Renin Inhibitors Containing a Pyridyl Amino Diol Derived C-Terminus

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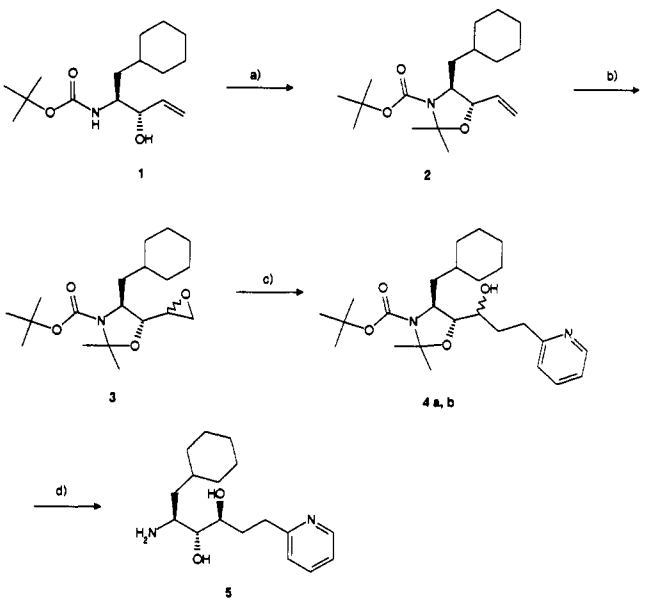
Based on the concept of transition-state analogs, a series of nonpeptide renin inhibitors with the new (2*S*,3*R*,4*S*)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexane moiety at the C-terminal functionality were synthesized and evaluated for inhibition of renin both *in vitro* and *in vivo*. All compounds exhibited potencies in the nanomolar or even subnanomolar range when tested *versus* human renin *in vitro*. Selected inhibitors were evaluated in anesthetized, sodium-depleted rhesus monkeys and produced a marked reduction in mean arterial blood pressure (MAP) upon intraduodenal administration of a dose of 2 mg/kg. Compound **38** (S 2864) containing an amino piperidyl succinic acid derived N-terminal is the most promising member in this series. **38** inhibited human renin with an IC_{50} of 0.38 nM, did not affect other human aspartic proteinases, and decreased mean arterial blood pressure significantly by 27% with a duration of action of 90 min after administration of 2 mg/kg id in anesthetized, sodium-depleted rhesus monkeys.

The renin–angiotensin system (RAS) is a multiregulated enzymatic-hormonal system controlling electrolyte homeostasis, fluid volume, and arterial blood pressure.[1] The clinical success of angiotensin-converting enzyme (ACE) inhibitors as antihypertensive agents in both normal and high renin forms of hypertension[2] demonstrate the widespread benefit of drugs targeted at the RAS. The therapeutic value of ACE inhibitors is diminished due to the occurrence of dry cough and the possible life-threatening angioneurotic edema with an incidence of 5–20% and 0.1–0.2%, respectively.[3] These adverse effects are not predictably associated with any other class of drugs and may be attributed to the low specificity of ACE, which degrades a variety of substances, e.g., bradykinin, enkephalins, and substance P besides angiotensin I.[4] However, angiotensinogen is the only known natural substrate of renin, and therefore inhibition of the highly specific enzyme renin might be a valuable alternative to ACE inhibition.

The most successful approach for the design of renin inhibitors has been based on the concept of tetrahedral transition-state peptidomimetics as non-hydrolyzable analogues of the Leu-Val cleavage site in angiotensinogen.[5] Potent renin inhibitors with significantly *in vivo* activity on either plasma renin activity (PRA) or MAP derived from this approach are (2*S*,3*R*,4*S*)-2-amino-1-cyclohexyl 3,4-diols.[5,6] The lack of long-lasting oral activity of many renin inhibitors even in the class of diols is due to poor oral bioavailability. This might be caused either by limited gastrointestinal absorption or high hepatic clearance. Our approach to overcome these limitations was to synthesize low molecular weight structures with increased hydrophilicity at the C-terminal moiety and to reduce the overall peptidic nature of the compounds by suitable N-terminal substitution. Recently, aminopentols[7] have been published in which the P_1' side chain was replaced by a pentahydroxy carbohydrate-derived moiety. These compounds exhibited a pronounced blood pressure lowering effect and demonstrated the scope of this kind of C-terminal modification. Here we describe the synthesis of pyridyl amino diols, which resulted after suitable selection of the remaining subunits, in renin inhibitors with substantial activity *in vitro* and *in vivo*.

Scheme I. Synthesis of the Pyridyl Amino Diol Moiety **5**[a]



[a] Key: (a) 2-methoxypropene, *p*-TosOH, DMF; (b) MCPBA, CH_2Cl_2; (c) 2-picoline, *n*-BuLi, THF; separation; (d) CF_3COOH, H_2O, CH_2Cl_2.

Synthesis[8]

C-Terminus. The synthesis of the pyridyl amino diol C-terminus **5** is outlined in Scheme I. Starting from the (3*S*,4*S*)-diastereomer of the allylic alcohol **1**,[6c] which was obtained from L-phenylalanine in five steps,[9,10] the BOC-NH function and the hydroxyl group were protected by an acid-catalyzed reaction of **1** with 2-methoxypropene. Epoxidation of the resulting acetonide **2**[11] using MCPBA produced **3** as a 2.7:1.0 mixture of diastereomers favoring the 1*S*-isomer. The opening of the epoxide with the lithiated 2-picoline provided a separable 2:1 mixture of the protected amino diols **4a,b**. The major diastereomer

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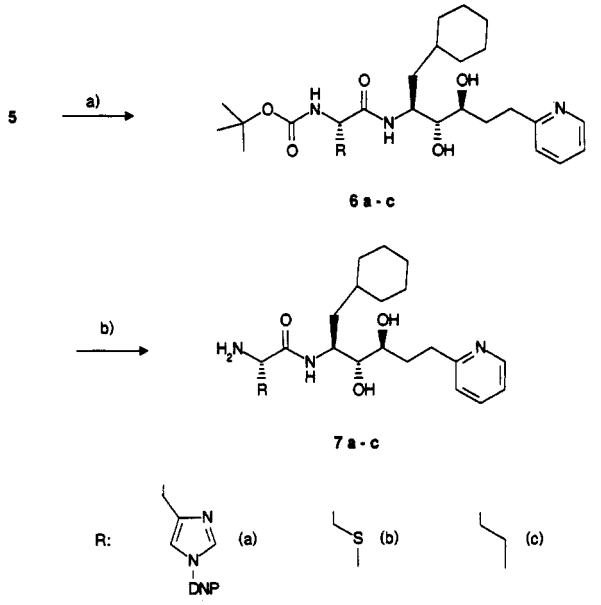
Scheme II. Coupling of the P_2-Amino Acids to 5[a]



[a] Key: (a) BOCNHCHRCOOH, DCC, HOBt, NEM, DMF; (b) CF_3COOH, CH_2Cl_2.

4a was converted to the free C-terminal 5 by treatment with aqueous trifluoroacetic acid. The configuration of the chiral centers in 5 was assumed to be 2*S*,3*R*,4*S* in accordance with structure–activity investigations of related amino diols[6b,c] and the superior *in vitro* activity *versus* renin of intact inhibitors derived from this fragment than that of corresponding inhibitors derived from the minor diastereomer 4b.[12]

Two alternative, stereoselective syntheses of 5 either by iterative homologation of L-cyclohexylalaninal *via* Dondoni's thiazole methodology[13] or by a chiral pool approach from D-(+)-mannose[14] suitable for large-scale preparations have been published recently.

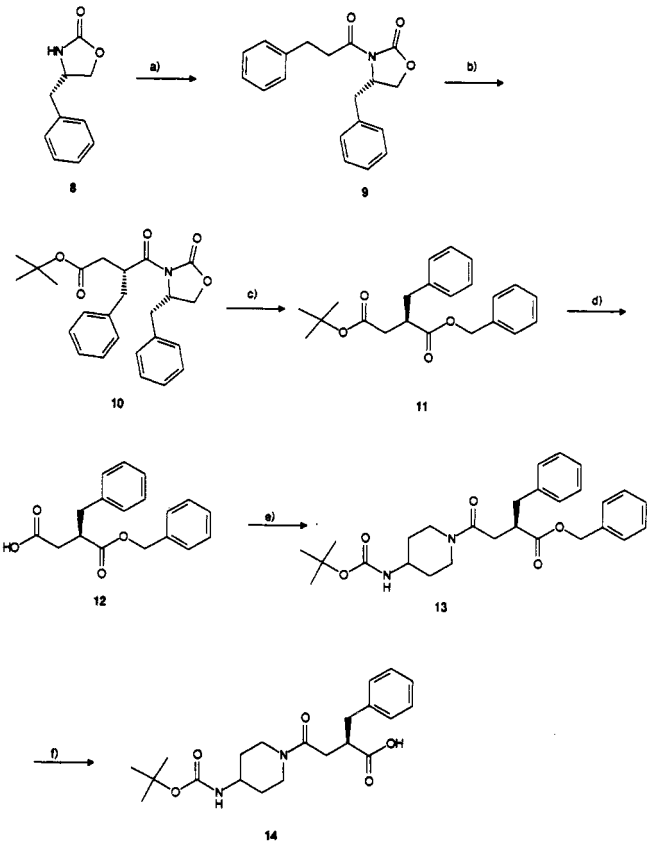
P_2 Extension. The N-terminal extension of the amino diol 5 at P_2 to the appropriate histidyl-, *S*-methylcysteinyl-, and norvalyl-containing fragments 7a–c was performed using standard solution peptide synthesis methodology (DCC/HOBt coupling, TFA-deprotection) *via* the intermediates 6a–c as shown in Scheme II.

N-Termini. The benzylsuccinic acid monoamide 14 was synthesized enantioselectively by application of the Evans' chiral enolate methodology (Scheme III).[6a,15] Thus, the lithium salt of (4*S*)-4-benzyloxazolidin-2-one (8) was acylated with 3-phenylpropionyl chloride to give 9. The oxazolidinone chiral auxiliary 8 was prepared according to previously reported methods.[15c] Deprotonation of 9 was followed by alkylation with *tert*-butyl bromoacetate to afford intermediate 10.[16] Successive steps of removal of the auxiliary, ester hydrolysis, condensation with 4-(BOC-amino)piperidine,[11] and cleavage of the benzyl ester by catalytic hydrogenation completed the synthesis.

An enantioselective, large-scale access to 14 *via* asymmetric hydrogenation in the presence of a tartaric acid derived cationic rhodium(I) complex has been developed recently.[17]

Enantioselective synthesis of (2*R*)-2-[(1-naphthyl)methyl]succinic acid monoamide 19 was achieved in the same way as described for 14 with minor modifications for similar N-termini (Scheme IV).[6d,18] Starting from chiral auxiliary 8 imide 15 was generated *via* acylation of 8 with (1-naphthyl)propionyl chloride. Deprotonation of 15 with

Scheme III. Synthesis of the Succinic Acid Derived N-Terminus 14[a]



[a] Key: (a) *n*-BuLi, THF, −78 °C; 3-phenylpropionyl chloride, T < 70 °C; (b) $NaN(SiMe_3)_2$, THF, T < −70 °C; $BrCH_2CO_2C(CH_3)_3$, THF, T < 70 °C; (c) $PhCH_2OH$, *n*-BuLi, THF, T < 5 °C; (d) CF_3COOH, CH_2Cl_2; (e) $(COCl)_2$, DMF, CH_2Cl_2; 4-BOCNH-piperidine; Et_3N, CH_2Cl_2; (f) H_2, Pd/C (10% Pd), EtOH.

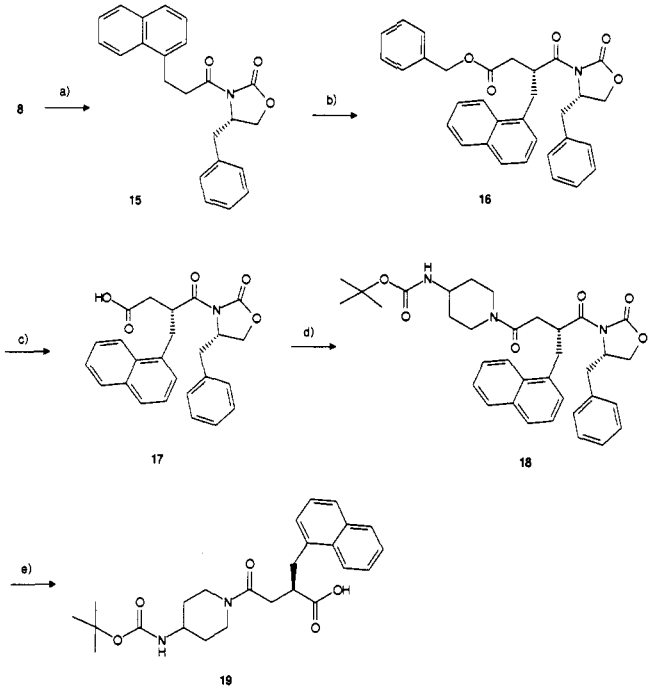
lithium diisopropylamide followed by reaction with benzyl bromoacetate afforded 16 diastereoselectivity.[16] After removal of the benzyl group by catalytic hydrogenation, HBTU-mediated coupling[17] of the resulting carboxylic acid 17 with 4-(BOC-amino)piperidine and hydrolysis of 18 provided the enantiomerically pure protected N-terminal acid 19. The overall yield following this sequence is somewhat lower than the one described in Scheme III due to the generation of the tetralin derivative of 17 during hydrogenation of 16.

The *O*-methyltyrosine derivative 22 was synthesized from protected *cis*-4-aminocyclohexanecarboxylic acid 20[20] by standard DCC/HOBt coupling to *O*-methyl L-tyrosine methyl ester and ester hydrolysis of 21 in quantitative yield (Scheme V).

The syntheses of the racemic N-terminal sulfonemethylene isosteres 27 and 32 are outlined in Schemes VI and VII, respectively. The key step in both pathways was the introduction of the sulfur functionality by nucleophilic addition of a thioacyl derivative to a benzyl acrylate ester.[21] As shown in Scheme VI, the route leading to N-terminus 27 started with the addition of thioacetic acid to benzyl 2-benzylacrylate. The resultant thioester 24 was converted to the sulfonyl chloride 25 by oxidation with chlorine in aqueous solution.[22] Condensation of 4-(BOC-amino)-piperidine with 25 in a Schotten–Baumann reaction and cleavage of the benzyl ester function provided the piperidinesulfonyl derivative 27.

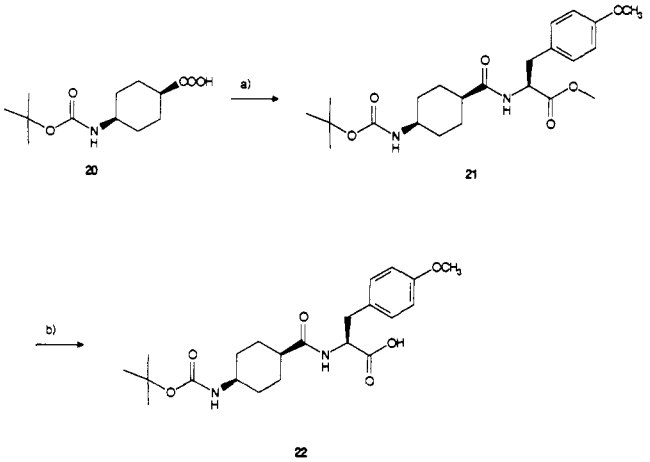
The synthesis of the corresponding cyclohexylsulfone 32 started with a Mitsunobu displacement[23] of the hydroxy

Scheme IV. Synthesis of the Naphthyl Succinic Acid Derived N-Terminus **19**[a]



[a] Key: (a) *n*-BuLi, THF, −78 °C; (1-naphthyl)propionyl chloride, THF, −78 °C; (b) LDA; benzyl 2-bromoacetate, THF, −78 °C → 0 °C; (c) H_2, Pd/C (10% Pd), EtOH; (d) 4-BOCNH-piperidine; HBTU, DMF; (e) LiOH, aqueous THF, 0 °C.

Scheme V. Synthesis of the (Aminocyclohexyl)-*O*-methyltyrosine N-Terminus **22**[a]



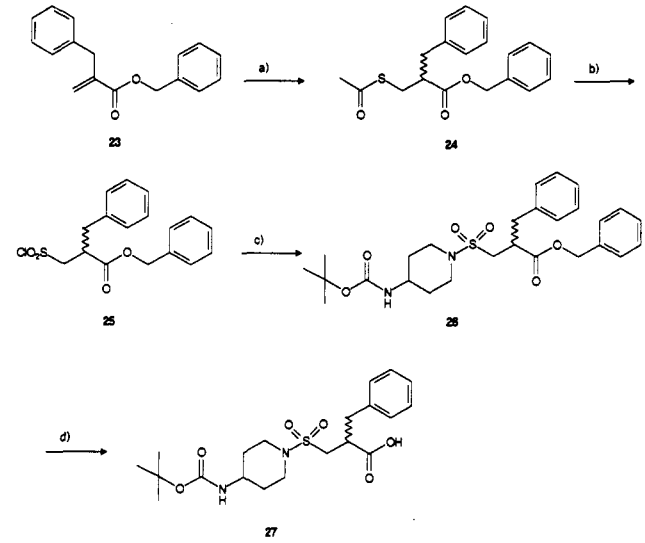
[a] Key: (a) *O*-methyl-L-tyrosine methyl ester, DCC, HOBt, NEM, DMF; (b) 1 N NaOH, EtOH.

group of 4-(BOC-amino)cyclohexanol by thioacetic acid and subsequent conversion of the resultant thioester **29** to the ethyl benzylpropionic acid derivative **30** by addition to ethyl 2-benzylacrylate.[24] Hydrolysis followed by oxidation of the sulfide **31** with potassium hydrogen persulfate[25] completed the synthesis (Scheme VII).

The adipic acid derived N-terminus **35** was synthesized by PPA-mediated coupling[26] of adipic acid monoethyl ester to *O*-benzyl L-phenylalanine **33** and subsequent hydrogenation of the intermediate **34** (Scheme VIII).

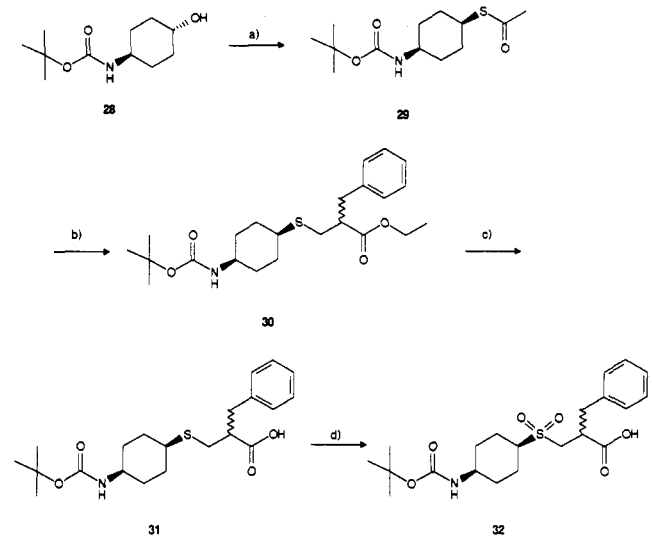
Completion of the Synthesis. The completion of the synthesis is exemplified by the preparation of the renin inhibitor **38** as shown in Scheme IX. Straightforward coupling of the N-terminal benzylsuccinic acid **14** to the N^{im}-protected amino diol–histidyl C-terminal **7a** using

Scheme VI. Preparation of the (4-Aminopiperidine)-sulfonyl Derived N-Terminus **27**[a]



[a] Key: (a) CH_3COSH, 70 °C; (b) Cl_2, H_2O; (c) 4-BOCNH-piperidine, Et_3N, CH_2Cl_2; (d) H_2, Pd/C (10% Pd), MeOH.

Scheme VII. Preparation of the (Aminocyclohexyl)-sulfonyl Derived N-Terminus **32**[a]

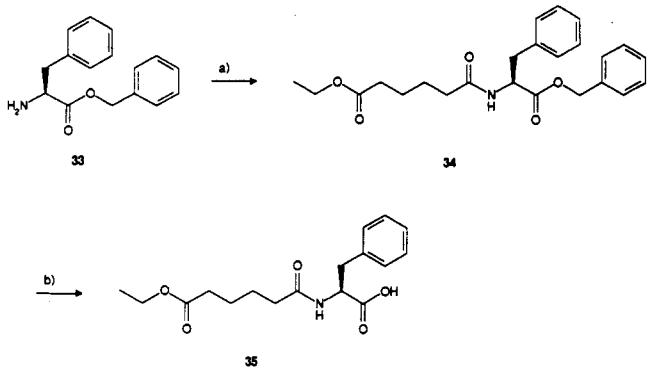


[a] Key: (a) CH_3COSH, DEAD, Ph_3P, THF; (b) $[(CH_3)_3Si]_2NNa$, ethyl 2-benzylacrylate, MeOH; (c) 1 N NaOH, DME; (d) oxone, $MeOH/H_2O$.

HBTU yielded the protected amide **36**. Successive cleavage of the DNP-group with thiophenol and acid-catalyzed BOC-deprotection followed by ion exchange afforded renin inhibitor **38** as an acetate (S 2864).

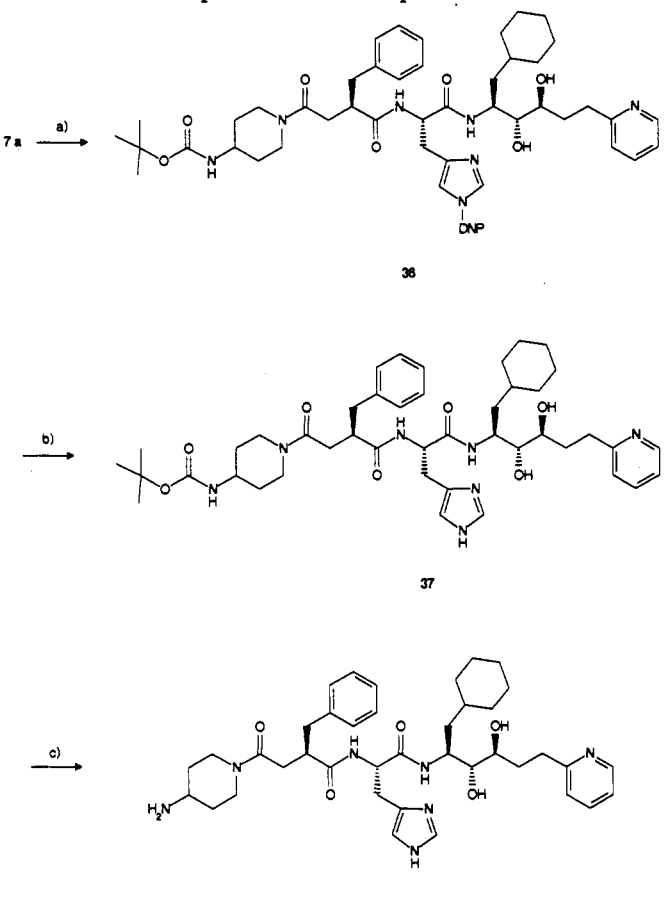
Likewise, 12 additional inhibitors **39–50** utilizing a pyridyl amino diol derived C-terminus were synthesized. Their structures are listed in Table I. For some of them, DCC/HOBt or PPA was used as coupling reagent instead of HBTU as described above. Compound **42** required a trityl protecting group on the histidyl residue and an acetonide protection on the amino diol residue of the P_2-elongated C-terminal coupling unit. The N-terminal sulfonyl-substituted acid components **27** and **32** were coupled as racemic mixture to the C-terminal fragment **7a**. The resulting diastereomeric mixture of protected amides could be separated by chromatography. The configuration of the chiral center of the acid components was assumed to be *R* in the diastereomer resulting in the

Scheme VIII. Preparation of the Adipic Acid Derived N-Terminus 35[a]



[a] Key: (a) $EtO_2C(CH_2)_4CO_2H$, PPA, THF; (b) H_2, Pd/C (10% Pd), EtOH.

Scheme IX. Preparation of the Peptide Derivative 38[a]



[a] Key: (a) 14, HBTU, HOBt, NEM, CH_3CN; (b) PhSH, CH_3CN; (c) CF_3COOH, CH_2Cl_2, IRA-93 ion exchange.

more potent inhibitor and to be *S* in the corresponding diastereomer resulting in the less potent inhibtor. (2*S*)-2-Benzyl-3-(*tert*-butylsulfonyl)propionic acid,[21] *cis*-*N*-[[4-[(*tert*-butyloxycarbonyl)amino]cyclohexyl]carbonyl]-L-phenylalanine,[7] (2*R*)-2-benzyl-3-(morpholinocarbonyl)-propionic acid,[6a] (2*S*)-[[[*N*-methyl-*N*-[2-[*N*-(morpholinocarbonyl)-*N*-methylamino]ethyl]amino]carbonyl]oxy]-2-phenylpropionic acid[7] and (2*S*)-2-[4-[(*tert*-butyloxycarbonyl)amino]-1-[(piperidylcarbonyl)oxy]-3-phenylpropionic acid[11] incorporated into renin inhibitors **39**, **40**, **43**, **44**, and **49** have been characterized as efficient N-terminal subunits of known competitive renin inhibitory structures and have been synthesized by analogy to described procedures.

Biological Results

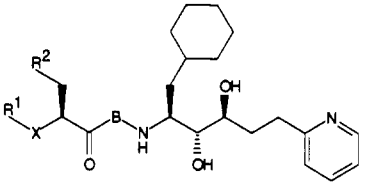
***In Vitro* Activity.** As shown in Table I, all renin inhibitors described elicit an *in vitro* activity in the purified kidney as well as in the physiologically more relevant human plasma renin assay predominantly in the subnanomolar range. The slight differences observed in compounds **38–50** gave evidence for the negligible influence of the selected N-terminal variations on the *in vitro* activity of the pyridyl amino diol derived renin inhibitors. Obviously, structurally different residues are tolerated in this region of the enzyme. Potency of compound **41** is decreased by a factor of 10 compared to **40**, indicating that a methoxy substituent on the phenyl ring in the P_3-residue decreases the affinity of renin for its synthetic inhibitor. Thus, the dominant influence on the *in vitro* activity of renin inhibitors **38–50** is the presence of the pyridyl amino diol moiety. Inhibitors derived from this C-terminus seems to be well accepted by the active side of the target enzyme tolerating a broad spectrum of N-terminal residues. This finding is supported by a comparison of the IC_{50} values of compounds **38–50** with those of the corresponding (2*S*,3*S*)-2-amino-1-cyclohexyl-3-hydroxy-6-(2-pyridyl)hexyl- and (2*S*,3*R*,4*S*)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-phenylhexyl derivatives, respectively.[27] The lack of the second hydroxy group or the substitution of the pyridyl by a phenyl ring on the C-terminal component in these analogs are correlated with a dramatic loss in renin inhibitory potency of approximately 2 orders of magnitude. This *in vitro* structure–activity relationship is in accordance with the *in vivo* experiments for both classes of compounds.[26] Variation of the amino acid in P_2 (compounds **47** and **48**) is with the little influence on the *in vitro* affinity to renin.

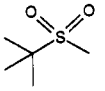
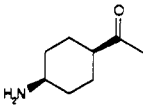
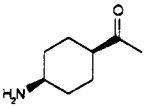
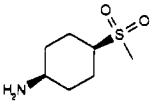
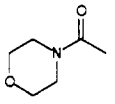
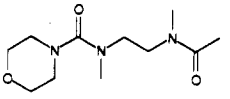
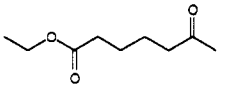
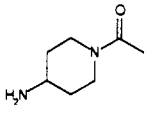
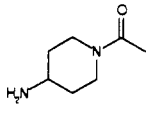
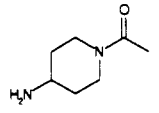
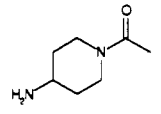
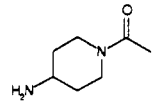
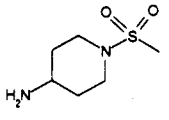
Enzyme Selectivity. The most promising compound **38** (S 2864) in this series of renin inhibitors was tested for activity against renin of various animal species and against human aspartic proteinases other than renin in concentrations up to 10^{-4} M. Measured IC_{50} values listed in Table II indicate the high specificity of compound **38** for human renin in comparison to the related human proteinases such as pepsin, gastricsin, cathepsin D, and cathepsin E with an activity split of a factor of $>10^5$ between these enzymes. **38** also exhibits high inhibitory efficacy against dog, sheep, guinea pig, and rhesus monkey plasma renin but only weak activity against rat plasma renin.

Enzymatic Stability. In order to investigate the enzymatic stabilities of selected compounds, representative renin inhibitors were studied in a chymotryptic digestion assay. Experimental half-lives ($t_{1/2}$) are listed in Table III. The values are in agreement with the fact that a decreased number of peptide bonds in the structure increases proteolytic stability. Thus, compound **40** with three native peptide bonds was rapidly cleaved by chymotrypsin. Compounds **39** and **50** with sulfonyl-derived N-termini are the most stable inhibitors due to their optimally reduced peptidic nature. Compounds **38** and **41** exhibit a moderate but substantial stability *versus* chymotrypsin degradation with $t_{1/2} \approx 90$ min.

***In Vivo* Activity.** The compounds **38**, **41**, **42**, **43**, and **44** were chosen, as representative members of the amino diol derived inhibitors, to investigate their blood pressure lowering effects in sodium-depleted, anesthetized rhesus monkeys (Figures 1 and 2). Figure 1 shows the MAP response of inhibitors **41–42** after intraduodenal administration of a dose of 2 mg/kg of each compound. In

Table I. *In Vitro* Renin Inhibition of the Pyridyl Amino Diols **38–50**



	R¹	X	R²	B	IC_{50}[a] [nM] human plasma renin	IC_{50}[a] [nM] kidney renin
39		CH_2	Ph	L-His	0.43 (3)	0.17 (2)
40		NH	Ph	L-His	0.47 (6)	0.50 (4)
41		NH	pCH_3OPh	L-His	5.3 (4)	4.2 (3)
42		CH_2	Ph	L-His	0.31 (2)	0.31 (3)
43		CH_2	Ph	L-His	1.10 (2)	1.10 (1)
44		O	Ph	L-His	0.14 (3)	0.16 (2)
45		NH	Ph	L-His	0.75 (2)	0.69 (3)
38		CH_2	Ph	L-His	0.38 (17)	0.39 (4)
46		CH_2	1-Naphthyl	L-His	0.79 (4)	0.13 (1)
47		CH_2	Ph	L-Cys(Me)	0.25 (2)	0.26 (2)
48		CH_2	Ph	L-Nva	1.30 (2)	0.68 (2)
49		O	Ph	L-His	0.37 (2)	0.53 (4)
50		CH_2	Ph	L-His	0.54 (5)	0.70 (1)

[a] Individual data differed for $n \geq 2$ by not more than 20% from the mean, except for **43** and **46** (27%). n = number of determinations.

contrast to the *in vitro* structure–activity relationships the different incorporated N-termini are of decisive importance for the hypotensive efficacy of these inhibitors reflecting their influence on water solubility and especially on the hydrophilic/hydrophobic balance of the structures.

Compound **44** had no effect on MAP at the selected dose. The lack of *in vivo* activity of this compound might be explained mainly as a result of poor gastrointestinal absorption, possibly accompanied by fast hepatic clearance due to the lipophilicity of the N-terminus and the high

Table II. Enzyme Selectivity of Inhibitor 38

aspartic proteinase	IC_{50} [M]
human pepsin	$>10^{-4}$
human gastricsin	$>10^{-4}$
human cathepsin D	$>10^{-4}$
human cathepsin E	$>10^{-4}$
rat plasma renin	$2.55 \pm 0.66 \times 10^{-6}$
dog plasma renin	$15.0 \pm 3.0 \times 10^{-9}$
sheep plasma renin	$12.5 \pm 3.0 \times 10^{-9}$
guinea pig plasma renin	5.5×10^{-9}
rhesus monkey plasma renin	$2.4 \pm 0.3 \times 10^{-10}$
human plasma renin	$3.8 \pm 0.07 \times 10^{-10}$

Table III. Stability versus Chymotrypsin

compd	$t_{1/2}$ (min)	compd	$t_{1/2}$ (min)
38	91	**41**	~90
39	171	**43**	22
40	<3	**50**	~300

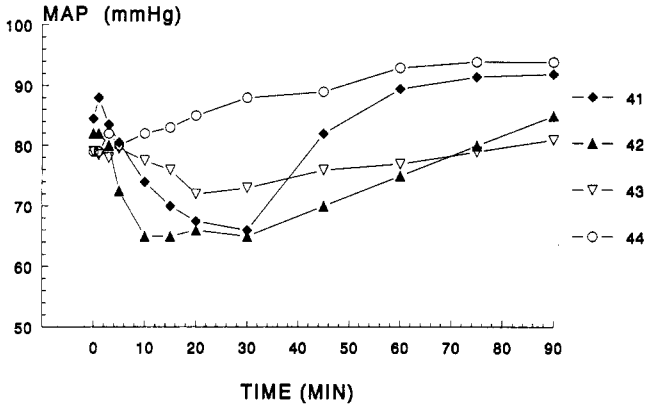


Figure 1. Effects on mean arterial blood pressure (MAP) of intraduodenal administration of 2 mg/kg of renin inhibitors 41–44 in salt-depleted, anesthetized rhesus monkeys.

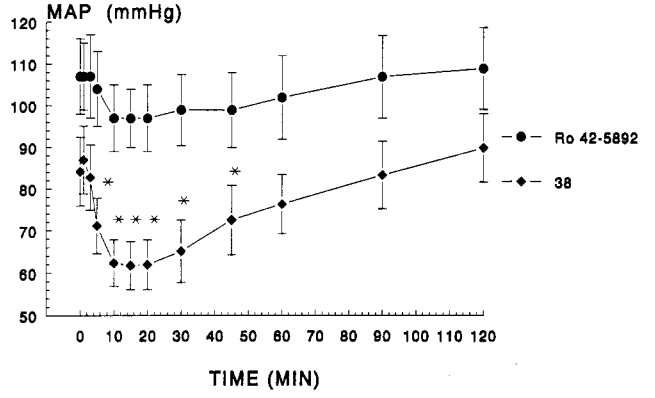


Figure 2. Comparison of blood pressure responses of salt-depleted, anesthetized rhesus monkeys to Ro 42–5892 (Remikiren) and renin inhibitor 38 (S 2864) after intraduodenal administration of 2 mg/kg (values are mean ± SEM, *: $p < 0.05$ vs Ro 42–5892).

molecular weight (804) of the inhibitor. On the contrary, inhibitors 41–43 exhibit a significant blood pressure lowering effect differing in onset, degree, and duration of action. Reduction of MAP was more pronounced by 41 and 42 than by 43 and returned to baseline levels after 40–50 min for 41 and after 70–80 min for 42 and 43 postdose. The only transient effect of compound 43 might be caused by its low solubility and the rapid degredation by chymotrypsin, whereas the weak and short effect of compound 41 might be correlated with its only moderate *in vitro* activity failing to block the compensatory renin release during inhibition of the RAS. Compound 42 was the most active inhibitor of these four candidates due to suitable solubility, chymotrypsin stability, and *in vitro* activity closely related to that of compound 38.

Figure 2 shows a comparison of the blood pressure response following intraduodenal administration of 2 mg/kg of compound 38 (S 2864), as the most active and promising candidate of this class of inhibitors *in vivo*, and the renin inhibitor clinical candidate Ro 42–5892 (Remikiren), which was described to be very potent after oral administration in small monkeys[6h] and has already demonstrated oral efficacy in man.[28] Inhibitor 38 lowered MAP from 84 to 62 mmHg (−27%) lasting for 90 min. Ro 42–5892 decreased MAP by 15 mmHg (−9%) lasting for 60 min. Plasma renin activity was significantly reduced during the whole course of the experiments for both compounds. These data demonstrate the superiority of 38 (S 2864) over a renin inhibitor in clinical trials, with statistically greater potency and duration of action in the selected *in vivo* model.

A full paper covering detailed results of the evaluation of S 2864 (plasma renin activity, plasma drug levels, plasma angiotensin II levels, bioavailability) is in preparation.

Conclusion

A new series of selective, nonpeptide renin inhibitors with a pyridyl amino diol derived C-terminus has been developed, demonstrating the high efficacy of the pyridyl moiety on the C-terminal residue of renin inhibitors. These compounds exhibited nanomolar or even subnanomolar activity in the human plasma renin assay. Several selected compounds of this series produced a significant to moderate short-lived reduction in blood pressure on intraduodenal administration to sodium-deficient rhesus monkeys. The outstanding member of these novel inhibitors, S 2864 (38), inhibited human plasma renin with an IC_{50} value of 0.38 nM and did not affect other human aspartic proteinases. It also exhibited a considerable, long-lasting blood pressure lowering effect after intraduodenal administration of 2 mg/kg in anesthetized, sodium-depleted rhesus monkeys. This *in vivo* activity was found to be superior to that of the known renin inhibitor clinical candidate Ro 42–5892 when tested in the same primate model.

Experimental Section

Solvents and other reagents were used without further purification unless otherwise stated. Product solutions were dried over anhydrous Na_2SO_4 prior to evaporation on a rotary evaporator. Column chromatography was carried out on E. Merck silica gel 60 (0.04–0.063 mm). Thin-layer chromatography was performed on silica gel F_{254} plates from E. Merck. Visualization was done with UV and by using bis[4-(dimethylamino)phenyl]-methane (TDM) or phosphomolybdic acid reagents. Ion exchange was carried out on Amberlite ion-exchange resin IRA-93 from Fluka AG. The NMR spectra were recorded on a Bruker AM 270. The 60-MHz spectra and one 400-MHz spectrum noted in the text were measured on a Bruker WP 60 and AM 400, respectively. Chemical shifts are reported as δ values (parts per million) from an internal tetramethylsilane standard. Positive FAB mass spectra were obtained on a Kratos MS 902 in a 3-nitrobenzylic alcohol matrix using xenon as the target gas. DCI mass spectra were determined on a Kratos MS 80 RFA using isobutane as reagent gas. GC analysis of compound 3 was performed on a HP 5890 using a J+W DB5+ column (30 m) at 180 °C and 1.0 bar H_2. Optical rotations at the sodium D line were measured on a Perkin-Elmer 241 polarimeter. Elemental analyses were determined by the analytical laboratories, Hoechst AG.

General Procedures. General Procedure A. Removal of BOC Protection. One mmol of the BOC-protected component

was dissolved in 2 mL/mmol of CH_2Cl_2, and an equal volume of trifluoroacetic acid was added to the stirred solution. After 3 h at room temperature, volatiles were evaporated. For preparation of the free base, the residue was dissolved in 20 mL of ethyl acetate, washed with saturated aqueous $NaHCO_3$, and brine, dried, and concentrated *in vacuo*. For preparation of the acetate salts, the residue was dissolved in water, treated with a sufficient amount (pH ~5) of ion-exchange resin (acetate form), filtered, and lyophilized.

General Procedure B. Amide Bond Formation with DCC/HOBt. One mmol of the amino fragment was dissolved in 10 mL of anhydrous DMF. After sequential addition of 1 mmol of HOBt × H_2O, 1 mmol of the carboxy component, and 1 mmol of DCC, the pH value of the reaction mixture was adjusted to 9 by adding an appropriate amount of *N*-ethylmorpholine. After being stirred for 24 h at room temperature, the mixture was filtered free of solids and evaporated to dryness. The residue was dissolved in a sufficient amount of ethyl acetate and washed with 1 N $NaHCO_3$ solution, water, and brine, followed by drying, evaporation, and chromatographic purification.

General Procedure C. Amide Bond Formation with HBTU. To a solution of 1 mmol of the amino fragment in 20 mL of acetonitrile were added sequentially 1 mmol of HOBt × H_2O, 1.5 mmol of *N*-ethylmorpholine, 1 mmol of HBTU, and 1 mmol of the carboxylic acid component. The mixture was stirred at room temperature for 2 h. Ten mL of brine was added and the mixture extracted with ethyl acetate. The combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine, dried, and chromatographed to homogeneity.

General Procedure D. Removal of N^{Im}-DNP Protection. A solution of 1 mmol N^{Im}-DNP-histidyl derivative and 8 mmol of thiophenol in 15 mL of acetonitrile was stirred at room temperature for 2 h. The reaction mixture was concentrated and the residue purified by chromatography.

(4*S*,5*S*)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-dimethyl-5-vinyloxazolidine (2). To a solution of 83.1 g (0.29 mol) of (3*S*,4*S*)-4-[(*tert*-butyloxycarbonyl)amino]-5-cyclohexyl-3-hydroxy-1-pentene (1)[6c] in 750 mL of dry DMF were added 71.0 mL (0.74 mol) of methoxypropene and 1.14 g of *p*-toluenesulfonic acid. After being stirred at ambient temperature for 3 h, the mixture was poured into water and extracted with ethyl acetate. The combined organic phases were washed with saturated $NaHCO_3$ solution, water, and brine and then dried and evaporated to afford 93.2 g (99.5%) of the oxazolidine as an oil: TLC R_f = 0.66 (cyclohexane/ethyl acetate); ^{1}H NMR ($CDCl_3$) δ = 5.95 (ddd, J = 16.6, 10.4, 7.2 Hz, 1H), 5.33 (m, 1H), 5.21 (m, 1H), 4.27 (dd, J = 3.6, 7.2 Hz, 1H), 3.71 (br m, 1H), 1.60 (s, 3H), 1.52 (s, 3H), 1.48 (s, 9H), 1.82–0.93 (br m, 13H); DCI MS *m/e* 324 (M + H)$^+$.

(4*S*,5*R*,1′*RS*)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-dimethyl-5-(1,2-epoxyethyl)oxazolidine (3). A solution of 28.0 g (86.7 mmol) of oxazolidine 2 in 770 mL of CH_2Cl_2 was treated with 64.1 g (260.1 mmol) of MCPBA (70% pure) in 500 mL of CH_2Cl_2 and the mixture refluxed for 3 h. The same amount of MCPBA was added and refluxing continued for an additional 4 h. After the mixture was cooled to 0 °C, 1.5 L of saturated $NaHSO_3$ solution was added and the mixture extracted with ethyl acetate. The combined organic phases were washed with saturated $NaHCO_3$ solution and brine, dried, and evaporated. A total of 28.5 g (96.8%) of the desired epoxide was obtained as an oil with a 1*S*/1*R* diastereomer ratio of 2.7:1.0 (GC analysis): TLC R_f = 0.20 (ethyl acetate/cyclohexane). For the major isomer: ^{1}H NMR ($CDCl_3$) δ = 3.96 (br m, 1 H), 3.56 (br m, 1H), 3.08 (m, 1H), 2.87 (t, J = 4.8 Hz, 1 H), 2.63 (dd, J = 2.2, 4.8 Hz, 1H), 1.90–0.85 (br, m, 13H), 1.63 (s, 3H), 1.53 (s, 3H), 1.49 (s, 9H); DCI MS *m/e* 340 (M + H)$^+$. For the minor isomer: ^{1}H NMR ($CDCl_3$) δ = 3.96 (br m, 1H), 3.81 (br m, 1H), 3.08 (m, 1H), 2.83 (dd, J = 4.0, 4.4 Hz, 1H), 2.63 (dd, J = 2.2, 4.8 Hz, 1H), 1.90–0.85 (br m, 13H), 1.61 (s, 3H), 1.53 (s, 3H), 1.49 (s, 9H); DCI MS *m/e* 340 (M + H)$^+$.

(4*S*,5*R*)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-dimethyl-5-[(1*S*)-3-(2-pyridyl)-1-hydroxypropyl]oxazolidine (4a) and (4*S*,5*R*)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-dimethyl-5-[(1*R*)-3-(2-pyridyl)-1-hydroxypropyl]oxazolidine (4b). A solution of 34.2 mL (0.35 mol) of picoline in 1.1 L of dry THF was treated at −78 °C with 246 mL (0.35 mol) of *n*-butyllithium (1.4 M in *n*-hexane). After being stirred for 1 h at ambient temperature, the mixture was cooled to −78 °C. At this temperature a solution of 39.0 g (0.115 mol) of epoxide 3 was added dropwise. The mixture was stirred for 5 h, poured into 1 L of water, and extracted with ethyl acetate. The combined organic phases were washed with brine, dried, and evaporated. Chromatography of the residue on silica gel with toluene/*tert*-butyl methyl ether afforded 11.2 g (22.5%) of the desired 1*S* isomer **4a** as an oil and 4.9 g (9.8%) of the 1*R* isomer **4b** as a white solid.

1*S* isomer **4a**: TLC R_f = 0.27; $[\alpha]^{25}_D$ = −20.0° (c = 1, methanol); ^{1}H NMR ($CDCl_3$) δ = 8.48 (d, J = 4.4 Hz, 1H), 7.62 (dt, J = 1.6, 8.0 Hz, 1H), 7.17 (m, 2H), 4.16 (br, 1H), 3.63 (m, 2H), 3.15 (ddd, J = 4.0, 8.8, 13.0 Hz, 1H), 3.02 (ddd, J = 4.0, 8.0, 13.0 Hz, 1H), 2.29 (br m, 1H), 2.0–0.9 (br m, 14H), 1.67 (s, 3H), 1.52 (s, 3H), 1.48 (s, 9H); DCI MS *m/e* 433 (M + H)$^+$.

1*R* isomer **4b**: TLC R_f = 0.19; $[\alpha]^{25}_D$ = +15.3° (c = 1, methanol); mp 42–46 °C; ^{1}H NMR ($CDCl_3$) δ = 8.51 (d, J = 4.8 Hz, 1H), 7.60 (dt, J = 2.0, 8.0 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.13 (m, 1H), 3.88 (br m, 1H), 3.70 (dd, J = 3.2, 7.4 Hz, 1H), 3.55 (br m, 1H), 3.02 (m, 2H), 2.0–0.9 (br m, 14H), 1.62 (s, 3H), 1.52 (s, 3H), 1.45 (s, 9H); DCI MS *m/e* 433 (M + H)$^+$.

(2*S*,3*R*,4*S*)-2-Amino-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexane (5). Oxazolidine **4a** (9.3 g, 21.50 mmol) in 20 mL of CH_2Cl_2 was treated with 10 mL of trifluoroacetic acid at room temperature for 1 h. After addition of 0.5 mL of water, stirring was continued for 3 h. The mixture was evaporated to dryness and the residue dissolved in ethyl acetate, washed with saturated $NaHCO_3$ solution and brine, and then dried and evaporated to afford 6.2 g (98.6%) of a pale yellow foam: TLC R_f = 0.10 (CH_2Cl_2/methanol (4:1)), $[\alpha]^{21}_D$ = +0.6° (c = 1, methanol); ^{1}H NMR ($CDCl_3$) δ = 8.45 (dd, J = 5.0 Hz, 1H), 7.74 (dt, J = 2.0, 7.5 Hz, 1H), 7.26 (m, 2H), 3.94 (br m, 1H), 3.63 (br m, 2H), 3.06 (br m, 2H), 1.92 (br m, 3H), 1.63 (br m, 8H), 1.42–1.06 (br m, 6H), 0.88 (br m, 2H); DCI MS *m/e* 293 (M + H)$^+$.

***N*-[*N*-(*tert*-Butyloxycarbonyl)-N^{Im}-(2,4-dinitrophenyl)-L-histidyl]-(2*S*,3*R*,4*S*)-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)-hexan-2-amine (6a).** Amino diol (3.2 g, 11.0 mmol) and 4.6 g (11.0 mmol) of BOC-L-His(DNP)-OH were coupled using general procedure B. Chromatography with CH_2Cl_2/methanol (20:1) yielded 5.0 g (65.3%) of a yellow amorphous solid: TLC R_f = 0.44 (CH_2Cl_2/methanol (9:1)), $[\alpha]^{25}_D$ = −31.8° (c = 1, methanol); ^{1}H NMR ($CDCl_3$) δ = 8.82 (d, J = 2.4 Hz, 1H), 8.53 (dd, J = 2.0, 8.2 Hz, 1H), 8.42 (d, J = 4.8 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.67 (s, 1H), 7.58 (dt, J = 1.6, 7.2 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.08 (t, J = 6.0 Hz, 1H), 6.92 (s, 1H), 6.54 (br d, J = 8.8 Hz, 1H), 5.88 (br d, J = 6.4 Hz, 1H), 4.45 (m, 1H), 4.30 (m, 1H), 3.28 (m, 2H), 3.05 (m, 3H), 2.83 (m, 1H), 2.20 (m, 1H), 1.88 (m, 1H), 1.75–0.78 (br m, 13H), 1.45 (s, 9H); FAB MS *m/e* 702 (M + Li)$^+$.

***N*-[*N*-(*tert*-Butyloxycarbonyl)-*S*-methyl-L-cysteinyl]-(2*S*,3*R*,4*S*)-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexan-2-amine (6b).** Amino diol (276.0 mg, 0.94 mmol) and 221.0 mg (0.94 mmol) of BOC-L-Cys(Me)-OH were processed using general procedure B. Chromatography with CH_2Cl_2/methanol (20:1) yielded 270.2 mg (56.5%) of a white amorphous solid: TLC R_f = 0.42 (CH_2Cl_2/methanol (9:1)); ^{1}H NMR ($CDCl_3$) δ = 8.47 (d, J = 4.8 Hz, 1H), 7.60 (dt, J = 1.6, 8.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.12 (m, 1H), 6.52 (br d, J = 8.8 Hz, 1H), 5.33 (br d, J = 7.2 Hz, 1H), 4.28 (m, 2H), 3.38 (m, 2H), 3.16–2.73 (m, 4H), 2.23 (m, 1H), 2.12 (s, 3H), 1.98 (m, 1H), 1.80–0.8 (br m, 13H), 1.45 (s, 9H); FAB MS *m/e* 510 (M + H)$^+$.

***N*-[*N*-(*tert*-Butyloxycarbonyl)-L-norvalyl]-(2*S*,3*R*,4*S*)-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexan-2-amine (6c).** Amino diol **5** (210.0 mg, 0.72 mmol) and 156.3 mg (0.72 mmol) of BOC-L-Nva-OH were processed using general procedure B. Chromatography with CH_2Cl_2/methanol (20:1) yielded 224.4 mg (63.4%) of a white amorphous solid: TLC R_f = 0.44 (CH_2Cl_2/methanol (9:1)); ^{1}H NMR ($CDCl_3$) δ = 8.45 (d, J = 6.0 Hz, 1H), 7.62 (dt, J = 1.6, 8.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.12 (m, 1H), 6.26 (br d, J = 8.0 Hz, 1H), 4.92 (br d, J = 7.2 Hz, 1H), 4.29 (ddd, J = 4.8, 9.6, 14.4 Hz, 1H), 4.03 (m, 1H), 3.16–2.92 (m, 2H), 2.23 (m, 1H), 1.98 (m, 1H), 1.77–1.12 (br m, 17H), 1.43 (s, 9H), 0.87 (t, J = 7.2 Hz, 3H); MS FAB *m/e* 492 (M + H)$^+$.

***N*-[N^{Im}-(2,4-Dinitrophenyl)-L-histidyl]-(2*S*,3*R*,4*S*)-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexan-2-amine (7a).** Amide **6a** (300.0 mg, 0.43 mmol) was BOC-deprotected using

general procedure A. A yellow foam (244.7 mg, 95.3%) [TLC R_f = 0.31 (CH_2Cl_2/methanol (9:1))] was obtained, which was used without further purification.

N-(S-Methyl-L-cysteinyl)-(2S,3R,4S)-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexan-2-amine (7b). Amide **6b** (90.3 mg, 0.18 mmol) was processed using general procedure A to yield 70.4 mg (95.5%) of a pale yellow foam [TLC R_f = 0.40 (CH_2Cl_2/methanol (9:1))], which was used without further purification.

N-(L-Norvalyl)-(2S,3R,4S)-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexan-2-amine (7c). Amide **6c** (70.5 mg, 0.14 mmol) was deprotected using general procedure A to yield 54.8 mg (97.9%) of a pale yellow foam [TLC R_f = 0.19 (CH_2Cl_2/methanol (9:1))] used without further purification.

(4S)-3-(3-Phenylpropionyl)-4-benzyloxazolidin-2-one (9). To a stirred solution of 60.0 g (0.34 mol) of (4S)-benzyloxazolidin-2-one (8)[15c] in 1 L of anhydrous THF was added dropwise 215.0 mL (0.34 mol) of *n*-butyllithium (1.6 M in *n*-hexane) at −78 °C under an argon atmosphere. The mixture was stirred for 2 h at −78 °C, after which 55.0 mL (0.37 mol) of 3-phenylpropionyl chloride was added during 1 h. The mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched by adding 45 mL of saturated aqueous NH_4Cl. The volatiles were evaporated, the resulting aqueous residue was extracted with ethyl acetate, and the combined organic phases were washed with brine, dried, and evaporated. Recrystallization from ethyl acetate/*n*-heptane provided 94.0 g (89.4%) of a white solid: TLC R_f = 0.56 (ethyl acetate/*n*-heptane (1:1)), mp 107 °C, $[\alpha]^{23}_D$ = +107.4° (*c* = 1, methanol), ^{1}H NMR ($CDCl_3$) δ = 7.35–7.15 (m, 10H), 4.67 (m, 1H), 4.17 (m, 2H), 3.27 (m, 3H), 3.03 (m, 2H), 2.75 (dd, *J* = 8.8, 13.2 Hz, 1H); DCI MS *m/e* 310 (M + H)$^+$.

(4S)-3-[(2R)-2-[(*tert*-Butyloxycarbonyl)methyl]-3-phenylpropionyl]-4-benzyloxazolidin-2-one (10). A 1 M solution of sodium hexamethyldisilylamide (334.0 mL, 0.334 mol) in THF was added dropwise (1 h) under an argon atmosphere at −70 °C to a stirred solution of 94.0 g (0.304 mol) of oxazolidinone **9** in 1 L of anhydrous THF. After the mixture was stirred for 45 min at −65 °C, a solution of 58.0 mL (0.396 mol) of *tert*-butyl bromoacetate in 200 mL of THF was added over 2 h, and the resulting mixture was stirred for 3 h at −70 °C. The reaction was quenched by adding 750 mL of saturated aqueous NH_4Cl and stirring for 12 h at room temperature. The volatiles were removed by rotary evaporation, and the remaining aqueous solution was extracted with ethyl acetate. The combined organic layers were washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine, dried, and evaporated to provide the title compound as an oil, which crystallized after treatment with 400 mL of diisopropyl ether/*n*-heptane (1:1) and stirring for 30 min. Filtration and additional chromatographic workup (*n*-heptane/ethyl acetate (8:2)) gave 92.0 g (71.5%) of the desired product as a white solid: TLC R_f = 0.24 (*n*-heptane/ethyl acetate); mp 108–110 °C; $[\alpha]^{25}_D$ = +119.6° (c = 1, methanol); ^{1}H NMR ($CDCl_3$) δ = 7.47–7.20 (m, 10 H), 4.52 (m, 2H), 4.08 (dd, *J* = 2.4, 8.8 Hz, 1H), 3.93 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.32 (dd, *J* = 3.2, 13.2 Hz, 1H), 3.02 (dd, *J* = 6.4, 13.2 Hz, 1H), 2.35 (dd, *J* = 11.2, 16.8 Hz, 1H), 2.72 (dd, *J* = 10.8, 12.8 Hz, 1H), 2.64 (dd, *J* = 8.8, 12.8 Hz, 1H), 2.48 (dd, *J* = 4.0, 16.8 Hz, 1H), 1.48 (s, 9H); DCI MS *m/e* 424 (M + H)$^+$.

Benzyl (2R)-2-[(*tert*-Butyloxycarbonyl)methyl]-3-phenylpropionate (11). Under an argon atmosphere 1.35 mL (13.0 mmol) of benzyl alcohol was dissolved in 80 mL of anhydrous THF, and 8.2 mL (13.0 mmol) of a 1.6 M solution of *n*-butyllithium in *n*-hexane was added dropwise at −5 °C. To this solution was added at 0 °C 4.3 g (10.2 mmol) of oxazolidinone **10** in 5 mL of anhydrous THF. After the mixture was stirred for 3 h at 0 °C, the reaction was quenched by adding 20 mL of saturated aqueous NH_4Cl. After the mixture was stirred overnight at room temperature, water was added, the organic layer separated, and the aqueous layer extracted three times with ethyl acetate. The combined organic phases were washed with water and brine, dried, and concentrated. Chromatography with *n*-heptane/ethyl acetate (10:1) provided 2.7 g (74.7%) of a colorless oil: TLC R_f = 0.40 (*n*-heptane/ethyl acetate (8:2)); ^{1}H NMR ($CDCl_3$) δ = 7.37–7.12 (m, 10H), 5.08 (d, *J* = 4.0 Hz, 2H), 3.13 (m, 1H), 3.02 (dd, *J* = 6.8, 13.2 Hz, 1H), 2.78 (dd, *J* = 8.0, 13.2 Hz, 1H), 2.61 (dd, *J* = 8.8, 16.0 Hz, 1H), 2.35 (dd, *J* = 5.2, 16.0 Hz, 1H0, 1.38 (s, 9H); DCI MS *m/e* 355 (M + H)$^+$.

Benzyl (2R)-2-(Carboxymethyl)-3-phenylpropionate (12). Propionate **11** (2.57 g, 7.25 mmol) was dissolved in 20 mL of CH_2Cl_2 and cooled to 0 °C. Ten mL of trifluoroacetic acid was added, and the mixture was stirred overnight at room temperature. The volatiles were removed *in vacuo* and the resulting residue dissolved in 50 mL of ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried, and evaporated to give 2.0 g (92.5%) of a colorless oil with sufficient purity to be employed in subsequent steps: TLC R_f = 0.28 (CH_2Cl_2/methanol (8:2)); $[\alpha]^{25}_D$ = +11.3° (*c* = 1, methanol); ^{1}H NMR ($CDCl_3$) δ = 7.38–7.10 (m, 10H), 5.10 (s, 2H), 3.15 (m, 1H), 3.06 (dd, *J* = 6.4, 13.2 Hz, 1H), 2.80 (*J* = 8.4, 13.2 Hz, 1H), 2.73 (dd, *J* = 9.2, 17.2 Hz, 1H), 2.46 (dd, *J* = 4.8, 17.2 Hz, 1H); DCI MS *m/e* 299 (M + H)$^+$.

Benzyl (2R)-3-[1-[[4-[(*tert*-Butyloxycarbonyl)amino]piperidinyl]carbonyl]-2-benzyl]propionate (13). To 1.0 g (3.36 mmol) of acid **12** in 50 mL of CH_2Cl_2 was added at 0 °C 0.313 mL (3.64 mmol) of oxalyl chloride and 15 drops of DMF. Stirring at 0 °C was continued for 1 h. The volatiles were removed *in vacuo* and the resultant residue diluted with 25 mL of CH_2Cl_2. A solution of 0.67 g (3.36 mmol) of 4-[(*tert*-butyloxycarbonyl)-amino]piperidine and 0.47 mL (3.36 mmol) of triethylamine in 50 mL of CH_2Cl_2 was added dropwise at 0 °C. After addition was complete, the mixture was stirred for 3 h at 0 °C and then concentrated. The residual oil was dissolved in 100 mL of ethyl acetate and was washed successively with 2 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried, filtered, and evaporated to give 1.35 g (83.6%) of an oil: TLC R_f = 0.30 (CH_2Cl_2/methanol (8:2)); ^{1}H NMR ($CDCl_3$) δ = 7.35–7.10 (m, 10H), 5.10 (m, 2H), 4.38 (br m, 2H), 3.67 (br m, 2H), 3.32 (br m, 1H), 3.03 (br m, 2H), 2.75 (br m, 3H), 2.33 (m, 1H), 1.90 (br t, 2H), 1.45 (s, 9H), 1.20 (br m, 2H); rotamers; DCI MS *m/e* 481 (M + H)$^+$.

(2R)-3-[1-[[4-[(*tert*-Butyloxycarbonyl)amino]piperidinyl]-carbonyl]-2-benzyl]propionic Acid (14). A solution of 1.40 g (2.91 mmol) of ester **13** in 60 mL of ethanol was hydrogenated at 1 atm of H_2 with 200.0 mg of 10% Pd on charcoal for 1.5 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. Crystallization of the residue from diethyl ether yielded 1.10 g (96.8%) of a white solid: TLC R_f = 0.15 (CH_2Cl_2/methanol (20:1)); mp 135 °C $[\alpha]^{21}_D$ = +1.7° (*c* = 1, methanol); ^{1}H NMR ($CDCl_3$) δ = 7.33–7.17 (m, 5H), 4.45 (br m, 1H), 3.61 (br t, 2H), 3.19 (br m, 2H), 3.07–2.38 (br m, 5H), 1.90 (br m, 2H), 1.43 (s, 9H), 1.25 (br m, 2H); rotamers; DCI MS *m/e* 391 (M + H)$^+$.

(4S)-3-[3-(1-Naphthyl)propionyl]-4-benzyloxazolidin-2-one (15). This compound was obtained in 63.3% yield (6.2 g) from 4.83 g (27.3 mmol) of 8[14c] using the procedure described for the oxazolidinone **9** but replacing the 3-phenylpropionyl chloride with the 3-(1-naphthyl)propionyl chloride: TLC R_f = 0.52 (ethyl acetate/*n*-heptane (1:1)); $[\alpha]^{23}_D$ = +78.2° (*c* = 1, methanol); ^{1}H NMR ($CDCl_3$) δ = 8.11 (d, *J* = 8.4 Hz, 1H), 7.87 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.74 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.57–7.18 (m, 9H), 4.68 (m, 1H), 4.17 (m, 2H), 3.53–3.28 (m, 5H), 2.78 (dd, *J* = 9.6, 13.2 Hz, 1H); DCI MS *m/e* 360 (M + H)$^+$.

(4S)-4-Benzyl-3-[(2R)-3-(benzyloxycarbonyl)-2-[(1-naphthyl)methyl]propionyl]oxazolidin-2-one (16). A solution of 4.2 g (11.70 mmol) of **15** in 20 mL of dry THF was added at −78 °C to a stirred solution of 1.95 mL (13.85 mmol) of diisopropylamine and 8.0 mL (12.85 mmol) of *n*-butyllithium (1.6 M solution in *n*-hexane) in 10 mL of dry THF under an argon atmosphere. The mixture was stirred for 1 h, and then a solution of 5.55 mL (35.10 mmol) of benzyl bromoacetate in 20 mL of dry THF was added. The reaction mixture was stirred for 4 h at −78 °C and then warmed to ambient temperature. The reaction was quenched by adding 10 mL of brine and neutralized with 1 N HCl. The organic layer was separated and the aqueous layer extracted with ethyl acetate. The combined organic phases were washed with water and brine, dried, and evaporated. The residue was purified by chromatography with *n*-heptane/ethyl acetate (95:5) as eluent. Crystallization from cyclohexane afforded 2.5 g (42.1%) of white crystals: TLC R_f = 0.24; mp 91–93 °C; ^{1}H NMR ($CDCl_3$) δ = 8.21 (d, *J* = 8.4 Hz, 1H), 7.83 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.74 (dd, *J* = 3.2, 6.8 Hz, 1H), 7.57–7.15 (m, 14H), 5.04 (s, 2H), 4.82 (m, 1H), 4.38 (m, 1H), 3.94 (dd, *J* = 2.4, 8.8 Hz, 1H), 3.72 (t, *J* = 8.8 Hz, 1H), 3.53 (dd, *J* = 7.2, 13.2 Hz, 1H), 3.18 (m,

2H), 3.07 (dd, J = 10.8, 16.8 Hz, 1H), 2.44 (m, 2H); FAB MS m/e 508 $(M + H)^+$.

(4*S*)-4-Benzyl-3-[(2*R*)-3-carboxy-2-[(1-naphthyl)methyl]propionyl]oxazolidin-2-one (17). Benzyl ester **16** (2.4 g, 4.72 mmol) in 240 mL of ethanol was hydrogenated using 200 mg of 10% Pd on charcoal overnight. Filtration and removal of the solvent gave 1.8 g (91.4%) of a white foam: TLC R_f = 0.23 (ethyl acetate/*n*-heptane (2:1)); ^{1}H-NMR ($CDCl_3$) δ = 8.18 (d, J = 8.8 Hz, 1H), 7.83 (dd, J = 1.2, 8.0 Hz, 1H), 7.73 (dd, J = 3.6, 6.4 Hz, 1H), 7.57–7.17 (m, 9H), 4.73 (m, 1H), 4.42 (m, 1H), 3.99 (dd, J = 2.0, 8.8 Hz, 1H), 3.73 (t, J = 8.8 Hz, 1H), 3.52 (dd, J = 7.6, 13.2 Hz, 1H), 3.25–2.96 (m, 3H), 2.68 (dd, J = 9.2, 13.2 Hz, 1H), 2.40 (dd, J = 4.0, 17.2 Hz, 1H); FAB MS m/e 424 $(M + Li)^+$.

(4*S*)-4-Benzyl-3-[(2*R*)-3-[(1-[4-[(*tert*-butyloxycarbonyl)amino]piperidinyl]]carbonyl]-2-[(1-naphthyl)methyl]oxazolidin-2-one (18). The title compound was synthesized using general procedure C using dry DMF as solvent. Acid **17** (400.0 mg, 0.96 mmol) and 192.0 (0.96 mmol) of 4-[(*tert*-butyloxycarbonyl)amino]piperidine afforded after chromatographic purification (ethyl acetate/*n*-heptane (1:1)) 353.0 mg (61.3%) of an oil: TLC R_f = 0.38 (ethyl acetate/*n*-heptane (2:1)); ^{1}H NMR ($CDCl_3$) δ = 8.26 (d, J = 8.8 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.75 (dd, J = 1.6, 7.6 Hz, 1H), 7.58–7.22 (m, 9H), 4.82 (m, 1H), 4.40 (m, 2H), 3.98 (dd, J = 2.0, 8.8 Hz, 1H), 3.77–3.47 (br m, 4H), 3.33 (dd, J = 3.6, 12.8 Hz, 1H), 3.20 (m, 1H), 3.02 (br m, 2H), 2.67 (br m, 2H), 2.36 (m, 1H), 1.86 (br m, 2H), 1.43 (s, 9H), 1.17 (br m, 2H); FAB MS m/e 600 $(M + H)^+$.

(2*R*)-3-[[1-[4-[(*tert*-Butyloxycarbonyl)amino]piperidinyl]]carbonyl]-2-[(1-naphthyl)methyl]propionic Acid (19). To a solution of 143.0 mg (0.24 mmol) of amide **18** in 4 mL of aqueous THF (20% water) was added 20.1 mg (0.48n mmol) of $LiOH \times H_2O$ at 0 °C. After the solution was stirred for 3 h at 0 °C, the solvents were removed *in vacuo*, and the residue was dissolved in 10% NaOH. This solution was extracted with CH_2Cl_2, dried, and evaporated. Chromatography of the residue with CH_2Cl_2/methanol (9:1) afforded 68.2 mg (64.5%) of an oil: TLC R_f = 0.13; ^{1}H NMR ($CDCl_3$) δ = 8.10 (d, J = 8.0 Hz, 1H), 7.87 (dd, J = 1.6, 8.0 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.52 (m, 2H), 7.40 (t, J = 8.0 Hz, 1H), 7.32 (d, J = 7.2 Hz, 1H), 4.38 (br m, 1H), 3.75 (br m, 1H), 3.56 (br m, 1H), 3.35 (br m, 2H), 3.17 (br dd, J = 11.2, 13.2 Hz, 1H), 2.90 (br m, 1H), 2.78–2.45 (br m, 3H), 1.83 (br m, 2H), 1.45 (s, 9H), 1.23 (br m, 2H); DCI MS m/e 441 $(M + H)^+$.

***N*-[[*cis*-4-[(*tert*-Butyloxycarbonyl)amino]cyclohexyl]carbonyl]-*O*-methyl-L-tyrosine Methyl Ester (21).** A solution of 6.85 g (27.9 mmol) of *O*-methyl-L-tyrosine methyl ester, 6.80 g (27.9 mmol) of *cis*-4-[(*tert*-butyloxycarbonyl)amino]cyclohexanecarboxylic acid (**20**),[19] and 17.9 mL (139.50 mmol) of triethylamine in 250 mL of dry DMF was treated with 28 mL of a 50% solution of *n*-propanephosphonic anhydride in ethyl acetate at 0 °C. The mixture was stirred for 18 h and then quenched by pouring into water. Extraction with ethyl acetate and washing of the combined organic layers with 10% aqueous citric acid, saturated aqueous $NaHCO_3$, and brine gave a residue, which was purified by chromatography with cyclohexane/ethyl acetate (1:1) to yield 11.91 g (98.2%) of a colorless oil: ^{1}H NMR ($CDCl_3$) δ = 7.02 (m, 2H), 6.83 (m, 2H), 5.88 (br d, J = 7.6 Hz, 1H), 4.77 (m, 1H), 4.70 (br, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 3.64 (br m, 1H), 3.09 (dd, J = 6.0, 13.6 Hz, 1H), 2.98 (dd, J = 6.8, 13.6 Hz, 1H), 2.17 (m, 1H), 1.70–1.54 (br m, 8H), 1.42 (s, 9H); DCI MS m/e 435 $(M + H)^+$.

***N*-[[*cis*-4-[(*tert*-butyloxycarbonyl)amino]cyclohexyl]carbonyl]-*O*-methyl-L-tyrosine (22).** A solution of 11.85 g (27.3 mmol) of ester **21** and 27.3 mL of 1 N NaOH in 200 mL of dioxane/water (1:1) was stirred for 3 h at room temperature. The mixture was concentrated *in vacuo* and extracted with ethyl acetate. The combined organic layer was washed with brine, dried, and evaporated to yield 11.2 g (97.6%) of the desired product: ^{1}H NMR ($CDCl_3$) δ = 7.07 (d, J = 8.8 Hz, 1H), 6.82 (d, J = 8.8 Hz, 1H), 4.83 (m, 1H), 3.77 (s, 3H), 3.18 (m, 2H), 2.20 (br m, 2H), 1.72–1.45 (br m, 9H), 1.45 (s, 9H); DCI MS m/e 421 $(M + H)^+$.

Benzyl (2*RS*)-2-Benzyl-3-(acetylthio)propionate (24). A solution of 6.1 g (24.18 mmol) of benzyl 2-benzylacrylate (**23**) and 3.44 mL (48.36 mmol) of thioacetic acid was stirred for 16 h at 70 °C. The volatiles were removed *in vacuo*, and the resultant residue was purified by chromatography with cyclohexane/ethyl acetate (9:1) to yield 7.14 g (89.5%) of a pale yellow oil: TLC R_f = 0.18; ^{1}H NMR (60 MHz, $CDCl_3$) δ = 7.40–7.15 (m, 10H), 5.12 (s, 2H), 3.08 (m, 4H), 2.30 (s, 3H), 1.20 (m, 1H); DCI MS m/e 329 $(M + H)^+$.

Benzyl (2*RS*)-2-Benzyl-3-(chlorosulfonyl)propionate (25). Chlorine was passed through a stirred suspension of 656.0 mg (2.0 mmol) of propionate **24** in 24 mL of water for 30 min. The excess of chlorine was removed *in vacuo*, the remaining aqueous solution extracted with CH_2Cl_2, and the combined extracts washed with brine. Drying and concentration gave 677.0 mg (99.5%) of a yellow oil [TLC R_f = 0.15 (cyclohexane/ethyl acetate (9:1))], which was used without further purification.

Benzyl (2*RS*)-2-Benzyl-3-[[*N*-[4-[(*tert*-butyloxycarbonyl)amino]piperidinyl]]sulfonyl]propionate (26). A solution of 400.0 mg (2.0 mmol) of 4-[(*tert*-butyloxycarbonyl)amino]-piperidine and 0.27 mL (2.0 mmol) of triethylamine in 6 mL of CH_2Cl_2 was added dropwise to a solution of 677.0 mg (2.0 mmol) of crude **25** in 3 mL of CH_2Cl_2 at −10 °C. After being stirred for 15 min at −10 °C, the reaction was quenched by acidification with 2 N HCl. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2. The combined organic phases were washed with water and brine, dried, and evaporated. Chromatography of the residue with cyclohexane/ethyl acetate (8:2) provided 716.2 mg (74.0%) of white crystals: TLC R_f = 0.08; mp 115–117 °C; ^{1}H NMR ($CDCl_3$) δ = 7.36–7.10 (m, 10H), 5.08 (s, 2H), 3.38 (br m, 1H), 3.58 (br m, 2H), 3.45 (dd, J = 8.8, 14.0 Hz, 1H), 3.24 (m, 1H), 3.06 (dd, J = 7.2, 14.0 Hz, 1H), 2.97–2.60 (m, 4H), 1.92 (br m, 2H), 1.45 (s, 9H), 1.35 (br m, 2H); DCI MS m/e 517 $(M + H)^+$.

(2*RS*)-2-Benzyl-3-[[*N*-[4-[(*tert*-butyloxycarbonyl)amino]-piperidinyl]]sulfonyl]propionic Acid (27). Benzyl ester **26** (710.0 mg, 1.47 mmol) in 50 mL of methanol was hydrogenated in the presence of 10% Pd on charcoal for 3 h at atmospheric pressure. The catalyst was removed by filtration, and the colorless filtrate was concentrated. Purification of the residue by chromatography with CH_2Cl_2/methanol (95:5) afforded 387.4 mg (61.9%) of white crystals: TLC R_f = 0.28; mp 161–163 °C; ^{1}H NMR ($CDCl_3$) δ = 7.35–7.17 (m, 5H), 5.47 (br m, 1H), 3.65–2.70 (br m, 9H), 1.92 (br m, 2H), 1.43 (s, 9H), 1.35 (br m, 2H); DCI MS m/e 427 $(M + H)^+$.

***cis*-4-[(*tert*-Butyloxycarbonyl)amino]-1-(acetylthio)cyclohexane (29).** To a solution of 15.3 g (58.33 mmol) of triphenylphosphine in 100 mL of dry THF was added a solution of 9.0 mL (57.15 mmol) of diethyl azodicarboxylate in 50 mL of dry THF at a temperature from −70 to −60 °C. The mixture was stirred for 10 min, followed by subsequent addition of a solution of 4.3 mL (60.44 mmol) of thioacetic acid in 50 mL of dry THF and a solution of 10.0 g (46.45 mmol) of *trans*-4-[(*tert*-butyloxycarbonyl)amino]cyclohexanol (**28**) in 130 mL of dry THF at the same temperature. Stirring was continued for 1 h at −60 °C and for 14 h at room temperature. The solvent was removed and the resultant residue chromatographed twice with cyclohexane/ethyl acetate (8:2) and CH_2Cl_2/methanol (99:1), respectively, to yield 3.78 g (29.8%) of a pale yellow oil: TLC R_f = 0.27 (cyclohexane/ethyl acetate (8:2)); ^{1}H NMR ($CDCl_3$) δ = 4.48 (br d, 1H), 3.76 (m, 1H), 3.54 (br m, 1H), 2.32 (s, 3H), 1.90–1.68 (br m, 6H), 1.53–1.48 (br m, 2H), 1.45 (s, 9H); DCI MS m/e 274 $(M + H)^+$.

Ethyl (2*RS*)-2-Benzyl-3-[[4-[(*tert*-butyloxycarbonyl)amino]cyclohexyl]thio]propionate (30). Under an argon atmosphere a solution of 12.3 mL (12.3 mmol) of sodium hexamethyldisilylamide (1 molar in THF) in 55 mL of methanol was added to a solution of 3.44 g (12.58 mmol) of thioester **29** in 55 mL of methanol at 0 °C. After being stirred for 1 h at room temperature, the mixture was cooled to 0 °C and a solution of 2.60 g (13.66 mmol) of ethyl 2-benzylacrylate was added. Stirring was continued for 1 h at room temperature. The reaction was quenched by addition of 12.5 mL of 1 N HCl, and then the mixture was concentrated. The residue was dissolved in ethyl acetate, washed with brine, dried, and evaporated. Chromatography with cyclohexane/ethyl acetate (7:3) afforded 4.83 g (94.3%) of an oil: TLC R_f = 0.23; ^{1}H NMR ($CDCl_3$) δ = 7.31–7.13 (m, 5H), 4.52 (br d, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.54 (br m, 1H), 3.02–2.59 (m, 6H), 1.80–1.57 (br m, 8H), 1.45 (s, 9H), 1.17 (t, J = 7.2 Hz, 3H); DCI MS m/e 422 $(M + H)^+$.

(2*RS*)-2-Benzyl-3-[[4-[(*tert*-butyloxycarbonyl)amino]cyclohexyl]thio]propionic Acid (31). A solution of 3.54 g (8.39 mmol) of ester **30** and 25 mL of 1 N NaOH in 40 mL of

dimethoxyethane was stirred for 2 d. The solvent was removed and the residue dissolved in ethyl acetate, washed with brine, and evaporated to yield 3.30 (100%) of an oil: TLC R_f = 0.11 (CH_2Cl_2/methanol (20:1)); ^1H NMR (60 MHz, $CDCl_3$) δ = 7.27 (m, 5H), 4.20 (br d, 1H), 3.52 (br m, 1H), 3.10–2.60 (br m, 6H), 1.70 (br m, 8H), 1.48 (s, 9H); DCI MS *m/e* 394 $(M + H)^+$.

(2*RS*)-2-Benzyl-3-[[4-[(*tert*-Butyloxycarbonyl)amino]cyclohexyl]sulfonyl]propionic Acid (32). A solution of 2.26 g (5.74 mmol) of thioether **31** and 9.9 g (16.10 mmol) of oxone in 50 mL of methanol and 40 mL of water was stirred for 40 h at room temperature. The insoluble salts were removed by filtration, and the organic solvent was evaporated. After addition of 2 N NaOH to pH 5, the aqueous solution was extracted with ethyl acetate, and the combined extracts were washed with brine, dried, and evaporated to yield 1.26 g (51.6%) of a white foam: TLC R_f = 0.30 (CH_2Cl_2/methanol (1:1)); ^1H NMR ($CDCl_3$) δ = 7.35–7.18 (m, 5H), 7.00 (br s, 1H), 4.75 (br m, 1H), 3.78 (br m, 2H), 3.41 (br m, 2H), 3.23 (dd, J = 6.4, 13.6 Hz, 2H), 2.87 (br m, 4H), 2.03–1.62 (br m, 4H), 1.46 (s, 9H); DCI MS *m/e* 426 $(M + H)^+$.

***O*-Benzyl-*N*-(*O*-ethyladipoyl)-L-phenylalanine (34).** To a mixture of 700.0 mg (1.64 mmol) of *O*-benzyl-L-phenylalanine *p*-toluenesulfonate (**33**), 285.0 mg (1.64 mmol) of adipic acid monoethyl ester, and 1.37 mL (13.12 mmol) of triethylamine in 5 mL of freshly dried THF was added 1.07 mL of a 50% solution of *n*-propanephosphonic acid anhydride in THF at 0 °C. After 2 h at 0 °C the mixture was allowed to stand at room temperature for 16 h. The mixture was diluted with 100 mL of ethyl acetate and washed with 5% aqueous $NaHSO_4$, saturated aqueous Na_2CO_3, and brine. The organic layer was dried and concentrated, and the residue was purified by chromatography with diisopropyl ether/methyl *tert*-butyl ether (1:1) as eluent to provide 480.0 mg (72.0%) of a pale yellow oil: TLC R_f = 0.10 (diisopropyl ether); ^1H NMR (60 MHz, $CDCl_3$) δ = 6.90–7.50 (m, 10H), 5.90 (d, J = 9.0 Hz, 2H), 5.15 (s, 2H), 5.05–4.70 (m, 1H), 4.10 (q, J = 7.0 Hz, 2H), 3.12 (d, J = 6.2 Hz, 2H), 1.70–1.35 (m, 4H), 1.25 (t, J = 7.0 Hz, 3H); DCI MS *m/e* 412 $(M + H)^+$.

***N*-(*O*-Ethyladipoyl)-L-phenylalanine (35).** Benzyl ester **34** (460.0 mg, 1.43 mmol) in 20 mL of ethanol was hydrogenated in the presence of 50 mg of 10% Pd on charcoal for 12 h to yield 220.0 mg (63.0%) of a colorless oil: TLC R_f = 0.10 (diisopropyl ether/methyl *tert*-butyl ether (1:1)); ^1H NMR (60 MHz, $CDCl_3$) δ = 7.30 (m, 5H), 6.15 (d, J = 9.0 Hz, 1H), 5.60–5.15 (br s, 1H), 5.10–4.70 (br s, 1H), 4.10 (q, J = 7 Hz, 2H), 3.25–3.00 (m, 2H), 2.55–2.05 (m, 2H), 1.90–1.28 (m, 2H), 1.25 (t, J = 7.0 Hz, 3H); DCI MS *m/e* 322 $(M + H)^+$.

(2*S*,3*R*,4*S*)-*N*-[*N*-[(2*R*)-2-Benzyl-3-[[4-[(*tert*-butyloxycarbonyl)amino]piperidyl]carbonyl]propionyl]N^{im}-(2,4-dinitrophenyl)-L-histidinyl]-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexan-2-amine (36). The C-terminal amino fragment **7a** (3.61 g, 6.07 mmol) and 2.37 g (6.07 mmol) of the N-terminal carboxylic acid fragment **14** were coupled using general procedure C. Purification by chromatography with CH_2Cl_2/methanol (20:1) afforded 6.16 g (87.8%) of a pale yellow foam: TLC R_f = 0.09; ^1H NMR ($CDCl_3$) δ = 8.80 (d, J = 2.4 Hz, 1H), 8.53 (br d, J = 8.8 Hz, 1H), 8.38 (br m, 1H), 7.80 (br dd, J = 4.4, 8.8 Hz, 2H), 7.71 (br d, J = 6.8 Hz, 1H), 7.38–7.04 (m, 11H), 4.78–4.50 (br m, 3H), 4.30 (br m, 2H), 3.65–3.30 (br m, 4H), 3.18–2.86 (br m, 8H), 2.78–2.58 (br m, 3H), 2.21 (br m, 1H), 1.86 (br m, 3H), 1.67–1.02 (br m, 11H), 1.42 (s, 9H), 0.83 (br m, 2H), rotamers; FAB MS *m/e* 974 $(M + Li)^+$.

(2*S*,3*R*,4*S*)-*N*-[*N*-[(2*R*)-2-Benzyl-3-[[4-[(*tert*-butyloxycarbonyl)amino]piperidyl]carbonyl]propionyl]-L-histidinyl]-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexan-2-amine (37). Tripeptide **36** (5.16 g, 5.33 mmol) was N^{im}-deprotected following general procedure D. Chromatography with CH_2Cl_2/methanol/NH_4OH (10:1:0.1) yielded 3.16 g (76.3%) of a yellow foam: TLC R_f = 0.29; ^1H NMR ($CDCl_3$) δ = 8.46 (t, J = 6.0 Hz, 1H), 7.59 (m, 2H), 7.33–7.07 (m, 7H), 6.87 (d, J = 2.0 Hz, 1H), 4.78 (br m, 1H), 4.66 (br m, 1H), 4.37 (br d, J = 12.8 Hz, 1H), 4.15 (br m, 1H), 3.63 (br m, 2H), 3.27–2.58 (br m, 13H), 2.18 (br m, 1H), 2.00–1.78 (br m, 2H), 1.70–1.53 (br m, 6H), 1.43 (s, 9H), 1.90–1.08 (br m, 5H), 0.85 (br m, 2H), rotamers; FAB MS *m/e* 802 $(M + H)^+$.

(2*S*,3*R*,4*S*)-*N*-[*N*-[(2*R*)-3-[[4-(Aminopiperidyl)]carbonyl]-2-benzylpropionyl]-L-histidinyl]-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexan-2-amine Acetate (38). BOC-protected tripeptide **37** (3.20 g, 3.99 mmol) was deprotected using general procedure A to yield after treatment with IRA-93 2.94 g (96.7%) of the monoacetate as an amorphous solid: TLC R_f = 0.07 (CH_2Cl_2/methanol/NH_4OH (9:1:0.2)); ^1H NMR (400 MHz, DMSO-d_6) δ = 8.43 (d, J = 3.0 Hz, 1H), 8.26 (br, 1H), 7.63 (dt, J = 1.8, 7.2 Hz, 1H), 7.51 (d, J = 1.8 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.28–7.12 (m, 7H), 6.82 (d, J = 1.8 Hz, 1H), 4.42 (br m, 1H), 4.21 (br m, 1H), 4.13 (br m, 1H), 3.71 (br m, 1H), 3.07 (m, 2H), 3.02–2.77 (br m, 7H), 2.68–2.48 (br m, 4H), 2.06 (br m, 2H), 1.83 (s, 3H), 1.74 (br m, 3H), 1.64–1.40 (br m, 6H), 1.28–1.05 (br m, 7H), 0.87 (br m, 1H), 0.76 (br m, 1H), rotamers; ^{13}C NMR (100 MHz, BB, DMSO-d_6) δ = 137.60, 172.60, 171.34, 168.97, 168.91, 162.10, 148.65, 139.37, 136.12, 134.39, 132.90, 128.83 (2C), 128.02 (2C), 125.89, 122.42, 120.76, 117.47, 75.30, 69.93, 52.91, 47.48, 46.66, 43.34, 43.11, 39.56, 39.48, 38.92, 37.73, 34.00, 33.50, 33.30, 33.29, 33.24, 33.02, 32.89, 32.33, 32.19, 32.22, 29.31, 26.08, 25.73, 25.56, 22.05; FAB MS *m/e* 702 $(M + H)^+$.

Tartrate. A crystalline salt of **38** was obtained by treatment of the free base (basic workup after deprotection) with 1 equiv L-tartaric acid in ethanol and recrystallization from ethanol: mp 154 °C.

(2*S*,3*R*,4*S*)-*N*-[*N*-[(2*R*)-2-Benzyl-3-(*tert*-butylsulfonyl)-propionyl]-L-histidinyl]-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexan-2-amine (39). (2*S*)-2-Benzyl-3-(*tert*-butylsulfonyl)propionic acid[21] (180.0 mg, 0.63 mmol) and 375.2 mg (0.63 mmol) of the amino fragment **7a** were coupled using general procedure B. Purification by chromatography with CH_2Cl_2/methanol (12:1) provided 300.0 mg (68.1%) of the protected peptide as pale yellow foam. Subsequent removal of the N^{im}-protection by use of general procedure D and chromatographic purification with CH_2Cl_2/methanol (10:1) afforded 249.5 mg (95.2%) of the desired compound as an amorphous pale yellow solid: TLC R_f = 0.24; ^1H NMR ($CDCl_3$) δ = 8.43 (d, J = 4.8 Hz, 1H), 7.68 (s, 1H), 7.62 (t, J = 1.8, 8.0 Hz, 1H), 7.46 (br, 1H), 7.32–7.17 (m, 6H), 7.12 (t, J = 6, 8 Hz, 1H), 6.96 (br s, 1H), 6.75 (br d, J = 8.4 Hz, 1H), 4.22 (br, 1H), 4.13 (m, 2H), 3.65 (m, 2H), 3.35–2.77 (br m, 9H), 2.14 (br m, 1H), 1.75–1.15 (br m, 10H), 1.34 (s, 9H), 0.89 (br m, 2H), rotamers: FAB MS *m/e* 696 $(M + H)^+$.

(2*S*,3*R*,4*S*)-*N*-[*N*-[[(*cis*-4-Aminocyclohexyl)carbonyl]-L-phenylalanyl]-L-histidyl]-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexan-2-amine Acetate (40). *cis*-*N*-[[4-[(*tert*-butyloxycarbonyl)amino]cyclohexane]carbonyl]-L-phenylalanine[7] (320.0 mg 0.82 mmol) and 488.4 mg (0.82 mmol) of amino fragment **7a** were processed according to general procedure B. Chromatography with CH_2Cl_2/methanol (20:1) as eluent gave 560 mg (74.4%) of the protected peptide as foam. Use of 45.7 mg (0.09 mmol) of this compound provided after subsequent removal of the protecting groups using general procedures D and A 20.0 mg (28.5%, two steps) of the acetate as an amorphous solid: TLC R_f = 0.12 (CH_2Cl_2/methanol (4:1)); ^1H NMR (DMSO-d_6) δ = 9.00 (br s, 1H), 8.56 (br d, J = 6.0 Hz, 1H), 8.46 (br d, J = 8.0 Hz, 1H), 7.98 (br d, J = 8.0 Hz, 1H), 7.70 (br m, 2H), 7.45 (br m, 2H), 7.27–7.14 (m, 6H), 4.67 (br m, 1H), 4.52 (br m, 1H), 4.17 (br m, 2H), 3.18–2.70 (br m, 10H), 2.27 (br m, 2H), 1.78–1.08 (br m, 18H), 0.86 (br m, 2H), rotamers; FAB MS *m/e* 702 $(M + H)^+$.

(2*R*,3*R*,4*S*)-*N*-[*N*-[[*cis*-4-Aminocyclohexyl)carbonyl]-*O*-methyl-L-tyrosyl]-L-histidyl]-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexan-2-amine Acetate (41). Coupling of 302.0 mg (0.72 mmol) of acid **22** and 428.8 mg (0.72 mmol) of amino fragment **7a** *via* general procedure B yielded 671.2 mg (92.3%) of the protected peptide as a pale yellow foam. This product was then subjected to N^{im}- and BOC-deprotection following general procedures D and A to yield 378.0 mg (68.6%, two steps) of the acetate as a pale yellow amorphous solid: TLC R_f = 0.07 (CH_2Cl_2/methanol/NH_4OH (10:1:0.2)); ^1H NMR (D_2O) δ = 8.43 (d, J = 4, 8 Hz, 1H), 8.15 (dd, J = 4.4, 0.8 Hz, 1H), 7.92 (m, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.35 (m, 1H), 7.17 (d, J = 8.8 Hz, 1H), 7.12 (m, 1H), 7.04 (s, 1H), 6.94 (t, J = 8.4 Hz, 2H), 4.65–4.50 (m, 2H), 4.16 (br m, 1H), 3.80 (s, 3H), 3.37 (br m, 2H), 3.22–2.78 (m, 8H), 2.44 (br m, 1H), 2.06 (br m, 1H), 1.92 (s, 3H), 1.83–1.33 (br m, 16H), 1.12 (br m, 4H), 0.85 (br m, 2H), rotamers: FAB MS *m/e* 732 $(M + H)^+$.

(2*S*,3*R*,4*S*)-*N*-[*N*-[(2*R*)-3-[(*cis*-4-Aminocyclohexyl)sulfonyl]-2-benzylpropionyl]-L-histidyl]-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexan-2-amine acetate (42). (2*R*,3*S*,4*R*)-2-Amino-1-cyclohexyl-3,4-dihydroxyhexane-6-(2-pyridyl)-3,4-acetonide[14] (1.60 g, 4.81 mmol) and 3.07 g (4.80 mmol) of Trt-

L-His(Trt)-OH were coupled *via* general procedure C to yield after chromatographic purification with ethyl acetate/methanol (99:1) as eluent 3.24 g (70.5%) of the protected amide as a white solid: TLC R_f = 0.42 (ethyl acetate); mp 85–95 °C; ^{1}H NMR ($CDCl_3$) δ = 8.52 (dd, J = 0.8, 4.8 Hz, 1H), 8.00 (d, J = 8.8 Hz, 1H), 7.54–7.40 (m, 7H), 7.30–7.00 (m, 28H), 6.21 (s, 1H), 4.17 (m, 4H), 3.68 (br d, J = 8.0 Hz, 1H), 3.45 (br m, 1H), 3.5 (m, 1H), 2.92 (m, 1H), 2.63 (dd, J = 3.6, 14.0 Hz, 1H), 2.17 (m, 2H), 1.87 (br m, 2H), 1.68–1.53 (br m, 4H), 1.46 (s, 3H), 1.37 (s, 3H), 1.31 (br m, 2H), 1.08 (br m, 3H), 0.92–0.68 (br m, 2H). A 2.00-g (2.10 mmol) portion of the above described amide provided, after stirring in 20 mL of glacial acetic acid and 2 mL of 5 N HCl for 10 min, addition of 70 mL of water, extraction with diethyl ether, addition of saturated aqueous Na_2CO_3 to pH 8, extraction with ethyl acetate, drying of the combined organic layers, and evaporation, 1.25 g (100%) of (2*S*,3*R*,4*S*)-*N*-(N^{im}-trytyl-L-histidyl)-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexan-2-amine as a colorless oil: TLC R_f = 0.37 (CH_2Cl_2/methanol (9:1)). The obtained amino fragment and 965.0 mg (2.27 mmol) of acid **32** were coupled *via* general procedure C. Diastereoisomers were separated by chromatography with CH_2Cl_2/methanol (97:3) in 38% yield (860.0 mg, less polar isomer) and 24% yield (540.0 mg, more polar isomer), respectively. A 460.0-mg (0.43 mmol) portion of the more polar 2*R* isomer was deprotected by stirring in 4.0 mL of trifluoroacetic acid and 0.2 mL of water for 2.5 h, addition of water, extraction with diisopropyl ether, addition of ion-exchange resin to the aqueous phase up to pH 5, filtration, and lyophilization of the filtrate to yield 277.2 mg (74.4%) of the acetate as an amorphous solid: TLC R_f = 0.20 (CH_2Cl_2/methanol/acetic acid/H_2O (100:50:10:5)), ^{1}H NMR (DMSO-d_6) δ = 8.50 (d, J = 7.6 Hz, 1H), 8.45 (dd, J = 0.8, 4.8 Hz, 1H), 7.64 (dt, J = 1.6, 8.0 Hz, 1H), 7.52 (s, 1H), 7.33–7.13 (m, 6H), 6.86 (s, 1H), 4.52 (m, 1H), 4.16 (br m, 1H), 3.48 (br m, 1H), 3.19 (br m, 1H), 3.10–2.54 (br m, 10H), 2.04 (br m, 1H), 1.87 (s, 3H), 1.82–1.07 (br m, 20H), 0.85 (br m, 2H), rotamers; FAB MS *m/e* 737 (M + H)$^+$.

(2*S*,3*R*,4*S*)-*N*-[*N*-[(2*R*)-2-Benzyl-3-(morpholinocarbonyl)propionyl]-L-histidyl]-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexan-2-amine (43). (2*R*)-2-Benzyl-3-(morpholinocarbonyl)propionic acid[6a] (103.0 mg, 0.37 mmol) and 221.3 mg (0.37 mmol) of amino fragment **7a** were coupled *via* general procedure B. Chromatography with CH_2Cl_2/methanol (25:1) gave 233.0 mg (73.7%) of the protected peptide as a pale yellow foam, which afforded after N^{im}-deprotection *via* general procedure D 91.0 mg (46.4%) of the desired product as a tan amorphous solid: TLC R_f = 0.18 (CH_2Cl_2/methanol (9:1)); ^{1}H NMR (CD_3OD) δ = 8.40 (dd, J = 0.8, 4.8 Hz, 1H), 7.74 (s, 1H), 7.70 (dd, J = 1.6, 8.0 Hz, 1H), 7.32–7.14 (m, 7H), 6.95 (s, 1H), 4.55 (dd, J = 5.6, 7.6 Hz, 1H), 4.24 (m, 1H), 3.62–3.33 (m, 9H), 3.22–2.94 (m, 6H), 2.85–2.62 (m, 3H), 2.33 (dd, J = 4.0, 16.0 Hz, 1H), 2.14 (m, 1H), 1.85–1.52 (br m, 7H), 1.37–1.15 (br m, 5H), 0.92 (br m, 2H), rotamers; FAB MS *m/e* 689 (M + H)$^+$.

(2*S*,3*R*,4*S*)-*N*-[(2*S*)-2-[[[*N*-methyl-*N*-[2-[*N*-(morpholinocarbonyl)-*N*-methylamino]ethyl]amino]carbonyl]oxy]-3-phenylpropionyl]-L-histidyl]-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexan-2-amine (44). (2*S*)-2-[[[*N*-Methyl-*N*-[2-[*N*-(morpholinocarbonyl)-*N*-methylamino]ethyl]amino]carbonyl]-oxy]-2-phenylpropionic acid[7] (53.0 mg 0.135 mmol) and 80.5 mg (0.135 mmol) of amino fragment **7a** were coupled using general procedure B. The crude amide [TLC R_f = 0.2 (ethyl acetate/methanol (5:1))] was N^{im}-deprotected *via* general procedure D and purified by chromatography with CH_2Cl_2/methanol/NH_4OH (9:1:0.1) to yield 43.0 mg (38.5%) of a pale yellow foam: TLC R_f = 0.2; ^{1}H NMR (DMSO-d_6) δ = 4.42 (d, J = 4.0 Hz, 1H), 8.34 (m, 1H), 7.65 (ddd, J = 1.8, 8.0, 8.0 Hz, 1H), 7.75 (s, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.30–7.10 (m, 8H), 6.70 (d, J = 12.0 Hz, 1H), 5.00 (m, 1H), 4.90–4.65 (br s, 1H), 4.55–4.40 (m, 1H), 4.20–4.02 (m, 1H), 3.50–2.60 (br m, 27H), 2.10–1.95 (m, 2H), 1.80–1.30 (br m, 6H), 1.30–1.00 (br m, 5H), 1.00–0.65 (br m, 2H), rotamers; FAB MS *m/e* 805 (M + H)$^+$.

(2*S*,3*R*,4*S*)-*N*-[*N*-[(*O*-Ethyladipoyl)-L-phenylalanyl]-L-histidyl]-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexane-2-amine (45). Acid **35** (64.2 mg, 0.20 mmol) and 121.0 mg (0.20 mmol) of amino fragment **7a** were processed using general procedure B and the N^{im}-deprotection removed from the crude amide *via* general procedure D. Chromatographic purification with ethyl acetate/methanol (3:1) afforded 103.4 mg (69.1%) of a pale yellow foam: TLC R_f = 0.2; ^{1}H NMR ($CDCl_3$) δ = 8.45 (d, J = 2.5 Hz, 1H), 8.12 (br d, J = 7.6 Hz, 1H), 7.62 (m, 2H), 7.36–7.13 (m, 9H), 6.90 (s, 1H), 6.47 (br m, 1H), 4.68 (br m, 1H), 4.48 (m, 1H), 4.10 (m, 2H), 3.96 (br m, 1H), 3.38–2.62 (m, 9H), 2.24 (t, J = 7.0 Hz, 3H), 2.25–2.05 (br m, 2H), 1.80–1.42 (br m, 8H), 1.28–1.06 (m, 8H), 0.95–0.76 (br m, 2H), rotamers; FAB MS *m/e* 733 (M + H)$^+$.

(2*S*,3*R*,4*S*)-*N*-[*N*-[(2*R*)-3-[(4-Aminopiperidyl)carbonyl]-2-[(1-naphthyl)methyl]propionyl]-L-histidinyl]-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexan-2-amine Acetate (46). Acid **19** (39.2 mg, 0.09 mmol) and 52.4 mg (0.09 mmol) of amino fragment **7a** were coupled according to general procedure C and purified by chromatography with CH_2Cl_2/methanol (20:1) to provide 58.8 mg (64.1%) of the corresponding amide as an amorphous solid: TLC R_f = 0.31. The BOC- and the N^{im}-DNP-protecting groups were removed *via* general procedures A and D, respectively. Ion exchange and lyophilization afforded 36.1 mg (75.2%) of the desired acetate as an amorphous solid: TLC R_f = 0.09 (CH_2Cl_2/methanol/NH_4OH (9:1:0.1)); ^{1}H NMR (D_2O) δ = 8.36 (br m, 1H), 8.08 (br m, 1H), 7.78 (br m, 2H), 7.60 (br m, 2H), 7.43 (br m, 1H), 7.34–7.21 (br m, 3H), 6.88 (s, 1H), 4.44–4.30 (br m, 2H), 4.07 (br m, 1H), 3.65 (dd, J = 4.4, 11.6 Hz, 1H), 3.54 (dd, J = 6.8, 11.6 Hz, 1H), 3.30–2.62 (br m, 12H), 2.47 (br m, 1H), 2.04 (br m, 2H), 1.92 (s, 3H), 1.77–1.47 (br m, 9H), 1.32–1.06 (br m, 5H), 0.87 (br m, 2H), rotamers; FAB MS *m/e* 752 (M + H)$^+$.

(2*S*,3*R*,4*S*)-*N*-[*N*-[(2*R*)-3-[(4-Aminopiperidyl)carbonyl]-2-benzylpropionyl]-*S*-methyl-L-cysteinyl]-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexan-2-amine Acetate (47). Acid **14** (67.4 mg, 0.17 mmol) and 70.0 mg (0.17 mmol) of amino fragment **7b** were processed *via* general procedure C to give 90.0 mg (67.7%) of the protected amide as a pale yellow foam: TLC R_f = 0.38 (CH_2Cl_2/methanol (9:1)). A 58.0-mg (0.074 mmol) portion of this amide yielded after removal of the BOC protection *via* general procedure A, ion exchange, and lyophilization 51.0 mg (91.8%) of the acetate as a pale yellow amorphous solid: TLC R_f = 0.31 (CH_2Cl_2/methanol/NH_4OH (7:3:0.1)); ^{1}H NMR (D_2O) δ = 8.43 (br m, 1H), 7.80 (dt, J = 1.2, 8.0 Hz, 1H), 7.42–7.23 (br m, 7H), 4.40 (br m, 2H), 4.18 (br m, 1H), 3.98 (br m, 1H), 3.39 (br m, 3H), 3.02 (br m, 2H), 2.99–2.67 (br m, 9H), 2.57 (br m, 2H), 2.06 (s, 3H), 1.93 (s, 3H), 1.76–1.57 (br m, 6H), 1.45 (br m, 2H), 1.30–1.13 (br m, 4H), 0.92 (br m, 2H), rotamers; FAB MS *m/e* 682 (M + H)$^+$.

(2*S*,3*R*,4*S*)-*N*-[*N*-[(2*R*)-3-[(4-Aminopiperidyl)carbonyl]-2-benzylpropionyl]-L-norvalyl]-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexane-2-amine Acetate (48). Acid **14** (55.3 mg, 0.14 mmol) and 53.0 mg (0.14 mmol) of amino fragment **7c** were coupled *via* general procedure C. Chromatography with CH_2Cl_2/methanol (20:1) gave 67.7 mg (63.3%) of the corresponding amide (TLC R_f = 0.28), which provided after deprotection using general procedures A followed by subsequent ion exchange and lyophilization 55.4 mg (85.8%) of the desired acetate as an amorphous white solid: TLC R_f = 0.15 (CH_2Cl_2/methanol/NH_4OH (10:1:0.1)); ^{1}H NMR (D_2O) δ = 8.45 (br m, 1H), 7.82 (br t, J = 7.2 Hz, 1H), 7.42–7.23 (br m, 7H), 4.42 (br m, 1H), 4.17 (br m, 1H), 4.00 (br m, 1H), 3.68 (dd, J = 2.4, 11.6 Hz, 1H), 3.57 (dd, J = 6.8, 11.6 Hz, 1H), 3.41 (br m, 2H), 3.30–2.72 (br m, 8H), 2.56 (br m, 1H), 2.09 (br m, 3H), 1.94 (s, 3H), 1.80–1.45 (br m, 10H), 1.33–1.15 (br m, 6H), 0.88 (br m, 4H), rotamers: FAB MS *m/e* 664 (M + H)$^+$.

(2*S*,3*R*,4*S*)-*N*-[*N*-[(2*S*)-2-[[(4-Aminopiperidyl)carbonyl]-oxy]-3-phenylpropionyl]-L-histidyl-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexan-2-amine Acetate (49). (2*S*)-2-[[[4-[(*tert*-Butyloxycarbonyl)amino]-1-piperidyl]carbonyl]oxy]-3-phenylpropionic acid[11] (225.7 mg, 0.575 mmol) and 342.4 mg (0.575 mmol) of amino fragment **7a** were processed *via* general procedure B. Purification by chromatography with CH_2Cl_2/methanol (20:1) afforded 357.0 mg (64.0%) of the protected amide: TLC R_f = 0.35 (CH_2Cl_2/methanol (10:1)). A 135.0-mg (0.139 mmol) portion of this amide provided after subsequent use of general procedures D and A, ion exchange, and lyophilization 93.2 mg (85.7%) of the desired acetate as a tan amorphous solid: TLC R_f = 0.11 (CH_2Cl_2/methanol/NH_4OH (9:1:0.1)); ^{1}H NMR (DMSO-d_6, 90 °C) δ = 8.43 (dd, J = 0.8, 4.8 Hz, 1H), 8.28 (br s, 1H), 8.00 (br d, J = 7.6 Hz, 1H), 7.63 (dt, J = 1.2, 8.0 Hz, 1H), 7.27–7.08 (m, 7H), 7.04 (s, 1H), 5.04 (dd, J = 4.0, 8.4 Hz, 1H), 4.57 (br m,

1H), 4.14 (br m, 1H), 3.92 (br m, 2H), 3.18 (br m, 2H), 3.12–2.74 (br m, 8H), 2.05 (br m, 1H), 1.87 (br m, 2H), 1.75–1.56 (br m, 6H), 1.44–1.13 (br m, 9H), 0.92 (br m, 2H), rotamers; FAB MS *m/e* 704 $(M + H)^+$.

(2*S*,3*R*,4*S*)-*N*-[*N*-[(2*R*)-3-[(4-Aminopiperidyl)sulfonyl]-2-benzylpropionyl]-L-histidyl]-1-cyclohexyl-3,4-dihydroxy-6-(2-pyridyl)hexan-2-amine (50). Acid **27** (213.2 mg, 0.50 mmol) and 297.8 mg (0.50 mmol) of amino fragment **7a** were coupled *via* general procedure B. Separation of the resultant two diastereomers by chromatography with CH_2Cl_2/methanol (96:4) yielded 201.0 mg (40.1%) of the less polar 2*S* diastereomer [$[\alpha]^{20}_D$ = −35.9° (*c* = 1, methanol), TLC R_f = 0.33] and 194.0 mg (38.7%) of the more polar 2*R* diastereomer [$[\alpha]^{20}_D$ = −24.8° (*c* = 1, methanol), TLC R_f = 0.30] as amorphous pale yellow solids. A 168.1-mg (0.17 mmol) portion of the more polar diastereomer was N^{im}-deprotected using general procedure D to afford after chromatographic purification with CH_2Cl_2/methanol/acetic acid (100:5:1) as eluent 121.8 mg (92.6%) of a pale yellow solid: TLC R_f = 0.24; mp 183–187 °C; $[\alpha]^{20}_D$ = −25.8° (*c* = 0.22, methanol). A 108.4-mg (0.13 mmol) portion of this compound was processed using general procedure A. Chromatography with CH_2Cl_2/methanol/NH_4OH (100:20:1) yielded 82.3 mg (85.9%) of the desired compound: TLC R_f = 0.08 $[\alpha]^{20}_D$ = −22.9° (*c* = 1, methanol); ^1H NMR ($CDCl_3$) δ = 8.43 (dd, *J* = 0.8, 4.4 Hz, 1H), 7.59 (dt, *J* = 1.2, 6.8 Hz, 1H), 7.53 (s, 1H), 7.32–7.15 (m, 6H), 7.10 (m, 1H), 6.94 (s, 1H), 6.81 (br d, *J* = 8.4 Hz, 1H), 4.68 (br dd, *J* = 2.4, 7.2 Hz, 1H), 4.22 (br m, 1H), 3.64–3.47 (br m, 3H), 3.26 (d, *J* = 8.4 Hz, 1H), 3.12–2.93 (br m, 6H), 2.87–2.63 (br m, 6H), 2.18 (br m, 1H), 1.87–1.51 (br m, 9H), 1.45–1.08 (br m, 7H), 0.87 (br m, 2H), rotamers; FAB MS *m/e* 738 $(M + H)^+$.

***In Vitro* Enzyme Inhibition.** Inhibition of plasma renin activity was assayed by measuring the endogenous angiotensin I production in plasma samples at 37 °C in the presence of appropriate concentrations of the test compounds. A commercial radioimmunoassay kit (Renin-MAIA, Serono Diagnostika) was used for the generation and quantitation of angiotensin I. Inhibitors were dissolved and diluted in DMSO (final assay concentration 1%). IC_{50} values were read from semilogarithmic plots of renin activity (% of control without test compound) *versus* inhibitor concentration.

Purified human kidney renin (Calbiochem) was assayed at pH 7.5 using the tetradecapeptide corresponding to the first 14 N-terminal amino acids of human angiotensinogen Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Asn (Bachem) at pH = 7.5 as substrate. Angiotensin I was determined as mentioned above.

The inhibition of human pepsin, gastricsin, and cathepsin D and E was determined as described previously.[29]

***In Vivo* Activity.** Following the previously described protocol,[7] experiments were carried out in two to six furosemide-treated, pentobarbitone-Na anesthetized rhesus monkeys of either sex weighing between 5 and 13 kg. For intraduodenal administration, compounds were dissolved in 0.1 M citric acid and delivered by a gastric fiberscope into the duodenum. Monitoring of systolic and diastolic blood pressure and periodic collection of blood samples were performed after surgically manipulation of one radial artery and the saphenous vein, respectively.

Stability Study. The stability of the inhibitors **38**, **39**, **40**, **41**, **43**, and **50** toward enzymatic degradation by chrymotrypsin were examined by reversed-phase HPLC on nucleosil C-18 (7 μm, eluent: 60% methanol/40% water/0.1% ammonium acetate) at 254 nM as described previously.[7]

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