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Design and Synthesis of a Novel Series of HIV-1 Protease Inhibitors

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Abstract—The synthesis and the SAR study of novel pseudo symmetric inhibitors of HIV-1 protease are described. Michael addition of amino acid derivatives to vinyl ketones was utilized to derive a potent (nM) series of HIV-1 protease inhibitors.

Introduction

Replication of the HIV virus requires processing of the proteins encoded by the *gag* and *gag-pol* genes by a virally encoded aspartyl protease (HIV-1 protease).[1–3] As such, inhibition of HIV-1 protease (HIV-1PR) offers an attractive target for the treatment of acquired immunodeficiency syndrome (AIDS).[4–9] Progress in the treatment of AIDS leading to an effective therapy has been slow, but recent results with new AIDS drugs, notably the HIV-1 PR inhibitors, allow for cautious optimism. Four HIV PR inhibitors, namely saquinavir, ritonavir, indinavir and nelfinavir, have been approved for clinical use by the FDA.[10]

AHPBA (3(*S*)-amino-2(*S*)-hydroxy-4-phenylbutanoic acid) is one of the promising peptide-mimic isosters in the design of HIV-1 PR inhibitors. Kiso[11–13] and our group[14–16] independently discovered that AHPBA-derived inhibitors showed potent inhibitory activity against HIV-1 PR. In these compounds, AHPBA and proline derivatives were linked via amide bonds. To reduce the peptide-like characteristics, we concentrated our efforts on connecting the two components without using peptide bonds.[5,12,15,16]

Recent reports indicated that HIV-1 does develop resistance to some protease inhibitors. Different HIV-1 protease inhibitors are expected to produce distinctly different patterns of resistance.[5,10] To overcome drug resistance, a combined use of different protease inhibitors is needed. Therefore, inhibitors with a new skeleton are always required. Our strategy is shown below (Fig. 1).

A, vinyl ketones, were synthesized from α-amino acids by known procedure.[17–20] **B**, amines, were commercially available. Here **A** was used as Michael acceptors and **B** was employed as donors. After joining **A** and **B**, a hydroxyl group, which would interact with HIV PR aspartate groups, was introduced by reduction. We demonstrated that inhibitors with a 3-hydroxy-2-methylbenzoyl group at the P_2 site were very potent.[16] In this study, the 3-hydroxy-2-methylbenzoyl group[21–23] was incorporated into our novel backbone as the P_2 group.

Results and Discussion

Chemistry and structure–activity relationship

First we chose vinyl ketone **1-a**, derived from Boc-phenylalanine,[17–19] as a Michael acceptor and benzylmethylamine (**2**) as the donor (Scheme 1).

Michael addition of **2** to **1-a** gave ketone **3**. Because **3** was unstable, in situ reduction was required. Although there remained the important problem of stereocontrol, reduction with $NaBH_4$ afforded the expected (*R*)-alcohol **4** as the major product in ca. 3:1 ratio.[17] Most of the reducing agents tested, such as diisobutylaluminum hydride (DIBAL-H) gave complex mixtures and use of L-Selectride® afforded undesirable (*S*)-alcohol (epi-**4**) as the major product.[24] Treatment of **4** and epi-**4** with NaH

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in DMF gave the oxazolidinones. The configurations of the hydroxyl groups in **4** and epi-**4** were assigned by NMR analysis of the oxazolidinones.[25–27] The NOE was observed only in the *cis* oxazolidinone, derived from the *R*-epimer **4** (Fig. 2).

The hydroxyl group in **4** was protected to give an acetate **5**. Hydrogenolysis of the benzyl group in **5** gave a secondary amine, which was then sulfonated under usual conditions to give **6**. Boc groups in **6** were removed by 4 N-HCl/1,4-dioxane to give a primary amine, which was then coupled with 3-hydroxy-2-methylbenzoic acid,[28] followed by removal of the acetyl group to give **7**. Compounds **8**–**13** were also synthesized by this method.

The resulting compounds had one carbon extended to the hydroxyethylamine isoster of VX-478.[29–33] HIV-1 PR inhibitory activity of the sulfonamide bearing compounds is shown in Table 1.

Among these compounds, **11** and **13** were potent. In our previous paper,[16] we reported that compounds with an *ortho*-methyl group at the P_2 benzene ring were good inhibitors. Here, **13**, with an *ortho*-methyl group, was also potent. The repulsion between the substituent and sulfonamide plane may have been the cause of favorable interaction at the S_2 pocket.[34,35]

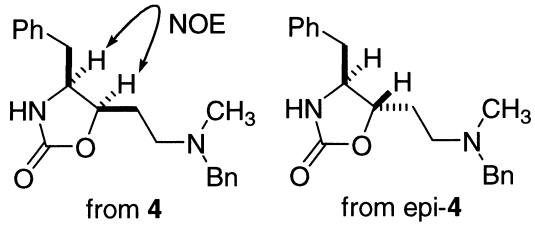


Figure 2. Stereochemical assignments of the oxazolidinones.

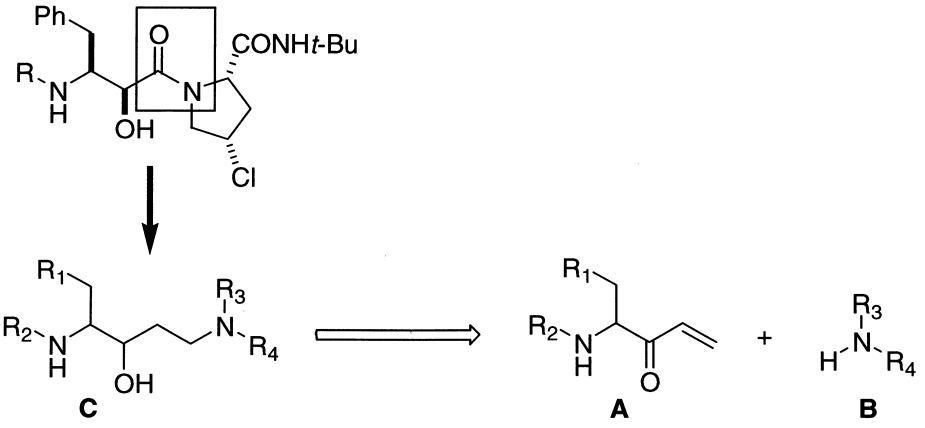
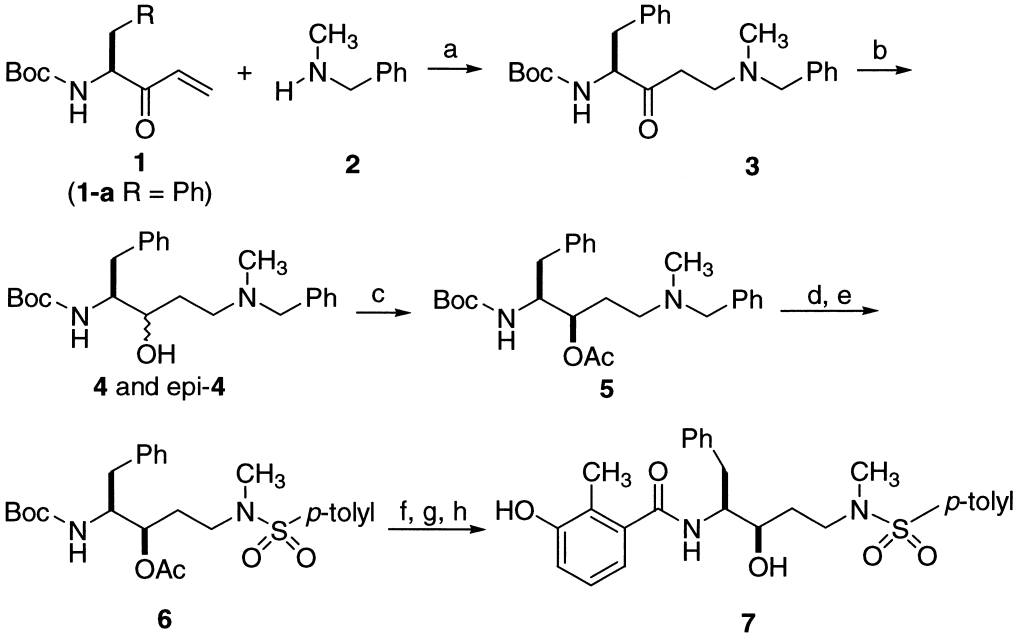


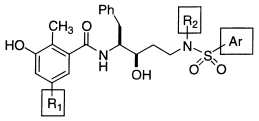
Figure 1. Design of inhibitors with novel backbones.

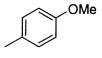
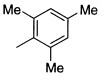


Scheme 1. Synthesis of sulfonamide bearing compounds. (a)/EtOH; (b) $NaBH_4$/EtOH (36%, 2 steps); (c) Ac_2O, Et_3N, DMAP (cat.)/CH_2Cl_2 (81%); (d) H_2, Pd-C, AcOH/EtOH; (e) *p*-toluenesulfonyl chloride, Et_3N/CH_2Cl_2 (41%, 2 steps); (f) 4 N HCl/1,4-dioxane; (g) 3-hydroxy-2-methylbenzoic acid, EDCl·HCl, HOBt, Et_3N/DMF; (h) 1 N NaOHaq./MeOH 45%, 3 steps).

Our strategy proved to be effective by the above results. We next turned our attention to changing the Michael donors from benzyl amines to amino acid derivatives, which means inhibitors with two amino acid units became our targets.[36–40] Scheme 2 describes our initial attempt.

Table 1. HIV-1 PR inhibitor activity of sulfonamide bearing compounds

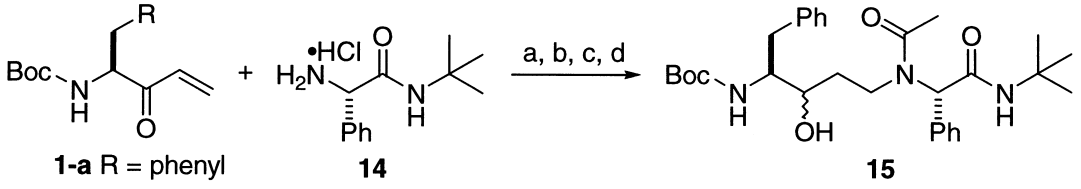


No	R_1	R_2	Ar	IC_{50} (nM)
7	H	Me		1300
8	H	Et		1600
9	H	isopropyl		1500
10	Me	isopropyl		2500
11	H	Et		900
12	H	hydroxyethyl		6500
13	H	Et		800

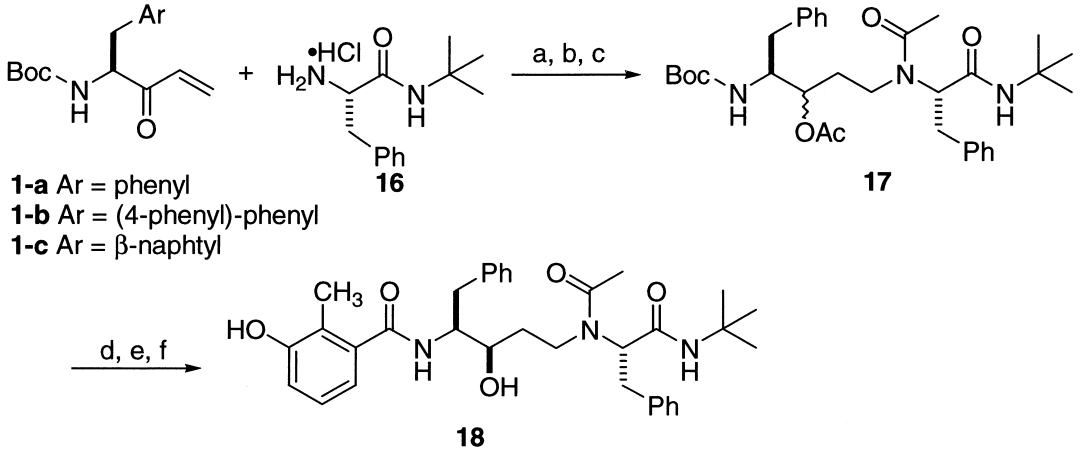
(*S*)-phenylglycine *tert*-butylamide **14** attacked the conjugated double bond of **1-a** to afford the corresponding ketone. This ketone was reduced with $NaBH_4$ in situ and treatment of the crude alcohol with Ac_2O and NEt_3 produced *N*- and *O*- diacylated compound. Saponification with aqueous NaOH gave **15**. Although **15** was assayed as a diastereomixture, it showed good inhibitory activity ($IC_{50} = 500$ nM). This result encouraged us to investigate detailed structure–activity relationship with regards to inhibitors with two amino acid units. We next adopted a 3-hydroxy-2-methylbenzamide as the P_2 moiety instead of a Boc group.[16,21–23] The preparation of the representative compound **18** is outlined in Scheme 3.

For linkage of vinylketone **1-a** and **16**, the above method was also employed to afford **17** (64%, 3 steps). The Boc group in **17** was removed under acidic conditions (4 N-HCl/1,4-dioxane), which was then coupled with 3-hydroxy-2-methylbenzoic acid using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide·hydrochloride (EDCI·HCl) and 1-hydroxybenzotriazole (HOBt). Hydrolysis in alkaline condition gave **18** in 43% yield (3 steps). Chromatographic separation of the diastereomers was carried out in this step.[41] Compounds **19**–**39** were also prepared in this way.

The inhibitory activity of these compounds is shown in Table 2.

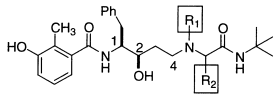


Scheme 2. Preparation of compound having two amino acid units. (a) Et_3N/EtOH; (b) $NaBH_4$/EtOH; (c) Ac_2O, Et_3N, DMAP/CH_2Cl_2 (78%, 3 steps); (d) 1 N NaOHaq./MeOH (89%).



Scheme 3. Preparation of pseudo symmetric compounds containing 3-hydroxy-2-methylbenzamide. (a) Et_3N/EtOH; (b) $NaBH_4$/EtOH; (c) Ac_2O, Et_3N, DMAP/CH_2Cl_2 (64%, 3 steps); (d) 4 N HCl/1,4-dioxane; (e) 3-hydroxy-2-methylbenzoic acid, EDCl·HCl, HOBt, Et_3N/DMF (h) 1 N NaOHaq./MeOH (43%, 3 steps).

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



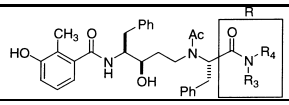
No	R_1	R_2	IC_{50} (nM)	No	R_1	R_2	IC_{50} (nM)
18	Ac		90	**25**	Ac		3600
19	H		16900	**26**			380
20	Me		26200	**27***	Ac		2500
21*	Bn		4300				
22	H		1800	**28**	Ac		> 100,000
23*	Ac		800	**29**	Ac		3800
24	H		6000	**30**	Ac		1500

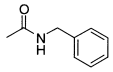
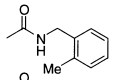
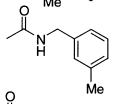
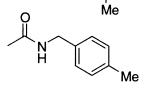
*Tested as a diastereomixture.

It is clearly shown that the nitrogen atom at the *C*-4 position should be acylated for good inhibition. A basic nitrogen would not have the same effect (**18** versus **19** versus **20** versus **21**) (**22** versus **23**) (**18** versus **26**). Oxygen atoms in the sulfonamides in **11** or **13** and in the acyl group of **18** may form hydrogen bonds to the structural water. The structural water acts as a bridge to Ile50 and Ile50′.

Compared with **18**, inhibitors with a larger aromatic ring or a substituted benzene ring as R_2 groups, were not good inhibitors (**18** versus **30**) (**18** versus **27** versus **28** versus **29**). It is likely that these substitutents disturb the hydrophobic interaction at this site. Comparing **18** and **25**, L-amino acid was apparently favorable. To develop more active compounds, our attention was then focused on changing the *tert*-butyl amide group to other groups (Table 3).

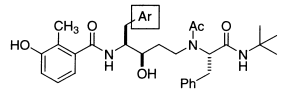
Table 3. HIV-1 PR inhibitor activity of compounds with various amide groups



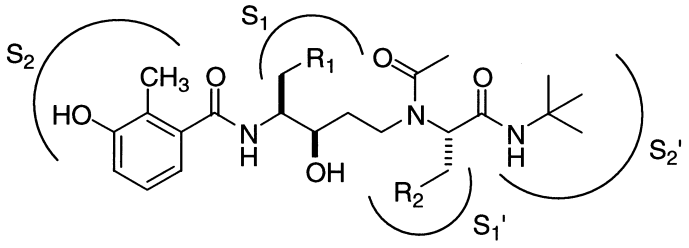
No	R	IC_{50} (nM)
18		90
31		2200
32*		1500
33*		1800
34*		1100
35*		1600
36*		100,000
37		5000

*Tested as a diastereomixture.

Table 4. HIV-1 PR inhibitory activity of compounds with various Ar groups



No	Ar	IC_{50} (nM)
18		90
38		29
39		41



18 R_1 = Ph, R_2 = Ph
38 R_1 = (4-phenyl)-phenyl, R_2 = Ph
39 R_1 = β-naphtyl, R_2 = Ph

Figure 3. Proposed enzyme-inhibitor interaction.

Unfortunately, no potent compounds appeared among the inhibitors we synthesized. This result stimulated us to change the P_1 aromatic moiety (Table 4).

As shown in Table 4, inhibitors with larger aromatic rings were more potent than those with a phenyl group. Their superior potency suggested that there may be extra room in the S_1 hydrophobic pocket. Figure 3 represents the proposed enzyme–inhibitor interaction.

Since they are composed of two β-arylalanine portions, the potent inhibitors **18**, **38** and **39** seem to have pseudo symmetry. It is presumed that the high potency of these compounds was due to this structural feature.

Conclusion

HIV-1 protease inhibitors with a novel backbone have been designed. We developed an efficient method for the construction of α-amino alcohol using Michael addition of amine to α,β-unsaturated ketone followed by reduction of the ketone moiety. The resulting pseudo-symmetric structure served as a peptide-mimic isoster where two amino acid analogues were connected without an amide bond. Further work for investigating more active compounds and determining the structure of the protease/inhibitor complex 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 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.

[1(*S*)-(Biphenyl-4-yl)-methyl-2-oxo-but-3-enyl]-carbamic acid *tert*-butyl ester (1-b). A solution of Boc-(4-phenyl)-Phe-OH (8 g, 21 mmol), *N*, *O*-dimethylhydroxylamine·hydrochloride (3.5 g, 35 mmol), EDCI·HCl (6 g, 31 mmol) and NEt_3 (3.5 g, 35 mmol) in CH_2Cl_2 (60 mL) was stirred for 10 h at room temperature. The reaction mixture was diluted with CH_2Cl_2, washed (brine) and dried (Na_2SO_4). After removal of the solvent in vacuo, the residue (6 g) was used in the next step.

To the solution of the above crude product (6 g) in THF (100 mL) was added a solution of vinyl magnesium bromide (1 N, 65 mL) at 0°C and stirred for 20 min at this temperature. The reaction mixture was poured into ice-cold aqueous HCl (3 N) and extracted with EtOAc. The organic extracts were washed (saturated aqueous $NaHCO_3$), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane: EtOAc = 75:25) to give **1-b** (3.4 g) in 34% yield (2 steps).

Mp 94°C; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 3.04 (dd, 1H, $J_1 = 13.8$, $J_2 = 6.3$ Hz), 3.21 (dd, 1H, $J_1 = 13.8$, $J_2 = 6.3$ Hz), 4.91 (ddd, 1H, $J_1 = J_2 = J_3 = 6.3$ Hz), 5.27 (d, 1H, $J = 6.3$ Hz), 5.88 (d, 1H, $J = 10.2$ Hz), 6.39 (d, 1H, $J = 17.4$ Hz), 6.49 (dd, 1H, $J_1 = 17.4$, $J_2 = 10.2$ Hz), 7.17–7.19 (m, 2H), 7.33–7.38 (m, 1H), 7.41–7.45 (m, 2H), 7.46–7.56 (m, 2H), 7.57–7.61 (m, 2H); IR (KBr) 3360, 2986, 1704, 1683, 1612, 1508, 1404, 1301, 1250, 1168, 831, 733 cm^{-1}; $[\alpha]_D^{25}$ +77.6° (*c* 1.13, $CHCl_3$). Anal. calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.24; H, 7.39; N., 3.77; mass m/z 352 $[M+H]^+$.

[1(*S*)-(2-Naphthyl)-methyl-2-oxo-but-3-enyl]-carbamic acid *tert*-butyl ester (1-c). Mp 77°C; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 3.19 (dd, 1H, $J_1 = 14.2$, $J_2 = 5.6$ Hz), 3.34 (d, 1H, $J_1 = 14.2$, $J_2 = 6.2$ Hz), 5.26–5.29 (m, 1H), 5.84 (d, 1H, $J = 11.6$ Hz), 6.36 (d, 1H, $J = 17.5$ Hz), 6.48 (dd, 1H, $J_1 = 17.5$, $J_2 = 11.6$ Hz), 7.26–7.28 (m, 1H), 7.44–7.49 (m, 2H), 7.58 (s, 1H), 7.77–7.87 (m, 3H); IR (KBr) 3350, 1688, 1512, 1404, 1370, 1248, 1168, 823 cm^{-1}; $[\alpha]_D^{25}$ +82.6° (*c* 0.232, $CHCl_3$). Anal. calcd for $C_{20}H_{23}NO_3 \cdot 1/5H_2O$: C, 73.03; H, 7.17; N, 4.26. Found: C, 73.35; H, 7.55; N, 3.78; mass m/z 326 $[M+H]^+$.

[1(*S*)-Benzyl-4-(benzyl-methyl-amino)-2(*R*)-hydroxy-butyl]-carbamic acid *tert*-butyl ester (4). A solution of **1-a** (383 mg, 1.39 mmol) and benzylmethylamine (354 mg, 2.92 mmol) in EtOH (5 mL) was stirred for 2 h at room temperature. After cooling to 0°C, $NaBH_4$ (50.4 mg, 1.33 mmol) was added to the reaction mixture and stirred for 1 h at this temperature. The reaction was stopped by adding CH_3CO_2H and the mixture was continuously stirred for 5 min. To this mixture was added saturated aqueous $NaHCO_3$ and the products were extracted with EtOAc. The combined organic extracts were washed (brine), dried (Na_2SO_4) and concentrated in vacuo. Purification by PTLC (hexane:EtOAc:acetone = 4:5:1) afforded **4** (200 mg, 36.1%) as a colorless crystalline and epi-**4** (78.9 mg, 14.2%) as a colorless oil.

Mp 82°C; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9H), 1.55–1.59 (m, 1H), 1.71–1.79 (m, 1H), 2.22 (s, 3H), 2.60 (dd, 1H, $J_1 = 12.6$, $J_2 = 3.7$ Hz), 2.73 (dd, 1H, $J_1 = 12.6$, $J_2 = 2.5$ Hz), 2.83–2.88 (m, 1H), 3.01 (dd, 1H, $J_1 = 14.0$, $J_2 = 4.0$ Hz), 3.41 (d, 1H, $J = 12.8$ Hz), 3.65 (d, 2H, $J = 12.8$ Hz), 3.80 (br, 1H), 4.53 (d, 1H, $J = 8.9$ Hz), 7.17–7.36 (m, 5H) ; IR ($CHCl_3$) 3358, 2980, 1739, 1686, 1525, 1496, 1454, 1367, 1247, 1171, 1044, 1018, 861, 741, 699 cm^{-1} ; $[\alpha]_D^{25}$ −10.5° (*c* 1.35, $CHCl_3$); mass m/z 399 $[M+H]^+$.

[1(*S*)-Benzyl-4-(benzyl-methyl-amino)-2(*S*)-hydroxy-butyl]-carbamic acid *tert*-butyl ester (epi-4). ^{1}H NMR ($CDCl_3$) δ 1.22–1.31 (m, 1H), 1.40 (s, 9H), 1.83–1.92 (m, 1H), 2.19 (m, 3H), 2.45–2.50 (m, 1H), 2.72–2.78 (m, 1H), 2.88 (d, 2H, $J = 7.6$ Hz), 3.35 (d, 1H, $J = 12.8$ Hz), 3.63–3.70 (m, 2H),

3.73 (d, 1H, $J = 10.4$ Hz), 5.09 (d, 1H, $J = 9.5$ Hz), 7.17–7.44 (m, 5H); IR ($CHCl_3$) 2985, 1730, 1375, 1254, 1046, 940 cm^{-1}; $[\alpha]_D^{25} + 0.89°$ (c 0.71, $CHCl_3$); mass m/z 399 $[M + H]^+$.

[1(*S*)-Benzyl-4-(benzyl-methyl-amino)-2(*R*)-acetoxy-butyl]-carbamic acid *tert*-butyl ester (5). A solution of **4** (66.4 mg, 0.167 mmol), Ac_2O (96.5 mg, 0.944 mmol), NEt_3 (94.1 mg, 0.930 mmol) and a catalytic amount of DMAP in CH_2Cl_2 (3 mL) was stirred for 4 h at room temperature. The reaction was quenched with brine and the mixture was extracted (EtOAc) and dried (Na_2SO_4). After removal of the solvent in vacuo, the residue was purified by PTLC (hexane:EtOAc = 5:5) to afford **5** (59.5 mg) in 81% yield.

Mp 61°C; ^1H NMR ($CDCl_3$) δ 1.33 (s, 9H), 1.77–1.89 (m, 2H), 1.99 (s, 3H), 2.21 (s, 3H), 2.49 (dd, 2H, $J_1 = J_2 = 7.1$ Hz), 2.66 (dd, 1H, $J_1 = 14.0$, $J_2 = 9.1$ Hz), 2.86 (dd, 1H, $J_1 = 14.0$, $J_2 = 5.5$ Hz), 3.52–3.59 (m, 2H), 4.10–4.15 (m, 1H), 4.93 (d, 1H, $J = 3.5$ Hz), 5.08 (d, 1H, $J = 8.7$ Hz) 5.36 (br, 1H), 7.16–7.48 (m, 5H); IR ($CHCl_3$) 3444, 2980, 1711, 1498, 1455, 1368, 1252, 1167, 1046, 1025, 873 cm^{-1}; mass m/z 441 $[M + H]^+$.

{1(*S*)-Benzyl-2(*R*)-acetoxy-4-[methyl-(*p*-toluenesulfonyl)-amino]-butyl}-carbamic acid *tert*-butyl ester (6). A suspension of **5** (290 mg, 0.658 mmol), AcOH (62.5 mg, 1.04 mmol) and 10% Pd–C (40 mg) in EtOH (5 mL) was stirred under H_2 (1 atm) at room temperature for 1 day. After changing the atmosphere to N_2, the mixture was diluted with EtOAc. The mixture was filtered through a Celite pad (washed with EtOAc), and the mixture was washed (saturated aqueous $NaHCO_3$), dried (Na_2SO_4) and concentraed in vacuo. The residue (105 mg) was used in the next step without further purification.

To the stirred solution of the above crude amine (105 mg) and NEt_3 (64.1 mg, 0.633 mmol) in CH_2Cl_2 (4 mL) was added *p*-toluenesulfonyl chloride (80.4 mg, 0.422 mmol) at 0°C and stirred for 3 h at this temperature. The reaction was stopped by adding saturated aqueous $NaHCO_3$ and the mixture was extracted with EtOAc. The combined organic extracts were washed (brine), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified with PTLC (hexane:EtOAc = 6:4) to give **6** (62.2 mg) in 41.0% yield (2 steps).

^1H NMR ($CDCl_3$) δ 1.32 (s, 9H), 1.79–1.97 (m, 2H), 2.09 (s, 3H), 2.43 (s, 3H), 2.54–2.79 (m, 1H), 2.69 (s, 3H) 2.81–3.19 (m, 3H), 3.98–4.16 (m, 1H), 4.55–4.70 (m, 1H), 4.83–5.00 (m, 1H), 7.17–7.33 (m, 7H), 7.62–7.67 (m, 2H); mass m/z 505 $[M + H]^+$.

***N*-[1(*S*)-Benzyl-4-(methyl-*p*-toluenesulfonyl-amino)-2(*R*)-hydroxy-butyl]-3-hydroxy-2-methylbenzamide (7).** A solution of **6** (61.5 mg, 0.122 mmol) in 1,4-dioxane (4 mL, contained 4 N HCl) was stirred for 2 h at room temperature. After removal of the solvent in vacuo the residue was used in the next step.

The suspension of the above crude product, EDCI (58.8 mg, 0.307 mmol), HOBt (21.2 mg, 0.157 mmol), 3-hydroxy-2-methylbenzoic acid (45 mg, 0.296 mmol) and NEt_3 (52 mg, 0.514 mmol) in DMF (4 mL) was stirred for 1 day at room temperature. The reaction was quenched with H_2O and the mixture was extracted with EtOAc. The organic extracts were washed (H_2O), dried (Na_2SO_4) and concentrated in vacuo. The residue was used in the next step without further purification.

The solution of the above crude product and aqueous NaOH (1 N, 0.3 mL) in MeOH (3 mL) was stirred for 30 min at room temperature. Brine was added and this reaction mixture was extracted with EtOAc. After removal of the solvent in vacuo, the residue was purified by PTLC (hexane:EtOAc = 4:6) to afford **7** in 45% yield (3 steps).

Mp 78°C; ^1H NMR ($CDCl_3$) δ 1.61–2.11 (m, 2H), 1.98 (s, 3H), 2.44 (s, 3H), 2.66–2.91 (m, 3H), 2.76 (s, 3H), 3.02–3.16 (m, 2H), 3.40–3.54 (m, 1H), 3.96–4.16 (m, 1H), 4.35–4.49 (m, 1H), 6.02 (d, 1H, $J = 8.6$ Hz), 6.58 (d, 1H, $J = 7.8$ Hz), 6.76 (d, 1H, $J = 7.8$ Hz), 6.95 (t, 1H, 7.8 Hz), 7.19–7.35 (m, 7H), 7.59–7.70 (m, 2H); IR (KBr) 3350, 2925, 1638, 1585, 1528, 1456, 1333, 1158, 1088, 949, 722 cm^{-1}; mass m/z 497 $[M + H]^+$.

***N*-[1(*S*)-Benzyl-4-(ethyl-*p*-toluenesulfonyl-amino)-2(*R*)-hydroxy-butyl]-3-hydroxy-2-methylbenzamide (8).** Mp 73°C; ^1H NMR ($CDCl_3$) δ 1.26 (t, 3H, $J = 7.1$ Hz), 1.63–1.97 (m, 3H), 2.00 (s, 3H), 2.42 (s, 3H), 2.81 (dd, 1H, $J_1 = 14.1$, $J_2 = 10.4$ Hz), 3.00–3.34 (m, 4H), 3.42–3.66 (m, 1H), 3.86–4.06 (m, 2H), 4.35–4.48 (m, 1H), 5.57 (s, 1H), 5.97 (d, 1H, $J = 7.8$ Hz), 6.58 (d, 1H, $J = 7.8$ Hz), 6.77 (d, 1H, $J = 7.8$ Hz), 6.97 (d, 1H, $J = 7.8$ Hz), 7.16–7.44 (m, 6H), 7.60–7.71 (m, 2H); IR (KBr) 3349, 2930, 1638, 1585, 1527, 1496, 1466, 1330, 1285, 1153, 1089, 911, 730, 700 cm^{-1}; mass m/z 511 $[M + H]^+$.

***N*-[1(*S*)-Benzyl-4-(isopropyl-*p*-toluenesulfonyl-amino)-2(*R*)-hydroxy-butyl]-3-hydroxy-2-methylbenzamide (9).** Mp 66°C; ^1H NMR ($CDCl_3$) δ 0.96 (d, 3H, $J = 6.7$ Hz), 1.11 (d, 3H, $J = 6.7$ Hz), 1.74–1.98 (m, 2H), 2.05 (s, 3H), 2.42 (s, 3H), 2.83 (dd, 1H, $J_1 = 14.3$, $J_2 = 10.3$ Hz), 3.02–3.20 (m, 1H), 3.22–3.48 (m, 2H), 3.77–4.17 (m, 3H), 4.33–4.46 (m, 1H), 5.50 (s, 1H), 5.93 (d, 1H, $J = 7.3$ Hz), 6.58 (d, 1H, $J = 7.3$ Hz), 6.78 (d, 1H, $J = 7.3$ Hz), 6.96 (t, 1H, $J = 7.8$ Hz), 7.16–7.35 (m, 7H), 7.61–7.72 (m, 2H); IR (KBr) 3347, 2975, 2928, 1638, 1532, 1467, 1455, 1327, 1285, 1149, 1119, 1088, 870, 731, 700 cm^{-1}; mass m/z 525 $[M + H]^+$.

***N*-[1(*S*)-Benzyl-4-(isopropyl-*p*-toluenesulfonyl-amino)-2(*R*)-hydroxy-butyl]-3-hydroxy-2,5-dimethylbenzamide (10).** Mp 53°C; ^1H NMR ($CDCl_3$) δ 0.97 (d, 3H, $J = 8.8$ Hz), 1.12 (d, 3H, $J = 6.7$ Hz), 1.71–1.96 (m, 1H), 1.99 (s, 3H), 2.17 (s, 3H), 2.42 (s, 3H), 2.82 (dd, 1H, $J_1 = 14.3$, $J_2 = 10.5$ Hz), 3.13 (dd, 1H, $J_1 = 14.3$, $J_2 = 4.9$ Hz), 3.22–3.47 (m, 2H), 3.86–4.17 (m, 3H), 4.30–4.45 (m, 1H), 5.26 (s, 1H), 5.86 (d, 1H, $J = 7.1$ Hz), 6.34 (s, 1H), 6.59 (s, 1H), 7.19–7.38 (m, 7H), 7.59–7.74 (m, 2H); IR (KBr) 3347, 2975, 2926, 1640, 1527, 1496, 1454, 1327, 1149, 1088, 867, 700 cm^{-1}; mass m/z 539 $[M + H]^+$.

***N*-{1(*S*)-Benzyl-4-[ethyl-(*p*-methoxy)-benzenesulfonyl-amino]-2(*R*)-hydroxy-butyl}-3-hydroxy-2-methylbenzamide (11).** Mp 52°C; ^1H NMR ($CDCl_3$) δ 1.10 (t, 1H, $J = 7.2$ Hz), 1.61–1.92 (m, 3H), 1.99 (s, 3H), 2.82 (dd,

1H, $J_1 = 14.3$, $J_2 = 10.4$ Hz), 3.01–3.35 (m, 4H), 3.45–3.59 (m, 1H), 3.86 (s, 3H), 3.96–4.09 (m, 1H), 4.31–4.48 (m, 1H), 6.00 (d, 1H, $J = 7.9$ Hz), 6.57 (d, 1H, $J = 7.9$ Hz), 6.76 (d, 1H, $J = 7.9$ Hz), 6.87–6.99 (m, 3H), 7.20–7.34 (m, 6H), 7.66–7.71 (m, 2H); IR (KBr) 3348, 2937, 1638, 1597, 1526, 1465, 1329, 1260, 1150, 1091, 1026, 911, 835, 804, 702 cm^{-1}; mass m/z 527 $[M+H]^+$.

***N*-[1(*S*)-Benzyl-4-(hydroxyethyl-*p*-toluenesulfonyl-amino)-2(*R*)-hydroxy-butyl]-3-hydroxy-2-methylbenzamide (12).** Mp 69°C; ^1H NMR ($CDCl_3$) δ 1.60–1.91 (m, 5H), 1.99 (s, 3H), 2.43 (s, 3H), 2.28 (dd, 1H, $J_1 = 14.5$, $J_2 = 10.7$ Hz), 3.01–3.20 (m, 3H), 3.22–3.33 (m, 1H), 3.45–3.67 (m, 1H), 3.72–3.88 (m, 2H), 4.08–4.23 (m, 1H), 4.31–4.41 (m, 1H), 6.11 (d, 1H, $J = 7.7$ Hz), 6.58 (d, 1H, $J = 7.7$ Hz), 6.76 (d, 1H, $J = 7.7$ Hz), 6.94 (t, 1H, $J = 7.7$ Hz), 7.19–7.66 (m, 7H), 7.67–7.71 (m, 2H); IR (KBr) 3352, 2927, 1637, 1585, 1528, 1455, 1332, 1285, 1156, 1088, 911, 732, 700 cm^{-1}; mass m/z 527 $[M+H]^+$.

***N*-{1(*S*)-Benzyl-4-[ethyl-(2,4,6-trimethyl)-benzenesulfonyl-amino]-2(*R*)-hydroxy-butyl}-3-hydroxy-2-methylbenzamide (13).** Mp 61°C; ^1H NMR ($CDCl_3$) δ 1.02 (t, 3H, $J = 7.2$ Hz), 1.68–1.89 (m, 1H), 1.96 (s, 3H), 2.27 (s, 3H), 2.59 (s, 6H), 2.74 (dd, 1H, $J_1 = 14.4$, $J_2 = 10.6$ Hz), 2.97–3.10 (m, 1H), 3.11–3.32 (m, 3H), 3.38–3.45 (m, 1H), 3.50–3.60 (m, 1H), 3.82–3.88 (m, 2H), 4.14–4.37 (m, 1H), 5.95 (d, 1H, $J = 7.2$ Hz), 6.26 (s, 1H), 6.51 (d, 1H, $J = 7.6$ Hz), 6.83 (d, 1H, $J = 8.0$ Hz), 6.88–6.99 (m, 2H), 7.19–7.40 (m, 6H); IR (KBr) 3342, 2972, 2938, 1638, 1523, 1467, 1382, 1307, 1286, 1146, 1056, 906, 734, 701 cm^{-1}; mass m/z 539 $[M+H]^+$.

{4-[Acetyl-(1(*S*)-*tert*-butylcarbamoyl-1-pheny-methyl)-amino]-1(*S*)-benzyl-2(*R*,*S*)-hydroxy-butyl}-carbamic acid *tert*-butyl ester (15). A solution of **1-a** (141 mg, 0.512 mmol), NEt_3 (130 mg, 1.28 mmol) and (*S*)-phenylglycine *tert*-butyl amide·hydrochloride **14** (100 mg, 0.413 mmol) in EtOH (4 mL) was stirred for 3 h at room temperature. The reaction mixture was cooled to 0°C and to this was added $NaBH_4$ (22.8 mg, 0.603 mmol). It was then stirred for 2 h at this temperature. The reaction was stopped by adding of CH_3CO_2H and stirred for another 5 min. The mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$. The organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue (276 mg) was used in the next step without further purification.

The solution of the above crude product (276 mg), Ac_2O (124 mg, 1.21 mmol), NEt_3 (131 mg, 1.29 mmol) and a catalytic amount of DMAP in CH_2Cl_2 (3 mL) was stirred for 1 day. The reaction was quenched with brine and the mixture was extracted with EtOAc and dried (Na_2SO_4). After removal of the solvent in vacuo, the residue was purified by PTLC (hexane:EtOAc = 4:6) to give diacetate (182 mg) in 78% yield.^1H NMR ($CDCl_3$) δ 1.10–1.57 (m, 2H), 1.33 (s, 9H), 1.37 (s, 9H), 2.00 (s, 3H), 2.20 (s, 3H), 2.53–2.72 (m, 2H), 3.22–3.46 (m, 3H), 3.95–4.03 (m, 1H), 4.50–4.68 (m, 1H), 5.34–5.94 (m, 2H), 7.08–7.48 (m, 10H); mass m/z 568 $[M+H]^+$.

The solution of the above diacetate (44 mg) and aqueous NaOH (1 N, 0.3 mL) in MeOH (4 mL) was stirred for 3 h at room temperature. To this mixture was added brine. Then the mixture was extracted (EtOAc), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by PTLC (hexane:EtOAc = 3:7) to afford **15** (33.4 mg) in 89% yield.

Mp 73°C; ^1H NMR ($CDCl_3$) δ 1.29 (s, 9H), 1.35 (s, 9H), 2.22 (s, 3H), 2.71–2.84 (m, 4H), 3.37–3.74 (m, 4H), 4.55–4.65 (m, 1H), 5.29–5.39 (m, 1H), 5.60–5.70 (m, 1H), 5.75–5.84 (m, 1H), 7.13–7.49 (m, 10H); IR (KBr) 3319, 2973, 1683, 1626, 1496, 1365, 1032, 743, 700 cm^{-1}. Anal. calcd for $C_{30}H_{43}N_3O_5 \cdot 1/2H_2O$: C, 67.39; H, 8.29; N, 7.86. Found: C, 67.19; H, 8.21; N., 8.07; mass m/z 526 $[M+H]^+$.

{4-[Acetyl-(1(*S*)-*tert*-butylcarbamoyl-2-phenyl-ethyl)-amino]-1(*S*)-benzyl-2(*R*,*S*)-acetoxy-butyl}-carbamic acid *tert*-butyl ester (17). A solution of H-Phe-NH-*tert*-butyl·hydrochloride **16** (1.15 g, 4.44 mmol), **1-a** (1.04 g, 3.78 mmol) and NEt_3 (1.16 g, 11.5 mmol) in EtOH (15 mL) was stirred for 3 h at room temperature. To this mixture was added $NaBH_4$ (212 mg, 5.6 mmol) at 0°C and stirred for 2 h at this temperature. The reaction was stopped by adding CH_3CO_2H (0.5 mL) and diluted with EtOAc. The mixture was washed with saturated aqueous $NaHCO_3$ and concentrated in vacuo. The residue was diluted with EtOAc, washed (brine), dried (Na_2SO_4) and concentrated in vacuo. The residue was used in the next step without further purification.

The solution of the above crude product, Ac_2O (1.59 g, 15.5 mmol), NEt_3 (1.61 g, 15.9 mmol) and catalytic amount of DMAP in CH_2Cl_2 (10 mL) was stirred for 12 h. The reaction mixture was quenched with brine and extracted with EtOAc. After removal of the solvent in vacuo, the residue was purified by flash column chromatography (hexane:EtOAc:Acetone = 5:4:1) to afford **17** (1.4 g) in 64% yield (3 steps) as a diastereomixture (colorless oil).

Mp 51°C; ^1H NMR ($CDCl_3$) δ 1.27 (s, 9H), 1.33 (s, 9H), 1.75–1.85 (m, 2H), 2.04 (s, 3H), 2.10 (s, 3H), 2.56–2.86 (m, 2H), 3.03–3.31 (m, 4H), 4.06–4.08 (m, 1H), 4.39–4.65 (m, 1H), 4.74–4.85 (m, 2H), 6.27–6.43 (m, 1H), 7.14–7.40 (m, 10H); IR (KBr) 3325, 2973, 1740, 1712, 1631, 1526, 1366, 1170, 1024, 749, 700 cm^{-1}. Anal. calcd for $C_{33}H_{47}N_3O_6 \cdot H_2O$: C, 66.09; H, 8.23; N, 7.01. Found: C, 66.29; H, 8.10; N, 6.67; mass m/z 582 $[M+H]^+$.

{4-[Acetyl-(1(*S*)-*tert*-butylcarbamoyl-2-phenyl-ethyl)-amino]-1(*S*)-benzyl-2(*R*)-hydroxy-butyl}-3-hydroxy-2-methylbenzamide (18). A solution of **17** (308 mg, 0.529 mmol) in 1,4-dioxane (5 mL, contained 4 N HCl) was stirred for 2 h at room temperature. After removal of the solvent in vacuo, the residue was used in the next step.

The solution of the above crude product, EDCI·Cl (223 mg, 1.16 mmol), HOBt (70 mg, 0.46 mmol), 3-hydroxy-2-methylbenzoic acid (158 mg, 1.04 mmol) and NEt_3 (113 mg, 1.12 mmol) in DMF (8 mL) was stirred for 1 day. The reaction was stopped by the addition of brine and the mixture was extracted with EtOAc. The combined organic extracts were washed (brine), dried

(Na_2SO_4) and concentrated in vacuo. The residue was used in the next step without further purification.

The solution of the above crude product and aqueous NaOH (1 N, 1.5 mL) in MeOH (4 mL) was stirred for 3 h at room temperature. To this mixture was added 5% aqueous $KHSO_4$ and extracted with EtOAc. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by PTLC (EtOAc:acetone = 8:2) to afford **18** (130 mg) in 43% yield (3 steps).

Mp 55°C; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 9H), 1.42 (br, 1H), 1.65–1.69 (m, 1H), 1.93 (d, 1H, J = 8.7 Hz), 1.98 (s, 3H), 2.11 (s, 3H), 2.73 (dd, 1H, J_1 = 14.0, J_2 = 10.7 Hz), 2.95 (dd, 1H, J_1 = 14.1, J_2 = 4.5 Hz), 3.21 (d, 2H, J = 7.7 Hz), 3.40–3.46 (m, 2H), 3.63–3.73 (m, 1H), 4.15–4.19 (m, 1H), 4.64–4.66 (m, 1H), 6.00 (d, 1H, J = 7.7 Hz), 6.49 (d, 1H, J = 8.4 Hz), 6.81 (d, 1H, J = 8.2 Hz), 6.91 (t, 1H, J = 7.8 Hz), 7.13–7.32 (m, 12H); IR (KBr) 3308, 2965, 2930, 1635, 1522, 1454, 1365, 1283, 1223, 1175, 1079, 834, 701 cm^{-1}; mass m/z 574 $[M+H]^+$.

{4-[(1(*S*)-*tert*-Butylcarbamoyl-2-phenyl-ethyl)-amino]-1(*S*)-benzyl-2(*R,S*)-hydroxy-butyl}-3-hydroxy-2-methylbenzamide (19). ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 9H), 1.68–1.76 (m, 1H), 1.94 (d, 1H, J = 2.9 Hz), 2.29 (s, 3H), 2.43–3.00 (m, 7H), 3.17–3.45 (m, 1H), 3.66–3.79 (m, 1H), 4.23–4.31 (m, 1H), 6.49–6.62 (m, 1H), 6.71–6.79 (m, 1H), 6.92–7.00 (m, 1H), 7.19–7.33 (m, 13H); mass m/z 532 $[M+H]^+$.

{4-[Methy-(1(*S*)-*tert*-butylcarbamoyl-2-phenyl-ethyl)-amino]-1(*S*)-benzyl-2(*R*)-hydroxy-butyl}-3-hydroxy-2-methylbenzamide (20). Mp 75°C; ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 9H), 1.72–1.86 (m, 1H), 1.90 (s, 3H), 2.46 (s, 3H), 2.47–2.58 (m, 2H), 2.70–3.00 (m, 4H), 3.04–3.20 (m, 3H), 3.62–3.79 (m, 1H), 3.87–3.90 (m, 1H), 4.26–4.37 (m, 1H), 6.03 (d, 1H, J = 9.2 Hz), 6.51 (d, 1H, J = 7.4 Hz), 6.65–6.80 (m, 1H), 6.87–7.07 (m, 1H), 7.14–7.75 (m, 12H); IR (KBr) 3296, 2965, 2858, 1739, 1643, 1521, 1455, 1285, 1223, 1032, 749, 700 cm^{-1}; mass m/z 546 $[M+H]^+$.

{4-[Benzyl-(1(*S*)-*tert*-butylcarbamoyl-2-phenyl-ethyl)-amino]-1(*S*)-benzyl-2(*R,S*)-hydroxy-butyl}-3-hydroxy-2-methylbenzamide (21). Mp 75°C; ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 9H), 1.63–1.80 (m, 2H), 1.90 (s, 3H), 2.86–3.34 (m, 7H), 3.54–3.79 (m, 2H), 3.90–4.15 (m, 2H), 4.77 (br, 1H), 5.99–6.02 (m, 1H), 6.45–6.51 (m, 1H), 6.73–6.78 (m, 1H), 6.88–6.91 (m, 1H), 7.15–7.53 (m, 15H) ; IR (KBr) 3309, 2962, 1645, 1585, 1518, 1454, 1284, 1076, 745, 700 cm^{-1}. Anal. calcd for $C_{39}H_{47}N_3O_4 \cdot H_2O$: C, 73.21; H, 7.72; N, 6.57. Found: C, 73.60; H, 7.58; N, 6.40.; mass m/z 622 $[M+H]^+$.

{4-[(1(*S*)-*tert*-Butylcarbamoyl-1-pheny-methyl)-amino]-1(*S*)-benzyl-2(*R*)-hydroxy-butyl}-3-hydroxy-2-methylbenzamide (22). Mp 48°C; ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 9H), 1.85–2.05 (m, 3H), 2.65–2.73 (m, 2H), 3.22–3.74 (m, 4H), 4.77–4.93 (m, 4H), 6.51–7.05 (m, 4H), 7.18–7.89 (m, 11H); IR (KBr) 3311, 1739, 1633, 1584, 1530, 1455, 1283, 1080, 701 cm^{-1}; mass m/z 519 $[M+H]^+$.

{4-[Acetyl-(1(*S*)-*tert*-butylcarbamoyl-1-pheny-methy)]-amino}-1(*S*)-benzyl-2(*R,S*)-hydroxy-butyl}-3-hydroxy-2-methylbenzamide (23). Mp 51°C; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.70–1.89 (m, 1H), 1.91 (s, 3H), 1.93–2.17 (m, 2H), 2.20 (s, 3H), 2.47–2.94 (m, 3H), 3.56–3.63 (m, 2H), 4.09–4.27 (m, 1H), 5.82 (d, 1H, J = 13.8 Hz), 6.02–6.17 (m, 1H), 6.44–6.52 (m, 1H), 6.75–6.77 (m, 1H), 6.85–6.91 (m, 1H), 7.10–7.54 (m, 10H); IR (KBr) 3309, 1633, 1520, 1454, 1365, 1283, 1223, 1080, 701 cm^{-1}; mass m/z 560 $[M+H]^+$.

{4-[(1(*S*)-*tert*-Butylcarbamoyl-1-*tert*-butyl-methy)]-amino}-1(*S*)-benzyl-2(*R*)-hydroxy-butyl}-3-hydroxy-2-methylbenzamide (24). Mp 47°C; ^{1}H NMR ($CDCl_3$) δ 1.00 (s, 9H), 1.04–1.36 (m, 2H), 1.37 (s, 9H), 1.64–1.68 (m, 1H), 1.94 (s, 3H), 2.79–2.88 (m, 2H), 3.14 (dd, 1H, J_1 = 14.6, J_2 = 4.0 Hz), 3.87 (d, 1H, J = 5.5 Hz), 4.40–4.45 (m, 1H), 5.93–6.00 (m, 2H), 6.55 (d, 1H, J = 7.8 Hz), 6.77 (d, 1H, J = 7.8 Hz), 6.93 (d, 1H, J = 7.8 Hz), 7.19–7.33 (m, 8H); IR (KBr) 3308, 2962, 1644, 1522, 1455, 1365, 1283, 1224, 1081, 700 cm^{-1}; mass m/z 498 $[M+H]^+$.

{4-[Acetyl-(1(*R*)-*tert*-butylcarbamoyl-2-phenyl-ethyl)-amino]-1(*S*)-benzyl-2(*R*)-hydroxy-butyl}-3-hydroxy-2-methylbenzamide (25). Mp 98°C; ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 9H), 1.40–1.75 (m, 2H), 1.91 (s, 3H), 2.07 (s, 3H), 2.65–2.79 (m, 1H), 2.89–3.01 (m, 1H), 3.06–3.74 (m, 6H), 4.16–4.27 (m, 1H), 6.34 (d, 1H, J = 8.6 Hz), 6.48 (d, 1H, J = 7.5 Hz), 6.76 (t, 1H, J = 7.7 Hz), 6.84 (t, 1H, J = 7.7 Hz), 7.10–7.38 (m, 12H); IR (KBr) 3306, 2966, 1635, 1526, 1454, 1365, 1284, 1223, 1175, 1080, 750, 701 cm^{-1}; mass m/z 574 $[M+H]^+$.

{4-[Propionyl-(1(*S*)-*tert*-butylcarbamoyl-2-phenyl-ethyl)-amino]-1(*S*)-benzyl-2(*R*)-hydroxy-butyl}-3-hydroxy-2-methylbenzamide (26). Mp 98°C; ^{1}H NMR ($CDCl_3$) δ 1.11 (dd, 3H, J_1 = 14.4, J_2 = 7.3 Hz), 1.26 (s, 9H), 1.98 (s, 3H), 2.28–2.42 (m, 2H), 2.73–3.00 (m, 2H), 3.01–3.23 (m, 2H), 3.41–3.75 (m, 3H), 4.21–4.32 (m, 1H), 4.69–4.73 (m, 1H), 5.84–6.08 (m, 1H), 6.50–6.62 (m, 1H), 6.77–6.83 (m, 1H), 6.93–6.99 (m, 1H), 7.14–7.34 (m, 13H); IR (KBr) 3315, 2966, 1637, 1527, 1455, 1365, 1283, 1222, 1071, 750, 701cm^{-1}; mass m/z 588 $[M+H]^+$.

{4-[Acetyl-(1(*S*)-*tert*-butylcarbamoyl-2-(*p*-chloro)-phenyl-ethyl)-amino]-1(*S*)-benzyl-2(*R,S*)-hydroxy-butyl}-3-hydroxy-2-methylbenzamide (27). Mp 91°C; ^{1}H NMR (CD_3OD) δ 1.26 (s, 9H), 1.65–1.90 (m, 1H), 1.97 (s, 3H), 2.12 (s, 3H), 2.36–2.50 (m, 2H), 2.56–2.70 (m, 1H), 2.83–3.29 (m, 3H), 3.47–3.76 (m, 4H), 4.16–4.45 (m, 1H), 6.56 (d, 1H, J = 7.5 Hz), 6.75 (d, 1H, J = 7.1 Hz), 6.90–6.96 (m, 1H), 7.02–7.75 (m, 12H); IR (KBr) 3306, 2965, 2932, 1739, 1631, 1527, 1455, 1283, 1225, 1170, 1015, 701 cm^{-1}; mass m/z 609 $[M+H]^+$.

{4-[Acetyl-(1(*S*)-*tert*-butylcarbamoyl-2-(*p*-hydroxy)-phenyl-ethyl)-amino]-1(*S*)-benzyl-2(*R*)-hydroxy-butyl}-3-hydroxy-2-methylbenzamide (28). Mp 109°C; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 9H), 1.58–1.91 (m, 2H), 2.02 (s, 3H), 2.26 (s, 3H), 2.49–2.65 (m, 3H), 2.83–3.16 (m, 4H), 3.24–3.36 (m, 1H), 3.62–3.79 (m, 3H), 4.60–4.77 (m, 1H), 4.89–4.92 (m, 1H), 5.96 (d, 1H, J = 9.3 Hz), 6.53–

9.78 (m, 3H), 6.84–7.00 (m, 3H), 7.12–7.44 (m, 9H); IR (KBr) 3301, 2965, 2931, 1740, 1643, 1517, 1455, 1367, 1227, 1032, 834, 751, 701 cm^{-1}; mass *m/z* 632 $[M+H]^+$.

{4-[Acetyl-(1(*S*)-*tert*-butylcarbamoyl-2-(*p*-benzyloxy)-phenyl-ethyl)-amino]-1(*S*)-benzyl-2(*R*)-hydroxy-butyl}-3-hydroxy-2-methylbenzamide (29). Mp 104°C; ^1H NMR ($CDCl_3$) δ 1.26 (s, 9H), 1.52–1.99 (m, 2H), 2.02 (s, 3H), 2.14 (s, 3H), 2.57–3.16 (m, 5H), 3.44–3.48 (m, 1H), 3.66–3.74 (m, 2H), 4.24 (br, 1H), 4.62 (br, 1H), 4.97 (s, 2H), 5.71–5.86 (m, 1H), 6.51–6.58 (m, 1H), 6.70–6.80 (m, 2H), 6.85–6.97 (m, 2H), 7.05–7.14 (m, 2H), 7.16–7.40 (m, 11H); IR (KBr) 3304, 2964, 2931, 1739, 1625, 1512, 1454, 1364, 1283, 1120, 1080, 832, 699 cm^{-1}, Anal. calcd for $C_{41}H_{49}N_3O_6 \cdot 3/2H_2O$: C, 69.67; H, 7.41; N, 5.94. Found: C, 69.87; H, 7.06; N, 5.67; mass *m/z* 680 $[M+H]^+$.

{4-[Acetyl-(1(*S*)-*tert*-butylcarbamoyl-2-(β-naphtyl)-ethyl)-amino]-1(*S*)-benzyl-2(*R*)-hydroxy-butyl}-3-hydroxy-2-methylbenzamide (30). Mp 45°C; ^1H NMR ($CDCl_3$) δ 1.26 (s, 9H), 1.41–1.92 (m, 2H), 1.92 (s 3H), 2.08 (s, 3H), 2.56–2.74 (m, 3H), 3.36–3.70 (m, 6H), 4.80 (br, 1H), 5.90 (br, 1H), 6.43 (br, 1H), 6.83 (br, 1H), 7.09–7.43 (m, 10H), 7.51–7.84 (m, 5H); IR (KBr) 3307, 2965, 1635, 1522, 1455, 1365, 1284, 1223, 1174, 1080, 748, 701 cm^{-1}. Anal. calcd for $C_{38}H_{45}N_3O_5 \cdot 3/2H_2O$: C, 70.13; H, 7.43; N, 6.46. Found: C, 70.26; H, 7.09; N, 6.08; mass *m/z* 624 $[M+H]^+$.

{4-[Acetyl-(1(*S*)-ethylcarbamoyl-2-phenyl-ethyl)-amino]-1(*S*)-benzyl-2(*R*)-hydroxy-butyl}-3-hydroxy-2-methylbenzamide (31). Mp 175°C; ^1H NMR ($CDCl_3$) δ 1.05 (t, 3H, $J=7.2$ Hz), 1.62–1.82 (m, 2H), 1.98 (s, 3H), 2.11 (s, 3H), 2.73 (dd, 1H, $J_1=14.2$, $J_2=10.6$ Hz), 2.94 (dd, 1H, $J_1=14.5$, $J_2=4.7$ Hz), 3.12–3.35 (m, 4H), 3.37–3.49 (m, 2H), 3.60–3.69 (m, 1H), 4.23–4.28 (m, 1H), 4.62–4.69 (m, 1H), 5.98 (d, 1H, $J=7.8$ Hz), 6.51 (t, 1H, $J=7.6$ Hz), 6.80 (d, 1H, $J=7.6$ Hz), 6.92 (t, 1H, $J=7.6$ Hz), 7.04–7.38 (m, 12H); IR (KBr) 3308, 2930, 1639, 1536, 1454, 1375, 1284, 1174, 1032, 750, 701 cm^{-1}; mass *m/z* 546 $[M+H]^+$.

{4-[Acetyl-(1(*S*)-benzylcarbamoyl-2-phenyl-ethyl)-amino]-1(*S*)-benzyl-2(*R,S*)-hydroxy-butyl}-3-hydroxy-2-methylbenzamide (32). Mp 58°C; ^1H NMR ($CDCl_3$) δ 1.24–1.30 (m 1H), 1.70–1.96 (m, 1H), 2.01 (s, 3H), 2.13 (s, 3H), 2.56–2.70 (m, 1H), 2.80–2.99 (m, 2H), 3.24–3.75 (m, 5H), 4.19–4.44 (m, 3H), 4.70–4.81 (m, 1H), 5.60–5.89 (m, 2H), 6.53 (dd, 1H, $J_1=14.0$, $J_2=7.3$ Hz), 6.79 (dd, 1H, $J_1=11.9$, $J_2=7.9$ Hz), 6.93–7.00 (m, 1H), 7.04–7.42 (m, 15H); IR (KBr) 3291, 1636, 1527, 1454, 1284, 1175, 1079, 1030, 749 cm^{-1}; mass *m/z* 608 $[M+H]^+$.

{4-[Acetyl-(1(*S*)-(*o*-methyl)-benzylcarbamoyl-2-phenyl-ethyl)-amino]-1(*S*)-benzyl-2(*R,S*)-hydroxy-butyl}-3-hydroxy-2-methylbenzamide (33). Mp 55°C; ^1H NMR ($CDCl_3$) δ 1.50–1.90 (m, 1H), 1.92 (s, 3H), 2.04 (s, 3H), 2.15 (s, 3H), 2.57 (dd, 1H, $J_1=14.1$, $J_2=10.5$ Hz), 2.75–2.82 (m, 1H), 3.23–3.63 (m, 6H), 4.08–4.39 (m, 4H), 4.76 (br, 1H), 6.00 (d, 1H, $J=7.9$ Hz), 6.21–6.70 (m, 1H), 6.71–7.00 (m, 2H), 7.04–7.45 (m, 15H); IR (KBr) 3296, 1638, 1527, 1455, 1284, 1175, 1074, 745, 701 cm^{-1}. Anal. calcd for $C_{38}H_{43}N_3O_5 \cdot 3/2H_2O$: C, 70.24; H, 7.29; N, 6.47. Found: C, 70.20; H, 6.85; N, 6.24; mass *m/z* 622 $[M+H]^+$.

{4-[Acetyl-(1(*S*)-(*m*-methyl)-benzylcarbamoyl-2-phenyl-ethyl)-amino]-1(*S*)-benzyl-2(*R,S*)-hydroxy-butyl}-3-hydroxy-2-methylbenzamide (34). Mp 111°C; ^1H NMR ($CDCl_3$) δ 1.70–1.98 (m, 2H), 1.94 (s, 3H), 2.08 (s, 3H), 2.23 (s, 3H), 2.60 (dd, 1H, $J_1=14.4$, $J_2=10.6$ Hz), 2.81 (dd, 1H, $J_1=14.4$, $J_2=4.3$ Hz), 2.92–2.98 (m, 1H), 3.25–3.64 (m, 5H), 4.09–4.38 (m, 3H), 4.74 (br, 1H), 5.92 (d, 1H, $J=7.2$ Hz), 6.46 (t, 1H, $J=7.2$ Hz), 6.69–6.77 (m, 1H), 6.81–7.00 (m, 3H), 7.03–7.47 (m, 13H); IR (KBr) 3297, 2927, 1638, 1525, 1455, 1284, 1173, 1075, 834, 749, 700 cm^{-1}; mass *m/z* 622 $[M+H]^+$.

{4-[Acetyl-(1(*S*)-(*p*-methyl)-benzylcarbamoyl-2-phenyl-ethyl)-amino]-1(*S*)-benzyl-2(*R,S*)-hydroxy-butyl}-3-hydroxy-2-methylbenzamide (35). Mp 126°C; ^1H NMR ($CDCl_3$) δ 1.64–1.88 (m, 2H), 1.94 (s, 3H), 2.11 (s, 3H), 2.33 (s, 3H), 2.57–2.67 (m, 1H), 2.75–2.86 (m, 1H), 3.20–3.75 (m, 5H), 4.11–4.37 (m, 4H), 4.80 (br, 1H), 6.07 (d, 1H, $J=8.3$ Hz), 6.48 (dd, 1H, $J_1=11.6$, $J_2=7.6$ Hz), 6.75 (t, 1H, $J=9.3$ Hz), 6.89 (dd, 1H, $J_1=15.0$, $J_2=7.6$ Hz), 7.00–7.09 (m, 5H), 7.12–7.43 (m, 11H); IR (KBr) 3296, 1640, 1584, 1536, 1454, 1284, 1174, 1074, 1032, 747, 700 cm^{-1}; mass *m/z* 622 $[M+H]^+$.

{4-[Acetyl-(1(*S*)-cyclohexylcarbamoyl-2-phenyl-ethyl)-amino]-1(*S*)-benzyl-2(*R*)-hydroxy-butyl}-3-hydroxy-2-methylbenzamide (36). Mp 112°C; ^1H NMR ($CDCl_3$) δ 1.00–1.95 (m, 12H), 1.99 (s, 3H), 2.15 (s, 3H), 2.73–2.81 (m, 1H), 2.92–3.04 (m, 1H), 3.22–3.30 (m, 2H), 3.41–3.57 (m, 1H), 3.63–3.76 (m, 2H), 4.12–4.35 (m, 1H), 4.56–4.74 (m, 1H), 6.13 (d, 1H, $J=8.2$ Hz), 6.54 (dd, 1H, $J_1=11.8$, $J_2=7.5$ Hz), 6.81 (t, 1H, $J=9.3$ Hz), 6.95 (dd, 1H, $J_1=13.2$, $J_2=7.8$ Hz), 7.17–7.41 (m, 13H); IR (KBr) 3291, 2932, 1637, 1531, 1453, 1284, 1175, 750, 700 cm^{-1}. Anal. calcd for $C_{36}H_{45}N_3O_5 \cdot H_2O$: C, 69.93; H, 7.67; N, 6.80. Found: C, 70.19; H, 7.42; N, 6.49; mass *m/z* 600 $[M+H]^+$.

{4-[Acetyl-(1(*S*)-pyrrolidylcarbonyl-2-phenyl-ethyl)-amino]-1(*S*)-benzyl-2(*R*)-hydroxy-butyl}-3-hydroxy-2-methylbenzamide (37). Mp 115°C; ^1H NMR ($CDCl_3$) δ 1.50–2.12 (m, 6H), 1.97 (s, 3H), 2.10 (s, 3H), 2.75–3.11 (m, 5H), 3.16–3.79 (m, 4H), 4.02–4.15 (m, 1H), 4.31–4.79 (m, 3H), 5.16–5.59 (m, 1H), 6.52 (t, 1H, $J=7.8$ Hz), 6.79 (d, 1H, $J=7.6$ Hz), 6.87 (t, 1H, $J=7.6$ Hz), 7.13–7.72 (m, 11H); IR (KBr) 3303, 2931, 2877, 1628, 1453, 1283, 1081, 1032, 751, 701 cm^{-1}. Anal. calcd for $C_{34}H_{41}N_3O_5 \cdot 3/2H_2O$: C, 68.21; H, 7.41; N, 7.01. Found: C, 68.12; H, 7.08; N, 7.24; mass *m/z* 594 $[M+Na]^+$.

{4-[Acetyl-(1(*S*)-*tert*-butylcarbamoyl-2-phenyl-ethyl)-amino]-1(*S*)-(4-phenyl)-benzyl-2(*R*)-hydroxy-butyl}-3-hydroxy-2-methyl-benzamide (38). Mp 106°C; ^1H NMR ($CDCl_3$) δ 1.26 (s, 9H), 1.33–1.49 (m, 1H), 1.66–1.79 (m, 1H), 1.99 (s, 3H), 2.11 (s, 3H), 2.75–2.86 (m, 1H), 2.94–3.10 (m, 1H), 3.21 (d, 2H, $J=7.8$ Hz), 3.40–3.47 (m, 2H), 3.61–3.68 (m, 1H), 3.72–3.78 (m, 1H), 4.22 (br, 1H), 4.66 (br, 1H), 6.08 (d, 1H, $J=7.9$ Hz), 6.79 (d, 1H, $J=7.3$ Hz), 6.89 (t, 1H, $J=7.8$ Hz), 7.13–7.35 (m, 11H), 7.38–7.44 (m, 2H), 7.47–7.57 (m, 4H); IR (KBr) 3309, 2965, 1631,

1521, 1454, 1365, 1283, 1223, 1077, 1039, 762, 699 cm^{-1}. Anal. calcd for $C_{40}H_{47}N_3O_5 \cdot 3/2H_2O$: C, 70.98; H, 7.44; N, 6.21. Found : C, 71.24; H, 7.09; N, 5.95; mass *m/z* 650 $[M+H]^+$.

{4-[Acetyl-(1(*S*)-*tert*-butylcarbamoyl-2-phenyl-ethyl)-amino]-1(*S*)-β-napthylmethy-2(*R*)-hydroxy-butyl}-3-hydroxy-2-methyl-benzamide (39). Mp 115°C; ^1H NMR ($CDCl_3$) δ 1.25 (s, 9H), 1.43–1.52 (m,1H), 1.70–1.79 (m, 1H), 1.91 (s, 3H), 2.10 (s, 3H), 2.90–3.00 (m, 2H), 3.08–3.14 (m, 2H), 3.21 (d, 2H, $J=7.6$ Hz), 3.35–3.48 (m, 2H), 3.67–3.76 (m, 1H), 4.24 (br, 1H), 4.68 (br, 1H), 6.08 (d, 1H, $J=7.8$ Hz), 6.46 (d, 1H, $J=7.5$ Hz), 6.70–6.89 (m, 3H), 7.11–7.26 (m, 5H), 7.33–7.46 (m, 3H), 7.63–7.82 (m, 4H); IR (KBr) 3308, 2964, 1634, 1523, 1454, 1365, 1284, 1223, 1079, 750, 701 cm^{-1}. Anal. calcd for $C_{38}H_{45}N_3O_5 \cdot 2H_2O$: C, 69.17; H, 7.49; N, 6.37. Found : C, 69.74; H, 7.10; N, 6.00.; mass *m/z* 624 $[M+H]^+$.

References and Notes

1. Mitsuya, H.; Yarchoan, R.; Broder, S. *Science* **1990**, *249*, 1533.
2. Yarchoan, R.; Mitsuya, H.; Broder, S. *Trends in Pharmacol. Sci.* **1993**, *14*, 196 and references cited therein.
3. Hellen, C. U. T.; Kräusslich, H-G.; Wimmer, E. *Biochemistry* **1989**, *28*, 9881.
4. For excellent reviews on HIV-1 protease inhibitors, see: Wlodawer, A.; Erickson, J. W. *Annu. Rev. Biochem.* **1993**, *62*, 543.
5. West, M. L.; Fairlie, D. P. *Trends in Pharmacol. Sci.* **1995**, *16*, 67.
6. Meek, T. D. *J. Enzyme Inhibition* **1992**, *6*, 65.
7. Barry, M.; Gibbons, S.; Back, D.; Mulcahy, F. *Clin. Pharmacokinet.* **1997**, *32*, 194.
8. Lunney, E. A. *Med. Chem. Res.* **1998**, *8*, 352.
9. Patick, A. K.; Potts, K. E. *Clinic. Microb. Rev.* **1998**, *11*, 614.
10. Boden, D.; Markowitz, M. *Antimicrob. Agents Chemother.* **1998**, *42*, 2775.
11. 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.
12. Mimoto, T.; Imai, J.; Tanaka, S.; Hattori, N.; Kisanuki, S.; Akaji, K.; Kiso, Y. *Chem. Pharm. Bull.* **1991**, *39*, 3088.
13. Mimoto, T.; Imai, J.; Kisanuki, S.; Enomoto, H.; Hattori, N.; Akaji, K.; Kiso, Y. *Chem. Pharm. Bull.* **1992**, *40*, 2251.
14. Sakurai, M.; Higashida, S.; Sugano, M.; Komai, T.; Yagi, R.; Ozawa, Y.; Handa, H.; Nishigaki, T.; Yabe, Y. *Bioorg. Med. Chem.* **1994**, *2*, 807.
15. 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.
16. Takashiro, E.; Watanabe, T.; Nitta, T.; Kasuya, A.; Miyamoto, S.; Ozawa, Y.; Yagi, R.; Nishigaki, T.; Shibayama, T.; Nakagawa, A.; Iwamoto, A.; Yabe, Y. *Bioorg. Med. Chem.* **1998**, *6*, 595.
17. Spaltenstein, A.; Leban, J. J.; Huang, J. J.; Reinhardt, K. R; Viveros, O. H.; Sigafoos, J.; Crouch, R. *Tetrahedron. Lett.* **1996**, *37*, 1343.
18. Kim, B. M.; Guare, J. P.; Hanifin, C. M.; Arford-Bickerstaff, D. J.; Vacca, J. P.; Ball, R. G. *Tetrahedron. Lett.* **1994**, *35*, 5153.
19. Ohba, T.; Ikeda, E.; Takei, H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1875.
20. Hanson, G. J.; Lindberg, T. *J. Org. Chem.* **1985**, *50*, 5399.
21. For the studies of P_2 benzamides, see: 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.
22. Kempf, D. J.; Flentge, C. A.; Wideburg, N. E.; Saldivar, A.; Vasavanonda, S.; Norbeck, D. W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2725.
23. 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.
24. For the reduction of α-amino ketones, see: Dondoni, A., Perrone, D. *Synthesis* **1993**, 1162 and references cited therein.
25. For the assignment of the absolute stereochemistry based on the vicinal coupling, see: Futagawa, S.; Inui, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3308.
26. Rich, D. H.; Sun, E. T. O. *J. Med. Chem.* **1980**, *23*, 27.
27. Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *Tetrahedron* **1985**, *41*, 163.
28. Houbion, J. A.; Miles, J. A.; Paton, J. A. *Org. Prep. Proc. Int.* **1979**, *11*, 27.
29. For sulfonamide bearing compounds, see: Kim, E. E.; Baker, C. T.; Dwyer, M. D.; Murcko, M. A.; Rao, B. G.; Tung, R. D.; Navia, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 1181.
30. Vazquez, M. L.; Bryant, M. L.; Clare, M. C.; DeCrescenzo, G. A.; Doherty, E. M.; Freskos, J. N.; Getman, D. P.; Houseman, K. A.; Julien, J. A.; Kocan, G. P.; Mueller, R. A.; Shieh, H.-S.; Stallings, W. C.; Stegeman, R. A.; Talley, J. J. *J. Med. Chem.* **1995**, *38*, 581.
31. Baker, C. T.; Salituro, F. G.; Court, J. J.; Deininger, D. D.; Kim, E. E.; Li, B.; Novak, P. M.; Rao, B. G.; Pazhanisamy, S.; Schairer, W. C.; Tung, R. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3631.
32. Salituro, F. G.; Baker, C. T.; Court, J. J.; Deininger, D. D.; Kim, E. E.; Li, B.; Novak, P. M.; Rao, B. G.; Pazhanisamy, S.; Porter, M. D.; Schairer, W. C.; Tung, R. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3637.
33. For the chemistry of hydroxyethylamine, see: Shiabata, N.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1997**, *38*, 619 and references cited therein.
34. Kaldor et al. reported that *o*-methyl-*N*-methylbenzamide exhibited a preference for an orientation in which the amide carbonyl and benzene ring were not coplanar. In this case, the *ortho*-methyl group might affected the conformation of sulfonamide, see: Kaldor, S. W.; Hammond, M.; Dressmen, B. A.; Fritz, J. E.; Crowell, T. A.; Hermann, R. A. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1385.
35. For the conformation of *N,N*-dialkyl-benzenesulfonamides, see: 29 and references cited therein.
36. For acyclic symmetric inhibitors, see: Housur, M. V., Bhat, T. N., Kempf, D. J., Baldwin, E. T., Liu, B., Gulnik, S., Wideburg, N. E., Norbeck. D. W., Appelt, K., Erickson, J. W. *J. Am. Chem. Soc.* **1994**, *116*, 847.
37. Greer, J.; Erickson; J. W.; Baldwin, J. J.; Varney, M. D. *J. Med. Chem.* **1994**, *37*, 1035.
38. For carbohydrate based symmetric inhibitors, see: Zuccarello, G.; Bouzide, A.; Kvarnström, I.; Niklasson, G.; Svensson, S. C. T.; Brisander, M.; Danielsson, H.; Nillroth, U.; Karlén, A.; Hallberg, A.; Classon, B.; Samuelsson, B. *J Org. Chem.* **1998**, *63*, 4898.
39. Alterman, M.; Björsne, M.; Mühlman, A.; Classon, B.; Kvarnström, I.; Danielson, H.; Markgren, P-O.; Nillroth, U.; Unge, T.; Hallberg, A.; Samuelsson, B. *J Med. Chem.* **1998**, *41*, 3782.
40. For cyclic compounds with C_2 symmetric structure, see: Rodgers, J. D.; Lam, P. Y.-S.; Johnson, B. L.; Wang, H.; Ko, S. S.; Seitz, S. P.; Trainor, G. L.; Anderson, P. S.; Kalbe, R. M.; Bacheler, L. T.; Cordova, B.; Garber, S.; Reid, C.; Wright, M. R.; Chang, C.-H.; Erickson-Viitanen, S. *Chemistry & Biology* **1998**, *5*, 597 and references cited therein.

41. Compounds **19**, **21**, **23**, **27**, **32**, **33**, **34**, **35** and **36** could not be separated by PTLC. They were assayed as diastereomixtures.