Supporting Information for:

Selective Fowler reductions: asymmetric total syntheses of isofagomine and other 1-azasugars from methyl nicotinate

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Synthesis of 6: Fowler reduction of methyl nicotinate

To a suspension of methyl nicotinate (10 g, 72.6 mmol) and sodium borohydride (2.89 g, 72.6 mmol) in methanol (200 mL) at –78 °C was added phenyl chloroformate (9.11 mL, 72.6 mmol) in a dropwise manner, over an interval of 40 min. The mixture was stirred for 3 h and then poured onto 800 mL of distilled water to give a yellow precipitate. The precipitate was filtered and washed with distilled water (150 mL) and dried under vacuum to give **6** (18 g, 97%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42 - 7.35 (m, 2 H), 7.28 - 7.21 (m, 1 H), 7.18 - 7.13 (m, 3 H), 7.02 (d, 1 H, J = 3.0 Hz), 5.44 - 5.37 (m, 1 H), 4.77 (s, 1 H), 4.63 (s, 1 H), 3.77 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 66.1 and 165.7, 150.9 and 150.8, 132.7, 131,2. 129.8 and 129.7, 126.5-126.4, 121.7 and 121.6, 120.4, 118.5, 105.1 and 105.0, 52.1 and 51.9, 43.4 and 43.0; IR (CH_2Cl_2) 2950, 1740, 1720, 1230, 1190 cm^{-1}; EIMS *m/z* 259 (M$^+$, 87%), 77 (100 %).

Synthesis of 16: Oxidation of 6

To a solution of **6** (10 g, 39 mmol) in methylene chloride (250 mL) at –78 °C was added *m*-chloroperoxybenzoic acid (10 g, 77 mmol). The reaction was stirred at –78 °C for 2 h and then at 0 °C for 4 h. Saturated sodium bisulfate solution (50 mL) was added and the mixture was stirred for 15 min after which the organic layer was washed with saturated sodium bisulfate solution, saturated sodium bicarbonate solution and brine and then dried ($MgSO_4$) and evaporated. Chromatography on SiO_2 (4:1 hexanes: ethyl acetate) gives **16** as a glassy white semi-solid (16 g, 92%), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09 – 7.67 (m, 2H), 7.75 – 6.86 (8 H), 6.5 (br, 1 H), 4.5 (br, 1 H), 4.2 H (b, 1 H) 3.80 (br. s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164. 7 and 164.4, 150.6, 134.5, 133.5, 133.2, 129.7, 129.3, 65.8, 51.8; IR (film) 3400, 1730, 1250, 1235, 760 cm^{-1}; ESIMS *m/z* 430 (M – H, 100%).

Synthesis of (±)-17: Reduction of 16

To a solution of **16** (7.36 g, 17.1 mmol) in methylene chloride (250 mL) at –78 °C was added trimethylsilyl trifluoromethanesulfonate (6.4 mL, 3.0 equiv) and borane-tetrahydrofuran complex

(1.0 M in THF, 32 mL, 32 mmol). The reaction was stirred at –78 °C for 3 h and then gradually warmed up to 0 °C and stirred for 3 h. Saturated sodium bicarbonate solution (50 mL) was added and the reaction mixture was warmed to rt. The organic phase washed with water (3 x 50 mL) and brine (3 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on SiO_2 (2:1 hexane/ethyl acetate) gave (±)- **17** (3.6 g, 77%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 - 7.32 (m, 2 H), 7.24 - 7.16 (m, 1 H), 7.11 - 7.08 (m, 2 H), 7.02 (br. s, 1 H), 4.42 - 4.25 (m, 3 H), 3.94 (dd, 1 H, *J* = 4.2 Hz and 8.7 Hz), 3.79 (s, 3 H), 3.60 - 2.33 (m, 1 H), 1.70 (s, 1 H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.6, 154.5, 151.3, 139.7, 138.9, 129.6, 125.9, 121.9, 63.5 and 63.4, 52.4, 47.8, 47.0, 43.3, 43.2; IR (CH_2Cl_2) 3450, 2980, 1730, 1650, 1440, 1220, 755 cm^{-1}; EIMS *m/z* 277 (M^+, 26) 140 (100).

Synthesis of 18: Oxidation of (±)-17

To a solution of (±)-**17** (2.0 g, 7.3 mmol) in acetone (14 mL) was added Jones reagent (2.7 M, 2.7 mL, 7.3 mmol) dropwise at O °C. After 20 min, 2-propanol (2 mL) was added followed by water (25 mL) and ether (100 mL). The organic layer was washed with 3M sodium acetate solution (30 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated to give enone **18** (2.0 g, 99%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (dd, *J* = 7.5 Hz and 8.1 Hz, 2 H), 7.22 (dd, *J* = 7.5 Hz and 8.1 Hz, 1 H), 6.94 (br, 1 H), 4.68 (s, 1 H), 4.37 (s, 1 H), 4.26 (s, 1 H), 3.89 (s, 3 H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.0, 153.6, 151.0, 145.2, 131.7, 131.6, 129.7, 126.1, 121.8, 53.3, 52.1 and 51.4, 43.2 and 43.0; IR (CH_2Cl_2) 2930, 1725, 1700, 1820, 1200, 750 cm^{-1}; EIMS *m/z* 275 (2 %), 94 (100 %).

Synthesis of (+)-17: Asymmetric reduction of 18

To a solution of (1R, 2S) – (-) – N – methylephedrine (1.88 g, 10.5 mmol) in dry ether (30 mL) was added a solution of lithium aluminum hydride (1.0 M in ether, 9.3 mL, 9.3 mmol) dropwise. The mixture was refluxed for 1 h and cooled to 0 °C. 2-Ethylaminopyridine (3.2 g, 20.4 mmol) was added to the above mixture. The resulting mixture was refluxed for 1 h and then cooled to

–78°C. A solution of **18** (1.6 g, 5.8 mmol) in ether (20 mL) was slowly added the above suspension at –78 °C. The mixture was stirred for 3 h and 1.5 mL of acetic acid was added. The reaction mixture was stirred for 5 min at –78 °C, further diluted with 3 *N* HCl (45 mL), and then extracted with ether (3 x 40 mL). The extracts were washed with saturated sodium bicarbonate solution and brine, dried ($MgSO_4$) and concentrated in vacuo. Chromatography on SiO_2 of the residue (2:1 hexane/ ethyl acetate) gave (+)- **17** (1.40 g, 85%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38 - 7.32 (m, 2 H), 7.24 - 7.16 (m, 1 H), 7.11 - 7.08 (m, 2 H), 7.02 (br. s, 1 H), 4.42 - 4.25 (m, 3 H), 3.94 (dd, 1 H, J = 4.2 Hz and 8.7 Hz), 3.79 (s, 3 H), 3.60 - 2.33 (m, 1 H), 1.70 (s, 1 H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.6, 154.5, 151.3, 139.7, 138.9, 129.6, 125.9, 121.9, 63.5 and 63.4, 52.4, 47.8, 47.0, 43.3, 43.2; IR (CH_2Cl_2) 3450, 2980, 1730, 1650, 1440, 1220, 755 cm^{-1}; EIMS *m/z* 277 (M^+, 26%) 140 (100%); $[\alpha]^D_{25} = +17^o$ (c=1.0, MeOH).