Design and Synthesis of Renin Inhibitors: Incorporation of Transition-State Isostere Side Chains That Span from the S1 to the S3 Binding Pockets and Examination of P3-Modified Renin Inhibitors

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A series of renin inhibitors were designed to examine the topography of the contiguous binding pocket of renin that is normally occupied by the P1 and P3 side chains. Molecular modeling suggested that extending the P1 hydrophobic side chain into the adjacent hydrophobic S3 enzyme pocket was feasible. Novel transition state isosteres with modified P1 → P3 side chains were synthesized and provided enhanced binding affinity when incorporated into renin inhibitors in which the P3 Phe was substituted by Gly. In a complementary approach, the binding affinities of a variety of P3–P4-modified peptidomimetic renin inhibitors that lacked substantial hydrophobic side chains at these sites were measured.

Introduction

The renin–angiotensin system (RAS) is intimately involved in the control of blood pressure and the retention of water and sodium, which is mediated through aldosterone release. The clinical success of angiotensin-converting enzyme (ACE) inhibitors as antihypertensive agents demonstrates the importance of drugs targeting the RAS. Recently, ACE inhibitors have also been shown to be an effective treatment for patients with congestive heart failure.[1] ACE inhibitors, however, also prevent the metalloprotease from degrading other important peptides such as bradykinin, enkephalins, and substance P, possibly accounting for some of the observed adverse effects of this class of drug.[2] Other potential means for intervention of the RAS include orally active nonpeptide angiotensin II (AII) antagonists of the type 1 receptor[3] and inhibitors of renin, a highly specific and rate-limiting enzyme in the proteolytic cascade leading to the pressor agent AII. Some AII antagonists are currently in clinical trials. However, a potential concern with this approach is the increased AII concentration and the resulting potential effect on the type 2 receptor, whose function remains unclear.[4] Inhibition of renin remains an attractive therapeutic target because in addition to lowering levels of AII, renin has only one known substrate, angiotensinogen.

Renin inhibitors are classically substrate based, employing an isostere that mimics the transition state of the hydrolysis of the scissile amide bond found between Leu10-Val11 of angiotensinogen. Potent inhibitors typically extend two or three amino acid residues from either the C- or N-terminus of the transition state mimetic and bind in an extended β-strand conformation.[5] The transition state isosteres employed in our work are derivatives of (2*S*,3*R*,4*S*)-1-alkyl-2-amino-6-methylheptane-3,4-diol, which have been previously described as key substructural components of various potent inhibitors.[6] The lack of long lasting oral activity observed with many renin inhibitors is thought to be due to poor absorption and/or rapid hepatic elimination of the inhibitors which are still, to some degree, peptidic in nature and often have molecular weights over 500.[3,7]

Our method for addressing these liabilities employed two complementary approaches. The first was topographical and based on the observation that many potent renin inhibitors have a hydrophobic cyclohexylmethyl moiety as the P1 group and typically an aromatic amino acid side chain at the P3 site.[8] In the bound inhibitor with a β-strand structure, and P1 and P3 side chains are adjacent and indeed occupy a continuous binding pocket.[5] Therefore, the synthesis of inhibitors with an aromatic group extending from the diol of the transition state mimetic directly into the contiguous S1–S3 enzyme pocket was proposed. By combining the two P1 and P3 hydrophobic side chains into one unit, advantage may be gained by prearranging the hydrophobic units into positions that would result from hydrophobic collapse.[9] Conceptually, by tethering an aromatic moiety from the P1 cyclohexylmethyl group to reach the S3 binding pocket, truncation of the peptide backbone might be possible. This approach may result in a lower molecular weight renin inhibitor with decreased peptidic nature, which may favorably affect absorption and excretion of the inhibitor.[10]

Recently, the Hanessian group independently published a strategy similar to ours[11] that employs extending hydrophobic groups from the transition state isostere into the S3 pocket.[12] A topographical approach has been previously employed for inhibitors of the aspartyl protease pepsin, which binds in an extended β-strand conformation, where the P1 and P3 hydrophobic groups are replaced by a hydrophobic macrocycle.[13] Hydrophilic side chains have also been tethered from P1 and P1′ hydrophobic groups in HIV protease inhibitors, allowing interaction with a polar environment.[14] In a more direct analogy with our work, potent HIV protease inhibitors with hydrophobic groups that occupy a continuous binding pocket have also been substituted by

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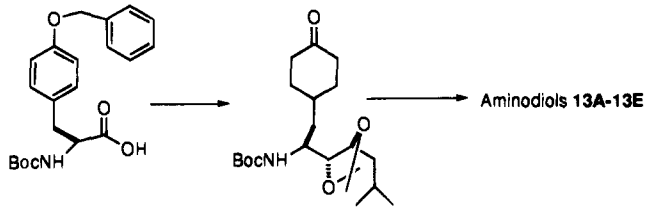
Scheme 1. Derivation of Amino Diols **13A–E**



the extended P1 side chain of a 4-benzoylphenylalanine-derived hydroxyethylene isostere.[15]

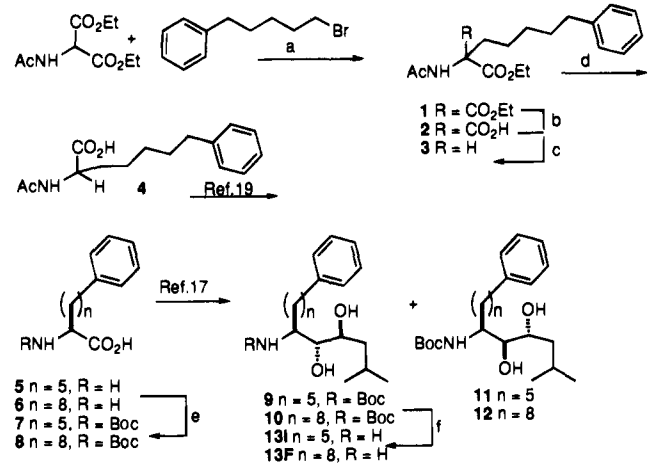
The second approach examined the viability of inhibitor truncation by exploring the importance of hydrogen bonds involving the amide groups linking P4–P3 and P3–P2 when no aromatic side chain occupies the S3 binding pocket. We have previously shown that when the P3 amino acid is derived from phenylalanine, isosteres of the P3–P2 amide offer a variety of binding affinities, implying the importance of conformation and hydrogen bonding at this site.[16] Taken collectively, these two approaches are expected to systematically provide insight into the relative contribution to the binding affinity of the P3 aromatic side chain and the hydrogen bonds formed by the P4–P3 and P3–P2 amide groups. At the outset it was hoped that the contribution of the aromatic group tethered from the diol transition state mimetic would be larger than the relative contribution of the hydrogen-bonding backbone amide groups, which would allow for truncation of the inhibitor.

Chemistry

The synthesis of transition state isosteres that extend through the S1–S3 binding pocket will be illustrated by representative examples. The synthesis of the isosteres where the S1 pocket is occupied by a cyclohexylmethyl moiety, **13A–E**, has been schematically described in a recent communication.[11] Spectral data for these amino diols can be found in the supporting information. Briefly, **13A–E** were obtained by converting Boc-*O*-benzyltyrosine to a ketone-containing intermediate, employing a standard aminodiol synthesis,[17] from which the transition state isosteres were derived (Scheme 1).

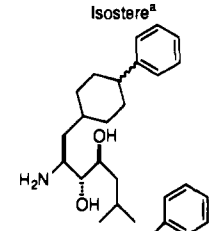
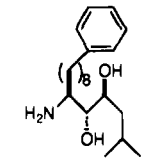
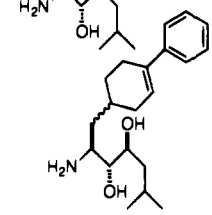
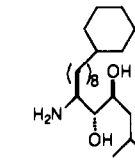
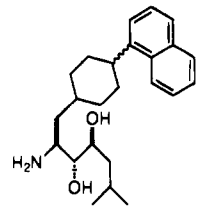
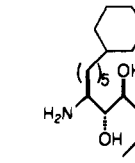
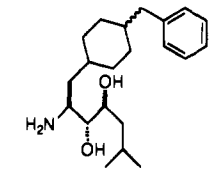
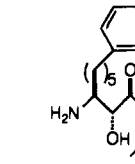
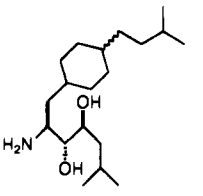
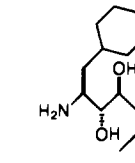
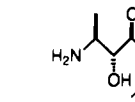
Synthesis of the isosteres in which the S3 pocket is reached by a phenyl or cyclohexyl ring appended to a linear alkyl chain originating at the P1 site is outlined in Scheme 2. Alkylation of acetamidomalonate with 1-bromo-5-phenylpentane[18] provided **1**. The diethyl ester was monohydrolyzed, giving **2**, which was decarboxylated by refluxing in dioxane providing **3**. The acetamido ester, **3**, was hydrolyzed to the acid, **4**, which was resolved to the L-isomer, **5**, by selective acetamide hydrolysis employing acylase following a literature procedure.[19] In a similar manner the 8-phenyloctyl amino acid, **6**, was obtained. Both **5** and **6** were protected as Boc derivatives **7** and **8**, which were converted to the Boc amino diols **9–12**. Deprotection provided pentyl derivative **13I** and octyl derivative **13F** (Scheme 2). The stereochemistry shown is based upon the assumption that the 2*S*,3*R*,4*S* stereoisomer is the more biologically active isomer.[17] The phenyl substituent of the 2*S*,3*R*,4*S* Boc amino diols, **9** and **10**, reduces with hydrogen in the presence of 10% Rh/C, providing the cyclohexyl-substituted side chain and upon removal of the Boc group provides the amino diols **13G** and **13H**.

Scheme 2.[a] Synthesis of Extended Alkyl Chain-Containing Transition-State Isosteres



[a] Conditions: (a) EtONa, EtOH, 50 °C; (b) EtOH/H_2O/NaOH, room temperature; (c) dioxane, reflux; (d) EtOH/H_2O/NaOH, room temperature; (e) Boc_2O, dioxane, NaOH; (f) HCl(g), CH_2Cl_2.

Table 1. Amino Diol Transition-State Isosteres

Compound No.	Isostere[a]	Compound No.	Isostere
13A		**13F**	
13B		**13G**	
13C		**13H**	
13D		**13I**	
13E		**13J**	
		13K	

[a] Wavy line indicates ~1:1 mixture of *cis/trans*-cyclohexane isomers or in the case of **13B**, ~1:1 mixture of diasteromers.

The amino diols **13A–K** (Table 1) were then coupled to Boc-allylglycine (Boc-Alg) employing standard carbodiimide coupling conditions (Scheme 3). Deprotection provided an amine which was then coupled with either (morpholinosulfonyl)phenylalanine[20] (SMO-Phe) **15B** or

Scheme 3. General Synthesis of Renin Inhibitors

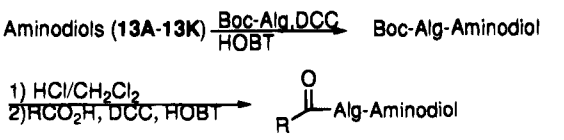
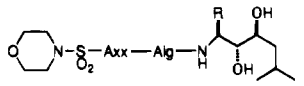
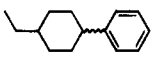
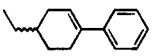
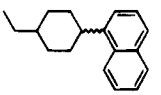
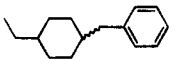
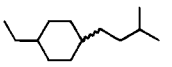


Table 2. In Vitro Binding Affinity of Renin Inhibitors that Span the P1 → P3 Sites



Compd Axx = Gly	Affinity (nM) IC_{50}	R	Compd Axx = Phe	Affinity (nM) IC_{50}
14A	60		14B	16.1
14C	18.5		14D	21.3
14E	11.0		14F	21.0
14G	202		14H	3.6
14I	29% at 10^{-6}		14J	23.8
14K	1200		14L	116
14M	20% at 10^{-6}		14N	21% at 10^{-6}M
14O	479		14P	25.1
14Q	23% at 10^{-6}		14R	6.1
14S	82		14T	0.2
....		CH_3	14U	16% at 10^{-6}M

(morpholinosulfonyl)glycine[21] (SMO-Gly) **15A**, providing renin inhibitors **14A**–**R** (Table 2).

The renin inhibitors **14S** and **14T**, which serve as reference compounds, were prepared from 2(*S*)-amino-1-cyclohexyl-3(*R*),4(*S*)-dihydroxy-6-methylheptane (ACDMH), **13J**.[17] The renin inhibitor **14U**, which also serves as a reference compound, is derived from 2(*S*)-amino-3(*R*),4(*S*)-dihydroxy-6-methylheptane, **13K**.

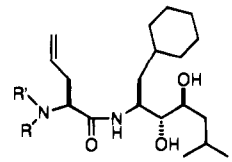
The second portion of our strategy required synthesis of the renin inhibitors that emphasize hydrogen-binding interactions between the P4–P3 and P3–P2 amide groups and the enzyme. Removing the aryl group from the P3 moiety provides opportunity for assessment of the contributions due to amide–enzyme interactions in this region. Focus was placed on coupling (*S*)-allylglycine–ACDMH with low molecular weight fragments **15C**–**K**, providing the renin inhibitors **16A**–**J**. (Table 3). Construction of the inhibitors was accomplished in one of three manners: (A) The morpholinosulfonyl amino acid derivatives[21] **15C**–**E** were coupled with (*S*)-allylglycine–ACDMH providing inhibitors **16A**–**C** by employing the general method described in Scheme 3. (B) (*E*)-1-Sulfonylmorpholineprop-1-en-3-oic acid, **15K**, was synthesized (Scheme 4) and coupled by employing the general method described in Scheme 3 to provide inhibitor **16J**. (C) The remaining acids, **15F**–**J**, are easily synthesized from commercially available anhydrides or half-acid esters and morpholine; their synthesis can be found in the Experimental Section. The acids, **15F**–**J**, once obtained, were then coupled with (*S*)-allylglycine–ACDMH, employing the general method described in Scheme 3 to provide the renin inhibitors **16D**–**I**.

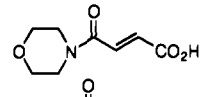
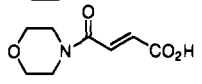
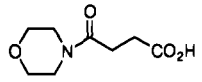
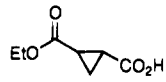
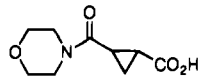
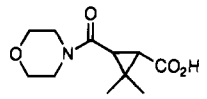
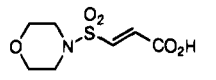
Results and Discussion

Molecular modeling studies involving structure-based design with a renin model were carried out to determine enzyme-compatible ligand structures that could extend from the P1 cyclohexyl group directly into the S3 pocket, while removing a side chain at the P3 position. The structures in Figure 1 were docked in the renin enzyme model by following the general binding scheme reported for inhibitors of the aspartic proteases.[22] The P1 hydroxyl group was positioned between the two catalytic aspartic acids, and the amide bonds were engaged in hydrogen bonds with the flap region and the base of the enzyme. A phenyl and, separately, a 1-naphthyl group were built on the equatorial 4-position of the cyclohexyl ring. Steric conformational searches of the P1 → P3 side chains run without the confines of the cleft region indicated that the lowest energy conformer from each analysis was compatible with the enzyme binding cleft. Compounds **14A** and **14E** were compared with the bound conformation of an inhibitor extracted from an endothiapepsin crystal complex[23] and manually oriented in the renin cleft model without altering the conformation. As can be seen from the upper part of Figure 2, the phenyl group in **14A** does not extend to completely fill the S3 binding site. However, the group at this position is compatible with the enzyme binding site and could result in favorable hydrophobic binding. In the renin model, Phe112 and Phe117 (pepsin numbering) are found proximal to the tethered phenyl binding site; however, the side chain of Phe117 is oriented away from the binding cavity. In examining the crystal structure of the homologous enzyme porcine pepsin,[24] Phe117 is found to be oriented toward the cleft, and thus, it is reasonable to suspect that this orientation might also be found in the renin crystal structure. This could provide a favorable aromatic environment for the phenyl attached to the cyclohexyl side chain. Subsequently, the human renin crystal structure was solved, and it indeed presents the Phe117 side chain toward the binding site. With the other tethered derivative, the naphthyl group does enter the S3 site but adopts a twisted plane orientation relative to the Phe side chain in the inhibitor crystal structure (Figure 2, lower part). The modeling work supported the syntheses of analogs in which the novel P1 → P3 moieties would be coupled onto an inhibitor fragment containing P2–P4 residues with no P3 phenyl side chain.

Compounds **14A** and **14E** contain the modeled phenyl and naphthyl P1 → P3 moieties, respectively, coupled to a SMO-Gly-Alg amino terminus. Both compounds proved to be potent inhibitors with the naphthyl having the better affinity: 11 nM versus 60 nM for the phenyl derivative. This was not surprising since, as indicated in Figure 2, the naphthyl group more fully occupied the S3 binding site. The results indicate that the concept

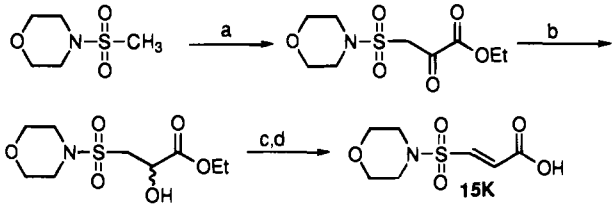
Table 3. In Vitro Binding Affinity of Renin Inhibitors Lacking a P3 Aromatic Group



Acid compd No.	R (as Acids)[a]	R'	Inhibitor compd No.	Affinity (nM) IC_{50}
15A	SMO-Gly	H	14S	82
15B	SMO-Phe	H	14T	0.2
15C	SMO-Ala	H	16A	89
15D	SMO-D-Ala	H	16B	28
15E	SMO-Val	H	16C	1.4
15F		H	16D	74
15F		CH_3	16E	5% at 10^{-6}M
15G		H	16F	832
15H		H	16G	131
15I		H	16H	19
15J		H	16I	85
15K		H	16J	32

[a] SMO refers to the morpholinosulfonyl group.

Scheme 4.[a] Synthesis of **15K**



[a] Conditions: (a) *n*-BuLi, diethyl oxalate, −20 °C; (b) EtOH, PtO_2, H_2, 50 psi; (c) $MeSO_2Cl$, Et_3N; (d) NaOH/THF/H_2O.

of extending to the S3 site directly from the P1 side chain was indeed valid, and thus related analogs were targeted.

Other groups were substituted at position 4 of the P1 cyclohexyl group, while retaining the SMO-Gly-Alg amino terminus. Although these inhibitors were synthesized as mixtures, the trans isomers were considered to be the more active analogs, based on the original modeling. The benzyl derivative, **14G**, exhibited a 20-fold drop in activity relative to **14E**, while the substitution of a 4-isopentyl group, as seen in **14I**, resulted in a more dramatic loss in potency. The latter result may be related to the lack of an aromatic moiety in the P1 extension. The preference for an aromatic moiety directly attached to the cyclohexyl group may be traced

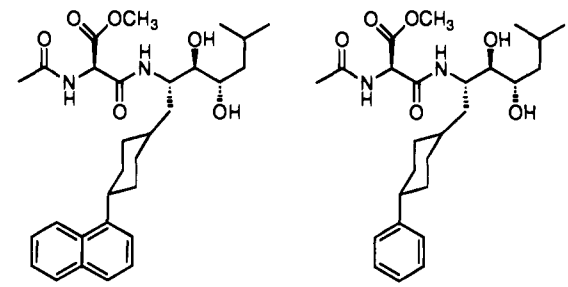


Figure 1. Tethered analogs modeled in the renin model active site. The P1 side chains extend to the S3 binding region through either a phenyl or naphthyl group.

to the S1 → S3 binding region described above. Replacing the cyclohexyl group with a more rigid cyclohexene ring, as in **14C**, resulted in a 3-fold increase in activity relative to **14A** and essentially equal potency when compared to the naphthyl analog **14E**. The cyclohexyl group of the P1 → P3 moiety was also replaced by more flexible linkers containing five and eight methylene units, each attached to a terminal phenyl group (**14K** and **14O**). In both cases the activity was diminished relative to **14A**, with the octyl analog exhibiting the lesser affinity of 1200 nM. The increased entropy of the side chains can account at least in part for the diminished potency for the two analogs and correlates with

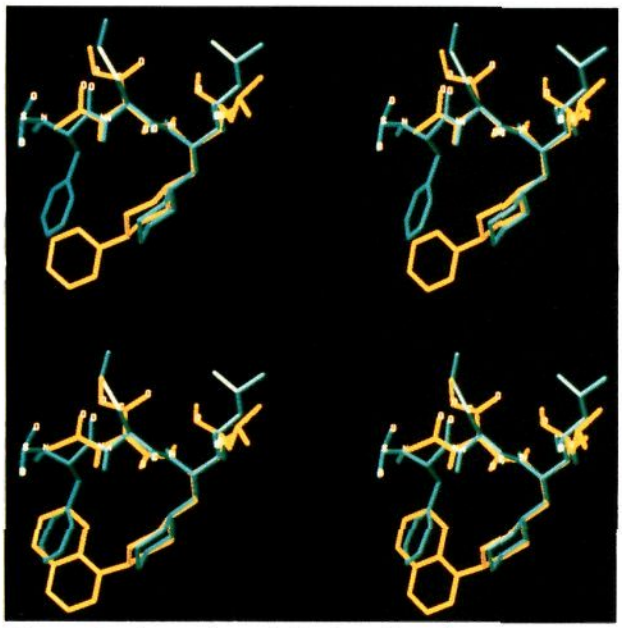


Figure 2. Stereoview of the bound conformation of the phenyl-tethered analog (upper, yellow) and the naphthyl-tethered analog (lower, yellow) overlaid with a diol inhibitor extracted from an endothiapepsin X-ray crystal complex[23] and orientated in the renin model active site (upper, lower, cyan).

the activities. The derivatives of **14K** and **14O** in which the P1 → P3 phenyl group was replaced with a cyclohexyl substituent, as seen in **14M** and **14Q**, showed diminished activity relative to the corresponding phenyl analogs and again reflected the loss of an aromatic group in the P1 extension.

To assess better the binding gained by tethering the P3 group to the P1 side chain, an inhibitor with Gly at P3 and the standard methylene cyclohexyl group at P1, **14S**, was tested. Surprisingly, the potency of **14S** was 82 nM, even though no aromatic group was introduced into the S3 site. This reflected an 8-fold decrease in activity relative to **14E** and was essentially equipotent to **14A**. Therefore, the naphthyl group contributed favorably to binding, whereas the phenyl group had little overall impact on the affinity. Furthermore, the activity of **14S** would suggest that for the analogs lacking a P3 aromatic moiety described above, **14I**, **14M**, and **14Q**, the drop in potency is due not only to the loss of the aromatic group but also to the detrimental effect of having the alkyl substituents in the S3 pocket, in addition to an unfavorable entropic factor.

An analog of **14S**, having a Phe at P3, **14T**, was 400-fold more potent than the P3-Gly analog. Truncating the P1 group of **14T** to a methyl group while retaining the P3 Phe group, as in **14U**, abolished meaningful binding affinity. Therefore, the P1 side chain is apparently more critical for binding in this series of inhibitors than the P3 side chain.

The P3 Phe derivatives of the tethered compounds were not predicted to be very potent inhibitors, since the tethered group was expected to compete with the P3 Phe side chain for the S3 binding site. Surprisingly, with the exception of the P3 Phe-containing naphthyl analog, **14F**, in which slightly poorer affinity was observed, the P3 Phe derivatives were more potent or equipotent to the corresponding P3 Gly analogs. The most dramatic increase in affinity was with **14R**, which bound with nanomolar affinity, in contrast to its Gly counterpart, **14Q**, which was essentially inactive at micromolar concentration.

To determine possible modes of binding for these unexpectedly potent inhibitors, **14P** was manually docked in the binding site of the renin crystal structure.[25] This structure had a smaller S3 binding site than that predicted in the model due to a shift of a helix. The binding mode in Figure 3 shows that the inhibitor can be accommodated by the cleft but involves changes relative to the standard binding, including an orientation of the P3 side chain more toward solvent (Figure 4). It would follow that **14E**, with a rigid extension to P3, would be less apt to adapt to the cleft, and this is reflected in the 2-fold drop in activity in the P3 Phe analog **14F**. However, with the enzyme crystal structure or with the renin model, one can only speculate about the binding modes for this novel series of inhibitors. An X-ray crystal structure with the human renin enzyme is needed for this determination.

Though the survey of P1 linking groups has been limited to cyclohexylmethyl, pentyl, and octyl, and the groups appended to their termini are not extensive, one can conclude that the concept of extending from the diol transition state isostere directly into the contiguous S1–S3 pocket is a plausible approach in designing novel renin inhibitors. The most favored side chain contains a cyclohexylmethyl linking group (P1) appended with a 4-(1-naphthyl) moiety. Prior to optimizing the tethered side chain in this topographically based approach, prudence indicated that the importance of hydrogen bonding at the P4–P3 and P3–P2 amide groups be investigated.

This investigation centered around improving the binding affinity of the P3 glycine analog **14S** (82 nM), while minimizing any increases in the molecular weight of the N-terminal functional groups. Use of Alg-ACDMH as the C-terminal fragment allows systematic investigation of the N-terminal acyl groups. Coupling SMO-L-Ala **15C** and SMO-D-Ala **15D** with Alg-ACDMH provides **16A** and **16B**, respectively. The activity of **16A** shows little change when compared to the P3 glycine derivative **14S** (89 vs 82 nM); however, the D-amino acid analog **16B** has a binding affinity of 28 nM.[26] In contrast, the SMO-Val analog, **16C**, displays greatly increased potency when compared with **14S** (1.4 vs 82 nM). Thus, the expedient of adding an isopropyl group to the α-carbon atom of glycine derivative **14S** results in 60-fold enhancement in binding affinity. Constraining the isopropyl group provides the dimethylcyclopropane derivative, **16I**, which has reduced binding affinity, 85 nM. Removal of the two methyl groups provides **16H**, with a binding affinity of 19 nM, indicating that the constrained isopropyl group is somewhat sterically unfavorable.[27] The cyclopropyl ester derivative, **16G**, shows a 7-fold drop in potency when compared to the cyclopropylmorpholinamide derivative, **16H** (131 vs 19 nM). This change in binding affinity may be partly attributed to the decreased hydrogen bond-accepting ability of the ester carbonyl versus the morpholinamide carbonyl. Replacement of the cyclopropane group in **16H** with another rigidifying group, a trans-olefin, provides **16D** and results in decreased binding affinity (19 vs 74 nM). N-Methylation of the P2 allylglycine unit provides **16E** and results in a loss of activity. This drop

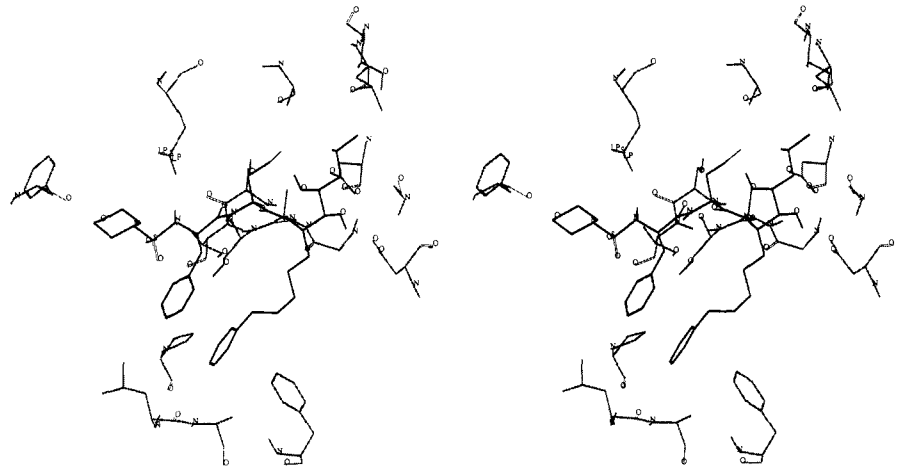


Figure 3. Stereoview of analog **14P** (black lines) docked in the renin binding site (gray lines) extracted from the human renin X-ray crystal structure.[25]

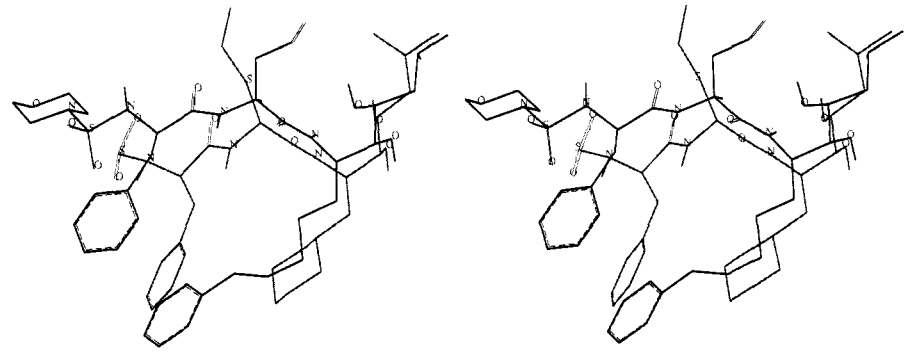


Figure 4. Stereoview of the bound conformation of **14P** (black lines) overlaid with a diol inhibitor extracted from an endothiapepsin X-ray crystal complex[23] and oriented in the renin active site (gray lines) of the X-ray crystal structure.[25]

in binding affinity may be attributed partially to the loss of a hydrogen bond donor interaction with the Thr77 side chain as observed in an X-ray crystal structure of renin bound with an inhibitor.[28] Furthermore, N-methylation can lead to an unfavorable increase in conformers containing a cis-amide bond. Reduction of the trans-olefin in **16D** gives inhibitor **16F** with greater backbone rotational freedom. Inhibitor **16F** displays a 10-fold drop in binding affinity versus **16D** presumably due to the increased entropy (74 vs 832 nM).[29] Comparison of **16D** with analog **16J** indicates that the sulfonamide functionality is preferred (74 vs 32 nM) by approximately 2-fold relative to the amide carbonyl possibly due to its increased hydrogen bond-accepting ability.

Collectively, these results suggest (a) a secondary amide unit linking P3 and P2 is preferred over tertiary amide group (**16E**), (b) the amide linking P4–P3 is adequate and is only improved slightly by incorporation of a sulfonamide (**16J**) while an ester (**16G**) is not as well-tolerated, and (c) small nonaromatic P3 side chains can provide an increase in binding affinity over the parent SMO-Gly analog **14S**.

Conclusion

This work demonstrates that the concept of extending from the transition state isostere directly into relatively distant binding pockets without involving the peptide backbone is a viable strategy. This strategy may be exploited in designing inhibitors targeting other enzymes which bind in an extended β-strand conformation and have P1 and P3 side chains that occupy contiguous binding pockets. The concept of tethering side chains from the transition state isostere offers the opportunity to increase the effectiveness of the mimetic, permitting the design of smaller substrate-based inhibitors. Such inhibitors may overcome absorption and excretion problems associated with more peptide-like inhibitors. As shown here, and in previous work,[16] the complementary approach of examining the binding affinity attributed to the hydrogen bond-accepting and -donating of P2–P3 and P3–P4 amide groups is apparently indispensible. This information guides how effective the P1–P3 hydrophobic extention must be to allow trunctation of the inhibitor and elimination of these amide groups. Unfortunately, in the case of renin, hydrogen-bonding interactions distant from the transition state isostere are of great significance and would indicate that truncation of the inhibitor would not be easily accomplished.

Experimental Section

Molecular Modeling. Molecular modeling studies were carried out using the Sybyl Molecular Modeling Software Package[30] (Versions 5 and 6) on a Silicon Graphics workstation or an Evans and Sutherland graphics terminal coupled to a VAX computer. The human renin model used was derived from the crystal structure of endothiapepsin, a fungal enzyme homologous to renin.[31] The conformational search analysis[32] for **14A** and **14E** was carried out without the confines of the cleft region, rotating the three bonds in the P1 → P3 side chains. The torsion angles were driven in 10° increments, a 5 kcal/mol energy cutoff was applied, and electrostatics were not included. The optimization of **14P** in the cleft extracted from the crystal structure of human renin[25] was carried out using the Tripos force field[33] and without electrostatics. All hydrogens were placed on the inhibitor, and only essential

hydrogens were added to the enzyme residues in the cleft region. The cleft and the inhibitor P1 oxygen bound at the catalytic dyad were defined as a fixed aggregate.

Biological Methods. In vitro renin inhibition was measured according to methods modified from Haber et al.[34] The in vitro angiotensin I generation step utilized 550 μL of monkey plasma (containing native renin and angiotensinogen), 50 μL of maleate buffer (pH 6.0), 5 μL of phenylmethanesulfonyl fluoride (PMSF), and 2 μL of appropriate concentration of inhibitor in dimethyl sulfoxide (DMSO) solution. Incubation was for 60 min at 37 °C. Following incubation, each mixture was analyzed with ^{125}I-labeled angiotensin I and carried out in tubes coated with rabbit anti-angiotensin I antibody (Gamma Coat RIA Kit, Dade Clinical Assays). Monkey plasma renin activity ranged from 3 to 8 ng/mL per h. Values for inhibitor tubes were compared to vehicle control tubes for estimation of percent inhibition. At the concentration used, DMSO inhibits the generation of angiotensin I by <10%. The inhibition results were expressed as IC_{50} values, which were obtained by plotting six inhibitor concentrations and estimating the concentration producing 50% inhibition using nonlinear regression analysis. All measurements were determined in duplicate.

Chemistry. ^{1}H NMR spectra were recorded on a Bruker AM250 (250 MHz) or XL300 (300 MHz) spectrometers and were run in either $CDCl_3$ or d_6-DMSO (DMSO). Chemical ionization mass spectra were recorded on either a Finnigan 4500 MS using methane as the reagent gas or a Fisions (VG Biotech) Trio-2A using 1% ammonia in methane as the reagent gas. All IR spectra and microanalytical data were obtained by the Parke-Davis Analytical Chemistry Section. The IR spectra were recorded on a Mattson Cygnus 100 FT-IR. Silica gel column chromatography was performed using either Keiselgel 60 (70–230 mesh or 230–400 mesh for flash). Thin layer chromatography employed EM science silica gel 60 F_{254} glass-backed plates. Solvents were dried according to Perrin and Armarego or purchased dry and used fresh from the suppliers.

General Methods. General Method A: Dicyclohexylcarbodiimide (DCC) and 1-Hydroxybenzotriazole (HOBT) Coupling Procedure. The acidic component (1 mmol) was dissolved in DMF or a suitable solvent (10 mL). The solution was sequentially treated with the free amine component (1 mmol), HOBT (1 mmol), and then DCC (1 mmol). The reaction mixture was stirred 8–24 h and then was filtered to remove solids. The DMF was removed under reduced pressure, and the residue was dissolved typically in ethyl acetate and partially purified by an extractive workup. The organic phase was dried over magnesium sulfate, and the solvent was removed under reduced pressure. The residue was then purified by chromatography over silica gel.

General Method B: Removal of Boc Protection. The Boc-protected amine component (1 mmol) was dissolved in dichloromethane (10–20 mL), and the solution was saturated with HCl gas. After 1–4 h at room temperature the solvent was removed under reduced pressure to provide the amine hydrochloride. The free base was obtained by washing the salt in ethyl acetate with saturated sodium bicarbonate and then brine. After drying over magnesium sulfate, the solvent was removed under reduced pressure, providing the free base that was generally utilized without purification.

Diethyl Acetamido(5-phenylpentyl)malonate (1). To 100 mL of absolute ethanol was added 3.3 g (0.143 mol) of sodium metal. When all had reacted, 31.2 g (0.143 mol) of diethyl acetamidomalonate and 25 mL of absolute ethanol was added, and the solution warmed at 50 °C for 1 h. The solution was then treated with 32.6 g (0.143 mol) of 1-bromo-5-phenylpentane[18] and heated at reflux overnight. The solvent was removed under reduced pressure and the residue taken up in ether and washed twice with water and then brine. Drying over $MgSO_4$ and removal of the solvent under reduced pressure gave a solid. Trituration with ether and dilution with hexane gave **1** (27.6 g, 53%) as a white solid: mp 93–95 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.16 (m, 2 H), 1.22 (t, 6 H), 1.34 (m, 2 H), 1.62 (m, 2 H), 2.04 (s, 3 H), 2.34 (m, 2 H), 2.60 (t, 2 H), 4.22 (q, 4 H), 6.78 (s, 1 H), 7.10–7.32 (m, 5 H); MS (CI, 1% NH_3 in CH_4) *m/z* 364 ($M + H^+$). Anal. ($C_{20}H_{29}NO_5$) C, H, N.

Acetamido(5-phenylpentyl)malonic Acid Monoethyl Ester (2). A solution of 27.6 g (0.076 mol) of 1 in 425 mL of ethanol was treated with a solution of 7.5 g (0.114 mol) of KOH in 15 mL of water and allowed to stir at room temperature for 3 h. The pH was adjusted to 5 with concentrated HCl and the mixture concentrated under reduced pressure at 35 °C. The residue was taken up in water and acidified to pH 2 with dilute HCl. The product was collected and washed with water, giving 24.95 g (98.2%) of a white solid: mp 127–128 °C eff; ^{1}H NMR (250 MHz, $CDCl_3$ + DMSO) δ 1.08–1.42 (m, 2 H), 1.62 (m, 2 H), 2.02 (s, 3 H), 2.34 (m, 2 H), 2.58 (t, 2 H), 4.02 (q, 2 H), 6.98 (s, 1 H), 7.10–7.32 (m, 5 H); MS (CI, 1% NH_3 in CH_4) *m/z* 336 ($M + H^+$). Anal. ($C_{18}H_{25}NO_5$) C, H, N.

Ethyl 2-Acetamido-7-phenylheptanoate (3). A solution of 24.95 g (0.074 mol) of **2** in 200 mL of dioxane was heated at reflux overnight. Removal of the solvent under reduced pressure gave **3** (21.7 g, 100%) as an oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.30 (t, 3 H), 1.38 (m, 4 H), 1.54–1.94 (m, 4 H), 2.02 (s, 3 H), 2.60 (t, 2 H), 4.20 (q, 2 H), 4.60 (m, 1 H), 6.04 (d, 1 H), 7.14–7.34 (m, 5 H); MS (CI + 1% NH_3 in CH_4) *m/z* 292 ($M + H^+$).

2-Acetamido-7-phenylheptanoic Acid (4). A solution of 21.7 g (0.074 mol) of **3** in 200 mL of ethanol was treated with a solution of 5.9 g (0.089 mol) of KOH in 20 mL of water and the solution stirred at room temperature for 1.5 h. The solvent was removed under reduced pressure and the residue taken up in water. Acidification with dilute HCl gave the crude product. Recrystallization from methanol/water gave **4** (18.64 g, 95.1%) as a white solid: mp 130–132 °C; ^{1}H NMR (250 MHz, $CDCl_3$ + DMSO) δ 1.38 (m, 4 H), 1.54–1.94 (m, 4 H), 2.04 (s, 3 H), 2.60 (t, 2 H), 4.50 (m, 1 H), 6.80 (d, 1 H), 7.12–7.34 (m, 5 H); MS (CI, 1% NH_3 in CH_4) *m/z* 264 ($M + H^+$). Anal. ($C_{15}H_{21}NO_3$) C, H, N.

L-2-Amino-7-phenylheptanoic Acid (5). A suspension of 17.6 g (0.067 mol) of **4** in 200 mL of water was treated with 70 mL of 1 N NaOH and the mixture worked with a spatula to effect solution. A few particles were filtered off and the solution adjusted to pH 7.6 with 1 N HCl. A filtered solution of 5.0 g of acylase (Acylase, Amano International Enzyme Co., 30 000 units/g) in 50 mL of water was then added, followed by a solution of 12 mg of $CoCl_2$ in 30 mL of water. The temperature was raised and maintained at 37 °C for 3 days with stirring. A solid started to appear after 10 min. The solid was collected and washed with water, ethanol, and then ether. There was obtained 6.7 g (90.7%) of **5** as a white solid: mp 232–235 °C dec; MS (CI, 1% NH_3 in CH_4) *m/z* 222 ($M + H^+$); $[\alpha]^{23}_D$ +10.2° (*c* 0.588 in 1 N NaOH). Anal. ($C_{13}H_{19}NO_2$) C, H, N.

L-2-Amino-10-phenyldecanoic Acid (6). In a manner similar to the above, but using 2-acetamido-10-phenyldecanoic acid (supporting information), there was obtained **6** (4.5 g, 95.7%) as a white solid: mp 243–247 °C dec; MS (CI, 1% NH_3 in CH_4) *m/z* 264 ($M + H^+$); $[\alpha]^{23}_D$ + 2.9° (*c* 0.977 in 1 N NaOH). Anal. ($C_{16}H_{25}NO_2$) C, H, N.

L-2-(Boc-amino)-7-phenylheptanoic Acid (7). A solution of 6.64 g (30 mmol) of **5** in 100 mL of dioxane was treated with 15 mL (30 mmol) of 2 N NaOH and then treated in portions with 7.5 g (33 mmol) of di-*tert*-butyl dicarbonate. In a few minutes a solid appeared. An additional 15 mL (30 mmol) of 2 N NaOH was then added, effecting solution. The solution was allowed to stir at room temperature overnight. The mixture was diluted with water, the pH was brought to 9.0 with 1 N NaOH, and the mixture was then extracted twice with ether. The aqueous phase was brought to pH 2.5 with dilute HCl and the mixture extracted with ether. The ether was washed with brine and then dried over $MgSO_4$. Removal of the ether under reduced pressure left 9.64 g (100%) of **7** as an oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.38 (m, 4 H), 1.42 (s, 9 H), 1.62 (m, 3 H), 1.84 (m, 1 H), 2.60 (t, 2 H), 4.50 (m, 1 H), 4.98 (d, 1 H), 7.14–7.34 (m, 5 H); MS (CI, 1% NH_3 in CH_4) *m/z* 322 ($M + H^+$).

L-2-(Boc-amino)-10-phenyldecanoic Acid (8). In a manner similar to above, but using **6**, there was obtained 6.2 g

(100%) of the product as an oil: MS (CI, 1% NH_3 in CH_4) *m/z* 364 ($M + H^+$).

[4*S*-(4*R,5*S**,6*R**)]-6-(Boc-amino)-2-methyl-11-phenylundecane-4,5-diol (9).** In a manner similar to that previously described,[17] the Boc-protected amino acid **7** was converted into the diols **9** and **11**. Chromatography on silica gel, eluting with 99:1 dichloromethane/methanol, followed by combining fractions and rechromatography on silica gel eluting with a gradient of 95:5 to 80:20 dichloromethane/ethyl acetate gave 4.03 g of the fast eluting isomer **9**: mp 72–75 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 (d, 3 H), 0.98 (d, 3 H), 1.32–1.74 (m, 20 H), 1.96 (m, 1 H), 2.62 (m, 1 H), 3.22 (m, 1 H), 3.34 (m, 1 H), 3.88 (m, 1 H), 4.64 (d, 1 H), 7.14–7.34 (m, 5 H); MS (CI, 1% NH_3 in CH_4) *m/z* 394 ($M + H^+$). Anal. ($C_{23}H_{39}NO_4$) C, H, N.

[4*R*-(4*S,5*R**,6*R**)]-6-(Boc-amino)-2-methyl-11-phenylundecane-4,5-diol (11).** Continued elution from the column gave 1.87 g of the slow eluting isomer **11**: mp 108–110 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 (d, 3 H), 0.99 (d, 3 H), 1.20–1.52 (m, 17 H), 1.64 (m, 2 H), 1.80 (m, 2 H), 2.42 (bs, 2 H), 2.60 (m, 2 H), 3.42 (m, 1 H), 3.72 (m, 1 H), 4.62 (d, 1 H), 7.14–7.34 (m, 5 H); MS (CI, 1% NH_3 in CH_4) *m/z* 394 ($M + H^+$). Anal. ($C_{23}H_{39}NO_4$) C, H, N.

[4*S*-(4*R,5*S**,6*R**)]-6-(Boc-amino)-2-methyl-14-phenyltetradecane-4,5-diol (10).** In a manner similar to that described for **9** but using Boc-amino acid **8**, there was obtained 2.67 g of the fast eluting isomer **10**: mp 64–66 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 0.90 (d, 3 H), 0.98 (d, 3 H), 1.22–1.78 (m, 26 H), 1.96 (m, 1 H), 2.62 (m, 2 H), 3.20–3.30 (m, 2 H), 3.88 (q, 1 H), 4.18 (d, 1 H), 4.60 (d, 1 H), 7.12–7.32 (m, 5 H); MS (FAB, thioglycerol) *m/z* 436 ($M + H^+$). Anal. ($C_{26}H_{45}NO_4$) C, H, N.

[4*R*-(4*S,5*R**,6*R**)]-6-Amino-2-methyl-14-phenyltetradecane-4,5-diol (12).** Continued elution from the column gave 1.81 g of the slower eluting isomer **12**: mp 81–83 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 0.96 (d, 3 H), 1.00 (d, 3 H), 1.20–1.92 (m, 26 H), 2.10 (m, 1 H), 2.60 (m, 2 H), 2.82 (d, 1 H), 3.42 (m, 1 H), 3.72 (m, 2 H), 4.62 (d, 1 H), 7.12–7.36 (m, 5 H); MS (FAB, thioglycerol) *m/z* 436 ($M + H^+$). Anal. ($C_{26}H_{45}NO_4$) C, H, N.

[4*S*-(4*R,5*S**,6*R**)]-6-Amino-2-methyl-11-phenylundecane-4,5-diol Hydrochloride (13I).** A solution of 2.8 g (7.1 mmol) of **9** in 30 mL of dichloromethane was treated with HCl gas for 5 min and then stirred for 1 h. Removal of the solvent under reduced pressure gave 2.24 g (95.7% yield) of the product as a viscous oil. The material was used directly in subsequent reactions.

[4*S*-(4*R,5*S**,6*R**)]-6-Amino-2-methyl-14-phenyltetradecane-4,5-diol Hydrochloride (13F).** In a manner similar to the above, but using **10**, there was obtained 1.11 g (100% yield) of the product as an oil. The material was used directly in subsequent reactions.

[4*S*-(4*R,5*S**,6*R**)]-6-Amino-11-cyclohexyl-2-methylundecane-4,5-diol (13H).** A solution of 1.09 g (2.8 mmol) of **9** in 100 mL of 2-propanol was treated with 0.4 g of 10% Rh/C and reduced at 25 °C, 50 psi. Removal of the solvent under reduced pressure gave 1.1 g (100% yield) of an oil which crystallized on standing: ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 (d, 3 H), 0.98 (d, 3 H), 1.06–1.80 (m, 34 H), 1.98 (m, 1 H), 3.22–3.46 (m, 2 H), 3.90 (m, 1 H), 4.60 (bs, 1 H); MS (CI, 1% NH_3 in CH_4) *m/z* 400 ($M + H^+$). A solution of 1.1 g (2.8 mmol) of the above protected amine in 20 mL of dichloromethane was treated peridically over 3.5 h with HCl gas. The solvent was then removed under reduced pressure, and the residue taken up in dichloromethane and washed with 0.25 N NaOH. The dichloromethane was dried over $MgSO_4$ and the solvent removed under reduced pressure, giving 0.7 g (85.4%) of a white solid: mp 104–106 °C; MS (CI + 1% NH_3 in CH_4) *m/z* 300 ($M + H^+$). Anal. ($C_{18}H_{37}NO_2 \cdot 0.05CH_2Cl_2$) C, H, N.

[4*S*-(4*R,5*S**,6*R**)]-6-Amino-14-cyclohexyl-2-methyltetradecane-4,5-diol (13G).** In a manner similar to the above, but using **10**, there was obtained 1.33 g (100%) of the product as an oil which crystallized on standing: ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (d, 3 H), 0.98 (d, 3 H), 1.06–1.74 (m, 39 H), 1.92 (m, 1 H), 3.20–3.40 (m, 2 H), 3.90 (m, 1 H), 4.14 (m, 1 H), 4.60 (d, 1 H); MS (FAB, thioglycerol) *m/z* 442 ($M + H^+$). Treatment of 1.41 g (3.2 mmol) of the Boc-amine in a manner similar to that described for **13H** gave **13G** (0.84 g, 95.4%) as a white solid: mp 112–114 °C; MS (CI + 1% NH_3 in CH_4) *m/z* 342 ($M + H^+$).

[4*S*-(4*R,5*S**,6*R**)]-2-Amino-6-methylheptane-3,4-diol (13K).** The Boc-amino diol (1.51 g) was synthesized in a manner similar to that previously described:[17] ^1H NMR ($CDCl_3$) δ 0.90 (dd, 6 H, J = 13.0 Hz, J = 6.6 Hz), 1.20 (d, 3 H, J = 6.8 Hz), 1.45 (s, 11 H), 1.90 (m, 1 H), 2.70 (bs, 2 H), 3.15 (m, 1 H), 3.30 (m, 1 H), 4.08 (m, 1 H), 4.67 (bs, 1 H); MS (CI, 1% NH_3 in CH_4) *m/z* 262 ($M + H^+$). Anal. ($C_{13}H_{27}NO_4$) C, H, N. This Boc-amino diol (1.40 g, 5.3 mmol) was deprotected by employing general method B to provide amino diol **13K** as a hydroscopic hydrochloride salt: ^1H NMR (DMSO) δ 0.90 (t, 6 H, J = 7.2 Hz), 1.20 (d, 3 H, J = 6.8 Hz), 1.35 (m, 2 H), 1.80 (m, 1 H), 3.18 (m, 1 H), 3.45 (m, 2 H).

[1*S*-(1*R,2*S**,3*R**)]-2-[[2-[(Morpholinosulfonyl)amino]acetyl]amino]pent-4-enoic Acid [2,3-Dihydroxy-5-methyl-1-[(4-phenylcyclohexyl)methyl]amide (14A).** The amino diol **13A** (180 mg, 0.56 mmol) was coupled with Boc-Alg, employing general method A. Chromatography of the crude reaction mixture (7:1 ethyl acetate/dichloromethane) provided a colorless solid (266 mg, 92%): ^1H NMR ($CDCl_3$) δ 0.94 (dd, 6 H, J = 14.8, 6.6 Hz), 1.46 (s, 1 H), 1.00–2.00 (m, 16 H), 2.55 (m, 2 H), 3.30 (m, 2 H), 4.10 (m, 2 H), 4.20–4.45 (m, 1 H), 4.92 (bs, 1 H), 5.22 (m, 2 H), 5.75 (m, 1 H), 6.25 (m, 1 H), 7.15–7.35 (m, 5 H); MS (CI, 1% NH_3 in CH_4) *m/z* 517 ($M + H^+$). Anal. ($C_{30}H_{48}N_2O_5$) C, H, N.

The Boc-protecting group was removed by employing general method B to provide the amine (116 mg, 0.28 mmol) as a colorless solid which was coupled, without purification, employing general method A and **15A** (63 mg, 0.31 mmol). Chromatography of the crude reaction mixture (2:5 acetone/dichloromethane) provided **14A** a colorless solid (153 mg, 91%): ^1H NMR (DMSO) δ 0.80 (d, 3 H, J = 6.8 Hz), 0.88 (d, 3 H, J = 6.8 Hz), 0.90–1.93 (m, 16 H), 2.23–2.60 (m, 3 H), 3.00 (m, 6 H), 3.58 (s, 4 H), 4.10 (m, 1 H), 4.48 (s, 2 H), 4.80 (d, 1 H, J = 6.1 Hz), 5.05 (m, 2 H), 5.72 (m, 1 H), 7.10–7.30 (m, 5 H), 7.69 (bs, 1 H), 7.87 (t, 1 H, J = 8.0 Hz), 8.03 (d, 1 H, J = 7.2 Hz); MS (FAB) *m/z* 624 ($M + H^+$). Anal. ($C_{31}H_{50}N_4O_9S$) C, H, N.

[1*S*-(1*R,2*S**,3*R**)]-2-[[2-[(Morpholinosulfonyl)amino]-3-phenylpropionyl]amino]pent-4-enoic Acid [2,3-Dihydroxy-5-methyl-1-[(4-phenylcyclohexyl)methyl]hexyl]-amide (14B).** The amine (121 mg, 0.29 mmol) resulting from the above Boc deprotection was coupled, employing general method A, with **15B** (100 mg, 0.32 mmol). Chromatography of the crude reaction mixture (1:4 acetone/dichloromethane) gave **14B** as a colorless foam (156 mg, 75%): ^1H NMR ($CDCl_3$) δ 0.96 (t, 6 H, J = 7.2 Hz), 1.0–2.0 (m, 14 H), 2.55–3.00 (m, 9 H), 3.17–3.60 (m, 7 H), 3.97 (m, 1 H), 4.25–4.45 (m, 2 H), 4.53 (m, 1 H), 5.00 (d, 1 H, J = 4 Hz), 5.25 (m, 2 H), 5.74 (m, 1 H), 6.74 (d, 1 H, J = 8 Hz), 6.93 (m, 1 H), 7.15–7.45 (m, 10 H); MS (CI, 1% NH_3 in CH_4) *m/z* 713 ($M + H^+$). Anal. ($C_{38}H_{56}N_4O_7S$) C, H, N.

[1-[1*R(*RS*),2*S**,3*R**]]-2-[[2-[(Morpholinosulfonyl)amino]acetyl]amino]pent-4-enoic Acid [2,3-Dihydroxy-5-methyl-1-[(4-phenylcyclohex-3-enyl)methyl]hexyl]-amide (14C).** The amino diol **13B** (188 mg, 0.59 mmol) was coupled with Boc-Alg by employing general procedure A. Chromatography of the reaction mixture (3:1 dichloromethane/ethyl acetate) provided a colorless solid (161 mg, 53%): ^1H NMR ($CDCl_3$) δ 0.92 (dd, 6 H, J = 15.0, 6.5 Hz), 1.42 (s, 9 H), 1.35–2.05 (m, 12 H), 2.25–2.65 (m, 4 H), 3.25 (m, 2 H), 4.13 (m, 1 H), 4.43 (m, 1 H), 4.94 (bs, 1 H), 5.20 (m, 2 H), 5.72 (m, 1 H), 6.18 (bs, 1 H), 6.45 (m, 1 H), 7.27–7.42 (m, 5 H); MS (CI, 1% NH_3 in CH_4) *m/z* 515 ($M + H^+$). The Boc-protecting group was removed by employing general method B to provide the amine hydrochloride that was coupled, without purification, with **15A** by employing general method A. Chromatography of the crude reaction mixture provided **14C** as a colorless oil (98 mg, 55%): ^1H NMR (DMSO) δ 0.85 (dd, 6 H, J = 14.8, 6.3 Hz), 1.00–2.00 (m, 10 H), 2.40 (m, 4 H), 3.05 (bs, 6 H), 3.59 (bs, 6 H), 4.20 (m, 1 H), 4.50 (m, 2 H), 4.87 (d, 1 H, J = 5.6 Hz), 5.10 (m, 2 H), 5.75 (m, 1 H), 6.13 (bs, 1 H), 7.15–7.50 (m, 5 H), 7.80 (m, 1 H), 7.88 (d, 1 H, J = 7, Hz), 8.05 (ds, 1 H,

J = 7 Hz); MS (CI, 1% NH_3 in CH_4) m/z 621 ($M + H^+$). Anal. ($C_{31}H_{48}N_4O_7S$) C, H, N.

[1S-(1R*(RS),2S*,3R*)]-2-[[2-[(Morpholinosulfonyl)amino]-3-phenylpropionyl]amino]pent-4-enoic Acid [2,3-Dihydroxy-5-methyl-1-[(4-phenylcyclohex-3-enyl)methyl]hexyl]amide (14D). The amine (127 mg, 0.31 mmol) resulting from the above Boc deprotection was coupled, employing general method A, with **15B** (106 mg, 0.34 mmol). Chromatography of the crude reaction mixture (1:4 acetone/dichloromethane) gave **14D** as a colorless foam (75 mg, 34%): ^1H NMR ($CDCl_3$) δ 0.95 (t, 6 H, J = 7.3 Hz), 1.00–2.00 (m, 13 H), 2.18–2.78 (m, 7 H), 2.92 (m, 2 H), 3.15–3.60 (m, 6 H), 3.95 (m, 2 H), 4.15–4.55 (m, 3 H), 5.18 (m, 2 H), 5.70 (m, 2 H), 6.08 (s, 1 H), 6.76 (m, 1 H), 6.95 (m, 1 H), 7.15–7.45 (m, 10 H); MS (CI, 1% NH_3 in CH_4) m/z 711 ($M + H^+$).

[1S-(1R*,2S*,3R*)]-2-[[2-[(Morpholinosulfonyl)amino]-acetyl]amino]pent-4-enoic Acid [2,3-Dihydroxy-5-methyl-1-[(4-naphthalen-1-ylcyclohexyl)methyl]hexyl]-amide (14E). The amino diol **13C** (325 mg, 0.88 mmol) was coupled with Boc-Alg by employing general method A. The crude product was chromatographed (4:1 dichloromethane/ethyl acetate) to give a colorless foam (275 mg, 56%): ^1H NMR ($CDCl_3$) δ 0.95 (dd, 6 H, J = 14.2, 6.4 Hz), 1.47 (s, 9 H), 1.15–2.15 (m, 15 H), 2.55 (m, 2 H), 2.75 (m, 1 H), 3.30 (m, 3 H), 4.12 (m, 2 H), 4.43 (m, 1 H), 4.95 (bs, 1 H), 5.22 (m, 2 H), 5.75 (m, 1 H), 6.31 (m, 1 H), 7.35–7.55 (m, 5 H), 7.71 (d, 1 H, J = 7 Hz), 7.85 (d, 1 H, J = 7 Hz), 8.10 (d, 1 H, J = 7 Hz); MS (CI, 1% NH_3 in CH_4) m/z 567 ($M + H^+$). Anal. ($C_{34}H_{50}N_2O_5$) C, H, N. The Boc protecting group was removed by employing general method B to provide the amine that was coupled, without purification, with **15A** by employing general method A. The crude product was chromatographed (5% of 8:1 ethanol/ammonium hydroxide in dichloromethane), giving **14E** as a colorless solid (97 mg, 71%): ^1H NMR ($CDCl_3$) δ 0.95 (dd, 6 H, J = 15.3, 6.3 Hz), 1.20–2.13 (m, 13 H), 2.62 (m, 2 H), 2.75 (m, 1 H), 3.20 (m, 4 H), 3.30 (m, 2 H), 3.73 (m, 6 H), 4.40 (m, 1 H), 4.58 (m, 1 H), 5.22 (m, 2 H), 5.43 (bs, 1 H), 5.78 (m, 1 H), 6.53 (m, 1 H), 6.78 (m, 1 H), 7.33–7.55 (m, 5 H), 7.70 (d, 1 H, J = 7.8 Hz), 7.85 (d, 1 H, J = 6.7 Hz), 8.08 (d, 1 H, J = 7.2 Hz). Anal. ($C_{35}H_{52}N_4O_7S$) C, H, N.

[1S-(1R*,2S*,3R*)]-2-[[2-[(Morpholinosulfonyl)amino]-3-phenylpropionyl]amino]pent-4-enoic Acid [2,3-Dihydroxy-5-methyl-1-[(4-naphthalen-1-ylcyclohexyl)methyl]-hexyl]amide (14F). The amine (89 mg, 0.19 mmol) resulting from the above Boc deprotection was coupled, employing general method A, with **15B** (66 mg, 0.21 mmol). Chromatography of the crude reaction mixture by MPLC (2.5% of 8:1 ethanol/ammonium hydroxide in dichloromethane) gave **14F** as a colorless oil (129 mg, 89%): ^1H NMR ($CDCl_3$) δ 0.95 (t, 6 H, J = 7.0 Hz), 1.10–2.10 (m, 13 H), 2.50–2.85 (m, 6 H), 2.95 (m, 2 H), 3.18–3.40 (m, 4 H), 3.50 (m, 4 H), 3.97 (m, 1 H), 4.15–4.60 (m, 3 H), 4.80 (d, 1 H, J = 3 Hz), 5.25 (m, 2 H), 5.75 (m, 1 H), 6.75 (d, 1 H, J = 9 Hz), 6.90 (m, 1 H), 7.20–7.55 (m, 10 H), 7.70 (d, 1 H, J = 8 Hz), 7.85 (d, 1 H, J = 8 Hz), 8.10 (d, 1 H, J = 8 Hz); MS (FAB) m/z 763 ($M + H^+$). Anal. ($C_{42}H_{58}N_4O_7S \cdot {}^1/_3H_2O$) C, H, N.

[1S-(1R*,2S*,3R*)]-2-[[2-[(Morpholinosulfonyl)amino]-acetyl]amino]pent-4-enoic Acid [1-[(4-benzylcyclohexyl)-methyl]-2,3-dihydroxy-5-methylhexyl]amide (14G). The amino diol **13D** (165 mg, 0.50 mmol) was coupled with Boc-Alg by employing general method A. Chromatography of the crude product (2:1 hexane/ethyl acetate) gave a colorless foam (242 mg, 91%): ^1H NMR ($CDCl_3$) δ 0.95 (m, 6 H), 1.45 (s, 9 H), 1.15–2.00 (m, 18 H), 2.55 (m, 3 H), 3.25 (m, 2 H), 4.10 (q, 1 H, J = 6.4 Hz), 4.32 (m, 1 H), 4.90 (m, 1 H), 5.20 (m, 2 H), 7.73 (m, 1 H), 6.25 (m, 1 H), 7.07–7.30 (m, 5 H); MS (CI, 1% NH_3 in CH_4) m/z 531 ($M + H^+$). Anal. ($C_{31}H_{50}N_2O_5$) C, H, N. The Boc protecting group was removed, employing general procedure B, to provide the amine that was coupled, without purification, with **15A** by employing general method A. The crude product was chromatographed (30% acetone in dichloromethane) to give **14G** a colorless solid (90 mg, 81%): ^1H NMR (DMSO) δ 0.85 (m, 6 H), 1.05–1.85 (m, 15 H), 2.30 (m, 1 H), 2.45 (m, 3 H), 3.00 (m, 6 H), 3.56 (m, 6 H), 4.07 (m, 1 H), 4.46 (bs, 1 H), 4.78 (m, 1 H), 5.06 (m, 2 H), 5.73 (m, 1 H), 7.12 (m, 3 H), 7.25 (m, 2 H), 7.68 (s, 1 H), 7.81 (m, 1 H), 8.03 (d, 1 H, J = 8.3 Hz); MS (CI, 1% NH_3 in CH_4) m/z 637 ($M + H^+$). Anal. ($C_{32}H_{52}N_4O_7S$) C, H, N.

[1S-(1R*,2S*,3R*)]-2-[[2-[(Morpholinosulfonyl)amino]-3-phenylpropionyl]amino]pent-4-enoic Acid [1-[(4-benzylcyclohexyl)methyl]-2,3-dihydroxy-5-methylhexyl]-amide (14H). The amine (71 mg, 0.17 mmol) resulting from the above Boc deprotection was coupled, employing general method A, with **15B** (57 mg, 0.19 mmol). Chromatography of the crude reaction mixture (1:1.5 ethyl acetate/dichloromethane) gave **14H** as a colorless solid (105 mg, 85%): ^1H NMR ($CDCl_3$) δ 0.95 (m, 6 H), 1.15–2.00 (m, 15 H), 2.45–2.78 (m, 7 H), 2.95 (m, 2 H), 3.10–3.40 (m, 4 H), 3.50 (m, 5 H), 3.95 (m, 1 H), 4.25 (m, 2 H), 4.49 (m, 1 H), 4.78 (d, 1 H, J = 4 Hz), 5.20 (m, 1 H), 5.70 (m, 2 H), 6.67 (t, 1 H, J = 9 Hz), 6.85 (d, 1 H, J = 9 Hz), 7.08–7.25 (m, 5 H), 7.25–7.45 (m, 5 H); MS (FAB) m/z 727 (M^+). Anal. ($C_{39}H_{58}N_4O_7S$) C, H; N: calcd, 7.71; found, 8.13.

[1S-(1R*,2S*,3R*)]-2-[[2-[(Morpholinosulfonyl)amino]-acetyl]amino]pent-4-enoic Acid [2,3-Dihydroxy-5-methyl-1-[[4-(3-methylbutyl)cyclohexyl]methyl]hexyl]amide (14I). The amino diol **13E** (**773** mg, 2.5 mmol) was coupled with Boc-Alg by employing general method A. The crude product was chromatographed (6% acetone in dichloromethane), giving a colorless foam (791 mg, 63%): ^1H NMR ($CDCl_3$) δ 0.90 (m, 12 H), 1.45 (s, 9 H), 1.05–2.00 (m, 22 H), 2.55 (m, 2 H), 3.25 (m, 2 H), 4.10 (q, 1 H, J = 6.6 Hz), 4.30 (m, 1 H), 4.92 (bs, 1 H), 5.20 (m, 2 H), 5.71 (m, 1 H), 6.23 (m, 1 H); MS (CI, 1% NH_3 in CH_4) m/z 511 ($M + H^+$). Anal. ($C_{29}H_{54}N_2O_5$) C, H, N. The Boc protecting group was removed by employing general procedure B to provide the amine that was coupled, without purification, with **15A**, employing general procedure A. The crude product was chromatographed (6% of 8:1 ethanol/ammonium hydroxide in dichloromethane) to give **14I** as a colorless solid: ^1H NMR (DMSO) δ 0.83 (m, 12 H), 1.05–1.55 (m, 18 H), 1.70 (m, 3 H), 3.05 (m, 5 H), 4.08 (m, 1 H), 4.45 (m, 2 H), 5.05 (m, 2 H), 5.70 (m, 1 H), 7.65–8.05 (m, 3 H); MS (CI, 1% NH_3 in CH_4) m/z 617 ($M + H^+$). Anal. ($C_{30}H_{56}N_4O_7S$) C, H, N.

[1S-(1R*,2S*,3R*)]-2-[[2-[(Morpholinosulfonyl)amino]-3-phenylpropionyl]amino]pent-4-enoic Acid [2,3-Dihydroxy-5-methyl-1-[[4-(3-methylbutyl)cyclohexyl]methyl]-hexyl]amide (14J). The amine (100 mg, 0.24 mmol) resulting from the above Boc deprotection was coupled, employing general method A, with **15B** (84 mg, 0.27 mmol). Chromatography of the crude reaction mixture (1:6 acetone/dichloromethane) gave **14J** as a colorless solid (171 mg, 100%): ^1H NMR ($CDCl_3$) δ 0.85 (d, 6 H, J = 6.6 Hz), 0.95 (t, 6 H, J = 6.8 Hz), 1.05–2.00 (m, 23 H), 2.50–2.80 (m, 5 H), 2.93 (m, 2 H), 3.12–3.40 (m, 3 H), 3.50 (m, 4 H), 3.95 (m, 1 H), 4.28 (m, 2 H), 4.50 (m, 1 H), 5.07–5.25 (m, 2 H), 5.73 (m, 1 H), 6.70 (d, 1 H, J = 8.7 Hz), 6.93 (d, 1 H, J = 7.3 Hz), 7.38 (m, 5 H); MS (FAB) m/z 707 ($M + H^+$). Anal. ($C_{37}H_{62}N_4O_7S$) C, H, N.

[1S-(1R*,2S*,3R*)]-2-[[2-[(Morpholinosulfonyl)amino]-acetyl]amino]pent-4-enoic Acid [1-(1,2-Dihydroxy-4-methylpentyl)-9-phenylnonyl]amide (14K). The amino diol **13F** (1.12 g, 3.0 mmol) and Boc-Alg (649 mg, 3.0 mmol) was coupled by employing general method A. The crude product (1.6 g, 100% yield), a tan foam, was employed without further purification: ^1H NMR (250 MHz, $CDCl_3$) δ 0.89 (d, J = 6.5 Hz, 3 H), 0.94 (d, J = 6.7 Hz, 3 H), 1.32 (broad s, 11 H), 1.44 (s, 9 H), 1.60 (m, 4 H), 1.74 (broad s, 1 H), 1.92 (m, 1 H), 2.28 (broad s, 1 H), 2.56 (m, 4 H), 3.24 (m, 2 H), 4.14 (m, 3 H), 4.96 (d, J = 6.4 Hz, 1 H), 5.20 (m, 2 H), 5.74 (m, 1 H), 6.41 (d, J = 9.1 Hz, 1 H), 7.14–7.32 (m, 5 H); MS (CI + 1% NH_3 in CH_4) m/z 533 ($M + 1$). The Boc protecting group was removed by employing general method B to provide an amine (1.13 g, 86.9%) as an oil which crystallized on standing. This amine (0.53 g, 1.2 mmol) was coupled with **15A** (275 mg, 1.2 mmol), employing general method A. The crude product was chromatographed on silica gel (97:3 chloroform/methanol), and then recrystallization from methanol/water gave **14K** (0.37 g, 47.3%) as a cream-colored solid: mp 150–153 °C; ^1H NMR (250 MHz, DMSO) δ 0.79 (d, J = 6.4 Hz, 3 H), 0.87 (d, J = 6.6 Hz, 3 H), 1.22 (broad s, 12 H), 1.46 (m, 5 H), 1.78 (m, 1 H), 2.32 (m, 1 H), 2.42 (m, 1 H), 2.60 (m, 1 H), 3.00 (m, 6 H), 3.58 (broad s, 6 H), 3.94 (m, 1 H), 4.44 (m, 2 H), 4.77 (d, J = 6.1 Hz, 1 H),

5.02 (m, 2 H), 5.76 (m, 1 H), 7.10–7.32 (m, 5 H), 7.66 (m, 1 H), 7.81 (d, J = 8.8 Hz, 1 H), 8.02 (d, J = 8.1 Hz, 1 H); MS (FAB, thioglycerol) m/z 639 (M + H^+). Anal. ($C_{32}H_{54}N_4O_7S \cdot 0.4H_2O$) C, H; N: calcd, 8.67; found, 8.13.

[1*S*-(1*R,2*S**,3*R**)]-2-[[2-[(Morpholinosulfonyl)amino]-3-phenylpropionyl]amino]pent-4-enoic Acid [1-(1,2-dihydroxy-4-methylpentyl)-9-phenylnonyl]amide (14L).** Via the procedure above, but using **15B**, there was obtained 1.07 g of the crude product. Chromatography on silica gel (99:1 chloroform/methanol), followed by recrystallization from acetonitrile/water and then recrystallization from ethyl acetate/hexane, gave **14L** (434 mg, 43%) as a white solid: mp 134–135 °C; ^{1}H NMR (250 MHz, DMSO) δ 0.80 (d, J = 6.5 Hz, 3 H), 0.86 (d, J = 6.6 Hz, 3 H), 1.06–1.34 (m, 11 H), 1.50 (m, 6 H), 1.78 (m, 1 H), 2.34 (m, 1 H), 2.62 (m, 5 H), 2.82–3.20 (m, 3 H), 3.40 (broad s, 6 H), 3.98 (m, 2 H), 4.40 (M, 2 H), 4.83 (d, J = 6.1 Hz, 1 H), 5.06 (m, 2 H), 5.78 (M, 1 H), 7.10–7.38 (m, 10 H), 7.60 (d, J = 8.9 Hz, 1 H), 7.75 (d, J = 9.6 Hz, 1 H), 8.40 (d, J = 8.0 Hz, 1 H); MS (FAB, thioglycerol) m/z 729 (M + H^+). Anal. ($C_{39}H_{60}N_4O_7S$) C, H, N.

[1*S*-(1*R,2*S**,3*R**)]-2-[[2-[(Morpholinosulfonyl)amino]-acetyl]amino]pent-4-enoic Acid [9-Cyclohexyl-1-(1,2-dihydroxy-4-methylpentyl)nonyl]amide (14M).** By use of general method A, amino diol **13G** was coupled with Boc-Alg, providing 1.37 g of the crude product. Trituration with hexane gave 0.88 g (66.7% yield) of the product, MS (CI + 1% NH_3 in CH_4) m/z 539 (M + H^+). The Boc protecting group was removed by employing general method B to provide the amine (0.67 g, 93.6%) as a white foam. This amine was coupled with **15A** by employing general method A. The reaction mixture was taken up in ethyl acetate and diluted with hexane. A white solid separated and was recrystallized from methanol/water to give 294 mg of the product as a white solid. Chromatography of the crude product (97:3 chloroform/methanol) followed by recrystallization from methanol/water gave **14M** (113 mg, 25.6%) as a white solid: mp 158–160 °C; ^{1}H NMR (250 MHz, DMSO) δ 0.79 (d, J = 6.5 Hz, 3 H), 0.87 (d, J = 6.7 Hz, 3 H), 1.06–1.38 (m, 20 H), 1.46 (m, 3 H), 1.64 (m, 6 H), 1.80 (m, 1 H), 2.32 (m, 1 H), 2.42 (m, 1 H), 3.02 (m, 6 H), 3.58 (m, 6 H), 3.96 (m, 1 H), 4.04 (m, 2 H), 4.78 (d, J = 6.1 Hz, 1 H), 5.06 (m, 2 H), 5.72 (m, 1 H), 7.69 (t, J = 6.2 Hz, 1 H), 7.82 (d, J = 8.7 Hz, 1 H), 8.02 (d, J = 8.1 Hz, 1 H); MS (FAB, thioglycerol) m/z 645 (M + H^+). Anal. ($C_{32}H_{60}N_4O_7S$) C, N; H: calcd, 9.38; found, 8.82.

[1*S*-(1*R,2*S**,3*R**)]-2-[[2-[(Morpholinosulfonyl)amino]-3-phenylpropionyl]amino]pent-4-enoic Acid [9-Cyclohexyl-1-(1,2-dihydroxy-4-methylpentyl)nonyl]amide (14N).** Following the procedure above, but using **15B**, there was obtained 660 mg of the crude product. Chromatography of the crude reaction mixture (98:2 chloroform/methanol) gave **14N** (410 mg, 66.2%) as a white foam: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.78–1.02 (m, 8 H), 1.08–1.38 (m, 20 H), 1.46 (m, 2 H), 1.70 (m, 5 H), 1.92 (m, 3 H), 2.60 (m, 4 H), 2.78 (m, 1 H), 2.90 (m, 2 H), 3.26 (m, 3 H), 3.44 (m, 4 H), 3.98 (m, 1 H), 4.18 (m, 1 H), 4.52 (m, 1 H), 5.20 (d, J = 12.9 Hz, 2 H), 5.38 (d, J = 5.5 Hz, 1 H), 5.76 (m, 1 H), 6.79 (d, J = 8.8 Hz, 1 H), 7.03 (d, J = 6.6 Hz, 1 H), 7.22–7.46 (m, 5 H); MS (FAB, thioglycerol) m/z 735 (M + H^+). Anal. ($C_{39}H_{66}N_4O_7S \cdot 0.2CHCl_3$) C, H, N.

[1*S*-(1*R,2*S**,3*R**)]-2-[[2-[(Morpholinosulfonyl)amino]-acetyl]amino]pent-4-enoic Acid [2,3-Dihydroxy-5-methyl-1-(5-phenylpentyl)hexyl]amide (14O).** By employing general method A, the amino diol **13I** was coupled with Boc-Alg to give the crude product that was triturated with hexane, providing **14O** (2.15 g, 72%) as a white solid: mp 109–111 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (d, J = 6.6 Hz, 3 H), 0.93 (d, J = 6.7 Hz, 3 H), 1.22–1.54 (m, 15 H), 1.60 (m, 4 H), 1.90 (m, 1 H), 2.22–2.64 (m, 5 H), 3.22 (m, 2 H), 4.16 (m, 3 H), 4.96 (d, J = 6.6 Hz, 1 H), 5.20 (m, 2 H), 5.76 (m, 1 H), 6.43 (d, J = 9.1 Hz, 1 H), 7.12–7.36 (m, 5 H); MS (FAB, thioglycerol) m/z 491 (M + H^+). Anal. ($C_{28}H_{46}N_2O_5$) C, H, N. The Boc protecting group was removed by employing general method B, giving the amine (1.66 g, 100%) as an oil which crystallized on standing. This amine was coupled with **15A** via general method A. Chromatography of the crude reaction mixture (97:3 chloroform/methanol) followed by recrystallization from methanol/water gave **14O** (508 mg, 48%) as a white solid: mp 167–169 °C; ^{1}H NMR (250 MHz, DMSO) δ 0.79 (d, J = 6.4 Hz, 3 H), 0.87 (d, J = 6.6 Hz, 3 H), 1.06–1.62 (m, 10 H), 1.78 (m, 1 H), 2.20–2.60 (m, 4 H), 3.02 (m, 6 H), 3.58 (broad s, 6 H), 3.94 (m, 1 H), 4.46 (m, 2 H), 4.79 (d, J = 5.9 Hz, 1 H), 5.04 (m, 2 H), 5.76 (m, 1 H), 7.12–7.36 (m, 5 H), 7.66 (m, 1 H), 7.84 (d, J = 8.6 Hz, 1 H), 8.03 (d, J = 8.0 Hz, 1 H); MS (FAB, 3-nitrobenzyl alcohol) m/z 597 (M + H^+). Anal. ($C_{29}H_{48}N_4O_7S$) C, H, N.

[1*S*-(1*R,2*S**,3*R**)]-2-[[2-[(Morpholinosulfonyl)amino]-3-phenylpropionyl]amino]pent-4-enoic Acid [2,3-Dihydroxy-5-methyl-1-(5-phenylpentyl)hexyl]amide (14P).** Via the procedure above, but using **15B**, there was obtained 1.2 g of the crude product. Chromatography of the crude product (98:2 chloroform/methanol) followed by recrystallization from methanol/water gave **14P** (462 mg, 42.4%) as a cream-colored solid: mp 167–169 °C; ^{1}H NMR (250 MHz, DMSO) δ 0.80 (d, J = 6.5 Hz, 3 H), 0.86 (d, J = 6.7 Hz, 3 H), 1.04–1.68 (m, 11 H), 1.80 (m, 1 H), 2.22–3.20 (m, 9 H), 3.40 (broad s, 6 H), 4.00 (m, 2 H), 4.42 (m, 2 H), 4.84 (d, J = 6.1 Hz, 1 H), 5.12 (m, 2 H), 5.80 (m, 1 H), 7.10–7.40 (m, 10 H), 7.61 (d, J = 8.8 Hz, 1 H), 7.75 (d, J = 9.6 Hz, 1 H), 8.39 (d, J = 8.0 Hz, 1 H); MS (FAB, thioglycerol) m/z 687 (M + H^+). Anal. ($C_{36}H_{54}N_4O_7S$) C, H, N.

[1*S*-(1*R,2*S**,3*R**)]-2-[[2-[(Morpholinosulfonyl)amino]-acetyl]amino]pent-4-enoic Acid [1-(5-Cyclohexylpentyl)-2,3-dihydroxy-5-methylhexyl]amide (14Q).** Via general method A, the amino diol **13H** was coupled with Boc-Alg to give 1.2 g of the crude product. Chromatography (99:1 chloroform/methanol), followed by another chromatography, eluting with a gradient (95:5–80:20 dichloromethane/ethyl acetate), gave the product as a white foam (0.77 g, 77.8%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.78–1.00 (m, 8 H), 1.08–2.80 (m, 31 H), 1.92 (m, 2 H), 2.54 (m, 2 H), 3.24 (m, 2 H), 4.16 (m, 2 H), 4.96 (broad s, 1 H), 5.20 (m, 2 H), 5.76 (m, 1 H), 6.40 (d, J = 8.8 Hz, 1 H); MS (CI + 1% NH_3 in CH_4) m/z 498 (M + H^+). The Boc protecting group was removed by employing general method B to provide the amine (470 mg, 77%) as a white solid: MS (CI + 1% NH_3 in CH_4) m/z 397 (M + H^+). By employing general method A, this amine was coupled with **15A**. The crude product was taken up in ethyl acetate and diluted with hexane to give **14Q** (162 mg, 53.3%) as an amorphous white solid: ^{1}H NMR (250 MHz, DMSO) δ 0.79 (d, J = 6.5 Hz, 3 H), 0.87 (d, J = 6.7 Hz, 3 H), 1.00–1.88 (m, 24 H), 2.36 (m, 2 H), 3.02 (m, 6 H), 3.58 (m, 6 H), 3.96 (m, 1 H), 4.44 (m, 2 H), 4.78 (d, J = 6.1 Hz, 1 H), 5.04 (m, 2 H), 5.72 (m, 1 H), 7.68 (m, 1 H), 7.82 (d, J = 8.8 Hz, 1 H), 8.02 (d, J = 8.2 Hz, 1 H); MS (FAB, thioglycerol) m/z 603 (M + H^+). Anal. ($C_{29}H_{54}N_4O_7S$) C, H, N.

[1*S*-(1*R,2*S**,3*R**)]-2-[[2-[(Morpholinosulfonyl)amino)-3-phenylpropionyl]amino]pent-4-enoic Acid [1-(5-Cyclohexylpentyl)-2,3-dihydroxy-5-methylhexyl]amide (14R).** By following the procedure above, but using **15B**, there was obtained 530 mg of the crude product. Chromatography on silica gel (98:2 chloroform/methanol), followed by another chromatography (99:1, chloroform/methanol), gave **14R** (300 mg, 69% yield) as a white foam: ^{1}H NMR (250 MHz, DMSO) δ 0.82 (m, 8 H), 0.96–1.90 (m, 24 H), 2.22–2.78 (m, 9 H), 2.80–3.20 (m, 3 H), 3.98 (m, 2 H), 4.40 (m, 2 H), 4.82 (d, J = 6.1 Hz, 1 H), 5.10 (m, 2 H), 5.78 (m, 1 H), 7.16–7.38 (m, 5 H), 7.58 (d, J = 8.6 Hz, 1 H), 7.74 (d, J = 9.4 Hz, 1 H), 8.40 (d, J = 7.9 Hz, 1 H); MS (FAB, thioglycerol) m/z 693 (M + H^+). Anal. ($C_{36}H_{60}N_4O_7S$) C, H, N.

[1*S*-(1*R,2*S**,3*R**)]-2-[[2-[(Morpholinosulfonyl)amino]-acetyl]amino]pent-4-enoic Acid [1-(Cyclohexylmethyl)-2,3-dihydroxy-5-methylhexyl]amide (14S).** By employing general method A, the amine Alg-ACDMH (170 mg, 0.50 mmol) was coupled with **15A** (102 mg, 0.50 mmol). After chromatography (5% of 8:1 ethanol/ammonium hydroxide in dichloromethane), **14S** was isolated as a colorless solid (183 mg, 67%): ^{1}H NMR (DMSO) δ 0.72–0.95 (m, 6 H), 1.05–1.85 (m, 16 H), 2.30 (m, 1 H), 2.45 (m, 1 H) 3.00 (m, 6 H), 3.57 (bs, 6 H), 4.10 (m, 1 H), 4.48 (m, 2 H), 4.68 (d, 1 H), 5.05 (m, 2 H), 5.73 (m, 1 H), 7.68 (bs, 1 H), 7.82 (d, 1 H), 8.02 (d, 1 H); MS (CI, 1% NH_3 in CH_4) m/z 547 (M + H^+). Anal. ($C_{25}H_{46}N_4O_2S$) C, H, N.

[1S-(1R*,2S*,3R*)]-2-[[2-[(Morpholinosulfonyl)amino]-3-phenylpropionyl]amino]pent-4-enoic Acid [1-(Cyclohexylmethyl)-2,3-dihydroxy-5-methylhexyl]amide (14T). By employing general method A, the amine Alg-ACDMH (957 mg, 2.8 mmol) was coupled with **15B** (870 mg, 2.8 mmol). Chromatography of the residue (49:1 chloroform/methanol) provided **14T** as a foam (1.31 g, 74%): ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 6 H), 1.07–1.48 (m, 6 H), 1.54–1.75 (m, 8 H), 1.92 (m, 1 H), 2.50–2.85 (m, 4 H), 2.90–3.05 (m, 3 H), 3.10–3.60 (m, 8 H), 3.97 (m, 1 H), 4.28 (m, 2 H), 4.90 (q, 1 H), 4.90 (d, 1 H), 5.15–5.30 (m, 2 H), 5.70 (m, 1 H), 6.69 (d, 1 H), 6.90 (d, 1 H), 7.25–7.45 (m, 6 H); MS (CI, 1% NH_3 in CH_4) *m/z* 637 ($M + H^+$). Anal. ($C_{32}H_{52}N_4O_7S \cdot {}^1/_8CHCl_3$) C, H, N.

[1S-(1R*,2S*,3R*)]-2-[[2-[(Morpholinosulfonyl)amino]-3-phenylpropionyl]amino]pent-4-enoic Acid (2,3-Dihydroxy-1,5-dimethylhexyl)amide (14U). The hydrochloride salt of amino diol **13K** (400 mg, 2 mmol) was coupled with Boc-Alg (479 mg, 2.2 mmol) by employing general method A. Chromatography of the residue (1:4 acetone/dichloromethane) provided a colorless solid (433 mg, 60%): ^{1}H NMR ($CDCl_3$) δ 0.93 (dd, 6 H, J = 14.8 Hz, J = 6.5 Hz), 1.25 (d, 3 H, J = 6.9 Hz), 1.45 (s, 11 H), 1.92 (m, 1 H), 2.50 (m, 4 H), 3.20 (d, 1 H, J = 7 Hz), 3.30 (m, 1 H), 4.10 (q, 1 H, J = 6.5 Hz), 4.36 (m, 1 H), 4.95 (m, 1 H), 5.20 (m, 2 H), 5.75 (m, 1 H), 6.31 (d, 1 H, J = 9.0 Hz); MS (CI, 1% NH_3 in CH_4) *m/z* 359 ($M + H^+$).

The Boc protecting group was removed by general method B to provide the amine hydrochloride (322 mg, 1.1 mmol), which was coupled by employing general method A with **15B** (386 mg, 1.2 mmol). Chromatography of the crude reaction mixture (7% of 8:1 ethanol/ammonium hydroxide in dichloromethane) gave **14U** as a colorless oil (226 mg, 37%): ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 6 H, J = 6.6 Hz), 1.23 (d, 3 H, J = 6.4 Hz), 1.45 (m, 2 H), 1.90 (m, 1 H), 2.60 (m, 4 H), 2.75 (m, 1 H), 3.25 (m, 3 H), 3.50 (m, 4 H), 3.95 (m, 2 H), 4.30–4.60 (m, 2 H), 5.02 (d, 1 H, J = 4 Hz), 5.20 (m, 2 H), 5.75 (m, 1 H), 6.80 (d, 1 H, J = 8 Hz), 6.90 (1 H, J = 8 Hz), 7.45 (m, 5 H); MS (CI, 1% NH_3 in CH_4) *m/z* 555 ($M + H^+$). Anal. ($C_{26}H_{42}N_4O_7S$) C, H, N.

[1S-(1R*,2S*,3R*)]-L,L-2-[[2-[(Morpholinosulfonyl)-amino]propionyl]amino]pent-4-enoic Acid (1-(Cyclohexylmethyl)-2,3-dihydroxy-5-methylhexyl)amide (16A). Via general method A, the amine Alg-ACDMH (420 mg, 1.2 mmol) was coupled with **15C** (175 mg, 1.3 mmol). Chromatography of the residue (2.5–5% methanol in dichloromethane) provided **16A** as a colorless solid (280 mg, 41%): ^{1}H NMR (DMSO) δ 0.70–0.90 (m, 8 H), 1.10–1.30 (m, 9 H), 1.35–1.85 (m, 8 H), 2.20–2.50 (m, 2 H), 2.85–3.15 (m, 6 H), 3.60 (m, 4 H), 3.88 (m, 1 H), 4.12 (m, 1 H), 4.40 (m, 2 H), 4.80 (d, 1 H), 4.95–5.15 (m, 2 H), 5.65–5.82 (m, 1 H), 7.58 (d, 1 H, J = 8 Hz), 7.75 (d, 1 H, J = 8 Hz), 8.10 (d, 1 H, J = 8 Hz); MS (CI, 1% NH_3 in CH_4) *m/z* 561 ($M + H^+$). Anal. ($C_{26}H_{48}N_4O_7S$) C, H, N.

[1S-(1R*,2S*,3R*)]-D,L-2-[[2-[(Morpholinosulfonyl)-amino]propionyl]amino]pent-4-enoic Acid [1-(Cyclohexylmethyl)-2,3-dihydroxy-5-methylhexyl]amide (16B). By employing general method A, the amine Alg-ACDMH (800 mg, 2.3 mmol) was coupled with **15D** (560 mg, 2.3 mmol). Chromatography of the residue (2.5–5% methanol in dichloromethane) provided **16B** as a colorless solid (970 mg, 74%): ^{1}H NMR (DMSO) δ 0.78–0.90 (m, 8 H), 1.08–1.30 (m, 9 H), 1.40–1.79 (m, 8 H), 2.29 (m, 1 H), 2.41 (m, 1 H), 2.85–3.15 (m, 6 H), 3.54 (m, 4 H), 3.91 (m, 1 H), 4.11 (m, 1 H), 4.50 (m, 2 H), 4.78 (d, 1 H, J = 4 Hz), 4.99–5.09 (m, 2 H), 5.68 (m, 1 H), 7.72 (d, 1 H, J = 8 Hz), 7.78 (d, 1 H, J = 8 Hz), 8.08 (d, 1 H, J = 8 Hz); MS (CI, 1% NH_3 in CH_4) *m/z* 561 ($M + H^+$). Anal. ($C_{26}H_{48}N_4O_7S$) C, H, N.

[1S-(1R*,2S*,3R*)]-2-[[3-Methyl-2-[(morpholinosulfonyl)-amino]butyryl]amino]pent-4-enoic Acid [1-(Cyclohexylmethyl)-2,3-dihydroxy-5-methylhexyl]amide (16C). The acid **15E** (200 mg, 0.751 mmol) was coupled with Alg-ACDMH by employing general method A. Chromatography of the crude product (9:1 dichloromethane/methanol) gave **16C** as a colorless solid (340 mg, 76%): ^{1}H NMR (DMSO) δ 0.75–0.92 (m, 12 H), 1.05–1.34 (m, 6 H), 1.38–1.52 (m, 2 H), 1.54–1.78 (m, 6 H), 1.82–1.94 (m, 2 H), 2.24–2.47 (m, 2 H), 2.84–3.13 (m, 4 H), 3.48–3.66 (m, 4 H), 4.12 (bs, 1 H), 4.48–4.52 (m, 2 H), 4.76 (d, 1 H, J = 6.2 Hz), 4.99–5.19 (m, 2 H), 5.68–5.74 (m, 1 H), 7.48 (d, 1 H, J = 9.7 Hz), 7.72 (d, 1 H, J = 8.5 Hz), 8.18 (d, 1 H, J = 8.1 Hz); MS (CI, 1% NH_3 in CH_4) *m/z* 589 ($M + H^+$). Anal. ($C_{28}H_{52}N_4O_7S$) C, H, N.

[1S-(1R*[R*(E)],2S*,3R*)]-2-[(4-Morpholin-4-yl-4-oxobut-2-enoyl)amino]pent-4-enoic Acid [1-(Cyclohexylmethyl)-2,3-dihydroxy-5-methylhexyl]amide (16D). By employing general method A, the amine Alg-ACDMH (200 mg, 0.58 mmol) was coupled with **15F** (110 mg, 0.58 mmol). Chromatography of the residue (1:2 ethyl acetate/hexane) gave **16D** as a colorless solid (60 mg, 20%): ^{1}H NMR (DMSO) δ 0.79 (d, 3 H, J = 6.1 Hz), 0.87 (d, 3 H, J = 6.4 Hz), 1.05–1.28 (m, 6 H), 1.38–1.75 (m, 8 H), 2.24–2.41 (m, 2 H), 2.91–3.18 (m, 2 H), 3.59 (m, 8 H), 4.13 (bs, 1 H), 4.42–4.50 (m, 2 H), 4.78 (d, 1 H, J = 6.0 Hz), 5.00–5.15 (m, 2 H), 5.70 (m, 1 H), 6.92 (d, 1 H, J = 15.1 Hz), 7.24 (d, 1 H, J = 15.1 Hz), 7.71 (d, 1 H, J = 8.9 Hz), 8.66 (d, 1 H, J = 7.9 Hz); MS (EI) *m/z* 508 (M^+). Anal. ($C_{27}H_{45}O_8N_3$) C, H, N.

[1S-(1R*[R*(E)],2S*,3R*)]-2-[Methyl(4-morpholin-4-yl-4-oxobut-2-enoyl)amino]pent-4-enoic Acid [1-(Cyclohexylmethyl)-2,3-dihydroxy-5-methylhexyl]amide (16E). By employing general method A, the amine *N*-methyl-Alg-ACDMH (200 mg, 0.56 mmol) was coupled with **15F** (104 mg, 0.56 mmol). Chromatography of the residue (50:1 dichloromethane/methanol) gave **16E** as a colorless solid (90 mg, 30%): ^{1}H NMR (DMSO) δ 0.81 (d, 3 H, J = 6.7 Hz), 0.88 (d, 3 H, J = 6.6 Hz), 1.02–1.28 (m, 6 H), 1.38–1.70 (m, 7 H), 1.77 (m, 1 H), 2.37 (m, 1 H), 2.65 (m, 1 H), 2.84 (s, 1 H), 2.96 (s, 3 H), 3.07 (m, 1 H), 3.57 (bs, 8 H), 4.10 (m, 1 H), 4.40 (m, 1 H), 4.72 (m, 1 H), 4.84 (d, 1 H, J = 6.7 Hz), 5.08 (m, 3 H), 5.67 (m, 1 H), 7.30 (m, 2 H), 7.97 (d, 1 H, J = 8.5 Hz); MS (CI, 1% NH_3 in CH_4) *m/z* 522 ($M + H^+$). Anal. ($C_{28}H_{48}N_3O_6$) C, H, N.

[1S-(1R*(R*),2S*,3R*)]-2-[(4-Morpholin-4-yl-4-oxobutyryl)amino]pent-4-enoic Acid [1-(Cyclohexylmethyl)-2,3-dihydroxy-5-methylhexyl]amide (16F). By employing general method A, the amine Alg-ACDMH (150 mg, 0.44 mmol) was coupled with acid **15G** (82 mg, 0.44 mol). Chromatography of the residue (1:9 acetone/dichloromethane) afforded **16F** as a colorless solid (70 mg, 31%): ^{1}H NMR (DMSO) δ 0.79 (d, 3 H, J = 6.5 Hz), 0.86 (d, 3 H, J = 6.8 Hz), 1.15–1.34 (m, 6 H), 1.41–1.54 (m, 2 H), 1.58–1.79 (m, 6 H), 2.22–2.42 (m, 3 H), 2.93 (m, 1 H), 3.07 (m, 1 H), 3.52 (m, 4 H), 4.10 (bs, 1 H), 4.27 (m, 1 H), 4.42 (d, 1 H, J = 4.6 Hz), 4.62 (d, 1 H, J = 7.0 Hz), 5.05 (m, 2 H), 5.73 (m, 1 H), 7.44 (d, 1 H, J = 9.1 Hz), 8.06 (d, 1 H, J = 8.0 Hz); MS (CI, 1% NH_3 in CH_4) *m/z* 510 ($M + H^+$). Anal. ($C_{27}H_{47}N_3O_6$) C, H, N.

[1S-(1R*(R*),2S*,3R*)]-2-[[1-[[1-(Cyclohexylmethyl)-2,3-dihydroxy-5-methylhexyl]carbamoyl]-but-3-enyl]-carbamoyl]cyclopropanecarboxylic Acid Ethyl Ester (16G). The acid **15H** (93 mg, 0.59 mmol) was coupled with the amine Alg-ACDMH (200 mg, 0.59 mmol) by employing general method A. Chromatography of the residue (33:1 dichloromethane/methanol) provided **16G** as a colorless foam (100 mg, 35%): ^{1}H NMR ($CDCl_3$) δ 0.79 (d, 3 H, J = 6.2 Hz), 0.87 (d, 3 H, J = 6.7 Hz), 1.12–1.25 (m, 10 H), 1.47–1.38 (m, 2 H), 1.51–1.75 (m, 5 H), 1.82 (m, 2 H), 2.26 (m, 2 H), 2.40 (m, 1 H), 2.93 (m, 1 H), 3.04 (m, 1 H), 4.03 (m, 3 H), 4.38 (m, 2 H), 4.75 (t, 1 H), 5.06 (m, 2 H), 5.73 (m, 1 H), 7.60 (t, 1 H), 8.54 (t, 1 H); MS (CI, 1% NH_3 in CH_4) *m/z* 481 ($M + H^+$). Anal. ($C_{26}H_{44}N_2O_6$) C, H, N.

[1S-(1R(R*)*,2S*,3R*)]-2-(Morpholin-4-ylcarbonyl)-cyclopropanecarboxylic Acid [1-[[1-cyclohexylmethyl)-2,3-dihydroxy-5-methylhexyl]carbamoyl]but-3-enyl]-amide (16H). The acid **15I** (123 mg, 618 mmol) was coupled with Alg-ACDMH by employing general method A. Chromatography of the residue (9:1 dichloromethane/methanol) gave **16H** as a colorless foam (237 mg, 73%): mp 185–187 °C; ^{1}H NMR (DMSO) δ 0.78 (d, 3 H, J = 6.4 Hz), 0.98–1.33 (m, 8 H), 1.34–1.53 (m, 2 H), 1.56–1.81 (m, 6 H), 2.06–2.20 (m, 2 H), 2.24–2.32 (bs, 1 H), 2.34–2.48 (m, 1 H), 2.94 (t, 1 H), 3.00–3.11 (bs, 1 H), 3.35–3.46 (m, 2 H), 3.48–3.63 (m, 6 H), 4.05–4.18 (bs, 1 H), 4.28–4.46 (m, 2 H), 4.76 (t, 1 H), 4.97–5.16 (m, 1 H), 5.65–5.74 (m, 1 H), 7.53 (t, 1 H), 8.45 (d, 1 H, J = 7.94 Hz); MS (CI, 1% NH_3 in CH_4) *m/z* 522 ($M + H^+$). Anal. ($C_{28}H_{47}N_3O_6$): C, H, N.

[1*S*-[1*R(*R**),2*S**,3*R**)]-2,2-Dimethyl-3-(morpholin-4-ylcarbonyl)cyclopropanecarboxylic Acid [1-[[1-(Cyclohexylmethyl)-2,3-dihydroxy-5-methylhexyl]carbamoyl]but-3-enyl]amide (16I).** The acid **15J** (170 mg, 0.730 mmol) was coupled with Alg-ACDMH by employing general method A. Chromatography of the crude product (9:1 dichloromethane/methanol) gave **16I** as a colorless solid (130 mg, 32%): ^{1}H NMR (DMSO) δ 0.79 (d, 3 H, J = 6.4 Hz), 0.87 (d, 3 H, J = 6.6 Hz), 1.01 (s, 3 H), 1.02–1.24 (m, 9 H), 1.37–1.76 (m, 8 H), 2.12–2.18 (m, 2 H), 2.23–2.32 (m, 1 H), 2.37–2.48 (m, 1 H), 2.88–2.98 (m, 1 H), 3.03–3.12 (m, 1 H), 3.44–3.72 (m, 8 H), 4.12 (bs, 1 H), 4.34–4.47 (m, 2 H), 4.75 (d, 1 H, J = 6.4 Hz), 4.99–5.11 (m, 2 H), 5.67–5.80 (m, 1 H), 7.58 (d, 1 H, J = 8.7 Hz), 8.37 (d, 1 H, J = 8.1 Hz); MS (CI, 1% MH_3 in CH_4) *m/z* 550 (M + H^+). Anal. ($C_{30}H_{51}N_3O_6$) H, N; C: calcd, 65.54; found, 64.95.

[1*S*-(1*R[*R**(*E*)],2*S**,3*R**)]-2-[[3-(Morpholinosulfonyl)-acryloyl]amino]pent-4-enoic Acid [1-(Cyclohexylmethyl)-2,3-dihydroxy-5-methylhexyl]amide (16J).** The acid **15K**, whose synthesis is described in the supporting information (300 mg, 0.881 mmol), was coupled with Alg-ACDMH by employing general method A. Chromatography of the crude product (9:1 dichloromethane/methanol) gave **16J** as a colorless solid (50 mg, 10%): ^{1}H NMR (DMSO) δ 0.79 (d, 3 H, J = 6.7 Hz), 0.86 (d, 3 H, J = 6.6 Hz), 1.08–1.24 (m, 6 H), 1.41–1.50 (m, 2 H), 1.54–1.69 (m, 6 H), 1.71–1.83 (m, 1 H), 2.26–2.37 (m, 1 H), 2.43–2.48 (m, 1 H), 2.92–2.99 (m, 1 H), 3.07 (s, 4 H), 3.62–3.64 (m, 4 H), 4.08–4.17 (bs, 1 H), 4.40 (d, 1 H, J = 4.8 Hz), 4.47–4.53 (m, 1 H), 4.76 (d, 1 H, J = 6.6 Hz), 5.10–5.13 (m, 2 H), 5.67–5.82 (m, 1 H), 6.97 (d, 1 H, J = 14.6 Hz), 7.17 (d, 1 H, J = 14.6 Hz), 7.76 (d, 1 H, J = 8.7 Hz), 8.87 (d, 1 H, J = 8.4 Hz); MS (FAB) *m/z* 544 (M + H^+). Anal. ($C_{26}H_{45}N_3O_7S_1$) C, H; N: calcd, 7.73; found, 7.16.

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Supporting Information Available: Synthesis and spectral data of the amino diols **13A–E** and compounds **15J** and **15K** (4 pages). Ordering information is given on any current masthead page.

References

(1) (a) Wyvratt, M. J.; Patchett, A. A. Recent developments in the design of angiotensin-converting enzyme inhibitors. *Med. Res. Rev.* **1985**, *5*, 483–531. (b) Gavras, H.; Gavras, I. Angiotensin converting enzyme inhibitors. Properties and side effects. *Hypertension* **1988**, *11* (3), Suppl. 11, 37–41.

(2) (a) McEwan, J. R.; Fuller, R. W. Angiotensin converting enzyme inhibitors and cough. *J. Cardiovasc. Pharmacol.* **1989**, *13* (Suppl. 3), S67–S69. (b) Skidgel, R. A.; Engelbrecht, S.; Johnson, A. R.; Erdos, E. G. Hydrolysis of substance P and neurotensin by converting enzyme and neutral endopeptidase. *Peptides* **1984**, *5*, 769–776.

(3) (a) Greenlee, W. J.; Siegel, P. K. S. Angiotensin/renin modulators. In *Annual Reports of Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: Amsterdam, 1992; Vol. 27, pp 59–68; 1991, Vol. 26, pp 63–72. (b) Duncia, J. V.; Carini, D. J.; Chiu, A. T.; Johnson, A. L.; Price, W. A.; Wong, P. C.; Wexler, R. R.; Timmermans, P. B. M. W. M. The discovery of DuP 753. A potent orally active nonpeptide angiotensin II receptor antagonist. *Med. Res. Rev.* **1992**, *12*, 149–191.

(4) Hodges, J. C.; Hamby, J. M.; Blankley, C. J. Angiotensin II receptor binding inhibitors. *Drugs Future* **1992**, *17*, 575–593.

(5) (a) Greenlee, W. J. Renin inhibitors. *Med. Res. Rev.* **1990**, *10*, 173–236. (b) Hutchins, C.; Greer, J. Comparative modeling of proteins in the design of novel renin inhibitors. *Crit. Rev. Biochem. Mol. Biol.* **1991**, *26* (1), 77–127.

(6) Heitsch, H.; Henning, R.; Kleemann, H.-W.; Linz, W.; Nickel, W.-U.; Ruppert, D.; Urbach, H.; Wagner, A. Renin inhibitors containing a pyridyl amino diol derived C-terminus. *J. Med. Chem.* **1993**, *36*, 2788–2800 and references cited therein.

(7) Hamilton, H.; Steinbaugh, B.; Blankley, J.; Taylor, M.; Chan, O. O.; Stewart, B.; Schroeder, R.; Ryan, M.; Rapundalo, S.; Cook, J.; Bernabei, A.; Stewart, C. Evaluation of the intestinal permeability and hepatic handling of peptidomimetic analogues. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 813–818.

(8) P_n–P_n' refers to the side chain position of the peptide substrate relative to the cleavage site: S_n–S_n' refers to the enzyme pocket occupied by the respective side chain. See: Schechter, I.; Berger, A. *Biochem. Biophys. Res. Commun.* **1967**, *27*, 157–162.

(9) Rich, D. H. Effect of hydrophobic collapse on enzyme-inhibitor interactions. Implications for the design of peptidomimetics. *Perspectives in Medicinal Chemistry*; Testa, B., Ed.; Verlag Helvetica Chim Acta: Basel, 1993; pp 15–25.

(10) Bertrams, A. A.; Ziegler, K. New substrates of the multispecific bile acid transporter in liver cells: Interference of some linear renin inhibiting peptides with transport protein(s) for bile acids. *Biochim. Biophys. Acta* **1991**, 213–220.

(11) Plummer, M.; Hamby, J. M.; Hingorani, G.; Batley, B. L.; Rapundalo, S. T. Peptidomimetic inhibitors of renin incorporating topographically modified isosteres spanning the P_1(→P_3)-P_1' sites. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2119–2124.

(12) Hanessian, S.; Raghavan, S. Design and synthesis of a prototypical non-peptidic inhibitor model for the enzyme renin. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1697–1702.

(13) Szewczuk, Z.; Rebholz, K. L.; Rich, D. H. Synthesis and biological activity of new conformationally restricted analogues of pepstatin. *Int. J. Pept. Protein Res.* **1992**, *40*, 233–242.

(14) Thompson, W. J.; Fitzgerald, P. M. D.; Holloway, M. K.; Emini, E. A.; Darke, P. L.; McKeever, B. M.; Scleif, W. A.; Quintero, J. C.; Zugay, J. A.; Tucker, T. J.; Schwering, J. E.; Homnick, C. F.; Nunberg, J.; Springer, J. P.; Huff, J. R. Synthesis and antiviral activity of a series of HIV-1 protease inhibitors with functionality tethered to the P_1 or P_1' phenyl substituents: X-ray crystal structure assisted design. *J. Med. Chem.* **1992**, *35*, 1685–1701.

(15) Romeo, S.; Houseman, K.; Mueller, R. A.; Rich, D. H. Protease inhibitors with potential P_3-P_1 bridging ligands. Synthesis of HIV-1 protease inhibitors. MEDI 54, 205th ACS National Meeting; March 28–April 2, 1993.

(16) Kaltenbronn, J. S.; Hudspeth, J. P.; Lunney, E. A.; Michniewicz, B. M.; Nicolaides, E. D.; Repine, J. T.; Roark, W. H.; Stier, M. A.; Tinney, F. J.; Woo, P. K. W.; Essenburg, A. D. Renin inhibitors containing isosteric replacements of the amide bond connecting the P_3 and P_2 sites. *J. Med. Chem.* **1990**, *33*, 838–845.

(17) Luly, J. R.; BaMaung, N.; Soderquist, J.; Fung, A. K. L.; Stein, H.; Kleinert, H. D.; Marcotte, P. A.; Egan, D. A.; Bopp, B.; Merits, I.; Bolis, G.; Greer, J.; Perun, T. J.; Plattner, J. J. Renin inhibitors. Dipeptide analogues of angiotensinogen utilizing a dihydroxyethylene transition-state mimic at the scissile bond to impart greater inhibitor potency. *J. Med. Chem.* **1988**, *31*, 2264–2276.

(18) Collins, R. F.; Davis, M. The chemotherapy of schistosomiasis Part IV. Some ethers of 4-amino-2-methoxyphenol. *J. Chem. Soc.* **1961**, *31*, 1863–1879.

(19) Shimohigashi, Y.; Lee, S.; Izumiya, N. Resolution of amino acids XII. Preparation of L-2-amino-5-amylpentanoic acids, constituent amino acids in AM- toxins. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3280–3284.

(20) Repine, J. T.; Himmelsbach, R. J.; Hodges, J. C.; Kaltenbronn, J. S.; Sircar, I.; Skeean, R. W.; Brennan, S. T.; Hurley, T. R.; Lunney, E.; Humblet, C. C.; Weishaar, R. E.; Rapundalo, S.; Ryan, M. J.; Taylor, D. G., Jr.; Olson, S. C.; Michniewicz, B. M.; Kornburg, B. E.; Belmont, D. T.; Taylor, M. D. Renin inhibitors containing esters at the P_2- position. Oral activity in a derivative of methyl aminomalonate. *J. Med. Chem.* **1991**, *34*, 1935–1943.

(21) The morpholinosulfonyl-containing amino acid derivatives were synthesized in a manner similar to that described in ref 20.

(22) Blundell, T. L.; Cooper, J.; Foundling, S. I. On the rational design of renin inhibitors: X-ray studies of aspartic proteinases complexed with transition-state analogues. *Biochemistry* **1987**, *26*, 5585–5595.

(23) Lunney, E. A.; Hamilton, H. W.; Hodges, J. C.; Kaltenbronn, J. S.; Repine, J. T.; Baddasso, M.; Cooper, J. B.; Dealwis, C.; Wallace, B. A.; Lowther, W. T.; Dunn, B. D.; Humblet, C. Analyses of ligand binding in five endothiapepsin crystal complexes and their use in the design and evaluation of novel renin inhibitors. *J. Med. Chem.* **1993**, *36*, 3809–3820.

(24) Cooper, J. B.; Khan, G.; Taylor, G.; Tickle, I. J.; Blundell, T. L. X-ray analyses of aspartic proteases II. Three-dimensional structure of the hexagonal crystal form of porcine pepsin at 2.3 Å resolution. *J. Mol. Biol.* **1990**, *214*, 199–222.

(25) Dhanaraj, V.; Dealwis, C. G.; Frazao, C.; Badasso, M.; Sibanda, B. L.; Tickle, I. J.; Cooper, J. B.; Driessen, H. P. C.; Newman, M.; Aguilar, C.; Wood, S. P.; Blundell, T. L.; Hobart, P. M.; Geoghegan, K. F.; Ammirati, M. J.; Danley, D. E.; O'Connor, B. A.; Hoover, D. J. X-ray analyses of peptide-inhibitor complexes define the structural basis of specificity for human and mouse renins. *Nature (London)* **1992**, *357*, 466–472.

(26) Increasing the size of the side chain from methyl to ethyl and isopropyl resulted in decreased binding affinity in the D-isomer series and increased binding affinity of the L-isomer. Data not shown.

(27) 1,2,3-Substituted cyclopropane derivatives have previously been employed in the P3 position of renin inhibitors. See: Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Baker, W. R.; Condon, S. L.; deLara, E.; Rosenberg, S. H.; Spina, K. P.; Stein, H. H.; Cohen, C.; Kleinert, H. D. 1,2,3-Trisubstituted cyclopropanes as conformationally restricted peptide isosteres: Application to the design and synthesis of novel renin inhibitors. *J. Med. Chem.* **1992**, *35*, 1710–1721.
(28) Rahuel, J.; Priestle, J. P.; Grutter, M. G. The crystal structures of recombinant glycosylated human renin alone and in complex with a transition state analog inhibitor. *J. Struct. Biol.* **1991**, *107*, 227–236.
(29) Williams, D. H. The molecular basis of biological order. *Aldrichchimica Acta* **1991**, *24*, 71–80.
(30) Sybyl Molecular Modeling Software, Versions 5 and 6, Tripos Associates Inc., 1699 S. Hanley Rd., Suite 303, St. Louis, MO 63144.
(31) Sibanda, B. L.; Blundell, T.; Hobart, P. M.; Fogliano, M.; Bindra, J. S.; Dominy, B. W.; Chirgwin, J. M. Computer graphics modelling of human renin. Specificity, catalytic activity and intron-exon junctions. *FEBS Lett.* **1984**, *174*, 102–111.
(32) Motoc, I.; Dammkoehler, R. A.; Mayer, D.; Labanowski, J. Three-dimensional quantitiative structure-activity relationships I. General approach to the pharmacophore model validation. *Quant. Struct.-Act. Relat.* **1986**, *5*, 99–105.
(33) Clark, M.; Cramer, R. D. III; Van Opdenbosch, N. Validation of the general purpose Tripos 5.2 Force Field. *J. Comput. Chem.* **1989**, *10*, 982–1012.
(34) Haber, E.; Koerner, T.; Page, L. B.; Kilman, B.; Purnode, A. Application of radioimmunoassay for angiotensin I to the physiologic measurements of plasma renin activity in normal human subjects. *J. Clin. Endocrinol.* **1969**, *29*, 1349–1355.

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