β-Substituted Cyclohexanecarboxamide: A Nonpeptidic Framework for the Design of Potent Inhibitors of Cathepsin K

Sheldon N. Crane,*,† W. Cameron Black,† James T. Palmer,‡ Dana E. Davis,‡ Eduardo Setti,‡ Joel Robichaud,† Julie Paquet,† Renata M. Oballa,† Christopher I. Bayly,† Daniel J. McKay,† John R. Somoza,‡ Natalie Chauret,† Carmai Seto,† John Scheigetz,† Greg Wesolowski,§ Frederic Massé,† Sylvie Desmarais,† and Marc Ouellet†

Merck Frosst Centre for Therapeutic Research, 16711 TransCanada Highway, Kirkland, Quebec, Canada, H9H 3L1, Celera Genomics, 180 Kimball Way, South San Francisco, California 94080, and Merck Research Laboratories, West Point, Pennsylvania 19486

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A new series of nonpeptidic cathepsin K inhibitors that are based on a β-substituted cyclohexanecarboxamide motif has been developed. Lead optimization yielded compounds with sub-nanomolar potency and exceptional selectivity profiles against cathepsins B, L, and S. Use of fluorine atoms to block metabolism on the cyclohexyl ring led to compounds with excellent pharmacokinetic properties. Considering the well-established role of cathepsin K in osteoclast-mediated bone turnover, compounds such as (−)-**34a** (hrab Cat K IC_{50} 0.28 nM; >800-fold selectivity vs Cat B, L, and S; PK data in dogs: F 55%, $t_{1/2}$ = 15 h) exhibit great potential for development as an orally bioavailable therapeutic for treatment of diseases that involve bone loss.

Introduction

Cathepsin K is a lysosomal cysteine protease that plays a fundamental role in the osteoclast-mediated degradation of the collagen framework of bone.[1] Consequently, it has become an attractive target for therapeutic intervention in diseases involving pathophysiological bone resorption.[2] Our efforts in this area have been focused on the identification of a once-daily, orally bioavailable cathepsin K inhibitor for the prevention and treatment of osteoporosis. We have recently shown that replacement of the P2−P3 amide bond in dipeptide-nitrile inhibitor **1**[3a,b] with an aryl ring in **2** (Figure 1) was an effective strategy for the development of potent and selective cathepsin K inhibitors that exhibit superior pharmacokinetic profiles as compared to their peptidic counterparts.[4a] We now wish to report that further research in this area has identified a β-substituted cyclohexanecarboxamide scaffold as a promising new entity for the construction of cathepsin K inhibitors.

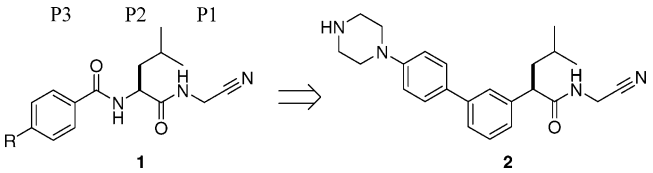

Figure 1. Replacement of the P2−P3 peptide bond in **1** with an aryl ring in **2**.

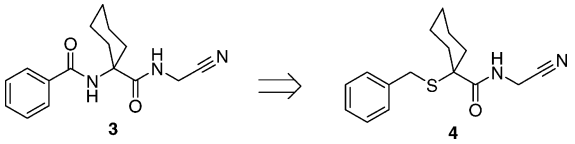

Figure 2. Replacement of the P2−P3 peptide bond with a methyl thioether.

Discovery and Initial SAR Studies

The cyclohexanecarboxamide series of cathepsin K inhibitors were borne out of an attempt to replace the P2−P3 amide bond in **3**[3b] with a methylene-thioether moiety in **4** (Figure 2).

As shown in Scheme 1, treatment of a mixture of bromoester **5a** and benzyl mercaptan with K_2CO_3 in methanol did not generate **6** as hoped, but rather produced **7** (syn:anti 13:1) via a 1,4-addition of the thiolate anion onto the in situ generated α,β-unsaturated ester **5b**. Saponification of the ester functionality in **7** with NaOH followed by HATU-mediated coupling of the resulting acid with aminoacetonitrile afforded syn-isomer **8a**, the corresponding anti-isomer **8b**, and elimination product **8c** in a ratio of 26:1:14.

Anti-isomer **8b** was found to have a potency similar to that of **3** against human cathepsin K (hCat K IC_{50} = 52 and 78 nM, respectively) despite the loss of a hydrogen-bonding interaction of the P2−P3 amide N−H with the carbonyl oxygen of Gly[66] in the active site of the enzyme.[5a] The syn-isomer **8a** was 5-fold less potent (hCat K IC_{50} = 280 nM) than **8b**. Excision of the P3 benzyl thioether and introduction of a conjugated double bond in **8c** resulted in a dramatic loss of activity against cathepsin K (hCat K IC_{50} = 3400 nM). The difficulties associated with the preparation of the more potent isomer **8b**, because of the tendency of **7** to expel benzyl mercaptan under strongly basic conditions, prompted us to transpose the carbon and sulfur atoms in the P2−P3 linker. This was accomplished as illustrated in Scheme 2. Starting from *trans*-cyclohexanecarboxylic acid anhydride (**9**), the warhead portion of the inhibitor was introduced by reaction with aminoacetonitrile in the presence of DMAP to yield **10**. Reduction of the carboxylic acid moiety in **10**, via treatment of an in situ generated mixed anhydride with sodium borohydride, was followed by reaction of the resulting alcohol with tosyl chloride to yield **11**. Nucleophilic displacement of the tosylate with thiophenolate anion produced **12a** (Ar═Ph). Fortunately, only a modest loss in potency was associated with reorganization of the methylene-thioether linker (hCat K IC_{50} = 140 nM for **12a** vs 52 nM for **8b**).

From intermediate **11**, we prepared a wide variety of thioether analogues and studied the effect of varying P3 on human and humanized-rabbit (hrab) cathepsin K[6] inhibition and selectivity

* To whom correspondence should be addressed. Telephone: (514) 428-3934. Fax: (514) 428-4939. E-mail: sheldon_crane@merck.com.
† Merck Frosst Centre for Therapeutic Research.
‡ Celera Genomics.
§ Merck Research Laboratories.

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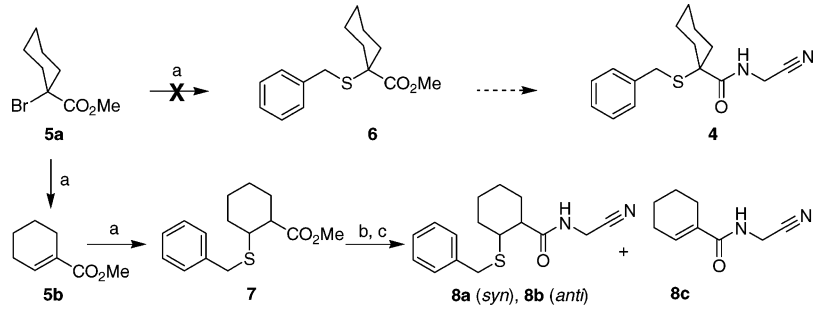
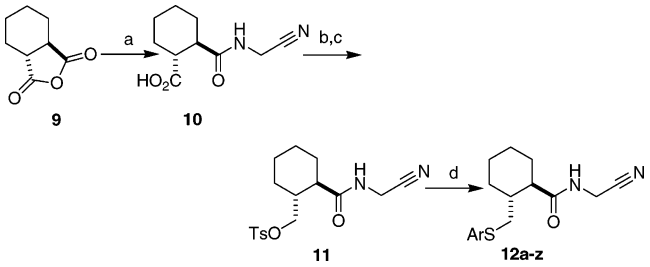
Scheme 1[a]



[a] Conditions: (a) benzyl mercaptan, K_2CO_3, CH_3OH, room temperature; (b) NaOH, H_2O, CH_3OH, reflux; (c) $H_2NCH_2CN{\cdot}HCl$, *i*-Pr_2NEt, HATU, DMF, room temperature.

Scheme 2[a]



[a] Conditions: (a) $H_2NCH_2CN{\cdot}HCl$, Et_3N, 4-DMAP, THF, room temperature, 82%; (b) *i*-BuOCOCl, *N*-methyl-morpholine, THF, −78 °C, then $NaBH_4$, MeOH, −78 °C to room temperature, 73%; (c) TsCl, pyr, CH_3CN, room temperature, 72%; (d) ArSH, K_2CO_3, DMF, room temperature.

Table 1. Potency and Selectivity Profiles of *para*-Substituted Phenyl Analogues of **12**

Compound	Ar = 4-**R**-Ph	hrabCat K[6] IC_{50} (nM)[a]	Selectivity Ratios[a]		
			Cat L/K	Cat B/K	Cat S/K
12a	H	172	150	31	28
12b	F	30	120	145	35
12c	Cl	30	120	>3400	330
12d	Br	33	71	>3100	>3100
12e	I	17	52	>5800	>5800
12f	CH_3S	4.2	2200	>24000	3200
12g	CH_3	100	110	380	180
12h	OH	21	1700	880	110
12i	CH_3O	28	810	>3500	960
12j	NH_2	100	350	>990	120

[a] Each value represents an average of at least three independent determinations.

in our counterscreen against cathepsins B, L, and S. We found that placing a *para*-substituted phenyl moiety in P3 yielded the most potent inhibitors of cathepsin K (Table 1). Additional tuning of the P3 SAR identified a methylthioether as the optimal group in the *para*-position (**12f**, Table 1). This feature further distinguishes this series of compounds from their dipeptide counterparts, which require a basic amine moiety in P3 to attain similar levels of potency and selectivity.[5a,b] Introduction of *meta*- or di- and trisubstituted aromatics (Table 2), as well as mono- and bicyclic-heteroaromatic rings (Table 3), in P3 generally produced less potent inhibitors.

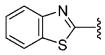
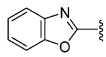
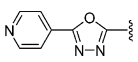
We next turned our attention to studying the effect of further modification of the P2−P3 linker on cathepsin enzyme activity. Oxidation of the thioether in **12b** to the corresponding sulfone with Oxone followed by a S_NAr displacement of the fluorine atom by reaction with 10 equiv of $NaSCH_3$ in DMF afforded **13b** in 93% yield for the two steps (Scheme 3). It should be noted that the electrophilic nitrile functionality was stable to these reaction conditions.

Table 2. Cat K Potency of *meta*-, Di-, and Trisubstituted Phenyl Analogues of **12**

Compound	Ar = **R**-Ph	hrabCat K[6] IC_{50} (nM)[a]	Compound	Ar = **R**-Ph	hrabCat K[6] IC_{50} (nM)[a]
12k	3-F	350	**12p**	3-NH_2	700
12l	3-Cl	200	**12q**	3,5-Cl_2	280
12m	3-Br	150	**12r**	2,4-Cl_2	110
12n	3-OH	330	**12s**	2,5-Cl_2	150
12o	3-CH_3O	370	**12t**	2,4,5-Cl_3	460

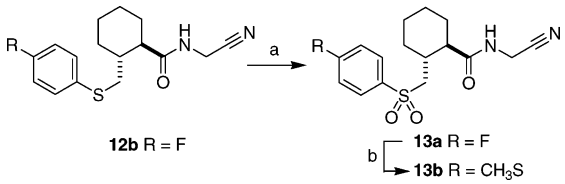
[a] Each value represents an average of at least three independent determinations.

Table 3. Cat K Potency of Heteroaromatic Analogues of **12**

Compound	Ar	hrabCat K[6] IC_{50} (nM)[a]	Compound	Ar	hrabCat K[6] IC_{50} (nM)[a]
12u		410	**12x**		990
12v		200	**12y**		490
12w		480	**12z**		950

[a] Each value represents an average of at least three independent determinations.

Scheme 3[a]

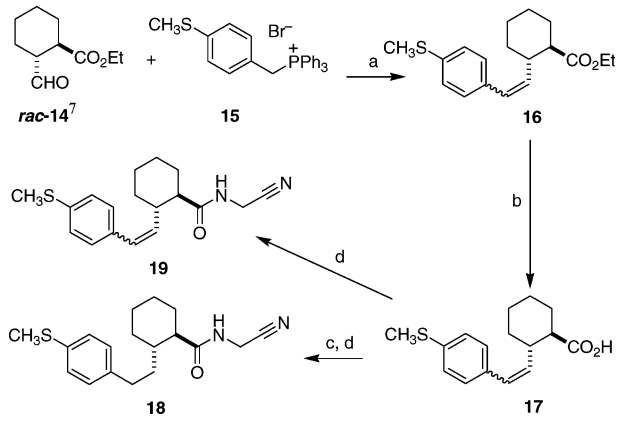


[a] Conditions: (a) Oxone, $NaHCO_3$, THF, MeOH, H_2O, room temperature; (b) $NaSCH_3$, DMF, room temperature, 93% from **12b**.

Hydrocarbon-based P2−P3 linkers were introduced as shown in Scheme 4. Reaction of known aldehyde **14**[7] with Wittig reagent **15** afforded alkene **16** (*Z*/*E* 5.7:1). Subsequent ester saponification, double bond hydrogenation, and coupling of the resulting acid **17** with aminoacetonitrile afforded the fully saturated hydrocarbon linker in **18**. Omission of the double bond reduction step from this sequence produced the corresponding alkene analogue **19**.

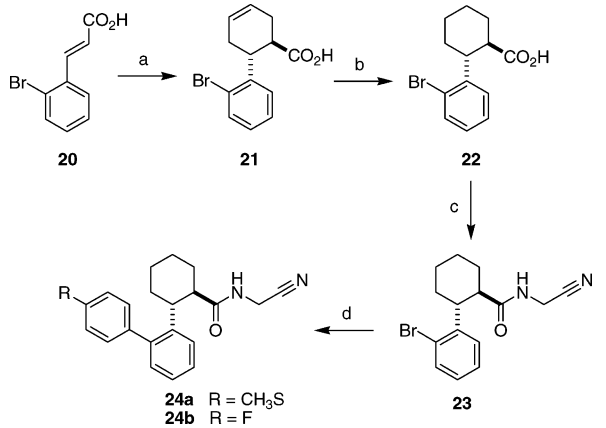
Replacement of the styrene moiety in **19** with a chemically and more metabolically robust biphenyl in **24a** was accomplished as shown in Scheme 5. Diels−Alder addition of *ortho*-bromocinnamic acid **20** to 1,4-butadiene under forcing conditions in a steel bomb gave **21** in 82% yield. Exposure of **21** to an atmosphere of hydrogen in the presence of palladium on charcoal preferentially reduced the double bond in the presence

Scheme 4[a]



[a] Conditions: (a) *t*-BuOK, THF, PhMe, 50 °C, 62%; (b) LiOH, DME, MeOH, H_2O, 60 °C; (c) 40 PSI H_2, 10% Pd/C, EtOAc; (d) H_2NCH_2CN·HCl, PyBOP, Et_3N, DMF, room temperature, 51% for **18**, 61% for **19**.

Scheme 5[a]



[a] Conditions: (a) 1,4-butadiene, PhMe, 200 °C, steel bomb, 82%; (b) 1 atm H_2, 10% Pd/C, EtOAc, room temperature; (c) H_2NCH_2CN·HCl, PyBOP, Et_3N, DMF, room temperature, 97%; (d) 4-methylthiophenylboronic acid or 4-fluorophenylboronic acid, 5 mol % $PdCl_2$(dppf), Na_2CO_3, H_2O, DMF, 85 °C, 66% for **24a**, 85% for **24b**.

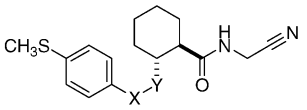
of the hindered *ortho*-substituted aryl bromide. Subsequent coupling of the carboxylic acid functionality to aminoacetonitrile yielded intermediate **23** from which a variety of biaryl analogues were prepared, including **24a** and **24b**, via a Suzuki−Miyaura cross coupling reaction.

A summary of the effect of varying the P2−P3 linker on cathepsin K potency and anti-target selectivities can be found in Table 4. Compound **13b**, possessing a methylene-sulfone P2−P3 linker, was equipotent to the methylene-thioether linked analogue (**12f**) against cathepsin K, but proved to be slightly less selective in the counterscreen assays. Replacing the sulfur atom in **12f** with a methylene unit in **18** yielded a 2-fold increase in potency; however, cathepsin L selectivity was eroded as a result of this change. Introduction of a unit of unsaturation in **19** produced a sub-nanomolar inhibitor of cathepsin K and restored cathepsin L selectivity to the level observed with **12f**. Phenyl-linked analogue **24a** retained the impressive selectivity profile exhibited by **12f** and **19** while maintaining low nanomolar potency against cathepsin K.

Pharmacokinetics and Metabolism I

The pharmacokinetic profiles of **13b** and **24a** were evaluated by intravenous dosing in male Sprague−Dawley rats. Both of these compounds were rapidly cleared from circulation ($t_{1/2}$ = 5 min, Cl = 38 mL/min/kg for **13b**; $t_{1/2}$ = 44 min, Cl = 35 mL/min/kg for **24a**). Incubation of **13b** and **24a** with rat or human hepatocytes produced two major metabolites in each case. These were identified as the corresponding P3 sulfoxides and sulfones (**25a**−**d**, Figure 3) through LC−MS analysis of the incubation media, and comparison with authentic standards prepared by the chemical oxidation of **13b** and **24a** with *m*-CPBA.

Table 4. P2−P3 Linker SAR



Compound	X-Y	hrabCat K[6] IC_{50} (nM)[a]	Selectivity Ratios[a]		
			Cat L/K	Cat B/K	Cat S/K
12f	S-CH_2	4.2	2200	>24000	3200
13b	SO_2-CH_2	5.0	740	2000	1800
18	CH_2-CH_2	1.7	700	>6100	3400
19	CH=CH	0.5	2200	>18000	6800
24a	*ortho*-phenyl	2.6	2800	>3800	>3800

[a] Each value represents an average of at least three independent determinations.

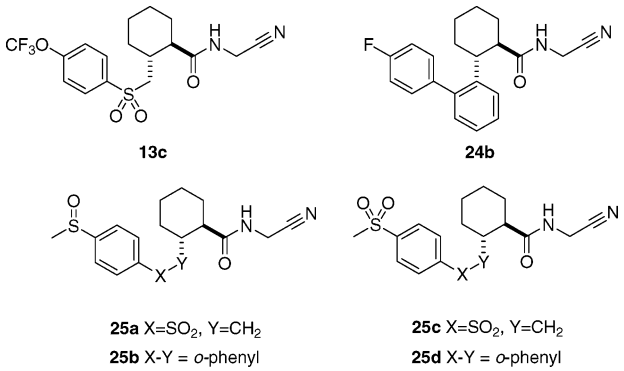


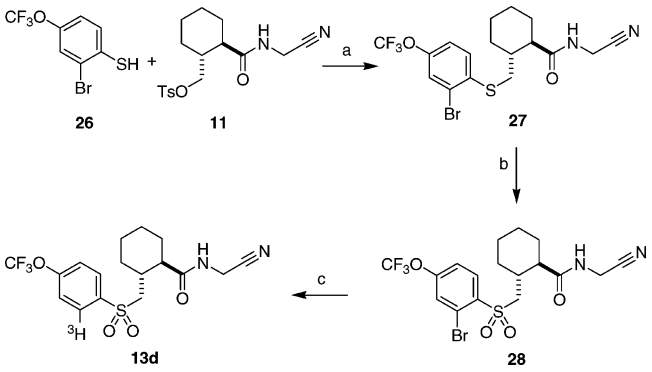
Figure 3. Cathepsin K inhibitors possessing metabolically robust groups in P3.

Poor pharmacokinetics was also exhibited by analogues **13c** ($t_{1/2}$ = 20 min, Cl = 42 mL/min/kg) and **24b** ($t_{1/2}$ = 45 min, Cl = 50 mL/min/kg) despite the absence of a group susceptible to metabolic oxidation in P3 (Figure 3). This prompted us to consider that other portions of these inhibitors were susceptible to cytochrome P450-mediated metabolism. LCMS analysis of the rat hepatocyte incubations of **13c** and **24b** revealed that several M+16 metabolites were indeed produced. MS-fragmentation analysis for each metabolite identified the cyclohexyl portion as the main site of oxidation. The radiolabeled compound **13d**, prepared by palladium-catalyzed tritiation of aryl bromide **28** (Scheme 6), was also incubated with rat hepatocytes. The additional sensitivity offered by radio-HPLC analysis enabled us to determine that the metabolic oxidation of **13b** was even more extensive than that revealed by LCMS analysis alone (Figure 4). Obtaining acceptable pharmacokinetic profiles for this class of compounds would obviously require a dramatic improvement in metabolic stability. Thus, a study of the P2-SAR aimed at achieving this was initiated.

X-ray Structure and Molecular Modeling

An X-ray crystal structure of P3-methoxy analogue **13e** bound to the active site of cathepsin K revealed that this series of inhibitors adopt a binding orientation similar to their peptidic counterparts.[5a] The salient features of this enzyme−inhibitor complex are illustrated in Figure 5a. These include the thio-

Scheme 6[a]



[a] Conditions: (a) K_2CO_3, MeOH, room temperature, 90%; (b) Oxone, $NaHCO_3$, THF, MeOH, H_2O, 40 °C, >99%; (c) $^3H_2$, 10% Pd/C, Et_3N, THF.

imidate moiety formed by covalent union of the nitrile carbon and the sulfur of Cys[25], the hydrogen bond between the thioimidate N−H and terminal oxygen of Gln[19], hydrogen-bonding contacts between the P1−P2 amide of the inhibitor with the N−H of Gly[66] and the carbonyl oxygen of Asn[158]. Note also the deep penetration of the cyclohexyl ring into S2, and the manner in which the aromatic plate of the inhibitor neatly fits into the region of S3 bordered by the aromatic ring of Tyr[67] and the shelf-like structure formed by Gly[65] and Gly[66].

Starting from the X-ray structure of **13e** bound to cathepsin K, molecular dynamics calculations were carried out in AMBER[8] to identify the positions and nature of substituents that would maintain or improve binding to the S2 pocket. Particular attention was paid to electron-withdrawing substituents such as fluorine or chlorine atoms, as a means of reducing oxidative metabolism of the cyclohexyl ring. Figure 5b shows the modeled structure of **13f** with two fluorine atoms added to the cyclohexyl ring of **13e**, which the calculations indicated would be well tolerated by the protein.

Synthesis of Halogenated P2 Analogues

The synthetic route that was used to prepare the *gem*-dihalogenated-cyclohexyl analogues of **24a** and **24b** is shown in Scheme 7. Diels−Alder adduct **21** from Scheme 5 was converted to bromolactone **29** using Iwata's conditions.[9a] Treatment of **29** with sodium methoxide in methanol opened the lactone to afford bromohydroxyester **30**. Oxidation of the alcohol functionality in **30** with Jones reagent followed by reductive debromination of the resulting α-bromoketone with activated zinc dust gave **31** in 31% overall yield from **21**. Conversion of the ketone functionality in **31** to a *gem*-difluoro moiety in **32a** was effected with diethylaminosulfur trifluoride (DAST).[9b] Under a variety of reaction conditions, **32a** was invariably contaminated with two isomeric halogenated alkenes (**32b**,**c**) that were not separable from the desired product by flash chromatography. Fortunately, treatment of the crude product mixture with excess ozone at −78 °C followed by oxidative workup with 30% H_2O_2 was successful in converting the fluoroalkene byproducts to the corresponding diacids, which were easily removed by washing with an aqueous solution of sodium carbonate. Compound **32a** was converted to **33** by a two-step sequence involving ester saponification with LiOH followed by coupling of the resulting acid with aminoacetonitrile. Conversion of aryl bromide **33** to a variety of biaryls[10] including **34a** and **34b** was accomplished in good yield using a Suzuki−Miyaura reaction under standard conditions with $PdCl_2$(dppf) as catalyst.

Both enantiomers of **34a** were also accessed using the chemistry shown in Scheme 7 following resolution of **21** with (*S*)- and (*R*)-α-methylbenzylamine to afford (+)- and (−)-**21**, respectively, in 93% ee. The more potent enantiomer of **34a**, prepared from (−)-**21**, was determined to be the (−)-antipode. The absolute configurations of (+)-**34a** and (−)-**34a** were established as (1*S*,2*S*)- and (1*R*,2*R*)-, respectively, by conversion of (+)-**21** to the known compound (+)-**35** (Scheme 8).[11,12]

Results and Discussion

Installation of a *gem*-difluoro in *rac*-**34a** yielded a 5-fold increase in potency against Cat K (Table 5) as compared to the nonhalogenated inhibitor **24a**. The more potent enantiomer (−)-**34a** retained an acceptable selectivity profile against cathepsins L, B, and S and exhibited good potency (IC_{50} = 16 nM, n = 3) in our functional bone resorption assay that evaluates the degradation of the type I collagen matrix of bovine bone by isolated rabbit osteoclasts.[4b] Introduction of a *gem*-chloro in *rac*-**34c**[13] resulted in a 5-fold potency boost against cathepsin K; however, cathepsin S selectivity was diminished as a consequence of this modification. The presence of a single axial or equatorial fluorine on the cyclohexyl ring in *rac*-**38a** and *rac*-**38b**, respectively[14] (Scheme 9), had little effect on Cat K IC_{50}. Thus, it appears that both fluorine substituents act cooperatively in **34a** to produce a synergistic enhancement of inhibitor binding to S2 of the Cat K active site.

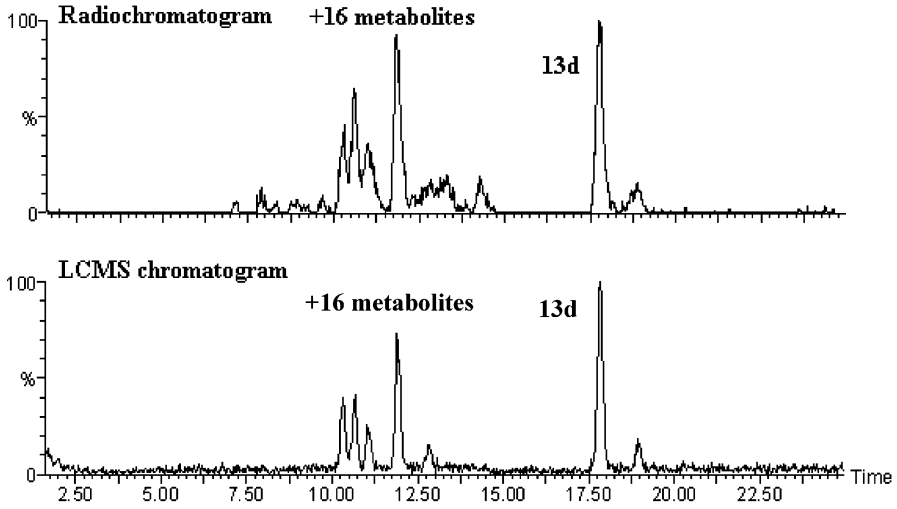


Figure 4. Radio-HPLC and LC−MS chromatograms of rat hepatocyte incubations of **13d**.

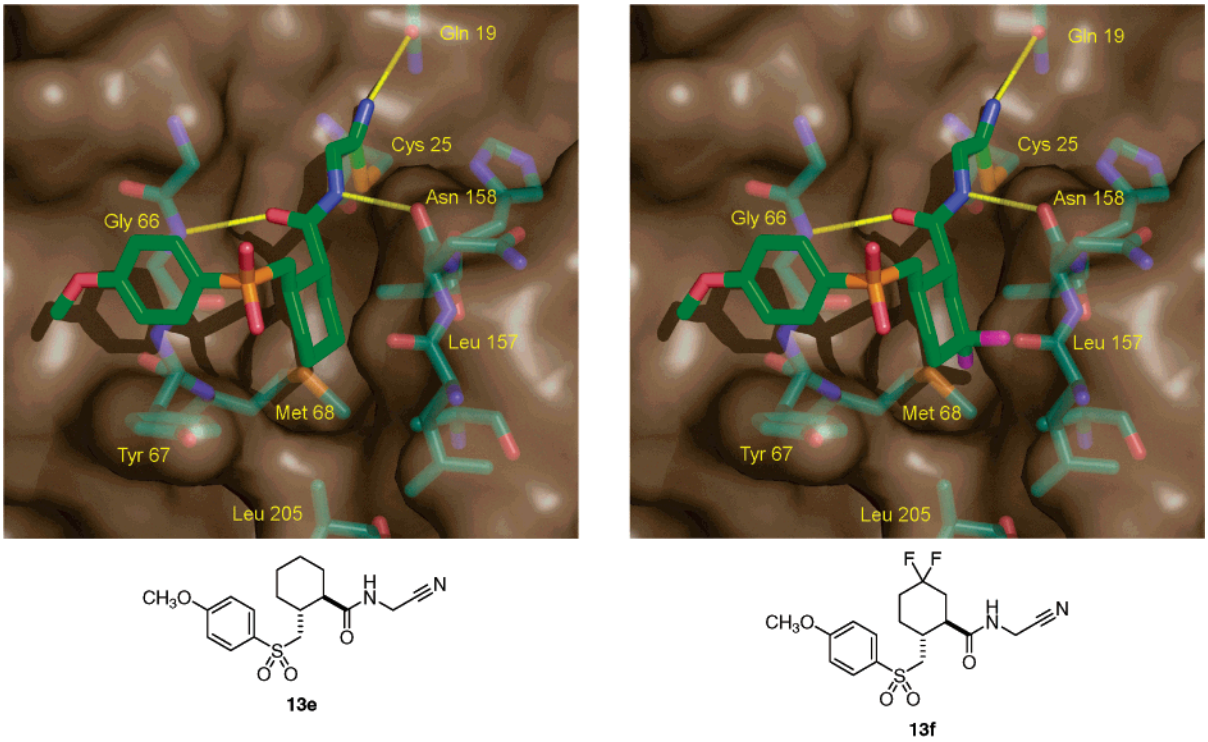
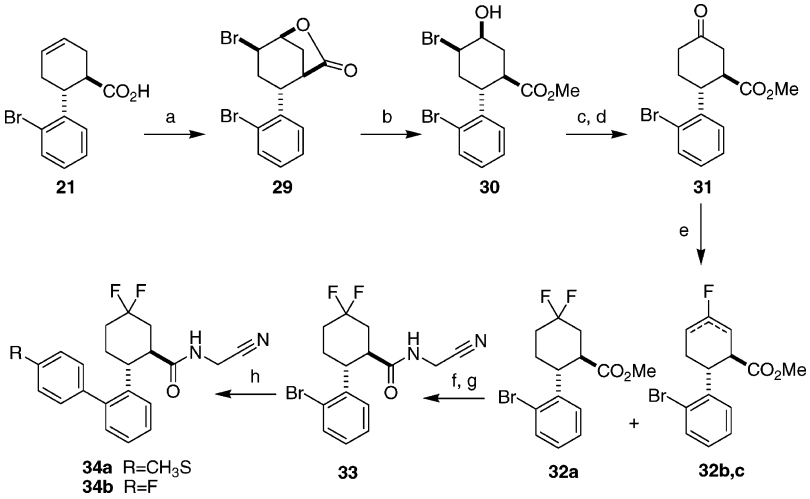


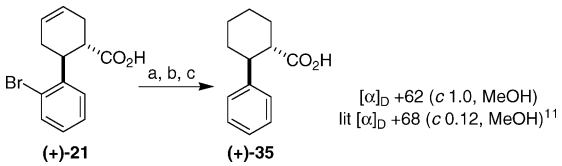
Figure 5. (a) X-ray structure of **13e** bound to cathepsin K. (b) Modeled structure of **13f** bound to cathepsin K.

Scheme 7[a]



[a] Conditions: (a) $(CH_3)_3SiBr$, Me_2SO, *i*-Pr_2NEt, $CHCl_3$, reflux; (b) NaOMe, MeOH, room temperature; (c) Jones oxidation; (d) Zn, KH_2PO_4, THF, H_2O, room temperature, 31% from **21**; (e) DAST, CH_2Cl_2, room temperature; (f) LiOH, H_2O, MeOH, THF, room temperature; (g) H_2NCH_2CN·HCl, PyBOP, Et_3N.

Scheme 8[a]

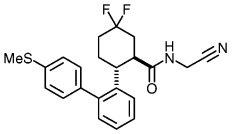
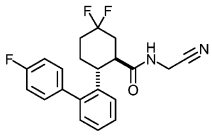
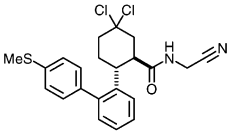
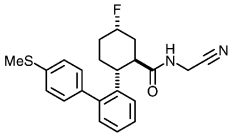
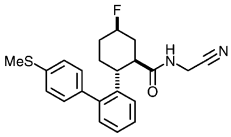


[a] Conditions: (a) CH_2N_2, Et_2O; (b) 1 atm H_2, 10% Pd/C, EtOAc, Et_3N; (c) LiOH, H_2O, THF, MeOH, 75% overall.

Pharmacokinetics and Metabolism II. Introduction of the *gem*-difluoro group onto the cyclohexyl ring also achieved the desired improvement in pharmacokinetics (Table 6). Acceptable terminal half-lives ($t_{1/2}$) and oral bioavailabilities (%*F*) were observed for (−)-**34a** in the three animal species shown with a particularly impressive PK profile being observed in dog (F = 55%, $t_{1/2}$ = 15 h). *gem*-Difluorination of the cyclohexyl ring likewise resulted in an increase in $t_{1/2}$ in rats from 45 min for **24b** to 4.5 h for *rac*-**34b**. A comparable enhancement of half-life in rats was also achieved with chlorine substituents in *rac*-**34c** ($t_{1/2}$ = 3.1 h). Introduction of a single fluorine at the 5-position in *rac*-**38a** improved the half-lives of this class of Cat K inhibitors from a few minutes to over an hour in rats. However, the terminal half-life observed in squirrel monkeys for *rac*-**38a** ($t_{1/2}$ = 0.8 h) was far shorter than that seen for (−)-**34a** ($t_{1/2}$ = 8.8 h).

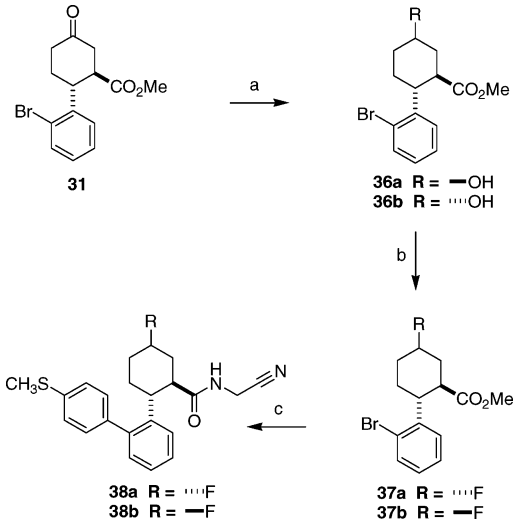
In contrast with the metabolic profile presented in Figure 4, incubation of *rac*-**34b** with rat hepatocytes led to the production of only one major M+16 metabolite. It was not possible to ascertain by MS-fragmentation analysis if oxygenation was occurring on the cyclohexyl or aromatic portion of the inhibitor.

Table 5. Potency and Selectivity of P2-Halogenated Cathepsin K Inhibitors

Compound	Structure	hrab Cat K[6] IC_{50} (nM)[a]	rabCat K IC_{50} (nM)[a]	Selectivity Ratios[a]		
				Cat L/K	Cat B/K	Cat S/K
rac-**34a**		0.46	0.50	880	>120000	1100
(–)-**34a**		0.28	0.32	780	>36000	940
(+)-**34a**		7.1	9.2	–	–	–
rac-**34b**		36	19	–	–	–
rac-**34c**		0.58	0.59	450	>17000	52
rac-**38a**		4.2	3.7	1600	>2400	1500
rac-**38b**		3.7	12	2000	>2700	180

[a] Each value represents an average of at least three independent determinations.

Scheme 9[a]



[a] Conditions: (a) $NaBH_4$, MeOH, room temperature; (b) DAST, CH_2Cl_2, −78 to −10 °C; (c) Scheme 7, steps f, g, and h.

Similar incubation of (−)-**34a** with rat and human hepatocytes revealed that oxidative metabolism was predominantly confined to the P3-thioether. This produced both the corresponding sulfoxide (**39a**) and the sulfone (**39b**) metabolites, which were determined to be 100-fold less potent than the parent compound. The structures of **39a** and **39b** were confirmed by LCMS analysis through comparison with synthetic standards.

Kinetic Characterization of (−)-34a. The reversibility of inhibition of humanized-rabbit cathepsin K by (−)-**34a** was demonstrated in experiments in which a 1:1 enzyme−inhibitor mixture (125 nM) was preincubated for 15 min, followed by a 500-fold dilution into substrate-containing buffer (0.2 μM citrate). After dilution, the cathepsin K enzyme activity was initially >95% inhibited, and slowly recovered with a first-order rate constant of 0.0081 s^{-1} ($t_{1/2}$ = 86 s). The final steady-state enzyme activity was ~80% that of control, demonstrating the reversibility of the formation of the (−)-**34a**−cathepsin K complex.

Table 6. Phamacokinetic Profiles of P2-Halogenated Cathepsin K Inhibitors

Compound	Species	%F	$T_{1/2}$ (h)	Cl (mL/min/kg)
rac-**34a**	Rat	53	3.5	15
(–)-**34a**	Rat	39	3.5	8.7
	Sq. Monkey	78	8.8	17
	Dog	55	15	3.6
rac-**34b**	Rat	26	4.5	37
rac-**34c**	Rat	75	3.1	51
rac-**38a**	Rat	88	1.5	25
	Sq. Monkey	28	0.8	21

Conclusion

A new class of nonpeptidic cathepsin K inhibitors that employ a nitrile-warhead on a β-substituted cyclohexanecarboxamide scaffold has been developed. SAR optimization of our initial lead (**8b**) culminated in the identification of (−)-**34a**, a compound that exhibited sub-nanomolar inhibition of cathepsin K, excellent selectivity against the closely related cathepsins

B, L, and S, and an acceptable pharmacokinetic profile in a number of animal species. Thus, the β-substituted cyclohexanecarboxamide moiety has been validated as a promising new scaffold for the development of orally bioavailable cathepsin K inhibitors as bone anti-resorptive agents.

Experimental Section

General. Zinc dust was activated by successive washing in a sintered glass filter funnel with dilute HCl solution, water, ethanol, and ether followed by drying under a stream of nitrogen and finally under high vacuum. *m*-Chloroperoxybenzoic acid (*m*-CPBA) was purified by washing a benzene solution of commercial material with two portions of pH 7.4 phosphate buffer followed by recrystallization from ether/hexanes. All other reagents were obtained commercially and used without further purification. Proton (^{1}H NMR) magnetic resonance spectra were recorded on a Bruker 500 MHz instrument. All spectra were recorded in d_6-acetone (unless otherwise indicated) using residual solvent as internal standard. Signal multiplicity was designated according to the following abbreviations: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, q = quartet, dt = doublet of triplets, td = triplet of doublets, dq = doublet of quartets, m = multiplet, br = broad. Elemental analyses were provided by Prevalere Life Sciences Inc., Whitesboro, NY. Rotations were measured on a Perkin-Elmer model 241 polarimeter. Reactions were carried out with continuous stirring under a positive pressure of nitrogen except where noted. Flash chromatography was carried out with silica gel 60, 230−400 mesh.

Enzyme Expression and Purification. See ref 4a.

Enzyme Activity Assays. See ref 15.

Pharmacokinetic and Bioavailability Experiments. Single compounds were dosed orally as suspensions in 1% methocel and intravenously via the jugular vein as solutions in PEG-200/H_2O (3:2). Dosing volumes used for oral administration were 10 mL/kg for rats and rabbits, 1 mL/kg for monkeys, and 5 mL/kg for dogs. Intravenous dosing volumes of 1 mL/kg were used for all species. Animals receiving the oral suspensions were fasted overnight prior to a.m. dosing. Plasma samples were collected at regular intervals and analyzed by LC−MS following a protein precipitation with 1.5 volumes of acetonitrile and centrifugation. All animal procedures were conducted in accordance with Institutional Animal Care and Use Committee guidelines.

Hepatocyte Incubations. For hepatocyte incubations, 1×10^6 cells diluted in 0.5 mL of Krebs-Henseleit buffer were first prepared at 37 °C for 20 min under 95%:5% O_2:CO_2 (BOC gases; Montreal, Canada) in a 48-well plate, and then 5 μL of 10 mM solution of compound dissolved in acetonitrile was added to each well to a final concentration of 50 μM. After 2 h of incubation at 37 °C under 95%:5% O_2:CO_2 atmosphere, one volume of acetonitrile was added in each well. A quenched incubation spiked with the parent compound and a blank were also prepared as controls. Once transferred, samples were centrifuged for 10 min at 14 000 rpm using an Eppendorf 5415C centrifuge (Hamburg, Germany), and the supernatant was used for LC/UV/MS analysis.

X-ray Structure Determination of 13e Bound to Cathepsin K. A mutant of rabbit cathepsin K was expressed and purified as described previously.[16] Compound **13e** was cocrystallized with the mutant cathepsin K at room temperature using the hanging drop vapor diffusion method. The reservoir consisted of 0.18 M magnesium formate, and the drop was formed by 2 μL of a solution of 10 mg/mL cathepsin K in 25 mM sodium acetate (pH 3.9) and by 2 μL of the reservoir solution. Crystals formed within 4 days, and diffraction data were collected on a Rigaku R-AXIS IV area detector, using X-rays produced by a Rigaku RU200 rotating anode generator. The data were reduced using the HKL package, and refinement was carried out by iterating between manual rebuilding using Quanta (MSI, Inc.) and automated refinement using CNX (MSI, Inc.). Data and refinement statistics for the final model are shown in Table S1 of the Supporting Information. The coordinates and observed structure factors have been deposited in the Protein Data Bank under accession code 2F7D.

Methyl 2-(Benzylthio)cyclohexanecarboxylate (7). A mixture of **5a** (520 mg, 2.35 mmol) and milled K_2CO_3 (990 mg, 7.20 mmol) was suspended in MeOH (10 mL). Benzyl mercaptan (0.50 mL, 4.2 mmol) was added, and the mixture was stirred for 6 days at room temperature before partitioning between ethyl acetate and 1 M NaOH. The organic phase was washed with 1 M NaOH and brine, then dried over Na_2SO_4 and concentrated. Purification by flash chromatography (5/95 to 12/88 ethyl acetate/hexanes) provided the title compound (syn:anti 13:1) as a faint-yellow oil 157 mg (25%). ^{1}H NMR: major isomer (syn) δ 7.35 (4H, m), 7.25 (1H, m), 3.77 (1H, d, J = 13 Hz), 3.73 (1H, d, J = 13 Hz), 3.60 (3H, s), 3.28 (1H, m), 2.73 (1H, td, J = 3.8, 11 Hz), 1.88 (1H, m), 1.70 (5H, m), 1.45 (1H, m), 1.30 (1H, m); discernible signals for the minor isomer (anti) δ 3.65 (3H, s), 2.41 (1H, dt, J = 3.8, 11 Hz). Alternatively, the title compound can be prepared by refluxing a mixture of **5b** (1.00 g, 7.14 mmol), benzyl mercaptan (1.07 g, 8.63 mmol), and K_2CO_3 (1.52 g, 11.0 mmol) in acetonitrile (4 mL) for 24 h. Substitution of water for 1 M NaOH in the workup procedure above and flash chromatography on silica eluting with 12/88 EtOAc/hexanes provides **7** as a colorless oil (1.62 g, 86%, syn:anti 13:1).

(1*R*/*S*,2*R*/*S*)-2-(Benzylthio)-*N*-(cyanomethyl)cyclohexanecarboxamide (8a), (1*R*/*S*,2*S*/*R*)-2-(Benzylthio)-*N*-(cyanomethyl)-cyclohexanecarboxamide (8b), and *N*-(Cyanomethyl)cyclohex-1-ene-1-carboxamide (8c). A solution of **7** (650 mg, 2.50 mmol) in a 1:1 mixture of MeOH and THF (4 mL) was treated with 2 M NaOH (4 mL, 8 mmol) followed by heating to reflux for 1 h (strong smell of benzyl mercaptan). The mixture was cooled, diluted with water, and extracted with ether. The aqueous layer was acidified with 1 M HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give 370 mg of a colorless oil that was combined with HATU (1.20 g, 3.20 mmol), aminoacetonitrile hydrochloride (0.70 g, 7.6 mmol), and Hunig's base (2.0 mL, 12 mmol) in DMF (3 mL) with stirring at room temperature overnight. The mixture was then added to 1 M HCl and extracted with ethyl acetate (2×). The organic phase was washed with saturated brine and $NaHCO_3$ aqueous solutions, dried over Na_2SO_4, and concentrated to afford a brown syrup that ^{1}H NMR analysis revealed to be composed of the title compounds in a ratio of 26:14:1 (**8a**:**8b**:**8c**). Purification by flash chromatography on silica gel eluting with 2/3 to 3/2 EtOAc/hexanes provided 134 mg of the syn-isomer (**8a**), 6 mg of the anti-isomer (**8b**), and 55 mg of the elimination product **8c** as colorless solids. R_f values in 1/1 EtOAc/hexanes: **8a** (0.42), **8b** (0.50), **8c** (0.33). ^{1}H NMR for **8a**: δ 7.58 (1H, br s), 7.39 (2H, m), 7.31 (2H, m), 7.25 (1H, m), 4.20 (2H, m), 3.77 (2H, m), 3.26 (1H, m), 2.67 (1H, td, J = 3.9, 9.7 Hz), 1.94 (1H, m), 2.70 (5H, m), 1.45 (1H, m), 1.30 (1H, m). For **8b**: δ 7.87 (1H, br s), 7.38 (2H, m), 7.29 (2H, m), 7.22 (1H, m), 4.26 (2H, d, J = 5.8 Hz), 3.84 (1H, d, J = 13 Hz), 3.79 (1H, d, J = 13 Hz), 2.82 (1H, dt, J = 3.9, 11 Hz), 2.32 (1H, dt, J = 3.9, 11 Hz), 2.00 (1H, m), 1.85 (1H, m), 1.72 (2H, m), 1.53 (1H, m), 1.30 (3H, m). For **8c**: δ 7.73 (1H, br s), 6.70 (1H, m), 4.25 (2H, d, J = 5.8 Hz), 2.27−2.24 (2H, m), 2.19−2.14 (2H, m), 1.70−1.64 (2H, m), 1.63−1.57 (2H, m).

(1*R*/*S*,2*R*/*S*)-2-{[(Cyanomethyl)amino]carbonyl}-cyclohexanecarboxylic Acid (10). A 0 °C suspension of anhydride **9** (1.00 g, 6.49 mmol), aminoacetonitrile hydrochloride (1.30 g, 14.0 mmol), and 4-(dimethylamino)pyridine (70 mg, 0.57 mmol) in THF (20 mL) was treated with triethylamine (2.0 mL, 14 mmol) and stirred at room temperature overnight (16 h). The mixture was then poured into 1 M HCl and extracted with EtOAc. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated to afford the title compound as a colorless solid (1.05 g, 78%). ^{1}H NMR: δ 10.60 (1H, br s), 7.71 (1H, br s), 4.32−4.00 (2H, m), 2.62 (1H, m), 2.47 (1H, m), 2.07 (1H, m), 1.88 (1H, m), 1.80−1.68 (2H, m), 1.43−1.20 (4H, m).

(1*R*/*S*,2*R*/*S*)-(2-{[(Cyanomethyl)amino]carbonyl}-cyclohexyl)-methyl-4-methylbenzenesulfonate (11). A solution composed of **10** (970 mg, 4.60 mmol) and *N*-methylmorpholine (0.51 mL, 4.6 mmol) in THF (10 mL) was cooled to −78 °C and treated with

isobutylchloroformate (0.60 mL, 4.6 mmol). The resulting colorless slurry was stirred at this temperature for 5 min and then at 0 °C for 30 min. The mixture was recooled to −78 °C, and $NaBH_4$ (450 mg, 12.0 mmol) was added in one portion followed by the dropwise addition of methanol (10 mL) with slow warming to room temperature over 1.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the mixture was poured into brine and extracted with ethyl acetate (3×). The combined organics were dried (Na_2SO_4) and concentrated, and the residue was suspended in toluene (15 mL) with stirring at room temperature overnight (16 h). Filtration afforded (1*R*/S,2*R*/*S*)-*N*-(cyanomethyl)-2-(hydroxymethyl)cyclohexanecarboxamide as a colorless solid (660 mg, 73% yield). ^{1}H NMR (d_4-methanol): δ 3.48 (1H, dd, *J* = 3.0, 9.4 Hz), 3.33 (2H, s), 3.32 (1H, overlapped dd), 2.09 (1H, br t), 1.93 (1H, m), 1.81 (1H, m), 1.78−1.72 (3H, overlapped m), 1.52 (1H, br q), 1.40−1.22 (2H, m), 1.15 (1H, br q). A solution of (1*R*/*S*,*2R*/*S*)-*N*-(cyanomethyl)-2-(hydroxymethyl)cyclohexanecarboxamide (372 mg, 1.90 mmol) and toluene-4-sulfonyl chloride (430 mg, 2.30 mmol) in acetonitrile (6 mL) was treated with pyridine (0.23 mL, 2.8 mmol) and stirred at room temperature until the solution cleared (3 h). The reaction vessel contents were then partitioned between water and ethyl acetate, and the layers were separated. The organic phase was dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography on silica gel eluting with 4/96 MeOH/$CHCl_3$ to afford the title compound as a pale-yellow foam (591 mg, 89%). ^{1}H NMR: δ 7.86 (1H, br s), 7.76 (2H, d, *J* = 8.3 Hz), 7.47 (2H, d, *J* = 8.3 Hz), 4.15 (1H, dd, *J* = 6.0, 17 Hz), 4.05 (1H, dd, *J* = 5.5, 17 Hz), 3.91 (1H, dd, *J* = 3.2, 9.6 Hz), 3.79 (1H, dd, *J* = 5.5, 9.6 Hz), 2.45 (3H, s), 2.16 (1H, dt, *J* = 3.8, 11 Hz), 1.92 (1H, m), 1.82 (1H, m), 1.75−1.67 (3H, m), 1.39 (1H, dq, *J* = 3.6, 13 Hz), 1.39−0.90 (3H, m).

General Procedure for the Preparation of 12a−z. A 0.35 M DMF solution of **11** was treated with the appropriate benzenethiol (1.1 equiv) and K_2CO_3 (4 equiv) with stirring at room temperature overnight (16 h). The mixture was then partitioned between ethyl acetate and water, and the layers were separated. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography on silica gel using the indicated solvent mixture afforded the desired thioether in high purity and generally in >90% yield.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-[(phenylthio)methyl]cyclohexanecarboxamide (12a). 2/3 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 7.83 (1H, br s), 7.36 (2H, d, *J* = 7.5 Hz), 7.30 (2H, t, *J* = 7.5 Hz), 7.17 (1H, t, *J* = 7.5 Hz), 4.30−4.22 (2H, m), 3.18 (1H, dd, *J* = 3.0, 13 Hz), 2.64 (1H, dd, *J* = 9.3, 13 Hz), 2.23−2.13 (2H, m), 1.95 (1H, m), 1.86 (1H, m), 1.79−1.72 (2H, m), 1.48 (1H, m), 1.30−1.22 (2H, m), 1.06 (1H, m). Anal. ($C_{16}H_{20}N_2OS$) C, calcd 66.63; found 65.85; H, calcd 6.99; found 6.93; N, calcd 9.71; found 9.30.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-[(4-fluorophenylthio)methyl]cyclohexanecarboxamide (12b). 2/3 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 7.81 (1H, br s), 7.39 (2H, dd, *J* = 5.2, 8.9 Hz), 7.07 (2H, t, *J* = 8.9 Hz), 4.25−4.20 (2H, m), 3.10 (1H, dd, *J* = 3.1, 13 Hz), 2.60 (1H, dd, *J* = 9.4, 13 Hz), 2.19−2.08 (2H, m), 1.89 (1H, m), 1.82 (1H, m), 1.76−1.68 (2H, m), 1.44 (1H, m), 1.30−1.17 (2H, m), 1.03 (1H, m). Anal. ($C_{16}H_{19}FN_2OS$) C, calcd 62.72; found 62.01; H, calcd 6.25; found 6.04; N, calcd 9.14; found 8.87.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-[(4-chlorophenylthio)methyl]cyclohexanecarboxamide (12c). 2/3 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 7.85 (1H, br s), 7.37 (2H, d, *J* = 8.7 Hz), 7.33 (2H, d, *J* = 8.7 Hz), 4.30−4.22 (2H, m), 3.17 (1H, dd, *J* = 3.0, 13 Hz), 2.65 (1H, dd, *J* = 9.6, 13 Hz), 2.20 (1H, m), 2.15 (1H, m), 1.94 (1H, m), 1.86 (1H, m), 1.80−1.70 (2H, m), 1.47 (1H, m), 1.32−1.19 (2H, m), 1.05 (1H, m). Anal. ($C_{16}H_{19}ClN_2OS$) C, calcd 59.52; found 58.60; H, calcd 5.93; found 5.61; N, calcd 8.68; found 8.26.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-[(4-bromophenylthio)methyl]cyclohexanecarboxamide (12d). 2/3 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 7.86 (1H, br s), 7.47 (2H, d, *J* = 8.6 Hz), 7.31 (2H, d, *J* = 8.6 Hz), 4.31−4.25 (2H, m), 3.17 (1H, dd, *J* = 3.1, 13 Hz), 2.64 (1H, dd, *J* = 9.5, 13 Hz), 2.23−2.13 (2H, m), 1.94 (1H, m), 1.86 (1H, m), 1.78−1.71 (2H, m), 1.46 (1H, m), 1.28−1.22 (2H, m), 1.05 (1H, m). Anal. ($C_{16}H_{19}BrN_2OS$) C, calcd 52.32; found 51.65; H, calcd 5.21; found 5.00; N, calcd 7.63; found 7.28.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-[(4-iodophenylthio)methyl]cyclohexanecarboxamide (12e). 2/3 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 7.87 (1H, br s), 7.64 (2H, d, *J* = 8.5 Hz), 7.18 (2H, d, *J* = 8.5 Hz), 4.31−4.21 (2H, m), 3.17 (1H, dd, *J* = 2.9, 13 Hz), 2.64 (1H, dd, *J* = 9.6, 13 Hz), 2.20 (1H, m), 2.14 (1H, m), 1.95 (1H, m), 1.86 (1H, m), 1.79−1.71 (2H, m), 1.47 (1H, m), 1.32−1.21 (2H, m), 1.05 (1H, m). Anal. ($C_{16}H_{19}IN_2OS$) C, calcd 46.38; found 46.50; H, calcd 4.62; found 4.42; N, calcd 6.76; found 6.60.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-[(4-(methylthio)phenylthio)methyl]cyclohexanecarboxamide (12f). 2/3 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 7.82 (1H, br s), 7.32 (2H, d, *J* = 8.6 Hz), 7.22 (2H, d, *J* = 8.6 Hz), 4.30−4.20 (2H, m), 3.15 (1H, dd, *J* = 3.1, 13 Hz), 2.62 (1H, dd, *J* = 9.5, 13 Hz), 2.49 (3H, s), 2.17 (1H, m), 1.98−1.90 (2H, m), 1.85 (1H, m), 1.80−1.72 (2H, m), 1.48 (1H, m), 1.33−1.22 (2H, m), 1.06 (1H, m). Anal. ($C_{17}H_{22}N_2OS_2$) C, calcd 61.04; found 60.25; H, calcd 6.63; found 6.23; N, calcd 8.37; found 7.90.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-[(4-methylphenylthio)methyl]cyclohexanecarboxamide (12g). 2/3 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 7.80 (1H, br s), 7.26 (2H, d, *J* = 8.4 Hz), 7.12 (2H, d, *J* = 8.4 Hz), 4.32−4.19 (2H, m), 3.13 (1H, dd, *J* = 3.2, 13 Hz), 2.61 (1H, dd, *J* = 9.4, 13 Hz), 2.30 (3H, s), 2.23−2.15 (2H, m), 1.94 (1H, m), 1.84 (1H, m), 1.80−1.71 (2H, m), 1.47 (1H, m), 1.32−1.20 (2H, m), 1.06 (1H, m). Anal. ($C_{17}H_{22}N_2OS$) C, calcd 67.51; found 66.67; H, calcd 7.33; found 6.69; N, calcd 9.26; found 8.88.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-[(4-hydroxyphenylthio)methyl]cyclohexanecarboxamide (12h). 55/45 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 8.41 (1H, br s), 7.75 (1H, m), 7.26 (2H, d, *J* = 8.6 Hz), 6.81 (2H, d, *J* = 8.6 Hz), 4.28−4.17 (2H, m), 3.03 (1H, dd, *J* = 3.1, 13 Hz), 2.56 (1H, dd, *J* = 9.1, 13 Hz), 2.20−2.12 (2H, m), 1.90−1.79 (2H, m), 1.77−1.71 (2H, m), 1.46 (1H, m), 1.29−1.21 (2H, m), 1.04 (1H, m). Anal. ($C_{16}H_{20}N_2O_2S$) C, calcd 63.13; found 62.18; H, calcd 6.62; found 6.33; N, calcd 9.20; found 8.83.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-[(4-methoxyphenylthio)methyl]cyclohexanecarboxamide (12i). 2/3 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 7.76 (1H, br s), 7.34 (2H, d, *J* = 8.8 Hz), 6.89 (2H, d, *J* = 8.8 Hz), 4.27−4.18 (2H, m), 3.80 (3H, s), 3.07 (1H, dd, *J* = 3.1, 13 Hz), 2.58 (1H, dd, *J* = 9.2, 13 Hz), 2.19−2.12 (2H, m), 1.92−1.80 (2H, m), 1.78−1.71 (2H, m), 1.46 (1H, m), 1.32−1.19 (2H, m), 1.04 (1H, m). Anal. ($C_{17}H_{22}N_2O_2S$) C, calcd 64.12; found 63.83; H, calcd 6.96; found 6.70; N, calcd 8.80; found 8.63.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-[(4-aminophenylthio)methyl]cyclohexanecarboxamide (12j). 5/95 MeOH/CH_2Cl_2, thick colorless syrup. ^{1}H NMR: δ 7.68 (1H, br s), 7.15 (2H, d, *J* = 8.5 Hz), 6.63 (2H, d, *J* = 8.5 Hz), 4.74 (2H, br s), 4.24−4.16 (2H, m), 2.96 (1H, dd, *J* = 3.2, 13 Hz), 2.51 (1H, dd, *J* = 8.8, 13 Hz), 2.20−2.12 (2H, m), 1.89−1.79 (2H, m), 1.74 (2H, m), 1.46 (1H, m), 1.29−1.22 (2H, m), 1.04 (1H, m). Anal. ($C_{16}H_{21}N_3OS$) C, calcd 63.33; found 59.07; H, calcd 6.98; found 6.86; N, calcd 13.85; found 12.89.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-{[(3-fluorophenyl)thio]methyl}cyclohexanecarboxamide (12k). 2/3 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 7.87 (1H, br), 7.30 (1H, m), 7.14−7.10 (2H, m), 6.88 (1H, dt, *J* = 2.3, 8.5 Hz), 4.34−4.19 (2H, m), 3.17 (1H, dd, *J* = 3.0, 13 Hz), 2.63 (1H, dd, *J* = 9.5, 13 Hz), 2.18 (1H, dt, *J* = 3.6, 12 Hz), 2.13 (1H, m), 1.97 (1H, m), 1.83 (1H, m), 1.78−1.69 (2H, m), 1.46 (1H, m), 1.26−1.20 (2H, m), 1.03 (1H, m). Anal. ($C_{16}H_{19}FN_2OS$) C, calcd 62.72; found 62.70; H, calcd 6.25; found 6.43; N, calcd 9.14; found 9.39.

(1*R*/*S*,2*R*/*S*)-2-{[(3-Chlorophenyl)thio]methyl}-*N*-(cyanomethyl)cyclohexanecarboxamide (12l). 1/1 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 7.86 (1H, s), 7.37 (1H, d, *J* = 1.0 Hz), 7.33−7.31 (2H, m), 7.20−7.18 (1H, m), 4.31−4.23 (2H, m), 3.20 (1H,

dd, $J = 3.1$, 13 Hz), 2.68 (1H, dd, $J = 9.5$, 13 Hz), 2.21 (1H, m), 2.15 (1H, m), 2.08 (1H, overlapped m), 1.97 (1H, m), 1.87 (1H, m), 1.80−1.72 (2H, m), 1.48 (1H, m), 1.32−1.22 (2H, m), 1.07 (1H, m). Anal. ($C_{16}H_{19}ClN_2OS$) C, calcd 59.52; found 59.52; H, calcd 5.93; found 5.88; N, calcd 8.68; found 8.53.

(1*R*/*S*,2*R*/*S*)-2-{[(3-Bromophenyl)thio]methyl}-*N*-(cyanomethyl)cyclohexanecarboxamide (12m). 1/1 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 7.85 (1H, br m), 7.47 (1H, m), 7.32 (2H, overlapping t), 7.22 (1H, t, $J = 7.9$ Hz), 4.32−4.19 (2H, m), 3.16 (1H, dd, $J = 3.1$, 13 Hz), 2.64 (1H, dd, $J = 9.5$, 13 Hz), 2.18 (1H, dt, $J = 3.6$, 11 Hz), 2.12 (1H, m), 1.94 (1H, m), 1.83 (1H, m), 1.75−1.70 (2H, m), 1.45 (1H, m), 1.32−1.18 (2H, m), 1.04 (1H, m). Anal. ($C_{16}H_{19}BrN_2OS$) C, calcd 52.32; found 52.68; H, calcd 5.21; found 5.19; N, calcd 7.63; found 7.68.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-{[(3-hydroxyphenyl)thio]methyl}cyclohexanecarboxamide (12n). 1/1 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 8.33 (1H, s), 7.80 (1H, br m), 7.09 (1H, t, $J = 7.9$ Hz), 6.80 (1H, d, $J = 7.8$ Hz), 6.78 (1H, m), 6.61 (1H, dd, $J = 1.9$, 7.8 Hz), 4.20−4.17 (2H, m), 3.10 (1H, dd, $J = 3.2$, 13 Hz), 2.60 (1H, dd, $J = 9.3$, 13 Hz), 2.17 (1H, dt, $J = 3.7$, 12 Hz), 2.13 (1H, m), 1.93 (1H, m), 1.82 (1H, m), 1.78−1.68 (2H, m), 1.46 (1H, m), 1.32−1.20 (2H, m), 1.02 (1H, m). Anal. ($C_{16}H_{20}N_2O_2S$) C, calcd 63.13; found 62.79; H, calcd 6.62; found 6.55; N, calcd 9.20; found 8.95.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-{[(3-methoxyphenyl)thio]methyl}cyclohexanecarboxamide (12o). 1/1 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 7.85 (1H, br s), 7.19 (1H, t, $J = 7.9$ Hz), 6.91 (2H, m), 6.72 (1H, dd, $J = 2.4$, 8.2 Hz), 4.29−4.22 (2H, m), 3.85 (3H, s), 3.20 (1H, dd, $J = 3.0$, 13 Hz), 2.60 (1H, dd, $J = 9.7$, 13 Hz), 2.22−2.16 (2H, m), 1.96 (1H, m), 1.86 (1H, m), 1.76 (2H, m), 1.48 (1H, m), 1.26 (2H, m), 1.05 (1H, m). Anal. ($C_{17}H_{22}N_2O_2S$) C, calcd 64.12; found 63.40; H, calcd 6.96; found 6.90; N, calcd 8.80; found 8.50.

(1*R*/*S*,2*R*/*S*)-2-{[(3-Aminophenyl)thio]methyl}-*N*-(cyanomethyl)cyclohexanecarboxamide (12p). 5/95 MeOH/CH_2Cl_2, colorless solid. ^{1}H NMR: δ 7.79 (1H, br s), 6.97 (1H, t, $J = 7.8$ Hz), 6.68 (1H, s), 6.57 (1H, d, $J = 7.6$ Hz), 6.47 (1H, dd, $J = 2.1$, 8.0 Hz), 4.61 (2H, br s), 4.29−4.21 (2H, m), 3.11 (1H, dd, $J = 3.0$, 13 Hz), 2.59 (1H, dd, $J = 9.2$, 13 Hz), 2.19 (1H, m), 2.14 (1 H, m), 1.95 (1H, m), 1.84 (1H, m), 1.76−1.74 (2H, m), 1.48 (1H, m), 1.31−1.24 (2H, m), 1.04 (1H, m). Anal. ($C_{16}H_{21}N_3OS$) C, calcd 63.33; found 62.87; H, calcd 6.98; found 6.98; N, calcd 13.85; found 13.60.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-{[(3,5-dichlorophenyl)thio]methyl}cyclohexanecarboxamide (12q). 2/3 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 7.89 (1H, br s), 7.34 (2H, d, $J = 1.8$ Hz), 7.24 (1H, t, $J = 1.8$ Hz), 4.31−4.24 (2H, m), 3.21 (1H, dd, $J = 3.1$, 13 Hz), 2.70 (1H, t, $J = 6.6$ Hz), 2.22 (1H, m), 2.15 (1H, m), 1.99 (1H, m), 1.89 (1H, m), 1.80−1.74 (2H, m), 1.48 (1H, m), 1.30−1.26 (2H, m), 1.09 (1H, m). Anal. ($C_{16}H_{18}Cl_2N_2OS$) C, calcd 53.78; found 53.38; H, calcd 5.08; found 4.92; N, calcd 7.84; found 7.66.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-{[(2,4-dichlorophenyl)thio]methyl}cyclohexanecarboxamide (12r). 2/3 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 7.92 (1H, br s), 7.53 (1H, d, $J = 8.6$ Hz), 7.48 (1H, d, $J = 2.2$ Hz), 7.36 (1H, dd, $J = 2.2$, 8.5 Hz), 4.32−4.24 (2H, m), 3.19 (1H, dd, $J = 2.9$, 13 Hz), 2.69 (1H, dd, $J = 9.8$, 13 Hz), 2.24 (1H, m), 2.18 (1H, m), 1.98 (1H, m), 1.89 (1H, m), 1.82−1.72 (2H, m), 1.49 (1H, m), 1.32−1.28 (2H, m), 1.10 (1H, m). Anal. ($C_{16}H_{18}Cl_2N_2OS$) C, calcd 53.78; found 53.37; H, calcd 5.08; found 4.85; N, calcd 7.84; found 7.70.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-{[(2,5-dichlorophenyl)thio]methyl}cyclohexanecarboxamide (12s). 2/3 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 7.92 (1H, br s), 7.52 (1H, d, $J = 2.3$ Hz), 7.41 (1H, d, $J = 8.5$ Hz), 7.19 (1H, dd, $J = 2.4$, 8.4 Hz), 4.34−4.24 (2H, m), 3.20 (1H, dd, $J = 3.0$, 13 Hz), 2.73 (1H, dd, $J = 9.7$, 13 Hz), 2.25 (1H, m), 2.18 (1H, m), 2.05 (1H, overlapped m), 1.92 (1H, m), 1.82−1.75 (2H, m), 1.51 (1H, m), 1.32−1.28 (2H, m), 1.13 (1H, m). Anal. ($C_{16}H_{18}Cl_2N_2OS$) C, calcd 53.78; found 53.45; H, calcd 5.08; found 4.87; N, calcd 7.84; found 7.67.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-{[(2,4,5-trichlorophenyl)thio]methyl}cyclohexanecarboxamide (12t). 2/3 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 7.93 (1H, br s), 7.70 (1H, s), 7.65 (1H, s), 4.33−4.25 (2H, m), 3.21 (1H, dd, $J = 2.9$, 13 Hz), 2.74 (1H, dd, $J = 9.8$, 13 Hz), 2.25 (1H, m), 2.18 (1H, m), 2.02 (1H, overlapped m), 1.92 (1H, m), 1.82−1.75 (2H, m), 1.48 (1H, m), 1.34−1.27 (2H, m), 1.12 (1H, m). Anal. ($C_{16}H_{17}Cl_3N_2OS$) C, calcd 49.06; found 48.62; H, calcd 4.37; found 4.29; N, calcd 7.15; found 7.03.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-[(1*H*-imidazol-2-ylthio)methyl]cyclohexanecarboxamide (12u). 95/5 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 11.4 (1H, br), 8.63 (1H, br s), 7.12 (2H, br s), 4.26 (2H, s), 3.26 (1H, dd, $J = 2.9$, 14 Hz), 2.72 (1H, dd, $J = 8.9$, 14 Hz), 2.22 (1H, m), 2.10 (1H, overlapped m), 2.01−1.93 (2H, m), 1.79−1.73 (2H, m), 1.45 (1H, m), 1.33−1.25 (2H, m), 1.13−1.05 (1H, m). Anal. ($C_{13}H_{18}N_4OS$) C, calcd 56.09; found 55.36; H, calcd 6.52; found 6.48; N, calcd 20.13; found 19.46.

(1*R*/*S*,2*R*/*S*)-2-[(1,3-Benzothiazol-2-ylthio)methyl]-*N*-(cyanomethyl)cyclohexanecarboxamide (12v). 2/3 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 7.96 (1H, d, $J = 8.0$ Hz), 7.95 (1H, overlapped br s), 7.87 (1H, d, $J = 8.0$ Hz), 7.48 (1H, t, $J = 7.5$ Hz), 7.37 (1H, t, $J = 7.5$ Hz), 4.37−4.21 (2H, m), 3.58 (1H, dd, $J = 3.3$, 13 Hz), 3.30 (1H, dd, $J = 8.2$, 13 Hz), 2.29 (1H, m), 2.16 (1H, m), 2.10 (1H, overlapped m), 1.91 (1H, m), 1.82−1.71 (2H, m), 1.54 (1H, m), 1.39−1.27 (2H, m), 1.19 (1H, m). Anal. ($C_{17}H_{19}N_3OS_2$) C, calcd 59.10; found 58.22; H, calcd 5.54; found 5.36; N, calcd 12.16; found 11.54.

(1*R*/*S*,2*R*/*S*)-2-[(1,3-Benzoxazol-2-ylthio)methyl]-*N*-(cyanomethyl)cyclohexanecarboxamide (12w). 2/3 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 7.96 (1H, br s), 7.62 (1H, d, $J = 6.9$ Hz), 7.56 (1H, d, $J = 7.1$ Hz), 7.33 (2H, m), 4.35−4.21 (2H, m), 3.54 (1H, d, $J = 13$ Hz), 3.26 (1H, dd, $J = 8.0$, 13 Hz), 2.28 (1H, m), 2.16 (1H, m), 2.10 (1H, overlapped m), 1.91 (1H, m), 1.85−1.70 (2H, m), 1.52 (1H, m), 1.35−1.27 (2H, m), 1.19 (1H, m). Anal. ($C_{17}H_{19}N_3O_2S$) C, calcd 61.98; found 59.99; H, calcd 5.81; found 5.74; N, calcd 12.76; found 11.97.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-[(pyrimidin-2-ylthio)methyl]cyclohexanecarboxamide (12x). 95/5 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 8.59 (2H, d, $J = 4.8$ Hz), 7.84 (1H, br s), 7.15 (1H, t, $J = 4.8$ Hz), 4.28−4.22 (2H, m), 3.39 (1H, dd, $J = 3.1$, 13 Hz), 3.04 (1H, dd, $J = 8.1$, 13 Hz), 2.22 (1H, m), 2.08 (1H, overlapped m), 1.98 (1H, m), 1.87 (1H, m), 1.80−1.71 (2H, m), 1.51 (1H, m), 1.32−1.25 (2H, m), 1.15 (1H, m). Anal. ($C_{14}H_{18}N_4OS$) C, calcd 57.91; found 57.29; H, calcd 6.25; found 5.99; N, calcd 19.29; found 18.76.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-[(1,3-thiazol-2-ylthio)methyl]cyclohexanecarboxamide (12y). 3/2 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 7.86 (1H, br s), 7.66 (1H, d, $J = 3.4$ Hz), 7.47 (1H, d, $J = 3.4$ Hz), 4.28−4.16 (2H, m), 3.39 (1H, dd, $J = 3.2$, 13 Hz), 3.07 (1H, dd, $J = 8.2$, 13 Hz), 2.20 (1H, m), 2.09−1.98 (2H, overlapped m), 1.86 (1H, m), 1.78−1.69 (2H, m), 1.48 (1H, m), 1.30−1.22 (2H, m), 1.11 (1H, m). Anal. ($C_{13}H_{17}N_3OS_2$) C, calcd 52.85; found 52.75; H, calcd 5.80; found 5.59; N, calcd 14.22; found 13.95.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-{[(5-pyridin-4-yl-1,3,4-oxadiazol-2-yl)thio]methyl}cyclohexanecarboxamide (12z). 95/5 EtOAc/hexanes, colorless solid. ^{1}H NMR: δ 8.84 (2H, d, $J = 4.5$ Hz), 8.00 (2H, dd, $J = 4.4$ Hz), 7.92 (1H, br s), 4.31−4.23 (2H, m), 3.54 (1H, dd, $J = 3.2$, 13 Hz), 3.17 (1H, dd, $J = 8.4$, 13 Hz), 2.32−2.24 (1H, m), 2.18−2.06 (2H, overlapped m), 1.92 (1H, m), 1.83−1.75 (2H, m), 1.52 (1H, m), 1.34−1.28 (2H, m), 1.19 (1H, m). Anal. ($C_{17}H_{19}N_5O_2S$) C, calcd 57.12; found 56.48; H, calcd 5.36; found 5.00; N, calcd 19.59; found 18.92.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-{[(4-fluorophenyl)sulfonyl]methyl}cyclohexanecarboxamide (13a). Compound **12b** (105 mg, 0.344 mmol), Oxone (595 mg, 0.970 mmol), and $NaHCO_3$ (595 mg, 7.1 mmol) were stirred together in a mixture of MeOH (2 mL), THF (2 mL), and H_2O (2 mL) at room temperature until completion of the reaction as judged by TLC (7 h). The mixture was then poured into water and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated to afford the title compound in high purity as a colorless solid (110 mg, 95%). ^{1}H NMR: δ 7.95 (2H, m), 7.75 (1H, br s), 7.40 (2H, m), 4.14 (2H, d,

J = 5.8 Hz), 3.14 (1H, dd, J = 2.4, 14 Hz), 3.05 (1H, dd, J = 9.4, 14 Hz), 2.31 (1H, m), 2.20 (1H, dt, J = 3.6, 11 Hz), 2.10 (1H, m), 1.81 (1H, m), 1.76−1.64 (2H, m), 1.42 (1H, m), 1.32−1.15 (3H, m). Anal. ($C_{16}H_{19}FN_2O_3S$) C, calcd 55.71; found 55.50; H, calcd 6.05; found 5.81; N, calcd 7.64; found 7.35.

(*1R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-{[(4-(methylthio)-phenylsulfonyl]methyl}cyclohexanecarboxamide (13b). A mixture of **13a** (22 mg, 64 μmol) and sodium thiomethoxide (50 mg, 700 μmol) was stirred together in DMF (1.5 mL) at room temperature overnight (16 h). The reaction vessel contents were then partitioned between water and EtOAc, and the layers were separated. The organic phase was washed with brine and dried (Na_2SO_4). Concentration in vacuo and flash chromatography of the residue on silica gel eluting with 15/85 acetone/benzene gave the title compound as a colorless solid (21 mg, 93%). ^{1}H NMR: δ 7.75 (2H, d, J = 8.6 Hz), 7.74 (1H, br s), 7.45 (2H, d, J = 8.6 Hz), 4.15 (2H, d, J = 5.8 Hz), 3.12 (1H, dd, J = 2.4, 14 Hz), 3.01 (1H, dd, J = 9.4, 14 Hz), 2.58 (3H, s), 2.31 (1H, m), 2.20 (1H, dt, J = 3.9, 11 Hz), 2.12 (1H, overlapped m), 1.82 (1H, m), 1.73−1.66 (2H, m), 1.43 (1H, m), 1.29−1.18 (3H, m). Anal. ($C_{17}H_{22}N_2O_3S_2$) C, calcd 55.71; found 55.50; H, calcd 6.05; found 5.81; N, calcd 7.64; found 7.35.

Synthesis of Radiolabeled Compound 13d. A 4 M aqueous solution of sodium nitrite (7.0 mL) was added to a slurry of 2-bromo-4-trifluoromethoxyaniline in 6 M HCl (10 mL) at 0 °C. This heterogeneous mixture was added dropwise to a 70 °C solution of potassium xanthate (5.0 g, 31 mmol) in water (70 mL) with stirring at this temperature for 45 min. The solution was then cooled to room temperature and extracted with two portions of ether. The extracts were dried (Na_2SO_4) and concentrated, the residue was taken up in a mixture of ethanol (40 mL) and 2 M KOH (40 mL), and the solution was heated to 85 °C for 2 h, before being cooled to room temperature and extracted with ether (3×, discard). The aqueous phase was acidified to pH 2−3 with 6 M HCl and extracted with ether (3×). The second set of ether extracts were combined, washed with water and brine, and dried (Na_2SO_4). Concentration in vacuo and flash chromatography of the residue on silica gel eluting with 2/98 ethyl acetate/hexanes yielded 2-bromo-4-trifluoromethoxythiophenol as a colorless oil (2.19 g, 31%). A mixture of this thiophenol (60 mg, 220 μmol), **11** (51 mg, 150 μmol), and K_2CO_3 (100 mg, 730 μmol) in DMF (0.40 mL) was stirred together at room temperature for 22 h. The reaction vessel contents were then poured into water and extracted with ethyl acetate (3×). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated, and the residue was flashed on silica gel eluting with 1/5 acetone/benzene to give 2-({[2-bromo-4-(trifluoromethoxy)-phenyl]thio}methyl)-*N*-(cyanomethyl)cyclohexanecarboxamide (**27**) as a colorless solid (59 mg, 90%). Compound **27** (56 mg, 120 μmol) was dissolved in a mixture of methanol, ethyl acetate, and water (1 mL each) and treated with $NaHCO_3$ (300 mg, 3.60 mmol) and Oxone (300 mg, 490 mol) with heating at 40 °C for 1 h. Water was added to dissolve the salts, and the mixture was extracted with ethyl acetate (2×). The combined organics were washed with brine, dried (Na_2SO_4), and concentrated to afford 2-({[2-bromo-4-(trifluoromethoxy)phenyl]sulfonyl}methyl)-*N*-(cyanomethyl)cyclohexanecarboxamide (**28**) as a colorless solid (60 mg, 99%). Compound **28** (3.6 mg, 7.5 μmol) was dissolved in THF (0.60 mL) containing Et_3N (50 μL) and stirred with 10% Pd on charcoal (4 mg) under an atmosphere of tritium gas (P = 598 mmHg) overnight. The mixture was then filtered (Celite) and the filtrate was concentrated and the residue was purified by reverse phase HPLC (C_{18} radial pack, 65/35 MeOH/10 mM NH_4OAc aqueous buffer, 17 mL/min flow rate, λ 220 nM) to afford **13d** (1.2 mg, specific activity 12 Ci/mmol).

(*1R*/*S*,2*S*/*R*)-2-{(*Z*)-2-[4-(Methylthio)phenyl]vinyl}-cyclohexanecarboxylate (16). A mixture of *p*-(methylthio)benzyl bromide (2.24 g, 13.1 mmol) and PPh_3 (3.43 g, 13.1 mmol) was heated at 90 °C for 15 h. The resulting slurry was then cooled to room temperature and treated with potassium *tert*-butoxide (11.7 mL, 1.0 M in THF) with stirring for 30 min prior to transfer via cannula into a 0 °C solution of ethyl (1*R*/*S*,2*R*/*S*)-2-formylcyclohexanecarboxylate (**14**)[7] (1.82 g, 10.0 mmol) in THF (10 mL). The reaction vessel contents were warmed to room temperature and then slowly to 50 °C for 1 h. Water was added at room temperature, and the mixture was extracted with ether (2×). The combined organics were washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography of the residue on silica gel eluting with 1/9 EtOAc/hexanes gave the title compound as a colorless, thick oil (1.88 g, 62%, *Z*/*E* 5.7:1). ^{1}H NMR: δ 7.29 (2H, d, J = 8.3 Hz), 7.19 (2H, d, J = 8.3 Hz), 6.33 (1H, d, J = 16 Hz), 6.08 (1H, dd, J = 8.2, 16 Hz), 4.05−3.95 (2H, m), 2.46 (3H, s), 2.32 (1H, m), 2.20 (1H, m), 1.90−1.68 (4H, m), 1.48 (1H, m), 1.40−1.20 (3H, m), 1.09 (3H, t, J = 7.1 Hz); discernible signals for *E*-isomer, δ 7.25 (2H, d, J = 8.6 Hz), 7.22 (2H, d, J = 8.6 Hz), 5.40 (1H, t, J = 10 Hz), 4.00−3.90 (2H, m).

(*1R*/*S*,2*S*/*R*)-2-{(*Z*)-2-[4-(Methylthio)phenyl]vinyl}-cyclohexanecarboxylic Acid (17). A 2 M aqueous solution of lithium hydroxide (9 mL) was added to a solution of **16** (280 mg, 0.921 mmol) in DME (15 mL) and methanol (2 mL) with rapid stirring at 60 °C for 5 h. The reaction mixture was then cooled to room temperature, diluted with water, and extracted with ether prior to acidification to pH 2 with 2 M HCl and extraction with ethyl acetate (2×). The combined ethyl acetate extracts were washed with brine, dried (Na_2SO_4), and concentrated to afford the title compound as a faint-yellow foam (180 mg, 71%, *Z*/*E* 5.2:1). ^{1}H NMR: δ 10.50 (1H, br s), 7.29 (2H, d, J = 8.3 Hz), 7.18 (2H, d, J = 8.3 Hz), 6.37 (1H, d, J = 16 Hz), 6.14 (1H, dd, J = 8.1, 16 Hz), 2.46 (3H, s), 2.38 (1H, m), 2.25 (1H, m), 1.95 (1H, m), 1.87−1.68 (3H, m), 1.50 (1H, m), 1.45−1.20 (3H, m); discernible signals for *E*-isomer, δ 6.30 (1H, d, J = 12 Hz), 5.45 (1H, t, J = 11 Hz), 2.48 (3H, s).

(*1R*/*S*,2*S*/*R*)-*N*-(Cyanomethyl)-2-{(*Z*)-2-[4-(methylthio)phenyl]-vinyl}cyclohexanecarboxamide (18). A mixture of **17** (180 mg, 0.655 mmol), benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP, 375 mg, 0.721 mmol), and aminoacetonitrile hydrochloride (134 mg, 1.44 mmol) in DMF (5.0 mL) was cooled to 0 °C and treated with triethylamine (0.33 mL, 2.3 mmol). The resulting slurry was stirred at room temperature for 2.5 h and then poured into saturated $NaHCO_3$ aqueous solution and extracted with ether (2×). The combined extracts were washed with brine and dried (Na_2SO_4). Concentration in vacuo and chromatography of the residue on silica eluting with 2/3 EtOAc/hexanes yielded the title compound as a colorless foam (177 mg, 86%, *Z*/*E* 3.4:1). ^{1}H NMR: δ 7.31 (2H, d, J = 8.3 Hz), 7.30 (1H, overlapped m), 7.19 (2H, d, J = 8.3 Hz), 6.36 (1H, d, J = 16 Hz), 6.12 (1H, dd, J = 7.8, 16 Hz), 4.24−4.05 (2H, m), 2.48 (3H, s), 2.42 (1H, m), 2.18 (1H, m), 1.90−1.65 (4H, m), 1.60 (1H, m), 1.45−1.15 (3H, m); discernible signals for *E*-isomer, δ 7.34 (2H, d, J = 8.2 Hz), 7.23 (2H, d, J = 8.2 Hz), 5.42 (1H, t, J = 11 Hz), 4.12−4.02 (2H, m), 2.51 (3H, s). Anal. ($C_{18}H_{22}N_2OS$) C, calcd 68.32; found 68.35; H, calcd 7.64; found 7.57; N, calcd 8.85; found 8.72.

(*1R*/*S*,2*S*/*R*)-*N*-(Cyanomethyl)-2-{2-[4-(methylthio)phenyl]-ethyl}cyclohexanecarboxamide (19). A solution of **17** (410 mg, 0.830 mmol) in a mixture of equal portions of methanol, ethyl acetate, and acetic acid was stirred under 40 PSI of hydrogen in the presence of 10% Pd on charcoal (400 mg) until the reaction was judged complete by TLC (6 h). The reaction flask contents were filtered through Celite, and the filtrate was concentrated. Flash chromatography of the residue on silica gel eluting with 1/4 EtOAc/hexanes containing 0.5% acetic acid gave 220 mg (59%) of material that was coupled to aminoacetonitrile as for **18** to afford the title compound as a colorless foam (217 mg, 87%). ^{1}H NMR: δ 7.74 (1H, br s), 7.20−7.07 (4H, m), 4.20 (2H, m), 2.56 (1H, m), 2.44 (3H, s), 2.44 (1H, overlapped m), 2.05−1.92 (3H, m), 1.85−1.59 (4H, m), 1.45 (1H, m), 1.38−1.16 (3H, m), 1.00 (1H, m). Anal. ($C_{18}H_{24}N_2OS$) C, calcd 68.75; found 67.92; H, calcd 7.05; found 6.83; N, calcd 8.91; found 8.64.

(1*R*/*S*,6*R*/*S*)-6-(2-Bromophenyl)cyclohex-3-ene-1-carboxylic Acid (21). A mixture of 2-bromocinnamic acid (20) (90 g, 400 mmol), toluene (240 mL), 1,4-hydroquinone (0.50 g), and 1,4-butadiene (150 mL) was heated together in a stainless steel bomb at 200 °C

for 24 h. After being cooled to room temperature, the bomb was cooled in an ice/water bath and the solid that crystallized from the reaction mixture was collected by suction filtration, washed with cold toluene (3×), and dried in air, then in vacuo, to afford the title compound as a colorless solid (92 g, 82% yield). ^{1}H NMR: δ 10.58 (1H, br s), 7.55 (1H, d, J = 8.6 Hz), 7.41 (1H, d, J = 7.8 Hz), 7.33 (1H, t, J = 7.6 Hz), 7.11 (1H, t, J = 7.8 Hz), 5.78 (2H, m), 3.59 (1H, m), 3.07 (1H, m), 2.50−2.32 (3H, m), 1.98 (1H, overlapped m). Resolution procedure: A solution of **21** (10.0 g, 36 mmol) in THF (100 mL) was maintained at 60 °C with stirring in an oil bath. (*R*)-Phenethylamine (4.6 mL, 36 mmol) was slowly added, and the solution was cooled slowly to room temperature (crystallization started at 45 °C) over 1.5 h while immersed in the oil bath. The solid was collected by suction filtration and washed with the minimum amount of THF (3×) required to cover the solid. The product was dried under a stream of nitrogen and then under high vacuum to afford the amine salt as a colorless solid (6.66 g). The free acid was liberated from the salt by treatment with 2 M HCl and extraction with ethyl acetate to afford (−)-**21** as a colorless solid (2.82 g, $[\alpha]_D$ −62 (c = 1.0, $CHCl_3$)) in 93% ee as determined by HPLC analysis (Chiralpak AD, 1 mL/min, 2-propanol:hexanes 1:140, λ = 227 nm) of the corresponding methyl ester. The same procedure using (*S*)-phenethylamine gave (+)-**21** as a colorless solid in 93% ee, $[\alpha]_D$ +60 (c = 0.98, $CHCl_3$).

(1*R*/*S*,2*R*/*S*)-2-(2-Bromophenyl)cyclohexanecarboxylic Acid (22). A solution of **21** (5.30 g, 18.9 mmol) in EtOAc (110 mL) was stirred under an atmosphere of hydrogen in the presence of 10% Pd on charcoal (0.50 g) for 12 h. The mixture was filtered (Celite) and concentrated to afford the title compound as a pale yellow solid (5.23 g, 98% yield). ^{1}H NMR: δ 10.45 (1H, br s), 7.55 (1H, d, J = 8.6 Hz), 7.39 (1H, d, J = 7.8 Hz), 7.30 (1H, t, J = 7.6 Hz), 7.09 (1H, t, J = 7.8 Hz), 3.30 (1H, m), 2.83 (1H, m), 2.12 (1H, m), 1.92−1.68 (3H, m), 1.57 (1H, m), 1.50−1.35 (2H, m), 1.26 (1H, m).

(1*R*/*S*,2*R*/*S*)-2-(2-Bromophenyl)-*N*-(cyanomethyl)cyclohexanecarboxamide (23). A mixture of **22** (5.23 g, 18.5 mmol), PyBOP (10.58 g, 20.3 mmol), and aminoacetonitrile hydrochloride (3.81 g, 41.2 mmol) in DMF (50 mL) was cooled to 0 °C and treated with triethylamine (9.0 mL, 65 mmol). The resulting slurry was stirred at room temperature for 2 h and then poured into saturated $NaHCO_3$ aqueous solution and extracted with ethyl acetate (2×). The combined extracts were washed with brine and dried (Na_2SO_4). Concentration in vacuo and chromatography of the residue on silica eluting with 1/4 acetone/benzene yielded the title compound as a pale-yellow solid (5.76 g, 97%). ^{1}H NMR: δ 7.67 (1H, br s), 7.52 (1H, d, J = 8.6 Hz), 7.36 (1H, d, J = 7.8 Hz), 7.27 (1H, t, J = 7.6 Hz), 7.06 (1H, t, J = 7.8 Hz), 4.00 (2H, m), 3.40 (1H, m), 2.80 (1H, m), 2.00 (1H, m), 1.93−1.75 (3H, m), 1.63 (1H, m), 1.54−1.32 (2H, m), 1.21 (1H, m).

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-[4′-(methylthio)biphenyl-2-yl]cyclohexanecarboxamide (24a). Compound **23** (498 mg, 1.55 mmol), 4-(methylthio)benzeneboronic acid (286 mg, 1.70 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (62 mg, 0.076 mmol, 5 mol %), and 2 M Na_2CO_3 aqueous solution (1.2 mL, 2.4 mmol) were heated at 85 °C in DMF (3.0 mL). After 16 h at this temperature, the reaction mixture was cooled to room temperature and partitioned between ethyl acetate and water, and the layers were separated. The aqueous phase was extracted with additional ethyl acetate, and the combined organics were washed with brine and dried (Na_2SO_4). Concentration in vacuo and chromatography of the residue on silica gel eluting with 1/1 ethyl acetate/hexanes gave the title compound as a faint-yellow foam (370 mg, 66%). ^{1}H NMR: δ 7.79 (1H, br s), 7.42−7.33 (3H, m), 7.32−7.28 (2H, m), 7.27 (1H, m), 7.16 (1H, t, J = 7.5 Hz), 7.06 (1H, d, J = 7.6 Hz), 4.04 (2H, m), 3.11 (1H, m), 2.75 (1H, m), 2.52 (3H, s), 1.87 (1H, m), 1.73−1.59 (3H, m), 1.44 (1H, m), 1.38−1.24 (2H, m), 1.12 (1H, m). Anal. ($C_{22}H_{24}N_2OS$) C, calcd 72.49; found 71.70; H, calcd 6.64; found 6.59; N, calcd 7.69; found 7.48.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-[4′-fluorobiphenyl-2-yl]cyclohexanecarboxamide (24b). Compound **23** (132 mg, 0.410 mmol), 4-fluorobenzeneboronic acid (69 mg, 0.49 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (18 mg, 0.022 mmol, 5 mol %), and 2 M Na_2CO_3 aqueous solution (0.31 mL, 0.62 mmol) were heated at 85 °C in DMF (1.2 mL). After 16 h at this temperature, the reaction mixture was cooled to room temperature and partitioned between ethyl acetate and water, and the layers were separated. The aqueous phase was extracted with additional ethyl acetate, and the combined organics were washed with brine and dried (Na_2SO_4). Concentration in vacuo and chromatography of the residue on silica gel eluting with 8/92 acetone/benzene gave the title compound as a faint-yellow foam (117 mg, 85%). ^{1}H NMR: δ 7.53 (1H, br s), 7.44 (2H, m), 7.40 (1H, d, J = 7.8 Hz), 7.28 (1H, t, J = 7.4 Hz), 7.17 (3H, m), 7.07 (1H, d, J = 7.5 Hz), 3.97 (2H, m), 3.04 (1H, m), 2.75 (1H, m), 1.87 (1H, m), 1.76−1.58 (3H, m), 1.42 (1H, m), 1.37−1.23 (2H, m), 1.08 (1H, m). Anal. ($C_{21}H_{21}FN_2O$) C, calcd 74.98; found 73.99; H, calcd 6.29; found 6.00; N, calcd 8.33; found 8.18.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-({[4-(methylsulfinyl)phenyl]sulfonyl}methyl)-cyclohexanecarboxamide (25a) and (1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-({[4-(methylsulfonyl)-phenyl]sulfonyl}methyl)cyclohexanecarboxamide (25c). A solution of **13b** (35 mg, 96 μmol) in CH_2Cl_2 (0.5 mL) was treated at 0 °C with *m*-CPBA (18 mg, 100 μmol) with stirring at this temperature for 1 h. Calcium hydroxide (50 mg) was then added, and the mixture was stirred at room temperature for 15 min before filtration through a plug of Celite and washing well with CH_2Cl_2. Concentration of the filtrate and flash chromatography of the residue on silica gel eluting first with EtOAc and then 30/70 THF/EtOAc afforded **25a** as a colorless foam (28 mg) and **25c** as a colorless solid (5 mg). For **25a** (1:1 mixture of diastereomeric sulfoxides): ^{1}H NMR δ 8.09 (2H, d, J = 8.4 Hz), 7.97 (2H, d, J = 8.0 Hz), 7.78 (1H, br s), 4.18−4.16 (2H, m), 3.22 (1H, d, J = 13 Hz), 3.13 (1H, dd, J = 9.1, 14 Hz), 2.821 (3H, s, methyl of one diastereomer), 2.819 (3H, s, methyl of the other diastereomer), 2.36 (1H, m), 2.28−2.22 (2H, m), 2.19 (1H, m), 2.09 (1H, overlapped m), 1.85 (1H, m), 1.77−1.70 (2H, m), 1.44 (1H, m), 1.28 (1H, m). For **25c**: ^{1}H NMR δ 8.24 (2H, d, J = 8.5 Hz), 8.18 (2H, d, J = 8.5 Hz), 7.80 (1H, br s), 4.17 (2H, d, J = 5.8 Hz), 3.29−3.23 (1H, m), 3.26 (3H,s), 3.19 (1H, m), 2.37 (1H, m), 2.26 (1H, m), 2.19 (1H, m), 1.86 (1H, m), 1.79−1.71 (2H, m), 1.45 (1H, m), 1.36−1.21 (3H, m).

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-[4′-(methylsulfinyl)biphenyl-2-yl]cyclohexanecarboxamide (25b) and (1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-2-[4′-(methylsulfonyl)biphenyl-2-yl]cyclohexanecarboxamide (25d). The procedure was the same as for the preparation of **25a** and **25c**. Flash chromatography was conducted using 22/78 acetone/benzene to elute **25d** and then 1/2 acetone/benzene to elute **25b**. For **25b** (1:1 mixture of diastereomeric sulfoxides): colorless foam. ^{1}H NMR: δ 7.77 (1H, d, J = 8.5 Hz), 7.67−7.64 (2H, m), 7.56 (1H, br m), 7.46 (1H, d, J = 7.9 Hz), 7.34 (1H, t, J = 7.5 Hz), 7.23 (1H, t, J = 7.5 Hz), 7.14 (1H, d, J = 7.6 Hz), 4.06−3.96 (2H, m), 3.07 (1H, m), 2.80 (1H, overlapped m), 1.93 (1H, m), 1.77−1.71 (2H, m), 1.67 (1H, m), 1.49−1.28 (3H, m), 1.13 (1H, m). For **25d**: colorless foam. ^{1}H NMR: δ 7.99 (2H, d, J = 8.6 Hz), 7.69 (2H, m), 7.56 (1H, m), 7.45 (1H, d, J = 7.8 Hz), 7.34 (1H, t, J = 7.4 Hz), 7.22 (1H, t, J = 7.5 Hz), 7.11 (1H, d, J = 6.5 Hz), 3.97 (2H, m), 3.19 (3H, s), 3.00 (1H, dt, J = 2.9, 11 Hz), 2.77 (1H, dt, J = 3.2, 11 Hz), 1.87 (1H, m), 1.75−1.68 (2H, m), 1.66 (1H, m), 1.45−1.27 (3H, m), 1.12 (1H, m).

(1*R*,2*R*,4*R*,5*S*)-4-Bromo-2-(2-bromophenyl)-6-oxabicyclo[3.2.1]octan-7-one (29). Bromotrimethylsilane (1.96 mL, 15.1 mmol) was added dropwise to a 0 °C solution of dimethyl sulfoxide (1.10 mL, 15.5 mmol) in chloroform (15 mL) with stirring at this temperature for 30 min. Compound (−)-**21** (4.24 g, 15.1 mmol) was then added as a solid with stirring at room temperature for 1 h. The mixture was recooled to 0 °C prior to the addition of diisopropylethylamine (2.65 mL, 15.2 mmol) followed by heating at reflux for 24 h. The reaction vessel contents were cooled to room temperature, diluted with ethyl acetate, and washed in succession with water, 5% HCl, water, and brine, and the organic phase was dried over sodium sulfate. Concentration in vacuo afforded an oily solid that was used directly in the next step. Flash chromatography of a portion on silica gel eluting with 7.5/92.5 acetone/benzene (R_f = 0.76) afforded an analytical sample of the title compound as a colorless foam. ^{1}H

NMR: δ 7.71 (1H, dd, J = 1.4, 7.8 Hz), 7.65 (1H, dd, J = 1.2, 8.0 Hz), 7.45 (1H, dt, J = 1.2, 7.5 Hz), 7.26 (1H, dt, J = 1.5, 7.7 Hz), 5.08 (1H, dd, J = 6.8, 11.5 Hz), 5.00 (1H, dd, J = 6.8, 11.5 Hz), 3.78 (1H, m), 3.03 (1H, m), 2.74 (1H, dd, J = 6.7, 16 Hz), 2.57 (1H, ddd, J = 8.2, 12, 15 Hz), 2.35 (1H, m), 1.98 (1H, d, J = 13 Hz).

Methyl (1*R*,2*R*,4*R*,5*S*)-4-Bromo-2-(2-bromophenyl)-5-hydroxycyclohexanecarboxylate (30). Freshly prepared sodium methoxide (35 mL, 0.45M in methanol) was added to a methanol (20 mL) solution of **29** (5.43 g, 15.1 mmol) with stirring at room temperature for 1.5 h. The mixture was then treated with 0.5 M HCl (50 mL), and the methanol was removed by rotary evaporation under reduced pressure. The residue was partitioned between water and ethyl acetate, and the layers were separated. The aqueous phase was extracted with additional ethyl acetate, and the combined organics were washed with water, 5% Na_2CO_3 (2 × 75 mL) and brine, and dried (Na_2SO_4). Concentration in vacuo yielded the title compound as a faint-yellow solid (2.50 g, 42% yield for two steps) after trituration with ether/hexanes. ^{1}H NMR: δ 7.57 (1H, dd, J = 1.2, 8.0 Hz), 7.40 (1H, d, J = 6.5 Hz), 7.31 (1H, t, J = 7.6 Hz), 7.12 (1H, dt, J = 1.7, 7.9 Hz), 4.19 (1H, m), 4.00 (1H, m), 3.82 (1H, m), 3.43 (3H, s), 3.16 (1H, m), 2.80 (1H, m), 2.18−1.97 (4H, m).

Methyl (1*R*,2*R*)-2-(2-Bromophenyl)-5-oxocyclohexanecarboxylate (31). Jones reagent (2.7 M, 7.0 mL) was added at 0 °C to an acetone (25 mL) solution of **30** (2.50 g, 6.38 mmol) with stirring at room temperature for 40 min. The mixture was then diluted with water and extracted with ether (3×). The combined extracts were washed with water, saturated aqueous sodium bicarbonate, and brine solutions, and dried (Na_2SO_4). Concentration in vacuo gave the α-bromoketone product as a colorless, thick syrup (2.49 g) that was taken up in THF (58 mL) and treated with zinc dust (21 g, 330 mmol) and a 1 M solution of KH_2PO_4 (32 mL) with rapid stirring at room temperature for 1 h. The mixture was then filtered (Celite), and the pad was washed well with ethyl acetate and water. The filtrate was transferred to a separatory funnel, shaken, and the layers were separated. The organic phase was washed with brine and dried (Na_2SO_4). Concentration in vacuo provided the title compound as a colorless solid (1.71 g, 86% yield for two steps). ^{1}H NMR: δ 7.59 (1H, dd, J = 1.1, 8.0 Hz), 7.46 (1H, dd, J = 1.5, 7.9 Hz), 7.34 (1H, t, J = 7.6 Hz), 7.15 (1H, dt, J = 1.6, 7.9 Hz), 3.85 (1H, dt, J = 3.5, 12 Hz), 3.42 (3H, s), 3.38 (1H, m), 2.78 (1H, t, J = 14 Hz), 2.70 (1H, dt, J = 6.3, 14 Hz), 2.52 (1H, m), 2.35 (1H, m), 2.16 (1H, m), 1.85 (1H, dq, J = 4.3, 14 Hz).

Methyl (1*R*,2*R*)-2-(2-Bromophenyl)-5,5-difluorocyclohexanecarboxylate (32a). A solution of **31** (1.69 g, 5.46 mmol) in CH_2Cl_2 (23 mL) was treated with methanol (22 μL, 10 mol %) and diethylaminosulfur trifluoride (DAST) (1.73 mL, 13.1 mmol) with stirring at room temperature for 2 h. The reaction vessel contents were then diluted with dichloromethane and washed with water, saturated sodium bicarbonate aqueous solution, and brine, and dried (Na_2SO_4). A 20% volume of methanol was introduced to the dichloromethane solution, and the mixture was cooled to −78 °C and treated with excess ozone until a blue-green color persisted (about 30 min). A solution of 30% H_2O_2 (10 mL) in methanol (10 mL) was then added, and the reaction vessel contents were warmed to room temperature and concentrated. The residue was taken up in ether and washed with 10% Na_2CO_3 aqueous solution, water, and brine, and dried (Na_2SO_4/$MgSO_4$). Concentration in vacuo afforded a cloudy, faint-yellow syrup (1.81 g) that was used directly in the next step. Purification of a portion of this material by flash chromatography on silica gel eluting with 1/9 ethyl acetate/hexanes afforded an analytical sample of the title compound as a colorless syrup. ^{1}H NMR: δ 7.57 (1H, dd, J = 1.2, 8.0), 7.41 (1H, dd, J = 1.5, 7.8 Hz), 7.34 (1H, dt, J = 1.1, 7.5 Hz), 7.14 (1H, m), 3.48 (1H, m), 3.42 (3H, s), 3.13 (1H, m), 2.39 (1H, m), 2.24−2.06 (3H, m), 1.97 (1H, m), 1.64 (1H, m).

(1*R*,2*R*)-2-(2-Bromophenyl)-*N*-(cyanomethyl)-5,5-difluorocyclohexanecarboxamide (33). A 2 M aqueous solution of lithium hydroxide (26 mL) was added to a solution of **32a** (1.81 g, 5.46 mmol) in a mixture of methanol (20 mL) and THF (10 mL) with rapid stirring at room temperature for 15 h. The reaction mixture was then diluted with water and extracted with ether prior to acidification to pH 2 with 2 M HCl and extraction with ethyl acetate (2×). The combined ethyl acetate extracts were washed with brine, dried (Na_2SO_4), and concentrated to afford crude (1*R*,2*R*)-2-(2-bromophenyl)-5,5-difluorocyclohexanecarboxylic acid as a tan foam (1.63 g). A mixture of the crude acid (820 mg, 2.58 mmol), PyBOP (1.49 g, 2.86 mmol), and aminoacetonitrile hydrochloride (530 mg, 5.73 mmol) in DMF (5.0 mL) was cooled to 0 °C and treated with triethylamine (1.26 mL, 9.04 mmol). The resulting slurry was stirred at room temperature for 2.5 h and then poured into water and extracted with ethyl acetate (3×). The combined extracts were washed with brine and dried (Na_2SO_4). Concentration in vacuo and chromatography of the residue on silica gel eluting with 2/3 EtOAc/hexanes yielded the title compound as a faint-yellow foam (579 mg, 63% yield for three steps). ^{1}H NMR: δ 7.83 (1H, br, s), 7.55 (1H, d, J = 8.0 Hz), 7.39 (1H, d, J = 7.0 Hz), 7.30 (1H, t, J = 7.3 Hz), 7.11 (1H, m), 4.02 (2H, m), 3.54 (1H, m), 3.12 (1H, m), 2.30 (1H, m), 2.24−1.93 (4H, m), 1.54 (1H, m).

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-5,5-dichloro-[4′-(methylthio)-1,1′-biphenyl-2-yl]cyclohexanecarboxamide (*rac*-34c). A solution of *rac*-**31** (663 mg, 2.12 mmol) in toluene (7 mL) was added to a 0 °C solution of PCl_5 (1.40 g, 6.70 mmol) in toluene (7 mL) followed by stirring at room temperature for 4 h. The mixture was then recooled to 0 °C, and a 2 M aqueous solution of NaOH was added to pH 9 followed by extraction with two portions of ether. The combined organics were washed with water and saturated NaCl aqueous solution before drying over $MgSO_4$. Concentration in vacuo and flash chromatography of the residue on silica gel eluting with 5/95 ethyl acetate/hexanes afforded methyl (1*R*/*S*,2*R*/*S*)-2-(2-bromophenyl)-5,5-dichlorocyclohexanecarboxylate as a colorless solid (377 mg, 43%). ^{1}H NMR: δ 7.57 (1H, d, J = 7.8 Hz), 7.40−7.33 (2H, m), 7.18−7.12 (1H, m), 3.50 (1H, m), 3.44 (3H, s), 3.29 (1H, m), 2.84 (1H, m), 2.65−2.50 (3H, m), 1.80 (1H, m), 0.87 (1H, m). A 2 M aqueous solution of lithium hydroxide (5.2 mL) was added to a solution of the above compound (377 mg, 1.03 mmol) in a mixture of methanol (7 mL) and THF (2.5 mL) with rapid stirring at room temperature for 15 h. The reaction mixture was then diluted with water and extracted with ether prior to acidification to pH 2 with 2 M HCl and extraction with ethyl acetate (2×). The combined ethyl acetate extracts were washed with brine, dried (Na_2SO_4), and concentrated to afford crude (1*R*/*S*,2*R*/*S*)-2-(2-bromophenyl)-5,5-dichlorocyclohexanecarboxylic acid as a tan foam (343 mg). A mixture of this crude material (343 mg, 0.97 mmol), PyBOP (555 mg, 1.07 mmol), and aminoacetonitrile hydrochloride (198 mg, 2.14 mmol) in DMF (4.8 mL) was cooled to 0 °C and treated with triethylamine (0.50 mL, 3.6 mmol). The resulting slurry was stirred at room temperature for 16 h and then was poured into water and extracted with ethyl acetate (3×). The combined extracts were washed with brine and dried (Na_2SO_4). Concentration in vacuo and chromatography of the residue on silica gel eluting with 2/3 EtOAc/hexanes yielded the (1*R*/*S*,2*R*/*S*)-2-(2-bromophenyl)-*N*-(cyanomethyl)-5,5-dichlorocyclohexanecarboxamide as a colorless solid (343 mg, 91% yield for two steps). ^{1}H NMR: δ 7.94 (1H, br m), 7.56 (1H, d, J = 7.8 Hz), 7.41 (1H, m), 7.32 (1H, m), 7.13 (1H, m), 4.05−4.00 (2H, m), 3.56 (1H, m), 3.30 (1H, m), 2.78 (1H, m), 2.67−2.48 (3H, m), 1.62 (1H, m), 0.87 (1H, m). A mixture of this compound (100 mg, 0.26 mmol), 4-(methylthio)benzeneboronic acid (66 mg, 0.39 mmol), $PdCl_2$-(dppf)·CH_2Cl_2 (11 mg, 0.013 mmol, 5 mol %), and 2 M Na_2CO_3 aqueous solution (0.46 mL, 0.91 mmol) was heated at 85 °C in DMF (0.65 mL). After 17 h at this temperature, the reaction mixture was cooled to room temperature and partitioned between ethyl acetate and water, and the layers were separated. The aqueous phase was extracted with additional ethyl acetate, and the combined organics were washed with brine and dried (Na_2SO_4). Concentration in vacuo and chromatography of the residue on silica gel eluting with 35/65 EtOAc/hexanes gave the title compound as a colorless foam (78 mg, 70%). ^{1}H NMR: δ 7.77 (1H, br m), 7.43 (1H, d, J = 7.9 Hz), 7.35−7.28 (5H, m), 7.22 (1H, m), 7.11 (1H, d, J = 6.9 Hz), 3.99 (2H, m), 3.22 (1H, m), 2.62 (1H, m), 2.54 (3H, s), 2.50 (1H, m), 2.38 (1H, m), 2.18 (1H, m), 1.92−1.79 (2H, m), 0.88

(1H, m). Anal. ($C_{22}H_{22}Cl_2N_2OS$) C, calcd 60.97; found 62.14; H, calcd 5.96; found 5.22; N, calcd 6.46; found 5.43.

(1*R*,2*R*)-*N*-(Cyanomethyl)-5,5-difluoro-[4′-(methylthio)-1,1′-biphenyl-2-yl]cyclohexanecarboxamide (−)-34a. Compound **33** (579 mg, 1.62 mmol), 4-(methylthio)benzeneboronic acid (342 mg, 2.04 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (68 mg, 0.083 mmol, 5 mol %), and 2 M Na_2CO_3 aqueous solution (1.2 mL, 2.4 mmol) were heated at 85 °C in DMF (4.6 mL). After 17 h at this temperature, the reaction mixture was cooled to room temperature and partitioned between ethyl acetate and water, and the layers were separated. The aqueous phase was extracted with additional ethyl acetate, and the combined organics were washed with brine and dried (Na_2SO_4). Concentration in vacuo and chromatography of the residue on silica gel eluting with 35/65 EtOAc/hexanes gave the title compound as a faint-yellow foam (563 mg, 86%), $[\alpha]_D$ −10 (c = 1.2, $CHCl_3$). ^{1}H NMR: δ 7.67 (1H, br s), 7.41 (1H, d, J = 7.0 Hz), 7.36−7.28 (5H, m), 7.22 (1H, dt, J = 1.3, 7.5 Hz), 7.10 (1H, dd, J = 1.2, 7.6 Hz), 4.00 (2H, m), 3.20 (1H, m), 3.05 (1H, m), 2.83 (3H, s), 2.18 (1H, m), 2.01 (1H, overlapped m), 1.95 (1H, m), 1.85 (1H, m), 1.75 (1H, m), 1.68 (1H, m). Anal. ($C_{22}H_{22}F_2N_2OS$) C, calcd 65.98; found 64.63; H, calcd 5.54; found 5.22; N, calcd 6.99; found 6.85.

(1*R*/*S*,2*R*/*S*)-*N*-(Cyanomethyl)-5,5-difluoro-2-[4′-fluorobiphenyl-2-yl]cyclohexanecarboxamide (*rac*-34b). 4-Fluorobenzeneboronic acid (27 mg, 0.19 mmol), *rac*-**33** (55 mg, 0.15 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (7 mg, 0.009 mmol, 5 mol %), and 2 M Na_2CO_3 aqueous solution (0.12 mL, 0.24 mmol) were heated at 85 °C in DMF (0.60 mL). After 16 h at this temperature, the reaction mixture was cooled to room temperature and partitioned between ethyl acetate and water, and the layers were separated. The aqueous phase was extracted with additional ethyl acetate, and the combined organics were washed with brine and dried (Na_2SO_4). Concentration in vacuo and chromatography of the residue on silica gel eluting with 35/65 EtOAc/hexanes gave the title compound as a faint-yellow solid (49 mg, 85%). ^{1}H NMR: δ 7.69 (1H, br s), 7.42 (3H, m), 7.33 (1H, t, J = 7.6 Hz), 7.22 (1H, t, J = 7.5 Hz), 7.17 (2H, m), 7.12 (1H, d, J = 7.6 Hz), 3.99 (2H, m), 3.14 (1H, m), 3.06 (1H, m), 2.18 (1H, m), 2.01 (1H, overlapped m), 1.91 (1H, m), 1.83 (1H, m), 1.74 (1H, m), 1.66 (1H, m). Anal. ($C_{21}H_{19}F_3N_2O$) C, calcd 67.73; found 66.92; H, calcd 5.14; found 4.88; N, calcd 7.52; found 7.27.

Methyl (1*R*/*S*,2*R*/*S*,5*R*/*S*)-2-(2-Bromophenyl)-5-hydroxycyclohexanecarboxylate (*rac*-36a) and Methyl (1*R*/*S*,2*R*/*S*,5*S*/*R*)-2-(2-Bromophenyl)-5-hydroxycyclohexanecarboxylate (*rac*-36b). Compound *rac*-**31** (2.05 g, 6.61 mmol) was dissolved in methanol (50 mL) and treated with $NaBH_4$ (0.32 g, 8.4 mmol) portionwise at room temperature. After 30 min, 2 M HCl (16 mL) was added, and the methanol was evaporated by rotary evaporation under reduced pressure. The residue was partitioned between ethyl acetate and water, and the layers were separated. The organic phase was washed with brine, dried (Na_2SO_4/$MgSO_4$), and concentrated. ^{1}H NMR analysis of the crude mixture revealed it to be composed of two diastereomeric alcohols *rac*-**36a** and *rac*-**36b** in a ratio of 15:1. Flash chromatography of the residue on silica gel eluting with 3/2 ethyl acetate/hexanes afforded analytical samples of major diastereomer *rac*-**36a** (1.48 g, R_f = 0.35) and minor diastereomer *rac*-**36b** (78 mg, R_f = 0.40) as thick, colorless syrups. For *rac*-**36a**: ^{1}H NMR δ 7.57 (1H, d, J = 8.0 Hz), 7.42−7.36 (1H, m), 7.32 (1H, t, J = 7.5 Hz), 7.13−7.11 (1H, m), 3.92 (1H, m, OH), 3.76 (1H, m, baseline width = 48 Hz), 3.43 (3H, s), 3.34 (1H, m), 3.02 (1H, m), 2.27 (1H, m), 2.05 (1H, overlapped m), 1.91 (1H, m), 1.56 (1H, q, J = 12 Hz), 1.49−1.42 (2H, m). For *rac*-**36b**: ^{1}H NMR δ 7.57 (1H, d, J = 8.0 Hz), 7.37−7.33 (2H, m), 7.12 (1H, m), 4.19 (1H, narrow m, baseline width = 22 Hz), 3.84 (1H, s, OH), 3.42 (3H, s), 3.40−3.32 (2H, m), 2.15−2.09 (2H, m), 1.88 (1H, m), 1.82−1.69 (2H, m), 1.66 (1H, m).

Methyl (1*R*/*S*,2*R*/*S*,5*S*/*R*)-2-(2-Bromophenyl)-5-fluorocyclohexanecarboxylate (*rac*-37a) and Methyl (1*R*/*S*,2*R*/*S*,5*R*/*S*)-2-(2-Bromophenyl)-5-fluorocyclohexanecarboxylate (*rac*-37b). Equatorial alcohol *rac*-**36a** and axial alcohol *rac*-**36b** were separately converted into the axial and equatorial fluoro-compounds (*rac*-**37a** and *rac*-**37b**, respectively[14]) by treatment of a CH_2Cl_2 solution (0.25 M in alcohol) with DAST (1.5 equiv) at −78 °C followed by slow warming to −10 °C over 2 h, aqueous workup, and flash chromatography on silica gel eluting with 1/9 ethyl acetate/hexanes (R_f = 0.30). For *rac*-**37a**: thick colorless syrup; 25% yield. ^{1}H NMR: δ 7.60 (1H, d, J = 7.7 Hz), 7.43−7.35 (2H, m), 7.15 (1H, m), 5.05 (1H, dm, doublet J_{H-F} = 48 Hz, multiplet baseline width = 15 Hz), 3.46 (1H, overlapped m), 3.45 (3H, s), 3.21 (1H,m), 2.36 (1H, m), 2.11 (1H, overlapped m), 1.98 (1H, m), 1.88 (1H, m), 1.77 (1H, m), 1.67 (1H, m). For *rac*-**37b**: thick colorless syrup; 6% yield. ^{1}H NMR: δ 7.59 (1H, d, J = 7.9 Hz), 7.40 (1H, d, J = 7.0 Hz), 7.34 (1H, t, J = 7.5 Hz), 7.14 (1H, t, J = 6.9 Hz) (1H, dm, doublet J_{H-F} = 48 Hz, multiplet baseline width = 40 Hz), 3.45 (3H, s), 3.40 (1H, m), 3.11 (1H, m), 2.42 (1H, m), 2.22 (1H, m), 1.98 (1H, m), 1.78 (1H, m), 1.68 (1H, m), 1.52 (1H, m).

(1*R*/*S*,2*R*/*S*,5*S*/*R*)-*N*-(Cyanomethyl)-5-fluoro-2-[4′-(methylthio)biphenyl-2-yl]cyclohexanecarboxamide (*rac*-38a) and (1*R*/*S*,2*R*/*S*,5*R*/*S*)-*N*-(Cyanomethyl)-5-fluoro-2-[4′-(methylthio)biphenyl-2-yl]cyclohexanecarboxamide (*rac*-38b). Compounds *rac*-**36a** and *rac*-**36b** were separately transformed as per steps f, g, and h in Scheme 7 to yield the title compounds as colorless solids. For *rac*-**38a**: ^{1}H NMR δ 7.65 (1H, br s), 7.44 (1H, d, J = 7.7 Hz), 7.39−7.31 (5H, m), 7.22 (1H, t, J = 7.4 Hz), 7.12 (1H, d, J = 7.5 Hz), 4.90 (1H, dm, doublet J_{H-F} = 48 Hz, multiplet baseline width = 16 Hz), 4.04−3.96 (2H, m), 3.18 (1H, m), 3.11 (1H, m), 2.57 (3H, s), 2.14 (1H, m), 1.96 (1H, m), 1.80 (1H, m), 1.74−1.64 (2H, m), 1.60 (1H, m). Anal. ($C_{22}H_{23}FN_2OS$) C, calcd 69.08; found 67.04; H, calcd 6.06; found 5.93; N, calcd 7.32; found 6.92. For *rac*-**38b**: ^{1}H NMR δ 7.57 (1H, s), 7.43 (1H, d, J = 7.5 Hz), 7.39−7.33 (4H, m), 7.30 (1H, d, J = 8.0 Hz), 7.22 (1H, d, J = 7.0 Hz), 7.12 (1H, dd, J = 1.1, 7.5 Hz), 4.67 (1H, dm, doublet J_{H-F} = 49 Hz, multiplet baseline width = 40 Hz), 4.01 (2H, m), 3.14 (1H, m), 2.97 (1H, m), 2.58 (3H, s), 2.25 (1H, m), 2.07 (1H, overlapped m), 1.84 (1H, m), 1.65 (1H, m), 1.54 (1H, m), 1.34 (1H, m).

(1*R*,2*R*)-*N*-(Cyanomethyl)-5,5-difluoro-2-[4′-(methylsulfinyl)-biphenyl-2-yl]cyclohexanecarboxamide (39a) and (1*R*,2*R*)-*N*-(Cyanomethyl)-5,5-difluoro-2-[4′-(methylsulfonyl)biphenyl-2-yl]cyclohexanecarboxamide (39b). A solution of (−)-**34a** (147 mg, 0.367 mmol) in CH_2Cl_2 (0.50 mL) was cooled to −15 °C and treated with *m*-CBPA (70 mg, 0.40 mmol). The mixture was stirred at this temperature for 1 h and then warmed slowly to room temperature over an additional 2 h. CH_2Cl_2 (3 mL) containing dimethyl sulfide (10 μL) was added followed 5 min later by $Ca(OH)_2$ (200 mg, 2.7 mmol). After being stirred at room temperature for 15 min, the mixture was filtered (Celite) and concentrated. Flash chromatography of the residue on silica gel eluting first with 22/78, then with 1/2 acetone/benzene, afforded **39a** (1:1 mixture of sulfoxide diastereomers) as a colorless solid (137 mg) after trituration with ether, and sulfone **39b** as a colorless solid (13 mg) after trituration with a mixture of acetone and hexanes. For **39a**: R_f = 0.13 (22/78 acetone/benzene). ^{1}H NMR: δ 7.76 (2H, m), 7.75 (1H, br s), 7.63 (2H, m), 7.48 (1H, d, J = 7.8 Hz), 7.38 (1H, t, J = 7.6 Hz), 7.29 (1H, d, J = 7.2 Hz), 7.18 (1H, d, J = 7.6 Hz), 4.02 (2H, m), 3.20 (1H, m), 3.10 (1H, m), 2.80 (3H, s), 2.43 (1H, m), 2.05 (1H, overlapped m), 2.00−1.86 (2H, m), 1.83−1.76 (2H, m). For **39**b: R_f = 0.37 (22/78 acetone/benzene). ^{1}H NMR: δ 8.02 (2H, m), 7.75 (1H, br s), 7.70 (2H, m), 7.50 (1H, d, J = 7.7 Hz), 7.42 (1H, t, J = 7.4 Hz), 7.31 (1H, t, J = 7.7 Hz), 7.19 (1H, d, J = 8.0 Hz), 4.08−3.98 (2H, m), 2.29 (3H, s), 3.18−3.06 (2H, m), 2.26−2.16 (2H, m), 2.01−1.88 (2H, m), 1.87−1.68 (2H, m).

Supporting Information Available: Data and refinement statistics for the X-ray structure of **13e** bound to the active site of cathepsin K. This material is available free of charge via the Internet at http://pubs.acs.org.

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