Aminodiol HIV Protease Inhibitors. Synthesis And Structure−Activity Relationships Of P_1/P_1' Compounds: Correlation between Lipophilicity and Cytotoxicity

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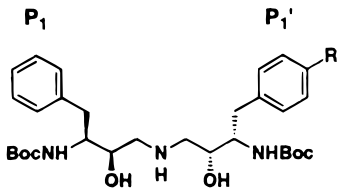
A series of novel aminodiol inhibitors of HIV protease based on the lead compound **1** with structural modifications at P_1' were synthesized in order to reduce the cytotoxicity of **1**. We have observed a high degree of correlation between the lipophilicity and the cytotoxicity of this series of inhibitors. It was found that appropriate substitution at the *para* position of the P_1' phenyl group of **1** resulted in the identification of equipotent (both against the enzyme and in cell culture) compounds (**10l**, **10m**, **10n**, and **15c**) which possess significantly decreased cytotoxicity.

Introduction

Human immunodeficiency virus (HIV), the causative agent of acquired immunodeficiency syndrome (AIDS), encodes an aspartyl protease that processes the gag and gag/pol viral polyproteins into the structural proteins and enzymes of the virus.[1] The demonstration that inactivation of HIV protease prevents infectious virion formation[2] has resulted in intensive investigations into the inhibition of this enzyme as a strategy for the treatment of HIV infection.[3,4]

In an earlier paper,[4a] we disclosed the C_2 symmetric aminodiol **1**, a potent and selective HIV protease inhibitor. Interestingly, **1** demonstrates comparable activity against the isolated enzyme (IC_{50} = 125 nM), HIV-1, and HIV-2 in cell culture (ED_{50} = 80 and 120 nM, respectively), a result which suggests good cell membrane penetration by this compound.[5] In addition, aminodiol **1** shows a promising pharmacokinetic profile in rats, with 40% oral bioavailability and a plasma elimination half-life of 4 h. On the other hand, **1** displays significant cytotoxicity in cell culture (CC_{50} = 8.5 μM), resulting in a modest *in vitro* therapeutic index of *ca.* 100.

During our initial structure−activity studies,[4a] the tyrosine-derived analog **2** was prepared, in which the P_1' phenyl substituent[6] of **1** is replaced by a more polar *p*-phenol moiety. Although this compound displays enzymatic and antiviral activity comparable to **1** (IC_{50} = 100 nM and ED_{50} = 90 nM), it is *ca.* 4-fold less cytotoxic (CC_{50} = 32 μM) than **1**. Thompson and coworkers[7a] have reported that polar substitution on the hydrophobic P_1' side chain of a structurally distinct class of HIV protease inhibitors is tolerated since these substituents are near the exterior surface of the active site and are thus directed into solvent. The effect of these substitutions on cytotoxicity was not disclosed; however, correlations between lipophilicity and cytotoxicity for other classes of drugs have previously been observed.[8] As part of our effort to improve the *in vitro* therapeutic index of aminodiol **1** *via* the reduction of its cytotoxicity, we investigated the effects of P_1' structural modifications of the aminodiols **1** and **2** on both activity and cytotoxicity. We therefore prepared the following: (1) analogs in which the P_1' phenyl group of **1** is replaced with heteroaromatic groups and (2) compounds in which various polar groups are tethered to the P_1'-phenolic hydroxyl group of **2**. In this paper, we report the observation of a significant correlation between lipophilicity and cytotoxicity for these P_1'-modified aminodiol inhibitors and the application of this observation to improve the *in vitro* therapeutic index of these compounds.



1: R = H
2: R = OH

Chemistry

The synthesis of the two regioisomers **7c** and **7d** of the aminodiol **2** followed a standard route starting from 3- and 2-*O*-benzyl-*N*-Boc-L-tyrosine **3c** and **3d**,[9] respectively (Scheme 1). Epoxides **4** were prepared following a four-step protocol:[4a] (1) diazo ketone formation; (2) conversion of the diazo ketone to the corresponding α-halo ketone; (3) reduction of the α-halo ketone to the halohydrin, typically resulting in a 4:1 diastereomeric mixture with the desired (*S*) isomer as the major product; and (4) base-induced epoxide formation. Reaction of the amino alcohol **5**[4a] with epoxides **4c** and **4d** followed by removal of the phenolic benzyl group afforded the required unsymmetrical aminodiols **7c** and **7d**.

Tethered P_1'-substituted analogs were prepared by the routes outlined in Schemes 2 and 3. Our initial

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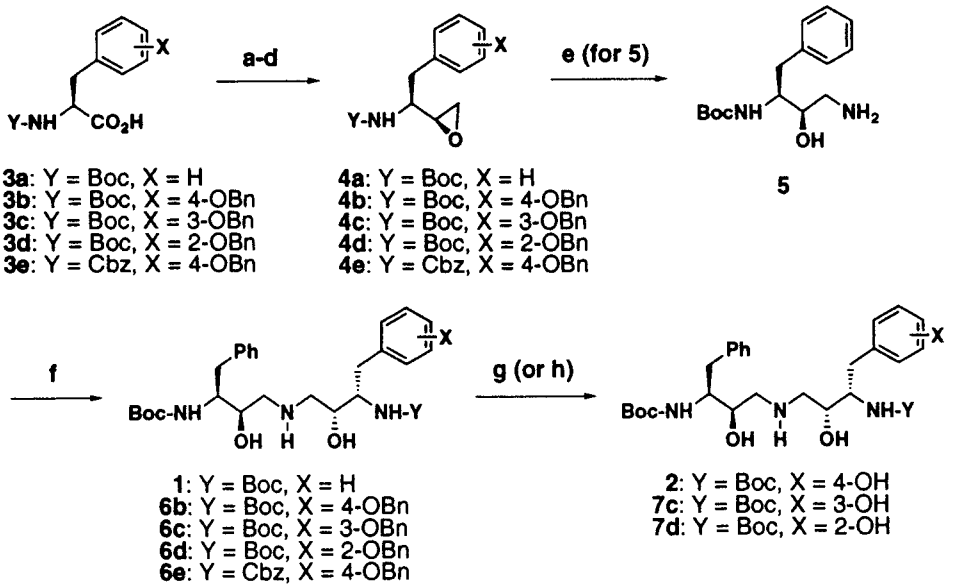
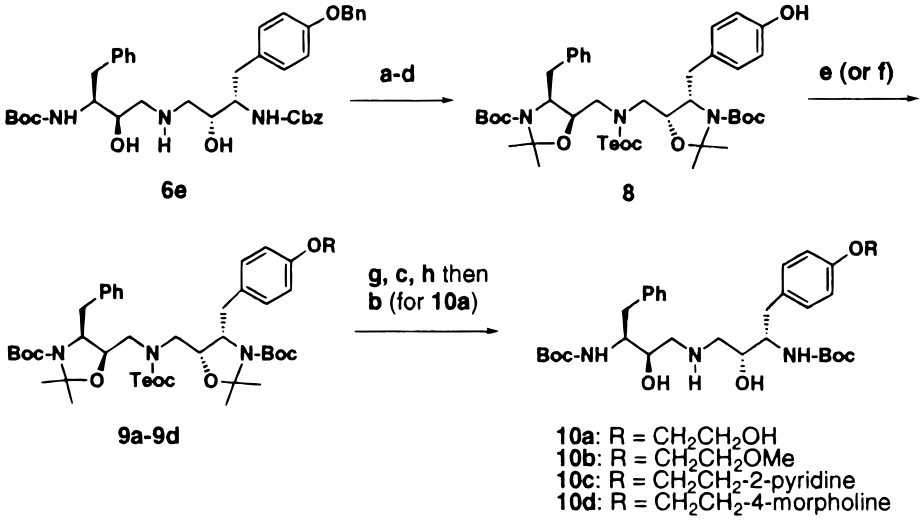
Scheme 1[a]



[a] (a) *i*-BuO_2CCl, 4-methylmorpholine, THF, then CH_2N_2, Et_2O, 0 °C; (b) HCl, dioxane, 0 °C; (c) $NaBH_4$ (4:1 diastereoselectivity); (d) KOH, EtOH; (e) NH_3, MeOH; (f) **4a** (for **1**), or **4c** (for **6c**), or **4d** (for **6d**), or **4e** (for **6e**), MeOH, 50 °C; (g) H_2, $Pd(OH)_2$/C, MeOH; then Boc_2O, Et_3N, MeOH (for **2** from **6e**); (h) H_2, $Pd(OH)_2$/C, MeOH (for **7c** from **6c** and **7d** from **6d**).

Scheme 2[a]



[a] (a) Teoc-Cl, *i*-Pr_2NEt, DMF; (b) H_2, $Pd(OH)_2$/C, MeOH; (c) Boc_2O, Et_3N, MeOH; (d) *p*-TSA, $Me_2C(OMe)_2$, toluene, Δ; (e) ROH, Ph_3P, DEAD, THF (for **10a**: R = CH_2CH_2OBn; for **10b**: R = CH_2CH_2OMe; for **10c**: R = CH_2CH_2-2-pyridine); (f) RCl, K_2CO_3, DMF, Δ (for **10d**: R = CH_2CH_2-4-morpholine); (g) HCO_2H, 0 °C; (h) *n*-Bu_4NF, THF, 55 °C.

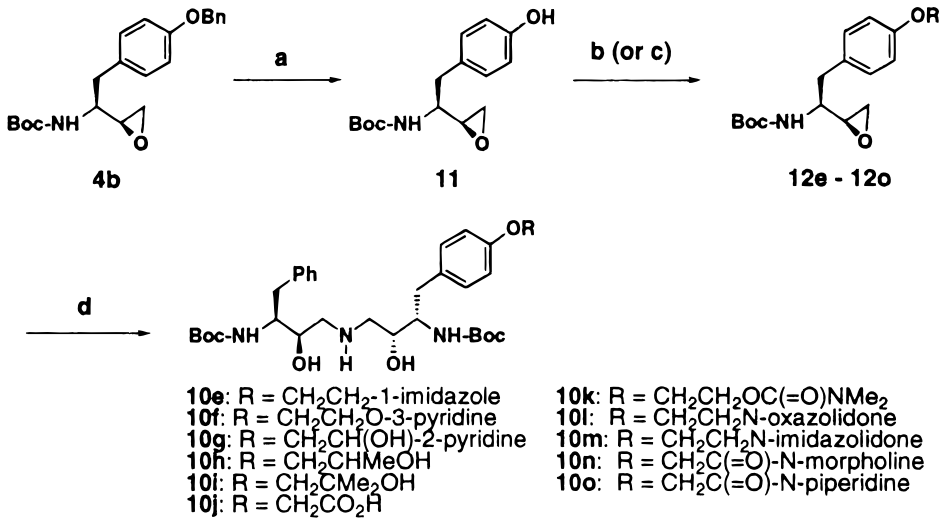
synthesis involved converting the readily available unsymmetric aminodiol **6e**[4a] by a four-step sequence to the key intermediate **8**, wherein the secondary amine and the diol functionalities are protected as the (trimethylsilyl)ethyl (Teoc) carbamate and the *N*,*O*-isopropylidene ketal, respectively. Aryl ethers **9a**−**d** were prepared either by Mitsunobu reaction of **8** with the corresponding alcohol or by alkylation of the potassium phenoxide of **8** with an appropriately functionalized halide. A three-step deprotection/reprotection protocol provided the required analogs **10a**−**d**.

Alternatively, a more efficient sequence to the desired aminodiols **10e**−**o** (Scheme 3) involved coupling of phenol **11** (obtained from carefully controlled hydrogenolysis[10] of benzyl ether **4b**) with an appropriate alcohol (*via* Mitsunobu reaction) or an alkyl halide (under alkylation conditions) to give aryl ethers **12e**−**o**. The functionalized phenoxy epoxides **12e**−**o** were then reacted with amino alcohol **5** to provide aminodiols **10e**−**o**.

For the synthesis of analogs **15a**−**c** (Scheme 4), the unnatural amino acids **13a**−**c** were required. **13a** and **13b** were obtained (see Experimental Section) according to literature methods.[11] The preparation of the unnatural amino acid **13c** is outlined in Scheme 5. The triflate **17**, obtained from *N*-Boc-L-tyrosine methyl ester **16**, was coupled with benzyl acrylate under Heck conditions[12] to give benzyl cinnamate **18** as a single (*E*) isomer. Diester **18** was converted into the *N*-Boc amino acid **13c** in three steps (hydrogenation, EDCI coupling with morpholine, and methyl ester hydrolysis). Epoxides **14a**−**c**, derived from **13a**−**c** according to the general protocol shown in Scheme 1, were individually coupled with amino alcohol **5** to give aminodiol analogs **15a**−**c**.

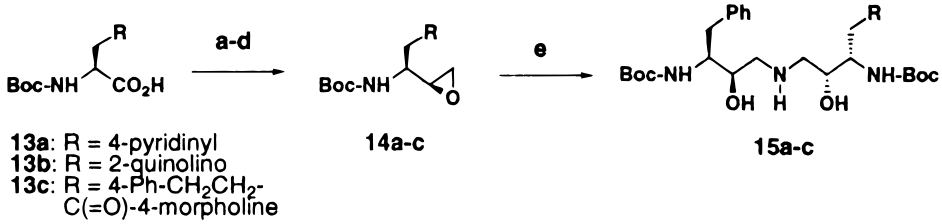
The synthesis of the carbon-linked P_1' analog **23** is shown in Scheme 6. Olefin **20**, obtained from triflate **19** *via* a Pd(0)-catalyzed Stille reaction,[13] was converted to alcohol **21** by ozonolysis and subsequent reduction. Reaction of alcohol **21** with *N*,*N*′-disuccinimidyl carbon-

Scheme 3[a]



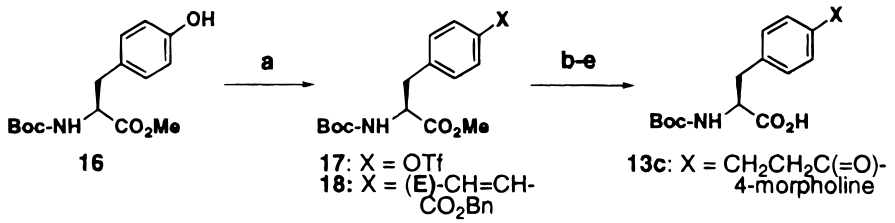
[a] (a) H_2, $Pd(OH)_2$/C, EtOH−EtOAc (4:1); (b) ROH, Ph_3P, DEAD, THF [for **10e**: R = CH_2CH_2-1-imidazole; for **10f**: R = CH_2CH_2O-3-pyridine; for **10h**: R = $CH_2CH(OBn)CH_3$, for **10k**: R = $CH_2CH_2OC(=O)NMe_2$; for **10l**: R = CH_2CH_2N-oxazolidone; for **10m**: R = CH_2CH_2N-imidazolidone]; for **10g**: (i) $HOCH_2CH(OSiMe_2$-*t*-Bu)-2-pyridine, Ph_3P, DEAD, THF; (ii) *n*-$Bu_4N^+F^-$, THF; (c) for **10i**, (i) $BrCH_2CO_2Et$, $NaN(TMS)_2$, THF; (ii) MeMgCl (3×); for **10j**, $BrCH_2CO_2Et$, $NaN(TMS)_2$, THF; for **10n**, $BrCH_2C(=O)$-4-morpholine, $NaN(TMS)_2$, THF; for **10o**, R = $BrCH_2C(=O)$-4-piperidine; (d) **5** (from Scheme 1), MeOH, 50 °C or DMF, 100 °C; for **10h**, (i) **5**, MeOH, 50 °C; (ii) H_2, $Pd(OH)_2$, MeOH; for **10j**, (i) **5**, MeOH, 50 °C; (ii) LiOH, THF, H_2O.

Scheme 4[a]



[a] (a−d) same as (a−d) of Scheme 1; (e) **5** (from Scheme 1), MeOH, 50 °C or DMF, 100 °C.

Scheme 5[a]



[a] (a) $(TfO)_2NPh$, Et_3N, CH_2Cl_2; (b) $CH_2{=}CHCO_2Bn$, $(Ph_3P)_2PdCl_2$, DMF, 90 °C; (c) H_2, $Pd(OH)_2$, MeOH; (d) morpholine, WSC, HOBT, NMM; (e) LiOH, THF−H_2O.

ate followed by treatment with morpholine furnished carbamate **22**.[14] Finally, epoxide **22** was coupled with amino alcohol **5** to furnish aminodiol **23**.

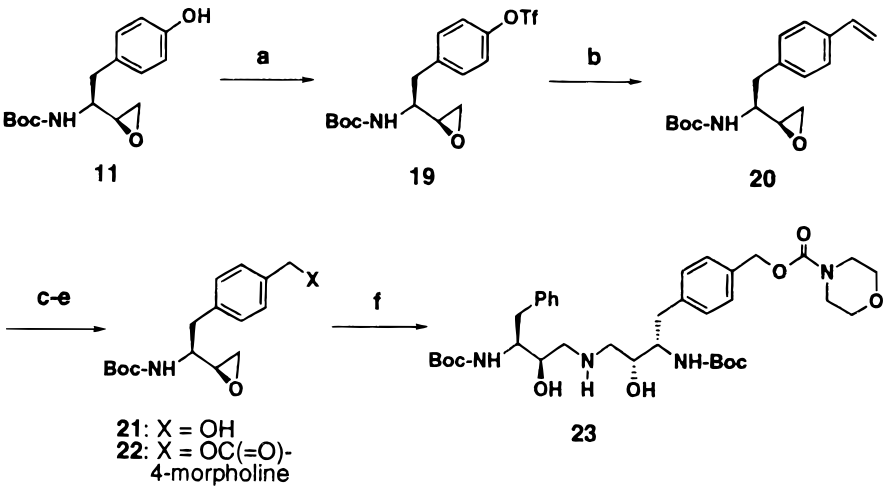
Results and Discussion

We initially examined the replacement of the P_1' phenyl group of **1** with various aromatic heterocycles; two representative examples are shown in Table 1. The quinoline analog **15b**, while showing good potency against the HIV virus, is slightly more cytotoxic than **2**. Although the pyridyl analog **15a** is somewhat less cytotoxic than **2**, it displays decreased enzymatic inhibitory potency (IC_{50}) and antiviral activity (ED_{50}). Our results suggest that replacement of the P_1' phenyl group of **1** with these aromatic heterocycles provides no overall improvement in either potency or cytotoxicity. Next we investigated **7c** and **7d**, the two isomeric phenol analogs of the *p*-tyrosine-derived aminodiol **2**. Among the three regioisomers, the *o*-phenol analog **7d** appears to be least potent, both against HIV protease and in cell culture, and the *p*-phenol analog **2** is least cytotoxic.

Appendage of a polar heteroaromatic imidazole group to the phenol substituent of **2** results in an equipotent analog (**10e**), which shows no improvement in cytotoxicity. The pyridylethyl analog **10c** displays a slight increase in potency and antiviral activity but remains cytotoxic. Increasing the polarity of **10c** *via* insertion of an oxygen atom (**10f**) or incorporation of a secondary hydroxyl group (**10g**) results in diminished (3−10-fold) cytotoxicity with respect to **10c** (Table 2).

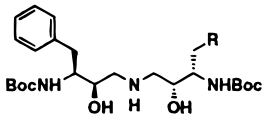
Tethering various alcohol, ether and carboxyl substituents to the *para* position of the P_1 phenol in **2** provided analogs **10a**, **10b**, and **10h**−**j** (Table 3). The hydroxyethoxy analog **10a** shows a small increase in intrinsic potency and decreased cytotoxicity relative to **2**, resulting in an *in vitro* therapeutic index of 933. The less polar methoxyethyl ether analog **10b** is equipotent to **10a** but is more cytotoxic. Neither the secondary nor

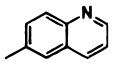
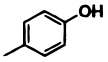
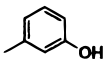
Scheme 6[a]



[a] (a) $(TfO)_2NPh$, Et_3N, CH_2Cl_2; (b) CH_2=$CHSnBu_3$, Pd_2dba_3, LiCl, Ph_3As, NMP; (c) O_3, Me_2S, then $NaBH_4$; (d) $(SuO)_2O$, Et_3N; (e) morpholine, Et_3N; (f) **5** (from Scheme 1), DMF, 100 °C.

Table 1. Structure–Activity at P_1/P_1' Positions of Aminodiols



No.	R	IC_{50}[a] (nM)	ED_{50}[b] (μM)	CC_{50}[c] (μM)	mp, °C	log k'[d]	formula[e] (anal.)
1		125	0.08	8.5	178-180	1.39	$C_{30}H_{45}N_3O_6 \cdot 0.80H_2O$ (CHN)
15a		400	0.54	67	foam	0.80	$C_{30}H_{45}N_3O_7 \cdot 0.70H_2O$ (CHN)
15b		130	0.03	15	105-112	--	$C_{33}H_{46}N_4O_6$ (HR-MS)
2		100	0.09	32	151-153	0.79	$C_{30}H_{45}N_3O_7 \cdot 0.70H_2O$ (CHN)
7c		200	0.15	17	193-196	0.92	$C_{30}H_{45}N_3O_7$ (HR-MS)
7d		300	1.2	17	156-160	1.16	$C_{30}H_{45}N_3O_7 \cdot 1.18H_2O$ (CHN)

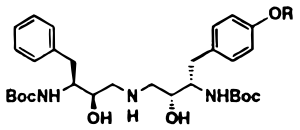
[a] Concentration needed to inhibit cleavage of substrate [V-S-Q-N-(β-naphthylalanine)-P-I-V][5,20a] by 50%. [b] Concentration needed to inhibit virus replication by 50% as determined by an XTT endpoint.[5,20b] Average of at least two determinations. [c] Concentration needed to inhibit cell growth by 50%. [d] The measurement of *k'* values is described in the Experimental Section. [e] Water content was not experimentally determined.

the tertiary hydroxyl analogs **10h** and **10i** provide a significant advantage over the corresponding primary alcohol **10c**. The carboxylic acid **10j** is slightly less potent against the enzyme than **2**, but it is poorly active in cell culture, presumably due to poor cell penetration by this polar compound.

A variety of tethered amide and carbamate analogs were tested (Table 4). The *N*,*N*-dimethylcarbamate analog **10k** displays improved (2-fold) enzymatic and comparable cell culture activity to **2** but is twice as cytotoxic. However, the more polar cyclic carbamate **10l** shows improved intrinsic potency, comparable antiviral activity, and diminished cytotoxicity relative to **1** and **2**. Related analogs, such as urea **10m** and morpholinamide **10n**, demonstrate similar properties. Replacement of the ether linker of **10n** with carbon (**15c**) also is well tolerated. Further permutations of the cyclic carbamate tether of **10n** provides morpholine **10d**, piperidine amide **10o**, and carbamate **23**. Only **23** demonstrates a modest improvement in intrinsic potency and antiviral activity while maintaining a level of cytotoxicity similar to **2**. Most noteworthy among the results delineated in this series is the finding that the polar morpholinamide analog **10n** displays significantly reduced cytotoxicity in comparison to **2**, thereby resulting in an *in vitro* therapeutic index of >1000.[15]

A notable feature of the entire series of P_1'-modified aminodiols is the similar activity displayed by these

Table 2. Structure–Activity at P_1/P_1' Positions of Aminodiols



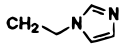
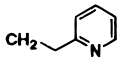
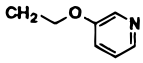
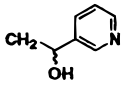
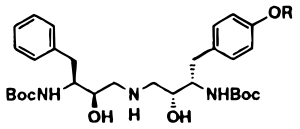
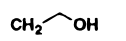
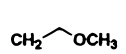
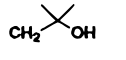
No.	R	IC_{50} (nM)	ED_{50} (μM)	CC_{50} (μM)	mp, °C	log k'	formula (anal.)
2	H	100	0.09	32	151-153	0.79	$C_{30}H_{45}N_3O_7 \cdot 0.70H_2O$ (CHN)
10e		90	0.05	22	130-135 (dec.)	0.96	$C_{35}H_{51}N_5O_7 \cdot 0.52H_2O$ (CHN)
10c		50	0.04	5	125-127	1.39	$C_{37}H_{52}N_4O_7 \cdot 0.53H_2O$ (CHN)
10f		60	0.04	18	127-130	1.25	$C_{37}H_{52}N_4O_8 \cdot 0.80H_2O$ (CHN)
10g		110	0.2	58	68-72 (dec.)	0.81	$C_{37}H_{53}N_4O_8$ (HR-MS)

Table 3. Structure–Activity at P_1/P_1' Positions of Aminodiols

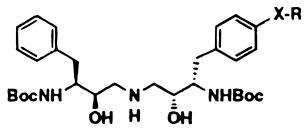


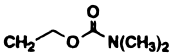
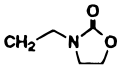
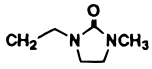
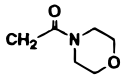
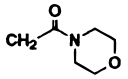
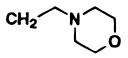
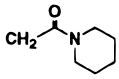
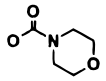
No.	R	IC_{50} (nM)	ED_{50} (μM)	CC_{50} (μM)	mp, °C	log k'	formula (anal.)
2	H	100	0.09	32	151-153	0.79	$C_{30}H_{45}N_3O_7 \cdot 0.70H_2O$ (CHN)
10a		64	0.06	56	152-154	0.82	$C_{32}H_{49}N_3O_8 \cdot 1.16H_2O$ (CHN)
10b		72	0.07	20	136-138	1.19	$C_{33}H_{51}N_3O_8 \cdot 0.83H_2O$ (CHN)
10h		49	0.07	22	145-147	1.02	$C_{33}H_{51}N_3O_8 \cdot 0.94H_2O$ (CHN)
10i		120	0.09	49	85-88	1.22	$C_{34}H_{53}N_3O_8$ (HR-MS)
10j		150	74	>100	182-187 (dec.)	0.12	$C_{32}H_{47}N_3O_9$ (HR-MS)

compounds against HIV protease; i.e., an approximately 3-fold spread is observed among the entire set of compounds. Our working hypothesis is that any substituent tethered to the *para* position of the P_1' phenyl group of the aminodiols is directed into solvent and thus is not directly involved in binding to the enzyme. This speculation is supported by molecular modeling studies on **10n** based on the single-crystal X-ray of analog **1** complexed with HIV protease. The model of **10n** (as shown in Figure 1) was constructed from the enzyme-bound X-ray crystal structure of **1**[16] utilizing the Macromodel program[17] and the Amber force field.[18]

During the course of our investigation, we observed a high correlation between the lipophilicity of the P_1'-modified analogs and their cytotoxicity.[7] Lipophilicity was determined experimentally by the measurement of k' values[19] using a reverse-phase C-18 HPLC column with a pH 7 buffer as eluent.[20] The observed positive correlation ($r^2 = 0.802$, $n = 24$) between the lipophilicity (log k') and cytotoxicity (log CC_{50}) of individual P_1'-substituted analogs[21] is shown in Figure 2. This result suggests that, within this set of compounds, the lipophilicity of a particular analog plays a major role in determining its *in vitro* cytotoxicity (i.e. increased

Table 4. Structure–Activity at P_1/P_1' Positions of Aminodiols



No.	R	X	IC_{50} (nM)	ED_{50} (μM)	CC_{50} (μM)	mp, °C	log k'	formula (anal.)
2	H	O	100	0.09	32	151-153	0.79	$C_{30}H_{45}N_3O_7 \cdot 0.70H_2O$ (CHN)
10k		O	40	0.12	16	128-132	1.24	$C_{35}H_{54}N_4O_9 \cdot 0.54H_2O$ (CHN)
10l		O	40	0.08	52	131-134	0.82	$C_{35}H_{52}N_4O_9 \cdot 0.25H_2O$ (CHN)
10m		O	60	0.05	50	63-66	1.04	$C_{36}H_{55}N_5O_8$ (HR-MS)
10n		O	100	0.1	>100	118-120	0.87	$C_{36}H_{54}N_4O_9 \cdot 0.30H_2O$ (CHN)
15c		CH_2	85	0.21	58	112-113	1.03	$C_{37}H_{56}N_4O_8 \cdot 0.48H_2O$ (CHN)
10d		O	100	0.07	25	140-141	1.18	$C_{36}H_{56}N_4O_8 \cdot 0.42H_2O$ (CHN)
10o		O	90	0.07	17	116-118	1.33	$C_{37}H_{56}N_4O_8 \cdot 0.53H_2O$ (CHN)
23		CH_2	30	0.04	27	116-118	1.23	$C_{36}H_{54}N_4O_9 \cdot 0.47H_2O$ (CHN)

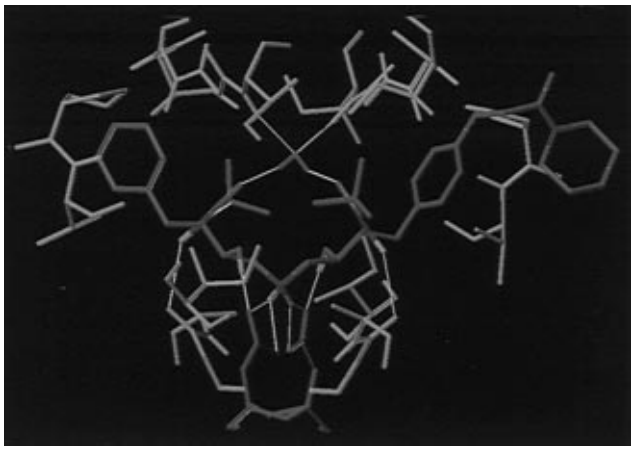


Figure 1. A 3-D representation of the modeled structure of **10n** (shown in green) bound to the active site of HIV protease (shown in light blue) with the morpholinamide group extending into the solvent. The catalytic aspartic acids and water are shown in red. The hydrogen bonds between the inhibitor, the water molecule, and the enzyme are shown in yellow.

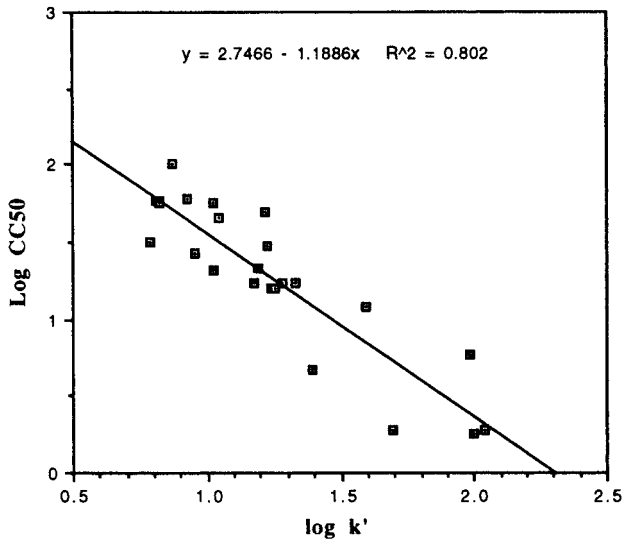
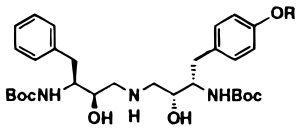


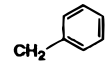
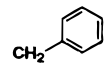
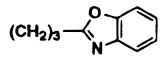
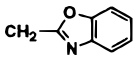
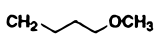
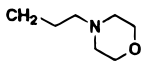
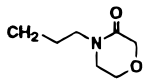
Figure 2. log k' vs log CC_{50} of P_1' aminodiol analogs.

lipophilicity leads to increased cytotoxicity). A similar correlation ($r^2 = 0.703$; $n = 174$) between log CC_{50} and log k' is observed for several additional series of aminodiol inhibitors (Figure 3; the 174 aminodiol analogs in this broad study incorporate a very wide variety of structural features encompassing hydroxylated carbamates,[4b] α-hydroxy amide,[22a] and α-amino amide[22b,c] compounds extended to the S_2 and S_3 subsites).

The delicate balance between polarity, antiviral activity, and cytotoxicity is demonstrated by the observation that very hydrophilic analogs (with low cytotoxicity), such as **15a** and **10j**, are usually poorly active against HIV-infected cells, apparently reflecting their inability to penetrate cell membranes. On the other hand, compounds which are intermediate in polarity, such as **10c**, **10l**, **10m**, and **10n**, generally demonstrated good antiviral activity along with acceptable cytotoxicity (>50 μM).

Table 5. Structure–Activity at P_1/P_1' Positions of Aminodiols



No.	R	IC_{50} (nM)	ED_{50} (μM)	CC_{50} (μM)	mp, °C	log k'	formula (anal.)
i		300	0.17	1.8	159-161	2.00	$C_{35}H_{51}N_3O_7$ (HR-MS)
ii	 (meta-substituted; O-benzyl ether of 7c)	140	0.09	1.9	125-130	2.04	$C_{37}H_{51}N_3O_7 \cdot 0.59H_2O$ (HR-MS)
iii		280	1.50	5.9	121-126	1.98	$C_{40}H_{54}N_4O_8 \cdot 1.28H_2O$ (CHN)
iv		320	0.11	1.9	145-150	1.69	$C_{38}H_{50}N_4O_8 \cdot 1.09H_2O$ (CHN)
v		50	<0.030	12.0	118-125	1.60	$C_{35}H_{55}N_3O_8 \cdot 1.39H_2O$ (CHN)
vi		86	0.04	17.0	122-124	1.28	$C_{37}H_{58}N_4O_8 \cdot 0.39H_2O$ (HR-MS)
vii		80	0.056	59.0	108-111	0.92	$C_{36}H_{54}N_4O_9$ (HR-MS)

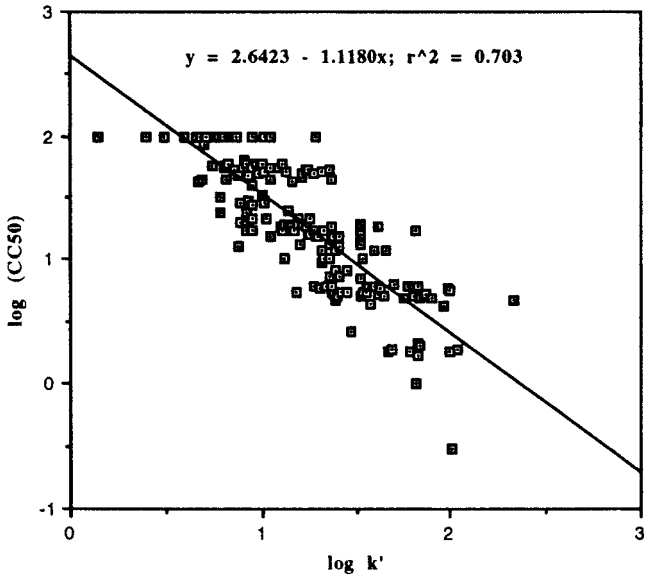


Figure 3. log k' vs log CC_{50} of all classes of aminodiols.

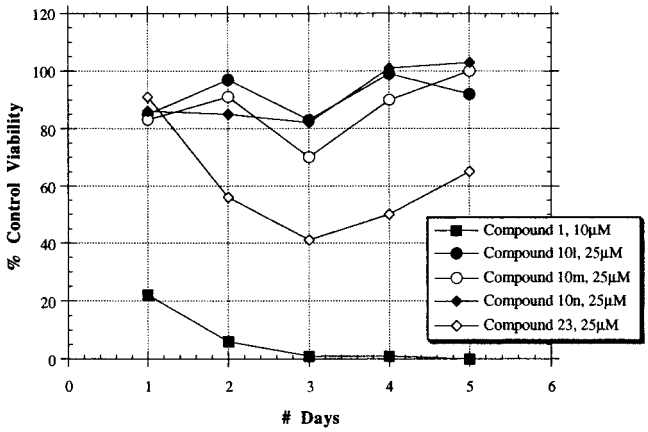


Figure 4. H9 (human T cell lymphoma) cells were cultured in RPMI 1640 medium containing 10% fetal bovine serum, 55 μM 2-mercaptoethanol, 2 mM L-glutamine, and 0.1 mM sodium pyruvate. Compounds were dissolved in DMSO and added to medium for testing at a final concentration of 0.12% DMSO. H9 cells were maintained for a total of 5 days. Each day, viable cell numbers were determined by Trypan Blue dye exclusion. Percent control viability was determined as the number of viable cells grown in the presence of each compound, as compared to the number of viable cells grown in the presence of 0.12% DMSO. Because higher concentrations were extremely cytotoxic, compound **1** was tested at 10 μM. All other compounds were tested at 25 μM.

To further explore the observed aminodiol cytotoxicity, a more rigorous study using a cell growth assay[23a] was undertaken with some representative P_1'-substituted analogs. The cell growth assay involved exposure of H9 cells (a human T-cell lymphoma cell line) to the aminodiol inhibitors, with daily cell counts over a 5-day period. Cells were counted daily, and the number of viable cells was determined by Trypan Blue dye exclusion. By comparison, the standard cytotoxicity studies were performed using replicating CEM-SS cells, which were incubated for 5 days with the inhibitor, with cell viability determined solely on the basis of the activity of a single set of cellular enzymes, the dehydrogenases.[23b] As shown in Figure 4, the increase in cell count in cultures treated with 25 μM aminodiols **10l**, **10m**, and **10n** is virtually identical to that of untreated cultures. In contrast, the cell counts obtained from cultures treated with 25 μM **1** were significantly reduced. With the notable exception of compound **1**, no evidence of cell

membrane rupture was observed upon exposure to the aminodiols over the 5-day period.

In conclusion, we have observed a significant correlation between inhibitor polarity and cytotoxicity within a series of P_1'-modified aminodiols. Appropriate substitution of the *p*-phenol moiety on the tyrosine-derived aminodiol **2** results in modification of the overall polarity of the resulting compounds without affecting intrinsic potency. This led to the identification of analogs (**10l**, **10m, 10n**, and **15c**) with potent antiviral activity and significantly reduced cytotoxicity with respect to **1**. Additional characterization of these compounds will be reported in due course.[24]

Experimental Section

Inhibition of HIV Protease (Enzyme Assay). IC_{50} values are determined by inhibition of the cleavage of the peptidic substrate [V-S-Q-N-(β-naphthylalanine)-P-I-V].[25a] The IC_{50} value represents the concentration of inhibitor required to inhibit cleavage of substrate by 50%. The assay is performed by addition of purified enzyme to a mixture of inhibitor and the above substrate at pH 5.5. The reaction medium is incubated for 30 min at 37 °C followed by quenching with H_3PO_4 and then analyzed by reverse phase HPLC UV (λ = 220 nm) detection.

Antiviral Activity (Cell Culture Assay). The antiviral activity (ED_{50}) is measured by a microculture method which determines the increase in cell viability of an infected culture when drug is added.[25b] ED_{50} is the concentration needed to inhibit virus replication by 50%. The CC_{50} value represents the concentration of inhibitor which results in 50% inhibition in cell growth. The assay is performed in a 96-well format by infecting suspensions of CEM-SS cell (5000 cells/well) with the RF strain of HIV-1. Inhibitors are added at day 1 to both the infected and uninfected control cells. Untreated (infected and uninfected) cells are included as controls. Following incubation for 6 days at 37 °C, viable cells are quantitated by an XTT assay (metabolic reduction of tetrazolium reagent by viable cells to a colored formazan product and measurement of the visible light absorbance at 450 nm).

Cell Growth Assay. H9 cells (human T-cell lymphoma) were maintained in RPMI 1640 medium containing 10% fetal bovine serum, 2 mM L-glutamine, 1 mM sodium pyruvate, and 55 μM 2-mercaptoethanol. Compounds were dissolved in DMSO and added to media at a final concentration of 0.12% DMSO. H9 cells were cultured in 24-well plates at a density of 5×10^4 cells/mL in media containing compounds dissolved in DMSO, or DMSO alone. Cells were allowed to grow for 5 days in the presence of compounds. Every 24 h, cells were stained in 0.2% Trypan Blue dye, and viable cells were counted on a hemacytometer. All cell counts are averages of duplicate wells.

log *k′* Measurements. log *k′* is defined by the equation $\log k' = \log(t_R - t_0/t_0)$, where t_R is the retention time of a peak and t_0 is the elution time of a standard unretained compound ($NaNO_2$). Compounds were eluted isocratically [65:35 MeOH: 10 mM aqueous KH_2PO_4 buffer (pH = 7.0)] at a flow rate of 1.5 mL/min on a Waters Nova-Pak C18 column (150 × 3.9mm; 4 μm particle size; thermostated at 30 °C) with detection at 210 nm. Each compound was injected twice. All retention times were reproducible. With the exception of diastereomeric compounds, the retention times were averaged when they were not identical.

Chemistry. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton and carbon nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were obtained on a GE QE300, JEOL GX-270 or GSX-400 spectrometer; all values are reported in parts per million (δ) from tetramethylsilane (internal reference) unless otherwise specified. Mass spectra were obtained on Finnigan TSQ-4600, JEOL HX-110, or SX-102 mass spectrometers. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by the Analytical Chemistry Department of the Bristol-Myers Squibb Pharmaceutical Research Institute.

Reactions were run under anhydrous conditions under an inert atmosphere (nitrogen or argon) unless otherwise specified. Solvents used were anhydrous unless otherwise specified. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Dichloromethane was distilled from calcium hydride.

Flash chromatography was performed on silica gel (Merck silica gel 60, 230−400 mesh), unless otherwise specified. Analytical thin-layer chromatography (TLC) was run on Merck silica gel 60 F_{254} plates. Analytical high-performance liquid chromatography (HPLC) was performed on a Shimadzu SCL-6B liquid chromatograph using a YMC A-312-3, S-3 120 Å C_{18} column (72 cm × 50 mm i.d.), with a UV wavelength detector set at either 217 or 254 nM. Preparative high-performance liquid chromatography (HPLC) was performed on a SepTech liquid chromatograph using a YMC SH-365-10, S-10 120 Å column, with a UV wavelength detector set at either 217 or 254 nM.

3-BnO-*N*-Boc-L-*m*-tyrosine (3c). L-*m*-Tyrosine (0.473 g, 2.61 mmol) was reacted with di-*tert* butyl dicarbonate (0.613 g, 2.81 mmol) in EtOH (20 mL) overnight at room temperature. Volatiles were removed *in vacuo*, and the residue was dissolved in EtOAc (400 mL) and washed with water (2×), brine (2×), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was chromatographed ($CHCl_3$−MeOH−HOAc, 97:2:1) and then recrystallized from $CHCl_3$ to yield Boc-L-*m*-tyrosine (0.41 g; 59%). ^1H NMR (CD_3OD) δ 1.39 (s, 9H), 3.18 (dd, *J* = 5, 8.9 Hz, 2H), 4.34 (m, 1 H), 6.64−6.71 (m, 3H), 7.08 (t, *J* = 7.7 Hz, 1H).

A mixture of Boc-L-*m*-tyrosine (0.41 g, 1.46 mmol), benzyl bromide (0.51 g, 2.98 mmol) and Cs_2CO_3 (0.97 g, 2.96 mmol) in DMF (2.5 mL) was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (200 mL), and the organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was recrystallized from ether−hexane (1:1) to yield 0.54 g (81%) of *O*-benzyl Boc-L-*m*-tyrosine benzyl ester: ^1H NMR ($CDCl_3$) δ 1.41 (s, 9H), 3.06 (t, *J* = 4.2 Hz, 2H), 4.40−4.64 (m, 1H), 4.97 (s, 2H), 5.11 (d, *J* = 8.1 Hz, 2H), 6.73 (s, 1H), 6.83 (dd, *J* = 2.1 Hz, 1H), 7.20 (d, *J* = 7.2 Hz, 1H), 7.26−7.41 (m, 10H), 7.90 (t, *J* = 7.90 Hz, 1H).

A solution of *O*-Benzyl Boc-L-*m*-tyrosine benzyl ester (1.147 g; 2.49 mmol) in THF (2.5 mL) and 1 N aqueous LiOH (2.5 mL) was stirred at room temperature for 20 min. Additional THF (2.0 mL) was added, and the reaction mixture was stirred for 40 min. The solution was neutralized with aqueous HCl (2.5 mL of a 1 N solution) at 0 °C and then concentrated *in vacuo* to a minimal volume. The aqueous solution was extracted with EtOAc (3 × 50 mL), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was dissolved in saturated aqueous $NaHCO_3$ (15 mL) and washed with ether (3×). The aqueous solution was neutralized with aqueous HCl and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to yield 0.84 g (91%) of *O*-benzyl-Boc-L-*m*-tyrosine (**3c**): ^1H NMR (CD_3OD) δ 1.37 (s, 9H), 3.00 (dd, *J* = 4.9, 9.1 Hz, 2H), 4.33 (m, 1H), 5.05 (s, 2H), 6.80-6.89 (m, 3H), 7.15−7.44 (m, 6H).

[*S*-(*R,*R**)]-[2-[4-(Benzyloxy)phenyl]-1-oxiranylethyl]-carbamic Acid, 1,1-Dimethylethyl Ester (4b). 4b** was prepared according to the previously reported[4a] general procedure using 4-*O*-benzyl-*N*-Boc-L-tyrosine (**3b**) as starting material: ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H), 2.71−2.97 (m, 5H), 3.64 (bs, 1H), 4.43 (bs, 1H), 5.06 (s, 2H), 6.93 (d, *J* = 8.55 Hz, 2H), 7.13 (d, *J* = 8.55 Hz, 2H), 7.30−7.49 (m, 5H).

[*S*-(*R,*R**)]-[2-[3-(Benzyloxy)phenyl]-1-oxiranylethyl]-carbamic Acid, 1,1-Dimethylethyl Ester (4c). 4c** was prepared according to the previously reported general procedure[4a] using 3-*O*-benzyl-*N*-Boc-L-tyrosine (**3c**) as starting material: ^1H NMR ($CDCl_3$) δ 1.31 (s, 9H), 2.64−2.88 (m, 4H), 3.60 (m, 1 H), 4.44 (br d, *J* = 8.1 Hz, 1H), 4.96 (s, 2H), 6.72−6.79 (m, 3H), 7.11−7.36 (m, 6H).

[[*S*-(*R,*R**)]-[2-[2-(Benzyloxy)phenyl]-1-oxiranylethyl]-carbamic Acid, 1,1-Dimethylethyl Ester (4d). 4d** was prepared by a procedure analogous to that for **4a** starting from 2-*O*-benzyl-*N*-Boc-L-tyrosine (**3d**):[9] ^1H NMR (CD_3OD) δ 1.31 (s, 9H), 2.58−2.75 (m, 3H), 2.90 (m, 1H), 3.09 (dd, *J* = 4.5,

13.5 Hz, 1H), 3.80 (m, 1H), 5.11 (s, 2H), 6.86 (dt, $J_d = 1.0$ Hz $J_t = 7.4$ Hz, 1H), 6.98 (d, $J = 8.4$ Hz, 1H), 7.16 (d, $J = 7.3$, 1.0 Hz, 2 H), 7.25-7.42 (m, 3H), 7.49 (d, $J = 7.3$ Hz, 2H).

[*S*-(*R,*R**)]-[2-[4-(Benzyloxy)phenyl]-1-oxiranylethyl]-carbamic Acid, Benzyl Ester (4e). 4e** was prepared by a procedure analogous to that for **4a** starting from 4-*O*-benzyl-*N*-Cbz-L-tyrosine (**3e**): ^{1}H NMR ($CDCl_3$) δ 2.65−2.90 (m, 5H), 3.71 (m, 1H), 4.68 (br s, 1H), 5.03 (s, 2H), 5.04 (s, 2H), 6.91 (d, $J = 8.5$ Hz, 2H), 7.11 (d, $J = 8.5$ Hz, 2H), 7.25−7.44 (m, 10H).

[*S*-(*R,*R**)]-[2-phenyl-1-(2-amino-1-hydroxyethyl)ethyl]carbamic Acid, 1,1-Dimethylethyl Ester (5).** A solution of **4a** (15.0 g, 56.96 mmol) in EtOH (350 mL) was added, with stirring, over 1 h to NH_4OH (350 mL) at 0 °C. NH_3 gas was bubbled through the reaction mixture during the addition and for 1 h afterward. The reaction mixture was allowed to warm to room temperature and stirred overnight. The resulting slurry was diluted with EtOAc (800 mL), and the organic layer was washed with brine (3×) and dried ($MgSO_4$). Concentration *in vacuo*, followed by trituration with 10% *i*-PrOH−EtOAc (overnight stirring), afforded **5** (4.37 g) as a white solid. The mother liquors were concentrated *in vacuo* and triturated again as above to give an additional quantity of **5** (5.73 g; 63% total yield): ^{1}H NMR (CD_3OD) δ 1.29 (s, 9H), 2.55 (dd, $J =$ 10.5, 3.5 Hz, 1H), 2.63 (dd, $J = 7$, 13.5 Hz, 1H), 2.76 (dd, $J =$ 3, 13.5 Hz, 1H), 3.11 (dd, $J = 3$, 13.5 Hz, 1H), 3.40 (m, 1H), 3.65 (m, 1H), 7.10−7.30 (m, 5H).

Preparation of Aminodiols 6b−e. The general method by which aminodiols **6b−e** were synthesized has previously been described.[4a]

[1*S*-[1*R,2*S**(2*S**,3*R**)]]-[3-[[3-[[(1,1-Dimethylethoxy)-carbonyl]amino]-2-hydroxy-4-[4-(benzyloxy)phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (6b):** ^{1}H NMR (DMSO-d_6, 70 °C) δ 1.27 (s, 18H), 2.46−2.72 (m, 4H), 2.86−3.01 (m, 2H), 3.03−3.18 (m, 2H), 3.42−3.66 (m, 4H), 5.05 (s, 2H), 6.35 (br s, 1H), 6.87 (d, $J = 8.55$ Hz, 2H), 7.09 (d, $J = 8.55$ Hz, 2H), 7.10−7.46 (m, 10H). ^{13}C NMR (DMSO-d_6, 70 °C) δ 28.2, 35.2, 36.2, 52.2, 55.2, 69.4, 71.3, 71.4, 77.4, 79.1, 114.5, 125.5, 127.4, 127.6, 127.8, 128.3, 129.1, 130.0, 131.9, 137.4, 139.6, 155.2, 156.7. Anal. ($C_{37}H_{51}N_3O_7$) C, H, N.

[1*S*-[1*R,2*S**(2*S**,3*R**)]]-[3-[[3-[[(1,1-Dimethylethoxy)-carbonyl]amino]-2-hydroxy-4-[3-(benzyloxy)phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (6c):** ^{1}H NMR (DMSO-d_6, 60 °C) δ 1.25 (s, 9H), 1.26 (s, 9H), 2.52−2.64 (m, 6H), 2.92−3.00 (m, 2H), 3.47−3.57 (m, 4H), 5.04 (s, 2H), 6.76−6.80 (m, 1H), 6.88 (br s, 1H), 7.10−7.42 (m, 11H); ^{13}C NMR (CD_3OD) δ 28.7, 28.8, 37.9, 52.9, 56.8, 70.8, 72.7, 79.9, 80.0, 113.5, 117.0, 123.1, 127.0, 128.5, 128.8, 129.1, 129.4, 130.1, 130.4, 138.7, 140.1, 141.7, 157.9, 158.0, 160.0.

[1*S*-[1*R,2*S**(2*S**,3*R**)]]-[3-[[3-[[(1,1-Dimethylethoxy)-carbonyl]amino]-2-hydroxy-4-[2-(benzyloxy)phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (6d):** ^{1}H NMR (DMSO-d_6, 70 °C) δ 1.27 (s, 18H), 2.54−3.05 (m, 6H), 3.54−3.84 (m, 4H), 5.1 (s, 2H), 7.1−7.55 (m, 14H); ^{13}C NMR (DMSO-d_6) δ 27.8, 30.5, 35.6, 50.7, 53.2, 56.0, 69.3, 77.4, 118.0, 119.9, 125.4, 126.8, 127.2, 127.5, 128.0, 128.7, 130.3, 137.1, 138.8, 154.9, 156.2. Anal. ($C_{37}H_{51}N_3O_7$) C, H, N.

[1*S*-[1*R,2*S**(2*S**,3*R**)]]-[3-[[3-[[(Benzyloxy)carbonyl]-amino]-2-hydroxy-4-[4-(benzyloxy)phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1, 1-dimethylethyl ester (6e):** ^{1}H NMR (DMSO-d_6, 70 °C) δ 1.26 (s, 9H), 2.50−2.82 (m, 6H), 2.96 (m, 2H), 3.50−3.69 (m, 4H), 4.82 (br s, 1H), 4.92 (m, 2H), 5.05 (s, 2H), 6.41 (br s, 1H), 6.87 (d, $J = 8.55$ Hz, 2H), 7.11 (d, $J = 8.55$ Hz, 2H), 7.13−7.48 (m, 15H); ^{13}C NMR (DMSO-d_6) δ 28.1, 35.0, 36.0, 51.8, 55.0, 56.0, 64.7, 69.1, 70.8, 77.3, 114.2, 125.6, 1127.1, 127.4, 127.5, 127.7, 127.8, 128.1, 128.3, 129.0, 130.0, 131.4, 137.2, 137.3, 139.5, 155.2, 155.8, 156.5; MS (Fab) 684$^+$ (M + H)$^+$. Anal. ($C_{40}H_{49}N_3O_7$) C, H, N.

[1*S*-[1*R,2*S**(2*S**,3*R**)]]-[3-[[3-[[(1,1-Dimethylethoxy)-carbonyl]amino]-2-hydroxy-4-(3-hydroxyphenyl)butyl]-amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic Acid, 1,1-Dimethylethyl Ester (7c).** A mixture of **6c** (0.177 g, 0.177 mmol) and 20% $Pd(OH)_2$/C in MeOH was stirred under the hydrogen atmosphere. After filtration (through a 45 μm Nylon filter), concentration of the filtrate *in vacuo*, and chromatography (CH_2Cl_2−MeOH−NH_4OH, 90:10:1), **7c** (53 mg; 51%) was obtained as a white solid: ^{1}H NMR (CD_3OD, 50 °C) δ 7.32−7.01 (m, 6H), 6.75−5.99 (m, 3H), 3.85−3.65(m, 4H), 3.0−3.18 (m, 4H), 2.83-2.92 (m, 2H), 2.53−2.64 (m, 2H), 1.58−1.60 (br d, 18H); ^{13}C NMR (CD_3OD, 50 °C) δ 28.7, 37.8, 52.5, 56.7, 56.8, 71.4, 71.5, 80.1, 80.2, 114.1, 117.4, 121.7, 127.1, 129.2, 130.1, 130.4, 139.9, 158.1, 158.2 (three aliphatic and two aromatic signals unresolved); accurate mass measurement (M + H)$^+$ calcd for $[C_{37}H_{52}N_3O_7]^+$ 560.3336, found 560.3343 ($\Delta_{ppm} = 1.3$).

[1*S*-[1*R,2*S**(2*S**,3*R**)]]-[3-[[3-[[(1,1-Dimethylethoxy)-carbonyl]amino]-2-hydroxy-4-(2-hydroxyphenyl)butyl]-amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic Acid, 1,1-Dimethylethyl Ester (7d). 7d** was prepared from **6d** in the same manner as **7c** from **6c**: ^{1}H NMR (CD_3OD, 55 °C) δ 1.32 (s, 18H), 2.58−2.78 (m, 2H), 2.84−3.15 (m, 6H), 3.68−3.8 (m, 3H), 6.72−7.40 (m, 9H); ^{13}C NMR (CD_3OD) δ 28.7, 31.8, 37.8, 52.5, 56.0, 56.8, 72.0, 80.3, 115.9, 120.6, 125.9, 127.2, 128.6, 129.3, 130.4, 132.4, 140.0., 156.6, 158.3, 158.4. Anal. $C_{30}H_{45}N_3O_7$ (C, H, N).

[4*S*-[4α,5α(4*R,5*S**)]]-5-[[[[3-[(1,1-Dimethylethoxy)carbonyl]-4-[(4-hydroxyphenyl)methyl]-2,2-dimethyl-5-oxazolidinyl]methyl][[2-(trimethylsilyl)ethoxy]carbonyl]amino]methyl]-2,2-dimethyl-4-(phenylmethyl)-3-oxazolidinecarboxylic acid, 1,1-Dimethylethyl Ester (8).** To a 0 °C solution of **6e** (420 mg, 0.61 mmol) in DMF (5.0 mL) was added *N*,*N*′-diisopropylethylamine (171 μL, 0.98 mmol), followed by (trimethylsilyl)ethyl chloroformate (133 mg, 0.74 mmol). The mixture was stirred for 2 h at 0 °C. Water was then added, and the aqueous phase was extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give an oil. This was purified by flash chromatography ($CHCl_3$−EtOAc, 10:1 to 4:1) to give the Teoc carbamate diol (468 mg; 92%) as a colorless oil.

A suspension of the above diol (278 mg, 0.34 mmol) and 20% $Pd(OH)_2$/C (85 mg) in EtOH (4 mL) was stirred under an atmosphere of H_2 overnight. Filtration and concentration *in vacuo* gave the aminodiol as a colorless oil.

The mixture of the above aminodiol (0.34 mmol), di-*tert*-butyl dicarbonate (98 μL, 0.43 mmol), and Et_3N (71 μL, 0.51 mmol) in MeOH (5 mL) was stirred for 4 h. Concentration *in vacuo* followed by chromatography (CH_2Cl_2−MeOH, 100:0 to 97:3) afforded the bis-Boc diol (211 mg; 90%) as a colorless oil.

A mixture of the above aminodiol (211 mg, 0.30 mmol), 2,2-dimethoxypropane (250 mg, 2.4 mmol), and *p*-TsOH (1.5 mg) in benzene (1.6 mL) was refluxed for 3 h in a Dean−Stark apparatus. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, and dried (Na_2SO_4). Concentration *in vacuo* followed by flash chromatography (hexane−EtOAc, 10:1 to 5:1) afforded **8** (231 mg; 98%) as a white foam. ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 9H), 0.95 (m, 2H), 1.25−1.94 (m, 30H), 2.81−3.06 (m, 4H), 3.20−3.64 (m, 4H), 4.04−4.38 (m, 6H), 6.65−7.40 (m, 11H).

Preparation of Aminodiols 10a−d (*via* Fully Protected Intermediate 8): (a) Mitsunobu Reaction (General Procedure). To a mixture of **8** (1.0 equiv), alcohol (2.0 equiv), and Ph_3P (2.0 equiv) in THF (a 0.5 M solution of **8**) was added dropwise diethyl azodicarboxylate (2.0 equiv). The resulting yellow-orange solution was stirred at room temperature overnight. Concentration *in vacuo* followed by flash chromatography (hexane−ethyl acetate) on silica gel afforded the corresponding ether.

[4*S*-[4α,5α(4*R,5*S**)]]-5-[[[[3-[(1,1-Dimethylethoxy)carbonyl]-4-[[4-[2-(phenylmethoxy)ethoxy]phenyl]methyl]-2,2-dimethyl-5-oxazolidinyl]methyl][[2-(trimethylsilyl)-ethoxy]carbonyl]amino]methyl]-2,2-dimethyl-4-(phenylmethyl)-3-oxazolidinecarboxylic Acid, 1,1-Dimethylethyl Ester (9a).** Flash chromatography (hexane−ethyl acetate, 10:1 to 8:1) after the Mitsunobu reaction afforded **9a** (251 mg, 86%) as a white foam. ^{1}H NMR ($CDCl_3$) δ 0.02 (s, 9H), 0.93 (m, 2H), 1.30−1.80 (m, 30H), 2.75−3.02 (m, 4H), 3.20−3.60 (m, 4H), 3.80−3.90 (m, 2H), 4.05−4.37 (m, 9H), 4.66 (s, 2H), 6.80−6.90 (m, 2H), 7.10−7.40 (m, 12H).

[4*S*-[4α,5α(4*R,5*S**)]]-5-[[[[3-[(1,1-Dimethylethoxy)carbonyl]-4-[[4-(2-methoxyethoxy)phenyl]methyl]-2,2-dimethyl-5-oxazolidinyl]methyl][[2-(trimethylsilyl)ethoxy]carbonyl]amino]methyl]-2,2-dimethyl-4-(phenylmethyl)-3-oxazolidinecarboxylic Acid, 1,1-Dimethylethyl Ester (9b).** Flash chromatography (hexane−ethyl acetate, 10:1 to 7:1) after the Mitsunobu reaction afforded **9b** (225 mg, 84%) as a white foam. ^{1}H NMR ($CDCl_3$) δ 0.02 (s, 9H), 0.80−1.00 (m, 2H), 1.24−1.85 (m, 30H), 2.74−3.06 (m, 4H), 3.19−3.58 (m, 4H), 3.47 (s, 3H), 3.72−3.82 (m, 2H), 4.02−4.36 (m, 9H), 6.79−6.92 (m, 2H), 7.11−7.38 (m, 7H).

[4*S*-[4α,5α(4*R,5*S**)]]-5-[[[[3-[(1,1-Dimethylethoxy)carbonyl]-4-[[4-[2-(2-pyridinyl)ethoxy]phenyl]methyl]-2,2-dimethyl-5-oxazolidinyl]methyl][[2-(trimethylsilyl)ethoxy]carbonyl]amino]methyl]-2,2-dimethyl-4-(phenylmethyl)-3-oxazolidinecarboxylic Acid, 1,1-Dimethylethyl Ester (9c).** Flash chromatography (hexane−ethyl acetate, 4:1) after the Mitsunobu reaction afforded **9c** (143 mg, 69%) as a colorless oil: ^{1}H NMR (CD_3OD) δ 0.03 (s, 9H), 0.84−1.06 (m, 2H), 1.28−1.79 (m, 30H), 2.76−3.00 (m, 4H), 3.26 (t, J = 6.4 Hz, 2H), 3.32−3.54 (m, 4H), 4.12−4.39 (m, 8H), 6.87 (d, J = 7.3 Hz, 2H), 7.13−7.38 (m, 8H), 7.43 (d, J = 7.7 Hz, 1H), 7.79 (m, 1H), 8.49 (d, J = 5.1 Hz, 1H).

(b) Alkylation: [4*S*-[4α,5α(4*R,5*S**)]]-5-[[[[3-[(1,1-Dimethylethoxy)carbonyl]-4-[[4-[4-morpholinyl)ethoxy]phenyl]methyl]]-2,2-dimethyl-5-oxazolidinyl]methyl][[2-(trimethylsilyl)ethoxy]carbonyl]amino]methyl]-2,2-dimethyl-4-(phenyl]methyl)-3-oxazolidinecarboxylic Acid, 1,1-Dimethylethyl Ester (9d).** A mixture of **8** (200 mg, 0.26 mmol), 2-(chloroethyl)morpholine (191 mg, 1.28 mmol), and powdered K_2CO_3 (88 mg, 0.64 mmol) in DMF (1.0 mL) was heated at 100 °C for 14 h. The mixture was diluted with EtOAc, washed (H_2O, saturated aqueous $NaHCO_3$, brine), and dried (Na_2SO_4). Concentration *in vacuo* followed by flash chromatography (CH_2Cl_2−MeOH−NH_4OH, 100:0:0 to 99:1:0.1) afforded **9d** (163 mg, 71%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 9H), 0.82−1.03 (m, 2H), 1.29−1.83 (m, 30H), 2.51−2.68 (m, 4H), 2.72-3.03 (m, 6H), 3.18−3.62 (m, 4H), 3.76 (t, J = 4.7 Hz, 4 H), 4.01−4.38 (m, 7H), 6.76−6.92 (m, 2H), 7.08−7.40 (m, 7H).

(c) Deprotection (General Procedure). To the bis-*N*,*O*-isopropylidene ketals **9a**−**d** was added cold 98% formic acid (<5 °C; 0.02−0.05 mM concentrations), and the mixture was stirred for 15−20 min at 5 °C. The reaction mixture was lyophilized to give an oily residue, which was mixed with Et_3N (1.5 equiv) and di-*tert*-butyl dicarbonate (1.0 equiv) in MeOH; the mixture was then stirred overnight. Concentration *in vacuo* followed by chromatography afforded the corresponding bis-Boc diol Teoc carbamates (for **10a**, the *O*-benzyl group was then removed by hydrogenolysis with 20% $Pd(OH)_2$/C in MeOH). The bis-Boc diol Teoc carbamates and Bu_4NF (3.0 equiv) were heated in THF (0.25−0.5 M concentrations) at 50 °C for 4−6 h until all starting material was consumed. Volatiles were removed *in vacuo*, and the residue was chromatographed to give **10a**−**d** as white solids.

[1*S*-[1*R,2*S**(2*S**,3*R**)]]-[3-[[3-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-(2-hydroxyethoxy)phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic Acid, 1,1-Dimethylethyl Ester (10a).** Flash chromatography (CH_2Cl_2−MeOH−NH_4OH, 100:0:0 to 94:6:0.6) afforded **10a** (122 mg; 74% from **9a**) as a white solid: ^{1}H NMR (CD_3OD) δ 1.29 and 1.31 (both s, 18H), 2.40−2.84 (m, 6H), 3.06 (m, 2H), 3.55−3.75 (m, 4H), 3.84 (t, J = 4.7 Hz, 4H), 3.99 (t, J = 4.7 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H), 7.10−7.30 (m, 5H); ^{13}C NMR (CD_3OD) δ 28.51, 28.77, 37.03, 37.93, 53.11, 56.88, 56.99, 61.80, 70.64, 73.15, 73.24, 79.95, 115.49, 127.10, 129.20, 130.50, 130.67, 131.43, 132.45, 140.30, 158.08, 158.13, 158.93 (two carbons unresolved). Anal. ($C_{32}H_{49}N_3O_8$·1.16H_2O) C, H, N.

[1*S*-[1*R,2*S**(2*S**,3*R**)]]-[3-[[3-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-(2-methoxyethoxy)phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic Acid, 1,1-Dimethylethyl Ester (10b).** Flash chromatography (CH_2Cl_2−MeOH−NH_4OH, 100:0:0 to 94:6:0.6) followed by hexane−ether trituration afforded **10b** (128 mg; 78% from **9b**) as a white solid: ^{1}H NMR (CD_3OD) δ 1.30 and 1.31 (both s, 18H), 2.40−2.90 (m, 6H), 3.06 (m, 2H), 3.40 (s, 3H), 3.55−3.70 (m, 4H), 3.71 (t, J = 4.70 Hz, 4H), 4.06 (t, J = 4.70 Hz, 2H), 6.83 (d, J = 8.54 Hz, 2H), 7.13 (d, J = 8.54 Hz, 2H), 7.10−7.30 (m, 5H); ^{13}C NMR (CD_3OD) δ 28.44, 28.52, 36.97, 37.86, 52.86, 56.85, 56.97, 59.24, 68.48, 72.29, 72.60, 72.68, 80.08, 115.54, 127.15, 129.24, 130.48, 131.45, 132.45, 140.19, 158.15, 158.18, 158.80 (two carbons unresolved). Anal. ($C_{33}H_{51}N_3O_8$·0.83H_2O) C, H, N.

[1*S*-[1*R,2*S**(2*S**,3*R**)]]-[3-[[3-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-(4-[2-(2-pyridinyl)ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic Acid, 1,1-Dimethylethyl Ester (10c).** Flash chromatography (CH_2Cl_2−MeOH−NH_4OH, 98:2:0.2 to 95:5:0.5) followed by trituration with ether−hexane afforded **10c** (40 mg; 37% from **9c**) as a light yellow solid: ^{1}H NMR (CD_3OD) δ 1.30 (s, 18H), 2.35−2.83 (m 6H), 2.95−3.15 (m, 2H), 3.21 (t, J = 6.41 Hz, 2H), 3.54−3.23 (m, 4H), 4.28 (t, J = 6.41 Hz, 2H), 6.79 (d, J = 8.34 Hz, 2H), 7.11 (d, J = 8.34 Hz, 2H), 7.12−7.30 (m, 6H), 7.39 (d, J = 7.69 Hz, 1H), 7.75 (dt, J_d = 1.71 Hz, J_t = 7.69 Hz, 1H), 8.45 (m, 1H); ^{13}C NMR (CD_3OD) δ 28.5, 28.7, 37.0, 37.9, 53.1, 56.8, 56.9, 68.2, 73.0, 73.2, 79.9, 115.4, 123.2, 125.4, 127.0, 129.2, 130.5, 131.4, 132.4, 138.6, 140.3, 149.7, 158.0, 158.6, 159.9 (three carbons unresolved). Anal. ($C_{37}H_{52}N_4O_7$·0.53H_2O) C, H, N.

[1*S*-[1*R,2*S**(2*S**,3*R**)]]-[3-[[3-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[2-(4-morpholinyl)ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic Acid, 1,1-Dimethylethyl Ester (10d).** Flash chromatography (CH_2Cl_2−MeOH−NH_4OH, 99:1:0.1 to 95:5:0.5) afforded **10d** (65 mg; 61% from **9d**) as a white solid: ^{1}H NMR (CD_3OD) δ 1.29 (s, 9H), 1.31 (s, 9H), 2.46−2.86 (m, 10H), 2.78 (t, J = 5.56 Hz, 2H), 3.07 (m, 2H), 3.55−3.75 (m, 4H), 3.70 (t, J = 4.70 Hz, 4H), 4.09 (t, J = 5.56 Hz, 2H), 6.83 (d, J = 8.55 Hz, 2H), 7.13 (d, J = 8.55 Hz, 2H), 7.13−7.30 (m, 5H); ^{13}C NMR (CD_3OD) δ 28.8, 37.1, 37.9, 53.1, 55.2, 56.9, 57.0, 58.8, 66.5, 67.6, 73.1, 73.2, 79.9, 115.4, 127.1, 129.3, 130.5, 131.5, 132.6, 140.3, 158.1, 158.6 (three carbons unresolved). Anal. ($C_{36}H_{56}N_4O_8$·0.42H_2O) C, H, N.

[*S*-(*R,*R**)]-[2-(4-Hydroxyphenyl)-1-oxiranylethyl]carbamic Acid, 1,1-Dimethylethyl Ester (11).** A mixture of **4b** (5.0 g, 13.5 mmol) and $Pd(OH)_2$−C (500 mg) in EtOH (100 mL) and EtOAc (25 mL) was stirred under an atmosphere of H_2 for 4.5 h. The catalyst was removed by filtration, and the catalyst was washed with EtOH, MeOH, and EtOAc. The combined filtrates were concentrated *in vacuo* to give **11** (3.8 g; 99%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H), 2.70−2.83 (m, 3H), 2.84−2.95 (m, 2H), 3.62 (br s, 1H), 4.55 (br s, 1H), 6.77 (d, J = 8.3 Hz, 2H), 7.06 (d, J = 8.3 Hz, 2H).

[*S*-(*R,*R**)]-[2-[4-[2-(1H-imidazol-1-yl)ethoxy]phenyl]-1-oxiranylethyl]carbamic Acid, 1,1-Dimethylethyl Ester (12e).** A mixture of imidazole (2.0 g, 29.0 mmol), ethyl bromoacetate (3.2 mL, 29 mmol), and K_2CO_3 (8.1g, 58.0 mmol) in DMF (30 mL) was heated at 65 °C for 18 h. After cooling, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was chromatographed (95:5 CH_2Cl_2−MeOH) to give the ethyl ester (2.1 g; 49%) as a light orange oil: ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J = 7 Hz, 3H), 4.25 (q, J = 7 Hz, 2H), 4.70 (s, 2H), 6.97 (s, 1H), 7.10 (s, 1H), 7.51 (s, 1H).

A solution of the above ethyl ester (1 g, 6.5 mmol) in Et_2O (15 mL) was added dropwise over 15 min to a suspension of $LiAlH_4$ (0.52 g, 13 mmol) in Et_2O (50 mL) at 0 °C. After 1 h, H_2O (0.52 mL) was added, followed by aqueous NaOH (0.52 mL of a 15% solution) and additional H_2O (1.56 mL). The suspension was stirred for 1 h, $MgSO_4$ was added, and the mixture was filtered. The filter cake was washed with hot EtOAc (100 mL), and the combined filtrates were concentrated *in vacuo* to afford the corresponding alcohol (0.70 g; 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.86 (t, J = 4.5 Hz, 2H), 4.02 (t, J = 4.5 Hz, 2H), 6.88 (s, 1H), 6.90 (s, 1H), 7.33 (s, 1H).

Diethyl azodicarboxylate (0.35 mL, 2.15 mmol) was added dropwise to a suspension of **11** (200 mg, 0.72 mmol), Ph_3P (564 mg, 2.15 mmol), and the above alcohol (267 mg; 2.15 mmol) in THF (1.8 mL) at room temperature. The reaction mixture was stirred at room temperature for 18 h. Volatiles were removed *in vacuo* to give a residue, which was purified by flash chromatography (5% MeOH in CH_2Cl_2 followed by EtOAc−MeOH, 100:0 to 90:10) gave **12e** (230 mg; 86%) as a light

yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 9H), 2.78 (m, 3H), 2.88 (m, 2H), 3.61 (m, 1H), 4.20 (t, J = 5 Hz, 2H), 4.33 (t, J = 4.5, 5.5 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 7.04 (s, 1H), 7.06 (s, 1H), 7.15 (d, J = 8.5 Hz, 2H), 7.59 (s, 1H).

[*S*-(*R,*R**)]-[2-[4-[2-(3-Pyridinyloxy)ethoxy]phenyl]-1-oxiranylethyl]carbamic Acid, 1,1-Dimethylethyl Ester (12f).** To a 0 °C suspension of 3-hydroxypyridine (1.00 g; 10.5 mmol), Ph_3P (7.08 g; 27.0 mmol), and bromoethanol (1.91 mL; 27.0 mmol) in THF (30 mL) was added dropwise DEAD (4.25 mL; 27.0 mmol) over 15 min. The yellow solution was warmed to room temperature and stirred for 36 h. Volatiles were removed *in vacuo* to give a brown residue, which was dissolved in EtOAc (30 mL) and Et_2O (30 mL). This was extracted with aqueous HCl (3 × 15 mL of a 1 M solution). The combined aqueous extracts were basified at 0 °C with excess aqueous 1 M NaOH and then extracted with EtOAc (4 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give an orange-brown oil, which was chromatographed (3:1 to 1:2 hexanes−EtOAc) to give 3-(2-bromoethoxy)pyridine (1.27 g; 60%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.63−3.68 (m, 2H), 4.32−4.37 (m, 2H), 7.20−7.24 (m, 2H), 8.26 (m, 1H), 8.34 (m, 1H).

To a 0 °C suspension of NaH (0.032 g of a 60% suspension in oil) in anhydrous DMF (1.0 mL) was added dropwise a solution of phenol **11** in DMF (1.0 mL). The solution was stirred at room temperature for 1 h and then cooled to 0 °C. A solution of 3-(2-bromoethoxy)pyridine (0.167 g; 0.827 mmol), *n*-Bu_4NI (0.015 g; 0.039 mmol), and 15-crown-5 (0.159 mL; 0.80 mmol) in DMF (1.0 mL) was added dropwise. The reaction mixture was stirred at room temperature for 24 h. Volatiles were removed *in vacuo*, and the residue was partitioned between H_2O and EtOAc (10 mL each). The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with water (2 × 20 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give a yellow-orange oil, which was chromatographed (3:1 to 1:3 hexane−EtOAc) to give ether **12f** (0.168 g; 59%) as a white solid and recovered phenol **11** (0.041g; 21%): ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H), 2.76−2.95 (m, 5H), 3.63 (br s, 1H), 4.30−4.39 (m, 4H), 4.60 (br s, 1H), 6.90 (d, J = 9.1 Hz, 2H), 7.15 (d, J = 8.6 Hz, 2H), 7.21−7.29 (m, 2H), 8.24 (m, 1H), 8.36 (m, 1H).

[*S*-(*R,*R**)]-[2-[4-[2-Hydroxy-2-(3-pyridinyl)ethoxy]phenyl]-1-oxiranylethyl]carbamic Acid, 1,1-Dimethylethyl Ester (12g).** To a 0 °C solution of vinylmagnesium bromide (41.0 mL of a 1.0 M solution in THF) was added dropwise over 1 h a solution of pyridine-3-carboxaldehyde (4.00 g, 37.3 mmol) in THF (50 mL). The resultant orange-yellow solution was stirred for 24 h at room temperature. The reaction was quenched at 0 °C by addition of aqueous NH_4Cl (55 mL of a 1 M solution). EtOAc (200 mL) was added, and the resulting emulsion was filtered through Celite. The aqueous layer was extracted with EtOAc (4 × 200 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a red oil, which was chromatographed (1:1 to 1:5 hexane−EtOAc) to give the allylic alcohol (3.89 g; 77%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 5.18−5.22 (m, 2H), 5.34 (m, 1H), 5.45 (br s, 1H), 6.01 (m, 1H), 7.25 (dd, J = 4.9, 7.9 Hz, 1H), 7.74 (m, 1H), 8.36 (dd, J = 1.6, 4.9 Hz, 1H), 8.46 (d, J = 2.0 Hz, 1H).

To a 0 °C solution of the above allylic alcohol (0.400 g; 2.96 mmol) in DMF (3.0 mL) were successively added TBSCl (0.535 g; 3.55 mmol), Et_3N (0.467 g; 4.62 mmol), and DMAP (.036 g; 0.296 mmol). The mixture was stirred at room temperature overnight; volatiles were removed *in vacuo*, and the residue was partitioned between aqueous $NaHCO_3$ (20 mL of a 50% saturated solution) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 20 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give an orange oil, which was chromatographed (10:1 hexane−EtOAc) to furnish the TBS ether (0.744; 100%) as a very pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.02 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 5.11−5.35 (m, 3H), 5.90 (m, 1H), 7.25 (m, 1H), 7.67 (m, 1H), 8.50 (dd, J = 1.4, 4.8 Hz, 1H), 8.57 (d, J = 1.9 Hz, 1H).

A stream of O_3 was bubbled into a −78 °C solution of the above olefin (0.650 g; 2.61 mmol) in CH_2Cl_2 (10 mL) for 15 min until the solution was faintly blue. After stirring for a further 30 min at −78 °C, N_2 was bubbled into the solution for 15 min to discharge the blue color. Diisobutylaluminum hydride (10.4 mL of a 1.0 M solution in hexane; 10.4 mmol) was added dropwise over 5 min, followed by 10 mL of dry hexane. The solution was stirred at −78 °C for 1 h and at −20 °C for 2 h; MeOH (3.0 mL) was added at −78 °C to quench the reaction. The solution was allowed to warm to room temperature, and brine (5.0 mL), Et_2O (100 mL), and $MgSO_4$ (15 g) were added. The mixture was stirred for 2 h, filtered, and concentrated *in vacuo* to give a yellow oil, which was chromatographed (1:1 to 1:4 hexane−EtOAc) to give the corresponding alcohol (0.234g; 35%) as a clear viscous oil: ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 3H), 0.16 (s, 3H), 0.98 (s, 9H), 2.70 (br s, 1 H), 3.64−3.73 (m, 2H), 4.87 (m, 1H), 7.34 (m, 1H), 7.75 (m, 1H), 8.56 (dd, J = 1.6 Hz, 4.8 Hz, 1H), 8.61 (d, J = 2.0 Hz, 1H).

The alcohol prepared above (0.331g; 1.31 mmol) and epoxide **11** (0.183 g; 0.655 mmol) were reacted with DEAD (0.228 g; 1.31 mmol) and Ph_3P (0.343 g; 1.31 mmol) in THF for 24 h according to the general procedure described above. The yellow-orange solution was concentrated *in vacuo* and chromatographed (5:5 to 1:1 hexane−EtOAc) to give epoxide (0.301 g; contaminated with 1,2 dicarbethoxyhydrazine) as a yellow viscous oil: ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 3H), 0.11 (s, 3H), 0.90 (s, 9H), 1.38 (s, 9 H), 2.70−2.88 (m, 5H), 3.60 (br s, 1H), 3.84−4.12 (m, 2H), 4.40 (br s, 1H), 5.08 (m, 1H), 6.81 (d, J = 8.6 Hz, 2H), 7.11 (d, J = 8.6 Hz, 2H), 7.30 (m, 1H), 7.77 (m, 1H), 8.54 (dd, J = 1.7, 4.8 Hz, 1H), 8.66 (d, J = 2.1 Hz, 1H).

The above epoxide (0.301 g) was dissolved in anhydrous THF, and *n*-$Bu_4NF{\cdot}3H_2O$ (0.204 g; 0.779 mmol) was added. The yellow solution was stirred at room temperature for 1.5 h. Volatiles were removed *in vacuo*, and the yellow residue was chromatographed (1:1 to 1:10 hexane−EtOAc) to give epoxide **12g** (0.096 g; 37% for 2 steps) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H), 2.73−2.92 (m, 5H), 3.62 (br s, 1H), 3.99−4.13 (m, 2H), 4.42 (br s, 1H), 5.16 (dd, J = 3.5, 8.3 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 7.14 (d, J = 8.7 Hz, 2H), 7.34 (m, 1H), 7.83 (m, 1H), 8.58 (dd, J = 1.7, 4.8 Hz, 1H), 8.68 (d, J = 2.1 Hz, 1 H).

[*S*-(*R,*R**)]-[2-[4-[2-(Benzyloxy)propoxy]phenyl]-1-oxiranylethyl]carbamic Acid, 1,1-Dimethylethyl Ester (12h).** To a 0 °C suspension of NaH in THF (1.0 g of a 60% suspension in oil; 25 mmol; washed with 2 × 5 mL THF) was added dropwise a solution of methyl lactate (2.10 mL; 22.0 mmol) in THF (10 mL) over 15 min. The reaction mixture was stirred at room temperature for 30 min. The solution was cooled to 0 °C, and benzyl bromide (2.97 mL; 25 mmol) in THF (5 mL) was added, followed by *n*-Bu_4NI (0.092 g; 0.25 mmol). The reaction mixture was stirred at room temperature for 24 h and then partitioned between H_2O and EtOAc (40 mL each). The aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with H_2O (2 × 20 mL), and brine (40 mL) and dried (Na_2SO_4). Volatiles were removed *in vacuo* to give a yellow oil, which was chromatographed (hexane to 10% EtOAc−hexane) to give *O*-benzyl methyl lactate (2.46 g; 57%) as a clear, colorless oil.

To a 0 °C suspension of $LiAlH_4$ (380 mg; 10 mmol) in THF (75 mL) was added dropwise a solution of *O*-benzyl methyl lactate (2.4 g; 12.4 mmol) in THF (20 mL) over 15 min. The reaction mixture was stirred at room temperature for 14 h, cooled to 0 °C, and quenched by dropwise addition of saturated aqueous Na_2SO_4 (10 mL). The white slurry was stirred at room temperature for 30 min and then filtered through Celite. The residue was washed with EtOAc (2 × 50 mL). The combined filtrates were concentrated *in vacuo* to give the alcohol (2.10 g; 100%) as a pale yellow oil.

The above alcohol (336 mg; 2.03 mmol) was coupled to phenol **11** (250 mg; 0.90 mmol) using the same general procedure as described above. The crude product was chromatographed (90:10 to 84:16 hexane−EtOAc) to afford **12h** (190 mg; 47%) as a beige solid. ^{1}H NMR ($CDCl_3$) δ 1.31 (d, J = 6.1 Hz, 3H), 1.39 (s, 9H), 2.72−2.95 (m, 5H), 3.63 (br s, 1H), 3.87−4.08 (m, 3H), 4.42 (br s, 1H), 4.67 (s, 2H), 6.86 (d, J = 8.6 Hz, 2H), 7.13 (d, J = 8.6 Hz, 2H), 7.27−7.39 (m, 5H).

[*S*-(*R,*R**)]-[2-[4-(2-Hydroxy-2-methylpropoxy)phenyl]-1-oxiranylethyl]carbamic Acid, 1,1-Dimethylethyl Ester (12i).** A solution of phenol **11** (200 mg; 0.71 mmol) in DMF

(0.75 mL) was reacted with $NaN(TMS)_2$ in THF (0.74 mL of a 1.0 M solution; 0.74 mmol), ethyl bromoacetate in DMF (0.74 mL of a 1.0 M solution; 0.74 mmol), and *n*-Bu_4NI (27.5 mg) as described in the synthesis of **12j**. The crude product was purified by chromatography (hexane−EtOAc, 90:10 to 84:16) to give 260 mg (88%) of the ester as a beige solid (contaminated with ethyl bromoacetate).

To a −23 °C solution of the above ester (204 mg; 0.56 mmol; contaminated with ethyl bromoacetate) in dry THF (0.56 mL) was added a solution of CH_3MgCl (1.67 mL of a 1.0 M solution in THF; 1.67 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 24 h, after which aqueous NH_4Cl (25 mL of a 1 M solution) was added. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The white residue was chromatographed (10:90 to 55:45 EtOAc-hexane) to afford 85 mg (43%) of **12i** as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3H), 1.39 (s, 3H), 1.40 (s, 9H), 2.73−3.02 (m, 5H), 3.66 (m, 1H), 3.79 (s, 2H), 3.82 (br s, 1H), 4.45 (br s, 1H), 6.86 (d, J = 8.6 Hz, 2H), 7.13 (d, J = 8.6 Hz, 2H).

[*S*-(*R,*R**)]-[2-[4-(Ethoxycarbomethoxy)phenyl]-1-oxiranylethyl]carbamic Acid, 1,1-Dimethylethyl Ester (12j).** To a 0 °C solution of phenol **11** (0.080 g; 0.286 mmol) in DMF (0.60 mL) was added dropwise a solution of $NaN(TMS)_2$ in THF (0.30 mL of a 1.0 M solution; 0.30 mmol). The solution was stirred at 0 °C for 1 h; ethyl bromoacetate in DMF (0.30 mL of a 1.0 M solution; 0.30 mmol) was then added dropwise, followed by *n*-Bu_4NI (0.011 g; 0.029 mmol). The yellow solution was then stirred at room temperature for 18 h. Volatiles were removed *in vacuo*, and the residue was partitioned between water and EtOAc (20 mL each). The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with water (3 × 20 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give a beige solid, which was chromatographed (10:1 to 1:2 hexane−EtOAc) to give 100 mg (95%) of **12j** as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.1 Hz, 3H), 1.39 (s, 9H), 2.73−2.95 (m, 5H), 3.63 (broad s, 1H), 4.27 (q, J = 7.1 Hz, 2H), 4.48 (broad s, 1H), 4.60 (s, 2H), 6.86 (d, J = 8.6 Hz, 2H), 7.14 (d, J = 8.6 Hz, 2H).

[*S*-(*R,*R**)]-[2-[4-[2-[[(Dimethylamino)carbonyl]oxy]-ethoxy]phenyl]-1-oxiranylethyl]carbamic Acid, 1,1-Dimethylethyl Ester (12k).** To a stirred solution of phosgene in toluene (8.5 mL of a 1.93M solution; 16.4 mmol) at −60 °C was added dropwise a solution of 2-(benzyloxy)ethanol (500mg, 3.28 mmol) and pyridine (583 μL, 7.22 mmol) in CH_2Cl_2 (3 mL). Additional CH_2Cl_2 (20 mL) was added to the reaction mixture, which was allowed to warm to 15 °C over 15 min. After cooling to −20 °C, excess anhydrous *N*,*N*-dimethylamine was bubbled through the turbid mixture, which was stirred at room temperature overnight. The brown solution was washed with water (2 × 5 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford a brown liquid, which was purified by chromatography (EtOAc−hexane, 1:4 to 1:3) to afford the corresponding carbamate (490 mg; 67%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.92 (s, 6H), 3.68 (t, J = 5.0 Hz, 2H), 4.26 (t, J = 5.0 Hz, 2H), 4.57 (s, 2H), 7.25−7.40 (m, 5H).

A mixture of above benzyl ether-protected carbamate (490 mg, 2.20 mmol) and 20% $Pd(OH)_2$ (40 mg) in EtOH (15 mL) was stirred under the hydrogen atmosphere for 6 h. The reaction mixture was filtered through Celite and concentrated to afford an oil which was azeotroped twice from toluene to afford the corresponding alcohol (290 mg; 99%) as a colorless oil. This material was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 2.93 (s, 6H), 3.00, (br s, 1H), 3.81 (m, 2H), 4.23 (m, 2H).

Under standard Mitsunobu conditions, the above alcohol (280 mg, 2.10 mmol) was reacted with epoxide **11** (391 mg, 1.40 mmol) in the presence of Ph_3P (735 mg, 2.80 mmol) and DEAD (488 mg, 441μL, 2.8 mmol) in THF (3.5mL). The crude product was chromatographed (30:70 to 70:30 EtOAc−hexane) to afford **12k** (191 mg, 35% yield) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H), 2.70−2.95 (m, 11H), 3.62 (br s, 1H), 4.16 (t, J = 5.5 Hz, 2H), 4.41 (t, J = 5.5 Hz, 2H), 4.44 (br s, 1H), 6.87 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H).

[*S*-(*R,*R**)]-[2-[4-[2-(2-Oxo-3-oxazolidinyl)ethoxy]phenyl]-1-oxiranylethyl]carbamic Acid, 1,1-Dimethylethyl Ester (12l).** To a solution of diethanolamine (2.0 g, 0.019 mol) in aqueous KOH (2.44 g, 0.043 mol; in 20 mL H_2O) at 0 °C was added phosgene (9.9 mL of a 1.93 M solution in toluene, 0.019 mol), and the reaction mixture was allowed to warm to room temperature and stirred for 15 h. The resulting mixture was extracted with hexane, and the aqueous layer was concentrated *in vacuo* to give an oily solid residue, which was washed with hot EtOAc (5×). The combined organic extracts were evaporated *in vacuo* to give the carbamate−alcohol (1.5 g, 60%).

Under standard Mitsunobu conditions, the alcohol prepared above (223 mg, 1.70 mmol) was reacted with Ph_3P (445 mg, 1.69 mmol), DEAD (268 μL, 1.70 mmol), and epoxide **11** (236 mg, 0.845 mmol) in THF (2 mL). The reaction residue was purified by flash chromatography (EtOAc−CH_2Cl_2, 1:4 to 1:3) to give epoxide **12l** (138 mg, contaminated with 11% Ph_3P═O; 37%): ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H), 2.70−2.98 (m, 5H), 3.66 (t, J = 4.9 Hz, 2H), 3.77 (t, J = 7.9 Hz, 2H), 4.13 (t, J = 4.9 Hz, 2H), 4.32 (t, J = 7.9 Hz, 2H), 4.55 (br s, 1H), 6.83 (d, J = 8.6 Hz, 2H), 7.14 (d, J = 8.6 Hz, 2H).

[*S*-(*R,*R**)]-[2-[4-[2-(3-Methyl-2-oxo-1-imidazolidinyl)-ethoxy]phenyl]-1-oxiranylethyl]carbamic Acid, 1,1-Dimethylethyl Ester (12m).** 3-(1-Hydroxyethyl)-2-oxazolidinone (333 mg; 2.30 mmol[26]) was coupled with phenol **11** (323 mg; 1.15 mmol) in the presence of Ph_3P (602 mg; 2.30 mmol) and DEAD (362 μL, 2.30 mmol) using the general Mitsunobu procedure described above. The crude product was chromatographed (hexane−EtOAc, 80:20 to 0:100) to afford **12m** (342 mg; 54%) as a beige solid: ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H), 2.71−2.95 (m, 5H), 2.79 (s, 3H), 3.22−3.32 (m, 2H), 3.45−3.53 (m, 2H), 3.59 (t, J = 4.9 Hz, 2H), 4.08 (t, J = 4.9 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H).

[*S*-(*R,*R**)]-[2-[4-[2-(4-Morpholinyl)-2-oxoethoxy]phenyl]-1-oxiranylethyl]carbamic Acid, 1,1-Dimethylethyl Ester (12n).** To a 0 °C suspension of NaH (48 mg of a 60% dispersion in oil, 1.2 mmol; prewashed with hexanes 2×) in DMF (1.0 mL) was added a solution of **11** (280 mg, 1.0 mmol) in DMF (1.5 mL). The mixture was stirred at 0 °C for 30 min, followed by the addition of 4-(2-bromoacetyl)morpholine[7a] (270 mg, 1.3 mmol) and *n*-$Bu_4N^+I^-$ (185 mg, 0.5 mmol). The reaction mixture was stirred at room temperature overnight. After cooling to 0 °C, water was added and the mixture was extracted with EtOAc (3×). The combined extracts were washed with water and brine and dried (Na_2SO_4). Concentration *in vacuo* followed by flash chromatography (hexane−EtOAc, 1:1 to 1:4) on silica gel afforded **12n** (92 mg; 96%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H), 2.72−2.96 (m, 5H), 3.55−3.72 (m, 9H), 4.45 (br s, 1H), 4.67 (s, 2H), 6.89 (d, J = 8.6 Hz, 2H), 7.14 (d, J = 8.6 Hz, 2H).

[*S*-(*R,*R**)]-[2-[4-(2-Piperidinylethoxy)phenyl]-1-oxiranylethyl]carbamic Acid, 1,1-Dimethylethyl Ester (12o).** To a 0 °C suspension of NaH (62 mg, 60% dispersion in oil, 1.55 mmol; washed with hexane) in DMF (3.0 mL) was added a solution of **11** (360 mg, 1.29 mmol) in DMF (3.0 mL). The mixture was stirred at 0 °C for 30 min, followed by addition of 4-(2-bromoacetyl)piperidine [prepared by a procedure analogous to that of 4-(2-bromoacetyl)morpholine] (350 mg, 1.68 mmol) and *n*-$Bu_4N^+I^-$ (240 mg, 0.65 mmol). The reaction mixture was stirred at room temperature overnight. After cooling to 0 °C, water was added and the mixture was extracted with EtOAc (3×). The combined organic extracts were washed with water and brine and dried (Na_2SO_4). Concentration *in vacuo* followed by flash chromatography (hexane−EtOAc, 1:1) afforded **12o** (300 mg; 55%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H), 1.43−1.75 (m, 6H), 2.70−2.97 (m, 5H), 3.48 (t, J = 5.3 Hz, 2H), 3.56 (t, J = 5.3 Hz, 2H), 3.60 (m, 1H), 4.42 (br s, 1H), 4.66 (s, 2H), 6.90 (d, J = 8.5 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H).

Coupling (General Procedure): [1*S*-[1*R,2*S**(2*S**,3*R**)]]-[3-[[3-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[2-(1*H*-imidazol-1-yl)ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic Acid, 1,1-Dimethylethyl Ester (10e).** A mixture of **12e** (220 mg, 0.59 mmol) and **5** (165 mg, 0.59 mmol) in DMF (0.50 mL) was heated at 100 °C for 4.5 h. After cooling, volatiles were

removed *in vacuo* and the residue was purified by flash chromatography (CH_2Cl_2−MeOH−NH_4OH, 98:2:0 to 90:10:1) to afford, after trituration with Et_2O overnight, **10e** (103 mg; 27%) as a white solid: ^{1}H NMR (CD_3OD) δ 1.29 (s, 18H), 2.55 (m, 2H), 2.78 (m, 4H), 3.03 (m, 1H), 3.11 (m, 1H), 3.61 (m, 4H), 4.20 (t, J = 4.5, 5 Hz, 2H), 4.39 (t, J = 4.5, 5 Hz, 2H), 6.80 (d, J = 8.5 Hz, 2H), 6.96 (s, 1H), 7.12 (d, J = 8 Hz, 2H), 7.21 (m, 6H), 7.71 (s, 1H). ^{13}C NMR (CD_3OD) δ 28.8, 37.0, 37.9, 47.7, 52.9, 56.9, 57.0, 68.7, 72.7, 80.1, 115.5, 121.1, 127.2, 129.0, 130.5, 131.6, 133.0, 138.9, 140.2, 158.2, 158.3 (two carbons unresolved). Anal. ($C_{35}H_{51}N_5O_7$) C, H, N.

[1*S*-[1*R,2*S** (2*S**, 3*R**)]]-[3-[[3-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[2-(3-pyridinyloxy)ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic Acid, 1,1-Dimethylethyl Ester (10f).** Epoxide **12f** (0.160 g; 0.400 mmol) was reacted with amino alcohol **5** in DMF at 100 °C for 5 h. Volatiles were removed *in vacuo*, and the residue was purified by chromatography (CH_2Cl_2−MeOH−NH_4OH, 99:1:0.1 to 90:10:1) to afford a white solid (0.125 g, 46%). This material was further purified by preparative HPLC (using as eluent a stepwise gradient from 50:50 to 75:25 A:B; A = 90:10:0.05 MeOH−H_2O−TFA; B = 90:10:0.05 H_2O−MeOH−TFA) to furnish 91 mg (34%) of aminodiol **10f** as a white solid: ^{1}H NMR (CD_3OD; 50 °C) δ 1.29 (broad s, 9 H), 2.56−2.81 (m, 6 H), 3.03−3.10 (m, 2 H), 3.61−3.78 (m, 4 H), 4.28−4.31 (m, 2 H), 4.35−4.38 (m, 2 H), 6.86 (d, J = 8.5 Hz, 2 H), 7.14 (d, J = 8.4 Hz, 2 H), 7.21−7.28 (m, 5 H), 7.33 (m, 1 H), 7.43 (m, 1 H), 8.12 (d, J = 4.6 Hz, 1 H), 8.26 (d, J = 2.7 Hz, 1 H); ^{13}C NMR (CD_3OD; 50 °C) δ 28.7, 37.0, 37.8, 46.0, 53.2, 56.9, 68.1, 68.7, 71.1, 73.2, 80.1, 115.8, 123.6, 125.7, 127.1, 129.2, 130.5, 131.5, 133.0, 138.9, 140.3, 142.6, 157.1, 158.0, 158.7 (four carbons unresolved). Anal. ($C_{37}H_{52}N_4O_8$) C, H, N.

[1*S*-[1*R,2*S**(2*S**,3*R**)]]-[3-[[3-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[2-hydroxy-2-(3-pyridinyl)ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic Acid, 1,1-Dimethylethyl Ester (10g).** Epoxide **12g** (0.030 g; 0.075 mmol) and amino alcohol **5** (0.025 g; 0.090 mmol) were heated in MeOH (0.20 mL) at 60 °C for 4 h. Volatiles were removed *in vacuo*, and the residue was purified by chromatography (CH_2Cl_2−MeOH−NH_4OH, 99:1:0.1 to 92:8:0.8) to afford a white solid (0.026 g, 52%). This was further purified by preparative HPLC (Waters Delta Prep 4000 HPLC; Polymer Labs PLRP-S column, 25 × 300 mm, 10 mm particle size, stepwise gradient from 70:30 to 40:60 A:B; A = 90:10:0.2 H_2O−MeCN−NH_4OH; B = 90:10:0.2 MeCN−H_2O−NH_4OH; flow rate 25 mL/min) and then lyophilized from dioxane−H_2O to give **10g** (0.021 g; 41%) as a white solid: ^{1}H NMR (CD_3OD; 55 °C) δ 1.28 (br s, 9 H), 2.51−2.78 (m,6 H), 2.96−3.08 (m, 2 H), 3.58−3.76 (m, 4 H), 4.08−4.14 (m, 2 H), 5.04 (dd, J = 5.3, 5.9 Hz, 1 H), 6.82 (d, J = 8.8 Hz, 2 H), 7.11 (d, J = 8.7 Hz, 2 H), 7.13−7.25 (m, 5 H), 7.40 (m, 1 H), 7.91 (m, 1 H), 8.43 (dd, J = 1.6, 4.9 Hz, 1 H), 8.61 (d, J = 1.7 Hz, 1 H); ^{13}C NMR (CD_3OD; 55 °C) δ 28.7, 37.0, 37.8, 53.0, 56.9, 71.2, 72.8, 74.0, 80.3, 115.8, 116.2, 124.9, 127.1, 129.2, 130.4, 131.5, 132.8, 136.4, 139.5, 140.2, 148.8, 149.3, 158.1, 158.7 (three aliphatic carbons unresolved); accurate mass measurement (M + H)$^+$ calcd for $[C_{37}H_{53}N_4O_8]^+$ 681.3863, found 681.3872 (Δ_{ppm} = 1.3).

[1*S*-[1*R, 2*S** (2*S**, 3*R**)]-[3-[[3-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-(2-hydroxypropoxy)phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic Acid, 1,1-Dimethyl Ester (10h).** The epoxide **12h** (190 mg; 0.44 mmol) was reacted with amino alcohol **5** (124 mg; 0.44 mmol) using the general procedure as described for **10e**. The crude product was chromatographed (CH_2Cl_2−MeOH−NH_4OH, 98:2:0.2 to 92:8:0.8) to yield *O*-benzyl-**10h** (140 mg; 63%) as a beige solid.

To a suspension of 10% Pd/C (60 mg) in MeOH (2.5 mL) was added *O*-benzyl-**10h** (64 mg; 0.09 mmol) followed by aqueous HCl (900 μL of a 0.1 N solution), and the reaction mixture was stirred under an atmosphere of H_2 for 1 h. The reaction mixture was neutralized with aqueous NaOH (900 μL of a 0.1 M solution), filtered through Celite and concentrated *in vacuo*. The crude product was purified by chromatography (CH_2Cl_2−MeOH−NH_4OH, 98:2:0.2 to 92:8:0.8) to yield **10h** (35 mg; 65%, 1:1 mixture of diastereomers) as a white solid: ^{1}H NMR (CD_3OD, 60 °C) δ 1.23 (d, 3H), 1.30 (broad s, 18H), 2.52−2.81 (m, 6H), 2.98−3.12 (m, 2H), 3.61-3.78 (m, 4H), 3.82 (d, J = 5.3 Hz, 2H), 4.07 (m, 1H), 6.83 (d, J = 8.6 Hz, 2H), 7.12 (d, J = 8.6 Hz, 2H), 7.21−7.25 (m, 5H); ^{13}C NMR (CD_3OD, 60 °C) δ 18.3, 27.2, 35.5, 36.4, 51.8, 55.4, 55.5, 65.6, 71.8, 73.2, 78.5, 114.2, 125.5, 127.7, 129.0, 130.0, 131.1, 138.8, 156.5, 157.5. Anal. ($C_{33}H_{51}N_3O_8$) C, H, N.

[1*S*-[1*R,2*S**(2*S**,3*R**)]]-[3-[[3[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-(2-hydroxy-2-methylpropoxy)phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic Acid, 1,1-Dimethylethyl Ester (10i).** Epoxide **12i** (85 mg; 0.242 mmol) was reacted with amino alcohol **5** (68 mg; 0.242 mmol) using the same general procedure as described above. The crude product was purified by chromatography (CH_2Cl_2−MeOH−NH_4OH, 99:1:0.1 to 92:8:0.8) to give a white solid (45 mg; 30%). This was further purified by preparative HPLC as described in the synthesis of **10h** and finally lyophilized from dioxane−water to give **10i** (20 mg; 18%) as a white lyophilate: ^{1}H NMR (CD_3OD; 55 °C) δ 1.38 (broad s, 18 H), 1.40 (s, 6H), 2.48−2.82 (m, 6H), 2.95−3.15 (m, 2H), 3.58−3.80 (m, 4H), 3.73 (s, 2H), 6.84 (d, J = 8.7 Hz, 2H), 7.12 (d, J = 8.7 Hz, 2H), 7.20−3.28 (m, 5H). ^{13}C NMR (CD_3OD, 55 °C) δ 25.0, 27.1, 27.2, 36.3, 51.8, 55.3, 69.4, 71.8, 114.1, 125.5, 127.4, 129.0, 129.9, 131.0, 138.7, 156.5, 157.7; accurate mass measurement (M + H)$^+$ calcd for $[C_{34}H_{54}N_3O_8]^+$ 632.3911, found 632.8887 (Δ_{ppm} = −3.8).

[1*S*-[1*R,2*S**(2*S**,3*R**)]]-[4-[4-(Carboxymethoxy)phenyl]-3-[[3-[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic Acid, 1,1-Dimethylethyl Ester (10j).** Epoxide **12j** (0.037 g; 0.102 mmol) and amino alcohol **5** (0.029 g; 0.102 mmol) were heated in DMF (0.20 mL) for 4 h as described above. Volatiles were removed *in vacuo*, and the residue was purified by chromatography (CH_2Cl_2−MeOH−NH_4OH, 99:1:0.1 to 92:8:0.8) to afford aminodiol ester (0.028 g, 43%) as a white solid: ^{1}H NMR (CD_3OD) δ 1.26 (t, J = 7.1 Hz, 3 H), 1.29 (s, 9 H), 1.30 (s, 9 H), 2.50−2.69 (m, 2 H), 2.73−2.92 (m, 4 H), 3.01−3.17 (m, 2 H), 3.63−3.78 (m, 4 H), 4.22 (q, J = 7.1 Hz, 2 H), 4.61 (s, 2 H), 6.83 (d, J = 8.7 Hz, 2 H), 7.14 (d, J = 8.7 Hz, 2 H), 7.21−7.24 (m, 5 H).

The above aminodiol ester (0.010g; 0.0156 mmol) was hydrolyzed using aqueous LiOH (82 μL of a 0.2 M solution) in THF (0.10 mL) for 24 h at 0 °C. More aqueous LiOH (90 mL of a 0.2 M solution) was added, and the reaction mixture was stirred for an additional 24 h. Aqueous HCl (35 mL of a 1 M solution) was added and the pH adjusted to 5.5 with aqueous LiOH. EtOAc (2 mL) was added, and the aqueous layer was further extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a white solid, which was lyophilized from dioxane−water to furnish **10j** (7.1 mg; 74%) as a white solid: ^{1}H NMR (CD_3OD) δ 1.31 (s, 9 H), 1.33 (s, 9 H), 2.57−2.63 (m, 4 H), 3.02−3.30 (m, 4 H), 3.62−3.77 (m, 2 H), 3.80−3.89 (m, 2 H), 4.59 (s, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 7.16 (d, J = 8.7 Hz, 2 H), 7.20−7.25 (m, 5 H); accurate mass measurement (M + H)$^+$ calcd for $[C_{32}H_{48}N_3O_9]^+$ 618.3391, found 618.3386 (Δ_{ppm} = −0.8).

[1*S*-[1*R,2*S**(2*S**,3*R**)]]-[3-[[4-[4-[2-[[(Dimethylamino)carbonyl]oxy]ethoxy]phenyl]-3-[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxybutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic Acid (10k).** A solution of epoxide **12k** (155 mg, 0.39 mmol) and amino alcohol **5** (132 mg, 0.47 mmol) in DMF (1 mL) was stirred at 100 °C for 4 h. Volatiles were removed *in vacuo*, and the crude product was purified by chromatography (CH_2Cl_2−MeOH−NH_4OH, 98:1.8:0.2 to 94:5.4:0.6) to afford **10k** (88 mg; 33%) as a white solid: ^{1}H NMR (CD_3OD) δ 1.29 and 1.31 (two singlets) with 1.18 (s, minor rotamer) and 1.21 (s, minor rotamer, 18H), 2.54 (m, 2H), 2.72 (m, 4H), 3.08 (m, 2H), 3.61 (m, 4H), 4.14 (t, J = 4.7 Hz, 2H), 4.35 (t, J = 4.7 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 7.13 (d, J = 8.6 Hz, 2H), 7.22 (m, 5H); ^{13}C NMR (CD_3OD) δ 28.8, 36.2, 36.6, 37.0, 37.9, 53.1, 56.9, 57.0, 65.4, 67.6, 73.0, 73.2, 79.9, 115.5, 127.1, 129.2, 130.5, 131.5, 132.7, 140.3, 158.1, 158.3, 158.7 (4 carbons unresolved). Anal. ($C_{35}H_{54}N_4O_9$) C, H, N.

[1*S*-[1*R,2*S**(2*S**,3*R**)]]-[3-[[3-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[2-(2-oxo-3-oxazolidinyl)ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic Acid, 1,1-Dimethylethyl Ester (10l).**

Under standard coupling conditions, epoxide **12l** (<87 mg, 0.197 mmol, contaminated with 11% $Ph_3P{=}O$) and amino alcohol **5** (65 mg, 0.232 mmol) were reacted in MeOH (0.5 mL) at 60 °C for 4 h. The reaction residue was purified by flash chromatography ($MeOH-NH_4OH-CH_2Cl_2$, 5:0.5:94.5 and then 6:0.6:93.4) to give aminodiol **10l** (62 mg, 47%) as a colorless solid: ^{1}H NMR (CD_3OD) δ 1.29 [1.18 rotamer] (s, 9 H), 1.31 [1.21 rotamer] (s, 9 H), 2.49−2.80 (m, 6 H), 3.00−3.15 (m, 2 H), 3.60−3.70 (m, 6 H), 3.72−3.78 (m, 2 H), 4.05−4.15 (m, 2 H), 4.30−4.35 (m, 2 H), 6.84 (d, J = 8.6 Hz, 2 H), 7.14 (d, J = 8.6 Hz, 2 H), 7.16−7.30 (m, 5 H); ^{13}C NMR (CD_3OD) δ 28.5 [rotamer or Boc], 28.8, 37.0, 37.9, 45.0, 46.7, 53.1, 56.9, 57.0, 63.9, 67.1, 73.1, 73.2, 80.0, 115.5, 127.1, 129.2, 130.5, 131.6, 132.9, 140.3, 158.1, 158.5, 161.1 [four carbons unresolved]. Anal. ($C_{35}H_{52}N_4O_9$) C, H, N.

[1*S*-[1*R,2*S**(2*S**,3*R**)]]-[3-[[3-[[(1,1-Dimethylethoxy)-carbonyl]amino]-2-hydroxy-4-[4-[2-(3-methyl-2-oxo-1-imidazolidinyl)ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic Acid, 1,1-Dimethylethyl Ester (10m).** The epoxide **12m** (150 mg; 0.37 mmol; contaminated with $(Ph)_3P{=}O$) was reacted with amino alcohol **5** (73 mg; 0.26 mmol) in DMF (260 μL) using the same general procedure as described above. The crude product was purified by chromatography ($CH_2Cl_2-MeOH-NH_4OH$, 99:1:0.1 to 92:8:0.8) to give a white solid (85 mg), which was further purified by preparative HPLC as described in the synthesis of **10h** and finally lyophilized from dioxane−water to give **10m** (60 mg; 34%) as a white lyophilate: ^{1}H NMR (CD_3OD) δ 1.29 (s, 9H), 1.31 (s, 9 H), 2.41−2.65 (m, 2H), 2.67−2.90 (m, 4H), 2.76 (s, 3H), 2.98−3.15 (m, 2H), 3.22−3.36 (m, 2H), 3.44−3.56 (m, 4H), 3.57−3.72 (m, 4H), 4.01−4.10 (m, 2H), 6.83 (d, J = 8.5 Hz, 2H), 7.08−7.29 (m, 5H), 7.12 (d, J = 8.5 Hz, 2H); accurate mass measurement $(M + H)^+$ calcd for $[C_{36}H_{56}N_5O_8]^+$ 686.4129, found 681.4100 ($\Delta_{ppm} = -4.2$).

[1*S*-[1*R,2*S**(2*S**,3*R**)]]-[3-[[3-[[(1,1-Dimethylethoxy)-carbonyl]amino]-2-hydroxy-4-[4-[2-(4-morpholinyl)-2-oxoethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic Acid, 1,1-Dimethylethyl Ester (10n).** Flash chromatography (100% $CHCl_3$ to $CHCl_3-MeOH-NH_4OH$, 95:5:0.5) followed by trituration with $CHCl_3$−hexane afforded aminodiol **10n** (114 mg; 82%) as a white solid: ^{1}H NMR (CD_3OD) δ 1.30 (s, 9H), 1.32 (s, 9H), 2.40−2.84 (m, 6H), 3.00−3.14 (m, 2H), 3.50−3.72 (m, 12H), 4.74 (s, 2H), 6.87 (d, J = 8.55 Hz, 2H), 7.15 (d, J = 8.55 Hz, 2H), 7.10−7.30 (m, 5H); ^{13}C NMR (CD_3OD) δ 28.7, 28.8, 37.0, 37.9, 43.6, 46.8, 53.1, 56.9, 57.0, 67.8, 67.9, 73.1, 73.2, 79.5, 80.0, 115.6, 127.1, 129.2, 130.5, 131.6, 133.4, 140.3, 158.0, 158.1, 169.2 (one carbon unresolved). Anal. ($C_{36}H_{54}N_4O_9$) C, H, N.

[1*S*-[1*R,2*S**(2*S**,3*R**)]]-[3-[[3-[[(1,1-Dimethylethoxy)-carbonyl]amino]-2-hydroxy-4-[4-(2-piperidinylethoxy)-phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic Acid, 1,1-Dimethylethyl Ester (10o).** A mixture of **12o** (180 mg, 0.43 mmol) and **5** (130 mg, 0.48 mmol) in DMF (0.43 mL) was heated to 100 °C for 5 h. Concentration *in vacuo* followed by flash chromatography ($CH_2Cl_2-MeOH-NH_4OH$, 98:2:0.2 to 89:10:1) afforded, after trituration with ether−pentane, **10o** (136 mg; 28%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 18H), 1.53−1.62 (m, 6H), 2.64−3.00 (m, 8H), 3.45−3.57 (m, 8H), 3.73−3.82 (m, 2H), 4.60−4.70 (m, 3H), 6.88 (d, J = 9 Hz, 2H), 7.13 (d, J = 9 Hz, 2H), 7.20−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.3, 24.5, 25.6, 26.5, 28.3, 35.4, 36.3, 43.3, 46.5, 51.6, 53.9, 65.9, 67.8, 71.1, 71.2, 77.6 79.7, 114.7, 126.4, 128.5, 129.5, 130.6, 137.8, 137.9, 156.1, 156.8, 166.2 [three carbons unresolved]. Anal. ($C_{37}H_{56}N_4O_8$) C, H, N.

***N*-[(1,1-Dimethylethoxy)carbonyl]-3-(4-pyridinyl)-L-alanine (13a).** Compound **13a** was prepared according to a literature procedure:[11b] ^{1}H NMR (CD_3OD) δ 1.30 (s, 9H), 2.96 (m, 1H), 3.27 (m, 1H), 4.41 (m, 1H), 7.37 (m, 2H), 8.44 (br s, 2H).

***N*-[(1,1-Dimethylethoxy)carbonyl]-3-(6-quinolinyl)-L-alanine (13b).** Compound **13b** was prepared according to a literature procedure:[11a] ^{1}H NMR (DMSO-d_6) δ 1.28 (s, 9H), 3.07 (m, 1H), 3.26 (m, 1H), 4.21 (m, 1H), 6.63 (br s, 1H), 7.46 (dd, J = 4.3, 8.1 Hz, 1H), 7.64 (dd, J = 1.7, 8.6 Hz, 1H), 7.75 (d, J = 1.7 Hz, 1H), 7.91 (d, J = 8.6 Hz, 1H), 8.22 (dd, J = 8.1, 4.3 Hz, 1H), 8.82 (dd, J = 1.7, 4.3 Hz, 1H).

***N*-[(1,1-Dimethylethoxy)carbonyl]-4-[3-(4-morpholinyl)-3-oxopropyl]-L-phenylalanine (13c).** Benzyl ester **18** (1.9 g, 4.4 mmol) was stirred over 20% $Pd(OH)_2$ (0.25 g) in MeOH (56 mL) under an atmosphere of H_2 for 1 h. The reaction mixture was filtered through Celite, washed with hot MeOH followed by HOAc−MeOH (1:99). The combined filtrates were concentrated *in vacuo* to give a white solid (1.4 g). This was combined with crude product (1.7 g) from a previous reaction and chromatographed (EtOAc−hexane−HOAc, 50:49:1) to afford, after azeotroping with CH_2Cl_2−heptane (1:1, 3×), the corresponding acid (2.4 g; 76%) as a white solid.

To a mixture of the above acid (1.8g, 5.1 mmol) and morpholine (0.3 mL, 5.1 mmol) in DMF at 0 °C was added HOBT (0.82 g, 6.1 mmol) followed by *N*-methylmorpholine (0.7 mL, 6.1 mmol) and WSC (1.0 g, 5.1 mmol). The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 18 h. Additional HOBT (0.4 g, 3.1 mmol), morpholine (0.15 mL, 2.5 mmol), *N*-methylmorpholine (0.33 mL, 3.1 mmol), and WSC (0.5 g, 2.5 mmol) were added sequentially at 0 °C at this point. Stirring was continued at 0 °C for 1 h and at room temperature for 18 h. The reaction mixture was diluted with EtOAc, and the organic phase was washed with H_2O, saturated aqueous $NaHCO_3$, 5% aqueous citric acid, and brine and dried (Na_2SO_4). Concentration *in vacuo* gave a yellow oil, which was further purified by chromatography (CH_2Cl_2-MeOH, 95:5) to afford the corresponding morpholinamide (1.95 g; 82%) as a light yellow oil.

Aqueous LiOH (9.04 mL of a 1 M solution) was added to a rapidly stirred solution of the above morpholinamide (1.9 g, 4.5 mmol) in THF (22 mL) and H_2O (13 mL) at room temperature. After 3 h, volatiles were removed *in vacuo*, and the remaining aqueous phase was acidified to pH 1 with 1 N aqueous HCl and extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to yield the acid **13c** (1.8 g; 100%) as a colorless foam: ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 2.60 (t, J = 7.7 Hz, 2H), 2.90 (t, J = 7.7 Hz, 2H), 3.12 (m, 1H), 3.33 (m, 2H), 3.50 (m, 2H), 3.61 (br s, 5H), 4.59 (m, 1H), 5.09 (d, J = 8.1 Hz, 1H), 6.94 (br s, 1H), 7.03−7.35 (m, 4H).

[*S*-(*R,*R**)]-[2-(4-Pyridinylmethyl)-1-oxiranylethyl]carbamic acid, 1,1-dimethylethyl ester (14a):** ^{1}H ($CDCl_3$) δ 1.30 (s, 9H), 2.69−2.95 (m, 5H), 3.69 (m, 1H), 4.70 (br d, J = 8.2 Hz, 1H), 7.09 (d, J = 4.8 Hz, 1H), 8.44 (d, J = 4.6 Hz, 1H).

[*S*-(*R,*R**)]-[2-(6-Quinolinylmethyl)-1-oxiranylethyl]-carbamic acid, 1,1-dimethylethyl ester (14b):** ^{1}H NMR (CD_3OD) δ 1.23 (s, 9H), 2.61−2.75 (m, 2H), 2.83 (m, 1H), 2.92 (m, 1H), 3.19 (dd, J = 4.3, 13.8 Hz, 1H), 3.65 (m, 1H), 7.40 (dd, J = 4.3, 8.1 Hz, 1H), 7.59 (dd, J = 1.7, 8.6 Hz, 1H), 7.68 (d, J = 1.7 Hz, 1H), 7.85 (d, J = 8.6 Hz, 1H), 8.20 (dd, J = 4.3, 8.1 Hz, 1H), 8.67 (dd, J = 1.7, 4.3 Hz, 1H).

[*S*-(*R,*R**)]-[2-[4-[3-(4-Morpholinyl)-3-oxopropyl]phenyl]-1-oxiranylethyl]carbamic acid, 1,1-dimethylethyl ester (14c):** ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H), 2.60 (t, J = 7.7 Hz, 2H), 2.70−3.15 (m, 7H), 3.38 (m, 2H), 3.54 (m, 2H), 3.63 (m, 5H), 4.50 (br s, 1H), 7.16 (m, 5H).

[1*S*-[1*R,2*S**(2*S**,3*R**)]]-[3-[[3-[[(1,1-Dimethylethoxy)-carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(4-pyridinylmethyl)propyl]carbamic Acid, 1,1-Dimethylethyl Ester (15a).** A solution of epoxide **14a** (35.2 mg, 0.13 mmol) and amino alcohol **5** (38.0 mg, 0.135 mmol) in DMF (0.14 mL) was heated at 100 °C for 4 h. The reaction mixture was concentrated *in vacuo* and purified by chromatography ($CH_2Cl_2-MeOH-NH_4OH$, 99:1:0.1 to 90:10:1) to yield **15a** (3.4 mg; 4.8%) as a white solid: ^{1}H NMR (CD_3OD; 50 °C) δ 1.29 (br s, 18H), 2.60−2.85 (m, 6H), 3.05−3.27 (m, 2H), 3.76−3.59 (m, 4H), 7.31−7.14 (m, 7H), 8.39−8.37 (m, 2H); accurate mass measurement $(M + H)^+$ calcd for $[C_{29}H_{45}N_4O_6]^+$ 545.3347, found 545.3339 ($\Delta_{ppm} = 1.5$).

[1*S*-[1*R,2*S**(2*S**,3*R**)]]-[3-[[3-[[(1,1-Dimethylethoxy)-carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(6-quinolinylmethyl)propyl]carbamic Acid, 1,1-Dimethylethyl Ester (15b).** Epoxide **14b** (100.9 mg, 0.321 mmol) was reacted with amino alcohol **5** (90 mg, 0.321 mmol) as described for the synthesis of **10e**. After a similar workup **15b** (0.114g; 59.4%) was obtained as a white solid: ^{1}H NMR (CD_3OD, 50 °C) δ 1.18−1.29 (2 s, 18H), 2.82−3.29 (m, 7H), 3.64−3.77 (m, 4H), 7.15−7.24 (m, 5H), 7.48 (m, 1H), 7.67−

7.76 (m, 2 H), 7.94 (d, J = 7.8 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H), 8.76 (m, 1H), 1H overlapped with the solvent peak; ^{13}C NMR (CD_3OD) δ 28.5, 28.7, 37.8, 37.9, 52.5, 52.7, 56.6, 56.8, 73.3, 80.0, 122.4, 127.1, 130.6, 129.7, 129.2, 129.0, 128.6, 133.3, 137.9, 139.4, 140.0, 147.5, 150.4, 158.9, 158.1 (two aromatic and two aliphatic carbons unresolved); accurate mass measurement $(M + H)^+$ calcd for $[C_{33}H_{47}N_4O_6]^+$ 595.3496, found 595.3471 ($\Delta_{ppm} = -4.2$).

[1*S*-[1*R,2*S**(2*S**,3*R**)]]-[3-[[3-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[3-(4-morpholinyl)-3-oxopropyl]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic Acid, 1,1-Dimethylethyl Ester (15c).** A mixture of epoxide **14c** (0.24 g, 0.59 mmol) and amino alcohol **5** (0.22 g, 0.59 mmol) in MeOH (0.6 mL) was heated at 55 °C for 18 h. Volatiles were removed *in vacuo*, and the resulting colorless oil was purified by chromatography (CH_2Cl_2−MeOH−NH_4OH, 97.8:2.0:0.2 to 95.6:4.0:0.4) to afford the crude aminodiol (0.37 g; 80%) as a colorless oil.

A mixture of the aminodiol (0.27 g, 0.35 mmol) and 20% $Pd(OH)_2$/C (30 mg) in MeOH (1.75 mL) and glacial acetic acid (1.75 mL) was stirred under an atmosphere of H_2 for 2 h. The mixture was filtered through Celite, which was washed with excess MeOH. The combined filtrates were concentrated *in vacuo*. Water was added to the residue, and the aqueous layer was neutralized with aqueous 30% NH_4OH and then extracted with EtOAc (2×). The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated *in vacuo* to give a colorless gel. This material was purified by chromatography (CH_2Cl_2−MeOH−NH_4OH, 97.8:2.0:0.2 to 95.6:4.0:0.4) to afford **15c** (0.152 g; 64%) as a white crystalline solid: ^{1}H NMR ($CDCl_3$) δ 1.1−1.5 (s, 18H), 2.5−3.1 (m, 12H), 3.3−3.4 (m, 2H), 3.5−3.7 (m, 7H), 3.8−3.9 (m, 1H), 4.5−4.8 (m, 1H), 7.0−7.5 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 28.3, 31.0, 34.8, 35.9, 36.3, 42.0, 46.0, 51.7, 54.0, 66.5, 66.9, 71.3, 79.7, 126.4, 128.4, 128.5, 129.5, 129.7, 135.7, 137.8, 139.1, 156.1, 170.9 (five carbons unresolved). Anal. ($C_{37}H_{56}N_4O_8$) C, H, N.

***N*-Boc-L-tyrosine, Methyl Ester (16).** To a 0 °C solution of L-tyrosine methyl ester hydrochloride (5.0 g, 21.65 mmol) in MeOH (22 mL) was added Et_3N (9.0 mL, 64.95 mmol) and di-*tert*-butyl dicarbonate (5.19 g, 23.82 mmol). The reaction mixture was stirred for 15 min at 0 °C and for 2 h at room temperature and then was concentrated *in vacuo*. This crude material was purified by chromatography (EtOAc−hexane, 1:1) to give *N*-Boc-L-tyrosine methyl ester (**16**) (7.2 g; 100%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 2.81−3.12 (m, 2H), 3.71 (s, 3H), 4.52 (m, 1H), 5.05 (d, J = 8.1 Hz, 1H), 6.62 (br s, 1 H), 6.74 (d, J = 8.6 Hz, 2H), 6.96 (d, J = 8.6 Hz, 2H).

***N*-[(1,1-Dimethylethoxy)carbonyl]-4-[[(trifluoromethyl)sulfonyl]oxy]-L-phenylalanine, Methyl Ester (17).** Et_3N (3.6 mL, 26.0 mmol) was added dropwise to a solution of *N*-Boc-L-tyrosine methyl ester (7.0 g, 23.7 mmol) and *N*-phenyltrifluoromethanesulfonimide (9.3 g, 26.1 mmol) in CH_2Cl_2 (65 mL) at 0 °C, and the reaction mixture was stirred at 0 °C for 1 h and at room temperature for 1 h. The mixture was diluted with Et_2O (200 mL) and then successively washed with water (100 mL), 1 N aqueous NaOH (100 mL), water (100 mL), and brine (100 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to furnish a yellow oil, which was purified by chromatography (hexane−EtOAc, 4:1) to give triflate **17** (8.3 g; 82%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H), 3.05 (m, 1H), 3.18 (m, 1H), 3.72 (s, 3H), 4.60 (m, 1H), 5.05 (d, J = 6.8 Hz, 1H), 7.12−7.36 (m, 5H).

***N*-[(1,1-Dimethylethoxy)carbonyl]-4-[3-oxo-3-(phenylmethoxy)-1-propenyl]-L-phenylalanine (18).** To a degassed solution of **17** (4.0 g, 9.40 mmol) in DMF (24 mL) were successively added benzyl acrylate (2.8 mL, 18.4 mmol), Et_3N (7.9 mL, 54.2 mmol), and $(Ph_3P)_2PdCl_2$ (0.70 g) at room temperature. The solution was heated at 90 °C for 48 h and then concentrated *in vacuo* to give a dark brown residue, which was purified by chromatography (hexane−EtOAc, 3:1 to 2:1) to give benzyl cinnamate **18** (2.85 g; 68%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H), 3.04 (m, 1H), 3.15 (m, 1H), 3.72 (s, 3H), 4.59 (m, 1H), 4.98 (m, 1H), 5.25 (s, 2H), 6.46 (d, J = 16.2 Hz, 1H), 7.15 (d, J = 8.1 Hz, 1H), 7.29−7.53 (m, 8 H), 7.70 (d, J = 16.2 Hz).

[*S*-(*R,*R**)]-[2-[4-[(Trifluoromethyl)sulfonyl]phenyl]-1-oxiranylethyl]carbamic Acid, 1,1-Dimethylethyl Ester (19).** To a 0 °C suspension of phenol **11** (1.9 g, 6.80 mmol) in CH_2Cl_2 (10 mL) was added *N*-phenyltrifluoromethanesulfonimide (2.67 g, 7.48 mmol), followed by addition of Et_3N (1.2 mL, 8.16 mmol). The mixture was stirred for 1 h at 0 °C and for 40 min at room temperature. DMF (3 mL) was added, and the mixture was stirred for 1 h. The reaction mixture was partitioned between EtOAc (50 mL) and water (50 mL). The aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic extracts were washed with aqueous 1.0 N NaOH, water, and brine and then dried (Na_2SO_4). Flash chromatography (hexane−EtOAc, 4:1 to 2:1) afforded triflate **19** (2.36 g, 84%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 9H), 2.68−3.10 (m, 5H), 3.75 (br s, 1H), 4.45 (br s, 1H), 7.22 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H).

[*S*-(*R,*R**)]-[2-(4-Vinylphenyl)-1-oxiranylethyl]carbamic Acid, 1,1-Dimethylethyl Ester (20).** To a solution of compound **19** (206 mg, 0.5 mmol) in anhydrous 1-methyl-2-pyrrolidinone (3 mL) was added LiCl (freshly flame-dried under vacuum, 64 mg, 1.5 mmol) and triphenylarsine (31 mg, 0.1 mmol). The mixture was purged with argon for 10 min; tris(dibenzylideneacetone)dipalladium (23.3 mg, 0.024 mmol) was then added, and the reaction mixture was stirred for 5 min. Vinyltributyltin (175.5 μL, 0.6 mmol) was added, and the mixture was stirred for 2 h at room temperature and then heated overnight (20 h) at 45 °C. The mixture was partitioned between 1:1 saturated aqueous $NaHCO_3$−EtOAc, and the aqueous layer was extracted with EtOAc (3×). The combined organic extracts were washed with water (3×) and brine (1×) and dried (Na_2SO_4). Flash chromatography (hexane−EtOAc, 9:1 to 2:1) afforded compound **20** (81 mg; 56%) as a yellow-brown solid: mp 115−116 °C; MS (FAB) 290^+ $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H), 2.72−3.02 (m, 5H), 3.69 (br s, 1H), 4.44 (br s, 1H), 5.23 (d, J = 10.9 Hz, 1H), 5.73 (d, J = 17.6 Hz, 1H), 6.70 (dd, J = 10.9, 17.6 Hz, 1H), 7.19 (d, J = 8.1 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H).

[*S*-(*R,*R**)]-[2-[4-(Hydroxymethyl)phenyl]-1-oxiranylethyl]carbamic Acid, 1,1-Dimethylethyl Ester (21).** Ozone was bubbled for 10 min into a −78 °C solution of compound **20** (200 mg, 0.69 mmol) in MeOH (6.5 mL) until a blue color developed. The reaction mixture was then purged with N_2 for 5 min, and $NaBH_4$ (131 mg, 3.46 mmol) was added. The mixture was stirred for 10 min at −78 °C, allowed to warm to 0 °C, and stirred for 30 min. Saturated aqueous NH_4Cl was added, and the mixture was extracted with EtOAc (2×). The combined organic extracts were washed with brine and dried (Na_2SO_4). Flash chromatography (hexane−EtOAc, 1:1) afforded **21** (187 mg; 92%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H), 2.70−3.00 (m, 6H), 3.68 (br s, 1H), 4.47 (br s, 1H), 4.67 (s, 2H), 7.22 (d, J = 7.7 Hz, 2H), 7.32 (d, J = 7.7 Hz, 2H).

[*S*-(*R,*R**)]-[2-[4-[[(4-Morpholinylcarbonyl)oxy]methyl]phenyl]-1-oxiranylethyl]carbamic Acid, 1,1-Dimethylethyl Ester (22).** To a solution of compound **21** (117 mg, 0.4 mmol) in CH_3CN (2 mL) was added Et_3N (167 μL, 1.2 mmol), followed by *N*,*N*′-disuccinimidyl carbonate (154 mg, 0.6 mmol). The mixture was stirred for 2 h and concentrated *in vacuo*, and the residue was dissolved in EtOAc. The solution was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated *in vacuo* to afford the mixed carbonate, which was used without further purification. A solution of the carbonate in CH_2Cl_2 (0.8 mL) was added to a solution of morpholine (42 mL, 0.48 mmol) and Et_3N (84 mL, 0.60 mmol) in CH_2Cl_2 (2 mL). The resulting mixture was stirred for 1 h, then diluted with additional CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and brine, and then dried (Na_2SO_4). Concentration *in vacuo* followed by flash chromatography (hexane−EtOAc, 2:1) afforded carbamate **22** (145 mg; 90%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 9H), 2.72−3.05 (m, 5H), 3.49 (m, 4H), 3.65 (m, 5H), 4.45 (br s, 1H), 5.12 (s, 2H), 7.22 (d, J = 7.9 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H).

[1*S*-[1*R,2*S**(2*S**,3*R**)]]-[3-[[3-[[(1,10-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[[(4-morpholinylcarbonyl)oxy]methyl]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic Acid, 1,1-Dimethylethyl Ester (23).** A mixture of **22** (76 mg, 0.187 mmol) and amino alcohol **5** (63 mg, 0.224 mmol) in DMF (0.5 mL) was heated at 100 °C for 4.5 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography

($CHCl_3$−MeOH−NH_4OH, 98:2:0.2 to 95:5:0.5). Successive triturations with $CHCl_3$-hexane and with Et_2O gave aminodiol **23** (82 mg; 64%) as a white solid: ^{1}H NMR (CD_3OD) δ 1.28 (s, 9H), 1.29 (s, 9H), 2.40−2.85 (m, 6H), 3.10 (m, 2H), 3.45 (m, 4H), 3.52−3.72 (m, 8H), 5.08 (s, 2H), 7.10−7.35 (m, 9H); ^{13}C NMR (CD_3OD) δ 28.4, 28.7, 37.6, 37.9, 45.3, 53.1, 56.8, 56.9, 67.6, 68.3, 73.1, 79.9, 127.1, 129.0, 129.2, 130.5, 130.7, 135.7, 140.3, 140.5, 157.0, 158.1 (three carbons unresolved). Anal. ($C_{36}H_{54}N_4O_9$) C, H, N.

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	IC_{50} (nM)	ED_{50} (nM)
A-77003 (Abbott)	2.3 (<1)	50 (200)
Ro 31−8959 (Roche)	0.85 (<0.4)	4 (2)
Sc-52151 (Monsanto-Searle)	4.0 (6.0)	20 (21)
L-735,524 (Merck)	1.1 (0.4)	10 (CIC_{95} = 50)

(6) The standard P_1/P_1' (S_1/S_1') nomenclature is used in this paper. For simplicity, the tyrosine-derived moiety of amino diols **10a**−**o** is defined to be binding in the S_1' subsite (i.e. the alkylated phenol group is the P_1' substituent).

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(15) An additional benefit of the increase in polarity is enhanced aqueous solubility. For example, the solubility of **10n** at pH 7 is 200 μM compared to 5 μM for the parent compound **1**.

(16) The X-ray structure of **1** complexed to HIV protease shows that the phenyl and Boc groups occupy the S_1 and S_2 subsites of the enzyme, respectively. The *para* position of the P_1' phenyl group is exposed to the solvent, thereby allowing substitution at this position. Molecular modeling was performed by attachment of the morpholinamide group to the *para* position and subsequent geometrical optimization. The atomic positions were fixed to the crystal structure coordinates with the *para* substituent being allowed to freely move. Several low-energy conformations were found, all of which place the morpholinamide group in the solvent and interacting with surface amino acids (Arg8, Phe53, Pro81, and Val82).

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(19) For a recent example of relating log k' with log *P* values, see: Henczi, M.; Nagy, J.; Weaver, D. F. Determination of Octanol-Water Partition Coefficients for a Series of Imidazolidinediones by a Novel Combination of Micro Shake-Flask and HPLC Techniques. *J. Liq. Chromatogr.* **1994**, *17*, 2605 and references cited therein.

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(21) The P_1' analogs used in this correlation comprise the amino diol compounds found in Tables 1−4 (with the exception of **15a** and **15b**, which are neither phenylalanine nor tyrosine-derived) as well as the compounds in Table 5, which are not further discussed in the text. Compound **10j** is not included in this correlation as we concluded from its poor IC_{50}/ED_{50} ratio that this analog does not penetrate cells and therefore its cytotoxicity value would not appear to be meaningful.

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