Studies of HIV-1 Protease Inhibitors. II. Incorporation of Four Types of Hydroxyethylene Dipeptide Isosteres at the Scissile Site of Substrate Sequences[1)]

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Human immunodeficiency virus type 1 (HIV-1) protease inhibitors containing four types of hydroxyethylene dipeptide isosteres were designed and synthesized. These inhibitors consist of eight stereoisomers of phenylalanylproline (Phe-ψ[H.E.]-Pro), four stereoisomers of phenylalanylalanine (Phe-ψ[H.E.]-Ala), and one stereoisomer each of phenylalanylglycine (Phe-ψ[H.E.]-Gly) and cyclohexylalanylalanine (Cha-ψ[H.E.]-Ala) hydroxyethylene dipeptide isosteres. For the synthesis of the latter two isosteres, a newly developed synthetic method for γ-lactone was applied. The inhibitory activities of these peptides were evaluated by cleavage assay of partially purified *gag* proteins or purified synthetic peptide. Of the inhibitors examined, compounds 2c (Z–Asn–(2*S*,3*R*,4*S*,5*S*)-Phe-ψ[H.E.]-Pro–NHBu^n; Bu^n = *n*-butyl, $K_i = 0.50\ \mu M$), 21a (Z–Asn–(2*R*,4*S*,5*S*)-Phe-ψ[H.E.]-Ala–NHBu^n, $K_i = 0.34\ \mu M$) and 23 (Z–Asn–(2*R*,4*S*,5*S*)-Cha-ψ[H.E.]-Ala–NHBu^n, $K_i = 0.46\ \mu M$) were moderately potent inhibitors. The results revealed that the alkyl substituent at C2 is essential, and the stereochemistry of the hydroxyethylene dipeptide isosteres greatly affected their inhibitory activities.

Keywords AIDS; HIV-1 protease inhibitor; hydroxyethylene dipeptide isostere; pepstatin A

The hydroxyethylene dipeptide isostere is an attractive dipeptide mimic which is stable and resembles the tetrahedral intermediate formed during hydrolysis of a peptide (Fig. 1).[2)] Furthermore, it has been found that potent aspartic protease inhibitors, especially inhibitors of renin, can be generated by introducing this hydroxyethylene isostere at the scissile site of substrates.[3)]

The protease of human immunodeficiency virus type-1 (HIV-1), the causative virus of acquired immunodeficiency syndrome (AIDS), is a member of the aspartic proteases, and it proteolytically processes huge precursor *gag* and *gag–pol* proteins to form components such as core proteins of the virus.[4)] It has been reported that deactivation of this protease by site-directed mutagenesis leads to the formation of non-infectious virions.[5)] Accordingly, HIV-1 protease inhibitors are promising candidates for a new type of anti-AIDS drug with a different mechanism from the reverse transcriptase inhibitors, such as azidothymidine (AZT), dideoxyinosine (DDI), and dideoxycytidine (DDC).[6)]

In our previous paper, we showed that 4-amino-3-hydroxy-5-phenylpentanoic acid (AHPPA) derivatives exhibited moderate inhibitory activity against HIV-1 protease.[1)] Now we report the result of a second approach in our search for inhibitors of HIV-1 protease. Peptides containing the four types of hydroxyethylene dipeptide isosteres shown in Fig. 2 were prepared and evaluated.[7)]

Chemistry The amino acid sequences of substrates of HIV-1 protease around their cleavage sites are shown in

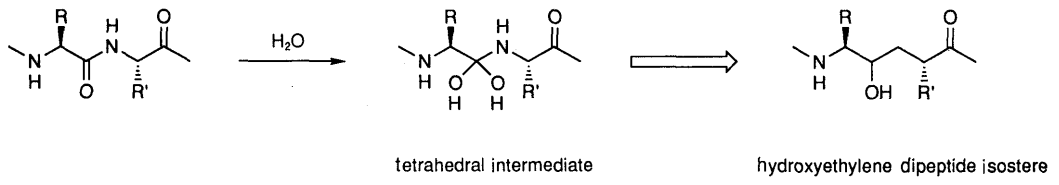
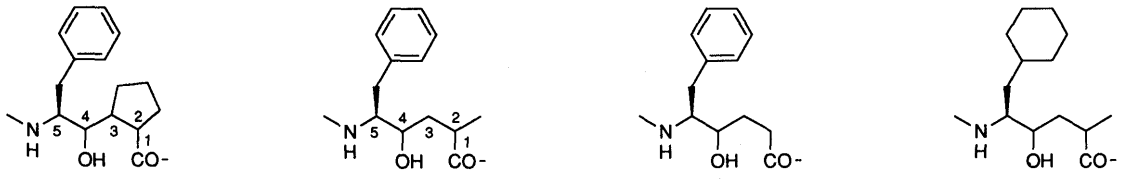
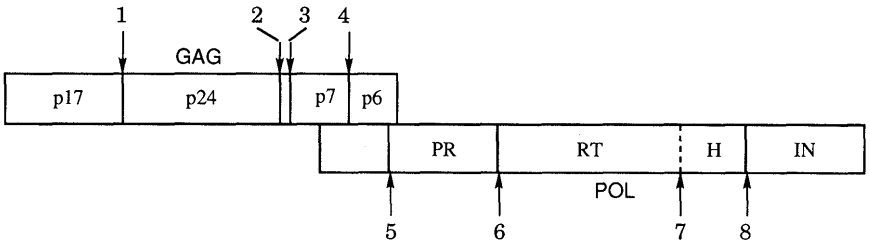


Fig. 1



I II III IV

Fig. 2



1	p17 * p24	Ser-Gln-Asn-**TYR** * **PRO**-Ile-Val-Gln
2	p24 * X	Ala-Arg-Val-**LEU** * **ALA**-Glu-Ala-Met
3	X * p7	Ala-Thr-Ile-**MET** * **MET**-Gln-Arg-Gly
4	p7 * p6	Pro-Gly-Asn-**PHE** * **LEU**-Gln-Ser-Arg
5	* PR	Ser-Phe-Asn-**PHE** * **PRO**-Gln-Ile-Thr
6	PR * RT	Thr-Leu-Asn-**PHE** * **PRO**-Ile-Ser-Pro
7	RT51* RNaseH	Ala-Glu-Thr-**PHE** * **TYR**-Val-Asp-Gly
8	RT * IN	Arg-Lys-Ile-**LEU** * **PHE**-Leu-Asp-Gly

Fig. 3. Sites of Scission of the Substrates of HIV-1 Protease

PR = protease, RT = reverse transcriptase, H = ribonuclease H, IN = integrase.

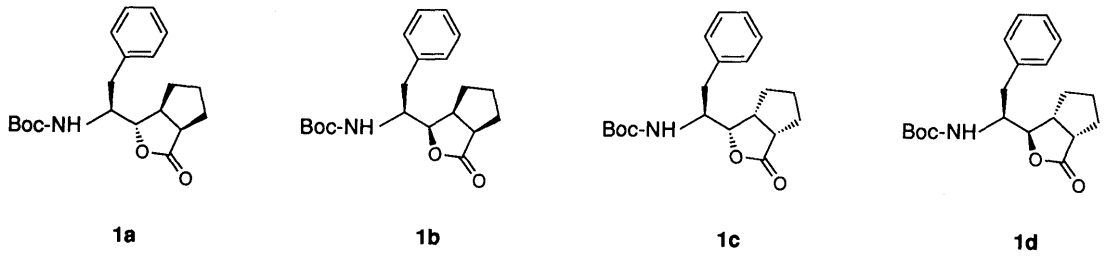


Fig. 4

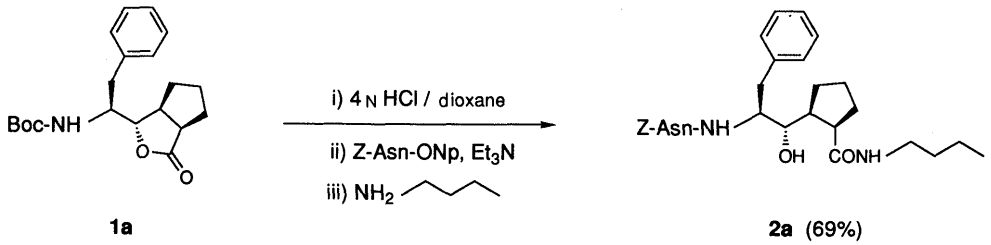
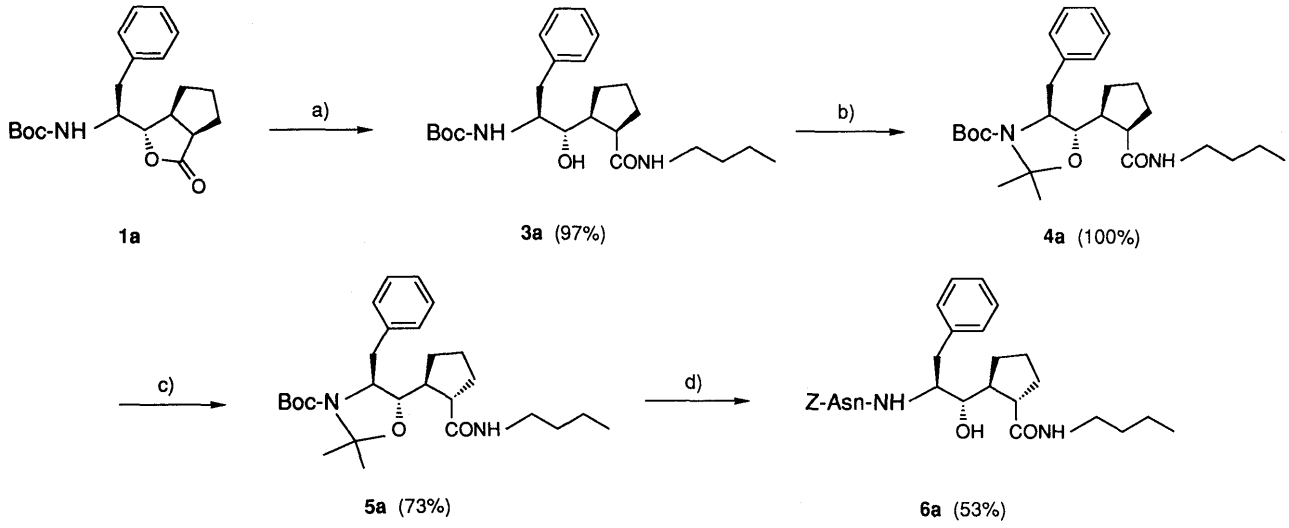


Chart 1

Fig. 3. Since there are three Tyr/Phe–Pro sequences (substrate sequences 1, 5 and 6) and the enzyme specificity is expected due to few mammalian aspartic proteases cleaving the peptide bond in front of a Pro residue,[8] peptides containing phenylalanylproline hydroxyethylene isostere (Phe-ψ[H.E.]-Pro, I in Fig. 2) were first designed. Until recently, only the pioneering work of Dreyer *et al.* on peptides containing the four stereoisomers of Phe-ψ[H.E.]-Pro had been reported.[9] Since this hydroxyethylene dipeptide isostere has four successive asymmetric carbons, sixteen stereoisomers exist. Although the stereochemistry of this isostere was expected to influence greatly the inhibitory activity, we decided to synthesize only eight of the sixteen possible stereoisomers, since the configuration at the carbon bearing the amino group should be identical with the L-phenylalanine (*S*)-configuration. In the design process, constraints were made to keep the molecular size minimal. Therefore, benzyloxycarbonyl (Z)–Asn and aminobutyl groups were introduced at the amino and carboxyl terminals of the isostere, respectively. The starting materials were the γ-lactones **1a**—**d** shown in Fig. 4; the synthesis of these γ-lactones will be reported elsewhere. Since the compounds with *cis* substituents on the cyclopentane ring were easily cyclized to form the corresponding γ-lactones under acidic conditions, **2a**—**d** were synthesized as follows: initial removal of the *tert*-butoxycarbonyl (Boc) group of the lactone **1a** by using 4 N hydrogen chloride in dioxane and coupling with Z–Asn *p*-nitrophenylester (ONp), followed by ring opening of the lactone with *n*-butylamine, afforded the objective compound **2a** (Chart 1). On the other hand, more steps were needed for the synthesis of compounds with *trans* substituents on the cyclopentane ring. Treatment of **1a** with *n*-butylamine, followed by protection of the hydroxyl and Boc-amino groups with 2-methoxypropene and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS), gave **4a**. Epimerization of the C2 carbon with potassium *tert*-butoxide led to the *N*,*O*-protected *trans* isomer **5a** in a good yield. Removal of the Boc and isopropylidene groups with 4 N hydrogen chloride in dioxane and coupling with Z–Asn–ONp afforded the desired compound **6a** (Chart 2). The other compounds **2b**—**d** and **6b**—**d** were obtained in the same way, but their



a) *n*-butylamine, room temp. b) 2-methoxypropene, PPTS, CH_2Cl_2, room temp. c) *tert*-BuOK, DMF-*tert*-BuOH, 90°C d) i) 4N HCl / dioxane, room temp. ii) Z-Asn-ONp, Et_3N, DMF, 4°C

Chart 2

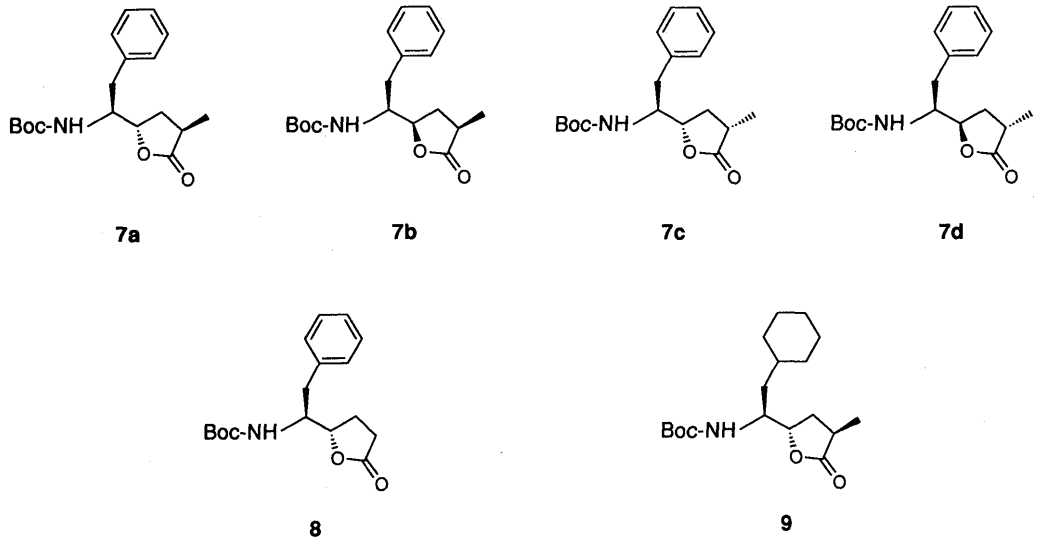
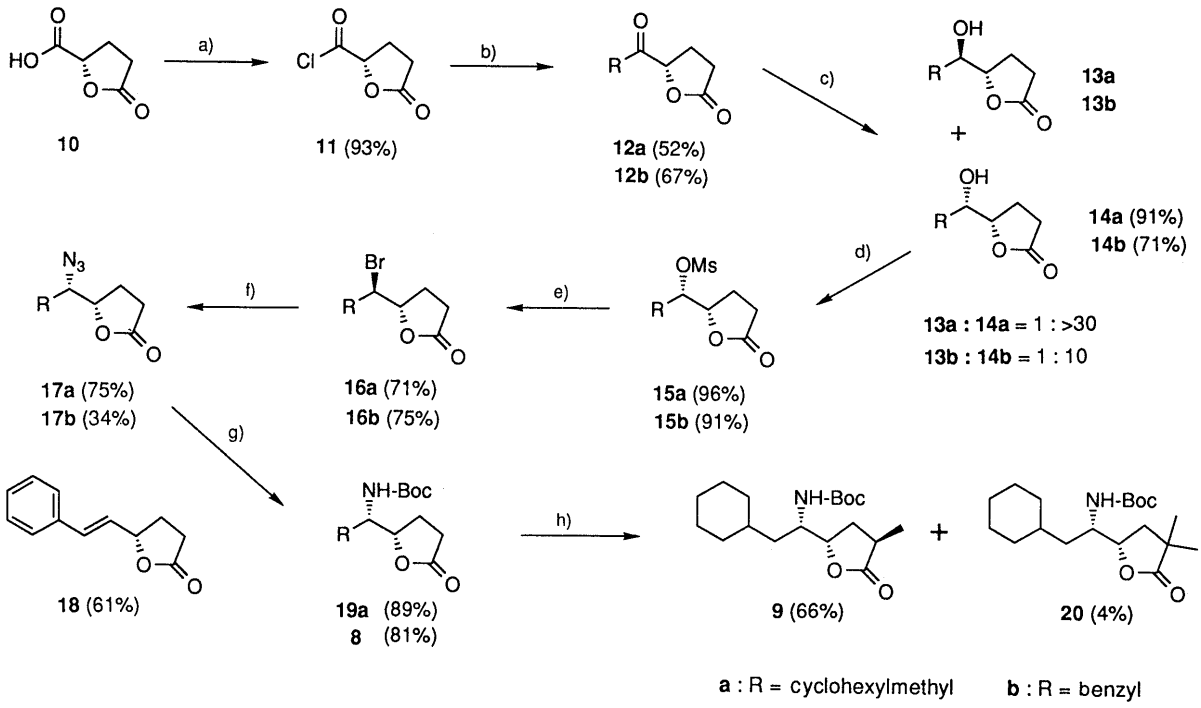


Fig. 5

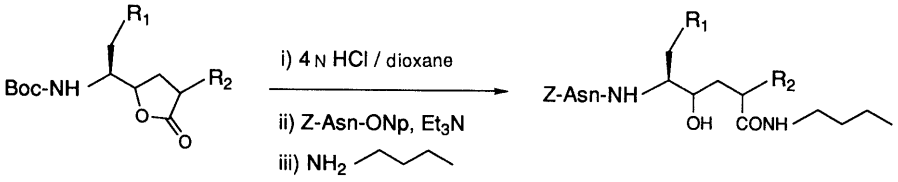
streochemistry influenced the coupling yields between Z–Asn–ONp and amino-γ-lactones, probably due to steric factors.

Peptides containing phenylalanylalanine (Phe-ψ[H.E.]-Ala, II in Fig. 2) and phenylalanylglycine (Phe-ψ[H.E.]-Gly, III in Fig. 2) hydroxyethylene dipeptide isosteres were synthesized, in order to examine the difference between cyclic and acyclic hydroxyethylene isosteres. Only half of the eight possible stereoisomers of Phe-ψ[H.E.]-Ala were prepared for the same reason as in the case of Phe-ψ[H.E.]-Pro. Only one diastereomer of Phe-ψ[H.E.]-Gly was prepared, because Dreyer *et al.* reported that Ser–Ala–Ala–(4*S*,5*S*)-Phe-ψ[H.E.]-Gly–Val–Val–OMe was about 80-fold more potent than the corresponding peptide which contains (4*R*,5*S*)-Phe-ψ[H.E.]-Gly.[9a] Furthermore, an inhibitor possessing (2*R*,4*S*,5*S*)-cyclohexylalanylalanine hydroxyethylene dipeptide isostere (Cha-ψ[H.E.]-Ala, IV in Fig. 2), which is not only a homolog of Phe-ψ[H.E.]-Ala but also an isostere of the Leu–Ala bond in substrate sequence 2, was prepared and examined. The preparation of the four γ-lactones **7a**—**d** leading to Phe-ψ[H.E.]-Ala will be reported elsewhere, together with that for Phe-ψ[H.E.]-Pro, but we disclose here our stereocontrolled synthesis of the γ-lactones **8** and **9**, leading to (4*S*,5*S*)-Phe-ψ[H.E.]-Gly and (2*R*,4*S*,5*S*)-Cha-ψ[H.E.]-Ala, respectively (Fig. 5, Chart 3).[10] Our synthesis of γ-lactones employed (*S*)-(+)-5-oxo-2-tetrahydrofurancarboxylic acid, which is readily available from the cheap L-glutamic acid, as a starting material.[11] The carboxylic acid **10** was converted into the acid chloride **11** using thionyl chloride, which was then treated with Grignard reagents to give the ketones **12a** and **12b**. Next these ketones were submitted to reduction with some reducing agents. While reduction of the ketones with sodium borohydride afforded a *ca.* 2 : 1 mixture of *anti* and *syn* alcohols, the *syn* alcohols **14a** and **14b** were diastereoselectively obtained by reducing



a) $SOCl_2$, reflux b) cyclohexylmethylmagnesium bromide or benzylmagnesium chloride, THF, -78°C c) L-Selectride®, THF, -78°C d) MsCl, Et_3N, CH_2Cl_2, 0°C e) LiBr, THF, reflux f) NaN_3, DMPU, room temp. g) H_2, Pd-C, $(Boc)_2O$, AcOEt, room temp. h) LDA, then MeI, THF, -78°C

Chart 3



7 : R_1 = Ph, R_2 = Me
a : (2*R*, 4*S*, 5*S*)
b : (2*R*, 4*R*, 5*S*)
c : (2*S*, 4*S*, 5*S*)
d : (2*S*, 4*R*, 5*S*)
8 : R_1 = Ph, R_2 = H (4*S*, 5*S*)
9 : R_1 = cyclohexyl, R_2 = Me (2*R*, 4*S*, 5*S*)

21 : R_1 = Ph, R_2 = Me
a : (2*R*, 4*S*, 5*S*)
b : (2*R*, 4*R*, 5*S*)
c : (2*S*, 4*S*, 5*S*)
d : (2*S*, 4*R*, 5*S*)
22 : R_1 = Ph, R_2 = H (4*S*, 5*S*)
23 : R_1 = cyclohexyl, R_2 = Me (2*R*, 4*S*, 5*S*)

Chart 4

the ketones with L-Selectride® (**13a** : **14a** = 1 : >30 and **13b** : **14b** = 1 : 10).[12] The configuration of the newly generated asymmetric carbon was confirmed by comparison of the spectral data with the reported values.[13] The next stage was to convert these *syn* alcohols into the desired *syn* amino γ-lactones. Mesylation of the *syn* alcohols **14a** and **14b** with mesyl chloride and triethylamine followed by two *S*N2 processes, substitution with LiBr and azidation with NaN_3, yielded the azides **17a** and **17b**, respectively. While the yield of **17a** was good, only a modest yield of **17b** was achieved, because a large amount of the elimination product **18** was produced during the treatment of **16b** with NaN_3. Catalytic hydrogenation of the azides **17a** and **17b** over Pd/C in the presence of $(Boc)_2O$ afforded the desired *N*-Boc-γ-lactones **19a** and **8**, respectively.[14] Further, deprotonation of **19a** by treatment with lithium diisopropylamide (LDA) followed by the addition of MeI gave predominantly the *trans* methylated γ-lactone. After purification by silica gel chromatography, the pure *trans* γ-lactone **9** and a small amount of the dimethyl γ-lactone **20** were obtained, but the *cis*-methylated γ-lactone could not be isolated. The structure of the *trans* methylated γ-lactone **9** was confirmed by the absence of a nuclear Overhauser effect (NOE) between the C2 and C4 protons, as NOE between the C2 and C4 protons was observed in the case of **7b** and **7c** with the *cis* relationship. Since these six γ-lactones were in hand, the objective peptides **21a—d**, **22** and **23** were prepared by ring opening of the lactone

with *n*-butylamine after coupling with Z–Asn–ONp as mentioned above (Chart 4).

Inhibitory Activity and Discussion Evaluation of the HIV-1 protease inhibitors was performed by using recombinant *gag* substrates and the protease as described in the previous report.[1] The remaining amount of the 55 kDa *gag* protein in the presence of a synthetic inhibitor was compared with the remaining amount in the presence of pepstatin A (Iva–Val–Val–Sta–Ala–Sta–OH; Iva = isovaleryl, Sta = statine, $K_i = 1.1\ \mu M$). The inhibitory activity shown in the table represents the concentration that is approximately equipotent with 1 μM pepstatin A. Furthermore, the inhibition constants (K_i) were determined for the active compounds using the partially purified protease and a synthetic substrate, Ac–Ser–Gln–Asn–Tyr–Pro–Ile–Val–NH_2.

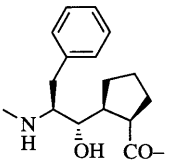
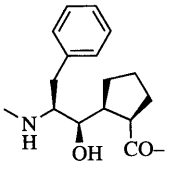
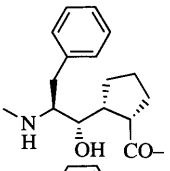
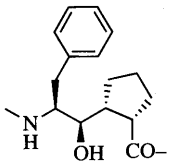
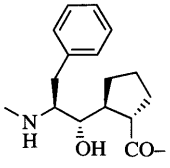
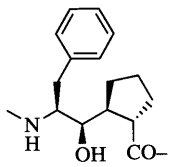
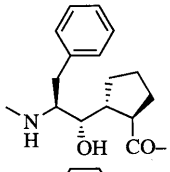
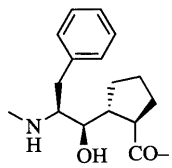
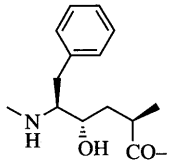
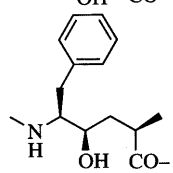
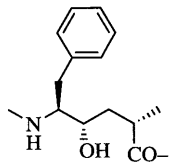
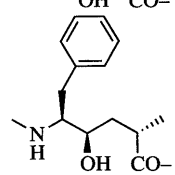
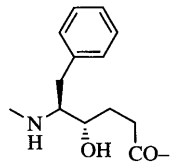
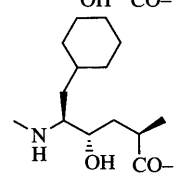
The results for the peptides synthesized here are shown in Table I. Initially, in the case of the peptides containing Phe-ψ[H.E.]-Pro, three of the eight stereoisomers were found to be potent inhibitors. Concerning the alcohol configuration, two (*S*)-diastereomers and one (*R*)-diastereomer were over 100 times more potent than their epimers, respectively (**2a** *vs.* **2b**, **2c** *vs.* **2d**, and **6b** *vs.* **6a**). To our knowledge, the latter is the first case in which (*R*)-configuration is preferred in a hydroxyethylene-type inhibitor of aspartic proteases. This fact may imply that the peptide with an (*R*)-hydroxyl group can fit the active site more easily due to the configuration of the substituents on the cyclopentane ring. Moreover, the fact that three stereoisomers are potent inhibitors suggests that HIV-1 protease has some degree of flexibility around the active center. In this series, the most potent stereoisomer is **2c** ($K_i = 0.50\ \mu M$), which has a (2*S*,3*R*,4*S*,5*S*)-configuration[7] and *cis* substituents on the cyclopentane ring. The reason why this compound has the highest potency among the eight stereoisomers is under investigation by using molecular modeling. On the other hand, Dreyer *et al.* reported four heptapeptides which correspond to our compounds **6a—d** with *trans*-substituents on the cyclopentane ring.[9a] While the (2*S*,3*S*,4*R*,5*S*)-configuration (compound **6b**)[7] gave the most potent activity among our *trans*-substituted compounds, they reported that Ser–Ala–Ala–(2*R*,3*R*,4*S*,5*S*)-Phe-ψ[H.E.]-Pro–Val–Val–OMe ($K_i = 0.50\ \mu M$), which corresponds to compound **6c** in terms of configuration, was 50 to 80 fold more potent than the other diastereomers. This inconsistency may be due to the difference in chain length.

Secondly, among the peptides containing Phe-ψ[H.E.]-Ala, the most potent of the four diastereomers was compound **21a** ($K_i = 0.34\ \mu M$) with a (2*R*,4*S*,5*S*)-configuration, which is identical with the configuration of potent inhibitors of other aspartic proteases. Nevertheless, other stereoisomers still possessed inhibitory activity. This fact contrasts with the results for Phe-ψ[H.E.]-Pro, and may reflect the flexibility of this acyclic isostere.

Peptide **22** contains Phe-ψ[H.E.]-Gly, which lacks the alkyl substituent at the C2 carbon, and it was 10-fold less potent than the Phe-ψ[H.E.]-Ala containing peptide **21a**. Moreover, compound **22** was much less potent than Ala–Ala–(4*S*,5*S*)-Phe-ψ[H.E.]-Gly–Val–Val–OMe ($K_i = 0.018\ \mu M$) reported by Dreyer *et al.*[9a] As was suggested earlier, this discrepancy may be due to our compound having a shorter backbone.[15]

TABLE I. The Inhibitory Activities of Peptides Containing Hydroxyethylene Dipeptide Isostere

Z–Asn–Phe-ψ[H.E.]-A.A.–NH

Compd.	Phe-ψ[H.E.]-A.A.	Inhibitory activity[a] (μM)	Compd.	Phe-ψ[H.E.]-A.A.	Inhibitory activity[a] (μM)
2a		1	**2b**		>100
2c		0.3 (0.50)[b]	**2d**		300
6a		>100	**6b**		1
6c		100	**6d**		100
21a		0.3 (0.34)[b]	**21b**		10
21c		3	**21d**		3
22		3	**23**		0.3 (0.46)[b]

a) Inhibitory activity is given as the concentration which is equipotent with 1 μM pepstatin A. *b*) K_i (μM).

We can summarize the results with the three types of hydroxyethylene dipeptide isosteres as follows: 1) the substituent at C2 is necessary for potent inhibitory activity (**21a** *vs.* **22**), 2) cyclization using the C2 and C3 carbons does not necessarily improve the inhibitory activity (**2a** *vs.* **21a**), 3) restriction of the peptide conformation due to cyclization clearly distinguishes between active and inactive conformations (**2a—d**, **6a—d** *vs.* **21a—d**), 4) the (*S*)-alcohol configuration is preferred (**2a**, **2c**, **21a** *vs.* **2b**, **2d**, **21b**) except for one case (**6a** *vs.* **6b**).

Finally, the peptide **23** ($K_i = 0.46\ \mu M$) with (2*R*,4*S*,5*S*)-Cha-ψ[H.E.]-Ala was found to be as potent as the peptide

21a with (2*R*,4*S*,5*S*)-Phe-ψ[H.E.]-Ala, although there are reports that replacement of the benzyl side chain with a cyclohexylmethyl group at the P_1 site led to a decrease in potency.[16]

In conclusion, we synthesized peptides containing four types of hydroxyethylene dipeptide isostere and examined their inhibitory activity against HIV-1 protease. Of the compounds examined here, **2c** with (2*S*,3*R*,4*S*,5*S*)-Phe-ψ[H.E.]-Pro,[7] **21a** with (2*R*,4*S*,5*S*)-Phe-ψ[H.E.]-Ala, and **23** with (2*R*,4*S*,5*S*)-Cha-ψ[H.E.]-Ala were moderately potent inhibitors. In particular, our results on the Phe-ψ[H.E.]-Pro containing peptides show that their stereochemistry greatly affects the inhibitory protency. Since Phe-ψ[H.E.]-Pro can be considered a conformationally restricted compound, it should be possible to identify the active conformation from these results. Further investigation to find more active inhibitors of HIV-1 protease is in progress.

Experimental

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

(1*R*,2*S*,1′*S*,2′*S*)-2-{2′-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-1′-hydroxy-3′-phenylpropyl}cyclopentane-1-carboxylic Acid *n*-Butylamide (2a) (1*R*,4*S*,5*S*,1′*S*)-4-(1′-*N*-*tert*-Butoxycarbonylamino-2′-phenyl)ethyl-3-oxobicyclo[3.3.0]octan-2-one (**1a**, 24 mg, 0.070 mmol) was added to 4 N hydrogen chloride in dioxane (2 ml), and this solution was stirred for 30 min at room temperature. The solvent was removed *in vacuo*, and the residue was evaporated with benzene. The residue was dried *in vacuo* for 2 h. This solid was dissolved in *N*,*N*-dimethylformamide (DMF, 1 ml), and then Z-Asn–ONp (40 mg, 0.10 mmol) and triethylamine (24 μl, 0.17 mmol) were added at 0 °C. The reaction mixture was stirred for 24 h at 4 °C, then the solvent was removed *in vacuo*. The residue was precipitated with 5% $NaHCO_3$, and the precipitate was washed with 1 N HCl and water. Purification by reprecipitation from diethylether afforded (1*R*,4*S*,5*S*,1′*S*)-4-{1′-(*N*-benzyloxycarbony-L-asparaginyl)amino-2′-phenyl}ethyl-3-oxobicyclo[3.3.0]octan-2-one. This compound was dissolved in *n*-butylamine (2 ml), and this solution was left for 3 d at room temperature. The solvent was removed *in vacuo*, and the remaining solid was evaporated with chloroform. Purification by precipitation from AcOEt–diethylether afforded **2a** (27 mg, 69%) as a white solid. mp 147—148 °C. $[\alpha]_D^{25}$ −37.6° (*c*=0.47, DMF). *Anal.* Calcd for $C_{31}H_{42}N_4O_6 \cdot 0.5H_2O$: C, 64.67; H, 7.53; N, 9.73. Found: C, 64.50; H, 7.41; N, 9.87. IR (KBr) 3329, 1699, 1656 cm^{-1}. ^{1}H-NMR (DMF-d_7) δ: 0.89 (t, 3H, *J*=7.3 Hz), 1.20—1.80 (m, 10H), 2.02—2.19 (m, 1H), 2.59—2.65 (m, 2H), 2.75—2.90 (m, 3H), 3.02—3.10 (m, 2H), 3.49—3.59 (m, 1H), 3.98—4.09 (m, 1H), 4.47—4.56 (m, 1H), 5.01 (d, 1H, *J*=6.4 Hz), 5.11 (s, 2H), 6.94 (br s, 1H), 7.13—7.53 (m, 14H). MS *m*/*z*: 548 (M^+ −18), 476, 440, 402, 228, 158, 108, 91, 79.

The compounds mentioned below were prepared as described above for **2a** using the corresponding starting materials instead of **1a**.

(1*R*,2*S*,1′*R*,2′*S*)-2-{2′-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-1′-hydroxy-3′-phenylpropyl}cyclopentane-1-carboxylic Acid *n*-Butylamide (2b) Yield 34%. mp 206—208 °C. $[\alpha]_D^{25}$ −36.7° (*c*=0.17, DMF). *Anal.* Calcd for $C_{31}H_{42}N_4O_6 \cdot 1.25H_2O$: C, 63.95; H, 7.61; N, 9.52. Found: C, 62.95; H, 7.19; N, 9.75. IR (KBr) 3311, 1699, 1652 cm^{-1}. ^{1}H-NMR (DMF-d_7) δ: 0.89 (t, 3H, *J*=7.3 Hz), 1.25—1.50 (m, 5H), 1.62—1.98 (m, 5H), 2.33—2.55 (m, 3H), 2.71—2.85 (m, 2H), 3.05—3.20 (m, 3H), 3.59—3.65 (m, 1H), 3.93—4.05 (m, 1H), 4.38—4.47 (m, 1H), 5.07 (ABq, 2H, *J*=9.3 Hz, Δ=0.06 ppm), 5.25 (d, 1H, *J*=2.9 Hz), 6.87 (br s, 1H), 7.09—7.45 (m, 11H), 7.55—7.65 (m, 2H), 8.13—8.18 (m, 1H). MS *m*/*z*: 548 (M^+ −18), 440, 301, 228, 158, 108, 91, 79.

(1*S*,2*R*,1′*S*,2′*S*)-2-{2′-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-1′-hydroxy-3′-phenylpropyl}cyclopentane-1-carboxylic Acid *n*-Butylamide (2c) Yield 26%. mp 225—227 °C. $[\alpha]_D^{25}$ −11.8° (*c*=0.22, DMF). *Anal.* Calcd for $C_{31}H_{42}N_4O_6 \cdot 1.5H_2O$: C, 62.71; H, 7.64; N, 9.44. Found: C, 62.85; H, 7.40; N, 9.45. IR (KBr) 3311, 1698, 1649 cm^{-1}. ^{1}H-NMR (DMF-d_7) δ: 0.89 (t, 3H, *J*=7.3 Hz), 1.25—1.50 (m, 5H), 1.61—1.91 (m, 5H), 1.99—2.11 (m, 1H), 2.58—2.70 (m, 3H), 2.81 (d, 2H, *J*=7.3 Hz), 2.95—3.09 (m, 2H), 3.64—3.71 (m, 1H), 4.17 (dd, 1H, *J*=7.8, 15.1 Hz), 4.51 (dd, 1H, *J*=7.3, 14.2 Hz), 4.99 (d, 1H, *J*=5.9 Hz), 5.10 (ABq, 2H, *J*=12.2 Hz, Δ=0.05 ppm), 6.94 (br s, 1H), 7.12—7.51 (m, 13H), 7.61—7.66 (m, 1H). MS *m*/*z*: 567 (M^+ +1), 549, 441, 301, 228, 198, 108, 91, 79.

(1*S*,2*R*,1′*R*,2′*S*)-2-{2′-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-1′-hydroxy-3′-phenylpropyl}cyclopentane-1-carboxylic Acid *n*-Butylamide (2d) Yield 65%. mp 234—236 °C. $[\alpha]_D^{25}$ −31.9° (*c*=0.30, DMF). *Anal.* Calcd for $C_{31}H_{42}N_4O_6 \cdot 0.5H_2O$: C, 64.67; H, 7.53; N, 9.73. Found: C, 64.86; H, 7.56; N, 9.83. IR (KBr) 3314, 1696, 1645 cm^{-1}. ^{1}H-NMR (DMF-d_7) δ: 0.88 (t, 3H, *J*=7.3 Hz), 1.24—1.88 (m, 10H), 2.18—2.30 (m, 1H), 2.52 (d, 2H, *J*=7.3 Hz), 2.80—2.90 (m, 1H), 3.02 (dd, 1H, *J*=3.4, 13.2 Hz), 3.13 (q, 2H, *J*=6.4 Hz), 3.58—3.68 (m, 1H), 3.99—4.11 (m, 1H), 4.38—4.48 (m, 1H), 5.07 (s, 2H), 5.16 (d, 1H, *J*=6.8 Hz), 6.90 (br s, 1H), 7.10—7.44 (m, 12H), 7.64—7.74 (m, 2H). MS *m*/*z*: 567 (M^+ +1), 548, 440, 301, 228, 198, 158, 91, 79.

(1*R*,2*S*,1′*S*,2′*S*)-2-(2′-*tert*-Butoxycarbonylamino-1′-hydroxy-3′-phenylpropyl)cyclopentane-1-carboxylic Acid *n*-Butylamide (3a) Compound **1a** (76 mg, 0.22 mmol) was dissolved in *n*-butylamine (2 ml), and this solution was left for 2 d at room temperature. The solvent was removed *in vacuo*, and the residue was extracted with AcOEt. The organic layer was washed with 5% citric acid, 5% $NaHCO_3$, and brine. Drying followed by evaporation and crystallization from *n*-hexane afforded **3a** (89 mg, 97%) as colorless crystals. mp 98—99 °C. $[\alpha]_D^{25}$ −28.7° (*c*=0.22, $CHCl_3$). *Anal.* Calcd for $C_{24}H_{38}N_2O_4$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.76; H, 8.86; N, 6.73. IR (KBr) 3329, 1686 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.94 (t, 3H, *J*=7.3 Hz), 1.19—1.89 (m, 19H), 2.02—2.19 (m, 1H), 2.73—2.87 (m, 3H), 2.99—3.18 (m, 2H), 3.50—3.64 (m, 1H), 3.73—3.81 (m, 1H), 7.10—7.28 (m, 5H). MS *m*/*z*: 419 (M^+ +1), 319, 227, 198, 154, 91, 57.

The compounds mentioned below were prepared as described above for **3a** using the corresponding starting materials instead of **1a**.

(1*R*,2*S*,1′*R*,2′*S*)-2-(2′-*tert*-Butoxycarbonylamino-1′-hydroxy-3′-phenylpropyl)cyclopentane-1-carboxylic Acid *n*-Butylamide (3b) Yield 95%. mp 123—124 °C. $[\alpha]_D^{25}$ −21.3° (*c*=0.30, $CHCl_3$). *Anal.* Calcd for $C_{24}H_{38}N_2O_4 \cdot 0.1H_2O$: C, 68.57; H, 9.16; N, 6.66. Found: C, 68.48; H, 9.14; N, 6.63. IR (KBr) 3311, 1692 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.94 (t, 3H, *J*=7.3 Hz), 1.12—1.58 (m, 14H), 1.75—1.97 (m, 5H), 2.31—2.60 (m, 2H), 2.65—2.79 (m, 1H), 3.06—3.20 (m, 3H), 3.50—3.71 (m, 2H), 7.10—7.25 (m, 5H). MS *m*/*z*: 419 (M^+ +1), 345, 301, 271, 227, 198, 154, 91, 57.

(1*S*,2*R*,1′*S*,2′*S*)-2-(2′-*tert*-Butoxycarbonylamino-1′-hydroxy-3′-phenylpropyl)cyclopentane-1-carboxylic Acid *n*-Butylamide (3c) Yield 97%. mp 123—124 °C. $[\alpha]_D^{25}$ +22.5° (*c*=0.15, $CHCl_3$). *Anal.* Calcd for $C_{24}H_{38}N_2O_4 \cdot 0.5H_2O$: C, 67.41; H, 9.19; N, 6.55. Found: C, 67.71; H, 9.17; N, 6.47. IR (KBr) 3306, 1687 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.93 (t, 3H, *J*=7.3 Hz), 1.21—1.61 (m, 14H), 1.69—1.91 (m, 5H), 1.99—2.13 (m, 1H), 2.61—2.69 (m, 1H), 2.76 (d, 2H, *J*=7.3 Hz), 2.82—2.95 (m, 1H), 3.01—3.11 (m, 1H), 3.57 (dd, 1H, *J*=1.5, 9.3 Hz), 3.78 (dd, 1H, *J*=1.5, 7.3 Hz), 7.10—7.25 (m, 5H). MS *m*/*z*: 419 (M^+ +1), 345, 327, 227, 198, 154, 91, 57.

(1*S*,2*R*,1′*R*,2′*S*)-2-(2′-*tert*-Butoxycarbonylamino-1′-hydroxy-3′-phenylpropyl)cyclopentane-1-carboxylic Acid *n*-Butylamide (3d) Yield 67%. mp 190—192 °C. $[\alpha]_D^{25}$ +6.7° (*c*=0.18, $CHCl_3$). *Anal.* Calcd for $C_{24}H_{38}N_2O_4$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.82; H, 9.16; N, 6.65. IR (KBr) 3315, 1652 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.94 (t, 3H, *J*=7.3 Hz), 1.19—2.00 (m, 19H), 2.15—2.28 (m, 1H), 2.59 (dd, 1H, *J*=10.8, 14.2 Hz), 2.82—2.90 (m, 1H), 2.98 (dd, 1H, *J*=3.4, 14.2 Hz), 3.17 (t, 2H, *J*=6.8 Hz), 3.60—3.79 (m, 2H), 7.13—7.26 (m, 5H). MS *m*/*z*: 419 (M^+ +1), 345, 301, 271, 227, 198, 154, 91, 57.

(4*S*,5*S*,1′*S*,2′*R*)-4-Benzyl-3-*N*-*tert*-butoxycarbonyl-5-(2′-*n*-butylaminocarbonyl)cyclopentyl-2,2-dimethyloxazolidine (4a) Compound **3a** (55 mg, 0.13 mmol) was dissolved in dichloromethane (CH_2Cl_2, 2 ml), and to this solution, 2-methoxypropene (63 μl, 0.66 mmol) and PPTS (3.3 mg, 0.013 mmol) were added at 0 °C. The reaction mixture was stirred for 1.5 h at room temperature, then CH_2Cl_2 and 5% $NaHCO_3$ were added, and the organic layer was washed with brine. Drying followed by evaporation and crystallization from *n*-hexane afforded **4a** (60 mg, 100%) as colorless crystals. mp 123—124 °C. $[\alpha]_D^{25}$ −1.3° (*c*=0.39, $CHCl_3$). *Anal.* Calcd for $C_{27}H_{42}N_2O_4$: C, 70.71; H, 9.23; N, 6.11. Found: C, 70.68; H, 9.26; N, 5.99. IR (KBr) 3282, 1691 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.94 (t, 3H,

J=6.8 Hz), 1.10—1.85 (m, 25H), 2.09—2.21 (m, 1H), 2.70—3.09 (m, 4H), 3.15—3.28 (m, 1H), 3.82—3.95 (m, 1H), 4.02—4.09 (m, 1H), 7.15—7.20 (m, 5H). MS *m/z*: 459 ($M^+ + 1$), 367, 267, 194, 91, 57.

The compounds mentioned below were prepared as described above for **4a** using the corresponding starting materials instead of **3a**.

(4*S*,5*R*,1′*S*,2′*R*)-4-Benzyl-3-*N*-*tert*-butoxycarbonyl-5-(2′-*n*-butylaminocarbonyl)cyclopentyl-2,2-dimethyloxazolidine (4b) Yield 82%. mp 101—102 °C. $[\alpha]_D^{25}$ −94.4° (c=0.37, $CHCl_3$). *Anal.* Calcd for $C_{27}H_{42}N_2O_4 \cdot 0.4H_2O$: C, 69.61; H, 9.26; N, 6.01. Found: C, 69.77; H, 9.07; N, 5.96. IR (KBr) 3297, 1696 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.92—0.94 (m, 3H), 1.08—2.05 (m, 25H), 2.27—2.35 (m, 1H), 2.55—2.62 (m, 1H), 2.68—2.80 (m, 1H), 2.85—2.96 (m, 1H), 3.14—3.23 (m, 2H), 4.05—4.21 (m, 2H), 7.18—7.30 (m, 5H). MS *m/z*: 458 (M^+), 367, 301, 268, 194, 91, 57.

(4*S*,5*S*,1′*R*,2′*S*)-4-Benzyl-3-*N*-*tert*-butoxycarbonyl-5-(2′-*n*-butylaminocarbonyl)cyclopentyl-2,2-dimethyloxazolidine (4c) Yield 92%. mp 130—132 °C. $[\alpha]_D^{25}$ +30.2° (c=0.18, $CHCl_3$). *Anal.* Calcd for $C_{27}H_{42}N_2O_4$: C, 70.71; H, 9.23; N, 6.11. Found: C, 71.02; H, 9.33; N, 6.00. IR (KBr) 3294, 1696 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.89—0.95 (m, 4H), 1.18—1.64 (m, 19H), 1.69—1.90 (m, 5H), 2.15—2.28 (m, 1H), 2.58—3.00 (m, 4H), 3.15—3.28 (m, 1H), 3.85—3.91 (m, 1H), 4.09—4.15 (m, 1H), 7.15—7.30 (m, 5H). MS *m/z*: 459 ($M^+ + 1$), 367, 267, 194, 91, 57.

(4*S*,5*R*,1′*R*,2′*S*)-4-Benzyl-3-*N*-*tert*-butoxycarbonyl-5-(2′-*n*-butylaminocarbonyl)cyclopentyl-2,2-dimethyloxazolidine (4d) Yield 91%. mp 117—118 °C. $[\alpha]_D^{25}$ −24.6° (c=0.34, $CHCl_3$). *Anal.* Calcd for $C_{27}H_{42}N_2O_4 \cdot 0.2H_2O$: C, 70.15; H, 9.25; N, 6.06. Found: C, 70.16; H, 9.22; N, 6.05. IR (KBr) 3356, 1703 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.93 (t, 3H, J=7.3 Hz), 1.05—1.85 (m, 25H), 2.18—2.30 (m, 1H), 2.72—3.05 (m, 4H), 3.15—3.27 (m, 1H), 3.97—4.18 (m, 2H), 7.14—7.29 (m, 5H). MS *m/z*: 459 ($M^+ + 1$), 367, 267, 194, 91, 57.

(4*S*,5*S*,1′*S*,2′*S*)-4-Benzyl-3-*N*-*tert*-butoxycarbonyl-5-(2′-*n*-butylaminocarbonyl)cyclopentyl-2,2-dimethyloxazolidine (5a) Compound **4a** (110 mg, 0.24 mmol) was dissolved in a mixture of DMF–*tert*-butanol (2 ml, 1 : 1, v/v), and then potassium *tert*-butoxide (135 mg, 1.20 mmol) was added. The reaction mixture was stirred for 4 h at 90 °C, and the solvent was removed *in vacuo*. The residue was extracted with AcOEt, and the organic layer was washed with 5% citric acid, 5% $NaHCO_3$, and brine. Drying followed by evaporation and purification by PTLC (*n*-hexane : AcOEt = 2 : 1) afforded **5a** (80 mg, 73%) as colorless crystals. mp 117—118 °C. $[\alpha]_D^{25}$ +0.8° (c=0.37, $CHCl_3$). *Anal.* Calcd for $C_{27}H_{42}N_2O_4$: C, 70.71; H, 9.23; N, 6.11. Found: C, 70.47; H, 9.33; N, 6.11. IR (KBr) 3274, 1698 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.45—0.73 (m, 1H), 0.93 (t, 3H, J=7.3 Hz), 1.23—1.69 (m, 23H), 1.72—1.87 (m, 1H), 2.28—2.53 (m, 2H), 2.68—2.91 (m, 1H), 3.05—3.18 (m, 3H), 3.65—3.75 (m, 1H), 3.78—3.92 (m, 1H), 7.18—7.34 (m, 5H). MS *m/z*: 459 ($M^+ + 1$), 367, 300, 267, 133, 91, 57.

The compounds mentioned below were prepared as described above for **5a** using the corresponding starting materials instead of **4a**.

(4*S*,5*R*,1′*S*,2′*S*)-4-Benzyl-3-*N*-*tert*-butoxycarbonyl-5-(2′-*n*-butylaminocarbonyl)cyclopentyl-2,2-dimethyloxazolidine (5b) Yield 45%. mp 161—162 °C. $[\alpha]_D^{25}$ −8.3° (c=0.29, $CHCl_3$). *Anal.* Calcd for $C_{27}H_{42}N_2O_4 \cdot 0.2H_2O$: C, 70.15; H, 9.25; N, 6.06. Found: C, 70.18; H, 9.27; N, 5.99. IR (KBr) 3288, 1696 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.94 (t, 3H, J=7.3 Hz), 1.01 (s, 6H), 1.25—1.81 (m, 17H), 1.94—2.06 (m, 2H), 2.39—2.48 (m, 1H), 2.50—2.63 (m, 2H), 2.79 (dd, 1H, J=2.9, 13.2 Hz), 3.18—3.26 (m, 1H), 3.84 (dd, 1H, J=4.4, 9.5 Hz), 4.13—4.24 (m, 1H), 7.11—7.28 (m, 5H). MS *m/z*: 459 ($M^+ + 1$), 367, 267, 91, 57.

(4*S*,5*S*,1′*R*,2′*R*)-4-Benzyl-3-*N*-*tert*-butoxycarbonyl-5-(2′-*n*-butylaminocarbonyl)cyclopentyl-2,2-dimethyloxazolidine (5c) Yield 74%. mp 101—102 °C. $[\alpha]_D^{25}$ −35.9° (c=0.11, $CHCl_3$). *Anal.* Calcd for $C_{27}H_{42}N_2O_4 \cdot 0.2H_2O$: C, 70.15; H, 9.25; N, 6.06. Found: C, 70.19; H, 9.12; N, 6.01. IR (KBr) 3275, 1695 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.95 (t, 3H, J=7.3 Hz), 1.22—1.84 (m, 25H), 2.26—2.39 (m, 1H), 2.82—3.22 (m, 4H), 3.72—3.90 (m, 2H), 7.14—7.29 (m, 5H). MS *m/z*: 459 ($M^+ + 1$), 367, 194, 91, 57.

(4*S*,5*R*,1′*R*,2′*R*)-4-Benzyl-3-*N*-*tert*-butoxycarbonyl-5-(2′-*n*-butylaminocarbonyl)cyclopentyl-2,2-dimethyloxazolidine (5d) Yield 53%. mp 116—117 °C. $[\alpha]_D^{25}$ −42.5° (c=0.88, $CHCl_3$). *Anal.* Calcd for $C_{27}H_{42}N_2O_4 \cdot 0.4H_2O$: C, 69.61; H, 9.26; N, 6.01. Found: C, 69.63; H, 9.06; N, 6.06. IR (KBr) 3303, 1686 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.96 (t, 3H, J=7.3 Hz), 0.99—1.89 (m, 25H), 2.41—2.53 (m, 1H), 2.73—2.94 (m, 2H), 3.03—3.11 (m, 1H), 3.79—3.87 (m, 1H), 4.11—4.21 (m, 1H), 7.13—7.32 (m, 5H). MS *m/z*: 459 ($M^+ + 1$), 367, 267, 194, 91, 57.

(1*S*,2*S*,1′*S*,2′*S*)-2-{2′-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-1′-hydroxy-3′-phenylpropyl}cyclopentane-1-carboxylic Acid *n*-Butylamide (6a) Compound **5a** (46 mg, 0.10 mmol) was added to 4 N hydrogen chloride in dioxane (2 ml), and the solution was stirred for 30 min at room temperature. The solvent was removed *in vacuo*, and the residue was evaporated with benzene. The residue was dried *in vacuo* for 2 h. This solid was dissolved in DMF (1 ml), and then Z–Asn–ONp (58 mg, 0.15 mmol) and triethylamine (35 μl, 0.25 mmol) were added at 0 °C. The reaction mixture was stirred for 24 h at 4 °C, then the solvent was removed *in vacuo*. The residue was precipitated with 5% $NaHCO_3$, and the precipitate was washed with 1 N HCl and water. Purification by reprecipitation from AcOEt afforded **6a** (30 mg, 53%) as a white solid. mp 206—207 °C. $[\alpha]_D^{25}$ −9.2° (c=0.25, DMF). *Anal.* Calcd for $C_{31}H_{42}N_4O_6 \cdot 0.5H_2O$: C, 64.67; H, 7.53; N, 9.73. Found: C, 64.53; H, 7.23; N, 9.65. IR (KBr) 3312, 1691, 1662 cm^{-1}. ^{1}H-NMR (DMF-d_7) δ: 0.87 (t, 3H, J=7.3 Hz), 0.95—1.11 (m, 1H), 1.25—1.55 (m, 6H), 1.70—1.83 (m, 3H), 2.25—2.35 (m, 1H), 2.50—2.65 (m, 3H), 2.70—2.90 (m, 2H), 3.06—3.21 (m, 2H), 3.24—3.34 (m, 1H), 4.05—4.17 (m, 1H), 4.46—4.57 (m, 1H), 5.11 (s, 2H), 5.44 (d, 1H, J=5.4 Hz), 6.93 (br s, 1H), 7.14—7.46 (m, 11H), 7.53—7.58 (m, 2H), 7.62—7.68 (m, 1H). MS *m/z*: 549 ($M^+ - 17$), 458, 198, 168, 108, 91.

The compounds mentioned below were prepared as described above for **6a** using the corresponding starting materials instead of **5a**.

(1*S*,2*S*,1′*R*,2′*S*)-2-{2′-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-1′-hydroxy-3′-phenylpropyl}cyclopentane-1-carboxylic Acid *n*-Butylamide (6b) Yield 81%. mp 230—232 °C. $[\alpha]_D^{25}$ −21.3° (c=0.14, DMF). *Anal.* Calcd for $C_{31}H_{42}N_4O_6 \cdot 0.5H_2O$: C, 64.67; H, 7.53; N, 9.73. Found: C, 64.61; H, 7.23; N, 9.77. IR (KBr) 3327, 1696, 1654 cm^{-1}. ^{1}H-NMR (DMF-d_7) δ: 0.88 (t, 3H, J=7.3 Hz), 1.25—1.91 (m, 10H), 2.45—2.75 (m, 5H), 3.06—3.31 (m, 3H), 3.45—3.52 (m, 1H), 3.95—4.05 (m, 1H), 4.38—4.48 (m, 1H), 4.89 (d, 1H, J=5.9 Hz), 5.09 (d, 2H, J=2.4 Hz), 6.92 (br s, 1H), 7.09—7.41 (m, 10H), 7.51 (br s, 1H), 7.65—7.77 (m, 3H). MS *m/z*: 566 (M^+), 549, 458, 369, 301, 198, 168, 108, 91.

(1*R*,2*R*,1′*S*,2′*S*)-2-{2′-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-1′-hydroxy-3′-phenylpropyl}cyclopentane-1-carboxylic Acid *n*-Butylamide (6c) Yield 53%. mp 235—237 °C. $[\alpha]_D^{25}$ −47.6° (c=0.47, DMF). *Anal.* Calcd for $C_{31}H_{42}N_4O_6 \cdot 0.2H_2O$: C, 65.29; H, 7.49; N, 9.83. Found: C, 65.14; H, 7.47; N, 9.72. IR (KBr) 3317, 1691, 1666 cm^{-1}. ^{1}H-NMR (DMF-d_7) δ: 0.88 (t, 3H, J=7.3 Hz), 1.23—1.73 (m, 10H), 2.25—2.37 (m, 1H), 2.48—2.69 (m, 3H), 2.70—2.90 (m, 2H), 3.05—3.17 (m, 2H), 3.45—3.55 (m, 1H), 4.01—4.11 (m, 1H), 4.44—4.53 (m, 1H), 4.97 (d, 1H, J=4.9 Hz), 5.09 (s, 2H), 6.94 (br s, 1H), 7.13—7.41 (m, 10H), 7.52—7.64 (m, 4H). MS *m/z*: 549 ($M^+ - 17$), 458, 369, 301, 253, 198, 168, 108, 91.

(1*R*,2*R*,1′*R*,2′*S*)-2-{2′-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-1′-hydroxy-3′-phenylpropyl}cyclopentane-1-carboxylic Acid *n*-Butylamide (6d) Yield 85%. mp 224—226 °C. $[\alpha]_D^{25}$ −68.4° (c=0.31, DMF). *Anal.* Calcd for $C_{31}H_{42}N_4O_6 \cdot 0.8H_2O$: C, 64.07; H, 7.56; N, 9.64. Found: C, 63.80; H, 7.23; N, 9.60. IR (KBr) 3309, 1692, 1655 cm^{-1}. ^{1}H-NMR (DMF-d_7) δ: 0.89 (t, 3H, J=7.3 Hz), 1.28—1.92 (m, 10H), 2.28—2.40 (m, 1H), 2.48—2.81 (m, 4H), 2.89—2.99 (m, 1H), 3.10—3.19 (m, 2H), 3.45—3.55 (m, 1H), 4.01—4.11 (m, 1H), 4.42—4.50 (m, 1H), 5.08 (s, 2H), 5.47 (d, 1H, J=4.9 Hz), 6.91 (br s, 1H), 7.11—7.40 (m, 11H), 7.51 (br s, 1H), 7.62—7.67 (m, 1H), 7.85 (br d, 1H, J=8.8 Hz). MS *m/z*: 549 ($M^+ - 17$), 458, 367, 301, 198, 168, 108, 91.

(*S*)-γ-Butyrolactone-γ-carboxylic Acid Chloride (11) A mixture of (*S*)-5-oxo-2-tetrahydrofurancarboxylic acid **10** (10.0 g, 76.9 mmol) and thionyl chloride (18.3 g, 0.15 mol) was refluxed for 2 h and left overnight at room temperature. Excess thionyl chloride was removed *in vacuo* and the residue was distilled, to afford **11** (10.6 g, 93%) as a colorless oil. bp 122—125 °C (10 mmHg).

(*S*)-5-(2′-Cyclohexyl-1′-oxoethyl)dihydrofuran-2(3*H*)-one (12a) A solution of cyclohexylmagnesium bromide prepared from magnesium (2.13 g, 87.6 mmol) and cyclohexyl bromide (9.16 ml, 65.6 mmol) in tetrahydrofuran (THF, 40 ml) was added to a solution of compound **11** (6.50 g, 43.8 mmol) in THF (30 ml) at −78 °C for 10 min. The reaction mixture was stirred at the same temperature for 30 min, and then quenched by the addition of saturated ammonium chloride solution. After acidification with 1 N HCl, AcOEt was added to this mixture, and the organic layer was washed with 5% $NaHCO_3$ and brine. Drying followed by evaporation and purification by silica gel chromatography (*n*-hexane : AcOEt = 4 : 1) afforded **12a** (4.82 g, 52%) as colorless crystals. mp 56—58 °C. $[\alpha]_D^{20}$ +21.3° (c=1, MeOH). *Anal.* Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.64; H, 8.32. IR (KBr) 1774, 1724 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.86—1.37 (m, 5H), 1.62—1.74 (m, 5H), 1.81—1.96 (m, 1H), 2.16—2.29 (m, 1H), 2.38—2.56 (m, 5H), 4.76—4.82 (m, 1H). MS *m/z*: 210 (M^+), 125, 97, 55.

(*S*)-5-(1′-Oxo-2′-phenylethyl)dihydrofuran-2(3*H*)-one (12b) The title compound **12b** was prepared as described above for **12a** using benzylmagnesium chloride instead of cyclohexylmagnesium bromide, to yield colorless crystals (2.36 g, 67%). mp 53—54 °C. $[\alpha]_D^{25}$ +15.7° (c=0.99, $CHCl_3$). *Anal.* Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.74;

H, 6.20. IR (KBr) 1785, 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.07—2.56 (m, 4H), 3.91 (s, 2H), 4.86—4.92 (m, 1H), 7.20—7.38 (m, 5H). MS *m/z*: 204 (M^+), 119, 91, 85.

(5*S*,1′*S*)-5-(2′-Cyclohexyl-1′-hydroxyethyl)dihydrofuran-2(3*H*)-one (14a) A solution of compound **12a** (10.0 g, 47.6 mmol) in THF (100 ml) was treated with 1.0 M lithium tri-*sec*-butylborohydride in THF (L-Selectride®, 95.1 ml, 95.1 mmol) at −78 °C under a nitrogen atmosphere. The mixture was stirred for 30 min at the same temperature, and then the reaction was quenched by the addition of saturated ammonium chloride solution. To this mixture was added AcOEt, and the organic layer was washed with brine. Drying followed by evaporation and purification by silica gel chromatography (*n*-hexane : AcOEt = 3 : 1) afforded **14a** (9.21 g, 91%) as colorless crystals. The diastereoselectivity of this reaction was determined to be **14a** : **13a** = > 30 : 1, because **13a** could not be detected by ^{1}H-NMR or high-performance liquid chromatography (HPLC) analysis (column, Senshu Pak Silica-1251-N 4.6 i.d. × 250 mm; eluent, 15 : 85 iso-PrOH–*n*-hexane mixture; flow rate 1.0 ml/min; t_R of **14a**, 6.8 min; t_R of **13a**, 6.3 min). mp 71—72 °C. $[\alpha]_D^{20}$ +16.0° (*c* = 1, MeOH). *Anal.* Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.91; H, 9.45. IR (KBr) 1794 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.78—1.35 (m, 6H), 1.44—1.84 (m, 6H), 1.94 (d, 1H, *J* = 6.4 Hz), 2.02—2.31 (m, 2H), 2.47—2.69 (m, 2H), 3.64—3.74 (m, 1H), 4.38 (dt, 1H, *J* = 4.9, 7.3 Hz). MS *m/z*: 212 (M^+), 109, 86.

(5*S*,1′*S*)-5-(1′-Hydroxy-2′-phenylethyl)dihydrofuran-2(3*H*)-one (14b) The title compound **14b** was prepared as described above for **14a** using **12b** (204 mg, 1.00 mmol) instead of **12a**, to yield a colorless oil (146 mg, 71%). The diastereoselectivity of this reaction was determined to be **14b** : **13b** = 10 : 1 by HPLC analysis (column, Senshu Pak Silica-1251-N 4.6 i.d. × 250 mm; eluent, 40 : 60 AcOEt–*n*-hexane mixture; flow rate 2.0 ml/min; t_R of **14b**, 7.0 min; t_R of **13b**, 6.6 min). $[\alpha]_D^{25}$ +61.7° (*c* = 0.69, $CHCl_3$). *Anal.* Calcd for $C_{12}H_{14}O_3 \cdot 0.1H_2O$: C, 69.28; H, 6.88. Found: C, 69.23; H, 7.01. IR (film) 3436, 1769 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.05—2.29 (m, 3H), 2.43—2.72 (m, 2H), 2.92 (d, 2H, *J* = 7.3 Hz), 3.83 (dt, 1H, *J* = 3.3, 7.3 Hz), 4.45 (dt, 1H, *J* = 3.3, 7.3 Hz), 7.22—7.36 (m, 5H). MS *m/z*: 206 (M^+), 188, 121, 92, 86.

(5*S*,1′*S*)-5-(2′-Cyclohexyl-1′-methanesulfonyloxyethyl)dihydrofuran-2(3*H*)-one (15a) Methanesulfonyl chloride (0.29 ml, 3.75 mmol) was added to a solution of compound **14a** (725 mg, 3.42 mmol) and triethylamine (0.71 ml, 5.09 mmol) in CH_2Cl_2 (20 ml) at 0 °C under a nitrogen atmosphere, and the reaction mixture was stirred for 2 h at the same temperature. Then CH_2Cl_2 was added, and the organic layer was separated and washed with 5% citric acid, 5% $NaHCO_3$, and brine. Drying followed by evaporation and purification by silica gel chromatography (*n*-hexane : AcOEt = 4 : 1) afforded **15a** (950 mg, 96%) as colorless crystals. mp 72—74 °C. $[\alpha]_D^{20}$ +2.6° (*c* = 1, MeOH). *Anal.* Calcd for $C_{13}H_{22}O_5S$: C, 53.77; H, 7.64; S, 11.04. Found: C, 53.90; H, 7.35; S, 11.21. IR (KBr) 1797, 1343, 1170 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.85—1.37 (m, 5H), 1.42—1.77 (m, 7H), 1.82—1.94 (m, 1H), 2.05—2.20 (m, 1H), 2.29—2.41 (m, 1H), 2.46—2.73 (m, 2H), 3.12 (s, 3H), 4.59 (dt, 1H, *J* = 5.4, 7.3 Hz), 4.78—4.86 (m, 1H). MS *m/z*: 291 ($M^+ + 1$), 109, 85.

(5*S*,1′*S*)-5-(1′-Methanesulfonyloxy-2′-phenylethyl)dihydrofuran-2(3*H*)-one (15b) The title compound **15b** was prepared as described above for **15a** using **14b** (108 mg, 0.52 mmol) instead of **14a** to yield a colorless oil (135 mg, 91%). $[\alpha]_D^{25}$ −11.8° (*c* = 0.74, $CHCl_3$). *Anal.* Calcd for $C_{13}H_{16}O_5S \cdot 0.5H_2O$: C, 53.23; H, 5.84; S, 10.93. Found: C, 52.94; H, 5.66; S, 10.84. IR (film) 1781, 1355, 1174 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.20—2.80 (m, 7H), 3.16 (d, 2H, *J* = 7.9 Hz), 4.60 (ddd, 1H, *J* = 2.6, 5.9, 7.9 Hz), 4.93 (dt, 1H, *J* = 2.6, 7.3 Hz), 7.25—7.38 (m, 5H). MS *m/z*: 284 (M^+), 188, 160, 91, 85.

(5*S*,1′*R*)-5-(1′-Bromo-2′-cyclohexylethyl)dihydrofuran-2(3*H*)-one (16a) Lithium bromide (2.69 g, 31.0 mmol) was added to a solution of compound **15a** (900 mg, 3.10 mmol) in THF (10 ml), and the reaction mixture was refluxed for 8 h under a nitrogen atmosphere. The solvent was removed *in vacuo*, and the residue was extracted with AcOEt. The organic layer was washed with brine. Drying followed by evaporation and purification by silica gel chromatography (*n*-hexane : AcOEt = 5 : 1) afforded **16a** (601 mg, 71%) as colorless crystals. mp 80—82 °C. $[\alpha]_D^{20}$ +63.5° (*c* = 1, MeOH). *Anal.* Calcd for $C_{12}H_{19}BrO_2$: C, 52.38; H, 6.96; Br, 29.04. Found: C, 52.68; H, 6.84; Br, 28.75. IR (KBr) 1777 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.77—1.36 (m, 5H), 1.54—1.83 (m, 8H), 2.09—2.26 (m, 1H), 2.36—2.71 (m, 3H), 4.17 (ddd, 1H, *J* = 4.4, 6.4, 10.3 Hz), 4.59 (q, 1H, *J* = 6.4 Hz). MS *m/z*: 274, 113, 85.

(5*S*,1′*R*)-5-(1′-Bromo-2′-phenylethyl)dihydrofuran-2(3*H*)-one (16b) The title compound **16b** was prepared as described above for **16a** using **15b** (90 mg, 0.32 mmol) instead of **15a**, to yield colorless crystals (64 mg, 75%). mp 74—76 °C. $[\alpha]_D^{25}$ +15.0° (*c* = 1.18, $CHCl_3$). *Anal.* Calcd for $C_{12}H_{13}BrO_2$: C, 53.55; H, 4.87; Br, 29.69. Found: C, 53.32; H, 4.82; Br, 29.91. IR (KBr) 1773 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.12—2.30 (m,1H), 2.38—2.73 (m, 3H), 3.16 (dd, 1H, *J* = 8.3, 14.7 Hz), 3.36 (dd, 1H, *J* = 4.9, 14.7 Hz), 4.28 (ddd, 1H, *J* = 4.9, 6.8, 8.3 Hz), 4.50 (q, 1H, *J* = 6.8 Hz), 7.21—7.38 (m, 5H). MS *m/z*: 268, 129, 91, 85.

(5*S*,1′*S*)-5-(1′-Azido-2′-cyclohexylethyl)dihydrofuran-2(3*H*)-one (17a) Sodium azide (247 mg, 3.80 mmol) was added to a solution of compound **16a** (920 mg, 3.17 mmol) in *N*,*N*′-dimethylpropyleneurea (DMPU, 5 ml), and the reaction mixture was stirred for 5 d at room temperature under a nitrogen atmosphere. The mixture was poured into ice water, and the water layer was extracted with diethylether. Drying followed by evaporation and purification by silica gel chromatography (*n*-hexane : AcOEt = 4 : 1) afforded **17a** (564 mg, 75%) as a colorless oil. $[\alpha]_D^{20}$ −13.8° (*c* = 1, MeOH). *Anal.* Calcd for $C_{12}H_{19}N_3O_2$: C, 60.74; H, 8.07; N, 17.71. Found: C, 60.53; H, 7.94; N, 17.70. IR ($CHCl_3$) 2100, 1780 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.83—1.82 (m, 13H), 2.01—2.17 (m, 1H), 2.23—2.37 (m, 1H), 2.46—2.72 (m, 2H), 3.41 (dt, 1H, *J* = 4.0, 9.9 Hz), 4.49 (dt, 1H, *J* = 4.0, 7.3 Hz). MS *m/z*: 238 ($M^+ + 1$), 124, 85, 55.

(5*S*,1′*S*)-5-(1′-Azido-2′-phenylethyl)dihydrofuran-2(3*H*)-one (17b) The title compound **17b** was prepared as described above for **17a** using **16b** (1.49 g, 5.54 mmol) instead of **16a**, to yield a colorless oil (430 mg, 34%) along with the elimination product **18** (640 mg, 61%). Further purification of **17b** by HPLC (column, Chemcosorb 7CN 10 i.d. × 250 mm; eluent, 7 : 93 iso-PrOH–*n*-hexane mixture; flow rate 4.0 ml/min; t_R of **17b**, 32 min), to remove a small amount of **18**, gave analytical samples. **17b**: $[\alpha]_D^{25}$ +61.4° (*c* = 0.17, $CHCl_3$). *Anal.* Calcd for $C_{12}H_{13}N_3O_2 \cdot 0.1C_3H_8O$: C, 62.26; H, 5.86; N, 17.71. Found: C, 62.34; H, 6.12; N, 17.78. IR (film) 2111, 1779 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.10—2.45 (m, 2H), 2.56—2.77 (m, 2H), 3.08 (d, 2H, *J* = 7.3 Hz), 3.58 (dt, 1H, *J* = 3.3, 7.3 Hz), 4.48 (dt, 1H, *J* = 3.3, 6.6 Hz), 7.27—7.40 (m, 5H). MS *m/z*: 232 ($M^+ + 1$), 188, 118, 91, 85. **18**: mp 104—106 °C. *Anal.* Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.60; H, 6.52. IR (KBr) 1767 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.01—2.18 (m, 1H), 2.41—2.68 (m, 3H), 5.05—5.17 (m, 1H), 6.20 (dd, 1H, *J* = 6.6, 15.8 Hz), 6.68 (d, 1H, *J* = 15.8 Hz), 7.24—7.41 (m, 5H). MS *m/z*: 188 (M^+), 160, 146, 133, 104.

(5*S*,1′*S*)-5-(1′-*tert*-Butoxycarbonylamino-2′-cyclohexylethyl)dihydrofuran-2(3*H*)-one (19a) A suspension of 10% palladium on carbon (20 mg) in AcOEt was stirred for 1 h at toom temperature under a hydrogen atmosphere. To this suspension was added a solution of compound **17a** (202 mg, 0.85 mmol) and di-*tert*-butyl dicarbonate (223 mg, 1.02 mmol) in AcOEt (2 ml), and the reaction mixture was stirred for 3 h under a hydrogen atmosphere. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (*n*-hexane : AcOEt = 4 : 1), to afford **19a** (237 mg, 89%) as colorless crystals. mp 62—64 °C. $[\alpha]_D^{20}$ −28.6° (*c* = 1, MeOH). *Anal.* Calcd for $C_{17}H_{29}NO_4$: C, 65.57; H, 9.39; N, 4.50. Found: C, 65.42; H, 9.37; N, 4.46. IR ($CHCl_3$) 1770, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.78—1.85 (m, 22H), 2.08—2.30 (m, 2H), 2.49—2.56 (m, 2H), 3.83—3.95 (m, 1H), 4.39—4.55 (m, 2H). MS *m/z*: 311 (M^+), 170, 126, 57.

(5*S*,1′*S*)-5-(1′-*tert*-Butoxycarbonylamino-2′-phenylethyl)dihydrofuran-2(3*H*)-one (8) The title compound **8** was prepared as described above for **19a** using **17b** (400 mg, 1.73 mmol) instead of **17a**, to yield colorless crystals (410 mg, 81%). mp 94—95 °C. $[\alpha]_D^{25}$ +1.2° (*c* = 0.85, $CHCl_3$). *Anal.* Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.77; H, 7.40; N, 4.52. IR (KBr) 1775, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (s, 9H), 2.07—2.18 (m, 2H), 2.47—2.57 (m, 2H), 2.88 (dd, 1H, *J* = 8.8, 13.5 Hz), 2.96 (dd, 1H, *J* = 7.2, 13.5 Hz), 4.01 (q, 1H, *J* = 8.6 Hz), 4.47 (dt, 1H, *J* = 1.2, 7.4 Hz), 4.61 (br d, 1H, *J* = 9.7 Hz), 7.20—7.35 (m, 5H). MS *m/z*: 249, 214, 120, 114, 91, 57.

(3*R*,5*S*,1′*S*)-5-(1′-*tert*-Butoxycarbonylamino-2′-cyclohexylethyl)-3-methyldihydrofuran-2(3*H*)-one (9) A solution of diisopropylamine (0.99 ml, 7.07 mmol) in THF (20 ml) was treated with 2.5 M *n*-butyllithium in *n*-hexane (2.83 ml, 7.07 mmol) at −78 °C under a nitrogen atmosphere, and this solution was stirred for 30 min at the same temperature. A solution of compound **19a** (1.00 g, 3.20 mmol) in THF (10 ml) was added to the above solution, and the reaction mixture was stirred for another 30 min at −78 °C. Methyl iodide (0.44 ml, 7.07 mmol) was added, and the whole was stirred for 1.5 h at the same temperature. The reaction was quenched by the addition of saturated ammonium chloride solution, and the water layer was extracted with AcOEt. The organic layer was washed with 5% citric acid, 5% $NaHCO_3$, and brine. Drying followed by evaporation and purification by silica gel chromatography (*n*-hexane : AcOEt = 8 : 1) afforded the desired **9** (690 mg, 66%) and the dimethylated γ-lactone **20** (42 mg, 4%) as more and less polar crystals, respectively. **9**: *Rf* 0.57 (*n*-hexane : AcOEt = 5 : 2), mp 80—82 °C. $[\alpha]_D^{20}$ −24.5° (*c* = 1, $CHCl_3$).

Anal. Calcd for $C_{18}H_{31}NO_4$: C, 66.43; H, 9.60; N, 4.30. Found: C, 66.24; H, 9.67; N, 4.38. IR (KBr) 1769, 1757, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.76—1.97 (m, 26H), 2.35—2.47 (m, 1H), 2.62—2.77 (m, 1H), 3.81—3.93 (m, 1H), 4.34 (br d, 1H, J=9.5 Hz), 4.44—4.52 (m, 1H). MS *m/z*: 325 (M^+), 226, 170, 126. **20**: *Rf* 0.67 (*n*-hexane : AcOEt = 5 : 2). mp 103—105 °C. *Anal.* Calcd for $C_{19}H_{33}NO_4$: C, 67.22; H, 9.80; N, 4.13. Found: C, 66.99; H, 9.71; N, 4.09. ^{1}H-NMR ($CDCl_3$) δ: 0.76—1.88 (m, 28H), 1.93 (dd, 1H, J=9.9, 13.2 Hz), 2.03 (dd, 1H, J=6.6, 13.2 Hz), 3.78—3.88 (m, 1H), 4.38—4.47 (m, 2H). MS *m/z*: 339 (M^+), 226, 170, 126, 57.

The compounds mentioned below were prepared as described above for **2a** using the corresponding starting materials among **7a—d**, **8**, and **9**, instead of **1a**.

(2*R*,4*S*,5*S*)-5-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-4-hydroxy-2-methyl-6-phenylhexanoic Acid *n*-Butylamide (21a) Yield 69%. mp 227—229 °C. $[\alpha]_D^{25}$ −42.1° (*c*=0.52, DMF). *Anal.* Calcd for $C_{29}H_{40}N_4O_6$: C, 64.42; H, 7.46; N, 10.36. Found: C, 64.09; H, 7.48; N, 10.25. IR (KBr) 3316, 1693, 1665 cm^{-1}. ^{1}H-NMR (DMF-d_7) δ: 0.87 (t, 3H, J=7.3 Hz), 0.99 (d, 3H, J=6.8 Hz), 1.23—1.45 (m, 5H), 1.63—1.73 (m, 1H), 2.51—2.81 (m, 4H), 2.85—2.95 (m, 1H), 3.04—3.12 (m, 2H), 3.54—3.63 (m, 1H), 3.93—4.02 (m, 1H), 4.45—4.55 (m, 1H), 5.04 (d, 1H, J=5.4 Hz), 5.10 (s, 2H), 6.94 (br s, 1H), 7.13—7.42 (m, 11H), 7.50—7.60 (m, 3H). MS *m/z*: 541 (M^++1), 523, 432, 275, 172, 108, 91.

(2*R*,4*R*,5*S*)-5-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-4-hydroxy-2-methyl-6-phenylhexanoic Acid *n*-Butylamide (21b) Yield 87%. mp 218—220 °C. $[\alpha]_D^{25}$ −28.4° (*c*=0.55, DMF). *Anal.* Calcd for $C_{29}H_{40}N_4O_6 \cdot 0.75H_2O$: C, 62.85; H, 7.55; N, 10.11. Found: C, 62.81; H, 7.60; N, 9.94. IR (KBr) 3308, 1693, 1656 cm^{-1}. ^{1}H-NMR (DMF-d_7) δ: 0.87 (t, 3H, J=7.3 Hz), 1.04 (d, 3H, J=7.3 Hz), 1.26—1.35 (m, 2H), 1.38—1.48 (m, 2H), 1.59—1.75 (m, 2H), 2.48—2.60 (m, 3H), 2.78 (dd, 1H, J=9.5, 13.9 Hz), 3.02 (dd, 1H, J=3.7, 13.9 Hz), 3.09—3.18 (m, 2H), 3.57—3.65 (m, 1H), 3.96—4.03 (m, 1H), 4.42—4.50 (m, 1H), 4.82 (d, 1H, J=6.6 Hz), 5.08 (ABq, 2H, J=12.5 Hz, Δ=0.03 ppm), 6.93 (br s, 1H), 7.12—7.48 (m, 12H), 7.61—7.66 (m, 1H), 7.76 (br d, 1H, J=9.5 Hz). MS *m/z*: 541 (M^++1), 431, 369, 172, 120, 91.

(2*S*,4*S*,5*S*)-5-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-4-hydroxy-2-methyl-6-phenylhexanoic Acid *n*-Butylamide (21c) Yield 60%. mp 220—222 °C. $[\alpha]_D^{25}$ −23.9° (*c*=0.50, DMF). *Anal.* Calcd for $C_{29}H_{40}N_4O_6 \cdot 0.1H_2O$: C, 64.21; H, 7.47; N, 10.33. Found: C, 64.05; H, 7.52; N, 10.17. IR (KBr) 3312, 1695, 1663 cm^{-1}. ^{1}H-NMR (DMF-d_7) δ: 0.88 (t, 3H, J=7.3 Hz), 0.98 (d, 3H, J=6.6 Hz), 1.25—1.48 (m, 5H), 1.73—1.84 (m, 1H), 2.38—2.47 (m, 1H), 2.55—2.65 (m, 2H), 2.79 (dd, 1H, J=7.3, 13.9 Hz), 2.88 (dd, 1H, J=6.6, 13.2 Hz), 2.99—3.11 (m, 2H), 3.55—3.60 (m, 1H), 4.04—4.12 (m, 1H), 4.48—4.54 (m, 1H), 4.90 (d, 1H, J=5.9 Hz), 5.10 (s, 2H), 6.94 (br s, 1H), 7.13—7.43 (m, 11H), 7.47—7.53 (m, 2H), 7.63—7.69 (m, 1H). MS *m/z*: 541 (M^++1), 432, 369, 172, 91.

(2*S*,4*R*,5*S*)-5-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-4-hydroxy-2-methyl-6-phenylhexanoic Acid *n*-Butylamide (21d) Yield 60%. mp 215—218 °C. $[\alpha]_D^{25}$ −26.9° (*c*=0.48, DMF). *Anal.* Calcd for $C_{29}H_{40}N_4O_6$: C, 64.42; H, 7.46; N, 10.36. Found: C, 64.15; H, 7.45; N, 10.26. IR (KBr) 3309, 1698, 1667 cm^{-1}. ^{1}H-NMR (DMF-d_7) δ: 0.88 (t, 3H, J=7.3 Hz), 1.09 (d, 3H, J=6.6 Hz), 1.29—1.48 (m, 5H), 1.91—1.99 (m, 1H), 2.52—2.75 (m, 4H), 3.01 (dd, 1H, J=3.7, 13.9 Hz), 3.11—3.19 (m, 2H), 3.46—3.55 (m, 1H), 3.92—4.02 (m, 1H), 4.41—4.50 (m, 1H), 4.93 (d, 1H, J=6.6 Hz), 5.08 (s, 2H), 6.94 (br s, 1H), 7.12—7.42 (m, 11H), 7.52 (br s, 1H), 7.71—7.76 (m, 2H). MS *m/z*: 541 (M^++1), 432, 369, 275, 172, 91.

(4*S*,5*S*)-5-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-4-hydroxy-6-phenylhexanoic Acid *n*-Butylamide (22) Yield 51%. mp 208—210 °C. $[\alpha]_D^{25}$ −35.8° (*c*=0.41, DMF). *Anal.* Calcd for $C_{28}H_{38}N_4O_6 \cdot 0.3H_2O$: C, 63.21; H, 7.31; N, 10.53. Found: C, 63.25; H, 7.26; N, 10.54. IR (KBr) 3317, 1692, 1643 cm^{-1}. ^{1}H-NMR (DMF-d_7) δ: 0.86 (t, 3H, J=7.3 Hz), 1.23—1.46 (m, 4H), 1.65—1.78 (m, 2H), 2.21 (t, 2H, J=7.3 Hz), 2.54—2.68 (m, 2H), 2.74—2.82 (m, 1H), 2.87—2.95 (m, 1H), 3.05—3.13 (m, 2H), 3.51—3.60 (m, 1H), 3.96—4.08 (m, 1H), 4.45—4.55 (m, 1H), 5.10 (s, 2H), 5.18 (d, 1H, J=5.4 Hz), 6.92 (br s, 1H), 7.13—7.43 (m, 11H), 7.47—7.58 (m, 2H), 7.64—7.73 (m, 1H). MS *m/z*: 509 (M^+ − 17), 418, 261, 158, 128, 91.

(2*R*,4*S*,5*S*)-5-(*N*-Benzyloxycarbonyl-L-asparaginyl)amino-6-cyclohexyl-4-hydroxy-2-methylhexanoic Acid *n*-Butylamide (23) Yield 90%. mp 220—222 °C. $[\alpha]_D^{25}$ −41.3° (*c*=0.61, DMF). *Anal.* Calcd for $C_{29}H_{46}N_4O_6$: C, 63.71; H, 8.48; N, 10.25. Found: C, 63.91; H, 8.50; N, 10.27. IR (KBr) 3304, 1697, 1663 cm^{-1}. ^{1}H-NMR (DMF-d_7) δ: 0.76—1.85 (m, 25H), 2.54—2.71 (m, 3H), 3.09—3.18 (m, 2H), 3.45—3.55 (m, 1H), 3.85—3.96 (m, 1H), 4.46—4.54 (m, 1H), 4.76 (d, 1H, J=5.4 Hz), 5.09 (s, 2H), 6.94 (br s, 1H), 7.26—7.42 (m, 7H), 7.50—7.63 (m, 2H). MS *m/z*: 546 (M^++1), 266, 172, 108, 91, 79.

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