Chemistry and Biology of Diazonamide A: Second Total Synthesis of Diazonamide A and Biological Investigations

K. C. Nicolaou,* Junliang Hao, Mali V. Reddy, Paraselli Bheema Rao, Gerasimos Rassias, Scott A. Snyder, Xianhai Huang, David Y.-K. Chen, William E. Brenzovich, Nicolas Giuseppone, Paraskevi Giannakakou,[†] and Aurora O'Brate[†]

*Department of Chemistry and The Skaggs Institute for Chemical Biology
The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037 and
Department of Chemistry and Biochemistry, University of California, San Diego,
9500 Gilman Drive, La Jolla, California 92093*

Corresponding Author: kcn@scripps.edu

Supporting Information

Experimental Data for Compounds

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, diethyl ether (Et₂O), ethylene glycol dimethyl ether (DME), and methylene chloride (CH₂Cl₂) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (¹H 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, and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-600, DRX-500, AMX-500 or

[†] Emory University School of Medicine, Winship Cancer Institute

AMX-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, quin = quintuplet, sext = sextet, sep = septet, br = broad, app = apparent, AB = AB quartet. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on an API 100 Perkin Elmer SCIEX single quadrupole mass spectrometer at 4000V emitter voltage. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer using MALDI (matrix-assisted laser-desorption ionization).

Boronic ester 6. Bispinacolato diboron (3.310 g, 13.00 mmol, 2.5 equiv), Pd(dppf)Cl₂•CH₂Cl₂ (0.425 g, 0.52 mmol, 0.1 equiv), and KOAc (0.864 g, 8.82 mmol, 3.0 equiv) were all added to a flask containing compound **10** (3.00 g, 5.20 mmol, 1.0 equiv). This vessel was then equipped with an air condenser, and degassed 1,4-dioxane (15 mL, prepared by three iterations of the freeze-thaw method) was added at 25 °C. The reaction flask contents were then warmed to 95 °C and stirred for 6 hours. Upon completion, the reaction mixture was diluted with EtOAc (50 mL), filtered through a short plug of silica, and extracted with EtOAc (3 × 50 mL). The combined organic layers were then washed with water (2 × 50 mL) and brine (50 mL), dried (MgSO₄), and concentrated. The resultant yellow-green residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4) to give the boronate ester **6** (2.76 g, 85% yield) as a pale yellow solid. **6**: R_f = 0.68 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2931, 1632, 1426, 1364, 1104, 823, 740, 704, 506 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.86–7.83 (m, 4 H), 7.79 (dd, *J* = 7.0, 0.8 Hz, 1 H), 7.73 (dd, *J* = 8.5, 1.1 Hz, 1 H), 7.51–7.45 (m, 6 H), 7.40 (dd, *J* = 8.4, 7.3 Hz, 1 H), 7.38 (s, 1 H), 7.15 (s, 1 H), 5.57 (s, 2 H), 4.90 (s, 2 H), 3.36 (s, 3 H), 1.26 (s, 12 H), 1.17 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) δ 161.0, 147.0, 136.0, 135.6, 132.8, 130.8, 130.4, 129.8, 129.7 (2 C), 127.7, 124.8, 122.3, 112.9, 105.6, 83.4, 77.5, 59.3, 56.0, 26.6, 25.0, 24.7, 19.2; HRMS (MALDI-FTMS) calcd for C₃₆H₄₃BN₂O₅SiNa⁺ [M + Na⁺] 645.2926, found 645.2918.

7-Bromoisatin (9). Prepared via the procedure delineated in the previous manuscript in this series.

Tertiary alcohol 12. A solution of Na₂CO₃ (22.75 g, 215.8 mmol, 1.0 equiv) in water (125 mL) was added to a rapidly stirring suspension of L-tyrosine methyl ester hydrochloride (50.0 g, 215.8 mmol, 1.0 equiv) in CHCl₃ (800 mL) at 25 °C. The resultant biphasic mixture was then cooled to 0 °C, and benzyl chloroformate (32.44 mL, 215.8 mmol, 1.0 equiv) and Na₂CO₃ (2.0 M in H₂O, 100 mL) were added sequentially. After 3 hours of vigorous stirring at 25 °C, the reaction flask contents were diluted with water (100 mL) and the organic layer was separated, dried (MgSO₄), and concentrated to give Cbz-protected L-tyrosine methyl ester (70.88 g, 100%) as a yellow oil. Carrying this material forward without further purification, a portion (22.4 g, 66.0 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (500 mL) and isatin **9** (15.0 g, 66.0 mmol, 1.0 equiv) was added at 25 °C. After stirring the resultant solution for 5 minutes at 25 °C, TiCl₄ (79.2 mL, 1.0 M in CH₂Cl₂, 79.2 mmol, 1.2 equiv) was added dropwise over the course of 30 minutes. After 6 hours of additional stirring at 25 °C, the reaction mixture was quenched by the addition of saturated aqueous NH₄Cl (250 mL), stirred for an additional hour at 25 °C, and extracted with CH₂Cl₂ (2 × 250 mL). The combined organic layers were then washed with water (2 × 250 mL), dried (MgSO₄), and concentrated. The resultant dark brown solid was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give tertiary alcohol **12** (21.8 g, 58% yield) as a light brown solid. **12**: *R_f* = 0.25 (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\max}$ 3273, 2952, 1699, 1616, 1506, 1212, 1170, 738 cm⁻¹; ¹H NMR (500 MHz, CD₃CN, 1:1 mixture of diastereomers) δ 8.53 (s, 1 H), 7.58 (d, *J* = 7.3 Hz, 1 H), 7.39 (d, *J* = 6.5 Hz, 1 H), 7.35–7.28 (m, 7 H), 6.99 (dd, *J* = 8.4, 6.6 Hz, 2 H), 6.85 (t, *J* = 12.0 Hz, 1 H), 6.69 (d, *J* = 6.6 Hz, 1 H), 5.92 (m, 1 H), 5.02 (s, 2 H), 4.70 (s, 1 H), 3.65 (s, 3 H), 3.06 (dd, *J* = 13.9, 5.7 Hz, 0.5 H), 3.02 (dd, *J* = 7.2, 5.2 Hz, 0.5 H), 2.89 (dd, *J* = 14.0, 5.7 Hz, 0.5 H), 2.84 (dd, *J* = 13.6, 5.3 Hz, 0.5 H); ¹³C NMR (150 MHz, CD₃CN) δ 179.8, 172.6, 156.7, 153.4, 141.9 (2 C), 137.4, 133.7, 132.7, 130.7, 130.3, 128.8, 128.3, 128.2, 128.0, 125.9, 123.8 (2 C), 123.2, 122.4, 116.2, 102.6, 78.0,

66.5, 56.0, 52.2, 50.1, 36.9; HRMS (MALDI-FTMS) calcd for $C_{26}H_{23}BrN_2O_7Na^+$ [$M + Na^+$] 577.0581, found 577.0593.

Lactam 13. Neat $SOCl_2$ (30 mL) was added to tertiary alcohol **12** (30.0 g, 54.0 mmol) at 25 °C. After 10 hours of stirring at 25 °C, the reaction flask contents were concentrated directly to provide the desired intermediate tertiary chloride (27.9 g, 90% yield) as a brown solid: R_f = 0.53 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3253, 2951, 1695, 1614, 1507, 1435, 1213, 1054, 786, 769 cm^{-1} ; 1H NMR (500 MHz, CD_3CN , 1:1 mixture of diastereomers) δ 8.89 (s, 1 H), 7.73 (d, J = 2.2 Hz, 1 H), 7.46 (dd, J = 8.0, 1.3 Hz, 0.5 H), 7.45 (dd, J = 8.0, 1.1 Hz, 0.5 H), 7.35–7.25 (m, 5 H), 7.13–7.10 (dd, J = 8.0, 1.9 Hz, 1 H), 7.05–6.89 (m, 2 H), 6.75 (dd, J = 11.7, 3.3 Hz, 1 H), 6.03 (t, J = 4.5 Hz, 1 H), 5.10 (s, 2 H), 4.53–4.45 (m, 1 H), 3.72 (s, 3 H), 3.14 (dd, J = 11.7, 4.4 Hz, 0.5 H), 3.13 (dd, J = 11.7, 4.4 Hz, 0.5 H), 3.02 (dd, J = 11.7, 7.0 Hz, 0.5 H), 2.98 (dd, J = 11.5, 7.0 Hz, 0.5 H); ^{13}C NMR (125 MHz, CD_3CN) δ 175.3, 173.0, 164.0, 156.8, 153.0, 141.3, 137.8, 133.5, 132.1 (2 C), 131.2, 130.7, 129.5, 129.3, 129.1, 128.8, 128.4, 125.0, 124.0, 123.9, 123.0, 116.3, 116.0, 68.5, 67.0, 56.4, 37.3. With this operation complete, a portion of the newly synthesized material (20.0 g, 34.7 mmol, 1.0 equiv) was dissolved in CH_3CN (150 mL) and treated with $NaCNBH_3$ (6.4 g, 104.7 mmol, 3.0 equiv) at 0 °C. The reaction flask contents were then warmed slowly to 25 °C and stirred for 5 additional hours before being quenched by the addition of saturated aqueous sodium potassium tartrate (200 mL), poured into water (500 mL), and extracted with CH_2Cl_2 (2×250 mL). The combined organic layers were then washed with water (2×250 mL), dried ($MgSO_4$), and concentrated. The resultant dark brown solid was purified by flash column chromatography (silica gel, EtOAc/hexanes, 2:3) to give lactam **13** (15.7 g, 84% yield) as a light brown solid. **13**: R_f = 0.33 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3272, 2949, 1694, 1613, 1509, 1212, 1126, 1053, 737, 696 cm^{-1} ; 1H NMR (600 MHz, CD_3CN , 1:1 mixture of diastereomers) δ 8.76 (s, 1 H), 7.34–7.25 (m, 5 H), 6.98 (dd, J = 8.3, 1.7 Hz, 1 H), 6.90 (br s, 2 H), 6.82 (t, J = 7.0 Hz, 1 H), 6.75 (d, J = 8.34, 1 H), 5.92 (t, J = 7.0 Hz, 1 H), 5.02 (s, 2 H), 4.81 (s, 1 H), 4.36 (m, 1 H), 3.61 (s, 3 H), 2.97 (dd, J = 13.5, 8.2 Hz, 1 H), 2.87 (dd, J = 15.7, 8.3 Hz, 1 H); ^{13}C NMR (150 MHz, CD_3CN , 1:1

mixture of diastereomers) δ 178.1, 173.0, 156.7, 154.6, 142.5, 137.9, 132.4, 132.2, 131.4, 131.2, 130.6, 129.3, 128.7, 128.6, 128.5, 124.4, 124.3, 124.1, 116.5, 115.9, 102.5, 67.0, 56.4, 52.6, 50.4, 37.1; HRMS (MALDI-FTMS) calcd for $C_{26}H_{23}BrN_2O_6Na^+$ $[M + Na^+]$ 561.0632, found 561.0630.

Acetonide 14. Oxindole intermediate **13** (50.0 g, 92.7 mmol, 1.0 equiv) was dissolved in THF (500 mL), cooled to 0 °C, and treated with $LiBH_4$ (185.0 mL, 2.0 M in THF, 371 mmol, 4.0 equiv). The resultant slurry was then warmed to 25 °C and allowed to stir for an additional 2 hours. Upon completion, the contents were cooled to 0 °C and a mixture of 10% aqueous HCl (50 mL) and water (400 mL) were added dropwise over the course of 4 hours to quench any residual reducing agent. The reaction flask contents were then poured into EtOAc (400 mL), washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated. The resultant yellow oil was purified by flash column chromatography (silica gel, EtOAc/hexanes, 4:1) to give the desired intermediate alcohol (45.0 g, 97%) as a yellow oil: R_f = 0.30 (silica gel, EtOAc/hexanes, 4:1); IR (film) ν_{max} 3248, 3033, 2943, 2862, 1685, 1603, 1510, 1241, 1048, 737, 695 cm^{-1} ; 1H NMR (500 MHz, CD_3CN , 1:1 mixture of diastereomers) δ 8.89 (br s, 1 H), 7.35–7.25 (m, 5 H), 6.98 (d, J = 6.6 Hz, 1 H), 6.95 (s, 1 H), 6.88 (t, J = 6.5 Hz, 1 H), 6.80 (dd, J = 12.0, 5.8 Hz, 1 H), 6.72 (d, J = 6.9 Hz, 1 H), 5.63 (dd, J = 19.4, 7.3 Hz, 1 H), 4.96 (s, 2 H), 4.78 (s, 1 H), 3.76–3.71 (m, 1 H), 3.47–3.42 (m, 2 H), 3.12 (br s, 1 H), 2.72 (m, 1 H), 2.54 (m, 1 H), 2.35 (br s, 2 H); ^{13}C NMR (125 MHz, CD_3CN , 1:1 mixture of diastereomers) δ 178.5, 157.1, 154.1, 142.4, 138.2, 132.5, 132.4, 131.3, 131.2, 130.6, 129.2, 128.6, 128.4, 128.3, 124.2, 124.1 (2 C), 124.0, 116.4, 102.5, 66.6, 64.2, 55.5, 50.7, 36.7 (2 C); HRMS (MALDI-FTMS) calcd for $C_{25}H_{23}BrN_2O_5Na^+$ $[M + Na^+]$ 533.0682, found 533.0686. With this operation complete, the new intermediate (45.0 g, 90.5 mmol, 1.0 equiv) was dissolved in acetone (200 mL) and treated sequentially with 2,2-dimethoxypropane (111.3 mL, 905 mmol, 10 equiv) and *p*-TsOH (0.300 g, catalytic) at 25 °C. After stirring the resultant mixture for 2 hours at 25 °C, the reaction flask contents were poured into water (200 mL) and extracted with EtOAc (3 $\times$ 200 mL). The combined organic layers were then washed with water (200 mL) and brine (200 mL), dried

(MgSO₄), and concentrated. The resultant brown residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 3:2) to give acetonide **14** (47.5 g, 98% yield) as a light brown solid. **14**: R_f = 0.60 (silica gel, EtOAc/hexanes, 2:3); IR (film) ν_{max} 3215, 2981, 1698, 1613, 1452, 1406, 1351, 1241, 1208, 1092, 1052, 738 cm⁻¹; ¹H NMR (500 MHz, CD₃CN, 1:1 mixture of diastereomers) δ 8.78 (br s, 1 H), 7.38–7.25 (m, 5 H), 7.03–6.97 (m, 3 H), 6.83 (dd, J = 12.1, 6.6 Hz, 1 H), 6.73 (d, J = 6.5 Hz, 1 H), 5.05 (m, 2 H), 4.70 (m, 1 H), 4.03 (m, 1 H), 3.81 (m, 1 H), 3.81 (d, J = 5.0 Hz, 1 H), 3.73 (dd, J = 13.5, 6.9 Hz, 1 H), 2.87–2.85 (m, 1 H), 2.62–2.60 (m, 1 H), 1.44–1.42 (m, 6 H); ¹³C NMR (125 MHz, CD₃CN, 1:1 mixture of diastereomers) δ 178.3, 154.0, 152.9, 142.4, 137.9, 132.4, 131.4, 130.9, 130.7, 129.3, 128.9, 128.8, 127.0, 124.4, 124.2, 124.1, 116.6, 102.6, 94.7, 67.0, 59.5, 55.2, 50.7, 50.6, 39.2, 26.8, 24.8, 23.3; HRMS (MALDI-FTMS) calcd for C₂₅H₂₃BrN₂O₅Na⁺ [M + Na⁺] 573.0995, found 573.0997.

Hydroxymethylated adduct 15. Et₃N (9.1 mL, 90.5 mmol, 6.0 equiv) and TMSCl (7.8 g, 72.4 mmol, 4.0 equiv) were added sequentially to a solution of acetonide **14** (10 g, 18.1 mmol, 1.0 equiv) in CH₂Cl₂ (250 mL) at 0 °C. After stirring the resultant mixture for 2 hours at 0 °C, the reaction flask contents were poured into water and extracted with CH₂Cl₂ (2 × 250 mL). The combined organic layers were then washed with water (2 × 250 mL) and brine (250 mL), dried (MgSO₄), and concentrated to give the desired intermediate silylenol ether (12.0 g, 94% yield) as a light yellow solid. Pressing forward without any additional purification, this new compound (12.0 g, 17.1 mmol, 1.0 equiv) was dissolved in THF (50 mL) and treated sequentially with formalin (5.1 g, 37% in water, 171.1 mmol, 10 equiv) and Yb(OTf)₃ (2.6 g, 4.2 mmol, 0.25 equiv) at 25 °C. The resultant mixture was stirred for 24 hours at 25 °C. Upon completion, the reaction flask contents were poured into water (200 mL) and extracted with CH₂Cl₂ (3 × 100 mL). The combined organic layers were then washed with saturated aqueous NaHCO₃ (200 mL), water (200 mL), and brine (200 mL), dried (MgSO₄), and concentrated. The resultant brown residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:2→3:2) to give hydroxymethylated adduct **15** (7.38 g, 70% yield overall from **14**) as a light

yellow solid. **15**: R_f = 0.30 (silica gel, EtOAc/hexanes, 3:2); IR (film) $\nu_{\max}$ 3260, 2875, 1694, 1611, 1408, 1350, 1242, 1210, 1168, 1049 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN , 1:1 mixture of diastereomers) δ 8.71 (s, 1 H), 7.80 (d, J = 26.3 Hz, 1 H), 7.55–7.33 (m, 5 H), 7.06 (d, J = 13.1 Hz, 1 H), 6.97 (d, J = 5.4 Hz, 1 H), 6.88 (dd, J = 13.1, 6.9 Hz, 1 H), 6.83–6.69 (m, 1 H), 5.15–4.94 (m, 2 H), 4.25–4.20 (m, 1 H), 4.15–4.04 (m, 2 H), 3.85 (s, 1 H), 3.75 (dd, J = 9.8, 8.0 Hz, 1 H), 3.12–3.09 (d, J = 13.3 Hz, 1 H), 2.90 (d, J = 11.3 Hz, 1 H), 2.68–2.64 (m, 1 H), 1.43 (m, 6 H); ^{13}C NMR (125 MHz, CD_3CN , 1:1 mixture of diastereomers) δ 180.3, 154.1, 152.5, 142.4, 137.5, 133.7, 132.8, 131.1, 130.2, 129.6, 128.9, 128.4, 128.3, 126.4, 124.3, 123.7, 116.8, 114.2, 102.2 (2 C), 94.3, 94.1, 66.9, 66.7, 66.5, 65.5, 39.0, 37.6, 29.7, 27.0, 26.3; HRMS (MALDI-FTMS) calcd for $\text{C}_{29}\text{H}_{29}\text{BrN}_2\text{O}_6\text{Na}^+$ [$\text{M} + \text{Na}^+$] 603.1101, found 603.1084.

TBS-protected phenol 16. Imidazole (7.81 g, 115.1 mmol, 8.0 equiv) and TBSCl (8.63 g, 57.5 mmol, 4.0 equiv) were added sequentially to a solution of alcohol **15** (10.0 g, 14.3 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) at 25 °C. After 6 hours of stirring at 25 °C, the reaction mixture was poured into saturated aqueous NaHCO_3 (100 mL) and extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were then washed with water (200 mL) and brine (200 mL), dried (MgSO_4), and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4) to give the desired bis-TBS protected intermediate (10.7 g, 84% yield) as a white solid: R_f = 0.81 (silica gel, EtOAc/hexanes, 1:3); IR (film) $\nu_{\max}$ 3250, 2950, 2927, 1716, 1699, 1614, 1498, 1470, 1404, 1252, 1092, 907, 834, 776 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN , 1:1 mixture of diastereomers) δ 8.53 (s, 1 H), 7.42–7.19 (m, 7 H), 7.00–6.93 (m, 1 H), 6.78 (dd, J = 14.0, 6.6 Hz, 1 H), 6.70 (t, J = 7.8 Hz, 1 H), 5.15–4.95 (m, 2 H), 4.28 (t, J = 8.3 Hz, 1 H), 4.17 (dd, J = 8.7, 5.2 Hz, 1 H), 4.16–4.13 (m, 1 H), 3.90 (dd, J = 8.1, 6.1 Hz, 1 H), 3.82 (d, J = 8.7 Hz, 1 H), 3.08–2.98 (m, 1 H), 2.74–2.70 (m, 1 H), 1.56–1.51 (m, 6 H), 0.70 (s, 9 H), 0.67 (s, 9 H), 0.12 (s, 3 H), –0.02 (s, 3 H), –0.09 (s, 3 H), –0.22 (s, 3 H); ^{13}C NMR (150 MHz, CD_3CN , 1:1 mixture of diastereomers) δ 178.4, 152.5, 143.0, 137.7, 135.2, 130.8, 130.4, 129.5, 128.9, 128.6, 128.5, 128.3, 128.1, 128.0, 123.0, 122.5 (2 C), 119.5, 102.2, 94.3, 67.8 (2 C), 67.0, 66.5, 66.4, 64.8, 60.4, 59.7, 58.9, 57.6, 26.5, 26.4, 25.9, 25.6, 25.4,

22.9, 19.1, 13.9, 17.9, -3.9, -4.1, -6.0, -6.1; HRMS (MALDI-FTMS) calcd for $C_{41}H_{57}BrN_2O_6Si_2Na^+$ $[M + Na^+]$ 831.2831, found 831.2828. With this operation completed, the bis-silylated intermediate (12.0 g, 13.0 mmol, 1.0 equiv) was dissolved in DMF (30 mL) and treated with LiOH (1.01 g, 39.0 mmol, 3.0 equiv) at 25 °C. After stirring the resultant slurry for 5 hours at 25 °C, the reaction flask contents were poured into EtOAc (200 mL), washed with water (200 mL) and brine (200 mL), dried ($MgSO_4$), and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:2) to give TBS-protected phenol **16** (9.01 g, 80% yield) as a white solid. **16**: R_f = 0.35 (silica gel, EtOAc/hexanes, 1:2); IR (film) ν_{max} 3190, 2950, 2885, 1695, 1471, 1247, 1093, 834, 775 cm^{-1} ; 1H NMR (600 MHz, CD_3CN , 1:1 mixture of diastereomers) δ 8.73 (s, 1 H), 7.87 (d, J = 34.6 Hz, 1 H), 7.40–7.25 (m, 6 H), 7.08 (d, J = 5.8 Hz, 1 H), 6.98 (d, J = 7.0 Hz, 1 H), 6.90 (t, J = 7.4 Hz, 1 H), 6.86 (t, J = 8.3 Hz, 1 H), 6.72–6.68 (m, 1 H), 5.10–4.96 (m, 2 H), 4.36 (d, J = 9.1 Hz, 1 H), 4.25 (t, J = 7.4 Hz, 1 H), 4.09–4.04 (m, 1 H), 3.87–3.85 (m, 1 H), 3.76 (dd, J = 11.8, 9.6 Hz, 1 H), 3.10–2.90 (m, 1 H), 2.65 (m, 1 H), 1.52–1.43 (m, 6 H), 0.69 (s, 9 H), -0.02 (s, 3 H), -0.06 (s, 3 H); ^{13}C NMR (150 MHz, CD_3CN , 1:1 mixture of diastereomers) δ 180.0, 154.0, 152.5, 142.8, 137.6, 134.2, 133.9, 130.9, 130.3, 130.1, 130.0, 129.4, 128.9, 128.3, 128.1, 128.0, 124.1, 123.6 (2 C), 123.4, 117.0, 102.1, 94.3, 66.8, 66.4, 59.6, 58.9, 39.0, 37.7, 27.3, 26.3, 25.3, 24.3, 22.8, 17.8, -6.2 (2 C); HRMS (MALDI-FTMS) calcd for $C_{35}H_{43}BrN_2O_6Na^+$ $[M + Na^+]$ 717.1966, found 717.1964.

Di-benzylated lactam 17. KF•alumina (4.9 g, 40%, 86.5 mmol, 5.0 equiv) and benzyl bromide (11.7 g, 69.3 mmol, 4.0 equiv) were added sequentially to a solution of phenol **16** (14.0 g, 17.3 mmol, 1.0 equiv) in DME (100 mL) at 25 °C, and the resultant slurry was stirred for 12 hours. Upon completion, the reaction mixture was filtered through Celite (using extensive EtOAc washes to ensure high yield) and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4) to give di-benzylated lactam **17** (14.9 g, 85% yield) as a white solid. **17**: R_f = 0.71 (silica gel, EtOAc/hexanes, 1:4); IR (film) ν_{max} 2947, 2927, 1698, 1605, 1497, 1461, 1404, 1337, 1251, 1092, 1006, 834, 729, 694 cm^{-1} ; 1H

NMR (500 MHz, CD₃CN, 1:1 mixture of diastereomers) δ 7.40–7.30 (m, 10 H), 7.25–7.16 (m, 5 H), 7.02 (t, J = 6.9 Hz, 1 H), 6.91–6.79 (m, 5 H), 5.10 (dd, J = 23.7, 12.8 Hz, 1 H), 4.98 (d, J = 10.2 Hz, 0.5 H), 4.88 (d, J = 10.2 Hz, 0.5 H), 4.75–4.72 (m, 2 H), 4.68 (t, J = 9.1 Hz, 1 H), 4.42 (d, J = 7.3 Hz, 1 H), 4.35 (d, J = 13.5 Hz, 1 H), 4.32 (d, J = 7.3 Hz, 1 H), 4.20–4.12 (m, 1 H), 3.91 (dd, J = 10.5, 5.1 Hz, 1 H), 3.83 (d, J = 7.3 Hz, 1 H), 3.13–2.96 (m, 1 H), 2.84–2.74 (m, 1 H), 1.48–1.46 (m, 6 H), 0.73 (s, 9 H), –0.03 (s, 3 H), –0.09 (s, 3 H); ¹³C NMR (150 MHz, CD₃CN, 1:1 mixture of diastereomers) δ 180.1, 155.2, 153.0, 143.4, 139.6, 137.0, 136.8, 135.4, 133.9, 131.5, 131.3, 130.6, 130.4, 129.6, 129.3, 129.1, 129.0, 128.9, 128.8, 128.6, 128.5, 127.7, 127.4, 127.3, 123.9, 123.2, 118.2, 113.0, 102.2, 94.8, 70.8, 68.6 (2 C), 67.5, 66.9 (2 C), 60.1, 59.5 (2 C), 56.1, 45.6, 39.6, 27.0, 26.0, 24.9, 23.4, 18.8, 5.3; HRMS (MALDI-FTMS) calcd for C₄₉H₅₅BrN₂O₆SiNa⁺ [M + Na⁺] 897.2905, found 897.2885.

Indoline 7. 9-BBN (171 mL, 0.5 M solution in THF, 85.5 mmol, 5.0 equiv) was added dropwise over the course of 1 hour to a solution of lactam **17** (15 g, 17.1 mmol, 1.0 equiv) in THF (50 mL) at 25 °C. Once this operation was complete, the reaction mixture was warmed to 65 °C and stirred for an additional 36 hours. The reaction mixture was then cooled to 25 °C, concentrated, taken up in MeOH (50 mL), and treated with L-lysine (14.0 g, 85.5 mmol, 5.0 equiv). The resultant slurry was heated to reflux and stirred for ~1 hour (or until all suspended material had dissolved). The reaction flask contents were then cooled to 25 °C, poured into Et₂O (300 mL), washed extensively with 15% aqueous NaOH (6 × 100 mL), dried (MgSO₄), and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 0:1→1:9) to give indoline **7** (10.6 g, 72% yield) as a waxy white solid. **7**: R_f = 0.27 (silica gel, EtOAc/hexanes, 1:9); IR (film) $\nu_{\max}$ 3436, 2919, 2848, 1701, 1607, 1443, 1406, 1353, 1255, 1049, 1025, 843, 773, 702 cm⁻¹; ¹H NMR (600 MHz, CD₃CN, 1:1 mixture of diastereomers) δ 7.40–7.15 (m, 15 H), 7.10–7.01 (m, 3 H), 6.90–6.85 (m, 3 H), 6.58–6.54 (m, 1 H), 5.14–4.98 (m, 2 H), 4.88 (d, J = 11.4 Hz, 1 H), 4.76 (t, J = 14.4 Hz, 1 H), 4.15 (dd, J = 21.4, 15.8 Hz, 1 H), 4.10–4.02 (m, 1 H), 3.99–3.95 (m, 1 H), 3.85 (dd, J = 17.1, 10.0 Hz, 1 H), 3.79 (dd, J = 14.4, 7.2 Hz, 1 H), 3.72 (t, J = 6.9 Hz, 1 H), 3.60 (t, J = 10.0 Hz, 1 H), 3.55–3.54 (m, 2

H), 3.05–2.85 (m, 1 H), 2.58 (dd, $J = 11.7, 6.4$ Hz, 1 H), 1.52–1.50 (m, 6 H), 0.74 (s, 9 H), –0.12 (s, 3 H), –0.18 (s, 3 H); ^{13}C NMR (150 MHz, CD_3CN , 1:1 mixture of diastereomers) δ 156.1, 152.9, 150.3, 140.3, 139.2, 138.1, 137.7, 133.6, 132.2, 129.7, 130.6, 129.3, 129.1, 128.8, 128.6, 128.5 (2 C), 128.4, 128.3, 127.6, 125.3, 125.0, 119.9, 118.1, 113.5, 103.5, 90.5, 70.6, 68.1, 67.3, 67.2 (2 C), 66.8, 66.7, 63.2, 59.5, 54.9, 42.3, 39.6, 38.3, 27.7, 26.9, 26.0, 24.8, 23.3, 18.6, –5.3, –5.6; HRMS (MALDI-FTMS) calcd for $\text{C}_{49}\text{H}_{57}\text{BrN}_2\text{O}_5\text{SiNa}^+$ [$\text{M} + \text{Na}^+$] 883.3112, found 831.3082.

Lactam 20. TBAF (0.223 mL, 1.0 M in THF, 0.223 mmol, 1.3 equiv) was added to a solution of di-benzylated lactam **17** (0.150 g, 0.171 mmol, 1.0 equiv) in THF (10 mL) at 0 °C, and the resultant solution was stirred for 1 hour. Upon completion, the reaction flask contents were poured into saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were then washed with water (20 mL) and brine (20 mL), dried (MgSO_4), and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:10) to give the dehydroxymethylated lactam **20** (0.119 g, 95% yield) as a white amorphous solid. **20**: $R_f = 0.35$ (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2948, 1704, 1493, 1451, 1377, 1246, 1099, 1017, 706, 605 cm^{-1} ; ^1H NMR (500 MHz, 323 K, CD_3CN , 1:1 mixture of diastereomers) δ 7.46–7.34 (m, 6 H), 7.31–7.23 (m, 5 H), 7.15 (br d, $J = 5.9$ Hz, 2 H), 7.06–7.03 (m, 2 H), 6.96 (t, $J = 7.7$ Hz, 1 H), 5.14 (AB, $J = 16.9$ Hz, $\nu_{\text{ab}} = 60.2$ Hz, 2 H), 4.97 (AB, $J = 11.8$ Hz, $\nu_{\text{ab}} = 29.4$ Hz, 2 H), 4.92 (br s, 1 H), 4.18 (m, 1 H), 3.97 (m, 1 H), 3.88 (ddd, $J = 8.8, 4.8, 1.5$ Hz, 1 H), 3.70 (br s, 1.5 H), 3.65 (br s, 1.5 H), 3.09 (br t, $J = 6.4$ Hz, 1 H), 2.84 (m, 1 H), 1.60–1.54 (m, 6 H); ^{13}C NMR (150 MHz, 323 K, CD_3CN , 1:1 mixture of diastereomers) δ 177.9, 157.8, 142.0, 139.3, 137.6, 134.2, 134.0 (2 C), 132.0, 131.0, 130.9, 129.4, 129.2, 128.7, 128.5, 127.6, 126.6, 124.4, 123.9, 113.5, 113.4, 102.4, 94.7, 70.9, 67.3, 59.6, 52.2, 49.6, 45.3; HRMS (MALDI-FTMS) calcd for $\text{C}_{36}\text{H}_{35}\text{BrN}_2\text{O}_5\text{Na}^+$ [$\text{M} + \text{Na}^+$] 677.1621, found 677.1613.

Suzuki coupling product 21. $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (0.325 g, 0.4 mmol, 0.2 equiv), K_2CO_3 (1.374 g, 10.0 mmol, 5.0 equiv), and boronate **6** (2.056 g, 2.1 mmol, 1.05 equiv) were

added sequentially to a flask containing indoline **7** (1.280 g, 2.0 mmol, 1.0 equiv). This vessel was then equipped with a reflux condenser, and degassed DME (15 mL, prepared by three iterations of the freeze-thaw method) was added at 25 °C. The reaction flask contents were then heated at reflux for 12 hours. Upon completion, the reaction mixture was diluted with EtOAc (50 mL), filtered through a short plug of silica, and concentrated. The resultant brown residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:3) to give Suzuki coupling adduct **21** (1.982 g, 78% yield) as a pale yellow solid. **21**: R_f = 0.72 (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\max}$ 3072, 2943, 2872, 1708, 1408, 1349, 1086 cm^{-1} ; ^1H NMR (600 MHz, 323 K, CD_3CN , 1:1 mixture of diastereomers) δ 7.71 (app t, J = 8.2 Hz, 2 H), 7.64 (app t, J = 8.3 Hz, 2 H), 7.47–7.29 (m, 17 H), 7.27–7.23 (m, 2 H), 7.14 (m, 1 H), 7.04–6.95 (m, 7 H), 6.87–6.83 (m, 2 H), 6.73 (m, 1 H), 6.66–6.62 (m, 2 H), 5.79 (d, J = 12.0 Hz, 1 H), 5.50–5.42 (m, 3 H), 5.18–5.10 (m, 2 H), 4.95–4.90 (m, 1 H), 4.84–4.78 (m, 1 H), 4.62 (d, J = 11.0 Hz, 0.5 H), 4.60 (d, J = 10.9 Hz, 0.5 H), 4.35–4.35 (m, 1H), 4.07 (m, 1 H), 3.97 (d, J = 8.8 Hz, 0.5 H), 3.85–3.78 (m, 2 H), 3.73 (dd, J = 8.4, 6.3 Hz, 0.5 H), 3.62 (d, J = 12.1 Hz, 0.5 H), 3.55 (d, J = 9.2 Hz, 0.5 H), 3.49–3.42 (m, 1 H), 3.33–3.30 (m, 1 H), 3.20 (s, 1.5 H), 1.31 (s, 1.5 H), 2.97 (m, 1 H), 2.80 (m, 1 H), 1.52–1.46 (m, 6 H), 1.06–1.01 (m, 9 H), 0.73–0.71 (m, 9 H), –0.05 (m, 1.5 H), –0.15 (s, 1.5 H), –0.24 (m, 3 H); ^{13}C NMR (150 MHz, 323 K, CD_3CN , 1:1 mixture of diastereomers) δ 164.0, 160.5, 156.5, 150.9, 148.3, 140.0, 138.2, 138.0, 137.9, 136.4, 136.3, 134.0, 131.8, 131.6, 130.8, 129.6, 129.3, 129.2, 128.5, 128.2, 127.2, 125.3, 124.5, 123.4, 113.8, 113.7, 113.4, 113.3, 110.4, 106.8, 94.8, 78.3, 70.9, 69.4, 69.3, 68.2, 68.1, 67.0, 63.9, 62.3, 59.5, 56.1, 55.8, 55.7, 55.3, 55.2, 53.8, 53.7, 27.1, 26.1, 19.7, 18.6, 18.5, –5.2, –5.4, –5.5; HRMS (MALDI-FTMS) calcd for $\text{C}_{79}\text{H}_{89}\text{N}_4\text{O}_8\text{Si}_2^+$ [$\text{M} + \text{H}^+$] 1277.6213, found 1277.6208.

Oxime 5. Suzuki coupling product **21** (15.0 g, 11.7 mmol, 1.0 equiv) was dissolved in THF (100 mL) and treated with TBAF (70.0 mL, 1.0 M in THF, 70.0 mmol, 6.0 equiv) at 25 °C. After stirring for 20 minutes at 25 °C, the reaction solution was warmed to 45 °C and stirred for 2 additional hours. Upon completion, the reaction was quenched by the addition of saturated aqueous NH_4Cl (100 mL), poured into water (100 mL), and extracted with EtOAc (3 $\times$ 100 mL).

The combined organic layers were then washed with water (100 mL) and brine (100 mL), dried (MgSO_4), and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 5:1) to give the desired intermediate diol (10.2 g, 94% yield) as a yellow amorphous solid: $R_f = 0.29$ (silica gel, EtOAc/hexanes, 4:1); IR (film) ν_{max} 3311, 3030, 2930, 2871, 1695, 1403, 1352 cm^{-1} ; ^1H NMR (600 MHz, 323 K, CD_3CN , 1:1 mixture of diastereomers) δ 7.56 (s, 1 H), 7.47 (d, $J = 8.3$ Hz, 1 H), 7.37–7.15 (m, 14 H), 7.07–6.98 (m, 7 H), 6.95 (d, $J = 8.3$ Hz, 1 H), 6.79 (t, $J = 7.6$ Hz, 1 H), 6.68 (d, $J = 3.5$ Hz, 1 H), 5.95 (s, 1 H), 5.53–5.44 (m, 3 H), 5.10 (m, 2 H), 4.96 (d, $J = 11.9$ Hz, 1 H), 4.81 (dd, $J = 11.9, 2.2$ Hz, 1 H), 4.43 (s, 2 H), 4.06 (m, 1 H), 3.89–3.84 (m, 2 H), 3.77 (t, $J = 9.7$ Hz, 1 H), 3.60 (m, 1 H), 3.48 (dd, $J = 8.4, 6.4$ Hz, 0.5 H), 3.44 (dd, $J = 8.4, 2.2$ Hz, 0.5 H), 3.31 (m, 1 H), 3.15 (s, 3 H), 3.14 (d, $J = 11.4$ Hz, 0.5 H), 3.11 (d, $J = 11.4$ Hz, 0.5 H), 2.93 (m, 1.5 H), 2.80 (m, 0.5 H), 2.69 (m, 0.5 H), 2.58 (m, 0.5 H), 1.47–1.45 (m, 6 H); ^{13}C NMR (150 MHz, 323 K, CD_3CN , 1:1 mixture of diastereomers) δ 162.5, 156.5, 153.2, 151.2, 147.9, 140.1, 138.2, 137.8, 134.4, 133.2, 131.5, 131.4, 131.0, 129.8, 129.7, 129.5, 129.3, 128.7, 128.6, 128.5, 127.2, 125.7, 125.5, 124.3, 123.5, 123.4, 110.5, 106.4, 94.8, 78.3, 71.0, 67.1, 66.5, 63.1, 59.7, 57.5, 56.1, 55.3, 53.8, 27.0, 20.7, 13.7; HRMS (MALDI-FTMS) calcd for $\text{C}_{57}\text{H}_{57}\text{N}_4\text{O}_8^+$ $[\text{M} + \text{H}^+]$ 925.4171, found 925.4184. Next, Et_3N (1.6 mL, 11.0 mmol, 10 equiv) and $\text{SO}_3 \cdot \text{pyridine}$ (1.445 g, 9.1 mmol, 8.3 equiv) were added sequentially to a solution of the newly-formed diol (1.050 g, 1.1 mmol, 1.0 equiv) in $\text{CH}_2\text{Cl}_2/\text{DMSO}$ (1:1, 12 mL) at 0 °C. After stirring the resultant solution for 2 hours at 0 °C, the reaction mixture was diluted with EtOAc (30 mL), poured into saturated aqueous NH_4Cl (40 mL), and extracted with EtOAc (3×25 mL). The combined organic layers were then washed with water (100 mL) and brine (100 mL), dried (MgSO_4), and concentrated to give the desired dialdehyde (0.951 g, 91% yield) as a fluorescent yellow solid. Carrying this material forward without any additional purification, this new compound (0.951 g, 1.03 mmol, 1.0 equiv) was dissolved in DMSO (10 mL) and treated with $\text{MeONH}_2 \cdot \text{HCl}$ (0.431 g, 5.16 mmol, 5.0 equiv) at 25 °C. After stirring the resultant solution for 15 minutes at 25 °C, during which time the reaction color changed from bright yellow to clear, the contents were poured into water (25 mL)

and extracted with EtOAc (3×25 mL). The combined organic extracts were then washed with water (3×25 mL), dried (MgSO_4) and concentrated. The resultant light yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 5:1) to give the aldehyde-oxime **5** (0.895 g, 83% yield over two steps) as a light yellow foam. **5**: $R_f = 0.58$ (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3029, 2935, 2873, 1696, 1590, 1402, 1050 cm^{-1} ; ^1H NMR (600 MHz, 323 K, CD_3CN , 1:1 mixture of diastereomers) δ 9.51 (s, 0.5 H), 9.50 (s, 0.5 H), 7.78 (s, 1 H), 7.63 (d, $J = 4.9$ Hz, 1 H), 7.53 (d, $J = 8.0$ Hz, 1 H), 7.40–7.23 (m, 12 H), 7.17 (t, $J = 6.4$ Hz, 1 H), 7.10–7.01 (m, 7 H), 6.89 (m, 2 H), 6.78 (br t, $J = 5.2$ Hz, 1 H), 6.71 (d, $J = 4.8$ Hz, 1 H), 6.14 (br s, 0.5 H), 6.04 (d, $J = 11.0$ Hz, 0.5 H), 5.52–5.50 (m, 3 H), 5.24–5.05 (m, 2 H), 4.94 (s, 2 H), 4.21–4.14 (m, 1 H), 4.09–4.07 (m, 1 H), 3.97–3.92 (m, 1 H), 3.86 (m, 2 H), 3.78 (d, $J = 6.4$ Hz, 0.5 H), 3.71 (app t, $J = 4.6$ Hz, 0.5 H), 3.42 (m, 1 H), 3.20 (s, 3H), 3.19 (m, 1.5 H), 3.09 (dd, $J = 7.4, 4.4$ Hz, 0.5 H), 2.82 (m, 0.5 H), 2.61 (m, 0.5 H), 1.45–1.42 (m, 6 H); ^{13}C NMR (150 MHz, 323 K, CD_3CN , 1:1 mixture of diastereomers) δ 151.6, 148.5, 139.1, 139.0, 138.9, 137.7, 137.3, 137.2, 137.1, 133.0, 132.8, 132.7, 131.1, 130.9, 130.7, 130.5, 130.2, 128.9, 128.8, 128.3, 128.0, 127.9, 127.7, 127.0, 126.2, 124.9, 124.8, 124.6, 124.4, 123.8, 123.3, 112.9, 112.7, 110.5, 105.3, 105.1, 94.4, 77.9, 70.6, 63.0, 62.8, 62.7, 62.6, 61.9, 61.1, 61.0, 59.1, 55.9, 55.8, 54.7, 54.5, 27.2, 20.7, 17.4; HRMS (MALDI-FTMS) calcd for $\text{C}_{58}\text{H}_{55}\text{N}_5\text{O}_8\text{Na}^+$ [$\text{M} + \text{Na}^+$] 972.3943, found 972.3974.

SmI₂ solution (0.1 M in THF). To a suspension of samarium powder (0.825 g, 20 mesh, 5.41 mmol, 1.1 equiv) in freshly degassed THF (50 mL) was quickly added a concentrated solution of $\text{ICH}_2\text{CH}_2\text{I}$ (0.150 g) in THF (1.5 mL) at 25 °C, yielding a deep blue solution after 5 minutes of stirring. Once this task was accomplished, a second portion of $\text{ICH}_2\text{CH}_2\text{I}$ (1.25 g, 4.97 mmol total for both portions, 1.0 equiv total for both portions) in THF (48.5 mL) was added dropwise at 25 °C at a rate such that no yellow precipitates were formed (corresponding to the generation of SmI_3). Once this second addition was complete, the dark blue reaction solution was stirred for an additional 10 hours at 25 °C before use in any hetero-pinacol coupling reaction.

Hetero-pinacol cyclized product 4. Freshly prepared SmI_2 solution (100 mL, 0.1 M in THF, 10.0 mmol) was transferred via an argon-flushed syringe to an evacuated round-bottom flask. Once this operation was complete, DMA (3.9 mL, 40.0 mmol) was then added dropwise at 25 °C over the course of 5 minutes, and the resultant reddish-purple solution was stirred for 10 additional minutes at 25 °C. A portion of this newly formed reducing complex (7.6 mL, 0.756 mmol, 9.0 equiv) was then added dropwise over the course of 1 hour to a solution of oxime **5** (0.080 mg, 0.084 mmol, 1.0 equiv) in degassed THF (50 mL) at 25 °C. When the addition was complete, the reaction solution was a deep blue color, indicating that there was still excess SmI_2 /DMA present (Note: if the color was not deep blue, then an additional 1 to 2 mL portion of the SmI_2 /DMA complex was added dropwise to the reaction mixture). After stirring for an additional 30 minutes at 25 °C, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (20 mL), stirred for 1 hour at 25 °C, poured into brine (20 mL), and extracted with CH_2Cl_2 (8×100 mL). The combined organic extracts were then dried (MgSO_4) and concentrated to give the intermediate hetero-pinacol coupled amino alcohol. Pressing forward without any additional purification steps, this compound was dissolved in DMF (0.5 mL) and treated with a DMF solution (1 mL) containing Fmoc-protected L-valine (0.086 g, 0.25 mmol, 3.0 equiv), EDC $\cdot\text{H}_2\text{O}$ (0.048 g, 0.25 mmol, 3.0 equiv), and HOBt $\cdot\text{H}_2\text{O}$ (0.039 g, 0.25 mmol, 3.0 equiv) which had already been stirring at 25 °C for 30 minutes. Once this operation was complete, the resultant yellow mixture was stirred for 12 hours at 25 °C before it was diluted with EtOAc (5 mL), quenched with 10% aqueous HCl (5 mL), and extracted with EtOAc (3×50 mL). The combined organic extracts were then dried (MgSO_4) and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}/\text{hexanes}$, 5:5:4) to give hetero-pinacol coupled product **4** (0.052 g, 50% yield overall) as a yellow solid. **4**: R_f = 0.23 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3305, 2931, 2872, 1700, 1494, 1091 cm^{-1} ; ^1H NMR (600 MHz, 323 K, CD_3CN , several diastereomers) δ 7.80 (d, J = 7.4 Hz, 2 H), 7.61 (d, J = 7.9 Hz, 2 H), 7.49 (d, J = 7.9 Hz, 1 H), 7.43 (br s, 1 H), 7.39–7.23 (m, 13 H), 7.21–7.17 (m, 4 H), 7.06 (dd, J = 7.9, 7.7 Hz, 3 H), 6.96 (m, 2 H), 6.93–6.86 (m, 3 H), 6.51 (m, 2 H),

6.35 (d, $J = 4.2$ Hz, 1 H), 5.72 (br s, 1 H), 5.50–5.45 (m, 3 H), 5.14–5.04 (m, 2 H), 4.99 (dd, $J = 17.8, 6.6$ Hz, 1 H), 4.94 (m, 1 H), 4.85 (d, $J = 7.4$ Hz, 0.5 H), 4.83 (d, $J = 7.0$ Hz, 0.5 H), 4.32–4.29 (m, 2 H), 4.17–4.12 (m, 3 H), 4.00 (br d, $J = 11.4$ Hz, 1 H), 3.95 (br d, $J = 11.4$ Hz, 1 H), 3.87 (dd, $J = 8.8, 5.7$ Hz, 0.5 H), 3.84 (dd, $J = 8.7, 5.7$ Hz, 0.5 H), 3.77 (d, $J = 9.2$ Hz, 0.5 H), 3.72 (d, $J = 8.8$ Hz, 0.5 H), 3.69 (d, $J = 3.0$ Hz, 0.5 H), 3.66 (d, $J = 3.1$ Hz, 0.5 H), 3.50 (d, $J = 10.5$ Hz, 0.5 H), 3.42 (d, $J = 11.0$ Hz, 0.5 H), 3.29 (m, 2 H), 3.25 (s, 3 H), 2.98 (m, 0.5 H), 2.88 (m, 0.5 H), 2.68 (d, $J = 9.2$ Hz, 0.5 H), 2.66 (d, $J = 9.1$ Hz, 0.5 H), 2.12 (m, 1 H), 1.43–1.41 (m, 6 H), 0.86–0.83 (m, 6 H); ^{13}C NMR (150 MHz, 323 K, CD_3CN , several diastereomers) δ 130.8, 130.3, 129.6, 129.4, 129.3, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 127.9, 127.5, 127.4, 126.8, 126.7, 126.0, 123.5, 123.0, 120.7, 116.5, 116.4, 114.3, 110.6, 104.5, 94.8, 78.4, 77.7, 77.5, 71.1, 67.4, 63.9, 63.8, 56.3, 55.7, 54.5, 48.8, 48.6, 31.7, 31.5, 19.5, 19.3, 18.0; HRMS (MALDI-FTMS) calcd for $\text{C}_{77}\text{H}_{75}\text{N}_6\text{O}_{10}^+$ [$\text{M} + \text{H}^+$] 1243.5539, found 1243.5523.

Keto amide 22. To a solution of hetero-pinacol coupling product **4** (0.120 g, 0.096 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added 4Å molecular sieves (spatula tip full) at 25 °C, and the resultant slurry was stirred for 10 minutes. Once this operation was complete, NMO (0.060 g, 0.480 mmol, 5.0 equiv) and TPAP (0.030 g, 0.096 mmol, 1.0 equiv) were added sequentially at 25 °C, and the resultant mixture was stirred for 2 hours at 25 °C. Upon completion, the reaction flask contents were filtered through a pad of silica gel (using extensive washes with CH_2Cl_2 to ensure high yield) and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:5→1:1) to give keto amide **22** (0.078 g, 65% yield) as a yellow solid. **22**: $R_f = 0.48$ (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2933, 2875, 1699, 1494, 1352, 1211, 1091 cm^{-1} ; ^1H NMR (600 MHz, 323 K, CD_3CN , several diastereomers) δ 7.81 (dd, $J = 7.4, 2.6$ Hz, 2 H), 7.66 (m, 2 H), 7.53 (d, $J = 8.3$ Hz, 1 H), 7.49 (d, $J = 4.4$ Hz, 1 H), 7.40–7.23 (m, 13 H), 7.20–7.14 (m, 4 H), 7.10–7.05 (m, 3 H), 6.99 (m, 1 H), 6.90 (m, 0.5 H), 6.89 (s, 0.5 H), 6.82–6.72 (m, 4 H), 6.66 (m, 1 H), 6.31 (s, 1 H), 6.00 (m, 1 H), 5.98 (br s, 0.5 H), 5.71 (br s, 0.5 H), 5.52 (AB, $J = 11.0$ Hz, $\nu_{\text{ab}} = 36.0$ Hz, 2 H), 5.10–5.03 (m, 2 H), 4.92–4.87 (m, 2 H), 4.73 (dd, $J = 12.3, 4.4$ Hz, 1 H), 4.40 (m, 1.5 H),

4.30 (dd, $J = 10.5, 7.0$ Hz, 0.5 H), 4.24 (app t, $J = 7.0$ Hz, 1 H), 4.08 (m, 1.5 H), 3.98 (m, 0.5 H), 3.88 (m, 2 H), 3.73 (d, $J = 9.2$ Hz, 0.5 H), 3.68 (d, $J = 9.2$ Hz, 0.5 H), 3.61 (d, $J = 10.2$ Hz, 1 H), 3.29 (s, 3 H), 3.19 (d, $J = 12.3$ Hz, 1 H), 2.90 (br m, 0.5 H), 2.82 (br m, 0.5 H), 2.64 (m, 1 H), 2.08 (m, 1 H), 1.47–1.44 (m, 6 H), 0.91 (m, 3 H), 0.87 (d, $J = 7.0$ Hz, 3 H); ^{13}C NMR (150 MHz, 323 K, CD_3CN , several diastereomers) δ 220.6, 200.5, 171.5, 158.0, 157.9, 153.6, 151.1, 151.0, 145.7, 142.1, 137.1, 133.3, 131.9, 129.9, 129.6, 129.5, 129.4, 128.8, 128.5, 128.3, 128.2, 128.0, 127.6, 127.5, 126.9, 126.7, 126.1, 126.0, 125.3, 123.9, 123.6, 120.7, 113.1, 111.0, 104.0, 78.4, 71.3, 71.2, 67.6, 67.4, 64.7, 64.6, 61.6, 56.3, 54.4, 48.1, 31.9, 19.5, 17.9, 17.8; HRMS (MALDI-FTMS) calcd for $\text{C}_{77}\text{H}_{73}\text{N}_6\text{O}_{10}^+$ [$\text{M} + \text{H}^+$] 1241.5382, found 1241.5393.

Oxazole 3. POCl_3 (1.0 mL) was added to a solution of keto amide **22** (0.120 g, 0.097 mmol, 1.0 equiv) in pyridine (2.0 mL) at 25 °C. The resultant solution was then warmed to 70 °C and stirred for 6 hours. Upon completion, the reaction mixture was cooled to 25 °C, diluted with EtOAc (10 mL), poured into a cold (0 °C) solution of saturated aqueous NaHCO_3 (50 mL), and extracted with EtOAc (3×25 mL). The combined organic layers were then washed with water (50 mL) and brine (50 mL), dried (MgSO_4), and concentrated. The resultant dark yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1→2:1) to give oxazole **3** (0.041 g, 35% yield) as an off-white solid along with a significant portion of starting material (0.040 g, 53% yield based on r.s.m.). **3**: $R_f = 0.15$ (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2930, 2871, 1699, 1494, 1352, 1225, 1090 cm^{-1} ; ^1H NMR (600 MHz, 323 K, CD_3CN , 1:1 mixture of diastereomers) δ 7.80 (m, 2 H), 7.65–7.61 (m, 3 H), 7.52 (d, $J = 7.2$ Hz, 1 H), 7.39–7.29 (m, 11 H), 7.21 (br s, 1 H), 7.13–7.04 (m, 4 H), 6.99–6.61 (m, 9 H), 6.61 (m, 3 H), 5.91 (m, 1 H), 5.55 (m, 1 H), 5.44 (m, 2 H), 5.05–4.91 (m, 3 H), 4.43 (app t, $J = 6.4$ Hz, 1 H), 4.21 (m, 2 H), 4.10–4.00 (m, 3 H), 3.88 (d, $J = 14.0$ Hz, 1 H), 3.81 (d, $J = 13.6$ Hz, 1 H), 3.71–3.61 (m, 3 H), 3.21 (s, 3 H), 2.80 (d, $J = 8.7$ Hz, 0.5 H), 2.74 (d, $J = 8.8$ Hz, 0.5 H), 2.65 (d, $J = 6.9$ Hz, 0.5 H), 2.63 (d, $J = 6.9$ Hz, 0.5 H), 1.00 (m, 1 H), 1.41–1.39 (m, 6 H), 0.80 (d, $J = 5.7$ Hz, 1.5 H), 0.78 (d, $J = 5.6$ Hz, 1.5 H), 0.74 (m, 3 H); ^{13}C NMR (150 MHz, 323 K, CD_3CN , 1:1 mixture of diastereomers) δ 130.3, 129.4, 129.1, 128.8, 128.7, 128.6, 128.4, 128.0, 127.8, 127.5,

126.3, 126.2, 126.1, 125.1, 123.8, 123.3, 123.2, 120.8, 119.8, 113.1, 111.1, 104.9, 94.8, 78.2, 70.6, 67.2, 67.0, 66.8, 59.3, 56.3, 55.8, 55.7, 52.4, 47.8, 39.4, 32.3, 32.1, 31.3, 26.7, 26.6, 24.8, 23.3, 19.2, 19.1, 18.4, 18.2, 13.9; HRMS (MALDI-FTMS) calcd for $C_{77}H_{70}N_6O_9Na^+$ [$M + Na^+$] 1245.5096, found 1245.5080.

Macrolactam 24. HF (2.0 mL, 48% in water, excess) was added to a solution of oxazole **3** (0.215 g, 0.180 mmol, 1.0 equiv) in MeCN (4 mL) at 0 °C, and the resultant solution was stirred for 2 hours at 0 °C. Upon completion, the reaction flask contents were diluted with EtOAc (20 mL), basified by the slow and careful addition of saturated aqueous $NaHCO_3$ (25 mL), poured into water (75 mL), and extracted with EtOAc (3×25 mL). The combined organic layers were then washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1→5:1) to give the desired alcohol intermediate (0.198 g, 95% yield) as a light yellow foam: $R_f = 0.36$ (silica gel, EtOAc/hexanes, 5:1); IR (film) ν_{max} 3395, 2924, 2324, 1702, 1493, 1449, 1218 cm^{-1} ; 1H NMR (600 MHz, 323 K, CD_3CN) δ 7.80 (d, $J = 8.4$ Hz, 2 H), 7.61 (m, 3 H), 7.53 (d, $J = 9.7$ Hz, 1 H), 7.39–7.22 (m, 12 H), 7.04–6.93 (m, 6 H), 6.88 (d, $J = 9.2$ Hz, 2 H), 6.63–6.58 (m, 3 H), 5.86 (br s, 1 H), 5.50 (AB, $J = 13.2$ Hz, $\nu_{ab} = 37.9$ Hz, 2 H), 5.43 (br s, 1 H), 5.00–4.93 (m, 4 H), 4.44 (br s, 1 H), 4.29 (m, 1 H), 4.20 (d, $J = 13.6$ Hz, 2 H), 4.11 (m, 1 H), 3.90 (d, $J = 8.8$ Hz, 0.5 H), 3.88 (d, $J = 8.8$ Hz, 0.5 H), 3.76 (m, 2 H), 3.62 (d, $J = 15.0$ Hz, 1 H), 3.47 (m, 2 H), 3.24 (s, 3 H), 2.76 (m, 2 H), 2.65 (dd, $J = 10.7, 7.7$ Hz, 0.5 H), 2.60 (dd, $J = 10.6, 7.7$ Hz, 0.5 H), 2.08 (m, 1 H), 0.80–0.71 (m, 6 H); ^{13}C NMR (150 MHz, 323 K, CD_3CN) δ 131.3, 130.9, 130.8, 130.6, 129.7, 129.4, 129.3, 128.8, 128.7, 128.6, 128.2, 128.1, 127.9, 127.8, 127.5, 127.4, 126.9, 126.4, 125.6, 124.6, 123.3, 123.0, 119.0, 112.9, 112.8, 110.5, 104.8, 77.9, 70.4, 69.7, 69.5, 66.9, 66.3, 64.0, 63.7, 55.9, 55.5, 55.3, 55.2, 47.6, 47.5, 37.0, 32.0, 18.6, 18.5, 18.1, 17.8; HRMS (MALDI-FTMS) calcd for $C_{74}H_{67}N_6O_9^+$ [$M + H^+$] 1183.4964, found 1183.4966. Next, a solution of IBX (0.235 g, 0.359 mmol, 5.0 equiv) in DMSO (5 mL) was added to a solution containing a portion of the newly-formed alcohol intermediate (0.198 g, 0.167 mmol, 1.0 equiv) in DMSO (5 mL) at 25 °C. After stirring for 4 hours at 25 °C, the

reaction mixture was poured into EtOAc (25 mL) and washed extensively with saturated aqueous Na_2SO_3 (3×15 mL) to remove the IBA by-product and any residual IBX. The organic layer was then dried (MgSO_4) and concentrated to give the desired aldehyde (0.192 g, 97% yield) as a yellow solid. Pressing forward without any additional purification, this compound (0.192 g, 0.163 mmol, 1.0 equiv) was dissolved in DMSO (2 mL) and treated sequentially at 0 °C with resorcinol (0.090 g, 0.813 mmol, 5.0 equiv), a solution of $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ (0.112 g, 0.813 mmol, 5.0 equiv) in water (0.1 mL), and a solution of NaClO_2 (0.076 g, 0.813 mmol, 5.0 equiv) in water (0.1 mL). The reaction mixture was then warmed to 25 °C and stirred for 1 hour. Upon completion, the reaction flask contents were poured into saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (3×25 mL). The combined organic layers were then washed with water (20 mL) and brine (20 mL), dried (MgSO_4), and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/MeOH, 1:0→19:1) to give the desired carboxylic acid intermediate (0.179 g, 92% yield) as an amorphous light yellow solid. Next, a portion of this newly-formed product (0.064 g, 0.053 mmol, 1.0 equiv) was dissolved in THF (2 mL) and treated with Et_2NH (0.4 mL, excess) at 25 °C. After stirring the resultant mixture for 4 hours at 25 °C, the reaction flask contents were concentrated directly (using several benzene co-evaporations to ensure the complete removal of all Et_2NH) to give carboxylic acid-amine **23** (0.051 g, 97% yield) as a white solid. This intermediate was then dried under high vacuum for 12 hours. Once this operation was complete, the material (0.051 g, 0.052 mmol, 1.0 equiv) was dissolved in DMF/ CH_2Cl_2 (1:2, 192 mL, final concentration of **23** = 1.0×10^{-4} M) and treated sequentially at 25 °C with 2,4,6-collidine (0.038 g, 0.312 mmol, 6.0 equiv) and HATU (0.039 g, 0.104 mmol, 2.0 equiv). After stirring the resultant mixture for 7 days at 25 °C, the reaction flask contents were concentrated directly. The residue was then dissolved in EtOAc (100 mL), washed with 10% aqueous HCl (50 mL), saturated aqueous NaHCO_3 (50 mL), and brine (50 mL), dried (MgSO_4), and concentrated. The resultant yellow residue was purified by preparative TLC (silica gel, EtOAc/hexanes, 2:1) to give macrolactam **24** (6.7 mg, 13%) as a pale yellow foam. **24**: R_f = 0.18 (silica gel, EtOAc); IR (film) ν_{max} 3104, 2935, 1702, 1664, 1542, 1248,

1021, 667 cm^{-1} ; ^1H NMR (600 MHz, 323 K, CD_3CN) δ 8.02 (br s, 1 H), 7.71 (app s, 4 H), 7.76 (d, $J = 7.2$ Hz, 1 H), 7.61 (app s, 4 H), 7.47–7.37 (m, 11 H), 7.23 (m, 1 H), 7.12 (d, $J = 7.4$ Hz, 1 H), 6.94–6.72 (m, 3 H), 5.91 (br s, 1 H), 5.54 (AB, $J = 6.4$ Hz, $v_{\text{ab}} = 25.7$ Hz, 2 H), 5.14 (s, 2 H), 4.99 (AB, $J = 6.6$ Hz, $v_{\text{ab}} = 33.4$ Hz, 2 H), 4.61 (t, $J = 4.6$ Hz, 1 H), 4.34–4.25 (m, 3 H), 4.15 (dd, $J = 7.4, 5.2$ Hz, 1 H), 4.08 (m, 1 H), 3.60 (m, 1 H), 3.31 (s, 3 H), 3.29 (m, 1 H), 2.72 (d, $J = 7.8$ Hz, 1 H), 2.04 (m, 1 H), 0.94–0.92 (m, 6 H); ^{13}C NMR (150 MHz, 323 K, CD_3CN) attempted, but only decomposition was observed after long acquisition times; HRMS (MALDI-FTMS) calcd for $\text{C}_{59}\text{H}_{53}\text{N}_6\text{O}_7^+$ [$\text{M} + \text{H}^+$] 957.3970, found 957.3979.

Chlorinated lactam 35. 4Å molecular sieves (spatula tip full) and $\text{Pd}(\text{OH})_2/\text{C}$ (0.010 g, 20 wt %, excess) were added sequentially to a solution of macrolactam **24** (6.5 mg, 0.0068 mmol, 1.0 equiv) in EtOH (0.5 mL) at 25 °C. The resultant suspension was then equipped with a balloon containing hydrogen gas (pressure of ~1 atm) and allowed to stir for 12 hours at 25 °C. Upon completion, the reaction flask contents were filtered through Celite and concentrated to give the desired amine (2.1 mg, 96%) as a clear oil. This crude material was then dissolved in 1,4-dioxane (0.4 mL), and saturated aqueous NaHCO_3 (0.2 mL) and benzyl chloroformate (4.8 μL , 0.034 mmol, 5.0 equiv) were added sequentially at 25 °C. After stirring the resultant solution for 24 hours at 25 °C, the reaction flask contents were poured into water (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried (MgSO_4), and concentrated. The resultant yellow residue was purified by preparative TLC (silica gel, EtOAc/hexanes, 2:1) to give lactam **25** (2.2 mg, 35% over two steps). Pressing forward, this new intermediate (2.2 mg, 0.0024 mmol, 1.0 equiv) was dissolved in THF/ CCl_4 (1:1, 0.5 mL) and treated with freshly recrystallized *N*-chlorosuccinimide (1.3 mg, 0.0095 mmol, 4.0 equiv) at 25 °C. The resultant solution was then warmed to 60 °C and stirred for 4 hours. Upon completion, the reaction flask contents were cooled to 25 °C and concentrated directly without any additional work-up to provide the desired bis-chlorinated intermediate **34** as a yellow oil. Taking this crude material forward, it was immediately dissolved in CH_2Cl_2 (0.5 mL), cooled to –78 °C, and treated with BCl_3 (0.011 mL, 1.0 M in

CH₂Cl₂, 0.011 mmol, 5.0 equiv). After two hours of stirring at –78 °C, the reaction flask contents were diluted with THF (1 mL); 10% aqueous NaOH (0.5 mL) was then added, and the resultant biphasic mixture was stirred for 10 minutes at 25 °C. Upon completion, the reaction flask contents were poured into saturated aqueous NH₄Cl (25 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried (MgSO₄), and concentrated. The resultant yellow residue was purified by preparative TLC (silica gel, EtOAc/hexanes, 2:1) to give chlorinated macrolactam **35** (1.5 mg, 75% over two steps) as a white foam, identical in all respects to the same material encountered from the first successful total synthesis of diazonamide A (based on ¹H and ¹³C NMR, IR, TLC, optical rotation, and HRMS) – see Ref. 1.

(–)-Diazonamide A (1). Intermediate **35** was elaborated to diazonamide A using the procedure delineated in the preceding article (see Ref. 1) in this series in comparable yields. As expected, its physical and spectral properties were identical in all respects with an authentic sample of the natural product.

Analog 39. Phenolic lactam **38** (0.030 g, 0.044 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (3 mL) and treated with DIBAL-H (1.78 mL, 1.0 M in toluene, 1.78 mmol, 40 equiv) at –78 °C. The reaction mixture was then warmed to 25 °C over the course of 30 minutes and allowed to stir for an additional 12 hours. Upon completion, the reaction flask contents were quenched at 25 °C by the slow and careful addition of water (5 mL), poured into water (25 mL), and extracted with CH₂Cl₂ (3 × 25 mL). The combined organic layers were then washed with water (25 mL) and brine (50 mL), dried (MgSO₄), and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 5:1→1:0) to give phenol **39** (0.021 g, 73% yield) as a clear film. **39**: R_f = 0.22 (silica gel, EtOAc/hexanes, 5:1); [α]_D²⁰ = –184.7 (*c* = 1.0, MeOH); IR (film) ν_{max} 3303, 2950, 1711, 1682, 1653, 1529, 1500, 1453, 1288, 1235, 1147, 1118, 1012, 753, 695 cm^{–1}; ¹H NMR (600 MHz, CD₃CN) δ 8.27 (br s, 1 H), 7.38–7.33 (m, 6 H), 7.12 (br s, 1 H), 7.02 (d, *J* = 7.0 Hz, 1 H), 6.92 (d, *J* = 7.9 Hz, 1 H), 6.90 (m, 2 H), 6.04 (br s, 1 H), 6.00 (br s, 1 H), 5.13–5.06 (m, 3 H), 4.45 (br t, *J* = 6.4 Hz, 1 H), 4.39

(d, $J = 4.8$ Hz, 1 H), 4.08 (br t, $J = 5.4$ Hz, 1 H), 3.97 (br m, 2 H), 3.78 (d, $J = 4.9$ Hz, 1 H), 2.97 (br t, $J = 6.8$ Hz, 1 H), 2.89 (br s, 1 H), 2.60 (br d, $J = 5.4$ Hz, 1 H), 2.01 (br m, 1 H), 1.02 (br s, 3 H), 0.94 (br s, 3 H); ^{13}C NMR (125 MHz, CD_3CN) δ 172.5, 162.8, 153.5, 149.9, 148.6, 137.6, 137.8, 133.1, 132.7, 131.7, 129.5, 128.9, 128.3, 128.2, 127.5, 124.4, 121.7, 66.5, 57.2, 57.0, 56.3, 55.8, 55.3, 38.2, 29.9, 19.2, 19.0; HRMS (MALDI-FTMS) calcd for $\text{C}_{33}\text{H}_{34}\text{BrN}_4\text{O}_6^+$ [$\text{M} + \text{H}^+$] 661.1656, found 661.1659.

Aminal-alcohol 40. Phenol **40** (10.0 mg, 0.015 mmol, 1.0 equiv) was dissolved in benzene (1 mL) and treated with activated MnO_2 (13.0 mg, 0.15 mmol, 10 equiv) at 25 °C. The resultant slurry was then warmed to 80 °C and allowed to react for 1 hour with vigorous stirring. Upon completion, the reaction flask contents were cooled to 25 °C, filtered through Celite, and concentrated. The resultant yellow oil was purified by preparative TLC (silica gel, EtOAc/hexanes, 5:1) to give aminal-alcohol **40** (4.8 mg, 48% yield) as a clear film and aminal-aldehyde **41** (2.3 mg, 23% yield) as a clear film. **40**: $R_f = 0.32$ (silica gel, EtOAc/hexanes, 5:1); IR (film) ν_{max} 3141, 2956, 1704, 1660, 1542, 1443, 1254, 1020, 750 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 7.38–7.32 (m, 6 H), 7.25 (d, $J = 7.4$ Hz, 1 H), 7.12 (d, $J = 7.2$ Hz, 1 H), 6.86 (br s, 1 H), 6.80 (d, $J = 8.3$ Hz, 1 H), 6.72 (d, $J = 6.8$ Hz, 1 H), 6.71 (t, $J = 7.9$ Hz, 1 H), 6.47 (d, $J = 2.2$ Hz, 1 H), 6.19 (d, $J = 2.3$ Hz, 1 H), 6.04 (br t, $J = 6.7$ Hz, 1 H), 5.03 (s, 2 H), 4.51 (t, $J = 6.1$ Hz, 1 H), 4.00 (ddd, $J = 12.9, 12.4, 5.4$ Hz, 1 H), 3.98 (dd, $J = 12.7, 5.3$ Hz, 1 H), 3.88 (dd, $J = 13.1, 6.1$ Hz, 1 H), 2.99 (t, $J = 6.8$ Hz, 1 H), 2.82 (m, 2 H), 2.08 (m, 1 H), 0.98–0.92 (m, 6 H); ^{13}C NMR (150 MHz, CD_3CN) δ 172.7, 158.0, 147.9, 139.4, 132.7, 130.9, 130.1, 129.3, 128.8, 128.6, 124.0, 121.8, 110.9, 103.4, 103.1, 67.0, 58.9, 56.3, 55.9, 30.7, 19.2 (2 C); HRMS (MALDI-FTMS) calcd for $\text{C}_{33}\text{H}_{32}\text{BrN}_4\text{O}_6^+$ [$\text{M} + \text{H}^+$] 659.1500, found 659.1520.

Aminal-aldehyde 41: Clear oil, $R_f = 0.66$ (silica gel, EtOAc/hexanes, 5:1); IR (film) ν_{max} 3157, 2932, 1723, 1704, 1664, 1505, 1247, 1028, 730 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 9.31 (s, 1 H), 7.37–7.32 (m, 5 H), 7.25 (d, $J = 7.4$ Hz, 1 H), 7.17 (br d, $J = 7.9$ Hz, 1 H), 7.03 (s, 1 H), 6.85 (d, $J = 8.3$ Hz, 1 H), 6.78 (br d, $J = 7.4$ Hz, 1 H), 6.70 (t, $J = 7.9$ Hz, 1 H), 6.65 (d, $J = 2.6$ Hz, 1 H), 6.29 (d, $J = 2.5$ Hz, 1 H), 6.08 (br d, $J = 7.1$ Hz, 1 H), 5.07 (s, 2 H), 4.68 (t, $J = 5.2$ Hz,

1 H), 4.04 (m, 1 H), 3.56 (m, 1 H), 3.04 (t, $J = 11.8$ Hz, 1 H), 2.82 (d, $J = 12.3$ Hz, 1 H), 2.08 (m, 1 H), 0.95 (d, $J = 6.5$ Hz, 3 H), 0.92 (d, $J = 6.6$ Hz, 3 H); HRMS (MALDI-FTMS) calcd for $C_{33}H_{29}BrN_4O_6Na^+$ $[M + Na^+]$ 679.1163, found 679.1176.

Brominated macrocycle 42. $Pd(OH)_2/C$ (0.002 g, 20 wt %, catalytic) was added to a solution of lactam **38** (10.0 mg, 0.015 mmol, 1.0 equiv) in EtOH (5 mL) at 25 °C. The resultant suspension was then equipped with a balloon containing hydrogen gas (pressure of ~2 atm) and allowed to stir for 1.5 hours at 25 °C. Upon completion, the reaction flask contents were filtered through Celite and concentrated to give the desired amine (9.2 mg, 97%) as a clear oil. This intermediate (9.2 mg, 0.014 mmol, 1.0 equiv) was then dissolved in DMF (1.0 mL) and treated sequentially at 25 °C with L-isovaleric acid (1.9 mg, 0.016 mmol, 1.1 equiv), $NaHCO_3$ (9.4 mg, 0.111 mmol, 7.5 equiv), EDC• H_2O (4.2 mg, 0.022 mmol, 1.5 equiv), and HOBT• H_2O (3.5 mg, 0.022 mmol, 1.5 equiv). After 12 hours of stirring at 25 °C, the reaction flask contents were poured into saturated aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (3×5 mL). The combined organic layers were then washed with 1 N aqueous HCl (5 mL), water (5 mL), and brine (5 mL), dried ($MgSO_4$), and concentrated. The resultant yellow residue was purified by preparative TLC (silica gel, EtOAc) to give brominated macrocycle **42** (4.5 mg, 47% yield over two steps) as a clear film and desbromo macrocycle **43** (1.7 mg, 21% yield over two steps) as a clear film. **42**: $R_f = 0.20$ (silica gel, EtOAc); $[\alpha]_D^{20} = -185.3$ ($c = 1.0$, MeOH); IR (film) ν_{max} 3400, 2918, 1719, 1660, 1613, 1513, 1454, 1254, 1160, 1125, 1019, 749 cm^{-1} ; 1H NMR (600 MHz, CD_3CN) δ 8.68 (br s, 1 H), 7.47 (d, $J = 8.1$ Hz, 1 H), 7.35 (br d, $J = 6.9$ Hz, 1 H), 7.31 (br s, 1 H), 7.17 (br d, $J = 7.1$ Hz, 1 H), 7.07 (d, $J = 6.8$ Hz, 1 H), 7.02 (d, $J = 6.6$ Hz, 1 H), 6.91 (t, $J = 7.9$ Hz, 1 H), 6.71 (d, $J = 8.3$ Hz, 1 H), 6.20 (d, $J = 1.8$ Hz, 1 H), 4.48 (t, $J = 6.4$ Hz, 1 H), 4.38 (t, $J = 6.8$ Hz, 1 H), 3.84 (m, 1 H), 3.71–3.60 (m, 3 H), 3.04 (dd, $J = 6.8, 6.5$ Hz, 1 H), 2.81 (m, 1 H), 2.60 (d, $J = 12.2$ Hz, 1 H), 2.07 (m, 1 H), 2.01 (m, 1 H), 1.01 (d, $J = 6.5$ Hz, 3 H), 0.97 (d, $J = 7.0$ Hz, 3 H), 0.91 (d, $J = 6.6$ Hz, 3 H), 0.81 (d, $J = 7.0$ Hz, 3 H); HRMS (MALDI-FTMS) calcd for $C_{30}H_{33}BrN_4O_7Na^+$ $[M + Na^+]$ 663.1425, found 663.1422.

Desbromo macrocycle 43: Clear oil, $R_f = 0.12$ (silica gel, EtOAc); $[\alpha]_D^{20} = -171.3$ ($c = 1.0$, MeOH); IR (film) $\nu_{\max}$ 3235, 1707, 1660, 1536, 1513, 1472, 1325, 1272, 1155, 1019, 749, 667 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 8.51 (s, 1 H), 7.34 (d, $J = 7.4$ Hz, 1 H), 7.31 (t, $J = 7.9$ Hz, 1 H), 7.18–7.12 (m, 2 H), 7.07 (d, $J = 7.0$ Hz, 1 H), 7.01–6.96 (m, 3 H), 6.68 (d, $J = 8.3$ Hz, 1 H), 6.21 (d, $J = 2.2$ Hz, 1 H), 4.46 (t, $J = 7.7$ Hz, 1 H), 4.37 (t, $J = 8.8$ Hz, 1 H), 3.85 (app s, 1 H), 3.63–3.57 (m, 3 H), 3.05 (app t, $J = 10.6$ Hz, 1 H), 2.71 (m, 1 H), 2.60 (d, $J = 10.6$ Hz, 1 H), 2.09 (m, 1 H), 2.07 (m, 1 H), 1.01 (d, $J = 6.5$ Hz, 3 H), 0.97 (d, $J = 7.0$ Hz, 3 H), 0.91 (d, $J = 6.6$ Hz, 3 H), 0.82 (d, $J = 7.0$ Hz, 3 H); HRMS (MALDI-FTMS) calcd for $\text{C}_{30}\text{H}_{34}\text{N}_4\text{O}_7\text{Na}^+$ [$\text{M} + \text{Na}^+$] 585.2320, found 585.2299.

Keto amide 44. *trans*-2-amino-1-cyclohexanol hydrochloride (0.91 g, 6.0 mmol, 1.5 equiv) was dissolved in CH_2Cl_2 (60 mL), and then EDC $\cdot\text{H}_2\text{O}$ (1.44 g, 7.5 mmol, 1.5 equiv), HOBt $\cdot\text{H}_2\text{O}$ (1.15 g, 7.5 mmol, 1.5 equiv), and benzoic acid (0.61 g, 5.0 mmol, 1.0 equiv) were added sequentially at 25 °C. After stirring the resultant mixture for 4 hours at 25 °C, the reaction flask contents were poured into saturated aqueous NaHCO_3 (100 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were then washed with 1 N HCl (50 mL), saturated aqueous NaHCO_3 (50 mL), and brine (50 mL), dried (MgSO_4), and concentrated to give the desired hydroxyamide (0.83 g, 95%) as a white powder. Pressing forward without any additional purification, a portion of the hydroxyamide (0.201 g, 0.91 mmol, 1.0 equiv) was suspended in CH_2Cl_2 (15 mL) and treated sequentially at 0 °C with solid NaHCO_3 (0.84 g, 10.0 mmol, 11 equiv) and Dess-Martin periodinane (0.423 g, 1.0 mmol, 1.1 equiv). After stirring the resultant mixture for 1 hour at 0 °C, it was warmed to 25 °C and allowed stirred for 3 more hours. Upon completion, the reaction flask contents were poured into saturated aqueous NaHCO_3 (30 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were then washed with water (30 mL), saturated aqueous NaHCO_3 (30 mL), and brine (30 mL), dried (MgSO_4) and concentrated to give keto amide **44** (0.183 g, 93% yield) as a white powder. **44.** $R_f = 0.32$ (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\max}$ 3324, 3062, 2939, 2863, 1720, 1644, 1535, 1487, 1450, 1320, 1129, 1072, 711, 530 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.82–7.80 (m, 2 H), 7.51–7.40

(m, 3 H), 7.22 (br s, 1 H), 4.65 (dtd, $J = 12.3, 6.1, 0.9$ Hz, 1 H), 2.83–2.76 (m, 1 H), 2.60–2.40 (m, 2 H), 2.20–2.14 (m, 1 H), 1.95–1.61 (m, 3 H), 1.41 (qd, $J = 12.3, 4.4$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 207.9, 166.8, 134.1, 131.6, 128.5, 127.0, 58.4, 41.2, 35.5, 28.1, 24.0; HRMS (MALDI-FTMS) calcd for $\text{C}_{13}\text{H}_{16}\text{NO}_2^+$ [$\text{M} + \text{H}^+$] 218.1175, found 218.1177.

Keto amide 46. Keto amide **46** was prepared in a manner analogous to keto amide **44** by replacing *trans*-2-amino-1-cyclohexanol hydrochloride with 2-amino-1-phenylethanol in the opening coupling and using IBX instead of DMP for the subsequent oxidation. This protocol ultimately yielded **46** (0.22 g, 92% yield) as an off-white powder. **46**: $R_f = 0.39$ (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3348, 3061, 2921, 1695, 1647, 1600, 1532, 1486, 1447, 1358, 1302, 1225, 1070, 997, 924, 753, 689, 564 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.11 (dd, $J = 8.4, 1.1$ Hz, 2 H), 7.97 (dd, $J = 8.2, 1.3$ Hz, 2 H), 7.74–7.70 (m, 1 H), 7.62–7.59 (m, 3 H), 7.56–7.53 (m, 2 H), 7.41 (br s, 1 H), 5.45 (d, $J = 4.0$ Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 194.8, 167.8, 134.8, 134.7, 134.3, 132.2, 129.4, 129.1, 128.4, 127.6, 47.3; HRMS (MALDI-FTMS) calcd for $\text{C}_{15}\text{H}_{14}\text{NO}_2^+$ [$\text{M} + \text{H}^+$] 240.1019, found 240.1020.

Keto amide 50. Tryptamine (0.960 g, 6.0 mmol, 1.5 equiv) was dissolved in CH_2Cl_2 (60 mL), and then EDC $\cdot\text{H}_2\text{O}$ (1.44 g, 7.5 mmol, 1.5 equiv), HOBT $\cdot\text{H}_2\text{O}$ (1.15 g, 7.5 mmol, 1.5 equiv), and benzoic acid (0.61 g, 5.0 mmol, 1.0 equiv) were added sequentially at 25 °C. After stirring the resultant mixture for 4 hours at 25 °C, the reaction flask contents were poured into saturated aqueous NaHCO_3 (100 mL) and extracted with EtOAc (3 $\times$ 50 mL). The combined organic layers were then washed with 1 N HCl (50 mL), saturated aqueous NaHCO_3 (50 mL), and brine (50 mL), dried (MgSO_4), and concentrated to give the desired amide (1.35 g, 95% yield) as a white powder. A portion of this compound (0.237 g, 1.0 mmol, 1.0 equiv) was then dissolved in THF/ H_2O (9:1, 20 mL) and treated with DDQ (8.54 g, 37.6 mmol, 2.0 equiv) at 0 °C to yield a deep red solution. After 4 hours of stirring at 0 °C, the reaction mixture was poured into EtOAc (50 mL) and washed extensively with saturated aqueous NaHCO_3 (4 $\times$ 50 mL) to remove any excess DDQ and its colored by-products. The organic layer was then dried (MgSO_4) and concentrated. The resultant yellow solid was purified by flash column chromatography to

give keto amide **50** (0.203 g, 81% yield) as a light yellow solid. **50**: R_f = 0.44 (silica gel, EtOAc); IR (film) $\nu_{\max}$ 3354, 3213, 1625, 1572, 1514, 1420, 1373, 1296, 1232, 1126, 920, 715, 609 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6) δ 8.79 (t, J = 5.7 Hz, 1 H), 8.50 (s, 1 H), 8.15 (dd, J = 7.0, 1.8 Hz, 1 H), 7.92 (d, J = 7.8 Hz, 2 H), 7.58–7.48 (m, 4 H), 7.20 (quind, J = 7.3, 1.4 Hz, 2 H), 4.65 (d, J = 5.6 Hz, 2 H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 190.2, 166.5, 136.6, 134.2, 133.8, 131.3, 128.4, 127.3, 125.6, 122.9, 121.9, 121.2, 114.1, 112.4, 46.3; HRMS (MALDI-FTMS) calcd for $\text{C}_{17}\text{H}_{15}\text{N}_2\text{O}_2^+$ [$\text{M} + \text{H}^+$] 279.1128, found 279.1130.

Keto amide 52. Keto amide **52** was prepared in a manner analogous to **50** by substituting nicotinic acid for benzoic acid in the initial coupling step, ultimately affording **52** (0.197 g, 79% yield) as an off-white solid. **52**: R_f = 0.24 (silica gel, EtOAc/MeOH, 19:1); IR (film) $\nu_{\max}$ 3225, 3107, 2918, 1638, 1519, 1425, 1302, 1237, 1143, 926, 744 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6) δ 9.08 (dd, J = 2.2, 0.9 Hz, 1 H), 9.03 (t, J = 5.7 Hz, 1 H), 8.52 (s, 1 H), 8.26 (dt, J = 8.2, 1.8 Hz, 1 H), 8.16 (dt, J = 7.9, 1.0 Hz, 1 H), 7.55 (ddd, J = 7.9, 4.7, 0.9 Hz, 1 H), 7.50 (m, 1 H), 7.22 (quind, J = 7.0, 1.2 Hz, 2 H), 4.69 (d, J = 5.9 Hz, 2 H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 189.9, 165.2, 152.0, 148.5, 136.5, 135.1, 133.8, 129.7, 125.5, 123.6, 123.0, 121.9, 121.2, 114.1, 112.3, 46.2; HRMS (MALDI-FTMS) calcd for $\text{C}_{16}\text{H}_{14}\text{N}_3\text{O}_2^+$ [$\text{M} + \text{H}^+$] 280.1080, found 280.1080.

Boc-protected L-valine keto amide 54: R_f = 0.39 (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\max}$ 3287, 2972, 1695, 1647, 1602, 1518, 1435, 1369, 1308, 1245, 1162, 1106, 1012, 915, 734 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 10.27 (s, 1 H), 8.28 (dd, J = 7.3, 2.6 Hz, 1 H), 8.11 (s, 1 H), 7.97 (t, J = 5.5 Hz, 1 H), 7.89 (d, J = 3.7 Hz, 1 H), 7.40 (dd, J = 8.5, 3.7 Hz, 1 H), 7.27–7.20 (m, 3 H), 5.35 (d, J = 11.4 Hz, 1 H), 4.77 (dd, J = 11.4, 7.7 Hz, 1 H), 4.71 (d, J = 5.9 Hz, 2 H), 2.17 (sep, J = 8.5 Hz, 1 H), 1.47 (s, 9 H), 0.91 (m, 6 H); ^{13}C NMR (125 MHz, CDCl_3) δ 188.4, 163.9, 160.8, 155.5, 140.9, 136.4, 135.7, 132.0, 125.2, 123.7, 122.8, 121.8, 114.8, 111.9, 80.3, 54.3, 45.7, 32.6, 28.3, 18.6, 18.0; HRMS (MALDI-FTMS) calcd for $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_5\text{Na}^+$ [$\text{M} + \text{Na}^+$] 463.1952, found 463.1958.

Thioamide 58. A solution of tryptamine derivative **3-6** (0.340 g, 1.25 mmol, 1.0 equiv) in water (25 mL) was added to a solution of *S*-(thiobenzoyl)thioglycolic acid (0.535 g, 2.50 mmol, 2.0 equiv) and Na₂CO₃ (0.190 g, 1.80 mmol, 1.45 equiv) in water (25 mL) at 25 °C. After stirring the resultant mixture for 1 hour at 25 °C, the reaction flask contents were filtered. The resultant crude solid was then washed with saturated NaHCO₃ (5 mL) and CH₂Cl₂ (5 mL), dissolved in MeOH (10 mL), and triturated with Et₂O (10 mL). The organic layer was then filtered, concentrated, and purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:2) to give the thioamide **58** (0.069 g, 19% yield) as a yellow solid. **58**: R_f = 0.22 (silica gel, Et₂O/hexanes, 2:1); IR (film) $\nu_{\max}$ 3300, 3105, 3048, 2921, 1641, 1518, 1486, 1361, 1245, 1155, 1113, 953, 919, 749, 694 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.52 (t, *J* = 5.6 Hz, 1 H), 8.55 (d, *J* = 3.0 Hz, 1 H), 8.17 (d, *J* = 7.4 Hz, 1 H), 7.86 (d, *J* = 7.3 Hz, 1 H), 7.55–7.45 (m, 4 H), 7.26–7.19 (m, 2 H), 5.19 (d, *J* = 5.6 Hz, 2 H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 198.2, 188.1, 140.8, 136.4, 138.8, 130.9, 128.1, 127.3, 125.4, 123.0, 121.9, 114.2, 112.3, 52.3; HRMS (MALDI-FTMS) calcd for C₂₃H₂₆N₄O₄Na⁺ [M + Na⁺] XXXX, found XXXX.

Cyclohexane thiazoline 60. *trans*-2-amino-1-cyclohexanol hydrochloride (0.91 g, 6.0 mmol, 1.5 equiv) was dissolved in CH₂Cl₂ (60 mL), and then EDC•H₂O (1.44 g, 7.5 mmol, 1.5 equiv), HOBT•H₂O (1.15 g, 7.5 mmol, 1.5 equiv), and benzoic acid (0.61 g, 5.0 mmol, 1.0 equiv) were added sequentially at 25 °C. After stirring the resultant mixture for 4 hours at 25 °C, the reaction flask contents were poured into saturated aqueous NaHCO₃ (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were then washed with 1 N HCl (50 mL), saturated aqueous NaHCO₃ (50 mL), and brine (50 mL), dried (MgSO₄), and concentrated to give the desired hydroxy amide (0.830 g, 95% yield) as a white powder. Pressing forward without any additional purification, a portion of this compound (0.110 g, 0.5 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (10 mL), and then 4-DMAP (0.122 g, 1.0 mmol, 1.0 equiv) and Ac₂O (0.070 mL, 0.75 mmol, 1.5 equiv) were added sequentially at 25 °C. After stirring the resultant mixture for 30 minutes at 25 °C, the reaction flask contents were poured into saturated aqueous NaHCO₃ (50 mL) and extracted with EtOAc (3 × 35 mL). The combined organic layers were

then washed with concentrated aqueous citric acid (50 mL), saturated aqueous NaHCO₃ (50 mL), and brine (50 mL), dried (MgSO₄), and concentrated to give the desired acetate (0.130 g, 99% yield) as a clear oil. With this material in hand, it (0.100 g, 0.38 mmol, 1.0 equiv) was dissolved in benzene (10 mL), and then Lawesson's reagent (0.185 g, 0.46 mmol, 1.2 equiv) was added at 25 °C. The resulting yellow solution was then heated at 80 °C for 2 hours. Upon completion, the reaction flask contents were cooled to 25 °C, poured into saturated aqueous NaHCO₃ (40 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with saturated aqueous NH₄Cl (40 mL), saturated aqueous NaHCO₃ (40 mL), and brine (40 mL), dried (MgSO₄) and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:2) to give the hydroxy sulfamide **62** (0.068 g, 76% yield) as a yellow powder. **62**: R_f = 0.39 (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\max}$ 3259, 3048, 2930, 2848, 1526, 1448, 1378, 1219, 1131, 1055, 973, 767, 690 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.74 (d, J = 7.0 Hz, 3 H), 7.45 (t, J = 7.3 Hz, 1 H), 7.37 (t, J = 7.7 Hz, 2 H), 4.54 (m, 1 H), 3.56 (td, J = 10.3, 4.4 Hz, 1 H), 2.31 (m, 1 H), 2.07 (m, 1 H), 1.75 (m, 2 H), 1.47–1.22 (m, 4 H); ¹³C NMR (125 MHz, CDCl₃) δ 200.6, 142.7, 131.7, 128.9, 127.3, 75.5, 62.0, 35.4, 30.9, 24.7, 24.6; HRMS (MALDI-FTMS) calcd for C₁₃H₁₈NSO⁺ [M + H⁺] 236.1104, found 236.1105.

Biphenyl thiazoline precursor 62: Hydroxysulfamide **62** was prepared in a manner analogous to compound **60** by substituting 2-amino-1-phenylethanol for *trans*-2-amino-1-cyclohexanol hydrochloride, ultimately affording **62** (0.177 g, 72% yield) as a yellow powder. **62**: R_f = 0.42 (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\max}$ 3282, 3200, 3036, 2918, 1531, 1449, 1390, 1319, 1202, 1084, 1041, 949, 757, 694 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.09 (br s, 1 H), 7.74 (dd, J = 8.4, 1.3 Hz, 2 H), 7.49–7.32 (m, 8 H), 5.15 (dd, J = 8.6, 3.5 Hz, 1 H), 4.42 (ddd, J = 14.3, 7.0, 3.5 Hz, 1 H), 3.80 (ddd, J = 14.3, 8.6, 4.4 Hz, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 200.3, 142.1, 141.6, 131.7, 129.2, 129.0, 128.8, 127.2, 126.2, 72.6, 53.7; HRMS (MALDI-FTMS) calcd for C₁₅H₁₆NSO⁺ [M + H⁺] 258.0947, found 258.0943.

General procedure for heterocycle synthesis using pyridine-buffered POCl₃. POCl₃ (0.5 mL) was added to a solution of the appropriate starting material (1 mmol, 1.0 equiv) in pyridine (2.5 mL) at 25 °C. The resultant solution was then stirred for 3 hours. Upon completion, the reaction mixture was diluted with EtOAc (10 mL), poured into a cold (0 °C) solution of saturated aqueous NaHCO₃ (25 mL), and extracted with EtOAc (3 × 15 mL). The combined organic layers were then washed with water (25 mL) and brine (25 mL), dried (MgSO₄), and concentrated. The resultant residue was purified by flash column chromatography in an appropriate solvent system to deliver the desired product in high purity.

Cyclohexane oxazole 45: White solid, *R_f* = 0.64 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2931, 2837, 1637, 1542, 1478, 1443, 1284, 1055, 920, 767, 709 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.07 (dd, *J* = 8.1, 1.2 Hz, 2 H), 7.52–7.45 (m, 3 H), 2.78–2.67 (m, 4 H), 2.00–1.89 (m, 4 H); ¹³C NMR (100 MHz, CDCl₃) δ 159.7, 146.9, 135.0, 129.6, 128.6, 128.0, 125.8, 23.1, 23.0, 22.9, 21.9; HRMS (MALDI-FTMS) calcd for C₁₃H₁₄NO⁺ [*M* + *H*⁺] 200.1070, found 200.1068.

Diphenyl oxazole 47: Light yellow solid, *R_f* = 0.62 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3045, 1584, 1483, 1443, 1126, 1062, 1020, 944, 908, 820, 760, 683 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.12 (dd, *J* = 7.7, 1.5 Hz, 2 H), 7.74 (dd, *J* = 8.2, 1.3 Hz, 2 H), 7.51–7.44 (m, 6 H), 7.35 (t, *J* = 7.5 Hz, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 161.5, 151.7, 130.8, 129.4, 129.3, 128.9, 128.4, 127.9, 126.7, 124.6, 123.9; HRMS (MALDI-FTMS) calcd for C₁₅H₁₂NO⁺ [*M* + *H*⁺] 222.0913, found 222.0914.

Indole-oxazole 49: See physical data reported in the first manuscript in this series.

Tryptamine benzoic acid oxazole 51: Off-white solid, *R_f* = 0.63 (silica gel, EtOAc); IR (film) ν_{max} 3413, 3154, 2919, 1625, 1602, 1443, 1361, 1249, 1120, 914, 767, 726 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.10–8.07 (m, 2 H), 7.98–7.95 (m, 2 H), 7.60–7.48 (m, 5 H), 7.25–7.17 (m, 2 H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 158.0, 148.3, 136.4, 130.1, 129.2, 127.2, 125.5, 123.9, 123.5, 122.3, 120.8, 120.3, 119.6, 112.2, 103.6; HRMS (MALDI-FTMS) calcd for C₁₇H₁₃N₂O⁺ [*M* + *H*⁺] 261.1022, found 261.1021.

Tryptamine nicotinic acid oxazole 53: Yellow solid, $R_f = 0.59$ (silica gel, EtOAc/MeOH, 19:1); IR (film) $\nu_{\max}$ 3173, 2919, 1755, 1628, 1431, 1331, 1255, 1120, 1008, 920, 803, 750, 703, 614 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6) δ 9.27 (s, 1 H), 8.69 (d, $J = 5.0$ Hz, 1 H), 8.41 (d, $J = 6.7$ Hz, 1 H), 8.01 (d, $J = 2.4$ Hz, 1 H), 7.97 (d, $J = 7.9$ Hz, 1 H), 7.67 (s, 1 H), 7.59 (dd, $J = 7.9, 5.0$ Hz, 1 H), 7.49 (d, $J = 7.9$ Hz, 1 H), 7.25–7.17 (m, 2 H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 155.9, 150.6, 149.0, 136.4, 132.8, 124.2, 124.1, 123.5, 123.4, 122.3, 120.9, 120.4, 119.6, 112.2, 103.4; HRMS (MALDI-FTMS) calcd for $\text{C}_{16}\text{H}_{12}\text{N}_3\text{O}^+$ [$\text{M} + \text{H}^+$] 262.0975, found 262.0972.

Boc-protected L-valine oxazole 55: Light yellow solid, $R_f = 0.62$ (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\max}$ 3313, 2971, 1697, 1631, 1504, 1454, 1367, 1253, 1165, 1114, 1093, 1010, 915, 736 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.89 (br s, 1 H), 8.15 (s, 1 H), 7.86 (d, $J = 7.0$ Hz, 1 H), 7.61 (d, $J = 2.4$ Hz, 1 H), 7.45 (dd, $J = 6.8, 1.8$ Hz, 1 H), 7.37 (s, 1 H), 7.30–7.22 (m, 3 H), 5.42 (d, $J = 9.1$ Hz, 1 H), 4.85 (dd, $J = 9.1, 5.9$ Hz, 1 H), 2.24 (sep, $J = 6.5$ Hz, 1 H), 1.45 (s, 9 H), 0.97 (m, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.2, 155.5, 152.7, 148.0, 137.4, 136.2, 130.7, 124.0, 123.0, 122.5, 121.1, 120.9, 119.8, 111.7, 105.2, 80.0, 54.3, 33.0, 28.3, 18.7, 18.0; HRMS (MALDI-FTMS) calcd for $\text{C}_{23}\text{H}_{26}\text{N}_4\text{O}_4\text{Na}^+$ [$\text{M} + \text{Na}^+$] 445.1846, found 445.1854.

Thiazole 59: Yellow solid, $R_f = 0.30$ (silica gel, Et_2O /hexanes, 2:1); IR (film) $\nu_{\max}$ 3399, 3170, 2912, 1562, 1487, 1452, 1421, 1337, 1245, 1120, 978, 911, 740, 689, 630 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.85 (m, 2 H), 7.47–7.38 (m, 3 H), 4.26 (dt, $J = 11.0, 5.5$ Hz, 1 H), 3.82 (dt, $J = 8.8, 5.8$ Hz, 1 H), 2.28 (m, 1 H), 1.89–1.80 (m, 2 H), 1.70–1.51 (m, 4 H), 1.37–1.29 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.1, 138.4, 136.4, 133.8, 132.7, 129.7, 129.0, 126.3, 125.4, 123.1, 122.8, 121.0, 119.7, 111.6, 108.3; HRMS (MALDI-FTMS) calcd for $\text{C}_{17}\text{H}_{13}\text{N}_2\text{S}^+$ [$\text{M} + \text{H}^+$] 277.0794, found 277.0788.

Cyclohexane thiazoline 61: White solid, $R_f = 0.68$ (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\max}$ 3060, 2919, 2849, 1572, 1484, 1443, 1302, 1243, 1078, 997, 950, 761, 686, 609 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.85 (m, 2 H), 7.47–7.38 (m, 3 H), 4.26 (dt, $J = 11.0, 5.5$ Hz, 1

H), 3.82 (dt, $J = 8.8, 5.8$ Hz, 1 H), 2.28 (m, 1 H), 1.89–1.80 (m, 2 H), 1.70–1.51 (m, 4 H), 1.37–1.29 (m, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 134.4, 131.5, 128.8, 128.6, 75.2, 51.6, 30.2, 29.0, 23.5, 22.1; HRMS (MALDI-FTMS) calcd for $\text{C}_{13}\text{H}_{16}\text{NS}^+$ [$\text{M} + \text{H}^+$] 218.0998, found 218.0997.

Diphenyl thiazoline 63: Yellow solid, $R_f = 0.61$ (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3056, 3021, 2915, 2833, 1602, 1488, 1441, 1306, 1236, 1171, 1077, 1000, 942, 760, 689, 601 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.88 (dd, $J = 8.3, 1.3$ Hz, 2 H), 7.51–7.26 (m, 8 H), 5.08 (dd, $J = 8.8, 5.5$ Hz, 1 H), 4.79 (dd, $J = 16.1, 8.8$ Hz, 1 H), 4.63 (dd, $J = 16.1, 5.5$ Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 167.7, 142.1, 133.1, 131.3, 128.8, 128.5, 128.4, 127.8, 127.0, 73.2, 54.5; HRMS (MALDI-FTMS) calcd for $\text{C}_{15}\text{H}_{14}\text{NS}^+$ [$\text{M} + \text{H}^+$] 240.0841, found 240.0837.

Diphenyl furan 65: White solid, $R_f = 0.68$ (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3115, 3056, 3032, 2915, 2857, 1717, 1599, 1476, 1259, 1076, 1024, 918, 796, 759, 689 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.75 (dd, $J = 8.4, 1.1$ Hz, 4 H), 7.41 (t, $J = 7.9$ Hz, 4 H), 7.27 (t, $J = 7.5$ Hz, 2 H), 6.75 (s, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 130.7, 128.7, 127.3, 123.7, 107.2; HRMS (MALDI-FTMS) calcd for $\text{C}_{16}\text{H}_{12}\text{O}^+$ [M^+] 220.0882, found 220.0883.

Methylphenyl furan 67: Light brown oil, $R_f = 0.71$ (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3056, 2915, 2856, 1723, 1594, 1547, 1482, 1441, 1259, 1206, 1065, 1018, 959, 912, 783, 689 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.65 (m, 2 H), 7.37 (m, 2 H), 7.23 (m, 1 H), 6.55 (d, $J = 3.3$ Hz, 1 H), 6.07 (dq, $J = 3.3, 1.1$ Hz, 1 H), 2.39 (d, $J = 1.1$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 152.7, 152.4, 131.6, 129.0, 127.2, 123.7, 108.1, 106.3, 14.2; HRMS (MALDI-FTMS) calcd for $\text{C}_{11}\text{H}_{10}\text{O}^+$ [M^+] 158.0726, found 158.0729.