The Development of Cyclic Sulfolanes as Novel and High-Affinity P_2 Ligands for HIV-1 Protease Inhibitors

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Design and synthesis of a novel series of protease inhibitors incorporating conformationally constrained cyclic ligands for the S_2-substrate binding site of HIV-1 protease is described. We recently reported urethanes of 3-tetrahydrofuranyl as P_2 ligands for HIV-1 protease inhibitors. Subsequently, we have found that the urethane of 3(*S*)-hydroxysulfolane further increased the *in vitro* potency of these inhibitors. Furthermore, introduction of a small 2-alkyl group *cis* to the 3-hydroxyl group of either heterocyclic system further enhanced enzyme affinity. The *cis*-2-isopropyl group thus far offered optimum enhancement of the inhibitory properties. This led to the discovery of inhibitor **43** (IC_{50} 3.5 nM, CIC_{95} 50 ± 14 nM) of comparable *in vitro* antiviral potency to the current clinical candidate 1 (Ro 31-8959) but of reduced molecular weight due to the exclusion of the P_3 quinoline ligand. Also, it has been demonstrated that the octahydropyrindene derivative **34** is an effective replacement of the P_1' decahydroisoquinoline derivative.

The development of an effective therapeutic agent for the treatment of AIDS continues to be a challenging problem in medicinal research. Since the discovery that a virally encoded HIV protease is vital for propagation, inhibition of this enzyme became a major therapeutic target for AIDS chemotherapy.[1] Consequently, numerous efforts aimed at developing potent and selective inhibitors of HIV protease have appeared in the literature.[2] During the course of our research, we have designed and synthesized a number of conformationally constrained cyclic ligands for the HIV protease substrate binding site.[3-5] We recently reported that the incorporation of an unnatural amino acid such as (2*S*,3′*R*)-tetrahydrofuranylglycine in place of asparagine at the P_2 subsite of the present clinical candidate 1 (Ro 31-8959)[6] led to inhibitor **2** with enhanced enzyme affinity as well as antiviral potency.[3] Subsequently, we have found that the removal of the P_3 quinoline ligand and incorporation of a urethane of (3*S*)-tetrahydrofuran as the P_2 ligand resulted in inhibitor **3** with an IC_{50} value of 132 nM.[5] The urethanes of 3(*S*)-hydroxysulfolane provided further potency enhancement relative to the heterocycle (3*S*)-tetrahydrofuran. Furthermore, introduction of a small 2-alkyl group *cis* to the 3-alkoxycarbonyl group of either heterocycle system significantly enhances enzyme affinity. Successful optimization of these findings led to identification[4] of inhibitor **43** with reduced molecular weight and comparable *in vitro* antiviral potency to present clinical candidate 1 (Ro 31-8959). Also, consistent with molecular modeling, an octahydropyrindene derivative **34** was found to be an effective replacement of the P_1' decahydroisoquinoline derivative. In this paper, we report the synthesis, enzyme inhibition, and antiviral potencies of a structurally new class of protease inhibitors which incorporate various conformationally constrained cyclic ligands designed to interact at the HIV-1 protease substrate binding site.

Chemistry

As described in Scheme 1, enantiomerically pure 3(*S*)-hydroxytetrahydrothiophene required for the preparation of various target inhibitors was synthesized from (3*S*)-dimethyl malate.[7] The hydroxyl group was first protected as the tetrahydropyranyl ether by treatment with dihydropyran and a catalytic amount of *p*-TsOH in diethyl ether. Reduction of the resulting ester with lithium aluminum hydride (LAH) in diethyl ether afforded the diol which was then mesylated with mesyl chloride and triethylamine in methylene chloride to provide the bis-mesylate **5**. Exposure of the bis-mesylate **5** with an excess of lithium sulfide in DMF at 60 °C furnished the protected tetrahydrothiophene **6**. The removal of tetrahydropyranyl protecting group with *p*-TsOH in methanol afforded the 3(*S*)-hydroxytetrahydrothiophene **7**. Similarly, starting from optically pure (3*R*)-dimethyl malate, the 3(*R*)-hydroxytetrahydrothiophene was prepared. Both enantiomers of *cis*-3-hydroxy-4-methyltetrahydrothiophenes utilized for the preparation of inhibitors **60** and **61** were synthesized from optically pure (3*S*)- and (3*R*)-diethyl malates. As shown in Scheme 2 (3*S*)-diethyl malate (**8**) was methylated according to the procedure of Seebach and co-workers[8] to provide **9** as a mixture (8:1) of diastereomers by ^{1}H NMR analysis. The resulting diester was converted to 3(*S*)-hydroxy-4(*R*)-methyltetrahydrothiophene (**11**) by following the same sequence utilized for converting **4** to **7**. The synthesis of racemic *cis*-3-hydroxy-5-methyltetrahydrothiophenes (**15**) is outlined in Scheme 3. Commercially available ethyl 3-bromobutyrate (**12**) was condensed with ethyl 2-mercaptoacetate in ethanol in the presence of sodium ethoxide to afford the diester **13**. Dieckman cyclization followed by hydrolysis and decarboxylation of the resulting keto ester resulted in the ketone **14** in good yield. Reduction of the ketone **14** with DIBAL-H in methylene chloride at −78 °C afforded a 3:1 mixture (by ^{1}H NMR analysis) of *cis*/*trans* alcohols **15** and **16**. The desired *cis* isomer **15** was separated from the mixture by silica gel chromatography with 25% ethyl acetate in hexane.

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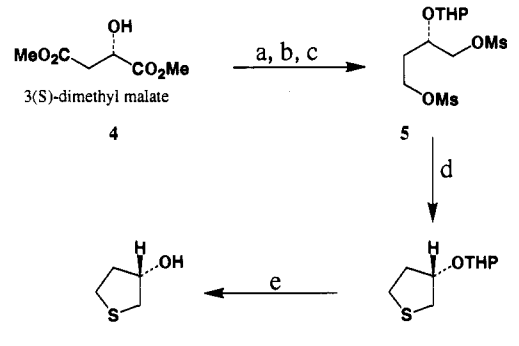
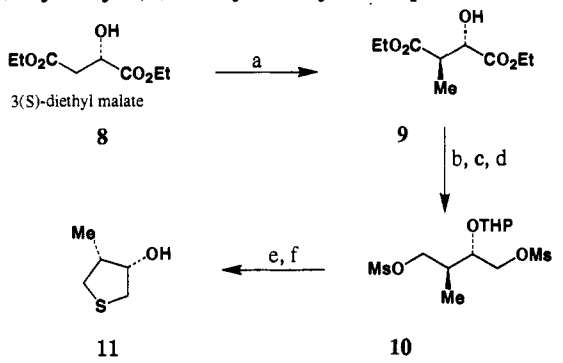
Scheme 1. Synthesis of 3(*S*)-Hydroxytetrahydrothiophene[a]



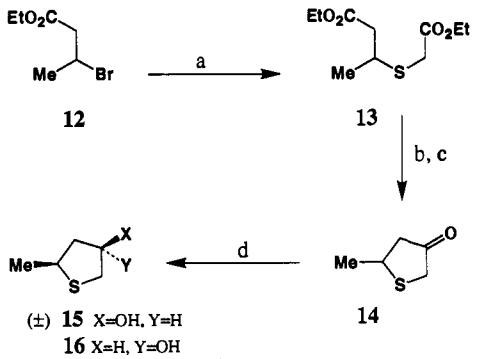
[a] Key: (a) DHP, *p*-TsOH, Et_2O; (b) LAH, Et_2O; (c) MsCl, Et_3N, CH_2Cl_2; (d) Li_2S, DMF; (e) *p*-TsOH, MeOH.

Scheme 2. Synthesis of 3(*S*)-Hydroxy-4(*R*)-methyltetrahydrothiophene[a]



[a] Key: (a) LDA, MeI, THF; (b) DHP, *p*-TsOH, Et_2O; (c) LAH, Et_2O; (d) MsCl, Et_3N, CH_2Cl_2; (e) Li_2S, DMF; (f) *p*-TsOH, MeOH.

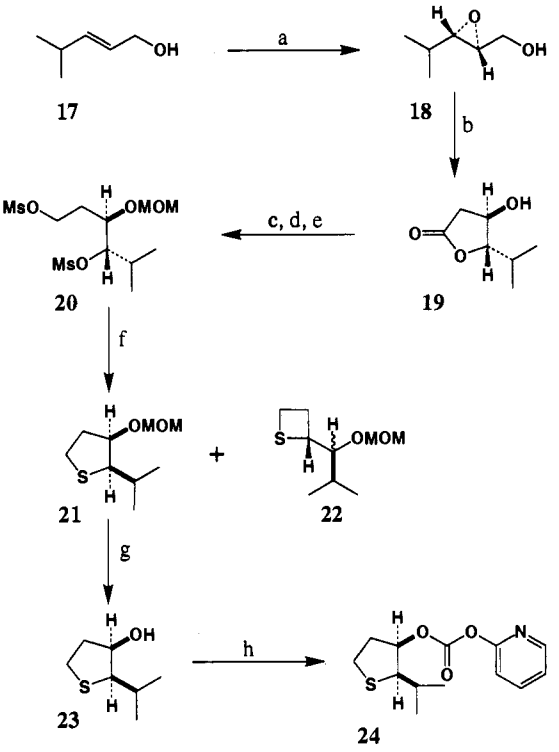
Scheme 3. Synthesis of *cis*-(±)-3-Hydroxy-5-methyltetrahydrothiophene[a]



[a] Key: (a) NaOEt, $HSCH_2CO_2Et$, EtOH; (b) NaOEt, PhMe; (c) aqueous HCl, MeOH, reflux; (d) DIBAL-H, CH_2Cl_2.

The synthesis of various enantiomerically pure *cis*-2-alkyl-3-hydroxytetrahydrothiophene derivatives utilized for the preparation of target inhibitors was accomplished by the procedure for preparing compound **24** as described in Scheme 4. The *trans* allylic alcohol **17** was readily prepared by Horner–Emmons olefination[9] of isobutyraldehyde and triethyl phosphonoacetate followed by DIBAL-H reduction of the resulting *trans* α,β-unsaturated ester (*trans*/*cis* ratio 50:1) in methylene chloride at −78 °C for 2 h. Sharpless epoxidation[10] of the allylic alcohol **17** with (+)-diethyl L-tartrate furnished the epoxide **18**.[11] Epoxide **18** was then converted to the lactone **19** by reaction with sodium cyanide in refluxing ethanol followed by careful acidification with concentrated hydrochloric acid according to the procedure of Ganem and Wrobel.[12]

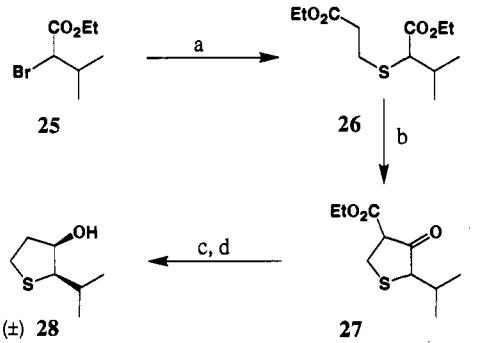
Scheme 4[a]



[a] Key: (a) tBuOOH, (+)-DET, $Ti(OiPr)_4$, CH_2Cl_2, −22 °C; (b) NaCN, EtOH, 80 °C, 12 h, then H_3O^+; (c) MOMCl, iPr_2NEt, CH_2Cl_2; (d) LAH, Et_2O; (e) MsCl, Et_3N, CH_2Cl_2; (f) Li_2S, DMF; (g) PhSH, BF_3·OEt_2, CH_2Cl_2; (h) DPC, CH_2Cl_2.

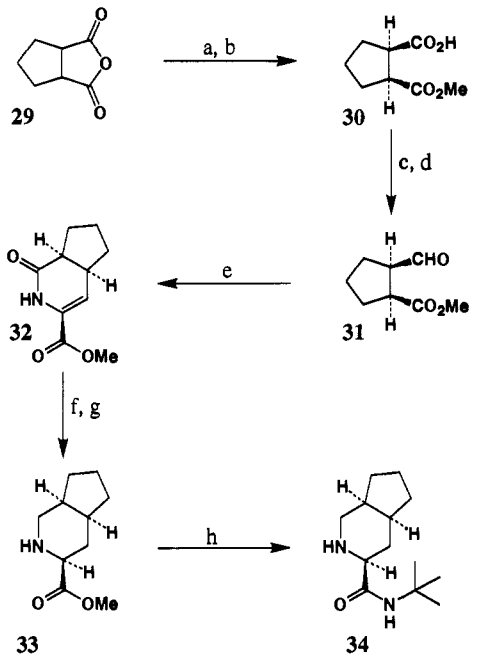
Lactone **19** was first protected as the MOM ether and then transformed into the bis-mesylate **20** in a two-step sequence: (1) LAH reduction[13] of the MOM-protected lactone to the corresponding diol and (2) mesylation of the resulting diol with mesyl chloride and triethylamine to the bis-mesylate **20**. Exposure of the bis-mesylate **20** with an excess of lithium sulfide in DMF provided a mixture (3:1) of desired tetrahydrothiophene derivative **21** and the thietane derivative **22**. Interestingly, the ratio of the cyclization products **21** and **22** depends on the choice of the protecting group. For example, when the hydroxyl group of the bis-mesylate was protected as the THP ether, the mixture ratio was 1:1 (76% combined yield). As expected, bis-mesylate cyclization with C-2 primary alkyl side chains provided mainly the corresponding tetrahydrothiophene derivatives (60–75% yield) and a small amount of thietane byproduct (3–8%). The desired tetrahydrothiophene derivative was separated by silica gel chromatography (5% ethyl acetate–hexane), and the MOM protecting group was removed by exposure to BF_3·OEt_2 and thiophenol to furnish the enantiomerically pure alcohol **23**.[14] Similarly, the corresponding 2(*S*)-alkyl-3(*S*)-hydroxytetrahydrothiophene derivatives were prepared by utilizing (−)-diethyl D-tartrate in the Sharpless epoxidation step. Racemic *cis*-3-hydroxy-2-isopropyltetrahydrothiophene (**28**) was prepared as shown in Scheme 5.[15] Commercially available ethyl 2-bromoisovalarate was reacted with the sodium salt of ethyl 3-mercaptopropionate to provide the diester **26**. Dieckman cyclization of the diester **26** with sodium ethoxide in refluxing ethanol afforded the keto ester **27** as a mixture (*cis*/*trans*). Keto ester **27** was subjected to aqueous acid under refluxing conditions to effect ester hydrolysis followed by decarboxylation to furnish the corresponding ketone. Reduction of the resulting ketone with DIBAL-H provided the *cis*

Scheme 5[a]



[a] Key: (a) NaOEt, $HS(CH_2)_2CO_2Et$, EtOH; (b) NaOEt, PhMe, 120 °C; (c) 10% aqueous H_2SO_4, reflux; (d) $NaBH_4$, EtOH.

Scheme 6[a]

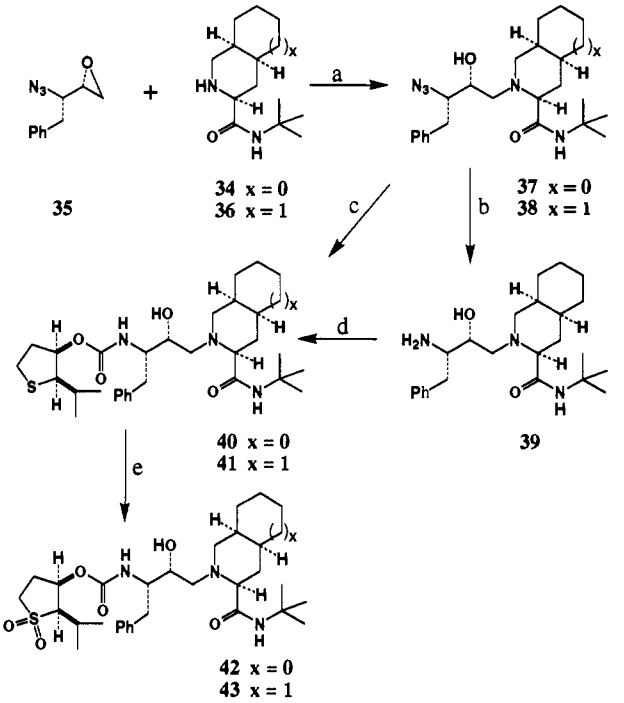


[a] Key: (a) MeOH, reflux; (b) crystallize with (+)-ephedrine; (c) PhMe, $(COCl)_2$; (d) H_2, 10% Pd–C, 2,6-lutidine, THF; (e) LiHMDS, $PhCH{=}NCH_2CO_2Me$, THF; then AcOH, MeOH; (f) H_2, 5% Pd–C, THF; (g) $BH_3{\cdot}Me_2S$, THF then H_3O^+; (h) Me_3Al, Me_3CNH_2.

alcohol **28** exclusively. Sodium borohydride reduction in ethanol also provided only the *cis* isomer **28**. For an easy access to racemic ligands, the above synthetic route is convenient and quite general.[16] This route has been employed for the preparation of inhibitors **45**, **69**, and **71–77**. Alkoxycarbonylation of the amine **39** with the racemic 2-alkyl-3-hydroxytetrahydrothiofuran provided diastereomers which were separated by column chromatography over silica gel. The stereochemistry at the 2- and 3-positions of the thiophene ring was assigned by comparison of ^1H NMR (300 MHz) spectra of the compounds with known configuration.

The synthesis of octahydropyrindene derivative **34** has been accomplished (Scheme 6) by using the chemistry developed by Houpis and co-workers.[17] The key starting material, *cis*-cyclopentane-1,2-dicarboxylic acid anhydride (**29**)[18] was refluxed with methanol, and the resulting racemic monoester was resolved with (+)-ephedrine to provide the desired enantiomer **30**. Monoester **30** was converted to aldehyde **31** by the following two-step sequence: (1) treatment with oxalyl chloride in toluene afforded the corresponding acid chloride and (2) Rosenmund reduction of the resulting acid chloride with 10% Pd–C under 50 psi of hydrogen in the presence of 2,6-lutidine resulted in the aldehyde **31**. Reaction of aldehyde **31** with the lithium enolate of the benzylidene derivative of glycine methyl ester prepared according to the procedure of Stork and co-workers[19] furnished the pyridine derivative **32** after acidic workup and silica gel chromatography. Saturation of the double bond by catalytic hydrogenation with 5% Pd–C under 50 psi of hydrogen followed by removal of the lactam carbonyl group by treatment with borane methyl sulfide complex in THF provided the octahydropyrindene derivative **33**. The methyl ester of **33** was then converted to the carboxamide derivative **34** by Weinreb amidation protocol.[20] Thus, treatment of **33** with the aluminum reagent obtained from the reaction of trimethylaluminum and *tert*-butylamine furnished **34** in good yield.

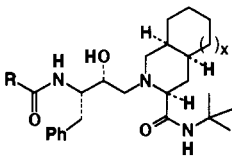
Scheme 7[a]

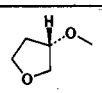
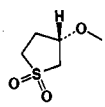
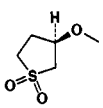
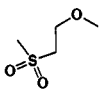
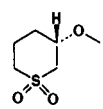
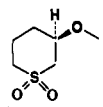
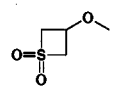


[a] Key: (a) iPrOH, 80 °C; (b) H_2, 10% Pd–C, AcOH, MeOH–THF; (c) H_2, 10% Pd–$BaSO_4$, mixed carbonate **16**, Et_3N; (d) Mixed carbonate **16**, CH_2Cl_2, Et_3N; (e) OsO_4 (cat.), NMO, acetone–H_2O.

Synthesis of various inhibitors with sulfolanes as the P_2 ligands and decahydroisoquinolinecarboxamide or the octahydropyrindenecarboxamide as the P_1' ligand was carried out according to Scheme 7. Opening of epoxide **35** with the octahydropyrindenecarboxamide **34** and the decahydroisoquinolinecarboxamide **36**[21,22] in refluxing 2-propanol afforded the corresponding azides **37** and **38**. Catalytic hydrogenation of **38** with 10% Pd–C in the presence of acetic acid provided the amine **39**. Amine **39** was transformed into various target inhibitors listed in Tables 1–3 by an alkoxycarbonylation of the respective alcohol.[23] For example, reaction of alcohol **23** with dipyridyl carbonate and triethylamine in methylene chloride afforded the active carbonate **24**. Treatment of the active carbonate with amine **39** in methylene chloride furnished the urethane **40** in good yield. Selective oxidation[24] of the ring sulfur with a catalytic amount of osmium tetraoxide and an excess of 4-methylmorpholine *N*-oxide in a mixture (3:1) of acetone and water afforded the inhibitor **43**. Inhibitor **42** with octahydropyrindene derivative was prepared by a catalytic hydrogenation of

Table 1. Structure and Inhibitory Potencies of Various Sulfone Derivatives



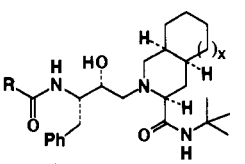
compd	R	X	IC_{50} (mM)	CIC_{95} (nM)
3		1	132 ± 30 (n = 72)	800 (n = 3)
44		0	61 ± 38 (n = 4)	400
45		1	132	
46		1	220	
47		1	76 ± 12 (n = 14)	364 ± 44 (n = 17)
48		0	11.3	>200
49		1	140	>800
50		1	1030	
51		1	1745	
52		1	2068	
53		1	104	

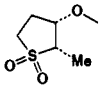
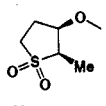
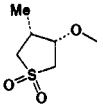
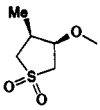
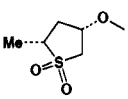
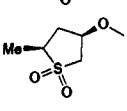
azide **37** over Pd–$BaSO_4$ in the presence of active carbonate **24** and triethylamine in THF.[25] Osmium tetraoxide-mediated oxidation of the ring sulfur afforded the inhibitor **42**. Various other inhibitors listed in Tables 1–3 were prepared from azide **37** and amine **39**, via the procedure described above.

Results and Discussion

As reported previously,[3] the replacement of asparagine of inhibitor **1** (Ro 31-8959, IC_{50}(HIV-1) 0.23 ± 0.1 nM; CIC_{95} 22 ± 7 nM) with (2*S*,3′*R*)-tetrahydrofuranylglycine (compound **2**, IC_{50}(HIV-1) 0.054 ± 0.027 nM; CIC_{95} 8 ± 4 nM) not only increased the enzyme affinities but led to significant enhancement of antiviral potencies compared to **1**. Energy-minimized modeled structures[26] of compounds **1** and **2** revealed a possible explanation for the facile replacement of asparagine by tetrahydrofuranylglycine. It appeared that the carbonyl oxygen of the asparagine of **1** and the tetrahydrofuran ring oxygen of inhibitor **2** are within hydrogen-bonding distance of the Asp 29 and Asp 30 NH present in the S_2 binding domain of the HIV-1 protease.[29] In order to obtain further insight into the ligand binding site interactions in this region, we subsequently removed the P_3 quinoline ligand of inhibitor **2** and incorporated a urethane of (3S)-tetrahydrofuran as

Table 2. Structure and Inhibitory Potencies of Various Substituted Sulfone Derivatives

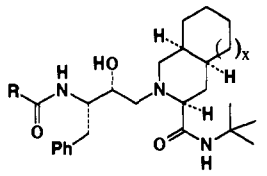


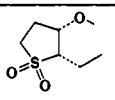
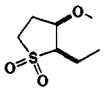
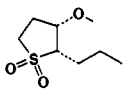
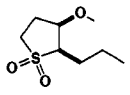
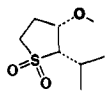
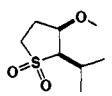
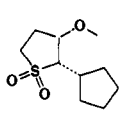
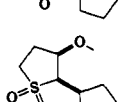
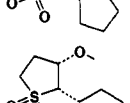
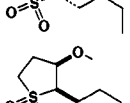
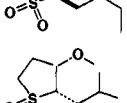
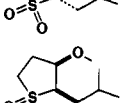
compd	R	X	IC_{50} (nM)	CIC_{95} (nM)
54		1	52.4	400
55		1	169	1600
56		1	11.4	200
57		0	12.6	100
58		1	22.3	200
59		1	70	800
60		1	216	800
61		1	82	>400
62		1	1600	

the P_2 ligand. This resulted in the lead inhibitor **3** with an IC_{50} value of 132 nM. As expected, this compound was significantly less potent than inhibitors **1** and **2**; however, a preliminary X-ray crystal structure[30] of the inhibitor **3** complexed with HIV-1 protease suggested a number of structural changes on the tetrahydrofuran ring that could lead to improved binding. The regions of the tetrahydrofuranyl ligand considered for structural modifications are labeled A–C (Figure 1). Thus, the optimization of this ligand was basically viewed as a three-variable matrix problem. Assuming each variable is independent, our approach to structure-based design of inhibitors was to optimize substituents in each region individually and then combine the features together to obtain inhibitors with high affinity.

As seen in Table 1, replacement of ring heteroatom of **3** with sulfur resulted in no change in inhibitory potency (compound **45**, IC_{50} 132 nM). The corresponding 3(*R*)-isomer showed an IC_{50} value of 220 nM, a greater than 3-fold potency enhancement compared to the (3*R*)-tetrahydrofuranylurethane (IC_{50} 694 nM) reported previously.[6] Oxidation of ring sulfur to the corresponding sulfone afforded (compound **47**, IC_{50} 76 nM) nearly a 2-fold potency enhancement over lead compound **3**. More importantly, compound **47** has prevented the spread of HIV-1 in MT4 human T-lymphoid cells infected with IIIb isolate[31] at an average concentration (n = 17) of 364 nM (CIC_{95}), again a 2-fold improvement over inhibitor **3**. An open chain sulfone (compound **50**) provided evidence that the cyclic ring is essential for potency enhancement.

Table 3. Structure and Inhibitory Potencies of Various 2-Substituted Sulfone Derivatives



compd	R	X	IC_{50} (nM)	CIC_{95} (nM)
63		1	5.4	400
64		1	13.1	800
65		1	6.2	400
66		1	20.1	800
67		1	11 ± 1.5 (n = 2)	200 (n = 2)
42		0	3 ± 0.15 (n = 2)	100
43		1	3.5 ± 0.8 (n = 7)	50 ± 14 (n = 7)
68		1	6.2	400
69		1	22.6	1500
70		1	14.9	400
71		1	45.8	800
72		1	12	400
73		1	30	1500

Evaluation of compounds **49–53** established that a five-membered heterocyclic ring is preferred by the S_2 binding region of HIV-1 protease. We were unable to obtain a crystal structure of compound **47** complexed with HIV-1 protease; however, in order to gain information regarding the protein–ligand interaction, an active model of inhibitor **47** bound to the enzyme was created. On the basis of superposition of the modeled structure onto the protein–ligand complex of **3**, it appeared that the sulfone oxygen *cis* to 3-hydroxyl group was in close proximity to Asp 29 and Asp 30. Therefore, it is likely that the *cis* sulfone oxygen makes a hydrogen-bonding interaction with the residues in this region (Figure 2). With respect to region B, we have investigated this area as an independent variable. Examination of the enzyme–inhibitor complex of **3** suggested that an alkyl group *cis* to the 3-alkoxy-

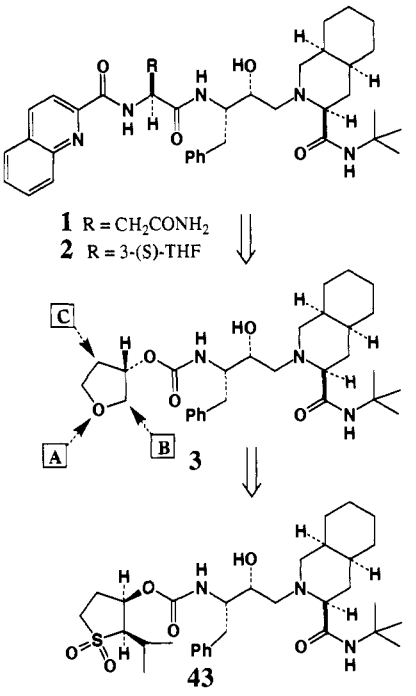


Figure 1.

carbonyl functionality could fill the hydrophobic pocket present in the region, resulting in improved binding. To test this hypothesis, the readily available tetrahydrofuranyl derivatives with a methyl group *cis* to the 3-alkoxycarbonyl group were prepared.[32] Indeed, results in Table 2 show that a *cis*-2-methyl-substituted 3(*S*)-tetrahydrofuranylurethane not only afforded improved inhibitory potency (compound **54**, IC_{50} 52.4 nM) but also resulted in enhanced antiviral potency (CIC_{95} 400 nM).[33] Interestingly, a *cis*-2-methyl substituent in the 3(*R*)-tetrahydrofuranylurethane also exhibited (compound **55**, IC_{50} 169 nM) greater than 4-fold potency enhancement compared to the 3(*R*)-tetrahydrofuranylurethane (IC_{50} 694 nM) reported previously.[5] *In vivo* pharmacokinetic properties of inhibitors **3** and **47** were evaluated in dogs. Since, the sulfolane-derived inhibitor **47** exhibited improved pharmacokinetic properties[34] compared to inhibitor **3**, we examined the substituent effect on the sulfolane ring. As indicated in Table 2, attachment of a *cis*-methyl group in sulfolane **47** afforded the inhibitor **56** with an IC_{50} value of 11.4 nM, a greater than 6-fold potency enhancement over the corresponding unsubstituted derivative. Furthermore, introduction of a *cis*-2-methyl substituent in 3(*R*)-sulfolane **49** resulted in (compound **58**; IC_{50} 22.3 nM) a greater than 6-fold increase in enzyme affinity. With respect to region C, incorporation of a *cis*-4-methyl group showed no appreciable effect on the enzyme inhibitory or antiviral potencies. Similarly, introduction of a *cis*-5-methyl substituent in (3*S*)-sulfolane exhibited no potency-enhancing effect, whereas a *cis*-methyl group in (3*R*)-sulfolane resulted in 8-fold reduction in potency.

Based on the above results, we have examined the effect of various alkyl substituents with 2*S*,3*S* and 2*R*,3*R* absolute configurations. The results are shown in Table 3. As is evident, increasing the size of the alkyl group from methyl to ethyl afforded roughly a 2-fold improvement in enzyme inhibitory potency (compound **63**, IC_{50} 5.4; compound **64**, 13.1 nM). In contrast to methyl substituents, ethyl side chains led to a reduction in antiviral potencies. Further increase in chain length from ethyl to propyl indicated only little effect. However, changing from a propyl to a

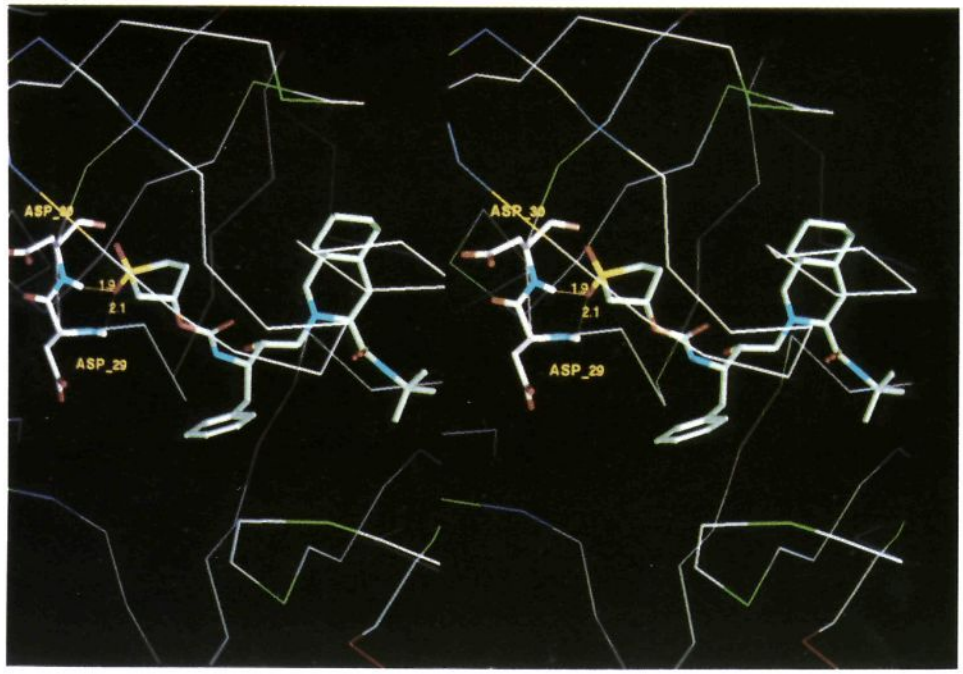


Figure 2. Stereoview of the optimized bound conformation of compound **47** in the L-689,502 inhibited HIV-1 protease active site.[31]

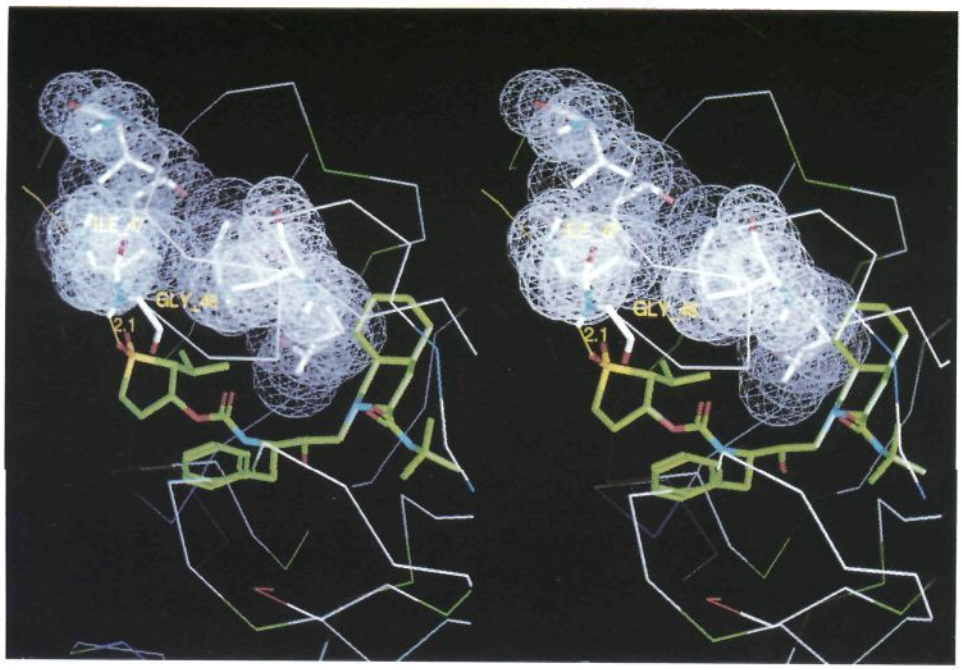


Figure 3. Stereoview of the optimized bound conformation of compound **43** in the L-689,502 inhibited HIV-1 protease active site.[31]

branched-chain isopropyl substituent resulted in a significant effect on potency. Sulfolane with a 2*S*,3*S* configuration (compound **67**) resulted in 2-fold loss in inhibitory potency compared to isomer **65**. On the other hand, the isomer with a 2*R*,3*R* configuration (compound **43**) was the most potent inhibitor in this series. Inhibitor **43** had an IC_{50} value of 3.5 nM, a greater than 5-fold potency enhancement compared to the corresponding *n*-propyl-derived isomer **66**. Furthermore, compound **43** exhibited an antiviral potency of 50 nM ($n = 7$), an impressive 16-fold improvement over compound **66**. Molecular modeling studies did not suggest any clear preferences for larger or smaller alkyl substituents in this region. To gain some insight into the molecular-binding properties, a modeled energy-minimized structure of **43** was created. On the basis of this modeling, one possible explanation for this results is that the size of the isopropyl group in inhibitor **43** is optimum to fill in the shallow hydrophobic cavity present in the S_2 region of the HIV-1 protease substrate binding site. Also, it appeared that the sulfolane oxygen *cis* to the isopropyl substituent is within hydrogen-bonding distance to Gly 48 (bonding distance 2.1 Å) present in the region (Figure 3). The actual contributions of the substituents of this novel ligand, however, should await a solution of the X-ray crystal structure of the protein–ligand complex of **43**.[35]

Consistent with molecular modeling, an octahydropyrindene derivative **34** was found to be an effective replacement of the P_1' decahydroisoquinoline derivative. Incorporation 3(*S*)-tetrahydrofuranylurethane as a P_2

Table 4. Inhibitory Potencies (HIV-2) of Selected Compounds

compd	IC_{50} (nM) (HIV-2)[35]	compd	IC_{50} (nM) (HIV-2)[35]
1	0.5	43	17.5
2	0.24	44	340
3	961	47	640 ± 180 (n = 2)

ligand into the octahydropyrindenecarboxamide containing a hydroxyethylamine isostere afforded a 2-fold potency enhancement (compound 44, IC_{50} 60 nM). Introduction of (3S)-sulfolane exhibited an impressive 6-fold potency-enhancing effect (compound 48, IC_{50} 11.3 nM). Although, octahydropyrindenecarboxamide as a P_1' ligand considerably improved the enzyme-inhibitory potencies for inhibitors 44 and 48, it has little effect on their antiviral potencies. Furthermore, incorporation of sulfolane ligand corresponding to compound 42 showed similar inhibitory potency enhancing effect (compound 42, IC_{50} 3.0 nM).

The inhibitory potency for HIV-2 protease[36] was evaluated for selected inhibitors in this series. As shown in Table 4 3(S)-tetrahydrofuranyl-derived inhibitor as P_2 ligand has an IC_{50} value of 961 nM. Incorporation of octahydropyrindenecarboxamide as the P_1' ligand resulted in nearly a 3-fold potency enhancement compared to compound 3. Inhibitor 47 with (3S)-sulfolane carbamate as the P_2 ligand exhibited an IC_{50} value of 640 nM, again a 1.5-fold improvement over 3(S)-tetrahydrofuranyl-derived inhibitor 3. Finally, inhibitor 43 with (2R)-3(R)-isopropylsulfolane displayed an IC_{50} value of 17.5 nM.

Conclusion

In conclusion, replacement of P_3 2-quinolinoyl and P_2 asparagine ligands of the present clinical candidate 1 (Ro 31-8959) with urethanes of *cis*-2-alkyl-3-hydroxysulfolanes as the P_2 ligands resulted in a novel series of HIV protease inhibitors. These ligands were prepared in optically pure form utilizing Sharpless epoxidation followed by Payne rearrangement of the resulting epoxide as the key steps. Of particular interest, thus far (2R)-3(R)-isopropylsulfolane is the optimum ligand which led to the discovery of a potent HIV protease inhibitor 43 (HIV-1, IC_{50} 3.5 nM; for HIV-2, IC_{50} 17.5 nM). More importantly, the inhibitor 43 has displayed (CIC_{95} 50 ± 14 nM) *in vitro* antiviral potency comparable to inhibitor 1 (CIC_{95} 22 ± 7 nM). Furthermore, it has been demonstrated that the octahydropyrindenecarboxamide 34 is an effective replacement of the P_1' decahydroisoquinolinecarboxamide. Incorporation of this ligand resulted in inhibitors with improved enzyme inhibitory potencies. The present work provides a basis for the design of further ligand with improved enzyme affinity and antiviral potency. Investigations are currently in progress.

Experimental Section

All melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton magnetic resonance spectra were recorded on a Varian XL-300 spectrometer using TMS as internal standard. Significant ^1H NMR data for representative compounds are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constant(s) in hertz. FAB mass spectra were recorded on a VG Model 7070 mass spectrometer, and relevant data are tabulated as m/z. Elemental analyses were performed by the analytical department, Merck Research Laboratories, West Point, PA, and were within ±0.4% of the theoretical values. Anhydrous solvents were obtained as follows: methylene chloride, distillation from P_4O_{10}; tetrahydrofuran, distillation from sodium/benzophenone; dimethylformamide and pyridine, distillation from CaH_2. All other solvents were HPLC grade. The abbreviations DME, DMF, THF, HOBT, and EDC refer to 1,2-dimethoxyethane, *N*,*N*-dimethylformamide, tetrahydrofuran, 1-hydroxybenzotriazole hydrate, and 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride. Column chromatography was performed with E. Merck 240–400-mesh silica gel under a low pressure of 5–10 psi. Thin-layer chromatography (TLC) was carried out with E. Merck silica gel 60 F-254 plates.

2(*S*)-(Tetrahydropyranyloxy)-1,4-bis((methylsulfonyl)-oxy)butane (5). To a solution of dimethyl malate (30 g, 190 mmol) and dihydropyran (51 mL, 560 mmol) in anhydrous ethyl ether (500 mL) at 24 °C was added *p*-TsOH (0.3 g). The resulting solution was stirred for 12 h. After this period, the reaction was quenched with saturated aqueous $NaHCO_3$ (200 mL). The layers were separated, and the organic layer was washed with brine (200 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure afforded the corresponding protected diester which was distilled under reduced pressure to give 36 g (78% yield) of the protected dimethyl malate derivative as a colorless oil.

To a suspension of LAH (8.7 g, 230 mmol) in anhydrous ethyl ether (150 mL) at 0 °C was added a solution of above protected diester (22.5 g, 91 mmol) in ether (30 mL) dropwise over a period of 15 min. The resulting mixture was stirred at 24 °C for 12 h and then heated, at reflux for 1 h. The mixture was cooled to 0 °C, and then water (7 mL) and 20% aqueous NaOH (7 mL) followed by water (15 mL) were added carefully. The resulting mixture was diluted with THF (100 mL), stirred for 1 h at 24 °C, and filtered through Celite. The filtercake was washed thoroughly with THF, and the combined filtrates were concentrated under reduced pressure to give 15.5 g of diol as a clear colorless oil.

The above diol (15.0 g, 79 mmol) was dissolved in dry methylene chloride (75 mL), triethylamine (37 mL) was added, and the resulting solution was cooled to −10 °C. Methanesulfonyl chloride (15.3 mL, 200 mmol) was added dropwise over 10 min. The resulting mixture was then stirred at −10 °C to 24 °C for 12 h. After this period, the solvent was evaporated under reduced pressure, and the residue was partitioned between ethyl acetate (250 mL) and saturated aqueous $NaHCO_3$ (150 mL). The layers were separated, and the organic layer was washed with water (150 mL) and brine and then dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure afforded 12 g of the title compound as a brown oil which was used without further purification.

3(*S*)-(Tetrahydropyranyloxy)tetrahydrothiophene (6). To a stirred solution of bis-mesylate 5 (12 g, 33 mmol) in dry DMF (250 mL) was added solid lithium sulfide (8 g, 165 mmol), and the resulting mixture was heated at 60 °C for 6 h. After this period, the mixture was cooled to 0 °C, and ether (400 mL) followed by water (400 mL) was added. The layers were separated, and the aqueous layer was extracted with ether (100 mL). The combined organic layers were washed with water (150 mL) and brine and then dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent gave a residue which was chromatographed over silica gel to afford 4.2 g of the title compound as a yellow oil.

3(*S*)-Hydroxytetrahydrothiophene (7). A solution of 3(S)-(tetrahydropyranyloxy)tetrahydrothiophene (6) (4.2 g, 24 mmol) and *p*-TsOH, monohydrate (0.10 g) in methanol (25 mL) was stirred for 12 h. After this period, saturated aqueous $NaHCO_3$ (10 mL) was added, and stirring was continued for 30 min. The resulting mixture was then evaporated to give a residue which was partitioned between ethyl acetate (100 mL) and water (10 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 × 20 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure gave a residue which was purified by silica gel chromatography (1:1 ethyl acetate/hexane) to afford 2.2 g (88% yield) of 3(S)-hydroxytetrahydrothiophene 7 as a colorless oil: ^1H NMR ($CDCl_3$) δ 4.6 (m, 1 H), 2.8–3.0 (m, 3 H), 2.1–2.2 (m, 1 H), 1.8–1.9 (m, 2 H).

Diethyl 2(*S*)-Hydroxy-3(*R*)-methylsuccinate (9). To a solution of diisopropylamine (3.1 mL, 0.022 mol) in THF (15 mL) at 0 °C was added a solution of 1.6 M *n*-BuLi in hexanes

(12.5 mL) dropwise, keeping the internal temperature below 6 °C. After 15 min at 0 °C the mixture was allowed to warm to 18 °C over 15 min and then cooled to −78 °C. A solution of diethyl D-malate (1.9 g, 0.01 mol) in THF (10 mL) was added dropwise, keeping the internal temperature below −66 °C. After 1 h at −78 °C, neat methyl iodide (1.3 mL, 0.02 mol) was added to the yellow enolate suspension. After stirring at −78 °C for 30 min, the reaction mixture was placed in a 0 °C freezer for 12 h and then quenched with 10% citric acid (15 mL) and water (25 mL). The mixture was extracted with ethyl acetate (2×), and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oily residue was chromatographed over silica gel (50% EtOAc/hexane) to give 1.4 g (69% yield) of the desired methylated diethyl malate as a 6:1 mixture of diastereomers.

2(*R*)-Methyl-3-(*S*)-(tetrahydropyranyloxy)-1,4-dimesylbutane (10). To a solution of diethyl malate (1.3 g, 6.4 mmol) and dihydropyran (1.7 mL, 20 mmol) in anhydrous ethyl ether (50 mL) at 24 °C was added *p*-TsOH (0.1 g). The resulting solution was stirred for 12 h. After this period, the reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL). The layers were separated, and the organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure afforded the corresponding protected diester which was distilled under reduced pressure to give 1.7 g (91% yield) of a protected diethyl malate derivative as a colorless oil.

To a suspension of LAH (0.56 g, 15 mmol) in anhydrous ethyl ether (15 mL) at 0 °C was added a solution of the above protected diester (1.7 g, 5.9 mmol) in ether (10 mL) dropwise over a period of 15 min. The resulting mixture was stirred at 24 °C for 12 h and then heated at reflux for 1 h. The mixture was cooled to 0 °C and then water (0.6 mL) and 20% aqueous NaOH (0.6 mL) followed by water (1.2 mL) were added carefully. The resulting mixture was diluted with THF (10 mL), stirred for 1 h at 24 °C, and filtered through Celite. The filtercake was washed thoroughly with THF, and the combined filtrates were concentrated under reduced pressure to give 1.1 g of diol as a clear colorless oil.

The above diol (1.1 g, 5.9 mmol) was dissolved in dry methylene chloride (15 mL), triethylamine (4 mL) was added, and the resulting solution was cooled to −10 °C. Methanesulfonyl chloride (1.14 mL, 14.7 mmol) was added dropwise over 10 min. The resulting mixture was then stirred at −10 °C to 24 °C for 12 h. After this period, the solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate (50 mL) and saturated aqueous $NaHCO_3$ (25 mL). The layers were separated, and the organic layer was washed with water (15 mL) and brine and then dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure afforded 2 g of the title compound as a brown oil which was used directly without further purification.

3(*S*)-Hydroxy-4(*R*)-methyltetrahydrothiophene (11). To a stirred solution of bis-mesylate **10** (2 g, 5.6 mmol) in dry DMF (30 mL) was added solid lithium sulfide (1.3 g, 28 mmol), and the resulting mixture was heated at 60 °C for 6 h. After this period, the mixture was cooled to 0 °C, and ether (80 mL) followed by water (80 mL) was added. The layers were separated, and the aqueous layer was extracted with ether (50 mL). The combined organic layers were washed with water (15 mL) and brine and then dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent gave a residue which was chromatographed over silica gel to afford 1.2 g of the protected tetrahydrothiophene derivative as a yellow oil.

A solution of 3(*S*)-(tetrahydropyranyloxy)tetrahydrothiophene (1.2 g) and *p*-TsOH, monohydrate (0.10 g) in methanol (10 mL) was stirred for 12 h. After this period, saturated aqueous $NaHCO_3$ (5 mL) was added, and stirring was continued for 30 min. The resulting mixture was then evaporated to give a residue which was partitioned between ethyl acetate (50 mL) and water (10 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 × 20 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure gave a residue which was purified by silica gel chromatography (1:3 ethyl acetate/hexane) to afford 0.3 g of 3(*S*)-hydroxytetrahydrothiophene 11 (45% yield) as a colorless oil: $[\alpha]^{25}D$ −11.5° (*c* = 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.3 (m, 1H), 3.1 (m, 1H), 2.9 (m, 2H), 2.6 (m, 1H), 2.2 (m, 1H), 1.2 (d, *J* = 7.1 Hz, 3H).

Ethyl 3-[(Ethoxycarbonyl)methyl]butyrate (13). To a stirred solution of $HSCH_2CO_2Et$ (2.97 g, 25 mmol) in ethanol (5 mL) at −30 °C was added the bromide **12** (4.8 g, 25 mmol) in ethanol (5 mL) dropwise. After the mixture was stirred for 3 h at 0 °C, the solvents were removed under reduced pressure. The resulting residue was partitioned between ethyl acetate and saturated NH_4Cl. The layers were separated, and the aqueous layer was extracted with EtOAc (2×). The combined organic layers were dried over $MgSO_4$. Filtration and concentration of the solvents gave 5.08 g of the crude mixture of esters as an oil.

4,5-Dihydro-5-methylthiophen-3(2*H*)-one (14). Treatment of the above diester **13** with NaOEt (10 mL, 21% in EtOH) in toluene (20 mL) followed by refluxing of the resulting mixture for 4 h afforded the corresponding Dieckman cyclization product. The mixture was cooled to room temperature, and 1 N HCl was added. The resulting mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$. Filtration and concentration of the solvents gave 4.5 g of an oil which was taken up in MeOH (25 mL) and concentrated HCl (17 mL). After refluxing for 4 h, the mixture was cooled to room temperature and neutralized with 1 N NaOH and extracted thoroughly with CH_2Cl_2. The combined extracts were dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvents under reduced pressure provided the crude ketone 14 (1.7 g) as an oil: ^1H NMR ($CDCl_3$) δ 3.5 (m, 1H), 3.3 (s, 2H), 2.8 (m, 1H), 2.3 (m, 1H), 1.4 (d, *J* = 6.9 Hz, 3H).

***cis*-Tetrahydro-5-methylthiophene-3-ol (15).** To a solution of the above ketone (1.7 g, 15 mmol) in CH_2Cl_2 (30 mL) at −78 °C was added 1.0 M DIBAL in hexanes (22 mL) dropwise. After 30 min at −78 °C, the mixture was allowed to warm to 24 °C and quenched with 1 N HCl until all salts dissolved. The resulting mixture (3:1) was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Chomatography of the resulting oil over silica gel (25% EtOAc/hexane) afforded the desired alcohol 15: ^1H NMR ($CDCl_3$) δ 4.5 (m, 1H), 3.5 (m, 1H), 3.1 (m, 1H), 2.9 (m, 1H), 2.3 (m, 1H), 1.7 (m, 1H), 1.4 (d, *J* = 7.0 Hz, 3H).

***trans*-4-Methyl-2-penten-1-ol (17).** To a stirred suspension of NaH (60% NaH, 11 g; washed with 200 mL of hexane) in toluene (200 mL) at 24 °C was added triethyl phosphonoacetate (50 g, 223 mmol) dropwise via an addition funnel over a period of 10 min. The resulting mixture was stirred for 30 min and then cooled to 20 °C. A solution of isobuteraldehyde (16 g, 220 mmol) in toluene (70 mL) was added dropwise, keeping the internal temperature between 24 and 26 °C throughout the addition (20 min). A thick precipitate formed, and the mixture was allowed to stand for 10 min. After this period, the reaction was carefully quenched with water (500 mL) and the layers were separated. The aqueous layer was extracted with ether (100 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure afforded crude unsaturated ester which was distilled (bp 64–70 °C, 10–15 mmHg) to give 21 g (64% yield) of unsaturated ester as an oil.

To a solution of above ester (21 g, 150 mmol) in dry CH_2Cl_2 (200 mL) at −78 °C under nitrogen was added dropwise via an addition funnel a solution of 1.0 M DIBAL in hexane (460 mL, 460 mmol), keeping the internal temperature below −72 °C. The resulting mixture was then stirred for 2 h at −78 °C. After this period, the reaction was quenched with glacial acetic acid (150 mL) followed by 10% aqueous citric acid (500 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic layers were carefully washed with saturated aqueous $NaHCO_3$ until the aqueous wash was basic. The organic layer was then dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure afforded crude allylic alcohol which was distilled (bp 60 °C, 20 mmHg) to give 13 g of allyl alcohol 17 as an oil: ^1H NMR ($CDCl_3$), δ 5.6 (m, 2 H), 4.1 (m, 2 H), 2.3 (m, 1 H), 1.0 (d, *J* = 7.0 Hz, 6H).

(2*S*,3*S*)-3-(1-Methylethyl)oxiranemethanol (18). To a stirred solution of titanium isopropoxide (1.39 mL, 4.8 mmol) and diethyl L-tartrate (1.05 mL, 6.1 mmol) in dry CH_2Cl_2 (300 mL) were added powdered sieves (6 g), and the resulting mixture was cooled to −30 °C. To this mixture was added a solution of

3 M *tert*-butyl hydroperoxide in trimethylpentane (70 mL, 210 mmol), and the resulting mixture was stirred for 25 min at −30 °C to −20 °C. Then, alcohol **17** (10 g, 100 mmol) in CH_2Cl_2 (40 mL) was added dropwise, keeping internal temperature at −20 °C. The mixture was allowed to stand at −20 °C for 48 h and then warmed to 0 °C. Water (40 mL) was added, the mixture was stirred to 24 °C for 30 min, a solution of 30% NaOH (w/v) in saturated brine (6 mL) was added, and stirring was continued for 1 h. The layers were separated, and the organic layer was dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent gave a residue which was chromatographed over silica gel (50% EtOAc/hexane) to afford 7.5 g (65% yield) of the title epoxide as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.9 (dd, J = 2, 10.5 Hz, 1 H), 3.6 (dd, J = 2.2, 10.4 Hz, 1 H), 3.0 (m, 1 H), 2.78 (dd, J = 2.45, 4.39 Hz, 1 H), 1.75 (br s, 1 H), 1.6 (m, 1 H), 1.0 (d, J = 7.1 Hz, 3 H), 0.95 (d, J = 7.1 Hz, 3 H).

4(*S*)-(1-Methylethyl)-3(*R*)-hydroxy-γ-butyrolactone (19). To a stirred solution of epoxide **18** (6.4 g, 55 mmol) in ethanol (60 mL) and water (90 mL) was added granulated NaCN (9.5 g, 190 mmol), and the resulting solution was heated to reflux for 12 h. After the solution was cooled to 24 °C, the ethanol was removed under reduced pressure and the remaining aqueous solution was washed with ether (50 mL). The layers were separated, and the aqueous layer was carefully acidified with concentrated HCl at 0 °C and concentrated. The remaining residue was taken up in CH_2Cl_2 and dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent gave a residue which was chromatographed over silica gel (50% EtOAc/hexane) to afford 5.2 g (66% yield) of lactone as a clear, colorless oil: IR (neat) 3426 (br), 1767 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.4 (m, 1 H), 4.1 (m, 1 H), 2.8–2.9 (dd, J = 7.19, 10.98 Hz, 1 H), 2.5–2.6 (dd, J = 4.0, 14.2 Hz, 1H), 1.8–1.9 (m, 1H), 1.0 (m, 6 H); MS (70 eV) m/z 145 (m^+ + H).

3(*R*)-[(Methoxymethyl)oxy]-4(*S*)-(1-methylethyl)-1,4-bis-[(methylsulfonyl)oxy]butane (20). To a stirred solution of above lactone **19** (5.0 g, 34.7 mmol) in dry CH_2Cl_2 (100 mL) were added diisopropylethylamine (35 mL, 200 mmol) and (chloromethoxy)methyl ether (10.5 mL, 140 mmol) followed by 4-(dimethylamino)pyridine (100 mg). The resulting mixture was stirred for 12 h. After this period, the solvents were removed under reduced pressure and the residue was partitioned between ethyl acetate (200 mL) and 10% aqueous citric acid (200 mL). The layers were separated, and the organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4. Filtration and concentration under reduced pressure afforded a residue which was chromatographed over silica gel (50% EtOAc/hexane) to give 2.9 g (45% yield) of protected lactone as a colorless oil.

To a suspension of LAH (1.3 g, 34 mmol) in anhydrous ethyl ether (75 mL) at 0 °C under nitrogen was added dropwise a solution of above protected lactone (2.9 g, 15.4 mmol) in ether (15 mL) for 10 min. The resulting mixture was heated to reflux for 2 h. After this period, the mixture was cooled to 0 °C, and water (13 mL) followed by 20% aqueous NaOH (1.3 mL) and then water (4 mL) were added carefully. The mixture was stirred at 24 °C for 30 min, THF (25 mL) was added, and the resulting mixture was continued to stir for another 30 min. The mixture was then filtered through Celite, and the filtercake was washed thoroughly with a mixture of THF and EtOAc. The filtrate was evaporated under reduced pressure to afford 2.1 g of the corresponding diol as a colorless oil.

To a stirred solution of above diol (1.5 g, 7.8 mmol) and triethylamine (6.5 mL, 47 mmol) in dry methylene chloride (15 mL) at −40 °C was added methanesulfonyl chloride (1.8 mL, 23 mmol) dropwise for a period of 10 min. The resulting mixture was stirred at −40 to 24 °C for 12 h. The mixture was then concentrated under reduced pressure and the residue was partitioned between ethyl acetate (100 mL) and saturated aqueous $NaHCO_3$ (100 mL). The layers were separated, and the organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure afforded 3.6 g of the title compound as a brown oil.

3(*R*)-[(Methoxymethyl)oxy]-2(*R*)-(1-methylethyl)tetrahydrothiophene (21). To a stirred solution of bis-mesylate **20** (3.6 g) in dry DMF (40 mL) was added lithium sulfide (2.3 g, 50 mmol), and the resulting mixture was heated at 60 °C for 6 h. After this period, the mixture was cooled to 0 °C, and ether (100 mL) followed by water (100 mL) was added. The layers were separated, and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were washed with brine (75 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure afforded a mixture of products which were separated by chromatography over silica gel (5% EtOAc/hexane) to afford 0.98 g (50% yield) of the title tetrahydrothiophene derivative **21** as a colorless oil [^{1}H NMR ($CDCl_3$) δ 4.75 (d, J = 7.1 Hz, 1 H), 4.67 (d, J = 7.08 Hz, 1 H), 4.29 (m, 1 H), 3.4 (s, 3 H), 3.0–3.1 (m, 2 H), 2.9 (m, 1 H), 2.4 (m, 1 H), 2.15 (m, 1 H), 1.8 (m, 1 H), 1.0 (m, 6 H)] and thietane byproduct **22** (240 mg) as colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.65 (m, 2 H), 4.1 (m, 1 H), 3.35 (s, 3 H), 3.0 (m, 1 H), 2.8 (m, 1 H), 2.65 (m, 1 H), 2.1 (m, 1 H), 1.8 (m, 2 H), 0.9 (d, J = 7.1 Hz, 3 H), 0.88 (d, J = 6.9 Hz, 3 H).

2(*R*)-(1-Methylethyl)-3(*R*)-hydroxytetrahydrothiophene (23). To a stirred solution of MOM ether **21** (600 mg, 3.2 mmol) in dry methylene chloride (25 mL) at 0 °C under nitrogen was added thiophenol (0.483 mL, 4.7 mmol) followed by boron trifluoride etherate (0.466 mL, 3.8 mmol). The resulting mixture was continued to stir at 0 °C for 30 min and then allowed to warm to 24 °C for 1 h. After this period, saturated aqueous $NaHCO_3$ (10 mL) was added, and stirring was continued for another 30 min. The layers were separated, and the aqueous layer was extracted with methylene chloride (25 mL). The combined organic layers were washed with 10% aqueous NaOH (10 mL) and brine (10 mL) and then dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure gave a residue which was purified by silica gel chromatography (1:3 ethyl acetate/hexane) to afford 0.45 g (96% yield) of the title compound **23** as a white semisolid: $[\alpha]^{25}_D$ +26.8° (c = 2.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.37 (m, 1 H), 2.9–3.1 (m, 3 H), 2.2–2.3 (M, 1 H), 1.8–2.0 (m, 2 H), 1.1 (d, J = 7.1 Hz, 3 H), 1.0 (d, J = 7.1 Hz, 3 H).

Ethyl 2-[[2-(Ethoxycarbonyl)ethyl]thio]-3-methylbutyrate (26). Commercial (±)-2-bromo-3-methylbutyric acid (25 g, 138 mmol) was dissolved in ethanol (50 mL) and benzene (100 mL) at room temperature. Sulfuric acid (0.05 mL) was added, and the resulting mixture was heated to a reflux with a Dean–Stark apparatus for 2 days. After cooling to 24 °C, the mixture was washed successively with water (50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL). Evaporation of the solvents gave a residue which was distilled under reduced pressure to yield 23 g (80% yield) of bromo ester as a liquid.

To a stirred solution of ethyl 3-mercaptopropionate (3.2 mL, 24.8 mmol) in ethanol (5 mL) was added NaOEt (14 mL, 21% in EtOH). The resulting mixture was cooled to −30 °C, and the above bromo ester (5 g, 23.9 mmol) in ethanol (2 mL) was added dropwise. After the mixture was stirred for 3 h, the solvents were removed under reduced pressure. The resulting residue was partitioned between ethyl acetate and saturated NH_4Cl. The layers were separated, and the aqueous layer was extracted with EtOAc (2×). The combined organic layers were dried over Na_2SO_4. Filtration and concentration of the solvents gave 6.2 g of the crude mixture of esters as an oil.

***cis*-2-(1-Methylethyl)-3-hydroxytetrahydrothiophene (28).** Treatment of the above diester with NaOEt (2.5 g) in toluene (20 mL) followed by refluxing of the resulting mixture for 6 h afforded the corresponding Dieckman cyclization product. The mixture was cooled to room temperature, and 1 N HCl (70 mL) was added. The resulting mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$. Filtration and concentration of the solvents gave 6.2 g of an oil which was taken up in 10% aqueous H_2SO_4 (75 mL). After 12 h at reflux, the mixture was cooled, neutralized with 40% NaOH, and extracted with ether. Drying (Na_2SO_4) and evaporation of the solvents under reduced pressure provided the crude Ketone (5 g) as an oil.

To a solution of the above ketone (5 g) in EtOH (15 mL) at 0 °C was added solid $NaBH_4$ (1.32 g) in three portions. Aftr 2 h at 0 °C, the mixture was quenched with 10% citric acid until all salts dissolved. The solvents were concentrated to dryness and extracted with EtOAc (3 × 50 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Chromatography of the resulting oil over silica gel (25% EtOAc/hexane) afforded 2.5 g (74% yield) of the desired alcohol.

1-Methyl (1*S*,2*R*)-Cyclopentanedicarboxylic Acid Monoester (30). A mixture of 40 g (290 mmol) of *cis*-cyclopentane-1,2-dicarboxylic acid anhydride and 300 mL of methanol was refluxed for 3 h, concentrated, and dried under vacuum. The resulting monoester, 50 g, was dissolved in 100 mL of ethyl acetate, and a solution of 50 g of (+)-ephedrine hemihydrate in 250 mL of hot ethyl acetate was added. On cooling and standing for 24 h, 40 g of white crystals was formed. The resolved monoester was liberated by dissolving the salt in 100 mL of 2 N sulfuric acid and extracting with 3 × 300 mL of ethyl acetate. After drying, 20.5 g (44% yield) of resolved monoester was obtained: $[\alpha]^{25}_D$ +5° (*c* = 1.4, MeOH); ^{1}H NMR ($CDCl_3$) δ 3.7 (s, 3 H), 3.05 (m, 2 H), 1.9–2.1 (m, 4 H), 1.61–1.85 (m, 2 H).

Methyl (1*S*,2*R*)-2-Formylcyclopentanecarboxylate (31). A solution of 1-methyl (1*S*,2*R*)-cyclopentanedicarboxylic acid monoester, 24 g (150 mmol) and 30 mL of oxalyl chloride in 1.3 L of toluene was stirred for 28 h under a stream of nitrogen to remove HCl. Concentration of the resulting solution gave 23 g of acid chloride as on oil. A solution of the acid chloride in 750 mL of dry tetrahydrofuran containing 15 mL of redistilled 2,6-lutidine and 3 g of 10% palladium on carbon was shaken under 50 psi of hydrogen for 18 h, filtered, and concentrated under reduced pressure at 25 °C. The residue was diluted with 300 mL of ethyl acetate, washed with 30 mL of 1 N hydrochloric acid and 30 mL of saturated sodium bicarbonate, and dried ($MgSO_4$). Removal of solvents under reduced pressure gave 20 g of pure *cis*-aldehyde, homogeneous by HPLC and TLC (10% EtOAc/hexanes development): $[\alpha]^{25}_D$ +60.7° (*c* = 1.57, MeOH); ^{1}H NMR ($CDCl_3$) δ 9.7 (br s, 1 H), 3.8 (s, 3 H), 3.05 (m, 2 H), 1.9–2.1 (m, 4 H), 1.6–1.8 (m, 2 H).

Methyl 2-Oxohexahydro-(4a*S*,7a*S*)-1*H*-pyrindene-3-carboxylate (32). To a stirred solution of 100 mL of commercial 1 M lithium bis(trimethylsilyl)amide in THF diluted in 200 mL of THF cooled to −40 °C was added a solution of 18 g of the benzylidene derivative of glycine methyl ester as a solution in 70 mL of THF while maintaining the temperature between −40 and −35 °C. After 30 min, a solution of 16 g (110 mmol) of methyl (1*S*,2*R*)-2-formylcyclopentanecarboxylate in 35 mL of THF was added over 15 min. After 45 min at −40 °C, the reaction was quenched with 30 mL of AcOH and 60 mL of MeOH. After concentration to near dryness, the residue was dissolved in 25 mL of AcOH and 175 mL of MeOH. The resulting mixture was aged for 7 days at 25 °C and then concentrated to dryness. Column chromatography using a gradient of 20–30% EtOAc/hexane gave 12 g (56% yield) of the methyl 1-oxohexahydro-(4a*S*,7a*S*)-1*H*-pyrindene-3-carboxylate. The earlier fractions contained 5 g of lactones which were converted into 2.6 g of additional product (68% overall yield) by retreatment with 20 mL of AcOH and 100 mL of MeOH: ^{1}H NMR ($CDCl_3$) δ 7.5 (br s, 1 H), 6.15 (s, 1 H), 3.8 (s, 3 H), 3.0 (m, 1 H), 2.8 (m, 1 H), 1.9–2.2 (m, 4 H), 1.5–1.8 (m, 2 H).

Methyl Octahydro-(3*S*,4a*S*,7a*S*)-1*H*-pyrindene-3-carboxylate (33). Hydrogenation of 12 g (61.5 mmol) of methyl 1-oxohexahydro-(4a*S*,7a*S*)-1*H*-pyrindene-3-carboxylate in 120 mL of dry THF with 1.1 g of 5% Pd/C under 50 psi of hydrogen on a shaker gave 12 g of product as a crystalline solid: mp 55–58 °C.

A solution of 3 g (15.2 mmol) of methyl 1-oxooctahydro-(3*S*,4a*S*,7a*S*)-1*H*-pyrindene-3-carboxylate in 50 mL of dry THF was cooled to 0 °C and treated dropwise with 3.2 mL of borane methyl sulfide complex, maintaining the temperature at 0–5 °C. Aftr being stirred for 3 h at 25 °C, the mixture was cooled and quenched by dropwise addition of 85 mL of 2 N HCl, maintaining the temperature between 0–5 °C. The mixture was allowed to warm to 15 °C and stand for 12 h in the refrigerator. The pH was adjusted to 10 with 5 N NaOH and the mixture extracted with 2 × 300 mL of ethyl acetate. The combined extracts gave, after drying ($MgSO_4$) and concentration under reduced pressure, 1.9 g (68% yield) of amino ester product as an oil: ^{1}H NMR ($CDCl_3$) δ 3.7 (s, 3 H), 3.65 (m, 1 H), 3.3 (m, 1 H), 3.2 (m, 1 H), 2.9 (m, 2 H), 2.1–2.3 (m, 2 H), 1.5–1.9 (m, 6 H).

***N*-*tert*-Butyloctahydro-(3*S*,4a*S*,7a*S*)-1*H*-pyrindene-3-carboxamide (34).** A solution of 12 mL of trimethylaluminum (2.0 m in toluene) and 2.6 mL of *tert*-butylamine in 10 mL of THF was warmed to 40–45 °C for 30 min. A solution of 1.2 g (6.6 mmol) of methyl octahydro-(3*S*,4a*S*,7a*S*)-1*H*-pyrindene-3-carboxylate in 10 mL of THF was added and the mixture aged at 25 °C for 24 h. The resulting mixture was added to 100 mL of ice-cold saturated sodium potassium tartrate and 100 mL of ethyl acetate. After the mixture was stirred vigorously for 1 h, the organic layer was separated, dried ($MgSO_4$), and concentrated to dryness. There was obtained 1.2 g of crude *tert*-butylamide which was essentially homogeneous by TLC: ^{1}H NMR ($CDCl_3$) δ 5.7 (br s, 1 H), 5.1 (br s, 1 H), 4.15 (m, 1 H), 3.2–3.55 (m, 2 H), 2.3 (m, 1 H), 1.95 (m, 3 H), 1.5–1.8 (m, 6 H), 1.3 (s, 9 H).

***N*-*tert*-Butyl-2-[2(*R*)-hydroxy-4-phenyl-3(*S*)-azidobutyl]-octahydro-(3*S*,4a*S*,7a*S*)-1*H*-pyrindene-3(*S*)-carboxamide (37).** A mixture of 3 g of *N*-*tert*-butyloctahydro-(3*S*,4a*S*,7a*S*)-1*H*-pyrindene-3-carboxamide and 4 g of 3(*S*)-azido-1,2(*R*)-epoxy-4-phenylbutane in 50 mL of 2-propanol was heated to 80 °C overnight and then concentrated to dryness under reduced pressure. Recrystallization from ethyl acetate–hexanes gave 2.16 g (39% yield) of product: mp 91–93 °C; ^{1}H NMR ($CDCl_3$) δ 7.2–7.35 (m, 5 H), 6.45 (br s, 1 H), 3.6 (m, 2 H), 3.0 (m, 1 H), 2.6–2.9 (m, 6 H), 2.15 (m, 1 H), 2.0 (m, 1 H), 1.4–1.95 (m, 8 H), 1.3 (s, 9 H). Anal. ($C_{23}H_{35}N_5O_2$) C, H, N.

***N*-*tert*-Butyl-2-[2(*R*)-hydroxy-4-phenyl-3(*S*)-azidobutyl]-decahydro(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (38).** A mixture of 6.46 g (27 mmol) of *N*-*tert*-butyldecahydro-(4a*R*,-8a*S*)-isoquinoline-3(*S*)-carboxamide (**36**) ($[\alpha]^{23}_D$ −70 °C (*c* = 1.0, MeOH)) and 10.3 g (54.8 mmol) of 3(*S*)-azido-1,2(*R*)-epoxy-4-phenylbutane (**35**) in 200 mL of 2-propanol was heated to 80 °C overnight and then concentrated to dryness under reduced pressure. Recrystallization from ethyl acetate–hexanes gave 9.63 g (84% yield) of product: mp 149–50 °C. Anal. ($C_{24}H_{37}N_5O_2$) C, H, N.

***N*-*tert*-Butyloctahydro-2-[2(*R*)-hydroxy-4-phenyl-[[[3(*S*)-tetrahydrofuranyloxy]carbonyl]amino]butyl]-(3*S*,4a*S*,7a*S*)-1*H*-pyrindene-3-carboxamide (44).** A mixture of 0.10 g (24 mmol) of *N*-*tert*-butyl 2-[2(*R*)-hydroxy-4-phenyl-3(*S*)-azidobutyl]octahydro-(3*S*,4a*S*,7a*S*)-1*H*-pyrindene-3(*S*)-carboxamide, 0.066 g of 3(*S*)-tetrahydrofuranyl succinimidyl carbonate, 0.05 g (0.23 mmol) of 10% Pd/C, and 0.067 mL of Et_3N in 15 mL of THF was stirred under an atmosphere of hydrogen for 48 h. Removal of the catalyst by filtration, concentration under reduced pressure, and purification by preparative TLC, eluting with ethyl acetate, gave 0.10 g (85% yield) of product as a white solid: mp 95–96 °C; ^{1}H NMR ($CDCl_3$) δ 7.2–7.35 (m, 5 H), 6.65 (br s, 1 H), 5.15 (m, 1 H), 5.05 (m, 1 H), 3.7–3.9 (m, 6 H), 3.6 (m, 1 H), 2.95 (m, 2 H), 2.3–2.7 (m, 4 H), 2.15 (m, 1 H), 2.0 (m, 1 H), 1.4–1.95 (m, 10 H), 1.3 (s, 9 H). Anal. ($C_{28}H_{43}N_3O_5 \cdot 0.2CHCl_3$) C, H, N.

***N*-*tert*-Butyldecahydro-2-[2(*R*)-hydroxy-4-phenyl-3(*S*)-[[[[2′(*R*)-(1-methylethyl)-(3′*R*)-1′,1′-dioxotetrahydrothiophene-3′-yl]oxy]carbonyl]amino]butyl]-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (43).** To a stirred solution of 2(*R*)-isopropyl-3(*R*)-hydroxytetrahydrothiophene (**21**) (210 mg, 0.14 mmol) and di(2-pyridyl) carbonate (470 mg, 0.22 mmol) in dry methylene chloride (10 mL) was added triethylamine (0.30 mL, 0.22 mmol). The resulting mixture was stirred at 24 °C for 12 h. The mixture was then diluted with methylene chloride, washed with saturated aqueous $NaHCO_3$ (10 mL) and brine, and dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure gave a residue which was purified by silica gel chromatography (1:3 ethyl acetate/hexane) to afford 0.34 g (91% yield) of the mixed active carbonate **24** as an oil.

To a stirred solution of active carbonate **24** (340 mg, 1.27 mmol) in methylene chloride (30 mL) was added *cis*-*N*-butyldecahydro-2-[2(*R*)-hydroxy-4-phenyl-3(*S*)-aminobutyl]-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (**39**) (610 mg, 1.53), and the resulting mixture was stirred at 24 °C for 12 h. The mixture was then diluted with methylene chloride, and the resulting solution was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine and dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure gave a residue which was purified by silica gel chromatography (1:1 ethyl acetate/hexane) to afford 0.47 g (65% yield) of the compound **41** as a white solid: mp 106–8 °C.

To a stirred solution above urethane derivative **41** (470 mg, 0.82 mmol) and 4-methylmorpholine *N*-oxide (215 mg, 1.83 mmol) in a mixture of acetone (30 mL) and water (10 mL) at 0 °C was added a solution of osmium tetraoxide (2.5%) in 2-methyl-2-propanol (0.35 mL). The resulting mixture was stirred at 24 °C

for 12 h and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate (50 mL) and water (20 mL), and the layers were separated. The organic layer was then washed with brine and dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure gave a residue which was purified by silica gel chromatography (5:95 methanol/chloroform) to afford 0.46 g (92% yield) of the title compound **43** as a white solid: mp 124–26 °C; ^{1}H NMR ($CDCl_3$) δ 7.2–7.4 (m, 5 H), 5.8 (s, 1 H), 5.35 (d, J = 8 Hz, 1 H), 5.26 (br s, 1 H), 3.95 (m, 1 H), 3.83 (m, 1 H), 2.8–3.2 (m, 6 H), 2.5–2.65 (m, 4 H), 2.4 (m, 1 H), 2.2 (m, 1 H), 1.4–1.95 (m, 12 H), 1.3 (s, 9 H), 1.2 (d, J = 6.9 Hz, 3 H), 0.9 (d, J = 7.1 Hz, 3 H); MS (70 eV) m/z 606 (m^+ + H). Anal. ($C_{28}H_{43}N_3O_5 \cdot 0.2CHCl_3$) C, H, N.

***N-tert*-Butyldecahydro-2-[2(*R*)-hydroxy-4-phenyl-3(*S*)-[[[[(3*S*)-1,1-dioxotetrahydrothiophene-3-yl]oxy]carbonyl]-amino]butyl]-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (47).** To a stirred solution of 3(*S*)-hydroxytetrahydrothiophene (7) (150 mg, 1.4 mmol) and di(2-pyridyl) carbonate (470 mg, 2.2 mmol) in dry methylene chloride (10 mL) was added triethylamine (0.3 mL, 2.2 mmol). After being stirred for 12 h, the mixture was diluted with methylene chloride, washed with saturated aqueous $NaHCO_3$ (10 mL) and brine, and then dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure gave a residue which was purified by silica gel chromatography (1:3 ethyl acetate/hexane) to afford 0.3 g (93% yield) of the corresponding active pyridyl carbonate as an oil.

A solution of above pyridyl carbonate (300 mg, 1.3 mmol) and *cis-N-tert*-butyldecahydro-2-[2(*R*)-hydroxy-4-phenyl-3(*S*)-aminobutyl]-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (**39**) (400 mg, 1.0 mmol) in dry methylene chloride (30 mL) was stirred for 12 h. The mixture was diluted with methylene chloride, washed with saturated aqueous $NaHCO_3$ (10 mL) and brine, and dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure gave a residue which was purified by silica gel chromatography (1:1 ethyl acetate/hexane) to afford 0.35 g (66% yield) of the corresponding urethane derivative.

To a stirred solution of above urethane derivative (0.350 g, 0.65 mmol) and 4-methylmorpholine N-oxide (230 mg, 1.95 mmol) in acetone (30 mL) and water (10 mL) at 0 °C was added a solution of osmium tetraoxide (2.5%) in 2-methyl-2-propanol (0.35 mL). The resulting mixture was stirred at 24 °C for 12 h and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate (50 mL) and water (20 mL), and the layers were separated. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure gave a residue which was purified by silica gel chromatography (5:95 methanol/chloroform) to afford 0.325 g (89% yield) of *cis-N-tert*-butyldecahydro-2-[2(*R*)-hydroxy-4-phenyl-3(*S*)-[[[[(3*S*)-1,1-dioxotetrahydrothiophene-3-yl]oxy]carbonyl]amino]butyl]-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (**47**) as a white solid: mp 111–13 °C; ^{1}H NMR ($CDCl_3$) δ 7.2–7.4 (m, 5 H), 5.8 (s, 1 H), 5.7 (d, 1 H), 5.25 (m, 1 H), 3.95 (m, 1 H), 3.85 (m, 1 H), 2.8–3.1 (m, 9 H), 2.6 (m, 2 H), 2.4 (m, 3 H), 2.0 (m, 1 H), 1.4–1.8 (m, 10 H), 1.3 (s, 9 H); MS (70 eV) m/z 564 (m^+ + H). Anal. ($C_{29}H_{45}N_3O_6S \cdot 0.25CHCl_3$) C, H, N.

***N-tert*-Butyldecahydro-2-[2(*R*)-hydroxy-4-phenyl-3(*S*)-[[[[(3*R*)-1,1-dioxotetrahydrothiophene-3-yl]oxy]carbonyl]-amino]butyl]-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (49).** The corresponding 3(*R*)-hydroxytetrahydrothiophene was prepared starting from optically pure (3*R*)-dimethyl malate, via the procedure for compound **7**. From 3(*R*)-hydroxytetrahydrothiophene, using the procedures described above for **47**, was obtained a white solid: mp 99–101 °C; MS (70 eV) m/z 564 (m^+ + H). Anal. ($C_{29}H_{45}N_3O_6S \cdot 0.25CHCl_3$) C, H, N.

***N-tert*-Butyldecahydro-2-[2(*R*)-hydroxy-4-phenyl-3(*S*)-[[[[2′(*S*)-methyl-(3′*S*)-1′,1′-dioxotetrahydrothiophene-3′-yl]-oxy]carbonyl]amino]butyl]-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (56).** The corresponding 2(*S*)-methyl-3(*R*)-hydroxytetrahydrothiophene was prepared via the procedure for compound **23**. From 2(*S*)-methyl-3(*R*)-hydroxytetrahydrothiophene using the procedures described above for **47** was obtained a white solid: mp 104–06 °C; MS (70 eV) m/z 578 (m^+ + H). Anal. ($C_{30}H_{47}N_3O_6S \cdot 0.7H_2O$) C, H, N.

***N-tert*-Butyldecahydro-2-[2(*R*)-hydroxy-4-phenyl-3(*S*)-[[[[2′(*R*)-methyl-(3′*R*)-1′,1′-dioxotetrahydrothiophene-3′-yl]-oxy]carbonyl]amino]butyl]-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (58)**: mp 109–11 °C; MS (70 eV) m/z 578 (m^+ + H). Anal. ($C_{30}H_{47}N_3O_6S \cdot 1.0H_2O$) C, H, N.

***N-tert*-Butyldecahydro-2-[2(*R*)-hydroxy-4-phenyl-3(*S*)-[[[[4′(*R*)-methyl-(3′*S*)-1′,1′-dioxotetrahydrothiophene-3′-yl]-oxy]carbonyl]amino]butyl]-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (59).** From 4(*R*)-methyl-3(*S*)-hydroxytetrahydrothiophene (**11**) using the procedures described above for **47** was obtained a white solid: mp 111–13 °C; MS (70 eV) m/z 578 (m^+ + H). Anal. ($C_{30}H_{47}N_3O_6S \cdot 0.15CHCl_3$) C, H, N.

***N-tert*-Butyldecahydro-2-[2(*R*)-hydroxy-4-phenyl-3(*S*)-[[[[4′(*S*)-methyl-(3′*R*)-1′,1′-dioxotetrahydrothiophene-3′-yl]-oxy]carbonyl]amino]butyl]-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (60).** The corresponding 4(*S*)-methyl-3(*R*)-hydroxytetrahydrothiophene was prepared via the procedure for compound **11**. From 4(*S*)-methyl-3(*R*)-hydroxytetrahydrothiophene using the procedures described above for **47** was obtained a white solid: mp 99–01 °C; MS (70 eV) m/z 578 (m^+ + H). Anal. ($C_{30}H_{47}N_3O_6S \cdot 0.7H_2O$) C, H, N.

***N-tert*-Butyldecahydro-2-[2(*R*)-hydroxy-4-phenyl-3(*S*)-[[[[5′(*R*)-methyl-3′(*S*)-1′,1′-dioxotetrahydrothiophene-3′-yl]-oxy]carbonyl]amino]butyl]-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (61)**: mp 88–90 °C; MS (70 eV) m/z 578 (m^+ + H). Anal. ($C_{30}H_{47}N_3O_6S$) C, H, N.

***N-tert*-Butyldecahydro-2-[2(*R*)-hydroxy-4-phenyl-3(*S*)-[[[[5′(*S*)-methyl-(3′*R*)-1′,1′-dioxotetrahydrothiophene-3′-yl]-oxy]carbonyl]amino]butyl]-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (62)**: mp 109–11 °C; MS (70 eV) m/z 578 (m^+ + H). Anal. ($C_{30}H_{47}N_3O_6S \cdot 1.0H_2O$) C, H, N.

***N-tert*-Butyldecahydro-2-[2(*R*)-hydroxy-4-phenyl-3(*S*)-[[[[2′(*S*)-(1-methylethyl)-(3′*S*)-1′,1′-dioxotetrahydrothiophene-3′-yl]oxy]carbonyl]amino]butyl]-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (67).** The corresponding 2(*S*)-(1-methylethyl)-3(*R*)-hydroxytetrahydrothiophene was prepared via the procedure for compound **23**. From 2(*S*)-(1-methylethyl)-3(*R*)-hydroxytetrahydrothiophene using the procedures described above for **43** was obtained a white solid: mp 110–12 °C; MS (70 eV) m/z 606 (m^+ + H). Anal. ($C_{32}H_{51}N_3O_6S \cdot 0.15CHCl_3$) C, H, N.

***N-tert*-Butyldecahydro-2-[2(*R*)-hydroxy-4-phenyl-3(*S*)-[[[[2′(*S*)-(2-methylpropyl)-(3′*S*)-1′,1′-dioxotetrahydrothiophene-3′-yl]oxy]carbonyl]amino]butyl]-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (72)**: mp 106–108 °C; MS (70 eV) m/z 620 (M^+ + H). Anal. ($C_{33}H_{53}N_3O_6S$) C, H. N.

***N-tert*-Butyldecahydro-2-[2-(*R*)-hydroxy-4-phenyl-3(*S*)-[[[[2′(*R*)-(2-methylpropyl)-(3′*R*)-1′,1′-dioxotetrahydrothiophene-3′-yl]oxy]carbonyl]amino]butyl]-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (73)**: mp 196–98 °C; MS (70 eV) m/z 620 (m^+ + H). Anal. ($C_{33}H_{53}N_3O_6S$) C, H, N.

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(30) A preliminary model of the X-ray crystal structure of the inhibitor **3** complexed with the HIV-1 protease at 2.5-Å resolution has been provided by Dr. Paula Fitzgerald, Department of Biophysical Chemistry. The final coordinates of the fully refined structure will be published in due course.

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(33) Unless otherwise indicated, all determinations were $n = 1$.

(34) When administered in dogs following an oral dose of 10 mg/kg dissolved in 10% citric acid solution, for compound **3** average (2 dogs) C_{max} was 3380 nM (after 30 min) compared to 6600 nM (after 40 min) for compound **47**. More importantly, compound **3** cleared much faster than compound **47**. After 3 h, the plasma level for compound **3** was slightly above 100 nM, whereas compound **47** maintained plasma levels above 100 nM even after 6 h. Oral bioavailability for compounds **3**, **43**, and **47** were measured to be 20%, 20%, and 15%, respectively. Personal communication, Dr. Juinn Lin, Department of Animal Pharmacology, Merck Research Laboratories, West Point, PA. Details of these experiments will be published elsewhere.

(35) Examination of a preliminary X-ray crystal structure model of an enzyme–inhibitor complex of compound **43** bound to HIV-1 protease revealed that the *cis*-sulfone oxygen is within hydrogen-bonding distance to the Asp 29 (distance 2.1 Å) and Asp 30 NH (distance 3.9 Å). Personal communication, Dr. Paula Fitzgerald, Department Biophysical Chemistry, Merck Research Laboratories, Rahway, NJ. Details of this experiment will be published in due course.

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