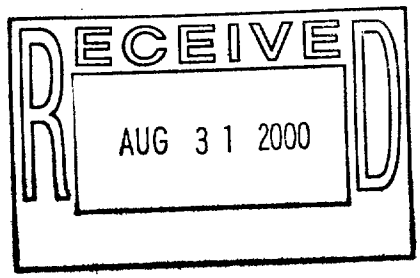
Design, Synthesis, and Evaluation of a Pyrrolinone-Based Matrix Metalloprotease Inhibitor



SUPPORTING INFORMATION

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EXPERIMENTAL PROCEDURES

All reactions were carried out in oven-dried or flame-dried glassware under an argon atmosphere, unless otherwise noted. *All* solvents were reagent or high performance liquid chromatography (HPLC) grade. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone under argon prior to use unless otherwise noted. Triethylamine and diisopropylethylamine were distilled from calcium hydride and stored over potassium hydroxide. Anhydrous dimethylformamide was purchased from Aldrich and used without purification. *n*-Butyllithium was purchased from Aldrich and standardized by titration with *sec*-butyl alcohol. All reactions were magnetically stirred and monitored by thin layer chromatography using 0.25 mm E. Merck pre-coated silica gel plates. Flash column chromatography was performed with the indicated solvents using silica gel-60 (particle size 0.040-0.062 mm) supplied by E. Merck. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. The IR and NMR spectra were obtained for $CHCl_3$ and $CDCl_3$ solutions respectively unless otherwise noted. Infrared spectra were recorded with a Perkin-Elmer 1600 series FTIR spectrometer. Proton and carbon-13 NMR spectra were recorded on a Bruker AM-500 spectrometer and obtained at 305 K. Chemical shifts are reported relative to chloroform (δ 7.26 for proton and δ 77.0 for carbon-13). Optical rotations were obtained with a Perkin-Elmer model 341 polarimeter in the solvent indicated. High-resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Service Center on a Micromass (UK) AutoSpec spectrometer in electrospray or chemical ionization mode.

Oxazolidinone (+)-4. To a solution of (*S*)-propionyl-oxazolidinone (8 g, 34 mmol) in THF (125 mL) at -78 °C was added 1.0 M NaHMDS in THF (41 mL, 41 mmol) over 1 h. The resulting solution was stirred for 15 min and then freshly distilled prenyl bromide (11.83 mL, 103 mmol) was added dropwise via syringe over 30 min. The clear yellow solution was stirred for 15 min at -78 °C and then warmed to 0 °C and stirred 45 min, where upon the solute became cloudy. The solution was then poured into 10 % aqueous $NaHSO_4$ (100 mL). The resulting biphasic mixture was extracted with EtOAc (2 x 100 mL) and the organic phase washed with saturated $NaHCO_3$ and brine (100 mL each), dried over $MgSO_4$ and concentrated in vacuo. The resulting yellow oil was purified by flash chromatography using ethyl acetate - hexanes (1:5) as eluant to afford the alkylated oxazolidinone (6.6 g, 64% yield, >98% ee) as a clear colorless oil: $[\alpha]^{23}_D$ +40.9° (*c* 1.70, $CHCl_3$); IR (neat, film) 3380 (w), 2973 (s), 2917 (s), 1770 (s), 1694 (s), 1289 (s), 1212 (s), 1100 (s), 1055 (s), 1016 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (m, 5

H), 5.19 (t, J = 7.4 Hz, 1 H), 4.70 (m, 1 H), 4.17 (m, 2 H), 3.82 (sx, J = 6.7 Hz, 1 H), 3.25 (dd, J = 3.3 Hz, 1 H), 2.74 (dd, J = 9.3 Hz, 1 H), 2.47 (m, 1 H), 2.21 (m, 1 H), 1.72 (s, 3 H), 1.66 (s, 3 H), 1.18 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.88, 152.99, 135.32, 133.77, 129.30, 128.80, 127.18, 121.04, 65.82, 55.10, 37.83, 37.79, 32.28, 25.70, 17.76, 16.32; high resolution mass spectrum (CI, CH_4) *m/z* 302.1746 $[(M + H)]^+$, calcd for $C_{18}H_{24}NO_3$ 302.1756

Alcohol (+)-5. To a solution of (+)-**4** (13.9 g, 46 mmol) in Et_2O (700 mL) at 0 °C was added H_2O (2.65 g, 147 mmol) and 2.0 M $LiBH_4$ in THF (25 mL, 50 mmol) dropwise over 30 min. The resulting solution was stirred for 1 h and then warmed to room temperature. The reaction was quenched with saturated $NaHCO_3$ (200 mL). The resulting biphasic mixture was extracted with Et_2O (3 x 125 mL), dried over $NaSO_4$, and concentrated in vacuo. The resulting yellow oil was purified by flash chromatography using Et_2O - hexanes (1:1) as eluant to afford the alcohol (5.1 g, 86% yield) as a volatile clear colorless oil: $[\alpha]^{23}_D$ +4.3° (*c* 1.40, CH_2Cl_2); IR ($CHCl_3$) 3626 (m), 3450 (b), 3009 (s), 2965 (s), 2929 (s), 2877 (s), 1672 (w), 1377 (s), 1028 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.16 (m, 1 H), 3.52 (m, J = 6.0, Hz, 1 H), 3.44 (dd, J = 6.3, 6.0, Hz, 1 H), 2.07 (m, 1 H), 1.88 (m, 1 H), 1.71 (s, 3 H), 1.69 (m, 1 H), 1.62 (s, 3 H), 1.37 (s, 1 H), 0.92 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.47, 122.56, 67.96, 36.47, 31.80, 25.70, 17.66, 16.48; high resolution mass spectrum (CI, CH_4) *m/z* 128.1201 $(M)^+$, calcd for $C_8H_{16}O$ 128.1201.

SEM Ether. To a solution of (+)-**5** (4.81 g, 38 mmol) in dichloromethane (18 mL) at 0 °C was added (i-Pr)$_2$NEt (33.10 mL, 190 mmol) dropwise over 15 min. To the resulting solution was added SEM-Cl (20.18 mL, 114 mmol) dropwise over 15 min. and stirred for 2 h. The solution was then poured into 10 % aqueous $NaHSO_4$ (100 mL). The resulting biphasic mixture was extracted with Et_2O (3 x 100 mL), dried over $MgSO_4$ and concentrated in vacuo. The resulting orange oil was purified by flash chromatography using ethyl acetate - hexanes (1:5) as eluant to afford the corresponding prenyl SEM ether (9.81 g, 99% yield) as a clear colorless oil: $[\alpha]^{23}_D$ -1.9° (*c* 2.59, $CHCl_3$); IR (neat, film) 2953 (s), 2921 (s), 1248 (s), 1109 (s), 1058 (s), 1038 (s), 859 (s), 835 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.12 (m, 1 H), 4.65 (s, 2 H), 3.61 (m, 2 H), 3.40 (dd, J = 3.6, 6.0 Hz, 1 H), 3.30 (m, J = 6.7 Hz, 1 H), 2.07 (m, 1 H), 1.85 (m, 1 H), 1.74 (sx, J = 6.7 Hz, 1 H), 1.69 (s, 3 H), 1.59 (s, 3 H), 0.93 m, 2 H), 0.91 (d, J = 6.7 Hz,

3 H), 0.01 (s , 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.38, 122.56, 94.94, 72.86, 64.82, 34.27, 31.98, 25.76, 18.11, 17.74, 16.96, -1.45; high resolution mass spectrum (CI, NH_3) *m/z* 276.2360 $[(M + NH_4)]^+$, calcd for $C_{14}H_{30}O_2Si{\bullet}NH_4$ 276.2359. Anal. Calcd for $C_{14}H_{30}O_2Si$: C, 65.06; H, 11.70. Found: C, 65.26; H, 11.95.

Aldehyde (+)-6. Ozone was bubbled through a solution of (-)-prenyl SEM ether (6.6 g, 26 mmol) in dichloromethane (200 mL) at -78 °C until a pale blue color persisted. At -78 °C, Ph_3P (6.69 g, 26 mmol) was then added and the reaction mixture allowed to stir and warm to room temperature ovemight. The resulting clear oil was purified by flash chromatography using ethyl acetate - hexanes (1:5 then 3:10) as eluant to afford the aldehyde (4.2 g, 71% yield) as a clear colorless oil: $[\alpha]^{23}_D$ +6.6° (*c* 1.07, $CHCl_3$); IR (neat, film) 2954 (m), 1732 (s), 1713 (s), 1416 (m), 1250 (m), 1057 (s), 859 (s), 835 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.69 (t, *J* = 2.0 Hz, 1 H), 4.56 (m, 2 H), 3.53 (m, 2 H), 3.40 (m, 1 H), 3.31 (m, *J* = 7.1, Hz, 1 H), 3.26 (dd, *J* = 7.5, 7.1 Hz, 1 H), 1.00 (m, 5 H), 0.86 (m, 2 H), -0.05 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.07, 94.86, 72.08, 65.08, 38.11, 29.00, 18.10, 17.08, -1.45; high resolution mass spectrum (CI, NH_3) *m/z* 250.1828 $[(M + NH_4)]^+$, calcd for $C_{11}H_{24}O_3Si{\bullet}NH_4$ 250.1838.

Monopyrrolinone (+)-8. To a solution of (-)-**7** (2.0 g, 8.6 mmol) in toluene (60 mL) was added to (+)-**6** (2.4 g, 8.6 mmol). Condensation was effected by allowing the solution to stir for 15 min; then the solution was concentrated in vacuo and the residue azeotropically dehydrated with additional toluene (5 x 60 mL).

To a solution of the residue in THF (80 mL) was added 0.5 M KHMDS in toluene (43 mL, 21 mmol) rapidly via syringe. The resulting yellow-orange solution was stirred for 20 min and then 10 % aqueous $NaHSO_4$ (100 mL) was added and diluted with EtOAc (100 mL). The resulting biphasic mixture was extracted with EtOAc (2 x 100 mL) and washed with saturated $NaHCO_3$ and brine (100 mL each). The resultant yellow solution was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography using methnaol - dichloromethane (1:19) as eluant to afford the monopyrrolinone (3.3 g, 93% yield) as a yellow oil: $[\alpha]^{23}_D$ +38.5° (*c* 1.07, $CHCl_3$); IR ($CHCl_3$) 3425 (m), 3008 (s), 2956 (s), 2873 (s), 2836 (m), 1710 (m), 1661 (s), 1583 (s), 1465 (s), 1422 (s), 1368 (s), 1250 (s), 1121 (s), 1057 (s), 861 (s), 837 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 3.7 Hz, 1 H), 5.61 (s, 1 H), 4.65 (s, 2 H), 4.47 (dd, *J* = 4.1, 4.5 Hz, 1 H), 3.61 (m, 3 H), 3.42 (m, *J* = 6.7 Hz, 1 H), 3.35 (s, 3 H), 3.28 (s, 3 H), 2.81 (sx, *J* = 6.7 Hz, 1 H), 1.91 (dd, *J* = 4.1 Hz, 1 H), 1.66 (m, 2 H), 1.52 (m, 2 H), 1.16 (d, *J* = 7.1

Hz, 3 H), 0.93 (m, 2 H), 0.85 (d, J = 6.3 Hz, 3 H), 0.81 (d, J = 6.7 Hz, 3 H), 0.02 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.80, 160.54, 115.81, 102.30, 94.96, 71.76, 67.99, 64.92, 54.00, 53.14, 43.66, 40.29, 28.56, 24.33, 24.26, 24.13, 18.06, 16.85, -1.45; high resolution mass spectrum (ESI) *m/z* 438.2667 [(M + Na)]$^+$, calcd for $C_{21}H_{41}NO_5SiNa$ 438.2652.

Monopyrrolinone Aldehyde. To a solution of (+)-**8** (2.1 g, 5 mmol) in a 3:1 mixture of THF and water (70 mL) was added *p*-TsOH hydrate (943 mg, 5 mmol). The solution was heated at 50 °C for 4 h and was then cooled to room temperature and diluted with EtOAc (400 mL) and saturated $NaHCO_3$ (300 mL). The resulting biphasic mixture was extracted with EtOAc (2 x 200 mL) and washed with brine (200 mL). The yellow solution was then dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography using methnaol - dichloromethane (3:47) as eluant to afford the monopyrrolinone aldehyde (1.82 g, 99% yield) as a yellow oil: $[\alpha]^{23}_D$ -43.8° (*c* 0.95, $CHCl_3$); IR ($CHCl_3$) 3447 (m), 3008 (s), 2957 (s), 2928 (s), 2873 (s), 1722 (s), 1661 (s), 1582 (s), 1452 (m), 1426 (m), 1368 (m), 1250 (s), 1212 (s), 1058 (s), 1029 (s), 861 (s), 837 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (d, J = 2.6 Hz, 1 H), 7.81 (d, J = 3.7 Hz, 1 H), 5.59 (s, 1 H), 4.64 (s, 2 H), 3.61 (m, 3 H), 3.45 (m, J = 6.7 Hz, 1 H), 2.81 (m, 1 H), 2.76 (m, J = 2.6 Hz, 1 H), 2.56 (d, J = 16.8 Hz, 1 H), 1.73 (m, J = 5.6 Hz, 1 H), 1.66 (m, J = 6.7 Hz, 1 H), 1.58 (m, 1 H), 1.16 (d, J = 6.7 Hz, 3 H), 0.93 (m, 2 H), 0.88 (d, J = 6.7 Hz, 3 H), 0.81 (d, J = 6.7 Hz, 3 H), 0.02 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.44, 200.10, 160.51, 115.13, 94.88, 71.45, 67.41, 64.92, 50.34, 44.42, 28.56, 24.26, 18.02, 16.82, -1.48; high resolution mass spectrum (ESI) *m/z* 392.2224 [(M + Na)]$^+$, calcd for $C_{19}H_{35}NO_4SiNa$ 392.2233.

Bispyrrolinone (-)-9. To a solution of (-)-**7** (1.0 g, 4.5 mmol) in toluene (60 mL) was added to (-)-monopyrrolinone aldehyde (1.8 g, 5 mmol). Condensation was effected by allowing the solution to stir for 15 min, then the solution was concentrated in vacuo and the residue azeotropically dehydrated with additional toluene (5 x 30 mL).

To a solution of the residue in THF (40 mL) was added 0.5 M KHMDS in toluene (45 mL, 22 mmol) rapidly via syringe. The resulting yellow-orange solution was stirred for 45 min, and then 10 % aqueous $NaHSO_4$ (100 mL) was added and diluted with EtOAc (100 mL). The resulting biphasic mixture was extracted with EtOAc (2 x 100 mL) and washed with saturated $NaHCO_3$ and brine (100 mL each). The yellow solution was dried over $MgSO_4$

and concentrated in vacuo. The residue was purified by flash chromatography using ethyl acetate as eluant to afford the bispyrrolinone (2.3 g, 84% yield) as a yellow oil: $[\alpha]^{23}_D$ -97.2° (*c* 1.21, $CHCl_3$); IR (neat, film) 3272 (s), 2953 (s), 1708 (s), 1643 (s), 1556 (s), 1468 (s), 1248 (s), 1188 (s), 1122 (s), 1057 (s), 860 (s), 836 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 4.1 Hz, 1 H), 7.80 (d, *J* = 3.4 Hz, 1 H), 7.03.(d, *J* = 3.4 Hz, 1 H), 5.99 (d, *J* = 3.7 Hz, 1 H), 4.65 (s, 2H), 4.48 (q, *J* = 3.7, 4.1 Hz, 1 H), 3.60 (m, 3 H), 3.44 (d, *J* = 7.1 Hz, 1 H), 3.42 (d, *J* = 7.4 Hz, 1 H), 3.35 (s, 3 H), 3.01 (s, 3H), 2.80 (m, 1 H), 1.93 (dd, *J* = 3.7, 4.1 Hz, 1 H), 1.86 (dd, *J* = 4.1, 4.5 Hz, 1 H), 1.72 (dd, *J* = 7.5, 7.4 Hz, 1 H), 1.61 (m, 2 H), 1.38 (hp, *J* = 6.7 Hz, 1 H), 1.16 (m, 1 H), 1.12 (d, *J* = 7.1 Hz, 3 H), 1.02 (d, *J* = 6.7 Hz, 1 H), 0.94 (m, 2 H), 0.87 (d, *J* = 6.3 Hz, 3 H), 0.85 (d, *J* = 6.3 Hz, 3 H), 0.77 (d, *J* = 6.7 Hz, 3 H), 0.69 (d, *J* = 6.3 Hz, 3 H), 0.01 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.02, 202.95, 161.48, 160.89, 114.82, 110.28, 102.00, 94.93, 71.80, 68.72, 67.78, 64.88, 53.91, 53.23, 47.62, 43.72, 39.88, 28.45, 24.79, 24.47, 24.29, 24.05, 23.72, 18.06, 16.92, -1.44; high resolution mass spectrum (ESI) *m/z* 575.3475 $[(M + Na)]^+$, calcd for $C_{29}H_{52}N_2O_6SiNa$ 575.3492.

Protected Bispyrrolinone (+)-10 To a solution of (-)-**9** (2.1 g, 3.7 mmol) in THF (40 mL) at a -78 °C was added 1.0 M NaHMDS in THF (11 mL, 11 mmol) dropwise over 30 min. The resulting yellow solution was stirred for 5 min and then benzyl chloroformate (1.6 mL, 11 mmol) was added dropwise via syringe over 30 min. The yellow solution was stirred for 15 min at -78 °C and was warmed to room temperature. The solution was then poured into 10 % aqueous $NaHSO_4$ (300 mL). The resulting biphasic mixture was extracted with EtOAc (2 x 200 mL) and the organic phase washed with saturated $NaHCO_3$ and brine (200 mL each), dried over $MgSO_4$ and concentrated in vacuo. The resulting yellow oil was purified by flash chromatography using ethyl acetate - hexanes (3:7) as eluant to afford the dibenzyloxy carbonyl - bispyrrolinone (2.5 g, 80% yield) as a yellow oil: $[\alpha]^{23}_D$ +47.9° (*c* 1.07, $CHCl_3$); IR (neat, film) 2955 (m), 1698 (s), 1614 (s), 1402 (s), 1278 (s), 1057 (s), 860 (m), 836 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.65 (br s), 8.41 (m), 8.25 (s), 8.35 (m), 5.24 (m), 4.60 (s), 4.08 (m), 3.57 (m), 3.50 (d, *J* = 6.3 Hz), 3.48 (d, *J* = 6.7 Hz), 3.23 (br s), 3.13 (br s), 3.04 (m), 2.81 (m), 2.43 (m), 2.11 (m), 1.84 (m), 1.55 (m), 1.42 (br s), 1.34 (br s), 1.17 (m), 0.90 (m), 0.79 (m), 0.70 (m), 0.57 (m), -0.01 (br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ (complex spectrum due to rotomers); high resolution mass spectrum (ESI) *m/z* 843.4225 $[(M + Na)]^+$, calcd for $C_{45}H_{64}N_2O_{10}SiNa$ 843.4228.

Alcohol (+)-11. To a solution of (+)-**10** (640 mg, 0.78 mmol) in a 1:1 mixture of THF and methanol (60 mL) was added *p*-TsOH (445 mg, 2.3 mmol). The solution was heated at 40 °C for 2.5 h and was then cooled to room temperature and diluted with Et_2O and saturated $NaHCO_3$ (200 mL each). The resulting biphasic mixture was extracted with Et_2O (2 x 100 mL) and washed with brine (100 mL). The yellow solution was then dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography using ethyl acetate - hexanes (1:1) as eluant to afford the dibenzyloxy carbonyl - bispyrrolinone alcohol (500 mg, 93% yield) as a yellow oil: $[\alpha]^{23}_D$ +22.0° (*c* 1.22, $CHCl_3$); IR ($CHCl_3$) 3520 (b), 2956 (m), 1722 (m), 1693 (m), 1682 (m), 1606 (m), 1402 (m), 1203 (m), 1148 (m), 1062 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.13 (s), 8.44 (m), 8.24 (m), 7.35 (m), 5.27 (m), 5.06 (m), 4.07 (m), 3.93 (m), 3.73 (m), 3.52 (m), 3.44 (m), 3.18 (br s), 3.11 (br s), 3.04 (br s), 2.96 (br s), 2.92 (br s), 2.67 (m), 2.50 (m), 2.16 (m), 1.90 (m), 1.60 (m), 1.41 (m), 1.23 (m), 1.15 (d, J = 7.1 Hz), 0.82 (m), 0.74 (m), 0.66 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ (complex spectrum due to rotomers); high resolution mass spectrum (ESI) *m/z* 713.3416 $[(M + Na)]^+$, calcd for $C_{39}H_{50}N_2O_9Na$ 713.3414.

Bispyrrolinone Acid. To a solution of (+)-**11** (426 mg, 0.62 mmol) in dichloromethane (8 mL) was added Dess-Martin periodinane (928 mg, 2.5 mmol). The heterogeneous mixture was stirred under air for 1.5 h. To the mixture was added saturated $NaHCO_3$ (30 mL), $Na_2S_2O_3$ (30 mL), and Et_2O (40 mL). The mixture was stirred until the Et_2O layer was clear (ca. 30 min). The resulting biphasic mixture was extracted with Et_2O (3 x 40 mL) and the organic phase washed with saturated $NaHCO_3$ and brine (40 mL each), dried over $MgSO_4$ and concentrated in vacuo.

To a solution of the above residue in *t*-BuOH (20 mL) was added 2-methyl-2-butene (1.21 mL, 2.4 mmol) and premixed $NaClO_2$ (164 mg, 1.8 mmol) and $Na_2H_2PO_4$ (142 mg, 0.9 mmol) in water (4 mL). The solution was stirred for 2 h and then 10 % aqueous $NaHSO_4$ (80 mL) and Et_2O (80 mL) was added. The resulting biphasic mixture was extracted with Et_2O (3 x 80 mL) and dried over $NaSO_4$ and concentrated in vacuo. The resulting clear oil was purified by flash chromatography using ethyl acetate - acetic acid - hexanes (49:1:50) as eluant to afford the dibenzyloxy carbonyl - bispyrrolinone acid (350 mg, 81 % yield, 2 steps) as a clear oil: $[\alpha]^{23}_D$ +67.4° (*c* 2.78, $CHCl_3$); IR ($CHCl_3$) 2956 (m), 1698 (m), 1605 (m), 1402 (m), 1360 (m), 1200 (m), 1147 (m), 1091 (m), 1058 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.69 (br s), 8.58 (br s), 8.43 (br s), 7.35 (m), 5.27 (m), 5.14 (m), 4.09 (m), 3.54 (m),

3.23 (br s), 3.13 (br s), 3.04 (br s), 2.97 (br s), 2.46 (m), 2.23 (m), 2.09 (m), 1.87 (m), 1.56 (br s), 1.42 (m), 1.24 (m), 0.79 (m), 0.70 (br s), 0.59 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ (complex spectrum due to rotomers); high resolution mass spectrum (ESI) *m/z* 727.3224 [(M + Na)]$^+$, calcd for $C_{39}H_{48}N_2O_{10}Na$ 727.3207.

Ester (+)-12. To a solution of (+)-bispyrrolinone acid (64 mg, 0.1 mmol) in DMF (3 mL) was added diisopropylcarbodiimide (34 mg, 0.3 mmol), 1-hydroxybenzotriazol (37 mg, 0.3 mmol), and DMAP (ca. 1 mg). After 5 min, absolute ethanol (0.02 mL, 0.3 mmol) was added and the solution stirred for 7 h. The solution was diluted water and Et_2O (40 mL each), separated, and washed with brine (50 mL). The solution was then dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography using ethyl acetate - hexanes (4:6) as eluant to afford the dibenzyloxy carbonyl - bispyrrolinone ethyl ester (39 mg, 58% yield) as a light yellow oil: $[\alpha]^{23}_D$ +89.9° (*c* 2.00, $CHCl_3$); IR ($CHCl_3$) 3019 (m), 3012 (m), 2961 (m), 1726 (s), 1608 (m), 1404 (s), 1224 (s), 1060 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.67 (br s), 8.54 (br s), 8.42 (br s), 7.38 (m), 5.26 (m), 4.12 (m, 4 H), 4.07 (br s), 3.51 (q, *J* = 7.1 Hz, 1 H), 3.45 (m), 3.24 (br s), 3.14 (br s), 3.05 (br s), 2.98 (br s), 2.45 (m), 2.10 (m), 1.86 (m), 1.56 (m), 1.41 (m), 1.26 (br s), 1.21 (t, *J* = 7.1 Hz), 0.80 (m), 0.72 (br s), 0.59 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ (complex spectrum due to rotomers); high resolution mass spectrum (ESI) *m/z* 755.3535 [(M + Na)]$^+$, calcd for $C_{41}H_{52}N_2O_{10}Na$ 755.3520.

Acid (+)-13. To a solution of (+)-**12** (70 mg, 0.1 mmol) in wet THF (3 mL) was added *p*-TsOH (184 mg, 1 mmol). The solution was heated at 40 °C for 3 h and was then cooled to room temperature and diluted with Et_2O (20 mL) and saturated $NaHCO_3$ (30 mL). The resulting biphasic mixture was extracted with Et_2O (3 x 20 mL) and washed with brine (20 mL). The solution was then dried over $MgSO_4$ and concentrated in vacuo.

To a solution of the above residue in *t*-BuOH (3.5 mL) was added 2-methyl-2-butene (0.19 mL, 0.38 mmol) and premixed $NaClO_2$ (26 mg, 0.3 mmol) and $Na_2H_2PO_4$ (22 mg, 0.14 mmol) in water (0.7 mL). The solution was chilled to 0 °C and stirred for 1.5 h. To the mixture was added 10 % aqueous $NaHSO_4$ (50 mL) and Et_2O (50 mL). The resulting biphasic mixture was extracted with Et_2O (3 x 40 mL) and dried over $NaSO_4$ and concentrated in vacuo. The resulting clear oil was purified by flash chromatography using ethyl acetate - acetic acid - hexanes (49:1:50) as eluant to afford the dibenzyloxy carbonyl - bispyrrolinone acid (40 mg, 59 % yield, 2 steps) as a light

yellow oil: $[\alpha]^{23}_D$ +68.2° (*c* 1.54, $CHCl_3$); IR ($CHCl_3$) 3019 (m), 2962 (w), 1727 (s), 1609 (w), 1405 (s), 1212 (s), 1091 (w), 1061 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.46 (m), 7.36 (m), 5.22 (m), 4.12 (m,), 3.54 (m), 3.20 (br s), 2.74 (m), 2..49 (br s), 2.20 (m), 2.04 (m), 1.79 (br s), 1.58 (br s), 1.40 (m), 1.26 (br s), 1.21 (t, *J* = 7.1 Hz), 0..78 (m), 0.71 (m), 0.69 (m), 0.63 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ (complex spectrum due to rotomers); high resolution mass spectrum (ESI) *m/z* 725.3046 $[(M + Na)]^+$, calcd for $C_{39}H_{46}N_2O_{10}Na$ 725.3050.

Protected Bispyrrolinone. To a solution of (+)-**13** (25 mg, 0.04 mmol) in dichloromethane (2 mL) at 0 °C was added EDCI•HCl (10 mg, 0.054 mmol) and 1-hydroxybenzotriazole (7 mg, 0.054 mmol) and stirred for 30 min. The solution was warmed to room temperature for 1 h then cooled to 0 °C. To the solution was added *O*-benzylhydroxylamine•HCl (17 mg, 0.108 mmol) and diisopropylethylamine (0.04 mL, 0.252 mmol) and stirred for 4 h. The solution was diluted with water and Et_2O (30 mL each) then washed with saturated $NaHCO_3$ and brine (20 mL each), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography using methnaol - dichloromethane (3:47) as eluant to afford the dibenzyloxycarbonyl-bispyrrolinone *O*-benzylhydroxyl-amide (26 mg, 90% yield) as a light yellow oil: $[\alpha]^{23}_D$ +72.6° (*c* 0.34, $CHCl_3$); IR ($CHCl_3$) 3018 (w), 3010 (w), 2962 (w), 1726 (s), 1607 (w), 1404 (s), 1210 (s), 1091 (w), 1061 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.41 (m, 3H), 7.34 (m), 5.28 (m), 5.08 (m), 4.81 (m), 4.12 (q, *J* = 7.1 Hz, 2 H), 3.52 (m, 1 H), 2.86 (br s), 2.48 (br s), 2.16 (br s), 2.00 (br s), 1.88 (m), 1.59 (m), 1.39 (m), 1.26 (br s), 1.21 (t, *J* = 7.1 Hz, 3 H), 0.88 (m), 0.78 (m), 0.69 (m), 0.62 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ (complex spectrum due to rotomers); high resolution mass spectrum (ESI) *m/z* 830.3664 $[(M + Na)]^+$, calcd for $C_{46}H_{53}N_3O_{10}Na$ 830.3629.

Bispyrrolinone Hydroxamic Acid (-)-1. To a solution of (+)-dibenzyloxycarbonyl-bispyrrolinone *O*-benzylhydroxylamide (26 mg, 0.032 mmol) in ethanol (6 mL) was added 5% $Pd/BaSO_4$ (26 mg) and stirred under a hydrogen atmosphere (hydrogen filled balloon) for 17 h. The heterogeneous mixture was filtered through a 0.45 μm filter disc syringe 1/4 filled with celite and then concentrated in vacuo. The resulting residue was purified by flash chromatography using isopropyl alcohol - hexanes (3:7) as eluant to afford the hydroxamic bispyrrolinone (8 mg, 57 % yield) as a light yellow film: $[\alpha]^{23}_D$ -172.5° (*c* 0.80, $CHCl_3$); IR ($CHCl_3$) 3243 (w), 3021 (w), 2959 (w), 2929 (w), 2872 (w), 1724 (w), 1650 (m), 1576 (m), 1446 (w), 1174 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (concentration

dependent spectrum) 10.10 (s br, 1 H), 8.31 (s, 1 H), 8.01 (d, J = 3.7 Hz, 1 H), 7.51 (s, 1 H), 7.27 (s, 1 H), 4.12 (q, J = 6.9, 7.4 Hz, 2 H), 3.49 (q, J = 6.9, 7.4 Hz, 1 H), 2.54 (d, J = 13.9 Hz, 1 H), 2.29 (d, J = 14.3 Hz, 1 H), 1.94 (m, 1H), 1.63 (m, 5 H), 1.40 (s, 1 H), 1.32 (d, J = 7.4 Hz, 3 H), 1.23 (t, J = 6.9 Hz, 3 H), 0.86 (d, J = 6.0 Hz, 3 H), 0.81 (d, J = 6.5 Hz, 3 H), 0.78 (d, J = 6.5 Hz, 3 H), 0.66 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.39, 201.62, 174.95, 167.01, 162.57, 162.04, 111.49, 108.98, 68.93, 68.09, 60.71, 46.45, 43.51, 40.45, 33.79, 24.58, 24.49, 24.29, 24.15, 23.78, 23.48, 17.44, 14.14; high resolution mass spectrum (ESI) *m/z* 472.2432 [(M + Na)]$^+$, calcd for $C_{23}H_{35}N_3O_6Na$ 472.2424.

Bispyrrolinone Carboxylic Acid (-)-14. To a solution of (+)-**13** (11 mg, 0.016 mmol) in ethanol (3 mL) was added 5% Pd/$BaSO_4$ (10 mg) and stirred under a hydrogen atmosphere (hydrogen filled balloon) for 2 h. The heterogeneous mixture was filtered through a 0.45 μm filter disc syringe 1/4 filled with celite and concentrated in vacuo. The resulting residue was purified by flash chromatography using acetic acid - methanol - dichloromethane (1:10:90) as eluant to afford the carboxylic bispyrrolinone (4 mg, 58 % yield) as a light yellow film: $[\alpha]^{23}_D$ -235.1° (*c* 0.70, $CHCl_3$); IR ($CHCl_3$) 3436 (m), 3026 (m), 3018 (m), 2958 (s), 2932 (s), 2872 (m), 1723 (s), 1648 (s), 1576 (s), 1448 (s), 1368 (m), 1168 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (concentration dependent spectrum) 8.30 (d, J = 3.3 Hz, 1 H), 7.98 (d, J = 2.9 Hz, 1 H), 7.12 (s, 1 H), 6.72 (s, 1 H), 4.12 (q, J = 7.5, 7.0 Hz, 2 H), 3.50 (q, J = 7.1 Hz, 1 H), 2.69 (d, J = 16.4 Hz, 1 H), 2.41 (d, J = 16.8 Hz, 1 H), 1.95 (m, 1H), 1.82 (dd, J = 14.1, 4.8 Hz, 1 H), 1.63 (m, 4 H), 1.42 (m, 1 H), 1.31 (d, J = 7.1 Hz, 3 H), 1.23 (t, J = 7.1 Hz, 3 H), 0.87 (d, J = 6.3 Hz, 3 H), 0.82 (d, J = 6.3 Hz, 3 H), 0.80 (d, J = 6.7 Hz, 3 H), 0.67 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.48, 201.62, 174.84, 173.38, 162.04, 161.69, 111.68, 108.89, 68.12, 67.96, 60.72, 46.67, 43.31, 41.23, 33.68, 24.62, 24.42, 24.27, 24.23, 23.79, 23.38, 17.53, 14.14; high resolution mass spectrum (ESI) *m/z* 457.2317 [(M + Na)]$^+$, calcd for $C_{23}H_{34}N_2O_6Na$ 457.2315.