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Structure–Activity Relationships of HIV-1 PR Inhibitors Containing AHPBA

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Abstract—A series of Human Immunodeficiency Virus type-1 protease (HIV-1 PR) inhibitors that contain 3-amino-2-hydroxy-4-phenylbutanoic acid (AHPBA) at the scission site of the substrate were prepared and evaluated for their inhibitory activity. Preliminary studies on the chain length of inhibitors and the hydroxyl configuration of AHPBA indicated that small (2*S*,3*S*)-derivatives, composed of the regions between the P_3 and P_2' sites, showed enough inhibitory activity toward HIV-1 PR to become prototypes for further structural modification. Systematic replacement at the sites from P_3 to P_2' revealed that some bicyclic heteroarylcarbonyl derivatives possessed strong potency and good enzyme selectivity.

Introduction

HIV-1 is the causative agent of acquired immunodeficiency syndrome (AIDS). Numerous efforts to inhibit the replication cycle of HIV-1 have been reported.[1] HIV-1 protease (HIV-1 PR), which plays an important role in processing the huge precursor *gag* and *gag-pol* proteins encoded by the virus,[2] has attracted much attention as a therapeutic target of AIDS.[3] This homodimer protease, which hydrolyzes peptide bonds including the characteristic Tyr/Phe–Pro sequences found in retrovirus proteases' substrates, is a member of the aspartic protease family.[4] Therefore, the results of abundant research on the inhibitors of aspartic proteases, such as renin, pepsin, penicillopepsin, and cathepsin D, can be applied to the design of tight-binding inhibitors of HIV-1 PR.[5] One strategy, for example, is to incorporate dipeptide transition-state analogs into the scissile bonds of substrates.

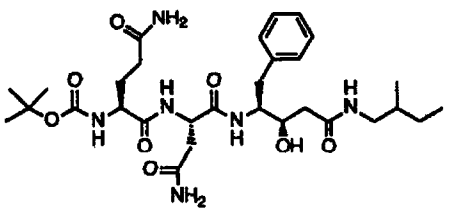
In previous papers, we reported some compounds that contain transition-state analogs, including some with a statine analog (4-amino-3-hydroxy-5-phenylpentanoic acid (AHPPA)[6]) and some with a homostatine analog (5-amino-6-cyclohexyl-4-hydroxy-2-methylhexanoic acid (cyclohexyl-alanylalanine hydroxyethylene dipeptide isostere; Cha-ψ[H.E.]-Ala)[7]) (Figure 1). AHPPA-containing peptide **1** showed only moderate inhibitory activity. Cha-ψ[H.E.]-Ala-containing peptide **2** was found to be a potent and selective inhibitor of HIV-1 PR, but its anti-HIV activity was not strong.

Recently, HIV-1 PR inhibitors containing a norstatine analog, AHPBA, have been reported by several research groups.[8] In particular, Kiso *et al.* described that two potent inhibitors, KNI-227 and 272, were selected as promising candidates for clinical trials. Their reports prompted us to disclose our own independent approach, which is the synthesis and *in vitro* evaluation of a series of AHPBA-containing peptides.[9]

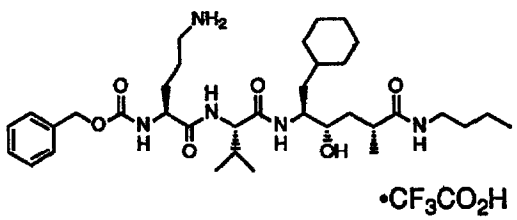
Results and Discussion

Chemistry

Except when stated otherwise, the inhibitors examined here were prepared by using diethylphosphoryl cyanide (DEPC)[10] as a condensation reagent and *p*-nitrophenyl active ester in a stepwise method of peptide synthesis as shown in Scheme I and Scheme II.

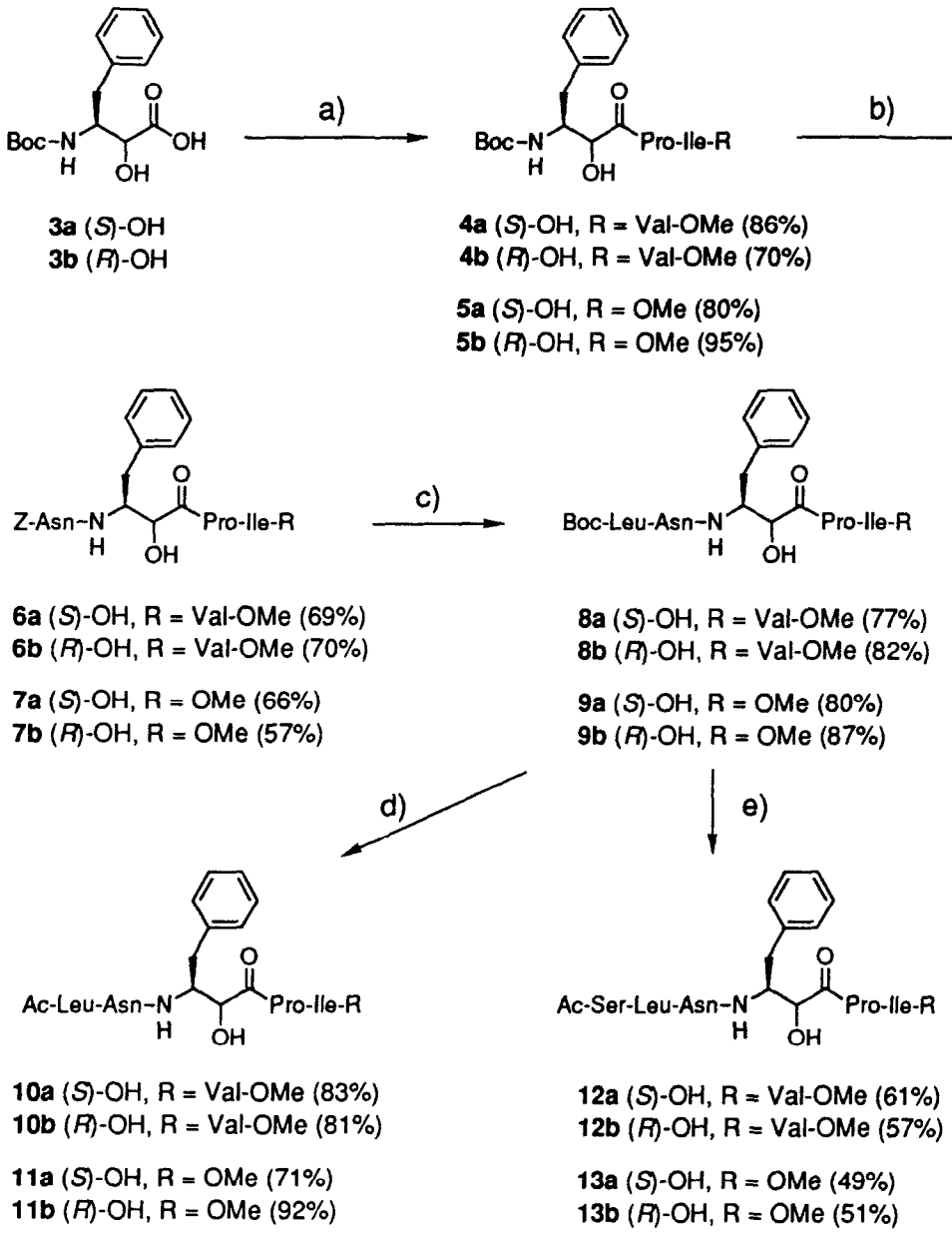


1 (K_i = 360 nM)



2 (K_i = 8nM)

Figure 1.

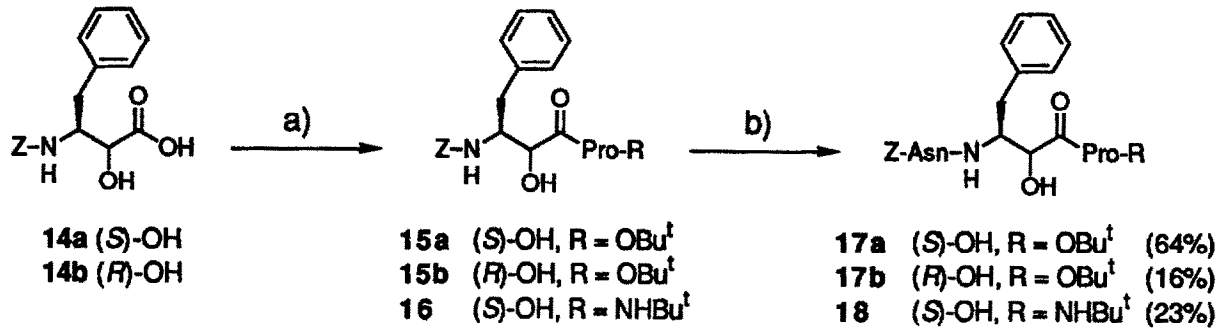


Reagents and conditions: (a) HCl·H-Pro–Ile–Val–OMe or HCl·H-Pro–Ile–OMe, DEPC, Et_3N, DMF, 4 °C; (b) i) 4 N HCl/dioxane, rt, ii) Z-Asn-ONp, Et_3N, DMF, rt; (c) i) H_2, Pd/C, MeOH, rt; ii) Boc–Leu–OH, DEPC, Et_3N, DMF, rt; (d) i) 4 N HCl/dioxane, rt; (ii) Ac_2O, Et_3N, DMF, 0 °C; (e) i) 4 N HCl/dioxane, rt; ii) Boc–Ser(Bzl)–OH, DEPC, Et_3N, DMF, rt; (iii) 4 N HCl/dioxane, rt; (iv) Ac_2O, Et_3N, DMF, 0 °C; (v) H_2, Pd/C, MeOH, rt.

Scheme I.

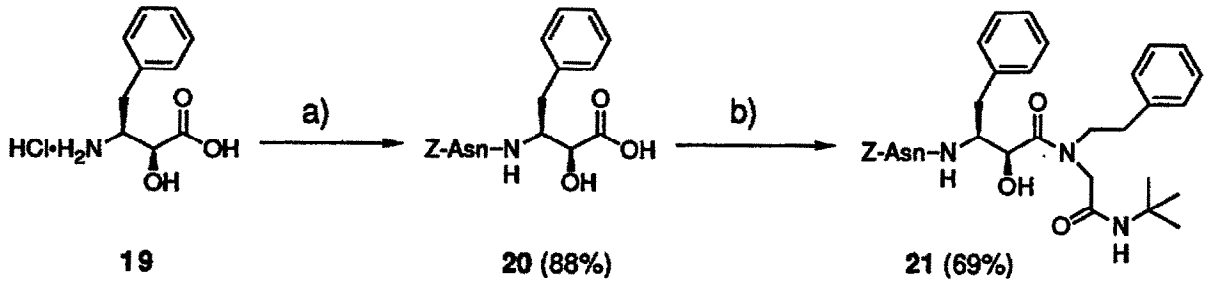
For the preparation of *N*-alkylated glycine derivatives, the fragment condensation method was employed (water soluble carbodiimide (WSCI)–1-hydroxybenzotriazole (HOBT)), as shown in Scheme III. That no epimerization occurred during this coupling reaction was confirmed by comparing compound **18** prepared by this method with that prepared in a stepwise manner. Preparation of *N*-2-phenethyl-L-alanine derivative **25** had to be performed using the stepwise method with the hydroxyl group protected and bromotris(pyrrolidino)phosphonium hexafluorophosphate (PyBrop®)[11] employed as a coupling agent (Scheme IV), because the coupling reaction by the other methods, including fragment condensation, did not proceed, due to the steric hindrance of the amine component.

For the synthesis of a variety of amides at the P_2' site, we found a convenient method. Acid treatment of compound **17a** gave the bicyclic compound **26**, which was transformed into the objective inhibitors with less sterically hindered amines as listed in Table 3, except in the case of *tert*-butylamine (Scheme V). The opening of compound **26** with bulky *tert*-butylamine was sluggish and led to a stereomeric mixture suggested from the data of 270 MHz ^1H NMR.



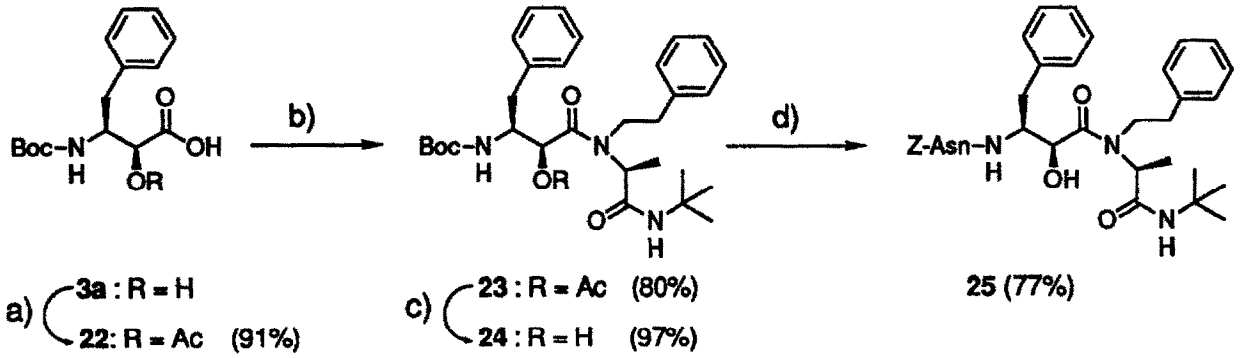
Reagents and conditions: (a) H-Pro-OBu^t or HCl·H-Pro-NHBu^t, DEPC, Et_3N, DMF, rt; (b) i) H_2, Pd/C, EtOH rt; ii) Z-Asn-ONp, Et_3N, DMF, rt.

Scheme II.



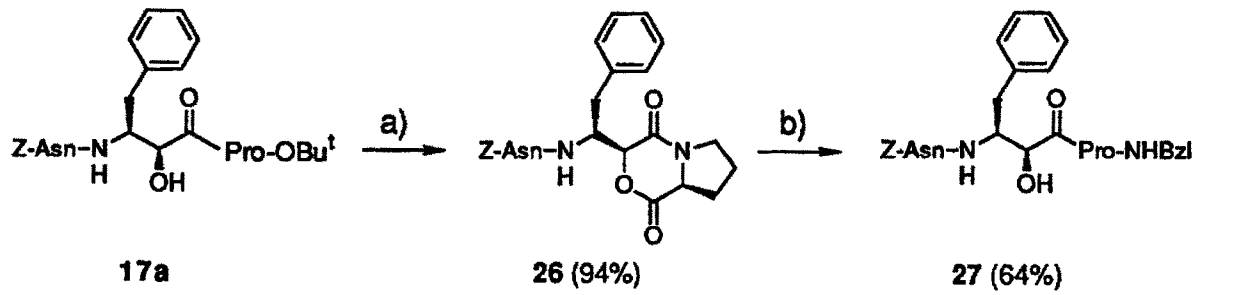
Reagents and conditions: (a) Z-Asn-ONp, Et_3N, DMF, 4 °C; b) *N*-2-phenethylglycine *tert*-butyl amide hydrochloride, WSCI-HOBT, Et_3N, DMF, 4 °C.

Scheme III.



Reagents and conditions: (a) Ac_2O, DMAP, CH_2Cl_2, 0 °C; (b) *N*-2-phenethyl- L-alanine *tert*-butyl amide hydrochloride, PyBrop®, Et_3N, DMF, rt; (c) 1 N NaOH, MeOH, 0 °C; (d) i) 4 N HCl/dioxane, rt.; ii) Z-Asn-ONp, Et_3N, DMF, rt.

Scheme IV.



Reagents and conditions: (a) i) 4 N HCl/dioxane, rt; ii) benzylamine, rt.

Scheme V.

Biological activity

The inhibitory activities of the compounds toward HIV-1 PR were determined by sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS–PAGE) assay and kinetic study as described in a previous report.[6] Initially, inhibitory activity relative to pepstatin A (Iva–Val–Val–Sta–Ala–Sta–OH; Iva = isovaleryl, Sta = statine, K_i = 1.1 μM) was determined using recombinant 55 kDa *gag* substrate and protease. Tables 1–6 display the concentrations that are approximately equipotent with 1 μM pepstatin A. The recombinant 55 kDa *gag* protein includes three scission sites (p17/p24, C terminus of p24, and N terminus of p7). Therefore, this assay system can simulate actual enzymatic process: the recognition and cleavage of the proteinic substrates. But it is difficult to evaluate the inhibitors quantitatively, since we visually judge the extent of disappearance of the 55 kDa substrate. Thus, K_i values were determined for active compounds using the partially purified protease and the synthetic substrate Ac–Ser–Gln–Asn–Tyr–Pro–Ile–Val–NH_2.

Structure–activity relationship

In order to ascertain the optimal length of inhibitors and the alcohol configuration of AHPBA, we prepared peptides containing AHPBA incorporated at the scission site analogous to p17/p24 (Table 1).

The chain length significantly affected the inhibitory activity. The potencies of the peptides extending from P_3' amino acid Val changed from moderate to strong with elongation in the N-terminal direction, and finally the longest compound **12a** showed the most potent activity (K_i = 16.5 nM). The difference in activity due to the configuration of the critical hydroxyl group varied between 2- and 9-fold. Deletion of Val, however, led to a significant loss of activity and enlargement of the difference between (*S*)- and (*R*)-alcohols. Transformation of Ile-OMe to OBu^t returned the lost potency, despite the peptide becoming smaller (**17a**). It is noteworthy that the corresponding amide derivative (**18**) was as potent as the ester derivative in our assay system; this is different from the result of Kiso *et al.*[8e]

The more active configuration of the crucial alcohol, which forms hydrogen bonds with the catalytic aspartic acids in the protease, is always (*S*)-configuration. This result reveals that these *erythro*-AHPBA-containing peptides occupy the active site, similar to our potent inhibitors with *erythro*-AHPPA, which is one-carbon longer than AHPBA.[6] Rich *et al.* reported that the preferred alcohol configuration of a hydroxyethylamine isostere, closely related to AHPBA, was inverted when the peptide chains were elongated.[12] In our inhibitors, however, such an inversion was not observed although the difference between (*S*)- and (*R*)-alcohols in inhibitory activity decreased.

Conversion of the phenyl group into a cyclohexyl group at the P_1 site resulted in a 3000-fold reduction of potency (**28**). This finding also proves that AHPBA-containing inhibitors do not correlate with the series of inhibitors containing Cha-ψ[H.E.]-Ala.[7] Compounds **17a** and **18** were selected as our prototypes to be carried out for further transformation; incidentally, the latter is identical with KNI-102.[8c]

Initially, the proline residue at the P_1' site was changed (Table 2). Conversion of proline into D-proline (**29**), glycine (**30**), and phenylalanine (**31**) made the inhibitors inactive. This result suggests that the configuration and imino moiety of L-proline are important for demonstrating inhibitory activity. Numerous reports insist that the protease has a large and hydrophobic pocket in the S_1' site. Success in fitting this pocket was exemplified in Ro-31-8959[13] and L-687,908,[14] which are subnanomolar

Table 1. Inhibitory Activity of HIV inhibitors Containing AHPBA and ACHBA

No.	Compound	Inhibitory Activity[a] (μM)	*Ki* (nM)
6a	Z-Asn-(2*S*, 3*S*)-AHPBA-Pro-Ile-Val-OMe	0.01	93
6b	Z-Asn-(2*R*, 3*S*)-AHPBA-Pro-Ile-Val-OMe	0.1	165
10a	Ac-Leu-Asn-(2*S*, 3*S*)-AHPBA-Pro-Ile-Val-OMe	0.01	24.5
10b	Ac-Leu-Asn-(2*R*, 3*S*)-AHPBA-Pro-Ile-Val-OMe	0.1	215
12a	Ac-Ser-Leu-Asn-(2*S*, 3*S*)-AHPBA-Pro-Ile-Val-OMe	0.01	16.5
12b	Ac-Ser-Leu-Asn-(2*R*, 3*S*)-AHPBA-Pro-Ile-Val-OMe	0.01	31.5
7a	Z-Asn-(2*S*, 3*S*)-AHPBA-Pro-Ile-OMe	0.1	
7b	Z-Asn-(2*R*, 3*S*)-AHPBA-Pro-Ile-OMe	100	
11a	Ac-Leu-Asn-(2*S*, 3*S*)-AHPBA-Pro-Ile-OMe	0.1	
11b	Ac-Leu-Asn-(2*R*, 3*S*)-AHPBA-Pro-Ile-OMe	30	
13a	Ac-Ser-Leu-Asn-(2*S*, 3*S*)-AHPBA-Pro-Ile-OMe	0.03	105
13b	Ac-Ser-Leu-Asn-(2*R*, 3*S*)-AHPBA-Pro-Ile-OMe	10	
17a	Z-Asn-(2*S*, 3*S*)-AHPBA-Pro-OBu^t	0.01	58
17b	Z-Asn-(2*R*, 3*S*)-AHPBA-Pro-OBu^t	1	
18	Z-Asn-(2*S*, 3*S*)-AHPBA-Pro-$NHBu^t$	0.01	57.5
28[b]	Z-Asn-(2*S*, 3*S*)-ACHBA-Pro-$NHBu^t$	30	

[a] Inhibitory activity is given as the concentration which is equipotent with 1 μM pepstatin A.
[b] ACHBA = 3-amino-4-cyclohexyl-2-hydroxybutanoic acid.

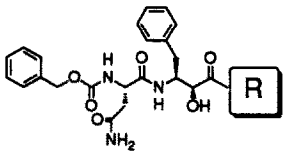
inhibitors. Thus, we also aimed at this hydrophobic pocket. The compounds with piperidine-2(*S*)-carbonyl (**32**), (4a*S*,8a*S*)-decahydroisoquinoline-3(*S*)-carbonyl (**33**), and 1,2,3,4-tetrahydroisoquinoline-3(*RS*)-carbonyl (**34**) groups were prepared. These compounds were shown to be poor inhibitors, in line with the suggestion of Krantz *et al.* that the monocyclic and bicyclic six-membered ring systems are disadvantageous in the AHPBA series.[8d]

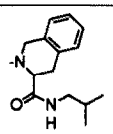
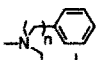
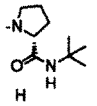
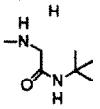
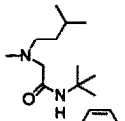
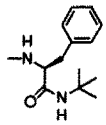
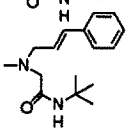
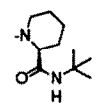
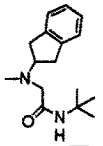
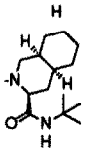
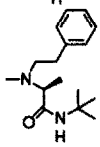
The importance of the tertiary amide bond between the P_1 and P_1' sites led to the *N*-alkylated glycine derivatives. Although *N*-benzyl derivative **35** became a weak inhibitor, the *N*-2-phenethyl and *N*-3-phenylpropyl derivatives (**21** and **36**) showed approximately one-third the potency of the reference compound **18**. However, the aliphatically substituted and conformationally restricted derivatives (**37–39**) led to a slight to significant decrease in potency. The inhibitory activity of *N*-2-phenethyl-L-alanine derivative **25** was reduced to 1 μM, while that of the corresponding glycine derivative **21** was 0.03 μM. These transformations revealed that the benzene ring of the *N*-2-phenethyl and *N*-3-phenylpropyl groups probably reaches the hydrophobic pocket, aided by the flexible structure of these compounds. However, these compounds did not satisfactorily occupy this subsite, and thus the compounds examined here could not exceed the reference compound **18**.

Subsequently, exploration at the P_2' site was conducted, with Z-Asn-AHPBA-Pro kept constant (Table 3). Neither a primary nor a tertiary amide could improve the potency (**40** and **41**), but some secondary amides with hydrophobic substituents (**42** and **27**) exhibited roughly the same potency as the reference compound **18**. Interestingly, the hydrophobic pocket at this site may not be wide, so that even a small transformation, such as the addition of a methyl group (**43** and **44**) or the insertion of a methylene group (**45**) into the methylene moiety of the benzyl amide (**27**), disrupts favorable interaction. Conversion of the benzene ring in compound **27** into a pyridine ring also decreased inhibitory activity (**46–48**).

Next, the side chain of the amino acid at the P_2 site was optimized (Table 4). Although incorporation of D-asparagine led to a weak inhibitor (**49**), aspartic acid had only a small reducing effect on potency (**50**). Therefore, several amide derivatives of aspartic acid were examined. Methyl, dimethyl, and piperidino amides decreased inhibitory activity (**51–53**). However, glutamine and

Table 2. P_1' Variations of HIV-1 PR Inhibitors Containing (2*S*,3*S*)-AHPBA



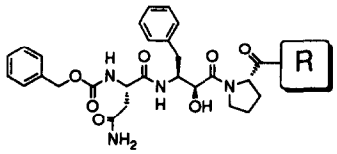
No.	R	Inhibitory Activity[a] (μM)	*Ki* (nM)	No.	R	Inhibitory Activity[a] (μM)	*Ki* (nM)
17a		0.01	58	**34**		1	
18		0.01	57.5	**35**		n=1 3	
				21		n=2 0.03	135
29		100		**36**		n=3 0.1	160
30		>100		**37**		3	
31		>100		**38**		10	
32		0.1		**39**		0.3	
33		0.3		**25**		1	

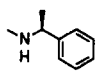
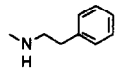
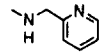
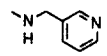
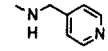
[a] inhibitory activity is given as the concentration which is equipotent with 1 μM pepstatin A.

glutamic acid exhibited one-third to one-half the potency of asparagine (**54** and **55**). Conversion into the other amino acids led to weak inhibitors (**56–61**). Our results suggest the importance of both hydrogen bond acceptors and donors at this site, although Kiso *et al.* have already reported that the peptides that contain hydrophobic amino acids without the hydrogen bonding interaction, such as methylthioalanine, valine, and isoleucine, are good inhibitors.[15]

Finally, the benzyloxycarbonyl group at the P_3 site was substituted (Table 5). Conversion of the benzyloxy moiety into a benzylamino moiety led to a decrease in potency (**62**). However, phenoxyacetyl derivative **63** had one-half the activity of compound **17a**. These results suggest that a hydrogen acceptor is necessary at this position. Therefore, pyridine-2-carbonyl and quinoline-2-carbonyl derivatives, which have a hydrogen acceptor in their ring systems, were introduced into this site (**64–66**). Interestingly, 5-*n*-

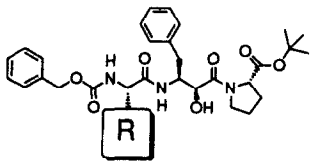
Table 3. P_2' Variations of HIV-1 PR Inhibitors Containing (2*S*,3*S*)-AHPBA

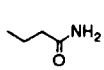
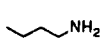
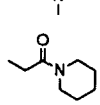


No.	R	Inhibitory Activity[a] (μM)	*Ki* (nM)	No.	R	Inhibitory Activity[a] (μM)
18		0.01	57.5	**44**		0.1
40		3		**45**		1
41		0.3				
42		0.03	45	**46**		0.1
27		0.03		**47**		0.1
43		0.3		**48**		0.1

[a] inhibitory activity is given as the concentration which is equipotent with 1 μM pepstatin A.

Table 4. P_2 Variations of HIV-1 PR Inhibitors Containing (2*S*,3*S*)-AHPBA



No.	R	Inhibitory Activity[a] (μM)	*Ki* (nM)	No.	R	Inhibitory Activity[a] (μM)	*Ki* (nM)
17a	 Asn	0.01	58	**54**	 Gln	0.03	185
49	 D-Asn	3		**55**	 Glu	0.03	95.5
50	 Asp	0.03	118	**56**	 Orn	0.3	
51		0.1		**57**		1	
				58	 Ser	0.3	
52		0.3		**59**	 Phe	0.3	
53		0.3		**60**	 His	0.3	
				61	H Gly	0.3	

[a] inhibitory activity is given as the concentration which is equipotent with 1 μM pepstatin A.

butylpyridine-2-carbonyl derivative **65** showed the same activity as phenoxyacetyl derivative **63**, and quinoline-2-carbonyl derivative **66** was 1.5 times more potent than the prototype compound **17a**. From comparison with pyridine-2-carbonyl derivative **64**, hydrophobic moieties such as the *n*-butyl group in compound **65** and the benzene ring in compounds **63** and **66** were found to be crucial for demonstrating reasonable inhibitory activity. While the extent of the loss in potency of naphthalene-2-carbonyl derivative **67** was small, the potency of naphthalene-2-sulfonyl derivative **68** decreased significantly. Quinoline-3-carbonyl derivative **69** as well as 2-carbonyl derivative **66** were strong inhibitors, in contrast with 4-carbonyl derivative **70**. We were also eventually able to substitute the quinoline-2-carbonyl group with quinoxaline-, indole-, and benzofuran-2-carbonyl groups without loss of activity (**71–73**). This systematic transformation indicates that some bicyclic heteroarylcarbonyl groups are suitable for this site. This result also implies that both hydrophobic interaction and hydrogen bonding between inhibitors and HIV-1 PR play an important role at this site.

Moreover, conversion of the *tert*-butyl esters into the *tert*-butyl amides was found to increase inhibitory activity by factors of 1.5 to 4 (**74–76**). Thus, several excellent inhibitors could be obtained.

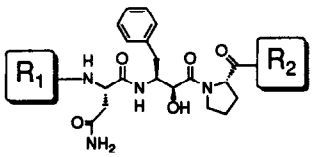
Enzyme selectivity

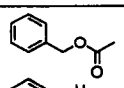
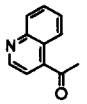
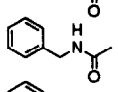
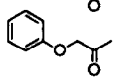
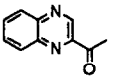
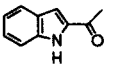
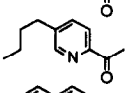
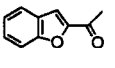
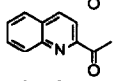
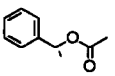
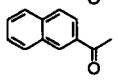
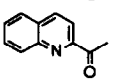
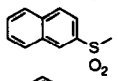
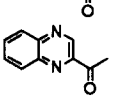
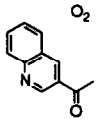
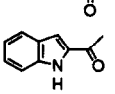
Some of the potent inhibitors obtained in this study were examined for enzyme selectivity. The inhibitory activities of compounds **17a**, **66**, **67** and **75** toward the closely-related aspartic proteases, pepsin,[16] cathepsin D,[17] and renin,[18] are shown in Table 6. None of the compounds tested showed any significant inhibition of these mammalian enzymes even at 30 μM. This high enzyme selectivity is probably due to the *erythro*-configuration of AHPBA; the *threo*-configuration of aminoalcohols as transition-state analogs is strictly conserved among the potent inhibitors of the mammalian enzymes.[5, 19]

Conclusion

We prepared AHPBA-containing inhibitors, and evaluated their inhibitory activity against HIV-1 PR. Systematic replacement at the sites from P_3 to P_2' gave several compounds with strong potency and high enzyme selectivity. In particular, the inhibitors containing bicyclic heteroarylcarbonyl groups at the P_3 and *tert*-butyl amide group at the P_2' have K_i values near to 10^{-9} M and molecular weights of around 600. Studies to determine the antiviral activity and oral bioavailability of a number of these compounds are currently in progress.

Table 5. P_3 Variations of HIV-1 PR Inhibitors Containing (2*S*,3*S*)-AHPBA



No.	R_1	R_2	Inhibitory Activity[a] (μM)	*Ki* (nM)	No.	R_1	R_2	Inhibitory Activity[a] (μM)	*Ki* (nM)
17a		OBu^t	0.01	58	**70**		OBu^t	0.1	
62		OBu^t	0.3						
63		OBu^t	0.03	130	**71**		OBu^t	0.01	45
64		OBu^t	0.3		**72**		OBu^t	0.01	25
65		OBu^t	0.03	160	**73**		OBu^t	0.01	36.5
66		OBu^t	0.01	36	**18**		NHBu^t	0.01	57.5
67		OBu^t	0.01	47	**74**		NHBu^t	0.01	27
68		OBu^t	0.3		**75**		NHBu^t	0.01	11
69		OBu^t	0.01	32.5	**76**		NHBu^t	0.01	18

[a] inhibitory activity is given as the concentration which is equipotent with 1 μM pepstatin A.

Table 6. Enzyme selectivity

No.	HIV-1 Protease		Pepsin	Cathepsin D	Renin
	Inhibitory Activity (M) [a]	*Ki* (M)	IC_{50} (M)	IC_{50} (M)	IC_{50} (M)
17a	1×10^{-8}	5.8×10^{-8}	7.8×10^{-4}	2.2×10^{-4}	0% at 3.0×10^{-5}
66	1×10^{-8}	3.6×10^{-8}	3.4×10^{-4}	2.6×10^{-4}	—
67	1×10^{-8}	4.7×10^{-8}	2.5×10^{-4}	6.1×10^{-4}	—
75	1×10^{-8}	1.1×10^{-8}	1.0×10^{-3}	$>8.6 \times 10^{-4}$	$>2.5 \times 10^{-3}$

[a] inhibitory activity is given as the concentration which is equipotent with 1 μM pepstatin A.

Experimental

Melting points were determined with a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were measured with a Nic 5SXC FT-IR spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL JNM-GX 270 FT-NMR. Chemical shifts are expressed in δ ppm from the internal standard tetramethylsilane. Mass spectra (MS) were taken on a JEOL JMS-D 300 mass spectrometer. Column chromatography was carried out on Kieselgel 60 F_{254} (Merck, 70–230 mesh). Preparative thin-layer chromatographies were run on Kieselgel 60 F_{254} plates (Merck art. 5717 or art. 5744). The organic solutions were dried over Na_2SO_4 before vacuum evaporation.

*(2S, 3S)-3-*tert*-Butoxycarbonylamino-2-hydroxy-4-phenylbutyryl-L-prolyl-L-isoleucyl-L-valine methyl ester (Boc-(2S,3S)-AHPBA-Pro-Ile-Val-OMe* **4a***)*

tert*-Butoxycarbonyl-L-prolyl-L-isoleucyl-L-valine methyl ester (Boc-Pro-Ile-Val-OMe).* Boc-Ile-Val-OMe[6] (1.30 g, 3.77 mmol) was added to 4 N HCl/dioxane solution (5 mL), and this solution was stirred for 30 min at room temperature. The solvent was removed *in vacuo*, and the remaining solid was evaporated with benzene. The residue was dried *in vacuo* for 2 h. This solid was dissolved in DMF (4 mL), and then Boc-Pro-OH (893 mg, 4.15 mmol), 93 % diethylphosphoryl cyanide (DEPC; 0.68 mL, 4.15 mmol), and triethylamine (1.29 mL, 9.30 mmol) were added at 0 °C. The mixture was stirred for 2 h at room temperature, then the solvent was removed *in vacuo*. The residue was extracted with ethyl acetate (AcOEt), and the organic layer was washed with 5 % citric acid, 5 % $NaHCO_3$, and brine. Drying followed by evaporation and purification by crystallization from *n*-hexane afforded Boc-Pro-Ile-Val-OMe (1.61 g, 97 %) as colorless crystals. mp 110–111 °C. $[\alpha]_D^{25}$ −88.9 ° (c = 0.63, $CHCl_3$). Anal. calcd for $C_{22}H_{39}N_3O_6$: C, 59.84; H, 8.90; N, 9.52; found: C, 59.61; H, 8.78; N, 9.44. IR (KBr) 3312, 1751, 1699, 1646 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.86–0.97 (m, 12H), 1.05–1.25 (m, 1H), 1.37–1.57 (m, 10H), 1.81–2.40 (m, 6H), 3.45 (br s, 1H), 3.73 (s, 3H), 4.21–4.40 (m, 2H), 4.51 (dd, *J* = 4.9, 8.8 Hz, 1H), 6.60 (br s, 1H). MS m/z : 441 (M^++1), 340, 283, 227, 170, 114, 86, 70, 57.

*(2S,3S)-3-*tert*-Butoxycarbonylamino-2-hydroxy-4-phenylbutyryl-L-prolyl-L-isoleucyl-L-valine methyl ester (Boc-(2S, 3S)-AHPBA-Pro-Ile-Val-OMe,* **4a***).* Boc-Pro-Ile-Val-OMe (344 mg, 0.78 mmol) was added to 4N HCl/dioxane solution (4 mL), and this solution was stirred for 30 min at room temperature. The solvent was removed *in vacuo*, and the remaining solid was evaporated with benzene. The residue was dried *in vacuo* for 2 h. This solid was dissolved in DMF (4 mL), and then Boc-(2*S*,3*S*)-AHPBA-OH[8b] **3a** (241 mg, 0.82 mmol), 93 % DEPC (0.14 mL, 0.86 mmol), and triethylamine (0.22 mL, 1.56 mmol) were added at 0 °C. The mixture was stirred for 16 h at 4 °C, then the solvent was removed *in vacuo*. The residue was extracted with AcOEt, and the organic layer was washed with 5 % citric acid, 5 % $NaHCO_3$, and brine. Drying followed by evaporation and purification by preparative thin layer chromatography (PTLC) (CH_2Cl_2:MeOH = 10:1) afforded **4a** (414 mg, 86 %) as a white solid. Mp 77–79 °C. $[\alpha]_D^{25}$ −56.1 ° (c = 0.47, MeOH). Anal. calcd for $C_{32}H_{50}N_4O_8 \cdot H_2O$: C, 60.35; H, 8.23; N, 8.80; found: C, 60.44; H, 8.07; N, 8.56. IR (KBr) 3316, 1744, 1695, 1653 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.79–0.99 (m, 12H), 1.10–1.65 (m, 13H), 1.80–2.15 (m, 4H), 2.62–2.84 (m, 2H), 3.65–3.86 (m, 5H), 4.02–4.38 (m, 3H), 4.45–4.62 (m, 3H), 5.06 (br d, *J* = 9.9 Hz, 1H), 6.28 (br d, *J* = 8.6 Hz, 1H), 6.78 (br d, *J* = 8.6 Hz, 1H), 7.15–7.34 (m, 5H). MS m/z : 619 (M^++1), 399, 342, 268, 247, 183, 132, 120, 86, 70, 57.

The compounds mentioned below were prepared as described above for **4a** using the corresponding starting materials instead of **3a** and/or Boc-Ile-Val-OMe.

*(2R,3S)-3-*tert*-Butoxycarbonylamino-2-hydroxy-4-phenylbutyryl-L-prolyl-L-isoleucyl-L-valine methyl ester (Boc-(2R,3S)-AHPBA-Pro-Ile-Val-OMe,* **4b***).* Yield 70 %. Mp 79–81 °C. $[\alpha]_D^{25}$ −147.0 ° (c = 0.03, MeOH). Anal. calcd for $C_{32}H_{50}N_4O_8 \cdot 0.75H_2O$: C, 60.75; H, 8.21; N, 8.86; found: C, 60.67; H, 7.56; N, 8.77. IR (KBr) 3309, 2971, 1746, 1704, 1651 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.85–1.45 (m, 25H), 1.86–2.29 (m, 4H), 2.81–2.97 (m, 2H), 3.11–3.20 (m, 1H), 3.34–3.45 (m, 1H), 3.72 (s, 3H), 3.89–4.01 (m, 1H), 4.08–4.25 (m, 3H), 4.36 (d, *J* = 6.6 Hz, 1H), 4.50 (dd, *J* = 5.3, 8.6 Hz, 1H), 4.88 (br d, *J* = 9.9 Hz, 1H), 6.40 (br d, *J* = 8.6 Hz, 1H), 7.08 (br d, *J* = 7.9 Hz, 1H), 7.21–7.37 (m, 5H). MS m/z: 637 (M^+), 486, 337, 229, 91, 84.

*(2S,3S)-3-*tert*-Butoxycarbonylamino-2-hydroxy-4-phenylbutyryl-L-prolyl-L-isoleucine methyl ester (Boc-(2S,3S)-AHPBA-Pro-Ile-OMe,* **5a***).* Yield 80 %. Oil. $[\alpha]_D^{25}$ −8.3 °

(c = 0.42, $CHCl_3$). Anal. calcd for $C_{27}H_{41}N_3O_7 \cdot 1.5H_2O$: C, 59.32; H, 8.11; N, 7.69; found: C, 59.17; H, 7.66; N, 6.93. IR (Film) 3332, 1741, 1688 cm^{-1}. ^1H NMR (CD_3OD) δ: 0.87–0.97 (m, 6H), 1.19–1.59 (m, 12H), 1.65–2.27 (m, 4H), 2.63 (dd, *J* = 10.7, 13.7 Hz, 1H), 2.81 (dd, *J* = 3.4, 13.7 Hz, 1H), 3.69–3.82 (m, 5H), 4.00–4.10 (m, 1H), 4.38–4.47 (m, 2H), 4.55–4.62 (m, 1H), 7.12–7.31 (m, 5H). MS m/z: 520 (M^++1), 420, 300, 273, 243, 183, 164, 155, 146, 128, 120, 91, 86, 70, 57.

*(2R,3S)-3-*tert*-Butoxycarbonylamino-2-hydroxy-4-phenylbutyryl-L-prolyl-L-isoleucine methyl ester (Boc-(2R,3S)-AHPBA-Pro-Ile-OMe, 5b).* Yield 95 %. Mp 37–39 °C. $[\alpha]_D^{25}$ –59.8 ° (c = 0.22, $CHCl_3$). Anal. calcd for $C_{27}H_{41}N_3O_7 \cdot 0.5H_2O$: C, 61.34; H, 8.01; N, 7.95; found: C, 61.32; H, 7.89; N, 7.68. IR (KBr) 3332, 1744, 1701, 1693 cm^{-1}. ^1H NMR (CD_3OD) δ: 0.88–0.97 (m, 6H), 1.15–1.55 (m, 12H), 1.81–2.18 (m, 4H), 2.84 (dd, *J* = 7.3, 13.2 Hz, 1H), 2.94 (dd, *J* = 7.8, 13.2 Hz, 1H), 3.28–3.45 (m, 2H), 3.69 (s, 3H), 4.05–4.14 (m, 1H), 4.21–4.25 (m, 1H), 4.30–4.40 (m, 2H), 7.18–7.42 (m, 5H). MS m/z:520 (M^++1), 428, 300, 273, 247, 243, 183, 155, 146, 120, 91, 70, 57.

(2S,3S)-3-(N-Benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutyryl-L-prolyl-L-isoleucyl-L-valine methyl ester (Z-Asn-(2S,3S)-AHPBA-Pro-Ile-Val-OMe, 6a). Boc-(2*S*,3*S*)-AHPBA-Pro-Ile-Val-OMe **4a** (385 mg, 0.62 mmol) was added to 4N HCl/dioxane solution (5 mL), and this solution was stirred for 30 min at room temperature. The solvent was removed *in vacuo*, and the remaining solid was evaporated with benzene. The residue was dried *in vacuo* for 2 h. This solid was dissolved in DMF (3 mL), and then Z-Asn–ONp (289 mg, 0.75 mmol) and triethylamine (0.21 mL, 1.49 mmol) were added at 0 °C. The reaction mixture was stirred for 24 h at room temperature, then the solvent was removed *in vacuo*. The residue was extracted with AcOEt, and the organic layer was washed with 5 % citric acid, 5 % $NaHCO_3$, and brine. Purification by crystallization from diethylether afforded **6a** (330 mg, 69 %) as colorless crystals. Mp 126–129 °C. $[\alpha]_D^{25}$ –64.1 ° (c = 0.36, MeOH). Anal. calcd for $C_{39}H_{54}N_6O_{10} \cdot H_2O$: C, 59.68; H, 7.19; N, 10.71; found: C, 59.50; H, 6.91; N, 10.59. IR (KBr) 3315, 1736, 1697, 1649 cm^{-1}. ^1H NMR (CD_3OD) δ: 0.84–0.98 (m, 12H), 1.13–1.20 (m, 1H), 1.53–1.65 (m, 1H), 1.75–2.27 (m, 6H), 2.42 (dd, *J* = 7.8, 15.1 Hz, 1H), 2.55 (dd, *J* = 5.4, 15.4 Hz, 1H), 2.73–2.95 (m, 2H), 3.68–3.78 (m, 5H), 4.24–4.34 (m, 3H), 4.42–4.52 (m, 3H), 5.08 (s, 2H), 7.09–7.37 (m, 10H). MS m/z: 749 (M^+-17), 500, 415, 399, 386, 301, 273, 260, 183, 155, 132, 120, 91, 86, 70.

The compounds mentioned below were prepared as described above for **6a** using the corresponding starting materials instead of **4a**.

(2R,3S)-3-(N-Benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutyryl-L-prolyl-L-isoleucyl-L-valine methyl ester (Z-Asn-(2R,3S)-AHPBA-Pro-Ile-Val-OMe, 6b)

Yield 70 %. Mp 168–169 °C. $[\alpha]_D^{25}$ –92.3 ° (c = 0.50, MeOH). Anal. calcd for $C_{39}H_{54}N_6O_{10} \cdot 0.25H_2O$: C, 60.72; H, 7.12; N, 10.90; found: C, 60.68; H, 7.04; N, 10.90. IR (KBr) 3295, 1743, 1705, 1657 cm^{-1}. ^1H NMR (CD_3OD) δ: 0.84–0.99 (m, 12H), 1.07–1.22 (m, 1H), 1.49–1.63 (m, 1H), 1.73–1.93 (m, 4H), 2.02–2.18 (m, 2H), 2.48 (dd, *J* = 7.8, 15.1 Hz, 1H), 2.65 (dd, *J* = 4.9, 15.1 Hz, 1H), 2.82–3.04 (m, 2H), 3.25–3.38 (m, 2H), 3.69 (s, 3H), 4.20–4.31 (m, 4H), 4.33–4.47 (m, 2H), 5.09 (s, 2H), 7.19–7.39 (m, 10H). MS m/z: 749 (M^+-17), 500, 415, 387, 301, 273, 260, 183, 155, 132, 120, 91, 86, 70.

(2S,3S)-3-(N-Benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutyryl-L-prolyl-L-isoleucine methyl ester (Z-Asn-(2S,3S)-AHPBA-Pro-Ile-OMe, 7a)

Yield 66 %. Mp 96–99 °C. $[\alpha]_D^{25}$ –40.0 ° (c = 0.60, MeOH). Anal. calcd for $C_{34}H_{45}N_5O_9 \cdot 0.5H_2O$: C, 60.34; H, 6.85; N, 10.35; found: C, 60.07; H, 6.56; N, 10.31. IR (KBr) 3331, 1732, 1670 cm^{-1}. ^1H NMR (CD_3OD) δ: 0.85–0.95 (m, 6H), 1.18–1.34 (m, 1H), 1.40–1.55 (m, 1H), 1.81–2.29 (m, 5H), 2.43 (dd, *J* = 8.3, 15.1 Hz, 1H), 2.60 (dd, *J* = 5.4, 15.1 Hz, 1H), 2.73–2.94 (m, 2H), 3.69–3.79 (m, 5H), 4.29–4.49 (m, 4H), 4.51–4.58 (m, 1H), 5.07 (s, 2H), 7.09–7.38 (m, 10H). MS m/z: 650 (M^+-17), 560, 387, 300, 290, 155, 120, 91, 86, 70.

(2R,3S)-3-(N-Benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutyryl-L-prolyl-L-isoleucine methyl ester (Z-Asn-(2R,3S)-AHPBA-Pro-Ile-OMe, 7b)

Yield 57 %. Mp 123–124 °C. $[\alpha]_D^{25}$ –84.9 ° (c = 0.70, MeOH). Anal. calcd for $C_{34}H_{45}N_5O_9 \cdot 0.75H_2O$: C, 59.94; H, 6.88; N, 10.28; found: C, 59.95; H, 6.70; N, 10.25. IR (KBr) 3303, 1736, 1704, 1656 cm^{-1}. ^1H NMR (CD_3OD) δ: 0.84–0.93 (m, 6H), 1.12–1.28 (m, 1H), 1.40–1.52 (m, 1H), 1.79–1.97 (m, 4H), 2.02–2.18 (m, 1H), 2.48 (dd, *J* = 8.3, 15.1 Hz, 1H), 2.65 (dd, *J* = 4.9, 15.1 Hz, 1H), 2.81–3.01 (m, 2H), 3.23–3.35 (m, 2H), 3.68 (s, 3H), 4.23–4.45 (m, 5H), 5.09 (s, 2H), 7.15–7.38 (m, 10H). MS m/z: 650 (M^+-17), 560, 387, 300, 290, 273, 155, 146, 120, 91, 86, 70.

(2S,3S)-3-(N-tert-Butoxycarbonyl-L-leucyl-L-asparaginyl)-amino-2-hydroxy-4-phenylbutyryl-L-prolyl-L-isoleucyl-L-valine methyl ester (Boc-Leu-Asn-(2S,3S)-AHPBA-Pro-Ile-Val-OMe, 8a)

A mixture of **6a** (200 mg, 0.26 mmol), 1 N HCl (0.29 mL, 0.29 mmol), and 10 % Pd/C (50 mg) in MeOH (4 mL) was stirred under a hydrogen atmosphere for 1 h at room temperature. The catalyst was filtered off and the filtrate was concentrated. The residue was dissolved in DMF (3 mL), and then Boc–Leu–OH·H_2O (85 mg, 0.34 mmol), 93 % DEPC (55 μL, 0.34 mmol), and triethylamine (91 μL, 0.65 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature for 2 h, and precipitated with 5 % $NaHCO_3$. The precipitate was washed with 0.5 N HCl and water. Purification by reprecipitation from diethylether afforded **8a** (169 mg, 77 %) as a white solid. Mp 126–129 °C. $[\alpha]_D^{25}$ –56.5 ° (c = 0.18, MeOH). Anal. calcd for $C_{42}H_{67}N_7O_{11} \cdot 0.75H_2O$: C, 58.69; H, 8.03; N, 11.41; found: C, 58.67; H, 7.93; N, 11.39. IR (KBr) 3316, 1742, 1657 cm^{-1}. ^1H NMR (CD_3OD) δ: 0.86–0.98 (m, 18H), 1.05–1.19 (m, 1H),

1.35–2.35 (m, 19H), 2.49–2.59 (m, 2H), 2.78 (dd, J = 10.3, 14.2 Hz, 1H), 2.91 (dd, J = 3.9, 14.2 Hz, 1H), 3.69–3.80 (m, 5H), 3.99–4.09 (m, 1H), 4.21–4.35 (m, 3H), 4.45–4.65 (m, 3H), 7.10–7.30 (m, 5H).

The compounds mentioned below were prepared as described above for **8a** using the corresponding starting materials instead of **6a**.

*(2R,3S)-3-(*N-tert-*Butoxycarbonyl-L-leucyl-L-asparaginyl)-amino-2-hydroxy-4-phenylbutyryl-L-prolyl-L-isoleucyl-L-valine methyl ester (Boc–Leu–Asn–(2R,3S)-AHPBA-Pro–Ile–Val–OMe, **8b**)*

Yield 82 %. Mp 198–200 °C. $[\alpha]_D^{25}$ −94.1 ° (c = 0.28, MeOH). Anal. calcd for $C_{42}H_{67}N_7O_{11}\cdot 0.5H_2O$: C, 59.00; H, 8.02; N, 11.47; found: C, 58.85; H, 7.92; N, 11.45. IR (KBr) 3297, 1745, 1649 cm^{-1}. ^1H NMR (CD_3OD) δ: 0.85–0.99 (m, 18H), 1.10–1.23 (m, 1H), 1.40–1.92 (m, 17H), 2.03–2.19 (m, 2H), 2.59 (dd, J = 6.8, 15.1 Hz, 1H), 2.69 (dd, J = 5.4, 15.1 Hz, 1H), 2.86 (dd, J = 6.3, 13.2 Hz, 1H), 2.99 (dd, J = 8.8, 13.2 Hz, 1H), 3.19–3.42 (m, 2H), 3.70 (s, 3H), 4.03–4.11 (m, 1H), 4.19–4.41 (m, 5H), 4.57–4.64 (m, 1H), 7.20–7.31 (m, 5H).

*(2S,3S)-3-(*N-tert-*Butoxycarbonyl-L-leucyl-L-asparaginyl)-amino-2-hydroxy-4-phenylbutyryl-L-prolyl-L-isoleucine methyl ester (Boc–Leu–Asn–(2S,3S)-AHPBA-Pro–Ile–OMe, **9a**)*

Yield 80 %. Mp 110–112 °C. $[\alpha]_D^{25}$ −36.9 ° (c = 0.42, MeOH). Anal. calcd for $C_{37}H_{58}N_6O_{10}\cdot 1.5H_2O$: C, 57.42; H, 7.95; N, 10.86; found: C, 57.33; H, 7.94; N, 10.73. IR (KBr) 3329, 1738, 1672 cm^{-1}. ^1H NMR (CD_3OD) δ: 0.85–0.97 (m, 12H), 1.20–1.72 (m, 14H), 1.82–2.28 (m, 5H), 2.54 (dd, J = 6.4, 15.1 Hz, 1H), 2.63 (dd, J = 6.4, 15.1 Hz, 1H), 2.74 (dd, J = 10.3, 14.2 Hz, 1H), 2.88 (dd, J = 3.4, 14.2 Hz, 1H), 3.69–3.81 (m, 5H), 3.98–4.06 (m, 1H), 4.30–4.45 (m, 3H), 4.52–4.62 (m, 2H), 7.10–7.30 (m, 5H). MS m/z: 729 (M^+-17), 647, 501, 328, 300, 243, 228, 183, 146, 120, 86, 70, 56, 41.

*(2R,3S)-3-(*N-tert-*Butoxycarbonyl-L-leucyl-L-asparaginyl)-amino-2-hydroxy-4-phenylbutyryl-L-prolyl-L-isoleucine methyl ester (Boc–Leu–Asn–(2R,3S)-AHPBA-Pro–Ile–OMe, **9b**)*

Yield 87 %. Mp 128–130 °C. $[\alpha]_D^{25}$ −84.9 ° (c = 0.65, MeOH). Anal. calcd for $C_{37}H_{58}N_6O_{10}\cdot H_2O$: C, 58.10; H, 7.91; N, 10.99; found: C, 57.83; H, 7.65; N, 10.96. IR (KBr) 3302, 1738, 1651 cm^{-1}. ^1H NMR (CD_3OD) δ: 0.88–0.97 (m, 12H), 1.15–1.30 (m, 1H), 1.40–1.58 (m, 12H), 1.62–1.73 (m, 1H), 1.81–1.96 (m, 4H), 2.03–2.16 (m, 1H), 2.60 (dd, J = 6.8, 15.1 Hz, 1H), 2.69 (dd, J = 5.4, 15.1 Hz, 1H), 2.86 (dd, J = 6.3, 13.2 Hz, 1H), 2.98 (dd, J = 8.8, 13.2 Hz, 1H), 3.20–3.31 (m, 2H), 3.69 (s, 3H), 4.03–4.11 (m, 1H), 4.21 (d, J = 1.5 Hz, 1H), 4.29–4.41 (m, 3H), 4.55–4.63 (m, 1H), 7.18–7.33 (m, 5H). MS m/z: 746 (M^+), 729, 647, 501, 328, 300, 243, 228, 183, 146, 120, 100, 86, 70, 57, 41.

*(2S,3S)-3-(*N-Acetyl-L-leucyl-L-asparaginyl)*amino-2-hydroxy-4-phenylbutyryl-L-prolyl-L-isoleucyl-L-valine methyl ester (Ac–Leu–Asn–(2S,3S)-AHPBA-Pro–Ile–Val–OMe, **10a**)*

Boc–Leu–Asn–(2*S*, 3*S*)-AHPBA-Pro–Ile–Val–OMe **8a** (40 mg, 0.047 mmol) was added to 4 N HCl/dioxane solution (1 mL), and this solution was stirred for 30 min at room temperature. The solvent was removed *in vacuo*, and the remaining solid was evaporated with benzene. The residue was dried *in vacuo* for 2 h. The residue was dissolved in DMF (1 mL), and then Ac_2O (4.9 μL, 0.052 mmol) and triethylamine (14.5 μL, 0.104 mmol) were added at 0 °C. The reaction mixture was stirred at the same temperature for 30min, and quenched by the addition of MeOH. The solvent was removed *in vacuo*, and the residue was purified by PTLC (CH_2Cl_2: MeOH = 6:1). Precipitation from *n*-hexane–diethylether (3:1) afforded **10a** (31 mg, 83 %) as a white solid. Mp 223–224 °C. $[\alpha]_D^{25}$ −64.2 ° (c = 0.13, MeOH). Anal. calcd for $C_{39}H_{61}N_7O_{10}\cdot 2.25H_2O$: C, 56.54; H, 7.97; N, 11.84; found: C, 56.33; H, 7.60; N, 11.81. IR (KBr) 3305, 1744, 1653 cm^{-1}. ^1H NMR (CD_3OD) δ: 0.83–0.98 (m, 18H), 1.15–1.29 (m, 1H), 1.48–2.22 (m, 13H), 2.53–2.59 (m, 2H), 2.80 (dd, J = 10.3, 14.2 Hz, 1H), 2.92 (dd, J = 3.9, 14.2 Hz, 1H), 3.69–3.81 (m, 5H), 4.27–4.35 (m, 4H), 4.46–4.61 (m, 3H), 7.10–7.30 (m, 5H). MS m/z: 788 (M^++1), 612, 527, 399, 344, 268, 183, 156, 132, 128, 120, 91, 86, 70.

The compounds mentioned below were prepared as described above for **10a** using the corresponding starting materials instead of **8a**.

*(2R,3S)-3-(*N-Acetyl-L-leucyl-L-asparaginyl)*amino-2-hydroxy-4-phenylbutyryl-L-prolyl-L-isoleucyl-L-valine methyl ester (Ac–Leu–Asn–(2R,3S)-AHPBA-Pro–Ile–Val–OMe, **10b**)*

Yield 81 %. Mp 212–214 °C. $[\alpha]_D^{25}$ −105.1 ° (c = 0.06, MeOH). Anal. calcd for $C_{39}H_{61}N_7O_{10}\cdot 2.5H_2O$: C, 56.23; H, 7.99; N, 11.77; found: C, 56.03; H, 7.36; N, 11.76. IR (KBr) 3300, 1745, 1656 cm^{-1}. ^1H NMR (CD_3OD) δ: 0.85–0.99 (m, 18H), 1.10–1.23 (m, 1H), 1.51–2.18 (m, 13H), 2.60 (dd, J = 7.3, 15.6 Hz, 1H), 2.70 (dd, J = 5.4, 15.6 Hz, 1H), 2.86 (dd, J = 6.4, 13.2 Hz, 1H), 2.99 (dd, J = 8.8, 13.2 Hz, 1H), 3.22–3.39 (m, 2H), 3.70 (s, 3H), 4.20–4.41 (m, 6H), 4.54–4.60 (m, 1H), 7.18–7.32 (m, 5H). MS m/z: 770 (M^+-17), 527, 499, 399, 268, 183, 156, 128, 120, 91, 86, 70.

*(2S,3S)-3-(*N-Acetyl-L-leucyl-L-asparaginyl)*amino-2-hydroxy-4-phenylbutyryl-L-prolyl-L-isoleucine methyl ester (Ac–Leu–Asn–(2S,3S)-AHPBA-Pro–Ile–OMe, **11a**)*

Yield 71 %. Mp 145–148 °C. $[\alpha]_D^{25}$ −57.1 ° (c = 0.08, MeOH). Anal. calcd for $C_{34}H_{52}N_6O_9\cdot 1.5H_2O$: C, 57.04; H, 7.74; N, 11.74; found: C, 56.88; H, 7.69; N, 11.39. IR (KBr) 3316, 1741, 1662 cm^{-1}. ^1H NMR (CD_3OD) δ: 0.85–0.98 (m, 12H), 1.20–1.35 (m, 1H), 1.42–1.71 (m, 4H), 1.82–2.26 (m, 8H), 2.49–2.66 (m, 2H), 2.77 (dd, J = 10.3, 14.2 Hz, 1H), 2.88 (dd, J = 3.9, 14.2 Hz, 1H), 3.68–3.83 (m, 5H), 4.18–4.46 (m, 4H), 4.51–4.60 (m, 2H),

7.10–7.30 (m, 5H). MS m/z: 689 (M^++1), 671, 501, 300, 243, 183, 155, 146, 128, 120, 86, 70.

(2R,3S)-3-(N-Acetyl-L-leucyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutyryl-L-prolyl-L-isoleucine methyl ester (Ac–Leu–Asn–(2R,3S)-AHPBA-Pro–Ile–OMe, 11b)

Yield 92 %. Mp 118–119 °C. $[\alpha]_D^{25}$ –88.0 ° (c = 0.45, MeOH). Anal. calcd for $C_{34}H_{52}N_6O_9 \cdot 1.75H_2O$: C, 55.69; H, 7.77; N, 11.67; found: C, 56.69; H, 7.53; N, 11.58. IR (KBr) 3299, 1741, 1655 cm^{-1}. ^1H NMR (CD_3OD) δ: 0.87–0.98 (m, 12H), 1.15–1.31 (m, 1H), 1.40–1.71 (m, 4H), 1.80–2.18 (m, 8H), 2.60 (dd, *J* = 6.8, 15.6 Hz, 1H), 2.70 (dd, *J* = 5.9, 15.6 Hz, 1H), 2.86 (dd, *J* = 6.4, 13.2 Hz, 1H), 2.99 (dd, *J* = 8.8, 13.2 Hz, 1H), 3.20–3.34 (m, 2H), 3.69 (s, 3H), 4.22 (d, *J* = 2.0 Hz, 1H), 4.29–4.40 (m, 4H), 4.55–4.61 (m, 1H), 7.18–7.31 (m, 5H). MS m/z: 689 (M^++1), 671, 499, 300, 243, 183, 155, 146, 128, 120, 86, 70.

(2S,3S)-3-(N-Acetyl-L-seryl-L-leucyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutyryl-L-prolyl-L-isoleucyl-L-valine methyl ester (Ac–Ser–Leu–Asn–(2S,3S)-AHPBA-Pro–Ile–Val–OMe, 12a)

Boc–Leu–Asn–(2*S*,3*S*)-AHPBA-Pro–Ile–Val–OMe **8a** (95 mg, 0.11 mmol) was added to 4 N HCl/dioxane solution (2 mL), and this solution was stirred for 30 min at room temperature. The solvent was removed *in vacuo*, and the remaining solid was evaporated with benzene. The residue was dried *in vacuo* for 2 h. The residue was dissolved in DMF (2 mL), and then Boc–Ser(Bzl)-OH (45 mg, 0.15 mmol), 93 % DEPC (25 μL, 0.15 mmol), and triethylamine (41 μL, 0.29 mmol) were added at 0°C. The reaction mixture was stirred at room temperature for 2 h, and precipitated with 0.5 N HCl. The precipitate was washed with 5 % $NaHCO_3$ and water. Purification by reprecipitation from diethylether afforded (2*S*,3*S*)-3-(O^{β}-benzyl-N^{α}-*tert*-butoxycarbonyl-L-seryl -L- leucyl -L- asparaginyl) amino -2- hydroxy -4- phenylbutyryl -L- prolyl -L-isoleucyl-L-valine methyl ester (94 mg, 82 %) as a white solid. This compound (50 mg, 0.049 mmol) was added to 4 N HCl/dioxane solution (1 mL), and this solution was stirred for 30 min at room temperature. The solvent was removed *in vacuo*, and the remaining solid was evaporated with benzene. The residue was dried *in vacuo* for 2 h. The residue was dissolved in DMF (1 mL), and then Ac_2O (5.1 μL, 0.054 mmol) and triethylamine (15.0 μL, 0.108 mmol) were added at 0 °C. The reaction mixture was stirred at the same temperature for 30 min, and quenched by the addition of MeOH. The solvent was removed *in vacuo*, and the residue was dissolved in MeOH (1 mL). To this solution were added a drop of AcOH and 10 % Pd/C (40 mg). This reaction mixture was stirred under a hydrogen atmosphere for 1 h at room temperature. The catalyst was filtered off and the filtrate was concentrated. The residue was purified by PTLC (CH_2Cl_2: MeOH = 5:1), and then precipitation from *n*-hexane–diethylether (3:1) afforded **12a** (32 mg, 74 %; 61 % from **8a**) as a white solid. Mp 224–227 °C;.$[\alpha]_D^{25}$ –64.3 ° (c = 0.11, MeOH). Anal. calcd for $C_{42}H_{66}N_8O_{12} \cdot 2.5H_2O$: C, 54.83; H, 7.78; N, 12.18; found: C, 54.58; H, 7.42; N, 12.05. IR (KBr) 3304, 1742, 1645 cm^{-1}. ^1H NMR (CD_3OD) δ: 0.85–0.98 (m, 18H), 1.15–1.30 (m, 1H), 1.55–2.25 (m, 13H), 2.44 (dd, *J* = 7.8, 15.1 Hz, 1H), 2.55 (dd, *J* = 5.4, 15.1 Hz, 1H), 2.80 (dd, *J* = 10.7, 14.2 Hz, 1H), 2.91 (dd, *J* = 3.4, 14.2 Hz, 1H), 3.68–3.88 (m, 7H), 4.25–4.58 (m, 8H), 7.10–7.30 (m, 5H).

The compounds mentioned below were prepared as described above for **12a** using the corresponding starting materials instead of **8a**.

(2R,3S)-3-(N-Acetyl-L-seryl-L-leucyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutyryl-L-prolyl-L-isoleucyl-L-valine methyl ester (Ac–Ser–Leu–Asn–(2R,3S)-AHPBA-Pro–Ile–Val–OMe, 12b)

Yield 57 %. Mp 207–209 °C. $[\alpha]_D^{25}$ –144.7 ° (c = 0.06, MeOH). Anal. calcd for $C_{42}H_{66}N_8O_{12} \cdot 2.25H_2O$: C, 55.09; H, 7.76; N, 12.24; found: C, 54.88; H, 7.20; N, 11.97. IR (KBr) 3289, 1745, 1646 cm^{-1}. ^1H NMR (CD_3OD) δ: 0.86–0.99 (m, 18H), 1.10–1.24 (m, 1H), 1.53–2.18 (m, 13H), 2.53 (dd, *J* = 8.3, 15.1 Hz, 1H), 2.78 (dd, *J* = 4.9, 15.1 Hz, 1H), 2.87 (dd, *J* = 6.3, 13.7 Hz, 1H), 3.00 (dd, *J* = 8.8, 13.7 Hz, 1H), 3.24–3.36 (m, 2H), 3.69 (s, 3H), 3.77 (dd, *J* = 6.4, 11.2 Hz, 1H), 3.84 (dd, *J* = 5.4, 11.2 Hz, 1H), 4.20–4.45 (m, 7H), 4.55–4.63 (m, 1H), 7.18–7.32 (m, 5H).

(2S,3S)-3-(N-Acetyl-L-seryl-L-leucyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutyryl-L-prolyl-L-isoleucine methyl ester (Ac–Ser–Leu–Asn–(2S,3S)-AHPBA-Pro–Ile–OMe, 13a)

Yield 49 %. Mp 127–129 °C. $[\alpha]_D^{25}$ –48.9 ° (c = 0.18, MeOH). Anal. calcd for $C_{37}H_{57}N_7O_{11} \cdot 1.5H_2O$: C, 55.35; H, 7.53; N, 12.21; found: C, 55.21; H, 7.31; N, 12.15. IR (KBr) 3308, 1743, 1651 cm^{-1}. ^1H NMR (CD_3OD) δ: 0.85–0.98 (m, 12H), 1.20–1.35 (m, 1H), 1.44–1.79 (m, 4H), 1.82–2.28 (m, 8H), 2.47 (dd, *J* = 7.8, 15.1 Hz, 1H), 2.57 (dd, *J* = 5.4, 15.1 Hz, 1H), 2.77 (dd, *J* = 10.3, 14.2 Hz, 1H), 2.88 (dd, *J* = 3.9, 14.2 Hz, 1H), 3.70–3.85 (m, 7H), 4.31–4.46 (m, 5H), 4.52–4.60 (m, 2H), 7.10–7.31 (m, 5H).

(2R,3S)-3-(N-Acetyl-L-seryl-L-leucyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutyryl-L-prolyl-L-isoleucine methyl ester (Ac–Ser–Leu–Asn–(2R,3S)-AHPBA-Pro–Ile–OMe, 13b)

Yield 51 %. Mp 134–136 °C. $[\alpha]_D^{25}$ –80.7 ° (c = 0.45, MeOH). Anal. calcd for $C_{37}H_{57}N_7O_{11} \cdot 2H_2O$: C, 54.73; H, 7.57; N, 12.08; found: C, 54.83; H, 7.24; N, 11.95. IR (KBr) 3298, 1744, 1646 cm^{-1}. ^1H NMR (CD_3OD) δ: 0.85–0.99 (m, 12H), 1.15–1.33 (m, 1H), 1.41–2.18 (m, 12H), 2.54 (dd, *J* = 8.3, 15.6 Hz, 1H), 2.68 (dd, *J* = 4.9, 15.6 Hz, 1H), 2.87 (dd, *J* = 6.3, 13.2 Hz, 1H), 3.00 (dd, *J* = 8.8, 13.2 Hz, 1H), 3.21–3.38 (m, 2H), 3.69 (s, 3H), 3.77 (dd, *J* = 6.3, 10.7 Hz, 1H), 3.85 (dd, *J* = 5.4, 10.7 Hz, 1H), 4.23 (d, *J* = 2.0 Hz, 1H), 4.30–4.47 (m, 5H), 4.59 (dd, *J* = 4.9, 8.3 Hz, 1H), 7.17–7.34 (m, 5H).

(2S,3S)-3-(N-Benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutyryl-L-proline tert*-butyl ester (Z-Asn–(2S,3S)-AHPBA-Pro–OBu^t, 17a)*

Z-(2*S*,3*S*)-AHPBA-OH[20] **14a** (183 mg, 0.56 mmol) and

H-Pro–OBu^t (105 mg, 0.61 mmol) were dissolved in DMF (5 mL), and then 93 % DEPC (0.10 mL, 0.61 mmol) and triethylamine (85 μL, 0.61 mmol) were added at 0 °C. The mixture was stirred for 3h at room temperature, then the solvent was removed *in vacuo*. The residue was extracted with AcOEt, and the organic layer was washed with 5 % citric acid, 5 % $NaHCO_3$, and brine. Drying followed by evaporation afforded (2*S*,3*S*)-3-benzyloxycarbonylamino-2-hydroxy-4-phenylbutyryl-L-proline *tert*-butyl ester **15a** (260 mg, 96 %) as a colorless oil. A mixture of **15a** (260 mg, 0.54 mmol), 1 N HCl (0.61 mL, 0.61 mmol), and 10 % Pd/C (60 mg) in EtOH (20 mL) was stirred under a hydrogen atmosphere for 1 h at room temperature. The catalyst was filtered off and the filtrate was concentrated. The residue was dissolved in DMF (5 mL), and then Z-Asn-ONp (217 mg, 0.56 mmol) and triethylamine (85 μL, 0.61 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature for 14h, and then the solvent was removed *in vacuo*. The residue was extracted with AcOEt, and the organic layer was washed with 5 % citric acid, 5 % $NaHCO_3$, and brine. Drying followed by evaporation and crystallization from diethylether afforded **17a** (215 mg, 67 %; 64 % from **14a**) as colorless crystals. Mp 109–112 °C. $[\alpha]_D^{25}$ –42.8 ° (c = 0.33, MeOH). Anal. calcd for $C_{31}H_{40}N_4O_8 \cdot 0.5H_2O$: C, 61.47; H, 6.82; N, 9.25; found: C, 61.25; H, 6.62; N, 9.32. IR (KBr) 3299, 1733, 1681, 1643 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.46 (s, 9H), 1.88–2.14 (m, 3H), 2.16–2.31 (m, 1H), 2.51 (dd, *J* = 6.4, 14.7 Hz, 1H), 2.65–2.80 (m, 2H), 2.84 (dd, *J* = 4.4, 14.2 Hz, 1H), 3.59–3.80 (m, 2H), 3.91–4.01 (m, 1H), 4.37–4.54 (m, 4H). 5.10 (s, 2H), 5.24 (br s, 1H), 5.72 (br s, 1H), 6.15 (br d, *J* = 6.8 Hz, 1H), 7.12–7.41 (m, 11H). MS m/z: 522 (M^+-74), 505, 414, 368, 260, 155, 120, 108, 91, 70.

*(2R,3S)-3-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutyryl-L-proline tert-butyl ester (Z-Asn-(2R,3S)-AHPBA-Pro-OBu^t, 17b)*

The title compound **17b** was prepared as described above for **17a** using Z-(2*R*,3*S*)-AHPBA-OH **14b** instead of Z-(2*S*,3*S*)-AHPBA-OH **14a**, to yield colorless crystals (16 % from **14b**). Mp 188–193 °C. $[\alpha]_D^{25}$ –86.2 ° (c = 0.51, MeOH). Anal. calcd for $C_{31}H_{40}N_4O_8 \cdot 0.5H_2O$: C, 61.47; H, 6.82; N, 9.25; found: C, 61.74; H, 6.56; N, 9.46. IR (KBr) 3309, 1735, 1714, 1685, 1662 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 1.36 (s, 9H), 1.70–1.90 (m, 3H), 1.92–2.04 (m, 1H), 2.24 (dd, *J* = 9.3, 13.2 Hz, 1H), 2.35 (dd, *J* = 4.4, 15.1 Hz, 1H), 2.74 (dd, *J* = 7.8, 13.2 Hz, 1H), 2.87 (dd, *J* = 5.9, 13.2 Hz, 1H), 3.29–3.41 (m, 2H), 4.05–4.32 (m, 4H), 4.82 (d, *J* = 6.4 Hz, 1H). 5.01 (s, 2H), 6.88 (br s, 1H), 7.15–7.38 (m, 12H), 7.73 (d, *J* = 8.8 Hz, 1H). MS m/z: 579 (M^+-17), 505, 478, 414, 257, 155, 108, 91, 79, 70.

*(2S,3S)-3-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutyryl-L-proline* tert*-butyl amide (Z-Asn-(2S,3S)-AHPBA-Pro-NHBu^t, 18)*

N-tert-*Butoxycarbonyl-L-proline* tert*-butyl amide (Boc-Pro-NHBu^t).* Boc–Pro–OH (21.5g, 100 mmol) was dissolved in THF (100 mL), and then triethylamine (15.3 mL, 110 mmol) and isobutyl chloroformate (14.3 mL, 110 mmol) were added at –40 °C. The mixture was stirred for 20min at –20 °C, then *tert*-butylamine (15.8 mL, 150 mmol) was added into this mixture at –40 °C. The mixture was stirred for 7 h at 0 °C, and then AcOEt was added into this reaction mixture. The organic layer was washed with 5 % citric acid, 5 % $NaHCO_3$, and brine. Drying followed by evaporation and crystallization from *n*-hexane afforded Boc–Pro–NHBu^t (25.0g, 93 %) as colorless crystals. Mp 124–125 °C. $[\alpha]_D^{25}$ –109.5 ° (c = 1.53, $CHCl_3$). Anal. calcd for $C_{14}H_{26}N_2O_3$: C, 62.19; H, 9.69; N, 10.36; found: C, 61.94; H, 9.28; N, 10.20. IR (KBr) 3329, 1698, 1657 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.34 (s, 9H), 1.47 (s, 9H), 1.80–2.38 (m, 4H), 3.34–3.54 (m, 2H), 4.05–4.22 (m, 1H), 5.82 (br s, 1H). MS m/z: 271 (M^++1), 215, 171, 114, 70, 57.

*(2S,3S)-3-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutyryl-L-proline* tert*-butyl amide (Z-Asn-(2S,3S)-AHPBA-Pro-NHBu^t, 18).* The title compound **18** was prepared as described above for **17a** using HCl·H–Pro–NHBu^t derived from Boc–Pro–NHBu^t instead of H–Pro–OBu^t, to yield colorless crystals (23 % from **14a**). Mp 101–102 °C. $[\alpha]_D^{25}$ –36.9 ° (c = 0.62, MeOH). Anal. calcd for $C_{31}H_{41}N_5O_7 \cdot 1.5H_2O$: C, 59.79; H, 7.12; N, 11.25; found: C, 60.00; H, 6.83; N, 11.30. IR (KBr) 3332, 1667 cm^{-1}. ^{1}H NMR (CD_3OD) δ: 1.31 (s, 9H), 1.84–2.23 (m, 4H), 2.43 (dd, *J* = 7.8, 15.6 Hz, 1H), 2.61 (dd, *J* = 5.4, 15.6 Hz, 1H), 2.72–2.94 (m, 2H), 3.68–3.79 (m, 2H), 4.29–4.48 (m, 4H), 5.08 (s, 2H), 7.09–7.39 (m, 10H). MS m/z: 579 (M^+-16), 479, 388, 273, 228, 129, 91, 70.

*(2S,3S)-3-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoic acid (Z-Asn-(2S,3S)-AHPBA-OH, 20)*

(2*S*,3*S*)-3-Amino-2-hydroxy-4-phenylbutanoic acid hydrochloride **19** (900 mg, 3.89 mmol), which is derived from Boc–(2*S*,3*S*)-AHPBA-OH, was dissolved in DMF (15 mL), and then Z-Asn-ONp (2.26g, 5.84 mmol) and triethylamine (1.89 mL, 13.6 mmol) were added at 0 °C. The mixture was stirred for 2 days at 4 °C, and precipitated with 1N HCl. The precipitate was washed with 1N HCl and water. Purification by reprecipitation from AcOEt afforded 20 (1.52g, 88 %) as a white solid. Mp 225–227 °C. $[\alpha]_D^{25}$ –23.0 ° (c = 0.49, DMF). Anal. calcd for $C_{22}H_{25}N_3O_7 \cdot H_2O$: C, 57.26; H, 5.90; N, 9.11; found: C, 57.33; H, 5.61; N, 9.18. IR (KBr) 3332, 1692, 1642 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 2.20–2.40 (m, 2H), 2.61–2.73 (m, 2H), 3.99 (d, *J* = 3.9 Hz, 1H), 4.19–4.36 (m, 2H), 5.01 (s, 2H), 5.55 (br s, 1H), 6.85 (br s, 1H), 7.10–7.40 (m, 12H), 7.73 (br d, *J* = 8.8 Hz, 1H), 12.60 (br s, 1H). MS m/z: 425 (M^+-17), 350, 274, 248, 120, 108, 91, 79.

*(2S,3S)-3-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutyryl-*N*'-2'-phenethylglycine* tert*-butyl amide (21)*

N-tert-*Butoxycarbonylglycine* tert*-butyl amide (Boc-Gly-NHBu^t).* The title compound Boc–Gly–NHBu^t was prepared as described above for Boc–Pro–NHBu^t using Boc–Gly–OH instead of Boc–Pro–OH, to yield colorless crystals (94 %); mp 69–70 °C. Anal. calcd for $C_{11}H_{22}N_2O_3$: C, 57.37; H, 9.63; N, 12.16; found: C, 57.14; H, 9.24; N,

12.00. IR (KBr) 3412, 3348, 1710, 1682 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.35 (s, 9H), 1.45 (s, 9H), 3.68 (d, J = 5.3 Hz, 2H), 5.32 (br s, 1H), 5.99 (br s, 1H). MS m/z: 230 (M^+), 175, 131, 75, 57.

N-*2-Phenethylglycine* tert-*butyl amide hydrochloride.* Boc–Gly–NHBu^t (2.76g, 12.0 mmol) was added to 4 N HCl/dioxane solution (5 mL), and this solution was stirred for 30 min at room temperature. The solvent was removed *in vacuo*, and the remaining solid was evaporated with benzene. The residue was dried *in vacuo* for 2 h. The residue was dissolved in DMF (2 mL), and then phenylacetaldehyde (1.54 mL, 13.2 mmol), triethylamine (1.00 mL, 7.20 mmol), and sodium cyanoborohydride (0.45g, 7.20 mmol) were added at 0 °C. The reaction mixture was stirred for 14 h at 4 °C, and quenched by the addition of 4 N HCl/dioxane solution (3 mL). The solvent was removed *in vacuo*, and the residue was extracted with AcOEt. The organic layer was washed with 5 % $NaHCO_3$ and brine. The organic solvent was removed *in vacuo*, and the residue was dissolved in MeOH (10 mL). Into this solution was added 4 N HCl/dioxane solution (3 mL), and the solvent was removed *in vacuo*. The remaining solid was evaporated with benzene, and then crystallization from AcOEt afforded the title compound (2.02 g, 62 %) as colorless crystals. Mp 210–212 °C. Anal. calcd for $C_{14}H_{22}N_2O$·HCl: C, 62.09; H, 8.56; N, 10.34; Cl, 13.09; found: C, 61.88; H, 8.36; N, 10.52; Cl, 12.90. IR (KBr) 1695 cm^{-1}. ^1H NMR (CD_3OD) δ: 1.36 (s, 9H), 2.97–3.06 (m, 2H), 3.22–3.29 (m, 2H), 3.73 (s, 2H), 7.25–7.40 (m, 5H). MS m/z: 235 (M^++1), 143, 134, 105, 87.

*(2S,3S)-3-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutyryl-*N*′-2′-phenethylglycine* tert-*butyl amide (21).* Z-Asn-(2*S*,3*S*)-AHPBA-OH **20** (67 mg, 0.15 mmol) and *N*-2-phenethylglycine *tert*-butyl amide hydrochloride (203 mg, 0.75 mmol) were dissolved in DMF (1 mL), and then 1-hydroxybenzotriazole (HOBT; 24 mg, 0.18 mmol), 1-(3'-dimethylamino)propyl-3-ethylcarbodiimide hydrochloride (water soluble carbodiimide hydrochloride (WSCI·HCl); 35 mg, 0.18 mmol), and triethylamine (0.16 mL, 1.13 mmol) were added at 0 °C. The mixture was stirred for 14 h at 4 °C, then the solvent was removed *in vacuo*. The residue was extracted with AcOEt, and the organic layer was washed with 5 % citric acid, 5 % $NaHCO_3$, and brine. Drying followed by evaporation and purification by PTLC (CH_2Cl_2: MeOH = 10:1) afforded **21** (69 mg, 69 %) as a white solid. Mp 96–98 °C. $[\alpha]_D^{25}$ –3.4 ° (c = 0.47, MeOH). Anal. calcd for $C_{36}H_{45}N_5O_7$·0.5H_2O: C, 64.65; H, 6.93; N, 10.47. Found: C, 64.33; H, 6.96; N, 10.33. IR (KBr) 3311, 1656 cm^{-1}. ^1H NMR (CD_3OD) δ: 1.31, 1.32 (each s, 9H), 2.39–2.50 (m, 2H), 2.75–2.91 (m, 4H), 3.44–3.68 (m, 2H), 3.75–3.93 (m, 2H). 4.05–4.13 (m, 1H), 4.19–4.35 (m, 1H), 4.40–4.49 (m, 1H), 5.05 (s, 2H), 7.10–7.37 (m, 15H). MS m/z: 642 (M^+-17), 569, 478, 321, 260, 219, 188, 134, 105, 91.

*(2S,3S)-2-Acetoxy-3-*tert-*butoxycarbonylamino-4-phenylbutanoic acid (22)*

Boc-(2*S*, 3*S*)-AHPBA-OH **3a** (500 mg, 1.67 mmol) was dissolved in THF (5 mL), and then acetic anhydride (0.18 mL, 1.86 mmol) and 4-*N*,*N*′-dimethylaminopyridine (DMAP; 21 mg, 0.17 mmol) were added at 0 °C. The mixture was stirred for 2 h at the same temperature, then AcOEt was added into this reaction mixture. The organic layer was washed with 5 % citric acid and brine. Drying followed by evaporation and purification by crystallization from *n*-hexane afforded **22** (520 mg, 91 %) as colorless crystals. Mp 157–160 °C. $[\alpha]_D^{25}$ –6.9 ° (c = 0.27, $CHCl_3$). Anal. calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15; found: C, 60.47; H, 6.94; N, 4.12. IR (KBr) 3281, 1757, 1717, 1707 cm^{-1}. ^1H NMR (CD_3OD) δ: 1.31 (s, 9H), 2.12 (s, 3H), 2.70–2.89 (m, 2H), 4.28–4.40 (m, 1H), 5.18 (d, J = 4.0 Hz, 1H), 7.15–7.30 (m, 5H). MS m/z: 337 (M^+), 249, 190, 146, 128, 57.

*(2S,3S)-2-Acetoxy-3-*tert-*butoxycarbonylamino-4-phenylbutyryl-N-2′-phenethyl-L-alanine* tert-*butyl amide (23)*

N-tert-*Butoxycarbonyl-L-alanine* tert-*butyl amide (Boc–Ala–NHBu^t).* The title compound Boc–Ala–NHBu^t was prepared as described above for Boc–Pro–NHBu^t using Boc–Ala–OH instead of Boc–Pro–OH, to yield colorless crystals (91 %). Mp 103–104 °C. $[\alpha]_D^{25}$ –48.4 ° (c = 1.41, $CHCl_3$). Anal. calcd for $C_{12}H_{24}N_2O_3$: C, 58.99; H, 9.90; N, 11.47; found: C, 58.92; H, 9.42; N, 11.42. IR (KBr) 3324, 1692, 1660 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.28–1.39 (m, 12H), 1.45 (s, 9H), 3.97–4.09 (m, 1H), 5.07 (br s, 1H), 6.00 (br s, 1H). MS m/z: 245 (M^+), 189, 145, 88, 57, 44.

N-*2-Phenethyl-L-alanine* tert-*butyl amide hydrochloride.* The title compound was prepared as described above for *N*-2-phenethylglycine *tert*-butyl amide hydrochloride using Boc–Ala–NHBu^t instead of Boc–Gly–NHBu^t, to yield colorless crystals (36 %). Mp 200–202 °C. $[\alpha]_D^{25}$ –8.3 ° (c = 1.01, MeOH). Anal. calcd for $C_{15}H_{24}N_2O$·HCl: C, 63.25; H, 8.85; N, 9.84; Cl, 12.45; found: C, 63.06; H, 8.99; N, 9.88; Cl, 12.31. IR (KBr) 1684 cm^{-1}. ^1H NMR (CD_3OD) δ: 1.36 (s, 9H), 1.50 (d, J = 6.6 Hz, 3H), 2.95–3.23 (m, 4H), 3.82 (q, J = 6.6 Hz, 1H), 7.25–7.40 (m, 5H). MS m/z: 249 (M^++1), 148, 105.

*(2S,3S)-2-Acetoxy-3-*tert-*butoxycarbonylamino-4-phenylbutyryl-N-2′-phenethyl-L-alanine* tert-*butyl amide (23).* Compound **22** (130 mg, 0.39 mmol) and *N*-2-phenethyl-L-alanine *tert*-butyl amide hydrochloride (100 mg, 0.35 mmol) were dissolved in DMF (2 mL), and then bromotris(pyrrolidino)phosphonium hexafluorophosphate (PyBrop®; 172 mg, 0.37 mmol) and triethylamine (0.15 mL, 1.09 mmol) were added at 0 °C. The mixture was stirred for 1.5 h at room temperature, then the solvent was removed *in vacuo*. The residue was extracted with AcOEt, and the organic layer was washed with 5 % citric acid, 5 % $NaHCO_3$, and brine. Drying followed by evaporation and purification by PTLC (*n*-hexane: AcOEt = 10:1) afforded 23 (160 mg, 80 %) as a foam. $[\alpha]_D^{25}$ –36.4 ° (c = 0.12, $CHCl_3$). Anal. calcd for $C_{32}H_{45}N_3O_6$: C, 67.70; H, 7.99; N, 7.40; found: C, 67.50; H, 8.19; N, 7.38. IR (KBr) 3370, 1735, 1701, 1661 cm^{-1}. ^1H NMR (CD_3OD) δ: 0.95–1.37 (m, 18H), 1.51–1.60 (m, 3H), 2.19, 2.20 (each s, 3H), 2.60–2.81 (m, 2H), 2.87–3.23 (m, 3H), 3.48–3.70

(m, 1H). 4.10–4.26 (m, 1H), 4.39–4.50 (m, 0.5H), 4.87–4.97 (m, 0.5H), 5.38 (d, J = 6.8 Hz, 0.5H), 5.47 (d, J = 3.4 Hz, 0.5H), 7.13–7.33 (m, 10H). MS m/z: 567 (M^+), 467, 367, 264, 148, 105, 57.

*(2S,3S)-3-*tert*-Butoxycarbonylamino-2-hydroxy-4-phenylbutyryl-N-2'-phenethyl-L-alanine* tert*-butyl amide (24)*

Compound **23** (120 mg, 0.21 mmol) was dissolved in MeOH (2 mL), and then 1N LiOH (0.23 mL, 0.23 mmol) was added at 0 °C. The mixture was stirred for 4.5 h at the same temperature. The reaction mixture was neutralized with 1 N HCl (0.23 mL, 0.23 mmol), then the solvent was removed *in vacuo*. The residue was extracted with AcOEt, and the organic layer was washed with 5 % citric acid, 5 % $NaHCO_3$, and brine. Drying followed by evaporation afforded **24** (108 mg, 97 %) as a foam. $[\alpha]_D^{25}$ –45.5 ° (c = 0.25, $CHCl_3$). Anal. calcd for $C_{30}H_{43}N_3O_5$: C, 68.54; H, 8.25; N, 7.99; found: C, 68.24; H, 8.57; N, 7.75. IR (KBr) 3340, 1694, 1638 cm^{-1}. ^1H NMR (CD_3OD) δ: 1.02–1.50 (m, 21H), 2.67–3.00 (m, 4H), 3.23–3.35 (m, 0.5H), 3.54–3.70 (m, 1H). 3.84–4.03 (m, 1.5H), 4.45 (d, J = 4.9 Hz, 0.5H), 4.53 (d, J = 4.4 Hz, 0.5H), 4.68–4.84 (m, 1H), 7.14–7.31 (m, 10H). MS m/z: 526 (M^++1), 426, 369, 325, 306, 249, 233, 148, 91, 57.

*(2S,3S)-3-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutyryl-*N*'-2'-phenethyl-L-alanine* tert*-butyl amide (25)*

The title compound **25** was prepared as described above for **6a** using **24** instead of **4a**, to yield colorless crystals (77 %). Mp 85–87 °C. $[\alpha]_D^{25}$ –46.3 ° (c = 0.37, MeOH). Anal. calcd for $C_{37}H_{47}N_5O_7 \cdot 0.5H_2O$: C, 65.08; H, 7.09; N, 10.26; found: C, 64.94; H, 6.90; N, 10.20. IR (KBr) 3335, 1671 cm^{-1}. ^1H NMR (CD_3OD) δ: 1.25–1.35 (m, 10.5H), 1.42 (d, J = 6.8 Hz, 1.5H), 2.42–2.95 (m, 6H), 3.23–3.38 (m, 0.5H), 3.45–3.82 (m, 1.5H), 4.30–4.40 (m, 1H). 4.42–4.53 (m, 2H), 4.65–4.78 (m, 1H), 5.05, 5.07 (each s, 2H), 7.11–7.39 (m, 15H). MS m/z: 674 (M^++1), 656, 556, 465, 335, 306, 249, 233, 148, 108, 91, 79.

*(3S,6S,1'S)-3-{1'-(*N*-Benzyloxycarbonyl-L-asparaginyl)-amino-2'-phenethyl}-1-aza-4-oxa-bicyclo[4.3.0]nonan-2, 5-dione (26)*

Compound **17a** (800 mg, 1.34 mmol) was added to 4 N HCl/dioxane solution (10 mL), and this solution was stirred for 9 h at room temperature. The solvent was removed *in vacuo*, and the remaining solid was evaporated with benzene. Crystallization from diethylether afforded **26** (660 mg, 94 %) as colorless crystals. Mp 260–262 °C. $[\alpha]_D^{25}$ –113.1 ° (c = 0.40, DMF). Anal. calcd for $C_{27}H_{30}N_4O_7 \cdot 0.25H_2O$: C, 61.53; H, 5.83; N, 10.63; found: C, 61.37; H, 5.78; N, 10.51. IR (KBr) 3300, 1753, 1691, 1652 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 1.78–2.11 (m, 3H), 2.19–2.40 (m, 3H), 2.78 (d, J = 6.8 Hz, 2H), 3.38–3.48 (m, 2H), 4.28–4.39 (m, 1H), 4.51–4.70 (m, 2H), 4.98–5.11 (m, 3H), 6.85 (br s, 1H), 7.12–7.39 (m, 11H), 8.08 (br d, J = 8.3 Hz, 2H), MS m/z: 505 (M^+-17), 414, 260, 155, 108, 91, 79.

*(2S,3S)-3-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutyryl-L-proline benzyl amide (27)*

Compound **26** (68 mg, 0.13 mmol) was dissolved in DMF (2 mL), and then benzylamine (71 μL, 0.65 mmol) was added at room temperature. The mixture was left for 14 h at room temperature, then the solvent was removed *in vacuo*. The residue was extracted with AcOEt, and the organic layer was washed with 5 % citric acid, 5 % $NaHCO_3$, and brine. Drying followed by evaporation and purification by PTLC (CH_2Cl_2: MeOH = 8:1) afforded **27** (52 mg, 64 %) as colorless crystals. Mp 97–99 °C. $[\alpha]_D^{25}$ –33.9 ° (c = 0.40, MeOH). Anal. calcd for $C_{34}H_{39}N_5O_7$: C, 64.85; H, 6.24; N, 11.12; found: C, 64.80; H, 6.18; N, 11.18. IR (KBr) 3321, 1669 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.84–2.38 (m, 4H), 2.51 (dd, J = 6.4, 15.1 Hz, 1H), 2.60–2.82 (m, 3H), 3.51–3.65 (m, 2H), 3.98–4.10 (m, 1H), 4.25–4.58 (m, 6H), 5.07 (s, 2H), 5.28–5.42 (m, 1H), 5.78 (br s, 1H), 6.15 (d, J = 7.3 Hz, 1H), 6.87–6.97 (m, 1H), 7.07–7.39 (m, 16H). MS m/z: 612 (M^+-17), 521, 290, 273, 262, 257, 205, 155, 120, 106, 91, 79, 70.

*(2S,3S)-3-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-4-cyclohexyl-2-hydroxybutyryl-L-proline* tert*-butyl amide (28)*

The title compound **28** was prepared as described above for **6 a** using (2*S*,3*S*)-3-*tert*-butoxycarbonylamino-4-cyclohexyl-2-hydroxybutanoic acid[21] (Boc-(2*S*,3*S*)-ACHBA-OH) and Boc–Pro–NHBu^t, to yield colorless crystals (51 % from Boc-(2*S*,3*S*)-ACHBA-OH). Mp 112–114 °C. $[\alpha]_D^{25}$ –70.3 ° (c = 0.39, MeOH). Anal. calcd for $C_{31}H_{47}N_5O_7 \cdot 1.5H_2O$: C, 59.21; H, 8.02; N, 11.14. Found: C, 59.18; H, 7.85; N, 11.04. IR (KBr) 3319, 1667 cm^{-1}. ^1H NMR (CD_3OD) δ: 0.80–2.18 (m, 26H), 2.50 (dd, J = 8.3, 15.1 Hz, 1H), 2.68 (dd, J = 4.9, 15.1 Hz, 1H), 3.55–3.72 (m, 2H), 4.12–4.19 (m, 1H), 4.30–4.48 (m, 3H), 5.09 (s, 2H), 7.25–7.38 (m, 5H). MS m/z: 601 (M^+), 484, 393, 296, 279, 228, 171, 155, 126, 108, 91, 79, 70, 51, 41.

The compounds shown in Table 2 were prepared as described above for **6a** or **21**. Their melting points, elemental analyses, and 270 MHz ^1H NMR data are shown in Table 7.

The compounds shown in Table 3 were prepared as described above for **27**. Their melting points, elemental analyses, and 270 MHz ^1H NMR data are shown in Table 8.

The compounds shown in Table 4 were prepared as described above for **17a**, with DEPC employed as a coupling reagent instead of *p*-nitrophenyl active ester. Their melting points, elemental analyses, and 270 MHz ^1H NMR data are shown in Table 9.

The compounds shown in Table 5 were prepared as described above for **8a**. Their melting points, elemental analyses, and 270 MHz ^1H NMR data are shown in Table 10.

Table 7. Analytical Data of the Compounds shown in Table 2

No.	Formula	Analysis (%) Calcd (Found) C	H	N	mp (°C)	270MHz ^{1}H-NMR (CD_3OD) δ: ppm (J = Hz)
29	$C_{31}H_{41}N_5O_7 \cdot 1.5H_2O$	59.79 (59.88	7.12 6.63	11.25 11.14)	110-112	1.28, 1.32 (each s, 9H), 1.80-2.11 (m, 4H), 2.46 (dd, J = 7.8, 15.6, 1H), 2.58 (dd, J = 5.9, 15.6, 1H), 2.66-2.97 (m, 2H), 3.51-3.72 (m, 2H), 4.10-4.25 (m, 1H), 4.28-4.47 (m, 3H), 5.07 (s, 2H), 7.10-7.40 (m, 10H).
30[a]	$C_{28}H_{37}N_5O_7 \cdot 1.5H_2O$	57.72 (57.99	6.92 6.68	12.02 11.87)	174-176	1.31 (s, 9H), 2.52-2.60 (m, 2H), 2.76-2.85 (m, 2H), 3.71-3.92 (m, 2H), 4.20-4.24 (m, 1H), 4.43-4.58 (m, 2H), 5.07 (ABq, J = 12.7, Δ = 0.03ppm, 2H), 6.30 (br s, 1H), 6.95 (br s, 1H), 7.10-7.41 (m, 10H), 7.52-7.60 (m, 2H), 7.93-8.11 (m, 2H).
31[b]	$C_{35}H_{43}N_5O_7 \cdot 0.5H_2O$	64.20 (64.27	6.77 6.30	10.70 10.77)	223-225	1.22 (s, 9H), 2.08-2.50 (m, 4H), 2.85-2.96 (m, 2H), 3.90-3.96 (m, 1H), 4.14-4.34 (m, 2H), 4.61-4.70 (m, 1H), 5.00 (s, 2H), 6.02 (d, J = 5.4, 1H), 6.86 (s, 1H), 6.96-7.38 (m, 17H), 7.62-7.70 (m, 3H).
32	$C_{32}H_{43}N_5O_7$	63.04 (63.00	7.10 7.10	11.49 11.24)	102-104	1.32 (s, 9H), 1.45-1.78 (m, 5H), 2.03-2.13 (m, 1H), 2.38-2.95 (m, 4H), 3.58-3.70 (m, 1H), 3.98-4.09 (m, 1H), 4.30-4.51 (m, 3H), 4.63-4.80 (m, 1H), 5.07 (s, 2H), 7.09-7.39 (m, 10H).
33	$C_{36}H_{49}N_5O_7 \cdot 0.5H_2O$	64.27 (64.41	7.49 7.63	10.41 10.22)	110-115	1.18-1.97 (m, 20H) including 1.33 (s, 9H), 2.01-2.11 (m, 1H), 2.38-2.86 (m, 4H), 3.74-3.84 (m, 1H), 4.04-4.26 (m, 1H), 4.35-4.53 (m, 2H), 4.63-4.76 (m, 1H), 4.81-4.93 (m, 1H), 5.08 (s, 2H), 7.07-7.40 (m, 10H).
34	$C_{36}H_{43}N_5O_7 \cdot H_2O$	63.98 (63.67	6.71 6.19	10.36 10.06)	185-187	0.60-0.83 (m, 6H), 1.45-1.71 (m, 1H), 2.41-2.70 (m, 3H), 2.79-3.29 (m, 5H), 4.28-4.69 (m, 4H), 4.76-5.09 (m, 4H), 6.80-6.90 (m, 1H), 7.04-7.40 (m, 14H).
35	$C_{35}H_{43}N_5O_7 \cdot 0.75H_2O$	63.76 (63.93	6.80 6.92	10.62 10.24)	88-90	1.27, 1.29 (each s, 9H), 2.38-2.49 (m, 1H), 2.53-2.68 (m, 1H), 2.78-2.97 (m, 2H), 3.67 (d, J = 15.6, 0.5H), 4.03-4.30 (m, 2.5H), 4.33-4.52 (m, 2H), 4.56-4.75 (m, 2H), 5.06 (s, 2H), 7.09-7.39 (m, 15H).
36	$C_{37}H_{47}N_5O_7 \cdot H_2O$	64.23 (64.46	7.14 7.07	10.12 10.06)	80-82	1.29, 1.30 (each s, 9H), 1.77-1.98 (m, 2H), 2.38-2.51 (m, 1H), 2.53-2.69 (m, 3H), 2.73-2.92 (m, 2H), 3.31-3.67 (m, 2H), 3.80 (d, J = 15.6, 0.5H), 4.01-4.17 (m, 1.5H), 4.19-4.35 (m, 1H), 4.40-4.59 (m, 2H), 5.05, 5.07 (each s, 2H), 7.09-7.39 (m, 15H).
37	$C_{33}H_{47}N_5O_7 \cdot 0.5H_2O$	62.44 (62.24	7.62 7.74	11.03 11.10)	85-88	0.85-0.96 (m, 6H), 1.32, 1.33 (each s, 9H), 1.35-1.62 (m, 3H), 2.40-2.51 (m, 1H), 2.55-2.68 (m, 1H), 2.75-2.95 (m, 2H), 3.30-3.68 (m, 2H), 3.80 (d, J = 15.6, 0.5H), 4.02-4.16 (m, 1.5H), 4.20-4.37 (m, 1H), 4.41-4.58 (m, 1H), 5.07 (s, 2H), 7.09-7.39 (m, 10H).
38	$C_{37}H_{45}N_5O_7 \cdot 0.5H_2O$	65.27 (65.44	6.81 6.77	10.29 10.25)	99-100	1.25, 1.29 (each s, 9H), 2.40-2.51 (m, 1H), 2.55-2.69 (m, 1H), 2.75-2.96 (m, 2H), 3.90 (d, J = 16.1, 0.5H), 4.04-4.50 (m, 6H), 4.66-4.72 (m, 0.5H), 5.06 (s, 2H), 6.09-6.30 (m, 1H), 6.50-6.65 (m, 1H), 7.06-7.41 (m, 15H).
39	$C_{37}H_{45}N_5O_7 \cdot 0.5H_2O$	65.27 (65.22	6.81 6.77	10.29 10.08)	106-108	1.25, 1.28 (each s, 9H), 2.39-2.51 (m, 4H), 2.61 (dd, J = 5.9, 15.1, 1H), 2.71-3.39 (m, 6H), 3.64 (d, J = 15.6, 0.7H), 3.90 (d, J = 15.6, 0.7H), 4.04 (d, J = 3.4, 0.6H), 4.22-4.50 (m, 2H), 4.72-4.80 (m, 1H), 5.07 (s, 2H), 5.11-5.27 (m, 1H), 7.10-7.38 (m, 14H).

[a] ^{1}H-NMR (DMF-d_7).
[b] ^{1}H-NMR (DMSO-d_6).

Table 8. Analytical Data of the Compounds shown in Table 3

No.	Formula	Analysis (%) Calcd (Found) C	H	N	mp (°C)	270MHz ^{1}H-NMR (CD_3OD) δ: ppm (J = Hz)
40	$C_{27}H_{33}N_5O_7 \cdot 2H_2O$	55.47	6.55	11.98	122-124	1.81-2.30 (m, 4H), 2.42 (dd, J = 8.3, 15.1, 1H), 2.58 (dd, J = 5.4, 15.1, 1H), 2.74-3.00 (m, 2H), 3.67-
		(55.07	6.82	11.59)		3.79 (m, 2H), 4.30-4.50 (m, 4H), 5.08 (s, 2H), 7.07-7.40 (m, 10H).
41	$C_{29}H_{37}N_5O_7 \cdot 1.5H_2O$	58.57	6.78	11.78	100-102	1.79-2.12 (m, 3H), 2.25-2.47 (m, 2H), 2.63 (dd, J = 5.4, 15.1, 1H), 2.78 (dd, J = 10.1, 13.7, 1H), 2.86-
		(58.91	6.42	11.43)		2.96 (m, 4H), 3.13 (s, 3H), 3.70-3.82 (m, 2H), 4.31-4.48 (m, 3H), 4.86-4.94 (m, 1H), 5.07 (s, 2H), 7.10-7.39 (m, 10H).
42	$C_{31}H_{41}N_5O_7 \cdot 0.25H_2O$	62.03	6.97	11.67	91-93	0.85-0.95 (m, 3H), 1.27-1.53 (m, 4H), 1.82-2.28 (m, 4H), 2.42 (dd, J = 8.3, 15.1, 1H), 2.58 (dd, J = 5.4,
		(61.98	6.87	11.53)		15.1, 1H), 2.75-2.98 (m, 2H), 3.09-3.21 (m, 2H), 3.68-3.78 (m, 2H), 4.29-4.46 (m, 4H), 5.07 (s, 2H), 7.09-7.39 (m, 10H).
43	$C_{35}H_{41}N_5O_7 \cdot H_2O$	63.52	6.55	10.58	100-102	1.44 (d, J = 7.2, 3H), 1.87-2.02 (m, 2H), 2.05-2.15 (m, 1H), 2.17-2.27 (m, 1H), 2.37 (dd, J = 8.2, 15.3,
		(63.35	6.20	10.40)		1H), 2.54 (dd, J = 5.4, 15.3, 1H), 2.68-2.82 (m, 2H), 3.68-3.75 (m, 2H), 4.24-4.31 (m, 1H), 4.39-4.53 (m, 3H), 4.95-5.09 (m, 3H), 7.06-7.40 (m, 15H).
44	$C_{35}H_{41}N_5O_7 \cdot 0.5H_2O$	64.40	6.49	10.73	98-99	1.42 (d, J = 6.8, 3H), 1.76-2.09 (m, 3H), 2.11-2.24 (m, 1H), 2.42 (dd, J = 8.3, 15.1, 1H), 2.62 (dd, J =
		(64.29	6.50	10.55)		5.4, 15.1, 1H), 2.82 (dd, J = 9.8, 13.7, 1H), 2.93 (dd, J = 4.4, 13.7, 1H), 3.65-3.77 (m, 2H), 4.22-4.51 (m, 4H), 4.87-5.09 (m, 3H), 7.08-7.38 (m, 15H).
45	$C_{35}H_{41}N_5O_7$	65.38	6.42	10.88	93-95	1.74-2.05 (m, 3H), 2.09-2.20 (m, 1H), 2.42 (dd, J = 8.2, 15.3, 1H), 2.57 (dd, J = 5.3, 15.3, 1H), 2.71-
		(65.28	6.39	10.94)		2.88 (m, 3H), 2.95 (dd, J = 3.9, 13.9, 1H), 3.32-3.50 (m, 2H), 3.65-3.75 (m, 1H), 4.27-4.47 (m, 4H), 5.06 (s, 2H), 7.10-7.38 (m, 15H).
46	$C_{33}H_{38}N_6O_7 \cdot 0.5H_2O$	61.96	6.07	13.14	97-99	1.88-2.31 (m 4H), 2.40 (dd, J = 8.3, 15.1, 1H), 2.56 (dd, J = 5.4, 15.1, 1H), 2.75-2.97 (m, 2H), 3.69-
		(61.73	6.29	13.08)		3.80 (m, 2H), 4.26-4.60 (m, 6H), 5.05 (s, 2H), 7.07-7.38 (m, 11H), 7.47-7.54 (m, 1H), 7.71-7.81 (m, 1H), 8.37-8.42 (m, 1H).
47	$C_{33}H_{38}N_6O_7 \cdot H_2O$	61.10	6.22	12.96	109-111	1.87-2.31 (m 4H), 2.40 (dd, J = 8.3, 15.1, 1H), 2.57 (dd, J = 5.4, 15.1, 1H), 2.73-2.94 (m, 2H), 3.68-
		(61.20	6.28	12.64)		3.78 (m, 2H), 4.26-4.53 (m, 6H), 5.04 (s, 2H), 7.08-7.38 (m, 11H), 7.76-7.85 (m, 1h), 8.34-8.40 (m, 1H), 8.49-8.54 (m, 1H).
48	$C_{33}H_{38}N_6O_7 \cdot H_2O$	61.10	6.22	12.96	109-111	1.89-2.31 (m 4H), 2.39 (dd, J = 8.3, 15.1, 1H), 2.56 (dd, J = 5.4, 15.1, 1H), 2.73-2.95 (m, 2H), 3.70-
		(61.41	6.37	12.67)		3.80 (m, 2H), 4.25-4.55 (m, 6H), 5.05 (s, 2H), 7.05-7.41 (m, 12H), 8.37-8.42 (m, 2H).

Table 9. Analytical Data of the Compounds shown in Table 4

No.	Formula	Analysis (%) Calcd (Found) C	H	N	mp (°C)	270MHz ^{1}H-NMR (CD_3OD) δ: ppm (J = Hz)
49	$C_{31}H_{40}N_4O_8 \cdot 0.5H_2O$	61.47 (61.78	6.82 6.84	9.25 9.22)	87-89	1.46 (s, 9H), 1.90-2.12 (m, 3H), 2.20-2.39 (m, 3H), 2.69-2.79 (m, 1H), 2.89 (dd, J = 3.6, 14.1, 1H), 3.65-3.85 (m, 2H), 4.33-4.50 (m, 4H), 5.08 (s, 2H), 7.11-7.40 (m, 10H).
50	$C_{31}H_{39}N_3O_9 \cdot 2H_2O$	58.75 (58.91	6.84 6.33	6.63 6.52)	121-123	1.46 (s, 9H), 1.89-2.13 (m, 3H), 2.19-2.30 (m, 1H), 2.36-2.66 (m, 2H), 2.72-2.93 (m, 2H), 3.65-3.84 (m, 2H), 4.32-4.55 (m, 4H), 5.06 (s, 2H), 7.07-7.41 (m, 10H).
51	$C_{32}H_{42}N_4O_8 \cdot 0.5H_2O$	62.02 (62.14	6.99 6.91	9.04 9.02)	162-164	1.46 (s, 9H), 1.87-2.10 (m, 3H), 2.19-2.30 (m, 1H), 2.41 (dd, J = 8.0, 14.9, 1H), 2.58 (dd, J = 5.7, 14.9, 1H), 2.66 (s, 3H), 2.77 (dd, J = 10.5, 13.9, 1H), 2.89 (dd, J = 3.9, 13.9, 1H), 3.64-3.80 (m, 2H), 4.32-4.48 (m, 4H), 5.07 (s, 2H), 7.09-7.40 (m, 10H).
52	$C_{33}H_{44}N_4O_8$	63.44 (63.10	7.10 7.24	8.97 8.54)	59-62	1.46 (s, 9H), 1.88-2.09 (m, 3H), 2.19-2.29 (m, 1H), 2.57-3.01 (m, 10H) including 2.88 (s, 3H) and 2.97 (s, 3H), 3.66-3.80 (m, 2H), 4.32-4.52 (m, 4H), 5.08 (s, 2H), 7.09-7.40 (m, 10H).
53	$C_{36}H_{48}N_4O_8 \cdot 0.5H_2O$	64.17 (64.01	7.33 7.37	8.31 8.09)	64-66	1.25-1.67 (m, 15H), 1.89-2.09 (m, 3H), 2.19-2.29 (m, 1H), 2.61 (dd, J = 7.3, 15.9, 1H), 2.65-2.77 (m, 2H), 2.89 (dd, J = 4.0, 14.1, 1H), 3.32-3.52 (m, 4H), 3.66-3.81 (m, 2H), 4.34-4.51 (m, 4H), 5.08 (s, 2H), 7.09-7.40 (m, 10H), 7.97 (d, J = 8.9, 1H).
54	$C_{32}H_{42}N_4O_8 \cdot 0.5H_2O$	62.02 (61.89	6.99 6.65	9.04 8.82)	92-94	1.46 (s, 9H), 1.68-2.31 (m, 8H), 2.76 (dd, J = 9.8, 13.7, 1H), 2.90 (dd, J = 3.4, 13.7, 1H), 3.65-3.84 (m, 2H), 4.03 (dd, J = 5.9, 8.3, 1H), 4.35-4.48 (m, 3H), 5.07 (s, 2H), 7.06-7.40 (m, 10H).
55	$C_{32}H_{41}N_3O_9 \cdot 0.5H_2O$	61.92 (61.99	6.82 6.83	6.77 6.85)	80-82	1.46 (s, 9H), 1.70-2.30 (m, 8H), 2.76 (dd, J = 11.0, 13.8, 1H), 2.90 (dd, J = 2.9, 13.8, 1H), 3.66-3.84 (m, 2H), 4.01-4.10 (m, 1H), 4.34-4.46 (m, 3H), 5.07 (s, 2H), 7.07-7.40 (m, 10H).
56	$C_{32}H_{44}N_4O_7 \cdot H_2O$	62.52 (62.34	7.54 7.41	9.11 8.88)	66-68	1.40-1.73 (m, 13H), 1.86-2.30 (m, 4H), 2.64-2.94 (m, 4H), 3.64-3.84 (m, 2H), 3.96-4.07 (m, 1H), 4.34-4.46 (m, 3H), 5.07 (s, 2H), 7.07-7.40 (m, 10H).
57	$C_{31}H_{38}N_4O_7 \cdot 2H_2O$	60.57 (60.34	6.89 6.62	9.12 9.68)	76-77	1.44 (s, 9H), 1.89-2.06 (m, 3H), 2.18-2.27 (m, 1H), 2.68-2.96 (m, 4H), 3.66-3.81 (m, 2H), 4.25-4.33 (m, 1H), 4.36-4.50 (m, 3H), 5.11 (s, 2H), 7.10-7.41 (m, 10H).
58	$C_{30}H_{39}N_3O_8 \cdot H_2O$	61.32 (61.42	7.03 6.63	7.15 7.41)	63-65	1.46 (s, 9H), 1.88-2.10 (m, 3H), 2.18-2.28 (m, 1H), 2.78 (dd, J = 10.7, 13.9, 1H), 2.90 (dd, J = 3.7, 13.9, 1H), 3.55-3.81 (m, 4H), 4.07-4.20 (m, 1), 4.35-4.47 (m, 3H), 5.09 (s, 2H), 7.09-7.40 (m, 10H).
59	$C_{36}H_{43}N_3O_7$	68.66 (68.75	6.88 7.17	6.67 6.44)	66-69	1.45 (s, 9H), 1.89-2.10 (m, 3H), 2.19-2.30 (m, 1H), 2.69 (dd, J = 9.5, 13.9, 1H), 2.77 (dd, J = 10.5, 13.9, 1H), 2.89 (dd, J = 3.5, 14.0, 1H), 2.97 (dd, J = 5.8, 14.0, 1H), 3.59-3.82 (m, 2H), 4.25-4.45 (m, 1H), 4.99 (s, 2H), 7.10-7.35 (m, 15H).
60	$C_{33}H_{41}N_5O_7$	63.96 (63.74	6.67 6.63	11.30 11.44)	94-98	1.45, 1.46 (each s, 9H), 1.90-2.10 (m, 3H), 2.19-2.31 (m, 1H), 2.70-2.98 (m, 4H), 3.64-3.81 (m, 2H), 4.25-4.50 (m, 4H), 5.02, 5.04 (each s, 2H), 6.50, 6.73 (each s, 1H), 7.10-7.37 (m, 10H), 7.53, 7.55 (each s, 1H).
61	$C_{29}H_{37}N_3O_7 \cdot 0.5H_2O$	63.49 (63.65	6.98 6.90	7.66 7.70)	65-68	1.46 (s, 9H), 1.89-2.10 (m, 3H), 2.20-2.30 (m, 1H), 2.76 (dd, J = 11.0, 13.9, 1H), 2.90 (dd, J = 3.6, 13.9, 1H), 3.56-3.80 (m, 4H), 4.33-4.50 (m, 3H), 5.08 (s, 2H), 7.10-7.40 (m, 10H), 8.03 (d, J = 8.7, 1H).

Table 10. Analytical Data of the Compounds shown in Table 5

No.	Formula	Analysis (%) Calcd (Found) C	H	N	mp (°C)	270MHz ^{1}H-NMR (CD_3OD) δ: ppm (J = Hz)
62	$C_{31}H_{41}N_3O_7$	62.50 (62.19	6.94 6.93	11.76 11.59)	179-180	1.46, 1.47 (each s, 9H), 1.89-2.10 (m, 3H), 2.17-2.30 (m, 1H), 2.45-2.65 (m, 2H), 2.72-2.92 (m, 2H), 3.65-3.76 (m, 2H), 4.27-4.44 (m, 5H), 4.48-4.58 (m, 1H), 7.09-7.34 (m, 10H).
63	$C_{31}H_{40}N_4O_6 \cdot 0.5H_2O$	61.47 (61.53	6.82 6.76	9.25 9.08)	87-90	1.44, 1.46 (each s, 9H), 1.87-2.11 (m, 3H), 2.18-2.42 (m, 1H), 2.56-2.70 (m, 2H), 2.76 (dd, J = 10.3, 13.7, 1H), 2.88 (dd, J = 3.9, 13.7, 1H), 3.65-3.83 (m, 2H), 4.34-4.54 (m, 5H), 4.70-4.80 (m, 1H), 6.94-7.36 (m, 10H).
64	$C_{29}H_{37}N_3O_7 \cdot 0.25H_2O$	60.88 (60.80	6.61 6.65	12.24 11.97)	104-106	1.44, 1.46 (each s, 9H), 1.85-2.16 (m, 3H), 2.19-2.30 (m, 1H), 2.67-2.82 (m, 3H), 2.88 (dd, J = 3.9, 13.7, 1H), 3.66-3.86 (m, 2H), 4.34-4.42 (m, 2H), 4.50 (d, J = 3.4, 1H), 4.85-4.94 (m, 1H), 6.92-7.08 (m, 3H), 7.18-7.27 (m, 2H), 7.53-7.60 (m, 1H), 7.93-8.02 (m, 1H), 8.08-8.15 (m 1H), 8.60-8.67 (m, 1H).
65	$C_{33}H_{45}N_5O_7 \cdot 0.5H_2O$	62.64 (62.55	7.33 7.24	11.07 10.98)	83-85	0.97 (t, J = 7.3, 3H), 1.33-1.48 (m, 11H), 1.60-1.70 (m, 2H), 1.89-2.11 (m, 3H), 2.20-2.30 (m, 1H), 2.65-2.80 (m, 5H), 2.87 (dd, J = 3.7, 13.9, 1H), 3.68-3.83 (m, 2H), 4.35-4.41 (m, 2H), 4.49 (d, J = 2.9, 1H), 4.85-4.90 (m, 1H), 6.91-7.06 (m, 3H), 7.19-7.27 (m, 2H), 7.79 (dd, J = 2.2, 8.1, 1H), 8.01 (d, J = 8.1, 1H), 8.46 (d, J = 2.2, 1H).
66	$C_{33}H_{39}N_5O_7 \cdot H_2O$	62.35 (62.29	6.50 6.50	11.02 10.60)	109-112	1.41, 1.47 (each s, 9H), 1.88-2.11 (m, 3H), 2.20-2.30 (m, 1H), 2.71-2.92 (m, 4H), 3.69-3.85 (m, 2H), 4.35-4.45 (m, 2H), 4.51 (d, J = 3.2, 1H), 4.90-4.97 (m, 1H), 6.87 (t-like, J = 7.5, 1H), 6.99 (t-like, J = 7.5, 2H), 7.12-7.27 (m, 2H), 7.68-7.73 (m, 1H), 7.82-7.88 (m, 1H), 8.00-8.05 (m, 1H), 8.14-8.26 (m, 2H), 8.48-8.52 (m, 1H).
67	$C_{34}H_{40}N_4O_7 \cdot H_2O$	64.34 (64.53	6.67 6.47	8.83 8.84)	134-140	1.43, 1.47 (each s, 9H), 1.88-2.10 (m, 3H), 2.18-2.30 (m, 1H), 2.68 (dd, J = 7.3, 15.4, 1H), 2.71-2.86 (m,2H), 2.89 (dd, J = 4.0, 14.1, 1H), 3.68-3.85 (m, 2H), 4.35-4.45 (m, 2H), 4.50 (d, J = 3.1, 1H), 4.95-5.01 (m, 1H), 6.94-7.05 (m, 3H), 7.13-7.28 (m, 2H), 7.55-7.64 (m, 2H), 7.83-7.88 (m, 1H), 7.91-8.00 (m, 3H), 8.32-8.36 (m, 1H).
68[a]	$C_{33}H_{40}N_4O_6S \cdot 0.5H_2O$	59.89 (59.86	6.25 6.19	8.47 8.32)	115-117	1.44, 1.46 (each s, 9H), 1.80-2.01 (m, 3H), 2.11-2.27 (m, 1H), 2.29-2.50 (m, 2H), 2.62 (dd, J = 10.3, 14.2, 1H), 2.76 (dd, J = 4.4, 14.2, 1H), 3.42-3.61 (m, 2H), 4.08-4.21 (m, 2H), 4.27 (d, J = 3.4, 1H), 4.33-4.40 (m, 1H), 7.04-7.27 (m, 5H), 7.58-7.80 (m, 3H), 7.88-8.03 (m, 3H), 8.38-8.42 (m, 1H).
69	$C_{33}H_{39}N_5O_7 \cdot H_2O$	62.35 (62.10	6.50 6.40	11.02 10.92)	122-124	1.42, 1.48 (each s, 9H), 1.89-2.10 (m, 3H), 2.20-2.30 (m, 1H), 2.68 (dd, J = 7.5, 15.4, 1H), 2.75-2.94 (m, 1H), 2.75-2.94 (m, 3H), 3.70-3.85 (m, 2H), 4.36-4.47 (m, 2H), 4.51 (d, J = 3.4, 1H), 4.95-5.03 (m, 1H), 6.95 (t-like, J = 7.5, 1H), 7.04 (t-like, J = 7.5, 2H), 7.14-7.29 (m, 2H), 7.69-7.76 (m, 1H), 7.87-7.94 (m, 1H), 8.06-8.14 (m, 2H), 8.73-8.76 (m, 1H), 9.18-9.22 (m, 1H).
70	$C_{33}H_{39}N_5O_7 \cdot 3H_2O$	59.00 (58.83	6.75 6.10	10.43 9.79)	138-140	1.45, 1.47 (each s, 9H), 1.90-2.11 (m, 3H), 2.20-2.31 (m, 1H), 2.59-2.69 (m, 1H), 2.78-2.98 (m, 3H), 3.70-3.82 (m, 2H), 4.19-4.50 (m, 3H), 5.05 (dd, J = 5.4, 8.3, 1H), 7.09-7.26 (m, 3H), 7.30-7.38 (m, 2H), 7.48-7.57 (m, 1H), 7.61-7.69 (m, 1H), 7.77-7.86 (m, 1H), 8.05-8.11 (m, 1H), 8.14-8.20 (m, 1H), 8.88-8.92 (m, 1H).
71	$C_{32}H_{38}N_6O_7 \cdot H_2O$	60.36 (60.31	6.33 5.92	13.20 13.06)	116-118	1.40, 1.47 (each s, 9H), 1.87-2.11 (m, 3H), 2.20-2.29 (m, 1H), 2.74-2.84 (m, 3H), 2.88 (dd, J = 4.2, 14.4, 1H), 3.70-3.85 (m, 2H), 4.34-4.45 (m, 2H), 4.51 (d, J = 3.4, 1H), 4.91-4.96 (m, 1H), 6.87 (t-like, J = 7.5, 1H), 7.00 (t-like, J = 7.5, 2H), 7.12-7.27 (m, 2H), 7.93-8.02 (m, 2H), 8.17-8.26 (m, 2H), 9.45-9.51 (m, 1H).
72	$C_{32}H_{39}N_5O_7 \cdot 3.5H_2O$	57.47 (57.23	6.93 6.27	10.47 10.06)	140-143	1.43, 1.47 (each s, 9H), 1.87-2.11 (m, 3H), 2.20-2.30 (m, 1H), 2.62 (dd, J = 7.3, 15.4, 1H), 2.68-2.84 (m, 2H), 2.87 (dd, J = 3.9, 14.1, 1H), 3.69-3.85 (m, 2H), 4.35-4.43 (m, 2H), 4.50 (d, J = 3.0, 1H), 4.92-4.98 (m, 1H), 6.89-7.00 (m, 3H), 7.04-7.14 (m, 2H), 7.25-7.33 (m, 3H), 7.44-7.50 (m, 1H), 7.60-7.66 (m, 1H).
73	$C_{32}H_{38}N_4O_6 \cdot H_2O$	61.52 (61.53	6.45 6.15	8.97 8.85)	114-116	1.43, 1.47 (each s, 9H), 1.88-2.10 (m, 3H), 2.20-2.30 (m, 1H), 2.64-2.93 (m, 4H), 3.67-3.85 (m, 2H), 4.35-4.43 (m, 2H), 4.50 (d, J = 3.3, 1H), 4.88-4.96 (m, 1H), 6.93 (t-like, J = 7.5, 1H), 7.02 (t-like, J = 7.5, 2H), 7.12-7.27 (m, 2H), 7.31-7.37 (m, 1H), 7.45-7.53 (m, 2H), 7.57-7.63 (m, 1H), 7.73-7.78 (m, 1H).
74	$C_{33}H_{40}N_6O_6 \cdot H_2O$	62.44 (62.16	6.67 6.49	13.24 13.15)	133-135	1.27, 1.35 (each s, 9H), 1.85-1.95 (m, 2H), 2.05-2.18 (m, 2H), 2.70-2.91 (m, 4H), 3.70-3.82 (m, 2H), 4.33-4.48 (m, 3H), 4.88-4.95 (m, 1H), 6.88 (t-like, J = 7.5, 1H), 7.00 (t-like, J = 7.5, 2H), 7.10-7.26 (m, 2H), 7.66-7.74 (m, 1H), 7.81-7.88 (m, 1H), 7.98-8.05 (m, 1H), 8.13-8.23 (m, 2H), 8.47-8.52 (m, 1H).
75	$C_{32}H_{39}N_7O_6 \cdot 0.5H_2O$	61.33 (61.48	6.43 6.62	15.64 15.23)	134-136	1.26, 1.35 (each s, 9H), 1.88-1.97 (m, 2H), 2.09-2.17 (m, 2H), 2.72-2.90 (m, 4H), 3.74-3.79 (m, 2H), 4.27-4.48 (m, 3H), 4.93 (t, J = 6.3, 1H), 6.86 (t-like, J = 7.3, 1H), 7.01 (t-like, J = 7.3, 2H), 7.12-7.27 (m, 2H), 7.93-8.01 (m, 2H), 8.17-8.25 (m, 2H), 9.48-9.50 (m, 1H).
76	$C_{32}H_{40}N_4O_6 \cdot H_2O$	61.72 (62.03	6.80 6.61	13.50 13.30)	152-154	1.29, 1.34 (each s, 9H), 1.86-1.97 (m, 2H), 2.06-2.19 (m, 2H), 2.60 (dd, J = 7.3, 15.4, 1H), 2.66-2.92 (m, 3H), 3.72-3.80 (m, 2H), 4.33-4.40 (m, 2H), 4.47 (d, J = 4.0, 1H), 4.90-4.96 (m, 1H), 6.89-7.02 (m, 3H), 7.04-7.14 (m, 2H), 7.20-7.28 (m, 3H), 7.43-7.49 (m, 1H), 7.60-7.65 (m, 1H).

[a] Anal. Calcd for $C_{33}H_{40}N_4O_8S$ 0.5H2O: S, 4.85. Found: S, 4.85.

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