Supplementary Information for

Concise Total Synthesis of Naamine G and Naamidine H

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1. Experimental procedures and characterization data for 9, 6, 12-14, 16-17, 5, 20, 2-3 – S2-S9.

2. Copies of $^1$H and $^{13}$C NMR spectra for 9, 6, 12,14, 16, 17, 5, 20, 2-3 – S10-S29.
(4-Benzylxoy-3,5-dimethoxyphenyl)-(5-iodo-2-methyl-2H-imidazol-1-yl)-methanol (9): 

EtMgBr (3.0 M solution in ether, 7.54 ml, 22.6 mmol) was added to a solution of 4,5-diiodo-1-methyl-1H-imidazole (7.19 g, 21.5 mmol) in dry CH$_2$Cl$_2$ (100 ml) at rt over ~10 min. The resulting mixture was stirred at rt for 20 min and 4-benzoyloxy-4,5-dimethylbenzaldehyde$^1$ (6.46 g, 23.7 mmol) was added and stirred at rt for 48 h. Sat. NH$_4$Cl (10 ml) was added to the reaction and the resulting pale yellow solid was filtered and the filtrate was partitioned with CH$_2$Cl$_2$. The organic layer was dried (Na$_2$SO$_4$) and concentrated to give a pale yellow solid. The resulting solid was triturated with hexanes, recrystallized with CH$_2$Cl$_2$ to give 9 (9.68 g, 95%) as a white solid; m.p = 173-175 °C; $^1$H NMR (CDCl$_3$): \( \delta = 7.44 \) (d, \( J = 6.9 \) Hz, 2H), 7.31-7.24 (m, 4H), 6.57 (s, 2H), 5.98 (s, 1H), 5.18 (s, 1H), 4.98 (s, 2H), 3.75 (s, 6H), 3.43 (s, 3H); $^{13}$C NMR: \( \delta = 153.6, 141.1, 137.8, 136.6, 135.9, 135.2, 128.6, 128.2, 127.9, 102.7, 84.6, 75.0, 67.1, 56.3, 33.5 \); IR (cm$^{-1}$): 3253 (br), 3104, 1585, 1501, 1411, 1338, 1226, 1140, 1033, 908; HR-DART-MS (m/z): Calc. for C$_{20}$H$_{21}$IN$_2$O$_4$ [M]$^+$: 480.0546; found: 480.0546; Calc. for C$_{20}$H$_{22}$IN$_2$O$_4$ [M+H]$^+$ 481.0624; found: 481.0624

4-(4-Benzylxoy-3,5-dimethoxy)benzyl-5-iodo-1-methyl-1H-imidazol (6): Et$_3$SiH (1.00 ml, 6.25 mmol) and TFA (0.40 ml, 5.20 mmol) were added to a solution of 9 (0.50 g, 1.04 mmol) in anhydrous CHCl$_3$ (20 ml) at rt and the resulting mixture was heated at reflux temperature for 24 h under nitrogen atmosphere. Then, the reaction was quenched by the addition of saturated aqueous solution of NaHCO$_3$. The aqueous layer was extracted with CHCl$_3$ several times and the combined extracts were dried (Na$_2$SO$_4$) and
concentrated. The residue was purified by chromatography (EtOAc) to isolate 6 (0.14 g, 28%) as a pale brown semi solid; $^1$H NMR (CDCl$_3$): $\delta = 7.44$ (d, $J = 6.9$ Hz, 2H), 7.36 (s, 1H), 7.30 (t, $J = 6.9$ Hz, 2H), 7.25 (d, $J = 6.9$ Hz, 1H), 6.31 (s, 2H), 4.95 (s, 2H), 3.87 (s, 2H), 3.73 (s, 6H), 3.40 (s, 3H); $^{13}$C NMR: $\delta = 153.8$, 139.6, 137.9, 135.9, 133.1, 128.5, 128.2, 127.9, 105.2, 85.0, 75.1, 56.3, 32.7, 31.0; IR (cm$^{-1}$): 3107, 2939, 1588, 1494, 1460, 1420, 1237, 1215, 1187, 1100, 978, 758; HR-ESIMS (m/z): Calc. for C$_{20}$H$_{22}$N$_2$O$_3$ [M+H]$^+$ 465.0670; found: 465.0669.

5-[(4-Benzyl-oxy-3,5-dimethoxyphenyl)-hydroxy-methyl]-1-methyl-1H-imidazole-4-carbaldehyde (12): EtMgBr (3.0 M in ether, 13.8 ml, 41.4 mmol) was added into a solution of 9 (9.03 g, 18.8 mmol) in dry THF (200 ml) at rt, and the resulting mixture was stirred at rt for 20 min. N-Methylformanilide (2.78 ml, 22.6 mmol) was added and the resulting mixture was stirred at rt for 33 h. Half saturated NH$_4$Cl (30 ml) was added to quench the reaction and the organic layer was extracted with EtOAc, dried (Na$_2$SO$_4$) and concentrated to give the crude product, which was purified through a short plug of silica gel (EtOAC→Acetone) to give 12 as a pale yellow solid (5.52 g, 77%); m.p = 132-134 °C; $^1$H NMR (CDCl$_3$): $\delta = 9.82$ (s, 1H), 7.42 (d, $J = 7.3$ Hz, 2H), 7.38 (s, 1H), 7.29 (t, $J = 7.3$ Hz, 2H), 7.25 (m, 1H), 6.50 (s, 2H), 6.23 (s, 1H), 4.94 (s, 2H), 3.71 (s, 6H), 3.47 (s, 3H); $^{13}$C NMR: $\delta = 188.4$, 153.8, 141.7, 139.9, 138.0, 137.7, 136.6, 136.2, 128.5, 128.2, 127.9, 103.4, 75.1, 66.7, 56.3, 33.1; IR (cm$^{-1}$): 3253 (br), 3106, 2938, 1680, 1587, 1502, 1450, 1415, 1230, 1100, 1056, 824; HR-DART-MS (m/z): Calc. for C$_{21}$H$_{23}$N$_2$O$_5$ [M+H]$^+$ 383.1601; found: 383.1597
{5-[(4-Benzoyloxy-3,5-dimethoxyphenyl)-hydroxy-methyl]-1-methyl-1H-imidazol-4-yl}-(4-methoxyphenyl)methanol (13): A few drops of p-bromoanisole (from 7.23 ml, 56.5 mmol) were added dropwise to a two necked round-bottom flask containing freshly-crushed, oven-dried, magnesium turnings (1.35 g, 56.5 mmol) and a small crystal of iodine in THF (100 ml). This mixture was then heated at 45 °C under nitrogen until the iodine color faded. The remainder of the p-bromoanisole was added dropwise while maintaining gentle reflux. After the addition was completed, the mixture was heated to reflux for 1 h, cooled to rt, and then a solution of 12 (5.40 g, 14.1 mmol) in THF (100 ml) was added. The resulting mixture was stirred at reflux overnight. After cooling to 0 °C, sat. NH₄Cl (50 ml) was added and the organic layer was extracted with EtOAc (3 x 100 ml), washed once with brine, dried (Na₂SO₄), and concentrated to give a thick, brown oil. The crude product was purified through a short plug of silica gel (EtOAc) to give 13 (4.38 g, 63%) as a pale yellow oil, which was used in the next step directly.

6-Benzoyloxy-5,7-dimethoxy-4-(4-methoxyphenyl)-1-methyl-1H-naphtho[2,3-d]imidazole (14): Et₃SiH (11.41 ml, 71.44 mmol) and TFA (4.81 ml, 62.5 mmol) were added to a solution of 13 (4.38 g, 8.93 mmol) in anhydrous CH₂Cl₂ (100 ml) at rt and the resulting mixture was stirred for 24 h under nitrogen atmosphere. Then, the reaction was quenched by the addition of saturated aqueous solution of NaHCO₃. The aqueous layer was extracted with CH₂Cl₂ several times and the combined extracts were dried (Na₂SO₄) and concentrated. The residue was purified by chromatography (EtOAc→acetone) to provide 14.
(3.30 g, 81%) as a pale brown solid; m.p = 194- 197 ºC; $^1$H NMR (CDCl$_3$): $\delta = 7.87$ (s, 1H), 7.61 (s, 1H), 7.53 (d, $J = 6.9$ Hz, 2H), 7.45 (d, $J = 8.7$ Hz, 2H), 7.36 (t, $J = 6.9$ Hz, 2H), 7.30 (m, 1H), 7.08 (s, 1H), 7.05 (d, $J = 8.7$ Hz, 2H), 5.10 (s, 2H), 3.96 (s, 3H), 3.89 (s, 3H), 3.74 (s, 3H), 3.37 (s, 3H); $^{13}$C NMR: $\delta = 158.2, 152.1, 150.6, 146.6, 142.9, 139.8, 138.0, 134.4, 132.4, 131.6, 130.9, 129.7, 128.4, 128.3, 127.9, 119.6, 112.7, 104.0, 102.3, 75.2, 60.9, 55.8, 55.4, 31.0; IR (cm$^{-1}$): 2929, 2831, 1607, 1514, 1451, 1330, 1274, 1145, 1075, 1027, 826, 740; HR-DART-MS ($m/z$): Calc. for C$_{28}$H$_{27}$N$_2$O$_4$ [M+H]$^+$ 455.1971; found: 455.1983.

4-Iodo-5-(4-methoxy-benzyl)-1-(N,N-dimethylsulfonyl)-1H-imidazole (16): EtMgBr (3.0 M solution in ether, 8.60 ml, 25.8 mmol) was added to a solution of 4,5-diiodo-1-(N,N-dimethylsulfonyl)-1H-imidazole 15 (7.19 g, 21.5 mmol) in dry CH$_2$Cl$_2$ (150 ml) at rt. The resulting mixture was stirred at rt for 20 min and 1.0 M solution of CuCN.2LiCl in dry THF (26 ml, 26 mmol) was added followed by 4-methoxybenzyl bromide (3.80 ml, 25.8 mmol) was added. The orange reaction solution was stirred at rt for 48 h and poured into half Sat. NH$_4$Cl containing 2% concentrated NH$_3$ (50 ml). After stirring for 20 min the resulting solid was filtered off and the filtrate was partitioned with CH$_2$Cl$_2$ (3x50 ml). The organic layer was dried (Na$_2$SO$_4$) and concentrated and purified by chromatography (EtOAc/hexane, 3:7) to afford 16 (6.41 g, 65%) as a pale yellow solid; m.p. = 76-78 ºC; $^1$H NMR (CDCl$_3$): $\delta = 7.87$ (s, 1H), 6.99 (d, $J = 8.7$ Hz, 2H), 6.77 (d, $J = 8.7$ Hz, 2H), 6.37 (s, 2H), 4.09 (s, 2H), 3.71 (s, 3H), 2.49 (s, 6H); $^{13}$C NMR: $\delta = 158.5, 139.7, 137.9, 132.5, 129.1, 114.0, 90.6, 55.4, 37.6, 29.9; IR (cm$^{-1}$): 3111, 2919, 1514, 1459, 1415, 1240, 1173, 1174, 1095, 960, 802; HR-DART-MS ($m/z$): Calc. for C$_{13}$H$_{17}$IN$_3$O$_3$S [M+H]$^+$ 422.0030; found: 422.0047.
4-(4-Benzylmethoxy-3,5-dimethoxybenzyl)-5-(4-methoxybenzyl)-1-(N,N-dimethylsulfonyl)-1H-imidazole (17): Following the above procedure, EtMgBr (3.0 M solution in ether, 4.98 ml, 14.95 mmol), 16 (5.72 g, 13.6 mmol) in dry CH₂Cl₂ (150 ml), 1.0 M solution of CuCN.2LiCl in dry THF (16.3 ml, 16.3 mmol) and 4-benzylmethoxy-3,5-dimethoxybenzyl bromide (10)² (6.87 g, 20.4 mmol) were used to produce 17 (5.18 g, 70%) as a pale yellow oil after the purification by chromatography (EtOAc:hexane, 1:1); ¹H NMR (CDCl₃): δ = 7.94 (s, 1H), 7.48 (d, J = 7.4 Hz, 2H), 7.35-7.26 (m, 3H), 6.94 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 6.37 (s, 2H), 4.94 (s, 2H), 4.14 (s, 2H), 3.78 (s, 2H), 3.75 (s, 3H), 3.71 (s, 6H), 2.57 (s, 6H); ¹³C NMR: δ = 158.4, 153.4, 141.3, 138.1, 138.0, 135.6, 134.8, 130.3, 129.9, 128.9, 128.5, 128.2, 127.8, 114.0, 106.0, 75.1, 56.1, 55.4, 37.5, 34.0, 28.1; IR (cm⁻¹): 2929, 2857, 1691, 1507, 1393, 1252, 1124, 909, 836, 779; HR-DART-MS (m/z): Calc. for C₂₉H₃₄N₃O₆S [M+H]⁺ 552.2163; found: 552.2180.

5-(4-Benzylmethoxy-3,5-dimethoxybenzyl)-4-(4-methoxybenzyl)-1-methyl-1H-imidazole (5): Methyl trifluoromethanesulfonate (0.95 ml, 8.66 mmol) was added dropwise to a solution of 17 (3.96 g, 7.18 mmol) in CH₂Cl₂ (50 ml), at 0 ºC under N₂ and stirred for 4 h at the same temperature. The solvent was evaporated under reduced pressure and the crude pale yellow oil was dissolved in dry acetonitrile (30 ml) and benzylamine (0.95 ml, 8.67 mmol) was added to it. Then the resulting solution was heated at 80
°C for 10 h. The solvent was evaporated to give a crude oil, which was purified with a gradient column (EtOAc:hexanes, 3:1→EtOAc:acetone; 1:1) to get 5 (2.96 g, 90%) as a pale brown oil; 1H NMR (CDCl₃): δ = 7.45 (d, J = 7.4 Hz, 2H), 7.40 (s, 1H), 7.38-7.26 (m, 3H), 7.19 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 6.15 (s, 2H), 4.96 (s, 2H), 3.88 (s, 2H), 3.87 (s, 2H), 3.75 (s, 3H), 3.64 (s, 6H), 3.34 (s, 3H); 13C NMR: δ = 157.9, 153.8, 138.8, 137.9, 136.8, 135.5, 134.1, 133.1, 129.5, 128.5, 128.2, 127.9, 125.5, 113.9, 105.1, 75.1, 56.1, 55.3, 32.8, 31.9, 29.5; IR (cm⁻¹): 2929, 2857, 1691, 1507, 1391, 1251, 1176, 1150, 910; HR-ESIMS (m/z): Calc. for C₂₈H₃₁N₂O₄ [M+H]⁺ 459.2278; found: 459.2278.

2-Azido-5-(4-benzyloxy-3,5-dimethoxybenzyl)-4-(4-methoxybenzyl)-1-methyl-1H-imidazole (20): n-Butyl lithium (1.6 M solution in hexanes, 1.31 ml, 2.09 mmol) was added dropwise to a stirred solution of 5 (870 mg, 1.90 mmol) in dry THF (20 ml) at -78 °C and the reaction was stirred for 1 h at the same temperature. The cooling bath was removed for 10 min, then the reaction mixture was re-cooled to -78 °C, and then TrisN₃ (706 mg, 2.28 mmol) was added. After stirring for an additional 45 min at -78 °C, the reaction mixture was quenched by the addition of sat. NH₄Cl (5 ml). The aqueous layer was extracted with EtOAc (3x15 ml), and the combined organic extracts were dried (Na₂SO₄) and concentrated to give a pale brown oil, which was purified through a short column of silica gel (hexane/EtOAc, 7:3) to give azide 20 (600 mg, 63%) as a pale brown oil; 1H NMR (CDCl₃): δ = 7.46 (d, J = 7.7 Hz, 2H), 7.38-7.26 (m, 3H), 7.21 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.4 Hz, 2H), 6.16 (s, 2H), 4.95(s, 2H), 3.85 (s, 2H), 3.80 (s, 2H), 3.76 (s, 3H), 3.64 (s, 6H), 3.08 (s, 3H); 13C NMR: δ = 158.0, 153.7, 139.2, 137.9, 136.5, 135.5, 134.0, 132.9, 129.5,
128.6, 128.2, 127.9, 124.6, 113.9, 105.0, 75.0, 56.1, 55.3, 32.7, 30.0, 29.6; IR (cm⁻¹): 2929, 2857, 2129, 1691, 1507, 1391, 1252, 1150, 1124, 909, 836, 779; HR-ESIMS (m/z): Calc. for C₂₈H₃₀N₅O₄ [M+H]⁺ 500.2292; found: 500.2290.

**Naamine G (2):** Azide 20 (600 mg, 1.20 mmol) was dissolved in EtOH (15 ml) and stirred overnight under a hydrogen atmosphere (55 psi) in the presence of 20% Pd(OH)₂ on charcoal (100 mg) at rt. The catalyst was filtered through a pad of Celite and the filtrate was concentrated to give naamine G, 2 (430 mg, 95%) as a greenish-yellow solid; m.p. = 218-220 °C; ¹H NMR (CD₃OD): δ = 7.17 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.34 (s, 2H), 3.92 (s, 2H), 3.84 (s, 2H), 3.74 (s, 3H), 3.69 (s, 6H), 3.23 (s, 3H); ¹³C NMR: δ = 158.8, 148.3, 146.5, 134.3, 129.8, 129.2, 127.3, 122.8, 122.4, 114.0, 105.2, 55.5, 54.5, 28.8, 28.3, 27.9; IR (cm⁻¹): 3244 (br), 3004, 2836, 1667, 1654, 1609, 1500, 1461, 1429, 1245, 1216, 1110, 1022; HR-DART-MS (m/z): Calc. for C₂₁H₂₆N₃O₄ [M+H]⁺ 384.1918; found: 384.1907.

**Naamidine H (3):** N,O-Bis(trimethylsilyl)acetamide (0.63 ml, 2.58 mmol) was added to a solution of 1-Methyeparabanic acid (331 mg, 4.11 mmol) in dry CH₃CN (10 ml) under an N₂ atmosphere and the resulting mixture was heated at reflux temperature for 1.5 h. Then, the solvent was removed by distillation and
to the resulting yellow residue was added naamine G (198 mg, 0.52 mmol) under N₂. After, this mixture was heated at 80 °C overnight in dry toluene (5 ml), water (5 ml) was added and the organic layer was extracted into EtOAc. The dried organic layer (Na₂SO₄) was concentrated and the yellow residue was purified over silica gel (EtOAc/hexanes, 4/6) to provide naamidine H (3) as a yellow amorphous solid (205 mg, 80%); m.p. = 204-205 °C; ¹H NMR (CDCl₃): δ = 7.13 (d, J = 8.7 Hz, 2H), 6.98 (br, 1H), 6.78 (d, J = 8.7 Hz, 2H), 6.14 (s, 2H), 3.89 (s, 2H), 3.88 (s, 2H), 3.75 (s, 3H), 3.69 (s, 6H), 3.49 (s, 3H), 3.47 (s, 3H), 3.16 (s, 3H); ¹³C NMR δ = 162.3, 158.3, 155.5, 147.4, 146.6, 144.7, 136.1, 133.7, 131.7, 129.4, 128.1, 126.7, 114.1, 104.7, 56.3, 55.4, 32.3, 30.0, 29.7, 24.8; IR (cm⁻¹): 3501, 3212, 2929, 2837, 1784, 1718, 1652, 1511, 1392, 1113, 1039, 1020, 918; HR-DART-MS (m/z): Calc. for C₂₅H₂₈N₅O₆ [M+H]⁺ 494.2034; found: 494.2049.

References:

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![Chemical structure image](image)

![NMR spectrum image](image)

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X: parts per Million (ppm)
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