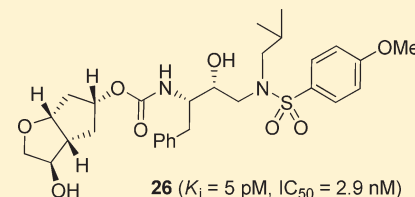


Design of HIV-1 Protease Inhibitors with C3-Substituted Hexahydrocyclopentafuranyl Urethanes as P2-Ligands: Synthesis, Biological Evaluation, and Protein–Ligand X-ray Crystal Structure[†]Arun K. Ghosh,^{*,‡} Bruno D. Chapsal,[‡] Garth L. Parham,[‡] Melinda Steffey,[‡] Johnson Agniswamy,[§] Yuan-Fang Wang,[§] Masayuki Amano,^{||} Irene T. Weber,[§] and Hiroaki Mitsuya^{||,⊥}[‡]Departments of Chemistry and Medicinal Chemistry, Purdue University, West Lafayette, Indiana 47907, United States[§]Department of Biology, Molecular Basis of Disease, Georgia State University, Atlanta, Georgia 30303, United States^{||}Departments of Hematology and Infectious Diseases, Kumamoto University Graduate School of Medical and Pharmaceutical Sciences, Kumamoto 860-8556, Japan[⊥]Experimental Retrovirology Section, HIV and AIDS Malignancy Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, United States

S Supporting Information

ABSTRACT: We report the design, synthesis, biological evaluation, and the X-ray crystal structure of a novel inhibitor bound to the HIV-1 protease. Various C3-functionalized cyclopentanyltetrahydrofurans (Cp-THF) were designed to interact with the flap Gly48 carbonyl or amide NH in the S2-subsite of the HIV-1 protease. We investigated the potential of those functionalized ligands in combination with hydroxyethylsulfonamide isosteres. Inhibitor **26** containing a 3-(*R*)-hydroxyl group on the Cp-THF core displayed the most potent enzyme inhibitory and antiviral activity. Our studies revealed a preference for the 3-(*R*)-configuration over the corresponding 3-(*S*)-derivative. Inhibitor **26** exhibited potent activity against a panel of multidrug-resistant HIV-1 variants. A high resolution X-ray structure of **26**-bound HIV-1 protease revealed important molecular insight into the ligand-binding site interactions.



■ INTRODUCTION

Human immunodeficiency virus 1 (HIV-1) protease inhibitors are critical components of antiretroviral therapies.^{1,2} However, the emergence of drug resistance has raised serious questions about long-term treatment options.^{3,4} Our structure-based design of inhibitors targeting the protein backbone has led to the discovery of a variety of novel HIV-1 protease inhibitors (PIs) with broad-spectrum activity against multidrug-resistant HIV-1 variants.^{5,6} One of these inhibitors, darunavir (**1**, Figure 1), was approved by the FDA for the treatment of HIV/AIDS patients.^{7–9} In an effort to address drug resistance, our inhibitor design strategy focused on maximizing active site interactions with the protease, particularly by promoting extensive hydrogen bonding interactions with backbone atoms throughout the active site.^{5,6}

We have recently reported a number of potent inhibitors incorporating a stereochemically defined (3*aS*,5*R*,6*aR*)-hexahydro-2*H*-cyclopenta[*b*]furan-5-yl (Cp-THF) as the P2-ligand with a modified hydroxyethylsulfonamide isostere as in inhibitor **3**.¹⁰ The X-ray crystal structure of **3**-bound HIV-1 protease revealed the formation of an extensive hydrogen-bonding network between the inhibitor and the active site. On the basis of this molecular insight, we subsequently incorporated a stereochemically defined lactam at the P1'-position to further enhance backbone interactions.¹¹ Interestingly, the resulting inhibitor **4**

retained full potency against a range of multidrug-resistant HIV-1 variants.¹² The X-ray structural studies of **4**-bound HIV-1 protease evidenced enhanced backbone interactions with the Gly27' carbonyl at the S1'-subsite. The Cp-THF ligand appears to fit within the S2-subsite, and the cyclic ether oxygen is involved in a close hydrogen bonding interaction with the backbone NH of Asp29 (2.8 Å). On the basis of this molecular insight, we have now investigated structural modifications of the Cp-THF ligand to further optimize ligand binding, particularly hydrogen bonding ability, in the S2-subsite. The X-ray structure of **3**-bound HIV-1 protease indicated that the C3 methylene of the Cp-THF is in proximity to the protease flap region. In fact, the X-ray data suggested a weak C3–H···O interaction with the Gly48 backbone carbonyl group.¹⁰ We therefore envisioned that introduction of a polar substituent at the C3 position may lead to additional interactions of the Cp-THF ligand with the protease flap residues. Furthermore, an inhibitor that makes tight interactions with the protease flap region could conceivably delay its dissociation via opening of the flaps. Herein, we report the design, synthesis, and biological evaluation of a series of protease inhibitors that incorporate a stereochemically defined functionality at the C3 position of the Cp-THF ligand. Inhibitor **26**,

Received: May 20, 2011

Published: July 29, 2011

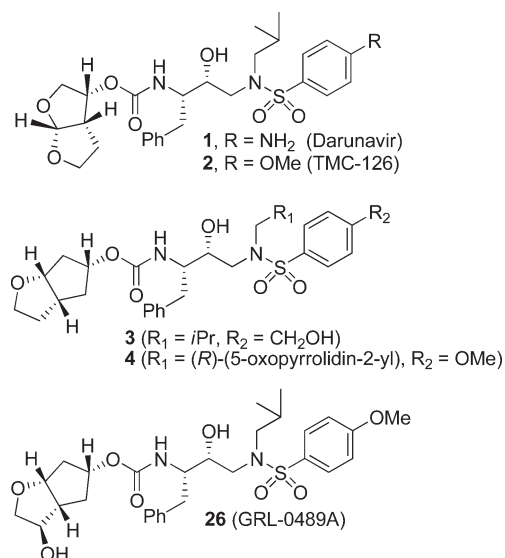
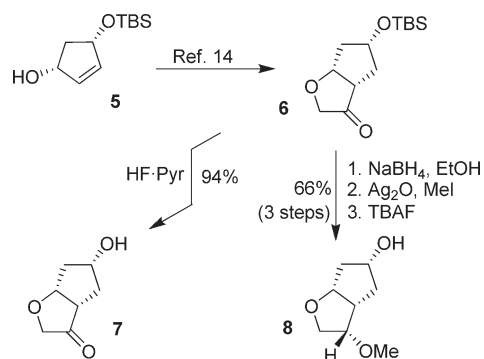


Figure 1. Structures of potent HIV-1 protease inhibitors 1–4 and 26.

Scheme 1. Syntheses of Optically Pure P2 Ligands 7 and 8



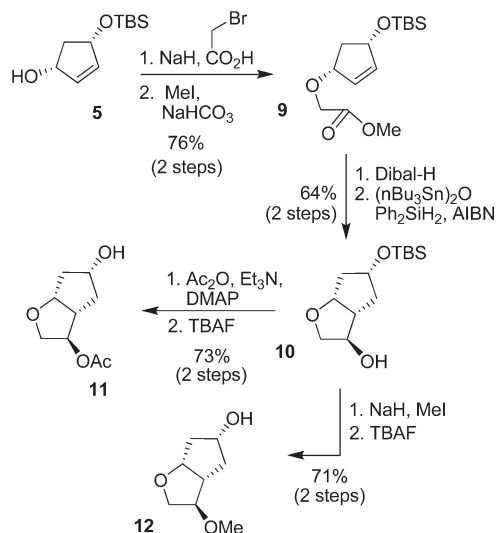
incorporating a 3-(*R*)-hydroxyl group, was the most potent PI ($K_i = 5$ pM; antiviral $IC_{50} = 2.9$ nM). This inhibitor also maintained excellent potency against a range of multidrug-resistant HIV-1 variants. The protein–ligand X-ray structure of 26-bound HIV-1 protease revealed important insights into the ligand-binding site interactions of the inhibitor with the flap region as well as other regions of the HIV-1 protease active site.

CHEMISTRY

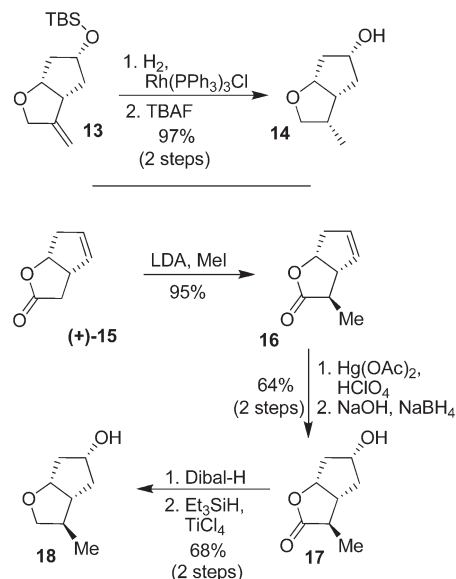
The syntheses of 3-keto and 3-(*S*)-methoxy Cp-THF ligands are shown in Scheme 1. Optically active alcohol 5 was prepared in multigram quantities as described previously.^{13,14} This was efficiently converted to ketone 6 as reported by us.¹⁴ The removal of TBS ether by exposure to HF–pyridine afforded keto alcohol 7 in 94% yield. Ketone 6 was converted to 3-(*S*)-methoxy derivative 8 in a three-step sequence involving (1) reduction of the ketone with NaBH₄ in ethanol at –25 °C to provide the corresponding alcohol as a single diastereomer, (2) methylation of the resulting alcohol with MeI in the presence of Ag₂O in acetonitrile, and (3) removal of the silyl group with TBAF in THF to provide 8 in 66% yield, in three steps.

The syntheses of 3-(*R*)-acetoxy and 3-(*R*)-methoxy ligands 11 and 12 are outlined in Scheme 2. Treatment of alcohol 5 with

Scheme 2. Syntheses of Ligands 11 and 12

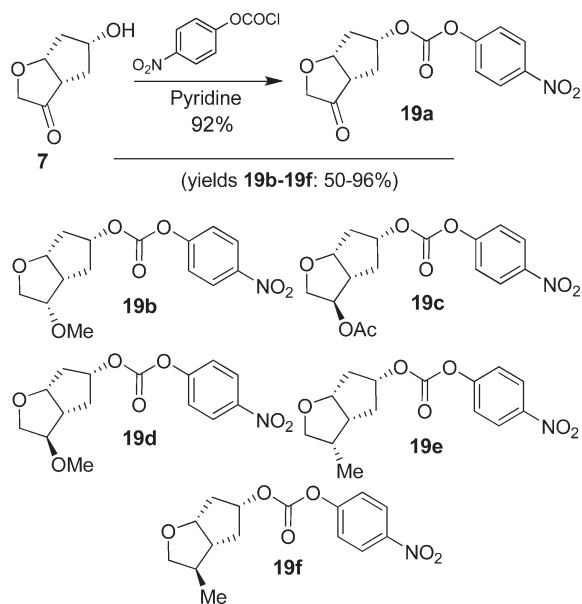


Scheme 3. Syntheses of C3-Methyl-Substituted Ligands 14 and 18



NaH and 2-bromoacetic acid in THF provided the corresponding alkylated acid. The resulting acid was reacted with methyl iodide in the presence of NaHCO₃ to provide methyl ester 9 in 76% yield (two steps). DIBAL-H reduction of ester 9 followed by radical cyclization¹⁵ of the resulting alkene using a catalytic amount of (*n*-Bu₃Sn)₂O, Ph₂SiH₂ and ethanol (2 equiv) in the presence of a catalytic amount of AIBN in benzene provided 3-(*R*)-hydroxy derivative 10 in 64% yield, in two steps. The ¹H NMR results showed a diastereomeric ratio of 10:1. The major isomer was separated by silica gel chromatography and used for the subsequent reactions. Reaction of alcohol 10 with acetic anhydride and triethylamine in the presence of a catalytic amount of DMAP afforded the corresponding acetate. The removal of the silyl group with TBAF in THF provided ligand 11 in 73% yield, in two steps. Alcohol 10 was converted to methoxy derivative 12 by

Scheme 4. Syntheses of Activated Mixed Carbonates 19a–f

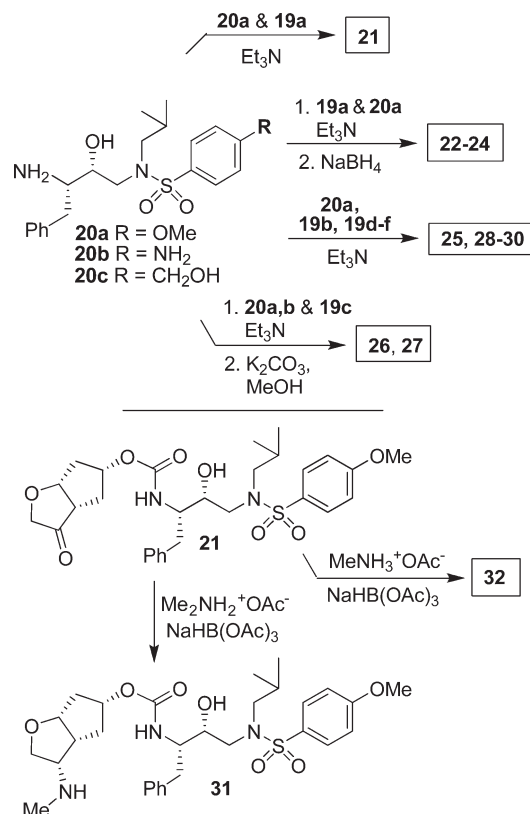


alkylation with NaH and MeI in THF followed by removal of the silyl group in 71% yield (two steps).

We also planned to synthesize stereochemically defined 3-methyl derivatives to compare with the effects of alkoxy and hydroxy groups. Toward this goal, we have carried out stereoselective syntheses of 3-(*S*)- and 3-(*R*)-methyl derivatives, and the synthetic routes are shown in Scheme 3. Optically active olefin **13** was synthesized as described previously.¹⁴ Catalytic hydrogenation of **13** in the presence of Wilkinson's catalyst under a hydrogen filled balloon at 23 °C for 3 h followed by removal of the silyl group using TBAF afforded 3-(*S*)-methyl derivative **14**.¹⁶ For the synthesis of the 3-(*R*)-methyl derivative, commercially available optically active lactone (+)-**15** was methylated using LDA and MeI at –78 °C to provide methyl derivative **16** with high diastereoselectivity (*dr* = 20:1) and in 95% yield. Olefin **16** was then subjected to oxymercuration condition with Hg(OAc)₂ and HClO₄. The resulting organomercurial derivative was treated with aqueous sodium hydroxide solution followed by NaBH₄ reduction to afford *endo*-alcohol **17** in 64% yield. The lactone was then reduced to the corresponding lactol with DIBAL-H. Further reduction of the resulting lactol using Et₃SiH and TiCl₄ furnished 3-(*R*)-methyl derivative **18** in 68% yield. Results from the ¹H NMR NOESY experiments fully corroborated the assignment of 3-(*S*)- and 3-(*R*)-stereochemistry of methyl derivatives **14** and **18**, respectively.

Various optically active ligand alcohols **7**, **8**, **11**, **12**, **14**, and **18** were converted to the respective mixed activated carbonates. As shown in Scheme 4, reactions of ligand alcohols with 4-nitrophenyl chloroformate in the presence of pyridine in CH₂Cl₂ provided activated carbonates **19a–f** in 50–96% yield.¹⁷ The syntheses of designed inhibitors were carried out by coupling these activated carbonates with various hydroxyethylsulfonamide isosteres containing functionalized P2'-phenylsulfonamide ligands. As shown in Scheme 5, amines **20a–c** were readily prepared as described previously.^{10,17} Reaction of amine **20a** with carbonate **19a** provided inhibitor **21**. Inhibitors **22–24** were prepared by reaction of carbonate **19a** with respective amines **20a–c** followed by NaBH₄ reduction of the resulting ketone derivatives.

Scheme 5. Syntheses of Inhibitors 21–32

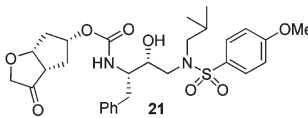
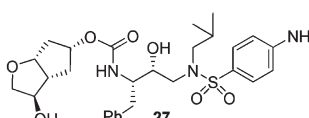
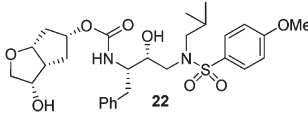
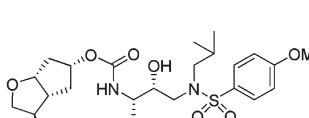
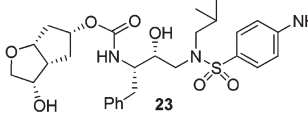
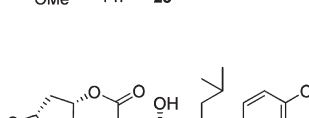
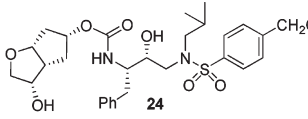
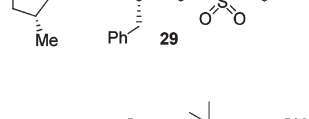
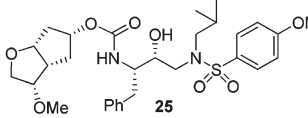
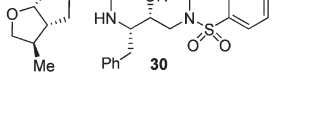
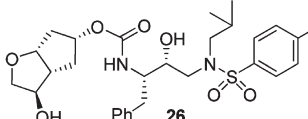


The inhibitor structures are shown in Table 1. Inhibitors **25** and **28–30** were prepared by reactions of amine **20a** with mixed carbonates **19b** and **19d–f**, respectively. The synthesis of inhibitors **26** and **27** was carried out by reactions of mixed carbonate **19c** with amines **20a** and **20b** followed by removal of the acetyl group with K₂CO₃ in methanol. All inhibitors were prepared in good to excellent overall (41–96%) yields. The synthesis of inhibitor **31** containing a dimethylamine functionality was carried out by reductive amination of ketone **21** with Me₂NH₂⁺OAc[–] in the presence of NaHB(OAc)₃. We have also attempted to prepare the corresponding methylamine derivative by reductive amination with MeNH₃⁺OAc[–]. However, the resulting 3-(*S*)-methylamine derivative **32** turned out to be unstable.

RESULTS AND DISCUSSION

As mentioned previously, inhibitors were designed to make additional interactions in the S2-subsite of the protease, especially with the Gly48 backbone atoms in the flap region of the enzyme. All inhibitors in Table 1 were first evaluated in enzyme inhibitory assay developed by Toth and Marshall.¹⁸ Inhibitors that exhibited potent *K_i* were subsequently evaluated for in vitro antiviral assays. As can be seen in the Table 1, all inhibitors displayed subnanomolar to low picomolar inhibitory potencies. Inhibitor **22**, with a 3-(*S*)-hydroxy group on the Cp-THF, was significantly more potent than the keto derivative **21** (entries 1 and 2). The 3-(*S*)-hydroxy Cp-THF ligand was also investigated in combination with other phenylsulfonamide substituents. Inhibitor **23** with a *p*-aminophenylsulfonamide as the P2'-ligand displayed impressive inhibitory potency; however, its antiviral

Table 1. Enzymatic Inhibitory and Antiviral Activity of Inhibitors 21–31

Entry	Inhibitor	K _i (nM)	IC ₅₀ (nM) ^a	Entry	Inhibitor	K _i (nM)	IC ₅₀ (nM) ^a
1		0.95	14	7		0.006	36
2		0.077	7	8		0.006	3.4
3		0.079	25	9		0.16	25
4		0.06	19	10		0.017	---
5		0.39	37	11		12.5	---
6		0.005	2.9				

^a Values are the mean of at least two experiments. Human T-lymphoid (MT-2) cells (2×10^3) were exposed to 100 TCID₅₀ of HIV-1_{LAI} and cultured in the presence of each PI, and IC₅₀ values were determined using the MTT assay. The IC₅₀ values of amprenavir (APV), saquinavir (SQV), indinavir (IDV), and darunavir (DRV) were 0.03, 0.015, 0.03, and 0.003 μ M, respectively.

activity was 3-fold lower than **22**. Inhibitor **24** with a *p*-hydroxymethylphenylsulfonamide as the P2'-ligand has shown a reduction in potency. Inhibitor **25**, which contains a 3-(*S*)-methoxy substituent, exhibited a significant loss of potency and a near 5-fold loss of antiviral activity compared to **22**. Interestingly, inhibitor **26** with 3-(*R*) configuration displayed an impressive enzyme inhibitory and antiviral activity. Inhibitor **27** with the 4-aminophenylsulfonamide isostere also showed comparable enzyme inhibitory activity. Inhibitor **28**, with a 3-(*R*)-methoxy group, also exhibited comparable inhibitory potency.

In order to probe the importance of the C3- oxygen on the Cp-THF ring, inhibitors **29** and **30** with a methyl group in place of a C3-hydroxyl were synthesized. Inhibitor **29**, which contains a 3-(*S*)-methyl group, showed a significant reduction in potency compared to **22**. Similarly, inhibitor **30** with a 3-(*R*)-methyl group has shown a reduction in enzyme K_i compared to the corresponding hydroxy derivative **26**. We have also investigated an amine substitution on the Cp-THF ligand. Inhibitor **31** with C3-dimethylamine exhibited a substantially lower enzyme inhibitory potency compared to the corresponding hydroxy or methoxy derivatives.

Inhibitors **22** with a 3-(*S*)-hydroxyl group and **26** with a 3-(*R*)-hydroxyl group on the Cp-THF ligand were tested against a panel of multidrug-resistant HIV-1 variants. Their antiviral activity was compared against other clinically available

PIs including APV and DRV. The results are shown in Table 2. All inhibitors in Table 2 exhibited high antiviral activity against the wild-type HIV-1 laboratory strain, HIV-1_{ERS104pre}, isolated from a drug-naïve patient.⁷ Compound **26** provided the most potent activity with an IC₅₀ of 2.9 nM, comparable to that of DRV. When tested against various multidrug-resistant HIV-1 strains, the IC₅₀ of inhibitor **26** remained in the low nanomolar range (2.9–29 nM) and fold-change in IC₅₀ did not exceed 10. Interestingly, isomeric inhibitor **22** displayed lower activity against the wild-type viral strain (IC₅₀ = 20 nM). It also exhibited a much larger IC₅₀ fold change and in some cases only marginal activity against multidrug-resistant HIV-1 variants. Such a stark contrast in antiviral activity of **22** compared to **26** emphasizes the importance of the stereochemistry at the C3-position of the Cp-THF ligand. Inhibitor **26** displayed a superior profile compared to another approved PI, APV. Overall, inhibitor **26** maintained impressive potency against all tested multidrug-resistant HIV-1 strains. It compared favorably with DRV, which is the leading PI for the treatment of multidrug resistant HIV infection.

In order to gain molecular insight into the ligand/binding-site interactions responsible for the activity of inhibitor **26**, we have determined the X-ray crystal structure of the inhibitor-bound wild-type HIV-1 protease that was refined to a 1.45 Å resolution. The protease dimer binds with the inhibitor in two orientations

Table 2. Comparison of the Antiviral Activity of 22, 26, and Other PIs against Multidrug Resistant HIV-1 Variants

virus ^a	IC ₅₀ ± SD, μ M (fold change) ^b			
	APV	DRV	22	26
HIV-1 _{ERS104pre} (wt)	0.030 ± 0.006	0.0037 ± 0.0001	0.020 ± 0.004	0.0029 ± 0.0008
HIV-1 _{MDR/B}	0.93 ± 0.28 (31)	0.036 ± 0.013 (10)	>1 (>50)	0.029 ± 0.007 (10)
HIV-1 _{MDR/C}	0.26 ± 0.03 (9)	0.013 ± 0.0004 (4)	>1 (>50)	0.022 ± 0.003 (7)
HIV-1 _{MDR/G}	0.38 ± 0.03 (12)	0.0023 ± 0.0006 (1)	0.27 ± 0.02 (13)	0.0045 ± 0.0007 (2)
HIV-1 _{MDR/TM}	0.19 ± 0.06 (6)	0.0019 ± 0.0003 (1)	0.041 ± 0.004 (2)	0.0031 ± 0.002 (1)

^a Amino acid substitutions identified in the protease-encoding region compared to the consensus type B sequence cited from the Los Alamos database: L10I, L33I, M36I, M46I, F53L, K55R, I62 V, L63P, A71 V, G73S, V82A, L90M, and I93L in HIV-1_{MDR/B}; L10I, I15 V, K20R, L24I, M36I, M46L, I54 V, I62 V, L63P, K70Q, V82A, and L89 M in HIV-1_{MDR/C}; L10I, V11I, T12E, I15 V, L19I, R41K, M46L, L63P, A71T, V82A, and L90 M in HIV-1_{MDR/G}; L10I, K14R, R41K, M46L, I54V, L63P, A71V, V82A, L90M, I93L in HIV-1_{MDR/TM}. HIV-1_{ERS104pre} served as a source of wild-type HIV-1.

^b IC₅₀ values were determined by using PHA-PBMs as target cells, and inhibition of p24 Gag protein production by each drug was used as an end point. Numbers in parentheses represent *n*-fold changes of IC₅₀ for each isolate compared to IC₅₀ for the wild-type HIV-1_{ERS104pre}. All assays were conducted in duplicate or triplicate, and data shown represent mean values (±1 standard deviation) derived from results of three independent experiments. PHA-PBMs were derived from a single donor in each independent experiment. DRV: darunavir. APV: amprenavir.

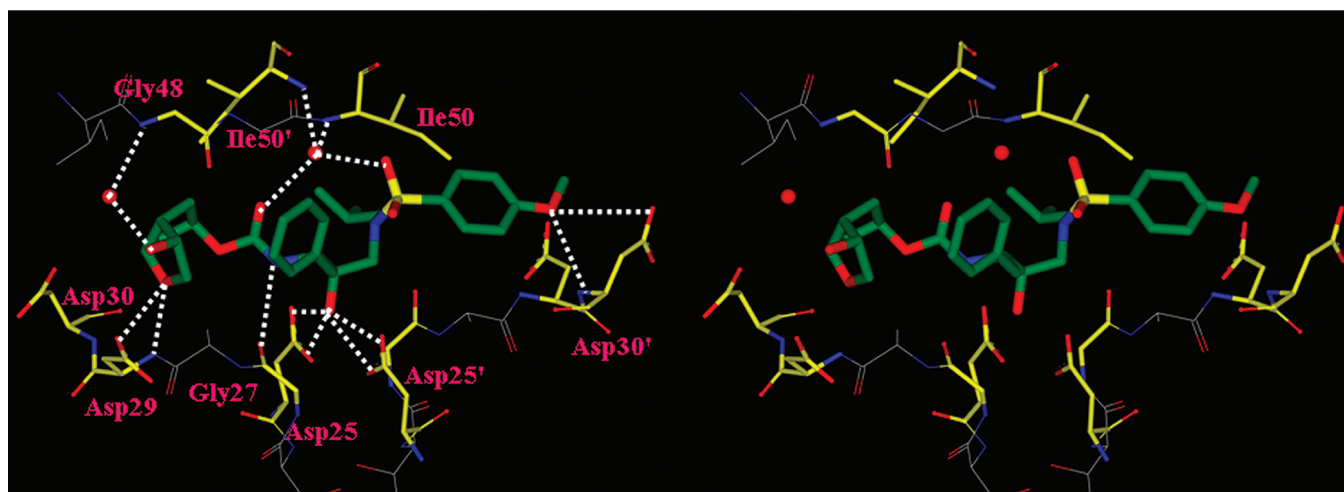


Figure 2. Stereoview of the X-ray structure of inhibitor 26 bound to the active site of the wild-type HIV-1 protease.

related by a 180° rotation with a 0.55/0.45 ratio. The protease backbone structure showed a very low rms deviation of 0.15 Å for all C α atoms compared to protease complexes of **2** or darunavir.^{19,20} The inhibitor makes extensive interactions from the P2 to P2' ligands with the protease atoms and most notably displays favorable polar interactions including hydrogen bonds, weaker C—H $\cdots$ O and C—H $\cdots$ π interactions, as shown in Figure 2. The central hydroxyl group forms hydrogen bonds with the side chain carboxylate oxygen atoms of the catalytic Asp25 and Asp25' residues. The inhibitor hydrogen-bonds with the protease backbone atoms of the amide of Asp30', the carbonyl oxygen of Gly27, and forms water-mediated interactions with the amides of Ile50 and Ile50', which are generally conserved in the majority of protease complexes with inhibitors²¹ or substrate analogues.^{22,23} The inhibitor interactions with atoms in the binding cavity resemble those of darunavir and **2** (TMC-126) with the exception of the interactions of the new P2-ligand that replaces the bis-THF group. The 3-(*R*)-hydroxyl of the Cp-THF ligand extends toward the flap region and forms a new water-mediated hydrogen bond interaction with the backbone amide NH of Gly48, with interatomic distances of 2.5 and 3.1 Å for the major inhibitor orientation or 2.7 and 3.1 Å for the minor

orientation. Also, the Cp-THF ether oxygen forms a strong hydrogen bond with the backbone amide NH of Asp29. These new interactions with the backbone atoms of Gly48 are likely to be responsible for the impressive antiviral activity and drug resistance properties of this inhibitor. The C3-functionality on the Cp-THF appears to enhance the affinity of the inhibitor. The new water-mediated interaction with the backbone NH of Gly48 on the protease flap may promote thermodynamic stabilization of the closed conformation of the protease–ligand complex. This may slow the kinetics of dissociation of the inhibitor through flexible opening of the protease flap.

CONCLUSION

In summary, we have designed a number of C3-substituted hexahydrocyclopentafuranyurethanes as P2-ligands to enhance interactions with the protein backbone in the S2-subsite. The ligands were stereoselectively synthesized in optically active form. Incorporation of these ligands in (*R*)-hydroxyethylsulfonyl isosteres resulted in a series of novel and highly potent HIV-1 protease inhibitors. In particular, inhibitor **26** displayed remarkable enzyme inhibitory and antiviral potency. Also, inhibitor **26** has shown excellent activity against multi-PI-resistant

variants compared to other FDA approved inhibitors. A protein–ligand X-ray structure of **26**-bound HIV-1 protease was determined at 1.45 Å resolution. The inhibitor appeared to make extensive interactions throughout the active site. Of particular interest, the 3-(*R*)-hydroxyl of the Cp-THF ligand formed a new water-mediated hydrogen bond interaction with the backbone amide NH of Gly48, and the Cp-THF ether oxygen formed a strong hydrogen bond with backbone amide NH of Asp29. The extensive interactions with the protein backbone may be responsible for inhibitor **26**'s impressive antiviral activity and drug resistance profile. The design of inhibitors targeting the protein backbone has led us to develop inhibitors characterized by high potency against both wild-type and multidrug-resistant HIV-1 strains. Further design and optimization of inhibitors utilizing this molecular insight are in progress.

■ EXPERIMENTAL SECTION

General. All anhydrous solvents were obtained according to the following procedures. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone under argon. Toluene, methanol, acetonitrile, and dichloromethane were distilled from calcium hydride, and benzene was distilled from sodium. Other solvents were used without purification. All moisture-sensitive reactions were carried out in flame-dried flasks under argon atmosphere. Reactions were monitored by thin layer chromatography (TLC) using Silicycle 60A-F254 silica gel precoated plates. Flash column chromatography was performed using Silicycle 230–400 mesh silica gel. Yields refer to chromatographically and spectroscopically pure compounds. Optical rotations were recorded on a Perkin-Elmer 341 polarimeter. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Inova-300 (300 and 75 MHz, respectively), Bruker Avance ARX-400 (400 and 100 MHz), and Bruker Avance ARX-500 (500 and 125 MHz). High and low resolution mass spectra were carried out by the Mass Spectroscopy Center at Purdue University, IN. The purity of all test compounds was determined by HRMS and HPLC analyses in the different solvent systems. All test compounds showed $\geq 95\%$ purity.

(3a*S*,5*R*,6a*R*)-5-Hydroxytetrahydro-2*H*-cyclopenta[*b*]furan-3(3a*H*)-one (7). A solution of ketone **6** (23 mg, 0.09 mmol) in CH_3CN (0.5 mL) was cooled to 0 °C under argon. Pyridine (50 μL) was added followed by dropwise addition of HF–pyridine (0.18 mL). The solution was stirred at 0 °C for 4 h. The reaction was quenched by addition of saturated aqueous NaHCO_3 solution followed by solid NaHCO_3 . The aqueous phase was extracted multiple times with EtOAc, and the combined organic layer was dried over Na_2SO_4 . Following careful evaporation of the solvent, the residue was purified by column chromatography on silica gel using hexanes/EtOAc (1:1 and then 1:2) as the eluent to yield the desired ketone **7** (12 mg, 94%) as a colorless oil. TLC, R_f = 0.32 (hexanes/EtOAc = 1:2); $[\alpha]_D^{20}$ +96.1 (*c* 0.86, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 5.04 (t, *J* = 6.6 Hz, 1H), 4.38 (t, *J* = 4.0 Hz, 1H), 4.20 (d, *J* = 17.0 Hz, 1H), 3.97 (d, *J* = 17.0 Hz, 1H), 2.85 (t, *J* = 8.4 Hz, 1H), 2.21 (d, *J* = 13.9 Hz, 1H), 2.15 (d, *J* = 15.2 Hz, 1H), 2.01 (ddd, *J* = 3.9, 10.5, 14.1 Hz, 1H), 1.95 (ddd, *J* = 4.5, 6.0, 15.1 Hz, 1H), 1.90 (br s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 217.7, 84.0, 72.9, 70.8, 48.8, 43.4, 40.7.

(3*S*,3a*S*,5*R*,6a*R*)-3-Methoxyhexahydro-2*H*-cyclopenta[*b*]furan-5-ol (8). Ketone **6** (35.6 mg, 0.14 mmol) was dissolved in EtOH (1 mL) under argon and cooled to –25 °C. To the solution was added NaBH_4 (10 mg, 0.26 mmol) in one portion, and the resulting mixture was stirred at this temperature for 20 min. Saturated aqueous NH_4Cl solution was added and the volume of solvent reduced under vacuum. Additional water was added, and the aqueous phase was extracted several times with EtOAc. The combined organic layer was washed with brine, dried (Na_2SO_4), and evaporated in vacuo. Purification of the crude alcohol by column chromatography on silica gel using

hexanes/EtOAc (5:1) as the eluent provided the corresponding alcohol (32.2 mg, 90%) as a colorless oil. TLC, R_f = 0.22 (hexanes/EtOAc = 5:1); $[\alpha]_D^{20}$ +21.5 (*c* 1.05, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz) δ 4.55 (br s, 1H), 4.42 (t, *J* = 7.0 Hz, 1H), 4.34 (t, *J* = 4.5 Hz, 1H), 4.11 (m, 1H), 3.87 (d, *J* = 9.9 Hz, 1H), 3.48 (dd, *J* = 3.6, 9.9 Hz, 1H), 2.89 (dt, *J* = 7.8, 10.2 Hz, 1H), 2.13 (dd, *J* = 2.4, 14.7 Hz, 1H), 1.99 (dd, *J* = 2.4, 14.7 Hz, 1H), 1.78–1.65 (m, 2H), 0.89 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 85.3, 77.3, 74.9, 72.9, 48.1, 41.8, 34.8, 25.7, 18.0, –4.7, –5.2. HRMS-Cl (*m/z*): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{27}\text{O}_3\text{Si}$ 259.1729, found 259.1731. To a solution of the above alcohol (27 mg, 0.1 mmol) in CH_3CN (1 mL) was added MeI (0.3 mL, excess) followed by Ag_2O (50 mg, 0.2 mmol). The mixture was gently refluxed for 12 h under argon, and then additional MeI (0.3 mL) and Ag_2O (50 mg) were added. Reflux was continued for an additional 12 h until all SM disappeared. The resulting mixture was diluted in Et_2O and filtered on Celite. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using hexanes/EtOAc (8:1) as the eluent to yield the corresponding 3-(*S*)-methoxy intermediate as a clear oil (23 mg, 85%). TLC, R_f = 0.38 (hexanes/EtOAc = 5:1); $[\alpha]_D^{20}$ +42.6 (*c* 1.02, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz) δ 4.41 (dt, *J* = 5.1, 7.2 Hz, 1H), 4.12 (m, 1H), 3.93 (m, 1H), 3.87–3.70 (m, 2H), 3.32 (s, 3H), 2.61 (m, 1H), 2.18 (m, 1H), 1.90–1.75 (m, 2H), 1.63 (m, 1H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 82.5, 81.1, 73.5, 69.0, 57.8, 42.6, 33.5, 25.8, 18.1, –4.8. To a solution of the above intermediate (16 mg, 0.059 mmol) in THF (1 mL) was added TBAF (1 M solution in THF, 0.1 mmol, 100 μL). The solution was stirred at room temperature for 2 h. The solvent was evaporated and the residue purified by flash column chromatography on silica gel using hexanes/EtOAc (1:1 and then 1:2.5) to furnish **8** as a colorless oil (8 mg, 86%). TLC, R_f = 0.32 (CHCl_3 /3% EtOH); ^1H NMR (CDCl_3 , 500 MHz) δ 4.41 (t, *J* = 4.4 Hz, 1H), 4.21 (dt, *J* = 5.1, 10.1 Hz, 1H), 4.08 (d, *J* = 10.3 Hz, 1H), 3.85 (dd, *J* = 3.0, 7.3 Hz, 1H), 3.83 (d, *J* = 10.3 Hz, 1H), 3.42 (s, 3H), 2.94–2.86 (m, 1H), 2.13 (d, *J* = 14.5 Hz, 1H), 2.08 (dd, *J* = 2.4, 15.1 Hz, 1H), 1.81 (ddd, *J* = 5.3, 10.6, 14.5 Hz, 1H), 1.74 (ddd, *J* = 5.3, 6.0, 15.0 Hz, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 86.0, 82.1, 73.6, 71.6, 57.4, 47.2, 42.0, 34.0.

Methyl 2-((1*R*,4*S*)-4-((*tert*-Butyldimethylsilyl)oxy)cyclopent-2-en-1-yloxy)acetate (9). To an ice-cold suspension of NaH (60% suspension in oil, 360 mg, 9 mmol) in dry THF (5 mL) under argon was slowly added a solution of 2-bromoacetic acid (520 mg, 3.75 mmol) in dry THF (3 mL + 3 mL rinse). The resulting mixture was stirred at room temperature for 30 min and then cooled back to 0 °C. Desymmetrized *meso*-cyclopentenediol **5** (642 mg, 3 mmol) in dry DMF (10 mL) was slowly added to this solution, and the mixture was allowed to warm to room temperature and was stirred for 24 h. A pH 4 phosphate buffer solution was added at 0 °C, and the aqueous phase was extracted with EtOAc ($\times 4$). The combined organic phase was dried (Na_2SO_4), filtered, and evaporated in vacuo to give the corresponding crude carboxylic acid along with residual DMF. The acid was diluted with additional DMF (10 mL). The solution was cooled to 0 °C, and NaHCO_3 (630 g, 7.5 mmol) was added at once followed by MeI (14 mmol, 1.98 g, 871 μL). After the mixture was stirred at room temperature for 12 h, saturated aqueous NH_4Cl solution was added (10 mL), then water (10 mL), and the aqueous phase was successively extracted with hexanes/ Et_2O , 1:1 ($\times 3$). The combined organic phase was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc (20:1 and then 15:1) to give methyl ester **9** as a colorless oil (654 mg, 76%, two steps). TLC, R_f = 0.45 (hexanes/EtOAc = 3:1); ^1H NMR (CDCl_3 , 300 MHz) δ 5.92 (s, 2H), 4.63 (dd, *J* = 4.8, 7.0 Hz, 1H), 4.53 (dd, *J* = 5.1, 7.2 Hz, 1H), 4.10 (s, 2H), 3.74 (s, 3H), 2.64 (dt, *J* = 7.2, 13.8 Hz, 1H), 1.60 (dt, *J* = 4.9, 13.7 Hz, 1H), 0.87 (s, 9H), 0.065 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 171.2, 138.4, 131.9, 82.4, 74.6, 64.7, 51.8, 40.5, 25.8, 18.0, –4.7.

(3*R*,3a*R*,5*R*,6a*R*)-5-((*tert*-Butyldimethylsilyl)oxy)hexahydro-2*H*-cyclopenta[*b*]furan-3-ol (10). A solution of methyl ester **9** (87.2 mg,

0.304 mmol) in dry CH_2Cl_2 (8 mL) was cooled to -78°C under argon. DIBAL-H (1 M solution in hexanes, 0.40 mL) was added slowly, and the reaction mixture was stirred for 1 h at this temperature. The reaction was quenched by addition of MeOH (100 μL), and the mixture was warmed to room temperature. A pH 7 phosphate buffer (0.5 M solution, 2 mL) was added. The aqueous phase was extracted with CH_2Cl_2 ($\times 3$) and the combined organic phase washed with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo. The crude aldehyde solution was passed through a short plug of silica gel, deactivated with 1% Et_3N using hexanes/EtOAc (5:1) as the eluent. After evaporation, the crude product was directly submitted to the next step. The residue was dissolved in dry benzene (degassed, 2 mL) under argon and the solution transferred into a sealable tube. (*n*- Bu_3Sn) $_2\text{O}$ (22.5 μL , 26.3 mg, 44 μmol), Ph_2SiH_2 (42 μL , 41.6 mg, 0.22 mmol), EtOH (45 μL), and AIBN (10 mg) were successively added. The sealed tube was placed with stirring in an oil bath at 80°C for 6 h. After cooling to room temperature, the reaction mixture was diluted with Et_2O (2 mL) and aqueous 0.5 M HCl solution (2 mL) was added. After the mixture was stirred at room temperature for 15 min, the aqueous phase was extracted with Et_2O ($\times 3$). The combined organic phase was washed with saturated aqueous NaHCO_3 solution, brine, dried (MgSO_4), filtered, and evaporated. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc (6:1 to 2:1) to afford the (*R*)-alcohol **10** (50 mg, 64%, over two steps) as a white solid; 5 mg of the other 3-(*S*)-diastereoisomer was also isolated, and only traces of 1,2 reduction product was observed. TLC, $R_f = 0.46$ (hexanes/EtOAc = 3:1); $[\alpha]_D^{20} +22.3$ (*c* 0.67, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz) δ 4.69 (dt, *J* = 3.8, 7.2 Hz, 1H), 4.19–4.02 (m, 3H), 3.72 (d, *J* = 9.8 Hz, 1H), 2.48 (q, *J* = 7.5 Hz, 1H), 2.13–1.96 (m, 2H), 1.70–1.55 (m, 1H), 1.47–1.25 (m, 1H), 0.86 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 82.2, 78.3, 73.1, 72.7, 50.9, 42.4, 39.0, 25.8, 17.5, –4.8, –4.9.

(3*R*,3*S*,5*R*,6*aR*)-5-Hydroxyhexahydro-2*H*-cyclopenta[*b*]furan-3-yl Acetate (11). Alcohol **10** (45 mg, 0.175 mmol) was diluted in CH_2Cl_2 (5 mL), and the solution was cooled to 0°C under argon. Et_3N (0.525 mmol, 53 mg, 75 μL) and DMAP (1 crystal) were added followed by acetic anhydride (25 μL , 0.23 mmol). The mixture was warmed to room temperature and stirred overnight. The solution was evaporated to dryness, and purification of the residue by flash column chromatography on silica gel using hexanes/EtOAc (20:1) furnished the corresponding acetate derivative (38 mg, 73%). TLC, $R_f = 0.24$ (hexanes/EtOAc = 10:1); ^1H NMR (CDCl_3 , 300 MHz) δ 5.02 (d, *J* = 3.8 Hz, 1H), 4.69 (dt, *J* = 3.2, 7.2 Hz, 1H), 4.22 (dd, *J* = 4.0, 10.4 Hz, 1H), 4.11 (m, 1H), 3.80 (d, *J* = 10.4 Hz, 1H), 2.56 (m, 1H), 2.09–1.97 (m, 2H), 2.04 (s, 3H), 1.71 (m, 1H), 1.68–1.54 (m, 1H), 0.86 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 170.8, 82.9, 81.2, 72.8, 70.9, 48.5, 42.7, 39.2, 25.8, 21.2, 18.0, –4.9. The acetate (28 mg, 0.093 mmol) was diluted in THF (1.5 mL). TBAF (1 M solution of THF, 200 μL , 0.2 mmol) was added at 0°C , and the mixture was stirred for 2.5 h while warming to 23°C . The solvent was evaporated and the residue purified by flash column chromatography on silica gel using hexanes/EtOAc (3:1 to 1:1) to give pure alcohol **11** as a colorless oil (17.5 mg, quant). TLC, $R_f = 0.18$ (EtOAc, 100%); ^1H NMR (CDCl_3 , 300 MHz) δ 5.11 (m, 1H), 4.70–4.62 (m, 1H), 4.32 (dd, *J* = 5.0, 10.4 Hz, 1H), 4.28–4.20 (m, 1H), 3.71 (dd, *J* = 3.2, 10.4 Hz, 1H), 2.65–2.56 (m, 1H), 2.30–2.13 (m, 2H), 2.06 (s, 3H), 1.99–1.88 (m, 1H), 1.77–1.68 (m, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 170.8, 84.8, 81.1, 73.4, 71.9, 48.9, 41.9, 39.5, 21.1.

(3*R*,3*S*,5*R*,6*aR*)-3-Methoxyhexahydro-2*H*-cyclopenta[*b*]furan-5-ol (12). A solution of alcohol **10** (30 mg, 0.116 mmol) in dry DMF (1 mL) was cooled to 0°C under argon, and NaH (60% suspension in oil, 15 mg, 0.348 mmol) was added in one portion. The mixture was warmed to room temperature, stirred for 30 min, and then cooled to 0°C . MeI (22 μL , 50 mg, 0.35 mmol) was added to the solution, and the mixture was warmed to 23°C and stirred for 3.5 h. Saturated aqueous NH_4Cl solution was added, and the aqueous phase was extracted with Et_2O /hexanes (1:1). The combined organic phase

was washed with brine, dried (Mg_2SO_4), filtered, and evaporated in vacuo. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc (10:1 and then 8:1) to afford the corresponding TBS-protected methoxy compound (28.6 mg, 86%) as a clear oil. TLC, $R_f = 0.61$ (hexanes/EtOAc = 3:1); $[\alpha]_D^{20} +20.6$ (*c* 1.52, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 4.63 (dt, *J* = 3.6, 7.2 Hz, 1H), 4.11 (m, 1H), 4.05 (dd, *J* = 4.1, 9.9 Hz, 1H), 3.81 (dd, *J* = 1.3, 9.9 Hz, 1H), 3.74 (m, 1H), 3.31 (s, 3H), 2.54 (td, *J* = 7.7, 8.3 Hz, 1H), 2.10–1.96 (m, 2H), 1.70–1.60 (m, 1H), 1.47 (m, 1H), 0.87 (s, 9H), 0.04 (6H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 87.7, 82.5, 72.9, 70.3, 56.6, 47.4, 42.5, 39.5, 25.8, 18.0, –4.8, –4.9. To an ice-cold solution of the above methoxy intermediate (27 mg, 0.1 mmol) in THF (2 mL) under argon was added TBAF (1 M solution in THF, 0.2 mL, 0.2 mmol). The mixture was stirred for 1.5 h. The solvent was evaporated, and the crude residue was purified by flash column chromatography on silica gel using hexanes/EtOAc (1:1) as the eluent to furnish alcohol **12** as a clear oil (13 mg, 82%). TLC, $R_f = 0.17$ (hexanes/EtOAc = 1:2); ^1H NMR (CDCl_3 , 300 MHz) δ 4.63 (t, *J* = 5.5 Hz, 1H), 4.26 (m, 1H), 4.20 (dd, *J* = 5.3, 9.7 Hz, 1H), 3.89 (dt, *J* = 2.0, 4.8 Hz, 1H), 3.65 (dd, *J* = 4.4, 9.7 Hz, 1H), 3.34 (s, 3H), 2.64–2.54 (m, 1H), 2.40 (br s, 1H), 2.16 (ddd, *J* = 5.5, 10.6, 14.3 Hz, 1H), 2.02 (dd, *J* = 1.7, 14.7 Hz, 1H), 1.87 (dt, *J* = 5.1, 14.7 Hz, 1H), 1.77–1.61 (m, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 88.4, 85.1, 74.0, 71.9, 57.0, 48.4, 41.8, 40.2.

(3*S*,3*aR*,5*R*,6*aR*)-3-Methylhexahydro-2*H*-cyclopenta[*b*]furan-5-ol (14). To a solution of olefin **13** (29.7 mg, 0.12 mmol) in toluene (3 mL) was added Wilkinson's catalyst, $\text{RhCl}(\text{PPh}_3)_3$ (18 μmol , 17 mg). The resulting solution was then placed under a hydrogen atmosphere and stirred for 3 h. After dilution with additional toluene, the solution was filtered on a Celite pad, and the pad was rinsed with toluene. Evaporation of the solvent and purification of the residue on silica gel using hexanes/EtOAc (100:1 and then 50:1) as the eluent furnished the corresponding 3-(*S*)-methyl compound (29 mg, 97%). TLC, $R_f = 0.28$ (hexanes/EtOAc = 20:1); $[\alpha]_D^{20} +22.7$ (*c* 1.01, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 4.43 (m, 1H), 4.03 (m, 1H), 3.81 (dd, *J* = 7.4, 8.0 Hz, 1H), 3.42 (dd, *J* = 8.0, 10.7 Hz, 1H), 2.43 (m, 1H), 2.32–2.18 (m, 2H), 1.72 (m, 1H), 1.51 (ddd, *J* = 4.8, 8.6, 13.5 Hz, 1H), 1.44 (m, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 82.6, 73.2, 71.6, 44.5, 43.2, 36.2, 34.7, 25.9, 18.2, 11.3, –4.7, –4.8. HRMS-Cl (*m/z*): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{29}\text{O}_2\text{Si}$ 257.1937, found 257.1936. A solution of methyl-based ligand (28 mg, 0.1 mmol) in THF (2 mL) was treated with TBAF (1 M solution in THF, 150 μL) and stirred at room temperature for 2.5 h. The reaction mixture was diluted with Et_2O and filtered on a short silica pad. The solvent containing the alcohol was carefully reduced, and essentially pure alcohol **14** was directly used in the next step without purification (>99% pure). TLC, $R_f = 0.26$ (hexanes/EtOAc = 1:1); ^1H NMR (CDCl_3 , 400 MHz) δ 4.46 (dt, *J* = 2.7, 5.5 Hz, 1H), 4.20 (m, 1H), 3.88 (t, *J* = 7.8 Hz, 1H), 3.48 (t, *J* = 9.2 Hz, 1H), 2.59–2.40 (m, 2H), 2.22 (d, *J* = 6.9 Hz, 1H), 2.08 (dt, *J* = 5.9, 14.1 Hz, 1H), 1.87 (ddd, *J* = 6.0, 9.5, 13.7 Hz, 1H), 1.83 (m, 1H), 1.68–1.54 (m, 1H), 1.01 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 85.3, 73.8, 72.9, 46.3, 42.4, 36.5, 34.5, 12.7.

(3*R*,3*aR*,6*aR*)-3-Methyl-3*a*,6*a*-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one (16). To a solution of lithium diisopropylamide, prepared by adding *n*-BuLi (2.5 M solution in hexanes, 1.36 mL, 3.39 mmol) to diisopropylamine (477 μL , 3.39 mmol) in THF (15 mL) at 0°C , was added a precooled solution of known (3*aS*,6*aR*)-3*a*,6*a*-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one (+)-**15** (350 mg, 2.82 mmol) in THF (5 mL + 3 mL rinse) at -78°C , dropwise. The reaction mixture was stirred at this temperature for 30 min. Then methyl iodide (352 μL , 5.65 mmol) was added dropwise and the reaction mixture was stirred at -78°C for 6 h. The reaction mixture was quenched with 2 M aqueous HCl. The aqueous phase was extracted with Et_2O ($\times 3$). The combined organic layer was dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel using hexanes/ Et_2O (5:1)

to yield lactone **16** (369 mg, 95%) as a brown oil. TLC, R_f = 0.54 (hexanes/EtOAc = 2:1); $[\alpha]_D^{20}$ +54.2 (c 1.0, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 5.74 (m, 1H), 5.59 (m, 1H), 5.12 (t, J = 5.6 Hz, 1H), 3.13 (dd, J = 3.8, 1.8 Hz, 1H), 2.65 (m, 2H), 2.52 (q, J = 7.6 Hz, 1H), 1.33 (d, J = 7.6 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 180.0, 130.9, 129.4, 81.3, 53.8, 39.9, 39.2, 17.4.

(3R,3aR,5R,6aR)-5-Hydroxy-3-methylhexahydro-2H-cyclopenta[b]furan-2-one (17). To an ice-cold yellow solution of Hg(OAc)₂ (1.45 g, 4.57 mmol) in THF/H₂O (2.5:1 ratio, 23 mL) was added perchloric acid (~0.7 mL) until the solution became colorless. A solution of lactone **16** (350 mg, 2.54 mmol) in THF (7 mL) was then added at 0 °C, and the mixture was stirred for 1 h. Additional Hg(OAc)₂ (646 mg, 2.03 mmol) similarly pretreated with perchloric acid in THF/H₂O (2.5:1, 10 mL) was added, and stirring was continued for 2 h at 0 °C. The pH of the mixture was then adjusted to ~10 by addition of a 1 M aqueous NaOH solution. Stirring was then continued for 1 h at room temperature. The solution was cooled to 0 °C, and NaBH₄ (145 mg, 3.81 mmol) was added in small portions. After 1 h, the reaction mixture was acidified to pH 2 with concentrated HCl, and stirring was continued for 1 h. The reaction solution was saturated with NaCl and the aqueous phase extracted several times with EtOAc. The combined organic phase was dried (Na₂SO₄), filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel using 2% MeOH in CH₂Cl₂ to yield alcohol **17** (252 mg, 64%) as a colorless oil. TLC, R_f = 0.31 (CHCl₃/MeOH = 9:1); $[\alpha]_D^{20}$ +53.5 (c 1.0, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 4.98 (dt, J = 8.0, 14.9 Hz, 1H), 4.55 (m, 1H), 2.69 (qd, J = 3.9, 7.6 Hz, 1H), 2.58 (m, 1H), 2.55 (m, 1H), 2.09 (d, J = 15.0 Hz, 1H), 1.94 (m, 2H), 1.83 (m, 1H), 1.26 (d, J = 7.6 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 181.0, 83.8, 74.6, 51.2, 45.5, 43.9, 41.3, 18.4.

(3R,3aR,5R,6aR)-3-Methylhexahydro-2H-cyclopenta[b]furan-5-ol (18). To a solution of lactone **17** (205 mg, 1.31 mmol) in CH₂Cl₂ (9 mL) was added DIBAL-H (1 M solution in CH₂Cl₂, 1.45 mL, 1.45 mmol) dropwise at -78 °C. The mixture was stirred for 3 h and then quenched with saturated Rochelle's salt solution. After the mixture was stirred overnight at room temperature, the phases were separated and the aqueous phase was extracted with EtOAc (×3). The combined organic phase was dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using 2% MeOH in CH₂Cl₂ to yield the corresponding lactol (150 mg, 72%). To a solution of this lactol (143 mg, 0.9 mmol) in CH₂Cl₂ (9 mL) at -78 °C was added TiCl₄ (100 μ L, 0.9 mmol) dropwise, and the mixture was stirred for 20 min. Et₃SiH (289 μ L, 1.81 mmol) was then added, and the solution was stirred for an additional 1 h. The reaction was quenched with saturated NaHCO₃ solution once completion was reached as observed by TLC. The aqueous phase was extracted with Et₂O, dried (Na₂SO₄), filtered, and concentrated under reduced pressure at 25 °C. The residue was purified by column chromatography on silica gel using 2% MeOH in CH₂Cl₂ to yield alcohol **18** (122 mg, 95%) as a colorless oil. TLC, R_f = 0.38 (CHCl₃/MeOH = 9:1); $[\alpha]_D^{20}$ +12.6 (c 1.0, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 4.47 (t, J = 5.7 Hz, 1H), 4.22 (m, 1H), 4.06 (dd, J = 6.5, 8.7 Hz, 1H), 3.18 (t, J = 8.4 Hz, 1H), 2.60 (d, J = 7.2 Hz, 1H), 2.27–2.18 (m, 1H), 2.18–2.12 (m, 1H), 2.00 (dd, J = 1.5, 16.2 Hz, 1H), 1.98–1.91 (m, 1H), 1.80 (dt, J = 5.2, 14.6 Hz, 1H), 1.69 (ddd, J = 2.3, 5.4, 13.9 Hz, 1H), 1.03 (d, J = 6.7 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 85.4, 75.1, 74.7, 50.3, 43.2, 41.6, 41.5, 17.6.

Synthesis of Activated Mixed Carbonates. (3aS,5R,6aR)-3-Oxoheptahydro-2H-cyclopenta[b]furan-5-yl (4-nitrophenyl)carbonate (19a). To a solution of ketone **7** (20 mg, 0.14 mmol) in CH₂Cl₂ (1 mL) was added pyridine (30 μ L). The solution was cooled to 0 °C under argon, and 4-nitrophenyl chloroformate (42 mg, 0.21 mmol) was added at once. A white suspension formed. The solution was stirred at this temperature and slowly warmed to room temperature until all starting material was consumed. The reaction mixture was evaporated to

dryness and the residue purified by column chromatography on silica gel using hexanes/EtOAc (3:1 and then 2:1) as eluent to furnish pure mixed carbonate **19a** (39 mg, 92%) as a white solid. TLC, R_f = 0.25 (hexanes/EtOAc = 2:1); ¹H NMR (CDCl₃, 400 MHz) δ 8.27 (d, J = 9.2 Hz, 2H), 7.34 (d, J = 9.2 Hz, 2H), 5.23 (t, J = 4.2 Hz, 1H), 5.13 (t, J = 6.9 Hz, 1H), 4.19 (d, J = 17.1 Hz, 1H), 4.06 (d, J = 17.1 Hz, 1H), 2.99 (dd, J = 8.7, 8.8 Hz, 1H), 2.54–2.41 (m, 2H), 2.22–2.08 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 216.8, 155.3, 151.5, 145.4, 125.3, 121.9, 82.4, 81.0, 70.6, 48.5, 41.2, 37.1.

(3S,3aS,5R,6aR)-3-Methoxyhexahydro-2H-cyclopenta[b]furan-5-yl (4-nitrophenyl)carbonate (19b). The title compound was obtained from **8** in 82% yield as described for **7** after purification by column chromatography on silica gel using hexanes/EtOAc (3:1 to 2:1) as the eluent (white solid). TLC, R_f = 0.25 (hexanes/EtOAc = 2:1); ¹H NMR (CDCl₃, 300 MHz) δ 8.27 (d, J = 9.2 Hz, 2H), 7.38 (d, J = 9.2 Hz, 2H), 5.15 (tt, J = 4.5, 6.2 Hz, 1H), 4.56 (dt, J = 2.8, 6.1 Hz, 1H), 4.04 (dt, J = 6.3, 7.5 Hz, 1H), 3.87 (AB, dd, J = 5.2, 9.1 Hz, 1H), 3.86 (AB, dd, J = 6.6, 9.1 Hz, 1H), 3.34 (s, 3H), 2.83 (m, 1H), 2.38–2.02 (m, 4H); ¹³C NMR (CDCl₃, 75 MHz) δ 155.6, 152.1, 145.2, 125.2, 121.8, 83.7, 81.4, 77.2, 70.3, 57.9, 44.2, 39.6, 30.2.

(3R,3aS,5R,6aR)-5-((4-Nitrophenoxy)carbonyloxy)hexahydro-2H-cyclopenta[b]furan-3-yl Acetate (19c). The title compound was obtained from **11** in 96% yield as described for **7** after purification by column chromatography on silica gel using hexanes/EtOAc (6:1 and then 4:1) as the eluent (white solid). TLC, R_f = 0.26 (hexanes/EtOAc = 3:1); ¹H NMR (CDCl₃, 300 MHz) δ 8.27 (d, J = 9.1 Hz, 2H), 7.37 (d, J = 9.1 Hz, 2H), 5.20–5.12 (m, 1H), 5.12–5.08 (m, 1H), 4.76 (dt, J = 2.0, 6.0 Hz, 1H), 4.27 (dd, J = 4.6, 10.4 Hz, 1H), 3.80 (dd, J = 2.5, 10.4 Hz, 1H), 2.79–2.70 (m, 1H), 2.37 (ddd, J = 6.0, 10.2, 15.0 Hz, 1H), 2.29–2.19 (m, 1H), 2.15 (dt, J = 5.6, 15.6 Hz, 1H), 2.07 (s, 3H), 2.02–1.92 (m, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 170.7, 155.4, 151.9, 145.3, 125.3, 121.8, 83.2, 81.0, 80.5, 71.7, 48.8, 39.6, 35.9, 21.1.

(3R,3aS,5R,6aR)-3-Methoxyhexahydro-2H-cyclopenta[b]furan-5-yl (4-Nitrophenyl)carbonate (19d). The title was obtained from **12** in 93% yield as described for **7** after purification by column chromatography on silica gel using hexanes/EtOAc (6:1 to 4:1) as the eluent (white solid). TLC, R_f = 0.40 (hexanes/EtOAc = 3:1); ¹H NMR (CDCl₃, 400 MHz) δ 8.27 (d, J = 9.2 Hz, 2H), 7.37 (d, J = 9.2 Hz, 2H), 5.19–5.12 (m, 1H), 4.74–4.67 (m, 1H), 4.13 (dd, J = 5.4, 5.5 Hz, 1H), 3.84–3.78 (m, 2H), 3.35 (s, 3H), 2.75–2.68 (m, 1H), 2.36 (ddd, J = 6.1, 10.0, 14.8 Hz, 1H), 2.25–2.11 (m, 2H), 1.82 (dddd, J = 1.2, 3.8, 5.5, 14.7 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 155.5, 151.9, 145.3, 125.3, 121.8, 87.5, 83.0, 81.3, 71.3, 56.9, 48.2, 39.4, 36.2.

(3S,3aR,5R,6aR)-3-Methylhexahydro-2H-cyclopenta[b]furan-5-yl (4-Nitrophenyl)carbonate (19e). The title compound was obtained from **14** in 83% yield as described for **7** after purification by column chromatography on silica gel using hexanes/EtOAc (10:1 and then 7:1) as the eluent (white solid). TLC, R_f = 0.25 (hexanes/EtOAc = 3:1); ¹H NMR (CDCl₃, 300 MHz) δ 8.27 (d, J = 9.0 Hz, 2H), 7.37 (d, J = 9.0 Hz, 2H), 5.09 (m, 1H), 4.57 (dt, J = 2.8, 6.2 Hz, 1H), 3.93 (t, J = 8.1 Hz, 1H), 3.51 (dd, J = 8.1, 10.4, 1H), 2.65 (m, 1H), 2.46 (m, 1H), 2.38 (m, 1H), 2.11 (m, 1H), 2.02 (ddd, J = 2.7, 5.5, 14.8 Hz, 1H), 1.81 (m, 1H), 1.02 (d, J = 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 155.5, 152.0, 145.3, 125.3, 121.8, 83.4, 80.8, 72.3, 45.8, 39.7, 36.5, 31.0, 11.8.

(3R,3aR,5R,6aR)-3-Methylhexahydro-2H-cyclopenta[b]furan-5-yl (4-Nitrophenyl)carbonate (19f). The title compound was obtained from **18** in 50% yield as described for **7** following column chromatography on silica gel using hexanes/EtOAc (10:1 and then 7:1) as the eluent (white solid). TLC, R_f = 0.29 (hexanes/EtOAc = 3:1); $[\alpha]_D^{20}$ +40.6 (c 1.0, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 8.26 (d, J = 9.3 Hz, 2H), 7.39 (d, J = 9.3 Hz, 2H), 5.19–5.12 (m, 1H), 4.57 (dt, J = 2.0, 6.8 Hz, 1H), 4.07 (dd, J = 6.3, 8.6 Hz, 1H), 3.31 (dd, J = 7.1, 8.6 Hz, 1H), 2.35–2.25 (m, 1H), 2.23–2.17 (m, 2H), 2.17–2.07 (m, 2H), 1.88 (ddd, J = 3.8, 5.3, 14.5 Hz, 1H), 1.05 (d, J = 6.8 Hz, 3H); ¹³C NMR

(CDCl₃, 100 MHz) δ 155.6, 151.9, 145.2, 125.2, 121.8, 83.3, 82.2, 74.9, 50.4, 41.8, 39.5, 37.3, 17.5.

General Method for the Synthesis of HIV-Protease Inhibitors. (3aS,5R,6aR)-3-Oxohexahydro-2H-cyclopenta[b]furan-5-yl [(2S,3R)-3-Hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl]carbamate (21). The *N*-Boc-protected isostere **20a** (82 mg, 0.16 mmol) was dissolved in a 2:1 mixture CH₂Cl₂/TFA and stirred at room temperature for 2 h. The solution was then evaporated and dried in vacuo. The residue was redissolved in CH₃CN (1 mL) and the solution cooled down to 0 °C under argon. Et₃N (100 μ L) was added followed by a solution of activated carbonate **19a** (40 mg, 0.13 mmol) in THF (1 mL). The solution was stirred for 36 h and the solution evaporated in vacuo. The residue was purified by column chromatography on silica gel using hexanes/EtOAc (3:1 to 1.5:1) as the eluent to furnish inhibitor **21** (46 mg, 61%) as a white solid. TLC, *R_f* = 0.23 (hexanes/EtOAc = 1:1); ¹H NMR (CDCl₃, 500 MHz) δ 7.70 (d, *J* = 8.8 Hz, 2H), 7.34–7.28 (m, 2H), 7.25–7.19 (m, 3H), 6.98 (d, *J* = 8.8 Hz, 2H), 5.03 (t, *J* = 6.9 Hz, 1H), 4.99 (m, 1H), 4.71 (d, *J* = 8.7 Hz, 1H), 3.97 (s, 2H), 3.87 (s, 3H), 3.89–3.85 (m, 1H), 3.83–3.70 (m, 2H), 3.09 (dd, *J* = 8.0, 15.2 Hz, 1H), 3.00 (dd, *J* = 3.0, 15.1 Hz, 1H), 2.99–2.89 (m, 3H), 2.89–2.82 (m, 1H), 2.79 (dd, *J* = 6.8, 13.4 Hz, 1H), 2.24–2.12 (m, 2H), 2.06–1.94 (m, 2H), 1.81 (m, 1H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.86 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 216.2, 163.0, 155.4, 137.5, 129.8, 129.6, 129.5, 128.5, 126.6, 114.3, 82.9, 76.3, 72.2, 70.6, 58.8, 55.6, 55.1, 53.7, 48.7, 41.2, 37.3, 35.1, 27.3, 20.1, 19.9. HRMS-ESI (*m/z*): [M + Na]⁺ calcd for C₂₉H₃₈N₂O₈SNa 597.2247, found 597.2251.

(3S,3aR,5R,6aR)-3-Hydroxyhexahydro-2H-cyclopenta[b]furan-5-yl [(2S,3R)-3-Hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl]carbamate (22). A solution of keto inhibitor **21** (10 mg, 17 μ mol) in EtOH was cooled to –25 °C, and NaBH₄ (6 mg) was added at once. The solution was stirred for 30 min. Then saturated aqueous NH₄Cl solution was added. The aqueous phase was extracted with EtOAc ($\times$ 4). The combined organic layer was dried, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using hexanes/EtOAc (2:1, 1:1, then 1:2) as the eluent to afford the desired inhibitor **22** (8 mg, 80%) as a white solid. TLC, *R_f* = 0.39 (hexanes/EtOAc = 1:5); ¹H NMR (CDCl₃, 500 MHz) δ 7.70 (d, *J* = 8.8 Hz, 2H), 7.32–7.19 (m, 5H), 6.97 (d, *J* = 8.8 Hz, 2H), 5.07 (m, 1H), 4.89 (d, *J* = 7.2 Hz, 1H), 4.38 (t, *J* = 6.8 Hz, 1H), 4.21 (m, 1H), 3.87 (s, 3H), 3.88–3.74 (m, 4H), 3.54 (dd, *J* = 3.2, 9.6 Hz, 1H), 3.10 (dd, *J* = 7.8, 15.0 Hz, 1H), 3.05–2.82 (m, 5H), 2.78 (dd, *J* = 6.8, 13.4 Hz, 1H), 2.42 (br s, 1H), 2.18–2.04 (m, 2H), 1.94–1.76 (m, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 163.0, 155.3, 137.6, 129.9, 129.6, 129.5, 128.6, 126.5, 114.3, 84.9, 78.1, 76.3, 73.0, 72.2, 58.7, 55.6, 55.3, 53.7, 47.3, 39.1, 35.4, 31.3, 27.2, 20.1, 19.9; LRMS-ESI (*m/z*): [M + Na]⁺ 599.3.

(3S,3aR,5R,6aR)-3-Hydroxyhexahydro-2H-cyclopenta[b]furan-5-yl [(2S,3R)-4-(4-Amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl]carbamate (23). The ketone intermediate was first synthesized from the coupling of **19a** with isostere **20b** as described for **21** after stirring 48 h at room temperature in a CH₂Cl₂/THF (1:1) mixture. Purification of the crude compound by column chromatography on silica gel using chloroform with 1–3% EtOH as the eluent afforded the corresponding ketone inhibitor (60%, white solid). TLC, *R_f* = 0.18 (chloroform/3% EtOH); ¹H NMR (CDCl₃, 500 MHz) δ 7.54 (d, *J* = 8.6 Hz, 2H), 7.34–7.28 (m, 2H), 7.25–7.18 (m, 3H), 6.68 (d, *J* = 8.6 Hz, 2H), 5.02 (t, *J* = 6.9 Hz, 1H), 4.99 (m, 1H), 4.68 (d, *J* = 8.8 Hz, 1H), 4.14 (br s, 2H), 3.98 (s, 2H), 3.91 (m, 1H), 3.84–3.72 (m, 2H), 3.08 (dd, *J* = 8.4, 15.1 Hz, 1H), 3.00–2.83 (m, 5H), 2.76 (dd, *J* = 8.7, 13.4 Hz, 1H), 2.22–2.15 (m, 2H), 2.05–1.97 (m, 2H), 1.80 (m, 1H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 216.9, 155.4, 150.6, 137.5,

129.6, 129.5, 128.5, 126.5, 126.3, 114.1, 82.9, 76.3, 72.2, 70.6, 58.9, 55.0, 53.8, 48.7, 41.2, 37.3, 35.2, 27.3, 20.2, 19.9. HRMS-ESI (*m/z*): [M + Na]⁺ calcd for C₂₈H₃₇N₃O₇SNa 582.2250, found 582.2246. The title compound was obtained in 82% yield by reduction of the above ketone intermediate as described for **22**, followed by column chromatography on silica gel using hexanes/EtOAc (1:2 to 1:5) as the eluent. Off-white solid. TLC, *R_f* = 0.12 (hexanes/EtOAc = 1:2); ¹H NMR (CDCl₃, 500 MHz) δ 7.54 (d, *J* = 8.8 Hz, 2H), 7.34–7.18 (m, 5H), 6.68 (d, *J* = 8.8 Hz, 2H), 5.07 (m, 1H), 4.87 (d, *J* = 7.2 Hz, 1H), 4.38 (t, *J* = 6.8 Hz, 1H), 4.24–4.19 (m, 1H), 4.14 (s, 2H), 3.86 (br s, 1H), 3.85–3.75 (m, 3H), 3.55 (dd, *J* = 3.6, 9.6 Hz, 1H), 3.10 (dd, *J* = 8.2, 15.0 Hz, 1H), 3.04–2.79 (m, 5H), 2.76 (dd, *J* = 6.8, 13.2 Hz, 1H), 2.37 (d, *J* = 11.6 Hz, 1H), 2.10 (t, *J* = 14.4 Hz, 2H), 1.94–1.75 (m, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 155.3, 150.6, 137.6, 129.6, 129.5, 128.5, 126.5, 126.4, 114.1, 84.9, 78.0, 70.3, 73.0, 72.2, 58.8, 55.2, 53.7, 47.3, 39.1, 35.5, 31.3, 27.3, 20.2, 19.9. HRMS-ESI (*m/z*): [M + Na]⁺ calcd for C₂₈H₃₉N₃O₇SNa 584.2406, found 584.2410.

(3S,3aR,5R,6aR)-3-Hydroxyhexahydro-2H-cyclopenta[b]furan-5-yl [(2S,3R)-3-Hydroxy-4-[4-(hydroxymethyl)-N-isobutylphenylsulfonamido]-1-phenylbutan-2-yl]carbamate (24). The ketone intermediate was first synthesized from the coupling of **19a** with isostere **20c** as described for **21**. Purification of the crude compound by column chromatography on silica gel using hexanes/EtOAc (2:1 to 1:2) as the eluent afforded the corresponding ketone inhibitor in 49% yield as a white solid. TLC, *R_f* = 0.38 (hexanes/EtOAc = 1:3); ¹H NMR (CDCl₃, 500 MHz) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.34–7.28 (m, 2H), 7.25–7.20 (m, 3H), 5.02 (t, *J* = 6.9 Hz, 1H), 4.96 (m, 1H), 4.79 (s, 2H), 4.67 (d, *J* = 8.4 Hz, 1H), 3.98–3.93 (m, 2H), 3.84–3.75 (m, 2H), 3.75–3.67 (m, 1H), 3.10 (dd, *J* = 8.2, 15.1 Hz, 1H), 3.07–2.80 (m, 5H), 2.83 (dd, *J* = 6.9, 13.5 Hz, 1H), 2.23–2.15 (m, 2H), 2.04–1.96 (m, 2H), 1.88–1.76 (m, 1H), 0.90 (dd, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H). The title compound was obtained in 83% yield by reduction of the above ketone intermediate as described for **22**, followed by column chromatography on silica gel using hexanes/EtOAc (1:1 to 1:3 and then 100% EtOAc) as the eluent. White solid. TLC, *R_f* = 0.23 (hexanes/EtOAc = 1:3); ¹H NMR (CDCl₃, 400 MHz) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.34–7.27 (m, 2H), 7.24–7.20 (m, 3H), 5.06 (m, 1H), 4.82 (d, *J* = 7.8 Hz, 1H), 4.76 (s, 2H), 4.38 (t, *J* = 7.0 Hz, 1H), 4.21 (m, 1H), 3.85–3.68 (m, 4H), 3.55 (dd, *J* = 3.5, 9.8 Hz, 1H), 3.11 (dd, *J* = 8.3, 15.1 Hz, 1H), 3.05–2.79 (m, 6H), 2.38 (d, *J* = 8.3 Hz, 1H), 2.15–1.99 (m, 2H), 1.94–1.80 (m, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H). HRMS-ESI (*m/z*): [M + Na]⁺ calcd for C₂₉H₄₀N₂O₈SNa 599.2403, found 599.2401.

(3S,3aS,5R,6aR)-3-Methoxyhexahydro-2H-cyclopenta[b]furan-5-yl [(2S,3R)-3-Hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl]carbamate (25). The title compound was obtained in 73% yield from **19b** and **20a** as described for **21** following column chromatography on silica gel using hexanes/EtOAc (1:1) as the eluent. White solid. TLC, *R_f* = 0.21 (hexanes/EtOAc = 1:1); ¹H NMR (CDCl₃, 500 MHz) δ 7.70 (d, *J* = 8.9 Hz, 2H), 7.33–7.19 (m, 5H), 6.97 (d, *J* = 8.9 Hz, 2H), 4.97–4.90 (m, 1H), 4.78 (d, *J* = 7.5 Hz, 1H), 4.47–4.42 (m, 1H), 3.99 (q, *J* = 6.9 Hz, 1H), 3.87 (s, 3H), 3.88–3.82 (m, 2H), 3.81–3.76 (m, 2H), 3.70 (dd, *J* = 6.9, 9.0 Hz, 1H), 3.30 (s, 3H), 3.14–3.06 (dd, *J* = 7.8, 14.9 Hz, 1H), 3.04–2.88 (m, 4H), 2.78 (dd, *J* = 6.7, 13.4 Hz, 1H), 2.70 (m, 1H), 2.14 (m, 1H), 1.93 (dd, *J* = 6.3, 8.6 Hz, 2H), 1.86–1.76 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 163.0, 156.3, 137.5, 129.9, 129.6, 129.5, 128.5, 126.5, 114.3, 83.5, 81.3, 76.3, 72.3, 70.0, 58.7, 57.8, 55.6, 54.9, 53.7, 43.8, 39.5, 35.5, 30.4, 27.2, 20.1, 19.9. HRMS-ESI (*m/z*): [M + H]⁺ calcd for C₃₀H₄₃N₂O₈S 591.2740, found 591.2742.

(3R,3aR,5R,6aR)-3-Hydroxyhexahydro-2H-cyclopenta[b]furan-5-yl [(2S,3R)-3-Hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl]carbamate (26). The

acetyl intermediate was first synthesized in 84% yield by coupling of **19c** with **20a** as described for **21** followed by purification by column chromatography on silica gel using hexanes/EtOAc (3:1 to 1:1) as the eluent. White solid. TLC, R_f = 0.23 (hexanes/EtOAc = 1:2); ^1H NMR (CDCl_3 , 300 MHz) δ 7.71 (d, J = 8.9 Hz, 2H), 7.34–7.19 (m, 5H), 6.97 (d, J = 8.9 Hz, 2H), 4.91 (m, 1H), 4.88 (m, 1H), 4.75 (d, J = 8.2 Hz, 1H), 4.67 (m, 1H), 3.98 (dd, J = 4.1, 10.4 Hz, 1H), 3.87 (s, 3H), 3.85–3.77 (m, 3H), 3.73 (dd, J = 1.5, 10.4 Hz, 1H), 3.19–2.92 (m, 4H), 2.90–2.72 (m, 2H), 2.67–2.55 (m, 1H), 2.23–2.09 (m, 1H), 2.06 (s, 3H), 2.04–1.76 (m, 3H), 1.50–1.43 (m, 1H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 170.6, 163.0, 156.0, 137.6, 129.8, 129.5, 128.5, 126.6, 114.3, 83.5, 80.6, 76.1, 72.6, 71.6, 58.8, 55.6, 54.9, 53.7, 48.5, 39.6, 36.2, 35.7, 27.2, 21.1, 20.1, 19.9. The acetate intermediate (18 mg, 0.029 mmol) was diluted in MeOH (1.5 mL) at 0 °C. K_2CO_3 (5 mg, 0.04 mmol) was added, and the solution was stirred for 6 h. Saturated aqueous NH_4Cl solution (1 mL) was added, and the solvent was reduced under vacuum. The aqueous phase was diluted and extracted with EtOAc ($\times 4$). The combined organic phase was dried (MgSO_4), filtered, and evaporated. The residue was purified by column chromatography on silica gel using (chloroform)/(0.5–3% EtOH) as the eluent to provide inhibitor **26** (15.9 mg, 94%) as a white solid. TLC, R_f = 0.26 (hexanes/EtOAc = 1:5); ^1H NMR (CDCl_3 , 500 MHz) δ 7.71 (d, J = 8.9 Hz, 2H), 7.33–7.25 (m, 1H), 7.24–7.19 (m, 3H), 6.98 (d, J = 8.9 Hz, 2H), 4.86 (m, 1H), 4.81 (d, J = 8.3 Hz, 1H), 4.69 (t, J = 5.4 Hz, 1H), 4.01 (m, 1H), 3.91–3.76 (m, 4H), 3.87 (s, 3H), 3.64 (dd, J = 2.0, 9.7 Hz, 1H), 3.12 (dd, J = 8.2, 15.1 Hz, 1H), 3.11–3.05 (m, 1H), 3.03 (dd, J = 2.7, 15.2 Hz, 1H), 2.95 (dd, J = 8.3, 13.4 Hz, 1H), 2.85–2.75 (m, 2H), 2.52 (m, 1H), 2.12 (ddd, J = 6.1, 10.0, 14.7 Hz, 1H), 1.99 (dt, J = 6.1, 15.0 Hz, 1H), 1.93–1.79 (m, 3H), 1.35 (m, 1H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 163.0, 156.0, 137.8, 129.8, 129.5, 128.4, 126.4, 114.3, 83.1, 78.3, 76.3, 73.8, 72.7, 58.8, 55.6, 54.8, 53.7, 51.3, 39.5, 36.1, 35.8, 27.2, 20.1, 19.9. HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{41}\text{N}_2\text{O}_8\text{S}$ 577.2584, found 577.2572.

(3R,3aR,5R,6aR)-3-Hydroxyhexahydro-2H-cyclopenta[b]furan-5-yl [(2S,3R)-4-(4-Amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl]carbamate (27). The acetyl intermediate was first synthesized in 63% yield by coupling of **19c** with **20b** as described for **21** followed by purification by column chromatography on silica gel using (CHCl_3)/(0.25–1.5% EtOH) as the eluent. White solid. TLC, R_f = 0.44 (hexanes/EtOAc = 1:3); ^1H NMR (CDCl_3 , 500 MHz) δ 7.54 (d, J = 8.7 Hz, 2H), 7.32–7.27 (m, 2H), 7.25–7.19 (m, 3H), 6.67 (d, J = 8.7 Hz, 2H), 4.94 (m, 1H), 4.90–4.85 (m, 1H), 4.75 (d, J = 8.7 Hz, 1H), 4.66 (t, J = 5.4 Hz, 1H), 4.16 (br s, 2H), 3.99 (dd, J = 4.1, 10.4 Hz, 1H), 3.88–3.77 (m, 3H), 3.74 (d, J = 10.3 Hz, 1H), 3.11 (dd, J = 8.5, 15.1 Hz, 1H), 3.05 (dd, J = 4.0, 14.1 Hz, 1H), 2.98 (dd, J = 1.5, 15.2 Hz, 1H), 2.93 (dd, J = 8.4, 13.2 Hz, 1H), 2.84 (dd, J = 8.8, 13.9 Hz, 1H), 2.77 (dd, J = 6.7, 13.3 Hz, 1H), 2.64–2.56 (m, 1H), 2.20–2.12 (m, 1H), 2.07 (s, 3H), 2.00 (dt, J = 6.1, 15.2 Hz, 1H), 1.95–1.88 (m, 1H), 1.81 (m, 1H), 1.51–1.44 (m, 1H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 170.6, 155.9, 150.6, 137.7, 129.5, 128.5, 126.5, 126.2, 114.1, 83.5, 80.6, 76.0, 72.6, 71.5, 58.9, 54.9, 53.8, 48.5, 39.6, 36.2, 35.7, 27.3, 21.1, 20.2, 19.9. The title compound was obtained from the above acetate intermediate in 88% yield as described for **26** following purification by column chromatography on silica gel using a gradient, 1–5% EtOH in CHCl_3 , as the eluent. White solid. TLC, R_f = 0.4 (CHCl_3 /10% EtOH); ^1H NMR (CDCl_3 , 500 MHz) δ 7.55 (d, J = 8.7 Hz, 2H), 7.31–7.26 (m, 2H), 7.24–7.19 (m, 3H), 6.67 (d, J = 8.7 Hz, 2H), 4.89–4.83 (m, 1H), 4.79 (d, J = 8.9 Hz, 1H), 4.69 (t, J = 5.4 Hz, 1H), 4.16 (br s, 2H), 4.01 (m, 1H), 3.88 (dd, J = 3.7, 9.9 Hz, 1H), 3.87–3.76 (m, 3H), 3.65 (dd, J = 1.4, 9.8 Hz, 1H), 3.14–3.04 (m, 2H), 2.99 (dd, J = 2.9, 15.1 Hz, 1H), 2.92 (dd, J = 8.3, 13.3 Hz, 1H), 2.81 (dd, J = 9.1, 14.0 Hz, 1H), 2.78 (dd, J = 6.8, 13.3 Hz, 1H), 2.54–2.47 (m, 1H), 2.11 (ddd, J = 6.2, 10.2, 14.6 Hz,

1H), 2.00 (dt, J = 6.1, 15.1 Hz, 1H), 1.93–1.85 (m, 1H), 1.85–1.76 (m, 2H), 1.35 (m, 1H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 156.0, 150.7, 137.8, 129.5, 128.4, 126.4, 126.2, 114.1, 83.1, 78.3, 76.2, 73.7, 72.7, 58.9, 54.8, 53.8, 51.3, 39.5, 36.0, 35.8, 27.3, 20.2, 19.9. HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{39}\text{N}_3\text{O}_7\text{S}$ 584.2406, found 584.2398.

(3R,3aS,5R,6aR)-3-Methoxyhexahydro-2H-cyclopenta[b]furan-5-yl [(2S,3R)-3-Hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl]carbamate (28). The title compound was obtained in 57% yield from **19d** and **20a** as described for **21** following purification by column chromatography on silica gel using hexanes/EtOAc (2:1 to 1:1) as the eluent. White solid. TLC, R_f = 0.34 (hexanes/EtOAc = 1:2); ^1H NMR (CDCl_3 , 500 MHz) δ 7.71 (d, J = 8.8 Hz, 2H), 7.33–7.25 (m, 2H), 7.26–7.20 (m, 3H), 6.98 (d, J = 8.8 Hz, 2H), 4.89 (m, 1H), 4.78 (d, J = 8.3 Hz, 1H), 4.61 (t, J = 5.7 Hz, 1H), 3.93–3.85 (m, 1H), 3.88 (s, 3H), 3.85–3.79 (m, 2H), 3.73 (d, J = 2.7, 9.8 Hz, 1H), 3.60 (m, 1H), 3.31 (s, 3H), 3.13 (dd, J = 8.3, 15.2 Hz, 1H), 3.10–3.00 (m, 2H), 2.95 (dd, J = 8.4, 13.4 Hz, 1H), 2.88–2.77 (m, 1H), 2.80 (dd, J = 7.0, 13.3 Hz, 1H), 2.62–2.53 (m, 1H), 2.19–2.09 (m, 1H), 1.99 (dt, J = 6.0, 15.1 Hz, 1H), 1.92 (m, 1H), 1.90–1.78 (m, 2H), 1.47–1.38 (m, 1H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 163.0, 156.1, 137.7, 129.9, 129.5, 128.5, 126.5, 114.3, 87.6, 83.3, 76.5, 72.7, 71.1, 58.8, 56.7, 55.6, 54.9, 53.7, 48.0, 39.5, 36.6, 35.8, 27.2, 20.1, 19.9. HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{30}\text{H}_{42}\text{N}_2\text{O}_8\text{SNa}$ 613.2560, found 613.2555.

(3S,3aR,5R,6aR)-3-Methylhexahydro-2H-cyclopenta[b]furan-5-yl [(2S,3R)-3-Hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl]carbamate (29). The title compound was obtained from **19e** and **20a** in 78% yield as described for **21** following purification by column chromatography on silica gel using hexanes/EtOAc (3:1 to 2:1) as the eluent. White solid. TLC, R_f = 0.32 (hexanes/EtOAc = 1:1); ^1H NMR (CDCl_3 , 300 MHz) δ 7.71 (d, J = 8.9 Hz, 2H), 7.34–7.19 (m, 5H), 6.98 (d, J = 8.9 Hz, 2H), 4.84 (m, 1H), 4.75 (d, J = 8.2 Hz, 1H), 4.49–4.40 (m, 1H), 3.87 (s, 3H), 3.86–3.76 (m, 4H), 3.32 (dd, J = 8.3, 10.5 Hz, 1H), 3.11 (dd, J = 7.8, 15.1 Hz, 1H), 3.06–2.84 (m, 4H), 2.79 (dd, J = 6.7, 13.4 Hz, 1H), 2.54–2.45 (m, 1H), 2.40–2.31 (m, 1H), 2.18 (dt, J = 6.5, 14.8 Hz, 1H), 1.90–1.77 (m, 2H), 1.74–1.66 (m, 1H), 1.50–1.40 (m, 1H), 0.91 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 162.7, 156.3, 137.6, 129.8, 129.5, 128.5, 126.5, 114.3, 83.5, 76.0, 72.6, 72.2, 58.7, 55.6, 54.9, 53.7, 45.6, 39.8, 36.4, 35.6, 31.3, 27.2, 20.1, 19.8, 11.8. LRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ 597.3, $[\text{M} + \text{H}]^+$ 575.1.

(3R,3aR,5R,6aR)-3-Methylhexahydro-2H-cyclopenta[b]furan-5-yl [(2S,3R)-3-Hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl]carbamate (30). The title compound was obtained from **19f** and **20a** in 96% yield as described for **21** following purification by column chromatography on silica gel using hexanes/EtOAc (5:1) as the eluent. White solid. TLC, R_f = 0.50 (hexanes/EtOAc = 1:1); $[\alpha]_D^{20}$ +24.5 (c 1.0, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 7.70 (d, J = 8.8 Hz, 2H), 7.30–7.16 (m, 5H), 6.96 (d, J = 8.8 Hz, 2H), 4.88 (m, 1H), 4.80 (d, J = 7.1 Hz, 1H), 4.46 (m, 1H), 3.91 (dd, J = 6.1, 8.5 Hz, 1H), 3.86 (s, 3H), 3.80 (m, 3H), 3.22 (dd, J = 7.5, 14.8 Hz, 1H), 3.15–2.99 (m, 3H), 2.94 (dd, J = 8.2, 13.4 Hz, 1H), 2.87–2.75 (m, 2H), 2.14 (m, 1H), 2.00–1.77 (m, 5H), 1.50 (d, J = 12.3 Hz, 1H), 0.98 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 162.9, 156.2, 137.7, 129.8, 129.4, 128.4, 126.4, 114.3, 83.7, 77.2, 74.7, 72.5, 58.7, 55.6, 54.8, 53.7, 50.2, 41.8, 39.4, 37.7, 35.7, 27.2, 20.1, 19.8, 17.6. LRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ 597.1, $[\text{M} + \text{H}]^+$ 575.3.

(3S,3aR,5R,6aR)-3-(Dimethylamino)hexahydro-2H-cyclopenta[b]furan-5-yl [(2S,3R)-3-Hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl]carbamate (31). To a solution of AcOH ($\sim 15 \mu\text{L}$) in dichloromethane (1 mL), a slow

stream of Me₂NH gas was bubbled briefly at 0 °C for 5 min. After the flask was flushed with argon, a solution of ketone inhibitor **21** (13 mg, 0.02 mmol) in dichloroethane (0.5 mL) was added at 0 °C, and after 15 min, NaBH(OAc)₃ (10 mg, 0.05 mmol) was added. The resulting solution was warmed to room temperature. After 24 h, another 10 mg portion of NaBH(OAc)₃ was added and the solution stirred for 48 h. The reaction was quenched by addition of saturated aqueous NaHCO₃ solution, adjusting the pH to 10 with 1 M NaOH solution. The aqueous phase was extracted multiple times with EtOAc. The combined organic phase was dried (Na₂SO₄), filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using ethanol (0.5–2%) in CHCl₃ to furnish the corresponding dimethylamine inhibitor **31** (11.3 mg, 82%) as a white solid. TLC, *R*_f = 0.35 (CHCl₃/8% EtOH); ¹H NMR (CDCl₃, 500 MHz) δ 7.70 (d, *J* = 8.9 Hz, 2H), 7.32–7.26 (m, 2H), 7.25–7.19 (m, 3H), 6.97 (d, *J* = 8.9 Hz, 2H), 4.92 (m, 1H), 4.86 (m, 1H), 4.55 (m, 1H), 3.90–3.85 (m, 1H), 3.87 (s, 3H), 3.83–3.75 (m, 2H), 3.70–3.63 (m, 1H), 3.30–3.20 (m, 1H), 3.10 (dd, *J* = 3.14, 3.06 Hz, 1H), 3.04–2.88 (m, 4H), 2.79 (dd, *J* = 6.9, 13.4 Hz, 1H), 2.64–2.55 (m, 1H), 2.23–2.18 (m, 1H), 2.24 (br s, 6H), 2.18–2.10 (m, 1H), 2.06–1.97 (m, 1H), 1.88–1.75 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 163.0, 156.4, 137.6, 130.0, 129.6, 129.5, 128.5, 126.5, 114.3, 83.8, 77.2, 76.0, 72.3, 69.4, 58.7, 55.6, 55.0, 53.7, 45.4, 45.3, 40.1, 35.5, 31.4, 27.2, 20.1, 19.9. LRMS-ESI (*m/z*): [M + H]⁺ 604.3

Determination of X-ray Structure of HIV-1 Protease Inhibitor Complex. The optimized HIV-1 protease was expressed and purified as previously described.²³ The protease–inhibitor complex was crystallized by the hanging drop vapor diffusion method with well solutions of 1.2 M ammonium chloride and 0.1 M sodium acetate buffer (pH 4.8). Diffraction data were collected on a single crystal cooled to 90 K at SER-CAT BM beamline 22, Advanced Photon Source, Argonne National Laboratory (Chicago, IL, U.S.), with an X-ray wavelength of 1.0 Å and processed by HKL-2000²⁴ with *R*_{merge} of 7.2%. The PR structure was used in molecular replacement by PHASER^{25,26} in the CCP4i suite^{27,28} and refined to 1.45 Å resolution using SHELX-97^{29,30} and COOT³¹ for manual modification. PRODRG-2³² was used to construct the inhibitor and the restraints for refinement. Alternative conformations were modeled, anisotropic atomic displacement parameters (*B* factors) were applied for all atoms including solvent molecules, and hydrogen atoms were added in the final round of refinement. The final refined solvent structure comprised two Cl[−] ions and 142 water molecules. The crystallographic statistics are listed in Table 3 in the Supporting Information. The coordinates and structure factors of the PR with **26** complex have been deposited in Protein Data Bank³³ with code 3ST5.

■ ASSOCIATED CONTENT

S Supporting Information. HPLC, LRMS, and HRMS data of inhibitors **21**–**31**; crystallographic data collection and refinement statistics for inhibitor **26**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Accession Codes

[†]The PDB accession code for **26**-bound HIV-1 protease X-ray structure is 3ST5.

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■ ACKNOWLEDGMENT

This research was supported by the National Institutes of Health (Grant GM53386 to A.K.G. and Grant GM62920 to I.T. W.). This work was also supported by the Intramural Research Program of the Center for Cancer Research, National Cancer Institute, National Institutes of Health, and in part by a Grant-in-Aid for Scientific Research (Priority Areas) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (Monbu Kagakusho), a Grant for Promotion of AIDS Research from the Ministry of Health, Welfare, and Labor of Japan, and the Grant to the Cooperative Research Project on Clinical and Epidemiological Studies of Emerging and Reemerging Infectious Diseases (Renkei Jigyo) of Monbu-Kagakusho.

■ ABBREVIATIONS USED

bis-THF, bis-tetrahydrofuran; Cp-THF, hexahydrocyclopentafuran; PI, protease inhibitor; APV, amprenavir; DRV, darunavir; SQV, saquinavir; IDV, indinavir; TBS, *tert*-butyldimethylsilyl; DIBAL, diisobutylaluminum hydride

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