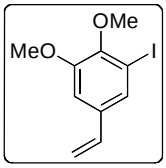
Supporting Information

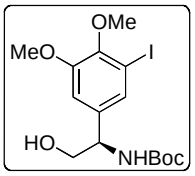
Total Synthesis of Chloropeptin II (Complestatin) and Chloropeptin I

Joie Garfunkle, F. Scott Kimball, John D. Trzupek, Shinobu Takizawa, Hiroyuki Shimamura, Masaki Tomishima, and Dale L. Boger*

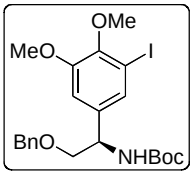
Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037



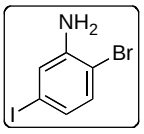
1-Iodo-2,3-dimethoxy-5-vinylbenzene (11). A solution of 3-iodo-4,5-dimethoxybenzaldehyde (**10**, 20.5 g, 70.2 mmol) in anhydrous THF (580 mL) was treated with K_2CO_3 (19.4 g, 140 mmol), CH_3PPh_3Br (50.2 g, 140 mol), and 18-crown-6 (3.08 g, 15% w/w). After 25 h at reflux, the mixture was filtered with Et_2O and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, 8 × 21 cm, 0–10% EtOAc–hexanes) to provide **11** as a yellow oil, which is light and heat sensitive, and must be stored at –20 ºC (21 g, 99%): ^{1}H NMR (acetone-d_6, 500 MHz) δ 7.41 (d, 1H, J = 1.9 Hz), 7.14 (d, 1H, J = 1.9 Hz), 6.62 (dd, 1H, J = 10.8, 17.5 Hz), 5.77 (d, 1H, J = 17.5 Hz), 5.21 (d, 1H, J = 10.8 Hz), 3.88 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 153.3, 149.3, 136.4, 135.8, 128.9, 114.5, 111.2, 92.6, 60.3, 56.1; HRMS-ESI-TOF *m/z* 290.9883 ($[M+H]^+$, $C_{10}H_{11}IO_2$ requires 290.9882).



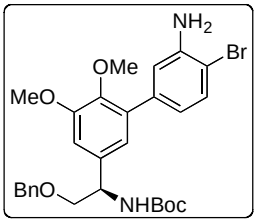
(*R*)-*tert*-Butyl 2-Hydroxy-1-(3-iodo-4,5-dimethoxyphenyl)ethyl carbamate (12). A 0.407 M solution of aqueous NaOH (8.50 mL, 138 mg, 3.45 mmol) was treated with a 0.77 M solution of *t*-butylcarbamate in *n*-PrOH (4.50 mL, 404 mg, 3.45 mmol) followed by slow addition of freshly prepared *t*-BuOCl (0.38 mL, 3.5 mmol). The homogenous solution was stirred for 15 min and was cooled to 0 ºC. A 0.015 M solution of $(DHQD)_2PHAL$ (4.5 mL, 53 mg, 0.068 mmol) in *n*-PrOH was added, followed by addition of **11** in *n*-PrOH (6.7 mL, 330 mg, 1.14 mmol, 0.17 M). Fresh $K_2OsO_4 \bullet 2H_2O$ (17 mg, 0.046 mmol) was added and the mixture was immediately warmed to ambient temperature. After 1 h, the reaction was quenched with the addition of saturated aqueous Na_2SO_3 and after 5 min the *n*-PrOH was removed by rotary evaporation. The residue was diluted with EtOAc, washed with H_2O (3×) and saturated aqueous NaCl. The organic layer was collected, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (SiO_2, 2.5 × 20 cm, 20–50% EtOAc–hexanes) afforded **12** as a white solid (431 mg, 75%, >98% ee) and a separable amount of the regioisomer (85 mg, 15%). For **12**: $[\alpha]^{25}_D$ –41 (*c* 1.0, $CHCl_3$); ^{1}H NMR (acetone-d_6, 500 MHz) δ 7.24 (d, 1H, J = 1.8 Hz), 7.21 (br s, 1H), 7.00 (s, 1H), 4.80 (t, 1H, J = 5.9 Hz), 4.44 (m, 1H), 3.79 (s, 3H), 3.67 (s, 3H), 3.45 (t, 2H, J = 9.2 Hz), 1.37 (s, 9H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 155.9, 153.1, 148.3, 140.6, 129.0, 112.8, 92.0, 78.7, 65.9, 60.0, 56.8, 56.0, 28.3; HRMS-ESI-TOF *m/z* 424.0614 ($[M+H]^+$, $C_{15}H_{22}INO_5$ requires 424.0621). The ee was determined by comparison with *S*-enantiomer on an analytical ChiralCel OJ column, 2.5% *i*-PrOH/hexanes, α = 1.37.



(*R*)-*tert*-Butyl 2-(Benzyloxy)-1-(3-iodo-4,5-dimethoxyphenyl) ethylcarbamate (13). A suspension of NaH (60% dispersion, 709 mg, 17.9 mmol) in anhydrous DMF (40 mL) at –5 ºC was treated with a solution of compound **12** (5.0 g, 12 mmol) in anhydrous DMF (20 mL). After 20 min, benzyl bromide (1.55 mL, 13.0 mmol) was added dropwise to the suspension. The reaction was complete at 2 h and was quenched by addition of H_2O. Following dilution with EtOAc, the organic phase was washed with H_2O (3×) and saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (SiO_2, 7 × 20 cm, 30% EtOAc–hexanes) provided **13** as a pale yellow oil (5.6 g, 92%): $[\alpha]^{25}_D$ –28 (*c* 1.0, $CHCl_3$); ^{1}H NMR (acetone-d_6, 500 MHz) δ 7.38 (s, 1H), 7.35–7.25 (m, 5H), 7.12 (s, 1H), 6.50 (br s, 1H), 4.85 (br s, 1H), 4.64 (d, 1H, *J* = 12.1 Hz), 4.60 (d, 1H, *J* = 12.1 Hz), 3.82 (s, 3H), 3.74 (s, 3H), 3.67–3.65 (m, 2H), 1.38 (s, 9H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 155.8, 153.1, 148.4, 140.2, 139.2, 129.0, 128.7, 128.1, 127.9, 112.8, 92.0, 78.7, 73.6, 73.0, 60.0, 56.0, 54.2, 28.3; HRMS-ESI-TOF *m/z* 514.1084 ($[M+H]^+$, $C_{22}H_{28}INO_5$ requires 514.1092).

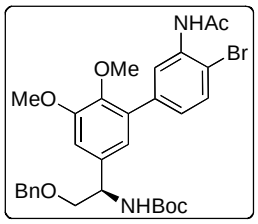


2-Bromo-5-iodoaniline (14). A solution of 3-iodoaniline (7.2 mL, 60 mmol) in benzene (2 L) was treated with freshly recrystallized NBS (10.2 g, 57.2 mmol). The mixture was allowed to stir at room temperature for 20 h, and then was concentrated. The resultant red-brown oil was dissolved in Et_2O (750 mL), washed with H_2O (3 × 200 mL) and saturated aqueous NaCl (150 mL), dried over Na_2SO_4, and concentrated. Column chromatography (SiO_2, 10% EtOAc/hexanes) afforded **14** as an orange-yellow solid (7.3 g, 41%): ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.24 (d, 1H, *J* = 2.0 Hz), 7.14 (d, 1H, *J* = 8.2 Hz), 6.86 (dd, 1H, *J* = 2.1, 8.2 Hz), 5.14 (br s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.6, 134.1, 128.4, 124.2, 109.2, 93.3; MS *m/z* 297 ([M]+, C_6H_5BrIN requires 297).

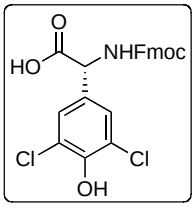


(*R*)-*tert*-Butyl 1-(3'-Amino-4'-bromo-5,6-dimethoxybiphenyl-3-yl)-2-(benzyloxy)ethylcarbamate (15). Compound **13** (1.0 g, 1.9 mmol) in anhydrous THF (18 mL) at 0 ºC was treated dropwise with *i*-PrMgCl (2.0 M in THF, 2.44 mL, 4.87 mmol). After 1 h, the yellow solution was cooled to –78 ºC and *n*-BuLi (2.5 M in hexane, 1.87 mL, 4.68 mmol) was added dropwise to the vigorously stirring solution. After 30 min, $B(OMe)_3$ (1.76 mL, 15.8 mmol) was added dropwise, and the reaction mixture was allowed to slowly warm to ambient temperature and left for 18 h. The white suspension was acidified to pH 3 with aqueous 1 N HCl, and stirred for 30 min. The resultant yellow solution was diluted with EtOAc, and washed with H_2O (3×) and saturated aqueous NaCl. The aqueous extracts were washed with EtOAc (3×) and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated to give the crude boronic acid product. The crude boronic acid product was combined with the 2-bromo-5-iodoaniline (**14**, 835 mg, 2.81 mmol), $(PPh_3)_4Pd$ (360 mg, 0.311 mmol), and aqueous 1 M $NaHCO_3$ (6.24 mL, 6.24 mmol) and dissolved by the addition of 15.6 mL DME. The reaction solution was stirred at 80 °C for 28 h before being cooled to ambient temperature and filtered through filter paper with EtOAc. The organic phase was washed

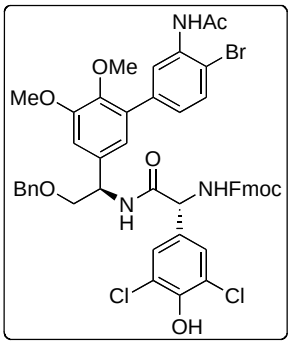
with H_2O (2×) and saturated aqueous NaCl. The combined aqueous phases were washed with EtOAc (2×). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, 5 × 15 cm, 10–25% EtOAc–hexanes) to afford **15** as a white foam (1.08 g, 98%): $[\alpha]^{25}_D$ –26 (*c* 1.0, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.39 (d, 1H, *J* = 8.2 Hz), 7.31–7.25 (m, 5H), 7.11 (d, 1H, *J* = 2.0 Hz), 7.02 (d, 1H, *J* = 2.1 Hz), 6.93 (d, 1H, *J* = 1.9 Hz), 6.68 (dd, 1H, *J* = 2.2, 8.2 Hz), 6.49 (br s, 1H), 4.95 (m, 3H), 4.55 (d, 1H, *J* = 12.0 Hz), 4.52 (d, 1H, *J* = 12.0 Hz), 3.86 (s, 3H), 3.71 (d, 2H, *J* = 6.3 Hz), 3.58 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 156.7, 154.5, 146.8, 146.5, 140.4, 140.1, 138.5, 136.1, 133.9, 130.8, 129.7, 129.6, 121.8, 120.6, 117.7, 112.3, 108.3, 79.4, 74.7, 73.7, 61.1, 56.8, 55.6, 29.1; HRMS-ESI-TOF *m/z* 579.1470 ([M+Na]$^+$, $C_{28}H_{33}BrN_2O_5$ requires 579.1477).



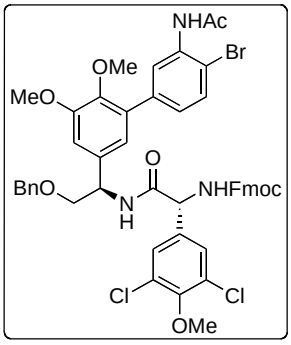
(*R*)-*tert*-Butyl 1 - (3' - Acetamido - 4' - bromo - 5,6 - dimethoxy biphenyl-3-yl)-2-(benzyloxy)ethylcarbamate (16). The aniline **15** (4.27 g, 7.65 mmol) was dissolved in CH_2Cl_2 (12.0 mL), Ac_2O (4.5 mL, 47 mmol) was added, and the mixture was stirred for 1 h. The reaction mixture was diluted with equal amounts of EtOAc and saturated aqueous $NaHCO_3$ and stirred for 5 min. The crude product was extracted with EtOAc and washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (SiO_2, 0–33% EtOAc–hexanes) provided **16** as a white solid (4.4 g, 96%): $[\alpha]^{24}_D$ –29 (*c* 0.1, $CHCl_3$); ^{1}H NMR (acetone-d_6, 600 MHz) δ 8.56 (s, 1H), 8.26 (s, 1H), 7.64 (d, 1H, *J* = 8.4 Hz), 7.30 (m, 4H), 7.25 (m, 1H), 7.20 (d, 1H, *J* = 8.4 Hz), 7.15 (d, 1H, *J* = 2.4 Hz), 6.99 (d, 1H, *J* = 2.4 Hz), 6.54 (d, 1H, *J* = 6.6 Hz), 4.95 (br s, 1H), 4.57 (d, 1H, *J* = 12.0 Hz), 4.53 (d, 1H, *J* = 12.0 Hz), 3.87 (s, 3H), 3.73 (d, 2H, *J* = 6.6 Hz), 3.64 (s, 3H), 2.20 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (acetone-d_6, 150 MHz) δ 170.0, 157.1, 155.0, 147.3, 140.50, 140.46, 139.1, 138.2, 135.7, 133.8, 130.0, 129.3, 129.2, 128.4, 127.0, 122.1, 113.2, 79.9, 75.1, 74.2, 61.8, 57.2, 56.1, 29.6, 25.1; HRMS-ESI-TOF *m/z* 599.1743 ([M+H]$^+$, $C_{30}H_{35}BrN_2O_6$ requires 599.1751).



(*R*)-2-(((9*H*-Fluoren-9-yl)-methoxy)carbonylamino)-2-(3,5-dichloro-4-hydroxyphenyl)acetic Acid (17). (*R*)-2-Amino-2-(3,5-dichloro-4-hydroxyphenyl)acetic acid (1.02 g, 4.42 mmol) in 160 mL dioxane:H_2O (1:1) was treated with Fmoc-Cl (1.5 g, 4.5 mmol) and $NaHCO_3$ (392 mg, 4.66 mmol). The suspension was stirred for 12 h, during which it became a homogeneous solution. After concentration in vacuo, the residue was extracted with EtOAc (3×), and the combined organic layers were washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (SiO_2, 2% MeOH–$CHCl_3$) afforded **17** as a white solid (1.91 g, 94%): $[\alpha]^{25}_D$ –81 (*c* 0.63, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 7.78 (d, 2H, *J* = 7.5 Hz), 7.65 (d, 2H, *J* = 7.5 Hz), 7.37–7.35 (m, 4H), 7.29 (m, 2H), 5.17 (s, 1H), 4.36 (d, 2H, *J* = 7.0 Hz), 4.22 (t, 1H, *J* = 7.0 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 173.3, 158.2, 150.8, 145.4, 145.2, 142.7, 131.5, 128.9, 128.6, 128.3, 126.4, 123.6, 121.0, 120.9, 68.3, 58.4; HRMS-ESI-TOF *m/z* 480.0376 ([M+Na]$^+$, $C_{23}H_{17}Cl_2NO_5$ requires 480.0378).

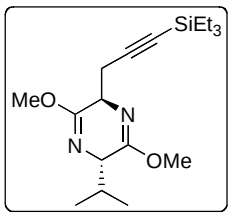


(9*H*-Fluoren-9-yl)methyl (*R*)-2-((*R*)-1-(3'-Acetamido-4'-bromo - 5,6 - dimethoxybiphenyl - 3 - yl) - 2 -(benzyloxy)ethyl amino) - 1 - (3,5 - dichloro - 4 - hydroxyphenyl) - 2 - oxoethyl carbamate (18). Compound **16** (1.5 g, 2.5 mmol) was stirred in formic acid (20 mL, 0.12 M) for 4 h and then diluted with toluene (2 × 10 mL) and the reaction solution was condensed under a stream of air. The residue was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and aqueous 2 M Na_2CO_3 at 0 ºC, then washed with H_2O and finally with saturated aqueous NaCl. The aqueous phase was back extracted with EtOAc (2×) and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was dissolved in 53 mL CH_2Cl_2:DMF (6:1) and the reaction mixture was cooled to –20 ºC and HOAt (493 mg, 3.62 mmol), EDCI (694 g, 3.62 mmol), and **17** (1.54 g, 3.38 mmol) were added as solids. The reaction mixture was stirred for 16 h, quenched with the addition of H_2O at –20 ºC, and warmed to ambient temperature. The organic product was extracted with CH_2Cl_2 (2×). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (SiO_2, 4 × 19 cm, 0–20% acetone–toluene) followed by precipitation with hexanes of the isolated material from THF (2×) afforded **18** as a white solid (2.2 g, 98%): ^{1}H NMR (THF-d_8, 600 MHz) δ 9.03 (br s, 1H), 8.41 (s, 1H), 8.31 (s, 1H), 8.06 (d, 1H, J = 7.8 Hz), 7.76 (d, 2H, J = 7.2 Hz), 7.64 (d, 2H, J = 7.2 Hz), 7.54 (d, 1H, J = 8.4 Hz), 7.45 (s, 2H), 7.44 (d, 1H, J = 8.4 Hz), 7.34–7.16 (m, 10H), 7.05 (s, 1H), 6.97 (s, 1H), 5.28 (d, 1H, J = 7.8 Hz), 5.25 (m, 1H), 4.48 (d, 1H, J = 12.0 Hz), 4.44 (d, 1H, J = 12.0 Hz), 4.30 (m, 2H), 4.18 (t, 1H, J = 7.2 Hz), 3.82 (s, 3H), 3.65 (d, 2H, J = 5.4 Hz), 3.62 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (THF-d_8, 600 MHz) δ 145.1, 145.0, 142.1, 142.0, 139.5, 139.2, 137.2, 136.8, 134.9, 132.8, 132.4, 129.0, 128.9, 128.8, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.6, 127.1, 126.0, 125.9, 125.8, 125.7, 73.5, 73.2, 60.5, 58.1, 56.1, 53.4, 48.1, 31.0; HRMS-ESI-TOF *m/z* 938.1602 ($[M+H]^+$, $C_{48}H_{42}BrCl_2N_3O_8$ requires 938.1605).

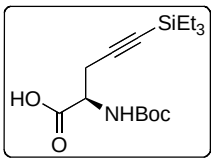


(9*H*-Fluoren-9-yl)methyl (*R*)-2-((*R*)-1-(3'-Acetamido-4'-bromo - 5,6 - dimethoxybiphenyl - 3 - yl)-2-(benzyloxy)ethyl amino) - 1 - (3 , 5 - dichloro - 4 - methoxyphenyl) - 2 - oxoethyl carbamate (**19).** Compound **18** (110 mg, 0.117 mmol) was dissolved in 12 mL benzene:MeOH (3:2) and treated dropwise with $TMSCHN_2$ (2.0 M in hexanes, 0.88 mL, 0.18 mmol). The reaction solution was stirred at ambient temperature for 2 h after which acetic acid (0.5 mL) was slowly added to quench the reaction until the yellow solution turned clear. The solvent was removed in vacuo to give **19** as a white solid (110 mg, 99%): $[\alpha]^{24}_D$ –26 (*c* 0.7, $CHCl_3$); ^{1}H NMR (THF-d_8, 600 MHz) δ 8.42 (s, 1H), 8.31 (s, 1H), 8.12 (d, 1H, J = 8.2 Hz), 7.76 (d, 2H, J = 7.4 Hz), 7.63 (d, 2H, J = 7.3 Hz), 7.54 (m, 4H), 7.34–7.14 (m, 10H), 7.05 (s, 1H), 6.97 (s, 1H), 5.35 (d, 1H, J = 8.3 Hz), 5.24 (dd, 1H, J = 5.6, 13.2 Hz), 4.48 (d, 1H, J = 12.0 Hz), 4.44 (d, 1H, J = 12.0 Hz), (m, 2H), 4.30 (m, 2H), 4.18 (t, 1H, J = 7.0 Hz), 3.84 (s, 3H), 3.82 (s, 3H), 3.66 (d, 2H, J = 5.5 Hz), 3.61 (s, 2H), 2.13 (s, 3H); ^{13}C NMR (THF-d_8, 600 MHz) δ 169.2, 168.3, 156.6, 154.0, 152.6,

146.7, 145.1, 145.0, 142.1, 142.0, 139.4, 139.2, 138.1, 137.2, 136.7, 134.9, 132.4, 129.7, 128.8, 128.20, 128.17, 128.0, 127.7, 127.6, 127.1, 125.9, 125.8, 125.7, 121.1, 120.44, 120.42, 112.4, 73.5, 73.2, 60.7, 60.5, 58.1, 56.1, 53.5, 48.0, 31.0; HRMS-ESI-TOF *m/z* 952.1753 ($[M+H]^+$, $C_{49}H_{44}BrCl_2N_3O_8$ requires 952.1761).

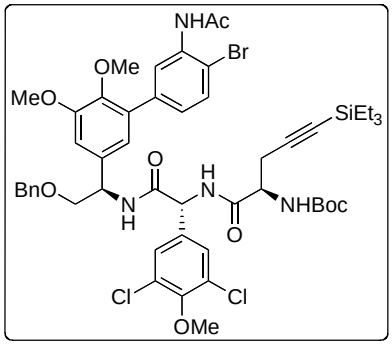


(2*S*,5*R*)-2-Isopropyl-3,6-dimethoxy-5-(3-(triethylsilyl)prop-2-ynyl)-2,5-dihydropyrazine (9). A chilled solution of 3-(triethylsilyl)prop-2-yn-1-ol (100 mg, 0.587 mmol) and diphenyl chlorophosphate (122 μL, 0.589 mmol) in 1 mL anhydrous Et_2O at –5 ºC was treated with KOH (50 mg, 0.89 mmol). The reaction mixture was stirred at –5 ºC overnight. Upon workup, the white precipitate was removed by filtration and the resultant colorless solution was concentrated in vacuo, azeotropically dried with anhydrous benzene, and dried under vacuum for at least 30 min. A separate vessel containing the (*S*)-Schöllkopf reagent (105 μL, 0.586 mmol) in anhydrous THF (0.8 mL) at –75 ºC was slowly treated with *n*-BuLi (2.3 M in anhydrous THF, 0.28 mL, 0.64 mmol). After stirring for 30 min, the freshly prepared phosphate **7** (in 0.2 mL of anhydrous THF) was slowly added to the solution containing the anion of the Schöllkopf reagent. The reaction mixture was stirred at –73 ºC for 1.5 h and then allowed to warm to room temperature and stirring was continued 30 min. The reaction was quenched by the addition of H_2O and diluted with Et_2O and the organic layer was collected. The aqueous layer was back-extracted with Et_2O (2×). The combined organic layers were dried over Na_2SO_4, concentrated, and the crude product was purified by flash chromatography (SiO_2, 5% EtOAc/hexanes) to afford **9** as a clear, colorless oil (145 mg, 73%): $[\alpha]^{25}_D$ –40 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.12 (m, 1H), 4.01 (t, 1H, *J* = 3.2 Hz), 3.71 (s, 6H), 2.84 (dd, 1H, *J* = 4.4, 16.8 Hz), 2.71 (dd, 1H, *J* = 4.0, 16.8 Hz), 2.27 (m, 1H), 1.04 (d, 3H, *J* = 8.0 Hz), 0.94 (t, 9H, *J* = 8.0 Hz), 0.66 (d, 3H, *J* = 8.0 Hz), 0.49 (q, 6H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 164.7, 161.7, 104.2, 83.6, 61.0, 54.6, 52.4, 31.6, 26.4, 19.0, 16.6, 7.3, 4.4; HRMS-ESI-TOF 337.2307 ($M + H^+$, $C_{18}H_{32}N_2O_2Si$ requires 337.2306).

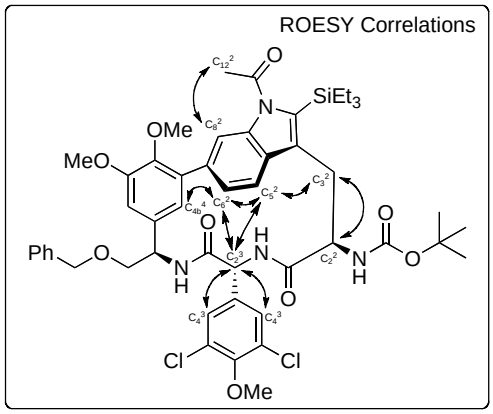


(*R*)-2-(*tert*-Butoxycarbonylamino)-5-(triethylsilyl)pent-4-ynoic Acid (6). Compound **9** (1.67 g, 4.97 mmol) was dissolved in 98 mL of THF and cooled to 0 ºC. This solution was treated with a chilled solution of aqueous 1 N HCl (98 mL) and the reaction mixture was stirred at 0 ºC for 2 h. The reaction was quenched by addition of 78 mL of saturated aqueous NH_4OH affording a basic aqueous layer. The solution was diluted with CH_2Cl_2:H_2O (1:1) and the aqueous phase was back-extracted with CH_2Cl_2 (2×). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. After vacuum drying, the amine was treated with $NaHCO_3$ (1.39 g, 16.4 mmol) and Boc_2O (3.35 g, 15.4 mmol) in THF (92 mL). The reaction mixture was stirred with mild heating (35 ºC) overnight. The reaction mixture was concentrated by rotary evaporation and purified by flash chromatography (SiO_2, 5% EtOAc–hexanes) to afford product as a white solid. The partially pure product (1.98 g) in 40 mL of THF:H_2O (3:1) was treated with $LiOH•H_2O$ (2.40 g, 57.2 mmol). After stirring for 2 h, the mixture was added to a

solution of CH_2Cl_2:1 N HCl (1:1). The organic layer was collected and the aqueous layer was back-extracted with CH_2Cl_2 (2×). The combine organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (SiO_2, 20% EtOAc–hexanes) afforded **6** as a colorless oil (1.62 g, 99%): $[\alpha]^{25}_D$ –52 (*c* 1.0, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 6.02 (d, 1H, *J* = 8.4 Hz), 4.36 (m, 1H), 2.81 (m, 2H), 1.42 (s, 9H), 0.98 (t, 9H, *J* = 8.0 Hz), 0.58 (q, 6H, *J* = 8.0 Hz); ^{13}C NMR (acetone-d_6, 150 MHz) δ 173.3, 156.9, 105.4, 85.6, 80.5, 54.2, 29.5, 25.0, 8.7, 6.0; HRMS-ESI-TOF *m/z* 350.1762 ($[M+Na]^+$, $C_{16}H_{29}NO_4Si$ requires 350.1758).

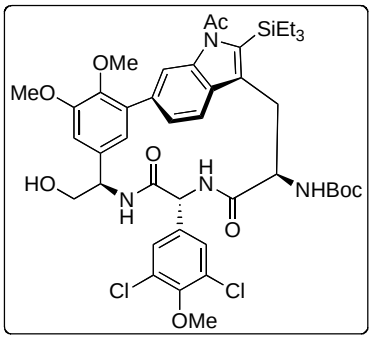


20. Compound **19** (51 mg, 0.053 mmol) was dissolved in 6 mL of MeCN:DMF (2:1) and treated with morpholine (46 μL, 0.53 mmol). The reaction mixture was stirred for 16 h before the MeCN was removed in vacuo. The residue was diluted with EtOAc and washed with aqueous 1 N HCl (1×). The aqueous phase was back-extracted with EtOAc. The combined organic phases were washed with aqueous 1 N HCl (3×) and then dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was then dissolved in 2.5 mL DMF, cooled to 0 ºC, and treated with HOAt (16 mg, 0.11 mmol), **6** (32 mg, 0.99 mmol, in 0.13 mL DMF), and EDCI (21 g, 0.11 mmol). After 30 min, the reaction mixture was warmed to ambient temperature and stirred for 48 h before the reaction mixture was quenched with the addition of EtOAc:1 N HCl (1:1). The crude product was extracted with EtOAc and the aqueous phase was back-extracted with EtOAc. The combined organic phases were washed with aqueous 1 N HCl and 5% aqueous Na_2SO_3 (2×) and then dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, 0–20% acetone–toluene) to give **21** as a white solid (46 mg, 83%): $[\alpha]^{28}_D$ –13.6 (*c* 0.1, $CHCl_3$); ^{1}H NMR (acetone-d_6, 600 MHz) δ 8.53 (s, 1H), 8.24 (s, 1H), 8.17 (d, 1H, *J* = 8.4 Hz), 7.97 (d, 1H, *J* = 6.6 Hz), 7.64 (d, 1H, *J* = 8.3 Hz), 7.55 (s, 2H), 7.28–7.13 (m, 5H), 7.12 (d, 1H, *J* = 2.0 Hz), 6.98 (d, 1H, *J* = 2.0 Hz), 6.43 (d, 1H, *J* = 7.5 Hz), 5.55 (d, 1H, *J* = 7.0 Hz), 5.23 (dd, 1H, *J* = 6.3, 13.7 Hz), 4.46 (d, 1H, *J* = 12.0 Hz), 4.42 (d, 1H, *J* = 12.0 Hz), 4.31 (m, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.71 (m, 2H), 3.64 (s, 3H), 2.66 (m, 2H), 2.21 (s, 3H), 1.40 (s, 9H), 0.93 (t, 9H, *J* = 7.9 Hz), 0.52 (q, 6H, *J* = 7.9 Hz); ^{13}C NMR (acetone-d_6, 125 MHz) δ 171.7, 170.11, 170.05, 157.3, 155.0, 153.5, 147.5, 140.3, 140.2, 138.8, 138.1, 137.6, 135.9, 133.8, 130.7, 130.06, 129.99, 129.84, 129.77, 129.4, 129.2, 129.1, 122.2, 113.5, 113.4, 106.1, 85.3, 80.8, 74.4, 62.0, 61.8, 57.5, 57.3, 55.4, 55.0, 33.2, 29.5, 24.4, 8.8, 6.0; HRMS-ESI-TOF *m/z* 1039.2799 ($[M+H]^+$, $C_{50}H_{61}BrCl_2N_4O_9Si$ requires 1039.2841).

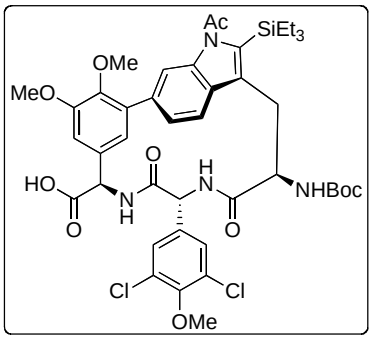


21. A solution of $Pd(OAc)_2$ (12 mg, 0.053 mmol) and D*t*PBF ligand (30 mg, 0.063 mmol) in 12 mL MeCN/toluene (1:1) was treated with distilled Et_3N (8.7 μL, 0.063 mmol) at ambient temperature. This solution was slowly added to a refluxing solution of 24 mL MeCN/toluene (1:1) in a three-necked flask equipped with a reflux condenser to give a clear orange solution. Compound **20** (50 mg, 0.048 mmol in 12 mL MeCN/toluene (1:1)) was slowly added to the reaction vessel and the mixture was stirred at reflux. The reaction was complete after 1 h as indicated by the appearance of the products on TLC ((*R*)-atropisomer R_f = 0.5, (*S*)-atropisomer R_f = 0.6, 15% acetone/toluene). The reaction solution was cooled to ambient temperature before the solvent was removed in vacuo. The crude product was purified and separated from the (*S*)-atropisomer by flash chromatography (SiO_2, 0–5% acetone–toluene) to afford **21** (41 mg, 89% (4:1 *R*:*S*)) as a mixture of atropisomers and 33 mg, 71% of the pure (*R*)-atropisomer **21** after atropisomer separation as a white solid. For (*R*)-**21**: $[\alpha]^{29}_D$ +8.6 (*c* 0.35, $CHCl_3$); ^{1}H NMR (acetone-d_6, 600 MHz) δ 7.87 (d, 1H, *J* = 8.9 Hz), 7.67 (s, 1H), 7.65 (d, 1H, *J* = 8.5 Hz), 7.49 (s, 2H), 7.22–7.45 (m, 5H), 6.92 (d, 1H, *J* = 8.6 Hz), 6.89 (d,1H, *J* = 2.3 Hz), 6.50 (d, 1H, *J* = 8.3 Hz), 5.87 (s, 1H), 5.84 (d, 1H, *J* = 8.5 Hz), 4.93 (m, 1H), 4.55 (d, 1H, *J* = 12.0 Hz), 4.50 (d, 1H, *J* = 12.0 Hz), 4.05 (s, 3H), 3.89 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.70 (dd, 1H, *J* = 13.7, 10.3 Hz), 3.59 (m, 1H), 3.12 (d, 1H, *J* = 13.7 Hz), 2.84 (s, 3H), 1.33 (s, 9H), 0.90–0.12 (m, 15 H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 173.1, 171.3, 171.1, 156.7, 155.2, 153.6, 145.6, 141.2, 140.2, 139.6, 139.0, 136.3, 136.0, 135.4, 133.8, 133.1, 131.2, 130.7, 130.1, 129.5 (2C), 129.3, 126.1, 122.6, 119.0, 110.1, 80.5, 74.6, 72.5, 62.5, 62.0, 61.5, 57.6, 56.5, 55.1, 31.6, 29.6, 26.8, 9.6, 7.3; HRMS-ESI-TOF *m/z* 959.3564 ($M + H^+$, $C_{50}H_{60}Cl_2N_4O_9Si$ requires 959.3579); The 2D ^{1}H–^{1}H ROESY spectrum (acetone-d_6, 600 MHz) displayed the following diagnostic NOE crosspeaks: C_2^3-H (5.84)/C_4^3-H (7.49), C_{4b}^4-H (5.87)/C_6^2-H (7.22), C_6^2-H (7.22)/C_2^3-H (5.84), C_5^2-H (7.65)/C_2^3-H (5.84), C_5^2-H (7.65)/C_3^2-H (3.70, 3.59), C_3^2-H (3.70, 3.59)/C_2^2-H (3.12), C_8^2-H (7.67)/C_{12}^2-H (2.84).

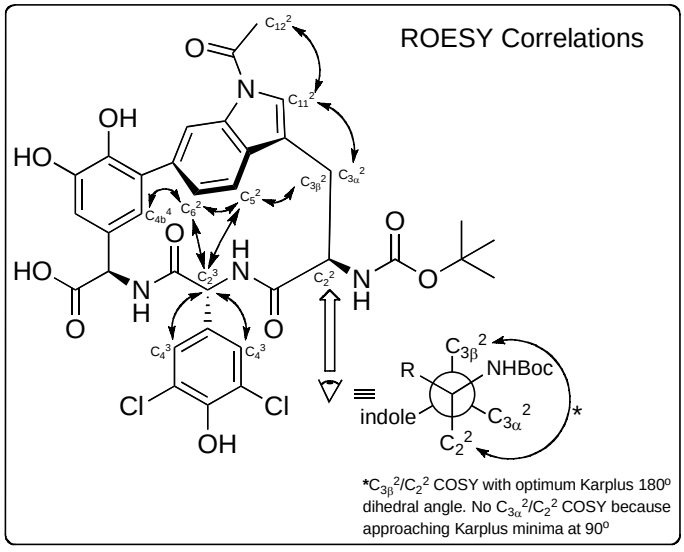
For (*S*)-**21**: $[\alpha]^{29}_D$ –70 (*c* 0.1, $CHCl_3$); ^{1}H NMR (acetone-d_6, 600 MHz) δ 7.81 (m, 2H), 7.64 (s, 1H), 7.33 (s, 2H), 7.30 (s, 2H, *J* = 7.1 Hz), 7.27 (s, 2H, *J* = 7.3 Hz), 7.11 (d, 1H, *J* = 7.6 Hz), 6.91 (d, 1H, *J* = 2.2 Hz), 6.83 (d, 1H, *J* = 7.8 Hz), 6.69 (d, 1H, *J* = 8.0 Hz), 5.39 (d, 1H, *J* = 1.5 Hz), 5.05 (m, 1H), 4.94 (d, 1H, *J* = 7.9 Hz), 4.87 (m, 1H), 4.51 (d, 1H, *J* = 12.0 Hz), 4.49 (d, 1H, *J* = 12.0 Hz), 4.02 (d, 3H), 3.87 (d, 3H), 3.84 (m, 2H), 3.82 (s, 3H), 3.51 (dd, 1H, *J* = 14.0, 12.0 Hz), 3.32 (dd, 1H, *J* = 14.1, 5.7 Hz), 1.42 (s, 9H), 0.95–1.02 (m, 15H); ^{13}C NMR (acetone-d_6, 150 MHz) δ 171.2, 171.0, 170.1, 157.7, 154.6, 153.5, 145.2, 141.0, 140.2, 140.1, 138.9, 137.9, 136.0, 133.2, 132.5, 131.8, 130.7, 130.0, 129.5, 129.3, 129.0, 128.9, 127.6, 121.4, 117.9, 110.9, 80.7, 74.6, 72.7, 62.4, 61.9, 57.5, 56.9, 55.2, 55.0, 30.8, 29.8, 27.2, 9.5, 7.5; HRMS-ESI-TOF *m/z* 959.3567 ($M + H^+$, $C_{50}H_{60}Cl_2N_4O_9Si$ requires 959.3579).



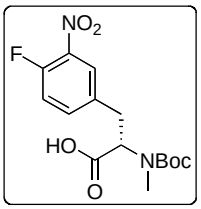
22. Compound **21** (76 mg, 0.079 mmol) was dissolved in THF (4 mL), treated with 20% $Pd(OH)_2$ (78 mg), and the reaction vessel evacuated and refilled with H_2 gas (4×). The reaction mixture was stirred under H_2 (1 atm) for 1 h. The mixture was diluted with EtOAc and filtered through a pad of Celite. The solvent was removed in vacuo and the residue was purified by flash chromatography (SiO_2, 7 × 22 cm, 0–20% acetone–toluene) to afford **22** (71 mg, 99%) as a white solid: $[\alpha]^{29}_D$ +8.6 (*c* 0.42, $CHCl_3$); ^{1}H NMR (acetone-d_6, 600 MHz) δ 7.73 (d, 1H, *J* = 8.9 Hz), 7.67 (s, 1H), 7.66 (d, 1H, *J* = 7.4 Hz), 7.48 (s, 2H), 7.28 (d, 1H, *J* = 8.4 Hz), 6.90 (m, 2H), 6.53 (d, 1H, *J* = 8.4 Hz), 5.89 (m, 2H), 4.76 (td, 1H, *J* = 4.5, 8.8 Hz), 4.08 (br s, 1H), 4.04 (s, 3H), 4.01 (m, 1H), 3.93 (m, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.71 (dd, 1H, *J* = 10.2, 13.8 Hz), 3.58 (t, 1H, *J* = 9.4 Hz), 3.12 (d, 1H, *J* = 13.7 Hz), 2.84 (s, 3H), 1.33 (s, 9H), 0.97 (m, 15H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 173.1, 171.4, 171.1, 156.7, 155.3, 153.5, 145.6, 141.2, 139.6, 139.0, 136.3, 135.9, 135.5, 134.1, 133.1, 131.4, 130.7, 129.6, 126.0, 122.7, 119.0, 110.2, 80.5, 64.8, 62.5, 62.0, 61.5, 57.6, 57.3, 29.5, 26.8, 9.6, 7.3; HRMS-ESI-TOF *m/z* 869.3099 ($[M+H]^+$, $C_{43}H_{54}Cl_2N_4O_9Si$ requires 869.3110).



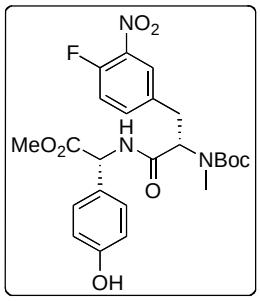
23. The alcohol **22** (200 mg, 0.230 mmol) in CH_2Cl_2 (11.5 mL) was cooled to 0 °C, treated with Dess–Martin periodinane (293 mg, 0.690 mmol) and warmed to room temperature. After 2.5 h, the reaction mixture was quenched with the addition of a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ and stirred for 30 min. The mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The aldehyde was unstable and taken directly into the second oxidation reaction. The residue was dissolved in a 4:1 solution of *t*-BuOH:2-methyl-2-butene (15 mL), cooled to 0 °C, and treated with $NaClO_2$ (25 mg, 0.28 mmol) in aqueous 1 M NaH_2PO_4 (0.69 mL). The reaction mixture was stirred for 90 min at 0 °C. The reaction solution was diluted with EtOAc/H_2O and the crude product was extracted with EtOAc and then dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, 4 × 13 cm, 0–2% AcOH–EtOAc) to afford **23** (187 mg, 92%) as a white solid: $[\alpha]^{25}_D$ +14 (*c* 0.31, acetone); ^{1}H NMR (6:1 acetone-d_6/D_2O, 600 MHz) δ 7.60 (m, 2H), 7.55 (d, 1H, *J* = 9.0 Hz), 7.48 (s, 2H), 7.33 (d, 1H, *J* = 8.4 Hz), 7.01 (s, 1H), 6.77 (d, 1H, *J* = 7.8 Hz), 5.92 (d, 1H, *J* = 8.4 Hz), 5.85 (s, 1H), 5.20 (s, 1H), 4.00 (s, 3H), 3.83 (s, 3H), 3.75 (s, 3H), 3.63 (m, 2H), 3.04 (d, 1H, *J* = 13.2 Hz), 2.76 (s, 3H), 1.25 (s, 9H), 0.88 (m, 15H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 173.5, 171.3, 170.7, 170.2, 156.6, 154.7, 153.2, 145.2, 141.1, 139.3, 138.5, 136.6, 135.7, 135.3, 135.1, 133.2, 132.3, 130.5, 129.2, 126.0, 122.5, 118.6, 110.3, 80.6, 62.5, 61.8, 60.9, 57.47, 57.44, 56.5, 33.0, 29.3, 26.6, 9.4, 7.1; HRMS-ESI-TOF *m/z* 883.2884 ($[M+H]^+$, $C_{43}H_{52}Cl_2N_4O_{10}Si$ requires 883.2893).



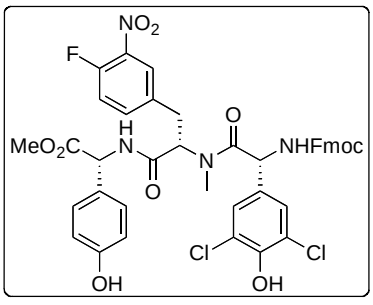
4. In a 10 mL microwave vial sealed with a septa, a solution of **23** (13 mg, 0.015 mmol) in anhydrous CH_2Cl_2 at ambient temperature under Ar was treated with boron tribromide (1 M in CH_2Cl_2, 0.37 mL) to give a cloudy yellow solution. The reaction progress was monitored by LCMS and determined to be complete after 17 h of stirring. Upon completion, two volume equivalents of hexanes were added. The reaction solution was tritrated and the mother liquor discarded. To the remaining solid, 3 mL CH_2Cl_2:hexanes (1:2) was added and the crude product was tritrated two additional times. The crude product was then dried under a stream of N_2 with vigorous stirring for 24 h. (High vacuum was not found to be adequate to completely dry the crude product which was necessary for the subsequent Boc-reprotection step to proceed well.) After drying, the crude solid was taken up in 1.4 mL anhydrous DMF and filtered through a nylon 13 mm 0.45 μm syringe filter to remove trace insoluble material. The DMF solution was collected in a new reaction vessel and purged with Ar before Boc_2O (6.4 mg, 0.029 mmol) and anhydrous Et_3N (6.2 μL, 0.044 mmol) were added. The reaction solution was stirred at 40 °C for 5 h with the reaction progress monitored by LCMS. Upon completion, the crude reaction solution was filtered through a nylon 13 mm 0.45 μm syringe filter and directly purified by HPLC using a 10–90% MeCN–H_2O (0.07% TFA) gradient over 40 min. The desired product **4** eluted at 27.5 min and was concentrated to give a light tan solid (10 mg, 94%): $[\alpha]^{25}_D$ +39 (*c* 0.52, THF); ^{1}H NMR (THF-d_8, 600 MHz) δ 8.30 (m, 2H), 7.77 (d, 1H, *J* = 8.6 Hz), 7.67 (d, 1H, *J* = 7.5 Hz), 7.58 (m, 2H), 7.29 (s, 2H), 7.19 (d, 1H, *J* = 7.9 Hz), 6.77 (s, 1H), 6.36 (d, 1H, *J* = 8.3 Hz), 5.62 (d, 1H, *J* = 7.9 Hz), 5.47 (s, 1H), 5.25 (d, 1H, *J* = 8.6 Hz), 3.86 (t, 1H, *J* = 8.4 Hz), 3.43 (t, 1H, *J* = 11.8 Hz), 2.82 (d, 1H, *J* = 12.9 Hz), 2.56 (s, 3H), 1.35 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 172.1, 171.4, 169.9, 168.8, 155.9, 149.9, 147.7, 140.8, 140.7, 137.0, 133.5, 130.6, 130.3, 128.6, 128.2, 126.5, 126.1, 124.4, 122.6, 120.9, 120.8, 119.8, 111.1, 79.1, 59.8, 56.6, 56.1, 29.6, 28.6, 23.8; HRMS-ESI-TOF *m/z* 727.1555 ($[M+H]^+$, $C_{34}H_{32}Cl_2N_4O_{10}$, requires 727.1568). The 2D ^{1}H–^{1}H ROESY spectrum (THF-d_8, 600 MHz) displayed the following diagnostic NOE crosspeaks: C_2^3-H (5.62)/C_4^3-H (7.29), C_{4b}^4-H (5.47)/C_6^2-H (7.19), C_6^2-H (7.19)/C_2^3-H (5.62), C_5^2-H (7.59)/C_2^3-H (5.62), C_5^2-H (7.59)/$C_{3\beta}^2$-H (3.43), $C_{3\alpha}^2$-H (2.82)/C_{11}^2-H (7.57), C_{11}^2-H (7.57)/C_{12}^2-H (2.56).



(*S*)-*N*-(*tert*-Butoxycarbonyl)-*N*-methyl-(4-fluoro-3-nitrophenyl) alanine (5). A solution of (*S*)-*N*-(*tert*-butyloxycarbonyl-4-fluoro-3-nitrophenylalanine (890 mg, 2.71 mmol) in THF (25 mL) at 0 ºC (ice bath) was treated with NaH (325 mg, 60% (oil), 8.13 mmol). The slurry was stirred at 0 ºC for 5 min before MeI (1.69 mL, 27.1 mmol) and DMF (2 mL) were added. The slurry was stirred at 0 ºC for 1 h, then at room temperature for 12 h. The solution was diluted with EtOAc and extracted with saturated aqueous $NaHCO_3$ (2×). The aqueous layers were acidified with aqueous 2 N HCl and extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl and the aqueous layers were back extracted with EtOAc (2×). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude oil was purified by flash chromatography (SiO_2, first purification: 0–3% AcOH–$CHCl_3$; second purification: 60% EtOAc–hexanes (1% AcOH)) to provide **5** as a yellow oil (680 mg, 73%; typically 70–95%): $[\alpha]^{25}_D$ –67 (*c* 0.6, MeOH); rotomer 1: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.39 (br s, 1H), 7.92 (m, 1H), 7.44 (m, 1H), 7.21 (m, 1H), 4.85 (ddd, 1H, *J* = 5.7, 10.8, 15.7 Hz), 3.36 (m, 1H), 3.09 (m, 1H), 2.75 (s, 3H), 1.38 (s, 9H); rotomer 2: ^{1}H NMR (acetone-d_6, 500 MHz) δ 9.39, (br s, 1H), 7.72 (m, 1H), 7.51 (m, 1H), 7.11 (m, 1H), 4.60 (m, 1H), 3.30 (m, 1H), 3.14 (m, 1H), 2.76 (s, 3H), 1.38 (s, 9H).

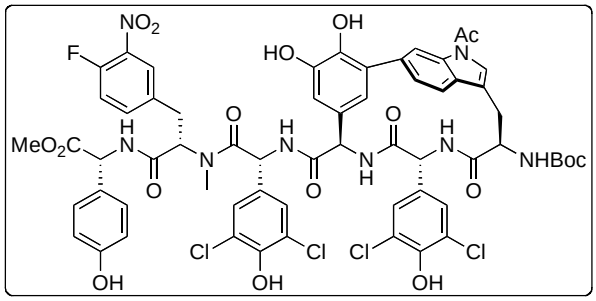


A solution of (*R*)-H_2N-Hpg-OMe (676 mg, 3.73 mmol) in a 3:1 mixture of CH_2Cl_2:DMF (28 mL) was treated with **5** (900 mg, 3.73 mmol). The solution was cooled to 0 °C (ice bath) and PyBOP (2.2 g, 4.23 mmol) was added. The solution was stirred for 2 h at 0 °C. The reaction mixture was diluted with EtOAc and washed with aqueous 0.5 N HCl, saturated aqueous $NaHCO_3$, H_2O, and saturated aqueous NaCl. The combined organic layers were dried over Na_2SO_4 and concentrated. The crude oil was purified by flash chromatography (SiO_2, 50% EtOAc–hexanes) to provide the dipeptide (1.02 g, 72%): $[\alpha]^{26}_D$ –55 (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.88 (dd, 1H, *J* = 2.3, 7.0 Hz), 7.47 (m, 1H), 7.07–7.19 (m, 4H), 6.74 (d, 2H, *J* = 8.6 Hz), 5.39 (m, 1H), 4.94 (m, 1H), 3.71 (s, 3H), 3.34–3.40 (m, 1H), 2.96 (dd, 1H, *J* = 5.6, 14.6 Hz), 2.83 (s, 3H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 171.1, 169.3, 157.1, 155.0, 153.3, 136.9, 136.2, 134.6, 128.4, 126.2, 118.3, 115.8, 69.7, 58.7, 56.1, 52.6, 32.8, 30.8, 28.0; HRMS-ESI-TOF *m/z* 506.1944 ($[M + H]^+$, $C_{24}H_{28}FN_3O_8$ requires 506.1933).



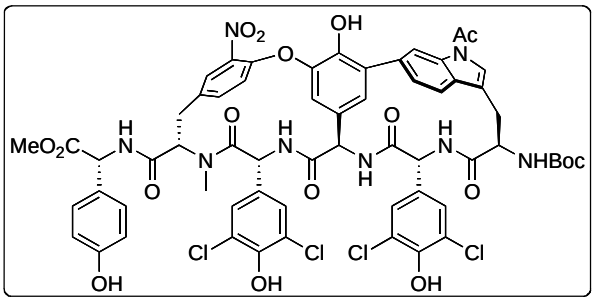
Fmoc protected 3. The dipeptide above (349 mg, 0.672 mmol) was dissolved in formic acid (6.72 mL) and the solution was stirred at room temperature for 2 h. The reaction mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The aqueous layers were back extracted with EtOAc, and the combined organic layers were dried over Na_2SO_4 and concentrated to provide the pure amine in quantitative yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.88 (dd, 1H, *J* = 2.3, 7.0 Hz), 7.74 (d, 1H, *J* = 7.8

Hz), 7.47 (ddd, 1H, *J* = 2.3, 4.1, 8.5 Hz), 7.22 (m, 2H), 7.19 (d, 1H, *J* = 8.5 Hz), 6.87 (m, 1H), 5.47 (d, 1H, *J* = 5.6 Hz), 3.80 (s, 3H), 3.71 (s, 3H), 3.27 (dd, 1H, *J* = 5.5, 7.4 Hz), 3.12 (dd, 1H, *J* = 5.5, 14.3 Hz), 3.01 (dd, 1H, *J* = 7.4, 14.0 Hz), 2.34 (s, 3H), 1.55 (s, 1H). The amine (503 mg, 1.24 mmol) in THF (12.4 mL) at 0 °C was treated with (*R*)-FmocHN-3,5-Cl_2Hpg-OH (**17**, 920 mg, 2.01 mmol), DEPBT (1.48 g, 4.96 mmol), and $NaHCO_3$ (1.04 g, 12.4 mmol). After 24 h at 0 °C, the reaction mixture was diluted with EtOAc and washed with aqueous 1 N HCl (3×) and saturated aqueous NaCl. The aqueous layer was back extracted with EtOAc and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude oil was purified by flash chromatography (SiO_2, 50% acetone–hexanes) to give Fmoc-protected **3** (870 mg, 83%) as a mixture of diastereoisomers (9:1). Recrystallization from CH_2Cl_2 provided pure product: $[\alpha]^{23}_D$ –51 (*c* 0.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) 7.97 (dd, 1H, *J* = 2.1, 7.4 Hz), 7.82 (d, 2H, *J* = 2.1 Hz), 7.70 (d, 1H, *J* = 7.1 Hz), 7.64 (d, 2H, *J* = 7.1 Hz), 7.55 (m, 1H), 7.38 (t, 2H, *J* = 12 Hz), 7.28 (m, 2H), 7.22 (d, 2H, *J* = 8.5 Hz), 7.17 (s, 2H), 7.04 (d, 1H, *J* = 6.5 Hz), 6.78 (d, 2H, *J* = 8.6 Hz), 5.76 (dd, 1H, *J* = 11.4, 4.81 Hz), 5.44 (d, 1H, *J* = 6.6 Hz), 5.40 (d, 1H, *J* = 7.2 Hz), 4.23 (m, 2H), 4.13 (t, 1H, *J* = 7.2 Hz), 3.66 (s, 3H), 3.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.0, 172.8, 170.7, 159.4, 157.4, 156.6, 154.8, 151.0, 145.9, 145.7, 143.0, 138.5, 138.3, 136.9, 131.2, 131.0, 129.9, 129.5, 128.9, 128.4, 128.1, 127.1, 123.4, 121.7, 119.7, 119.5, 117.3, 68.5, 58.7, 58.3, 56.2, 53.6, 48.8, 34.4, 32.7; HRMS-ESI-TOF *m/z* 845.1771 ($[M + H]^+$, $C_{42}H_{35}Cl_2FN_4O_{10}$ requires 845.1787).

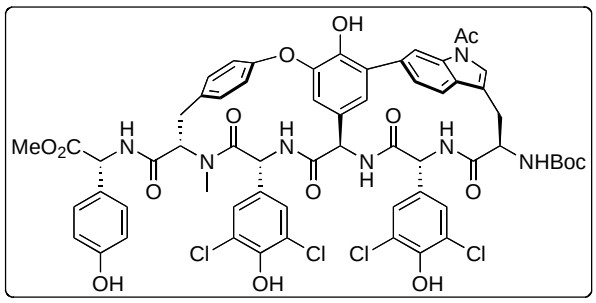


25. Fmoc protected **3** (20 mg, 0.024 mmol) was dissolved in THF (2.4 mL), cooled to 0 °C and treated dropwise with Bu_4NF (1.0 M in THF, 118 μL, 0.118 mmol). The reaction mixture was warmed to ambient temperature. After 1 h, the reaction mixture was diluted with 3 mL toluene and concentrated to half the volume. The crude mixture was directly purified by flash chromatography (SiO_2, 2.5 × 11 cm, 0–8% MeOH–CH_2Cl_2) to afford the free amine (15 mg, 99%) as an off-white solid. The free amine **3** (15 mg, 0.024 mmol), HOAt (7.2 mg, 0.053 mmol), $NaHCO_3$ (6 mg, 0.072 mmol) and **4** (26 mg, 0.036 mmol) were dissolved in a 3:1 mixture of CH_2Cl_2:DMF (2.4 mL), cooled to –5 °C, and EDCI (10 mg, 0.053 mmol) was added as a solid. The reaction mixture was stirred for 6 h, quenched with the addition of H_2O (1 mL) at –5 ºC, warmed to ambient temperature, and the volatiles were removed in vacuo. The product was dissolved in EtOAc and washed with aqueous 1 N HCl (1×) and saturated aqueous NaCl (1×). The organic layer was collected and the aqueous layer was back-extracted with EtOAc (3×), dried over Na_2SO_4 and concentrated in vacuo. Preparative thin layer chromatography (SiO_2, run 2× 40% acetone–toluene + 2% MeOH) afforded **25** (19 mg, 59%) as a light yellow solid: $[\alpha]^{25}_D$ –22 (*c* 0.36, THF); ^{1}H NMR (THF-d_8, 600 MHz) δ 9.19 (s, 1H), 8.88 (s, 1H), 8.53 (d, 1H, *J* = 6.3 Hz), 8.35 (s, 1H), 8.28 (s, 1H), 8.13 (s, 1H), 7.96 (d, 1H, *J* = 5.2 Hz), 7.93 (d, 1H, *J* = 7.1 Hz), 7.62 (d, 1H, *J* = 7.8 Hz), 7.58 (d, 1H, *J* = 8.3 Hz), 7.52 (d, 1H, *J* = 9.0 Hz), 7.56 (s, 1H), 7.45 (d, 1H, *J* = 7.3 Hz), 7.25 (s,

2H), 7.20 (d, 1H, *J* = 8.2 Hz), 7.15 (s, 2H), 7.11 (d, 2H, *J* = 8.4 Hz), 6.83 (d, 1H, *J* = 1.7 Hz), 6.65 (d, 2H, *J* = 8.4 Hz), 6.41 (d, 1H, *J* = 8.7 Hz), 5.71 (d, 1H, *J* = 6.4 Hz), 5.62 (dd, 1H, *J* = 5.9, 9.8 Hz), 5.55 (d, 1H, *J* = 7.2 Hz), 5.41 (d, 1H, *J* = 7.1 Hz), 5.36 (s, 1H), 5.26 (d, 1H, *J* = 9.0 Hz), 3.84 (t, 1H, *J* = 9.5 Hz), 3.63 (s, 3H), 3.44 (t, 1H, *J* = 11.8 Hz), 3.30 (dd, 1H, *J* = 5.7, 14.6 Hz), 3.03 (s, 3H), 2.94 (dd, 1H, *J* = 9.8, 14.8 Hz), 2.56 (s, 3H), 1.34 (s, 9H); ^{19}F NMR (THF-d_8, 400 MHz) δ –120.9; HRMS-ESI-TOF *m/z* 1331.2436 ($[M+H]^+$, $C_{61}H_{55}Cl_4FN_8O_{17}$, requires 1331.2496).

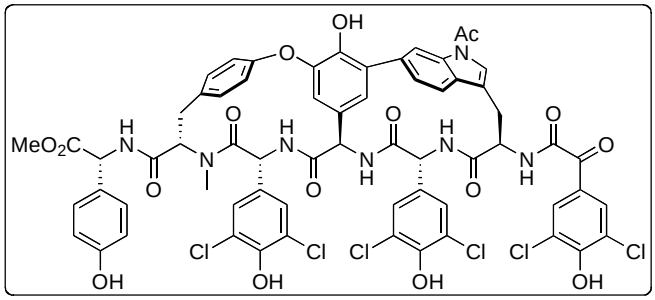


26. Compound **25** (5 mg, 0.004 mmol) was combined with vacuum oven dried K_2CO_3 (52 mg, 0.38 mmol) and catalytic amounts of 18-crown-6 and 4 Å molecular sieves (5 mg) in a 20 mL microwave vial. The solids were evacuated and refilled under an argon atmosphere. Freshly distilled THF (7.5 mL) was added, and the vessel was sealed and warmed at 62 °C for 2–3 d. The reaction progression was monitored every 24 h by LCMS. Upon disappearance of starting material (approx. 48 h), the reaction mixture was cooled to ambient temperature, diluted with EtOAc, and poured into a separatory funnel containing aqueous 1 N HCl. The organic layer was collected, washed with saturated aqueous NaCl, and the combined aqueous layer was back-extracted with EtOAc (3×). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Preparative thin layer chromatography (SiO_2, run 2× 40% acetone–toluene + 2% MeOH) afforded **26** (3.9 mg, 78%) as predominantly a single atropisomer of an inconsequential mixture atropisomers: $[\alpha]^{25}_D$ +20 (*c* 0.72, MeOH); ^{1}H NMR (DMSO-d_6, 600 MHz) δ 9.93 (s, 1H), 9.64 (s, 1H), 8.99 (d, 1H, *J* = 6.0 Hz), 8.57 (d, 1H, *J* = 5.4 Hz), 8.32 (d, 1H, *J* = 9.3 Hz), 8.22 (m, 1H), 8.05 (d, 1H, *J* = 8.6 Hz), 7.89 (d, 1H, *J* = 1.2 Hz), 7.78 (s, 1H), 7.53 (d, 1H, *J* = 8.0 Hz), 7.49 (d, 1H, *J* = 8.3 Hz), 7.30 (s, 2H), 7.24 (s, 2H), 7.13 (m, 6H), 6.78 (d, 2H, *J* = 8.4 Hz), 6.72 (d, 1H, *J* = 8.4 Hz), 5.59 (m, 2H), 5.17 (d, 1H, *J* = 1.8 Hz), 5.12 (d, 1H, *J* = 6.0 Hz), 5.00 (m, 1H), 3.72 (t, 1H, *J* = 9.1 Hz), 3.54 (s, 3H), 3.09 (m, 1H), 3.02 (s, 3H), 2.73 (d, 1H, *J* = 11.9 Hz), 2.62 (s, 3H), 1.25 (s, 9H); HRMS-ESI-TOF *m/z* 1311.2385 ($[M+H]^+$, $C_{61}H_{54}Cl_4N_8O_{17}$, requires 1311.2434), *m/z* 1333.2249 ($[M+Na]^+$, requires 1333.2253).



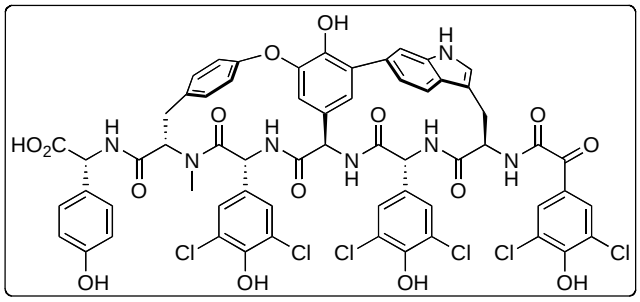
28. Compound **26** (10 mg, 0.0076 mmol) was placed in a 10 mL microwave vial, thoroughly dried, dissolved in anhydrous MeOH (0.8 mL) and cooled to 0 °C. Raney-Ni was washed with anhydrous MeOH (6×) and slurried in 0.2 mL of MeOH before addition to the cooled solution. H_2 gas was bubbled through the solution for 1 min. The reaction mixture was vigorously stirred at 0 °C under an

atmosphere of H_2 for 2 h before being warmed to ambient temperature. Upon disappearance of starting material (<6h), the mixture was filtered through a pad of Celite and washed with copious amounts of THF and MeOH. The solvent was removed in vacuo and the crude material was purified by preparative thin layer chromatography (SiO_2, run 2× 40% acetone–toluene + 2% MeOH) to afford the aniline **27** (8.5 mg, 87%), which was used immediately after purification. The aniline **27** (8.5 mg, 0.0066 mmol) was dissolved in freshly distilled THF (660 μL) and cooled to 0 °C. A solution of H_3PO_2 in distilled THF (50% aq, 220 μL of a 0.606 M) was added dropwise followed by dropwise addition of *t*-BuONO in distilled THF (66 μL of a 0.2 M), and the solution was vigorously stirred at 0 °C for 3 h. The reaction mixture was diluted with EtOAc and washed with H_2O (1×), saturated aqueous $NaHCO_3$ (1×), and saturated aqueous NaCl (1×). The aqueous phase was back extracted with EtOAc (6×) and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by preparative thin layer chromatography (SiO_2, run 1× 50% acetone–toluene + 4% MeOH) to afford **28** (6 mg, 72%) as a light yellow solid: $[\alpha]^{25}_D$ +48 (*c* 0.057, MeOH); ^{1}H NMR (DMSO-d_6, 600 MHz) δ 9.64 (m, 1H), 9.63 (s, 1H), 8.81 (d, 1H, *J* = 5.9 Hz), 8.66 (d, 1H, *J* = 4.2 Hz), 8.29 (d, 1H, *J* = 8.3 Hz), 8.18 (s, 1H), 7.77 (s, 1H), 7.74 (d, 1H, *J* = 8.2 Hz), 7.46 (dd, 1H, *J* = 4.1, 8.2 Hz), 7.42 (d, 1H, *J* = 8.1 Hz), 7.36 (d, 1H, *J* = 7.9 Hz), 7.33 (s, 2H), 7.23 (s, 2H), 7.21 (d, 1H, *J* = 7.1 Hz), 7.12 (m, 4H), 6.85 (dd, 1H, *J* = 1.6, 9.0 Hz), 6.78 (d, 2H, *J* = 8.5 Hz), 5.59 (d, 1H, *J* = 9.1 Hz), 5.49 (m, 2H), 5.17 (d, 1H, *J* = 6.4 Hz), 5.10 (d, 1H, *J* = 5.8 Hz), 5.04 (d, 1H, *J* = 2.0 Hz), 4.98 (m, 1H), 3.70 (dd, 1H, *J* = 6.0, 12.9 Hz), 3.52 (s, 3H), 3.11 (m, 1H), 3.03 (s, 3H), 2.99 (d, 1H, *J* = 11.2 Hz), 2.73 (d, 1H, *J* = 13.6 Hz), 2.61 (s, 3H), 1.26 (s, 9H); HRMS-ESI-TOF *m/z* 1266.2564 ($[M+H]^+$, $C_{61}H_{55}Cl_4N_7O_{15}$, requires 1266.2583).

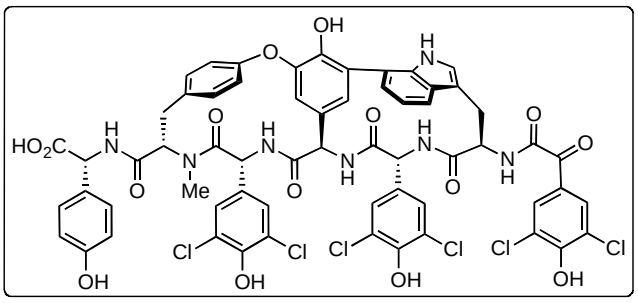


30. Compound **28** (3 mg, 0.002 mmol) was treated with 4 N HCl in 1,4-dioxane (300 μL) at ambient temperature and the reaction progress was monitored by LCMS. Upon disappearance of starting material (3 h), 300 μL of toluene was added, the volatiles were removed under a stream of N_2, and the crude material was used without purification. The amine, HOAt (0.5 mg, 0.003 mmol), $NaHCO_3$ (0.8 mg, 0.009 mmol) and **29** (0.9 mg, 0.003 mmol) were dissolved in a 5:1 mixture of CH_2Cl_2:DMF (0.48 mL), cooled to 0 °C, and EDCI (1.4 mg, 0.007 mmol) was added as a solid. The reaction mixture was stirred for 2 h at 0 °C, warmed to ambient temperature, and the volatiles were removed in vacuo. Preparative thin layer chromatography (SiO_2, run 3× 40% acetone–toluene + 2% MeOH) afforded **30** (1.8 mg, 54%) as a light yellow solid: $[\alpha]^{25}_D$ +43 (*c* 0.2, MeOH); ^{1}H NMR (DMSO-d_6, 600 MHz) δ 10.13 (s, 2H), 9.90 (s, 1H), 9.62 (s, 1H), 9.59 (s, 1H), 8.81 (d, 1H, *J* = 5.5 Hz), 8.70 (d, 1H, *J* = 4.8 Hz), 8.34 (d, 1H, *J* = 9.0 Hz), 8.20 (s, 1H), 7.97 (s, 1H), 7.84 (m, 1H), 7.74 (s, 2H), 7.49 (d, 1H, *J* = 8.0 Hz), 7.36 (s, 2H), 7.34 (s, 2H), 7.27 (s, 1H), 7.25 (d, 1H, *J* = 10.7 Hz), 7.21 (d, 1H, *J* = 7.6 Hz), 7.16 (d, 2H, *J* = 7.8 Hz), 7.11 (d, 1H, *J* = 6.9 Hz), 6.87 (m, 2H), 6.79 (d, 2H, *J* = 8.0 Hz), 5.59 (m, 2H), 5.50 (s, 1H),

5.19 (d, 1H, J = 5.2 Hz), 5.12 (d, 1H, J = 5.4 Hz), 5.08 (s, 1H), 4.99 (m, 1H), 4.26 (m, 1H), 3.53 (s, 3H), 3.33 (m, 1H), 3.11 (m, 1H), 3.04 (s, 3H), 2.97 (m, 1H), 2.87 (d, 1H, J = 13.2 Hz), 2.69 (s, 3H); HRMS-ESI-TOF *m/z* 1404.1261 ($[M+Na]^+$, $C_{64}H_{49}Cl_6N_7O_{16}$, requires 1404.1259).



Complestatin (1, chloropeptin II). Compound **30** (1.8 mg, 0.0013 mmol) was dissolved in freshly distilled THF (0.65 mL), cooled to 0 °C, and treated dropwise with aqueous 0.1 N LiOH (0.195 mL). The reaction progress was monitored by LCMS and upon disappearance of starting material (3 h), the reaction was quenched with the addition of aqueous 0.1 N HCl (0.2 mL) and warmed to ambient temperature. The THF was removed under a stream of N_2, and the crude material was diluted with EtOAc. The organic phase was washed with H_2O (1×), and the aqueous phase was back-extraced with EtOAc (5×). The combined organic phases were concentrated in vacuo, and the crude material was purified by HPLC (C18) using a 10–60% MeCN–H_2O(0.07% TFA) gradient over 60 min. Complestatin (**1**) eluted at 67 min and was concentrated to give **1** as a light yellow solid (1.0 mg, 58%): $[\alpha]^{24}_D$ +77 (*c* 0.2, DMSO-d_6) [authentic **1**: $[\alpha]^{24}_D$ +77 (*c* 0.2, DMSO-d_6)]; $[\alpha]^{24}_D$ +35 (*c* 0.6, DMSO) [authentic **1**: $[\alpha]^{24}_D$ +35 (*c* 0.6, DMSO)][S1]; ^{1}H NMR (DMSO-d_6, 600 MHz) δ 10.91 (s, 1H), 10.11 (s, 1H), 9.90 (s, 1H), 9.56 (s, 1H), 9.43 (s, 2H), 8.74 (d, 1H, J = 6.1 Hz), 8.57 (d, 1H, J = 6.2 Hz), 8.30 (d, 1H, J = 9.5 Hz), 7.82 (m, 3H), 7.76 (s, 2H), 7.43 (d, 1H, J = 8.6 Hz), 7.33 (s, 2H), 7.28 (s, 2H), 7.26 (s, 1H), 7.24 (s, 1H), 7.18 (d, 1H, J = 7.7 Hz), 7.11 (d, 2H, J = 8.6 Hz), 7.08 (d, 1H, J = 8.4 Hz), 6.86 (d, 1H, J = 10.5 Hz), 6.82 (d, 1H, J = 8.7 Hz), 6.76 (d, 2H, J = 8.7 Hz), 5.56 (d, 2H, J = 12.0 Hz), 5.46 (d, 1H, J = 1.7 Hz), 5.19 (d, 1H, J = 7.1 Hz), 5.09 (s, 1H), 5.05 (d, 2H, J = 6.6 Hz), 4.13 (t, 1H, J = 7.9 Hz), 3.39 (m, 1H), 3.05 (m, 2H), 2.98 (s, 3H), 2.86 (d, 1H, J = 12.7 Hz); HRMS-ESI-TOF *m/z* 1326.1149 ($[M+H]^+$, $C_{61}H_{45}Cl_6N_7O_{15}$, requires 1326.1177). HPLC coinjection of synthetic and authentic **1** revealed that the two samples coelute (NovaPak C_{18}, 3.9 x 300 mm, 10–40% MeCN–H_2O (0.07% TFA) gradient over 25 min then isocratic, flow rate 1 mL/min, t_R = 42.20 min).



Chloropeptin I (2). The clean acid-catalyzed conversion of **1** to **2** was conducted on a small scale with both synthetic and authentic **1** to further confirm the integrity of synthetic **1**, albeit on a scale where we do not have a preparative yield to report. The two samples behaved the same providing **2** and we found this was most conveniently conducted with 50% TFA/H_2O at 50 °C progressing at a rate that is easily monitored and that was cleaner on this scale than

when conducted with neat TFA (50 °C).[7] Thus, **1** (15–30 μg) was placed in 50% TFA/H_2O (70 μL) and the solution was stirred at 50 °C for 5 h. Periodic monitoring of the reaction by LCMS (Zorbax SB-C18, 4.6 × 50 mm, 10–65% MeCN + 0.01% TFA / H_2O + 0.1% TFA over 4 min then isocratic) over 5 h revealed the conversion of synthetic and authentic **1** (t_R = 5.36 min) to synthetic and authentic **2** (t_R = 5.52 min), Figure S2.

(S1). To quote the Merck isolation report[8a] "We encountered some difficulties in measurement of optical rotations of buff-colored DMSO solutions of complestatin (then thought to be isocomplestatin) and chloropeptin I. These solutions in polarimeter cells with 1 dm path length cause low energy (less than 60%) deflection and fluctuation presumably due to high viscosity and color of the sample. This problem was circumvented by substitution of cells with 1 cm path length. This problem could lead to some inconsistencies in the observed rotations of the samples." We believe this is due to the poor solubility of **1**, even in DMSO, and the long period of dissolution that is required to avoid (dissolve) aggregates. We measured our rotations of the synthetic and authentic natural samples at the same time, at the same concentration, in the same cells (0.5 dm path length) and with NMR samples (hence DMSO-d_6) after they displayed the crisp spectra (long dissolution times). These proved to be identical. Tanaka has reported the rotation of the **1** (+16.3 (*c* 1.6, DMSO)), both at a much higher concentration and at a much earlier date, and this may be a source of the discrepancy in the measured optical rotations, and Merck reported the rotation of **1** (at the time it was thought to be isocomplestatin)[8a,11] in the above article as –11.2 (*c* 1.6, DMSO).

In our hands, complestatin (which exhibits poor solubility properties) exhibited concentration dependent, time dependent, and moisture (H_2O) dependent ^1H NMR spectra that impact the sharpness of the spectra (see Figure S1), that leads to significant movement of the phenol OH and amide NH resonances and that even results in subtle chemical shift movements in some additional resonances (e.g. C_4^3-H and C_4^5-H). We attribute these to slow dissolution of aggregates even in DMSO.

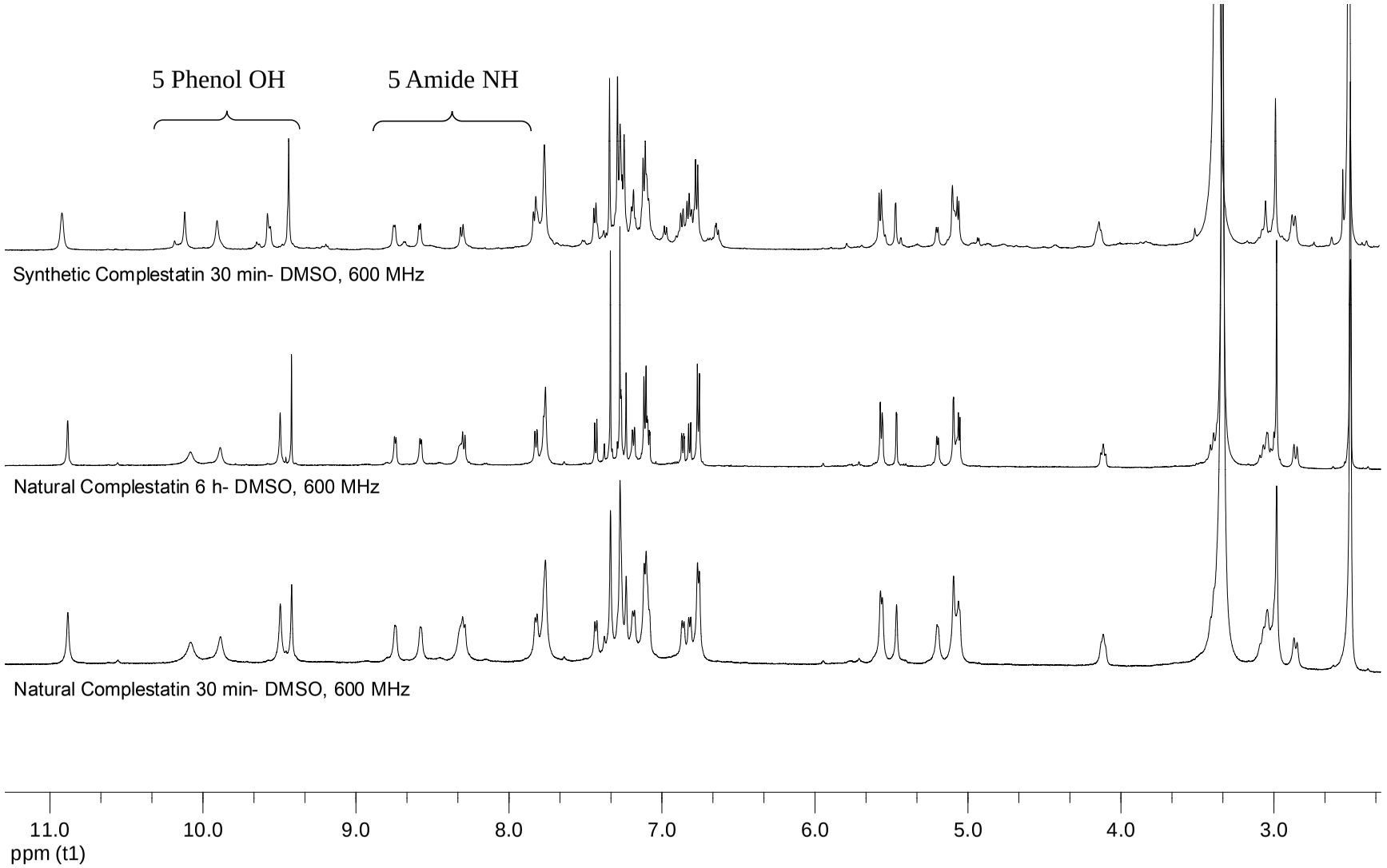


Figure S1. Comparison ^1H NMR (DMSO-d_6, 600 MHz) of natural and synthetic complestatin (**1**, chloropeptin II).

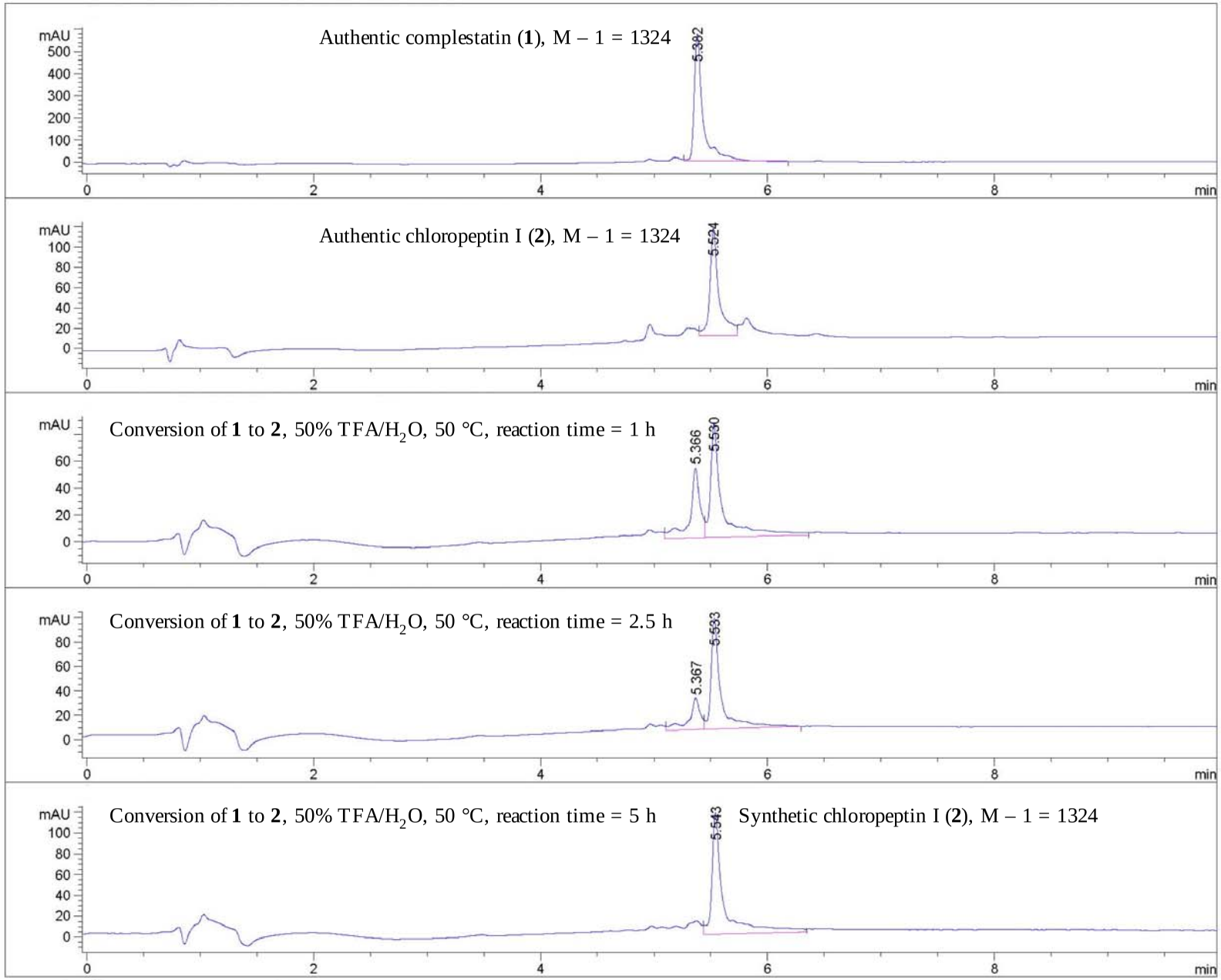
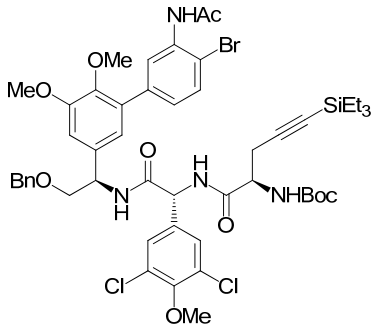
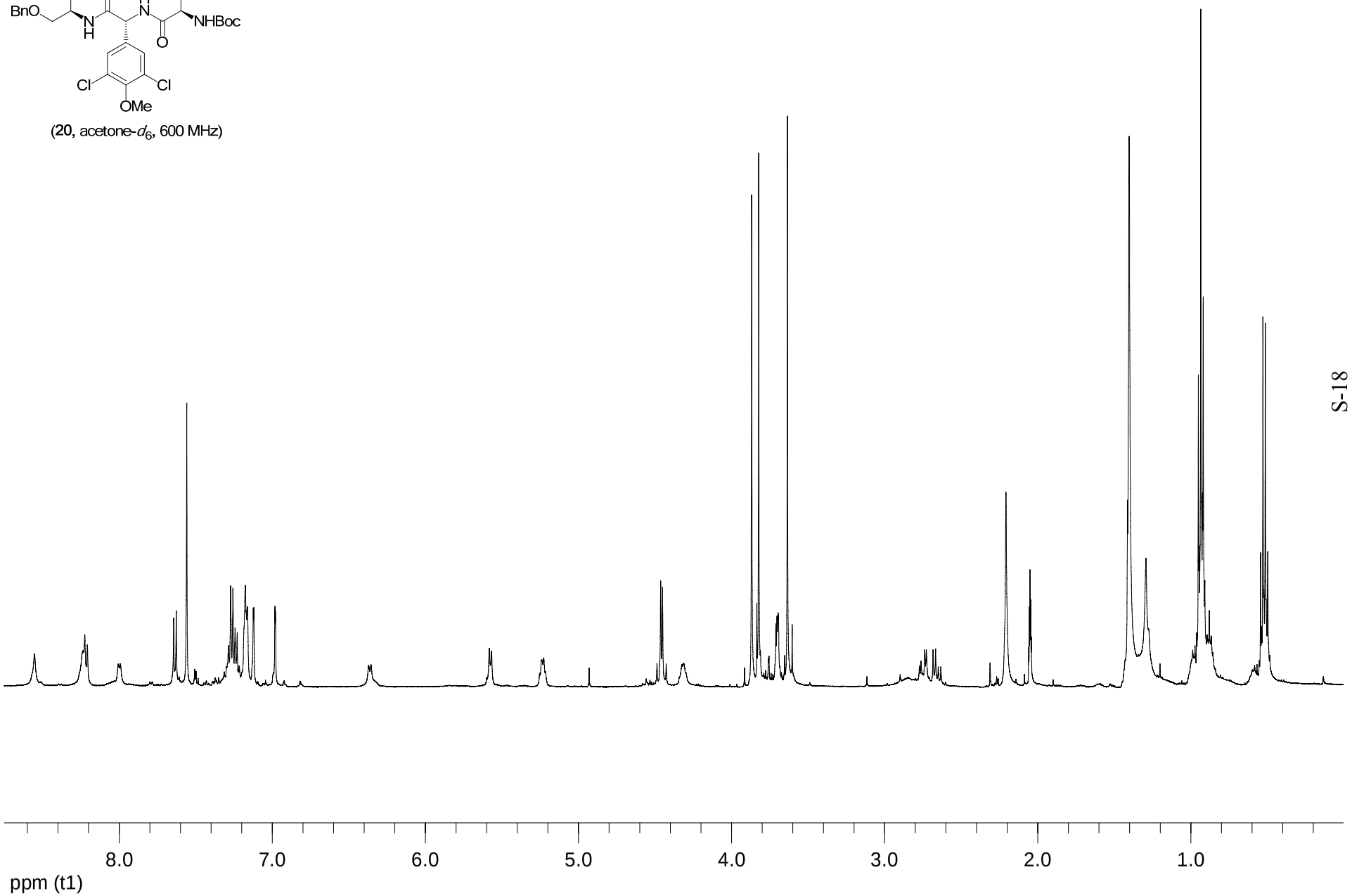
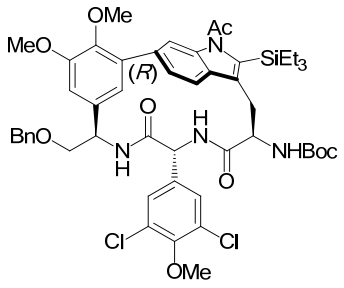


Figure S2. LCMS-scale conversion of complestatin (**1**) to chloropeptin I (**2**).



(**20**, acetone-d_6, 600 MHz)

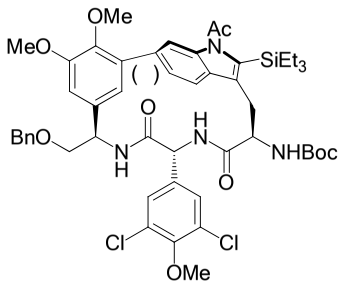




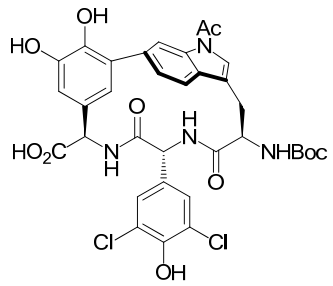
((*R*)-**21**, acetone-d_6, 600 MHz)

7.0 6.0 5.0 4.0 3.0 2.0 1.0

ppm (f1)



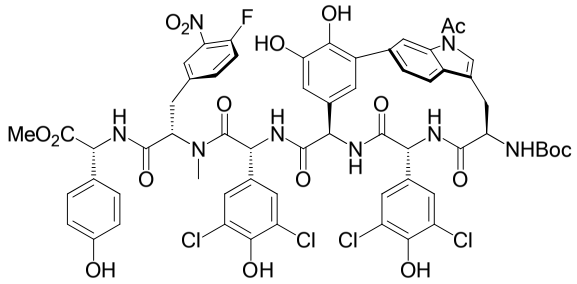
((*S*)-**21**, acetone-d_6, 600MHz)



(**4**, THF-d_8, 600 MHz)

9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0

ppm (t1)



(**25**, THF-d_8, 600 MHz)

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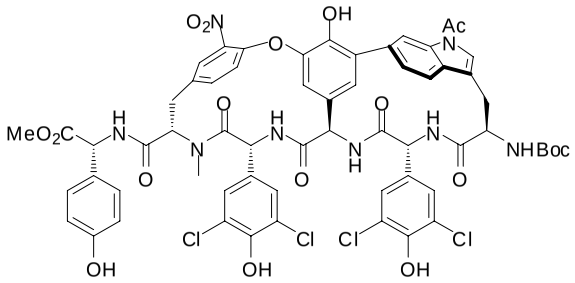
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0

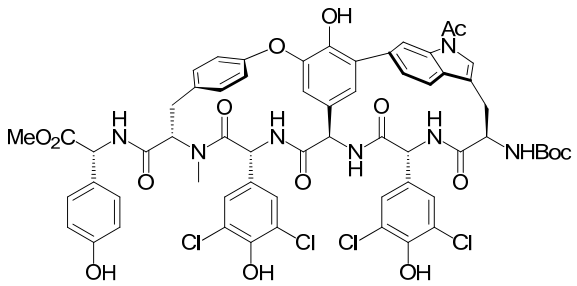
ppm (t1)



(**26**, DMSO-d_6, 600 MHz)

10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0

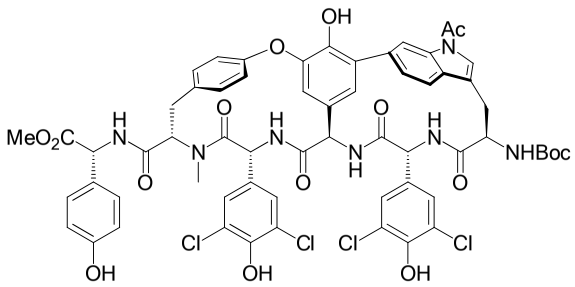
ppm (t1)



(**28**, THF-d_8, 600 MHz)

8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0

ppm (t1)



(**28**, DMSO-d_6, 600 MHz)

9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0

ppm (t1)