, *J* = 4.5, 10.2 Hz, 1H, C*H*$_2$OTBDMS), 4.50 (m, 1H, H11), 4.63 (dd, *J* = 5.6, 9.6 Hz, 1H, C*H*CH$_2$CHMe$_2$), 4.76 (m, 1H, H14), 4.86 (m, 1H, H8), 6.77 (dd, *J* = 2.3, 8.0 Hz, 1H, H4), 6.80 (d, *J* = 8.0 Hz, 1H, H6), 6.86 (s, 1H, H21), 7.09 (dd, *J* = 8.5, 10.5 Hz, 2H, H19 and NH), 7.18 (t, *J* = 8.0 Hz, 2H, H5 and H20), 7.69 (dd, *J* = 2.0, 6.9 Hz, 1H, H17), 7.83 (brs, 1H, NH), 7.93 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.4, 18.3, 18.6, 21.7, 23.9, 24.9, 25.9, 28.4, 29.4, 36.7, 38.0, 49.4, 53.9, 55.4, 57.0, 66.0, 81.1, 114.7, 118.3 (d, *J* = 21 Hz), 126.7, 128.8, 129.8, 132.2, 136.7, 141.2, 151.6, 154.0 (d, *J* = 262 Hz), 157.0, 168.3, 171.6, 175.8; FABMS (Thio/NaCl) *m*/*z* 798 ($M + Na^+$), 776 ($M + H^+$). Anal. Calcd for $C_{38}H_{58}FN_5O_9Si$: C, 58.82; H, 7.53. Found: C, 59.01; H, 7.81.

Compound 31. To a solution of compound **30** (77 mg, 0.1 mmol) in DMF (10 mL) was added dry CsF (304 mg, 2.0 mmol). The mixture was stirred at room temperature under argon for 15 h and then diluted with water. The aqueous solution was extracted with EtOAc. The combined organic phases were washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. Purification by preparative TLC (ether/EtOAc = 2/1) furnished the macrocycle **31** (40 mg, 63%); mp 120−121; $[\alpha]_D$ −71° (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) 3300−3400, 1720, 1600, 1530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 264K) δ 0.94 (d, *J* = 6.4 Hz, 3H, CH*Me*$_2$), 0.97 (d, *J* = 6.6 Hz, 3H, CH*Me*$_2$), 1.35 (d, *J* = 7.1 Hz, 3H, CH*Me*), 1.49 (s, 9H, Bu^t), 1.48−1.52 (m, 1H, C*H*Me$_2$), 1.73 (t, *J* = 7.4 Hz, 2H, C*H*$_2$CHMe$_2$), 2.75 (dd, *J* = 5.4, 13.1 Hz, 1H, H15), 2.91 (s, 3H, N*Me*), 3.65 (dd, *J* = 5.1, 13.1 Hz, 1H, H15′), 3.80 (m, 1H, C*H*$_2$OH), 3.88 (m, 1H, C*H*$_2$OH), 4.51 (m, 1H, H11), 4.66 (t, *J* = 7.4 Hz, 1H, C*H*CH$_2$CHMe$_2$), 5.01 (m, 2H, H8 and H14), 5.81 (s, 1H, H21), 6.72 (br s, 1H, NH), 6.79 (br d, *J* = 6.9 Hz, 1H, NH), 6.91 (d, *J* = 7.8 Hz, 1H, H6), 7.01 (d, *J* = 8.6 Hz, 1H, H19), 7.19 (dd, *J* = 2.0, 7.8 Hz, 1H, H4), 7.35 (t, *J* = 7.8 Hz, 1H, H5), 7.39 (br s, 1H, NH9), 7.54 (dd, *J* = 1.8, 8.6 Hz, 1H, H20), 7.83 (br s, 1H, H17); ^{13}C NMR ($CDCl_3$) δ 21.3, 21.7, 23.6, 24.3, 28.2, 36.5, 37.9, 39.3, 49.6, 53.6, 55.4, 56.8, 65.2, 81.4, 112.8, 116.8, 120.9, 125.3, 126.3, 130.4, 134.5, 137.2, 139.6, 143.1, 148.7, 157.1, 159.9, 168.8, 171.6, 172.3; FABMS (Thio/NaCl) *m*/*z* 664 ($M + Na^+$).

Compound 46a. Cyclization of **45a** under conditions described for **30** gave compound **46a** in 70−75% yield: mp 150−153 °C; $[\alpha]_D$ −90° (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) 3618, 3435, 1718, 1680, 1668, 1537, 1480, 1360 cm^{-1}; ^1H RMN (acetone-d_6) δ 1.33 (d, *J* = 7.0 Hz, 3H, CH_3Ala), 1.47 (s, 9H, Bu^t), 3.06 (m, 1H, H15), 3.50 (dd, *J* = 4.6, 13.1 Hz, 1H, H15′), 3.77 (m, 2H H22), 4.16 (br d, 1H, NHBoc), 4.45 (m, 1H, H11), 4.50 (m, 1H, H14), 4.70 (m, 1H, H8), 6.16 (br s, 1H, H21), 6.40 (br d, 1H, NH12), 6.95 (d, *J* = 8.1Hz, 1H, H6), 7.02 (d, *J* = 8.1Hz, 1H, H4), 7.07 (d, *J* = 8.3Hz, 1H, H19), 7.27 (t, *J* = 8.1Hz, 1H, H5), 7.45 (m, 2H, H20 + NH9), 8.05 (br s, 1H, H17); ^{13}C RMN ($CDCl_3$) δ 18.7, 28.3, 37.7, 49.7, 55.9, 56.0, 64.9, 81.0, 113.1, 116.9, 121.0, 125.6, 126.4, 130.2, 134.4, 136.9, 140.1, 143.0,

148.9, 155.3, 159.9, 169.4, 172.5; MS (CI) *m/z* 515 (M + 1) 497, 459, 415.

Compound 46b. Cyclization of **45b** under conditions described for **30** gave compound **46b** in 75% yield: $[\alpha]_D$ −115° (*c* = 0.1, $CHCl_3$); IR ($CHCl_3$) 3618, 3420, 1710, 1680, 1660, 1537, 1490, 1480 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (d, *J* = 6.8 Hz, 3H, MeAla), 1.49 (s, 9H, Bu^t), 2.70 (dd, *J* = 9.8, 13.3 Hz, 1H, H15), 3.31 (s, 3H, OMe), 3.53 (dd, *J* = 4.8, 13.3 Hz, 1H, H15′), 3.71 (m, 1H, H22), 3.78 (m, H22′), 4.20 (m, 1H, H11), 4.41 (m, 1H, H14), 4.98 (m, 1H, H8), 5.54 (d, *J* = 7.6 Hz, 1H, NHBoc), 5.91 (br s, 1H, H21), 5.98 (br d, 1H, NH12), 6.41 (br d, 1H, NH9), 6.92 (dd, *J* = 1.8, 7.9 Hz, 1H, H6), 7.13 (d, *J* = 8.4 Hz, 1H, H19), 7.17 (dd, *J* = 2.0, 7.9 Hz, 1H, H4), 7.34 (t, *J* = 7.9 Hz, 1H, H5), 7.60 (dd, *J* = 2.0, 8.4 Hz, 1H, H20), 7.67 (brs, 1H, H17); ^{13}C NMR ($CDCl_3$) δ 21.3, 28.3, 39.2, 49.1, 50.1, 52.8, 53.0, 59.2, 81.7, 113.7, 117.2, 120.7, 126.0, 126.9, 129.7, 130.2, 135.4−142.7 (4 C), 155.2, 156.8, 171.5; FABMS (Thio/NaCl) *m/z* 551 (M + Na^+), 529 (M + H^+); selected NOES H17-H15, NHBoc; **H20-H14**, H15′, H19; H6-H8, H22; NH9-H21, H8, MeAla; NH12-H14, NHBoc; H21-H8; NHBoc-H17, H12, H14, H15; H8-H6, NH9, H21, H22; **H14-H20**, H12, H15, H15′, NHBoc, H11-NH12, NH9; MeAla-NH9.

Compound 3. To a solution of **31** (38.5 mg, 0.06 mmol) in acetonitrile (6 mL) was added concentrated HCl (0.6 mL) dropwise. After being stirred for 1 h at room temperature, the solution was carefully basified (pH = 8) by addition of aqueous $NaHCO_3$, the pure product **3′** (26 mg, 82%) was obtained by simple extraction with AcOEt; mp 138−140 °C; $[\alpha]_D$ −70° (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) 3700, 3420, 3340, 1700−1670, 1590, 1530, 1250 cm^{-1}; ^1H NMR (400 MHz, 300K, 20 mg/0.4 mL $CDCl_3$) δ 0.96 (d, *J* = 6.4 Hz, 3H, CH_3Leu), 0.99 (d, *J* = 6.4 Hz, 3H, H28, C_3Leu), 1.24 (s, NHLeu), 1.35 (d, *J* = 6.9 Hz, 3H, CH_3 Ala), 1.41−1.76 (m, 3H, CH_2 Leu and CHLeu), 2.40 (s, 3H, N-CH_3), 2.75 (dd, *J* = 7.0, 13.3 Hz, 1H, H15), 3.07 (dd, *J* = 4.8, 9.0 Hz, 1H, H25), 3.55 (dd, *J* = 4.4, 13.3 Hz, 1H, H15′), 3.89 (m, 2H, C*H*$_2$OH), 4.32 (m, 1H, H11), 4.80 (m, 2H, H8 + H14), 5.62, 5.78 (br s, OH), 5.97 (s, 1H, H21), 6.48 (d, *J* = 6.2 Hz, 1H, NH12), 6.91 (d, *J* = 7.7 Hz, 1H, H6), 7.00 (d, *J* = 6.9 Hz, 1H, NH23), 7.02 (d, *J* = 8.6 Hz, 1H, H19), 7.17 (dd, *J* = 2.4, 8.1 Hz, 1H, H4), 7.37 (t, *J* = 7.9 Hz, 1H, H5), 7.56 (d, *J* = 1.8, 8.6 Hz, 1H, H20), 7.75 (s, *J* = 1.8 Hz, 1H, H17), 8.11 (br s, 1H, NH9); FABMS (Thio/NaCl) *m/z* 564 (M + Na^+), 542 (M +H^+).

Compound **3** was obtained by heating the acetone solution of **3′** for 30 min: mp 120−125 °C; $[\alpha]_D$ −160° (*c* 0.15, EtOH); IR ($CHCl_3$) 3450, 3320, 1700, 1660, 1530 cm^{-1}; ^1H NMR (400 MHz, Me_2CO-d_6) δ 0.84 (d, *J* = 6.6 Hz, 3H, *Me*Leu), 0.88 (d, *J* = 6.6 Hz, 3H, *Me*Leu), 1.22 (d, *J* = 7.2 Hz, 3H, *Me*Ala), 1.28 (m, 1H, N*H*Leu), 1.58 (m, 2H, CH_2Leu), 1.74 (m, 1H, C*H* Me_2-Leu), 2.42 (s, 3H, NMe), 3.24 (dd, *J* = 2.5, 7.5 Hz, 1H, N-C*H*COleu), 3.34 (dd, *J* = 14.0, 5.0Hz, 1H, H15), 3.50 (m, 2H, CH_2-O), 3.70 (dd, *J* = 14.0, 5.0Hz, 1H, H15′), 3.80 (t, *J* = 6.5 Hz, 1H, OH), 4.53 (m, 2H, H11 + H14), 4.90 (m, 1H, H8), 6.36 (s, 1H, H21), 6.92 (d, *J* = 7.5 Hz, 1H, H6), 7.00 (d, *J* = 8.5 Hz, 1H, H19), 7.09 (dd, *J* = 8 Hz, 3Hz, 1H, H4), 7.17 (d, *J* = 9 Hz, 1H, NH12), 7.26 (t, *J* =7.5 Hz, 1H, H5), 7.68 (d, *J* = 9 Hz, 1H, NH9), 7.79 (dd, *J* =7.5 Hz, 1H, H20), 7.91 (d, *J* = 2 Hz, 1H, H17); ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, *J* = 6.8 Hz, 3H, MeLeu), 0.88 (d, *J* = 6.8 Hz, 3H, MeLeu), 1.31 (d, *J* = 7.2 Hz, 3H, MeAla), 1.37 (m, 1H, CH_2Leu), 1.66 (m, 1H, CH_2-Leu), 1.72 (m, 1H *CH*Me_2Leu), 2.40 (s, 3H, NMe), 3.12 (dd, *J* = 5.2, 14.0 Hz, 1H, H15), 3.22 (dd, *J* = 2.6, 6.9 Hz, 1H, COC*H*NLeu), 3.46 (dd, *J* = 8.3, 11.3 Hz, 1H, OCH_2), 3.61 (dd, *J* = 4.6, 11.3 Hz, 1H, OCH_2), 3.76 (dd, *J* = 4.6, 14.0 Hz, 1H, H15′), 4.17 (m, 1H, H14), 4.65 (m, 1H, H11), 5.01 (dt, *J* = 4.6, 8.5 Hz, 1H, H8), 6.39 (s, 1H, H21), 6.68 (d, *J* = 9.1 Hz, 1H, NH12), 6.86 (d, *J* = 7.6 Hz, 1H, H6), 6.98 (d, *J* = 8.4 Hz, 1H, H19), 7.19 (dd, *J* = 2.5, 7.6 Hz, 1H, H4), 7.22 (br d, 1H, NH9), 7.25 (t, *J* = 7.6 Hz, 1H, H5), 7.72 (dd, *J* = 2.2, 8.4 Hz, 1H, H20), 7.74 (d, *J* = 2.2 Hz, 1H, H17); ^{13}C NMR ($CDCl_3$) δ 18.7, 22.6, 23.7, 26.2, 33.1, 36.9, 38.7, 49.7, 57.3, 58.3, 62.4, 67.2, 115.7, 116.6, 122.5, 126.2, 128.3, 129.9, 136.8, 139.0, 143.2, 150.8, 162.5, 167.5, 172.7; FABMS (Thio/NaCl) *m/z* 564 (M + Na^+), 542 (M + H^+).

Compound 35. A suspension of **34** (3.94 g, 10 mmol), Boc_2O (3.27 g, 15 mmol) and Pd/C (10%, 400 mg) in EtOAc was hydrogenated at 1 atm for 2 h. The reaction mixture was filtered through a short pad of Celite, the filtrate was evaporated *in vacuo* and purified by flash chromatography to afford **35** (4.3 g, 92%): mp 45 °C; $[\alpha]_D$ +165.8° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3450, 3010, 1793, 1706, 1600, 1387 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.31 (d, *J* = 6.0 Hz, 6H), 1.43 (s, 9H), 2.84 (dd, *J* = 10.2, 13.4 Hz, 1H), 3.39 (dd, *J* = 2.6, 13.4 Hz, 1H), 4.08 (dd, *J* = 7.3, 9.1 Hz, 1H), 4.13 (dd, *J* = 2.6, 9.1 Hz, 1H), 4.54 (septet, *J* = 6.0 Hz, 1H), 4.57 (m, 1H), 5.49 (d, *J* = 7.9 Hz, 1H), 6.57 (d, *J* = 7.9 Hz, 1H), 6.8−7.5 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 21.8, 28.1, 37.4, 55.5, 56.4, 66.0, 69.6, 79.9, 115.5, 116.0, 119.8, 123.4, 127.1, 128.8, 129.3, 129.7, 135.0, 137.0, 148.9, 152.1, 154.7, 158.0, 171.3. Anal. Calcd for $C_{26}H_{32}N_2O_6$: C, 66.65; H, 6.88; N, 5.98. Found: C, 66.37; H, 6.70; N, 5.71.

Compound 32. Following the procedure detailed for **12**, hydrolysis of **35** afforded compound **32** in 92% yield: $[\alpha]_D$ +109.5° (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) 3446, 3313, 2939, 1727, 4660, 1616, 1607, 1485, 1350 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 2 rotamers) δ 1.21 (s, OBu^t), 1.31 (d, *J* = 6.0 Hz, 6H, OCH*Me*$_2$), 1.41 (s, OBu^t), 4.52 (septet, *J* = 6.0 Hz, 1H, O*CH*Me_2), 5.06 (d, *J* = 4.3 Hz, ArC*H*), 5.27 (d, *J* = 6.8 Hz, ArC*H*), 5.50 (br s, 1H, NH), 6.8−7.2 (m, 4H, aromatics), 7.67 (brs, OH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 22.2 (22.3), 28.2 (28.5), 57.8 (59.1), 70.1, 80.6 (81.8), 114.7 (114.9), 115.9, 119.4 (119.7), 129.6 (130.1), 138.2 (139.9), 155.3 (157.1), 158.2 (158.4), 173.7 (175.3); MS (EI) *m/z* 309, 292, 264. Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 61.91; H, 7.52; N, 4.65.

Compound 36. To a solution of amino acid **32** (450 mg, 1.45 mml) in CH_2Cl_2 (10 mL) was added a solution of amino alcohol **16** (406 mg, 1.32 mmol) in CH_2Cl_2 (3 mL), HOBt (230 mg, 1.7 mmol) and EDC (300 mg, 1.6 mmol) at 0 °C. After being stirred for 30 min at 0 °C, the reaction mixture was diluted with aqueous NH_4Cl (15 mL) and was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography (SiO_2, EtOAc/heptane = 1/6) afforded dipeptide **36** (728 mg, 92%): mp = 85 °C; $[\alpha]_D$ +49.5° (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) 3418, 2987, 2956, 2937, 1718, 1680, 1606, 1490 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ −0.20 (s, 3H), −0.09 (s, 3H), 0.80 (s, 9H), 1.27 (d, *J* = 5.2 Hz, 3H), 1.29 (d, *J* = 5.2 Hz, 3H), 1.39 (s, 9H), 3.69 (dd, *J* = 3.6 Hz, 10.2 Hz, 1H), 3.88 (dd, *J* = 4.0 Hz, 10.2 Hz, 1H), 4.33 (br d, *J* = 5.2 Hz, 1H), 4.49 (septet, *J* = 5.2 Hz, 1H), 4.91 (td, *J* = 3.8, 7.6 Hz, 1H), 5.12 (br s, 1H), 5.25 (qd, *J* = 1.3, 10.5 Hz, 1H), 5.37 (qd, *J* = 1.3, 17.3 Hz, 1H), 5.84 (br s, 1H), 6.00 (tdd, *J* = 5.2, 10.5, 17.3 Hz, 1H), 6.44−6.52 (m, 3H), 6.71 (dd, *J* = 2.5, 8.1 Hz, 1H), 6.81−6.85 (m, 2H), 6.91 (d, *J* = 7.8 Hz, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 7.26 (t, *J* = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −5.7, −5.6, 18.2, 22.1, 25.9, 28.4, 54.7, 58.9, 66.3, 68.7, 69.9, 80.0, 112.6, 114.0, 114.2, 116.0, 117.5, 119.0, 119.4, 129.2, 130.3, 133.4, 141.5, 158.7, 169.2; MS *m/z* 598 (M^+), 541, 525, 497, 482. Anal. Calcd for $C_{33}H_{50}N_2SiO_6$: C, 66.19; H, 8.42; N, 4.68. Found: C, 66.49; H, 8.51; N, 4.52.

Compound 37. To a solution of dipeptide **36** (99 mg, 0.165 mmol) in THF (1 mL) was added $NaBH_4$ (38 mg, 1 mmol) and $Pd(PPh_3)_4$ (9.6 mg, 8.27 μmol) at 0 °C. After being stirred for 1 h at room temperature, the reaction mixture was diluted with aqueous NH_4Cl (10 mL), and the aqueous solution was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography (SiO_2, EtOAc/heptane = 1/6 then 1/3) afforded compound **37** (78.3 mg, 85%): $[\alpha]_D$ +60.6° (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) 3600, 3425, 2975, 2963, 2931, 1712, 1686, 1606, 1480 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ −0.27 (s, 3H), −0.10 (s, 3H), 0.75 (s, 9H), 1.27 (d, *J* = 6.0 Hz, 3H), 1.32 (d, *J* = 6.0 Hz, 3H), 1.43 (s, 9H), 3.67 (dd, *J* = 3.5 Hz, 10.1 Hz, 1H), 3.85 (dd, *J* = 3.8, 10.1 Hz, 1H), 4.52 (septet, *J* = 6.0 Hz, 1H), 4.85 (td, *J* = 3.8, 7.6 Hz, 1H), 5.17 (br s, 1H), 5.90 (br s, 1H), 6.18 (s, 1H), 6.46 (m, 2H), 6.61 (dd, *J* = 2.5, 8.0 Hz, 1H), 6.81−6.92 (m, 2H), 6.99 (d, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 7.9 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50.03 MHz) δ −5.8, −5.6, 18.2, 22.1, 25.9, 28.4, 54.7, 58.9, 66.1, 70.6, 80.2, 113.6, 114.4, 115.0, 116.2, 118.2, 120.2, 129.4, 130.3, 130.4, 140.5, 141.3, 156.0, 158.5, 169.5; MS *m/z* 558 (M^+), 501, 457; HRMS *m/z* 558.3110 ($C_{30}H_{46}N_2SiO_6$ requires 558.3125).

Compound 38. A solution of compound **37** (152 mg, 0.27 mmol), TBDMSOTf (375 μL, 1.63 mmol) and 2,6-lutidine (159 μL, 1.36 mmol) was stirred at room temperature for 20 min. The reaction was quenched by addition of aqueous NH_4Cl and acidified with 3 N HCl to pH = 2. The resulting mixture was stirred for 15 min, neutralized with phosphate buffer (pH = 7), and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography (SiO_2, EtOAc/heptane = 1/2 then 1/1) afforded compound **38** (145 mg, 76%): $[\alpha]_D$ +10.8° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3418, 3368, 2956, 2931, 2861, 1675, 1600, 1487 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ -0.11 (s, 3H, Me), −0.05 (s, 3H, Me), 0.19 (s, 6H, 2Me), 0.85 (s, 9H), 0.99 (s, 9H), 1.32 (d, *J* = 6.0 Hz, 6H), 3.75, (dd, *J* = 3.9 Hz, 10.1 Hz, 1H), 3.84 (dd, *J* = 4.3 Hz, 10.1 Hz, 1H), 4.50 (s, 1H), 4.51 (septet, *J* = 6.0 Hz, 1H), 4.94 (td, *J* = 4.1, 8.2 Hz, 1H), 6.6−7.3 (m, 8H), 7.68 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −5.6, −5.5, −4.3, 18.3, 22.2, 25.8, 25.9, 29.0, 54.1, 60.1, 66.2, 69.8, 114.7, 115.3, 118.9, 119.1, 120.1, 122.0, 129.2, 130.0, 142.0, 142.7, 155.7, 158.4, 172.3; MS (EI) *m*/*z* 572 (M^+), 557, 515, 457, 427. Anal. Calcd for $C_{31}H_{52}N_2Si_2O_4$: C, 64.99; H, 9.15; N, 4.89. Found: C, 65.19; H, 9.17; N, 4.74.

Compound 40. A solution of dipeptide **38** (82.5 mg, 0.145 mmol), amino acid **39** (43 mg, 0.131 mmol), EDC (30 mg, 0.15 mmol), and HOBt (26.5 mg, 0.19 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 40 min. The reaction mixture was diluted with phosphate buffer (pH = 7) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography (SiO_2, EtOAc/heptane = 1/3) afforded compound **40** (109 mg, 95%): mp 59 °C; $[\alpha]_D$ +40.6° (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) 3425, 2950, 2931, 1718, 1679, 1587, 1481 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ −0.19 (s, 3H), −0.10 (s, 3H), 0.12 (s, 6H), 0.78 (s, 9H), 0.95 (s, 9H), 1.30 (m, 6H), 1.39 (s, 9H), 2.95 (dd, *J* = 6.3, 13.5 Hz, 1H), 3.10 (dd, *J* = 6.5, 13.5 Hz, 1H), 3.68 (dd, *J* = 3.6, 10.1 Hz, 1H), 3.85 (dd, *J* = 4.1, 10.1 Hz, 1H), 4.4−4.6 (m, 2H), 4.85 (m, 1H), 5.14 (d, *J* = 8.3 Hz, 1H), 5.38 (d, *J* = 6.2 Hz, 1H), 6.3−7.4 (m, 12H), 7.71 (dd, *J* = 2.0, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ −5.7, −5.6, −4.4, 18.2, 22.1, 25.8, 25.9, 28.3, 29.8, 37.8, 54.8, 57.4, 66.2, 69.9, 80.5, 115.0, 115.9, 118.3 (d, *J* = 16.6 Hz), 118.9, 119.2 (d, *J* = 9.7 Hz), 126.9, 129.1, 130.5, 133.7, 136.5 (d, *J* = 7.7 Hz), 138.9, 141.3, 151.5, (d, *J* = 267.0 Hz), 158.7, 168.6, 169.7; FABMS *m*/*z* 883 (M + H^+). Anal. Calcd for $C_{45}H_{67}FN_4Si_2O_9$: C, 61.20; H, 7.65; N, 6.34. Found: C, 61.36; H, 7.82; N, 6.39.

Compound *Epi*-40: $[\alpha]_D$ -21.5° (*c* 0.6, $CHCl_3$); IR ($CHCl_3$) 3425, 2950, 2931, 2856, 2400, 1718, 1679, 1587, 1481 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ −0.20 (s, 3H, SiMe), −0.18 (s, 3H, SiMe), 0.19 (s, 6H, $SiMe_2$), 0.73 (s, 9H, Bu^t), 0.98 (s, 9H, Bu^t), 1.31 (d, *J* = 6.0 Hz, 3H, OCH*Me*$_2$), 1.32 (d, *J* = 6.0 Hz, 3H, OCH*Me*$_2$), 1.38 (s, 9H, OBu^t), 3.01 (dd, *J* = 6.5, 14.0 Hz, 1H, H15), 3.13 (dd, *J* = 6.0, 14.0 Hz, 1H, H15′), 3.64 (dd, *J* = 4.4, 10.3 Hz, 1H, H22), 3.67 (dd, *J* = 4.1, 10.3 Hz, 1H, H22′), 4.41 (m, 1H, H14), 4.51 (septet, *J* = 6.0 Hz, 1H, $OCHMe_2$), 4.86 (m, 1H, H8), 5.03 (d, *J* = 7.5 Hz, 1H, N*H*Boc), 5.28 (d, *J* = 7.3 Hz, 1H, H11), 6.32 (d, *J* = 7.3 Hz, 1H, NH9), 6.7−6.9 (m, 5H, aromatics), 6.90 (d, *J* = 7.7 Hz, 1H, aromatic), 7.01 (dd, *J* = 8.5, 10.6 Hz, 1H, H19), 7.18 (t, *J* = 7.8 Hz, 1H, H5), 7.22 (t, *J* = 7.8 Hz, 1H), 7.32 (m, 2H, H20, NH12), 7.82 (dd, *J* = 2.2 Hz, 7.0 Hz, 1H, H17); ^{13}C NMR ($CDCl_3$) δ −5.6, −4.2, 18.3, 22.1, 24.9, 25.8, 25.9, 28.3, 37.6, 55.0, 57.5, 65.8, 69.9, 80.6, 114.8, 115.6, 118.5 (d, *J* = 21.1 Hz), 118.8, 119.2 (d, *J* = 15.6 Hz), 119.8, 126.9, 129.5, 130.5, 133.8, 136.7 (d, *J* = 9.0 Hz), 139.1, 141.2, 155.5 (d, *J* = 264.2 Hz), 164.6, 168.7, 169.6; FABMS *m*/*z* 883 (M + H^+). Anal. Calcd for $C_{45}H_{67}FN_4Si_2O_9$: C, 61.20; H, 7.65; N, 6.34. Found: C, 61.01; H, 7.93; N, 6.42

Compound 41. A solution of tripeptide **40** (280 mg, 0.32 mmol) and anhydrous CsF (965 mg, 6.4 mmol) in dry DMF (30 mL) was stirred at room temperature for 15 h. The reaction mixture was diluted with aqueous NH_4Cl, acidified to pH = 4, and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography (SiO_2, EtOAc/heptane = 1/1) afforded compound **41** (171 mg, 84%): $[\alpha]_D$ −49° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3450, 3010, 1716, 1682, 1596, 1536, 1490, 1377, 1357 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (d, *J* = 6.0 Hz, 3H, OCH*Me*$_2$), 1.31 (d, *J* = 6.0 Hz, 3H, OCH*Me*$_2$), 1.45 (s, 9H, OBu^t), 2.78 (dd, *J* = 7.8, 13.8 Hz, 1H, H15), 3.55 (dd, *J* = 4.9, 13.8 Hz, 1H, H15′), 3.75 (dd, *J* = 3.3, 11.4 Hz, 1H, H22), 3.85 (dd, *J* = 4.8, 11.4 Hz, 1H, H22′), 4.49 (septet, *J* = 6.0 Hz, 1H, OC*H*Me$_2$), 4.52−4.75 (m, 3H, H8, H14, NH12), 5.10 (brs, 1H, NH), 5.45 (d, *J* = 7.8 Hz, 1H, H11), 6.03 (br s, 1H, H21), 6.31 (br s, 1H, NH), 6.54 (d, *J* = 8.0 Hz, 1H, H27), 6.71 (br s, 1H, H25), 6.78 (dd, *J* = 2.4, 8.0 Hz, 1H, H29), 6.87 (d, *J* = 7.9 Hz, 1H, H4), 7.08 (d, *J* = 8.5 Hz, 1H, H19), 7.19 (dd, *J* = 2.5, 7.9 Hz, 1H, H6), 7.24 (t, *J* = 8.0 Hz, 1H, H28), 7.32 (t, *J* = 7.9 Hz, 1H, H5), 7.60 (d, *J* = 8.5 Hz, 1H, H20), 7.85 (d, *J* = 1.7 Hz, 1H, H17); ^1H NMR (CD_3CN, 400 MHz, 313 K) δ 1.25 (d, *J* = 6.0 Hz, 6H, OCH*Me*$_2$), 1.44 (s, 9H, OBu^t), 2.97 (dd, *J* = 3.6, 13.9 Hz, 1H, H15), 3.44 (dd, *J* = 5.0, 13.9 Hz, 1H, H15′), 3.72 (m, 2H, H22), 4.43 (m, 1H, H14), 4.57 (m, 2H, H8 and OC*H*Me$_2$), 5.30 (d, *J* = 8.0 Hz, 1H, H11), 5.80 (br d, 1H, NH23), 6.17 (s, 1H, H21), 6.81 (m, 3H, H25, H27 and H29), 6.98 (m, 2H, H6 and NH9), 7.03 (br d, 1H, NH12), 7.11 (d, J = 8.5 Hz, 1H, H19), 7.15 (m, 1H), 7.21 (t, *J* = 7.6 Hz, 1H, H28), 7.38 (t, *J* = 7.9 Hz, 1H, H5), 7.47 (dd, *J* = 1.8, 8.5 Hz, 1H, H20), 8.03 (d, *J* = 1.7 Hz, 1H, H17); ^{13}C NMR (CD_3OD−$CDCl_3$) δ 22.0, 28.3, 37.7, 55.7, 57.3, 57.6, 64.7, 70.0, 81.0, 113.4, 115.1, 115.3, 117.0, 118.8, 121.1, 125.6, 126.2, 130.2, 134.3, 136.4, 138.1, 140.1, 142.9, 149.0, 155.2, 158.4, 159.6, 159.9, 169.4, 170.5; FABMS *m*/*z* 657 (M + Na^+), 635 (M + H^+); HRMS (CI) *m*/*z* 635.2745 ($C_{33}H_{38}N_4O_9$ + H^+ requires 635.2717); Selected NOES (CD_3CN, 400 MHz, 313 K) H17-H15; **H20-H14**, H11, H15′.

***Epi*-41.** Compound *epi*-**41** was obtained as described for compound **41**: mp 86−88; $[\alpha]_D$ −46.4° (*c* 0.55, $CHCl_3$); IR ($CHCl_3$) 3700, 3425, 2975, 1713, 1675, 1600, 1531, 1488 cm^{-1}; ^1H NMR (CD_3CN, 400 MHz, 323K) δ 1.28 (d, *J* = 6.0 Hz, 6H, *Me*$_2$CH), 1.48 (s, 9H, OBu^t), 2.86 (t, *J* = 12.4 Hz, 1H, H15), 2.89 (m, 1H, OH), 3.24 (dd, *J* = 5.3, 12.4 Hz, 1H, H15′), 3.65−3.83 (m, 2H, H22), 4.47 (m, 1H, H14), 4.59 (septet, *J* = 6.0 Hz, 1H, Me_2CH), 4.75 (m, 1H, H8), 5.28 (d, *J* = 8.5 Hz, 1H, H11), 6.09 (t, *J* = 1.2 Hz, 1H, H21), 6.8−7.2 (m, 10H, aromatics + NH), 7.38 (t, *J* = 7.9 Hz, 1H, H5), 7.73 (dd, *J* = 2.2, 8.4 Hz, 1H, H20), 7.78 (d, *J* = 2.2 Hz, 1H, H17); ^{13}C NMR ($CDCl_3$) δ 22.1, 28.3, 39.0, 54.0, 55.4, 56.4, 63.9, 69.7, 80.1, 112.5, 113.8, 115.3, 116.7, 117.9, 119.8, 125.6, 126.8, 129.9, 130.4, 134.9, 135.6, 138.9, 139.4, 139.6, 143.1, 147.4, 155.4, 158.2, 159.6, 169.9: FABMS *m*/*z* 657 (M + Na^+), 635 (M + H^+). Anal. Calcd for $C_{33}H_{38}N_4O_9$: C, 62.45; H, 6.04; N, 8.83. Found: C, 62.09; H, 6.32; N, 8.54.

Compound 42. To a solution of **41** (7.1 mg, 0.012 mmol) in CH_2Cl_2 (O.5 mL) was added BCl_3 (180 μL, 1M in CH_2Cl_2, 0.18 mmol) at 0 °C. After being stirred for 1 h at 0 °C, the reaction was quenched by slow addition of anhydrous MeOH. The volatile was evaporated, and the residue was dissolved in MeCN (1 mL) and concentrated HCl (0.1 mL) and was stirred at rom temperature for 1 h. The volatile was evaporated, and the residue was diluted with 4 mL of water and extracted with ether to remove the neutral species. The aqueous solution was then neutralized with phosphate buffer (pH = 7) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated to afford compound **42** (5.0 mg, 85%) which was used without further purification: mp = 277 °C; $[\alpha]_D$ +73.3° (*c* 0.1, $CHCl_3$/CH_3OH 20/1); ^1H NMR (CD_3OD, 400 MHz) δ 2.95 (dd, *J* = 3.6, 13.5 Hz, 1H, H15), 3.40 (dd, *J* = 4.3, 13.5 Hz, 1H, H15′), 3.79 (dd, *J* = 5.3, 11.3 Hz, 1H, H22), 3.84 (dd, *J* = 6.6, 11.3 Hz, 1H, H22′), 3.92 (t, *J* = 3.9 Hz, 1H, H14), 4.48 (dd, *J* = 5.3, 6.6 Hz, 1H, H8), 5.39 (s, 1H, H11), 6.21 (t, *J* = 1.9 Hz, 1H, H21), 6.68 (dd, *J* = 2.5, 8.0 Hz, 1H, H25), 6.80 (t, *J* = 2.0 Hz, 1H, H29), 6.84 (d, *J* = 7.8 Hz, 1H, H27), 6.95 (d, *J* = 8.0 Hz, 1H, H4), 7.07 (d, *J* = 8.5 Hz, 1H, H19), 7.10 (d, *J* = 8.0 Hz, 1H, H6), 7.12 (t, *J* = 7.9 Hz, 1H, H28), 7.31 (t, *J* = 8.0 Hz, 1H, H5), 7.40 (dd, *J* = 2.1, 8.5 Hz, 1H, H20), 8.09 (d, *J* = 2.1 Hz, 1H, H17); ^{13}C NMR (CD_3OD−$CDCl_3$, 50.03 MHz) δ 39.2, 55.8, 57.0, 59.0, 64.8, 113.0, 113.9, 115.5, 116.5, 118.2, 121.6, 125.9, 126.8, 130.1, 135.1, 136.3, 148.7, 157.9, 160.6, 171.6, 173.7; FABMS *m*/*z* 493 (M + H^+); HRMS (CI) *m*/*z* 493.1709 ($C_{25}H_{24}N_4O_7$ + H^+ requires 493.1723).

Compound 44. To a solution of **42** (8.1 mg, 0.016 mmol), (3-fluoro-4-nitrophenyl)acetic acid **39** (6.6 mg, 0.033 mmol) in DMF (1 mL) were added DPPA (8.8 μL) and Et_3N (8.0 μL,

0.057 mmol) at 0 °C. After being stirred for 5 h at room temperature, the reaction mixture was diluted with ether (50 mL), washed with water and brine, dried, and evaporated. Purification of crude product by preparative TLC (SiO_2, CH_2Cl_2/MeOH = 10/1) afforded compound **44** (10.4 mg, 94%): mp = 147 °C; $[\alpha]_D$ +37.3° (*c* 0.05, CH_3OH); IR ($CHCl_3$) 3605, 3010, 2995, 2980, 1675, 1606, 1531, 1488, 1463, 1394 cm^{-1}; ^1H NMR (CD_3OD, 250 MHz) δ 3.07 (dd, J = 3.5, 14.1 Hz, 1H, H15), 3.53 (dd, J = 5.6, 14.1 Hz, 1H, H15′), 3.81 (dd, J = 5.2, 11.5 Hz, 1H, H22), 3.84 (d, J = 14.8 Hz, 1H, H31), 3.92 (d, J = 14.8 Hz, 1H, H31′), 3.95 (m, 1H, H22′), 4.42 (dd, J = 5.4 Hz, 6.5 Hz, 1H, H8), 4.73 (dd, J = 3.5, 5.6 Hz, 1H, H14), 5.31 (s, 1H, H11), 6.29 (t, J = 1.8 Hz, 1H, H21), 6.7−6.8 (m, 3H, aromatics), 6.96 (br d, J = 8.5 Hz, 1H, aromatic), 7.0−7.5 (m, 3H, aromatics), 7.13 (d, J = 8.5 Hz, 1H, H19), 7.33 (t, J = 8.0 Hz, 1H, H5), 7.35 (dd, J = 1.2, 8.5 Hz, 1H, H6), 7.44 (dd, J = 1.8, 12.0 Hz, 1H, H37), 7.50 (dd, J = 2.1, 8.5 Hz, 1H, H20), 8.02 (t, J = 8.1 Hz, 1H, H36), 8.25 (d, J = 2.1 Hz, 1H, H17); ^{13}C NMR (CD_3OD) δ 36.9, 42.5, 56.4, 57.7, 59.7, 65.0, 114.1, 114.6, 116.0, 117.2, 118.5, 120.1 (d, J = 20.8 Hz), 122.3, 126.6 (d, J = 8.2 Hz), 126.9 (d, J = 14.5 Hz), 135.0, 137.4, 139.4, 142.2, 144.0, 145.3 (d, J = 3.1 Hz), 149.8, 156.2 (d, J = 261.4 Hz), 160.9, 170.3, 171.9, 172.4; FABMS m/z 674 ($M + H^+$)

Compound 4. A solution of tripeptide **44** (8 mg, 0.012 mmol), anhydrous K_2CO_3 (16.8 mg, 0.12 mmol), and a catalytic amount of 18-crown-6 in dry THF (1.5 mL) was stirred at room temperature for 30 h. The insoluble K_2CO_3 was removed by filtration through a short pad of Celite. The filtrate was evaporated *in vacuo* and purified directly by flash chromatography (SiO_2, CH_2Cl_2/MeOH = 30/1) to afford compound **4** as a white solid (6.8 mg, 87%): mp = 309−312 °C; $[\alpha]_D$ + 86.7° (*c* 0.02, $CHCl_3$/CH_3OH = 10/1); IR ($CHCl_3$) 3600, 3510, 3010, 2990, 1694, 1638, 1612, 1538, 1456, 1400, 1344 cm^{-1}; ^1H NMR (DMSO-d_6, 250 MHz) δ 3.13 (dd, J = 5.3, 14.4 Hz, 1H, H15), 3.53 (dd, J = 6.2, 14.4 Hz, 1H, H15′), 3.62−3.70 (m, 2H, H22), 3.72 (d, J = 15.3 Hz, 1H, H31), 3.98 (d, J = 15.3 Hz, 1H, H31′), 4.45 (br s, 1H, OH), 4.91 (br t, J = 5.3 Hz, 1H, H8), 4.96−5.02 (m, 1H, H14), 5.49 (br s, 1H, H11), 6.21 (br s, 1H, H21), 7.02 (d, J = 7.6 Hz, 1H, aromatic), 7.22 (dd, J = 2.6, 8.1 Hz, 1H, H4), 7.23−7.28 (m, 2H, aromatics), 7.28 (dd, J = 2.3, 8.1 Hz, 1H, H6), 7.32 (d, J = 8.3 Hz, 1H), 7.37−7.45 (m, 3H, aromatics), 7.49 (t, J = 8.1 Hz, 1H, H5), 7.59 (br d, J = 8.2 Hz, 1H, H20), 8.17 (d, J = 8.3 Hz, 1H, H36), 8.36 (br s, 1H, H17), 8.62 (br s, 1H, NH9), 8.70 (br s, 1H, NH12); ^{13}C NMR (DMSO-d_6) δ 35.8, 42.1, 54.5, 56.7, 57.5, 63.4, 112.0, 115.1, 118.2, 118.8, 121.2, 123.4, 124.7, 125.5, 125.8, 126.7, 129.3, 130.3, 135.2, 136.5, 141.1, 142.1, 143.2, 147.3, 148.3, 154.9, 159.3, 168.5, 168.8, 168.9; FABMS (Thio/NaCl) m/z 676 ($M + Na^+$).

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Supporting Information Available: ^1H NMR spectra of selected compounds (14 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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