Pergamon

Bioorganic & Medicinal Chemistry 7 (1999) 2063–2072

BIOORGANIC & MEDICINAL CHEMISTRY

Structure–Activity Relationship of HIV-1 Protease Inhibitors Containing α-Hydroxy-β-amino Acids. Detailed Study of P_1 Site

Eiji Takashiro,[a,*] Ichiro Hayakawa,[a] Tamayo Nitta,[a] Atsushi Kasuya,[a] Shuichi Miyamoto,[a] Yuji Ozawa,[b] Ryuichi Yagi,[b] Ikue Yamamoto,[b] Takahiro Shibayama,[c] Akihiko Nakagawa[c] and Yuichiro Yabe[a,*]

[a]*Exploratory Chemistry Research Laboratory, Sankyo Co. Ltd. 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan*
[b]*Biological Research Laboratory, Sankyo Co. Ltd. 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan*
[c]*Analytical and Metabolic Research Laboratories, Sankyo Co. Ltd. 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan*

Received 26 March 1999; accepted 6 May 1999

Abstract—The structure–activity relationship of HIV-1 protease (HIV-1 PR) inhibitors containing α-hydroxy-β-amino acids is discussed. We demonstrated that substituent groups on the P_1 aromatic rings of the inhibitors exert significant influence on their biological activity. Inhibitors bearing an alkyl or a fluorine atom at the *meta* and *para* position on their P_1 benzene ring were found to be good inhibitors. We also discovered that the substitution positions of the P_2 benzamides were crucial for good antiviral potency. In this study, inhibitor **48** was the most potent {IC_{90} (CEM/HIV-1 IIIB) 27 nM} and showed good pharmacokinetics in rats.

Introduction

The importance of HIV-1 protease inhibitors in the treatment of AIDS is now well established. (for selected reviews on HIV-1 protease inhibitors, see refs 1 and 2) More recent advances in inhibitor design have focused on structure modification to improve potency, oral bioavailability[3,4] and to circumvent drug resistance.[5–11] Despite its success, it is nearly impossible to treat all of the growing world-wide AIDS population based on currently available drugs. Therefore, the need for inexpensive and widely available HIV protease inhibitors still exists.

Pioneering work by Kiso et al. demonstrated that AHPBA (3(*S*)-amino-2(*S*)-hydroxy-4-phenylbutanoic acid) has great potential as a transition-state mimic for HIV-1 protease.[12–16] In previous papers, we also 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 also showed good anti-HIV activity.[17–19] Kaldor et al. reported that Nelfinavir with an *S*-phenyl (thiophenyl) group at the P_1 site was a potent inhibitor, which bound with an approximately 10-fold greater affinity than a phenyl analogue.[20,21] This shows that the lipophilic aromatic ring system which fits into the S_1 hydrophobic pocket is very important. Therefore, investigating the structure–activity relationship of the P_1 site became of interest to us. To the best of our knowledge there has been no previous effort carried out to discuss the importance of substitution positions on the P_1 benzene rings. In developing more active compounds, additional optimization work was focused on the P_1 phenylalanine portion (Fig. 1).

Results and Discussion

Chemistry

All commercially available benzoic acids were purchased, and others were prepared as follows. 3-Hydroxy-2-methylbenzoic acid,[22] 2,4-dimethyl-3-hydroxybenzoic acid[23] and 2,6-dimethyl-3-hydroxybenzoic acid[24] were prepared according to known methods. The preparation of 3-hydroxy-2,5-dimethylbenzoic acid was carried out by Charlesworth's procedure.[25] 5-Fluoro-3-hydroxy-2-methylbenzoic acid **1** was synthesized from 5-fluoro-2-methylbenzoic acid by nitration, reduction, diazotization and hydrolysis.

To enhance the interaction between inhibitor and protease at the P_1 site we chose AHPPA (3-amino-2-hydroxy-5-phenylpentanoic acid) as our first target molecule.

* Corresponding authors.

0968-0896/99/$ - see front matter
PII: S0968-0896(99)00127-3

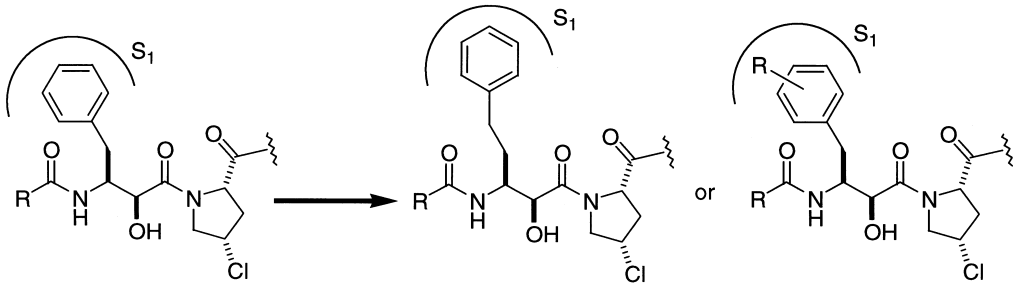


Figure 1. Design of HIV PR inhibitors with AHPPA (3-amino-2-hydroxy-5-phenylpentanoic acid) or substituted AHPBA (3-amino-2-hydroxy-4-phenylbutanoic acid).

Unfortunately, AHPPA could not be synthesized by the well-known Reetz's procedure,[26] so we had to develop a new synthetic route toward AHPPA (Scheme 1).

One of the most versatile synthetic methods of peptide isosteres involves the use of chiral amino aldehydes or Weinreb amides. Several approaches using the addition of organometallics have also appeared.[27] For our study, we used vinyl magnesium bromide.[28–31] *N*,*N*-Diethylamide[32] **2** derived from Boc-L-homophenylalanine (Boc = *tert*-butoxycarbonyl) was converted into the corresponding vinyl ketone **3** in 58% yield. Reduction with $NaBH_4/CeCl_3{\cdot}7H_2O$ gave a 3:1 mixture of diastereomers **4**.[33] Ozonolysis of **4**, followed by reduction with methylsulfide gave aldehyde, which was oxidized by $NaClO_2$[34] to give an acid. This acid was then converted into a methyl ester **5** in 52% yield from compound **4**. **5** was hydrolyzed in alkaline condition to afford diastereomerically pure acid **6**.

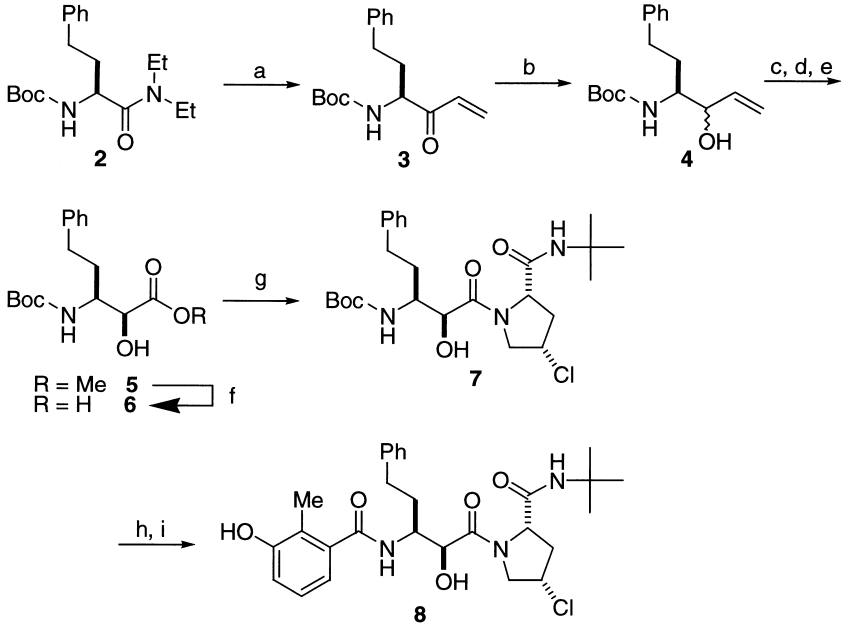
All other 3(*S*)-amino-2(*S*)-hydroxy-4-arylbutanoic acids were prepared by Dondoni's method[35] or Ajinomoto's procedure[36] from L-amino acids. All commercially available optically active amino acids were purchased and others were prepared by resolution of *N*-acyl DL-amino acids.[39] (For resolution of *N*-acyl DL-amino acids, see refs 37 and 38.)

The linkage of the above β-amino-α-hydroxy carboxylic acids and 4(*S*)-Cl-proline-*tert*-butylamide was carried out using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide·hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBt) in dimethyformamide (DMF). These dipeptides were coupled with substituted benzoic acids by the EDCI-HOBt method in good yield.

Structure–activity relationship

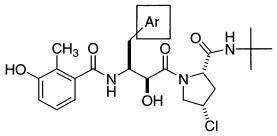
Table 1 shows the protease inhibitory activity of 3-hydroxy-2-methylbenzamide containing compounds.[18]

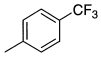
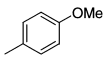
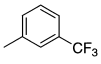
Because compound **8** showed good protease inhibitory activity ($IC_{50} = 1.4$ nM) but low cellular IC_{90} value (as shown in Table 3), we next turned attention to systematic replacement on P_1 benzene rings in AHPBA. Among compounds **9** to **27**, inhibitors **10**, **11**, **14**, **19**,



Scheme 1. (a) Vinyl magnesium bromide/THF 58%; (b) $NaBH_4$, $CeCI_3{\cdot}7H_2O$/MeOH 90%; (C) O_3, then methylsulfide; (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene/*t*-BuOH-H_2O; (e) $TMSCHN_2$/benzene–MeOH 52% (3 steps); (f) 1N-NaOHaq/MeOH; (g) 4(S)-Cl-Pro-*tert*-butylamide, EDCl·HCl, HOBt/DMF 78% (2 steps); (h) 4N-HCl/1,4-dioxane; (i) 3-hydroxy-2-methylbenzoic acid, EDCl·HCL HOBt/THF 60% (2 steps).

Table 1. HIV-1 PR inhibitory activity of 3-hydroxy-2-methylbenzamide bearing compounds



No.	Ar	IC_{50} (nM)	No.	Ar	IC_{50} (nM)	No.	Ar	IC_{50} (nM)
8		1.4	**15**		0.7	**22**		1.3
9		0.9	**16**		0.8	**23**		0.9
10		0.9	**17**		0.8	**24**		1.2
11		0.6	**18**		1.6	**25**		1.4
12		4.5	**19**		0.6	**26**		1.5
13		0.9	**20**		0.9	**27**		1.0
14		0.6	**21**		0.5			

and **23** were very potent; however, **12** was not a good inhibitor. The superior potency of the former compounds showed that *meta*- and *para*-substitutions were favourable. These results suggest that aromatic rings with *meta*- and *para*-substitutions at the P_1 site may bind favourably in inhibitor–protease complexes. Comparing **12** with **15**, the latter with an *ortho*-fluorine atom was more potent as a protease inhibitor. It was concluded that only smaller substituents were acceptable at the *ortho* position.

In our previous paper,[19] we found that the substitution positions of P_2 benzamides significantly influenced inhibitory activity, (for the studies of P_2 benzamides, see refs 40–42) but the best combination of P_1 and P_2 structures remained unknown. Therefore we were interested in optimizing P_1 and P_2 structures (Table 2).

It was clearly shown that inhibitors having a methyl group or a fluorine atom at the 5-position were potent. On the other hand, substitutions at the 4- and 6-position decreased their inhibitory activity (**9** versus **28** versus **29** versus **30** versus **31**) (**10** versus **41** versus **42**) (**19** versus **36** versus **37**) (**21** versus **32** versus **33** versus **34** versus **35**). Because we succeeded in developing highly active protease inhibitors, our interest was now in their anti-HIV activity. Table 3 summarizes the anti-HIV activity of selected inhibitors.[18]

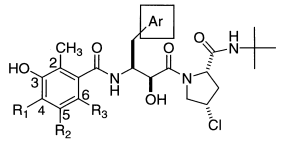
It is well known that protease inhibition is not always compatible with anti-HIV activity. Compound **8** with AHPPA showed good protease inhibition but a poor cellular IC_{90} value ($IC_{90} = 730$ nM). Although compounds **45** and **48** with a 3-hydroxy-2,5-dimethylbenzoyl group were of similar potency to **9** with a 3-hydroxy-2-methylbenzoyl group, **45** and **48** showed more potency than **9** in a cell-based assay. Although protease inhibition of **50** was equipotent to the other compounds, it was much more potent in terms of its anti-HIV activity. These results suggest that the 5-fluoro-3-hydroxy-2-methylbenzoyl or the 3-hydroxy-2,5-dimethylbenzoyl moieties are important not only for interaction with protease, but also for cellular penetration.

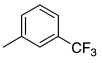
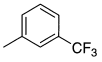
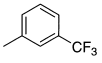
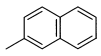
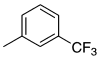
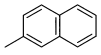
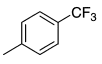
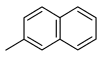
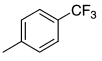
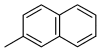
Compound **48** was a good candidate for anti-AIDS drugs among these inhibitors due to its good pharmacokinetic parameters. When **48** (10 mg/kg) was administered orally to rats, the AUC, C_{max}, T_{max}, $T_{1/2}$ and bioavailability were as follows: 3.10 μg·h/mL, 1.28 μg/mL, 0.33 h, 1.79 h and 48%, respectively.

Conclusion

Our study revealed that substitution positions of the P_1 benzene rings was crucial for their inhibitory activity. *Meta*- and *para*-substitutions on the P_1 benzene rings

Table 2. HIV-1 PR inhibitory activity of substituted benzamide bearing compounds



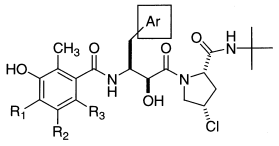
No.	Ar	R_1	R_2	R_3	IC_{50} (nM)	No.	Ar	R_1	R_2	R_3	IC_{50} (nM)
28		Me	H	H	8.2	**41**		Me	H	H	8.6
29		H	Me	H	1.3	**42**		H	H	Me	3.6
30		H	F	H	1.7	**43**		Me	H	H	49.9
31		H	H	Me	2.5	**44**		H	H	Me	34.3
32		Me	H	H	3.5	**45**		H	Me	H	1.3
33		H	Me	H	1.9	**46**		H	Me	H	1.2
34		H	F	H	2.1	**47**		Me	H	H	3.2
35		H	H	Me	4.6	**48**		H	Me	H	0.8
36		Me	H	H	6.3	**49**		H	H	Me	2.8
37		H	H	Me	3.9	**50**		H	F	H	1.2
38		Me	H	H	2.5	**51**		H	Me	H	1.5
39		H	Me	H	1.3	**52**		H	F	H	1.9
40		H	H	Me	3.4						

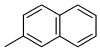
increased their biological activity. We also found that methyl or fluorine groups at the 5-positon of P_2 benzamide moiety significantly contributed to their anti-HIV activity. Further work to develop more active compounds is now in progress.

Experimental

All experiments dealing with air- and moisture-sensitive compounds were conducted under an atmosphere of dry N_2. Melting points (mp) were determined with a Yanaco 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 or a Varian Mercury 400 spectrometer. Chemical shifts were expressed in δ ppm from the internal standard tetramethylsilane (TMS). Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad peak. EI- and FAB-MS were taken on a JEOL JMS-D 300 mass spectrometer and relevant data

Table 3. Anti-HIV activity of selected inhibitors



No.	Ar	R_1	R_2	R_3	CEM/HIV-1 III_B IC_{90} (nM)
8		H	H	H	730
9		H	H	H	110
24		H	H	H	51
29		H	Me	H	115
45		H	Me	H	48
48		H	Me	H	27
50		H	F	H	31
51		H	Me	H	58
52		H	F	H	80

are tabulated as *m*/*z*. Column chromatography was carried out using SK-34 (Kishida, 70–230 mesh). Preparative thin-layer chromatography (PTLC) was performed using 60 F_{254} plates (Merck art. 5744). Optical rotations ($[\alpha]_D$) were measured on a Jasco DIP-360 polarimeter.

5-Fluoro-3-hydroxy-2-methylbenzoic acid (1). To a stirred solution of 5-fluoro-2-methylbenzoic acid (1.01 g, 6.55 mmol) in H_2SO_4 (98%, 8 mL) was added a mixture of HNO_3 (fuming, 0.33 mL, 7.9 mmol) and H_2SO_4 (98%, 1.5 mL) at −15°C. The reaction mixture was warmed to 0°C and stirred for 30 min at this temperature. The mixture was poured into ice-cold water, stirred for another 10 min and extracted with EtOAc. The combined organic layer was washed (brine), dried (Na_2SO_4) and concentrated in vacuo. The residue was used in the next step.

The solution of the above crude product, K_2CO_3 (1.0 g, 7.3 mmol) and benzylbromide (0.87 mL, 7.7 mmol) was stirred for 1 h at 50°C. The reaction was stopped by adding H_2O and extracted with EtOAc. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane:EtOAc = 3:1) to afford 5-fluoro-2-methyl-3-nitrobenzoic acid benzylester (780 mg, 41%) as a colourless crystalline. ^1H NMR ($CDCl_3$) δ 2.58 (s, 3H), 5.03 (s, 2H), 7.34–7.45 (m, 5H), 7.60 (dd, 1H, $J_1 = 8.2$, $J_2 = 2.8$ Hz), 7.75 (dd, 1H, $J_1 = 8.2$, $J_2 = 2.8$ Hz).

A suspension of 5-fluoro-2-methyl-3-nitrobenzoic acid benzylester (498 mg, 1.72 mmol) and 10% Pd–C (250 mg) was stirred under H_2 (1 atm) at room temperature for 20 h. After changing the atmosphere to N_2, the reaction mixture was diluted with EtOAc. The mixture was filtered through a Celite pad (washed with EtOAc) and concentrated in vacuo. The resulting crude product, 3-amino-5-fluoro-2-methylbenzoic acid (257 mg), was used in the next step without further purification. ^1H NMR (CD_3OD) δ 2.25 (s, 3H), 6.58 (dd, 1H, $J_1 = 9.5$, $J_2 = 2.6$ Hz), 6.75 (dd, 1H, $J_1 = 9.5$, $J_2 = 2.6$ Hz).

To the stirred solution of the above product (245 mg) in H_2SO_4 (98%, 3.0 mL) and H_2O (1.5 mL) was added a solution of $NaNO_2$ (105 mg, 1.52 mmol) in H_2O (2 mL) at 0°C and stirred for 2 h at this temperature. The mixture was added dropwise to almost boiling solution of 50% H_2SO_4 (4 mL). After cooling to room temperature, the mixture was diluted with Et_2O, washed (brine), dried (Na_2SO_4) and concentrated in vacuo. Crystallization from hexane:Et_2O gave 187 mg of 5-fluoro-3-hydroxy-2-methylbenzoic acid (64%). ^1H NMR (CD_3OD) δ 2.33 (s, 3H), 6.67 (dd, 1H, $J_1 = 9.4$, $J_2 = 2.7$ Hz), 6.98 (dd, 1H, $J_1 = 9.4$, $J_2 = 2.7$ Hz).

(*tert*-Butoxycarbonyl)-homophenylalanyl-diethylamide (2). To the stirred solution of boc-homophenylalanine (3.73 g, 13.4 mmol) and NEt_3 (3.7 mL, 26 mmol) were added isobutyl chloroformate (1.8 mL, 14 mmol) and diethylamine (1.4 mL, 14 mmol) successively at 0°C. After stirring the mixture for 5 h at this temperature, the reaction was stopped by adding brine and extracted with EtOAc. The combined organic extracts were washed successively with 5% aq citric acid, satd aq $NaHCO_3$ and brine. The organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane: CH_2Cl_2:Et_2O = 4:3:3) to afford **2** (2.45 g, 50%) as a colourless oil. ^1H NMR ($CDCl_3$) δ 1.07–1.15 (m, 6H), 1.49 (s, 9H), 1.85–1.94 (m, 2H), 2.59–2.78 (m, 2H), 3.08–3.32 (m, 3H), 3.45–3.59 (m, 1H), 4.53–4.62 (m, 1H), 5.40 (d, 1H, $J = 8.6$ Hz) 7.16–7.32 (m. 5H); IR (KBr) 2976, 2934, 2875, 1706, 1639, 1497, 1455, 1382, 1172, 1048, 1024, 701 cm^{-1}. Anal. calcd for $C_{19}H_{30}N_2O_3 \cdot 1/2H_2O$: C, 66.44; H, 9.10; N, 8.16. Found: C, 66.26; H, 9.23; N, 8.09; MS *m*/*z* 335 $(M+H)^+$; $[\alpha]_D^{25}$ −4.8° (*c* 1.1, $CHCl_3$).
(2-Oxo-1(*S*)-phenethyl-but-3-enyl)-carbamic acid *tert*-butyl ester (**3**).

To a stirred solution of **2** (2.41 g, 7.21 mmol) in tetrahydrofuran (THF) (45 mL), was added a solution of vinyl magnesium bromide (1M in THF, 35 mL) at 0°C and the reaction mixture was gradually warmed to room temperature. After stirring the mixture for 4 h, the reaction was quenched with 5% aq $KHSO_4$ and extracted

with EtOAc. The combined organic extracts were washed with successively satd aq $NaHCO_3$ and brine. The organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane:EtOAc = 8:2) to afford **3** (1.20 g, 58%) as a white crystalline solid: mp 46–48°C; ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 9H), 1.75–1.90 (m, 1H), 2.08–2.19 (m, 1H). 2.55–2.74 (m, 2H), 4.68–4.73 (m, 1H), 5.35 (d, 1H, J = 7.2 Hz), 5.85 (d, 1H, J = 10.2 Hz), 6.30 (d, 1H, J = 17.5 Hz), 6.45 (dd, 1H, J_1 = 17.5 Hz, J_2 = 10.2 Hz), 7.15–7.31 (m, 5H); IR (KBr) 3344, 2981, 2932, 1706, 1680, 1617, 1522, 1369, 1319, 1278, 1165, 876, 700 cm^{-1}. Anal. calcd for $C_{17}H_{23}NO_3 \cdot 1/4H_2O$: C, 69.48; H, 8.06; N, 4.77. Found: C, 69.36; H, 7.94; N, 4.65; MS m/z 290 $(M+H)^+$.

{2(*R*,*S*)-Hydroxy-1(*S*)-phenethyl-but-3-enyl}-carbamic acid *tert*-butyl ester (4). To a suspension of $CeCl_3 \cdot 7H_2O$ (745 mg, 2.0 mmol) and $NaBH_4$ (168 mg, 4.4 mmol) in EtOH (8 mL) was added **3** (1.20 g, 4.16 mmol) at 0°C and the reaction mixture was stirred for 4 h at this temperature. The reaction was quenched by adding CH_3CO_2H and stirred for 5 min and then the mixture was extracted with EtOAc. The combined organic layer was successively washed with saturated aqueous $NaHCO_3$ and brine. The organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane: Et_2O = 7:3) to afford **4** (1.12 g, 90%) as a diastereomixture (colourless oil): MS m/z 291 $(M)^+$.

(*tert*-Butoxycarbonyl)-2(*S*)-hydroxy-3(*S*)-amino-5-phenylpentanoic acid methy ester (5). O_3 (ca. 3% in O_2) was bubbled (25 mL/h) into a solution of **4** (213 mg, 0.73 mmol) in MeOH (10 mL) at −78°C for 4 h. Excess O_3 was purged by bubbling N_2. To this was added Me_2S (0.50 mL, 6.8 mmol) at −78°C and the reaction mixture was gradually warmed to room temperature and stirred for 30 min. After removal of the solvent in vacuo, the residue was used in the next step.

To the solution of this residue and 2-methyl-2-buten (0.40 mL, 3.8 mmol) in *tert*-butylalcohol (2 mL) was added an aq solution (2 mL) of $NaClO_2$ (230 mg, 2.54 mmol) and NaH_2PO_4 (340 mg, 2.83 mmol) at room temperature, and stirred continuously for 5 h. The reaction was stopped by adding brine and the mixture was extracted with EtOAc. The combined extracts were washed successively with satd aq NaS_2O_3 and brine. The organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue (291 mg) was used without further purification in the next step.

To the stirred solution of the residue (291 mg) in benzene: MeOH (2:1, 3 mL) was added a solution of tetramethyldiazometane in *n*-hexane (10%, 1.5 mL) and stirred for 20 min. After removal of the solvent in vacuo, the residue was purified by PTLC (hexane:EtOAc = 5:5) to afford **5** (123 mg, 52%) and epi-**5** {(*tert*-butoxycarbonyl)-2(*R*)-hydroxy-3(*S*)-amino-5-phenylpentanoic acid methyl ester} (36.5 mg, 16%). **5** mp 78–79°C; ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 9H), 1.50–1.64 (m, 1H), 1.70–1.86 (m, 1H), 2.54–2.80 (m, 2H), 3.15 (d, 1H, J = 5.6 Hz), 3.73 (s, 3H), 3.99–4.07 (m, 1H), 4.26–4.34 (m, 1H), 4.84 (d, 1H, J = 9.3 Hz) 7.14–7.31 (m. 5H); $[\alpha]_D^{25}$ +0.7° (c 0.76, $CHCl_3$). epi-**5** mp 90°C; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.86–2.07 (m, 2H), 2.61–2.80 (m, 2H), 3.14 (d, 1H, J = 5.0 Hz), 3.79 (s, 3H), 4.00–4.14 (m, 1H), 4.18 (d, 1H, J = 3.5 Hz), 4.68 (s, 1H), 7.10–7.31 (m. 5H); $[\alpha]_D^{27}$ −40.4° (c 0.84, $CHCl_3$).

(*tert*-Butoxycarbonyl)-2(*S*)-hydroxy-3(*S*)-amino-5-phenylpentanoic acid (6). A suspension of **5** (155 mg, 0.48 mmol) and $LiOH \cdot H_2O$ (361 mg, 8.5 mmol) in MeOH (5 mL) was stirred for 1 day at room temperature. The reaction was quenched by adding 5% aq citric acid and extracted with EtOAc. The extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue (152 mg) was used in the next step without further purification.

(*tert*-Butoxycarbonyl)-2(*S*)-hydroxy-3(*S*)-amino-5-phenylpentanoyl-4(*S*)-Cl-Pro-NH-*tert*-Bu (7). A solution of **6** (152 mg, 0.48 mmol), EDCI·HCl (293 mg, 1.53 mmol), HOBt (111 mg, 0.82 mmol) and 4(S)-Cl-Pro-*tert*-butylamide (311 mg, 1.50 mmol) in DMF (3 mL) was stirred for 1 day. The reaction mixture was diluted with EtOAc and successively washed with H_2O and brine. The organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by PTLC (CH_2Cl_2: MeOH = 9:1) to afford **7** (175 mg, 78%) as a colourless form. Mp 61°C; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 9H), 1.48 (s, 9H), 1.68–1.77 (m, 2H), 2.10–2.81 (m, 4H), 3.37–4.10 (m, 4H), 4.12–4.39 (m, 2H), 4.44 (d, 1H, J = 9.0 Hz), 4.93 (d, 1H, J = 9.0 Hz), 6.31 (s, 1H), 7.10–7.66 (m, 5H); IR (KBr) 3333, 2975, 1692, 1650, 1575, 1454, 17, 1170, 1027, 701 cm^{-1}. Anal. calcd for $C_{25}H_{38}N_3O_5Cl \cdot 3/4H_2O$: C, 58.92; H, 7.81; N, 8.25; Cl, 6.92. Found: C, 58.86; H, 7.32; N, 8.01; Cl, 6.82; MS m/z 496 $(M+H)^+$.

(3-Hydroxy-2-methylbenzoyl)-(2(*S*)-hydroxy-3(*S*)-amino-5-phenylpentanoyl)-4(*S*)-Cl-Pro-NH-*t*-Bu (8). A solution of **7** (24.5 mg, 49.4 μmol) in 1,4-dioxane (2 mL, contained 4N-HCl) was stirred for 4 h. After removal of the solvent in vacuo, the residue was used in the next step without further purification.

The solution of 3-hydroxy-2-methylbenzoic acid (19.1 mg, 0.126 mmol), EDCI·HCl (45.5 mg, 0.237 mmol), HOBt (16.6 mg, 0.123 mmol), NEt_3 (16.6 mg, 0.164 mmol) and the above crude compound in THF (1 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 PTLC (CH_2Cl_2: MeOH = 9:1) to afford **8** (15.6 mg) in 60% yield. Mp 111–112°C; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 9H), 1.80–1.90 (m, 2H), 2.35 (s, 3H), 2.26–2.81 (m, 3H), 3.51–3.83 (m, 4H), 4.18–4.59 (m, 4H), 6.13–6.50 (m, 2H), 6.85–7.65 (m, 9H); IR (KBr) 3325, 1646, 1529, 1455, 1367, 1283, 1119, 749, 700 cm^{-1}; MS m/z 530 $(M+H)^+$.

(3-Hydroxy-2-methylbenzoyl)-(2(*S*)-hydroxy-3(*S*)-amino-phenylbutanoyl)-4(*S*)-Cl-Pro-NH-*t*-Bu (9). 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 $C_{27}H_{34}N_3O_5Cl \cdot 1/2H_2O$: 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 $(M+)^+$.

(3-Hydroxy-2-methylbenzoyl)-(2(*S*)-hydroxy-3(*S*)-amino-4-*p*-tolylbutanoyl)-4(*S*)-Cl-Pro-NH-*t*-Bu (10). ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 2.02 (s, 3H), 2.32 (s, 3H), 2.63–2.84 (m, 4H), 3.81 (d, 1H, $J=6.4$ Hz), 3.99–4.08 (m, 2H), 4.30–4.39 (m, 2H), 4.41–4.60 (m, 1H), 4.67–4.73 (m, 1H), 6.06 (d, 1H, $J=8.1$ Hz), 6.28 (s 1H), 6.69–6.84 (m, 5H), 7.00–7.17 (m, 5H); MS m/z 530 $(M+H)^+$.

(3-Hydroxy-2-methylbenzoyl)-(2(*S*)-hydroxy-3(*S*)-amino-4-*m*-tolylbutanoyl)-4(*S*)-Cl-Pro-NH-*t*-Bu (11). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 2.02 (s, 3H), 2.27 (s, 3H), 2.62–2.84 (m, 4H), 3.66–3.77 (m, 2H), 4.00–4.10 (m, 2H), 4.31–4.41 (m, 2H), 4.50–4.62 (m, 1H), 4.69–4.72 (m, 1H), 6.08 (d, 1H, $J=8.6$ Hz), 6.29 (s, 1H), 6.68 (d, 1H, $J=8.6$ Hz), 6.74 (s, 1H), 6.64–7.06 (m, 4H), 7.15–7.23 (m, 1H); MS m/z 530 $(M+H)^+$.

(3-Hydroxy-2-methylbenzoyl)-(2(*S*)-hydroxy-3(*S*)-amino-4-*o*-tolylbutanoyl)-4(*S*)-Cl-Pro-NH-*t*-Bu (12). ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 2.08 (s, 3H), 2.36 (s, 3H), 2.59–2.72 (m, 3H), 3.95–4.00 (m, 1H), 4.06–4.15 (m, 1H), 4.32–4.40 (m, 2H), 4.47–4.52 (m, 1H), 4.69–4.75 (m, 1H), 4.76–4.82 (m, 1H), 5.36 (s, 1H), 6.12 (d, 1H, $J=8.5$ Hz), 6.33 (s, 1H), 6.62 (d, 1H, $J=7.1$ Hz), 6.76 (t, 1H, $J=8.3$ Hz), 6.97 (t, 1H, $J=7.8$ Hz), 7.04–7.26 (m, 4H); MS m/z 530 $(M+H)^+$.

(3-Hydroxy-2-methylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(4-fluoro)-phenylbutanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (13). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 2.03 (s, 3H), 2.53–2.71 (m, 2H), 2.74–2.86 (m, 2H), 3.96–4.01 (m, 1H), 4.08–4.19 (m, 1H), 4.30–4.45 (m, 3H), 4.55–4.64 (m, 2H), 6.20–6.29 (m, 2H), 6.65–6.81 (m, 3H), 6.94–7.03 (m, 3H), 7.11–7.25 (m,2H). Anal. calcd for $C_{27}H_{33}N_3O_5ClF \cdot 3/2H_2O$: C, 57.80; H, 6.47; N, 7.49; Cl, 6.32; F, 3.39. Found: C, 58.03; H, 6.02; N, 7.14; Cl, 6.03; F, 3.08; MS m/z 534 $(M+H)^+$.

(3-Hydroxy-2-methylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(3-fluoro)-phenylbutanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (14). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 2.06 (s, 3H), 2.61–2.70 (m, 2H), 2.74–2.90 (m, 2H), 3.91–4.14 (m, 2H), 4.29–4.36 (m, 1H), 4.41–4.49 (m, 1H), 4.60–4.70 (m, 2H), 5.56 (s, 1H), 6.11–6.16 (m, 2H), 6.69–7.06 (m, 6H), 7.24–7.30 (m, 2H). Anal. calcd for $C_{27}H_{33}N_3O_5ClF \cdot H_2O$: C, 58.74; H, 6.39; N, 7.61; Cl, 6.42; F, 3.44. Found: C, 58.61; H, 6.33; N, 7.45; Cl, 6.35; F, 3.27; MS m/z 534 $(M+H)^+$.

(3-Hydroxy-2-methylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(2-fluoro)-phenylbutanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (15). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 2.04 (s, 3H), 2.60–2.72 (m, 2H), 2.82–3.02 (m, 2H), 3.98–4.16 (m, 2H), 4.27–4.36 (m, 1H), 4.40–4.49 (m, m, 2H), 4.63–4.70 (m, 1H), 6.27 (s, 1H), 6.36 (s, 1H), 6.47 (s, 1H), 6.67–6.72 (m, 1H), 6.77–6.89 (m, 1H), 6.94–7.34 (m, 6H). Anal. calcd for $C_{27}H_{33}N_3O_5ClF \cdot 2/3H_2O$: C, 59.39; H, 6.34; N, 7.70; Cl, 6.49; F, 3.48. Found: C, 59.10; H, 6.48; N, 7.03; Cl, 6.06; F, 2.91; MS m/z 534 $(M+H)^+$.

(3-Hydroxy-2-methylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(3,4-difluoro)-phenylbutanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (16). ^{1}H NMR (CD_3OD) δ 1.34 (s, 9H), 2.01 (s, 3H), 2.67–2.81 (m, 2H), 3.03–3.09 (m, 1H), 3.84–3.91 (m, 1H), 4.06–4.17 (m, 1H), 4.32–4.58 (m, 5H), 6.95–7.01 (m, 1H), 7.14–7.19 (m, 3H), 7.26–7.36 (m, 2H); MS m/z 552 $(M+H)^+$.

(3-Hydroxy-2-methylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(3,5-difluoro)-phenylbutanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (17). ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9H), 2.09 (s, 3H), 2.50–2.90 (m, 4H), 3.89–4.03 (m, 2H), 4.27–4.48 (m, 4H), 4.60–4.69 (m, 2H), 5.97 (s, 1H), 6.16 (d, 1H, $J=8.9$ Hz), 6.67–6.91 (m, 5H), 7.06 (t, 1H, $J=7.7$ Hz); MS m/z 552 $(M+H)^+$.

(3-Hydroxy-2-methylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(2,4-difluoro)-phenylbutanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (18). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 2.06 (s, 3H), 2.47–2.66 (m, 2H), 2.84–2.97 (m, 2H), 3.96–4.06 (m, 2H), 4.28–4.47 (m, 3H), 4.59–4.67 (m, 2H), 5.83 (s, 1H), 6.15 (s, 1H), 6.33 (d, 1H, $J=8.5$ Hz), 6.76–6.89 (m, 3H), 6.98–7.11 (s, 2H), 7.29–7.38 (m, 1H); MS m/z 552 $(M+H)^+$.

(3-Hydroxy-2-methylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(4-trifluoromethyl)-phenylbutanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (19). ^{1}H NMR (DMSO-d_6) δ 1.24 (s, 9H), 1.72 (s, 3H), 1.91–2.00 (m, 1H), 2.69–2.92 (m,3H), 3.07–3.50 (m, 1H), 4.35–4.44 (m, 4H), 4.52–4.55 (m, 1H), 5.25 (d, 1H, $J=6.9$ Hz), 6.56 (d, 1H, $J=7.4$ Hz), 6.77 (d, 1H, $J=8.1$ Hz), 6.95 (t, 1H, 7.7 Hz), 7.55–7.62 (m, 5H), 8.27 (d, 1H, 8.4 Hz), 9.28 (s, 1H); MS m/z 584 $(M+H)^+$.

(3-Hydroxy-2-methylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(4-methoxy)-phenylbutanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (20). ^{1}H NMR (CD_3OD) δ 1.30 (s, 9H), 2.03 (s, 3H), 2.59–2.64 (m, 2H), 2.73–2.85 (m, 2H), 3.76 (s, 3H), 3.96–4.13 (m, 2H), 4.25–4.35 (m, 2H), 4.40–4.46 (m, 2H), 4.57–4.66 (m, 2H), 6.28 (t, 2H, $J=7.8$ Hz), 6.62–6.85 (m, 5H), 7.14 (d, 1H, $J=5.1$ Hz); MS m/z 546 $(M+H)^+$.

(3-Hydroxy-2-methylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(3-trifluoromethyl)-phenylbutanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (21). ^{1}H NMR (DMSO-d_6) δ 1.26 (s, 9H), 1.81 (s, 3H), 1.81–2.03 (m, 1H), 2.70–2.92 (m, 3H), 3.71–3.77 (m, 1H), 4.28–4.59 (m, 5H), 5.11 (d, 1H, $J=6.1$ Hz), 6.57 (d, 1H, $J=7.5$ Hz), 6.79 (d, 1H, $J=7.5$ Hz), 6.95 (t, 1H, $J=7.5$ Hz), 7.52–7.61 (m, 3H), 7.75 (t, 1H, $J=5.7$ Hz), 7.87 (s, 1H), 8.32 (d, 1H, $J=9.5$ Hz), 9.40 (s, 1H); MS m/z 584 $(M+H)^+$.

(3-Hydroxy-2-methylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(4-hydroxy)-phenylbutanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (22). ^{1}H NMR (CD_3OD) δ 1.33 (s, 9H), 1.89 (s, 3H), 2.60–3.03 (m, 4H), 3.84–3.90 (m, 1H), 4.40–5.51 (m, 5H), 6.61–6.77 (m, 5H), 6.95–7.17 (m, 2H); MS m/z 532 $(M+H)^+$.

(3-Hydroxy-2-methylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(4-phenyl)-phenylbutanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (23). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 2.05 (s, 3H), 2.61–2.66 (m, 2H), 2.83–2.97 (m, 2H), 3.95–4.11 (m, 2H), 4.28–4.36 (m, 2H), 4.42–4.48 (m, 1H), 4.67–4.75 (m, 2H), 6.22–6.29 (m, 1H), 6.60–6.99 (m, 2H), 7.13–7.57 (m, 12H); MS *m*/*z* 592 $(M+H)^+$.

(3-Hydroxy-2-methylbenzoyl)-2(*S*)-hydroxy-3(*S*)-amino-4-(3,4-dimethyl)-phenylbutanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (24). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 2.05 (s, 3H), 2.22 (s, 3H), 2.23 (s, 3H), 2.57–2.89 (m, 4H), 3.83–4.07 (m, 3H), 4.25–4.60 (m, 4H), 4.67–4.72 (m, 1H), 6.10 (d, 1H, $J=8.2$ Hz), 6.33 (s, 1H), 6.89–7.07 (m 6H); MS *m*/*z* 544 $(M+H)^+$.

(3-Hydroxy-2-methylbenzoyl)-2(*S*)-hydroxy-3(*S*)-amino-4-(benzo[*b*]thiophene-5-yl)-butanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (25). ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 1.85–1.98 (m, 3H), 2.59–3.31 (m, 6H), 3.93–4.03 (m, 1H), 4.27–4.38 (m, 2H), 4.41–4.46 (m, 1H), 4.58–4.71 (m, 2H), 6.24–6.41 (m, 2H), 7.06–7.29 (m, 5H), 7.41–7.44 (m, 1H), 7.59–7.68 (m, 1H), 7.73–7.81 (m, 1H); MS *m*/*z* 572 $(M+H)^+$.

(3-Hydroxy-2-methylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(α-naphtyl)-butanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (26). ^{1}H NMR (CD_3OD) δ 1.33 (s, 9H), 1.72 (s, 3H), 2.11–2.18 (m, 1H), 2.69–2.70 (m, 1H), 3.11–3.17 (m, 1H), 3.57–3.66 (m, 1H), 3.71–3.76 (m, 1H), 3.91 (dd, 1H, $J_1=11.1$, $J_2=7.6$ Hz), 4.39–4.54 (m, 4H), 6.52 (d, 1H, $J=7.0$ Hz), 6.72 (d, 1H, $J=7.9$ Hz), 6.89–6.93 (m, 1H), 7.38–7.59 (m, 4H), 7.77 (d, 1H, $J=7.9$ Hz), 7.87 (d, 1H, $J=7.8$ Hz), 8.34 (d, 1H, $J=8.4$ Hz); MS *m*/*z* 566 $(M+H)^+$.

(3-Hydroxy-2-methylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(β-naphtyl)-butanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (27). ^{1}H NMR (CD_3OD) δ 1.34 (s, 9H), 1.66 (s, 3H), 2.10–2.17 (m, 1H), 2.71–2.78 (m, 1H), 2.91 (dd, 1H, $J_1=14.0$, $J_2=11.5$ Hz), 3.25–3.31 (m, 2H), 3.91 (dd, 1H, $J_1=10.8$, $J_2=7.8$ Hz), 4.36–4.55 (m, 4H), 4.66–4.88 (m, 1H), 6.55 (d, 1H, $J=7.2$ Hz), 6.71 (d, 1H, $J=7.9$ Hz), 6.89 (t, 1H, $J=7.9$ Hz), 7.40–7.46 (m, 2H), 7.53 (dd, 1H, $J_1=8.2$, $J_2=1.4$ Hz), 7.71–7.83 (m, 4H); MS *m*/*z* 566 $(M+H)^+$.

(3-Hydroxy-2,4-dimethylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-phenylbutanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (28). ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 2.11 (s, 3H), 2.22 (s, 3H), 2.59–2.89 (m, 4H), 3.81 (d, 1H, $J=6.5$ Hz), 3.99–4.12 (m, 2H), 4.31–4.39 (m, 2H), 4.39–4.53 (m, 1H), 4.59–4.64 (m, 1H), 4.66–4.70 (m, 1H), 6.09 (d, 1H, $J=8.3$ Hz), 6.26 (s, 1H), 6.61 (d, 1H, $J=7.7$ Hz), 6.90 (d, 1H, 7.7 Hz), 7.15–7.33 (m, 5H); MS *m*/*z* 530 $(M+H)^+$.

(3-Hydroxy-2,5-dimethylbenzoyl)-(2(*S*)-hydroxy-3(*S*)-amino-4-phenylbutanoyl)-4(*S*)-Cl-Pro-NH-*t*-Bu (29). ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.93 (s, 3H), 2.19 (s, 3H), 2.40–2.96 (m, 4H), 3.86 (d, 1H, $J=6.5$ Hz), 3.97–4.12 (m, 2H), 4.31–4.42 (m, 2H), 4.48–4.59 (m, 1H), 4.60–4.74 (m, 2H), 6.03 (d, 1H, $J=8.2$ Hz), 6.25 (s, 1H), 6.46 (s, 1H), 6.64 (s, 1H), 7.16–7.52 (m, 5H); MS *m*/*z* 530 $(M+H)^+$.

(5-Fluoro-3-hydroxy-2-methylbenzoyl)-(2(*S*)-hydroxy-3(*S*)-amino-4-phenylbutanoyl)-4(*S*)-Cl-Pro-NH-*t*-Bu (30). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.90 (s, 3H), 2.41–2.96 (m, 4H), 3.98 (d, 1H, $J=4.0$ Hz), 4.00–4.14 (m, 1H), 4.30–4.42 (m, 1H), 4.48–4.52 (m, 1H), 4.58–4.71 (m, 1H), 5.65 (br, 1H), 6.06 (d, 1H, $J=8.4$ Hz), 6.18 (br, 1H), 6.35–6.47 (m, 1H), 6.52–6.61 (m, 1H), 7.15–7.34 (m, 5H); MS *m*/*z* 534 $(M+H)^+$.

(3-Hydroxy-2,6-dimethylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-phenylbutanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (31). Mp 134–136°C; H-NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.91 (s, 3H), 1.97 (s, 3H), 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 $C_{28}H_{36}N_3O_5Cl\cdot1.78H_2O$: 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-Hydroxy-2,4-dimethylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(3-trifluoromethyl)-phenylbutanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (32). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 2.05 (s, 3H), 2.22 (s, 3H), 2.56–2.96 (m, 4H), 3.83 (d, 1H, $J=6.1$ Hz), 3.97–4.17 (m, 2H), 4.30–4.36 (m, 2H), 4.40–4.48 (m, 1H), 4.61–4.79 (m, 2H), 6.04 (s, 1H), 6.11 (d, 1H, 8.7 Hz), 6.63 (d, 1H, 7.6 Hz), 6.91 (d, 1H, 7.6 Hz), 7.28–7.53 (m, 4H); MS *m*/*z* 598 $(M+H)^+$.

(3-Hydroxy-2,5-dimethylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(3-trifluoromethyl)-phenylbutanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (33). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.97 (s, 3H), 2.20 (s, 3H), 2.43–2.96 (m, 4H), 3.86 (d, 1H, $J=6.40$ Hz), 3.94–4.22 (m, 2H), 4.29–4.37 (m, 2H), 4.42–4.49 (m, 1H), 4.60–4.76 (m, 2H), 6.03 (br, 1H), 6.07 (d, 1H, $J=8.8$ Hz), 6.48 (s, 1H), 6.62 (s, 1H), 7.35–7.55 (m, 4H); MS *m*/*z* 598 $(M+H)^+$.

(5-Fluoro-3-hydroxy-2-methylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(3-trifluoromethyl)-phenylbutanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (34). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.91 (s, 3H), 2.45–2.96 (m, 4H), 3.87 (d, 1H, $J=6.2$ Hz), 3.94–4.06 (m, 1H), 4.07–4.37 (m, 2H), 4.44–4.48 (m, 1H), 4.62–4.71 (m, 2H), 5.48 (br, 1H), 5.97 (br, 1H), 6.11 (d, 1H, $J=8.8$ Hz), 6.41–6.46 (m, 1H), 6.54–6.62 (m, 1H), 7.35–7.54 (m, 4H); MS *m*/*z* 602 $(M+H)^+$.

(3-Hydroxy-2,6-dimethylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(3-trifluoromethyl)-phenylbutanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (35). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.85 (s, 3H), 1.92 (s, 3H), 2.42–3.09 (m, 4H), 3.77–3.80 (m, 1H), 4.00–4.20 (m, 2H), 4.29–4.44 (m, 2H), 4.46 (t, 1H, $J=7.8$ Hz), 4.54–4.88 (m, 3H), 6.01 (s, 1H), 6.65 (d, 1H, $J=8.2$ Hz), 6.78–6.87 (m, 1H), 7.30–7.54 (m, 4H); MS *m*/*z* 598 $(M+H)^+$.

(3-Hydroxy-2,4-dimethylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(4-trifluoromethyl)-phenylbutanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (36). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 2.00 (s, 3H), 2.23 (s, 3H), 2.57–2.88 (m, 4H), 3.82 (d, 1H, 6.4 Hz), 3.92–4.18 (m, 2H), 4.30–4.36 (m, 2H), 4.41–4.51 (m, 1H), 4.64–4.79 (m, 2H), 6.03 (s, 1H), 6.06 (d, 1H, $J=8.7$ Hz), 6.64 (d, 1H, $J=7.6$ Hz), 6.92 (d, 1H,

J = 7.6 Hz), 7.39 (d, 1H, 8.1 Hz), 7.56 (d, 1H, 8.1 Hz); MS m/z 598 $(M+H)^+$.

(3-Hydroxy-2,6-dimethylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(4-trifluoromethyl)-phenylbutanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (37). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.82 (s, 3H), 1.90 (s, 3H), 2.44–2.96 (m, 4H), 3.79 (d, 1H, J = 6.3 Hz), 4.00–4.19 (m, 1H), 4.31–4.39 (m, 2H), 4.44–4.52 (m, 1H), 4.66–4.75 (m, 2H), 4.82–4.85 (m, 1H), 5.94 (d, 1H, J = 8.7 Hz), 6.01 (s, 1H), 6.64 (d, 1H, 8.2 Hz), 6.81 (d, 1H, 8.2 Hz), 7.39 (d, 1H, J = 8.1 Hz), 7.56 (d, 2H, J = 8.1 Hz); MS m/z 598 $(M+H)^+$.

(3-Hydroxy-2,4-dimethylbenzoyl)-(2(*S*)-hydroxy-3(*S*)-amino-4-*m*-tolylbutanoyl)-4(*S*)-Cl-Pro-NH-*t*-Bu (38). ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 2.06 (s, 3H), 2.22 (s, 3H), 2.32 (s, 3H), 2.58–2.79 (m, 4H), 3.81 (d, 1H, J = 7.4 Hz), 4.00–4.10 (m, 2H), 4.31–4.39 (m, 2H), 4.51–4.61 (m, 2H), 4.70–4.74 (m, 1H), 6.07 (d, 1H, J = 8.2 Hz), 6.31 (s, 1H), 6.62 (d, 1H, J = 7.8 Hz), 6.70–6.97 (m, 2H), 7.00–7.05 (m, 2H), 7.13–7.21 (m, 1H); MS m/z 544 $(M+H)^+$.

(3-Hydroxy-2,5-dimethylbenzoyl)-(2(*S*)-hydroxy-3(*S*)-amino-4-*m*-tolylbutanoyl)-4(*S*)-Cl-Pro-NH-*t*-Bu (39). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.96 (s, 3H), 2.19 (s, 3H), 2.31 (s, 3H), 2.41–2.96 (m, 4H), 3.87 (d, 1H, J = 6.5 Hz), 3.96–4.14 (m, 2H), 4.32–4.49 (m, 2H), 4.51–4.61 (m, 2H), 4.69–4.73 (m, 1H), 6.04 (d, 1H, J = 8.2 Hz), 6.30 (s, H), 6.44 (s, 1H), 6.60 (s, 1H), 6.94–7.06 (m, 3H), 7.15–7.22 (m, 1H); MS m/z 544 $(M+H)^+$.

(3-Hydroxy-2,6-dimethylbenzoyl)-(2(*S*)-hydroxy-3(*S*)-amino-4-*m*-tolylbutanoyl)-4(*S*)-Cl-Pro-NH-*t*-Bu (40). ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.84 (s, 3H), 1.94 (s, 3H), 2.28 (s, 3H), 2.41–2.98 (m, 4H), 3.79 (d, 1H, J = 6.3 Hz), 4.00–4.14 (m, 2H), 4.31–4.40 (m, 2H), 4.50–4.65 (m, 2H), 4.76–4.85 (m, 1H), 5.98 (d, 1H, J = 8.1 Hz), 6.28 (s, H), 6.63–6.73 (m, 1H), 6.79–6.85 (m, 1H), 6.90–7.04 (m, 3H), 7.12–7.19 (m, 1H); MS m/z 544 $(M+H)^+$.

(3-Hydroxy-2,4-dimethylbenzoyl)-(2(*S*)-hydroxy-3(*S*)-amino-4-*p*-tolylbutanoyl)-4(*S*)-Cl-Pro-NH-*t*-Bu (41). ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 2.06 (s, 3H), 2.23 (s, 3H), 2.31 (s, 3H), 2.60–2.83 (m, 4H), 3.77 (d, 1H, J = 6.6 Hz), 3.97–4.10 (m, 2H), 4.31–4.39 (m, 2H), 4.51–4.67 (m, 2H), 4.69–4.72 (m, 1H), 6.03 (d, 1H, J = 8.3 Hz), 6.30 (s, 1H), 6.64 (d, 1H, J = 7.6 Hz), 6.91 (d, 1H, J = 7.6 Hz), 6.95–7.15 (m, 4H); m/z 544 $(M+H)^+$.

(3-Hydroxy-2,6-dimethylbenzoyl)-(2(*S*)-hydroxy-3(*S*)-amino-4-*p*-tolylbutanoyl)-4(*S*)-Cl-Pro-NH-*t*-Bu (42). ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.84 (s, 3H), 1.94 (s, 3H), 2.31 (s, 3H), 2.59–2.88 (m, 4H), 3.76 (d, 1H, J = 6.4 Hz), 4.00–4.14 (m, 2H), 4.31–4.40 (m, 2H), 4.51–4.63 (m, 2H), 4.76–4.88 (m, 1H), 5.93 (d, 1H, J = 8.2 Hz), 6.28 (s, H), 6.64 (d, 1H, J = 8.2 Hz), 6.80 (d, 1H, 8.2 Hz), 7.02–7.13 (m, 4H); MS m/z 544 $(M+H)^+$.

(3-Hydroxy-2,4-dimethylbenzoyl)-(2(*S*)-hydroxy-3(*S*)-amino-4-*o*-tolylbutanoyl)-4(*S*)-Cl-Pro-NH-*t*-Bu (43). ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 9H), 2.02 (s, 3H), 2.17 (s, 3H), 2.28 (s, 3H), 2.38–2.61 (m, 1H), 2.68–3.06 (m, 4H), 3.83–4.05 (m, 2H), 4.24–4.45 (m, 2H), 4.57–4.59 (m, 1H), 4.69–4.81 (m, 1H), 4.87 (t, 1H, J = 7.7 Hz), 5.21 (s, 1H), 6.26–6.30 (m, 1H), 6.62 (dd, 1H, J_1 = 27.9, J_2 = 7.7 Hz), 6.93 (dd, 1H, J_1 = 26.0, J_2 = 7.7 Hz) 7.01–7.07 (m, 2H), 7.08–7.15 (m, 2H); MS m/z 544 $(M+H)^+$.

(3-Hydroxy-2,6-dimethylbenzoyl)-(2(*S*)-hydroxy-3(*S*)-amino-4-*o*-tolylbutanoyl)-4(*S*)-Cl-Pro-NH-*t*-Bu (44). ^{1}H NMR ($CDCl_3$) δ 1.26–1.33 (m, 9H), 1.89 (s, 3H), 2.11 (s, 3H), 2.35 (s, 3H), 2.53–3.02 (m, 5H), 3.79–3.89 (m, 1H), 3.95–4.05 (m, 2H), 4.20–4.47 (m, 3H), 4.49–4.60 (m, H), 4.75–4.81 (m, 1H), 4.90 (t, 1H, J = 7.5 Hz), 6.84–6.92 (m, 1H), 7.04–7.14 (m, 5H); MS m/z 544 $(M+H)^+$.

(3-Hydroxy-2,5-dimethylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(4-phenyl)-phenylbutanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (45). ^{1}H NMR ($CDCl_3$) δ 1.31(s, 9H), 1.90 (s, 3H), 2.12 (s, 3H), 2.60–2.66 (m, 2H), 2.77–2.97 (m, 2H), 3.94–4.07 (m, 2H), 4.28–4.36 (m, 2H), 4.43–4.53 (m, 1H), 4.63–4.76 (m, 2H), 6.01 (s, 1H), 6.23 (s, 1H), 6.46–6.64 (m, 1H), 7.21–7.57 (m, 11H); MS m/z 606 $(M+H)^+$.

(3-Hydroxy-2,5-dimethylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(3,5-difluoro)-phenylbutanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (46). ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9H), 1.87 (s, 3H), 2.05–2.16 (m, 1H), 2.20 (s, 3H), 2.70–2.81 (m, 2H), 3.08 (d, 1H, J = 3.0 Hz), 3.88–3.89 (m, 1H), 4.40–4.58 (m, 5H), 6.46 (s, 1H), 6.61 (s, 1H), 6.74–6.83 (m, 1H), 7.00–7.07 (m, 2H); MS m/z 566$(M+H)^+$.

(3-Hydroxy-2,4-dimethylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(β-naphtyl)-butanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (47). ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.91 (s, 3H), 2.19 (s, 3H), 2.61–2.79 (m, 2H), 2.95–3.06 (m, 2H), 3.83 (d, 1H, J = 6.5 Hz), 3.92–4.07 (m, 2H), 4.33–4.45 (m, 2H), 4.54–4.57 (m, 1H), 4.61–4.77 (m, 2H), 6.11 (d, 1H, J = 8.2 Hz), 6.29 (s, 1H), 6.59 (d, 1H, J = 7.7 Hz), 6.84 (d, 1H, J = 7.7 Hz), 7.29–7.49 (m, 3H), 7.60–8.02 (m, 4H); MS m/z 580 $(M+H)^+$.

(3-Hydroxy-2,5-dimethylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(β-naphtyl)-butanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (48). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.84 (s, 3H), 2.05 (s, 3H), 2.62–3.06 (m, 4H), 3.89 (d, 1H, J = 6.5 Hz), 3.92–4.08 (m, 2H), 4.33–4.45 (m, 2H), 4.53–4.77 (m, 3H), 6.07 (d, 1H, J = 8.2 Hz), 6.28 (s, 1H), 6.31 (s, 1H), 6.55 (s, 1H), 7.29–7.52 (m, 4H), 7.61–7.83 (m, 4H); MS m/z 579 $(M)^+$.

(3-Hydroxy-2,6-dimethylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(β-naphtyl)-butanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (49). ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.70 (s, 3H), 1.83 (s, 3H), 2.63–3.02 (m, 4H), 3.79 (d, 1H, J = 6.1 Hz), 4.02–4.10 (m, 2H), 4.35–4.43 (m, 2H), 4.53–4.65 (m, 1H), 4.74–4.82 (m, 2H), 6.00 (d, 1H, J = 8.2 Hz), 6.28 (s, 1H), 6.60–6.67 (m, 1H), 6.74–6.83 (m, 1H), 7.29–7.52 (m, 3H), 7.59–7.82 (m, 4H); MS m/z 580 $(M+H)^+$.

(5-Fluoro-3-hydroxy-2-methylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(β-naphtyl)-butanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (50). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.77 (s, 3H), 2.63–2.76 (m, 2H), 2.95–3.07 (m, 2H), 3.86–4.04 (m, 2H), 4.31–4.43 (m, 3H), 4.51–4.76 (m, 3H), 5.41 (s, 1H), 6.13–6.58 (m, 4H), 7.29–7.67 (m, 4H), 7.73–7.83 (m, 3H); MS m/z 584 $(M+H)^+$.

(3-Hydroxy-2,5-dimethylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(benzo[*b*]thiophene-5-yl)-butanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (51). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.83–1.96 (m, 3H), 2.06–2.18 (m, 3H), 2.57–3.33 (m, 6H), 3.92–4.06 (m, 2H), 4.28–4.36 (m, 2H), 4.43–4.58 (m, 1H), 4.66–4.71 (m, 2H), 6.01 (s, 1H), 7.06–7.28 (m, 4H), 7.42–7.45 (m, 2H); MS *m*/*z* 586 $(M+H)^+$.

(5-Fluoro-3-hydroxy-2-methylbenzoyl)-{2(*S*)-hydroxy-3(*S*)-amino-4-(benzo[*b*]thiophene-5-yl)-butanoyl}-4(*S*)-Cl-Pro-NH-*t*-Bu (52). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.80 (s, 3H), 2.64–2.73 (m, 3H), 2.89–2.93 (m, 1H), 3.25–3.35 (m, 2H), 3.89–4.00 (m, 2H), 4.30–4.34 (m, 2H), 4.49–4.54 (m, 1H), 4.66–4.71 (m, 2H), 5.58–5.65 (m, 1H), 6.98–7.30 (m, 4H), 7.45 (d, 1H, $J=5.5$ Hz), 7.69 (s, 1H), 7.83 (d, 1H, $J=8.1$ Hz); MS *m*/*z* 590 $(M+H)^+$.

References

1. Wlodawer, A.; Erickson, J. W. *Annu. Rev. Biochem.* **1993**, *62*, 543.
2. Meek, T. D. J. *Enzyme Inhibition* **1992**, *6*, 65.
3. Barry, M.; Gibbons, S.; Back, D.; Mulcahy, F. *Clin. Pharmacokinet.* **1997**, *32*, 194.
4. West, M. L.; Fairlie, D. P. *Trends in Pharmacol. Sci.* **1995**, *16*, 67.
5. Boden, D.; Markowitz, M. *Antimicrob. Agents Chemother.* **1998**, *42*, 2775.
6. Preston, B. D.; Dougherty, J. P. *Trends in Microbiology* **1996**, *4*, 16.
7. Ala, P. J.; Huston, E. E.; Klabe, R. M.; McCabe, D. D.; Duke, J. L.; Rizzo, C. J.; Korant, B. D.; DeLoskey, R. J.; Lam, P. Y. S.; Hodge, C. N.; Chang, C.-H. *Biochemistry* **1997**, *36*, 1573.
8. Ridky, T. W.; Kikonyogo, A.; Leis, J. *Biochemistry* **1998**, *38*, 13835.
9. Molla, A.; Vasavanonda, S.; Kumar, G.; Sham, H. L.; Johnson, M.; Grabowski, B.; Denissen, J. F.; Kohlbrenner, W.; Plattner, J. J.; Leonard, J. M.; Norbeck, D. W.; Kempf, D. J. *Virology* **1998**, *250*, 255.
10. Chen, X.; Kempf, D. J.; Sham, H. L.; Green, B. E.; Molla, A.; Korneyeva, M.; Vasavanonda, S.; Wideburg, N. E.; Saldivar, A.; Marsh, K. C.; McDonard, E.; Norbeck, D. W.; Rodgers, J. D.; Lam, P. Y.-S.; Johnson, B. L.; Wang, H.; Ko, S. S.; Seitz, S. P.; Trainor, G. L.; Anderson, P. S.; Klabe, R. M.; Bacheler, L. T.; Cordova, B.; Garber, S.; Reid, C.; Wright, M. R.; Chang, C.-H.; Erickson-Viitanen, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3531.
11. Rodgers, J. D.; Lam, P. Y.-S.; Johnson, B. L.; Wang, H.; Ko, S. S.; Seitz, S. P.; Trainor, G. L.; Anderson, P. S.; Klabe, R. M.; Bacheler, L. T.; Cordova, B.; Garber, S.; Reid, C.; Wright, M. R.; Chang, C.-H.; Erickson-Viitanen, S. *Chemistry and Biology* **1998**, *5*, 597.
12. Mimoto, T.; Imai, J.; Tanaka, S.; Hattori, N.; Takahashi, O.; Kisanuki, S.; Nagano, Y.; Shintani, M.; Hayashi, H.; Sakikawa, H.; Akaji, K.; Kiso, Y. *Chem. Pharm. Bull.* **1991**, *39*, 2465.
13. Mimoto, T.; Imai, J.; Tanaka, S.; Hattori, N.; Kisanuki, S.; Akaji, K.; Kiso, Y. *Chem. Pharm. Bull.* **1991**, *39*, 3088.
14. Mimoto, T.; Imai, J.; Kisanuki, S.; Enomoto, H.; Hattori, N.; Akaji, K.; Kiso, Y. *Chem. Pharm. Bull.* **1992**, *40*, 2251.
15. Wang, Y.-X.; Freedberg, D. I.; Wingfield, P. T.; Stahl, S. J.; Kaufman, J. D.; Kiso, Y.; Bhat, T. N.; Erickson, J. W.; Torchia, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 12287.
16. For chemistry of AHPBA, see: Sasai, H.; Kim, W.-S.; Suzuki, T.; Shibasaki, M.; Mitsuda, M.; Hasegawa, J.; Ohashi, T. *Tetrahedron. Lett.* **1994**, *35*, 6123 and references cited therein.
17. Sakurai, M.; Higashida, S.; Sugano, M.; Komai, T.; Yagi, R.; Ozawa, Y.; Handa, H.; Nishigaki, T.; Yabe, Y. *Bioorg. Med. Chem.* **1994**, *2*, 807.
18. 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.
19. Takashiro, E.; Watanabe, T.; Nitta, T.; Kasuya, A.; Miyamoto, S.; Ozawa, Y.; Yagi, R.; Nishigaki, T.; Shibayama, T.; Nakagawa, A.; Iwatomo, A.; Yabe, Y. *Bioorg. Med. Chem.* **1998**, *6*, 595.
20. Kaldor, S. W.; Kalish, V. J.; Davies II, J. F.; Shetty, B. V.; Fritz, J. E.; Appelt, K.; Burgess, J. A.; Campanale, K. M.; Chirgadze, N. Y.; Clawson, D. K.; Dressman, B. A.; Hatch, S. D.; Khalil, D. A.; Kosa, M. B.; Lubbehusen, P. P.; Muesing, M. A.; Patick, A. M.; Reich, S. H.; Su, K. S.; Tatlock, J. H. *J. Med. Chem.* **1997**, *40*, 3979.
21. For Nelfinavir, see: Jarvis, B.; Faulds, D. *Drugs* **1998**, *56*, 147.
22. Houbion, J. A.; Miles, J. A.; Paton, J. A. *Org. Prep. Proc. Int.* **1979**, *11*, 27.
23. Agrawal, S. R.; Desai, V. B.; Kaushik, H. C.; Khan, M. S.; Merchant, J. R. *J. Ind. Chem. Soc.* **1962**, *39*, 759.
24. Mandell, L.; Caine, D.; Kilpatrick, G. E. *J. Am. Chem. Soc.* **1961**, *83*, 4457.
25. Charlesworth, E. H.; Levene, L. *Can. J. Chem.* **1963**, *41*, 1071.
26. Reetz, M. T.; Drewes, M. W.; Harm, K.; Reif, W. *Tetrahedron Lett.* **1988**, *29*, 3295.
27. Shimizu, M.; Wakioka, I.; Fujisawa, T. *Tetrahedron. Lett.* **1997**, *38*, 6027.
28. Ohba, T.; Ikeda, E.; Takei, H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1875.
29. Hanson, G. J.; Lindberg, T. J. *Org. Chem.* **1885**, *50*, 5399.
30. Spaltenstein, A.; Leban, J. J.; Huang, J. J.; Reinhardt, K. R; Viveros, O. H.; Sigafoos, J.; Crouch, R. *Tetrahedron. Lett.* **1996**, *37*, 1343.
31. Kim, B. M.; Guare, J. P.; Hanifin, C. M.; Arford-Bickerstaff, D. J.; Vacca, J. P.; Ball, R. G. *Tetrahedron. Lett.* **1994**, *35*, 5153.
32. In this reaction, use of *N*-methoxy-*N*-methyl amide led to the formation of a side product, derived from Michael addition of magnesium *N*-methoxy-*N*-methyl amide to vinyl ketone. Use of diethyl amide completely suppressed this side reaction.
33. The absolute stereochemistry of hydroxyl groups was established as follows: treatment of these allyl alcohols with NaH in DMF gave oxazolidinones, which were analyzed by spectroscopic means: see ref 31.
34. Lindgren, B. O.; Nilsson, T. *Acta. Chem. Scand.* **1973**, *27*, 888.
35. Dondoni, A.; Perrone, D. Synthesis 1993, 1162.
36. Suzuki, T.; Honda, Y.; Izawa, K. EP 0 767 168 A2.
37. Chenault, H. K.; Dahmer, J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989**, *111*, 6354.
38. Chibata, I.; Ishikawa, T.; Yamada, S. *Bull. Agr. Chem. Soc. Jpn.* **1957**, *21*, 304.
39. The details of preparing the L-amino acids and the corresponding α-hydroxy-β-amino acids will be reported elsewhere.
40. Randad, R. S.; Lubkowska, L. L.; Bhat, T. N.; Munshi, S. M.; Gulnik, S. V.; Yu, B.; Erickson, J. W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1707.
41. Kempf, D. J.; Flentge, C. A.; Wideburg, N. E.; Saldivar, A.; Vasavanonda, S.; Norbeck, D. W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2725.
42. Kalish, V. J.; Tatlock, J. H.; Davies II, J. F.; Kaldor, S. W.; Dressmen, B. A.; Reich, S.; Pino, M.; Nyugen, D.; Appelt, K.; Musick, L.; Wu, B.-W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 727.