Potent Human Immunodeficiency Virus Type 1 Protease Inhibitors That Utilize Noncoded D-Amino Acids as P_2/P_3 Ligands

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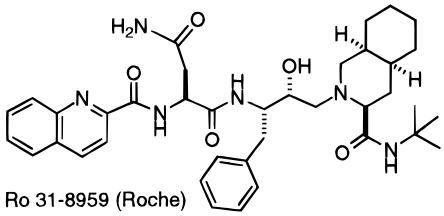
Noncoded D-amino acids have been designed to replace the quinaldic amide−asparaginyl moiety (P_2/P_3 ligand) found in several potent human immunodeficiency virus (HIV) protease inhibitors such as LY289612. The substituted nitrogen, optimally an *N*-methanesulfonyl moiety, served as a CH_2CONH_2 (asparagine side chain mimic), while the amino acid side chain became the backbone and P_3 ligand of these novel inhibitors. Compounds derived from *S*-aryl-D-cysteine proved to be potent HIV protease inhibitors which also exhibited potent whole cell antiviral activity. Oxidation of the cysteines to the sulfoxide or sulfone oxidation states resulted in significant improvements in potency. For example, the compound derived from *N*-(methylsulfonyl)-2-*S*-naphthylcysteine sulfone, **17c**, was a 3.5 nM inhibitor of HIV protease which inhibited the spread of virus in MT4 cells with an $IC_{50} = 4.3$ nM. Compounds **17c,g,i** were found to be orally bioavailable in a rat model.

Introduction

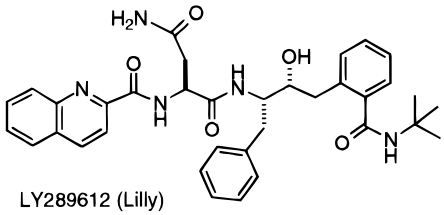
Human immunodeficiency virus type 1 (HIV-1) protease, an essential enzyme in the life cycle of HIV, remains an exciting target for anti-AIDS (acquired immune deficiency syndrome) chemotherapeutic agents.[1] Considerable effort has been spent on attempts to find potent, orally bioavailable, peptidomimetic inhibitors of this enzyme.[2] Representative examples include Ro 31-8959[3] and the MK-639,[2,4] both of which are in phase III clinical trails. The Lilly group recently reported[5] on our lead compound LY289612, and much of our continued effort in this area has focused on improving the antiviral potency and pharmacokinetic properties of this structure type.

The factors which determine why peptidomimetic compounds typically exhibit poor oral bioavailability while selected compounds such as MK-639 are well absorbed are not yet well understood.[6] Both Ro 31-8959 and LY289612 exhibit relatively low oral bioavailability in animal models.[7,8] The structural similarities between Ro 31-8959 and LY289612 are readily apparent; thus we reasoned one potential way to improve the pharmacokinetic properties might be to diverge from the quinaldic amide−asparagine moiety found in both inhibitors. A reduction in both the peptide-like nature of our inhibitor as well as the structural similarity to the Roche inhibitor could be achieved by replacing the only remaining natural amino acid, asparagine, which serves as the P_2 ligand. Of course modification of the asparagine moiety could have a negative effect on the enzyme inhibition and antiviral properties of any new inhibitor. For example, the Roche group systematically explored the structural requirements for each subsite, $P_3-P_{1'}$, of their HIV-1 protease inhibitor and reported "at the P_2 subsite no improvement over asparaginyl was found".[3]

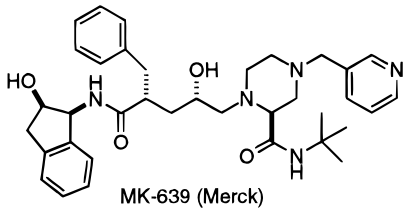
Several avenues of investigation were considered including either replacement of the asparagine with a noncoded L-amino acid or substitution of the natural L-amino acid with the corresponding D-amino acid.[9]



Ro 31-8959 (Roche)

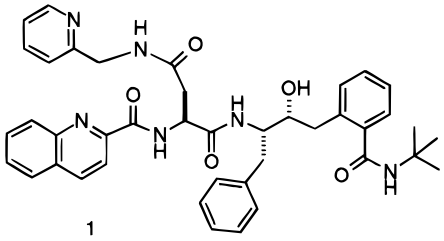


LY289612 (Lilly)



MK-639 (Merck)

While D-amino acid substitution might improve proteolytic stability, our knowledge of how LY289612 binds to the HIV protease suggested that a D-asparagine moiety at P_2 would have a negative effect on binding affinity to the enzyme's active site. Initially we decided to replace the asparagine moiety with a noncoded L-amino acid. For example, we prepared a series of carboxamides represented by **1**, a potent HIV-1 protease



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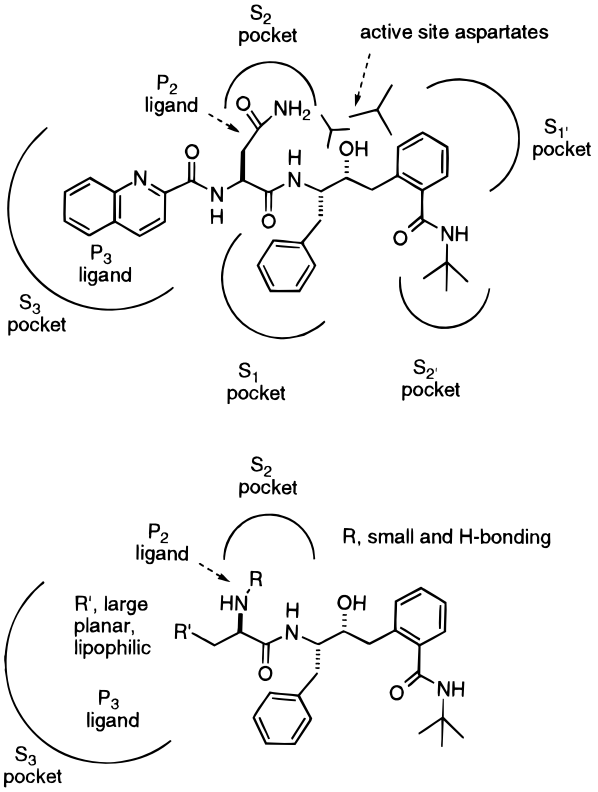


Figure 1. Cartoon depicting binding of LY289612 to HIV protease and proposed "role reversal" of the D-amino acid in the S_2-S_3 region.

inhibitor which also exhibits potent antiviral activity in vitro.[10] Unfortunately no significant improvement in oral bioavailability was found within this series.

The concept we wish to introduce herein is a hybrid of the noncoded L-amino acid and D-amino acid replacement ideas. We envisioned the design of a noncoded D-amino acid which would mimic the quinaldic amide–asparagine moiety found in our lead inhibitor. LY289612 binds to HIV-1 protease[11] with the quinaldic amide moiety fitting in the S_3 pocket of the enzyme's active site, while the asparagine side chain binds to the S_2 pocket as depicted in Figure 1. We postulated that inversion of the amino acid stereochemistry would require the substituted amino group to become the P_2 ligand (R group in Figure 1), while the aromatic P_3 ligand (R′ group in Figure 1) would be derived from the side chain of the D-amino acid. The ultimate success of this approach required the design of a relatively small nitrogen substituent which was capable of H-bonding ($CONH_2$ mimic). As the amino acid side chain now serves as the peptidomimetic's backbone, it must mimic the relatively large size and lipophilic nature of the quinaldic amide moiety. In a preliminary communication, we demonstrated the successful replacement of asparagine by appropriately substituted, commercially available, D-aspartic acid and D-cysteine analogs wherein the nitrogen was capped by either an acetyl or methanesulfonyl group.[12a] We now report on our efforts to expand our understanding of these structure–activity relationships (SAR).

Concept Evolution. The first compound we synthesized[12a] in order to test the "D-amino acid concept" was the benzyl *N*-acetyl-D-aspartate analog **4** (Scheme 1). While **4** proved to be more than 50-fold less potent (85 vs 1.5 nM) than LY289612 as an HIV protease inhibitor, we still considered this to be a remarkable

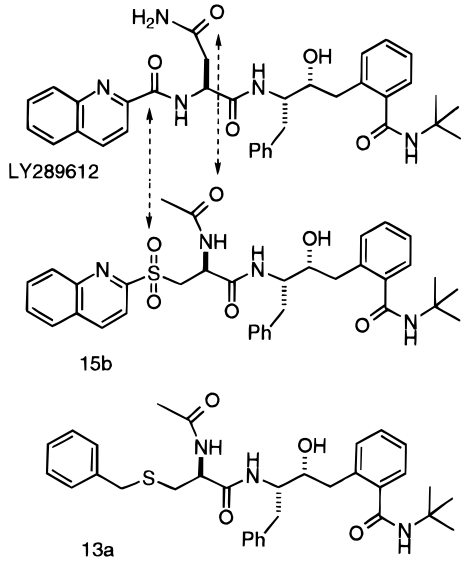


Figure 2. Evolution of the design concept.

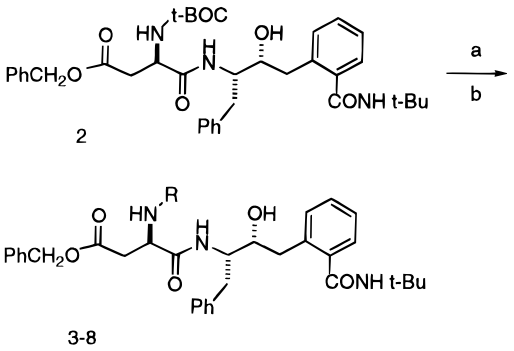
finding. The lack of enzyme inhibitory activity displayed by the corresponding L-isomer further supported the viability of this design concept. Several analogs were prepared (vide infra) in an attempt to optimize the nitrogen substituent (P_2 ligand) prior to turning our attention to the amino acid side chain (P_3 ligand). Early in our studies we concentrated on readily available D-amino acids such as aspartic acid amides, serine-based esters or ethers, and phenylalanine. None of these early compounds exhibited enzyme inhibitory or antiviral activity comparable to LY289612. We also investigated several *S*-alkylated cysteine analogs and found that the compound derived from *N*-acetyl-*S*-benzyl-D-cysteine, **13a** (Figure 2), was a 45 nM inhibitor of HIV protease. With the recognition that a sulfone can potentially act as an amide isostere,[13] we envisioned a D-cysteinesulfonyl moiety that would more closely mimic the quinaldic amide–asparagine moiety found in the Lilly, Roche, and Monsanto[14] inhibitors. Analog **15b**, derived from *N*-acetyl-*S*-quinolinylcysteine sulfone, appeared to be an attractive target for synthesis, and thus we turned our efforts in this direction (Figure 2).

Chemistry

In order to test the D-amino acid concept quickly, we searched for several commercially available, optically pure, *t*-BOC-protected amino acids which contain an aromatic moiety in the side chain. For example, we selected *N*-*t*-BOC-D-aspartic acid β-benzyl ester as our starting point. This material was coupled to amine **11**[5] providing amide **2** in 87% yield.[12a] Treatment of **2** with TFA gave rise to the corresponding free amine **3** as shown in Scheme 1. Amine **3** proved to be a useful intermediate which allowed us to explore a number of potential mimics of the $CONH_2$ moiety which binds to the S_2 pocket of the target enzyme. Thus, treatment of **3** with acetic anhydride gave the corresponding *N*-acetyl analog **4**. Acylation with propionyl chloride or butryl chloride provided propionate **5** and butyrate **6**, respectively. The urea analog **7** was synthesized by condensation with trimethylsilyl isocyanate. Sulfonamide **8** was obtained by treating amine **3** with methanesulfonyl chloride.

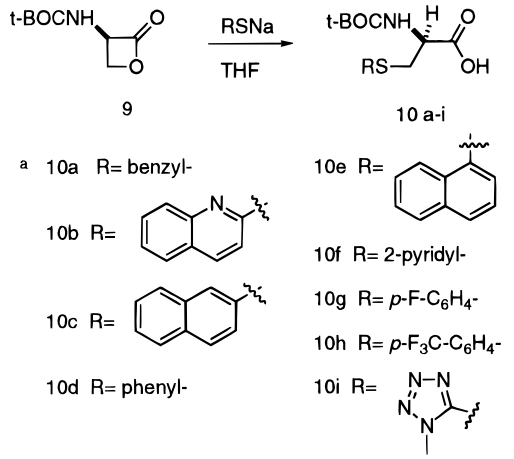
With the observation that cysteine-derived analogs such as **13a** were also HIV protease inhibitors, a general route to optically pure *S*-alkylated D-cysteine analogs

Scheme 1[a]



[a] (a) TFA/CH_2Cl_2 provided **3** (R = H); (b) compound **3** treated with Ac_2O/pyridine/CH_2Cl_2 provided **4** (R = CH_3CO), with EtCOCl/Et_3N/CH_2Cl_2 provided **5** (R = EtCO), with *n*-PrCOCl/Et_3N/CH_2Cl_2 provided **6** (R = *n*-PrCO), with $(CH_3)_3SiNCO$/THF provided **7** (R = $CONH_2$), or with $CH_3SO_2Cl/Et_3N/CH_2Cl_2$ provided **8** (R = SO_2CH_3).

Scheme 2[a]



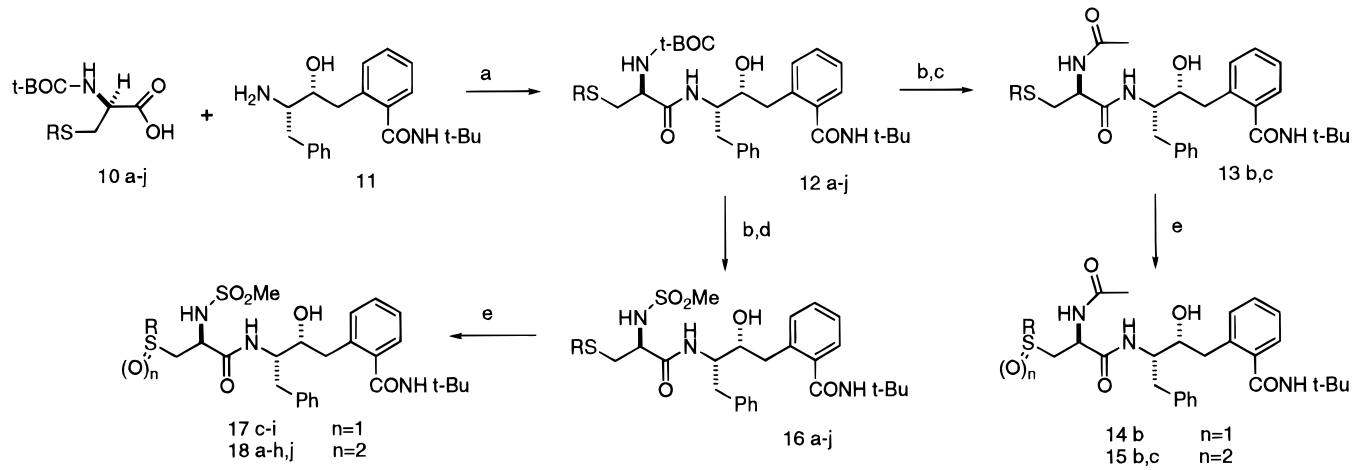
was required in order to elaborate on this SAR. To this end, we recognized that the ring-opening reaction of Vederas' *N*-*t*-BOC-D-serine β-lactone (**9**)[15] with a variety of mercaptans would provide the desired D-amino acids in a single step (Scheme 2). In practice the requisite cysteine analogs **10b**−**i** were obtained by adding the sodium salt of the appropriate arylmercaptan to β-lactone **9**. Alternatively, acids **10j,k** were prepared by thiolate displacement of the tosylate **19**,[16] which also proceeded without any apparent racemization (Scheme 4). Compound **10a**, R = benzyl, is commercially available.

To complete the synthesis of the target inhibitors, the acids **10a**−**j** were coupled to amine **11**[5] (DCC, HOBt) without any detectable racemization to give amides **12a**−**j** in good yield (Scheme 3). Trifluoroacetic acid-catalyzed removal of the *t*-BOC protecting group provided the corresponding free amines which were either acylated (AcCl, Ac_2O) or treated with methanesulfonyl chloride to give the *N*-acetyl analogs **13b,c** or the sulfonamides **16a**−**j**, respectively. Sulfide **13a** was obtained in one step by coupling amine **11** with *N*-acetyl-*S*-benzyl-D-cysteine. Sulfoxides **14b** and **17c**−**i** were obtained by treating the corresponding sulfides with 1 equiv of MCPBA. Both diastereomers of sulfoxide **17f** were isolated, while sulfoxides **14b** and **17c**−**e,g**−**i** were obtained as single diastereomers of undefined configuration at the sulfur center. Oxidation with excess Oxone provided sulfones **15c** and **18a,c,d,h,j**. Alternatively, sulfones **15b** and **18b,f,g** were obtained utilizing MCPBA as the oxidant. Sulfoxide **17e** was treated with MCPBA to provide sulfone **18e**.

We also developed a slightly more convergent approach to the target sulfones. As shown in Scheme 4, the *p*-chlorophenyl-substituted acid **10k** was oxidized to sulfone **20** utilizing Oxone. The standard coupling procedure (DCC, HOBt) with amine **11** gave rise to amide **21**. Finally, acid-catalyzed removal of the *t*-BOC protecting group followed by treatment with methanesulfonyl chloride provided target structure **18k**. Attempts to convert aryl sulfone-substituted D-amino acids such as **20** into the corresponding *N*-SO_2CH_3 analogs and then coupling with amine **11** led to significant racemization at some point in the process.

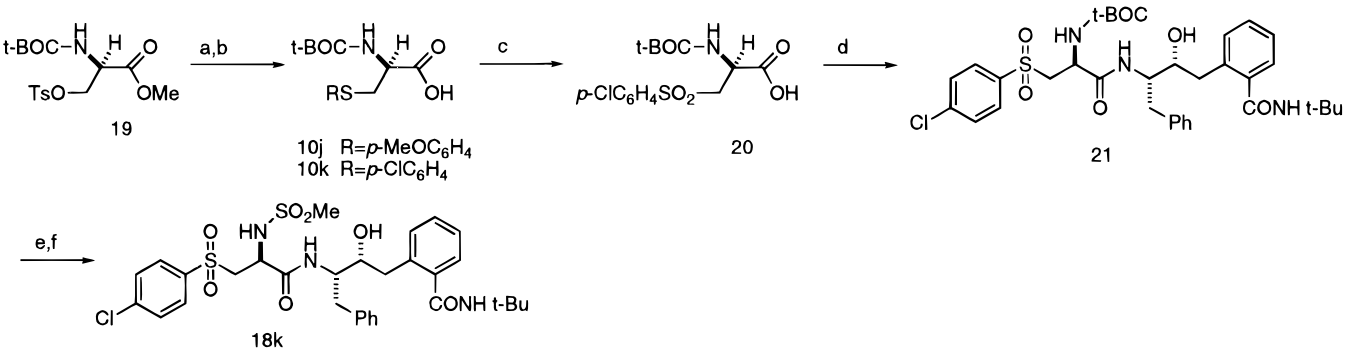
Compounds **13d** and **15d** were prepared as outlined in Scheme 5. D,L-*N*-Acetyl-*S*-phenylcysteine (**22**) was coupled to amine **11** in the usual fashion. The isomeric compounds **13d** and **23** were readily separated by flash chromatography. The more polar isomer was assigned structure **13d** on the basis of its enzyme inhibitory activity, while the less polar isomer **23** was inactive against HIV protease. In all other instances where both the D- and L-isomers have been unambiguously synthesized, the D-isomers were active against HIV protease while the L-isomers were found to be inactive.[12a] Sulfide **13d** was converted to the corresponding sulfone **15d** upon treatment with oxone.

Scheme 3[a]



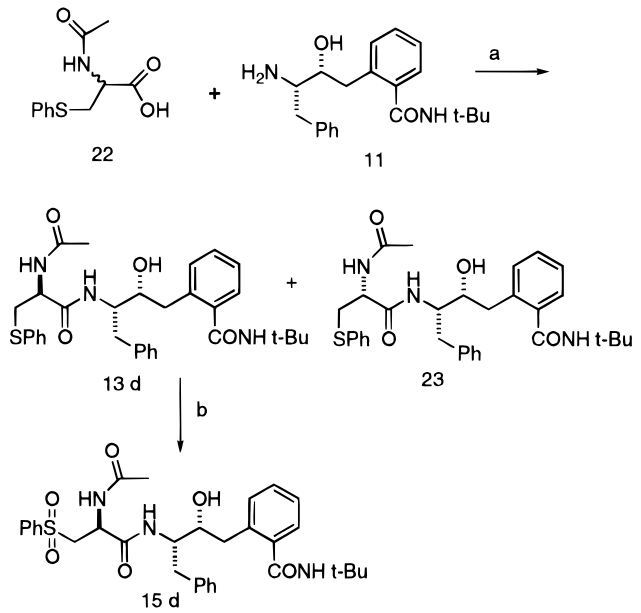
[a] (a) DCC/HOBt/THF; (b) TFA/CH_2Cl_2; (c) AcCl/CH_2Cl_2/Et_3N; (d) $CH_3SO_2Cl/CH_2Cl_2/Et_3N$; (e) Oxone/aqueous MeOH or MCPBA/CH_2Cl_2. R substituents for **a**−**k** are as defined in Schemes 2 and 4.

Scheme 4[a]



[a] (a) ArSNa/DMF; (b) LiOH/H_2O/THF; (c) Oxone/H_2O/MeOH; (d) **11**/DCC/HOBt/THF; (e) TFA/CH_2Cl_2; (f) $CH_3SO_2Cl/CH_2Cl_2/Et_3N$.

Scheme 5[a]



[a] (a) DCC/HOBt/THF; (b) Oxone/aqueous MeOH.

Results and Discussion

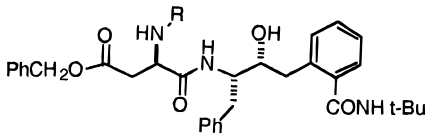
Having established that the benzyl *N*-acetylaspartate analog **4** was an 85 nM inhibitor of HIV protease, we undertook a brief study of what other nitrogen substitutions might effectively mimic the carboxamide P_2 ligand. The results are summarized in Table 1. Key intermediates in the synthesis of analogs, namely, the *N*-*t*-BOC compound **2** and the free amine **3**, were not active against HIV protease. Increasing the chain length from acetyl to propionyl, compound **4** vs **5**, had little effect on potency, but the *N*-butyryl analog **6** was significantly less active (323 nM), indicating an apparent size restriction for the nitrogen substituent. We anticipated that a simple urea, **7**, might effectively mimic a carboxamide moiety, and a slight improvement over acetyl was seen (51 vs 85 nM). Unfortunately none of these compounds demonstrated useful levels of whole cell antiviral activity, as all were >5 μM inhibitors of viral replication (Table 1). A significant increase in enzyme inhibitory activity (5.4 nM) as well as in whole cell antiviral activity (IC_{50} = 1 μM) was observed with sulfonamide analog **8**.

At this point it seemed appropriate to concentrate on optimization of the amino acid side chain (P_3 ligand) and to utilize the *N*-acetyl and *N*-methanesulfonyl groups as reasonably diverse choices for the P_2 ligand. Other commercially available D-amino acids which contained an aryl moiety in the side chain were investigated and generally gave poor results. However, the *S*-benzyl-D-cysteine-substituted compound **13a** was a comparable enzyme inhibitor (45 nM) to the benzyl aspartates (Table 2). The *N*-methanesulfonyl analog **16a** was an even more active enzyme inhibitor (14.7 nM), and oxidation of the sulfide to the corresponding sulfone **18a** provided an improvement in antiviral activity as well (IC_{50} = 800 nM, CEM cells).

At this juncture we recognized that the *S*-quinolinyl analogs **13b** and **16b** and their corresponding sulfones **15b** and **18b** represented, perhaps, optimal mimics of the quinaldic amide moiety found in LY289612. Both sulfides **13b** and **16b** were relatively weak enzyme inhibitors, 14.7 and 60 nM, respectively, and **16b** was only a weak antiviral agent (IC_{50} = 5.4 μM). We were delighted to find that the corresponding sulfones **15b** (0.28 nM) and **18b** (2.8 nM) were more potent enzyme inhibitors than the sulfides and that the *N*-acetyl analog **15b** exhibited potent antiviral activity as well (IC_{50} = 53 nM, CEM cells). Contrary to our observations with aspartate-based analogs (**4** vs **8**), the *N*-acetyl-*S*-quinolinyl-substituted compound **15b** was much more active than the corresponding *N*-methanesulfonyl-substituted compound **18b**.

These exciting results prompted us to further expand the *S*-arylcysteine SAR. As seen in Table 2, a variety of compounds were tested, including mono- and bicyclic aryl analogs, in an attempt to optimize enzyme inhibi-

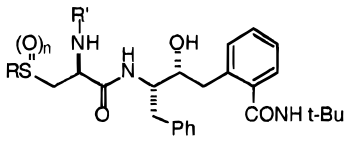
Table 1. Potential Carboxamide Mimics



		IC_{50} (nM)		
			antiviral activity[b]	
no.	R	enzyme inhibition[a]	CEM	MT2
2	*t*-BOC	>1000		
3	H	>1000		
4	Ac	85		
5	EtCO-	73	5200	9880
6	*n*-PrCO-	323	8700	24 200
7	H_2NCO-	51	22 400(1)	11 900
8	Ms	5.4	1090(1)	1270

[a] All entries are for a single determination. [b] All entries are the average of two determinations except where noted by a superscripted number in parentheses, performed at the Southern Research Institute, Birmingham, AL.

Table 2. D-Cysteine Analogs



				IC$_{50}$ (nM)			
					antiviral activity[b]		
no.	R	*n*	R′	enzyme inhibition[a]	CEM	MT2	CEM
13a	$PhCH_2$	0	Ac	45	2910	3120	
13b	2-quinolinyl	0	Ac	14.7			
13c	2-naphthyl	0	Ac	42	1130	1000(1)	
13d	Ph	0	Ac	220	5400	11 300	
14b	2-quinolinyl	1	Ac	0.25	72	180	
15b	2-quinolinyl	2	Ac	0.28	53	180	59
15c	2-naphthyl	2	Ac	0.32	11(4)	31(3)	
15d	Ph	2	Ac	20	815	820	
16a	$PhCH_2$	0	Ms	14.7	1650	926(1)	
16b	2-quinolinyl	0	Ms	60	5400	6440	
16c	2-naphthyl	0	Ms	1.8	530(3)	800(3)	
16d	Ph	0	Ms	44	4370	2750	
16e	1-naphthyl	0	Ms	1.2(2)	270	760	323
16f	2-pyridyl	0	Ms	910			
16g	*p*-F-C_6H_4	0	Ms	4.4	2130	2880	
16h	*p*-CF_3-C_6H_4	0	Ms	170	2930	5910	
16i	*N*-Me-tetrazole	0	Ms	17.5	6680	9260	
16j	*p*-MeO-C_6H_4	0	Ms	16	1800	1910	
17c	2-naphthyl	1	Ms	3.5(2)	<0.5	4.3	6.7
17d	Ph	1	Ms	1.9(2)	100	500	
17e	1-naphthyl	1	Ms	0.45	<0.5	6	0.8
17f	2-pyridyl	1	Ms	7.9	330	770	
17f′	2-pyridyl	1	Ms	19.3			474
17g	*p*-F-C_6H_4	1	Ms	0.38	165	900	
17h	*p*-CF_3-C_6H_4	1	Ms	2.3	53	116	
17i	*N*-Me-tetrazole	1	Ms	2.1			5010
18a	$PhCH_2$	2	Ms	19.4	800	730(1)	
18b	2-quinolinyl	2	Ms	2.8	2060	3030	5780
18c	2-naphthyl	2	Ms	0.3	<0.5	5	12
18d	Ph	2	Ms	5.7	72	176	83
18e	1-naphthyl	2	Ms	0.44	<0.5	8.8	49
18f	2-pyridyl	2	Ms	22			
18g	*p*-F-C_6H_4	2	Ms	0.77	59	440	32
18h	*p*-CF_3-C_6H_4	2	Ms	2	204	450	646
18j	*p*-MeO-C_6H_4	2	Ms	2.4	54	150	107
18k	*p*-Cl-C_6H_4	2	Ms	0.34	138	24	16

[a] All entries are for a single determination except where noted with a superscripted number in parentheses. [b] All entries are the average of two determinations except where noted by a superscripted number in parentheses. Antiviral activity in the first two columns was generated at the Southern Research Institute, Birmingham, AL. Data in the third column were generated at the Lilly Research Laboratories.

tory and antiviral activity. Sulfide analogs **13a**−**d** and **16a**−**j** were uniformly less active than their sulfoxide or sulfone counterparts. The most active sulfide, the 1-naphthyl-substituted **16e**, was a potent enzyme inhibitor (1.2 nM); however, its antiviral activity was a disappointing 270−760 nM.

Alternatives to the 2-quinolinesulfonyl moiety were explored such as 2-naphthylsulfonyl. In each instance (**15b** vs **15c**, **18b** vs **18c**) the naphthyl analogs exhibited comparable or improved enzyme inhibitory activity relative to the quinolines, and significantly improved antiviral activity was obtained with the naphthyl analogs as well. For example, the *N*-methanesulfonyl-2-naphthylsulfonyl analog **18c** was among the most potent antiviral agents within the series (IC$_{50}$ = 12 nM, CEM cells). It is interesting to note that the activity of the 1-naphthylsulfonyl analog **18e** is indistinguishable from that of the 2-naphthyl-substituted **18c**.

Bicyclic aryl substituents appeared to make better P_3 ligands than monocyclic aryl analogs. Pyridines **16f** and **18f** were significantly less active enzyme inhibitors than their quinoline counterparts **16b** and **18b**. Likewise, phenyl-substituted compounds were less active, both as enzyme inhibitors and as antiviral agents, than the corresponding naphthyl analogs; compare **13c** vs **13d**, **15c** vs **15d**, and **18c** vs **18d**. However, several 4-substituted phenyl analogs, **18g,j,k,** were good enzyme inhibitors, and each of these displayed respectable antiviral activity as well (IC$_{50}$s < 100 nM).

We also evaluated a number of sulfoxide analogs (**17c-i**). In each instance only a single diastereomer was obtained except for the pyridine analogs **17f**,**f′** where both sulfoxides were produced under the oxidation conditions employed. While there is an apparent 2-fold difference in enzyme inhibition between sulfoxide isomers **17f**,**f′**, they both exhibit comparable antiviral activity. The sulfoxides typically were about as active or slightly less active than the corresponding sulfones; thus we concentrated our effort on the sulfones, in order to avoid the ambiguity presented by the potential for having sulfoxide diastereomers. The 1-naphthylsulfinyl-substituted compound **17e** was the most potent inhibitor of viral replication (IC$_{50}$ = 0.8 nM, CEM cells) we found within this series of P_2/P_3 D-amino acid-substituted HIV protease inhibitors.

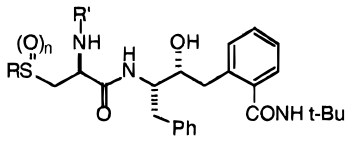
While we were excited by the fact that several of these novel inhibitors exhibited low-nanomolar IC$_{50}$s in acute viral infection assays, IC$_{95}$s are probably better indicators of a compound's potential to perform in the clinical setting. IC$_{95}$s were determined for several of our most potent analogs: **17c**, 24 nM; **17e**, 21 nM; **18c**, 50 nM; **18e**, 100 nM; **18k**, 94 nM. HIV protease inhibitors with antiviral IC$_{95}$s in the 25-100 nM range are competitive, in terms of whole cell activity, with compounds undergoing clinical evaluation such as Ro 31-8959 and MK-639.

Oral Bioavailability. A rapid prescreen in rats was developed to evaluate the potential oral absorption of the newly synthesized HIV protease inhibitors. Compounds were dissolved in an appropriate vehicle and dosed orally to Harlan Sprague−Dawley rats. Plasma was collected at several time points and assayed for HIV protease inhibitory activity rather than parent drug concentration. One cannot rule out the possibility that the antiviral activity observed in plasma was caused in part by the presence of active metabolites; however, this assay method was useful for quickly assessing the behavior of these compounds in animals. The compounds tested were selected on the basis of their antiviral activity as well as structural diversity considerations. While most of the compounds tested (Table 3) were poorly absorbed, three compounds showed modest absorption, the highly potent 2-naphthylsulfinyl-substituted **17c** as well as the weakly active *N*-methyltetrazole-substituted **17i**. The best absorption was obtained with the moderately active (*p*-fluorophenyl)-sulfinyl-substituted analog **17g** which gave a peak plasma concentration in excess of 2 μg/mL.

Conclusions

A number of D-amino acids were screened for their ability to act as mimics of the quinaldic amide−asparagine moiety found in our lead inhibitor LY289612. A brief SAR was developed in order to optimize the nitrogen substituent on D-aspartate analogs, and the *N*-methanesulfonyl-substituted compound **8** was found

Table 3. Oral Bioavailability Prescreen



no.	R	*n*	R′	C_{max} (μg/mL)[a]
15c	2-naphthyl	2	Ac	<0.1
17c	2-naphthyl	1	Ms	0.33
17e	1-naphthyl	1	Ms	<0.25
17f	2-pyridyl	1	Ms	<0.2
17g	*p*-F-C_6H_4	1	Ms	2.2
17h	*p*-CF_3-C_6H_4	1	Ms	<0.2
17i	*N*-Me-tetrazole	1	Ms	0.49
18c	2-naphthyl	2	Ms	<0.1
18d	Ph	2	Ms	<0.3
18g	*p*-F-C_6H_4	2	Ms	<0.3
18h	*p*-CF_3-C_6H_4	2	Ms	<0.3
18j	*p*-MeO-C_6H_4	2	Ms	<0.3
18k	*p*-Cl-C_6H_4	2	Ms	<0.3

[a] Each compound was delivered orally to rats (40 mg/kg) (n = 2). C_{max} is the maximum plasma concentration of HIV protease inhibitory activity observed based on the potency of the parent compound.

to be the most active. The best D-amino acids found to date were *S*-arylcysteine analogs. The Vederas β-lactone ring-opening procedure allowed for the rapid synthesis of a variety of *S*-arylcysteines which were elaborated into the proposed HIV protease inhibitors. The majority of these compounds are potent HIV protease inhibitors (IC_{50} < 10 nM), and several of these compounds possess potent antiviral activity, significantly more potent than lead structure LY289612.

There is no readily apparent correlation between the enzyme inhibitory activity and whole cell antiviral activity; however, several trends are apparent. Potent antiviral activity (IC_{50} < 500 nM) was only obtained with the best enzyme inhibitors (IC_{50} < 10 nM), as seen in Table 2. The sulfoxide and sulfone analogs tend to exhibit better potency both as enzyme inhibitors and as antivirals when compared to their sulfide counterparts. Perhaps these oxidized analogs serve as better mimics of the quinaldic amide bond present in LY289612 or the peptide backbone found in the natural substrates. Compounds containing bicyclic aryl substituents which can serve as P_3 ligands, naphthalene and quinoline, are more active than the corresponding phenyl or pyridyl analogs. Analogs with completely carbocyclic P3 aryl ligands are typically more active than their heterocyclic counterparts. Within the *S*-arylcysteine series of compounds, NSO_2Me-substituted compounds tended to be more active than the NAc analogs, except for the quinoline-containing compounds, e.g., **15b** vs **18b**.

Three compounds demonstrated measurable oral bioavailability in an animal model. These findings have significantly influenced our decision of which D-amino acids to couple to alternate isosteres in an attempt to find an HIV protease inhibitor which possesses both potent antiviral activity and good oral bioavailability. These studies will be the subject of a future report.

In summary, noncoded D-amino acids have been designed which effectively replace the P_2/P_3 ligands of the lead HIV-1 protease inhibitor LY289612 as evidenced by improved enzyme inhibitory and whole cell antiviral activity. This "D-amino acid concept" may find application in the design of peptidomimetic inhibitors of other proteolytic enzymes. We continue to explore this novel approach, and additional studies will be reported in due course.

Experimental Section

General Procedure. All reactions were run under a positive pressure of dry nitrogen. Fast atom bombardment mass spectra (FABMS) were obtained on a VG ZAB-3 instrument; field desorption mass spectra (FDMS) were obtained on a VG 70SE instrument. NMR spectra were obtained on a GE QE300 spectrometer. Optical rotations were obtained in MeOH solution. Flash chromatography was carried out on E. Merck Kieselgel 60 (230−400 mesh). The abbreviations THF, DMF, DCC, HOBt, Ac, Ms, TFA, and MCPBA refer to tetrahydrofuran, dimethylformamide, dicyclohexylcarbodiimide, 1-hydroxybenzotriazole hydrate, acetyl, methanesulfonyl, trifluoroacetic acid, and *m*-chloroperoxybenzoic acid, respectively. Anhydrous THF, 99.9%, was purchased from Aldrich and used directly.

Biological Methods. Protease inhibition assays[17] and whole cell antiviral testing[18] have been described previously.

Oral bioavailability was determined as follows. Test compounds were prepared for dosing in 100 g male, Harlan Sprague−Dawley rats as follows: Compound was micronized using a mortar and pestle and 20 mg transferred to a tare-weighted, silanized glass vial (2 mL capacity); 2 mL of dosing vehicle (10% acacia, 1% Tween 80 in water) was trickled down the side of the vial, to prevent clumping, yielding a concentration of 10 mg/mL. The vial was capped, vortexed vigorously for 30 s, and then sonicated in an ultrasonic water bath for 9 min. Alternate vortexing and sonicating was repeated twice. A stir bar was placed in the vial and the emulsion left to stir overnight on a magnetic stirplate.

After surgical implantation of a canula in the right jugular vein, rats were allowed to recover for at least 48 h prior to dose administration. Animals were fasted for 16−18 h prior to dosing. Compound was given by oral gavage at a dose of 40 mg/kg. Vehicle control animals received ca. 0.4 mL of the acacia/Tween vehicle. Typically two rats were given test compound. Blood draws (0.2 mL) were taken via canula at 0 (predose), 0.5, 1, 2, and 4 h time points. Blood was immediately transferred to a microtainer (Becton Dickson) and placed on ice. Plasma was separated from cell fraction by centrifugation. Plasma was stored at −70 °C until needed for assay.

Plasma samples were analyzed via a high-throughput fluorescence HPLC enzymatic assay which readily quantitates HIV protease inhibitor activity in biological fluids. HIV protease was incubated under optimal conditions (using appropriate diluents) with FITC-substrate (*N*-biotin-Gly-Ser-Gln-Asn-Tyr-Pro-Ile-Val-Gly-Lys(fluorescein isothiocyanate)-OH) and either a known amount of test compound (standard curve) or an unknown amount in plasma (sample analysis). Hydrolysis was allowed to procede for 5 h at 37 °C, and then the reaction was stopped with 0.1% TFA. An aliquot of this incubation mixture was injected onto a reverse-phase HPLC column. Only two fluorescent peaks are produced. By resolving and quantifying the fluorescence of the hydrolyzed and nonhydrolyzed FITC-substrate HPLC peaks, a percent hydrolysis is calculated for each injection (area of the hydrolyzed substrate peak/total area). The percent of substrate hydrolysis is inversely proportional to the amount of inhibitor in the incubation.

Ten concentrations of test compound prepared in 2% plasma, 10% DMSO, and MES buffer, pH 5.5 (20 mM MES, 20 mM NaCl, 0.2 mM EDTA, 1 mM DTT), were analyzed in duplicate along with a buffer control. Standard curves were prepared from a fresh weighing of the test compound. From an independent weighing, three concentration checks were prepared and assayed in triplicate along with the above standard curves. This defined the standard curve and validated the accuracy and precision of the compound stocks.

Plasma samples obtained from compound-dosed rats were prepared by making a 1:49 dilution of plasma with 10% DMSO and MES buffer and analyzed via the HPLC assay described

above. The concentrations of compound in plasma samples were extrapolated from the standard curve.

Preparation of (*R*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)-amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)-propyl]-2-amino-4-oxo-4-(benzyloxy)butanamide (3). To a solution of (*R*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-dimethylethyl)amino]-carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(*tert*-butoxycarbonyl)amino]-4-oxo-4-(benzoyloxy)butanamide (**2**)[12a] (0.91 g, 1.4 mmol) in CH_2Cl_2 (5 mL) was added TFA (3 mL). The mixture was stirred at room temperature for 3 h at which time TLC indicated the starting material had been consumed. The volatiles were removed in vacuo, and the residue was taken up in EtOAc. The EtOAc solution was washed with 5% aqueous NH_4OH solution, and the aqueous phase was then back-extracted with additional EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give 0.72 g of the amine as a white solid. Flash chromatography (4% MeOH/CH_2Cl_2 and then 6% MeOH/CH_2Cl_2) gave 0.56 g, 73% yield, of the title compound **3** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.57 (d, J = 9.1 Hz, 1H), 7.40−7.15 (m, 14H), 6.01 (br s, 1H), 5.07 (d, J = 1.2 Hz, 2H), 4.25 (m, 1H), 3.77 (m, 1H), 3.55 (dd, J = 3.9, 3.9 Hz, 1H), 3.12−2.75 (m, 5H), 2.58 (dd, J = 8.1, 8.1 Hz, 1H), 1.42 (s, 9H). $[\alpha]^{22}_D$ +2.8°. Anal. ($C_{32}H_{39}N_3O_5$) C,H,N.

Preparation of (*R*)-*N*-(1*S*,2*R*)-[3-[2-[[1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)-propyl]-2-(acetoxyamino)-4-oxo-4-(benzyloxy)butanamide (4). To a solution of amine **3** (1.35 g, 2.47 mmol) in CH_2Cl_2 (5 mL) were added pyridine (0.42 mL, 5.2 mmol) and acetic anhydride (0.26 mL, 2.72 mmol). The mixture was stirred at room temperature for 2 h and then diluted with additional CH_2Cl_2, washed with cold 0.1 N HCl solution, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (step gradient from 3% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2) gave 0.6 g, 40% yield, of the title compound **4** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.10−7.40 (m, 14H), 6.90 (d, J = 8 Hz, 1H), 6.70 (d, J = 6 Hz, 1H), 6.10 (s, 1H), 5.08 (s, 2H), 4.68 (m, 1H), 4.26 (m, 1H), 3.75 (m, 1H), 2.74−3.10 (m, 5H), 2.33 (d, J = 6 Hz, 1H), 1.90 (s, 3H), 1.45 (s, 9H). FABMS (M + 1): calcd, 588.3073; found, 588.3051.

Preparation of (*R*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)-amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)-propyl]-2-[(ethylcarbonyl)amino]-4-oxo-4-(benzyloxy)-butanamide (5). To a solution of amine **3** (0.15 g, 0.27 mmol) in CH_2Cl_2 (4 mL) were added Et_3N (0.076 mL, 0.55 mmol) and propionyl chloride (0.024 mL, 0.27 mmol). The mixture was stirred at room temperature for 30 min and then diluted with additional CH_2Cl_2, washed with cold 1 N HCl solution, dried (Na_2SO_4), and concentrated in vacuo to give 0.17 g, 100% yield, on the title compound **5** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.40−7.11 (m, 14H), 6.87 (d, J = 9.3 Hz, 1H), 6.64 (d, J = 7.8 Hz, 1H), 6.05 (s, 1H), 5.99 (d, J = 5.5 Hz, 1H), 5.07 (d, J = 2.1 Hz, 2H), 4.69 (m, 1H), 4.28 (m, 1H), 3.73 (m, 1H), 3.10−2.72 (m, 5H), 2.33 (dd, J = 6.8, 10.4 Hz, 1H), 2.15 (q, J = 7.6 Hz, 2H), 1.47 (s, 9H), 1.06 (t, J = 7.6 Hz, 3H). Anal. ($C_{35}H_{43}N_3O_6$) C,H,N.

Preparation of (*R*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)-amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)-propyl]-2-[(*n*-propylcarbonyl)amino]-4-oxo-4-(benzyloxy)-butanamide (6). To a solution of amine **3** (0.16 g, 0.29 mmol) in CH_2Cl_2 (4 mL) were added Et_3N (0.081 mL, 0.58 mmol) and *n*-butyryl chloride (0.03 mL, 0.29 mmol). The mixture was stirred at room temperature for 15 min and then diluted with additional CH_2Cl_2, washed with cold 1 N HCl solution, dried (Na_2SO_4), and concentrated in vacuo to give 0.18 g, 100% yield, of the title compound **6** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.40−7.12 (m, 14H), 6.88 (d, J = 9.3 Hz, 1H), 6.65 (d, J = 7.8 Hz, 1H), 6.11 (s, 1H), 5.99 (d, J = 5.5 Hz, 1H), 5.07 (d, J = 2.3 Hz, 2H), 4.69 (m, 1H), 4.25 (m, 1H), 3.75 (m, 1H), 3.10−2.72 (m, 5H), 2.33 (dd, J = 6.8, 10.4 Hz, 1H), 2.07 (t, J = 6.9 Hz, 2H), 1.55 (q, J = 7.6 Hz, 2H), 1.46 (s, 9H), 0.86 (t, J = 7.4 hz, 3H). Anal. ($C_{36}H_{45}N_3O_6$) C,H,N.

Preparation of (*R*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)-amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)-propyl]-2-(carbamoylamino)-4-oxo-4-(benzyloxy)butan-amide (7). To a solution of amine **3** (0.055 g, 0.1 mmol) in THF (2 mL) was added trimethylsilyl isocyanate (0.019 mL, 0.15 mmol). The mixture was stirred at room temperature for 30 min at which time an additional 0.035 mL of the isocyanate was added, and stirring was continued overnight. The mixture was diluted with EtOAc, washed with dilute aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated in vacuo to give 40 mg, 68% yield, of the title compound **7**. ^{1}H-NMR ($CDCl_3$): δ 7.10−7.39 (m, 14H), 7.05 (d, J = 8 Hz, 1H), 6.18 (s, 1H), 6.12 (d, J = 8 Hz, 1H), 5.93 (br s, 1H), 5.01 (s, 2H), 4.76 (s, 2H), 4.55 (m, 1H), 4.21 (m, 1H), 3.75 (m, 1H), 2.70−3.03 (m, 5H), 2.43 (dd, J = 6, 12 Hz, 1H), 1.43 (s, 9H). Anal. ($C_{33}H_{40}N_4O_6$) C, H, N.

Preparation of (*R*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)-amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)-propyl]-2-[(methylsulfonyl)amino]-4-oxo-4-(benzyloxy)-butanamide (8). To a 0 °C solution of amine **3** (0.75 g, 0.97 mmol, added as a bis-TFA salt) in CH_2Cl_2 (5 mL) were added Et_3N (0.4 mL, 2.9 mmol) and methanesulfonyl chloride (0.075 mL, 0.97 mmol). The mixture was stirred at 0 °C for 1 h and then at room temperature for 1 h. An additional 0.02 mL of both methanesulfonyl chloride and Et_3N was added and the mixture stirred for 1 h. The reaction mixture was poured into cold 1 N HCl solution and extracted with additional CH_2Cl_2. The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give 0.6 g of a beige solid. Flash chromatography (2% MeOH/CH_2Cl_2) gave 0.33 g, 54% yield, of the title compound **8** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.06−7.41 (m, 15H), 6.10 (s, 1H), 5.99 (d, J = 6 Hz, 1H), 5.80 (d, J = 8 Hz, 1H), 5.05 (s, 2H), 4.38 (m, 1H), 4.13 (m, 1H), 3.80 (m, 1H), 2.63−3.10 (m, 5H), 2.76 (s, 3H), 2.42 (dd, J = 6, 12 Hz, 1H), 1.45 (s, 9H). Anal. ($C_{33}H_{41}N_3O_7S$) C,H,N.

Preparation of (*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-(2-quinolinylthio)propionic Acid (10b). General Procedure for the Preparation of *S*-Arylcysteines. To a solution of 2-quinolinethiol (1.9 g, 11.8 mmol) in THF (15 mL) was added NaH (0.47 g, 11.8 mmol, 60% oil dispersion), and the resulting mixture was stirred at room temperature for 10 min. A solution of *N*-*t*-BOC-D-serine β-lactone (**9**)[15] (2.0 g, 10.7 mmol) in THF (15 mL) was added dropwise over 10 min; then stirring was continued at room temperature for 2 h. The reaction mixture was acidified by adding 10% aqueous $NaHSO_4$ solution and then extracted with ethyl acetate (EtOAc, 2 × 100 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to give a yellow foam. Flash chromatography eluting first with 2% MeOH/CH_2Cl_2 to remove any thiol and then increasing the polarity to 10% MeOH/0.1% AcOH/CH_2Cl_2 gave 2.0 g, 54% yield, of **10b** as a yellow solid. ^{1}H-NMR ($CDCl_3$): δ 8.05 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 7.3 Hz, 1H), 7.80−7.63 (m, 3H), 7.50 (t, J = 7.3 Hz, 1H), 7.32 (d, J = 8.7 Hz, 1H), 4.60 (m, 1H), 3.85 (dd, J = 3.1, 15.3 Hz, 1H), 3.44 (dd, J = 5.7, 15.3 Hz, 1H), 1.42 (s, 9H). Anal. ($C_{17}H_{20}N_2O_4S$) C,H,N.

Preparation of (*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-(2-naphthylthio)propionic Acid (10c). As above, naphthalenethiol (1.9 g, 11.9 mmol) in THF (15 mL) was treated with NaH (0.47 g, 11.8 mmol, 60% oil dispersion) followed by addition of lactone **9** (2.0 g, 10.7 mmol) in THF (15 mL) to give after flash chromatography (2% MeOH/CH_2Cl_2 followed by 5% MeOH/1% AcOH/CH_2Cl_2) 3.08 g, 84% yield, of **10c** as a white foam. ^{1}H-NMR ($CDCl_3$): δ 7.85 (s, 1H), 7.74 (m, 3H), 7.42 (m, 3H), 5.47 (d, J = 7.0 Hz, 1H), 4.62 (m, 1H), 3.49 (m, 2H), 1.38 (s, 9H).

Preparation of (*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-(phenylthio)propionic Acid (10d). As above, thiophenol (1 mL, 9.7 mmol) in THF (15 mL) was treated with NaH (0.39 g, 10.5 mmol, 60% oil dispersion) followed by addition of lactone **9** (1.7 g, 9.2 mmol) in THF (15 mL) to give after flash chromatography (2% MeOH/CH_2Cl_2 followed by 10% MeOH/1% AcOH/CH_2Cl_2) 1.9 g, 61% yield, of **10d** as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 7.39 (m, 2H), 7.20 (m, 3H), 5.48 (d, J = 7.0 Hz, 1H), 4.58 (m, 1H), 3.39 (m, 2H), 1.38 (s, 9H).

Preparation of (*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-(1-naphthylthio)propionic Acid (10e). As above, 1-naphthalenethiol (0.9 g, 5.6 mmol) in THF (5 mL) was treated with NaH (0.22 g, 5.5 mmol, 60% oil dispersion) followed by addition of lactone **9** (1 g, 5.3 mmol) in THF (5 mL) to give after flash chromatography (2% MeOH/CH_2Cl_2 followed by 10% MeOH/1% AcOH/CH_2Cl_2) 1.3 g, 70% yield, of **10e** as a white solid.

^{1}H-NMR ($CDCl_3$): δ 8.45 (d, J = 8.0 Hz, 1H), 7.88−7.39 (m, 7H), 5.26 (d, J = 2.5 Hz, 1H), 4.50 (m, 1H), 3.42 (m, 2H), 1.40 (s, 9H). Anal. ($C_{18}H_{21}NO_4S$) C,H,N.

Preparation of (*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-(2-pyridylthio)propionic Acid (10f). As above, 2-pyridinethiol (1 g, 9 mmol) in THF (8 mL) was treated with NaH (0.35 g, 8.8 mmol, 60% oil dispersion) followed by addition of lactone **9** (1.5 g, 8 mmol) in THF (8 mL) to give after flash chromatography (2% MeOH/CH_2Cl_2 followed by 5% MeOH/1% AcOH/CH_2Cl_2) 2.4 g, 100% yield, of **10f** as a yellowish-tinted solid. ^{1}H-NMR ($CDCl_3$): δ 8.42 (d, J = 4.8 Hz, 1H), 7.66 (t, J = 7.3 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.18 (t, J = 5.7 Hz, 1H), 6.62 (br s, 1H), 4.58 (br s, 1H), 3.78 (dd, J = 3.5, 15.1 Hz, 1H), 3.34 (dd, J = 5.4, 15.1 Hz, 1H), 1.41 (s, 9H).

Preparation of (*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-[(*p*-fluorophenyl)thio]propionic Acid (10g). As above, *p*-fluorothiophenol (1.2 mL, 11.2 mmol) in THF (10 mL) was treated with NaH (0.45 g, 11.2 mmol, 60% oil dispersion) followed by addition of lactone **9** (2 g, 10.7 mmol) in THF (10 mL) to give after flash chromatography (2% MeOH/CH_2Cl_2 followed by 10% MeOH/0.2% AcOH/CH_2Cl_2) 2.4 g, 71% yield, of **10g** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.40 (m, 2H), 6.96 (m, 2H), 5.33 (d, J = 7.0 Hz, 1H), 4.43 (m, 1H), 3.30 (m, 2H), 1.40 (s, 9H). $[\alpha]^{22}_D$ + 17.03°.

Preparation of (*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-[[*p*-(trifluoromethyl)phenyl]thio]propionic Acid (10h). As above, [*p*-(trifluoromethyl)phenyl]thiophenol (1 g, 5.6 mmol) in THF (5 mL) was treated with NaH (0.24 g, 5.9 mmol, 60% oil dispersion) followed by addition of lactone **9** (1 g, 5.3 mmol) in THF (5 mL) to give after flash chromatography (2% MeOH/CH_2Cl_2 followed by 10% MeOH/1% AcOH/CH_2Cl_2) 1.9 g, 95% yield, of **10h** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.50−7.10 (m, 4H), 5.40 (m, 1H), 4.58 (m, 1H), 3.42 (m, 2H), 1.39 (s, 9H).

Preparation of (*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-[(1-*N*-methyltetrazol-5-yl)thio]propionic Acid (10i). To a solution of 5-mercapto-1-methyltetrazole sodium salt (0.77 g, 5.6 mmol; Aldrich) in THF (9 mL) was added a solution of lactone **9** (1 g, 5.3 mmol) in THF (5 mL), and the mixture was worked up as above to give after flash chromatography (10% MeOH/0.2% AcOH/CH_2Cl_2) 1 g, 63% yield, of **10i** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 6.1 (br s, 1H), 4.50 (m, 1H), 3.81 (s, 3H), overlapping 3.80 (m, 1H), 3.58 (m, 1H), 1.36 (s, 9H).

Preparation of (*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-[(*p*-methoxyphenyl)thio]propionic Acid (10j). To a 0 °C slurry of NaH (0.283 g, 7.07 mmol) in DMF (7 mL) was added *p*-methoxythiophenol (0.96 mL, 7.8 mmol), and the resulting solution was stirred at 0 °C for 20 min. A solution of tosylate **19**[16] (2.64 g, 7.07 mmol) in DMF (13 mL) was added, and stirring was continued at 0 °C for 2 h. The reaction mixture was diluted with Et_2O, washed with water, saturated aqueous K_2CO_3 solution, and brine, and then dried (Na_2SO_4) and concentrated in vacuo to give an oil. Flash chromatography (30% EtOAc/hexanes) gave 2.17 g, 90% yield, of (*S*)-methyl 2-[(*tert*-butoxycarbonyl)amino]-3-[(*p*-methoxyphenyl)thio]propiolate. $[\alpha]^{22}_D$ +20.60°. Anal. C,H,N.

The ester (2.17 g, 6.07 mmol) was dissolved in dioxane (15 mL), and 0.5 M aqueous LiOH (14.6 mL) was added. The mixture was stirred at room temperature for 8 h, and then an additional 2 mL of 0.5 M aqueous LiOH was added and stirring continued to an additional 16 h. The dioxane was removed in vacuo and the residue partitioned between EtOAc and 1 N HCl. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give 1.97 g, 99% yield, of the title acid **10j** as a white powder. ^{1}H-NMR ($CDCl_3$): δ 7.4 (d, J = 9 Hz, 2H), 6.83 (d, J = 9 Hz, 2H), 5.27 (br s, 1H), 4.45 (m, 1H), 3.78 (s, 3H), 3.25 (m, 2H), 1.41 (s, 3H). $[\alpha]^{22}_D$ + 38.18°. Anal. ($C_{15}H_{21}NO_5S$) C,H,N.

Preparation of (*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-[(*p*-chlorophenyl)sulfonyl]propionic Acid (20). As above, NaH (0.285 g, 7.01 mmol) in DMF (10 mL) was treated with *p*-chlorothiophenol (1.08 g, 7.5 mmol) and then with a solution of tosylate **19**[16] (2.65 g, 7.1 mmol) in DMF (10 mL) which gave after workup 2.51 g, 100% yield, of (*S*)-methyl 2-[(*tert*-butoxycarbonyl)amino]-3-[(*p*-chlorophenyl)thio]propiolate as a waxy solid which was used without purification.

The ester (7.1 mmol theoretical) in dioxane (20 mL) was treated with 0.5 M aqueous LiOH (24 mL) for 22 h and then worked up as above to give (*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-[(*p*-chlorophenyl)thio]propionic acid (**10k**). The acid **10k** (7.1 mmol theoretical) was dissolved in MeOH (40 mL) and cooled to 0 °C. A solution of Oxone (5.26 g, 17 mmol equiv) in water (30 mL) was added, and the mixture was allowed to warm slowly to room temperature overnight. The methanol was removed in vacuo and the residue extracted several times with EtOAc. The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give 2.1 g, 81% yield, of the title compound **20** as a white foam. Material was used directly without further purification. ^{1}H-NMR ($CDCl_3$): δ 8.1 (br s, 1H), 7.85 (d, J = 9 Hz, 2H), 7.54 (d, J = 9 Hz, 2H), 5.57 (br d, J = 7 Hz, 1H), 4.64 (m, 1H), 3.83 (t, J = 5 Hz, 2H), 1.39 (s, 9H). $[\alpha]^{22}_D$ +8.19°. Anal. ($C_{14}H_{18}ClNO_6S$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(*tert*-butoxycarbonyl)amino]-3-(benzylthio)propanamide (12a). General Procedure for Coupling D-Amino Acids to Amine Isostere 11. *N*-*t*-BOC-*S*-benzyl-D-cysteine (**10a**) (0.5 g, 1.6 mmol; purchased from Bachem), amino alcohol **11**[5] (0.55 g, 1.6 mmol), and HOBt (0.22 g, 1.6 mmol) were dissolved in THF (5 mL) and DMF (1 mL). The mixture was cooled to 0 °C, and solid DCC (0.33 g, 1.6 mmol) was added. Stirring was continued at 0 °C for 2 h and then at room temperature overnight. The precipitate which formed was removed by filtration and the filter cake washed with EtOAc. The filtrate was diluted with additional EtOAc, washed with saturated aqueous $NaHCO_3$, water, 5% aqueous citric acid, and brine, dried (Na_2SO_4), and concentrated in vacuo to give 1 g of crude coupling product as a white solid. Flash chromatography (2% MeOH/CH_2Cl_2) gave 0.74 g, 73% yield, of the title compound **12a** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.40−7.13 (m, 14H), 6.79 (d, J = 9.0 Hz, 1H), 6.24 (s, 1H), 5.35 (d, J = 7.0 Hz, 1H), 4.30 (m, 1H), 4.18 (m, 1H), 3.75 (m, 1H), 3.62 (s, 2H), 3.03−2.32 (m, 7H), 1.44 (s, 9H), 1.41 (s, 9H). FDMS: M + 1, 634.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(*tert*-butoxycarbonyl)amino]-3-(2-quinolinylthio)propanamide (12b). Acid **10b** (1.8 g, 5.2 mmol), amine **11** (1.8 g, 5.3 mmol), and HOBt (0.7 g, 5.12 mmol) in THF (15 mL) and DMF (2 mL) were treated with DCC (1.1 g, 5.3 mmol) and then worked up as above. Flash chromatography (2% MeOH/CH_2Cl_2) followed by a second flash chromatography (35% EtOAc/toluene) gave 1.8 g, 51% yield, of the title compound **12b** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 8.04 (d, J = 8 Hz, 1H), 7.90 (d, J = 9 Hz, 1H), 7.70 (m, 2H), 7.46 (t, J = 7 Hz, 1H), 7.10−7.38 (m, 10H), 6.85 (d, J = 9 Hz, 1H), 6.02 (br s, 2H), 4.52 (q, J = 5 Hz, 1H), 4.30 (m, 1H), 3.65 (m, 1H), 3.57 (d, J = 4 Hz, 2H), 2.95 (m, 4H), 1.45 (s, 9H), 1.40 (s, 9H). FDMS: M^+, 670.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(*tert*-butoxycarbonyl)amino]-3-(2-naphthylthio)propanamide (12c). Acid **10c** (0.38 g, 1.1 mmol), amine **11** (0.37 g, 1.1 mmol), and HOBt (0.15 g, 1.1 mmol) in THF (5 mL) and DMF (1 mL) were treated with DCC (0.22 g, 1.1 mmol) and then worked up as above. Flash chromatography (2.5% MeOH/CH_2Cl_2) gave 0.48 g, 66% yield, of the title compound **12c** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.75 (m, 4H), 7.50−7.02 (m, 12H), 6.85 (d, J = 9.3 Hz, 1H), 6.25 (s, 1H), 5.44 (d, J = 7.6 Hz, 1H), 4.28 (m, 2H), 3.75 (m, 1H), 3.20 (m, 2H), 3.03−2.70 (m, 5H), 1.44 (s, 9H), 1.35 (s, 9H). Anal. ($C_{39}H_{47}N_3O_5S$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(*tert*-butoxycarbonyl)amino]-3-(phenylthio)propanamide (12d). Acid **10d** (1.9 g, 5.7 mmol), amine **11** (2.0 g, 5.9 mmol), and HOBt (0.8 g, 5.9 mmol) in THF (15 mL) and DMF (2 mL) were treated with DCC (1.2 g, 5.8 mmol) and then worked up as above. Flash chromatography (2.5% MeOH/CH_2Cl_2) gave 2.5 g, 69% yield, of the title compound **12d** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.40−7.15 (m, 14H), 6.55 (d, J = 9.0 Hz, 1H), 5.95 (s, 1H), 5.18 (br s, 1H), 4.30 (m, 1H), 4.15 (m, 1H), 3.73 (m, 1H), 3.10−2.70 (m, 6H), 1.44 (s, 9H), 1.40 (s, 9H). Anal. ($C_{35}H_{45}N_3O_5S$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(*tert*-butoxycarbonyl)amino]-3-(1-naphthylthio)propanamide (12e). Acid **10e** (1.2 g, 3.5 mmol), amine **11** (1.2 g, 3.5 mmol), and HOBt (0.47 g, 3.5 mmol) in THF (10 mL) and DMF (1.5 mL) were treated with DCC (0.71 g, 3.5 mmol) and then worked up as above. Flash chromatography (2% MeOH/CH_2Cl_2 and then 3% MeOH/CH_2Cl_2) gave 1.8 g, 78% yield, of the title compound **12e** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 8.35 (d, J = 8.0 Hz, 1H), 7.90−7.10 (m, 16H), 6.50 (m, 1H), 5.95 (br s, 1H), 5.18 (m, 1H), 4.32 (m, 1H), 4.18 (m, 1H), 3.72 (m, 1H), 3.20−2.75 (m, 6H), 1.45 (s, 9H), 1.39 (s, 9H). FDMS: M^+, 669.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(*tert*-butoxycarbonyl)amino]-3-(2-pyridylthio)propanamide (12f). Acid **10f** (0.88 g, 3 mmol), amine **11** (1.0 g, 3 mmol), and HOBt (0.4 g, 3 mmol) in THF (10 mL) and DMF (1.5 mL) were treated with DCC (0.61 g, 3 mmol) and then worked up as above. Flash chromatography (2% MeOH/CH_2Cl_2 and then 3% MeOH/CH_2Cl_2) gave 1.4 g, 78% yield, of the title compound **12f** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 8.50 (d, J = 7.0 Hz, 1H), 7.40−7.10 (m, 12H), 6.40 (m, 1H), 6.10 (m, 1H), 5.90 (br s, 1H), 4.40 (m, 2H), 3.80 (m, 1H), 3.20−2.80 (m, 6H), 1.48 (s, 9H), 1.38 (s, 9H). FDMS: M + 1, 621. $[\alpha]^{22}_D$ +3.80°.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(*tert*-butoxycarbonyl)amino]-3-[(*p*-fluorophenyl)thio]propanamide (12g). Acid **10g** (1.1 g, 3.5 mmol), amine **11** (1.2 g, 3.5 mmol), and HOBt (0.47 g, 3.5 mmol) in THF (10 mL) and DMF (1.5 mL) were treated with DCC (0.72 g, 3.5 mmol) and then worked up as above. Flash chromatography (3% MeOH/CH_2Cl_2) gave 1.7 g, 77% yield, of the title compound **12g** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.40−7.13 (m, 10H), 6.96 (m, 3H), 6.60 (d, J = 9.0 Hz, 1H), 5.95 (s, 1H), 5.19 (d, J = 7.0 Hz, 1H), 4.28 (m, 1H), 4.07 (m, 1H), 3.72 (m, 1H), 3.10−2.70 (m, 6H), 1.44 (s, 9H), 1.40 (s, 9H). Anal. ($C_{35}H_{44}FN_3O_5S$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(*tert*-butoxycarbonyl)amino]-3-[[*p*-(trifluoromethyl)phenyl]thio]propanamide (12h). Acid **10h** (1 g, 2.7 mmol), amine **11** (0.93 g, 2.7 mmol), and HOBt (0.37 g, 2.7 mmol) in THF (8 mL) and DMF (1 mL) were treated with DCC (0.56 g, 2.7 mmol) and then worked up as above. Flash chromatography (2% MeOH/CH_2Cl_2) gave 1.5 g, 79% yield, of the title compound **12h** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.50 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.36−7.10 (m, 9H), 6.58 (d, J = 9.0 Hz, 1H), 5.96 (br s, 1H), 5.20 (m, 1H), 4.34 (m, 1H), 4.19 (m, 1H), 3.75 (m, 1H), 3.10−2.70 (m, 6H), 1.45 (s, 9H), 1.39 (s, 9H). FDMS: M^+, 687. $[\alpha]^{22}_D$ +11.94°.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(*tert*-butoxycarbonyl)amino]-3-[(1-*N*-methyltetrazol-5-yl)thio]propanamide (12i). Acid **10i** (1 g, 3.3 mmol), amine **11** (1.12 g, 3.3 mmol), and HOBt (0.45 g, 3.3 mmol) in THF (10 mL) and DMF (1.5 mL) were treated with DCC (0.68 g, 3.3 mmol) and then worked up as above. Flash chromatography (3% MeOH/CH_2Cl_2) gave 1.1 g, 52% yield, of the title compound **12i** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.40−7.10 (m, 9H), 7.00 (m, 1H), 5.97 (s, 1H), 5.66 (d, J = 7.0 Hz, 1H), 4.45 (m, 1H), 4.32 (m, 1H), 3.85 (s, 3H), 3.78 (m, 1H), 3.42 (m, 1H), 3.21−3.08 (m, 2H), 3.02−2.78 (m, 3H), 1.44 (s, 9H), 1.38 (s, 9H). Anal. ($C_{31}H_{43}N_7O_5S$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(*tert*-butoxycarbonyl)amino]-3-[(*p*-methoxyphenyl)thio]propanamide (12j). Acid **10j** (1 g, 3.1 mmol), amine **11** (1.02 g, 3 mmol), and HOBt (0.43 g, 3.1 mmol) in THF (15 mL) and DMF (3 mL) were treated with DCC (0.65 g, 3.1 mmol) and then worked up as above. Flash chromatography (25−35% EtOAc/toluene) gave 1.07 g, 55% yield, of the title compound **12j** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.4−7.1 (m, 11H), 6.82 (d, J = 9 Hz, 2H), 6.55 (br d, J = 7 Hz, 1H), 5.98 (br m, 2H), 5.16 (br d, J = 7 Hz, 1H), 4.28 (m, 1H), 4.08 (m, 1H), 3.78 (s, 3H), 3.74 (m, 1H), 3.1−2.7 (m, 5H), 1.48 (s, 9H), 1.40 (s, 9H).

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(*tert*-butoxycarbonyl)amino]-3-[(*p*-chlorophenyl)sulfonyl]propanamide (21). Acid **20** (0.4 g, 1.1 mmol), amine **11** (0.37 g, 1.1 mmol), and HOBt (0.15 g, 1.1 mmol) in THF (4 mL) were treated with DCC (0.23 g, 1.1 mmol) and then worked up as above. Flash chromatography (2.5% MeOH/CH_2Cl_2) gave 0.58 g, 77% yield, of the title compound **21** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.78 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.38−7.10 (m, 9H), 6.32 (br s, 1H), 5.88 (d, J = 7.0 Hz, 1H), 5.63 (d, J = 9.0 Hz, 1H), 4.41 (m, 1H), 4.21 (m, 1H), 3.75 (m, 1H), 3.39 (m, 2H), 3.03−2.75 (m, 4H), 1.43 (s, 9H), 1.39 (s, 9H). FDMS: M^+, 686.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-(acetoxyamino)-3-(phenylthio)propanamide (13d). Acid **22** (0.2 g, 0.83 mmol; purchased from TCl), amine **11** (0.28 g, 0.83 mmol), and HOBt (0.11 g, 0.83 mmol) in THF (5 mL) and DMF (1 mL) were treated with DCC (0.17 g, 0.83 mmol) and then worked up as above. Flash chromatography (step gradient of 1.5% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2) gave, as the more polar isomer on TLC (5% MeOH/CH_2Cl_2), 0.13 g, 27% yield, of the title compound **13d** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.40−7.13 (m, 14H), 6.83 (d, J = 9.2 Hz, 1H), 6.36 (d, J = 7.5 Hz, 1H), 6.10 (s, 1H), 4.45 (m, 1H), 4.31 (m, 1H), 3.75 (m, 1H), 3.10−2.70 (m, 6H), 1.83 (s, 3H), 1.45 (s, 9H). Anal. ($C_{32}H_{39}N_3O_4S$) C,H,N.

The less polar isomer **23**, 0.13 g, 27% yield, was also obtained as a white solid. Anal. ($C_{32}H_{39}N_3O_4S$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-(acetoxyamino)-3-(2-quinolinylthio)propanamide (13b). To a solution of protected amine **12b** (1.8 g, 2.7 mmol) in CH_2Cl_2 (6 mL) was added TFA (6 mL), and the resulting solution was stirred at room temperature for 1 h; then the volatiles were removed in vacuo. The residue was taken up in EtOAc, washed with 5% aqueous NH_4OH solution and brine, dried (Na_2SO_4), and concentrated in vacuo to give 1.5 g of the amine as a white solid. Flash chromatography (step gradient of 3% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2) on 0.5 g of this material gave 0.43 g, 84% yield, of the free amine as a white solid. Anal. ($C_{33}H_{38}N_4O_3S$) C,H,N.

The amine (0.36 g, 0.63 mmol) was dissolved in CH_2Cl_2 (4 mL), and Et_3N (0.175 mL, 1.26 mmol) was added followed by acetyl chloride (0.045 mL, 0.63 mmol) and the resulting solution stirred at room temperature for 30 min. The mixture was diluted with CH_2Cl_2, washed with cold 1 N HCl solution, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (3% MeOH/CH_2Cl_2) gave 0.35 g, 90% yield, of the title *N*-acetyl compound **13b** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 8.00 (d, J = 7.0 Hz, 1H), 7.55 (m, 2H), 7.51 (m, 1H), 7.40−7.14 (m, 12H), 6.15 (m, 1H), 4.63 (m, 1H), 4.32 (m, 1H), 3.79 (m, 1H), 3.53 (m, 1H), 3.10−2.80 (m, 5H), 1.85 (s, 3H), 1.44 (s, 9H). FABMS (M + 1): calcd, 613.2849; found, 613.2876.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-(acetoxyamino)-3-(2-naphthylthio)propanamide (13c). To a solution of protected amine **12c** (3.9 g, 5.8 mmol) in CH_2Cl_2 (10 mL) was added TFA (7 mL), and the resulting solution was stirred at room temperature for 3 h; then the volatiles were removed in vacuo. The residue was taken up in EtOAc, washed with 5% aqueous NH_4OH solution and brine, dried, (Na_2SO_4), and concentrated in vacuo to give 3.4 g of the amine as a white solid. Flash chromatography (2.5% MeOH/CH_2Cl_2 and then 5% MeOH/CH_2Cl_2) gave 1.6 g, 48% yield, of the free amine as a white solid. $[\alpha]^{22}_D$ −16.08°. Anal. ($C_{34}H_{39}N_3O_3S$) C,H,N.

The amine (0.31 g, 0.54 mmol) was dissolved in CH_2Cl_2 (4 mL), Et_3N (0.15 mL, 1.1 mmol) was added followed by acetyl chloride (0.039 mL, 0.54 mmol), and the resulting solution was stirred at room temperature for 30 min. The mixture was diluted with CH_2Cl_2, washed with cold 1 N HCl solution, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (step gradient of 2% MeOH/CH_2Cl_2 to 5% MeOH/CH_2Cl_2) gave 0.32 g, 97% yield, of the title *N*-acetyl compound **13c** as a white

solid. ^{1}H-NMR ($CDCl_3$): δ 7.80−7.70 (m, 4H), 7.45−7.11 (m, 12H), 6.90 (d, J = 9 Hz, 1H), 6.45 (d J = 8 Hz, 1H), 6.08 (br s, 1H), 4.55 (m, 1H), 4.32 (m, 1H), 3.77 (m, 1H), 3.20−2.70 (m, 6H), 1.80 (s, 3H), 1.43 (s, 9H). Anal. ($C_{36}H_{41}N_3O_4S$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-(methylsulfonyl)amino]-3-(benzylthio)propanamide (16a). General Procedure for Deblocking and Preparation of *N*-Methanesulfonyl Analogs. To a solution of protected amine **12a** (0.72 g, 1.14 mmol) in CH_2Cl_2 (4 mL) was added TFA (3 mL), and the resulting solution was stirred at room temperature for 1 h; then the volatiles were removed in vacuo. The residue was taken up in EtOAc, washed with 5% aqueous NH_4OH solution and brine, dried (Na_2SO_4), and concentrated in vacuo to give 0.55 g of the amine as a white solid. Flash chromatography (4% MeOH/CH_2Cl_2 and then 6% MeOH/CH_2Cl_2) gave 0.47 g, 77% yield, of the free amine as a white solid. Anal. ($C_{31}H_{39}N_3O_3S$) C,H,N.

The amine (0.44 g, 0.82 mmol) was dissolved in CH_2Cl_2 (5 mL), Et_3N (0.23 mL, 1.6 mmol) was added followed by methanesulfonyl chloride (0.077 mL, 0.98 mmol), and the resulting solution was stirred at room temperature for 30 min. The mixture was diluted with CH_2Cl_2, washed with cold 1 N HCl solution, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (2.5% MeOH/CH_2Cl_2) gave 0.47 g, 94% yield, of the title *N*-methanesulfonyl compound **16a** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.42−7.17 (m, 14H), 6.78 (d, J = 9.4 Hz, 1H), 5.95 (s, 1H), 5.28 (d, J = 7.7 Hz, 1H), 4.40 (m, 1H), 3.82 (m, 2H), 3.70 (s, 2H), 3.10−2.80 (m, 4H), 2.81 (s, 3H), 2.65 (dd, J = 6, 10 Hz, 1H), 2.43 (dd, J = 6, 10 Hz, 1H), 1.50 (s, 9H). Anal. ($C_{32}H_{41}N_3O_5S_2$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-(2-quinolinylthio)propanamide (16b). The free amine was generated as described above in the preparation of compound **13b**. The amine (1 g, 1.7 mmol) in CH_2Cl_2 (5 mL) was treated with Et_3N (0.49 mL, 3.5 mmol) and methanesulfonyl chloride (0.16 mL, 2.1 mmol) and then worked up as above. Flash chromatography (2% MeOH/CH_2Cl_2) gave impure material which was rechromatographed (40% EtOAc/toluene) to give 0.54 g, 49% yield, of the title compound **16b** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 8.19 (br s, 1H), 7.98 (d, J = 7.0 Hz, 1H), 7.77 (m, 2H), 7.51 (m, 1H), 7.38−7.12 (m, 12H), 5.96 (s, 1H), 4.38 (m, 1H), 4.25 (m, 1H), 3.78 (m, 1H), 3.53 (m, 1H), 3.40−2.83 (m, 5H), 2.78 (s, 3H), 1.42 (s, 9H). Anal. ($C_{34}H_{40}N_4O_5S_2$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-(2-naphthylthio)propanamide (16c). The free amine was generated as described above in the preparation of compound **13c**. The amine (1.1 g, 1.93 mmol) in CH_2Cl_2 (15 mL) was treated with Et_3N (0.54 mL, 3.86 mmol) and methanesulfonyl chloride (0.16 mL, 2.12 mmol) and then worked up as above. Flash chromatography (1.8% MeOH/CH_2Cl_2) gave 1.1 g, 88% yield, of the title compound **16c** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.78 (m, 4H), 7.50−7.10 (m, 12H), 6.96 (d, J = 9 Hz, 1H), 5.96 (br s, 1H), 5.63 (d, J = 8 Hz, 1H), 4.39 (m, 1H), 3.91 (q, J = 7 Hz, 1H), 3.80 (m, 1H), 2.75 (s, 3H), 3.10−2.72 (m, 6H), 1.43 (s, 9H). Anal. ($C_{35}H_{41}N_3O_5S_2$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-(phenylthio)propanamide (16d). Protected amine **12d** (2.4 g, 3.8 mmol) in CH_2Cl_2 (6 mL) was treated with TFA (6 mL) and worked up as above. Flash chromatography (2.5% MeOH/CH_2Cl_2 and then 3.5% MeOH/CH_2Cl_2) gave 1.1 g, 55% yield, of the free amine as a white solid. Anal. ($C_{30}H_{37}N_3O_3S$) C,H,N.

The amine (1 g, 1.9 mmol) in CH_2Cl_2 (5 mL) was treated with Et_3N (0.53 mL, 3.8 mmol) and methanesulfonyl chloride (0.18 mL, 2.3 mmol) and then worked up as above. Flash chromatography (2% MeOH/CH_2Cl_2) gave 0.7 g, 64% yield, of the title compound **16d** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.42−7.15 (m, 14H), 6.83 (d, J = 9.3 Hz, 1H), 5.93 (s, 1H), 5.40 (d, J = 7.7 Hz, 1H), 4.39 (m, 1H), 3.85 (m, 1H), 3.80 (m, 1H), 3.10−2.80 (m, 6H), 2.77 (s, 3H), 1.45 (s, 9H). Anal. ($C_{31}H_{39}N_3O_5S_2 \cdot 0.5H_2O$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-(1-naphthylthio)propanamide (16e). Protected amine **12e** (1.8 g, 2.7 mmol) in CH_2Cl_2 (3 mL) was treated with TFA (3 mL) and worked up as above. Flash chromatography (2.5% MeOH/CH_2Cl_2) gave 0.8 g, 53% yield, of the free amine as a white solid. Anal. ($C_{34}H_{39}N_3O_3S$) C,H,N.

The amine (0.7 g, 1.2 mmol) in CH_2Cl_2 (5 mL) was treated with Et_3N (0.34 mL, 2.4 mmol) and methanesulfonyl chloride (0.1 mL, 1.3 mmol) and then worked up as above. Flash chromatography (1.5% MeOH/CH_2Cl_2 and then 3% MeOH/CH_2Cl_2) gave 0.69 g, 86% yield, of the title compound **16e** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 8.33 (d, J = 7.5 Hz, 1H), 7.90−7.12 (m, 15H), 6.81 (d, J = 8.0 Hz, 1H), 6.00 (m, 1H), 5.40 (m, 1H), 4.40 (m, 1H), 3.93 (m, 1H), 3.81 (m, 1H), 3.20−2.70 (m, 6H), 2.72 (s, 3H), 1.48 (s, 9H). Anal. ($C_{35}H_{41}N_3O_5S_2$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-(2-pyridylthio)propanamide (16f). Protected amine **12f** (1.3 g, 2.1 mmol) in CH_2Cl_2 (4 mL) was treated with TFA (4 mL) and worked up as above. Flash chromatography (step gradient of 2.5% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2) gave 0.84 g, 76% yield, of the free amine as a white solid. $[\alpha]^{22}_D$ −11.21°. The amine (0.76 g, 1.4 mmol) in CH_2Cl_2 (5 mL) was treated with Et_3N (0.4 mL, 2.9 mmol) and methanesulfonyl chloride (0.13 mL, 1.7 mmol) and then worked up as above. Flash chromatography (2% MeOH/CH_2Cl_2 and then 3% MeOH/CH_2Cl_2) gave 0.82 g, 94% yield, of the title compound **16f** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 8.42 (d, J = 7.0 Hz, 1H), 7.84 (d, J = 7.0 Hz, 1H), 7.38−7.03 (m, 11H), 6.20 (br s, 1H), 6.14 (br s, 1H), 4.35 (m, 1H), 4.05 (m, 1H), 3.75 (m, 1H), 3.40−2.70 (m, 6H), 2.80 (s, 3H), 1.44 (s, 9H). Anal. ($C_{30}H_{38}N_4O_5S_2$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-[(*p*-fluorophenyl)thio]propanamide (16g). Protected amine **12g** (1.7 g, 2.67 mmol) in CH_2Cl_2 (5 mL) was treated with TFA (5 mL) and worked up as above. Flash chromatography (2.5% MeOH/CH_2Cl_2 and then 3% MeOH/CH_2Cl_2) gave 0.83 g, 59% yield, of the free amine as a white solid. $[\alpha]^{22}_D$ −5.1°. Anal. ($C_{30}H_{36}FN_3O_3S$) C,H,N.

The amine (0.5 g, 0.93 mmol) in CH_2Cl_2 (5 mL) was treated with Et_3N (0.26 mL, 1.9 mmol) and methanesulfonyl chloride (0.086 mL, 1.1 mmol) and then worked up as above. Flash chromatography (2% MeOH/CH_2Cl_2) gave 0.46 g, 81% yield, of the title compound **16g** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.42−7.18 (m, 11H), 6.99 (t, J = 8.0 Hz, 2H), 6.88 (d, J = 9.3 Hz, 1H), 5.96 (s, 1H), 5.41 (d, J = 7.5 Hz, 1H), 4.39 (m, 1H), 3.80 (m, 2H), 3.10−2.75 (m, 6H), 2.80 (s, 3H), 1.44 (s, 9H). Anal. ($C_{31}H_{38}FN_3O_5S_2$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-[[*p*-(trifluoromethyl)phenyl]thio]propanamide (16h). Protected amine **12h** (1.4 g, 2 mmol) in CH_2Cl_2 (4 mL) was treated with TFA (4 mL) and worked up as above. Flash chromatography (2.5% MeOH/CH_2Cl_2 and then 3% MeOH/CH_2Cl_2) gave 1 g, 83% yield, of the free amine as a white solid. $[\alpha]^{22}_D$ −13.99°. Anal. ($C_{31}H_{36}F_3N_3O_3S$) C,H,N.

The amine (0.87 g, 1.48 mmol) in CH_2Cl_2 (5 mL) was treated with Et_3N (0.41 mL, 3 mmol) and methanesulfonyl chloride (0.14 mL, 1.8 mmol) and then worked up as above. Flash chromatography (2% MeOH/CH_2Cl_2) gave 0.9 g, 91% yield, of the title compound **16h** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.52−7.04 (m, 13H), 6.42 (d, J = 7.0 Hz, 1H), 6.19 (br s, 1H), 6.14 (d, J = 9.0 Hz, 1H), 4.38 (m, 1H), 3.89 (m, 2H), 3.10−2.62 (m, 6H), 2.72 (s, 3H), 1.43 (s, 9H). FABMS (M + 1): calcd, 666.2283; found, 666.2293. Anal. ($C_{32}H_{38}F_3N_3N_3O_5S_2$) H,N; C: calcd, 57.73; found, 58.60.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-[(1-*N*-methyltetrazol-5-yl)thio]propanamide (16i). Protected amine **12i** (1.1 g, 1.76 mmol) in CH_2Cl_2 (5 mL) was treated with TFA (5 mL) and worked up as above. Flash chromatography (4% MeOH/

CH_2Cl_2 and then 6% MeOH/CH_2Cl_2) gave 0.58 g, 63% yield, of the free amine as a white solid. FDMS: M^+, 526. The amine (0.58 g, 1.1 mmol) in CH_2Cl_2 (5 mL) was treated with Et_3N (0.3 mL, 2.1 mmol) and methanesulfonyl chloride (0.1 mL, 1.3 mmol) and then worked up as above. Flash chromatography (3% MeOH/CH_2Cl_2) gave 0.48 g, 73% yield, of the title compound **16i** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.40−7.13 (m, 9H), 5.94 (s, 1H), 5.90 (d, J = 7.5 Hz, 1H), 4.42 (m, 1H), 4.21 (m, 1H), 3.90 (s, 3H), 3.82 (m, 1H), 3.31−2.80 (m, 6H), 2.85 (s, 3H), 1.41 (s, 9H). Anal. ($C_{27}H_{37}N_7O_5S_2$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-[(*p*-methoxyphenyl)thio]propanamide (16j). Protected amine **12j** (1 g, 1.54 mmol) in CH_2Cl_2 (5 mL) was treated with TFA (5 mL) and worked up as above to give 0.8 g, 94% yield, of the free amine as a white solid. FDMS: M^+, 549. The amine (0.8 g, 1.46 mmol) in CH_2Cl_2 (3 mL) was treated with *N*-methylmorpholine (0.32 mL, 2.9 mmol) and methanesulfonyl chloride (0.12 mL, 1.6 mmol) and then worked up as above. Flash chromatography (2.5% MeOH/CH_2Cl_2) gave 0.77 g, 84% yield, of the title compound **16j** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.42−7.20 (11H), 6.85 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 9.2 Hz, 1H), 5.92 (br s, 1H), 5.35 (d, J = 7.4 Hz, 1H), 4.40 (m, 1H), 3.80 (m, 2H), overlapping 3.80 (s, 3H), 3.10−2.78 (m, 6H), 2.82 (s, 3H), 1.48 (s, 9H). Anal. ($C_{32}H_{41}N_3O_6S_2$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-[(*p*-chlorophenyl)sulfonyl]propanamide (18k). Protected amine **21** (0.58 g, 0.84 mmol) in CH_2Cl_2 (3 mL) was treated with TFA (3 mL) and worked up as above. Flash chromatography (step gradient of 1.5% MeOH/CH_2Cl_2 to 5% MeOH/CH_2Cl_2) gave 0.35 g, 70% yield, of the free amine as a white solid. FDMS: M^+, 586. The amine (0.35 g, 0.59 mmol) in CH_2Cl_2 (3 mL) was treated with Et_3N (0.17 mL, 1.2 mmol) and methanesulfonyl chloride (0.055 mL, 0.71 mmol) and then worked up as above. Flash chromatography (1.5% MeOH/CH_2Cl_2 and then 3% MeOH/CH_2Cl_2) gave 0.23 g, 58% yield, of the title compound **18k** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.82 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H), 7.42−7.08 (m, 9H), 6.02 (br s, 1H), 5.80 (d, J = 7.0 Hz, 1H), 4.44 (m, 1H), 4.37 (m, 1H), 3.82 (m, 1H), 3.22−2.72 (m, 6H), 2.92 (s, 3H), 1.48 (s, 9H). FDMS: M^+, 664. Anal. ($C_{31}H_{38}ClN_3O_7S_2$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-(acetoxyamino)-3-(2-quinolinylsulfinyl)propanamide (14b). General Method for the MCPBA-Catalyzed Oxidation to Sulfoxide and/or Sulfone Analogs. To a −78 °C solution of sulfide **13b** (0.15 g, 0.24 mmol) in CH_2Cl_2 (5 mL) was added a solution of MCPBA (0.073 g, 0.23 mmol; Lancaster, 50−55% peracid) in CH_2Cl_2 (2 mL). The resulting solution was stirred at −78 °C for 30 min at which time TLC (5% MeOH/CH_2Cl_2) indicated the reaction was essentially complete. The reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$ solution. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give 0.17 g of a white solid. Flash chromatography (step gradient of 3% MeOH/CH_2Cl_2 to 6% MeOH/CH_2Cl_2) gave 0.07 g, 47% yield, of the title compound **14b** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 8.55 (d, J = 8.5 Hz, 1H), 8.32 (d, J = 9.3 Hz, 1H), 8.05 (m, 3H), 7.93 (t, J = 5.8 Hz, 1H), 7.75 (t, J = 7.0 Hz, 1H), 7.42 (d, J = 7.3 Hz, 1H), 7.30−7.18 (m, 4H), 7.10 (d, J = 7.5 Hz, 2H), 6.98 (d, J = 7.3 Hz, 1H), 6.64 (t, J = 7.6 Hz, 2H), 6.25 (t, J = 7.3 Hz, 1H), 5.08 (m, 1H), 4.33 (m, 1H), 4.03 (m, 1H), 3.10−2.97 (m, 3H), 2.85−2.70 (m, 3H), 1.92 (s, 3H), 1.38 (s, 9H). Anal. ($C_{35}H_{40}N_4O_5S$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-(acetoxyamino)-3-(2-quinolinylsulfonyl)propanamide (15b). A 0 °C solution of sulfide **13b** (0.11 g, 0.18 mmol) in CH_2Cl_2 (5 mL) was treated with a solution of MCPBA (0.11 g, 0.35 mmol) in CH_2Cl_2 (2 mL) and after 30 min at 0 °C worked up as described above. Flash chromatography (4% MeOH/CH_2Cl_2) gave 0.08 g, 67% yield, of the title compound **15b** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 8.40 (d, J = 8.4 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.85 (t, J = 5.8 Hz, 1H), 7.72 (t, J = 5.8 Hz, 1H), 7.33 (m, 2H), 7.20 (m, 6H), 7.00 (t, J = 5.8 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.40 (br s, 1H), 5.03 (m, 1H), 4.23 (m, 1H), 3.81 (m, 1H), 3.50 (m, 1H), 3.10−2.75 (m, 4H), 1.72 (s, 3H), 1.42 (s, 9H). Anal. ($C_{35}H_{40}N_4O_5S$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-(2-quinolinylsulfonyl)propanamide (18b). A 0 °C solution of sulfide **16b** (0.17 g, 0.26 mmol) in CH_2Cl_2 (5 mL) was treated with a solution of MCPBA (0.18 g, 0.52 mmol) in CH_2Cl_2 (2 mL) and after 30 min at 0 °C worked up as described above. Flash chromatography (40% toluene/EtOAc) gave 0.11 g, 61% yield, of the title compound **18b** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 8.44 (d, J = 8 Hz, 1H), 8.30 (d, J = 9 Hz, 1H), 8.10 (d, J = 9 Hz, 1H), 7.90 (m, 2H), 7.72 (t, J = 8 Hz, 1H), 7.40−7.05 (m, 9H), 6.82 (d, J = 7 Hz, 1H), 6.06 (br s, 1H), 4.51 (m, 1H), 4.33 (m, 1H), 3.80 (m, 2H), 3.57 (dd, J = 3, 15 Hz, 1H), 3.12 (dd, J = 4, 14 Hz, 1H), 2.88 (s, 3H), 3.00−2.80 (m, 3H), 1.42 (s, 9H). FABMS (M + 1): calcd, 681.2417; found, 681.2433.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-(2-naphthylsulfinyl)propanamide (17c). A −10 °C solution of sulfide **16c** (1.1 g, 1.7 mmol) in CH_2Cl_2 (10 mL) was treated with a solution of MCPBA (0.48 g, 1.53 mmol) in CH_2Cl_2 (2 mL) and after 30 min at −10 °C worked up as described above. Flash chromatography (step gradient of 2% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2) gave 0.88 g, 86% yield, of the title compound **17c** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 8.24−7.93 (m, 4H), 7.80−7.20 (m, 8H), 7.08 (d, J = 7.5 Hz, 2H), 6.69 (t, J = 7.6 Hz, 2H), 6.49 (t, J = 7.3 Hz, 1H), 6.23 (br s, 1H), 5.80 (d, J = 9.3 Hz, 1H), 4.63 (m, 1H), 4.38 (m, 1H), 3.75 (m, 1H), 3.27 (dd, J = 3.0, 15.0 Hz, 1H), 3.02−2.80 (m, 3H), 2.98 (s, 3H), 2.60 (t, J = 12.4 Hz, 1H), 2.27 (t, J = 12.4 Hz, 1H), 1.43 (s, 9H). $[\alpha]^{22}_D$ +29.34°. FDMS: 664. Anal. ($C_{35}H_{41}N_3O_6S_2$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-(phenylsulfinyl)propanamide (17d). A 0 °C solution of sulfide **17d** (0.1 g, 0.16 mmol) in CH_2Cl_2 (4 mL) was treated with a solution of MCPBA (0.058 g, 0.16 mmol) in CH_2Cl_2 (2 mL) and after 30 min at 0 °C worked up as described above. Flash chromatography (70% EtOAc/toluene and then 85% EtOAc/toluene) gave 0.025 g, 24% yield, of the title compound **17d** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 8.30 (d, J = 10 Hz, 1H), 7.75−7.15 (m, 10H), 7.02 (d, J = 7 Hz, 2H), 6.60 (m, 3H), 6.28 (br s, 1H), 5.70 (d, J = 10 Hz, 1H), 4.53 (t, J = 9 Hz, 1H), 4.30 (m, 1H), 3.67 (q, J = 7 Hz, 1H), 3.25 (dd, J = 4, 14 Hz, 1H), 2.91 (s, 5H), 2.83 (dd, J = 3, 13 Hz, 1H), 2.52 (t, J = 12 Hz, 1H), 1.98 (t, J = 13 Hz, 1 H), 1.42 (s, 9H). Analytical HPLC on Waters C18 μ-Bondapak column eluting with 35% CH_3CN/35% MeOH/0.5% NH_4OAc/H_2O gave a retention time of 4.04 min, 90.5% purity (UV detection at 254 nM). FABMS (M + 1): calcd, 614.2359; found, 614.2387.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-(1-naphthylsulfinyl)propanamide (17e). A −10 °C solution of sulfide **16e** (0.4 g, 0.62 mmol) in CH_2Cl_2 (4 mL) was treated with a solution of MCPBA (0.17 g, 0.56 mmol) in CH_2Cl_2 (2 mL) and after 30 min at −10 °C worked up as described above. Flash chromatography (2.5% MeOH/CH_2Cl_2) gave 0.32 g, 86% yield, of the title compound **17e** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 8.38−8.10 (m, 4H), 7.92 (t, J = 7.5 Hz, 1H), 7.78−7.20 (m, 8H), 6.95 (d, J = 7.5 Hz, 2H), 6.42 (t, J = 7.5 Hz, 2H), 6.27 (br s, 1H), 5.88 (t, J = 7.5 Hz, 1H), 5.80 (d, J = 9.3 Hz, 1H), 4.70 (m, 1H), 4.38 (m, 1H), 3.70 (m, 1H), 3.25 (dd, J = 3.0, 15.0 Hz, 1H), 2.99 (s, 3H), 2.99−2.78 (m, 3H), 2.49 (t, J = 12.4 Hz, 1H), 2.27 (t, J = 12.4 Hz, 1H), 1.41 (s, 9H). FDMS: 664. Anal. ($C_{35}H_{41}N_3O_6S_2$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-(1-naphthylsulfonyl)propanamide (18e). A room temperature solution of sulfoxide **17e** (0.1 g, 0.15 mmol) in CH_2Cl_2 (3 mL) was treated with a solution of MCPBA (0.047 g, 0.15 mmol) in CH_2Cl_2 (1 mL)

and after 30 min at room temperature worked up as described above to give 0.1 g, 97% yield, of the title compound **18e** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 8.62 (d, J = 8.5 Hz, 1H), 8.31 (d, J = 8.5 Hz, 1H), 8.18 (d, J = 8.5 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.90−7.52 (m, 4H), 7.41−7.15 (m, 6H), 7.00 (t, J = 7.5 Hz, 2H), 6.88 (t, J = 7.5 Hz, 1H), 6.13 (br s, 1H), 5.81 (d, J = 8.7 Hz, 1H), 4.64 (m, 1H), 4.37 (m, 1H), 4.86 (m, 1H), 3.40−2.70 (m, 6H), 2.94 (s, 3H), 1.47 (s, 9H). Analytical HPLC on Waters C18 μ-Bondapak column eluting with 70% CH_3CN/0.5% NH_4OAc/H_2O gave a retention time of 2.63 min, 83.1% purity (UV detection at 254 nM). None of the sulfoxide **17e** was detected. FDMS: 679.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-(2-pyridylsulfinyl)propanamide (17f,f′) and (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-(2-pyridylsulfonyl)propanamide (18f). A −10 °C solution of sulfide **16f** (0.25 g, 0.42 mmol) in CH_2Cl_2 (4 mL) was treated with a solution of MCPBA (0.12 g, 0.38 mmol) in CH_2Cl_2 (2 mL) and after 30 min at −10 °C worked up as described above. Flash chromatography (step gradient of 2% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2) gave 0.01 g, 4% yield, of the sulfone **18f** (least polar spot on TLC, 5% MeOH/CH_2Cl_2) as a white solid. ^{1}H-NMR ($CDCl_3$): δ 8.78 (d, J = 7.0 Hz, 1H), 8.10−7.98 (m, 2H), 7.60 (m, 1H), 7.40−7.18 (m, 9H), 6.23 (d, J = 9.0 Hz, 1H), 6.08 (br s, 1H), 4.40 (m, 2H), 3.82 (m, 1H), 3.69 (dd, J = 7.0, 7.0 Hz, 1H), 3.40 (dd, J = 3.0, 15.0, Hz, 1H), 3.18 (dd, J = 3.0, 15.0 Hz, 1H), 3.00−2.82 (m, 3H), 2.90 (s, 3H), 1.48 (s, 9H). FDMS: 631.

Sulfoxide **17f′**, 0.05 g, 21% yield, was the second compound to elute (middle spot on TLC). ^{1}H-NMR ($CDCl_3$): δ 8.75 (d, J = 4.4 Hz, 1H), 8.02 (m, 2H), 7.80 (d, J = 7.5 Hz, 1H), 7.58−7.05 (m, 7H), 6.80 (m, 3H), 6.35 (br s, 1H), 5.91 (d, J = 7.5 Hz, 1H), 4.58 (m, 1H), 4.38 (m, 1H), 3.72 (m, 1H), 3.24 (dd, J = 3.0, 15.0 Hz, 1H), 3.00−2.53 (m, 5H), 2.92 (s, 3H), 1.42 (s, 9H). FDMS: M + 1, 615.

Sulfoxide **17f**, 0.13 g, 54% yield, was the third compound to elute (lowest spot on TLC). ^{1}H-NMR ($CDCl_3$): δ 8.60 (d, J = 4.4 Hz, 1H), 8.00−7.88 (m, 2H), 7.75 (d, J = 7.5 Hz, 1H), 7.41−7.20 (m, 9H), 6.11 (br s, 1H), 5.62 (d, J = 7.5 Hz, 1H), 4.40 (m, 1H), 4.31 (m, 1H), 3.80 (m, 1H), 3.25−2.80 (m, 6H), 2.69 (s, 3H), 1.45 (s, 9H). FABMS (M + 1): calcd, 615.2311; found, 615.2335.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-[(*p*-fluorophenyl)sulfinyl]propanamide (17g). A −78 °C solution of sulfide **16g** (0.22 g, 0.36 mmol) in CH_2Cl_2 (4 mL) was treated with a solution of MCPBA (0.11 g, 0.36 mmol) in CH_2Cl_2 (2 mL) and after 30 min at −78 °C worked up as described above. Flash chromatography (2.5% MeOH/CH_2Cl_2 and then 3% MeOH/CH_2Cl_2) gave 0.13 g, 57% yield, of the title compound **17g** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 8.16 (d, J = 9.5 Hz, 1H), 7.60 (m, 2H), 7.43−7.30 (m, 5H), 7.20 (m, 2H), 7.01 (d, J = 7.3 Hz, 2H), 6.83−6.68 (m, 3H), 6.31 (br s, 1H), 5.95 (d, J = 9.5 Hz, 1H), 4.55 (m, 1H), 4.31 (m, 1H), 3.68 (m, 1H), 3.22 (m, 1H), 2.91 (s, 3H), 2.72 (m, 1H), 2.55 (m, 1H), 2.07 (t, J = 12.6 Hz, 1H), 1.41 (s, 9H). FDMS: M + 1, 632. Anal. ($C_{31}H_{38}FN_3O_6S_2$) C,H,N.

Sulfoxide **18g**, 0.06 g, was also isolated from the reaction mixture.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-[(*p*-fluorophenyl)sulfonyl]propanamide (18g). A 0 °C solution of sulfide **16g** (0.19 g, 0.31 mmol) in CH_2Cl_2 (3 mL) was treated with a solution of MCPBA (0.19 g, 0.62 mmol) in CH_2Cl_2 (2 mL) and after 30 min at 0 °C worked up as described above. Flash chromatography (2.5% MeOH/CH_2Cl_2) gave 0.15 g, 75% yield, of the title compound **18g** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.91 (m, 2H), 7.40−7.02 (m, 11H), 6.11 (br s, 1H), 5.89 (d, J = 8.7 Hz, 1H), 4.45 (m, 1H), 4.33 (m, 1H), 3.80 (m, 1H), 3.20−2.70 (m, 6H), 2.91 (s, 3H), 1.43 (s, 9H). FDMS: M + 1, 648. Anal. ($C_{31}H_{38}FN_3O_7S_2$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-[[*p*-(trifluoromethyl)phenyl]sulfinyl]propanamide (17h). A −10 °C solution of sulfide **16h** (0.35 g, 0.53 mmol) in CH_2Cl_2 (4 mL) was treated with a solution of MCPBA (0.16 g, 0.51 mmol) in CH_2Cl_2 (2 mL) and after 30 min at −10 °C worked up as described above. Flash chromatography (2.5% MeOH/CH_2Cl_2) gave 0.2 g, 57% yield, of the title compound **17h** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.92 (d, J = 8.2 Hz, 2H), 7.69 (d, J = 8.2 Hz, 2H), 7.50−7.20 (m, 5H), 7.03 (d, J = 8.0 Hz, 2H), 6.80 (t, J = 7.0 Hz, 2H), 6.69 (t, J = 7.0 Hz, 1H), 6.20 (br s, 1H), 5.92 (d, J = 9.5 Hz, 1H), 5.78 (d, J = 5.3 Hz, 1H), 4.59 (m, 1H), 4.39 (m, 1H), 3.71 (m, 1H), 3.28 (dd, J = 3.0, 15.0 Hz, 1H), 3.00−2.90 (m, 2H), 2.96 (s, 3H), 2.71 (m, 1H), 2.58 (t, J = 12.5 Hz, 1H), 2.18 (t, J = 12.5 Hz, 1H), 1.45 (s, 9H). FDMS: M + 1, 682. Anal. ($C_{32}H_{38}F_3N_3O_6S_2$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-[(1-*N*-methyltetrazol-5-yl)sulfinyl]propanamide (17i). A −78 °C solution of sulfide **16i** (0.15 g, 0.25 mmol) in CH_2Cl_2 (4 mL) was treated with a solution of MCPBA (0.078 g, 0.25 mmol) in CH_2Cl_2 (2 mL), and after 30 min at −78 °C, the cooling bath was removed and stirring continued for an additional 30 min; then the mixture was worked up as described above. Flash chromatography (2.5% MeOH/CH_2Cl_2 and then 3% MeOH/CH_2Cl_2) gave 0.07 g, 47% yield, of the title compound **17i** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.60 (d, J = 9.3 Hz, 1H), 7.42−7.02 (m, 8H), 6.79 (t, J = 7.0 Hz, 1H), 6.08 (m, 2H), 4.38 (m, 2H), 4.21 (s, 3H), 3.86 (m, 1H), 3.22−2.70 (m, 6H), 2.88 (s, 3H), 1.44 (s, 9H). FDMS: M + 1, 620. Anal. ($C_{27}H_{37}N_7O_6S_2 \cdot 1.5H_2O$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-(acetoxyamino)-3-(2-naphthylsulfonyl)propanamide (15c). General Method for the Oxone-Catalyzed Oxidation of Sulfone Analogs. To a 0 °C solution of sulfide **13c** (0.31 g, 0.51 mmol) in MeOH (6 mL) was slowly added a solution of Oxone (0.37 g, 1.2 mmol equiv) in H_2O (2 mL). The resulting solution was stirred at 0 °C for 15 min and then at room temperature for 4 h at which time TLC (5% MeOH/CH_2Cl_2) indicated the reaction was essentially complete. The reaction mixture was poured into water and extracted several times with $CHCl_3$. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give 0.29 g, 88% yield, of the title compound **15c** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 8.45 (s, 1H), 8.00 (d, J = 9 Hz, 2H), 7.91 (d, J = 8 Hz, 1H), 7.79 (d, J = 7 Hz, 1H), 7.70−6.96 (m, 10H), 6.48 (d, J = 8 Hz, 1H), 6.13 (br s, 1H), 4.81 (m, 1H), 4.22 (m, 1H), 3.79 (m, 1H), 3.40 (m, 1H), 3.18 (m, 1H), 3.08−2.76 (m, 4H), 1.80 (s, 3H), 1.42 (s, 9H). Analytical HPLC on Waters C18 μ-Bondapak column eluting with 35% CH_3CN/35% MeOH/0.5% NH_4OAc/H_2O gave a retention time of 5.7 min, 99% purity (UV detection at 254 nM). FABMS (M + 1): calcd, 644.2794; found, 644.2827. Anal. ($C_{36}H_{41}N_3O_6S \cdot 1.7H_2O$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-(acetoxyamino)-3-(phenylsulfonyl)propanamide (15d). A 0 °C solution of sulfide **13d** (0.07 g, 0.12 mmol) in MeOH (5 mL) was treated with a solution of Oxone (0.079 g, 0.26 mmol equiv) in H_2O (2 mL). After stirring for 15 min at 0 °C and then at room temperature for 4 h, the mixture was worked up as described above to give 0.07 g, 95% yield, of the title compound **15d** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.85 (d, J = 8 Hz, 2H), 7.60 (m, 2H), 7.38−7.00 (m, 11H), 6.62 (d, J = 8 Hz, 1H), 6.35 (br s, 1H), 4.82 (m, 1H), 4.22 (m, 1H), 3.80 (m, 1H), 3.25 (m, 1H), 3.12−2.75 (m, 5H), 1.82 (s, 3H), 1.43 (s, 9H). FDMS: M + 1, 594. Anal. ($C_{32}H_{39}N_3O_6S_2$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-(benzylsulfonyl)propanamide (18a). A 0 °C solution of sulfide **16a** (0.26 g, 0.42 mmol) in MeOH (4 mL) was treated with a solution of Oxone (0.27 g, 0.87 mmol equiv) in H_2O (2 mL). After stirring for 15 min at 0 °C and then at room temperature for 4 h, the

mixture was worked up as described above. Flash chromatography (2.5% MeOH/CH_2Cl_2) gave 0.1 g, 37% yield, of the title compound **18a** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.41−7.10 (m, 15H), 6.00 (br s, 1H), 5.81 (d, J = 9 Hz, 1H), 4.38 (m, 2H), 4.26 (q, J = 4 Hz, 2H), 3.80 (m, 1H), 3.10 (m, 2H), 2.90 (s, 3H), 2.80 (m, 4H), 1.46 (s, 9H). FDMS: M + 1, 644. Anal. ($C_{32}H_{41}N_3O_7S_2$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-(2-naphthylsulfonyl)propanamide (18c). A 0 °C solution of sulfide **16c** (0.34 g, 0.52 mmol) in MeOH (5 mL) was treated with a solution of Oxone (0.39 g, 1.2 mmol equiv) in H_2O (2 mL). After stirring for 15 min at 0 °C and then at room temperature for 4 h, the mixture was worked up as described above. Flash chromatography (2% MeOH/CH_2Cl_2 and then 5% MeOH/CH_2Cl_2) gave 0.2 g, 56% yield, of the title compound **18c** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 8.50 (s, 1H), 8.00 (d, J = 8 Hz, 12H), 7.93 (d, J = 8 Hz, 1H), 7.83 (d, J = 7 Hz, 1H), 7.68 (m, 2H), 7.40−6.92 (m, 10H), 6.04 (br s, 1H), 5.73 (d, J = 8 Hz, 1H), 4.53 (m, 1H), 4.37 (m, 1H), 3.81 (m, 1H), 2.92 (s, 3H), 3.33−2.70 (m, 6H), 1.46 (s, 9H). FDMS: M + 1, 680. Anal. ($C_{35}H_{41}N_3O_7S_2$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-(phenylsulfonyl)propanamide (18d). A 0 °C solution of sulfide **16d** (0.51 g, 0.85 mmol) in MeOH (6 mL) was treated with a solution of Oxone (0.63 g, 2 mmol equiv) in H_2O (2 mL). After stirring for 10 min at 0 °C and then at room temperature for 4 h, the mixture was worked up as described above. Flash chromatography (2% MeOH/CH_2Cl_2) gave 0.47 g, 87% yield, of the title compound **18d** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.88 (d, J = 9.0 Hz, 2H), 7.60 (m, 2H), 7.40−7.04 (m, 9H), 5.95 (br s, 1H), 5.72 (d, J = 7.0 Hz, 1H), 4.39 (m, 2H), 3.81 (m, 1H), 3.31 (m, 1H), 3.15−2.80 (m, 5H), 2.95 (s, 3H), 1.43 (s, 9H). FDMS: M + 1, 630. Anal. ($C_{31}H_{39}N_3O_7S_2$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-[[*p*-(trifluoromethyl)phenyl]sulfonyl]propanamide (18h). A 0 °C solution of sulfide **16h** (0.41 g, 0.62 mmol) in MeOH (5 mL) was treated with a solution of Oxone (0.55 g, 1.8 mmol equiv) in H_2O (2 mL). After stirring for 10 min at 0 °C and then at room temperature for 4 h, the mixture was worked up as described above to give 0.42 g, 97% yield, of the title compound **18h** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 8.02 (d, J = 7.5 Hz, 2H), 7.81 (d, J = 7.5 Hz, 2H), 7.40−7.00 (m, 9H), 6.18 (br s, 1H), 6.01 (d, J = 9.0 Hz, 1H), 5.95 (d, J = 7.0 Hz, 1H), 4.53 (m, 1H), 4.35 (m, 1H), 3.83 (m, 1H), 3.20−2.64 (m, 6H), 2.88 (s, 3H), 1.44 (s, 9H). FDMS: M + 1, 699. Anal. ($C_{32}H_{38}F_3N_3O_7S_2 \cdot 0.8H_2O$) C,H,N.

Preparation of (*S*)-*N*-(1*S*,2*R*)-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(methylsulfonyl)amino]-3-[(*p*-methoxyphenyl)sulfonyl]propanamide (18j). A 0 °C solution of sulfide **16j** (0.24 g, 0.38 mmol) in MeOH (3 mL) was treated with a solution of Oxone (0.34 g, 1.1 mmol equiv) in H_2O (2 mL). After stirring for 10 min at 0 °C and then at room temperature for 3 h, the mixture was worked up as described above to give 0.25 g, 99% yield, of the title compound **18j** as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.82 (d, J = 7.5 Hz, 2H), 7.40−7.00 (m, 11H), 6.19 (br s, 1H), 5.86 (d, J = 7.5 Hz, 1H), 5.80 (br s, 1H), 4.50 (m, 1H), 4.33 (m, 1H), 3.90 (s, 3H), 3.80 (m, 1H), 3.20−2.70 (m, 6H), 2.93 (s, 3H), 1.45 (s, 9H). Analytical HPLC on Waters C18 μ-Bondapak column eluting with 35% MeOH/35% CH_3CN/0.5% NH_4OAc/H_2O gave a retention time of 3.94 min, 98.7% purity (UV detection at 254 nM). FDMS: M + 1, 660. Anal. ($C_{32}H_{41}N_3O_8S_2 \cdot 0.8H_2O$) C,H,N.

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