Structure-Based Design and Synthesis of Substituted 2-Butanols as Nonpeptidic Inhibitors of HIV Protease: Secondary Amide Series

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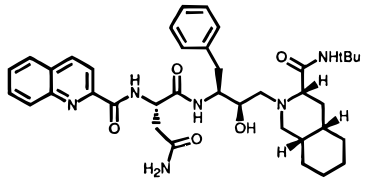
The design, synthesis, and crystallographic analysis of protein−inhibitor complexes is described for a novel series of nonpeptidic HIV protease (HIV Pr) inhibitors. Beginning with a cocrystal structure of a Phe-Pro peptidomimetic bound to the HIV Pr, design was initiated that resulted in the substituted 2-butanol compound **8** as the lead compound ($K_i = 24.5\ \mu$M, racemic mixture). Modifications on the initial compound were then made on the basis of its cocrystal structure with HIV Pr and inhibition data, resulting in compounds with enhanced potency against the enzyme (compound **18**, $K_i = 0.48\ \mu$M). These inhibitors were found to bind to the enzyme essentially as predicted on the basis of the original design hypothesis. Stereospecific synthesis of individual enantiomers confirmed the prediction of a binding preference for the *S* alcohol stereochemistry. Modest antiviral activity was demonstrated for several of the more potent HIV Pr inhibitors in a HIV-1 infected CEM-SS cell line.

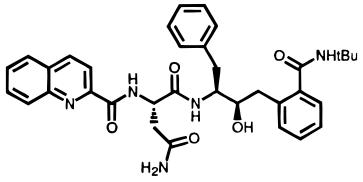
Introduction

Many RNA viruses rely upon expression of structural proteins and enzymes as a large polyprotein which require cleavage by a virally encoded protease as a fundamental component of the replication process. This simple strategy conserves genomic content and reduces the potential interference from host cell regulation. The HIV-1 protease (HIV Pr) catalyzes the cleavage of the gag/pol polyprotein into the constitutive structural proteins and enzymes. This proteolytic processing is required for the development of mature virions, and the HIV Pr enzyme has emerged as a promising therapeutic target for the treatment of acquired immune deficiency syndrome (AIDS).[1] As a result, considerable effort has been focused on both the design of HIV Pr inhibitors and studies of the enzyme crystallographically. While there are numerous examples of very potent peptide-based inhibitors of HIV Pr, the identifications of non-peptidic inhibitors has been more difficult.[2] We have previously described the design and optimization of a novel class of nonpeptidic HIV Pr inhibitors using iterative structure-based techniques.[3] We now provide a full account of the structure-based design, synthesis, and biological evaluation of these HIV Pr inhibitors.

The first HIV Pr inhibitor to reach the market was compound **1** (Saquanivir) from Roche (Figure 1).[4] It is characteristic of peptide-based HIV Pr inhibitors which utilize a transition-state analog to mimic the tetrahedral intermediate formed during cleavage of the scissile Phe-Pro amide bond of the natural substrate. A related inhibitor **2**, which has a comparable affinity for the enzyme, replaces the tetrahydroisoquinoline with the Phe-CH(OH)CH_2aryl as a Phe-Pro mimetic.[5] Both of these compounds are potent inhibitors of the HIV Pr enzyme and potent antivirals. However, they both suffer from poor oral bioavailability. This poor level of oral bioavailability will likely lead to replacement of compound **1** by more orally bioavailable second generation HIV Pr inhibitors.



1
Saquanivir (Ro31-8959)



2
LY289612

Figure 1. Peptide-based HIV Pr inhibitors which mimic the natural Phe-Pro substrate cleavage site.

Design of Inhibitors

The crystal structure of compound **2** complexed with the HIV Pr was solved to 2.5 Å resolution,[6] and this structure was used as a starting point for structure-based design. We reasoned that by retaining only the benzamide portion of the inhibitor the remaining peptidic residues from P1−P3 might be replaced with nonpeptidic fragments yielding an inhibitor with improved oral bioavailability. The challenge of this type of approach was maintaining the desired binding affinity with nonpeptide fragments. The cocrystal structure indicated that as expected, the *tert*-butylbenzamide portion of this inhibitor occupied the S1′ and S2′ pockets, albeit marginally. The benzamide carbonyl oxygen made a hydrogen bond to the flap water molecule (2.7 Å), the other being made by the P2 asparagine backbone carbonyl. These two hydrogen bonds to the flap water molecule are typically made by backbone carbonyls of residues at P2 and P1′ in peptidic inhibitors and presumably in the natural substrate. Modeling was

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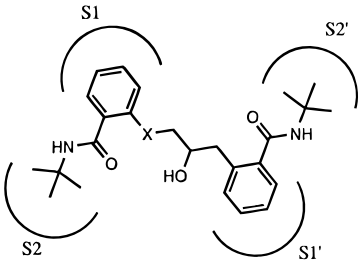


X = S, N, or C
-Benzamide carbonyls to accept H-bond from flap water molecule
-Central hydroxyl forms hydrogen bonds with catalytic aspartic acids

Figure 2. Modeled and observed binding mode of 2-butanol HIV Pr inhibitors.

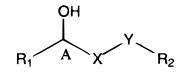
initiated by building off of the central hydroxyl carbon into the S1−S2 pockets. Due to the asymmetrical nature of the inhibited HIV Pr when complexed with an inhibitor a two-carbon fragment appended to the central hydroxyl was required to adequately access the S1 pocket. An acylated 2-aminophenyl group was initially appended to the hydroxyethyl fragment in an attempt to maintain the critical hydrogen bond to the flap water molecule. The first compound prepared to test this hypothesis was racemic sulfide **3** which had no measurable inhibition (Table 1). The sulfur for carbon replacement was used to simplify the synthesis and because the more acute C−S−C bond angle appeared to position the aromatic ring into the S1 pocket better. Further modeling revealed that the hydrogen bond to the flap water molecule could also be made by a 2-substituted benzamide by slightly rotating the phenyl ring. The core inhibitor structure as it was modeled into the subsites of the HIV Pr active site is depicted schematically in Figure 2. Gratifyingly, the bis-*tert*-butyl compound **4** did inhibit the HIV Pr, with a modest K_i of 83 μM.[7] While we synthesized and tested compound **4** as a racemic mixture, the *S* enantiomer was expected to bind preferentially based on the above modeling studies.

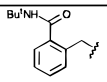
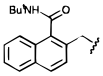
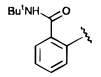
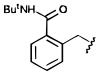
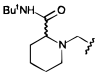
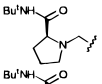
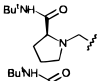
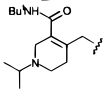
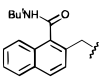
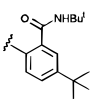
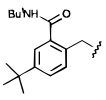
A number of derivatives of the parent sulfide compound **4** were designed to increase both water solubility and binding affinity to facilitate the initial solution of a cocrystal structure. These efforts met with uniform failure except for compound **5**. The naphthyl ring of **5** was able to fill the S1 pocket based on modeling studies and resulted in a 3-fold increase in potency relative to parent compound **4**. Shortening the central linker by one carbon or replacement of sulfur with nitrogen led to a loss in activity with compounds **6** and **7**.

Replacement of the sulfur atom of **4** with carbon (used in the original design) yielded compound **8** with a K_i of 24 μM, a 3-fold improvement in binding relative to sulfide **4**. The cocrystal structure of **8** complexed with the HIV Pr was solved at 2.2 Å resolution and is shown in Figure 3. Comparison of the bound conformation of **8** with the modeled conformation revealed only very minor differences. As anticipated the phenyl rings occupied the S1 and S1′ pockets while the *tert*-butyl groups occupied S2 and S2′ (see Figure 3). Both benzamide carbonyls of **8** made good hydrogen bonds (3 Å) with the flap water molecule. The two-carbon central linker was in an extended anti orientation in the cocrystal structure, which led us to consider a trans olefin as a more conformationally constrained derivative, and inhibitor **9** fit well when modeled into the active site of HIV Pr. However, when synthesized and tested, the trans olefin compound **9** and the corresponding acetylene compound **10**, which also seemed to be accommodated by the enzyme reasonably well, had only weak activity.

Various heterocyclic ring systems were modeled in

Table 1. Substituted 2-Butanol HIV Protease Inhibitors



Cmpd	R1	stereochem. A	X-Y	R_2	K_i (uM)
3		R, S	CH_2-S		>200*
4	"	R, S	CH_2-S		83 +/- 23
5		R, S	CH_2-S	"	25*
6		R, S	CH_2-S	"	>200*
7		R, S	CH_2-NH	"	120*
8	"	R, S	CH_2-CH_2	"	24 +/- 7
9	"	R, S	CH=CH (trans)	"	40% @ 200*
10	"	R, S	C≡C	"	200*
11		R, S	CH_2-CH_2	"	20% @ 100*
12	"	R, S	CH_2-CH_2	"	35% @ 100*
13		R	CH_2-CH_2	"	10% @ 10*
14		S	CH_2-CH_2	"	10% @ 10*
15		R, S	CH_2-CH_2	"	70*
16		R, S	CH_2-CH_2	"	2.2 +/- 0.12
17	"	R, S	CH_2-CH_2		1.4 +/- 0.08
18	"	S	CH_2-CH_2	"	0.48 +/- 0.10
19	"	R	CH_2-CH_2	"	25 +/- 7
20	"	R, S	CH_2-CH_2		1.2 +/- 0.4
21		R, S	CH_2-CH_2	"	7*

* IC_{50}

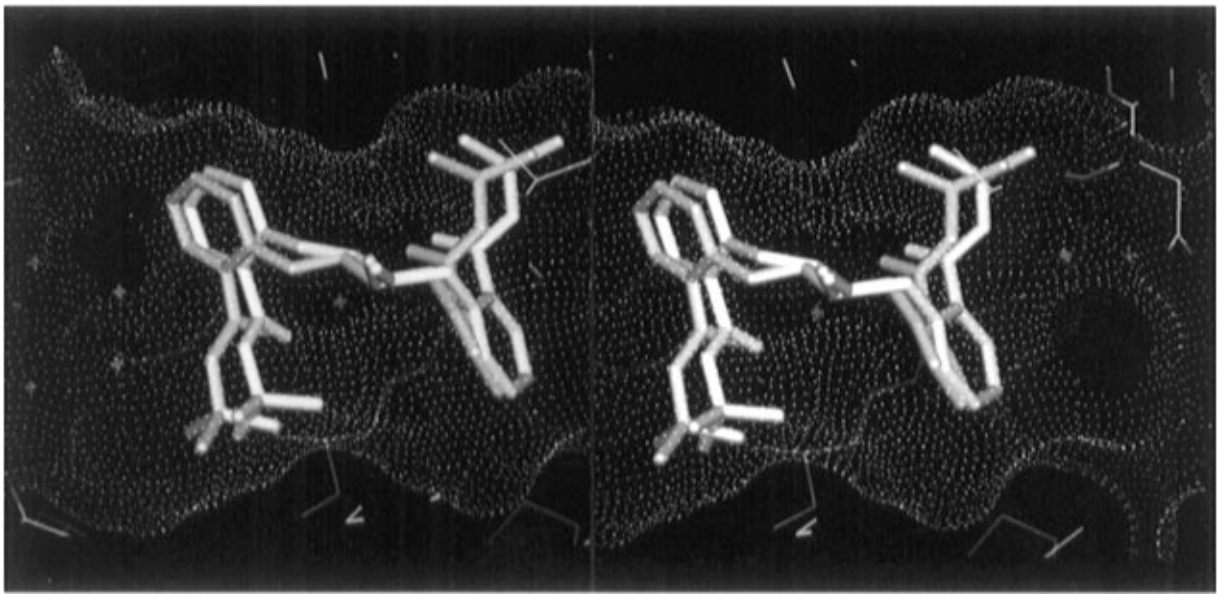


Figure 3. Stereoview of inhibitor **8** complexed with the HIV Pr. The expected (modeled) binding mode is shown in lavender and the observed binding mode is shown in orange. Water molecules are represented as red crosses. The proteins solvent accessable surface is shown in white and protein atoms are shown in green (carbon), red (oxygen), and blue (nitrogen).

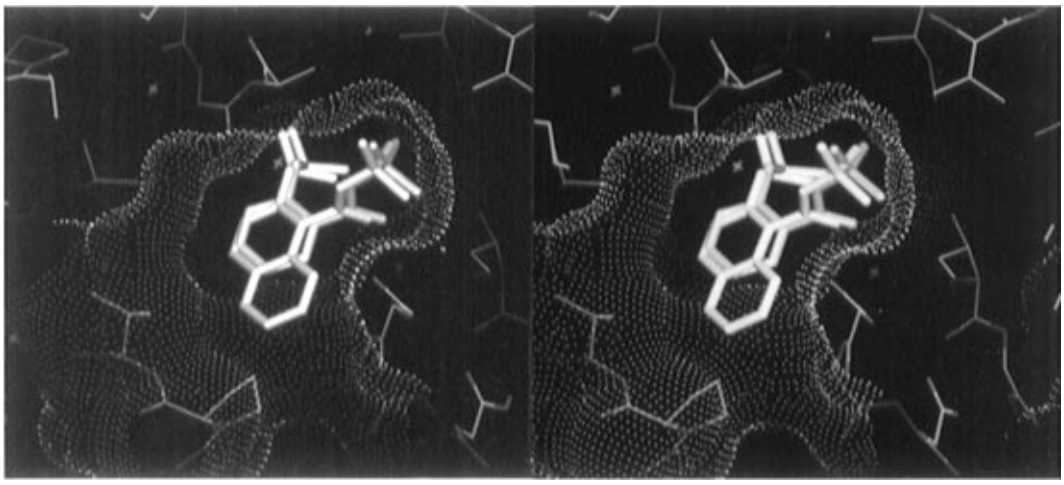


Figure 4. Stereoview of naphthalene-containing inhibitor **16** (shown in lavender) complexed with the HIV Pr. The monocyclic inhibitor **8** is shown in orange for comparison.

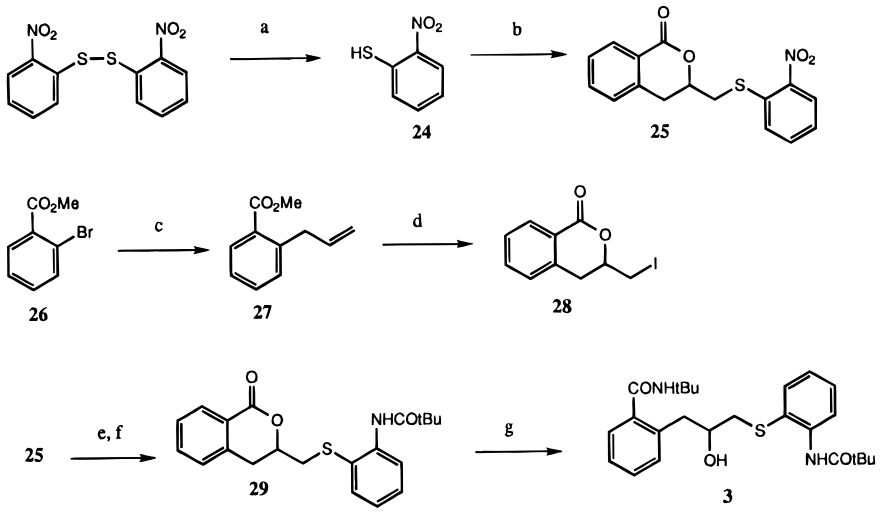
place of the disubstituted benzamides of inhibitor **8** with the intent of filling the lipophilic S1 and S1′ pockets more completely and potentially conferring greater water solubility to the inhibitors. Both the pipicolinic and proline ring systems proved ineffective as inhibitors of HIV Pr (compounds **11**−**14**). The tetrahydropyridine compound **15** designed to position an isopropyl group into the S1′ pocket was merely equipotent with the parent benzamide inhibitor **8**. This may be a result of a competing penalty for desolvation of the basic tetrahydropyridine nitrogen.

Inspection of the cocrystal structure of the relatively small inhibitor **8** (MW 600) revealed that much of the S2, S2′ and S3, S3′ pockets remained unoccupied. Extension of the benzamide to a naphthylamide, as used before with inhibitor **5**, led to a 6-fold improvement in binding with compound **16**. A cocrystal structure of inhibitor **16** was solved, indicating that it had rotated slightly in the active site, presumably to accommodate the larger naphthyl ring (Figure 4). This encouraging result prompted the design and synthesis of racemic bisnaphthyl compound **17** which provided an additional 3-fold enhancement in binding bringing the K_i down to 1 μM.

While it was clear from both the modeling and crystallographic data that it should be the *S* enantiomer which bound preferentially in the active site of HIV Pr, we had no direct evidence for this preference, and all inhibitors thus far had been prepared and tested as racemic mixtures. Therefore, individual enantiomers of racemic inhibitor **17** were prepared by an unambiguous asymmetric synthesis. The *S* enantiomer **18** (K_i = 0.48 μM) was found to be 52-fold more potent than the *R* enantiomer, validating our original design hypothesis.

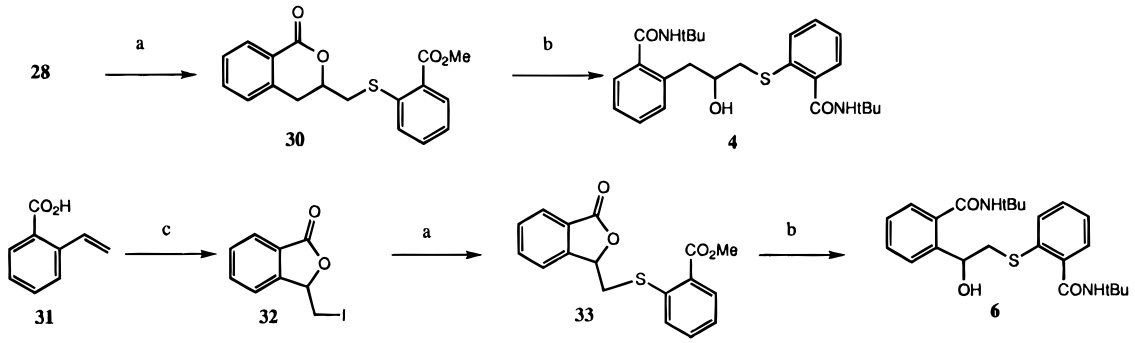
By substituting the 5-position of the benzamide ring of inhibitor **16**, the S1 and S3 pockets of the protease could be accessed based on the cocrystal structure. A *tert*-butyl group in this position was found to fill this pocket well; however inhibitor **20** showed only a modest 2-fold improvement over unsubstituted compound **16**. Substituting both benzamides in compound **8** with a *tert*-butyl group yielded inhibitor **21**, which showed a 3-fold improvement in activity.

Scheme 1[a]



[a] (a) NaSH, NaOH, EtOH; (b) KOH, EtOH–H_2O, **28**; (c) $CH{=}CHCH_2Sn(C_4H_9)_3$, $Pd(PPh_3)_4$, 100 °C; (d) I_2, CH_3CN; (e) Zn–AcOH; (f) pivaloyl chloride, pyridine–CH_2Cl_2; (g) $tBuNHAl(CH_3)_2$, $PhCH_3$.

Scheme 2[a]



[a] (a) Methyl 2-mercaptobenzoate, KOH; (b) $tBuNHAl(CH_3)_2$, $PhCH_3$; (c) I_2, CH_3CN.

Chemistry

The syntheses of compounds **2**–**21** are summarized in Schemes 1–8. Construction of the sulfur containing inhibitors **3**, **4**, and **6** was accomplished using iodo lactones as key intermediates (Scheme 1). Palladium-catalyzed allylation of methyl 2-bromobenzoate **26** followed by iodolactonization afforded intermediate racemic lactone **28**. Coupling of *o*-nitrothiophenol with **28** produced the sulfide **25** in good yield. Reduction of the nitro group, acylation with pivaloyl chloride, and finally treatment with the dimethylaluminum amide of *tert*-butylamine[8] under reflux produced the target sulfide **3**. The aluminum amide procedure was used in general for the direct conversion of intermediate esters and lactones to the corresponding amides.

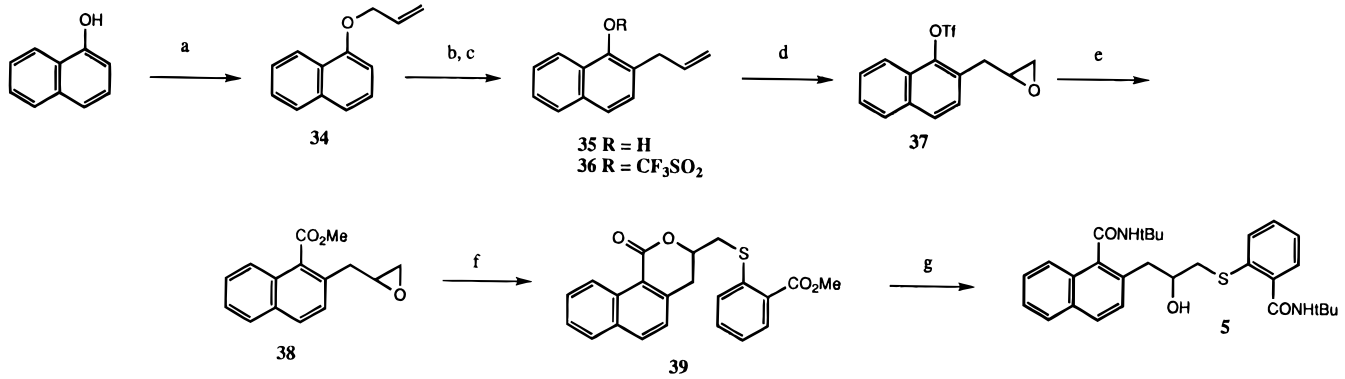
Preparation of the benzamide **4** utilized a similar strategy involving reaction of methyl 2-mercaptobenzoate with iodolactone **28** to yield di-*tert*-butylbenzamide **4** after aluminum amide treatment (Scheme 2). The sulfide **6** containing the shorter three-atom linker was prepared in an analogous fashion using iodo lactone **32** as the coupling partner. Naphthalene containing inhibitor **5** was prepared using a racemic epoxide as the coupling reagent as outlined in Scheme 3. 2-(Allyloxy)-naphthalene **34** was subjected to a Claisen rearrangement to provide naphthol **35**. Triflate formation, epoxidation, and finally palladium-catalyzed CO insertion yielded the key racemic epoxide–ester **38**. Opening of epoxide **38** to form lactone **39** followed by amide formation produced compound **5**.

The alkyne **10**, trans-olefin **9**, and fully reduced compound **8** were obtained from the intermediate ester–lactone **40** (Scheme 4). Lithiation of methyl 2-ethynylbenzoate[9] with LDA followed by quenching with 2-(carboxymethyl)phenylacetaldehyde afforded lactone **40** in modest yield. Hydrogenation to give reduced lactone **41** followed by standard amide formation gave compound **8**. Direct amidation of **40** with *tert*-butylaminodimethylaluminum yielded alkyne **10**. Alternatively, reduction of **40** with Lindlar catalyst produced cis-olefin **42**, which was isomerized with AIBN[10] to the desired trans-olefin and amidated to afford compound **9**.

Amine-containing inhibitors **7** and **11**–**15** were prepared as described in Scheme 5. Coupling of methyl anthranylate with racemic epoxide **38** using lithium perchlorate activation[11] gave aniline **44**, which was amidated under standard conditions to afford compound **7**. Pipicolinic acid amide-containing compounds **11** and **12** were obtained from reaction of racemic pipicolinic acid *tert*-butyl amide **48** with epoxide **46** which was in turn obtained via metalation of 2-methyl-*tert*-butylbenzamide and quenching with epibromohydrin. Final compounds **11** and **12** were obtained as separable diastereomers by flash chromatography. Enantiomeric proline amides **13** and **14** were obtained via coupling of L-proline *tert*-butyl amide with epoxides **66** and **67**, respectively, followed by amidation.

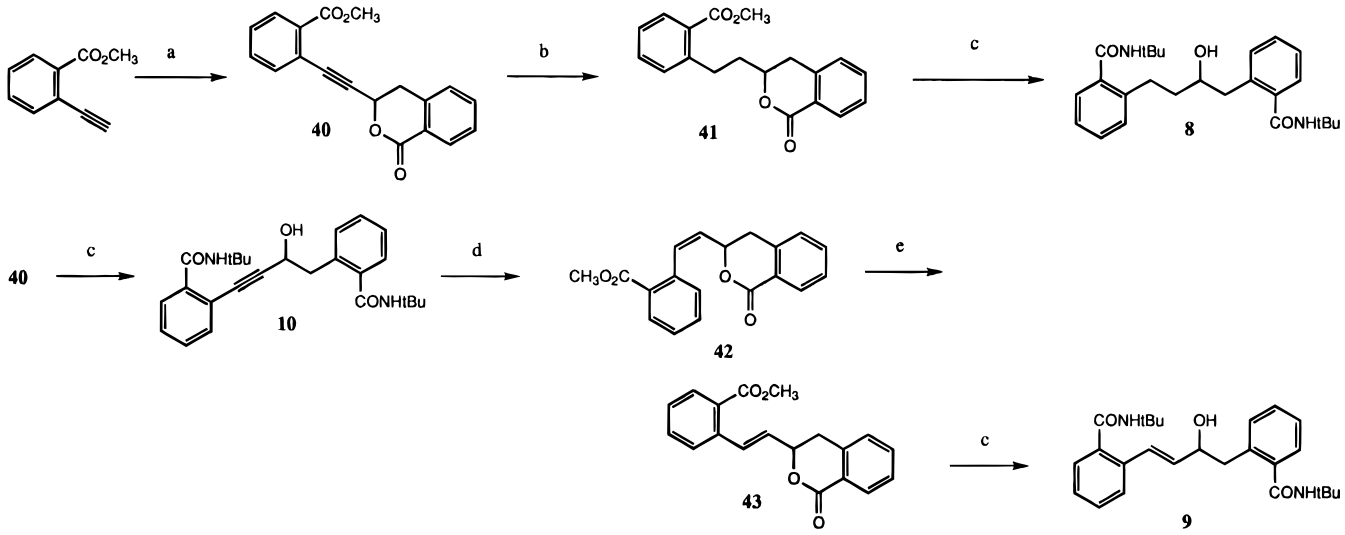
The synthesis of tetrahydropyridine **15** began with 3-cyano-4-methylpyridine, which was converted by a Ritter reaction to the corresponding *tert*-butyl amide

Scheme 3[a]



[a] (a) Allyl bromide, K_2CO_3; (b) $PhN(CH_3)_2$, reflux; (c) Tf_2O, pyridine; (d) mCPBA; (e) $Pd(OAc)_2$, dPPP, CO, MeOH; (f) methyl 2-mercaptobenzoate, KOH; (g) $tBuNHAl(CH_3)_2$, $PhCH_3$.

Scheme 4[a]



[a] (a) LDA, *o*-$(CO_2CH_3)PhCH_2CHO$ (**40a**), THF, −78 °C; (b) H_2, Pd−C, EtOAc; (c) $tBuNHAl(CH_3)_2$; (d) H_2, Lindlar catalyst; (e) PhSH, AIBN, $PhCH_3$.

which was alkylated to afford the isopropyl iodide salt **56**. Sodium borohydride reduction provided the desired intermediate tetrahydropyridine **57**. Metalation of *tert*-butyl amide **63** (vida infra) followed by treatment with ethylene oxide to give the primary alcohol, PDC oxidation to the acid, and finally reaction with *N*,*O*-dimethylhydroxylamine and EDC afforded amide **60**. Metalation of **57** with *s*-BuLi and subsequent treatment with amide **60** yielded alcohol **15** after reduction with sodium borohydride.

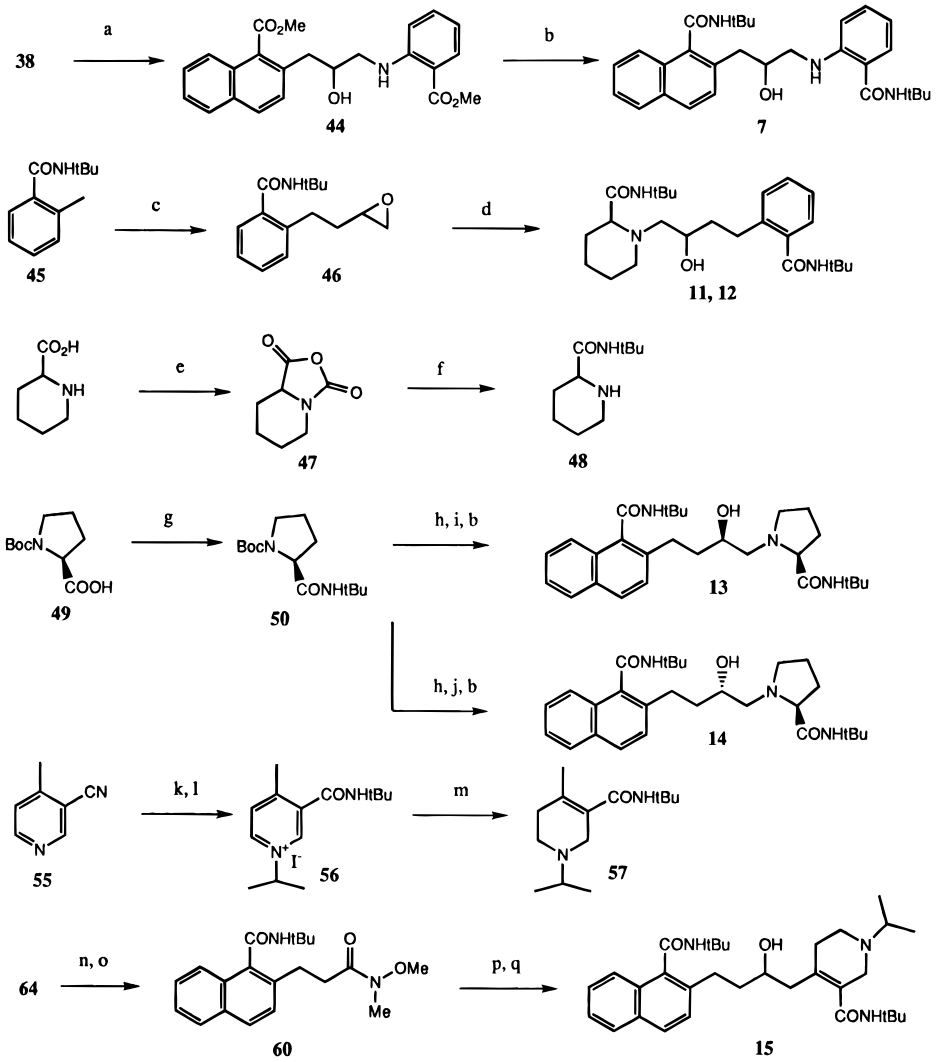
Preparation of bisnaphthalene inhibitors **17**−**19** utilized 2-methylnaphthoic acid *tert*-butyl amide **63** as a key starting material which was synthesized as outlined in Scheme 6. 1-Bromo-2-methylnaphthalene was converted to the 1-carboxylic acid by formation of the corresponding organolithium followed by quenching with CO_2. Standard acid chloride formation and treatment with *tert*-butylamine afforded amide **63**. Metalation and ethylene oxide treatment as before provided alcohol **64** which was oxidized with Collin's reagent to give aldehyde **65**. Metalation again of amide **63** and treatment with aldehyde **65** yielded racemic alcohol **17** directly albeit in modest yield. The individual *R* and *S* enantiomers of **17** were obtained by again metalating naphthalene-1-carboxylic acid *tert*-butyl amide followed by treatment with *S* and *R* glycidyl tosylate, respectively. The mononaphthalene compound **16** was prepared using the same approach used for inhibitor **8** as outlined in Scheme 7. Ozonolysis of olefin **36** provided the required aldehyde which was condensed with methyl 2-ethynylbenzoate as before to provide the alcohol **69**. Palladium-catalyzed CO insertion gave the lactone **71**, which yielded target **16** upon aluminum amide treatment.

The preparation of *tert*-butyl-substituted inhibitors **20** and **21** is summarized in Scheme 8. The *tert*-butyl amide **74** was prepared in a straightforward fashion from 4-*tert*-butyltoluene. Amide **74** was then elaborated into the methoxymethyl amide **77** as before. Coupling of lithiated amides **63** and **74** with **77** provided the expected ketones, which were reduced to the target alcohols **20** and **21**, respectively.

Antiviral Activity

The in vitro antiviral activity of the more potent inhibitors **16** and **17** was assessed using a cell viability assay as described previously.[3] While these are modest inhibitors of the HIV Pr with inhibition constants in the micromolar range, they nevertheless displayed a clear dose response with an antiviral IC_{50} of 63 and 11.5 μM, respectively. This provided us with enough encouragement to pursue optimization of the core structure represented by compound **8**, the details of which are described in the subsequent paper.[12]

Scheme 5[a]



[a] (a) Methyl anthranylate, $Mg(ClO_4)_2$; (b) $tBuNHAl(CH_3)_2$; (c) nBuLi, epibromohydrin; (d) **48**, EtOH, reflux; (e) triphosgene; (f) $tBuNH_2$; (g) iBuOCOCl, Et_3N, −10 °C, $tBuNH_2$; (h) TFA, CH_2Cl_2, 85%; (i) **67**, EtOH, 70 °C; (j) **66**, EtOH, 70 °C; (k) $AcOH-H_2SO_4$, tBuOH, 55 °C to give **56a**; (l) iPrI, CH_3CN, reflux; (m) $NaBH_4$, MeOH; (n) PDC, DMF to give **60b**; (o) HN(OMe)Me·HCl, EDC, HOBt, Et_3N; (p) **57**, sBuLi, TMEDA, −78 °C; (q) $NaBH_4$, MeOH.

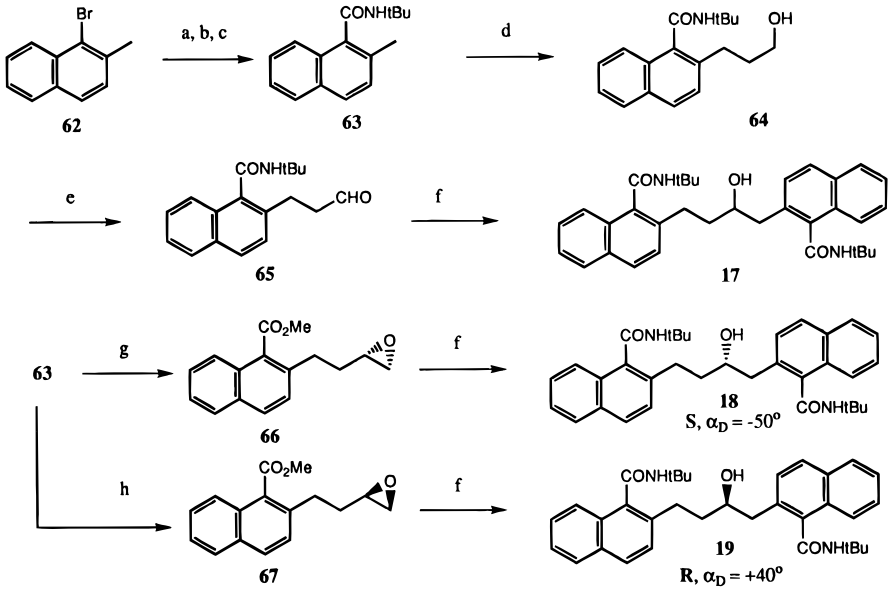
Conclusions

A novel class of nonpeptide HIV Pr inhibitors has been designed and synthesized using the enzyme structure as a guide. Based on initial cocrystal structure information and design, the *S* alcohol was predicted to be favored in binding to the enzyme active site. The prediction was verified through the analysis of crystal structures of several inhibitors complexed with the HIV Pr and also by stereospecific synthesis of each alcohol enantiomer. Some of the compounds were found to be good inhibitors of the HIV Pr enzyme with inhibition constants below 1 μM. The more potent compounds were tested in a primary antiviral assay and were shown to have modest but demonstrable antiviral activity in HIV-1-infected CEM cells, presumably a result of their inhibition of viral protein processing. While the potency of these compounds is modest, the ability to solve cocrystal structures of several of the inhibitors complexed with the HIV Pr enzyme has facilitated their optimization and has led to a related series of HIV Pr inhibitors with enhanced enzyme inhibition, antiviral activity, and oral availability.[12]

Experimental Section

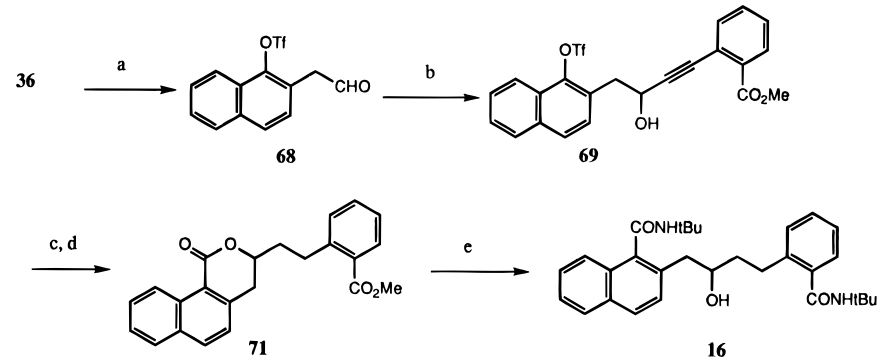
Melting points were determined on a Mel-Temp apparatus and are uncorrected. The structures of all compounds were confirmed by proton magnetic resonance spectroscopy, infrared spectroscopy, and either elemental microanalysis or mass spectrometry. Proton magnetic resonance spectra were determined using a General Electric QE-300 spectrometer operating at a field strength of 300 MHz. Chemical shifts are reported in parts per million (ppm) setting the references such that, in $CDCl_3$, the $CHCl_3$ peak is at 7.26 ppm, in DMSO-d_6, the DMSO peak is at 2.49 ppm, and in acetone-d_6, the acetone peak is at 2.04 ppm. Standard and peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; brs, broad singlet; brd, broad doublet; br, broad signal; and m, multiplet. Mass spectra were determined using a VG 7070E-HF high-resolution mass spectrometer. Infrared absorption spectra were taken on a Perkin-Elmer 457 spectrometer or a MIDAK high-resolution FT IR, and values are reported in cm^{-1}. Elemental microanalysis gave results for the elements stated within ±0.4% of the theoretical values. *N*,*N*-Dimethylformamide and *N*,*N*-dimethylacetamide was used as received from Aldrich. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen. Flash chromatography was performed using silica gel 60 (Merck Art. 9385) unless stated otherwise. Thin layer chro-

Scheme 6[a]



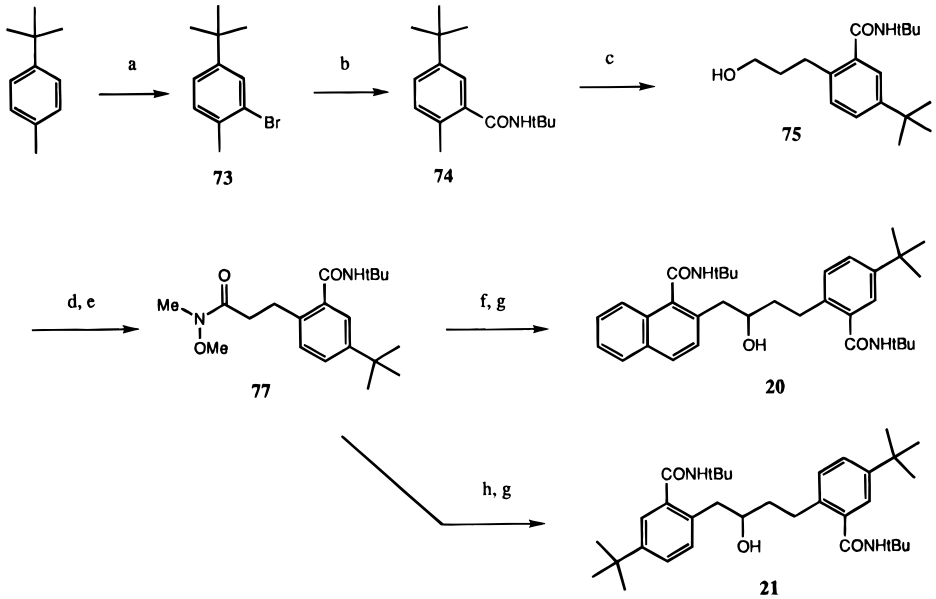
[a] (a) Li^0, Et_2O, reflux, CO_2; (b) $(COCl)_2$, DMF; (c) $tBuNH_2$; (d) nBuLi−TMEDA, ethylene oxide: (e) CrO_3−Pyr_2; (f) naphthalene-1-carboxylic acid *tert*-butyl amide, nBuLi−TMEDA; (g) sBuLi, *(R)*-glycidyl tosylate; (h) sBuLi, *(S)*-glycidyl tosylate.

Scheme 7[a]



[a] (a) O_3, MeOH, $(CH_3)_2S$; (b) LDA, **39a**; (c) H_2, Pd−C; (d) $Pd(OAc)_2$, DPPP, Et_3N, MeOH; (e) $tBuNHAl(CH_3)_2$.

Scheme 8[a]



[a] (a) Br_2, cat. I_2; (b) Li^0, tBuNCO; (c) nBuLi−TMEDA ethylene oxide; (d) PDC, DMF; (e) HN(OMe)Me·HCl, EDC, HOBt, Et_3N; (f) **63**, sBuLi, TMEDA, to give **78**; (g) $NaBH_4$, MeOH; (h) **74**, sBuLi, TMEDA.

matographs (TLC) were performed on precoated sheets of silica 60 F254 (Merck Art 5719).

2-Nitrothiophenol (24). To a refluxing suspension of 2-nitrophenyl disulfide (30.03 g, 97.40 mmol) in 100 mL of

ethanol was added, by dropping funnel, a solution of $NaSH \cdot H_2O$ (12.13 g, 163.79 mmol) and NaOH (5.02 g, 125.50 mmol) in 100 mL water over 15 min. The hot reaction mixture was poured into 500 mL of ice/water and filtered. The filtrate was slowly added to 1 L of ice water containing 80 mL of concentrated HCl, forming a yellow precipitate. The mixture was filtered, and the solid was dissolved in 500 mL of hot 2:1 CCl_4/petroleum ether. The aqueous layer was removed, and the hot organic layer was suction filtered. The filtrate was allowed to cool, forming yellow crystals which were collected and dried to give 17.50 g of **24** (112.78 mmol, 58%): mp 55−56 °C.

3-[[(2-Nitrophenyl)sulfanyl]methyl]isochroman-1-one (25). To a suspension of **24** (0.94 g, 6.05 mmol) in 12 mL of degassed ethanol at 0 °C was added a solution of 85% KOH (0.40 g, 6.09 mmol) in 2 mL of water. A solution of **28** (vide infra) (1.72 g, 5.96 mmol) in 6 mL of EtOH was added by dropping funnel over 40 min; the mixture was allowed to warm to 23 °C and stirred for 16 h. The mixture was poured into 0.5 N HCl, extracted twice with CH_2Cl_2, dried over $MgSO_4$, and concentrated. Purification by flash chromatography (20% hexanes/CH_2Cl_2, preadsorbed onto SiO_2 with CH_2Cl_2) gave **25** as a yellow solid: 1.19 g (3.78 mmol, 62%); mp 172−175 °C; ^{1}H NMR ($CDCl_3$) δ 8.21 (1H, d, J = 8.2 Hz), 8.10 (1H, d, J = 7.7 Hz), 7.61−7.51 (3H, m), 7.41 (1H, t, J = 7.6 Hz), 7.35−7.26 (2H, m), 4.74 (1H, m), 3.61 (1H, dd, J = 13.8, 4.1 Hz), 3.31−3.09 (3H, m); IR (neat) 1728, 1605, 1460, 1337, 1280, 1244, 1119, 1084, 733; HRMS, exact mass calculated for $C_{16}H_{13}NO_4S$, M^+ required 315.0566, found 315.0553. Anal. ($C_{16}H_{13}NO_4S$) C, H, N, S.

Methyl 2-Propenylbenzoate (27). A solution of methyl 2-bromobenzoate (12.0 mL, 83.42 mmol), allyltributyltin (32.0 mL, 103.22 mmol), and palladium tetrakis(triphenylphosphine) (1.92 g, 1.66 mmol) in 30 mL of benzene was heated to 100 °C in a sealed tube for 16 h. The mixture was filtered through a pad of silica gel (eluted with hexanes), and the solvent was removed. Distillation of the crude material at 1 mmHg gave a clear oil (79−90 °C), which contained approximately 90% product (14.3 g). The compound was further purified by flash chromatography (600 g SiO_2, 5% → 10% Et_2O/hexanes) to give 11.48 g of pure **27** (65.16 mmol, 78% yield based on methyl 2-bromobenzoate): ^{1}H NMR ($CDCl_3$) δ 7.88 (1H, m), 7.44 (1H, m), 7.28 (2H, m), 6.01 (1H, m), 5.02 (2H, m), 3.88 (3H, s), 3.75 (2H, d, J = 6.4 Hz); IR (neat) 3075, 2951, 1723, 1435, 1262, 1076, 916, 748.

3-(Iodomethyl)isochroman-1-one (28). A solution of **27** (2.00 g, 11.35 mmol) in 8 mL of acetonitrile at 23 °C was treated with iodine (5.70 g, 22.46 mmol) and stirred for 30 min. The reaction mixture was diluted with ethyl acetate (200 mL), washed twice with a saturated solution of sodium bisulfite, dried over $MgSO_4$, and concentrated to a pale yellow oil (3.22 g, 11.18 mmol, 98%) which needed no further purification: ^{1}H NMR ($CDCl_3$) δ 8.10 (1H, d, J = 7.7 Hz), 7.57 (1H, td, J = 7.5, 1.4 Hz), 7.41 (1H, t, J = 7.6 Hz), 7.28 (1H, d, J = 7.5 Hz), 4.55 (1H, m), 3.52 (1H, dd, J = 10.6, 4.6 Hz), 3.18 (1H, dd, J = 10.6, 7.2 Hz), 3.14−3.20 (2H, m); IR (neat) 3028, 1726, 1607, 1460, 1275, 1240, 1119, 1084, 745; HRMS, exact mass calculated for $C_{10}H_9O_2I$, M^+ required 287.9648, found 287.9655.

2,2-Dimethyl-*N*-[[(1-oxoisochroman-3-yl)methyl]sulfanyl]phenyl]propionamide (29). A solution of **25** (0.15 g, 0.48 mmol) in 4 mL of glacial acetic acid at 23 °C was treated with zinc (0.15 g, 2.33 mmol) and stirred for 1 h. The mixture was filtered through Celite, and the acetic acid was removed under vacuum. The residue was dissolved in ethyl acetate, washed with a saturated solution of $NaHCO_3$, dried over $MgSO_4$, and concentrated. The crude aniline was purified by flash chromatography (20% EtOAc/hexanes) to give a **25b** as a yellow oil: 0.08 g (0.29 mmol, 60%); ^{1}H NMR ($CDCl_3$) δ 8.07 (1H, d, J = 7.1 Hz), 7.53 (1H, dt, J = 7.5, 1.1 Hz), 7.39 (2H, t, J = 7.8 Hz), 7.26−7.11 (2H, m), 6.77−6.66 (2H, m), 4.40 (2H, brs), 4.55 (1H, m), 3.25−2.98 (4H, m); IR (neat) 3462, 3358, 3067, 2926, 1718, 1607, 1480, 1283, 1246, 1121, 1084, 745; HRMS, exact mass calculated for $C_{16}H_{15}NO_2S$, M + H required 286.0903, found 286.0890. Anal. ($C_{16}H_{15}NO_2S \cdot H_2O$) C, H, N, S. To a solution of **25b** (0.168 g, 0.59 mmol) and pyridine (0.07 mL, 0.69 mmol) in 4 mL of CH_2Cl_2 at 0 °C was added trimethylacetyl chloride (0.10 mL, 0.81 mmol). After 20 min, the reaction mixture was diluted with ethyl acetate, washed twice with water and then with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (20% EtOAc/hexanes) to affort 0.16 g (75%) of **29**: ^{1}H NMR ($CDCl_3$) δ 8.91 (1H, br s), 8.46 (1H, dd, J = 8.3, 1.2 Hz), 8.07 (1H, dd, J = 7.8, 1.0 Hz), 7.54 (2H, m), 7.38 (2H, m), 7.20 (1H, d, J = 7.5 Hz), 7.05 (1H, td, J = 7.6, 1.3 Hz), 4.50 (1H, m), 3.19 (1H, dd, J = 13.8, 6.6 Hz), 3.04 (3H, m), 1.36 (9H, s); IR (neat) 2963, 2878, 1730, 1682, 1580, 1510, 1431, 1300, 1246, 1159, 1121, 1084, 745; HRMS, exact mass calculated for $C_{21}H_{23}NO_3S$, M + H required 370.1480, found 370.1464.

Procedure A: Representative Procedure for Amide Formation Using Trimethylaluminum. *N*-*tert*-Butyl-2-{3-[[2-[(2,2-dimethylpropionyl)amino]phenyl]sulfanyl]-2-hydroxypropyl}benzamide (3) *tert*-Butylamine (0.09 mL, 0.83 mmol) was added to a cooled (−12 °C) solution of trimethylaluminum (0.86 mmol) in 4 mL of toluene. The solution was warmed to 23 °C for 45 min, cooled to 0 °C, and treated with lactone **29** (0.067 g, 0.18 mmol) in 1 mL of toluene. The reaction mixture was heated to reflux for 3 h during which all of **29** was consumed. The mixture was poured into 0.5 N HCl, extracted three times with ethyl acetate, dried over $MgSO_4$, and concentrated. Purification by flash chromatography (5% EtOAc/CH_2Cl_2) gave **3** as a white foam: 0.059 g (74%); ^{1}H NMR ($CDCl_3$) δ 9.07 (1H, br s), 8.43 (1H, d, J = 7.4 Hz), 7.59 (1H, dd, J = 7.7, 1.3 Hz), 7.38−7.18 (5H, m), 7.04 (1H, td, J = 7.5, 1.2 Hz), 5.91 (1H, br s), 5.84 (1H, d, J = 5.0 Hz), 3.79 (1H, m), 3.00−2.81 (4H, m), 1.45 (9H, s), 1.35 (9H, s); IR (neat) 3333, 2965, 2870, 1676, 1634, 1580, 1512, 1433, 1366, 1302, 1223, 1161, 1096, 1036, 920, 733; HRMS, exact mass calculated for $C_{25}H_{34}N_2O_3S$, M + H required 443.2371, found 443.2352. Anal. ($C_{25}H_{34}N_2O_3S \cdot 0.25H_2O$) C, H, N, S.

2-[[(1-Oxoisochroman-3-yl)methyl]sulfanyl]benzoic Acid Methyl Ester (30). A solution of 85% KOH (0.19 g, 2.88 mmol) in 10 mL of ethanol/2 mL of water (degassed) at 0 °C was treated with methyl thiosalicylate (0.40 mL, 2.91 mmol), and the resulting yellow solution was stirred for 20 min. Iodo lactone **2** in 5 mL of ethanol was introduced, and the mixture was warmed to 23 °C and stirred for 4 h. The reaction mixture was poured into 1 N HCl, extracted twice with ethyl acetate, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography (20% → 40% EtOAc/hexanes, preadsorbed onto SiO_2 with CH_2Cl_2) to give 0.805 g of **30** as a white solid (2.45 mmol, 84%): mp 79−82 °C; ^{1}H NMR ($CDCl_3$) δ 8.09 (1H, d, J = 7.7 Hz), 7.98 (1H, dd, J = 7.8, 1.4 Hz), 7.57−7.38 (4H, m), 7.26−7.18 (2H, m), 4.74 (1H, m), 3.93 (3H, s), 3.59 (1H, dd, J = 13.6, 3.9 Hz), 3.35−3.05 (3H, m); IR (neat) 1721, 1607, 1460, 1433, 1283, 1246, 1121, 1063, 743, 693. Anal. ($C_{18}H_{16}O_4S$) C, H, S.

***tert*-Butyl-2-[3-[[2-(*tert*-Butylcarbamoyl)phenyl]sulfanyl]-2-hydroxypropyl]benzamide (4).** Using procedure A described above for **3**, alcohol **4** was obtained as a white solid after flash chromatography (5−20% EtOAc/CH_2Cl_2) (81% yield): mp 69−76 °C; ^{1}H NMR ($CDCl_3$) δ 7.57 (1H, d, J = 7.8 Hz), 7.43−7.16 (7 H, m), 6.77 (1 H, br s), 6.17 (1 H, br s), 5.83 (1 H, d, J = 4.3 Hz), 3.89 (1H, m), 3.14 (1H, dd, J = 13.6, 4.5 Hz), 3.00 (1H, dd, J = 13.6, 8.2 Hz), 2.88 (2H, m), 1.46 (9H, s); IR (neat) 3297, 1638, 1545, 1452, 1364, 1321, 1223, 1096, 1044, 911, 878, 733; HRMS, exact mass calculated for $C_{25}H_{34}N_2O_3S$, M + H required 443.2370, found 443.2383. Anal. ($C_{25}H_{34}N_2O_3S$) C, H, N, S.

1-(Allyloxy)naphthalene (34). A solution of 1-naphthol (11.00 g, 76.29 mmol), allyl bromide (6.60 mL, 76.29 mmol), and K_2CO_3 (13.70 g, 99.18 mmol) in 100 mL of acetone was heated for 12 h at reflux. The mixture was filtered through Celite and concentrated to give 13.70 g (98% yield) of **34** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 8.21 (1H, m), 7.81 (1H, m), 7.46 (3H, m), 7.23 (1H, m), 6.12 (1H, m), 5.56 (1H, s), 5.30 (2H, m), 3.58 (2H, t, J = 5.8 Hz).

2-Allylnaphthalen-1-ol (35). The allyl ether **34** (10.00 g crude, 54.28 mmol) was added to 75 mL of dimethylaniline and refluxed for 4 h. The mixture was poured into 150 mL of water and extracted with diethyl ether. The organic layer was washed with 3 N HCl, dried over $MgSO_4$, and concentrated to the red oil **35** (9.40 g, 94% yield): ^{1}H NMR ($CDCl_3$) δ 8.32 (1H,

m), 7.81 (1H, m), 7.52−7.30 (4H, m), 6.82 (1H, d, J = 7.3 Hz), 6.16 (1H, m), 5.58−5.51 (1H, m), 5.37 (1H, m), 4.72 (2H, m).

Trifluoromethanesulfonic Acid 2-Allylnaphthalen-1-yl Ester (36). Trifluoromethanesulfonic anhydride (4.64 mL, 27.59 mmol) was added to a solution of **35** (4.84 g, 26.28 mmol) at 0 °C, and pyridine (2.22 mL, 27.59 mmol) in 60 mL of CH_2Cl_2 was added. The solution was warmed to 23 °C and stirred for 12 h. The mixture was poured into 75 mL of 1 N HCl and extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$, dried with $MgSO_4$, and concentrated to a crude white solid. Chromatography on silica (10%Et_2O−hexanes) yielded **36** as a white solid (5.32 g, 64% yield): mp 49−50 °C; ^{1}H NMR ($CDCl_3$) δ 8.09 (1H, d, J = 8.5 Hz), 7.80 (2H, m), 7.65−7.53 (2H, m), 7.42 (1H, d, J = 8.5 Hz), 5.95 (1H, m), 5.17 (2H, m), 3.69 (2H, d, J = 5.8 Hz); IR (neat film) 3441, 1642, 1406, 1217, 756. Anal. ($C_{14}H_{11}O_3SF_3$) C, H, S.

Trifluoromethanesulfonic Acid 2-(Oxiranylmethyl)-naphthalen-1-yl Ester (37). Compound **36** (5.77 g, 18.25 mmol) was treated with mCPBA (6.30 g, 36.51 mmol) in 55 mL of CH_2Cl_2 at 0 °C. The solution was stirred at 23 °C for 12 h, and the reaction mixture was poured into 75 mL of 1 N NaOH. Extraction of the aqueous layer with CH_2Cl_2, drying ($MgSO_4$), and purification by flash chromatography (20% Et_2O−hexanes) afforded 4.95 g (82%) of epoxide **37** as a white solid: mp 40−41 °C; ^{1}H NMR ($CDCl_3$) δ 8.10 (1H, d, J = 8.3 Hz), 7.87 (2H, m), 7.66−7.54 (3H, m), 3.35 (2H, m), 3.06 (1H, m), 2.83 (1H, t, J = 4.3 Hz), 2.60 (1H, m); IR (neat film) 3059, 3021, 2924, 1605, 1507, 1414, 1232, 1140, 1028, 880. Anal. ($C_{14}H_{11}O_4SF_3$) C, H, S.

2-(Oxiranylmethyl)naphthalene-1-carboxylic Acid Methyl Ester (38). A solution of epoxide **37** (4.86 g, 14.63 mmol), palladium acetate (0.21 g, 0.92 mmol), dppp (1.2-bis-(diphenylphosphino)ethane) (0.38 g, 0.92 mmol), triethylamine (2.7 mL), methanol (19 mL), and 1,2-dichloroethane (10 mL) in 30 mL of DMSO was heated to 70 °C under a balloon atmosphere of carbon monoxide. Arter 16 h of stirring, the reaction mixture was diluted with chloroform and washed with 1 N HCl and saturated aqueous $NaHCO_3$. Concentration of the organic layer and purification by chromatography (20% EtOAc−hexanes on silica) yielded 1.10 g (31% yield) of white solid **38**: ^{1}H NMR ($CDCl_3$) δ 7.85 (3H, m), 7.54−7.42 (3H, m), 4.06 (3H, s), 3.12 (1H, m), 3.05 (2H, q, J = 5.3 Hz), 2.80 (1H, t, J = 4.2 Hz), 2.58 (1H, m); IR (neat film) 3055, 2996, 2951, 1725, 1435, 1281, 1138, 750. Anal. ($C_{15}H_{14}O_3$) C, H.

2-[[(4-Oxo-1,4-dihydro-2*H*-3-oxaphenanthren-2-yl)methyl]sulfanyl]benzoic Acid Methyl Ester (39). A solution of methyl 2-mercaptobenzoate (170 μL, 1.23 mmol) and 1 N KOH (1.23 mL) and 3 mL of EtOH was stirred at 0 °C for 45 min. Epoxide **38** was added in 1 mL of EtOH. Warming the reaction mixture to 23 °C resulted in the formation of a white precipitate within 10 min. The reaction was diluted with EtOAc, washed with water and 0.5 N HCl, and concentrated to a light yellow solid. Flash chromatography (2:1 hexanes/EtOAc) provided the lactone **39** (0.25 g, 54%): mp 136−138 °C; ^{1}H NMR ($CDCl_3$) δ 9.19 (1H, d, J = 8.7 Hz), 7.99 (2H, t, J = 8.8 Hz), 7.85 (1H, d, J = 6.6 Hz), 7.67 (1H, m), 7.57−7.39 (3H, m), 7.33−7.18 (2H, m), 4.40 (1H, m), 3.93 (3H, s), 3.66−3.39 (2H, dd, J = 4.0, 3.2 Hz), 3.25 (2H, m); IR (neat film) 3021, 1715, 1215, 756; HRMS exact mass calcd for $C_{22}H_{19}O_4S$ (MH^+) 379.1004, found 379.1007.

2-[3-[[2-(*tert*-Butylcarbamoyl)phenyl]sulfanyl]-2-hydroxypropyl]naphthalene-1-carboxylic Acid *tert*-Butyl Amide (5). Compound **5** was prepared in 85% yield according to the general procedure A above: mp 92−95 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (1H, m), 7.75 (2H, m), 7.59 (1H, br s), 7.39 (4H, m), 7.30−7.10 (2H, m), 5.81 (1H, br s), 5.31 (1H, br s), 3.93 (1H, m), 3.25−2.79 (5H, m), 1.46−1.23 (18H, m); IR (neat film) 3422, 3302, 3019, 2974, 1651, 1514, 1217, 754; HRMS exact calcd for $C_{29}H_{37}N_2O_3S$ (MH^+) 493.2525, found 493.2535. Anal. ($C_{29}H_{36}N_2O_3S\cdot0.3H_2O$) C, H, N, S.

3-(Iodomethyl)-3*H*-isobenzofuran-1-one (32). Iodine (17.15 g, 0.068 mol) was added in one portion to a solution of 2-vinylbenzoic acid[12] (5.00 g, 0.034 mol) in 60 mL of degassed CH_3CN. The reaction mixture was stirred for 1 h at 23 °C and poured into 150 mL of saturated $Na_2S_2O_3$ solution. The mixture was extracted with three 50 mL portions of ethyl acetate. The combined organic phase was washed once with 100 mL portions each of water, saturated $NaHCO_3$ solution, and saturated $Na_2S_2O_3$ solution. The solution was dried over $MgSO_4$, and concentrated to a yellow solid. The crude product was purified by recrystallization from hot ethanol. A 5.78 g (62%) yield of iodo lactone **32** was isolated in two crops as a white solid: IR (film) 1765, 1286, 1059; ^{1}H NMR ($CDCl_3$) δ 7.73 (1 H, d, J = 7.8 Hz), 7.73 (1 H, m), 7.61 (2 H, m), 5.50 (1 H, t, J = 4.9 Hz), 3.66 (1 H, dd, J = 5.2, 11.0 Hz), 3.59 (1 H, dd, J = 4.8, 11.0 Hz).

2-[[(3-Oxo-1,3-dihydroisobenzofuran-1-yl)methyl]-sulfanyl]benzoic Acid Methyl Ester (33). A solution of methyl thiosalicylate (0.97 g, 0.79 mL, 5.75 mmol) in 18 mL of ethanol was degassed and treated with a solution of KOH (0.38 g, 5.75 mmol) in 2 mL of H_2O. The solution was stirred for 10 min, cooled to 0 °C, and treated with a solution of **32** (1.50 g, 5.48 mmol) in 7 mL of THF. The reaction mixture was stirred overnight at 23 °C, poured into 50 mL of H_2O, and extracted three times with 50 mL portions of CH_2Cl_2. The combined organic phase was washed with 50 mL portions of H_2O and brine and dried over $MgSO_4$. The solution was filtered and concentrated to give a viscous yellow oil. The product was isolated by flash chromatography (100 g of SiO_2, 20−25% ethyl acetate/hexanes) to yield 1.14 g (66%) of sulfide **33** as a white solid: IR (film) 1766, 1712, 1286, 1253, 1060; ^{1}H NMR ($CDCl_3$) δ 7.75 (2 H, m), 7.70−7.29 (5 H, series of m), 7.05 (1 H, m), 5.46 (1 H, dd, J = 5.1, 7.1 Hz), 3.74 (3 H, s), 3.44 (1 H, dd, J = 5.1, 13.8 Hz), 3.12 (1 H, dd, J = 7.3, 14.2 Hz).

2-[2-[2-[[(*tert*-Butylcarbamoyl)phenyl]sulfanyl]-1-hydroxyethyl]benzoic Acid *tert*-Butyl Amide (6). A solution of *n*-BuLi (1.6 M in hexanes, 0.94 mL, 1.50 mmol) was added dropwise to a solution of *tert*-butylamine (158 μL, 110 mg, 1.50 mmol) in 2 mL of dry THF cooled to 0 °C. The solution was stirred for 15 min at 0 °C, and a solution of sulfide **33** (157 mg, 0.50 mmol) in 2 mL of THF was added dropwise. The reaction mixture was stirred for 2.5 h at 0 °C and then quenched with 5 mL of dilute NH_4Cl solution. The mixture was extracted three times with 10 mL portions of ethyl acetate, and the combined organic phase was washed once with 15 mL portions of H_2O and brine. The organic solution was dried over $MgSO_4$, filtered, and concentrated to a yellow residue. The product was isolated by flash chromatography (SiO_2, 5−10% ethyl acetate/CH_2Cl_2) to yield 17 mg (8%) of **6** as a white solid: IR (film) 3290 (br), 2967, 1640, 1543, 1365, 1319, 1223; ^{1}H NMR ($CDCl_3$) δ 7.62 (1 H, dd, J = 1.0, 7.2 Hz), 7.52−7.29 (7 H, series of m), 6.38 (1 H, br s, NH), 6.29 (1 H, br s, NH), 4.75 (1 H, dd, J = 4.4, 9.2 Hz), 3.49 (1 H, dd, J = 4.5, 13.7 Hz), 3.24 (1 H, dd, J = 9.3, 13.7 Hz), 1.48 (9 H, s), 1.36 (9 H, s); HRFABMS calcd for $C_{24}H_{33}N_2O_3S$ 429.22119, found 429.22111.

2-[(1-Oxoisochroman-3-yl)ethynyl]benzoic Acid Methyl Ester (40). A solution of osmium tetraoxide (2.5% solution in *tert*-butyl alcohol, 1.4 mL, 0.036 g, 0.142 mmol) was added dropwise to a solution of methyl 2-(2-propenyl)benzoate (2.50 g, 14.19 mmol) in 50 mL of dioxane and 16 mL of H_2O. The mixture was stirred for 15 min during which time the solution turned brown. $NaIO_4$ (6.07 g, 28.38 mmol) was added portionwise over 30 min. A white precipitate formed, and the reaction mixture was stirred at 23 °C for 2.5 h. The mixture was diluted with 75 mL of H_2O and extracted three times with 60 mL portions of ether. The combined organic phase was washed once with 100 mL portions of H_2O and brine and dried over $MgSO_4$. The solution was filtered and concentrated to a tan oil. The aldehyde was isolated by flash chromatography (100 g silica gel, 30% ether/hexanes) to yield 1.39 g (55%) of aldehyde **40a** as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (1H, s, CHO), 8.05 (1 H, dd, J = 1.1, 7.8 Hz), 7.50 (1 H, dt, J = 1.3, 7.5 Hz), 7.37 (1 H, dt, J = 0.9, 7.8 Hz), 7.24 (1 H, t, J = 7.4 Hz), 4.04 (2 H, s), 3.86 (3 H, s). A solution of *n*-BuLi (1.6 M, 10.6 mL, 17.0 mmol) was added dropwise to a solution of diisopropylamine (2.62 mL, 1.89 g, 18.7 mmol) in 50 mL of dry THF cooled to −78 °C. The solution was warmed to 0 °C for 20 min and then cooled to −78 °C. A solution of methyl 2-ethynylbenzoate[9] (2.72 g, 17.0 mmol) in 8 mL of dry THF

was added dropwise, and the mixture was stirred for 30 min. A solution of aldehyde **40a** (2.75 g, 15.5 mmol) in 15 mL of THF was added dropwise, and the reaction mixture was stirred at −78 °C for 2 h during which time the mixture went from a reddish brown slurry to a yellow homogeneous solution. The reaction was quenched with 50 mL of dilute NH_4Cl solution and extracted three times with 80 mL portions of ethyl acetate. The organic extracts were washed once with 100 mL portions of 10% citric acid solution, H_2O, and brine and dried over MgSO4. The solution was filtered and concentrated to an orange solid. The product was isolated by flash chromatography (125 g of silica gel, 15−30% ethyl acetate/hexanes) to yield 1.50 g (32%) of the acetylenic lactone **40** as a white solid. The material was recrystallized from ethyl acetate/hexanes to give a white solid: mp 133.5−135 °C; IR (film) 2953, 1728, 1271, 1070; ^{1}H NMR ($CDCl_3$) δ 8.11 (1 H, d, J = 7.8 Hz), 7.91 (1 H, d, J = 7.7 Hz), 7.57 (1 H, t, J = 7.5 Hz), 7.48−7.26 (5 H, series of m), 5.59 (1 H, dd, J = 5.2, 7.2 Hz), 3.87 (3 H, s), 3.38 (2 H, m). Anal. ($C_{19}H_{14}O_4 \cdot 0.5H_2O$) C, H.

2-[2-(1-Oxoisochroman-3-yl)ethyl]benzoic Acid Methyl Ester (41). A mixture of alkyne **40** (140 mg, 0.36 mmol) and 10% palladium on carbon (96 mg) in 12 mL of ethyl acetate was stirred briskly under an atmosphere of H_2 gas. After 1.5 h the mixture was filtered through Celite and the filter pad washed with 25 mL of ethyl acetate. The solution was concentrated to yield a slightly yellow viscous oil which was purified by flash chromatography (50 g of silica gel, 25−35% ether/hexanes) to afford 127 mg (89%) of lactone **41** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 8.09 (1 H, dd, J = 0.9, 7.7 Hz), 7.91 (1 H, dd, J = 1.3, 7.8 Hz), 7.54−7.21 (6 H, series of m), 4.56 (1 H, m), 3.89 (3 H, s), 3.29−2.90 (4 H, series of m), 2.12 (2 H, m).

2-[4-[2-(*tert*-Butylcarbamoyl)phenyl]-2-hydroxybutyl]-benzoic Acid *tert*-Butyl Amide (8). **8** was prepared from lactone **41** using general procedure A above. The material was purified by flash chromatography (40 g of silica gel, 20−40% ethyl acetate/hexane) to yield 91 mg (83%) of diamide **8** as a white solid: mp 145.5−147 °C; IR (film) 3268 br, 2967, 1638, 1549, 1223; ^{1}H NMR ($CDCl_3$) δ 7.46 (1 H, br s, NH), 7.36 (1 H, dd, J = 1.4, 7.5 Hz), 7.30−7.08 (6 H, series of m), 7.03 (1 H, dd, J = 1.1, 7.6 Hz), 5.88 (1 H, br s, NH), 3.62 (1 H, m), 2.90−2.75 (3 H, series of m), 2.66 (1 H, dd, J = 3.4, 13.6 Hz), 1.97−1.84 (2 H, series of m), 1.35 (9 H, s), 1.34 (9 H, s); HRFABMS calculated for $C_{26}H_{37}N_2O_3$ 425.28042, found 425.28039. Anal. ($C_{26}H_{36}N_2O_3$) C, H, N.

2-[2-Hydroxy-3-[[2-(methoxycarbonyl)phenyl]amino]-propyl]naphthalene-1-carboxylic Acid Methyl Ester (44). A solution of **38** (0.26 g, 1.07 mmol) and methyl anthranylate (204 μL, 1.58 mmol) in 3.5 mL of CH_3CN was treated with $Mg(ClO_4)_2$ (0.35 g, 1.58 mmol) and stirred 12 h at 23 °C.[11] The solution was diluted with ethyl acetate, washed with water, and concentrated to a crude oil. Purification by flash chromatography on silica (1:1 Et_2O/hexanes) afforded 0.26 g (61%) of the foam **44**: ^{1}H NMR ($CDCl_3$) δ 8.03 (1H, m), 7.93−7.79 (4H, m), 7.48 (2H, m), 7.37 (2H, m), 6.72 (1H, d, J = 8.5 Hz), 6.72 (1H, t, J = 7.5 Hz), 4.20 (1H, m), 4.04 (3H, s), 3.85 (3H, s), 3.35 (2H, m), 3.15−2.96 (2H, dd, J = 4.4, 8.5 Hz), 2.86 (1H, d, J = 4.4 Hz); IR (neat film) 3368, 3019, 2953, 1723, 1682, 1582, 1520, 1260, 1217, 775. Anal. ($C_{23}H_{23}NO_5$) C, H, N.

2-[3-[[2-(*tert*-Butylcarbamoyl)phenyl]amino]-2-hydroxypropyl]naphthalene-1-carboxylic Acid *tert*-Butyl Amide (7). Using general procedure A described above, diester **44** was converted into diamide **7**. Purification by flash chromatography on silica (1:1 EtOAc/hexanes) gave a off-white solid: 0.17 g (60%); mp 86−89 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (1H, br s), 7.78 (2H, m), 7.48 (3H, m), 7.30 (3H, m), 6.80 (1H, d, J = 8.4 Hz), 6.61 (1H, br s), 4.67 (1H, br s), 4.28 (1H, br s), 4.05 (1H, br s), 3.45−3.05 (4H, m), 1.55 (9H, s), 1.44 (9H, s); IR (neat film) 3441, 3353, 3019, 1645, 1516, 1215, 758; HRMS exact mass calcd for $C_{29}H_{38}N_3O_3$ (MH^+) 476.2913, found 476.2907.

2-[4-[2-(*tert*-Butylcarbamoyl)phenyl]-2-hydroxybut-3-ynyl]benzoic Acid *tert*-Butyl Amide (10). **10** was prepared from lactone **40** using general procedure A above. The product was isolated by flash chromatography (20 g of silica gel, 20−40% ethyl acetate/hexanes) to yield 31 mg (32%) of diamide **10** as a yellowish white solid: IR (film) 3289 (br), 2967, 2243 (w), 1640, 1539, 1319, 1223; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (1 H, d, J = 9.2 Hz), 7.50−7.29 (7 H, series of m), 7.16 (1 H, br s, NH), 6.04 (1 H, br s, NH), 4.86 (1 H, dd, J = 5.0, 7.7 Hz), 3.24 (2 H, m), 1.47 (9 H, s), 1.46 (9 H, s); HRFABMS calcd for $C_{26}H_{33}N_2O_3$ 421.2491, found 421.2496.

2-[2-(1-Oxoisochroman-3-yl)vinyl]benzoic Acid Methyl Ester (42). A mixture of acetylenic lactone **10** (236 mg, 0.77 mmol), quinoline (60 μL), and Lindlar catalyst (65 mg) in 15 mL of ethyl acetate was stirred briskly under an atmosphere of H_2 gas for 1 h. The reaction mixture was filtered through Celite and the filter pad washed with 20 mL of ethyl acetate. The solution was concentrated to a yellow liquid which was purified by flash chromatography (75 g of silica gel, 15−30% ethyl acetate/hexanes). The isolated material was triturated several times with ether/hexanes to remove traces of quinoline to yield 208 mg (87%) of cis olefin−lactone **42** as a white solid: mp 120−122 °C; ^{1}H NMR ($CDCl_3$) δ 8.08 (1 H, dd, J = 1.0, 7.7 Hz), 8.00 (1 H, dd, J = 1.2, 7.9 Hz), 7.55−7.18 (7 H, series of m), 5.93 (1 H, dd, J = 9.6, 11.4 Hz), 5.14 (1 H, app ddd, J = 0.5, 3.4, 10.3 Hz), 3.91 (3 H, s), 3.14 (1 H, dd, J = 10.6, 16.4 Hz), 2.93 (1 H, dd, J = 3.5, 16.4 Hz). A solution of cis-olefin **42** (150 mg, 0.49 mmol), thiophenol (8.0 μL, 8.6 mg, 0.08 mmol), and 2,2′-azobisisobutyronitrile (AIBN)[10] (6.5 mg, 0.04 mmol) in 12 mL of benzene was heated to 80 °C for 2.5 h. Additional AIBN (6.0 mg) was added, and the heating was continued for 1.5 h. The reaction was cooled and concentrated to a colorless oil which was purified by flash chromatography (80 g of silica gel, 10−30% ethyl acetate/hexanes) to yield 112 mg (75%) of the trans-olefin **43** as a white solid: mp 88−90 °C; IR (film) 1720, 1263, 966; ^{1}H NMR ($CDCl_3$) δ 8.06 (1 H, d, J = 7.7 Hz), 7.86 (1 H, d, J = 7.8 Hz), 7.54−7.21 (7 H, series of m), 6.18 (1 H, dd, J = 6.7, 16.0 Hz), 5.19 (1 H, m), 3.84 (3 H, s), 3.13 (2 H, m).

2-[4-(*tert*-Butylcarbamoyl)phenyl]-2-hydroxybut-3-enyl]-benzoic Acid *tert*-Butyl Amide (9). **9** was prepared from lactone **43** using general procedure A above. The product was isolated by flash chromatography (15 g of silica gel, 20−45% ethyl acetate/hexanes) to yield 33 mg (48%) of diamide **9** as a white solid: mp 170−171 °C; IR (film) 3270 (br), 2969, 1638, 1547, 1225, 962; ^{1}H NMR ($CDCl_3$) δ 7.54 (1 H, d, J = 7.6 Hz), 7.46−7.24 (7 H, series of m), 6.96 (1 H, d, J = 15.8 Hz), 6.32 (1 H, dd, J = 5.5, 15.8 Hz), 6.19 (1 H, br s, NH), 5.65 (1 H, br s, NH), 4.51 (1 H, app q, J = 5.9 Hz), 3.03 (2 H, m), 1.46 (18 H, s); HRFABMS calcd for $C_{26}H_{35}N_2O_3$ 423.26477, found 423.26502. Anal. ($C_{26}H_{35}N_2O_3$) C, H, N.

***N*-*tert*-Butyl-2-(2-oxiranylethyl)benzamide (46).** A solution of 2-methyl-*N*-*tert*-butylbenzamide **45** (2.0 g, 10.4 mmol) and tetramethylenediamine (2.67g, 3.47 mL, 23.0 mmol) in 25 mL of dry THF was cooled to −78 °C. A solution of *n*-BuLi (1.6 M in hexane, 14.4 mL, 23 mmol) was added dropwise over 15 min, and the reaction mixture was stirred at −78 °C for an additional 60 min. Epibromohydrin (5.7 g, 3.6 mL, 41.6 mmol) was added over a 10 min period, and the reaction mixture was stirred for 70 min while warming to −15 °C. The reaction mixture was quenched with 10 mL of dilute NH_4Cl solution, and the mixture was poured into 125 mL of H_2O and extracted with twice with 50 mL portions of ethyl acetate. The combined organic phase was washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to an orange residue. The product was isolated by flash chromatography (150 g of silica gel, 50% ethyl acetate/hexane) to yield 1.64 g (63%) of epoxide **46** as a white solid: mp 86−88 °C; ^{1}H NMR ($CDCl_3$) δ 7.39−7.18 (4 H, m), 5.74 (1 H, br s, NH), 2.94 (3 H, m), 2.74 (1 H, m), 2.48 (1 H, m), 1.89 (2 H, m), 1.47 (9 H, s). Anal. ($C_{15}H_{21}NO_2$) C, H, N.

Piperidine-2-carboxylic Acid *tert*-Butyl Amide (48). Triphosgene (2.20 g, 7.4 mmol) was added in one portion to a stirred suspension of pipecolinic acid (2.40 g, 18.6 mmol) in 35 mL of dry THF. The reaction mixture was heated to 40 °C for 20 h. The mixture was cooled to 23 °C and filtered and the solid washed with 10 mL ether. The filtrate was concentrated to a yellow oil (2.41 g, 84% crude) which was dissolved in 10 mL of dry THF, and the solution was cooled to 0 °C. A solution of *tert*-butylamine (5.00 mL, 3.43 g, 47.0 mmol) in 10 mL of $CHCl_3$ was added dropwise, and the solution was stirred

at 0 °C for 2 h and at 23 °C for 14 h. The reaction mixture was concentrated to a red viscous oil which was purified by flash chromatography (200 g of silica gel, 2−5% MeOH saturated with NH_3/CH_2Cl_2) to yield 1.46 g (51%) of *tert*-butyl amide **48** as a tan solid. A sample recrystallized from hot hexanes gave colorless needles: IR (film) 3324 (br NH), 2932, 1661, 1520; ^{1}H NMR ($CDCl_3$) δ 6.70 (1 H, br s, NH), 3.03 (2 H, app dt, J = 3.3, 10.0 Hz), 2.65 (1 H, app dt, J = 2.8, 12.0 Hz), 1.95 (1 H, m), 1.76 (1 H, m), 1.56 (1 H, m), 1.37 (3 H, m), 1.34 (9 H, s).

1-[4-[2-(*tert*-Butylcarbamoyl)phenyl]-2-hydroxybutyl]-piperidine-2-carboxylic Acid *tert*-Butyl Amide (11 and 12). A solution of epoxide **46** (75 mg, 0.30 mmol) and *tert*-butyl amide **48** (62 mg, 0.33 mmol) in 4 mL of ethanol was heated to reflux for 24 h. The mixture was cooled and concentrated to a yellow residue. The crude product was purified by flash chromatography (16 g of silica gel, 40−50% ethyl acetate/hexanes containing 1.5% MeOH saturated with NH_3). The less polar diastereomer **11** (60 mg) was not pure, while the more polar diasteromer **12** was homogeneous by TLC (35 mg). More polar diastereomer **12**: mp 159−161 °C; ^{1}H NMR ($CDCl_3$) δ 7.35−7.16 (4 H, series of m), 6.58 (1 H, br s, NH), 5.82 (1 H, br s, NH), 5.10 (1 H, br s, OH), 3.50 (1 H, m), 3.17 (1 H, m), 2.93 (1 H, m), 2.74 (1 H, m), 2.58 (1 H, m), 2.38 (1 H, dd, J = 4.6, 12.0 Hz), 2.24 (1 H, dd, J = 7.7, 13.0 Hz), 2.03 (2 H, m), 1.84 (2 H, m), 1.66 (2 H, m), 1.45 (9 H, s), 1.40 (3 H, m), 1.21 (9 H, s); FABMS [M + H] 432. Anal. ($C_{24}H_{41}N_3O_3$) C, H, N. The less polar diastereomer was purified by flash chromatography (10 g of silica gel, 40−50% ethyl acetate/hexanes with 0.5% MeOH saturated with NH_3) to yield 15 mg of compound **12**: IR (film) 3304 (br), 2934, 1657, 1537, 1229; ^{1}H NMR ($CDCl_3$) δ 7.26 (4 H, m), 6.88 (1 H, br s, NH), 5.79 (1 H, br s, NH), 4.16 (1 H, OH), 3.66 (1 H, m), 2.94 (2 H, m), 2.83 (1 H, m), 2.53 (2 H, m), 2.04−1.90 (5 H, series of m), 1.76 (3 H, m), 1.48 (2 H, m), 1.46 (9 H, s), 1.35 (9 H, s); HRFABMS calcd for $C_{24}H_{41}N_3O_3$ 432.3226, found 432.3222.

(1*S*)-2-(*tert*-Butylcarbamoyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (50). To a flask containing *N*-Boc-L-proline **49** (0.55 g, 2.55 mmol) in 7 mL of THF was added triethylamine (0.34 mL, 2.55 mmol) at −12 °C. The cold solution was treated with isobutyl chloroformate (0.33 mL, 2.55 mmol) and stirred for 30 min. *tert*-Butylamine (0.27 mL, 2.55 mmol) was added, and the resulting mixture was stirred at −12 °C. After 1 h, the mixture was poured into water, extracted with EtOAc, dried over $MgSO_4$, and concentrated. Purification by flash chromatography (3:2 hexanes/EtOAc) on silica gave the white solid **50** (0.62 g, 96%): mp 122−124 °C; ^{1}H NMR (DMSO-d_6) δ 7.37 (1H, s), 3.98 (1H, m), 3.23 (2H, m), 2.05 (1H, m), 1.77 (3H, m), 1.33 (9H, s), 1.24 (9H, s); IR (neat film) 3424, 3019, 2978, 1674, 1393, 1215, 758.

50a. The *tert*-butyl-Boc-proline **50** (0.48 g, 1.89 mmol) was treated with a 15% solution of TFA/CH_2Cl_2 at room temperature. After 4 h, the reaction mixture was concentrated and the redissolved in EtOAc. Filtration of the solution through a plug of silica afforded 0.28 g (85% yield) of *(S)*-prolinamide **50a** as a white solid: mp 80−81 °C; ^{1}H NMR (DMSO) δ 7.89 (1H, br s), 3.68 (1H, br s), 2.92 (2H, br s), 2.10 (1H, m), 1.68 (3H, m), 1.25 (9H, s); IR (neat film) 3316, 3019, 2973, 1659, 1524, 1215, 756.

(2*S*)-1-[4-[1-(*tert*-Butylcarbamoyl)naphthalen-2-yl]-2-hydroxybutyl]pyrrolidine-2(*S*)-carboxylic Acid *tert*-Butyl Amide (14). *(S)*-Epoxide **66** (0.07 g, 0.24 mmol) and the *(S)*-prolinamide **50a** (0.04 g, 0.24 mmol) were heated to 70 °C in 7 mL EtOH. After 12 h, the reaction mixture was concentrated and purified on silica by flash chromatography (3% MeOH/CH_2Cl_2) to give **14** as a white solid (0.05 g, 46% yield): mp 83−85 °C; ^{1}H NMR ($CDCl_3$) δ 7.80 (2H, m), 7.43 (2H, m), 7.25 (2H, m), 5.90 (1H, br s), 4.83 (1H, br s), 3.22 (1H, br s), 3.15−2.74 (4H, m), 2.46 (2H, m), 2.25 (1H, m), 2.02−1.80 (3H, m), 1.71−1.62 (4H, m), 1.54 (9H, s), 1.07 (9H, s); IR (neat film) 3418, 3019, 2976, 1653, 1516, 1215, 769; HRMS exact mass calcd for $C_{28}H_{42}N_3O_3$ (MH^+) 468.3226, found 468.3214.

(2*R*)-1-[4-[1-(*tert*-Butylcarbamoyl)naphthalen-2-yl]-2-hydroxybutyl]pyrrolidine-2(*S*)-carboxylic Acid *tert*-Butyl Amide (13). Compound **13** was prepared from the *(R)*-epoxide **67** in a 50% yield according to the procedure described above for **14**: mp 105−108 °C; ^{1}H NMR ($CDCl_3$) δ 7.82 (2H, m), 7.45 (2H, m), 7.27 (2H, m), 5.87 (1H, br s), 4.20 (1H, br), 3.35 (1H, br s), 2.90 (5H, m), 2.58 (1H, m), 2.35 (2H, br s), 2.10 (2H, br s), 1.70 (4H, m), 1.55 (9H, s), 1.32 (9H, s); IR (neat film) 3418, 3019, 2973, 1649, 1516, 1215, 758. Anal. ($C_{28}H_{41}N_3O3\cdot0.25H_2O$) C, H, N.

3-(*tert*-Butylcarbamoyl)-1-isopropyl-4-methylpyridinium Iodide (56). A solution of 3-cyano-4-methylpyridine (11.60 g, 0.098 mol) in 20 mL of glacial acetic acid at 0 °C was treated with *tert*-butyl alcohol (9.26 mL, 0.098 mol), and a solution of 25 mL of AcOH/19 mL of sulfuric acid over 20 min. The reaction mixture was warmed to 55 °C. After 1 h, the mixture was allowed to cool and was made basic with 1 N NaOH. The aqueous layer was extracted with EtOAc, washed with water and brine, dried ($MgSO_4$), and concentrated to give 1.30 g (89%) of **56a** as a off-white solid that was used without further purification: mp 72−73 °C; ^{1}H NMR ($CDCl_3$) δ 8.41 (1H, d, J = 5.0 Hz), 8.37 (1H, s), 8.05 (1H, s), 7.24 (1H, d, J = 5.0 Hz), 2.34 (3H, s), 1.36 (9H, s); IR (neat film) 3428, 3291, 3017, 2976, 1667, 1592, 1514, 1217, 754. Anal. ($C_{11}H_{16}N_2O$) C, H, N. The amide **56a** (3.70 g, 19.25 mmol) was alkylated with isopropyl iodide (2.50 mL, 25.02 mmol) in 45 mL of refluxing acetonitrile. After 48 h, a crude salt precipitate was filtered from the orange-red mother liquor. The solid was washed with a solution of 1:1 hexanes/EtOAc, and the fine pale yellow salt **56** was collected and dried under vacuum (4.00 g, 57% yield): mp 205−210 °C; ^{1}H NMR (DMSO) δ 9.07 (2H, m), 8.39 (1H, s), 8.07 (1H, d, J = 6.0 Hz), 4.98 (1H, m), 2.55 (3H, s), 1.59 (6H, d, J = 6.5 Hz), 1.39 (9H, s); IR (neat film) 3437, 3235, 3019, 2955, 1671, 1535, 1215, 770. Anal. ($C_{14}H_{23}N_2OI$) C, H, N, I.

1-Isopropyl-4-methyl-1,2,5,6-tetrahydropyridine-3-carboxylic Acid *tert*-Butyl Amide (57). The pyridine salt **56** (2.0 g, 5.52 mmol) was reduced with sodium borohydride (0.84 g, 22.08 mmol) in 25 mL of methanol (−12 °C initially; warmed to 25 °C). After 4 h of stirring, the reaction mixture was quenched with water, extracted with EtOAc, washed with brine, and concentrated to the crude oil. Purification by flash chromatography on silica (6% methanol/CH_2Cl_2) yielded 0.86 g (66%) of the white solid **57**: mp 101−102 °C; ^{1}H NMR ($CDCl_3$) δ 5.42 (1H, br s), 3.20 (2H, d, J = 2.0 Hz), 2.81 (1H, m), 2.58 (2H, t, 5.8 Hz), 2.13 (2H, br s), 1.78 (1H, s), 1.36 (9H, s), 1.07 (6H, d, J = 6.5 Hz); IR (neat film) 3428, 3019, 2971, 2913, 1645, 1510, 1217, 669. Anal. ($C_{14}H_{26}N_2O$) C, H, N.

2-(2-Carboxyethyl)naphthalene-1-carboxylic Acid *tert*-Butyl Amide (60b). The alcohol **64** (2.0 g, 7.01 mmol) and PDC (9.24 g, 24.53 mmol) were added to a solution of 10 g of Celite in 75 mL of DMF. After 12 h of vigorous stirring at 23 °C, the dark suspension was poured into 100 mL of 1 N HCl and diluted with diethyl ether. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated to give a crude off-white solid. The impure solid was washed several times with a 1:1 mixture of hexanes/diethyl ether and collected to give 1.2 g (60% yield) of pure acid **60b**: mp 206−210 °C; ^{1}H NMR (DMSO) δ 12.16 (1H, br s), 8.24 (1H, s), 7.87 (2 H, m), 7.74 (1H, d, J = 8.1 Hz), 7.45 (3H, m), 2.90 (2H, d, J = 8.1 Hz), 2.59 (2H, t, J = 8.5 Hz), 1.42 (9H, s); IR (neat film) 3424, 3019, 1713, 1659, 1514, 1215, 748.

2-[2-(Methoxymethylcarbamoyl)ethyl]naphthalene-1-carboxylic Acid *tert*-Butyl Amide (60). A solution of acid **60b** (3.02 g, 10.02 mmol), *N,O*-dimethylhydroxylamine hydrochloride (0.98 g, 10.02 mmol), hydroxybenzotriazole (HOBT) (1.35 g, 10.02 mmol), and triethylamine (4.20 mL, 30.07 mmol) in 25 mL of DMF was treated with 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride (EDC) (1.92 g, 10.02 mmol) at 0 °C. The reaction mixture was allowed to warm to 25 °C and stirred for a total of 12 h. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give 2.60 g of a colorless oil. Chromatography on silica (3:2 hexanes/EtOAc) afforded 1.80 g (48%) of **60** as an oil that crystallized upon standing as a white solid: mp 120−121 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (1H, d, J = 8.2 Hz), 7.77 (2H, m), 7.50 (2H, m), 7.35 (1H, d, J = 8.6 Hz), 6.40 (1H, s), 3.64 (3H, s), 3.13 (3H, s), 3.10 (2H, br s), 2.91 (2H, m), 1.56 (9H, s);

IR (neat film) 3422, 3019, 2973, 1659, 1512, 1217, 772. Anal. ($C_{20}H_{26}N_2O_3$) C, H, N.

4-[4-[1-(*tert*-Butylcarbamoyl)naphthalene-2-yl]-2-hydroxybutyl]-1-isopropyl-1,2,5,6-tetrahydropyridine-3-carboxylic Acid *tert*-Butyl Amide (15). TMEDA (0.30 mL, 2.60 mmol) and *sec*-butyllithium (2.60 mmol) were added to a solution of **57** (0.31 g, 1.30 mmol) in 6 mL of THF at −78 °C. After the deep red anion was stirred for 1.5 h, the amide **60** (0.22 g, 0.65 mmol) in 6 mL of THF was added. After 1 h of stirring at −78 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with EtOAc, washed with brine, and concentrated to give a crude oil. The crude ketone (0.25 g) along with remaining **57** was immediately used in the reduction described below: ^{1}H NMR ($CDCl_3$) δ 7.84 (1H, d, J = 7.0 Hz), 7.77 (2H, t, J = 8.5 Hz), 7.48 (2H, m), 7.30 (1H, m), 6.48 (1H, s), 6.05 (1H, s), 5.40 (1H, br s), 3.35−3.20 (2H, m), 3.15 (1H, m), 3.03 (2H, br s), 2.72 (1H, m), 2.56 (2H, m), 2.49 (1H, br s), 2.20 (1H, br s), 1.99 (1H, br s), 1.80 (1H, s), 1.54 (9H, s), 1.37 (9H, s), 1.10 (6H, m). The crude ketone (0.25 g, 0.48 mmol) was reduced with sodium borohydride (0.84 g, 22.08 mmol) in 25 mL of methanol at 25 °C. After 2 h, the reaction mixture was concentrated to an oil, dissolved in EtOAc, washed with water and brine, concentrated, and purified by flash chromatography on silica (6% methanol/CH_2Cl_2). The tan solid **15** was precipitated twice from a mixture of diethyl ether/hexanes giving 0.30 g: mp 125−128 °C; ^{1}H NMR δ 7.90 (1H, br s), 7.83 (2H, m), 7.45 (2H, m), 7.35 (1H, d, J = 8.5 Hz), 5.90 (1H, m), 5.05 (1H, br s), 3.40 (2H, m), 2.92 (3H, m), 2.75−2.30 (5H, m), 1.97−1.65 (5H, m), 1.55 (9H, s), 1.38 (9H, s), 1.02 (6H, br s); IR (neat film) 3416, 3293, 3017, 2973, 1649, 1514, 1217, 772; HRMS exact mass calcd for $C_{32}H_{48}N_3O_3$ (MH^+) 522.3696, found 522.3701.

2-Methylnaphthalene-1-carboxylic Acid *tert*-Butyl Amide (63). A solution of 1-bromo-2-methylnaphthalene (10.0 g, 45.2 mmol) in 40 mL of ether was treated with lithium wire (0.624 g, 90.5 mmol, previously washed with hexanes) in portions. After an initial period of reflux (exotherm), the reaction mixture was stirred for an additional 2 h and the resulting mixture was transferred via canula into a solution of solid, crushed CO_2 in 50 mL of ether, forming a white precipitate. After 15 min, water was added followed by saturated aqueous $NaHCO_3$ to dissolve solids, and the separated aqueous layer was washed with ether. The aqueous layer was acidified and extracted with ether, dried ($MgSO_4$), and concentrated to afford 5.88 g of crude acid. Recrystallization provided 4.86 g (67%) of 1-carboxy-2-methylnaphthalene: ^{1}H NMR (acetone-d_6) δ 7.96 (1 H, d, J = 8.2 Hz), 7.88 (2 H, m), 7.53 (2 H, m), 7.40 (1 H, d, J = 8.4 Hz), 2.54 (3 H, s). Anal. ($C_{12}H_{10}O_2$) C, H. The above acid (2.0 g, 10.8 mmol) was taken up in 30 mL of toluene and treated with oxalyl chloride (3.0 g, 23.7 mmol) and DMF (250 μL) at 25 °C for 1 h. The volatiles were removed, and the crude acid chloride in 30 mL of CH_2Cl_2 was treated with *tert*-butylamine (1.65 g, 22.6 mmol) at 0 °C. After warming to 25 °C and stirring for 30 min the reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to afford a solid. Chromatography on silica (2:1 hexanes/ether) gave amide **63** (2.16 g, 83%) as a solid: mp 119−120 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (1 H, d, J = 8.2 Hz), 7.55 (2 H, m), 7.45 (2 H, m), 7.27 (1 H, d, J = 8.4 Hz), 2.51 (3 H, s), 1.55 (9 H, s). Anal. ($C_{16}H_{19}NO$) C, H, N.

2-(3-Hydroxypropyl)naphthalene-1-carboxylic Acid *tert*-Butyl Amide (64). TMEDA (3.28 mL, 21.67 mmol) was added to a solution of methyl-*tert*-butylnaphthalenamide **63** (2.50 g, 10.36 mmol) in 90 mL of THF at −78 °C. After 45 min of stirring, neat ethylene oxide (0.55 mL, 10.88 mmol) was added via syringe to the reaction mixture. The dark heterogeneous solution was slowly warmed to 23 °C over 2 h. The reaction mixture was poured into water, extracted with EtOAc, dried over $MgSO_4$, and concentrated to give a crude off-white solid. Purification by flash chromatography (2:1 hexanes/EtOAc) on silica and recrystallization in CH_2Cl_2 afforded 2.1 g (70% yield) of the alcohol **64**: mp 146−148 °C; ^{1}H NMR ($CDCl_3$) δ 7.82 (3H, m), 7.50 (2H, m), 7.32 (2H, d, J = 7.7 Hz), 5.88 (1H, s), 3.45 (3H, m), 2.89 (2H, br s), 2.08−1.90 (2H, m), 1.55 (9H, s); IR (neat film) 3422, 3019, 1649, 1514, 1215, 756. Anal. ($C_{18}H_{23}NO_2 \cdot 0.3H_2O$) C, H, N.

2-(3-Oxopropyl)naphthalene-1-carboxylic Acid *tert*-Butyl Amide (65). Chromium trioxide (0.32 g, 3.15 mmol) was added to a solution of pyridine (0.50 g, 6.3 mmol) in 10 mL of CH_2Cl_2 at 23 °C. After 15 min alcohol **64** (0.15 g, 0.53 mmol) in 2 mL of CH_2Cl_2 was added, and the mixture was stirred an additional 15 min, poured into ether, washed with 1 N NaOH, 1 N HCl, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Recrystallization from ether/hexanes afforded 0.1 g (67%) of aldehyde **65**: ^{1}H NMR ($CDCl_3$) δ 9.80 (1 H, s), 7.91 (1 H, d, J = 7.3 Hz), 7.78 (2 H, m), 7.50 (2 H, m), 7.29 (1 H, d, J = 7.5 Hz), 5.99 (1 H, bs), 3.09 (2 H, m), 2.95 (2 H, m), 1.55 (9 H, s); HRMS exact mass calcd for $C_{18}H_{21}NO_2$ 284.1650 (MH^+), found 284.1648.

2-[4-[2-(*tert*-Butylcarbamoyl)phenyl]-3-hydroxybutyl]-naphthalene-1-carboxylic Acid *tert*-Butyl Amide (17). A solution of amide **63** (0.136 g, 0.56 mmol) and TMEDA (0.132 g, 1.13 mmol) in 10 mL of THF was treated with *n*-BuLi (0.34 mL of 1.69 M in hexanes, 1.13 mmol) at −78 °C. After stirring for 45 min aldehyde **65** (0.08 g, 0.28 mmol) in 2 mL of THF was added, the reaction mixture was allowed to reach 23 °C and then poured into water, and the aqueous layer was extracted with ether. Combined organic fractions were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography (SiO_2, 1:1 ether−hexanes) afforded 0.35 g (23%) of the desired alcohol **17**: ^{1}H NMR ($CDCl_3$) identical with **18**. Anal. ($C_{34}H_{4O}N_2O_3 \cdot 0.1H_2O$) C, H, N.

***(R)*-2-(2-Oxiranylethyl)naphthalene-1-carboxylic Acid Methyl Ester (67).** To a solution of amide **63** (1.13 g, 4.68 mmol) in 15 mL of THF was added *sec*-butyllithium (9.36 mmol) at −78 °C. After the deep red solution was stirred for 1 h, *(S)*-glycidyl tosylate (Aldrich Chemical Co.) (1.07 g, 4.68 mmol, in 10 mL of THF) was added dropwise. After 1 h of stirring at −78 °C, the reaction mixture was poured into water, extracted with EtOAc, and concentrated to give an oil. Purification by flash chromatography on silica (20% THF/hexanes) gave *(R)*-epoxide **67** as an oil that solidified upon cooling (0.85 g, 61%): mp 84−85 °C; $[\alpha]_D$ = +15.2 (chloroform) at 25 °C; ^{1}H NMR ($CDCl_3$) δ 7.88 (1H, d, J = 8.2 Hz), 7.77 (2H, m), 7.48 (2H, m), 7.33 (1H, d, J = 7.5 Hz), 5.80 (1H, s), 2.93 (3H, m), 2.74 (1H, t, J = 4.5 Hz), 2.48 (1H, s), 2.03 (1H, br s), 1.83 (1H, m), 1.55 (9H, s); IR (neat film) 3422, 3019, 2978, 1661, 1512, 1217, 754. Anal. ($C_{19}H_{23}NO_2$) C, H, N.

***(S)*-2-(2-Oxiranylethyl)naphthalene-1-carboxylic Acid Methyl Ester (66).** The *(S)*-epoxide **66** was prepared in 55% yield using the same procedure described above for **67**: mp 84−85 °C; $[\alpha]_D$ = −23.0 (chloroform) at 25 °C; ^{1}H NMR and IR identical with that of compound **67**. Anal. ($C_{19}H_{23}NO_2$) C, H, N.

***(S)*-2-[2-(*tert*-Butylcarbamoyl)phenyl]-3-hydroxybutyl]-naphthalene-1-carboxylic Acid *tert*-Butyl Amide (18).** TMEDA (0.46 mL, 3.03 mmol) and *sec*-butyllithium (3.03 mmol) were added to a solution of *tert*-butylnaphthalenamide (0.34 g, 1.51 mmol) in 9 mL of THF at −78 °C. After the deep red anion was stirred for 1 h, the *(S)*-epoxide **66** (0.23 g, 0.76 mmol) in 5 mL of THF was added. After another 30 min at −78 °C the reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with EtOAc, washed with brine, and concentrated to give a crude foam. Flash chromatography on silica (25% THF/hexanes) afforded 0.06 g (15%) of *(S)*-**18** as a white solid: mp 118−122 °C; $[\alpha]_D$ = −50.1 (chloroform) at 25 °C; ^{1}H NMR ($CDCl_3$) δ 8.00 (1H, br s), 7.82−7.60 (5H, m), 7.47−7.30 (5H, m), 7.04 (1H, br s), 5.87 (2H, m), 4.05 (1H, m), 3.65 (1H, m), 2.97 (3H, br s), 2.75 (1H, m), 1.95 (2H, m), 1.65−1.40 (18H, br); IR (neat film) 3418, 3019, 1647, 1514, 1215, 774; HRMS exact mass calcd for $C_{34}H_{41}N_2O_3$ (MH^+) 525.3117, found 525.3121.

(3*R*)-2-[4-[2-(*tert*-Butylcarbamoyl)phenyl]-3-hydroxybutyl]naphthalene-1-carboxylic Acid *tert*-Butyl Amide (19). *(R)*-Alcohol **19** was prepared in 31% yield from *(R)*-epoxide **67** according to the general procedure described above for **18**: mp 118−122 °C; $[\alpha]_D$ = +40.0 (chloroform at 25 °C); ^{1}H NMR and IR identical to that of compound **18**; HRMS exact mass calcd for $C_{34}H_{41}N_2O_3$ (MH^+) 525.3117, found 525.3111. Anal. ($C_{34}H_{40}N_2O_3 \cdot 3.3H_2O$) C, H, N.

Trifluoromethanesulfonic Acid 2-(2-Oxoethyl)naphthalen-1-yl Ester (68). Ozone was bubbled through a rapidly stirring solution of olefin **36** (0.30 g, 0.95 mmol) in 7 mL of MeOH at −78 °C until a persistant blue color was observed. Excess dimethyl sulfide was added, the reaction was allowed to reach 23 °C, and the mixture was treated with 10 mL of water. The aqueous layer was extracted with ether, and the organic fractions were combined, dried ($MgSO_4$), and concentrated to give 0.41 g of crude material. Flash chromatography (SiO_2, 1:2 ether/hexanes) yielded 0.22 g (73%) of aldehyde **68**: ^{1}H NMR ($CDCl_3$) δ 9.83 (1 H, d, J = 1.1 Hz), 8.10 (1 H, d, J = 8.4 Hz), 7.89 (2 H, m), 7.64 (2 H, m), 7.35 (1 H, d, J = 8.4 Hz), 4.05 (2 H, d, J = 1.1 Hz), 3.09 (2 H, m), 2.95 (2 H, m), 1.55 (9 H, s).

2-{3-Hydroxy-4-[1-[[(trifluoromethyl)sulfonyl]oxy]-naphthalen-2-yl]but-1-ynyl}benzoic Acid Methyl Ester (69). The anion of methyl 2-ethynylbenzoate (0.45 g, 2.8 mmol, prepared from LDA as described for the preparation of **40**) in 10 mL of THF at −78 °C was treated with a solution of aldehyde **68** (0.90 g, 2.8 mmol, previously dried by evaporation of benzene, 2×) in 3 mL of THF. After 1 h the reaction mixture was poured into ice water, and the aqueous phase was extracted with ether. The combined organic fractions were dried ($MgSO_4$) and concentrated to 1.01 g of crude material. Flash chromatography (SiO_2, 1:1 ether/hexanes) afforded 0.51 g (17%) of **69** as a solid: ^{1}H NMR ($CDCl_3$) δ 9.83 (1 H, d, J = 1.1 Hz), 8.10 (1 H, d, J = 8.4 Hz), 7.89 (2 H, m), 7.64 (2 H, m), 7.35 (1 H, d, J = 8.4 Hz), 4.05 (2 H, d, J = 1.1 Hz), 3.09 (2 H, m), 2.95 (2 H, m), 1.55 (9 H, s).

2-[2-(4-Oxo-1,4-dihydro-2*H*-3-oxaphenanthren-2-yl)-ethyl]benzoic Acid Methyl Ester (71). Alkyne **69** (0.23 g, 0.48 mmol) in 15 mL of EtOAc was treated with 5% Pd−C (0.12 g) and placed under 1 atm of H_2 for 1 h. Filtration of the reaction through Celite to remove catalyst followed by concentration yielded 0.175 g (76%) of the desired triflate **70** which was taken on directly into the next step. The triflate **70** (0.17 g, 0.35 mmol) was taken up in 1.5 mL of MeOH, and 0.5 mL of dichloroethane, 2 mL of DMSO, triethylamine (0.07 g, 0.73 mmol), Pd(II) acetate (0.005 g, 0.02 mmol), and DPPP (0.009 g, 0.02 mmol) were added. The reaction flask was evacuated, CO (1 atm) was applied via balloon, and the reaction mixture was heated at 70 °C for 1 h. After cooling, the reaction mixture was diluted with ether and washed with water, aqueous critic acid, saturated $NaHCO_3$ and brine, and the combined organic fractions were dried ($MgSO_4$) and concentrated. Flash chromatography (SiO_2, 1:2 ether/hexanes) afforded 0.15 g (44%) of lactone **71**: ^{1}H NMR ($CDCl_3$) δ 9.22 (1 H, d, J = 8.7 Hz), 8.00 (1 H, d, J = 8.4 Hz), 7.92 (1 H, dd, J = 7.95, 1.0 Hz), 7.86 (1 H, d, J = 8.1 Hz), 7.68 (1 H, m), 7.65 (1 H, m), 7.56 (1 H, m), 7.42 (1 H, m), 7.30 (3 H, m), 4.60 (1 H, m), 3.91 (3 H, s), 3.25 (3 H, m), 3.04 (1 H, m), 2.19 (2 H, m); IR (film) 1715; HRMS exact mass calcd for $C_{23}H_{20}O_4$ 360.1362 (M^+), found 360.1371.

2-[4-[2-(*tert*-Butylcarbamoyl)phenyl]-2-hydroxybutyl]-naphthalene-1-carboxylic Acid *tert*-Butyl Amide (16). Using general procedure A above, lactone **71** (0.05 g, 0.16 mmol) was treated with 10 equiv of (*tert*-butylamino)dimethylaluminum. Standard workup followed by flash chromatography gave 0.05 g (68%) of racemic amide **16**: ^{1}H NMR ($CDCl_3$) δ 8.02 (1 H, m), 7.75 (3 H, m), 7.30 (6 H, m), 5.75 (1 H, bs), 5.30 (1 H, bs), 3.75 (1 H, m), 3.00 (2 H, m), 2.80 (2 H, m), 2.10 (1 H, m), 1.95 (1 H, m), 1.50 (9 H, s), 1.41 (9 H, s); IR (film) 3275, 2965, 2926, 1640, 1543; HRMS exact mass calcd for $C_{23}H_{20}O_4$ 360.1362 (M^+), found 360.1371.

2-Bromo-4-*tert*-Butyltoluene (73). Bromine (5.6 g, 35.4 mmol) was added to a stirred solution of 4-*tert*-butyltoluene (5.0 g, 33.7 mmol) and a crystal of iodine with occasional cooling in an ice bath. After stirring at 23 °C for 2 h water was carefully added and the aqueous layer was extracted with ether. The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to afford bromotoluene **73** (6.6 g, 86%) as an oil which was used directly in the next step.

***N*,5-Di-*tert*-butyl-2-methylbenzamide (74).** A mixture of the crude bromide **73** (3.0 g, 13.2 mmol) and lithium wire (0.2 g, 29.4 mmol) in 25 mL of ether was refluxed for 4 h. The reaction mixture was allowed to cool to 23 °C, and *tert*-butyl isocyanate (1.21 g, 14.5 mmol) was added. After 30 min the reaction mixture was poured into water and extracted with ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to yield 1.54 g (47%) of amide **74** after trituration with hexanes: ^{1}H NMR ($CDCl_3$) δ 7.32 (1 H, s), 7.29 (1 H, d, J = 8.6 Hz), 7.12 (1 H, d, J = 8.6 Hz), 5.55 (1 H, bs), 1.47 (9 H, s), 1.31 (9 H, s). Anal. ($C_{16}H_{25}NO$) C, H, N.

***N*,5-Di-*tert*-butyl-2-(3-hydroxypropyl)benzamide (75).** Same procedure as for **64** (72% yield): mp 146−148 °C; ^{1}H NMR ($CDCl_3$) δ 7.36 (1 H, m), 7.25 (1 H, d, J = 8.2 Hz), 7.18 (1 H, d, J = 8.2 Hz), 5.75 (1 H, bs), 3.47 (2 H, t, J = 5.4 Hz), 2.79 (2 H, t, J = 6.7 Hz), 1.90 (2 H, m), 1.47 (9 H, s), 1.31 (9 H, s). Anal. ($C_{18}H_{29}NO_2$) C, H, N.

***N*,5-Di-*tert*-butyl-2-[2-(methoxymethylcarbamoyl)ethyl]benzamide (77).** Oxidation as with **60**. Amide formation as with **60** (52%): ^{1}H NMR ($CDCl_3$) δ 7.38 (1 H, s), 7.35 (1 H, d, J = 8.2 Hz), 7.20 (1 H, d, J = 8.2 Hz), 6.43 (1 H, bs), 3.68 (3 H, s), 3.18 (3 H, s), 3.03 (2 H, t, J = 8.1 Hz), 2.90 (2 H, m), 1.49 (9 H, s), 1.31 (9 H, s).

2-[4-[4-*tert*-Butyl-2-(*tert*-butylcarbamoyl)phenyl]-2-hydroxybutyl]naphthalene-1-carboxylic Acid *tert*-Butyl Amide (20). Same procedure as with the conversion of **60** to **15**. Benzamide **63** was metalated as before and quenched with *N*-(methoxymethyl)amide **77** to afford ketone **78** (81%): ^{1}H NMR ($CDCl_3$) δ 7.94 (1 H, d, J = 8.4 Hz), 7.80 (1 H, d, J = 7.5 Hz), 7.77 (1 H, d, J = 7.0 Hz), 7.50 (2 H, m), 7.28 (2 H, m), 7.15 (1 H, d, J = 8.5 Hz), 7.10 (1 H, d, J = 8.0 Hz), 6.40 (1 H, bs), 5.88 (1 H, bs), 3.91 (2 H, bs), 2.90 (4 H, m), 1.43 (9 H, s), 1.34 (9 H, s), 1.29 (9 H, s). Anal. ($C_{34}H_{44}N_2O_3$) C, H, N. A solution of ketone **78** (0.1 g, 0.19 mmol) in 3 mL of EtOH was cooled in an ice bath and treated with $NaBH_4$ (0.011 g, 0.28 mmol) and stirred for 30 min at 0 °C and 30 min at 23 °C. The reaction mixture was poured into saturated $NaHCO_3$ and extracted with ether, and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated, affording 0.086 g (85%) of alcohol **20** after flash chromatography on SiO_2 (2:1 ether/hexanes): ^{1}H NMR ($CDCl_3$) δ 8.03 (1 H, m), 7.75 (2 H, m), 7.45 (3 H, m), 7.25 (3 H, m), 5.76 (1 H, bs), 5.20 (1 H, bs), 3.80 (1 H, m), 2.95 (3 H, m), 2.80 (2 H, m), 2.05 (1 H, m), 1.95 (1 H, m), 1.48 (9 H, s), 1.40 (9 H, s), 1.30 (9 H, s); IR (film) 3275, 2965, 2926, 1640, 1543, 1452. Anal. ($C_{34}H_{46}N_2O_3$) C, H, N.

***N*,5-Di-*tert*-butyl-2-[4-[4-*tert*-butyl-2-(*tert*-butylcarbamoyl)phenyl]-2-hydroxybutyl]benzamide (21).** Procedure identical to that used for **20** above to give **21** in 55% yield for two steps: ^{1}H NMR ($CDCl_3$) δ 7.60 (1 H, s), 7.46 (1 H, s), 7.43 (1 H, d, J = 9.3 Hz), 7.27 (3 H, m), 7.04 (1 H, d, J = 8.1 Hz), 5.86 (1 H, s), 4.55 (1 H, bs), 3.70 (1 H, m), 2.82 (4 H, m), 2.05 (1 H, m), 1.95 (1 H, m), 1.43 (9 H, s), 1.42 (9 H, s), 1.32 (9 H, s), 1.28 (9 H, s); IR (film) 3275, 2965, 2926, 1640, 1543, 1452. Anal. ($C_{34}H_{52}N_2O_3$) C, H, N.

Crystallization of HIV-1 Protease, Data Collection, and Structure Solution. The details of the cloning, expression, and purification of HIV-1 protease have been described previously.[3]

Determination of Inhibition Constants (K_i and IC_{50}) and Antiviral Activity (IC_{50}). The methods used were as previously reported.[3]

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(6) See ref 3 for crystallization conditions, data collection, and structure solution of HIV-Pr complexes.
(7) In retrospect, the lack of activity of compounds such as **3** is likely a result of their strong conformational preferences. Compound **3** contains an acylated aniline with only one ortho substituent (the thioalkyl chain), so that a conformation where the amide linkage is in the plane of the phenyl ring is of lower energy. In this conformation the amide carbonyl cannot reach the flap water molecule to form a hydrogen bond. This is not the case with benzamides such as **4**, where the in-plane conformation is of higher energy.
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