Pergamon

Bioorganic & Medicinal Chemistry 6 (1998) 595–604

BIOORGANIC & MEDICINAL CHEMISTRY

Structure–Activity Relationship of HIV-1 Protease Inhibitors Containing AHPBA. Part III: Modification of P_2 Site

Eiji Takashiro,[a,*] Takashi Watanabe,[a] Tamayo Nitta,[a] Atsushi Kasuya,[a] Shuichi Miyamoto,[a] Yuji Ozawa,[b] Ryuichi Yagi,[b] Takashi Nishigaki,[b] Takahiro Shibayama,[c] Akihiko Nakagawa,[c] Aikichi Iwamoto[d] and Yuichiro Yabe[a,*]

[a]*Exploratory Chemistry Research Laboratories, Sankyo Co. Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140, Japan*
[b]*Biological Research Laboratories, Sankyo Co. Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140, Japan*
[c]*Analytical and Metabolic Research Laboratories, Sankyo Co. Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140, Japan*
[d]*Institute of Medical Science, University of Tokyo, Shiroganedai, Minato-ku, Tokyo 108, Japan*

Received 18 September 1997; accepted 25 December 1997

Abstract—The structure–activity relationship of HIV-1 protease (HIV-1 PR) inhibitors containing AHPBA (3-amino-2-hydroxy-4-phenylbutanoic acid) is discussed. In order to solve the problem of poor oral bioavailability, small-sized dipeptide HIV-1 protease inhibitors containing cyclic urethanes or benzamides at the P_2 site were designed and prepared. The substitution patterns of the benzamides contributed significantly to their HIV-1 PR inhibitory activities, and it was shown that the choice of P_2-residues was very important. Highly potent inhibitors possessing subnanomolar IC_{50} values and exhibiting good antiviral potency have been identified. In this class, inhibitor **18** was the most potent (IC_{90} (CEM/HIV-1 IIIB) 0.11 μM) and showed good oral bioavailability in dogs.

Introduction

Treatment of acquired immunodeficiency syndrome (AIDS) continues to be one of the most challenging obstacles in chemotherapy. HIV-1 protease is an aspartic protease which is essential for viral replication, processing the *gag* and the *gag–pol* polyproteins to permit formation of mature protein.[1] Inhibition of HIV-1 protease offers an attractive target for the treatment of AIDS.[2] Numerous inhibitors have been developed and several of them are now on the market or undergoing clinical trial.[3,4]

In the previous paper, we reported that AHPBA-derived HIV-1 PR inhibitors having 4(*S*)-Cl-Pro at the P_1' site showed potent inhibitory activity against HIV-1 PR, and some of them showed good anti-HIV activity.[5] Unfortunately, their oral bioavailability was unsatisfactory. In order to improve this, we replaced the P_3–P_2 region with groups which are smaller in size (Figure 1).

Ghosh et al. reported that inhibitors incorporating cyclic ligands at the P_2 site showed high potency.[6] This result prompted us to synthesize compounds with cyclic urethanes as P_2 ligands. Benzamide groups were proved to be desirable P_2/P_2'-ligands in symmetric inhibitors by two groups,[7] and Kalish et al. disclosed that they were also very good P_2-ligands for hydroxyethylamine-type inhibitors.[8a] These results encouraged us to incorporate substituted benzoyl groups into the backbone structure of our HIV-1 PR inhibitors.

Results and Discussion

Chemistry

All alcohols used were either purchased or prepared according to known procedures. 5(*S*)-hydroxy-5,6-

*Corresponding author.

0968-0896/98/$19.00
PII: S0968-0896(98)00004-2

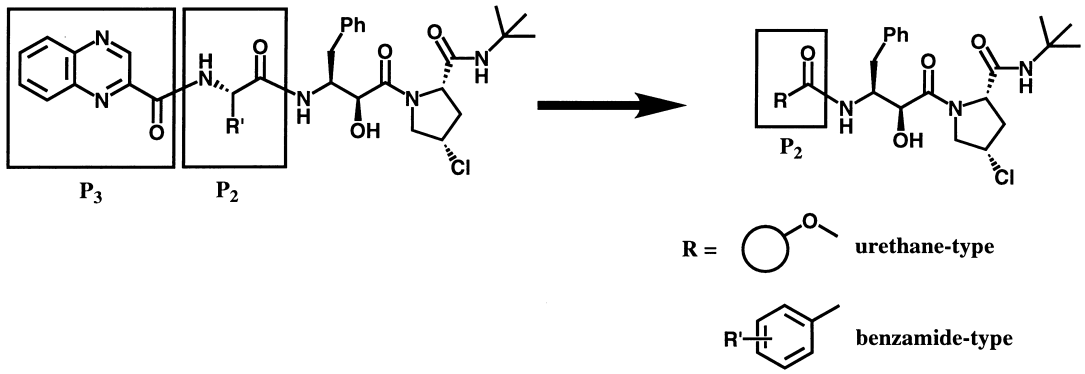


Figure 1. Design of reduced size inhibitors.

dihydro-2*H*-pyran, 5(*S*)-hydroxy-6(*R*)-methoxy-5,6-dihydro-2*H*-pyrane and their antipols were synthesized by Fleet's procedure.[9]

All commercially available benzoic acids were purchased, and others were prepared as follows. 3- Hydroxy-2-methylbenzoic acid,[10] 2,6-dimethyl-3-hydroxybenzoic acid[11] and 2-ethyl-3-hydroxybenzoic acid[12] were prepared according to known methods. 2-Bromo-3-hydroxybenzoic acid was obtained by oxidation[13] of the corresponding aldehyde.[14] 3-Hydroxy-2-*n*-propylbenzoic acid was synthesized according to Scheme 1.

Regioselective lithiation of aldehyde **1**, followed by alkylation of the corresponding aryllithium, afforded aldehyde **2** in good yield.[15] Oxidation of **2** with $NaClO_2$ gave benzoic acid,[13] which was then converted to methyl ester **3** in quantitative yield. Deprotection of the benzyl group in **3**, followed by alkaline hydrolysis of the methyl ester, gave desired benzoic acid **4**.

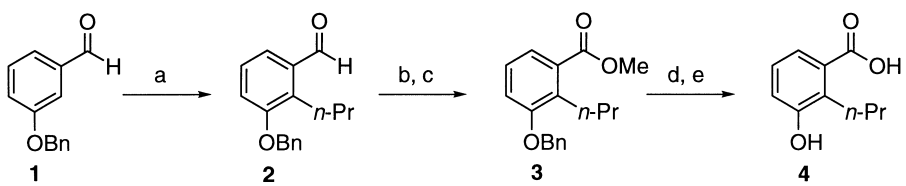
The formation of urethane- and benzamide-bearing structures was carried out in the following ways. (2*S*, 3*S*)-AHPBA-(4*S*)-Cl-Pro-NH-*t*-Bu was coupled with cyclic alcohols using DSC[16](*N*,*N*′-disuccinimidyl carbonate) to afford cyclic urethanes in good yield. Benzamide-bearing compounds, which included the most potent inhibitor **18**, were synthesized by treatment with benzoic acid, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide-hydrochloride (EDCI), 1-hydroxybenzotriazole (HOBt) and (2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu in tetrahydrofuran (THF), in quantitative yield.

Structure–activity relationship

Table 1 shows the inhibitory activities of AHPBA-based inhibitors possessing cyclic urethanes.

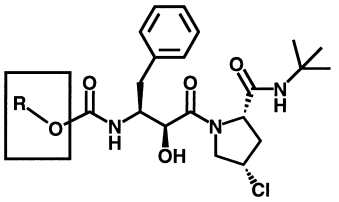
Among compounds **5**, **6**, **7**, **8** and **9**, inhibitor **6** was the most potent. The superior potency of **6** clearly showed that an oxygen atom is more effective than sulfur or nitrogen as a hetero ring atom. Because inhibitor **6**, which has a racemic alcohol, was equipotent to diastereomerically pure **10**, and compounds **12** and **13** were of similar potency, it was concluded that the configuration of the cyclic urethanes is not important.[17] The presence of unsaturated bonds in the six-membered ring increased the activity (**14** versus **15**)(**13** versus **17**). Although compound **6** showed good oral absorption in rats (data not shown), its anti-HIV activity was weak (IC_{90} (CEM/HIV-1 IIIB) 4.8 μM). Therefore, compound **6** did not satisfy our criteria, so we attempted to remove the oxygen atom from the urethanes. Compounds which have benzamide structure at the P_2 site were synthesized (Table 2).

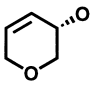
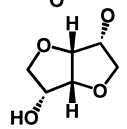
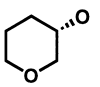
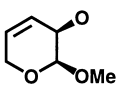
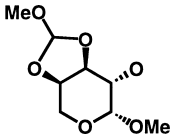
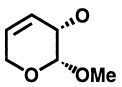
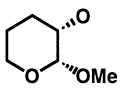
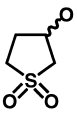
Among these compounds, **18** that has 3-hydroxy-2-methylbenzoyl group was the most potent.[7,8a] We were



Scheme 1. (a) $MeHNCH_2CH_2NMe_2$, *n*-BuLi/THF then **1**, PhLi, *n*-propyl–l (72%); (b) $NaClO_2$, $Na_2H_2PO_4$, 2-methyl-2-butene/acetone–H_2O; (c) $TMSCHN_2$/MeOH–benzene (83%, 2 steps); (d) H_2, Pd-black/MeOH (50%); (e) LiOH/MeOH, reflux (86%).

Table 1. HIV-1 PR inhibitory activity of urethane-type compounds



No.	R	IC_{50} (nM)	No	R	IC_{50} (nM)	No	R	IC_{50} (nM)
2		19	10		5.1	14		4.5
6		4.9	11		25	15		14
7		> 1000	12		35	16		> 1000
8		7.7	13		29	17		37
9		11						

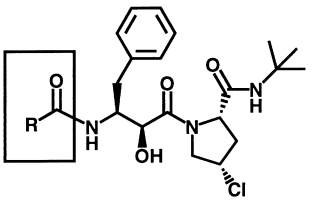
interested in investigating the relationship between substitution pattern and inhibitory activity. It was shown that *ortho*-substitution of the benzene ring is very important for high potency (**19** versus **20**∼**28**) and that inhibitors having an alkyl group or a halogen atom at this position were potent.

Randad et al. reported on inhibitors which showed strong activities when the aromatic ring and the amide carbonyl were not co-planar.[7a] Kaldor et al. found that *ortho*-substitution at the P_1' site affected amide conformation.[8b] Our computational studies on **18** showed that the benzamide carbonyl group is almost at right angle to the benzene ring.[18] In **18** and **20**–**23**, *ortho*-substitutions seemed to induce a repulsion between the aromatic ring and the amide carbonyl. Because of this repulsion, aromatic rings might occupy favorable positions in inhibitor–protease complexes. With the intention of enhancing the substituent-induced repulsion, we synthesized inhibitors **24** and **25**, which have a *n*-propyl group and a dimethyl group, respectively, at the *ortho*-position. Comparing these two compounds, two small substituents were found to be more effective than one large substituent.

On the other hand, compounds **26** and **27** exhibited very poor activity. The low-field singlet (δ 12.0 in **26** and 11.2 in **27**, respectively) in their respective ^{1}H NMR spectra suggests that hydrogen bondings occur between the *ortho*-hydroxyl groups and the amide carbonyls. It is concluded that this hydrogen bonding decreases the interactions between 'flap' water and the amide carbonyls.[19] Interestingly, compound **28** showed moderate activity. In **28**, the *ortho*-amino group possibly forms a hydrogen bond with the amide carbonyl, but this hydrogen bonding seems to be very weak because the aniline proton in **28** is less acidic than the phenolic proton in **26** or **27** (pKa values of phenol and aniline are 10.0 and 30.7, respectively). Thus, the difference between the inhibitory activity of **26** and that of **28** could be explained in this way.[20]

We also investigated the position of the hydroxyl group. According to our computational studies on **18**, the hydroxyl group seems to form a hydrogen bond with Asp29 or Asp30 in protease. This is consistent with the results of Randad et al.[7a] and Kalish et al.[8a] Inhibitors with hydroxyl group at the meta-position were generally more effective than the regioisomers or non-substituted

Table 2. HIV-1 PR Inhibitory activity of benzamide-type compounds



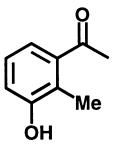
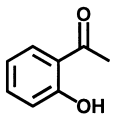
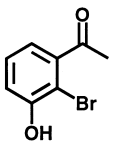
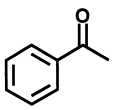
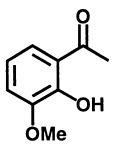
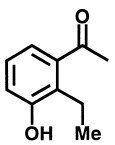
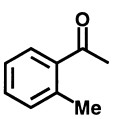
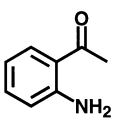
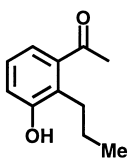
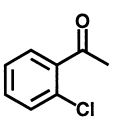
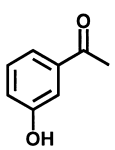
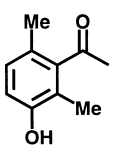
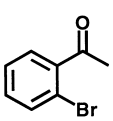
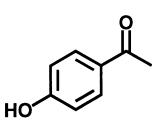
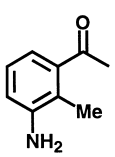
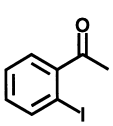
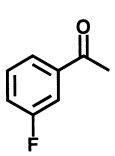
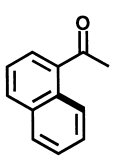
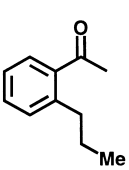
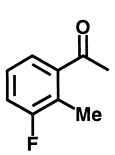
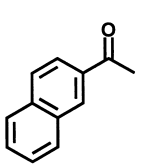
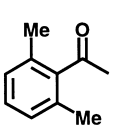
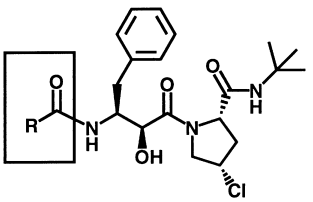
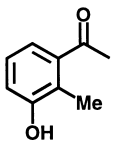
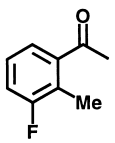
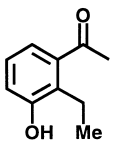
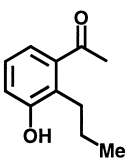
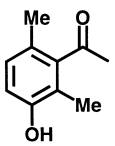
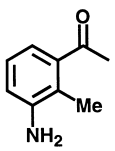
No.	R	IC_{50} (nM)	No	R	IC_{50} (nM)	No	R	IC_{50} (nM)
18		0.8	26		> 1000	33		1.5
19		26	27		> 1000	34		0.9
20		5.1	28		39	35		1.6
21		11	29		9.0	36		2.5
22		12	30		33	37		5.4
23		14	31		20	38		9.0
24		29	32		5.6	39		50
25		3.6						

Table 3. Anti-HIV activity of AHPBA-based inhibitors **18**, **32**, **34**, **35**, **36** and **37**



No.	R	CEM/HIV-1 III, B IC_{90} (nM)
18		110
32		> 500*
34		120
35		230
36		105
34		> 500*

*IC_{50} (nM)

compounds (e.g. **18** versus **20**, **19** versus **29**, **29** versus **30**, **22** versus **33**). Replacement of the methyl group with an ethyl group (**34**) or a *n*-propyl group (**35**) gave compounds with potent enzyme inhibitory activities, but their antiviral activities were less potent than that of **18** (Table 3). 2,6-Dimethyl-3-hydroxybenzamide **36** was also a good inhibitor, but it was a little less potent than **18**. A *n*-propyl group proved to be too large as a *ortho*-substitution as judged by the above results (**20** versus **24**, **18** versus **35**).

Comparing **37** with **18**, a hydroxyl group is more effective than an amino group for the formation of a hydrogen bond to Asp29 or Asp30. Moreover, compound **38** was more potent than compound **39**, suggesting that the boldface bond in **38** might work in a similar way to the methyl group in **18**.

Anti-HIV-1 activity

It is well known that protease inhibition is not always compatible with anti-HIV activity. Table 3 summarizes the anti-HIV activities of selected inhibitors.[5b]

Compound **18** with a 3-hydroxy-2-methylbenzoyl group was the best candidate among the compounds in this class. Although **34** and **35** showed almost equipotent protease inhibitory activities as **18**, they were much less potent than **18** in terms of anti-HIV activities. Interestingly, although **36** was less potent than **18** in protease inhibition, they were of similar potency in anti-HIV activity. These results suggest that the 2,6-dimethyl-3-hydroxybenzamide moiety is important not only for interaction with protease, but also for cellular penetration. However, the reason for superior penetration ability of the 2,6-dimethyl-3-hydroxybenzamide moiety compared to the other benzamide-bearing compounds is not clearly understood, nor is its cell penetration mechanism known.

Inhibitor **18** showed good oral bioavailability in dogs. When inhibitor **18** (10 mg/kg) was administered orally to dogs, the C_{max}, AUC and bioavailability were as follows: 5.0 μM, 8.7 μM hr and 27%, respectively.

Conclusion

We have succeeded in developing small-sized dipeptide HIV-1 protease inhibitors. During the course of this study, we found that inhibitors with benzamides as P_2-ligands in the peptide-based structure showed high potency. We also discovered that *ortho*-substitutions of benzene rings are crucial for biological activities. Further work to develop more active compounds is now in progress.

Experimental

Melting points were determined with a Yanagimoto melting point apparatus and are not corrected. Infrared (IR) spectra were measured with a Nic 5SXC FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on

a JEOL JNM-GX 270 FT-NMR spectrophotometer. Chemical shifts are expressed in δ ppm from the internal standard tetramethylsilane. EI- and FAB-MS were taken on a JEOL JMS-D 300 mass spectrometer and relevant data are tabulated as *m*/*z*. Column chromatography was carried out using SK-34 (Kishida, 70–230 mesh). Preparative thin-layer chromatography was performed using 60 F_{254} plates (Merck art. 5744).

Preparation of urethane-type inhibitors (5–17)

The representative compound **13** was prepared by the following method. A solution of 5(*S*)-hydroxy-6(*R*)-methoxy-5,6-dihydro-2*H*-pyrane (153 mg, 1.17 mmol), DSC (*N*,*N*′-disuccinimidyl carbonate) (450 mg, 1.76 mmol) and triethylamine (355 mg, 3.51 mmol) in acetonitrile (5 mL) was stirred for 5 h at room temperature. After removal of the solvent in vacuo, the residue was dissolved with CH_2Cl_2 (2 mL). To this was added a solution of (2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (580 mg, 1.17 mmol) in CH_2Cl_2 (2 mL) and a solution of triethylamine (180 mg, 1.78 mmol) in CH_2Cl_2 (2 mL), and the resulting solution was stirred for 1 day. The reaction was quenched with brine and the reaction mixture was extracted with EtOAc. The combined organic layer was successively washed with saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by flash column chromatography (hexane/EtOAc = 2/8 then EtOAc only) to afford **13** (343 mg) in 55% yield.

Preparation of benzamide-type inhibitors (18–39)

The representative compound **18** was coupled with (2*S*, 3*S*)-AHPBA-4*S*-Cl-Pro-NH-*t*-Bu in the following way. The solution of 3-hydroxy-2-methylbenzoic acid (1.51 g, 9.92 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide·hydrochloride (EDCI) (3.05 g, 15.9 mmol), 1-hydroxybenzotriazole (HOBt) (1.35 g, 9.96 mmol) and (2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (3.45 g, 9.02 mmol) in THF (80 mL) was stirred for 1 day at room temperature. The reaction was quenched with brine and this reaction mixture was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by flash column chromatography (CH_2Cl_2/MeOH = 9/1) to afford **18** (4.25 mg) in 91% yield.

3-Benzyloxy-2-*n*-propylbenzaldehyde (2). To the stirred solution of *N*,*N*,*N*′-trimethylethylenediamine (1.46 g, 14.3 mmol) in toluene (13 mL) was added *n*-butyllithium (5.46 mL, 2.5 M solution in *n*-hexane) at −20 °C. The cooling bath was removed and this solution was stirred for 10 min at room temperature. The reaction mixture was cooled to −20 °C and to this a THF solution (10 mL) of **1** (2.76 g, 13.0 mmol) was added and stirred for 5 min at room temperature. To this solution was added phenyllithium (40.4 mL, 1.0 M solution in cyclohexane) and THF (10 mL), and stirred for 30 min at room temperature. The reaction mixture was cooled to −78 °C and *n*-propyliodide (8.90 mL, 91.3 mmol) was added and then stirred for 17 h. After quenching by adding H_2O, the product was extracted with EtOAc and the combined organic layer was washed with brine. After removal of the solvent in vacuo, the residue was purified by flash column chromatography (hexane/CH_2Cl_2/Et_2O = 8/1/1) to give **2** in 72% yield: ^{1}H NMR δ 0.96 (t, 3H, *J* = 7.4 Hz), 1.75–1.88 (m, 1H), 1.95–2.09 (m, 1H), 3,11 (t, 2H, *J* = 7.8 Hz), 5.12 (s, 2H), 7.09–7.50 (m, 8H), 9.88 (s, 1H); MS *m*/*z* 254 (M^+).

Methyl(3-benzyloxy-2-*n*-propyl)benzoate (3). To the stirred solution of **2** (2.24 g, 8.80 mmol) and 2-methyl-2-butene (2.60 g, 37.0 mmol) in acetone (40 mL), was added a solution of $NaClO_2$ (2.45 g, 27.1 mmol) and $Na_2H_2PO_4$ (3.49 g, 29.1 mmol) in H_2O (20 mL), and the mixture was stirred for 18 h. The solution was acidified with 0.3 N HCl aq and extracted with EtOAc. The combined organic layer was successively washed with saturated aq $Na_2S_2O_3$ and brine. After removal of solvent in vacuo, the residue was used without purification in the next step.

To the stirred solution of the above crude benzoic acid in benzene/MeOH (20/10 mL) was added trimethylsilyldiazomethane (20 mL, 10% *n*-hexane solution) at room temperature. The reaction was stirred for 5 min and evaporated in vacuo. The resulting residue was purified by flash column chromatography (hexane/EtOAc = 9/1) to give **3** in 83% yield: ^{1}H NMR ($CDCl_3$) δ 0.98 (t, 3H, *J* = 7.3 Hz), 1.81–1.87 (m, 1H), 1.96–2.08 (m, 1H), 2.96 (t, 2H, *J* = 7.9 Hz), 3.89 (s, 3H), 5.10 (s, 2H), 6.99–7.70 (m, 8H); MS *m*/*z* 284 (M +).

3-Hydroxy-2-*n*-propylbenzoic acid (4). A suspension of the methyl ester **3** (578 mg, 2.0 mmol) and Pd-black (50 mg) in MeOH (5 mL) was stirred for 2 days under hydrogen (1 atm) at room temperature. After changing the atmosphere to N_2, the mixture was diluted with CH_2Cl_2 and filtered through a Celite pad (washed with CH_2Cl_2). After removal of the solvent in vacuo, the residue was used without purification in the next step (200 mg, 50%, as crude product): mp 80 °C; ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 3H, *J* = 7.4 Hz), 1.54–1.69 (m, 2H), 2.86–2.92 (m, 2H), 3.89 (s, 3H), 5.12 (s, 1H), 6.93 (d, 1H, *J* = 7.9 Hz), 7.11 (dd, 1H, $J_1 = J_2 = 7.9$ Hz), 7.39 (d, 1H, *J* = 7.9 Hz); IR (KBr) 3413, 1698 cm^{-1}; Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H,717; Found: C,67.85; H, 7.53.

The resulting crude methyl ester (116 mg, 596 μmol) and $LiOH·H_2O$ (125 mg, 299 μmol) in MeOH–H_2O (1 mL/1 mL) was stirred for 3 h at 100 °C. The reaction was

cooled to room temperature and acidified with 3 N aqueous HCI. The reaction mixture was extracted with EtOAc and washed with brine. After the removal of solvent in vacuo, the residue was purified with preparative TLC (EtOAc only) to give acid **4** (91.4 mg) in 85% yield: mp, 144–145 °C; ^{1}H NMR (DMSO-d_6) δ 0.89 (t, 3H, J = 7.8 Hz), 1.49 (tq, 2H, $J_1 = J_2$ = 7.8 Hz), 2.80 (t, 2H, J = 7.8 Hz), 6.94 (d, 1 H, J = 8.2 Hz), 7.05 (dd, 1H, $J_1 = J_2$ = 8.2 Hz), 7.13 (d, 1H, J = 8.2 Hz), 9.51 (s, 1H), 12.6 (br,1H); IR(KBr) 3386, 1699 cm^{-1}, Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; 11,6.71; Found: C, 66.41; H, 6.81.

[(Cyclopentyl)oxy]carbonyl - (2*S*,3*S*) - AHPBA - 4(*S*) - Cl-Pro-NH-*t*-Bu (5). Mp 70–79 °C; ^{1}H NMR (CD_3OD) δ 1.32 (s, 9H), 1.47–1.67 (m, 9H), 2.14–2.18 (m, 1H), 2.61–2.74 (m, 2H), 2.93 (dd, 1H, J_1 = 13.9, J_2 = 3.3 Hz), 3.78 (q, 1H, J = 10.6 Hz), 4.03–4.04 (m, 1H), 4.31–4.44 (m, 4H), 7.16–7.32 (in, 5H); IR (KBr).3339, 2968, 2489, 1655, 1528, 1455, 1227 cm^{-1}; MS m/z 495 (M^+).

[3(*R*,*S*)-(Tetrahydrofuranyl)oxy]carbonyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (6). Mp, 85–91 °C; ^{1}H NMR (CD_3OD) δ 1.35 (s, 9H), 1.96–2.18 (m, 3H), 2.61–2.72 (m, 3H), 2.94 (dd, 1H, J_1 = 13.9, J_2 = 3.3 Hz), 3.54–3.84 (m, 6H), 4.03–4.04 (m, 1H), 4.31–4.44 (m, 4H), 5.00–5.02 (m, 1H),7.16–7.32 (m, 5H); IR (KBr) 3339, 2970, 2875, 2489, 1706, 1426, 1226, 702 cm^{-1}; Anal. Calcd for $C_{24}H_{34}N_3O_6Cl\cdot\frac{1}{2}H_2O$: C, 57.08; H, 6.99; N, 8.32; Cl, 7.02; Found: C, 57.09; H, 6.90; N, 8.29; Cl, 7.02; MS m/z 496 (M^+).

[3(*R*,*S*)-(Pyrrolidyl)oxy]carbonyl-(2*S*, 3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu·HCl (7). Mp 112 °C; ^{1}H NMR (CD_3OD) δ 1.35 (s, 9H), 1.96–2.18 (m, 3H), 2.61–2.72 (m, 3H), 2.94 (dd, 1H, J_1 = 13.9, J_2 = 3.3 Hz), 3.54–3.84 (m, 6H), 4.03–4.04 (m, 1H), 4.31–4.44 (m, 4H), 5.00–5.02 (m, 1H), 7.16–7.32 (m, 5H); IR (KBr) 3293, 2970, 1718, 1651, 1534, 1455, 1228, 1032, 752, 702 cm^{-1}; Anal. Calcd for $C_{24}H_{35}N_4O_5C1\cdot HCl\cdot H_2O$: C, 52.46; H, 6.79; N, 10.20; Cl, 12.90; Found: C, 52.38; H, 7.3 1; N, 9.98; Cl, 13.68; MS m/z 494 ($M^+ + 1$).

[3(*R*, *S*) - (Tetrahydrothiophenyl)oxy]carbonyl - (2*S*, 3*S*) - AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (8). Mp 85–91 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.78–1.98 (m, 1H), 2.03–2.28 (m, 1H), 2.62–3.08 (m, 7H), 3.64–3.89 (m, 3H), 4.03–4.32 (m, 3H), 4.49–4.58 (m, 2H), 5.14 (br, 1H), 5.31 (br, 1H), 6.28 (br, 1H), 7.20–7.32 (m, 5H); Anal. Calcd for $C_{24}H_{34}N_3O_5SCl\cdot\frac{1}{2}H_2O$: C, 54.38; H, 6.66; N, 7.92; Cl, 6.69; S, 6.05; Found: C, 54.69; H, 6.34; N, 7.73; Cl, 6.72; S, 6.08; MS m/z 512 (M^+).

[3(*R*,*S*) - (1,1 - Dioxo - tetrahydrothiophenyl)oxy]carbonyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (9). Mp 90–94 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9H), 2.01–2.43 (m, 2H), 2.62–2.77 (m, 3H), 3.04–3.28 (m, 4H), 3.66–3.81 (m, 2H), 4.07–4.33 (m, 4H), 4.45–4.56 (m, 2H), 5.27–5.38 (m, 2H), 6.18 (br, 1H), 7.22–7.36 (m, 5H); MS m/z 544 (M^+).

[3(*S*)-(Tetrahydrofuranyl)oxy]carbonyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (10). Mp 73–86 °C; ^{1}H NMR (CD_3OD) δ 1.32 (s, 9H), 1.95–2.05 (m, 1H), 2.07–2.18 (m, 2H), 2.60–2.74 (m, 2H), 2.94 (dd, 1H, J_1 = 13.9, J_2 = 3.3 Hz), 3.52 (d, 1H, J = 10.6 Hz), 3.50–3.84 (m, 5H), 4.01–4.06 (m, 1H), 4.31–4.44 (m, 4H), 5.00–5.04 (m, 1H), 7.16–7.33 (m, 5H); IR (KBr) 3414, 3343, 2970, 2478, 1683, 1534, 1367, 1226, 1033, 702 cm^{-1}; Anal. Calcd for $C_{24}H_{34}N_3O_6C1\cdot\frac{1}{2}H_2O$: C, 57.08; H, 6.99; N, 8.32; Cl, 7.02; Found: C, 57.33; H, 6.96; N, 8.36; Cl, 7.31.

(1,4:3,6-Dianhydro-D-sorbitol)carbonyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (11). Mp 104–106 °C; ^{1}H NMR (CD_3OD) δ 1.32 (s, 9H), 2.13–2.18 (m, 1H), 2.64–2.74 (m, 3H), 2.89 (dd, 1H, J_1 = 13.9, J_2 = 3.3 Hz), 3.50 (t, 1H, J = 8.6 Hz), 3.66–3.93 (m, 5H), 3.99–4.04 (m, 1H), 4.17–4.22 (m, 1H), 4.31–4.49 (m, 5H), 4.63 (t, 1H, J = 5.3 Hz), 4.88–4.90 (m, 1H), 7.16–7.32 (m, 5H); IR (KBr) 3417, 3344, 2969, 1717, 1652, 1531, 1427, 1265, 751, 701 cm^{-1}; Anal. Calcd for $C_{26}H_{36}N_3O_8C1\cdot\frac{2}{3}H_2O$: C, 55.17; H, 6.65; N, 7.42; Cl, 6.26; Found: C, 55.06; H, 6.61; N, 7.45; Cl, 6.1 1; MS m/z 554 ($M^+ + 1$).

[5(*R*)-[6(*S*)-Methoxy-5,6-dihydro-2*H*-pyranyl]oxy]carbonyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (12). Mp 88–90 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 2.57–2.76 (m, 4H), 3.50 (s, 3H), 3.71–3.84 (m, 2H), 4.02–4.34 (m, 4H), 4.49–4.58 (m, 2H), 4.82–5.33 (m, 3H), 5.50 (dd, 1H, J_1 = 10.5, J_2 = 1.5 Hz), 5.87 (dd, 1H, J_1 = 10.5, J_2 = 2.0 Hz), 6.33 (s, 1H), 7.13–7.37 (m, 5H); IR (KBr) 3335, 2968, 2935, 1762, 1710, 1687, 1651, 1531, 1455, 1392, 1367, 1250, 1230, 1206, 1128, 1101, 1057, 967, 937, 888, 820, 752, 702 cm^{-1}; MS m/z 538 ($M^+ + 1$).

[5(*S*)-[6(*R*)-Methoxy-5,6-dihydro-2*H*-pyranyl]oxy]carbonyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (13). Mp 90–92 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 2.54–2.79 (m, 4H), 3.39 (s, 3H), 3.33–3.95 (m, 1H), 3.99–4.50 (m, 6H), 4.52–4.88 (m, 3H), 5.16 (s, 1H), 5.29 (d, 1H, J = 8.7 Hz), 5.69 (dd, 1H, J_1 = 10.5, J_2 = 1.8 Hz), 5.96 (dd, 1H, J_1 = 10.5, J_2 = 2.1 Hz), 6.36 (s, 1H), 7.13–7.38 (m, 5H); IR (KBr) 3366, 2965, 2934, 1762, 1700, 1688, 1650, 1128, 1102, 1059, 968, 937, 888, 753, 702 cm^{-1}; MS m/z 538 ($M^+ + 1$).

[5(*R*) - (5,6 - Dihydro - 2*H* - pyranyl)oxy]carbonyl - (2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (14). Mp 88–90 °C; δ 1.30 (s, 9H), 2.56–2.76 (m, 4H), 3.36 (s, 3H), 3.41–3.90 (m, 1H), 4.00–4.48 (m, 6H), 4.49–4.88 (m, 3H), 5.14 (s, 1H), 5.28 (d, 1H, J = 8.7 Hz), 5.63 (dd, 1H, J_1 = 10.5,

$J_2 = 1.8$ Hz), 5.90 (dd, 1H, $J_1 = 10.5$, $J_2 = 2.1$ Hz), 6.31 (s, 1H), 7.13–7.35 (m, 5H); MS m/z 508 ($M^+ + 1$).

[3(*S*)-(Tetrahydropyranyl)oxy]carbonyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (15). Mp 73–86 °C; ^{1}H NMR (CD_3OD) δ 1.32 (s, 9H), 1.95–2.05 (m, 2H), 2.07–2.20 (m, 2H), 2.55–2.98 (m, 5H), 3.50–3.84 (m, 7H), 4.01–4.12 (m, 1H), 4.31–4.44 (m, 4H), 5.00–5.04 (m, 1H), 7.16–7.33 (m, 5H); IR (KBr) 3414, 3343, 2970, 2478, 1683, 1534, 1367, 1226, 1033, 702 cm^{-1}; MS m/z 510 ($M^+ + 1$).

[3(*S*)-[2(*R*)-methoxy-(4(*S*),5(*R*)-methoxymethylene)tetrahydropyranyl]oxy]carbonyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (16). Mp 88–90 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 2.56–2.89 (m, 4H), 3.29–3.49 (m, 6H), 3.68–4.73 (m, 13H), 5.40 (d, 1H, $J = 9.0$ Hz), 5.79 (s, 1H), 6.30 (s, 1H), 7.15–7.39 (m, 5H); MS m/z 652 ($M^+ + K$).

[3(*S*)-[2(*R*)-Methoxy-tetrahydropyranyl]oxy]carbonyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (17). Mp 89–93 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 1.36–1.87 (m, 3H), 2.41–3.29 (m, 4H), 3.34 (s, 1H), 3.37–3.52 (m, 3H), 3.61–3.73 (m, 2H), 3.81–3.90 (m, 1H), 4.07–4.33 (m, 3H), 4.49–4.64 (m, 3H), 5.22 (d, 1H, $J = 8.6$ Hz), 6.30 (s, 1H), 7.00–7.32 (m, 5H); IR (KBr) 3338, 2965, 2880, 1707, 1690, 1648, 1535, 1455, 1392, 1366, 1320, 1265, 1225, 1156, 1126, 1086, 1058, 1031, 969, 752, 701 cm^{-1}; Anal. Calcd for $C_{26}H_{38}N_3O_7Cl \cdot \frac{1}{2}H_2O$: C, 56.88; H, 7.16; N, 7.65; Cl, 6.46; Found: C, 56.63; H, 7.27; N, 7.53; Cl, 6.72; MS m/z 540 (M^+).

(3-Hydroxy-2-methyl)benzoyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (18). Mp 117 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.96 (s, 3H), 2.21–2.77 (m, 4H), 3.48–4.18 (m, 2H), 4.30–4.73 (m, 4H), 5.94 (s, 1H), 6.17–6.84 (m, 3H), 6.93–7.03 (m, 1H), 7.14–7.33 (m, 5H); IR (KBr) 3325, 2969, 2931, 1648, 1586, 1526, 1455, 1367, 1282, 1225, 1208, 1176, 1112, 1093, 700 cm^{-1}; Anal. Calcd for $C_{27}H_{34}N_3O_5Cl \cdot \frac{1}{2}H_2O$: C, 61.77; H, 6.72; N, 8.00; Cl, 6.75. Found: C, 61.46; H, 6.77; N, 7.85; Cl, 6.64; MS m/z 515 (M^+).

Benzoyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (19). Mp 84–85 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 2.40–2.94 (m, 4H), 3.60–4.07 (m, 3H), 4.30–4.40 (m, 2H), 4.51–4.72 (m, 2H), 6.30 (s, 1H), 6.53 (d, 1H, $J = 8.0$ Hz), 7.17–7.70 (m, 10H); IR (KBr) 3413, 3340, 2968, 2931, 1648, 1531, 1488, 1454, 1391, 1366, 1272, 1226, 1113, 1074, 700 cm^{-1}; Anal. Calcd for $C_{26}H_{32}N_3O_4Cl \cdot \frac{1}{2}H_2O$: C, 63.09; H, 6.72; N, 8.49; Cl, 7.16. Found: C, 63.23; H, 6.75; N, 8.49; Cl, 6.89; MS m/z 486 ($M^+ + 1$).

2-Methylbenzoyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (20). Mp 83–84 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 2.18 (s, 3H), 2.41–2.93 (m, 4H), 3.61–4.14 (m, 3H), 4.32–5.06 (m, 4H), 6.08 (d, 1H, $J = 8.4$ Hz), 6.27 (s, 1H), 7.10–7.34 (m, 9H); IR (KBr) 3322, 2968, 1649, 1530, 1455, 1392, 1366, 1270, 1207, 1112, 746, 700 cm^{-1}; Anal. Calcd for $C_{27}H_{34}N_3O_4Cl \cdot \frac{1}{2}H_2O$: C, 63.71; H, 6.93; N, 8.25; Cl, 6.96. Found: C, 63.39; H, 6.52; N, 7.90; Cl, 7.08; MS m/z 500 ($M^+ + 1$).

2-Chlorobenzoyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (21). Mp 85 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 2.41–2.93 (m, 4H), 3.61–4.17 (m, 3H), 4.31–4.75 (m, 4H), 6.28 (s, 1H), 6.69 (d, 1H, $J = 8.2$ Hz), 7.17–7.48 (m, 9H); IR (KBr) 3341, 3324, 2968, 1652, 1530, 1391, 1365, 1205, 751 cm^{-1}; Anal. Calcd for $C_{26}H_{31}N_3O_4Cl_2 \cdot \frac{1}{2}H_2O$: C, 58.98; H, 6.09; N, 7.93; Cl, 13.39. Found: C, 58.62; H, 6.01; N, 7.64; Cl, 13.38; MS m/z 520 ($M^+ + 1$).

2-Bromobenzoyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (22). Mp 91 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 2.40–2.92 (m, 3H), 3.64–4.10 (m, 4H), 4.31–4.74 (m, 4H), 6.26–6.61 (m, 2H), 7.18–7.35 (m, 8H), 7.51–7.59 (m, 1H); IR (KBr) 3403, 3326, 2969, 2932, 2877, 1652, 1530, 1455, 1392, 1366, 1268, 1226, 1119, 1029, 750, 701 cm^{-1}; MS m/z 564 ($M^+ + 1$).

2-Iodobenzoyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (23). Mp 93–94 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 2.40–2.93 (m, 3H), 3.64–4.10 (m, 4H), 4.31–4.75 (m, 4H), 6.22–6.53 (m, 2H), 7.03–7.13 (m, 2H), 7.19–7.38 (m, 6H), 7.78–7.85 (m, 1H); IR (KBr) 3319, 2966, 1652, 1533, 1454, 1118, 1016, 872, 749, 700 cm^{-1}; MS m/z 612 ($M^+ + 1$).

2-*n*-Propylbenzoyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (24). Mp 73–75 °C; ^{1}H NMR ($CDCl_3$) δ 0.80 (t, 3H, $J = 7.7$ Hz), 1.30 (s, 9H), 1.42 (q, 2H, $J = 7.7$ Hz), 2.41–2.91 (m, 6H), 3.65–4.14 (m, 3H), 4.32–4.73 (m, 4H), 6.04–6.46 (m, 2H), 6.99–7.36 (m, 9H); IR (KBr) 3409, 3326, 1648, 1527, 1455, 1367, 1116, 700 cm^{-1}; Anal. Calcd for $C_{29}H_{38}N_3O_4Cl \cdot H_2O$: C, 63.78; H, 7.38; N, 7.69; Cl, 6.49. Found: C, 64.00; H, 7.20; N, 7.56; Cl, 6.83; MS m/z 528 ($M^+ + 1$).

2,6-Dimethylbenzoyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (25). Mp 93–97 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 2.00 (s, 6H), 2.61–2.91 (m, 3H), 3.60–4.21 (m, 4H), 4.31–4.83 (m, 4H), 6.13 (d, 1H, $J = 8.1$ Hz), 6.27 (s, 1H), 6.99–7.36 (m, 10H); Anal. Calcd for $C_{28}H_{36}N_3O_4Cl \cdot \frac{3}{2}H_2O$: C, 62.15; H, 7.26; N, 7.77; Cl, 6.55. Found: C, 62.34; H, 6.98; N, 7.44; Cl, 6.72; MS m/z 514 ($M^+ + 1$).

2-Hydroxybenzoyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (26). Mp 100 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9H), 2.43–3.00 (m, 4H), 3.62–3.94 (m, 4H), 4.05–4.66 (m, 4H), 6.20 (s 1H), 6.77–7.06 (m, 2H), 7.14–7.43 (m, 7H), 12.0 (s, 1H); IR (KBr) 3350, 2970, 1644, 1603, 1536, 1494, 1454, 1226, 754 cm^{-1}; Anal. Calcd for $C_{26}H_{32}N_3O_5$-

C1·H_2O: C, 60.05; H, 6.59; N, 8.08; Cl, 6.82. Found: C, 60.05; H, 6,38; N, 7.72; Cl, 6.48; MS *m*/*z* 501 (M^+).

(2-Hydroxy-3-methoxy)benzoyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (27). Mp 120–126 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 9H), 2.41–2.94 (m, 3H), 3.65–3.74 (m, 3H), 3.82–4.09 (m, 4H), 4.27–4.67 (m, 4H), 6.14–6.27 (m, 1H), 6.77–6.88 (m, 1H), 6.94–7.06 (m, 2H), 7.10–7.56 (m, 6H), 11.2 (s, 1H); IR (KBr) 3353, 2969, 2935, 1671, 1587, 1534, 1462, 1367, 1253, 1119, 936, 873, 835, 779, 747, 702 cm^{-1}; MS *m*/*z* 531 (M^+).

2-Aminobenzoyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (28). Mp 93–94 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 2.44–2.94 (m, 3H), 3.70–4.16 (m, 4H), 4.29–4.38 (m, 2H), 4.50–4.60 (m, 3H), 6.27–6.32 (m, 1H), 6.46 (d, 1H, J = 8.2 Hz), 6.60–6.71 (m, 3H), 7.13–7.32 (m, 7H); IR (KBr) 3348, 2968, 1644, 1521, 1453, 1366, 1266, 1118, 750, 702 cm^{-1}; Anal. Calcd for $C_{26}H_{33}N_4O_4C1\cdot\frac{5}{4}H_2O$: C, 59.65; H, 6.84; N, 10.70; Cl, 6.77. Found: C, 60.36; H, 6.51; N, 10.28; Cl, 6.62; MS *m*/*z* 501 (M^+).

3-Hydroxybenzoyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (29). Mp 112 °C; ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 9H), 2.35–4.61 (m, 8H), 4.61–5.06 (m, 3H), 6.46–8.25 (m, 11H); IR (KBr) 3406, 2968, 1648,1585, 1530, 1454, 1367, 1272, 1226, 1116, 811, 751, 700 cm^{-1}; Anal. Calcd for $C_{26}H_{32}N_3O_5Cl\cdot\frac{1}{2}H_2O$: C, 61.11; H, 6.52; N, 8.22; Cl, 6.94. Found: C, 61.25; H, 6.55; N, 7.95; Cl, 7.05; MS *m*/*z* 501 (M^+).

4-Hydroxybenzoyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (30). Mp 100 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 2.43–2.95 (m, 4H), 3.60–4.09 (m, 3H), 4.20–4.69 (m, 5H), 5.97–8.13 (m, 11H); IR (KBr) 3327, 2969, 2876, 1652, 1609, 1536, 1503, 1455, 1392, 1366, 1272, 1226, 1174, 1113, 851, 750 cm^{-1}; Anal. Calcd for $C_{26}H_{32}N_3O_5$-C1·H_2O: C, 60.05; H, 6.59; N, 8.08; Cl, 6.82. Found: C, 60.19; H, 6.78; N, 8.41; Cl, 6.98; MS *m*/*z* 501 (M^+).

3-Fluorobenzoyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (31). Mp 81–82 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 2.41–2.75 (m, 2H), 2.78–2.92 (m, 2H), 3.62–4.08 (m, 3H), 4.29–4.69 (m, 4H), 6.25 (s, 1H), 6.54 (d, 1H, J = 8.1 Hz), 7.13–7.49 (m, 9H); IR (KBr) 3337, 2969, 2932, 1649, 1455, 1366, 1271, 1224, 806, 751, 701 cm^{-1}; Anal. Calcd for $C_{26}H_{31}N_3O_4FCl\cdot\frac{1}{4}H_2O$: C, 61.41; H, 6.24; N, 8.26; F, 3.74; Cl, 6.97. Found: C, 61.40; H, 6.40; N, 8.20; F, 3.66; Cl, 6.74; MS *m*/*z* 504 (M^+ + 1).

(3-Fluoro-2-methyl)benzoyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (32). Mp 86–88 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 2.05 (s, 3H), 2.42–2.89 (m, 3H), 3.68–4.16 (m, 3H), 4.31–4.71 (m, 4H), 6.09 (d, 1H, J = 8.4 Hz), 6.22 (s, 1H), 6.90 (d, 1H, J = 7.4 Hz), 6.97–7.34 (m, 8H); IR (KBr) 3321, 2969, 2932, 1652, 1530, 1456, 1393, 1243, 1225, 1115, 830, 752, 700 cm^{-1}; Anal. Calcd for $C_{27}H_{33}N_3O_4FCl\cdot\frac{1}{2}H_2O$: C, 61.53; H, 6.51; N, 7.97; F, 3.60; Cl, 7.97. Found: C, 61.18; H, 6.71; N, 7.68; F, 3.47; Cl, 6.62; MS *m*/*z* 517 (M^+).

(2-Bromo-3-hydroxy)benzoyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (33). Mp 117–118 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 2.39–2.99 (m, 3H), 3.43–4.24 (m, 3H), 4.31–4.53 (m, 2H), 4.60–5.06 (m, 3H), 6.22–7.34 (m, 10H); IR (KBr) 3321, 2968, 2931, 1652, 1569, 1530, 1458, 1439, 1367, 1296, 1225, 1118, 1031, 873, 795, 750, 701 cm^{-1}; MS *m*/*z* 580 (M^+ + 1).

(2-Ethyl-3-hydroxy)benzoyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (34). Mp 111–116 °C; ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 3H, J = 7.6 Hz), 1.30 (s, 9H), 2.38–2.93 (m, 5H), 3.61–4.12 (m, 4H), 4.31–4.71 (m, 4H), 6.10 (d, 1H, J = 7.4 Hz), 6.43 (s, 1H), 6.64–7.34 (m, 8H); IR (KBr) 3326, 2967, 1648, 1522, 1455, 1367, 1287, 1099, 749, 700 cm^{-1}; Anal. Calcd for $C_{28}H_{36}N_3O_5Cl\cdot H_2O$: C, 61.36; H, 6.99; N, 7.67; Cl, 6.47. Found: C, 61.31; H, 6.01; N, 7.41; Cl, 6.35; MS *m*/*z* 5 30 (M^+ + 1).

(3-Hydroxy-2-*n*-propyl)benzoyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (35). Mp 108–112 °C; ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 3H, J = 7.4 Hz), 1.30 (s, 9H), 2.38–2.94 (m, 3H), 3.61–4.12 (m, 4H), 4.31–4.71 (m, 4H), 5.42 (s, 1 H), 6.10 (d, 1H, J = 7.6 Hz), 6.25 (s, 1 H), 6.63–7.34 (m, 8H); IR (KBr) 3327, 2964, 2871, 1648, 1584, 1522, 1455, 1367, 1290, 1223, 1105, 791, 742, 700 cm^{-1}; Anal. Calcd for $C_{29}H_{38}N_3O_5Cl\cdot H_2O$: C, 61.97; H, 7.17; N, 7.48; Cl, 6.3 1. Found: C, 62.14; fl, 6.93; N, 7.22; Cl, 6.60; MS *m*/*z* 544 (M^+).

(2,6-Dimethyl-3-hydroxy)benzoyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (36). Mp 134–136 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.91 (s, 3H), 1.97 (s, 311), 2.36–2.90 (m, 3H), 3.71–4.19 (m, 4H), 4.31–4.85 (m, 3H), 5.04–7.00 (m, 3H), 7.11–7.52 (m, 7H); IR (KBr) 3335, 2968, 1645, 1532, 1455, 1276, 1223, 1118, 872, 749, 700 cm^{-1}; Anal. Calcd for $C_{28}H_{36}N_3O_5Cl\cdot 1.78H_2O$: C, 59.84; H, 7.09; N, 7.47; Cl, 6.31. Found: C, 60.07; H, 6.75; N, 7.09; Cl, 6.57; MS *m*/*z* 529 (M^+).

(3-Amino-2-methyl)benzoyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (37). Mp 106–108 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.90 (dd, 2H, $J_1 = J_2$ = 22.5 Hz), 2.40–3.18 (m, 3H), 3.63–4.14 (m, 6H), 4.30–4.71 (m, 4H), 6.09–6.72 (m, 4H), 6.93–7.33 (m, 6H); IR (KBr) 3350, 1648, 1522, 1454, 1225, 1119, 873, 751, 701 cm^{-1}; Anal. Calcd for $C_{27}H_{35}N_4O_4Cl\cdot\frac{3}{4}H_2O$: C, 61.35; H, 6.96; N, 10.60; Cl, 6.70. Found: C, 61.48; H, 6.98; N, 9.69; Cl, 6.33; MS *m*/*z* 515 (M^+ + 1).

α-Naphthoyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (38). Mp 89–91 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H),

2.42–2.94 (m, 3H), 3.60–4.19 (m, 4H), 4.33–4.82 (m, 4H), 6.28–6.65 (m, 2H), 7.21–7.51 (m, 9H), 7.77–7.99 (m, 3H); IR (KBr) 3350, 1648, 1522, 1454, 1225, 1119, 873, 751, 701 cm^{-1}; Anal. Calcd for $C_{30}H_{34}N_3O_4Cl{\cdot}\frac{3}{4}H_2O$: C, 65.56; H, 6.5 1; N, 7.65; Cl, 6.45. Found: C, 65.53; H, 6.23; N, 7.57; Cl, 6.57; MS *m*/*z* 536 ($M^+ + 1$).

β-Naphthoyl-(2*S*,3*S*)-AHPBA-4(*S*)-Cl-Pro-NH-*t*-Bu (39). Mp 95 °C; ^1H NMR ($CDCl_3$) δ 1.32 (s, 9H), 2.42–5.06 (m, 11H), 6.29–8.19 (m, 14H); IR (KBr) 3334, 2968, 1648, 1531, 1455, 1391, 1366, 1269, 1228, 1205, 1136, 1115, 778, 761, 701 cm^{-1}; Anal. Calcd for $C_{30}H_{34}N_3O_4Cl{\cdot}\frac{3}{4}H_2O$: C, 65.57; H, 6.5 1; N, 7.65; Cl, 6.45. Found: C, 65.69; H, 6.3 1; N, 7.52; Cl, 6.29; MS *m*/*z* 536 ($M^+ + 1$).

References and Notes

1. (a) Mitsuya H.; Yarchoan, R.; Broder, S. *Science* **1990**, *249*, 1533. (b) Yarchoan, R.; Mitsuya, H.; Broder, S. *Trends in Pharmacol. Sci.* **1993**, *14*, 196 and references cited therein. (c) Hellen, C. U. T.; Kräusslich, H. H-G.; Wimmer, E. *Biochemstry* **1989**, *28*, 9881. (d) Rich, D. H. *J. Med. Chem.* **1985**, *85*, 263.

2. For excellent reviews on HIV-1 protease inhibitors, see: (a) Wlodawer, A.; Erickson, J. W. *Annu. Rev. Biochem.* **1993**, *62*, 543. (b) West, M. L.; Fairlie, D. P. *Trends Pep. Sci.* **1995**, *16*, 67. (c) Meek, T. D. *J. Enzyme Inhibition* **1992**, *6*, 65.

3. For AHPBA, see: Mimoto, T.; Imai, L; Kisanuki, S.; Enomoto, H.; Hattori, N.; Akaji, K.; Kiso, Y. *Chem. Pharm. Bull.* **1992**, *40*, 2251 and references cited therein.

4. Barry, M.; Gibbons, S.; Back, D.; Mulcahy, F. *Clin. Pharmacokinet.* **1997**, *32*, 194.

5. (a) Sakurai, M.; Higashida, S.; Sugano, M.; Kornai, T.; Yagi, R.; Ozawa, Y.; Handa, K; Nishigaki, T.; Yabe, Y. *Bioorg. Med. Chem.* **1994**, *2*, 807. (b) Komai, T.; Higashida, S.; Sakurai, M.; Nitta, T.; Kasuya, A.; Miyamoto, S.; Yagi, R.; Ozawa, Y.; Handa, H.; Mohri, H.; Yasuoka, A.; Oka, S.; Nishigaki, T.; Kimura, S.; Shimada, K.; Yabe, Y. *Bioorg. Med. Chem.* **1996**, *4*, 1365.

6. (a) Ghosh, A. K.; Thompson, W. L.; McKee, S. R.; Duong, T. T.; Lyle, T. A.; Chen, J. C.; Darke, P. L.; Zugay, J. A.; Emilio, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 292. (b) Ghosh, A. K.; Lee, H. Y.; Thompson, W. L.; Culberson, C.; Holloway, M. K.; McKee, S. R.; Munson, P. M.; Duong, T. T.; Smith, A. M.; Darke, P. L.; Zugay, J. A.; Emilio, E. A.; Scheif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1994**, *37*, 1177.

7. (a) Randad, R. S.; Lubkowska, L.; Bhat, T. N.; Munshi, S.; Gulnik, S. V.; Yu, B.; Erickson, J. W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1707. (b) Kempf, D. L.; Flentge, C. A.; Wideburg, N. E.; Saldivar, A.; Vasavanonda, S.; Norbeck, D. W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2725.

8. (a) Kalish, V. L.; Tatlock, J. H.; Davis, II, J. R.; Kaldor, S. W.; Dressman, B. A.; Reich, S.; Pino, M.; Nyugen, D.; Appelt, K.; Musick, L.; Wu, B-W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 727. (b) Kaldor S. W.; Hammond, M.; Dressman, B. A.; Fritz, J. E.; Crowell, T. A.; Hermann, R. A. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1385.

9. Fleet, G. W. L; Gough, M. L.; Shing, T. K. M. *Tetrahedron Lett.* **1983**, *24*, 3661.

10. Houbion, J. A.; Miles, J. A.; Paton, J. A. *Org. Prep. Proc. Int.* **1979**, *11*, 27.

11. Mandell, L.; Caine, D.; Kilpatrick, G. E. *J. Am. Chem. Soc.* **1961**, *83*, 4457.

12. Richtzenhain, H. *Chem. Ber.* **1944**, 1.

13. Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888.

14. Nicolaou, K. C.; Bunnage, M. E.; Kiode, K. *J. Am. Chem. Soc.* **1994**, *116*, 8402.

15. Comins, D. L.; Brown, J. D., *J. Org. Chem.* **1989**, *54*, 3730.

16. Ghosh, A. K.; Duong, T. T.; McKee, S. R.; Thompson, W. J. *Tetrahedron Lett.* **1992**, *33*, 2781.

17. Ghosh et al. reported that cyclic urethanes with 3*S*-configuration were more potent than ones with 3*R*-configuration (see Ref. 6).

18. The detailed computational studies will be reported elsewhere.

19. For structural water, see: Wang, Y.-X.; Freedberg, D. L.; Wingfield, P. T.; Stahl, S. L.; Kaufman, J. D.; Kiso, Y.; Bhat, T. N.; Erickson, J. W.; Torchia, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 12287 and references cited therein.

20. The conclusion described by Kempf et al. was that *ortho* is not a suitable position for interaction with Asp 29 or 30 (see Ref. 7b). But the hydrogen bond interaction between the carbonyls and the *ortho* hydroxyl groups is presumed to be more important than aforesaid interaction.