Lessons from the Total Synthesis of

(±) Phalarine: Insights Into the Mechanism of

the Pictet–Spengler Reaction

John D. Trzupek†, Chaomin Li§, Collin Chan§, Brendan M. Crowley†, Annekatrin C. Heimann†, and Samuel J. Danishefsky†§

†Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research,
1275 York Avenue, New York, New York 10065; and §Department of Chemistry,
Columbia University, Havemeyer Hall, 3000 Broadway, New York, New York 10027
**General.** All non-aqueous reactions were carried out in oven-dried glassware under a slight positive pressure of argon unless otherwise noted. All reagents were commercially available and used without further purification from Sigma-Aldrich, Acros, and Strem, unless indicated otherwise. Tetrahydrofuran (THF), diethyl ether (Et₂O), methylene chloride (CH₂Cl₂), benzene (PhH), and toluene (PhCH₃) were obtained from a dry solvent system (activated alumina columns, positive Argon pressure). All other solvents were used as received in Sure/Seal bottles (Aldrich). Triethylamine (Et₃N), pyridine, and chlorotrimethylsilane (TMSCl) were distilled from CaH₂ immediately prior to use. Reactions were magnetically stirred and monitored by thin layer chromatography on Merck silica gel 60-F₂₅₄ coated 0.25 mm plates. All reactions were performed at room temperature (ca 23 ºC) unless indicated otherwise. Flash chromatography was performed with E. Merck silica gel (60, particle size 40-63 µm), unless indicated otherwise. Yields reported are for isolated, spectroscopically pure compounds. Microwave experiments were performed using a Biotage microwave reactor. ¹H-NMR and ¹³C-NMR spectra were recorded on a Bruker DRX-500 MHz or Bruker AVII+600 MHz spectrometer. Chemical shifts are given in ppm relative to the residual undeuterated solvent peak and coupling constants are given in Hz. Residual solvent peaks were referenced as follows: acetone-₆ (¹H, δ = 2.05 ppm; ¹³C, δ = 29.9 ppm), CDCl₃ (¹H, δ = 7.26 ppm; ¹³C, δ = 77.0 ppm), and DMSO-₆ (¹H, δ = 2.50 ppm; ¹³C, δ = 39.5 ppm). Multiplicities and peak shape are labeled as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, pt = pseudo triplet, dd = doublet of doublets, etc. IR spectra were recorded on a JASCO FTIR-6100 instrument. Optical rotations were measured on a JASCO P-2000 polarimeter. Low resolution mass spectra were acquired at the Sloan-Kettering Institute Core Facility on a Perkin Elmer Sciex API 100 spectrometer.
**Table S1.** Lewis acid-mediated azaspiroindolenine formation. Under no circumstances was rearrangement of 68 to the core of phalarine (i.e. 69) observed.
Experimental Methods

Methods to prepare intermediates 2, 5, 10, 11, 15, 21–24, 26–31, 33–45, and final product 1 were reported previously and can be found elsewhere.1-3

A degassed solution (30 min, Ar bubbling) of 1-iodo-4-methoxy-2-(methoxymethoxy)benzene4 (500 mg, 1.70 mmol) in anhydrous DMF (4.0 mL) was treated sequentially with anhydrous, distilled Et,N (950 µL, 6.82 mmol, 4.00 equiv.), CuI (62 mg, 0.33 mmol, 0.19 equiv.), Pd(PPh3)4 (210 mg, 0.18 mmol, 0.11 equiv.), and 3-butyne-1-ol (350 µL, 4.62 mmol, 2.71 equiv.). This solution was heated to 60 ºC in an oil bath for 1.5 h. After cooling to room temperature, the reaction was diluted with EtOAc (15 mL) and washed with saturated aqueous NaHCO3 (25 mL). The aqueous layer was back-extracted with EtOAc (15 mL), and the combined organic layers were washed with saturated aqueous NaHCO3 (2 x 25 mL), brine (25 mL), dried over Na2SO4, and concentrated. Flash chromatography (SiO2, 40% EtOAc/hexanes) provided the product as a red-orange oil (306 mg, 402 mg theoretical, 76%): 1H NMR (acetone-d6, 500 MHz) δ 7.26 (d, 1H, J = 8.5 Hz), 6.71 (d, 1H, J = 2.4 Hz), 6.56 (d, 1H, J = 2.4, 8.5 Hz), 5.2 (s, 2H), 3.84 (t, 1H, J = 6.0 Hz), 3.79 (s, 3H), 3.71 (m, 2H), 3.47 (s, 3H), 2.60 (t, 2H, J = 7.0 Hz); 13C NMR (CH3OD, 125 MHz) δ 160.6, 159.0, 133.8, 107.0, 106.0, 102.0, 95.1, 88.8, 79.0, 61.1, 56.3, 55.4, 24.2; IR (neat) νmax 2954, 2936, 2911, 2837, 1606, 1571, 1504, 1465, 1450, 1430, 1397, 1293, 1261, 1239, 1217, 1192, 1152, 1075, 1039, 992, 922 cm−1; LRMS (ESI-TOF) m/z 258.9 ([M + Na]+, C13H16O4 requires 259.1).

An oven-dried microwave vial containing a solution of Pd(OAc)2 (11.8 mg, 0.008 mmol, 0.05 equiv.) and N-tosyl-2-idoaniline (59 mg, 0.158 mmol) in anhydrous, degassed NMP (1.5 mL) was treated with a solution of 56 (45 mg, 0.190 mmol, 1.20 equiv.) in anhydrous, degassed NMP (500 µL) and anhydrous, distilled Et,N (54 µL, 0.387 mmol, 2.50 equiv.). The reaction was heated to 125 ºC in a microwave reactor for 40 min, cooled to room temperature, diluted with EtOAc (20 mL), and washed with saturated aqueous NaHCO3 (20 mL). The aqueous layer was back-extracted with EtOAc (10 mL) and the combined organic layers were washed with saturated aqueous NaHCO3 (2 x 20 mL), dried over Na2SO4, and concentrated. Flash chromatography (SiO2, 30%
EtOAc/PhH) provided the product as a 2:1 mixture of regioisomers (63 mg, 76 mg theoretical, 83% conversion, 56% of desired regioisomer) that were further separated by flash chromatography (35% acetone/hexanes), affording the C2-aryl regioisomer as the major product: $^1$H NMR (acetone-$d_6$, 600 MHz) $\delta$ 8.21 (d, 1H, $J = 8.4$ Hz), 7.62 (d, 1H, $J = 7.8$ Hz), 7.50 (d, 2H, $J = 8.2$ Hz), 7.35 (apparent t, 1H, $J = 7.8$ Hz), 7.27 (m, 3H), 7.14 (d, 1H, $J = 8.4$ Hz), 6.84 (d, 1H, $J = 2.1$ Hz), 6.66 (dd, 1H, $J = 2.1, 8.4$ Hz), 5.17 (d, 1H, $J = 6.9$ Hz), 5.03 (d, 1H, $J = 6.9$ Hz), 3.86 (s, 3H), 3.60 (m, 3H), 3.38 (s, 3H), 2.74 (m, 1H), 2.69 (m, 1H), 2.31 (s, 3H); $^{13}$C NMR (acetone-$d_6$, 150 MHz) $\delta$ 162.8, 158.9, 145.7, 137.6, 137.1, 135.3, 134.1, 131.7, 130.4, 127.7, 125.2, 124.1, 120.9, 120.4, 115.9, 114.3, 106.2, 101.9, 95.5, 62.0, 56.3, 55.8, 29.2, 21.5; IR (neat) $\nu_{\text{max}}$ 3425, 2955, 1619, 1596, 1579, 1502, 1450, 1367, 1300, 1219, 1188, 1175, 1131, 1071, 1046, 997, 922 cm$^{-1}$; LRMS (ESI-TOF) m/z 504.1 ([M + Na]$^+$, C$_{26}$H$_{27}$NO$_6$S requires 504.1).

From the above protocol, the minor C3-aryl regioisomer was isolated: $^1$H NMR (acetone-$d_6$, 600 MHz) $\delta$ 8.17 (d, 1H, $J = 8.4$ Hz), 7.69 (d, 2H, $J = 8.4$ Hz), 7.33 (d, 2H, $J = 8.0$ Hz), 7.29 (apparent t, 1H, $J = 7.8$ Hz), 7.19 (m, 2H), 7.11 (d, 1H, $J = 7.8$ Hz), 6.85 (d, 1H, $J = 2.2$ Hz), 6.71 (dd, 1H, $J = 2.2, 8.4$ Hz), 4.99 (d, 1H, $J = 6.8$ Hz), 4.96 (d, 1H, $J = 6.8$ Hz), 3.84 (m, 5H), 3.71 (t, 1H, $J = 5.8$ Hz), 3.29 (m, 4H), 3.15 (m, 4H), 2.33 (s, 3H); $^{13}$C NMR (acetone-$d_6$, 150 MHz) $\delta$ 161.9, 157.2, 146.0, 137.7, 136.7, 136.6, 133.5, 132.6, 130.8, 129.2, 127.3, 125.1, 124.6, 123.0, 120.7, 116.0, 115.6, 107.6, 103.1, 95.6, 95.1, 82.8, 56.2, 55.8, 32.2, 21.5; IR (neat) $\nu_{\text{max}}$ 3418, 2956, 1702, 1599, 1575, 1506, 1451, 1360, 1296, 1255, 1217, 1188, 1173, 1155, 1126, 1090, 1028, 1002, 922 cm$^{-1}$; LRMS (ESI-TOF) m/z 504.1 ([M + Na]$^+$, C$_{26}$H$_{27}$NO$_6$S requires 504.1).

A solution of 57 (50 mg, 0.103 mmol) in anhydrous CH$_2$Cl$_2$ (1.0 mL) was treated with NaHCO$_3$ (26 mg, 0.309 mmol, 3.00 equiv.) and Dess–Martin periodinane (84 mg, 0.198 mmol, 1.90 equiv.). After 1.5 h, the reaction was diluted with CH$_2$Cl$_2$ (15 mL) and washed with saturated aqueous Na$_2$S$_2$O$_3$/saturated aqueous NaHCO$_3$ (2 x 15 mL, 1:1), dried over Na$_2$SO$_4$, and concentrated. Flash chromatography (SiO$_2$, 40%
EtOAc/hexanes) provided the product as a white foam (38.0 mg, 49.8 mg theoretical, 76%): \(^1\)H NMR (acetone-\(d_6\), 600 MHz) \(\delta\) 9.55 (s, 1H), 8.23 (d, 1H, \(J = 8.4\) Hz), 7.51 (m, 3H), 7.38 (apparent t, 1H, \(J = 7.4\) Hz), 7.29 (m, 3H), 7.10 (d, 1H, \(J = 8.4\) Hz), 6.83 (d, 1H, 2.3 Hz), 6.66 (dd, 1H, \(J = 2.3, 8.4\) Hz), 5.14 (d, 1H, \(J = 6.8\) Hz), 5.02 (d, 1H, \(J = 6.8\) Hz), 3.87 (s, 3H), 3.60 (d, 1H, \(J = 15.2\) Hz), 3.50 (d, 1H, \(J = 15.2\) Hz), 3.36 (s, 3H), 2.33 (s, 3H); \(^13\)C NMR (acetone-\(d_6\), 150 MHz) \(\delta\) 198.8, 163.1, 158.8, 145.9, 137.6, 137.0, 136.7, 134.2, 131.3, 130.5, 127.8, 125.7, 124.5, 120.2, 116.0, 115.5, 113.5, 108.0, 106.5, 103.4, 102.0, 95.7, 56.3, 55.8, 40.3, 21.5; IR (neat) \(\nu_{\text{max}}\) 2933, 2831, 1724, 1616, 1596, 1576, 1574, 1569, 1504, 1450, 1389, 1218, 1188, 1175, 1132, 1083, 1066, 1041, 995, 921 cm\(^{-1}\); LRMS (ESI-TOF) \(m/z\) 502.0 ([M + Na]\(^+\), \(C_{26}H_{25}NO_6S\) requires 502.1).

Iodine (164 mg, 0.646 mmol, 3.00 equiv.), PPh\(_3\) (204 mg, 0.778 mmol, 3.60 equiv.) and imidazole (66 mg, 0.969 mmol, 4.50 equiv.) were vigorously stirred in anhydrous CH\(_2\)Cl\(_2\) (8.0 mL) until the purple color disappeared. At this stage, S-2 was added (103 mg, 0.214 mmol in 1.1 mL of anhydrous CH\(_2\)Cl\(_2\)) and the reaction was stirred at room temperature for 45 min. The reaction mixture was diluted with CH\(_2\)Cl\(_2\) (10 mL) and washed with saturated aqueous Na\(_2\)S\(_2\)O\(_3\) (20 mL), saturated aqueous NaHCO\(_3\) (25 mL), dried over Na\(_2\)SO\(_4\), and concentrated. The crude material was purified by flash chromatography (SiO\(_2\), 15% EtOAc/hexanes) to afford the product as a brilliant white foam (108 mg, 127 mg theoretical, 85%): \(^1\)H NMR (acetone-\(d_6\), 600 MHz) \(\delta\) 8.22 (d, 1H, \(J = 8.4\) Hz), 7.64 (d, 1H, \(J = 7.8\) Hz), 7.49 (d, 2H, \(J = 8.4\) Hz), 7.37 (apparent t, 1H, \(J = 7.4\) Hz), 7.29 (m, 3H), 7.17 (d, 1H, \(J = 8.4\) Hz), 6.84 (d, 1H, 2.2 Hz), 6.68 (dd, 1H, \(J = 2.2, 8.4\) Hz), 5.16 (d, 1H, \(J = 6.8\) Hz), 5.03 (d, 1H, \(J = 6.8\) Hz), 3.88 (s, 3H), 3.39 (s, 3H), 3.27 (m, 2H), 3.12 (m, 1H), 3.03 (m, 1H), 2.33 (s, 3H); \(^13\)C NMR (acetone-\(d_6\), 125 MHz) \(\delta\) 163.0, 158.8, 145.9, 137.6, 137.1, 135.4, 134.1, 130.5, 130.5, 127.7, 125.5, 124.4, 122.9, 120.0, 116.0, 113.7, 106.4, 102.0, 95.6, 56.5, 55.8, 21.5; IR (neat) \(\nu_{\text{max}}\) 2956, 2835, 1735, 1616, 1594, 1574, 1504, 1450, 1369, 1304, 1239, 1218, 1188, 1176, 1131, 1090, 1060, 1034, 999, 922 cm\(^{-1}\); LRMS (ESI-TOF) \(m/z\) 614.3 ([M + Na]\(^+\), \(C_{26}H_{26}INO_5S\) requires 614.0).
A solution of S-2 (108 mg, 0.183 mmol) in CH$_2$NH$_2$ (1.8 mL, 2.0 M in THF) was heated to 50 °C for 18 h. After cooling, the crude reaction mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous NaHCO$_3$ (10 mL). The aqueous layer was back-extracted with EtOAc (2 x 10 mL) and the combined organic layers were washed with saturated aqueous NaHCO$_3$ (2 x 10 mL), dried over Na$_2$SO$_4$, and concentrated. Flash chromatography (SiO$_2$, 10% CH$_3$OH/CHCl$_3$) provided the product as a white foam (74 mg, 90 mg theoretical, 82%): $^1$H NMR (CDCl$_3$, 600 MHz) δ 8.29 (d, 1H, $J$ = 8.4 Hz), 7.56 (d, 1H, $J$ = 7.8 Hz), 7.40 (d, 2H, $J$ = 8.2 Hz), 7.36 (apparent t, 1H, $J$ = 7.6 Hz), 7.28 (apparent t, 1H, $J$ = 7.6 Hz), 7.10 (d, 2H, $J$ = 8.2 Hz), 6.88 (d, 1H, $J$ = 8.3 Hz), 6.85 (d, 1H, $J$ = 2.2 Hz), 6.57 (dd, 1H, $J$ = 2.2, 8.3 Hz), 5.14 (d, 1H, $J$ = 6.8 Hz), 5.03 (d, 1H, $J$ = 6.8 Hz), 3.88 (s, 3H), 3.44 (s, 3H), 2.68 (m, 4H), 2.30 (s, 3H), 2.25 (s, 3H); $^{13}$C NMR (CDCl$_3$, 150 MHz) δ 162.1, 158.6, 144.5, 137.0, 136.5, 134.4, 132.9, 130.5, 129.5, 127.0, 124.8, 123.4, 120.5, 119.2, 115.5, 113.4, 106.0, 101.3, 95.2, 56.4, 55.6, 51.1, 36.0, 24.5, 21.7; IR (neat) $\nu_{max}$ 2934, 2837, 1734, 1616, 1596, 1576, 1504, 1450, 1368, 1300, 1264, 1218, 1188, 1176, 1155, 1132, 1090, 1066, 1043, 999, 922 cm$^{-1}$; LRMS (ESI-TOF) m/z 495.4 ([M + H]$^+$, C$_{27}$H$_{30}$N$_2$O$_5$S requires 495.2).

A solution of 58 (16.0 mg, 0.032 mmol) in CH$_2$Cl$_2$ (600 µL) stirring at −10 °C was treated with 10% TFA/CH$_2$Cl$_2$ (600 µL). After 3 h, the reaction mixture was diluted with CH$_2$Cl$_2$ (5 mL) and quenched by addition of saturated NaHCO$_3$ (5 mL). The aqueous layer was back-extracted with CH$_2$Cl$_2$ (5 mL) and the combined organic phases were washed with saturated aqueous NaHCO$_3$ (10 mL), dried over Na$_2$SO$_4$, and concentrated. Flash chromatography (SiO$_2$, 4-10% MeOH/CHCl$_3$, gradient elution) provided the product as an off-white solid (12 mg, 14.6 mg theoretical, 82%): $^1$H NMR (CDCl$_3$, 500 MHz) δ 8.35 (d, 1H, $J$ = 8.4 Hz), 7.51 (d, 2H, $J$ = 8.4 Hz), 7.39 (m, 2H), 7.29 (apparent t, 1H, $J$ = 7.5 Hz), 7.10 (m, 3H), 6.53 (m, 2H), 3.85 (s, 3H), 3.01 (m, 1H), 2.79 (m, 2H), 2.63 (m, 1H), 2.27 (s, 3H), 2.12 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 161.8, 157.0, 144.4, 137.9, 135.8, 135.4, 135.3, 129.8, 129.3, 127.5, 125.2, 124.1, 120.8, 118.5, 116.9, 110.9, 105.9, 103.4, 55.4, 47.7, 35.8, 24.6, 21.7; IR (neat) $\nu_{max}$ 2921, 2845, 1618, 1596, 1450, 1638, 1175, 1131, 1024, 963 cm$^{-1}$; LRMS (ESI-TOF) m/z 451.1 ([M + H]$^+$, C$_{25}$H$_{26}$N$_2$O$_4$S requires 451.2).
An oven-dried microwave vial containing 4Å MS and CSA (3.3 mg, 0.014 mmol, 1.00 equiv.) was treated with a solution of 60 (6.5 mg, 0.014 mmol) in anhydrous toluene (0.70 mL) and formalin (1.4 µL, 0.017 mmol, 1.20 equiv.). The reaction vessel was sealed, heated to 120 ºC in an oil bath, and allowed to stir for 2 h. After cooling to room temperature, the crude reaction mixture was diluted with EtOAc (5 mL), filtered through celite, and concentrated. Flash chromatography (SiO$_2$, 40% EtOAc/hexanes) provided the product as a white solid (2.6 mg, 6.7 mg theoretical, 39%): $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.73 (d, 1H, $J = 8.4$ Hz), 7.63 (d, 1H, $J = 8.2$ Hz), 7.46 (d, 1H, $J = 7.6$ Hz), 7.39 (apparent t, 1H, $J = 7.4$ Hz), 7.14 (apparent t, 1H, $J = 7.4$ Hz), 7.03 (d, 2H, $J = 8.4$ Hz), 6.93 (d, 2H, $J = 8.4$ Hz), 6.61 (dd, 1H, $J = 2.0$, 8.4 Hz), 6.12 (d, 1H, $J = 2.0$ Hz), 4.23 (d, 1H, $J = 11.2$ Hz), 3.76 (s, 3H), 2.70 (m, 2H), 2.38 (d, 1H, $J = 12.2$ Hz), 2.32 (s, 3H), 2.25 (s, 3H), 2.00 (m, 1H), 1.80 (m, 1H); LRMS (ESI-TOF) $m/z$ 463.3 ([M + H$^+$], C$_{26}$H$_{26}$N$_2$O$_4$S requires 463.2).

A solution of S-2 (15 mg, 0.025 mmol) in anhydrous THF (300 µL) was treated with benzylamine (60 µL, 0.549 mmol, 22.00 equiv.) and heated to 50 ºC for 18 h. After cooling to room temperature, the crude reaction mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous NaHCO$_3$ (10 mL). The aqueous layer was back-extracted with EtOAc (5 mL) and the combined organic layers were washed with saturated aqueous NaHCO$_3$ (2 x 10 mL), dried over Na$_2$SO$_4$, and concentrated. Flash chromatography (SiO$_2$, 100% EtOAc) provided the product (12 mg, 13.4 mg theoretical, 90%): $^1$H NMR (CDCl$_3$, 600 MHz) δ 8.28 (d, 1H, $J = 8.4$ Hz), 7.50 (d, 1H, $J = 7.7$ Hz), 7.39 (d, 2H, $J = 8.4$ Hz), 7.35 (apparent t, 1H, $J = 7.4$ Hz), 7.26 (m, 3H), 7.21 (m, 1H), 7.14 (d, 2H, $J = 7.2$ Hz), 7.07 (d, 2H, $J = 9.0$ Hz), 6.91 (d, 1H, $J = 8.4$ Hz), 6.79 (d, 1H, $J = 2.2$ Hz), 6.56 (dd, 1H, $J = 2.2$, 8.4 Hz), 4.97 (d, 1H, $J = 6.9$ Hz), 4.89 (d, 1H, $J = 6.9$ Hz), 3.88 (s, 3H), 3.62 (m, 2H), 3.38 (s, 3H), 2.74 (m, 3H), 2.67 (m, 1H), 2.31 (s, 3H); $^{13}$C NMR (CDCl$_3$, 150 MHz) δ 162.0, 158.5, 144.4, 140.4, 137.0, 136.4, 134.4, 132.9, 130.6, 129.48, 129.46, 128.5, 128.09, 128.08, 128.03, 127.0, 124.7, 123.4, 120.8, 119.3, 115.6, 113.5, 105.9, 101.2, 94.9, 56.4, 55.6, 53.6, 48.6, 25.1, 21.7; IR (neat) ν$_{max}$ 3409, 2916, 2836, 1619, 1599, 1574, 1498, 1447, 1367, 1197, 1171, 1126 cm$^{-1}$; LRMS (ESI-TOF) $m/z$ 571.3 ([M + H$^+$], C$_{33}$H$_{34}$N$_2$O$_5$S requires 571.2).
A solution of 59 (6.0 mg, 0.011 mmol) in CH₂Cl₂ (300 µL) stirring at −10 °C was treated with 10% TFA/CH₂Cl₂ (300 µL). After 2 h, the reaction was diluted with CH₂Cl₂ (10 mL) and quenched by addition of saturated NaHCO₃ (10 mL). The aqueous layer was back-extracted with CH₂Cl₂ (10 mL) and the combined organic phases were washed with saturated aqueous NaHCO₃ (10 mL), dried over Na₂SO₄, and concentrated. Flash chromatography (SiO₂, 100% EtOAc) provided the product as a yellow solid (5.5 mg, 5.5 mg theoretical, quantitative conversion): ¹H NMR (CDCl₃, 600 MHz) δ 8.31 (d, 1H, J = 8.4 Hz), 7.50 (d, 2H, J = 8.2 Hz), 7.36 (m, 2H), 7.14 (d, 1H, J = 8.5 Hz), 7.07 (m, 2H), 6.89 (d, 2H, J = 8.0 Hz), 6.60 (d, 1H, J = 2.4 Hz), 6.55 (dd, 1H, J = 2.4, 8.5 Hz), 3.87 (s, 3H), 3.50 (apparent q, 2H), 2.99 (m, 1H), 2.79 (m, 2H), 2.65 (m, 1H), 2.18 (s, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 161.8, 156.5, 144.4, 138.3, 138.0, 135.4, 135.3, 135.1, 129.9, 129.3, 128.8, 128.4, 127.6, 127.4, 125.2, 124.1, 121.4, 118.6, 116.8, 111.1, 106.3, 103.4, 55.4, 53.7, 44.9, 25.3, 21.6; IR (neat) ν max 3408, 2922, 2846, 1736, 1621, 1596, 1496, 1451, 1370, 1294, 1232, 1188, 1175, 1130, 1090, 1027, 963 cm⁻¹; LRMS (ESI-TOF) m/z 527.3 ([M + H]+, C₃₁H₂₉N₂O₄S requires 527.2).

An oven-dried microwave vial containing 4Å MS and CSA (2.4 mg, 0.010 mmol, 1.00 equiv.) was treated with a solution of 61 (5.5 mg, 0.010 mmol) in anhydrous toluene (0.50 mL) and formalin (1.0 µL, 0.012 mmol, 1.20 equiv.). The reaction vessel was sealed, heated to 120 °C in an oil bath, and allowed to stir for 2 h. After cooling to room temperature, the crude reaction mixture was diluted with EtOAc (5 mL), filtered through celite, and concentrated. Flash chromatography (SiO₂, 40% EtOAc/hexanes) provided the product as a colorless, crystalline solid (4.5 mg, 5.6 mg theoretical, 80%): ¹H NMR (CDCl₃, 600 MHz) δ 7.64 (d, 1H, J = 7.8 Hz), 7.52 (d, 1H, J = 8.4 Hz), 7.4 (apparent t, 1H, J = 7.2 Hz), 7.32–7.23 (m, 5H), 7.13, (apparent t, 1H, J = 7.2 Hz), 6.99 (d, 2H, J = 7.8 Hz), 6.90 (d, 2H, J = 8.4 Hz), 6.59 (dd, 1H, J = 2.4, 8.4 Hz), 6.12 (d, 1H, J = 2.4 Hz), 4.19 (dd, 1H J = 1.8, 12.0 Hz), 3.79 (s, 3H), 3.61 (d, 1H, J = 13.2 Hz), 3.52 (d, 1H, J = 13.2 Hz), 2.72 (m, 1H), 2.67 (dd, 1H, J = 1.8, 12.0 Hz), 2.45 (d, 1H, J = 12.0 Hz), 2.24 (s, 3H), 2.02 (m, 1H), 1.91 (m, 1H); ¹³C NMR (CDCl₃, 150 MHz) δ 162.4, 161.8, 143.3, 142.9, 138.0, 137.2, 131.4, 129.1, 129.0, 128.7, 128.3, 127.5, 127.2, 126.2, 124.2, 123.5, 117.2, 114.6, 106.7, 96.4, 95.0, 78.6, 61.6, 58.4, 55.5, 48.8, 30.8, 21.3; IR (neat) ν max 2919, 2840, 1734, 1619, 1603, 1496, 1462, 1353, 1294,
An oven-dried microwave vial containing N-trifluoroacetyl-2-iodoaniline (70 mg, 0.233 mmol) in anhydrous, degassed NMP (1.0 mL) was treated with anhydrous, distilled Et$_3$N (120 µL, 0.861 mmol, 3.70 equiv.), compound 56 (78 mg, 0.330 mmol, 1.40 equiv.) in anhydrous, degassed NMP (600 µL), and Pd(OAc)$_2$ (9 mg, 0.040 mmol, 0.17 equiv.) in anhydrous, distilled NMP (600 µL). The reaction mixture was heated to 125 ºC in a microwave reactor for 30 min, cooled to room temperature, diluted with EtOAc (20 mL), and washed with saturated aqueous NaHCO$_3$ (20 mL). The aqueous layer was back-extracted with EtOAc (2 x 10 mL) and the combined organic layers were washed with saturated aqueous NaHCO$_3$ (2 x 20 mL) and saturated aqueous NaCl (20 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. Flash chromatography (SiO$_2$, 25% EtOAc/PhH) provided the product (29 mg, 76 mg theoretical, 38%) as a tan solid: $^1$H NMR (acetone-$d_6$, 600 MHz) δ 9.99 (br s, 1H), 7.60 (d, 1H, $J = 7.8$ Hz), 7.46 (d, 1H, $J = 8.4$ Hz), 7.36 (d, 1H, $J = 8.4$ Hz), 7.08 (apparent t, 1H, $J = 7.8$ Hz), 7.01 (apparent t, 1H, $J = 7.2$ Hz), 6.87 (d, 1H, $J = 2.4$ Hz), 6.72 (dd, 1H, $J = 2.4$, 8.4 Hz), 5.16 (s, 2H), 3.85 (s, 3H), 3.79 (m, 2H), 3.53 (t, 1H, $J = 6.0$ Hz), 3.33 (s, 3H), 2.98 (t, 2H, $J = 7.8$ Hz); $^{13}$C NMR (acetone-$d_6$, 150 MHz) δ 161.8, 157.4, 137.2, 133.5, 133.3, 129.7, 121.9, 119.5, 119.4, 116.7, 111.7, 110.4, 107.5, 103.4, 102.2, 96.1, 63.1, 56.4, 55.8; IR (neat) $\nu_{max}$ 3394, 2938, 1717, 1612, 1576, 1508, 1294, 1217, 1154, 1044, 996, 924 cm$^{-1}$; LRMS (ESI-TOF) m/z 328.2 ([M + H]$^+$, C$_{19}$H$_{21}$NO$_4$ requires 328.2).

The minor C3-aryl regioisomer provided from the above protocol was isolated: $^1$H NMR (acetone-$d_6$, 600 MHz) δ 10.04 (br s, 1H), 7.36 (d, 1H, $J = 8.4$ Hz), 7.27 (d, 1H, $J = 8.4$ Hz), 7.25 (d, 1H, $J = 7.8$ Hz), 7.05 (apparent t, 1H, $J = 8.4$ Hz), 6.94 (apparent t, 1H, $J = 7.2$ Hz), 6.87 (d, 1H, $J = 2.4$ Hz), 6.70 (dd, 1H, $J = 2.4$, 8.4 Hz), 5.03 (s, 2H), 3.90 (t, 1H, $J = 5.4$ Hz), 3.84 (m, 5H), 3.28 (s, 3H), 2.93 (t, 2H, $J = 6.6$ Hz); LRMS (ESI-TOF) m/z 350.2 ([M + Na]$^+$, C$_{19}$H$_{21}$NO$_4$ requires 350.1).
Iodine (61 mg, 0.240 mmol, 2.70 equiv.), PPh₃ (75 mg, 0.286 mmol, 3.20 equiv.), and imidazole (25 mg, 0.367 mmol, 4.10 equiv.) were vigorously stirred in anhydrous CH₂Cl₂ (3.4 mL) until the purple color disappeared. At this stage, 66 was added (29 mg, 0.089 mmol in 1.0 mL of anhydrous CH₂Cl₂) and the reaction was stirred at room temperature for 30 min. After this time, the reaction was diluted with CH₂Cl₂ (10 mL) and washed with a mixture of saturated aqueous Na₂S₂O₃/saturated aqueous NaHCO₃ (10 mL, 1:1). The aqueous layer was back-extracted with CH₂Cl₂ (10 mL), and the combined organic layers were washed with saturated aqueous Na₂S₂O₃ (15 mL) and saturated aqueous NaHCO₃ (15 mL), dried over Na₂SO₄, and concentrated. The crude material was purified by flash chromatography (SiO₂, 30% EtOAc/PhH) to afford the product (32 mg, 39 mg theoretical, 82%): ¹H NMR (acetone-d₆, 600 MHz) δ 10.14 (br s, 1H), 7.60 (d, 1H, J = 7.8 Hz), 7.39 (m, 2H), 7.11 (apparent t, 1H, J = 7.2 Hz), 7.05 (apparent t, 1H, J = 7.2 Hz), 6.90 (d, 1H, J = 8.4 Hz), 6.74 (dd, 1H, J = 2.4, 8.4 Hz), 5.18 (s, 2H), 3.86 (s, 3H), 3.41 (m, 2H), 3.34 (m, 5H); ¹³C NMR (acetone-d₆, 150 MHz) δ 162.1, 157.3, 137.1, 133.4, 133.0, 128.8, 122.3, 119.9, 119.0, 116.2, 113.3, 111.9, 107.7, 103.4, 96.2, 56.5, 55.8, 31.5; IR (neat) νmax 3399, 2955, 2830, 1611, 1576, 1498, 1457, 1293, 1217, 1154, 1128, 1077, 1052, 994, 923 cm⁻¹; LRMS (ESI-TOF) m/z 438.2 ([M + Na]⁺, C₁₉H₂₀INO₃ requires 438.1).

A solution of S-3 (32 mg, 0.073 mmol) in CH₃NH₂ (0.750 mL, 2.0 M in THF) was heated in a sealed microwave vial to 50 °C for 18 h. After cooling to room temperature, the crude mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous NaHCO₃ (10 mL). The aqueous layer was back-extracted with EtOAc (5 mL) and the combined organic layers were washed with saturated aqueous NaHCO₃ (10 mL), dried over Na₂SO₄, and concentrated. Flash chromatography (SiO₂, 5-10% CH₃OH/CHCl₃ gradient elution) provided desired product (22.5 mg, 24.9 mg theoretical, 90%): ¹H NMR (CDCl₃, 500 MHz) δ 8.41 (br s, 1H), 7.66 (d, 1H, J = 7.9 Hz), 7.40 (d, 1H, J = 8.5 Hz), 7.38 (m, 1H), 7.20 (apparent t, 1H, J = 7.1 Hz), 7.13 (apparent t, 1H, J = 7.1 Hz), 6.84 (d, 1H, J = 2.5 Hz), 6.69 (dd, 1H, J = 2.5, 8.5 Hz), 5.14 (s, 2H), 3.86 (s, 3H), 3.37 (s, 3H), 3.11 (t, 2H, J = 7.2 Hz), 2.98 (t, 2H, J = 7.2 Hz), 2.42 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 161.4, 156.1, 135.8, 132.8, 132.0, 128.0, 122.6, 120.1, 118.7, 114.8, 111.0,
108.2, 107.4, 103.7, 96.3, 56.8, 55.8, 49.4, 33.0, 21.8; IR (neat) ν_{\text{max}} 3289, 2924, 1684, 1612, 1576, 1489, 1458, 1396, 1294, 1242, 1217, 1154, 1130, 1077, 991, 921 cm^{-1}; LRMS (ESI-TOF) m/z 341.1 ([M + H]^+), C_{20}H_{24}N_{2}O_{3} requires 341.2.

Compound 72 (7.5 mg, 0.022 mmol) was placed in a flask, cooled to −10 °C, and treated with 4M HCl/dioxane (350 µL). After 2 h, the reaction mixture was diluted with EtOAc (10 mL) and quenched by addition of saturated NaHCO₃ (10 mL). The aqueous layer was back-extracted with EtOAc (10 mL) and the combined organic phases were washed with saturated aqueous NaHCO₃ (10 mL), dried over Na₂SO₄, and concentrated. Flash chromatography (SiO₂, 5-12% CH₃OH/CHCl₃ gradient elution) provided the desired product as a yellow solid (6.0 mg, 6.5 mg theoretical, 92%): ¹H NMR (CDCl₃, 600 MHz) δ 8.12 (br s, 1H), 7.53 (d, 1H, J = 8.4 Hz), 7.36 (d, 1H, J = 7.8 Hz), 7.15 (m, 2H), 7.09 (apparent t, 1H, J = 7.2 Hz), 6.67 (d, 1H, J = 2.4 Hz), 6.51 (dd, 1H, J = 2.4, 8.4 Hz), 3.80 (s, 3H), 3.23 (t, 2H, J = 6.0 Hz), 3.07 (t, 2H, J = 6.0 Hz), 2.38 (s, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 161.7, 136.3, 134.2, 131.8, 127.9, 122.4, 120.0, 118.2, 112.0, 111.4, 107.5, 107.0, 103.0, 55.6, 48.9, 34.2, 22.6; IR (neat) ν_{\text{max}} 2925, 2853, 1679, 1620, 1586, 1460, 1292, 1205, 1164, 1036, 960, 908 cm^{-1}; LRMS (ESI-TOF) m/z 297.2 ([M + H]^+), C_{18}H_{20}N_{2}O_{2} requires 297.2.

An oven-dried microwave vial containing 4Å MS and CSA (2.7 mg, 0.012 mmol, 1.00 equiv.) was treated with a solution of compound 67 (3.5 mg, 0.012 mmol) in anhydrous toluene (0.60 mL) and 37% aqueous formaldehyde (1.2 µL, 0.015 mmol, 1.25 equiv.). The reaction mixture was stirred at room temperature for 2 h. The crude reaction mixture was diluted with EtOAc (10 mL), washed with saturated aqueous NaHCO₃ (2 x 10 mL), dried over Na₂SO₄, and concentrated. The product was recovered as a yellow solid that required no further purification (3.1 mg, 3.6 mg theoretical, 86%): ¹H NMR (CDCl₃, 600 MHz) δ 14.67 (br s, 1H), 8.45 (d, 1H, J = 8.4 Hz), 7.50 (m, 2H), 7.34 (apparent t, 1H, J = 7.2 Hz), 7.23 (apparent t, 1H, J = 7.2 Hz), 6.60 (d, 1H, J = 2.4 Hz), 6.54 (dd, 1H, J = 2.4, 8.4 Hz), 3.86 (s, 3H), 3.40 (d, 1H, J = 10.2 Hz), 3.31 (m, 1H), 2.87 (m, 1H), 2.67 (d, 1H, J = 10.2 Hz), 2.61 (m, 1H), 2.54 (s, 3H), 2.00 (m, 1H); ¹H NMR (DMSO-d₆, 600 MHz) δ 14.40 (s, 1H), 8.51 (d, 1H, J = 9.0 Hz), 7.61 (d, 1H, J = 7.2 Hz), 7.55 (d, 1H, J = 7.8 Hz),
7.37 (apparent t, 1H, \(J = 7.8\) Hz), 7.29 (apparent t, 1H, \(J = 7.8\) Hz), 6.61 (dd, 1H, \(J = 2.4, 9.0\) Hz), 3.82 (s, 3H), 3.29 (m, 2H), 2.85 (m, 1H), 2.61 (d, 1H, \(J = 10.2\) Hz), 2.48 (s, 3H), 2.44 (m, 1H), 1.91 (m, 1H); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz) \(\delta\) 183.8, 165.0, 163.7, 151.0, 146.0, 131.6, 128.1, 125.9, 121.9, 119.1, 108.9, 106.9, 101.9, 65.3, 62.1, 57.5, 55.6, 41.9, 39.1; \(^{13}\)C NMR (DMSO-\(d_6\), 150 MHz) \(\delta\) 183.7, 163.8, 163.3, 149.9, 145.4, 131.3, 128.0, 126.0, 122.0, 118.5, 107.9, 106.6, 101.6, 64.6, 61.4, 59.7, 56.5, 55.4, 41.2, 38.7; IR (neat) \(\nu_{\text{max}}\) 2922, 2846, 2781, 1737, 1627, 1601, 1585, 1506, 1459, 1398, 1364, 1343, 1285, 1257, 1207, 1152, 1128, 1108, 1094, 1037 cm\(^{-1}\); LRMS (ESI-TOF) \(m/z\) 309.2 ([M + H]\(^+\), \(\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2\) requires 309.2).

References