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Total Synthesis of Exochelin MN and Analogues

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The first total synthesis of exochelin MN is described along with rationally designed analogues. The required L-*threo*-β-hydroxyamino acid components were constructed using either Sharpless asymmetric aminohydroxylation reactions or an aldol reaction of imidazolidinone **19**. A new concise procedure for the preparation of the constituent six-membered cyclic hydroxamate was developed. In addition, a plausible mechanism for exochelin MN-mediated iron(III) transport was proposed. Biological studies of these compounds will be used to evaluate this hypothesis.

Introduction

Exochelins are a class of extracellular siderophores (low-molecular mass iron chelators) isolated from a variety of microorganisms belonging to the genus *Mycobacteria*.[1−3] They play a crucial role in the iron(III) assimilation and transport process of mycobacteria.[4−6] Exochelins are responsible for the acquisition of iron(III) from the environment to form an iron(III)−exochelin complex, which can be recognized by receptors in the cell wall. The sequestered iron is then further transferred and utilized by the mycobacteria.[7−9] In 1996, a new compound in this family, exochelin MN (**1a**, Figure 1), was isolated by Ratledge and co-workers from culture broth of *M. neoaurum*.[10] The molecule possesses impressive biological properties. It can transport iron not only into *M. neoaurum* but also into *M. leprae* cells, which are causative agents of leprosy.[10] The fact that other exochelins do not mediate iron uptake in *M. leprae* suggests a specific uptake mechanism involving exochelin MN. Since the exochelin produced by *M. leprae* cannot be directly identified, studies concerning the mode of action of exochelin MN could advance our understanding of the iron acquisition mechanisms of this species and also facilitate the development of novel antileprosy and antimycobacterial agents in the future.

The structure of exochelin MN has been fully elucidated by spectroscopic techniques as well as derivatization and GC analysis.[10] Key features include a hexapeptide backbone characterized by two hydroxamic acid units and an unusual amino acid moiety, *threo*-β-hydroxy-L-histidine, which has only been reported as a key component of pseudobactin PF244.[11] Such challenging structural novelty combined with exciting biological activity makes exochelin MN an attractive target for total synthesis.

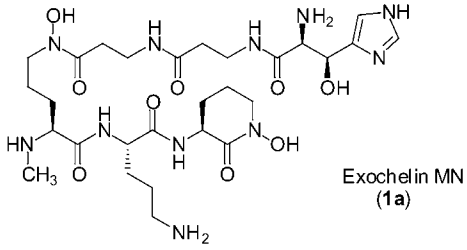

FIGURE 1.

Exochelin MN coordinates iron(III) octahedrally with its two *cis*-hydroxamate groups in addition to the hydroxy and imidazole nitrogen of the β-hydroxyhistidine.[10] As it is rare that nitrogen is involved in the chelation of iron(III) by siderophores, studies of the β-hydroxyhistidine moiety will provide insights into the function of this structural motif. Based on the unique properties of the imidazole functionality, we propose a novel mechanism for the reversible coordination of iron(III) by exochelin MN. We suggest that the iron binding ability of exochelin MN is strongly influenced by environmental pH. At neutral pH (~7.0), exochelin MN, a hexadentate ligand, should be able to acquire iron effectively from the growth media, while under slightly acidic conditions (pH < 6.5) protonation of the imidazole nitrogen of β-hydroxyhistidine would drastically reduce its affinity for iron (tetradentate ligand) and subsequently trigger the release of iron. In this way, the coordination of iron(III) by exochelin MN could be regulated by subtle changes of pH within the physiological range. A pH-dependent iron-

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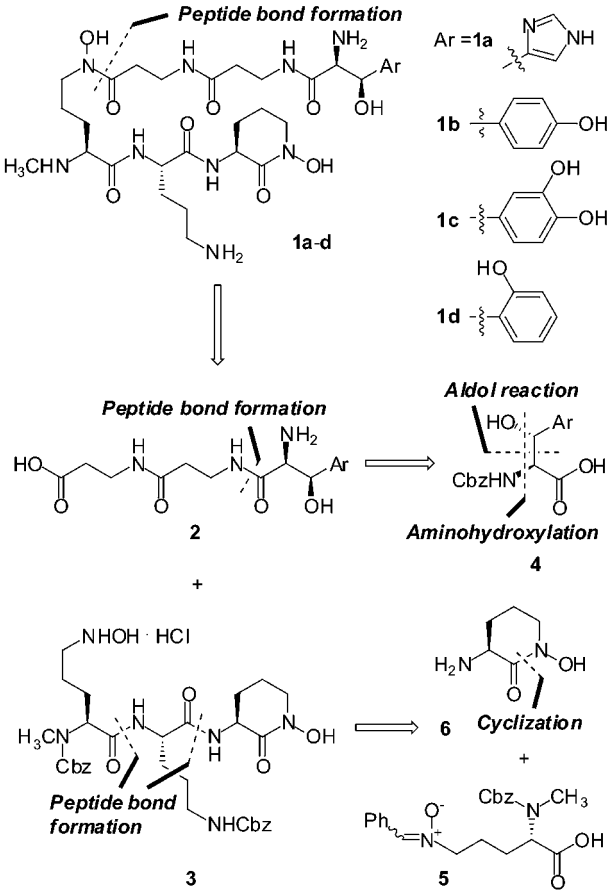


FIGURE 2. Retrosynthetic analysis.

binding study of exochelin MN is underway to evaluate this hypothesis.

As part of our studies in this area, several exochelin MN analogues were designed (**1b**−**d**, Figure 2). In these compounds, the imidazole of *β*-hydroxyhistidine was replaced by phenol and catechol, which are common iron-binding ligands found in siderophores. Evaluation of molecular models showed that these analogues could coordinate iron(III) in a fashion similar to that of exochelin MN. However, it is of special interest to note that these ligands, unlike imidazole, are not readily interconvertible between their protonated and depronated forms under physiological conditions. We expect that the results from iron-binding and growth promotion studies of these analogues could provide further evidence for our hypothesis regarding the reversible iron-binding mechanisms of exochelin MN.

Herein, we report the first total synthesis of exochelin MN and analogues thereof. Our journey toward this end witnessed the development of three generations of approach. Through the evolution of the synthetic strategy, a highly convergent and flexible approach has been devised, which culminated in the successful synthesis of the target molecules. Furthermore, this work provides a platform from which entry to other analogues of biological interest could also easily be realized.

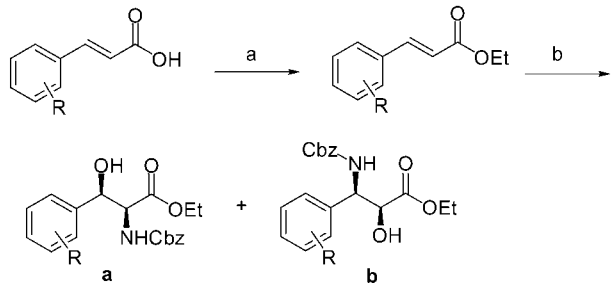
Results and Discussion

First-Generation Approach. Our first synthetic plan envisaged the cleavage at the middle peptide bond to generate two tripeptide fragments **2** and **3** as plausible precursors (Figure 2). Compound **2** could be further simplified to *β*-alanine and *threo*-*β*-hydroxy-L-amino acid **4**. L-Ornithine derivatives **5** and **6** were envisioned to be the building blocks for the construction of the other sector, **3**.

In developing our approach to the synthesis of **1a**−**d**, we viewed a practical preparation of highly functionalized *threo*-*β*-hydroxy-L-amino acid **4** as a pivotal step. We were intrigued by the possibility of exploiting the Sharpless asymmetric aminohydroxylation reaction (AA reaction) for enantioselectively introducing the amino and hydroxy groups in one step. Since it has been demonstrated that this protocol could be successfully applied to the preparation of the *threo*-*β*-hydroxy-L-tyrosine,[12] we decided to first prepare the *β*-hydroxyamino acid units of analogues **1b**−**d** utilizing this methodology.

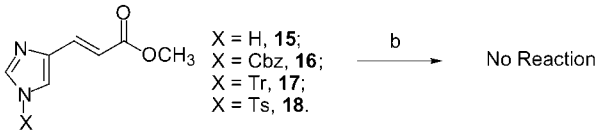
The substrates for the aminohydroxylation, **7**−**10**, were assembled by esterification and subsequent benzylation of the corresponding cinnamic acid derivatives (Scheme 1).[13,14] Under the optimal conditions established by Sharpless and co-workers, the AA reaction was performed on these compounds as summarized in Scheme 1. To our delight, most of the reactions gave satisfactory results as compounds **11**−**13** were able to be prepared in enantiomerically enriched form and in reasonable yields.[15,16]

SCHEME 1. Results of AA Reaction on Different Substrates[a]



Entry	R	a : b	yield% of a	ee% of a
1 (**7**)	4-OBn	3 :1	45% (**11**)	86%
2 (**8**)	3,4-di-OBn	2:1	34% (**12**)	undertermined
3 (**9**)	2-OBn	1:0	55% (**13**)	84%
4 (**10**)	3-OBn	1.6 :1	76% (**14**)*	N/A

* Inseparable mixture of **a** and **b**.



[a] Reagents and conditions: (a) EtOH, H_2SO_4, reflux; BnBr, K_2CO_3, DMF, rt, 82−87% for two steps; (b) $BnOCONH_2$, NaOH, $K_2[OsO_2(OH)_4]$, $(DHQD)_2AQN$, *t*-BuOCl, *n*-propanol/H_2O, rt.

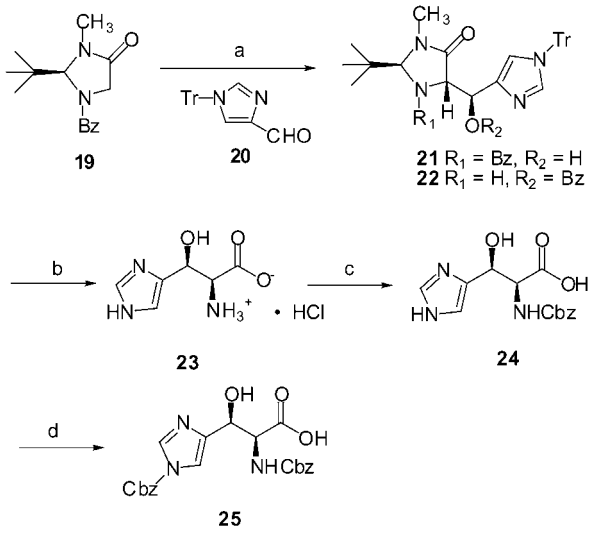
(12) Tao, B.; Schlingloff, G.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 2507−2510.
(13) Hamamichi, N.; Natrajan, A.; Hecht, S. M. *J. Am. Chem. Soc.* **1992**, 114, 6278−6291.
(14) Doherty, D. G. *J. Am. Chem. Soc.* **1955**, *77*, 4887−4892.

The only exception was the reaction of compound **10**, which produced an inseparable mixture of regioisomers.

Encouraged by these results, we set out to examine the possibility of a straightforward approach to (2*S*,3*S*)-*β*-hydroxyhistidine from urocanic acid methyl ester **15** (Scheme 1). Unfortunately, this strategy could not be implemented despite the structural similarity between cinnamic acid ester and **15**. The possible chelation of the imidazole with osmium(VIII) was assumed to be the reason for these failed attempts.[17] To test this hypothesis, compounds **16**−**18** (Scheme 1) were prepared and subjected to the aminohydroxylation conditions.[18,19] The goal of introducing these N^1 protecting groups was to block the possible coordination of the imidazole with osmium(VIII) through inductive or steric effects. However, attempts on these substrates were unsuccessful. These, as well as results from further studies,[20] indicated that the notion of extending the scope of the AA reaction to nitrogen-containing heterocycles was, in fact, problematic, and a new plan had to be devised.

After considering several possibilities, the approach that emerged as the most attractive commenced with the aldol reaction of imidazolidinone **19**[21] and known aldehyde **20**[22] followed by the exhaustive deprotection of the resulting adducts to afford amino acid **23**.[21] Employing the procedure developed by Oshima and co-workers,[23] aldol products **21** and **22** were obtained in good yield. Without separation, the mixture was hydrolyzed to generate (2*S*,3*S*)-*β*-hydroxyhistidine hydrochloride **23** with high optical purity,[24] which was then protected in two steps to provide bis-Cbz compound **25** (Scheme 2).[25]

SCHEME 2. Synthesis of (2*S*,3*S*)-*β*-Hydroxyhistidine by Asymmetric Aldol Reaction[a]



[a] Reagents and conditions: (a) Ti(O-*n*-Bu)$_4$, *t*-BuOK, **20**, THF, 0 °C, 56%; (b) 6 M HCl, reflux, 93%; (c) Cbz-S, TEA, dioxane/H_2O, 0 °C to rt, 54%; (d) CbzCl, $NaHCO_3$, H_2O, rt.

The rapid decomposition of compound **25** made it necessary to use the crude material immediately after preparation, and no full characterization was attempted.

With these important *β*-hydroxyamino acids in hand, we turned our attention to their coupling reactions with *β*-alanine dipeptide **29**,[26] as outlined in Scheme 3. By carefully monitoring the reactions, esters **11**−**13** were able to be saponified in excellent yields. The resulting acids **26**−**28** were then coupled with *β*-alanyl-*β*-alanine methyl ester hydrochloride **29** to afford the corresponding tripeptide methyl esters **30**−**32**.[27] In the next transformation, however, we found that the poor solubility of these esters and basic lability of the benzyl carbamate, especially with the participation of the neighboring hydroxy group, made the hydrolysis reactions quite problematic. Finally, after some experimentation, the combination of CH_3CN/MeOH/H_2O provided the best results. However, attempts to hydrolyze the methyl ester of compound **30** always led to the concomitant loss of the Cbz group and oxazolidinone **33** was obtained as the exclusive product.

Having addressed the synthesis of tripeptide **2**, the next task was the construction of fragment **3** from compounds **5** and **6**. The synthesis of compound **5** was accomplished by N-methylation of known nitrone **36** in good yield.[28,29] Hydroxamate **6** was prepared from the same precursor in a three-step sequence, involving deprotection of the nitrone, cyclization and hydrogenoly-

(15) The methyl ester derivatives of compounds **7** and **8** were not soluble in the solvent system. Reaction of the methyl ester version of compound **9** gave lower enantioselectivity (65% ee) despite the facile purification (the separation of compound **13** from excess benzyl carbamate was problematic).

(16) The enantiomeric excess of the aminohydroxylation products was determined by Mosher's reagent derivatization and ^{19}F NMR studies. In the case of compound **12**, it was found that the solvent ($CDCl_3$ or DMSO-d_6) employed for the experiment drastically affected the results. Currently, the enantiomeric excess of this compound has not been unequivocally determined and further studies are ongoing. The absolute configuration of representative product **11** was unambiguously determined by saponification and hydrogenolytic removal of the Cbz and benzyl groups, followed by comparison of the optical rotation of resulting *β*-hydroxytyrosine with the literature value. Herbert, R. B.; Wilkinson, B.; Ellames, G. J. *Can. J. Chem.* **1994**, *72*, 114−117.

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(18) Ilizuka, K.; Akahane, K.; Mosose, D.; Nakazawa, M.; Tanouchi, T. *J. Med. Chem.* **1981**, *24*, 1139−1148.

(19) Kosaka, K.; Maruyama, K.; Nakamura, H.; Ikeda, M. *J. Heterocycl. Chem.* **1991**, *28*, 1941−1944.

(20) Competition studies were performed to further explore this assumption. When a mixture of equal equivalents of **7** and **15** or **16** was subjected to aminohydroxylation conditions, compound **11** was not detected. In a separate experiment, when the reaction of **16** was conducted in the presence of a stoichiometric amount of osmium reagent, no consumption of the substrates was observed.

(21) (a) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277−5292. (b) Fitzi, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 345−346.

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(24) Taraz, K.; Wever, M.; Budzikiewicz, H. *Z. Naturforsch. Sect. B−A* **1998**, *53*, 1520−1524. The optical rotations of compound **23** and its enantiomer we synthesized matched the literature values at 589 nm (unpublished results obtained through personal correspondence with the author. We thank Dr. H. Budzikiewicz at Institut für Organische Chemie der Universität zu Köln for his help and discussion).

(25) Kitaka, A.; Sngano, Y.; Otasuka, M. *Tetrahedron* **1988**, *44*, 2811−2820. Coupling reactions of compound **24** generally gave very poor results (~10% yield).

(26) The general procedure for peptide synthesis was employed to prepare these *β*-alanine dipeptides. For example, **25**: Cbz protection of *β*-alanine (CbzCl, NaOH, 95%), coupling of this compound with *β*-alanine methyl ester hydrochloride (EDC, HOBt, DMAP, 91%) ,and removal of the Cbz protecting group from the resulting dipeptide by hydrogenolysis (H_2, Pd/C, 100%).

(27) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397−4398.

(28) Lin, Y.-M.; Miller, M. J. *J. Org. Chem.* **1999**, *64*, 7451−7458.

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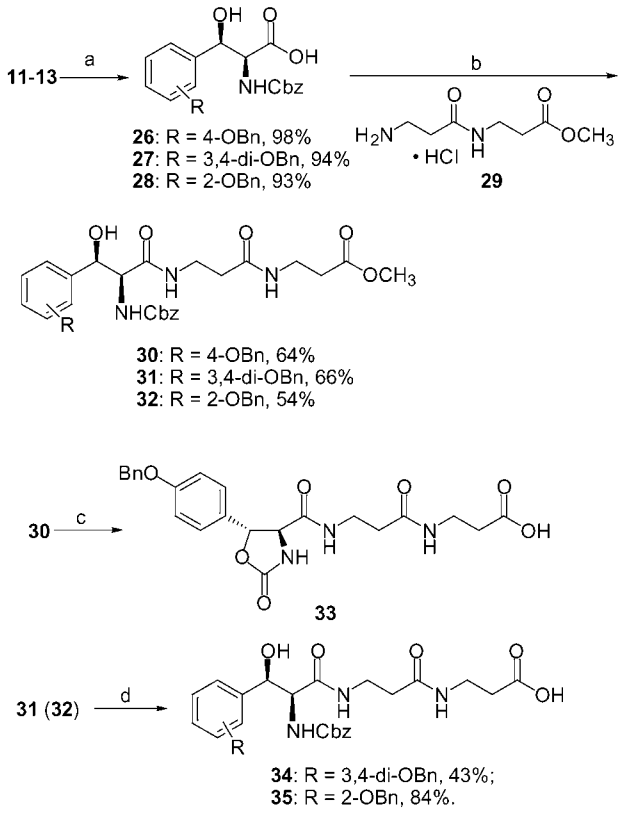
SCHEME 3. Synthesis of the Tripeptide Fragments[a]

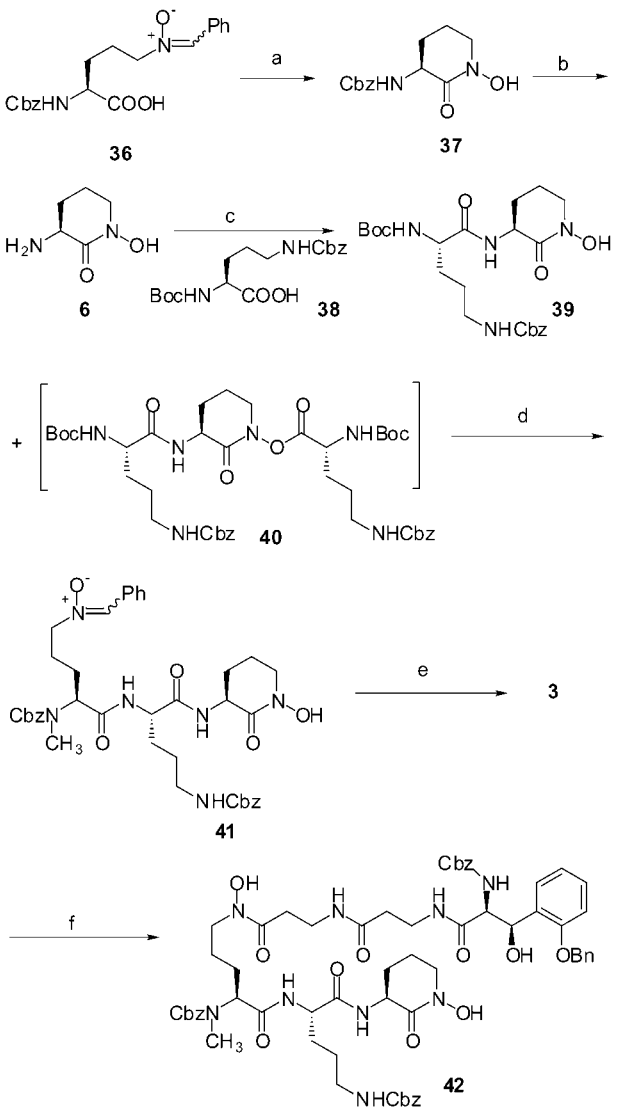


[a] Reagents and conditions: (a) LiOH, THF/H_2O, 0 °C; (b) EDC, HOAt, DMAP, **29**, CH_2Cl_2, 0 °C to rt; (c) LiOH, CH_3CN/MeOH/H_2O, 0 °C to rt, 88%; (d) **31**: CH_3CN/MeOH/H_2O, 0 °C; **32**: LiOH, THF/H_2O, 0 °C.

sis (Scheme 4). However, these deceptively simple transformations were found to be among the principal hurdles in the synthesis due to the highly variable yields, especially in the hydrogenolysis step. Although enough material was accumulated for the investigation of the following steps, possible remedies to this problem were sought later.

We encountered some unanticipated difficulties in the next several coupling reactions. Although ample literature precedent indicated that amino groups could be selectively acylated in the presence of hydroxamates,[30] we found that the carbodiimide-mediated coupling reaction of **6** and **38** always led to a mixture of the desired product **39** and bis-coupled product **40**. This competitive acylation of the hydroxamate seriously compromised the yields of this and subsequent coupling reactions. After TFA-mediated Boc deprotection of **39**, the reaction of the resulting amine salt and compound **5** generated tripeptide **41**. A number of other coupling reagents (HATU, BOP) were investigated in an attempt to improve the efficiency of these coupling reactions. Unfortunately, no satisfactory conditions surfaced during these studies. Finally, treatment of compound **41** with hydroxylamine hydrochloride removed the nitrone and furnished compound **3**.[31]

SCHEME 4. Synthesis of the Protected Analogue 42[a]



[a] Reagents and conditions: (a) TFA, H_2O, 60 °C; 1 M HCl, CH_2Cl_2, rt, 82%; EDC, HOBt, $NaHCO_3$, CH_3CN, rt, 65%; (b) H_2, 10% Pd/C, rt, 100%; (c) **38**, EDC, HOAt, DMAP, DMF, 0 °C to rt; TEA, rt, 58%; (d) TFA, CH_2Cl_2, 0 °C to rt; **5**, EDC, HOAt, DMAP, DMF, 0 °C to rt; TEA, rt, 35% for two steps; (e) NH_2OH·HCl, CH_3OH, 60 °C, 75%; (f) **35**, BOP, (i-Pr)$_2$EtN, DMF, 0 °C to rt, 41%.

With the preparation of the above fragments, an important stage in the synthesis had been reached. The remaining task was the union of fragments **3** and **2**. The preparation of the phenol analogue **42** was pursued first (Scheme 4). Several conditions were examined to effect the last coupling reaction. Eventually, the successful solution to the union of **3** and **35** was accomplished by utilizing BOP and (^{i}Pr)$_2$EtN to yield the protected analogue **42**.[32]

Second-Generation Approach. Despite the success described above, it was clear that considerable difficulties, notably arising from the assembly of fragment **2**, would be encountered if the above route were followed

(30) (a) Bergeron, R. J.; Phanstiel, O. IV *J. Org. Chem.* **1992**, *57*, 7140−7143. (b) Akiyama, M.; Shimizu, K.; Aiba, S.; Katoh, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1421−1425.

(31) Hu, J.; Miller, M. J. *J. Org. Chem.* **1994**, *59*, 4848−4861.

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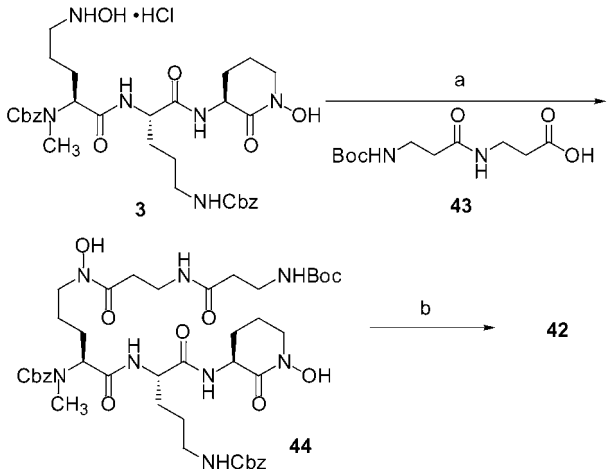
SCHEME 5. Synthesis of Protected Analogue 42[a]



[a] Reagents and conditions: (a) BOP, (*i*-Pr)$_2$EtN, **43**, DMF/CH_3CN, 0 °C to rt, 31%; (b) TFA, CH_2Cl_2, 0 °C to rt; **28**, EDC, HOAt, DMAP, DMF, 0 °C to rt, 37% for two steps.

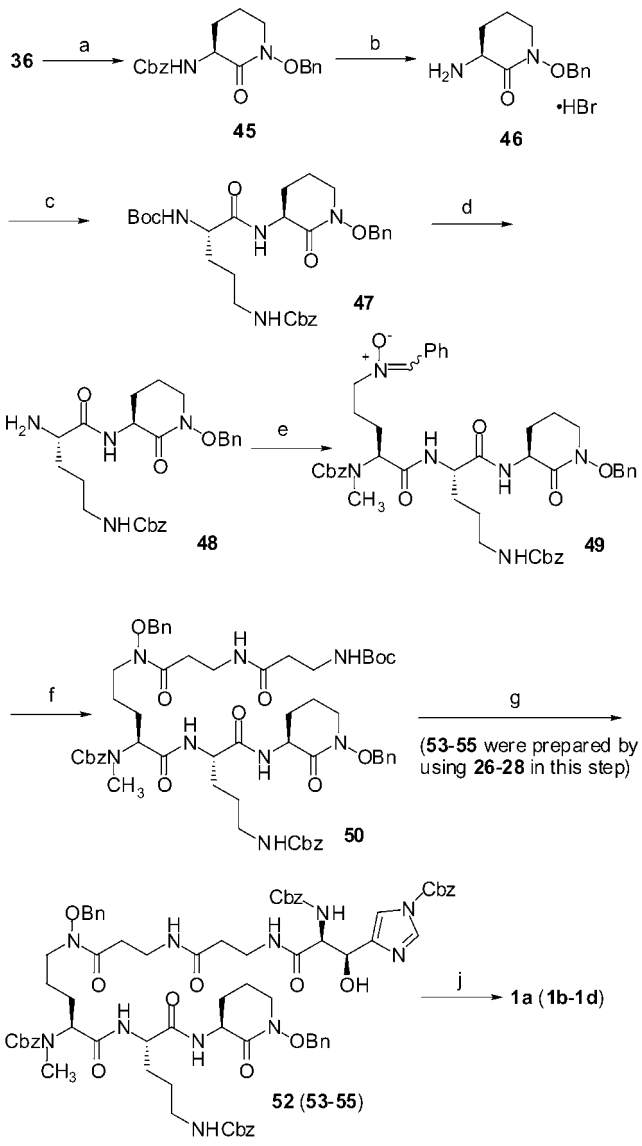
to access the target compounds. Recognizing the importance of developing a convergent synthesis of **1a**−**d**, an alternative synthetic plan was devised as shown in Scheme 5. According to this strategy, exochelin MN and its analogues could be derived from the common advanced intermediate, pentapeptide **44** (Scheme 5). Subsequent studies showed that the convergence provided by this approach was vital to the success of these syntheses.

In this alternative approach, an orthogonal protecting group had to be employed for the amino group of the β-alanine dipeptide to allow its selective removal at the later stage of the synthesis in the presence of both Cbz and benzyl protecting groups. After an extensive survey of a variety of candidates (Boc, Fmoc, and Alloc), Boc was found to best serve this purpose.[33] Therefore, the coupling reaction of *N*-Boc β-alanine dipeptide **43**[26] and compound **3** furnished pentapeptide **44**, which was exposed to TFA to remove the Boc group. The amine salt then reacted with carboxylic acid **28** to produce protected analogue **42** in moderate yield (Scheme 5). In this way, compounds **1a**−**d** should be readily accessed by adjusting the last β-hydroxyamino acids.

Third-Generation Approach. While the results of the second-generation approach were certainly gratifying, a more efficient route was desirable to render the synthesis practical. In appraisal of the setbacks involved in previous approaches, it was noted that the free cyclic hydroxamate was the primary source of frustration because of its apparent interference in acylation reactions. It should also be mentioned that all the intermediates containing a hydroxamate moiety had to be purified by careful reversed-phase chromatography, and the strong iron-binding ability of these compounds made their isolation and purification quite difficult. To circumvent these problems, we recognized the necessity of incorporating a hydroxamate protecting group strategy, and a benzyl group was selected for this purpose.

(33) The Fmoc group proved to be too labile under basic conditions and also caused solubility problems. On the other hand, the Alloc group could be easily introduced but was not able to be cleanly removed.

SCHEME 6. Synthesis of Exochelin MN[a]



[a] Reagents and conditions: (a) NH_2OH·HCl, 3 Å molecular sieves, TEA, CH_3OH, reflux; BnBr, K_2CO_3, DMF, rt, 65% for two steps; (b) HBr/HOAc, CH_2Cl_2, rt, 92%; (c) **38**, EDC, HOAt, DMAP, CH_2Cl_2, 0 °C to rt, 94%; (d) TFA, CH_2Cl_2, rt; $NaHCO_3$ (aq), 92%; (e) **5**, EDC, HOAt, CH_2Cl_2, 0 °C to rt, 92%; (f) NH_2OH·HCl, CH_3OH, 60 °C, 85%; **43**, BOP, (*i*Pr)$_2$EtN, DMF, 0 °C to rt; BnBr, K_2CO_3, DMF, rt, 74% for two steps; (g) TFA, CH_2Cl_2, 0 °C to rt; $NaHCO_3$ (aq); **25**, EDC, HOAt, 0 °C to rt, DMF, 44% for two steps; (j) H_2, $Pd(OH)_2$, rt, 36%.

The synthesis of exochelin MN by this revised route is outlined in Scheme 6. Compound **37** had previously been prepared from nitrone **36** in modest yield, and initially we believed the application of this method in conjunction with benzyl protection would provide the most expeditious means of obtaining compound **45**. However, after some experimentation, we developed a more concise and efficient protocol through a one-pot deprotection−cyclization reaction followed by benzylation. In this fashion, compound **45** was able to be obtained in good yield and in a short time! An added benefit of this approach was that this reaction proved very amenable to scale-up since it could be conducted in concentrated solution without polymerization.

The next challenge in our synthesis was to find a protocol to selectively remove the Cbz group in the presence of the hydroxamate−benzyl group. This could be readily achieved by treatment with 33% HBr in acetic acid.[34] Finally, we were pleased to find that, as expected, the introduction of hydroxamate−benzyl protecting group made the subsequent coupling and deprotection reactions proceed smoothly and exochelin MN was obtained in excellent overall yields (4.7% from the longest linear sequence). It should be pointed out that the second hydroxamate formed in this sequence was also protected as a benzyl ether to facilitate the purification. Interestingly, it seemed that this free hydroxamate was not reactive under coupling reaction conditions, which was consistent with the literature reports as mentioned before. In the last global deprotection reaction, we found that the employment of Pd/C led to serious iron(III) contamination of the products while $Pd(OH)_2$ proved to be a superior catalyst. The spectroscopic data of our synthetic sample (IR, MS, ^{1}H and ^{13}C NMR) matched those of the natural product kindly provided by Professor Colin Ratledge. Analogues **1b**−**d** were prepared in a similar fashion by varying the last β-hydroxyamino acid. It is worth noting that all intermediates in the third-generation approach were purified by regular-phase chromatography. This greatly simplified the procedures and contributed to the improved yields and overall efficiency.

Conclusions

In conclusion, the first total synthesis of exochelin MN and several analogues has been achieved. Biological assays and pH-dependent iron(III)-binding studies of these compounds are underway and will be published in due course. Investigations in this area will significantly augment the understanding of the iron transport processes of mycobacteria, especially the controlled iron(III) release by exochelin, and should also facilitate the search for potent remedies for mycobacterial infections. In this process, a new concise procedure for the preparation of the six-membered cyclic hydroxamate was developed. We have also shown that Sharpless asymmetric aminohydroxylation reaction and the asymmetric aldol reaction of imidazolidinone **19** provided an entry to a number of related β-hydroxyamino acids. We believe our efforts in this area will lead to an array of synthetically and biologically interesting moieties in the future.

Experimental Section

General Procedures. Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Methylene chloride (CH_2Cl_2), acetonitrile (CH_3CN), dioxane, and triethylamine (TEA) were distilled from CaH_2. *N*,*N*-Dimethylformamide (DMF) was distilled from CaH_2 and stored over 3 Å molecular sieves. All other reagents were used as received. Unless otherwise noted, all nonaqueous reactions were carried out under a dry argon atmosphere with oven-dried glassware (120 °C, at least 12 h). Melting points were measured on a capillary melting point apparatus and are uncorrected. Unless otherwise noted, all NMR spectra were recorded at 300 MHz. Silica gel flash column chromatography was performed using silica gel 60 (30−70 μm irregular particles). Reversed-phase chromatography was performed on C-18 silica gel (37−53 μm particles). During all hydrogenolysis reactions, the solvent was purged with argon prior to the addition of the catalyst.

(*E*)-Ethyl 2-Benzyloxycinnamate (9). To a solution of 2-hydroxycinnamic acid (1.0 g, 6.1 mmol) in absolute EtOH (20 mL) was added concentrated H_2SO_4 (0.5 mL) dropwise with vigorous stirring. After being refluxed for 5 h, the reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in EtOAc (30 mL), washed with H_2O (3 × 10 mL), dried ($MgSO_4$), filtered, and concentrated to give an off-white solid. To a mixture of this solid and K_2CO_3 (1.580 g, 11.5 mmol) in DMF (6 mL) was added benzyl bromide (0.979 g, 0.681 mL, 5.7 mmol). The mixture was stirred overnight at room temperature and partitioned between EtOAc (30 mL) and H_2O (15 mL). The organic layer was further washed with H_2O (3 × 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (1:10 EtOAc/hexanes) to afford **9** as a white solid (1.490 g, 87%): mp 45−47 °C; IR (neat) 1705, 1630 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, 1 H, J = 8.1 Hz), 7.53−6.90 (m, 9 H), 6.53 (d, 1 H, J = 8.1 Hz), 5.12 (s, 2 H), 4.23 (q, 2 H, J = 6.9 Hz), 1.33 (t, 3 H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 157.4, 140.0, 136.8, 131.5, 128.9, 128.8, 128.1, 127.3, 124.0, 121.2, 119.0, 113.0, 70.4, 60.5, 14.5; HRFABMS *m*/*z* calcd for $C_{18}H_{19}O_3$ $[MH]^+$ 283.1334, found 283.1351.

General Procedure for Aminohydroxylation Reactions: Ethyl (2*S*,3*R*)-2-Benzyloxycarbonylamino-3-(4-benzyloxyphenyl)-3-hydroxypropionate (11) and Ethyl (2*S*,3*R*)-3-Benzyloxycarbonylamino-3-(4-benzyloxyphenyl)-2-hydroxypropionate (11b). A 1 N NaOH solution (3.05 mL, 3.05 mmol) was diluted with H_2O (4.5 mL). Part of this solution (0.5 mL) was transferred into a vial to dissolve $K_2[OsO_2(OH)_4]$ (14.7 mg, 0.04 mmol). To the rest of the solution were added *n*-propanol (4 mL) and benzyl carbamate (469 mg, 3.1 mmol) with rigorous stirring, followed by dropwise addition of freshly prepared *tert*-butyl hypochlorite (331 mg, 0.346 mL, 3.05 mmol). After 5 min, an *n*-propanol solution (3.5 mL) of $(DHQD)_2AQN$ (34.3 mg, 0.04 mmol), α,β-unsaturated ester (**7**−**10**) (1.0 mmol), and the aqueous $K_2[OsO_2(OH)_4]$ solution were added. For compounds **11** and **12**: After being stirred for 2 h at room temperature, the reaction mixture was cooled to 0 °C, filtered, washed with cold H_2O/*n*-propanol (1:1), and dried to give the crude product. For compound **13** and **14**: After being stirred for 2 h at room temperature, the reaction mixture was quenched with $NaHSO_3$ (0.5 g) and diluted with EtOAc (8 mL). After separation of the layers, the aqueous layer was further extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude product. The crude material was purified by column chromatography (5:1 hexanes/EtOAc or 20:1 CH_2Cl_2/EtOAc) to afford the desired compounds. **11**: white crystals (45%); mp 104−106 °C; IR (KBr) 3482, 1726, 1690 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45−7.25 (m, 10 H), 7.26 (d, 2 H, J = 8.4 Hz), 6.94 (d, 2 H, J = 8.4 Hz), 5.55 (d, 1 H, J = 8.4 Hz), 5.19 (m, 1 H), 5.05 (s, 2 H), 5.03 (s, 2 H), 4.55 (d, 1 H, J = 5.4 Hz), 4.25 (q, 2 H, J = 7.2 Hz), 2.52 (m, 1 H), 1.23 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 159.8, 137.7, 132.2, 128.9, 128.7, 128.4, 128.2, 127.7, 127.5, 115.0, 73.8, 70.2, 67.3, 62.1, 60.1, 14.3; HRFABMS *m*/*z* calcd for $C_{26}H_{26}NO_6$ $[MH]^+$ 448.1760, found 448.1785. **11b**: a white solid; mp 118−120 °C; IR (KBr) 3364, 1719, 1692 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.70 (d, 1 H, J = 9.3 Hz), 7.45−7.30 (m, 15 H), 7.22 (d, 2 H, J = 8.4 Hz), 6.94 (d, 2 H, J = 8.4 Hz), 5.55 (d, 1 H, J = 7.8 Hz), 5.07 (s, 2 H), 5.01 (d, 2 H, J = 11.4 Hz), 4.97 (d, 2 H, J = 11.4 Hz), 4.87 (dd, 1 H, J = 5.1, 9.3 Hz), 4.22 (dd, 1 H, J = 5.4, 9.3 Hz), 3.95 (q, 2 H, J = 6.9 Hz), 1.01 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 158.7, 155.9, 137.2, 136.5, 128.9, 128.8, 128.4, 128.3, 127.7, 115.2, 73.7, 70.3, 67.2, 62.8, 56.2, 14.3; HRFABMS *m*/*z* calcd for $C_{26}H_{26}NO_6$ $[MH]^+$ 448.1760, found 448.1753.

(34) Okonya, J. F.; Kolasa, T.; Miller, M. J. *J. Org. Chem.* **1995**, *60*, 1932−1935.

Ethyl (2*S*,3*R*)-2-Benzyloxycarbonylamino-3-(3,4-dibenzyloxyphenyl)-3-hydroxypropionate (12) and Ethyl (2*S*,3*R*)-3-Benzyloxycarbonylamino-3-(3,4-dibenzyloxyphenyl)-2-hydroxypropionate (12b). 12: white crystals (34%); mp 109−110 °C; IR (KBr) 3359, 1733, 1697 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.44−7.25 (m, 15 H), 7.00 (s, 1 H), 6.88 (m, 2 H), 5.68 (d, 1 H, J = 9.0 Hz), 5.10 (s, 2 H), 5.07 (s, 2 H), 5.00 (s, 2 H), 4.53 (dd, 1 H, J = 9.6, 3.0 Hz), 4.13 (m, 2 H), 3.08 (s, br, 1 H), 1.19 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 156.5, 149.0, 148.8, 137.3, 136.3, 133.2, 128.6 (2), 128.2, 128.0 (2), 127.5, 127.4, 119.3, 114.7, 112.9, 73.5, 71.3, 71.2, 67.1, 61.9, 60.1, 14.2; FABMS *m*/*z* calcd for $C_{33}H_{33}NO_7$ $[M]^+$ 555, found 555. **12b**: A white solid; mp 104−105 °C; IR (KBr) 3450, 1722, 1691 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.45−7.26 (m, 15 H), 7.00 (s, 1 H), 6.90 (m, 2 H), 5.55 (d, 1 H, J = 10.5 Hz), 5.18 (m, 1 H), 5.14 (m, 4 H), 5.06 (d, 2 H, J = 4.8 Hz), 4.39 (m, 1 H), 4.23 (q, 2 H, J = 6.9 Hz), 3.08 (d, 1 H, J = 4.2 Hz), 1.26 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 155.8, 149.2, 148.9, 137.5, 137.3, 136.4, 132.5, 128.7, 128.6, 128.3, 128.0, 128.0, 127.7, 127.4, 120.0, 115.1, 114.2, 73.6, 71.6, 71.5, 67.2, 62.8, 56.2, 14.3; FABMS *m*/*z* calcd for $C_{33}H_{33}NO_7$ $[M]^+$ 555, found 555.

Ethyl (2*S*,3*R*)-2-benzyloxycarbonylamino-3-(2-benzyloxyphenyl)-3-hydroxypropinoate (13): a white solid (55%); mp 74−75 °C; IR (KBr) 3442, 1746, 1706 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.49−7.21 (m, 14 H), 6.94 (m, 2 H), 5.78 (d, 1 H, J = 9.0 Hz), 5.62 (m, 1 H), 5.15 (d, 2 H, J = 11.4 Hz), 5.06 (d, 2 H, J = 11.4 Hz), 4.94 (s, 2 H), 4.86 (dd, 1 H, J = 9.6, 2.4 Hz), 4.15 (m, 2 H), 3.31 (d, 1 H, J = 5.4 Hz), 1.19 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.2, 156.5, 155.2, 136.8, 136.5, 129.0, 128.5, 128.2, 128.0 (2), 127.9, 127.1, 120.8, 111.4, 70.0, 69.8, 66.8, 61.6, 58.1, 14.1; HRFABMS *m*/*z* calcd for $C_{26}H_{26}NO_6$ $[MH]^+$ 450.1917, found 450.1931.

(2*S*,3*S*)-β-Hydroxyhistidine (23). To a solution of Ti(O-*n*-Bu)$_4$ (0.507 mL, 2.5 mmol) in THF (6.5 mL) was added KO-*t*-Bu (260 mg, 2.5 mmol) at room temperature. After being stirred for 10 min, the solution was cooled to 0 °C and a solution of **19** (260 mg, 1.0 mmol) in THF (5 mL) was added in small portions. After the mixture was stirred for 10 min, a solution of **20** (507 mg, 1.5 mmol) in THF (7 mL) was added dropwise, and the mixture was stirred for 4 h at 0 °C. The reaction mixture was quenched with addition of 1 N HCl (3 mL) and diluted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (3 × 5 mL), dried ($MgSO_4$), filtered, and concentrated to generate a yellow gum. The crude product was purified by column chromatography (1−5% MeOH/CH_2Cl_2). The pale yellow partially crystalline mixture (286.1 mg, 56%) contained **21** and **22**.

The mixture (80.0 mg, 0.131 mmol) was refluxed with 6 N HCl (2 mL) for 8 h. After being cooled to room temperature, the mixture was washed with Et_2O (4 × 2 mL), filtered, and concentrated under reduced pressure. The crude product was purified by Dowex cation ion-exchange resin (50 × 8−400) to give **23** as a pale yellow solid (29 mg, 93%): $[\alpha]_D = -9$ (c = 1 M, H_2O, pH = 4.3); IR (KBr) 3401, 1702, 1607 cm^{-1}; ^1H NMR (300 MHz, D_2O, pH = 4.3) δ 8.52 (d, 1 H, J = 1.2 Hz), 7.27 (dd, 1 H, J = 1.2, 0.9 Hz), 5.41 (dd, 1 H, J = 3.6, 0.9 Hz), 4.25 (d, 1 H, J = 3.6 Hz); ^{13}C NMR (75 MHz, D_2O, pH = 4.3) δ 171.4, 135.5, 134.7, 116.5, 65.1, 59.3; HRFABMS *m*/*z* calcd for $C_6H_{10}N_3O_3$ $[MH]^+$ 172.0722, found 172.0727.

(2*S*,3*S*)-N^2-(Benzyloxycarbonyl)-β-hydroxyhistidine (24). To a solution of **23** (100.0 mg, 0.482 mmol) in H_2O (2.4 mL) was added a solution of Cbz-succinimide (158.6 mg, 0.578 mmol) in dioxane (2.4 mL) and TEA (0.221 mL, 1.592 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and then at room temperature overnight. The reaction mixture was treated with H_2O (10 mL) and washed with EtOAc (4 × 8 mL). The aqueous layer was concentrated under reduced pressure, and the residue was purified by column chromatography (35−50% MeOH/$CHCl_3$) to give **24** as light yellow crystals (79.1 mg, 54%): IR (KBr) 3422, 1702, 1607 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 7.82 (s, 1 H,), 7.27 (m, 5 H), 7.02 (s, 1 H), 5.24 (d, 1 H, J = 3.0 Hz), 5.04 (d, 1 H, J = 12.6 Hz), 4.99 (d, 1 H, J = 13.2 Hz), 4.37 (d, 1 H, J = 3.0 Hz); ^{13}C NMR (150 MHz, CD_3OD) δ 171.5, 157.2, 137.0, 134.5, 128.3, 127.8, 127.6, 116.4, 67.8, 66.4, 60.0; HRFABMS *m*/*z* calcd for $C_{14}H_{15}N_3O_5$ $[MH]^+$ 305.0722, found 305.0727.

General Procedure for Hydrolysis of Ethyl Esters 11−13. (2*S*,3*R*)-2-Benzyloxycarbonylamino-3-(4-benzyloxyphenyl)-3-hydroxypropioic Acid (26). To a solution of **11** (80.0 mg, 0.182 mmol) in THF/H_2O (1.6:1, 3 mL) was added 1 N LiOH solution (0.214 mL, 0.214 mmol) at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was concentrated under reduced pressure to remove the THF. The residue was diluted with H_2O (2 mL) and washed with Et_2O (3 × 2 mL). The aqueous layer was acidified to pH 3.0 with 10% citric acid and extracted with EtOAc (3 × 7 mL). The combined organic layers were washed with brine (3 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford **26** as white crystals (75.2 mg, 98%): mp 110−112 °C; IR (KBr) 3495, 1742, 1242 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.46−6.94 (m, 14 H), 5.13 (m, 1H), 5.08 (s, 2 H), 4.96 (s, 2 H), 4.26 (dd, 1 H, J = 9.0, 3.0 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.9, 171.3, 157.5, 156.2, 137.2, 137.1, 134.3, 128.5, 128.3, 127.8, 127.7, 127.4, 127.3, 114.1, 71.8, 69.2, 65.3, 60.5; HRFABMS *m*/*z* calcd for $C_{24}H_{24}NO_6$ $[MH]^+$ 422.1604, found 422.1587.

(2*S*,3*R*)-2-Benzyloxycarbonylamino-3-(3,4-dibenzyloxyphenyl)-3-hydroxypropioic acid (27): white crystals (94%); mp 103−104 °C; IR (KBr) 3419, 1734, 1269 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.44−6.88 (m, 18 H), 5.14 (d, 1H, J = 4.5 Hz), 5.09 (s, 2 H), 5.06 (s, 2 H), 4.95 (s, 2 H), 4.25 (dd, 1 H, J = 9.0, 4.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.6, 158.6, 156.9, 148.6, 148.0, 138.1, 135.9, 132.0, 129.1, 129.0, 128.5, 128.3, 128.2, 127.9, 119.6, 114.5, 113.5, 72.6, 71.0, 70.8, 65.9, 61.1; FABMS *m*/*z* 527 (M^+), 510 (M − 17).

(2*S*,3*R*)-2-Benzyloxycarbonylamino-3-(2-benzyloxyphenyl)-3-hydroxypropioic acid (28): colorless glass (93%); IR (neat) 3410, 1721, 1498 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.55−6.87 (m, 14 H), 5.80 (d, 1 H, J = 9.3 Hz), 5.73 (m, 1 H), 5.13 (d, J = 11.7 Hz), 5.04 (d, J = 12.0 Hz), 4.91 (m, 2 H), 4.41 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 156.9, 155.3, 136.9, 129.2, 128.9, 128.6, 128.2, 128.1, 127.2, 127.0, 121.1, 111.8, 107.3, 70.3, 69.7, 67.2, 58.0; HRFABMS *m*/*z* calcd for $C_{24}H_{24}NO_6$ $[MH]^+$ 422.1604, found 422.1620.

General Procedure for Coupling Reactions of 29 and 26−28. *N*-*N*-[(2*S*,3*R*)-2-Benzyloxycarbonylamino-3-(4-benyloxyphenyl)-3-hydroxypropionyl]-β-alanyl-β-alanine Methyl Ester (30). To a stirred solution of **29** (241.6 mg, 1.148 mmol), **26** (406.3 mg, 0.965 mmol), and HOAt (143.1 mg, 1.05 mmol) in CH_2Cl_2 (8 mL) at 0 °C were added EDC (220.4 mg, 1.148 mmol) and DMAP (294.3 mg, 2.412 mmol). After being stirred at room temperature overnight, the reaction mixture was partitioned between EtOAc (25 mL) and H_2O (7 mL). The organic layer was washed with 10% citric acid (3 × 5 mL), 5% $NaHCO_3$ (3 × 5 mL), and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated to give the crude product. This was purified by column chromatography (2−4% MeOH/CH_2Cl_2) to afford **30** as a white solid (356.3 mg, 64%): mp 188−190 °C; IR (KBr) 3294, 1737, 1696, 1649 cm^{-1}; ^1H NMR (300 Hz, DMSO-d_6) δ 7.97 (t, 1 H, J = 5.7 Hz), 7.92 (t, 1 H, J = 5.4 Hz), 7.45−6.88 (m, 14 H), 5.47 (d, 1 H, J = 6.0 Hz), 5.13 (m, 1 H), 5.07 (s, 2 H), 4.94 (m, 2 H), 4.14 (dd, 1 H, J = 12.6, 3.3 Hz), 3.58 (s, 3 H), 3.27 (m, 4 H), 2.48 (t, 2 H, J = 7.2 Hz), 2.17 (t, 2 H, J = 6.6 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.5, 171.2, 170.4, 158.1, 137.9, 135.2, 131.9, 129.1, 129.0, 128.5, 128.4, 128.0, 127.9, 115.5, 114.7, 100.2, 72.7, 69.8, 66.0, 61.9, 52.1, 36.1, 35.8, 35.4, 34.3; HRFABMS *m*/*z* calcd for $C_{33}H_{36}N_3O_8$ $[MH]^+$ 578.2502, found 578.2500.

***N*,*N*-[(2*S*,3*R*)-2-Benzyloxycarbonylamino-3-(3,4-dibenyloxyphenyl)-3-hydroxypropionyl]-β-alanyl-β-alanine methyl ester (31):** a white solid (66%); mp 187−188 °C; IR (KBr) 3294, 1738, 1696, 1649 cm^{-1}; ^1H NMR (300 Hz, DMSO-d_6) δ 7.96 (t, 1 H, J = 5.4 Hz), 7.90 (t, 1 H, J = 5.1 Hz), 7.43−6.95 (m, 18 H), 5.49 (s, br, 1 H), 5.08 (s, 2 H), 5.05 (s, 2 H),

4.97 (d, 1 H, J = 12.9 Hz), 4.89 (d, 1 H, J = 12.9 Hz), 4.15 (dd, 1 H, J = 9.0, 3.0 Hz), 3.57 (s, 3 H), 3.23 (m, 4 H), 2.44 (t, 2 H, J = 6.9 Hz), 2.18 (t, 2 H, J = 6.6 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.5, 171.2, 170.5, 156.6, 148.6, 148.0, 138.1, 138.0, 137.7, 136.1, 129.1, 129.0, 128.5, 128.4, 128.3, 128.1, 127.9, 119.7, 114.5, 113.5, 72.8, 71.0, 70.8, 66.0, 61.9, 52.1, 36.1, 35.8, 35.4, 34.3; HRFABMS m/z calcd for $C_{38}H_{41}N_3O_9$ [M + Na]$^+$ 706.2741, found 706.2722.

***N*,*N*-[(2*S*,3*R*)-2-Benzyloxycarbonylamino-3-(2-benyloxyphenyl)-3-hydroxypropionyl]-*β*-alanyl-*β*-alanine methyl ester (32):** a colorless glass (54%); IR (neat) 3339, 1728, 1654 cm^{-1}; ^{1}H NMR (300 Hz, $CDCl_3$) δ 7.46−6.88 (m, 14 H), 6.89 (t, 1 H, J = 5.4 Hz), 6.48 (t, 1 H, J = 5.7 Hz), 5.85 (t, 1 H, J = 8.4 Hz), 5.58 (s, br, 1 H), 5.13 (d, 1 H, J = 11.4 Hz), 5.06 (d, 1 H, J = 11.7 Hz), 4.92 (s, 2 H), 4.57 (dd, 1 H, J = 8.4, 1.8 Hz), 4.21 (d, 1 H, J = 4.2 Hz), 3.61 (s, 3 H), 3.52−3.31 (m, 4 H), 2.48 (t, 2 H, J = 6.3 Hz), 2.26 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 171.8, 171.4, 156.8, 155.1, 136.9, 136.4, 128.9, 128.6, 128.5, 128.2, 128.0, 127.5, 127.1, 121.1, 111.6, 77.4, 70.3, 68.8, 67.1, 58.5, 52.1, 36.2, 35.2, 33.9; HRFABMS m/z calcd for $C_{31}H_{36}N_3O_8$ [MH]$^+$ 578.2502, found 578.2503.

***N*,*N*-[(2*S*,3*R*)-2-Benzyloxycarbonylamino-3-(3,4-dibenyloxyphenyl)-3-hydroxypropionyl]-*β*-alanyl-*β*-alanine (34).** To a solution of **30** (15.2 mg, 0.022 mmol) in CH_3CN/MeOH (1:1, 0.6 mL) was added a 1 N LiOH solution (0.033 mL, 0.033 mmol) at 0 °C. After being stirred at 0 °C for 3 h, the reaction mixture was diluted with H_2O (2 mL) and washed with Et_2O (3 × 2 mL). The aqueous layer was acidified to pH 3.0 with 10% citric acid and extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine (1 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford **34** as a white solid (6.4 mg, 43%): IR (neat) 3321, 1726 cm^{-1}; ^{1}H NMR (300 Hz, DMSO-d_6) δ 8.28 (t, 1 H, J = 5.1 Hz), 7.98 (t, 1 H, J = 5.4 Hz), 7.51−6.88 (m, 18 H), 5.26 (d, 1 H, J = 6.9 Hz), 5.14 (s, 2 H), 5.12 (s, 2 H), 5.06 (m, 2 H), 4.09(d, 2 H, J = 5.4 Hz), 3.59 (d, 1 H, J = 6.0 Hz), 3.22 (m, 4 H), 2.36 (t, 2 H, J = 6.6 Hz), 2.25 (m, 2 H); ^{13}C NMR (75 Hz, DMSO-d_6) δ 171.8, 171.0, 170.1, 158.6, 149.0, 148.8, 137.4, 137.3, 131.9, 128.8, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 126.9, 119.5, 114.6, 112.6, 80.0, 72.8, 70.7, 70.4, 61.7, 43.2, 36.0, 35.3, 35.2, 34.1; FABMS m/z calcd for $C_{37}H_{40}N_3O_9$ [MH]$^+$ 670, found 670.

***N*,*N*-[(2*S*,3*R*)-2-Benzyloxycarbonylamino-3-(2-benyloxyphenyl)-3-hydroxypropionyl]-*β*-alanyl-*β*-alanine (35).** To a solution of **31** (32.6 mg, 0.056 mmol) in THF/H_2O (1:1, 1 mL) was added a 1 N LiOH solution (0.085 mL, 0.085 mmol) at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was concentrated to remove the THF. The residue was diluted with H_2O (2 mL) and washed with Et_2O (2 × 2 mL). The aqueous layer was acidified to pH 3.0 with 10% citric acid and extracted with EtOAc (3 × 4 mL). The combined organic layers were washed with brine (2 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford **35** as a colorless glass (26.7 mg, 84%): IR (neat) 3307, 1718, 1652 cm^{-1}; ^{1}H NMR (300 Hz, $CDCl_3$) δ 7.43−6.82 (m, 14 H), 6.11 (d, 1 H, J = 8.7 Hz), 5.71 (d, 1 H, J = 3.6 Hz), 5.66 (s, br), 5.04 (m, 2 H), 4.91 (d, 1 H, J = 12.6 Hz), 4.82 (d, 1 H, J = 12.6 Hz), 4.65 (m, 1 H), 4.17 (d, 1 H, J = 3.6 Hz), 3.36 (m, 4 H), 2.44 (m, 2 H), 2.30 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 172.9, 172.5, 171.3, 160.2, 157.1, 155.7, 155.0, 137.1, 136.5, 136.4, 130.4, 129.1, 128.9, 128.7, 128.2, 128.0, 127.9, 127.4, 127.3, 127.0, 126.6, 121.4, 121.0, 112.3, 111.7, 77.6, 73.3, 70.7, 70.2, 68.6, 67.0, 61.7, 59.1; HRFABMS m/z calcd for $C_{30}H_{34}N_3O_8$ [MH]$^+$ 564.2346, found 564.2346.

***N*^{2}-Benzyloxycarbonyl-*N*^{2}-methyl-*N*^{5}-phenylmethylene-*N*^{5}-oxide-L-ornithine (5).** To a suspension of **36** (100.0 mg, 0.271 mmol) and MeI (0.135 mL, 2.162 mmol) in THF (4 mL) was added NaH (60%) (32.4 mg, 0.810 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 24 h and quenched with addition of MeOH. The mixture was concentrated under reduced pressure and partitioned between Et_2O (20 mL) and H_2O (8 mL). After separation of the layers, the aqueous layer was acidified to pH 3 with 1 N HCl and extracted with EtOAc (3 × 15 mL). The combined extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a pale yellow oil. After trituration from hexanes and Et_2O, **5** was obtained as a light yellow powder (71.8 mg, 85%): mp 106−108 °C; IR (neat) 1698, 1454 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, 70 °C) δ 8.31 (m, 1 H), 7.93 (s, 1 H), 7.51−7.38 (m, 10 H), 5.16 (s, 2 H), 4.57 (s, br), 4.01 (m, 2 H), 2.87 (s, 3 H), 1.96−1.78 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C) δ 173.8, 173.6, 157.5, 156.7, 137.4,137.2, 136.6, 131.5, 130.0, 129.7, 128.8, 128.8, 128.3, 128.2, 128.0, 67.9, 65.9, 58.0, 30.9, 25.6, 24.5; HRFABMS m/z calcd for $C_{21}H_{25}N_2O_5$ [MH]$^+$ 385.1763, found 385.1751.

***(S)*-3-Benzyloxycarbonylamino-1-hydroxypiperidin-2-one (37).** A mixture of **36** (3.7 g, 10 mmol), hexanes (20 mL), 0.5 N HCl (40 mL), and TFA (10 mL) was heated at 60 °C for 15 min. The reaction mixture was concentrated under reduced pressure to give a light yellow oil. To this residue were added CH_2Cl_2 (40 mL) and 1 N HCl (60 mL). The mixture was heated at 40 °C briefly to dissolve the residue and allowed to stir at room temperature for 40 min. After separation of the layers, the aqueous phase was washed with CH_2Cl_2 (3 × 10 mL) and hexanes (5 mL), filtered, and concentrated to give *N*^{2}-benzyloxycarbonyl-*N*^{5}-hydroxy-L-ornithine hydrochloride (2.62 g, 82%) as a white foam: ^{1}H NMR (300 MHz, D_2O) δ 7.43 (m, 5 H), 5.13 (s, 2 H), 4.21 (m, 1 H), 3.29 (m, 2 H), 1.99−1.78 (m, 4 H).

To a mixture of the above compound (524.0 mg, 1.645 mmol) in CH_3CN (100 mL) were added HOBt (266.5 mg, 1.809 mmol), $NaHCO_3$ (359.3 mg, 4.277 mmol), and EDC (377.0 mg, 1.974 mmol) at 0 °C, and the mixture was stirred at room temperature for 24 h. The mixture was concentrated under reduced pressure to give a light yellow residue. The residue was treated with EtOAc (70 mL) and washed with 10% citric acid (2 × 15 mL) and 5% $NaHCO_3$ (3 × 10 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give crude **37** (282.2 mg, 65%) as an off-white solid. An analytical sample was obtained as a white solid by reversed-phase chromatography (H_2O/MeOH, 2:1−1:2): IR (neat) 3307, 1706, 1649 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 5 H), 5.68 (d, 2 H, J = 6.0 Hz), 5.12 (s, 2 H), 4.25 (m, 1 H), 3.65 (m, 2 H), 2.39−1.70 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 156.6, 137.6, 128.7, 128.3, 128.2, 67.1, 51.8, 50.4, 28.1, 20.4; HRFABMS m/z calcd for $C_{13}H_{17}N_2O_4$ [MH]$^+$ 265.1188, found 265.1183.

***(S)*-3-Amino-1-hydroxypiperidin-2-one (6).** Compound **37** (1.638 g, 6.204 mmol) was stirred in MeOH (40 mL) in the presence of 10% Pd/C (163.8 mg) under H_2 (1 atm) for 1 h. After the compound was filtered through a reversed-phase silica plug, the solvent was removed under reduced pressure to produce **6** (0.81 g, 100%) as a white foam: IR (neat) 3352, 1634 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 3.61 (t, 2 H, J = 3.3 Hz), 3.50 (m, 1 H), 2.20−1.59 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 51.6, 50.8, 29.3, 20.7; HRFABMS m/z calcd for $C_5H_{11}N_2O_2$ [MH]$^+$ 131.0821, found 131.0827.

***N*^{5}-Benzyloxycarbonyl-*N*^{2}-*tert*-butyloxycarbonyl-*N*-[(*S*)-1-hydroxy-2-oxo-3-piperidyl]-L-ornithinamide (39).** To a stirred solution of **6** (1.892 g, 5.173 mmol) and HOAt (0.744 g, 5.691 mmol) in CH_2Cl_2 (6 mL) was added EDC (1.19 g, 6.201 mmol) at 0 °C. After being stirred at 0 °C for 15 min, compound **38** (0.800 g, 6.20 mmol) was added followed by the addition of DMAP (0.946 g, 7.755 mmol). The mixture was stirred at room temperature for 9 h, and TEA (0.719 mL, 5.174 mmol) was added. After the mixture was stirred for another 24 h, the solvent was removed under reduced pressure. The resulting residue was partitioned between 10% citric acid (10 mL) and EtOAc (30 mL). The aqueous layer was further extracted with EtOAc (2 × 10 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was purified by reversed-phase chromatography (2:1 MeOH/H_2O) to give **39** (1.285 g, 58%) as an off-white foam: IR (neat) 3309, 2480, 1690, 1655

cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.33 (m, 5 H), 7.03 (s, br, 1 H), 6.73 (m, 1 H), 5.10 (s, br, 1 H), 5.06 (s, 2 H), 4.43 (dd, 1 H, J = 5.1, 10.2 Hz), 4.06 (s, br, 1 H), 3.60 (m, 2 H), 3.15 (m, 2 H), 2.09−1.54 (m, 8 H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, CD_3OD) δ 173.7, 166.1, 157.9, 156.6, 137.3, 128.3, 127.8, 127.7, 79.4, 66.2, 57.2, 54.5, 51.5, 50.3, 40.3, 29.7, 27.6, 26.3, 26.0, 20.6, 17.3; HRFABMS *m/z* calcd for $C_{23}H_{35}N_4O_7$ [MH]$^+$ 479.2506, found 479.2523.

***N*^{5}-Benzyloxycarbonyl-(*N*^{2}-benzyloxycarbonyl-*N*^{2}-methyl-*N*^{5}-phenylmethylene-*N*^{5}-oxide-L-ornithyl)-*N*-[(*S*)-1-hydroxy-2-oxo-3-piperidyl]-L-ornithinamide (41).** To a stirred solution of **39** (1.968 g, 4.12 mmol) in CH_2Cl_2 (10 mL) was added TFA (8 mL) at 0 °C. After the mixture was stirred at room temperature for 40 min, the solvent was removed under reduced pressure to give the amine TFA salt (2.030 g, 100%) as a light yellow foam. Employing the procedure described for the preparation of **39**, reaction of **5** and the above salt afforded compound **41** as an off-white foam (0.949 g, 31%) after reversed-phase column chromatography (3:1 MeOH/H_2O): IR (neat) 3306, 1686 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (m, 1 H), 7.74−7.27 (m, 15 H), 5.65 (s, br, 1 H), 5.11 (s, 2 H), 5.02 (s, 2 H), 4.72 (m, 1 H), 4.51 (m, 1 H), 4.26 (m, 1 H), 3.89 (m, 2 H), 3.51 (m, 2 H), 3.16 (m, 2 H), 2.85 (s, 3 H), 2.03−1.45 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 172.0, 170.7, 165.0, 157.3, 157.0, 136.8, 136.4, 135.7, 130.8, 130.7, 130.5, 128.9 (2), 128.7, 128.6, 128.3, 128.2, 127.9, 67.8, 66.7, 66.2, 58.5, 52.6, 50.4, 50.3, 40.2, 30.5, 29.7, 27.5, 25.9, 25.3, 24.3, 20.5; HRFABMS *m/z* calcd for $C_{39}H_{49}N_6O_9$ [MH]$^+$ 745.3561, found 745.3549.

***N*^{5}-Benzyloxycarbonyl-[*N*^{2}-benzyloxycarbonyl-*N*^{5}-*N*-*N*-[(2*S*,3*R*)-2-benzyloxycarbonylamino-3-(2-benyloxyphenyl)-3-hydroxypropionyl]-*β*-alanyl-*β*-alanyl-*N*^{5}-hydroxy-*N*^{2}-methyl-L-ornithyl]-*N*-[(*S*)-1-hydroxy-2-oxo-3-piperidyl]-L-ornithinamide (42).** To a stirred solution of **41** (74.7 mg, 0.10 mmol) in MeOH (2 mL) was added hydroxylamine hydrochloride (7.7 mg, 0.11 mmol). The mixture was warmed to 60−70 °C and stirred for 20 min. The solution was concentrated under reduced pressure, and the resulting residue was triturated using MeOH and Et_2O to give **3** as a light yellow foam (519.4 mg, 75%) that was used without purification.

To a stirred solution of compound **3** (48.0 mg, 0.07 mmol), compound **35** (39.4 mg, 0.07 mmol), and BOP (31.1 mg, 0.07 mmol) in DMF (0.8 mL) was added DIPEA (9.2 mg, 0.07 mmol) dropwise at 0 °C. The mixture was stirred at 0 °C for 15 min and at room temperature overnight. The reaction mixture was treated with EtOAc (6 mL), washed with 5% $NaHCO_3$ (2 × 3 mL), 10% citric acid (2 × 3 mL), and brine (3 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by reversed-phase chromatography (3:1 MeOH/H_2O) to yield **42** (37.6 mg, 41%) as a light yellow foam: IR (neat) 3307, 1654 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.11 (m, 1 H), 7.90 (m, 2 H), 7.56−6.92 (m, 24 H), 5.59 (m, 1 H), 5.16 (s, 2 H), 5.09 (s, br, 2 H), 4.99 (s, 2 H), 4.87 (d, 1 H, J = 10.2 Hz), 4.83 (d, 1 H, J = 10.2 Hz), 4.60 (s, br, 1 H), 4.44 (d, 1 H, J = 8.4 Hz), 4.30 (m, 1 H), 4.22 (m, 1 H), 3.45 (m, 2 H), 3.34−3.25 (m, 6 H), 2.94 (m, 2 H), 2.80 (s, 3 H), 2.44 (m, 2 H), 2.17 (m, 2 H), 1.88−1.44 (m, 12 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.4, 171.2, 170.9, 170.5, 169.9, 164.6, 158.2, 156.1, 155.9, 155.3, 154.3, 137.2, 137.0, 136.9, 136.7, 130.5, 129.9, 128.4, 128.3, 128.2, 127.9, 127.7, 127.4, 127.3, 126.9, 126.8, 126.6, 120.6, 120.0, 112.6, 111.5, 79.2, 75.8, 69.4, 69.0, 66.8, 66.4, 65.1, 60.4, 59.3, 57.8, 52.2, 51.2, 50.8, 49.5, 46.8, 34.6, 32.3, 32.0, 29.4, 27.5, 25.8, 23.3, 20.3; HRFABMS *m/z* calcd for $C_{62}H_{76}N_9O_{16}$ [MH]$^+$ 1201.5332, found 1201.5298.

***N*^{5}-Benzyloxycarbonyl-(*N*^{2}-benzyloxycarbonyl-*N*^{5}-*N*,*N*-*tert*-butyloxycarbonyl-*β*-alanyl-*β*-alanyl-*N*^{5}-hydroxy-*N*^{2}-methyl-L-ornithyl)-*N*-[(*S*)-1-hydroxy-2-oxo-3-piperidyl]-L-ornithinamide (44).** To a stirred solution of compound **3** (131.6 mg, 0.192 mmol) and **43** (56.4 mg, 0.192 mmol) in DMF (2 mL) was added BOP (84.9 mg, 0.192 mmol). A solution of DIPEA (24.8 mg, 0.192 mmol) in DMF (0.3 mL) was added dropwise to the above solution at 0 °C, and the mixture was stirred at 0 °C for 15 min. After being stirred at room temperature overnight, the reaction mixture was concentrated under reduced pressure. The residue was treated with EtOAc, washed with 5% $NaHCO_3$ (2 × 3 mL), 10% citric acid (2 × 3 mL), brine (2 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was purified by reversed-phase chromatography (3:1 MeOH/H_2O) to generate **44** (62.4 mg, 31%) as a light yellow foam: IR (neat) 3306, 1653, 1540 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.09 (d, 1 H, J = 6.0 Hz), 7.97 (m, 1 H), 7.88 (m, 1 H), 7.35−7.24 (m, 10 H), 6.72 (m, 1 H), 5.09 (s, br, 2 H), 4.99 (s, 2 H), 4.60 (m, 1 H), 4.30 (m, 1 H), 4.21 (m, 1 H), 3.45 (m, 2 H), 3.40 (m, 2 H), 3.23 (t, 2 H, J = 7.2 Hz), 3.10 (m, 2 H), 2.95 (m, 2 H), 2.80 (s, 3 H), 2.51 (m, 2 H), 2.19 (t, 2 H, J = 7.5 Hz), 1.89−1.42 (m, 12 H), 1.36 (s, 9 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.4, 171.2, 171.0, 170.4, 170.3, 164.7, 156.1, 155.4, 137.2, 136.9, 128.3, 127.8, 127.3, 79.2, 77.6, 66.4, 65.1, 57.8, 52.2, 51.2, 50.8, 49.5, 46.8, 35.7, 34.6, 32.4, 32.0, 29.8, 29.4, 28.2, 27.5, 25.8, 23.4, 20.3; HRFABMS *m/z* calcd for $C_{43}H_{63}N_8O_{13}$ [MH]$^+$ 899.4515, found 899.4510.

***N*^{5}-Benzyloxycarbonyl-[*N*^{2}-benzyloxycarbonyl-*N*^{5}-*N*-*N*-[(2*S*,3*R*)-2-benzyloxycarbonylamino-3-(2-benyloxyphenyl)-3-hydroxypropionyl]-*β*-alanyl-*β*-alanyl-*N*^{5}-hydroxy-*N*^{2}-methyl-L-ornithyl]-*N*-[(*S*)-1-hydroxy-2-oxo-3-piperidyl]-L-ornithinamide (42).** To a stirred solution of compound **44** (32.4 mg, 0.036 mmol) in CH_2Cl_2 (1 mL) was added TFA (1 mL) at 0 °C. After being stirred at room temperature for 45 min, the mixture was concentrated under reduced pressure and azeotroped with toluene twice. To a mixture of the above residue, **28** (15.2 mg, 0.036 mmol), and BOP (15.9 mg, 0.036 mmol) in DMF (0.8 mL) was added DIPEA (0.006 mL, 0.02 mmol) dropwise at 0 °C. The mixture was stirred at 0 °C for 15 min and at room temperature overnight. The reaction mixture was treated with EtOAc (6 mL), washed with 5% $NaHCO_3$ (2 × 2 mL), 10% citric acid (2 × 2 mL), and brine (2 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by reverse-phase chromatography (3:1 MeOH/H_2O) to yield **42** (16.0 mg, 37%) as a light yellow foam.

***(S)*-3-Benzyloxycarbonylamino-1-benzyloxypiperidin-2-one (45).** To a stirred solution of **36** (370.0 mg, 1.0 mmol) in MeOH (10 mL) was added hydroxylamine hydrochloride (73.2 mg, 1.05 mmol). The mixture was refluxed for 20 min. To this solution were then added 3 Å molecular sieves and TEA (202.0 mg, 2.0 mmol). The mixture was refluxed for an additional 1 h and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure, and the resulting residue was partitioned between EtOAc (25 mL) and H_2O (8 mL). After separation of the layers, the organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a red residue.

To a solution of the above compound in DMF (1.5 mL) were added K_2CO_3 (1.38 g, 10.0 mmol) and BnBr (0.595 mL, 5.0 mmol). The reaction mixture was stirred at room temperature overnight and diluted with EtOAc (50 mL). This mixture was washed with H_2O (3 × 15 mL) and brine (15 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2/EtOAc, 8:1) to provide **45** as white needles (230.1 mg, 65%): $[\alpha]_D = -45°$ (c = 1.0, CH_2Cl_2); mp 86−88 °C; IR (neat) 3326, 1718, 1670 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 10 H), 5.72 (s, br, 1 H), 5.12 (s, 2 H), 4.95 (d, 1 H, J = 10.5 Hz), 4.90 (d, 1 H, J = 10.2 Hz), 4.17 (m, 1 H), 3.41 (m, 1 H), 3.33 (m, 1 H), 2.41 (m, 1 H), 1.86 (m, 1 H), 1.79 (m, 1 H), 1.55 (dq, 1 H, J = 12.3, 4.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 162.2, 136.8, 135.8, 129.7, 128.9, 128.6, 128.2, 76.1, 67.0, 52.9, 51.4, 28.3, 20.9; HRFABMS *m/z* calcd for $C_{20}H_{23}N_2O_4$ [MH]$^+$ 355.1658, found 355.1641.

***(S)*-3-Amino-1-benzyloxypiperidin-2-one Hydrobromide (46).** To a solution of **45** (350 mg, 1.0 mmol) in CH_2Cl_2 (8 mL) was added HBr (33% w/v in acetic acid) (8 mL). After

being stirred at room temperature for 1 h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (20 mL) and concentrated again. The residue was triturated using $CHCl_3$ and hexanes to give **46** as a white solid (276 mg, 92%): mp 194−195 °C; IR (KBr) 3436, 1676 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 7.47 (m, 5 H), 4.98 (m, 2 H), 4.07 (m, 1 H), 3.61 (m, 2 H), 2.27 (m, 1 H), 2.07 (m, 1 H), 1.95−1.82 (m, 2 H), ^{13}C NMR (75 MHz, D_2O) δ 165.0, 134.2, 130.2, 129.6, 129.0, 76.1, 50.5, 49.9, 24.9, 19.9; HRFABMS *m/z* calcd for $C_{12}H_{17}N_2O_2$ $[MH]^+$ 221.1290, found 221.1291.

***N*⁵-Benzyloxycarbonyl-*N*-[(*S*)-1-benzyloxy-2-oxo-3-piperidyl]-*N*²-*tert*-butyloxycarbonyl-L-ornithinamide (47).** To a stirred suspension of **46** (295.1 mg, 0.980 mmol), **38** (422.0 mg, 1.151 mmol), and HOAt (160.0 mg, 1.176 mmol) in CH_2Cl_2 (5 mL) were added EDC (262.1 mg, 1.372 mmol) and DMAP (311.3 mg, 2.546 mmol) at 0 °C. After being stirred at 0 °C for 15 min and room temperature overnight, the reaction mixture was treated with EtOAc (40 mL) and H_2O (10 mL). After separation of the layers, the organic layer was washed with 5% $NaHCO_3$ (2 × 15 mL), 10% citric acid (2 × 15 mL), and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography (2% MeOH/CH_2Cl_2) to give **47** (523 mg, 94%) as a white solid: IR (neat) 3308, 1698, 1525 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (m, 10 H), 5.37 (m, 2H), 5.08 (s, 2 H), 4.93 (d, 2 H, J = 10.5 Hz), 4.88 (d, 2 H, J = 10.5 Hz), 4.43 (m, 1 H), 4.29 (m, 1 H), 3.32 (m, 4 H), 2.19−1.62 (m, 8 H), 1.50 (s, 9 H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 167.7, 157.1, 137.0, 135.4, 129.7, 129.0, 128.7, 128.7, 128.3, 128.2, 79.9, 76.1, 66.8, 53.7, 51.3, 40.2, 30.6, 30.6, 28.6, 28.0, 26.1, 21.1; HRFABMS *m/z* calcd for $C_{30}H_{41}N_4O_7$ $[MH]^+$ 569.2975, found 569.2981.

***N*⁵-Benzyloxycarbonyl-*N*-[(*S*)-1-benzyloxy-2-oxo-3-piperidyl]-L-ornithinamide (48).** To a solution of compound **47** (204.5 mg, 0.423 mmol) in CH_2Cl_2 (2 mL) was added TFA (2 mL) at 0 °C. After being stirred at room temperature for 40 min, the solution was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL), washed with 5% $NaHCO_3$ (2 × 6 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give **48** as a colorless glass (182.3 mg, 92%): IR (neat) 3316, 1660, 1254 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, 1 H, J = 6.9 Hz), 7.41−7.14 (m, 10 H), 5.57 (t, 2 H, J = 5.7 Hz), 5.06 (s, 2 H), 4.92 (d, 2 H, J = 10.5 Hz), 4.89 (d, 2 H, J = 10.5 Hz), 4.39 (m, 1 H, J = 6.3 Hz), 3.39 (m, 1 H), 3.29 (m, 2 H), 3.16 (m, 2 H), 2.24−1.50 (m, 8 H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 168.0, 156.9, 137.0, 135.4, 129.7, 129.2, 129.0, 128.7, 128.4, 128.3, 128.2, 76.1, 66.7, 54.9, 51.3, 51.1, 40.8, 32.5, 28.1, 26.2, 21.1; HRFABMS *m/z* calcd for $C_{25}H_{33}N_4O_5$ $[MH]^+$ 469.2451, found 469.2444.

***N*⁵-Benzyloxycarbonyl-(*N*²-benzyloxycarbonyl-*N*²-methyl-*N*⁵-phenylmethylene-*N*⁵-oxide-L-ornithyl)-*N*-[(*S*)-1-benzyloxy-2-oxo-3-piperidyl]-L-ornithinamide (49).** To a mixture of **48** (110.0 mg, 0.235 mmol), **5** (99.3 mg, 0.258 mmol), and HOAt (38.4 mg, 0.282 mmol) in CH_2Cl_2 (4 mL) was added EDC (58.4 mg, 0.305 mmol) at 0 °C. After being stirred at 0 °C for 15 min and room temperature overnight, the reaction mixture was diluted with EtOAc (15 mL) and H_2O (4 mL). After separation of the layers, the organic layer was washed with 5% $NaHCO_3$ (2 × 4 mL), 10% citric acid (2 × 4 mL), and brine (3 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography (4% MeOH/CH_2Cl_2) to give **49** (177.2 mg, 92%) as a white solid: IR (neat) 3307, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (m, 1 H), 7.36 (m, 20 H), 5.40 (m, 1H), 5.12 (s, 2 H), 5.05 (s, 2 H), 4.90 (d, 2 H, J = 10.5 Hz), 4.86 (d, 2 H, J = 10.5 Hz), 4.73 (m, 1 H), 4.59 (m, 1 H), 4.40 (m, 1 H), 3.92 (m, 2 H), 3.38−3.09 (m, 4 H), 2.87 (s, 3 H), 2.13−1.48 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 170.7, 167.6, 157.5, 157.2, 136.9, 136.6, 135.4, 135.1, 130.7, 129.7, 129.0, 128.9, 128.8, 128.8, 128.7, 128.4, 128.2, 128.1, 76.1, 68.0, 66.9, 66.4, 58.7, 52.4, 51.3, 40.0, 30.5, 30.1, 28.0, 26.1, 25.2, 24.4, 21.2; HRFABMS *m/z* calcd for $C_{46}H_{55}N_6O_9$ $[MH]^+$ 835.4031, found 835.4027.

***N*⁵-Benzyloxycarbonyl-(*N*⁵-benzyloxy-*N*²-benzyloxycarbonyl-*N*⁵-*N*,*N*-*tert*-butyloxycarbonyl-*β*-alanyl-*β*-alanyl-*N*²-methyl-L-ornithyl)-*N*-[(*S*)-1-benzyloxy-2-oxo-3-piperidyl]-L-ornithinamide (50).** To a stirred solution of **49** (332.2 mg, 0.398 mmol) in MeOH (5 mL) was added hydroxylamine hydrochloride (29.1 mg, 0.418 mmol). The mixture was warmed to 60−70 °C and stirred for 20 min. The solution was concentrated under reduced pressure, and the resulting residue was triturated with MeOH and Et_2O to give the hydroxylamine hydrochloride derivative (263.7 mg, 85%) as a white foam.

To a stirred solution of the above compound (260.6 mg, 0.333 mmol) and **43** (86.6 mg, 0.333 mmol) in CH_3CN/DMF (3:1, 2 mL) were added BOP (147.3 mg, 0.333 mmol) and DMAP (488.2 mg, 0.333 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min and at room temperature overnight. The reaction mixture was concentrated under reduced pressure and partitioned between EtOAc (45 mL) and H_2O (10 mL). The organic phase was further washed with 5% $NaHCO_3$ (2 × 8 mL), 10% citric acid (2 × 4 mL), and brine (3 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. To a solution of the above residue in DMF (1 mL) were added K_2CO_3 (229.8 mg, 1.665 mmol) and BnBr (0.158 mL, 1.332 mmol). After being stirred at room temperature overnight, the suspension was diluted with EtOAc (25 mL) and washed with H_2O (3 × 15 mL) and brine (15 mL). After separation of the layers, the organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (1−4% MeOH/CH_2Cl_2) to provide **50** as a white solid (266.1 mg, 74% for two steps): IR (neat) 3308, 1656, 1529 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−6.97 (m, 20 H), 5.32 (m, 1 H), 5.14 (s, 2 H), 5.07 (s, 2 H), 4.90 (d, 2 H, J = 10.5 Hz), 4.87 (d, 2 H, J = 10.5 Hz), 4.76 (m, 2 H), 4.55 (m, 1 H), 4.40 (m, 1 H), 3.96 (m, 1 H), 3.42−3.13 (m, 10 H), 2.89 (s, 3 H), 2.33 (m, 2 H), 2.07 (m, 2 H), 1.86−1.45 (m, 12 H), 1.39 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 171.4, 167.5, 157.3, 156.3, 136.9, 136.7, 135.4, 134.3, 129.7, 129.6, 129.4, 129.0, 128.8, 128.7, 128.7, 128.4, 128.2, 128.0, 79.2, 77.6, 76.7, 76.2, 67.9, 66.9, 57.9, 52.2, 44.2, 51.3, 40.0, 37.0, 36.0, 35.0, 32.5, 30.3, 30.1, 28.7, 28.0, 26.1, 25.2, 23.7, 21.2; HRFABMS *m/z* calcd for $C_{57}H_{75}N_8O_{13}$ $[MH]^+$ 1078.5375, found 1078.5387.

***N*⁵-Benzyloxycarbonyl-(*N*⁵-benzyloxy-*N*²-benzyloxycarbonyl-*N*⁵,*N*-*β*-alanyl-*β*-alanyl-*N*²-methyl-L-ornithyl)-*N*-[(*S*)-1-benzyloxy-2-oxo-3-piperidyl]-L-ornithinamide (51).** To a solution of compound **50** (85.2 mg, 0.082 mmol) in CH_2Cl_2 (1.0 mL) was added TFA (1.0 mL) at 0 °C. The reaction mixture was stirred at room temperature for 40 min and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) and washed with 5% $NaHCO_3$ (2 × 3 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give **51** as an oily solid (68.1 mg, 87%): IR (neat) 3319, 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (m, 1 H), 7.36−7.16 (m, 20 H), 5.36 (m, 1 H), 5.14 (s, 2 H), 5.07 (s, 2 H), 4.90 (d, 2 H, J = 10.5 Hz), 4.87 (d, 2 H, J = 10.5 Hz), 4.76 (m, 2 H), 4.55 (m, 1 H), 4.36 (m, 1 H), 3.82 (m, 1 H), 3.47−3.32 (m, 6 H), 3.13 (m, 2 H), 2.97 (t, 2 H, J = 6.0 Hz), 2.87 (s, 3 H), 2.33 (t, 2 H, J = 6.0 Hz), 2.17 (m, 2 H), 1.85−1.53 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 172.1, 171.4, 167.6, 156.8, 156.6, 136.9, 136.6, 135.4, 134.3, 129.8, 129.5, 129.4, 129.3, 129.0, 128.8, 128.8, 128.7, 128.5, 128.4, 128.3, 128.1, 125.8, 77.5, 76.7, 76.2, 67.9, 66.9, 58.1, 53.7, 51.4, 51.3, 40.0, 38.0, 38.4, 35.0, 32.5, 30.5, 30.0, 27.9, 26.1, 25.2, 23.4, 21.3; HRFABMS *m/z* calcd for $C_{52}H_{67}N_8O_{11}$ $[MH]^+$ 979.4929, found 979.4962.

General Procedure for the Final Coupling Reaction: *N*⁵-Benzyloxycarbonyl-[*N*⁵-benzyloxy-*N*²-benzyloxycarbonyl-*N*⁵,*N*,*N*-[(2*S*,3*S*)-2-benzyloxycarbonylamino-3-hydroxy-3-(4-imidazoylpropionyl)]-*β*-alanyl-*β*-alanyl-*N*²-methyl-L-ornithyl]-*N*-[(*S*)-1-benzyloxy-2-oxo-3-piperidyl]-

L-ornithinamide (52). To a solution of **24** (115.7 mg, 0.379 mmol) and $NaHCO_3$ (79.6 mg, 0.948 mmol) in H_2O (2 mL) was added CbzCl (0.057 mL, 0.398 mmol) dropwise with vigorous stirring at room temperature. After the mixture was stirred for 30 min, the same amounts of $NaHCO_3$ and CbzCl were added again. After an additional 30 min, the suspension was washed with Et_2O (2 × 3 mL). The aqueous layer was acidified to pH 3 with 10% citric acid and extracted with EtOAc (4 × 3 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give crude **25** as a clear glass (143.2 mg, 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1 H), 7.40 (m, 5 H), 7.32 (s, 1 H), 7.26 (m, 5 H), 6.01 (d, J = 8.4 Hz, 1 H), 5.37 (m, 2 H), 5.32 (m, 1 H), 5.01 (m, 2 H), 4.70 (m, 1 H).

To a solution of crude **25** (36.1 mg, 0.082 mmol), **51** (80.2 mg, 0.082 mmol), and HOAt (19.5 mg, 0.102 mmol) in CH_2Cl_2 (2 mL) was added EDC (19.5 mg, 0.102 mmol) at 0 °C. The mixture was stirred at 0 °C for 15 min and at room temperature overnight. The reaction mixture was treated with EtOAc (6 mL) and H_2O (2 mL). After separation of the layers, the organic phase was washed with 5% $NaHCO_3$ (2 × 3 mL), 10% citric acid solution (2 × 3 mL), and brine (3 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (5% MeOH/CH_2Cl_2) to produce **52** (45.6 mg, 44%) as a white solid: IR (neat) 3307, 1654 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.19 (m, 25 H), 7.19 (d, 2 H, J = 7.2 Hz), 6.85 (d, 2 H, J = 7.2 Hz), 5.22 (s, br, 1 H), 5.10−4.97 (m, 6 H), 4.88 (d, 2 H, J = 9.9 Hz), 4.84 (d, 2 H, J = 10.2 Hz), 4.76 (m, 2H), 4.57−3.96 (m, 3 H), 3.42−3.13 (m, 10 H), 2.89 (s, 3 H), 2.33 (m, 2 H), 2.26 (m, 2 H), 2.06−1.51 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 172.0, 171.8, 170.8, 170.6, 167.5, 157.1, 156.8, 148.6, 137.1, 136.6, 135.4, 134.2, 131.5, 129.7, 129.5 (2), 129,4, 129.1, 129.0, 128.7, 128.3, 128.2 (2), 127.7, 127.3, 127.0, 114.8, 77.4, 76.5, 76.2, 70.1, 68.6, 67.9, 67.2, 67.0, 66.8, 58.0, 52.1, 51.3, 43.8, 40.1, 36.6, 36.3, 35.1, 34.0, 32.6, 30.5, 28.0, 26.1, 25.0, 23.4, 21.2; FABMS m/z calcd for $C_{66}H_{80}N_{11}O_{15}$ $[MH]^+$ 1266, found 1266.

***N*^{5}-Benzyloxycarbonyl-[*N*^{5}-benzyloxy-*N*^{2}-benzyloxycarbonyl-*N*^{5}-*N*-*N*-[(2*S*,3*R*)-2-benzyloxycarbonylamino-3-(4-benzyloxyphenyl)-3-hydroxypropionyl]-*β*-alanyl-*β*-alanyl-*N*^{2}-methyl-L-ornithyl]-*N*-[(*S*)-1-benzyloxy-2-oxo-3-piperidyl]-L-ornithinamide (53):** a white solid (64%); IR (neat) 3314, 1652, 1513 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.19 (m, 32 H), 6.85 (d, 2 H, J = 8.1 Hz), 6.48 (m, 1 H), 6.16 (m, 1 H); 5.39 (m, 1 H), 5.25 (s, br, 1 H), 5.10 (m, 2 H), 5.02 (m, 2 H), 4.97 (s, 2 H), 4.88−4.75 (m, 4 H), 4.57 (m, 1 H), 4.41 (m, 1 H), 3.92 (s, br, 1 H), 3.58 (m, 2 H), 3.40 (m, 2 H), 3.31 (m, 2 H), 3.16 (m, 2 H), 2.84 (s, 3 H), 2.52 (m, 2 H), 2.39 (m, 2 H), 2.16 (m, 2 H), 2.00−1.50 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 172.0, 170.9, 167.5, 158.4, 157.2, 157.1, 156.8, 137.2, 136.8, 136.6, 135.3(2), 134.2, 132.8, 129.7, 129.6, 129.4, 129.3, 129.0, 128.9, 128.8, 128.7(2), 128.6, 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 127.4, 127.2, 114.7, 77.4, 76.5, 76.0, 72.4, 70.1, 67.9, 67.1, 66.8, 60.9, 57.9, 52.1, 51.2, 40.0, 36.6, 36.0, 35.2, 32.6, 30.5, 38.0, 27.8, 25.8, 23.4, 23.0, 21.1; FABMS m/z calcd for $C_{76}H_{88}N_9O_{16}$ $[MH]^+$ 1382, found 1382.

***N*^{5}-Benzyloxycarbonyl-[*N*^{5}-benzyloxy-*N*^{2}-benzyloxycarbonyl-*N*^{5},*N*,*N*-[(2*S*,3*R*)-2-benzyloxycarbonylamino-3-(3,4-dibenzyloxyphenyl)-3-hydroxypropionyl]-*β*-alanyl-*β*-alanyl-*N*^{2}-methyl-L-ornithyl]-*N*-[(*S*)-1-benzyloxy-2-oxo-3-piperidyl]-L-ornithinamide (54):** a white solid (72%); IR (neat) 3315, 1652, 1515 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.05 (m, 36 H), 6.85 (dt, 2 H, J = 8.7, 13.8 Hz), 6.52 (m, 1 H), 6.02 (m, 1 H); 5.37 (m, 1 H), 5.26 (m, 1 H), 5.11 (m, 2 H), 5.06 (m, 4 H), 4.95 (s, 2 H), 4.90−4.73 (m, 4 H), 4.40 (m, 2 H), 3.92 (s, br, 1 H), 3.55 (m, 2 H), 3.41 (m, 2 H), 3.38 (m, 2 H), 3.11 (m, 2 H), 2.84 (s, 3 H), 2.37 (m, 2 H), 2.08 (m, 2 H), 1.97−1.49 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 172.0, 171.9, 171.2, 170.4, 167.5, 157.1, 156.7, 149.0, 148.5, 137.6, 137.5, 136.8, 136.5, 135.3, 134.2, 133.9, 129.7, 129.6, 129.4, 129.3, 129.0, 128.7, 128.6, 128.3, 128.2, 128.0, 127.9, 127.6, 127.4, 119.2, 114.9, 113.0, 77.4, 76.4, 76.1, 72.5, 71.3, 67.9, 67.1, 66.8, 60.9, 57.9, 52.3, 51.2, 43.7, 40.1, 36.5, 35.9, 35.2, 32.7, 30.5, 27.8, 26.2, 25.9, 24.7, 23.0, 21.1; FABMS m/z calcd for $C_{83}H_{94}N_9O_{17}$ $[MH]^+$ 1488, found 1488.

***N*^{5}-Benzyloxycarbonyl-[*N*^{5}-benzyloxy-*N*^{2}-benzyloxycarbonyl-*N*^{5},*N*,*N*-[(2*S*,3*R*)-2-benzyloxycarbonylamino-3-(2-benzyloxyphenyl)-3-hydroxypropionyl]-*β*-alanyl-*β*-alanyl-*N*^{2}-methyl-L-ornithyl]-*N*-[(*S*)-1-benzyloxy-2-oxo-3-piperidyl]-L-ornithinamide (55):** a colorless glass (84%); IR (neat) 3319, 1656, 1528 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.14 (m, 32 H), 6.85 (m, 2 H), 6.62 (m, 1 H), 6.18 (m, 1 H); 5.60 (m, 1 H), 5.36 (m, 1 H), 5.12 (m, 2 H), 5.08 (s, 2 H), 5.04 (m, 2 H), 4.88−4.74 (m, 4 H), 4.64 (d, 1 H, J = 7.5 Hz), 4.58 (m, 1 H), 4.40 (m, 1 H), 3.92 (s, br, 1 H), 3.48 (m, 2 H), 3.40 (m, 2 H), 3.28 (m, 2 H), 3.08 (m, 2 H), 2.83 (s, 3 H), 2.52 (m, 2 H), 2.28 (m, 2 H), 2.07 (m, 2 H), 1.84−1.48 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 171.8, 171.6, 171.1, 167.6, 157.3, 157.0, 154.9, 137.0, 136.9, 136.5, 135.3, 134.3, 129.7, 129.5, 129.4, 129.3, 129.0, 128.8, 128.7, 128.6, 128.3, 128.1, 128.0, 127.9, 127.4, 127.2, 120.9, 111.4, 77.4, 76.3, 75.9, 70.1, 68.6, 67.9, 66.9, 66.7, 58.7, 57.9, 53.6, 52.4, 51.1, 43.8, 40.2, 36.6, 36.0, 35.0, 32.9, 30.6, 30.4, 27.7, 25.5, 21.1; FABMS m/z calcd for $C_{76}H_{88}N_9O_{16}$ $[MH]^+$ 1382, found 1382.

General Procedure for Deprotection: *N*^{5}-Hydroxy-*N*^{5},*N*-(*N*-*threo*-*β*-hydroxy-L-histidyl)-*β*-alanyl-*β*-alanyl-*N*^{2}-methyl-L-ornithyl-*N*-(*S*)-(1-hydroxy-2-oxo-3-piperidyl)-L-ornithinamide (1a). To a solution of **52** (51.7 mg, 0.037 mmol) in MeOH (2 mL) was added 10% $Pd(OH)_2$/C (42.1 mg). The reaction mixture was stirred under H_2 (1 atm) for 1 h and filtered through a reversed-phase silica plug. The filtrate was acidified to pH 6−7 with 1 N HCl, filtered, and concentrated under reduced pressure to give a light red glass. The product was further purified by reversed-phase chromatography (1% TFA in H_2O/MeOH, 10:1) and HPLC (2% MeOH/H_2O, 1% TFA at 1 mL min^{-1}, monitored at 221 nm) to give **1a** as a pink solid (9.1 mg, 36%): IR (neat) 3400, 1650 cm^{-1}; ^{1}H NMR (600 MHz, D_2O) δ 8.06 (s, 1 H Hz, Im), 7.56 (s, 1 H, Im), 4.96 (d, 1H, J = 3.3 Hz ImC*H*OH), 4.32 (m, 1 H, NHC*H*CO), 4.13 (m, 1 H, COC*H*NH_2), 3.81 (m, 2 H, 2 × NHC*H*CO), 3.50 (m, 4 H, 2 × CH_2NOH), 3.23 (m, 2 H, CH_2NH_2), 3.17 (t, 2 H, J = 6.0 Hz, CH_2NHCO), 2.89 (t, 2 H, J = 6.0 Hz, CH_2NHCO), 2.55 (s, 3 H, NCH_3), 2.11 (m, 2 H, CH_2CONH), 1.93 (m, 2 H, CH_2CONH), 1.88−1.52 (m, 12 H, 3 × CHCH_2CH_2CH_2); ^{13}C NMR (150 MHz, D_2O) δ 169.5, 168.5, 167.3, 164.6, 162.6, 159.3, 131.5, 120.2, 116.6, 66.3, 56.9, 49.9, 47.8, 46.4, 43.9, 43.3, 35.0, 31.5, 31.2, 31.0, 27.7, 24.0, 23.1, 22.7, 19.3, 17.3, 16.2; HRFABMS m/z calcd for $C_{28}H_{50}N_{11}O_9$ $[M + Na]^+$ 706.3612, found 706.3629.

***N*^{5},*N*,*N*-[(2*S*,3*R*)-2-Amino-3-hydroxy-3-(4-hydroxyphenyl)propionyl]-*β*-alanyl-*β*-alanyl-*N*^{5}-hydroxy-*N*^{2}-methyl-L-ornithyl-*N*-(*S*)-(1-hydroxy-2-oxo-3-piperidyl)-L-ornithinamide (1b):** HPLC (2% MeOH/H_2O, 1% TFA at 1 mL min^{-1}, monitored at 283 nm); a pink solid (67%); UV (MeOH) λ_{max} 283 nm; IR (neat) 3234, 1672, 1201 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.18 (dd, 2 H, J = 1.8, 8.7 Hz, Ar), 6.77 (dd, 2 H, J = 1.5, 8.7 Hz, Ar), 4.77 (m, 2H, NHC*H*CO, ArC*H*OH), 4.41 (m, 1 H, NHC*H*CO), 3.87 (m, 1 H, NHC*H*CO), 3.77 (d, 1 H, J = 7.8 Hz, COC*H*NH_2), 3.61 (m, 2 H, CH_2NOH), 3.38 (m, 2 H, CH_2NOH), 3.23 (m, 4 H, 2 × CH_2NHCO), 2.95 (m, 2 H, CH_2-NH_2), 2.64 (s, 3 H, NCH_3), 2.45 (t, 2 H, J = 6.6 Hz, CH_2CONH), 2.18 (m, 2 H, CH_2CONH), 2.10−1.67 (m, 12 H, 3 × CHCH_2CH_2-CH_2); ^{13}C NMR (75 MHz, CD_3OD) δ 173.0, 171.8, 167.9, 160.4, 159.9, 157.9, 130.1, 118.0, 115.3, 114.2, 72.5, 61.0, 59.9, 53.2, 51.9, 50.4, 39.0, 35.7, 35.2, 35.0, 33.4, 32.2, 31.3, 28.7, 28.3, 27.5, 23.7, 21.7, 20.2; HRFABMS m/z calcd for $C_{31}H_{52}N_9O_{10}$ $[MH]^+$ 710.3837, found 710.3818.

***N*^{5},*N*,*N*-[(2*S*,3*R*)-2-Amino-3-hydroxy-3-(3,4-dihydroxyphenyl)propionyl]-*β*-alanyl-*β*-alanyl-*N*^{5}-hydroxy-*N*^{2}-methyl-L-ornithyl-*N*-(*S*)-(1-hydroxy-2-oxo-3-piperidyl)-L-ornithinamide (1c):** HPLC (2% MeOH/H_2O, 1% TFA at 1 mL min^{-1}, monitored at 283 nm); a pink glass (44%); IR (neat) 3235, 1670, 1200 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 6.79−6.67 (m, 3 H, Ar), 4.70 (m, 1 H, J = 7.2 Hz, ArC*H*OH), 4.40

(m, 2 H, 2 × NHC*H*CO), 3.89 (m, 1 H, NHC*H*CO), 3.73 (d, 1 H, J = 7.2 Hz, COC*H*NH_2), 3.59 (m, 2 H, CH_2NOH), 3.37 (m, 2 H, CH_2NOH), 3.23 (m, 4 H, 2 × CH_2NHCO), 2.92 (m, 2 H, CH_2NH_2), 2.64 (s, 3 H, NCH_3), 2.19 (m, CH_2CONH), 2.09 (m, 2 H, CH_2CONH), 1.98−1.69 (m, 12 H, 3 × CHCH_2CH_2CH_2); ^{13}C NMR (75 MHz, CD_3OD) δ 173.3, 172.2, 167.9, 166.9, 160.2, 159.7, 145.7, 145.4, 131.0, 118.1, 117.9, 115.3, 114.1, 113.7, 72.5, 61.0, 60.0, 53.2, 52.0, 50.4, 39.1, 35.8, 35.2, 35.1, 32.3, 31.3, 28.7, 28.3, 27.5, 23.7, 21.7, 20.2; HRFABMS m/z calcd for $C_{31}H_{52}N_9O_{11}$ $[MH]^+$ 726.3786, found 726.3754.

***N*^{5},*N*,*N*-[(2*S*,3*R*)-2-Amino-3-hydroxy-3-(2-hydroxyphenyl)propionyl]-*β*-alanyl-*β*-alanyl-*N*^{5}-hydroxy-*N*^{2}-methyl-L-ornithyl-*N*-(*S*)-(1-hydroxy-2-oxo-3-piperidyl)-L-ornithinamide (1d):** HPLC (2% MeOH/H_2O, 1% TFA at 1 mL min^{-1}, monitored at 283 nm); a pink solid (65%); IR (neat) 1670, 1202 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.37 (d, 1 H, J = 7.8 Hz, Ar), 7.16 (t, 1 H, J = 7.2 Hz, Ar), 6.90−6.78 (m, 2 H, Ar), 5.24 (d, 1 H, J = 6.0 Hz, ArC*H*OH), 4.43 (m, 2 H, 2 × NHC*H*CO), 4.09 (d, 1 H, J = 6.3 Hz, COC*H*NH_2), 3.92 (m, 1 H, NHC*H*CO), 3.64 (m, 2 H, CH_2NOH), 3.37 (t, 2 H, J = 7.2 Hz, CH_2NOH), 3.26 (m, 4 H, 2 × CH_2NHCO), 2.96 (m, 2 H, CH_2NH_2), 2.65 (m, 3 H, NCH_3), 2.47 (t, 2 H, J = 6.9 Hz, CH_2CONH), 2.27 (m, 2 H, CH_2CONH), 2.10−1.67 (m, 12 H, 3 × CHCH_2CH_2CH_2); ^{13}C NMR (75 MHz, CD_3OD) δ 172.2, 171.8, 167.7, 166.9, 158.9, 157.9, 130.1, 129.8, 129.1, 127.9, 115.3, 72.4, 61.0, 59.9, 53.3, 51.6, 51.1, 50.2, 39.2, 35.7, 35.2, 35.0, 34.7, 33.4, 32.3, 31.3, 28.8, 27.5, 23.5, 20.6; HRFABMS m/z calcd for $C_{31}H_{52}N_9O_{10}$ $[MH]^+$ 710.3837, found 710.3834.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all compounds listed in the Experimental Section except **11b** and **12b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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