A General Method for the Catalytic Nazarov Cyclization of Heteroaromatic Compounds

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Supporting Information

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Supporting Information

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Materials and Methods

Reactions were carried out in oven-dried glassware. Dry solvents were obtained from solvent drying columns. Column chromatography was performed on EM Science silica gel 60 (230-400) mesh. Thin layer chromatography was performed on EMD Chemicals pre-coated, glass backed plates (Silica gel 60 F₂₅₄, 250 μ m thickness) and visualized with p-anis aldehyde/heat, potassium permanganate/heat, or a UV lamp. Chloroform-d was purchased from Cambridge Isotope. ¹H and ¹³C NMR spectroscopy was performed on a Bruker AMX 400 (400MHz /100MHz respectively) spectrometer, a Bruker AVANCE (400MHz /100MHz respectively) spectrometer, or a Bruker AVANCE (500MHz /125MHz respectively) at ambient temperature. IR spectra were collected on a Shimadzu-8400S FT-IR. All reagents were used as received unless otherwise noted. High-resolution mass spectra were collected by professor Alice Bergmann of the State University of New York at Buffalo.

CAUTION! metal perchlorates are potentially explosive and should be handled with care. However, no problems of that nature were encountered in the course of these experiments.

Lithium perchlorate (Aldrich) was powdered with an agate mortar and pestle and may be used as received. Two different lots of lithium perchlorate were compared in order to ensure consistent results. Powdered samples of each lot and samples from both lots that were dried under vacuum (48h, 120°C) were used in cyclization reactions (48h, 120°C). Comparison of the results showed only negligible differences in yield and rate.

Anhydrous scandium perchlorate was prepared by concentration of commercially available (Aldrich) 40% wt. solution (*aq.*) on a rotary evaporator to give a white solid followed by drying under vacuum (24h, 120°C) to give a clear yellow glass which was promptly stored in a glove box.¹

3-pyrrole carboxylic acid was prepared according to known procedures.² Preparation of acid chlorides was performed according to the method of Beccalli,³ and alkylations of aldehydes and acid chlorides were carried out using a modified version of Thomas' procedure where in diisopropyl amine was used instead of 1,1,1,3,3,3-hexamethyldisilazane.⁴ Oxidation of secondary alcohols was achieved with MnO₂ according to the method of Kundu.⁵ Nazarov substrates were prepared *via* TiCl₄ mediated Knoevenagel condensation of their parent β -ketoesters according to literature procedures.⁶

The 2-substituted indole **20** was not synthesized by the same method as the other substrates. An alternative route was employed and can be seen in scheme 1.

Scheme 1. Synthesis of β -ketoester **S-4**

Weinreb amide formation was conducted according to the method of Dodd.⁷ Protection of the indole nitrogen with Boc-anhydride was accomplished using the method of Grieco⁸ and the resulting carbamate **S-2** was used crude for the alkylation with MeLi. In the course of this reaction the Boc group was cleaved to give methyl ketone **S-3** which was condensed with dimethylcarbonate to give β -ketoester **S-4**. Knoevenagel condensation followed using the method referenced above.

Alkylation of Boc-protected Weinreb amide

A solution of the Boc-protected amide **S-2** (5.727g, 19.9 mmol) in 50 mL of dry Et₂O, under Argon was cooled to -78°C in a dry ice/acetone bath. Methyl lithium (1.6M, 46.04 mL, 73.7 mmol) was added dropwise to the solution in three portions (31.04 mL, 10 mL, 5 mL) over the course of an hour. Upon consumption of the starting material by TLC the reaction was allowed to warm to room temperature. The reaction was then slowly quenched by the addition of saturated NH₄Cl aq. (20 mL), and scaled up with 20 mL of EtOAc. The aqueous phase was separated, extracted with 10 mL of EtOAc, and the combined organic phases were washed with distilled water (40 mL) and brine (40 mL). The organic phase was then dried over MgSO₄, filtered, and concentrated. The residue was redissolved in a minimum amount of EtOAc and passed over a plug of silica. The filtrate was concentrated to afford methyl ketone **S-3** which was used without further purification. ¹H NMR (400MHz, CDCl₃) δ 9.27 (broad s, 1.00H), 7.72 (d, J=8.0Hz, 0.96H), 7.44 (d, J=7.6Hz, 1.08H), 7.36 (m, 1.15H), 7.22 (s, 0.97H), 7.17 (t, J=7.6Hz, 1.15H), 2.62 (s, 2.99H)

Condensation of **S-3** with dimethylcarbonate

A flask was charged with NaH (60% dispersion in mineral oil, 0.9604g, 2.4 mmol), and KH (30% dispersion in mineral oil, 3.2200g, 2.4 mmol) and then flushed with Argon. The hydrides were washed (2x 2 mL) with dry hexane and then suspended in 60 mL dry THF. The flask was then cooled to 0°C in a ice bath and a solution of **S-3** (2.9400g, 1.85 mmol) and dimethylcarbonate (5.46 mL, 6.48 mmol) in 8 mL dry THF was added with stirring. The reaction was then warmed to 40°C where it took on a deep red coloration. Upon consumption of the starting ketone (ca. 4 h) the reaction was cooled to room temperature and quenched with 30 mL of water. The reaction was scaled up with 30 mL EtOAc, and after separation, the organic phase was washed with 50 mL brine. The organic phase was dried over MgSO₄, filtered and concentrated. FCC (5:1 Hexane/EtOAc) of the resultant residue yielded β -ketoester **S-4** (2.86 g, 71%). ¹H NMR (500MHz, CDCl₃) δ 9.46 (broad s, 1.00H), 7.72 (d, J=8.0Hz, 1.05H), 7.46 (d, J=8.0Hz, 1.06H), 7.39 (t, J=7Hz, 1.11H), 7.27 (s, 1.19H), 7.18 (t, J=7.5Hz, 1.11H), 4.01 (s, 2.17H), 3.78 (s, 3.13H); ¹³C NMR (125MHz, CDCl₃) δ 184.5, 167.7, 137.9, 134.3, 127.4, 127.0, 123.3, 121.2, 112.4, 111.1, 52.6, 45.3.

Michael addition of o-iodophenol to ethylpropiolate was carried out according to the method of Pfaltz.⁹

(Silica gel 6:1 Hexane/EtOAc, 88%) IR (neat) 3077, 2979, 2904, 1708, 1648, 1630, 1573, 1465, 1439, 1313, 1220, 1123, 1122, 1041, 1020, 947, 833 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 7.79 (dd, $J=8.0$, 1.6Hz, 0.96H), 7.67 (dd, $J=12.0$, 2.0Hz, 0.97H), 7.32 (dt, $J=8.4$, 1.6Hz, 0.98H), 7.03 (dd, $J=8.4$, 1.6Hz, 0.98H), 6.91 (dt, $J=7.6$, 1.2Hz, 0.99H), 5.47 (dd, $J=12.4$, 1.6Hz, 0.95H), 4.16 (q, $J=7.2$ Hz, 2.00H), 1.25 (t, $J=7.2$ Hz, 3.00H); ^{13}C NMR (100MHz, CDCl_3) δ 166.8, 158.7, 155.1, 140.0, 129.9, 126.9, 119.1, 102.7, 87.9, 60.1, 14.3; HRMS m/z calc. for $\text{C}_{11}\text{H}_{11}\text{O}_3\text{I}$ ($\text{M} + \text{Na}^+$) 340.9645, found 340.96399

(Silica gel 6:1 Hexane/EtOAc, 7%) IR (neat) 3062, 2979, 2903, 1717, 1698, 1646, 1574, 1465, 1439, 1259, 1221, 1152, 1079, 1065, 1020, 942, 802, 752 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 7.81 (dd, $J=7.6$, 1.2Hz, 1.03H), 7.30 (dt, $J=7.6$, 0.8Hz, 1.03H), 7.00 (dd, $J=8.4$, 1.6Hz, 1.04H), 6.88 (dt, $J=7.6$, 1.2Hz, 1.05H), 6.71 (d, $J=6.8$ Hz, 1.02H), 5.19 (d, $J=6.8$ Hz, 1.00H), 4.21 (q, $J=6.8$ Hz, 2.09H), 1.30 (t, $J=6.8$ Hz, 3.05H); ^{13}C NMR (100MHz, CDCl_3) δ 164.4, 156.5, 153.1, 139.9, 129.8, 126.4, 117.5, 101.3, 87.3, 60.1, 14.4; HRMS m/z calc. for $\text{C}_{11}\text{H}_{11}\text{O}_3\text{I}$ ($\text{M} + \text{Na}^+$) 340.9645, found 340.96432

Intramolecular Heck reaction of *trans*-25

A flask containing a solution of *trans*-25 (0.1153 g, 0.36 mmol) in 5 mL CH_3CN was flushed with Argon. To this solution $\text{Pd}(\text{OAc})_2$ (0.00813 g, 0.036 mmol) and PPh_3 (0.0189 g, 0.072 mmol) was added, followed by 0.5 mL Et_3N . The flask was warmed to 80°C for 3 h, after which the solvent was removed *via* rotary evaporation. FCC of the resulting residue (7:1 Hexane/EtOAc) yielded benzofuran **26** (0.0575g, 84%). ^1H NMR (400MHz, CDCl_3) δ 8.27 (s, 1.00H), 8.08 (m, 1.03H), 7.54 (m, 1.06H), 7.37 (m, 2.24H), 4.42 (q, $J=7.2$ Hz, 2.15H), 1.44 (t, $J=7.2$ Hz, 3.35H)

6:1 E/Z

(Silica gel 3:1 Hexane/EtOAc, 63%) IR (neat) 3272 (broad), 2961, 2928, 2902, 2868, 1717, 1615, 1544, 1432, 1404, 1328, 1291, 1241, 1158, 1111, 1037, 1008, 888, 749 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 10.45 (broad s, 0.87H), 10.29 (broad s, 0.22H), 7.10 (m, 1.00H), 6.91 (d, $J=10.8$ Hz, 0.85H), 6.76 (m, 0.99H), 6.52 (d, $J=10.4$ Hz, 0.15H), 6.26 (m, 0.99H), 3.90 (s, 0.48H), 3.77 (s, 2.70H), 3.20 (m,

0.14H), 2.50 (m, 0.89H), 1.16 (d, $J=6.8\text{Hz}$, 0.89H), 1.01 (d, $J=6.8\text{Hz}$, 5.57H); ^{13}C NMR (100MHz, CDCl_3) δ 182.9, 181.8, 166.1, 165.4, 155.6, 153.8, 132.26, 131.4, 131.06, 130.6, 126.8, 126.3, 119.8, 119.0, 111.1, 110.9, 52.2, 51.9, 29.2, 28.9, 22.1, 21.9; HRMS m/z calc. for $\text{C}_{12}\text{H}_{15}\text{O}_3\text{N}$ ($\text{M} + \text{Na}^+$) 244.09496, found 244.09459

(Silica gel 3:1 Hexane/EtOAc, 68%) IR (neat) 3182 (broad), 2956, 2930, 2873, 1733, 1665, 1452, 1434, 1387, 1368, 1318, 1203, 1156, 1084, 912, 871, 839 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 11.11 (broad s, 1.00H), 7.34 (t, $J=2.4\text{Hz}$, 1.02H), 6.18 (t, $J=2.0\text{Hz}$, 1.02H), 3.76 (s, 3.11H), 3.63 (d, $J=2.8\text{Hz}$, 1.03H), 3.37 (dd, $J=6.4, 2.8\text{Hz}$, 1.02H), 1.97 (m, 1.04H), 0.97 (m, 6.35H); ^{13}C NMR (100MHz, CDCl_3) δ 184.9, 170.8, 155.8, 134.2, 132.7, 106.7, 62.5, 52.5, 45.9, 31.7, 20.1, 19.5; HRMS m/z calc. for $\text{C}_{12}\text{H}_{15}\text{O}_3\text{N}$ ($\text{M} + \text{Na}^+$) 244.09549, found 244.09459

(Silica gel 6:1 Hexane/EtOAc, 85%) IR (NaCl plate) 3434, 2962, 2933, 2872, 1722, 1668, 1560, 1508, 1245, 1153, 1022, 871, 602 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 7.88 (s, 0.91H), 7.46 (s, 1.03H), 6.89 (d, $J=8.8\text{ Hz}$, 0.86H), 6.82 (s, 0.78H), 6.78 (s, 0.15H), 6.50 (d, $J=8.0\text{ Hz}$, 0.14H), 3.79 (s, 0.60H), 3.74 (s, 2.52H), 3.11 (m, 0.15H), 2.48 (m, 0.82H), 1.12 (d, $J=5.2\text{Hz}$, 1.47H), 1.03 (d, $J=5.2\text{Hz}$, 5.76H); ^{13}C NMR (100MHz, CDCl_3 , E isomer) δ 187.8, 165.0, 153.9, 149.2, 144.7, 131.7, 128.4, 108.6, 52.3, 29.1, 21.9; HRMS m/z calc. for $\text{C}_{12}\text{H}_{14}\text{O}_4$ ($\text{M} + \text{Na}^+$) 245.0784, found 245.0785

(Silica gel 6:1 Hexane/EtOAc, 54%) IR (NaCl plate) 3148, 3124, 2961, 2935, 2876, 1740, 1713, 1589, 1437, 1325, 1254, 1159, 1117, 989, 899, 754 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 7.53 (d, $J=1.9\text{Hz}$, 1.00H), 6.50 (d, $J=2.0\text{Hz}$, 1.02H), 3.79 (s, 3.60H), 3.71 (d, $J=2.6\text{Hz}$, 1.22H), 3.53 (dd, $J=6.28, 2.56\text{Hz}$, 1.05H), 2.06 (m, 1.20H), 1.00 (m, 6.80H); ^{13}C NMR (100MHz, CDCl_3) δ 187.7, 184.3, 169.3, 150.1, 127.0, 105.2, 63.3, 52.8, 46.6, 30.5, 20.0, 19.6; HRMS m/z calc. for $\text{C}_{12}\text{H}_{14}\text{O}_4$ ($\text{M} + \text{Na}^+$) 245.0784, found 245.0784.

4.7:1 E/Z

(Silica gel 2:1 Hexane/EtOAc, 71%) IR (neat) 3273 (broad), 2958, 2934, 2873, 1715, 1611, 1543, 1432, 1402, 1270, 1248, 1224, 1109, 1074, 1036, 751 cm^{-1} ; ^1H NMR (500MHz, CDCl_3) δ 10.42 (broad s, 1H), 7.13 (m, 1.81H), 6.74 (m, 1.12H), 6.26 (m, 0.99H), 3.77 (s, 0.53H), 3.72 (2.55H), 2.55 (q, $J=7.5$ Hz, 0.34H), 2.13 (q, $J=7.5$ Hz, 1.78H), 1.55 (m, 0.35H), 1.46 (m, 1.66H), 0.99 (t, $J=5.0$ Hz, 0.59H), 0.88(t, $J=7.5$ Hz, 2.52H); ^{13}C NMR (125MHz, CDCl_3) δ 183.0, 181.8, 166.1, 165.3, 149.8, 148.1, 133.8, 133.0, 132.2, 131.1, 126.8, 126.4, 119.8, 119.0, 111.2, 111.0, 52.2, 51.1, 31.7, 31.5, 22.0, 21.8, 13.8, 13.7; HRMS m/z calc. for $\text{C}_{12}\text{H}_{15}\text{O}_3\text{N}$ ($\text{M} + \text{Na}^+$) 224.0944, found 224.09511

5.5:1 E/Z

(Silica gel 6:1 Hexane/EtOAc, 59%) IR (NaCl plate) 3134, 2960, 2935, 2873, 1724, 1666, 1560, 1510, 1437, 1286, 1251, 1227, 1157, 1074, 1018, 945, 872, 845, 748, 599 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 7.84 (s, 0.92H), 7.41 (m, 0.91H), 7.05 (t, $J=8.0$ Hz, 0.76H), 6.75 (d, $J=1.8$ Hz, 0.70H), 6.71 (m, 0.34H), 3.73 (s, 0.45H), 3.66 (s, 2.51H), 2.46 (q, $J=7.4$ Hz, 0.31H), 2.07 (q, $J=7.7$ Hz, 1.69H), 1.42 (m, 2.0H), 0.93 (t, $J=7.4$ Hz, 0.57H), 0.84 (t, $J=7.3$ Hz, 2.56H); ^{13}C NMR (100MHz, CDCl_3) δ 187.7, 185.8, 165.5, 164.6, 149.8, 149.2, 147.9, 144.5, 144.0, 135.5, 133.9, 128.0, 126.8, 109.3, 108.4, 52.0, 51.8, 31.4, 31.3, 21.8, 21.6, 13.6, 13.5; HRMS m/z calc. for $\text{C}_{12}\text{H}_{15}\text{O}_4$ ($\text{M} + \text{H}^+$) 223.0965, found 223.0959

10:1 E/Z

(Silica gel 3:1 Hexane/EtOAc, 96%) IR (NaCl plate) 3323 (broad), 3134, 2961, 2934, 2872, 1717, 1636, 1541, 1506, 1435, 1273, 1250, 1227, 1150, 1096, 1057, 791, 735, 604 cm^{-1} ; ^1H NMR (500MHz, CDCl_3) δ 8.72 (broad s, 1.00H), 7.33 (m, 0.96H), 7.07 (t, $J=8.0$ Hz, 0.91H), 6.81 (m, 1.005H), 6.65 (m, 1.05H), 3.76 (s, 0.27H), 3.73 (s, 2.92H), 2.53 (q, $J=7.5$ Hz, 0.16H), 2.13 (q, $J=7.5$ Hz, 1.84H), 1.56 (m, 0.46H), 1.46 (m, 2.02H), 0.98 (t, $J=7.5$ Hz, 0.39H), 0.89 (t, $J=7.5$ Hz, 3.15H); ^{13}C NMR (125MHz, CDCl_3) δ 189.0, 187.6, 166.4, 165.5, 148.6, 146.8, 136.0, 134.6, 126.2, 125.2, 125.0, 124.8, 120.0, 119.6, 109.9, 109.2, 52.1, 51.9, 31.5, 31.4, 22.1, 21.9, 13.9, 13.8; HRMS m/z calc. for $\text{C}_{12}\text{H}_{16}\text{O}_3\text{N}$ ($\text{M} + \text{H}^+$) 222.1125, found 222.11343

(Silica gel 5:1 Hexane/EtOAc, 5%) IR (neat) 3103, 2959, 2933, 2872, 1723, 1664, 1510, 1435, 1413, 1285, 1242, 1228, 1185, 1175, 1067, 851, 824, 779 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 7.96 (dd, $J=2.8, 1.2$ Hz 0.95H), 7.53 (dd, $J=5.2, 1.2$ Hz, 0.97H), 7.33 (dd, $J=5.2, 3.2$ Hz, 0.97H), 7.13 (t, $J=8.0$ Hz, 1.00H), 3.71 (s, 3.09H), 2.09 (q, $J=7.6$ Hz, 2.04H), 1.46 (m, 2.08H), 0.87 (t, $J=7.6$ Hz, 3.24H); ^{13}C NMR (100MHz, CDCl_3) δ 188.6, 165.6, 148.7, 143.0, 135.2, 134.7, 127.64, 127.55, 52.9, 32.2, 22.5, 14.4; HRMS m/z calc. for $\text{C}_{12}\text{H}_{14}\text{O}_3\text{S}$ ($\text{M} + \text{Na}^+$) 261.0556, found 261.05582

(Silica gel 3:1 Hexane/EtOAc, 99%) IR (neat) 3262 (broad), 2957, 2931, 1712, 1698, 1604, 1580, 1426, 1244, 1258, 1167, 1125, 1059, 906 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 8.46 (d, $J=7.6$ Hz, 1H), 7.74 (d, $J=3.2$ Hz, 1H), 7.49 (m, 1H), 7.34 (m, 2H), 7.18 (t, $J=7.6$ Hz, 1H), 3.74 (s, 3H), 2.19 (q, $J=7.2$ Hz, 2H), 1.48 (m, 2H), 0.89 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 189.7, 166.4, 147.7, 137.7, 135.7, 135.3, 125.9, 124.7, 123.7, 122.7, 118.8, 112.7, 52.9, 32.4, 22.5, 14.4; HRMS m/z calc. for $\text{C}_{16}\text{H}_{17}\text{O}_3\text{N}$ ($\text{M} + \text{Na}^+$) 294.1101, found 294.11066

5:1 E/Z

(Silica gel 5:1 Hexane/EtOAc, 40%) IR (neat) 3131, 3071, 2960, 2934, 2873, 1722, 1658, 1550, 1479, 1449, 1435, 1284, 1249, 1225, 1125, 1095, 1059, 751 cm^{-1} ; ^1H NMR (500MHz, CDCl_3) δ 8.28 (m, 0.79H), 8.18 (m, 0.16H), 8.08 (s, 0.87H), 7.54 (m, 0.94H), 7.39 (m, 1.98H), 7.20 (t, $J=8.0$ Hz, 0.83H), 6.74 (t, $J=8.0$ Hz, 0.16H), 3.78 (s, 0.52H), 3.73 (s, 2.50H), 2.59 (q, $J=7.5$ Hz, 0.32H), 2.17 (q, $J=7.5$ Hz, 1.68H), 1.57 (m, 0.45H), 1.49 (m, 1.81H), 1.01 (t, $J=7.5$ Hz, 0.56H), 0.90 (t, $J=7.5$ Hz, 2.76H); ^{13}C NMR (125MHz, CDCl_3) δ 188.4, 186.9, 165.7, 164.9, 156.0, 155.7, 153.3, 151.7, 150.2, 148.3, 135.6, 134.1, 126.0, 125.9, 124.8, 124.6, 123.9, 123.0, 122.83, 122.79, 121.7, 111.6, 111.5, 52.3, 52.0, 31.6, 22.0, 21.8, 13.9, 13.7; HRMS m/z calc. for $\text{C}_{16}\text{H}_{16}\text{O}_4$ ($\text{M} + \text{Na}^+$) 295.0941, found 295.09406

(Silica gel 6:1 Hexane/EtOAc, 43%) IR (NaCl plate) 3132, 2961, 2935, 2873, 1728, 1661, 1566, 1464, 1435, 1394, 1285, 1252, 1227, 1165, 1080, 1020, 974, 883, 770, 594 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 7.65 (d, $J=0.8$ Hz, 1.00H), 7.16 (m, (2.05H), 6.57 (dd, $J=3.6, 1.6$ Hz, 1.15H), 3.74 (s, 3.39H), 2.16 (q, $J=7.6$ Hz, 2.22H), 1.49 (m, 2.28H), 0.90 (t, $J=7.2$ Hz, 3.34H); ^{13}C NMR (100MHz, CDCl_3) δ 182.1, 165.5, 153.4, 150.3, 148.2, 133.3, 120.4, 113.2, 52.9, 32.2, 22.4, 14.4; HRMS m/z calc. for $\text{C}_{12}\text{H}_{14}\text{O}_4$ ($\text{M} + \text{H}^+$) 223.0965, found 223.09601

(Silica gel 6:1 Hexane/EtOAc, 65%) IR (NaCl plate) 3101, 2961, 2934, 2872, 1726, 1651, 1516, 1435, 1412, 1356, 1285, 1244, 1148, 1067, 1041, 841, 729 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 7.71 (dd, $J=5.2, 1.2$ Hz, 0.87H), 7.56 (dd, $J=3.6, 0.8$ Hz, 0.90H), 7.12 (m, 1.91H), 3.70 (s, 2.89H), 2.11 (q, $J=7.6$ Hz, 2.00H), 1.46 (m, 1.98H), 0.87 (t, $J=7.2$ Hz, 3.04H); ^{13}C NMR (125MHz, CDCl_3) δ 186.4, 164.7, 148.5, 144.1, 135.2, 134.3, 133.3, 128.4, 52.2, 31.6, 21.7, 13.7; HRMS m/z calc. for $\text{C}_{12}\text{H}_{14}\text{O}_3\text{S}$ ($\text{M} + \text{Na}^+$) 261.0556, found 261.05566

3:1 E/Z

(Silica gel 5:1 Hexane/EtOAc, 66%) IR (neat) 3314 (broad), 2957, 2933, 2872, 1714, 1630, 1618, 1520, 1435, 1418, 1340, 1246, 1225, 1172, 1152, 1021, 907 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 10.19 (broad s, 1H), 7.72 (m, 1.04H), 7.52 (m, 1.06H), 7.36 (m, 0.95H), 7.31 (t, $J=8.0$ Hz, 0.89H), 7.16 (t, $J=7.6$ Hz, 1.02H), 7.12 (m, 0.99H), 6.93 (t, $J=7.6$ Hz, 0.24H), 3.84 (s, 0.73H), 3.76 (s, 2.31H), 2.67 (q, $J=7.6$ Hz, 0.52H), 2.21 (q, $J=7.6$ Hz, 1.55H), 1.64 (m, 0.52H), 1.50 (m, 1.57H), 1.06 (t, $J=7.2$ Hz, 0.77H), 0.91 (t, $J=7.2$ Hz, 2.47H); ^{13}C NMR (100MHz, CDCl_3) δ 186.1, 184.5, 165.9, 165.2, 151.1, 149.0, 138.5, 138.3, 135.4, 134.4, 133.8, 132.8, 127.4, 126.9, 126.7, 123.3, 123.1, 121.1, 113.0, 112.7, 112.6, 112.0, 52.3, 52.1, 31.7, 31.6, 22.0, 21.8, 13.9, 13.7; HRMS m/z calc. for $\text{C}_{16}\text{H}_{17}\text{O}_3\text{N}$ ($\text{M} + \text{Na}^+$) 294.1101, found 294.10995

(Silica gel 6:1 Hexane/EtOAc, 60%) IR (neat) 3064, 2962, 2935, 2873, 2841, 1713, 1650, 1612, 1597, 1556, 1531, 1448, 1435, 1371, 1271, 1257, 1242, 1229, 1174, 1090, 1047, 885, 766, 752 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 7.68 (d, $J=8.0$ Hz, 1H), 7.55 (d, $J=8.4$ Hz, 1H), 7.45 (m, 2H), 7.29 (t, $J=8.0$ Hz, 1H), 7.22 (t, $J=8.0$ Hz, 1H), 3.70 (s, 3H), 2.16 (q, $J=7.6$ Hz, 2H), 1.47 (m, 2H), 0.86 (t, $J=7.6$ Hz, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 183.3, 164.5, 156.0, 152.3, 150.0, 132.3, 128.7, 126.8, 123.9, 123.4, 115.5, 112.5, 52.2, 31.5, 21.6, 13.6; HRMS m/z calc. for $\text{C}_{16}\text{H}_{16}\text{O}_4$ ($\text{M} + \text{Na}^+$) 295.0946, found 295.0935

General procedure for the Nazarov Cyclization

In a glove box under nitrogen $\text{Sc}(\text{OTf})_3$ (0.028 g, 0.056 mmol) and powdered LiClO_4 were added to a flask containing the substrate, **7** (0.25 g, 1.13 mmol) and a magnetic stir-bar. The flask was sealed and removed from the glove box whereupon the mixture was diluted (0.3 M w/r/t substrate) with dry dichloroethane. The reaction was warmed to 80°C in an oil bath. Upon consumption of the starting material the crude reaction mixture was concentrated onto silica gel and subjected to flash column chromatography to afford Nazarov product **8** (0.19 g, 75%).

(Silica gel 6:1 Hexane/EtOAc, 75%) IR (NaCl plate) 3148, 3124, 2959, 2934, 2874, 1742, 1715, 1591, 1437, 1261, 1227, 1198, 1159, 1122, 970, 899, 752 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 7.49 (d, $J=2.0$ Hz, 1.00H), 6.46 (d, $J=2.0$ Hz, 0.96H), 3.76 (s, 3.15H), 3.60 (m, 2.04H), 1.76 (m, 1.10H), 1.63 (m, 1.23H), 1.49 (m, 2.17H), 0.93 (t, $J=7.3$ Hz, 3.26H); ^{13}C NMR (100MHz, CDCl_3) δ 187.4, 185.0, 169.0, 150.0, 126.0, 105.2, 65.7, 52.6, 39.6, 34.5, 20.4, 13.7; HRMS m/z calc. for $\text{C}_{12}\text{H}_{14}\text{O}_4$ ($\text{M} + \text{H}^+$) 223.0965, found 223.09644

(Silica gel 1.5:1 Hexane/EtOAc, 68%) IR (NaCl plate) 3258 (broad), 3111, 2957, 2930, 2872, 1736, 1670, 1497, 1464, 1439, 1340, 1271, 1247, 1159, 1068, 976, 921, 744, 690 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 10.50 (broad s, 1H), 6.87 (m, 1.00H), 6.16 (m, 0.98H), 3.70 (s, 3.10H), 3.58 (m, 2.04H), 1.80 (m, 1.02H), 5.56 (m, 1.11H), 3.65 (m, 2.16H), 0.88 (t, $J=7.6$ Hz, 3.28H); ^{13}C NMR (100MHz, CDCl_3) δ 190.0, 170.4, 162.7, 126.9, 124.6, 102.5, 65.3, 52.4, 38.8, 35.7, 20.5, 13.7; HRMS m/z calc. for $\text{C}_{12}\text{H}_{15}\text{O}_3\text{N}$ ($\text{M} + \text{H}^+$) 222.1125, found 222.11302

(Silica gel 6:1 Hexane/EtOAc, 76%) IR (neat) 3085, 2956, 2929, 2873, 2862, 1737, 1701, 1516, 1463, 1434, 1397, 1334, 1240, 1226, 1201, 1155, 1004, 943 cm^{-1} ; ^1H NMR (500MHz, CDCl_3) δ 7.32 (d, $J=5.0$ Hz, 1.00H), 7.12 (d, $J=5.0$ Hz, 0.99H), 3.84 (m, 1.02H), 3.79 (s, 3.10H), 3.62 (d, $J=3.5$ Hz, 1.05H), 1.75 (m, 2.32H), 1.50 (m, 2.34H), 0.98 (t, $J=7.0$ Hz, 3.32H); ^{13}C NMR (125MHz, CDCl_3) δ 190.9, 174.7, 169.9, 144.2, 132.0, 120.3, 65.7, 53.4, 42.7, 38.5, 21.4, 14.5; HRMS m/z calc. for $\text{C}_{12}\text{H}_{14}\text{O}_3\text{S}$ ($\text{M} + \text{Na}^+$) 261.0556, found 261.05524

(Silica gel 3:1 Hexane/EtOAc, 80%) IR (NaCl plate) 3218 (broad), 2955, 2930, 2872, 1732, 1657, 1619, 1504, 1467, 1450, 1434, 1243, 1228, 1154, 909 cm^{-1} ; ^1H NMR (500MHz, CDCl_3) δ 9.43 (broad s, 1.04H), 7.86 (d, $J=7.5$ Hz, 1.00H), 7.40 (d, $J=8.0$ Hz, 1.05H), 7.25 (m, 2.56H), 3.83 (m, 1.02H), 3.78 (s, 3.05H), 3.70 (d, $J=3.0$ Hz, 1.10H), 1.89 (m, 1.08H), 1.70 (m, 1.49H), 1.49 (m, 2.18H), 0.97 (t, $J=7.0$ Hz, 3.29H); ^{13}C NMR (125MHz, CDCl_3) δ 188.9, 170.7, 170.6, 142.9, 124.3, 122.7, 121.3, 120.7, 118.6, 113.0, 64.9, 52.7, 39.5, 35.6, 29.7, 20.7, 13.9; HRMS m/z calc. for $\text{C}_{16}\text{H}_{17}\text{O}_3\text{N}$ ($\text{M} + \text{Na}^+$) 294.1101, found 294.10999

(Silica gel 6:1 Hexane/EtOAc, 66%) IR (neat) 2957, 2933, 2874, 1739, 1708, 1585, 1480, 1446, 1435, 1405, 1378, 1259, 1223, 1149, 1072, 976, 926 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 7.80 (m, 1.00H), 7.53 (m, 1.05H), 7.35 (m, 2.23H), 3.84 (m, 4.02H), 3.73 (d, $J=2.4$ Hz, 1.12H), 1.92 (m, 1.07H), 1.73 (m, 1.23H), 1.59 (m, 2.36H), 1.00 (t, $J=7.6$ Hz, 3.32H); ^{13}C NMR (100MHz, CDCl_3) δ 188.7, 187.2, 169.2, 161.4, 125.8, 124.9, 122.3, 121.6, 121.1, 112.4, 65.1, 52.9, 40.1, 34.5, 20.6, 13.9; HRMS m/z calc. for $\text{C}_{16}\text{H}_{16}\text{O}_4$ ($\text{M} + \text{Na}^+$) 294.0941, found 295.09402

(Silica gel 2:1 Hexane/EtOAc, 95%) IR (neat) 3196 (broad), 2955, 2929, 1735, 1664, 1452, 1434, 1404, 1381, 1256, 1227, 1194, 1156, 976, 915, 762 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 11.06 (broad s, 0.97H), 7.32 (m, 0.99H), 6.17 (s, 1.00H), 3.76 (s, 3.09H), 3.55 (d, $J=2.4$ Hz, 0.99H), 3.46 (m, 1.03H), 1.66 (m, 2.04H), 1.47 (m, 2.07H), 0.95 (t, $J=7.2$ Hz, 3.08H); ^{13}C NMR (100MHz, CDCl_3) δ 184.7, 170.6, 170.3, 157.4, 157.1, 134.3, 132.1, 105.9, 65.2, 52.5, 39.0, 37.5, 20.8, 14.0; HRMS m/z calc. for $\text{C}_{12}\text{H}_{15}\text{O}_3\text{N}$ ($\text{M} + \text{Na}^+$) 244.0944, found 244.09468

(Silica gel 6:1 Hexane/EtOAc, 36%) IR (NaCl plate) 3097, 2957, 2930, 2872, 1740, 1703, 1427, 1335, 1315, 1261, 1227, 1202, 1157, 970, 951, 743 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 7.94 (d, $J=4.8$ Hz, 1.00H), 7.08 (d, $J=4.8$ Hz, 1.09H), 3.80 (s, 3.15H), 3.66 (m, 2.06H), 1.83 (m, 1.16H), 1.60 (m, 2.52H), 1.45 (m, 2.37H), 0.98 (t, $J=7.3$ Hz, 3.37H); ^{13}C NMR (100MHz, CDCl_3) δ 189.3, 171.7, 169.4, 141.6, 138.7, 123.2, 64.4, 52.6, 41.4, 36.8, 20.6, 13.8; HRMS m/z calc. for $\text{C}_{12}\text{H}_{14}\text{O}_3\text{S}$ ($\text{M} + \text{Na}^+$) 261.0556, found 261.05624

(Silica gel 4:1 Hexane/EtOAc, 66%) IR (neat) 3250 (broad), 3076, 3003, 2957, 2930, 2872, 1738, 1670, 1620, 1570, 1541, 1481, 1435, 1373, 1323, 1248, 1232, 1153, 1103, 993 cm^{-1} ; ^1H NMR (500MHz, CDCl_3) δ 10.34 (s, 1.00H), 7.71 (d, $J=8.0$ Hz, 1.04H), 7.53 (d, $J=8.5$ Hz, 1.05H), 7.38 (t, $J=7.5$ Hz, 1.05H), 7.17 (t, $J=7.5$ Hz, 1.04H), 3.85 (m, 1.00H), 3.82 (s, 3.00H), 3.74 (d, $J=2.0$ Hz, 1.05H), 2.07 (m, 1.13H), 1.71 (m, 1.06H), 1.53 (m, 2.14H), 1.04 (t, $J=7.5$ Hz, 3.20H); ^{13}C NMR (125MHz, CDCl_3) δ 187.9, 170.5, 150.4, 144.9, 136.6, 127.9, 122.8, 122.1, 120.8, 114.2, 64.5, 52.7, 39.5, 37.2, 20.9, 14.1; HRMS m/z calc. for $\text{C}_{16}\text{H}_{17}\text{O}_3\text{N}$ ($\text{M} + \text{Na}^+$) 294.1101, found 294.11041

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3.620

JAM-D-150Etrans
02-01-06

JAM-D-150 trans
02-01-06

JAM-D-150cis
02-01-06

13.14

Standard Protoc
h1
SK Sur, D

sters

JAM-D-125
01-18-06

195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 ppm

DMF-d₂
01-18-06

183.013
181.787

166.076
165.287

149.778
148.122

133.765
132.962
132.167
131.080
126.838
126.370

119.828
118.963

111.167
110.954

77.346
77.091
76.837

52.189
51.920

31.660
31.538

22.035
21.805

13.847
13.728

JAM-D-130
01-19-06

ppm

JAM-B-129a
01-04-05

JAM-D-114
01-04-06

195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 ppm

JAN-D-114
01-04-06

- 190.941
- 174.686
- 169.855
- 144.204
- 131.961
- 120.307
- 77.975
- 77.721
- 77.467
- 65.699
- 53.417
- 42.666
- 38.464
- 21.429
- 14.509

JAM-C-002
03-01-04
protector

JAM-D-168
03-03-06

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190
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170
160
150
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130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

- 188.614
- 165.599
- 148.700
- 142.995
- 135.235
- 134.744
- 127.640
- 127.554
- 78.072
- 77.754
- 77.436
- 52.916
- 32.220
- 22.451
- 14.424

ppm