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Solid-Phase Synthesis of HTLV-1 Protease Inhibitors Containing Hydroxyethylamine Dipeptide Isostere

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An efficient method has been developed for the first solid-phase synthesis of HTLV-1 protease inhibitors that contain hydroxyethylamine isostere as a transition-state mimetic. The synthetic procedure was designed to allow the evaluation of stereostructure−activity relationships at the scissile site. All the possible configurations at the hydroxy- and side chain-bearing asymmetric centers of the isostere were constructed by an ester-derived asymmetric aldol reaction. Each inhibitor containing the isostere backbone was synthesized on solid support by using the newly developed succinate ester linker. The configuration at the hydroxy- and side chain-bearing asymmetric center showed remarkable effects on the inhibitory activity; the K_i value changed with approximately 2 orders of magnitude. The described approach enables an efficient preparation of the inhibitors containing secondary alcohol as a transition-state mimetic.

Introduction

Human T-cell leukemia virus type-1 (HTLV-1) isolated in the early 1980s was the first exogeneous retrovirus shown to be associated with adult T-cell leukemia and a number of other chronic diseases.[1] The genome of HTLV-1 is approximately 9 kb in length and contains several open reading frames that encode *gag*, *pol*, *env*, and regulatory proteins. As in other retroviruses including HIV, HTLV-1 proteins are initially translated as large precursor polyproteins that undergo proteolytic processing by the viral protease during virion assembly and maturation.[2] The protease is an aspartic protease that is encoded in a separate reading frame overlapping the *gag*/*pol* coding sequence of the virus genome. The protease itself is autoprocessed from a precursor protein and thus the function of the mature 125-amino acid-long HTLV-1 protease is crucial for virus replication. Although several studies have reported expression of the stabilized HTLV-1 protease in *Escherichia coli* as well as its kinetic characterization, the biochemical properties of the HTLV-1 protease have not been well-described because of the difficulties in obtaining sizable amounts of the protease.[3] To date, no structural information is available for the HTLV-1 protease. Thus, no effective HTLV-1 protease inhibitor has been reported; this contrasts with the numerous potent inhibitors of HIV protease reported. The inhibitors for HIV protease are unable to block the processing of HTLV-1 derived precursor proteins.[4] It is suggested that the substrate binding site of HTLV-1 protease is different from the substrate binding site of pepsin and HIV-1 protease.[4b] To address these difficulties, we have reported a total chemical synthesis of [L40I, C90A, C109A]-HTLV-1 protease, an auto-digestion resistant mutant of the protease, and evaluated its kinetic properties regarding enzymatic activity.[5] In this paper, we report the first solid-phase syntheses of HTLV-1 protease inhibitors containing the transition-state isostere mimetic and evaluation of the stereostructure−activity relationship of the inhibitors.[6] By using a newly developed succinic acid linker, each inhibitor containing the isostere mimetic was efficiently synthesized on solid support.

Results and Discussion

A key structural element in many of the aspartic protease inhibitors is a hydroxy or hydroxy-like structure that binds to the catalytic aspartates in the enzyme activation site.[7] Among numerous transition-state analogues based on this principle, we selected a hydroxyethylamine isostere, one of the most common transition-state isosteres utilized in peptide-like aspartic protease inhibitors.[8] The absolute configuration of the hydroxy-

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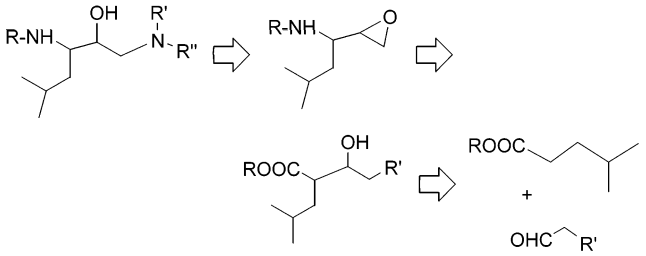
SCHEME 1



bearing asymmetric center of the isostere would have a pronounced effect on the inhibitory potency as in the case of HIV protease inhibitors.[9] In this study regarding the HTLV-1 protease inhibitors, we attempted to evaluate the effects of the amino acid derived substituent in combination with the hydroxy group. Thus, a synthetic scheme, in which the absolute configuration at the hydroxy- and side chain-bearing asymmetric centers of the scissile site can be selectively constructed, was adopted for the construction of the isostere backbone.

Stereoselective Construction of the Isostere Backbone. Scheme 1 shows our synthetic route for the hydroxyethylamine isostere. Aminoalkyl epoxide is selected as a key intermediate for the construction of the isostere backbone. In most of the previous syntheses of the aminoalkyl epoxide or related compounds, N-protected L-amino acid derivatives were employed as the starting materials.[10] These syntheses, however, have limitations in stereochemical control at the hydroxy-bearing centers as well as in the varieties of side-chain substituents. To avoid these limitations, several stereoselective syntheses of the aminoalkyl epoxide have been reported, in which the hydroxy group and the side-chain substituent were introduced successively.[11] In our synthetic scheme, we selected stereochemical control of both groups by a single step asymmetric aldol reaction, in which a chiral ester-derived titanium enolate was employed.[12] The enolate was reported to react with monodentate or bidentate aldehydes to provide *anti*- or *syn*-aldol product, respectively; thus each product would be selectively prepared by using the same chiral template, *cis*-1-arylsulfonamido-2-indanol derivative.

The *syn*-type aminoalkyl epoxide **5** was prepared according to the route developed by Ghosh et al.[13] (Figure 1). (1*S*,2*R*)-1-Arylsulfonamido-2-indanyl 4-methylvalerate **1** was converted to titanium enolate and then reacted with (benzyloxy)acetaldehyde according to the published procedure to maintain the aldol product as a single diastereomer. The chiral auxiliary of **2** was removed by hydrolysis and the crude product, without further purification, was subjected to Curtius rearrangement. Treatment of the mixture with diphenylphosphoryl azide and triethylamine gave the oxazolidinone **3** in 61% yield. The *syn* configuration at the asymmetric carbons of **3** was confirmed by homonuclear decoupling experiments. The coupling constant of the vicinal protons at the asymmetric carbons (J_{A-B} = 7.9 Hz) was consistent with that of the literature value of *syn* stereochemistry.[14] The oxazolidinone ring of **3** was then opened by hydrolysis with aqueous KOH. Without further purification, the amino group of the product was protected with a Boc group by reaction with di-*tert*-butyl dicarbonate in DMF to yield **4**. After purification, the benzyl group of **4** was removed by catalytic hydrogenation and the resulting diol product was converted to the desired aminoalkyl epoxide by Mitsunobu reaction. Exposure of the diol with triphenylphosphine and diethylazodicarboxylate gave **5** at 54% yield after chromatography. The enantiomer of **5** was similarly prepared starting from (1*R*,2*S*)-1-arylsulfonamido-2-indanyl ester-derived enolate.

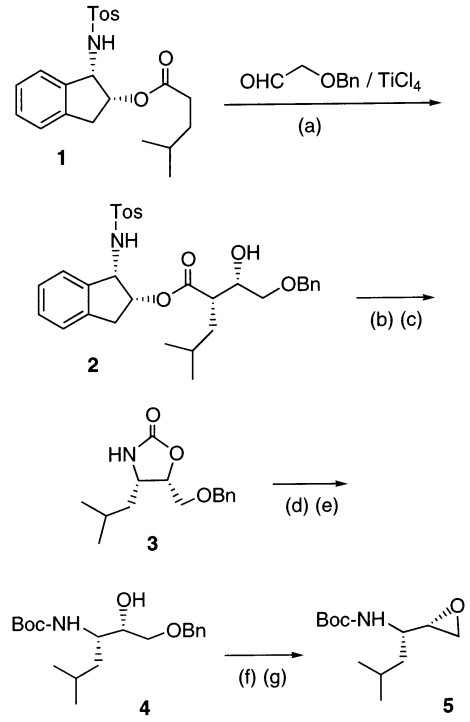


FIGURE 1. The preparation of the *syn*-type aminoalkyl epoxide **5**. Reagents and conditions: (a) −78 °C, 2 h; (b) 30% H_2O_2, LiOH, 23 °C, 12 h; (c) DPPA/Et_3N, 23 °C, 24 h; (d) KOH/EtOH−H_2O, reflux, 8 h; (e) di-*tert*-butyl dicarbonate, DIEA, 23 °C, 24 h; (f) H_2/Pd−C, 23 °C, 12 h; (g) Ph_3P/DEAD in $CHCl_3$, reflux, 6 h.

For preparation of the *anti*-type aminoalkyl epoxide, we first examined the synthesis of the *anti*-type oxazolidinone **22** using the same bidentate aldehyde as above,

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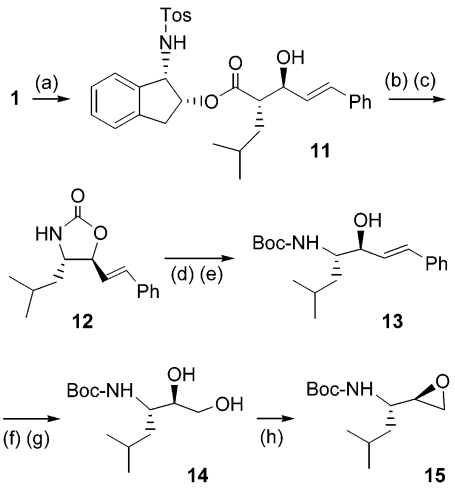

FIGURE 2. Synthetic route for the anti-type aminoalkyl epoxide **15**. Reagents and conditions: (a) cinnamaldehyde/ $^{n}Bu_2BOTf$, −78 °C, 1.5 h; (b) 30% H_2O_2, LiOH, 23 °C, 15 h; (c) DPPA/Et_3N in benzene, reflux, 10 h; (d) KOH/EtOH−H_2O, reflux, 15 h; (e) di-*tert*-butyl dicarbonate, DIEA, 23 °C, 4 h; (f) O_3, −78 °C, 30 min; (g) $NaBH_4$, 23 °C, 1 h; (h) Ph_3P/DEAD in $CHCl_3$, reflux, 6 h.

but containing a more sterically hindered TBDPS group instead of the Bn group. The steric bulk could hinder the effective chelation derived from the ether oxygen, which could result in conversion of the stereoselectivity.[12] The aldol condensation of the tosyl-indanyl ester **6** with the aldehyde precomplexed with $TiCl_4$ gave a single product, **21**, at 52% isolation yield leaving a small amount of the starting ester. The product could be converted to the desired *anti*-type oxazolidinone **22** according to the same route as that employed for the *syn*-oxazolidinone **3**. However, the cyclization yield was poor (less than 10%) probably due to the steric hindrance of the TBDPS group. Thus, we decided to use a monodentate aldehyde for preparation of the *anti*-type aldol product.

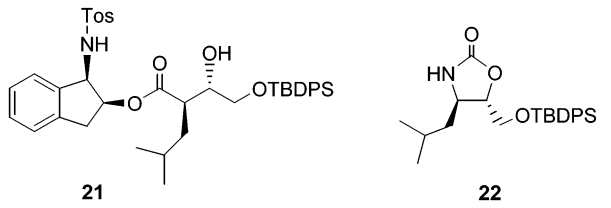

Figure 2 shows the synthetic route for the *anti*-type aminoalkyl epoxide **15**. Cinnamaldehyde was selected as the monodentate aldehyde according to a previous report.[13] Reaction of the enolate of **1** with cinnamaldehyde precomplexed with $^{n}Bu_2BOTf$ afforded the desired *anti*-product as a major product (6:1 ratio) in 28% isolated yield. Reaction with cinnamaldehyde precomplexed with $TiCl_4$, however, proceeded sluggishly and gave the undesired *syn*-product exclusively with 9% isolation yield. Oxazolidinone **12** was prepared from the aldol product **11** and the *anti* stereochemistry of **12** was established by the vicinal coupling constant (J_{A-B} = 6.3 Hz)[14] as described for the *syn*-type oxazolidinone **3**. Basic hydrolysis of **12** and subsequent Boc-protection produced **13** in 90% yield without difficulties. Ozonolysis of the double bond followed by reductive workup yielded the diol **14**, which was converted to the desired aminoalkyl epoxide by Mitsunobu reaction as described previously. The enantiomer of **15** was similarly prepared starting from (1*R*,2*S*)-1-arylsulfonamide-2-indanyl 4-methylvalerate. Thus, the four stereoisomers of the aminoalkyl epoxide were selectively prepared by using the asymmetric aldol reaction.

Solid-Phase Synthesis of Inhibitors. Although most of the previous syntheses of protease inhibitors were conducted with use of conventional solution-phase procedures, these methods were not suitable for library preparation. In addition, in the syntheses of inhibitors containing hydroxy-type isosters, formation of the byproducts derived from overreaction at the hydroxy group yielded homobislactone or a half-ester dimer.[15] To avoid these limitations, several solid-phase approaches were reported, in which a multistep conversion of the functional groups would be necessary for the chain elongation due to the acid-labile linkage to the solid support.[16] A key feature of our solid-phase approach is the development of an acid-stable linker, which can be incorporated by simple reaction with succinic anhydride. The linkage through the secondary alcohol of the isoster serves not only to anchor the inhibitor to the solid support, but also to protect the alcohol functionality. The linker can be easily cleaved under an aqueous basic condition.

The synthetic scheme for HTLV-1 protease inhibitor on solid support is shown in Figure 3. The aminoalkyl epoxide **5** was reacted with proline amide derivative (H-Pro-$NHCH_2C_6H_4I$)[17] at 70 °C to give the hydroxyethylamine product **23** in 65% yield. A succinic acid linker was introduced to the hydroxy group of **23** by reaction with succinic anhydride in the presence of DMAP. The resulting carbonyl group of the condensed product was then used for the reaction with the amino group on solid support to anchor the hydroxyethylamine derivative. As the solid support, glycyl *p*-methylbenzhydrylamine polystyrene resin was employed, and the anchoring reaction was carried out with DIPCDI-mediated reaction to yield **28**. The Boc group of **28** was removed by treatment with 50% TFA/CH_2Cl_2. After neutralization with DIEA, Boc-Ile-OH was condensed by reaction with DIPCDI and HOBt. The same deprotection/condensation procedure was employed for the successive introduction of Boc-Val-OH and Boc-Pro-OH to afford the desired inhibitor resin **29**. The product resin was then treated with HF at 4 °C for 30 min to cleave the inhibitor precursor **30** from the resin. The product showed a single major peak on an analytical HPLC without any purification step (Figure 4a). In addition, the crude product had the mass number expected for the precursor product. Finally, the precursor product **30** was treated with aqueous $AcONH_4$ at pH 8.0 to cleave the linker derivative.[18] The progress of the reaction could be easily monitored on an analytical

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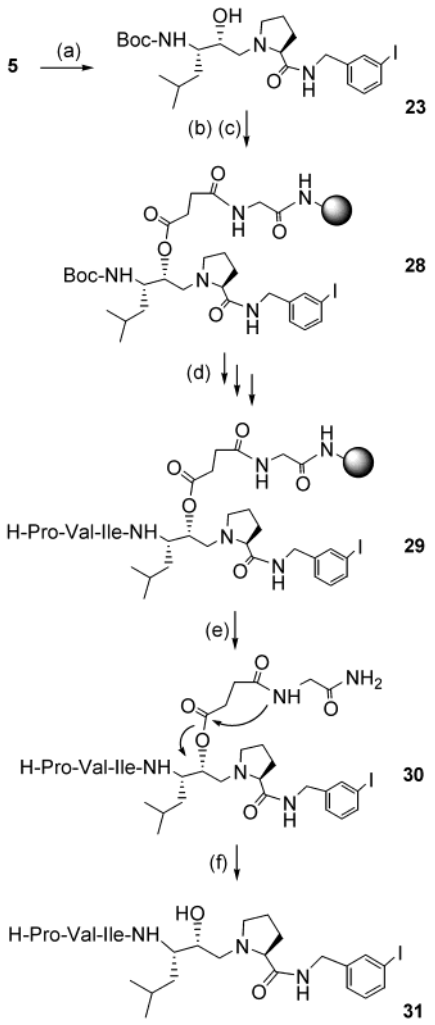


FIGURE 3. Synthetic scheme for HTLV-1 protease inhibitor on solid support. Reagents and conditions: (a) H-Pro-$NHCH_2C_6H_4I$ in 2-propanol, 70 °C, 4 h; (b) succinic anhydride/DMAP, 23 °C, 12 h; (c) H-Gly-MBHA resin, DIPCDI/HOBt, 23 °C, 15 h; (d) Boc-based solid-phase synthesis; (e) HF, 4 °C, 50 min; (f) 0.4 M $AcONH_4$, pH 8.0, 23 °C, 17 h.

HPLC. After 17 h of treatment, most of the precursor converted to the desired product having a single major peak on HPLC (Figure 4b) and a desired mass number. The product was purified by preparative HPLC to produce the inhibitor **31** with 46% yield calculated from the starting MBHA-resin. Three other diastereomers were also prepared according to the same route starting from the corresponding aminoalkyl epoxide synthesized above.

Inhibitory Activity. The activity of each inhibitor was examined by using the auto-digestion resistant protease mutant prepared by chemical synthesis.[5] Synthetic dodecapeptide, which contains the cleavage site corresponding to the C-terminal portion of the protease itself, was employed as the substrate. Cleavage of the substrate by the mutant enzyme was monitored on an analytical HPLC. Inhibitory activity of each inhibitor was evaluated by using the corresponding K_i value determined by the least-squares method in a Dixon plot.[19] For comparison, pepstatin was used as the standard inhibitor for aspartic protease.

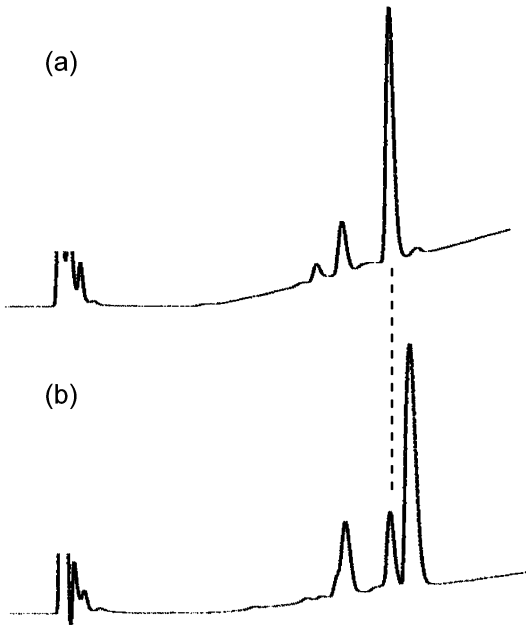
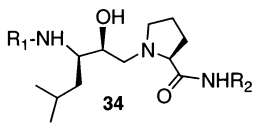
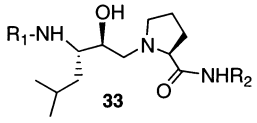
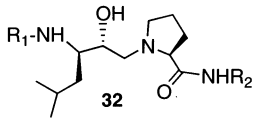
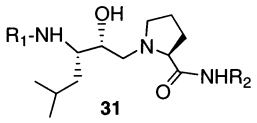


FIGURE 4. Analytical HPLC spectra. Reagents and conditions: (a) crude compound **30**; (b) after 17 h treatment at pH 8.0, HPLC; YMC AM302 (reversed phase C18, 4.6 × 150 mm), CH_3CN in 0.1% aq TFA (25% to 70%/30 min), 0.9 mL/min flow.

TABLE 1. K_i Values for 31−34[a]

compound	Ki
 **34**	4.94 ± 0.49 μM
 **33**	5.49 ± 0.33 μM
 **32**	292 ± 77 nM
 **31**	38 ± 8 nM

[a] R_1 = H-Pro-Val-Ile, R_2 = $CH_2C_6H_4I$.

As shown in Table 1, all four diastereomers prepared above inhibited the enzyme reaction more strongly than pepstatin. Among them, the inhibitor **31**, which has the hydroxyethylamine isoster composed of the *R*-configuration for the hydroxy group and the *S*-configuration for the scissile-site side chain, was most effective. The inhibitor **31** showed a K_i value of 38 nM, a 250-fold increase in potency over pepstatin. As expected, the

(19) Dixon, M. *Biochem. J.* **1953**, *55*, 170.

configuration at the hydroxy-bearing asymmetric center showed remarkable effects on the inhibitory activity. The K_i value decreased by about 2 orders of magnitude by the configuration change of the hydroxy group (compound **31** vs **33**). The decrease by the change at the side chain-bearing center was less than 1 order of magnitude (compound **31** vs **32**). Details of the structure−activity relationship are the subject of ongoing investigation, and will be published in the future.

Conclusion

We have achieved the first solid-phase synthesis of HTLV-1 protease inhibitor containing a hydroxyethylamine isostere backbone. The key features of the present synthesis are the stereoselective construction of the isostere by the ester-derived asymmetric aldol reaction and the development of a new succinic acid linker, which enables an efficient preparation of the inhibitors on solid support. Using the synthetic inhibitors prepared stereoselectively, we have succeeded in evaluating the stereostructure−activity relationship of HTLV-1 protease inhibitors. Configuration of the hydroxy group at the isostere backbone influenced the activity by 2 orders of magnitude, while the influence of the side chain at the scissile bond was less than 1 order of magnitude. The present synthetic approach should provide an efficient procedure to prepare the hydroxy-containing inhibitors on solid support. Application of this method in the construction of an HTLV-1 protease inhibitor library is currently in progress.

Experimental Section

General. Solvents were reagent grade and dried prior to use. Fmoc-Gly-OH, Boc amino acid derivatives, and *p*-methylbenzhydrylamine resin were obtained from Peptide Institute, Inc. (Osaka, Japan) and were used without further purification. Melting points were uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a 400-MHz spectrometer with TMS as an internal standard. HPLC was carried out on a reversed-phase column, which was eluted with CH_3CN in 0.1% aqueous TFA and detected at OD 220 nm.

(1*S*,2*R*)-*cis*-*N*-[2,3-Dihydro-2-(4-methyl-1-oxopentyloxy)-inden-1-yl]-4-methylbenzenesulfonamide (1). To a stirred solution of (1*S*,2*R*)-*cis*-*N*-tosyl-1-aminoindan-2-ol (7.76 g, 26 mmol) in $CHCl_3$ (100 mL) were added 4-methylvaleric acid (3.90 mL, 31 mmol), (dimethylamino)pyridine (DMAP, 940 mg, 7.7 mmol), diisopropylethylamine (DIEA, 4.50 mL, 26 mmol), and diisopropylcarbodiimide (DIPCDI, 6.10 mL, 0.45 mmol). The mixture was stirred at 25 °C for 24 h and then filtered. The filtrate was washed with H_2O and dried over anhydrous $MgSO_4$. The solvent was removed and the resulting residue was recrystallized from ether to yield 6.50 g (63%) of **1** as a white solid: mp 118−119.5 °C, $[\alpha]^{25}_D$ −77.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H), 1.36−1.42 (m, 2H), 1.44−1.52 (m, 1H), 2.14 (dd, J = 7.2, 7.2 Hz, 2H), 2.45 (s, 3H), 2.89 (d, J = 17.3 Hz, 1H), 3.09 (dd, J = 17.3, 5.0 Hz, 1H), 4.98 (dd, J = 10.2, 5.2 Hz, 1H), 5.14 (dd, J = 5.2, 5.0 Hz, 1H), 5.14 (d, J = 10.2 Hz, 1H), 7.16−7.29 (m, 4H), 7.31 (d, J = 8.2 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.53, 22.13, 27.56, 32.08, 33.39, 37.47, 59.51, 74.58, 124.27, 124.96, 126.93, 127.39, 128.62, 129.85, 137.88, 138.63, 139.71, 143.80, 172.81. Anal. Calcd for $C_{22}H_{27}O_4NS$: C, 65.70; H, 6.72; N, 3.48. Found: C, 65.59; H, 6.77; N, 3.56; HRFAB MS, *m*/*z* 402.1733 for $[M + H]^+$ (calcd for $C_{22}H_{28}O_4NS$ 402.1739).

The (1*R*,2*S*) derivative **6** was similarly prepared from (1*R*,2*S*)-*cis*-*N*-tosyl-1-aminoindan-2-ol (7.38 g, 24 mmol) to give 6.32 g (65%) of **6** as a white solid: mp 118−119 °C, $[\alpha]^{25}_D$ +73.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H), 1.37−1.41 (m, 2H), 1.43−1.53 (m, 1H), 2.13 (dd, J = 7.4, 7.4 Hz, 2H), 2.45 (s, 3H), 2.88 (d, J = 17.3 Hz, 1H), 3.08 (dd, J = 17.3, 5.0 Hz, 1H), 4.99 (dd, J = 10.3, 5.0 Hz, 1H), 5.12 (dd, J = 5.0, 5.0 Hz, 1H), 5.18 (d, J = 10.3 Hz, 1H), 7.19−7.23 (m, 4H), 7.32 (d, J = 8.2 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.55, 22.14, 27.55, 32.06, 33.35, 37.47, 59.49, 74.56, 124.25, 124.96, 126.91, 127.38, 128.61, 129.86, 137.81, 138.61, 139.68, 143.81, 172.82. Anal. Calcd for $C_{22}H_{27}O_4NS$: C, 65.70; H, 6.72; N, 3.48. Found: C, 65.62; H, 6.77; N, 3.48; HRFAB MS, *m*/*z* 402.1745 for $[M + H]^+$ (calcd for $C_{22}H_{28}O_4NS$ 402.1739).

(1*S*,2*R*)-*cis*-*N*−(2,3-Dihydro-2-[((2*S*,3*S*)-3-hydroxy-2-(isobutyl)-4-(phenylmethoxy)-1-oxobutoxy)inden-1-yl]-4-methylbenzenesulfonamide (2). To a solution of **1** (2.00 g, 5.0 mmol) in CH_2Cl_2 (15 mL) was added a 1 M solution of $TiCl_4$ (6.00 mL) in CH_2Cl_2 at 4 °C. The mixture was stirred at 23 °C for 15 min. To this solution was added DIEA (3.30 mL, 19 mmol) and the mixture was stirred for 2 h at 23 °C. The resulting solution was added to the aldehyde solution prepared at −78 °C by the addition of the 1 M solution of $TiCl_4$ (10.5 mL in CH_2Cl_2) to a stirred solution of (benzyloxy)acetaldehyde (1.57 g, 10 mmol) in CH_2Cl_2 (10 mL) followed by 15 min of stirring. The mixture was stirred at −78 °C for 2 h and then quenched by the addition of aqueous ammonium chloride. The organic layer was washed with H_2O, dried over $MgSO_4$, and rotary evaporated. The crude product was purified by silica gel column chromatography with $CHCl_3$ followed by flash chromatography with hexane:AcOEt 3:1 to yield 2.61 g (95%) of **2** as an oil: $[\alpha]^{25}_D$ −20.4 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H), 1.17 (ddd, J = 13.5, 9.4, 3.9 Hz, 1H), 1.34−1.41 (m, 1H), 1.55 (ddd, J = 13.5, 11.2, 4.5 Hz, 1H), 2.44 (s, 3H), 2.57−2.62 (m, 1H), 2.73 (d, J = 4.0 Hz, 1H), 2.86 (d, J = 17.2 Hz, 1H), 3.06 (dd, J = 17.2, 4.6 Hz, 1H), 3.33 (dd, J = 9.6, 7.3 Hz, 1H), 3.42 (dd, J = 9.6, 3.8 Hz, 1H), 3.93−3.98 (m, 1H), 4.39 (d, J = 11.8 Hz, 1H), 4.43 (d, J = 11.8 Hz, 1H), 4.92 (dd, J = 9.9, 4.8 Hz, 1H), 5.32 (dd, J = 4.8, 4.6 Hz, 1H), 5.82 (d, J = 9.9 Hz, 1H), 7.13−7.36 (m, 1H), 7.81 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.56, 21.61, 23.30, 26.33, 35.32, 37.19, 46.93, 59.67, 71.14, 71.53, 73.38, 75.83, 124.30, 124.77, 127.07, 127.40, 127.63, 127.83, 127.89, 128.00, 128.45, 128.47, 128.60, 129.79, 137.51, 137.91, 138.40, 140.01, 143.60, 173.04; HRFAB MS, *m*/*z* 552.2413 for $[M + H]^+$ (calcd for $C_{31}H_{38}O_6NS$ 552.2420).

The (1*R*,2*S*) derivative **7** was similarly prepared from **6** (1.00 g, 2.5 mmol) to give 1.29 g (94%) of **7** as an oil: $[\alpha]^{25}_D$ +19.0 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (d, J = 6.5 Hz, 3H), 0.83 (d, J = 6.5 Hz, 3H), 1.18 (ddd, J = 13.5, 9.4, 3.9 Hz, 1H), 1.34−1.41 (m, 1H), 1.55 (ddd, J = 13.5, 11.2, 4.4 Hz, 1H), 2.44 (s, 3H), 2.56−2.61 (m, 1H), 2.69 (d, J = 4.0 Hz, 1H), 2.86 (d, J = 17.2 Hz, 1H), 3.06 (dd, J = 17.2, 4.6 Hz, 1H), 3.33 (dd, J = 9.6, 7.3 Hz, 1H), 3.42 (dd, J = 9.6, 3.9 Hz, 1H), 3.92−3.97 (m, 1H), 4.39 (d, J = 11.8 Hz, 1H), 4.43 (d, J = 11.8 Hz, 1H), 4.92 (dd, J = 9.9, 4.8 Hz, 1H), 5.33 (dd, J = 4.8, 4.6 Hz, 1H), 5.78 (d, J = 9.9 Hz, 1H), 7.13−7.37 (m, 1H), 7.81 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.54, 21.61, 23.29, 26.34, 35.35, 37.19, 46.95, 59.67, 71.15, 71.54, 73.38, 75.83, 124.31, 124.76, 127.07, 127.39, 127.62, 127.82, 127.87, 128.02, 128.20, 128.46, 128.59, 129.78, 137.53, 137.95, 138.41, 140.02, 143.58, 173.04; HRFAB MS, *m*/*z* 552.2426 for $[M + H]^+$ (calcd for $C_{31}H_{38}O_6NS$ 552.2420).

(4*S*,5*S*)-4-Isobutyl-5-[(phenylmethyloxy)methyl]oxazolidin-2-one (3). To a stirred solution of **2** (2.61 g, 4.7 mmol) in THF:H_2O (3:1, 20 mL) were added 30% H_2O_2 (4.5 mL) and $LiOH\cdot H_2O$ (840 mg, 20 mmol), and the mixture was stirred at 23 °C for 12 h. Aqueous Na_2SO_3 (1.5 M) and saturated aqueous $NaHCO_3$ were added to the mixture, and the organic solvent was removed in vacuo. The resulting solution was acidified with AcOH, and then extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over $MgSO_4$, and rotary evapo-

rated. The residue was dissolved in CH_2Cl_2 (10 mL). To this solution were added Et_3N (2.79 mL, 20 mmol) and diphenylphosphoryl azide (4.30 mL, 20 mmol). The mixture was stirred at 23 °C for 24 h, and the solvent was removed in vacuo. The product was purified by silica gel column chromatography with $CHCl_3$ followed by flash chromatography with hexane:AcOEt 3:1 to yield 0.760 g (61%) of **3** as an oil: $[\alpha]^{25}_D$ −13.7 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 1.23 (ddd, J = 13.4, 10.0, 3.4 Hz, 1H), 1.50 (ddd, J = 13.4, 11.0, 4.3 Hz, 1H), 1.58−1.66 (m, 1H), 3.67 (d, J = 5.8 Hz, 2H), 3.93−3.99 (m, 1H), 4.53 (d, J = 12.0 Hz, 1H), 4.59 (d, J = 12.0 Hz, 1H), 4.71−4.76 (m, 1H), 7.06 (br s, 1H), 7.29−7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.83, 23.73, 24.61, 38.05, 52.53, 67.37, 73.48, 77.78, 127.69, 127.75, 128.33, 137.36, 159.72; HRFAB MS, *m*/*z* 264.1606 for $[M + H]^+$ (calcd for $C_{15}H_{22}O_3N$ 264.1600).

The (4*R*,5*R*) derivative **8** was similarly prepared from **7** (1.25 g, 2.3 mmol) to give 0.360 g (60%) of **8** as an oil: $[\alpha]^{25}_D$ +13.1 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H), 1.29 (ddd, J = 13.3, 9.7, 3.4 Hz, 1H), 1.50 (ddd, J = 13.3, 10.7, 4.4 Hz, 1H), 1.56−1.622 (m, 1H), 3.68 (d, J = 5.8 Hz, 2H), 3.94−3.99 (m, 1H), 4.54 (d, J = 12.0 Hz, 1H), 4.59 (d, J = 12.0 Hz, 1H), 4.72−4.77 (m, 1H), 6.07 (br s, 1H), 7.28−7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.05, 23.72, 24.95, 38.14, 52.66, 67.40, 73.66, 77.85, 127.82, 127.90, 128.46, 137.45, 159.16; HRFAB MS, *m*/*z* 264.1595 for $[M + H]^+$ (calcd for $C_{15}H_{22}O_3N$ 264.1600).

(2*S*,3*S*)-3-[*N*-(*tert*-Butyloxycarbonyl)amino]-5-methyl-1-(phenylmethyl)hexan-2-ol (4). To a stirred solution of **3** (0.750 g, 2.9 mmol) in EtOH (10 mL) was added 85% KOH (0.750 g, 11 mmol) in H_2O (4 mL), and the mixture was heated at reflux for 8 h. The solution was neutralized with 1 N HCl and the solvent was removed to dryness. The residue was suspended in DMF (5 mL), and di-*tert*-butyl dicarbonate (1.24 g, 5.7 mmol) and DIEA (400 μL, 2.3 mmol) were added to the suspension. The mixture was stirred at 23 °C for 24 h, and the solvent was removed in vacuo. The product was extracted with $CHCl_3$ and the organic layer was washed with H_2O, dried over $MgSO_4$, and rotary evaporated. The crude product was purified by silica gel column chromatography with $CHCl_3$ followed by flash chromatography with hexane:AcOEt 3:1 to yield 0.610 g (63%) of **4** as an oil: $[\alpha]^{25}_D$ −29.0 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 6.8 Hz, 6H), 1.25−1.37 (m, 2H), 1.43 (s, 9H), 1.65−1.67 (m, 1H), 2.85 (br s, 1H), 3.49−3.58 (m, 2H), 3.77 (br s, 2H), 4.55 (s, 2H), 4.72 (br d, J = 7.0 Hz, 1H), 7.29−7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.70, 23.55, 24.70, 28.34, 39.73, 51.55, 71.81, 73.04, 73.54, 79.30, 127.70, 127.78, 128.44, 137.86, 156.25; HRFAB MS, *m*/*z* 338.2327 for $[M + H]^+$ (calcd for $C_{19}H_{32}O_4N$ 338.2331).

The (2*R*,3*R*) derivative **9** was similarly prepared starting from **8** (0.750 g, 2.9 mmol) to give 0.650 g (68%) of **9** as an oil: $[\alpha]^{25}_D$ +26.2 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 6.8 Hz, 6H), 1.25−1.37 (m, 2H), 1.43 (s, 9H), 1.63−1.67 (m, 1H), 2.83 (br s, 1H), 3.49−3.58 (m, 2H), 3.77 (br s, 2H), 4.55 (s, 2H), 4.71 (br d, J = 6.5 Hz, 1H), 7.29−7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.71, 23.55, 24.71, 28.35, 39.74, 51.57, 71.81, 73.05, 73.55, 79.32, 127.71, 127.79, 128.45, 137.86, 156.26; HRFAB MS, *m*/*z* 338.2328 for $[M + H]^+$ (calcd for $C_{19}H_{32}O_4N$ 338.2331).

2(*S*)-[1′-(*S*)-*N*-(*tert*-Butyloxycarbonyl)amino-3′-methyl-2-butyl]oxirane (5). To a stirred solution of **4** (0.600 g, 1.8 mmol) in MeOH (10 mL) was added a catalytic amount of 10% Pd−C, and the mixture was stirred at 23 °C for 12 h under H_2 atmosphere. Pd−C was removed by filtration, and the filtrate was rotary evaporated. The residue was dissolved in $CHCl_3$ (5 mL), and Ph_3P (1.40 g, 5.3 mmol) and diethyl azodicarboxylate (1.20 mL, 7.5 mmol) were added to the solution. The mixture was heated at reflux for 6 h. After cooling, the reaction mixture was washed with H_2O, dried over $MgSO_4$, and rotary evaporated. The crude product was purified by silica gel column chromatography with $CHCl_3$ followed by flash chromatography with hexane:AcOEt 3:1 to yield 0.220 g (54%) of **5** as an oil: $[\alpha]^{25}_D$ −25.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 1.36−1.41 (m, 2H), 1.44 (s, 9H), 1.71−1.78 (m, 1H), 2.75 (br d, J = 3.8 Hz, 2H), 2.83−2.85 (m, 1H), 3.51 (br s, 1H), 4.41 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.79, 23.29, 24.44, 28.33, 40.82, 46.09, 50.30, 54.50, 79.42, 155.41; HRFAB MS, *m*/*z* 230.1750 for $[M + H]^+$ (calcd for $C_{12}H_{24}O_3N$ 230.1756).

The (2*R*,1′*R*)-oxirane **10** was similarly prepared starting from **9** (0.640 g, 1.9 mmol) to yield 0.240 g (55%) of **10** as an oil: $[\alpha]^{25}_D$ +25.1 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H), 1.35−1.41 (m, 2H), 1.44 (s, 9H), 1.71−1.78 (m, 1H), 2.75 (br d, J = 3.8 Hz, 2H), 2.83−2.85 (m, 1H), 3.51 (br s, 1H), 4.40 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.83, 23.33, 24.49, 28.37, 40.87, 46.14, 50.35, 54.54, 79.48, 155.44; HRFAB MS, *m*/*z* 230.1763 for $[M + H]^+$ (calcd for $C_{12}H_{24}O_3N$ 230.1756).

(1*S*,2*R*)-*N*-[2,3-Dihydro-2-((2*S*,3*S*)-(*E*)-3-hydroxy-5-phenyl-2-(isobutyl)-1-oxopent-4-enoxy)inden-1-yl]-4-methylbenzenesulfonamide (11). To a stirred solution of **1** (400 mg, 1.0 mmol) in CH_2Cl_2 (8 mL) was added a 1 M solution of $TiCl_4$ in CH_2Cl_2 (1.20 mL) at 4 °C, and the mixture was stirred at 23 °C for 15 min. To this solution was added DIEA (660 μL, 3.8 mmol). The mixture was stirred for 90 min at 23 °C, and then cooled to −78 °C. The aldehyde solution, prepared at −78 °C by the addition of a 1 M solution of ^{n}Bu$_2$BOTf (3.5 mL in CH_2Cl_2) to a stirred solution of cinnamaldehyde (440 μL, 3.5 mmol) in CH_2Cl_2 (8 mL) followed by 30 min of stirring, was added to the above solution at −78 °C. The mixture was stirred at −78 °C for 90 min. MeOH (3 mL), pH 7 buffer (2 mL), and 30% H_2O_2 (1 mL) were added successively, and the mixture was allowed to warm to 23 °C. $CHCl_3$ (10 mL) was added and the organic layer was washed with 5% aqueous $NaHCO_3$ and H_2O, dried over $MgSO_4$, and rotary evaporated. The crude product was purified by silica gel column chromatography with $CHCl_3$ followed by flash chromatography with hexane:AcOEt 6:1 to yield 150 mg (28%) of **11** (and 25 mg of a *syn*-diastereomer) as an oil: $[\alpha]^{25}_D$ −15.5 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H), 1.14−1.21 (m, 1H), 1.45−1.53 (m, 2H), 2.42 (s, 3H), 2.60−2.66 (m, 1H), 2.82 (d, J = 17.1 Hz, 1H), 2.83 (d, J = 4.7 Hz, 1H), 3.08 (dd, J = 17.1, 4.8 Hz, 1H), 4.20−4.25 (m, 1H), 4.83 (dd, J = 9.4, 5.0 Hz, 1H), 5.42 (dd, J = 5.0, 4.8 Hz, 1H), 6.05 (dd, J = 15.8, 7.3 Hz, 1H), 6.28 (d, J = 9.4 Hz, 1H), 6.54 (d, J = 15.8 Hz, 1H), 7.05−7.07 (m, 1H), 7.22−7.31 (m, 9H), 7.38−7.40 (m, 1H), 7.81 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.54, 21.66, 23.30, 26.18, 37.33, 38.09, 50.63, 59.68, 74.50, 74.91, 124.55, 124.76, 126.65, 127.23, 127.34, 128.10, 128.32, 128.62, 128.86, 129.70, 133.29, 135.98, 137.63, 138.37, 140.22, 143.46, 172.56; HRFAB MS, *m*/*z* 556.2141 for $[M + Na]^+$ (calcd for $C_{31}H_{35}O_5NSNa$ 556.2134).

The (1*R*,2*S*) derivative **16** was similarly prepared starting from **6** (1.26 g, 3.1 mmol) to give 0.430 g (26%) of **16** as an oil: $[\alpha]^{25}_D$ +14.9 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (d, J = 6.4 Hz, 3H), 0.88 (d, J = 6.4 Hz, 3H), 1.18−1.22 (m, 1H), 1.46−1.54 (m, 2H), 2.43 (s, 3H), 2.61−2.66 (m, 1H), 2.82 (d, J = 17.2 Hz, 1H), 2.78 (d, J = 4.5 Hz, 1H), 3.05 (dd, J = 17.2, 4.8 Hz, 1H), 4.21−4.26 (m, 1H), 4.84 (dd, J = 9.4, 5.0 Hz, 1H), 5.43 (dd, J = 5.0, 4.8 Hz, 1H), 6.06 (dd, J = 15.8 Hz, 7.3 Hz, 1H), 6.24 (d, J = 9.4 Hz, 1H), 6.56 (d, J = 15.8 Hz, 1H), 7.06−7.07 (m, 1H), 7.21−7.32 (m, 9H), 7.38−7.40 (m, 1H), 7.81 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.54, 21.68, 23.30, 26.20, 37.34, 38.13, 50.64, 59.70, 74.51, 74.94, 124.55, 124.77, 126.66, 127.24, 127.35, 128.12, 128.34, 128.63, 128.89, 129.72, 133.31, 135.99, 137.66, 138.38, 140.23, 143.48, 172.57; HRFAB MS, *m*/*z* 556.2128 for $[M + Na]^+$ (calcd for $C_{31}H_{35}O_5NSNa$ 556.2134).

(4*S*,5*S*)-4-Isobutyl-5-[(*E*)-phenylvinyl]oxazolidin-2-one (12). To a stirred solution of **11** (0.740 g, 1.4 mmol) in THF:H_2O (3:1, 20 mL) were added 30% H_2O_2 (1.6 mL) and $LiOH\cdot H_2O$ (0.290 g, 6.9 mmol), and the mixture was stirred at 23 °C for 15 h. Aqueous Na_2SO_3 (1.5 M) and saturated aqueous $NaHCO_3$ were added to the mixture and the organic

solvent was removed in vacuo. The resulting solution was acidified with AcOH and then extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over $MgSO_4$, and rotary evaporated. The residue was dissolved in benzene (10 mL). To this solution were added Et_3N (0.580 mL, 4.1 mmol) and diphenylphosphoryl azide (0.900 mL, 4.1 mmol). The mixture was stirred at reflux for 10 h, and the solvent was removed in vacuo. The product was purified by silica gel column chromatography with $CHCl_3$ followed by flash chromatography with hexane:AcOEt 3:1 to yield 0.225 g (66%) of **12** as an oil: $[\alpha]^{25}_D$ −59.4 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), 1.48 (ddd, J = 13.5, 8.3, 5.0 Hz, 1H), 1.57 (ddd, J = 13.5, 8.5, 6.0 Hz, 1H), 1.65−1.74 (m, 1H), 3.67−3.72 (m, 1H), 4.69−4.73 (m, 1H), 5.96 (br s, 1H), 6.22 (dd, J = 15.8, 7.5 Hz, 1H), 6.72 (d, J = 15.8 Hz, 1H), 7.30−7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.97, 23.01, 25.14, 43.64, 56.90, 83.64, 124.60, 126.82, 128.59, 128.71, 134.53, 135.45, 158.99; HRFAB MS, *m*/*z* 246.1499 for $[M + H]^+$ (calcd for $C_{15}H_{20}O_2N$ 246.1494).

The (4*R*,5*R*) derivative **17** was similarly prepared from **16** (0.420 g, 0.79 mmol) to yield 123 mg (64%) of **17** as an oil: $[\alpha]^{25}_D$ +65.4 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), 1.48 (ddd, J = 13.5, 8.2, 5.0 Hz, 1H), 1.57 (ddd, J = 13.5, 8.5, 6.0 Hz, 1H), 1.67−1.74 (m, 1H), 3.67−3.72 (m, 1H), 4.69−4.73 (m, 1H), 6.01 (br s, 1H), 6.22 (dd, J = 15.8 , 7.5 Hz, 1H), 6.72 (d, J = 15.8 Hz, 1H), 7.29−7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.98, 23.01, 25.14, 43.67, 56.92, 83.63, 124.64, 126.83, 128.56, 128.71, 134.52, 135.48, 159.02; HRFAB MS, *m*/*z* 246.1488 for $[M + H]^+$ (calcd for $C_{15}H_{20}O_2N$ 246.1494).

(3*S*,4*S*)-(*E*)-4-[*N*-(*tert*-Butyloxycarbonyl)amino]-6-methyl-1-phenylhept-1-ene-3-ol (13). To a stirred solution of **12** (220 mg, 0.90 mmol) in EtOH (5 mL) was added 85% KOH (240 mg, 3.6 mmol) in H_2O (5 mL), and the mixture was heated at reflux for 15 h. The solution was neutralized with 1 N HCl and the solvent was removed to dryness. The residue was suspended in DMF (5 mL), and di-*tert*-butyl dicarbonate (390 mg, 1.8 mmol) and DIEA (160 μL, 0.90 mmol) were added to the suspension. The mixture was stirred at 23 °C for 4 h, and the solvent was removed in vacuo. The product was extracted with $CHCl_3$ and the organic layer was washed with H_2O, dried, and rotary evaporated. The crude product was purified by flash chromatography with hexane:AcOEt 5:1 to yield 260 mg (91%) of **13** as an oil: $[\alpha]^{25}_D$ −15.5 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3H), 0.95 (s, 3H), 1.40 (s, 9H), 1.40−1.47 (m, 2H), 1.68−1.73 (m, 1H), 2.53 (br s, 1H), 3.75 (br s, 1H), 4.24 (br s, 1H), 4.64 (br d, J = 8.4 Hz, 1H), 6.23 (dd, J = 15.9, 6.4 Hz, 1H), 6.62 (d, J = 15.9 Hz, 1H), 7.21−7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.93, 23.34, 24.86, 28.31, 40.64, 53.35, 75.20, 79.44, 126.54, 127.64, 128.50, 129.52, 131.44, 136.68, 156.45; HRFAB MS, *m*/*z* 320.2221 for $[M + H]^+$ (calcd for $C_{15}H_{20}O_2N$ 320.2226).

The (3*R*,4*R*) derivative **18** was similarly prepared starting from **17** (120 mg, 0.49 mmol) to give 140 mg (90%) of **18** as an oil: $[\alpha]^{25}_D$ +18.8 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3H), 0.95 (s, 3H), 1.40 (s, 9H), 1.40−1.45 (m, 2H), 1.68−1.74 (m, 1H), 2.40 (br s, 1H), 3.74 (br s, 1H), 4.24 (br s, 1H), 4.61 (br d, J = 7.7 Hz, 1H), 6.23 (dd, J = 15.9, 6.4 Hz, 1H), 6.62 (d, J = 15.9 Hz, 1H), 7.21−7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.94, 23.35, 24.87, 28.32, 40.69, 53.38, 75.26, 79.46, 126.56, 127.66, 128.51, 129.53, 131.49, 136.68, 156.46; HRFAB MS, *m*/*z* 320.2230 for $[M + H]^+$ (calcd for $C_{15}H_{20}O_2N$ 320.2226).

(2*R*,3*S*)-3-[*N*-(*tert*-Buthyloxycarbonyl)amino]-3-isobutyl-2-hydroxypropan-1-ol (14). To a stirred solution of **13** (120 mg, 0.39 mmol) in EtOH (5 mL) was bubbled a stream of ozonized oxygen at −78 °C until the blue color persisted (30 min). The solution was flushed with N_2 for 5 min, and then $NaBH_4$ (150 mg, 3.9 mmol) in EtOH (5 mL) was added. The reaction mixture was stirred at 23 °C for 1 h, and acetone was added. The solvent was removed in vacuo and the residue was extracted with AcOEt. The organic layer was washed with H_2O, dried, and rotary evaporated. The product was purified by silica gel column chromatography with $CHCl_3$:MeOH 20:1 to yield 71 mg (76%) of **14** as an oil: $[\alpha]^{25}_D$ −26.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, J = 6.4 Hz, 3H), 0.94 (d, J = 6.4 Hz, 3H), 1.32 (ddd, J = 13.8, 8.5, 5.0 Hz, 1H), 1.45 (s, 9H), 1.53 (ddd, J = 13.8, 9.9, 5.5 Hz, 1H), 1.64−1.74 (m, 1H), 2.27 (br d, J = 5.0 Hz, 1H), 3.28 (br t, J = 6.5 Hz, 1H), 3.45−3.51 (m, 1H), 3.54−3.60 (m, 1H), 3.64−3.66 (m, 1H), 3.77−3.82 (m, 1H), 4.62 (br d, J = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.97, 23.07, 24.82, 28.31, 40.89, 49.21, 63.64, 73.69, 80.02, 157.23; HRFAB MS, *m*/*z* 248.1858 for $[M + H]^+$ (calcd for $C_{12}H_{26}O_4N$ 248.1862).

The (2*S*,3*R*) derivative **19** was similarly prepared starting from **18** (130 mg, 0.41 mmol) to yield 97 mg (96%) of **19** as an oil: $[\alpha]^{25}_D$ +30.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, J = 6.3 Hz, 3H), 0.94 (d, J = 6.3 Hz, 3H), 1.32 (ddd, J = 13.8, 8.7, 5.1 Hz, 1H), 1.45 (s, 9H), 1.53 (ddd, J = 13.8, 9.8, 5.5 Hz, 1H), 1.63−1.72 (m, 1H), 2.18 (br d, J = 5.1 Hz, 1H), 3.22 (br t, J = 6.5 Hz, 1H), 3.47−3.51 (m, 1H), 3.54−3.61 (m, 1H), 3.64−3.66 (m, 1H), 3.77−3.82 (m, 1H), 4.59 (br d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.97, 23.07, 24.82, 28.30, 40.88, 49.21, 63.65, 73.69, 80.03, 157.23; HRFAB MS, *m*/*z* 248.1866 for $[M + H]^+$ (calcd for $C_{12}H_{26}O_4N$ 248.1862).

2(*R*)-[1′-(*S*)-*N*-(*tert*-Butyloxycarbonyl)amino-3′-methyl-2-butyl]oxirane (15). To a stirred solution of **14** (60 mg, 0.24 mmol) in $CHCl_3$ (5 mL) were added Ph_3P (220 mg, 0.84 mmol) and diethyl azodicarboxylate (160 μL, 1.0 mmol), and the mixture was heated at reflux for 6 h. After cooling, the reaction mixture was washed with H_2O, dried, and rotary evaporated. The crude product was purified by flash chromatography with hexane:AcOEt 6:1 to yield 35 mg (63%) of **15** as an oil: $[\alpha]^{25}_D$ −9.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 3H), 0.97 (s, 3H), 1.43 (s, 9H), 1.43−1.51 (m, 2H), 1.70−1.77 (m, 1H), 2.59 (br s, 1H), 2.73 (t, J = 4.4 Hz, 1H), 2.98 (br s, 1H), 3.97 (br s, 1H), 4.29 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.12, 23.04, 24.70, 28.32, 42.34, 44.39, 47.18, 53.94, 79.38, 155.65; HRFAB MS, *m*/*z* 230.1760 for $[M + H]^+$ (calcd for $C_{12}H_{24}O_3N$ 230.1756).

The (2*S*,1′*R*)-oxirane **20** was similarly prepared starting from **19** (90 mg, 0.36 mmol) to yield 52 mg (62%) of **20** as an oil: $[\alpha]^{25}_D$ +10.5 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 3H), 0.96 (s, 3H), 1.43 (s, 9H), 1.43−1.51 (m, 2H), 1.70−1.77 (m, 1H), 2.59 (br s, 1H), 2.73 (t, J = 4.3 Hz, 1H), 2.98 (br s, 1H), 3.97 (br s, 1H), 4.29 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.12, 23.04, 24.70, 28.32, 42.34, 44.38, 47.18, 53.94, 79.38, 155.65; HRFAB MS, *m*/*z* 230.1752 for $[M + H]^+$ (calcd for $C_{12}H_{24}O_3N$ 230.1756).

(1*R*,2*S*)-*cis*-*N*-(2,3-Dihydro-2-[(2R,3S)-3-hydroxy-2-(isobutyl)-4-(*tert*-butyldiphenylsilyoxy)-1-oxobutoxy]inden-1-yl)-4-methylbenzenesulfonamide (21). To a stirred solution of **6** (400 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was added a 1 M solution of $TiCl_4$ in CH_2Cl_2 (1.2 mL) at 4 °C. The mixture was stirred at 23 °C for 15 min. To this solution was added DIEA (660 μL, 3.8 mmol), and the mixture was stirred for 90 min at 23 °C. The resulting solution was added to the aldehyde solution prepared at −78 °C by the addition of the 1 M $TiCl_4$/CH_2Cl_2 (3.9 mL) to a stirred solution of (*tert*-butyldiphenylsilyoxy)acetaldehyde (1.05 g, 3.5 mmol) in CH_2Cl_2 (10 mL) followed by 15 min of stirring. The mixture was stirred at −78 °C for 2 h and then quenched by the addition of aqueous ammonium chloride. The organic layer was washed with H_2O, dried, and rotary evaporated. The crude product was purified by silica gel column chromatography with $CHCl_3$ followed by flash chromatography with hexane:AcOEt 6:1 to yield 360 mg (52%) of **21** as a powder: mp 127−129 °C, $[\alpha]^{25}_D$ +17.0 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (d, J = 6.5 Hz, 3H), 0.78 (d, J = 6.5 Hz, 3H), 1.03 (s, 9H), 1.11 (ddd, J = 13.5, 9.4, 3.8 Hz, 1H), 1.27−1.34 (m, 1H), 1.52 (ddd, J = 13.5, 9.3, 4.4 Hz, 1H), 2.43 (s, 3H), 2.51−2.56 (m, 1H), 2.76 (d, J = 17.0 Hz, 1H), 2.77 (d, J = 3.1 Hz, 1H), 3.02 (dd, J = 17.0, 4.7 Hz, 1H), 3.53 (d, J = 6.2 Hz, 2H), 3.87−3.92 (m, 1H), 4.91 (dd, J = 9.9, 5.0 Hz, 1H), 5.31 (dd, J = 5.0, 4.7 Hz, 1H), 5.82 (d, J = 9.9 Hz,

1H), 7.03−7.05 (m, 1H), 7.18−7.45 (m, 11H), 7.58−7.62 (m, 4H), 7.80 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.14, 21.55, 21.56, 23.29, 26.36, 26.79, 34.62, 37.20, 46.51, 59.62, 65.38, 72.65, 75.63, 124.35, 124.71, 127.05, 127.34, 127.85, 128.40, 129.76, 129.90, 129.94, 132.77, 132.86, 135.49, 138.05, 138.33, 139.99, 143.53, 173.16; HRFAB MS, m/z 722.2945 for $[M + Na]^+$ (calcd for $C_{40}H_{49}O_6NSSiNa$ 722.2948).

(4*R*,5*S*)-4-Isobutyl-5-[(*tert*-butyldiphenylsilyloxy)-methyl]oxazolidin-2-one (22). To a stirred solution of **21** (350 mg, 0.50 mmol) in THF: H_2O (3:1, 4 mL) were added 30% H_2O_2 (450 μL) and LiOH·H_2O (84 mg, 2.0 mmol), and the mixture was stirred at 23 °C for 90 min. Aqueous Na_2SO_3 (1.5 M) and saturated aqueous $NaHCO_3$ were added to the mixture and the organic solvent was removed in vacuo. The resulting solution was acidified with AcOH and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried, and evaporated. The residue was extracted with hexane. *N*-Tosylaminoindanol was precipitated as a powder. The solvent of the extract was removed in vacuo and the residue was dissolved in CH_2Cl_2 (4 mL). To this solution were added Et_3N (280 μL, 2.0 mmol) and diphenylphosphoryl azide (430 μL, 2.0 mmol). The mixture was stirred at 23 °C for 48 h, and the solvent was removed in vacuo. The product was purified by silica gel column chromatography with $CHCl_3$ followed by flash chromatography with hexane:AcOEt 3:1 to yield 12 mg (6%) of **22** as an oil: $[\alpha]^{25}_D$ −15.3 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, J = 6.4 Hz, 3H), 0.93 (d, J = 6.4 Hz, 3H), 1.06 (s, 9H), 1.36−1.43 (m, 1H), 1.54−1.63 (m, 1H), 3.85 (d, J = 5.4 Hz, 2H), 3.97−4.02 (m, 1H), 4.60−4.65 (m, 1H), 5.65 (br s, 1H), 7.37−7.47 (m, 6H), 7.65−7.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.13, 21.16, 23.71, 25.15, 26.70, 38.14, 52.73, 61.37, 78.91, 127.83, 129.93, 132.65, 132.79, 135.55, 135.62, 159.08; HRFAB MS, m/z 412.2304 for $[M + H]^+$ (calcd for $C_{24}H_{34}O_3NSi$ 412.2308).

Solid-Phase Synthesis of Inhibitors. (a) General Procedure for the Deprotection of the N$^\alpha$-Boc Group. TFA (50%) in CH_2Cl_2 was added to a Boc-containing resin and the mixture was agitated at 23 °C for 3 min. After filtration, the resin was re-treated with 50% TFA/CH_2Cl_2 for 15 min. The resin was washed with CH_2Cl_2 and DMF, and then agitated with 5% DIEA/DMF for 30 s (three times). The resulting resin was washed with DMF, and was used for the next reaction.

(b) Hydroxyethylaminated Pro-amide, Boc-HEA[*S*-isobutyl,*R*-hydroxy]- Pro-NH-CH$_2$-C$_6$H$_4$I (23). To a stirred solution of anisole (0.760 mL, 7.0 mmol) in TFA (10 mL) in an ice bath was added Boc-Pro-NH-CH_2-C_6H_4I (1.50 g, 3.5 mmol), and the mixture was stirred at 4 °C for 60 min. The TFA was removed by azeotroping with hexane (three times) and the product was extracted with $CHCl_3$. The organic layer was washed with 5% $NaHCO_3$ and H_2O, dried over $MgSO_4$, and evaporated. The residue was triturated with hexane to yield a powder (0.780 g). The product was dissolved in 2-propanol (10 mL). To this solution was added the (2*S*,1′*S*)-aminoalkylepoxide **5** (220 mg, 1.0 mmol), and the mixture was stirred at 70 °C for 4 h. The solvent was removed in vacuo, and the residue was extracted with $CHCl_3$. The organic layer was washed with 5% citric acid and H_2O, dried over $MgSO_4$, and then rotary evaporated. The residue was triturated with hexane to yield 350 mg (65%) of **23** as a powder: mp 144−146 °C; $[\alpha]^{25}_D$ −54.8 (c 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 1.14−1.30 (m, 2H), 1.44 (s, 9H), 1.60 (br s, 1H), 1.70−1.77 (m, 2H), 1.95−2.00 (m, 1H), 2.13−2.23 (m, 1H), 2.46−2.53 (m, 1H), 2.55−2.65 (m, 1H), 3.10−3.14 (m, 1H), 3.22−3.26 (m, 1H), 3.49 (br s, 1H), 3.67 (br s, 1H), 4.36−4.39 (m, 2H), 4.48 (br d, J = 7.7 Hz, 1H), 7.06 (t, J = 7.7 Hz, 1H), 7.25 (d, J = 7.7 Hz, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.63 (br s, 1H), 8.00 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.56, 23.52, 24.56, 24.77, 28.33, 30.97, 39.13, 42.21, 52.68, 56.30, 59.20, 67.84, 73.75, 79.91, 94.49, 126.84, 130.33, 136.29, 136.53, 141.18, 156.69, 175.26; HRFAB MS, m/z 560.1990 for $[M + H]^+$ (calcd for $C_{24}H_{39}O_4N_3I$ 560.1985).

Three other diastereomers of **23** were similarly prepared starting from **10**, **15**, and **20**, respectively.

Boc-HEA[*R*-isobutyl,*S*-hydroxy]-Pro-NH-CH$_2$-C$_6$H$_4$I (24). Yield 77%; $[\alpha]^{25}_D$ −52.4 (c 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 090 (d, J = 6.6 Hz, 3H), 094 (d, J = 6.6 Hz, 3H), 1.10−1.17 (m, 1H), 1.30−1.37 (m, 1H), 1.43 (s, 9H), 1.59−1.68 (m, 1H), 1.76−1.83 (m, 2H), 1.87−1.95 (m, 1H), 2.18−2.25 (m, 1H), 2.27−2.35 (m, 1H), 2.44 (dd, J = 12.6, 1.5 Hz, 1H), 2.65 (dd, J = 12.6, 10.6 Hz, 1H), 3.19 (dd, J = 9.7, 5.5 Hz, 1H), 3.23−3.27 (m, 1H), 3.37 (br s, 1H), 3.67 (br s, 1H), 3.74−3.76 (m, 1H), 4.27−4.33 (m, 1H), 4.39−4.44 (m, 1H), 4.55 (br d, J = 7.0 Hz, 1H), 7.04 (t, J = 7.8 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.62 (br s, 1H), 8.20 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.62, 23.52, 24.20, 24.84, 28.33, 30.43, 38.74, 42.15, 52.74, 53.65, 58.26, 68.09, 73.04, 80.02, 94.41, 126.81, 130.26, 136.21, 136.55, 141.12, 174.69; HRFAB MS, m/z 560.1977 for $[M + H]^+$ (calcd for $C_{24}H_{39}O_4N_3I$ 560.1985).

Boc-HEA[*S*-isobutyl,*S*-hydroxy]-Pro-NH-CH$_2$-C$_6$H$_4$I (25). Yield 75%; $[\alpha]^{25}_D$ −116.4 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.919 (d, J = 6.6 Hz, 3H), 0.923 (d, J = 6.6 Hz, 3H), 1.22−1.29 (m, 2H), 1.43 (s, 9H), 1.43−1.52 (ms, 1H), 1.58−1.65 (m, 1H), 1.72−1.94 (m, 2H), 2.17−2.27 (m, 1H), 2.32−2.38 (m, 1H), 2.50−2.54 (m, 1H), 2.67−2.73 (m, 1H), 3.19−3.24 (m, 2H), 3.58 (br s, 1H), 3.64−3.67 (m, 1H), 4.34−4.44 (m, 2H), 4.63 (br d, J = 9.0 Hz, 1H), 7.07 (t, J = 7.8 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.65 (br s, 1H), 7.89 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.08, 23.22, 24.24, 24.77, 28.38, 30.42, 41.68, 42.21, 51.10, 53.94, 59.62, 68.18, 71.87, 76.68, 79.50, 94.47, 126.85, 130.34, 136.31, 136.54, 141.08, 156.21, 174.54; HRFAB MS, m/z 560.1979 for $[M + H]^+$ (calcd for $C_{24}H_{39}O_4N_3I$ 560.1985).

Boc-HEA[*R*-isobutyl,*R*-hydroxy]-Pro-NH-CH$_2$-C$_6$H$_4$I (26). Yield 75%; $[\alpha]^{25}_D$ −50.7 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 1.13−1.19 (m, 1H), 1.42 (s, 9H), 1.38−1.45 (m, 1H), 1.55−1.62 (m, 1H), 1.70−1.80 (m, 2H), 1.95−2.01 (m, 1H), 2.12−2.23 (m, 1H), 2.48−2.54 (m, 1H), 2.58−2.67 (m, 2H), 3.12−3.18 (m, 2H), 3.39 (br s, 1H), 3.59 (br s, 1H), 4.30−4.35 (m, 1H), 4.41−4.46 (m, 1H), 4.54 (br d, J = 9.4 Hz, 1H), 7.05 (t, J = 7.8 Hz, 1H), 7.26 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.65 (br s, 1H), 7.83 (br t, J = 5.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.05, 23.29, 24.54, 24.76, 28.35, 30.91, 42.01, 42.25, 50.84, 56.20, 60.53, 68.08, 72.31, 79.40, 94.53, 126.97, 130.38, 136.39, 136.67, 141.42, 156.28, 175.06; HRFAB MS, m/z 560.1981 for $[M + H]^+$ (calcd for $C_{24}H_{39}O_4N_3I$ 560.1985).

(c) H-Pro-Val-Ile-HEA[*S*-isobutyl,*R*-hydroxy](Gly-MBHA)-Pro-NH-CH$_2$-C$_6$H$_4$I (29). To a stirred solution of **23** (180 mg, 0.32 mmol) in $CHCl_3$ (3 mL) were added succinic anhydride (42 mg, 0.42 mmol) and DMAP (12 mg, 98 μmol), and the mixture was stirred at 23 °C for 12 h. The reaction mixture was washed with 5% citric acid and H_2O, dried over $MgSO_4$, and then evaporated. The product was purified by flash chromatography with hexane:AcOEt 1:5 followed by $CHCl_3$:MeOH 5:1 as the eluant to yield 105 mg (48%) of the desired carboxylic acid, Boc-HEA($COCH_2CH_2COOH$)-Pro-NH-CH_2-C_6H_4I (**27**):^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H), 1.15−1.18 (m, 2H), 1.42 (s, 9H), 1.55−1.71 (m, 2H), 1.76 (br s, 2H), 1.85−1.90 (m, 1H), 2.10−2.18 (m, 1H), 2.51−2.55 (m, 1H), 2.62−2.86 (m, 6H), 3.15−3.16 (m, 1H), 3.30−3.32 (m, 1H), 3.91 (br s, 1H), 4.23−4.28 (m, 2H), 4.41−4.53 (m, 1H), 4.56 (br d, J = 7.1 Hz, 1H), 4.82−4.86 (m, 1H), 7.04 (t, J = 7.7 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.65 (br s, 2H), 8.45 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.35, 23.53, 24.47, 24.56, 28.31, 29.03, 29.32, 30.93, 39.43, 42.10, 49.37, 55.59, 56.60, 68.82, 75.47, 79.64, 94.34, 127.01, 130.23, 136.11, 136.59, 141.39, 155.69, 172.15, 175.32, 176.04; HRFAB MS, m/z 660.2143 for $[M + H]^+$ (calcd for $C_{28}H_{43}O_7N_3I$ 660.2146).

To 100 mg of *p*-methylbenzhydrylamine resin (0.63 mmol/g resin) swelled in DMF (3 mL) were added. Fmoc-Gly-OH (49 mg, 0.16 mmol), *N*-hydroxybenzotriazole (HOBt, 25 mg, 0.16

mmol), DIEA (29 μL, 0.16 mmol), and DIPCDI (26 μL, 0.16 mmol) The mixture was agitated for 90 min at 23 °C. After the resin was washed with DMF, piperidine (20%) in DMF was added to the resin, and the mixture was agitated for 20 min at 23 °C. The N^{α}-deprotected resin was filtered and washed with DMF. To this resin were added the carboxylic acid **27** (90 mg, 0.13 mmol, 2 equiv for the resin) prepared above, HOBt (20 mg, 0.13 mmol), DIEA (29 μL, 0.16 mmol), and DIPCDI (26 μL, 0.16 mmol). The resin mixture was agitated for 15 h at 23 °C to yield the anchored resin **28**. After the resin was washed with DMF, the N^{α}-Boc group was removed by treatment with 50% TFA in CH_2Cl_2 according to the general procedure described above. Boc-Ile-OH was then introduced by a coupling reaction (90 min) with 0.16 mmol of each Boc-Ile-OH, HOBt, DIEA, and DIPCDI in DMF (3 mL). The Boc group of the resulting resin was removed with 50% TFA/CH_2Cl_2 as above. Boc-Val-OH and Boc-Pro-OH were then introduced by using the same coupling reaction followed by the N^{α}-deprotection reaction. The resin obtained was filtered, washed with MeOH, and dried to yield 120 mg of the desired resin **29**.

(d) H-Pro-Val-Ile-HEA[*S*-isobutyl,*R*-hydroxy]-Pro-NH-CH_2-C_6H_4I (31). An aliquot of the inhibitor resin **29** (50 mg) was treated with an anhydrous HF (5 mL) in the presence of anisole (0.10 mL) at 4 °C for 50 min. After evaporation of HF, ether (10 mL) was added to the reaction cylinder. The resulting precipitate was washed with ether (10 mL) and dissolved in 0.1% aqueous TFA. An analytical HPLC chromatogram of this solution is shown in Figure 4a. The solution was freeze-dried to yield 14.5 mg of the inhibitor precursor **30** as a white amorphous powder: HPLC, 15.08 min [YMC AM302 (4.6 × 150 mm), 0.9 mL/min, CH_3CN (25% to 70%, 30 min)], HRFAB MS, *m*/*z* 925.4056 for $[M + H]^+$ (calcd for $C_{41}H_{66}O_8N_8I$ 925.4048).

The precursor product **30** was dissolved in 0.4 M $AcONH_4$ (10 mL) and the pH of the solution was adjusted to 8.0. The mixture was stirred at 23 °C for 17 h, and then the pH was adjusted to 5.5 with 1 N AcOH. The solution was freeze−dried and the crude product was purified by preparative HPLC [YMC Pro C18 column (10 × 250 mm), CH_3CN (25−70%/60 min) in 0.1% aq TFA, 2.5 mL/min] to yield 7.1 mg (overall 46%) of inhibitor **31** as a white amorphous powder: HPLC, 15.98 min [YMC AM302 (4.6 × 150 mm), 0.9 mL/min, CH_3CN (25% to 70%, 30 min)], HRFAB MS, *m*/*z* 769.3520 for $[M + H]^+$ (calcd for $C_{35}H_{58}O_5N_6I$ 769.3513).

Three other inhibitors were prepared from the corresponding Boc-HEA-Pro-NH-CH_2-C_6H_4I, **24**, **25**, and **26**, using the same anchoring reaction followed by solid-phase synthesis.

H-Pro-Val-Ile-HEA[*R*-isobutyl,*S*-hydroxy]-Pro-NH-CH_2-C_6H_4I (32). Yield, overall 7% (white amorphous powder); HPLC, 16.96 min [YMC AM302 (4.6 × 150 mm), 0.9 mL/min, CH_3CN (25% to 70%, 30 min)], HRFAB MS, *m*/*z* 769.3535 for $[M + H]^+$ (calcd for $C_{35}H_{58}O_5N_6I$ 769.3513).

H-Pro-Val-Ile-HEA[*S*-isobutyl,*S*-hydroxy]-Pro-NH-CH_2-C_6H_4I (33). Yield, overall 9% (white amorphous powder); HPLC, 13.24 min [YMC AM302 (4.6 × 150 mm), 0.9 mL/min, CH_3CN (25% to 70%, 30 min)], HRFAB MS, *m*/*z* 769.3506 for $[M + H]^+$ (calcd for $C_{35}H_{58}O_5N_6I$ 769.3513).

H-Pro-Val-Ile-HEA[*R*-isobutyl,*R*-hydroxy]-Pro-NH-CH_2-C_6H_4I (34). Yield, overall 12% (white amorphous powder); HPLC, 17.16 min [YMC AM302 (4.6 × 150 mm), 0.9 mL/min, CH_3CN (25% to 70%, 30 min)], HRFAB MS, *m*/*z* 769.3518 for $[M + H]^+$ (calcd for $C_{35}H_{58}O_5N_6I$ 769.3513).

Measurement of Inhibitory Activity. Enzyme assays were carried out with use of the synthetic HTLV-1 protease mutant at an enzyme concentration of 5.6 nM. Hydrolyzate of the substrate in a reaction solution (0.5 M sodium acetate buffer, pH 5.6, containing 10% glycerol, 10 mM DTT and 4 M NaCl) were analyzed on a Cosmosil 5C18-AR11 column (4.6 × 250 mm), employing a linear gradient of CH_3CN (10−40%) in aq 0.1% TFA over 30 min. Under the two different substrate concentrations (30 and 15 μM), the initial velocities of the enzymatic reaction were measured in the presence of different amounts of the inhibitor. The incubation time was 12 min in the absence of the inhibitor and 40 min at the highest inhibitor concentration. Each experiment was repeated 3 times. The inhibitory constant, K_i, was then calculated from the Dixon plot. The K_i values obtained are summarized in Table 1.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compound **1**−**27**, and HPLC chromatograms for compound **31**−**34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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