Supporting Information

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Reduction of Peptide Character of HIV Protease Inhibitors that Exhibit Nanomolar Potency against Muti-drug Resistant HIV-1 Strains

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Experimental

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^{1}H NMR spectra were recorded using a JEOL EX-270 or a Bruker AC 300 spectrometer at 270 or 300 MHz ^{1}H frequency in $CDCl_3$ or CD_3OD. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane. Nominal (LRMS) and exact mass (HRMS) spectra were recorded on a JEOL JMS-01SG-2 or JMS-HX/HX 110A mass spectrometer. Ion-spray (IS)-mass spectrum was obtained with a Sciex API*III*E triple quadrupole mass spectrometer (Toronto, Canada). Optical rotations were measured in $CHCl_3$ with a JASCO DIP-360 digital polarimeter (Tokyo, Japan) or a Horiba high-sensitive polarimeter SEPA-200 (Kyoto, Japan). Melting points were measured by a hot stage melting point apparatus and are uncorrected. For flash column chromatographies, silica gel 60 H (silica gel for thin-layer chromatography, Merck) and Wakogel C-200 (silica gel for column chromatography) were employed. HPLC solvents were H_2O and CH_3CN, both containing 0.1% (v/v) TFA. For analytical HPLC, a Cosmosil 5C18-AR column (4.6 x 250 mm, Nacalai Tesque Inc., Kyoto, Japan) was eluted with a linear gradient of CH_3CN at a flow rate of 1 mL/min on a Waters model 600 (Nihon Millipore, Ltd., Tokyo, Japan). Preparative HPLC was performed on a Waters Delta Prep 4000 equipped with a Cosmosil 5C18-AR column (20 x 250 mm, Nacalai Tesque Inc.) using an isocratic mode of CH_3CN at a flow rate of 15 mL/min.

2-[2(*R*)-Hydroxy-4-phenyl-3(*S*)-[[*N*-(phenylmethoxy)carbonyl]amino]butyl]-*N*-*tert*-butyldecahydro-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide 2

To a stirred solution of epoxide **1** (500 mg, 1.68 mmol) in 2-propanol (5 mL) at room temperature was added *N*-(*tert*-butyl)-decahydroisoquinolinehydroxamide (399 mg, 1.68 mmol), and the mixture was refluxed for 5 h. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography over silica gel with *n*-hexane-EtOAc (3 : 1) to give 542 mg (1.01 mmol, 60.3 %) of hydroxyethylamine **2** as a colorless oil.

$[\alpha]^{28}_D$ –49.0 (*c* 1.47, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.23-2.04 (21H, m), 2.22-2.35 (2H, m), 2.59-2.69 (2H, m), 2.86-3.02 (3H, m), 3.82-3.92 (1H, br), 3.92-4.05 (1H, m), 4.99 (2H, s), 5.26-5.35 (1H, br), 5.97-6.03 (1H, br d), 7.18-7.35 (10H, m); *m/z* (FAB-LRMS) 536 (MH^+), 435, 138 (base peak), 91; Found (FAB): $(M+H)^+$, 536.3506.

Calcd for $C_{32}H_{46}O_4N_3$ (MH^+), 536.3488.

***N*-*tert*-Butyldecahydro-2-[2(*R*)-hydroxy-3(*S*)-[2(*S*)-[*N*-(methylsulfonyl)amino]-3-(2-naphthylsulfinyl)propanyl]amino-4-(phenyl)butyl]-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide 7**

To 61.2 mg (114 μmol) of **2** at 0 °C were added *m*-cresol (244 μL), thioanisole (600 μL), 1,2-ethanedithiol (100 μL), TFA (3.75 mL) and TMSBr (660 μL), and the mixture was stirred at 0 °C for 2 h. The mixture was concentrated under reduced pressure to give an oily residue of deprotected compound **3**, which was washed with *n*-hexane.

To a stirred solution of Boc-D-*S*-(2-naphthyl)cysteine (85.3 mg, 245 μmol) in DMF (3 mL) at 0 °C was added HOBt (37.6 mg, 245 μmol), BOP (109 mg, 245 μmol) and DIPEA (43.0 μL, 245 μmol), and the mixture was stirred at 0 °C for 10 min. The mixture and Et_3N (62.0 μL, 446 μmol) were added to a stirred solution of the above residue of **3** in DMF (2 mL) at 0 °C, and the reaction mixture was allowed to warm to room temperature and stirred at this temperature for 2.5 h. The mixture was extracted with EtOAc, and the extract was washed with saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was filtered through a pad silica gel to give a crude product **4**, which was used directly in the following step without further purification.

4 M HCl in 1,4-dioxane (1 mL, 4 mmol) was added to the above crude product **4** at 0 °C, and the mixture was allowed to warm to room temperature, stirred at this temperature for 1.5 h, and then concentrated under reduced pressure. To a stirred solution of the residue **5** in DMF (1 mL) at 0 °C were added DIPEA (50.1 μL, 288 μmol) and MsCl (7.4 μL, 95.9 μmol), and the reaction mixture was allowed to warm to room temperature, stirred at this temperature for 2h and extracted with EtOAc. The extract was washed with saturated aq. citric acid, saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was filtered through a pad silica gel to give a crude product **6**, which was used directly in the following step without further purification.

To a stirred solution of the crude mesylate **6** in MeOH (1 mL) at room temperature was added aq. 1 M $NaIO_4$ (43.0 μL, 43.0 μmol), and the mixture was stirred at room temperature overnight and extracted with EtOAc. The extract was washed with

brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by HPLC (H_2O : MeCN = 60 : 40) to give 6.14 mg (7.39 μmol, 6.5 % from **2**) of **7** as a white powder (1 TFA salt).

^{1}H NMR (270 MHz, CD_3OD) δ 1.30-1.45 (9H, m), 1.47-2.12 (12H, m), 2.43 (2H, t, *J* = 12.6 Hz), 3.05 (3H, s), 3.18-3.40 (4H, m), 3.53-3.61 (1H, m), 3.91-4.05 (3H, m), 4.14 (1H, dd, *J* = 12.2, 3.0 Hz), 6.23 (1H, t, *J* = 7.3 Hz), 6.73 (2H, t, *J* = 7.8 Hz), 7.03 (2H, d, *J* = 7.3 Hz), 7.54 (1H, dd, *J* = 8.6, 2.0 Hz), 7.68-7.73 (2H, m), 7.92-7.96 (1H, br), 8.06-8.11 (2H, m), 8.16-8.26 (2H, m); *m/z* (IS-MS) 725.5 (MH^+); Found (FAB): $(M+H)^+$, 725.3421. Calcd for $C_{38}H_{53}O_6N_4S_2$ (MH^+), 725.3407.

_N_-[3-[_N_-(4-Aminophenylsulfonyl)(2-methylpropyl)amino]-1(_S_)-benzyl-2(_R_)-hydroxypropyl]-2(_S_)-[_N_-(methylsulfonyl)amino]-3-(2-naphthylsulfinyl)propanamide 14

To a stirred solution of epoxide **1** (250 mg, 0.84 mmol) in 2-propanol (2.5 mL) at room temperature was added isobutylamine (85 μL, 0.84 mmol), and the mixture was refluxed for 5 h and concentrated under reduced pressure. To a stirred solution of the residue in $CHCl_3$ (2.5 mL) at 0 °C were added *p*-nitrobenzenesulfonylchloride (393 mg, 1.77 mmol) and triethylamine (245 μL, 1.77 mmol), and the mixture was allowed to warm to room temperature, stirred at this temperature for 2 days and extracted with EtOAc. The extract was washed with saturated aq. $NaHCO_3$, aq. 1 M HCl and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was filtered through a pad silica gel to give a crude product **8**, which was used directly in the following step without further purification.

By use of a procedure similar to that described for the preparation of **7** from **2**, the above crude product **8** was converted into crude mesylate **13**, which was used directly in the following step without further purification.

To a stirred solution of the crude mesylate **13** in MeOH (1 mL) at room temperature were added Zn (300 mg) and AcOH (300 μL), and the mixture was stirred at room temperature for 2 h. The residue was filtered through a pad silica gel and purified by HPLC (H_2O : MeCN = 58 : 42) to give 35.8 mg (43.2 μmol, 5.1 % from **1**) of **14** as a white powder (1 TFA salt).

^{1}H NMR (270 MHz, CD_3OD) δ 0.87 (3H, d, *J* = 6.6 Hz), 0.90 (3H, d, *J* = 6.3 Hz), 1.91-2.05 (1H, m), 2.10 (1H, dd, *J* = 13.5, 3.0), 2.32-2.41 (2H, m), 2.93 (3H, s), 2.77-3.05

(2H, m), 3.21 (1H, dd, J = 13.5, 3.3 Hz), 3.38 (1H, dd, J = 13.9, 3.3 Hz), 3.72-3.82 (1H, m), 4.03-4.17 (1H, m), 4.25 (1H, dd, J = 11.9, 3.3 Hz), 6.19 (1H, t, J = 7.3 Hz), 6.67 (2H, t, J = 7.8 Hz), 6.79 (2H, d, J = 8.6 Hz), 7.03 (2H, d, J = 6.9 Hz), 7.56 (3H, d, J = 8.6 Hz), 7.69-7.72 (2H, m), 8.06-8.09, (2H, m), 8.15-8.18 (2H, m), 8.26 (1H, d, J = 9.6 Hz); *m/z* (IS-MS) 715.5 (MH^+); Found (FAB): $(M+H)^+$, 715.2276. Calcd for $C_{34}H_{43}O_7N_4S_3$ (MH^+), 715.2294.

***tert*-Butyl 2(*R*)-benzyl-6-(2-naphthylthio)-5(*S*)-[[*N*-(phenylmethoxy)carbonyl]amino]hex-3(*E*)-enoate 16**

To a stirred solution of EADI **15** (3.29 g, 7.74 mmol) in $CHCl_3$ (16 mL) at 0 °C were added pyridine (3.76 mL, 46.5 mmol) and *p*-toluenesulfonylchloride (2.22 g, 11.6 mmol), and the reaction mixture was allowed to warm to room temperature and stirred at this temperature for 4h. *p*-Toluenesulfonylchloride (443 mg, 2.32 mmol) was added to the reaction mixture at 0 °C, and the mixture was stirred at room temperature for 4.5 h followed by quenching with saturated aq. citric acid at 0 °C. After evaporation of $CHCl_3$, the mixture was extracted with EtOAc. The extract was washed with saturated aq. citric acid and water, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was filtered through a pad silica gel to give a crude tosyl compound.

To a stirred slurry of NaH (200 mg, 8.32 mmol) in dry THF (5 mL) under argon at 0 °C was added dropwise 2-naphthalenethiol (1.33 g, 8.32 mmol) in THF (10 mL), and the mixture was allowed to warm to room temperature and stirred at this temperature for 15 min. A solution of the above crude tosylate in THF (20 mL) was added to the reaction mixture at 0 °C, and the reaction mixture was stirred at 0 °C for 2.5 h followed by quenching with saturated aq. citric acid at 0 °C. After evaporation of THF, the mixture was extracted with EtOAc. The extract was washed with saturated aq. citric acid, saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel with *n*-hexane-EtOAc (6 : 1) to give 3.16 g (5.57 mmol, 71.8 % from **15**) of EADI **16** as a colorless oil.

$[\alpha]^{29}_D$ −18.4 (*c* 1.41, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.34 (9H, s), 2.71 (1H, dd, J = 13.5, 6.9 Hz), 2.97 (1H, dd, J = 13.5, 7.9 Hz), 3.11-3.20 (3H, m), 4.39-4.50 (1H, m), 4.93-5.08 (3H, m), 5.49 (1H, dd, J = 15.5, 5.6 Hz), 5.70 (1H, dd, J = 15.5, 8.3 Hz), 7.08-7.49 (13H, m), 7.71-7.80 (4H, m); *m/z* (FAB-LRMS) 567 (M^+), 361, 294 (base peak),

173, 91, 57; Found (FAB): (M^+), 567.2442. Calcd for $C_{35}H_{37}O_4NS$ (M^+), 567.2443.

2(*R*)-Benzyl-6-(2-naphthylthio)-5(*S*)-[[*N*-(phenylmethoxy)carbonyl]amino]hex-3(*E*)-enoic acid 17

4 M HCl in 1,4-dioxane (30 mL, 120 mmol) was added to EADI **16** (3.16 g, 5.57 mmol) at 0 °C, and the mixture was allowed to warm to room temperature, stirred at this temperature over night and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel with *n*-hexane-EtOAc (2 : 1) to give 2.62 g (5.12 mmol, 92.0 %) of carboxylic acid free EADI **17** as a colorless oil.
$[\alpha]^{24}_D$ −19.9 (*c* 1.26, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 2.69-2.76 (1H, m), 3.01-3.09 (1H, m), 3.20-3.26 (1H, m), 3.58-3.64 (1H, m), 3.72-3.76 (1H, m), 4.36-4.46 (1H, br), 5.02 (2H, s), 4.98-5.18 (1H, br), 5.45 (1H, dd, *J* = 15.5, 5.6 Hz), 5.69 (1H, dd, *J* = 15.5, 8.6 Hz), 7.07-7.44 (13H, m), 7.68-7.77 (4H, m); *m/z* (FAB-LRMS) 511 (MH^+), 361, 338 (base peak), 294, 173, 91; Found (FAB): $(M+H)^+$, 512.1887. Calcd for $C_{31}H_{30}O_4NS$ (MH^+), 512.1896.

***N*-[1(*S*)-(2-Naphthylthiomethyl)-4(*R*)-[2(*R*,*S*)-oxiranyl]-5-phenylpent-2(*E*)-enyl](phenylmethoxy)formamide 20a, b**

To a stirred solution of EADI **17** (2.69 g, 5.08 mmol) in THF (10 mL) at −78 °C were added dropwise DIPEA (1.33 mL, 7.62 mmol) and isobutylchloroformate (989 μL, 7.62 mmol), and the mixture was stirred at −10 °C for 30 min. Diazomethane, which was bubbled in Et_2O, was added in the reaction mixture at −10 °C, and the mixture was stirred at 0 °C for 30 min followed by quenching carefully with AcOH at 0 °C. 4 M HCl in dioxane (12.7 mL, 50.8 mmol) was added to the mixture at 0 °C, and the mixture was allowed to warm to room temperature, stirred at this temperature for 1.5 h and concentrated under reduced pressure. The residue was extracted with EtOAc. The extract was washed with saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure to give a crude product **18**, which was used directly in the following step without further purification.

$NaBH_4$ (769 mg, 20.3 mmol) was added to a solution of the above crude compound **18** in THF (25 mL), MeOH (2.5 mL) and H_2O (2.5 mL) at 0 °C, and the mixture was stirred at 0 °C for 1 h followed by quenching with saturated aq. NH_4Cl. After evaporation of THF and MeOH, the mixture was extracted with EtOAc. The

extract was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give crude products **19a,b**, which were used directly in the following step without further purification.

0.5 M KOH in EtOH (10.2 mL, 5.08 mmol) was added to a stirred solution of the above crude compounds **19a,b** in EtOH (50 mL) at 0 °C, and the mixture was stirred at 0 °C for 1.5 h and at room temperature for 30 min and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel with *n*-hexane-EtOAc (3 : 1) to give 1.43 g (2.81 mmol, 55.0% from **17**) of epoxides **20a,b** as a diastereomixture.

^{1}H NMR (270 MHz, $CDCl_3$) δ 2.06-2.24 (1H, m), 2.26-2.32 (0.5H, m), 2.42-2.45 (0.5H, m), 2.57-2.60 (0.5H, m), 2.64-2.68 (2H, m), 2.71-2.81 (1H, m), 2.90 (0.5H, dd, J = 13.6, 5.3 Hz), 3.02-3.25 (2H, m), 4.34-4.51 (1H, br), 4.85-5.12 (3H, M), 5.33 (0.5H, dd, J = 15.5, 5.9 Hz), 5.43-5.53 (1H, m), 5.58 (0.5H, dd, J = 15.8, 7.3 Hz), 7.05-7.50 (13H, m), 7.71-7.80 (4H, m); *m/z* (FAB-LRMS) 510 (MH^+), 173 (base peak), 91; Found (FAB): $(M+H)^+$, 510.2096. Calcd for $C_{32}H_{32}O_3NS$ (MH^+), 510.2103.

***N*-*tert*-Butyldecahydro-2-[3(*R*)-benzyl-2(*R*,*S*)-hydroxy-6(*S*)-[*N*-(methylsulfonyl)amino]-7-(2-naphthylsulfinyl)hept-4(*E*)-enyl]-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide 23a,b and *N*-*tert*-butyldecahydro-2-[3(*R*)-benzyl-2(*R*,*S*)-hydroxy-6(*S*)-[*N*-(methylsulfonyl)amino]-7-(2-naphthylsulfonyl)hept-4(*E*)-enyl]-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide 24a,b**

To a stirred solution of epoxides **20a,b** (71.4 mg, 140 μmol) in 2-propanol (600 μL) at room temperature was added *N*-(*tert*-butyl)-decahydroisoquinolinehydroxamide (39.9 mg, 168 μmol) at room temperature, and the mixture was refluxed for 8 h. The reaction mixture was concentrated under reduced pressure and was filtered through a pad silica gel to give crude compounds **21a,b**.

To the crude compounds **21a,b** at 0 °C were added *m*-cresol (200 μL), thioanisole (200 μL), 1,2-ethanedithiol (200 μL), H_2O (200 μL) and TFA (3.2 mL), and the mixture was allowed to warm to room temperature and stirred at this temperature for 1 day. The mixture was concentrated under reduced pressure to give an oily residue of deprotected compounds, which were washed with *n*-hexane.

To a stirred solution of the deprotected compounds in DMF (1.5 mL) at 0 °C

were added MsCl (15.3 μL, 197 μmol) and DIPEA (105 μL, 606 μmol), and the mixture was allowed to warm to room temperature and stirred at this temperature overnight. Saturated aq. $NaHCO_3$ was added to the reaction mixture at 0 °C, and the mixture was extracted with EtOAc. The extract was washed with saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure to give crude mesyl compounds **22a,b**, which were used directly in the following step without further purification.

To a stirred solution of the crude mesylates **22a,b** in MeOH (1 mL) at 0 °C was added aq. 1 M $NaIO_4$ (87.0 μL, 87.0 μmol), and the mixture was allowed to warm to room temperature and stirred at this temperature for 5 h. The mixture was extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by HPLC (H_2O : MeCN = 45 : 55) to give 1.79 mg (2.18 μmol, 1.53 % from **20a,b**) of **23a**, 1.44 mg (1.75 μmol, 1.27 % from **20a,b**) of **23b**, 1.14 mg (1.36 μmol, 0.95 % from **20a,b**) of **24a** and 1.63 mg (1.94 μmol, 1.34 % from **20a,b**) of **24b** as white powders (1 TFA salt).

23a, ^{1}H NMR (270 MHz, CD_3OD) δ 0.88-0.98 (9H, m), 1.17-2.15 (12H, m), 2.58-2.77 (2H, m), 2.86 (1.5H, s), 2.97 (1.5H, s), 3.18-3.40 (4H, m), 3.76-3.85 (1H, m), 4.04-4.15 (1H, m), 4.21 (2H, d, J = 6.3 Hz), 4.24-4.35 (1H, m), 5.28 (0.5H, dd, J = 15.5, 7.3 Hz), 5.37 (0.5H, dd, J = 15.2, 7.6 Hz), 5.64 (0.5H, dd, J = 14.9, 4.6 Hz), 5.68 (0.5H, dd, J = 15.5, 4.6 Hz), 6.88 (1H, m), 7.08 (2H, d, J = 4.6 Hz), 7.17 (1H, d, J = 6.9 Hz), 7.24 (1H, d, J = 6.9 Hz), 7.60-7.78 (3H, m), 7.98-8.22 (5H, m); *m/z* (FAB-LRMS) 730 (MNa^+), 708 (MH^+), 692, 591, 532 (base peak), 431, 337, 245, 115, 91; Found (FAB): $(M+H)^+$, 708.3488. Calcd for $C_{39}H_{54}O_5N_3S_2$ (MH^+), 708.3505.

23b, ^{1}H NMR (270 MHz, CD_3OD) δ 0.88-0.99 (9H, m), 1.27-2.18 (12H, m), 2.62-2.77 (2H, m), 2.87 (1.5H, s), 2.98 (1.5H, s), 3.20-3.40 (4H, m), 3.95-4.12 (1H, m), 4.21 (2H, d, J = 5.4 Hz), 4.24-4.37 (1H, m), 4.60 (1H, br), 5.13 (0.5H, dd, J = 15.5, 8.2 Hz), 5.28-5.38 (0.5H, m), 5.40-5.45 (1H, m), 6.77 (1H, m), 7.03 (2H, d, J = 6.6 Hz), 7.17 (1H, d, J = 6.6 Hz), 7.23 (1H, d, J = 6.9 Hz), 7.60-7.75 (3H, m), 8.00-8.08 (3H, m), 8.12 (1H, d, J = 7.9 Hz), 8.18 (1H, d, J = 9.9 Hz); *m/z* (FAB-LRMS) 708 (MH^+), 692, 591, 532 (base peak), 431, 138, 91; Found (FAB): $(M+H)^+$, 708.3524. Calcd for $C_{39}H_{54}O_5N_3S_2$ (MH^+), 708.3505.

24a, $[\alpha]^{28}_D$ −17.54 (*c* 0.06, MeOH); ^{1}H NMR (270 MHz, CD_3OD) δ 0.82-1.00 (9H, m), 1.23-2.08 (12H, m), 2.69 (3H, s), 2.78-3.02 (2H, m), 3.17-3.40 (4H, m), 4.08-4.12 (1H,

m), 4.21 (2H, d, J = 5.6 Hz), 4.26-4.37 (1H, m), 4.58-4.80 (1H, m), 5.30-5.45 (1H, m), 5.58-5.80 (1H, m), 6.78-6.92 (1H, m), 7.00-7.25 (4H, m), 7.60-7.75 (3H, m), 8.00-8.07 (3H, m), 8.07-8.13 (2H, m); *m/z* (FAB-LRMS) 722 (MH^-), 708, 589 (base peak), 239, 138; Found (FAB): $(M-H)^-$, 722.3283. Calcd for $C_{39}H_{52}O_6N_3S_2$ $(M-H)^-$, 722.3297.

24b, $[\alpha]^{29}_D$ –333 (*c* 0.02, MeOH); ^1H NMR (270 MHz, CD_3OD) δ 0.83-0.99 (9H, m), 1.20-2.12 (12H, m), 2.58-2.82 (2H, m), 2.87 (1.5H, s), 2.98 (1.5H, s), 3.17-3.40 (4H, m), 4.10-4.18 (1H, m), 4.21 (2H, d, J = 5.6 Hz), 4.24-4.39 (1H, m), 4.56-4.80 (1H, m), 5.25 (0.5H, dd, J = 15.4, 7.2 Hz), 5.38 (0.5H, dd, J = 15.0, 8.2 Hz), 5.52-5.66 (1H, m), 6.82-6.92 (1H, m), 7.08 (2H, d, J = 4.3 Hz), 7.18 (1H, d, J = 6.3 Hz), 7.24 (1H, d, J = 7.6 Hz), 7.60-7.75 (3H, m), 8.00-8.08 (3H, m), 8.13 (1H, dd, J = 8.6, 6.3 Hz), 8.20 (1H, d, J = 7.3 Hz); *m/z* (FAB-LRMS) 724 (MH^+), 708, 239, 138 (base peak); Found (FAB): $(M+H)^+$, 724.3464. Calcd for $C_{39}H_{54}O_6N_3S_2$ $(MH)^+$, 724.3454.

***N,N*-[3(*R*)-Benzyl-2(*S*)-hydroxy-6(*S*)-[*N*-(methylsulfonyl)amino]-7-(2-naphthylthio)hept-4(*E*)-enyl](2-methylpropyl)[(4-nitrophenyl)sulfonyl]amine 27a and *N,N*-[3(*R*)-benzyl-2(*R*)-hydroxy-6(*S*)-[*N*-(methylsulfonyl)amino]-7-(2-naphthylthio)hept-4(*E*)-enyl](2-methylpropyl)[(4-nitrophenyl)sulfonyl]amine 27b**

To a stirred solution of epoxides **20a,b** (553.6 mg, 1.09 mmol) in 2-propanol (5 mL) at room temperature was added isobutylamine (169 μL, 1.68 mmol), and the mixture was refluxed for 18 h. The reaction mixture was concentrated under reduced pressure and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. To a stirred solution of the residue in $CHCl_3$ (4 mL) at 0 °C were added *p*-nitrobenzenesulfonylchloride (583 mg, 2.63 mmol) and triethylamine (797 μL, 5.74 mmol), and the mixture was allowed to warm to room temperature, stirred at this temperature for 2 days and extracted with EtOAc. The extract was washed with aq. 1 M HCl and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was filtered through a pad silica gel to give crude products **25a,b**, which were used directly in the following step without further purification.

To the crude compounds **25a,b** at 0 °C were added *m*-cresol (800 μL), thioanisole (800 μL), 1,2-ethanedithiol (800 μL), H_2O (800 μL) and TFA (12.8 mL), and the mixture was allowed to warm to room temperature and stirred at this temperature for 6 h. The mixture was concentrated under reduced pressure, and the residue was washed

with *n*-hexane and purified by HPLC (H_2O : MeCN = 53 : 47) to give 189 mg of **26a** and 160 mg of **26b** as yellow oils.

To a stirred solution of the above deprotected compound **26a** in DMF (2 mL) at 0 °C were added MsCl (19.6 μL, 253 μmol) and DIPEA (132 μL, 759 μmol), and the mixture was allowed to warm to room temperature, stirred at this temperature for 4 h and extracted with EtOAc. The extract was washed with aq. 1 M HCl, saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel with *n*-hexane-EtOAc (3 : 1) to give 66.0 mg (92.7 μmol, 8.53 % from **20a,b**) of **27a** as a yellow oil.

The other deprotected compound **26b** was converted into the corresponding mesyl compound **27b** (25.1 mg, 35.3 μmol, 3.25 % from **20a,b**) as yellow crystals in the same way.

27a, $[\alpha]^{23}_D$ +4.1 (*c* 1.47, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.83 (3H, d, *J* = 6.6 Hz), 0.88 (3H, d, *J* = 6.6 Hz), 1.73-1.87 (1H, m), 2.39-2.61 (2H, m), 2.81 (3H, s), 2.77-3.08 (6H, m), 3.17 (1H, d, *J* = 5.9 Hz), 3.70-3.78 (1H, m), 3.81-3.92 (1H, m), 4.69 (1H, d, *J* = 5.3 Hz), 5.21 (1H, dd, *J* = 15.2, 7.9 Hz), 5.40 (1H, dd, *J* = 15.5, 8.9 Hz), 7.08-7.38 (6H, m), 7.49-7.56 (2H, m), 7.75-7.84 (4H, m), 7.98 (2H, d, *J* = 8.9 Hz), 8.31 (2H, d, *J* = 8.9 Hz); *m/z* (FAB-LRMS) 711 (MH^+), 617 (base peak), 271, 173, 154, 136, 57; Found (FAB): $(M+H)^+$, 712.2177. Calcd for $C_{35}H_{42}O_7N_3S_3$ (MH^+), 712.2185.

27b, mp 163-165 °C [from EtOAc-hexane]; $[\alpha]^{23}_D$ -18.2 (*c* 0.39, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.79 (3H, d, *J* = 5.9 Hz), 0.82 (3H, d, *J* = 5.9 Hz), 1.66-1.79 (1H, m), 2.25-2.35 (1H, m), 2.80 (3H, s), 2.61-3.09 (7H, m), 3.29 (1H, dd, *J* = 14.5, 9.2 Hz), 3.75-3.80 (1H, m), 3.95-4.00 (1H, m), 4.78 (1H, d, *J* = 5.9 Hz), 5.30 (1H, dd, *J* = 15.5, 7.6 Hz), 5.70 (1H, dd, *J* = 15.3, 9.4 Hz), 7.09-7.31 (6H, m), 7.47-7.52 (2H, m), 7.75-7.83 (4H, m), 7.97 (2H, d, *J* = 8.6 Hz), 8.28 (2H, d, *J* = 8.6 Hz); *m/z* (FAB-LRMS) 712 (MH^+), 617 (base peak), 271, 173, 154, 136; Found (FAB): $(M+H)^+$, 712.2197. Calcd for $C_{35}H_{42}O_7N_3S_3$ (MH^+), 712.2185.

_N,N_-[(4-Aminophenyl)sulfonyl][3(_R_)-benzyl-2(_S_)-hydroxy-6(_S_)-[_N_-(methylsulfonyl)amino]-7-(2-naphthylsulfinyl)hept-4(_E_)-enyl](2-methylpropyl)amine 29a and _N,N_-[(4-aminophenyl)sulfonyl][3(_R_)-benzyl-2(_R_)-hydroxy-6(_S_)-[_N_-(methylsulfonyl)amino]-7-(2-naphthylsulfinyl)hept-4(_E_)-enyl](2-methylpropyl)amine 29b

By use of a procedure similar to that described for the preparation of **14** from **12**, compounds **27a** (11.9 mg, 16.8 μmol) and **27b** (9.7 mg, 13.7 μmol) were converted into 4.46 mg (5.49 μmol, 32.9%) of **29a** and 2.71 mg (3.34 μmol, 24.3 %) of **29b**, respectively, as white powders.

29a, ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.83 (1.5H, d, *J* = 6.6 Hz), 0.84 (1.5H, d, *J* = 6.6 Hz), 0.88 (3H, d, *J* = 6.6 Hz), 1.95-2.05 (1H, m), 2.37-2.57 (2H, m), 2.59-3.11 (4H, m), 2.77 (1.5H, s), 2.85 (1.5H, s), 3.66-3.79 (2H, m), 3.99-4.10 (1H, m), 4.22-4.33 (1H, m), 5.07 (0.5H, dd, *J* = 15.8, 8.6 Hz), 5.23 (0.5H, dd, *J* = 16.2, 8.6 Hz), 5.48-5.62 (1H, m), 6.70 (2H, dd, *J* = 8.9, 4.0 Hz), 6.95-7.21 (4H, m), 7.50 (2H, d, *J* = 8.6 Hz), 7.63-7.69 (3H, m), 7.98-8.05 (2H, m), 8.10-8.15 (2H, m), 8.19 (1H, d, *J* = 5.6 Hz); *m/z* (IS-MS) 698.5 (MH^+); Found (FAB): $(M+H)^+$, 698.2404. Calcd for $C_{35}H_{44}O_6N_3S_3$ (MH^+), 698.2392.

29b, ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.76 (3H, d, *J* = 6.6 Hz), 0.81 (3H, d, *J* = 6.3 Hz), 1.75 (1H, heptuplet), 2.42-2.62 (2H, m), 2.64-2.90 (2H, m), 2.84 (1.5H, s), 2.93 (1.5H, s), 3.03-3.17 (2H, m), 3.78 (2H, m), 4.12 (1H, dd, *J* = 14.5, 7.3 Hz), 4.34 (1H, m), 5.30 (0.5H, dd, *J* = 15.5, 7.6 Hz), 5.43 (0.5H, dd, *J* = 15.5, 7.9 Hz), 5.73 (0.5H, dd, *J* = 15.2, 9.6 Hz), 5.74 (0.5H, dd, *J* = 15.2, 9.6 Hz), 6.67 (3H, t, *J* = 8.9 Hz), 6.84 (1H, m), 7.07 (2H, d, *J* = 4.3 Hz), 7.15 (1H, d, *J* = 6.9 Hz), 7.21 (1H, d, *J* = 7.6 Hz), 7.44 (3H, t, *J* = 8.6 Hz), 7.62-7.72 (2H, m), 7.99-8.06 (2H, m), 8.12 (2H, dd, *J* = 8.9, 3.3 Hz), 8.23 (1H, s); *m/z* (FAB-LRMS) 698 (MH^+), 527 (base peak), 241, 156; Found (FAB): $(M+H)^+$, 698.2405. Calcd for $C_{35}H_{44}O_6N_3S_3$ (MH^+), 698.2392.

1(*R*)-[2-(*tert*-Butyldimethylsiloxy)-1(*R*)-[[*N*-(phenylmethoxy)carbonyl]amino]ethyl]prop-2-enyl acetate 32

To a stirred solution of an ester **30** (ref. Konradi, A. W., et al., *J. Am. Chem. Soc.* **1994**, *116*, 1316-1323; Jacobsen, E. J., et al., *J. Med. Chem.* **1999**, *42*, 1525-1536) (50.0 g, 136 mmol) in $CHCl_3$ (200 mL) and toluene (200 mL) under argon at -78 °C with stirring was added *via* syringe 204 mL (204 mmol) of a 1 M solution of DIBAL in toluene, and the stirring was continued for 1.5 h. To the reaction mixture at -78 °C with stirring was added successively *via* syringe 382 mL of a 1.07 M vinylMgCl (408 mmol) in THF containing $ZnCl_2$ (55.6 g, 408 mmol) and LiCl (17.3 g, 408 mmol), and the mixture was allowed to warm to room temperature and stirred at this temperature overnight followed by quenching with saturated aq. citric acid at 0 °C. The mixture was stirred at room

temperature for 2 h. Organic solvents were removed by evaporation, and the mixture was extracted with EtOAc. The extract was washed with saturated aq. citric acid, saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was filtered through a pad silica gel to give a crude product **31**, which was used directly in the following step without further purification.

To a stirred solution of the above crude allyl alcohol **31** in benzene (150 mL) at room temperature were added vinyl acetate (38.2 mL, 414 mmol) and NOVOZYM435 (*Candida antarctica* lipase, Novo Nordisk Bioindustry Ltd., ref. Fujiwara, Y., et al., *Tetrahedron: Asymmetry*, **1997**, *8*, 2793-2799) (2.00 g), and the mixture was stirred at room temperature for 3 days. Vinyl acetate (114 mL, 1.24 mol) and NOVOZYM435 (1.00 g) were added to the reaction mixture at room temperature, and the mixture was stirred at room temperature for 6 days. After removal of enzyme by filtration, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel with *n*-hexane-EtOAc (5 : 1) to give 23.3 g (57.2 mmol, 41.3 % from **30**) of **32** as a colorless oil. Stereochemical assignment for **32** was established by conversion of 1-(*tert*-butyldimethylsiloxy)-3(*R*)-hydroxy-2(*R*)-[*N*-(phenylmethoxycarbonyl)amino]-4-pentene into **32** by Ac_2O and pyridine.

$[\alpha]^{24}_D$ +1.7 (*c* 1.17, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.89 (9H, s), 2.01 (3H, s), 3.56 (1H , dd, *J* = 9.9, 5.9 Hz), 3.71 (1H, dd, *J* = 10.2, 3.6 Hz), 3.85-3.96 (1H, m), 5.03-5.17 (3H, m), 5.26 (1H, d, *J* = 9.6 Hz), 5.31 (1H, d, *J* = 15.7 Hz), 5.52 (1H, dd, *J* = 6.0, 5.6 Hz), 5.82 (1H, ddd, *J* = 17.2, 10.6, 6.6 Hz), 7.36 (5H, br s); *m/z* (FAB-LRMS) 408 (MH^+), 350, 348, 91, 73 (base peak); Found (FAB): $(M+H)^+$, 408.2198. Calcd for $C_{21}H_{34}O_5NSi$ (MH^+), 408.2206.

tert-Butyl 4(*R*)-acetoxy-6-(*tert*-butyldimethylsiloxy)-5(*R*)-[[*N*-(phenylmethoxy)carbonyl]amino]hex-2(*E*)-enoate 33

O_3 was bubbled through a solution of acetate **32** (25.0 g, 61.3 mmol) in EtOAc (200 mL) at -78 °C until a blue color persisted. N_2 was bubbled through the solution with stirring for 30 min during which time it was allowed to warm to 0 °C. To the solution at 0 °C was added dimethyl sulfide (22.5 mL, 307 mmol), and the mixture was stirred for 30 min and concentrated under reduced pressure to give an oily residue of a crude aldehyde. To a stirred slurry of LiCl (3.90 g, 92.0 mmol) in CH_3CN (40 mL) under argon at 0 °C were added a solution of diethylphosphono acetic acid *tert*-butyl ester (23.2 g, 92.0

mmol) in CH_3CN (40 mL) and DIPEA (16.0 mL, 92.0 mmol), followed by addition of the above residue of the crude aldehyde in CH_3CN (70 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred at this temperature overnight. Organic solvents were removed by evaporation, and the mixture was extracted with EtOAc. The extract was washed with saturated aq. citric acid and H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel with *n*-hexane-EtOAc (5 : 1) to give 17.3 g (34.1 mmol, 55.6 %) of **33** as a colorless oil.

$[\alpha]^{28}_D$ -11.6 (*c* 0.69, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.89 (9H, s), 1.48 (9H, s), 2.04 (3H, s), 3.56 (1H, dd, *J* = 9.9, 6.3 Hz), 3.73 (1H, dd, *J* = 10.1, 3.5 Hz), 3.90-4.01 (1H, m), 5.05-5.16 (3H, m), 5.66 (1H, dd, *J* = 5.3, 4.6 Hz), 5.89 (1H, d, *J* = 15.5 Hz), 6.75 (1H, dd, *J* = 15.7, 5.8 Hz), 7.36 (5H, br s); *m/z* (FAB-LRMS) 508 (MH^+), 452, 450 (base peak), 91, 73; Found (FAB): $(M+H)^+$, 508.2720. Calcd for $C_{26}H_{42}O_7NSi$ (MH^+), 508.2731.

Cbz-D-Ser(TBS)-ψ[(*E*)-CH=CH]-L-Phe-OBu^t 35

Na_2CO_3 (21.7 g, 205 mmol) was added to a stirred solution of **33** (17.3 g, 34.1 mmol) in MeOH (150 mL) at 0 °C, and the mixture was stirred at 0 °C for 30min and at room temperature for 1.5h. The mixture was filtered through celite and concentrated under reduced pressure, and the residue was extracted with EtOAc. The extract was washed with H_2O, dried over $MgSO_4$ and concentrated under reduced pressure to give a crude alcohol. To a stirred solution of the crude alcohol in $CHCl_3$ (120 mL) at 0 °C were added pyridine (13.8 mL, 171 mmol) and MsCl (7.92 mL, 102 mmol), and the mixture was allowed to warm to room temperature and stirred at this temperature 4 h. Pyridine (13.8 mL, 171 mmol) and MsCl (7.92 mL, 102 mmol) were added to the reaction mixture at 0 °C, and the mixture was allowed to warm to room temperature and stirred at this temperature overnight followed by quenching with saturated aq. $NaHCO_3$ at 0 °C. After evaporation of the organic solvents, the mixture was extracted with EtOAc. The extract was washed with saturated aq. $NaHCO_3$, saturated aq. citric acid and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was filtered through a pad silica gel to give a crude mesyl compound **34**, which was used directly in the following step without further purification.

To a stirred slurry of CuCN (11.3 g, 126 mmol) in dry THF (80 mL) under

argon at –78 °C was added by syringe 101 mL (126 mmol) of 1.25 M BnMgCl in THF, and the mixture was allowed to warm to 0 °C and stirred at this temperature for 15 min. $BF_3{\cdot}Et_2O$ (15.5 mL, 126 mmol) was added to the above mixture at –78 °C, and the mixture was stirred at –78°C for 15 min. To the mixture at –78 °C with stirring was added by syringe a solution of the crude mesylate **34** (17.1 g, 31.5 mmol) in THF (40 mL), and the stirring was continued for 30 min at –78 °C followed by quenching with saturated aq. NH_4Cl and aq. 28 % NH_3 (1 : 1) at 0 °C. The mixture was allowed to warm to room temperature and extracted with Et_2O. The extract was washed with H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel with *n*-hexane-EtOAc (7 : 1) to give 9.00 g (16.7 mmol, 49.0 % from **33**) of protected EADI **35** as a colorless oil.

$[\alpha]^{24}_D$ -24.1 (*c* 0.54, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.01 (6H, s), 0.86 (9H, s), 1.32 (9H, s), 2.75 (1H, dd, *J* = 13.5, 6.9 Hz), 2.99 (1H, dd, *J* = 13.5, 8.2 Hz), 3.15-3.23 (1H, m), 3.51-3.59 (1H, br), 3.64 (1H, dd, *J* = 9.9, 4.3 Hz), 4.15-4.25 (1H, br), 4.97-5.08 (1H, br), 5.11 (2H, s), 5.49 (1H, dd, *J* = 15.5, 5.9 Hz), 5.70 (1H, dd, *J* = 15.5, 7.9 Hz), 7.13-7.37 (10H, m); *m/z* (FAB-LRMS) 562 (MNa^+), 540 (MH^+), 484, 91, 72, 57 (base peak); Found (FAB): $(M+H)^+$, 540.3153. Calcd for $C_{31}H_{46}O_5NSi$ (MH^+), 540.3145.

Cbz-D-Ser-ψ[(*E*)-CH=CH]-L-Phe-OBu^t 15

Aq. 35 % H_2SiF_6 (7.62 mL, 25.0 mmol) was added to a stirred solution of protected EADI **35** (8.99 g, 16.7 mmol) in THF (40 mL) and CH_3CN (40 mL) in plastic vessel at 0 °C, and the mixture was stirred at 0 °C for 1 h followed by quenching with saturated aq. $NaHCO_3$ at 0 °C. After evaporation of the organic solvents, the mixture was extracted with EtOAc. The extract was washed with saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel with *n*-hexane-EtOAc (2 : 1) to give 7.28 g (17.1 mmol, 103 %) of protected EADI **15** as a white powder.

$[\alpha]^{24}_D$ –6.3 (*c* 0.63, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.36 (9H, s), 2.01-2.07 (1H, br), 2.76 (1H, dd, *J* = 13.5, 7.9 Hz), 3.03 (1H, dd, *J* = 13.5, 7.6 Hz), 3.19 (1H, ddd, *J* = 8.3, 7.9, 7.6 Hz), 3.43-3.63 (2H, br), 4.18-4.28 (1H, br), 5.09 (2H, s), 5.03-5.11 (1H, br), 5.34 (1H, dd, *J* = 15.8, 5.9 Hz), 5.69 (1H, dd, *J* = 15.8, 8.4 Hz), 7.11-7.34 (10H, m); *m/z* (FAB-LRMS) 448 (MNa^+), 426 (MH^+), 370, 91, 57 (base peak); Calcd for $C_{25}H_{32}O_5N$

(MH^+), 426.2280. Anal. ($C_{25}H_{31}O_5N$) Found: C, 70.19; H, 7.30; N, 3.33. Calcd: C, 70.57; H, 7.34; N, 3.29%.

Cells and viruses

MT-2 cells were grown in an RPMI 1640-based culture medium supplemented with 15% fetal calf serum (FCS, HyClone Laboratories, Logan, Utah, USA) plus 50 U of penicillin and 50 μg of streptomycin per mL. The following HIV-1 strains were used for a drug susceptibility assay: HIV-1_{LAI}, a clinical HIV-1 strain isolated from a drug-naive patient with AIDS, HIV-1_{104pre}, and three HIV-1 clinical isolates that were originally isolated from heavily pretreated patients, HIV-1_{TM}, HIV-1_{MM} and HIV-1_{JSL}, which were genotypically and phenotypically characterized as multi-drug-resistant HIV-1s. Amino acid substitutions identified in the protease-encoding region are as follows:

HIV-1_{104pre}	L63P
HIV-1_{TM}	L10I/K14R/S37N/R41K/M46I/I54V/L63P/A71V/V82A/L90M/I93L
HIV-1_{MM}	L10I/S37N/K43T/M46I/I54V/L63P/A71V/V82A/L90M/I93L
HIV-1_{JSL}	L10I/L24I/L33F/E35D/M36I/M46I/I54V/R57K/I62V/L63P/A71V/ G73S/V82A

Anti-HIV assay

The sensitivities of HIV-1_{LAI} against various agents were determined as previously described (ref. Yoshimura, K., et al., *J. Virol.* **2002**, *76*, 1349-1358). Briefly, MT-2 cells (2 x 10^3/well) were exposed to 100 50% tissue culture infective doses ($TCID_{50}$s) of HIV-1_{LAI} in the presence of various concentrations of agents in 96-well microculture plates and incubated at 37°C for 7 days (final volume: 200 μL/well). After the medium was removed from each well, 10 μL of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) solution (7.5 mg/mL) in PBS was added to each well in the plate, followed by incubation at 37°C for 2 h. After incubation, to dissolve the formazan crystals, 100 μL of acidified isopropanol containing 4% (v/v) Triton X-100 was added to each well, the optical density (OD570) was measured in a microplate reader (model 3550; Bio-Rad). All assays were performed in at least triplicate.

Phytohemagglutinin (PHA)-treated peripheral blood mononuclear cells (PBMC) (1 x 10^5/well) were exposed to 50 $TCID_{50}$s of each HIV-1 clinical isolate in the presence or absence of various concentrations of agents in 96-well microculture plates

(final volume: 200 μL/well). The amounts of p24 antigen produced by the cells were determined on day 7 in culture using a commercially available radioimmunoassay kit. Drug concentrations that resulted in 50% inhibition (IC_{50}) of p24 antigen production were determined by comparison with the p24 production level in drug-free control cell cultures as previously described. All assays were performed in triplicate or greater replicates.

HIV-1 protease inhibition assay

Recombinant HIV-1 protease (affinity purified, H-1256) was purchased from Bachem AG (Switzerland). HIV protease substrate 1 (H-2930, Arg-Glu-Ser-Gln-Asn-Tyr-Pro-Ile-Val-Gln-Lys-Arg) was purchased from Molecular Probes, Inc. (OR, USA). As an assay buffer was used 50 mM 2-(*N*-morpholino)ethanesulfonic acid-NaOH buffer (pH 6.0) containing 200 mM NaCl, 1 mM EDTA, 1 mM DTT and 0.1% Triton X-100. Various concentrations of test compounds (30 μL) were added to 10 μL of protease (5 ng, final concentration 9.1 nM), and incubated at 37°C for 5 min. After addition of 10 μL of the substrate (5-20 μM), the incubation was continued at 37°C for 20 min following by quenching with treatment at 95°C for 1 min. The parent peptide substrate was quantitated by surface-enhanced laser desorption/ionization (SELDI)-MS.

Mass spectra were recorded on a SELDI Protein Biology System II (Ciphergen Biosystems Inc., CA, USA) equipped with nitrogen laser (337 nm). The mass spectrometer was operated at an acceleration voltage of 20 kV and a detector voltage of 2.2 kV under a pressure below 1.2×10^{-6} torr. A 1 μL of analyte solution was spotted on a sample probe surface (NP1 chip from Ciphergen Biosystems Inc.), washed twice 5 μL of distilled water and dried under air followed by the addition of 0.5 μL of a matrix solution (0.17 mg/mL 2,5-dihydroxybenzoic acid (DHB) in ethanol) containing human ACTH peptide (0.5 pmol, MW 2933.5) as an internal standard. All the spectra obtained were averaged from 100 laser shots, and the peak intensities were normalized with the internal standard and were averaged from at least 2 spectra of different spots.

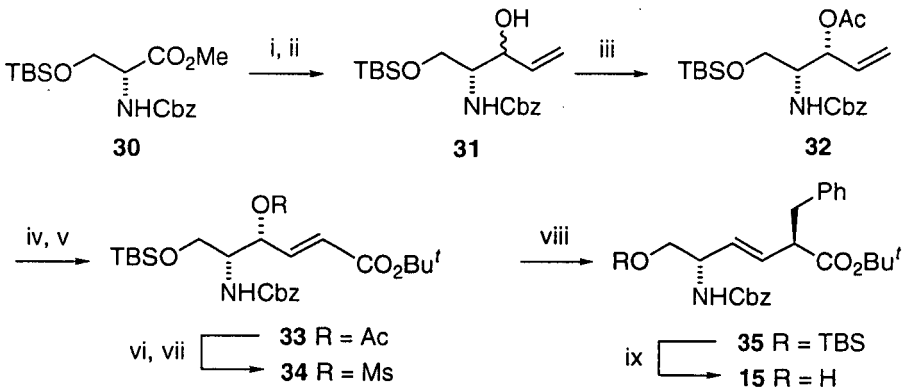
The substrate concentration used were 0, 5, 10, 15 and 20 μM for making a standard curve, which were plotted substrate concentration (x-axis) and peak height (y-axis). After digestion with HIV protease, the rest of parent peptide substrate was quantitated using the standard curve and amount of cleaved substrate was calculated. K_i

values were calculated according to Eq. (1). The values of K_m and V_0 were caluculated by Lineweaver-Burk plots of ($1/S$ versus $1/V$) based on the velocity data of the cleavage in the absence of inhibitors.

$$V = V_0/2Et\{\{[K_i(1 + S/K_m) + It - Et]^2 + 4K_i(1 + S/K_m)Et\}^{1/2} - [K_i(1 + S/K_m) + It - Et]\} \quad (1)$$

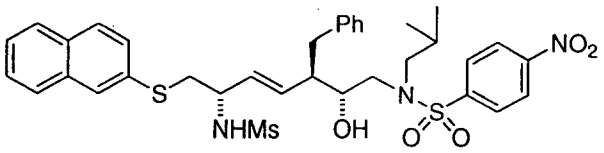
where V and V_0 are the initial velocities with an inhibitor and without an inhibitor, respectively, and S, Et and It are the concentrations of substrate, protease and inhibitor, respectively.

Scheme S1



Reagents: (i) DIBAL; (ii) vinylMgCl, $ZnCl_2$, LiCl; (iii) NOVOZYM435, vinyl acetate; (iv) O_3, then DMS; (v) $(EtO)_2P(O)CH_2CO_2Bu^t$, LiCl, DIPEA; (vi) Na_2CO_3, MeOH; (vii) MsCl, pyridine; (viii) $BnCu(CN)MgCl{\cdot}BF_3$; (ix) H_2SiF_6 aq.

X-ray crystallographic data of 27b



27b

Experimental

Data Collection

A colorless prismatic crystal of $C_{35}H_{41}N_3O_7S_3$ having approximate dimensions of 0.10 x 0.10 x 0.30 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC5R diffractometer with graphite monochromated Cu-Kα radiation and a rotating anode generator.

Cell constants and an orientation matrix for data collection , obtained from a least-squares refinement using the setting angles of 24 carefully centered reflections in the range $15.52 < 2\theta < 27.57°$ corresponded to a primitive monoclinic cell with dimensions:

a = 17.25(1) $\AA$

b = 5.86(1) $\AA$ $\quad \beta = 115.58(5)°$

c = 19.28(1) $\AA$

V = 1759(4) $\AA^3$

For Z = 2 and F.W. = 711.90, the calculated density is 1.34 g/cm^3. Based on the systematic absences of:

0k0: k $\neq$ 2n

packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$P2_1$ (#4)

The data were collected at a temperature of 23 $\pm$ 1°C using the ω-2θ scan technique to a maximum 2θ value of 120.3°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.48° with a take-off angle of 6.0°. Scans of (1.00 + 0.30 tan θ)° were made at a speed of 8.0°/min (in omega). The weak reflections (I < 10.0σ(I)) were rescanned (maximum of 3 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm, the crystal to detector distance was 258 mm, and the detector aperture was 9.0 x 13.0 mm (horizontal x vertical).

Data Reduction

Of the 5455 reflections which were collected, 2931 were unique (R_{int} = 0.322). The intensities of three representative reflection were measured after every 150 reflections. No decay correction was applied.

The linear absorption coefficient, μ, for Cu-Kα radiation is 23.6 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.39 to 0.98. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques[2]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[3] was based on 969 observed reflections ($I > 3.00\sigma(I)$) and 433 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.096$$

$$R_w = \sqrt{\Sigma w(|Fo| - |Fc|)^2/\Sigma wFo^2} = 0.099$$

The standard deviation of an observation of unit weight[4] was 3.58. The weighting scheme was based on counting statistics and included a factor (p = 0.017) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin\theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.43 and -0.48 $e^-/\AA^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[5] . Anomalous dispersion effects were included in Fcalc[6]; the values for Δf' and Δf" were those of Creagh and McAuley[7]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[8]. All calculations were performed using the teXsan[9] crystallographic software package of Molecular Structure Corporation.

References

(1) SHELXS86: Sheldrick, G.M. (1985). In: "Crystallographic Computing 3" (Eds G.M. Sheldrick, C. Kruger and R. Goddard) Oxford University Press, pp. 175-189.

(2) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M. (1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(3) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

where $w = \frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$

$\sigma_c(Fo)$ = e.s.d. based on counting statistics

p = p-factor

(4) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2/(No - Nv)}$$

where: No = number of observations

Nv = number of variables

(5) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(6) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(7) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(8) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(9) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{35}H_{41}N_3O_7S_3$
Formula Weight	711.90
Crystal Color, Habit	colorless, prismatic
Crystal Dimensions	0.10 X 0.10 X 0.30 mm
Crystal System	monoclinic
Lattice Type	Primitive
No. of Reflections Used for Unit Cell Determination (2θ range)	24 (15.5 - 27.6°)
Omega Scan Peak Width at Half-height	0.48°
Lattice Parameters	a = 17.25(1) Å b = 5.86(1) Å c = 19.28(1) Å β = 115.58(5)°
	V = 1759(4) Å^3
Space Group	$P2_1$ (#4)
Z value	2
D_{calc}	1.344 g/cm^3
D_{obs}	1.300 g/cm^3
F_{000}	752.00
μ(CuKα)	23.57 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC5R
Radiation	CuKα (λ = 1.54178 Å)

	graphite monochromated
Attenuator	Ni foil (factors = 1.00, 2.95, 7.98, 23.38)
Take-off Angle	6.0°
Detector Aperture	9.0 mm horizontal 13.0 mm vertical
Crystal to Detector Distance	258 mm
Temperature	23.0°C
Scan Type	ω-2θ
Scan Rate	8.0°/min (in ω) (up to 3 scans)
Scan Width	$(1.00 + 0.30 \tan\theta)°$
$2\theta_{max}$	120.3°
No. of Reflections Measured	Total: 5455 Unique: 2931 (R_{int} = 0.322)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.3865 - 0.9766)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELXS86)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$w = \frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$
p-factor	0.0170
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	969
No. Variables	433
Reflection/Parameter Ratio	2.24
Residuals: R; Rw	0.096 ; 0.099
Goodness of Fit Indicator	3.58

Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.43 $e^-/\AA^3$
Minimum peak in Final Diff. Map	-0.48 $e^-/\AA^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
S(1)	0.6230	0.4627	0.9571	4.5155
S(2)	0.9158	1.2154	0.9011	7.4405
S(3)	0.8429	1.1578	0.6485	6.8137
O(1)	0.8229	1.2752	1.2063	11.3693
O(2)	0.9334	1.1158	1.1942	12.1191
O(3)	0.5568	0.4115	0.9801	4.3606
O(4)	0.6756	0.2958	0.9488	5.4911
O(5)	0.6662	0.2914	0.7952	6.5648
O(6)	0.8993	1.4402	0.9056	10.4728
O(7)	0.9984	1.1205	0.9114	8.9915
N(1)	0.8638	1.1578	1.1900	9.1687
N(2)	0.5783	0.6415	0.8790	4.3964
N(3)	0.8456	1.1252	0.8118	8.6131
C(1)	0.6951	0.6648	1.0323	4.0585
C(2)	0.7818	0.6460	1.0498	5.2419
C(3)	0.8361	0.8171	1.1034	6.1475
C(4)	0.8012	0.9479	1.1281	5.8728
C(5)	0.7149	0.9952	1.1130	6.8136
C(6)	0.6617	0.8236	1.0617	6.9320
C(7)	0.5185	0.8053	0.8759	6.5302
C(8)	0.4548	0.8713	0.7940	9.0117
C(9)	0.3980	1.0390	0.8004	10.7652
C(10)	0.4025	0.6172	0.7505	9.8458
C(11)	0.6351	0.6796	0.8383	3.7134

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
C(12)	0.6188	0.5199	0.7712	3.6187
C(13)	0.6395	0.6066	0.7101	3.7645
C(14)	0.6191	0.4331	0.6410	5.9217
C(15)	0.5281	0.3921	0.6039	4.7081
C(16)	0.4906	0.1943	0.6115	6.0234
C(17)	0.4062	0.1290	0.5759	7.5413
C(18)	0.3515	0.3133	0.5301	6.8040
C(19)	0.3791	0.5044	0.5213	8.0994
C(20)	0.4712	0.5778	0.5556	7.3638
C(21)	0.7278	0.6745	0.7447	6.9374
C(22)	0.7671	0.8154	0.7379	6.4173
C(23)	0.8572	0.9033	0.7797	7.7775
C(24)	0.8820	1.0547	0.9573	6.5510
C(25)	0.9050	0.9487	0.7298	7.3048
C(26)	0.9260	1.2805	0.6338	5.8149
C(27)	0.8975	1.4933	0.5924	6.1477
C(28)	0.9532	1.6345	0.5741	6.0050
C(29)	1.0362	1.5310	0.5921	4.1666
C(30)	1.0947	1.6687	0.5736	5.9494
C(31)	1.1743	1.5677	0.5892	4.2144
C(32)	1.1992	1.3486	0.6326	5.3484
C(33)	1.1424	1.2534	0.6493	5.9948
C(34)	1.0605	1.3204	0.6343	4.4841
C(35)	1.0006	1.2102	0.6484	3.4330

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
H(1)	0.6697	0.2885	0.8489	7.8000
H(2)	0.7950	1.2091	0.7821	9.3494
H(3)	0.7992	0.5138	1.0287	6.1156
H(4)	0.8952	0.8149	1.1148	6.9388
H(5)	0.6951	1.1052	1.1363	7.7692
H(6)	0.6011	0.8280	1.0472	8.0868
H(7)	0.4823	0.7341	0.8995	8.9879
H(8)	0.5442	0.9327	0.9053	8.9879
H(9)	0.4848	0.9409	0.7657	10.2235
H(10)	0.4295	1.1516	0.8336	12.3676
H(11)	0.3578	1.0826	0.7541	12.3676
H(12)	0.3684	0.9507	0.8274	12.3676
H(13)	0.3725	0.5614	0.7781	10.8719
H(14)	0.3635	0.6428	0.6985	10.8719
H(15)	0.4443	0.5073	0.7525	10.8719
H(16)	0.6273	0.8346	0.8190	4.2775
H(17)	0.6942	0.6650	0.8748	4.2775
H(18)	0.5574	0.4843	0.7487	3.6860
H(19)	0.6082	0.7424	0.6883	4.3157
H(20)	0.6426	0.4808	0.6052	6.5023
H(21)	0.6544	0.2829	0.6623	6.5023
H(22)	0.5268	0.0777	0.6472	7.4249
H(23)	0.3826	-0.0126	0.5770	8.5614
H(24)	0.2889	0.2956	0.5053	7.6444

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
H(25)	0.3435	0.6259	0.4907	9.2350
H(26)	0.4952	0.7083	0.5504	7.8362
H(27)	0.7671	0.5303	0.7763	8.4859
H(28)	0.7235	0.9203	0.7031	6.8197
H(29)	0.8904	0.7982	0.8207	8.7812
H(30)	0.8291	1.1084	0.9560	6.7693
H(31)	0.8771	0.8982	0.9448	6.7693
H(32)	0.9245	1.0661	1.0121	6.7693
H(33)	0.9153	0.7927	0.7071	8.8712
H(34)	0.9662	0.9916	0.7603	8.8712
H(35)	0.8427	1.5436	0.5759	5.4584
H(36)	0.9371	1.7699	0.5516	5.5470
H(37)	1.0820	1.8155	0.5522	6.2972
H(38)	1.2089	1.6367	0.5694	5.7863
H(39)	1.2558	1.3029	0.6457	5.5534
H(40)	1.1617	1.0992	0.6744	7.0956
H(41)	1.0199	1.0573	0.6716	3.9392

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S(1)	0.0561	0.0611	0.0451	0.0017	0.0131	0.0077
S(2)	0.0884	0.1190	0.0521	-0.0037	0.0084	-0.0052
S(3)	0.0634	0.1334	0.0492	0.0050	0.0123	0.0271
O(1)	0.1241	0.1653	0.1113	-0.0146	0.0213	-0.0520
O(2)	0.1281	0.1476	0.1332	-0.0255	0.0078	-0.0676
O(3)	0.0557	0.0580	0.0364	-0.0015	0.0052	0.0283
O(4)	0.0748	0.0803	0.0345	0.0181	0.0056	-0.0048
O(5)	0.1250	0.0755	0.0389	0.0044	0.0259	-0.0365
O(6)	0.1389	0.1209	0.0754	0.0067	-0.0129	-0.0175
O(7)	0.0785	0.2062	0.0579	-0.0326	0.0304	-0.0573
N(1)	0.1475	0.0993	0.0833	-0.0095	0.0326	-0.0045
N(2)	0.0503	0.0588	0.0430	0.0118	0.0060	0.0031
N(3)	0.0850	0.1712	0.0490	-0.0009	0.0081	-0.0077
C(1)	0.0631	0.0380	0.0626	-0.0309	0.0360	0.0227
C(2)	0.0602	0.0886	0.0518	-0.0322	0.0256	0.0015
C(3)	0.0539	0.1300	0.0479	-0.0404	0.0202	-0.0171
C(4)	0.0738	0.0775	0.0637	-0.0081	0.0220	0.0305
C(5)	0.0857	0.1174	0.0479	0.0139	0.0214	-0.0516
C(6)	0.0540	0.1451	0.0544	-0.0202	0.0142	-0.0375
C(7)	0.0563	0.0829	0.0681	0.0113	-0.0117	-0.0608
C(8)	0.0966	0.1367	0.1044	0.0696	0.0390	0.0374
C(9)	0.1818	0.1226	0.0908	0.0700	0.0457	-0.0354
C(10)	0.0857	0.1909	0.0837	0.0236	0.0236	0.0152
C(11)	0.0491	0.0389	0.0312	-0.0279	-0.0033	-0.0144

Table 2. Anisotropic Displacement Parameters (continued)

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(12)	0.0385	0.0570	0.0211	-0.0303	-0.0067	-0.0168
C(13)	0.0382	0.0485	0.0538	0.0132	0.0174	0.0177
C(14)	0.0703	0.1264	0.0301	-0.0195	0.0233	-0.0002
C(15)	0.0643	0.1104	0.0192	-0.0167	0.0321	-0.0233
C(16)	0.0656	0.1103	0.0564	0.0121	0.0296	0.0360
C(17)	0.0968	0.1260	0.0571	-0.0319	0.0270	0.0071
C(18)	0.0823	0.0950	0.0682	-0.0439	0.0202	-0.0238
C(19)	0.0799	0.1207	0.0713	-0.0089	-0.0010	0.0697
C(20)	0.0706	0.1481	0.0564	-0.0064	0.0230	0.0073
C(21)	0.0605	0.1438	0.0626	-0.0295	0.0296	0.0382
C(22)	0.0746	0.0977	0.0383	-0.0421	-0.0069	0.0134
C(23)	0.0601	0.1423	0.0700	-0.0241	0.0063	-0.0057
C(24)	0.0787	0.0816	0.0768	-0.0053	0.0224	-0.0180
C(25)	0.0678	0.1220	0.0749	0.0429	0.0188	0.0200
C(26)	0.0510	0.1426	0.0219	0.0037	0.0105	-0.0107
C(27)	0.0696	0.1090	0.0280	0.0007	-0.0043	-0.0481
C(28)	0.0785	0.0977	0.0343	0.0168	0.0078	-0.0368
C(29)	0.0601	0.0628	0.0265	-0.0102	0.0103	-0.0194
C(30)	0.0876	0.0894	0.0327	-0.0205	0.0107	0.0152
C(31)	0.0729	0.0553	0.0261	-0.0547	0.0159	-0.0194
C(32)	0.0642	0.0989	0.0221	0.0023	0.0017	0.0108
C(33)	0.0641	0.1173	0.0438	0.0199	0.0208	0.0227
C(34)	0.0488	0.0852	0.0262	-0.0028	0.0067	0.0042
C(35)	0.0640	0.0271	0.0262	0.0207	0.0071	0.0389

Table 2. Anisotropic Displacement Parameters (continued)

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

Table 3. Bond Lengths(Å)

atom	atom	distance	atom	atom	distance
S(1)	O(3)	1.42(2)	S(1)	O(4)	1.39(2)
S(1)	N(2)	1.72(3)	S(1)	C(1)	1.87(3)
S(2)	O(6)	1.36(3)	S(2)	O(7)	1.46(2)
S(2)	N(3)	1.71(3)	S(2)	C(24)	1.72(4)
S(3)	C(25)	1.91(4)	S(3)	C(26)	1.73(3)
O(1)	N(1)	1.12(5)	O(2)	N(1)	1.19(4)
O(5)	C(12)	1.53(4)	O(5)	H(1)	1.01
N(1)	C(4)	1.73(5)	N(2)	C(7)	1.39(4)
N(2)	C(11)	1.51(3)	N(3)	C(23)	1.49(6)
N(3)	H(2)	0.95	C(1)	C(2)	1.39(3)
C(1)	C(6)	1.34(5)	C(2)	C(3)	1.45(5)
C(2)	H(3)	0.98	C(3)	C(4)	1.19(5)
C(3)	H(4)	0.95	C(4)	C(5)	1.42(4)
C(5)	C(6)	1.43(5)	C(5)	H(5)	0.93
C(6)	H(6)	0.96	C(7)	C(8)	1.53(4)
C(7)	H(7)	1.01	C(7)	H(8)	0.93
C(8)	C(9)	1.43(5)	C(8)	C(10)	1.76(6)
C(8)	H(9)	0.99	C(9)	H(10)	0.92
C(9)	H(11)	0.90	C(9)	H(12)	1.02
C(10)	H(13)	0.95	C(10)	H(14)	0.95
C(10)	H(15)	0.96	C(11)	C(12)	1.52(4)
C(11)	H(16)	0.97	C(11)	H(17)	0.96
C(12)	C(13)	1.46(4)	C(12)	H(18)	0.98
C(13)	C(14)	1.59(4)	C(13)	C(21)	1.43(3)

Table 3. Bond Lengths($\AA$) (continued)

atom	atom	distance	atom	atom	distance
C(13)	H(19)	0.95	C(14)	C(15)	1.44(3)
C(14)	H(20)	0.98	C(14)	H(21)	1.05
C(15)	C(16)	1.37(5)	C(15)	C(20)	1.49(5)
C(16)	C(17)	1.37(4)	C(16)	H(22)	0.98
C(17)	C(18)	1.46(5)	C(17)	H(23)	0.93
C(18)	C(19)	1.26(6)	C(18)	H(24)	0.98
C(19)	C(20)	1.50(4)	C(19)	H(25)	0.96
C(20)	H(26)	0.90	C(21)	C(22)	1.11(5)
C(21)	H(27)	1.09	C(22)	C(23)	1.50(4)
C(22)	H(28)	0.98	C(23)	C(25)	1.54(5)
C(23)	H(29)	0.97	C(24)	H(30)	0.96
C(24)	H(31)	0.94	C(24)	H(32)	0.99
C(25)	H(33)	1.06	C(25)	H(34)	0.99
C(26)	C(27)	1.45(5)	C(26)	C(35)	1.26(3)
C(27)	C(28)	1.42(5)	C(27)	H(35)	0.91
C(28)	C(29)	1.45(4)	C(28)	H(36)	0.89
C(29)	C(30)	1.45(4)	C(29)	C(34)	1.44(4)
C(30)	C(31)	1.40(4)	C(30)	H(37)	0.94
C(31)	C(32)	1.49(5)	C(31)	H(38)	0.93
C(32)	C(33)	1.28(4)	C(32)	H(39)	0.94
C(33)	C(34)	1.37(4)	C(33)	H(40)	1.01
C(34)	C(35)	1.34(4)	C(35)	H(41)	0.99

Table 4. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
O(3)	S(1)	O(4)	122(1)	O(3)	S(1)	N(2)	106(1)
O(3)	S(1)	C(1)	104(1)	O(4)	S(1)	N(2)	113(1)
O(4)	S(1)	C(1)	106(1)	N(2)	S(1)	C(1)	100(1)
O(6)	S(2)	O(7)	125(1)	O(6)	S(2)	N(3)	106(1)
O(6)	S(2)	C(24)	110(2)	O(7)	S(2)	N(3)	104(1)
O(7)	S(2)	C(24)	106(1)	N(3)	S(2)	C(24)	100(1)
C(25)	S(3)	C(26)	100(1)	C(12)	O(5)	H(1)	96.5
O(1)	N(1)	O(2)	147(4)	O(1)	N(1)	C(4)	110(3)
O(2)	N(1)	C(4)	102(3)	S(1)	N(2)	C(7)	120(2)
S(1)	N(2)	C(11)	113(1)	C(7)	N(2)	C(11)	120(3)
S(2)	N(3)	C(23)	121(2)	S(2)	N(3)	H(2)	121.0
C(23)	N(3)	H(2)	117.1	S(1)	C(1)	C(2)	115(2)
S(1)	C(1)	C(6)	120(2)	C(2)	C(1)	C(6)	124(3)
C(1)	C(2)	C(3)	114(3)	C(1)	C(2)	H(3)	116.9
C(3)	C(2)	H(3)	128.4	C(2)	C(3)	C(4)	116(3)
C(2)	C(3)	H(4)	117.0	C(4)	C(3)	H(4)	126.5
N(1)	C(4)	C(3)	117(3)	N(1)	C(4)	C(5)	106(3)
C(3)	C(4)	C(5)	135(3)	C(4)	C(5)	C(6)	107(3)
C(4)	C(5)	H(5)	127.5	C(6)	C(5)	H(5)	124.1
C(1)	C(6)	C(5)	121(2)	C(1)	C(6)	H(6)	120.6
C(5)	C(6)	H(6)	118.3	N(2)	C(7)	C(8)	113(3)
N(2)	C(7)	H(7)	106.7	N(2)	C(7)	H(8)	112.3
C(8)	C(7)	H(7)	105.2	C(8)	C(7)	H(8)	111.5
H(7)	C(7)	H(8)	106.6	C(7)	C(8)	C(9)	107(3)

Table 4. Bond Angles(°) (continued)

atom	atom	atom	angle	atom	atom	atom	angle
C(7)	C(8)	C(10)	105(3)	C(7)	C(8)	H(9)	111.2
C(9)	C(8)	C(10)	113(2)	C(9)	C(8)	H(9)	107.7
C(10)	C(8)	H(9)	111.7	C(8)	C(9)	H(10)	109.5
C(8)	C(9)	H(11)	111.9	C(8)	C(9)	H(12)	102.1
H(10)	C(9)	H(11)	117.3	H(10)	C(9)	H(12)	106.7
H(11)	C(9)	H(12)	108.0	C(8)	C(10)	H(13)	108.5
C(8)	C(10)	H(14)	110.8	C(8)	C(10)	H(15)	109.2
H(13)	C(10)	H(14)	109.9	H(13)	C(10)	H(15)	109.2
H(14)	C(10)	H(15)	109.2	N(2)	C(11)	C(12)	115(2)
N(2)	C(11)	H(16)	108.9	N(2)	C(11)	H(17)	109.0
C(12)	C(11)	H(16)	107.9	C(12)	C(11)	H(17)	108.5
H(16)	C(11)	H(17)	107.0	O(5)	C(12)	C(11)	113(2)
O(5)	C(12)	C(13)	105(2)	O(5)	C(12)	H(18)	106.3
C(11)	C(12)	C(13)	116(2)	C(11)	C(12)	H(18)	106.0
C(13)	C(12)	H(18)	108.2	C(12)	C(13)	C(14)	114(3)
C(12)	C(13)	C(21)	107(2)	C(12)	C(13)	H(19)	111.0
C(14)	C(13)	C(21)	111(2)	C(14)	C(13)	H(19)	106.7
C(21)	C(13)	H(19)	105.1	C(13)	C(14)	C(15)	108(2)
C(13)	C(14)	H(20)	113.5	C(13)	C(14)	H(21)	109.2
C(15)	C(14)	H(20)	113.1	C(15)	C(14)	H(21)	112.3
H(20)	C(14)	H(21)	99.7	C(14)	C(15)	C(16)	123(3)
C(14)	C(15)	C(20)	118(3)	C(16)	C(15)	C(20)	118(2)
C(15)	C(16)	C(17)	129(3)	C(15)	C(16)	H(22)	118.8
C(17)	C(16)	H(22)	111.9	C(16)	C(17)	C(18)	111(3)

Table 4. Bond Angles(°) (continued)

atom	atom	atom	angle	atom	atom	atom	angle
C(16)	C(17)	H(23)	128.4	C(18)	C(17)	H(23)	120.1
C(17)	C(18)	C(19)	124(3)	C(17)	C(18)	H(24)	120.4
C(19)	C(18)	H(24)	115.5	C(18)	C(19)	C(20)	126(3)
C(18)	C(19)	H(25)	124.5	C(20)	C(19)	H(25)	109.5
C(15)	C(20)	C(19)	110(3)	C(15)	C(20)	H(26)	118.8
C(19)	C(20)	H(26)	130.5	C(13)	C(21)	C(22)	137(3)
C(13)	C(21)	H(27)	109.0	C(22)	C(21)	H(27)	112.3
C(21)	C(22)	C(23)	137(3)	C(21)	C(22)	H(28)	102.8
C(23)	C(22)	H(28)	117.6	N(3)	C(23)	C(22)	103(2)
N(3)	C(23)	C(25)	108(3)	N(3)	C(23)	H(29)	110.6
C(22)	C(23)	C(25)	115(2)	C(22)	C(23)	H(29)	109.2
C(25)	C(23)	H(29)	109.5	S(2)	C(24)	H(30)	112.5
S(2)	C(24)	H(31)	112.9	S(2)	C(24)	H(32)	109.8
H(30)	C(24)	H(31)	109.5	H(30)	C(24)	H(32)	105.4
H(31)	C(24)	H(32)	106.3	S(3)	C(25)	C(23)	111(2)
S(3)	C(25)	H(33)	110.4	S(3)	C(25)	H(34)	113.5
C(23)	C(25)	H(33)	109.9	C(23)	C(25)	H(34)	113.1
H(33)	C(25)	H(34)	97.9	S(3)	C(26)	C(27)	109(2)
S(3)	C(26)	C(35)	131(3)	C(27)	C(26)	C(35)	118(3)
C(26)	C(27)	C(28)	122(2)	C(26)	C(27)	H(35)	121.9
C(28)	C(27)	H(35)	115.9	C(27)	C(28)	C(29)	113(3)
C(27)	C(28)	H(36)	122.5	C(29)	C(28)	H(36)	123.9
C(28)	C(29)	C(30)	115(3)	C(28)	C(29)	C(34)	120(2)
C(30)	C(29)	C(34)	123(2)	C(29)	C(30)	C(31)	115(3)

Table 4. Bond Angles(°) (continued)

atom	atom	atom	angle	atom	atom	atom	angle
C(29)	C(30)	H(37)	124.2	C(31)	C(30)	H(37)	120.1
C(30)	C(31)	C(32)	120(3)	C(30)	C(31)	H(38)	118.0
C(32)	C(31)	H(38)	121.8	C(31)	C(32)	C(33)	116(3)
C(31)	C(32)	H(39)	114.3	C(33)	C(32)	H(39)	128.9
C(32)	C(33)	C(34)	130(4)	C(32)	C(33)	H(40)	112.3
C(34)	C(33)	H(40)	117.0	C(29)	C(34)	C(33)	112(3)
C(29)	C(34)	C(35)	117(2)	C(33)	C(34)	C(35)	129(3)
C(26)	C(35)	C(34)	126(3)	C(26)	C(35)	H(41)	120.5
C(34)	C(35)	H(41)	112.8				

Table 5. Torsion Angles(°)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
S(1)	N(2)	C(7)	C(8)	-152(2)	S(1)	N(2)	C(11)	C(12)	93(2)
S(1)	C(1)	C(2)	C(3)	174(2)	S(1)	C(1)	C(6)	C(5)	-173(2)
S(2)	N(3)	C(23)	C(22)	141(2)	S(2)	N(3)	C(23)	C(25)	-95(3)
S(3)	C(25)	C(23)	N(3)	-58(3)	S(3)	C(25)	C(23)	C(22)	56(4)
S(3)	C(26)	C(27)	C(28)	178(2)	S(3)	C(26)	C(35)	C(34)	179(2)
O(1)	N(1)	C(4)	C(3)	176(4)	O(1)	N(1)	C(4)	C(5)	3(4)
O(2)	N(1)	C(4)	C(3)	0(5)	O(2)	N(1)	C(4)	C(5)	-174(3)
O(3)	S(1)	N(2)	C(7)	36(2)	O(3)	S(1)	N(2)	C(11)	-169(2)
O(3)	S(1)	C(1)	C(2)	146(2)	O(3)	S(1)	C(1)	C(6)	-38(3)
O(4)	S(1)	N(2)	C(7)	174(2)	O(4)	S(1)	N(2)	C(11)	-31(2)
O(4)	S(1)	C(1)	C(2)	14(3)	O(4)	S(1)	C(1)	C(6)	-169(2)
O(5)	C(12)	C(11)	N(2)	-84(2)	O(5)	C(12)	C(13)	C(14)	53(2)
O(5)	C(12)	C(13)	C(21)	-71(3)	O(6)	S(2)	N(3)	C(23)	165(3)
O(7)	S(2)	N(3)	C(23)	31(3)	N(1)	C(4)	C(3)	C(2)	-178(2)
N(1)	C(4)	C(5)	C(6)	179(2)	N(2)	S(1)	C(1)	C(2)	-103(2)
N(2)	S(1)	C(1)	C(6)	72(3)	N(2)	C(7)	C(8)	C(9)	179(3)
N(2)	C(7)	C(8)	C(10)	58(3)	N(2)	C(11)	C(12)	C(13)	152(2)
N(3)	C(23)	C(22)	C(21)	-110(6)	C(1)	S(1)	N(2)	C(7)	-71(2)
C(1)	S(1)	N(2)	C(11)	81(2)	C(1)	C(2)	C(3)	C(4)	2(5)
C(1)	C(6)	C(5)	C(4)	-4(5)	C(2)	C(1)	C(6)	C(5)	2(5)
C(2)	C(3)	C(4)	C(5)	-7(7)	C(3)	C(2)	C(1)	C(6)	0(5)
C(3)	C(4)	C(5)	C(6)	8(7)	C(7)	N(2)	C(11)	C(12)	-113(3)
C(8)	C(7)	N(2)	C(11)	55(4)	C(11)	C(12)	C(13)	C(14)	-178(2)
C(11)	C(12)	C(13)	C(21)	56(3)	C(12)	C(13)	C(14)	C(15)	63(3)

Table 5. Torsion Angles(°) (continued)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
C(12)	C(13)	C(21)	C(22)	-141(5)	C(13)	C(14)	C(15)	C(16)	-106(3)
C(13)	C(14)	C(15)	C(20)	72(3)	C(13)	C(21)	C(22)	C(23)	170(4)
C(14)	C(13)	C(21)	C(22)	92(6)	C(14)	C(15)	C(16)	C(17)	-175(3)
C(14)	C(15)	C(20)	C(19)	179(2)	C(15)	C(14)	C(13)	C(21)	-173(3)
C(15)	C(16)	C(17)	C(18)	-6(5)	C(15)	C(20)	C(19)	C(18)	0(5)
C(16)	C(15)	C(20)	C(19)	-1(4)	C(16)	C(17)	C(18)	C(19)	3(6)
C(17)	C(16)	C(15)	C(20)	5(5)	C(17)	C(18)	C(19)	C(20)	0(7)
C(21)	C(22)	C(23)	C(25)	131(6)	C(23)	N(3)	S(2)	C(24)	-78(3)
C(23)	C(25)	S(3)	C(26)	152(2)	C(25)	S(3)	C(26)	C(27)	-161(2)
C(25)	S(3)	C(26)	C(35)	23(3)	C(26)	C(27)	C(28)	C(29)	7(4)
C(26)	C(35)	C(34)	C(29)	-6(4)	C(26)	C(35)	C(34)	C(33)	179(3)
C(27)	C(26)	C(35)	C(34)	5(4)	C(27)	C(28)	C(29)	C(30)	179(2)
C(27)	C(28)	C(29)	C(34)	-8(3)	C(28)	C(27)	C(26)	C(35)	-5(4)
C(28)	C(29)	C(30)	C(31)	-178(2)	C(28)	C(29)	C(34)	C(33)	-177(2)
C(28)	C(29)	C(34)	C(35)	7(4)	C(29)	C(30)	C(31)	C(32)	-8(4)
C(29)	C(34)	C(33)	C(32)	0(5)	C(30)	C(29)	C(34)	C(33)	-5(4)
C(30)	C(29)	C(34)	C(35)	179(2)	C(30)	C(31)	C(32)	C(33)	4(4)
C(31)	C(30)	C(29)	C(34)	9(4)	C(31)	C(32)	C(33)	C(34)	0(5)
C(32)	C(33)	C(34)	C(35)	175(3)					