compound for 5 days, starting on the day of virus infection. The test compounds were formulated in 0.2% (w/w) sodium (carboxymethyl)cellulose, 0.2% Tween 80 in H_2O to give a solution or a homogeneous suspension. Twenty mice were used per group. Statistical significance of the differences in the final mortality rates (after 20 days of observation) was assessed by the χ^2 test with Yates correction for small numbers.[38]

The procedure for topical treatment of cutaneous HSV-1 or HSV-2 infection in hairless mice has been recently described.[39] The mice were inoculated intracutaneously in the lumbosacral area with either HSV-1 (Brand) at 1×10^6 PFU/0.025 mL per mouse or HSV-2 (K 979) at 1.8×10^5 PFU/0.025 mL per mouse. The test compounds were formulated in AZDMSO (5% azone [1-dodecylazacycloheptan-2-one], synthesized at the Sandoz Forschungsinstitut by the method of Swain et al.,[40] in dimethyl sulfoxide). They were applied in a volume of 50 μL topically four times a day (at 9 a.m., 11 a.m., 2 p.m., and 4 p.m.) for 5 days, starting immediately after virus infection. Ten mice were used per group.

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Registry No. **1a**, 951-78-0; **1b**, 50-89-5; **1c**, 54-42-2; **1d**, 90301-59-0; **1e**, 69304-47-8; **2a**, 115365-13-4; **2b**, 115365-14-5; **2c**, 115365-15-6; **2d**, 115365-16-7; **2e**, 115365-18-9; **2f**, 115365-19-0; **2g**, 115365-20-3; **2h**, 115365-21-4; **3a**, 115365-22-5; **3b**, 115365-23-6; **3c**, 115383-47-6; **4**, 115365-24-7; **5a**, 115365-25-8; **5b**, 115365-26-9; **5c**, 115365-27-0; **5d**, 115365-28-1; **6**, 115365-33-8; **7**, 115365-34-9; **8**, 115365-38-3; **9**, 115365-39-4; **10**, 115365-40-7; **11a**, 115365-29-2; **11b**, 115365-36-1; **11c**, 115365-30-5; **11d**, 115365-31-6; **11e**, 115365-32-7; **12a**, 115365-35-0; **12b**, 115365-37-2; EtOCOP(O)(OMe)Cl, 115365-12-3; $EtOCOCH_2P(O)(OMe)Cl$, 115365-17-8; $HOOCCH_2P(O)(OMe)_2$, 34159-46-1; $EtOCOCH_2P(O)(OH)_2$, 35752-46-6; $t\text{-}BuOCOCH_2P(O)(OH)_2$, 77530-32-6; $EtOCOP(O)(OH)_2$, 55920-71-3; $EtOCOP(O)(OH)_2{\cdot}PhNH_2$, 67472-32-6; $MeOCOP(O)(OH)_2$, 55920-68-8; $PhCH_2OCOP(O)(OH)_2$, 55920-74-6.

Synthesis and Biological Activity of Some Transition-State Inhibitors of Human Renin

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A series of renin inhibitors containing the dipeptide transition state mimics (2*S*,4*S*,5*S*)-5-amino-4-hydroxy-2-isopropyl-7-methyloctanoic acid ($\text{Leu}\overset{\text{OH}}{—}\text{Val}$) and (2*S*,4*S*,5*S*)-5-amino-4-hydroxy-2-isopropyl-6-cyclohexylhexanoic acid ($\text{Cha}\overset{\text{OH}}{—}\text{Val}$) was prepared. A structure–activity study with Boc-Phe-His-$\text{Leu}\overset{\text{OH}}{—}\text{Val}$-Ile-His-$NH_2$ (**8a**) as starting material led to *N*-[(2*S*)-2-[(*tert*-butylsulfonyl)methyl]-3-phenylpropionyl]-His-$\text{Cha}\overset{\text{OH}}{—}\text{Val}$-$NHC_4H_9$-*n* (**8i**) which has the length of a tetrapeptide and contains only one natural amino acid. Compound **8i** had an IC_{50} of 2×10^{-9} M against human renin and showed high enzyme specificity; IC_{50} values against the related aspartic proteinases pepsin and cathepsin D were (8×10^{-6} and 3×10^{-6} M, respectively). In salt-depleted marmosets, **8i** inhibited plasma renin activity PRA and lowered blood pressure for up to 2 h after oral administration of a dose of 10 mg/kg.

Renin, the rate-determining enzyme in the cascade leading to the vasopressor substance angiotensin II, plays a key role in the regulation of blood pressure.[1] Interruption of the renin-angiotensin system by inhibition of angiotensin converting enzyme (ACE) has led to the development of effective antihypertensive agents.[2] In principle, renin inhibitors should also provide a means of controlling blood pressure. Animal studies comparing an ACE inhibitor with a renin inhibitor have shown the two agents to be equieffective.[3] In addition, renin inhibitors may have advantages over ACE inhibitors, since, unlike ACE, which hydrolyzes a variety of bioactive peptides, renin is specific, having angiotensinogen as its only known substrate.[4] Human renin hydrolyzes the Leu^{10}-Val^{11} amide bond of angiotensinogen. A number of nonhydrolyzable equivalents of this dipeptide based on the transition state inhibitor concept have been prepared and incorporated into small peptides. Szelke and co-workers were the first to apply this concept to the synthesis of renin inhibitors.[5] These and subsequent efforts by others have produced a number of potent inhibitors of renin, but none of these have shown good oral activity.[6] Herein we report some

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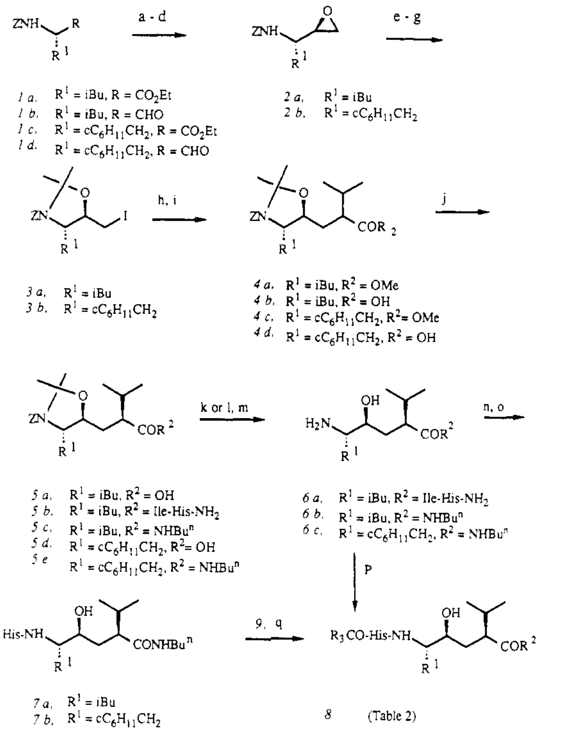
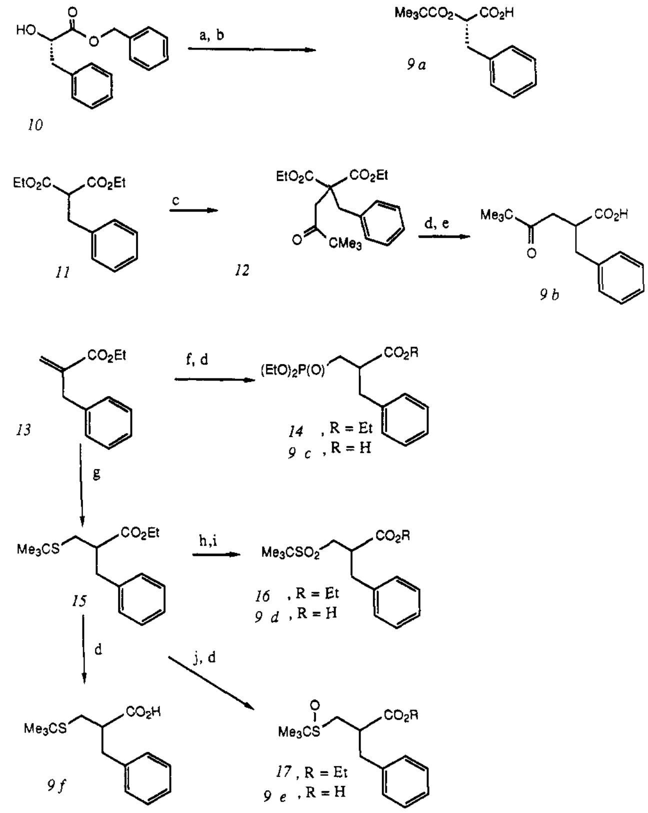
Scheme I.[a] Preparation of Leu$\underline{\text{OH}}$Val and Cha$\underline{\text{OH}}$Val Derivatives



[a] (a) DIBAL; (b) $H_2NNHCONH_2$; (c) HCHO, HCl; (d) Me_2SOCH_2Na; (e) NaI, Me_3SiCl; (f) KF; (g) $(MeO)_2CMe_2$, TsOH; (h) $Me_2CHCHLiCO_2Me$; (i) KO-*t*-Bu, H_2O; (j) chromatography; (k) Ile-His-NH_2, DCC, HOBT; (l) H_2N-*n*-Bu, DCC, HOBT; (m) H_2, Pd–C; (n) Z-His or *N,N'*-ditrityl-His, DCC, HOBT; (o) H_2, Pd–C; (p) Boc-Phe-His or pivaloyl-Phe-His, DCC, HOBT; (q) DCC, HOBT.

results from our studies based on hydroxyethylene isosteres of the dipeptides Leu-Val and Cha-Val[7] leading to the discovery of a potent inhibitor active after oral administration.

Scheme II.[a] Preparation of Phe Derivatives **9a–f**



[a] (a) Me_3CCOCl; (b) H_2, Pd–C; (c) Me_3CCOCH_2Br, NaH; (d) NaOH; (e) HCl, reflux; (f) $(EtO)_2POH$; (g) Me_3CSH; (h) $KHSO_5$; (i) 6 N HCl; (j) MCPBA.

Chemistry

The dipeptide derivatives Leu$\underline{\text{OH}}$Val and Cha$\underline{\text{OH}}$Val, which span the site of enzymatic cleavage, were prepared as depicted in Scheme I. A somewhat related approach to this class of dipeptide mimics has been reported.[9b] For Cha$\underline{\text{OH}}$Val, Z-L-cyclohexylalanine ethyl ester (**1c**) was reduced with diisobutylaluminum hydride to aldehyde **1d**. The product was isolated as its semicarbazone, purified, and regenerated in aqueous acid immediately prior to use. The aldehyde **1d** showed at least 90% optical purity according to HPLC analysis of the diastereomeric (−)-MTPA-amides (see the Experimental Section) of the reduced aldehyde. Conversion of **1d** to epoxide **2b** was carried out with dimethyloxosulfonium methylide.[8] This reaction produced a 5:1 mixture of diastereomers, with the desired isomer (**2b**) predominating. After ring opening of epoxide **2b** with iodotrimethylsilane,[10] the diastereomeric iodo alcohols were separated by flash column chromatography. Acetonide formation led to **3b**. The stereochemical assignment was based on ^{13}C NMR data of acetonide **3a** or **3b** and on the absolute configuration of the hydroxyl group in statine-containing renin inhibitors.[9,16] Alkylation

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(7) Abbreviations used are as follows: Z, benzyloxycarbonyl; Boc, *tert*-butoxycarbonyl; DCC, dicyclohexylcarbodiimide; HOBT, hydroxybenzotriazole; DIBAL, diisobutylaluminum hydride; TMSI, iodotrimethylsilane; Cha, β-cyclohexyl-L-alanine; Leu$\underline{\text{OH}}$Val, (2*S*,4*S*,5*S*)-5-amino-4-hydroxy-2-isopropyl-7-methyloctanoic acid; Cha$\underline{\text{OH}}$Val, (2*S*,4*S*,5*S*)-5-amino-4-hydroxy-2-isopropyl-6-cyclohexylhexanoic acid; TFA, trifluoroacetic acid; Piv, pivaloyl; Pla, L-phenyllactyl; Leu$\underline{\text{R}}$Val, *N*-[(2*S*)-2-amino-4-methylpentyl]-L-valine; MCPBA, 3-chloroperoxybenzoic acid.

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Table I. Characterization of Leu$\overset{\text{OH}}{-}$Val and Cha$\overset{\text{OH}}{-}$Val Derivatives (**8a–l**)[a]

no.[b]	TLC, R_f[c]	formula[d]	$[\alpha]_D$,[e] deg
8a	0.28 (*N*)	$C_{44}H_{68}N_{10}O_8$	−44.8 (*c* 0.50)
8b	0.31 (L), 0.17 (N)	$C_{44}H_{68}N_{10}O_7$	−38.4 (*c* 1.0)
8c	0.32 (L)	$C_{44}H_{67}N_9O_8$	−43.8 (*c* 0.85)
8d	0.47 (P)	$C_{36}H_{57}N_5O_6$	−33.7 (*c* 0.49)
8e	0.72 (N)	$C_{39}H_{61}N_5O_6$[f]	−37.7 (*c* 0.48)
8f	0.33 (P)	$C_{40}H_{63}N_5O_5$	−49.0 (*c* 0.50)
8g	0.46 (P), 0.66 (N)	$C_{39}H_{64}N_5O_7P$	−44.0 (*c* 0.50)
8h	0.44 (P), 0.67 (N)	$C_{39}H_{63}N_5O_6S$	−30.0 (*c* 0.50)
8i	0.24 (C)	$C_{39}H_{63}N_5O_6S$	−30.3 (*c* 0.95)
8j	0.31 (P)	$C_{39}H_{63}N_5O_6S$	−66.2 (*c* 0.47)
8k	0.53/0.63 (J)	$C_{39}H_{63}N_5O_5S$	−59.1 (*c* 0.20)
8l	0.42 (P)	$C_{39}H_{63}N_5O_4S$	−36.0 (*c* 0.50)

[a] See ref 7 for definition of Leu$\overset{\text{OH}}{-}$Val and Cha$\overset{\text{OH}}{-}$Val. [b] See Table II for structures. Each compound had NMR consistent with structure and expected M + H ion seen in FAB-MS. [c] See the Experimental Section for solvent systems (A–R). [d] Analyses for C, H, N were correct within ±0.4% unless otherwise indicated. [e] Rotations were determined in MeOH. [f] C, H, N analysis was within ±0.51%.

of methyl isovalerate with iodide **3b** generated **4c** as an approximately 1:1 mixture of diastereomers. The ester was hydrolyzed to yield a diastereomeric mixture of acids **4d**, which were separated by chromatography to give the desired *S,S,S* isomer **5d**.[11] The stereochemistry at the newly formed asymmetric center with the Val side chain was assigned on the basis of ^{1}H NMR coupling constants of the corresponding γ-butyrolactones. Acid **5d** was converted to *n*-butylamide **5e** and then deprotected by hydrogenolysis to generate the dipeptide mimic **6c**.

The final compounds **8e–l** were prepared by standard amide coupling procedures. Condensation of Z-L-histidine with **6c** followed by hydrogenolytic removal of the benzyloxycarbonyl group led to **7b**. Acylation of **7b** with acids **9a–f** yielded the final compounds **8e–l**.

The corresponding Leu$\overset{\text{OH}}{-}$Val derivatives **8c** and **8d** were prepared analogously with **1a** as starting material. Hexapeptide derivative **8a** was prepared from **6a** by amidation with Boc-Phe-His, and compound **8b** was derived from coupling of **6a** with pivaloyl-Phe-His.

The acids **9a–f**, which mimic phenylalanine, were prepared as summarized in Scheme II. *O*-Pivalyl-L-phenyllactic acid (**9a**) was obtained by acylation of benzyl-L-pivalate (**10**) followed by hydrogenolysis. 2-(Pivalylmethyl)hydrocinnamic acid (**9b**) was generated by alkylation of diethyl benzylmalonate (**11**) with bromopinacolone to give **12**, followed by hydrolysis and decarboxylation. Phosphonate **9c** was synthesized by Michael addition of diethylphosphite to ethyl 2-benzylacrylate (**13**)[12] with subsequent hydrolysis. The sulfur-containing acids **9d–f** were produced by 1,4-addition of *tert*-butyl mercaptan to **15** followed, if required, by the appropriate oxidation and hydrolysis. The optical isomers of **9d** were prepared by chromatographic separation of the corresponding diastereomeric amides formed with L-phenylalaninol followed by acid-catalyzed hydrolysis. Alternatively, the isomer contained in the final compound with greater biological activity, which presumably corresponds to the absolute configuration of L-phenylalanine, could be prepared by recrystallization of the diastereomeric salt formed with dehydroabietylamine.

Table II. In Vitro Human Renin Inhibition of Leu$\overset{\text{OH}}{-}$Val and Cha$\overset{\text{OH}}{-}$Val Derivatives (**8a–l**)

no.	structure[a]	human renin IC_{50},[b] nM
8a	Boc-Phe-His-Leu$\overset{\text{OH}}{-}$Val-Ile-His-NH_2	15
8b	Piv-Phe-His-Leu$\overset{\text{OH}}{-}$Val-Ile-His-NH_2	20
8c	Piv-Pla-His-Leu$\overset{\text{OH}}{-}$Val-Ile-His-NH_2	20
8d	Piv-Pla-His-Leu$\overset{\text{OH}}{-}$Val-NHC_4H_9-*n*	20
8e	Piv-Pla-His-Cha$\overset{\text{OH}}{-}$Val-NHC_4H_9-*n*	7
8f	Piv$\overset{\text{C}}{-}$Phe-His-Cha$\overset{\text{OH}}{-}$Val-NHC_4H_9-*n*[c]	6
8g	$(EtO)_2PO$$\overset{\text{C}}{-}$Phe-His-Cha$\overset{\text{OH}}{-}$Val-$NHC_4H_9$-*n*[d]	4
8h	*t*-$BuSO_2$$\overset{\text{C}}{-}$Phe-His-Cha$\overset{\text{OH}}{-}$Val-$NHC_4H_9$-*n*[e]	2
8i	*t*-$BuSO_2$$\overset{\text{C}}{-}$Phe-His-Cha$\overset{\text{OH}}{-}$Val-$NHC_4H_9$-*c*[e,f]	2
8j	*t*-$BuSO_2$$\overset{\text{C}}{-}$Phe-His-Cha$\overset{\text{OH}}{-}$Val-$NHC_4H_9$-*c*[e,f]	10
8k	*t*-BuSO$\overset{\text{C}}{-}$Phe-His-Cha$\overset{\text{OH}}{-}$Val-NHC_4H_9-*n*[g]	2
8l	*t*-BuS$\overset{\text{C}}{-}$Phe-His-Cha$\overset{\text{OH}}{-}$Val-NHC_4H_9-*n*[h]	4
H-142	Pro-His-Pro-Phe-His-Leu$\overset{\text{R}}{-}$Val-Ile-His-Lys	10[i]

[a] For definition of abbreviations see ref 7. Compounds **8f–h**, **8k**, and **8l** are diastereomeric at the center contained in the Phe-mimic subunit. [b] Purified human kidney renin (250 pg/mL) was incubated (37 °C) with human angiotensinogen at pH 7.2. Test details are described in ref 7. [c] Piv$\overset{\text{C}}{-}$Phe, from acylation of **9b**. [d] $(EtO)_2PO$$\overset{\text{C}}{-}$Phe, from acylation of **9c**. [e] *t*-$BuSO_2$$\overset{\text{C}}{-}$Phe, from acylation of **9d**. [f] Compound **8h** is a diastereomeric mixture of **8i** and **8j**. Compounds **8i** and **8j** contain resolved optical isomers of **9d**. [g] *t*-BuSO$\overset{\text{C}}{-}$Phe, from acylation of **9e**. [h] *t*-BuS$\overset{\text{C}}{-}$Phe, from acylation of **9f**. [i] Lit.[5] IC_{50} = 10 nM.

Results and Discussion

The starting point in the structure–activity study summarized in Table II was the hexapeptide derivative **8a**, which incorporates the amino acid side chains corresponding to positions 8–13 of human angiotensinogen. The goal of the investigation was to lower the molecular weight, minimize the number of peptide amide bonds, and enhance in vivo stability. The central dipeptide derivative Leu$\overset{\text{OH}}{-}$Val or Cha$\overset{\text{OH}}{-}$Val, which replaces the scissile amide bond and was designed to mimic the tetrahedral transition state of the enzymatic hydrolysis, was kept constant, and the left and right side attachments were varied.

On the amino side it was found that the terminal *tert*-butyl carbamate group in **8a** could be replaced by a pivalamide (compound **8b**) and further that this amide bond could be exchanged for an ester linkage (compound **8c**). This result implies that the NH of the amide at this position is not involved in an essential hydrogen bond with the enzyme. On the carboxy side of **8a** it was found that the dipeptide Ile-His-NH_2 could be replaced entirely with *n*-butylamide (compound **8d**) without loss of in vitro potency. In addition, replacement of the central dipeptide mimic Leu$\overset{\text{OH}}{-}$Val in **8d** with Cha$\overset{\text{OH}}{-}$Val led to enhanced potency (compound **8e**). A similar increase in potency has been reported for a series of statine-containing renin inhibitors.[6d]

Since the nitrogen of the N-terminal amide bond appeared to be unnecessary (compounds **8c** and **8d**), re-

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Table III. Comparison of Enzyme Inhibitions for 8i

enzyme	IC_{50},[a] nM
human kidney renin	2
human plasma renin	0.4
marmoset plasma renin	1
dog plasma renin	3
rat plasma renin	400
porcine pepsin	8200
bovine cathepsin D	3200

[a] Plasma renin activity was measured as the rate of angiotensin I formation after incubation (37 °C) of the endogenous renin and angiotensinogen in plasma at pH 7.2. Test details are described in ref 6a.

placement with carbon was investigated, and ketone **8f** was found to be an equipotent inhibitor. Potential isosteric replacements of the ketone functionality were also studied. Phosphonate **8g** and sulfone **8h** each showed good activity. The corresponding sulfoxide (**8k**) and sulfide (**8l**) were also equipotent. The two isomers of diastereomeric **8h**, compounds **8i** and **8j**, were found to differ by a factor of five in potency. Overall, the structure–activity study indicates that it is possible, starting from hexapeptide analogue **8a**, to remove three of the four natural amino acids and to isosterically replace an additional amide bond.

Sulfone derivative **8i** wass also assayed for specificity in other enzyme systems (Table III). The inhibitor showed similar potency against human, marmoset, and dog renin, but was only weakly active against rat renin. Although renin is a member of the same enzyme family, the aspartic proteinases pepsin and cathepsin D were inhibited by **8i** only at a 1000-fold higher dose.

In vivo, sulfone **8i** was studied with use of salt-depleted marmosets (Table IV). After intravenous administration the compound was found to produce complete inhibition of plasma renin activity (PRA) and significant reduction of blood pressure in dose of 0.1 mg/kg and above.

Oral administration of sulfone **8i** was also investigated. A dose of 1 mg/kg induced a substantial inhibition of PRA, with little influence on blood pressure. Doses of 3 mg/kg and above completely inhibited PRA and lowered blood pressure (BP). A dose of 10 mg/kg induced a significant fall in BP, which persisted over the 2-h test period.

In conclusion, structure–activity studies with hexapeptide derivative **8a** as the starting material led to compound **8i**, which has the length of a tetrapeptide and contains only one natural amino acid. The compound was found to be a potent and selective renin inhibitor in vitro and to effectively inhibit PRA and lower blood pressure after oral administration at a dose of 3–10 mg/kg. The compound, designated CGP 38 560 A, was therefore selected for extensive pharmacological characterization and for clinical investigation.

Experimental Section

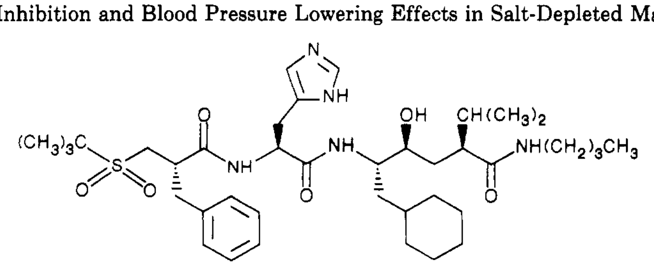
Proton NMR spectra were determined on a Bruker WM 250 or a Varian HA 100D spectrometer with Me_4Si as the internal standard. FAB mass spectra were recorded on a VG Analytical ZAB-HF spectrometer. Optical rotations were measured with a Perkin-Elmer 291 polarimeter. Melting points were taken on a Büchi 510 melting point apparatus and are uncorrected. All compounds were prepared by methods identical with those described below. Intermediate products were used directly without further purification. The experimental procedures for the biological tests have been described previously.[6a]

Systems used for TLC were as follows: A, 1:9 ethyl acetate–hexane; B, 1:2 ethyl acetate–hexane; C, 9:1 CH_2Cl_2–MeOH; D, 300:10:1 CH_2Cl_2–MeOH–H_2O; E, 1:4 ethyl acetate–hexane; F, 1:6 ethyl acetate–hexane; G, 4:1 CH_2Cl_2–ether; H, 4:1 CH_2Cl_2–MeOH; I, 9:1 CH_2Cl_2–ether; J, 1:1 ethyl acetate–hexane; K, 60:10:1 CH_2Cl_2–MeOH–NH_4OH; L, 40:10:1 CH_2Cl_2–MeOH–NH_4OH; M, 350:50:1 CH_2Cl_2–MeOH–NH_4OH; N, 750:270:50:5 CH_2Cl_2–MeOH–H_2O–acetic acid; O, 4:1 ethyl acetate–hexane; P, 90:10:1 CH_2Cl_2–MeOH–NH_4OH; Q, 20:1 hexane–ethyl acetate; R, 70:30:5 $CHCl_3$–MeOH–NH_4OH.

***N*-(Benzyloxycarbonyl)-3-cyclohexyl-L-alanine Ethyl Ester (1c).** To the dicyclohexylamine salt of Z-Cha[13] (243 g, 0.50 mol) in toluene (600 mL) and EtOH (900 mL) at 0 °C was added $SOCl_2$ (88.3 g, 0.74 mol) dropwise in 30 min. The reaction was stirred overnight at room temperature and filtered. The filtrate was evaporated, and the residue was purified by flash column chromatography (22.5 kg of silica gel, 2:1 ethyl acetate–hexane) to give **1c** (166 g, 99%) as an oil: R_f(A) 0.2; R_f(B) 0.52; $[\alpha]_D$ −19.3° (*c* 1.2, MeOH); NMR (Me_2SO-d_6) δ 0.85–1.4 (6 H, m), 1.18 (3 H, t, *J* = 7 Hz), 1.14–1.7 (7 H, m), 4.08 (3 H, m), 5.05 (2 H, s), 7.35 (5 H, s), 7.32 (1 H, d, *J* = 8 Hz).

2-[(Benzyloxycarbonyl)amino]-3-cyclohexyl-(2*S*)-propionaldehyde (1d). To **1c** (166.1 g, 0.50 mol) in toluene (2.2 L) at −65 °C was added 836 mL of diisobutylaluminum hydride (20% in toluene, 1.0 mol) in 30 min. The reaction was stirred for 20 min at −65 °C and quenched by dropwise addition of MeOH (84 mL) over 10 min. Aqueous potassium sodium tartrate (3 L) was added, and the reaction mixture was extracted with ether (5 L). The organic phase was washed with H_2O (2 L) and poured into a solution of semicarbazide hydrochloride (106 g, 0.92 mol) and sodium acetate (156.5 g, 1.9 mol) in 50% aqueous EtOH (1.3 L). After the reaction had stirred for 1 h at room temperature, the layers were separated. The aqueous phase was extracted with ether (2 × 1.5 L). The combined organic portions were dried ($MgSO_4$) and evaporated. The crude product was purified by flash column chromatography (2 kg of silica gel, 2:1 ethyl acetate–hexane) to give the semicarbazone of **1d** (132.3 g, 76%): mp 63–66

Table IV. In Vivo Plasma Renin Inhibition and Blood Pressure Lowering Effects in Salt-Depleted Marmosets for 8i[a]



dose, mg/kg	route of admin	% inhibition of PRA[b] 30 min	60 min	120 min	ΔBP,[c] mmHg 30 min	60 min	120 min
0.1	iv	100	98	94	−13	−5	−1
1	iv	100	100	100	−17	−13	−12
1	po	96	94	84	0	−5	−6
3	po	95	91	97	−6	−10	−8
10	po	100	100	100	−18	−23	−23

[a] The in vivo tests procedures were carried out as described in ref 6a. [b] Tabulated results indicate the percent inhibition of plasma renin activity measured 30, 60, and 120 min after administration of test compound to salt-depleted marmosets (*n* = 4). [c] Tabulated results indicate the reduction of blood pressure measured 30, 60, and 120 min after administration of test compound to salt-depleted marmosets.

°C; $[\alpha]_D$ −16.4° (*c* 1.0, MeOH); R_f(C) 0.51; NMR (Me_2SO-d_6) δ 0.85–1.45 (7 H, m), 1.62 (6 H, m), 4.17 (1 H, m), 5.04 (2 H, s), 6.24 (2 H, s) 7.07 (1 H, d, *J* = 2 Hz), 7.38 (5 H, s), 7.45 (1 H, d, *J* = 8 Hz), 9.90 (1 H, s). Anal. ($C_{18}H_{26}N_4O_3$) C, H, N.

To the above semicarbazone (130 g, 0.37 mol) in THF (1 L) at 0 °C were added 282 mL of 37% aqueous formaldehyde and 143 mL of 0.5 N HCl. The reaction was stirred for 2 h at room temperature and filtered. The filtrate was extracted with ether (3 × 300 mL). The combined organic portions were washed with H_2O (500 mL), 10% aqueous $NaHCO_3$ (500 mL), and H_2O (500 mL). The organic phase was dried ($MgSO_4$), diluted with THF (500 mL), concentrated to 250 mL, and used immediately. Optical purities were quantitatively determned by 360-MHz ^1H NMR analysis of the diastereomeric (−)-MTPA-amides[18] of the reduced and deprotected aldehyde **1d**. The aldehyde was first reduced by $NaBH_4$ in methanol at room temperature, and the resulting alcohol was hydrogenated over 10% Pd–C for 1 h at 25 °C in methanol. The amino alcohol reacted with (*S*)-(−)-α-methoxy-α-[(trifluoromethyl)phenyl]acetyl chloride in dichloromethane at 0 °C in presence of 1 equiv of hünigs base to give quantitatively the corresponding amide. The methoxy signal for the desired (*S*)-cyclohexylmethyl amide appers at 3.48 ppm, the (*R*)-cyclohexylmethyl amide at 3.39 ppm (360-MHz ^1H NMR, $CDCl_3$). The purities of the used aldehyde batches were at least 90%.

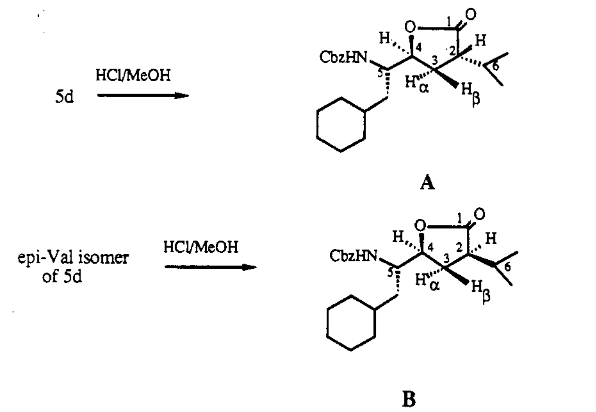
1-[1-[(Benzyloxycarbonyl)amino]-2-cyclohexyl-(1*S*)-ethyl]oxirane (2b). To NaH (18.9 g (0.43 mol) of 55% oil dispersion, washed free of oil with 3 × 50 mL of hexane) in THF (500 mL) was added trimethylsulfoxonium iodide (55.6 g, 0.25 mol). After being refluxed for 1 h, the reaction mixture was cooled to −70 °C, and **1d** (108.6 g, 0.37 mol) in THF (250 mL) was added. The reaction was stirred for 2 h at 0 °C, poured onto ice (500 g), and extracted with ether (2.5 L). The organic phase was washed with H_2O (200 mL), dried (Na_2SO_4), and evaporated. The residue was purified by flash column chromatography (2.5 kg of silica gel, 1:4 ethyl acetate–hexane) to yield **2b** (43.3 g, 38%): R_f(D) 0.71; R_f(E) 0.16; $[\alpha]_D$ −16.4° (*c* 1.5, MeOH). NMR indicated an approximately 5:1 ratio of isomers. For the major isomer: NMR (Me_2SO-d_6) δ 0.90 (2 H, m), 1.02–1.45 (6 H, m), 1.58 (5 H, m), 2.48 (1 H, m), 2.68 (1 H, t, *J* = 2 Hz), 2.91 (1 H, m), 3.45 (1 H, m), 5.02 (2 H, s), 7.25 (1 H, d, *J* = 6 Hz), 7.35 (5 H, m). For the minor isomer: NMR (Me_2SO-d_6) δ 0.90 (2 H, m), 1.01–1.45 (6 H, m), 1.52–1.80 (5 H, m), 2.58 (1 H, m), 2.65 (1 H, t), 2.84 (1 H, m), 3.42–3.58 (1 H, m), 5.00–5.05 (2 H, AB system, *J* = 12 Hz), 7.25 (1 H, d, *J* = 6 Hz), 7.35 (5 H, m).

3-(Benzyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-dimethyl-5-(iodomethyl)-(4*S*,5*R*)-1,3-oxazolidine (3b). To **2b** (42.3 g of a 5:1 isomer mixture, 0.14 mol) in MeCN (200 mL) at 0 °C was added NaI (20.9 g, 0.14 mol) followed by dropwise addition of chlorotrimethylsilane (15.1 g, 0.14 mol) over 30 min. The reaction mixture was stirred for 40 min at 0 °C, poured into ice water (700 mL), and extracted with ether (500 mL). The organic layer was washed with 5% aqueous $Na_2S_2O_3$ (750 mL) and brine (750 mL), dried (Na_2SO_4), and evaporated to give crude 3-[(benzyloxycarbonyl)amino]-4-cyclohexyl-1-iodo-2-[(trimethylsilyl)oxy]-(2*R*,3*S*)-butane (65.7 g). To the above TMS ether (65.7 g, 0.14 mol) in MeOH (290 mL) at 0 °C were added acetic acid (8.4 g, 0.14 mol) and KF (8.1 g, 0.14 mol). The reaction was stirred 4 h at room temperature, evaporated, and partitioned between 10% aqueous $NaHCO_3$ (750 mL) and ether (1.5 L). The aqueous phase was extracted with ether (2 × 400 mL). The combined organic portions were dried ($MgSO_4$) and evaporated. The residue was separated by flash column chromatography (2.5 kg of silica gel, 1:9 ethyl acetate–hexane) to give the major, less polar (2*R*,3*S*) iodo alcohol (49.3 g, 78%): R_f(E) 0.12; $[\alpha]_D$ −19.5° (*c* 0.64, MeOH); NMR (Me_2SO-d_6) δ 0.90 (2 H, m), 1.02–1.4 (6 H, m), 1.45–1.92 (5 H, m), 3.04 (1 H, m), 3.32 (1 H, m), 3.52 (1 H, m), 3.72 (1 H, m), 5.05 (2 H, dd, *J* = 12 Hz), 5.32 (1 H, d, *J* = 6 Hz), 6.90 (1 H, d, *J* = 8 Hz), 7.35 (5 H, m). The minor, polar 2*S*,3*S* isomer was removed during this chromatographic separation (10.0 g, 15.6%): NMR (Me_2SO-d_6) δ 0.90 (2 H, m), 1.02–1.4 (6 H, m), 1.45–1.92 (5 H, m), 3.10 (1 H, m), 3.30 (1 H, m), 3.34 (1 H, m), 3.55 (1 H, m), 5.03 (2 H, dd, *J* = 12 Hz), 5.31 (1 H, d, *J* = 6 Hz), 7.08 (1 H, d, *J* = 8 Hz), 7.35 (5 H, m). To the above major isomer (49.3 g, 0.11 mol) and *p*-toluenesulfonic acid (1.1 g) in CH_2Cl_2 (450 mL) was added 2,2-dimethoxypropane (118 g, 1.44 mol). The reaction mixture was stirred for 3 h at room temperature and extracted with 500 mL of saturated aqueous $NaHCO_3$. The organic phase was dried (Na_2SO_4), evaporated, and purified by flash column chromatography (3 kg of silica gel, 1:6 ethyl acetate–hexane) to yield **3b** (51.3 g, 95%): R_f(F) 0.46; $[\alpha]_D$ 24.5° (*c* 1.5, MeOH); NMR (Me_2SO-d_6) δ 0.80–1.0 (2 H, m), 1.0–1.95 (11 H, m), 1.42 (3 H, s), 1.50 (3 H, s), 3.27 and 3.54 (2 H, dd, *J* = 7, 10 Hz), 3.95 (1 H, m) 4.02 (1 H, m), 5.08 (2 H, m), 7.38 (5 H, m). Anal. ($C_{21}H_{30}NO_3I$) C, H, N, I. After the minor isomer has been converted by the same procedure into its oxazolidine derivative, the final assignment of the stereochemistry of **3b** and its isomer was made by comparison of the ^{13}C NMR data as described in literature.[16] For the major isomer **3b** (the compound appears as two rotamers relative to the amide bond): ^{13}C NMR ($CDCl_3$) δ 9.1/9.0 (CH_2C5), 42.0/41.0 (CH_2C4), 59.6/60.5 (C4), 81.3/81.1 (C5). For the minor isomer (the compound appears as two rotamers relative to the amide bond): ^{13}C NMR ($CDCl_3$) δ 0.2 (CH_2C5), 37.3/37.0 (CH_2C4), 57.1/56.4 (C4), 78.1/77.7 (C5).

Methyl 2-[[3-(Benzyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-dimethyl-(4*S*)-1,3-oxazolidin-5-yl]methyl]-3-methyl-2(*R*,*S*)-butyrate (4c). To diisopropylamine (10.2 g, 0.10 mol) in THF (200 mL) at 0 °C was added 65.8 mL (0.10 mol) of 1.6 M *n*-butyllithium in hexane. After being stirred for 20 min, the reaction mixture was cooled to −70 °C and treated with methyl isovalerate (11.7 g, 0.10 mol) followed by HMPT (320 mL). After being stirred at −70 °C for 10 min, the reaction mixture was treated with **3b** (43.4 g, 0.092 mol) in THF (110 mL). The reaction mixture was stirred 2.5 h at room temperature, poured into saturated aqueous NH_4Cl (1 L), and extracted with ethyl acetate (2 L). The organic phase was washed with H_2O (2 × 500 mL), dried ($MgSO_4$), evaporated, and purified by flash column chromatography (2.5 kg of silica gel, 1:10 ethyl acetate–hexane) to give **4c** (36 g, 78%) (R_f(E) 0.36, 0.34; R_f(A) 0.23, 0.21) as a mixture of diastereomers: NMR (Me_2SO-d_6) δ 0.80–0.98 (8 H, m), 1.0–1.92 (14 H, m), 1.40 (3 H, s), 1.48 (3 H, s), 2.18/2.38 (1 H, 2 m), 3.56/3.58 (3 H, 2 s), 3.65–3.80 (2 H, m), 4.99–5.17 (2 H, m), 7.37 (5 H, s).

2-[[3-(Benzyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-dimethyl-(4*S*)-1,3-oxazolidin-5-yl]methyl]-3-methyl-(2*S*)-butyric Acid (5d). To potassium *tert*-butoxide (16.5 g, 0.15 mol) and H_2O (1.8 mL, 0.10 mol) in ether (250 mL) at 5 °C was added **4c** (35.8 g, 0.078 mol) in ether (250 mL). The reaction mixture was stirred for 18 h at room temperature, poured into saturated aqueous NH_4Cl (500 mL), and extracted with ethyl acetate (2 × 500 mL). The organic phase was washed with brine (250 mL), dried (Na_2SO_4), and evaporated. The diastereomeric acids **(4d)** were purified by flash column chromatography (2.5 kg of silica gel, 1:4 ethyl acetate–hexane) to give **5d** and isomeric acid. **5d** (14.5 g, 42%): R_f(D) 0.20, R_f(G) 0.35; $[\alpha]_D$ −7.3° (*c* 1.4, MeOH); NMR (Me_2SO-d_6) δ 0.80–1.0 (8 H, m), 1.0–1.95 (14 H, m), 1.39 (3 H, s), 1.55 (3 H, s), 2.28 (1 H, m), 3.72 (2 H, m), 5.08 (2 H, m),

Scheme III[a]



[a] See the Experimental Section.

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7.35 (5 H, m), 12.25 (1 H, s). Isomeric acid (51.3 g, 51%): R_f(D 0.16, R_f(G) 0.30; $[\alpha]_D$ −7.0° (c 1.3, MeOH); NMR (Me_2SO-d_6) δ 0.8–1.0 (8 H, m), 1.0–1.92 (14 H, m), 1.37 (3 H, s), 1.55 (3 H, s), 2.02 (1 H, m), 3.72 (2 H, m), 5.07 (2 H, m), 7.38 (5 H, m), 12.20 (1 H, s). Anal. ($C_{26}H_{39}NO_5$) C, H, N. The acid **5d** and its 2*R* isomer were converted into the corresponding γ-butyrolactones A and B (Scheme III) by stirring them in methanol–HCl 1 N (1:1). The stereochemistry of the Val side chain in lactones A and B was then assigned unambiguously by comparing proton NMR data with results of similar compounds.[17] For lactone A: NMR ($CDCl_3$) δ 0.80–0.85 (1 H, m), 0.85–1.00 (6 H, m), 1.05–1.90 (14 H, m), 2.00–2.20 (3 H, m), 2.47 (1 H, ddd, $J_{2,3\beta}$ = 11 Hz, $J_{2,3\alpha}$ = 6.5 Hz, $J_{2,6}$ =5 Hz), 3.85–4.00 (1 H, m), 4.39–4.46 (1 H, ddd, $J_{3\alpha,4}$ = 8 Hz, $J_{3\beta,4}$ = 6 Hz, $J_{4,5}$ = 2 Hz), 4.60 (1 H, d), 5.11 (2 H, s), 7.33 (5 H, s). For (2*R*)-lactone B: NMR ($CDCl_3$) δ 0.80 (3 H, d), 0.90 (1 H, m), 0.97 (3 H, d), 1.10–1.90 (14 H, m), 2.07–2.21 (2 H, m), 2.57 (1 H, ddd, $J_{2,3\beta}$ = 12.5 Hz, $J_{2,3\alpha}$ = 9 Hz, $J_{2,6}$ = 5 Hz), 3.89–3.99 (1 H, m), 4.32–4.39 (1 H, ddd, $J_{3\alpha,4}$ = 6 Hz, $J_{3\beta,4}$ = 10 Hz, $J_{4,5}$ = 1.5 Hz), 4.69 (1 H, d), 5.10 (2 H, dd), 7.35 (5 H, s).

N-Z-N,O-Isopropylidene-Cha$\frac{OH}{}$Val-NH(CH_2)$_3$$CH_3$ (5e). To a solution of **5d** (40.1 g, 90 mmol) and HOBT (17.9 g, 117 mmol) in anhydrous DMF (700mL) was added DCC (24.1 g, 117 mmol) at 0–5 °C, and the solution was kept at 0 °C for 3 days. *n*-Butylamine (35.5 mL, 0.36 mol) was added, and the reaction was stirred for 2 h of 0 °C and for 24 h at room temperature. The reaction mixture was diluted with 1:1 acetic acid–H_2O (50 mL), stirred for 30 min, and then concentrated to $^1/_3$ of its original volume. The precipated urea was removed by filtration, and the filtrate was evaporated. The residue was partitioned between ethyl acetate (500 mL) and saturated $NaHCO_3$ solution (300 mL). The organic portion was washed with brine (100 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography on silica gel (1:4 ethyl acetate–hexane) to yield **5e** (43.2 g, 96%) as a light yellow oil: R_f(B) 0.39; $[\alpha]_D$ −10.6° (c 2.4, $CHCl_3$); EIMS, *m/e* 500 (M^+); NMR ($CDCl_3$) δ 0.93 (9 H, m), 1.1–2.1 (26 H, m), 3.27 (2 H, m), 3.70 (1 H, br s), 3.76 (2 H, m), 5.0–5.2 (2 H, m), 5.62 (1 H, br s), 7.3 (5 H, m); IR (CH_2Cl_2, cm^{-1}) 3440, 1700, and 1670. Anal. ($C_{30}H_{48}N_2O_4$) C, H, N.

Cha$\frac{OH}{}$Val-NH(CH_2)$_3$$CH_3$ (6c). A solution of **5e** (47.1 g, 94 mmol) in 95:5 MeOH–H_2O (500 mL) was hydrogenated over 10% Pd–C (5 g) for 4 h at 25 °C and atmospheric pressure. The catalyst was removed by filtration, and the colorless filtrate was evaporated. The remaining oil was dissolved in 1:1 H_2O–MeOH (400 mL) and stirred for 2 h at room temperature. The mixture was concentrated, and residual H_2O was removed by azeotropic distillation with toluene to yield **6c** (30.3 g, 99%) as a colorless oil, which could be crystallized from hexane: mp 91–92 °C; $[\alpha]_D$ −27.4° (c 1.15, $CHCl_3$); R_f(R) 0.5; FAB MS, *m/e* 327 (M^+ + 1); NMR ($CDCl_3$) δ 0.9–1.8 (31 H, m), 1.86 (1 H, m), 2.08 (1 H, ddd, *J* = 11.6, 8.6, 3.2 Hz), 2.57 (1 H, ddd, *J* = 9.1, 5.7, 3.1 Hz), 3.07 (1 H, ddd, *J* = 8.6, 5.7, 2.3 Hz), 3.22 (1 H, m), 3.30 (1 H, m), 5.79 (1 H, br t, *J* = 5.5 Hz); IR (CH_2Cl_2, cm^{-1}) 3460, 3380, 1670. Anal. ($C_{19}H_{38}N_2O_2$) C, H, N.

His-Cha$\frac{OH}{}$Val-NH(CH_2)$_3$$CH_3$ (7b). Method A. To a solution of *N,N'*-ditrityl-L-histidine (12.1 g, 18.9 mmol) and HOBT (2.9 g, 18.9 mmol) in DMF (120 mL) at 0 °C was added a solution of amine **6c** (4.4 g, 13.5 mmol) in DMF (20 mL) followed by DCC (4.46 g, 21.6 mmol). The reaction mixture was stirred at 0–5 °C for 6 h followed by 2 days at room temperature. The precipitated urea was filtered off at 0 °C, and the solvent was evaporated. The crude ditrityl intermediate was purified by flash chromatography (CH_2Cl_2–MeOH, 50:1). The trityl groups were then removed with 95% TFA (130 mL) for 30 min at 25 °C. The reaction mixture was concentrated, redissolved in 5:3:1 CH_2Cl_2–MeOH–NH_4OH (150 mL), and concentrated again. The residue was titurated with MeOH, filtered, and evaporated. The crude product (**7b**) was purified by flash chromatography on silica gel (80:10:1 → 50:10:1 CH_2Cl_2–MeOH–NH_4OH) and freeze-dried from *t*-BuOH to give **7b** (4.0 g, 64%) as a white powder.

Method B. To a solution of Z-His (19.5 g, 67.5 mmol), *N*-hydroxynorbornane-*exo*-2,3-dicarboximide[15] (12.3 g, 67.5 mmol) and **6c** (14.7 g, 45 mmol) in DMF (450 mL) was added DCC (13.9 g, 67.5 mmol), and the resulting mixture was stirred for 16 h at room temperature. The reaction mixture was diluted with 50% aqueous acetic acid (50 mL), stirred for 1 h at 25 °C, and concentrated to about half of its volume. The precipitated urea was removed by filtration, and the solvents were evaporated. The residue was partitioned between 4:1 CH_2Cl_2–MeOH (300 mL) and saturated $NaHCO_3$ solution (200 mL). The aqueous phase was reextracted (200 mL), and then the combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4), and concentrated. The crude product was recrystallized from EtOAc–MeOH to give the *N*-benzyloxycarbonyl derivative of **7b** (22.3 g, 83%) as white crystals: mp 204–205 °C; $[\alpha]_D$ −40.4° (c 0.7, EtOH); R_f(C) 0.2; FAB MS, *m/e* 598 (M^+ + 1); NMR (DMSO-d_6) δ 0.9–1.8 (29 H, m), 2.09 (1 H, m), 2.77 (1 H, dd, *J* = 14.5, 9.0 Hz), 2.91 (1 H, dd, *J* = 14.5, 4.5 Hz), 3.03 (2 H, m), 3.20 (1 H, br d, *J* = 10.0 Hz), 3.71 (1 H, m), 4.22 (1 H, m), 4.69 (1 H, br s), 4.97 (1 H, d, *J* = 12.8 Hz), 5.01 (1 H, d, *J* = 12.8 Hz), 6.79 (1 H, br s), 7.2–7.4 (6 H, m), 7.43 (1 H, d, *J* = 8.5 Hz), 7.52 (1 H, s), 7.76 (1 H, t, *J* = 6.0 Hz), 11.8 (1 H, br s); IR (KBr, cm^{-1}) 3400, 3320, 1695, and 1640. Anal. ($C_{33}H_{51}N_5O_5$) C, H, N.

A solution of Z-**7b** (22.0 g, 36.5 mmol) in MeOH (500 mL) was hydrogenated in the presence of 10% Pd–C (1.5 g) for 8 h at atmospheric pressure. The catalyst was removed by filtration, and the colorless filtrate was concentrated. The remaining glassy foam (18.2 g) was crystallized from EtOH–Et_2O to yield **7b** (16.4 g, 97%) as white crystals: mp 166–167 °C: $[\alpha]_D$ −41.6° (c 1.28, EtOH; R_f(R) 0.25: FAB MS, *m/e* 464 (M^+ + 1); NMR (DMSO-d_6) δ 0.85–1.80 (28 H, m), 2.10 (1 H, m), 2.53 (1 H, m), 2.87 (1 H, br d, *J* = 15 Hz), 3.00 (1 H, m), 3.07 (1 H, m), 3.23 (1 H, m), 3.37 (4 H, m), 3.69 (1 H, m), 4.69 (1 H, br s), 6.83 (1 H, br s), 7.53 (2 H, m), 7.68 (1 H, t, *J* = 6 Hz), 11.82 (1 H, br s); IR (KBr, cm^{-1}) 3350, 1685. Anal. ($C_{25}H_{45}N_5O_3$) C, H, N.

Pivaloyl-Phe-His-Leu$\frac{\Gamma H}{}$Val-Ile-His-NH$_2$ (8b). To an ice-cooled solution of **4b** (608 mg, 1.50 mmol) in 20 mL of DMF was added Ile-His-NH_2 (441 mg, 1.65 mmol), 1-hydroxybenzotriazole hydrate (230 mg, 1.50 mmol), and 1,3-dicyclohexylcarbodiimide (464 mg, 2.25 mmol). The mixture was stirred for 24 h with ice cooling and for 72 h at room temperature. The reaction mixture was filtered, and the filtrate was evaporated. The residue was stirred in a 94:3:3 mixture of methanol–acetic acid–H_2O (20 mL) for 1 h at 60 °C. The solvent was removed, and the residue was purified by flash chromatography (230 g of silica gel, 80:10:1 CH_2Cl–MeOH–NH_4OH) to give the product (**5b**) (796 mg, 81%), homogeneous by TLC (R_f (K) 0.28), used without further purification: $[\alpha]_D$ −42.3° (c 1.0, MeOH); NMR (Me_2SO-d_6) δ 0.82 (18 H, m), 1.00–1.84 (9 H, m), 1.38 (3 H, s), 1.56 (3 H, s), 2.30 (1 H, m), 2.84 (2 H, m), 3.62 (2 H, m), 4.14 (1 H, t), 4.41 (1 H, q), 5.07 (2 H, m), 6.80 (1 H, s), 7.00 (1 H, s), 7.18 (1 H, s), 7.38 (5 H, m), 7.48 (1 H, s), 7.93 (2 H, m), 12.24 (1 H, m).

A stirred solution of the above product (700 mg, 1.07 mmol) in a 9:1 mixture of methanol–H_2O was hydrogenated in the presence of 10% Pd–C (100 mg). After 0.5 h, the reaction mixture was filtered, and the filtrate was stirred for 1.5 h with 15 mL of H_2O at room temperature. The solvent was removed, and the residue was purified by flash chromatography (90 g silica gel, 40:10:1 CH_2Cl_2–MeOH–NH_4OH) to give the product (**6a**) (400 mg, 78%), homogeneous by TLC (R_f(L) 0.22), used without further purification: NMR (Me_2SO-d_6) δ 0.82 (18 H, m), 1.12 (3 H, m), 1.42 (2 H, m), 1.67 (4 H, m), 2.26 (1 H, m), 2.41 (1 H, m), 2.86 (2 H, m), 3.02 (1 H, m), 4.14 (1 H, t), 4.41 (1 H, q), 6.76 (1 H, s), 7.00 (1 H, s), 7.18 (1 H, s), 7.48 (1 H, s), 7.78 (1 H, d), 8.00 (1 H, d), 12.30 (1 H, m).

To an ice-cooled solution of L-2-pivalamido-3-phenylpropionic acid (1.25 g, 5.0 mmol) in 40 mL of DMF was added L-histidine methyl ester dihydrochloride (1.21 g, 5.0 mmol), 1-hydroxybenzotriazole hydrate (0.77 g, 5.0 mmol), 4-methylmorpholine (1.01 g, 10.0 mmol), and 1.3-dicyclohexylcarbodiimide (1.34 g, 6.5 mmol). The mixture was stirred for 5 h with ice cooling and for 20 h at room temperature. The reaction mixture was filtered, and the filtrate was evaporated. The residue was stirred in a 94:3:3 mixture of methanol–acetic acid–H_2O (40 mL) for 1 h at 60 °C. The solvent was removed, and the residue in 100 mL of saturated aqueous $NaHCO_3$ was extracted with 3 × 100 mL of ethyl acetate. The combined organic portions were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (260 g of silica gel, 350:50:1 CH_2Cl_2–MeOH–NH_4OH) to give an oil (1.64 g, 81%), homogeneous by TLC (R_f(M) 0.38; R_f(N) 0.61). To the above product (1.60 g, 4.0 mmol) in 16 mL of methanol was added 32 mL H_2O and 1.0 N aqueous NaOH (6.0 mL, 6.0 mmol). the reaction mixture was stirred for 45 min at room temperature. Aqueous HCl (1.0 N; 6.0 mL, 6.0 mmol) was added, and the reaction mixture was evaporated to give the crude product (1.80 g), containing approximately 13% NaCl, homogeneous by TLC (R_f(L) 0.06; R_f(N) 0.14), used without further purification: NMR (Me_2SO-d_6) δ 0.95 (9 H, s), 2.93 (4 H, m), 4.39 (1 H, m), 4.49 (1 H, m), 6.83 (1 H, s), 7.17 (1 H, m), 7.23 (5 H, d), 7.50 (1 H, d), 7.58 (1 H, s), 8.15 (1 H, d).

To an ice-cooled solution of the above acid (49 mg, 0.11 mmol) in 4 mL of DMF was added **6a** (48 mg, 0.10 mmol), 1-hydroxybenzotriazole hydrate (17 mg, 0.11 mmol), and 1,3-dicyclohexylcarbodiimide (27 mg, 0.13 mmol). The mixture was stirred for 24 h with ice cooling and for 24 h at room temperature. The reaction mixture was filtered, and the filtrate was evaporated. The residue was stirred in a 94:3:3 mixture of methanol–acetic acid–H_2O (5 mL) for 1 h at 60 °C. The solvent was removed, and the residue was purified by flash chromatography (40 g of silica gel, 60:10:1 CH_2Cl_2–MeOH–NH_4OH) and lyophilized in 2 mL of 2-methyl-2-propanol to give the product **8b** (52 mg, 61%), homogeneous by TLC (R_f(L) 0.31; R_f(N) 0.17): $[\alpha]_D$ −38.4° (*c* 1.0, MeOH); NMR (Me_2SO-d_6) δ 0.80 (18 H, m), 0.98 (9 H, s), 1.12 (3 H, m), 1.33 (4 H, m), 1.65 (2 H, m), 2.25 (2 H, m), 2.88 (4 H, m), 3.23 (2 H, m), 3.65 (1 H, m), 4.13 (1 H, t), 4.42 (3 H, m), 6.82 (2 H, d), 7.02 (1 H, s), 7.18 (7 H, m), 7.50 (1 H, d), 7.58 (2 H, m), 7.73 (1 H, m), 8.00 (1 H, d), 8.15 (1 H, m). Anal. ($C_{44}H_{68}N_{10}O_7{\cdot}2H_2O$) C, H, N.

Pivaloyl-L-phenyllactic Acid (9a). To a solution of L-(−)-phenyllactic acid (4.00 g, 24.1 mmol) in 70 mL of MeOH–H_2O (10:1) at room temperature was added 23 mL of aqueous $CsCO_3$ (20%, 14.1 mmol). After removal of the solvent, the crude cesium salt was dissolved in DMF (37 mL), benzyl bromide (3.2 mL, 26.9 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 24 h. After filtration and removal of the solvent, the residue was suspended in H_2O (50 mL), and the benzyl ester of L-phenyllactic acid was extracted with ether (3 × 100 mL). The organic phase was dried (Na_2SO_4) and evaporated to give a pale yellow oil (**10**) (6.20 g, 100%), which was used without further purification. The above oil (5.00 g, 19.5 mmol), 4-(dimethylamino)pyridine (238 mg, 1.95 mmol), and diisopropylethylamine (2.50 g, 19.5 mmol) were dissolved in CH_2Cl_2 (100 mL). Pivaloyl chloride (3.53 g, 29.2 mmol) was added dropwise at 0 °C. After being stirred at room temperature for 1 h, the reaction mixture was evaporated, and the product was chromatographed on silica gel with hexane–ethyl acetate (95:5) to give 3.8 g (57%) benzyl *O*-pivaloyl-L-phenyllactate as an oil [R_f(E) 0.52; $[\alpha]_D$ −25.2° (*c* 1, MeOH)], used without further purification. The above oil (2.50 g, 7.34 mmol) was dissolved in MeOH (30 mL), and this solution was hydrogenated in the presence of 0.250 g of Pd–C (10%). The solution was filtered and concentrated, giving 1.69 g (92%) of the acid **9a** as a colorless oil: R_f(H) 0.37; NMR (Me_2SO-d_6) δ 1.1 (9 H, s), 3.15 (2 H, m), 5.1 (1 H, dd), 7.25 (5 H, Ar), 12.5 (1 H, br).

2-Benzyl-3-pivaloylpropionic Acid (9b). To a solution of diethyl benzylmalonate (**11**) (100 g, 0.40 mol) and 1-bromopinacoline (78.7 g, 0.44 mol) in 1 L of DMF was added NaH (1.74 g, 0.40 mol, 55% suspension in oil) at room temperature. The reaction was stirred for 2 h. The solvent was removed, 2 L of 1 N HCl were added, and the product was extracted with CH_2Cl_2 (3 × 300 mL) to give a pale yellow oil (**12**) (134.4 g, 96%): R_f 0.30 (CH_2Cl_2); NMR (Me_2SO-d_6) δ 1.05 (9 H, s), 1.14 (6 H, t, J = 7 Hz), 2.98 (2 H, s), 3.29 (2 H, s), 4.10 (4 H, q, J = 7 Hz), 6.94 (2 H, m), 7.28 (3 H, m).

To the crude diester (**12**) in dioxane (670 mL) at room temperature were added H_2O (670 mL) and 2 N NaOH (578 mL). The reaction mixture was stirred for 3 h at 80 °C. After evaporation of approximately half of the solvent, 4 N HCl (500 mL) was added, and the diacid was extracted with CH_2Cl_2 (3 × 300 mL). After removal of the solvent, the crude diacid was decarboxylated by heating at 160 °C without solvent for 0.5 h. The product (**9b**) was crystallized in hexane (500 mL) to give colorless needles (79.6 g, 80%): mp 93–94 °C; NMR (Me_2SO-d_6) δ 1.04 (9 H, s), 2.50 (1 H, m), 2.70 (1 H, m), 2.88 (1 H, m), 2.93 (2 H, s), 7.36–7.14 (5 H, m), 12.15 (1 H, br, COOH). Anal. ($C_{15}H_{20}O_3$) C, H.

Ethyl 2-Benzyl-3-(diethoxyphosphoryl)propionate (14). A solution of EtOH (30 mL), NaOEt (4 mL of 1% solution in EtOH), α-benzylacrylic acid ethyl ester (**13**) (1 g, 5.26 mmol), and diethylphosphite (0.68 mL, 5.26 mmol) was stirred at 23 °C for 24 h. After addition of $NaH_2PO_4{\cdot}H_2O$ (0.2 g in 1 mL of H_2O), the solvent was evaporated. The residue in ether (100 mL) was washed with water (2 × 50 mL) and dried (Na_2SO_4). After removal of the solvent, the crude product was chromatographed on silica gel with CH_2Cl_2–ether (7:1) to give 0.75 g (43.5%) of **14** as a yellowish oil: R_f(I) 0.15; NMR (Me_2SO-d_6) δ 1.05 (3 H, t), 1.18 (6 H, t), 1.8–2.2 (2 H, m), 2.9 (3 H, m), 3.95 (6 H, m), 7.2 (5 H, m).

Benzyl 3-(diethoxyphosphoryl)-2(*R*,*S*)-propionic Acid (9c). A solution of **14** (0.745 g, 2.27 mmol) EtOH (5 mL), H_2O (4 mL), and 2 N KOH (1.13 mL) was stirred at 23 °C for 4 h and then neutralized with 2 N HCl (1.13 mL). After removal of the solvents, the crude product was chromatographed on silica gel with CH_2Cl_2–MeOH (95:5) to give 0.3g (44%) of **9c** as a pale oil: R_f(C) 0.46; NMR (Me_2SO-d_6) δ 1.2 (6 H, t, J = 7), 1.7 (1 H, m), 2.05 (1 H, m), 2.7–3.0 (3 H, m), 3.95 (4 H, m), 7.15–7.35 (5 H, m), 12.3 (1 H, br s). The product was used without further purification.

Piv$\overset{C}{-}$Phe-His-Cha$\overset{OH}{-}$Val-NH(CH_2)$_3$$CH_3$ (8f). A mixture of acid **9b** (40 mg, 0.16 mmol), histidine derivative **7b** (50 mg, 0.11 mmol), HOBT (25 mg, 0.16 mmol), and DCC (36 mg, 0.17 mmol) was stirred in DMF (2 mL) for 7 h at 0 °C, followed by 16 h at room temperature. After removal of the insoluble urea by filtration and evaporation of the solvent, the crude product was dissolved in 10 mL of MeOH–AcOH–H_2O (94:3:3) and stirred at 60 °C for 1 h. The solvent was evaporated, and the product was purified by flash column chromatography on silica gel with CH_2Cl_2–MeOH–NH_4OH (90:10:1) to give **8f** as an approximately 1:1 mixture of diastereomers (55 mg, 72%): R_f(P) 0.33; $[\alpha]_D$ −49.0° (*c* 0.50, MeOH); FAB-MS, *mz* M + H at 694; NMR (Me_2SO-d_6) δ 1.03/1.00 (2 s, 9 H), 3.76–3.62 (1 H, m), 4.47–4.30 (1 H, m), 4.72–4.56 (1 H, br, OH), 6.82/6.68 (2 s, 1 H, CH-imidazole), 7.31–7.07 (6 H, m), 7.53/7.50 (2 s, 1 H, CH-imidazole), 7.65 (q, 1 H, NH), 8.20/8.14 (2 d, 1 H, NH), 11.85 (1 H, br, NH-imidazole). Anal. ($C_{40}H_{63}N_5O_5{\cdot}0.5H_2O$) C, H, N.

Ethyl 2-Benzyl-3-(*tert*-butylsulfonyl)propionate (16). To a solution of ethyl 2-benzylacrylate (**13**)[12] (60 g, 0.315 mol) in anhydrous EtOH (600 mL) was added *tert*-butyl mercaptan (36.6 mL, 0.315 mol) at 0–5 °C and a catalytic amount of NaH (0.7 g, 50% dispersion in oil, 0.016 mol). The resulting light yellow solution was stirred for 2 h at 0–5 °C followed by 40 h at 25 °C. The reaction mixture was diluted with H_2O (500 mL) and acidified with 2 N H_2SO_4 (10 mL), and the crude thioether **15** was directly oxidized with potassium hydrogen persulfate[14] (261 g Oxone, 55% in $KHSO_5$, 0.945 mol), which was added in small portions at 0–5 °C. The resulting white slurry was stirred for 15 h at room temperature. The insoluble salts were removed by filtration, and the organic solvent was evaporated. The remaining aqueous solution was extracted with CH_2Cl_2 (2 × 500 mL), and the combined extracts were washed with brine (100 mL), dried (Na_2SO_4), and concentrated to give **16** as a light yellow oil (91.8 g, 93%), which crystallized on standing: mp 47–48 °C; R_f (Q) 043; EIMS, *m/e* 312 (M^+); NMR ($CDCl_3$) δ 2.95 (1 H, dd, J = 12, 8, 3.9 Hz), 3.01 (1 H, dd, J = 13.8, 7.4 Hz), 3.10 (1 H, dd, J = 13.8, 7.4 Hz), 3.42 (1 H, m), 3.46 (1 H, dd, J = 12.8, 8.4 Hz), 4.12 (2 H, q, J = 7.4 Hz), 7.25 (5 H, m); IR (film, cm^{-1}) 1735, 1300, and 1120. Anal. ($C_{16}H_{24}O_4S$) C, H, S.

Ethyl 2-Benzyl-3-(*tert*-butylsulfinyl)propionate (17). To a solution of **15** (4.48 g, 16 mmol) in CH_2Cl_2 (40 mL) was added the solution of *m*-chloroperbenzoic acid (3.06 g, 16 mmol) in CH_2Cl_2 (30 mL) at −78 °C. After being stirred for 2 h at −78 °C and for 17 h at 23 °C, the solution was washed with 1 N $NaHCO_3$ and (50 mL), H_2O (25 mL) and dried (Na_2SO_4). After removal of the solvent, the crude product was chromatographed on silica gel with ethyl acetate–hexane (1:1) to give 3.2 g (68%) of **17** as a colorless oil: R_f(J) 0.14; IR(CH_2Cl_2) 1723, 1205, 1172, 1033 cm^{-1}; NMR (Me_2SO-d_6) δ 1.0–1.2 (12 H, m), 2.6–3.2 (5 H, m), 4.0 (2 H, m), 7.3 (5 H, m). The product was used directly.

2-Benzyl-3-(*tert*-butylsulfinyl)propionic Acid (9e). To a solution of **17** (3.2 g, 10.8 mmol) in MeOH (30 mL) and H_2O (30 mL) was added 1 N NaOH (10.8 mL). The solution was stirred at 23 °C for 16 h. After addition of 1 N HCl (10.8 mL) and evaporation of the solvent, the crude product was chromatographed on silica gel with CH_2Cl_2–MeOH (4:1) to give 1.52 g (52%) of **9e** as a white foam; R_f(H) 0.38. The product was used directly without further purification.

2-Benzyl-3-(*tert*-butylthio)propionic Acid (9f). A solution of **15** (0.5 g, 1.78 mmol), THF (5 mL), 2 N KOH (1.8 mL), and H_2O (3.2 mL) was stirred for 30 h. After addition of 2 N HCl (1.8 mL) and evaporation of the solvent, the curde product was chromatographed on silica gel with CH_2Cl_2–MeOH (19:1) to give 60 mg (13%) of **9f** as a yellow oil: R_f(C) 0.57; NMR (Me_2SO-d_6) δ 1.25 (9 H, s), 2.55–2.9 (5 H, m), 7.22 (5 H, m), 12.4 (1 H, s). Anal. ($C_{14}H_{20}O_2S$) C, H, S.

2-Benzyl-3-(*tert*-butylsulfonyl)propionic Acid (9d). A solution of **16** (91.9 g, 0.3 mol) in 6 N aqueous HCl (500 mL) and acetic acid (100 mL) was heated at reflux for 15 h. The crude acid **9d**, which crystallized directly from the reaction mixture, was collected by filtration and twice recrystallized from ethyl acetate to yield **9d** (68.3 g, 80%) as white crystals: mp 147–148 °C; R_f(B) 0.4; EIMS, m/e 284 (M^+); NMR ($CDCl_3$) δ 1.35 (9 H, s), 2.97 (1 H, m), 3.05 (1 H, dd, J = 13.8, 7.4 Hz), 3.22 (1 H, dd, J = 13.8, 6.1 Hz), 3.45 (2 H, m), 7.25 (5 H, m), 8.5 (1 H, br s); IR (KBr, cm^{-1}) 3440, 1715, 1300, and 1110. Anal. ($C_{14}H_{20}O_4S$) C, H, S.

Resolution of 2-Benzyl-3-(*tert*-butylsulfonyl)propionic Acid (9d). Method A. From Diastereomeric Amides. The racemic acid **9d** (12.5 g, 44.0 mmol), L-phenylalaninol (7.32 g, 48.4 mmol), HOBT (7.41 g, 48.4 mol) and DCC (11.80 g, 57.22 mmol) were dissolved in DMF (400 mL) and stirred at room temperature for 21 h. After removal of the insoluble urea by filtration and evaporation of the solvent, the crude product was purified by flash column chromatography (silica gel, 1:1 ethyl acetate–hexane) to give 8.00 g (19.1 mmol, 43%) of the pure unpolar diasteriomeric amide and 5.10 g (12.2 mmol, 28%) of the pure polar diasteriomeric amide as white solids. **Unpolar amide**: R_f(O) 0.24; NMR (Me_2SO-d_6) δ 1.22 (9 H, s), 2.67–2.58 (1 H, m), 2.95–2.75 (4 H, m), 3.17–3.05 (2 H, m), 3.35–3.17 (2 H, m), 3.85 (1 H, m), 4.63 (1 H, t, OH), 7.32–7.11 (10 H, m), 7.95 (d, 1 H, NH); $[\alpha]^{22}_D$ +0.4° (c 1.0, MeOH). **Polar amide**: R_f(O) 0.12; NMR (Me_2SO-d_6) δ 1.20 (9 H, s), 2.58–2.45 (2 H, m), 2.97–2.62 (3 H, m), 3.13–3.03 (1 H, m), 3.31–3.20 (1 H, m), 3.48–3.35 (2 H, m), 3.88 (1 H, m), 4.66 (1 H, t, OH), 7.28–7.05 (10 H, m), 8.05 (d, 1 H, NM); $[\alpha]^{22}_D$ −47.4° (c 1.0, MeOH).

The unpolar amide (5 g, 12.0 mmol) was dissolved in 1:3 acetic acid–6 N HCl (100 mL) and stirred for 5 h at 90 °C. After removal of the solvent, the residue was dissolved in CH_2Cl_2 (150 mL), and the L-phenylalaninol was removed by extraction with 2 N HCl (2 × 100 mL). The organic phase was evaporated to give 6.6 g of an oily residue, which was purified by flash column chromatography (silica gel 400:10:1 CH_2Cl_2–MeOH–NH_4OH) to yield the unpolar acid (3.25 g, 95%), assigned on the basis of the biological activity as having the S configuration. (S)-**9d**: NMR (Me_2SO-d_6) δ 1.23 (9 H, s), 2.81–2.73 (dd, 1 H, part of AB system, J = 15 Hz), 2.93–2.83 (1 H, m), 3.12–3.00 (2 H, m), 3.58–3.48 (dd, 1 H, part of AB system, J = 15 Hz), 7.30–7.10 (5 H, m, Ar); $[\alpha]_D$ +7.1° (c 0.98, MeOH). R-**9d**: $[\alpha]_D$ −8.6° (c 1.01, MeOH).

(S)-(+)-2-Benzyl-3-(*tert*-butylsulfonyl)propionic Acid [(S)-9d]. Method B. From Diastereomeric Salts. To a solution of the racemic acid **9d** (142 g, 0.5 mol) in i-PrOH (2 L) were added purified (+)-dehydroabiethylamine (85.7 g, 0.3 mol) and NEt_3 (27.8 mL, 0.2 mol), and the precipitated salt was recrystallized from hot i-PrOH. After an additional three recrystallizations of the salt, the acid was liberated and twice recrystallized from EtOAc–hexane to give (S)-**9d** (25.5 g, 18%) in high optical purity (≥98% ee) as determined by GC analysis of its (−)-menthol ester: mp 99–101 °C; $[\alpha]_D$ +10.9° (c 0.91, CH_2Cl_2). Anal. ($C_{14}H_{20}O_4S$) C, H, S.

***N*-[(2*S*)-Benzyl-3-(*tert*-butylsulfonyl)propionyl]-His-Cha$\overset{OH}{__}$Val-NH$(CH_2)_3CH_3$ (8i).** To a solution of **7b** (13.9 g, 30 mmol), HOBT (5.7 g, 36 mmol), and (S)-**9d** (10.2 g, 36 mmol) in DMF (300 mL) was added at 0 °C DCC (8.1 g, 39 mmol), and the resulting solution was stirred for 2 h at 0 °C followed by 18 h at room temperature. The reaction mixture was acidified with 50% aqueous acetic acid (50 mL) and stirred for 1 h at 50 °C. The suspension was concentrated to about half of its original volume, cooled to 0 °C, and filtered. The filtrate was evaporated, and the residue was partitioned between ethyl acetate (300 mL) and $NaHCO_3$ solution (200 mL). The organic portion was washed with brine (100 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography (10:1 CH_2Cl_2–MeOH) and then crystallized from CH_2Cl_2–hexane to yield **8i** (19.2 g, 88%) as white crystals: mp 148–149 °C; $[\alpha]_D$ −30.3° (c 0.95, MeOH); R_f(C) 0.24; FAB MS, m/e 730 (M^+ + 1); NMR ($CDCl_3$) δ 0.85–0.95 (9 H, m), 1.39 (9 H, s), 1.1–1.9 (19 H, m), 2.1 (1 H, m), 2.84 (1 H, dd, J = 13, 9 Hz), 2.94 (1 H, dd, J = 13, 3 Hz), 3.0–3.4 (9 H, m), 3.46 (1 H, m), 3.60 (1 H, dd, J = 12, 9 Hz), 3.81 (1 H, m), 4.56 (1 H, m), 6.38 (1 H, br s), 6.43 (1 H, br d, J = 10 Hz), 6.84 (1 H, br s), 7.15–7.30 (5 H, m), 7.34 (1 H, br s), 7.48 (1 H, s), 11.8 (1 H, br s); IR (KBr, cm^{-1}) 3320, 1640, 1540, 1290, and 1120. Anal. ($C_{39}H_{63}N_5O_6S$) C, H, N, S.

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Registry No. **1c**, 105852-46-8; **1d**, 105852-47-9; **1d** (semicarbazone), 114469-32-8; (1S,2′R)-**2b**, 105852-48-0; (1S,2′S)-**2b**, 105852-30-0; (4S,5R)-**3b**, 105852-50-4; (4S,5S)-**3b**, 114469-19-1; (2S)-[4S,5S]-**4b**, 102522-22-5; (2R)-[4S,5S]-**4c**, 105852-51-5; (2S)-[4S,5S]-**4c**, 105857-29-2; **5b**, 102522-24-7; **5d**, 105852-42-4; **5d** (2R diastereomer), 105864-88-8; **5e**, 105852-65-1; **6a**, 102522-16-7; **6c**, 105852-64-0; **7b**, 105852-62-8; **7b** (N-Cbz derivative), 105852-63-9; **8a**, 102522-26-9; **8b**, 102522-56-5; **8c**, 114469-20-4; **8d**, 114469-21-5; **8e**, 105851-89-6; **8f** (diastereomer 1), 105851-79-4; **8f** (diastereomer 2), 105927-79-5; **8g** (diastereomer 1), 105928-01-6; **8g** (diastereomer 2), 105851-92-1; **8i**, 114469-22-6; **8j**, 114530-03-9; **8k** (diastereomer 1), 114469-23-7; **8k** (diastereomer 2), 114530-05-1; **8l** (diastereomer 1), 114469-24-8; **8l** (diastereomer 2), 114530-06-2; **9a**, 105852-83-3; **9b**, 105852-66-2; **9c**, 95272-47-2; **9d**, 114469-25-9; (S)-**9d**, 114530-04-0; **9e**, 114469-26-0; **9f**, 114469-27-1; **10**, 7622-21-1; **11**, 607-81-8; **12**, 114469-28-2; **13**, 20593-63-9; **14**, 95176-70-8; **15**, 114469-29-3; **16**, 114469-30-6; **17**, 114469-31-7; (R)-(−)-MTPA chloride, 39637-99-5; Z-Cha-OH·DCHA, 54594-40-0; trt-His-(trt)-OH, 74853-62-6; Z-His-OH, 14997-58-1; H-Ile-His-NH_2, 102522-23-6; Piv-Phe-OH, 32909-56-1; H-His-OMe·2HCl, 7389-87-9; Piv-Phe-His-OMe, 102522-57-6; Piv-Phe-His-OH, 102522-55-4; Piv-Cl, 3282-30-2; Piv-Pla-OCH_2Ph, 105852-84-4; H-Phe-ol, 3182-95-4; (S)-$CF_3CPh(OMe)CONH$-(S)-$CH(CH_2$-c-$C_6H_{11})$-CH_2OH, 114469-33-9; (S)-$CF_3CPh(OMe)CONH$-(R)-$CH(CH_2$-c-$C_6H_{11})CH_2OH$, 114469-34-0; Cbz-NH-(S)-$CH(CH_2$-c-$C_6H_{11})$-(R)-$CH(OSiMe_3)CH_2I$, 114469-35-1; Cbz-NH-(S)-$CH(CH_2$-c-$C_6H_{11})$-(S)-$CH(OSiMe_3)CH_2I$, 114469-36-2; Cbz-NH-(S)-CH-$(CH_2$-c-$C_6H_{11})$-(R)-$CH(OH)CH_2I$, 114469-37-3; Cbz-NH-(S)-CH-$(CH_2$-c-$C_6H_{11})$-(S)-$CH(OH)CH_2I$, 114469-38-4; $CH_3C(OMe)_2CH_3$, 77-76-9; $CH_3CH(CH_3)CH_2COOMe$, 556-24-1; $BuNH_2$, 109-73-9; $PhCH_2Br$, 100-39-0; $CH_3C(CH_3)_2COCH_2Br$, 5469-26-1; t-BuSH, 75-66-1; t-$BuSO_2CH_2$-(S)-$CH(CH_2Ph)CO$-L-Phe-ol, 114469-41-9; t-$BuSO_2CH_2$-(R)-$CH(CH_2Ph)CO$-L-Phe-ol, 114469-42-0; lactone A, 114469-39-5; lactone B, 114469-40-8; renin, 9015-94-5.