Synthesis of a Model Bicyclic CDE Ring System of Ristocetin A and Observation of a Facile Inversion of Configuration in a 16-Membered DE Ring Model

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Areneruthenium chemistry was used to effect intramolecular S_NAr reactions between phenoxide nucleophiles and chlorophenylalanine residues that are connected by a peptide chain, resulting in the construction of a bicyclic peptido aryl ether system that corresponds to the BCDF system of the glycopeptide antibiotics ristocetin A and teicoplanin. A facile and selective base-catalyzed complete inversion of configuration at the D ring arylglycine residue was observed when this unit is the carboxylate terminus on a 16-membered ring system corresponding to the DEF rings of the target molecules. The inversion appears to result from an overwhelming thermodynamic preference for the inverted system and is supported by molecular mechanics and semiempirical calculations on the minimized conformations of the epimeric molecules.

Introduction

Vancomycin (**1**) was isolated from *Streptomyces orientalis* in 1956 and is in clinical use as an effective antibiotic, especially for the treatment of methicillin-resistant infections.[1,2] Following its isolation, more than 200 compounds having similar structural features, collectively called glycopeptide antibiotics, have been isolated. Other members of this family include orienticin-A−D, ristocetin-A (**2**), aricidin, teicoplanin, and avoparcin. In general, they have a core heptapeptide backbone structure, containing amino acids made up of derivatives of phenylglycine, tyrosine, leucine, methionine, and asparagine. The aromatic rings are cross-linked by either biphenyl or by biaryl ether linkages, forming peptido macrocycles. Thus, vancomycin contains a 12-membered biphenyl macrocycle and two 16-membered macrocyclic ethers. During recent years, there has been observed an increasing occurrence of vancomycin-resistant strains of infectious bacteria.[3] This, coupled with the challenge presented by the structural complexity of these molecules, has promoted considerable interest in their chemical synthesis.[4]

One of the challenges associated with the synthesis of vancomycin and its relatives is the construction of the diaryl ether linkages, since these must be formed in the presence of quite sensitive amino acid and/or peptide functionality. Of particular significance in this regard are the arylglycine residues that are very labile under basic conditions,[5] which precludes the use of some of the more classical approaches, such as Ullmann coupling.[6] We have reported technology for ruthenium-promoted S_NAr reactions, which proceed under very mild conditions, and that can be used either inter-[7] or intramolecularly[8] for the construction of diaryl ethers of the type found in the vancomycin group. We describe in this paper ap-

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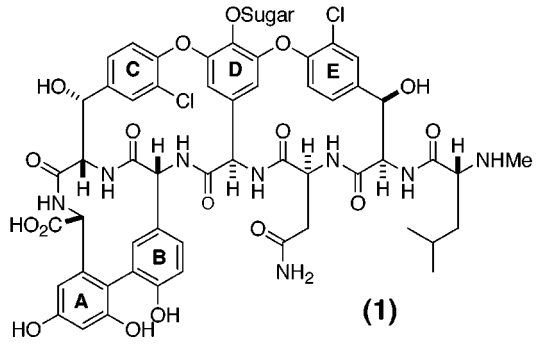
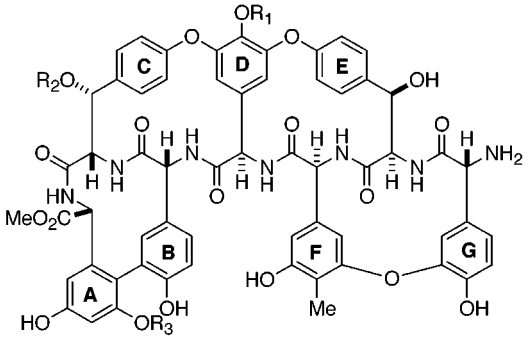


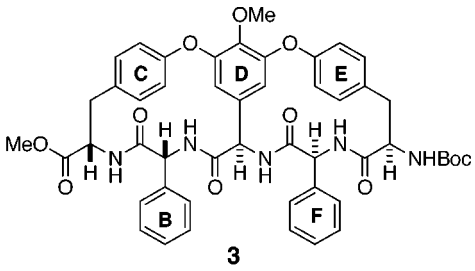
(1)

VANCOMYCIN



(2)

RISTOCETIN A



3

plications of this chemistry to the synthesis of a model bicyclic system, shown in structure **3**, representing the B/C/D/E/F rings of ristocetin and teicoplanin. This system was chosen primarily because the presence of three quite sensitive arylglycine residues would serve as an excellent test of any methodology chosen for its construction. We also disclose a thermodynamically driven selective inversion of the D-ring arylglycine residue when this is used as a carboxyl terminus. This has important implications concerning the choice of strategy for the general construction of these molecules, and it appears to have gone unnoticed in previous studies on these substances.

Our first retrosynthetic analysis of the target molecule **3** is presented in Scheme 1. This approach was chosen on the basis of the known mechanism of biological activity of vancomycin,[2b] which involves primarily the "right hand" half of the molecule, and so it appeared most expeditious to adopt a synthetic avenue that would furnish carboxylate binding pocket analogues relatively early in the sequence. By disconnecting the ether linkage between the amino acid residues **C** and **D**, we arrive at intermediate **I**. The target can be made by subjecting this complex to an intramolecular S_NAr reaction. Further disconnection at the amide bond between residues **C** and **B** results in the ruthenium complex **II** and the macrocycle **III**. The tetrapeptide intermediate **III** can be made by condensing a phenylglycine to the cyclic tripeptide **IV**, which can be made by an intramolecular S_NAr reaction of the corresponding linear tripeptide ruthenium complex **V**.

Results and Discussion

To implement the above strategy, we needed to prepare a tripeptide ruthenium complex corresponding to the intermediate **V**. Our synthesis started with the azido acid **4** (Scheme 2), previously reported by us.[9] The acid was esterified using MeOH and *p*-toluenesulfonic acid monohydrate to provide **5** in excellent yield. The azide was reduced and coupled with (*S*)-ZPhg to provide the dipeptide **6**, also in excellent yield. The amine was then deprotected and condensed with the ruthenium complex **7**, reported by us previously,[7,8] to provide the tripeptide ruthenium complex **8** that was then used for cycloetherification studies.

The cyclization reaction conditions initially tested (procedure A) involved addition, over 30 min, of a DMF solution of the ruthenium complex to a cooled THF solution (between −40 and −60 °C) of sodium 2,6-di-*tert*-butylphenoxide (2 equiv) over a period of 30 min to 1 h, followed by slow warming of the reaction mixture to 0 °C over a period of about 2 h, after which it was stirred for about 1 h at 0 °C and 2−3 h at room temperature. Thus, during the addition, an excess of base over complex is present. The crude product was subjected to photolysis, to disengage the RuCp moiety, and the product fractions were separated by preparative TLC. Thus, the phenolate of **8** was generated at low temperature and allowed to warm slowly so as to undergo the desired macrocyclization. The solution concentration was usually around 5−10 mM.

The tripeptide ruthenium complex **8**, when subjected to these cyclization conditions, underwent smooth conversion to two separable products in a ∼4:1 ratio with a combined yield of 46% (Scheme 3). Both compounds appeared to be cyclization products on the basis of their ^{1}H NMR spectra, which showed clearly the expected upfield shift of one of the ortho protons of ring **D**.[10] This was also confirmed by FABHRMS spectroscopy of each fraction. The chromatographically *more mobile* compound (TLC) was the *major* fraction and the *less mobile* compound (TLC) was the *minor* fraction.

Since the minor component also appeared to be a cyclization product, it suggested that partial epimerization was taking place at one of the stereogenic centers, most likely the amino acid residue **D**. Among the three amino acid residues, both **E** and **F** contain amide carbonyl, and only residue **D** contains the ester carbonyl, which should make its α-CH comparatively more acidic. When the cyclization was repeated, it was found that, depending on the reaction conditions, the ratio of the more mobile to less mobile product varied to a great extent (Table 1). By varying the procedure, one can produce either the more mobile product as the major one (entry 1 and 3) or exclusively the less mobile product (entry 4).

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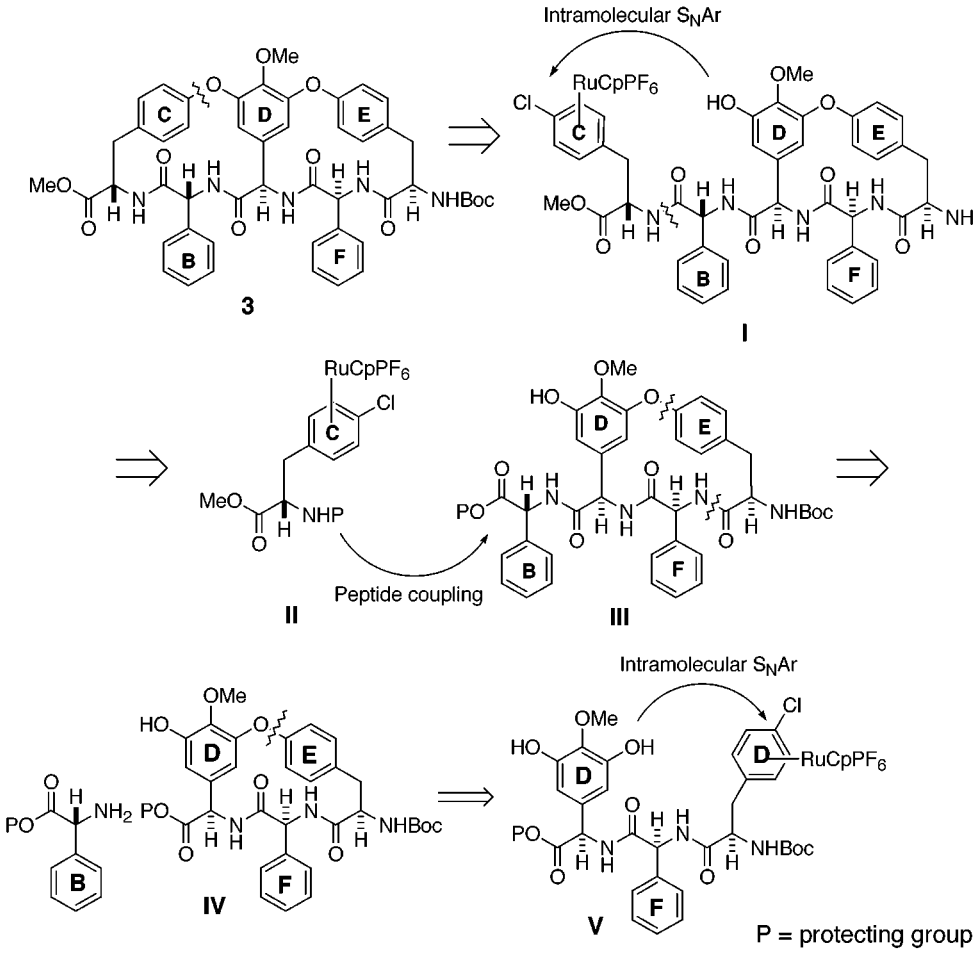
Scheme 1



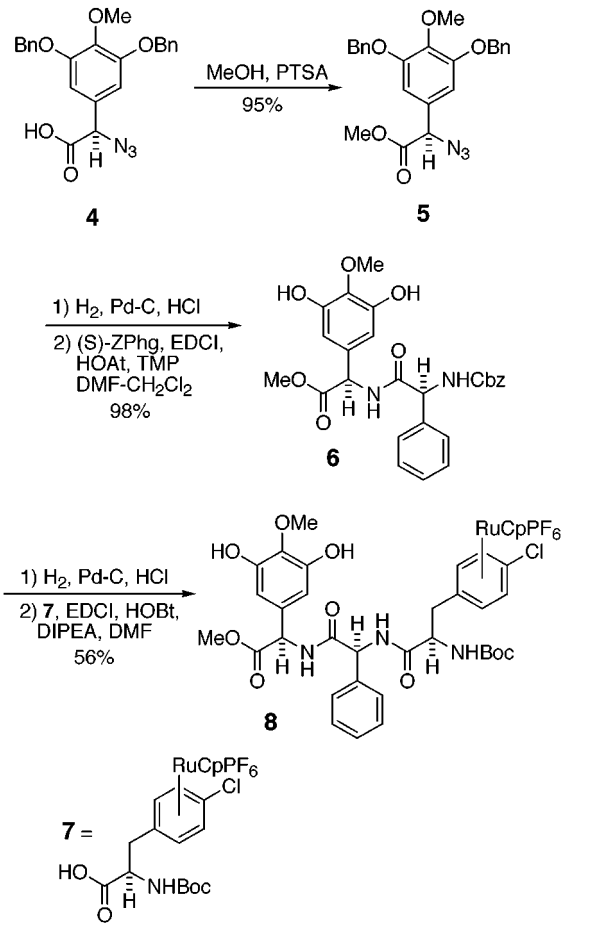
Since the latter result is obtained when excess base is not present during the reaction (as base is added slowly to the complex), we suspected that the less polar product is **9**, wherein the stereochemistry is retained. Variation of solvent has some effect on the outcome of the reaction (entry 2 vs entry 1), and the use of cesium carbonate at room temperature causes significant epimerization (entry 3; DMF was used as solvent to alleviate solubility problems with cesium carbonate). The use of DMF might be expected to promote epimerization, as a result of its cation-coordinating ability leading to the presence of "naked" phenolate, which would be a stronger base.

To confirm the site of epimerization, and which product was the desired one, the carboxy-terminal epimer of **8** was prepared. During the asymmetric synthesis of **4**, the azido carboximide **11** was obtained as a minor product (~10%).[9] Hydrolysis of this carboximide with LiOOH provided the azido acid **12** with the required (*S*) absolute configuration (Scheme 4), and this was esterified using MeOH−PTSA to provide **13**. The azide was reduced and then coupled with (*S*)-ZPhg to provide the dipeptide **14**, which was then converted into the tripeptide ruthenium complex **15**. This complex was subjected to the standard cyclization conditions (procedure A) using sodium 2,6-di-*tert*-butylphenoxide as the base. Demetalation afforded a *single* macrocyclic product (Scheme 4), which was in fact identical to the more mobile fraction **10** obtained from the cyclization of **8** (Scheme 3).

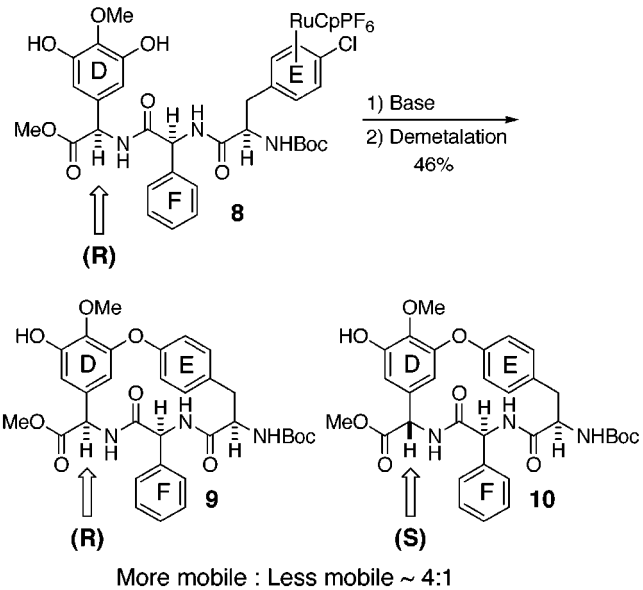
The absolute configurations of the two products **9** and **10** were thus confirmed by correlation with the product from **15**. Inspection of the product ratios in Table 1 reveals that the more mobile, epimeric macrocycle **10** is obtained as the major product when an excess of base is present during cyclization (Table 1, entries 1−3, where 2 equiv or greater amount of base was installed prior to addition of **8**). We believe that cyclization of the tripeptide **8** results in the RuCp complex of **9**, which undergoes a facile base-promoted epimerization to provide the thermodynamically more stable complex corresponding to **10**. Under the reaction conditions provided in entries 1 and 2 of Table 1, it is likely that the presence of excesses of sodium 2,6-di-*tert*-butylphenoxide can drive this equilibrium. To prevent this, we adopted procedure C (Table 1, entry 4) where the base is slowly added to a solution of the ruthenium complex using a syringe pump. In this way no excess of NaDTBP is present at any time, and only the nonepimerized macrocycle **9** was obtained.

To test this proposition and further our understanding of the configurational stability of these molecules, the NMR psectrum of the macrocycle **9** (about 1.5 mg in about 450 μL of 1:1 $CD_3CN-CDCl_3$) was recorded, and the solution was then treated with 50 μL of 1:1 $CD_3CN-CDCl_3$ containing DBU (5.0 equiv). The NMR spectrum was immediately recorded, showing *complete conversion* of **9** to **10** with no trace of residual starting material remaining. Since the product ratio is >99:1, this corresponds to at least 3 kcal/mol difference in free energy between these two compounds. *This is an extremely facile and selective thermodynamically driven inversion of configuration that probably also occurs with the intermediate ruthenium complexes.*

Scheme 2



Scheme 3



As far as we are aware, this is the first reported observation of such behavior during the construction of subunits of the vancomycin family. Earlier, we have reported the synthesis of 16-membered ring systems related to **9** and **10**, using both cycloamidation[7] and cycloetherification[8] strategies. Comparison of the present NMR spectra with our earlier data suggests that in both cases we had obtained the products of inversion at the carboxylate terminus, which went undetected (since mixtures were not produced). There are a number of reports in the literature[11] of similar model systems that have been constructed using more forcing conditions for the S_NAr process than those required for the Ru-promoted reactions described herein. Our results indicate that any inversion of configuration at the D-residue would probably not be detected under such conditions and are a forewarning of a general problem that is likely to occur in any approach to the target molecules that involve a "right-to-left" strategy.

Molecular Modeling. Molecular Dynamics (Insight/Discover molecular-modeling software package) simulations were employed to obtain global minima for the epimeric compounds **9** and **10**. The molecule was constructed using the Insight program and was then subjected to high-temperature MD simulation using the Discover program and CFF91 force field. The molecule was heated to 1000 K and equilibrated at this temperature for 20 000 fs with an integral time step of 1 fs. The temperature was maintained at 1000 K for 10^5 fs, and the conformers were sampled at every 1000 fs. Each of the resultant 100 conformers were then subjected to minimization using Discover. The minimized conformers were arranged in increasing order of total energy, and the lowest energy conformer was selected. This structure was further minimized using Discover, and the final energy corresponding to this global minimum was taken. The energy of the conformer corresponding to the global minimum of **9** was found to be −4.79 kcal/mol using CFF91. The energy corresponding to the epimer **10** was found to be somewhat lower at −5.52 kcal/mol.

We also performed semiempirical calculations on these molecules using the Spartan software package. The coordinates corresponding to the global minima of **9** and **10** from the Insight/Discover molecular mechanics calculations were imported into the Spartan program. These structures were then subjected to semiempirical minimization using the PM3, MNDO, and AM1 modules of Spartan, and the results are summarized in Table 2.

The heats of formation of **9** and **10** were found to be −245.82 kcal/mol and −248.76 kcal/mol (MNDO), respectively, from these calculations. Both the strain energy calculation using molecular mechanics and heat of formation using semiempirical methods consistently show that the epimeric macrocycle **10** is more stable than **9**.

Even though the required macrocycle **9** could be obtained as the sole product by choosing the appropriate cyclization conditions (Table 1, entry 4) deprotection of the methyl ester could not be realized with LiOH without extensive epimerization of the C-terminal chiral center. Acid-mediated removal of the methyl ester was not expected to be successful due to the presence of the acid-labile Boc group. Thus, we could not proceed satisfactorily to the intermediate **III** presented in Scheme 1. Before abandoning the approach presented in Scheme 1, we decided to prepare the macrocyclic tripeptide intermediate **VI** with a (trimethylsilyl)ethyl carboxyl blocking group, which can be removed under milder conditions. The synthesis started with the azido acid **4**, which was esterified using DCC/HOAt to provide the ester **16** in excellent yield (Scheme 5). The ester was converted to

(11) Generally, the conditions used for nitro-group-promoted S_NAr reactions that lead to formation of diaryl ethers of this type require the use of base at elevated temperature (ca. 40 °C) for extended periods of time. For examples, see ref 4b−d.

Table 1. Cyclization of 8 under Different Conditions

	base	solvent	reaction condns[a]	yield[b] (%)	ratio[c]
1	NaDTBP	1:1 DMF−THF	procedure A: addition of complex **8** to 2 equiv of base over 30 min, then 2 h at −60 °C, warming to 0 °C, then 1 h at 0 °C and 2 h at 20 °C	46	4:1
2	NaDTBP	2:5 DMF−THF	modified procedure A: 2 h at −60 °C to 0 °C then 1 h at 0 °C and 3 h at 20 °C	40	1:1
3	Cs_2CO_3	DMF	procedure B: addition of complex **8** to 5 equiv of Cs_2CO_3, then 6 h at rt	42	4:1
4	NaDTBP	2:9 DMF−THF	procedure C: addition of base by syringe pump to complex **8** over 2 h at 0 °C, then stirred for 30 min at 0 °C and 3 h at rt	29	0:1

[a] See the Experimental Section for the detailed procedures. [b] Yield represents the isolated yield after demtalation. [c] Ratio represents the ratio of the more mobile to less mobile product.

Scheme 4

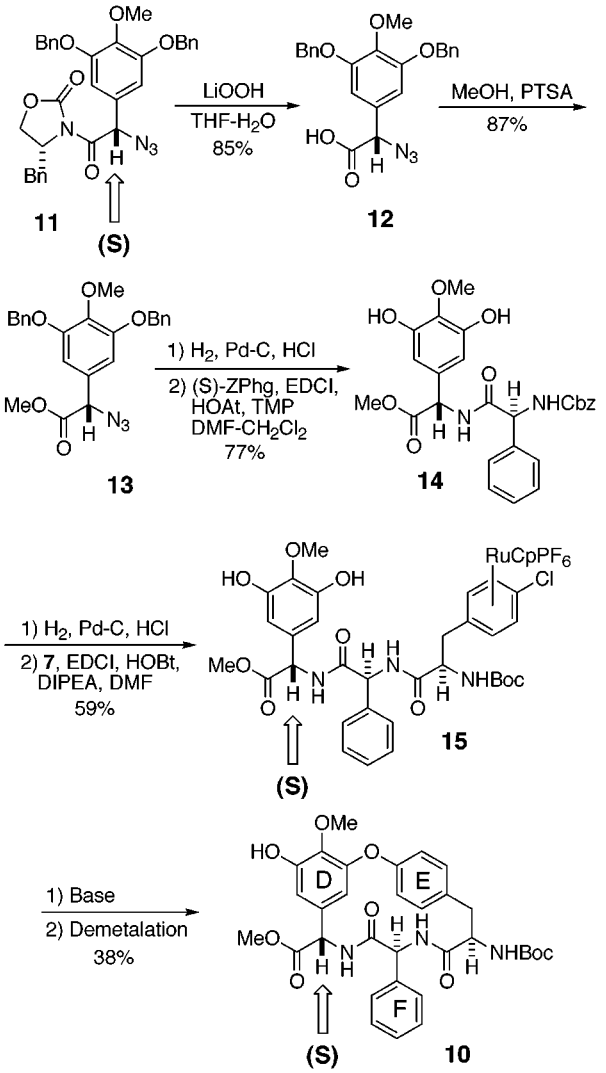


Table 2. Results of Calculations on Structures 9 and 10

	property	method	calculated (kcal/mol) **9**	**10**
1	strain energy	CFF91[a]	−4.79	−5.52
2	heat of formation	PM3[b]	−279.27	−280.27
3	heat of formation	MNDO[b]	−245.82	−248.76
4	heat of formation	AM1[b]	−265.05	−265.47

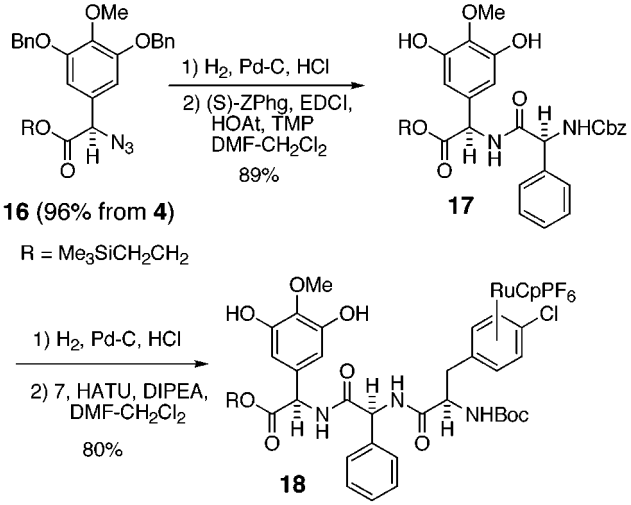
[a] Molecular mechanics calculation using Insight/Discover program. [b] Semiempirical calculations using Spartan program.

the dipeptide **17**, which was then transformed into the tripeptide ruthenium complex **18**.

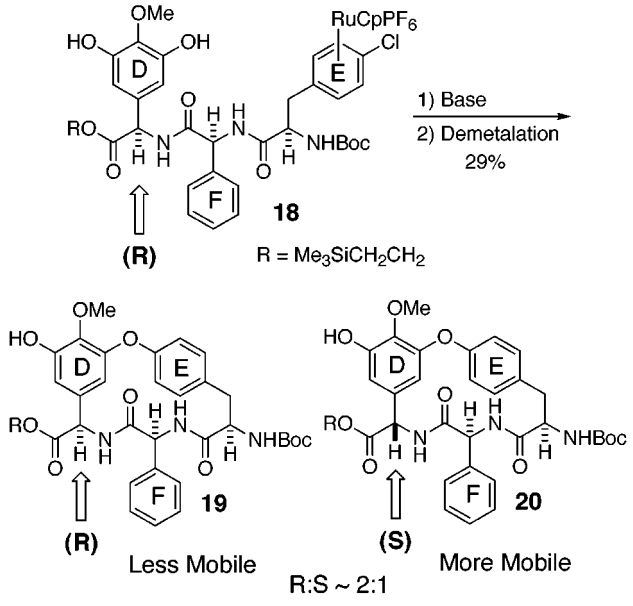
Cyclization of **18** under standard conditions with sodium 2,6-di-*tert*-butylphenoxide also provided two macrocyclic products arising from carboxyl-terminal epimerization (Scheme 6). ^{1}H NMR spectra of these products showed patterns similar to **9** and **10**. In contrast to the cyclization of **8**, we could not suppress the formation of the epimeric macrocycle **20** during the cyclization of **18** by varying the reaction conditions.

We also carried out TMSE deprotection and peptide coupling on **19**. When the ester **19** was treated with tetrabutylammonium fluoride, the TMSE group was cleaved to provide the acid. Analysis of the crude product by ^{1}H NMR showed very little epimerization. Owing to

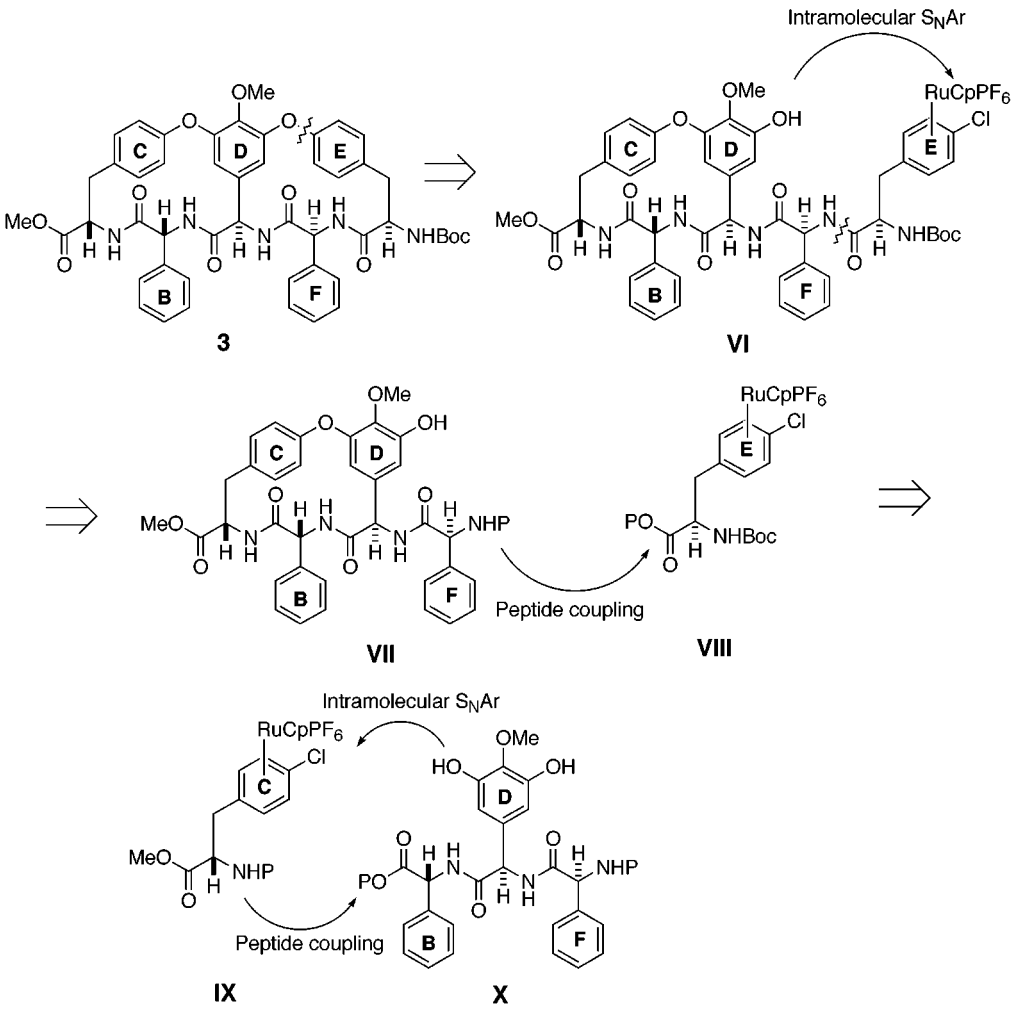
Scheme 5



Scheme 6



Scheme 7



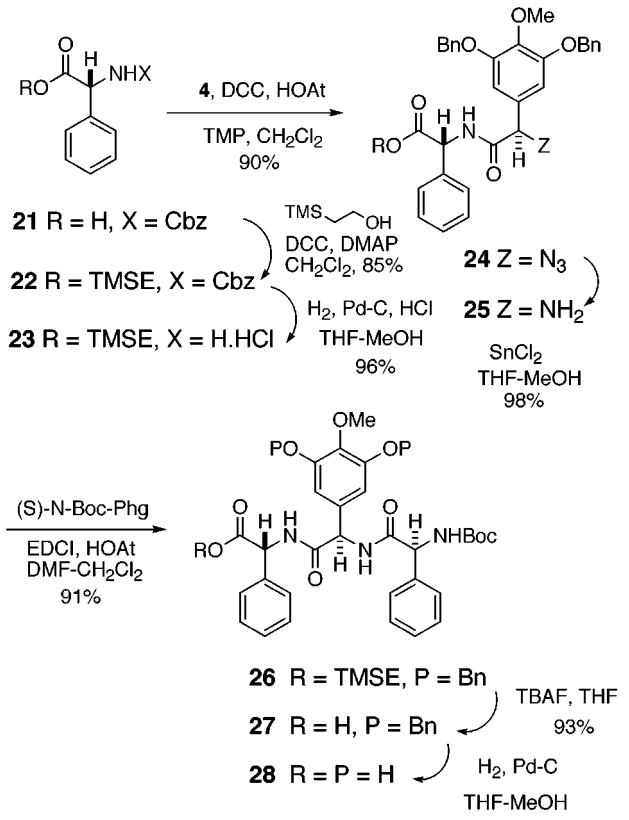
difficulty in purifying this product, the crude material was subjected immediately to peptide-coupling conditions (EDCI/HOAt) with phenylglycine methyl ester. However, analysis of the product showed extensive epimerization, suggesting once again the extreme lability of the D-residue stereogenic center. Thus, even if we could obtain the acid **19** without epimerization we could not proceed with the peptide coupling.

The "Left-to-Right" Strategy. Since the strategy outlined in the preceding paragraphs met with numerous tactical problems, we decided to construct the left side macrocycle (C−O−D ring) first and then add the right side macrocycle (D−O−E ring) as outlined in Scheme 7. It may be noted that this is in fact the coupling direction used by Evans in his synthesis of orienticin C.[4] Here, the synthesis requires the linear tripeptide **X**.

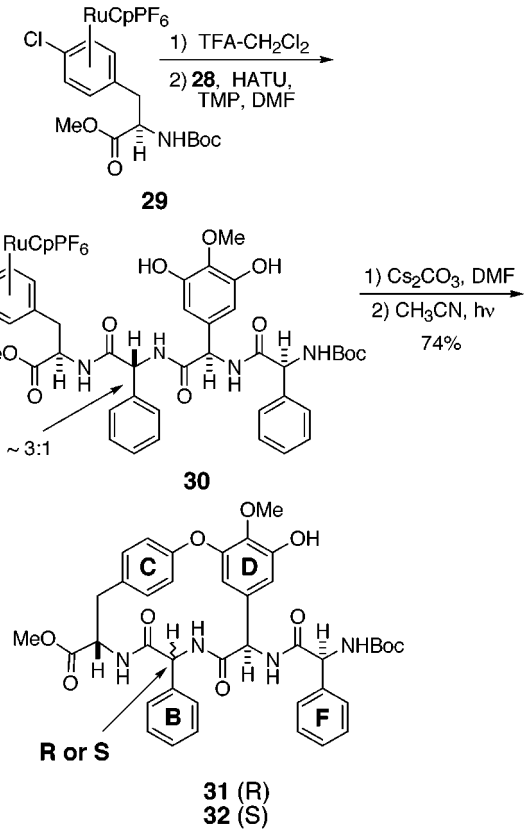
Our synthesis started with the (benzyloxy)carbonyl-protected (*R*)-phenylglycine **21** (Scheme 8). (*R*)-ZPhg was protected as its TMSE ester **22** using DCC/DMAP. The Cbz group was then cleaved by hydrogenolysis to provide the amine hydrochloride **23**, which was coupled with the azido acid **4** to furnish the dipeptide **24** in excellent yield. The azide reduction was then carried out using $SnCl_2$ to provide the amine **25** in near-quantitative yield. This is a clean reaction and provided the pure amine, which was homogeneous by NMR without chromatographic purification. Use of triphenylphosphine as the reducing agent also worked well for this reaction, but product purification was significantly more difficult. The amine was then coupled with Boc-protected (*S*)-phenylglycine, prepared by reaction of (*S*)-Phg with $(Boc)_2O$ in the presence of $NaHCO_3$ in THF−H_2O mixture. The tripeptide **26** was subjected to TMSE deprotection using TBAF to provide the acid **27** in high yield, and debenzylation using H_2/Pd−C afforded **28**.

It was found that the ^1H NMR spectrum of the tripeptide **26** in $CDCl_3$ was markedly concentration-dependent, showing two distinct NMR patterns at lower and higher concentrations. For example, at very low concentration (~2 mg/mL), the benzylic methylene protons appeared as a singlet (4H), while at higher concentrations (~40 mg/mL), they appeared as two (geminally coupled) doublets. Similar changes were observed for other resonances. This can be explained if the tripeptide is undergoing noncovalent dimer formation (via hydrogen bonding) in a relatively nonpolar solvent such as $CDCl_3$. At very low concentration only the monomer exists, giving the spectrum where the benzylic protons appear as a singlet. As the solution concentration is increased, an equilibrium between monomer and dimer is set up. The resultant NMR spectrum corresponds to a time-averaged structure. As the concentration is further increased it is possible that most of the molecules exist as dimers, resulting in the limiting pattern observed at higher concentrations, wherein restricted rotation about the benzyl ether bonds causes inequivalence of the methylene protons. It may be noted that many members of the vancomycin family are known to exist as dimers

Scheme 8



Scheme 9



in solution,[12] but the minimum structure that is required for this phenomenon to occur has not been evaluated.

The tripeptide **28** was then converted to the tetrapeptide ruthenium complex **30** (Scheme 9). The ruthenium complex **29** was prepared by complexation of the methyl ester of (*S*)-*N*-Boc-4-chlorophenylalanine[13] under the conditions reported for the (*R*) enantiomer.[7] The *tert*-butoxycarbonyl group of the complex **29** was removed in TFA−CH_2Cl_2 mixture, and the amine was then coupled with the tripeptide **28** using HATU.[14] In this case, partial epimerization at the B-ring residue was observed, since the peptide coupling is carried out at the C-terminal phenylglycine, which contains an *N*-acyl unit. The product mixture was subjected to cycloetherification, affording two separable macrocycles in the ratio of ~3:1. When sodium 2,6-di-*tert*-butylphenoxide (DMF−THF) was used as the base for cyclization, the yield was low and purification was difficult, but when Cs_2CO_3 (DMF) was used the macrocycles were obtained cleanly in 74% overall yield for cyclization and demetalation.

The major macrocycle **31** was then deprotected using the TFA−CH_2Cl_2 mixture in the presence of dimethyl sulfide, and the resultant amine was coupled with **7** to provide the pentapeptide ruthenium complex **33** in high yield (Scheme 10). This compound was treated with Cs_2CO_3 in DMF, resulting in a smooth intramolecular S_NAr reaction to afford the target molecule **3** in 70% yield after photolytic decomplexation. The successful cyclization was indicated by an upfield NMR shift of the second ortho proton of the residue **D**, and the identity of this compound was further confirmed by FABHRMS.

Summary

Ruthenium-promoted intramolecular S_NAr reactions can be successfully employed with structures of high complexity to afford systems related to the vancomycin group of antibiotics. The reaction conditions for the cycloetherification process are sufficiently mild to avoid epimerization of sensitive arylglycine residues except when these are at the carboxyl terminus. An extremely facile thermodynamically driven inversion at the D-ring arylglycine residue was observed in the 16-membered D−O−E macrocycle, which mandates a "left-to-right" strategy for the synthesis of the target structures. The chemistry developed here can now be extended to the total synthesis of members of the vancomycin family of antibiotics.

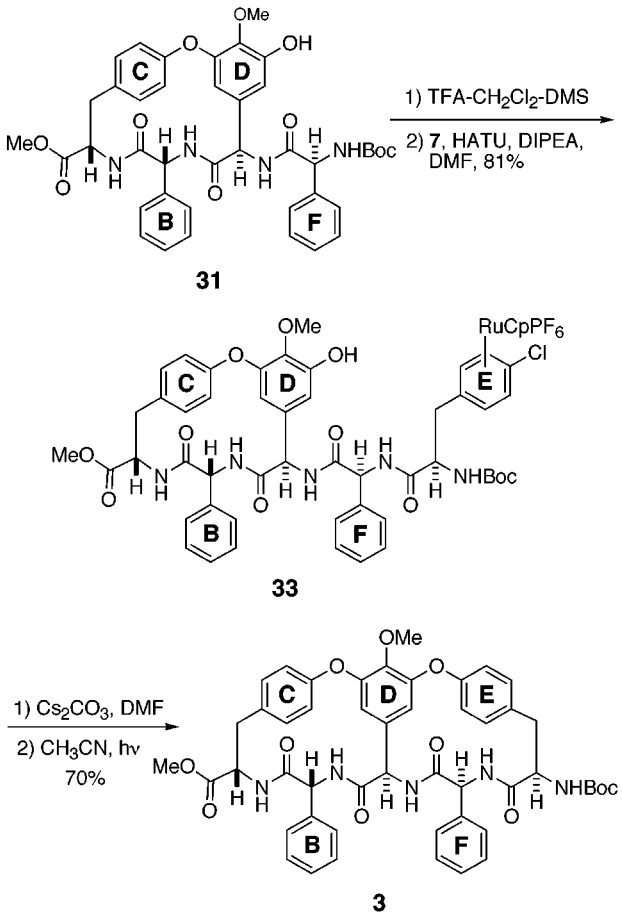
Experimental Section

General procedures are as described elsewhere.[7,8]

Methyl (2*R*)-2-Azido-2-[3,5-bis(benzyloxy)-4-methoxyphenyl]ethanoate (5). A solution of the azido acid **4** (520 mg, 1.24 mmol) and *p*-toluenesulfonic acid monohydrate (236 mg, 1.24 mmol) in 10 mL of MeOH was refluxed for 2.5 h. The solvent was evaporated, and the residue was dissolved in 75 mL of CH_2Cl_2. The organic phase was washed with 2 × 30 mL of aqueous $NaHCO_3$ and dried over Na_2SO_4. The solution was filtered, the solvent evaporated, and the residue chromatographed (SiO_2 gel, CH_2Cl_2) to obtain 510 mg of resin (95%): R_f 0.30 (100% CH_2Cl_2); $[\alpha]^{20}_D$ −69° (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.44−7.30 (10H), 6.64 (s, 2H), 5.13 (s, 4H), 4.81 (s, 1H), 3.89 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (75 MHz) δ

(12) Williams, D. H.; Searle, M. S.; Westwell, M. S.; Mackay, J. P.; Groves, P.; Beauregard, D. A. *Chemtracts: Org Chem.* **1994**, *7*, 133.
(13) Lee, K. Ph.D. Dissertation, Case Western Reserve University, 1995.
(14) We used various coupling methods and found less epimerization with those conditions described in this article, as reported by: Carpino, L. A.; Ionesco, D.; El-Faham, A. *J. Org. Chem.* **1996**, *61*, 2460. Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397. Carpino, L. A.; El-Faham, A. *J. Org. Chem.* **1994**, *59*, 695.

Scheme 10



169.28, 152.80, 140.14, 136.64, 128.81, 128.49, 127.89, 127.27, 107.26, 71.12, 65.10, 60.82, 52.84; IR ($CHCl_3$) 2113, 1750, 1440 cm^{-1}; HRMS (EI) *m/z* 433.1606 (M^+), $C_{24}H_{23}N_3O_5$ requires 433.1638.

Methyl (2*R*)-2-[(*S*)-1-{[(Benzyloxy)carbonyl]amino]}-1-(phenylmethyl)carboxamido]-2-(3,5-dihydroxy-4-methoxyphenyl)ethanoate (6). To a solution of the azide **5** (510 mg, 1.18 mmol) in 15 mL of THF−MeOH (1:1 v/v) was added 393 μL of 6 N HCl (2.36 mmol, 2.0 equiv) and 100 mg of 10% Pd−C. The suspension was stirred under 1 atm of H_2 (balloon) for 18 h. The mixture was filtered through Celite, and the solvent was evaporated. The residue was chased with dry ether and dried under vacuum to obtain the crude amine hydrochloride as a solid. To a solution of this amine hydrochloride, (*S*)-ZPhg (370 mg, 1.30 mmol, 1.1 equiv), and HOAt (241 mg, 1.77 mmol, 1.5 equiv) in 12 mL of DMF−CH_2Cl_2 (1:2 v/v) at 0 °C was added EDCI (340 mg, 1.77 mmol, 1.5 equiv) followed by TMP (156 μL, 1.18 mmol, 1.0 equiv). The mixture was stirred at 0 °C for 2 h and at room temperature for 11 h. The solution was diluted with 70 mL of EtOAc, and the organic phase was successively washed with 1 N HCl (2 × 30 mL), aqueous $NaHCO_3$ (2 × 30 mL), and brine (30 mL) and dried (Na_2SO_4). The solution was filtered, the solvent evaporated, and the residue chromatographed (30 g of SiO_2 gel, 5:95 MeOH−$CHCl_3$) to obtain 590 mg of foam (98%): R_f 0.28 (5:95 MeOH−$CHCl_3$); $[\alpha]^{22}_D$ −35° (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 1H, J = 3.3 Hz), 7.25−7.08 (10H), 6.83 (bs, 2H), 6.44 (s, 2H), 6.21 (d, 1H, J = 9.2 Hz), 5.61 (d, 1H, J = 7.7 Hz), 5.11 (d, 1H, J = 4.8 Hz), 4.77 (d, 1H, J = 12 Hz), 4.54 (d, 1H, J = 12 Hz), 3.67 (s, 3H), 3.58 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.65, 170.77, 156.10, 149.75, 136.87, 135.72, 135.01, 130.27, 128.87, 128.34, 128.02, 127.79, 127.08, 107.08, 67.14, 60.54, 57.97, 57.12, 52.98; IR ($CHCl_3$) 1741, 1712, 1677, 1513 cm^{-1}; HRMS (EI) *m/z* 494.1671 (M^+), $C_{26}H_{26}N_2O_8$ requires 494.1689.

(η^5-Cyclopentadienyl){methyl (2*R*)-2-{(*S*)-1-[(1*R*)-1-[(*tert*-butoxycarbonyl)amino]-2-((1,2,3,4,5,6-η)-4-chlorophenyl)ethylcarboxamido]-1-(phenylmethyl)carboxamido}-2-(3,5-dihydroxy-4-methoxyphenyl)ethanoate}ruthenium Hexafluorophosphate (8). A mixture of the dipeptide **6** (84 mg, 0.17 mmol), 10% Pd−C (19 mg), and 6 N HCl (84 μL, 0.5 mmol, 3.0 equiv) was stirred under 1 atm of H_2 (balloon) for about 12 h. The suspension was filtered through Celite and evaporated. The residue was chased with dry ether and dried under vacuum to obtain the amine hydrochloride. To a flask containing the ruthenium complex **7** (103 mg, 0.17 mmol) and HOBt (34 mg, 0.25 mmol, 1.5 equiv) in 0.75 mL of DMF at 0 °C was added EDCI (36 mg, 019 mmol, 1.1 equiv) and the mixture was stirred at 0 °C for 30 min. To this was added a solution of the above amine hydrochloride in 1.75 mL of DMF followed by DIPEA (30 μL, 0.17 mmol, 1.0 equiv). The mixture was stirred at 0 °C for 3 h and at room temperature for about 12 h. The solution was poured into 25 mL of cold water and extracted with 3 × 10 mL of propionitrile. The combined organic layer was washed with aqueous $NaHCO_3$ (10 mL) and 1 M $NaHSO_4$ (10 mL). The solution was dried (Na_2SO_4), filtered, and evaporated to give a residue, which was dissolved in 1 mL of 1:1 MeOH−MeCN and reprecipitated by the addition of 50 mL of dry ether. The fine precipitate was collected by filtration to give 90 mg (56%) of dark brown solid: ^{1}H NMR (CD_3CN) δ 7.56 (d, 1H, J = 6.6 Hz), 7.45 (d, 1H, J = 6.4 Hz), 7.34 (bs, 5H), 6.95 (bs, 2H), 6.40−6.30 (4H), 6.06 (d, 1H, J = 5.4 Hz), 6.00 (d, 1H, J = 6.0 Hz), 5.85 (bs, 1H), 5.43 (d, 1H, J = 6.6 Hz), 5.36 (s, 5H), 5.22 (d, 1H, J = 6.4 Hz), 4.29 (dd, 1H, J = 13.7 Hz, 7.8 Hz), 3.74 (s, 3H), 3.66 (s, 3H), 2.86 (dd, 1H, J = 13.8 Hz, 4.9 Hz), 2.86 (dd, 1H, J = 13.8 Hz, 8.0 Hz), 1.35 (s, 9H); ^{13}C NMR (CD_3CN) δ 172.00, 170.78, 170.51, 156.62, 151.53, 138.98, 136.40, 133.00, 130.08, 129.67, 128.81, 108.13, 105.94, 102.35, 88.18, 84.12, 81.96, 81.17, 61.42, 58.12, 57.65, 56.35, 53.64, 37.29, 28.77; FABHRMS (glycerol/NBA/CsI/NaI) *m/z* 773.2021 ($M^+ - PF_6$-Cl), $C_{37}H_{41}N_3O_9Ru$ requires 773.1880.

Cyclization of 8. Procedure A. A stock solution of sodium 2,6-di-*tert*-butylphenoxide was prepared by mixing 38 mg of 60% NaH (0.95 mmol) and 196 mg of 2,6-di-*tert*-butylphenol (0.95 mmol) in 10 mL of THF. To a flask containing 674 μL (0.064 mmol, 2.0 equiv) of this stock solution, 2.4 mL of THF and 1.6 mL of DMF at −60 °C, was added a solution of the ruthenium complex **8** (30 mg, 0.032 mmol) in 1 mL of DMF over a period of 30 min (final concentration 5 mM). The solution was allowed to warm slowly to 0 °C over a period of 2 h and stirred at 0 °C for 1 h and then at room temperature for 2 h. The reaction was quenched by the addition of 1 mL of 1 M $NaHSO_4$ at 0 °C, and the THF was evaporated under reduced pressure. The mixture was diluted with 15 mL of H_2O and extracted with 3 × 7 mL of propionitrile. The combined organic layer was evaporated, and the residue was dissolved in 20 mL of CH_3CN, degassed with Ar, and photolyzed (Rayonet, 350 nm) for 22 h. The solution was concentrated and purified by preparative TLC (0.5 mm thickness, SiO_2 gel, 4:96 MeOH−$CHCl_3$) to obtain 1.7 mg of **9** and 7.1 mg of **10** (46% combined yield).

Procedure B. To a flask containing the ruthenium complex **8** (94 mg, 0.099 mmol) and Cs_2CO_3 (161 mg, 0.49 mmol) was added 9.9 mL of DMF (10 mM concentration), and the mixture was stirred at room temperature for 6 h. The reaction was quenched by the addition of aqueous citric acid at 0 °C and diluted with 60 mL of propionitrile. The organic layer was washed with 3 × 30 mL of H_2O and evaporated to give a residue, which was dissolved in 20 mL of CH_3CN, degassed with Ar, and photolyzed (Rayonet, 350 nm) for 24 h. The solution was concentrated and purified by preparative TLC (SiO_2 gel, 0.5 mm thickness, 4:96 MeOH−$CHCl_3$) to obtain 5 mg of **9** and 20.4 mg of **10** (42% combined yield).

Procedure C. A stock solution of sodium 2,6-di-*tert*-butylphenoxide was prepared by mixing 76 mg of 60% NaH (1.94 mmol) and 400 mg of 2,6-di-*tert*-butylphenol (1.94 mmol) in 15 mL of THF. To a flask containing the ruthenium complex **8** (46 mg, 0.048 mmol) in 1 mL of DMF and 3.8 mL of THF at 0 °C was added 763 μL (2.0 equiv) of the above stock solution over a period of 2 h, using a syringe pump (~9 mM final concentration). The solution was stirred at 0 °C for 30

min and at room temperature for 3 h. The reaction was quenched by the addition of 1 mL of 1 M $NaHSO_4$ at 0 °C. The mixture was diluted with 20 mL of H_2O and extracted with 3 × 7 mL of propionitrile. The combined organic layer was evaporated, and the residue was dissolved in 20 mL of CH_3CN, degassed, and photolyzed (Rayonet, 350 nm) for 17 h. The solution was concentrated, and the residue was purified by preparative TLC (SiO_2 gel, 0.5 mm, 4:96 MeOH−$CHCl_3$) to obtain 7.8 mg of **9** (29%).

Methyl (8*R*,11*S*,14*R*)-14-[(*tert*-butoxycarbonyl)amino]-5-hydroxy-4-methoxy-10,13-dioxo-11-phenyl-2-oxa-9,12-diazatricyclo[14.2.2.1^{3,7}]henicosa-1(18),3,5,7(21),16,19-hexaene-8-carboxylate (9): R_f 0.30 (4:96 MeOH−$CHCl_3$); $[\alpha]^{21}_{Hg\text{-}578}$ −42° (*c* 0.3, $CHCl_3$); ^{1}H NMR (CD_3CN−$CDCl_3$) δ 7.37 (dd, 1H, J = 8.3 Hz, 2.4 Hz), 7.32−7.14 (6H), 7.20−7.15 (2H), 7.02 (d, 1H, J = 7.7 Hz), 6.91 (dd, 1H, J = 8.3 Hz, 2.4 Hz), 6.46 (d, 1H, J = 2.2 Hz), 5.71 (d, 1H, J = 2.2 Hz), 5.48 (d, 1H, J = 5.0 Hz), 5.32 (d, 1H, J = 7.7 Hz), 4.85 (d, 1H, J = 6.8 Hz), 4.42−4.37 (m, 1H), 3.98 (s, 3H), 3.54 (s, 3H), 3.39 (dd, 1H, J = 13.8 Hz, 4.8 Hz), 2.87 (dd, 1H, J = 13.8 Hz, 3.9 Hz), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.58, 169.46, 169.16, 155.57, 154.99, 152.74, 149.66, 136.14, 135.69, 134.21, 131.18, 130.34, 129.49, 129.13, 128.89, 127.35, 123.65, 122.66, 107.62, 106.31, 80.28, 61.45, 59.17, 55.80, 53.11, 39.14, 29.69, 28.30; FABHRMS (glycerol/NBA/CsI/NaI) *m*/*z* 738.1444 (MCs^+), $C_{32}H_{35}N_3O_9Cs$ requires 738.1424.

Methyl (8*S*,11*S*,14*R*)-14-[(*tert*-butoxycarbonyl)amino]-5-hydroxy-4-methoxy-10,13-dioxo-11-phenyl-2-oxa-9,12-diazatricyclo[14.2.2.1^{3,7}]henicosa-1(18),3,5,7(21),16,19-hexaene-8-carboxylate (10): R_f 0.35 (4:96 MeOH−$CHCl_3$); $[\alpha]^{21}_{Hg\text{-}578}$ +99° (c 0.4, $CHCl_3$); ^{1}H NMR (CD_3CN−$CDCl_3$) δ 7.47 (d, 1H, J = 8.8 Hz), 7.38 (dd, 1H, J = 8.5 Hz, 2.1 Hz), 7.35−7.25 (6H), 7.17 (dd, 1H, J = 8.5 Hz, 2.1 Hz), 7.08−7.03 (2H), 6.48 (dd, 1H, J = 2.3 Hz, 1.0 Hz), 5.78 (dd, 1H, J = 2.3 Hz, 1.0 Hz), 5.46 (bs, 1H), 5.43 (d, 1H, J = 8.8 Hz), 5.34 (d, 1H, J = 7.2 Hz), 3.98 (s, 3H), 3.77 (s, 3H), 3.36 (dd, 1H, J = 14.0 Hz, 2.8 Hz), 2.90 (dd, 1H, J = 14.0, 2.8 Hz), 1.47 (s, 9H); ^{13}C NMR (CD_3CN−$CDCl_3$) δ 169.90, 169.81, 169.72, 155.94, 155.46, 153.58, 150.81, 138.43, 136.56, 133.49, 131.80, 131.47, 130.95, 128.98, 128.44, 126.81, 123.60, 122.31, 106.94, 106.86, 106.27, 80.58, 61.45, 56.97, 56.11, 54.97, 53.07, 36.84, 28.29; FABHRMS (glycerol/NBA/CsI/NaI) *m*/*z* 628.2277 (MNa^+), $C_{32}H_{35}N_3O_9Na$ requires 628.2271.

(4*R*)-3-{(2*S*)-2-Azido-2-[3,5-bis(benzyloxy)-4-methoxyphenyl]ethanoyl}-4-benzyl-1,3-oxazolidin-2-one (11): R_f 0.23 (15:15:70 EtOAc−CH_2Cl_2−hexanes); $[\alpha]^{20}_D$ +64° (*c* 2.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.47 (d, 4H, J = 7.4 Hz), 7.35 (t, 4H, J = 7.4 Hz), 7.27−7.23 (5H), 6.94−6.91 (2H), 6.86 (s, 2H), 6.10 (s, 1H), 5.17 (ABq, 2H, J = 12.2 Hz), 5.10 (ABq, 2H, J = 12.2 Hz), 4.76−4.68 (m, 1H), 4.20 (t, 1H, J = 8.6 Hz), 4.08 (dd, 1H, J = 9.1, 3.3 Hz), 3.97 (s, 3H), 2.89 (dd, 1H, J = 13.6, 3.3 Hz), 2.40 (dd, 1H, J = 13.6, 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ 168.72, 152.76, 152.44, 140.12, 136.58, 134.28, 129.28, 128.72, 128.42, 127.90, 127.81, 127.16, 108.02, 70.93, 66.28, 62.88, 60.78, 54.59, 36.80; IR ($CHCl_3$) 2110, 1782, 1709, 1593, 1443, 1391, 1371, 1119 cm^{-1}; HRMS (EI) *m*/*z* 578.2192 (M^+), $C_{33}H_{30}N_4O_6$ requires 578.2165.

(2*S*)-2-Azido-2-[3,5-bis(benzyloxy)-4-methoxyphenyl]ethanoic Acid (12). A solution of the azido carboximide **11** (98 mg, 0.17 mmol), 30% H_2O_2 (77 mg, 0.68 mmol, 4.0 equiv), and LiOH·H_2O (15 mg, 0.36 mmol, 2.1 equiv) in 2 mL of THF−H_2O (3:1 v/v) was stirred at 0 °C for 1 h. The reaction was quenched by the addition of a solution of Na_2SO_3 (108 mg, 0.86 mmol, 5.0 equiv) in 1 mL of H_2O. The solution was stirred for 5 min, and to this was added 5 mL of 0.5 M solution of K_2CO_3 and 15 mL of H_2O. It was then washed with ether (3 × 20 mL) and acidified with 10% HCl to ∼pH 2. The aqueous phase was extracted with EtOAc (3 × 10 mL), and the combined organic layer was washed with brine (10 mL) and dried (Na_2SO_4). The solution was filtered and evaporated to obtain 60 mg of resin (85%), $[\alpha]^{24}_D$ +83° (*c* 1.3, $CHCl_3$). The compound showed spectral properties identical to its (*R*)-enantiomer **4**.

Methyl (2*S*)-2-Azido-2-[3,5-bis(benzyloxy)-4-methoxyphenyl]ethanoate (13). This compound was prepared from **12** using the procedure used for the preparation of **5**: yield 87%; $[\alpha]^{24}_D$ +68° (*c* 1.5, $CHCl_3$). The compound showed spectral properties identical to its (*R*)-enantiomer **5**.

Methyl (2*S*)-2-[(*S*)-1-{[(Benzyloxy)carbonyl]amino]}-1-(phenylmethyl)carboxamido]-2-(3,5-dihydroxy-4-methoxyphenyl)ethanoate (14). This compound was prepared from **13** using the procedure used for the preparation of **6**: yield 77% of foam; R_f 0.29 (4:96 MeOH−$CHCl_3$); $[\alpha]^{24}_D$ +63° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$), δ 7.91 (d, 1H, J = 6.8 Hz), 7.42−7.27 (10H), 6.65 (bs, 2H), 6.29 (s, 2H), 5.98 (d, 1H, J = 7.9 Hz), 5.75 (d, 1H, J = 7.9 Hz), 5.38 (d, 1H, J = 6.8 Hz), 5.07 (d, 1H, J = 12.2 Hz), 4.84 (d, 1H, J = 12.2 Hz), 3.83 (s, 3H), 3.59 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.09, 170.44, 156.28, 149.62, 136.80, 135.80, 134.99, 130.94, 128.92, 128.53, 128.39, 128.09, 128.02, 127.19, 106.77, 67.39, 60.55, 58.14, 56.42, 52.69; HRMS (EI) *m*/*z* 494.1680 (M^+), $C_{26}H_{26}N_2O_8$ requires 494.1689.

(η^5-Cyclopentadienyl){methyl (2*S*)-2-{(*S*)-1-[(1*R*)-1-[(*tert*-butoxycarbonyl)amino]-2-((1,2,3,4,5,6,-η)-4-chlorophenyl-)ethylcarboxamido]-1-(phenylmethyl)carboxamido}-2-(3,5-dihydroxy-4-methoxyphenyl)ethanoate}ruthenium Hexafluorophosphate (15). This compound was prepared from **14** using the procedure employed for the preparation of compound **8**: yield 59%; ^{1}H NMR (CD_3CN) δ 7.61 (d, 1H, J = 7.5 Hz), 7.58 (d, 1H, J = 9.0 Hz), 7.37 (bs, 5H), 6.39 (s, 2H), 6.36 (d, 1H, J = 6.0 Hz), 6.28 (d, 1H, J = 5.8 Hz), 6.03 (d, 1H, J = 6.0 Hz), 5.98 (d, 1H, J = 5.8 Hz), 5.86 (d, 1H, J = 7.0 Hz), 5.54 (d, 1H, J = 6.1 Hz), 5.34 (s, 5H), 5.25 (d, 1H, J = 7.0 Hz), 4.34 (bs, 1H), 3.76 (s, 3H), 3.58 (s, 3H), 2.83 (dd, 1H, J = 13.5 Hz, 5.2 Hz), 2.62 (dd, 1H, J = 13.5 Hz, 8.3 Hz), 1.32 (s, 9H); ^{13}C NMR (CD_3CN) δ 171.50, 170.50, 170.04, 156.29, 151.27, 138.63, 136.11, 132.98, 129.73, 129.34, 128.49, 107.86, 105.62, 101.94, 87.83, 83.78, 81.60, 80.81, 61.14, 57.48, 57.36, 56.02, 53.28, 37.07, 28.43; FABHRMS (NBA/glycerol) *m*/*z* 808.1564 ($M^+ - PF_6$) $C_{37}H_{41}N_3O_9ClRu$ requires 808.1568.

Cyclization of 15. A stock solution of sodium 2,6-di-*tert*-butylphenoxide was prepared by mixing 34 mg of 60% NaH (0. 85 mmol) and 176 mg of 2,6-di-*tert*-butylphenol (0.85 mmol) in 10 mL of THF. To a flask containing 1.04 mL of the above stock solution (0.9 mmol, 2.0 equiv), 1.2 mL of THF, and 0.7 mL of DMF at −60 °C was added a solution of the ruthenium complex **15** (42 mg, 0.044 mmol) in 1.5 mL of DMF over a period of few minutes (final concentration 10 mM). The solution was allowed to warm to 0 °C over a period of 2 h and stirred at 0 °C for 1 h and at room temperature for 2 h. To the solution was added 1 mL of 1 N $NaHSO_4$, the solution was diluted with 20 mL of H_2O, and the aqueous solution was extracted with 3 × 7 mL of propionitrile. The combined organic layer was evaporated, and the residue was dissolved in 20 mL of CH_3CN, degassed with Ar, and photolyzed (Rayonet, 350 nm) for 24 h. The solvent was evaporated, and the residue was subjected to preparative TLC (SiO_2 gel, 0.5 mm thickness, 4:96 MeOH−$CHCl_3$) to obtain 10 mg (38%) of **10**.

Equilibration Study on 9. A stock solution of DBU was prepared by dissolving 20 mg of DBU in 500 μL of CD_3CN−$CDCl_3$ (1:1 v/v) mixture. To an NMR tube containing 1.5 mg (2.5 μmol) of **9** in ∼450 μL of CD_3CN−$CDCl_3$ (shimmed) was added 50 μL of the above stock solution (13 μmol, 5.2 equiv). The sample was shimmed, and the ^{1}H NMR was taken immediately. The NMR showed complete downfield shift of CO_2Me peak (from 3.54 to 3.71 ppm). The solution was immediately diluted with 5 mL of EtOAc, washed with 1 N HCl (2 × 5 mL) and brine (5 mL), and dried (Na_2SO_4). The solution was filtered and evaporated, and the crude product was analyzed by ^{1}H NMR, which showed only the presence of **10**.

2-(Trimethylsilyl)ethyl (2*R*)-2-Azido-2-[3,5-bis(benzyloxy)-4-methoxyphenyl]ethanoate (16). To a mixture of the azido acid **4** (208 mg, 0.50 mmol), (trimethylsilyl)ethanol (118 mg, 1.0 mmol, 2.0 equiv), and HOAt (68 mg, 0.50 mmol, 1.0 equiv) in 5 mL of CH_2Cl_2 at 0 °C was added DCC (154 mg, 0.75 mmol, 1.5 equiv), and the cloudy solution was stirred for 3 h at 0 °C and 12 h at room temperature. To the mixture was added 2 mL of 1 N HCl at 0 °C and then 50 mL of EtOAc, and the solution was filtered through a Celite plug to remove

insolubles. The organic layer was washed with 1 N HCl (2 × 25 mL) and brine (25 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to a give a yellow residue that was chromatographed (SiO_2 gel, 3:7 hexanes−CH_2Cl_2) to provide 248 mg of colorless resin (96%): R_f 0.38 (CH_2Cl_2); $[\alpha]^{20}_D$ −42° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.44−7.32 (10H), 6.64 (s, 2H), 5.11 (s, 4H), 4.77 (s, 1H), 4.21−4.07 (2H), 3.88 (s, 3H), 0.95−0.89 (2H), −0.02 (s, 9H, TMS); ^{13}C NMR ($CDCl_3$) δ 168.83, 152.70, 139.98, 136.58, 128.98, 128.36, 127.76, 127.14, 107.19, 70.98, 65.12, 64.39, 60.66, 17.03, −1.73; IR ($CHCl_3$) 2110, 1739, 1596, 1505, 1439, 1256, 1115 cm^{-1}; HRMS (EI) *m*/*z* 519.2195 (M^+), $C_{28}H_{33}N_3O_5Si$ requires 519.2189.

2-(Trimethylsilyl)ethyl (2*R*)-2-[(*S*)-1-{[(Benzyloxy)carbonyl]amino}-1-(phenylmethyl)carboxamido]-2-(3,5-dihydroxy-4-methoxyphenyl)ethanoate (17). A mixture of the azide **16** (150 mg, 0.29 mmol), 6 N HCl (145 μL, 0.87 mmol, 3.0 equiv), and 35 mg of 10% Pd−C in 7 mL of 1:1 THF−MeOH was stirred under 1 atm of H_2 for 12 h. The slurry was filtered through a Celite plug and evaporated, and the residue was chased with dry ether and dried under vacuum to obtain the amine hydrochloride. To a solution of the amine hydrochloride, (*R*)-ZPhg (83 mg, 0.29 mmol, 1.0 equiv), HOAt (59 mg, 0.43 mmol, 1.5 equiv), and TMP (38 μL, 0.29 mmol, 1.0 equiv) in 3 mL of 1:2 DMF−CH_2Cl_2 at 0 °C was added EDCI (67 mg, 0.35 mmol, 1.2 equiv), and the solution was stirred for 3 h at 0 °C and 12 h at room temperature. The mixture was diluted with 20 mL of EtOAc, and the organic layer was washed successively with 1 N HCl (2 × 20 mL), aqueous $NaHCO_3$ (2 × 20 mL), and brine (20 mL). The organic layer was dried (Na_2SO_4) and filtered, and the solvent was evaporated to give a residue that was chromatographed (SiO_2 gel, 4:96 MeOH−$CHCl_3$) to obtain 150 mg of foam (89%): R_f 0.25 (4:96 MeOH−$CHCl_3$); $[\alpha]^{20}_D$ −5.8° (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.62 (bs, 1H), 7.34−7.21 (10H), 6.48 (s, 2H), 6.06 (d, 1H, *J* = 7.1 Hz), 5.61 (d, 1H, *J* = 5.6 Hz), 5.14 (d, 1H, *J* = 3.5 Hz), 4.86 (d, 1H, *J* = 12.0 Hz), 4.68 (d, 1H, *J* = 12.0 Hz), 4.33−4.24 (m, 1H), 4.17−4.08 (m, 1H), 3.81 (s, 3H), 0.97 (t, 2H), −0.02 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.31, 170.70, 156.07, 149.72, 136.91, 135.75, 134.91, 130.30, 128.95, 128.83, 128.32, 127.96, 127.73, 127.05, 107.09, 67.05, 64.76, 60.52, 57.83, 57.47, 16.89, −1.69; FABHRMS (glycerol/NaI/CsI) *m*/*z* 581.2298 (MH^+), $C_{30}H_{37}N_2O_8Si$ requires 581.2319.

(η^5-Cyclopentadienyl){2-(trimethylsilyl)ethyl (2*R*)-2-{(*S*)-1-[(1*R*)-1-[(*tert*-butoxycarbonyl)amino]-2-((1,2,3,4,5,6-η)-4-chlorophenyl)ethylcarboxamido]-1-(phenylmethyl)carboxamido}-2-(3,5-dihydroxy-4-methoxyphenyl)-ethanoate}ruthenium Hexafluorophosphate (18). To a solution of the dipeptide **17** (530 mg, 0.91 mmol) in 15 mL of MeOH was added 115 mg of 10% Pd−C and 305 μL of 6 N HCl, and the suspension was stirred under 1 atm of H_2 (balloon) for about 16 h. The suspension was filtered through Celite and evaporated, and the residue was chased with dry ether and dried under vacuum to obtain the amine hydrochloride salt. This salt was taken along with the ruthenium complex **7** (247 mg, 0.40 mmol, 1.0 equiv) and HATU (200 mg, 0.53 mmol, 1.3 equiv) in 4 mL of 1:1 DMF−CH_2Cl_2 and cooled to 0 °C. To this was added DIPEA (212 μL, 1.22 mmol, 3.0 equiv), and the solution was stirred at 0 °C for 1 h and at room temperature for 3 h. The mixture was poured into 50 mL of ice-cold water and extracted with 4 × 15 mL of propionitrile. The combined organic layer was washed with 1 N $NaHSO_4$ (2 × 15 mL) and aqueous $NaHCO_3$ (2 × 15 mL) and dried over Na_2SO_4. The solution was evaporated, the residue was dissolved in 2 mL of CH_3CN, and the product was precipitated by the addition of 40 mL of dry ether. The precipitate was filtered, washed with ether, and evaporated to give 337 mg of dark brown solid (80%). Due to the difficulty in purifying further, it was used for the next step as such.

Cyclization of 18. A stock solution of sodium 2,6-di-*tert*-butylphenoxide was prepared by mixing 40 mg of 60% NaH (1.0 mmol) and 206 mg of 2,6-di-*tert*-butylphenol (1.0 mmol) in 10 mL of THF. To a flask containing 770 μL (0.077 mmol, 2.0 equiv) of the stock solution, 1.7 mL of THF, and 1 mL of DMF at −40 °C was added a solution of the ruthenium complex **18** (40 mg, 0.039 mmol) in 1.4 mL of DMF over a period of 1 h (8 mM final concentration). The solution was allowed to warm slowly to 0 °C over a period of 2 h and stirred at 0 °C for 3 h. It was quenched with 1 mL of 1 N $NaHSO_4$ at 0 °C, the volatiles were removed under reduced pressure, and the residue diluted with 15 mL of H_2O. The aqueous phase was extracted with 3 × 7 mL of propionitrile, and the combined organic layer was evaporated. The residue was dissolved in 20 mL of CH_3CN, degassed with Ar, and photolyzed (Rayonet, 350 nm) for 24 h. The solution was concentrated, and the residue was subjected to preparative TLC (SiO_2 gel, 0.5 mm thickness, 2:98 MeOH−$CHCl_3$) to obtain 5.2 mg of **19** and 2.6 mg of **20** (29% combined yield).

2-(Trimethylsilyl)ethyl (8*R*,11*S*,14*R*)-14-[(*tert*-butoxycarbonyl)amino]-5-hydroxy-4-methoxy-10,13-dioxo-11-phenyl-2-oxa-9,12-diazatricyclo[14.2.2.1^{3,7}]henicosa-1(18),3,5,7(21),16,19-hexaene-8-carboxylate (19): R_f 0.28 (2:98 MeOH−$CHCl_3$); $[\alpha]^{21}_{Hg\text{-}578}$ = +116° (*c* 0.2, MeOH); ^{1}H NMR (CD_3CN−$CDCl_3$) δ 7.38 (dd, 1H, *J* = 8.5 Hz, 2.3 Hz), 7.30 (bs, 5H), 7.28 (d, 1H, *J* = 9.0 Hz), 7.20−7.15 (2H), 7.01 (d, 1H, *J* = 7.6 Hz), 6.93 (dd, 1H, *J* = 8.5 Hz, 2.3 Hz), 6.78 (s, 1H), 6.45 (d, 1H, *J* = 2.1 Hz), 5.72 (d, 1H, *J* = 2.1 Hz), 5.43 (bs, 1H), 5.29 (d, 1H, *J* = 7.6 Hz), 4.78 (d, 1H, *J* = 6.7 Hz), 4.40−4.34 (m, 1H), 4.05−3.96 (5H), 3.39 (dd, 1H, *J* = 13.8 Hz, 4.8 Hz), 2.88 (dd, 1H, *J* = 13.8 Hz, 4.0 Hz), 1.45 (s, 9H), 0.63 (t, 2H), −0.07 (s, 9H); ^{13}C NMR (CD_3CN−$CDCl_3$) δ 169.96, 169.71, 169.30, 155.65, 155.52, 153.51, 150.25, 138.12, 136.33, 133.36, 132.01, 131.78, 130.78, 129.02, 128.55, 127.18, 123.41, 122.45, 109.61, 106.26, 80.40, 64.10, 61.58, 56.93, 56.59, 37.13, 29.95, 28.30, 17.25, −1.66; FABHRMS (NBA/CsI/NaI) *m*/*z* 692.3008 (MH^+), $C_{36}H_{46}N_3O_9Si$ requires 692.3003.

2-(Trimethylsilyl)ethyl (8*S*,11*S*,14*R*)-14-[(*tert*-butoxycarbonyl)amino]-5-hydroxy-4-methoxy-10,13-dioxo-11-phenyl-2-oxa-9,12-diazatricyclo[14.2.2.1^{3,7}]henicosa-1(18),3,5,7(21),16,19-hexaene-8-carboxylate (20): R_f 0.22 (2:98 MeOH−$CHCl_3$); $[\alpha]^{21}_{Hg\text{-}578}$ = +65° (*c* 0.4, $CHCl_3$); ^{1}H NMR (CD_3CN−$CDCl_3$) δ 7.43 (d, 1H, *J* = 8.7 Hz), 7.36 (dd, 1H, *J* = 8.4 Hz, 2.1 Hz), 7.32−7.22 (6H), 7.14 (dd, 1H, *J* = 8.4 Hz, 2.1 Hz), 7.05−7.01 (2H), 6.88 (s, 1H), 6.49 (dd, 1H, *J* = 2.2 Hz, 1.0 Hz), 5.75 (dd, 1H, *J* = 2.2 Hz, 1.0 Hz), 5.46 (bs, 1H), 5.34 (d, 1H, *J* = 8.7 Hz), 5.33 (d, 1H, *J* = 7.3 Hz), 4.32−4.20 (3H), 3.95 (s, 3H), 3.33 (dd, 1H, *J* = 13.9 Hz, 5.2 Hz), 2.87 (dd, 1H, *J* = 13.9 Hz, 2.8 Hz), 1.44 (s, 9H), 1.03−0.97 (2H), −0.02 (s, 9H); ^{13}C NMR (CD_3CN−$CDCl_3$) δ 169.81, 169.77, 169.50, 155.99, 155.46, 153.59, 150.81, 138.49, 136.52, 133.52, 131.82, 131.62, 130.98, 128.99, 128.44, 126.80, 123.64, 122.34, 106.95, 106.29, 80.59, 64.88, 61.40, 56.98, 56.11, 55.10, 36.84, 28.30, 17.55, −1.60; FABHRMS (NBA/CsI/NaI) *m*/*z* 824.1979 (MCs^+), $C_{36}H_{45}N_3O_9SiCs$ requires 824.1979.

2-(Trimethylsilyl)ethyl (2*R*)-2-[(*tert*-Butoxycarbonyl)-amino]-2-phenylethanoate (22). To a flask containing **21** (500 mg, 1.75 mmol), (trimethylsilyl)ethanol (414 mg, 3.50 mmol, 1.2 equiv), and DMAP (214 mg, 1.75 mmol, 1.0 equiv) in 15 mL of CH_2Cl_2 at 0 °C was added DCC (542 mg, 2.63 mmol, 1.5 equiv), and the mixture was stirred at 0 °C for 4 h. The solution was quenched with aqueous HCl at 0 °C, diluted with 100 mL of EtOAc, and filtered through a Celite pad. The organic layer was washed with 2 × 50 mL of brine, dried over Na_2SO_4, and filtered. The solution was concentrated and chromatographed (SiO_2 gel, 10:90 EtOAc/hexanes) to give 575 mg of resin (85%): R_f 0.19 (10:90 EtOAc/hexanes); $[\alpha]^{20}_D$ −68° (*c* 2.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.36−7.28 (10H), 5.85 (d, 1H, *J* = 6.7 Hz), 5.34 (d, 1H, *J* = 6.7 Hz), 5.13 (ABq, 1H, *J* = 12.1 Hz), 5.07 (ABq, 1H, *J* = 12.1 Hz), 4.32−4.11 (2H), 0.94 (t, 2H), −0.02 (s, 9H); ^{13}C NMR (acetone-d_6) δ 171.42, 156.43, 137.83, 129.41, 129.07, 128.97, 128.77, 128.56, 128.35, 127.20, 66.85, 64.13, 59.20, 17.58, −1.54; IR ($CHCl_3$) 1729, 1724,1501, 1252, 1176, 1054 cm^{-1}; FABHRMS (NBA/NaI/CsI) *m*/*z* 386.1740 (M^+), $C_{21}H_{28}NO_4Si$ requires 386.1788.

[(*R*)-1-Phenyl-1-[2-[[(trimethylsilyl)ethyl]oxy]carbonyl]methyl]ammonium Chloride (23). To a solution of **22** (518 mg, 0.74 mmol) and 6 N HCl (372 μL, 2.23 mmol, 3.0 equiv) in 15 mL of 1:1 MeOH−THF was added 55 mg of 10% Pd−C, and the suspension was stirred under 1 atm of H_2 (balloon) for 18 h. The suspension was filtered through a

Celite pad and evaporated. The residue was chased with dry ether and dried under vacuum to obtain 370 mg of solid (96%): $[\alpha]^{20}_D$ −68° (*c* 0.9, MeOH); ^{1}H NMR (CD_3OD) δ 7.48 (bs, 5H), 5.12 (s, 1H), 4.35−4.28 (2H), 0.98−0.91 (2H); ^{13}C NMR (CD_3OD) δ 169.58, 133.32, 133.11, 130.52, 129.27, 66.22, 57.65, 17.87, −1.57; FABHRMS (glycerol) *m/z* 252.1421 ($M - Cl^+$) $C_{13}H_{22}NO_2Si$ requires 252.1420.

2-(Trimethylsilyl)ethyl (2*R*)-2-{(*R*)-1-Azido-1-[[3,5-bis(benzyloxy)-4-methoxyphenyl]methyl]carboxamido}-2-phenylethanoate (24). To a solution of the azido acid **4** (624 mg, 1.49 mmol), amine hydrochloride **23** (514 mg, 1.79 mmol, 1.2 equiv), HOAt (203 mg, 1.49 mmol, 1.0 equiv), and TMP (236 μL, 1.79 mmol, 1.0 equiv) in 15 mL of CH_2Cl_2 at 0 °C was added DCC (461 mg, 2.23 mmol, 1.5 equiv), and the cloudy mixture was stirred at 0 °C for 3 h and at room temperature for 12 h. The reaction was quenched with aqueous citric acid and diluted with 150 mL of EtOAc. The suspension was filtered through a Celite pad to remove the insolubles and then washed successively with 1 N HCl (2 × 50 mL), aqueous $NaHCO_3$ (2 × 50 mL), and brine (50 mL). The solution was dried (Na_2SO_4), filtered, and evaporated to give a crude product that was chromatographed (SiO_2 gel, 1:99 acetone−$CHCl_3$) to provide 874 mg (90%) of off-white solid: mp 106−109 °C; R_f 0.33 (1:99 acetone−$CHCl_3$); $[\alpha]^{21}_D = -120°$ (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.50 (d, 1H, J = 7.3 Hz), 7.41−7.25 (15H), 6.55 (s, 2H), 5.53 (d, 1H, J = 7.3 Hz), 5.01 (ABq, 1H, J = 11.8 Hz), 4.96 (ABq, 1H, J = 11.8 Hz), 4.95 (s, 1H), 4.35−4.14 (2H), 3.84 (s, 3H), 0.99−0.93 (2H), −0.01 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 170.30, 167.10, 152.84, 139.93, 136.60, 136.34, 129.86, 128.93, 128.57, 128.43, 127.87, 127.34, 127.18, 107.15, 71.02, 66.86, 64.59, 60.73, 56.42, 17.06, −1.67; IR ($CHCl_3$) 2116, 1736, 1685, 1596, 1505, 1499 cm^{-1}; FABHRMS (NBA/CsI/NaI) *m/z* 652.2744 (M^+), $C_{36}H_{40}N_4O_6Si$ requires 652.2717.

2-(Trimethylsilyl)ethyl (2*R*)-2-{(*R*)-1-Amino-1-[3,5-bis(benzyloxy)-4-methoxyphenyl]methyl]carboxamido}-2-phenylethanoate (25). A mixture of the azide **24** (509 mg, 0.78 mmol) and $SnCl_2$ (296 mg, 1.56 mmol, 2.0 equiv) in 10 mL of THF−MeOH (2:3 v/v) was stirred at 0 °C for 15 min and at room temperature for 5 h. The mixture was poured into 100 mL of aqueous $NaHCO_3$ and extracted with 3 × 50 mL of $CHCl_3$. The combined organic layer was washed with 50 mL of brine, dried over Na_2SO_4, filtered, and evaporated to give 480 mg (98%) of foamy resin that was homogeneous by NMR: $[\alpha]^{24}_D = -60°$ (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.17 (d, 1H, J = 7.7 Hz), 7.42−7.28 (15H), 6.61 (s, 2H), 5.55 (d, 1H, J = 7.7 Hz), 5.03 (ABq, 2H, J = 11.9 Hz), 4.97 (ABq, 2H, J = 11.9 Hz), 4.45 (s, 1H), 4.33−4.13 (2H), 3.83 (s, 3H), 0.96 (t, 2H, J = 8.6 Hz), −0.02 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.18, 170.51, 152.41, 138.62, 136.71, 136.54, 135.93, 128.61, 128.41, 128.16, 127.54, 127.10, 126.97, 106.05, 70.61, 63.95, 60.44, 59.26, 55.98, 16.81, −1.86; FABHRMS (glycerol/NBA/NaI/CsI) *m/z* 759.1861 (MCs^+), $C_{36}H_{43}N_2O_6SiCs$ requires 759.1866.

(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-2-phenylethanoic Acid. A mixture of (*S*)-phenylglycine (804 mg, 5.3 mmol), $(Boc)_2O$ (1.16 g, 5.3 mmol, 1.0 equiv), and $NaHCO_3$ (671 mg, 8.0 mmol, 1.5 equiv) was stirred with 30 mL of THF−H_2O mixture (1:1 v/v) at room temperature for 21 h. The THF was evaporated, and the mixture was diluted with 100 mL of H_2O. The aqueous solution was washed with 50 mL of ether, acidified with 10% HCl, and extracted with 3 × 40 mL of EtOAc. The combined organic layer was washed with 50 mL of brine, dried over Na_2SO_4, filtered, and evaporated to give 1.26 g (94%) of white foam: $[\alpha]^{24}_D = +135°$ (*c* 0.8, $CHCl_3$); ^{1}H NMR (CD_3NO_2) δ 7.48−7.36 (5H), 6.76 (bs, 1H), 6.03 (d, 1H, J = 5.7 Hz), 5.31 (d, 1H, J = 5.7 Hz), 1.41 (s, 9H); ^{13}C NMR (CD_3NO_2) δ 173.94, 156.74, 138.46, 130.28, 129.92, 128.74, 81.38, 58.88, 28.60; FABHRMS (glycerol/CsI/NaI) *m/z* 252.1235 (MH^+), $C_{13}H_{17}NO_4$ requires 252.1236.

2-(Trimethylsilyl)ethyl (2*R*)-2-{(*R*)-1-[(*S*)-1-[(*tert*-Butoxycarbonyl)amino]-1-(phenylmethyl)carboxamido]-1-[[3,5-bis(benzyloxy)-4-methoxyphenyl]methyl]carboxamido}-2-phenylethanoate (26). To a solution of the amine **25** (480 mg, 0.77 mmol), (*S*)-*N*-Boc-Phg (231 mg, 0.92 mmol, 1.2 equiv), and HOAt (104 mg, 0.77 mmol, 1.0 equiv) in 7.5 mL of DMF−CH_2Cl_2 mixture (1:2 v/v) at 0 °C was added EDCI (220 mg, 1.15 mmol, 1.5 equiv), and the mixture was stirred at 0 °C for 2 h and at room temperature for 13 h. The reaction was quenched with aqueous citric acid and diluted with 100 mL of EtOAc. The organic phase was washed successively with 1 N HCl (2 × 50 mL), aqueous $NaHCO_3$ (2 × 50 mL), and brine (50 mL) and dried over Na_2SO_4. It was filtered and evaporated, and the residue was chromatographed (SiO_2 gel, 1:99 MeOH−$CHCl_3$) to obtain 600 mg of white solid (91%): mp 158−161 °C; R_f 0.20 (1:99 MeOH−$CHCl_3$); $[\alpha]^{24}_D = -18°$ (*c* 2.5, $CHCl_3$); FABHRMS (glycerol/NBA/CsI/NaI) *m/z* 992.2918 (MCs^+), $C_{49}H_{57}N_3O_9SiCs$ requires 992.2919; ^{1}H NMR ($CDCl_3$, 2 mg/mL) δ 7.39−7.19 (20H), 6.95 (bs, 2H), 6.47 (s, 2H), 5.79 (bs, 1H), 5.41 (d, 1H, J = 6.8 Hz), 5.30 (d, 1H, J = 6.4 Hz), 5.17 (s, 1H), 4.81 (s, 4H), 4.23−4.03 (2H), 3.77 (s, 3H), 1.32 (s, 9H), 0.70 (dd, 2H, J = 9.4 Hz, 7.7 Hz), −0.09 (s, 9H); ^{1}H NMR ($CDCl_3$, 40 mg/mL) δ 8.14 (bs, 1H), 7.39−7.27 (19H), 7.12 (d, 2H, J = 3.7 Hz), 6.54 (s, 3H), 5.92 (d, 1H, J = 5.6 Hz), 5.37 (d, 2H, J = 6.7 Hz), 4.60 (d, 2H, J = 11.3 Hz), 4.44 (d, 2H, J = 11.3 Hz), 4.30−4.21 (m, 1H), 4.14−4.05 (m, 1H), 3.67 (s, 3H), 1.25 (s, 9H), 0.90 (t, 2H, J = 8.7 Hz), −0.06 (s, 9H); ^{1}H NMR (DMSO-d_6) δ 9.34 (d, 1H, J = 6.7 Hz), 8.86 (d, 1H, J = 8.6 Hz), 7.52 (d, 1H, J = 7.9 Hz), 7.43−7.16 (20H), 6.77 (s, 2H), 5.66 (d, 1H, J = 7.9 Hz), 5.46 (d, 1H, J = 7.9 Hz), 5.42 (d, 1H, J = 6.7 Hz), 4.92 (ABq, 2H, J = 11.5 Hz), 4.85 (ABq, 2H, J = 11.5 Hz), 4.15−4.00 (2H), 3.63 (s, 3H), 1.36 (s, 9H), 0.78 (t, 2H), −0.12 (s, 9H); ^{13}C NMR ($CDCl_3$, ∼40 mg/mL), δ 170.64, 170.08, 169.04, 154.79, 152.38, 150.40, 139.58, 138.18, 136.74, 132.94, 128.84, 128.61, 128.13, 127.99, 127.94, 127.67, 127.56, 127.19, 126.83, 104.51, 79.01, 69.98, 64.58, 60.45, 58.14, 57.22, 55.97, 27.95, 16.98, −1.81.

(2*R*)-2-{(*R*)-1-[(*S*)-1-[(*tert*-Butoxycarbonyl)amino]-1-(phenylmethyl)carboxamido]-1-[[3,5-bis(benzyloxy)-4-methoxyphenyl]methyl]carboxamido}-2-phenylethanoate (27). To a solution of the tripeptide **26** (595 mg, 0.69 mmol) in 7 mL of THF was added 1.39 mL of a 1 M solution of TBAF in THF (1.39 mmol, 2.0 equiv), and the mixture was stirred at room temperature for 8 h. The solution was poured into 100 mL of 1 N HCl, and the aqueous slurry was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (50 mL) and dried over Na_2SO_4. The solution was filtered and evaporated to provide a foam that was purified by chromatography (SiO_2 gel, 3:97 MeOH−EtOAc) to provide 488 mg (93%) of off-white solid: mp 156−159 °C; R_f 0.43 (3:97 MeOH−EtOAc); $[\alpha]^{24}_D$ −34° (*c* 0.6, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 9.19 (d, 1H, J = 5.4 Hz), 8.80 (d, 1H, J = 8.0 Hz), 7.54−7.25 (20H), 7.17 (d, 1H, J = 7.1 Hz), 6.76 (s, 3H), 5.67 (bs, 1H), 5.46 (d, 1H, J = 8.0 Hz), 5.31 (d, 1H, J = 7.1 Hz), 4.90 (ABq, 2H, J = 11.4 Hz), 4.82 (ABq, 2H, J = 11.4 Hz), 3.62 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 171.70, 169.70, 168.74, 154.75, 151.82, 139.00, 137.28, 136.78, 134.01, 130.26, 128.76, 128.64, 128.43, 128.14, 127.93, 127.84, 127.66, 127.46, 127.36, 105.33, 78.38, 70.08, 59.96, 57.21, 56.92, 56.88, 28.10; FABHRMS (glycerol/NBA/NaI/CsI) *m/z* 892.2225 (MCs^+), $C_{44}H_{45}N_3O_9Cs$ requires 892.2207.

(2*R*)-2-{(*R*)-1-[(*S*)-1-[(*tert*-Butoxycarbonyl)amino]-1-(phenylmethyl)carboxamido]-1-[[3,5-dihydroxy-4-methoxyphenyl]methyl]carboxamido}-2-phenylethanoate (28). To a solution of **27** (325 mg, 0.43 mmol) in 10 mL of 1:1 THF−MeOH mixture was added 50 mg of 10% Pd−C and the resulting mixture stirred under 1 atm of H_2 (balloon) for 12 h. The suspension was filtered through Celite and evaporated to obtain 230 mg of off-white solid (93%): $[\alpha]^{21}_{Hg\text{-}578}$ −59° (*c* 0.6, MeOH); ^{1}H NMR (acetone-d_6) δ 7.50−7.25 (13H), 6.47 (s, 2H), 5.54 (s, 2H), 5.41 (s, 1H), 3.74 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (acetone-d_6) δ 171.51, 170.29, 170.04, 151.08, 139.90, 138.05, 135.80, 134.44, 129.43, 129.18, 128.92, 128.47, 128.38, 128.26, 107.64, 79.53, 60.50, 59.35, 58.81, 57.32, 57.13; FABHRMS (glycerol/NBA/CsI/NaI) *m/z* 712.1249 (MCs^+), $C_{30}H_{33}N_3O_9Cs$ requires 712.1268.

η^6-{1-(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-oxo-3-methoxy]propyl-4-chloro}benzene-η^5-cyclopentadienylruthenium Hexafluorophosphate (29). A mixture of methyl ester or (*S*)-*N*-Boc-4-chlorophenylalanine (300 mg, 0.96 mmol) and $[CpRu(CH_3CN)_3]PF_6$ (600 mg, 1.39 mmol) was refluxed in dichloroethane for 4 h. The solution was cooled, filtered

through a Celite pad, and evaporated. The residue was dissolved in CH_3CN and filtered through neutral alumina, and the solution was evaporated to obtain 590 mg of dark brown foam (98%). The compound showed spectral properties identical to the (*R*)-enantiomer reported earlier by us.

(η^5-Cyclopentadien-1-yl){methyl (2*S*)-2-{(*R*)-1-[(*R*)-1-[(*S*)-1-[(*tert*-Butoxycarbonyl)amino]-1-(phenylmethyl)-carboxamido]-1-[(3,5-dihydroxy-4-methoxyphenyl)methyl]carboxamido]-1-(phenylmethyl)carboxamido}-3-((1,2,3,4,5,6,-η)-4-chlorophenyl)propanoate}ruthenium Hexafluorophosphate (30). To a flask containing the complex **29** (220 mg, 0.35 mmol) was added 3 mL of CH_2Cl_2 followed by 1 mL of trifluoroacetic acid, and the solution was stirred for 2 h at 0 °C. The solvent was evaporated, and the residue was dissolved in ~1 mL of MeOH. To this was added 120 μL of 6 N HCl (0.72 mmol, 2.0 equiv), and the solvent was evaporated. The residue was chased with dry ether and dried under vacuum to obtain the crude amine hydrochloride. To this were added tripeptide **28** (0.32 mmol), HATU (159 mg, 0.42 mmol, 1.5 equiv), and 3.5 mL DMF. The solution was cooled to 0 °C, and 128 μL of TMP was added (0.97 mmol, 3.0 equiv). The mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. It was quenched with aqueous citric acid and diluted with 50 mL of propionitrile. The organic layer was washed with 3 × 30 mL 1 N HCl and dried over Na_2SO_4. The solution was filtered and concentrated. It was treated with dry ether, and the resulting precipitate was collected by filtration to provide 209 mg of dark brown solid. Due to difficulty in purifying this product, it was used as such for the next step.

Cyclization of 30. To a flask containing the ruthenium complex **30** (40 mg, 37 μmol) and Cs_2CO_3 (60 mg, 0.18 mmol, 5 equiv) was added 4 mL of dry DMF, and the mixture was stirred at 22 °C for 6 h. The solution was cooled to 0 °C, quenched with aqueous citric acid, and diluted with 30 mL of propionitrile. The organic layer was washed with 2 × 15 mL of H_2O and then evaporated. The residue was dissolved in 20 mL of CH_3CN, degassed with Ar, and photolyzed for 22 h. The solution was concentrated, and the residue was purified by preparative TLC (SiO_2 gel, 0.5 mm thickness, 5:95 MeOH−$CHCl_3$) to provide 15 mg of **31** (less mobile) and 5 mg of **32** (more mobile) (74% combined yield).

Methyl (8*R*,11*R*,14*S*)-8-[(*S*)-1-amino-1-(phenylmethyl)carboxamido]-5-hydroxy-4-methoxy-9,12-dioxo-11-phenyl-2-oxa-10,13-diazatricyclo[14.2.2.1^{3,7}]henicosa-1(18),3(21),4,6,16,19-hexaene-14-carboxylate (31): R_f 0.24 (5:95 MeOH−$CHCl_3$); ^{1}H NMR (CD_3CN−$CDCl_3$) δ 7.51−7.15 (12H), 7.13 (d, 1H, J = 8.3 Hz), 7.12 (d, 1H, J = 8.3 Hz), 7.07 (d, 1H, J = 5.7 Hz), 6.89 (d, 1H, J = 8.3 Hz), 6.88 (d, 1H, J = 8.3 Hz), 6.37 (d, 1H, J = 5.1 Hz), 5.82 (bs, 1H), 5.71 (d, 1H, J = 2.1 Hz), 5.28 (d, 1H, J = 8.2 Hz), 5.09 (1H, J = 6.8 Hz), 4.99 (ddd, 1H, J = 12.9 Hz, 10.3 Hz, 4.5 Hz), 4.89 (d, 1H, J = 5.7 Hz), 3.96 (s, 3H), 3.73 (s, 3H), 3.45 (dd, 1H, J = 12.9 Hz, 4.5 Hz), 2.70 (t, 1H, J = 12.9 Hz), 1.34 (s, 9H); ^{13}C NMR (CD_3CN−$CDCl_3$) δ 182.74, 171.72, 171.10, 169.02, 154.84, 154.12, 151.01, 150.61, 138.33, 134.34, 133.06, 132.10, 130.92, 129.32, 129.05, 128.77, 128.32, 127.72, 126.80, 122.73, 122.13, 118.55, 117.14, 111.28, 106.74, 61.34, 59.61, 59.18, 55.64, 53.13, 52.79, 38.15, 29.41, 28.31; FABHRMS (glycerol/NBA/CsI/NaI) *m*/*z* 871.1936 (MCs^+), $C_{40}H_{42}N_4O_{10}Cs$ requires 871.1952.

Methyl (8*R*,11*S*,14*S*)-8-[(*S*)-1-amino-1-(phenylmethyl)carboxamido]-5-hydroxy-4-methoxy-9,12-dioxo-11-phenyl-2-oxa-10,13-diazatricyclo[14.2.2.1^{3,7}]henicosa-1(18),3(21),4,6,16,19-hexaene-14-carboxylate (32): $[\alpha]^{21}_{Hg\text{-}578}$ −46° (*c* 0.3, $CHCl_3$); ^{1}H NMR (CD_3CN) δ 7.70 (bs, 1H), 7.47 (d, 1H, J = 8.3 Hz), 7.46 (d, 1H, J = 8.3 Hz), 7.34−7.26 (10H), 7.07 (d, 1H, J = 8.2 Hz), 6.99 Hz (d, 1H, J = 8.3 Hz), 6.98 (d, 1H, J = 8.3 Hz), 6.66 (d, 1H, J = 7.1 Hz), 6.23 (bs, 1H), 5.83 (s, 2H), 5.49 (d, 1H, J = 8.2 Hz), 5.33 (d, 2H, J = 5.4 Hz), 4.20−4.14 (m, 1H), 3.91 (s, 3H), 3.58 (s, 3H), 3.47 (dd, 1H, J = 14.0 Hz, 4.5 Hz), 2.89 (dd, 1H, J = 14.0 Hz, 7.5 Hz), 1.34 (s, 9H); FABHRMS (glycerol/NBA/CsI/NaI) *m*/*z* 871.1952 (MCs^+), $C_{40}H_{42}N_4O_{10}Cs$ requires (871.1892).

(η^5-Cyclopentadien-1-yl){methyl (8*R*,11*R*,14*S*)-8-{(*S*)-1-[(1*R*)-1-[(*tert*-butoxycarbonyl)amino]-2-(4-chlorophenyl)-ethylcarboxamido]-1-(phenylmethyl)carboxamido}-5-hydroxy-4-methoxy-9,12-dioxo-11-phenyl-2-oxa-10,13-diazatricyclo[14.2.2.1^{3,7}]henicosa-1(18),3(21),4,6,16,19-hexaene-14-carboxylate}ruthenium Hexafluorophosphate (33). A solution of **31** (17 mg, 16 μmol) in 1.1 mL of 7:3:1 mixture of CH_2Cl_2−TFA−DMS was stirred at 0 °C for 2 h, after which time the solution was evaporated. The residue was dissolved in 1 mL of MeOH, and to this was added 1 drop of 6 N HCl. The solvent was evaporated, and the residue was chased with dry ether and dried under vacuum to obtain the amine hydrochloride. To this was added 19 mg (31 μmol, 2.0 equiv) of ruthenium complex **7**, 12 mg of HATU (32 μmol, 2.0 equiv), and 500 μL of DMF. The solution was cooled to 0 °C, and to this was added 11 μL of DIPEA (63 μmol, 4.0 equiv). The solution was stirred at 0 °C for 1 h and at 21 °C for 4 h. The reaction was quenched with aqueous citric acid and diluted with 15 mL of propionitrile. It was washed with 3 × 10 mL of 1 N HCl and 2 × 10 mL of aqueous $NaHCO_3$ and dried over Na_2SO_4. The solution was filtered, concentrated, and treated with dry ether and filtered to obtain 23 mg (81%) of dark solid: ^{1}H NMR (CD_3CN−$CDCl_3$) δ 7.52 (d, 1H, J = 8.2 Hz), 7.50 (d, 1H, J = 8.3 Hz), 7.48−7.16 (12H), 7.13 (d, 1H, J = 8.3 Hz), 7.12 (d, 1H, J = 8.4 Hz), 6.87 (d, 1H, J = 8.4 Hz), 6.86 (d, 1H, J = 8.3 Hz), 6.40−6.33 (3H), 6.07 (d, 1H, J = 6.1 Hz), 5.95 (d, 1H, J = 5.4 Hz), 5.76 (bs, 1H), 5.70 (d, 1H, J = 2.0 Hz), 5.43−5.22 (7H), 5.04−4.95 (m, 1H), 4.83 (d, 1H, J = 5.3 Hz), 4.31−4.24 (m, 1H), 3.94 (s, 3H), 3.70 (s, 3H), 3.46 (dd, 1H, J = 13.8 Hz, 4.7 Hz), 3.17 (dd, 1H, J = 12.6 Hz, 4.6 Hz), 2.73 (dd, 1H, J = 13.8 Hz, 13.0 Hz), 2.53 (dd, 1H, J = 12.6 Hz, 8.2 Hz), 1.32 (s, 9H).

Methyl (14*S*,17*R*,20*R*,23*S*,26*R*)-26-[(*tert*-Butoxycarbonyl)amino]-35-methoxy-16,19,22,25-tetraoxo-17,23-diphenyl-2,8-dioxa-15,18,21,24-tetraazapentacyclo[26.2.2.2^{9,12}.1^{3,7}.0^{5,20}]pentatriaconta-1(30),3(35),4,6,9,11,28,31,33-nonaene-14-carboxylate (3). To a flask containing the ruthenium complex **33** (20 mg, 16 μmol) and Cs_2CO_3 (27 mg, 83 μmol, 5.0 equiv) was added 3.3 mL of DMF (~5 mM concentration), and the solution was stirred at 25 °C for 6 h. The reaction was quenched with aqueous citric acid at 0 °C and diluted with 15 mL of propionitrile. It was washed with 3 × 10 mL of H_2O and evaporated, and the residue was dissolved in 20 mL of CH_3CN, degassed with Ar and photolyzed (Rayonet 350 nm) for 22 h. The solution was concentrated, and the product was purified by preparative TLC (SiO_2 gel, 0.5 mm thickness, 4:96 MeOH−$CHCl_3$) to obtain 10 mg (70%) of **3**: R_f 0.52 (4:96 MeOH−$CHCl_3$); $[\alpha]^{21}_{Hg\text{-}578}$ −66° (*c* 0.2, $CHCl_3$); ^{1}H NMR (CD_3CN−$CDCl_3$) δ 8.03 (bs, 1H), 7.62 (d, 1H, J = 8.0 Hz), 7.43−7.09 (15H), 7.04 (d, 2H, J = 7.6 Hz), 6.73 (d, 2H, J = 8.1 Hz), 6.35 (bs, 1H), 6.14 (d, 1H, J = 6.9 Hz), 5.89 (s, 1H), 5.63 (s, 1H), 5.57 (d, 1H, J = 6.9 Hz), 5.50 (d, 1H, J = 8.7 Hz), 5.13 (d, 1H, J = 8.0 Hz), 5.08−4.99 (m, 1H), 4.66−4.62 (m, 1H), 4.10 (s, 3H), 3.66 (s, 3H), 3.46 (dd, 1H, J = 8.0 Hz, 6.5 Hz), 3.11 (dd, 1H, J = 8.0 Hz, 7.1 Hz), 2.72 (dd, 1H, J = 12.5 Hz, 10.1 Hz), 2.61 (t, 1H, J = 12.5 Hz), 1.4 (s, 9H); FABHRMS (glycerol/NBA/NaI/CsI) *m*/*z* 1016.2485 (MCs^+), $C_{49}H_{49}N_5O_{11}Cs$ requires 1016.2486.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for new compounds, including concentration effects on the ^{1}H NMR spectrum of tripeptide **26** (45 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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