# Synthesis of a 14-Membered Cyclic Peptide Model of the CFG Rings of Ristocetin A and Observations on Atropdiastereoisomerism

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Two routes for the synthesis of a 14-membered heterodetic cyclic peptide as a model for the CFG ring system of the antibiotic ristocetin A (2) are described. The key aryl ether bonds for this molecule were constructed by using the reaction of phenoxides from (hydroxyaryl)glycine derivatives with tricarbonyl(3-methoxy-2-methylchlorobenzene)manganese hexafluorophosphate (11). This coupling reaction can be performed in the presence of protected amino acids and dipeptides without racemization of the sensitive arylglycine. Stereoselective introduction of the F-ring glycine side chain was accomplished by reaction of the aryl ether manganese complexes with Schöllkopf's bislactim glycine enolate equivalent. The product(s) from this reaction were demetalated and aromatized by treatment with *N*-bromosuccinimide. Deprotection of the aromatized compounds followed by cycloamidation furnished two atrodiastereomeric cyclic peptides corresponding to the target molecule, the structures of which were assigned on the basis of 2D-NMR NOESY experiments coupled with molecular modeling. One of the product molecules corresponds closely to the structure that has been proposed for the CFG ring system of ristocetin, except for the orientation of the $w_3$ amide group.

## Introduction

Vancomycin (1), ristocetin A (2), and teicoplanin (3) are representative members of a large and growing 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. The exact structure of each molecule varies mostly in the right-hand section, according to the amino acid subunits that constitute the peptide backbone.[1] These molecules represent an undeniable challenge for the synthetic organic chemist, not least because of the presence of arylglycine subunits that are especially sensitive toward racemization under mildly 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 couple directly two arylamino acid derivatives.[2] To date there has been no successful total synthesis of vancomycin or its relatives recorded in the literature, although Evans *et al.*[3] and Yamamura's group[4] have reported successful model studies 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] Superimposed on the difficulties of bond construction is the possibilty for atropdiastereomer formation in each of the heterodetic cyclic peptide subunits, as discussed later.

We have developed techniques that allow the construction of diaryl ethers which have amino acid and/or peptide functionalty on *both* aromatic rings and which are closely related to the F/G and C/F/G ring systems of ristocetin A.[6] The methodology that has been developed during these synthetic studies allows (a) diaryl ether formation without racemization of arylglycine subunits, (b) attachment of a second glycine side chain to the aryl ether system without racemization of a preexisting arylglycine component, and (c) the direct coupling of two protected arylamino acids or their derived peptides to give aryl ether derivatives. The objective of this most recent chapter in our studies was to construct a model CFG ring moiety of ristocetin A using arene–manganese chemistry in order to probe potential problems in a projected synthesis of this antibiotic.

Our approach requires formation of the cyclic peptide by using cycloamidation techniques. In a previous study, macrocyclization of a model compound which resembled the BC ring of ristocetin A failed,[7] and similar difficulties were also reported in a recent paper from Williams' group.[8] We were encouraged, however, by the report from the Chakraborty group which uses an essentially identical cycloamidation for the 14-membered ring formation in his teicoplanin model.[5]

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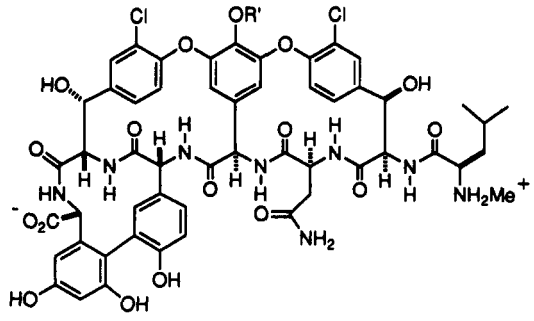
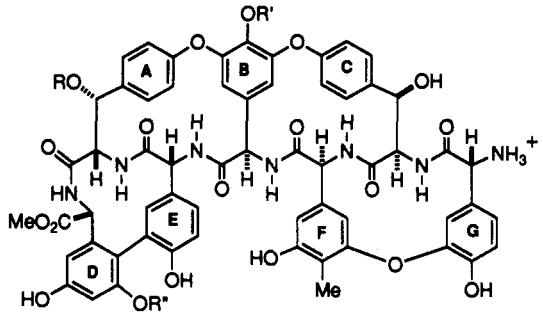
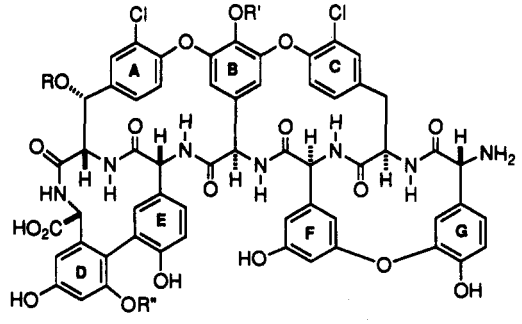


(1) **VANCOMYCIN** (R' = sugar unit)



(2) **RISTOCETIN A** (R, R' and R" = sugar units)



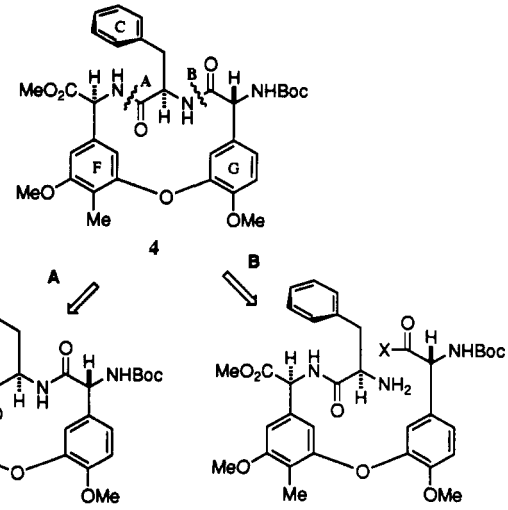
(3) **TEICOPLANIN** (R, R' and R" = sugar units)

For the synthesis of model compound **4**, it is possible to approach from two cycloamidation pathways as shown in Scheme 1. Since we anticipated that different results might be obtained at almost every point during the construction of the desired intermediates, as well as in the their cyclization, we have examined both pathways.

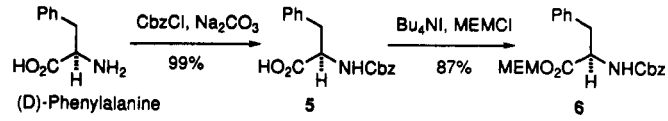
**Preparation of CFG Model Compound via Cycloamidation Pathway A.** The synthesis of the CFG model **4** started from the protected phenylalanine **6** which constitutes the C ring moiety. Protection of the amino group with benzyl chloroformate (CbzCl) was quantitive in the presence of saturated aqueous $Na_2CO_3$ (Scheme 2). This reaction in the presence of saturated $NaHCO_3$ solution was low yielding (38%).

Because of the base sensitivity of the F and G ring arylglycine units and the projected use of an acid-labile Boc protecting group on the G-ring subunit, it was necessary to employ a carboxyl protecting group which can be cleaved under neutral conditions. It is known that the (methoxyethoxy)methyl (MEM) ester can be deprotected by using $MgBr_2{\cdot}Et_2O$ in ether.[9] Accordingly, MEMCl in the presence of $Bu_4NI$[10] was employed in the protection of the carboxylic group, affording the MEM ester **6** in 87% yield.

**Scheme 1. Cycloamidation Pathways for the Synthesis of the CFG Model**



**Scheme 2. Protection of Phenylalanine**



For the synthesis of the C/G ring dipeptide **9**, the Cbz group of **6** was removed using Pd/C (10%) under $H_2$ atmosphere. However, the amine **7** was very unstable, and 4 h of stirring in EtOAc led to its complete destruction (no spot on TLC). Fortunately, hydrogenolysis was complete in 15 min in ethanol as solvent. The ethanol was removed *in vacuo* at room temperature followed by coevaporation with dichloromethane and then pumping (3 min), and the reaction mixture was immediately dissolved in dry dichloromethane. Coupling of this crude amine with the azidoarylacetic acid **8**, available from our previous studies,[11] afforded the dipeptide **9** in 90% yield (Scheme 3).

Generally, the diastereomeric ratio obtained from this coupling reaction was ~87% (14:1) based on $^1H$ NMR, which is almost the same as the enantiomeric ratio (13:1) of **8**,[11] suggesting that no racemization occurred during the peptide coupling. However, we also observed that addition of the coupling agent EDC to a cooled (0 °C) mixture of amine **7** with carboxylic acid **8** and HOBT consistently improved the ratio to 30:1–58:1. (In the initial studies the amine was added to the mixture of carboxylic acid/ EDC and HOBT at 0 °C or rt.) The origin of this seemingly abnormal high diastereomer ratio is not clear, but it is possible that the previously estimated optical purity of **8** is incorrect and too low, owing to some racemization during the preparation of its MTPA amide. Another possibility is that some kinetic resolution occurs during the peptide coupling, but further investigation was not undertaken.

We now required the conversion of the dipeptide **9** into the N-Boc-protected phenolic dipeptide, by simultaneous

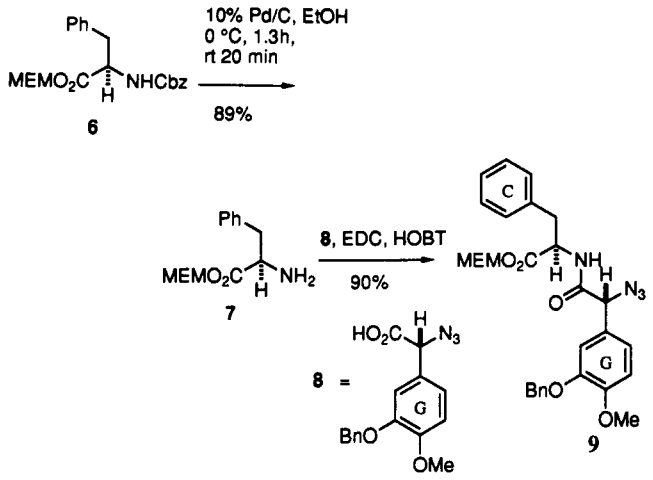
(8) Stone, M. J.; van Dyk, M. S.; Booth, P. M.; Williams, D. H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1629. For successful but low-yielding related cycloamidation, see: Mann, M. J.; Pant, N.; Hamilton, A. D. *J. Chem. Soc., Chem. Commun.* **1986**, 158. Pant, N.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 2002. Crimmin and Brown, ref 2.

(9) Kim, S.; Park, Y. H.; Kee, I. S. *Tetrahedron Lett.* **1991**, *32*, 3099.

(10) Marchelli, R.; Bocchi, V.; Casnati, G.; Dossena, A. *Synthesis* **1979**, 957.

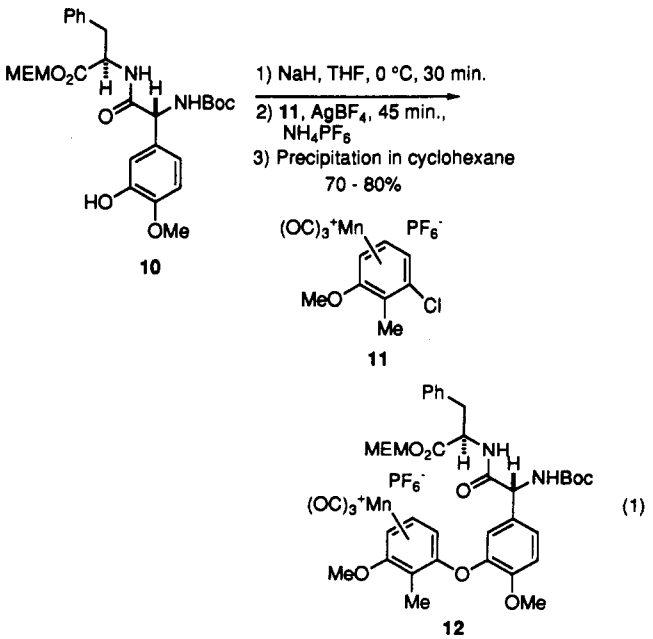
(11) Pearson, A. J.; Shin, H. *Tetrahedron* **1992**, *48*, 7527.

**Scheme 3. Synthesis of Dipeptide 9**



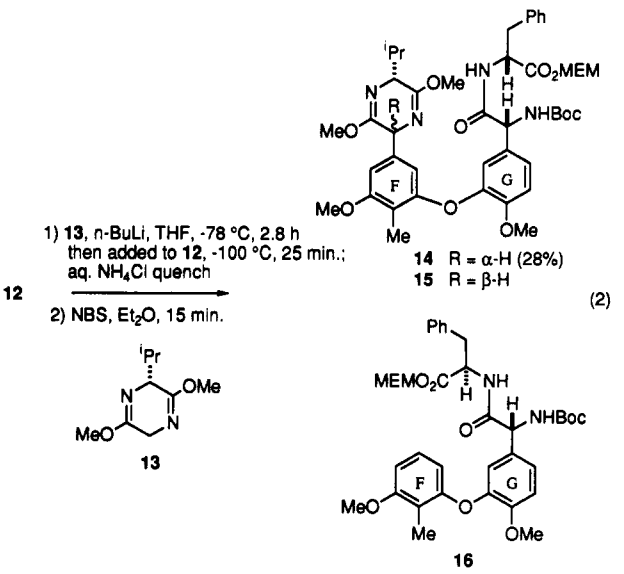

removal of the benzyl ether, reduction of the azide, and *in situ* protection of the resulting amino group. This transformation was attempted using hydrogen over 10% palladium on carbon in EtOAc solution, according to our earlier study on a simple arylglycine.[11] However, neither the azide reduction nor hydrogenolysis of the benzyl group occurred using this catalyst, even at 52 psi. The starting material was quite soluble in EtOAc and the different behavior of dipeptide **9** compared with the simpler arylglycine is somewhat puzzling. Satisfactory results were obtained, however, by employing 5% Pd/C and THF as the solvent, in the presence of $Boc_2O$. The yield of this reaction was 78% from 150 mg of **9**, but decreased somewhat when the reaction was carried out on a larger scale.

The aryl ether forming reaction was performed following the protocol as described in the earlier synthesis of a protected ristomycinic acid (eq 1).[11] Under optimum




conditions the yield of this reaction is 70–80%, but separation of the arenemanganese complex **12** from unreacted **11** by precipitation without significant losses was not completely successful (using an excess of **11** is necessary for high yields), best results being obtained by precipitation in cyclohexane. Contamination of **12** with the starting material **11** was usually *ca.* 5–10% according to NMR, and this material was found to be satisfactory for the next step.

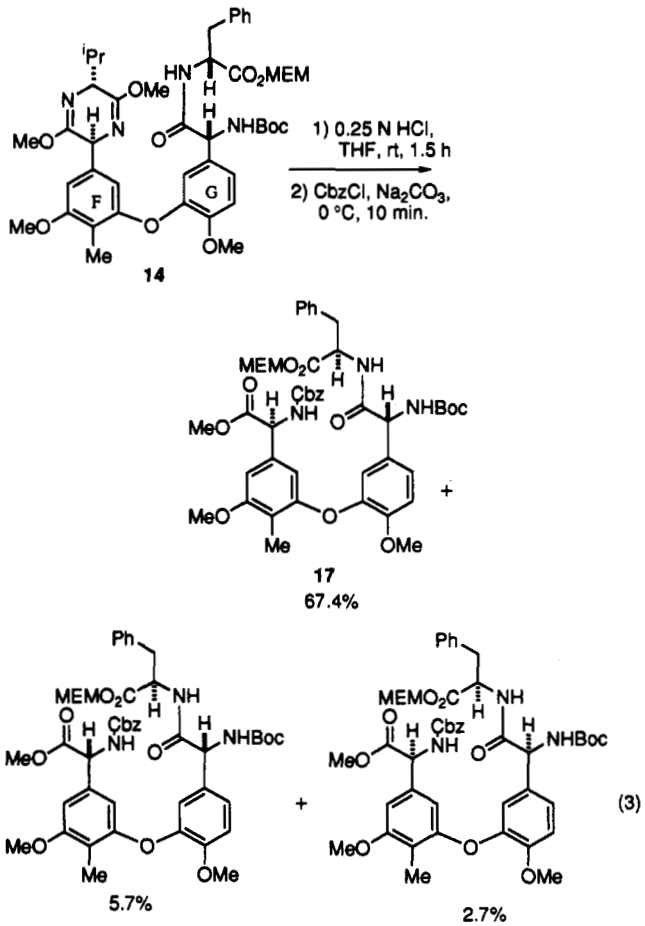
Reaction of the slightly contaminated arene–manganese complex **12** with the Schöllkopf bislactim anion **13**,[12] followed by rearomatization with concomitant demetalation, afforded the desired product along with its diastereomer and demetalated starting material (eq 2).




Separation of the desired product **14** from its diastereomer **15** could be achieved using HPLC (M20 10/25 silica gel column) but not from the side product **16**. The ratio of **14**:**15**:**16** was ~15:4:11 (i.e., de = 58%) by NMR on the basis of integration of the F-ring methyl resonance. After HPLC separation, the calculated yield of **14** was 28%. During subsequent studies, to be described later, we found that formation of the side product can be reduced by carrying out the oxidative demetalation in acetonitrile, leading to significant improvement in the yield of the desired aryl ether (*ca.* 56%). The bislactim **14** (and **16**, 54:46) was hydrolyzed to the corresponding amino ester which was found to be extremely unstable on silica gel and was immediately protected as its benzyloxycarbonyl (Cbz) urethane **17** by treatment with benzyloxycarbonyl chloride in the presence of sodium carbonate. While the use of weaker base ($NaHCO_3$) is more desirable for prevention of arylglycine racemization, these conditions did not yield significant quantities of **17**.

Although pure diastereomer **17** could be obtained by using HPLC ($t_R$ = 94 min, M20 10/25 silica gel column), it was accompanied by two side products, presumably diastereomers formed by partial racemization, in 1.6% and 3.5% yield ($t_R$ = 90, 110 min, respectively). The demetalated side product **16** was also recovered, showing that Boc and -OMEM protecting groups are stable under the bislactim hydrolysis conditions. However, this compound was also accompanied by a side product, presumably the epimer, in 0.9% yield ($t_R$ = 58 and 55 min, respectively), again from partial racemization. On the basis of HPLC analysis, it appears that *ca.* 7.5% racemization occurred at the F-ring unit chiral center and 3.5% at the G-ring unit chiral center.

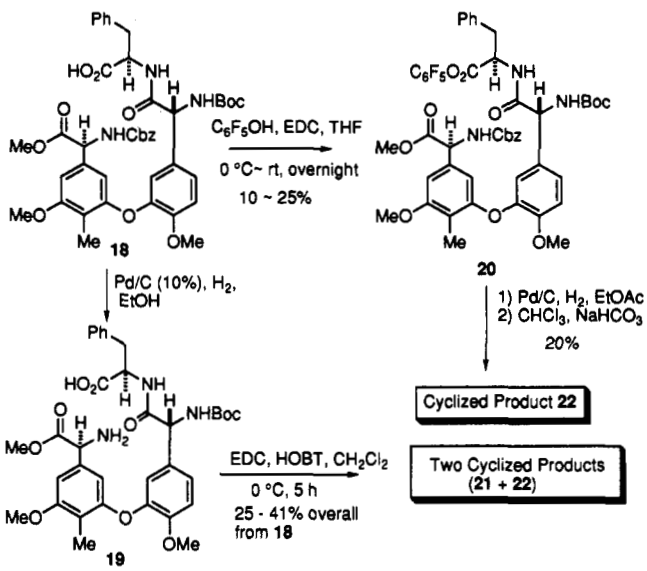
(12) Schöllkopf, U. *Pure Appl. Chem.* **1983**, *55*, 1799. Schöllkopf, U. *Top. Curr. Chem.* **1983**, *109*, 65.




The MEM ester of the pure diastereomer **17** was deprotected in ether solution in the presence of excess (5–7 equiv) magnesium bromide etherate. The yield was over 80%, but this compound was very labile and could not be purified by column chromatography or base extraction. It should be noted that the reaction mixture in ether solution does not show any spot on TLC until the product is hydrolyzed for 30 min with water or dilute acid. The crude carboxylic acid **18** was used for the cyclization studies. Macrocyclization was performed in dilute methylene chloride solution using either direct coupling effected by EDC or the active pentafluorophenyl ester. As a prerequisite to the EDC coupling, the Cbz protecting group of **18** was removed by using $H_2$ over 10% Pd/C in EtOH (Scheme 4), and after EtOH removal *in vacuo*, the resulting amino acid was directly dissolved in methylene chloride and added to a 0 °C solution of EDC and HOBT in the same solvent over 6–10 h. For the active ester method, the protected amino acid **18** was coupled with pentafluorophenol using EDC, and the Cbz group was removed to allow cyclization. The yield of the pentafluorophenyl ester was poor (10–25% yield). From both reactions, a cyclized product was obtained as shown in Scheme 4. Macrocyclization by the imide coupling agent (EDC) furnished the products **21** (trace–19% yield, depending on reaction conditions) and **22** (14–29% yield) whose HPLC retention times were $t_R$ = 25 min and 36 min (M20 10/25 silica gel column, hexanes:EtOAc = 2:3, 5 mL/min), respectively.

In the case of the cyclization by using the active ester, **21** was not observed. The compound **22** was obtained from this procedure as a mixture with an unknown side product, presumably from the macrocyclization of a diastereomer that is formed due to the basic conditions

**Scheme 4**




of this reaction (saturated $NaHCO_3/CHCl_3$/0 °C), since this showed a very similar structure (NMR) and it was inseparable from **22** by HPLC. Surprisingly, this racemization problem was not observed by Chakraborty[5] during cyclization of a closely related pentafluorophyl ester under more highly basic conditions. The ratio of **22**:side product was ~3:2 and the combined yield was ~30%. Because of the low yield of the active ester formation and side product formation during the macrocyclization, this method was not studied any further in the present case.

**Structure Determination of Cyclization Products.** One of the well-known problems of macrocyclization is the occurrence of undesired intermolecular peptide couplings including dimeric or oligomeric cyclization. To minimize this possibility, the cyclization of **19** was conducted at high dilution (0.2–0.8 mM). $^1H$ NMR spectra of products **21** and **22** were quite similar. High-resolution mass spectrometry (HRMS) of **22** by electron impact ionization at 70 eV showed the molcular ion peak corresponding to cyclic monomer at 633.2698 (calculated mass = 633.2686); however, there were many fragments at higher mass. The FAB mass spectrum also showed similar high molecular weight ions. With field-desorption mass spectroscopy, which usually shows only molecular ion peaks, monomer ($M^+Na$), "cyclic dimer" ($2M^+Na$ or associated monomer), and "trimer" ($3M^+Na$) peaks were obtained. Because association of molecules with $H^+$ or $Na^+$ during vaporization is sometimes observed in mass spectrometry,[13] it could not be concluded with certainty whether the $2M^+$ and $3M^+$ peaks originated from cyclic dimers and trimers or from association of two or three monomers.

Eventually, we obtained the mass spectra for **21** and **22** which showed no sign of high molecular weight fragmentation. Electron impact ionization (EI) was used at the lowest possible energy (18 eV for Kratos MS25A), along with stepwise increase of temperature. The molecular ion peak appeared from 220 to 250 °C for both compounds, corresponding only to the monomer ($M^+$ = 633.2684 for **21** and 633.2702 for **22**; calcd molecular mass = 633.2686), together with the expected fragmentations at lower mass in both cases. Thus, it is likely that the high molecular weight fragmentations observed in the earlier spectra

(13) Ganem, B.; Li, Y.-T.; Henion, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 7818; **1991**, *113*, 6294. Williams, D. H.; Butcher, D. W. *J. Am. Chem. Soc.* **1981**, *103*, 5697.

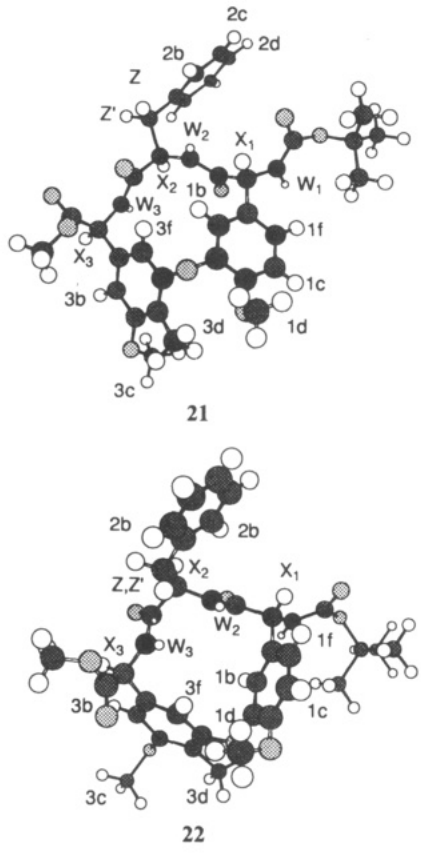



**Figure 1.** Minimized structures for **21** and **22** calculated using Biograf. Labeling of hydrogens is consistent with that used in the literature. For a line diagram see structure **4** (Scheme 1).

originated from sodium (or proton)-bound dimer and trimer. This was reinforced by tandem FAB mass spectrometry analysis with collisional activation of the dimeric fragments ($2MH^+$, observed mass = 1267.5) which produced predominantly the monomer ions ($MH^+$, observed mass = 634) as well as lower mass fragments. *In view of the observation of a single compound in the NMR spectra of **21** and **22**, these experiments establish that the cyclization products are atropisomeric cyclic monomers.* In support of this proposal, Evans has recently observed the formation atropdiastereomers during the construction of a vancomycin DE ring model.[14]

The conformations of **21** and **22**, shown in Figure 1, were deduced using 2D-NOESY experiments (Table 1) and molecular modeling (Biograf). The labeling of hydrogens is made to be consistent with those used in the literature. When the simulated structures are compared with published results, compound **21** is similar to the structures proposed for ristocetin A,[15] teicoplanin,[1] a molecule that is closely related to ristocetin A, and the teicoplanin model compound prepared by Chakraborty, except for the orientation of the bridging amide group ($W_3$) in all cases. In our case, no NOE was observed between proton $W_3$ and 3f, and instead, a large NOE was observed between $X_2$ and $W_3$. In the case of Charkraborty's synthetic CFG ring model of teicoplanin,[5] which is very similar to our molecule, a large NOE was also observed between $X_2$ and $W_3$ (11%), along with 9 and 3% NOE between $W_3$ and 3f and between $W_3$ and $X_3$, respectively. This may suggest that proton $W_3$ is pointing away from the F-ring unit, as is the case with our model, or at least lies in between 3f and $X_2$. ($W_3$ is reported to point in the direction of 3f.) It also suggests that the methyl group (3d), which is present in our model compound but not in Chakraborty's, has a significant effect on the overall conformation of the intermediate leading to cycloamidation. In ristocetin A, a large NOE was observed between proton $X_3$ and 3b and with proton 3f,[16] and the calculated distance between proton $X_3$ and 3b was 2.4 Å. Also, small NOE's were observed between $X_1$/1f and $X_1$/1b because of oscillation of the G-ring unit. In the case of **21**, a strong NOE between $X_3$ and 3b was observed but with weak NOE between $X_3$ and 3f. The calculated distance (by Biograf) between proton $X_3$ and 3b is 2.34 Å, in good agreement with the NOE data. The NOE's between $X_1$ and 1b, and between $X_1$ and 1f were both weak, suggesting a strong similarity between **21** and the conformation of ristocetin A (which has not been completely elucidated). In the case of Chakraborty's teicoplanin model, $X_3$ showed NOE both with 3b (8%) and 3f (2%) similar to our case. However, $X_1$ showed NOE only with proton 1b (7%) but not with 1f, suggesting that proton $X_1$ is almost parallel to 1b in their model.

**Table 1. Summary of Observed NOE's for Compounds 21 and 22, Compared with Ristocetin A**

| protons | compd **21** NOE/distance[a] | compd **22** NOE/distance[a] | ristocetin A[b] NOE/distance |
|---|---|---|---|
| z:z′ | Y(S)/1.76 | Y/1.76 | |
| z:2b | Y/2.39 | Y/2.58 | |
| z′:2b′ | Y/2.65 | Y/3.51 | |
| z/z′:$x_2$ | N/2.47 | Y/2.49 | |
| 1d:1c | Y(S)/2.94 | Y(S)/2.86 | |
| 3b:3c | Y(S)/2.73 | Y/2.79 | |
| $x_2$:2b | Y/2.59 | Y(S)/2.39 | |
| $x_2$:$w_3$ | Y(S)/2.18 | Y/3.62 | |
| $x_2$:$w_2$ | N/2.94 | Y/2.88 | |
| $x_1$:1f | Y/3.53 | Y(S)/2.38 | Y/2.5 |
| $x_1$:1b | Y/2.63 | N/3.76 | Y/3.7 |
| $x_1$:$w_2$ | Y/2.21 | Y/2.64 | |
| $x_3$:$w_3$ | Y/2.19 | N/2.91 | |
| $x_3$:3f | Y/3.78 | N/3.75 | Y/3.5 |
| $x_3$:3b | Y/2.34 | Y(S)/2.38 | Y/*ca.* 2.5–3.1 |
| $w_1$:1f | Y/2.22 | N/4.39 | |
| 1b:3f | Y(S)/2.32 | Y/3.38 | Y/2.7 |
| 3f:$w_3$ | N/3.62 | Y/2.48 | Y/*ca.* 2.6 |
| $w_1$:1b | N/4.52 | Y/2.43 | |

[a] Y = NOE observed, N = NOE not observed, S = strong; calculated distance in Å, from Biograf structures. [b] From ref 16; some data correspond to the ristocetin pseudoglycon–$Ac_2$-Lys-D-Ala-D-Ala complex.

The structure **22** appears to be unprecedented in this type of molecule and does not coincide with other structures so far reported. In contrast to the structure **21**, a large NOE was observed between $W_3$ and 3f, thus indicating that $W_3$ is pointing toward proton 3f as was suggested by Charkraborty's model. Also, there is a large NOE between $X_1$ and 1f and no NOE between $X_1$ and 1b, suggesting that $X_1$ is almost parallel with proton 1f. We have also carried out molecular modeling on structures corresponding to racemization of each arylglycine to confirm that none of these represents either of the cycloamidation products.

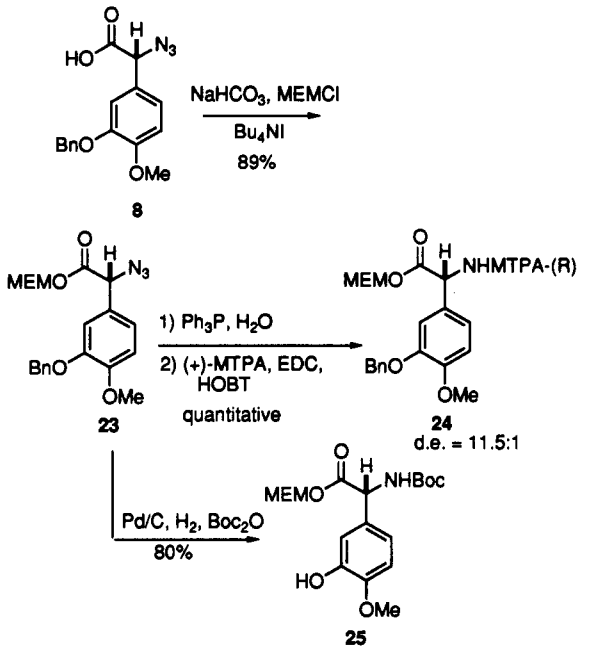
**Macrocyclization of CFG Model Compound via Pathway B.** Although it was possible to obtain a cyclized

(14) Evans, D. A.; Dinsmore, C. J.; Evrard, D. A.; DeVries, K. M. *J. Am. Chem. Soc.* **1993**, *115*, 6426. Evans, D. A.; Dinsmore, C. J. *Tetrahedron Lett.* **1993**, *34*, 6029.

(15) Harris, C. M.; Harris, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 363.

(16) Williams, D. H.; Waltho, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 2475. Fesik, S. W.; O'Donnell, T. J.; Gampe, R. T., Jr.; Olejniczak, E. T. *J. Am. Chem. Soc.* **1986**, *108*, 3165.

**Scheme 5**




product using pathway A, this strategy has some limitations. It was difficult to make large amounts of the phenolic dipeptide **10**, and rigorous purification of the arene–manganese complex **12** is impractical. To avoid these difficulties, and to test a different cycloamidation, pathway B (Scheme 1) was examined. During these experiments we have also partly solved the problem of low yield that was experienced during the oxidative demetalation of dienyl–Mn complexes which are the immediate products of the bislactim nucleophile addition.

The MEM ester **23** was prepared from the azido acid **8** using (methoxyethoxy)methyl (MEM) chloride in the presence of $Bu_4NI$. The enantiomeric excess (11.5:1) was measured by $^{19}F$ NMR of the (*R*)-MTPA amide **24** (as discussed earlier, this value may represent a lower limit). Hydrogenation of **23** and *in situ* protection of the resulting amine with Boc anhydride in THF afforded the arylglycine derivatives **25** in 80% yield (Scheme 5).

Coupling of **25** with the arene–manganese complex **11** afforded the diarene–manganese complex **26**. Precipitation of the crude product from pentane afforded almost pure compound, in contrast to the difficulties recorded with **12**. The bislactim addition to this compound was performed following the usual protocol. After the reaction was quenched with $NH_4Cl$, and extracted with methylene chloride, unreacted manganese complex **26** was recovered in 34% yield by precipitation from pentane. At this time, it was found that dealkylation of the resulting dienyl–manganese complexes (diastereomeric mixture), which occurs during the oxidative demetalation reaction using NBS, is minimized in $CH_3CN$ as solvent, and the product **27/28** was obtained in up to 56% yield (Scheme 6). The diastereoselectivity of the bislactim addition reaction/rearomatization was 3:1 to 4:1, and the side product **29** was obtained in *ca.* 23% yield. The diastereomer **28** could be separated using column chromatography. However, it was not possible to separate the desired product **27** from **29** even with HPLC. The partially purified mixture was therefore hydrolyzed using 0.25 N HCl, and the resulting crude amine was coupled directly with the protected phenylalanine **30** in *ca.* 93% yield using EDC and HOBT, followed by chromatographic removal of **29**. The resulting product **31** was contaminated with *ca.* 10% of a compound that was presumed to be a diastereomer and which was inseparable on HPLC (Scheme 7).

The MEM ester of the dipeptide **31** was deprotected following the earlier protocol to afford **32**; the Cbz protecting group was removed, and the product was cyclized following the reaction conditions used in pathway A. Cyclization via the pentafluorophenyl ester was also tested as shown in Scheme 7. The active ester **33** was obtained in 60% yield using DCC (without HOBT). It was observed that use of HOBT, or EDC instead of DCC, gave a poor yield of the pentafluorophenyl ester. Interestingly, **33** exists as a *ca.* 1:1 mixture of two conformers (NMR) at rt, probably due to amide resonance; at 50 °C, the NMR signals coalesced. Yields of **21** and **22** were *ca.* 5 and 12–53%, respectively, when **32** was cyclized using EDC. With the active ester method, the same products were obtained in 10 and 32% yield, respectively.

When pathway B is compared with pathway A, though pathway B is more accommodating for larger amounts of material, it afforded a decreased yield of **21** (which has the conformation closest to the CFG ring unit of ristocetin A) and an increased yield of **22** (undesired conformer). In pathway B, the cyclization reaction was not as clean as pathway A (HPLC).

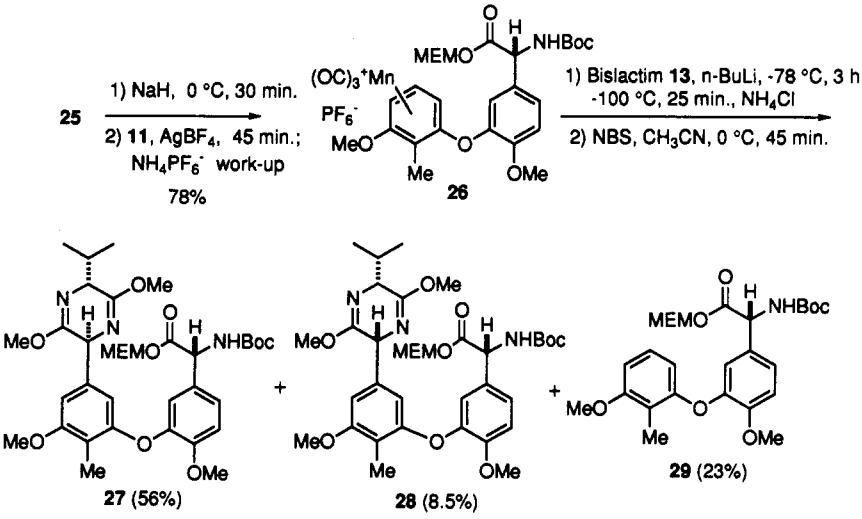
Possible interconversion of **21** and **22** was tested by NMR spectroscopy in hot DMSO-$d_6$. Pure atropisomer **21** did not show any change after 2 h at 115 °C, and after 2 h at 160 °C it was completely destroyed, giving several products. These products were combined with excess $Boc_2O$ and, after prolonged reaction time, compared with **22**. However, no matching products were found from the reaction, indicating a substantial activation barrier to this conformational "flip".

**Conclusions.** Cyclization of a model compound representing the the CFG ring moiety of ristocetin A was tested using two different methods and two different bond dissections. From pathway A (Scheme 1), two atropisomeric cyclic monomers **21** and **22** were obtained in 19 and 22% yield. According to NOESY experiments and molecular modeling, **21** is closer to the CFG ring moiety of ristocetin A, except for the orientation of proton $W_3$. Pathway B afforded the same pair of atropisomers. This method was easier than pathway A for the preparation of large amounts of material. However, **21** was obtained in *ca.* 5% yield, and **22** was obtained in 50% yield. Interconversion between **21** and **22** did not occur at 160 °C in DMSO-$d_6$. The active ester method for cycloamidation did not lead to improved results, and the requirement for base during this cyclization makes it a less attractive route owing to the potential for racemization of the arylglycine moieties. One significant feature of our model, compared with the only other related synthetic compound,[5] is the apparent effect of the F-ring methyl substituent on the outcome of cycloamidation. In our case, two atropisomers were obtained, in relative amounts depending on reaction conditions, while Chakraborty's model, which lacks this methyl group, is reportedly obtained as a single atropisomer. We propose to investigate this cyclization reaction in more detail in the near future.

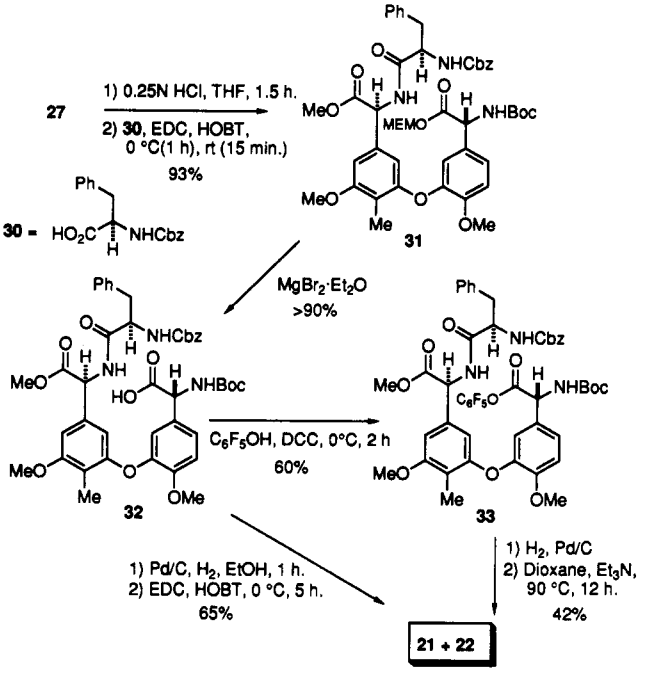
## Experimental Section

**General.** All reactions were conducted under a dry $N_2$ or Ar atmosphere, unless otherwise noted. THF, ether, benzene, and toluene were purified by distillation from Na/benzophenone, and

**Scheme 6**




**Scheme 7**




$CH_2Cl_2$ was distilled from $CaH_2$. For chromatography, distilled hexanes and EtOAc were used, and ether was distilled over $LiAlH_4$. Acetonitrile was used as purchased.

$^1H$, $^{13}C$, $^{19}F$, and $^{31}P$ NMR spectra were recorded using either Varian Gemini-300 (300 MHz) or Varian XL 200 (200 MHz) spectrometers using $CDCl_3$, benzene-$d_6$, $D_2O$, DMSO-$d_6$, $CD_3CN$, and $CD_2Cl_2$ solvents. $^1H$ NMR was referenced to TMS or $CHCl_3$ (7.26 ppm). $^{13}C$ was referenced to $CHCl_3$ (77.0 ppm) and the results of attached proton test (APT) are recorded as (+) or (−), multiplicity of the carbon is denoted as s, d, t, and q. $^{19}F$ NMR was referenced to $CFCl_3$ as a external standard. Mass spectra were recorded, in house, on a Kratos MS 25A instrument or performed by the Midwest Center, University of Nebraska, Lincoln, NE. Combustion analyses were performed by Galbraith Laboratories, Knoxville, TN.

Infrared spectra were recorded on a Perkin-Elmer Series 1600 FT-IR using $CHCl_3$ solution in NaCl chamber. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter. Melting points were measured on a Thomas-Hoover melting point apparatus and are uncorrected.

Preparative HPLC was performed on a Gilson HPLC using a M20 10/25 silica gel column.

***N*-[2(*R*)-Azido-2-[3-(benzyloxy)-4-methoxyphenyl]acetyl]-D-phenylalanine (Methoxyethoxy)methyl Ester (9).** A solution of Cbz-protected D-phenylalanyl ester **6** (742 mg, 1.92 mmol, 1.0 equiv) in EtOH (45 mL) was stirred with Pd/C (10%, 742 mg) for 15 min under an $H_2$ atmosphere until the starting material was consumed (TLC). The EtOH was evaporated *in vacuo* and the residue was coevaporated with $CH_2Cl_2$ (3 × 45 mL) and placed under high vacuum for 3 min. The resulting amine was dissolved in $CH_2Cl_2$ (45 mL), dried with $Na_2SO_4$, and then added in one portion, via cannula, to an ice-cooled solution of the azidoacetic acid **8** (599.5 mg, 1.91 mmol, 1.0 equiv) and HOBT (517.5 mg, 3.83 mmol, 2.0 equiv) in $CH_2Cl_2$ (36 mL). EDC (550.7 mg, 2.87 mmol, 1.50 equiv) was added to the mixture, which was then stirred for 1.3 h at 0 °C and 20 min at rt. The reaction mixture was washed with brine (2 × 25 mL), dried ($MgSO_4$), and filtered through $SiO_2$ (hexanes:EtOAc = 3:2) to afford 832.5 mg (79%) of a pale yellow solid which showed a 30:1 ratio (93.5% de) of diastereomers by NMR (300 MHz). An analytical sample was prepared using HPLC (Partisil M20 10/25, hexanes:EtOAc = 1:1, 5 mL/min, 254 nm, $t_R$ = 59 min): mp 93.5–94.5 °C; $R_f$ 0.66 (EtOAc); IR ($CHCl_3$) 3401, 3021, 3019, 3016, 2933, 2116 ($-N_3$), 1741, 1682, 1593, 1513, 1455, 1443, 1428 cm$^{-1}$ ; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.45–7.21 (m, 7H), 7.06–7.03 (m, 2H), 6.8 –6.75 (m, 4H), 5.41 (d, $J$ = 6.0 Hz, 1H), 5.37 (d, $J$ = 6.0 Hz, 1H), 5.08 (s, 2H), 4.94 (s, 1 H), 4.85 (ddd, $J$ = 8.1, 6.5, 5.8 Hz), 3.89 (s, 3H), 3.74–3.71 (m, 3H), 3.54–3.51 (m, 2H), 3.17 (dd, $J$ = 14.0, 5.8 Hz, 1H), 3.07 (dd, $J$ = 14.1, 6.5 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 170.66 (s, +), 167.80 (s, +), 150.33 (s, +), 148.44 (s, +), 136.58 (s, +), 135.33 (s, +), 129.19 (d, −), 128.59 (d, −), 128.52 (d, −), 127.94 (d, −), 127.45 (d, −), 127.15 (d, −), 126.78 (s, +), 120.77 (d, −), 113.06 (d, −), 111.79 (d, −), 90.47 (t, +), 71.33 (t, +), 71.06 (t, +), 69.80 (t, +), 66.85 (d, −), 59.03 (q, −), 55.96 (q, −), 53.07 (d, −), 37.43 (t, +); $[\alpha]_D$ −123.0° (*c* 1.17, $CHCl_3$); HRMS found 548.2216, calcd for $C_{29}H_{32}N_4O_7$ 548.2216; MS *m/e* 548 (0.4), 520 (1.3), 368 (1), 354 (0.4), 295 (0.6), 284 (1.3), 283 (0.6), 270 (0.6), 257 (1.1).

**2(*R*)-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-[(3-hydroxy-4-methoxyphenyl)acetyl]-D-phenylalanine (Methoxyethoxy)methyl Ester (10).** A mixture of azido dipeptide **9** (155.6 mg, 0.28 mmol, 1.0 eq), Pd/C (5%, 160.1 mg), and $Boc_2O$ (221.9 mg, 1.0 mmol, 2.6 equiv) in THF (34 mL) was stirred under $H_2$ atmosphere for 48 h. After evaporation of the solvent *in vacuo*, the crude product was column chromatographed over $SiO_2$ (hexanes:EtOAc = 1:1) to afford 125.3 mg (81%) of the product **10** as a yellow oil. The diastereomeric excess of the product was 96% by $^1H$ NMR. An analytical sample was prepared using HPLC (Partisil M20 10/25, hexanes:EtOAc = 1:4, 5 mL/min, 254 nm UV detector, $t_R$ = 27 min): $R_f$ 0.57 (EtOAc); IR ($CHCl_3$) 3539, 3420, 3020, 2933, 1743, 1710, 1684, 1507, 1456, 1443 cm$^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.33–7.23 (m, 3H), 7.05 (m, 2H), 6.84 (s, 2H), 6.78 (s, 2H), 6.18 (d, $J$ = 7.4 Hz, 1H), 5.78 (s, 1H), 5.64 (bs, 1H), 5.30 (d, $J$ = 6.0 Hz, 1H), 5.26 (d, $J$ = 6.0 Hz, 1H), 5.00 (bd, $J$ = 5.5 Hz, 1H), 4.81 (ddd, $J$ = 7.7, 5.9, 5.8 Hz), 3.86 (s, 3H), 3.64–3.61 (m, 2H), 3.51–3.48 (m, 2H), 3.17 (dd, $J$ = 14.0, 5.8 Hz, 1H), 3.09 (dd, $J$ = 14.0, 5.9 Hz, 1H), 1.41 (s, 9H);

$^{13}C$ NMR (75 MHz, $CDCl_3$) δ 170.87 (s, +), 170.39 (s, +), 155.44 (s, +), 147.16 (s, +), 146.39 (s, +), 135.87 (s, +), 131.12 (s, +), 129.68 (d, -), 128.98 (d, -), 127.50 (d, -), 119.52 (d, -), 113.68(d, -), 111.28 (d, -), 90.66 (t, +), 80.43 (s, +), 71.71 (t, +), 69.96 (t, +), 59.37 (q, -), 58.58(d, -), 56.25 (q, -), 53.88 (d, -), 37.80 (t, +), 28.64 (q, -); $[\alpha]_D$ -57.4° (c 0.74, $CHCl_3$); HRMS found 532.2414, calcd for $C_{27}H_{36}N_2O_9$ 532.2421; MS m/e 532 (0.7), 459 (0.9), 368 (1.0), 326 (0.8), 313 (0.9), 264 (0.9), 255 (1.9).

**[3-*O*-[(Tricarbonyl)(η⁶-2-methyl-3-methoxyphenyl)manganio]-*N*-(*tert*-butoxycarbonyl)-(*R*)-3-hydroxy-4-methoxyphenylglycinyl]-D-phenylalanine (Methoxyethoxy)methyl Ester Hexafluorophosphate (12).** To an ice-cold solution of phenolic dipeptide 10 (743.6 mg, 1.37 mmol, 1.0 equiv) in dichloromethane (53 mL) was added NaH (54.4 mg, 1.36 mmol, 0.99 equiv) in one portion, and the mixture was stirred for 30 min at 0 °C. The resulting phenoxide solution was transferred via cannula to a stirred suspension of arene–manganese complex 11 and $AgBF_4$ (1.07 g, 9.74 mmol, 7.0 equiv) in dichloromethane (97 mL), and the mixture was stirred 1 h at 0 °C. The reaction was quenched with 0.5 M $NH_4PF_6$ solution, and the resulting mixture was stirred vigorously for 30 min at rt. After separation of the organic layer, the aqueous layer was extracted with dichloromethane (3 × 70 mL), and the combined organic layer was washed with $NH_4PF_6$ solution (50 mL) and dried ($MgSO_4$). After filtration and evaporation of most of the solvent, the concentrated solution was added dropwise to cyclohexane (200 mL) to afford 900 mg (88%) of a yellow solid, 12 contaminated with small amounts of 11: IR ($CHCl_3$) 3411, 3016, 2980, 2932, 2070, 2004, 1746, 1709, 1683, 1601, 1511, 1486, 1472, 1427 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.37–6.97 (m, 7H), 6.61 (bs, 1H), 6.13 (m, 1H), 5.98 (d, J = 8.6 Hz, 1 H), 5.90 (bs, 1H), 5.50–5.14 (m, 4H), 5.06 (m, 1H), 4.80 (bs, 1H), 4.12 (s, 3H), 3.80 (s, 3H), 3.71 (s, 2H), 3.53 (s, 2H), 3.37 (s, 3/2H, diastereomer, chiral arene–Mn), 3.35 (s, 3/2H, diastereomer), 3.15 (bs, 2H), 2.40 (s, 3/2H, diastereomer), 2.39 (s, 3/2H, diastereomer), 1.41 (s, 9H).

**[3-[[2-Methyl-3-methoxy-5-[4(*R*)-isopropyl-3,6-dimethoxy-1,4-dihydropyrazinyl]phenyl]oxy]-*N*-(*tert*-butoxycarbonyl)-(*R*)-4-methoxyphenylglycinyl]-D-phenylalanine (Methoxyethoxy)methyl Ester (14).** To a cooled solution (-78 °C) of bislactim 13 (428 mg, 2.3 mmol, 7.0 equiv) in THF (21 mL) was added n-BuLi (2.5 M, 900 μL) dropwise, and the mixture was stirred for 3 h at -78 °C. Each of a one-third portion of the resulting solution was added every 6 min via cannula to a solution of arene–manganese complex 11 dissolved in THF (7.5 mL) at -100 °C. The reaction mixture was stirred for 18 min at -100 °C and quenched with saturated $NH_4Cl$ (140 mL). After warming, the mixture was extracted with ether (3 × 25 mL), dried ($Na_2SO_4$), filtered, and concentrated to ~40 mL. To this solution was added NBS (45 mg, 0.76 equiv), the mixture was stirred for 20 min at rt, and the reaction was quenched with $NaHSO_3$ (40 mL), washed with brine (2 × 30 mL), dried ($MgSO_4$), and evaporated. The product was purified with HPLC (M20 10/25 silica gel column, hexanes:EtOAc = 2:3, $t_R$ = 40 min) to provide a mixture of the desired bislactim adduct 14 and the demetalated starting material 16 in a ratio of 1.3:1. The calculated yield of 14 was 28%: $R_f$ 0.63 (hex:EtOAc = 1:2); $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.29–7.20 (m, 3H), 7.07–6.88 (m, 4H), 6.68 (s, 1H), 6.51 (s, 1H), 6.36 (s, 1H), 6.17 (d, J = 7.4 Hz, 1H), 5.45 (bs, 1H, 5.30 (d, J = 6.0 Hz, 1H), 5.26 (d, J = 6.0 Hz, 1H), 4.93 (d, J = 3.4 Hz, 1H), 4.76 (m, 1H), 4.02 (t, J = 3.2 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.67 (s, 3H), 3.65–3.62 (m, 2H), 3.60 (s, 3H), 3.52–3.47 (m, 2H), 3.36 (s, 3H), 3.14 (dd, J = 14.0, 6.0 Hz, 1H), 3.06 (dd, J = 14.1, 6.6 Hz, 1H, 2.32 (m, 1H), 2.06 (s, 3H), 1.39 (s, 9H), 1.07 (d, J = 6.8 Hz, 3H), 0.72 (d, J = 6.8 Hz, 3H).

**[*N*-(*tert*-Butoxycarbonyl)-(*R*)-3-hydroxy-4-methoxyphenylglycinyl]-D-phenylalanine (Methoxyethoxy)methyl Ester *O*-[*N*-(Benzyloxycarbonyl)-(*S*)-2-methyl-3-methoxyphenylglycine methyl ester] (17).** A mixture (122 mg, 64:58) of the bislactim adduct 14 and the side product 16 dissolved in THF (3.7 mL) was combined with of 0.25 N HCl (920 μL), and the mixture was stirred for 1.5 h at rt. Water (2.5 mL) was added to the mixture, and after evaporation of the THF *in vacuo*, ether (3.2 mL) was added to the mixture which was then cooled to 0 °C. The mixture was basified to pH = 8–9 with few drops of saturated $Na_2CO_3$, and benzyl chloroformate (38 mL, 0.27 mmol, 3.5 equiv) was added in one portion. After 12 min of stirring, the reaction was quenched with 0.25 N HCl (reaction mixture pH = 2), and the mixture was extracted with ether (3 × 20 mL) and dried over $MgSO_4$. The desired product 17 was obtained (45 mg, 67%) after purificaton using HPLC (M20 10/25 silica gel column, hexanes:EtOAc = 1:1, 5 mL/min, $t_R$ (17) = 104 min), along with two side products ($t_R$ = 96, 114 min; 2.7, 5.7%, respectively). Side product 16 was also recovered ($t_R$ = 62 min, 48.8 mg, 85%) along with its epimer (0.8 mg, 1.4%). For 17: $R_f$ 0.63 (hex:EtOAc = 1:2); IR ($CHCl_3$) 3683, 3425, 3067, 3020, 1741, 1718, 1684, 1579, 1510, 1476, 1421 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.29–7.16 (m, 9H), 7.08–7.02 (m, 2H), 7.01 (d, J = 2.0 Hz, 1H), 6.98 (d, J = 2.1 Hz, 1H), 6.93 (s, 1H), 6.90 (s, 1H), 6.77 (d, J = 1.8 Hz, 1H), 6.57 (s, 1H), 6.42 (s, 1H), 6.35 (bs, 1H), 5.89 (s, 1H), 5.57 (s, 1H), 5.26 (d, J = 5.97, 1H), 5.24 (d, J = 6.0, 1H), 5.14 (d, J = 7.2 Hz, 1H), 5.08 (d, J = 12.4 Hz, 1H), 5.03 (d, J = 12.6, 1H), 4.90 (d, J = 6.5 Hz, 1H), 4.71 (m, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.66 (s, 3H), 3.62–3.57 (m, 2H), 3.47–3.43 (m, 2H), 3.33 (s, 3H), 3.12 (dd, J = 14.0, 5.8 Hz, 1H), 3.02 (dd, J = 14.1, 6.7 Hz, 1H), 2.12 (s, 3H), 1.37 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 171.24 (s, +), 170.61 (s, +), 169.80 (s, +), 159.19 (s, +), 155.34 (s, +), 154.99 (s, +), 150.26 (s, +), 146.15 (s, +), 136.05 (s, +), 135.95 (s, +), 134.81 (s, +), 130.71 (d, -), 129.24 (d, -), 128.50 (d, -), 128.14 (d, -), 128.04 (d, -), 126.98 (d, -), 122.07 (d, -), 118.20 (s, +), 117.51 (d, -), 112.95 (d, -), 110.40 (d, -), 104.03 (d, -), 90.38 (t, +), 79.96 (s, +), 71.33 (t, +), 69.60 (t, +), 67.07 (t, +), 59.00 (q, -), 57.89 (d, -), 56.09 (q, -), 55.74 (q, -), 53.75 (d, -), 52.78 (q, -), 37.11 (t, +), 28.24 (q, -), 8.75 (q, -); $[\alpha]_D$ +9.2° (c = 1.32, $CHCl_3$); HRMS found 896.3594, calcd for $C_{46}H_{55}O_{14}N_3Na$ ($M^+Na$) 896.3582. Data for 16: $R_f$ 0.63 (hex:EtOAc = 1:2); IR ($CHCl_3$) 3419, 3025, 3018, 2981, 2935, 2839, 1745, 1711, 1684, 1582.2, 1506, 1489, 1473 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.29–7.22 (m, 3H), 7.08–6.90 (m, 5H), 6.70 (d, J = 1.9 Hz, 1H), 6.61 (d, J = 7.6 Hz, 1H), 6.37 (dd, J = 8.3, 1.0 Hz, 1H), 6.14 (d, J = 7.7 Hz, 1H), 5.50 (bs, 1H), 5.31 (d, J = 6.0 Hz, 1H), 5.27 (d, J = 6.0 Hz, 1H), 4.93 (bs, 1H), 4.78 (m, 1H), 3.84 (s, 3H), 3.65–3.61 (m, 2H), 3.50–3.48 (m, 2H), 3.36 (s, 3H), 3.14 (dd, J = 13.8, 6.0 Hz, 1H), 3.06 (dd, J = 14.0, 5.8 Hz, 1H), 2.13 (s, 3H), 1.39 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 170.4 (s, +), 169.6 (s, +), 158.7 (s, +), 155.4 (s, +), 154.9 (s, +), 150.6 (s, +), 146.6 (s, +), 135.4 (s, +), 130.4 (s, +), 129.3 (d, -), 128.6 (d, -), 127.2 (d, -), 126.4 (d, -), 122.4 (d, -), 117.5 (d, -), 117.4 (s, +), 112.8 (d, -), 110.6 (d, -), 105.5 (d, -), 90.3 (t, +), 80.1 (s, +), 71.3 (t, +), 69.7 (t, +), 59.0 (q, -), 58.1 (d, -), 56.1 (q, -), 55.6 (q, -), 53.4 (d, -), 37.5 (t, +), 28.2 (q, -), 8.7 (q, -); $[\alpha]_D$ -38.8° (c = 0.97, $CHCl_3$); HRMS found 652.3037, calcd 652.2996; MS m/e 652 (1), 578 (5), 503 (1), 502 (4), 489 (2), 472 (2), 460 (3), 447 (2), 446 (10), 374 (3), 373 (7).

**[*N*-(*tert*-Butoxycarbonyl)-(*R*)-3-hydroxy-4-methoxyphenylglycinyl]-D-phenylalanine *O*-[*N*-(Benzyloxycarbonyl)-(*S*)-2-methyl-3-methoxyphenylglycine methyl ester] (18).** A solution of the above MEM ester 17 in ether (25 mL) was combined with $MgBr_2$·$Et_2O$ (57 mg, 5.0 equiv), and the mixture was stirred for 26 h at rt. Water (14 mL) was added to the reaction mixture, and it was stirred for 30 min. After separation of the organic layer, the aqueous layer was extracted with dichloromethane (2 × 10 mL), and the combined organic layer was dried ($MgSO_4$) and evaporated to afford the desired product 18 in 82% yield. This product decomposes during column chromatography and was therefore used without purification in the next step: $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 8.0 Hz, 1H), 7.40–7.20 (m, 9H), 7.09 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 8.8 Hz, 1H), 6.58 (s, 1H), 6.48 (d, J = 2.1 Hz, 1H), 6.36 (s, 1H), 5.77 (bs, 1H), 5.45 (d, J = 8.0 Hz, 1H), 5.21 (d, J = 12.0 Hz, 1H), 5.14 (d, J = 12.0 Hz, 1H), 5.05 (d, J = 8.0 Hz, 1H), 4.93 (bs, 1H), 4.52 (m, 1H), 3.84 (s, 6H), 3.58 (s, 3H), 3.12 (dd, J = 14.4, 5.6 Hz, 1H), 3.00 (dd, J = 14.4, 8.0 Hz, 1H), 2.02 (s, 3H), 1.35 (s, 9H).

**Deprotection and Cycloamidation of 18.** A solution of the crude carboxylic acid 18 (18.6 mg, 0.025 mmol, 1.0 equiv) in EtOH (7.5 mL) was combined with Pd/C (10%, 42 mg) and stirred for 1 h under hydrogen atmosphere until all the starting material was consumed (TLC). The reaction mixture was filtered through the Celite, and the EtOH was removed *in vacuo*. To remove the EtOH completely, the resulting product was coevaporated with dichloromethane (2 × 20 mL) and placed under high vacuum for 30 min. The product was then dissolved in dichloromethane (6 mL), and this solution was slowly injected, over 5 h, into an ice-cooled solution of EDC (10.4 mg, 0.054 mmol, 2.2 equiv) and

HOBT (7.7 mg, 0.057 mmol, 2.3 equiv) in dichloromethane (27 mL). The reaction mixture was stirred for 4 h at 0 °C and 12 h at rt. The solvent was removed *in vacuo*, and the residue was purified using HPLC (M20 10/25 silica gel column, hexanes:EtOAc = 2:3, 5 mL/min). Two products **21** ($t_R$ = 26 min) and **22** ($t_R$ = 35 min) were obtained in 19 and 22% yield, respectively.

For **21**: IR ($CHCl_3$) 3019, 1734, 1718, 1701, 1696, 1676, 1653, 1601, 1583, 1560, 1517, 1437, 1420 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.31–7.21 (m, 5H), 7.20 (d, $J$ = 1.74 Hz, 1H), 7.17 (s, 1H), 7.09 (dd, $J$ = 8.4 Hz, 2.3 Hz, 1H), 6.97 (d, $J$ = 8.4 Hz, 1H), 6.75 (d, $J$ = 7.6 Hz, 1H), 6.67 (d, $J$ = 2.2 Hz, 1H), 6.48 (s, 1H), 6.27 (s, 1H), 5.90 (bd, $J$ = 8.9 Hz, 1H), 5.74 (bd, $J$ = 7.0 Hz, 1H), 5.42 (d, $J$ = 7.6 Hz, 1H), 4.97 (d, $J$ = 7.0 Hz, 1H), 4.60 (ddd, $J$ = 9.2, 8.9, 5.9 Hz, 1 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.70 (s, 3H), 3.10 (dd, $J$ = 13.6, 9.2 Hz, 1H), 2.90 (dd, $J$ = 13.6, 5.9 Hz, 1H), 2.18 (s, 3H), 1.41 (s, 9H); $[\alpha]_D$ −12.9° (*c* 0.21, $CHCl_3$); HRMS found 633.2684; calcd for $C_{34}H_{39}N_3O_9$ 633.2686; MS *m/e* 633 (8), 577 (20), 533 (52), 529 (27), 527 (30), 490 (64), 471 (28), 374 (74).

For **22**: IR ($CHCl_3$) 3684, 3589, 3419, 3027, 3013, 2959, 2933, 2854, 1884, 1735, 1690, 1599, 1581, 1516, 1478, 1420 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.36–7.25 (m, 4H), 7.19 (d, $J$ = 8.3 Hz, 1H), 7.11 (bd, $J$ = 1H), 6.98 (d, $J$ = 8.3 Hz, 1H), 6.65 (d, $J$ = 2.2 Hz, 1H), 6.56 (d, $J$ = 1.3 Hz, 1H), 6.46 (d, $J$ = 6.9 Hz, 1H), 5.61 (d, $J$ = 7.0 Hz, 1H), 5.55 (bd, $J$ = 6.7 Hz, 1H), 5.19 (d, $J$ = 6.9 Hz, 1H), 4.91 (bd, $J$ = 6.7 Hz, 1H), 4.65 (ddd, $J$ = 8.5, 7.0, 5.9, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.68 (s, 3H), 3.24 (dd, $J$ = 14.3, 5.9, 1H), 3.03 (dd, $J$ = 14.3, 8.5 Hz, 1H), 2.19 (s, 3H), 1.35 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 170.9, 170.1, 169.2, 159.0, 157.4, 151.4, 135.5, 135.0, 129.8, 129.0, 128.9, 127.4, 125.1, 118.1, 117.7, 113.3, 107.7, 105.5, 80.1, 57.5, 56.2, 55.9, 55.7, 52.8, 36.7, 28.2, 8.5; $[\alpha]_D$ −82.4° (*c* 0.29, $CHCl_3$); HRMS found 633.2702, calcd for $C_{34}H_{39}N_3O_9$ 633.2686; MS *m/e* 634 (1), 633 (2), 560 (2), 559 (4), 533 (17), 526 (7), 497 (3), 491 (8), 490 (25).

**(Methoxyethoxy)methyl 2(*R*)-Azido-2-[3-(benzyloxy)-4-methoxyphenyl]acetate (23).** A solution of the azido acid **8** (506.4 mg, 1.0 equiv) in dichloromethane (16 mL) was combined with $Bu_4NI$ dissolved in water (16 mL), and the mixture was cooled to 0 °C and then basified with saturated $NaHCO_3$ to pH = 8. (Methoxyethoxy)methyl chloride (220 $\mu$L, 1.2 equiv) was added, and the reaction mixture was stirred for 30 min, quenched with 2.5 N HCl to pH = 1, extracted with dichloromethane (2 × 20 mL), dried over $MgSO_4$, and evaporated. After column chromatography ($SiO_2$, hexanes:EtOAc = 3:1), the desired product **23** was obtained as a yellow oil (576 mg, 89%). $R_f$ 0.45 (1:1 hexanes:EtOAc); IR ($CHCl_3$) 2934, 2838, 2106, 1749, 1604, 1592, 1515, 1455, 1443, 1428 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.46–7.29 (m, 5H), 6.98–6.88 (m, 3H), 5.34 (d, $J$ = 6.0 Hz, 1H), 5.32 (d, $J$ = 6.0 Hz, 1H), 5.17 (d, $J$ = 12.7 Hz, 1H), 5.13 (d, $J$ = 12.7 Hz, 1H), 4.87 (s, 1 H), 3.89 (s, 3 H), 3.65–3.63 (m, 2H), 3.47–3.44 (m, 2H), 3.33 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 168.7 (s, +), 150.5 (s, +), 148.44 (s, +), 136.5 (s, +), 128.5 (d, −), 127.9 (d, −), 127.4 (d, −), 125.7 (s, +), 121.0 (d, −), 113.0 (d, −), 111.7 (d, −), 90.5 (t, +), 71.2 (t, +), 71.0 (t, +), 69.7 (t, +), 64.9 (d, −), 59.0 (q, −), 56.0 (q, −); $[\alpha]_D$ −76.6° (*c* 0.74, $CHCl_3$); HRMS found 401.1590, calcd for $C_{20}H_{23}N_3O_6$ 401.1586, MS *m/e* 401 (4), 373 (2), 297 (1), 270 (1).

**(Methoxyethoxy)methyl 2(*R*)-[[(1,1-Dimethylethoxy)-carbonyl]amino]-2-(3-hydroxy-4-methoxyphenyl)acetate (25).** A solution of azido (methoxyethoxy)methyl ester **23** (370 mg, 0.92 mmol, 1.0 equiv) in THF was combined with $Boc_2O$ (300 mg, 1.4 mmol, 1.5 equiv) and 10% Pd/C (105 mg). The mixture was then stirred for 38 h under hydrogen atmosphere and was column chromatographed ($SiO_2$, hexanes:EtOAc = 2:1) to afford the desired product **25**. An analytical sample was obtained using HPLC to afford a white solid: mp 91–92 °C; $R_f$ 0.51 (2:1 hexanes:EtOAc); IR ($CHCl_3$) 3542, 3439, 3016, 2981, 2937, 2844, 1747, 1711, 1596, 1511, 1496, 1456, 1444 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 6.93 (d, 2.1 Hz, 1 H), 6.89 (dd, $J$ = 8.2, 2.1 Hz, 1H), 5.74 (s, 1H, OH), 5.49 (bd, $J$ = 7.2 Hz, 1H), 5.40 (d, $J$ = 6.0 Hz, 1H), 5.28 (d, $J$ = 6.0 Hz, 1H), 5.23 (d, $J$ = 7.3 Hz, 1H), 3.88 (s, 3H), 3.66–3.63 (m, 2H), 3.47–3.44 (m, 2H), 3.34 (s, 3H), 1.43 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 170.8 (s, +), 154.77 (s, +), 146.76 (s, +), 145.9 (s, +), 129.7 (s, +), 119.2 (d, −), 113.3 (d, −), 110.8 (d, −), 90.1 (t, +), 80. (s, +), 71.3 (t, +), 69.4 (t, +), 58.9 (q, −), 57.2 (d, −), 55.9 (q, −), 28.2 (q, −); $[\alpha]_D$ −80.3° (*c* 1.22, $CHCl_3$); HRMS found 385.1739, calcd for $C_{18}H_{27}NO_8$ 385.1737; MS *m/e* 385 (1), 299 (1.1), 254 (1), 253 (9), 252 (16), 223 (7), 209 (9), 208 (1).

**3-*O*-[(Tricarbonyl)($\eta^6$-2-methyl-3-methoxyphenyl)manganio]-*N*-(*tert*-butoxycarbonyl)-(*R*)-3-hydroxy-4-methoxyphenylglycine (Methoxyethoxy)methyl Ester Hexafluorophosphate (26).** To an ice-cold solution of phenol **25** in dichoromethane (25 mL) was added NaH (60%, 51.7 mg, 0.99 equiv), and the mixture was stirred at 0 °C for 30 min. The mixture was then transferred to a mixture of arene–manganese complex **11** (546 mg, 1.1 equiv) and $AgBF_4$ (800 mg, 5.6 equiv) suspended in ice-cold dichloromethane (80 mL) and the resulting mixture stirred for 1 h at 0 °C and then for 5 min at rt. Ammonium hexafluorophosphate (0.5 M (aq), 65 mL) was added, and the mixture was stirred vigorously for 1 h. The resulting dark solution was filtered through Celite, extracted with $CH_2Cl_2$ (2 × 50 mL), dried over $MgSO_4$, and evaporated. The crude product was dissolved in ~3 mL of $CHCl_3$, and the solution was filtered through Celite to remove residual arene–manganese complex (**11**). The desired product (805 mg, 78.3%) was obtained as a yellow solid (mixture of diastereomers due to chiral racemic arene–Mn moiety) by precipitation with pentane (75 mL): mp 205 °C dec; IR ($CHCl_3$) 3691, 3433, 3118, 3046, 3012, 2985, 2937, 2846, 2070, 2004, 1748, 1711, 1618, 1602, 1558, 1534, 1513, 1497, 1471, 1444, 1428 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.40* (dd, $J$ = 8.7, 2.2 Hz, 1/2H), 7.39* (dd, $J$ = 8.6, 2.3 Hz, 1/2H), 7.28* (d, $J$ = 2.0 Hz, 1/2H), 7.24* (d, $J$ = 2.1 Hz, 1/2H), 7.07 (d, $J$ = 8.6 Hz, 1H), 6.65 (t, $J$ = 7.0 Hz, 1H), 6.06 (d, $J$ = 7.1 Hz, 1H), 5.73* (bd, $J$ = 6.6 Hz, 1/2H), 5.69* (bd, $J$ = 7.0 Hz, 1/2H), 5.46* (d, $J$ = 7.0 Hz, 1H), 5.38–5.33 (m, 2H), 5.29 (d, $J$ = 6.6 Hz, 1H), 4.13 (s, 3H), 3.82 (s, 3 H), 3.69–3.65 (m, 2H), 3.50–3.46 (m, 2H), 3.34* (s, 3/2H), 3.33* (s, 3/2H), 2.39 (s, 3H), 1.42 (s, 9H) (* peaks due to one diastereomer or the other; nonasterisked peaks are common for both diastereomers); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 215.34 (s, +, $Mn^+(CO)_3$), 170.04 (s, +), 154.81 (s, +), 150.19* (s, +), 150.12* (s, +), 148.91* (s, +), 148.82* (s, +), 147.11 (s, +), 130.71* (s, +), 130.56* (s, +), 127.67* (d, −), 127.46* (d, −), 121.07* (d, −), 120.77* (d, −), 120.98 (d, −), 113.62 (d, −), 100.69 (d, −), 90.69 (s, +), 88.41 (s, +), 80.41 (s, +), 75.78* (q, −, $Mn^{(+)}$–$ArOCH_3$), 75.68* (q, −, $Mn^{(+)}$–$ArOCH_3$), 73.36 (d, −), 71.31 (t, +), 69.72 (t, +) , 58.97* (d, −), 58.91* (d, −), 56.74 (q, −, $CH_3OAr$), 55.97 (d, −, ), 28.58 (q, −, $-CO_2C(CH_3)_3$), 9.47 (q, −, $Mn^{(+)}$–$ArCH_3$) (* peaks due to one diastereomer or the other; nonasterisked peaks are common for both diastereomers). Anal. Calcd: C, 44.12; H, 4.47; N, 1.77. Found: C, 42.01; H, 4.54; N, 2.06.

**3-[[2-Methyl-3-methoxy-5-[(1*R*,4*R*)-5-isopropyl-3,6-dimethoxy-2-pyrazinyl]phenyl]oxy]-*N*-(*tert*-butoxycarbonyl)-(*R*)-4-methoxyphenylglycine (Methoxyethoxy)methyl Ester (27).** To a cold (−78 °C) solution of 6(*R*)-isopropyl-2,5-dimethoxy-3,6-dihydropyrazine (**13**) in THF (14 mL) was added n-BuLi (2.4 M, 526 $\mu$L) in hexanes, and the mixture was stirred for 3 h. The resulting lithiated bislactim was transferred to a cold solution (−100 °C) of arene–manganese complex **26** dissolved in THF (14 mL), which was prepared just before the addition of lithiated bislactim to minimize any demetalation by THF, and the mixture was stirred in the dark for 30 min at −100 *to* −95 °C. The reaction was quenched with $NH_4Cl$ (50 mL) at −95 °C, and after warming, the mixture was separated, the aqueous layer was extracted with dichloromethane (4 × 25 mL), and the combined layers were dried over $MgSO_4$. After filtration and concentration of the solvent, the crude product was dissolved in $CHCl_3$ (5 mL) and was added portionwise to pentane (50 mL), centrifuged, and decanted to remove the unreacted arene–managnese complex **26** (170.2 mg, 34%) as a yellow precipitate. The supernatant was evaporated, and the resulting product was dissolved in ice-cold $CH_3CN$ (20 mL) and reacted with NBS (107 mg, 1.5 equiv) for 45 min at 0 °C. The reaction was quenched with $NaHSO_3$ (10% w/w, 20 mL), and after separation of the organic layer, the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extract was washed with brine (2 × 20 mL) and dried over $MgSO_4$. Column chromatography ($SiO_2$, hexanes:EtOAc = 2.5:1) afforded the product **27** (56%, $R_f$ 0.60, EtOAc/hexane, 1:1) as a 2.5:1 mixture with side product **29** (23%). Pure diastereomer **28** (8.5%, $R_f$ 0.52, EtOAc/hexane, 1:1) was also obtained from the chromatography. For **27**: $R_f$ 0.60 (hexanes:EtOAc = 1:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 6.94 (d, $J$ = 8.1 Hz, 1H), 6.73 (d, $J$ = 2.6 Hz, 1H), 6.55 (s, 1H,), 6.34 (s, 1H), 5.45–5.30 (m, 2H), 5.27 (d, $J$ =

6.0 Hz, 1H), 5.13 (d, $J$ = 7.1 Hz, 1H), 4.95 (d, $J$ = 3.2 Hz, 1 H), 4.00 (t, $J$ = 3.5 Hz, 1H), 3.87 (s, 6H), 3.67 (s, 3H), 3.63 (s, 3H), 3.63–3.55 (m, 2H), 3.44–3.40 (m, 2H), 3.33 (s, 3H), 2.33 (m, 1H), 2.07 (s, 3H), 1.41 (s, 9H), 1.08 (d, 7.9 Hz, 3H), 0.72 (d, 7.9 Hz, 3H).

For **28**: IR ($CHCl_3$) 3683, 3438, 3032, 3026, 3016, 2964, 2945, 2872, 2840, 2400, 1746, 1710, 1694, 1650, 1642, 1613, 1581, 1511, 1498, 1464, 1442, 1417 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$, 60 °C) $\delta$ 7.08 (dd, $J$ = 8.4, 2.1 Hz, 1H), 6.94 (d, $J$ = 8.4 Hz, 1H), 6.84 (d, $J$ = 2.1 Hz, 1H), 6.66 (s, 1H), 6.39 (s, 1H), 5.33 (d, $J$ = 6.0 Hz, 1H), 5.29 (d, $J$ = 6.0 Hz, 1H), 5.26 (bd, 1H), 5.16 (bd, $J$ = 8.7 Hz, 1H), 5.06 (d, $J$ = 5.0 Hz, 1H), 3.92 (t, $J$ = 4.8 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.68 (s, 3H), 3.64–3.61 (m, 5H), 3.45–3.42 (m, 2H), 3.33 (s, 3H), 2.12 (s, 3H), 2.16–2.02 (m, 1H), 1.00 (d, $J$ = 6.8 Hz, 3H), 0.68 (d, $J$ = 6.8 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 170.7 (s, +), 164.5 (s, +), 161.6 (s, +), 158.4 (s, +), 155.1 (s, +), 154.7 (s, +), 150.8 (s, +), 146.3 (s, +), 138.6 (s, +), 129.1 (s, +), 122.6 (d, –), 118.1 (d, –), 116.0 (s, +), 112.6 (d, –), 109.9 (d, –), 105.2 (d, –), 90.2 (t, +), 80.1 (s, +), 71.2 (t, +), 69.4 (t, +), 60.9 (d, –), 59.4 (d, –), 59.0 (q, –), 57.1 (d, –), 56.1 (q, –), 55.6 (q, –), 52.6 (q, –), 31.8 (d, –), 28.2 (q, –), 19.7 (q, –), 17.9 (q, –), 8.7 (q, –); HRMS found: 687.3366, calcd for $C_{35}H_{49}N_3O_{11}$ 687.3367; MS $m/e$ 688 (8), 687 (32), 466 (10), 455 (19), 454 (100), 452 (16), 450 (18).

Spectral data for **29**: IR ($CHCl_3$) 3683, 3438, 3032, 3026, 3016, 2964, 2945, 2872, 2840, 2400, 1746, 1710, 1694, 1650, 1642, 1613, 1581, 1511, 1498, 1464, 1442, 1417 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$, 60 °C ) $\delta$ 7.08 (dd, $J$ = 8.4, 2.1 Hz, 1H), 6.94 (d, $J$ = 8.4 Hz, 1H), 6.84 (d, $J$ = 2.1 Hz, 1H), 6.66 (s, 1H), 6.39 (s, 1H), 5.33 (d, $J$ = 6.0 Hz, 1H), 5.29 (d, $J$ = 6.0 Hz, 1H), 5.26 (bd, 1H), 5.16 (bd, $J$ = 8.7 Hz, 1H), 5.06 (d, $J$ = 5.0 Hz, 1H), 3.92 (t, $J$ = 4.8 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.68 (s, 3H), 3.64–3.61 (m, 5H), 3.45–3.42 (m, 2H), 3.33 (s, 3H), 2.12 (s, 3H), 2.16–2.02 (m, 1H), 1.00 (d, $J$ = 6.8 Hz, 3H), 0.68 (d, $J$ = 6.8 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 170.7 (s, +), 164.5 (s, +), 161.6 (s, +), 158.4 (s, +), 155.1 (s, +), 154.7 (s, +), 150.8 (s, +), 146.3 (s, +), 138.6 (s, +), 129.1 (s, +), 122.6 (d, –), 118.1 (d, –), 116.0 (s, +), 112.6 (d, –), 109.9 (d, –), 105.2 (d, –), 90.2 (t, +), 80.1 (s, +, 71.2 (t, +), 69.4 (t, +), 60.9 (d, –), 59.4 (d, –), 59.0 (q, –), 57.1 (d, –), 56.1 (q, –), 55.6 (q, –), 52.6 (q, –), 31.8 (d, –), 28.2 (q, –), 19.7 (q, –), 17.9 (q, –), 8.7 (q, –); HRMS found 505.2316, calcd for $C_{26}H_{35}NO_9$ 505.2312; MS $m/e$ 505 (2), 404 (1.3), 385 (1.1), 374 (2.2), 373 (10.7), 372 (9.5), 330 (3.3), 328 (6.6), 327 (2.5), 318 92.8), 317 (18.2).

**Compound 31.** To a solution of the mixture of bislactim adduct **27** and side product **29** in THF (13 mL) was added 0.25 N HCl (3.4 mL), and the mixture was stirred for 1.5 h at rt. The reaction mixture was then basified to pH = 8–9 with $NaHCO_3$, extracted with $CH_2Cl_2$ (3 × 10 mL), dried over $MgSO_4$, and filtered. This solution was added via cannula to an ice-cold solution of *N*-(benzyloxycarbonyl)-D-phenylalanine (186 mg, 2.2 equiv) and HOBT followed by EDC. The mixture was stirred for 1 h at 0 °C and 15 min at rt. After concentration, the resulting product was column chromatographed to afford the desired product **31** (205 mg, 93% based on **27**) as a white solid. This compound contains ~10% inseparable side product, and further purification was not attempted: $R_f$ 0.42 (1:2 hexanes:EtOAc); IR ($CHCl_3$) 3423, 3013, 2957, 2936, 1742, 1711, 1582, 1497, 1464, 1456, 1442, 1420 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$, 55 °C ) $\delta$ 7.29–7.23 (m, 3H), 7.13–7.10 (m, 3H), 7.08 (d, $J$ = 2.1 Hz, 1H), 7.05 (d, $J$ = 2.2 Hz, 1H), 7.03–6.99 (m, 2H), 6.94 (s, 1H), 6.91 (s, 1H), 6.80 (d, $J$ = 1.9 Hz, 1H), 6.66 (d, $J$ = 6.9 Hz, 1H), 6.43 (bs, 1H), 6.32 (s, 1H), 5.60 (bs, 1H), 5.33 (s, 1H), 5.31 (d, $J$ = 6.0, 1H), 5.24 (d, $J$ = 6.0, 1H), 5.13 (d, $J$ = 6.0, Hz, 1H), 5.03 (s, 2H), 4.39 (m, 1H), 3.80 (s, 3H, $ArOCH_3$), 3.78 (s, 3H), 3.63 (s, 3H), 3.60–3.56 (m, 2H), 3.40–3.36 (m, 2H), 3.27 (s, 3H), 3.01–2.97 (m, 2H), 2.13 (s, 3H), 1.38 (s, 9H); HRMS found 896.3601, calcd for $C_{46}H_{55}N_3O_{14}Na$ ($M^+Na$) 896.3582.

**Compound 32.** To a solution of **31** (60.5 mg, 0.07 mmol, 1.0 equiv) in methylene chloride (18 mL) was added $MgBr_2{\cdot}Et_2O$. After the solution was stirred for 36 h at rt, water (9 mL) was added, and the mixture was stirred for 30 min. The reaction mixture was acidified (pH = 2) with 2.5 N HCl and was extracted with EtOAc (2 × 10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The resulting compound was subjected to the next reaction without further purification: $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.39–6.90 (m), 6.97–6.90 (m), 6.84 (d, $J$ = 2.6 Hz, 1H), 6.51 (s, 1H), 6.26 (s, 1H), 5.48–5.17 (m), 5.17–4.92 (m), 3.92 (s, 3 H), 3.89 (s, 3H), 3.63 (s, 3H), 3.08–2.84 (m, 2H), 2.18 (s, 3H), 1.45 (s, 9H).

**3-[2-Methyl-3-methoxy-5-[[N-(benzyloxycarbonyl)-(*R*)-phenylalanyl]-*O*-methyl-(*S*)-glycinyl]oxy]-*N*-(*tert*-butoxycarbonyl)-(*R*)-4-methoxyphenylglycine Pentafluorophenyl Ester (33).** A solution of the carboxylic acid **32** (40.3 mg, 0.051 mmol, 1.0 equiv) in THF (1 mL) was combined with pentafluorophenol (28.3 mg, 0.15 mmol, 3.0 equiv) and the mixture was cooled to 0 °C. Dicyclohexylcarbodiimide (DCC, 16 mg, 0.077 mmol, 1.5 equiv) was added to the cooled solution, and the mixture was stirred for 2 h at 0 °C and overnight at rt. The reaction mixture was concentrated and purified by HPLC (M20 10/25 silica gel column, hexanes:EtOAc = 1:1) to afford the desired product (29 mg, 60%) as a colorless oil: $R_f$ 0.31 (1:1 hexanes: EtOAc); IR ($CHCl_3$) 3684, 3620, 3417, 3298, 3038, 3035, 3031, 3028, 3024, 3022, 3019, 3010, 3008, 2979, 2937, 2433, 2400, 1790, 1741, 1707, 1673, 1583, 1520, 1465, 1456, 1442, 1420 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.45 (d, $J$ = 9.21, 1/2H), 7.31 (bs, 4H), 7.23–7.14 (m, 3H), 7.07–6.94 (m, 4H), 6.85 (s, 1/2H), 6.81 (d, $J$ = 7.6 Hz, 1H), 6.73 (d, $J$ = 5.8 Hz, 1H), 6.56 (s, 1/2H), 6.42 (d, $J$ = 7.9 Hz, 1H), 5.95 (s, 1/2H), 5.82 (d, $J$ = 7.9 Hz, 1/2H), 5.52 (d, $J$ = 7.4 Hz, 1/2H), 5.39–5.28 (m, 3/2H), 5.16–4.99 (m, 1H), 5.03 (s, 3/2H), 4.38 (m, 1/2H), 4.31 (m, 1/2H), 3.92 (s, 3/2H), 3.88 (s, 3/2H), 3.82 (s, 1/2H), 3.80 (s, 3/2H), 3.69 (s, 1H), 3.67 (s, 3/2H), 3.65 (s, 1H), 3.64 (s, 1/2H), 3.05–2.98 (m, 3/2H), 2.83 (dd, $J$ = 12.7, 3.5 Hz, 1/2H), 2.23 (s, 3/2H), 2.14 (s, 3/2H), 1.42 (s, 9/2H), 1.41 (s, 9/2H); $[\alpha]_D$ +35.1° (*c* 2.76, $CHCl_3$).

**Macrocyclization reactions of 32 and 33.** These reactions were performed in an identical manner to those for compounds **19** and **20**, as discussed in the text.

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