INFORMATION

Studies Towards Diazonamide A: Initial Synthetic Forays Directed Towards the Originally Proposed Structure

K. C. Nicolaou,* Scott A. Snyder, Xianhai Huang, Klaus B. Simonsen, Alexandros E. Koumbis, and Antony Bigot

*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, benzene, 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 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, AB = AB quartet, app = apparent. 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).

MOM-protected aldehyde 13. To a solution of 2,6-dibromophenol (58.0 g, 230.2 mmol, 1.0 equiv) in THF (300 mL) at 0 °C was added NaH (13.8 g, 60% dispersion in mineral oil, 345.3 mmol, 1.5 equiv). After 5 minutes of stirring at 0 °C, MOMCl (22.5 mL, 300 mmol, 1.3 equiv) was added via syringe. The reaction mixture was then allowed to slowly warm to 25 °C, and following 2 hours of additional stirring at that temperature, the reaction mixture was poured into Et₂O (300 mL) and washed extensively with 3 M NaOH (3 × 75 mL) to remove any residual phenol starting material. The organic layer was then dried (MgSO₄) and concentrated to give MOM-protected 2,6-dibromophenol (66.2 g, 97% yield) as a yellow oil. With this initial operation accomplished, a portion of the intermediate product (31.2 g, 105.4 mmol, 1.0 equiv) was dissolved in THF (300 mL), cooled to -78 °C, and then treated with *n*-BuLi (69.2 mL, 1.6 M in hexanes, 110.7 mmol, 1.05 equiv). After 10 minutes of stirring at -78 °C, the yellow-colored reaction mixture was quenched at -78 °C by the rapid addition of DMF (40 mL) and allowed to stir for 10 additional minutes at 25 °C. The reaction mixture was poured into water (300 mL) and extracted with Et₂O (3 × 75 mL). The combined organic layers were then washed with water (100 mL) and brine (100 mL), dried (MgSO₄), and concentrated. The resultant light yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:10) to give MOM-protected aldehyde 13 (17.2 g, 67% yield) as a fluffy white solid. **13:** *R_f* = 0.23 (silica gel, EtOAc/hexanes, 1:10); IR (film) ν_{max} 2928, 1685, 1586, 1450, 1380, 1242, 1200, 1158, 1066, 930, 785, 706 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 10.31 (d, *J* = 1.1 Hz, 1 H), 7.79 (m, 2 H), 7.11 (t, *J* = 8.1 Hz, 1 H), 5.17 (s, 2 H), 3.59 (s, 3 H); ¹³C NMR (150 MHz, CDCl₃) δ 189.7, 157.2,

139.2, 131.6, 127.6, 126.0, 118.2, 100.9, 58.3; HRMS (MALDI-FTMS) calcd for $C_9H_9BrO_3Na^+$ $[M + Na^+]$ 266.9627, found 266.9630.

Biaryl ketone 14. Phenylmagnesium bromide (42.6 mL, 1.0 M in THF, 42.6 mmol, 1.5 equiv) was added to a solution of aldehyde **13** (3.2 g, 13.1 mmol, 1.0 equiv) in THF (50 mL) at $-78\text{ }^\circ\text{C}$. After 10 minutes of stirring at $-78\text{ }^\circ\text{C}$, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (5 mL), poured into water (200 mL), and extracted with Et_2O ($3 \times 75\text{ mL}$). The combined organic extracts 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, 1:5) to give the desired biaryl alcohol (4.2 g, 100% yield) as a yellow oil: $R_f = 0.08$ (silica gel, $EtOAc$ /hexanes, 1:10); IR (film) ν_{max} 3440, 2924, 1683, 1589, 1450, 1397, 1232, 1156, 1065, 950, 782, 750, 701 cm^{-1} ; 1H NMR (600 MHz, C_6D_6) δ 7.46 (d, $J = 7.7\text{ Hz}$, 2 H), 7.18 (dd, $J = 8.2, 1.6\text{ Hz}$, 1 H), 7.13 (d, $J = 7.1\text{ Hz}$, 2 H), 7.04 (t, $J = 8.2\text{ Hz}$, 2 H), 6.46 (t, $J = 7.7\text{ Hz}$, 1 H), 6.28 (s, 1 H), 4.76 (AB, $J = 6.1\text{ Hz}$, $\nu_{ab} = 21.0\text{ Hz}$, 2 H), 3.57 (br s, 1 H), 3.07 (s, 3 H); ^{13}C NMR (150 MHz, C_6D_6) δ 153.4, 143.3, 141.3, 132.9, 128.8, 128.4, 127.3, 126.8, 126.3, 117.5, 100.1, 70.0, 57.3; HRMS (MALDI-FTMS) calcd for $C_{15}H_{15}BrO_3Na^+$ $[M + Na^+]$ 345.0097, found 345.0092. Next, a solution of IBX (9.10 g, 32.7 mmol, 2.5 equiv) in DMSO (30 mL) was added to a solution of the intermediate biaryl alcohol (4.2 g, 19.5 mmol, 1.0 equiv) in THF/DMSO (1:1, 60 mL) at $25\text{ }^\circ\text{C}$. After stirring for 4 hours at $25\text{ }^\circ\text{C}$, the reaction mixture was poured into $EtOAc$ (300 mL) and washed extensively with saturated aqueous Na_2SO_3 ($3 \times 75\text{ mL}$) to remove the IBA by-product and any residual IBX. The organic layer was then dried ($MgSO_4$) and concentrated. The resultant light brown residue was purified by flash column chromatography (silica gel, $EtOAc$ /hexanes, 1:5) to give ketone **14** (3.88 g, 93% yield) as a white solid. **14**: $R_f = 0.21$ (silica gel, $EtOAc$ /hexanes, 1:10); IR (film) ν_{max} 2925, 1667, 1593, 1450, 1395, 1284, 1157, 1071, 929 cm^{-1} ; 1H NMR (600 MHz, C_6D_6) δ 7.80 (d, $J = 7.7\text{ Hz}$, 2 H), 7.31 (dd, $J = 7.7, 1.5\text{ Hz}$, 1 H), 7.06 (t, $J = 7.1\text{ Hz}$, 1 H), 6.98 (m, 3 H), 6.43 (t, $J = 7.7\text{ Hz}$, 1 H), 4.79 (s, 2 H), 2.97 (s, 3 H); ^{13}C NMR (150 MHz, C_6D_6) δ 194.0, 152.6,

137.5, 136.4, 135.5, 133.1, 130.3, 129.0, 128.5, 125.4, 118.5, 100.4, 57.3; HRMS (MALDI-FTMS) calcd for $C_{15}H_{13}BrO_3Na^+$ [$M + Na^+$] 342.9940, found 342.9942.

Phenol 15. Concentrated HCl (10 mL) was added to a solution of MOM-protected **14** (6.2 g, 19.4 mmol, 1.0 equiv) in MeOH/ CH_2Cl_2 (1:1, 100 mL) at 25 °C. After 12 hours of stirring at 25 °C, the reaction mixture was basified by the slow addition of saturated aqueous $NaHCO_3$, poured into water (100 mL), and extracted with CH_2Cl_2 (3×150 mL). The combined organic layers were then washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated to give phenol **15** (5.21 g, 97% yield) as a yellow oil which was carried forward without additional purification. **15**: R_f = 0.48 (silica gel, EtOAc/hexanes, 1:10); IR (film) ν_{max} 3447, 1623, 1469, 1426, 1324, 1249, 1186, 1121, 1076, 958, 828, 747, 701, 656 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, J = 7.7, 1.5 Hz, 1 H), 7.68 (dd, J = 8.1, 1.1 Hz, 2 H), 7.65–7.58 (m, 2 H), 7.52 (t, J = 8.1 Hz, 2 H), 6.81 (t, J = 8.1 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 159.6, 139.4, 137.3, 132.8, 132.4, 129.2, 128.5, 120.0, 119.4, 112.1; HRMS (MALDI-FTMS) calcd for $C_{13}H_{10}BrO_2^+$ [$M + H^+$] 276.9859, found 276.9860.

Phenyl sulfide epoxide 16. To a solution of phenol **15** (5.21 g, 18.8 mmol, 1.0 equiv) in acetone (100 mL) at 25 °C was added chloromethyl phenyl sulfide (5.04 mL g, 37.6 mmol, 2.0 equiv) and K_2CO_3 (3.89 g, 28.2 mmol, 1.5 equiv). The resultant suspension was then heated at reflux for 3 hours. Upon completion, the reaction mixture was cooled to 25 °C, poured into water (500 mL), and extracted with Et_2O (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 light yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4) to give the desired alkylated product (6.98 g, 93% yield) as a light yellow oil. With this alkylation complete, epoxide formation was then sought by treating a DMSO solution of trimethylsulfonium iodide (2.02 g, 10.15 mmol, 1.5 equiv) at 0 °C with $KOt-Bu$ (8.12 mL, 1.0 M in THF, 1.2 equiv). After 5 minutes of stirring at 0 °C, a portion of the newly-generated phenyl sulfide intermediate (2.7 g, 6.77 mmol, 1.0 equiv) was added dropwise as a solution in DMSO (10 mL). Following 10 minutes of additional stirring at 0 °C, the reaction

mixture was poured into saturated aqueous NH_4Cl (50 mL) and extracted with Et_2O (3×50 mL). The combined organic layers were then washed with water (100 mL) and brine (100 mL), dried (MgSO_4), and concentrated to give epoxide **16** (2.71 g, 96% yield) as a clear oil which was carried forward without additional purification. **16**: $R_f = 0.65$ (silica gel, EtOAc /hexanes, 1:2); IR (film) ν_{max} 3060, 2919, 1807, 1624, 1427, 1324, 1250, 1179, 1122, 744, 699, 656 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.62 (dd, $J = 7.7, 1.5$ Hz, 1 H), 7.49 (dd, $J = 7.7, 1.5$ Hz, 1 H), 7.43 (m, 2 H), 7.30 (m, 3 H), 7.24–7.18 (m, 5 H), 7.10 (t, $J = 7.8$ Hz, 1 H), 5.37 (AB, $J = 10.6$ Hz, $\nu_{\text{ab}} = 65.3$ Hz, 2 H), 3.23 (AB, $J = 5.1$ Hz, $\nu_{\text{ab}} = 101.2$ Hz, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 153.8, 139.1, 135.1, 135.0, 134.0, 130.2, 129.3, 128.8, 128.2, 127.8, 126.8, 126.3, 125.8, 117.7, 77.6, 59.6, 56.8; MS (ESI) calcd for $\text{C}_{21}\text{H}_{17}\text{BrO}_2\text{SNa}^+ [\text{M} + \text{Na}^+]$ 435, found 435.

Phenyl sulfoxide 17. Solid NaHCO_3 (1.37 g, 16.3 mmol, 2.5 equiv) and *m*-CPBA (2.05 g, 55%, 6.52 mmol, 1.0 equiv) were added sequentially to a solution of phenyl sulfide **16** (2.71 g, 6.52 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL) at -10 °C to give a milk-colored slurry. After stirring this mixture for 30 minutes at -10 °C, the reaction contents were poured into water (40 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were then washed with 50 mL portions of 3 M NaOH until all organic by-products were removed as indicated by TLC, dried (MgSO_4), and concentrated to give phenyl sulfoxide **17** (2.41 g, 86% yield) as a light yellow foam which was carried forward without additional purification. **17**: $R_f = 0.23$ (silica gel, EtOAc /hexanes, 1:2); IR (film) ν_{max} 2931, 2849, 1636, 1443, 1232, 1088, 1018, 756, 694 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3 , 1:1 mixture of diastereomers) δ 7.55 (m, 4 H), 7.50–7.41 (m, 10 H), 7.28 (m, 6 H), 7.12 (m, 4 H), 7.08 (t, $J = 7.4$ Hz, 2 H), 4.79 (AB, $J = 8.8$ Hz, $\nu_{\text{ab}} = 67.1$ Hz, 2 H), 4.76 (AB, $J = 8.8$ Hz, $\nu_{\text{ab}} = 137.2$ Hz, 2 H), 3.29 (AB, $J = 5.3$ Hz, $\nu_{\text{ab}} = 20.6$ Hz, 2 H), 3.26 (AB, $J = 5.3$ Hz, $\nu_{\text{ab}} = 68.8$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3 , 1:1 mixture of diastereomers) δ 153.7, 153.6, 140.7, 139.1, 138.9, 134.7, 134.6, 134.2, 134.1, 131.4 (2 C), 129.3 (2 C), 129.1, 129.0, 128.4 (3 C), 128.1, 128.0, 126.3, 126.2, 124.7 (2 C), 116.9 (2 C), 91.4, 90.4, 59.6, 59.4, 56.5, 56.4; HRMS (MALDI-FTMS) calcd for $\text{C}_{21}\text{H}_{17}\text{BrO}_3\text{SNa}^+ [\text{M} + \text{Na}^+]$ 450.9974, found 450.9975.

Phenyl sulfoxide 18. Solid NaHCO₃ (2.74 g, 32.6 mmol, 5.0 equiv) and *m*-CPBA (4.10 g, 55%, 13.0 mmol, 2.0 equiv) were added sequentially to a solution of phenyl sulfide **16** (2.71 g, 6.52 mmol, 1.0 equiv) in CH₂Cl₂ (25 mL) at 25 °C to give a milk-colored slurry. After stirring this mixture for 1 hour at 25 °C, the reaction contents were poured into water (40 mL) and extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layers were then washed with 50 mL portions of 3 M NaOH until all organic by-products were removed as indicated by TLC, dried (MgSO₄), and concentrated to give phenyl sulfone **18** (2.65 g, 91% yield) as a light yellow foam which was carried forward without additional purification. **18**: R_f = 0.55 (silica gel, EtOAc/hexanes, 1:2); IR (film) ν_{max} 3060, 2908, 1725, 1666, 1584, 1443, 1309, 1150, 1081, 1032, 748, 686, 526 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.79 (dd, *J* = 8.3, 1.3 Hz, 2 H), 7.62 (t, *J* = 8.8 Hz, 1 H), 7.52 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.43 (m, 3 H), 7.25–7.21 (m, 3 H), 7.08 (t, *J* = 7.9 Hz, 1 H), 7.01 (m, 2 H), 4.92 (AB, *J* = 10.1 Hz, ν_{ab} = 182.4 Hz, 2 H), 3.16 (AB, *J* = 4.8 Hz, ν_{ab} = 71.0 Hz, 2 H); ¹³C NMR (150 MHz, CDCl₃) δ 151.8, 138.6, 136.8, 134.9, 134.2, 134.0, 129.4, 129.2, 128.9, 128.3, 127.9, 126.6, 126.2, 116.6, 84.0, 59.3, 56.4; HRMS (MALDI-FTMS) calcd for C₂₁H₁₈BrO₄S⁺ [M + H⁺] 445.0104, found 445.0111.

Biaryl alkene 19. KO^{*t*}-Bu (14.8 mL, 1.0 M in THF, 14.8 mmol, 1.2 equiv) was added to a suspension of methylenetriphenylphosphonium bromide (6.18 g, 17.3 mmol, 1.4 equiv) in THF (80 mL) at 0 °C. After 15 minutes of stirring at 0 °C, ketone **14** (3.96 g, 12.3 mmol, 1.0 equiv) was added via cannula as a solution in THF (50 mL), and the resultant mixture was allowed to react for 6 additional hours at 0 °C. Upon completion, the reaction mixture was quenched by the addition of water (100 mL) and extracted with Et₂O (3 × 75 mL). The combined organic layers were then washed with water (100 mL) and brine (100 mL), dried (MgSO₄), and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:10) to give the desired MOM-protected alkene (3.60 g, 92% yield) as a clear oil: R_f = 0.23 (silica gel, EtOAc/hexanes, 1:10); IR (film) ν_{max} 2956, 1616, 1437, 1395, 1235, 1202, 1158, 1068, 951, 779, 756, 709 cm⁻¹; ¹H NMR (600 MHz, C₆D₆) δ 7.35 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.20 (m, 2 H), 7.04 (m, 3 H), 6.93 (dd, *J* = 7.9, 1.7 Hz, 1 H), 6.54 (t, *J* = 7.4 Hz, 1 H),

5.55 (d, $J = 0.9$ Hz, 1 H), 5.20 (d, $J = 0.9$ Hz, 1 H), 4.86 (s, 2 H), 3.21 (s, 3 H); ^{13}C NMR (150 MHz, C_6D_6) δ 152.8, 146.7, 140.5, 137.7, 33.2, 131.2, 128.5, 128.0, 127.0, 125.3, 118.6, 116.8, 99.2, 57.5; MS (ESI) calcd for $\text{C}_{16}\text{H}_{17}\text{BrO}_2^+$ [$\text{M} + \text{H}^+$] 321, found 321. Next, concentrated HCl (0.5 mL) was added to a solution of MOM-protected alkene (3.6 g, 11.3 mmol, 1.0 equiv) in MeOH/ CH_2Cl_2 (1:1, 50 mL) at 25 °C. After 12 hours of stirring at 25 °C, the reaction mixture was basified by the slow addition of saturated aqueous NaHCO_3 , poured into water (100 mL), and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were then washed with water (100 mL) and brine (100 mL), dried (MgSO_4), and concentrated to give phenol **19** (3.10 g, 99% yield) as a yellow oil which was carried forward without additional purification. **19**: R_f = 0.35 (silica gel, EtOAc/hexanes, 1:10); IR (film) ν_{max} 3499, 1456, 1321, 1236, 1175, 1112, 1065, 908, 858, 823, 778, 741, 703 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.50 (dt, $J = 7.9, 1.2$ Hz, 1 H), 7.34 (m, 6 H), 7.17 (dt, $J = 7.3, 1.2$ Hz, 1 H), 6.85 (td, $J = 7.6, 1.2$ Hz, 1 H), 5.84 (s, 1 H), 5.61 (br s, 1 H), 5.42 (s, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 149.7, 145.5, 139.6, 132.1, 130.3, 129.4, 128.5, 128.2, 126.7, 121.4, 116.9, 110.4; HRMS (MALDI-FTMS) calcd for $\text{C}_{14}\text{H}_{12}\text{BrO}^+$ [$\text{M} + \text{H}^+$] 275.0066, found 275.0066.

Trimethylsilyl epoxide 20. To a solution of phenol **19** (3.11 g, 11.3 mmol, 1.0 equiv) in acetone (50 mL) at 25 °C was added chloromethyltrimethylsilane (2.36 mL, 17.0 mmol, 1.5 equiv) and K_2CO_3 (3.12 g, 22.6 mmol, 2.0 equiv). The resultant suspension was then heated at reflux for 15 hours. Upon completion, the reaction mixture was cooled to 25 °C, poured into water (50 mL), and extracted with Et_2O (3×50 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, 1:10) to give the desired alkylated alkene (3.48 g, 85% yield) as a clear oil. Next, solid NaHCO_3 (2.41 g, 28.8 mmol, 3.0 equiv) and *m*-CPBA (4.51 g, 55%, 14.4 mmol, 1.5 equiv) were added sequentially to a solution of the intermediate trimethylsilyl alkene (3.48 g, 9.6 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) at 25 °C to give a milk-colored slurry. After stirring this mixture for 6 hours at 25 °C, the reaction contents were poured into water (40 mL) and extracted with CH_2Cl_2 ($3 \times$

50 mL). The combined organic layers were then washed with 50 mL portions of 3 M NaOH until all organic by-products were removed as indicated by TLC, dried (MgSO_4), and concentrated to give trimethylsilyl epoxide **20** (2.61 g, 72% yield) as a light yellow foam which was carried forward without additional purification. **20**: R_f = 0.43 (silica gel, EtOAc/hexanes, 1:10); IR (film) ν_{max} 2943, 1666, 1442, 1420, 1249, 975, 860, 755, 698 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.58 (dd, J = 7.9, 1.3 Hz, 1 H), 7.42 (dd, J = 7.4, 1.3 Hz, 1 H), 7.31–7.28 (m, 3 H), 7.25–7.23 (m, 2 H), 7.02 (t, J = 7.9 Hz, 1 H), 3.65 (AB, J = 11.8 Hz, ν_{ab} = 84.2 Hz, 2 H), 3.31 (AB, J = 5.3 Hz, ν_{ab} = 89.9 Hz, 2 H), 0.05 (s, 9 H); ^{13}C NMR (150 MHz, CDCl_3) δ 157.8, 139.8, 134.3, 134.0, 129.5, 128.1, 127.7, 126.2, 124.7, 117.8, 67.9, 59.6, 56.9, –3.1; HRMS (MALDI-FTMS) calcd for $\text{C}_{18}\text{H}_{22}\text{BrO}_2\text{Si}^+$ [$\text{M} + \text{H}^+$] 377.0567, found 377.0576.

Cyano epoxide 21. To a solution of phenol **19** (3.11 g, 11.3 mmol, 1.0 equiv) in acetone (50 mL) at 25 °C was added chloroacetonitrile (1.10 mL, 17.0 mmol, 1.5 equiv) and K_2CO_3 (3.12 g, 22.6 mmol, 2.0 equiv), and the resultant suspension was heated at reflux for 3 hours. Upon completion, the reaction mixture was cooled to 25 °C, poured into water (50 mL), and extracted with Et_2O (3×50 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, 1:10) to give the desired alkylated alkene (3.22 g, 90% yield) as a clear oil. Next, solid NaHCO_3 (2.56 g, 30.6 mmol, 3.0 equiv) and *m*-CPBA (4.80 g, 55%, 15.3 mmol, 1.5 equiv) were added sequentially to a solution of the newly-formed cyano alkene (3.22 g, 10.2 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) at 25 °C to give a milk-colored slurry. After stirring this mixture for 6 hours at 25 °C, the reaction contents were poured into water (40 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were then washed with 50 mL portions of 3 M NaOH until all organic by-products were removed as indicated by TLC, dried (MgSO_4), and concentrated to give cyano epoxide **21** (2.46 g, 73% yield) as a light yellow foam which was carried forward without additional purification. **21**: R_f = 0.57 (silica gel, EtOAc/hexanes, 1:10); IR (film) ν_{max} 3062, 2928, 1767, 1727, 1661, 1594, 1443, 1254, 1219, 1077, 1016, 933, 908, 760, 701 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.61 (dd, J =

8.3, 1.7 Hz, 1 H), 7.49 (dd, $J = 7.9, 1.3$ Hz, 1 H), 7.33 (m, 3 H), 7.26 (m, 2 H), 7.15 (t, $J = 7.9$ Hz, 1 H), 4.61 (s, 2 H), 3.31 (AB, $J = 5.2$ Hz, $v_{ab} = 41.6$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3) δ 153.5, 138.9, 135.3, 134.2, 129.1, 128.5, 128.2, 126.7, 126.0, 117.5, 115.0, 59.9, 57.7, 56.2; HRMS (MALDI-FTMS) calcd for $\text{C}_{16}\text{H}_{13}\text{BrNO}_2\text{Si}^+ [\text{M} + \text{H}^+]$ 330.0124, found 330.0127.

5-*exo*-tet cyclization product 25. KO t -Bu (69.2 mL, 1.0 M in THF, 69.2 mmol, 1.4 equiv) was added dropwise over 5 minutes to a solution of cyano epoxide **21** (16.3 g, 49.5 mmol, 1.0 equiv) in THF/DMF (1:1, 300 mL) at -78 °C. After 5 minutes of additional stirring at -78 °C, the reaction mixture was quenched by the rapid addition of 1 M HCl (100 mL), poured into saturated aqueous NH_4Cl (150 mL), and extracted with Et_2O (3×150 mL). The combined organic layers were then washed with saturated aqueous NH_4Cl (150 mL), water (150 mL), and brine (10 mL), dried (MgSO_4), and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:10 $\rightarrow$ 1:1) to give the desired 5-*exo*-tet cyclization product **25** (12.22 g, 76% yield) as a white foam along with a significant portion of 3-phenylbenzofuran **22** (1.65 g, 12% yield) as yellow oil. **25**: $R_f = 0.11$ (silica gel, EtOAc/hexanes, 1:4); IR (film) ν_{max} 3457, 2932, 1709, 1582, 1497, 1448, 1265, 1216, 1065, 1010, 951, 837, 765, 736, 702 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.49 (dd, $J = 7.7, 1.1$ Hz, 1 H), 7.42–7.37 (m, 3 H), 7.26 (m, 2 H), 7.08 (dd, $J = 7.3, 1.1$ Hz, 1 H), 6.96 (t, $J = 7.7$ Hz, 1 H), 5.70 (s, 1 H), 4.22 (AB, $J = 11.4$ Hz, $v_{ab} = 30.1$ Hz, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 156.1, 137.4, 133.3, 129.7, 129.1, 128.9, 127.6, 124.1, 124.0, 114.9, 103.9, 66.2, 61.5; HRMS (MALDI-FTMS) calcd for $\text{C}_{16}\text{H}_{13}\text{BrNO}_2^+ [\text{M} + \text{H}^+]$ 330.0124, found 330.0124.

3-phenylbenzofuran 22: $R_f = 0.85$ (silica gel, EtOAc/hexanes, 1:10); IR (film) ν_{max} 3060, 1716, 1612, 1491, 1443, 1421, 1335, 1265, 1226, 1099, 865, 825, 780, 759, 738, 698 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.87 (s, 1 H), 7.78 (dd, $J = 7.7, 0.8$ Hz, 1 H), 7.63 (dt, $J = 8.1, 1.5$ Hz, 2 H), 7.53 (dd, $J = 7.7, 7.0$ Hz, 1 H), 7.50 (t, $J = 6.2$ Hz, 2 H), 7.41 (tt, $J = 7.3, 1.5$ Hz, 1 H), 7.21 (t, $J = 7.7$ Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 152.8, 141.8, 131.4, 129.0, 127.8 (2 C), 127.6 (2 C), 124.3, 123.1, 119.6, 104.6; HRMS (MALDI-FTMS) calcd for $\text{C}_{14}\text{H}_9\text{BrO}^+ [\text{M}^+]$ 271.9831, found 271.9833.

TBS-protected 26. Imidazole (5.03 g, 73.9 mmol, 2.0 equiv) and TBSCl (8.36 g, 55.5 mmol, 1.5 equiv) were added sequentially to a solution of alcohol **25** (12.2 g, 37.0 mmol, 1.0 equiv) in DMF (100 mL) at 25 °C. After 12 hours of stirring at 25 °C, the reaction mixture was poured into saturated aqueous NaHCO₃ (300 mL) and extracted with Et₂O (3 × 150 mL). The combined organic layers were then washed with water (100 mL) and brine (100 mL), dried (MgSO₄), and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:10) to give the desired TBS-protected intermediate **26** (15.1 g, 92% yield) as a white foam. **26**: R_f = 0.43 (silica gel, EtOAc/hexanes, 1:10); IR (film) ν_{max} 2929, 2857, 1450, 1256, 1217, 1118, 838, 778, 699 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.46 (d, *J* = 7.9 Hz, 1 H), 7.40–7.34 (m, 5 H), 7.03 (d, *J* = 7.3 Hz, 1 H), 6.93 (t, *J* = 7.7 Hz, 1 H), 5.76 (s, 1 H), 4.18 (AB, *J* = 10.1 Hz, ν_{ab} = 207.7 Hz, 2 H), 0.81 (s, 9 H), 0.06 (s, 3 H), –0.09 (s, 3 H); ¹³C NMR (150 MHz, CDCl₃) δ 156.1, 137.9, 132.7, 130.6, 128.7, 128.6, 127.8, 124.1, 123.5, 115.2, 103.4, 77.2, 67.5, 61.6, 25.5, 17.9, –5.6, –5.9; MS (ESI) calcd for C₂₂H₂₇BrNO₂Si⁺ [*M* + *H*⁺] 444, found 444.

Lactone 27. LiHMDS (12.85 mL, 1.0 M in THF, 12.85 mmol, 1.8 equiv) was added to a solution of protected cyanide **26** (3.17 g, 7.14 mmol, 1.0 equiv) in THF (75 mL) at –78 °C. After 5 minutes, a balloon filled with oxygen gas and equipped with a long syringe was inserted into the reaction vessel, and oxygen gas was bubbled directly into the solution for 30 minutes at –78 °C. The reaction mixture was then quenched at –78 °C by the addition of a solution of SnCl₂ (0.133 g, 0.714 mmol, 0.1 equiv) in 1 M aqueous HCl (16 mL). After 5 minutes of additional stirring, the reaction contents were poured into 1 M aqueous HCl (40 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were then washed with 1 M HCl (3 × 50 mL), saturated aqueous NaHCO₃ (50 mL), and brine (50 mL), dried (MgSO₄), and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:10) to give lactone **27** (2.94 g, 94% yield) as a white foam. **27**: R_f = 0.51 (silica gel, EtOAc/hexanes, 1:10); IR (film) ν_{max} 2926, 2855, 1814, 1445, 1255, 1116, 1029, 957, 837, 778, 697 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.51 (dd, *J* = 8.2, 1.1 Hz, 1 H), 7.42 (d, *J* =

8.1 Hz, 2 H), 7.38–7.32 (m, 3 H), 7.29 (dd, $J = 7.6, 1.1$ Hz, 1 H), 7.12 (t, $J = 7.7$ Hz, 1 H), 4.39 (AB, $J = 9.2$ Hz, $\nu_{ab} = 163.2$ Hz, 2 H), 0.68 (s, 9 H), –0.02 (s, 3 H), –0.18 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 175.4, 152.0, 134.8, 132.4, 130.5, 128.9, 128.4, 127.0, 125.0, 124.0, 103.6, 68.9, 59.7, 25.3, 17.8, –5.8; HRMS (MALDI-FTMS) calcd for $\text{C}_{21}\text{H}_{25}\text{BrO}_3\text{SiNa}^+ [\text{M} + \text{Na}^+]$ 455.0648, found 455.0654.

Trans-disposed methylated adduct 28. DIBAL-H (25.40 mL, 1.0 M in toluene, 25.4 mmol, 2.0 equiv) was added dropwise to a solution of protected lactone **27** (5.53 g, 12.7 mmol, 1.0 equiv) in toluene (60 mL) at –78 °C over the course of 15 minutes. After 1 hour of further stirring at –78 °C, the reaction mixture was quenched at –78 °C by the dropwise addition of MeOH (10 mL) followed by Rochelle's salt (40 mL). After stirring the resultant slurry for 4 additional hours at 25 °C, the reaction contents were poured into water (40 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were then washed with water (3 × 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, 1:4) to give the desired intermediate lactol (5.11 g, 92% yield) as a white foam: $R_f = 0.65$ (silica gel, EtOAc/hexanes, 1:4); IR (film) ν_{max} 3426, 2954, 1602, 1454, 1255, 1104, 837, 778, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.43 (dd, $J = 8.1, 1.1$ Hz, 1 H), 7.36–7.27 (m, 5 H), 7.12 (dd, $J = 7.7, 1.1$ Hz, 1 H), 6.89 (t, $J = 7.7$ Hz, 1 H), 6.03 (br d, $J = 11.8$ Hz, 1 H), 5.97 (br d, $J = 12.1$ Hz, 1 H), 4.30 (AB, $J = 10.3$ Hz, $\nu_{ab} = 322.0$ Hz, 2 H), 0.74 (s, 9 H), 0.00 (s, 3 H), –0.21 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 156.3, 140.5, 132.2, 129.7, 128.6, 127.7, 126.7, 124.7, 121.8, 111.5, 103.2, 68.3, 30.3, 25.6, –5.7, –5.9; MS (ESI) calcd for $\text{C}_{21}\text{H}_{26}\text{BrO}_3\text{Si}^- [\text{M} - \text{H}]^-$ 433, found 433. With this compound in hand, a portion (1.31 g, 3.0 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (30 mL) in a reaction vessel protected from light, and then MeI (5.61 mL, 90.0 mmol, 30 equiv) and Ag_2O (2.43 g, 10.5 mmol, 3.5 equiv) were added sequentially at 25 °C. The resultant slurry was stirred for three hours at 25 °C, filtered through Celite, and concentrated. The so-obtained yellow residue was then purified by flash column chromatography (silica gel, EtOAc/hexanes, 0:1→1:10) to give the desired *trans*-disposed methylated adduct **28** (5.11 g, 72% yield) as a

white foam, the *cis*-disposed methylated adduct **29** (0.851 g, 12% yield) as a yellow foam, and aldehyde **30** (0.832 g, 12% yield) as a yellow oil. **28**: R_f = 0.62 (silica gel, EtOAc/hexanes, 1:10); IR (film) $\nu_{\max}$ 2943, 1636, 1454, 1254, 1196, 1112, 837, 774, 698 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.29–7.27 (m, 3 H), 7.26–7.23 (m, 3 H), 6.95 (dd, J = 7.4, 1.3 Hz, 1 H), 6.80 (t, J = 7.4 Hz, 1 H), 5.63 (s, 1 H), 3.96 (AB, J = 10.1 Hz, ν_{ab} = 135.9 Hz, 2 H), 3.42 (s, 3 H), 0.80 (s, 9 H), –0.02 (s, 3 H), –0.12 (s, 3 H); ^{13}C NMR (150 MHz, CDCl_3) δ 156.2, 137.5, 132.6, 131.8, 129.1, 127.6, 127.0, 124.8, 122.0, 111.2, 103.2, 68.0, 60.9, 56.9, 25.6, 18.0, –5.7, –5.9; MS (ESI) calcd for $\text{C}_{22}\text{H}_{29}\text{BrO}_3\text{SiNa}^+ [\text{M} + \text{Na}^+]$ 471, found 471.

Cis-Disposed methylated adduct 29: R_f = 0.53 (silica gel, EtOAc/hexanes, 1:10); IR (film) $\nu_{\max}$ 2929, 2855, 1640, 1603, 1448, 1367, 1329, 1253, 1210, 1110, 934, 838, 776, 684 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.38 (d, J = 7.9 Hz, 2 H), 7.28–7.25 (m, 3 H), 7.22 (m, 2 H), 6.86 (t, J = 7.9 Hz, 1 H), 5.59 (s, 1 H), 4.19 (AB, J = 10.1 Hz, ν_{ab} = 106.6 Hz, 2 H), 3.58 (s, 3 H), 0.75 (s, 9 H), –0.07 (s, 3 H), –0.15 (s, 3 H); ^{13}C NMR (150 MHz, CDCl_3) δ 155.4, 141.6, 132.6, 131.8, 127.5, 126.9, 125.8, 122.3, 115.0, 103.3, 65.2, 59.8, 57.1, 25.6, 18.1, –5.7, –5.9; HRMS (MALDI-FTMS) calcd for $\text{C}_{22}\text{H}_{29}\text{BrO}_3\text{SiNa}^+ [\text{M} + \text{Na}^+]$ 471.0962, found 471.0978.

Aldehyde 30: R_f = 0.63 (silica gel, EtOAc/hexanes, 1:10); IR (film) $\nu_{\max}$ 2950, 2856, 1722, 1462, 1415, 1252, 1109, 1000, 839, 778, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.98 (s, 1 H), 7.61 (dd, J = 7.7, 1.5 Hz, 1 H), 7.41 (tt, J = 7.7, 1.5 Hz, 2 H), 7.37–7.33 (m, 3 H), 7.19 (dd, J = 8.1, 1.8 Hz, 1 H), 7.05 (t, J = 8.1 Hz, 1 H), 4.46 (AB, J = 10.3 Hz, ν_{ab} = 109.0 Hz, 2 H), 3.60 (s, 3 H), 0.86 (s, 9 H), 0.01 (s, 3 H), –0.05 (s, 3 H); ^{13}C NMR (150 MHz, CDCl_3) δ 197.8, 155.3, 138.7, 137.2, 133.3, 130.8, 129.0, 128.3, 127.3, 124.9, 116.7, 65.7, 63.1, 60.8, 25.7, 18.1, –5.8, –5.9; HRMS (MALDI-FTMS) calcd for $\text{C}_{22}\text{H}_{29}\text{BrO}_3\text{SiNa}^+ [\text{M} + \text{Na}^+]$ 471.0961, found 471.0979.

Boronate ester 31. HF (10.0 mL, 48 % in H_2O) was added to a solution of the *trans*-disposed methylated adduct **28** (3.00 g, 6.70 mmol, 1.0 equiv) in MeCN (100 mL) at 0 °C, and the resultant mixture was stirred for 1 hour at 0 °C. Upon completion, the reaction mixture was quenched at 0 °C by the slow and careful addition of saturated aqueous NaHCO_3 (50 mL) and extracted with EtOAc (3 $\times$ 50 mL). The combined organic layers were then washed with water

(3 × 50 mL) and brine (50 mL), dried (MgSO₄), and concentrated to give the desired intermediate alcohol (2.23 g, 99% yield) as a clear foam. Carrying this material forward directly, the newly-formed alcohol (2.23 g, 6.65 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (100 mL), cooled to 0 °C, and then treated sequentially with NaHCO₃ (5.59 g, 66.5 mmol, 10.0 equiv) and Dess–Martin periodinane (4.80 g, 9.98 mmol, 1.5 equiv). After stirring the resultant slurry for 2 hours at 0 °C, the reaction contents were poured into CH₂Cl₂ (100 mL) and washed extensively with saturated aqueous Na₂SO₃ (3 × 100 mL). The organic layer was then dried (MgSO₄) and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4) to give the desired intermediate aldehyde (2.13 g, 96% yield) as a white foam. With this adduct synthesized, a portion (0.333 g, 1.00 mmol, 1.0 equiv) was dissolved in THF (40 mL) and treated with the Tebbe reagent (3.0 mL, 0.5 M in toluene, 1.50 mmol, 1.5 equiv) at 0 °C, yielding a blood-red solution. After 10 minutes of stirring at 0 °C, the reaction mixture was quenched at 0 °C by the addition of a few drops of 10% aqueous NaOH. The reaction contents were then diluted with Et₂O (causing some bubbling to occur), filtered through Celite, and concentrated. The resultant brown residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4) to give the desired intermediate alkene (0.245 g, 74% yield) as a yellow oil. Finally, bispinacolato diboron (0.226 g, 0.89 mmol, 1.2 equiv), Pd(dppf)Cl₂•CH₂Cl₂ (0.121 g, 0.015 mmol, 0.2 equiv), and KOAc (0.218 g, 2.22 mmol, 3.0 equiv) were all added to a flask containing the just-formed alkene (0.245 g, 0.74 mmol, 1.0 equiv). This vessel was then equipped with an air condenser and degassed DMSO (5 mL, prepared by three iterations of the freeze-thaw method) was added at 25 °C. The reaction contents were then warmed to 90 °C and stirred for 6 hours. Upon completion, the reaction mixture was diluted with EtOAc (15 mL), filtered through a short plug of silica, and extracted with EtOAc (3 × 25 mL). The combined organic layers were then washed with water (2 × 25 mL) and brine (25 mL), dried (MgSO₄), and concentrated. The resultant yellow-green residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4) to give boronate ester **31** (0.118 g, 42% yield) as a white foam. **31**: R_f = 0.73 (silica gel, EtOAc/hexanes, 1:1); IR

(film) $\nu_{\max}$ 2978, 2932, 1618, 1476, 1429, 1366, 1281, 1127, 985, 923, 872, 848, 752, 701 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.66 (dd, $J = 7.5, 1.3$ Hz, 1 H), 7.33 (d, $J = 7.5$ Hz, 2 H), 7.30 (t, $J = 7.0$ Hz, 2 H), 7.26 (t, $J = 7.0$ Hz, 1 H), 7.16 (dd, $J = 7.5, 1.3$ Hz, 1 H), 6.98 (t, $J = 7.4$ Hz, 1 H), 6.31 (dd, $J = 17.5, 10.5$ Hz, 1 H), 5.62 (s, 1 H), 5.19 (d, $J = 10.5$ Hz, 1 H), 5.06 (d, $J = 17.5$ Hz, 1 H), 3.39 (s, 3 H), 1.38 (s, 9 H), 1.35 (s, 6 H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.2, 140.6, 138.7, 135.6, 131.1, 129.2, 128.8, 127.5, 126.8, 120.7, 114.7, 111.3, 83.5, 60.5, 56.1, 24.9, 24.4; HRMS (MALDI-FTMS) calcd for $\text{C}_{23}\text{H}_{27}\text{BO}_4^+$ [M^+] 378.2002, found 378.2004.

Lactone 34. To a stirred suspension of mandelic acid (0.500 g, 3.29 mmol, 1.0 equiv) in 70% aqueous H_2SO_4 (10 mL) at 0 $^\circ\text{C}$ was added 2-bromophenol (0.682 g, 3.95 mmol, 1.2 equiv). Once dissolution was complete, the solution was warmed to 70 $^\circ\text{C}$ over the course of 15 minutes and allowed to react for an additional 2 hours at 70 $^\circ\text{C}$ with vigorous stirring. The reaction contents were then cooled to 25 $^\circ\text{C}$, poured into ice water (100 mL), and extracted with Et_2O (3×50 mL). The combined organic layers were then washed with water (2×25 mL), dried (MgSO_4), and concentrated. The resultant pinkish-red residue was purified by flash column chromatography (silica gel, EtOAc /hexanes, 1:10 $\rightarrow$ 1:5) to give lactone **34** (0.401 g, 42% yield) as a clear oil. **34**: $R_f = 0.68$ (silica gel, EtOAc /hexanes, 1:5); IR (film) $\nu_{\max}$ 3037, 1817, 1608, 1445, 1067, 1046, 888, 738, 698 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.53 (dd, $J = 8.1, 1.1$ Hz, 1 H), 7.41–7.37 (m, 3 H), 7.24–7.21 (m, 2 H), 7.14 (dd, $J = 7.2, 1.1$ Hz, 1 H), 7.08 (t, $J = 7.4$ Hz, 1 H), 5.00 (s, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.3, 151.8, 134.4, 132.7, 129.3, 128.5, 128.2, 125.6, 124.1, 103.7, 50.6; MS (ESI) calcd for $\text{C}_{14}\text{H}_9\text{BrO}_2^+$ [M^+] 288, found 288.

5-*exo*-tet product 35. Freshly prepared LDA (5.07 mL, 1.0 M in THF, 5.07 mmol, 1.5 equiv) was added dropwise over 5 minutes to a solution of phenylsulfoxide epoxide **17** (1.45 g, 3.38 mmol, 1.0 equiv) in THF (40 mL) at -78 $^\circ\text{C}$. After 5 minutes of additional stirring at -78 $^\circ\text{C}$, the reaction mixture was quenched by the rapid addition of 1 M HCl (10 mL), poured into saturated aqueous NH_4Cl (50 mL), and extracted with Et_2O (3×50 mL). The combined organic layers were then washed with saturated aqueous NH_4Cl (50 mL), water (50 mL), and brine (50 mL), dried (MgSO_4), and concentrated. The resultant residue was purified by flash column

chromatography (silica gel, EtOAc/hexanes, 1:10→1:1) to give the desired 5-*exo*-tet cyclization product **35** (0.812 g, 56% yield) as a white foam and 3-phenylbenzofuran **22** (0.256 g, 28% yield) as a yellow oil. **35**: R_f = 0.23 (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\max}$ 3401, 3060, 1643, 1606, 1445, 1212, 1084, 1044, 908, 733, 697 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.78 (dd, J = 6.2, 2.6 Hz, 2 H), 7.55 (m, 3 H), 7.40–7.29 (m, 6 H), 7.13 (d, J = 7.4 Hz, 1 H), 6.92 (t, J = 7.9 Hz, 1 H), 5.16 (s, 1 H), 4.89 (dd, J = 12.3, 4.4 Hz, 1 H), 4.21 (dd, J = 12.3, 9.2 Hz, 1 H), 3.98 (dd, J = 8.8, 4.4 Hz, 1 H); ^{13}C NMR (150 MHz, CDCl_3) δ 156.8, 141.8, 138.7, 132.4, 132.0, 130.7, 129.2, 129.1, 128.0, 126.5, 125.8, 124.3, 123.4, 106.4, 103.0, 66.4, 62.0; HRMS (MALDI-FTMS) calcd for $\text{C}_{21}\text{H}_{17}\text{BrO}_3\text{Na}^+ [\text{M} + \text{Na}^+]$ 450.9974, found 450.9954.

Aldehyde 36. A solution of IBX (0.691 g, 2.46 mmol, 1.3 equiv) in DMSO (10 mL) was added to a solution of alcohol **35** (0.812 g, 1.89 mmol, 1.0 equiv) in THF/DMSO (1:1, 10 mL) at 25 °C. After stirring for 1 hour at 25 °C, the reaction mixture was poured into EtOAc (50 mL) and washed extensively with saturated aqueous Na_2SO_3 (3×25 mL) to remove the IBA by-product and any residual IBX. The organic layer was then dried (MgSO_4) and concentrated. The resultant light yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give aldehyde **36** (0.671 g, 83% yield) as a white solid. **36**: R_f = 0.33 (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\max}$ 3060, 1724, 1444, 1213, 1086, 1053, 997, 740, 695, 593 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 10.19 (s, 1 H), 7.71 (d, J = 7.4 Hz, 2 H), 7.49–7.45 (m, 4 H), 7.30 (m, 3 H), 7.21 (d, J = 7.4 Hz, 1 H), 7.04 (d, J = 7.0 Hz, 2 H), 6.94 (t, J = 7.9 Hz, 1 H), 5.50 (s, 1 H); ^{13}C NMR (150 MHz, CDCl_3) δ 193.3, 138.7, 137.4, 133.5, 131.9, 129.4, 129.0, 128.6, 127.3, 126.2, 126.0, 125.1, 123.5, 105.7, 103.3, 69.9, 60.4; HRMS (MALDI-FTMS) calcd for $\text{C}_{21}\text{H}_{15}\text{BrO}_3\text{SNa}^+ [\text{M} + \text{Na}^+]$ 448.9817, found 448.9827.

Phenylsulfide 37. Aldehyde **36** (0.427 g, 1.00 mmol, 1.0 equiv) was dissolved in THF (40 mL) and treated with the Tebbe reagent (4.40 mL, 0.5 M in toluene, 2.20 mmol, 2.2 equiv) at –20 °C, yielding a blood-red solution. After 10 minutes of stirring at –20 °C, the reaction mixture was warmed to 0 °C and stirred for an additional hour. Upon completion, the contents were quenched by the addition of a few drops of 10% aqueous NaOH. The reaction mixture was

then diluted with Et₂O (causing some bubbling to occur), filtered through Celite, and concentrated. The resultant brown residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:10→1:4) to give phenylsulfide **37** (0.319 g, 78% yield) as a yellow oil. **37**: *R_f* = 0.76 (silica gel, EtOAc/hexanes, 1:4); IR (film) ν_{max} 3072, 1636, 1484, 1444, 1216, 1091, 938, 907, 738, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.70–7.68 (m, 2 H), 7.50 (dd, *J* = 8.1, 1.1 Hz, 1 H), 7.43–7.37 (m, 7 H), 7.35 (m, 1 H), 7.11 (dd, *J* = 7.1, 1.1 Hz, 1 H), 6.98 (t, *J* = 7.4 Hz, 1 H), 6.58 (dd, *J* = 16.9, 10.3 Hz, 1 H), 6.26 (s, 1 H), 5.54 (dd, *J* = 10.3, 1.1 Hz, 1 H), 5.09 (dd, *J* = 17.2, 0.8 Hz, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 142.7, 137.3, 134.5, 133.8, 132.7, 132.3, 132.1, 129.0, 128.6, 128.0, 127.5, 127.1, 125.6, 122.6, 118.9, 104.0, 102.3, 83.3, 62.2; HRMS (MALDI-FTMS) calcd for C₂₂H₁₈BrOS⁺ [*M* + H⁺] 409.0256, found 409.0275.

Alkene 38. [Bis(trifluoroacetoxy)iodo]benzene (0.503 g, 1.17 mmol, 1.5 equiv) was added in a single portion to a solution of phenylsulfide **37** (0.319 g, 0.078 mmol, 1.0 equiv) in MeOH (10 mL) at 25 °C, and the resultant solution was stirred for 3 hours. Upon completion, the reaction mixture was poured into water (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were then dried (MgSO₄) and concentrated. The resultant light yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:10→1:4) to give alkene **38** (0.214 g, 83% yield) as a white oil. **38**: *R_f* = 0.71 (silica gel, EtOAc/hexanes, 1:4); IR (film) ν_{max} 2931, 1635, 1602, 1446, 1110, 905, 763, 701 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.40 (dd, *J* = 8.1, 1.5 Hz, 1 H), 7.34–7.26 (m, 5 H), 7.01 (dd, *J* = 7.7, 1.5 Hz, 1 H), 6.87 (t, *J* = 8.1 Hz, 1 H), 6.30 (dd, *J* = 17.3, 10.7 Hz, 1 H), 5.64 (s, 1 H), 5.26 (d, *J* = 10.6 Hz, 1 H), 5.11 (d, *J* = 17.6 Hz, 1 H), 3.45 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 155.3, 140.1, 138.1, 133.2, 131.8, 129.1, 127.7, 127.2, 124.6, 122.6, 115.0, 112.1, 103.8, 61.8, 56.9; HRMS (MALDI-FTMS) calcd for C₁₇H₁₅BrO₂⁺ [*M*⁺] 330.0250, found 330.0252.

4-bromoindole (44). A suspension of 2-methyl-3-nitroaniline (38.87 g, 225 mmol, 1.0 equiv) in water (325 mL) was heated to reflux and HBr (48% aqueous, 130 mL) was added over the course of 5 minutes with an additional funnel. Following 20 minutes of additional heating at reflux, the resultant red solution was then cooled to 0 °C, ultimately yielding a cloudy

suspension. A solution of NaNO_2 (17.56 g, 225 mmol, 1.0 equiv) in water (90 mL) was then added dropwise to this mixture at a rate such that the internal temperature of the reaction media never rose above 5 °C. The resultant yellow-brown solution was stirred for 15 additional minutes at 0–5 °C, and then was added quickly via cannula to a rapidly stirring suspension of CuBr (42.03 g, 293 mmol, 1.3 equiv) in HBr (48% aqueous, 86 mL) and water (225 mL) at 25 °C. Once the addition was complete, the reaction contents were then heated at 100 °C for 20 minutes, cooled back down to 25 °C, poured into water (500 mL), and extracted with Et_2O (3 × 250 mL). The combined organic layers were then washed with 3 N aqueous NH_4OH (4 × 200 mL) to remove any copper-containing by-products, dried (MgSO_4), and concentrated to give the desired 1-bromo-2-methyl-3-nitrobenzene (49.26 g, 90% yield) as an orange solid. This material was then dissolved in DMF (300 mL), to which was added *N,N*-dimethylformamide dimethyl acetal (90.9 mL, 684 mmol, 3.0 equiv) and pyrrolidine (19.03 mL, 228 mmol, 1.0 equiv) at 25 °C. The resultant blood-red solution was heated at 110 °C for 5 hours. Upon completion, the reaction mixture was cooled to 25 °C, poured into water (500 mL), and extracted with Et_2O (3 × 300 mL). The combined organic layers were then washed with water (2 × 500 mL), dried (MgSO_4), and concentrated to give the desired intermediate (59.1 g, 98% yield) as a brown solid. Without executing any additional purification steps, this crude product (59.1 g, 216 mmol, 1.0 equiv) was dissolved in HOAc (80% aqueous, 1.0 L), heated to 75 °C, and treated with zinc granules (127 g, 20 mesh, 1948 mmol, 9.0 equiv). The resultant suspension was then warmed to 85 °C and heated for an additional 3 hours. Upon completion, the reaction mixture was cooled to 25 °C, poured into water (500 mL), and extracted with Et_2O (3 × 300 mL). The combined organic layers were then carefully washed with saturated aqueous NaHCO_3 (3 × 500 mL) to neutralize any residual HOAc , dried (MgSO_4), and concentrated. The resultant brown residue was purified by flash column chromatography (silica gel, CH_2Cl_2 /hexanes, 1:5→1:1) to give **44** (25.2 g, 60% yield) as a light brown oil. **44**: R_f = 0.51 (silica gel, CH_2Cl_2 /hexanes, 1:1); IR (film) ν_{max} 3419, 1608, 1563, 1484, 1425, 1413, 1335, 1178, 1014, 888, 748 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 8.28 (br s, 1 H), 7.33 (d, J = 7.7 Hz, 1 H), 7.29 (d, J = 7.9 Hz, 1 H), 7.25 (m, 11 H),

7.06 (t, $J = 7.9$ Hz, 1 H), 6.61 (m, 1 H); ^{13}C NMR (150 MHz, CDCl_3) δ 136.0, 128.6, 124.7, 122.9, 122.7, 114.7, 110.2, 103.0; HRMS (MALDI-FTMS) calcd for $\text{C}_8\text{H}_7\text{NBr}^+$ [$\text{M} + \text{H}^+$] 195.9756, found 195.9759.

Dimethylamino nitroethylene (45). *N,N*-dimethylformamide dimethyl acetal (20.0 mL, 161 mmol, 1.0 equiv) and nitromethane (8.16 mL, 161 mmol, 1.0 equiv) were mixed at 25 °C and then heated in the absence of solvent at 80 °C for 30 minutes. Upon completion, the contents were cooled to 25 °C and concentrated directly. The resultant dark brown solid was purified by flash column chromatography (silica gel, EtOAc) to give **45** (12.1 g, 65% yield) as a light yellow solid. **45**: $R_f = 0.43$ (silica gel, EtOAc); IR (film) ν_{max} 3119, 1635, 1501, 1453, 1384, 1326, 1295, 1236, 1130, 1016, 983, 765, 713 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 8.12 (d, $J = 10.9$ Hz, 1 H), 6.61 (d, $J = 10.9$ Hz, 1 H), 3.20 (s, 3 H), 2.87 (s, 3 H); ^{13}C NMR (150 MHz, CDCl_3) δ 151.2, 112.0, 45.5, 38.0; HRMS (MALDI-FTMS) calcd for $\text{C}_3\text{H}_9\text{N}_2\text{O}_2^+$ [$\text{M} + \text{H}^+$] 117.0659, found 117.0660.

4-bromo-3-nitroethylene indole derivative 46. To a mixture of 4-bromoindole (10.9 g, 55.6 mmol, 1.0 equiv) and dimethylamino nitroethylene (6.45 g, 55.6 mmol, 1.0 equiv) was added TFA (25 mL) at 25 °C. After 30 minutes of stirring at 25 °C, the reaction was quenched by adding it dropwise to a rapidly stirring solution of saturated aqueous NaHCO_3 (300 mL), and the resultant green slurry was extracted with EtOAc (3×150 mL). The combined organic layers were then washed with water (2×500 mL), dried (MgSO_4), and concentrated to give the desired indole derivative **46** (13.4 g, 90% yield) as a brown solid which was carried forward without additional purification. **46**: $R_f = 0.11$ (silica gel, CH_2Cl_2); IR (film) ν_{max} 3401, 3225, 2919, 1608, 1547, 1484, 1420, 1298, 1261, 1185, 1025, 997, 773, 741 cm^{-1} ; ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 9.13 (d, $J = 11.0$ Hz, 1 H), 8.57 (s, 1 H), 8.13 (d, $J = 11.0$ Hz, 1 H), 7.56 (d, $J = 7.0$ Hz, 1 H), 7.43 (d, $J = 6.2$ Hz, 1 H), 7.17 (d, $J = 6.6$ Hz, 1 H); ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ 139.8, 134.6, 133.4, 133.3, 127.3, 125.4, 125.2, 114.2, 114.0, 108.8; GC/MS (ESI) calcd for $\text{C}_{10}\text{H}_7\text{BrN}_2\text{O}_2^+$ [M^+] 266, found 266.

TBDPS-protected glycolic acid 48. To a solution of glycolic acid (7.6 g, 100 mmol, 1.0 equiv) in THF (400 mL) at 0 °C was added 4-DMAP (0.300 g, catalytic) and Et₃N (14.7 mL, 102.5 mmol, 1.01 equiv). Following five minutes of stirring at 0 °C, TMSCl (12.7 mL, 105 mmol, 1.05 equiv) was added dropwise via syringe over the course of 15 minutes, yielding a white slurry. This suspension was stirred for an additional hour at 0 °C, and then mixed for a second hour at 25 °C. A second portion of Et₃N (14.7 mL, 102.5 mmol, 1.01 equiv) was added at 25 °C followed by the introduction of TBDPSCl (26.4 mL, 105 mmol, 1.05 equiv), and the resultant slurry was stirred for 8 hours at 25 °C. Upon completion, the reaction was quenched by the addition of an aqueous solution of HOAc (90 mL in 280 mL of H₂O), stirred for 1 hour at 25 °C, poured into water, and extracted with Et₂O (3 × 250 mL). The combined organic layers were then washed with water (2 × 500 mL), dried (MgSO₄), and concentrated. The resultant light yellow oil was purified by flash column chromatography (silica gel, Et₂O/hexanes, 1:1) to give TBDPS-protected glycolic acid **48** (25.6 g, 82% yield) as a light yellow oil. **48**: *R*_f = 0.18 (silica gel, Et₂O/hexanes, 1:1); IR (film) ν_{max} 3436, 2943, 1730, 1649, 1467, 1427, 1249, 1138, 1112, 822, 740, 703, 611, 504 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.72 (dd, *J* = 7.8, 1.5 Hz, 4 H), 7.53 (dd, *J* = 7.3, 1.5 Hz, 2 H), 7.49 (t, *J* = 7.3 Hz, 4 H), 4.29 (s, 2 H), 1.19 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) δ 172.8, 135.4, 131.6, 130.3, 128.1, 61.9, 26.6, 19.1; HRMS (MALDI-FTMS) calcd for C₁₈H₂₂O₃SiNa⁺ [*M* + Na⁺] 337.1236, found 337.1225.

4-bromotryptamine derivative 49. LiAlH₄ (15.6 g, 412 mmol, 6.0 equiv) was added slowly to a solution of 4-bromo-3-nitroethylene indole derivative **46** (18.4 g, 68.7 mmol, 1.0 equiv) in THF (450 mL) at 0 °C. Once the addition was complete, the resultant brown slurry was heated at reflux for 6 hours. Upon completion, the solution was cooled to 0 °C, quenched with saturated aqueous sodium potassium tartrate (200 mL), and stirred for an additional 8 hours at 25 °C. The reaction mixture was then filtered through Celite using extensive EtOAc washes (3 × 300 mL) to ensure high yield. The organic layer of the filtrate was then separated, washed with water (2 × 500 mL), dried (MgSO₄), and concentrated to give 4-bromotryptamine **47** (14.2 g, 87% yield) as a dark brown oil. Carrying this material forward without any additional

purification, the newly formed intermediate (14.2 g, 59.7 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (400 mL), and then glycolic acid derivative **48** (18.7 g, 59.7 mmol, 1.0 equiv), EDC $\cdot\text{H}_2\text{O}$ (11.4 g, 59.7 mmol, 1.0 equiv), and HOBt $\cdot\text{H}_2\text{O}$ (9.00 g, 5.97 mmol, 1.0 equiv) were added sequentially at 25 °C. After stirring the resultant brown mixture for 6 hours at 25 °C, the reaction contents were poured into water (500 mL) and extracted with CH_2Cl_2 (2 $\times$ 200 mL). The combined organic layers were then washed with water (2 $\times$ 500 mL), dried (MgSO_4), and concentrated. The resultant dark brown oil was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give 4-bromotryptamine derivative **49** (25.1 g, 79% yield) as a light brown solid. **49**: R_f = 0.53 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3411, 3275, 2930, 1666, 1533, 1427, 1336, 1110, 910, 821, 738, 703 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.11 (br s, 1 H), 7.52 (dd, J = 8.1, 1.1 Hz, 4 H), 7.39 (m, 2 H), 7.32 (m, 4 H), 7.26 (dd, J = 11.0, 7.4 Hz, 2 H), 6.98 (t, J = 7.7 Hz, 4 H), 6.95 (m, 2 H), 4.12 (s, 2 H), 3.70 (q, J = 7.0 Hz, 2 H), 3.25 (t, J = 6.6 Hz, 2 H), 1.01 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.6, 137.9, 135.3, 132.2, 130.2, 128.0, 125.3, 124.1, 123.0, 114.2, 113.5, 110.7; HRMS (MALDI-FTMS) calcd for $\text{C}_{28}\text{H}_{31}\text{BrN}_2\text{O}_2\text{SiNa}^+ [\text{M} + \text{Na}^+]$ 557.1236, found 557.1257.

Ketone 50. To a solution of 4-bromotryptamine derivative **49** (10.0 g, 18.8 mmol, 1.0 equiv) in THF/ H_2O (9:1, 220 mL) at 0 °C was added DDQ (8.54 g, 37.6 mmol, 2.0 equiv), yielding a deep red solution. After 4 hours of stirring at 0 °C, the reaction mixture was poured into EtOAc (500 mL) and washed extensively with saturated aqueous NaHCO_3 (4 $\times$ 500 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 alcohol (8.4 g, 82%) as a light brown foam. Carrying this material forward without any additional purification, the newly generated synthetic intermediate (8.4 g, 15.3 mmol, 1.0 equiv) was dissolved in THF (80 mL) and a solution of IBX (12.9 g, 45.8 mmol, 3.0 equiv) in DMSO (40 mL) was then added at 25 °C. After 4 hours of stirring at 25 °C, the reaction mixture was poured into EtOAc (300 mL) and washed extensively with saturated aqueous Na_2SO_3 (3 $\times$ 75 mL) to remove the IBA by-product and any residual IBX. The organic layer was then dried (MgSO_4) and concentrated. The resultant light brown residue

was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:2→1:0) to give ketone **50** (7.12 g, 85% yield) as a white solid. **50**: R_f = 0.15 (silica gel, EtOAc/hexanes, 2:1); IR (film) $\nu_{\max}$ 3395, 3244, 2930, 1697, 1664, 1518, 1412, 1108, 934, 820, 740, 703, 500 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 10.10 (br s, 1 H), 8.10 (br t, J = 4.4 Hz, 1 H), 7.79 (d, J = 3.1 Hz, 1 H), 7.69 (d, J = 7.0 Hz, 4 H), 7.47–7.43 (m, 3 H), 7.39 (m, 4 H), 7.33 (d, J = 8.3 Hz, 1 H), 7.07 (t, J = 8.0 Hz, 1 H), 4.62 (d, J = 4.9 Hz, 2 H), 4.23 (s, 2 H), 1.16 (s, 9 H); ^{13}C NMR (150 MHz, CDCl_3) δ 187.9, 171.6, 138.3, 135.5, 132.1, 132.0, 130.1, 128.0, 127.8, 124.7, 124.6, 116.1, 114.1, 111.2, 63.9, 47.4, 26.8, 19.2; HRMS (MALDI-FTMS) calcd for $\text{C}_{28}\text{H}_{29}\text{BrN}_2\text{O}_3\text{SiNa}^+ [\text{M} + \text{Na}^+]$ 571.1023, found 571.1039.

Indole-oxazole 51. Ph_3P (2.40 g, 9.12 mmol, 2.0 equiv) and hexachloroethane (2.14 g, 9.12 mmol, 2.0 equiv) were dissolved in CH_2Cl_2 (100 mL) at 25 °C. Et_3N (2.56 mL, 18.2 mmol, 4.0 equiv) was then added, and after 5 minutes of stirring at 25 °C, a solution of ketoamide **50** (2.5 g, 4.56 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL) was introduced to the dehydrating mixture over the course of 5 minutes. After 4 hours of stirring at 25 °C, the reaction mixture was poured into water (300 mL) and extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layers were then washed with water (2 × 200 mL), dried (MgSO_4), and concentrated. The resultant dark orange oil was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give indole-oxazole **51** (2.00 g, 82% yield) as a light yellow solid. Alternatively, the same dehydration could be carried out more conveniently on a larger scale by treating a solution of ketoamide **50** (9.0 g, 16.4 mmol, 1.0 equiv) in CH_2Cl_2 (200 mL) sequentially with TFAA (7.0 mL, 49.2 mmol, 3.0 equiv) and TFA (1.5 mL, 16.4 mmol, 1.0 equiv) at 0 °C, and then stirring the resultant mixture for 8 hours at 25 °C. Upon completion, the reaction mixture was poured into water (300 mL) and extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layers were then washed with water (2 × 200 mL), dried (MgSO_4), and concentrated. The resultant dark orange oil was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give indole-oxazole **51** (8.44 g, 97% yield) as a light yellow solid. **51**: R_f = 0.48 (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\max}$ 3416, 3152, 2930, 1562, 1426, 1112, 823, 737, 703 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3)

δ 8.82 (br s, 1 H), 7.75 (dd, J = 8.1, 1.5 Hz, 4 H), 7.42–7.37 (m, 8 H), 7.17 (s, 1 H), 7.10 (t, J = 7.7 Hz, 1 H), 4.82 (s, 2 H), 1.08 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 161.8, 145.5, 137.0, 135.7, 132.9, 129.8, 127.8, 126.8, 126.1, 125.3, 123.7, 114.0, 110.8, 105.1, 59.2, 26.7, 19.3; HRMS (MALDI-FTMS) calcd for $\text{C}_{28}\text{H}_{27}\text{BrN}_2\text{O}_2\text{SiNa}^+ [\text{M} + \text{Na}^+]$ 553.0923, found 553.0937.

Methyl-protected indole-oxazole 52. Tetra-*n*-butylammonium hydrogensulfate (2.88 g, 8.48 mmol, 1.1 equiv) and 10% aqueous NaOH (excess, ~50 mL) were added sequentially to a solution of indole-oxazole **51** (4.10 g, 7.71 mmol, 1.0 equiv) in benzene (100 mL) at 25 °C. The resultant biphasic system was stirred at 25 °C for 5 minutes, and then MeI (0.960 mL, 14.2 mmol, 2.0 equiv) was added. After 20 minutes of additional stirring at 25 °C, the reaction contents were poured into water (250 mL) and extracted with CH_2Cl_2 (3 $\times$ 250 mL). The combined organic extracts were then washed with water (300 mL) and brine (300 mL), dried (MgSO_4), and concentrated to give the desired methyl-protected indole-oxazole (4.12 g, 98% yield) as a yellow oil. Carrying this material forward without any additional purification, the newly-formed oxazole (4.12 g, 7.54 mmol, 1.0 equiv) was then dissolved in THF (250 mL) and treated with TBAF (11.3 mL, 1.0 M in THF, 11.3 mmol, 1.5 equiv) at 25 °C. After stirring the resultant light brown solution for 15 minutes at 25 °C, the reaction contents were concentrated, and the resultant dark brown residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1 $\rightarrow$ 1:0) to give indole-oxazole **52** (2.86 g, 88% yield over two steps) as a light yellow solid. **52**: R_f = 0.08 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3166, 2919, 2849, 1625, 1561, 1449, 1331, 1185, 1096, 1033, 761, 724 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.35 (d, J = 7.9 Hz, 1 H), 7.30 (d, J = 7.9 Hz, 1 H), 7.27 (s, 1 H), 7.14 (s, 1 H), 7.11 (t, J = 7.9 Hz, 1 H), 4.80 (s, 2 H), 4.02 (br s, 1 H), 3.81 (s, 3 H); ^{13}C NMR (150 MHz, CDCl_3) δ 145.5, 137.9, 131.3, 125.7, 125.5, 125.0, 123.3, 113.9, 109.0, 102.9, 57.6, 33.3; HRMS (MALDI-FTMS) calcd for $\text{C}_{13}\text{H}_{12}\text{BrN}_2\text{O}_2^+ [\text{M} + \text{H}^+]$ 307.0077, found 307.0079.

Olefinated indole-oxazole 53. A solution of IBX (0.843 g, 3.00 mmol, 3.0 equiv) in DMSO (5 mL) was added to a solution of the alcohol **52** (0.305 g, 1.00 mmol, 1.0 equiv) in THF/DMSO (1:1, 10 mL) at 25 °C. After stirring for 3 hours at 25 °C, the reaction mixture was

poured into EtOAc (300 mL) and washed extensively with saturated aqueous Na_2SO_3 (3×75 mL) to remove the IBA by-product and any residual IBX. The organic layer was then dried (MgSO_4) and concentrated. The resultant bright yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give the desired aldehyde (0.273 g, 90% yield) as a fluorescent yellow solid. Next, $\text{KO}^t\text{-Bu}$ (1.17 mL, 1.0 M in THF, 1.17 mmol, 1.3 equiv) was added to a suspension of methylenetriphenylphosphonium bromide (0.484 g, 1.35 mmol, 1.5 equiv) in THF (10 mL) at 0 °C. After 15 minutes of stirring at 0 °C, the newly-formed aldehyde intermediate (0.273 g, 0.90 mmol, 1.0 equiv) was added via cannula as a solution in THF (5 mL), and the resultant mixture was allowed to react for 15 minutes at 0 °C. Upon completion, the reaction mixture was quenched by the addition of water (20 mL) and extracted with Et_2O (3×50 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 olefinated indole-oxazole **53** (0.796 g, 89% yield) as a yellow solid. **53**: R_f = 0.39 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2939, 1624, 1597, 1525, 1445, 1417, 1332, 1196, 1098, 986, 929, 839, 770, 735, 679 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.38 (d, J = 7.4 Hz, 1 H), 7.34 (d, J = 8.5 Hz, 1 H), 7.32 (s, 1 H), 7.22 (s, 1 H), 7.14 (t, J = 7.7 Hz, 1 H), 6.66 (dd, J = 17.6, 11.4 Hz, 1 H), 6.21 (dd, J = 17.6, 1.1 Hz, 1 H), 5.60 (dd, J = 11.0, 1.1 Hz, 1 H), 3.92 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 144.9, 138.0, 131.1, 127.0, 125.5, 125.1, 123.8, 123.3, 120.8, 114.0, 109.0, 103.3, 65.8, 33.3; HRMS (MALDI-FTMS) calcd for $\text{C}_{14}\text{H}_{12}\text{BrN}_2\text{O}^+$ [$\text{M} + \text{H}^+$] 303.0128, found 303.0124.

Suzuki coupling product 54. $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (0.082 g, 0.010 mmol, 0.2 equiv), K_2CO_3 (0.345 g, 2.50 mmol, 5.0 equiv), and boronate **31** (0.189 g, 0.500 mmol, 1.0 equiv) were added to a flask containing indole-oxazole **53** (0.151 g, 0.500 mmol, 1.0 equiv). This vessel was then equipped with a reflux condenser, and degassed DME (5 mL, prepared by three iterations of the freeze-thaw method) was added at 25 °C. The reaction contents were then heated at reflux (85 °C) for 6 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, 1:4→1:1) to give Suzuki coupling product **54** (0.147 g, 62% yield) as a bright yellow oil (Note: all purification steps were carried out in minimal light to avoid photodecomposition of the product). **54**: R_f = 0.51 (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\max}$ 2931, 2837, 1690, 1612, 1531, 1449, 1414, 1331, 1190, 1112, 926, 748 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.41–7.36 (m, 3 H), 7.33–7.28 (m, 6 H), 7.23 (br s, 1 H), 7.02 (d, J = 7.0 Hz, 1 H), 6.95 (br s, 1 H), 6.40 (dd, J = 17.0, 10.9 Hz, 1 H), 6.20 (dd, J = 17.5, 10.9 Hz, 1 H), 5.90 (br d, J = 16.3 Hz, 2 H), 5.39 (d, J = 11.4 Hz, 1 H), 5.32 (s, 1 H), 5.17 (d, J = 10.6 Hz, 1 H), 5.05 (br d, J = 14.5 Hz, 1 H), 3.88 (s, 3 H), 3.18 (br s, 3 H); ^{13}C NMR (150 MHz, CDCl_3) δ 140.7, 137.6, 131.9, 130.4, 129.6, 129.3, 127.7, 127.5, 126.8, 124.8, 124.2, 123.5, 123.4, 122.8, 122.4, 120.9, 119.7, 114.1, 109.8, 109.1, 99.7, 64.4, 61.2, 57.0, 56.6, 33.2, 30.6, 24.8, 19.1; HRMS (MALDI-FTMS) calcd for $\text{C}_{31}\text{H}_{27}\text{N}_2\text{O}_3^+$ [$\text{M} + \text{H}^+$] 475.2016, found 475.2017.

Phosphonate 59. A solution of indole-oxazole **52** (0.470 g, 1.54 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) and added slowly to a mixture of Ph_3P (0.685 g, 2.61 mmol, 1.7 equiv), imidazole (0.209 g, 3.07 mmol, 2.0 equiv), and iodine (0.592 g, 2.30 mmol, 1.5 equiv) in CH_2Cl_2 (30 mL) that had already been stirring for 15 minutes at 0 °C. After 20 additional minutes of stirring at 0 °C, the reaction contents were poured into water (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were then washed with water (50 mL) and brine (50 mL), dried (MgSO_4), and concentrated to give the desired iodide (0.604 g, 94% yield) as a yellow solid: R_f = 0.43 (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\max}$ 2912, 1635, 1596, 1547, 1448, 1410, 1328, 1306, 1197, 1153, 1096, 983, 906, 830, 769, 731 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.38 (dd, J = 7.4, 0.8 Hz, 1 H), 7.32 (dd, J = 8.5, 0.8 Hz, 1 H), 7.30 (s, 1 H), 7.14 (s, 1 H), 7.13 (t, J = 8.1 Hz, 1 H), 4.48 (s, 2 H), 3.38 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.7, 146.2, 137.9, 131.2, 126.9, 125.5, 125.1, 123.4, 114.0, 109.0, 103.0, 33.3, -9.7; HRMS (MALDI-FTMS) calcd for $\text{C}_{13}\text{H}_{10}\text{BrN}_2\text{O}^+$ [$\text{M} - \text{I}^+$] 288.9971, found 288.9981. Carrying this intermediate (0.604 g, 1.45 mmol, 1.0 equiv) forward without further purification, it was

dissolved in THF (10 mL) and added dropwise to a THF solution of the anion of dimethylphosphite which had been prepared by adding NaH (0.099 g, 60% dispersion in mineral oil, 2.47 mmol, 1.7 equiv) to a solution of dimethylphosphite (0.319 g, 2.90 mmol, 2.0 equiv) in THF (30 mL) at 0 °C. After 10 minutes of stirring at 0 °C, the reaction contents were poured into water (50 mL) and extracted with EtOAc (3 × 50 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/MeOH, 1:0→19:1) to give indole-oxazole phosphonate **59** (0.497 g, 86% yield) as a clear oil. **59**: *R_f* = 0.35 (silica gel, MeOH/CH₂Cl₂, 1:19); IR (film) $\nu_{\max}$ 3560, 2954, 1637, 1561, 1449, 1331, 1261, 1196, 1096, 1032, 826 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.33 (d, *J* = 8.1 Hz, 1 H), 7.29 (d, *J* = 8.1 Hz, 1 H), 7.25 (s, 1 H), 7.10 (m, 2 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.48 (br s, 1 H), 3.44 (br s, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 155.2, 145.9, 137.9, 131.3, 126.6, 125.7, 124.9, 123.3, 113.9, 109.0, 103.0, 53.2, 53.1, 33.3, 27.1, 26.0; HRMS (MALDI-FTMS) calcd for C₁₅H₁₇BrN₂O₄P⁺ [*M* + *H*⁺] 399.0104, found 399.0099.

trans-Methoxy boronate. Bispinacolato diboron (0.480 g, 3.53 mmol, 1.2 equiv), Pd(dppf)Cl₂•CH₂Cl₂ (0.480 g, 0.588 mmol, 0.2 equiv), and KOAc (0.864 g, 8.82 mmol, 3.0 equiv) were all added to a flask containing compound **28** (1.32 g, 2.94 mmol, 1.0 equiv). This vessel was then equipped with an air condenser, and degassed DMSO (18 mL, prepared by three iterations of the freeze-thaw method) was added at 25 °C. The reaction contents were then warmed to 85 °C and stirred for 8 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 desired boronate ester (0.729 g, 50% yield) as a white foam. *R_f* = 0.59 (silica gel, EtOAc/hexanes, 1:4); IR (film) $\nu_{\max}$ 2930, 2857, 1619, 1433, 1366, 1255, 1192, 1111, 940, 838, 778, 698 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.63 (d, *J* = 7.4 Hz, 1 H), 7.41 (d, *J* = 7.4 Hz, 2 H), 7.28–7.21 (m, 3 H), 7.12 (d, *J* = 7.2

Hz, 1 H), 6.90 (t, $J = 7.4$ Hz, 1 H), 5.58 (s, 1 H), 3.96 (AB, $J = 10.0$ Hz, $v_{ab} = 25.9$ Hz, 2 H), 3.39 (s, 3 H), 1.30 (s, 12 H), 0.76 (s, 9 H), -0.06 (s, 3 H), -0.12 (s, 3 H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.8, 138.2, 135.7, 130.9, 129.5, 129.4, 127.3, 126.6, 120.2, 110.1, 83.5, 67.7, 59.4, 56.2, 25.7, 25.2, 24.5, 18.1, -5.7 , -5.8 ; HRMS (MALDI-FTMS) calcd for $\text{C}_{28}\text{H}_{41}\text{BO}_5\text{SiNa}^+$ [$\text{M} + \text{Na}^+$] 519.2708, found 519.2709.

Suzuki coupling product 60. $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (0.245 g, 0.30 mmol, 0.2 equiv), K_2CO_3 (1.04 g, 7.50 mmol, 5.0 equiv), and the newly prepared *trans*-methoxy boronate (0.818 g, 1.65 mmol, 1.1 equiv) were added to a flask containing indole-oxazole phosphonate **59** (0.600 g, 1.50 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 contents were then heated at reflux (85 °C) for 8 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, 1:4→1:0) to give Suzuki coupling product **60** (0.691 g, 67% yield) as a light brown foam. **60**: $R_f = 0.28$ (silica gel, EtOAc); IR (film) ν_{max} 3442, 2953, 2855, 1634, 1565, 1439, 1334, 1256, 1193, 1103, 1033, 941, 838, 779, 748, 700 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 7.50 (d, $J = 7.0$ Hz, 1 H), 7.48 (s, 1 H), 7.36–7.31 (m, 3 H), 7.30 (br t, $J = 7.4$ Hz, 2 H), 7.24 (br t, $J = 7.0$ Hz, 1 H), 7.17 (dd, $J = 7.9, 1.7$ Hz, 1 H), 7.09 (br d, $J = 6.6$ Hz, 1 H), 7.03 (br d, $J = 6.7$ Hz, 1 H), 6.95 (t, $J = 7.5$ Hz, 1 H), 5.85 (br s, 1 H), 5.24 (s, 1 H), 3.98 (AB, $J = 6.6$ Hz, $v_{ab} = 46.9$ Hz, 2 H), 3.88 (s, 3 H), 3.65 (dd, $J = 14.0, 11.0$ Hz, 6 H), 3.09 (dd, $J = 21.4, 4.8$ Hz, 2 H), 3.04 (br s, 3 H), 0.70 (s, 9 H), -0.03 (br s, 3 H), -0.11 (br s, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 154.5, 153.4, 148.0, 137.9, 131.6, 130.8, 130.1, 130.0, 127.7, 127.0, 125.7, 124.4, 123.7, 122.9, 122.6, 122.4, 120.5, 111.1, 110.0, 98.3, 68.4, 53.2, 53.1, 33.1, 26.3, 25.5, 25.2, 20.9, 18.1, 17.0, -6.0 , -6.2 ; HRMS (MALDI-FTMS) calcd for $\text{C}_{37}\text{H}_{46}\text{N}_2\text{O}_7\text{PSi}^+$ [$\text{M} + \text{Na}^+$] 689.2806, found 689.2781.

Aldehyde-phosphonate 61. HF (7.0 mL, 48% in water) was added to a solution of the Suzuki coupling product **60** (0.691 g, 1.0 mmol, 1.0 equiv) in MeCN (9 mL) at 0 °C, and the

resultant solution was stirred at 0 °C for 45 minutes. Upon completion, the reaction mixture was basified by the slow and careful addition of saturated aqueous NaHCO₃ (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 (MgSO₄), and concentrated to give the desired alcohol (0.556 g, 97% yield) as a yellow foam which was carried forward without any additional purification. Next, oxalyl chloride (0.422 mL, 4.85 mmol, 5.0 equiv) was added to a solution of DMSO (0.686 mL, 9.70 mmol, 10 equiv) in CH₂Cl₂ (50 mL) at -78 °C. After 10 minutes of stirring at -78 °C, the newly-formed intermediate alcohol (0.556 g, 0.97 mmol, 1.0 equiv) was added dropwise as a solution in CH₂Cl₂ (5 mL) at -78 °C. Following 45 minutes of stirring at -78 °C, Et₃N (2.70 mL, 19.6 mmol, 20 equiv) was added and the mixture was allowed to warm slowly to 25 °C. The reaction contents were then poured into water (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were then washed with water (50 mL), 1 N aqueous HCl (50 mL), saturated aqueous NaHCO₃ (50 mL), and brine (50 mL), dried (MgSO₄), and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, EtOAc/MeOH, 1:0→19:1) to give aldehyde-phosphonate **61** (0.488 g, 88% yield) as a light yellow oil. **61**: R_f = 0.13 (silica gel, EtOAc); IR (film) $\nu_{\max}$ 2943, 1725, 1596, 1437, 1326, 1261, 1190, 1114, 1031, 926, 814, 744, 697 cm⁻¹; ¹H NMR (600 MHz, CD₃CN) δ 9.48 (s, 1 H), 7.50 (d, *J* = 8.3 Hz, 1 H), 7.46 (s, 1 H), 7.43 (t, *J* = 7.0 Hz, 2 H), 7.38–7.34 (m, 2 H), 7.27 (t, *J* = 7.4 Hz, 2 H), 7.18 (d, *J* = 7.0 Hz, 2 H), 7.12–7.08 (m, 2 H), 5.84 (app s, 2 H), 3.87 (s, 3 H), 3.66 (app t, *J* = 11.0 Hz, 6 H), 3.11 (d, *J* = 10.6 Hz, 2 H), 3.08 (s, 3 H); ¹³C NMR (150 MHz, CD₃CN) δ 193.6, 157.7, 154.6, 148.1, 138.3, 133.6, 132.3, 130.8, 130.2, 129.5, 129.1, 126.2, 125.9, 124.1, 123.3, 123.2, 123.0 (2 C), 122.1, 110.7, 108.3, 104.0, 71.3, 56.8, 53.6, 53.5, 33.6, 26.6, 25.7; HRMS (MALDI-FTMS) calcd for C₃₁H₃₀N₂O₇P⁺ [*M* + H⁺] 573.1785, found 573.1769.

Macrocyclic alkene 55. LiHMDS (0.873 mL, 1.0 M in THF, 0.873 mmol, 5.0 equiv) was added dropwise over the course of 2 minutes to a solution of aldehyde-phosphonate **61** (0.100 g, 0.174 mmol, 1.0 equiv) in THF at 0 °C, and the resultant yellow reaction mixture was

stirred for 2 hours at 0 °C. Upon completion, the reaction was poured into water (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic extracts were then washed with water (50 mL) and brine (50 mL), dried (MgSO₄), and concentrated. The resultant yellow-orange oil was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1→1:0) to give macrocyclic alkene **55** (0.019 g, 25% yield) as a dark yellow foam. **55**: *R_f* = 0.18 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2925, 1591, 1492, 1446, 1373, 1225, 1190, 928, 747 cm⁻¹; ¹H NMR (600 MHz, CD₃CN) δ 7.53 (dd, *J* = 8.3, 0.8 Hz, 1 H), 7.46 (s, 1 H), 7.42–7.38 (m, 5 H), 7.33–7.29 (m, 1 H), 7.20 (dd, *J* = 7.0, 0.9 Hz, 1 H), 6.97 (dd, *J* = 8.5, 1.3 Hz, 1 H), 6.95 (dd, *J* = 8.3, 1.3 Hz, 1 H), 6.90 (d, *J* = 12.7 Hz, 1 H), 6.86 (s, 1 H), 6.81 (t, *J* = 7.4 Hz, 1 H), 6.46 (d, *J* = 12.7 Hz, 1 H), 5.99 (s, 1 H), 3.88 (s, 3 H), 3.17 (s, 3 H); ¹³C NMR (150 MHz, CD₃CN) δ 159.0, 146.0, 143.0, 138.5, 132.5, 131.9, 131.0, 130.9, 130.2, 129.4, 128.7, 127.9, 127.8, 126.4, 126.3, 124.5, 124.0, 123.3, 123.0, 122.0, 121.6, 119.1, 116.7, 110.9, 61.0, 57.9, 33.7; HRMS (MALDI-FTMS) calcd for C₂₉H₂₃N₂O₃Si⁺ [*M* + H⁺] 447.1703, found 447.1707.

Oxime 62. Finely powdered KMnO₄ (0.052 g, 0.328 mmol, 6.0 equiv) was added in small portions over the course of 45 minutes to a rapidly stirring solution of alkene **55** (0.024 g, 0.055 mmol, 1.0 equiv) and Cu(OAc)₂•H₂O (0.066 g, 0.328 mmol, 6.0 equiv) in Ac₂O (5 mL) at 0 °C. The resultant dark purple solution was then stirred for an additional 45 minutes at 0 °C. Upon completion, the reaction contents were diluted with EtOAc (5 mL), poured into saturated aqueous Na₂S₂O₃ (15 mL), and extracted with EtOAc (3 × 15 mL). The combined organic extracts were then washed with water (25 mL) and brine (25 mL), dried (MgSO₄), and concentrated. The resultant bright yellow oil was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1→1:0) to give the desired diketone intermediate (0.008 g, 31% yield) as a bright yellow oil. This compound (0.008 g, 0.017 mmol, 1.0 equiv) was then dissolved in EtOH (5 mL, absolute) and treated with MeONH₂•HCl (0.042 g, 0.505 mmol, 30 equiv) at 25 °C. After stirring the resultant solution for 12 hours at 25 °C, during which time the reaction color lightened from bright yellow to a light yellow, the reaction contents were poured into saturated aqueous NaHCO₃ (15 mL) and extracted with EtOAc (3 × 15 mL). The combined

organic extracts were then washed with water (25 mL) and brine (25 mL), dried (MgSO_4), and concentrated. The resultant light yellow oil was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1→1:0) to give the desired oxime **62** (0.009 g, 98% yield) as a light yellow oil. **62**: R_f = 0.62 (silica gel, EtOAc/hexanes, 2:1); IR (film) ν_{max} 2932, 1717, 1674, 1615, 1597, 1513, 1465, 1359, 1262, 1047, 900, 806, 743 cm^{-1} ; ^1H NMR (400 MHz, CD_3CN) δ 7.63 (dd, J = 7.8, 6.8 Hz, 3 H), 7.58 (t, J = 7.7 Hz, 2 H), 7.54–7.50 (m, 4 H), 7.28 (dd, J = 7.2 Hz, 1 H), 6.99 (s, 1 H), 6.98 (d, J = 6.8 Hz, 1 H), 6.94 (s, 1 H), 6.03 (s, 1 H), 3.98 (s, 3 H), 3.59 (s, 3 H), 3.31 (s, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 199.3, 160.8, 153.8, 149.1, 146.6, 138.3, 133.1, 131.9, 131.5, 130.5, 129.8, 129.1, 129.0 (2 C), 128.6, 128.0, 126.5, 125.4, 125.1, 123.7, 122.1, 122.0, 111.0, 110.4, 63.1, 56.5, 33.6; HRMS (MALDI-FTMS) calcd for $\text{C}_{30}\text{H}_{24}\text{N}_3\text{O}_5^+$ [$\text{M} + \text{H}^+$] 506.1710, found 506.1693.

Ketoamide 63. Pd/C (2.0 mg, 10 wt %, excess) was added to a solution of oxime **52** (1.1 mg, 0.0022 mmol, 1.0 equiv) in degassed MeOH/ CF_3COOH (4:1, 2.5 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 12 hours at 25 °C. Upon completion, the reaction contents were filtered through Celite (using several benzene washes to ensure high yield) and concentrated to give the desired amine•TFA salt as a white amorphous solid. This intermediate was then immediately dissolved in CHCl_3 (2 mL) and treated sequentially at 25 °C with Et_3N (0.2 mL, excess) and AcCl (0.1 mL, excess). After stirring the resultant solution for 30 minutes at 25 °C, the reaction contents were poured into saturated aqueous NH_4Cl (15 mL) and extracted with EtOAc (3×15 mL). The combined organic extracts were then washed with water (25 mL) and brine (25 mL), dried (MgSO_4), and concentrated. The resultant light yellow oil was purified by preparative TLC (silica gel, EtOAc) to give the ketoamide **63** (0.9 mg, 80% yield over two steps) as a light yellow oil. **63**: R_f = 0.15 (silica gel, EtOAc); IR (film) ν_{max} 3315, 2920, 1746, 1697, 1615, 1519, 1471, 1369, 1099, 745 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.41 (d, J = 6.6 Hz, 1 H), 7.39–7.36 (m, 6 H), 7.24 (m, 2 H), 7.15 (s, 1 H), 6.98 (d, J = 7.4 Hz, 1 H), 6.93 (t, J = 7.9

Hz, 1 H), 6.65 (s, 1 H), 6.42 (br d, $J = 6.4$ Hz, 1 H), 6.01 (d, $J = 7.9$ Hz, 1 H), 5.97 (s, 1 H), 3.85 (s, 3 H), 3.25 (s, 3 H), 2.05 (s, 3 H); MS (ESI) calcd for $C_{31}H_{26}N_3O_5^+$ [$M + H^+$] 520, found 520.

Oxazole 64. *p*-TsOH (2.0 mg, excess) was added to a solution of ketoamide **63** (0.9 mg, 0.0017 mmol, 1.0 equiv) in benzene (6 mL) at 25 °C. The resultant mixture was then heated at 80 °C for 20 hours, using a Dean-Stark trap to drive the desired elimination of water. Upon completion, the reaction contents were poured into EtOAc (15 mL), washed with saturated aqueous $NaHCO_3$ (5 mL), water (25 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated. The resultant light yellow oil was purified by preparative TLC (silica gel, EtOAc) to give the oxazole **64** (0.4 mg, 50% yield) as a clear oil. **64**: $R_f = 0.52$ (silica gel, EtOAc); IR (film) ν_{max} 2920, 1735, 1698, 1651, 1519, 1465, 1369, 1099 cm^{-1} ; 1H NMR (600 MHz, $CDCl_3$) δ 7.62 (d, $J = 7.9$ Hz, 1 H), 7.44–7.37 (m, 4 H), 7.34–7.24 (m, 4 H), 7.08 (d, $J = 7.4$ Hz, 1 H), 6.99 (d, $J = 7.5$ Hz, 1 H), 6.92 (s, 1 H), 6.82 (t, $J = 7.8$ Hz, 1 H), 6.08 (s, 1 H), 3.88 (s, 3 H), 3.23 (s, 3 H), 2.45 (s, 3 H); HRMS (MALDI-FTMS) calcd for $C_{31}H_{24}N_3O_4^+$ [$M + H^+$] 502.1761, found 502.1744.

Methyl-protected indole-oxazole 65. Tetra-*n*-butylammonium hydrogensulfate (0.075 g, 0.220 mmol, 1.1 equiv) and 10% aqueous NaOH (excess, ~5 mL) were added sequentially to a solution of indole-oxazole **51** (0.106 g, 0.200 mmol, 1.0 equiv) in benzene (10 mL) at 25 °C. The resultant biphasic system was stirred at 25 °C for 5 minutes, and then MeI (0.037 mL, 0.600 mmol, 3.0 equiv) was added. After 20 minutes of additional stirring at 25 °C, the reaction contents were poured into water (25 mL) and extracted with CH_2Cl_2 (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) to give methyl-protected indole-oxazole **65** (0.099 g, 88% yield) as a yellow oil. **65**: $R_f = 0.54$ (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2932, 1636, 1559, 1469, 1424, 1099, 822, 737, 703, 611, 505 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 7.77 (dd, $J = 8.1, 1.8$ Hz, 4 H), 7.45–7.38 (m, 7 H), 7.33 (d, $J = 8.1$ Hz, 1 H), 7.23 (s, 1 H), 7.16 (s, 1 H), 7.14 (t, $J = 7.0$ Hz, 1 H), 4.83 (s, 2 H), 3.83 (s, 3 H), 1.10 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6,

145.5, 137.9, 135.7, 132.9, 131.2, 129.8, 127.8, 126.0, 125.6, 125.0, 123.2, 114.1, 108.9, 103.5, 59.2, 33.3, 26.7, 19.3; HRMS (MALDI-FTMS) calcd for $C_{23}H_{23}BrN_2O_2Si^+$ [$M - C_6H_6^+$] 467.0785, found 467.0795.

Benzyl-protected indole-oxazole 67. NaH (0.060 g, 60% dispersion in mineral oil, 1.41 mmol, 5.0 equiv) was added slowly to a solution of indole-oxazole **51** (0.150 g, 0.280 mmol, 1.0 equiv) in DMF (15 mL) at 25 °C. The resultant slurry was stirred at 25 °C until all bubbling ceased (~5 minutes), and then benzyl bromide (0.160 g, 0.860 mmol, 3.0 equiv) was added in a single portion. After 2 hours of additional stirring at 25 °C, the reaction was quenched with water (50 mL) and extracted with CH_2Cl_2 (3 × 30 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) to give benzyl-protected indole-oxazole **67** (0.130 g, 74% yield) as a light yellow oil. **67**: R_f = 0.82 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2955, 1636, 1429, 1173, 1110, 1085, 820, 732, 702 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 7.75 (m, 4 H), 7.43–7.28 (m, 12 H), 7.17 (m, 3 H), 7.09 (t, J = 8.1 Hz, 1 H), 5.35 (s, 2 H), 4.81 (s, 2 H), 1.09 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.8, 137.5, 135.9, 135.6, 132.7, 130.7, 129.8, 129.0, 128.2, 127.8, 126.9, 125.7, 125.3, 125.0, 123.5, 114.1, 109.5, 103.7, 99.6, 58.9, 50.6, 26.7, 19.2; HRMS (MALDI-FTMS) calcd for $C_{35}H_{34}BrN_2O_2Si^+$ [$M + H^+$] 621.1567, found 621.1544.

MOM-protected indole-oxazole 69. NaH (0.406 g, 60% dispersion in mineral oil, 10.16 mmol, 2.0 equiv) was added slowly to a solution of indole-oxazole **51** (2.7 g, 5.08 mmol, 1.0 equiv) in THF (125 mL) at 0 °C. The resultant slurry was stirred at 0 °C until all bubbling ceased (~5 minutes), and then chloromethyl methyl ether (0.501 mL, 0.220 mmol, 1.1 equiv) was added in a single portion. After 20 minutes of additional stirring at 0 °C, the reaction was quenched with water (50 mL) and extracted with CH_2Cl_2 (3 × 75 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 MOM-protected indole-oxazole **69** (2.75 g, 95% yield) as a

light yellow, amorphous solid. **69**: R_f = 0.35 (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\max}$ 2930, 1636, 1473, 1428, 1394, 1183, 1099, 1006, 905, 823, 738, 702 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.79 (d, J = 6.6 Hz, 4 H), 7.52 (d, J = 8.3 Hz, 1 H), 7.47–7.41 (m, 7 H), 7.36 (s, 1 H), 7.21 (s, 1 H), 7.17 (t, J = 7.9 Hz, 1 H), 5.47 (s, 2 H), 4.85 (s, 2 H), 3.31 (s, 3 H), 1.12 (s, 9 H); ^{13}C NMR (150 MHz, CDCl_3) δ 161.8, 145.0, 137.4, 135.6, 132.8, 130.3, 129.8 (2 C), 127.7, 126.3, 125.8, 123.9, 114.1, 109.7, 104.9, 77.8, 59.1, 56.1, 26.7, 19.2; HRMS (MALDI-FTMS) calcd for $\text{C}_{30}\text{H}_{31}\text{BrN}_2\text{O}_3\text{SiNa}^+$ [$\text{M} + \text{Na}^+$] 597.1179, found 597.1162.

Ethyl carbamate-protected indole-oxazole 71. Et_3N (0.105 mL, 0.755 mmol, 4.0 equiv) and ethyl chloroformate (0.036 mL, 0.377 mmol, 2.0 mmol) were added sequentially to a solution of indole-oxazole **51** (0.100 g, 0.188 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at 0 °C. After 15 minutes of stirring at 0 °C, the reaction contents were poured into Et_2O (50 mL), washed with saturated aqueous NaHCO_3 (50 mL) and brine (50 mL), dried (MgSO_4), and concentrated. The resultant yellow oil was purified by flash column chromatography (silica gel, EtOAc/hexanes 1:1) to give ethyl carbamate-protected indole-oxazole **71** (0.087 g, 79% yield) as a yellow oil. **71**: R_f = 0.69 (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\max}$ 1749, 1636, 1470, 1424, 1376, 1256, 1179, 1117, 741, 703 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 8.34 (d, J = 8.3 Hz, 1 H), 7.89 (s, 1 H), 7.81 (dd, J = 7.9, 1.3 Hz, 4 H), 7.54 (d, J = 7.9 Hz, 1 H), 7.50–7.44 (m, 6 H), 7.30 (t, J = 7.9 Hz, 1 H), 7.27 (s, 1 H), 4.88 (s, 2 H), 4.59 (q, J = 7.0 Hz, 2 H), 1.55 (t, J = 7.4 Hz, 3 H), 1.14 (s, 9 H); ^{13}C NMR (150 MHz, CDCl_3) δ 162.4, 150.1, 143.6, 136.4, 135.5, 132.7, 129.8, 128.1, 127.7 (2 C), 127.6, 127.1, 126.1, 114.5, 114.0, 109.5, 64.0, 59.0, 26.6, 19.2, 14.3; HRMS (MALDI-FTMS) calcd for $\text{C}_{31}\text{H}_{32}\text{BrN}_2\text{O}_4\text{Si}^+$ [$\text{M} + \text{H}^+$] 603.1309, found 603.1306.

***t*-Butyl carbamate-protected indole-oxazole 73.** Et_3N (0.592 mL, 4.24 mmol, 1.5 equiv), 4-DMAP (0.035 g, 0.283 mmol, 0.1 equiv), and Boc_2O (1.17 g, 3.68 mmol, 1.3 mmol) were added sequentially to a solution of indole-oxazole **51** (1.50 g, 2.83 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at 0 °C. After 10 minutes of stirring at 0 °C, the reaction contents were poured into saturated aqueous NaHCO_3 (100 mL) and extracted with EtOAc (3 $\times$ 75 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 *t*-butyl carbamate-protected indole-oxazole **73** (1.68 g, 98% yield) as a yellow oil. **73**: *R*_f = 0.83 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 1737, 1636, 1453, 1427, 1368, 1242, 1154, 1110, 1057, 740, 703, 611, 506 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.25 (br d, *J* = 6.5 Hz, 1 H), 7.89 (s, 1 H), 7.81 (d, *J* = 7.9 Hz, 1 H), 7.78 (d, *J* = 6.6 Hz, 4 H), 7.46–7.41 (m, 6 H), 7.36 (t, *J* = 7.9 Hz, 1 H), 7.32 (s, 1 H), 4.88 (s, 2 H), 1.73 (s, 9 H), 1.13 (s, 9 H); ¹³C NMR (150 MHz, CDCl₃) δ 161.0, 146.5, 135.6, 132.7, 129.9, 127.8, 126.6, 125.1, 123.4, 122.7, 122.0, 120.1, 115.5, 109.4, 99.5, 84.4, 59.0, 28.2, 26.7, 19.3, 17.4; MS (ESI) calcd for C₃₃H₃₆BrN₂O₄Si⁺ [*M* + H⁺] 631, found 631.

Tosyl-protected indole-oxazole 75. Tetra-*n*-butylammonium hydrogensulfate (0.075 g, 0.220 mmol, 1.1 equiv) and 10% aqueous NaOH (excess, ~5 mL) were added sequentially to a solution of indole-oxazole **51** (0.106 g, 0.200 mmol, 1.0 equiv) in benzene (10 mL) at 25 °C. The resultant biphasic system was stirred at 25 °C for 5 minutes, and then *p*-TsCl (0.042 g, 0.220 mmol, 1.1 equiv) was added. After 20 minutes of additional stirring at 25 °C, the reaction contents were poured into water (25 mL) and extracted with CH₂Cl₂ (3 × 25 mL). The combined organic extracts 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 tosyl-protected indole-oxazole **75** (0.123 g, 91% yield) as a white amorphous solid. **75**: *R*_f = 0.68 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2955, 1636, 1412, 1378, 1177, 1152, 1089, 1041, 817, 738, 704, 611, 574 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.03 (d, *J* = 8.0 Hz, 1 H), 7.83 (d, *J* = 8.4 Hz, 1 H), 7.80 (s, 1 H), 7.75 (dd, *J* = 7.9, 1.3 Hz, 4 H), 7.48–7.38 (m, 7 H), 7.29 (d, *J* = 8.3 Hz, 2 H), 7.23 (d, *J* = 7.9 Hz, 1 H), 7.21 (s, 1 H), 4.83 (s, 2 H), 2.39 (s, 3 H), 1.10 (s, 9 H); ¹³C NMR (150 MHz, CDCl₃) δ 162.6, 145.9, 143.1, 135.7, 135.6, 134.6, 132.7, 130.2, 129.9, 128.4, 128.1, 127.8, 127.1, 126.1, 114.3, 112.7, 59.0, 26.7, 21.6, 19.3; HRMS (MALDI-FTMS) calcd for C₃₅H₃₃BrN₂O₄SSiNa⁺ [*M* + Na⁺] 707.1011, found 707.0987.

General procedure for chlorinations. Freshly recrystallized *N*-chlorosuccinimide (0.026 g, 0.2 mmol, 2.0 equiv) was added to a solution of the appropriate indole-oxazole (0.1 mmol, 1.0 equiv) in THF/CCl₄ (1:1, 5 mL) at 25 °C, and the resultant solution was heated to 65 °C. Once TLC analysis indicated reaction completion (typically in 6–8 hours), the reaction mixture was cooled to 25 °C, poured into water (25 mL), and extracted with CH₂Cl₂ (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 the desired products as yellow films in yields which ranged from 56–84% (see Table 2).

66: *R_f* = 0.45 (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\max}$ 2931, 1741, 1605, 1459, 1425, 1361, 1326, 1109, 820, 740, 703, 609, 504 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.68 (d, *J* = 6.8 Hz, 4 H), 7.45–7.35 (m, 6 H), 7.28 (m, 2 H), 6.87 (d, *J* = 7.4 Hz, 1 H), 4.69 (s, 2 H), 3.27 (s, 3 H), 1.03 (s, 9 H); ¹³C NMR (150 MHz, CDCl₃) δ 161.4, 144.8, 137.5, 135.5, 132.5, 132.4, 132.3, 130.0, 128.1, 127.9, 127.8, 125.1, 121.6, 108.0, 99.2, 58.8, 30.9, 26.5, 19.2; HRMS (MALDI-FTMS) calcd for C₂₉H₂₇BrCl₂N₂O₂Si⁺ [*M* + H⁺] 635.0294, found 635.0292.

68: *R_f* = 0.86 (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\max}$ 2932, 2857, 1647, 1560, 1428, 1388, 1228, 1163, 1107, 823, 737, 702, 613 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.75 (dd, *J* = 8.1, 1.5 Hz, 4 H), 7.45–7.30 (m, 10 H), 7.26 (d, *J* = 8.1 Hz, 1 H), 7.15 (d, *J* = 7.4 Hz, 2 H), 7.09 (t, *J* = 8.1 Hz, 1 H), 5.49 (s, 2 H), 4.79 (s, 2 H), 1.09 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) δ 161.7, 137.7, 136.3, 135.6, 135.5, 132.5, 130.6, 129.9, 129.0, 128.3, 128.0, 127.8, 126.4, 125.9, 125.8, 123.8, 113.1, 109.5, 99.0, 59.1, 47.7, 26.7, 19.2; HRMS (MALDI-FTMS) calcd for C₃₅H₃₁BrCl₂N₂O₂SiNa⁺ [*M* + Na⁺] 711.0607, found 711.0603.

70: *R_f* = 0.68 (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\max}$ 2933, 1648, 1561, 1472, 1430, 1393, 1203, 1103, 1055, 917, 824, 738, 703, 613, 505 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.83–7.81 (m, 3 H), 7.60 (dd, *J* = 8.1, 0.8 Hz, 1 H), 7.53–7.45 (m, 7 H), 7.26 (t, *J* = 8.1 Hz, 1 H), 5.58 (s, 2 H), 4.85 (s, 2 H), 3.39 (s, 3 H), 1.16 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) δ 160.8,

139.4, 137.2, 135.6, 132.5, 131.4, 130.0, 128.6, 127.8, 127.0, 125.8, 124.1, 113.9, 109.8, 102.0, 78.0, 59.0, 56.2, 26.7, 19.2; MS (ESI) calcd for $C_{30}H_{31}BrClN_2O_3Si^+$ $[M - Cl]^+$ 609, found 609.

72: $R_f = 0.74$ (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2925, 1752, 1643, 1564, 1469, 1425, 1376, 1258, 1177, 1116, 1055, 823, 740, 704 cm^{-1} ; 1H NMR (600 MHz, $CDCl_3$) δ 8.29 (d, $J = 8.3$ Hz, 1 H), 7.90 (s, 1 H), 7.74 (d, $J = 7.0$ Hz, 4 H), 7.50 (d, $J = 7.9$ Hz, 1 H), 7.46–7.39 (m, 6 H), 7.28 (t, $J = 7.9$ Hz, 1 H), 4.78 (s, 2 H), 4.56 (q, $J = 7.4$ Hz, 2 H), 1.52 (t, $J = 7.0$ Hz, 3 H), 1.08 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.3, 150.1, 138.0, 136.3, 135.6, 134.8, 132.5, 129.9, 129.5, 129.1, 128.0, 127.7, 126.3, 114.6, 113.8, 106.9, 64.1, 59.0, 26.6, 19.2, 14.3; HRMS (MALDI-FTMS) calcd for $C_{31}H_{30}BrClN_2O_4SiNa^+$ $[M + Na^+]$ 659.0739, found 659.0728.

74: $R_f = 0.70$ (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2943, 1747, 1637, 1450, 1351, 1309, 1257, 1149, 1113, 824, 742, 703, 504 cm^{-1} ; 1H NMR (600 MHz, $CDCl_3$) δ 8.12 (d, $J = 8.3$ Hz, 1 H), 7.71 (d, $J = 7.4$ Hz, 4 H), 7.50 (d, $J = 7.4$ Hz, 1 H), 7.42 (m, 2 H), 7.39–7.35 (m, 5 H), 7.27 (t, $J = 7.4$ Hz, 1 H), 4.79 (s, 2 H), 1.72 (s, 9 H), 1.08 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.8, 148.6, 138.6, 137.4, 135.6, 135.2, 132.4, 130.0, 127.9, 126.2, 125.2, 124.9, 123.7, 119.5, 115.2, 85.8, 59.0, 28.1, 26.6, 19.2, 17.4; MS (ESI) calcd for $C_{33}H_{33}BrN_2O_4Si^-$ $[M - HCl^-]$ 627, found 627.

76: $R_f = 0.71$ (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2943, 1648, 1561, 1413, 1379, 1177, 1147, 1089, 1020, 918, 821, 741, 705, 574 cm^{-1} ; 1H NMR (600 MHz, $CDCl_3$) δ 8.02 (d, $J = 8.3$ Hz, 1 H), 7.86 (s, 1 H), 7.83 (d, $J = 8.3$ Hz, 1 H), 7.71 (dd, $J = 7.4, 0.9$ Hz, 4 H), 7.45 (m, 3 H), 7.39 (t, $J = 7.4$ Hz, 4 H), 7.31 (d, $J = 8.8$ Hz, 2 H), 7.24 (t, $J = 7.9$ Hz, 1 H), 4.76 (s, 2 H), 2.40 (s, 3 H), 1.07 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.4, 146.0, 137.5, 135.6, 135.5, 134.4, 132.4, 130.2, 129.9, 129.6, 129.5, 128.3, 127.8, 127.1, 126.3, 114.1, 112.7, 107.8, 99.8, 59.0, 26.7, 21.7, 19.2; HRMS (MALDI-FTMS) calcd for $C_{35}H_{32}BrClN_2O_4SSiNa^+$ $[M + Na^+]$ 741.0622, found 741.0586.

77: $R_f = 0.53$ (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3447, 2695, 1739, 1618, 1450, 1110, 702 cm^{-1} ; 1H NMR (600 MHz, $CDCl_3$) δ 8.48 (br s, 1 H), 7.70–7.67 (m, 4 H),

7.46–7.42 (m, 2 H), 7.41–7.38 (m, 4 H), 7.28 (dd, $J = 8.1, 1.1$ Hz, 1 H), 7.25 (t, $J = 8.1$ Hz, 1 H), 6.94 (dd, $J = 7.3, 1.5$ Hz, 1 H), 4.72 (s, 1 H), 1.05 (s, 9 H); ^{13}C NMR (150 MHz, CDCl_3) δ 161.6, 141.8, 137.2, 135.5, 132.6, 132.4, 132.3, 130.0, 128.5, 127.9, 127.8, 125.5, 121.7, 109.9, 58.9, 26.6, 19.2; MS (ESI) calcd for $\text{C}_{28}\text{H}_{25}\text{BrCl}_2\text{N}_2\text{O}_2\text{SiNa}^+ [\text{M} + \text{Na}^+]$ 621, found 621.

L-Tyrosine-derived phenol 79. A solution of Na_2CO_3 (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 CHCl_3 (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 Na_2CO_3 (2.0 M in H_2O , 100 mL) were added sequentially. After 3 hours of vigorous stirring at 25 °C, the reaction contents were diluted with water (100 mL) and the organic layer was separated, dried (MgSO_4), 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, the newly-formed intermediate (70.88 g, 215 mmol, 1.0 equiv) was dissolved in THF (1000 mL), cooled to 0 °C, and treated with solid LiBH_4 (14.80 g, 645 mmol, 3.0 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% HCl (50 mL) and water (400 mL) were added dropwise over the course of 4 hours to quench any residual reducing agent. Subsequent extraction with EtOAc (3 $\times$ 400 mL), followed by washing the combined organic layers with water (100 mL) and brine (100 mL), ultimately afforded the desired intermediate alcohol (64.86 g, 99% yield) as a yellow oil upon concentration. With this operation complete, the new intermediate (64.86 g, 216 mmol, 1.0 equiv) was then dissolved in acetone (300 mL) and treated sequentially with 2,2-dimethoxypropane (265 mL, 2.16 mol, 10 equiv) and *p*-TsOH (0.300 g, catalytic) at 25 °C. After 30 minutes of additional stirring at 25 °C, the reaction 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 (MgSO_4), and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:5) to give L-tyrosine-derived phenol **79** (71.3 g, 97% yield) as a colorless

oil. **79**: R_f = 0.43 (silica gel, EtOAc/hexanes, 1:5); IR (film) $\nu_{\max}$ 3374, 2984, 1680, 1613, 1515, 1415, 1355, 1252, 1096, 826, 764, 698 cm^{-1} ; ^1H NMR (500 MHz, 340 K, CD_3CN) δ 7.52–7.47 (m, 4 H), 7.45–7.41 (m, 1 H), 7.06 (br s, 2 H), 6.79 (d, J = 8.5 Hz, 2 H), 6.74 (br s, 1 H), 5.21 (br m, 3 H), 4.13 (m, 1 H), 3.93 (dd, J = 8.8, 5.6 Hz, 1 H), 3.84 (dd, J = 9.2, 1.8 Hz, 1 H), 3.04 (br d, J = 11.0 Hz, 1 H), 2.73 (dd, J = 13.2, 9.9 Hz, 1 H), 1.60 (br s, 3 H), 1.54 (s, 3 H); ^{13}C NMR (125 MHz, 340 K, CD_3CN) δ 155.9, 137.7, 130.8, 130.1, 128.9, 128.3, 115.6, 94.3, 66.7, 59.4, 39.0, 26.5, 23.1; HRMS (MALDI-FTMS) calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_4\text{Na}^+$ [$\text{M} + \text{Na}^+$] 364.1519, found 364.1519.

Iodinated building block 80. K_2CO_3 (89.4 g, 649 mmol, 10 equiv) and MeI (20.2 mL, 325 mmol, 5.0 equiv) were added sequentially to a solution of phenol **79** (22.1 g, 64.9 mmol, 1.0 equiv) in DMF (500 mL) at 25 °C, and the resultant slurry was stirred vigorously for 10 hours. Upon completion, the reaction contents were poured into water (1000 mL) and extracted with Et_2O (3×400 mL). The combined organic layers were then washed with water (400 mL) and brine (400 mL), dried (MgSO_4), and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, Et_2O /hexanes, 1:1) to give the desired methylated intermediate (21.2 g, 92% yield) as a colorless oil. With this operation complete, this newly-formed compound (21.2 g, 59.7 mmol, 1.0 equiv) was dissolved in CHCl_3 (500 mL). Silver trifluoroacetate (19.8 g, 89.6 mmol, 1.5 mmol) was then added at 25 °C, and the resultant slurry was treated with a solution of iodine (19.8 g, 77.6 mmol, 1.2 equiv) in CHCl_3 (500 mL) added at a rate such that discoloration of the iodine solution occurred immediately upon its introduction into the reaction flask (~4 hours for completion using an additional funnel). Once this operation was complete, the reaction was quenched with saturated aqueous Na_2SO_3 (100 mL), filtered through a bed of Celite to remove insoluble particulates, and extracted with EtOAc (3×400 mL). The combined organic layers were then washed with water (400 mL) and brine (400 mL), dried (MgSO_4), and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, Et_2O /hexanes, 1:1) to give iodinated building block **80** (28.2 g; 77% yield) as a yellow oil. **80**: R_f = 0.53 (silica gel, Et_2O /hexanes, 1:1); IR (film) $\nu_{\max}$ 2939, 1700,

1597, 1490, 1457, 1407, 1353, 1254, 1093, 1051, 1019, 763, 699 cm^{-1} ; ^1H NMR (600 MHz, 340 K, CD_3CN) δ 7.58 (br s, 1 H), 7.40 (m, 4 H), 7.35 (m, 1 H), 7.13 (m, 1 H), 6.84 (d, $J = 8.3$ Hz, 1 H), 5.11 (AB, $J = 12.2$ Hz, $\nu_{\text{ab}} = 33.7$ Hz, 2 H), 4.08 (m, 1 H), 3.88 (dd, $J = 8.8, 5.7$ Hz, 1 H), 3.82 (s, 3 H), 3.75 (d, $J = 7.4$ Hz, 1 H), 2.93 (br d, $J = 13.1$ Hz, 1 H), 2.71 (dd, $J = 12.7, 9.2$ Hz, 1 H), 1.50 (br s, 3 H), 1.45 (s, 3 H); ^{13}C NMR (125 MHz, 340 K, CD_3CN) δ 157.5, 140.4, 137.6, 133.3, 131.1, 128.9, 128.4, 128.3, 114.3, 111.8, 94.3, 85.6, 66.8, 59.1, 56.6, 38.5, 26.5, 23.0; HRMS (MALDI-FTMS) calcd for $\text{C}_{21}\text{H}_{24}\text{INO}_4\text{Na}^+$ [$\text{M} + \text{Na}^+$] 504.0642, found 504.0647.

Biaryl alcohol 81. Freshly prepared isopropylmagnesium bromide (42.6 mL, 1.0 M in THF, 42.6 mmol, 1.5 equiv) was added to a solution of iodide **80** (15.0 g, 31.2 mmol, 1.1 equiv) in THF (50 mL) at -20 $^\circ\text{C}$. Once TLC analysis (hexanes/ Et_2O , 1:1) indicated the formation of the desired Grignard reagent, typically after 10 to 15 minutes of stirring at -20 $^\circ\text{C}$, this solution was quickly added via cannula to a solution of aldehyde **13** (6.95 g, 28.4 mmol, 1.0 equiv) in THF (150 mL) at -78 $^\circ\text{C}$. After 10 minutes of additional stirring at -78 $^\circ\text{C}$, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (5 mL), poured into water (200 mL), and extracted with Et_2O (3×100 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, 1:3 $\rightarrow$ 1:1) to give alcohol **81** (11.7 g, 69% yield) as a white solid. **81**: $R_f = 0.46$ (silica gel, EtOAc /hexanes, 1:1); IR (film) ν_{max} 3439, 2941, 1698, 1500, 1450, 1408, 1354, 1249, 1157, 1068, 1030, 953, 762, 698 cm^{-1} ; ^1H NMR (600 MHz, 340 K, CD_3CN , 1:1 mixture of diastereomers) δ 7.53–7.49 (m, 1 H), 7.45–7.42 (m, 5 H), 7.20 (br q, $J = 7.9$ Hz, 2 H), 7.07 (br q, $J = 7.9$ Hz, 1 H), 6.98 (dt, $J = 7.9, 3.5$ Hz, 1 H), 6.84 (dd, $J = 8.3, 4.8$ Hz, 1 H), 6.38 (d, $J = 4.4$ Hz, 1 H), 5.11 (m, 4 H), 4.09 (m, 1 H), 3.86 (m, 1 H), 3.75 (ddd, $J = 15.8, 9.2, 1.7$ Hz, 1 H), 3.69 (d, $J = 3.1$ Hz, 3 H), 3.64 (m, 1 H), 3.58 (m, 3 H), 2.99 (br s, 1 H), 2.69 (m, 1 H), 1.46 (m, 6 H); ^{13}C NMR (125 MHz, 340 K, CD_3CN , 1:1 mixture of diastereomers) δ 155.7, 155.6, 152.4, 140.4, 137.7, 132.8, 132.0, 131.9, 130.7, 130.6, 129.8, 129.7, 128.9, 128.8, 128.7, 128.3, 128.2 (2 C), 126.0, 111.4 (2 C), 100.3,

98.4, 94.3, 67.7, 66.6, 65.4 (2 C), 64.2, 60.3, 59.3, 57.7, 55.6, 39.1, 26.5, 23.0, 16.7, 13.9; HRMS (MALDI-FTMS) calcd for $C_{30}H_{34}BrNO_7Na^+$ [$M + Na^+$] 622.1411, found 622.1437.

Epoxide 82. A solution of IBX (6.57 g, 23.4 mmol, 1.2 equiv) in DMSO (30 mL) was added to a solution of alcohol **81** (11.7 g, 19.5 mmol, 1.0 equiv) in THF/DMSO (1:1, 170 mL) at 25 °C. After stirring for 4 hours at 25 °C, the reaction mixture was poured into EtOAc (300 mL) and washed extensively with saturated aqueous Na_2SO_3 (3×75 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 biaryl ketone (11.5 g, 98% yield) as a white solid which was carried forward without additional purification. Next, $KOt-Bu$ (39.8 mL, 1.0 M in THF, 39.8 mmol, 1.5 equiv) was added to a suspension of methylenetriphenylphosphonium bromide (18.95 g, 53.0 mmol, 2.0 equiv) in THF (300 mL) at 0 °C. After 15 minutes of stirring at 0 °C, the newly-formed ketone intermediate (15.86 g, 26.5 mmol, 1.0 equiv) was added via cannula as a solution in THF (50 mL), and the resultant mixture was allowed to react for 6 additional hours at 0 °C. Upon completion, the reaction mixture was quenched by the addition of water (200 mL) and extracted with Et_2O (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, 1:3→1:1) to give the desired biaryl alkene (13.7 g, 86% yield) as a white solid: $R_f = 0.59$ (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2943, 1702, 1608, 1497, 1449, 1405, 1352, 1245, 1202, 1157, 1089, 1026, 950, 760 cm^{-1} ; 1H NMR (600 MHz, 340 K, CD_3CN) δ 7.50 (dd, $J = 7.9, 1.3$ Hz, 1 H), 7.41–7.36 (m, 4 H), 7.32 (br t, $J = 7.0$ Hz, 1 H), 7.12 (d, $J = 7.4$ Hz, 1 H), 7.07 (br s, 1 H), 7.00 (br s, 1 H), 6.97 (t, $J = 7.9$ Hz, 1 H), 6.84 (d, $J = 7.9$ Hz, 1 H), 5.61 (s, 2 H), 5.10 (m, 2 H), 4.96 (s, 2 H), 4.08 (dd, $J = 14.0, 7.0$ Hz, 1 H), 3.87 (dd, $J = 9.2, 6.2$ Hz, 1 H), 3.77 (d, $J = 9.2$ Hz, 1 H), 3.55 (s, 3 H), 3.46 (s, 3 H), 2.99 (br d, $J = 11.9$ Hz, 1 H), 2.69 (t, $J = 12.7$ Hz, 1 H), 1.50 (s, 3 H), 1.46 (s, 3 H); ^{13}C NMR (125 MHz, 340 K, CD_3CN) δ 156.1, 151.5, 144.3, 138.6, 137.6, 132.6, 131.7, 131.0, 130.9, 130.5, 130.4, 128.9, 128.3 (2 C), 125.5, 120.2, 118.0, 112.3, 99.3, 94.3, 66.7, 59.3, 57.8, 55.6, 39.0, 26.5, 23.0; HRMS (MALDI-FTMS) calcd for $C_{31}H_{34}BrNO_6Na^+$ [$M + Na^+$] 618.1462, found

618.1458. With this operation complete, concentrated HCl (10 mL) was added to a solution of the alkene (15.6 g, 26.2 mmol, 1.0 equiv) in MeOH/CH₂Cl₂ (1:1, 400 mL) at 25 °C. After 12 hours of stirring at 25 °C, the reaction mixture was basified by the slow addition of saturated aqueous NaHCO₃, poured into water (100 mL), and extracted with CH₂Cl₂ (3 × 150 mL). The combined organic layers were then washed with water (100 mL) and brine (100 mL), dried (MgSO₄), and concentrated to give the desired phenol (14.71 g, 98% yield) as a yellow oil. Carrying this intermediate forward without additional purification, the phenol (14.71 g, 28.7 mmol, 1.0 equiv) was dissolved in acetone (400 mL), and then chloroacetonitrile (4.36 g, 57.4 mmol, 2.0 equiv) and K₂CO₃ (5.94 g, 43.1 mmol, 1.5 equiv) were added at 25 °C. The resultant suspension was heated at reflux for 3 hours. Upon completion, the reaction mixture was then cooled to 25 °C, poured into water (500 mL), and extracted with Et₂O (3 × 150 mL). The combined organic layers were then washed with water (100 mL) and brine (100 mL), dried (MgSO₄), and concentrated to give the desired alkylated product (15.2 g, 95% yield) as an orange oil which was carried forward without additional purification. Next, 2,2-dimethoxypropane (50 mL, large excess) and *p*-TsOH (0.10 g, catalytic) were added to a solution of this newly-formed product (18.7 g, 33.4 mmol, 1.0 equiv) in acetone (300 mL) at 25 °C. After 30 minutes of stirring at 25 °C, the reaction mixture was poured into water (200 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were then washed with saturated aqueous NaHCO₃ (100 mL), water (100 mL), and brine (100 mL), dried (MgSO₄), and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:3) to give the desired acetonide product (16.9 g, 86% yield) as a clear viscous oil. Finally, solid NaHCO₃ (8.11 g, 96.6 mmol, 3.0 equiv) and *m*-CPBA (14.4 g, 77%, 64.4 mmol, 2.0 equiv) were added sequentially to a solution of this intermediate (19.0 g, 32.2 mmol, 1.0 equiv) in CH₂Cl₂ (450 mL) at 0 °C to give a milk-colored slurry. After stirring this mixture for 8 hours at 0 °C, the reaction contents were poured into water (400 mL) and extracted with CH₂Cl₂ (3 × 150 mL). The combined organic layers were then washed with 50 mL portions of 3 M NaOH until all organic by-products were removed as indicated by TLC, dried (MgSO₄),