A Convergent Synthesis of 14-Membered F–O–G Ring Analogs of the Teicoplanin Binding Pocket *via* Intramolecular S_NAr Reaction

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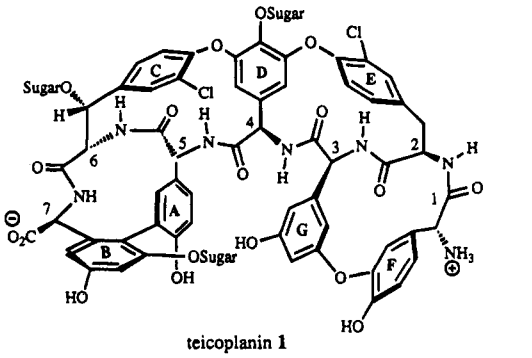
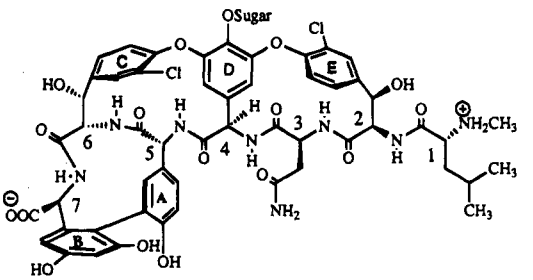
An intramolecular S_NAr reaction for efficient macrocyclization *via* biaryl ether formation was developed for syntheses of the 14-membered macrocycles **2** and **3** related to F–O–G ring of teicoplanin **1**. Chloride as well as fluoride could be used as the leaving group in this reaction. However, the latter was preferred since it required milder conditions. Both *ortho* and *para* nitro, fluoro disubstituted aromatic rings were suitable for the macrocyclization reaction with tethered aryl oxides. The nonproteinogenic α-amino acid **23**, required for the synthesis of **3**, was prepared *via* an asymmetric Strecker synthesis using (*R*)-phenylglycinol as a chiral auxiliary. The overall synthetic strategy was convergent, and the cyclization could be performed in the presence of the highly sensitive arylglycine unit without racemization.

Introduction

Teicoplanin **1**,[1] a glycopeptide related to vancomycin and ristocetine,[2] is an antibiotic produced by *Actinoplanes teichomyceticus*. The compound has recently been introduced into clinical practice for treatment of infections caused by methicillin-resistant *Staphylococcus aureus* and Gram-positive organisms. *In vitro* and *in vivo* studies[3] have shown that teicoplanin is superior to vancomycin, having lower toxicity and higher activity. Moreover, *in vivo*, it exhibits substantially different pharmacokinetic behavior, having a half-life of 40 h in man. 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.[4] A structure for the drug–receptor complex has been proposed by Williams and co-workers on the basis of extensive NMR studies. It was concluded[2,4] that the complex is stabilized by five hydrogen bonds in addition to hydrophobic interactions and an electrostatic attraction between the protonated terminal ammonium group of the antibiotic and peptide carboxylate anion (Figure 1).

Although remarkable achievements have been registered in recent years, especially in Evans' group[5] toward the long-awaited total synthesis of vancomycin, the difficulties associated with preparation of the tripeptide





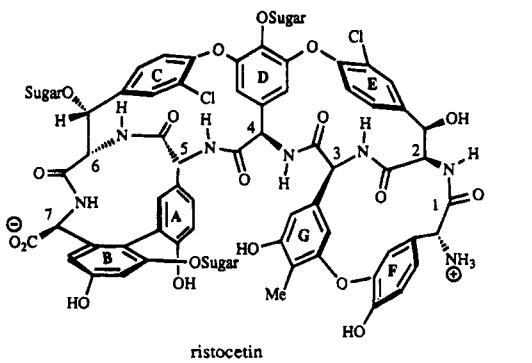


Figure 1.

binding pocket composed of C–O–D, D–O–E 16-membered rings,[5a,6] F–O–G 14-membered ring,[7] as well as

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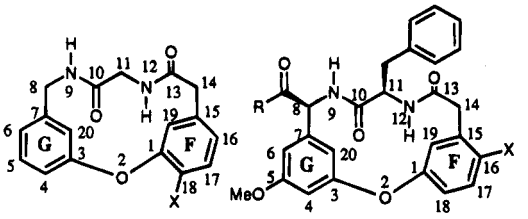
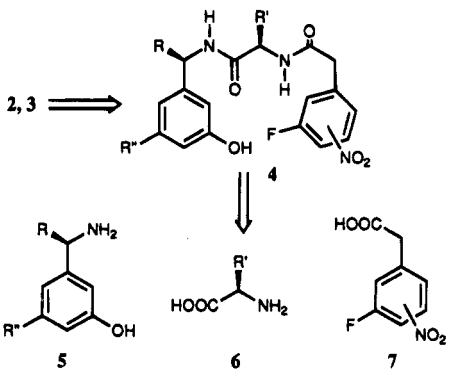


Figure 2.

the A–B 12-membered biaryl macrocycle[5b,c,8] have been recognized. Our interest in this field hinges upon a new and efficient macrocyclization procedure based on intramolecular nucleophilic substitution (S_NAr) reaction *via* biaryl ether formation.[9] The method has been successfully applied to the synthesis of a 16-membered vancomycin model[10] and the naturally occuring 17-membered cyclic tripeptide K-13.[11] In addition to high yield and minimal racemization, an important advantage of our approach is that the nitro functionality *ortho* to the diaryl ether linkage, after serving as an activator, can be transformed into other groups[10,11] (H, Cl, OH) found in natural products.

Structurally, teicoplanin is very similar to vancomycin but has an extra 14-membered macrocycle involving an ether bond between the aryl moieties of amino acid 1 and 3. Two syntheses of the 14-membered F–O–G segment of ristocetin and teicoplanin have been reported by Chakraborty[7a] and Pearson,[7b] both employing macrolactamization for formation of the cyclic peptide. These syntheses have involved the preparation of a simple biaryl ether followed by stepwise construction of the desired amino acid side chains, presumably due to the incompatibility of the amino acid with the harsh reaction conditions required for preparation of biaryl ethers.[12] Consequently, both these synthetic routes are linear.

Scheme 1



Detailed here is the use of an intramolecular S_NAr reaction for the preparation of 14-membered F–O–G analogs **2** and **3** related to teicoplanin (Figure 2).[13]

As shown in the retrosynthetic scheme (Scheme 1), our strategy is conceptually different and operationally more convergent. It involves (1) elaboration of peptide backbone chain **4** from the corresponding amino acids *via* classical peptide chemistry and (2) macrocyclization *via* biaryl ether bond formation at the final stage of the synthesis. The synthesis of **3a** constitutes the first example wherein macrocyclization was carried out with an activating nitro group located *para* to the leaving group (fluoride).

Synthesis of Model Compound 2

Access to the desired macrocyclization precursor for the synthesis of compounds **2a** and **2b** required 3-fluoro-4-nitrophenylacetic acid (**10a**). Reaction of 3-fluoro-4-nitrobenzyl bromide with either KCN or Et_4NCN under various conditions did not give any appreciable amount of 3-fluoro-4-nitrobenzyl cyanide, probably due to the high acidity of the methylene protons.[14] Attempts to switch the reaction course from S_N2 to $S_{RN}1$ mechanism[15] also failed to give consistent results. Alternatively, nitration of 3-fluorophenylacetic acid (**8a**) under standard conditions (H_2SO_4, HNO_3) gave exclusively 3-fluoro-6-nitrophenylacetic acid (**9a**) in 95% yield (Scheme 2). In order to get the other regioisomer **10a** needed for the macrocyclization studies, the acid **8a** was first esterified to give **8b**, nitration of which under the same conditions afforded, in this case, two separable regioisomers **9b** and **10b** in a 3:1 ratio. Hydrolysis of these esters (6 N HCl, reflux) gave then the two corresponding products 3-fluoro-6-nitrophenylacetic acid (**9a**) and 3-fluoro-4-nitrophenylacetic acid (**10a**), respectively, in nearly quantitative yield.

The structures of **9a** and **10a** were assigned by the proton splitting pattern in ^1H NMR spectra. Proton H-4 of **9a** appeared as a dt (δ = 7.42 ppm, J_{H4-H2} = 2.9, J_{H4-F} = J_{H4-H5} = 8.9 Hz), while H-2 of **10a** was a dd (δ = 7.50 ppm, J_{H2-H6} = 1.6, J_{H2-F} = 12.3 Hz), in agreement with the proposed structure. This assignment was supported by ^{13}C NMR spectral studies. Thus, C-3 in compounds **9a** and **10a** resonated at δ = 173.7 ppm (d, J = 252.0 Hz) and 156.0 ppm (d, J = 264.0 Hz), respectively, in accordance with the substitutent effect of nitro group.[16]

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(16) Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. *Tables of Spectral Data for Structure Determination of Organic Compounds*, 2nd ed.; Springer-Verlag: Berlin, Heidelberg, 1989; p C120.

Scheme 2

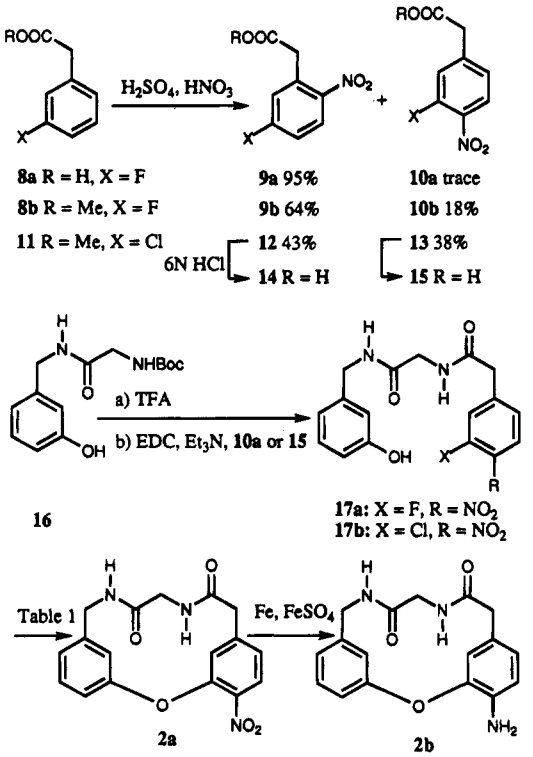


Table 1. Representative Results of the Macrocyclization Reaction[a]

entry	base (equiv)	additive	T (°C), time	yield (%)
		X = F		
1	K_2CO_3 (3)	no	rt, 20 h	66
2	CsF (5)	no	rt, 20 h	62
3	K_2CO_3 (3)	18-crown-6	rt. 6 h	82
4	Li_2CO_3 (30)	no	rt, 4 days	no reaction
5	$NaHCO_3$ (3)	no	rt, 2 days	trace
		X = Cl		
6	K_2CO_3 (3)	no	rt, 2 days	no reaction
7	K_2CO_3 (3)	no	40, 24 h	degradation
8	K_2CO_3 (3)	18-crown-6	rt, 2 days	degradation
9	K_2CO_3 (3)	no	80, 6 h	80%

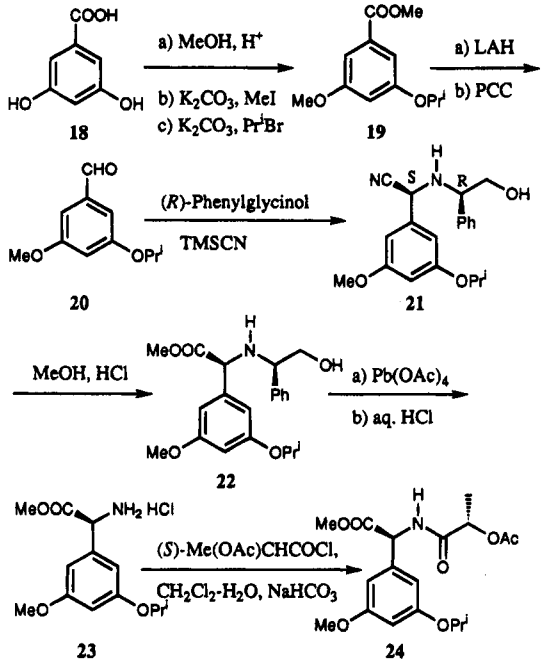
[a] All reactions were run in dry DMF at a concentration of 0.01 M.

The electronic effect in conjuction with anchimeric assistance of the carboxyl group may explain the observed high regioselectivity in the nitration of acid **8a**.

Chloro derivatives **14** and **15** were prepared in the same fashion as described for **9a** and **10a**. Nitration of methyl 3-chlorophenylacetate (**11**) under the same conditions gave methyl 3-chloro-6-nitrophenyl acetate (**12**) and methyl 3-chloro-4-nitrophenylacetate (**13**) in comparable amounts. Hydrolysis of them under acidic conditions afforded the corresponding acids **14** and **15** in 95% yield.

Scheme 2 shows a synthesis of the immediate precursor for the macrocyclization study, i.e., the linear peptide **17a**. Specifically, mild acidic deprotection (TFA, CH_2Cl_2) of the known dipeptide **16**[10b] followed by reaction with 3-fluoro-4-nitrophenylacetic acid (**10a**) employing EDC as coupling agent furnished **17a** in 90% yield. To our delight, when **17a** was submitted to our previously established cyclization conditions[10,11] (Table 1, entry 1), the 14-membered macrocycle **2a** was obtained in 66% yield after a simple extraction and recrystallization procedure.[13] This transformation appeared to be almost quantitative, but some loss occurred during extraction and purification. In fact, compound **2a** is very insoluble

Scheme 3



in common organic solvents, and the isolated yield may simply reflect an inefficient extraction. No higher molecular weight species resulting from dimerization or oligomerization were detected in the mass spectra of the crude reaction product.

In searching for even milder reaction conditions, macrocyclization of **17a** to **2a** was examined under a range of experimental conditions. Table 1 indicates that CsF[17] was an excellent base to promote the desired intramolecular S_NAr reaction, while Li_2CO_3 and $NaHCO_3$ were ineffective presumably due to insufficient basicity. An appropriate crown ether accelerate the reactions dramatically (entry 3). Increased nucleophilicity of alkoxide due to complexation of K^+ apparently leads to a more reactive "naked" anion.[18]

Reduction of nitro group was realized efficiently employing Fe–$FeSO_4$,[19] and compound **2b** was obtained in 85% yield.

In view of the ready availability of chloro-substituted aromatic compounds, macrocyclization using chloride as leaving group was also studied. Linear peptide **17b** was prepared in a fashion which parallels that described for **17a** (Scheme 3). Unlike **17a**, no cyclization reaction occurred under our standard conditions (entry 6), and the starting material was recovered quantitatively, in agreement with the low "leaving ability" of chloride relative to fluoride in S_NAr reactions.[9] At 40 °C, cyclization did occur; however, the conversion was low. Prolonged stirring at this temperature led to degradation, indicating that either **17b** or the cyclized product **2a** was unstable at this temperature. No beneficial effect was observed either when 18-crown-6 (entry 8) was added. Curiously, the optimized conditions for the cyclization of **17b** require heating to 80 °C for a shorter period of time (6h, entry 9); compound **2a** was then isolated in 80% yield. In view of this reactivity difference and sensitivity of the arylglycine unit toward racemization, the fluoride was used as leaving group in the following studies.

(17) Clark J. H. *Chem. Rev.* **1980**, *80*, 429–452.
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Synthesis of F–O–G Analog of Teicoplanin

It was desirable to synthesize 14-membered macrocycles of type **3** in order to determine the minimal functional units needed for the antibacterial activity. In this regard, the presence of an aromatic amino group, though less basic than the aliphatic one, may facilitate formation of an initial "loose" complex with carboxylate anion.[20–23] Secondly, the presence of an amino substitutent in the aromatic ring may rigidify the cyclic framework, and this would be beneficial to the binding interactions. Finally, this provided an opportunity to test macrocyclization in the hitherto unknown case wherein the nitro group is located *para* to the leaving group (fluoride).

Our preparation of L-[(*S*)-3-(isopropyloxy)-5-methoxyphenyl]gly-OMe (**23**) is shown in Scheme 3. A conventional five-step sequence starting from 3,5-dihydroxybenzoic acid (**18**) gave the 3-(isopropyloxy)-5-methoxybenzaldehyde (**20**) in 44% overall yield. A diastereoselective Strecker synthesis was the key step for the synthesis of the desired (*S*) amino acid **23**.[24] Thus, treatment of aldehyde **20** with (*R*)-phenylglycinol in dichloromethane at room temperature for 3 h followed by sequential addition of methanol and TMSCN at 0 °C afforded a mixture of two readily separable diastereoisomers (4:1) from which the desired compound **21** was isolated in 73% yield. The high yield of this reaction (>90%) compensated the somewhat moderate diastereoselectivity (4:1). The stereochemistry of the newly created chiral center of **21** was determined according to the literature procedure.[25] Thus, the signal of the α_{CH} of the major diastereoisomer (*S,R*) appeared at higher field than that of the minor (*R,R*) counterpart.[25] Hydrolysis of α-amino nitrile **21** occurred smoothly with gaseous HCl saturated MeOH to give the α-amino ester **22** in 91% yield. Oxidative cleavage of the chiral auxiliary with a slight excess of lead tetraacetate[26] in CH_2Cl_2–MeOH (2:1) at 0 °C afforded an unstable aldimine which was immediately hydrolyed with aqueous HCl into the desired amino ester **23**. This compound was not very stable; it was best stored as its hydrochloride salt. Conversion of **23** to the (*S*)-lactamide **24** [(*S*)-MeCH(OAc)COCl, $NaHCO_3$, CH_2Cl_2–H_2O][13b] gave an 8:1 ratio of diastereoisomers, corresponding to an enantiomeric excess of *ca.* 80%. Product **23** was used in the following reactions without further enhancement of enantiomeric purity.

(20) Thomas and co-workers have recently shown that, unlike vancomycin, the formation of a bent salt bridge between the terminal amino group of the antibiotic and the carboxylate anion of cell wall peptide (electrostatic interaction) plays only a minor role in complex formation and bioactivity of ristocetine and teicoplanin: Herrin, T. R.; Thomas, A. M.; Perun, T. J.; Mao, J. C.; Fesik, S. W. *J. Med. Chem.* **1985**, *28*, 1371–1375. Trani and co-workers[21] have prepared deaminoteicoplanin and demonstrated that the loss of the terminal amino group reduces the *in vitro* activity against *staphylococcal* and *streptococcal* to one-half that of teicoplanin. More recent research from Pratt's group[22] also suggested that the N-terminal ammonium ion is advantageous but not essential for strong binding. On the basis of these results, Hamilton and co-workers[23] have recently prepared a series of simple neutral amides as receptors for carboxylates.

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(23) Hamilton, A. D.; Albert, J. S. *Tetrahedron Lett.* **1993**, *34*, 7363–7366.

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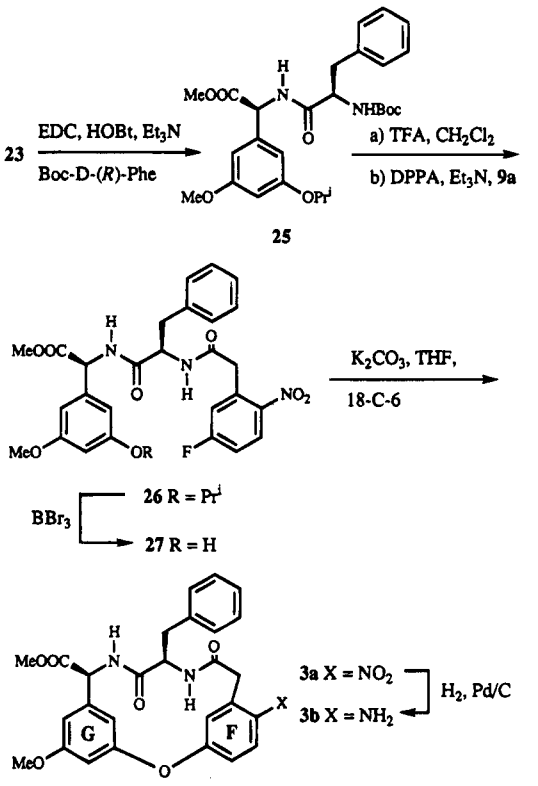
Scheme 4



Synthesis and macrocyclization of the tripeptide **27** was shown in Scheme 4. Coupling of **23**·HCl with Boc-D-Phe using EDC as coupling reagent in the presence of Et_3N (1 equiv) furnished the dipeptide **25**. Mild acid deprotection (TFA, CH_2Cl_2) followed by amide bond formation with 3-fluoro-6-nitrophenylacetic acid (**9a**) employing DPPA[27] as coupling agent provided the tripeptide **26** very efficiently. Chemoselective deprotection of isopropyl ether in the presence of methoxy group was realized using BBr_3[28] to afford the linear tripeptide **27** in 92% yield.

The macrocyclization of **27** was first run under the previously established conditions (K_2CO_3, DMF, 0.01 M, rt). Cyclization did occur to give **3a**, but the reaction proceeded slowly, and prolonged reaction time led to degradation of the starting material. After searching for the different reaction parameters, we found that anhydrous THF in the presence of K_2CO_3 with a catalytic amount of 18-crown-6 was ideal. Conversely, in the absence of this complexing agent, the reaction did not proceed at all. Compound **3a**, isolated in 71% yield, has spectral data (^1H and ^{13}C NMR, IR, HRMS) consistent with the proposed macrocyclic structure. A high-resolution mass spectrum of **3a** showed the molecular ion peak corresponding to the cyclized monomer of molecular formula: $C_{27}H_{25}N_3O_8$. The splitting pattern of H-17 in the ^1H NMR spectrum was also indicative of the cyclized product. Thus, for compound **27**, H-17 appeared as a doublet of doublets (δ = 8.01 ppm, $J_{H18-H17}$ = 9.1 Hz, J_{H17-F} = 5.1 Hz) whereas for the macrocycle **3a**, the signal of this proton was a doublet (δ = 8.01 ppm, $J_{H18-H17}$ = 9.0 Hz). A minor isomer of the cyclic monomer was isolated in 10% yield. We reasoned that it could be either an atropisomer of **3a** or *epi*-**3a** due to the epimerization

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(28) Sala, T.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2593–2598.

of the sensitive chiral center at C-8. Attempts to distinguish between these two possibilities *via* NOE experiments[10b] were inconclusive. Taking into account the enantiomeric purity of the amino ester **23**, we speculate that the minor product is *epi*-**3a**, but, no further studies have been carried out.

In contrast to compound **27**, the macrocycle **3a** was configurationally stable under mild basic conditions (1 N NaOH–DMSO, rt). We reasoned that the extra ring constraints introduced by the enolization of ester function as well as the noncoplanarity of C-8 and the aromatic ring G may explain the reduced kinetic acidity of H-8 and thus increased configurational stability. It is worthy noting that teicoplanin was readily epimerized at the α-carbon center of amino acid **3** under relatively harsh basic conditions ($NaHCO_3$, reflux).[29]

Completion of the synthesis of the F–O–G ring analog of teicoplanin was as follows. Reduction of **3a** using Fe–$FeSO_4$ as described earlier gave a low isolated yield of **3b**. However, hydrogenation (Pd/C, MeOH–CH_2Cl_2, 1 h) afforded this amino compound in excellent yield, and no ring-opened compound resulting from the possible debenzylation was observed. Interestingly, in the ^1H NMR spectrum, H-20 of **3b** ($\delta = 6.02$ ppm) was shifted upfield compared to that of **3a** ($\delta = 6.48$ ppm); hence, conformational changes seem to be induced by the reduction of the nitro to the amino group. The relative position of the two aromatic rings F and G was changed in such a way that H-20 was now located under the plane of ring F and in its shielding region. A 2D ^1H–^1H-NOESY NMR spectrum of **3b** exhibited crosspeaks for H-20/H-19, NH-9; H-19/NH-12, H-14; H-8/H-6, NH-9; NH-9/H-11; NH-12/H-11, H-14, from which it seems probable that the conformation of **3b** is very similar to that of the structure prepared by Chakraborty.[7a] The only difference is that the latter shows an additional NOE, *albeit* small (2%), between H-8 and H-20.

Discussion and Conclusion

Given that the 14-membered *meta*, *meta'* cyclophane systems of compounds **2** and **3** are obviously strained, the relatively facile cyclization reported here is remarkable. A high dilution technique was not needed, so the solution conformation of the cyclization precursor may be such that the two reactive sites are close.[30] Several distinct structural factors may favor such prearrangement, namely (1) π–π interactions[31] between the electron-deficient fluoro, nitro substituted aromatic ring and an electron-rich phenoxide ring[32] (electron donor–acceptor (EDA) or charge transfer (CT) model) or an attractive electrostatic interaction arising from positively and negatively charged atoms (the atomic charge model);[33] (2) intramolecular hydrogen bonds;[34] and (3) the presence of glycine or D-amino acids in the peptide chain which could favor bent conformations over β-pleated sheets.[35]

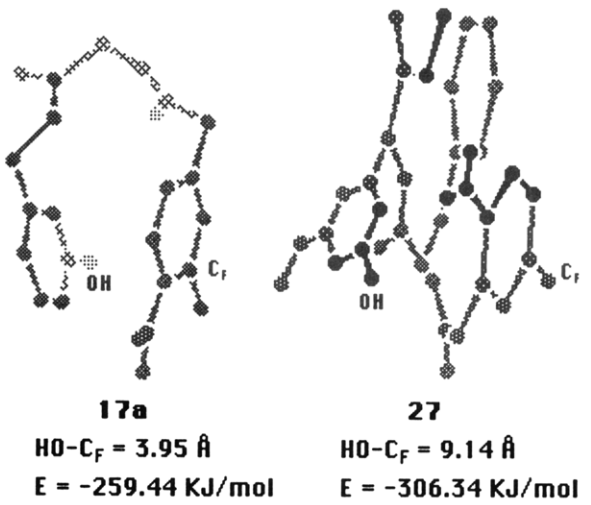

Figure 3.

If the prearranged conformation was really necessary for such macrocyclization (proximity effects),[30b,36] then this last point should not be determinant for the conformational preferences as shown in our successful synthesis of K-13 where the peptide chain is comprised of L-(*S*)-amino acids.[11] In fact, Haase et al.[37] have recently shown that there was no remarkable dependence of the cyclization yields on the position of the D-residues in the macrolactamization.

To gain information regarding the solution conformations of the cyclization precursor, we have carried out computational simulation (macromodel, Batchmin Version 3.5a, Oplsa force field, water set).[38] Figure 3 shows the lowest energy conformation observed for the two cyclization precursor **17a** and **27**. For compound **17a**, the lowest energy conformer has a bent orientation where a parallel face-to-face π stacked geometry between two aromatic rings is evident and the two reactive sites (HO and C_F) were thus placed within 3.95 Å, resulting in a low activation energy and favorable entropy for cyclization. For compound **27**, the lowest energy conformer is folded such that the three aromatic rings have a mutual edge-to-face orientation. The distance between two reactive sites (HO and C_F, 9.14 Å) is larger than anticipated for an easy cyclization, which may explain the reactivity difference between **17a** and **27** (*vide supra*). The presence of a third aromatic ring (phenylalanine) in **27** may account for, in part, such conformational preferences. Moreover, the fact that the fluoride is located *para* to the nitro group probably played an important role in the proximity of two reactive sites (HO and C_F).

In conclusion, we have described an efficient method for preparation of 14-membered macrocycles related to teicoplanin. Both chloride and fluoride could serve as leaving groups in the pivotal intramolecular S_NAr reaction, but the latter was preferred in view of the milder conditions. The requisite nitro activating group could be either *ortho* or *para* to the leaving group. Conformational preferences suggest that the *ortho* nitro, fluoro disubstituted aromatic system is a better macrocyclization pre-

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cursor than the *para* nitro, fluoro disubstituted one. This observation may be pertinent to future applications of related macrocyclization techniques. These results, in conjunction with earlier studies from this laboratory, demonstrate the feasibility of intramolecular S_NAr reaction in the total synthesis of teicoplanin and related antibiotics.

Experimental Section

General procedures and methods for characterization are described elewhere.[10b] Melting points are uncorrected.

Compound 9a. To the solution of 3-fluorophenylacetic acid (**8a**) (616 mg, 4 mmol) in concd H_2SO_4 (1.03 mL, 20 mmol) at 0 °C was added HNO_3 (187 μL, 4 mmol) slowly. The resulting reaction mixture was stirred under argon for 2 h at 0 °C and poured into ice–water. The white solide was precipitated, and the aqueous phase was extracted with EtOAc (4 × 30 mL). The organic phase was washed with brine, dried (Na_2SO_4), and evaporated. Recrystallization from EtOAc/heptane gave **9a** (756 mg, 95%) as a white solid: mp 152–154 °C; IR ($CHCl_3$) 3550, 1731, 1631, 1600, 1525, 1356 cm^{-1}; ^1H NMR (200 MHz, Me_2CO-d_6) δ 4.10 (s, 2H, CH_2COOH), 7.34 (dd, J = 2.9, 8.7 Hz, 1H, H-2), 7.42 (dt, J = 2.9, 8.9 Hz, 1H, H-4), 8.21 (dd, J = 5.2, 8.9 Hz, 1H, H-5); ^{13}C NMR (CD_3OD) δ 48.9, 125.1 (d, J = 23.2 Hz), 130.1 (d, J = 24.4 Hz), 137.7 (d, J = 10.3 Hz), 144.0 (d, J = 10.3 Hz), 154.8, 173.7 (d, J = 252.0 Hz), 180.5; MS *m/z* 199, 154. Anal. Calcd for $C_8H_6FNO_4$: C, 48.25; H, 3.04; N, 7.03; Found: C, 48.51; H, 2.99; N, 6.85.

Compound 10a. Nitration of **8b** as detailed above afforded two compounds **9b** and **10b** in 64 and 18% yield, respectively. Hydrolysis in refluxing 6 N HCl gave the corresponding acids **9a** and **10a** in 90% yield. **Compound 10a**: mp 153 °C (Et_2O/heptane); IR ($CHCl_3$) 3525, 1731, 1537, 1356 cm^{-1}; ^1H NMR (200 MHz, Me_2CO-d_6) δ 3.85 (s, 2H, CH_2COOH), 7.41 (dd, J = 1.6, 8.3 Hz, 1H, H-6), 7.50 (dd, J = 1.6, 12.3 Hz, 1H, H-2), 8.10 (t, J = 8.3 Hz, 1H, H-5); ^{13}C NMR δ 40.6, 119.4 (d, J = 21.0 Hz), 125.7, 125.9 (d, J = 22.8 Hz), 126.2 (d, J = 3.1 Hz), 143.2 (d, J = 7.8 Hz), 156.0 (d, J = 264.0 Hz), 172.1; MS *m/z* 199, 154. Anal. Calcd for $C_8H_6FNO_4$: C, 48.25; H, 3.04; N, 7.03; Found: C, 48.08; H, 3.25; N, 6.81.

Compound 15. Compound **15** was prepared as detailed for **10a**: mp 118–120 °C (Et_2O/heptane); IR ($CHCl_3$) 3525, 1731, 1537, 1356 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.85 (s, 2H, CH_2COOH), 7.55 (d, J = 8.4 Hz, 1H, H-6), 7.67 (s, 1H, H-2), 8.01 (d, J = 8.4 Hz, 1H, H-5), 11.10 (br s, 1H, COOH); ^{13}C NMR δ 40.5, 126.7, 130.9, 131.0, 133.9, 138.1, 143.1, 177.9; MS *m/z* 217, 215. Anal. Calcd for $C_8H_6ClNO_4$: C, 44.57; H, 2.81; N, 6.49; Found: C, 44.56; H, 2.84; N, 6.49.

Compound 17a. The solution of dipeptide **16** (196 mg, 0.7 mmol) in TFA–CH_2Cl_2 was stirred at room temperature under argon for 30 min. The volatile was removed in vacuo, and the residue was dissolved in CH_2Cl_2 (9 mL), DMF (1 mL), and Et_3N (200 μL, 1.4 mmol). After being stirred at room temperature for 30 min, the mixture was cooled to 0 °C, EDC (134 mg, 0.7 mmol) and **10** (140 mg, 0.7 mmol) were added, and stirring was continued for 4 h. The reaction was quenched with aqueous NH_4Cl and extracted with CH_2Cl_2. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated. The crude mixture was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH = 9/1) to give **17a** (226 mg, 90%) as a white solid: mp 180–181 °C; IR (KBr) 3390, 3315, 2931, 1650, 1530 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 3.71 (s, 2H, H-14), 3.89 (s, 2H, H-8), 4.31 (s, 2H, H-11), 6.70 (m, 3H, H-aromatics), 7.11 (t, J = 7.8 Hz, 1H, H-5), 7.30 (dd, J = 1.7, 8.1 Hz, 1H, H-16), 7.40 (dd, J = 1.7, 12.1 Hz, 1H, H-19), 8.05 (t, J = 8.1 Hz, 1H, H-17); ^{13}C NMR δ 42.7, 43.8, 44.0, 115.1, 115.3, 119.5, 120.1 (d, J = 21.4 Hz), 126.5 (d, J = 21.2 Hz), 127.0 (d, J = 6.5 Hz), 130.5, 141.2, 156.2 (d, J = 264.0 Hz), 158.7, 171.2, 172.4; MS *m/z* 361; HRMS *m/z* 361.1087 ($C_{17}H_{16}FN_3O_5$ requires 361.1074).

Compound 17b. Compound **17b** was prepared as detailed for **17a**: mp 140–142 °C; IR ($CHCl_3$) 3395, 3325, 1675, 1531, 1463, 1356 cm^{-1}; ^1H NMR (200 MHz, Me_2CO-d_6) δ 3.73 (s, 2H, H-14), 3.95 (d, J = 5.7 Hz, 2H, H-8), 4.31 (d, J = 6.0 Hz, 2H, H-11), 6.70 (m, 3H, H-aromatics), 7.09 (t, J = 7.6 Hz, 1H, H-5), 7.41 (dd, J = 1.4, 8.3 Hz, 1H, H-16), 7.5–7.8 (m, H-aromatics + 2NH), 7.91 (d, J = 8.3 Hz, 1H, H-17), 8.33 (s, 1H, OH); ^{13}C NMR δ 42.7, 43.8, 44.1, 115.2, 115.7, 119.7, 126.7, 130.6, 130.7, 132.4, 132.8, 133.8, 142.1, 158.9, 170.0, 170.6; MS *m/z* 379, 377.

Compound 2a. To the solution of compound **17a** (10.0 mg, 0.027 mmol) in DMF (2.7 mL, 0.01M) was added K_2CO_3 (11.5 mg, 0.083 mmol). The mixture was stirred at room temperature for 20 h. DMF was evaporated in vacuo, and the residue was dissolved in water and acidified with 1 N HCl. The aqueous solution was extracted with EtOAc (5 × 10 mL), and the organic phase was washed with brine, dried (Na_2SO_4), and evaporated. Recrystallization from EtOAc gave product **2a** as a white solid (6.3 mg, 66%): mp 341 °C dec; IR (KBr) 3343, 3281, 3080, 1638, 1510 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 3.61 (s, 2H, H-14), 3.75 (d, J = 5.4 Hz, 2H, H-8), 4.29 (d, J = 5.5 Hz, 2H, H-11), 7.05 (s, 1H, H-20), 7.25 (t, J = 6.8 Hz, 2H, H-6, H-19), 7.45 (d, J = 8.2 Hz, 1H, H-16), 7.52 (t, J = 6.8 Hz, 2H, H-4, H-5), 8.12 (d, J = 8.2 Hz, 1H, H-17), 8.61 (t, 1H, J = 5.4 Hz, NH-9), 8.68 (t, 1H, J = 5.5 Hz, NH-12); ^{13}C NMR δ 41.6, 42.4, 43.3, 114.5, 117.2, 119.9, 123.4, 125.1, 125.5, 129.9, 139.6, 142.3, 143.6, 148.0, 155.5, 168.5, 169.1; MS *m/z* 341, 311; HRMS *m/z* 341.1016 ($C_{17}H_{15}N_3O_5$ requires 341.1012).

Compound 2b. To the suspension of compound **2a** (30.0 mg, 0.088 mmol) in refluxing water was added Fe (49.1 mg, 0.88 mmol) and $FeSO_4$ (13.4 mg, 0.088 mmol). The reaction mixture was refluxed for 3 h, filtrated through Celite, and washed thoroughly with CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL) and EtOAc (3 × 15 mL). The organic phase was washed with brine, dried (Na_2SO_4), and evaporated. The crude mixture was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH = 9/1) to give **2b** (23.0 mg, 84%) as a white solid: mp 287–288; IR (KBr) 3443, 3287, 1635 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 3.35 (s, 2H, H-14), 3.70 (s, 2H, H-8), 4.25 (s, 2H, H-11), 6.8–7.0 (m, 5H, H-aromatics), 7.05 (dd, J = 1.9, 8.0 Hz, 1H, H-16), 7.25 (t, J = 7.8 Hz, 1H, H-5); ^{13}C NMR δ 40.1, 41.9, 43.2, 112.7, 115.4, 116.4, 119.1, 120.9, 123.6, 125.2, 129.2, 138.3, 140.7, 141.3, 157.3, 168.6, 170.8; MS *m/z* 311; HRMS *m/z* 311.1255 ($C_{17}H_{17}N_3O_3$ requires 311.1270).

Methyl 3-Methoxy-5-(isopropyloxy)benzoate (19). A solution of 3,5-dihydroxybenzoic acid (**7**) (20.0 g, 129.9 mmol) in dry methanol (100 mL) and H_2SO_4 (1 mL) was refluxed for 20 h. The volatile was removed in vacuo, and the residue was redissolved in EtOAc and washed with aqueous $NaHCO_3$, H_2O, and brine. The organic phase was dried (Na_2SO_4) and evaporated to give methyl 3,5-dihydroxybenzoate as a white solid (21.2 g, 98%): mp 170 °C (lit.[7a] mp 168–170 °C); ^1H NMR (200 MHz, $CDCl_3$) δ 3.85 (s, 3H, OMe), 6.55 (t, J = 2.2 Hz, 1H, H-4), 7.05 (d, J = 2.2 Hz, 2H, H-2 and H-6). To the solution of methyl 3,5-dihydroxybenzoate (20.3 g, 121 mmol) in dry acetone were added potassium carbonate (34.0 g, 246.0 mmol) and tetraethylammonium iodide (3.1 g, 12 mmol) followed by dimethyl sulfate (15.3 g, 121.0 mmol). The reaction mixture was refluxed for 5 h, cooled to room temperature, and filtrated. The filtrate was concentrated in vacuo, and the residue was partitioned between EtOAc and water. The aqueous phase was acidified to pH = 6 and extracted with EtOAc. The organic phase was dried (Na_2SO_4), evaporated, and purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH = 50/1) to give methyl 5-hydroxy-3-methoxybenzoate as a white solid (13.7 g, 62.2%): mp 95 °C (lit.[7a] mp 93–95 °C); ^1H NMR (200 MHz, $CDCl_3$) δ 3.78 (S, 3H, OMe), 3.92 (s, 3H, OMe), 5.90 (s, 1H, OH), 6.61 (t, 1H, J = 2.2 Hz, H-4), 7.14 (t, 1H, J = 2.2 Hz, H-2), 7.16 (t, 1H J = 2.2 Hz, H-6). To the solution of methyl 5-hydroxy-3-methoxybenzoate (15.0 g, 82.4 mmol) in DMF (60 mL) were added potassium carbonate (22.4 g, 162.1 mmol) and isopropyl bromide (22 mL, 234.0 mmol). The reaction mixture was heated at 100 °C for 90 min. Following the usual workup procedure, methyl 3-methoxy-5-(isopropyloxy)benzoate (**19**) was obtained as a colorless oil (18.1 g, 98%): IR ($CHCl_3$) 1722, 1596 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.33 (d, J = 6.1 Hz, 6H, OCHMe_2), 3.78 (s, 3H, OMe), 3.91 (s, 3H, OMe), 4.53 (septet, J = 6.1 Hz, 1H, OCHMe$_2$), 6.68 (t, J = 2.2 Hz, 1H, H-4), 6.9–7.0 (m, 2H, H-2 and H-6); ^{13}C NMR δ 22.1, 52.3,

55.7, 70.4, 107.1, 107.6, 109.1, 132.1, 158.9, 160.8, 173.1; MS *m/z* 224, 209, 193. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.19; H, 7.02.

3-Methoxy-5-(isopropyloxy)benzaldehyde (20). To the solution of compound **19** (18.5 g, 82.6 mmol) in THF (300 mL) at 0 °C was added LAH (6.3 g, 165.8 mmol). After being stirred at room temperature for 2 h, the reaction was quenched by 1 N NaOH and H_2O, and the white precipitate was filtrated through Celite. The filtrate was evaporated in vacuo to give the corresponding alcohol which was dissolved in dry CH_2Cl_2 and stirred in the presence of PCC for 2 h at room temperature. The reaction mixture was diluted with Et_2O, filtrated through Celite, and washed thoroughly with Et_2O. The filtrate was evaporated in vacuo and purified by flash chromatography (SiO_2, EtOAc/heptane = 1/5) to give **20** (1.92 g, 73%) as a colorless oil: IR ($CHCl_3$) 3043, 2940, 2847, 1705, 1596, 1495 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.35 (d, J = 6.1 Hz, 6H, OCH*Me*$_2$), 3.80 (s, 3H, OMe), 4.53 (septet, J = 6.1 Hz, 1H, O*CH*Me$_2$), 6.68 (t, J = 2.3 Hz, 1H, H-4), 6.9–7.0 (m, 2H, H-2 and H-6), 9.90 (s, 1H, CHO); ^{13}C NMR δ 22.0, 55.6, 70.3, 106.8, 107.8, 108.8, 108.9, 138.4, 159.6, 192.0; MS *m/z* 194. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.99; H, 7.30.

Compound 21. To a solution of **20** (1.50 g, 7.73 mmol) in CH_2Cl_2 was addded (*R*)-phenylglycinol (1.06 g, 7.73 mmol). After being stirred at room temperature for 3 h, the reaction mixture was cooled to 0 °C, and dry MeOH (4 mL) followed by TMSCN (1.54 mL, 11.60 mmol) were added successively. The reaction mixture was stirred at room temperature for 15 h. Concentration in vacuo followed by flash chromatography (SiO_2, Et_2O/heptane = 1/2) gave **21** (1.92 g, 73%) as a colorless oil: $[\alpha]_D$ = −41° (*c* = 0.33, $CHCl_3$); IR ($CHCl_3$) 3598, 2195, 1596, 1463, 1435 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.31 (d, J = 6.0 Hz, 6H, OCH*Me*$_2$), 3.55 (m, 1H, PhCH*CH*$_2$OH), 3.75 (s, 3H, OMe), 3.85 (m, 1H, PhCH*CH*$_2$OH), 4.25 (dd, J = 4.0, 9.1 Hz, 1H, Ph*CH*CH$_2$OH), 4.38 (brs, 1H, NCC*H*NH), 4.52 (septet, J = 6.0 Hz, 1H, O*CH*Me$_2$), 6.40 (t, J = 2.2 Hz, 1H, H-aromatic), 6.6–6.7 (m, 2H, H-aromatics), 7.30 (m, 5H, H-aromatics); ^{13}C NMR δ 22.1, 52.2, 55.6, 63.4, 67.5, 70.4, 102.6, 105.3, 107.5, 118.8, 127.5, 127.7, 128.6, 137.4, 138.4, 159.4, 161.4; MS *m/z* 314 (M^+ − 26), 282.

Compound 22. The solution of aminonitrile **21** (7.5 g, 20.58 mmol) in hydrochloride-saturated dry methanol was stirred at room temperature for 4 h. The volatile was removed in vacuo, and the residue was neutralized with phosphate buffer (pH 7). The aqueous phase was extracted with CH_2Cl_2. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated. The crude product was purified by flash chromatography (SiO_2, EtOAc/heptane = 1/2) to give **22** (7.0 g, 91%) as a colorless oil: $[\alpha]_D$ = −9.3° (*c* = 0.87, $CHCl_3$); IR ($CHCl_3$) 3626, 3339, 1738, 1599, 1468, 1435 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.31 (d, J = 6.0 Hz, 6H, OCH*Me*$_2$), 3.60 (m, 1H, PhCH*CH*$_2$OH), 3.68 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.6–3.7 (m, 1H, PhCH*CH*$_2$OH), 3.80 (dd, J = 4.2, 8.2 Hz, 1H, Ph*CH*CH$_2$OH), 4.21 (s, 1H, MeO$_2$CC*H*NH), 4.48 (septet, J = 6.0 Hz, 1H, O*CH*Me$_2$), 6.33 (t, J = 2.2 Hz, 1H, H-aromatic), 6.41 (m, 2H, H-aromatic), 7.30 (m, 5H, H-aromatics); ^{13}C NMR δ 21.9, 52.2, 55.2, 62.8, 63.2, 67.1, 69.8, 101.5, 105.0, 107.1, 127.5, 127.7, 128.6, 139.9, 140.3, 159.2, 160.9, 173.8; MS *m/z* 342 (M − OMe). Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 66.92; H, 7.24; N, 3.69.

Compound 23. To the solution of compound **22** (1.15 g, 3.1 mmol) in CH_2Cl_2 (20 mL) and MeOH (10 mL) at 0 °C was added $Pb(OAc)_4$ (1.51 g, 3.4 mmol). The reaction mixture was stirred at 0 °C for 10 min and diluted with phosphate buffer (pH 7), and stirring was continued for another 30 min. The precipitate was filtrated through Celite. The aqueous phase was extracted with CH_2Cl_2. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated to give the crude aldimine which was dissolved in ether (20 mL) and HCl (3 N, 20 mL). The reaction mixture was stirred at room temperature for 2 h. The aqueous phase was extracted with Et_2O to remove the neutral material. Water was evaporated in vacuo to give the pure hydrochloride salt of **23** (766 mg, 86%): mp 91–93 °C; $[\alpha]_D$ = +133° (*c* = 0.06, EtOH); IR ($CHCl_3$) 3580, 2983, 2955, 2846, 1756, 1602, 1465, 1437 cm^{-1}; ^1H NMR (200 MHz, Me_2CO-d_6) δ 1.28 (d, J = 6.0 Hz, 6H, OCH*Me*$_2$), 3.71 (s, 3H, OMe), 3.74 (s, 3H, OMe), 4.65 (septet, J = 6.0 Hz, 1H, O*CH*Me$_2$), 5.30 (s, 1H, ArC*H*), 6.45 (t, J = 1.8 Hz, 1H, H-4), 6.85 (d, J = 1.8 Hz, 1H, H-2), 6.87 (d, J = 1.8 Hz, H-6); ^{13}C NMR δ 22.4, 53.8, 56.1, 57.4, 70.7, 104.1, 107.2, 108.9, 134.9, 160.4, 162.2, 169.5; FABMS 254 (M − HCl + 1). Anal. Calcd for $C_{13}H_{20}ClNO_4$: C, 53.89; H, 6.96; N, 4.83. Found: C, 53.62; H, 7.03; N, 4.65.

Compound 24. To the solution of **23** (29 mg, 0.1 mmol) in CH_2Cl_2 (3 mL) and H_2O (2 mL) was added (*S*)-MeCH(OAc)-COCl (29 μL, 0.25 mmol) and solid $NaHCO_3$ until pH = 6. The reaction mixture was stirred at room temperature for 1 h, diluted with aqueous NH_4Cl, and extracted with CH_2Cl_2. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated. The crude mixture was purified by preparative chromatography (SiO_2, EtOAc/heptane = 1/2) to give **24** (26 mg, 71%): $[\alpha]_D$ = +83° (*c* = 0.13, $CHCl_3$); IR ($CHCl_3$) 3694, 3431, 1743, 1687, 1600, 1512, 1468 cm^{-1}; ^1H NMR (250MHz, $CDCl_3$) δ 1.32 (d, J = 6.0 Hz, 6H, OCH*Me*$_2$), 1.45 (d, J = 6.8 Hz, 3H, Me), 2.18 (s, 3H, *Me*CO), 3.71 (s, 3H, OMe), 3.79 (s, 3H, OMe), 4.55 (sept, J = 6.0 Hz, 1H, O*CH*Me$_2$), 5.22 (q, J = 6.8 Hz, 1H, *CH*OCOMe), 5.48 (d, J = 7.3 Hz, 1H, ArC*H*-COOMe), 6.38 (t, J = 2.2 Hz, 1H, H-aromatic), 6.4–6.5 (m, 2H, H-aromatics), 7.08 (d, J = 7.3 Hz, 1H, ArCHN*H*); ^{13}C NMR δ 17.8, 21.1, 22.1, 53.0, 55.4, 56.0, 70.1, 70.5, 102.1, 105.1, 106.9, 138.2, 161.3, 169.5, 169.8, 171.0; MS *m/z* 367, 308.

Compound 25. To the solution of compound **23** (784 mg, 2.71 mmol) in DMF was added Et_3N (830 μL, 5.92 mmol), *N*-Boc-Phe (789 mg, 2.98 mmol), and DPPA (642 μL, 2.98 mmol) at 0 °C. After being stirred for 2 h at 0 °C and 15 h at room temperature, the reaction was diluted with aqueous NH_4Cl and extracted with EtOAc. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated. The crude mixture was purified by flash chromatography (SiO_2, EtOAc/heptane = 1/2) to give **25** (900 mg, 66.4%): mp 89 °C (EtOAc/heptane); $[\alpha]_D$ = +72° (*c* = 0.12, $CHCl_3$); IR ($CHCl_3$) 3400, 3050, 2990, 1756, 1706, 1688, 1600, 1488, 1375 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.31 (d, J = 6.1 Hz, 6H, OCH*Me*$_2$), 1.39 (s, 9H, O*Bu*^{t}), 3.05 (m, 2H, Ph*CH*$_2$), 3.70 (s, 3H, OMe), 3.75 (s, 3H, OMe), 4.40 (m, 1H, PhCH$_2$C*H*), 4.51 (sept, J = 6.1 Hz, 1H, O*CH*Me$_2$), 5.05 (brs, 1H, NHBoc), 5.41 (d, J = 7.1 Hz, 1H, ArC*H*COOMe), 6.3–6.4 (m, 3H, H-aromatics), 6.78 (d, J = 7.1 Hz, 1H, ArCHN*H*), 7.1–7.3 (m, 5H, H-aromatics); ^{13}C NMR δ 22.1, 28.4, 38.5, 52.8, 55.5, 56.0, 56.7, 70.2, 80.5, 102.4, 105.3, 107.4, 127.0, 128.7, 129.4, 129.5, 136.6, 138.1, 159.6, 161.4, 170.7, 170.9; MS *m/z* 500, 427, 385. Anal. Calcd for $C_{27}H_{36}N_2O_7$: C, 64.78; H, 7.25; N, 5.60. Found: C, 64.47; H, 7.43; N, 5.69.

Compound 26. Compound **25** (240 mg, 0.47 mmol) was dissolved in dry CH_2Cl_2 (9 mL) and TFA (4.5 mL) and was set aside at room temperature for 1 h. The solvent was removed in vacuo and dried over an oil pump, and the so produced amine salt was dissolved in CH_2Cl_2 (16 mL) and Et_3N (145 μL, 0.94 mmol). After 30 min, the reaction mixture was cooled at 0 °C, and EDC (99 mg, 0.52 mmol) and **9a** (103 mg, 0.52 mmol) were added. After being stirred for 2 h at room temperature, the reaction was quenched with aqueous NH_4Cl and extracted with CH_2Cl_2. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated. The crude mixture was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH = 20/1) to give **26** (262 mg, 96%): mp 69 °C; $[\alpha]_D$ = +54° (*c* = 0.34, $CHCl_3$); IR ($CHCl_3$) 3690, 3420, 3025, 2950, 2843, 1743, 1675, 1600, 1525 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.28 (d, J = 6.0 Hz, 6H, OCH*Me*$_2$), 3.05 (d, J = 6.9, 2H, PhC*H*$_2$), 3.70 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.85 (s, 2H, H-14), 4.48 (sept, J = 6.0 Hz, 1H, O*CH*Me$_2$), 4.75 (q, J = 6.9 Hz, 1H, H-11), 5.36 (d, J = 7.1 Hz, 1H, H-8), 6.4–6.5 (m, 3H, H-aromatics), 6.68 (d, J = 7.1 Hz, 1H, NH-9), 6.85 (d, J = 6.9 Hz, 1H, NH-12), 6.9–7.3 (m, 7H, H-aromatics), 8.10 (dd, J = 5.2, 8.8 Hz, 1H, H-17); ^{13}C NMR δ 22.1, 38.2, 41.0, 52.8, 54.6, 55.5, 56.8, 70.2, 102.5, 105.4, 107.5, 115.5 (d, J = 23.0 Hz), 120.4 (d, J = 24.3 Hz), 127.1, 128.1 (d, J = 9.5 Hz), 128.7, 129.4, 133.8 (d, J = 9.1 Hz), 136.3, 137.9, 144.8 (d, J = 2.2 Hz), 159.6, 161.3, 165.5 (d, J = 256.0 Hz), 168.5, 170.1, 170.8; MS *m/z* 581, 550, 522. Anal. Calcd for $C_{30}H_{32}FN_3O_8$: C, 61.96; H, 5.51; N, 7.23. Found: C, 61.86; H, 5.29; N, 6.96.

Compound 27. To the solution of **26** (260 mg, 0.45 mmol) in dry CH_2Cl_2 at −78 °C was added BBr_3 (6.7 mL, 6.70 mmol), precooled at −78 °C. After being stirred for 7 min at −78 °C, the reaction mixture was quenched with aqueous NH_4Cl. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated. Recrystallization from EtOAc/heptane afforded **27** as a white solid (221 mg, 91%): mp 81 °C; $[\alpha]_D$ = +46° (*c* = 0.31, $CHCl_3$); IR ($CHCl_3$) 3400, 1749, 1663, 1629, 1609, 1530, 1337 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.90 (dd, *J* = 7.6, 13.8 Hz, 1H, PhCH_2), 3.05 (dd, *J* = 6.4, 13.8 Hz, 1H, PhCH_2), 3.63 (s, 3H, OMe), 3.67 (s, 2H, H-14), 3.73 (s, 3H, OMe), 4.91 (q, *J* = 7.2 Hz, 1H, H-11), 5.15 (d, *J* = 5.7 Hz, 1H, H-8), 6.34 (s, 2H, H-6 and H-20), 6.42 (s, 1H, H-4), 6.7−7.1 (m, 8H, H-aromatics + NH-12), 7.52 (s, 1H, OH), 7.80 (d, *J* = 5.7 Hz, 1H, NH-9), 8.01 (dd, *J* = 5.1, 9.1 Hz, 1H, H-17); ^{13}C NMR δ 38.3, 40.6, 52.9, 54.5, 55.4, 57.1, 101.9, 105.6, 106.7, 115.6 (d, *J* = 23.0 Hz), 120.2 (d, *J* = 24.2 Hz), 126.9, 127.8 (d, *J* = 10.5 Hz), 128.6, 129.3, 133.6 (d, *J* = 9.0 Hz), 136.2, 137.5, 144.9 (d, *J* = 2.9 Hz), 158.2, 161.2, 164.5 (d, *J* = 256.7 Hz), 169.3, 171.2, 171.4; MS *m/z* 539, 508. Anal. Calcd for $C_{27}H_{26}FN_3O_8$: C, 60.11; H, 4.82; N, 7.79. Found: C, 59.89; H, 4.91; N, 7.53.

Compound 3a. To the solution of compound **27** (35.0 mg, 0.065 mmol)) in THF (6.5 mL, 0.01M) was added K_2CO_3 (36.0 mg, 0.26 mmol) and 18-crown-6 (8.6 mg, 0.03 mmol). The mixture was stirred at room temperature for 20 h. Inorganic salt was filtrated out, the filtrate was evaporated in vacuo and the residue was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH = 100/1) to give **3a** as a pale yellow solid (27.3 mg, 81%): mp 280 °C dec; $[\alpha]_D$ = +120° (*c* = 0.1, $CHCl_3$/MeOH = 10/1); IR ($CHCl_3$) 3690, 3630, 1723, 1687, 1581, 1518, 1469 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.91 (dd, *J* = 7.8, 14.0 Hz, 1H, PhCH_2), 3.20 (dd, *J* = 7.4, 14.0 Hz, 1H, PhCH_2), 3.52 (d, *J* = 5.5 Hz, 1H, H-14), 3.74 (s, 3H, OMe), 3.83 (s, 3H, OMe), 4.10 (d, *J* = 5.5 Hz, 1H, H-14), 4.78 (m, 1H, H-11), 5.48 (d, *J* = 7.8 Hz, 1H, H-8), 6.12 (d, *J* = 9.0 Hz, 1H, NH-12), 6.48 (brs, 1H, H-20), 6.6−6.7 (m, 2H, H-4 and H-6), 6.90 (d, *J* = 2.6 Hz, 1H, H-19), 7.10 (dd, *J* = 2.6, 9.0 Hz, 1H, H-18), 7.2−7.4 (m, 6H, H-aromatics, NH-9), 8.05 (d, *J* = 9 Hz, 1H, H-17); ^{13}C NMR δ 36.8, 37.9, 40.7, 52.5, 53.0, 55.6, 104.3, 107.4, 110.9, 118.3, 118.6, 126.2, 127.5, 128.1, 129.0, 133.5, 137.5, 141.2, 144.6, 156.0, 159.0, 160.7, 168.2, 169.3, 169.6; MS *m/z* 519, 488, 460; HRMS *m/z* 519.1642 ($C_{27}H_{25}N_3O_8$ requires 519.1618).

Compound 3b. Compound **3a** (5.2 mg, 0.01 mmol) in MeOH was stirred at 1 atm of H_2 over Pd/C (10%) for 1 h. The reaction was filtrated through Celite, and the filtrate was evaporated and purified by preparative TLC (SiO_2, CH_2Cl_2/MeOH = 10/1) to give **3a** as a pale yellow solid (4.3 mg, 89%): mp 229 °C dec; $[\alpha]_D$ = +227° (*c* = 0.1, $CHCl_3$); IR ($CHCl_3$) 3410, 2928, 2856, 1742, 1665, 1611, 1593, 1504, 1456, 1438, 1295 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.91 (dd, *J* = 6.0, 13.4 Hz, 1H, PhCH_2), 3.02 (d, *J* = 12.7 Hz, 1H, H-14), 3.08 (dd, *J* = 9.2, 13.4 Hz, 1H, PhCH_2), 3.52 (d, *J* = 12.7 Hz, 1H, H-14), 3.65 (s, 3H, OMe), 3.77 (s, 3H, OMe), 4.62 (dt, *J* = 6.0, 9.2 Hz, 1H, H-11), 5.33 (d, *J* = 6.3 Hz, 1H, H-8), 6.02 (t, *J* = 1.5 Hz, 1H, H-20), 6.24 (d, *J* = 9.2 Hz, 1H, NH-12), 6.60 (m, 2H, H-4 and H-6), 6.66 (d, *J* = 2.6 Hz, 1H, H-19), 6.72 (d, *J* = 8.5 Hz, 1H, H-17), 6.81−6.84 (m, 2H, H-aromatic + NH-9), 7.1−7.3 (m, 5H, H-aromatics); ^{13}C NMR δ 32.0, 37.6, 39.2, 53.5, 55.5, 56.5, 103.4, 104.0, 108.7, 118.4, 120.1, 121.8, 123.3, 126.8, 128.5, 129.3, 136.6, 138.8, 141.5, 148.2, 160.9, 161.0, 169.6, 172.3, 173.1; MS *m/z* 489; HRMS *m/z* 489.1915 ($C_{27}H_{27}N_3O_6$ requires 489.1900).

Supporting Information Available: ^1H NMR spectra of **2a,b**, **3a,b**, **17a,b**, and **24** (7 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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