A Concise Asymmetric Synthesis of the ADE Fragment of Nakadomarin A

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Supporting Information

General Experimental. Unless otherwise noted, all reagents were obtained from commercial suppliers and were used without further purification. Reactions were carried out in oven-dried glassware under an inert Ar atmosphere. Organic extracts were dried over Na₂SO₄ and solvents were removed with a rotary evaporator. Flash column chromatography was carried out using Merck 60 230-400 mesh silica gel. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Optical rotations were measured on a Rudolph Research 589/546-10 polarimeter. IR spectra were recorded on a Nicolet Avatar 320 Fourier Transform infrared spectrometer and only partial data are listed. ¹H and ¹³C NMR spectra were recorded on either a Varian 300 MHz or Varian 400 MHz instrument, as noted. NMR spectra are internally referenced to the residual protio solvent signal. Data for ¹H NMR are reported as chemical shift (ppm), multiplicity, coupling constant (Hz), and integration. Data for ¹³C NMR are reported as chemical shift (ppm). Mass spectra were obtained from the Colorado State University Central Instrumentation Facility.

Compound 10. 6-Oxo-2,3-diphenyl-morpholine-4-carboxylic acid tert-butyl ester¹ (30.0 g, 84.9 mmol) was suspended in CH₂Cl₂ (425 mL). The reaction flask was placed in a room temperature water bath. A 4M solution of HCl in dioxane (106 mL, 425 mmol) was slowly added. The solution was stirred at room temperature for 5 h, until TLC analysis indicated complete removal of the *tert*-butyl carbamate. The majority of the solvent was then removed *in vacuo*, and Et₂O was added to precipitate the hydrochloride salt. The white solid was filtered, rinsed with Et₂O, and dried to provide 24.0 g (98% yield) of 5,6-diphenyl-morpholin-2-one hydrochloride. The hydrochloride salt was dissolved in CH₂Cl₂ (300 mL) and sat. NaHCO₃ (5 mL) was slowly added, followed by solid NaHCO₃ (10.0 g). The reaction mixture was stirred for 3 h. Anhydrous MgSO₄ was added, the solution was filtered through celite and concentrated to yield 21.5 g of the title compound as a white solid (89% yield). Spectral data were consistent with those previously reported¹: ¹H NMR (300 MHz, CDCl₃) δ 7.24-7.15 (m, 6H), 6.94-6.92 (m, 2H), 6.83-6.82 (m, 2H), 5.69 (d, *J* = 3.8 Hz, 1H), 4.64 (d, *J* = 3.8 Hz, 1H), 4.14 (d, *J* = 18.3, 1H), 4.03 (d, *J* = 18.3 Hz, 1H).

Compound 11. To a solution of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (6.56 g, 25.0 mmol) in CH₂Cl₂ (60 mL) was added a solution of saturated NaHCO₃ (3.0 mL). NaIO₄ (8.02 g, 37.5 mmol) was added slowly, and the suspension was stirred vigorously

¹ (a) Aldrich Chemical Co.: (+)-enantiomer, catalog No. 33,181-3 (CAS Registry No. 112741-50-1); (-)-enantiomer, catalog No. 33,184-8 (CAS Registry No. 112741-49-8). (b) Williams, R. M. *Aldrichim. Acta* **1992**, 25, 11. (c) Williams, R. M.; Sinclair, P. J.; DeMong, D. E.; Chen, D.; Zhai, D. *Org. Syn.* **2002**, 80, 18.

for 2 h until TLC analysis indicated the reaction was complete. Anhydrous MgSO₄ was added, and the reaction mixture was filtered and concentrated to provide 5.68 g of the title compound as a clear oil (87% yield). Spectral data were consistent with those previously reported²: ¹H NMR (300 MHz, CDCl₃) δ 9.73 (s, 1H), 4.41-4.37 (m, 1H), 4.21-4.09 (m, 3H), 1.50 (s, 3H), 1.44 (s, 3H).

Compound 17. A solution of LiOEt was freshly prepared by the addition of Li (1.09 g, 157 mmol) to anhydrous EtOH (140 mL). The solution was cooled to 0 °C, and diethyl oxalate (22.9 g, 157 mmol) was added. To this mixture was added *N*-Boc-4-piperidinone (28.5 g, 143 mmol). The reaction mixture was stirred for 12 h, after which the EtOH was removed *in vacuo*. The residue was diluted with Et₂O (500 mL), cooled to 0 °C, and 1N HCl (160 mL) was added slowly (litmus paper indicated acidic solution). The organic layer was extracted, washed with H₂O (4 x 100 mL) and brine (100 mL). The organic layer was dried, filtered, and concentrated. SiO₂ purification (20% EtOAc/hex with 1% AcOH) afforded 21.2 g of the title compound as an orange oil (50% yield): IR (film) 2979, 1733, 1699, 1622, 1575, 1418, 1367, 1243, 1165, 1106 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.46 (s, 2H), 4.37 (q, *J* = 7.1, 2H), 3.65 (t, *J* = 5.9, 2H), 2.59 (t, *J* = 5.9, 2H), 2.11 (s, 1H), 1.48 (s, 9H), 1.40 (t, *J* = 7.1, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 192.5, 173.2, 162.3, 154.5, 107.3, 81.3, 62.6, 41.6, 39.2, 33.7, 28.6, 14.3; FAB-HRMS calcd. for C₁₄H₂₂N₁O₆ [M+H]⁺ 300.1447, found 300.1434.

² Earle, M. J.; Abdur-Rashid, A.; Priestley, N. D. *J. Org. Chem.* **1996**, *61*, 5697.

Compound 12. To a mixture of compound **17** (10.0 g, 33.4 mmol) and aqueous formaldehyde (37%, 8.2 mL, 100 mmol) in THF (85 mL), a solution of NaOH (1.34 g, 33.4 mmol) and H₂O (5 mL) was added slowly. The reaction mixture was stirred for 20 min, after which TLC analysis indicated no remaining starting material. The reaction mixture was then diluted with Et₂O (300 mL) and washed with H₂O (2 x 100 mL) and brine (50 mL). The organic layer was dried, filtered, and concentrated (water bath temperature <25 °C) to afford the title compound, which was immediately used in the dipolar cycloaddition reaction: ¹H NMR (300 MHz, CDCl₃) δ 6.13 (br, 1H), 5.38 (br, 1H), 4.38 (s, 2H), 3.75 (t, *J* = 6.2 Hz, 2H), 2.59 (t, *J* = 6.2 Hz, 2H), 1.47 (s, 9H).

Compound 9. Freshly prepared ene-one **12** was immediately added to a solution of morpholinone **10** (2.82 g, 11.1 mmol) and aldehyde **11** (1.52 g, 11.7 mmol) in toluene (65 mL). The reaction mixture was stirred over 3Å molecular sieves (previously flame dried under high vacuum) at 50 °C for 16 h. The reaction mixture was then filtered through celite, concentrated, and purified by SiO₂ chromatography (25% EtOAc/hex) to afford 2.24 g of the title compound as a white foam (35% yield): m.p. 88-92 °C; [α]_D²³ -49.5° (*c* 1.0, CHCl₃); IR (film) 2981, 2932, 1733, 1696, 1477, 1454, 1423, 1367, 1381, 1275, 1239, 1166, 1092, 1057, 1032, 974, 856, 735, 699 cm⁻¹; ¹H NMR (500 MHz, CD₃OD, 50 °C) δ 7.27-7.22 (m, 3H), 7.16-7.09 (m, 5H), 6.98-6.95 (m, 2H), 6.18 (d, *J* =

3.2 Hz, 1H), 4.91 (d, $J = 3.2$ Hz, 1H), 4.32 (d, $J = 13.1$ Hz, 1H), 4.24-4.18 (m, 1H), 4.14 (s, 1H), 4.03-3.98 (m, 1H), 3.93-3.89 (m, 1H), 3.81 (d, $J = 13.1$ Hz, 1H), 3.72-3.68 (m, 1H), 3.45-3.39 (m, 1H), 3.35-3.26 (m, 1H), 2.94-2.86 (m, 1H), 2.47-2.42 (m, 1H), 2.20 (dd, $J = 6.3, 13.0$ Hz, 1H), 1.86 (dd, $J = 10.6, 13.0$ Hz, 1H), 1.50 (s, 9H), 1.44 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $\text{d}_6\text{-DMSO}$, 100 $^\circ\text{C}$) δ 210.0, 171.4, 154.6, 138.5, 137.5, 129.2, 128.7, 128.3, 128.2, 127.6, 126.7, 109.5, 79.5, 78.9, 66.3, 64.4, 63.9, 62.1, 61.8, 52.8, 42.9, 38.1, 36.5, 28.7, 27.1, 25.8; FAB-HRMS calcd. for $\text{C}_{33}\text{H}_{41}\text{N}_2\text{O}_7$ $[\text{M}+\text{H}]^+$ 577.2914, found 577.2912.

Compound 8. To a solution of compound **9** (3.40 g, 5.90 mmol) in EtOH/EtOAc (1:1, 40 mL), $\text{Pd}(\text{OH})_2/\text{C}$ (830 mg, 20 wt% Pd, moist) was added. The reaction flask was flushed with H_2 , and stirred under a H_2 balloon for 16 h, after which it was filtered through celite. The filtrate was concentrated then re-concentrated with toluene to remove residual water from the catalyst. Trituration of the residue with pentane and filtration of the resulting precipitate afforded 2.15 g of the title compound as a white powder (91% yield): m.p. 118-124 $^\circ\text{C}$; $[\alpha]_D^{23} -27.5^\circ$ (c 1.0, CHCl_3); IR (film) 3445, 2980, 2934, 1695, 1634, 1479, 1423, 1367, 1311, 1245, 1167, 1067, 855, 736 cm^{-1} ; ^1H NMR (300 MHz, CD_3OD , 50 $^\circ\text{C}$) δ 4.29-4.22 (m, 1H), 4.14-3.91 (m, 4H), 3.88 (s, 1H), 3.78-3.69 (m, 2H), 3.63-3.49 (m, 1H), 2.65-2.61 (m, 2H), 2.47-2.41 (m, 1H), 1.89-1.81 (m, 1H), 1.51 (s, 9H), 1.48 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 208.0, 169.9, 155.4, 110.5, 80.8, 75.6, 66.1, 65.8, 60.3, 57.9, 50.1, 42.0, 37.5, 27.5, 25.6, 24.3, 22.3; FAB-HRMS calcd. for $\text{C}_{19}\text{H}_{31}\text{N}_2\text{O}_7$ $[\text{M}+\text{H}]^+$ 399.2131, found 399.2132.

5-Hexenoyl chloride. Catalytic DMF (1 drop) was added to 5-hexeneoic acid (400 mg, 3.50 mmol). Oxalyl chloride (370 μ L, 4.20 mmol) was added slowly. The reaction mixture was stirred for 15 min after the evolution of gas subsided, then diluted with Et₂O and filtered. Concentration of the filtrate afforded 380 mg of the title compound as a clear oil (82%). Spectral data were consistent with those previously reported³: ¹H NMR (300 MHz, CDCl₃) δ 5.83-5.69 (m, 1H), 5.10-5.04 (m, 2H), 2.91 (t, J = 7.4, 2H), 2.18-2.11 (m, 2H), 1.88-1.78 (m, 2H).

Compound 19. To a solution of compound **8** (2.00 g, 5.02 mmol) in CH₂Cl₂ (10 mL) was added NEt₃ (2.10 mL, 15.1 mmol). The solution was stirred for 15 min, then cooled to 0 °C. A solution of 5-hexenoyl chloride (732 mg, 5.52 mmol) in CH₂Cl₂ (10 mL) was slowly added. The reaction mixture was stirred at 0 °C for 1 h, then gradually warmed to room temperature and stirred an additional 1 h. The reaction mixture was then cooled to 0 °C, diluted with CH₂Cl₂ (100 mL), and 1N HCl (20 mL) was added. The organic layer was extracted, washed with H₂O (2 x 25 mL) and brine (25 mL). The organic layer was dried, filtered, and concentrated. SiO₂ purification afforded 1.87 g of the title compound as a white foam (75% yield): m.p. 62-66 °C; [α]_D²³ +51.8° (c 1.0, CHCl₃); IR (film) 3304, 2980, 2935, 1775, 1699, 1668, 1423, 1369, 1264, 1221, 1162, 1108, 1058, 973, 915, 857, 735 cm⁻¹; ¹H NMR (400 MHz, d₆-DMSO, 100 °C) δ 5.86-

³ Cekovik, Z. *Tetrahedron Lett.* **1972**, 13, 749.

5.75 (m, 1H), 5.04-4.93 (m, 2H), 4.57 (s, 1H), 4.49-4.36 (m, 1H), 4.33-4.20 (m, 2H), 4.13-4.02 (m, 1H), 4.00-3.94 (m, 1H), 3.65-3.59 (m, 1H), 3.24-3.09 (m, 2H), 2.84-2.69 (m, 1H), 2.65-2.30 (m, 5H), 2.08-2.04 (m, 2H), 1.68-1.59 (m, 2H), 1.45 (s, 9H), 1.38 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, d_6 -DMSO, 100 °C) δ 207.2, 175.2, 171.5, 154.6, 138.9, 115.4, 109.4, 80.5, 78.5, 66.9, 58.8, 51.0, 42.6, 39.7, 39.3, 34.5, 33.2, 31.9, 28.6, 26.8, 25.9, 25.8, 24.7; FAB-HRMS calcd. for $\text{C}_{25}\text{H}_{39}\text{N}_2\text{O}_8$ $[\text{M}+\text{H}]^+$ 495.2706, found 495.2711.

Compound 20. To a solution of compound **19** (88 mg, 0.177 mmol) in MeOH (1 mL) was added TMS-diazomethane (2.0 M solution in hexanes) until a yellow color persisted. The solution was stirred for 5 min then concentrated. The residue was dissolved in H_2O saturated CH_3NO_2 (1 mL), and $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (40 mg, 0.177 mmol) was slowly added in small portions. The reaction mixture was stirred for 1 h, after which no starting material was observed by TLC. Saturated NaHCO_3 (1 mL) was added and the reaction mixture was diluted with EtOAc (20 mL). The organic layer was separated, washed with H_2O (3 x 5 mL), then dried, filtered, and concentrated. SiO_2 purification (2.5% MeOH/ CH_2Cl_2) afforded 66 mg of the title compound as a colorless amorphous solid (80% yield); $[\alpha]_D^{23} +7.2^\circ$ (c 1.0, CHCl_3); IR (film) 3399, 2974, 1742, 1695, 1635, 1428, 1367, 1350, 1312, 1245, 1168, 1146, 1107, 671 cm^{-1} ; ^1H NMR (400 MHz, d_6 -DMSO, 100 °C) δ 5.86-5.74 (m, 1H), 5.04-4.94 (m, 2H), 4.90-4.83 (m, 1H), 4.58 (s, 1H), 4.36-4.26 (m, 2H), 4.19-4.12 (m, 1H), 4.09-4.01 (m, 1H), 3.68-3.61 (m, 1H), 3.53 (s,

3H), 3.51-3.39 (m, 2H), 3.39-3.29 (m, 1H), 3.26-3.20 (m, 1H), 2.76-2.66 (m, 1H), 2.65-2.54 (m, 1H), 2.35-2.27 (m, 1H), 2.07-2.00 (m, 2H), 1.77-1.69 (m, 1H), 1.66-1.56 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, d_6 -DMSO, 100 °C) δ 206.0, 175.8, 170.6, 154.7, 138.9, 115.4, 80.6, 74.8, 67.2, 67.1, 64.8, 60.1, 59.2, 52.4, 51.3, 51.2, 42.8, 34.4, 33.1, 28.7, 24.5; FAB-HRMS calcd. for $\text{C}_{23}\text{H}_{37}\text{N}_2\text{O}_8$ $[\text{M}+\text{H}]^+$ 469.2550, found 469.2546.

Compound 7. To a solution of compound **20** (400 mg, 0.854 mmol), PPh_3 (896 mg, 3.42 mmol), and imidazole (233 mg, 3.42 mmol) in toluene (17 mL) at 80 °C was slowly added I_2 in small portions (650 mg, 2.56 mmol). The reaction mixture was stirred for 2 h at 80 °C after the addition of I_2 was complete. The reaction mixture was then diluted with Et_2O (100 mL) and washed with a solution of $\text{Na}_2\text{S}_2\text{O}_3$ (2% aq, 25 mL). The organic layer was washed with H_2O (2 x 25 mL) and brine (25 mL). The Et_2O layer was dried, filtered, and concentrated. SiO_2 purification (25 % EtOAc /hex) afforded 223 mg of the title compound as a clear oil (60% yield): $[\alpha]_D^{23} -9.2^\circ$ (c 0.52, CHCl_3); IR (film) 2976, 1743, 1700, 1652, 1423, 1367, 1350, 1279, 1239, 1199, 1268, 1145, 922 cm^{-1} ; ^1H NMR (400 MHz, d_6 -DMSO, 100 °C) δ 6.00-5.90 (m, 1H), 5.84-5.72 (m, 1H), 5.30-5.19 (m, 2H), 5.04-4.94 (m, 2H), 4.72-4.63 (m, 1H), 4.64 (s, 1H), 4.35-4.28 (m, 1H), 4.15-4.06 (m, 1H), 3.52 (s, 3H), 3.34-3.21 (m, 1H), 3.14-3.08 (m, 1H), 3.04-2.92 (m, 1H), 2.66-2.55 (m, 1H), 2.50-2.40 (m, 1H), 2.32-2.23 (m, 2H), 2.07-1.99 (m, 2H), 1.69-1.55 (m, 3H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, d_6 -DMSO, 100 °C) δ 205.6, 173.9, 170.3,

154.5, 141.1, 138.8, 116.1, 115.5, 80.6, 66.2, 66.1, 58.7, 52.3, 51.0, 42.7, 36.5, 33.6, 33.4, 33.0, 28.6, 24.3; FAB-HRMS calcd. for C₂₃H₃₅N₂O₆ [M+H]⁺ 435.2495, found 435.2499.

Compound 6. To a solution of compound **7** (48.0 mg, 0.111 mmol) in CH₂Cl₂ (100 mL) was added a solution of Grubb's second-generation catalyst (4.70 mg, 0.011 mmol) in CH₂Cl₂ (10 mL). The reaction mixture was refluxed for 2.5 h, upon which TLC analysis indicated the consumption of the starting material. The reaction mixture was cooled to room temperature and the solvent removed *in vacuo*. The residue was purified by SiO₂ (50% EtOAc/hex) to afford 29.0 mg of the title compound as a white solid (65% yield): m.p. 184-186 °C; [α]_D²³ -4.9° (*c* 0.51, CHCl₃); IR (film) 2954, 2921, 2849, 1753, 1698, 1655, 1650, 1461, 1422, 1366, 1277, 1241, 1166, 1145 cm⁻¹; ¹H NMR (400 MHz, d₆-DMSO, 100 °C) δ 5.74-5.65 (m, 1H), 5.52-5.47 (m, 1H), 4.88-4.82 (m, 1H), 4.58 (s, 1H), 4.29-4.23 (m, 1H), 4.13-4.04 (m, 1H), 3.53 (s, 3H), 3.37-3.28 (m, 1H), 3.18-3.11 (m, 1H), 3.02-2.92 (m, 1H), 2.75-2.48 (m, 4H), 2.19-2.12 (m, 1H), 2.04-1.95 (m, 1H), 1.87-1.67 (m, 2H), 1.66-1.59 (m, 1H), 1.45 (s, 9H); ¹³C NMR (100 MHz, d₆-DMSO, 100 °C) δ 204.6, 172.2, 169.0, 153.7, 133.5, 125.4, 79.6, 64.9, 57.7, 56.9, 51.0, 49.4, 41.7, 39.0; 35.3, 31.6, 27.5, 25.1, 22.2; FAB-HRMS calcd. for C₂₁H₃₁N₂O₆ [M+H]⁺ 407.2182, found 407.2174.

S10 - Compound 10, CDCl₃, 300 MHz

S11 - Compound 11, CDCl₃, 300 MHz

S12 - Compound 17, CDCl₃, 300 MHz

S13 - Compound 12, CDCl₃, 300 MHz

S14 - Compound 9, CD3OD, 500 MHz, 50 oC

S15 - gCOSY of compound 9 in CD3OD, 500 MHz, 50 oC

03OD, 500 MHz, 50 oC

S17 - Compound 8, CD3OD, 50 oC, 300 MHz

S18 - CDCl₃, 300 MHz

S 19 - Compound 19, d6-DMSO, 100 oC, 400 MHz

S20 - Compound 20, d6-DMSO, 100 °C, 400 MHz

S21 - Compound 7, d6-DMSO, 100 oC, 400 MHz

S22 - Compound 6, d6-DMSO, 100 oC, 400 MHz