Synthesis of a 16-Membered Cyclic Peptide Model of the BCF Rings of Ristocetin A Using Arene–Ruthenium Chemistry Coupled with Cycloamidation

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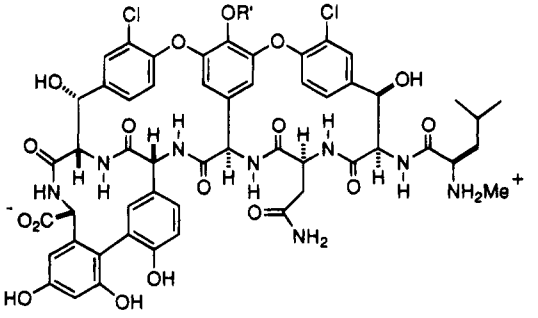
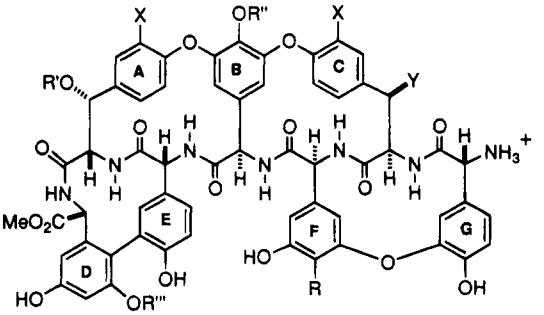
A convergent synthetic approach to the cyclic peptide **4**, which is a model for the B/C/F ring system of ristocetin B, is described. A key reaction is the coupling of the phenolic dipeptide **5**, constructed from arylglycine subunits, with the chlorophenylalanine–RuCp cationic complex **6**, followed by demetalation of the product to give the diaryl ether **7**, without epimerization at any of the amino acid residues. Deprotection of **7** followed by cycloamidation affords the target molecule **4**, produced as a mixture of atropdiastereomers which were separated and characterized by NMR spectroscopy.

Introduction

Vancomycin (**1**), ristocetin A (**2**), and teicoplanin (**3**) are representative members of an important family of glycopeptide antibiotics, the molecular structures of which are characterized by the presence of a heptapeptide backbone that is cross linked by aryl ether bonds.[1] A considerable challenge to the synthetic chemist is the presence of arylglycine subunits that are especially sensitive toward racemization under basic conditions, thereby restricting the methods that may be applied in the formation of the aryl ether linkages. Moreover, there exist very few methods for diaryl ether formation that may be used to directly couple two arylamino acid derivatives.[2] To date, there have been no reported total syntheses of vancomycin or its relatives, although Evans *et al.*[3] and Yamamura's group[4] have reported considerable progress on the construction of peptido aryl ethers related to vancomycin and Chakraborty has described methodology for the construction of an N-terminal 14-membered ring model of teicoplanin.[5] A recent report from our laboratory disclosed a successful approach to a similar 14-membered ring model for ristocetin A, based on the use of arene–manganese chemistry to set in place the requisite diaryl ether, followed by cycloamidation to connect the peptide ring.[6] For this approach to be successful for construction of the entire ristocetin molecule, there still remains the challenge of effecting cycloamidation for the formation of the 16-membered rings that characterize the A/B/C ring system, *in the presence of arylglycine functionality*.



(1) VANCOMYCIN (R' = sugar unit)



(2) X= H; Y = OH; R = Me: **RISTOCETIN A**

(3) X = Cl; Y = H; R = H: **TEICOPLANIN**

(R', R'' and R''' = sugar units)

We report in this paper a reinvestigation of methodology for construction of the 16-membered cyclic peptide **4**

[⊗] Abstract published in *Advance ACS Abstracts,* October 1, 1995.

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(2) The standard Ullmann coupling reaction for the preparation of diaryl ethers cannot be applied when *both* aromatic substrates have protected amino acid or peptide side chains; see: Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063. Boger, D. L.; Yohannes, D. *Tetrahedron Lett.* **1989**, *30*, 2053. Crimmin, M. J.; Brown, A. G. *Tetrahedron Lett.* **1990**, *31*, 2017. For studies on the construction of aryl thioethers that are related to vancomycin, see: Hobbs, D. W.; Still, W. C. *Tetrahedron Lett.* **1987**, *28*, 2805. For recent studies on the use of intramolecular S_NAr reactions to construct vancomycin models, see: Beugelmans, R.; Zhu, J.; Husson, N.; Bois-Choussy, M; Singh, G. P. *J. Chem. Soc., Chem. Commun.* **1994**, 439–440. Beugelmans, R.; Singh, G. P.; Bois-Choussy, M.; Chastanet, J.; Zhu, J. *J. Org. Chem.* **1994**, *59*, 5535–5542.

(3) Evans, D. A.; Ellman, J. A.; DeVries, K. M. *J. Am. Chem. Soc.* **1989**, *111*, 8912.

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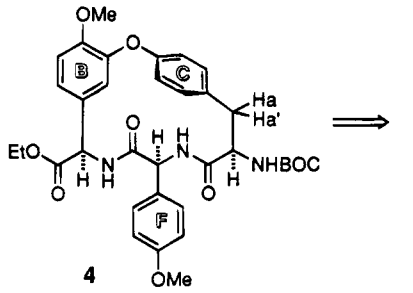
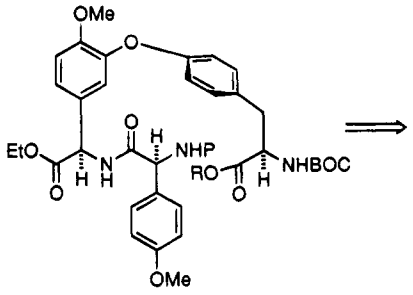
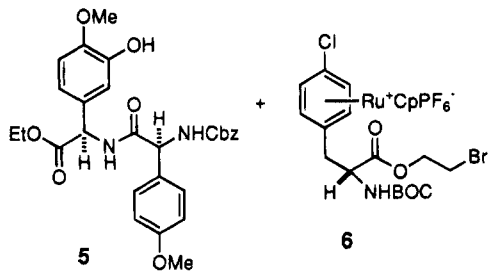
Scheme 1



4



7 P = Cbz, R = $BrCH_2CH_2$



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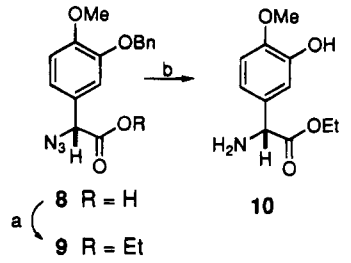
that is characteristic of the BC ring structure of ristocetin A, which illustrates the considerable utility of chloroarene–ruthenium complexes for effecting direct aryl ether formation between highly functionalized arylamino acid derivatives. Our approach requires formation of the cyclic peptide by using known cycloamidation techniques. In a previous study, macrocyclization of a simpler ristocetin model compound failed,[7] and similar difficulties were also reported from Williams' group.[8] Other groups have reported low-yielding cycloamidations, but none of these models carried sensitive arylglycine functionality in order to test for racemization or other problems that might accompany the ring closure.[9] The present model study reveals that the cycloamidation approach is a viable strategy for the construction of these systems, that arylglycine epimerization does not occur, but that the formation of atropdiastereomers is a secondary problem that is to some extent dependent on cycloamidation reaction conditions.

Results and Discussion

Our strategy for the construction of the model **4** is illustrated in Scheme 1. The 4-methoxyphenyl group as a substitute for the ristocetin F ring was chosen in order to lessen any possibility of base-promoted epimerization

Scheme 2[a]



[a] Reaction conditions, reagents, and yields: (a) PTSA/EtOH, reflux, 8 h, 71%; (b) H_2, Pd–C (10%), THF/MeOH (1:1), rt, 24 h, 99%.

of the amino acid side chain. We have also subsequently carried through an unsubstituted F-ring without epimerization problems, but in the interest of brevity this will not be discussed here (this obsevation implies the substitution pattern present in the natural products would not be problematic). Reaction of the phenolic dipeptide **5** with the chlorophenylalanine–ruthenium complex **6**, followed by demetalation, is expected to produce the diaryl ether **7** without racemization of the arylglycines, according to our earlier observations.[7]

Complex **6** was prepared, in essentially quantitative yield from the protected 4-chlorophenylalanine, according to the method described in our previous paper;[7] the protected amino acid components for the dipeptide **5** were each prepared by using Evans' asymmetric azidation reactions.[10] Azido acid **8**, which was used in our synthesis of the 14-membered ring peptide model,[6] was converted to ethyl ester **9** by standard Fischer esterification, and simultaneous hydrogenolysis of the benzyl ether and azide groups furnished the amino ester **10** in *ca.* 70% overall yield (Scheme 2). The N-protected 4-methoxyphenylglycine **15** was prepared starting from 4-methoxyphenylacetic acid (**11**) as outlined in Scheme 3. Azidation of **12** proceeded with *ca.* 95:5 diastereoselectivity (by ^1H NMR spectroscopy), and flash chromatography, followed by recrystallization, afforded diastereomerically pure **13**, which was converted to **15** by standard methods. Carbodiimide-promoted coupling of **10** with **15** (EDC/HOBT), followed by flash chromatographic purification, afforded the diastereomerically pure protected dipeptide **5** in 71% yield (Scheme 3).

Reaction of **5** with complex **6** was carried out using sodium 2,6-di-*tert*-butyl phenoxide as base, which we have previously found to allow the reaction to proceed without epimerization of the arylglycine residues. The NMR spectrum of the product complex **16** indicated the presence of two components, but owing to the relative thermal sensitivity of these complexes, we did not attempt further separation or characterization of this apparent mixture, but converted it directly to the uncomplexed diaryl ether **7**, as shown in Scheme 4. It should be noted that $[CpRu(CH_3CN)_3]PF_6$ is generally obtained in 75–85% yield from the decomplexation reaction; since this complex is used to attach the RuCp group to the protected chlorophenylalanine in the preparation of complex **6**, and since the latter is formed in essentially quantitative yield, this ability to recycle the ruthenium partly compensates for its stoichiometric use. The limiting factor for efficient recycling lies in the coupling reaction itself; while in general we have obtained

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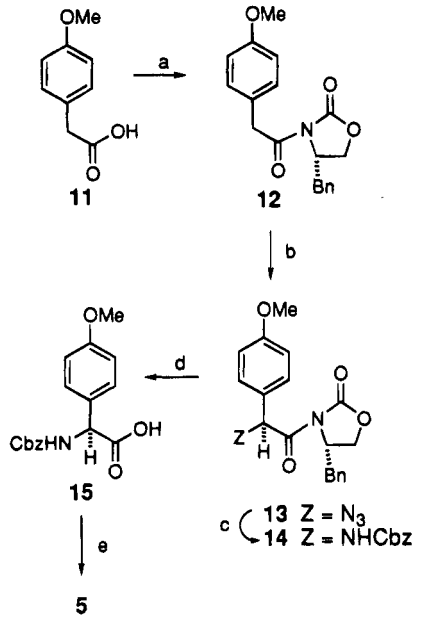
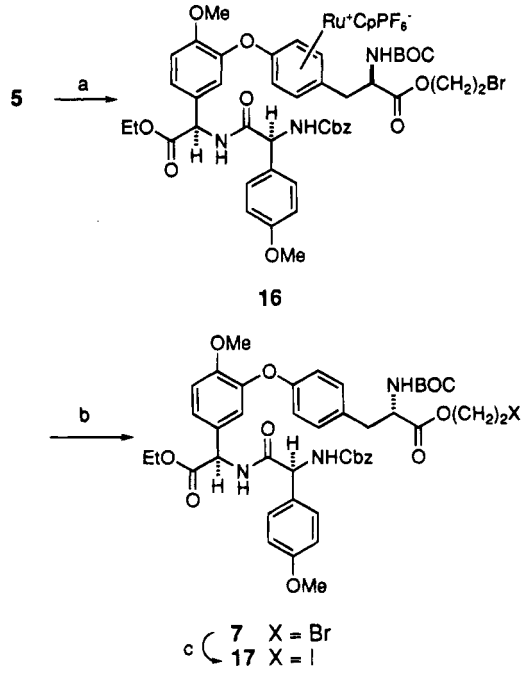
(8) Stone, M. J.; van Dyk, M. S.; Booth, P. M.; Williams, D. H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1629.
(9) Mann, M. J.; Pant, N.; Hamilton, A. D. *J. Chem. Soc., Chem. Commun.* **1986**, 158. Pant, N.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 2002. Crimmin, M. J.; Brown, A. G. Reference 2.
(10) Evans, D. A.; Britton, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 6881.

Scheme 3[a]



[a] Reaction conditions, reagents, and yields: (a) Et_3N, pivaloyl chloride, (4*S*)-4-(phenylmethyl)-2-oxazolidinone/*n*-BuLi, 79%; (b) KHMDS, trisyl azide, 68%; (c) H_2 (1 atm), Pd–C (10%), HCl (2.0 equiv), 8 h, rt, then CbzCl (1.5 equiv), $NaHCO_3$, 0 °C, 4 h, 80%; (d) LiOH (2.0 equiv), 0 °C, 1 h, quantitative; (e) **10**, EDC, HOBT, THF, 0 °C, 4 h, rt, 15 h, 71%.

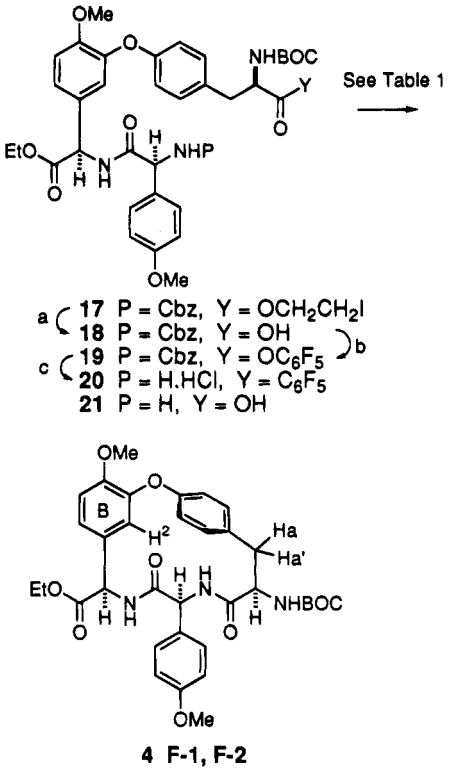
Scheme 4[a]



[a] Reaction conditions, reagents, and yields: (a) Na 2,6-di-*tert*-butylphenoxide (1.0 equiv), 0 °C, N_2, 15 min; **6** (1.0 equiv), 15 min (−78 °C) then 1.5 h (rt), 84%; (b) sun lamp (275 W), CH_3CN, N_2, 20–24 h, three times, 55%; (c) NaI (5.0 equiv), acetone, reflux, 5 h, N_2, 80%.

yields greater than 80% for this reaction, the present work gave only 55% for the formation of **16**. Again, two components were observed in the ^1H NMR spectrum of the purified compound **7** (see Experimental Section for details). That this phenomenon is a result of restricted rotation about a C–N bond, due to amide resonance, was readily established by the observation that **7** is a single

Scheme 5[a]



[a] Reaction conditions, reagents, and yields: (a) SmI_2 (6.5 equiv), DMPU (39.0 equiv), THF, 10 °C, 5 min, rt, 1 h, 79%; (b) pentafluorophenol (3.0 equiv), DCC (1.5 equiv), dichloromethane, 64%; (c) H_2 (1 atm), Pd–C (10%), EtOH, THF, HCl.

compound according to TLC and HPLC analysis and by variable temperature NMR studies in CD_3NO_2 as solvent: at 90 °C coalescence into a single set of resonances occurred; the doubling of peaks reappeared on cooling again to ambient temperature. Furthermore, control experiments in which an excess of **5** was subjected to the coupling reaction with **6** showed that no epimerization of **5** (recovered) had occurred, thereby ruling out the possibility of diastereomer formation during any events prior to the coupling reaction itself.

The next steps of our strategy required deprotection of the bromoethyl ester, removal of the *N*-benzyloxycarbonyl protecting group, and cycloamidation of the resulting amine/acid. We have previously noted problems with direct conversion of bromoethyl ester to carboxylic acid,[7] and we recently published a solution to this problem in which conversion to iodoethyl ester is followed by deblocking on exposure to samarium(II) iodide.[11] In these studies we have found that the early use of iodoethyl ester as blocking group leads to lower yields during the ruthenium complexation and subsequent reaction with phenoxides, and the most efficient strategy is to use complex **6**, followed by the deprotection tactics shown in Scheme 5, which furnished the carboxylic acid **18** in 70% overall yield from **7**. With this material in hand we were in a position to examine the cycloamidation using different methods. Our first choice was to use the activated pentafluorophenyl ester method, for which **18** was converted to **19**. Unmasking of the amine of **19** was followed by direct cyclization of **20** under standard conditions (high dilution, Et_3N, dioxane, 90 °C, 4 h; Scheme 5). Two

(11) Pearson, A. J.; Lee, K. *J. Org. Chem.* **1994**, *59*, 2304. Pearson, A. J.; Lee, K. *J. Org. Chem.* **1994**, *59*, 2257.

Table 1. Results of Cycloamidation Studies for Construction of 21

entry	starting mat.	concn (mM)	reagent used	base used (equiv)	reaction[a,b] condns	combined yield (%)	ratio[c] (F1/F2)
1	**20**	0.3		Et_3N (5)	(a) n.a. (b) 90 °C, 1,4-dioxane, 4 h	14	70:30
2	**22**	0.3	DCC/HOAT[d]	none	(a) 0 °C, CH_2Cl_2, 10 h (b) rt, 14 h	2	25:75
3	**22**	1.5	HAPyU[e]	(*i*-Pr)$_2$NEt (3.0)	(a) rt, DMF, 4.5 h (b) rt, 20 h	3	40:60
4	**22**	0.3	FDPP[f]	(*i*-Pr)$_2$NEt (2.0)	(a) 0 °C, DMF, 4 h (b) rt, 20 h	3	40:60

[a] Conditions for addition of starting material to the solution of coupling reagent. [b] Reaction time and temperature after addition. [c] Ratio was determined by ^{1}H NMR prior to HPLC separation of the mixture. [d] HOAT = 7-aza-1-hydroxybenzo triazole.[12a] [e] HAPyU = *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate.[12b] [f] FDPP = pentafluorophenyl diphenylphosphinate.[12c]

products were isloated by HPLC, both of which were shown to be cyclic monomers **4** by HRMS (M^+ = 633.2660 for fraction F-1 and 633.2701 for F-2; calcd = 633.2686; F-1 and F-2 refer to the faster and slower eluting products, respectively, from HPLC separation; see Experimental Section for further details). ^{1}H NMR spectroscopy provides further evidence for the cycloamidation, since the aromatic proton B-*H*^{2} is shifted to higher field (6.11 ppm for F-1 and 6.26 ppm for F-2, compared with between 6.7 and 7.5 for all other aromatic protons in both **4** and the acyclic precursors) as a result of shielding from the neighboring aromatic C-ring, a well-known feature in the NMR spectra of compounds in this series.[1,9] Table 1 summarizes the results of this and other cycloamidation reactions.

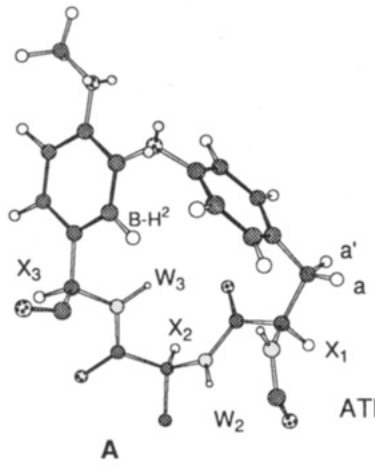
Two possibilities could account for the above observation: (1) products F-1 and F-2 are epimers, formed by partial racemization at one of the amino acid residues during amidation; (2) products F-1 and F-2 are atropisomers that are not readily interconvertible. We concluded that the latter explanation is the more likely, based on the following observations, coupled with molecular modeling. Conversion of **18** to the amine/acid **21**, followed by cycloamidation to **4** under mild conditions, using coupling reagents that are known to give racemization-free peptide bond formation[12] (Table 1) still gave *both* products F-1 and F-2, albeit in different ratios, and also in much lower yield. The only noteworthy difference between the ^{1}H NMR spectra of the two products is in the resonance corresponding to one of the phenylalanine methylene protons (labeled a and a′ in structure **4** and Figure 1). Thus, for the product labeled F-1, Ha′ appeared as a doublet of doublets with small vicinal coupling to Hx_1 (J_{gem} = 12.2, J_{vic} = 5.2 Hz) and Ha appeared as a doublet of doublets with *large* vicinal coupling (J_{gem} = 12.2, J_{vic} = 12.1 Hz); for product F-2, Ha′ and Ha both showed small vicinal coupling to Hx_1 (J_{gem} = 14.0, J_{vic} = 5.2 and 2.9 Hz, respectively). The couplings observed for protons x_3 and x_2 were similar for both compounds, in the range 7−9 Hz, and therefore not useful for structure determination (see Figure 1 for labeling of protons and Experimental Section for assignments; copies of spectra are included in the supporting information).

Figure 1 summarizes MM2 molecular modeling that we used to characterize F-1 and F-2 (Chem 3D Plus). There are two atropisomers that differ by the relative orientations of the aromatic B-ring and the peptide backbone, together with appropriate orientations of the side chains (see **A** and **A′**). We considered all epimers of each atropisomer that would arise by inversion at each amino acid residue. Focusing on atropisomer **A**, we can see that the calculated dihedral angles between Hx_1 and Ha or Ha′ match with the coupling constants found for product F-2. Epimerization at either of the arylglycine centers would not alter the expected couplings, whereas epimerization at the phenylalanine residue could account for the couplings that are shown by compound F-1 (a′:x_1 dihedral angle = 178°). But epimerization of phenylalanine residues under the conditions used here for cycloamidation is extremely unlikely. On the other hand, atropisomer **A′** has dihedral angles for a:x_1 and a′:x_1 that correspond to the coupling constants observed for F-1; the only way this conformation could produce a compound corresponding to F-2 is again by (unlikely) epimerization of the phenylalanine residue. It may be noted that all possible structural variations would lead to the couplings of 7−9 Hz that are observed for Hx_2 and Hx_3. On the basis of these considerations we assign the structures **A** and **A′** to the cycloamidation products F-2 and F-1, respectively. We did examine possible interconversion of these two products by variable temperature NMR, but no change was observed up to 140 °C, which is similar to observations made in our earlier work on the 14-membered cyclic peptides that were prepared as models for the ristocetin B/F/G ring system.[6] In further support of this proposal, we observed that exposure of compound F-2 to the reaction conditions used for cyclization of the pentafluorophenyl ester **4** produced no change, indicating that the mixture obtained from this cycloamidation is not a thermodynamic mixture of epimeric products, which are formed by base-catalyzed epimerization at the phenylalanine (or any other) residue. The observations made earlier concerning amide resonance for uncyclized systems may have some bearing on the cycloamidation reaction, but at this stage we have no experimental data that allow assignments to be made for the two equilibrating conformations.

Conclusions

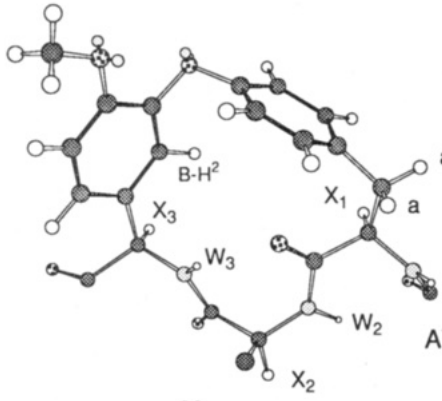
The reaction of chloroarene−ruthenium complexes with phenoxide nucleophiles allows formation of diaryl ethers under conditions that are sufficiently mild to tolerate sensitive functionality in both the chloroarene and the phenolic partners. In particular, dipeptides constructed from arylglycines can be used as the nucleophiles which can be coupled to chlorophenylalanine via its ruthenium complex. The use of stoichiometric ruthenium in these reactions is not considered to be a major drawback to the methodology because it can be recovered in high yield as $[CpRu(CH_3CN)_3]PF_6$, which is the reagent

(12) (a) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397. (b) Carpino, L. A.; El-Faham, A. *J. Org. Chem.* **1994**, *59*, 695. (c) Chen, S.; Xu, J. *Tetrahedron Lett.* **1991**, *32*, 6711.



A

		X_2 EPIMER	X_3 EPI	X_1 EPI
ENERGY	10.62	12.75	14.36	15.66
DIHEDRAL a/X_1	73°	72°	72°	61°
DIHEDRAL a'/X_1	43°	44°	44°	178°
DIHEDRAL X_2/W_2	146°	14°	148°	138°
DIHEDRAL X_3/W_3	140°	127°	134°	134°



A'

		X_2 EPIMER	X_3 EPI	X_1 EPI
ENERGY	15.92	14.30	15.72	16.02
DIHEDRAL a/X_1	179°	177°	179°	43°
DIHEDRAL a'/X_1	62°	61°	64°	73°
DIHEDRAL X_2/W_2	7°	147°	19°	7°
DIHEDRAL X_3/W_3	131°	127°	135°	133°

Figure 1. MM2-minimized structures corresponding to atropisomers (A and A′) of compound **4**, showing effect on dihedral angles between Ha/x_1 and Ha′/x_1 of epimerization at amino acid residues. Atoms corresponding to ester OEt, BOC OBu^t, and part of aromatic F-ring are hidden for viewing convenience. "X_2 (X_3, X_1) epimer", etc., refers to the structures resulting from inversion at X_2 (X_3, X_1); the structures are not included for clarity of presentation of the actual atropisomers that correspond to the products.

used to attach the RuCp group to the chloroarene. Subsequent manipulation of the diaryl ether, followed by cycloamidation, leads to a convergent approach for construction of the cyclic peptide ring system of compounds related to the B/C section of vancomycin and ristocetin A, though the cycloamidation does introduce a secondary problem, the formation of atropdiastereomers.

Experimental Section

General procedures are as described elsewhere.[6]

(2*R*)-2-Azido-2-[(3-(benzyloxy)-4-methoxy)phenyl]acetic Acid Ethyl Ester (9). The azido acid **8**[6] (2.03 g) was dissolved in 30 mL of dry EtOH, followed by addition of *p*-toluenesulfonic acid (2.24 g, 2.0 equiv), and the resulting mixture was heated under reflux overnight under N_2. The solvent was removed *in vacuo*, and the residue was dissolved in CH_2Cl_2 (80 mL). The organic layer was washed successively with 5% aqueous $NaHCO_3$ and saturated aqueous NaCl and dried over Na_2SO_4, and the solvent was removed *in vacuo*. Flash chromatography of the crude product on silica gel (hexanes/EtOAc, 8/2) provided 1.42 g (71%) of **9** as a white solid: mp 43.0−45.0 °C; $[\alpha]^{22}_D$ −93.5 (*c* 0.49, $CHCl_3$); R_f 0.37 (hexanes/EtOAc,7/3); IR ($CHCl_3$) 3019, 2996, 2935, 2117, 1741, 1601, 1523, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45−7.26 (m, 5H), 6.97−6.88 (m, 3H), 5.15 (s, 2H), 4.82 (s, 1H), 4.24−4.11 (m, 2H), 3.89 (s, 3H), 1.20 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 169.2, 150.4, 148.4, 136.6, 128.5, 127.9, 127.4, 126.1, 121.0, 113.0, 111.7, 71.0, 65.0, 62.0, 56.0, 14.0; HRMS calcd for $C_{18}H_{19}N_3O_4$ 341.1375, found 341.1369.

D-[(3-Hydroxy-4-methoxy)phenyl]glycine Ethyl Ester (10). To a slurry of preactivated (with H_2, 30 min) Pd−C (10%, 140.0 mg) in 40 mL of mixed solvent (THF/MeOH, 1/1) was added α-azido ethyl ester **9** (1.36 g, 3.98 mmol), and the resulting mixture was stirred for 24 h at rt under H_2 (1 atm). The solid Pd−C catalyst was filtered off through a Celite pad (1 × 2 cm), and the filter cake was washed well with MeOH (30 mL). The combined organic layers were concentrated *in vacuo* and dried under vacuum to furnish α-amino ethyl ester **10** (887.0 mg, 99%) as an off-white solid. The crude product was judged (NMR) to be sufficiently pure for the next reaction: mp 114.5−116.5 °C; $[\alpha]^{23}_D$ −97.6 (*c* 0.50, $CHCl_3$); R_f 0.36 (EtOAc/MeOH, 9/1); IR ($CHCl_3$) 3546, 3018, 2981, 1731, 1595, 1514, 1215 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.94 (d, 1H, J = 2.0 Hz), 6.84 (dd, 1H, J = 8.3, 2.0 Hz), 6.78 (d, 1H, J = 8.3 Hz), 4.54 (s, 1H), 4.27−4.08 (m, 4H), 3.84 (s, 3H), 1.20 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 173.5, 146.7, 145.9, 132.5, 118.5, 113.4, 110.9, 61.4, 58.0, 55.9, 14.0; HRMS calcd for $C_{11}H_{15}NO_4$ 225.1001, found 225.0999.

(4*S*)-3-[2-(4-Methoxyphenyl)-1-oxoethyl]-4-(phenylmethyl)-2-oxazolidinone (12). Freshly distilled Et_3N (2.25 mL, 1.30 equiv) and pivaloyl chloride (2.06 mL, 1.10 equiv) were added sequentially to a precooled (−78 °C), stirred solution of *p*-methoxyphenylacetic acid (**11**, 2.53 g, 15.2 mmol) in 70 mL of THF under N_2. The mixture was stirred for 20 min at −78 °C then 50 min at rt and cooled again to −78 °C. Into a separate flask containing 2.64 g (1.05 equiv) of (4S)-4-benzyl-2-oxazolidinone in 60 mL of THF at −78 °C was added *n*-BuLi (10.6 mL, 1.05 equiv, 1.51 M in hexanes), and the mixture was stirred for 30 min at −78 °C under N_2. The latter solution was then transferred to the mixed anhydrides solution via cannula, and the resulting mixture was stirred for 30 min at −78 °C and for 20 h at rt under N_2. The reaction was quenched with $NaHSO_4$ (100 mL, 1.0 N), and THF was removed *in vacuo* to give a pale-brown oily residue which was extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were washed with dilute $NaHCO_3$ and brine, dried over $MgSO_4$, and then filtered and concentrated. Flash column chromatography (SiO_2, hexanes/EtOAc, 7/3) provided a pale-yellow oil, which solidified in the refrigerator (3.88 g, 79%): mp 81.0−83.0 °C; $[\alpha]^{23}_D$ +64.6 (*c* 0.68, $CHCl_3$); R_f 0.28 (hexanes/EtOAc,7/3); IR ($CHCl_3$) 3024, 2981, 1781 1700, 1619, 1514, 1222 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.32−7.20 (m, 5H), 7.14 (d, 2H, J = 7.7 Hz), 6.89 (d, 2H, J = 7.7 Hz), 4.69−4.64 (m, 1H), 4.31−4.13 (m, 4H), 3.80 (s, 3H, −OC*H*$_3$), 3.26 (dd, 1H, J = 13.3, 3.3 Hz), 2.75 (dd, 1H, J = 13.3, 9.4 Hz); ^{13}C NMR ($CDCl_3$) δ 171.4, 158.8, 153.4, 135.1, 130.8, 129.4, 128.9, 127.3, 125.4, 114.0, 66.1, 55.3, 55.2, 40.7, 37.7; HRMS calcd for $C_{19}H_{19}NO_4$ 325.1314, found 325.1311.

(2*S*,4*S*)-3-[2-Azido-2-(4-methoxyphenyl)-1-oxoethyl]-4-(phenylmethyl)-2-oxazolidinone (13). KHMDS (14.3 mL, 0.5 M in toluene, 1.10 equiv) was added by syringe to a stirred, precooled (−78 °C) solution of imide **12** (2.11 g, 6.48 mmol) in 80 mL of THF, and the resulting solution was stirred for 30 min at −78 °C under N_2. Into this was transferred a precooled (−78 °C) solution of trisyl azide (2.51 g, 1.25 equiv) in 40 mL of THF via cannula, and the resulting mixture was stirred for 2 min at −78 °C and then rapidly quenched by addition of 1.30 mL (3.5 equiv) of glacial acetic acid and warmed immediately to *ca.* 35 °C with a water bath. The mixture was stirred for an additional 5 h at rt, diluted with 150 mL of Et_2O, was then washed with brine. The aqueous layer was extracted

with Et_2O (10 mL × 2) and the combined organic layers were washed successively with dilute $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a pale-brown residue. The diastereomer ratio in the crude product was determined to be 95:5 by ^{1}H-NMR (integration of MeO resonances). Flash column chromatography on silica gel (hexanes/EtOAc, 8/2) and subsequent recrystallization from hexanes/Et_2O gave 1.62 g (68%) of α-azido imidate **13** in a diastereomerically pure form: mp 120.0−121.5 °C; $[\alpha]^{22}_D$ +289.8 (*c* 0.51, $CHCl_3$); R_f 0.31 (hexanes/EtOAc, 7/3); IR ($CHCl_3$) 3689, 3627, 3030, 2981, 2110, 1787, 1706, 1613, 1514, 1222, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40−7.22 (m, 7H), 6.93 (d, 2H, *J* = 8.8 Hz), 6.11 (s, 1H), 4.67−4.61 (m, 1H), 4.19−4.07 (m, 2H), 3.81 (s, 3H), 3.41 (dd, 1H, *J* = 13.4, 3.1 Hz), 2.85 (dd, 1H, *J* = 13.4, 9.7 Hz); ^{13}C NMR ($CDCl_3$) δ 169.5, 160.4, 152.3, 134.8, 130.0, 129.4, 129.0, 127.5, 124.7, 114.5, 66.4, 63.2, 55.7, 55.3, 37.7; HRMS calcd for $C_{19}H_{18}N_2O_4$ $(M - N_2)^+$ 338.1266, found 338.1279.

(2*S*,4*S*)-3-[2-[[(Phenylmethoxy)carbonyl]amino]-2-(4-methoxyphenyl)-1-oxoethyl]-4-(phenylmethyl)-2-oxazolidinone (14). To preactivated (with H_2, 30 min) Pd−C (10%, 73.0 mg) in 40 mL of organic solvent (THF/MeOH, 1/1) were added 702.5 mg (1.92 mmol) of α-azido imidate **13** and 767 μL (2.0 equiv) of 5 N HCl, and the resulting slurry was stirred for 8 h at rt under H_2 (1 atm). The mixture was filtered through a Celite pad (1 × 5 cm), and the filter cake was washed well with MeOH (20 mL × 2). The combined organic layers were concentrated *in vacuo* and dried under high vacuum. The crude amine·HCl salt thus obtained above was dissolved in 25 mL of CH_2Cl_2, and the solution was cooled to 0 °C with an ice bath. To this was added 410.9 μL (1.50 equiv) of benzyl chloroformate followed by 25 mL of saturated $NaHCO_3$, and the resulting mixture was stirred for 4 h at 0 °C and then diluted with 20 mL of CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted further with CH_2Cl_2 (10 mL × 2). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Flash column chromatography on silica gel (hexanes/EtOAc, 7/3) afforded 723.2 mg (80%) of pure **14** as a white solid: mp 143.0−144.5 °C; $[\alpha]^{22}_D$ +166.2 (*c* 0.69, $CHCl_3$); R_f 0.56 (hexanes/EtOAc, 5/5); IR ($CHCl_3$) 3441, 3019, 2956, 2919, 1789, 1703, 1611, 1514, 1394, 1215 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.13 (d, 1H, *J* = 7.5 Hz), 7.38−7.26 (m, 12H), 6.90 (d, 1H, *J* = 8.6 Hz), 6.39 (d, 1H, *J* = 7.5 Hz), 5.10 (s, 2H), 4.69 (bs, 1H), 4.29−4.16 (m, 2H), 3.73 (s, 3H), 3.00 (bs, 2H); ^{13}C NMR (DMSO-d_6) δ 171.1, 159.9, 155.2, 152.2, 136.2, 135.1, 129.6, 129.4, 129.0, 128.5, 128.1, 127.6, 127.3, 114.3, 67.0, 66.2, 56.3, 55.7, 55.2, 37.6; HRMS calcd for $C_{27}H_{25}N_2O_6$ 473.1712, found 473.1684.

***N*-[*N*-[(Phenylmethoxy)carbonyl]-L-(4-methoxyphenyl)-glycinyl]-D-[(3-hydroxy-4-methoxyphenyl)glycine Ethyl Ester (5).** To a stirred, precooled (0 °C) solution of *N*-Cbz-imidate **14** (1.71g, 3.61 mmol) dissolved in 45 mL of THF was added dropwise LiOH (14.4 mL, 0.5 M in H_2O, 2.0 equiv), and the resulting suspension was stirred for 1 h at 0 °C. The mixture was diluted with 50 mL of Et_2O and separated. The aqueous layer was washed further with Et_2O (20 mL × 2) and then acidified with 10% HCl to ca. pH 2 and extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were dried over $MgSO_4$, evaporated, and dried under vacuum to give a white solid **15** (983.5 mg, 87%) which was used for the next coupling reaction without purification. A solution of amine **15** (702.6 mg, 3.12 mmol), acid **10** (983.5 mg, 1.0 equiv), and HOBT·H_2O (506.1 mg, 1.20 equiv) in 30 mL of THF was cooled to 0 °C with an ice bath. To this solution was added EDC (598.3 mg, 1.0 equiv; as hydrochloride salt, *not* methidide) in one portion, and the resulting mixture was stirred for 4 h at 0 °C and for 15 h at rt under Ar. The solvent was removed *in vacuo* at rt, and the residue was dissolved in 50 mL of CH_2Cl_2. The organic layer was washed with water (20 mL), $NaHSO_4$ (20 mL, 1.0 N), and brine, dried over $MgSO_4$, and then evaporated *in vacuo* to furnish a pale-brown residue. Flash column chromatography on silica gel (hexanes/THF, 6/4) and subsequent recrystallization from hexanes/THF (8/2) afforded the pure product **5** as white needles (1.14g, 71%): mp 163.0−165.0 °C; $[\alpha]^{23}_D$ +21.2 (*c* 0.68, $CHCl_3$); R_f 0.35 (hexanes/THF, 5/5); IR ($CHCl_3$) 3549, 3410, 3025, 2984, 1736, 1689, 1607, 1515, 1223, 1039 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5H), 7.24 (d, 2H, *J* = 8.5 Hz), 6.85−6.62 (m, 6H), 6.04 (d, 1H, *J* = 5.1 Hz), 5.78 (s, 1H), 5.37 (d, 1H, *J* = 6.7 Hz), 5.30 (d, 1H, *J* = 5.1 Hz), 5.04 (d, 1H, *J* = 12.3 Hz), 4.98 (d, 1H, *J* = 12.3 Hz), 4.20 (dq, 1H, *J* = 10.7, 7.1 Hz), 4.09 (dq, 1H, *J* = 10.7, 7.1 Hz), 3.82 (s, 3H), 3.78 (s, 3H), 1.19 (dd, 3H, *J* = 7.1, 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 170.5, 169.4, 159.6, 155.6, 146.7, 145.8, 136.1, 129.8, 128.8, 128.6, 128.4, 128.0, 118.8, 114.4, 113.1, 110.6, 66.9, 62.0, 58.0, 56.3, 55.8, 55.2, 13.9; HRMS calcd for $C_{28}H_{30}N_2O_8$ 522.2002, found 522.2035.

[η^6-(2*R*,2′*R*)-4-[[2-Methoxy-5-[1-[*N*-[[(phenylmethoxy)-carbonyl]-L-(4-methoxyphenyl)glycinyl]amino]-2-ethoxy-2-oxoethyl]phenoxy]-1-[2-[[(1,1-dimethylethoxy)carbonyl]-amino]-3-oxo-3-(2-bromoethoxy)propyl]benzene](η^5-cyclopentadienyl)ruthenium Hexafluorophosphate (16). A stock solution of sodium 2,6-di-*tert*-butylphenoxide was prepared as follows: Into a 50 mL round bottom flask containing 395.6 mg (1.92 mmol) of 2.6-di-*tert*-butylphenol and NaH (76.6 mg, 1.0 equiv, 60% in mineral oil) was added 30 mL of freshly distilled THF by syringe. The resulting slurry was stirred for 30 min at rt and then cooled to 0 °C with an ice bath under N_2. To a stirred, precooled (0 °C) solution of dipeptide **5** (162.5 mg) in 10 mL of THF was added 5.3 mL (1 equiv) of this stock solution by syringe, and the resulting mixture was stirred for 15 min at 0 °C under N_2. This cooled (0 °C) solution was then trasferred via cannula into a precooled (−78 °C) solution of arene−Ru complex **6** (241 mg, 1 equiv) in 10 mL of THF, and the resulting mixture was stirred under N_2 for 30 min at −78 °C and 1.5 h at rt and then evaporated *in vacuo* to afford a dark brown residue which was dissolved in 10 mL of CH_3CN. The CH_3CN solution was then filtered through a neutral alumina column (1 × 5 cm), and the column was washed further with 15 mL of CH_3CN. The combined filrate was concentrated to *ca.* 1 mL and then diluted with 40 mL of Et_2O. The ethereal mixture was cooled in a refrigerator for 1 h and decanted carefully. The pale-brown residue was washed further with cold Et_2O (10 mL × 2) and then dried under vacuum to provide the Ru complex **16** (330 mg, 84%) as a pale-brown solid foam, which was judged to be pure enough for the next reaction by ^{1}H NMR: IR ($CHCl_3$) 3640, 3422, 3024, 2981, 1744, 1713 (br), 1514, 1220, 1035, 849 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37−6.73 (m, 14H), 6.46−5.79 (m, 5H), 5.46−5.00 (m, 9H), 4.53−4.41 (m, 3H), 4.30−4.10 (m, 2H), 3.85 and 3.84 (2 × s, 3/2H each, $-OCH_3$ amide resonance), 3.83 and 3.79 (2 × s, 3/2H each, $-OCH_3$), 3.63−3.56 (m, 2H), 3.12−2.82 (m, 2H), 1.43 (s, 9H), 1.27−1.17 (m, 3H).

(2*R*)-3-[4-[2-[[(1,1-Dimethylethoxy)carbonyl]amino]-3-oxo-3-(2-bromoethoxy)propyl]phenoxy]-4-methoxy-*N*-[*N*-[(phenylmethoxy)carbonyl]-L-(4-methoxyphenyl)glycinyl]-D-phenylglycine Ethyl Ester (7). The arene−Ru complex **16** (290 mg, 0.24 mmol) was dissolved in 25 mL of dry CH_3CN in a quartz cell (1.5 × 20 cm), and the solution was degassed by bubbling with N_2 for 20−30 min. The resulting solution was irradiated with a sunlamp (275 W) for 20−24 h under N_2 (caution: no refluxing, slightly heated) and then cooled to rt and concentated *in vacuo* to *ca.* 1 mL, which was diluted with 40 mL of Et_2O. The etheral suspension was set aside for 2 h at rt to allow the $[CpRu(CH_3CN)_3]PF_6$ to settle and then filtered. The ether-insoluble filter cake was washed well with an additional 30 mL of Et_2O. The combined ether extracts were concentrated under reduced pressure to give a pale-brown residue which was purified by flash column chromatography (SiO_2, hexanes/EtOAc, 6/4), providing 85 mg of product **7** as an off-white solid. The filter cake and dark-brown deposits inside the flask were recovered in 25 mL of CH_3CN, and the resulting solution was bubbled with N_2 and then subjected to the same photochemical reaction conditions. Repeating the whole procedure twice provided an additional 41 mg of pure product. A total of 85.0 mg (80%) of crude $[CpRu(CH_3CN)_3]PF_6$ was recovered: total yield, 116 mg (55%); $[\alpha]^{22}_D$ +47.9 (*c* 0.56, $CHCl_3$); R_f 0.39 (hexanes/EtOAc, 5/5); IR ($CHCl_3$) 3432-(br), 3027, 2985, 1733, 1716, 1683, 1609, 1509, 1221, 1171, 1032 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30−6.73 (m, 17H), 6.05 (bs, 1H), 5.42 and 5.37 (2 × d, 1/2H each, *J* = 6.9 Hz, $-CHNHCbz$, amide resonance), 5.27 (d, 1H, *J* = 4.5 Hz), 5.09−4.98 (m, 3H,

two doublets of $-OCH_2Ph$ overlapped with $-NHBOC$) 5.08 (d, 1H, J = 12.4 Hz), 5.00 (d, 1H, J = 12.4 Hz), 4.58 (bs, 1H), 4.41–4.35 (m, 2H), 4.19–4.05 (m, 2H), 3.79 and 3.77 (2 × s, 3/2H each, $-OCH_3$, amide resonance), 3.768 and 3,75 (2 × s, 3/2H each, $-OCH_3$, amide resonance), 3.46–3.4 (m, 2H), 3.06 (bs, 2H), 1.41 (s, 9H), 1.19–1.10 (m, 3H); ^{1}H NMR (CD_3NO_2, 90 °C) 7.36–6.77 (m, 17H), 6.07 (d, 1H, J = 4.9 Hz), 5.44–5.40 (m, 1H), 5.27–5.23 (m, 2H), 5.07 (s, 2H), 4.49–4.42 (m, 3H), 4.21–4.08 (m, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.60–3.56 (m, 2H), 3.16 (dd, 1H, J =14.2, 5.9 Hz), 3.00 (dd, 1H, J =14.2, 8.2 Hz), 1.38 (s, 9H); HRMS FAB (m-NBA) calcd for $C_{44}H_{51}N_3O_{12}Br$ $(MH)^+$ (^{79}Br, ^{81}Br), 892.2656, 894.2635 found $(MH)^+$ (^{79}Br, ^{81}Br) 892.2612, 894.2592. Anal. Calcd for $C_{44}H_{50}N_3O_{12}Br$: C, 59.19; H, 5.64; N, 4.71. Found: C, 59.40; H, 5.85; N, 4.48.

(2*R*)-3-[4-[2-[[(1,1-Dimethylethoxy)carbonyl]amino]-3-oxo-3-(2-iodoethoxy)propyl]phenoxy]-4-methoxy-*N*-[*N*-[(phenylmethoxy)carbonyl]-L-(4-methoxyphenyl)glycinyl]-D-phenylglycine Ethyl Ester (17). To a stirred solution of bromoethyl ester **7** (137 mg, 0.16 mmol) in 10 mL of dry acetone was added 119 mg (5.0 equiv) of anhydrous NaI in one portion, and the resulting slurry was heated under reflux for 6 h under N_2. The reaction mixture was cooled to rt and then filtered, and the filter cake was washed well with acetone (10 mL × 2). Solvent was removed *in vacuo* to afford a solid residue which was taken up in 30 mL of CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtered, and then evaporated. The product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 5/5) to give 135 mg (89%) of **17** as a white foam: R_f 0.37 (hexanes/EtOAc, 5/5); $[\alpha]^D_{22}$ +41.2 (c 0.5, $CHCl_3$); IR ($CHCl_3$) 3422(br), 3024, 2962, 1734, 1712, 1685, 1612, 1508, 1222, 1171, 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.31–6.66 (m, 17H), 6.01 (bs, 1H), 5.42 and 5.37 (2 × d, 1/2H each, J = 7.0 Hz, $-CHNHCbz$), 5.23 (bs, 1H), 5.10–4.99 (m, 3H, two doublets of $-OCH_2Ph$ overlapped with $-NHBOC$), 5.08 (d, 1H, J = 12.5 Hz), 5.01 (d, 1H, J = 12.5 Hz), 4.57 (bs, 1H), 4.36-4.31 (m, 2H), 4.17–4.06 (m, 2H), 3.81 and 3.76 (2 × s, 3/2H each, $-OCH_3$), 3.25–3.19 (m, 2H), 3.11–3.07 (m, 2H), 1.42 (s, 9H), 1.25–1.11 (m, 3H); LRMS FAB (m-NBA) calcd for $C_{44}H_{51}N_3O_{12}I$ $(MH)^+$ 940, found $(MH)^+$ 940. Anal. Calcd for $C_{44}H_{50}N_3O_{12}I$: C, 56.23; H, 5.36; N, 4.47. Found: C, 56.52; H, 5.57; N, 4.30.

(*R*)-4-[2-Methoxy-5-[1-[*N*-[[(Phenylmethoxy)carbonyl]-L-(4-methoxy phenyl)glycinyl]amino]-2-ethoxy-2-oxoethyl]phenoxy]-*N*-[(1,1-dimethylethoxy)carbonyl]-D-phenylalanine (18). To a stirred solution of **17** (77.7 mg, 0.083 mmol) in 8 mL of THF was added by syringe DMPU (390.0 μL, 39.0 equiv), and the resulting solution was cooled to 10 °C with an ice/water bath under Ar. To this was added by syringe 5.38 mL of SmI_2 solution (6.5 equiv, 0.1 M in THF). The solution color immediately changed to a dark purple (suspension). After the solution was stirred for 5 min at 10 °C and then an additional 1 h at rt, the color of the suspension slowly changed to pale yellow. Stirring was continued for 1 h at rt, and the reaction mixture was diluted with 50 mL of CH_2Cl_2 and then treated with 10 mL of 0.1 N HCl. The organic layer was separated, and the aqueous layer was extracted further with CH_2Cl_2 (10 mL × 3). The combined organic extracts were washed with 10 mL of $Na_2S_2O_3$ (0.2 M) and brine and dried over $MgSO_4$. The solvent was evaporated in *vacuo* to give a pale-yellow oil which was purified by flash chromatography on silica gel (hexanes/EtOAc/AcOH, 35/65/1% then CH_2Cl_2/EtOAc/AcOH, 75/25/1%). The fractions containing product were diluted with heptane (30 mL) and concentrated under reduced pressure while the bath temperature was maintained below 10 °C. The concentrated solution was diluted again with heptane (10 mL) and evaporated in *vacuo* under 10 °C to give 51 mg (79%) of **18** as a white powder: R_f 0.48 (EtOAc/hexanes/AcOH, 8/2/1%); $[\alpha]^{24}_D$ +36.9 (c 0.51, $CHCl_3$); IR ($CHCl_3$) 3683, 3615, 3434 (br), 3018, 2981, 1730, 1709 (br), 1684, 1613, 1514, 1427, 1222, 1041, 936 cm^{-1}; ^{1}H NMR ($CD_3CN/CDCl_3$, 7/3) shows amide resonance: δ 7.32–6.70 (m, 17H), 6.28 (d, 1H, J = 1.5 Hz), 5.39 (bs, 1H), 5.33 (d, 1H, J = 7.0 Hz), 5.22 (d, 1H, J = 7.3 Hz), 5.07 (d, 1H, J = 12.6 Hz), 5.01 (d, 1H, J = 12.6 Hz), 4.33–4.29 (m, 1H), 4.16–4.02 (m, 2H), 3.78 and 3.77 (2 × s, 3/2H each, $-OCH_3$), 3.752 and 3.746 (2 × s, 3/2H, $-OCH_3$), 3.08 (dd, 1H, J = 13.8, 5.2 Hz), 2.89 (dd, 1H, J = 13.8, 8.3 Hz), 1.37 (s, 9H), 1.15 and 1.09 (2 × t, 3/2H each, J = 7.2 Hz); HRMS FAB (m-NBA) calcd for $C_{42}H_{48}N_3O_{12}$ $(MH)^+$ 786.3238, found 786.3241. Anal. Calcd for $C_{42}H_{47}N_3O_{12}$: C, 64.19; H, 6.03; N, 5.35. Found: C, 63.75; H, 6.37; N, 5.03.

(*R*)-4-[3-[1-[*N*-[*N*-[(Phenylmethoxy)carbonyl]-L-(4-methoxyphenyl)glycinyl]amino]-2-(ethoxycarbonyl)ethyl]-4-methoxyphenoxy]-*N*-[(1,1-dimethylethoxy)carbonyl]-D-phenylalanine Pentafluorophenyl Ester (19). To a stirred, precooled (0 °C) solution of **18** (57 mg, 0.073 mmol) and pentafluorophenol (40 mg, 3.0 equiv) in 10 mL of CH_2Cl_2 was added DCC (23 mg, 1.5 equiv), and the resulting mixture was stirred for 3 h at 0 °C and then for 12 h at rt under Ar. The reaction mixture was diluted with 40 mL of CH_2Cl_2 and then washed with dilute $NaHCO_3$, dried over $MgSO_4$, and filtered. Removal of the solvent under reduced pressure afforded a pale yellow residue, which was purified by flash chromatography on silica gel (hexanes/EtOAc) to give 44 mg (64%) of **19**. After the ^{1}H NMR spectrum was obtained, the product was subjected to the next reaction *immediately* without further purification: ^{1}H NMR ($CDCl_3$) shows amide resonance: δ 7.36–6. (m, 17H), 6.81 (bs, 1H), 5.94 (d, 1H, J = 5.2 Hz), 5.42 and 5.36 (2 × d, 1/2H each, J = 6.8 Hz, $-CHNHCbz$), 5.18 (bs, 1H), 5.09 (d, 1H, J = 12.3 Hz), 5.02 (d, 1H, J = 12.3 Hz), 4.97–4.84 (m, 1H), 4.16–4.02 (m, 2H), 3.81 and 3.79 (2 × s, 3/2H each, $-OCH_3$), 3.78 and 3.76 (2 × s, 3/2H each, $-OCH_3$), 3.29–3.13 (m, 2H), 1.43 (s, 9H), 1.20–1.07 (m, 3H).

(1*R*,2*R*)-[*N*-[1-[3-[4-[2-[[(1,1-Dimethylethoxy)carbonyl]-amino]-3-oxo-3-(pentafluorophenoxy)propyl]phenoxy]-4-methoxyphenyl]-2-ethoxy-2-oxoethyl]amino]-(*S*)-(4-methoxyphenyl)glycine Hydrochloride (20). To a stirred slurry of 10% Pd–C (44.0 mg) in 10 mL of 30% EtOH in THF were added **19** (44.1 mg, 0.0464 mmol) and 18.5 μL of HCl (5.0N, 2.0 equiv). The resulting slurry was stirred for 3 h under H_2 (1atm). The mixture was filtered through a Celite pad (1 × 2 cm), and the filter cake was washed with 20 mL of THF. The combined filtrate and washings were evaporated to afford a pale yellow residue which was dissolved in 20 mL of CH_2Cl_2. Removal of the solvent gave a solid residue which was dried under high vacuum for 30 min and then subjected to the cyclization reaction without characterization.

(1*R*,2*R*)-[*N*-[1-[3-[4-[2-[[(1,1-Dimethylethoxy)carbonyl]-amino]-3-hydroxy-3-oxopropyl]phenoxy]-4-methoxy]phenyl]-2-ethoxy-2-oxoethyl]amino]-(*S*)-(4-methoxyphenyl)-glycine (21). To a stirred slurry of Pd–C(10%, 38.6mg) in 10 mL of organic solvent (30% EtOH in THF) was added **18** (38.6 mg, 0.0492 mmol), and the resulting slurry was stirred for 4 h under H_2 (1 atm). The reaction mixture was filtered through Celite, and the filter cake was washed with 20 mL of THF. The combined filtrate and washings were evaporated to give a solid residue which was dissolved again in 20 mL of CH_2Cl_2. Removal of the solvent afforded a pale yellow residue which was dried under vacuum for 3 h and then subjected to the cyclization reaction without characterization.

Cycloamidation Reactions. (i) Pentafluorophenyl ester/Et$_3$N method. The pentafluorophenyl ester–amine·HCl salt **20** (0.04 mmol) dissolved in 15 mL of dry 1,4-dioxane was added slowly to a stirred, warmed (90 °C) solution of Et_3N (32.3 μL, 5.0 equiv) in 150 mL of 1,4-dioxane by syringe pump over 3 h under Ar atmosphere. After being stirred for an additional 1 h at 90 °C, the mixture was cooled to rt, and then the solvent was removed *in vacuo* to give a brown residue, which was dissolved again in 30 mL of CH_2Cl_2. The solution was washed with 10 mL of HCl (1.0 N) and brine, dried over $MgSO_4$, filtered, and evaporated. By TLC analysis (silica gel, hexanes/EtOAc, 5/5), several UV-active substances were observed. By the first HPLC analysis (column: Whatman Partisil M20 10/25; eluent: CH_2Cl_2/EtOAc, 75/25; flow rate: 6 mL/min), combined fractions (4.2 mg, 14%) of **4** (F-1) (t_R = 32.2 min) and **4** (F-2) (t_R = 33.4 min) were separated, and ^{1}H-NMR was taken to show that this was a mixture of two cyclization products with a ratio of 70:30. By a second HPLC separation (column: silica gel Whatman Magnum 9; eluent: hexanes/EtOAc, 1:1; flow rate 5 mL/min), the mixture was separated into two fractions **4** (F-1) (1.5 mg, t_R = 14.9 min) and **4** (F-2) (0.8 mg, t_R = 20.8 min). **4** (F-1): R_f 0.50 (EtOAc/hexanes, 6/4); $[\alpha]^{22}_D$ +31.1 (c 0.15, MeOH); IR ($CHCl_3$) 3687, 3622, 3413 (br),

3019, 2979, 2939, 1735, 1708, 1667, 1603, 1512, 1425, 1227, 929 cm^{-1}; ^1H NMR ($CD_3CN/CDCl_3$, 7/3) δ 7.40–6.81 (m, 12H), 6.13 (s, 1H, B – H^2), 5.41–5.38 (m, 2H), 5.40 (d, 1H, J = 8.2 Hz, Hx_3), 5.25 (d, 1H, J = 7.1 Hz, Hx_2), 4.31–4.18 (m, 3H), 3.93 (s, 3H), 3.75 (s, 3H), 3.17 (dd, 1H, J = 12.2, 5.2 Hz, Ha'), 2.74 (dd, 1H, J = 12.2, 12.1 Hz, Ha), 1.41 (s, 9H), 1.30–1.26 (m, 3H); HRMS calcd for $C_{34}H_{39}N_3O_9$ 633.2686, found 633.2660; MS *m/e* 634 (9), 633 (29), 577 (56), 560 (25), 533 (67), 516 (33), 490 (100), 443 (18), 415 (20), 401 (15).

4 (F-2): R_f 0.38 (EtOAc/hexanes, 6/4); $[\alpha]^{22}_D$ +12.3 (*c* 0.08, $CHCl_3$); IR ($CHCl_3$) 3689, 3615, 3018, 2981, 1776, 1714, 1670, 1602, 1526, 1421, 1215, 929 cm^{-1}; ^1H NMR ($CD_3CN/CDCl_3$, 7/3) δ 7.45–6.77 (m, 12H), 6.23 (s, 1H, B – H^2), 5.50–5.40 (m, 2H), 5.48 (d, 1H, J = 9.2 Hz, Hx_3), 5.24 (d, 1H, J = 7.0 Hz, Hx_2), 4.34–4.29 (m, 1H), 4.28–4.16 (m, 2H), 3.93 (s, 3H), 3.76 (s, 3H), 3.35 (dd, 1H, J = 14.0, 5.2 Hz, Ha'), 2.90 (dd, 1H, J = 14.0, 2.9 Hz, Ha), 1.47 (s, 9H), 1.31–1.26 (m, 3H); HRMS calcd for $C_{34}H_{39}N_3O_9$ 633.2686, found 633.2701; MS *m/e* 633 (2), 577 (6), 533 (100), 516 (12), 505 (26), 490 (96), 475 (7), 460 (9), 432 (10), 415 (14).

(ii) (DCC/HOAT) Method. The acid amine salt **21** (0.0492 mmol) dissolved in 20 mL of CH_2Cl_2 was slowly added to a stirred, precooled (0 °C) solution of DCC (22.2 mg, 2.2 equiv) and HOAT (19.9 mg, 3.0 equiv) in 160 mL of CH_2Cl_2 by syringe pump over 10 h. The resulting solution was stirred further for 14 h at rt under Ar and then washed with 20 mL of HCl (1.0 N) and brine, dried over $MgSO_4$, filtered, and concentrated. By using the same first HPLC analysis conditions as in method i, the overlapping fraction of **4** (F-1) and **4** (F-2) was collected and the ratio was determined to be 20:80 by ^1H-NMR.

(iii) HAPyU Method. To a stirred solution of the acid amine salt **21** (0.0490 mmol) in 35 mL of dry DMF were added HAPyU (923.4 mg, 1.10 equiv) and (i-Pr)$_2$NEt (25.7 μL, 3.0 equiv), and the resulting solution was stirred for 4.5 h at rt under Ar. The solvent was removed under vacuum with warming (40 °C), and the resulting brown residue was dissolved again in 30 mL of CH_2Cl_2. The CH_2Cl_2 layer was washed with 10 mL of HCl (1.0 N) and brine, dried over $MgSO_4$, filtered, and concentrated. By using the same first HPLC analysis conditions as the (pentafluorophenyl ester/Et_3N) method, the overlapping fraction of **4** (F-1) and **4** (F-2) was collected and the ratio was determined to be 40:60) by ^1H-NMR.

(iv) FDPP Method. The acid amine salt **21** (0.0545 mmol) dissolved in 20 mL of dry DMF was added slowly to a solution of FDPP (25.1 mg, 1.20 equiv) and (i-Pr)$_2$NEt (1.90 μL, 2.0 equiv) by syringe over 4 h under Ar. The resulting solution was stirred further for 20 h at rt. The solvent was removed under high vacuum with warming (40 °C), and the residue was worked up as in iii. The ratio of **4** (F-1) and **4** (F-2) was determined to be 40:60 by ^1H-NMR.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for all new compounds (20 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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