CHEMISTRY
A EUROPEAN JOURNAL

Supporting Information

Dynamic Kinetic Asymmetric Transformation of Butadiene Monoepoxide: Enantioselective Synthesis of DMDP, Bulgecinine, and Broussonetine G

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Experimental Section

General:

All reactions were run under an atmosphere of argon unless otherwise indicated. Anhydrous solvents were transferred by an oven-dried syringe or cannula. Flasks were flame-dried under vacuum and cooled under a stream of nitrogen or argon. Benzene, pyridine, diisopropylamine, triethylamine, diisopropylethylamine, and dimethylsulfoxide were distilled from calcium hydride. Acetonitrile, toluene, diethyl ether, and dichloromethane were purified with a Solv-Tek solvent purification system by passing through a column of activated alumina. Tetrahydrofuran (THF), and dimethoxyethane (DME) were distilled from sodium benzophenone ketyl. Acetone was distilled from calcium sulfate, and hexane was distilled from sodium. Methanol was distilled from magnesium methoxide.

Analytical thin layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (DC-Fertigplatten Krieselgel 60 F_{254}). Preparative column chromatography employing silica gel was performed according to the method of Still. Solvents for chromatography are listed as volume:volume ratios.

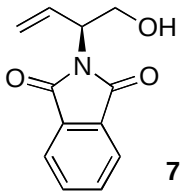
Melting points were determined on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. Absorbance frequencies are reported in reciprocal centimeters (cm^{-1}). Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona. High resolution mass spectra (HRMS) were obtained from the Mass Spectrometry Regional Center of the University of California-San Francisco on a Kratos MS-90 mass spectrometer with an ionizing current of 98 A and an ionizing voltage of 79 eV and reported as m/e (relative intensity). Accurate masses are reported for the molecular ion (M^+) or a suitable fragment ion. Low resolution CI mass spectral data was obtained using an AX-505H mass spectrometer (JEOL, USA, Inc.).

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded using a Varian UI-500 (500 MHz), Varian XL-400 (400 MHz), Varian Gemini 300 (300 MHz), or Varian Gemini 200 (200 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, part per million (ppm) downfield from tetramethylsilane (TMS) or in ppm relative to the singlet at 7.24 ppm for deuterochloroform. Coupling constants are reported in Hertz (Hz). The following abbreviations are used: s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet.

Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded using a Varian UI-500 (125 MHz), Varian XL-400 (100 MHz), Varian Gemini 300 (75 MHz), or Varian Gemini 200 (50 MHz) spectrometer. Chemical shifts are reported in delta (δ) units,

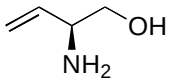
part per million (ppm) relative to the center line of the triplet at 77.00 ppm for deuterochloroform. ^{13}C NMR spectra were routinely run with broadband decoupling.

Optical rotation data was obtained with a Jasco DIP-360 digital polarimeter at the sodium D line (589 nm) in the solvent and concentration indicated.



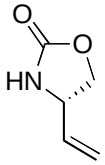
7

(*S*)-N-(1-hydoxymethyl-2-propenyl)phthalimide (7). To a 500 mL flask was added sodium carbonate (171 mg, 1.61 mmol) and the flask was flame-dried under vacuum. After cooling under nitrogen, phthalimide **5** (4.75 g, 32 mmol, recrystallized from hot ethanol), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (47 mg, 0.13 mmol), and (*R*,*R*)-**6** (307 mg, 0.39 mmol) were added and the flask flushed with 3 times with argon. 325 mL dry CH_2Cl_2 (degassed with argon for 30 min) was added and the orange/yellow suspension stirred 15 min. Butadiene monoxide **4** (2.10 g, 30.0 mmol) was added and the yellow solution stirred at rt for 10 h. The reaction was concentrated and the orange residue purified by flash chromatography (silica gel, gradient elution 2:3 PE:Et_2O) to yield 5.85 g **7** (90%) as a white solid. Enantiomeric excess was determined to be 98% ee by chiral HPLC (Chiralpak OD, 90:10 heptane:*i*PrOH, 1.0 mL/min, 13.25 min *R* and 17.40 min *S*). mp 56-57 °C (PE/Et_2O) [lit. mp 58 °C]; $[\alpha]_D^{25}$ = -74 (c 1.02, CH_2Cl_2); R_f = 0.23 (1:1 PE/Et_2O); IR (thin film) 3464, 1774, 1710, 1468, 1388, 1360, 1064, 1027, 719 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 2H), 7.74 (m, 2H), 6.17 (ddd, J=17.1, 10.5, 6.6 Hz, 1H), 5.29 (d, J=10.5 Hz, 1H), 5.28 (d, J=17.1 Hz, 1H), 4.94 (m, 1H), 4.66 (m, 1H, OH), 4.15 (ddd, J=11.7, 8.7, 7.8 Hz, 1H), 3.98 (ddd, J=11.7, 4.5, 3.9 Hz, 1H) ppm; ^{13}C NMR (75 MHZ, $CDCl_3$) δ 168.5, 134.0, 131.9, 131.6, 123.3, 118.8, 62.6, 55.9 ppm.



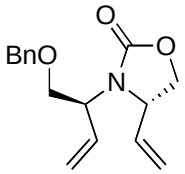
(*S*)-2-amino-3-buten-1-ol To a solution of **7** (49.79 g, 0.230 mol) in 800 mL ethanol was added ethylenediamine (31 mL, 0.46 mol) and the solution was heated to reflux for 4 h. The solution was cooled to room temperature and the white solid removed by filtration through a pad of Celite. The solid was washed with 2x100 mL EtOH and the combined washings were dried over $MgSO_4$ and concentrated. The crude was distilled under nitrogen (oil bath

temperature 180 °C) and the remaining residue was then distilled under vacuum (100-10 torr) to yield 24g clear light yellow oil consisting of a mixture of (*S*)-2-amino-3-buten-1-ol and ethylenediamine. The residue was then further purified by flash chromatography (silica gel, MeOH) to yield 16.8 g (*S*)-2-amino-3-buten-1-ol (84%) as a clear, colorless oil. $[\alpha]_D^{25}$ = -20 (c 1.01, CH_2Cl_2); R_f = 0.25 (MeOH); IR (thin film) 3354, 2869, 1644, 1591, 1458, 1425, 1361, 1143, 1052, 996, 922, 859, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (ddd, J=17.4, 10.5, 5.7 Hz, 1H), 5.24 (dd, J=17.1, 0.9 Hz, 1H), 5.16 (dd, J=10.5, 0.9 Hz, 1H), 3.62 (dd, J=10.2, 3.9 Hz, 1H), 3.47 (m, 2H), 3.36 (dd, J=10.2, 7.5 Hz, 1H), 1.99 (bs, 2H, NH_2) ppm; ^{13}C NMR (75 MHZ, $CDCl_3$) δ 139.3, 115.4, 66.2, 55.5 ppm. Anal: Calc'd for $C_7H_7NO_2$: C, 55.15; H, 10.41; N, 16.08; found: C, 55.31; H, 10.78; N, 16.35.



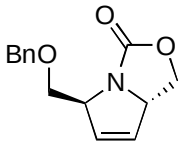
8

(*S*)-4-vinyl-1,3-oxazolidin-2-one (8). To a solution of (*S*)-2-amino-3-buten-1-ol (15.0 g, 17.2 mmol) in 500 mL 10% aqueous $NaHCO_3$ and 125 mL toluene was added a solution of triphosgene (17.0 g, 57 mmol) in 100 mL toluene at 0°C over 1 h. The reaction was stirred at 0 °C for 1h, then warmed to room temperature and stirred an additional 4 h. The crude reaction mixture was diluted with 300 mL CH_2Cl_2, extracted, then the aqueous layer was extracted with 2 x 300 mL additional CH_2Cl_2, the organic layers were combined, dried over $MgSO_4$ and concentratrated *in vacuo*. The crude residue was purified by flash chromatography (silica gel, 50:1 Et_2O:MeOH) to yield 16.6 g **8** (85%) as a clear, colorless oil. $[\alpha]_D^{25}$ = -23 (c 1.07, CH_2Cl_2); R_f = 0.50 (20:1 Et_2O:MeOH); IR (thin film) 3286, 2988, 2914, 1748, 1647, 1538, 1480, 1401, 1349, 1320, 1290, 1236, 1095, 1050, 1024, 992, 935, 770, 724 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.17 (bs, 1H, NH), 5.83 (ddd, J=17.1, 10.2, 7.2 Hz, 1H), 5.33 (dd, J=17.1, 0.6 Hz, 1H), 5.26 (d, J=10.2 Hz, 1H), 4.55 (dd, J=8.6 Hz, 1H), 4.40 (dd, J=7.5, 0.9 Hz, 1H), 4.07 (dd, J=8.6, 6.5 Hz, 1H) ppm; ^{13}C NMR (75 MHZ, $CDCl_3$) δ 159.3, 135.6, 118.8, 69.9, 55.2 ppm. Anal: Calc'd for $C_7H_7NO_2$: C, 53.09; H, 6.24; N, 12.38; found: C, 53.17; H, 6.31; N, 12.78.



11

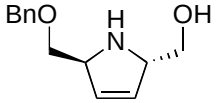
[4*S*,3(1*S*)]-3-[1-benzyloxymethyl-allyl]-4-vinyl-oxazolidin-2-one (11). To a mixture of dienol *anti*-**9** (2.20 g, 12.0 mmol) and tetrabutylammonium iodide (221 mg, 0.60 mmol) in 10 mL THF was added sodium hydride (518 mg, 13.0 mmol, 60% in mineral oil) portionwise over 5 min. The reaction was stirred for 5 min and THF, 5 mL was added to rinse the residue from the sides of the flask. Benzyl bromide (2.16 g, 12.6 mmol) was added over 2 min and the reaction stirred at rt for 18 h under N_2. The reaction was quenched with 20 mL saturated aqueous NH_4Cl and extracted with 1 x 100 mL and 2 x 50 mL Et_2O. The organic layers were combined, dried over $MgSO_4$, and concentrated to yield an oily residue that was purified by flash chromatography (silica gel, 1:1 PE:Et_2O) to yield 2.75 g **11** (84%) as a clear, colorless oil. $[\alpha]_D^{25}$ = -6.2 (c 1.15, CH_2Cl_2); R_f = 0.24 (1:1 Et_2O:PE); IR (thin film) 2959, 2928, 2885, 1752, 1463, 1335, 1110, 943, 820, 763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5H), 5.82 (ddd, J=17.3, 10.2, 7.5 Hz, 1H), 5.70 (ddd, J=17.6, 8.3, 1.2 Hz, 1H), 5.23 (m. 4H), 4.60 (d, J=12.0 Hz, 1H), 4.45 (d, J=12.0 Hz, 1H), 4.51-4.26 (m, 3H), 4.00-3.80 (m, 2H), 3.62 (dd, J=10.3, 5.4 Hz, 1H) ppm; ^{13}C NMR (125 MHZ, $CDCl_3$) δ 157.8, 137.8, 136.1, 133.3, 128.3, 127.8, 127.7, 120.3, 118.5, 72.8, 68.5, 67.1, 58.7, 56.1 ppm. Anal: Calc'd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12; found: C, 70.20; H, 6.90; N, 5.27.



12

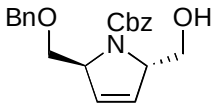
(3*S*,6a*S*)-1,2-Dehydro-3-benzyloxymethyl-5-oxapyrrolizidin-4-one (12). To a solution of diene **2.28** (23.53 g, 86.1 mmol) in 450mL CH_2Cl_2 was degassed with argon for 30 min and the solution was heated to 40 °C. Grubbs' II catalyst, 2 portions (650 mg + 250 mg, 1.06 mmol, 1.2 mol%) in CH_2Cl_2 (each 2 mL) were added after (0 h and 12 h). The reaction was stirred an additional 3 h for a total of reaction time of 15 h then cooled to rt and concentrated. The residue was purified by flash chromatography (silica gel, 4:1 Et_2O:PE) to yield 20.0 g **12** as a pink solid (product contains colored Ru byproducts). The product was dissolved in 500 mL CH_2Cl_2 and 5 mL DMSO was added, the reaction was stirred 12 h under N_2 and chromatographed (silica gel, gradient elution 4:1 ? 9:1 Et_2O:PE) to yield 19.1g **12** (91%, 77.9 mmol) as white crystalline solid. Recrystalization from hot Et_2O (300 mL/5 g product) yields white prisms. mp 156-160 °C; $[\alpha]_D^{25}$ = -135 (c 1.01, CH_2Cl_2); R_f = 0.18 (4:1 PE:Et_2O);

IR (thin film) 2992, 2929, 1746, 1385, 1366, 1222, 1126, 1031, 746 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 5H) 6.00 (d, J=6.1 Hz, 1H), 5.93 (d, J=6.1 Hz, 1H), 4.74 (m, 2H), 4.54 (m, 3H), 4.19 (dd, J=8.5, 5.1 Hz, 1H), 3.53 (d, J=4.9 Hz, 2H) ppm; ^{13}C NMR (75 MHZ, $CDCl_3$) δ 158.2, 133.2, 127.4, 125.5, 123.6, 122.9, 122.7, 68.4, 66.4, 64.0, 62.1, 59.7 ppm. Anal: Calc'd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71; found: C, 68.71; H, 6.02; N, 5.57.



36

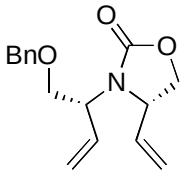
(2*S*,5*S*)-(5-Benzyloxymethyl-2,5-dihydro-1H-pyrrol-2-yl)-methanol (36). To benzyl ether **12** (17.7 g, 80.0 mmol) was added 400 mL 3:1 ethanol:H_2O 1.25 M NaOH. The reaction was heated with a 100 °C oil bath and allowed to reflux for 24 h. The flask was cooled to rt and concentrated to 100 mL. The residue was added to a 200 mL capacity continuous extractor and 100 mL CH_2Cl_2 was added and the solution extracted for 18 h. The CH_2Cl_2 layer was concentrated to yield 15.8 g crude **36** (quantitative, 80.0 mmol) as a brown solid. $[\alpha]_D^{25}$ = -187 (c 0.98, CH_2Cl_2); R_f = 0.10 (20:1 CH_2Cl_2:MeOH); IR (thin film) 3404, 2930, 2865, 1478, 1392, 1219, 970, 805, 740, 670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.78 (d, J=6.1 Hz, 1H), 5.74 (d, J=6.1 Hz, 1H), 4.53 (s, 2H), 4.21 (bs, 2H, -NH,-OH), 3.70-3.49 (m, 4H), 3.45-3.34 (m, 2H) ppm; ^{13}C NMR (75 MHZ, $CDCl_3$) δ 133.2, 125.9, 125.8, 123.6, 122.9, 68.4, 68.1, 61.5, 60.1, 59.7 ppm; $C_{13}H_{17}NO_2$: C, 54.19; H, 5.85; N, 9.03. Found: C, 53.93; H, 6.03; N, 8.90. HRMS (EI+) m/z calculated for $C_{13}H_{18}NO_2$ $[M + H]^+$: 220.1338, found 220.1341.



13

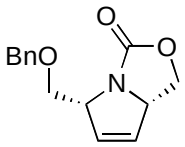
(2*S*,5*S*)-2-Benzyloxymethyl-5-hydroxymethyl-2,5-dihydro-pyrrole-1-carboxylic acid benzyl ester (13). The crude dihydropyrrole **36** (15 g, 68.4 mmol) was added to a solution of 125 mL H_2O with Na_2CO_3 (7.2 g, 68 mmol) and $NaHCO_3$ (7.2 g, 68 mmol). The suspension was stirred in a 0 °C ice bath 20 min and degassed with argon, then benzylchloroformate (23.3 g, 137 mmol) was added dropwise. The reaction was stirred at 0 °C 2.5 h. The reaction was diluted with 100 mL H_2O, extracted with 3 x 150 mL EtOAc, the combined organic layers dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, 100:1 CH_2Cl_2:MeOH) to yield 24.0 g (99%, 67.9 mmol) **13** as a clear, light yellow, viscous oil. $[\alpha]_D^{25}$ = -187 (c 1.019, CH_2Cl_2); R_f = 0.56 (20:1

CH_2Cl_2:MeOH); IR (thin film) 3428, 2920, 1701, 1454, 1416, 1356, 1318, 1105, 735, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 4:1 mixture of amide rotamers **Major**: δ 7.39-7.22 (m, 10H), 5.88 (dt, J=6.3, 2.1 Hz, 1H), 5.68 (dt, J=6.3, 1.7 Hz, 1H), 5.08 (s, 2H), 4.76 (m, 1H), 4.66 (m, 1H), 4.43 (d, J=12.2 Hz, 1H), 4.38 (d, J=12.3 Hz, 1H), 3.86 (dd, J=12.1, 1.5 Hz, 1H), 3.68 (dd, J=9.4, 2.7 Hz, 1H), 3.65 (dd, J=12.2, 6.3 Hz, 1H), 3.54 (dd, J=9.3, 6.1 Hz, 1H) ppm; **Minor**: δ 7.39-7.22 (m, 10H), 5.98 (d, J=6.5 Hz, 1H), 5.77 (d, J=6.5 Hz, 1H), 5.17 (d, J=12.3 Hz, 1H), 5.11 (d, J=12.3 Hz, 1H), 4.76 (m, 1H), 4.66 (m, 1H), 4.49 (m, 2H), 3.85 (m, 2H) ppm; ^{13}CNMR (125 MHZ, $CDCl_3$) δ 156.2, 138.4, 136.3, 129.8, 128.9, 128.8, 128.7, 128.6, 128.5, 128.5, 128.4, 128.0, 127.7, 73.6, 73.5, 70.6, 69.7, 69.4, 67.7, 67.3, 67.2, 66.6, 66.0, 65.4, 63.7 ppm; HRMS (EI+) m/z calculated for $C_{21}H_{23}NO_4$ $[M - CH_2OH]^+$: 322.1446, found: 322.1443.



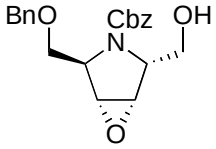
14

[4*S*,3(1*R*)]-3-[1-benzyloxymethyl-allyl]-4-vinyl-oxazolidin-2-one (14). To a mixture of dienol *syn*-**9** (220 mg, 1.2 mmol) and tetrabutylammonium iodide (10 mg, 0.027 mmol) in 1 mL THF was added sodium hydride (52 mg, 1.3 mmol, 60% in mineral oil). The reaction was stirred for 10 min then benzyl bromide (216 mg, 1.26 mmol) was added and the reaction stirred at rt for 12 h under N_2. The reaction was quenched with 2 mL saturated aqueous NH_4Cl, diluted with 2 mL H_2O, and extracted with 1 x 5 mL then 2 x 50 mL Et_2O. The organic layers were combined, dried over $MgSO_4$, and concentrated to yield an oily residue that was purified by flash chromatography (silica gel, 1:1 PE:Et_2O) to yield 277 mg **14** (84%) as a clear, colorless oil. $[\alpha]_D^{26}$ = -3.2 (c 1.17, CH_2Cl_2); R_f = 0.40 (4:1 Et_2O:PE); IR (thin film) 3086, 3030, 3985, 2907, 2865, 1748, 1644, 1496, 1479, 1454, 1404, 1336, 1248, 1224, 1104, 1062, 992, 933, 738, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.97 (ddd, J=17.6, 10.7, 6.8 Hz, 1H), 5.72 (ddd, J=16.8, 9.8, 8.3 Hz, 1H), 5.30 (d, J=17.3 Hz, 1H), 5.24-5.21 (m, 3H), 4.52 (m, 2H), 4.38 (m, 2H), 4.25 (m, 1H), 3.90 (m, 2H), 3.57 (dd, J=9.8, 5.6 Hz, 1H) ppm; ^{13}C NMR (75 MHZ, $CDCl_3$) δ 157.4, 138.0, 136.0, 132.6, 128.3, 127.8, 127.6, 120.4, 118.8, 73.0, 69.8, 67.3, 60.2, 56.1 ppm. Anal: Calc'd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12; found: C, 70.44; H, 7.10; N, 5.21.



15

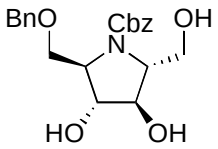
(3*R*,6a*S*)-1,2-Dehydro-3-benzyloxymethyl-5-oxapyrrolizidin-4-one (15). A solution of diene **14** (50 mg, 0.18 mmol) in 0.5 mL CH_2Cl_2 was degassed with argon for 5 min and the solution was heated to 40°C. Grubbs' II catalyst, 3 portions (4.7, 2.3, and 2.5 mg, 0.011 mmol, 6 mol%) were added after (0 h, 8 h, and 4 h). The reaction was stirred an additional 10 h for a total of reaction time of 24 h then cooled to rt and concentrated. The residue was purified by flash chromatography (silica gel, gradient elution 1:1 ? 2:1 Et_2O:PE) to yield 38 mg **15** (85%) as a clear, light yellow oil. $[\alpha]_D^{25}$ = -10.7 (c 2.54, CH_2Cl_2); R_f = 0.18 (4:1 Et_2O:PE); IR (thin film) 3030, 2870, 1748, 1454, 1364, 1261, 1212, 1111, 1075, 1034, 819, 734, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5H) 5.87 (dt, J=6.3, 1.7 Hz, 1H), 5.83 (dt, J=6.1, 1.7 Hz, 1H), 4.97 (m, 1H), 4.60 (d, J=11.6 Hz, 1H), 4.49-4.41 (m, 1H), 4.44 (d, J=11.6 Hz, 1H), 4.38 (m, 1H), 4.22 (dd, J=9.9, 3.8 Hz, 1H), 4.00 (dd, J=10.2, 7.9 Hz, 1H), 3.78 (dd, J=9.9, 2.0 Hz, 1H) ppm; ^{13}C NMR (75 MHZ, $CDCl_3$) δ 159.3, 138.0, 133.1, 128.3, 127.8, 127.6, 126.8, 73.1, 69.7, 67.0, 65.2, 64.9 ppm; EA calculated for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71; found: C, 68.48; H, 6.10, N, 5.89.



16

(1*R*,2*R*,4*R*,5*S*)-*N*-Benzyloxycarbonyl-2-benzyloxymethyl-4-hydroxymethyl-6-oxa-3-aza-bicyclo[3.1.0]hexane (16). To a flame-dried test tube with methyltrioxorhenium(VII) [MTO] (12 mg, 0.047 mmol, 5 mol%) and urea hydrogen peroxide complex [UHP] (170 mg, 1.8 mmol) under N_2 is added 1 mL CH_2Cl_2 and the resulting yellow solution stirred 10 min at rt. A solution of **13** (270 mg, 0.77 mmol) in 1 mL CH_2Cl_2 was added via syringe and the solution stirred at rt 68 h. The resulting white suspension was diluted with 5 mL CH_2Cl_2, extracted with 5 mL H_2O, 5 mL saturated aqueous $Na_2S_2O_3$, 5 mL saturated aqueous NaCl, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (silica gel, gradient elution 4:1 ? 2:1 PE:EtOAc) to yield 215 mg **16** (76%) as a clear, colorless oil. The compound is isolated as a single diastereomer by ^1H NMR analysis (>25:1 dr).$[\alpha]_D^{23}$ = -93 (c 1.08, $CHCl_3$); R_f = 0.40 (1:1 PE:EtOAc); IR (NaCl, thin film) 3435, 3063, 3032, 2903, 2864, 1682, 1497, 1454, 1428, 1397, 1356, 1330, 1114, 1038, 979, 861, 774, 740, 700 cm^{-1}; ^1H

NMR (500 MHz, $CDCl_3$) 9:1 mixture of amide rotamers **Major** δ 7.32 (m, 10H) 5.06 (d, J=12.1 Hz, 1H), 5.01 (d, J=12.2 Hz, 1H), 4.86 (d, J=9.8 Hz, 1H), 4.43 (d, J=12.2 Hz, 1H), 4.37 (d, J=12.2 Hz, 1H), 4.17 (d, J=2.6 Hz, 1H), 4.04-3.88 (m, 3H), 3.71 (m, 1H), 3.61 (dd, J=9.8, 4.9 Hz, 1H), 3.58 (d, J=3.2 Hz, 1H), 3.56 (d, J=9.9 Hz, 1H) ppm; ^{13}C NMR (125 MHZ, $CDCl_3$ with DEPT) δ 156.2 (C), 137.5 (C), 135.7 (C), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.0 (CH), 127.7 (CH), 127.3 (CH), 73.1 (CH_2), 68.1 (CH_2), 67.4 (CH_2), 63.3 (CH_2), 63.0 (CH), 59.7 (CH), 57.6 (CH), 55.4 (CH) ppm; EA calculated for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.12; H, 6.35; N, 3.67; HRMS (EI+) m/z calculated for $C_{21}H_{23}NO_5$ $[M]^+$: 369.1576, found: 369.1581.



16a

(2*R*,3*R*,4*R*,5*R*)-*N*-Benzyloxycarbonyl-2-benzyloxymethyl-3,4-dihydroxy-5-hydroxymethylpyrrolidine (16a). To a solution of **16** (230 mg, 0.59 mmol) in 12 mL 3:2 THF:H_2O is added TFA (50 μL, 0.64 mmol). The reaction is stirred at 65 °C for 12 h, only 25% conversion (TLC). An additional portion of TFA (100 μL, 1.28 mmol) is added and the reaction stirred 22 h at 65 °C at which time the reaction is complete. The reaction is quenched with 5 mL saturated aqueous $NaHCO_3$ and extracted with 3 x 5 mL Et_2O. The organic layers were combined, washed with 5 mL saturated aqueous NaCl, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (silica gel, 4:1 EtOAc:PE) to yield 165 mg **16a** (72%) as a clear, colorless oil. $[\alpha]_D^{28}$ = -79 (c 1.56, $CHCl_3$); R_f = 0.10 (1:1 EtOAc:PE); IR (NaCl, thin film) 3392, 2929, 1698, 1676, 1417, 1353, 1077, 1026, 740, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) Spectra complicated by 1:1 mixture of amide rotamers δ 7.34 (m, 12H) 7.24 (m, 8H), 5.16 (d, J=12.4 Hz, 1H), 5.12 (d, J=12.4 Hz, 1H), 5.07 (d, J=12.1 Hz, 1H), 5.00 (d, J=12.1 Hz, 1H), 4.92 (d, J=11.9 Hz, 1H), 4.82 (d, J=11.6 Hz, 1H), 4.63 (bs, 2H), 4.56 (d, J=11.7 Hz, 1H), 4.49 (d, J=13.3 Hz, 1H), 4.45 (s, 1H), 4.40 (d, J=11.9 Hz, 1H), 4.26 (dd, J=9.8, 2.8 Hz, 1H), 4.12 (dd, J=11.3, 3.7 Hz, 1H), 4.00 (m, 9H), 3.90 (dd, J=9.8, 3.2 Hz, 1H), 3.74 (dd, J=10.7, 1.9 Hz, 1H), 3.69 (d, J=10.4 Hz, 1H), 3.59 (dd, J=9.8, 1.5 Hz, 1H), 3.53 (dd, J=9.8, 1.4 Hz, 1H), 2.81 (bs, 2H) ppm; ^{13}C NMR (100 MHZ, $CDCl_3$) δ 154.7, 154.6, 136.4, 136.0, 128.7, 128.62, 128.61, 128.56, 128.4, 128.3, 128.24, 128.20, 128.1, 128.0, 127.9, 127.8, 80.3, 80.0, 79.3, 79.1, 73..8, 73.6, 69.9, 69.2, 68.9, 68.5, 67.6, 67.5, 67.2, 67.1, 62.0, 61.1 ppm; EA calculated for $C_{20}H_{22}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.12; H, 6.35; N, 3.67; MS (+ESI) m/z calculated for $C_{21}H_{26}NO_6$ [M +

H]$^+$: 388.3, found: 388.2; HRMS (EI+) m/z calculated for $C_{20}H_{22}NO_5$ (M^+ – CH_2OH) : 356.1498, found: 356.1508.

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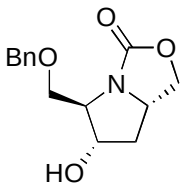
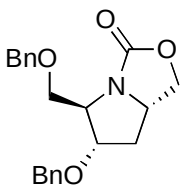


18

(5*R*,6*S*,7a*S*)-5-Benzyloxymethyl-6-hydroxy-tetrahydro-pyrrolo[1,2-c]oxazol-3-one (18).

To a solution of freshly prepared 9-BBN dimer (450 mg, 1.84 mmol) in 2.5 mL THF at rt is added a solution of oxazolidinone **12** (744 mg, 3.03 mmol) in 2.5 mL THF via cannula, 1 mL THF used to rinse flask. The reaction was stirred 21 h at rt. The reaction was cooled to 0 °C, and 10 mL 3 M aqueous NaOH was added followed by dropwise addition of 1 mL 30% aqueous H_2O_2. The reaction was stirred at 0 °C 1 h, then warmed to rt and stirred an additional 4 h. The reaction was diluted with 50 mL H_2O and extracted with 4 x 25 mL Et_2O. The combined organic layers were then washed with 20 mL saturated aqueous K_2CO_3, dried over Na_2SO_4 and concentrated to yield 950 mg crude product as a clear oil. The crude product contains cyclooctane-1,5-diol which is difficult to separate by silica gel chromatography and required two successive columns (silica gel, 1:1 EtOAc:PE) to obtain 597 mg **18** (75%, 2.27 mmol) as a clear white solid. $[\alpha]_D^{25}$ = -48 (c 1.06, $CHCl_3$); R_f = 0.15 (2:1 EtOAc:PE); IR (thin film) 3418, 2920, 2860, 1732, 1454, 1394, 1229, 1121, 1055, 1004, 733, 740, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.26 (m, 5H), 4.57-4.50 (m, 4H), 4.20 (dd, J=8.7, 4.8 Hz, 1H), 4.11-4.06 (m, 1H), 3.93 (dt, J=5.6, 3.8 Hz, 1H), 3.69 (dd, J=9.6, 4.1 Hz, 1H), 3.52 (dd, J=9.6, 6.0 Hz, 1H), 2.40 (p, J=6.1 Hz, 1H), 1.73 (ddd, J=12.9, 7.8, 6.1 Hz, 1H) ppm; ^{13}C NMR (75 MHZ, $CDCl_3$) δ 162.2, 137.7, 128.5, 127.8, 127.6, 76.0, 73.5, 70.4, 69.2, 66.5, 57.4, 40.1 ppm. Anal: Calc'd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 64.00; H, 6.65; N, 5.43.

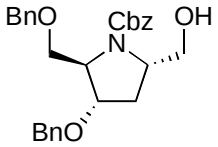


22

(5*R*,6*S*,7a*S*)-6-Benzyloxy-5-benzyloxymethyl-tetrahydro-pyrrolo[1,2-c]oxazol-3-one (22).

To a solution of **18** (263 mg, 1.0 mmol) in 3 mL THF under N_2 is added NaH (47 mg, 60 % in

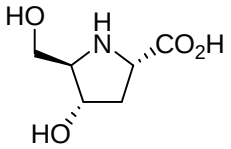
mineral oil, 1.2 mmol). The reaction was stirred at rt 20 min then a solution of TBAI (15 mg, 0.041 mmol, 4 mol%) and benzyl bromide (257 mg, 1.5 mmol) in 2 mL THF was added via cannula. The reaction was stirred 5 h at rt, then quenched with 5 mL half saturated aqueous $NaHPO_4$. The reaction was extracted with 3 x 5 mL Et_2O, the organic layers combined, dried over Na_2SO_4, and concentrated to yield a yellow oil. The residue was purified by flash chromatography (silica gel, 4:1 EtOAc:PE) to yield 165 mg **22** (92%) as a clear, colorless oil. $[\alpha]_D^{26}$ = -34 (c 0.81, $CHCl_3$); R_f = 0.70 (4:1 EtOAc:PE); IR (thin film) 3030, 2919, 2859, 1750, 1454, 1387, 1215, 1064, 737, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.25 (m, 10H), 4.53 (dd, J=12.0, 4.6 Hz, 2H), 4.51 (dd, J=8.5, 4.1 Hz, 2H), 4.41 (d, J=11.7 Hz, 1H), 4.25 (m, 1H), 4.15 (dd, J=8.5, 4.6 Hz, 1H), 4.08 (m, 1H), 3.59 (dd, J=9.9, 4.0 Hz, 1H), 3.55 (dd, J=10.0, 5.1 Hz, 1H), 2.41 (ddd, J=13.2, 7.3, 6.1 Hz, 1H), 1.73 (ddd, J=12.7, 7.3, 4.6 Hz, 1H) ppm; ^{13}C NMR (75 MHZ, $CDCl_3$) δ 161.8, 137.8, 137.6, 128.4, 127.9, 127.73, 127.68, 127.5, 81.9, 73.3, 71.4, 70.4, 69.1, 63.8, 57.5, 38.5 ppm. Anal: Calc'd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.20; H, 6.66; N, 4.13.



23

(2*R*,3*S*,5*S*)--N-Benzyloxycarbonyl-3-benzyloxy-2-benzyloxymethyl-5-hydroxymethyl-pyrrolidine (23). A solution of **22** (50 mg, 0.141 mmol) in 1.5 mL 3:1 EtOH:1.3 M aqueous NaOH was heated in a 85 °C oil bath 12 h. The reaction was cooled to rt and concentrated to yield the amino alcohol as a brown/tan solid. The crude material was carried into the subsequent step without purification. The crude amino alcohol was dissolved in 1.5 mL H_2O, Na_2CO_3 (100 mg, 0.9 mmol) and $NaHCO_3$ (100 mg, 1.2 mmol) were added and the solution was cooled to 0 °C and benzyl chloroformate (100 mg, 0.59 mmol) was added. The reaction was stirred 3 h at 0 °C then warmed to rt. The reaction was extracted with 3 x 5 mL EtOAc, the organic layers combined, washed with 5 mL saturated aqueous NaCl and concentrated to yield 55 mg crude product as a yellow oil. The residue was purified by flash chromatography (silica gel, gradient elution 5:1 ? 2:1 PE:Et_2O) to yield 55 mg **23** (85%) as a clear, light yellow oil. $[\alpha]_D^{27}$ = -21.4 (c 2.12, $CHCl_3$); R_f = 0.21 (2:1 PE:EtOAc); IR (NaCl, thin film) 3422, 1688, 1431, 1356, 1113, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) Spectra complicated by 1:1 mixture of amide rotamers δ 7.33-7.16 (m, 15H) 5.12 (m, 4H), 4.69 (m, 0.5H), 4.55-4.40 (m, 3H), 4.35 (d, J=9.8 Hz, 0.5H), 4.31 (d, J=9.8 Hz, 0.5H), 4.22-4.17 (m, 2H), 4.09=4.04 (m, 2H), 3.70 (dd, J=9.5, 2.7 Hz, 0.5H), 3.57 (dd, J=9.6, 6.4 Hz, 0.5H), 3.53 (dd, J=9.3, 3.5 Hz,

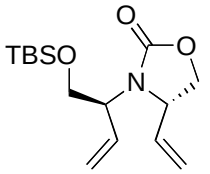
0.5H), 3.31 (dd, J=9.7, 7.1 Hz, 0.5H), 2.17 (m, 2H) ppm; ^{13}C NMR (100 MHZ, $CDCl_3$) δ 154.3, 154.0, 137.8, 136.4, 128.6, 128.55, 128.49, 128.40, 128.37, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 127.4, 81.4, 80.5, 78.6, 73.3, 70.6, 69.7, 69.2, 68.5, 68.1, 67.1, 64.0, 56.5, 56.1, 32.5, 31.3, 29.7 ppm. Anal: Calc'd for $C_{28}H_{31}NO_5$: C, 72.86; H, 6.77; Found: C, 72.45; H, 6.37.



2

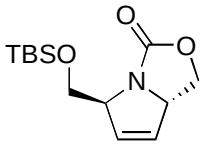
(-)-Bulgecinine (2). To a solution of alcohol **23** (10 mg, 0.022 mmol) in 500 μL acetone is added 100 μL 5% aqueous $NaHCO_3$. The reaction is cooled to 0 °C and KBr (0.5 mg, $4x10^{-3}$ mmol), TEMPO (0.8 mg, $5x10^{-3}$ mmol), and bleach (85 μL, 5.5% in H_2O, 0.06 mmol) were added. The reaction was stirred at 0 °C 2 h, then 2 mL 5% aqueous $NaHCO_3$ was added and the solution concentrated *in vacuo* to remove the acetone. The remaining aqueous solution was extracted with 2 x 5 mL Et_2O. The aqueous layer acidified to pH 4-5 with solid $KHSO_4$ and extracted with 2 x 5 mL EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude acid, 7.8 mg (75%, 0.016 mmol) as a clear, colorless oil.

To a vial with the crude acid from above (6.5 mg, 0.014 mmol) is added 10% Pd/C (5 mg, 0.005 mmol, 34 mol%). The vial was flushed with N_2, then 500 μL MeOH was added followed by one drop concentrated HCl. A baloon of H_2 was bubbled through the reaction 5 min., then the reaction was stirred under H_2 balloon 6.5 h. The reaction was filtered through a plug of Celite and the plug washed with 2 x 3 mL MeOH. The filtrates were combined and concentrated *in vacuo* to yield the crude HCl salt as yellow oil/solid. Purification by ion exchange chromatrography (DOWEX50W-X2) by dissolving in 1 mL H_2O with 1 drop 10% aqueous HCl, and gradient elution with 20 mL H_2O, then 20 mL 1M NH_4OH. The NH_4OH fractions were collected and concentrated *in vacuo* to yield 2.1 mg **2** (95%, 0.0013 mmol) as a clear oil. $[\alpha]_D^{23}$= -13.8 (c=0.21, H_2O); Lit.[1] $[a]_D^{27}$ = -16 (c=2, H_2O); IR (thin film) 3425-2930, 2903, 1633, 1405, 1082, 1043, 764, 707 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 4.31 (m, 1H), 4.11 (dd, J=9.0, 6.5 Hz), 3.91 (dd, J=13.8, 6.6 Hz, 1H), 3.71-3.63 (m, 2H), 2.59 (ddd, J=13.8, 9.0, 5.9 Hz, 1H), 2.08 (ddd, J=13.8, 6.5, 5.1 Hz, 1H) ppm; ^{13}C NMR (100 MHZ, D_2O, CD_3OD standard) δ 174.5, 71.4, 67.3, 59.7, 59.0, 37.3 ppm; EA calculated for $C_6H_{12}NO_4$: C, 44.72; H, 6.88; N, 8.69. Found: C, 44.92; H, 6.66; N, 8.47.



11b

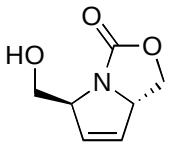
[4*S*,3(1*S*)]-3-[1-(tert-butyldimethylsilyloxy)-methyl-allyl]-4-vinyl-oxazolidin-2-one (11b). A mixture of dienol *anti*-**9** (6.47 g, 35.31 mmol), tert-butyldimethylsilyl chloride (6.90 g, 45.77 mmol), triethylamine (9.71 g, 95.9 mmol), and DMAP (90.0 mg, 0.737 mmol) in 70 mL THF was heated at 50 °C for 20 h. Due to incomplete conversion, tert-butyldimethylsilyl chloride (1.50 g, 10.0 mmol) was added and the reaction stirred an additional 24 h at 50 °C. The reaction was cooled, and 100 mL H_2O was added. Et_2O, 100 mL, was added and the layers separated. The aqueous layer was extracted with 3 x 100 mL Et_2O, the organic layers combined, and dried over $MgSO_4$. The solution was concentrated to yield a residue that was purified by flash chromatography (silica gel, gradient elution 4:1 ? 2:1 PE:Et_2O) to yield 9.79 g **11b** (93%) as a clear, colorless oil. $[\alpha]_D^{25}$ = -6.2 (c 1.15, CH_2Cl_2); R_f = 0.43 (2:1 PE:Et_2O); IR (thin film) 2956, 2930, 2886, 2858, 1756, 1472, 1404, 1338, 1252, 1112, 932, 838, 778 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (ddd, J=18.0, 10.5, 7.8 Hz, 1H), 5.76 (ddd, J=18.3, 9.4, 8.4 Hz, 1H), 5.31 (d, J=16.2 Hz, 1H), 5.27 (d, J=9.0 Hz, 1H), 5.20 (d, J=17.1 Hz, 1H), 5.17 (d, J=10.2 Hz, 1H), 4.37 (m, 2H), 4.07 (m, 1H), 3.94 (m, 1H), 3.93 (dd, J=10.5, 9.0 Hz, 1H), 3.76 (dd, J=10.5, 5.7 Hz, 1H), 0.87 (s, 9H), 0.05 (s, 6H) ppm; ^{13}CNMR (75 MHZ, $CDCl_3$) δ 157.8, 136.4, 133.4, 120.1, 118.5, 67.1, 62.1, 59.1, 58.9, 25.7, 18.1, -5.4, -5.5 ppm. Anal: Calc'd for $C_{15}H_{27}NO_3Si$: C, 60.57; H, 9.15; N, 4.71; found: C, 60.65; H, 8.98; N, 4.83.



12b

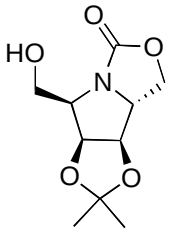
(3*S*,6a*S*)-1,2-dehydro-3-(tert-butyldimethylsilyloxy)methyl-5-oxapyrrolizidin-4-one (12b). To a solution of diene **9a** (8.06g, 27.1 mmol) was added 287 mL CH_2Cl_2 and the solution was degassed with argon for 30 min. The solution was heated to 40 °C and 4 portions of Grubbs' catalyst (each 120 mg, 0.0146 mmol, 0.54%) in CH_2Cl_2 (each 2mL) were added after (0 h, 21.5 h, 64.5 h, and 74.5 h). The reaction was stirred an additional 40 h for a total of reaction time of 4.75 days then cooled to rt and concentrated. The residue was purified by flash chromatography (silica gel, 2:1 PE:Et_2O) to yield recovered starting material, 1.37g (17%) **11b** and 6.02 g **12b** (83%, 99% BRSM, 22.3 mmol) as a clear, slightly gray oil. $[\alpha]_D^{25}$ = -135 (c 1.01, CH_2Cl_2); R_f = 0.20 (2:1 PE:Et_2O); IR (thin film) 2955, 2929,

2858, 1760, 1472, 1384, 1254, 1217, 1130, 1107, 838, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (dd, J=18.6, 6.0 Hz, 1H), 5.94 (dd, J=18.6, 6.0 Hz, 1H), 4.74 (m, 1H), 4.63 (m, 1H), 4.58 (t, J=8.7 Hz, 1H), 4.20 (dd, J=8.7, 5.7 Hz, 1H), 3.71 (m, 2H), 0.88 (s, 9H), 0.04 (s, 6H) ppm; ^{13}CNMR (75 MHZ, $CDCl_3$) δ 162.7, 132.5, 129.9, 68.9, 68.5, 64.8, 64.6, 25.8, 18.2, -5.5 5 ppm. Anal: Calc'd for $C_{13}H_{23}NO_3Si$: C, 57.96; H, 8.60; N, 5.20; found: C, 58.17; H, 8.60; N, 5.29.



30

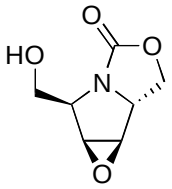
(3S,6aS)-1,2-dehydro-3-hydroxymethyl-5-oxapyrrolizidin-4-one (30). To a solution of silyl ether **12b** (1.01 g, 3.75 mmol) in 15 mL THF was added a solution of tetrabutylammonium fluoride (8.0 mL, 1.0 M in THF, 8.0 mmol) and the reaction was stirred at rt for 10 h. The reaction mixture was concentrated and purified by flash chromatography (silica gel, 20:1 CH_2Cl_2:MeOH) to yield 567.2 mg **30** (98%) as a clear, colorless oil. $[\alpha]_D^{25}$ = -169 (c 1.06, CH_2Cl_2); R_f = 0.28 (20:1 CH_2Cl_2:MeOH); IR (thin film) 3427, 2921, 2877, 1732, 1482, 1392, 1358, 1223, 1120, 1029, 965, 801, 738, 666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (s, 2H), 4.83 (m, 1H), 4.70 (m, 1H), 4.64 (t, J=8.7 Hz, 1H), 4.26 (dd, J=8.7, 6.0 Hz, 1H), 3.79 (dd, J=11.7, 3.9 Hz, 1H), 3.55 (dd, J=11.4, 6.3 Hz, 1H), 2.32 (bs, 1H, OH) ppm; ^{13}CNMR (75 MHZ, $CDCl_3$) δ 163.3, 131.2, 130.5, 69.3, 69.2, 64.4, 63.9 ppm. Anal: Calc'd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03; found: C, 53.93; H, 6.03; N, 8.90.



31

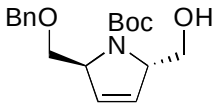
(5*R*,6*R*,7*S*,7a*R*)-6,7-(2,2-dimethyl-[1,3]dioxolane)-5-hydroxymethyl-tetrahydro-pyrrolo[1,2-c]oxazol-3-one (31). To a test tube containing **30** (57.5 mg, 0.371 mmol) under Ar is added a solution of NMO (59.2 mg, 0.505 mmol) in 2.5 mL CH_2Cl_2. The solution was stirred at rt as OsO_4 (115 μL, 4% in H_2O, 0.018 mmol) was added. After 1 h the reaction was flushed through a plug of silica gel and eluted with 25 mL MeOH. The combined washings were concentrated to yield the crude triol as a light green oil which was used in the subsequent step without purification. To the crude triol in 5 mL acetone (distilled from

$CaSO_4$) was added *p*-TsOH•H_2O (10 mg, 0.053 mmol, 14 mol%). The reaction was stirred 17 h at rt then concentrated to yield a white/grey solid. The product was purified by flash chromatography (silica gel, 20:1 CH_2Cl_2:MeOH) to yield 53.9 mg **31** (63%) as a light grey amorphous solid. mp 67-71 °C; $[\alpha]_D^{23}$ = -9.1 (c 0.84, $CHCl_3$); R_f = 0.20 (20:1 CH_2Cl_2:MeOH); IR (thin film) 3437, 2987, 2938, 1732, 1473, 1401, 1376, 1214, 1160, 1103, 1077, 1024, 874, 772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.80 (d, J=5.4 Hz, 1H), 4.61 (t, J=4.6 Hz, 1H), 4.52 (dd, J=8.5, 2.9 Hz, 1H), 4.39 (t, J=8.5 Hz, 1H), 4.19-4.16 (m, 1H), 4.08 (t, J=4.2 Hz, 1H), 3.77-3.65 (m, 2H), 2.63 (bs, 1H), 1.42 (s, 3H), 1.29 (s, 3H) ppm; ^{13}CNMR (75 MHZ, $CDCl_3$) δ 157.4, 107.6, 79.5, 75.6, 61.2, 58.44, 58.36, 57.4, 21.5, 19.4 ppm; HRMS (EI+) m/z calculated for $C_{10}H_{10}NO_5$ $[M + H]^+$: 230.1028, found 230.1028.



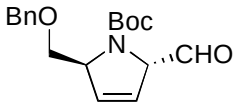
33

(1*R*,2*S*,3*R*,6a*R*)-1,2-Epoxy-3-hydroxymethyl-5-oxapyrrolizidin-4-one (33). To a solution of methyltrioxorhenium (MTO) (1.55 mg, 0.0062 mmol, 1 mol%) in 1 mL CH_2Cl_2 was added urea-hydrogen peroxide complex (UHP) (146.0 mg, 1.55 mmol). The solution was stirred for 10 min then a solution of olefin **30** (100.9 mg, 0.650 mmol) in 1 mL CH_2Cl_2 was added. The reaction was stirred for 20 h at rt. Due to incomplete conversion, evidenced by the yellow color of the active epoxidation catalyst being absent, MTO (1.50 mg, 0.006 mmol) was added and the reaction stirred an additional 9 h. The crude reaction mixture was directly purified by flash column chromatography (silica gel, 20:1 CH_2Cl_2:MeOH) to yield 80.8 mg **33** (73%, 0.472 mmol) as a single diastereomer by ^1H NMR; as a clear, colorless oil. $[\alpha]_D^{25}$ = -62 (c 0.91, CH_2Cl_2); R_f = 0.20 (20:1 CH_2Cl_2:MeOH); IR (thin film) 3419, 2924, 2884, 1732, 1411, 1376, 1230, 1073, 1029, 1004, 858, 784, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.56 (t, J=8.7 Hz, 1H), 4.48 (dd, J=8.7, 4.2 Hz, 1H), 4.14 (m, 2H), 3.78 (m, 2H), 3.72 (s, 2H), 2.78 (bs, 1H, OH) ppm; ^{13}CNMR (75 MHZ, $CDCl_3$) δ 163.0, 65.2, 61.9, 61.8, 58.4, 57.3, 55.8 ppm. Anal: Calc'd for $C_7H_9NO_4$: C, 49.12; H, 5.30; N, 8.18; found: C, 49.01; H, 5.43; N, 8.09.



37

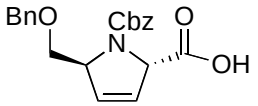
(2*S*,5*S*)-2-Benzyloxymethyl-5-hydroxymethyl-2,5-dihydro-pyrrole-1-carboxylic acid tert-butyl ester (37). To a solution of dihydropyrrole **12a** (806 mg, 3.67 mmol) in 12 mL CH_2Cl_2 was added NEt_3 (1.21g, 12.0 mmol) and DMAP (10mg, 0.08 mmol). The reaction was stirred under N_2 and BOC anhydride (2.62g, 12.0 mmol) was added dropwise via syringe. The reaction was stirred at rt for 18.5 h then concentrated and purified by flash column chromatography (silica gel, 2:1 PE:Et_2O) to yield the bis-Boc compound as 1.05 g light yellow oily solid. To the crude bis-Boc compound prepared above (1.05 g) was added 20 mL methanol and K_2CO_3 (691 mg, 5 mmol). The reaction was stirred under N_2 for 48 h then filtered through Celite. The filter cake was washed with 3 x 15 mL methanol and the combined washings concentrated to yield a brown/white oily solid. The residue was purified by flash chromatography (silica gel, 40:1 CH_2Cl_2:MeOH) to yield 591 mg (50%, 1.83 mmol) **37** as a clear, colorless, viscous oil. $[\alpha]_D^{25}$ = -162 (c 0.92, CH_2Cl_2); R_f = 0.42 (20:1 CH_2Cl_2:MeOH); IR (thin film) 3420, 2975, 2866, 1699, 1635, 1456, 1323, 1255, 1177, 1077, 855, 814, 771, 734, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 5:1 mixture of amide rotamers **Major**: δ 7.30 (m, 5H), 5.91 (m, 1H), 5.65 (d, J=6.6 Hz, 1H), 4.93 (bs, 1H), 4.70 (m, 1H), 4.58 (m, 1H), 4.52 (m, 2H), 3.78 (m, 2H), 3.60 (dd, J=12.2, 6.8 Hz, 1H), 3.52 (dd, J=9.0, 6.6 Hz, 1H), 1.42 (s, 9H) ppm; **Minor**: δ 7.30 (m, 5H), 5.98 (m, 1H), 5.74 (d, 1H), 4.94 (bs, 1H), 4.70 (m, 1H), 4.58 (m, 1H), 4.52 (m, 2H), 3.94 (m, 2H), 3.87 (d, 1H), 3.78 (m, 1H), 3.70 (m, 1H), 1.50 (s, 9H) ppm; ^{13}CNMR (125 MHZ, $CDCl_3$) δ 155.7, 130.3, 128.7, 128.6, 127.7, 127.7, 127.6, 127.5, 73.6, 71.3, 69.6, 66.8, 65.1, 64.5, 64.4, 64.0, 28.7, 27.9 ppm: Anal: Calc'd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39; found: C, 67.52; H, 7.71; N, 4.21.



38

(2*S*,5*S*)-2-Benzyloxymethyl-5-formyl-2,5-dihydro-pyrrole-1-carboxylic acid tert-butyl ester (38). To a solution of oxalyl chloride (293 mg, 2.31 mmol) in 2 mL CH_2Cl_2 under argon balloon at -78 °C was added a solution of DMSO (384 mg, 4.91 mmol) in 1 mL CH_2Cl_2 via cannula. The solution was stirred for 15 min, then alcohol **37** (154 mg, 0.482 mmol) in 1 mL CH_2Cl_2 was added and the resulting suspension stirred at -78 °C for 45 min. Triethylamine (650 μL, 4.66 mmol) was added and the suspension stirred 15 min, then warmed to -20 °C and stirred an additional 30 min. H_2O, 2 mL, was added and the reaction

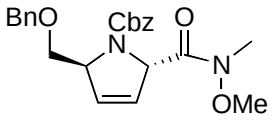
warmed to rt. The reaction was extracted with 3 x 15 mL CH_2Cl_2, the organic layers combined, washed with 15 mL saturated aqueous $NaHCO_3$, and 15 mL saturated aqueous NaCl. The organic layer was dried over $MgSO_4$ and concentrated to yield 134.6 mg **38** (88%, 0.424 mmol) as a clear, light yellow oil. The crude product is of sufficient purity for spectroscopic analysis and subsequent reactions. R_f = 0.44 (1:1 PE:Et_2O); IR (thin film) 2977, 2929, 2864, 1738, 1694, 1454, 1392, 1257, 1175, 1131, 737, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 2:1 mixture of amide rotamers **Major**: δ 9.23 (d, J=3.7 Hz, 1H), 7.30 (m, 5H), 6.15 (m, 1H), 5.58 (d, J=6.1 Hz, 1H), 4.85 (m, 1H), 4.78 (m, 1H), 4.53 (s, 2H), 3.85 (dd, J=9.3, 2.7 Hz, 1H), 3.80-3.72 (m, 1H), 1.42 (s, 9H) ppm; **Minor**: δ 9.29(d, J=3.7 Hz, 1H), 7.30 (m, 5H), 6.15 (m, 1H), 5.63 (d, J= 6.4 Hz, 1H), 4.85 (m, 1H), 4.72 (m, 1H), 4.55 (s, 2H), 3.80-3.72 (m, 1H), 3.54 (dd, J=9.0, 6.4 Hz, 1H), 1.43 (s, 9H) ppm; ^{13}CNMR (125 MHZ, $CDCl_3$) δ 200.1, 155.9, 138.1, 129.2, 128.2, 126.2, 126.1, 125.8, 125.4, 72.1, 71.3, 69.2, 65.9, 65.8, 65.3, 65.2, 64.5, 29.2, 28.1 ppm. Anal: Calc'd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41; found: C, 68.05; H, 7.46; N, 4.32.



40

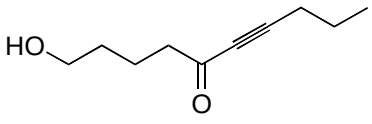
(2*S*,5*S*)-5-Benzyloxymethyl-2,5-dihydro-pyrrole-1,2-dicarboxylic acid 1-benzyl ester (40). To a solution of alcohol **13** (16.5 g, 46.7 mmol) in 200 mL acetone was added 40 mL 5% aqueous $NaHCO_3$. To the solution was added KBr (554 mg, 4.65 mmol, 10 mol%) and TEMPO (730 mg, 4.67 mmol). The solution as cooled to 0 °C in an ice bath and and bleach (150 mL, 5.5% in H_2O, 100 mmol) was added slowly. The reaction was stirred at 0 °C 2.5 h. To the reaction was added 50 mL 5% aqueous $NaHCO_3$ and the acetone removed *in vacuo*. The remaining aqueous solution was extracted with 2 x 100 mL Et_2O. The aqueous layer was acidified to pH 4 with solid $KHSO_4$, then extracted with 2 x 100 mL EtOAc. The EtOAc extractions were combined, dried over $MgSO_4$ and concentrated to yield 15.3 g (89%, 41.6 mmol) **40** as a clear, colorless, viscous oil. $[\alpha]_D^{25}$= -204 (c 1.094, CH_2Cl_2); R_f = 0.10 (2:1 EtOAc:PE); IR (thin film) 3400-2500, 3033, 2925, 1715, 1418, 1357, 1303, 1206, 1109, 1002, 912, 737, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 11:9 mixture of amide rotamers **Major**: δ 9.90 (bs, 1H), 7.35-7.20 (m, 10H), 6.04 (m, 1H), 5.77 (dt, J=6.4, 2.0 Hz, 1H), 5.12-5.04 (m, 3H), 4.88 (m, 1H), 4.50 (m, 2H), 3.87 (dd, J=9.6, 2.9 Hz, 1H), 3.78 (dd, J=9.6, 5.7 Hz, 1H), 3.65 (dd, J=12.2, 6.3 Hz, 1H), 3.54 (dd, J=9.3, 6.1 Hz, 1H) ppm; **Minor**: δ 9.90 (bs, 1H), 7.35-7.20 (m, 10H), 6.04 (m, 1H), 5.83 (dt, J=6.3, 1.8 Hz, 1H), 5.12-5.04 (m, 3H), 4.78 (m, 1H), 4.70 (m, 2H), 3.71 (dd, J=9.5, 2.7 Hz, 1H), 3.55 (dd, J=9.6, 6.1 Hz, 1H) ppm;

^{13}CNMR (125 MHZ, $CDCl_3$ with DEPT) δ 175.4(C), 174.7(C), 154.3(C), 153.7(C), 138.1(C), 137.9(C), 136.0(C), 135.9(C), 132.5(CH), 132.5(CH), 128.5(CH), 128.4(CH), 128.3(CH), 128.3(CH), 128.1(CH), 128.0(CH), 127.9(CH), 127.7(CH), 127.7(CH), 127.6(CH), 127.5(CH), 127.4(CH), 124.4(CH), 124.2(CH), 73.3(CH_2), 73.2(CH_2), 70.0(CH_2), 69.0(CH_2), 67.6(CH_2), 67.5(CH_2), 67.2(CH), 67.1(CH), 65.3(CH), 64.4(CH) ppm; HRMS (EI+) m/z calculated for $C_{21}H_{22}NO_5$ $[M + H]^+$: 368.1498, found: 368.1492.



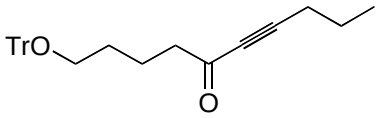
41

(2*S*,5*S*)-2-Benzyloxymethyl-5-(methoxy-methyl-carbamoyl)-2,5-dihydro-pyrrole-1-carboxylic acid benzyl ester (41). To a solution of acid **40** (5.64, 15.4 mmol) in a solution of 100 mL CH_2Cl_2 was added N,O-dimethyl-hydroxylamine hydrochloride (3 g, 30.7 mmol), Hünig's base (6.4 g, 49.3 mmol), and py-BOP reagent (8.0 g, 15.4 mmol). The reaction was stirred at rt 36 h. The reaction was extracted with 3 x 50 mL 3 M aqueous HCl, 50 mL saturated aqueous $NaHCO_3$, 50 mL saturated aqueous NaCl, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (silica gel, 8:1 ? 1:1 PE:EtOAc) to yield 5.12 g **41** (81%, 12.5 mmol) as a clear, colorless, viscous oil. $[\alpha]_D^{25}$= -193 (c 7.18, $CHCl_3$); R_f = 0.52 (2:1 EtOAc:PE); IR (thin film) 3402, 2969, 2870, 1714, 1694, 1682, 1455, 1392, 1088, 1014, 915, 708 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 11:9 mixture of amide rotamers **Major**: δ 7.35-7.23 (m, 10H), 6.01 (dt, J=6.3, 2.0 Hz, 1H), 5.73 (dt, J=6.3, 2.1 Hz, 1H), 5.37 (m, 1H), 5-18-4.96 (m, 2H), 4.95 (m, 1H), 4.56 (s, 2H), 3.90 (dd, J=9.6, 3.1 Hz, 1H), 3.81 (dd, J=9.5, 5.7 Hz, 1H), 3.38 (s, 3H), 3.07 (s, 3H) ppm; **Minor**: δ 7.35-7.23 (m, 10H), 5.99 (dt, J=6.3, 2.0 Hz, 1H), 5.81 (dt, J=6.3, 2.0 Hz, 1H), 5.51 (m, 1H), 5-18-4.96 (m, 2H), 4.85 (m, 1H), 4.45 (d, J=12.5 Hz, 2H), 4.41 (d, J=12.5 Hz, 1H), 3.81 (s, 3H), 3.74 (dd, J=9.5, 2.8 Hz, 1H), 3.59 (dd, J=9.5, 6.0 Hz, 1H), 3.23 (s, 3H) ppm; ^{13}CNMR (125 MHZ, $CDCl_3$) δ 170.0, 169.7, 154.3, 153.9, 138.2, 138.0, 136.2, 136.1, 131.7, 131.6, 128.4, 128.4, 128.3, 129.2, 128.2, 128.0, 127.9, 127.6, 127.5, 127.4, 124.5, 124.3, 73.3, 73.1, 70.3, 69.4, 67.2, 67.1, 65.7, 65.4, 65.2, 64.4, 61.3, 63.8, 32.3, 32.1 ppm; HRMS (EI+) m/z calculated for $C_{23}H_{27}N_2O_5$ $[M + H]^+$: 411.1920, found: 411.1932.



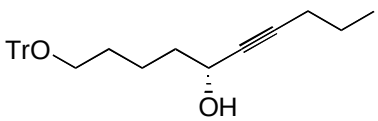
43

1-hydroxy-dec-6-yn-5-one[1] (43). To a solution of 1-pentyne (11.53 g, 169 mmol) in 140 mL THF at -15 °C was added *n*-BuLi (106 mL, 1.6M in hexanes, 169 mmol) over 5 min. The resulting yellow suspension was warmed to rt and stirred 15 min, then recooled to -78 °C. A solution of δ-valerolactone (14.53 g, 145 mmol) in 20 mL THF was added dropwise over 8 min and the reaction stirred 1 h then warmed to -15 °C. The reaction was poured onto 500 mL ice cold saturated aqueous NH_4Cl and stirred 30 min. The solution was then extracted with 3 x 500 mL ether, the organic layers combined, dried over $MgSO_4$, and concentrated to yield a yellow oil. The residue was purified by flash chromatography (silica gel, 1:1 EtOAc:PE) to yield 22.83g **43** (94%, 136 mmol) as a clear, colorless, viscous oil. R_f = 0.44 (1:1 EtOAc:PE); IR (thin film) 3446, 2965, 2876, 2212, 1732, 1715, 1592, 1456, 1380, 1252, 1169, 1081, 968, 802 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)**Fehler! Textmarke nicht definiert.** δ 3.65 (m, 2H), 2.60 (t, J=7.2 Hz, 2H), 2.35 (t, J=7.2 Hz, 2H), 1.76 (m, 2H), 1.68-1.55 (m, 5H), 1.05 (t, J=7.2 Hz, 3H) ppm; ^{13}CNMR (125 MHZ, $CDCl_3$) δ 172.8, 94.4, 80.9, 62.2, 45.0, 31.8, 21.2, 20.8, 20.1, 13.4 ppm.



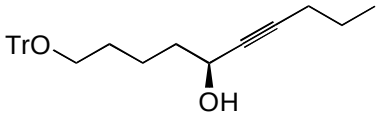
44

1-Trityloxy-dec-6-yn-5-one (44). To a solution of alcohol **43** (18.2 g, 0.108 mol), NEt_3 (27 mL, 0.194 mol), and DMAP (660 mg, 5.4 mmol) in 100 mL DMF was added a solution of trityl chloride (33.07 g, 0.119 mol) in 50 mL DMF. The reaction was stirred for 26 h at rt then poured into 500 mL ice water and extracted with 3 x 500 mL CH_2Cl_2. The combined organic layers were washed with 500 mL saturated aqueous NH_4Cl, 500 mL H_2O, dried over Na_2SO_4, and concentrated to yield a yellow oily solid. The residue was purified by flash chromatography (silica gel, 20:1 PE:Et_2O) to yield 34.1 g **44** (77%, 83 mmol) as a clear, light yellow, highly viscous oil. R_f = 0.53 (4:1 PE:Et_2O); IR (thin film) 3059, 3032, 2961, 2872, 2212, 1674, 1491, 1449, 1223, 1161, 1073, 1034, 899, 762, 705, 648, 633 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.44 (m, 6H), 7.34 (m, 9H), 3.07 (t, J=6.2 Hz, 2H), 2.51 (t, J=6.5 Hz, 2H), 2.33 (t, J=7.0 Hz, 2H), 1.84-1.54 (m, 6H), 1.00 (t, J=7.3 Hz, 3H) ppm; ^{13}CNMR (75 MHZ, $CDCl_3$) δ 183.5, 139.6, 123.9, 122.9, 122.0, 89.4, 81.6, 76.2, 58.2, 40.5, 24.5, 16.5, 16.3, 16.1 ppm. Anal: Calc'd for $C_{29}H_{30}O_2$: C, 84.84; H, 7.37; found: C, 84.88; H, 7.30.



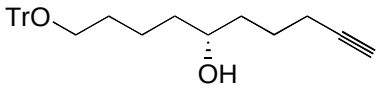
46

(5*R*)-1-Trityloxy-dec-6-yn-5-ol (46). To a solution of ynone **44** (64.0 g, 156 mmol), in 900 mL *i*-PrOH (freshly distilled from Na°/$NaBH_4$) was added ruthenium(II) catalyst (*R*,*R*)-**45** (940 mg, 1.56 mmol, 1.0 mol%) The reaction was stirred under argon balloon for 4 h. An additional portion of catalyst (*R*,*R*)-**45** (940 mg, 1.56 mmol, 1 mol%) was added and the reaction stirred an additional 12 h to effect completion of the reaction. The solution was concentrated to yield a brown/yellow oil. The residue was purified by flash chromatography (silica gel, gradient elution 10:1 ? 1:1 PE:Et_2O) to yield 58.3 g **46** (91%, 141 mmol) as a clear, light yellow, highly viscous oil. $[\alpha]_D^{24}$ = -2.2 (c 2.63, CH_2Cl_2); R_f = 0.39 (4:1 PE:Et_2O); IR (thin film) 3405, 3087, 2936, 2870, 1958, 1817, 1597, 1491, 1449, 1381, 1221, 1077, 1033, 900, 746, 699, 633 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (m, 6H), 7.30-7.18 (m, 9H), 4.33 (bs, 1H), 3.07 (t, J=6.4 Hz, 2H), 2.16 (dt, J=2.0, 7.1 Hz, 2H), 1.71 (d, J=3.4 Hz, 1H, -OH), 1.68-1.47 (m, 8H), 0.95 (t, J=7.3 Hz, 3H) ppm; ^{13}CNMR (75 MHZ, $CDCl_3$) δ 139.7, 123.9, 122.9, 122.0, 81.6, 80.7, 76.6, 58.6, 57.9, 33.2, 24.9, 17.3, 17.2, 15.9, 8.7 ppm; HRMS (EI+) m/z calculated for $C_{29}H_{31}O_2$ $[M - H]^+$: 411.2324, found: 411.2321. Enantiomeric excess was determined to be 96% ee by chiral HPLC (Chiralpak OD, 97:3 heptane:*i*-PrOH, 1.0 mL/min, major enantiomer (5*R*) t_R=9.43 min and minor enantiomer (5*S*) t_R=16.97 min)



(*ent*)-**46**

(5*S*)-1-Trityloxy-dec-6-yn-5-ol [(*ent*)-46]. To a solution of ruthenium(II) catalyst (*S*,*S*)-**45** (2.20 g, 3.67 mmol, 2.2 mol) in 800 mL *i*-PrOH (freshly distilled from Na°/$NaBH_4$) was added a solution of ynone **44** (69.0 g, 168 mmol), in 200 mL *i*-PrOH. The reaction was stirred under argon balloon for 12 h. The solution was concentrated to yield a brown/yellow oil. The residue was purified by flash chromatography (silica gel, gradient elution 10:1 ? 1:1 PE:Et_2O) to yield 65.3 g **(*ent*)-46** (94%, 158 mmol) as a clear light yellow highly viscous oil. $[\alpha]_D^{24}$ = +2.9 (c 1.70, CH_2Cl_2). Enantiomeric excess was determined to be 97% ee by chiral HPLC (Chiralpak OD, 97:3 heptane:*i*-PrOH, 1.0 mL/min, minor enantiomer (5*R*) t_R=10.73 min and major enantiomer (5*S*) t_R=19.36 min)



47

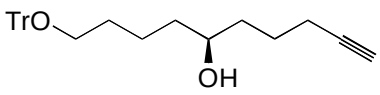
(5*R*)-1-Trityloxy-dec-9-yn-5-ol (47). To a flame-dried 250 mL three-necked flask equipped with a mechanical stirrer was added potassium hydride (10.3 g, 35% in mineral oil, 90 mmol) and the flask flushed with N_2. The suspension was washed with 3 x 25 mL freshly distilled

hexane via cannula to remove the mineral oil. 1,3-Diaminopropane, 90 mL, was added via cannula to yield a brown foaming mixture and the suspension stirred for 2 h at rt until the foaming had subsided and a brown/green suspension results. A solution of yne-ol **46** (5.0 g, 12.1 mmol) in 10 mL THF was added to the suspension via cannula. The gray/green solution turned bright red upon addition of the substrate. The reaction was stirred for 24 h, then poured very slowly into a vigorously stirred 100 mL ice/saturated aqueous NH_4Cl suspension, under N_2 stream. The solution was diluted with 100 mL ether, then extracted. The aqueous layer was extracted with 2 x 100 mL additional ether, the organic layers combined, and washed with 50 mL 1M HCl, 50 mL saturated aqueous $NaHCO_3$, and 50 mL saturated aqueous NaCl. The organic layer was then dried over $MgSO_4$ and concentrated to yield a clear brown oil. The residue was purified by flash chromatography (silica gel, 4:1 PE:Et_2O) to yield 3.86 g **47** (77%, 9.36 mmol) as a clear, light yellow oil. $[\alpha]_D^{23}$ = +1.1 (c 1.033, CH_2Cl_2); R_f = 0.40 (1:1 PE:Et_2O); IR (thin film) 3584, 3388, 3058, 2937, 2867, 2116, 1959, 1821, 1597, 1490, 1449, 1266, 1074, 1032, 900, 764, 740, 707, 648, 603 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (m, 6H), 7.32-7.20 (m, 9H), 3.59 (bs, 1H), 3.07 (t, J=6.4 Hz, 2H), 2.21 (dt, J=3.6, 6.3 Hz, 2H), 1.94 (t, J=2.5 Hz, 1H), 1.68-1.47 s(m, 11H) ppm; ^{13}CNMR (75 MHZ, $CDCl_3$) δ 139.7, 123.9, 122.9, 122.1, 81.6, 79.6, 66.5, 58.6, 32.6, 31.5, 25.2, 19.8, 17.5, 13.6 ppm; HRMS (EI+) m/z calculated for $C_{29}H_{32}O_2$ $[M]^+$: 412.2402, found: 412.2416. Anal: Calc'd for $C_{29}H_{32}O_2$: C, 84.43; H, 7.82; found: C, 84.27; H, 7.70.

Larger Scale:

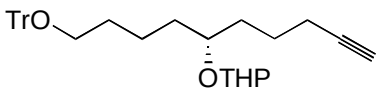
To a flame-dried 1L three-necked flask equipped with a mechanical stirrer was added potassium hydride (103 g, 35% in mineral oil, 0.9 mol) and the flask flushed with N_2. The suspension was washed with 3 x 100 mL freshly distilled hexane via cannula to remove the mineral oil. 1,3-Diaminopropane, 900 mL, was added via cannula to yield a brown foaming mixture and the suspension stirred for 2 h at rt until the foaming had subsided and a brown/green suspension results. A solution of yne-ol **46** (50.0 g, 121 mmol) in 50 mL THF was added to the suspension via cannula. The gray/green solution turned bright red upon addition of the substrate. The reaction was stirred for 24 h, then poured very slowly into a vigorously stirred 250 mL ice/saturated aqueous NH_4Cl suspension, under N_2 stream (warning, fire is probable if not quenched this way on large scale). The solution was diluted with 1 L ether, then extracted. The aqueous layer was extracted with 2 x 1 L additional ether, the organic layers combined, and washed with 500 mL 1M HCl, 500 mL saturated aqueous $NaHCO_3$, and 500 mL saturated aqueous NaCl. The organic layer was then dried over

$MgSO_4$ and concentrated to yield a clear brown oil. The residue was purified by flash chromatography (silica gel, 4:1 PE:Et_2O) to yield 26.4 g **47** (53%, 64 mmol) as a clear light yellow oil. The low yield of this reaction is attributed to the use of old KH. Repeat of this reaction with the other enantiomer of starting material and smaller scales (example below) gives reproducible yields of 75-84% on scales of 250 mg to 25 g.



(*ent*)-**47**

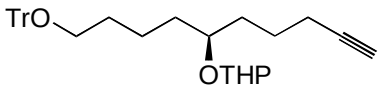
(5*S*)-1-Trityloxy-dec-9-yn-5-ol [(*ent*)-47]. To a flame-dried 500 mL three-necked flask equipped with a mechanical stirrer was added potassium hydride (20.9 g, 35% in mineral oil, 182 mmol) and the flask flushed with N_2. The suspension was washed with 3 x 50 mL freshly distilled hexane via cannula to remove the mineral oil. 200 mL 1,3-Diaminopropane (freshly distilled from CaH_2 was added via cannula to yield a brown foaming mixture. The suspension was stirred for 2 h at rt until the foaming had subsided and a brown/green suspension results. A solution of alkynol **(*ent*)-46** (15.0 g, 36.4 mmol) in 50 mL THF was added to the suspension via cannula. The gray/green solution turned bright red upon addition of the substrate. The reaction was stirred for 15 h, then poured very slowly into a vigorously stirred 250 mL ice/saturated aqueous NH_4Cl suspension, under N_2 stream. The solution was diluted with 100 mL ether, then extracted. The aqueous layer was extracted with 2 x 100 mL additional ether, the organic layers combined, and washed with 100 mL 1M HCl, 100 mL saturated aqueous $NaHCO_3$, and 100 mL saturated aqueous NaCl. The organic layer was then dried over $MgSO_4$ and concentrated to yield a clear, brown oil. The residue was purified by flash chromatography (silica gel, 4:1 PE:Et_2O) to yield 11.90 g **(*ent*)-47** (79%, 28.8 mmol) as a clear, light yellow oil. $[\alpha]_D^{25} = -1.4$ (c 1.27, CH_2Cl_2).



48

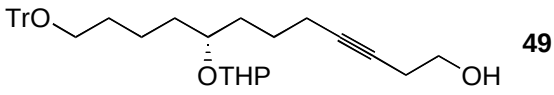
(5*R*)-1-Trityloxy-5-(tetrahydro-pyran-2-yloxy)-dec-9-yne (48). To a flask with alcohol **47** (25.0 g, 60.6 mmol) in 150 mL CH_2Cl_2 was added 3,4-dihydro-2H-pyran (15.3 g, 182 mmol) the reaction was stirred at rt and PPTS (1.53 g, 6.06 mmol) was added quickly and the reaction flushed with N_2. The reaction was stirred for 10 h at rt. The reaction was then washed with 200 mL half saturated aqueous NaCl, the aqueous layer back extracted with 50 mL CH_2Cl_2, the organic layers combined, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (silica gel, gradient elution 20:1 ? 10:1 PE:Et_2O) to

yield 27.7 g **48** (92%, 55.8 mmol) as a clear, colorless, highly viscous oil. $[\alpha]_D^{28}$ = -1.2 (c 1.00, CH_2Cl_2); R_f = 0.75 (1:1 PE:Et_2O); IR (thin film) 3305, 3058, 2940, 2868, 1597, 1491, 1449, 1200, 1154, 1076, 1032, 1002, 902, 774, 707 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) Splitting complicated by mixture of THP diastereomers δ 7.44 (m, 6H), 7.27 (m, 6H), 7.20 (m, 3H) 4.62 (m, 1H), 3.87 (m, 1H), 3.62 (m, 1H), 3.44 (m, 1H), 3.06 (m, 2H), 2.19 (m, 2H), 1.90 (m, 1H), 1.80 (m, 1H), 1.67-1.40 (m, 15H) ppm; ^{13}CNMR (75 MHZ, $CDCl_3$) Double peaks due to THP diastereomers δ 144.8, 144.7, 129.0, 128.0, 127.9, 127.1, 97.9, 97.7, 86.6, 86.5, 84.9, 84.6, 76.3, 76.2, 68.8, 68.6, 63.6, 63.2, 62.9, 35.1, 34.3, 33.8, 32.7, 31.5, 31.4, 30.5, 30.4, 25.8, 24.8, 24.2, 22.9, 22.7, 22.1, 20.4, 20.2, 18.9, 18.8 ppm; HRMS (EI+) m/z calculated for $C_{28}H_{35}O_3$ $[M - C_6H_5]^+$: 419.2586, found: 419.2590; calculated for $C_{29}H_{31}O_2$ [M -C_5H_9O (THP)]$^+$: 411.2324, found: 411.2308. Anal: Calc'd for $C_{34}H_{40}O_3$: C, 82.22; H, 8.12; found: C, 81.98; H, 7.97.



(*ent*)-**48**

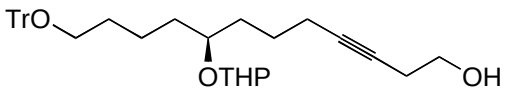
(5*S*)-1-Trityloxy-5-(tetrahydro-pyran-2-yloxy)-dec-9-yne [(*ent*)-48]. To a flask with alcohol **(*ent*)-47** (32.0 g, 77.6 mmol) in 150 mL CH_2Cl_2 was added 3,4-dihydro-2H-pyran (19.6 g, 233 mmol) the reaction was stirred at rt and PPTS (1.95 g, 7.76 mmol, 10 mol%) was added quickly and the reaction flushed with N_2. The reaction was stirred for 12 h at rt. The reaction was then washed with 200 mL half saturated aqueous NaCl, the aqueous layer back extracted with 50 mL CH_2Cl_2, the organic layers combined, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (silica gel, gradient elution 20:1 →10:1 PE:Et_2O) to yield 35.8 g **(*ent*)-48** (93%, 72.1 mmol) as a clear, colorless, highly viscous oil. $[\alpha]_D^{26}$ = -1.1 (c 1.16, CH_2Cl_2).



49

(5*R*)-1-Trityloxy-5-(tetrahydro-pyran-2-yloxy)-dodec-9-yn-12-ol (49). To a flame-dried 1 L flask with **48** (25.7 g, 51.7 mmol) under Ar was added 150 mL Et_2O. The reaction was cooled to -78 °C and *n*-BuLi (20.7 mL, 2.5 M in hexanes, 51.7 mmol) was added over 5 min. The reaction was stirred 45 min until a bright pink, clear solution resulted, then $AlMe_3$ (25.8 mL, 2.0 M in toluene, 51.7 mmol) was added over 2 min, and stirred an additional 15 min at -78 °C. The reaction was warmed to -40 °C (CO_2/CH_3CN bath) and stirred 25 min. After recooling to -78 °C, ethylene oxide (4.8 g, 108.6 mmol) and $BF_3{\cdot}OEt_2$ (7.2 mL (8.07 g), 56.9

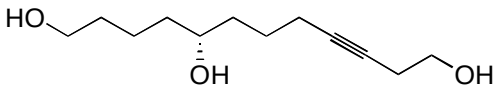
mmol) was added. And the reaction stirred for 16.8 h at -78 °C. The reaction was quenched with 50 mL MeOH and warmed to 0 °C. Saturated aqueous NH_4Cl, 150 mL, was added and the reaction warmed to rt. The mixture was diluted with 200 mL ether and 200 mL H_2O. The organic layer was separated and the aqueous layer was extracted with 2 x 200 mL ether. The combined organic layers were washed with 150 mL saturated aqueous $NaHCO_3$, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, gradient elution 5:1 ? 1:1 PE:Et_2O) to yield 21.21 g **49** (76%, 39.22 mmol) as a clear, colorless, highly viscous oil. $[\alpha]_D^{24}$ = -1.2 (c 1.00, CH_2Cl_2); R_f = 0.27 (1:1 PE:Et_2O); IR (thin film) 3442, 3059, 2941, 2868, 1490, 1449, 1200, 1133, 1113, 1076, 1032, 1002, 909, 733, 707 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) Splitting complicated by mixture of THP diastereomers δ 7.44 (m, 6H), 7.32-7.20 (m, 9H), 4.63 (m, 1H), 3.87 (m, 1H), 3.63 (m, 3H), 3.49 (m, 1H), 3.06 (t, J=6.2 Hz, 2H), 2.39 (m, 2H), 2.17 (m, 2H), 2.04 (bs, 1H), 1.86-1.40 (m, 16H) ppm; ^{13}CNMR (50 MHZ, $CDCl_3$) Double peaks due to THP diastereomers δ 142.3, 142.2, 126.4, 125.4, 124.5, 95.6, 94.8, 83.9, 79.8, 73.9, 73.5, 67.8, 61.1, 60.9, 60.5, 60.1, 59.0, 32.4, 31.7, 31.1, 30.1, 28.8, 28.7, 27.7, 23.1, 22.5, 21.9, 20.7, 20.0, 19.4, 17.6, 17.3, 16.5, 16.4 ppm; HRMS (+ESI) m/z calculated for $C_{36}H_{44}NaO_4$ $[M + Na]^+$: 563.314, found: 563.279. Anal: Calc'd for $C_{36}H_{44}O_4$: C, 79.96; H, 8.20; found: C, 79.86; H, 7.95.



(*ent*)-**49**

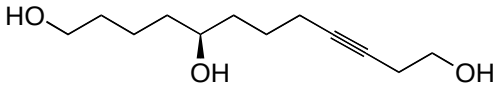
(5*S*)-1-Trityloxy-5-(tetrahydro-pyran-2-yloxy)-dodec-9-yn-12-ol [(*ent*)-49]. To a flame-dried 1 L flask with **(*ent*)-48** (28 g, 56.4 mmol) under Ar was added 200 mL Et_2O. The reaction was cooled to -78 °C and *n*-BuLi (20.7 mL, 2.5 M in hexanes, 51.7 mmol) was added over 5 min. The reaction was stirred 50 min until a bright pink, clear solution resulted, then $AlMe_3$ (29 mL, 2.0 M in toluene, 58 mmol) was added over 5 min at -78 °C. The reaction was warmed to -40 °C (CO_2/CH_3CN bath) and stirred 1 h. After recooling to -78 °C, ethylene oxide (32 mL, 3.7 M in Et_2O, 118 mmol) and $BF_3{\cdot}OEt_2$ (9.0 g, 63 mmol) were added and the reaction stirred for 8 h at -78 °C. The reaction was quenched with 20 mL MeOH and warmed to 0 °C. Saturated aqueous NH_4Cl, 200 mL, was added and the reaction warmed to rt. The mixture was filtered through a plug of Celite, and the solid rinsed with 200 mL ether. The combined washings were then extracted, the organic layer was separated, and the aqueous layer was extracted with 2 x 200 mL ether. The combined organic layers were washed with 150 mL saturated aqueous $NaHCO_3$, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, gradient elution 5:1 ? 1:1 PE:Et_2O) to yield

5.58 g (20%) recovered **(*ent*)-2.47** and 18.0 g **(*ent*)-2.48** (59%, 33.3 mmol, 74% BRSM) as a clear, colorless, highly viscous oil. $[\alpha]_D^{26}$ = -1.1 (c 1.16, CH_2Cl_2).



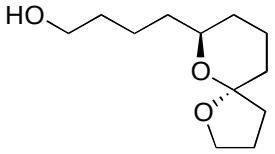
50

(5*R*)-Dodec-9-yne-1,5,12-triol (50). To a 500 mL flask containing 100 mL HCl in MeOH (freshly prepared from 4 mL acetyl chloride and 100 mL MeOH) at 0 °C was added alkynol **49** (20.5 g, 37.9 mmol) in 100 mL MeOH, with 50 mL additional MeOH used to rinse flask. The reaction was stirred at 0 °C 15 min, then warmed to rt and stirred an additional 2 h. The solution was filtered through a scintered glass funnel to remove the solid TrOMe by product. The filter cake was washed with 100 mL CH_2Cl_2 and the combined filtrates concentrated. The product was purified by flash column chromatography (silica gel, gradient elution 20:1 ? 4:1 CH_2Cl_2:MeOH) to yield 7.73 g **50** (95%, 36.1 mmol) as a clear, light yellow, highly viscous oil. $[\alpha]_D^{24}$ = +5.8 (c 1.20, MeOH); R_f = 0.20 (10:1 CH_2Cl_2:MeOH); IR (thin film) 3333, 2937, 1457, 1434, 1374, 1335, 1048 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.68 (m, 5H), 2.43 (m, 2H), 2.21 (m, 3H), 1.73 (bs, 2H), 1.67-1.43 (m, 10H) ppm; ^{13}CNMR (75 MHZ, $CDCl_3$) δ 81.7, 76.8, 70.7, 62.1, 60.8, 36.5, 36.0, 32.0, 24.5, 22.7, 21.4, 18.3 ppm; Anal: Calc'd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35; found: C, 67.16; H, 10.26.



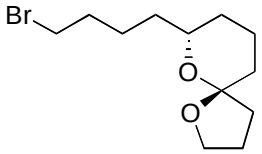
(*ent*)-**50**

(5*S*)-Dodec-9-yne-1,5,12-triol [(*ent*)-50]. To a 500 mL flask containing 100 mL HCl in MeOH (freshly prepared from 4 mL acetyl chloride and 100 mL MeOH) at 0 °C was added alkynol **(*ent*)-49** (24.5 g, 45.3 mmol) in 100 mL MeOH, with an additional 50 mL MeOH used to rinse the flask. The reaction was stirred at 0 °C 15 min, then warmed to rt and stirred an additional 2 h. The solution was filtered through a scintered glass funnel to remove the solid TrOMe by product, the filter cake was washed with 100 mL CH_2Cl_2, the filtrates combined and concentrated, and the product purified by flash column chromatography (silica gel, gradient elution 20:1 →10:1 CH_2Cl_2:MeOH) to yield 8.75 g **(*ent*)-50** (90%, 40.8 mmol) as a clear, light yellow, highly viscous oil. $[\alpha]_D^{29}$ = -5.7 (c 0.42, MeOH).



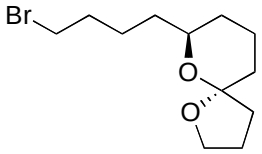
(*ent*)-**51**

4-[(5*S*,7*S*)-1,6-Dioxa-spiro[4.5]dec-7-yl]-butan-1-ol [(*ent*)-51]. A flame-dried 250 mL flask with triol **(*ent*)-50** (6.0 g, 28 mmol) in 167 mL 3:2 CH_3CN:THF was degassed with Ar by bubbling for 15 min. To this solution was quickly added solid $PdCl_2(PhCN)_2$ (322 mg, 0.84 mmol, 3 mol%) and the reaction was stirred at rt under Ar baloon 10 h. The resulting yellow/green solution was concentrated and purified by flash column chromatography (silica gel, 4:1 Et_2O:PE) to yield 4.75 g (79%, 22.2 mmol) **(*ent*)-51** as a clear, colorless, oil. $[\alpha]_D^{24}$= -67.4 (c 1.00, MeOH).



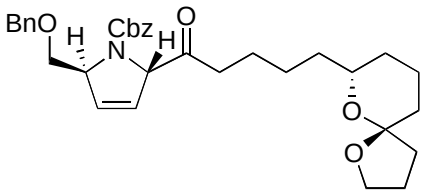
52

(5*R*,7*S*)-7-(4-Bromo-butyl)-1,6-dioxa-spiro[4.5]decane (52). To a 100 mL flask with Ph_3PBr_2 (8.8 g, 20.8 mmol) under N_2 was added THF and the suspension cooled to 0 °C. A solution of alcohol **51 (**3.74 g, 17.45 mmol) and imidazole (2.14 g, 31.4 mmol) in 5 mL THF was added via cannula, 5 mL additional THF rinse. The suspension was stirred 30 min, then allowed to warm to rt and stirred 12 h. The reaction was filtered through a plug of celite to remove solid triphenylphosphine oxide, and the plug rinsed with 3 x 25 mL Et_2O. The combined filtrates were filtered again through a celite plug, 3 x 50 mL Et_2O rinse. The filtrates were concentrated and the residue purified by flash column chromatography (silica gel, 20:1 PE:Et_2O to yield 4.41 g (91%, 15.9 mmol) **52** as a clear, colorless oil. $[\alpha]_D^{25}$ = +64 (c 1.250, $CHCl_3$); R_f = 0.81 (4:1 Et_2O:PE); IR (thin film) 2938, 2870, 1457, 1439, 1216, 1081, 1041 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.88 (m, 2H), 3.70 (m, 1H), 3.41 (t, J=6.8Hz, 2H), 2.04 (m, 1H), 1.94-1.77 (m, 5H), 1.71-1.64 (m, 4H), 1.59-1.36 (m, 5H), 1.21 (ddd, J=16.5, 13.0, 3.5 Hz, 1H) ppm; ^{13}CNMR (125 MHZ, $CDCl_3$) δ 105.8, 69.8, 66.8, 37.8, 35.2, 34.0, 32.8, 32.7, 30.9, 24.3, 23.7, 20.4 ppm; HRMS (EI+) m/z calculated for $C_{12}H_{21}BrO_2$ $[M + H]^+$: 277.0800, found: 277.0803.



(*ent*)-**52**

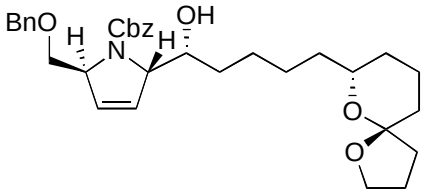
(5*S*,7*R*)-7-(4-Bromo-butyl)-1,6-dioxa-spiro[4.5]decane [(*ent*)-52]. To a 25 mL flask with Ph_3PBr_2 (5.0 g, 12 mmol) under N_2 was added 15 mL THF and the suspension cooled to 0 °C. A solution of alcohol **(*ent*)-51 (**2.1 g, 9.8 mmol) and imidazole (1.2 g, 18 mmol) in 10 mL THF was added via cannula. The suspension was stirred 1h, ~ 50% conversion by TLC. The reaction was warmed to rt and stirred 2 h. Additional Ph_3PBr_2 (1 g, 2.4 mmol) was added and the reaction stirred an additional 1 h. The reaction was filtered through a plug of celite to remove solid triphenylphosphine oxide, plug rinsed with 300 mL Et_2O. The filtrates were concentrated and the oily residue containing a large quantity of triphenylphosphine oxide was purified by flash column chromatography (silica gel, 20:1 PE:Et_2O to yield 2.47 g **(*ent*)-52** (91%, 8.91 mmol) as a clear, colorless oil. $[\alpha]_D^{26}$ = -73 (c 1.32, $CHCl_3$).



56

(2*S*,5*S*)-2-Benzyloxymethyl-5-[5-{(5*R*,7*R*)-1,6-dioxa-spiro[4.5]dec-7-yl}-pentanoyl]-2,5-dihydro-pyrrole-1-carboxylic acid benzyl ester (58). Mg chips (Aldrich, 99.95%) were washed successively in a Büchner funnel with vacuum filtration with: 10 % aqueous HCl, H_2O, EtOH, acetone, and Et_2O and dried overnight under vacuum. To a 25 mL flask was added the Mg chips (0.5 g, 20.5 mmol) and the flask flame-dried under vacuum. The flask was purged with Ar 3 times and 1 mL THF was added followed by bromide **52** (500 mg, 1.80 mmol). The reaction was placed in a 65 °C oil bath and stirred 2 h. The resulting green-black solution was cooled to rt and a solution of Weinreb amide **41** (616 mg, 1.5 mmol) in a solution of 1 mL benzene was added and the reaction was stirred at rt 2 h. The reaction was poured into 25 mL saturated aqueous NH_4Cl, diluted with 20 mL Et_2O, the organic layer separated, and the aqueous phase washed with 2 x 20 mL ether. The combined organic layers were washed with 25 mL saturated aqueous $NaHCO_3$, 25 mL satuarated aqueous NaCl, dried over Na_2SO_4, and concentrated to yield a yellow oil. The residue was purified by flash chromatography (silica gel, 4:1 PE:EtOAc) to yield 527 mg **58** (65%, 0.96 mmol) as a clear, colorless oil. $[\alpha]_D^{26}$= -207 (c 1.38, $CHCl_3$); R_f = 0.68 (1:1 PE:EtOAc); IR (thin film) 2938, 2868, 1713, 1497, 1455, 1410, 1352, 1105, 1008, 737, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 3:2 mixture of amide rotamers **Major**: δ 7.37-7.22 (m, 10H), 6.04 (dt, J=6.4, 2.0 Hz, 1H), 5.65 (dt, J=6.3, 2.0 Hz, 1H), 5.14-5.09 (m, 3H), 4.89 (m, 1H), 4.54 (d, J=12.2 Hz, 1H), 4.50 (d, J=12.2 Hz, 1H), 3.90-3.78 (m, 3H), 3.73 (dd, J=9.5, 2.9 Hz, 1H), 3.62 (m, 2H), 2.25 (ddd,

J=17.7, 8.7, 6.4Hz, 1H), 2.10 (ddd, J=17.7, 8.7, 6.4 Hz, 1H), 2.01 (m, 1H), 1.92-1.75 (m, 3H), 1.71-1.53 (m, 6H), 1.47-1.09 (m, 6H) ppm; **Minor**: δ 7.35-7.22 (m, 10H), 6.01 (dt, J=6.4, 1.8 Hz, 1H), 5.71 (dt, J=6.4, 1.8 Hz, 1H), 5.00 (m, 3H), 4.79 (m, 1H), 4.42 (d, J=12.2 Hz, 1H), 4.39 (d, J=12.2 Hz, 1H), 3.90-3.78 (m, 3H), 3.61 (m, 3H), 2.47 (ddd, J=17.1, 10.5, 6.5 Hz, 1H), 2.33 (ddd, J=17.1, 10.5, 6.5 Hz, 1H), 2.01 (m, 1H), 1.92-1.75 (m, 3H), 1.71-1.53 (m, 6H), 1.47-1.09 (m, 6H) ppm; ^{13}CNMR (125 MHZ, $CDCl_3$) δ 207.1, 206.5, 154.1, 153.6, 138.2, 138.0, 136.2, 135.9, 132.2, 132.1, 128.5, 128.4, 128.4, 128.3, 128.2, 128.2, 128.1, 128.1, 127.9, 127.8, 127.7, 127.6, 127.4, 126.5, 125.0, 124.9, 105.7, 74.4, 74.3, 73.3, 73.3, 73.2, 72.0, 70.2, 70.0, 69.9, 69.1, 67.3, 67.1, 66.6, 65.6, 65.4, 64.5, 38.1, 37.8, 36.9, 35.9, 32.8, 30.9, 25.2, 25.1, 23.6, 22.2, 23.1, 20.4 ppm; MS (+ESI) m/z calculated for $C_{33}H_{42}NO_6$ $[MH]^+$: 548.3, found: 548.4; HRMS (EI+) m/z calculated for $C_{20}H_{20}NO_3$ $[M - C_{13}H_{21}NO_3]^+$: 322.1443, found: 322.1445, m/z calculated for $C_{13}H_{21}O_3$ $[M - C_{20}H_{20}NO_3]^+$: 225.1491, found: 225.1490.

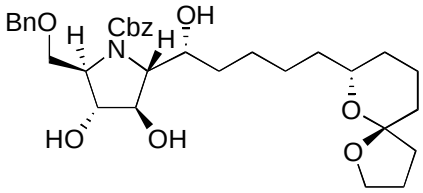


57

(2*S*,5*S*)-2-Benzyloxymethyl-5-[(1*R*)-5-{(5*R*,7*R*)-1,6-dioxa-spiro[4.5]dec-7-yl}-1-hydroxy-pentyl]-2,5-dihydro-pyrrole-1-carboxylic acid benzyl ester (59). To a solution of ketone **58** (200 mg, 0.37 mmol) in 2 mL Et_2O at 0 °C was added DIBAL-H (0.75 mL, 1.0 M in heptane, 0.75 mmol) dropwise over 2 min. The reaction was stirred 1 h, then quenched with 4 mL H_2O and 250 mg potassium sodium tartrate. The reaction was stirred vigorously for 20 min, the reaction extracted with 3 x 5 mL Et_2O. The organic layers were combined, extracted with 5 mL saturated aqueous NaCl, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography (silica gel, gradient elution 1:2 ? 2:1 Et_2O:PE) to yield 27 mg of diastereomer **60** (14%, 0.049 mmol) [R_f=0.69 (1:1 EtOAc:PE)] and 122 mg of diastereomer **59** (61%, 0.27 mmol) as clear, colorless oils. Total yield 76%, 4.5:1 dr. $[\alpha]_D^{24}$ = -95 (c 1.54, $CHCl_3$); R_f = 0.53 (1:1 EtOAc:PE); IR (thin film) 3440, 3032, 2936, 1694, 1634, 1455, 1417, 1354, 1328, 1214, 1105, 1009, 958, 916, 826, 736, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 4:1 mixture of amide rotamers **Major**: δ 7.36-7.23 (m, 10H), 5.88 (dt, J=6.4, 2.0 Hz, 1H), 5.70 (dt, J=6.4, 1.8 Hz, 1H), 5.10 (d, J=12.2 Hz, 1H), 5.06 (d, J=12.2 Hz, 1H), 4.87 (m, 1H), 4.63 (m, 1H), 4.42 (d, J=12.2, Hz, 1H), 4.37 (d, J=12.2 Hz, 1H), 4.12 (d, J=9.5 Hz, 1H), 3.85 (m, 3H), 3.69 (m, 2H), 3.56 (dd, J=9.3, 6.0 Hz, 1H), 2.03 (m, 1H), 1.92-1.55

(m, 8H), 1.44-1.11 (m, 9H) ppm; **Minor**: δ 7.36-7.23 (m, 10H), 6.02 (d, J=6.5 Hz, 1H), 5.73 (d, J=6.5 Hz, 1H), 5.19 (d, J=12.2 Hz, 1H), 5.12 (d, J=12.2 Hz, 1H), 4.74 (m, 1H), 4.63 (m, 1H), 4.50 (s, 2H), 4.04 (m, 1H), 3.85 (m, 4H), 3.69 (m, 2H), 2.03 (m, 1H), 1.92-1.11 (m, 17H) ppm; ^{13}CNMR (125 MHZ, $CDCl_3$) δ 155.7, 138.1, 136.1, 129.5, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.6, 127.5, 127.4, 105.8, 73.1, 72.6, 72.1, 70.2, 67.4, 66.6, 65.3, 37.8, 36.3, 32.9, 31.3, 30.9, 29.7, 26.4, 25.7, 23.7, 20.5 ppm; MS (+ESI) m/z calculated for $C_{33}H_{43}NNaO_6$ $[M + Na]^+$: 572.3, found: 572.3.4, m/z calculated for $C_{33}H_{44}NO_6$ $[M + H]^+$: 550.3, found: 550.4; HRMS (EI+) m/z calculated for $C_{26}H_{36}NO_5$ $[M - C_7H_7O\ (OBn)]^+$: 442.2593, found: 442.2586.

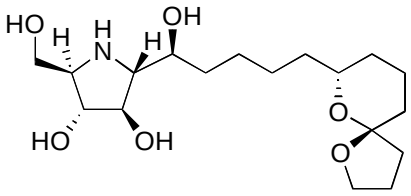
The absolute stereochemistry of the secondary alcohol was determined by formation of (*R*)- and (*S*)-O-methylmandelate esters and analysis of their ^{1}H NMR spectra.[1]



61

(2*R*,3*R*,4*R*,5*R*)-2-Benzyloxymethyl-5-[(1*R*)-5-{(5*R*,7*R*)-1,6-dioxa-spiro[4.5]dec-7-yl}-1-hydroxy-pentyl]-3,4-dihydroxy-pyrrolidine-1-carboxylic acid benzyl ester (63). To a vial with alkene **59** (100 mg, 0.182 mmol) was added 1 mL CH_3CN, and 400 μL $4x10^{-4}$ M EDTA in H_2O. The solution was cooled to 0 °C and 1,1,1-trifluoroacetone (407 μL, 4.5 mmol) was added. A mixture of solid Oxone (1.12 g, 1.82 mmol) and $NaHCO_3$ (350 mg, 4.5 mmol) was added in 4 portions over 45 min. The reaction was stirred 2 h, then diluted with 10 mL H_2O, and extracted with 3 x 20 mL CH_2Cl_2. The organic layers were combined, and concentrated to yield the crude epoxide as a mixture of diastereomers. The product was purified by flash chromatography (silica gel, gradient elution 1:2 ? 2:1 Et_2O:PE) to yield 69.5 mg **62** (68%, 0.123 mmol) as a mixture of epoxides. To a vial containing the mixture of epoxides **62** (50.3 mg, 0.088 mmol) was added 300 μL 10% TFA in 3:2 THF:H_2O. The reaction was stirred under N_2 and heated in an 70 °C oil bath 4 h. The reaction was cooled to rt, quenched with 5 mL saturated aqueous $NaHCO_3$, and extracted with 3 x 5 mL Et_2O. The organic layers were combined, dried over Na_2SO_4, and concentrated. The product was purified by flash chromatography (silica gel, gradient elution 1:1 ? 4:1 Et_2O:PE) to yield 38.0 mg **63** (74%, 0.065 mmol) as a clear oil. $[\alpha]_D^{24}$ = -11 (c 0.70, $CHCl_3$); R_f = 0.39 (2:1 EtOAc:PE); IR (thin film) 3374, 2930, 1700, 1455, 1412, 1348, 1213, 1084, 1010, 736, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 1.3:1 mixture of amide rotamers **Major**: δ 7.37-7.21 (m, 10H), 5.13 (m, 1H),

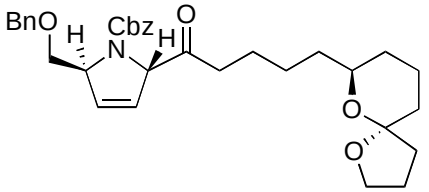
5.06 (d, J=12.1 Hz, 1H), 4.98 (d, J=12.2 Hz, 1H), 4.78 (d, J=12.1 Hz, 1H), 4.60 (m, 1H), 4.44 (d, J=12.0 Hz, 1H), 4.36 (d, J=11.8, Hz, 1H), 4.13 (bt, J=5.7 Hz, 1H), 4.06 (d, J=12.0 Hz, 1H), 4.00 (m, 1H), 3.87 (m, 4H), 3.69 (m, 1H), 3.51 (d, J=8.6 Hz, 1H), 2.73 (bs, 1H), 2.03 (m, 1H), 1.85 (m, 2H), 1.71-1.15 (m, 13H) ppm; **Minor**: δ 7.36-7.21 (m, 10H), 5.17 (d, J=12.4 Hz, 1H), 5.13 (m, 1H), 5.11 (d, J=12.4 Hz, 1H), 4.84 (d, J=12.1 Hz, 1H), 4.55 (d, J=12.0 Hz, 1H), 4.49 (d, J=12.0 Hz, 1H), 4.30 (dd, J=9.8, 2.8 Hz, 1H), 4.05 (d, J=11.8 Hz, 1H), 4.00 (m, 2H), 3.87 (m, 4H), 3.69 (m, 1H), 3.57 (d, J=9.8 Hz, 1H), 2.03 (m, 1H), 1.85 (m, 2H), 1.71-1.15 (m, 13H) ppm; ^{13}CNMR (125 MHZ, $CDCl_3$) δ 154.5, 154.3, 136.5, 136.4, 136.3, 136.2, 128.7, 128.6, 128.6, 128.6, 128.3, 128.2, 128.0, 127.9, 127.9, 105.9, 80.5, 79.6, 76.5, 75.8, 73.8, 73.6, 73.4, 72.7, 71.2, 70.1, 69.4, 69.0, 68.3, 67.6, 66.9, 66.7, 37.8, 35.9, 35.8, 34.4, 34.2, 32.8, 30.9, 29.7, 25.9, 25.7, 25.5, 25.3, 23.6, 20.4 ppm; HRMS (EI+) m/z calculated for $C_{25}H_{38}NO_6$ $[M - OCOBn]^+$: 448.2699, found: 448.2684.



64

(2*R*,3*R*,4*R*,5*R*)-2-[(1*S*)-5-{(5*R*,7*R*)-1,6-Dioxa-spiro[4.5]dec-7-yl}-1-hydroxy-pentyl]-5-hydroxymethyl-pyrrolidine-3,4-diol (66). To a solution of ketone **58** (150 mg, 0.27 mmol) in 2 mL MeOH at 0 °C was added $NaBH_4$ (21 mg, 0.056 mmol) in one portion. The reaction was stirred at 0°C 2.5 h, then quenched with 5 mL H_2O, the reaction stirred 15 min, then warmed to rt. H_2O, 25 mL, was added and the reaction extracted with 3 x 25 mL Et_2O. The organic layers were combined, dried over Na_2SO_4, and concentrated. The product was purified by flash chromatography (silica gel, gradient elution 1:2 ? 2:1 Et_2O:PE) to yield 34.7 mg of diastereomer **59** (23%, 0.063 mmol) [R_f=0.53 (1:1 EtOAc:PE)] and 90.7 mg of diastereomer **60** (60%, 0.17 mmol) as clear, colorless oils. Total yield 83%, 2.6:1 dr. To a vial with alkene **60** (61 mg, 0.11 mmol) was added 1 mL CH_3CN, and 500 μL $4x10^{-4}$ M EDTA in H_2O. The solution was cooled to 0 °C and 1,1,1-trifluoroacetone (400 μL, 4.5 mmol) was added. A mixture of solid Oxone (650 mg, 1.05 mmol) and Na_2CO_3 (111 mg, 1.05 mmol) was added in 4 portions over 45 min. The reaction was stirred 1.5 h, then diluted with 5 mL H_2O, and extracted with 3 x 10 mL CH_2Cl_2. The organic layers were combined, and concentrated to yield the crude epoxide as a mixture of diastereomers. The product was

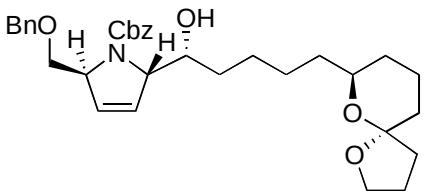
purified by flash chromatography (silica gel, gradient elution 1:2 ? 2:1 Et_2O:PE) to yield 46.6 mg (75%, 0.082 mmol) of a mixture of epoxides. To a vial containing the mixture of epoxides **60** (46.6 mg, 0.082 mmol) was added 300 μL 10% TFA in 3:2 THF:H_2O. The reaction was stirred under N_2 and heated in an 70 °C oil bath 4 h. The reaction was cooled to rt, quenched with 5 mL saturated aqueous $NaHCO_3$, and extracted with 3 x 5 mL Et_2O. The organic layers were combined, dried over Na_2SO_4, and concentrated. The product was purified by flash chromatography (silica gel, gradient elution 1:1 ? 4:1 Et_2O:PE) to yield 30.0 mg **65** (63%, 0.051 mmol) as a clear oil. The combined yield over 2 steps is 47%. To a vial with triol **65** (25.0 mg, 0.043 mmol) is added 10% Pd/C (11.4 mg, 0.010 mmol, 25 mol%). The flask was flushed with N_2, and 500 μL MeOH was added via syringe, followed by 2 drops concentrated HCl. A baloon of H_2 was bubbled through the stirring solution 5 min, then the reaction stirred under H_2 at rt 2 h. The reaction was filtered through a plug of Celite, the plug rinsed with 10 mL MeOH, and the combined filtrates concentrated. Purification of the product by ion exchange chromatography [DOWEX50W-X2 (H^+ form), gradient elution H_2O then 1 M aqueous NH_4OH] provides 12.5 mg **66** (81%, 0.035 mmol) as a light white film. $[\alpha]_D^{25}$ = -35 (c 1.25, MeOH); R_f = 0.80 (5:1:1 $CHCl_3$:MeOH:56% aq. NH_4OH); IR (thin film 3356, 2937, 1683, 1458, 1202 cm^{-1}; ^1H NMR (500 MHz, pyridine-d_5) δ 6.89 (bs, 1H, -OH), 6.72 (bs, 1H, -OH), 6.30 (bs, 1H, -OH), 6.01 (bs, 1H, -OH), 4.80 (t, J=5.4 Hz, 1H), 4.66 (t, J=6.0 Hz, 1H), 4.33 (dd, J=9.8, 5.3 Hz, 1H), 4.20 (dd, J=10.0, 4.8 Hz, 1H), 4.17 (dd, J=9.8, 5.3 Hz, 1H), 3.92-3.74 (m, 5H), 2.00-1.71 (m, 6H), 1.71-1.55 (m, 7H), 1.50-1.37 (m, 4H), 1.10 (m, 1H) ppm; ^{13}CNMR (125 MHZ, pyridine-d_5) δ 105.8, 80.9, 80.6, 74.1, 70.4, 67.5, 66.3, 66.3, 63.7, 38.4, 36.9, 35.0, 33.1, 31.6, 26.7, 26.1, 24.4, 21.0 ppm. HRMS (EI+) m/z calculated for $C_{18}H_{33}NO_6$ $[M]^+$: 359.2308, found: 359.2284.



65

(2*S*,5*S*)-2-Benzyloxymethyl-5-[5-{(5*S*,7*S*)-1,6-dioxa-spiro[4.5]dec-7-yl}-pentanoyl]-2,5-dihydro-pyrrole-1-carboxylic acid benzyl ester (67). Mg chips (Aldrich, 99.95%) were washed successively in a Büchner funnel with vacuum filtration with: 10 % aqueous HCl, H_2O, EtOH, acetone, and Et_2O and dried overnight under vacuum. To a 25 mL flask was added the Mg chips (450 mg, 18.5 mmol) and $HgCl_2$ (5 mg, 0.018 mmol) the flask flame-dried under vacuum. The flask was purged with Ar 3 times and 1 mL THF was added

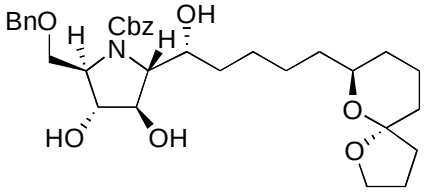
followed by bromide **(*ent*)-52** (307 mg, 1.10 mmol). The reaction was placed in a 65 °C oil bath and stirred 30 min. The resulting green-black solution was cooled to rt and a solution of Weinreb amide **41** (381 mg, 0.93 mmol) in a solution of 600 μL benzene was added and the reaction was stirred at rt 3 h. The reaction was poured into 25 mL saturated aqueous NH_4Cl, stirred vigourously 30 min, diluted with 30 mL Et_2O, the organic layer separated, and the aqueous phase washed with 2 x 30 mL ether. The combined organic layers were washed with 25 mL saturated aqueous $NaHCO_3$, 25 mL satuarated aqueous NaCl, dried over Na_2SO_4, and concentrated to yield a yellow oil. The residue was purified by flash chromatography (silica gel, 4:1 PE:EtOAc) to yield 325 mg **67** (65%, 0.59 mmol) as a clear, light yellow oil. $[\alpha]_D^{26}$ = -230 (c 1.02, $CHCl_3$); R_f = 0.74 (1:1 PE:EtOAc); IR (thin film) 2938, 2868, 1711, 1455, 1411, 1352, 1214, 1104, 1008, 738, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 3:2 mixture of amide rotamers **Major**: δ 7.36-7.22 (m, 10H), 6.05 (dt, J=6.3, 2.0 Hz, 1H), 5.65 (dt, J=6.2, 2.1 Hz, 1H), 5.14-5.09 (m, 3H), 4.89 (m, 1H), 4.53 (d, J=12.2 Hz, 1H), 4.50 (d, J=12.2 Hz, 1H), 3.91-3.78 (m, 3H), 3.73 (dd, J=9.4, 2.8 Hz, 1H), 3.62 (m, 2H), 2.25 (dt, J=17.5, 7.5 Hz, 1H), 2.09 (dt, J=17.5, 7.5 Hz, 1H), 2.01 (m, 1H), 1.92-1.75 (m, 3H), 1.71-1.50 (m, 6H), 1.43-1.07 (m, 6H) ppm; **Minor**: δ 7.36-7.22 (m, 10H), 6.01 (dt, J=6.3, 2.0 Hz, 1H), 5.71 (dt, J=6.4, 2.0 Hz, 1H), 5.00 (m, 3H), 4.79 (m, 1H), 4.44 (d, J=12.3 Hz, 1H), 4.40 (d, J=12.3 Hz, 1H), 3.91-3.78 (m, 3H), 3.62 (m, 3H), 2.48 (ddd, J=17.3, 8.4, 6.2 Hz, 1H), 2.35 (ddd, J=17.4, 8.4, 6.5 Hz, 1H), 2.01 (m, 1H), 1.92-1.07 (m, 15H) ppm; ^{13}C NMR (125 MHZ, $CDCl_3$) δ 207.07, 206.44, 154.10, 133.54, 138.12, 137.95, 136.14, 135.87, 136.14, 135.87, 132.15, 132.10, 128.44, 128.42, 128.32, 128.18, 128.15, 128.09, 128.05, 127.62, 127.52, 127.39, 124.91, 124.84, 105.69, 74.32, 74.26, 73.30, 73.15, 70.11, 69.95, 69.90, 69.01, 67.26, 67.09, 66.59, 65.41, 64.49, 38.10, 37.73, 36.93, 35.84, 32.76, 30.83, 25.16, 25.11, 23.60, 23.13, 23.04, 20.35 ppm; MS (+ESI) m/z calculated for $C_{33}H_{42}NO_6$ $[M + H]^+$: 548.4, found: 548.4; HRMS (EI+) m/z calculated for $C_{25}H_{32}NO_5$ $[M - C_8H_9O (CH_2OBn)]^+$: 426.2285, found: 426.2262.



66

(2*S*,5*S*)-2-Benzyloxymethyl-5-[(1*R*)-5-{(5*S*,7*S*)-1,6-dioxa-spiro[4.5]dec-7-yl}-1-hydroxy-pentyl]-2,5-dihydro-pyrrole-1-carboxylic acid benzyl ester (68). To a solution of ketone **67** (300 mg, 0.55 mmol) in 2 mL Et_2O at 0 °C was added DIBAL-H (1.0 mL, 1.0 M in hexanes, 1.0 mmol) dropwise over 2 min. The reaction was stirred 1 h, then quenched with 4

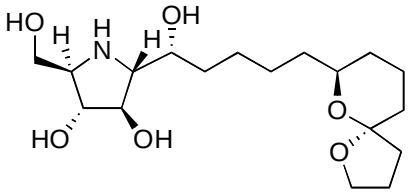
mL H_2O and 250 mg potassium sodium tartrate. The reaction was stirred vigorously for 20 min, the reaction extracted with 3 x 5 mL Et_2O. The organic layers were combined, extracted with 5 mL saturated aqueous NaCl, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography (silica gel, gradient elution 1:2 ? 2:1 Et_2O:PE) to yield 45 mg of diastereomer **71** (15%, 0.082 mmol) [R_f=0.69 (1:1 EtOAc:PE)] and 189 mg of diastereomer **68** (63%, 0.345 mmol) as clear, colorless oils. Total yield 78%, 4.2:1 dr. $[\alpha]_D^{24}$ = -159 (c 0.62, $CHCl_3$); R_f = 0.53 (1:1 EtOAc:PE); IR (thin film) 3439, 3032, 2936, 2864, 1704, 1633, 1455, 1417, 1354, 1327, 1214, 1106, 1009, 958, 916, 826, 738, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 4:1 mixture of amide rotamers **Major**: δ 7.35-7.22 (m, 10H), 5.88 (dt, J=6.4, 2.1 Hz, 1H), 5.70 (dt, J=6.4, 1.9 Hz, 1H), 5.09 (d, J=12.2 Hz, 1H), 5.06 (d, J=12.2 Hz, 1H), 4.86 (m, 1H), 4.63 (m, 1H), 4.42 (d, J=12.2, Hz, 1H), 4.37 (d, J=12.2 Hz, 1H), 4.14 (d, J=9.5 Hz, 1H), 3.87 (m, 3H), 3.71 (dd, J=9.3, 2.7 Hz, 1H), 3.67 (m, 1H), 3.56 (dd, J=9.3, 6.0 Hz, 1H), 2.02 (m, 1H), 1.93-1.55 (m, 8H), 1.44-1.11 (m, 9H) ppm; **Minor**: δ 7.35-7.22 (m, 10H), 6.02 (d, J=6.5 Hz, 1H), 5.72 (d, J=6.5 Hz, 1H), 5.18 (d, J=12.2 Hz, 1H), 5.11 (d, J=12.2 Hz, 1H), 4.73 (m, 1H), 4.63 (m, 1H), 4.50 (s, 2H), 4.04 (m, 1H), 3.87 (m, 4H), 3.67 (m, 2H), 2.03 (m, 1H), 1.92-1.11 (m, 17H) ppm; ^{13}CNMR (125 MHZ, $CDCl_3$) δ 155.7, 153.8, 138.4, 138.1, 136.1, 132.0, 131.2, 129.5, 128.5, 128.3, 128.25, 128.17, 128.1, 128.0, 127.6, 127.5, 127.4, 125.1, 105.7, 73.2, 73.1, 72.6, 72.0, 71.2, 70.2, 70.1, 68.8, 67.3, 66.9, 66.6, 65.6, 65.3, 37.8, 36.1, 33.6, 32.8, 31.3, 30.9, 29.6, 26.4, 26.3, 25.7, 25.5, 23.6, 20.4 ppm; MS (+ESI) m/z calculated for $C_{33}H_{43}NNaO_6$ $[M + Na]^+$: 572.3, found: 572.4, m/z calculated for $C_{33}H_{44}NO_6$ $[M + H]^+$: 550.3, found: 550.4; HRMS (EI+) m/z calculated for $C_{31}H_{40}NO_5$ $[M – C_2H_3O]^+$: 506.2906, found: 506.2917.



67

(2*R*,3*R*,4*R*,5*R*)-2-Benzyloxymethyl-5-[(1*R*)-5-{(5*S*,7*S*)-1,6-dioxa-spiro[4.5]dec-7-yl}-1-hydroxy-pentyl]-3,4-dihydroxy-pyrrolidine-1-carboxylic acid benzyl ester (69). To a vial with alkene **68** (140 mg, 0.255 mmol) was added 2.5 mL CH_3CN, and 1 mL $4x10^{-4}$ M EDTA in H_2O. The solution was cooled to 0 °C and 1,1,1-trifluoroacetone (800 μL, 8.9 mmol) was added. A mixture of solid Oxone (1.3 g, 2.11 mmol) and Na_2CO_3 (350 mg, 4.2 mmol) was added in 4 portions over 45 min. The reaction was stirred 2 h, then diluted with 20 mL H_2O, and extracted with 3 x 25 mL CH_2Cl_2. The organic layers were combined, and concentrated

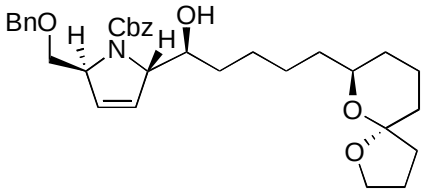
to yield the crude epoxide as a mixture of diastereomers. The product was purified by flash chromatography (silica gel, gradient elution 1:2 ? 2:1 Et_2O:PE) to yield 98.5 mg (68%, 0.174 mmol) of a mixture of epoxides. To a vial containing the mixture of epoxides (78 mg, 0.138 mmol) was added 300 μL 10% TFA in 3:2 THF:H_2O. The reaction was stirred under N_2 and heated in an 70 °C oil bath 12 h. The reaction was cooled to rt, quenched with 5 mL saturated aqueous $NaHCO_3$, and extracted with 3 x 5 mL Et_2O. The organic layers were combined, dried over Na_2SO_4, and concentrated. The product was purified by flash chromatography (silica gel, gradient elution 1:1 ? 4:1 Et_2O:PE) to yield 66.0 mg **69** (82%, 0.113 mmol) as a clear oil. $[\alpha]_D^{24}$ = -49 (c 2.11, $CHCl_3$); R_f = 0.39 (2:1 EtOAc:PE); IR (thin film) 3375, 2935, 1702, 1456, 1213, 1085, 1010, 916, 739, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 1.3:1 mixture of amide rotamers **Major**: δ 7.37-7.20 (m, 10H), 5.06 (d, J=12.0 Hz, 1H), 4.97 (d, J=12.0 Hz, 1H), 4.78 (d, J=12.1 Hz, 1H), 4.48-4.41 (m, 1H), 4.44 (d, J=11.9 Hz, 1H), 4.35 (d, J=11.9, Hz, 1H), 4.10-4.01 (m, 1H), 3.98(d, J=6.1 Hz, 1H), 3.91-3.78 (m, 4H), 3.68 (m, 1H), 3.51 (d, J=8.5 Hz, 1H), 2.03 (m, 1H), 1.93-1.12 (m, 17H) ppm; **Minor**: δ 7.37-7.20 (m, 10H), 5.15 (d, J=12.3 Hz, 1H), 5.10 (d, J=12.3 Hz, 1H), 4.84 (d, J=12.1 Hz, 1H), 4.55 (d, J=11.8 Hz, 1H), 4.49 (d, J=11.8 Hz, 1H), 4.28 (dd, J=9.9, 2.8 Hz, 1H), 4.10-4.01 (m, 2H), 3.91-3.78 (m, 4H), 3.56 (d, J=9.8 Hz, 1H), 2.03 (m, 1H), 1.93-1.12 (m, 17H) ppm; ^{13}CNMR (125 MHZ, $CDCl_3$) δ 154.5, 154.4, 136.4, 136.2, 128.69, 128.62, 128.58, 128.55, 128.3, 128.2, 128.0, 127.9, 127.8, 105.9, 80.5, 79.5, 76.4, 75.8, 73.8, 73.6, 73.5, 72.8, 71.2, 70.1, 69.3, 69.0, 68.2, 67.5, 66.9, 66.7, 37.8, 35.7, 34.22, 34.15, 32.8, 30.9, 29.7, 25.9, 25.5, 25.3, 23.6, 20.4 ppm; MS (ESI+) m/z calculated for $C_{33}H_{46}NO_8$ $[M + H]^+$: 584.4, found: 584.3; HRMS (EI+) m/z calculated for $C_{25}H_{38}NO_6$ $[M - C_8H_7O_2 (OCOBn)]^+$: 448.2699, found: 448.2680.



68

(2*R*,3*R*,4*R*,5*R*)-2-[(1*R*)-5-{(5*S*,7*S*)-1,6-Dioxa-spiro[4.5]dec-7-yl}-1-hydroxy-pentyl]-5-hydroxymethyl-pyrrolidine-3,4-diol (70). To a vial with triol **69** (20 mg, 0.034 mmol) is added 10% Pd/C (10 mg, 0.0094 mmol, 28 mol%). The flask was flushed with N_2, and 500 μL MeOH was added via syringe, followed by 2 drops concentrated HCl. A baloon of H_2 was bubbled through the stirring solution 5 min, then the reaction stirred under H_2 at rt 2 h. The reaction was filtered through a plug of Celite, the plug rinsed with 10 mL MeOH, and the combined filtrates concentrated. Purification of the product by ion exchange chromatography

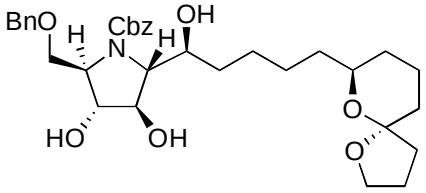
(DOWEX50W-X2 (H^+ form), gradient elution H_2O then 1 M aqueous NH_4OH) provides 11.7 mg **70** (96%, 0.033 mmol) as a light white film. $[\alpha]_D^{26}$ = -19 (c 1.17, MeOH); R_f = 0.80 (5:1:1 $CHCl_3$:MeOH:56% aq. NH_4OH); IR (thin film) 3356, 2937, 1683, 1458, 1202 cm^{-1}; ^1H NMR (500 MHz, pyridine-d_5) δ 6.92 (d, J=5.6 Hz, 1H, -OH), 6.78 (dd, J=7.9, 5.1 Hz, 1H, -OH), 6.31 (t, J=5.2 Hz, 1H, -OH), 6.01 (d, J=4.4 Hz, 1H, -OH), 4.93 (q, J=6.0 Hz, 1H), 4.71 (q, J=5.7 Hz, 1H), 4.21 (m, 1H), 4.18 (m, 1H), 3.83-3.77 (m, 4H), 3.62 (t, J=5.2 Hz, 1H), 2.00-1.71 (m, 6H), 1.71-1.54 (m, 7H), 1.48-1.37 (m, 4H), 1.12 (m, 1H) ppm; ^{13}CNMR (125 MHZ, pyridine-d_5) δ 105.83, 80.55, 80.39, 74.07, 70.22, 67.52, 66.68, 65.86, 63.51, 38.11, 36.71, 35.03, 33.30, 31.30, 26.79, 26.23, 24.08, 20.92 ppm. HRMS (EI+) m/z calculated for $C_{18}H_{33}NO_6$ $[M]^+$: 359.2308, found: 359.2199.



69

(2*S*,5*S*)-2-benzyloxymethyl-5-[(1*S*)-5-{(5*S*,7*S*)-1,6-dioxa-spiro[4.5]dec-7-yl}-1-hydroxy-pentyl]-2,5-dihydro-pyrrole-1-carboxylic acid benzyl ester (71). To a solution of ketone **67** (430 mg, 0.79 mmol) in 5 mL MeOH at 0 °C was added $NaBH_4$ (60 mg, 1.58 mmol) in one portion. The reaction was stirred at 0°C 2 h, then quenched with 10 mL H_2O, the reaction stirred 15 min, then warmed to rt. H_2O, 50 mL, was added and the reaction extracted with 3 x 50 mL Et_2O. The organic layers were combined, dried over Na_2SO_4, and concentrated. The product was purified by flash chromatography (silica gel, gradient elution 1:2 ? 2:1 Et_2O:PE) to yield 100 mg of diastereomer **68** (23%, 0.18 mmol) [R_f=0.53 (1:1 EtOAc:PE)] and 270 mg of diastereomer **71** (63%, 0.49 mmol) as clear, colorless oils. Total yield 83%, 2.7:1 dr. $[\alpha]_D^{24}$ = -206 (c 1.08, $CHCl_3$); R_f = 0.69 (1:1 EtOAc:PE); IR (thin film) 3453, 2937, 2864, 1704, 1454, 1413, 1354, 1324, 1213, 1105, 1016, 738, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 5:2 mixture of amide rotamers **Major**: δ 7.36-7.21 (m, 10H), 5.86 (m, 2H), 5.08 (d, J=12.8 Hz, 1H), 5.04 (d, J=12.8 Hz, 1H), 4.67 (m, 1H), 4.62 (m, 1H), 4.40 (d, J=12.2, Hz, 1H), 4.35 (d, J=12.2 Hz, 1H), 3.95-3.80 (m, 3H), 3.68 (dd, J=9.3, 2.6 Hz, 1H), 3.54 (dd, J=9.3, 6.0 Hz, 1H). 2.02 (m, 1H), 1.93-1.10 (m, 17H) ppm; **Minor**: δ 7.36-7.21 (m, 10H), 5.95 (d, J=6.3 Hz, 1H), 5.86 (m, 1H), 5.19 (d, J=12.2 Hz, 1H), 5.06 (m, J=12.2 Hz, 1H), 5.06 (m, 1H), 4.71 (m, 1H), 4.50 (m, 2H), 4.14 (m, 1H), 3.95-3.80 (m, 3H), 3.66 (m, 3H), 2.02 (m, 1H), 1.92-1.10 (m, 17H) ppm; ^{13}CNMR (125 MHZ, $CDCl_3$) δ 155.9, 153.8, 138.4, 138.1, 136.4, 136.0,

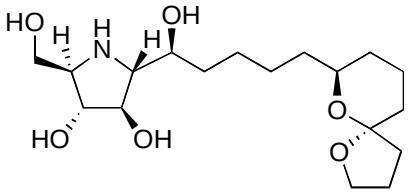
129.6, 129.0, 128.5, 128.4, 128.3, 128.2, 128.1, 127.6, 127.41, 127.36, 127.1, 126.8, 105.8, 74.3, 73.2, 73.1, 72.0, 71.8, 70.23, 70.17, 69.2, 68.9, 67.4, 66.8, 66.6, 65.7, 64.8, 37.8, 36.2, 33.0, 32.8, 30.9, 30.5, 29.7, 26.0, 25.7, 25.6, 25.3, 23.6, 20.4 ppm; MS (+ESI) m/z calculated for $C_{33}H_{43}NNaO_6$ $[M + Na]^+$: 572.3, found: 572.3.4; HRMS (EI+) m/z calculated for $C_{26}H_{35}NO_5$ $[M – (H + OBn)]^+$: 441.2515, found: 441.2487.



70

(2*R*,3*R*,4*R*,5*R*)-2-Benzyloxymethyl-5-[(1*S*)-5-{(5*S*,7*S*)-1,6-dioxa-spiro[4.5]dec-7-yl}-1-hydroxy-pentyl]-3,4-dihydroxy-pyrrolidine-1-carboxylic acid benzyl ester (72). To a vial with alkene **71** (50 mg, 0.091 mmol) was added 1 mL CH_3CN, and 500 μL $4x10^{-4}$ M EDTA in H_2O. The solution was cooled to 0 °C and 1,1,1-trifluoroacetone (300 μL, 3.4 mmol) was added. A mixture of solid Oxone (660 mg, 1.07 mmol) and Na_2CO_3 (113 mg, 1.07 mmol) was added in 4 portions over 45 min. The reaction was stirred 2 h, then diluted with 10 mL H_2O, and extracted with 3 x 20 mL CH_2Cl_2. The organic layers were combined, and concentrated to yield the crude epoxide as a mixture of diastereomers. The product was purified by flash chromatography (silica gel, gradient elution 1:2 ? 2:1 Et_2O:PE) to yield 31 mg (60%, 0.055 mmol) of a mixture of epoxides. R_f=0.8 (2:1 EtOAc:PE). To a vial containing the mixture of epoxides (31 mg, 0.055 mmol) was added 2 mL 10% TFA in 3:2 THF:H_2O. The reaction was stirred under N_2 and heated in an 70 °C oil bath 5 h. The reaction was cooled to rt, quenched with 5 mL saturated aqueous $NaHCO_3$, and extracted with 3 x 5 mL Et_2O. The organic layers were combined, dried over Na_2SO_4, and concentrated. The product was purified by flash chromatography (silica gel, gradient elution 1:1 ? 4:1 Et_2O:PE) to yield 25.0 mg **72** (78%, 0.043 mmol) as a clear oil. $[\alpha]_D^{24}$ = -100 (c 1.07, $CHCl_3$); R_f = 0.69 (2:1 EtOAc:PE); IR (thin film) 3407, 2929, 1674, 1455, 1412, 1349, 1213, 1088, 1010, 736, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 1.2:1 mixture of amide rotamers δ 7.37-7.21 (m, 10H), 5.16 (m, 0.6H), 5.07 (m, 1.6H), 4.69 (d, J=11.7 Hz, 1.2H), 4.55 (d, J=11.2 Hz, 0.5H), 4.50 (d, J=9.7 Hz, 0.5H), 4.46 (d, J=11.5 Hz, 0.5H), 4.35 (d, J=12.1 Hz, 0.6H), 4.31 (d, J=12.1 Hz, 0.6H), 4.09-3.80 (m, 9 H), 3.69 (bt, J=5.7 Hz, 0.6 H), 3.63 (m, 0.5 H), 3.56 (d, J=9.5 Hz, 0.5 H), 3.45 (d, J=10.0 Hz, 0.6H), 3.00 (bs, 0.5 H), 2.02-0.87 (m, 21H) ppm; ^{13}CNMR (125 MHZ, $CDCl_3$) δ 155.0, 154.8, 136.4, 136.3, 128.7, 128.6, 128.4, 128.3, 127.9, 121.8, 105.8, 94.7, 81.7, 81.0, 79.6, 75.2, 74.8, 74.6, 73.7, 73.5, 72.6, 71.2, 70.2, 68.6,

67.6, 67.4, 67.1, 66.7, 37.8, 36.0, 32.9, 30.9, 29.7, 29.3, 25.8, 25.3, 23.7, 20.4 ppm; MS (ESI+) m/z calculated for $C_{33}H_{46}NO_8$ $[M + H]^+$: 584.3, found: 584.4. HRMS (EI+) m/z calculated for $C_{25}H_{38}NO_6$ $[M - C_8H_7O_2 (OCOBn)]^+$: 448.2699, found: 448.2697.



71

(2*R*,3*R*,4*R*,5*R*)-2-[(1*S*)-5-{(5*S*,7*S*)-1,6-Dioxa-spiro[4.5]dec-7-yl}-1-hydroxy-pentyl]-5-hydroxymethyl-pyrrolidine-3,4-diol (73). To a vial with triol **72** (15.0 mg, 0.027 mmol) is added 10% Pd/C (10 mg, 0.009 mmol, 30 mol%). The flask was flushed with N_2, and 1 mL MeOH was added via syringe, followed by 2 drops concentrated HCl. A baloon of H_2 was bubbled through the stirring solution 5 min, then the reaction stirred under H_2 at rt 4 h. The reaction was filtered through a plug of Celite, the plug rinsed with 10 mL MeOH, and the combined filtrates concentrated. Purification of the product by ion exchange chromatography (DOWEX50W-X2 (H^+ form), gradient elution H_2O then 1 M aqueous NH_4OH) provides 8.5 mg **73** (88%, 0.024 mmol) as a light white film. $[\alpha]_D^{25}$ = +27 (c 1.01, MeOH); R_f = 0.80 (5:1:1 $CHCl_3$:MeOH:56% aq. NH_4OH); IR (thin film) 3356, 2937, 1683, 1458, 1202 cm^{-1}; ^1H NMR (500 MHz, pyridine-d_5) δ 6.85 (bs, 1H, -OH), 6.73 (bs, 1H, -OH), 6.35 (bs, 1H, -OH), 6.02 (bs, 1H, -OH), 4.81 (t, J=5.2 Hz, 1H), 4.65 (t, J=5.7 Hz, 1H), 4.15 (dd, J=9.8, 5.5 Hz, 1H), 4.29 (dd, J=9.8, 4.0 Hz, 1H), 4.25 (dd, J=6.4, 4.8 Hz, 1H), 3.92-3.76 (m, 5H), 2.00-1.71 (m, 6H), 1.72-1.55 (m, 7H), 1.50-1.37 (m, 4H), 1.10 (m, 1H) ppm; ^{13}CNMR (125 MHZ, pyridine-d_5) δ 105.8, 81.0, 80.8, 74.1, 70.4, 67.4, 66.3, 66.1, 63.7, 38.4, 36.9, 35.0, 33.1, 31.5, 26.6, 26.2, 24.3, 21.0 ppm. HRMS (EI+) m/z calculated for $C_{18}H_{33}NO_6$ $[M]^+$: 359.2308, found: 359.2291.