Supporting Information for

Two Syntheses of the 16- and 17-Membered DEF Ring Systems of Chloropeptin and Complestatin

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General: All reaction were carried out under an atmosphere of nitrogen using flame-dried glassware. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium metal-benzophenone ketyl. Aldrich Chemical Company supplied Dimethylformamide (DMF) in Sure-Seal bottles. Hexanes was redistilled (reagent grade, Fisher). Absolute ethanol was purchased from AAPER alcohol and chemical company. All other solvents were used without further purification. Triethylamine (TEA) and N-methylmorpholine (NMM) were purchased from Aldrich Chemical Company and stored over potassium hydroxide. All amino acids were purchased from Aldrich and Chem-Impex. N-toluenesulfonylisocyanate was obtained from Aldrich and the (S)-Tol-BINAP and $PdCl_2$(dppf) were purchased from Strem Chemical. All other reagents were purchased from Aldrich.

^{1}H NMR spectra were taken on a 300 MHz Bruker Aspect 3000 system in $CDCl_3$ unless noted otherwise. Chemical shifts were reported in ppm (δ units) downfield from tetramethylsilane. Electron Impact mass spectra (EIMS) and high-resolution mass spectra (HRMS) were determined on a Kratos MS-80RFA spectrometer. LSIMS and high-resolution mass spectra (HRMS) were determined on a VG Auto Spec spectrometer.

Experimental Procedures:

(R)-6-Bromo-N-tosyl-trytophan ethyl ester (10). To a dry 10 mL round bottom flask was added 0.010g of Cu(I)$(CH_3CN)_4ClO_4$ (0.030 mmol) and 0.026g of (S)-Tol-BINAP (0.038 mmol) in 0.7 mL of BTF. The heterogeneous mixture was allowed to stir at R.T. for 1 hour, during which time the reaction became a yellow homogenous solution. To the above mixture, α–iminoester (0.184g, 0.63 mmol) was added and 6-bromo-N-tosyl-3-methyleneindoline (0.230g, 0.63 mmol) in 3.5 ml BTF. The reaction was allowed to stir at room temperature for 4h, during which time a precipitate formed. The reaction was cooled in an ice bath and the precipitate was filtered to give 0.282g of a white precipitate a 76% yield. When the product did not precipitate out, the product was purified by flash chromatography with silica gel 20% EtOAc/ 80% Hexane to 25% EtOAc/ 75% Hexane. R_f = 0.36 in 30% EtOAc/ 70% Hexane. ^{1}H NMR ($CDCl_3$, 300MHz) δ 1.05 (t, 3H, J = 7.2 Hz), 2.34 (s, 3H), 2.38 (s, 3H), 3.00 (dd, 1H, J = 7.2, 11.1 Hz), 3.12 (dd, 1H, J = 4.8, 14.1 Hz), 3.92 (dq, 2H, J = 2.4, 6.6 Hz), 4.12 (q, 1H, 5.7 Hz), 5.28 (d, 1H, J = 8.7 Hz), 7.12 (d, 2H, J = 7.8 Hz), 7.25 (m, 4H), 7.34 (s, 1H), 7.53 (d, 2H, J = 8.1 Hz), 7.73 (d, 2H, J = 7.8 Hz), 8.08 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.8, 21.5, 21.6, 28.9, 55.5, 62.1, 116.2, 116.6, 118.5, 120.6, 125.3, 126.5, 126.8, 126.9, 129.2, 129.5, 130.1, 134.8, 135.5, 136.1, 143.8, 145.3, 170.7; HRMS (EI)*m/z* calcd for $C_{27}H_{27}N_2O_6S_2Br$ 618.0495, obsd. 618.0494.

(R,R)-{1-[2-*tert*-Butyl-diphenyl-silanyloxy)-1-(4-methoxy-phenyl)-ethyl carbamoyl]-2-phenyl-ethyl}-carbamic acid *tert*-butyl ester (4). To a mixture of Boc-D-phenylalanine (0.184g, 0.56mmol) in 4 mL of acetonitrile were added EDCI (0.129g, 0.67 mmol) and HOBt (0.121g, 0.89 mmol). The reaction was allowed to stir at room temperature and a solution of R-2-amino-2-(3-iodo-4-methoxy)-phenyl)-ethanol in 1mL of acetonitrile was added, followed by the addition of NMM (0.717mL, 0.59 mmol). The

reaction was allowed to stir for 2h at room temperature and concentrated down. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted 3x EtOAc. The organic were washed with brine and dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography with silica gel 50% Hexane/ 50% EtOAc to obtain 75% yield. $R_f = 0.33$ in 50% EtOAc/ 50% Hexane. ^1H NMR (CD_3OD, 300MHz) δ 1.35 (s, 9H), 2.85 (dd, 1H, J = 9.0, 13.8 Hz), 3.05(dd, 1H, J = 5.7, 13.8 Hz), 3.60(d, 2H, J = 6.0 Hz), 3.80 (s, 3H), 4.34 (t, 1H, J = 6.9 Hz), 4.82 (q, 1H, J = 5.7 Hz), 6.83 (d, 1H, J = 8.4 Hz), 7.25 (m, 8H), 7.72 (d, 1H, J = 1.8 Hz); ^{13}C NMR (CD_3OD) δ 28.9, 39.1, 55.4, 56.8, 57.3, 65.6, 80.6, 86.4, 111.8, 127.6, 129.2, 129.4, 130.2, 135.1, 138.4, 139.0, 158.8, 173.8; HRMS *m/z* (EI) calcd for $C_{23}H_{29}N_2O_5I$ 540.1130, obsd 540.1121.

(R,R)-{1-[2-*tert*-Butyl-diphenyl-silanyloxy)-1-(3-iodo-4-methoxy-phenyl)-ethyl carbamoyl]-2-phenyl-ethyl}-carbamic acid *tert*-butyl ester (5). The 4-methoxy-3-iodophenyl glycinol **4** (0.120g, 0.21 mmol) was added to 1.4 mL of CH_2Cl_2, followed by imidazole (0.021g, 0.43 mmol) and TBDPSiCl (0.059g, 0.22 mmol). The reaction was allowed to stir at room temperature for 4h, during which time a white precipitate formed. The organic layer was added to 1N HCl and the organic were separated, the aqueous was then extracted 2x with CH_2Cl_2. The organics were collected, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The oil was purified by flash column chromatography with silica gel 25% EtOAc/75% Hexane. $R_f = 0.27$ in 20% EtOAc/ 80% Hexane. ^1H NMR ($CDCl_3$, 300MHz) δ 0.88 (s, 9H), 1.28 (s, 9H), 2.93 (d, 2H, J = 7.0 Hz), 3.47 (dd, 1H, J = 5.1, 10.2 Hz), 3.54 (dd, 1H, J = 3.4, 10.2 Hz), 3.69 (s, 3H), 4.31 (q, 1H, J = 6.6 Hz), 4.74 (m, 1H), 5.14 (d, 1H, J = 8.4 Hz), 6.53 (d, 1H, J = 8.4 Hz), 6.77 (d, 1H, J = 6.9 Hz), 6.97 (dd, 1H, J = 2.1, 8.7 Hz), 7.01-7.31 (m, 13H), 7.40 (dd, 2H, J = 1.8, 8.1 Hz), 7.49 (d, 1H, J = 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 18.9, 26.6, 28.1, 38.2, 53.3, 56.2, 66.4, 80.0, 85.8, 110.3, 126.7, 127.4, 127.5, 127.6, 128.5, 129.1, 129.2, 129.6, 129.7, 132.3, 132.5, 133.9,

134.7, 135.3, 135.4, 136.6, 137.6, 157.2, 170.5; HRMS (FAB$^+$) $C_{39}H_{47}IN_2O_5Si$ (M+Na$^+$) 801.2197, obsd 801.2230

(R,R)-(1-{2-*tert*-Butyl-diphenyl-silanyloxy)-1-(4-methoxy-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2yl)-phenyl]-ethyl carbamoyl}-2-phenyl-ethyl}-carbamic acid *tert*-butyl ester (11). Iodide **5** (0.165g, 0.200 mmol) was dissolved in 1.4 ml of degassed DMSO. Bis(pinacolato)diboron (0.057g, 0.22 mmol) and KOAc (0.060g, 0.611 mmol) were added to the above mixture and evacuated with nitrogen. The palladium catalyst, $PdCl_2$(dppf) (0.012g, 0.014 mmol), was weighted out under nitrogen and added to the reaction mixture. The reaction was allowed to heat at 80 ° C for 40h, the mixture was allowed to cool to room temperature and diluted with EtOAc and water. The EtOAc was allowed to separate and removed, the water was extracted twice more with EtOAc. The organic were collected, washed 3 times with water and once with brine, then dried over $MgSO_4$. The oily residue was purified by flash chromatography with silica gel 20% EtOAc/ 80% Hexane to give a yellow oil in 75% yield and a R_f = 0.46 in 30% EtOAc/70% Hexane. ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.97 (s, 9H), 1.21 (s, 9H), 1.36 (s, 12H), 3.05 (d, 2H, J = 8.1 Hz), 3.61 (dd, 1H, J = 5.1, 10.5Hz), 3.70 (dd, 1H, J = 3.6, 10.2 Hz), 3.83 (s, 3H), 4.40 (q, 1H, J = 4.8 Hz), 4.93 (q, 1H, J = 6.7 Hz), 5.11 (d, 1H, J = 9.9 Hz), 6.75 (d, 1H, J = 10.2 Hz), 6.80 (d, 1H, J = 9.8 Hz), 7.11-7.46 (m, 13H), 7.52 (dd, 2H, J = 1.8, 9.0 Hz), 7.59 (d, 1H, J = 2.4 Hz), 7.35 (d, 2H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) 19.0, 24.8, 26.8, 28.2, 38.7, 54.0, 56.0, 66.5, 79.9, 83.3, 110.3, 126.8, 127.6, 127.7, 128.5, 129.3, 129.7, 129.7, 131.2, 131.3, 132.7, 132.8, 135.5, 135.6, 136.8, 163.7, 170.2; HRMS (FAB$^+$) $C_{45}H_{59}BN_2O_7Si$ (M+Na$^+$) 800.4119, obsd 800.4112.

(R,R,R)-3-[6-{5-[1-(2-*tert*-Butoxycarbonylamino-3-phenyl-propionylamino)-2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-2-methoxy-phenyl}-1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-2-(toluene-4-sulfonylamino)-propionic acid ethyl ester (12): To a 25 mL

RBF were added phenylalanine boronate **11** (0.407g, 0.53 mmol), N-tosyl-6-bromo-tryptophan **10** (0.207g, 0.35 mmol), K_2CO_3 (0.243g, 1.76 mmol), and $PdCl_2$(dppf) (0.020g) in 4 mL of degassed DME. The reaction was heated to 80 ° C for 20 h. The reaction was cooled to room temperature and the DME was concentrated off. The brown residue was partitioned between EtOAc/ H_2O. The aqueous layer was extracted twice with EtOAc, collected, washed once with brine, dried over $MgSO_4$, filtered, and concentrated down. The brown oil was purified by flash column chromatography with silica 20% EtOAc/ 80% Hexane to 30% EtOAc/70% Hexane to give 0.231g a white solid in 55% yield and a R_f = 0.34 in 30% EtOAc/70% Hexane. ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.97 (s, 9H), 1.02(dt, 3H, J = 3.4, 7.2 Hz), 1.32 (s, 9H), 2.29 (s, 3H), 2.34 (s, 3H), 3.10 (m, 4H), 3.71 (dd, 1H, J = 4.8, 10.2 Hz), 3.78 (dd, 1H, J = 5.1, 10.2 Hz), 3.83 (s, 3H), 3.88 (dq, 2H, J = 3.0, 7.2 Hz), 4.20 (m, 1H), 4.44 (q, 1H, J = 4.5 Hz), 4.97 (q, 1H, J = 4.5 Hz), 5.17 (bs, 1H), 5.40 (dd, 1H, J = 4.5, 8.9 Hz), 6.83 (d, 1H, J = 6.9 Hz), 6.91 (d, 1H, J = 8.1 Hz), 7.09-7.43 (m, 23H), 7.51 (dd, 2H, J = 1.8, 7.8 Hz), 7.59 (dd, 1H, J = 4.8, 8.4 Hz), 7.74 (d, 2H, J = 8.4 Hz), 8.12 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 13.8, 19.1, 21.5 (2), 24.8, 26.7, 28.1, 29.1, 38.3, 54.1, 55.5, 55.7, 61.9, 66.8, 80.1, 81.8, 111.1, 114.7, 116.1, 118.7, 125.0, 126.8, 127.0, 127.6, 127.7, 128.5, 129.3, 129.5, 129.7, 129.8, 130.4, 132.1, 132.6, 132.7, 134.8, 135.1, 135.4, 135.5, 136.4, 136.8, 143.7, 144.8, 155.7, 170.5 170.7; HRMS (FAB$^+$) $C_{66}H_{74}N_4O_{11}S_2Si$ (M+Na$^+$) 1213.4463,obsd 1213.4502

(R,R,R)-3-[6-{5-[1-(2-*tert*-Butoxycarbonylamino-3-phenyl-propionylamino)-2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-2-methoxy-phenyl}-1*H*-indol-3-yl)-2-(toluene-4-sulfonylamino)-propionic acid ethyl ester (13). To a 10 mL RBF was added the corresponding ester **12** (0.190g, 0.17 mmol) dissolved in 1.2 mL of dry EtOH. To the above mixture was added 0.020g of magnesium turnings and ammonium chloride. The reaction was allowed to stir at room temperature for 5h, during which time an evolution of gas was seen and a precipitate formed. The reaction was filtered and the ethanol was

evaporated. The residue was partitioned between aqueous NH_4Cl and ethyl acetate. The aqueous layer was extracted 3x with EtOAc. The organic were collected together and washed 1x with brine and dried over $Mg_2SO_{4,}$ filtered and concentrated down to a white residue. The white residue was purified by flash column chromatography with silica gel 30% EtOAc/70% Hexane to give 0.175g a white solid in 97% yield and a R_f = 0.2 in 30% EtOAc/70% Hexane ^1H NMR ($CDCl_3$, 300MHz) δ 0.97 (s, 9H), 1.01 (t, 3H, J = 6.9 Hz), 1.34 (s, 9H), 2.35 (s, 3H), 3.05 (d, 2H, J = 8.1 Hz), 3.25 (d, 2H, J = 5.4 Hz), 3.66 (dd, 1H, J = 4.5, 10.5 Hz), 3.77 (dd, 1H, J = 3.3, 10.8 Hz), 3.79 (s, 3H), 3.81 (dq, 2H, J = 1.5, 7.2 Hz), 4.26 (dt, 2H, J = 4.8, 9.3 Hz), 4.41 (q, 1H, J = 7.5 Hz), 4.95 (m, 1H), 5.02 (bd, 1H, J = 2.4 Hz), 5.16 (d, 1H, J = 9.0 Hz), 6.70 (d, 1H, J = 6.6 Hz), 6.88 (d, 1H, J = 8.4 Hz), 7.04 (d, 1H, J = 2.4 Hz), 7.10-7.45 (m, 22H), 7.50 (dd, 1H, J = 1.2, 6.9 Hz), 7.64 (dd, 1H, J = 0.9, 8.4 Hz), 8.01 (bs, 1H); ^{13}C NMR ($CDCl_{3,}$ 62.5 MHz) 13.8, 19.1, 21.5, 24.8, 26.8, 28.2, 29.4, 38.6, 54.2, 55.8, 61.6, 63.7, 66.9, 80.2, 82.5, 117.9, 123.6, 126.4, 126.5, 126.9, 127.1, 127.7, 127.7, 128.6, 129.3, 129.5, 129.7, 129.8, 132.7, 135.5, 135.6, 136.7, 155.8, 170.4, 170.5; HRMS (FAB^+) $C_{59}H_{68}N_4O_9SSi$ ($M+Na^+$) 1059.4374, obsd 1059.4355.

Cyclic (R,R,R)-3-(6-{5-(2-Amino-3-phenyl-propionylamino)-2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-2-methoxy-phenyl}-1*H*-indol-3-yl)-2-(toluene-4-sulfonylamino)-propionamide (15). The biphenyl **13** (0.160g, 0.150 mmol) was dissolved in dry THF (1.0 mL) and methanol (0.2 mL) and a solution of freshly prepared LiOH (0.007g, 0.30 mmol) in 0.2 mL of water was added. The reaction was stirred at room temperature for 18h and concentrated down to remove the MeOH and THF. The resulting aqueous solution was diluted with water and 2N HCl was added to give a white solid. The solid was filtered and washed twice with 2N HCl then dried in vacuum, yielding 0.150g of a white solid (90%). The acid was dissolved in EtOAc and a HCl saturated solution of ethyl acetate was added. The reaction was allowed to stir at room temperature for 1h and concentrated down and

diluted 3x with ether and concentrated down to remove the excess HCl. The white residue, which remained, was carried directly onto the cyclization. Free amine **14** was dissolved in DMF under high dilution conditions to a concentration of $5x10^{-3}$ mol/L (27.7 ml) and 0.054g of DIEA (0.42 mmol) and FDPP (0.064g, 0.166 mmol) were added. The reaction was allowed to stir at room temperature for 3 days. The reaction was concentrated to an oily residue and trituated with water to give a light brown solid. The solid was purified by flash column chromatography with silica gel 2% MeOH/ 98% CH_2Cl_2 to 5% MeOH / 95% CH_2Cl_2 to give a white solid in 36.5% yield over the 3-steps with a $R_f = 0.34$ in 30% EtOAc/ 70% Hexane. ^{1}H NMR ($CDCl_3$, 300MHz) δ 1.01 (s, 9H), 2.31 (s, 3H), 2.50 (dd, 1H, J = 8.7, 14.9 Hz), 2.88 (dd, 1H, J = 7.8, 13.8 Hz), 3.07 (dt, 2H, J = 4.8, 14.7 Hz), 3.64 (dd, 1H, J = 6.0, 10.8 Hz), 3.67(m, 1H), 3.78 (dd, 1H, J = 6.6, 10.2 Hz), 3.85 (s, 3H), 4.77 (d, 1H, J = 3.3 Hz), 4.79 (q, 1H, J = 7.5 Hz), 4.95 (q, 1H, 5.7 Hz), 5.72 (s, 1H), 6.65 (d, 1H, J = 7.81 Hz), 6.70 (m, 2H), 6.75 (s, 1H), 6.78 (d, 1H, J = 4.2 Hz), 6.79 (s, 1H), 6.84 (d, 1H, J= 7.8 Hz), 6.99 (s, 2H), 7.16-7.40 (m, 16H), 7.49 (dd, 1H, J = 1.8, 8.1 Hz), 7.54 (d, 1H, J = 1.5, 7.8 Hz), 8.09 (bs, 1H); MS MALDI-TOF $C_{52}H_{54}N_4O_6SSi$ 890.4, obsd 890.6

Linear System

(R,R,R)-3-(6-Bromo)-1*H*-indol-3-yl)-N-(1-{2-(*tert*-butyl-diphenyl-silanyloxy)-1-[4-methoxy-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-ethylcarbamoyl}-2-phenyl-ethyl)-2-(toluene-4-sulfonylamino)-propionamide (19). To a solution of R-3-(6-Bromo)-1*H*-indol-3-yl)-2-(toluene-4-sulfonylamino)-propionic acid, **18**, (0.020g, 0.049 mmol) in 0.5 mL of acetonitrile was added EDCI (0.011g, 0.059 mmol), HOBt (0.011g, 0.078 mmol) and 0.2 mL of DMF for solubility reasons. To the above mixture was added 0.036g of the HCl amine salt **17** (0.053 mmol) and 0.006mL of NMM. The reaction was allowed to stir at room temperature for 3h. The reaction was concentrated

down and diluted with water and ethyl acetate. The aqueous layer was extracted 3x with ethyl acetate. The organics were collected together and washed 1x HCl, 1x 1N NaOH and 1x with brine. The organics were dried over Mg_2SO_4 and concentrated down. The oily residue was purified by flash column chromatography with silica gel 45% EtOAc/ 55% Hexane to 55% EtOAc/45% Hexane to give 0.039g of a white solid in 75% yield and a R_f = 0.29 in 50% EtOAc/50% Hexane. ^1H NMR ($CDCl_3$, 300MHz) δ 0.98 (s, 9H), 1.33 (s, 12H), 2.30 (s, 3H), 2.53 (dd, 1H, J = 8.9, 15.6 Hz), 2.86 (dd, 1H, J = 7.8, 14.1 Hz), 3.08 (dt, 2H, J = 6.0, 14.1 Hz), 3.65 (dd, 1H, J = 5.7, 9.9 Hz), 3.81 (m, 2H), 3.86 (s, 3H), 4.75 (q, 1H, J = 7.2 Hz), 4.92 (m, 1H), 5.21 (d, 1H J = 5.4 Hz), 6.48 (d, 1H, J = 8.4 Hz), 6.60 (d, 1H, J = 2.4 Hz), 6.70-7.45 (m, 21 H), 7.46 (d, 2H, J = 6.3 Hz), 7.51 (d, 2H, J = 6.9 Hz), 7.62 (d, 1H, J = 1.8 Hz), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 14.1, 19.1, 21.5, 24.8, 26.8, 28.2, 29.0, 38.1, 54.1,, 54.5, 55.9, 56.5, 66.5, 83.6, 109.1, 110.6, 114.2, 114.2, 115.8, 119.5, 122.8, 124.1, 125.1, 127.6, 127.6, 127.7, 128.5, 129.1, 129.4, 129.5, 129.7, 131.3, 133.0, 133.1, 135.5, 135.6, 136.5, 137.1, 163.6, 169.5, 170.1; LRMS (FAB^+) $C_{58}H_{66}BBrN_4O_8SSi$ ($M+Na^+$) 1121.4, obsd 1121.4

Cyclic (R,R,R)-3-(6-{5-(2-Amino-3-phenyl-propionylamino)-2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-2-methoxy-phenyl}-1*H*-indol-3-yl)-2-(toluene-4-sulfonylamino)-propionamide (15). To a solution of the bromo boronate **19** was added K_2CO_3 (10.007g, 0.050mmol) and $PdCl_2$(dppf) in 0.5mL of degassed DME. The reaction was heated to 40 ° C for 5 h then cooled to room temperature. The DME was concentrated off and the brown residue was partitioned between EtOAc/ H_2O. The aqueous layer was extracted 2x more with EtOAc, collected, and washed once with brine, dried over $MgSO_4$, filtered, and concentrated. The brown oil was purified by flash column chromatography with silica 2% MeOH/ 98% CH_2Cl_2 to 5% MeOH/ 95% CH_2Cl_2 to give a white solid in 56% yield and a R_f = 0.34 in 30% EtOAc/70% Hexane. (See previous characterization)