Bis Tertiary Amide Inhibitors of the HIV-1 Protease Generated via Protein Structure-Based Iterative Design

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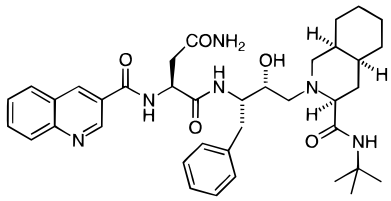
A series of potent nonpeptide inhibitors of the HIV protease have been identified. Using the structure of compound **3** bound to the HIV protease, bis tertiary amide inhibitor **9** was designed and prepared. Compound **9** was found to be about 17 times more potent than **3**, and the structure of the protein−ligand complex of **9** revealed the inhibitor binds in an inverted binding mode relative to **3**. Examination of the protein−ligand complex of **9** suggested several modifications in the P1 and P1′ pockets. Through these modifications it was possible to improve the activity of the inhibitors another 100-fold, highlighting the utility of crystallographic feedback in inhibitor design. These compounds were found to have good antiviral activity in cell culture, were selective for the HIV protease, and were orally available in three animal models.

Introduction

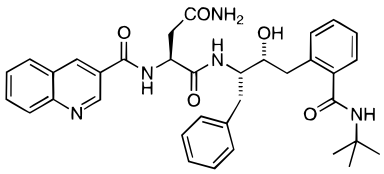
The spread of acquired immunodeficiency disease (AIDS) continues to be a health problem of global proportions, and the search for useful therapeutics to help combat and control the disease continues. One encouraging approach involves inhibiting the virally encoded protease (HIV-PR). This aspartyl protease is responsible for the cleavage of the *gag* and *gag-pol* polyproteins into the structural and functional proteins of the mature virion. The HIV-PR is essential for viral replication and when disabled via mutation or inhibition produces immature virions which are replication incompetent.[1] Thus the HIV-PR represents an ideal target for interruption of the viral life cycle, and several HIV-PR inhibitors are currently being evaluated in the clinic.[2]

Crystallographic studies have shown that the HIV-PR is a *C*2 symmetric homodimer. Each monomer contains one of the catalytic aspartic acid residues and a β turn or flap region. These flap regions fold onto the substrate or inhibitor, making several hydrogen bonding contacts upon binding. Since its discovery, the HIV-PR has undergone extensive structural studies and is arguably one of the best characterized proteases to date.[3] The protease is unique in its substrate specificity, cleaving phenylalanine (tyrosine)−proline peptide bonds. Taken together, this increases the attractiveness of the HIV-PR as a therapeutic target.[1]

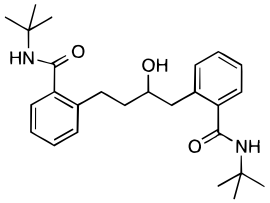
Early inhibitors of the HIV-PR were substrate analogs, examples of which include Ro31-8959 (Saquinivar, **1**)[4] and LY289612 (**2**).[5] Unfortunately these inhibitors were peptidic in nature and displayed poor pharmacokinetic properties (short half-life, low availability) in animal models. These shortcomings were generally attributed to the poor solubility and high molecular weight of these inhibitors. A great deal of work has been spent attempting to convert peptidic lead molecules into compounds with superior properties, and in some cases this has been successful.[6] More recently, nonpeptide inhibitors of the HIV-PR have been identified either by rational design[7] or by broad screening of compound libraries.[8] Thus, in order to avoid the inherent difficulties associated with developing peptidic lead compounds into drugs, it would appear necessary to identify nonpeptide inhibitors of the HIV-PR early in the drug discovery process.



1 Ro31-8959, Saquanivir™



2 LY289612



3 AG1132

In a previous report, a series of novel inhibitors of the HIV-PR based on the structural information of LY219612 (**2**) bound to the HIV-PR was described.[9] This resulted in the discovery of AG1132 (**3**), a nonpeptide inhibitor with good inhibitory activity (IC_{50} = 20 μM). More significantly, the structure of the complex of **3** bound to the HIV-PR was obtained, and with appropriate modifications the activity of **3** was improved by 20-fold. In this report, a new series of inhibitors based on the structure of **3** is presented. By the use of structure-

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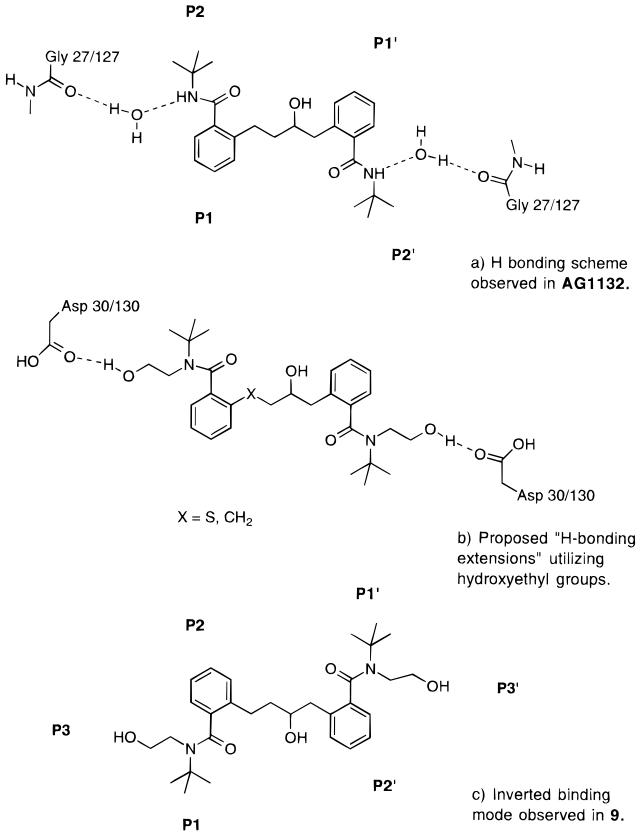


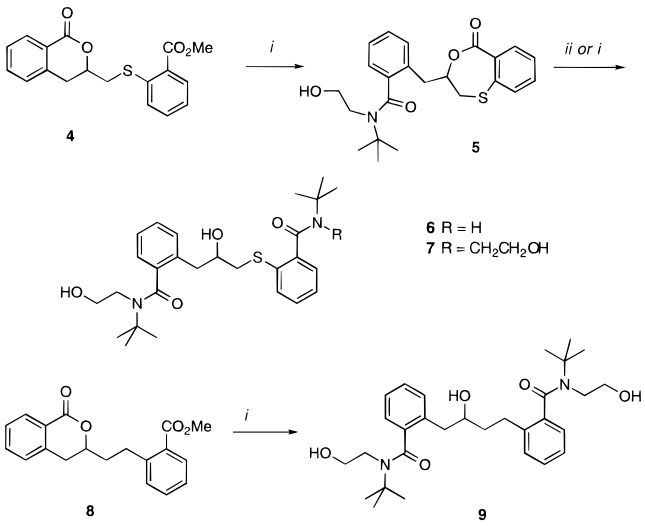
Figure 1. Design of inhibitor **9** based on the binding mode of **3**: (a) binding mode of **3**; (b) proposed binding mode of **9**; (c) experimentally observed binding mode of **9**.

based iterative ligand design, a series of bis tertiary amides was identified which has undergone a critical change in binding. This change in binding mode was exploited, improving activity over **3** by greater than 1000-fold and producing inhibitors which possess both good antiviral and pharmacological properties.[10]

Inhibitor Design

In our previous report, the optimization of the P1 and P1′ groups of **3** was described; however, no effort was made with regard to the amide groups.[9] Upon inspection of the structure of **3** bound to the HIV-PR, it was apparent that the amide NH's were not interacting directly with the protein, but rather were undergoing hydrogen bonding through ordered water molecules to the carbonyl of glycine 27/127 (Figure 1a). One modification would be to extend alkyl chains off the amide nitrogens, producing tertiary amides. The initial idea was to utilize hydroxyethyl groups to act as hydrogen-bonding "extentions" which could potentially donate a hydrogen bond to the carboxylate side chain of aspartic acid 30/130 (Figure 1b). Thus the ligand could interact through the hydroxyl groups directly with the protein as well as allow the inhibitor to access the P3 and P3′ binding sites. This idea was originally explored in the sulfide series (Figure 1b, X = S). Both the mono and bis hydroxyethyl tertiary amides were prepared (Scheme 1), and these compounds were modest improvements over the parent inhibitor (data not shown), but were similar in activity to **3** (Table 1, compounds **6** and **7**). It was known from the AG1132 series that substituting a methylene for sulfur produced a 3−5-fold improvement

Scheme 1[a]



[a] Reagents: (i) Me_3Al, $HOCH_2CH_2NH^tBu$, $PhCH_3$, Δ; (ii) Me_3Al, H_2N^tBu, $(ClCH_2)_2$, Δ.

Table 1. Biological Activity of HIV Protease Inhibitors

compd	R_1[a]	R_4[a]	K_i (μM)[b]	ED_{50} (μM)[c]	TC_{50}[d]
1	Ro31-8959		0.0009(0.00002)[e]	0.002[e]	>10
2	LY219612		0.002(0.0006)[f]	0.020[f]	122
3	AG1132		20(4.4)	nd[g]	nd
6	−	−	34(9.6)	nd	nd
7	−	−	18(4.1)	nd	nd
9	−	−	1.1(0.12)	36	>150
40	a	b	0.090(0.033)	3.4	>150
40	a	d	0.11(0.03)	3.7	nd
40	a	e	1.3(0.12)	nd	nd
40	b	b	0.021(0.006)	2.2	122
40	a	f	0.145(0.038)	7.2	nd
40	a	g	0.064(0.014)	7.6	nd
41	a	b	0.15(0.034)	4.9	nd
42	a	b	0.063(0.016)	4.2	nd
42	b	b	0.018(0.004)	0.81	nd
42	c	b	0.008(0.002)	0.78	103
42	c	h	0.0004(0.0005)	0.79	nd
42	c	d	0.006(0.003)	1.37	nd
42	c	i	0.035(0.006)	1.11	nd
43	c	b	0.002(0.001)	0.72	97
44	−	−	0.004(0.003)	0.59	nd
45	−	−	0.010(0.003)	0.95	nd
47	−	−	0.051(0.011)	1.7	nd
49	−	−	0.010(0.004)	0.86	nd
56	−	−	0.006(0.0014)	0.88	nd
58	−	−	0.002(0.001)	0.65	nd
62	−	−	0.009(0.003)	0.84	nd

[a] See Scheme 4 for R_1 and R_4 groups. [b] Standard deviation is in parentheses. [c] Antiviral activity in CEM cells. [d] Concentration (μM) at which 50% of the cells were viable. [e] See ref 4. [f] See ref 5. [g] Not determined.

in activity.[9] Thus the methylene version of **7** (Figure 1b, X = CH_2) was prepared (Scheme 1, **9**) as a racemic mixture and found to be a good inhibitor of the HIV-PR (K_i = 1.1 μM, Table 1). This represented a nearly 17-fold improvement over **3**, and the HIV-PR-ligand complex of **9** was determined in order to ascertain the binding mode.

The HIV-PR complex of **9** was solved at 2.4 Å resolution and revealed a very interesting and unexpected result. The inhibitor was found to bind in an inverted mode compared to **3** (see Figure 1c and compare with 1a). In this manner, it appeared the active enantiomer was the *R* configuration (as inferred from the crystal structure), while for **3**, it was found to be the *S* enantiomer by synthesis.[9,10] Several interest-

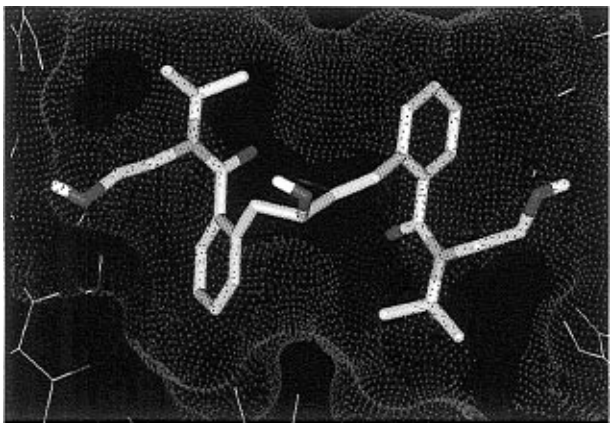


Figure 2. Crystal structure of **9** complexed to the HIV-PR determined at 2.4 Å resolution. Carbon atoms are in green, nitrogen atoms are in blue, and oxygen atoms are in red. A solvent accessible surface is seen in purple.

ing features should be noted (see Figure 2). With the reversal of the binding mode, the phenyl rings were now located in P2 and P2′ (in **3** they were located in P1 and P1′ pockets), while the *tert*-butyl groups were in P1 and P1′ (in **3** they were found in the P2 and P2′ pockets). Interestingly, ordered water molecules were observed interacting with the π clouds of the aromatic rings and accepting a hydrogen bond from the amide NH of aspartic acid 30/130. In this inverted binding mode, the hydroxyethyl groups were unable to hydrogen bond to the side chain carboxylates of aspartic acid 30/130, but instead were found to be hydrogen bonded to the same ordered water molecule interacting with the aromatic rings. This new binding mode resulted in improved bond vectors for reaching deeper into P1 and P1′ which by inspection of the protein−ligand complex were only marginally occupied.

This last observation cannot be over emphasized. A new structure/binding mode is only as useful as its ability to access all binding pockets. In **3**, the phenyl rings allowed additional access to P1 and P1′, but the bond vectors of the phenyl ring allowed for only limited changes. As will be discussed in detail below, the *tert*-butyl substituent permits access to the P1 and P1′ pockets from all three methyl groups, thus allowing a variety of changes in these binding pockets. Also the phenyl rings in P2 and P2′ appeared to be ideally located for placement of additional substituents and the hydroxyethyl groups allowed access to P3 and P3′.

As mentioned above, the P1 and P1′ sites of the structure of the HIV-PR complexed with **9** were only marginally occupied by the *tert*-butyl groups. The first modifications were directed at improving binding in the P1′ pocket which by inspection had a lipophilic cavity which could be filled by replacing a methyl group with a larger substituent. On the basis of modeling studies using the crystal structure of **9** (Figure 3A), it was decided to replace a methyl of the P1′ *tert*-butyl group with a phenyl ring. In order for this group to fit, the protein residues in this vicinity (threonine 80/180-proline 181/181-valine 82/182) would have to move about 2 Å. Such movement has been previously observed in the structure of Ro 31-8959 (**1**) complexed to the HIV-PR.[11] In this case, the large decahydroisoquinoline system effected the protein movement. Thus it was predicted that the protein could accommodate the larger phenyl group. This compound (**40ab** in Table 1) was prepared and found to be about 11-fold more active than **9** (K_i = 0.090 nM). Solution of the protein−ligand complex of **40ab** at 2.35 Å resolution indicated that the compound bound as anticipated (see Figure 3B and compare with 3A) with the necessary protein movement to accommodate the phenyl group (proline 81/181 was observed to move approximately 2.1 Å relative to its position in **9**). An additional point that should be made is that this modification did not alter the new binding mode.

Encouraged by these results, the protein−ligand complexes of **9** and **40ab** were further scrutinized for binding pockets which were not adequately filled. It was quickly realized that the P1 pocket could also be filled with a dimethylbenzyl group and this modification was successful, although the improvement in activity was not as large (about 4-fold) as observed with the P1′ dimethylbenzyl group (**40bb** in Table 1). Although this change might be expected to produce an equal or nearly equal improvement in activity (compared to the P1′ dimethylbenzyl), it must be realized that although the active site of the HIV-PR is symmetrical, the inhibitor is not. Thus the second dimethylbenzyl group does not interact with the protein in completely the same manner. This phenomenon has been previously observed in the secondary amide series.[9,10] Careful inspection of the P2′ phenyl ring revealed a small pocket which could be filled nicely by a methyl group in the 5 position. This resulted in a slight improvement in activity (compare **40ab** with **42ab**, see Table 1). Interestingly a similar pocket exists on the P2 phenyl ring; however, this modification resulted in an almost 2-fold loss in activity (compare **41ab** and **40ab** in Table 1). It is not clear from the structure of **40ab** why there is a loss of potency in this case. Perhaps there is some subtle communication between binding pocket residues in this case.

New structural leads were also generated with a Monte Carlo *de novo* ligand generation (MCDNLG) program which was performed on both the P1 and P1′ sites to produce several new ideas.[12] In P1′ two new ideas were suggested that were synthetically viable. In the first case, a 1,1-diethylbutyl group replaced the *tert*-butyl group to produce a potent inhibitor (**40ad**, Table 1) being about 11-fold more potent than **9**. An alternative suggestion was the use of a *cis*-perhydroindan system. This idea was particularly interesting since the saturated indan ring system would have to place one ring into the active site parallel to the butyl connecting chain ("doubling back on itself"), thus filling space that has not been addressed by previous inhibitors in this series. This modification was prepared as an inseparable mixture of diasteriomers, but the mixture was found to be quite active, about 20-fold more potent than **9** (**40ag**, Table 1). Structures of these compounds (**40ad** and **40ag**) complexed to the HIV-PR were determined at 2.1 and 2.2 Å resolution, respectively, and can be seen in Figure 3C,D. Both **40ad** and **40ag** bound essentially as predicted. In the perhydroindan case we could not unambiguously determine which ring was located in the active site parallel to the butyl chain although the cyclopentyl ring appeared to fit the data best.

On the P1 side, MCDNLG suggested a three-carbon homologation in the form of a 1-ethylcyclopentyl group to replace the *tert*-butyl group. Like the perhydroindan system, this would require either the ethyl group or the

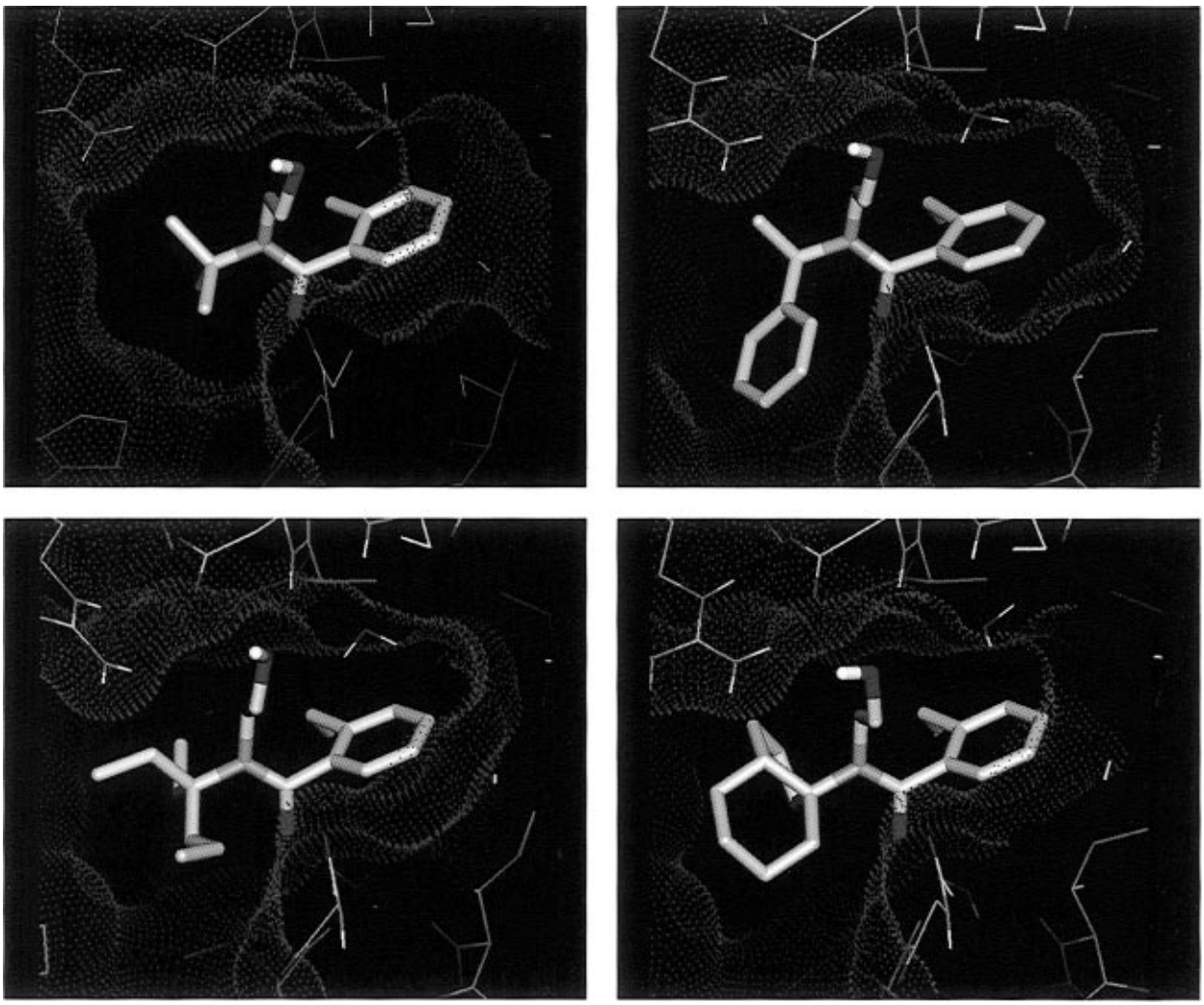


Figure 3. Modifications of **9** in P1′: (A, top left) P1′ group of **9** (*tert*-butyl); (B, top right) P1′ group of **40ab** (dimethylbenzyl); (C, bottom left) P1′ group of **40ad** (1,1-diethylbutyl); (D, bottom right) P1′ group of **40ag** (*cis*-perhydroindan). Atom colors are the same as in Figure 2.

cyclopentyl ring to double back on the inhibitor, filling space not addressed by previous inhibitors. This group was a 7-fold improvement over the *tert*-butyl group in P1 (compare **42cb** with **42ab** in Table 1). Thus the combination of the cyclopentyl ethyl (in P1) with the dimethylphenyl (in P1′) and the 5-methyl group in P2′ produced the highly potent inhibitor **42cb**. This represents a greater than 2000-fold improvement over AG1132 (**3**) and an over 100-fold improvement over **9**. A structure of **42cb** bound to the HIV-PR was determined and revealed excellent complimentarity with the active site.[10]

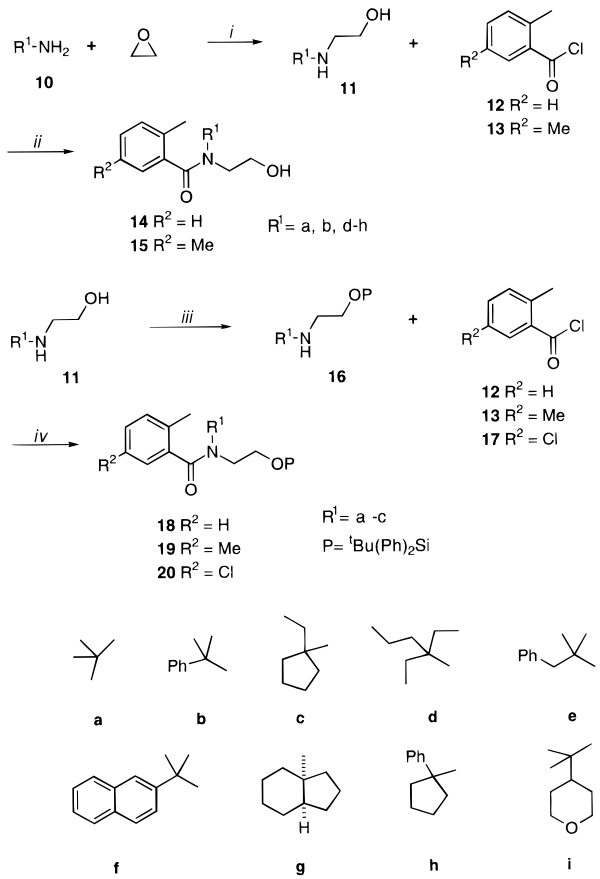
Chemistry

Initially, the sulfide analogs **6** and **7** were prepared because they were synthetically more accessible. These compounds were prepared by the chemistry in Scheme 1. Reaction of lactone ester **4**[9] with a 6-fold excess of the aluminum amide derived from hydroxyethyl-*tert*-butylamine produced the lactone amide **5**.[13] This material was reacted with aluminum amides derived from either *tert*-butylamine or hydroxyethyl-*tert*-butylamine to produce the final compounds **6** or **7**, respectively.

The synthesis of the carbon analog **9** was accomplished in one step from the known intermediate[9] **8** (Scheme 1). Thus both the ester and lactone were reacted simultaneously with the aluminum amide derived from hydroxyethyl-*tert*-butylamine and trimethylaluminum to produce **9** in modest yield. However, this chemistry was not ammendable to preparing compounds with two different amide groups, so an alternate synthesis was developed, which is outlined in Scheme 4. The key step was the coupling of an *o*-toluoyl anion[14] with the *N*,*O*-dimethylamides **34** or **35** to generate ketones[15] **36**−**39**, which were easily reduced and deprotected to give the final inhibitors.

In Schemes 2 and 3 the synthesis of the tertiary amide precursers is described. The starting amines **10b**−**h** were either literature compounds or were prepared by known methods (see the Experimental Section). In the case of amine **10i**, the synthesis was carried out according to Scheme 3. The known pyran-4-carboxylic acid[16] (**28**) was converted to the tertiary carbinol **29** with methyllithium. The alcohol was treated with KCN and H_2SO_4 in acetic acid to give amine **10i** after acidic hydrolysis of the formamide intermediate. The amines **10b**−**i** were alkylated with ethylene oxide in the presence of $LiClO_4$,[17] and the resultant alcohol was protected as a *tert*-butyldiphenylsilyl ether to produce compounds **16b**−**h** (Scheme 2). In addition (Scheme 3) amine **21** was prepared by reaction of **10b**

Scheme 2[a]



[a] Reagents: (i) $LiClO_4$, THF/CH_3CN; (ii) (1) TEA, CH_2Cl_2, (2) KOH, aqueous MeOH; (iii) $^tBu(Ph)_2SiCl$, TEA, CH_2Cl_2; (iv) TEA, CH_2Cl_2.

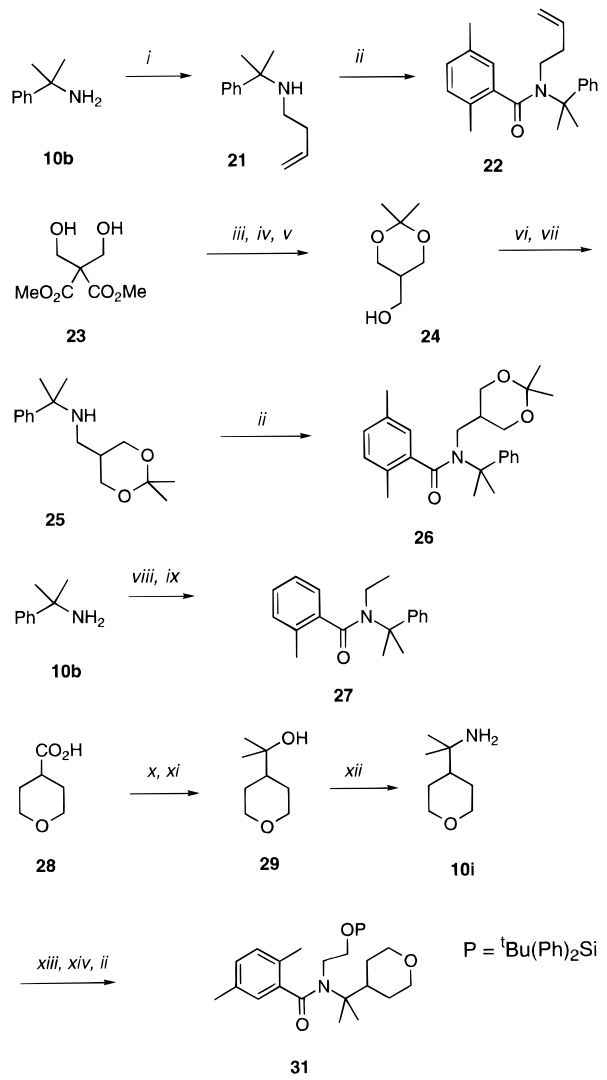
with 4-bromobutene. Reductive amination of **10b** with acetaldehyde followed by acylation with **12** produced amide **27**. Alkylation of **10b** with the mesylate derived from **24** produced amine **25**.

Acylation of the amines with *o*-toluoyl chloride (**12**), 2,5-dimethylbenzoyl chloride (**13**) or 5-chloro-2-methylbenzoyl chloride (**17**) furnished the toluamides **18a**−**c, 19a**,**b**,**d, 20b**, **22**, **26**, and **31**. In some cases, the hydroxyethylamines **11** were acylated directly with **12** or **13** to form an ester amide which was treated with sodium hydroxide to produce the hydroxyamides **14a**, **b**, **d**−**h** or **15a** (Scheme 2).

The toluoyl amide **18a**−**c** or **19a** was ortho metalated with *sec*-butyllithium in THF at −78 °C, and the resultant anion was quenched with excess ethylene oxide yielding the homologated alcohol (Scheme 4). Oxidation with either Jones reagent or pyridinium dichromate (PDC) produced the carboxylic acids **32** or **33**. The carboxylic acids **32a**−**c** or **33a** were coupled with *N*,*O*-dimethylhydroxylamine using either (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) or diethylphosphoryl cyanide (DEPC) to produce the amides **34a**−**c** or **35a**.

The compounds were completed by C-acylation of the requisite toluoyl anions generated by deprotonation of amides **14a**,**b**,**d**−**h**, **18b**, **19b**,**d**, **20b**, **22**, **26**, **27**, or **31** with *s*-BuLi followed by reaction with *N*,*O*-dimethylamides **34a**−**c** or **35a** (Scheme 4). This produced ketones **36**−**39**, which were subsequently reduced with $NaBH_4$ and deprotected with tetrabutylammonium fluoride (TBAF) to produce the final compounds **40**−**43**

Scheme 3[a]



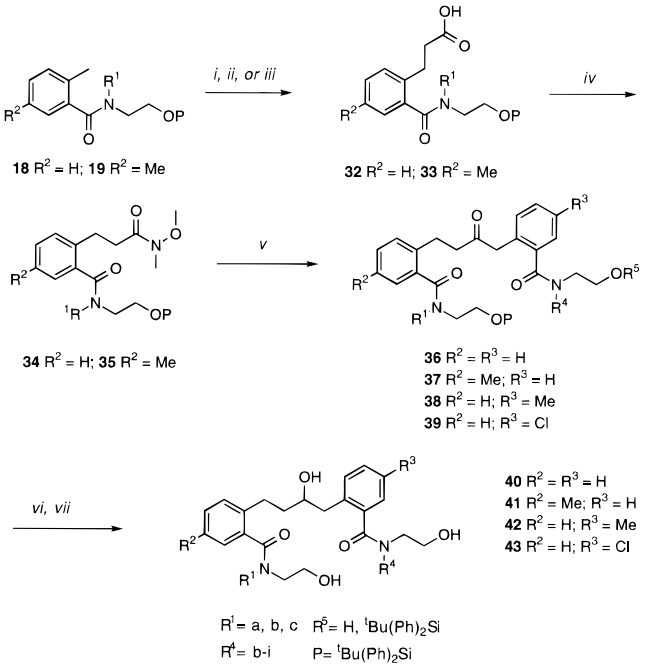
[a] Reagents: (i) 4-bromobutene, Hunig's base, 110 °C; (ii) TEA, **13**, CH_2Cl_2; (iii) $C(Me)_2(OMe)_2$, *p*-TSA, CH_2Cl_2; (iv) NaCl, H_2O, DMSO, Δ; (v) $LiAlH_4$, Et_2O; (vi) $MeSO_2Cl$, TEA, 0 °C; (vii) **10b**, Hunig's base; (viii) acetaldehyde, $NaCNBH_3$, MeOH/H_2O; (ix) TEA, **12**, CH_2Cl_2; (x) MeLi, THF, −78 °C; (xi) MeLi, THF, 0 °C; (xii) (1) KCN, HOAc, H_2SO_4, 55 °C, (2) concentrated HCl, Δ;(xiii) $LiClO_4$, ethylene oxide, THF/CH_3CN; (xiv) $^tBu(Ph)_2SiCl$, TEA, CH_2Cl_2.

as racemic mixtures. In most cases we found we could take the crude ketone directly into the reduction and deprotection step and purify the product at the end.

Compounds **44**, **45**, **47**, and **49** were prepared in an analogous fashion (Scheme 5). In the case of **45**, the final step involved acidic deprotection of the acetal **44** to produce the tetrol. Compound **49** was prepared by *cis* hydroxylation of **48** with OsO_4 to produce the tetrol.

The synthesis of phenol **56** and O-alkylated derivatives **58** and **62** can be seen in Schemes 6 and 7. The requisite amine **52** was prepared from 4-isopropylphenol (**50**) by silyl protection and oxidative nucleophilic substitution with trimethylsilyl azide, followed by azide reduction to yield the amine.[18] Standard alkylation with ethylene oxide, silyl protection, and acylation gave the desired toluamide **54**. The toluamide **54** was C-acylated with *N*,*O*-dimethylamide **34c** under our standard conditions to produce ketone **55** which could be reduced and deprotected in standard fashion to yield final compound **56**. Alternately, **55** could be selectively desilated at the phenol hydroxyl with TBAF at −50 °C

Scheme 4[a]



[a] Reagents: (i) *s*-BuLi, ethylene oxide, THF, −78 °C; (ii) PDC, DMF; (iii) Jones reagent, acetone; (iv) BOP or DEPC, Me(MeO)NH−HCl, Hunigs base, CH_2Cl_2; (v) *s*-BuLi, **14a**,**b**,**d**−**h**, **18b**, **19b**,**d**, **20b**, **31**, THF −78 °C; (vi) $NaBH_4$, MeOH; (vii) TBAF (2 equiv), THF.

followed by *O*-alkylation with 3-(chloromethyl)pyridine to yield ketone **57**. Again reduction and deprotection produced the final compound **58**. Finally morpholine derivative **62** (Scheme 7) was prepared from amide **54** by selective deprotection with TBAF at 0 °C followed by *O*-alkylation with chloroethylmorpholine to give the amide **60**. Ortho metalation of **60** followed by reaction with **34c** produced ketone **61**. The final compound **62** was obtained by reduction and deprotection in the usual fashion.

Results

The biological results for the various compounds are summarized in Table 1. Clearly the carbon analogs were superior to the sulfur-linked inhibitors (compare **7** and **9**). As was discussed in the ligand design section, increasing the bulk of the P1 and P1′ groups of the inhibitor generally improved activity. In P1′, increasing the size of the inhibitor from *tert*-butyl to dimethylbenzyl to cyclopentylphenyl (compare **9** with **40ab** and **42cb** with **42ch**) produced a dramatic increase in activity versus the enzyme. Interestingly the 1,1-diethylbutyl group appeared as effective as the dimethylbenzyl group (compare **40ad** with **40ab**), while the perhydroindan **40ag** was even better, especially if one takes into account that it is a mixture of four diastereomers. Some P1′ modifications were not as successful, such as the dimethylnaphthyl **40af**, which was less active than the dimethylbenzyl. Also, the 1,1-dimethyl-2-phenethyl group in P1′ **40ae** had essentially the same activity as a *tert*-butyl group in P1′ (**9**), indicating that the phenyl group is probably not interacting with the protein. Saturated rings such as a 4-pyran were also tolerated, compare **42cb** with **42ci**.

Replacing the hydrogen in the 5-position of the P2′ phenyl with a methyl group resulted also in an improvement in activity. Changing to chloro improved activity even more (compare **43cb** with **42cb**), presumably by inductive effects. Substituents larger than methyl did not result in further improvements (data not shown) even though the crystal structure indicated that somewhat larger substitutents could be accommodated.

On the P1 side, a trend similar to P1′ was found in that going from *tert*-butyl to dimethylbenzyl improved activity but not as dramatically as in the P1′ side (about a 4 fold improvement compare **40ab** with **40bb**). Better results were obtained with the 1-ethylcyclopentyl group which produced a larger increase (**42ab** versus **42cb**). Interestingly there appeared to be a pocket of the P2 side of the inhibitor which could also be filled by a methyl group in the 5-position. Yet this modification did not improve activity (compare **41ab** with **40ab)**. On the basis of the above SAR the combination of a dimethylbenzyl in P1′, methyl in P2′ and cyclopentylethyl in P1 were found to be the optimal both from an activity and chemistry standpoint. We utilized this optimal framework to explore some changes in the P3′ site that could improve antiviral and pharmacological properties.

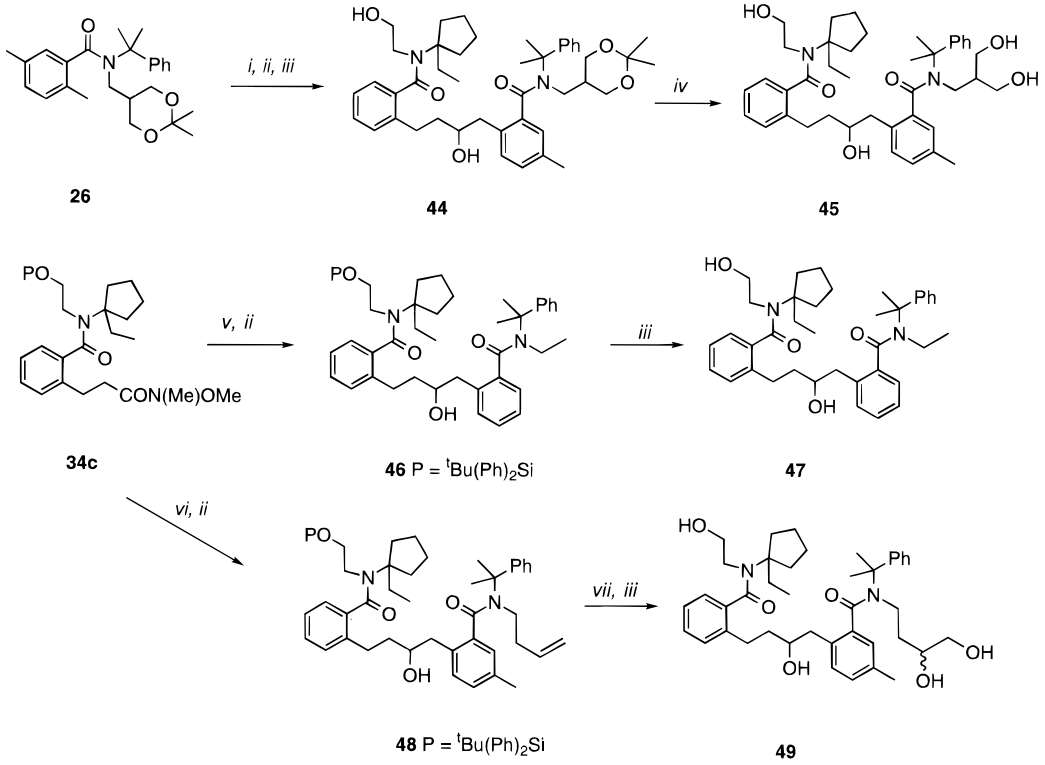
It was found that the hydroxyl groups (of the hydroxyethyl groups) appear to be important for good activity as the data for **47** indicated. The P3′ region appeared to be able to accommodate a variety of structural diols such as compounds **49** and **45.** Interestingly, the precursor to **45**, acetal **44**, was also a potent inhibitor, although this modification was not pursued due to the lability of the acetal group.

It was also discovered from the structure of **40ab** and **42cb** that the 4-position of the phenyl ring in P1′ was directed toward solvent and would be an ideal position to attach groups to improve solubility. This was accomplished with a phenol, which could be selectively alkylated with a suitable group. As the data in Table 1 indicates, the phenol **44** had activity nearly identical to that of **42cb**. Functionalizing the phenol with a 3-methylpyridine group or an ethylmorpholine group produced the potent compounds **58** and **62**, respectively.

The antiviral data from cell culture in CEM cells can be seen in Table 1. One notices a good correlation of antiviral activity with K_i for the less potent compounds, but as the K_i improved antiviral activity only improved marginally. For example the antiviral activity in going from **9** to **40ab** parallels the K_i data very nicely, but when one compares the antiviral activity of **42cb** with that of **40ab** the improvement is not as dramatic as one might anticipate. One also notices that as the compounds become more lipophilic in P1′ the antiviral data begins to drop off as well. For example the compounds **40ag** and **40af** are similar in activity to **40ab** versus the enzyme, but are both less potent in the antiviral assay. Also compare the antiviral activity of compound **42cb** with **42ch** and **42cd**. This phenomenom has been observed with other HIV PR inhibitors and may be due to the highly lipophilic nature of the inhibitors.[19]

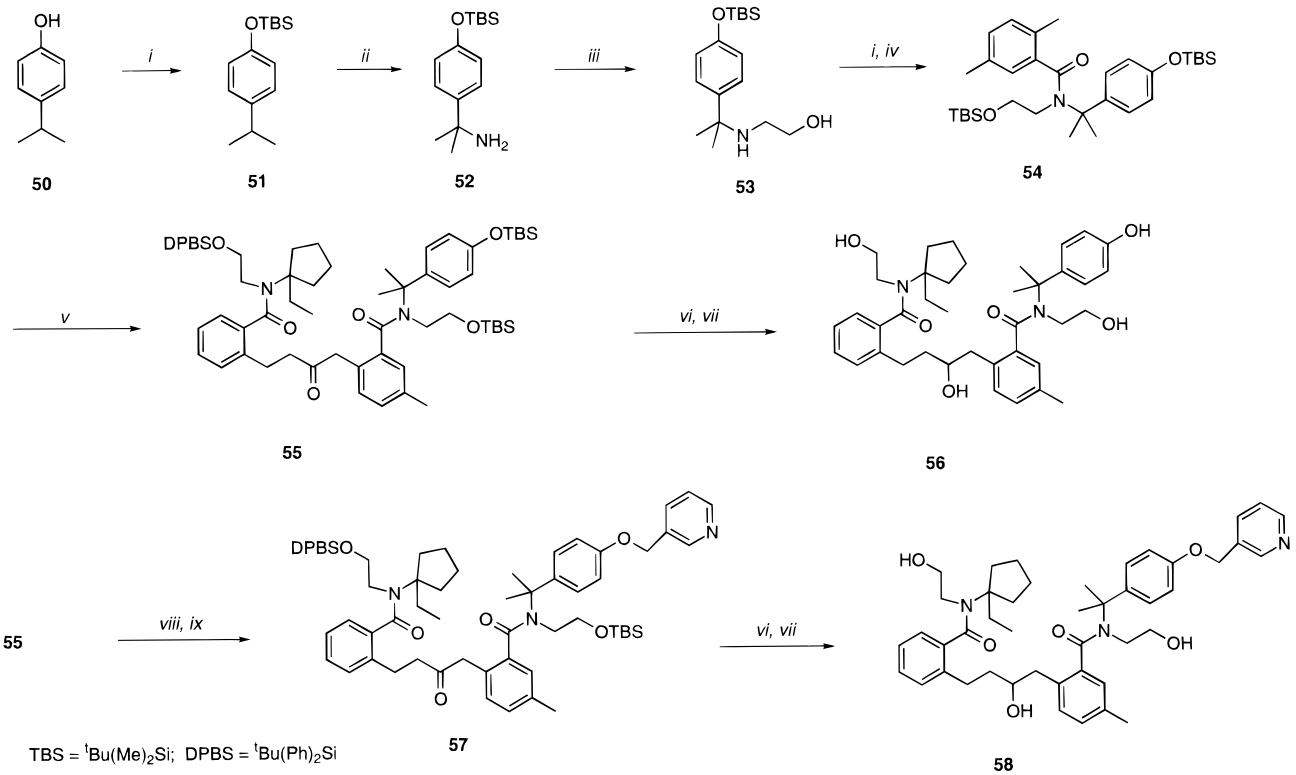
Attempts to improve antiviral activity by altering the properties of **42cb** was attempted, and examples can be seen in Table 1. Thus incorporation of an additional hydroxyl as seen in **45** and **49** did not effect the K_i

Scheme 5[a]



[a] Reagents: (i) *s*-BuLi, **34c**, THF, −78 °C; (ii) $NaBH_4$, MeOH; (iii) TBAF, THF; (iv) *p*-TSA MeOH; (v) *s*-BuLi, **27**, THF, −78 °C; (vi) *s*-BuLi, **22**, THF, −78 °C; (vii) OsO_4, NMMNO, acetone/H_2O.

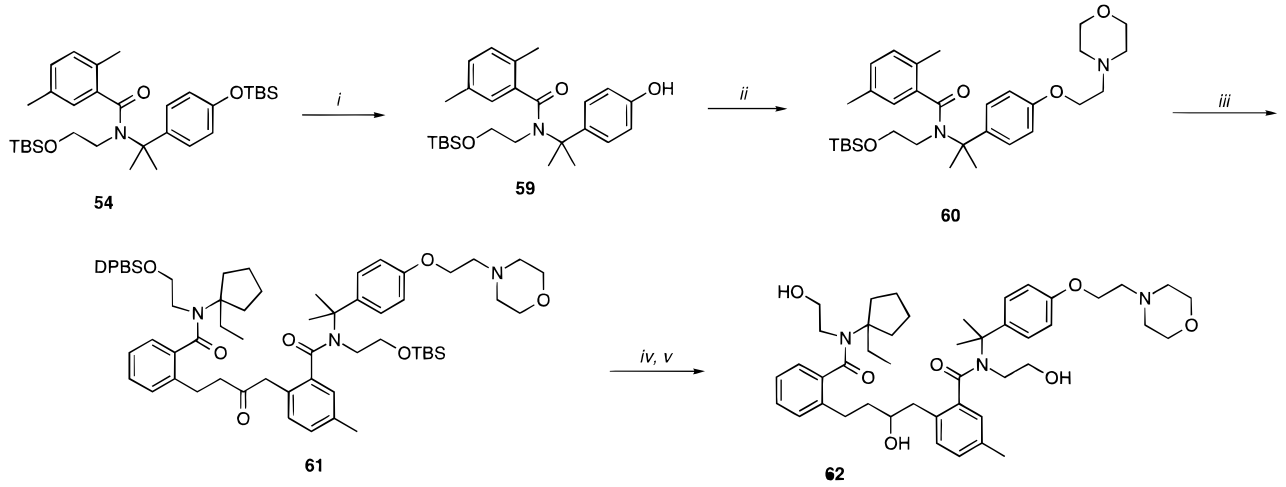
Scheme 6[a]



[a] Reagents: (i) $^tBu(Me)_2SiCl$, imidazole, DMF; (ii) (1) Me_3SiN_3, DDQ, $CHCl_3$, (2) Pd/$BaSO_4$, H_2, EtOH; (iii) ethylene oxide, $LiClO_4$, THF; (iv) **13**, TEA, THF; (v) *s*-BuLi, **34c**, THF, −78 °C; (vi) $NaBH_4$, MeOH; (vii) TBAF, THF; (viii) TBAF, THF/hexanes, −50 °C; (ix) 3-(chloromethyl)pyridine, Cs_2CO_3, KI, acetone.

significantly, but no improvement in antiviral activity was observed. Effectively the same results were observed for phenol **44**, 3-pyridyl compound **58**, and morpholino compound **62**. The parent structural skeleton **42cb** being highly lipophilic, it may require more dramatic structural changes in order to significantly alter the physical properties of these molecules. Nonetheless, several compounds possessed good antiviral activity and their pharmacological properties were investigated in several animal models.

Scheme 7[a]



[a] Reagents: (i) TBAF, $PhCH_3$, 0 °C; (ii) Cs_2CO_3, chloroethyl morpholine, dioxane, 80 °C; (iii) *s*-BuLi, **34c**, THF, −78 °C; (iv) $NaBH_4$, MeOH; (v) TBAF, THF.

Table 2. Pharmacokinetic Parameters of Selected Compounds in the Rat

compd	dose[a] (mg/kg)	route[b] (unfasted)	C_{max} (μg/mL)	$T_{1/2}$[c] (h)	% F[d]
42bb	50	iv	88.9	0.5	−
	50	po	1.2	nc	34
42cb	50	iv	88.35	1.3	−
	50	po	2.78	nc[e]	39
43cb	50	iv	110.9	1.7	−
	50	po	1.4	nc	31
45	50	iv	52.2	1.0	−
	50	po	1.16	nc	7
49	50	iv	110.8	1.3	−
	50	po	0.84	nc	2
56	50	iv	41.3	1.4	−
	50	po	no levels	−	0
58	60	iv	87.2	1.0	−
	50	po	0.86	nc	5[f]

[a] All compounds dosed in propylene glycol/water. [b] iv = intravenous, po = oral. [c] Half life. [d] Fraction of compound bioavailable. [e] Not calculated. [f] Dose corrected.

Table 3. Pharmacokinetic Parameters of Selected Compounds in the Dog and Monkey

compd	dose (mg/kg)	route (unfasted)	C_{max} (μg/mL)	$T^{1/2}$ (h)	% F
		Dog			
42bb	15	po	0.39	2.07	nc[a]
42cb	15	iv	15.95	0.24	−
	15	po	0.38	nc	3
	30	po	0.69	nc	nc
	30 + antacid[b]	po	3.26	0.52	33
43cb	15	po	0.59−2.25	nc	nc
45	15	po	1.17	0.34	nc
		Monkey			
42bb	25	po	0.86[c]	−	−
42cb	25	iv	18.28	1.08	−
	25	po	1.91	1.07	32
43cb	25	po	no levels	−	−
45	25	po	0.81	nc	nc

[a] nc = not calculated. [b] $CaCO_3$ (500 mg) dosed orally 10 min prior to and 60 min postdosing of **42cb**. [c] No levels detected in second monkey.

Pharmacology

In order to ascertain if this series of inhibitors possessed good pharmacological properties, it was decided to dose compound **9** in mice. Using propylene glycol/water as vehicle, **9** was dosed at 100 mg/kg both intravenously and intraperitoneally. Compound **9** displayed a C_{max} = 9.7 μg/mL and an availablilty of 46%. Likewise when **40ab** was dosed in mice under the same conditions, a C_{max} of 4.6 μg/mL and an availability of 11% was observed.

With these encouraging results in hand, several of the more potent inhibitors were dosed in rats intravenously and orally. This data can be seen in Table 2. The rat studies involved **42cb** and derivatives of this structure. **42cb** actually gave good results when dosed both intravenously and orally in rats at 50 mg/kg. Various other derivatives also gave encourgaing results as can be seen in Table 2. Most notable are **42bb** and **43cb**, which were both comparable to **42cb**. Phenol **56** produced no detectable levels of drug when dosed orally. This was found to be due to its very high acid sensitivity in which it loses the phenolic residue. Other modifications (**45**, **49**, **58**) designed to improve solubility gave marginal results.

Since it was not possible to distinguish between some of our compounds in the rat model, several compounds were also examined in dogs and monkeys. These results are found in Table 3. In the case of dogs, when dosed at 15 mg/kg, quite variable results were observed among our compounds although it appeared **43cb** had the best overall results. Because **42cb** was also found to have some acid instability, it was decided to dose it at 30 mg/kg along with $CaCO_3$ as an antacid. In this case much better results were obtained. Due to compound supply, we could not dose all of the compounds with this alternate protocol, although **43cb** was considerably more stable than **42cb** under acidic conditions, perhaps explaining its good availability.

Finally several of our compounds were tested in monkeys, and these results are also in Table 3. In this case only **42cb** displayed good results. Strangely, with **43cb** no levels of compound could be detected when dosed orally. On the basis of these results, it appeared that **42cb** had the best overall pharmacokinetic properties after oral administration, with oral bioavailability of greater than 30% and plasma levels maintained at or above the antiviral IC_{90} beyond 5 h when dosed in rats at 50 mg/kg, dogs at 30 mg/kg, and monkeys at 25 mg/kg.

Because selectivity is also a concern for a protease inhibitor, **42cb** was assayed against the following human proteases: renin, cathepsin D and E, and pepsin.[20]

Excellent selectivity was observed in that **42cb** possesed only micromolar inhibition against these proteases.

Conclusions

Through the use of protein structure-based iterative ligand design, a new series of potent inhibitors of the HIV-1 protease has been identified. Starting from our lead structure **3**, a series of bis tertiary amides was designed which had improved activity due to an inversion in binding mode. This new binding mode allowed for improved access to all the binding pockets, and it was possible to improve activity of **3** by over 1000-fold with a minimum of compound preparation. These new compounds were selective for the HIV-PR and possesed good antiviral activity and good pharmacological properties in three animal models. This work emphasizes the critical importance of structural feedback when either designing new classes of inhibitors or modifying existing ones whose binding modes may be speculative.

Experimental Section

All melting points and boiling points are uncorrected. Melting points were obtained on a Mel-Temp melting point apparatus. Infrared spectra were obtained with a Midac FT infrared spectrophotometer. ^{1}H NMR spectra were obtained with a QE300 spectrometer. Mass spectra were obtained from the mass spectroscopy facilities of UC Rivereside, UC Berkeley, and the Scripps Research Institute (La Jolla, CA). Elemental analyses were obtained from Atlantic Microlab Inc. (Norcross, GA). Tetrahydrofuran was distilled from Na/benzophenone ketyl. All other solvents were used as received. The following amines were prepared according to literature methods: 1-methyl-1-phenylethylamine (**10b**),[21] 1,1-diethylbutylamine (**10d**),[22] 1-ethylcyclopentylamine (**10c**),[23] 2-methyl-3-phenyl-2-aminopropane (**10e**),[24] *cis*-octahydroinden-3a-ylamine (**10g**),[25] 1-phenylcyclopentylamine (**10h**).[26]

***N-tert*-Butyl-*N*-(2-hydroxyethyl)-2-[(9-oxo-6,7-dihydro-9*H*-8-oxa-5-thiabenzocyclohepten-7-yl)methyl]benzamide (5).** A solution of trimethylaluminum (2.0 M in hexane, 3.66 mL, 7.32 mmol) was added dropwise to a solution of *tert*-butylhydroxyethylamine (863 mg, 7.32 mmol) in 15 mL toluene at 0 °C. The mixture was stirred for 45 min at room temperature, a solution of lactone **4** (400 mg, 1.22 mmol) in 5 mL of toluene was added dropwise, and the mixture was heated to 90 °C for 18 h. The reaction mixture was cooled and quenched with 5 mL of dilute NH_4Cl solution and extracted with three 15 mL portions of ethyl acetate. The organic phase was washed with 10 mL of H_2O, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash chromatography (75 g of silica gel, 5−10% ethyl acetate/CH_2Cl_2) to yield 160 mg (32%) of lactone **5** as a white solid: IR (film) 3449 (br OH), 1726, 1626 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58−7.14 (8 H, series of m), 4.52 (1 H, br m), 3.63−2.94 (8 H, series of m), 1.53 and 1.39 (9 H, s, *tert*-butyl rotomers); HRFABMS calcd for $C_{23}H_{28}NO_4S$ 414.1791, found 414.1735.

***N-tert*-Butyl-2-[[2-hydroxy-3-[2-[(2-hydroxyethyl)-*tert*-butylcarbamoyl]phenyl]propyl]thio]benzamide (6).** A solution of trimethylaluminum (2.0 M in hexane, 0.36 mL, 0.73 mmol) was added dropwise to a solution of *tert*-butylamine (53 mg, 76 μL, 0.73 mmol) in 3 mL of dichloroethane at 0 °C. The mixture was stirred for 45 min at room temperature, a solution of lactone **5** in 0.5 mL of dichloroethane was added, and the mixture was heated to 60 °C for 18 h. The reaction mixture was cooled, quenched with dilute NH_4Cl solution, and extracted three times with 10 mL portions of ethyl acetate. The solution was dried over $MgSO_4$, filtered, and concentrated to a yellow oil. The crude material was purified by flash chromatography (20 g of silica gel, 15−30% ethyl acetate/CH_2Cl_2) to yield 45 mg (76%) of diamide **6** as a colorless solid: IR (film) 3302 (br OH), 1638, 1613 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51−7.08 (8 H, series of m), 6.50 and 6.25 (1 H, br s, NH rotomers), 5.40 and 4.85 (1 H, br s, OH rotomers), 3.93 and 3.82 (1 H, m, rotomers), 3.52−2.57 (8 H, series of m), 1.49 and 1.44 (9 H, rotomers), 1.47 and 1.45 (9 H, rotomers); HRFABMS calcd for $C_{27}H_{39}N_2O_4S$ 487.2631, found 487.2638. Anal. ($C_{27}H_{38}N_2O_4S\cdot1.25H_2O$) C, H, N, S.

***N-tert*-Butyl-*N*-(2-hydroxyethyl-2-[[2-hydroxy-3-[2-[(2-hydroxyethyl)-*tert*-butylcarbamoyl]phenyl]propyl]thio]-benzamide (7).** A solution of trimethylaluminum (2.0 M in hexane, 0.73 mL, 1.45 mmol) was added dropwise to a solution of *tert*-butylhydroxyethylamine (170 mg, 1.45 mmol) in 5 mL of toluene at 0 °C. The mixture was stirred for 45 min at room temperature, a solution of lactone **5** (400 mg, 1.22 mmol) in 1 mL dichloroethane was added dropwise, and the mixture was heated to 110 °C for 5 h. The reaction mixture was cooled and quenched with 5 mL of dilute NH_4Cl solution and extracted with three 10 mL portions of ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash chromatography (15 g of silica gel, 3% MeOH/CH_2Cl_2) to yield 18 mg (23%) of diamide **7** as a pink solid: IR (film) 3393 (br OH), 1611 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53−7.09 (8 H, series of m), 3.84−3.79 (1 H, br m), 3.56−2.63 (12 H, series of br m), 1.53, 1.47, and 1.44 (18 H, *tert*-butyl rotomers); HRFABMS calcd for $C_{29}H_{43}N_2O_5S$ 531.2893, found 531.2904. Anal. ($C_{29}H_{42}N_2O_5S\cdot0.25H_2O$) C, H, N, S.

***N-tert*-Butyl-*N*-(2-hydroxyethyl)-2-[3-hydroxy-4-[2-[(2-hydroxyethyl)-*tert*-butylcarbamoyl]phenyl]butyl]-benzamide (9).** A solution of 2-(*N-tert*-butylamino)ethanol (0.55 g, 4.72 mmol) in toluene (5 mL) was cooled in an ice bath, after which a solution of trimethylaluminum (2.0 M in hexanes, 2.4 mL, 4.72 mmol) was added over a period of 8 min. The reaction mixture was allowed to stir at ambient temperature for 45 min, after which a solution of lactone **8** (0.15 g, 0.47 mmol) in toluene (2 mL) was added. The reaction mixture was heated for 14 h at 90 °C and at reflux for an additional 6 h. It was treated with 0.5 N NH_4Cl (5 mL) and H_2O (30 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to leave a yellow oily residue (0.26 g) which was purified by column chromatography (EtOAc) to give the product **9** as a white foam: yield 0.075 g, 31%; IR (film) 3391, 1612 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.10−7.30 (8 H, series of m), 1.40−3.80 (36 H, series of m); HRFABMS calcd for $C_{30}H_{45}N_2O_5$ 513.3328, found 513.3304. Anal. ($C_{30}H_{44}N_2O_5\cdot0.5H_2O$) C, H, N.

***N-tert*-Butyl-[2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-amine (16a).** To a solution of 2-(*tert*-butylamino)ethanol **(11a)** (11.72 g, 0.1 mol) and imidazole (8.85 g, 0.13 mol, 1.3 equiv) in CH_2Cl_2 (50 mL) cooled to 0 °C was added *tert* -butyldiphenylsilyl chloride (28 g, 0.102 g, 1.02 equiv) over a 15 min period while the temperature was maintained between 0 and 10 °C. The reaction mixture was allowed to stir at room temperature for 18 h, after which it was treated with saturated $NaHCO_3$ (100 mL), poured into H_2O (600 mL), and extracted with 200 mL of Et_2O. The organic layer was washed with H_2O (600 mL), dried (Na_2SO_4), and concentrated to give the product **16a** as a clear colorless oil: yield 31.2 g, 88%.

***N-tert*-Butyl-*N*-[2-(*tert*-butyldiphenylsilyl)oxy]ethyl]-2-methylbenzamide (18a).** A solution of **16a** (25.5 g, 71.7 mmol) and its HCl salt (5.1 g, 13 mmol) in CH_2Cl_2 (50 mL) was treated with Et_3N (18 mL, 130 mmol) and cooled to 0°C. *o*-Toluoyl chloride **(12)** (13.1 g, 85 mmol) was added to the solution over a 5 min period, after which the reaction was stirred at room temperature for 21 h. The mixture was washed with saturated $NaHCO_3$ (100 mL) and H_2O (2 × 500 mL), dried over Na_2SO_4, and evaporated to give an orange oil (21.6 g) which was Kugelrohr distilled (230 °C, 1.9 Torr) to give a product still contaminated with *o*-tolouyl chloride. Chromatography on SiO_2 eluting with 10−100% EtOAc/hexane gave **18a** as a light yellow oil: yield 9.69 g, 42%; ^{1}H NMR ($CDCl_3$) δ 7.55−7.00 (14 H, series of m), 3.60−3.20 (4 H, m), 2.20 (3 H, s), 1.50 (9 H, s, *tert*-butyl), 0.90 (9 H, s, *tert*-butyl).

3-[2-[*N-tert*-Butyl-[2-[(*tert*-butyldiphenylsilyl)oxy]-ethyl]carbamoyl]phenyl]propionic Acid (32a). A solution of **18a** (9.06 g, 19.1 mmol) and diisopropylamine (0.4 mL, 2.9 mmol, 0.15 equiv) in THF (100 mL) was cooled to −78 °C and treated with 1.2 M *sec*-butyllithium (19.1 mL, 23 mmol) over

a 15 min period while the temperature was maintained at −70 °C. The resulting deep purple solution was stirred for 1.5 h, after which ethylene oxide (2.8 mL, 57 mmol, 3 equiv) was added in one portion and the reaction mixture allowed to warm to room temperature for 16 h. It was then quenched with 0.5 N NH_4Cl (10 mL), poured into H_2O (600 mL), and extracted with EtOAc (2 × 200 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo to leave a peach-colored viscous oil (9.98 g) which was chromatographed on SiO_2 (45% EtOAc/hexanes) to give the homologated alcohol as a viscous yellow oil: yield 7.08 g, 72%; IR (film) 3420, 1622 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51−6.99 (14 H, series of m), 3.50−1.70 (11 H, series of m), 1.48 (9 H, s, *tert*-butyl), 0.93 (9 H, s, *tert*-butyl). Anal. ($C_{32}H_{43}NO_3Si$) C, H, N.

A solution of the alcohol (7.0 g, 13.5 mmol) and pyridinum dichromate (25.43 g, 67.6 mmol) in DMF (50 mL) was stirred at room temperature for 17 h, after which it was poured into H_2O (3 L) and extracted with EtOAc (2 × 500 mL). The combined organic layers were washed with H_2O (2 L), dried (Na_2SO_4), and evaporated to a viscous brown oil (4.85 g) which was purified by column chromatography (10% MeOH/CH_2Cl_2) to give 2.31 g (32%) of carboxylic acid **32a** as a brown oil: ^1H NMR ($CDCl_3$) δ 7.50−7.01 (14 H, series of m), 3.54−2.52 (8 H, series of m), 1.46 (9 H, s, *tert*-butyl), 0.94 (9 H, s, *tert*-butyl). Anal. ($C_{32}H_{41}NO_4Si$) H, N; C: calcd, 72.28; found, 71.82.

***N*-*tert*-Butyl-*N*-[2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-2-[2-(methoxymethylcarbamoyl)ethyl]benzamide (34a).** A solution of **32a** (2.31 g, 4.3 mmol), BOP (2.02 g, 4.56 mmol, 1.05 equiv), *N*,*O*-dimethylhydroxylamine hydrochloride (0.47 g, 4.78 mmol, 1.1 equiv) and diisopropylethylamine (2.1 mL, 11.9 mmol, 2.75 equiv) in CH_2Cl_2 (15 mL) was stirred at ambient temperature for 2 h, after which it was washed with H_2O (200 mL), dried (Na_2SO_4), and evaporated to leave a brown residue (3.52 g) which was purified by column chromatography (1:1 EtOAc/hexane) to give **34a** as a clear, colorless oil: yield 1.48 g, 59%; IR (film) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.53−7.01 (14 H, series of m), 3.58 (3 H, s, OCH_3), 3.15 (3 H, s, CH_3), 3.52−2.60 (8 H, series of m), 1.45 (9 H, s, *tert*-butyl), 0.94 (9 H, s, *tert*-butyl). Anal. ($C_{34}H_{46}N_2O_4Si$) C, H, N.

1-Methyl-1-phenylethylamine (10b) was prepared by the method of Kalir;[21] however, the azide was reduced with $LiAlH_4$ instead of Raney nickel/NH_2NH_2. The amine was purified by vacuum distillation (60 °C, 3.2 Torr) as a colorless liquid: yield 46.82 g, 74%.

2-[(1-Methyl-1-phenylethyl)amino]ethanol (11b). To THF (25 mL) cooled to −78 °C was added ethylene oxide (5.4 mL, 0.11 mol, 1.1 equiv), after which was suspended $LiClO_4$ (10.64 g, 0.1 mol) and the mixture was warmed to 0 °C. After stirring at 0 °C for 10 min, a solution of **10b** (13.52 g, 0.1 mol) in CH_3CN (12.5 mL) was added over a 2 min period followed by stirring at ambient temperature for 3 h. The mixture was poured into brine (200 mL) and extracted with Et_2O (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, and the oily residue was Kugelrohr distilled at 180 °C (2 Torr) to give **11b** as a colorless, viscous oil: yield 10.80 g, 60%; IR (film) 3320 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44−7.19 (5 H, m), 3.56 (2 H, t, J = 5.2 Hz), 2.48 (2 H, t, J = 5.2 Hz), 1.47 (6 H, s, CH_3). Anal. ($C_{11}H_{17}NO$) C, H, N.

***N*-(2-Hydroxyethyl)-2-methyl-*N*-(1-methyl-1-phenylethyl)benzamide (14b).** To a solution of **11b** (5.0 g, 28 mmol) and DMAP (0.51 g, 4 mmol, 0.15 equiv) in pyridine (40 mL) cooled to 0 °C was added *o*-toluoyl chloride (**12**) (17.2 g, 14.5 mL, 11 mmol, 4 equiv) over a 10 min period. The solution was stirred for 15 h at 120 °C and poured into H_2O (100 mL), treated with 1 N HCl (400 mL), and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with 1 N HCl (300 mL) followed by H_2O (500 mL), dried (Na_2SO_4), and evaporated to give an orange oil (16.8 g), which was treated with a solution of 90% aqueous MeOH (175 mL) and 50% NaOH (15 mL) and stirred at room temperature for 20 min. The reaction mixture was poured into H_2O (1500 mL) and extracted with Et_2O (2 × 100 mL) and CH_2Cl_2 (100 mL). The combined organic layers were dried and evaporated to give an orange solid (4.5 g) which was triturated with a 1:1 hexane/EtOAc mixture (40 mL) followed by additional hexanes (75 mL). After standing in the freezer for 2 h, the resulting off-white solid was filtered and washed with a 1:1 hexane/EtOAc mixture (50 mL) to yield 3.96 g (48%) of amide **14b**: mp 139−141 °C; IR (film) 1609 cm^{-1}; ^1H NMR (DMSO-d_6) 7.41−7.11 (4 H, series of m), 4.75 (1H, t, OH), 3.45−3.33 (4 H, m), 2.18 (3 H, s, CH_3), 1.72 (6 H, s, CH_3). Anal. ($C_{19}H_{23}NO_2$) C, H, N.

***N*-*tert*-Butyl-*N*-(2-hydroxyethyl)-2-[3-hydroxy-4-[2-[(2-hydroxyethyl)(1-methyl-1-phenylethyl)carbamoyl]-phenyl]butyl]benzamide (40ab).** To a solution of **14b** (0.12 g, 0.42 mmol) and diisopropylamine (0.009 mL, 0.063 mmol, 0.15 equiv) in THF (5 mL) cooled to −78 °C was added 1.3 M *sec*-butyllithium (0.71 mL, 0.92 mmol, 2.2 equiv) over a 5 min period. The resulting deep red solution was stirred for an additional 50 min, after which a solution of **34a** (0.25 g, 0.42 mmol) in THF (5 mL) was added. The mixture was allowed to warm to room temperature over 17.5 h, quenched with 0.5 N NH_4Cl, diluted with H_2O (75 mL), and extracted with EtOAc (2 × 25 mL). The combined organic layers were dried and evaporated leaving the crude ketone **36ab**, which was dissolved in EtOH (5 mL), treated with $NaBH_4$ (0.045 g, 1.2 mmol), and stirred for 45 min. The reaction was quenched with saturated $NaHCO_3$ (4 mL), poured into brine (40 mL), and extracted with EtOAc (2 × 25 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to give the crude alcohol, which was dissolved in THF (5 mL), treated with a solution of tetrabutylammonium fluoride (1.0 M in THF, 0.7 mL, 0.68 mmol), and stirred at room temperature for 18 h. The reaction was quenched with saturated $NaHCO_3$ (2 mL), poured into brine (40 mL), and extracted with EtOAc (2 × 15 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to give an oil (0.32 g). Purification by column chromatography (EtOAc) afforded product **40ab** as a white foam: yield 111 mg, 46% from **14b**; IR (film) 3383, 1613 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34−7.10 (13 H, series of m), 3.69−1.51 (34 H, series of m); HRFABMS calcd for MH^+ 575.3485, found 575.3481. Anal. ($C_{35}H_{46}N_2O_5 \cdot 0.5H_2O$) C, H, N.

2-[(1,1-Diethylbutyl)amino]ethanol (11d). 1,1-Diethylbutylamine (910 mg, 7.05 mmol) was alkylated with ethylene oxide in the same fashion as amine **10b** to yield 630 mg (52%) of **11d** as a colorless liquid. The product was purified by kugelrohr distillation at reduced pressure (bp 90−95 °C, 0.5 Torr): ^1H NMR ($CDCl_3$) δ 3.59 (2 H, t, J = 5.3 Hz), 2.59 (2 H, t, J = 5.3 Hz), 2.01 (2 H, br s, NH, OH), 1.32 (4 H, q, J = 7.5 Hz), 1.23 (4 H, m), 0.90 (3 H, m), 0.78 (6 H, t, J = 7.4 Hz). Anal. ($C_{10}H_{23}NO \cdot 0.25H_2O$) C, H, N.

***N*-(1,1-Diethylbutyl)-*N*-(2-hydroxyethyl)-2-methylbenzamide (14d).** Amine **11d** (500 mg, 2.89 mmol) was acylated with *o*-toluoyl chloride **(12)** in the same fashion as amine **11b** to produce 90 mg (11%) of amide **14d** after chromatography: IR (film) 3402 (br), 1614 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20−7.03 (4 H, m), 3.35 and 3.12 (4 H, br m rotomers), 2.28 (3 H, s), 2.20 and 1.90 (6 H, br m, rotomers), 1.25 (2 H, m), 0.94 (3 H, t, J = 7.2 Hz), 0.85 (6 H, t, J = 7.4 Hz). Anal. ($C_{18}H_{29}NO_2$) C, H, N.

***N*-*tert*-Butyl-*N*-(2-hydroxyethyl)-2-[3-hydroxy-4-[2-[(2-hydroxyethyl)(1,1-diethylbutyl)carbamoyl]phenyl]butyl]-benzamide (40ad).** Amide **14d** (0.087 g, 0.3 mmol) was ortho metalated with *s*-butyllithium and acylated with *N*,*O*-dimethylamide **34a** in the same fashion as compound **14b** to yield ketone **36ad**. The crude product was reduced and deprotected without purification in fashion identical to compound **36ab**. The crude product was purified by column chromatography on SiO_2 eluting with EtOAc followed by chromaography on SiO_2 eluting with 25% EtOAc/hexane to yield 0.040 g (23% over three steps) of **40ad** as a white solid: IR (neat) 3376, 1609 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30−7.10 (8 H, series of m), 3.80−0.80 (44 H, series of m); HRFABMS calcd for $C_{34}H_{53}N_2O_5$ 569.3954, found 569.3954. Anal. ($C_{34}H_{52}N_2O_5$) C, H, N.

2-[(1-Ethylcyclopentyl)amino]ethanol (11c). 1-Ethylcyclopentylamine (58 g, 0.51 mol) was alkylated with ethylene oxide in the same fashion as amine **10b** to yield 52 g (65%) of **11c** as a colorless low-melting solid after kugelrohr distillation (bp 75−80 °C, 0.4 Torr): ^1H NMR ($CDCl_3$) δ 3.58 (2 H, t, J = 5.1 Hz), 2.63 (2 H, t, J = 5.2 Hz), 2.23 (2 H, br s, NH, OH), 1.69−1.41 (10 H, series of m), 0.85 (3 H, t, J = 7.4 Hz).

***N*-[2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl]-*N*-(1-ethylcyclopentyl)-2-methylbenzamide (18c).** (Hydroxyethyl)-cyclopentylamine **11c** (25.0 g, 0.16 mol) was silated with diphenyl-*tert*-butylsilyl chloride and acylated with *o*-toluoyl chloride **(12)** in the same manner as amine **11b** to produce 57 g (79%) of amide **18c** as a white solid. The product was isolated by crystallization from hexanes: ^{1}H NMR ($CDCl_3$) δ 7.51−7.00 (14 H, series of m), 3.46 and 3.27 (4 H, br m, rotomers), 2.21 (3 H, s), 2.05 and 1.94 (6 H, br m, rotomers), 1.61 (4 H, br m), 0.95 (9 H, s), 0.88 (3 H, t, J = 7.4 Hz). Anal. ($C_{33}H_{43}NO_2Si$) C, H, N.

***N*-[2-(*tert*-Butyldiphenylsiloxy)ethyl]-*N*-(1-ethylcyclopentyl)-2-[2-(methoxymethylcarbamoyl)ethyl]-benzamide (34c).** *o*-Toluoyl amide **18c** (47.0 g, 0.092 mol) was ortho metalated and alkylated with ethylene oxide in the same fashion as amide **18a** to produce after chromatography 45 g (88%) of the homologated alcohol as a tan viscous oil: IR (film) 3422 (br), 1620, 1111 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.51−7.01 (14 H, series of m), 3.79 (1 H, br t, J = 6.1 Hz, OH), 3.36 (4 H, m), 2.45 (2 H, m), 2.30 (1 H, m), 2.13 (1 H, m), 1.95−1.59 (12 H, series of m), 0.93 (9 H, s), 0.89 (3 H, t, J = 7.5 Hz). This material was oxidized (14.01 g, 0.025 mol) to the carboxylic acid with Jones reagent in the same fashion as the alcohol derived from **32b** to produce 12.6 g (88%) of the crude carboxylic acid **32c** as a tan foam which was used without purification in the next step.

N,*O*-Dimethylamide **34c** was prepared from carboxylic acid **32c** (12.6 g, 0.022 mol) in similar fashion as amide **34a**. Diethylphosphonocyanide (DEPC) was utilized as the coupling reagent (instead of BOP). The product was isolated by flash chromatography (350 g of silica gel, 25−40% ethyl acetate/hexanes) to yield 10.5 g (78%) of the desired diamide as a colorless viscous glass: IR (film) 1667, 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53−7.05 (14 H, series of m), 3.62 (3 H, s), 3.54−3.30 (4 H, br m), 3.19 (3 H, s), 2.89−2.70 (4 H, br m), 2.08−1.61 (10 H, series of br m), 0.98 (9 H, s), 0.92 (3 H, t, J = 7.5 Hz).

***N*-*tert*-Butyl-*N*-[2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-2,5-dimethylbenzamide (19a).** A suspension of 2,5-dimethylbenzoic acid (5.0 g, 33 mmol) in toluene (50 mL) was cooled in an ice bath followed by the addition of oxalyl chloride (9.3 g, 73 mmol, 2.2 equiv) and DMF (0.8 mL, 1 mmol, 0.3 equiv). After the addition, the reaction mixture was allowed to warm to room temperature, during which time all solid had gone into solution. After 40 min the solvent was evaporated and THF was added (20 mL), and the resulting mixture added to a 0 °C solution of **16a** (11.84 g, 33 mmol) and Et_3N (2.65 mL, 37 mmol, 1.1 equiv) in THF (50 mL) over a 5 min period. After stirring overnight, the reaction mixture was poured into H_2O (1 L) followed by extraction with EtOAc (2 × 200 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to give an orange-colored oil (20.7 g), which was purified by column chromatography (15% EtOAc/hexanes) to give **19a** as a cream-colored solid: yield 3.75 g, 23%; mp 92−94 °C; ^{1}H NMR ($CDCl_3$) δ 7.50−6.85 (13 H, series of m), 3.55−3.28 (4 H, s), 2.16 (6 H, s, CH_3), 1.48 (9 H, s, *tert*-butyl), 0.95 (9 H, s, *tert*-butyl). Anal. ($C_{19}H_{41}NO_2Si$) C, H, N.

3-[2-[*tert*-Butyl[2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-carbamoyl]-4-methylphenyl]propionic acid (33a) was prepared from **19a** (3.75 g, 7.7 mmol) in two steps by the same method used to prepare **32a**. The homologated alcohol was purified by column chromatography (1:1 EtOAc/hexanes) to give a light green solid: yield 2.29 g, 60%; IR (film) 1624 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.51−6.81 (13 H, series of m), 3.62−3.28 (8 H, series of m), 2.43 (2 H, m), 2.21 (3 H, s), 1.49 (9 H, s, *tert*-butyl), 0.94 (9 H, s, *tert*-butyl). Anal. ($C_{33}H_{45}NO_3Si$) C, H, N.

This material (2.29 g, 4.3 mmol) was oxidized with PDC in the same fashion as the material used to prepare **32a** and the product purified by column chromatography (10% MeOH/CH_2Cl_2) to give 635 mg (27%) of carboxylic acid **33a** as a light orange oil: IR (film) 1719 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.02−6.85 (13 H, series of m), 3.60−2.20 (8 H, series of m), 2.16 (3 H, s, CH_3), 1.48 (9 H, s, *tert*-butyl), 0.95 (9 H, s, *tert*-butyl); HRFABMS calcd for $C_{33}H_{43}NO_4Si$ 546.3039, found 546.3046.

***N*-*tert*-Butyl-*N*-[2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-2-[2-(methoxymethylcarbamoyl)ethyl]-5-methylbenzamide (35a)** was prepared from **33a** (0.64 g, 1.2 mmol) in the same manner as **34a** with a reaction time of 16 h at room temperature. The product was purified by column chromatography (1:1 EtOAc/hexane) to give 318 mg (46%) of *N*,*O*-dimethylamide **35a** as a clear viscous oil: IR (neat) 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.53−6.85 (13 H, series of m), 3.58 (3 H, m, OCH_3), 3.50−3.30 (4 H, m), 3.14 (3 H, s, CH_3), 2.79 (4 H, m), 2.15 (3 H, s, CH_3), 1.47 (9 H, s, *tert*-butyl), 0.95 (9 H, s, *tert*-butyl). Anal. ($C_{35}H_{48}N_2O_4Si$) C, H, N.

***N*-*tert*-Butyl-*N*-(2-hydroxyethyl)-4-methyl-2-[3-hydroxy-4-[2-[(2-hydroxyethyl)(1-methyl-1-phenylethyl)carbamoyl]phenyl]butyl]benzamide (41ab)** was prepared from amide **15b** (0.20 g, 0.7 mmol) and *N*,*O*-dimethylamide **35a** (0.4 g, 0.7 mmol) in the same fashion as **40ab**. The product was purified by column chromatography (EtOAc) to afford 155 mg (38% overall) of **41ab** as a white foam: IR (film) 3387, 1614 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.54−6.98 (12 H, series of m), 3.65−1.58 (27 H, series of m), 0.96 (9 H, s, *tert*-butyl); HRFABMS calcd for $C_{36}H_{49}N_2O_5$ 589.3641, found 589.3654. Anal. ($C_{36}H_{48}N_2O_5 \cdot 0.9H_2O$) C, H, N.

1-Methyl-1-naphth-2-ylethylamine (10f). To a solution of CH_3MgBr (3 M in diethyl ether, 47 mL, 0.14 mol) and Et_2O (30 mL) was added a solution of 2′-acetonaphthone in Et_2O (70 mL) over a 5 min period at room temperature during which time a white precipitate formed. The mixture was heated at reflux for 45 min and treated with 10% aqueous H_2SO_4 (100 mL) and ice (50 g) followed by extraction by Et_2O (2 × 100 mL). The combined organic layers were washed with a 5% bisulfite solution (100 mL) and evaporated to give an oil which was purified by column chromatography using a gradient of $CHCl_3$ to CH_2Cl_2 to give the alcohol (15 g) as a white solid. To a solution of this alcohol (5 g, 26.8 mmol) in $CHCl_3$ (30 mL) was susupended NaN_3 (3.49 g, 54 mmol, 2 equiv), and the mixture was cooled to 0 °C followed by addition of trifluoroacetic acid (10.3 mL, 15.3 g, 134 mmol, 5 equiv) in $CHCl_3$ over a 15 min period. The mixture was stirred at room temperature for 17 h and treated with NH_4OH (150 mL) and H_2O (125 mL). The organic layer was dried (Na_2SO_4) and evaporated to give the crude azide as a clear oil (5.15 g, 91%), which was dissolved in Et_2O (15 mL) and added to a suspension of $LiAlH_4$ (15.7 g, 41 mmol, 1.7 equiv) at 0 °C over 30 min. After 30 min of stirring at ambient temperature, the mixture was recooled in ice and carefully quenched with 25% NaOH (100 mL), extracted with Et_2O (2 × 75 mL), dried (Na_2SO_4), concentrated and Kugelrohr distilled (180 °C, 2 Torr) to give the amine **10f** as a colorless liquid: yield 3.52 g, 48% overall; ^{1}H NMR ($CDCl_3$) δ 7.41−6.92 (7 H, series of m), 1.68 (s, 2H, NH_2), 1.58 (6 H, s, CH_3). Anal. ($C_{13}H_{15}N$) C, H, N.

2-[(1-Methyl-1-naphth-2-ylethyl)amino]ethanol (11f). To a suspension of $LiClO_4$ (1.07 g, 10.2 mmol) in THF (4 mL) cooled to −78 °C was added ethylene oxide (0.55 mL, 11.2 mmol, 1.1 equiv) followed by **10f** in CH_3CN (8 mL), and the reaction mixture was stirred at 0 °C for 1 h. After an additional 7 h of stirring at ambient temperature, the reaction mixture was recooled to −78 °C and treated with an additional 3 equiv of ethylene oxide. After 26 h of stirring at ambient temperature, the reaction mixture was poured into saturated brine (100 mL) and extracted with EtOAc (2 × 25 mL). The combined organic layers were dried and evaporated to give the desired product **11f** as a viscous orange oil (2.51 g, 100%) of sufficient purity to use in the next step. An analytical sample prepared by Kugelrohr distillation had bp 250 °C, 1.8 Torr: IR (film) 3306 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.83−7.44 (7 H, series of m), 1.58 (s, 6 H, CH_3), 3.56 (2 H, t, J = 5.2 Hz), 2.51 (2 H, t, J = 5.2 Hz), 1.78 (2 H, bs, NH,OH). Anal. ($C_{15}H_{16}NO \cdot 0.2H_2O$) C, H, N.

***N*-(2-Hydroxyethyl)-2-methyl-*N*-(1-methyl-1-naphth-2-ylethyl)benzamide (14f)** was prepared from **11f** (2.52 g, 8.7 mmol) in the same fashion as **14b**. The product, an oil which solidified slowly, was swirled with 1:1 EtOAc/hexanes and filtered to give 1.1 g (37%) of amide **14f** as a cream-colored solid: mp 149−151 °C; IR (film) 3308, 1606 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.83−7.13 (11 H, series of m), 1.57−1.86 (s and bs,

6 H, CH_3), 3.70−3.40 (4 H, m), 2.32 (3 H, s, CH_3). Anal. ($C_{23}H_{25}NO_2$) C, H, N.

***N*-*tert*-Butyl-*N*-(2-hydroxyethyl)-2-[3-hydroxy-4-[2-[(2-hydroxyethyl)-(1-methyl-1-(naphth-2-ylethyl)carbamoyl]-phenyl]butyl]benzamide (40af)** was prepared from amide **14f** (0.1 g, 0.29 mmol) and *N*,*O*-dimethylamide **34a** (0.17 g, 0.29 mmol) in the same fashion as **40ab**. Purification by column chromatography (10% hexane/EtOAc) afforded 84 mg (46% overall) of **36af** as a white foam: IR (neat) 3370, 1613 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.80−7.11 (15 H, series of m), 3.78−1.24 (series of m, 33 H); FABMS 625.6 $[M + H]^+$. Anal. ($C_{36}H_{48}N_2O_5 \cdot 0.5H_2O$) C, H, N.

[2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl](1-methyl-1-phenylethyl)amine (16b). To a solution of **11b** (0.8 g, 4.5 mmol) and Et_3N (0.8 mL, 5.82 mmol) in CH_2Cl_2 (6 mL) was added the *tert*-butyldiphenylsilyl chloride (1.24 g, 4.53 mmol) in CH_2Cl_2 (3 mL) and stirred at room temperature for 2.5 h, after which the reaction mixture was poured into H_2O (40 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with saturated Na_2CO_3 (30 mL), dried (Na_2SO_4), and evaporated to give a crude colorless oil (1.56 g) which was Kugelrohr distilled (250 °C, 1.8 Torr) to remove impurities, leaving behind the product as a light yellow oil: yield 1.0 g, 54%; ^1H NMR ($CDCl_3$) δ 7.70−7.11 (15 H, series of m), 3.74 (2 H, t, J = 5.2 Hz), 2.47 (2 H, t, J = 5.2 Hz), 1.46 (6 H, s, CH_3), 1.06 (s, 9 H, *tert*-butyl). Anal ($C_{27}H_{35}NOSi$) C, H, N.

***N*-[2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl]-2-methyl-*N*-(1-methyl-1-phenylethyl)benzamide (18b).** To a solution of **16b** (13.5 g, 32.2 mmol) and Et_3N (13.5 mL, 64.5 mmol) in CH_2Cl_2 (65 mL) cooled to 0 °C was added *o*-toluoyl chloride (8.4 mL, 64.5 mmol) over a 2 min period, and the mixture was stirred at room temperature for 5 h, after which it was poured into H_2O (500 mL) and extracted with CH_2Cl_2 (100 mL). The organic layer was dried, concentrated, and purified by column chromatography (70% EtOAc/hexane) to give a colorless oil. The mixed fractions were rechromatographed (15−40% EtOAc/hexane) to give a total yield of 9.0 g (52%) of amide **18b**: IR (film) 1649 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70−7.00 (19 H, series of m), 3.70−3.40 (4 H, bs), 2.20 (3 H, s, CH_3), 1.70 (6 H, bs, CH_3), 0.30 (9 H, s, *tert*-butyl). Anal. ($C_{35}H_{41}NO_2Si$) C, H, N.

3-[2-[2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl](1-methyl-1-phenylethyl)carbamoyl]phenyl]propionic Acid (32b) was prepared in two steps in a manner similar to **32a**. Amide **18b** (1.8 g, 3.4 mmol) was homologated with *s*-BuLi and ethylene oxide to produce 1.46 g (75%) of the alcohol as a viscous oil after chromatography (30% hexane/EtOAc): IR (film) 3424, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45−6.90 (19 H, series of m), 3.70−1.51 (26 H, series of m). Anal. ($C_{37}H_{45}NO_3Si$) C, H, N. A solution of 2.67 M Jones reagent (9.62 mL, 0.26 mmol) was added to an ice-cooled solution of the alcohol (5.96 g, 0.1 mmol) in acetone (120 mL) over a 6 min period. The reaction mixture was warmed to ambient temperature over 30 min. Upon recooling in an ice bath, the reaction was quenched with isopropyl alcohol (10 mL), and the Cr salts were filtered off and washed with acetone (2 × 30 mL). The filtrate was concentrated to a bluish residue which was dissolved in Et_2O (150 mL) and washed with H_2O (500 mL) and saturated NaCl (300 mL). The Cr salts were dissolved in H_2O (150 mL) and extracted with Et_2O (2 × 125 mL). The combined organic layers were dried and concentrated, and the resulting residue was taken up in C_6H_6 (100 mL) and concentrated to give 5.36 g (88%) of the crude carboxylic acid **32b** as a nearly colorless viscous oil suitable for further use: IR (film) 1711, 1626 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.80−7.00 (19 H, series of m), 3.70−1.00 (23 H, series of m).

***N*-[2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl]-2-[2-(methoxymethylcarbamoyl)ethyl]-*N*-(1-methyl-2-phenylethyl)-benzamide (34b)** was prepared in the same manner as **34a**, except that DEPC (1.5 mL, 9.9 mmol, 1.1 equiv) was used as the coupling reagent instead of BOP. The product was purified by column chromatography (1:1 EtOAc/hexane) to give 3.94 g (69%) of *N*,*O*-dimethylamide **34b** as a colorless oil: IR (film) 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51−6.99 (19 H, series of m), 3.60−1.26 (20 H, series of m), 0.95 (9 H s, *tert*-butyl). Anal. ($C_{39}H_{48}N_2O_4Si \cdot 0.2H_2O$) C, H, N.

***N*-[2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl]-2,5-dimethyl-*N*-(1-methyl-1-phenylethyl)benzamide (19b).** A solution of **16b** (12.87 g, 30.8 mmol) and Et_3N (12.9 mL, 9.2 mmol, 3 equiv) in CH_2Cl_2 (70 mL) was cooled in an ice bath followed by addition of **13** (10.0 g, 59.6 mmol) (prepared by the procedure for the preparation of **19c**) over a 2 min period followed by stirring for 19 h at room temperature. The reaction mixture was poured into H_2O (500 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic layers were washed with H_2O (500 mL), dried ($MgSO_4$), and evaporated to leave an orange oil (20.7 g) which was purified by column chromatography (15−30% EtOAc/hexane) to give **19b** as a viscous oil: yield 11.4 g, 67%; IR (film) 3289, 1640 cm^{-1}.

***N*-(1-Methyl-1-phenylethyl)-*N*-(2-hydroxyethyl)-2-[3-hydroxy-4-[2-[(2-hydroxyethyl)(1-methyl-1-phenylethyl)-carbamoyl]-4-methylphenyl]butyl]benzamide (42bb)** was prepared from amide **19b** (3.94 g, 6.2 mmol) and *N*,*O*-dimethylamide **34b** (3.40 g, 6.2 mmol) in the same fashion as **40ab**. The product was purified by column chromatography (EtOAc) to give 1.99 g (49% overall) of **42bb** as a white foam: IR (film) 3372, 1616 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45−6.97 (17 H, series of m), 3.80−1.58 (33 H, series of m); HRFABMS calcd for $C_{41}H_{51}N_2O_5$ 651.3798, found 651.3825. Anal. ($C_{41}H_{50}N_2O_5 \cdot 1.2H_2O$) C, H, N.

2-[(Octahydroinden-3a-yl)amino]ethanol (11g) was prepared from *cis*-2-octahydroinden-3a-ylamine (**10g**) in the same fashion as **11b** with a reaction time of 13.5 h. The crude product was purified by Kugelrohr distillation (200 °C, 2.3 torr) to give **11g** as a clear liquid: yield 1.94 g, 62%; ^1H NMR ($CDCl_3$) δ 3.62−1.18 (21 H, series of m). Anal. ($C_{11}H_{21}NO \cdot 0.3H_2O$) C, H, N.

***N*-(2-Hydroxyethyl)-2-methyl-*N*-(octahydroinden-3a-yl)benzamide (14g)** was prepared in the same manner as **14b**, with a reaction time of 18 h and saponification time of 1 h. The crude oily product (0.72 g) was purified by column chromatography (1:1 EtOAc/hexane) to give **14g** as an amber oil: yield 0.4 g, 34%; IR (film) 3383, 1612 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23−7.16 (4 H, m), 3.60−1.30 (23 H, series of m). Anal. ($C_{19}H_{27}NO_2$) C, H, N.

***N*-*tert*-Butyl-*N*-(2-hydroxyethyl)-2-[3-hydroxy-4-[2-[(2-hydroxyethyl)(*cis*-octahydroinden-3a-yl)carbamoyl]-phenyl]butyl]benzamide (40ag)** was prepared from **14g** (0.15 g, 0.5 mmol) and *N*,*O*-dimethylamide **34a** (0.29 ng, 0.5 mmol) in the same manner as **40ab**. The crude product was purified by column chromatography (EtOAc) to give 99 mg (34% overall) of **40ag** as a white foam: IR (film) 3374, 1608 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29−7.03 (8 H, series of m), 3.70−1.39 (42 H, series of m); HRFABMS calcd for $C_{35}H_{51}N_2O_5$ 579.3798, found 579.3798. Anal. ($C_{35}H_{50}N_2O_5 \cdot 0.3H_2O$) C, H, N.

***N*-(1-Ethylcyclopentyl)-*N*-(2-hydroxyethyl)-2-[3-hydroxy-4-[2-[(2-hydroxyethyl)(1-methyl-1-phenylethyl)-carbamoyl]-4-methylphenyl]butyl]benzamide (42cb)** was prepared from amide **19b** (11.38 g, 20.7 mmol) and *N*,*O*-dimethylamide **34c** in the same fashion as **40ab**. The crude product was purified by column chromatography (EtOAc) to give the **42cb** as a white foam: yield 7.7 g, 59% overall; IR (film) 3372, 1611 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.00 (12 H, m), 3.70−0.91 (40 H, series of br m); HRFABMS calcd for $C_{39}H_{53}N_2O_5$ 629.3924, found 629.3964. Anal. ($C_{39}H_{52}N_2O_5$) C, H, N.

2-[(1-Phenylcyclopentyl)amino]ethanol (11h) was prepared in the same manner as **11b**, starting with 2-(1-phenylcyclopentyl)amine **10h** (2.76 g, 17 mmol) and a reaction time of 1 h 45 min. The product was purified by Kugelrohr distillation to give the starting amine **10h** (1.6 g, 145 °C, 2 Torr) and **11h** (0.86 g, 177 °C, 2 Torr) as a viscous oil: yield 0.86 g, 61% (based on recovered starting material); IR (film) 3318 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39−7.18 (5 H, series of m), 3.46 (2 H, m), 2.39 (2 H, m), 2.05−1.67 (10 H, series of m). Anal. ($C_{13}H_{19}NO$) C, H, N.

***N*-(2-Hydroxyethyl)-2-methyl-*N*-(1-phenylcyclopentyl)benzamide (14h)** was prepared in the same manner as **14a**, starting with **11h** (0.99 g, 5.0 mmol) and a reaction time of 65 h and a 45 min saponification time. The product was

purified by column chromatography (1:1 EtOAc/hexane) to give 0.98 g (59%) of amide **14h** as an amber oil: IR (film) 3383, 1622 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−6.99 (8 H, series of m), 3.60−1.6 (19 H, series of br m). Anal. ($C_{22}H_{27}NO_2 \cdot 0.5H_20$) C, H, N.

***N*-(1-Ethylcyclopentyl)-*N*-(2-hydroxyethyl)-2-[3-hydroxy-4-[2-[(2-hydroxyethyl)(1-cyclopentyl-1-phenyl)carbamoyl]-4-methylphenyl]butyl]benzamide (42ch)** was prepared from amide **14h** (0.14 g, 0.40 mmol) and *N*,*O*-dimethylamide **34c** (0.25 g, 0.4 mmol) in the same fashion as **40ab**. The crude product was purified by column chromatography (EtOAc) to yield 0.070 g (27%) of **42ch** as a white foam: IR (film) 3380, 1611 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60−6.80 (12 H, series of m), 3.40−0.90 (42 H, series of m); HRFABMS calcd for $C_{41}H_{55}N_2O_5$ 655.4111, found 655.4115. Anal. ($C_{41}H_{54}N_2O_5$) C, H, N.

***N*-Ethyl-2-methyl-*N*-(1,1-dimethyl-1-phenylethyl)-benzamide (27).** A solution of amine **10b** (1.0 g, 7.4 mmol) in MeOH was cooled to 0 °C and treated with acetaldehyde (326 mg, 7.4 mmol). The solution's pH was adjusted to 6−7 by the addition of 0.5 N HCl and then treated with $NaBH_3CN$ (418 mg, 6.6 mmol). The mixture was stirred at 0 °C for several hours, gradually warmed to room temperature, and stirred overnight. The solvent was evaporated, leaving a slurry that was taken up in H_2O (20 mL). The aqueous mixture was made alkaline with 1 N NaOH to a pH of 11. The basic solution was treated with saturated NaCl (5 mL) and was extracted with Et_2O (3 × 50 mL). All organic extracts were combined, washed with H_2O (3 × 50 mL), dried over $MgSO_4$, and concentrated to give 750 mg (63%) of the secondary amine as a light yellow liquid: ^1H NMR ($CDCl_3$) δ 7.43 (5 H, m), 2.39 (2 H q, J = 7.2 Hz), 1.74 (1 H, s), 1.46 (6 H, s), 1.06 (3 H, t, J = 7.1 Hz). The amine was acetylated with *o*-toluoyl chloride in the same fashion as **16b** to yield 600 mg of an orange oil. Purification by column chromatography eluting with 20% ethyl acetate/hexanes gave the amide **27** as a light yellow oil: yield 325 mg (68%); ^1H NMR ($CDCl_3$) δ 7.48 (10 H, m), 3.51 (2 H, br m), 2.28 (3 H, s), 1.82 (6 H, s), 1.56 (1 H, s), 1.14 (3 H, t, J = 7.3 Hz).

1-[2-[*N*-(α,α-dimethylbenzyl)-*N*-ethylcarbamoyl]phenyl]-4-[2-[*N*-(1-ethylcyclopentyl)-*N*-(2-hydroxyethyl)carbamoyl]phenyl]-2-butanol (47). The compound was prepared from amide **27** (87 mg, 0.31 mmol) and *N*,*O*-dimethylamide **34c** (189.7 mg, 0.31 mmol) following the same procedure used to prepare **40ab**. The product was purified by column chromatography eluting with 20% ethyl acetate/hexanes to yield 65 mg (68%) of **47** as a white amorphous solid: IR (film) 3396 (br), 1609 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (13 H, m), 3.46 (2 H, br m), 2.75 (1 H, br m), 2.01 (1 H, br m), 1.87 (3 H, br m), 1.80 (6 H, br m), 1.60 (6 H, s), 1.20 (3 H, m), 0.93 (3 H, t, J = 6.9 Hz); HRFABMS calcd for $C_{38}H_{51}N_2O_4$ 599.3849, found 599.3849. Anal. ($C_{38}H_{50}N_2O_4 \cdot 0.5H_2O$) C, H, N.

***N*-But-3-enyl-1,1-dimethylbenzylamine (21).** A solution of amine **10b** (10.0 g, 37.0 mmol), 4-bromo-1-butene (5.0 g, 37.0 mmol), and Hunig's base (4.77 g, 37.0 mmol) was heated to 140 °C under argon for 2.5 h. A white precipitate fell out of solution during heating, and the solution turned yellow. The mixture was cooled to room temperature and was diluted with Et_2O (25 mL) and stirred until the HBr salt of Hunig's base precipitated out. The solution was filtered and the filtrate concentrated to a dark yellow liquid. The residual salt was filtered and the filtrate distilled (60−70 °C, 0.5 Torr) to give amine **21** as a clear liquid: yield 5.31 g (76%); ^1H NMR ($CDCl_3$) δ 7.42 (5 H, m), 5.85 (1 H, m), 5.04 (2 H, t, J = 1.2 Hz), 4.75 (1 H, s), 2.40 (2 H, t, J = 7.0 Hz), 2.20 (2 H q, J = 7.1 Hz), 1.49 (6 H, s).

***N*-But-3-enyl-2,5-dimethyl-*N*-(1,1-dimethylbenzyl)-benzamide (22)** was prepared from amine **21** (471 mg, 2.49 mmol) and toluoyl chloride **13** (837 mg, 4.98 mmol) by the same method used to prepare **18b**. The product was purified by column chromatography with ethyl ether/hexanes (95:5) as elutant to give 455 mg (59%) of amide **22** as a white solid: IR (film) 1642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41 (8 H, m), 5.49 (1 H, m), 4.95 (2 H, t, J = 1.2 Hz), 3.50 (2 H, br m), 2.33 (3 H, s), 2.29 (3 H, s), 1.82 (6 H, s).

1-[2-[*N*-(α,α-Dimethylbenzyl)-*N*-but-3-enylcarbamoyl]-4-methylphenyl]-4-[2-(*N*-(1-ethylcyclopentyl)-*N*-[2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]carbamoyl]phenyl]-2-butanol (48). Amide **22** (300 mg, 0.93 mmol) was combined with diisopropylamine (20 μL, 0.14 mmol) in anhydrous THF (5 mL) and was cooled to −78 °C under argon. *sec*-Butyllithium (1.6 M solution in cyclohexane, 1.31 mL, 2.05 mmol) was added, and the deep red solution was stirred for 35 min at −78 °C. *N*,*O*-Dimethylamide **34c** (574 mg, 0.93 mmol) in THF (5 mL) was added, and the solution was gradually warmed to room temperature. After 1 h the solution was quenched with 0.5 N ammonium chloride and extracted with ethyl acetate (3 × 15 mL). The organic layers were combined, washed with H_2O (3 × 15 mL), dried over $MgSO_4$, and evaporated to give 687 mg of an amber-colored residue. Purification by column chromatography eluting with hexanes/ethyl acetate (95:5) gave the ketone as a white amorphous solid: yield 387 mg (48%); IR (film) 1717, 1643 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36 (22 H, m), 5.49 (1 H, m), 4.95 (2 H, m), 3.50 (4 H, br m), 2.75 (2 H, m), 2.32 (2 H, br m), 2.01 (2 H, m), 1.77 (3 H, s), 1.56 (6 H, s), 0.92 (9 H, br m). The ketone (387 mg, 0.44 mmol) was combined with absolute EtOH (10 mL) and treated with $NaBH_4$ (64 mg, 1.56 mmol) at room temperature. The alcoholic mixture was diluted with H_2O (15 mL), extracted with diethyl ether (3 × 20 mL), dried over $MgSO_4$, and evaporated to afford 378 mg of the alcohol **48** as a white amorphous solid: yield 99%; IR (film) 3350 cm^{-1}.

1-[2-[*N*-(α,α-Dimethylbenzyl)-*N*-(3,4-dihydroxybutyl)-carbamoyl]-4-methylphenyl]-4-[2-[*N*-(1-ethylcyclopentyl)-*N*-(2-hydroxyethyl)carboxamido]phenyl]-2-butanol (49). *N*-Methylmorpholine *N*-oxide (21.8 mg, 0.181 mmol) was combined with *tert*-butyl alcohol (0.05 mL) in H_2O (4.8 mL). This mixture was treated with OsO_4 (2% solution in *tert*-butyl alcohol, 0.6 mL, 0.002 mmol) and stirred for 20 min under argon. Alcohol **48** (150 mg, 0.174 mmol) in acetone (4 mL) was added, and the mixture was stirred under argon overnight. The mixture was acidified with H_2SO_4 to a pH of 3 and added to a slurry of florasil in H_2O (25 mg in 5 mL). The slurry mixture was stirred for 10 min and diluted with ethyl acetate (20 mL). The organic layer was washed with H_2O (3 × 10 mL), dried over $MgSO_4$, and evaporated to give the diol as an amber residue: yield 140 mg (89%); ^1H NMR ($CDCl_3$) δ 7.50 (22 H, series of m), 3.50 (4 H, br m), 2.75 (2 H, br m), 2.32 (2 H, br m), 2.01 (2 H, br m), 1.77 (3 H, br m), 1.56 (6 H, br m), 0.92 (9 H, br m). The diol (139 mg, 0.16 mmol) was combined with THF (10 mL) and reacted with tetrabutylammonium fluoride (1.0 M in THF, 0.47 mL, 0.47 mmol) at room temperature. The solution was stirred for 2 h, diluted with H_2O (5 mL), and extracted with ethyl acetate (3 × 10 mL). All organic extracts were combined, washed with H_2O (3 × 10 mL), dried over $MgSO_4$, and evaporated to give 119 mg of a light brown residue. Purification by column chromatography eluting with hexanes and ethyl acetate (1:1) gave 65 mg of **49** as a light brown amorphous solid: yield (68%); IR (film) 3387, 1609 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49 (12 H, br m), 3.85 (2 H, br m), 3.50 (4 H, br m), 2.75 (2 H, br m), 2.25 (2 H, br m), 1.68 (6 H, br m), 1.71 (8 H, br m), 1.60 (6 H, br m), 1.21 (4 H, br m), 0.98 (8 H, br m); HRFABMS calcd for $C_{41}H_{56}N_2O_6Cs$ 805.3193, found 805.3199. Anal. ($C_{41}H_{56}N_2O_6 \cdot 1.5H_2O$) C, H, N.

***N*-(1,1-Diethylbutyl)-*N*-[2-*tert*-butyldiphenylsiloxy)-ethyl]amine (16d)** was prepared from amine **11d** and *tert*-butyldiphenylsilyl chloride in the same fashion as amine **16a**: ^1H NMR (CDCl3) δ 7.69−7.26 (10 H, series of m), 3.75 (2 H, t, J = 5.3 Hz), 2.53 (2 H, t, J = 5.3 Hz), 1.55−0.74 (12 H, series of m). Anal. ($C_{26}H_{41}NOSi$) C, H, N.

***N*-(1,1-Diethylbutyl)-*N*-[2-(*tert*-butyldiphenylsiloxy]-ethyl]-2,4-dimethylbenzamide (19d).** Amide **19d** was prepared from amine **16d** and 2,5-dimethylbenzoyl chloride(**13**) in the same fashion as **19a**: ^1H NMR ($CDCl_3$) δ 7.75−7.00 (13 H, series of m), 3.60−3.20 (4 H, series of m), 2.20−0.75 (18 H, series of m). Anal. ($C_{35}H_{49}NO_2Si$) C, H, N.

***N*-(1-Ethylcyclopentyl)-*N*-(2-hydroxyethyl)-2-[3-hydroxy-4-[2-[(2-hydroxyethyl)(1,1-diethylbutyl)carbamoyl]-4-methylphenyl]butyl]benzamide (42cd)** was prepared from *N*-(1,1-diethylbutyl)-*N*-[2-(*tert*-butyldiphenylsiloxy)ethyl]-2,4-dimethylbenzamide **19d** (0.30 g, 0.55 mmol) and *N*,*O*-di-

methylamide **34c** (0.34 g, 0.55 mmol) in the same manner as **40ab**. The product was purified by column chromatography (EtOAc) to give **42cd** as a white foam (0.14 g, 40% overall): IR (film) 3368, 1609 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−6.70 (7 H, series of m), 3.80−0.90 (51 H, series of m); HRFABMS calcd for $C_{38}H_{59}N_2O_5$ 623.4424, found 623.4436. Anal. ($C_{38}H_{58}N_2O_5$) C, H, N.

2-(Tetrahydropyran-4-yl)propan-2-ol (29). To an ice-cooled solution of tetrahydropyran-4-carboxylic acid[16] (**28**) (15 g, 115 mmol) in THF (300 mL) was added a solution of methyllithium (1.4 M in Et_2O, 82 mL, 115 mmol) over a 25 min period during which time a white solid formed and then gradually disappeared during addition. After stirring at 0 °C for 2 h, the reaction was quenched with 0.5 N HCl, allowed to stir for 10 min, and then extracted with Et_2O (2 × 100 mL). The combined organic layers were dried and azeotroped from benzene (30 mL), and the material was again dissolved in THF (300 mL), cooled, and treated again with methyllithium (1.4 M in Et_2O, 82 mL, 115 mmol) over a 20 min period. The mixture was allowed to warm to ambient temperature over 30 h and was followed by recooling and quenching with 0.5 N HCl (100 mL). It was extracted with Et_2O (2 × 100 mL), dried, and evaporated, and the product **29** was Kugelrohr distilled (125 °C, 4 Torr): yield 8.78 g, 53%; IR (film) 3413 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.08 (4 H, d, J = 7.1 Hz), 3.40 (4 H, t, J = 11.5 Hz), 1.52 (1 H, m), 1.21 (6 H, s).

1-Methyl-1-(tetrahydropyran-4-yl)ethylamine (30). To a cooled slurry of HOAc (7 mL) and NaCN (1.6 g, 33.3 mmol) was added a solution of H_2SO_4 (7 mL) in HOAc (3.5 mL) over a 10 min period, keeping the temperature below 20 °C, after which **29** (4.0 g, 27.7 mmol) was added over 3 min followed by stirring at 15 °C for 45 min and 2 h at 80 °C. The mixture was then removed from heat, poured onto cracked ice (100 mL), brought to pH 9 with Na_2CO_3, and extracted with Et_2O (100 mL), salt was added to the aqueous layer, and the mixture was extracted once more with Et_2O (100 mL). The combined organic layers were dried and evaporated to give the crude formamide which was treated with concentrated HCl (2.5 mL) and heated at reflux for 2 h 45 min. The mixture was then treated with H_2O (5 mL) and extracted with Et_2O (2 × 25 mL). The organic layer was discarded and the aqueous layer brought to pH 13 with 50% NaOH and extracted with Et_2O (25 mL). NaCl was added to the aqueous layer and extracted once more with Et_2O (25 mL). The combined organic layers were dried, evaporated at 30 °C, and Kugelrohr distilled (95 °C, 2.5 Torr) to give **30** as a colorless oil: yield 0.23 g, 6%.

***N*-[2-(*tert*-Butyldiphenylsiloxy)ethyl]-2,5-dimethyl-*N*-[1-methyl-1-(tetrahydropyran-4-yl)ethyl]benzamide (31).** To THF (2 mL) cooled to −78 °C was added a cooled solution of ethylene oxide (0.35 mL, 7.14 mmol) followed by $LiClO_4$ (0.69 g, 7.14 mmol) and stirring for 5 min. A solution of **30** (0.93 g, 6.49 mmol) in CH_3CN (2 mL) was added over a 3 min period. The mixture was allowed to warm to ambient temperature over 4 h. The solvents were evaporated, and the residue was dissolved in EtOAc (20 mL) and washed with brine (2 × 10 mL). The organic layer was dried and evaporated, and the product was Kugelrohr distilled (170 °C, 2 Torr) to a clear colorless oil: yield 424 mg, 35%; ^1H NMR ($CDCl_3$) δ 1.02 (s, 6 H, CH_3), 1.60−4.00 (series of m, 15 H). Anal. ($C_{10}H_{21}NO_2 \cdot 0.1H_2O$) C, H, N. To a solution of above hydroxyethylamine (0.42 g, 2.21 mmol) and imidazole (0.33 g, 4.9 mmol) in 7 mL of CH_2Cl_2 was added *tert*-butyldiphenylsilyl chloride (1.34 g, 4.9 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred for 2 h at room temperature after which the reaction mixture was washed with H_2O (50 mL) and the aqueous layer extracted with CH_2Cl_2 (10 mL). The organic layers were combined, dried, and evaporated, and the residue was purified by column chromatography (5% MeOH/CH_2Cl_2) to give the product as a viscous oil: yield 620 mg, 66%; ^1H NMR ($CDCl_3$) δ 1.00 (s, 9H, *tert*-butyl), 1.04 (s, 6 H, CH_3), 1.60−4.00 (series of m, 14 H), 7.26−7.67 (series of m, 10 H). Anal. ($C_{26}H_{39}NO_2Si$) C, H, N. A solution of the siloxyamine (0.6 g, 1.4 mmol), 2,5-dimethylbenzoyl chloride (**13**) (0.47 g, 2.8 mmol), and Et_3N (0.6 mL, 4.2 mmol) in CH_2Cl_2 (3 mL) was stirred for 24 h at room temperature followed by addition of CH_2Cl_2 (10 mL) and washing with H_2O (100 mL). The aqueous layer was washed once with CH_2Cl_2 (100 mL), the combined organics were dried and evaporated, and the residue was purified twice by column chromatography (5% MeOH/CH_2Cl_2 followed by 25% EtOAc/hexane) to give **31** as a clear, viscous oil: yield 534 mg, 68%; ^1H NMR ($CDCl_3$) δ 7.47−7.01 (13 H, series of m), 2.13 (3 H, s, CH_3), 4.02−1.34 (19 H, series of m), 0.93 (9 H, s, *tert*-butyl). Anal. ($C_{35}H_{47}NO_3Si$) C, H, N.

***N*-(1-Ethylcyclopentyl)-*N*-(2-hydroxyethyl)-2-[3-hydroxy-4-[2-[(2-hydroxyethyl)[1-methyl-1-(tetrahydropyran-4-yl)ethyl]carbamoyl]-4-methylphenyl]butyl]-benzamide (42ci)** was prepared from amide **31** (0.3 g, 0.54 mmol) and *N*,*O*-dimethylamide **34c** (0.3 g, 0.54 mmol) in the same manner as **40ab**. The product was purified by column chromatography (EtOAc) to give **42ci** as a white foam: yield 92 mg, 27% overall; ^1H NMR ($CDCl_3$) δ 7.30−6.80 (7 H, series of m), 4.00−0.90 (49 H, series of m); HRFABMS calcd for $C_{38}H_{57}N_2O_6$ 637.4217, found 637.4220. Anal. ($C_{38}H_{56}N_2O_6 \cdot 0.5H_2O$) C, H, N.

***N*-(Hydroxyethyl)-2-methyl-3-phenyl-2-aminopropane (11e)** was prepared in the same manner as amine **11b** to yield a viscous oil (Kugelrohr, 170 °C/2 Torr, 59% yield). ^1H NMR ($CDCl_3$) δ 7.30 (3 H, m), 7.27 (1 H, d, J = 7.6 Hz), 7.16 (1 H, d, J = 8.0 Hz), 3.61 (2 H, t, J = 5.2 Hz), 2.80 (2 H, t, J = 5.1 Hz), 2.69 (2 H, s), 2.05 (1 H, br), 1.07 (6 H, s).

[*N*-(Hydroxyethyl)-*N*-(2-methyl-3-phenylpropyl)-benzamide (14e) was prepared in the same manner as amide **14b** to yield a viscous oil. (58% yield): ^1H NMR ($CDCl_3$) δ 7.32 (5 H, m), 7.16 (3 H, m), 7.14 (1 H, m), 3.97 (1 H, bd, J = 12.6 Hz), 3.22 (1 H, m), 2.99 (3 H, m), 2.88 (2 H, d, J = 12.9 Hz), 2.29 (3 H, s), 1.63 (3 H, s), 1.47 (3 H, s). Anal. ($C_{20}H_{25}NO_2$) C, H, N.

2-[4-[2-(*tert*-Butyl(2-hydroxyethyl)carbamoyl]phenyl]-2-hydroxybutyl]-*N*-(1,1-dimethyl-2-phenylethyl)-*N*-(2-hydroxyethyl)benzamide (40ae) was prepared in the same fashion as **40ab**. Amide **14e** was lithiated with *s*-BuLi and quenched with Weinreb amide **34a** to give crude ketone **36ae**, which was reduced ($NaBH_4$) and deprotected (n-Bu_4NF) to give **40ae** as an amorphous solid after column chromatography on silica (3:1 EtOAc/hexanes) (35% yield from **14e**): ^1H NMR ($CDCl_3$) δ 7.10−7.40 (13 H, m), 4.45 (2 H, m), 3.25−3.80 (5 H, m), 2.55−2.95 (4 H, m), 1.60−2.10 (3 H, m), 1.55 (18 H, bs). Anal. ($C_{36}H_{48}N_2O_5 \cdot 0.5H_2O$) C, H, N.

***N*-(1,1-Dimethylethyl)-*N*-(2-hydroxyethyl)-2,5-dimethylbenzamide (15b)** was prepared in the same manner as amide **14b** from 2,5-dimethylbenzoic acid (12% yield, three steps): IR (film) 3316, 2953, 1607 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (6 H, m), 7.01 (2 H, bs), 6.81 (1 H, bs), 3.66 (2 H, bs), 3.51 (2 H, m), 2.26 (3 H, s), 2.25 (3 H, s), 1.75 (6 H, bs).

***N*-*tert*-Butyl-*N*-(2-hydroxyethyl)-2-[3-hydroxy-4-[2-[(2-hydroxyethyl)(1-methyl-1-phenylethyl)carbamoyl]-4-methylphenyl]butyl]benzamide (42ab)** was prepared in the same fashion as **40ab**. Amide **15b** was lithiated with *s*-BuLi and quenched with Weinreb amide **34a** to give crude ketone **38ab** which was reduced ($NaBH_4$) and deprotected (n-BuN_4F) to give **42ab** as an amorphous solid (17% yield from **15b**): ^1H NMR ($CDCl_3$) δ 6.80−7.60 (13 H, m), 4.45 (2 H, m), 3.20−3.85 (5 H, m), 2.40−3.00 (4 H, m), 2.29 (3 H, m), 1.20−2.00 (21 H, m). Anal. ($C_{36}H_{48}N_2O_5 \cdot 0.5H_2O$) C, H, N.

***tert*-Butyl(4-isopropylphenoxy)dimethylsilane (51).** A solution of 4-isopropylphenol (**50**) (20 g, 146.8 mmol) in 250 mL of DMF was treated with imidazole (15.0 g, 220 mmol) and *tert*-butyldimethylsilyl chloride (24.3 g, 162 mmol) portionwise at 25 °C. After 3 h the reaction mixture was poured into 500 mL water and ether was added. The aqueous layer was separated and extracted with ether. The combined organic layer was washed with 0.1 N HCl and saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated to afford a clear oil which was used without further purification (36.6 g, 100%): ^1H NMR ($CDCl_3$) δ 7.07 (2 H, d, J = 8.4 Hz), 6.76 (2 H, d, J = 8.4 Hz), 2.85 (1 H, m), 1.21 (6 H, d, J = 7.0 Hz), 1.02 (9 H, s), 0.19 (6 H, s).

1-[4-[(*tert*-Butyldimethylsilyl)oxy]phenyl]-1-methylethylamine (52). The silyl ether **51** (20 g, 79.8 mmol) in 140 mL of $CHCl_3$ was treated with azidotrimethylsilane[18] (36.8 g, 319 mmol) and dichlorodicyanobenzoquinone (DDQ, 36.2 g, 160 mmol) portionwise at 25 °C. After 3 h the reaction was carefully

poured into a solution of saturated $NaHCO_3$, and the aqueous layer was extracted with ether, washed with brine, dried ($MgSO_4$), and concentrated to afford 33 g of a crude amber oil. This material was filtered through a plug of silica, eluting with 7:1 hexanes/ether, yielding 12.5 g of crude azide. The azide in 140 mL of EtOH was treated with 2 g of 5% Pd-$BaSO_4$ and placed under 1 atm of H_2 at 25 °C. After 5 h starting azide was still present and an additional gram of catalyst was added. After 28 h the reaction was complete and the solution was filtered through a pad of Celite and concentrated to afford a light yellow oil (10.5 g, 50%): ^{1}H NMR ($CDCl_3$) δ 7.33 (2 H, d, J = 8.7 Hz), 6.78 (2 H, d, J = 8.7 Hz), 1.64 (2 H, bs), 1.47 (6 H, s), 0.99 (9 H, s), 0.20 (6 H, s).

2-[[1-[4-[(*tert*-Butyldimethylsilyl)oxy]phenyl]-1-methylethyl]amino]ethanol (53). The amine **52** (5.22 g, 19.7 mmol) was treated with ethylene oxide and $LiClO_4$ as described previously to afford alcohol **53** (73% yield), after chromatography on silica (5% MeOH/CH_2Cl_2 with NH_3): ^{1}H NMR ($CDCl_3$) δ 7.30 (2 H, d, J = 8.6 Hz), 6.82 (2 H, d, J = 8.6 Hz), 3.67 (2 H, bt, J = 5.0 Hz), 2.60 (2 H, bt, J = 5.0 Hz), 2.46 (2 H, bs), 1.58 (6 H, s), 0.98 (9 H, s), 0.20 (6 H, s). Anal. ($C_{17}H_{31}NO_2Si\cdot 0.6H_2O$) C, H, N.

***N*-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-*N*-[1-[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]-1-methylethyl]-2,5-dimethylbenzamide (54).** Alcohol **53** was silylated using the procedure described for **50** to afford compound **54** as an oil (95%). Amine was acylated with 2,5-dimethylbenzoyl chloride as described previously to give amide **54** in 67% yield as an oil after flash chromatography (12:1 hexanes/EtOAc): ^{1}H NMR ($CDCl_3$) δ 7.36 (1 H, s), 7.24 (1 H, s), 7.00 (2 H, s), 6.89 (1 H, bs), 6.79 (1 H, s), 6.76 (1 H, s), 3.58 (2 H, m), 3.38 (2 H, m), 2.28 (3 H, s), 2.21 (3 H, s), 1.79 (6 H, bs), 0.97 (9 H, s), 0.79 (9 H, s), 0.19 (6 H, s), −0.14 (6 H, s). Anal. ($C_{32}H_{53}NO_3Si_2$) C, H, N.

***N*-(1-Ethylcyclopentyl)-*N*-(2-hydroxyethyl)-2-[3-hydroxy-4-[2-[(2-hydroxyethyl)[1-(4-hydroxyphenyl)-1-methylethyl]carbamoyl]-4-methylphenyl]butyl]benzamide (56)** was prepared in the same fashion as **40ab**. Amide **54** was lithiated with *s*-BuLi and quenched with Weinreb amide **34c** to give purified ketone **55** (63%) which was reduced ($NaBH_4$) and deprotected (*n*-Bu_4NF) to give **56** as an amorphous solid after column chromatography on silica (1:4 EtOAc/hexanes) (78% yield from **54**): ^{1}H NMR ($CDCl_3$) δ 6.60−7.35 (13 H, m), 4.45 (2 H, m), 3.10−3.80 (5 H, m), 2.40−2.80 (4 H, m), 2.29 (2 H, bs), 2.26 (2 H, bs), 1.50−2.10 (17 H, m), 0.93 (3 H, m). Anal. ($C_{36}H_{48}N_2O_5$) C, H, N.

***N*-(1-Ethylcyclopentyl)-*N*-(2-hydroxyethyl)-2-[3-hydroxy-4-[2-[(2-hydroxyethyl)[1-methyl-1-[4-(pyridin-3-ylmethoxy)phenyl]ethyl]carbamoyl]-4-methylphenyl]butyl]-benzamide (58).** A solution of ketone **55** (3.80 g, 3.42 mmol) in 60 mL of THF and 65 mL of hexanes was cooled to −50 °C and treated with *n*-Bu_4NF (3.44 mmol, 3.44 mL of a 1 M solution in THF). After stirring for 2.5 h the reaction was diluted with water and EtOAc. The organic layer was dried (Na_2SO_4) and concentrated to give 4.0 g of an oil. Purification using chromatography on silica (20−30% EtOAc/hexanes) afforded 2.8 g (83%) of phenol as an amorphous solid: ^{1}H NMR ($CDCl_3$) δ 6.90−7.50 (19 H, m), 6.50 (2 H, d, J = 8.5 Hz), 3.65 (4 H, bs), 3.42 (2 H, m), 3.20−3.35 (3 H, m), 3.07 (1 H, br), 2.35−2.62 (8 H, m), 2.31 (3 H, s), 1.50−2.20 (16 H, m), 0.91 (9 H, s), 0.83 (9 H, s), −0.06 (3 H, s), −0.08 (3 H, s). The phenol (1.83 g, 1.83 mmol) was treated with 3-(chloromethyl)pyridine (0.47 g, 3.66 mmol), Cs_2CO_3 (1.2 g, 3.66 mmol), and KI (0.04 g, 0.24 mmol) in 60 mL of dry acetone, and the mixture was heated to 53 °C for 4 h. After the reaction mixture was allowed to cool to 25 °C, the solution was concentrated and the residue taken up in EtOAc, washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated to afford 1.42 g (71%) of ketone **57** after chromatography on silica (1:1 hexanes/EtOAc). Ketone **57** was reduced ($NaBH_4$) and deprotected (nBu_4NF) to give **58** as an amorphous solid (82%) after chromatography on silica (100% EtOAc): ^{1}H NMR ($CDCl_3$) δ 8.59 (2 H, m), 7.78 (1 H, br), 6.80−7.50 (12 H, m), 5.02 (2 H, m), 3.20−3.80 (8 H, m), 2.70 (3 H, br), 2.28 (1.5 H, bs), 2.25 (1.5 H, bs), 1.50−2.10 (23 H, m), 0.92 (3 H, bt). Anal. ($C_{45}H_{57}N_3O_6\cdot 0.3H_2O$) C, H, N.

(2,2-Dimethyl[1,3]dioxan-5-yl)methanol (24). A mixture of diethyl bis(hydroxymethyl)malonate **23** (25 g, 113 mmol), 50 mL of dimethoxymethane, and *p*-toluenesulfonic acid monohydrate (1.0 g, 5.2 mmol) was combined and stirred for 54 h. The reaction mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to afford 28.9 g (98%) of a yellow oil. The crude diester (15 g, ca. 57.6 mmol) in a mixture of 75 mL of DMSO and 2 mL of H_2O was treated with NaCl (3.37 g, 57.6 mmol) and heated to reflux for 12 h. Upon cooling, the reaction was diluted with water and extracted with ether. The ether layer was washed with brine, dried ($MgSO_4$), and concentrated to afford 7.4 g (69%) of monoester as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 4.19 (2 H, q, J = 7.1 Hz), 4.05 (4 H, m), 2.80 (1 H, m), 1.45 (3 H, s), 1.41 (3 H, s), 1.27 (3 H, t, J = 7.1 Hz). To a solution of $LiAlH_4$ (1.04 g, 27.5 mmol) and 120 mL of ether was added a solution of ester (4.7 g, 24.9 mmol) in 20 mL of ether so as to maintain a gentle reflux. The reaction was carefully quenched by the slow addition of 1 mL of H_2O, followed by 1 mL of 15% aqueous NaOH and then 3 mL of additional H_2O followed by vigorous stirring for 1 h. The solution was filtered from the white precipitate that had formed, the precipitate was washed with EtOAc, and the combined organic layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated to afford 3.56 g of crude oil. Flash chromatography (SiO_2, 2:1 ether/hexanes) gave 2.86 g (78%) of alcohol **24** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 4.03 (2 H, dd, J = 4.2 Hz), 3.82 (5 H, m), 1.85 (1 H, m), 1.45 (3 H, s), 1.41 (3 H, s). Anal. ($C_7H_{14}O_3$) C, H.

[(2,2-Dimethyl[1,3]dioxan-5-yl)methyl](1-methyl-1-phenylethyl)amine (25). Formation of the mesylate of alcohol **24** as described above and displacement with 1,1-dimethylbenzylamine afforded amine **25** in 56% yield for the two steps: ^{1}H NMR ($CDCl_3$) δ 7.42 (2 H, d, J = 6.4 Hz), 7.35 (2 H, t, J = 6.4 Hz), 7.21 (1 H, m), 3.93 (2 H, dd, J = 11.9, 3.5 Hz), 3.59 (2 H, dd, J = 11.9, 8.0 Hz), 2.29 (2 H, d, J = 7.0 Hz), 1.80 (1 H, m), 1.44 (6 H, s), 1.40 (3 H, s), 1.35 (3 H, s).

N-[(2,2-Dimethyl[1,3]dioxan-5-ylmethyl]-*N*-(1-methyl-1-phenylethyl)benzamide (26) was prepared by the same procedure used to prepare amide **14b**, as a viscous oil (45% yield from amine **25**): ^{1}H NMR ($CDCl_3$) δ 7.40 (2 H, d, J = 7.5 Hz), 7.33 (2 H, t, J = 7.3 Hz), 7.23 (1 H, t, J = 5.3 Hz), 7.00 (2 H, s), 6.84 (1 H, bs), 3.82 (2 H, br), 3.35−3.65 (4 H, m), 2.26 (6 H, s), 1.85 (4 H, m), 1.75 (3 H, bs), 1.35 (3 H, s), 1.16 (3 H, s). Anal. ($C_{25}H_{33}NO_3\cdot 0.2H_2O$) C, H, N.

***N*-(1-Ethylcyclopentyl)-2-[4-[2-[(2,2-dimethyl[1,3]dioxan-5-yl)methyl](1-methyl-1-phenylethyl)carbamoyl]-4-methylphenyl]-3-hydroxybutyl]-*N*-(2-hydroxyethyl)benzamide (44)** was prepared in the same manner as **40ab**. Amide **26** was lithiated with *s*-BuLi and quenched with Weinreb amide **34c** to give crude ketone which was reduced ($NaBH_4$)and deprotected (*n*-Bu_4NF) to give **44** as an amorphous solid after column chromatography on silica (1:1 EtOAc/hexanes) (48% yield from **26**): ^{1}H NMR ($CDCl_3$) δ 7.00−7.45 (16 H, m), 4.60 (1 H, br), 3.75−3.85 (4 H, m), 3.25−3.60 (7 H, m), 2.50−2.85 (4 H, m), 1.65−2.10 (18 H, m), 1.34 (3 H, bs), 1.08 (4 H, m), 0.96 (3 H, t, J = 7.2 Hz); HRFABMS calculated for $C_{44}H_{60}N_2O_6\cdot Cs$ 845.3506, found 845.3491.

***N*-(1-Ethylcyclopentyl)-*N*-(2-hydroxyethyl)-2-[3-hydroxy-4-[2-[[3-hydroxy-2-(hydroxymethyl)propyl](1-methyl-1-phenylethyl)carbamoyl]-4-methylphenyl]butyl]-benzamide (45). 44** was deprotected (*p*-TosOH−MeOH) to give **45** as an amorphous solid after column chromatography on silica (12:1 EtOAc/hexanes) (67% yield): ^{1}H NMR ($CDCl_3$) δ 7.00−7.40 (16 H, m), 4.25 (1 H, br), 3.50−3.80 (6 H, m), 3.45 (5 H, m), 2.45−2.80 (4 H, m), 1.60−2.35 (18 H, m), 1.27 (3 H, bs), 0.96 (3 H, m). Anal. ($C_{41}H_{56}N_2O_6$) C, H, N.

***N*-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-*N*-[1-(4-hydroxyphenyl)-1-methylethyl]-2,5-dimethylbenzamide (59).** Silyl ether **54** (2.2 g, 3.9 mmol) in 20 mL of toluene was treated with *n*-Bu_4NF (3 mmol, 3 mL of 1 M solution in THF) at 0 °C, and after 5 min water was added. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried (Na_2SO_4) and concentrated to yield 3 g of a crude oil. Chromatography (SiO_2, 2% MeOH/CH_2Cl_2) afforded 1.08 g (82%) of phenol **59** as a white amorphous solid: ^{1}H NMR

($CDCl_3$) δ 7.20 (2 H, d, J = 8.5 Hz), 7.02 (2 H, s), 6.89 (1 H, bs), 6.59 (2 H, d, J = 8.5 Hz), 6.13 (1 H, bs), 3.60 (3 H, bs), 3.40 (1 H, br), 2.29 (3 H, s), 2.21, (3 H, s), 1.78 (6 H, bs), 0.80 (9 H, s), −0.12 (6 H, s).

***N*-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2,5-dimethyl-*N*-[1-methyl-1-[4-(2-morpholin-4-ylethoxy)phenyl]ethyl]-benzamide (60).** A mixture of phenol **59** (264 mg, 0.59 mmol), $CsCO_3$ (780 mg, 2.4 mmol), and 2-(chloroethyl)morpholine (free base, prepared from the hydrochloride salt via extraction with EtOAc-saturated $NaHCO_3$ and $MgSO_4$ drying; 893 mg, 6.0 mmol) in 30 mL of dry dioxane was heated to 80 °C for 1 h. After cooling to 25 °C the reaction was filtered, concentrated, taken up in EtOAc, washed with water and brine, dried ($MgSO_4$), and concentrated again. Chromatography (SiO_2, 100% EtOAc) yielded 182 mg (55%) of ether **60** as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 7.32 (2 H, d, J = 8.7 Hz), 7.00 (2 H, s), 6.86 (1 H, bs), 6.86 (2 H, d, J = 8.7 Hz, overlapping bs), 4.10 (2 H, t, J = 7.7 Hz), 3.74 (4 H, t, J = 4.6 Hz), 3.58 (4 H, br s), 2.79 (2 H, t, J = 5.7 Hz), 2.58 (4 H, t, J = 4.6 Hz), 2.28 (3 H, s), 2.21 (3 H, s), 1.79 (6 H, bs), 0.80 (9 H, s), −0.13 (6 H, s).

***N*-(1-Ethylcyclopentyl)-*N*-(2-hydroxyethyl)-2-[3-hydroxy-4-[2-[(2-hydroxyethyl)[1-methyl-1-[4-(2-morpholin-4-ylethoxy)phenyl]ethyl]carbamoyl]-4-methylphenyl]-butyl]benzamide (62)** was prepared as described previously. Amide **60** was lithiated with *s*-BuLi and quenched with Weinreb amide **34c** to give ketone **61** (75%) which was reduced ($NaBH_4$) and deprotected (n-Bu_4NF) to give **62** as an amorphous solid after preparative thin layer chromatography on silica (10% MeOH/CH_2Cl_2) (35% yield from **60**): ^{1}H NMR ($CDCl_3$) δ 7.00−7.40 (9 H, m), 6.86 (2 H, m), 4.60 (1 H, br), 4.10 (2 H, m), 3.74 (4 H, bt), 3.48 (10 H, br), 3.25 (1 H, br), 3.0 (1 H, br), 2.65−2.75 (4 H, m), 2.58 (6 H, br s), 2.29 (3 H, bs), 2.26 (3 H, bs), 2.00 (2 H, br), 1.60−1.85 (12 H, br), 0.95 (3 H, br). Anal. ($C_{45}H_{63}N_3O_7 \cdot 1.0H_2O$) C, H, N.

***N*-[2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl]-5-chloro-2-methyl-*N*-(1-methyl-1-phenylethyl)benzamide (20b).** 3-Chloro-5-methylbenzoic acid[27] was converted to the acid chloride as described previously ($(COCl)_2$, catalytic DMF) and treated with amine **16b** to afford the amide **20b** in 73% yield after chromatography (SiO_2, 7:1 hexanes/EtOAc).

***N*-[2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl]-2-[4-[2-[[2-[(*tert*-butyldiphenylsilyl)oxy]ethyl](1-methyl-1-phenylethyl)carbamoyl]-4-chlorophenyl]-3-oxobutyl]-*N*-(1-ethylcyclopentyl]benzamide (39bc)** was prepared as described previously. Amide **20b** was lithiated with *s*-BuLi and quenched with Weinreb amide **34c** to give ketone **39bc** (35%) after chromatography (SiO_2, 20−33% hexanes/EtOAc): ^{1}H NMR ($CDCl_3$) δ 7.00−7.70 (32 H, m), 3.73 (2 H, m), 3.65 (2 H, m), 3.48 (5 H, m), 3.25 (1 H, br), 2.70 (4 H, m), 1.75−2.00 (8 H, m), 1.70 (8 H, bs), 1.05 (9 H, s), 0.95 (9 H, s), 0.85 (3 H, t, J = 7.2 Hz). Anal. ($C_{70}H_{83}N_2O_5Si_2Cl$) C, H, N, Cl.

2-[4-[4-Chloro-2-[(2-hydroxyethyl)(1-methyl-1-phenylethyl)carbamoyl]phenyl]-3-hydroxybutyl]-*N*-(1-ethylcyclopentyl)-*N*-(2-hydroxyethyl)benzamide Alcohol (43bc). Ketone **39bc** was reduced ($NaBH_4$) and deprotected (n-Bu_4NF) as described previously to give **43bc** as an amorphous solid after chromatography on silica (2:1 EtOAc/hexanes) (84% yield from **39bc**): ^{1}H NMR ($CDCl_3$) δ 7.46 (1 H, bs), 7.00−7.40 (11 H, m), 4.95 (1 H, bs), 3.90 (1 H, bs), 3.40−3.75 (7 H, m), 3.23 (1 H, m), 2.55−2.75 (4 H, m), 2.10−2.30 (2 H, m), 1.90 (8 H, m), 1.50−1.75 (10 H, m), 0.96 (3 H, t, J = 7.2 Hz). Anal. ($C_{38}H_{49}N_2O_5Cl \cdot 0.4H_2O$) C, H, N, Cl.

Crystallography. The crystallization conditions, data collection, and structure solution methods have been previously reported.[10] The resolution limit of the diffraction data and the final crystallographic R factors for the structures are as follows: compound **9**, 2.4 Å and R = 0.174; compound **40ab**, 2.35 Å and R = 0.186; compound **40ad**, 2.2 Å and R = 0.213; compound **40ag**, 2.1 Å and R = 0.211; and compound **42bc**, 2.3 Å and R = 0.189.

Biology and Pharmacology. The details of the method used to determine K_i values has been described previously.[10] The ability of the compounds to prevent HIV-1-induced cell death was determined at Southern Research Institute (Birmingham, AL). Cell viability was measured by metabolism of the tetrazolium dye MTT in CEM-SS cells. The concentrations of compounds required to produce 50% inhibition of HIV-1 induced cell death (ED50) were determined and are listed in Table 1. The concentration of compound that produced a 50% reduction in the number of viable cells (uninfected with virus) as determined by metabolism of MTT is designated the TC_{50} in Table 1. The details of the methods used in the pharmacokinetic studies have been reported previously.[10]

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