Supporting Information

ONE-POT, DIVERSITY-ORIENTED SYNTHESIS OF ARYL-SUBSTITUTED BENZOXACYCLES INCLUDING BENZOFURAN, COUMARIN, AND BENZOXAZEPINE

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EXPERIMENTAL

General

NMR spectra were recorded on a JEOL Model ECA-500 instrument. Chemical shifts are reported in parts per million (ppm) relative to the signal for the internal standard tetramethylsilane (0.0 ppm) or the solvent $CDCl_3$ (7.26 ppm, ^1H NMR; or 77.1 ppm, ^{13}C NMR) peaks. Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectrum data are reported as follows: chemical shift (δ ppm), and where applicable, multiplicity and coupling constants. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; sp, septet; m, multiplet; br, broad; and J, coupling constants in Hertz. Only the strongest and/or structurally relevant IR peaks are reported (cm^{-1}). All reactions were monitored by thin-layer chromatography performed using 0.2 mm E. Merck silica gel plate (60F-254). The reactants and products were visualized using UV light (254 nm), or by heating after treatment with p-anisaldehyde solution, ceric sulfate solution, or 10% ethanolic phosphomolybdic acid. Column chromatography separations were performed using silica gel (Merck). ESI-TOF Mass spectra were acquired on a Waters LCT PremierTM XE. HRMS (ESI-TOF) were calibrated using a standard curve obtained using leu-enkephalin.

Methyl 4-hydroxymandelate (14)[1]

To a solution of 4-hydroxymandelic acid (3.00 g, 17.9 mmol, 1.00 equiv.) in methanol (35.8 mL) was added conc. H_2SO_4 (286 μL, 5.39 mmol, 0.300 equiv.) at room temperature. After being stirred at the same temperature for 2 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with two portions of ethyl acetate. The combined organic layer was washed with brine, dried

over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was recrystallized from ethyl acetate to give methyl 4-hydroxymandelate (1.64 g, 8.95 mmol, 50%) as a pale white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 8.5 Hz, 2H), 5.82 (s, 1H), 4.96 (s, 1H), 3.59 (s, 3H).

Methyl 4-benzyloxymandelate (15)[2]

To a solution of methyl 4-hydroxymandelate (1.50 g, 8.19 mmol, 1.00 equiv.) in DMF (24.6 mL) was added potassium carbonate (3.40 g, 24.6 mmol, 3.00 equiv.), potassium iodide (680 mg, 4.10 mmol, 0.500 equiv.), and benzyl bromide (1.46 mL, 12.3 mmol, 1.50 equiv.) at room temperature. After being stirred at the same temperature for 15 h, the reaction mixture was poured into 1 M HCl and the aqueous layer was extracted with two portions of diethyl ether. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2:1) to give methyl 4-benzyloxymandelate (2.08 g, 6.54 mmol, 76%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.34-7.32 (m, 4H), 6.97 (d, *J* = 9.0 Hz, 2H), 5.13 (d, *J* = 5.7 Hz, 1H), 5.06 (s, 2H), 3.75 (s, 3H).

Methyl 2-bromo-2-[4-(benzyloxy)phenyl]acetate (2)

To a solution of 4-benzyloxymandelate (1.00 g, 3.67 mmol, 1.00 equiv.) in diethyl ether (4.59 mL) was added phosphorus tribromide (174 μL, 1.84 mmol, 0.500 equiv.) at room temperature. After being stirred at the same temperature for 2 h, the reaction mixture was poured into methanol and the aqueous layer was extracted with two portions of ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 9:1) to give methyl 2-bromo-2-[4-(benzyloxy)phenyl]acetate (879 mg, 2.62 mmol, 71%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.7 Hz, 2H), 7.43-7.38 (m, 4H), 7.34 (t, *J* = 7.2 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 2H), 5.34 (s, 1H), 5.06 (s, 2H), 3.78 (s, 3H).

General procedure for one-pot synthesis of benzofuran analogs

To a solution of 2-aryloyl phenol (1.00 equiv.) and methyl 2-bromocarboxylate (1.00 equiv) in DMF was added K_2CO_3 (3.00 equiv.) at room temperature. After being stirred at the same temperature for 1 h, to the reaction mixture was added NaH (3.00 equiv.) at room temperature. After being stirred at the same temperature, the reaction mixture was poured into 1 M HCl and the aqueous layer was extracted with two portions of diethyl ether. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered,

and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give benzofuran analog.

2-[4-(Benzyloxy)phenyl]-6-methoxy-3-phenylbenzofuran (3)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.9 Hz, 2H), 7.51-7.33 (m, 11H), 7.09 (s, 1H), 6.92 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 1H), 5.07 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 158.7, 155.4, 150.4, 137.3, 133.7, 130.3, 129.5, 128.7, 128.6, 128.1, 128.0, 124.4, 120.5, 116.6, 115.4, 112.3, 96.3, 70.6, 56.4, 30.3; FT-IR 3035, 2937, 2835, 1739, 1608, 1591, 1511, 1492, 1454, 1439, 1417, 1380, 1344, 1300, 1271, 1246, 1195, 1175, 1152, 1492, 1454, 1439, 1417, 1380, 1344, 1300, 1271, 1246, 1195, 1175, 1152, 1130, 1111, 1064, 1026, 967, 943, 832, 770, 744, 701, 633, 586, 534 (cm^{-1}).

Methyl 6-methoxy-3-phenylbenzofuran-2-carboxylate (9)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.9 Hz, 2H), 7.51-7.33 (m, 11H), 7.09 (s, 1H), 6.92 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 1H), 5.07 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 160.3, 155.9, 139.0, 130.7, 130.1, 130.0, 128.5, 128.3, 122.6, 121.6, 114.1, 95.6, 55.8, 52.1.

General procedure for one-pot synthesis of coumarin analogs

To a solution of 2-aryloyl phenol (1.00 equiv.) in trans-decalin (1.00 mL) was added 2,2,6-trimethyl-1,3-dioxin-4-one (10.0 equiv) at room temperature. After being stirred at the reflux temperature for 12 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give coumarin analog.

3-Acetyl-7-methoxy-4-phenylcoumarin (4)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.48 (m, 3H), 7.29-7.26 (m, 2H), 7.10 (d, *J* = 8.7 Hz, 1H), 6.87 (s, 1H), 6.76 (d, *J* = 8.8 Hz), 3.89 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 163.7, 155.5, 152.9, 129.6, 129.5, 128.9, 128.5, 113.1, 113.0, 100.8, 56.0, 31.5; FT-IR 2941, 2844, 1715, 1614, 1550, 1509, 1492, 1463, 1444, 1372, 1295, 1285, 1263, 1204, 1166, 1135, 1117, 1077, 1044, 1025, 996, 964, 839, 776, 753, 703, 655, 622, 566, 540, 482 (cm^{-1}).

3-Butyryl-7-methoxy-4-phenylcoumarin (11)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21-4.17 (m, 1H), 1.92 (d, *J* = 6.8 Hz, 3H), 1.87-1.79 (m, 1H), 1.62-1.44 (m, 3H), 1.41-1.33 (m, 1H), 1.24-1.12 (m, 2H), 0.88 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 43.2, 38.1, 31.0, 29.0, 27.9, 27.6, 22.7, 22.6.

2-Iodo-6-methylheptane (16)

To a solution of 6-methyl-2-heptanol (7.91 mL, 50.0 mmol, 1.00 equiv.) in dichloromethane (150 mL) were added iodine (15.2 g, 60.0 mmol, 1.20 equiv.), PPh_3 (13.1 g, 50.0 mmol, 1.00 equiv.), and 1*H*-imidazole (3.40 mL, 50.0 mmol, 1.00 equiv.) at room temperature. After being stirred at the same temperature for 1 h, the reaction mixture was poured into $Na_2S_2O_3$ and the aqueous layer was extracted with two portions of dichloromethane. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane) to give 2-iodo-6-methylheptane (11.4 g, 53.7 mmol, quant.) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21-4.17 (m, 1H), 1.92 (d, *J* = 6.8 Hz, 3H), 1.87-1.79 (m, 1H), 1.62-1.44 (m, 3H), 1.41-1.33 (m, 1H), 1.24-1.12 (m, 2H), 0.88 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 43.2, 38.1, 31.0, 29.0, 27.9, 27.6, 22.7, 22.6; FT-IR 2954, 2928, 2868, 1466, 1377, 1367, 1277, 1245, 1314, 1172, 1139, 1075, 992, 961, 895, 833, 806, 736, 857, 487 (cm^{-1}).

2-(2-Benzyloxyphenyl)-2-hydroxyacetonitrile (18)[3]

To a solution of 2-(benzyloxy)benzaldehyde (6.34 g, 30.0 mmol, 1.00 equiv.) in dichloroethane (90.0 mL) were added trimethylsilyl cyanide (7.44 mL, 60.0 mmol, 2.00 equiv.), and magnesium bromide ethyl etherate (2.23 g, 9.00 mmol, 0.300 equiv.) at room temperature. After being stirred at the same temperature for 12 h, the reaction mixture was poured into 1 M HCl and the aqueous layer was extracted with two portions of dichloromethane. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 4:1) to give 2-(2-benzyloxyphenyl)-2-hydroxyacetonitrile (7.18 mg, 21.3 mmol, 71%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.0 Hz, 2H), 7.42-7.35 (m, 5H), 7.05-7.02 (m, 2H) 5.57 (d, *J* = 9.0 Hz, 1H), 5.21 (dd, *J* = 3.9 Hz, 2H), 3.47 (d, *J* = 9.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 156.2, 131.3, 129.6, 128.4, 127.8, 124.2, 121.5, 114.3, 112.6, 70.7, 61.3, 55.4; FT-IR 3416, 3065, 1706, 1602, 1490, 1453, 1382, 1288, 1264, 1243, 1191, 1180, 1164, 1114, 1047, 1023, 917, 857, 822, 732, 697, 649, 623, 487, 456 (cm^{-1}).

1-(2-Benzyloxyphenyl)-2,6-dimethylheptan-1-one (19)

To a solution of 2-(2-(benzyloxy)phenyl)-2-hydroxyacetonitrile (3.59 g, 15.0 mmol, 1.00 equiv.) in dichloroethane (90.0 mL) was added pyridinium *p*-toluenesulfonate (377 mg, 60.0 mmol, 2.00 equiv.) and ethyl vinyl ether (2.16 mL, 22.5 mmol, 1.50 equiv.) at 0 °C. After being stirred at the same temperature for 1 h, the reaction mixture was poured into $NaHCO_3$ and the aqueous layer was extracted with two portions

of dichloromethane. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a solution of the residue (2.59 g, 8.33 mmol, 1.00 equiv.) in THF (25.0 mL) was added LHMDS in THF (1.0 M, 25.0 mL, 25.0 mmol, 3.00 equiv.) at 0 °C. After being stirred at the same temperature for 15 min, to the mixture was added 2-iodo-6-methylheptane (3.00 g, 12.5 mmol, 1.50 equiv.) at 0 °C. After being stirred at the same temperature for 3 min, the reaction mixture was poured into NH_4Cl and the aqueous layer was extracted with two portions of ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a solution of the residue (2.59 g, 8.33 mmol, 1.00 equiv.) in MeOH (6.81 mL) was added *p*-toluenesulfonic acid monohydrate (432 mg, 2.27 mmol, 1.00 equiv.) at the room temperature. After being stirred at the same temperature for 5 min, the reaction mixture was poured into 10% NaOH and the aqueous layer was extracted with two portions of diethyl ether. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 9:1) to give 1-(2-benzyloxyphenyl)-2,6-dimethylheptan-1-one (514 mg, 2.27 mmol, 65% in 3 steps) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 7.5 Hz, 1H), 7.33-7.42 (m, 6H), 7.01-6.98 (m, 2H), 5.12 (s, 2H), 1.71-1.64 (m, 1H), 1.46-1.39 (m, 1H), 1.32-0.985 (m, 9H), 0.871 (d, J = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4, 132.5, 130.1, 128.7, 128.3, 127.7, 121.1, 112.7, 70.7, 45.4, 39.1, 33.5, 27.9, 25.1, 22.7, 22.6, 16.5; FT-IR 3067, 3034, 2952, 2931, 2869, 1674, 1596, 1498, 1482, 1447, 1382, 1285, 1234, 1162, 1111, 1080, 1050, 1006, 969, 916, 857, 817, 751, 696, 645, 622, 522, 493 (cm^{-1}).

1-(2-Hydroxyphenyl)-2,6-dimethylheptan-1-one (20)

To a solution of 1-(2-benzyloxyphenyl)-2,6-dimethylheptan-1-one (474 mg, 1.46 mmol, 1.00 equiv.) in THF (4.00 ml) was added 5 wt% Pd/C (311 mg, 0.146 mmol, 0.100 equiv.) at room temperature. After being stirred under an atmosphere of H_2 (balloon pressure) at the same temperature for 3.5 h, the reaction mixture was filtered through a short plug of Celite. The filtrate was collected and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 50:1) to give 1-(2-hydroxyphenyl)-2,6-dimethylheptan-1-one (344 mg, 1.47 mmol, 98%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 6.91 (t, J = 7.8 Hz, 1H), 3.55-3.48 (m, 1H), 1.84-1.77 (m, 1H), 1.56-1.40 (m, 2H), 1.39-1.10 (m, 7H), 0.85 (d, J = 6.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.0, 163.3, 136.3, 129.9, 118.9, 118.8, 118.7, 40.2, 39.0, 34.1, 27.9, 25.3, 22.7, 17.6; FT-IR 2953, 2932, 2869, 1635, 1612, 1582, 1487, 1446, 1383, 1367, 1349, 1289, 1241, 1209, 1161, 1148, 1125, 1099, 1035, 976, 860, 810, 752, 700, 656, 561, 529 (cm^{-1}).

General procedure for one-pot synthesis of benzoxazepine analogs

To a solution of 2-aryloyl phenol (1.00 equiv.) and 2-(*tert*-butoxycarbonylamino)-1-ethanol (1.20 equiv.) in THF (12.0 mL) were added triphenyl phosphine (1.20 equiv.) and DMEAD (1.20 equiv.) at room temperature. After being stirred at the same temperature for 12 h, to the reaction mixture was added TFA at room temperature. After being stirred at 60 °C for 25 h, the reaction mixture was poured into triethylamine and the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give benzoxazepine analog.

8-Methoxy-5-phenyl-2,3-dihydrobenzo[*f*][1,4]oxazepine (8)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.4 Hz, 2H), 7.54 (t, *J* = 6.7 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.08 (d, *J* = 8.6 Hz, 1H), 6.67-6.64 (m, 2H), 4.75 (t, *J* = 4.7 Hz, 2H), 4.00 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 162.5, 158.5, 140.1, 132.5, 130.1, 129.2, 128.2, 119.8, 109.2, 106.3, 78.4, 55.6, 51.5; FT-IR 3056, 3004, 2937, 1895, 1720, 1603, 1574, 1562, 1497, 1444, 1378, 1323, 1284, 1259, 1238, 1194, 1159, 1123, 1110, 1706, 1059, 1030, 1001, 969, 930, 861, 815, 777, 759, 735, 723, 697, 666, 636, 618, 854, 552, 538, 513, 474 (cm^{-1}).

5-(6-Methylheptan-2-yl)-2,3-dihydrobenzo[*f*][1,4]oxazepine (12)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 8.5 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 4.56-4.51 (m, 2H), 3.66-3.54 (m, 2H), 2.91-2.85 (m, 1H), 1.69-1.62 (m, 1H), 1.52-1.06 (m, 9H), 1.52 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 155.1, 131.1, 130.1, 127.4, 123.6, 121.9, 78.5, 49.9, 41.5, 39.1, 35.4, 27.9, 25.0, 22.7, 22.6, 18.6; FT-IR 3067, 2953, 2930, 2869, 1725, 1629, 1600, 1571, 1482, 1458, 1445, 1384, 1367, 1335, 1263, 1232, 1205, 1154, 1111, 1048, 998, 943, 881, 795, 761, 737, 704, 683, 636, 572, 458, 510 (cm^{-1}).

3,4-Dihydro-9-methoxy-6-phenyl-2H-benzo[1,5-b]oxazocine (13)[4]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.0 Hz, 2H), 7.40-7.34 (m, 3H), 6.82 (d, *J* = 9.0 Hz, 1H), 6.49 (d, *J* = 7.0 Hz, 1H), 6.47 (s, 1H), 4.37 (s, 1H), 4.11-4.05 (m, 2H), 3.52 (s, 1H), 3.80 (s, 3H), 2.10 (s, 1H), 1.91 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 161.8, 160.3, 141.6, 133.1, 129.8, 129.1, 128.2, 114.2, 108.0, 103.8, 65.9, 55.4, 49.6, 26.5; FT-IR 2957, 2859, 1720, 1649, 1608, 1577, 1499, 1464, 1445, 1375, 1353, 1317, 1287, 1243, 1226, 1200, 1169, 1125, 1112, 1060, 1039, 1009, 975, 900, 839, 810, 779, 762, 737, 698, 641, 616, 527 (cm^{-1}).

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