Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Supporting information

Variations of the P2 Group in HIV-1 Protease Inhibitors Containing a Tertiary Alcohol in the Transition-State Mimicking Scaffold

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Chemistry

General information. Analytical LC-MS was performed on a Gilson HPLC system with a Finnigan AQA quadropole mass spectrometer using a Chromolith Performance RP-18e 4.6 × 100 mm (Merck KGaA) column, with a gradient of CH_3CN in 0.05% aqueous HCOOH as mobile phase at a flow rate of 4 mL/min. Preparative reverse-phase LC-MS was done under similar conditions but using a Zorbax SB-C8, 5 μm 21.2 × 150 mm (Agilent technologies) column, at a flow rate of 15 mL/min. Flash chromatography was performed on Merck silica gel 60 (40–63 μm) or Merck silica gel 60 RP-18 (40–63 μm). Analytical thin layer chromatography was done using aluminum sheets precoated with silica gel 60 F_{254}. UV light and an ethanolic solution of phosphomolybdic acid followed by heating visualized components. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter. Specific rotations ($[\alpha]_D$) are reported in deg/dm and the concentration (*c*) is given as g/100 mL in the specified solvent. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury Plus instruments; ^1H at 300 MHz and ^{13}C at 75.45 MHz, ^1H at 399.9 MHz and ^{13}C at 100.6 MHz or ^1H at 399.8 MHz and ^{13}C at 100.5 MHz. Analytische Laboratorien, Lindlar, Germany, performed elemental analyses. Exact molecular masses were determined on Micromass Q-Tof2 mass spectrometer equipped with an electrospray ion source. Crystallization and collection of X-ray data for compound **18** were performed at the Latvian Institute of Organic Synthesis, Riga, Latvia.

2-Benzyl-acrylic acid [(*S*)-1-ethoxycarbonyl-ethyl] ester (**3**). 2-Benzyl acrylic acid[1] (3.16 g, 19.5 mmol) was dissolved in $SOCl_2$ (30 mL). The reaction mixture was stirred at room temp for 3 h and then the $SOCl_2$ was evaporated to give 2-benzyl-acryloyl chloride as a colourless oil (3.37 g, 96%) which was used in the following step without further purification. ^1H NMR ($CDCl_3$) δ 7.39–7.18 (m, 5H), 6.66 (m, 1H), 5.94 (m, 1H), 3.70 (m, 2H). 2-Benzyl-acryloyl chloride (9.25 g, 51.1 mmol) was dissolved in CH_2Cl_2 and cooled to 0 °C. A solution of ethyl-(*S*)-lactate (7.13 mL, 61.7 mmol) and DMAP (8.01 g, 64.2 mmol) in CH_2Cl_2 was added drop wise and then the mixture was stirred at room temp for 3 h. After filtration through a plug of silica the crude product was concentrated under reduced pressure and purified by flash chromatography (silica, EtOAc/pentane, 2.5:97.5–5:95) affording **3** (10.1 g, 75%) as a colourless oil. $[\alpha]^{19}_D$ -16 ° (*c* 1.1, CD_3OD); ^1H NMR ($CDCl_3$) δ 7.32–7.19 (m, 5H), 6.33 (m, 1H), 5.53 (m, 1H), 5.09 (q, *J* = 7.07 Hz, 1H), 4.19 (q, *J* = 7.11 Hz, 1H), 4.18 (q, *J* = 7.11 Hz, 1H), 3.66 (s, 2H), 1.50 (d, *J* = 7.07 Hz, 3H), 1.24 (t, *J* = 7.13 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.9, 166.3, 139.6, 138.7, 129.2, 128.5, 127.4, 126.5, 69.2, 61.4, 38.0, 17.0, 14.2. Anal. ($C_{15}H_{18}O_4$) C, H.

(2*S*)-2-Benzyl-oxirane-2-carboxylic acid [(*S*)-1-ethoxycarbonyl-ethyl] ester ((*S*)-4) and (2*R*)-2-Benzyl-oxirane-2-carboxylic acid [(*S*)-1-ethoxycarbonyl-ethyl] ester ((*R*)-4). Compound **3** (10.1 g, 38.6 mmol) was dissolved in CH_2Cl_2 and mCPBA (77%, 17.3 g, 77.1 mmol) was added. The reaction mixture was refluxed for 24 h and thereafter washed with 10% $Na_2S_2O_3$ (aq.), saturated $NaHCO_3$ (aq.) and brine. The combined $NaHCO_3$ and brine phases were re-extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and evaporated. The crude product was purified by flash chromatography (EtOAc/isohexane, 10:90–25:75) two times, yielding pure (*S*)-**4**, mixed fractions and pure (*R*)-**4** (3.27 g, 0.78 g and 4.19 g respectively) as colourless oils (total 8.24 g, 77%). (*S*)-**4**: R_f = 0.47 (EtOAc/isohexane 20:80); $[\alpha]^{19}_D$ -48 ° (*c* 1.2, CD_3OD); ^{1}H NMR (CD_3OD) δ 7.31–7.19 (m, 5H), 5.00 (q, *J* = 7.03 Hz, 1H), 4.14 (q, *J* = 7.10 Hz, 2H), 3.46 (d, *J* = 15.3 Hz, 1H), 3.03 (d, *J* = 15.3 Hz, 1H), 3.01 (d, *J* = 5.86 Hz, 1H), 2.83 (d, *J* = 5.86 Hz, 1H), 1.43 (d, *J* = 7.03 Hz, 3H), 1.21 (t, *J* = 7.10 Hz, 3H); ^{13}C NMR (CD_3OD) δ 171.7, 171.1, 137.2, 130.8, 129.3, 127.9, 71.2, 62.6, 58.2, 52.1, 37.8, 16.9, 14.3. Anal. ($C_{15}H_{18}O_5$) C, H. (*R*)-**4**: R_f = 0.58 (EtOAc/isohexane 20:80); $[\alpha]^{19}_D$ -4.3 ° (*c* 1.2, CD_3OD); ^{1}H NMR (CD_3OD) δ 7.30–7.19 (m, 5H), 5.03 (q, *J* = 7.03 Hz, 1H), 4.15 (q, *J* = 7.07 Hz, 1H), 4.14 (q, *J* = 7.07 Hz, 1H), 3.42 (d, *J* = 14.8 Hz, 1H), 3.08 (d, *J* = 5.85 Hz, 1H), 3.05 (d, *J* = 14.8 Hz, 1H), 2.80 (d, *J* = 5.85 Hz, 1H), 1.43 (d, *J* = 7.03 Hz, 3H), 1.21 (t, *J* = 7.07 Hz, 3H); ^{13}C NMR (CD_3OD) δ 171.8, 171.2, 137.0, 130.9, 129.2, 127.9, 71.0, 62.6, 58.1, 52.1, 37.5, 16.9, 14.4. Anal. ($C_{15}H_{18}O_5$) C, H.

General procedure for preparation of (2*R* or 2*S*)-2-benzyl-oxirane-2-carboxylic acids (*S*)-5 and (*R*)-5. Compound (*S*)-**4** or (*R*)-**4** was dissolved in THF (10 mL/g) and a solution of 1 M NaOH (2 equiv) in THF (twice the volume of the 1 M NaOH) was added. The solution was stirred at room temp for 1 h and then the solvent was evaporated. The reaction mixture was neutralized with 1 M HCl (2 equiv) and extracted with 2 × CH_2Cl_2. The organic phase was dried (Na_2SO_4) and evaporated to give the products as colourless oils in quantitative yield, which were used in the amide coupling reactions without further purification. ^{1}H NMR (CD_3OD) δ 7.30–7.18 (m, 5H), 3.42 (d, *J* = 14.95 Hz, 1H), 2.98 (d, *J* = 14.95 Hz, 1H), 2.96 (d, *J* = 5.86 Hz, 1H), 2.74 (d, *J* = 5.86 Hz, 1H); ^{13}C NMR (CD_3OD) δ 173.5, 137.4, 130.7, 129.2, 127.7, 78.5, 52.0, 37.7.

General procedures for amide coupling reactions.
Method A. Carboxylic acid, EDC, HOBT and NMM were stirred in EtOAc at room temp for 30 min. The amine was added and stirring continued overnight. The reaction mixture was washed with saturated $NaHCO_3$ (aq.) and brine, the combined water phases were re-extracted with EtOAc. Drying (Na_2SO_4) of the combined organic phases followed by evaporation afforded the crude product, which was purified as described below.
Method B. Carboxylic acid, amine and PyBOP were dissolved in dry CH_2Cl_2 and thereafter diisopropylamine was added. The reaction mixture was stirred at room temp over night and thereafter washed with saturated $NaHCO_3$ (aq.) and brine followed by drying (Na_2SO_4) of the organic phase. Evaporation afforded the crude product, which was purified as described below.
Method C. Carboxylic acid, amine and HATU were dissolved in dry CH_2Cl_2 and thereafter DIEA was added. The reaction mixture was stirred at room temp for 3.5 h and then washed with 2 × NaOAc buffer (pH 4), $NaHCO_3$ (5%, aq.) and brine followed by drying (Na_2SO_4) of the organic phase. Evaporation afforded the crude product, which was purified as described below.

(2*S*)-2-Benzyl-oxirane-2-carboxylic acid benzylamide (**6a**). Compound **6a** was prepared according to Method A using (*S*)-**5** (0.201 g, 1.18 mmol), EDC (0.249 g, 1.30 mmol), HOBT (0.176 g, 1.30 mmol), NMM (0.156 mL, 1.42 mmol) and benzylamine (0.142 mL, 1.30 mmol). Purification by reverse-phase LC-MS (35 min gradient of 20–70% CH_3CN in 0.05% aqueous formic acid) afforded **6a** (0.0504 g, 32%) as a white solid. $[\alpha]^{20}_D$ -45 ° (*c* 1.0, $CHCl_3$); ^{1}H NMR (CD_3OD) δ 7.32–7.13 (m, 8H), 6.97 (m, 2H), 4.36 (d, *J* = 15.0 Hz, 1H), 4.14 (d, *J* = 15.0 Hz, 1H), 3.64 (d, *J* = 14.7 Hz, 1H), 2.88 (d, *J* = 5.1 Hz, 1H), 2.83 (d, *J* = 5.1 Hz, 1H), 2.74 (d, *J* = 14.7 Hz, 1H); ^{13}C NMR (CD_3OD) δ 172.1, 139.6, 137.4, 130.8, 129.4, 129.3, 128.02, 127.95, 127.8, 60.7, 53.3, 43.3, 38.0. Anal. ($C_{17}H_{17}NO_2 \times H_2O$) C, H, N.

(2*S*)-2-Benzyl-oxirane-2-carboxylic acid ((3*R*)-tetrahydro-furan-3-yl)-amide (**6b**). Compound **6b** was prepared according to Method A using (*S*)-**5** (0.156 g, 0.876 mmol), EDC (0.185 g, 0.964 mmol), HOBT (0.130 g, 0.964 mmol), NMM (0.128 mL, 1.16 mmol) and *R*-(+)-3-aminotetrahydrofuran toluene-4-sulfonate (0.250 g, 0.964 mmol, as a solution in EtOAc with Et_3N 0.134 mL, 0.964 mmol). Purification by flash chromatography (silica, EtOAc/iso-hexane, 50:50–80:20) afforded **6b** (0.0691 g, 32%) as a white solid. $[\alpha]^{19}_D$ -22 ° (*c* 1.0, CH_3OH); ^{1}H NMR (CD_3OD) δ 7.29–7.15 (m, 5H), 4.26 (m, 1H), 3.80–3.63 (m, 3H), 3.58 (d, *J* = 14.6 Hz, 1H), 3.49 (dd, *J* = 3.74, 9.23 Hz, 1H), 2.83 (d, *J* = 5.04 Hz, 1H), 2.81 (d, *J* = 5.04 Hz, 1H), 2.77 (d, *J* = 14.6 Hz, 1H), 2.06 (m, 1H), 1.62 (m, 1H); ^{13}C NMR (CD_3OD) δ 172.1, 137.3, 130.8, 129.2, 127.8, 73.2, 67.9, 60.5, 53.1, 51.2, 37.8, 33.1. Anal. ($C_{14}H_{17}NO_3$) C, H, N.

(2*S*)-2-Benzyl-oxirane-2-carboxylic acid (3-hydroxy-2-methyl-phenyl)-amide (**6c**). Compound **6c** was prepared according to Method B using (*S*)-**5** (0.358 g, 2.01 mmol), 3-amino-2-methylphenol (0.297 g, 2.41 mmol), PyBOP (1.05 g, 2.01 mmol) and (iPr)$_2$NH (0.560 mL, 4.02 mmol + 0.280 mL, 2.01 mmol, added after stirring for 5 h). Purification by flash chromatography (silica, EtOAc/iso-hexane, 20:80–50:50) afforded **6c** (0.264 g, 46%) as a white solid. $[\alpha]^{19}_D$ -27 ° (*c* 0.45, CH_3OH); ^{1}H NMR (CD_3OD) δ 7.40–7.22 (m, 5H), 6.86 (m, 1H), 6.60 (m, 1H), 6.16 (m, 1H), 3.56 (d, *J* = 15.2 Hz, 1H), 3.24 (d, *J* = 5.86 Hz, 1H), 3.11 (d, *J* = 15.2 Hz, 1H), 2.98 (d, *J* = 5.86 Hz, 1H), 1.65 (s, 3H); ^{13}C NMR (CD_3OD) δ 170.3, 150.8, 148.5, 137.4, 130.8, 129.4, 128.0, 127.6, 115.9, 114.2, 111.7, 58.6, 52.3, 38.2, 9.9. Anal. ($C_{17}H_{17}NO_3$) C, H, N.

(2*S*)-2-Benzyl-oxirane-*N*-[quinoline-2-amine-1-yl]-2-carboxylic acid amide (**6d**). Compound **6d** was prepared according to Method B using (*S*)-**5** (0.349 g, 1.96 mmol), quinoline-2-amine (0.339 g, 2.35 mmol), PyBOP (1.02 g, 1.96 mmol) and (iPr)$_2$NH (0.551 mL, 3.92 mmol + 0.275 mL, 1.96 mmol, added after stirring for 8 h). Purification by flash chromatography (silica, EtOAc/iso-hexane/Et_3N, 10:88:2–20:78:2) afforded **6d** (0.231 g, 39%) as a white solid. $[\alpha]^{18}_D$ -9.3 ° (*c* 0.27, CD_3OD); ^{1}H NMR (CD_3OD) δ 8.30-8.19 (m, 2H) 7.81-7.42 (m, 4H) 7.32-7.10 (m, 5H), 3.70 (d, *J* = 14.8 Hz, 1H), 3.06 (d, *J* = 4.77 Hz, 1H), 2.99 (d, *J* = 14.8 Hz, 1H), 2.95 (d, *J* = 4.77 Hz, 1H); ^{13}C NMR (CD_3OD) δ 170.0, 150.6, 146.8, 139.8, 135.9, 131.0, 130.4, 129.0, 128.3, 127.6, 127.2, 126.3, 114.6, 60.3, 53.0, 36.5 (2 aromatic carbon signals overlapping). Anal. ($C_{19}H_{16}N_2O_2 \times 0.25\ H_2O$) C, H, N.

(2*S*)-2-Benzyl-oxirane-2-carboxylic acid ((1*S*)-2-methyl-1-methylcarbamoyl-propyl)-amide (**6e**). Compound **6e** was prepared according to Method C using (*S*)-**5** (0.0880 g, 0.494 mmol), HATU (0.225 g, 0.593 mmol), DIEA (0.344 mL, 1.98 mmol), and H-Val-NHMe (0.0794 g, 0.544 mmol). Purification by reverse-phase LC-MS (35 min gradient of 10–65% CH_3CN in 0.05% aqueous formic acid) afforded **6e** and the corresponding (1*R*)-diastereomer

in a 7:1 mixture (0.0854 g, 60%) as a white solid. $[\alpha]^{20}_D$ -28 ° (*c* 0.93, CH_3OH); ^{1}H NMR (**6e**, CD_3OD) δ 7.30–7.16 (m, 5H), 4.04 (d, *J* = 7.48 Hz, 1H), 3.56 (d, *J* = 14.9 Hz, 1H), 2.85 (d, *J* = 14.9 Hz, 1H), 2.86 (s, 2H), 2.65 (s, 3H), 1.95 (m, 1H), 0.85 (d, *J* = 6.79 Hz, 3H), 0.82 (d, *J* = 6.79 Hz, 3H); ^{13}C NMR (**6e**, CD_3OD) δ 173.5, 171.9, 137.1, 130.8, 129.3, 127.9, 60.5, 59.5, 53.3, 37.4, 32.2, 26.2, 19.6, 18.5. Anal. ($C_{16}H_{22}N_2O_3$) C, H, N.

(2*S*)-2-Benzyl-oxirane-2-carboxylic acid [(1*S*)-1-(2-methoxy-ethylcarbamoyl)-2-methyl-propyl]-amide (**6f**). Compound **6f** was prepared according to Method A using (*S*)-**5** (0.104 g, 0.584 mmol), EDC (0.123 g, 0.642 mmol), HOBT (0.0867 g, 0.642 mmol), NMM (0.0770 mL, 0.701 mmol) and H-Val-NH$(CH_2)_2$OMe (0.112 g, 0.642 mmol). Purification by flash chromatography (silica, EtOAc/pentane, 50:50–70:30) afforded **6f** and the corresponding (1*R*)-diastereomer in a 6:1 mixture (0.0870 g, 45%) as a colorless semi-solid. $[\alpha]^{20}_D$ -26 ° (*c* 1.0, CH_3OH): ^{1}H NMR (**6f**, CD_3OD) δ 7.28–7.15 (m, 5H), 4.08 (d, *J* = 7.36 Hz, 1H), 3.56 (d, *J* = 14.8 Hz, 1H), 3.41–3.20 (m, 7H), 2.85 (s, 3H), 1.95 (m, 1H), 0.87 (d, *J* = 6.84 Hz, 3H), 0.83 (d, *J* = 6.84 Hz, 3H); ^{13}C NMR (**6f**, CD_3OD) δ 173.0, 171.8, 137.1, 130.7, 129.3, 127.8, 71.8, 60.4, 59.4, 58.9, 53.3, 40.1, 37.3, 32.4, 19.5, 18.6. Anal. ($C_{18}H_{26}N_2O_4$×0.25 HCOOH) C, H, N.

(2*S*)-2-Benzyl-oxirane-2-carboxylic acid ((1*S*)-3-methyl-1-methylcarbamoyl-butyl)-amide (**6g**). Compound **6g** was prepared according to Method A using (*S*)-**5** (0.210 g, 1.18 mmol), EDC (0.249 g, 1.30 mmol), HOBT (0.176 g, 1.30 mmol), NMM (0.156 mL, 1.42 mmol) and H-Leu-NHMe (0.204 g, 1.42 mmol). Purification by reverse-phase LC-MS (35 min gradient of 10–65% CH_3CN in 0.05% aqueous formic acid) afforded **6g** and the corresponding (1*R*)-diastereomer in a 5:1 mixture (0.135 g, 38%) as a white solid. $[\alpha]^{20}_D$ -22 ° (*c* 2.3, isopropanol); ^{1}H NMR (**6g**, $CD_3OD/CDCl_3$, 6:1) δ 7.28–7.15 (m, 5H), 4.29 (m, 1H), 3.55 (d, *J* = 14.8 Hz, 1H), 2.84 (d, *J* = 14.8 Hz, 1H), 2.82 (d, *J* = 5.00 Hz, 1H), 2.78 (d, *J* = 5.00 Hz, 1H), 2.60 (s, 3H), 1.56-1.37 (m, 3H), 0.87 (d, *J* = 6.25 Hz, 3H), 0.84 (d, *J* = 6.25 Hz, 3H); ^{13}C NMR (**6g**, $CD_3OD/CDCl_3$, 6:1) δ 174.2, 171.5, 136.7, 130.6, 129.1, 127.7, 60.3, 52.9, 52.3, 41.7, 37.3, 26.4, 25.7, 23.3, 21.9. Anal. ($C_{17}H_{24}N_2O_3$) C, H, N.

(1*S*)-2-Benzyl-oxirane-2-carboxylic acid ((1*S*)-1-methylcarbamoyl-2-phenyl-ethyl)-amide (**6h**). Compound **6h** was prepared according to Method A using (*S*)-**5** (0.138 g, 0.775 mmol), EDC (0.164 g, 0.853 mmol), HOBT (0.115 g, 0.853 mmol), NMM (0.102 mL, 0.930 mmol) and H-Phe-NHMe (0.152 g, 0.853 mmol). Purification by reverse-phase LC-MS (35 min gradient of 10–60% CH_3CN in 0.05% aqueous formic acid) afforded **6h** and the corresponding (1*R*)-diastereomer in a 3:1 mixture (0.0455 g, 17%) as a white solid. $[\alpha]^{20}_D$ -3.6 ° (*c* 1.0, isopropanol); ^{1}H NMR (**6h**, $CD_3OD/CDCl_3$, 6:1) δ 7.28–7.07 (m, 10H), 4.48 (dd, *J* = 5.47, 9.52 Hz, 1H), 3.47 (d, *J* = 14.8 Hz, 1H), 3.10 (dd, *J* = 5.47, 13.9 Hz, 1H), 2.77 (m, 2H), 2.62 (d, *J* = 5.13 Hz, 1H), 2.60 (s, 3H), 2.26 (d, *J* = 5.13 Hz, 1H); ^{13}C NMR (**6h**, $CD_3OD/CDCl_3$, 6:1) δ 172.9, 171.4, 137.7, 136.6, 130.5, 130.0, 129.9, 129.2, 129.0, 127.6, 60.1, 54.7, 52.6, 38.5, 37.1, 26.4. Anal. ($C_{20}H_{22}N_2O_3$×0.25 H_2O) C, H, N.

(2*S*)-2-(2-Benzyl-acryloylamino)-3,3,*N*-trimethyl-butyramide (**7**). Compound **7** was prepared according to Method A using 2-benzyl acrylic acid[1] (2.00 g, 12.3 mmol), EDC (2.60 g, 13.6 mmol), HOBT (1.83 g, 13.6 mmol), NMM (1.63 mL, 14.8 mmol) and L-*tert*-leucine-methylamide (1.96 g, 13.6 mmol). Purification by flash chromatography (silica, EtOAc/pentane, 50:50–70:30) afforded **7** (1.91 g, 54%) as a white solid. $[\alpha]^{20}_D$ -6.3 ° (*c* 1.8, EtOAc); ^{1}H NMR (CD_3OD) δ 7.32–7.14 (m, 5H), 5.81 (m, 1H), 5.40 (m, 1H), 4.23 (s, 1H), 3.72 (m, 1H), 3.64 (m, 1H), 2.69 (s, 3H), 0.81 (s, 9H); ^{13}C NMR (CD_3OD) δ 171.8, 168.9,

144.1, 138.4, 128.7, 128.5, 126.5, 120.2, 60.9, 38.5, 34.4, 25.8, 24.9. Anal. ($C_{17}H_{24}N_2O_2$) C, H, N.

(2*R* or *S*)-2-Benzyl-oxirane-2-carboxylic acid ((1*S*)-2,2-dimethyl-1-methylcarbamoyl-propyl)-amide ((*S*)-**8** and (*R*)-**8**). Compound **7** (1.72 g, 5.98 mmol) was dissolved in $ClCH_2CH_2Cl$ and mCPBA (77%, 3.35 g, 14.9 mmol) was added. The reaction mixture was heated to 45 °C and then AIBN (0.004 g, 0.0243 mmol) was added followed by reflux of the resulting solution over night. Washing of the mixture with 10% $Na_2S_2O_3$ (aq.), saturated $NaHCO_3$ (aq.) and brine followed by drying (Na_2SO_4) and evaporation afforded the crude product. Purification by flash chromatography (silica, EtOAc/pentane, 50:50–100:0) yielded the diastereomeric epoxides (*S*)-**8** (0.664 g) and (*R*)-**8** (0.712 g) as separate white solids in a total yield of 76%. (*S*)-**8**: $[\alpha]^{20}_D$ -5.3 ° (*c* 1.1, EtOAc); ^{1}H NMR (CD_3OD + 2 drops of D_2O) δ 7.28–7.14 (m, 5H), 4.12 (s, 1H), 3.55 (d, *J* = 15.0 Hz, 1H), 2.86 (s, 2H), 2.84 (d, *J* = 15.0 Hz, 1H), 2.65 (s, 3H), 0.89 (s. 9H); ^{13}C NMR (CD_3OD + 2 drops of D_2O) δ 171.3, 170.3, 135.8, 129.6, 128.2, 126.7, 60.1, 59.5, 52.3, 36.2, 34.6, 25.8, 25.0. Anal. ($C_{17}H_{24}N_2O_3$) C, H, N. (*R*)-**8**: $[\alpha]^{20}_D$ +22 ° (*c* 0.91, EtOAc); ^{1}H NMR (CD_3OD) δ 7.33–7.14 (m, 5H), 4.05 (s, 1H), 3.64 (d, *J* = 14.7 Hz, 1H), 2.96 (d, *J* = 4.87 Hz, 1H), 2.86 (d, *J* = 4.87 Hz, 1H), 2.69 (d, *J* = 14.7 Hz, 1H), 2.67 (s, 3H), 0.71 (s, 9H); ^{13}C NMR (CD_3OD) δ 171.4, 169.6, 136.2, 129.6, 128.2, 126.8, 60.0, 59.9, 52.3, 36.8, 34.3, 25.6, 24.9. Anal. ($C_{17}H_{24}N_2O_3$) C, H, N.

General procedure for the epoxide ring opening reactions. Epoxide and hydrazide **9**[2] were stirred in *i*-PrOH at 80 ºC (time as stated below). Evaporation of the solvent and then purification by reverse-phase LC-MS gave the pure products.

{(1*S*)-1-[*N*'-((2*S*)-2-Benzylcarbamoyl-2-hydroxy-3-phenyl-propyl)-*N*'-(4-bromo-benzyl)-hydrazinocarbonyl]-2,2-dimethyl-propyl}-carbamic acid methyl ester (**10**). Compound **10** was prepared according to the general procedure using **9** (0.0834 g, 0.224 mmol) and **6a** (0.0499 g, 0.187 mmol) by heating for 7 days. Reverse-phase LC-MS (35 min gradient of 15–100% CH_3CN in 0.05% aqueous formic acid) afforded **10** (0.0648 g, 54%) as a white solid. $[\alpha]^{19}_D$ -64 ° (*c* 0.79, $CH_3OH/CHCl_3$ 1:1); ^{1}H NMR ($CD_3OD/CDCl_3$ 1:1) δ 7.28 (m, 2H), 7.24–7.04 (m, 10H), 6.83 (m, 2H), 4.20 (d, *J* = 14.9 Hz, 1H), 4.06 (d, *J* = 14.9 Hz, 1H), 3.96 (d, *J* = 14.3 Hz, 1H), 3.87 (d, *J* = 14.3 Hz, 1H), 3.76 (d, *J* = 13.9 Hz, 1H), 3.60 (s, 3H), 3.56 (s, 1H), 2.95 (d, *J* = 13.3 Hz, 1H), 2.81 (d, *J* = 13.9 Hz, 1H), 2.74 (d, *J* = 13.3 Hz, 1H), 0.57 (s, 9H); ^{13}C NMR ($CD_3OD/CDCl_3$ 1:1) δ 175.8, 171.6, 158.1, 138.0, 137.2, 136.5, 131.8, 131.1, 130.7, 128.9, 128.4, 128.0, 127.7, 127.1, 121.7, 78.5, 68.0, 61.9, 61.6, 52.7, 43.54, 43.46, 34.6, 26.3. Anal. ($C_{32}H_{39}BrN_4O_5$) C, H, N.

((1*S*)-1-{*N*'-(4-Bromo-benzyl)-*N*'-[(2*S*)-2-hydroxy-3-phenyl-2-((3*R*)-tetrahydro-furan-3-ylcarbamoyl)-propyl]-hydrazinocarbonyl}-2,2-dimethyl-propyl)-carbamic acid methyl ester (**11**). Compound **11** was prepared according to the general procedure using **9** (0.0681 g, 0.183 mmol) and **6b** (0.0377 g, 0.153 mmol) by heating for 7 days. Reverse-phase LC-MS (40 min gradient of 10–90% CH_3CN in 0.05% aqueous formic acid) afforded **11** (0.0494 g, 52%) as a white solid. $[\alpha]^{19}_D$ -72 ° (*c* 0.98, CH_3OH); ^{1}H NMR (CD_3OD) δ 7.37 (m, 2H), 7.28–7.14 (m, 7H), 4.12 (m, 1H), 4.00 (d, *J* = 14.4 Hz, 1H), 3.95 (d, *J* = 14.4 Hz, 1H), 3.77 (d, *J* = 13.7 Hz, 1H), 3.64–3.42 (m, 8H), 2.90 (d, *J* = 13.3 Hz, 1H), 2.86 (m, 1H), 2.73 (d, *J* = 13.3 Hz, 1H), 1.88 (m, 1H), 1.27 (m, 1H), 0.61 (s, 9H); ^{13}C NMR (CD_3OD) δ 176.6, 172.4, 159.0, 138.4, 137.4, 132.4, 131.6, 131.4, 128.8, 127.6, 122.1, 79.0, 72.9, 68.5, 67.7, 62.9, 62.0, 52.7, 51.2, 44.0, 34.9, 33.4, 26.6. Anal. ($C_{29}H_{39}BrN_4O_6$) C, H, N.

((1*S*)-1-{*N*'-(4-Bromo-benzyl)-*N*'-[(2*S*)-2-hydroxy-2-(3-hydroxy-2-methyl-phenylcarbamoyl)-3-phenyl-propyl]-hydrazinocarbonyl}-2,2-dimethyl-propyl)-carbamic acid methyl ester (**12**). Compound **12** was prepared according to the general procedure using **9** (0.162 g, 0.437 mmol) and **6c** (0.103 g, 0.364 mmol) by heating for 7 days. Reverse-phase LC-MS (35 min gradient of 30–100% CH_3CN in 0.05% aqueous formic acid) afforded **12** (0.0168 g, 7%) as a white solid. $[\alpha]^{19}_D$ -42 ° (*c* 0.90, CH_3OH); ^{1}H NMR (CD_3OD) δ 7.51–7.18 (m, 9H), 6.82 (m, 1H), 6.57 (m, 1H), 6.12 (m, 1H), 4.12 (d, *J* = 13.7 Hz, 1H), 4.07 (d, *J* = 13.7 Hz, 1H), 3.71 (d, *J* = 14.2 Hz, 1H), 3.65 (s, 1H), 3.60 (s, 3H), 3.14 (m, 3H), 1.75 (s, 3H), 0.68 (s, 9H); ^{13}C NMR (CD_3OD) δ 174.7, 172.3, 159.0, 151.1, 148.4, 138.0, 137.1, 132.3, 131.9, 131.8, 129.1, 127.9, 127.3, 122.2, 116.0, 113.9, 112.2, 79.9, 68.2, 62.9, 62.7, 52.7, 44.0, 35.0, 26.7, 10.4. Anal. ($C_{32}H_{39}BrN_4O_6$) C, H, N.

((1*S*)-1-{*N*'-(4-Bromo-benzyl)-*N*'-[(2*S*)-2-hydroxy-3-phenyl-2-(quinolin-2-ylcarbamoyl)-propyl]-hydrazinocarbonyl}-2,2-dimethyl-propyl)-carbamic acid methyl ester (**13**). Compound **13** was prepared according to the general procedure using **9** (0.142 g, 0.383 mmol) and **6d** (0.0970 g, 0.319 mmol) by heating for 7 days. Reverse-phase LC-MS (35 min gradient of 30–100% CH_3CN in 0.05% aqueous formic acid) afforded **13** (0.0229 g, 11%) as a white solid. $[\alpha]^{19}_D$ -6.5 ° (*c* 0.54, $CHCl_3$); ^{1}H NMR ($CD_3OD/CDCl_3$, 1:1) δ 8.18 (m, 2H), 7.77 (m, 2H), 7.65 (m, 1H), 7.44 (m, 1H), 7.28–7.03 (m, 9H), 4.02 (d, *J* = 14.2 Hz, 1H), 3.93 (d, *J* = 14.2 Hz, 1H), 3.85 (d, *J* = 14.0 Hz, 1H), 3.62 (s, 3H), 3.56 (s, 1H), 3.08 (d, *J* = 13.4 Hz, 1H), 2.93 (d, *J* = 14.0 Hz, 1H), 2.86 (d, *J* = 13.4 Hz, 1H), 0.57 (s, 9H); ^{13}C NMR ($CD_3OD/CDCl_3$, 1:1) δ 175.7, 171.6, 158.1, 150.4, 146.9, 139.5, 136.8, 136.0, 131.8, 130.9, 130.8, 128.4, 128.2, 127.5, 127.2, 127.0, 126.1, 121.7, 114.2, 78.9, 67.3, 62.0, 61.9, 52.7, 43.7, 34.6, 26.3 (2 aromatic carbon signals overlapping). HRMS ($M+H^+$): 676.2135, $C_{34}H_{39}N_5O_5Br$ requires 676.2154.

{(1*S*)-1-{*N*'-(4-Bromo-benzyl)-*N*'-[(2*S*)-2-hydroxy-2-((1*S*)-2-methyl-1-methylcarbamoyl-propylcarbamoyl)-3-phenyl-propyl]-hydrazinocarbonyl}-2,2-dimethyl-propyl}-carbamic acid methyl ester (**14**). Compound **14** was prepared according to the general procedure using **9** (0.0916 g, 0.246 mmol) and **6e** (0.0595 g, 0.205 mmol) by heating for 7 days. Reverse-phase LC-MS (35 min gradient of 10–80% CH_3CN in 0.05% aqueous formic acid) afforded **14** (0.0565 g, 46%) as a white solid and 0.0056 g recovered epoxide. $[\alpha]^{20}_D$ -69 ° (*c* 1.0, CH_3OH); ^{1}H NMR (CD_3OD) δ 7.37 (m, 2H), 7.26 (m, 2H), 7.18 (m, 5H), 4.04 (d, *J* = 14.3 Hz, 1H), 3.98 (d, *J* = 14.3 Hz, 1H), 3.89 (d, *J* = 6.75 Hz, 1H), 3.68 (d, *J* = 14.1 Hz, 1H), 3.63 (s, 1H), 3.59 (s, 3H), 2.91 (m, 2H), 2.78 (d, *J* = 13.5 Hz, 1H), 2.59 (s, 3H), 1.84 (m, 1H), 0.77 (d, *J* = 5.11 Hz, 3H), 0.76 (d, *J* = 5.11 Hz, 3H), 0.65 (s, 9H); ^{13}C NMR (CD_3OD) δ 176.7, 173.0, 172.4, 159.0, 138.1, 137.2, 132.3, 131.5, 131.4, 128.9, 127.5, 122.1, 79.0, 68.1, 62.9, 62.2, 59.9, 52.7, 44.4, 34.9, 32.6, 26.7, 26.2, 19.4, 18.9. Anal. ($C_{31}H_{44}BrN_5O_6$) C, H, N.

{(1*S*)-1-(*N*'-(4-Bromo-benzyl)-*N*'-{(2*S*)-2-hydroxy-2-[(1*S*)-1-(2-methoxy-ethylcarbamoyl)-2-methyl-propylcarbamoyl]-3-phenyl-propyl}-hydrazinocarbonyl)-2,2-dimethyl-propyl}-carbamic acid methyl ester (**15**). Compound **15** was prepared according to the general procedure using **9** (0.0522 g, 0.140 mmol) and **6f** (0.0391 g, 0.117 mmol) by heating for 7 days. Reverse-phase LC-MS (35 min gradient of 10–75% CH_3CN in 0.05% aqueous formic acid) afforded **15** (0.0389 g, 73%) as a white solid and 0.0137 g recovered epoxide. $[\alpha]^{20}_D$ -66 ° (*c* 1.0, CH_3OH); ^{1}H NMR (CD_3OD) δ 7.37 (m, 2H), 7.26 (m, 2H), 7.17 (m, 5H), 4.04 (d, *J* = 14.5 Hz, 1H), 3.98 (d, *J* = 14.5 Hz, 1H), 3.94 (d, *J* = 6.74 Hz, 1H), 3.68 (d, *J* = 14.3 Hz, 1H), 3.62 (s, 1H), 3.59 (s, 3H), 3.38 (m, 2H), 3.32 (s, 3H), 3.17 (m, 2H), 2.90 (m, 2H), 2.77 (d, *J* = 13.4 Hz, 1H), 1.84 (m, 1H), 0.80 (d, *J* = 4.70 Hz, 3H), 0.78 (d, *J* = 4.70

Hz, 3H), 0.64 (s, 9H); ^{13}C NMR (CD_3OD) δ 176.8, 172.5, 172.4, 159.0, 138.1, 137.2, 132.3, 131.5, 131.4, 128.9, 127.5, 122.1, 79.0, 71.8, 68.0, 62.9, 62.2, 59.8, 58.9, 52.7, 44.3, 40.1, 34.9, 32.8, 26.6, 19.4, 18.9. Anal. ($C_{33}H_{48}BrN_5O_7$) C, H, N.

{(1*S*)-1-{*N*'-(4-Bromo-benzyl)-*N*'-{(2*S*)-2-hydroxy-2-[(1*S*)-3-methyl-1-methylcarbamoyl-butylcarbamoyl)-3-phenyl-propyl]-hydrazinocarbonyl}-2,2-dimethyl-propyl)-carbamic acid methyl ester (**16**). Compound **16** was prepared according to the general procedure using **9** (0.125 g, 0.335 mmol) and **6g** (0.0850 g, 0.279 mmol) by heating for 7 days. Reverse-phase LC-MS (35 min gradient of 10–80% CH_3CN in 0.05% aqueous formic acid) afforded **16** (0.0664 g, 35%) as a white solid. $[\alpha]^{19}_D$ -87 ° (*c* 0.87, CH_3OH); ^{1}H NMR (CD_3OD) δ 7.38 (m, 2H), 7.29–7.14 (m, 7H), 4.20 (m, 1H), 4.00 (d, *J* = 14.7 Hz, 1H), 3.96 (d, *J* = 14.7 Hz, 1H), 3.70 (d, *J* = 14.0 Hz, 1H), 3.63 (s, 1H), 3.59 (s, 3H), 2.91 (d, *J* = 13.3 Hz, 1H), 2.89 (d, *J* = 14.0 Hz, 1H), 2.76 (d, *J* = 13.3 Hz, 1H), 2.54 (s, 3H), 1.36 (m, 3H), 0.67 (s, 3H), 0.65 (s, 3H), 0.64 (s, 9H); ^{13}C NMR (CD_3OD) δ 176.6, 174.3, 172.4, 159.0, 138.2, 137.3, 132.4, 131.6, 131.2, 128.9, 127.6, 122.0, 78.8, 68.4, 63.0, 61.8, 52.9, 52.7, 44.3, 42.9, 34.9, 26.7, 26.5, 25.7, 23.0, 22.1. Anal. ($C_{32}H_{46}BrN_5O_6$) C, H, N.

{(1*S*)-1-{*N*'-(4-Bromo-benzyl)-*N*'-{(2*S*)-2-hydroxy-2-[(1*S*)-1-methylcarbamoyl-2-phenyl-ethylcarbamoyl)-3-phenyl-propyl]-hydrazinocarbonyl}-2,2-dimethyl-propyl)-carbamic acid methyl ester (**17**). Compound **17** was prepared according to the general procedure using **9** (0.0345 g, 0.0928 mmol) and **6h** (0.262 g, 0.0774 mmol) by heating for 8 days. Reverse-phase LC-MS (35 min gradient of 20–80% CH_3CN in 0.05% aqueous formic acid) afforded **17** (0.0214 g, 39%) as a white solid. $[\alpha]^{19}_D$ -53 ° (*c* 1.0, CH_3OH); ^{1}H NMR (CD_3OD) δ 7.38 (m, 2H), 7.29–7.05 (m, 12H), 4.34 (t, *J* = 7.14 Hz, 1H), 3.95 (d, *J* = 13.9 Hz, 1H), 3.91 (d, *J* = 13.9 Hz, 1H), 3.64 (s, 1H), 3.58 (s, 3H), 3.49 (d, *J* = 14.2 Hz, 1H), 2.96-2.71 (m, 5H), 2.47 (s, 3H), 0.67 (s, 9H); ^{13}C NMR (CD_3OD) δ 176.4, 173.0, 172.5, 159.0, 138.1, 137.9, 137.4, 132.4, 131.6, 131.5, 130.3, 129.5, 128.9, 127.8, 127.5, 122.2, 79.0, 67.9, 62.9, 62.2, 55.8, 52.7, 44.1, 39.6, 34.9, 26.7, 26.3. Anal. ($C_{35}H_{44}BrN_5O_6$) C, H, N.

{(1*S*)-1-[*N*'-(4-Bromo-benzyl)-*N*'-((2*S*)-2-((1*S*)-2,2-dimethyl-1-methylcarbamoyl-propylcarbamoyl)-2-hydroxy-3-phenyl-propyl)-hydrazinocarbonyl]-2,2-dimethyl-propyl}-carbamic acid methyl ester (**18**). Compound **18** was prepared according to the general procedure using **9** (0.184 g, 0.493 mmol) and (*S*)-**8** (0.125 g, 0.411 mmol) by heating for 4 days. Reverse-phase LC-MS (35 min gradient of 35–80% CH_3CN in 0.05% aqueous formic acid) afforded **18** (0.136 g, 49%) as a white solid. $[\alpha]^{20}_D$ -63 ° (*c* 0.82, CH_3OH); ^{1}H NMR (CD_3OD) δ 7.36 (m, 2H), 7.27 (m, 2H), 7.15 (m, 5H), 4.02 (d, *J* = 14.6 Hz, 1H), 3.99 (d, *J* = 14.6 Hz, 1H), 3.87 (s, 1H), 3.72 (d, *J* = 14.1 Hz, 1H), 3.64 (s, 1H), 3.59 (s, 3H), 2.94 (d, *J* = 14.1 Hz, 1H), 2.87 (d, *J* = 13.3 Hz, 1H), 2.74 (d, *J* = 13.3 Hz, 1H), 2.56 (s, 3H), 0.77 (s, 9H), 0.65 (s, 9H); ^{13}C NMR (CD_3OD) δ 176.4, 172.4, 172.0, 159.0, 138.0, 137.1, 132.3, 131.4, 131.3, 128.8, 127.4, 122.1, 79.0, 68.2, 62.9, 62.1, 62.0, 61.9, 52.7, 44.6, 35.8, 34.9, 27.0, 26.6. Anal. ($C_{32}H_{46}BrN_5O_6$) C, H, N.

{(1*S*)-1-[*N*'-(4-Bromo-benzyl)-*N*'-((2*R*)-2-((1*S*)-2,2-dimethyl-1-methylcarbamoyl-propylcarbamoyl)-2-hydroxy-3-phenyl-propyl)-hydrazinocarbonyl]-2,2-dimethyl-propyl}-carbamic acid methyl ester (**19**). Compound **19** was prepared according to the general procedure using **9** (0.203 g, 0.544 mmol) and (*R*)-**8** (0.138 g, 0.454 mmol) by heating for 4 days. Reverse-phase LC-MS (35 min gradient of 35–80% CH_3CN in 0.05% aqueous formic acid) afforded **19** (0.212 g, 69%) as a white solid. $[\alpha]^{20}_D$ +35 ° (*c* 0.86, CH_3OH); ^{1}H NMR (CD_3OD) δ 7.39–7.26 (m, 4H), 7.24-7.08 (m, 5H), 4.03-3.80 (m, 3H), 3.64 (d, *J* = 14.0

Hz, 1H), 3.59 (s, 3H), 3.57 (s, 1H), 2.97–2.78 (m, 3H), 2.49 (s, 3H), 0.77 (s, 9H), 0.69 (s, 9H); ^{13}C NMR (CD_3OD) δ 176.1, 172.5, 172.0, 158.8, 137.7, 137.2, 132.1, 131.8, 131.7, 129.0, 127.7, 121.8, 79.3, 67.7, 62.8, 61.84, 61.75, 61.5, 52.8, 43.9, 35.4, 34.9, 26.9, 26.8. Anal. ($C_{32}H_{46}BrN_5O_6$) C, H, N.

Table 1. Elemental Analysis Data

Cmpd no	Formula	Theoretical			Analyzed		
		C	**H**	**N**	**C**	**H**	**N**
3	$C_{15}H_{18}O_4$	68.68	6.92		68.51	7.91	
(*S*)-**4**	$C_{15}H_{18}O_5$	64.74	6.52		64.88	6.28	
(*R*)-**4**	$C_{15}H_{18}O_5$	64.74	6.52		64.60	6.44	
6a	$C_{17}H_{17}NO_2 \times H_2O$	71.56	6.71	4.91	71.53	6.58	4.78
6b	$C_{14}H_{17}NO_3$	68.00	6.93	5.66	67.84	6.82	5.57
6c	$C_{17}H_{17}NO_3$	72.07	6.05	4.94	71.84	6.20	5.09
6d	$C_{19}H_{16}N_2O_2 \times 0.25\ H_2O$	73.89	5.38	9.07	73.84	5.19	8.68
6e	$C_{16}H_{22}N_2O_3$	66.18	7.64	9.65	65.93	7.68	9.62
6f	$C_{18}H_{26}N_2O_4 \times 0.25$ HCOOH	63.37	7.72	8.10	63.58	7.35	8.36
6g	$C_{17}H_{24}N_2O_3$	67.09	7.95	9.20	66.85	7.91	9.17
6h	$C_{20}H_{22}N_2O_3 \times 0.25\ H_2O$	70.05	6.61	8.17	69.80	6.73	8.52
7	$C_{17}H_{24}N_2O_2$	70.80	8.39	9.71	70.60	8.48	9.66
(*S*)-**8**	$C_{17}H_{24}N_2O_3$	67.08	7.95	9.20	66.82	7.96	9.11
(*R*)-**8**	$C_{17}H_{24}N_2O_3$	67.08	7.95	9.20	66.88	7.87	9.12
10	$C_{32}H_{39}BrN_4O_5$	60.09	6.15	8.76	60.08	6.32	8.65
11	$C_{29}H_{39}BrN_4O_6$	56.22	6.34	9.04	56.11	6.51	8.86
12	$C_{32}H_{39}BrN_4O_6$	58.63	6.00	8.55	58.36	6.14	8.38
14	$C_{31}H_{44}BrN_5O_6$	56.19	6.69	10.57	56.08	6.65	10.41
15	$C_{33}H_{48}BrN_5O_7$	56.09	6.85	9.91	56.31	6.96	9.82
16	$C_{32}H_{46}BrN_5O_6$	56.80	6.85	10.35	56.44	6.73	10.18
17	$C_{35}H_{44}BrN_5O_6$	59.15	6.24	9.85	58.88	6.08	9.71
18	$C_{32}H_{46}BrN_5O_6$	56.80	6.85	10.35	56.59	6.88	10.24
19	$C_{32}H_{46}BrN_5O_6$	56.80	6.85	10.35	56.52	6.92	10.20

Biological Evaluations

HIV-1 Protease Inhibition. The HIV-1 protease was cloned and heterologously expressed in *Escherichia coli* and purified as described elsewhere.[3] The K_i-values were determined by a fluorometric assay.[4]

Cell Based Anti-HIV Activity. The in vitro anti-HIV activity was assayed in MT4 cells according to a previously published procedure[4] using the colorimetric XTT assay to monitor the cytopathogenic effects.

Stability in Liver Microsomes. A final concentration of 2 μM test compound (dissolved in 0.1% DMSO) was incubated with rat or human liver microsomes at 37 ºC for 10, 20 and 30 min (triplicate incubations). The samples contained 0.5 mg/mL of microsomal protein in 100 mM potassium phosphate buffer pH 7.4. The reaction was initiated by the addition of NADPH (1 mM) and terminated by the addition of acetonitrile. Control incubation was

performed as described above except that NADPH was omitted. Calculation of the in vitro clearance: The ln (residual concentration) versus time was plotted. The slope of the line will give the elimination rate constant (k) from which the elimination half-life (t½) can be calculated in accordance with a one-compartment pharmacokinetic model. $k = 0.693/t_{1/2}$ and an equation expressing Cl_{int} in terms of $t_{1/2}$ can be derived

$$Cl = \frac{Volume \times 0.693}{t_{1/2}}$$

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