Design and Synthesis of Plasmepsin I and Plasmepsin II Inhibitors with Activity in *Plasmodium falciparum*-Infected Cultured Human Erythrocytes

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A series of protease inhibitors targeted at the malarial enzymes plasmepsin I and II, and encompassing a basic hydroxyethylamine transition state isostere scaffold, was prepared. The substituents in the P1′ position were varied and the biological activities expressed in K_i-values ranged from 60 to >2000 nM. A more than 4-fold selectivity for either of the plasmepsins could be achieved. All of the active compounds exhibited high preference for the plasmepsins over cathepsin D, the most closely related human protease. A few active compounds were shown to inhibit parasite growth in cultured infected human erythrocytes. An ED_{50} value as low as 1.6 μM was observed for one of the inhibitors despite K_i values of 115 nM (Plm I) and 121 nM (Plm II).

Introduction

Malaria is one of the leading causes of morbidity and mortality in the tropics. The parasitic disease afflicts hundreds of millions of people and causes 0.7 to 2.7 million deaths per year.[1] Nearly all of the fatal cases are caused by *Plasmodium falciparum*. New efficient therapy is urgently needed since the parasite's resistance to conventional antimalarials such as chloroquine is increasing at an alarming rate.[2] In fact, some *P. falciparum* strains have now been identified that are resistant to all known antimalarial drugs, giving rise to a need for new macromolecular targets for malaria therapy. The plasmepsin aspartyl proteases of *P. falciparum*, hemoglobin-degrading enzymes located in the acidic parasite food vacuole, have been recognized recently as promising targets for drug intervention.[3,4] In 1996 the crystal structure of plasmepsin II complexed with pepstatin A was published.[5] In a subsequent structure-based design process,[5] with pepstatin A as lead, a series of phenylalanine-statin analogues were synthesized, and among these, the peptidic picoline derivative **1** exerted an impressive inhibitory activity (K_i = 0.56 nM) and a 38-fold selectivity over the structurally very similar human aspartyl protease cathepsin D (K_i = 21 nM) (Figure 1). This compound inhibited the growth of *P. falciparum* in culture, although with modest activity. As deduced from a frequency analysis of a large encoded combinatorial library containing the statine core structure,[6,7] a β-branched carbon is strongly preferred in the P2 position and a hydrophobic side-chain, such as a benzyl or isobutyl group, in the P1 position of a plasmepsin II inhibitor (Figure 2). In addition it has been suggested that the P2 and P3 substituents impart selectivity to statine-based inhibitors, and the most potent inhibitor in the encoded library, compound **2**, exhibited a K_i value of 50 nM and a 6-fold selectivity over cathepsin D. More recently Ellman's group used several iterative focused libraries to identify a series of very potent and selective plasmepsin II inhibitors: these lack the branched aliphatic P2 substituent present in **1** and **2** and contain a hydroxyethylamine core structure.[8] One of the most promising inhibitors from these libraries, compound **3** (a druglike molecule with an acceptable molecular weight) inhibited plasmepsin II and cathepsin D with K_i values of 4.3 nM and 63 nM, respectively. This compound and two structurally related potent inhibitors bearing amine groups were, in addition, found to be moderately more potent against plasmepsin I than plasmepsin II and were determined to have 1−2 μM IC_{50} values for inhibition of parasite growth in cultured parasite-infected human erythrocytes.

We were attracted by the high potency and selectivity of **1** and **3** and by the finding of Ellman's group that large P1′ substituents are readily accommodated in the flexible S1′ site of plasmepsin II. We decided to examine the bioactivity of compounds with the generic structure **4**. Compared to **1**, which exhibits a high plasmepsin II/cathepsin D selectivity, these compounds are characterized by (a) a transition state mimicking scaffold, comprising a basic secondary amine, (b) one prime side amino acid residue to minimize the size and the peptidic nature of the inhibitor, and (c) large P1′ substituents.

We herein report inhibitors with K_i-values in the 60−130 nM range exhibiting selectivity for plasmepsin II [K_i (Plm I)/K_i (Plm II) > 4] or alternatively selectivity for plasmepsin I [K_i (Plm II)/K_i (Plm I) > 4]. These inhibitors are devoid of activity in the cathepsin D assay.

Chemistry

The target compounds **6**, **11a**−**g**, **16a**−**d**, and **17a**−**d** were prepared as outlined in Schemes 1−4. The hy-

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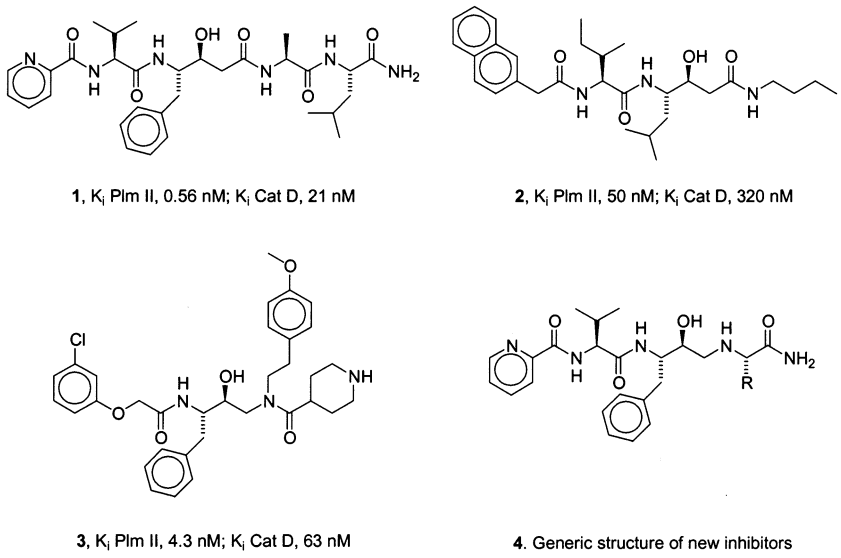
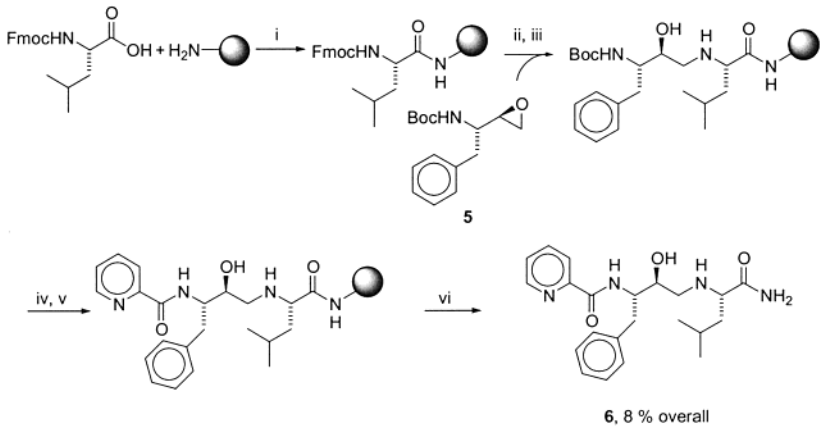


Figure 1.

Scheme 1[a]



[a] Reagents and conditions: (i) TBTU, DIEA, DMF, 2 h, rt; (ii) piperidine−DMF (1:4), 5 min, rt; (iii) *t*-BuOH, 24 h, 70 °C; (iv) TFA-CH_2Cl_2 (1:1), 10 min, rt; (v) picolinic acid, TBTU, DIEA, DMF, 1 h, rt; (vi) *hν*, DMF, 3 h, rt.

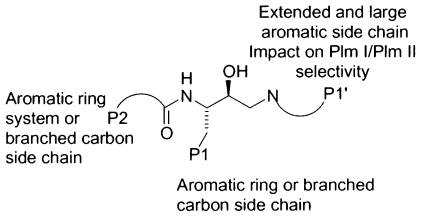
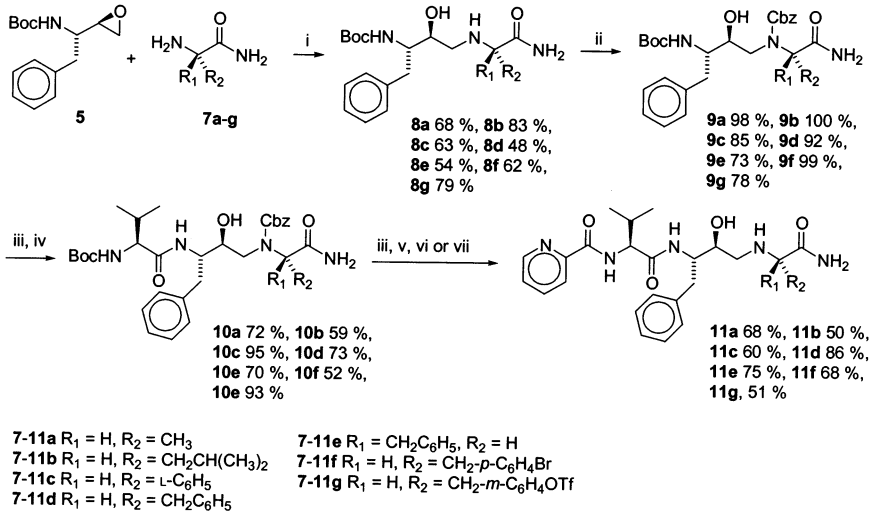


Figure 2. Strucural requirements of a hydroxyethylamine-based inhibitor of plasmepsin I and plasmepsin II.

droxyethylamine transition-state mimicking fragment was prepared by selective ring-opening of the chiral epoxide **5**,[9] with protected amino acids either on solid phase or in solution.

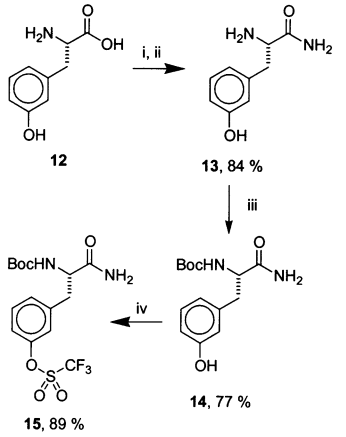
In the initial experiments we utilized solid-phase synthesis techniques and compound **6**, which lacks the valine residue, was selected as the first target molecule. Fmoc-protected leucine was coupled to a photosensitive linker attached to tentagel using TBTU as the coupling agent (Scheme 1).[10,11] The Fmoc-group was removed by treatment with piperidine and the resulting free amine was allowed to react with the epoxide **5**, which was prepared by the method of Romeo and Rich.[9] After subsequent removal of the Boc group with TFA, the liberated primary amine was coupled with picolinic acid. Cleavage from the resin by UV-light delivered **6**, which was then purified by preparative HPLC. The total yield for the reaction sequence was 8%. This low yield was accounted for by a predominant, competing acylation of the internal secondary amine rather than the terminal primary amine. Attempts were therefore made to protect the secondary amine either with a trifluoroacetyl or a Fmoc group prior to the reaction with the picolinic acid, but no significant improvement of the total yield was effected by these methods. The outcome from the solid-phase synthesis was not satisfying, and therefore for the preparation of **11a**−**g**, **16a**−**d**, and **17a**−**d**, solution chemistry was employed as an alternative. The epoxide **5** was warmed to 50 °C with the amino acid amides **7a**−**g** in 2-propanol overnight to deliver the Boc-derivatives **8a**−**g** (Scheme 2). The secondary amines were subsequently protected with the Cbz-group to give the compounds **9a**−**g**. After acid-mediated removal of the Boc-group, the resulting primary amines were coupled with Boc-protected valine using TBTU as the coupling agent to afford **10a**−**g**. After deprotection of the Boc group of the amines followed by coupling with picolinic acid, the Cbz-protecting group was removed by catalytic hydrogenation using Pd/C and ammonium

Scheme 2[a]



[a] Reagents and conditions: (i) 2-propanol, overnight, 50 °C; (ii) Cbz-Cl, Na_2CO_3, THF−H_2O (1:1), 30 min, rt; (iii) HCl, EtOAc, 15 min, rt; (iv) BocValOH, TBTU, DIEA, DMF, 2 h, rt; (v) picolinic acid, TBTU, DIEA, DMF, 1 h, rt; (vi) ammonium formate, Pd−C, EtOH, 1 h, rt; (vii) TfOH, anisole, CH_2Cl_2, 1 h, rt.

Scheme 3[a]



[a] Reagents and conditions: (i) AcCl−MeOH (1:4), overnight, rt; (ii) NH_3 (sat.), MeOH, overnight, rt; (iii) Boc_2O, $NaHCO_3$, THF−H_2O (1:1), overnight, rt; (iv) *N*-phenyltrifluoromethanesulfonimide, K_2CO_3, triethylamine, CH_2Cl_2, 30 min, reflux.

formate in ethanol. Alternatively, the deprotection could be conducted by acidic hydrolysis using triflic acid in methylene chloride, with anisole as a scavenger. All reactions employed to obtain **11a**−**g** proceeded in fair to good yields. Two of the target compounds, the *p*-bromo derivative **11f** and the *m*-trifluoromethanesulfonyloxy derivative **11g** were used for further functionalizations.

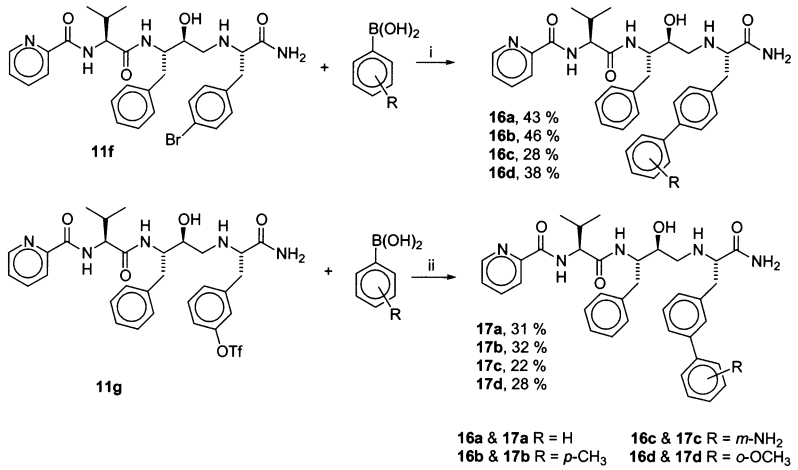
The starting material *p*-bromophenylalanine amide (**7f**) was prepared from *p*-bromophenylalanine by the formation of the methyl ester, followed by treatment with ammonia-saturated methanol in 98% total yield. The *m*-(trifluoromethanesulfonyloxy)phenylalanine amide (**7g**) was synthesized from commercially available DL-*m*-tyrosine (Scheme 3). After resolution according to the method of Tong et al,[12] the pure L-amino acid **12** was esterified using acetyl chloride in methanol, and the primary amide **13** was formed using ammonia in methanol. The primary amine function of **13** was Boc-protected, and the phenol function was thereafter transformed into the triflate ester using *N*-phenyltrifluoromethanesulfonimide, potassium carbonate, and triethylamine in methylene chloride to afford **15** in 89% yield. Removal of the Boc-group delivered **7g** used directly for ring-opening of the epoxide **5**.

For the preparation of **16a**−**d** and **17a**−**d** with biphenyl-extended P1′ groups, microwave-promoted Suzuki couplings were conducted.[13,14] Thus, **11f** and **11g** were reacted with four randomly chosen substituted phenylboronic acids (Scheme 4). For the synthesis of **16a**−**d**, a mixture of dimethoxyethane, ethanol and water was used as solvent. With **11g** as reactant, used for the synthesis of **17a**−**d**, the water was not used in the solvent mixture to avoid the unwanted hydrolysis of the triflate ester that otherwise occurred under the extreme flash heating conditions in the microwave cavity.

While investigating this Suzuki coupling with the Z-group still attached to the secondary amine, a spontaneous hydantoin ring formation was found to occur smoothly under the basic conditions employed.[15,16] This reaction was utilized for the synthesis of **18** and **19**: also potential plasmepsin inhibitors (Scheme 5). The coupled product from the deprotected compound **10e** and picolinic acid was stirred in ethanol with two equivalents of cesium carbonate for 1 h at room temperature, to give compound **18** in 45% total yield. A subsequent Suzuki coupling with phenylboronic acid using the same conditions as above gave compound **19** in 15% yield. The structural determination of **18** was performed using selective decoupling, COSY, HETCOR, COLOC, and selective INEPT NMR experiments.

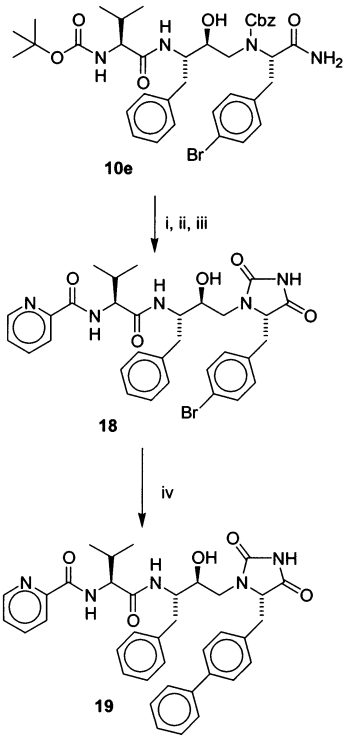
Biological Evaluation. To evaluate the enzyme inhibitory effects of compounds **6**, **11a**−**g**, **16a**−**d**, and **17a**−**d** plasmepsin I (Plm I), plasmepsin II (Plm II), and human cathepsin D (Cat D) were used. The results are summarized in Table 1. A picolinoyl (**6**) or Boc group (not shown) in the P2 position gave inactive inhibitors. An N-terminal P3 picolinic residue and valine at P2 enabled a series of compounds to be examined where the P1′ group had been altered (**11a**−**g**, **16a**−**d**, and **17a**−**d**). As demonstrated by the results obtained, appreciable activity is obtained only after incorporation

Scheme 4[a]



[a] Reagents and conditions: (i) $Pd(PPh_3)_2Cl_2$, Na_2CO_3, EtOH, DME, H_2O, 20 min, 140 °C, microwave irradiation. (ii) $Pd(PPh_3)_2Cl_2$, Cs_2CO_3, EtOH, DME, 20 min, 140 °C, microwave irradiation.

Scheme 5[a]



[a] Reagents and conditions: (i) TFA−CH_2Cl_2 (1:4), 15 min, rt; (ii) picolinic acid, TBTU, DIEA, DMF; (iii) 2 h, rt; Cs_2CO_3, EtOH, 1 h, rt; (iv) $PhB(OH)_2$, $Pd(PPh_3)_2Cl_2$, Cs_2CO_3, EtOH, DME, 20 min, 140 °C, microwave irradiation.

of a large group in the P1′ position. To illustrate this, even a phenylalanine residue at this position exhibits a very high K_i value in Plm I, Plm II in addition to the Cat D assays (**11c**). Also substitution with D-Phenylalanine yields essentially inactive inhibitors (**11d**). In contrast, substitutions in the 4-position of the phenyl group of phenylalanine with a bromine, a phenyl group, or with three differently substituted phenyl groups delivered inhibitors with activity both in the Plm I and Plm II assays (**11e** and **16a**−**d**). Furthermore, some of these compounds showed approximately 10- to 20-fold selectivity in these assays as compared to Cat D. Substitution with phenyl groups in the 3-position, rather than in the 4-position, provided derivatives with lower inhibitory activities in the Plm I assay (**17a**−**d**). One compound (**17c**) exhibited a 4-fold selectivity for Plm II over Plm I. Four compounds, **11f**, **16b**, **16c**, and **17c** were selected for studies of their ability to inhibit the growth of *P. falciparum* in infected red blood cells. The results are summarized in Table 1. Furthermore one compound, the biphenyl **16a** was subjected to an uptake study in Caco-2 cells and the result is presented in Table 1.

Discussion

The cleavage of the peptide bond is proposed to go via a tetrahedral intermediate bound to a protonated form of one of the aspartic acids in the active site of an aspartic protease. This mechanism is consistent with pH kinetics.[17] Prior to cleavage of the scissile bond, protonation of the substrate occurs on nitrogen, and then the generated zwitterionic intermediate collapses and liberates the products. Among all of the tetrahedral intermediate mimics previously disclosed, the noncyclic hydroxyethyl secondary amine transition state isostere in **4**, first exploited by Tucker for the design of HIV protease inhibitors,[18] seemed particularly attractive. Incorporating such an isostere should allow the protonated nitrogen to interact favorably with one of the catalytically active aspartic acids in Plm I and Plm II, respectively, as deduced by modeling. Furthermore it is anticipated that the presence of a basic nitrogen in plasmepsin inhibitors should be especially attractive considering the acidic environment in the vacuoles where the hemoglobin digestion occurs.

As demonstrated in Table 1 an expansion of the P1′-side-chain results in increased affinity for the aforementioned enzymes. The most marked effect is observed when hydrogen in the *para* position in compound **11d** is exchanged with bromine (**11f**). This manipulation leads to more than a 20-fold increase in Plm I inhibitory activity. In the Plm II assay this change has a lesser effect, thus **11f** is a moderately selective Plm I inhibitor.

The rigid biphenyl substituents in **16a**−**c** seem to be accommodated easily in the flexible S1′ pocket of both Plm I and II and the high selectivity ratio versus cathepsin D is retained. With one exception (**16d**) these compounds tend to be slightly more potent as Plm I

Table 1

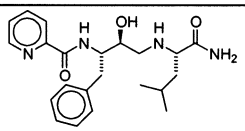
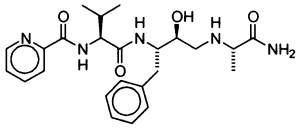
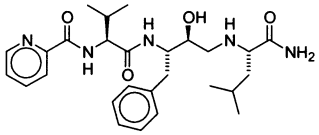
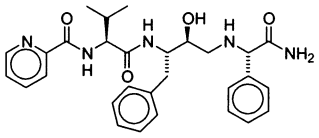
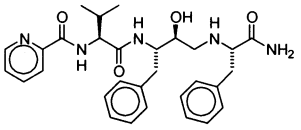
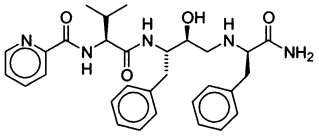
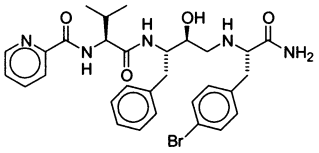
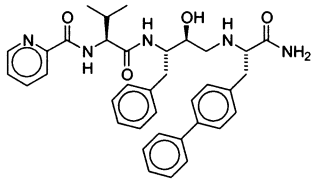
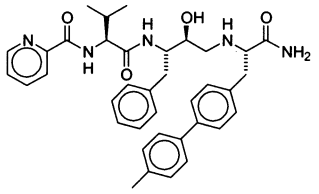
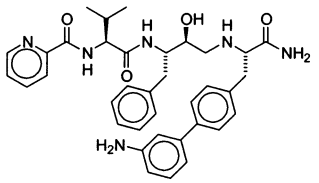
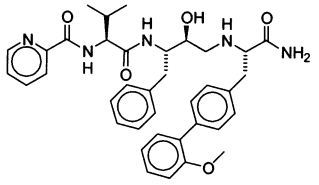
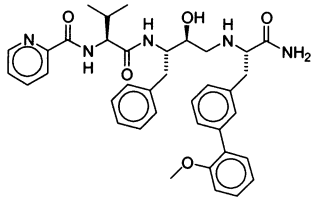
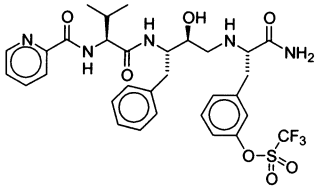
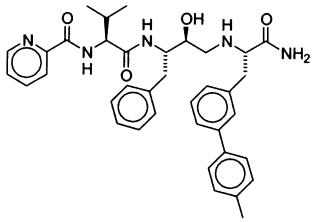
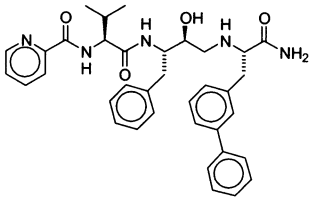
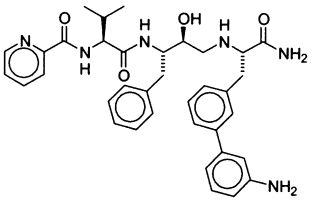
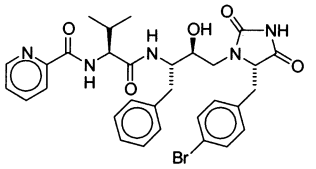
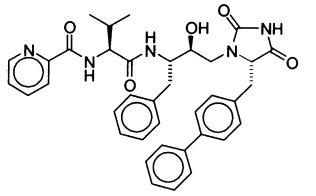
Structure	Compound	K_i (Plm I / nM)	K_i (Plm II / nM)	K_i (Cat D / nM)
	**6**	>2000	>2000	>2000
	**11a**	>2000	>2000	>2000
	**11b**	~2900	~3300	>2800
	**11c**	>2000	>2000	>2000
	**11d**	~2100	~3200	>2800
	**11e**	~8000	~3500	>2000
	**11f**[a]	98	540	>2000
	**16a**[b]	68	117	>2000
	**16b**[c]	115	121	~1700
	**16c**[d]	63	150	~1000
	**16d**	437	379	~1700

Table 1 (Continued)

Structure	Compound	K_i (Plm I / nM)	K_i (Plm II / nM)	K_i (Cat D / nM)
	**17d**	1300	1430	>2000
	**11g**	469	>2000	1700
	**17b**	1100	930	1900
	**17a**	1000	579	1600
	**17c**[e]	530	129	>2000
	**18**	>2000	1900	>2000
	**19**	2046	928	>2000

[a] Inhibition on *P. falciparum* infected red blood cells; 35% inhibition @ 5 μM; solubility at pH 7.5 = ~50 μM. [b] Permeability in Caco-2 cells determined; Papp value = 10.3×10^{-6} cm/s;[19] solubility at pH 7.5 = ~25 μM. [c] Inhibition on *P. falciparum* infected red blood cells; ED_{50} = 1.6 μM; solubility at pH 7.5 > 6 μM. [d] Inhibition on *P. falciparum* infected red blood cells; 77% inhibition @ 5 μM; solubility at pH 7.5 > 6 μM. [e] Inhibition on *P. falciparum* infected red blood cells; 69% inhibition @ 5 μM; solubility at pH 7.5 > 6 μM.

inhibitors than as Plm II inhibitors. The observation that the substitution with an *o*-methoxy group as in **16d** rendered an inhibitor with 6-fold lower activity in the Plm I assay as compared to **16a**, while the activity against Plm II was less affected (3-fold) suggested to us that fine-tuning of substituents in proximity to the bond between the aromatic rings could allow selective Plm II inhibitors to be made. Attachment of the *o*-methoxyphenyl ring to the 3 rather than 4-position of the P1′ phenylalanine residue provided an inhibitor, **17d**, with poor potency against both plasmepsins. The triflate, compound **11g**, from which **17d** was derived is also a selective Plm I inhibitor, although with only moderate potency (K_i = 469 nM). A comparison of the parent biphenyls **16a** (*para*) and **17a** (*meta*) reveals that **16a** is almost 2 times more active versus plasmepsin I, while the opposite is true for **17a**, which is more active in the plasmepsin II assay. Potency was gained by the

introduction of the *meta* amino group to **17a** (to give **17c**) and the selectivity versus Plm II was even more pronounced.

Thus it seems likely that further manipulation in the P1′ site of the inhibitors might give access to inhibitors with fair activity and with moderate selectivity for either one of the plasmepsins. With the assumption that inhibitors of the generic structure **4** have similar binding interactions in the nonprime side of both plasmepsins, the results herein suggest, that the character of the S1′ site of Plm I and Plm II differs considerably. In Figure 2, the characteristic features of hydroxyethylamine based Plm I/Plm II inhibitors are depicted.

With the objective of assessing whether partially selective inhibition of Plm I or Plm II has an impact on the parasite growth in infected red blood cells, we compared the structurally and physicochemically similar aniline-based inhibitors **16c** and **17c**. The dual Plm I/Plm II inhibitor **16c** resulted in 77% inhibition at 5 μM, while a 69% inhibition was obtained with the somewhat less potent and more selective Plm I inhibitor **17c** at the same concentration. The inhibitor **11f**, which exhibited the greatest Plm I/Plm II selectivity in the series achieved only 35% inhibition at 5 μM. Although many factors determine the outcome in blood cell assays, these results suggest that inhibition of Plm II might have a greater impact on parasite growth than inhibition of Plm I. However, it should be kept in mind that the parasite has an additional eight aspartyl proteases in its genome, of which at least two are both expressed and active in the hemoglobin degrading process.[19,20] The function of the other proteases remains partly unclear, but the compounds discussed herein might interact with any of these in addition to interacting with Plm I and Plm II. To assess the effect of the aniline amino group on activity, **16c** (solubility at pH 7.5 > 6 μM) was compared to the equipotent but more lipophilic plasmepsin inhibitor **16b** (solubility at pH 7.5 > 6 μM), with both having similar molecular weights. The latter suppressed parasite growth completely at 5 μM with an ED_{50} of 1.6 μM determined. The high potency in the infected blood assay is remarkable considering the K_i values of 115 nM (Plm I) and 121 nM (Plm II) in the enzyme assays.

One of the inhibitors in the series, the parent compound **16a** (solubility at pH 7.5 = ~25 μM, structurally similar to **16b**) was selected for an absorption study in Caco-2 cells. Good cell penetration was observed, suggesting that compounds containing the scaffold **4** might be suitable candidates for further development.[21]

Conclusion

In summary it has been demonstrated that rigid biphenyl side-chains furnish suitable extended P1′ substituents for the S1′ sites of both plasmepsin I and II. These biphenyls were prepared by fast microwave-promoted Suzuki couplings. While the S1′ site of Plm II seems to be able to accommodate both 3- and 4-substituted derivatives, the data suggests that 4-substituted derivatives are preferred in the S1′ site of Plm I, suggesting large steric differences in the S1′ sites of the two plasmepsins. We believe that access to selective plasmepsin inhibitors will provide valuable research tools for future efforts to elucidate the significance of the various aspartyl proteases in the lifecycle of *P. falciparum*. Although all compounds reported herein are less potent than **1** and **3** as plasmepsin II inhibitors, the relatively good activity observed on infected blood cells (e.g., **16b**, ED_{50} = 1.6 μM) despite only moderate activity in the enzyme assays is encouraging and suggests that further optimization of inhibitors of the generic structure **4** would be fruitful.

Experimental Section

Plasmepsin Assay and K_i Determination. Pro-plasmepsin II was a generous gift from Helena Danielson (Department of Biochemistry, Uppsala University, Uppsala, Sweden), and the expression and purification of plasmepsin I will be published elsewhere (manuscript in preparation). Human liver cathepsin D was purchased from Sigma-Aldrich, Sweden. The activities of plasmepsin I (Plm I), plasmepsin II (Plm II) and cathepsin D was measured essentially as described earlier,[8] using a total reaction volume of 100 μL. The concentration of pro-Plm II was 3 nM, the amount of Plm I was adjusted to give similar catalytic activity, and 50 ng/mL pro-cathepsin D was used. The pro-sequence of Plm II was cleaved off by preincubation in the assay reaction buffer (100 mM sodium acetate buffer [pH 4.5], 10% glycerol, and 0.01% Tween 20) at room temperature for 40 min, and Cathepsin D was activated by incubation in the same reaction buffer at 37 °C for 20 min. The reaction was initiated by the addition of 3 μM substrate (DABCYL-Glu-Arg-Nle-Phe-Leu-Ser-Phe-Pro-EDANS, AnaSpec Inc, San Jose, CA) and hydrolysis was recorded as the increase in fluorescence intensity over a 10 min time period, during which the rate increased in a linear fashion with time.

Stock solutions of inhibitors in DMSO were serially diluted in DMSO and added directly before addition of substrate, giving a final DMSO concentration of 1%.

IC_{50} values were obtained by assuming competitive inhibition and fitting a Langmuir isotherm ($v_i/v_o = 1/(1 + [I]/IC_{50})$) to the dose response data (Grafit), where v_i and v_o are the initial velocities for the inhibited and uninhibited reaction respectively and [I] is the inhibitor concentration.[22] The K_i was subsequently calculated by using $K_i = IC_{50}/(1 + [S]/K_m)$[23] and a K_m value determined according to Michaelis−Menten.

The *P. falciparum*-Infected Erythrocyte Assay was performed as earlier described by DesJardins et al.[24] The Caco-2 cell Penetration Assay was performed as earlier described by Artursson and Karlsson.[21]

General Procedures. All microwave reactions were conducted in heavy-walled glass Smith process vials sealed with aluminum crimp caps fitted with a silicon septum. The microwave heating was performed in a Smith Synthesizer single-mode microwave cavity producing continuous irradiation at 2450 MHz (Personal Chemistry AB, Uppsala, Sweden). Reaction mixtures were stirred with a magnetic stirring bar during the irradiation. The temperature, pressure, and irradiation power were monitored during the course of the reaction. After completed irradiation, the reaction tube was cooled with high-pressure air until the temperature had fallen below 39 °C. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX 270 spectrometer at 270.2 and 67.8 MHz, respectively, or on a JEOL JNM-EX400 spectrometer at 399.8 and 100.5 MHz, respectively. Chemical shifts are reported as δ values (ppm) indirectly referenced to TMS by the solvent residual signal. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter. Specific rotations ($[\alpha]_D$) are reported in deg/dm, and the concentration (c) is given in g/100 mL in the specified solvent. Elemental analysis were performed by Mikro Kemi AB, Uppsala, Sweden. Flash column chromatography was performed on Merck silica gel 60, 0.04−0.063 mm. Thin-layer chromatography was performed using aluminum sheets precoated with silica gel 60 F_{254} (0.2 mm; E. Merck) and visualized with UV light and ninhydrin. Analytical RP-LC-MS was performed on a Gilson HPLC system with a Zorbax SB−C8, 5 μm 4.6 × 50 mm (Agilent technologies) column, with a Finnigan AQA quadropole mass spectrometer, at a flow rate

of 1.5 mL/min. Preparative RP-LC-MS was performed on Gilson HPLC system with a Zorbax SB−C8, 5μm 21.2 × 150 mm (Agilent technologies) column, with a Finnigan AQA quadropole mass spectrometer, at a flow rate of 15 mL/min.

(2*S*,5*S*,6*R*)-3-Aza-5-hydroxy-2-isobutyl-7-phenyl-6-(picolylamino)heptanoyl Amide (6). P-linker 1 (0.2 g, loading 0.16 mmol/g),[10,11] FmocLeuOH (54 mg, 0.16 mmol), TBTU (52 mg, 0.16 mmol), and DIEA (54 μL, 0.32 mmol) were suspended in a Teflon test tube. DMF (5 mL) was added, and the mixture was allowed to stand for 2 h at room temperature with an occasional mixing. The solvent was filtered off, and the solid phase was washed three times with DMF (5 mL) and then suspended in 20% piperidine in DMF (5 mL) for 5 min. This solution was filtered off, and another 5 mL of 20% piperidine in DMF was added and filtered off after 5 min. The solid phase was washed three times with DMF (5 mL) and three times with MeOH (5 mL). (2*R*,3*S*)-3-[*N*-(*tert*-butyloxycarbonyl)amino]-1,2-epoxy-4-phenylbutane (**5**, 0.42 g, 0.32 mmol)[9] and *t*-BuOH (5 mL) were added, and the mixture was shaken for 24 h at 70 °C. The solvent was filtered off, and the solid phase was washed three times with MeOH, three times with DMF, and twice with CH_2Cl_2. A mixture of CH_2Cl_2 and TFA (1:1) was added, and the mixture was allowed to stand for 10 min. The solvents were filtered off, and the solid phase was washed three times with CH_2Cl_2, and three times with DMF. Picolinic acid (5.8 mg, 48 μmol), TBTU (16 mg, 48 μmol), DIEA (1.6 μL, 96 μmol), and DMF (5 mL) were added, and the mixture was allowed to stand for 1 h at room temperature. The solvent was filtered off, and the solid phase was washed three times with DMF (5 mL), twice with MeOH (5 mL), and twice with CH_2Cl_2 (5 mL). DMF (15 mL) was added to the solid phase, and it was subjected to UV-light for 3 h. The solid phase was filtered away and washed three times with DMF (5 mL) and three times with MeOH (5 mL), the solvents were pooled and evaporated, and the residue was purified by HPLC (Vydac C18, 22 × 250 mm, particle size 10 μm, gradient 20% → 60% AcCN in 0.1% TFA (aq), 30 min) to give **6** (6.4 mg, 8%), as a white solid. **6**: $[\alpha]^{22}_D = -51.3$ ($c = 0.4$, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 0.91−1.18 (m, 6 H, 2 CH_3), 1.59−1.87 (m, 3 H, $(CH_3)_2CHCH_2$), 2.83−3.15 (m, 4 H, C4H_2 and C7H_2), 3.76−3.90 (m, 1 H, C5H), 4.04−4.19 (m, 1 H, C6H), 4.28−4.51 (m, 1 H, C2H), 7.10−7.40 (m, 5 H, Ph-H), 7.50−7.67 (m, 1 H, C5H on pyridine), 7.88−8.11 (m, 2 H, C3H and C4H on pyridine), 8.58−8.72 (m, 1 H, C6H on pyridine). ^{13}C NMR (100.5 MHz, CD_3OD) δ 2.4, 23.0, 25.7, 38.5, 40.7, 50.6, 54.8, 60.4, 68.5, 123.3, 127.7, 128.1, 129.5, 130.3, 138.9, 139.0, 149.8, 150.2, 166.9, 171.4. Anal. ($C_{22}H_{30}N_4O_3 \cdot 0.5H_2O$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-6-[(*tert*-butyloxycarbonyl)amino]-5-hydroxy-2-methyl-7-phenylheptanoyl Amide (8a). Alanine amide (**7a**, 120 mg, 1.36 mmol) and epoxide **5** (180 mg, 0.67 mmol) were dissolved in 2-propanol (20 mL) and refluxed overnight. The mixture was cooled, the solvent was removed by evaporation, and the product was purified by column chromatography (EtOAc−MeOH 9:1) to give **8a** (149 mg, 68%) as a white powder. **8a**: $[\alpha]^{22}_D = -25.5$ ($c = 1.1$, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.12−1.50 (m, 12 H), 2.43−2.76 (m, 2 H), 2.80−2.99 (m, 2 H), 3.06−3.24 (m, 1 H), 3.50−3.70 (m, 1 H), 3.70−3.93 (m, 1 H), 5.10−5.23 (m, 1 H), 6.12 (br s, 1 H), 7.07 (br s, 1 H), 7.12−7.35 (m, 5 H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.5, 28.3, 38.6, 51.9, 53.7, 58.1, 69.9, 79.4, 126.3, 128.4, 129.3, 138.2, 156.1, 178.5. Anal. ($C_{18}H_{29}N_3O_4$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-3-(benzyloxycarbonyl)-6-[(*tert*-butyloxycarbonyl)amino]-5-hydroxy-2-methyl-7-phenylheptanoyl Amide (9a). The secondary amine **8a** (26 mg, 74.0 μmol) was suspended in a mixture of THF and water (1:1, 20 mL). Na_2CO_3 (10 mg, 84.7 μmol) and Z-Cl (38 mg, 0.223 mmol) were added, and the mixture was stirred at room temperature for 30 min, extracted twice with EtOAc, dried, filtered, and evaporated. The product was purified by column chromatography (toluene−EtOAc 1:2) to give **9a** (34 mg, 98%) as a white powder. **9a**: $[\alpha]^{22}_D = -52.1$ ($c = 1.1$, $CHCl_3$); ^{1}H NMR (270 MHz, CD_3OD) δ 1.15−1.60 (m, 12 H), 2.67−2.95 (m, 2 H), 3.16−3.40 (m, 1 H), 3.45−3.60 (m, 1 H), 3.62−3.83 (m, 1 H), 3.83−4.04 (m, 1 H), 4.17−4.38 (m, 1 H), 4.98−5.20 (m, 2 H), 6.25−6.40 (m, 1 H), 7.10−7.43 (m, 10 H). Anal. ($C_{26}H_{35}N_3O_6$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-3-(benzyloxycarbonyl)-6-{[(*tert*-butyloxycarbonyl)-L-valinyl]amino}-5-hydroxy-2-methyl-7-phenylheptanoyl Amide (10a). The protected primary amine **9a** (91 mg, 0.156 mmol) was stirred in EtOAc saturated with HCl (5 mL) for 15 min. A saturated aqueous solution of $NaHCO_3$ was added until pH > 6, and the organic phase was dried, filtered, and evaporated. The residue was dissolved in DMF (1.5 mL). BocValOH (87 mg, 0.400 mmol), TBTU (128 mg, 0.399 mmol), and DIEA (137 μL, 0.800 mmol) were added, and the mixture was stirred for 2 h at room temperature. CH_2Cl_2 (5 mL) was added, and the mixture was washed with aqueous $NaHCO_3$ (1 M, 10 mL), dried, filtered, and evaporated. The product was purified by column chromatography (toluene−EtOAc 1:2) to give **10a** (80 mg, 72%) as a white powder. **10a**: $[\alpha]^{22}_D = 62.1$ ($c = 0.9$, $CHCl_3$); ^{1}H NMR (270 MHz, CD_3OD) δ 0.63−1.00 (m, 6 H), 1.28−1.58 (m, 12 H), 1.83−2.05 (m, 1 H), 2.71−3.00 (m, 2 H), 3.01−3.25 (m, 1 H), 3.36−3.58 (m, 1 H), 3.70−3.88 (m, 1 H), 3.88−4.25 (m, 3 H), 4.96−5.20 (m, 2 H), 7.07−7.41 (m, 10 H). Anal. ($C_{31}H_{44}N_4O_7$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-5-hydroxy-2-methyl-7-phenyl-6-[(picolyl-L-valinyl)amino]-heptanoyl Amide (11a). The protected primary amine **10a** (80 mg, 0.137 mmol) was stirred in EtOAc saturated with HCl (5 mL) for 15 min. A saturated aqueous solution of $NaHCO_3$ was added until pH > 6, and the organic phase was dried, filtered, and evaporated. The residue was dissolved in a mixture of DMF and CH_2Cl_2 (1:1, 1.5 mL). Picolinic acid (18 mg, 0.146 mmol), TBTU (46 mg, 0.143 mmol), and DIEA (49 μL, 0.294 mmol) were added, and the mixture was stirred for 2 h at room temperature. CH_2Cl_2 (5 mL) was added, and the mixture was washed with aqueous $NaHCO_3$ (1 M, 10 mL), dried, filtered, and evaporated. The peptide coupling product was purified by column chromatography (EtOAc) and dissolved in a saturated solution of ammonium formate in ethanol (95%, 5 mL). Palladium on active carbon (10%, 5 mg) was added, and the mixture was stirred at room temperature for 2 h, filtered through Celite, evaporated, and freeze-dried to give **11a** (42.4 mg, 68%) as a white solid. **11a**: $[\alpha]^{22}_D = -57.7$ ($c = 1.1$, CH_3OH), ^{1}H NMR (270 MHz, CD_3OD) δ 0.85 (d, $J = 6.8$ Hz, 3 H, Val-CH_3), 0.99 (d, $J = 6.9$ Hz, 3 H, Val-CH_3), 1.55 (d, $J = 6.9$ Hz, 3 H, C2-CH_3), 1.98−2.20 (m, 1 H, Val-$(CH_3)_2CH$), 2.74−3.15 (m, 4 H, C4H_2 and C7H_2), 3.73−3.95 (m, 1 H, C5H), 3.95−4.11 (m, 1 H, C6H), 4.11−4.22 (m, 1 H, C2H), 4.22−4.40 (m, 1 H, Val-CHNH), 6.88−7.03 (m, 1 H, *p*-CH), 7.03−7.18 (m, 2 H, *m*-CH), 7.18−7.34 (m, 2 H, *o*-CH), 7.51−7.70 (m, 1 H, C5H on pyridine), 7.92−8.07 (m, 1 H, C4H on pyridine), 8.07−8.20 (m, 1 H, C3H on pyridine), 8.59−8.86 (m, 1 H, C6H on pyridine). ^{13}C NMR (67.8 MHz, CD_3OD) δ 17.1, 18.7, 19.91, 32.22, 38.36, 50.51, 54.61, 57.34, 60.70, 69.30, 123.3, 127.3, 128.0, 129.3, 130.3, 138.9, 139.3, 149.8, 150.4, 166.2, 173.4, 173.8. Anal. ($C_{24}H_{33}N_5O_4 \cdot 1.5H_2O$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-6-[(*tert*-butyloxycarbonyl)amino]-2-isobutyl-5-hydroxy-7-phenylheptanoyl Amide (8b). Compound **8b** (91 mg, 83%) was prepared from leucine amide (**7b**, 200 mg, 1.54 mmol) and epoxide **5** (73 mg, 0.273 mmol) using the same procedure as in the synthesis of **8a**. **8b**: $[\alpha]^{22}_D = -30.9$ ($c = 0.6$, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.80−1.01 (m, 6 H), 1.33 (s, 9 H), 1.60−1.82 (m, 1 H), 2.45−2.74 (m, 2 H), 2.79−2.98 (m, 2 H), 2.98−3.15 (m, 1 H), 3.51−3.68 (m, 1 H), 5.95−5.12 (m, 1 H), 5.79 (br s, 1 H), 6.9 (br s, 1 H), 7.12−7.40 (m, 5 H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.8, 23.2, 24.8, 28.3, 38.7, 42.9, 51.9, 53.6, 61.2, 69.9, 79.5, 126.4, 128.4, 129.3, 138.2, 156.1, 178.3. Anal. ($C_{21}H_{35}N_3O_4$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-3-(benzyloxycarbonyl)-6-[(*tert*-butyloxycarbonyl)amino]-2-isobutyl-5-hydroxy-7-phenylheptanoyl Amide (9b). Compound **9b** (135 mg, 100%) was prepared from **8b** (100 mg, 0.254 mmol), K_2CO_3 (35 mg, 0.253 mmol), and Z-Cl (130 μL, 0.911 mmol) using the same procedure as in the synthesis of **9a**. **9b**: $[\alpha]^{22}_D = -65.0$ ($c = 0.4$, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.79−1.08 (m, 6 H), 1.44 (s, 9 H), 1.51−1.77 (m, 1 H), 2.10−2.25 (m, 2 H), 2.79−3.02 (m, 2 H), 3.02−3.33 (m, 1 H), 3.53−3.85 (m, 2 H), 3.85−

4.15 (m, 2 H), 4.86−5.38 (m, 3 H), 5.55−7.00 (m, 2 H), 7.06−7.50 (m, 10 H). Anal. ($C_{29}H_{41}N_3O_6$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-3-(benzyloxycarbonyl)-6-{[(*tert*-butyloxycarbonyl)-L-valinyl]amino}-2-isobutyl-5-hydroxy-7-phenylheptanoyl Amide (10b). Compound **10b** (87 mg, 59%) was prepared from **9b** (124 mg, 0.235 mmol), BocValOH (51 mg, 0.235 mmol), TBTU (75 mg, 0.234 mmol), and DIEA (80 μL, 0.467 mmol) using the same procedure as in the synthesis of **10a**. **10b**: $[\alpha]^{22}_D = -74.0$ (c = 0.8, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.70−1.10 (m, 12 H), 1.37−1.75 (m, 11 H), 1.96−2.16 (m, 2 H), 2.80−2.24 (m, 3 H), 3.53−3.82 (m, 1 H), 3.82−4.27 (m, 4 H), 4.72−5.29 (m, 2 H), 5.29−6.88 (m, 3 H), 7.06−7.48 (m, 10 H). Anal. ($C_{34}H_{50}N_4O_7$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-2-isobutyl-5-hydroxy-7-phenyl-6-[(picolyl-L-valinyl)amino]heptanoyl Amide (11b). Compound **11b** (48 mg, 50%) was prepared from **10b** (122 mg, 0.195 mmol), picolinic acid (24 mg, 0.195 mmol), TBTU (62 mg, 0.193 mmol), and DIEA (66 μL, 0.386 mmol) using the same procedure as in the synthesis of **11a**. **11b**: $[\alpha]^{22}_D = -53.4$ (c = 0.9, MeOH), ^{1}H NMR (270 MHz, CD_3OD) δ 0.70−1.28 (m, 12 H, 4 CH_3), 1.45−1.73 (m, 2 H, $(CH_3)_2CHCH_2$), 1.74−1.92 (m, 1 H, $(CH_3)_2CHCH_2$), 2.03−2.30 (m, 1 H, Val-$(CH_3)_2CH$), 2.68−2.80 (m, 2 H, C7H_2), 2.80−3.15 (m, 2 H, C4H_2), 3.21−3.38 (m, 1 H, C5H), 3.76−4.00 (m, 1 H, C6H), 4.12−4.32 (m, 1 H, C2H), 4.32−4.60 (d, J = 7.4 Hz, 1 H, Val-CHNH), 6.88−7.13 (m, 1 H, *p*-CH), 7.13−7.20 (m, 2 H, *m*-CH), 7.20−7.50 (m, 2 H, *o*-CH), 7.56−7.80 (m, 1 H, C5H on pyridine), 7.99−8.12 (m, 1 H, C4H on pyridine), 8.12−8.39 (m, 1 H, C3H on pyridine), 8.71−8.85 (m, 1 H, C6H on pyridine). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 18.6, 20.0, 23.0, 25,9, 32.4, 38.7, 42.9, 51.8, 54.6, 60.4, 61.5, 70.8, 123.3, 127.2, 128.0, 129.2, 130.3, 138.9, 139.5, 149.8, 150.4, 166.1, 173.5, 177.2. Anal. ($C_{27}H_{39}N_5O_4\cdot H_2O$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-6-[(*tert*-butyloxycarbonyl)amino]-5-hydroxy-2,7-diphenylheptanoyl Amide (8c). Compound **8c** (260 mg, 63%) was prepared from phenylglycine amide (**7c**, 435 mg, 2.90 mmol) and epoxide **5** (263 mg, 1.00 mmol) using the same procedure as in the synthesis of **8a** except the product was purified by recrystallization from 2-propanol. **8c**: $[\alpha]^{22}_D$ = +20.0 (c = 1.0, MeOH−$CHCl_3$ 1:1); mp 214−215 °C; ^{1}H NMR (270 MHz, $CDCl_3$−CD_3OD 9:1) δ 1.29 (s, 9 H), 2.42−2.63 (m, 2 H), 2.68−2.88 (m, 2 H), 3.57−3.80 (m, 2 H), 3.95−4.12 (m, 1 H), 7.01−7.38 (m, 10 H). ^{13}C NMR (67.8 MHz, $CDCl_3$−CD_3OD 9:1) δ 28.1, 38.4, 51.7, 53.9, 67.0, 69.7, 79.4, 126.1, 127.1, 128.1, 128.2, 128.6, 129.1, 138.1, 138.5, 156.2, 175.9. Anal. ($C_{23}H_{31}N_3O_4$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-3-(benzyloxycarbonyl)-6-[(*tert*-butyloxycarbonyl)amino]-5-hydroxy-2,7-diphenylheptanoyl Amide (9c). Compound **9c** (270 mg, 85%) was prepared from **8c** (240 mg, 0.58 mmol), K_2CO_3 (160 mg, 1.16 mmol), and Z-Cl (91 μL, 0.64 mmol) using the same procedure as in the synthesis of **9a**. **9c**: $[\alpha]^{22}_D = -40.8$ (c = 0.9, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.31 (s, 9 H), 2.60−2.90 (m, 3 H), 3.25−3.49 (m, 2 H), 3.53−3.70 (m, 1 H), 4.55−4.91 (m, 1 H), 4.91−5.19 (m, 2 H), 5.35−5.65 (m, 1 H), 5.85−7.54 (m, 2 H), 6.81−7.41 (m, 15 H). Anal. ($C_{31}H_{37}N_3O_6\cdot 0.2H_2O$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-3-(benzyloxycarbonyl)-6-{[(*tert*-butyloxycarbonyl)-L-valinyl]amino}-5-hydroxy-2,7-diphenylheptanoyl Amide (10c). Compound **10c** (280 mg, 95%) was prepared from **9c** (250 mg, 0.457 mmol), BocValOH (109 mg, 0.503 mmol), TBTU (161 mg, 0.503 mmol), and DIEA (175 μL, 1.01 mmol) using the same procedure as in the synthesis of **10a**. **10c**: $[\alpha]^{22}_D = -67.7$ (c = 0.8, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.50−0.93 (m, 12 H), 1.38 (s, 9 H), 1.80−2.12 (m, 1 H), 2.60−2.99 (m, 4 H), 3.10−3.41 (m, 1 H), 3.60−3.95 (m, 3 H), 4.80−5.20 (m, 2 H), 5.26−5.57 (m, 1 H), 5.76−6.15 (m, 2 H), 6.38−6.67 (m, 1 H), 6.85−7.38 (m, 15 H). Anal. ($C_{36}H_{46}N_4O_7$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-5-hydroxy-2,7-diphenyl-6-[(picolyl-L-valinyl)amino]-heptanoyl Amide (11c). Compund **11c** (120 mg, 60%) was prepared from **10c** (250 mg, 0.387 mmol), picolinic acid (52 mg, 0.426 mmol), TBTU (137 mg, 0.426 mmol), and DIEA (145 μL, 0.851 mmol) using the same procedure as in the synthesis of **11a**. **11c**: $[\alpha]^{22}_D = -7.9$ (c = 0.8, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.80 (d, J = 6.8 Hz, Val-CH_3), 0.98 (d, J = 6.6 Hz, 3 H, Val-CH_3), 2.08−2.32 (m, 1 H, Val-$(CH_3)_2CH$), 2.53−2.74 (m, 2 H, C7H_2), 2.74−3.01 (m, 2 H, C4H_2), 3.59−3.78 (m, 1 H, C5H), 4.05−4.25 (m, 1 H, C6H), 4.13 (s, 1 H, C2H), 4.34 (dd, J = 7.3, 1 H, Val-CHNH), 6.31 (br s, 1 H, NH), 6.78−6.91 (m, 1 H, NH), 6.91−7.00 (m, 1 H, *p*-CH), 7.00−7.20 (m, 5 H, 5 Ar-H), 7.20−7.40 (m, 5 H, 4 Ar-H and NH), 7.40−7.53 (m, 1 H, NH), 7.76−7.91 (m, 1 H, C5H on pyridine), 8.05−8.20 (m, 1 H, C4H on pyridine), 8.35−8.50 (m, 1 H, C3H on pyridine), 8.50−8.66 (m, 1 H, C6H on pyridine). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 18.0, 19.6, 30.5, 38.3, 51.9, 52.7, 59.2, 67.3, 70.1, 122.3, 126.1, 126.5, 127.4, 128.2, 128.8, 129.2, 137.3, 137.9, 138.8, 148.3, 149.0, 164.5, 170.9, 175.3. Anal. ($C_{29}H_{35}N_5O_4$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-2-benzyl-6-[(*tert*-butyloxycarbonyl)-amino]-5-hydroxy-7-phenylheptanoyl Amide (8d). Compound **8c** (78 mg, 48%) was prepared from phenylalanine amide (**7d**, 100 mg, 0.609 mmol) and epoxide **5** (100 mg, 0.380 mmol) using the same procedure as in the synthesis of **8a**. **8d**: $[\alpha]^{22}_D = -86.1$ (c = 1.2, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.43 (s, 9 H), 1.83 (br s, 1 H), 2.55−2.68 (m, 2 H), 2.70−2.98 (m, 3 H), 3.12−3.25 (m, 1 H), 3.25−3.39 (m, 1 H), 3.40−3.56 (m, 1 H), 3.71−3.85 (m, 1 H), 4.95−5.12 (m, 1 H), 5.85 (br s, 1 H), 7.0 (br s, 1 H), 7.13−7.42 (m, 10 H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 28.3, 38.7, 39.3, 51.8, 53.8, 63.8, 69.4, 79.4, 126.4, 126.9, 128.4, 128.8, 129.0, 129.3, 137.4, 138.1, 156.0, 176.8. Anal. ($C_{24}H_{33}N_3O_4$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-2-benzyl-3-(benzyloxycarbonyl)-6-[(*tert*-butyloxycarbonyl)amino]-5-hydroxy-7-phenylheptanoyl Amide (9d). Compound **9d** (158 mg, 92%) was prepared from **8d** (131 mg, 0.307 mmol), K_2CO_3 (64 mg, 0.463 mmol) and Z-Cl (130 μL, 0.911 mmol) using the same procedure as in the synthesis of **9a**. **9d**: $[\alpha]^{22}_D = -151.7$ (c = 0.9, $CHCl_3$); ^{1}H NMR (270 MHz, CD_3OD) δ 1.05−1.5 (m, 9 H), 2.12−2.4 (m, 1 H), 2.54−2.87 (m, 2 H), 3.01−3.28 (m, 3 H), 3.41−3.61 (m, 1 H), 3.76−3.99 (m, 1H), 4.0−4.23 (m, 1H), 5.01−5.35 (m, 2 H), 6.14−6.30 (m, 1 H), 6.9−7.55 (m, 15 H). Anal. ($C_{32}H_{39}N_3O_6\cdot 0.2H_2O$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-2-benzyl-3-(benzyloxycarbonyl)-6-{[(*tert*-butyloxycarbonyl)-L-valinyl]amino}-5-hydroxy-7-phenylheptanoyl Amide (10d). Compound **10d** (79 mg, 73%) was prepared from **9d** (92 mg, 0.164 mmol), BocValOH (36 mg, 0.166 mmol), TBTU (58 mg, 0.181 mmol), and DIEA (57 μL, 0.333 mmol) using the same procedure as in the synthesis of **10a**. **10d**: $[\alpha]^{22}_D = -132.9$ (c = 0.8, $CHCl_3$); ^{1}H NMR (270 MHz, CD_3OD) δ 0.62−0.91 (m, 6 H), 1.13−1.57 (m, 10 H), 1.77−1.98 (m, 1 H), 2.19−2.46 (m, 1 H), 2.61−2.90 (m, 2 H), 2.95−3.23 (m, 2 H), 3.70−4.23 (m, 4 H), 5.01−5.30 (m, 2 H), 6.85−7.53 (m, 15 H). Anal. ($C_{37}H_{48}N_4O_7\cdot 0.1H_2O$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-2-benzyl-5-hydroxy-7-phenyl-6-[(picolyl-L-valinyl)amino]heptanoyl Amide (11d). Compound **11d** (46 mg, 86%) was prepared from **10d** (66 mg, 99.9 μmol), picolinic acid (24 mg, 97.5 μmol), TBTU (62 mg, 99.7 μmol), and DIEA (66 μL, 0.199 mmol) using the same procedure as in the synthesis of **11a**. **11d**: $[\alpha]^{22}_D = -45.8$ (c = 0.6, MeOH), ^{1}H NMR (270 MHz, CD_3OD) δ 0.76−1.08 (m, 6 H, 2 CH_3), 1.94−2.18 (m, 1 H, Val-$(CH_3)_2CH$), 2.50−2.72 (m, 2 H, C2CH_2), 2.72−3.13 (m, 4 H, C4H_2 and C7H_2), 3.42−3.59 (m, 1 H, C5H), 3.68−3.90 (m, 1 H, C6H), 4.07−4.23 (m, 1 H, Val-CHNH), 4.26−4.42 (m, 1 H, C2H), 6.85−6.99 (m, 1 H, *p*-CH), 7.00−7.12 (m, 2 H, *m*-CH), 7.12−7.50 (m, 7 H, 7 Ar-H), 7.48−7.65 (m, 1 H, C5H on pyridine), 7.90−8.04 (m, 1 H, C4H on pyridine), 8.05−8.19 (m, 1 H, C3H on pyridine), 8.55−8.70 (m, 1 H, C6H on pyridine). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 18.6, 20.0, 32.4, 38.7, 39.9, 52.1, 54.6, 60.3, 64.6, 71.1, 123.3, 127.1, 127.9, 129.2, 129.6, 130.3, 130.5, 138.0, 138.9, 139.6, 149.7, 150.4, 166.0, 173.3, 177.0. Anal. ($C_{30}H_{37}N_5O_4\cdot H_2O$) C, H, N.

(2*R*,5*S*,6*R*)-3-Aza-2-benzyl-6-[(*tert*-butyloxycarbonyl)-amino]-5-hydroxy-7-phenylheptanoyl Amide (8e). Compound **8e** (0.60 g, 54%) was prepared from D-phenylalanine amide (**7e**, 0.94 g, 5.7 mmol) and epoxide **5** (0.68 g, 2.6 mmol) using the same procedure as in the synthesis of **8a**. **8e**: $[\alpha]^{22}_D = -7.6$ (c = 0.4, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.11−1.29 (m, 1 H), 1.40 (s, 9 H), 2.43−2.74 (m, 2 H), 2.74−3.03 (m, 3 H), 3.03−3.22 (m, 1 H), 3.22−3.42 (m, 1 H), 3.47−3.70 (m, 1

H), 3.78−3.97 (m, 1 H), 5.04−5.27 (m, 1 H), 5.98 (br s, 1 H), 7.00 (br s, 1 H), 7.11−7.48 (m, 10 H). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 28.2, 38.6, 39.1, 51.5, 53.5, 64.1, 70.1, 79.3, 126.2, 126.8, 128.3, 128.6, 129.0, 129.2, 137.2, 138.2, 156.1, 176.73. Anal. ($C_{24}H_{33}N_3O_4$) C, H, N.

(2*R*,5*S*,6*R*)-3-Aza-2-benzyl-3-(benzyloxycarbonyl)-6-[(*tert*-butyloxycarbonyl)amino]-5-hydroxy-7-phenylheptanoyl Amide (9e). Compound **9e** (0.55 g, 73%) was prepared from **8e** (0.57 g, 0.98 mmol) using the same procedure as in the synthesis of **9a**. **9e**: $[\alpha]^{22}_D = +12.8$ (c = 0.3, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.13−1.70 (m, 9 H), 2.77−3.00 (m, 2 H), 3.00−3.56 (m, 5 H), 3.56−3.79 (m, 1 H), 3.79−3.98 (m, 1 H), 4.55−4.78 (m, 1 H), 4.85−5.48 (m, 3 H), 6.89−7.67 (m, 16 H). Anal. ($C_{32}H_{39}N_3O_6$) C, H, N.

(2*R*,5*S*,6*R*)-3-Aza-2-benzyl-3-(benzyloxycarbonyl)-6-{[(*tert*-butyloxycarbonyl)-L-valinyl]amino}-5-hydroxy-7-phenylheptanoyl Amide (10e). Compound **10e** (0.43 g, 70%) was prepared from **9e** (0.52 g, 0.164 mmol) using the same procedure as in the synthesis of **10a**. **10e**: $[\alpha]^{22}_D = +1.3$ (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.58−0.98 (m, 6 H), 1.26−1.53 (m, 10 H), 1.85−2.03 (m, 1 H), 2.61−3.04 (m, 4 H), 3.04−3.31 (m, 2 H), 3.63−4.06 (m, 4 H), 4.39−4.63 (m, 1 H), 4.75−5.11 (m, 2 H), 5.11−5.33 (m, 1 H), 6.85−7.53 (m, 17 H). Anal. ($C_{37}H_{48}N_4O_7 \cdot 2.5H_2O$) C, H, N.

(2*R*,5*S*,6*R*)-3-Aza-2-benzyl-5-hydroxy-7-phenyl-6-[(picolyl-L-valinyl)amino]heptanoyl Amide (11e). Compound **11e** (0.24 g, 75%) was prepared from **10e** (0.40 g, 0.61 mmol) using the same procedure as in the synthesis of **11a**. **11e**: $[\alpha]^{22}_D = -33.4$ (c = 0.4, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.77 (d, J = 6.9 Hz, 3 H, Val-CH_3), 1.00 (d, J = 6.8 Hz, 3 H, Val-CH_3), 2.05−2.35 (m, 1 H, Val-$(CH_3)_2CH$), 2.45 (dd, J = 8.3, 11.9 Hz, 1 H, C2-C*H*), 2.64 (dd, J = 5.4, 12.0 Hz, 1 H, C2-C*H*), 2.71−2.95 (m, 3 H, C4H and C7H_2), 2.95−3.20 (m, 1 H, C4H), 3.20−3.40 (m, 1 H, C5H), 3.47−3.70 (m, 1 H, C6H), 4.06−4.21 (m, 1 H, Val-C*H*NH), 4.28 (dd, J = 6.8, 8.9 Hz, 1 H, C2H), 6.13 (br s, 1 H, NH), 6.85−7.61 (m, 13 H, 10 Ar-H and 3 NH), 7.71−7.94 (m, 1 H, C5H on pyridine), 8.00−8.20 (m, 1 H, C4H on pyridine), 8.30−8.50 (m, 1 H, C3H on pyridine), 8.50−8.66 (m, 1 H, C6H on pyridine). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 17.7, 19.5, 30.1, 38.0, 38.8, 51.1, 52.1, 59.2, 64.0, 70.0, 122.2, 125.6, 126.1, 126.6, 126.7, 128.2, 128.5, 129.1, 137.1, 137.4, 137.76, 148.3, 148.8, 164.7, 171.1, 176.4. Anal. ($C_{30}H_{37}N_5O_4 \cdot 0.5H_2O$) C, H, N.

***p*-L-Bromophenylalanine Amide (7f).** *p*-Bromophenylalanine (2.00 g, 8.19 mmol) was suspended in methanol (60 mL). Acelyl chloride (30 mL) was added slowly under ice cooling, and the mixture was stirred overnight at room temperature and evaporated. The solid residue was dissolved in EtOAc (30 mL), washed with aqueous saturated $NaHCO_3$, dried, filtered, and evaporated. The crude residue was stirred overnight with ammonia saturated methanol (200 mL), evaporated, and purified by crystallization from MeOH−ether to give **7f** (1.96 g, 98%) as white crystals. **7f**: $[\alpha]^{22}_D = +14.0$ (c = 1.1, MeOH), mp 153−5 °C; ^{1}H NMR (270 MHz, CD_3OD) δ 2.71−2.88 (dd, J = 7.26, 13.36 Hz, 1 H), 2.90−3.04 (dd, J = 6.10, 13.36 Hz, 1 H), 3.49−3.60 (dd, J = 6.27, 7.42, 1 H), 7.10−7.23 (m, 2 H), 7.40−7.52 (m, 2 H). ^{13}C NMR (67.8 MHz, CD_3OD) δ 41.8, 57.2, 121.5, 132.4, 138.2, 179.3. Anal. ($C_9H_{11}BrN_2O$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-2-(*p*-bromobenzyl)-6-[(*tert*-butyloxycarbonyl)amino]-5-hydroxy-7-phenylheptanoyl Amide (8f). Compound **8f** (1.01 g, 62%) was prepared from **8f** (1.00 g, 0.609 mmol) and epoxide **5** (0.85 g, 3.23 mmol) using the same procedure as in the synthesis of **8a**. **8f**: $[\alpha]^{22}_D = -22.1$ (c = 0.7, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.29 (s, 9 H), 1.46−1.92 (m, 1 H), 2.30−2.60 (m, 2 H), 2.60−2.87 (m, 3 H), 2.87−3.05 (m, 1 H), 3.05−3.30 (m, 1 H), 3.30−3.47 (m, 1 H), 3.47−3.82 (m, 1 H), 4.80−5.02 (m, 1 H), 5.80 (br s, 1 H), 6.87 (br s, 1 H), 6.93−7.08 (m, 2 H), 7.08−7.29 (m, 5 H), 7.29−7.42 (m, 2 H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 28.4, 38.8, 50.8, 51.9, 53.8, 63.9, 69.9, 79.7, 120.9, 126.5, 128.6, 129.4, 130.9, 131.9, 136.4, 138.2, 156.2, 176.6. Anal. ($C_{24}H_{32}BrN_3O_4$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-3-(benzyloxycarbonyl)-2-(*p*-bromobenzyl)-6-[(*tert*-butyloxycarbonyl)amino]-5-hydroxy-7-phenylheptanoyl Amide (9f). Compound **9f** (1.05 g, 99%) was prepared from **8f** (0.85 g, 1.68 mmol), Na_2CO_3 (212 mg, 2.00 mmol), and Z-Cl (0.50 mL, 4.62 mmol) using the same procedure as in the synthesis of **9a**. **9f**: $[\alpha]^{22}_D = -175.0$ (c = 0.4, $CHCl_3$); ^{1}H NMR (270 MHz, CD_3OD) δ 1.08−1.45 (m, 9 H), 2.21−2.40 (m, 1 H), 3.00−3.42 (m, 4 H), 3.45−3.66 (m, 1 H), 3.79−4.00 (m, 1 H), 4.00−4.24 (m, 1 H), 5.00−5.38 (m, 2 H), 6.80−7.00 (m, 2 H), 7.07−7.52 (m, 12 H). Anal. ($C_{32}H_{38}BrN_3O_6$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-3-(benzyloxycarbonyl)-2-(*p*-bromobenzyl)-6-{[(*tert*-butyloxycarbonyl)-L-valinyl]amino}-5-hydroxy-7-phenylheptanoyl Amide (10f). Compound **10f** (0.554 g, 52%) was prepared from **9f** (0.90 g, 1.43 mmol), BocValOH (0.375 g, 1.73 mmol), TBTU (0.555 g, 1.73 mmol), and DIEA (0.590 mL, 3.45 mmol) using the same procedure as in the synthesis of **10a** except **10f** was purified by recrystallization from MeOH−ether. **10f**: $[\alpha]^{22}_D = -172.9$ (c = 1.0, $CHCl_3$−MeOH 1:1); ^{1}H NMR (400 MHz, CD_3OD−$CDCl_3$ 1:1) δ 0.85−1.04 (m, 6 H), 1.65 (s, 9 H), 2.01−2.17 (m, 1 H), 2.40−2.62 (m, 1 H), 2.88−3.09 (m, 2 H), 3.19−3.37 (m, 2 H), 3.37−3.63 (m, 2 H), 3.85−3.98 (m, 1 H), 3.98−4.33 (m, 3 H), 5.01−5.50 (m, 2 H), 6.95−7.16 (m, 2 H), 7.24−7.69 (m, 12 H). Anal. ($C_{37}H_{47}BrN_4O_7$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-2-(*p*-bromobenzyl)-5-hydroxy-7-phenyl-6-[(picolyl-L-valinyl)amino]heptanoyl Amide (11f). The protected primary amine **10f** (0.200 mg, 0.269 mmol) was stirred in EtOAc saturated with HCl (5 mL) for 15 min. A saturated aqueous solution of $NaHCO_3$ was added until pH > 6, and the organic phase was dried, filtered, and evaporated. The residue was dissolved in a mixture of DMF and CH_2Cl_2 (1:1, 1.5 mL). Picolinic acid (40 mg, 0.325 mmol), TBTU (0.104 g, 0.324 mmol), and DIEA (0.11 mL, 0.643 mmol) were added, and the mixture was stirred for 2 h at room temperature. CH_2Cl_2 (5 mL) was added, and the mixture was washed with aqueous $NaHCO_3$ (1 M, 10 mL), dried, filtered, and evaporated. The peptide coupling product was purified by column chromatography (EtOAc) and dissolved in a CH_2Cl_2 (40 mL). Anisole (0.29 g, 2.69 mmol) and triflic acid (1.00 g, 6.72 mmol) were added, and the mixture was stirred att room temperature for 5 min. Saturated aqueous Na_2CO_3 was added until pH > 6, and the organic phase was dried, filtered, and evaporated. The product was purified by column chromatography (CH_2Cl_2−MeOH 9:1) to give **11f** (0.112 g, 68%) as a white solid. **11f**: $[\alpha]^{22}_D = -37.7$ (c = 0.5, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$, CD_3OD 9:1) δ 0.74 (d, J = 6.9 Hz, 3 H, Val-CH_3), 0.79 (d, J = 6.8 Hz, 3 H, Val-CH_3), 1.98−2.15 (m, 1 H, Val-$(CH_3)_2CH$), 2.53 (dd, J = 8.7, 12.4 Hz, 1 H, C2-C*H*), 2.60 (dd, J = 4.6, 12.5 Hz, 1 H, C2-C*H*), 2.72 (dd, J = 8.8, 13.7 Hz, 1 H, C7H), 2.81 (dd, J = 6.6, 13.8 Hz, 1 H, C7H), 2.84 (dd, J = 7.1, 13.6 Hz, 1 H, C4H), 2.93 (dd, J = 6.8, 13.6 Hz, 1 H, C4H), 3.43−3.49 (m, 1 H, C5H), 3.62−3.71 (m, 1 H, C6H), 4.01−4.10 (m, 1 H, Val-C*H*NH), 4.14−4.25 (m, 1 H, C2H), 6.86−6.93 (m, 1 H, *p*-CH), 6.98−7.13 (m, 6 H, 6 Ar-H), 7.28−7.36 (m, 2 H, Ar-H *meta* to CBr), 7.37−7.45 (m, 1 H, C5H on pyridine), 7.77−7.85 (m, 1 H, C4H on pyridine), 8.00−8.07 (m, 1 H, C3H on pyridine), 8.48−8.54 (m, 1 H, C6H on pyridine). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 17.9, 19.4, 30.3, 37.9, 38.3, 51.5, 52.6, 59.8, 63.51, 70.2, 120.7, 122.2, 126.5, 128.2, 129.1, 130.9, 131.6, 136.0, 137.4, 137.8, 148.3, 148.8, 164.6, 171.1, 176.1. Anal. ($C_{30}H_{36}BrN_5O_4 \cdot 0.5H_2O$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-5-hydroxy-7-phenyl-2-(*p*-phenylbenzyl)-6-[(picolyl-L-valinyl)amino]heptanoyl Amide (16a). In a microwave test tube were mixed compound **11f** (44 mg, 72 μmol), phenylboronic acid (26 mg, 0.213 mmol), $Pd(PPh_3)_2Cl_2$ (1.6 mg, 2.3 μmol), aqueous Na_2CO_3 (2 M, 0.11 mL, 0.22 mmol), EtOH (0.3 mL), DME (1.2 mL), and H_2O (0.9 mL). The test tube was heated in a microwave oven to 140 °C for 20 min and cooled, and the solvents were evaporated. The residue was dissolved in a mixture of water, AcCN, and formic acid (10:10:1, 2 mL) and then filtered and purified by preparative HPLC (Zorbax C8, 20 × 150 mm, particle size 5 μm) using a gradient (H_2O−AcCN (0.1% formic acid) 95:5 → 4:6) over a period of 30 min. The fractions containing the pure product (measured with MS) were pooled and freeze-dried to give **16a** (19 mg, 43%) as a white solid. **16a**: $[\alpha]^{22}_D = -30.4$ (c = 0.6,

$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (d, J = 7.0 Hz, 3 H, Val-CH_3), 0.83 (dd, J = 6.8 Hz, 3 H, Val-CH_3), 2.11−2.33 (m, 1 H, Val-$(CH_3)_2CH$), 2.56−2.79 (m, 2 H, C2CH_2), 2.79−2.91 (m, 2 H, C7H_2), 2.97 (dd, J = 8.1, 13.5 HZ, 1 H, C4H), 3.15 (dd, J = 6.1, 13.4 Hz, 1 H, C4H), 3.50−3.64 (m, 1 H, C5H), 3.64−3.84 (m, 1 H, C6H), 4.09−4.23 (m, 1 H, Val-C*H*NH), 4.33 (dd, J = 6.8, 9.0 Hz, 1 H, C2H), 6.02−6.20 (br s, 1 H, NH), 6.76−7.66 (m, 17 H, 14 Ar-H and 3 NH), 7.79−7.91 (m, 1 H, C5H on pyridine), 8.08−8.20 (m, 1 H, C4H on pyridine), 8.35−8.50 (m, 1 H, C3H on pyridine), 8.50−8.63 (m, 1 H, C6H on pyridine). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 17.8, 19.6, 30.2, 38.1, 38.5, 51.4, 52.7, 59.4, 63.7, 69.6, 122.3, 126.2, 126.4, 126.7, 126.8, 126.9, 127.0, 127.4, 127.6, 128.4, 128.5, 128.8, 129.2, 129.6, 129.7, 136.1, 137.4, 137.5, 137.7, 139.8, 140.5, 148.3, 149.0, 164.8, 171.1, 175.8. Anal. ($C_{36}H_{41}N_5O_4$·1.3H_2O) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-2-[*p*-(*p*-methylphenyl)benzyl]-5-hydroxy-7-phenyl-6-[(picolyl-L-valinyl)amino]heptanoyl Amide (16b). Compound **16b** (21 mg, 46%) was prepared from **11f** (44 mg, 72 μmol) and 4-methylphenylboronic acid (26 mg, 0.19 mmol) using the same procedure as in the synthesis of **16a**. **16b**: $[\alpha]^{22}_D$ = −39.9 (c = 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, J = 6.9 Hz, 3 H, Val-CH_3), 0.91 (d, J = 6.8 Hz, 3 H, Val-CH_3), 2.14−2.20 (m, 1 H, Val-$(CH_3)_2CH$), 2.20 (s, 3 H, Ar-CH_3), 2.60−2.77 (m, 2 H, C2-CH_2), 2.77−3.01 (m, 3 H, C4H and C7H_2), 3.08−3.22 (m, 1 H, C4H), 3.41−3.55 (m, 1 H, C5H), 3.59−3.72 (m, 1 H, C6H), 4.05−4.22 (m, 1 H, Val-C*H*NH), 4.32 (dd, J = 6.5, 8.7 Hz, 1 H, C2H), 5.78−5.98 (br s, 1 H, NH), 6.64−6.78 (m, 1 H, NH), 6.85−6.99 (m, 1 H, NH), 6.99−7.09 (m, 1 H, Ar-H), 7.09−7.19 (m, 4 H, 4 Ar-H), 7.19−7.39 (m, 4 H, 4 Ar-H), 7.48−7.60 (m, 5 H, 4 Ar-H, NH), 7.78−7.91 (m, 1 H, C5H on pyridine), 8.07−8.22 (m, 1 H, C4H on pyridine), 8.33−8.49 (m, 1 H, C3H on pyridine), 8.53−8.67 (m, 1 H, C6H on pyridine). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 17.7, 19.6, 21.1, 30.1, 38.2, 38.9, 51.5, 52.6, 59.3, 63.9, 69.7, 122.3, 126.3, 126.5, 126.8, 127.2, 127.4, 128.4, 128.6, 129.2, 129.5, 136.1, 136.8, 137.4, 137.7, 139.7, 148.3, 149.1, 164.7, 170.9, 176.2. Anal. ($C_{37}H_{43}N_5O_4$·H_2O·HCOOH) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-2-[*p*-(*m*-aminophenyl)benzyl]-5-hydroxy-7-phenyl-6-[(picolyl-L-valinyl)amino]heptanoyl Amide (16c). Compound **16c** (13 mg, 28%) was prepared from **11f** (46 mg, 75 μmol) and 3-aminophenylboronic acid (42 mg, 0.31 mmol) using the same procedure as in the synthesis of **16a** except the HPLC gradient was changed (H_2O (0.1% HCOOH) → H_2O−AcCN 7:3 (0.1% HCOOH)). **16c**: $[\alpha]^{22}_D$ = −22.2 (c = 0.5, $CHCl_3$−MeOH 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, CD_3OD 1:1); δ 0.87 (d, J = 6.6 Hz, 3 H, Val-CH_3), 0.93 (d, J = 6.7 Hz, 3 H, Val-CH_3)), 1.27 (br s, 2 H, ArNH_2), 2.18−2.33 (m, 1 H, Val-$(CH_3)_2CH$), 2.55−2.77 (m, 2 H, C2-CH_2), 2.77−3.01 (m, 3 H, C4H and C7H_2), 3.01−3.27 (m, 1 H, C4H), 3.27−3.48 (m, 1 H, C5H), 3.48−3.71 (m, 1 H, C6H), 4.00−4.20 (m, 1 H, Val-C*H*NH), 4.20−4.38 (m, 1 H, C2H), 5.40−5.61 (br s, 1 H, NH), 6.29−6.52 (m, 1 H, Ar-H), 6.55−6.80 (m, 1 H, Ar-H), 6.80−7.00 (m, 2 H, 2 Ar-H), 7.00−7.33 (m, 8 H, 6 Ar-H, 2 NH),7.33−7.65 (m, 4 H, 3 Ar-H, NH), 7.72−7.96 (m, 1 H, C5H on pyridine), 7.96−8.22 (m, 1 H, C4H on pyridine), 8.22−8.45 (m, 1 H, C3H on pyridine), 8.45−8.66 (m, 1 H, C6H on pyridine). ^{13}C NMR (100.5 MHz, CD_3OD) δ 17.0, 30.1, 36.5, 36.6, 49.4, 52.4, 58.7, 61.6, 67.6, 113.3, 114.1, 116.6, 121.5, 125.6, 126.2, 126.6, 127.5, 128.4, 128.9, 133.1, 137.0, 140.0, 140.8, 146.5, 147.8, 148.3, 164.40, 171.4, 171.8. Anal. ($C_{36}H_{42}N_6O_4$·H_2O·0.8HCOOH) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-5-hydroxy-2-[*p*-(*o*-methoxyphenyl)-benzyl]-7-phenyl-6-[(picolyl-L-valinyl)amino]heptanoyl Amide (16d). Compound **16d** (18 mg, 38%) was prepared from **11f** (45 mg, 74 μmol) and 2-methoxyphenylboronic acid (34 mg, 0.22 mmol) using the same procedure as in the synthesis of **16a**. **16d**: $[\alpha]^{22}_D$ = −41.9 (c = 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, J = 6.8 Hz, 3 H, Val-CH_3), 0.93 (dd, J = 6.8 Hz, 3 H, Val-CH_3), 2.11−2.32 (m, 1 H, Val-$(CH_3)_2CH$), 2.51−2.70 (m, 2 H, C2-CH_2), 2.70−2.90 (m, 3 H, C4H and C7H_2), 3.16−3.30 (dd, J = 5.4, 13.4 Hz, 1 H, C4H), 3.47−3.51 (m, 1 H, C5H), 3.51−3.69 (m, 1 H, C6H), 3.73 (s, 3 H, OCH_3), 4.00−4.14 (m, 1 H, Val-C*H*NH), 4.22−4.42 (dd, J = 6.8, 8.9 Hz, 1 H, C2H), 5.83−6.03 (br s, 1 H, NH), 6.68−6.81 (m, 1 H, NH), 6.85−7.39 (m, 12 H, 11 Ar-H and NH), 7.30−7.53 (m, 3 H, 2 Ar-H and NH), 7.73−7.86 (m, 1 H, C5H on pyridine), 8.02−8.21 (m, 1 H, C4H on pyridine), 8.33−8.46 (m, 1 H, C3H on pyridine), 8.46−8.60 (m, 1 H, C6H on pyridine). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 17.8, 19.6, 30.3, 38.3, 38.9, 51.5, 52.7, 55.5, 59.2, 63.7, 69.2, 111.1, 120.8, 122.3, 126.3, 126.4, 126.8, 128.4, 128.6, 128.7, 128.8, 129.2, 129.9, 129.9, 133.9, 135.6, 136.0, 137.4, 137.7, 148.3, 149.1, 156.3, 164.7, 170.9, 176.3. Anal. ($C_{37}H_{43}N_5O_5$·1.6H_2O) C, H, N.

***m*-L-Tyrosine Amide (13).** Compound **13** (0.25 g, 84%) was prepared from *m*-tyrosine (**12**, 0.30 g, 1.66 mmol)[12] according to the method for the preparation of **7f** except **13** was purified by column chromatography (EtOAc−MeOH 4:1) to give **13** as a colorless glue. **13**: $[\alpha]^{22}_D$ = +5.2 (c = 1.2, MeOH), ^{1}H NMR (400 MHz, CD_3OD) δ 2.63−2.82 (m, 1 H), 2.90−3.09 (m, 1 H), 3.49−3.64 (m, 1 H), 6.57−6.96 (m, 3 H), 6.99−7.27 (m, 1 H). ^{13}C NMR (67.8 MHz, CD_3OD) δ 42.4, 57.2, 114.9, 117.2, 121.4, 130.5, 140.2, 158.7, 179.5. Anal. ($C_9H_{12}N_2O_4$·0.7H_2O) C, H, N.

***N*-(*tert*-Butyloxycarbonyl)-*m*-L-Tyrosine Amide (14).** The primary amine **13** (0.36 g, 2.0 mmol), Boc_2O (0.88 mg, 4.0 mmol) and $NaHCO_3$ (0.34, 4.0 mmol) were suspended in a mixture of water and THF (1:1, 30 mL) and stirred overnight. The mixture was extracted with EtOAc (30 mL), and the organic phase was dried, filtered, and evaporated. The product was purified by column chromatography (CH_2Cl_2−MeOH 9:1) to give **14** (0.43 g, 77%) as a white powder. **14**: $[\alpha]^{22}_D$ = +21.8 (c = 1.0, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.38 (s, 9 H), 2.77−3.10 (m, 2 H), 4.30−4.49 (m, 1 H), 5.48−5.70 (m, 1 H), 6.44 (br s, 1 H), 6.55−6.83 (m, 4 H), 6.98−7.16 (m, 1 H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 28.2, 38.3, 55.4, 80.5, 114.3, 116.2, 121.0, 129.7, 137.8, 155.8, 156.5, 175.1. Anal. ($C_{14}H_{20}N_2O_4$) C, H, N.

***N*-(*tert*-Butyloxycarbonyl)-*m*-(trifluoromethanesulfonyloxy)-L-phenylalanineamide (15).** Compound **14** (0.760 g, 2.71 mmol), *N*-phenyltrifluoromethanesulfonimide (1.94 g, 5.43 mmol), K_2CO_3 (0.75 g, 5.43 mmol), and triethylamine (1.88 mL, 13.56 mmol) were refluxed in CH_2Cl_2 (100 mL) for 30 min. The mixture was washed with water, dried, filtered, and evaporated. The product was purified by column chromatography to give **15** (1.00 g, 89%) as a white powder. **15**: $[\alpha]^{22}_D$ = +1.63 (c = 1.0, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.41 (s, 9 H), 2.93−3.31 (m, 2 H), 4.30−4.59 (m, 1 H), 5.10−5.37 (m, 1 H), 5.81 (br s, 1 H), 6.22 (br s, 1 H), 7.00−7.56 (m, 4 H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 28.2, 37.9, 54.8, 80,5, 118.7 (q, J = 320 Hz), 119.8, 122.3, 129.5, 130.3, 139.8, 149.5, 155.4, 173.2. Anal. ($C_{15}H_{19}F_3N_2O_6S$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-6-[(*tert*-butyloxycarbonyl)amino]-5-hydroxy-7-phenyl-2-[*m*-(trifluoromethanesulfonyloxy)-benzyl]heptanoyl Amide (8g). Compound **15** (0.32 g, 0.78 mmol) was dissolved in a mixture of TFA and CH_2Cl_2 (1:1, 10 mL), and the mixture was stirred for 15 min and evaporated. The residue was dissolved in CH_2Cl_2 and washed twice with Na_2CO_3 (aq, 1 M). The organic phase was dried, filtered, and evaporated. The residue and epoxide **5** (0.15 g, 0.57 mmol) were reacted according to the procedure as in the synthesis of **8a** to give **8g** (0.26 g, 79%). **8g**: $[\alpha]^{22}_D$ = −3.0 (c = 1.6, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.39 (s, 9 H), 1.46−1.92 (m, 1 H), 2.47−2.73 (m, 2 H), 2.73−3.02 (m, 3 H), 3.02−3.21 (m, 1 H), 3.21−3.38 (m, 1 H), 3.40−3.60 (m, 1 H), 3.67−3.98 (m, 1 H), 4.77−5.00 (m, 1 H), 5.60 (br s, 1 H), 6.78 (br s, 1 H), 7.03−7.48 (m, 10 H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 28.1, 38.5, 51.6, 53.7, 63.3, 69.7, 79.3, 118.5 (q, J = 321 Hz), 119.5, 122.0, 126.2, 128.3, 129.1, 130.3, 138.1, 140.3, 149.4, 150.1, 176.3. Anal. ($C_{33}H_{38}F_3N_3O_9S$·0.5H_2O) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-3-(benzyloxycarbonyl)-6-[(*tert*-butyloxycarbonyl)amino]-5-hydroxy-7-phenyl-2-[*m*-(trifluoromethanesulfonyloxy)benzyl]heptanoyl Amide (9g). Compound **9g** (0.25 g, 78%) was prepared from **8g** (0.26 g, 0.45 mmol), Na_2CO_3 (96 mg, 0.90 mmol), and Z-Cl (0.13 mL, 0.90 mmol) using the same procedure as in the synthesis of **9a**. **9g**: $[\alpha]^{22}_D$ = −140.6 (c = 1.1, $CHCl_3$); ^{1}H NMR (270 MHz, CD_3OD) δ 1.05−1.45 (m, 9 H), 2.22−2.44 (m, 1 H), 2.52−2.88 (m, 2 H), 3.08−3.37 (m, 3 H), 3.43−3.66 (m, 1 H), 3.80−4.05 (m, 1

H), 4.10−4.29 (m, 1 H), 4.92−5.35 (m, 2 H), 6.89−7.51 (m, 14 H). Anal. ($C_{33}H_{38}F_3N_3O_9S$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-3-(benzyloxycarbonyl)-6-{[(*tert*-butyloxycarbonyl)-L-valinyl]amino}-5-hydroxy-7-phenyl-2-[*m*-(trifluoromethanesulfonyloxy)benzyl]heptanoyl Amide (10g). Compound **10g** (0.17 g, 93%) was prepared from **9g** (0.16 g, 0.23 mmol), BocValOH (49 mg, 0.23 mmol), TBTU (72 mg, 0.23 mmol), and DIEA (77 μL, 0.46 mmol) using the same procedure as in the synthesis of **10a**. **10g**: $[\alpha]^{22}_D = -162.4$ ($c = 0.6$, $CHCl_3$); ^{1}H NMR (270 MHz, $CD_3OD-CDCl_3$ 1:1) δ 0.54−0.94 (m, 6 H), 1.45 (s, 9 H), 1.81−2.01 (m, 1 H), 2.21−2.45 (m, 1 H), 2.61−2.90 (m, 2 H), 2.98−3.50 (m, 3 H), 3.73−4.10 (m, 3 H), 4.10−4.30 (m, 1 H), 4.99−5.35 (m, 2 H), 6.42−6.60 (m, 1 H), 6.95−7.51 (m, 14 H). Anal. ($C_{38}H_{47}F_3N_4O_{10}S$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-5-hydroxy-7-phenyl-6-[(picolyl-L-valinyl)amino]-2-(*m*-(trifluoromethanesulfonyloxy)benzyl)-heptanoyl Amide (11g). Compound **11g** (60 mg, 51%) was prepared from **10g** (0.14 g, 0.17 mmol), picolinic acid (23 mg, 0.19 mmol), TBTU (61 mg, 0.19 mmol), and DIEA (62 μL, 0.38 mmol) using the same procedure as in the synthesis of **11a**. **11g**: $[\alpha]^{22}_D = -44.0$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$, CD_3OD 9:1) δ 0.78 (d, $J = 6.9$ Hz, 3 H, Val-CH_3), 0.83 (d, $J = 6.8$, 3 H, Val-CH_3), 2.03−2.19 (m, 1 H, Val-$(CH_3)_2CH$), 2.51−2.69 (m, 2 H, C2-CH_2), 2.76 (dd, $J = 8.6$, 13.9 Hz, 1 H, C7H), 2.84 (dd, $J = 6.8$, 13.7 Hz, 1 H, C7H), 2.73−3.21 (m, 2 H, C4H_2), 3.48−3.57 (m, 1 H, C5H), 3.67−3.76 (m, 1 H, C6H), 4.04−4.14 (m, 1 H, Val-$(CH_3)_2CH$), 4.14−4.28 (m, 1 H, C2H), 6.91−7.00 (m, 1 H, Ar-H), 7.00−7.22 (m, 6 H, Ar-H), 7.22−7.39 (m, 2 H, Ar-H), 6.82−7.72 (m, 12 H, 9 Ar-H and 3 NH), 7.40−7.49 (m, 1 H, C5H on pyridine), 7.79−7.88 (m, 1 H, C4H on pyridine), 8.04−8.12 (m, 1 H, C3H on pyridine), 8.52−8.59 (m, 1 H, C6H on pyridine). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 17.8, 19.5, 30.2, 38.5, 51.6, 52.5, 59.2, 63.5, 70.4, 118.6 (q, $J = 321$ Hz), 119.5, 122.2, 126.2, 126.5, 128.2, 129.1, 129.4, 130.2, 137.4, 137.8, 140.5, 148.3, 148.8, 149.4, 164.6, 171.0, 176.1. Anal. ($C_{31}H_{36}F_3N_5O_7S$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-5-hydroxy-7-phenyl-2-(*m*-phenylbenzyl)-6-[(picolyl-L-valinyl)amino]heptanoyl Amide (17a). In a microwave test tube were mixed compound **11g** (31 mg, 46 μmol), phenylboronic acid (17 mg, 0.213 mmol), $Pd(PPh_3)_2Cl_2$ (1.6 mg, 2.3 μmol), Cs_2CO_3 (59 mg, 0.18 mmol), EtOH (0.5 mL), and DME (2.0 mL). The solvents were heated in a microwave oven to 140 °C for 20 min and cooled, and the solvents were evaporated. The residue was dissolved in a mixture of water, AcCN, and formic acid (10:10:1, 2 mL), filtered, and purified by preparative HPLC (Zorbax C8, 20 × 150 mm, particle size 5 μm) using a gradient (H_2O−AcCN 95:5 → 4:6) over a period of 20 min. The fractions containing the pure product (measured with MS) were pooled and freeze-dried to give **17a** (9 mg, 31%) as a white solid. **17a**: $[\alpha]^{22}_D = -28.7$ ($c = 0.2$, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 0.61−0.96 (m, 6 H, 2 Val-CH_3), 1.93−2.08 (m, 1 H, Val-$(CH_3)_2CH$), 2.72−3.06 (m, 4 H, $C2CH_2$ and $C7CH_2$), 3.06−3.25 (m, 1 H, C4H), 3.36−3.54 (m, 1 H, C4H), 3.90−4.24 (m, 4 H, Val-C*H*NH, C2H, C5H, and C6H), 6.85−7.00 (m, 1 H, Ar-H), 7.00−7.60 (m, 13 H, 13 Ar-H), 7.60−7.75 (m, 1 H, C5H on pyridine), 7.75−7.93 (m, 1 H, C4H on pyridine), 8.35−8.50 (m, 1 H, C3H on pyridine), 8.50−8.63 (m, 1 H, C6H on pyridine). Anal. ($C_{36}H_{41}N_5O_4 \cdot 3.7\ H_2O \cdot 2.5HCOOH$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-2-[*m*-(*p*-methylphenyl)benzyl]-5-hydroxy-7-phenyl-6-[(picolyl-L-valinyl)amino]heptanoyl Amide (17b). Compound **17b** (18 mg, 32%) was prepared from **11g** (61 mg, 90 μmol) and 4-methylphenylboronic acid (46 mg, 0.34 mmol) using the same procedure as in the synthesis of **17a**. **17b**: $[\alpha]^{22}_D = -31.5$ ($c = 0.2$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, CD_3OD 3:1) δ 0.72−1.14 (m, 6 H, 2 Val-CH_3), 2.10−2.20 (m, 1 H, Val-$(CH_3)_2CH$), 2.40 (s, 3 H, Ar-CH_3), 2.58−2.93 (m, 3 H, C2CH_2 and C7H), 2.93−3.20 (m, 3 H, C4H_2 and C7H), 3.51−3.70 (m, 1 H, C5H), 3.70−3.95 (m, 1 H, C6H), 3.95−4.20 (m, 1 H, Val-C*H*NH), 4.20−4.42 (m, 1 H, C2H), 6.83−7.72 (m, 14 H, Ar-H), 7.88−8.05 (m, 1 H, C4H on pyridine), 8.05−8.25 (m, 1 H, C3H on pyridine), 8.56−8.87 (m, 1 H, C6H on pyridine). Anal. ($C_{37}H_{43}N_5O_4 \cdot H_2O \cdot 1.7HCOOH$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-2-[*m*-(*m*-aminophenyl)benzyl]-5-hydroxy-7-phenyl-6-[(picolyl-L-valinyl)amino]heptanoyl Amide (17c). Compound **17c** (8 mg, 22%) was prepared from **11g** (41 mg, 60 μmol) and 3-nitrophenylboronic acid (34 mg, 0.25 mmol) using the same procedure as in the synthesis of **17a** except the HPLC gradient was changed ($H_2O \rightarrow H_2O$−AcCN 7:3). **17a**: $[\alpha]^{22}_D = -28.8$ ($c = 0.1$, MeOH), ^{1}H NMR (400 MHz, CD_3OD) δ 0.85 (d, $J = 6.8$ Hz, 3 H, Val-CH_3), 0.86 (d, $J = 6.8$ Hz, 3 H, Val-CH_3), 1.20−1.43 (m, 2 H, NH or OH), 1.96−2.11 (m, 1 H, Val-$(CH_3)_2CH$), 2.45−2.62 (m, 2 H, C2CH_2), 2.76 (dd, $J = 9.4$, 13.6 Hz, 1 H, C7H), 2.81−2.95 (m, 2 H, C7H and C4H), 3.00 (dd, $J = 7.1$, 12.9 Hz, 1 H, C4H), 3.31−3.42 (m, 1 H, C5H), 3.61−3.73 (m, 1 H, C2H), 4.08−4.18 (m, 1 H, Val-C*H*NH), 4.24−4.34 (dd, $J = 7.3$, 14.3 Hz, 1 H, C2H), 4.64 (br s, 2 H, NH_2), 6.67−6.73 (m, 1 H, Ar-H), 6.85−6.91 (m, 1 H, Ar-H), 6.91−6.96 (m, 1 H, Ar-H), 6.96−7.00 (m, 1 H, Ar-H), 7.00−7.07 (m, 2 H, *m*-H on C7Ph), 7.08−7.23 (m, 4 H, Ar-H), 7.28−7.36 (m, 1 H, Ar-H), 7.39−7.48 (m, 1 H, Ar-H), 7.52−7.61 (m, 1 H, C5H on pyridine), 7.90−8.01 (m, 1 H, C4H on pyridine), 8.03−8.14 (m, 1 H, C3H on pyridine), 8.59−8.65 (m, 1 H, C6H on pyridine). Anal. ($C_{36}H_{42}N_6O_4 \cdot H_2O \cdot 2HCOOH$) C, H, N.

(2*S*,5*S*,6*R*)-3-Aza-5-hydroxy-2-[*m*-(*o*-methoxyphenyl)-benzyl]-7-phenyl-6-[(picolyl-L-valinyl)amino]heptanoyl Amide (17d). Compound **17d** (16 mg, 28%) was prepared from **11g** (60 mg, 88 μmol) and 2-methoxyphenylboronic acid (52 mg, 0.34 mmol) using the same procedure as in the synthesis of **17a**. **17d**: $[\alpha]^{22}_D = -25.5$ ($c = 0.1$, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$, CD_3OD 3:1) δ 0.60 (d, $J = 7.0$, 3 H, Val-CH_3), 0.68 (d, $J = 6.8$, 3 H, Val-CH_3), 1.80−2.03 (m, 1 H, Val-$(CH_3)_2CH$), 2.58−2.87 (m, 3 H, C2CH_2 and C7H), 2.94−3.11 (m, 1 H, C7H), 3.20−3.37 (m, 2 H, C4H_2), 3.54−3.69 (m, 2 H, C5H and C6H), 3.63 (s, 3 H, OCH_3), 3.80−4.04 (m, 2 H, Val-C*H*NH and C2H), 6.75−7.32 (m, 13 H, Ar-H), 7.32−7.49 (m, 1 H, C5H on pyridine), 7.71−7.91 (m, 1 H, C4H on pyridine), 7.91−8.10 (m, 1 H, C3H on pyridine), 8.36−8.54 (m, 1 H, C6H on pyridine). Anal. ($C_{37}H_{43}N_5O_5 \cdot H_2O \cdot 2.5HCOOH$) C, H, N.

(5*S*)-5-(*p*-Bromobenzyl)-1-{(2*S*,3*R*)-2-hydroxy-4-phenyl-3-[(picolyl-L-valinyl)amino]butyl}imidazolidine-2,4-dione (18). The protected primary amine **7e** (110 mg, 0.148 mmol) was stirred in a mixture of TFA and CH_2Cl_2 (1:4, 10 mL) for 15 min. The solvent was removed by evaporation, and the residue was extracted with CH_2Cl_2 and a saturated aqueous solution of $NaHCO_3$. The organic phase was dried, filtered, and evaporated. The residue was dissolved in a mixture of DMF and CH_2Cl_2 (1:1, 1.5 mL). Picolinic acid (30 mg, 0.244 mmol), TBTU (71 mg, 0.244 mmol), and DIEA (77 μL, 0.488 mmol) were added, and the mixture was stirred for 2 h at room temperature. CH_2Cl_2 (5 mL) was added, and the mixture was washed with aqueous $NaHCO_3$ (1 M, 10 mL), dried, filtered, and evaporated. The peptide coupling product was purified by column chromatography (EtOAc) and dissolved in absolute ethanol (99.5%, 1 mL). Cs_2CO_3 (97 mg, 0.296 mmol) was added, and the mixture was stirred at room temperature for 1 h. CH_2Cl_2 (20 mL) was added, and the mixture was washed with water (2 × 5 mL), dried, filtered, and evaporated. The residue was purified using column chromatography (CH_2Cl_2−MeOH 39:1) to give **18** (43 mg, 45%) as a white solid. **18**: $[\alpha]^{22}_D = -28.4$ ($c = 0.6$, CH_3OH), ^{1}H NMR (400 MHz, $CDCl_3-CD_3OD$ 9:1) δ 0.70−0.87 (d, $J = 6.8$ Hz, 3 H, Val-CH_3), 0.87−1.00 (d, $J = 6.8$ Hz, 3 H, Val-CH_3), 2.06−2.27 (m, 1 H, Val-$(CH_3)_2CH$), 2.64−2.81 (dd, $J = 8.7$, 13.8 Hz, 1 H, *p*-BrPhC*H*), 2.81−2.98 (dd, $J = 6.6$, 13.8 Hz, 1 H, *p*-BrPhC*H*), 2.98−3.22 (m, 3 H, C4′H_2 and C1′H), 3.47−3.65 (m, 1 H, C1′H), 3.73−3.90 (m, 1 H, C2′H), 3.95−4.11 (m, 1 H, C3′H), 4.17−4.32 (m, 1 H, Val-C*H*NH), 4.40−4.54 (m, 1 H, C5H), 6.80−6.96 (m, 2 H, CH *ortho* to CBr), 6.96−7.05 (m, 1 H, *p*-CH), 7.05−7.19 (m, 4 H, *o*- and *m*-CH on Ph), 7.19−7.36 (m, 2 H, CH *meta* to CBr), 7.36−7.53 (m, 1 H, C5H on pyridine), 7.73−7.91 (m, 1 H, C4H on pyridine), 8.00−8.12 (m, 1 H, C3H on pyridine), 8.48−8.61 (m, 1 H, C6H on pyridine). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 17.8, 19.4, 30.2, 33.2, 37.3, 45.2, 53.8, 59.3, 63.5, 70.7, 121.1, 122.2, 126.3, 126.6, 128.3, 129.0, 131.1, 131.5,

133.1, 137.4, 137.5, 148.2, 148.7, 156.9, 164.7, 171.6, 173.8. Anal. ($C_{31}H_{34}BrN_5O_5 \cdot 0.7H_2O$) C, H, N.

(5*S*)-1-{(2*S*,3*R*)-2-Hydroxy-4-phenyl-3-[(picolyl-L-valinyl)amino]butyl}-5-(*p*-phenylbenzyl)imidazolidine-2,4-dione (19). Compound **19** (3.2 mg, 15%) was prepared from **18** (22 mg, 35 μmol) using the same procedure as in the synthesis of **17a**. **19**: $[\alpha]^{22}_D = -40.6$ ($c = 0.2$, CH_3OH); ^{1}H NMR (270 MHz, $CDCl_3$, CD_3OD 9:1) δ 0.79 (d, $J = 6.8$ Hz, 3 H, Val-CH_3), 0.88 (d, $J = 6.8$ Hz, 3 H, Val-CH_3), 2.00−2.21 (m, 1 H, Val-$(CH_3)_2CH$), 2.60−2.81 (m, 2 H, C5CH_2), 2.81−3.18 (m, 3 H, C4′H_2 and C1′H), 3.45−3.70 (m, 2 H, C1′H and C2′H), 3.85−4.00 (m, 1 H, C3′H), 4.20 (d, $J = 7.3$ Hz, 1 H, Val-C*H*NH), 4.29−4.40 (m, 1 H, C5H), 6.81−7.17 (m, 7 H, 7 Ar-H), 7.17−7.53 (m, 8 H, 8 Ar-H), 7.77−7.90 (m, 1 H, C4H on pyridine), 8.01−8.14 (m, 1 H, C3H on pyridine), 8.44−8.58 (m, 1 H, C6H on pyridine). ^{13}C NMR (67.8 MHz, $CDCl_3$, CD_3OD 9:1) δ 17.8, 19.2, 30.4, 34.2, 37.6, 44.3, 52.6, 59.4, 61.6, 68.0, 122.5, 126.1, 126.7, 127.0, 127.1, 128.1, 128.6, 129.0, 129.6, 137.4, 138.3, 139.9, 140.2, 147.6, 148.2, 157.5, 164.1, 171.3, 173.8. Anal. ($C_{37}H_{39}N_5O_5 \cdot H_2O \cdot HCOOH$) C, H, N.

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