Chemistry and Biology of Diazonamide A: First Total Synthesis and Confirmation of the True Structure

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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) 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 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).

7-Bromoisatin (21). Sodium sulfate (25.56 g, 180 mmol, 18 equiv), a solution of 2-bromoaniline (1.72 g, 10.0 mmol, 1.0 equiv) in water (36 mL), concentrated HCl (1.35 mL, 30.0 mmol, 3.0 equiv), and a solution of HONH₂•HCl (2.1 g, 30.0 mmol, 3.0 equiv) in water (10 mL) were added sequentially to a solution of chloral hydrate (1.81 g, 11.0 mmol, 1.1 equiv) in water (24 mL) at 25 °C. The resulting suspension was then warmed to 80 °C and stirred for 1 hour. Upon completion, the reaction flask contents were cooled to 0 °C, yielding 2-bromohydroxyiminoacetanilide as a yellow solid (1.75 g, 72% yield) which was collected by filtration. Next, this intermediate (1.75 g, 7.20 mmol, 1.0 equiv) was added to a flask containing hot (50 °C) concentrated H₂SO₄ (15 mL) at a rate such that the internal temperature of the solution did not rise above 65 °C. Upon completion, the reaction flask contents were then heated to 80 °C and stirred for an additional 15 minutes. The reaction mixture was then cooled to 25 °C, poured into ice water, and extracted with EtOAc (3 × 25 mL). The combined organic layers were then washed with water (50 mL) and brine (50 mL), dried (MgSO₄), and concentrated. The resultant red residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give 7-bromoisatin (0.781 g, 48% yield) as a red amorphous solid. **21**: R_f = 0.48 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3097, 1736, 1610, 1468, 1425, 1315, 1167, 1124, 956, 757 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.24 (br s, 1 H), 7.70 (d, *J* = 7.9 Hz, 1 H), 7.57 (d, *J* = 7.5 Hz, 1 H), 7.05 (t, *J* = 7.9 Hz, 1 H); ¹³C NMR (150 MHz, CDCl₃) δ 182.4, 158.4, 148.0, 140.8, 125.0, 124.4, 119.5; HRMS (MALDI-FTMS) calcd for C₈H₄BrNO₂Na⁺ [M + Na⁺] 247.9318, found 247.9321.

Tertiary alcohol 22. Phenylmagnesium chloride (0.58 mL, 1.9 M in THF, 1.10 mmol, 2.5 equiv) was added dropwise to a solution of 7-bromoisatin (0.100 g, 0.442 mmol, 1.0 equiv) in THF (2.0 mL) at 0 °C. After stirring for 5 minutes at 0 °C, the reaction mixture was quenched by the addition of saturated aqueous NH₄Cl (25 mL), poured into water (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 (MgSO₄), and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give tertiary alcohol **22** (0.129 g, 96% yield) as a light yellow oil. **22**: *R_f* = 0.40 (silica gel, EtOAc/hexanes, 1:1); ¹H NMR (400 MHz, CDCl₃) δ 8.27 (s, 1 H), 7.41–7.35 (m, 3 H), 7.33–7.28 (m, 3 H), 7.17 (d, *J* = 7.3 Hz, 1 H), 6.93 (dd, *J* = 8.2, 7.6 Hz, 1 H), 4.03 (br s, 1 H); ¹³C NMR (150 MHz, CDCl₃) δ 178.3, 139.8, 139.3, 133.3, 128.7, 128.6, 125.2, 124.8, 124.1, 103.4, 28.3; HRMS (MALDI-FTMS) calcd for C₁₄H₁₀BrNO₂Na⁺ [*M* + Na⁺] 325.9787, found 325.9792.

Phenolic lactam 24. A solution of TfOH (0.81 mL, 8.55 mmol, 5.0 equiv) in CH₂Cl₂ (1.0 mL) was added dropwise to a solution of tertiary alcohol **23** (0.52 g, 1.71 mmol, 1.0 equiv) and acetylated tyrosine methyl ester **23** (0.59 g, 1.80 mmol, 1.05 equiv) in CH₂Cl₂ (10 mL) at 0 °C. After 20 minutes of stirring at 0 °C, the reaction mixture was poured carefully into a cold (0 °C) solution of saturated aqueous NaHCO₃ (50 mL), ensuring that the aqueous layer of the resultant biphasic system was slightly basic as measured by standard pH paper. This mixture was then poured into water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried (MgSO₄), and concentrated to give the desired intermediate free amine (0.81 g, 98% yield) as a white foam. Carrying this material forward without any further purification, this intermediate product (0.81 g, 1.67 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (5 mL), and then Ac₂O (0.81 mL, 8.55 mmol, 5.0 equiv) was added at 25 °C. After 20 minutes of stirring at 25 °C, the reaction mixture was concentrated directly, and the resultant yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 2:1) to give phenolic lactam **24** (0.78 g, 84% yield over two steps) as a clear oil. **24**: *R_f* = 0.17 (silica gel, EtOAc/hexanes, 3:1); IR (film) ν_{max} 3272,

1719, 1649, 1614, 1508, 1443, 1367, 1214, 1126, 1032, 908, 732 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3 , 1:1 mixture of diastereomers) δ 9.54 (s, 1 H), 9.50 (s, 1 H), 8.99 (s, 1 H), 8.92 (s, 1 H), 7.34 (d, $J = 7.9$ Hz, 1 H), 7.33 (d, $J = 7.9$ Hz, 1 H), 7.27–7.19 (m, 5 H), 6.99 (t, $J = 7.4$ Hz, 1 H), 6.93–6.88 (m, 2 H), 6.79 (d, $J = 5.7$ Hz, 1 H), 6.40 (d, $J = 7.9$ Hz, 1 H), 6.38 (d, $J = 7.9$ Hz, 1 H), 4.77 (dd, $J = 13.1, 5.7$ Hz, 1 H), 4.73 (dd, $J = 13.6, 6.1$ Hz, 1 H), 3.60 (s, 3 H), 3.47 (s, 3 H), 2.98 (dd, $J = 14.0, 5.7$ Hz, 1 H), 2.96 (dd, $J = 12.3, 3.5$ Hz, 1 H), 2.89 (dd, $J = 13.1, 5.7$ Hz, 1 H), 2.87 (dd, $J = 13.6, 5.3$ Hz, 1 H), 1.83 (s, 3 H), 1.74 (s, 3 H); ^{13}C NMR (150 MHz, CDCl_3 , 1:1 mixture of diastereomers) δ 182.0, 181.9, 172.3, 170.5, 170.4, 155.2 (2 C), 140.1, 139.8, 138.9, 134.0, 131.3, 131.2, 130.8 (2 C), 130.2, 130.1, 128.9, 128.8, 128.0, 127.9, 127.5, 127.3, 127.0 (2 C), 126.5, 126.1, 125.6, 124.2 (2 C), 119.0, 118.6, 103.7, 103.6, 63.3, 63.0, 60.5, 53.3, 52.5, 52.2, 37.1, 37.0, 22.8, 22.6; HRMS (MALDI-FTMS) calcd for $\text{C}_{26}\text{H}_{23}\text{BrN}_2\text{O}_5\text{H}^+$ $[\text{M} + \text{H}^+]$ 523.0863, found 523.0872.

Aminal 27. $\text{BH}_3 \cdot \text{SMe}_2$ (0.023 mL, 0.383 mmol, 4.0 equiv) was added to a solution of lactam **24** (0.050 g, 0.0957 mmol, 1.0 equiv) in THF (1.5 mL) at 0 $^\circ\text{C}$. After 10 minutes of stirring at 0 $^\circ\text{C}$, the reaction mixture was warmed slowly to 25 $^\circ\text{C}$ and stirred for 2 additional hours. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous NaHCO_3 (10 mL) and extracted with EtOAc (3×15 mL). The combined organic layers were then washed with water (50 mL) and brine (50 mL), dried (MgSO_4), and concentrated. The resultant light yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 3:1) to give aminal **27** (0.019 g, 40% yield) as a clear oil. **27**: $R_f = 0.33$ (silica gel, EtOAc/hexanes, 3:1); IR (film) ν_{max} 3354, 2919, 1731, 1649, 1602, 1484, 1437, 1372, 1343, 1243, 1208, 1120, 1049, 750, 691 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3 , 1:1 mixture of diastereomers) δ 7.41–7.34 (m, 5 H), 7.18–7.13 (m, 3 H), 7.01 (m, 1 H), 6.97 (dd, $J = 5.2, 1.8$ Hz, 1 H), 6.96 (dd, $J = 5.2, 1.8$ Hz, 1 H), 6.90 (d, $J = 4.0$ Hz, 1 H), 6.89 (d, $J = 4.0$ Hz, 1 H), 6.79 (t, $J = 7.4$ Hz, 1 H), 6.77 (t, $J = 7.4$ Hz, 1 H), 6.24 (s, 1 H), 5.92 (t, $J = 6.6$ Hz, 1 H), 5.30 (br s, 1 H), 4.91 (dd, $J = 12.8, 5.9$ Hz, 1 H), 4.89 (dd, $J = 12.8, 5.9$ Hz, 1 H), 3.74 (s, 3 H), 3.68 (s, 3 H), 3.15 (m, 2 H), 2.03 (s, 3 H), 1.97 (s, 3 H); ^{13}C NMR (150 MHz, CDCl_3) δ 172.2, 169.7 (2 C),

159.2, 147.3 (2 C), 142.4 (2 C), 133.2, 133.0, 131.9, 131.7, 131.3, 129.8, 129.1 (2 C), 128.9, 127.9 (2 C), 127.8, 125.9, 125.8, 123.7, 123.6, 121.3, 110.3 (2 C), 105.2 (2 C), 103.0, 66.8, 53.5, 53.4, 52.6, 52.5, 37.4, 37.3, 23.4, 23.3; HRMS (MALDI-FTMS) calcd for $C_{26}H_{23}BrN_2O_4H^+$ [$M + H^+$] 507.0914, found 507.0908.

Oxazole 12. L-Serine methyl ester (214.7 g, 138 mmol, 1.0 equiv), EDC•H₂O (278 g, 145 mmol, 1.05 equiv), and HOBt•H₂O (223 g, 145 mmol, 1.05 equiv) were added sequentially to a solution of Boc-protected L-valine (300 g, 138 mmol, 1.0 equiv) in CH₂Cl₂ (2.5 L) at 25 °C. The resultant mixture was stirred for 5 minutes at 25 °C, and then Et₃N (386 mL, 276 mmol, 2.0 equiv) was added. After stirring for 12 hours at 25 °C, the reaction mixture was poured into water (500 mL) and extracted with CH₂Cl₂ (2 × 300 mL). The combined organic layers were then washed with water (3 × 500 mL), dried (MgSO₄), and concentrated. The resultant product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give amide **30** (404 g, 92% yield) as a light yellow solid. Next, Burgess reagent (3.57 g, 15.0 mmol, 1.5 equiv) was added to a solution of a portion of this amide intermediate (3.18 g, 10.0 mmol, 1.0 equiv) in THF (50 mL) at 25 °C, and the resultant mixture was heated to reflux and stirred for 4 hours. Upon completion, the reaction flask contents were poured into water (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 (MgSO₄), and concentrated. The resultant light yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give oxazoline **31** (2.40 g, 80% yield) as a clear oil. Finally, this new intermediate (2.40 g, 8.0 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (150 mL) and treated sequentially at 0 °C with DBU (1.32 mL, 8.8 mmol, 1.1 equiv) and a solution of BrCCl₃ (0.87 mL, 8.8 mmol, 1.1 equiv) in CH₂Cl₂ (50 mL). The resultant mixture was then warmed to 25 °C and stirred for 3 hours. Upon completion, the reaction flask contents were poured into water (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 (MgSO₄), and concentrated. The resultant light yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give oxazole **12** (2.15 g, 90% yield) as a

clear oil. **12**: $R_f = 0.48$ (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\max}$ 3322, 2968, 1712, 1583, 1520, 1453, 1367, 1322, 1245, 1169, 1109, 1000 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.17 (s, 1 H), 5.30 (d, $J = 9.2$ Hz, 1 H), 4.77 (dd, $J = 9.2, 5.9$ Hz, 1 H), 3.88 (s, 3 H), 2.16 (dq, $J = 5.8, 5.5$ Hz, 1 H), 1.40 (s, 9 H), 0.89 (app t, $J = 8.3$ Hz, 6 H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.6, 162.0, 155.8, 144.3, 133.5, 80.4, 54.7, 52.6, 33.3, 28.7, 19.1, 18.4; HRMS (MALDI-FTMS) calcd for $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_5\text{Na}^+ [\text{M} + \text{Na}^+]$ 321.1421, found 321.1425.

TFA salt of Boc-protected tryptamine (6). Saturated aqueous NaHCO_3 (15 mL) and Boc_2O (2.76 g, 12.68 mmol, 1.5 equiv) were added sequentially to a solution of tryptamine (1.36 g, 8.5 mmol, 1.0 equiv) in 1,4-dioxane (30 mL) at 25 °C. After stirring the resultant suspension for 2 hours at 25 °C, the reaction flask contents were poured into water (100 mL) and extracted with EtOAc (3×150 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, 1:1) to give the desired Boc-protected intermediate (2.03 g, 92%) as an amorphous white solid. This compound (2.03 g, 7.81 mmol, 1.0 equiv) was then dissolved in THF/ H_2O (9:1, 110 mL), and DDQ (3.54 g, 15.6 mmol, 2.0 equiv) was added at 0 °C, yielding a deep red solution. After 2 hours of stirring at 0 °C, the reaction mixture was poured into EtOAc (250 mL) and washed extensively with saturated aqueous NaHCO_3 (4×250 mL) to remove any excess DDQ and its colored by-products. The organic layer was then dried (MgSO_4) and concentrated to give the desired intermediate ketone (1.86 g, 87%) as a yellow solid: $R_f = 0.19$ (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\max}$ 3331, 3260, 1687, 1646, 1535, 1514, 1432, 1361, 1296, 1243, 1167, 1126, 920, 732 cm^{-1} ; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.46 (d, $J = 3.3$ Hz, 1 H), 8.22 (d, $J = 7.3$ Hz, 1 H), 7.54 (d, $J = 7.3$ Hz, 1 H), 7.28 (dt, $J = 7.3, 1.5$ Hz, 1 H), 7.23 (dt, $J = 7.3, 1.5$ Hz, 1 H), 7.07 (t, $J = 5.9$ Hz, 1 H), 4.36 (d, $J = 5.9$ Hz, 2 H), 2.56 (m, 1 H), 1.47 (s, 9 H); ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$) δ 191.7, 156.8, 137.2, 134.2, 126.2, 123.7, 122.6, 122.0, 114.8, 113.0, 78.7, 47.7, 29.1; HRMS (MALDI-FTMS) calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3\text{Na}^+ [\text{M} + \text{Na}^+]$ 297.1210, found 297.1213. When this fragment was needed for coupling, a portion of the ketone intermediate (0.074 g, 0.274 mmol, 1.0 equiv)

was treated with neat TFA (5 mL) at 25 °C. After stirring the resultant solution for 10 minutes at 25 °C, the solvent was removed in vacuo (using several benzene co-evaporations to ensure the complete removal of all TFA) to give the keto tryptamine TFA salt **6** (0.069 g, 99% yield) as a white solid which was used immediately.

MOM-protected 7-bromoisatin (13). Vinyl magnesium bromide (800 mL, 1.0 M in THF, 800 mmol, 3.0 equiv) was added quickly via cannula to a solution of 2-bromonitrobenzene (53.9 g, 266.7 mmol, 1.0 equiv) in THF (800 mL) at –45 °C. After stirring the resultant yellow solution for 45 minutes at –45 °C, the reaction was quenched by the addition of saturated aqueous NH₄Cl (50 mL) and the pH was then adjusted to a value of 6 by the careful addition of 1 N aqueous HCl. The resultant biphasic system was extracted with EtOAc (3 × 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, hexanes/EtOAc, 1:0→1:8) to give 7-bromoindole (33.0 g, 63% yield) as a yellow-orange solid. This newly-formed product (33.0 g, 168.4 mmol, 1.0 equiv) was then dissolved in DMF (150 mL) and freshly ground KOH (23.4 g, 420.9 mmol, 2.5 equiv) was added at 0 °C. The resultant mixture was stirred for 5 minutes at 0 °C, and then a solution of I₂ (44.8 g, 176.8 mmol, 1.05 equiv) in DMF (50 mL) was added at 0 °C. After 15 minutes of additional stirring at 0 °C, the reaction mixture was poured into water (400 mL) and extracted with Et₂O (3 × 200 mL). The combined organic layers were then washed with water (200 mL) and brine (200 mL), dried (MgSO₄), and concentrated to give 3-iodo-7-bromoindole (49.4 g, 91% yield) as a red solid. Without further purification, this newly-formed intermediate (49.4 g, 153.4 mmol, 1.0 equiv) was dissolved in THF (500 mL), cooled to –78 °C, and treated with LiHMDS (184 mL, 1.0 M in THF, 184.0 mmol, 1.2 equiv). Following 15 minutes of stirring at –78 °C, MOMCl (16.1 mL, 214.7 mmol, 1.4 equiv) was added at –78 °C, and the reaction mixture was allowed to warm to 25 °C. After 2 hours of additional stirring at 25 °C, the reaction was quenched by the addition of saturated aqueous NH₄Cl (100 mL) and extracted with EtOAc (3 × 200 mL). The combined organic layers were then washed with water (200 mL) and brine (200

mL), dried (MgSO₄), and concentrated to give *N*-MOM-protected 3-iodo-7-bromoindole (54.0 g, 96% yield) as a brown solid. This crude product (54.0 g, 147.5 mmol, 1.0 equiv) was then dissolved in CH₃CN/THF/water (8.3:1.0:1.7, 660 mL), cooled to 0 °C, and treated sequentially with RuCl₃•3H₂O (3.77 g, 14.8 mmol, 0.1 equiv) and NaIO₄ (94.7 g, 442.68 mmol, 3.0 equiv). The resultant suspension was stirred for 30 minutes at 0 °C before it was filtered through a short pad of silica gel. Following subsequent removal of the residual solvent in vacuo, the residue was taken up in EtOAc (200 mL) and washed with saturated aqueous Na₂S₂O₃ (50 mL), water (50 mL), and brine (50 mL), dried (MgSO₄), and concentrated. The resultant dark red residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 0:1→40:1) to give the desired 7-bromoisatin **7** (27.2 g, 68% yield over 3 steps) as a red-orange solid. **7**: *R*_f = 0.42 (silica gel, EtOAc/hexanes, 1:3); IR (film) ν_{max} 1737, 1608, 1461, 1426, 1337, 1284, 1173, 1085, 1008, 773 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.75 (d, *J* = 7.5 Hz, 1 H), 7.62 (d, *J* = 7.5 Hz, 1 H), 7.05 (t, *J* = 7.5 Hz, 1 H), 5.50 (s, 2 H), 3.39 (s, 3 H); ¹³C NMR (150 MHz, CDCl₃) δ 182.2, 159.2, 147.5, 144.3, 125.7, 124.9, 120.8, 105.4, 71.5, 56.8; HRMS (MALDI-FTMS) calcd for C₁₀H₈BrNO₃Na⁺ [*M* + Na⁺] 291.9580, found 291.9587.

Benzylated oxazole 36. LiBH₄ (301.6 mL, 2.0 M in THF, 603.3 mmol, 3.0 equiv) and absolute EtOH (58.6 mL, 1005 mmol, 5.0 equiv) were added sequentially to a solution of oxazole **12** (60.0 g, 201.1 mmol, 1.0 equiv) in THF (500 mL) at 0 °C. The reaction mixture was then warmed to 25 °C and allowed to stir for 3 hours. EtOAc (200 mL) was then added dropwise at 25 °C, and after an additional 30 minutes had transpired, the reaction mixture was cooled to 0 °C and quenched by the careful addition of 1 N aqueous HCl (~300 mL) until the evolution of hydrogen gas ceased, poured into water (200 mL), and extracted with EtOAc (3 × 300 mL). The combined organic layers were then washed with water (200 mL) and brine (200 mL), dried (MgSO₄), and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, CH₂Cl₂/EtOAc, 1:0→2:1) to give the desired intermediate alcohol (45.0 g, 83% yield) as a transparent oil: *R*_f = 0.43 (silica gel, EtOAc/hexanes, 3:1); [α]_D²⁰ = -33.7 (*c* = 1.0, MeOH); IR (film) ν_{max} 3307, 2954, 2872, 1701, 1519, 1464, 1367, 1247, 1170,

1040 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.51 (s, 1 H), 5.58 (d, $J = 8.0$ Hz, 1 H), 4.71 (dd, $J = 8.0, 5.5$ Hz, 1 H), 4.53 (s, 2 H), 4.43 (s, 1 H), 2.10 (dq, $J = 5.8, 5.5$ Hz, 1 H), 1.41 (s, 9 H), 0.89 (d, $J = 5.8$ Hz, 3 H), 0.86 (d, $J = 5.8$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.3, 163.6, 155.9, 135.4, 80.2, 56.4, 54.8, 33.4, 28.7, 19.1, 18.5; HRMS (MALDI-FTMS) calcd for $\text{C}_{13}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}^+$ [$\text{M} + \text{Na}^+$] 293.1472, found 293.1466. Next, NaHMDS (277.4 mL, 1.0 M in THF, 277.4 mmol, 2.0 equiv) was added to a solution of this alcohol (50.0 g, 138.7 mmol, 1.0 equiv) in THF (1.0 L) at -78°C over the course of 30 minutes. Benzyl bromide (15.1 mL, 138.7 mmol, 1.0 equiv) and $n\text{-Bu}_4\text{NI}$ (0.100 g, catalytic) were then added at -78°C , and the resulting mixture was warmed to 25°C and stirred for 36 hours. Upon completion, the reaction mixture was poured into brine (300 mL) and extracted with EtOAc (3×300 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, 1:20 $\rightarrow$ 1:4) to give oxazole **36** (36.0 g, 72% yield) as a transparent oil. **36**: $R_f = 0.42$ (silica gel, EtOAc/hexanes, 3:10); $[\alpha]_D^{20} = -26.6$ ($c = 1.0$, MeOH); IR (film) ν_{max} 3318, 2954, 1707, 1501, 1448, 1360, 1243, 1167, 1084, 737 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.51 (s, 1 H), 7.33–7.29 (m, 5 H), 5.28 (d, $J = 7.6$ Hz, 1 H), 4.73 (dd, $J = 7.6, 4.7$ Hz, 1 H), 4.57 (s, 2 H), 4.43 (s, 2 H), 2.16 (dq, $J = 6.4, 4.7$ Hz, 1 H), 1.41 (s, 9 H), 0.89 (d, $J = 6.4$ Hz, 3 H), 0.88 (d, $J = 6.4$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 164.6, 163.5, 155.8, 138.1, 136.4, 128.8, 128.3, 80.1, 72.9, 64.3, 54.7, 33.3, 28.7, 19.0, 18.3; HRMS (MALDI-FTMS) calcd for $\text{C}_{28}\text{H}_{28}\text{N}_2\text{O}_4\text{Na}^+$ [$\text{M} + \text{Na}^+$] 383.1941, found 383.1938.

Tertiary alcohol 11. To a solution of oxazole **36** (20.0 g, 55.5 mmol, 1.0 equiv) in THF (300 mL) at -78°C was added $n\text{-BuLi}$ (69.3 mL, 1.6 M in hexanes, 111.0 mmol, 2.0 equiv) over the course of 5 minutes, during which time the initial pale yellow color of the solution deepened to a dark brown. After 30 minutes of further stirring at -78°C , a solution of isatin derivative **13** (15.7 g, 58.3 mmol, 1.05 equiv) in THF (60 mL) was then added dropwise via cannula over the course of 5 minutes. Upon completion, the reaction mixture was quenched immediately with saturated aqueous NH_4Cl (200 mL) and extracted with EtOAc (3×200 mL). The combined

organic layers were then washed with water (200 mL) and brine (200 mL), dried (MgSO₄), and concentrated. The resultant orange residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 10:1→2:1) to give tertiary alcohol **11** (25.5 g, 73% yield) as a yellow foam. **11**: *R*_f = 0.65 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3330, 2966, 2931, 2872, 1707, 1607, 1501, 1367, 1172, 1090, 744 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.50 (d, *J* = 8.2 Hz, 1 H), 7.49 (d, *J* = 8.2 Hz, 1 H), 7.40–7.25 (m, 12 H), 6.95 (dd, *J* = 8.2, 7.4 Hz, 1 H), 6.94 (dd, *J* = 8.2, 7.6 Hz, 1 H), 6.17 (s, 1 H), 6.11 (s, 1 H), 5.48 (d, *J* = 10.8 Hz, 1 H), 5.45 (s, 2 H), 5.42 (d, *J* = 10.8 Hz, 1 H), 5.12 (d, *J* = 9.1 Hz, 1 H), 5.11 (d, *J* = 8.8 Hz, 1 H), 4.81–4.52 (m, 10 H), 3.37 (s, 3 H), 3.36 (s, 3 H), 2.00–1.97 (m, 2 H), 1.40 (s, 9 H), 1.39 (s, 9 H), 0.82–0.77 (m, 12 H); ¹³C NMR (100 MHz, CDCl₃) δ 177.0, 175.9, 162.6 (2 C), 155.2 (2 C), 145.2, 145.1, 139.6, 139.6, 136.4, 136.2, 135.7, 135.5, 131.3, 131.1, 128.5 (2 C), 128.3 (2 C), 128.2 (2 C), 125.7 (2 C), 125.0, 124.9, 124.5, 124.4, 103.6 (2 C), 79.5 (2 C), 73.3 (2 C), 73.2, 73.1, 71.5 (2 C), 65.2, 65.1, 56.2, 56.1, 54.0, 53.8, 32.7 (2 C), 28.2 (2 C), 18.4, 18.3, 17.8, 17.6; HRMS (MALDI-FTMS) calcd for C₃₀H₃₆BrN₃O₇Na⁺ [*M* + Na⁺] 652.1629, found 652.1634.

Triaryl intermediate 8. Cbz-protected L-tyrosine **9** (41.8 g, 126.8 mmol, 4.0 equiv) and *p*-TsOH•H₂O (24.1 g, 126.8 mmol, 4.0 equiv) were added sequentially to a solution of tertiary alcohol **11** (20 g, 31.7 mmol, 1.0 equiv) in 1,2-dichloroethane at 25 °C. The resultant mixture was then heated to reflux, and after 25 minutes of further stirring, the reaction flask contents were quickly cooled to 0 °C, poured into saturated aqueous NaHCO₃ (300 mL), and extracted with EtOAc (3 × 300 mL). The combined organic layers were then washed with water (3 × 200 mL), dried (MgSO₄), and concentrated. The resultant black residue was purified quickly by flash column chromatography (silica gel, EtOAc/CH₂Cl₂, 0:1→3:1; then EtOAc/MeOH, 10:1) to give amine **38** (12.0 g, 47% yield) as a dark foam. This intermediate (12.0 g, 15.0 mmol, 1.0 equiv) was then dissolved in 1,4-dioxane (30 mL), and saturated aqueous NaHCO₃ (15 mL) and Boc₂O (2.76 g, 12.68 mmol, 1.5 equiv) were added sequentially at 25 °C. After stirring the resultant suspension for 2 hours at 25 °C, the reaction flask contents were poured into water (100 mL) and extracted with EtOAc (3 × 150 mL). The combined organic layers were then washed with water

(100 mL) and brine (100 mL), dried (MgSO₄), and concentrated. The resultant brown residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:20→1:2) to give the desired triaryl product **8** and its diastereomer **39** (4.6 g each, 33% combined yield over two steps) as pale yellow foams. **8**: *R_f* = 0.38 (silica gel, EtOAc/hexanes, 1:1); [α]_D²⁰ = +153.8 (*c* = 1.0, MeOH); IR (film) ν_{max} 3312, 2966, 2872, 1725, 1619, 1507, 1454, 1372, 1249, 1166, 1601, 748 cm⁻¹; ¹H NMR (600 MHz, 323 K, CD₃CN) δ 8.78 (s, 1 H), 7.82 (s, 1 H), 7.43 (dd, *J* = 7.9, 0.8 Hz, 1 H), 7.35–7.17 (m, 10 H), 7.05 (dd, *J* = 7.9, 2.2 Hz, 1 H), 6.90 (dd, *J* = 8.3, 8.2 Hz, 1 H), 6.78 (d, *J* = 7.9 Hz, 1 H), 6.77 (d, *J* = 1.7 Hz, 1 H), 5.86 (s, 1 H), 5.63 (s, 1 H), 5.04 (d, *J* = 12.7 Hz, 1 H), 5.00 (d, *J* = 12.7 Hz, 1 H), 4.37–4.32 (m, 1 H), 4.23 (d, *J* = 11.8 Hz, 1 H), 4.20 (d, *J* = 11.8 Hz, 1 H), 4.07 (d, *J* = 11.9 Hz, 1 H), 3.94 (d, *J* = 11.9 Hz, 1 H), 3.66–3.62 (m, 1 H), 3.56 (s, 3 H), 2.99 (dd, *J* = 14.2, 5.3 Hz, 1 H), 2.80 (dd, *J* = 14.2, 8.6 Hz, 1 H), 2.05–2.00 (m, 1 H), 1.36 (s, 9 H), 0.87 (d, *J* = 6.8 Hz, 3 H), 0.79 (d, *J* = 6.8 Hz, 3 H); ¹³C NMR (150 MHz, 323 K, CD₃CN) δ 177.4, 172.8, 164.1, 156.8, 156.5, 155.2, 145.3, 141.7, 139.3, 138.0, 135.7, 132.8, 132.1, 131.6, 130.9, 129.4, 129.4, 129.1, 128.8, 128.6, 128.5, 128.3, 126.1, 126.1, 124.9, 118.4, 103.6, 80.1, 72.7, 67.2, 64.4, 58.1, 56.5, 55.7, 52.6, 37.6, 32.9, 28.5, 19.0, 18.7; HRMS (MALDI-FTMS) calcd for C₄₆H₄₉BrN₄O₁₀Na⁺ [*M* + Na⁺] 919.2524, found 919.2517.

39: *R_f* = 0.35 (silica gel, EtOAc/hexanes, 1:1); [α]_D²⁰ = –119.3 (*c* = 0.7, MeOH); IR (film) ν_{max} 3295, 2977, 2930, 1719, 1613, 1513, 1442, 1366, 1254, 1225, 1167, 1066, 749 cm⁻¹; ¹H NMR (600 MHz, 323 K, CD₃CN) δ 8.87 (s, 1 H), 8.10 (s, 1 H), 7.41 (dd, *J* = 8.3, 0.8 Hz, 1 H), 7.35–7.17 (m, 10 H), 7.06 (dd, *J* = 7.9, 2.2 Hz, 1 H), 6.89 (dd, *J* = 8.3, 8.3 Hz, 1 H), 6.82 (d, *J* = 1.7 Hz, 1 H), 6.78 (d, *J* = 7.9 Hz, 1 H), 6.01 (s, 1 H), 5.71 (s, 1 H), 5.05–4.96 (m, 2 H), 4.50–4.47 (m, 1 H), 4.37–4.33 (m, 1 H), 4.20 (s, 2 H), 4.01 (d, *J* = 11.4 Hz, 1 H), 3.95 (d, *J* = 11.4 Hz, 1 H), 3.65–3.60 (m, 1 H), 3.61 (s, 3 H), 3.03–2.99 (m, 1 H), 2.78 (dd, *J* = 14.4, 8.8 Hz, 1 H), 2.03–2.00 (m, 1 H), 1.37 (s, 9 H), 0.87 (d, *J* = 6.8 Hz, 3 H), 0.79 (d, *J* = 6.8 Hz, 3 H); ¹³C NMR (150 MHz, 323 K, CD₃CN) δ 177.2, 172.9, 164.0, 156.9, 156.6, 155.0, 145.2, 141.7, 139.3, 138.0, 135.7, 132.8, 131.9, 131.4, 130.9, 129.5, 129.3, 129.1, 128.7, 128.6, 128.4, 128.3, 126.2, 125.1, 124.8, 118.4, 103.5, 80.1, 72.7, 67.0, 64.4, 58.0, 56.6, 56.5, 52.6, 37.6, 32.8, 28.5, 18.9,

18.7; HRMS (MALDI-FTMS) calcd for $C_{46}H_{49}BrN_4O_{10}Na^+$ $[M + Na^+]$ 919.2524, found 919.2528.

Bis-MOM protected intermediate 40. K_2CO_3 (31.9 g, 230.8 mmol, 40 equiv) and MOMCl (8.8 mL, 115.4 mmol, 20 equiv) were added sequentially to a solution of phenol **8** (5.17 g, 5.77 mmol, 1.0 equiv) in acetone (500 mL) at 0 °C. After 10 minutes of stirring at 0 °C, the reaction mixture was warmed to 25 °C and stirred for an additional hour. Upon completion, the reaction mixture was filtered through a short pad of $MgSO_4$, concentrated, and purified by flash column chromatography (silica gel, EtOAc/hexanes, 0:1→3:2) to give bis-MOM protected intermediate **40** (4.85 g, 85% yield) as a pale yellow solid. **40**: R_f = 0.42 (silica gel, EtOAc/hexanes, 1:1); $[\alpha]_D^{20}$ = -47.6 (c = 1.0, MeOH); IR (film) ν_{max} 3331, 2954, 1725, 1696, 1578, 1496, 1455, 1361, 1337, 1243, 1208, 1161, 1073, 996, 914, 732, 697 cm^{-1} ; 1H NMR (600 MHz, CD_3CN) δ 7.48 (d, J = 7.4 Hz, 1 H), 7.36–7.23 (m, 10 H), 7.16 (dd, J = 8.3, 1.7 Hz, 1 H), 7.10 (d, J = 7.0 Hz, 1 H), 6.96 (d, J = 8.3 Hz, 1 H), 6.92 (d, J = 2.2 Hz, 1 H), 6.86 (t, J = 7.9 Hz, 1 H), 5.95 (br s, 1 H), 5.71 (br s, 1 H), 5.39 (AB, J = 10.5 Hz, ν_{ab} = 45.1 Hz, 2 H), 5.06 (AB, J = 12.2 Hz, ν_{ab} = 29.3 Hz, 2 H), 4.85 (AB, J = 6.6 Hz, ν_{ab} = 57.4 Hz, 2 H), 4.56 (br s, 1 H), 4.41 (m, 1 H), 4.29 (AB, J = 11.7 Hz, ν_{ab} = 11.8 Hz, 2 H), 4.05 (AB, J = 10.6 Hz, ν_{ab} = 13.6 Hz, 2 H), 3.62 (s, 3 H), 3.32 (s, 3 H), 3.10 (dd, J = 13.6, 4.9 Hz, 1 H), 3.04 (s, 3 H), 2.86 (dd, J = 13.6, 8.8 Hz, 1 H), 2.07 (m, 1 H), 1.40 (s, 9 H), 0.91 (d, J = 6.6 Hz, 3 H), 0.83 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 176.5, 172.8, 164.5, 153.7, 144.2, 141.1, 139.4, 137.0, 135.4, 133.2, 131.6, 131.2, 131.0, 129.3, 129.0, 128.8, 128.7, 128.6, 128.4, 128.2, 125.7, 124.8, 115.2, 103.3, 94.7, 72.9, 72.6, 67.1, 64.4, 56.2, 56.1, 52.6, 37.8, 32.7, 28.5, 19.0, 18.7; HRMS (MALDI-FTMS) calcd for $C_{50}H_{57}BrN_4O_{12}Na^+$ $[M + Na^+]$ 1007.3048, found 1007.3024.

Macrolactam 42. Solid LiOH (0.85 g, 20.32 mmol, 20 equiv) was added to a solution of **40** (1.0 g, 1.02 mmol) in THF/ CH_3OH/H_2O (10:2:1, 39 mL) at 25 °C and the resultant mixture was heated at reflux for 20 minutes. The reaction mixture was then poured into EtOAc (100 mL) and washed with 1 N aqueous HCl (3 × 25 mL). The combined aqueous layers were then reextracted with EtOAc (3 × 25 mL), and the combined organic layers were washed with water

(50 mL) and brine (50 mL), dried (MgSO₄), and concentrated to the intermediate carboxylic acid (0.961 g, 96% yield) as a white foam. This intermediate (0.961 g, 0.976 mmol, 1.0 equiv) was immediately treated with neat TFA (10 mL) at 25 °C, and after 10 minutes of exposure, the solvent was removed *in vacuo* (using several benzene co-evaporations to ensure the complete removal of all TFA) to give amino acid **41** (0.820 g, 98% yield) as a white oil. This newly-formed adduct (0.820 g, 0.940 mmol, 1.0 equiv) was then dissolved in CH₂Cl₂/DMF (2:1, 3.0 L, final concentration of 3×10^{-4} M), and HATU (0.857 g, 2.24 mmol, 2.2 equiv) and 2,4,6-collidine (1.14 mL, 6.70 mmol, 6.6 equiv) were added sequentially at 25 °C. After 12 hours of stirring at 25 °C, the reaction flask contents were concentrated; the residue was taken up in EtOAc (100 mL) and washed with saturated aqueous NaHCO₃ (2 × 25 mL). The combined aqueous layers were then reextracted with EtOAc (2 × 25 mL), and the combined organic layers were washed with water (50 mL) and brine (50 mL), dried (MgSO₄), and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 0:1→1:0) to give the bis-MOM protected macrolactam **42** (0.140 g, 16% yield) and the mono-MOM protected macrolactam **43** (0.220 g, 27% yield) as amorphous white solids.

42: R_f = 0.66 (silica gel, EtOAc/hexanes, 2:1); $[\alpha]_D^{20}$ = -177.0 (c = 0.57, MeOH); IR (film) $\nu_{\max}$ 3295, 2931, 1791, 1666, 1531, 1496, 1455, 1331, 1243, 1155, 1073, 991, 914, 732, 697 cm⁻¹; ¹H NMR (600 MHz, CD₃CN) δ 7.53 (d, J = 7.9 Hz, 1 H), 7.38–7.27 (m, 9 H), 7.20 (d, J = 7.4 Hz, 2 H), 7.14 (d, J = 7.0 Hz, 2 H), 6.91 (t, J = 8.3 Hz, 1 H), 6.90 (d, J = 8.8 Hz, 1 H), 6.35 (s, 1 H), 6.06 (br d, 1 H), 5.37 (AB, J = 10.1 Hz, ν_{ab} = 75.4 Hz, 2 H), 5.08 (AB, J = 12.7 Hz, ν_{ab} = 21.0 Hz, 2 H), 4.91 (AB, J = 6.5 Hz, ν_{ab} = 25.9 Hz, 2 H), 4.46 (t, J = 7.9 Hz, 1 H), 4.14 (t, J = 8.8 Hz, 1 H), 4.09 (AB, J = 11.4 Hz, ν_{ab} = 15.4 Hz, 2 H), 3.68 (AB, J = 11.4 Hz, ν_{ab} = 25.4 Hz, 2 H), 3.30 (s, 3 H), 3.11 (t, J = 12.7 Hz, 1 H), 3.05 (s, 3 H), 2.66 (d, J = 12.7 Hz, 1 H), 2.02 (m, 1 H), 1.02 (d, J = 6.1 Hz, 3 H), 0.90 (d, J = 6.1 Hz, 3 H); ¹³C NMR (150 MHz, CD₃CN) δ 176.1, 173.5, 164.8, 152.8, 145.9, 141.3, 138.9, 138.0, 136.8, 136.0, 133.5, 130.7, 130.5, 130.3, 130.1, 129.3, 129.2, 128.8, 128.7, 128.6, 128.4, 125.9, 125.0, 114.4, 103.4, 94.2, 72.9, 72.3, 67.0, 64.1,

57.4, 57.1, 56.3, 55.9, 38.2, 30.7, 19.7, 19.3; HRMS (MALDI-FTMS) calcd for $C_{44}H_{45}BrN_4O_9Na^+$ $[M + Na^+]$ 875.2262, found 875.2257.

43: R_f = 0.43 (silica gel, EtOAc/hexanes, 2:1); IR (film) ν_{max} 3413, 2943, 1713, 1660, 1508, 1455, 1337, 1284, 1243, 1214, 1173, 1090, 1087, 750, 697 cm^{-1} ; 1H NMR (600 MHz, CD_3CN) δ 7.53 (d, J = 8.3 Hz, 1 H), 7.38–7.27 (m, 9 H), 7.20 (d, J = 7.0 Hz, 2 H), 7.13 (d, J = 7.4 Hz, 1 H), 7.03 (br d, J = 7.4 Hz, 1 H), 6.91 (t, J = 7.5 Hz, 1 H), 6.69 (d, J = 7.9 Hz, 1 H), 6.26 (s, 1 H), 6.07 (br d, 1 H), 5.34 (AB, J = 11.0 Hz, ν_{ab} = 15.8 Hz, 2 H), 5.07 (AB, J = 12.3 Hz, ν_{ab} = 22.0 Hz, 2 H), 4.45 (t, J = 7.5 Hz, 1 H), 4.10 (t, J = 7.5 Hz, 1 H), 4.08 (AB, J = 4.4 Hz, ν_{ab} = 16.2 Hz, 2 H), 3.63 (AB, J = 11.4 Hz, ν_{ab} = 22.8 Hz, 2 H), 3.31 (s, 3 H), 3.08 (t, J = 11.8 Hz, 1 H), 2.62 (d, J = 11.8 Hz, 1 H), 2.00 (m, 1 H), 1.01 (d, J = 5.7 Hz, 3 H), 0.89 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 176.2, 173.5, 164.7, 156.2, 152.8, 146.3, 141.3, 138.9, 138.0, 136.6, 136.0, 133.6, 130.8, 130.6, 129.3, 129.2, 128.8, 128.7, 128.6, 128.4, 127.6, 125.9, 124.9, 116.2, 103.2, 72.9, 72.4, 67.0, 64.1, 57.6, 57.0, 56.5, 38.3, 30.7, 19.7, 19.3; HRMS (MALDI-FTMS) calcd for $C_{42}H_{41}BrN_4O_8Na^+$ $[M + Na^+]$ 831.2000, found 831.2001.

Deprotected macrolactam 7. BCl_3 (7.6 mL, 1.0 M in CH_2Cl_2 , 7.6 mmol, 20 equiv) was added dropwise to a solution of bis-MOM protected macrolactam **43** (0.325 g, 0.38 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) at $-78^\circ C$ over the course of 2 minutes. After 2 hours of additional stirring at $-78^\circ C$, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL) and then enough THF was added to generate a biphasic system. Aqueous 3 N $NaOH$ (4 mL) was added at $25^\circ C$ and the mixture was stirred for an additional hour. The resultant mixture was poured into water (50 mL) and extracted with EtOAc (2×25 mL). The residual aqueous layer was acidified with 1 N aqueous HCl and reextracted with EtOAc (2×25 mL), and the combined organic layers were then washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated. The resultant light yellow residue was purified by flash column chromatography (silica gel, $CH_2Cl_2/MeOH$, 1:0→9:1) to give the deprotected macrolactam **7** (0.167 g, 65% yield) as an off-white solid. **7:** R_f = 0.41 (silica gel, EtOAc); $[\alpha]_D^{20}$ = -230.3 (c = 0.31, MeOH); IR (film) ν_{max} 3392, 1715, 1649, 1614, 1508, 1455, 1261, 1220, 1126, 1090, 1020, 750, 597 cm^{-1} ;

^1H NMR (600 MHz, CD_3CN) δ 8.66 (s, 1 H), 7.47 (d, J = 8.3 Hz, 1 H), 7.37–7.32 (m, 5 H), 7.27 (br s, 1 H), 7.22 (s, 1 H), 7.07 (d, J = 7.4 Hz, 1 H), 7.02 (d, J = 7.9 Hz, 1 H), 6.90 (t, J = 7.9 Hz, 1 H), 6.70 (d, J = 7.9 Hz, 1 H), 6.23 (s, 1 H), 6.03 (br d, J = 6.3, Hz 1 H), 5.07 (AB, J = 12.3 Hz, ν_{ab} = 21.9 Hz, 2 H), 4.45 (t, J = 7.9 Hz, 1 H), 4.11 (t, J = 8.3 Hz, 1 H), 3.63 (ABX, J = 10.1, 5.7 Hz, ν_{ab} = 15.8 Hz, 2 H), 3.06 (t, J = 12.7 Hz, 1 H), 2.78 (br t, J = 5.6 Hz, 1 H), 2.62 (d, J = 12.7 Hz, 1 H), 2.00 (m, 1 H), 1.01 (d, J = 6.1 Hz, 3 H), 0.91 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 175.5, 173.4, 164.6, 156.2, 153.0, 144.7, 142.4, 139.0, 138.0, 133.6, 133.0, 130.6, 130.0, 129.3, 129.0, 128.7, 128.6, 127.7, 125.4, 124.2, 116.2, 102.9, 67.0, 57.6, 57.0, 55.8, 38.4, 30.7, 19.6, 19.3; HRMS (MALDI-FTMS) calcd for $\text{C}_{33}\text{H}_{31}\text{BrN}_4\text{O}_7\text{Na}^+$ [$\text{M} + \text{Na}^+$] 697.1268, found 697.1266. Note: use of the same procedure served to convert **42** into **7** in comparable yields; mixtures of **42** and **43** could also be transformed into **7** with equal facility with this protocol.

Macrocyclic precursor 46. Boc-protected tertiary alcohol **11** (0.200 g, 0.318 mmol, 1.0 equiv) was treated with neat TFA (2 mL) at 25 °C. After stirring the resultant solution for 10 minutes at 25 °C, the solvent was removed in vacuo (using several benzene co-evaporations to ensure the complete removal of all TFA) to give amine **44** (0.168 g, 99% yield) as a white foam. This intermediate (0.168 g, 0.318 mmol, 1.0 equiv) was then dissolved in DMF (5 mL) and Cbz-protected L-tyrosine (0.150 g, 0.477 mmol, 1.5 equiv), HOBT• H_2O , (0.073 g, 0.477 mmol, 1.5 equiv), and EDC• H_2O (0.092 g, 0.477 mmol 1.5 equiv) were added sequentially at 25 °C. The resultant mixture was cooled to 0 °C, and then Et_3N (0.133 mL, 0.953 mmol, 3.0 equiv) was added. After 5 minutes of stirring at 0 °C, the reaction mixture was warmed to 25 °C and stirred for 12 additional hours. Upon completion, the reaction flask contents were poured into saturated aqueous NaHCO_3 (10 mL) and extracted with EtOAc (3×25 mL). The combined organic layers were then washed with 1 N aqueous HCl (3×10 mL) and brine (25 mL), dried (MgSO_4), and concentrated. The resultant yellow oil was purified by flash chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{EtOAc}$, 1:0→3:1) to give the desired macrocyclic precursor **46** (0.167 g, 63% yield) as a yellow foam. **46**: R_f = 0.34 (silica gel, EtOAc/hexanes, 2:1); IR (film) ν_{max} 3307, 3060, 2966,

1738, 1673, 1620, 1521, 1462, 1350, 1244, 743 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 7.45 (t, J = 8.8 Hz, 2 H), 7.40–6.95 (m, 10 H), 7.22 (d, J = 7.0 Hz, 4 H), 7.10 (d, J = 8.3 Hz, 1 H), 7.08 (d, J = 8.3 Hz, 1 H), 7.00–6.90 (m, 4 H), 6.64 (d, J = 7.0 Hz, 4 H), 5.96 (d, J = 8.7 Hz, 1 H), 5.95 (d, J = 8.7 Hz, 1 H), 5.59 (s, 2 H), 5.35–5.30 (m, 4 H), 5.05–4.90 (m, 4 H), 4.80–4.70 (m, 2 H), 4.50–4.40 (m, 8 H), 4.30–4.20 (m, 2 H), 3.28 (s, 3 H), 3.27 (s, 3 H), 2.85 (dd, J = 14.0, 9.3 Hz, 1 H), 2.78 (dd, J = 14.0, 9.3 Hz, 1 H), 2.64 (dd, J = 14.0, 9.1 Hz, 1 H), 2.56 (dd, J = 14.0, 9.1 Hz, 1 H), 2.10–2.00 (m, 2 H), 0.83 (d, J = 6.6 Hz, 3 H), 0.82 (d, J = 6.6 Hz, 3 H), 0.75 (d, J = 6.6 Hz, 3 H), 0.72 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 176.4, 176.3, 172.4 (2 C), 163.1, 163.0, 156.9, 156.8, 156.5, 156.4, 146.0, 145.9, 140.4, 140.3, 138.9 (2 C), 137.9 (2 C), 137.1, 137.0, 136.1, 136.0, 132.7, 132.6, 129.4 (2 C), 129.3 (4 C), 129.2 (2 C), 129.1 (4 C), 129.0 (2 C), 128.9 (2 C), 128.8 (2 C), 128.7 (2 C), 128.6 (2 C), 128.4 (2 C), 115.9 (2 C), 104.0 (2 C), 74.3, 74.1, 73.1, 73.0, 72.3, 72.2, 67.0, 66.9, 64.8, 64.7, 57.1 (2 C), 56.3 (2 C), 53.7, 53.6, 37.8, 37.7, 19.0, 18.9, 18.6, 18.5; HRMS (MALDI-FTMS) calcd for $\text{C}_{42}\text{H}_{43}\text{BrN}_4\text{O}_9\text{Na}^+$ [$\text{M} + \text{Na}^+$] 849.2111, found 849.2112.

Boc-protected primary alcohol 47. Boc_2O (0.061 g, 0.28 mmol, 1.05 equiv), Et_3N (0.081 mL, 0.588 mmol, 2.2 equiv) and 4-DMAP (0.003 g, 0.0267 mmol, 0.1 equiv) were added sequentially to a solution of deprotected macrolactam **7** (0.180 g, 0.267 mmol, 1.0 equiv) in 1,4-dioxane (5.5 mL) at 25 $^\circ\text{C}$. After 1 hour of stirring at 25 $^\circ\text{C}$, the reaction mixture was diluted with EtOAc (5 mL), quenched by the addition of 0.5 N aqueous HCl (5 mL), poured into water (25 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 light yellow residue was purified by flash column chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 1:0 $\rightarrow$ 9:1) to give Boc-protected primary alcohol **47** (0.145 g, 70% yield) as an off-white solid. **47**: R_f = 0.31 (silica gel, EtOAc/hexanes, 5:1); $[\alpha]_D^{20}$ = -204.8 (c = 0.73, MeOH); IR (film) ν_{max} 3413, 2919, 1713, 1660, 1502, 1449, 1284, 1249, 1214, 1143, 1020, 738, 650, 609 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 8.86 (s, 1 H), 7.49 (d, J = 7.9 Hz, 1 H), 7.38–7.30 (m, 5 H), 7.23 (br d, 1 H), 7.08 (d, J = 7.4 Hz, 1 H), 7.06 (d, J = 8.3 Hz, 1 H), 6.91 (t, J = 7.9 Hz, 1 H), 6.40 (s, 1

H), 6.08 (br d, 1 H), 5.08 (AB, $J = 12.3$ Hz, $\nu_{ab} = 20.6$ Hz, 2 H), 4.46 (t, $J = 7.4$ Hz, 1 H), 4.17 (t, $J = 8.8$ Hz, 1 H), 3.64 (AB, $J = 12.7$ Hz, $\nu_{ab} = 22.8$ Hz, 2 H), 3.16 (t, $J = 12.2$ Hz, 1 H), 2.82 (br s, 1 H), 2.73 (d, $J = 12.2$ Hz, 1 H), 2.01 (m, 1 H), 1.38 (s, 9 H), 1.02 (d, $J = 5.7$ Hz, 3 H), 0.92 (d, $J = 7.0$ Hz, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 174.9, 173.2, 164.9, 151.1, 147.2, 143.7, 142.2, 139.5, 134.8, 133.6, 133.5, 133.2, 130.6, 129.3 (2 C), 128.8, 128.6, 125.7, 124.6, 123.6, 103.4, 84.4, 67.0, 57.2, 57.0, 55.8, 38.4, 30.6, 27.4, 19.6, 19.3; HRMS (MALDI-FTMS) calcd for $\text{C}_{38}\text{H}_{39}\text{BrN}_4\text{O}_9\text{Na}^+ [\text{M} + \text{Na}^+]$ 797.1792, found 797.1791.

Amide 5. A solution of IBX (0.174 g, 0.612 mmol, 5.0 equiv) in DMSO (2.0 mL) was added to a solution of Boc-protected alcohol **47** (0.095 g, 0.123 mmol, 1.0 equiv) in DMSO (1.5 mL) at 25 °C. After stirring for 2 hours at 25 °C, the reaction mixture was poured into EtOAc and washed extensively with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (3×25 mL) to remove the IBA by-product and any residual IBX. The combined organic layers were then washed with water (3×20 mL) and brine (20 mL), dried (MgSO_4), and concentrated to give the desired aldehyde (0.084 g, 89% yield) as a yellow foam. Pressing forward without any further purification, this newly-formed intermediate (0.084 g, 0.108 mmol, 1.0 equiv) was dissolved in DMSO (3 mL) and treated sequentially at 25 °C with resorcinol (0.0671 g, 0.613 mmol, 5.0 equiv), a solution of $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ (0.094 g, 0.613 mmol, 5.0 equiv) in water (0.3 mL), and a solution of NaClO_2 (0.045 g, 0.613 mmol, 5.0 equiv) in water (0.3 mL). After stirring for 2 hours at 25 °C, the reaction mixture was 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/hexanes, 4:1 $\rightarrow$ 1:0; then MeOH/EtOAc, 1:4 $\rightarrow$ 1:1) to give the desired free acid (0.072 g, 74% yield) as a white oil. This intermediate (0.072 g, 0.091 mmol, 1.0 equiv) was then dissolved in DMF (2.0 mL) and treated sequentially at 25 °C with freshly prepared keto tryptamine TFA salt **6** (0.074 g, 0.274 mmol, 3.0 equiv), NaHCO_3 (0.122 g, 1.37 mmol, 15 equiv), $\text{EDC} \cdot \text{H}_2\text{O}$ (0.053 g, 0.274 mmol, 3.0 equiv) and $\text{HOBt} \cdot \text{H}_2\text{O}$ (0.043 g, 0.274 mmol, 3.0 equiv). After 12 hours of stirring at 25 °C, the reaction mixture was poured into

saturated aqueous NaHCO_3 (25 mL) and extracted with EtOAc (3×25 mL). The combined organic layers were then washed with 1 N aqueous HCl (20 mL), water (20 mL), and brine (20 mL), dried (MgSO_4), and concentrated. The resultant light yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 0:1 $\rightarrow$ 1:0) to give amide **5** (0.066 g, 76% yield) as a yellow solid. **5**: $R_f = 0.36$ (silica gel, EtOAc/hexanes, 1:1); $[\alpha]_D^{20} = -133.5$ ($c = 0.49$, MeOH); IR (film) ν_{max} 3262, 1726, 1662, 1538, 1503, 1426, 1280, 1244, 1209, 1144, 1039, 751 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 10.02 (s, 1 H), 8.91 (s, 1 H), 8.22 (d, $J = 7.4$ Hz, 1 H), 8.01 (s, 1 H), 7.65 (s, 1 H), 7.50 (d, $J = 7.4$ Hz, 1 H), 7.37–7.22 (m, 10 H), 7.04 (br d, 1 H), 6.96 (br d, 1 H), 6.74 (t, $J = 7.4$ Hz, 1 H), 6.58 (s, 1 H), 6.25 (d, $J = 7.4$ Hz, 1 H), 5.10 (m, 2 H), 4.57 (br t, 1 H), 4.35 (AB, $J = 14.6$ Hz, $\nu_{\text{ab}} = 39.1$ Hz, 2 H), 4.25 (br t, 1 H), 3.18 (t, $J = 11.4$ Hz, 1 H), 2.79 (d, $J = 11.4$ Hz, 1 H), 2.05 (m, 1 H), 1.40 (s, 9 H), 1.03 (br d, 3 H), 0.94 (br d, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 189.7, 174.1, 173.2, 164.1, 160.3, 156.2, 151.2, 150.1, 146.9, 142.4, 138.0, 137.3, 134.5, 134.2, 134.0, 133.7, 133.0, 132.6, 131.1, 130.5, 129.3, 128.8, 128.6, 126.3, 124.9, 124.5, 124.2, 123.9, 123.2, 122.3, 115.1, 112.9, 102.8, 84.4, 67.0, 57.2, 56.7, 46.5, 38.3, 30.6, 27.5, 19.6, 19.3; HRMS (MALDI-FTMS) calcd for $\text{C}_{48}\text{H}_{45}\text{BrN}_6\text{O}_{10}\text{Na}^+$ [$\text{M} + \text{Na}^+$] 967.2273, found 967.2269.

Oxazole 4. POCl_3 (3.0 mL) was added to a solution of amide **5** (0.380 g, 0.402 mmol, 1.0 equiv) in pyridine (12.0 mL) at 25 $^\circ\text{C}$. After 2 hours of stirring at 25 $^\circ\text{C}$, the reaction mixture was diluted with EtOAc (10 mL), poured into a cold (0 $^\circ\text{C}$) 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 light yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 0:1 $\rightarrow$ 1:0) to give oxazole **4** (0.188 g, 52% yield) as an off-white solid. **4**: $R_f = 0.57$ (silica gel, EtOAc/hexanes, 1:1); $[\alpha]_D^{20} = -199.7$ ($c = 0.69$, MeOH); IR (film) ν_{max} 3279, 2927, 1733, 1700, 1652, 1612, 1535, 1506, 1453, 1247, 1212, 1141, 1059, 742 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 9.86 (s, 1 H), 9.20 (s, 1 H), 7.69 (d, $J = 7.9$ Hz, 1 H), 7.50–7.17 (m, 11 H), 7.08 (s, 2 H), 6.92 (d, $J = 7.9$ Hz, 1 H), 6.68 (d, $J = 7.4$ Hz, 1 H), 6.43 (m, 2 H), 6.28 (br d, 1 H),

5.09 (AB, $J = 12.3$ Hz, $\nu_{ab} = 22.8$ Hz, 2 H), 4.60 (t, $J = 5.7$ Hz, 1 H), 4.23 (t, $J = 8.8$ Hz, 1 H), 3.23 (t, $J = 11.8$ Hz, 1 H), 2.76 (d, $J = 11.8$ Hz, 1 H), 2.05 (m, 1 H), 1.37 (s, 9 H), 1.05 (d, $J = 5.7$ Hz, 3 H), 0.94 (d, $J = 7.0$ Hz, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 174.3, 173.5, 165.8, 156.3, 151.6, 151.2, 149.7, 148.6, 147.0, 142.4, 138.0, 137.4, 135.0, 133.2, 132.9, 130.8, 129.4, 129.2, 129.1, 128.8, 128.6, 124.6 (2 C), 124.2, 124.1, 123.9, 123.4, 121.7, 121.4, 120.2, 112.8, 104.5, 103.4, 84.5, 67.1, 57.4, 57.2, 57.1, 38.4, 30.7, 27.4, 19.7, 19.3; HRMS (MALDI-FTMS) calcd for $\text{C}_{48}\text{H}_{43}\text{BrN}_6\text{O}_9\text{H}^+$ $[\text{M} + \text{H}^+]$ 927.2347, found 927.2335.

Wiktop photocyclization product 3. To a solution of oxazole **4** (11.8 mg, 0.013 mmol, 1.0 equiv) in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (3:1, 4.8 mL) at 25 °C was added $\text{LiOAc}\cdot\text{H}_2\text{O}$ (51.8 μL of a solution containing 100 mg in 2.0 mL of H_2O , 0.026 mmol, 2.0 equiv) and epichlorohydrin (70.9 μL of a solution containing 100 mg in 2.0 mL of CH_3CN , 0.039 mmol, 3.0 equiv). A balloon filled with argon gas and equipped with a long syringe was then inserted into the reaction vessel, and argon gas was bubbled directly into the reaction solution for 7 minutes to remove any dissolved gases. The resulting reaction mixture was exposed to UV light (200 nm) for 15 minutes at 25 °C. Upon completion, the contents were poured into water (10 mL) and extracted with EtOAc (3×25 mL). The combined organic layers were then washed with water (25 mL) and brine (25 mL), dried (MgSO_4), and concentrated. The resultant bright yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 0:1 $\rightarrow$ 1:0) to give the desired photocyclization product **3** (3.6 mg, 33% yield) as a yellow solid along with a significant portion of recovered starting material (4.2 mg, 51% yield of **3** based on r.s.m.). **3**: $R_f = 0.25$ (silica gel, EtOAc/hexanes, 5:1); $[\alpha]_D^{20} = -172.26$ ($c = 0.31$, MeOH); IR (film) ν_{max} 3342, 2919, 1719, 1655, 1496, 1443, 1278, 1255, 1143, 1055, 750 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 9.87 (s, 1 H), 8.68 (s, 1 H), 7.60 (d, $J = 7.9$ Hz, 1 H), 7.43–7.30 (m, 9 H), 7.14 (d, $J = 6.6$ Hz, 1 H), 7.13 (d, $J = 7.9$ Hz, 1 H), 6.97 (s, 1 H), 6.87–6.86 (m, 2 H), 6.83 (d, $J = 7.4$ Hz, 1 H), 6.75 (t, $J = 7.0$ Hz, 1 H), 6.24 (d, $J = 7.4$ Hz, 1 H), 5.09 (AB, $J = 12.7$ Hz, $\nu_{ab} = 17.1$ Hz, 2 H), 4.54 (t, $J = 7.0$ Hz, 1 H), 4.31 (ddd, $J = 11.8, 8.3, 3.1$ Hz, 1 H), 3.32 (t, $J = 12.3$ Hz, 1 H), 2.80 (d, $J = 12.7$ Hz, 1 H), 1.98 (m, 1 H), 1.41 (s, 9 H), 1.00 (d, $J = 6.2$ Hz, 3 H), 0.90 (d, $J = 6.2$ Hz, 3 H); ^{13}C NMR (150

MHz, CD₃CN) δ 174.4, 173.6, 164.0, 156.3, 154.7, 151.4, 150.4, 148.9, 147.1, 143.3, 138.0, 137.6, 134.7, 134.6, 132.2, 131.1, 130.9, 130.5, 129.4, 128.8, 128.6, 128.2, 128.0, 127.8, 126.5, 124.9, 124.1 (2 C), 123.9, 123.4, 123.2, 121.7, 113.1, 103.5, 84.1, 67.1, 57.5, 57.0, 56.5, 38.0, 31.0, 27.6, 19.7, 19.1; HRMS (MALDI-HRMS) calcd for C₄₈H₄₂N₆O₉H⁺ [M + H⁺] 847.3086, found 847.3110.

Bis-chlorinated intermediate 49. *N*-chlorosuccinimide (1.10 mL of a solution containing 25 mg in 2 mL of 1:1 THF/CCl₄, 0.102 mmol, 4.4 equiv) was added to a solution of macrocycle **3** (19.7 mg, 0.023 mmol, 1.0 equiv) in THF/CCl₄ (1:1, 19 mL) at 25 °C. The resulting mixture was then heated at 60 °C for 2 hours before it was purified directly by preparative TLC (silica gel, EtOAc/hexanes, 5:1) to give the bis-chlorinated product **49** (11.0 mg, 50% yield) as a yellow solid. **49**: R_f = 0.60 (silica gel, EtOAc/hexanes, 5:1); $[\alpha]_D^{20}$ = -208.2 (c = 0.22, MeOH); IR (film) $\nu_{\max}$ 3260, 2966, 1725, 1666, 1502, 1443, 1273, 1243, 1208, 1143, 1055, 750 cm⁻¹; ¹H NMR (600 MHz, CD₃CN) δ 10.4 (s, 1 H), 8.62 (s, 1 H), 7.55 (d, J = 8.3 Hz, 1 H), 7.41–7.31 (m, 7 H), 7.17 (d, J = 7.0 Hz, 1 H), 7.13 (d, J = 7.9 Hz, 1 H), 6.93–6.90 (m, 3 H), 6.84 (t, J = 7.9 Hz, 1 H), 6.19 (d, J = 7.9 Hz, 1 H), 5.10 (AB, J = 12.3 Hz, ν_{ab} = 16.6 Hz, 2 H), 4.54 (t, J = 7.9 Hz, 1 H), 4.29 (ddd, J = 11.8, 8.3, 2.6 Hz, 1 H), 3.32 (t, J = 12.2 Hz, 1 H), 2.80 (d, J = 12.7 Hz, 1 H), 2.00 (m, 1 H), 1.41 (s, 9 H), 1.01 (d, J = 6.2 Hz, 3 H), 0.91 (d, J = 6.2 Hz, 3 H); ¹³C NMR (150 MHz, CD₃CN) δ 174.3, 173.6, 164.4, 156.3, 154.4, 152.0, 151.3, 147.1, 143.0, 140.6, 138.0, 135.9, 134.7, 134.6, 131.9, 130.8, 130.6, 129.9, 129.6, 129.4, 128.8, 128.6, 127.7, 127.3, 127.2, 126.9, 124.6, 124.1, 123.9, 123.5, 123.0, 122.7, 112.5, 98.2, 84.1, 67.1, 57.5, 57.0, 56.4, 37.9, 30.9, 27.5, 19.7, 19.1; HRMS (MALDI-FTMS) calcd for C₄₈H₄₀Cl₂N₆O₉Na⁺ [M + Na⁺] 937.2126, found 937.2136.

Phenolic lactam 50. Bis-chlorinated intermediate **49** (11.0 mg, 0.0117 mmol, 1.0 equiv) was treated with neat TFA (1.0 mL) at 25 °C. After stirring the resultant solution for 10 minutes at 25 °C, the solvent was removed in vacuo (using several benzene co-evaporations to ensure the complete removal of all TFA) to give phenolic lactam **50** (8.6 mg, 90% yield) as an amorphous white solid. **50**: R_f = 0.35 (silica gel, EtOAc/hexanes, 5:1); $[\alpha]_D^{20}$ = -277.3 (c = 0.40, MeOH);

IR (film) $\nu_{\max}$ 3260, 2919, 1713, 1660, 1602, 1496, 1443, 1401, 1302, 1261, 1214, 1155, 1055, 750 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 10.38 (s, 1 H), 8.42 (s, 1 H), 7.54 (d, $J = 7.9$ Hz, 1 H), 7.42–7.33 (m, 7 H), 7.27 (br m, 1 H), 7.22 (d, $J = 7.0$ Hz, 1 H), 7.10 (d, $J = 7.4$ Hz, 1 H), 6.89–6.87 (m, 2 H), 6.82 (t, $J = 7.9$ Hz, 1 H), 6.77 (d, $J = 7.9$ Hz, 1 H), 6.73 (s, 1 H), 6.15 (d, $J = 7.9$ Hz, 1 H), 5.08 (AB, $J = 12.7$ Hz, $\nu_{\text{ab}} = 17.1$ Hz, 2 H), 4.55 (t, $J = 7.4$ Hz, 1 H), 4.24 (ddd, $J = 11.4, 8.8, 3.1$ Hz, 1 H), 3.23 (t, $J = 12.7$ Hz, 1 H), 2.68 (d, $J = 11.4$ Hz, 1 H), 2.00 (m, 1 H), 1.01 (d, $J = 6.1$ Hz, 3 H), 0.91 (d, $J = 6.1$ Hz, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 174.9, 173.8, 164.3, 156.3, 154.6, 152.9, 152.8, 143.2, 140.6, 138.0, 135.9, 134.5, 131.6, 130.6, 130.0, 129.4, 129.3, 128.8, 128.6, 128.2, 127.2, 126.9, 124.8, 124.5, 123.2, 122.7, 116.6, 112.4, 98.3, 67.0, 57.8, 57.0, 56.4, 37.8, 31.0, 19.6, 19.0; HRMS (MALDI-FTMS) calcd for $\text{C}_{43}\text{H}_{32}\text{Cl}_2\text{N}_6\text{O}_7\text{H}^+$ [$\text{M} + \text{H}^+$] 815.1782, found 815.1778.

Aminal 52. A portion of phenolic lactam **50** (5.0 mg, 0.0061 mmol, 1.0 equiv) was dissolved in THF (5 mL) and treated with DIBAL-H (0.012 mL, 1.0 M in toluene, 0.012 mmol, 2.0 equiv) at -78 $^{\circ}\text{C}$. The reaction flask contents were then warmed to 25 $^{\circ}\text{C}$ over the course of 30 minutes. Upon completion, the reaction mixture was cooled back down to -78 $^{\circ}\text{C}$, treated with another portion of DIBAL-H (0.012 mL, 1.0 M in toluene, 0.012 mmol, 2.0 equiv), and again allowed to warm to 25 $^{\circ}\text{C}$ over the course of 30 minutes. This cycle was repeated three more times, and, once accomplished, the reaction mixture was quenched at 25 $^{\circ}\text{C}$ by the slow and careful addition of water (5 mL), poured into water (25 mL), and extracted with EtOAc (3×25 mL). The combined organic layers were then washed with water (25 mL) and brine (50 mL), dried (MgSO_4), and concentrated. The resultant yellow residue was purified by preparative TLC (silica gel, EtOAc/hexanes, 1:1) to give aminal **52** (2.7 mg, 56% yield) as a clear film. **52**: $R_f = 0.40$ (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\max}$ 3366, 2923, 2849, 1701, 1660, 1490, 1449, 1396, 1376, 1343, 1255, 1202, 1120, 750, 597 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 10.41 (s, 1 H), 7.51 (d, $J = 7.0$ Hz, 1 H), 7.40 (m, 5 H), 7.31 (dd, $J = 7.0, 6.6$ Hz, 1 H), 7.30 (s, 1 H), 7.20 (d, $J = 7.0$ Hz, 1 H), 7.19 (d, $J = 8.3$ Hz, 1 H), 6.98 (d, $J = 6.6$ Hz, 1 H), 6.88 (d, $J = 7.0$ Hz, 1 H), 6.87 (d, $J = 7.5$ Hz, 1 H), 6.78 (d, $J = 7.8$ Hz, 1 H), 6.63 (dd, $J = 7.8, 7.5$ Hz, 1 H), 6.38 (d, $J =$

4.4 Hz, 1 H), 6.17 (d, $J = 8.0$ Hz, 1 H), 5.88 (d, $J = 4.4$ Hz, 1 H), 5.09 (s, 2 H), 4.85 (dd, $J = 8.3$, 5.7 Hz, 1 H), 4.17 (m, 1 H), 3.28 (dd, $J = 12.3$, 12.0 Hz, 1 H), 2.80 (dd, $J = 12.3$, 3.0 Hz, 1 H), 2.11 (m, 1 H), 0.98 (d, $J = 7.2$ Hz, 3 H), 0.90 (d, $J = 7.2$ Hz, 3 H); HRMS (MALDI-FTMS) calcd for $C_{43}H_{32}Cl_2N_6O_6Na^+$ [$M + Na^+$] 821.1653, found 821.1669.

(–)-Diazonamide A (1). $Pd(OH)_2/C$ (0.002 g, 20 wt %, catalytic) was added to a solution of aminal **52** (2.7 mg, 0.0034 mmol, 1.0 equiv) in EtOH (1 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 2 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 intermediate (2.1 mg, 0.0032 mmol, 1.0 equiv) was then dissolved in DMF (1.0 mL) and treated sequentially at 25 °C with L-2-hydroxyisovaleric acid (1.9 mg, 0.0162 mmol, 5.0 equiv), $NaHCO_3$ (4.0 mg, 0.0490 mmol, 15 equiv), EDC• H_2O (3.0 mg, 0.0162 mmol, 5.0 equiv), and HOBt• H_2O (2.4 mg, 0.0162 mmol, 5.0 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/hexanes, 1:1) to give (–)-diazonamide A (2.1 mg, 82% yield over two steps) as a clear film, a compound whose physical and spectral properties were identical in all respects with an authentic sample (based on 1H NMR, optical rotation, HPLC, and TLC in a variety of solvents).¹ For the purpose of direct comparison with C-37 *epi*-diazonamide A (**53**), we are providing the 1H NMR data that we obtained for synthetic **1** which is in complete accordance with that originally reported by Fenical, Clardy, and co-workers: 1H NMR (600 MHz, CD_3OD) δ 7.45 (d, $J = 7.9$ Hz, 1 H), 7.36 (dd, $J = 8.3$, 7.3 Hz, 1 H), 7.33 (s, 1 H), 7.19 (app d, $J = 6.6$ Hz, 2 H), 7.00 (d, $J = 7.4$ Hz, 1 H), 6.86 (d, $J = 7.0$ Hz, 1 H), 6.77 (d, $J = 8.3$ Hz, 1 H), 6.66 (dd, $J = 7.4$, 7.3 Hz, 1 H), 6.35 (s, 1 H), 4.85 (d, $J = 6.7$ Hz, 1 H), 4.60 (dd, $J = 11.5$, 3.4 Hz, 1 H), 3.88 (dd, $J = 3.9$ Hz, 1 H), 3.38 (dd, $J = 12.8$, 11.9 Hz, 1 H), 2.78 (dd, $J = 12.7$, 3.5 Hz, 1 H), 2.19 (dq, $J = 6.4$, 6.9, 6.9 Hz, 1 H), 2.11 (dq, $J = 3.3$, 6.8, 6.7 Hz, 1 H),

1.05 (d, $J = 6.6$ Hz, 3 H), 1.01 (d, $J = 7.0$ Hz, 3 H), 0.96 (d, $J = 6.5$ Hz, 3 H), 0.92 (d, $J = 6.5$ Hz, 3 H).

C-37 *epi*-Diazonamide A (53). Pd(OH)₂/C (0.002 g, 20 wt %, catalytic) was added to a solution of aminal **52** (2.4 mg, 0.0030 mmol, 1.0 equiv) in EtOH (1 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 2 hours at 25 °C. Upon completion, the reaction flask contents were filtered through Celite and concentrated to give the desired amine (1.9 mg, 94%) as a clear oil. This intermediate (1.9 mg, 0.0029 mmol, 1.0 equiv) was then dissolved in DMF (1.0 mL) and treated sequentially at 25 °C with D-2-hydroxyisovaleric acid (1.7 mg, 0.0145 mmol, 5.0 equiv), NaHCO₃ (3.6 mg, 0.0435 mmol, 15 equiv), EDC•H₂O (2.7 mg, 0.0145 mmol, 5.0 equiv), and HOBT•H₂O (2.2 mg, 0.0145 mmol, 5.0 equiv). After 12 hours of stirring at 25 °C, the reaction flask contents were poured into saturated aqueous NaHCO₃ (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 (MgSO₄), and concentrated. The resultant yellow residue was purified by preparative TLC (silica gel, EtOAc/hexanes, 1:1) to give C-37 *epi*-diazonamide A (1.8 mg, 77% yield over two steps) as a clear film. **53**: ¹H NMR (600 MHz, CD₃OD) δ 7.44 (d, $J = 7.8$ Hz, 1 H), 7.36 (dd, $J = 8.3, 7.3$ Hz, 1 H), 7.33 (s, 1 H), 7.19 (app d, $J = 6.5$ Hz, 2 H), 7.00 (d, $J = 7.4$ Hz, 1 H), 6.86 (d, $J = 6.9$ Hz, 1 H), 6.77 (d, $J = 8.3$ Hz, 1 H), 6.66 (dd, $J = 7.3, 7.2$ Hz, 1 H), 6.34 (s, 1 H), 4.85 (d, $J = 6.6$ Hz, 1 H), 4.62 (dd, $J = 11.5, 3.4$ Hz, 1 H), 3.91 (dd, $J = 3.8$ Hz, 1 H), 3.41 (dd, $J = 12.7, 11.8$ Hz, 1 H), 2.77 (dd, $J = 12.7, 3.5$ Hz, 1 H), 2.19 (dq, $J = 6.4, 6.9, 6.8$ Hz, 1 H), 2.11 (dq, $J = 3.2, 6.7, 6.7$ Hz, 1 H), 1.04 (d, $J = 6.7$ Hz, 3 H), 1.01 (d, $J = 6.8$ Hz, 3 H), 0.95 (d, $J = 6.6$ Hz, 3 H), 0.91 (d, $J = 6.7$ Hz, 3 H).²

Notes

1. An authentic sample was obtained from Professor Patrick G. Harran (who obtained it from Professor William Fenical) after the publication of our original communication regarding the first total synthesis of diazonamide A.

2. Copies of spectra are available upon request for all compounds presented in the supplemental material section of this manuscript.