Enantioselective Total Synthesis of Avrainvillamide and the Stephacidins

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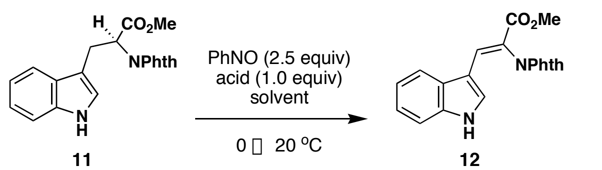
Supporting Information

General procedures. All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), benzene, toluene, acetonitrile (MeCN), *N*, *N*-dimethylformamide (DMF) and methanol (MeOH) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns unless otherwise stated. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate; *p*-anisaldehyde in ethanolic HOAc/H_2SO_4; or potassium permanganate in aqueous NaOH as developing agents. NMR spectra were recorded on Bruker DRX 600, DRX 500, AMX 400, or Varian INOVA 400 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were recorded on a Perkin-Elmer Spectrum BX FT-IR instrument. High resolution mass spectrometry data (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer using MALDI (matrix assisted laser desorption ionization). Melting points (m.p.) are uncorrected and were recorded on a Fisher-Johns 12-144 melting point apparatus. LCMS data were recorded on an Agilent 1100 series LC system coupled to an ESI Agilent MSD.

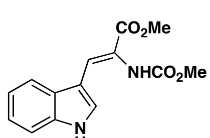
Screening for acid catalysts for the nitrosobenzene-mediated dehydrogenation. The general procedure below was used to screened the following acids for this reaction.



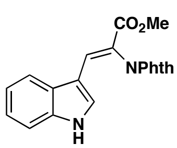
Entry	Acid	Solvent	Yield (%)[a]
1	$ZrCl_4$	CH_3CN	ca 20
2	$ZnCl_2$	CH_2Cl_2	0
3	$TiCl_4$	CH_2Cl_2	60
4	$SnCl_4$	CH_2Cl_2	25
5	$AlCl_3$	CH_2Cl_2	63
6	$ZrCl_4$	Et_2O	42
7	$ZrCl_4$	CH_2Cl_2	82
8	$ZrCl_4$	toluene	82
9	TsOH	MeOH	80

[a] Isolated yield.

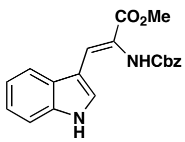
Table S1. Lewis and Brønstead acid screen for the PhNO-mediated dehydrogenation.



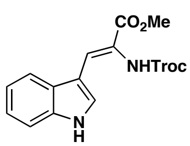
General procedure for nitroso ene reaction (synthesis of compounds **10**, **12**, **14**, **16**, **18**, **20**, **22**). To a solution of **9** (149 mg, 0.54 mmol) and nitrosobenzene (145 mg, 1.35 mmol, 2.5 equiv) in toluene (4 mL, 0.14 *M*) at 0 °C was added $ZrCl_4$ (126 mg, 0.54 mmol, 1.0 equiv) in one portion. The cooling bath was removed and he reaction mixture was stirred for two hours and turned from an initial green color to dark brown. Once the reaction was complete as judged by TLC, the reaction mixture was filtered through Celite® and concentrated. The crude residue was purified by flash column chromatography (silica gel, 10:1 → 2:1 hexanes:EtOAc) and crystallized from 1:1 hexanes:EtOAc furnishing 120 mg (81%) of **10**: white cubes; m.p. = 200 – 202 °C; R_f = 0.30 (silica gel, 2:1 hexanes:EtOAc); IR (film) ν_{max} 3302, 2954, 2260, 1706, 1684, 1618, 1508, 1458, 1431, 1329, 1272, 1224, 1132, 1056, 722 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.78 (bs, 1 H), 7.88 (s, 1 H), 7.77 (d, J = 8.0 Hz, 1 H), 7.73 (s, 1 H), 7.48 (d, J = 8.0 Hz, 1 H), 7.21 (t, J = 7.2 Hz, 1 H) 7.15 (t, J = 7.2 Hz, 1 H), 3.75 (s, 3 H), 3.64 (bs, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.8, 155.2, 135.6, 128.6, 126.9, 122.3, 120.4, 120.0, 119.8, 118.1, 112.0, 108.8, 51.8 (2 C); HRMS (ESI-TOF) calculated for $C_{14}H_{14}N_2O_4Na$ [M + Na^+] 297.0846, found 297.0848.



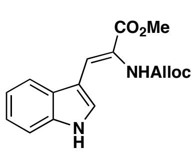
12. Yield: 82%. Yellow plates; m.p. 246 – 247 ˚C; R_f = 0.35 (silica gel, 2:1 hexanes:EtOAc); IR (film) ν_{max} 3370, 1786, 1725, 1700, 1628, 1518, 1424, 1309, 1263, 1239, 1115, 1074, 888, 752, 734 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.87 (bs, 1 H), 8.39 (s, 1 H), 8.06 – 8.01 (m, 2 H), 7.98 – 7.94 (m, 2 H), 7.80 (d, J = 8.0 Hz, 1 H), 7.69 (d, J = 2.8 Hz, 1 H), 7.49 (d, J = 8.0 Hz, 1 H), 7.22 (t, J = 7.4 Hz , 1 H), 7.15 (t, J = 7.4 Hz, 1 H), 3.77 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.9 (2 C), 164.2, 135.8, 135.1 (2 C), 134.8, 131.6 (2 C), 129.5, 126.8 (2 C), 123.9, 122.7, 121.1, 118.1, 112.9, 112.4, 107.9, 52.4; HRMS (ESI-TOF) calculated for $C_{20}H_{14}N_2O_4Na$ [M + Na^+] 369.0851, found 369.0843.



14. Yield: 30%, 67% based on recovered starting material. Yellow cubes; m.p. 198 – 200 ˚C; R_f = 0.48 (silica gel, 1:1 hexanes:EtOAc); IR (film) ν_{max} 3392, 2922, 2259, 1714, 1633, 1517, 1458, 1431, 1244, 1043, 744 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.95 (bs, 0.67 H), 8.67 (bs, 0.33 H), 7.90 (bs, 1 H), 7.78 (d, J = 8.0 Hz, 1 H), 7.77 (s, 1 H), 7.50 (d, J = 8.5 Hz, 1 H), 7.48 – 7.40 (m, 3 H), 7.40 – 7.30 (m, 1 H), 7.28 – 7.24 (m, 1 H), 7.22 (t, J = 7.5 Hz, 1 H), 7.15 (t, J = 7.5 Hz, 1 H), 5.16 (s, 2 H), 5.06 (bs, 1 H), 3.75 (bs, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.7, 154.7, 137.0, 135.6, 128.7, 128.3, 127.8, 127.6, 127.2 , 126.8, 122.3 (2 C), 120.4 (2 C), 119.9, 118.2, 112.0, 108.9, 65.7, 51.8; HRMS (ESI-TOF) calculated for $C_{20}H_{18}N_2O_4Na$ [M + Na^+] 373.1164, found 373.1173.

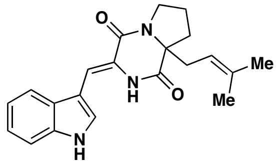


16. Yield: 33%, 47% based on recovered starting material. White cubes; m.p. 164 – 166 °C (dec.); R_f = 0.45 (silica gel, 1:1 hexanes:EtOAc); IR (film) ν_{max} 3317, 1717, 1628, 1517, 1431, 1330, 1260, 1250, 1134, 1094, 748, 603, 568 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 9.95 (s, 1 H), 7.89 (bs, 1 H), 7.83 (s, 1 H), 7.78 (d, J = 8.0 Hz, 1 H), 7.48 (d, J = 8.0 Hz, 1 H), 7.33 (bs, 1 H), 7.24 (t, J = 8.5 Hz, 1 H), 7.19 (t, J = 8.5 Hz, 1 H), 4.86 (s, 2 H), 3.78 (s, 3 H); ^{13}C NMR (125 MHz, CD_3CN) δ 166.6, 154.1, 136.8, 129.5, 128.1, 123.9, 121.9, 120.2, 119.4, 113.0, 110.3, 96.7, 75.2, 52.8, 30.9; HRMS (ESI-TOF) calculated for $C_{15}H_{13}Cl_3N_2O_4$ [M + Na^+] 412.9839, found 412.9837.

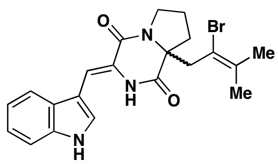


18. Yield: 45%. White cubes; m.p. 152 – 154 ˚C; R_f = 0.29 (silica gel, 1:1 hexanes:EtOAc); IR (film) ν_{max} 3398, 1693, 1629, 1517, 1432, 1329, 1290, 1132, 1053, 747 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 9.90 (bs, 1 H), 7.82 (s, 2 H) , 7.77 (d, J = 8.0 Hz, 1 H), 7.49 (d, J = 8.0 Hz, 1 H), 7.23 (t, J = 8.0 Hz, 1 H), 7.18 (t, J = 8.0 Hz, 1 H), 6.95

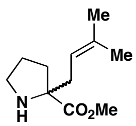
(bs,1 H), 5.96 (bs, 1 H), 5.37 (bs, 1 H), 5.23 (d, J = 6.8 Hz, 1 H), 4.60 (bs, 2 H), 3.78 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 156.0, 137.1, 134.6, 129.7, 128.9, 128.5, 124.1, 122.1, 121.4, 119.7, 118.1, 113.3, 110.8, 66.8, 53.0; HRMS (ESI-TOF) calculated for $C_{16}H_{16}N_2O_4Na$ [M + Na^+]: 323.1008, found 323.1005.



20. Yield 92%. White cubes; m.p. 180 – 182 ˚C; R_f = 0.29 (silica gel, 4:1 EtOAc:hexanes); IR (film) ν_{max} 3216, 2360, 1686, 1654, 1596, 1442, 1382, 1353, 1240, 1132, 1109, 1024, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (bs, 1 H), 7.70 (d, J = 6.2 Hz, 1 H), 7.58 (s, 1 H), 7.42 (d, 6.6 Hz, 1 H), 7.40 (s, 1 H), 7.28 (t, J = 6.2 Hz, 1 H), 7.21 (t, J = 6.2 Hz, 1 H), 7.17 (s, 1 H), 5.16 (t, J = 5.9 Hz, 1 H), 3.88 (dt, J = 11.3, 6.6 Hz, 1 H), 3.70 – 3.59 (m, 1 H), 2.56 (dd, J = 11.4, 6.4 Hz, 1 H), 2.48 (dd, J = 11.0, 6.3 Hz, 1 H), 2.30 – 2.18 (m, 2 H), 2.13 – 2.01 (m, 2 H), 1.62 (s, 3 H), 1.60 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 158.7, 138.3, 136.0, 126.5, 125.5, 123.4 (2C) , 121.0, 119.4, 116.8, 111.5, 110.2, 107.8, 68.6, 45.1, 37.1, 34.2, 26.1, 20.3, 17.8; HRMS (ESI-TOF) calculated for $C_{21}H_{24}N_3O_2$ [M + H^+]: 350.1869, found 350.1858.

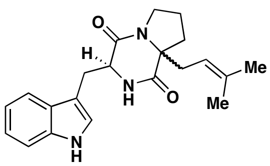


22. Yield: 79%. White needles; m.p. 216 – 220 ˚C; R_f = 0.4 (silica gel, 1:1 hexanes:EtOAc); IR (film) ν_{max} 3221, 1690, 1597, 1447, 1241, 1132, 748, cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.71 (s, 1 H), 7.87 (d, J = 2.7 Hz, 1 H), 7.64 (d, J = 7.8 Hz, 1 H), 7.42 (d, J = 8.1 Hz, 1 H), 7.17 (t, J = 8.1 Hz, 1 H), 7.10 (t, J = 7.9 Hz, 1 H), 6.87 (s, 1 H), 3.70 – 3.62 (m, 1 H), 3.50 (td, J = 9.5, 3.4 Hz, 1 H), 3.03 (d, J = 15.4 Hz, 1 H), 2.97 (d, J = 15.4 Hz, 1 H), 2.16 – 1.98 (m, 3 H), 1.97 – 1.88 (m, 1 H), 1.69 (s, 3 H), 1.48 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.4, 159.2, 136.8, 135.5, 127.0, 126.3, 124.3, 121.9, 119.8, 117.9, 114.0, 111.8, 108.0, 106.9, 67.6, 45.2, 44.9, 35.0, 25.6, 20.6, 19.6; HRMS (ESI-TOF) calculated for $C_{21}H_{23}BrN_3O_2$ [M + H^+] 428.0968, found 428.0963.



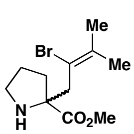
Prenylated proline 26. To a solution of **23** (4.74 g, 20.7 mmol) in THF (21 mL, 1 *M*) at –78 °C was added LHMDS (22.8 mL from a 1.0 *M* solution, 22.8 mmol, 1.1 equiv) over 5 min. After the addition, the reaction mixture was maintained at –78 °C and allowed to react for 35 min, during which time the solution turned yellow. To the resulting enolate was added prenyl bromide (2.63 mL, 22.7 mmol, 1.1 equiv) over 5 min. After the addition, the cooling bath was removed and the reaction was allowed to warm to room temperature. After 2 h, the reaction was quenched with saturated aqueous NH_4Cl (100 mL), followed by H_2O (100 mL). The product mixture was extracted with EtOAc (3 × 100 mL) and the combined EtOAc layers were washed with saturated aqueous NaCl (200 mL), dried with anhydrous $MgSO_4$, concentrated *in vacuo*, and purified by flash column chromatography (silica gel, 6:1 hexanes:EtOAc) furnishing 5.11 g (83%) of **25** as a clear colorless oil. To a solution of this compound (5.11 g, 17.2 mmol) in toluene (84 mL, 0.2 *M*) was added *p*-TsOH• H_2O (3.27, 17.2 mmol, 1.0 equiv). The resulting suspension was stirred vigorously and heated at reflux whereupon the acid dissolved. After 2.5 h, the reaction was deemed complete by TLC and the solvent was removed *in vacuo*. The residue was dissolved in $CHCl_3$ (100 mL) and ammonia was bubbled through the suspension for 20 min, during which time the mixture became a cloudy, white suspension. The reaction mixture was filtered and the cake was rinsed with additional $CHCl_3$ (50 mL). The filtrate was concentrated furnishing 2.85 g (84%) of amine **26**: clear oil; R_f = 0.30 (silica gel, EtOAc); IR (film) ν_{max} 2952, 1729, 1437, 1376, 1223, 1193, 1173, 1098, 998 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.05 (tt, *J* = 7.2, 1.3 Hz, 1 H), 3.67 (s, 3 H), 2.94 (t, *J* = 6.8

Hz, 2 H), 2.51 (dd, J = 14.2, 7.6 Hz, 1 H), 2.36 (bs, 1 H), 2.26 (dd, J = 14.2, 6.9 Hz, 1 H), 2.16 – 2.08 (m, 1 H), 1.79 – 1.66 (m, 3 H), 1.66 (d, J = 1.0 Hz, 3 H), 1.57 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 134.8, 119.3, 69.7, 52.2, 46.5, 38.2, 35.3, 26.0, 25.1, 18.0; HRMS (ESI-TOF) calculated for $C_{11}H_{20}NO_2$ [M + H^+] 198.1488, found 198.1485.



Diketopiperazine 19. To a solution of *N*-Boc tryptophan (252 mg, 0.828 mmol, 1.0 equiv) and the prenylated amine **26** (163 mg, 0.828 mmol, 1.0 equiv) in CH_2Cl_2 (8.28 mL, 0.1 *M*) was added bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl, 232 mg, 0.911 mmol, 1.1 equiv). After 1 min, *i*-Pr_2EtN (0.433 mL freshly distilled from CaH_2, 2.48 mmol, 3.0 equiv) was added. The reaction mixture was allowed to stir for 24 h. It was then diluted with EtOAc (30 mL) and H_2O (30 mL). The mixture was extracted with EtOAc (2 $\times$ 30 mL). The combined organic layers were washed with 1 *M* aqueous HCl (50 mL) then with saturated aqueous NaCl (50 mL). The organic portion was dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash column chromatography (silica gel, 3:1 hexanes:EtOAc) furnishing 165 mg (41%) of an inseparable mixture of diastereomeric amides. 144 mg (0.298 mmol) of this diastereomeric mixture was then subjected to heating without solvent under a nitrogen atmosphere at 190 °C for 45 min furnishing 83 mg (79%) of the corresponding diketopiperazines as a 1:1 mixture that could be separated by flash column chromatography (1:1 hexanes:EtOAc, then EtOAc). Upper diastereomer: white foam; R_f = 0.38 (silica gel, EtOAc); IR (film) ν_{max} 3257, 2929, 1640, 1435, 1342, 1103, 1031, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (bs, 1 H), 7.56 (d, J = 7.9 Hz, 1 H), 7.38 (d, J = 8.2 Hz, 1 H), 7.22 (t, J = 8.1 Hz, 1 H), 7.11 (t, J = 7.9 Hz, 1 H), 7.02 (d, J = 2.0 Hz, 1 H), 5.74 (bs, 1 H), 5.09 (t, J = 7.9 Hz, 1 H), 4.39 (dd, J = 11.1, 3.4 Hz, 1 H), 3.90 – 3.79 (m, 1 H), 3.78 (dd, J =

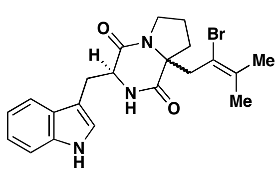
14.9, 3.0 Hz, 1 H), 3.55 (ddd, *J* = 12.9, 9.0, 4.4 Hz 1 H), 2.85 (dd, *J* = 14.8, 11.2 Hz, 1 H), 2.47 (dd, *J* = 14.2, 7.7 Hz, 1 H), 2.40 (dd, *J* = 14.2, 8.3 Hz, 1 H), 2.15 – 2.10 (m, 2 H), 2.06 – 1.93 (m, 2 H), 1.68 (s, 3 H), 1.56 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 165.6, 137.9, 136.9, 126.7, 123.6, 122.7, 119.9, 118.6, 117.2, 111.7, 109.9, 68.6, 54.5, 45.2, 36.1, 34.6, 28.3, 26.1, 20.5, 17.9; HRMS (ESI-TOF) calculated for $C_{21}H_{26}N_3O_2$ [M + H^+] 352.2019, found 352.2034. Lower diastereomer: white flakes; R_f = 0.18 (silica gel, EtOAc); IR (film) ν_{max} 3252, 2920, 1735, 1664, 1620, 1451, 1330, 1245, 1101, 1045, 743, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (bs, 1 H), 7.62 (d, *J* = 7.9 Hz, 1 H), 7.37 (d, *J* = 8.1 Hz, 1 H), 7.21 (t, *J* = 7.3 Hz, 1 H), 7.13 (t, *J* = 7.3 Hz, 1 H), 7.02 (s, 1 H), 5.78 (bs, 1 H), 5.22 (t, *J* = 7.8 Hz, 1 H), 4.18 (dd, *J* = 11.4, 1.5 Hz, 1 H), 4.07 – 4.00 (m, 1 H), 3.62 (dd, *J* = 14.2, 2.9 Hz, 1 H), 3.51 – 3.43 (m, 1 H), 2.99 (dd, *J* = 14.2, 11.4 Hz, 1 H), 2.59 (dd, *J* = 14.2, 7.7 Hz, 1 H), 2.38 (dd, *J* = 14.2, 7.7, 1 H), 2.24 – 2.16 (m, 1 H), 2.07 – 1.93 (m, 3 H), 1.80, (s, 3 H), 1.68 (s, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.0, 165.0, 137.4, 136.6, 126.8, 123.3, 122.6, 120.0, 118.8, 118.2, 111.6, 110.4, 67.9, 58.1, 44.8, 36.3, 35.3, 31.9, 26.5, 19.7, 18.2; HRMS (ESI-TOF) calculated for $C_{21}H_{26}N_3O_2$ [M + H^+] 352.2019, found 352.2023.



Vinyl bromide 35. To a solution of **23** (4.36 g, 19.0 mmol) in THF (190 mL, 0.1 *M*) at –78 °C was added LHMDS (22.8 mL from a 1.0 *M* solution, 22.8 mmol, 1.2 equiv) over 5 min. After the addition, the reaction mixture was maintained at –78 °C and allowed to react for 35 min, during which it turned yellow. To the resulting enolate was added 1,2-dibromo-3-methyl-2-butene[1] (**33**, 4.33 g, 19.0 mmol, 1.0 equiv) over 5 min. After the addition, the cooling bath was removed and the reaction was allowed to warm to room temperature. After

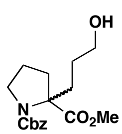
[1] Wijnberg, J. B. P. A.; Wiering, P. G.; Steinberg, H. *Synthesis*, **1981**, *11*, 901-903.

2 h, the reaction was quenched with saturated aqueous NH_4Cl (100 mL) followed by H_2O (100 mL). The aqueous portion was extracted with EtOAc (3 × 100 mL) and the combined EtOAc layers were washed with saturated aqueous NaCl (200 mL), dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and purified by flash column chromatography furnishing **35** (5.91 g, 83%) as a clear colorless oil. To a solution of this compound (5.91 g, 15.7 mmol) in toluene (79 mL, 0.2 *M*) was added *p*-TsOH• H_2O (2.99 g, 15.8 mmol, 1.0 equiv). The resulting suspension was stirred vigorously and heated at reflux whereupon the acid dissolved. The reaction was heated for 2 h at which point all starting material had been consumed by TLC. The solvent was then removed *in vacuo* and replaced with $CHCl_3$ (100 mL). Ammonia was bubbled through the suspension for 30 min, during which time the mixture became a cloudy, white suspension. The reaction mixture was filtered and the cake was rinsed with addition $CHCl_3$ (50 mL). The filtrate was concentrated furnishing 3.7 g (85%) of **35**: pale yellow oil; R_f = 0.2 (silica gel, 1:1 hexanes:EtOAc); IR (film) ν_{max} 2948, 2360, 1730, 1433, 1206, 1021, 899, 764, 606 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3 H), 3.05 (d, *J* = 14.8 Hz, 1 H), 3.03 – 2.87 (m, 2 H), 2.90 (d, *J* = 14.8 Hz, 1 H), 2.65 (bs, 1 H), 2.24 – 2.16 (m, 1 H), 1.83 (s, 3 H), 1.80 – 1.60 (m, 3 H), 1.75 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 134.7, 115.8, 69.7, 52.2, 46.3, 45.9, 35.9, 25.8, 24.1, 21.3; HRMS (ESI-TOF) calculated for $C_{11}H_{19}BrNO_2$ [M + H^+] 276.0594, found 276.0596.



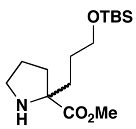
Vinyl bromide DKP 21. To a solution of *N*-Boc tryptophan (1.900 g, 6.24 mmol, 1.0 equiv) and the vinyl bromide amine **35** (1.72 g, 6.24 mmol, 1.0 equiv) in CH_2Cl_2 (62 mL, 0.1 *M*) was added bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl, 1.746 g, 6.86 mmol, 1.1 equiv). After 1 min, *i*-Pr_2EtN

(3.26 mL, 18.7 mmol, 3.0 equiv) was added. The reaction mixture was allowed to stir for 12 h at ambient temperature. After 12 h, all starting material had been consumed as judged by TLC and the reaction was then diluted with EtOAc (100 mL) and H_2O (100 mL). The mixture was extracted with EtOAc (2×50 mL). The combined organic layers were washed with 1 *M* aqueous HCl (100 mL) then with saturated aqueous NaCl (100 mL). The organic portion was dried over anhydrous $MgSO_4$, filtered, concentrated, and purified by flash column chromatography (silica gel, 2:1 hexanes:EtOAc) furnishing 1.9 g (54%) of an inseparable mixture of diastereomeric amides. To a solution of a mixture of the amides thus prepared (1.84 g, 3.27 mmol) in toluene (32.7 mL, 0.1 *M*) was added *p*-TsOH•H_2O (622 mg, 3.27 mmol, 1.0 equiv). The resulting suspension was heated at reflux whereupon the acid dissolved until all starting material had been consumed as judged by TLC (2.5 h). The solvent was then evaporated *in vacuo* and replaced with $CHCl_3$ (100 mL). Ammonia was bubbled through the suspension for 20 min, during which the mixture became a cloudy, white suspension. The reaction mixture was filtered and the cake was rinsed with additional $CHCl_3$ (50 mL). The filtrate was concentrated and the residue dissolved in toluene (32.7 mL) and heated at reflux for 4 h. The solvent was evaporated and the residue purified by flash column chromatography (2:1 $\rightarrow$ 1:1 hexanes:EtOAc $\rightarrow$ EtOAc) furnishing a total of 646 mg (46%) of vinyl bromide **21**: upper diastereomer: white foam; R_f = 0.32 (silica gel, EtOAc); IR (film) ν_{max} 3276, 1648, 1426, 1104, 739, 418 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.37 (bs, 1 H), 7.66 (d, *J* = 7.9 Hz, 1 H), 7.40 (d, *J* = 8.1 Hz, 1 H), 7.22 (t, *J* 7.8 Hz, 1 H), 7.5 Hz, 1 H), 7.08 (s, 1 H), 5.82 (s, 1 H), 4.22 (dt, *J* = 11.7, 6.5 Hz, 1 H), 4.08 – 4.01 (m, 1 H), 3.68 (d, *J* = 14.2, 2.3 Hz, 1 H), 3.64 – 3.58 (m, 1 H), 3.37 (d, *J* = 15.2 Hz, 1 H), 2.92 – 2.82 (m, 2 H), 2.23 – 2.16 (m, 1 H), 2.09 – 1.99 (3 H), 1.98 (s, 3 H), 1.89 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 165.9, 137.5, 136.8, 126.6, 123.6, 122.6, 119.8, 118.7, 113.6, 111.7, 109.6, 68.4, 54.5, 45.5, 44.5, 35.9, 28.0, 26.0, 20.9, 20.2; HRMS (ESI-TOF) calculated for $C_{21}H_{25}BrN_3O_2$ [M + H^+] 430.1125, found 430.1127. Lower diastereomer : white foam; R_f = 0.14 (silica gel, EtOAc); IR (film) ν_{max} 3226, 2983, 1664, 1650, 1456, 1373, 1246, 1045, 742, 611 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (bs, 1 H), 7.57 (d, *J* = 7.9 Hz, 1 H), 7.39 (d, *J* = 8.2 Hz, 1 H), 7.23 (t, *J* = 7.8 Hz, 1 H), 7.13 (d, *J* = 7.5 Hz, 1 H), 7.09 (s, 1 H), 5.72 (s, 1 H), 4.44 (dd, *J* = 11.3, 3.4 Hz, 1 h), 3.88 – 3.80 (m, 1 H), 3.77 (dd, *J* = 15.0, 3.4 Hz, 1 H), 3.67 – 3.61 (m, 1 H), 3.18 (d, *J* = 15.2 Hz, 1 H), 2.89 (d, *J* = 15.2 Hz, 1 H), 2.86 (dd, *J* = 15.0, 11.5 Hz, 1 H), 2.17 – 2.07 (m, 2 H), 2.06 – 1.98 (m, 2 H), 1.85 (s, 3 H), 1.66 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 164.8, 137.5, 137.0, 126.6, 123.5, 122.5, 119.8, 118.7, 114.3, 111.7, 110.3, 67.8, 57.9, 45.4, 44.0, 36.5, 32.0, 26.3, 21.3, 19.5; HRMS (ESI-TOF) calculated for $C_{21}H_{25}BrN_3O_2$ [M + H^+] 430.1125, found 430.1136.

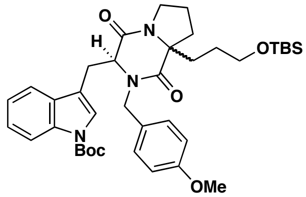


Proline derivative 38. To a solution of (±)-*N*-Cbz-2-allylproline methyl ester (1.0 g, 3.30 mmol, 1.0 equiv) in THF (11 mL) was added 9-BBN (0.5 M in THF, 13.2 mL, 6.60 mmol, 2.0 equiv). The mixture was stirred for 3 h at room temperature. It was then subjected to oxidative workup by adding 3 *M* aqueous NaOH (30 mL) immediately followed by careful and dropwise addition of 35% aqueous H_2O_2 (30 mL) with vigorous stirring. The reaction mixture was stirred for 1 h and then extracted with EtOAc (3 × 300 mL), washed with saturated aqueous NaCl (3 × 500 mL), dried with anhydrous $MgSO_4$, concentrated *in vacuo*, and purified by flash column chromatography (silica gel, 4:1 hexanes:EtOAc) furnishing 973 mg (92%) of **38** as a clear colorless oil: R_f = 0.55 (silica gel, 1:1 hexanes:EtOAc); IR (film) ν_{max} 3452, 2951, 1737, 1701, 1405, 1355, 1276, 1208, 1131, 1169, 1025, 770, 745, 699, 621 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, data for both rotamers reported) δ 7.37 – 7.28, (m, 5 H), 5.18 – 5.06

(m, 2 H), 3.83 – 3.71 (m, 0.5 H), 3.69 (s, 1.5 H), 3.67 – 3.61 (m, 1.5 H) 3.57 – 3.45 (m, 2 H), 3.48 (s, 1.5 H), 2.35 (ddd, J = 16.7, 11.9, 4.6 Hz, 0.5 H), 2.15 – 1.80 (m, 4 H), 1.69 – 1.35 (m, 3.5 H); ^{13}C NMR (100 MHz , $CDCl_3$, data for both rotamers reported) δ 175.0, 174.8, 154.5 (2 C), 136.8, 136.4, 128.5, 128.5 (2 C), 128.3, 128.1, 127.9, 127.7 (2 C), 127.6 (2 C), 68.5, 67.6, 67.1, 66.7, 62.7, 52.5, 52.3, 52.1, 49.2, 48.5, 37.5, 36.1, 31.3, 30.2, 27.0, 26.9, 23.1, 22.7; HRMS (ESI-TOF) calculated for $C_{17}H_{24}NO_5$ [M + H$^+$] 322.1649, found 322.1650.



Proline derivative 39. To a solution of compound **38** (630 mg, 1.96 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL, 0.2 *M*) at room temperature, was added imidazole (160 mg, 2.35 mmol, 1.2 equiv) and the solution was stirred for 5 minutes. TBSCl (325 mg, 2.16 mmol, 1.1 equiv) was then added and the mixture was stirred for 30 min. The solution was concentrated *in vacuo* and purified by passing the residue through a short plug of silica gel (silica gel, 2:1 hexanes:EtOAc) furnishing 820 mg (96%) of the silylated product as a colorless oil. To a solution of this compound so prepared (700 mg, 1.60 mmol, 1.0 equiv) in MeOH (20 mL, 0.08 *M*) was added 10% Pd/C (20% w/w). Hydrogen gas was bubbled through the suspension and after 3 h, all starting material had been consumed as judged by TLC. The mixture was filtered through Celite®, and the filter cake was rinsed with CH_2Cl_2 (60 mL). The mixture was concentrated furnishing 480 mg (100%) of **39** as a clear colorless oil; R_f = 0.22 (silica gel, ether); IR (film) ν_{max} 2952, 1730, 1462, 1253, 1197, 1095, 1004, 834, 774, 625, 459, 448, 418 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3 H), 3.58 (m, 2 H), 2.96 (t, J = 6.5 Hz, 2 H), 2.34 (bs, 1 H, D_2O exchangeable), 2.15 (m, 1 H), 1.82 – 1.31 (m, 7 H), 0.88 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 69.5, 63.0, 52.3, 46.3, 35.9, 35.8, 28.6, 25.9, 24.7, 18.3 (3 C), – 5.3 (2 C); HRMS calculated for $C_{15}H_{31}SiNO_3Na$ [M + Na$^+$] 324.1971; found 324.1964.



Compound 43. Amine **39** (2.03 g, 6.7 mmol, 1.0 equiv) and tryptophan **40**[2] (2.95 g, 6.73 mmol, 1.0 equiv) were combined and dried azeotropically with benzene. DMF (135 mL, 0.05 *M*) was added to this mixture followed by *O*–(7–azabenzotriazol–1–yl)–*N, N, N', N'*–tetramethyluromoium hexafluorophosphate (HATU, 2.81 g, 7.40 mmol, 1.1 equiv). *i*-Pr_2EtN (3.52 mL freshly distilled from CaH_2, 20.2 mmol, 3.0 equiv) was then added dropwise. The reaction mixture was stirred overnight at which point TLC analysis indicated complete consumption of the starting material. The reaction was quenched by the addition of EtOAc (100 mL) and 1 *M* aqueous HCl (100 mL). The mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with H_2O (5 × 100 mL), then with saturated aqueous NaCl (200 mL), dried with anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude product mixture which was purified by flash column chromatography (silica gel, 10:1 hexanes:EtOAc) to provide 3.84 g (79%) combined weight of diastereomers. Both diastereomers could be carried on to compound **43**. The lower diastereoisomer (2.62 g, 3.64 mmol) was dissolved in EtOAc:MeOH (1:1, 0.1 M), 20% Pd/C (10% w/w) was added, and H_2(g) was bubbled through the solution. After 5 h, the reaction was deemed complete by TLC and the free amine was filtered through Celite®. The filter cake was washed with a MeOH:CH_2Cl_2 (1:1, 50 mL) and the washings concentrated *in vacuo* to obtain the free amine (1.5 g, 70%). This residue (1.5 g, 2.55 mmol) was dissolved in toluene (51 mL, 0.05 *M*) and the solution refluxed for 4 h to obtain the crude diketopiperazine which was be purified by flash column chromatography (silica gel, 4:1 hexanes:EtOAc) to give **42** (1.04 g, 74%). **42** (0.8 g, 1.44 mmol, 1.0 equiv) was dissolved in DMF (14.4 mL, 0.1 *M*), cooled to 0 °C, and NaH

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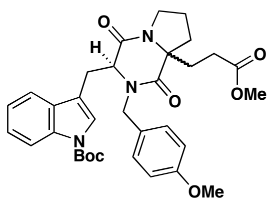
2 Abato, P.; Yuen, C. M.; Cubanski, J. Y.; Seto, C. T. *J. Org. Chem.* **2002**, *67*, 1184–1191.

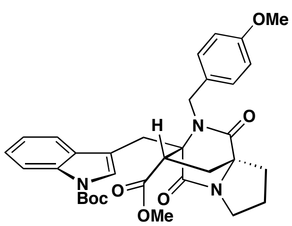
(0.69 g, 1.73 mmol, 1.2 equiv used as a 60% dispersion in mineral oil) was added and stirred for 30 min. After 30 min, *p*-methoxybenzyl chloride (0.235 mL, 1.73 mmol, 1.2 equiv) was added and the mixture was stirred for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL), diluted with 1:1 H_2O:EtOAc (50 mL) and then extracted with EtOAc (3 $\times$ 30 mL). The EtOAc extracts were combined and washed with H_2O (3 $\times$ 40 mL), then saturated aqueous NaCl (100 mL), dried with anhydrous $MgSO_4$, concentrated and purified by flash column chromatography (silica gel, 6:1 hexanes:EtOAc) to provide 0.84 g (72%) of **43**: white foam; R_f = 0.31 (silica gel, EtOAc); $[\alpha]_D$ = –39.7 (c 1.7, $CHCl_3$); IR (film) ν_{max} 2955, 1734, 1654, 1513, 1452, 1370, 1252, 1157, 1086, 835, 767, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (bd, *J* = 7.6 Hz, 1 H), 7.59 (d, *J* = 8.0 Hz, 1 Hz), 7.42 (s, 1 H), 7.35 (t, *J* = 8.0 Hz, 1 H), 7.26 (t, *J* = 8.0 Hz, 1 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 6.73 (d, *J* = 8.8 Hz, 2 H), 5.26 (d, *J* = 14.8 Hz, 1 H), 4.26 (dd, *J* = 6.8, 4.8 Hz, 1 H), 3.86 (m, 1 H), 3.76 (s, 3 H), 3.48 (d, *J* = 14.8 Hz, 1 H), 3.50 – 3.27 (m, 5 H), 2.26 (m, 1 H), 1.93 (m, 3 H), 1.68 (s, 9 H), 1.51 (m, 3 H), 1.25 (m, 1 H), 0.87 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (100 MHz , $CDCl_3$) δ 169.3, 165.1, 159.4, 149.6, 135.6, 130.3, 129.9 (2 C), 128.1, 125.1, 124.6, 123.1, 119.5, 116.1 (2 C), 115.6, 114.3, 84.1, 67.2, 62.4, 60.6, 55.4, 47.0, 44.9, 34.6, 29.6, 28.4 (3 C), 26.1 (3 C), 20.0, 18.4 (3 C), –5.1 (2 C); HRMS (ESI-TOF) calculated for $C_{38}H_{54}N_3O_6Si$ [M + H^+] 676.3776, found 676.3791. Lower diastereomer: white foam; R_f = 0.44 (silica gel, 1:1 hexanes:EtOAc); $[\alpha]_D$ = –37.8 (c 3.0, $CHCl_3$); IR (film) ν_{max} 2953, 1733, 1654, 1513, 1455, 1371, 1254, 1157, 1083, 835, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (bd, *J* = 8.0 Hz, 1 H), 7.55 (d, *J* = 7.3 Hz, 1 H), 7.31 (t, *J* = 6.8 Hz, 1 H), 7.30 (td, *J* = 7.3, 1.1 Hz, 1 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 7.22 (td, *J* = 7.3, 1.1 Hz, 1 H), 6.87 (d, *J* = 6.6 Hz, 2 H), 5.62 (d, *J* = 14.7 Hz, 1 H), 4.24 (dd, *J* = 4.8, 2.6 Hz, 1 H), 3.87 (d, *J* =14.7 Hz, 1 H), 3.80 (s, 3 H), 3.61 (m, 1 H), 3.53 (dd, *J* = 16.5, 1.5 Hz, 1 H), 3.49 (m, 2H), 3.31 (dd, *J* = 15.8, 4.8 Hz, 1 H), 3.10 (m, 1 H), 1.80 (m, 2 H), 1.65 (s, 9 H), 1.26 (m, 3 H), 1.28 (m, 2 H), 1.08 (m, 1 H), 0.84 (s, 9 H), -0.01 (s, 6 H); ^{13}C NMR (100 MHz , $CDCl_3$) δ 168.9, 164.4, 159.6, 149.6, 135.2, 130.5, 130.3 (2 C), 127.5, 124.9, 124.6, 122.7, 119.6, 115.2, 114.5 (2 C), 113.9, 84.0, 67.3, 62.4, 58.4, 55.5, 45.9, 43.8, 34.9, 34.6, 28.4 (3 C), 27.3, 26.2, 26.1 (3 C), 19.5, 18.4, –5.1, –5.2. HRMS (ESI-TOF) calculated for $C_{38}H_{54}N_3O_6Si$ [M + H$^+$] 676.3776, found 676.3784.



Compound 44. To a solution of **43** (diastereomers of **43** were carried forward independently; 710 mg, 1.05 mmol) in THF (11 mL, 0.1 *M*) was added TBAF (3.15 mL from a 1 *M* solution in THF, 3.15 mmol, 3.0 equiv). All starting material was consumed after 2 h as judged by TLC. The reaction was quenched with saturated aqueous NH_4Cl (10 mL). The mixture was diluted with H_2O:EtOAc (1:1, 50 mL) and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 30 mL). The combined organic portions were washed with saturated aqueous NaCl (30 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resulting crude alcohol was dissolved in CH_2Cl_2 (11 mL, 0.1 *M*). Dess-Martin periodinane (0.490 g, 1.16 mmol, 1.1 equiv) was added and the mixture was stirred open to the atmosphere. After 1.5 h, all starting material had been consumed as judged by TLC. The reaction mixture was poured into a separatory funnel and diluted with saturated aqueous $NaHCO_3$ (20 mL) and CH_2Cl_2 (20 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (100 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. To a vigorously stirring solution of this crude aldehyde in THF (11 mL, 0.1 M) was added 2-methyl-2-butene (2.22 mL, 21.0 mmol, 20.0 equiv) and NaH_2PO_4•H_2O (0.435 g in 1.05 mL H_2O, 3.15 mmol, 3.0 equiv). $NaClO_2$ (266 mg in 1.05 mL

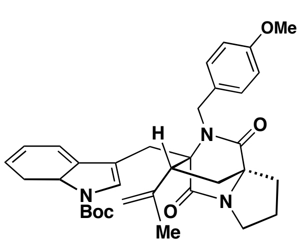
H_2O, 2.94 mmol, 2.8 equiv) was then added dropwise to this mixture. After 30 min, all starting material had been consumed as judged by TLC and the reaction mixture was diluted with H_2O (20 mL) and EtOAc (20 mL) and the layers were separated. The aqueous portion was back extracted with EtOAc (20 mL). The combined organic layers were washed with saturated aqueous NaCl (40 mL), dried over $MgSO_4$, and concentrated *in vacuo* to approximately 10 mL. This crude solution was diluted with MeOH:benzene (1:1, 20 mL) and cooled to 0 °C. Ethereal CH_2N_2 was carefully added dropwise to the stirring solution of crude acid until a yellow color persisted. Excess CH_2N_2 was quenched with glacial AcOH and the solution was concentrated *in vacuo* and purified by flash column chromatography (silica gel, 8:1 hexanes:EtOAc) to furnish **43** (0.45 g, 72 %) as separable diastereomers. Upper diastereomer: white foam; R_f = 0.84 (silica gel, EtOAc); $[\alpha]_D$ = –29.3 (c 0.40, $CHCl_3$); IR (film) ν_{max} 2977, 1732, 1651, 1513, 1452, 1370, 1253, 1155, 1082, 1035, 851, 750, 589 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.08 (bd, *J* = 7.7 Hz, 1 H), 7.54 (d, *J* = 7.8 Hz, 1 H), 7.30 (d, *J* = 8.6 Hz, 2 H), 7.30 – 7.26 (m, 2 H), 7.22 (t, *J* = 7.0 Hz, 1 H), 6.90 (d, *J* = 8.6 Hz, 2 H), 5.57 (d, *J* = 14.5 Hz, 1 H), 4.27 (dd, *J* = 4.3, 2.5 Hz, 1 H), 3.93 (d *J* = 14.5 Hz, 1 H), 3.82 (s, 3 H), 3.60 – 3.53 (m, 1 H), 3.59 (s, 3 H), 3.54 (dd, *J* = 15.8, 3.1 Hz, 1 H), 3.30 (dd, *J* = 15.2, 4.6 Hz, 1 H), 3.10 – 3.04 (m, 1 H), 2.12 – 2.00 (m, 3 H), 1.93 – 1.86 (m, 1 H), 1.72 (ddd, *J* = 12.3, 10.1, 1.5 Hz, 1 H), 1.66 (s, 9 H), 1.63 – 1.55 (m, 1 H), 1.03 – 0.95 (m, 1 H), 0.65 (q, *J* = 10.2 Hz, 1 H); ^{13}C NMR (150 MHz , $CDCl_3$) δ 172.9, 168.1, 164.5, 159.7, 149.5, 135.1, 130.3 (3 C), 127.3, 124.9 (2 C), 122.7, 119.7, 115.2, 114.5 (2 C), 113.7, 84.1, 67.0, 60.5, 58.8, 55.5, 52.1, 46.2, 44.0, 34.8, 32.9, 29.1, 28.3, 26.4, 19.3; HRMS (ESI-TOF) calculated for $C_{33}H_{40}N_3O_7$ [M + H^+] 590.2861, found 590.2863. Lower diastereomer: white foam; R_f = 0.68 (silica gel, EtOAc); $[\alpha]_D$ = –42.1 (c 0.24, $CHCl_3$); IR (film) ν_{max} 2977, 1733, 1654, 1513, 1452, 1371, 1335, 1307, 1254, 1158, 1086, 1034, 750 cm^{-1}; ^1H NMR (600

MHz, $CDCl_3$) δ 8.14 (bs, 1 H), 7.60 (d, *J* = 7.8 Hz, 1 H), 7.49 (s, 1 H), 7.33 (t, *J* = 8.1 Hz, 1 H), 7.26 (t, *J* = 8.1 Hz, 1 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 6.74 (d, 8.3 Hz, 2 H), 5.28 (d, *J* = 14.5, 1 H), 4.26 (t, *J* = 5.5 Hz, 1 H), 3.88 – 3.81 (m, 1 H), 3.76 (s, 3 H), 3.67 (s, 3 H), 3.57 (d, *J* = 14.5 Hz, 1 H), 3.41 (d, *J* = 5.3 Hz, 2 H), 3.35 – 3.28 (m, 1 H), 2.27 (t, *J* = 8.0 Hz, 2 H), 2.23 – 2.15 (m, 1 H), 1.95 – 1.85 (m, 3 H), 1.79 – 1.72 (m, 1 H), 1.68 (s, 9 H), 1.45 – 1.37 (m, 1 H); ^{13}C NMR (150 MHz , $CDCl_3$) δ 173.0, 168.6, 165.0, 159.4, 149.6, 135.6, 130.1, 129.9 (2 C), 127.9, 125.0, 124.9, 123.0, 119.4, 115.6, 115.5, 114.3 (2 C), 83.9, 66.4, 60.4, 55.4, 52.0, 46.8, 44.7, 34.2, 32.1, 29.4, 29.0, 28.4 (3 C), 19.7; HRMS (ESI-TOF) calculated for $C_{33}H_{40}N_3O_7$ [M + H^+] 590.2861, found 590.2866.



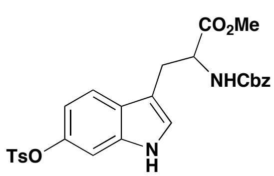
Compound 45. (Note: The THF used in this reaction, including that used for preparing solutions of LDA and $Fe(acac)_3$, was purified by distillation over excess sodium metal and benzophenone. The solvent was collected immediately prior to use and always transferred *via* dry, oxygen-free syringes. LDA was prepared by standard methods with care taken to exclude oxygen. $Fe(acac)_3$ was dissolved in benzene and dried azeotropically prior to dissolution in THF.) Compound **44** (single diastereomer, 189 mg, 0.32 mmol, 1.0 equiv) was dried azeotropically with benzene and dissolved in THF (6.6 mL, 0.05 *M*). The solution was cooled to – 78 °C. LDA (0.99 mL, 0.70 mmol, 2.2 equiv, 0.7 *M* in THF) was added as rapidly as possible through an 18 gauge needle and the resulting yellow solution was maintained at – 78 °C for 5 min. Immediately after the 5 min enolization time, $Fe(acac)_3$ (3.56 mL, 0.70 mmol, 0.2 *M* in THF) was added as rapidly as possible through an 18 gauge needle. The reaction became a dark green/brown color and was maintained at –78 °C for 5 min. After 5 min, the cooling bath was removed and the reaction

allowed to warm to room temperature, and stirred for an additional 45 min during which TLC showed disappearance of all the starting material. The reaction was quenched by pouring the mixture into saturated aqueous NH_4Cl (30 mL) and diluted with EtOAc (30 mL). The layers were separated and the organic portion was extracted it with EtOAc (2 × 30 mL). The combined EtOAc layers were washed with 1 *M* aqueous HCl (60 mL), saturated aqueous NaCl (50 mL), dried with anhydrous $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (silica gel, 2:1 hexanes:EtOAc → 1:1 hexanes:EtOAc) furnishing 122 mg (65%) of **46**: white foam; R_f = 0.58 (silica gel, EtOAc); IR (film) ν_{max} 2974, 2358, 1732, 1690, 1513, 1452, 1371, 1251, 1158, 1083, 913, 731, 615 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.05 (bs, 1 H), 7.49 (s, 1 H), 7.43 (d, *J* = 7.7 Hz, 1 H), 7.32 (t, *J* = 7.2 Hz, 1 H), 7.25 (t, *J*= 7.4 Hz, 1 H), 6.79 (d, *J* = 8.6 Hz, 2 H), 6.72 (d, *J* = 8.7 Hz, 2 H), 4.76 (d, *J* = 15.8, 1 H), 4.34 (d, *J* = 15.7 Hz, 1 H), 3.77 (s, 3 H), 3.72 – 3.65 (m, 1 H), 3.64 – 3.58 (m, 1 H), 3.48 (d, *J* = 17.1 Hz, 1 H), 3.43 (s, 3 H), 3.45 – 3.39 (m, 1 H), 3.20 (dd, *J* = 9.8, 3.8 Hz, 1 H), 2.92 – 2.86 (m, 1 H), 2.29 – 2.22 (m, 1 H), 2.15 (dd, *J* = 12.9, 4.6 Hz, 1 H), 2.11 – 2.05 (m, 2 H), 1.95 – 1.90 (m, 1 H), 1.66 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 171.8, 166.0, 158.8, 149.8, 134.8, 131.2, 129.7, 127.9 (2 C), 125.2, 124.6, 122.6, 118.8, 115.2, 114.0 (2 C), 113.9, 83.9, 68.3, 65.8, 55.3, 52.3, 48.6, 45.7, 44.6, 35.1, 29.8, 28.3 (3 C), 24.4, 24.3; HRMS (ESI-TOF) calculated for $C_{33}H_{38}N_3O_7$ [M + H^+] 588.2704, found 588.2687.

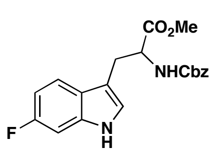


Compound 46. Compound **45** (66 mg, 0.112 mmol, 1.0 equiv.) was dried azeotropically from benzene then dissolved in THF (2 mL, 0.06 *M*) and cooled to 0 °C. Once cooled, MeMgBr (1.4 *M* solution in toluene:THF (3:1), 0.40 mL, 0.562 mmol, 5.0 equiv) was added rapidly in one portion turning

the reaction mixture yellow. After 2 h the reaction was deemed complete by TLC, quenched with saturated aqueous NH_4Cl (5 mL) and diluted with EtOAc (10 mL) and H_2O (15 mL). The layers were separated and the aqueous layer was back-extracted with EtOAc (2 × 10 mL), the combined EtOAc layers were washed with saturated aqueous NaCl (10 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The concentrate was purified by flash column chromatography (silica gel, 8:92 acetone:CH_2Cl_2) to obtain a mixture of the corresponding alcohol and ketone. This mixture was dissolved in benzene (2.4 mL, 0.05 M) and Burgess reagent (80.3 mg, 0.337 mmol, 3.0 equiv) was added. The flask was sealed and introduced in to an oil bath preheated to 50 ^{o}C, heating for 20 min. The mixture was concentrated and purified by flash column chromatography (silica gel, 2:1 hexane:EtOAc → 1:3 hexane:EtOAc) furnishing 26.5 mg (41%) of **46** and 25 mg (39%) of the corresponding methyl ketone.

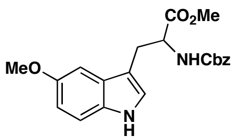


Tryptophan derivative 56. *N*-Cbz-L-pyroglutamate methyl ester (100 mg, 360 μmol) was dissolved in THF (3.6 mL, 0.1 *M*) and cooled to –78 °C. After 5 min at –78 °C, lithium triethylborohydride (0.40 mL from a 1 *M* solution in THF, 0.40 mmol, 1.1 equiv) was added over 30 sec. After 10 min of stirring, saturated aqueous NH_4Cl (5 mL) was added to the cold reaction solution. The reaction was allowed to warm to ambient temperature and H_2O (10 mL) and EtOAc (10 mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (10 mL). The organic layers were combined and washed with saturated aqueous NaCl (15 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. To the resultant crude clear oil was added compound **55** (156 mg, 0.40 mmol, 1.1 equiv), diazabicyclo[2.2.2]octane (DABCO, 120 mg, 1.1 mmol, 3.0 equiv), and TBAI (133 mg, 0.36 mmol, 1.0 equiv). The mixture was azeotropically dried using benzene (5 mL). The reaction flask was evacuated under high vacuum and backfilled with N_2. DMF (1.2 mL, 0.3 *M*) was added to the reaction flask followed by $Pd(OAc)_2$ (4.0 mg, 0.018 mmol, 0.05 equiv). The reaction flask was degassed under high vacuum once more and backfilled with N_2 then placed in an oil bath preheated to 105 °C. After 4 h the reaction was removed from the heat and water (5 mL) was added. The reaction was extracted with EtOAc (5 × 10 mL) and the organic portions were washed with saturated aqueous NaCl (15 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give a crude orange foam. This material was purified by flash column chromatography (silica gel, 1:6 → 1:1 EtOAc:hexanes) to yield 141 mg (75%) of compound **56**: white foam; R_f = 0.38 (silica gel, 1:1 EtOAc:hexanes); IR (neat) ν_{max} 3406, 1707, 1598, 1508, 1457, 1364, 1213, 1177, 1089, 950, 841, 814, 733, 551 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.27 (s, 1 H), 7.63 (d, *J* = 8.0 Hz, 2 H), 7.28 (m, 5 H), 7.21 (d, *J* = 7.2 Hz, 3 H), 7.06 (s, 1 H), 6.91 (s, 1 H), 6.49 (d, *J* = 8.5, 1 H), 5.26 (d, *J* = 7.8 Hz, 1 H), 5.05 (d, *J* = 12.0 Hz, 1 H), 5.00 (d, *J* = 12.0 Hz, 1 H), 4.63 – 4.60 (m, 1 H), 3.57 (s, 3 H), 3.21 – 3.12 (m, 2 H), 2.36 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 155.9, 145.6, 145.4, 136.3, 135.7, 132.6, 129.8 (2 C), 128.7 (3 C), 128.4 (2 C), 128.2 (2 C), 126.5, 124.6, 119.0, 114.3, 110.0, 105.8, 67.1, 54.6, 52.5, 28.0, 21.8; HRMS (ESI-TOF) calculated for $C_{27}H_{27}N_2O_7S$ [M + H^+] 523.1533, found 523.1536.

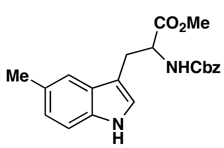


Substituted tryptophan 58. All of the following tryptophan derivatives were synthesized according to the conditions used to synthesize compound **56**. Yield: 45%. Pale yellow viscous semisolid; R_f = 0.55 (silica gel, 1:1 EtOAc:hexanes); IR (neat) ν_{max} 3300, 2923, 1714, 1498, 1455, 1211, 742, 697, 610 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (bs, 1H), 7.71 (m, 5H), 7.01 (dd, *J* = 9.5, 2.0 Hz, 1 H), 6.93 (s, 1 H), 6.83 (dt, *J* = 9.5, 2.0 Hz, 2

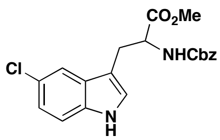
H), 5.31 (d, *J* = 8 Hz, 1 H), 5.10 (m, 2H), 4.70 (m, 1H), 3.68 (s, 3 H), 3.27 (d, *J* = 5.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 161.0, 159.4, 155.9, 136.4, 136.2, 128.7, 128.4, 128.3, 124.3, 123.2, 119.6, 119.5, 110.3, 108.7, 97.7, 67.1, 54.6, 52.6, 28.2; HRMS (ESI-TOF) calculated for $C_{21}H_{20}FN_2O_4$ [M+H$^+$] 371.1402, found 371.1407; HRMS (ESI-TOF) calculated for $C_{21}H_{19}FN_2O_4Na$ [M+H$^+$] 393.1221, found 393.1224.



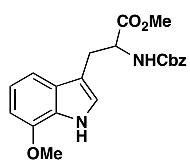
Substituted tryptophan 59. Yield: 20%. White foam; R_f = 0.48 (silica gel, 1:1 EtOAc:hexanes); IR (neat) ν_{max} 3349, 2953, 1706, 1486, 1439, 1349, 1214, 1061, 1027, 738, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (bs, 1 H), 7.39 – 7.29 (m, 5 H), 7.22 (d, *J* = 8.8 Hz, 1 H), 6.98 (d, *J* = 1.9 Hz, 1 H), 6.93 (d, *J* = 2.2 Hz, 1 H), 6.84 (dd, *J* = 8.8, 2.2 Hz, 1 H), 5.35 (d, *J* = 8.1 Hz, 1 H, D_2O exchangeable), 5.13 – 5.07 (m, 2 H), 4.76 – 4.69 (m, 1 H), 3.80 (s, 3 H), 3.69 (s, 3 H), 3.28 (d, *J* = 5.3 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 156.0, 154.4, 136.4, 131.4, 128.7, 128.4 (2 C), 128.3 (2 C), 128.2, 123.7, 112.9, 112.2, 109.9, 100.5, 67.2, 56.0, 54.7, 52.6, 28.3; HRMS (ESI–TOF) calculated for $C_{21}H_{23}N_2O_5$ [M + H$^+$] 383.1601, found 383.1599.



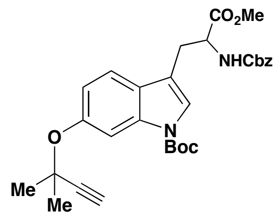
Substituted tryptophan 60. Yield: 69%. Pale yellow viscous semisolid; R_f = 0.54 (silica gel, 1:1 EtOAc:hexanes); IR (neat) ν_{max} 3394, 2922, 1701, 1507, 1436, 1213, 1060, 794, 736, 696, 603 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (bs, 1 H), 7.33 (m, 6 H), 7.24 (d, *J* = 8.4 Hz, 1 H), 7.02 (d, *J* = 8.4 Hz, 1 H), 6.93 (bs, 1 H), 5.31 (d, *J* = 7.2 Hz, 1 H), 5.11 (s, 2 H), 4.72 (m, 1 H), 3.70 (s, 3 H), 3.29 (d, *J* = 5.2 Hz, 2 H), 2.43 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 155.9, 136.4, 134.6, 128.9, 128.6, 128.3, 128.2, 127.8, 123.9, 123.1, 118.3, 111.0, 109.3, 67.0, 54.6, 52.4, 28.0, 21.6; HRMS (ESI-TOF) calculated for $C_{21}H_{23}N_2O_4$ [M + H$^+$] 367.1652, found 367.1649.



Substituted tryptophan 61. Yield: 55%. White foam, R_f = 0.47 (silica gel, 1:1 EtOAc:hexanes); IR (neat) ν_{max} 3333, 2366, 1701, 1508, 1464, 1348, 1286, 1214, 1057, 910 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (bs, 1 H), 7.49 (s, 1 H), 7.39 – 7.28 (m, 5 H), 7.21 (d, *J* = 8.6 Hz, 1 H), 7.12 (d, *J* = 8.6 Hz, 1 H), 6.94 (s, 1 H), 5.37 (d, *J* = 7.9 Hz, 1 H, D_2O exchangeable), 5.15 – 5.08 (m, 2 H), 4.74 – 4.67 (m, 1 H), 3.70 (s, 3 H), 3.32 – 3.21 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 156.2, 136.6, 134.9, 129.2, 129.0 (3 C), 128.7, 128.6, 125.9, 124.8, 123.0, 118.6, 112.8, 110.0, 67.5, 54.8, 52.9, 28.3; HRMS (ESI–TOF) calculated for $C_{20}H_{19}N_2O_4Na$ [M + Na$^+$] 409.0925, found 409.0923.



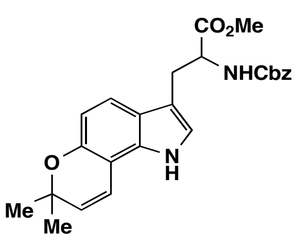
Substituted tryptophan 62. Yield: 27%. Colorless needles; m.p. 122 – 124 °C (Et_2O); R_f = 0.64 (silica gel, 1:1 EtOAc:hexanes); IR (neat) ν_{max} 3350, 2925, 1716, 1578,1506, 1456, 1339, 1260, 1212, 1053, 779, 735, 609 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.24 (bs, 1 H), 7.35 (m, 5 H), 7.12 (d, *J* = 7.1 Hz, 1 H), 7.12 (t, *J* = 7.8 Hz, 1 H), 6.94 (s, 1 H), 6.64 (d, *J* = 7.2 Hz, 1 H), 5.30 (m, *J* = 12.0 Hz, 1 H), 5.13 (d, *J* = 12.0 Hz, 1 H), 5.08 (d, *J* = 12.0 Hz, 1 H), 4.71 (m, 1 H), 3.95 (s, 3 H), 3.69 (s, 3 H), 3.30 (d, *J* = 4.8 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 155.9, 1463, 136.8, 136.5, 129.1. 128.7 (2 C), 128.3, 126.9, 122.5, 120.3, 111.6, 110.5, 102.2, 67.1, 55.5, 54.5, 54.7, 52.5, 28.3; HRMS (ESI-TOF) calculated for $C_{21}H_{23}N_2O_4$ [M + H$^+$] 383.1601, found 383.1603.



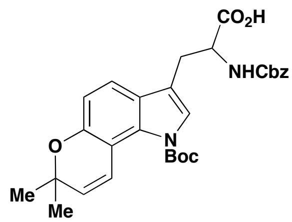
Tryptophan derivative 66. Tryptophan derivative **56** (120 mg, 0.23 mmol) was dissolved in CH_2Cl_2:CH_3CN (1:1, 2.3 mL, 0.1 *M*) and 4-dimethylaminopyridine (DMAP, 0.3 mg, 0.0023 mmol, 0.01 equiv) followed by di-*tert*-butyl dicarbonate (Boc_2O, 50 mg, 0.23 mmol, 1.0 equiv) were added. After 30 min, the reaction was concentrated *in vacuo* and purified by flash column chromatography (silica gel, 1:6 → 1:3 EtOAc:hexanes) to afford 136 mg (95%) of the *N*-Boc protected tryptophan. The *N*-Boc protected tryptophan (4.343 g, 6.98 mmol) so prepared was dissolved in MeOH (70 mL, 0.1 *M*) and cooled to 0 °C. Mg turnings (1.697 g, 69.8 mmol, 10 equiv) were added to the reaction solution and the ice bath was removed. After 2.5 h, the reaction was poured through a cotton plug and EtOAc (100 mL) was used to rinse the plug. The reaction mixture was washed with 1 *M* aqueous HCl (100 mL) upon which a white gel formed in the separatory funnel that dissolved upon vigorous shaking. The layers were separated and the aqueous portion was extracted with EtOAc (2 × 50 mL). Organic layers were combined and washed with saturated aqueous NaCl (100 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to produce a yellow foam. The crude free phenol was dissolved in CH_3CN (70 mL, 0.1 *M*). 1,1-dimethylprop-2-ynyl methyl carbonate[3] (**65**, 2.97 g, 20.9 mmol, 3.0 equiv) and $CuCl_2$ (0.9 mg, 0.00698 mmol, 0.001 equiv) were added to the reaction mixture and the solution was cooled to 0 °C. Once cooled to 0 °C, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 3.13 mL, 20.9 mmol, 3.0 equiv) was added dropwise over 10 min. Color change was observed from a light yellow color through red to a clear brown-green color. After 24 h, the reaction was diluted with EtOAc (50 mL) and 1 *M* aqueous HCl (100 mL) was added at 0 °C. The layers were separated

[3] Tisdadle, E. J.; Vong, B. G.; Li, H.; Kim, S. H.; Chowdhury, C.; Theodorakis, E. A. *Tetrahedron*, **2003**, *59*, 6873-6887

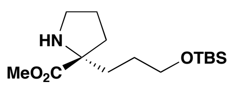
and the aqueous portion was extracted with EtOAc (2 × 50 mL). Organics were combined and washed with saturated aqueous NaCl (100 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (silica gel, 1:6 EtOAc:hexanes) to give 2.81 g (75% over two steps) of **66**: white foam; R_f = 0.51 (silica gel, 1:1 EtOAc:hexanes); IR (neat) ν_{max} 2985, 1725, 1477, 1438, 1380, 1254, 1212, 1155, 1084, 956, 818, 768, 698, 682, 565; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1 H), 7.34 (m, 7 H), 7.09 (d, *J* = 8.5 Hz, 1 H), 5.43 (d, *J* = 7.9 Hz, 1 H), 5.14 (d, *J* = 12.0 Hz, 1 H), 5.09 (d, *J* = 12.0 Hz, 1 H), 4.74 – 4.69 (m, 1 H), 3.69 (s, 3 H), 3.26 – 3.16 (m, 2 H), 2.56 (s, 1 H), 1.67 (s, 6 H), 1.66 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 155.9, 153.3, 149.7, 136.4, 135.7, 128.7 (2 C), 128.4, 128.3 (2 C), 126.5, 124.0, 118.7, 118.4, 114.8, 109.4, 86.4, 83.9, 74.1, 73.2, 67.2, 54.3, 54.7, 29.9 (2 C), 28.4 (3 C), 28.0; HRMS (ESI-TOF) calculated for $C_{30}H_{35}N_2O_7$ [M + H^+] 535.2444, found 535.2428.



Tryptophan derivative 67. Tryptophan derivative **66** (1.00 g, 1.87 mmol) was dissolved in 1,2–dichlorobenzene (100 mL, 10 mg / 1 mL) and placed in a 190 °C preheated oil bath for 10 min. After 10 min, reaction was removed from heating and allowed to cool to room temperature at which time it was loaded onto silica gel and flushed with hexanes (300 mL). This crude material was purified by flash chromatography (silica gel, 1:2 → 2:1 Et_2O:hexanes) furnishing 800 mg (80%) of **67** along with 122 mg (15 %) of the *N*-Boc-deprotected benzopyran (95 %).



Tryptophan derivative 52. Tryptophan derivative **67** (310 mg, 0.713 mmol) was dissolved in CH_2Cl_2:CH_3CN (1:1, 7 mL, 0.3 *M*). 4-dimethylaminopyridine (DMAP, 0.9 mg, 0.00713 mmol, 0.01 equiv) was added followed by the dropwise addition of di-*tert*-butyl dicarbonate (Boc_2O, 156 mg, 0.713 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL). After 30 min of stirring at ambient temperature, the reaction was concentrated *in vacuo*. The resultant brown-orange oil was purified by flash column chromatography (silica gel, 1:3 $\rightarrow$ 2:1 Et_2O:hexanes) furnishing 293 mg (77%) of the indole *N*-Boc compound. The indole *N*-Boc compound so prepared (534 mg, 1.00 mmol) was dissolved in THF:H_2O (1:1, 10 mL, 0.1 *M*) and the reaction was cooled to 0 °C. LiOH (360 mg, 15.0 mmol, 15.0 equiv) was added and the reaction was allowed to warm to room temperature and stirred for 3 h. The reaction was acidified with 1 *M* aqueous HCl and extracted with EtOAc (3 $\times$ 15 mL). The organics were washed with saturated aqueous NaCl (20 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude foam was passed through a plug of silica and eluted with 15 % MeOH in CH_2Cl_2 until the acid was no longer detected by TLC. The fractions were concentrated to give 520 mg (100%) tryptophan derivative **52**. Data given for methyl ester of **52**: white needles; m.p. 109 – 111 °C (1:99 CH_2Cl_2:Et_2O); R_f = 0.63 (silica gel, 1:2 EtOAc:hexanes); IR (neat) ν_{max} 3344, 2975, 2359, 1371, 1508, 1370, 1352, 1275, 1216, 1154, 1119, 1087, 1056, 812, 768 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 5 H), 7.23 (s, 1 H), 7.20 (d, *J* = 8.0 Hz, 1 H), 7.00 (d, *J* = 10.0 Hz, 1 H), 6.79 (d, *J* = 8.0 Hz, 1 H), 5.61 (d, *J* = 10.0 Hz, 1 H), 5.35 (d, *J* = 8.0 Hz, 1 H, D_2O exchangeable), 5.13 (d, *J* = 12.0 Hz, 1 H), 5.10 (d, *J* = 12.0 Hz, 1 H), 4.70 (dd, *J* = 13.5, 6.0 Hz, 1 H), 3.69 (s, 3 H), 3.23 – 3.11 (m, 2 H), 1.61 (s, 9 H), 1.48 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 155.8, 152.0, 149.9, 136.4, 132.4, 128.7 (2 C), 128.4 (2 C), 128.2 (2 C), 127.0, 125.9, 125.1, 121.9, 119.1, 115.1, 113.8, 110.0, 83.9, 75.0, 67.2, 54.2, 52.6, 28.3 (3 C), 27.4, 27.3; HRMS calculated for $C_{30}H_{34}N_2O_7Na^+$ [M + Na^+] 557.2264, found 557.2252.



Proline derivative 71. To a solution of (*R*)-2-allylproline hydrochloride[4,5] (1.00 g, 5.22 mmol) in MeOH:benzene (1:1, 20 mL, 0.3 *M*) at 0 °C was added dropwise a solution of CH_2N_2 in Et_2O until the yellow color persisted. The mixture was stirred for 30 min. Unreacted diazomethane was quenched by the dropwise addition of glacial acetic acid. The mixture was concentrated *in vacuo* and suspended in a solution of saturated aqueous $NaHCO_3$ (30 mL, 0.17 *M*) which was cooled to 0 °C. To this mixture was added benzyl chloroformate (CbzCl, 1.77 g, 10.4 mmol, 2.0 equiv) dropwise with vigorous stirring. The reaction mixture was then gradually allowed to attain ambient temperature by removing the ice bath and then stirred at 50 °C for 4 h. The product mixture was extracted with EtOAc (3 × 30 mL), washed with saturated aqueous NaCl (30 mL), dried with anhydrous $MgSO_4$, concentrated *in vacuo*, and purified by flash column chromatography (silica gel; 1:6 EtOAc:hexanes). To remove any traces of benzyl alcohol the product obtained was subjected to heating to 110 °C under high vacuum to furnish 1.17 g (74%) of *N*-Cbz-(*R*)-allylproline methyl ester (**68**). To a solution of this ester (1.00 g, 3.30 mmol) in THF (11 mL, 0.3 *M*), was added 9-borabicyclo[3.3.1]nonane (9-BBN, 13.2 mL from a 0.5 *M* in THF, 6.60 mmol, 2.0 equiv). The mixture was stirred for 3 h at room temperature. It was subjected to oxidative workup by adding 3 *M* aqueous NaOH (30 mL) immediately followed by careful and dropwise addition of 35% aqueous H_2O_2 (30 mL) with vigorous stirring. The reaction mixture was stirred vigorously for 1

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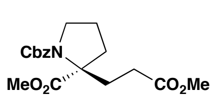
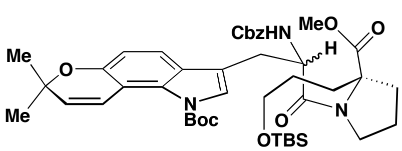
[4] D. Seebach, M. Boes, R. Naef, W. B. Schweizer, *J. Am. Chem. Soc.* **1983**, *105*, 5390 – 5398.
[5] M. G. Hinds, J. H., Welsh, D. M. Bernnand, J. Fisher, M. J. Glennie, N. G. J. Richards, D. L. Turner, J. A. Robinson, *J. Med. Chem.* **1991**, *34*, 1777 – 1789.

h and then extracted with EtOAc (3 × 300 mL), washed with saturated aqueous NaCl (3 × 500 mL), dried with anhydrous $MgSO_4$, concentrated *in vacuo*, and purified by flash column chromatography (silica gel, 1:4 EtOAc:hexanes) furnishing 0.97 g (92%) of the primary alcohol. To a solution of this alcohol (630 mg, 1.96 mmol) in CH_2Cl_2 (10 mL, 0.2 *M*) at room temperature, was added imidazole (160 mg, 2.35 mmol, 1.2 equiv) and the solution was stirred for 5 min. *tert*-Butyldimethylsilyl chloride (TBSCl, 325 mg, 2.16 mmol, 1.1 equiv) was then added and the mixture stirred for 30 min. The solution was concentrated *in vacuo* and purified by flash column chromatography (silica gel, 1:2 EtOAc:hexanes) furnishing the protected alcohol (**69**, 0.82 g, 96%). To this alcohol (**69**, 700 mg, 1.60 mmol) was added 10% Pd/C (140 mg, 20% w/w). The flask was flushed with nitrogen gas and MeOH (20 mL) was added. The flask was evacuated using low vacuum and flushed with nitrogen. Hydrogen gas was then bubbled through the suspension until the reaction was complete by TLC. The suspension was filtered through Celite® using CH_2Cl_2. The filtrate was concentrated *in vacuo* and the resulting residue was passed through a short pad of silica gel furnishing 480 mg (100%) of proline derivative **71**: colorless oil; R_f = 0.22 (silica gel, Et_2O); $[\alpha]_D$ = – 9.3 (c 1.8, $CHCl_3$); IR (neat) ν_{max} 2952, 1730, 1462, 1253, 1197, 1095, 1004, 834, 774, 625, 459, 448, 418 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3 H), 3.58 (m, 2 H), 2.96 (t, *J* = 6.5 Hz, 2 H) 2.34 (bs, 1 H, D_2O exchangeable), 2.15 (m, 1 H), 1.82 – 1.31 (m, 7 H), 0.88 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 69.5, 63.0, 52.3, 46.3, 35.9, 35.8, 28.6, 25.9, 24.7, 18.3 (3 C), – 5.3 (2 C). HRMS (ESI-TOF) calculated for $C_{15}H_{31}SiNO_3Na^+$ $[M + Na^+]$ 324.1971, found 324.1964.



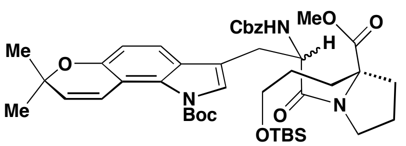
Proline derivative 70. The same procedures used to obtain proline **69** including hydroboration were used starting from (*S*)-2-allylproline hydrochloride. The alcohol was not protected as its TBS ether. Instead, the resulting alcohol (0.98g, 3.05 mmol) from hydroboration was dissolved in MeCN (22.5 mL) and H_2O (7.5 mL) (3:1, 0.1 *M*). To the stirring solution was added $PhI(OAc)_2$ (2.16 g, 6.71 mmol, 2.2 equiv) followed by 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO, 95.3 mg, 0.61 mmol, 0.2 equiv) and the reaction was stirred for 5 h. The reaction mixture was then poured into a separatory funnel and diluted with EtOAc (200 mL) and quenched with 1 *M* aqueous HCl (100 mL). The layers were separated and the aqueous layer was back extracted with EtOAc (2 × 50 mL). The organic layers were combined and washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude oil was dissolved in EtOAc (50 mL) and treated with ethereal CH_2N_2. The esterification was monitored by TLC and when deemed complete, the excess diazomethane was quenched with glacial acetic acid and the reaction was once again concentrated *in vacuo*. The crude oil was purified by flash column chromatography (silica gel, 1:5 → 1:3 EtOAc:hexanes) to give 0.92 g (86%) of **70**.



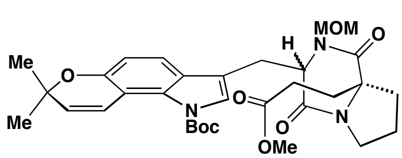
Amide 72. To a dry solution of acid **52** (809 mg, 1.55 mmol, 1.0 equiv) and amine **71** (703 mg, 2.33 mmol, 1.5 equiv) in CH_2Cl_2 (15.5 mL, 0.1 *M*) at 0 °C was added bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl, 435 mg, 1.71 mmol, 1.1 equiv). The resultant suspension was allowed to stir vigorously for 1 min after which *i*-Pr_2EtN (freshly distilled from CaH_2, 0.298 mL, 1.71 mmol, 1.1 equiv) was injected rapidly in one portion. After 5 min the cooling bath was removed, and the reaction was allowed to warm to ambient temperature. The reaction was allowed to run for 10 h at room temperature before being diluted with EtOAc (10 mL) and quenched with 1 *M* aqueous HCl (20 mL). The reaction mixture was poured into a

separatory funnel and the layers were separated. The aqueous layer was extracted with additional EtOAc (20 mL). The organic portions were combined, washed with saturated aqueous NaCl (20 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel; 2:1 Et_2O:hexanes) to furnish **72** (678 mg of the lower diastereomer and 102 mg of the upper diastereomer, 62%). Major diastereomer: white foam; R_f = 0.62 (silica gel, 1:2 EtOAc:hexanes); $[□]_D$ = + 1.7 ° (c 2.14, CH_2Cl_2); IR (neat) $□_{max}$ 2954, 1735, 1648, 1447, 1370, 1253, 1156, 982, 836, 735 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) □ 7.43 (d, *J* = 8.3 Hz, 1 H), 7.42 (s, 1 H), 7.35 – 7.27 (m, 5 H), 7.03 (d, *J* = 9.9 Hz, 1 H), 6.84 (d, *J* = 8.3 Hz, 1 H), 5.61 (d, *J* = 9.9 Hz, 1 H), 5.54 (d, *J* = 8.6 Hz, 1 H, D_2O exchangeable), 5.08 (s, 2 H), 4.80 (dd, *J* = 14.6, 7.8 Hz, 1 H), 3.69 (s, 3 H), 3.61 – 3.56 (m, 1 H), 3.55 – 3.50 (m, 1 H), 3.47 (dd, *J* = 17.0, 7.7 Hz, 1 H), 3.32 – 3.26 (m, 1 H), 3.08 (dd, *J* = 14.6, 7.7 Hz, 1 H), 2.95 (dd, *J* = 14.6, 5.9 Hz, 1 H), 2.31 – 2.24 (m, 1 H), 2.00 (t, *J* = 7.2 Hz, 2 H), 1.98 – 1.92 (m, 1 H), 1.81 – 1.72 (m, 2 H), 1.68 – 1.62 (m, 1 H), 1.60 (s, 9 H), 1.49 (s, 3 H), 1.47 (s, 3 H), 1.34 – 1.26 (m, 1 H), 0.87 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) □ 173.5, 169.5, 155.5, 151.4, 149.6, 136.1, 131.8, 128.2 (2 C), 127.7, 127.5 (2 C), 126.6, 125.6, 125.2, 121.5, 118.8, 114.8, 113.5, 109.6, 83.1, 74.5, 68.6, 66.4, 62.8, 52.0, 51.9, 48.3, 35.2, 29.7, 28.0, 27.8 (3 C), 27.0, 26.9, 26.8, 25.7 (3 C), 23.4, 18.0, – 5.5, – 5.6; HRMS (ESI-TOF) calculated for $C_{44}H_{62}N_3O_9Si$ [M + H^+] 804.4250, found 804.4287. Minor diastereomer: white foam; R_f = 0.51 (1:2 EtOAc:hexanes); $[□]_D$ = – 3.9 ° (c 0.75, CH_2Cl_2); IR (neat) $□_{max}$ 2955, 1736, 1641, 1449, 1370, 1255, 1156, 982, 774 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) □ 7.39 (d, *J* = 8.4 Hz, 1 H), 7.37 – 7.28 (m, 6 H), 7.00 (d, *J* = 9.9 Hz, 1 H), 6.82 (d, *J* = 8.4 Hz, 1 H), 5.61 (d, *J* = 9.9 Hz, 1 H), 5.55 (d, *J* = 8.7 Hz, 1 H, D_2O exchangeable), 5.10 (s, 2 H), 4.90 (dd, *J* = 15.1, 8.1 Hz, 1 H), 3.87 – 3.81 (m, 1 H), 3.63 (s, 3 H), 3.53 – 3.48 (m, 1 H), 3.46 – 3.40 (m, 1 H), 3.14 (dd, *J* = 16.9, 7.6 Hz, 1 H), 3.05 (dd, *J* =

14.5, 7.9 Hz, 1 H), 2.96 (dd, J = 14.4, 6.1 Hz, 1 H), 2.08 – 1.88 (m, 6 H), 1.79 – 1.71 (m, 1 H), 1.60 (s, 9 H), 1.49 (s, 3 H), 1.47 (s, 3 H), 1.38 – 1.29 (m, 1 H), 0.86 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 173.9, 169.6, 155.7, 151.7, 149.7, 136.2, 132.1, 128.4 (2 C), 128.0, 127.7 (2 C), 126.7, 125.6, 124.9, 121.6, 119.0, 115.4, 113.6, 109.8, 83.5, 74.7, 68.9, 66.7, 62.8, 52.1, 48.9, 35.1, 30.2, 29.7, 28.9, 28.0 (3 C), 27.3, 27.0, 26.8, 25.9 (3 C), 23.6, 18.2, – 5.35 (2 C); HRMS (ESI-TOF) calculated. for $C_{44}H_{62}N_3O_9Si$ [M + H^+] 804.4250; found 804.4251. Both diastereomers could be carried forward to hexacycle **76** using identical procedures; however, only data for compounds derived from the major diastereomer are presented.

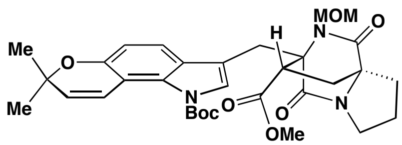


Diketopiperazine 75 (*via* 71). To a solution of amide **72** (608 mg, 0.756 mmol, major diastereomer) in CH_2Cl_2 (15 mL, 0.05 *M*) were added Et_3SiH (4.83 mL, 30.2 mmol, 40 equiv), Et_3N (0.211 mL, 1.51 mmol, 2.0 equiv), and Pd_2dba_3•$CHCl_3$ (157 mg, 0.151 mmol, 0.2 equiv) at room temperature. The reaction vessel was sealed with a plastic stopper and Parafilm M®. The reaction mixture was stirred for 4 h, rapidly turning from a purple solution to a black suspension. Upon completion of the reaction, the reaction mixture was diluted with EtOAc and passed through a tightly packed anhydrous $MgSO_4$-on-Celite® plug. The filtrate was passed through a second plug (only Celite®) to remove any remaining palladium. The resultant yellow filtrate was concentrated *in vacuo*. The residue was dissolved in MeOH (20 mL, 0.008 *M*) and heated at vigorous reflux for 30 min to cleave the intermediate silyl carbamate. The solution was evaporated *in vacuo* and the residue was suspended in toluene (20 mL, 0.008 *M*). The suspension was heated at reflux for 2 h during which dissolution occurred. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel, 1:2 $\rightarrow$ 2:3 EtOAc:hexanes) furnishing 256 mg (53%) of unprotected diketopiperazine: white foam; R_f = 0.43 (silica gel, 1:1 EtOAc:hexanes); $[\alpha]_D$ = – 29.4° (c 0.81, CH_2Cl_2); IR (neat) ν_{max} 2931, 1735, 1655, 1395, 1358, 1277, 1256, 1156, 982, 835, 772, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1 H), 7.26 (d, J = 8.4 Hz, 1 H), 7.01 (d, J = 9.9 Hz, 1 H), 6.83 (d, J = 8.4 Hz, 1 H), 5.69 (bs, 1 H, D_2O exchangeable), 5.63 (d, J = 9.9 Hz, 1 H), 4.31 (dd, J = 10.8, 2.9 Hz, 1 H), 3.86 – 3.77 (m, 1 H), 3.68 (dd, J = 15.0, 2.3 Hz, 1 H), 3.59 – 3.47 (m, 4 H), 2.75 (dd, J= 14.8, 11.0 Hz, 1 H), 2.15 (t, J = 7.2 Hz, 2 H), 2.00 – 1.89 (m, 2 H), 1.84 – 1.71 (m, 2 H), 1.64 (s, 9 H), 1.51 – 1.45 (m, 7 H), 0.83 (s, 9 H), – 0.01 (s, 3 H), – 0.02 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 164.8, 152.2, 149.5, 132.7, 127.1, 125.3, 124.6, 121.5, 118.8, 114.9, 113.9, 110.2, 84.1, 77.2, 74.9, 67.9, 62.1, 53.7, 45.0, 33.6, 33.3, 28.1 (3 C), 27.6, 27.2, 27.1, 25.8 (3 C), 20.5, 18.2, – 5.4 (2 C); HRMS (ESI-TOF) calculated for $C_{35}H_{52}N_3O_6Si$ [M + H^+] 638.3620, found 638.3623. To a solution of this unprotected diketopiperazine (220 mg, 0.345 mmol, major diastereomer) in DMF (3.45 mL, 0.1 *M*) at 0 °C was added NaH (17 mg, 0.414 mmol, 1.2 equiv used as a 60 % dispersion in mineral oil). The suspension was stirred vigorously for 30 min before chloromethyl methyl ether (MOMCl, 0.029 ml, 0.379 mmol, 1.1 equiv) was added to the orange suspension. The reaction was allowed to stir for 1 h during which the color changed from orange to yellow. The cooling bath was removed and the reaction was immediately quenched by the addition of saturated aqueous NH_4Cl (5 mL). The resulting suspension was diluted with water (5 mL) and EtOAc (10 mL). The mixture was poured into a separatory funnel and the layers were separated. The aqueous portion was extracted with EtOAc (10 mL). The organic portions were combined, washed with saturated aqueous NaCl (10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 1:4 $\rightarrow$ 1:2 EtOAc:hexanes) furnishing 153 mg (65%) of **74**: white foam; R_f = 0.44 (silica gel; 1:2 EtOAc:hexanes); $[\alpha]_D$ = + 10.0 (c 0.59, CH_2Cl_2); IR (neat) ν_{max} 2929, 1741, 1657, 1431, 1393, 1276, 1257, 1156, 1090, 983, 835, 774 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.4 Hz, 1 H), 7.09 (s, 1 H), 6.95 (d, *J* = 9.9 Hz, 1 H), 6.80 (d, *J* = 8.4 Hz, 1 H), 5.59 (d, *J* = 9.9 Hz, 1 H), 5.23 (d, *J* = 10.2 Hz, 1 H), 4.65 (d, *J* = 10.2 Hz, 1 H), 4.47 (bs, 1 H), 3.68 – 3.47 (m, 4 H), 3.42 (s, 3 H), 3.26 (dd, *J* = 15.4, 4.6 Hz, 1 H), 3.21 – 3.14 (m, 1 H), 1.88 – 1.82 (m, 1 H), 1.82 – 1.75 (m, 1 H), 1.70 – 1.63 (m, 2 H), 1.59 (s, 9 H), 1.46 (s, 3 H), 1.45 (s, 3 H), 1.45 – 1.36 (m, 2 H), 1.27 – 1.20 (m, 1 H), 1.09 (dd, *J* = 22.2, 10.2 Hz, 1 H), 0.84 (s, 9 H), 0.01 (s, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.0, 164.2, 151.7, 149.6, 131.8, 126.8, 125.6 (2 C), 121.6, 119.7, 114.2, 113.5, 109.6, 83.6, 75.4, 74.8, 67.4, 62.1, 58.5, 57.3, 43.9, 34.6, 34.0, 28.0 (3 C), 27.3, 27.2, 26.9, 26.0, 25.8 (3 C), 19.5, 18.2, – 5.4 (2 C); HRMS (ESI-TOF) calculated for $C_{37}H_{55}N_3NaO_7Si$ [M + Na^+] 704.3707 found 704.3686. To a solution of **74** (146 mg, 0.214 mL) in THF (4.3 mL, 0.05 *M*) was added tetrabutylammonium fluoride (TBAF, 0.642 mL of a 1 *M* wet solution in THF, 3.0 equiv). After 1 h, the reaction was complete as judged by TLC and was diluted with EtOAc (10 mL), saturated aqueous NH_4Cl (5 mL), H_2O (5 mL) and was poured into a separatory funnel. The layers were separated and the aqueous portion was extracted with EtOAc (10 mL). The organic portions were combined, washed with saturated aqueous NaCl (10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude residue was dissolved in CH_2Cl_2 (4.3 mL, 0.05 *M*, wet CH_2Cl_2) and Dess-Martin periodinane (DMP, 136 mg, 0.321 mmol, 1.5 equiv) was added. The reaction vessel was left open to the ambient atmosphere. The reaction was stirred vigorously for 2 h during which the reaction produced a white cloudy precipitate. Once complete, the reaction mixture was diluted with EtOAc (15 mL). The contents of the reaction vessel were poured into a separatory funnel and washed with H_2O:saturated aqueous $NaHCO_3$ (1:1, 4 $\times$ 10 mL). The aqueous portions were combined and extracted with EtOAc (15 mL). The organic portions were combined, washed with saturated aqueous NaCl (15 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude residue was dissolved in THF (4.3 mL, 0.05 *M*) and 2-methyl-2-butene (0.453 mL, 4.28 mmol, 20 equiv) was added. NaH_2PO_4•H_2O (89 mg, 0.642 mmol, 3.0 equiv) was dissolved in H_2O (0.214 mL) and added *via* pipette to the vigorously stirring THF solution. $NaClO_2$ (54 mg, 0.599 mmol, 2.8 equiv) was dissolved H_2O (0.214 mL) and added *via* pipette dropwise over 30 sec to the vigorously stirring biphasic mixture. The reaction turned an intense yellow color soon after addition of the oxidant. The reaction was stirred vigorously for 20 min after which it was diluted with EtOAc (10 mL), saturated aqueous NH_4Cl (5 mL), and H_2O (5 mL) and was poured into a separatory funnel. The layers were separated and the aqueous portion was extracted with EtOAc (10 mL). The organic portions were combined, washed with saturated aqueous NaCl (10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude reside was dissolved in MeOH (approximately 5 mL) and treated with an ethereal solution of diazomethane (1 mL portions) until the starting material had been consumed. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel, 1:1 → 2:1 EtOAc:hexanes) furnishing 88 mg (69%) of diketopiperazine **75**.



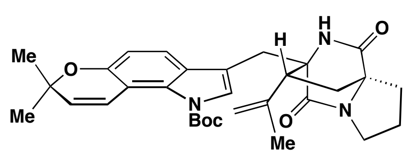
Diketopiperazine 75 (*via* 53). Proline derivative **70** (1.62 g, 4.65 mmol) was dissolved in MeOH:EtOAc (1:1, 46.6 mL, 0.1 *M*). 10% Pd/C (324 mg, 20% w/w**)** was added and hydrogen was bubbled through the vigorously stirring solution. After 30 min the reaction was complete and was filtered through Celite® and concentrated to a clear, yellow oil. (Note: The resulting amine could be isolated but required storage at –78 °C to prevent lactamization.) This oil was immediately combined with tryptophan acid **52** (2.42 g, 4.65 mmol, 1 equiv) and this mixture was dried azeotropically using benzene (20 mL). Once dry, the mixture was dissolved in DMF (93 mL) and *O*–(7–azabenzotriazol–1–yl)–*N, N, N', N'*–tetramethyluromoium hexafluorophosphate (HATU, 1.95 g, 5.12 mmol, 1.1 equiv) was added followed by the dropwise addition of *i*-Pr_2EtN (freshly distilled over CaH_2, 2.44 mL, 14.0 mmol, 3.0 equiv). The reaction was stirred for 12 h after which it was diluted with EtOAc (500 mL) and quenched with 1 *M* aqueous HCl (1.5 L). The layers were separated and the aqueous layer was back extracted with EtOAc (100 mL). Organics were combined and washed with saturated aqueous NaCl (2×1 L), dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel, 1:5 $\rightarrow$ 1:1 EtOAc:hexanes) furnishing 2.71 g (81 %) of amide **73**. Amide **73** (100 mg, 0.139 mmol) was dried azeotropically from benzene (10 mL) and dissolved in CH_2Cl_2 (14 mL, 0.01 *M*). Et_3SiH (0.89 mL, 5.57 mmol, 40 equiv) and Et_3N (0.039 mL, 0.279 mmol, 2 equiv) were added to the stirring solution followed by Pd_2dba_3•$CHCl_3$ (29 mg, 27.8 mmol, 0.2 equiv). The reaction was stirred for 2.5 h at which point all of the starting material amide had been consumed. The reaction was passed through two successive $MgSO_4$-Celite® pads eluting with MeOH (100 mL) then CH_2Cl_2 (100 mL) to remove the palladium. The filtrate was heated at 60 °C and the CH_2Cl_2 was boiled off using a Dean-Stark trap. After 30 min, DMF (50 mL) was added to the MeOH solution and the heating was increased to 110 °C. The MeOH was also removed using the Dean-Stark trap. The reaction was complete after 2.5 h as indicated by TLC and was concentrated *in vacuo*. The crude reaction material was purified by column chromatography (silica gel, 1:1 $\rightarrow$ EtOAc) furnishing 1.08 g (80%) of the unprotected diketopiperazines. Upper diastereomer: white foam; R_f = 0.45 (silica gel, EtOAc); $[\alpha]_D$ = +17.6 (c 0.34, $CHCl_3$); IR (neat) ν_{max} 2977, 2360, 2249, 1735, 1655, 1420, 1370, 1279, 1200, 1155, 982, 912 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (s, 1 H), 7.28 (d, *J* = 8.4 Hz, 1 H), 7.14 (d, *J* = 10.0 Hz, 1 H), 6.85 (d, *J* = 8.4 Hz, 1 H), 5.73 (s, 1 H), 4.38 (dd, *J* = 10.8, 3.1 Hz, 1 H), 3.86 – 3.76 (m, 1 H), 3.63 (s, 3 H), 3.55 – 3.46 (m, 1 H), 2.77 (dd, *J* = 15.0, 10.9 Hz, 1 H), 2.36 (t, *J* = 7.9 Hz, 2 H), 2.14 – 1.92 (m, 8 H), 1.64 (s, 9 H), 1.48 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 170.6, 165.0, 152.4, 149.7, 132.9, 127.2, 125.5, 124.8, 121.7, 119.1, 115.0, 114.2, 110.3, 84.4, 75.2, 67.5, 54.0, 52.2, 45.3, 33.8, 31.5, 29.4, 28.3 (3 C), 27.8, 27.4, 27.3, 20.6; HRMS (ESI-TOF) calculated for $C_{30}H_{38}N_3O_7$ [M + H$^+$] 552.2710, found 552.2705. Lower diastereomer: white foam; R_f = 0.25 (silica gel, EtOAc); $[\alpha]_D$ = – 93.9 (c 0.44, $CHCl_3$); IR (neat) ν_{max} 2976, 1754, 1654, 1473, 1370, 1276, 1156, 982 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (s, 1 H), 7.35 (d, *J* = 8.43 Hz, 1 H), 7.00 (d, *J* = 9.94 Hz, 1 H), 6.83 (d, *J* = 8.43 Hz, 1 H), 5.82 – 5.79 (m, 1 H), 5.62 (d, *J* = 9.94 Hz, 1 H), 4.22 (dt, *J* = 10.9, 3.08 Hz, 1 H), 3.99 – 3.91 (m, 1 H), 3.70 (s, 3 H), 3.50 – 3.41 (m, 2 H), 3.04 (dd, *J* = 14.3, 10.9 Hz, 1 H), 2.48 – 2.36 (m, 2 H), 2.19 – 2.14 (m, 1 H), 2.14 – 2.06 (m, 1 H), 2.04 – 1.93 (m, 4 H), 1.63 (s, 9 H), 1.48 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 169.3, 164.8, 152.3, 149.9, 132.7, 127.2, 125.7, 124.9, 121.8, 119.2, 115.1, 114.1, 110.3, 84.2, 75.1, 66.7, 57.6, 52.2, 44.9, 34.0, 32.4, 31.3, 29.5, 28.3 (3 C), 27.4, 27.3, 19.7; HRMS (ESI-TOF) calculated for $C_{30}H_{37}N_3O_7Na$ [M + Na$^+$] 574.2529, found 574.2514. (Note: MOM protection of the intermediate diketopiperazinewas carried out in individual batches keeping diastereomers separate. This was necessary for ease of purification.) This unprotected amide (685 mg, 1.24 mmol) was dried azeotropically from benzene (15 mL) and then dissolved in THF (12.4 mL, 0.1 *M*). The stirring solution was cooled to –78 °C for 10 min and then sodium bis(trimethylsilyl)amide (NaHMDS, 0.68 mL from a 2 *M* solution in THF, 1.36 mmol, 1.1 equiv) was added dropwise. The brown solution was stirred for 30 min and then chloromethyl methyl ether (MOMCl, freshly distilled over CaH_2, 0.13 mL, 1.74 mmol, 1.4

equiv) was added dropwise. The cooling bath was removed and the reaction allowed to attain ambient temperature. After 1 h, the reaction was quenched with saturated aqueous NH_4Cl (5 mL) and diluted with EtOAc (50 mL) and H_2O (50 mL). The layers were separated and the aqueous layer was back extracted with EtOAc (10 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude reaction material was purified by flash column chromatography (silica gel, 1:1 EtOAc:hexanes) to yield 465 mg (62%) of **75**. Upper diastereomer: white foam; R_f = 0.61 (silica gel, EtOAc); $[\alpha]_D$ = – 16.5 (c 0.20, $CHCl_3$); IR (neat) ν_{max} 2974, 1737, 1660, 1433, 1371, 1276, 1156, 1119, 983 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.5 Hz, 1 H), 7.11 (s, 1 H), 6.93 (d, *J* = 10.0 Hz, 1 H), 6.80 (d, *J* = 8.5 Hz, 1 H), 5.59 (d, *J* = 10.0 Hz, 1 H), 5.19 (d, *J* = 10.1 Hz, 1 H), 4.73 (d, *J* = 10.1 Hz, 1 H), 4.49 – 4.44 (m, 1 H), 3.63 (s, 3 H), 3.61 – 3.51 (m, 2 H), 3.47 (s, 3 H), 3.25 (dd, *J* = 15.0, 4.6 Hz, 1 H), 3.16 – 3.08 (m, 1 H), 2.29 – 2.16 (m, 2 H), 2.09 – 2.01 (m, 1 H), 1.99 – 1.91 (m, 1 H), 1.81 – 1.75 (m, 1 H), 1.71 – 1.63 (m, 1 H), 1.59 (s, 9 H), 1.46 (s, 3 H), 1.45 (s, 3 H), 1.15 – 1.05 (m, 1 H), 0.92 – 0.83 (m, 1 H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 169.5, 164.5, 152.0, 149.9, 132.0, 127.1, 126.3, 125.7, 121.7, 120.1, 114.2, 113.7, 109.8, 84.0, 76.1, 75.1, 67.3, 59.2, 57.7, 52.2, 44.3, 34.8, 32.7, 29.4, 28.2 (3 C), 27.4, 27.2, 26.8, 19.5; HRMS (ESI-TOF) calculated for $C_{32}H_{41}N_3O_8Na$ [M + Na^+] 618.2786, found 618.2785. Lower diastereomer: white foam; R_f = 0.33 (silica gel, EtOAc); $[\alpha]_D$ = + 14.2 (c 0.70, $CHCl_3$); IR (neat) ν_{max} 2977, 1736, 1655, 1432, 1370, 1274, 1200, 1155, 1120, 1093, 982 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.34 (m, 2 H), 7.02 (d, *J* = 10.0 Hz, 1 H), 6.81 (d, *J* = 8.5 Hz, 1 H), 5.58 (d, *J* = 10.0 Hz, 1 H), 4.99 (d, *J* = 10.1 Hz, 1 H), 4.46 (d, *J* = 5.1 Hz, 1 H), 4.43 (d, *J* = 10.1 Hz, 1 H), 3.91 – 3.83 (m, 1 H), 3.62 (s, 3 H), 3.39 – 3.28 (m, 2 H), 3.24 (s, 3 H), 2.24 (t, *J* = 8.4 Hz, 2 H), 2.18 – 2.13 (m, 1 H), 1.92 – 1.83 (m, 4 H), 1.74 – 1.67 (m, 1 H), 1.60 (s, 9 H), 1.47 (s, 3 H), 1.44 (s, 3 H), 1.36 –1.28 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) □ 172.8, 169.8, 165.0, 152.0, 149.8, 132.3, 126.8, 126.0, 125.5, 122.0, 119.6, 115.3, 114.0, 110.1, 83.8, 75.7, 75.0, 66.5, 60.9, 57.0, 52.0, 44.8, 34.1, 31.9, 29.3, 29.2, 28.2 (3 C), 27.5, 27.0, 19.7; HRMS (ESI-TOF) calculated for $C_{32}H_{42}N_3O_8$ [M + H^+] 596.2966, found 596.2951.



Hexacycle 76. (Note: The THF used in this reaction, including that used for preparing solutions of LDA and $Fe(acac)_3$, was purified by distillation over excess sodium metal and benzophenone. The solvent was collected immediately prior to use and always transferred *via* dry, oxygen-free syringes. LDA was prepared by standard methods with care taken to exclude oxygen. $Fe(acac)_3$ was dissolved in benzene and dried azeotropically prior to dissolution in THF.) To a solution of diketopiperazine **75** (1.212 mg, 2.03 mmol) in dry THF (40.6 mL, 0.05 *M*) at –78 °C was added LDA (8.94 mL from a 0.5 *M* solution in THF, 4.47 mmol, 2.2 equiv) in one portion as rapidly as possible through two syringes fitted with 18 gauge needles. The reaction immediately turned yellow. The bis-enolate was allowed to form for 5 min after which $Fe(acac)_3$ (22.35 mL from a 0.2 *M* solution in THF, 4.47 mmol, 2.2 equiv) was added in one portion as quickly as possible using two syringes both fitted with 18 gauge needles to the reaction mixture at –78 °C. The reaction immediately turned dark green-brown and was allowed to stir for 5 min at –78 °C. The cooling bath was removed and the reaction was allowed to stir without the cooling bath for an additional 20 min. The reaction was quenched by the addition of 100 mL saturated aqueous NH_4Cl. The biphasic mixture was poured into a separatory funnel and diluted with additional EtOAc (200 mL) and 1 *M* aqueous HCl (200 mL). The layers were separated and the aqueous portion was extracted with EtOAc (100 mL). The organic portions were combined, washed with saturated

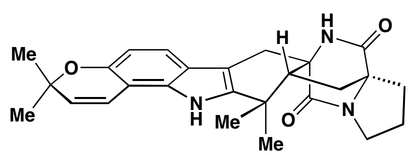
aqueous NaCl (300 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, 1:2 $\rightarrow$ 3:1 EtOAc:hexanes) furnishing 736 mg (61%) of hexacycle **76** along with recovered **75** (96.5 mg, 8%). White foam; R_f = 0.53 (silica gel, 4:1 EtOAc:hexanes); $[\alpha]_D$ = – 5.8 (c 0.24, CH_2Cl_2); IR (neat) ν_{max} = 2928, 1737, 1697, 1370, 1276, 1156, 1085, 982, 813, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1 H), 7.38 (d, *J* = 8.5 Hz, 1 H), 6.96 (d, *J* = 9.9 Hz, 1 H), 6.84 (d, *J* = 8.5 Hz, 1 H), 5.60 (d, *J* = 9.9 Hz, 1 H), 4.84 (d, *J* = 10.6 Hz, 1 H), 4.63 (d, *J* = 10.6 Hz, 1 H), 3.70 – 3.56 (m, 2 H), 3.53 (s, 3 H), 3.50 – 3.44 (m, 3 H), 3.17 (s, 3 H), 2.85 – 2.78 (m, 1 H), 2.28 (dd, *J* = 13.3, 10.4 Hz, 1 H), 2.13 (dd, *J* = 13.3, 4.8 Hz, 1 H), 2.09 – 1.99 (m, 2 H), 1.92 – 1.85 (m, 1 H), 1.61 (s, 9 H), 1.48 (s, 3 H), 1.47 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 171.9, 165.9, 151.8, 149.9, 131.6, 126.7, 126.5, 126.1, 121.8, 118.9, 114.1, 113.5, 109.7, 83.9, 74.9, 73.3, 67.3, 65.9, 65.6, 56.5, 52.4, 44.4, 29.7, 29.6, 28.1 (3 C), 27.3, 26.9, 23.1, 21.9; HRMS (ESI-TOF) calculated for $C_{32}H_{39}N_3O_8Na^+$ [M + Na^+] 616.2629, found 616.2639. Stereochemistry confirmed using ROESY. Peak assignments made using HMBC, HMQC and COESY analysis.



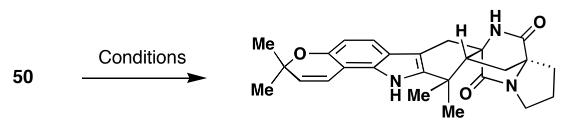
Olefin 50. To a solution of hexacycle **76** (34 mg, 0.0572 mmol) in CH_2Cl_2 (1.1 mL, 0.05 *M*) at 0 °C was added *B*-bromocatecholborane (0.430 mL from a 0.2 *M* solution in CH_2Cl_2, 1.5 equiv). The reaction was allowed to stir for 10 min and was quenched with 2 *M* aqueous NaOH (1 mL). The reaction mixture was diluted with EtOAc (5 mL) followed by 2 *M* aqueous NaOH (10 mL) and this mixture was stirred vigorously for 15 min. The mixture was poured into a separatory funnel and the layers were separated. The organic portion was washed again with 2 *M* aqueous NaOH (10 mL). The aqueous portions were combined and extracted with EtOAc (10 mL). The organic

portions were combined, washed with saturated aqueous NaCl (10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by PTLC (silica gel, EtOAc) furnishing 21 mg (63 %) of de(methoxy)methyl hexacycle. To a solution of de(methoxy)methyl hexacycle (21 mg, 0.0361 mmol) in toluene (0.722 mL) at ambient temperature was added MeMgBr (0.155 mL, 1.4 *M* solution (3:1 toluene:THF) 0.0216 mmol, 6 equiv). The solution immediately turned yellow and gas evolution was observed. The reaction was allowed to stir until starting material had been consumed, approximately 10 min. The reaction was quenched by the dropwise addition of saturated aqueous NH_4Cl (1 mL). The reaction mixture was diluted with water (10 mL) and EtOAc (10 mL). The biphasic mixture was poured into a separatory funnel and the layers were separated. The aqueous portion was extracted with EtOAc (10 mL). The organic portions were combined, washed with saturated aqueous NaCl (10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo.* The crude residue was dissolved in benzene (approximately 0.5 mL) and treated with the Burgess reagent (17 mg, 0.0722 mmol, 2.0 equiv). The solution was sealed with a plastic stopper and Parafilm M®. The reaction vessel was immersed in an oil bath preheated to 50 °C for 30 min. The reaction vessel was then removed from the bath and TLC was used to determine the extent of reaction. Once complete, the solvent was removed *in vacuo* and the residue was purified by PTLC (silica gel, 4:1 EtOAc:hexanes) furnishing 17 mg (88%) of olefin **50**: white foam, $[\alpha]_D$ = + 6.3 (c 0.54, CH_2Cl_2); R_f = 0.61 (silica gel; 4:1 EtOAc:hexanes); IR (neat) ν_{max} 3391, 2975, 1687, 1371, 1276, 1155, 982, 814 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (s, 1 H), 7.31 (d, *J* = 8.4 Hz, 1 H), 6.99 (d, *J* = 9.9 Hz, 1 H), 6.84 (d, *J* = 8.4 Hz, 1 H), 5.79 (bs, 1 H, D_2O exchangeable), 5.62 (d, *J* = 9.9 Hz, 1 H), 5.00 (bs, 2 H), 3.62 – 3.55 (m, 1 H), 3.54 – 3.49 (m, 1 H), 3.50 (d, *J* = 15.2 Hz, 1 H), 2.98 (dd, *J* = 10.4, 5.6 Hz, 1 H), 2.94 (d, *J* = 15.4 Hz, 1 H), 2.73 – 2.67 (m, 1 H), 2.26 (dd, *J* = 13.4, 10.4 Hz, 1 H), 2.04

– 1.93 (m, 2 H), 1.80 – 1.74 (m, 2 H), 1.74 (s, 3 H), 1.63 (s, 9 H), 1.48 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 168.4, 152.1, 149.6, 143.3, 132.1, 127.1, 126.8, 126.2, 121.5, 118.5, 116.1, 114.1, 113.1, 110.1, 84.0, 74.9, 66.5, 63.4, 52.3, 44.2, 36.7, 29.1, 28.1 (3 C), 27.2, 27.1, 24.4, 23.6, 19.3; HRMS (ESI-TOF) calculated for $C_{31}H_{38}N_3O_5H^+$ [M + H$^+$] 532.2811, found 532.2788.



Stephacidin A (1). Olefin **6** (5 mg, 0.0094 mmol) was transferred to a new round bottom flask. Any solvent was removed first by exposure to a stream of dry nitrogen followed by exposure to high vacuum. The reaction vessel was sealed and attached to a source of dry nitrogen. The reaction vessel was immersed in an oil bath preheated to 200 °C and removed after 1 h of heating. Once at room temperature, the residue was dissolved in CH_2Cl_2 and purified by PTLC (silica gel; 4:1 EtOAc:hexanes) furnishing 1.8 mg (45%) of stephacidin A (**1**) along with recovered *N*-Boc deprotected olefin (0.4 mg). Synthetic stephacidin A displayed identical spectroscopic properties to that reported for natural stephacidin A (^{1}H NMR in two solvents, ^{1}H-H COESY, HRMS; DMSO-d_6 spectra attached).

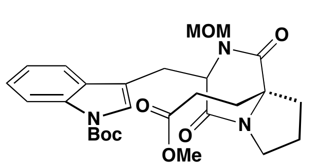


***ent*-1:** (–)-stephacidin A

Entry	Conditions	Result
1	CF_3CH_2OH, 120 °C, 18 h	Boc cleavage
2	H_2O, 200 °C	Boc cleavage
3	AcOH, 160 °C, 48 h	Boc cleavage
4	*p*-TsOH (1.5 equiv), toluene, reflux, 10 min	decomposition
5	1 *M* HCl, 100 °C, 1 h	decomposition
6	THF:10% H_2SO_4, (3:1), 100 °C, 2 h	decomposition
7	THF:1 *M* HCl (3:1), 100 °C, 24 h	20% product
8	neat, 200 °C, 1 h	28-45% product

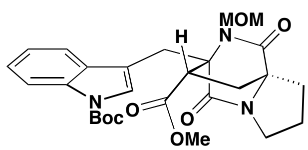
Table S2. Attempted deprotection/cyclization of olefin **50**.

Procedure for entry 7: Compound **50** (5.5 mg, 0.0103 mmol) was dissolved in THF:1 *M* aqueous HCl (3:1, 3 mL:1 mL, 2.58 mM) and the reaction vessel was sealed. The reaction mixture was immersed in a preheated 100 °C oil bath for 24 hr. The solvent was removed *in vacuo* and the residue was purified by preparatory TLC (3:1:0.1, EtOAc:hexanes:MeOH) providing **1** (0.9 mg, 20%) along with *N*-Boc-deprotected **50** (0.5 mg, 11 %).

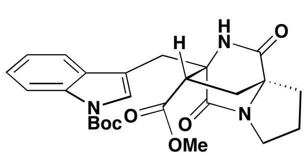


Model diketopiperazine 83. A mixture of racemic **53** (122 mg, 0.567 mmol, 1 equiv) and **81** (273 mg, 0.623 mmol, 1.1 equiv) was dried azeotropically using benzene (5 mL). Once dry, the mixture was dissolved in DMF (6.23 mL, 0.1 *M*) and *O*–(7–azabenzotriazol–1–yl)–*N, N, N', N'*–tetramethyluromoium hexafluorophosphate (HATU, 237 mg, 0.623 mmol, 1.1 equiv) followed by *i*-Pr_2EtN (0.296 mL, 1.70 mmol, 3.0 equiv). The mixture was allowed to react for approximately 12 h. The reaction vessel contents were then poured into separatory funnel and diluted with Et_2O (30 mL) and 1 *M* aqueous HCl (30 mL). The layers were separated and the aqueous portion was extracted a second time with additional Et_2O (30 mL). The organic portions were combined, washed with saturated aqueous NaCl, dried over $MgSO_4$, concentrated and purified by column chromatography (silica gel, 5:2 → 2:1 → 3:2 hexanes:EtOAc) furnishing 266 mg (74%) of **82** as an inseparable mixture of diastereomers. To a solution of **82** (4.793 g, 7.54 mmol) prepared as above in toluene (66 mL) was added 10% Pd/C (25% w/w). The suspension was stirred vigorously while hydrogen gas was bubbled through using a 20 gauge needle. After all starting material had been consumed (approximately 10 h), the reaction mixture was passed through a Celite®. The filter cake was washed with additional toluene (approximately 20 mL). The filtrate was then heated at reflux for 2 h then evaporated and the residue was purified by column chromatography (silica gel, 3:2 → 1:2 → 1:3 → 1:4 → hexanes:EtOAc then EtOAc) furnishing 1.512 g of the upper diastereomer of the unprotected diketopiperazine and 1.580 g of the lower diasteomer (3.092 g total, 87%). Upper diastereomer: white foam; R_f = 0.51 (silica gel, EtOAc); IR (neat) ν_{max} 2978, 1732, 1662, 1453, 1371, 1256, 1158, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (bd, *J* = 8.1 Hz, 1 H), 7.53 (d, *J* = 9.6 Hz, 1 H), 7.50 (s, 1 H), 7.34 (t, *J* = 9.2 Hz, 1 H), 7.25 (t, *J* = 9.6 Hz, 1 H), 5.95 (bs, 1 H), 4.42 (dd, *J* = 13.2, 4.1 Hz, 1 H), 3.85 – 3.75 (m, 1 H), 3.71 (dd, *J* = 18.7, 4.1 Hz, 1 H), 3.60 (s, 3 H), 3.55 – 3.45 (m, 1 H), 2.86 (dd, *J* = 18.7, 13.2 Hz, 1 H), 2.33 (t, *J* = 9.5 Hz, 2 H), 2.12 – 2.01 (m, 4 H), 2.01 – 1.88 (m, 2 H), 1.67 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 170.6, 164.9, 149.5, 135.9, 129.6, 125.2, 124.8, 123.0, 118.9, 115.7, 114.9, 84.2, 67.5, 54.0, 52.1, 45.2, 33.8, 31.4, 29.3, 28.3 (3 C), 27.8, 20.5; HRMS (ESI-TOF) calculated for $C_{25}H_{32}N_3O_6$ [M + H^+]: 470.2286, found 470.2288. Lower diastereomer:

white foam; R_f = 0.32 (silica gel, EtOAc); IR (neat) ν_{max} 2979, 1731, 1654, 1452, 1370, 1256, 1158, 1085, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.12 (bd, *J* = 9.2 Hz, 1 H); 7.59 (d, *J* = 9.6 Hz, 1 H), 7.57 (s, 1 H), 7.31 (t, *J* = 10.3 Hz, 1 H), 7.23 (t, *J* = 9.6 Hz, 1 H), 6.03 (bs, 1 H), 4.25 (dt, *J* = 13.2, 8.1, 4.1 Hz, 1 H), 3.93 (m, 1 H), 3.68 (s, 3 H), 3.50 (dd, *J* = 18.0, 2.6 Hz, 1 H), 3.50 – 3.39 (m, 1 H), 3.12 (dd, *J* = 18.0, 13.2 Hz, 1 H), 2.36 (t, *J* = 10.3 Hz, 2 H), 2.18 – 2.10 (m, 1 H), 2.10 – 2.00 (m, 1 H), 2.00 – 1.86 (m, 4 H), 1.66 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 169.4, 164.8, 149.6, 135.9, 129.7, 125.1, 125.0, 123.0, 119.1, 115.7, 115.0, 84.1, 66.6, 57.5, 52.1, 44.9, 33.9, 32.4, 31.3, 29.4, 28.4 (3 C), 19.6; HRMS (ESI-TOF) calculated for $C_{25}H_{32}N_3O_6$ [M + H^+]: 470.2286, found 470.2282. Each diastereomer was protected as described previously in generating **76**. The upper diastereomer of the unprotected diketopiperazine was protected in 86% yield furnishing the upper diastereomer of **83**: white foam; R_f = 0.53 (silica gel, 3:1 EtOAc:hexanes); IR (neat) ν_{max} 3111, 2248, 1732, 1659, 1557, 1454, 1371, 1328, 1257, 1157, 1083, 912 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 8.07 (bd, *J* = 7.7 Hz, 1 H), 7.55 (d, *J* = 7.7 Hz, 1 H), 7.28 (t, *J* = 7.7 Hz, 1 H), 7.25 (s, 1 H), 7.21 (t, *J* = 7.7 Hz, 1 H), 5.22 (d, *J* = 10.3 Hz, 1 H), 4.71 (d, *J* = 10.3 Hz, 1 H), 4.51 (t, *J* = 2.9 Hz, 1 H), 3.67 – 3.58 (m, 5 H), 3.46 (s, 3 H), 3.35 (dd, *J* = 15.4, 4.4 Hz, 1 H), 3.19 – 3.13 (m, 1 H), 2.30 – 2.17 (m, 2 H), 2.09 – 2.02 (m, 1 H), 1.99 – 1.92 (m, 1 H), 1.83 – 1.76 (m, 1 H), 1.72 – 1.65 (m, 1 H), 1.63 (s, 9 H), 1.17 – 1.08 (m, 1 H), 0.97 – 0.88 (m, 1 H); ^{13}C (125 MHz, $CDCl_3$) δ 172.9, 169.5, 149.6, 135.2, 130.4, 125.0, 124.8, 122.7, 119.7, 115.2, 114.2, 91.1, 83.9, 75.9, 67.3, 59.0, 57.7, 52.2, 44.4, 34.8, 32.6, 29.4, 28.3 (3 C), 26.6, 19.5; HRMS (ESI-TOF) calculated for $C_{27}H_{35}N_3O_7Na$ [M + Na^+] 536.2367, found 536.2365. The lower diastereomer of the unprotected diketopiperazine was protected in 92% yield furnishing the lower diastereomer of **83**: white foam; R_f = 0.35 (silica gel, 3:1 EtOAc:hexanes); IR (neat) ν_{max} 3109, 2248, 1732, 1660, 1557, 1455, 1372, 1339, 1257, 1160, 1085, 913 cm^{-1}; ^{1}H (500 MHz, $CDCl_3$) δ 8.11 (bs, 1 H), 7.62 (d, *J* = 7.7 Hz, 1 H), 7.51 (s, 1 H), 7.30 (t, *J* = 7.9 Hz, 1 H), 7.24 (t, *J* = 7.5 Hz, 1 H), 5.02 (d, *J* = 10.3 Hz, 1 H), 4.51 (t, *J* = 5.5 Hz, 1 H), 4.46 (d, *J* = 9.9 Hz, 1 H), 3.94 – 3.86 (m, 1 H), 3.64 (s, 3 H), 3.49 – 3.43 (m, 1 H), 3.41 – 3.37 (m, 2 H), 3.25 (s, 3H), 2.23 – 2.13 (m, 3 H), 1.95 – 1.84 (m, 3 H), 1.71 – 1.67 (m, 1 H), 1.65 (s, 9 H), 1.38 – 1.29 (m, 1 H); ^{13}C (125 MHz, $CDCl_3$) δ 173.1, 170.1, 165.2, 149.9, 135.9, 130.4, 125.5, 125.1, 123.3, 119.6, 115.7, 115.5, 90.9, 84.1, 75.9, 66.8, 61.1, 57.2, 52.3, 45.2, 34.4, 32.3, 29.6, 28.6 (3 C), 20.0; HRMS (ESI-TOF) calculated for $C_{27}H_{35}N_3O_7Na$ [M + Na^+] 536.2367, found 536.2365.

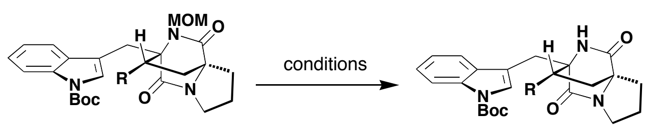


Pentacycle 84. The following compound was synthesized according to the procedures used to obtain compound **76** in 53% yield (after 1 recycle). White foam; R_f = 0.48 (silica gel, 3:1 EtOAc:hexanes); IR (neat) ν_{max} 3112, 2360, 1732, 1698, 1600, 1558, 1455, 1372, 1258, 1159, 1081, 909 cm^{-1}; ^{1}H (500 MHz, $CDCl_3$) δ 8.08 (bd, *J* = 7.4 Hz, 1 H), 7.65 (d, *J* = 7.4 Hz, 1 H), 7.61 (s, 1 H), 7.32 (t, *J* = 7.9 Hz, 1 H), 7.27 (t, *J* = 7.5 Hz, 1 H), 4.85 (d, *J* = 10.7 Hz, 1 H), 4.65 (d, *J* = 10.3 Hz, 1 H), 3.72 – 3.59 (m, 2 H), 3.58 (d, *J* = 5.2 Hz, 2 H), 3.55 – 3.50 (m, 4 H), 3.17 (s, 3 H), 2.85 – 2.77 (m, 1 H), 2.32 – 2.25 (m, 1 H), 2.18 – 2.14 (m, 1 H), 2.09 – 1.98 (m, 2 H), 1.93 – 1.86 (m, 1 H), 1.67 (s, 9 H); ^{13}C (125 MHz, $CDCl_3$) δ 174.2, 172.3, 166.3, 150.2, 135.1, 131.7, 125.4, 125.0, 123.0, 119.1, 115.5, 114.7, 84.3, 73.9, 67.7, 66.1, 56.9, 52.8, 48.8, 44.9, 35.4, 30.0, 28.6 (3 C), 24.5, 23.7; HRMS (ESI-TOF) calculated for $C_{27}H_{33}N_3O_7Na$ [M + Na^+] 534.2211, found 534.2211.



Hexacycle 85. The following compound was synthesized according to the procedures used to deprotect compound **76**. White foam; R_f = 0.35

(silica gel, 3:1 EtOAc:hexanes); IR ν_{max} 3110, 2356, 1732, 1695, 1558, 1454, 1371, 1310, 1258, 1158, 1093, 910 cm^{-1}; ^{1}H (500 MHz, $CDCl_3$) δ 8.15 (bd, *J* = 7.3 Hz, 1 H), 7.71 (s, 1 H), 7.58 (d, *J* = 7.7 Hz, 1 H), 7.35 (t, *J* = 7.30 Hz, 1 H), 7.29 (t, *J* = 7.2, 1 H), 5.77 (s, 1 H), 3.82 (s, 3 H), 3.67 – 3.57 (m, 3 H), 3.29 (dd, *J* = 9.9 , 4.4 Hz, 1 H), 3.18 (d, *J* = 15.8 Hz, 1 H), 2.73 – 2.64 (m, 1 H), 2.25 (dd, *J* = 13.6, 4.8 Hz, 1 H), 2.17 (dd, *J* = 13.6, 10.3 Hz, 1 H), 2.11 – 1.95 (m, 2 H), 1.85 – 1.77 (m, 1 H), 1.69 (s, 9 H); ^{13}C (125 MHz, $CDCl_3$) δ 172.8, 172.1, 166.9, 149.9, 135.8, 131.2, 126.7, 125.5, 123.8, 118.6, 116.1, 112.9, 84.6, 66.6, 63.9, 53.2, 48.5, 44.7, 35.2, 29.3, 28.6 (3 H), 24.7, 24.5; HRMS (ESI-TOF) calculated for $C_{25}H_{29}N_3O_6Na$ [M + Na^+] 490.1948, found 490.1948.



84: R = CO_2Me **85**: R = CO_2Me

Entry	Conditions	Product (% yield)[a]
1	BF_3•OEt_2, 1.0 equiv, EtSH, 3.0 equiv, CH_2Cl_2, 20 °C	recovered s.m.
2	BBr_3, 2.5 equiv, CH_2Cl_2, –78 °C, 10 min	complete decomposition
3	Ph_3CBF_4, 10 equiv, CH_2Cl_2, 0 °C, 70 min	5
4	PPh_3•Br_2, 2 equiv, CH_2Cl_2, 20 °C, 45 min	21
5	*B*-Br-9-BBN, 2 equiv, CH_2Cl_2, 0 °C, 15 min	35
6	TMSI, 10.0 equiv, CH_2Cl_2, –20°C, 10 min	49
7	*B*-bromocatecholborane, 2.0 equiv, CH_2Cl_2, 0 °C, 10 min; 1 recycle	68

[a] Isolated yield.

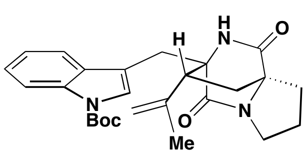
Table S3. Screening of MOM-deprotection conditions attempted on substrate **76**.

Procedure for entry 3: compound **84** (10 mg, 0.0195 mmol) was dissolved in CH_2Cl_2 (0.195 mL, 0.1 *M*) and cooled to 0 °C. Once cooled, Ph_3CBF_4 (0.234 mL, 0.0585 mmol, 0.25 *M* in CH_2Cl_2, 3 equiv) was added dropwise over 2 min. The reaction color changed from clear green-yellow to yellow, to yellow-brown upon full addition of the reagent. TLC analysis indicated that the majority of the remaining material was starting material. Ph_3CBF_4 (0.546 mL, 0.137 mmol, 0.25 *M* in CH_2Cl_2, 7 equiv) as added dropwise over 5 min after which the was allowed to stir at 0 °C. The reaction was quenched after 70 min with 2 *M* aq. NaOH (1 mL) and diluted with EtOAc (2 mL). The layers were separated and the aqueous layer was back-extracted with EtOAc (2 mL). The organic layers were combined, dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude residue was purified by preparatory TLC (9:1, CH_2Cl_2:acetone) providing **85** (1.2 mg, 12 %) along with **84** (0.5 mg, 5 %).

Procedure for entry 4: compound **84** (10 mg, 0.0195 mmol) was dissolved in CH_2Cl_2 (0.195 mL, 0.1 *M*). $PPh_3{\bullet}Br_2$ (0.390 mL, 0.039 mmol, 0.1 *M* in CH_2Cl_2, 2 equiv) was added dropwise to the solution over 1 min. The reaction was monitored by TLC for disappearance of starting material and was quenched with 2 *M* aqueous NaOH (1 mL) after 45 min. The reaction was diluted with EtOAc (2 mL) and the layers were separated. The aqueous layer was back-extracted with EtOAc (2 mL) and the organic layers were combined, dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude residue was purified by preparatory TLC (9:1, CH_2Cl_2:acetone) providing **85** (1.9 mg, 21 %) along with **84** (0.8 mg, 8 %).

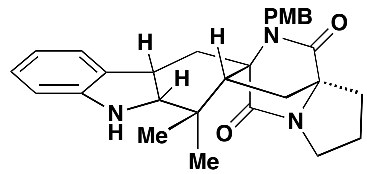
Procedure for entry 5: compound **84** (10 mg, 0.0195 mmol) was dissolved in CH_2Cl_2 (0.390 mL, 0.05 *M*) and cooled to 0 °C. Once cooled, *B*-Br-9BBN (0.039 mL, 0.039 mmol, 1 *M* in CH_2Cl_2, 2 equiv) was added in one portion. After 15 min, all starting material had been consumed by TLC and the reaction was quenched by adding 2 *M* aq. NaOH (1 mL). The reaction was diluted with EtOAc (2 mL) and the layers were separated. The aqueous layer was back-extracted with EtOAc (2 mL) and the organic layers were combined, dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude residue was purified by preparatory TLC (9:1, CH_2Cl_2:acetone) providing **85** (3.2 mg, 35 %).

Procedure for entry 6: compound **84** (10.1 mg, 0.0197 mmol) was dissolved in CH_2Cl_2 (0.394 mL, 0.05 *M*) and cooled to –20 °C. Once cooled, TMSI (0.028 mL, 0.197 mmol, 10 equiv) was added in one portion. After 10 min, the reaction was quenched with 6 *M* aq. NaOH (1 mL). The reaction was diluted with EtOAc (2 mL) and the layers were separated. The aqueous layer was back-extracted with EtOAc (2 mL) and the organic layers were combined, dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude material (4.5 mg, 49 %) was spectroscopically pure **85**.

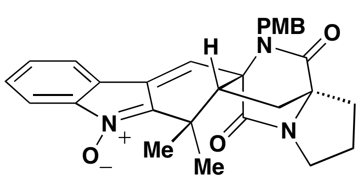


Olefin 86. The following compound was synthesized according to the procedures used to obtain compound **50**. White foam; R_f = 0.51 (silica gel, 3:1 EtOAc:hexanes); IR ν_{max} 2979, 1729, 1686, 1452, 1371, 1309, 1257, 1219, 1156, 1093, 1013, 904 cm^{-1}; ^{1}H (500 MHz, $CDCl_3$) δ 8.14 (bd, *J* = 7.4 Hz, 1 H), 7.61 (s, 1 H), 7.58 (d, *J* = 8.2 Hz, 1 H), 7.34 (t, *J* = 7.9 Hz, 1 H), 7.28 (t, *J* = 7.4 Hz, 1 H), 5.77 (s, 1 H), 5.02 (bs, 2 H), 3.63 – 3.55 (m, 2 H), 3.54 – 3.48 (m, 1 H), 3.05 – 2.97 (m, 2 H), 2.73 – 2.67 (m, 1 H), 2.27 (dd, *J* = 13.6, 10.3 Hz, 1 H), 2.06 – 1.93 (m, 2 H), 1.82 – 1.74 (m, 5 H), 1.68 (s, 9 H); ^{13}C (125 MHz, $CDCl_3$) δ 172.9, 168.6, 149.7, 143.4, 135.5, 131.1, 126.3, 125.1, 123.4, 118.6, 116.4, 115.8,

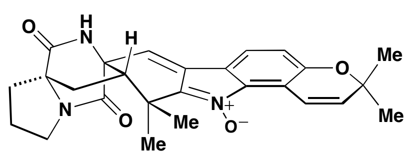
113.3, 84.2, 66.7, 63.7, 52.6, 44.4, 36.9, 29.4, 28.4 (3 C), 24.7, 24.0, 19.6; HRMS (ESI-TOF) calculated for $C_{26}H_{31}N_3O_4Na$ [M + Na^+] 472.2207, found 472.2207.



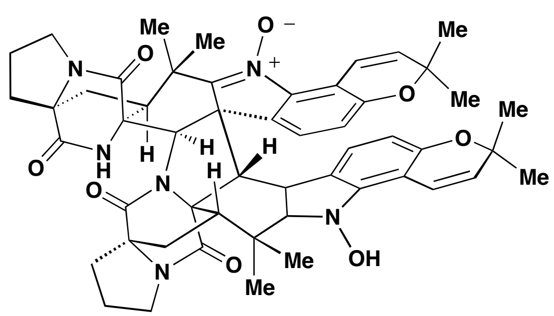
Model indoline 88. *CAUTION: The following procedure should be conducted in a well-ventilated fume hood as hydrogen cyanide gas is evolved upon addition of the reducing agent to the reaction mixture*. Compound **87** (10.3 mg, 0.0219 mmol) was dissolved in AcOH (0.220 mL, 0.1 *M*). $NaBH_3CN$ (13.8 mg, 0.219 mmol) was added in one portion. The reaction was allowed to stir at 25 °C for 12 h after which it was diluted with EtOAc (10 mL) and poured into a separatory funnel. The solution was basified to pH 14 by the addition of 3 *M* aqueous NaOH and gave a clear biphasic mixture. The layers were separated, and the aqueous portion was re-extracted with an addition 10 mL EtOAc. The combined organic portions were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by PTLC (4:1 CH_2Cl_2:acetone) and furnished 5.5 mg (53%) of **88**. We note that this reaction has not been optimized.



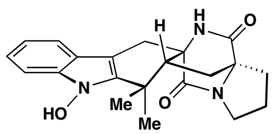
Model α,β-unsaturated nitrone 92. Compound **88** (3 mg, 0.064 mmol) was dissolved in methanol (0.2 mL). To this solution was added H_2O (0.050 mL), 35% aqueous H_2O_2 (0.0062 mL), and Na_2WO_4•$2H_2O$ (0.4 mg, 0.0013 mL). Sonication was used to aid dissolution of the catalyst. The reaction was allowed to stir for 6 h under an oxygen atmosphere after which the solution was diluted with H_2O (5 mL) and EtOAc (5 mL). The layers were separated in a separatory funnel and the aqueous portion was back-extracted with EtOAc (10 mL). The combined organic portions were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by PTLC (4:1 CH_2Cl_2:acetone) and furnished **92** (*ca.* 1 mg, *ca.* 30% yield) as a bright yellow film. R_f = 0.22 (silica gel, EtOAc); IR (neat) ν_{max} 2928, 2260, 1732, 1682, 1513, 1455, 1394, 1326, 1249, 1158, 1138, 1034, 841, 778 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 7.73 (d, *J* = 8.0 Hz, 1 H), 7.59 – 7.53 (m, 2 H), 7.53 – 7.48 (m, 1 H), 7.18 (d, *J* = 8.7 Hz, 2 H), 6.92 (s, 1 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 4.78 (d, *J* = 15.9 Hz, 1 H), 4.56 (d, *J* = 15.9 Hz, 1 H), 3.73 (s, 3 H), 3.53 – 3.47 (m, 1 H), 3.46 – 3.39 (m, 1 H), 2.81 – 2.73 (m, 1 H), 2.56 – 2.51 (m, 1 H), 2.21 – 1.95 (m, 5 H), 1.54 (s, 3 H), 1.12 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 166.8, 159.4, 130.3, 129.5, 129.1, 128.8, 128.6 (2 C), 124.8, 124.3, 120.5, 115.7, 115.6, 114.6 (2 C), 114.1, 67.3, 66.8, 55.5, 51.9, 45.4, 44.8, 36.2, 31.5, 30.2, 29.2, 24.7 (2 C); HRMS (ESI-TOF) calculated for $C_{29}H_{30}N_3O_4$ [$M + H^+$]: 484.2231; found 484.2227.



Avrainvillamide (3). *CAUTION: The following procedure should be conducted in a well-ventilated fume hood as hydrogen cyanide gas is evolved upon addition of the reducing agent to the reaction mixture*. To a solution of stephacidin A (**1**, 3.5 mg, 0.0081 mmol) in AcOH (0.650 mL, 0.0125 M) was added $NaBH_3CN$ (20.4 mg, 0.325 mmol) in one portion. The reaction was allowed to stir for 16 h after which it was quenched by pouring it into saturated aqueous $NaHCO_3$ (6 mL). The mixture was diluted with EtOAc (5 mL) and H_2O (5 mL) and poured into a separatory funnel. The layers were separated, and the aqueous portion was back-extracted with EtOAc (10 mL). The combined organic portions were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo.* The conversion was >95% as judged by ^1H NMR (inconsequential mixture of diastereomers). To a solution of the indoline (4 mg, 0.0092 mmol) in 1,4-dioxane (0.461 mL, 0.02 *M*) was added 35% aqueous H_2O_2 (0.0118 mL) followed by SeO_2 (0.26 mg; 0.0102 mL from a solution in water made by dissolving 10 mg SeO_2 in 0.4 mL H_2O). The reaction was allowed to stir for 40 h after which the solution was diluted with H_2O (3 mL) and EtOAc (3 mL). The layers were separated in a separatory funnel and the aqueous portion was back-extracted with EtOAc (3 mL). The combined organic portions were washed with saturated aqueous NaCl (5 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by PTLC (SiO_2, 100% EtOAc) and furnished starting material indoline (2.0 mg, 50%) and avrainvillamide (**3**, 1.1 mg, 27% yield) as a bright yellow amorphous solid. Synthetic **3** was identical to natural **3** as judged by LCMS, TLC in several solvent mixtures, ^1H NMR, and optical rotation (synthetic **3** $[\alpha]_D$ = +11 (c 0.1, $CHCl_3$); natural **3** $[\alpha]_D$ = 10.6 (c 0.17, $CHCl_3$).

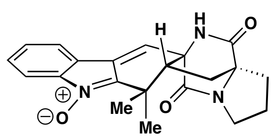


Stephacidin B (**2**). Procedure A:[6] To a solution of avrainvillamide (**3**, 0.5 mg, 0.0011 mmol) in CH_3CN (0.085 mL) was added Et_3N (0.015 mL). The reaction was allowed to stir at room temperature for 45 min. The resulting solution was evaporated and dried under high vacuum for 30 min. The residue was purified by PTLC (SiO_2, 100% EtOAc). Procedure B: avrainvillamide (**3**) was absorbed onto a prep plate and allowed to stand for 1 h before being eluted. Stephacidin B could be separated from avrainvillamide by eluting solvent twice during purification. This procedure gave a 15-20% yield of **2** along with recovered **3** (70-80%). Procedure C: avrainvillamide was dissolved in DMSO and then the solvent was removed *in vacuo* over 30 min to 1 h. ^1H NMR indicated a ratio of 2:1 (**3**:**2**) (avrainvillamide:stephacidin B) which could be separated by PTLC. Synthetic **2** was identical in all respects to a sample of natural **2** kindly provided by BMS (LCMS, TLC in several solvent mixtures, ^{1}H NMR, and optical rotation (synthetic (–)-**2**: $[\square]_D$ = –33 (c 0.1, CH_3CN); natural (–)-**2**: $[\square]_D$ = –21.1 (c 0.19, $CDCl_3$).

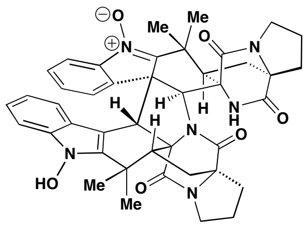


Model *N*-hydroxyindole 91. Compound **80** (142.6 mg, 0.41 mmol) was dissolved in glacial AcOH (4.1 mL, 0.1 *M*). To the stirring solution was added $NaBH_3CN$ (256 mg, 4.08 mmol, 10 equiv). The reaction was monitored by LCMS. When all starting material had been consumed, the reaction was quenched with 1 *M* aqueous NaOH (5 mL) and extracted with EtOAc (10 mL). The layers were separated, aqueous layer back-extracted with EtOAc (5 mL), organics combined and washed with saturated aqueous NaCl (10 mL), dried over $MgSO_4$, filtered, and solvent was removed *in vacuo*. This residue was dissolved in trifluoroethanol:H_2O (3:1, 40.8 mL, 0.01 *M*). To this solution was added Na_2WO_4•$2H_2O$ (269 mg, 0.82 mmol, 2 equiv) followed by 35% aqueous H_2O_2 (1.75 mL, 50 equiv). The reaction was monitored by LCMS for appearance of product mass and quenched after 50 min by adding H_2O (40 mL) and EtOAc (40 mL). The layers were separated and the aqueous layer was back-extracted with EtOAc (2 □ 10 mL). The organics were combined, washed with saturated aqueous NaCl (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue flash chromatographed on silica gel (4:1 □ 2:1 CH_2Cl_2:acetone) to give *N*-hydroxyindole **41** (81 mg, 54 %) as a white powder. R_f = 0.46 (silica gel, 2:1 CH_2Cl_2:acetone); IR (neat) $\square_{max}$ 2927, 1696, 1660, 1508, 1457, 1338, 1215, 1092, 914, 729, 610 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD) □ 7.44 (d, *J* = 7.8 Hz, 1 H), 7.30 (d, *J* = 8.1 Hz, 1 H), 7.12 (t, *J* = 8.0 Hz, 1 H), 7.00 (t, *J* = 7.8 Hz, 1 H), 5.50 (s, 1 H), 3.62 (d, *J* = 15.3 Hz, 1 H), 3.51 – 3.45 (m, 1 H), 3.42 – 3.36 (m, 1 H), 2.78 (d, *J* =

15.3 Hz, 1 H), 2.75 – 2.68 (m, 1 H), 2.65 – 2.61 (m, 1 H), 2.22 – 2.21 (m, 2 H), 2.12 – 2.05 (m, 1 H), 2.02 – 1.93 (m, 2 H), 1.52 (s, 3 H), 1.21 (s, 3 H); ^{13}C NMR (150 MHz, CD_3OD) δ 175.3, 170.7, 138.6, 136.7, 122.7, 122.0, 119.4, 118.2, 108.3, 100.9, 67.8, 61.1, 51.2, 44.6, 36.2, 31.1, 29.6, 27.3, 24.9, 24.7, 19.8; LC-MS (ESI-TOF) calculated for $C_{21}H_{24}N_3O_3$ [M + H^+]: 366.4; found 366.1.



Model avrainvillamide 93. Compound **91** (10 mg, 0.0274 mmol) was dissolved in THF (2.74 mL, 0.01 *M*) and to this solution was added chloranil (13.5 mg, 0.00548 mmol, 2 equiv). The resulting yellow solution was sealed with a plastic cap and heated in an oil bath preheated to 70 °C. After 30 min, the reaction was removed from the heat and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel (CH_2Cl_2 → 2:1 CH_2Cl_2:acetone) furnishing 8.8 mg (88%) of **93**: yellow film; R_f = 0.29 (silica gel, 2:1 CH_2Cl_2:acetone); IR (neat) ν_{max} 2967, 2360, 2341, 1685, 1516, 1457, 1403, 1380, 1317, 1218, 1149, 1087. 895, 764 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, J = 7.8 Hz, 1 H), 7.64 (d, J = 7.1 Hz, 1 H), 7.51 (t, J = 7.5 Hz, 1 H), 7.44 (t, J = 7.3 Hz, 1 H), 7.15 (bs, 1 H), 6.76 (s, 1 H), 3.62 – 3.55 (m, 1 H), 3.50 – 3.43 (m, 1 H), 2.85 – 2.79 (m, 1 H), 2.58 (dd, J = 16.5, 6.6 Hz, 1 H), 2.22 (dd, J = 23.5, 13.2 Hz, 1 H), 2.11 – 2.00 (m, 2 H), 1.96 – 1.86 (m, 2 H), 1.67 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0, 167.4, 146.6, 143.3, 134.8, 130.3, 128.8, 124.1, 122.4, 120.7, 114.1, 67.3, 63.1, 53.2, 44.6, 36.1, 31.2, 29.6, 24.8, 23.8, 16.1; HRMS (ESI-TOF) calculated for $C_{21}H_{22}N_3O_3$ [M + H^+]: 364.1656; found 364.1656.



Model Stephacidin B (95). Model avrainvillamide **93** (47.1 mg, 0.13 mmol) was dissolved in MeCN (1.3 mL, 0.1 *M*). To the yellow solution was added Et_3N (0.183 mL, 1.3 mmol, 100 equiv). After 15 min, the reaction color had become clear brown and after 1 h, TLC indicated that all starting material had been consumed. The solvent was removed *in vacuo*. The residue was purified by PTLC (3 □ 0.5 mm thick plates, 2:1 CH_2Cl_2:acetone) to yield 32.5 mg (69%) of **95**: yellow-white powder; R_f = 0.24 (silica gel, 2:1 CH_2Cl_2:acetone); IR (neat) $□_{max}$ 2360, 2341, 1683, 1558, 1540, 1507, 1457, 1395, 668 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) □ 10.84 (s, 1 H), 7.93 (d, *J* = 7.5 Hz, 1 H), 7.61 (s, 1 H), 7.21 (d, *J* = 8.4 Hz, 1 H), 7.14 (t, *J* = 7.6 Hz, 1 H), 7.10 (t, *J* = 8.2 Hz, 2 H), 7.00 (t, *J* = 7.2 Hz, 1 H), 6.89 (t, *J* = 7.6 Hz, 1 H), 5.37 (s, 1 H), 5.01 (s, 1 H), 4.55 (s, 1 H), 3.48 – 3.43 (m, 1 H), 3.42 –3.38 (m, 1 H), 3.30 – 3.25 (m, 2 H), 3.21 – 3.14 (m, 1 H), 2.82 (d, *J* = 9.6 Hz, 1 H), 2.71 – 2.60 (m, 2 H), 2.49 –2.43 (m, 1 H), 2.32 (d, *J* = 14.3 Hz, 1 H), 2.20 – 2.13 (m, 1 H), 2.12 (s, 1 H), 2.11 – 2.02 (m, 2 H), 2.01 – 1.94 (m, 1 H), 1.93 – 1.78 (m, 3 H), 1.74 (s, 3 H), 1.59 (s, 3 H), 1.40 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR (150 MHz, DMSO-d_6) □; HRMS (ESI-TOF) calculated for $C_{42}H_{42}N_6O_6$ [$M + H^+$]: 727.3244; found 727.3264.