Asymmetric Synthesis of

3-Azide-4-fluoro-L-phenylalanine

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Supporting Information

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General Experimental

Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Infrared spectra (IR) were recorded on a JASCO FT/IR-8300 spectrophotometer and are reported in wave number (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker ARX-400 (400 MHz) spectrometer. NMR samples were dissolved in CDCl_3 and DMSO, and chemical shifts are reported in ppm relative to the residual undeuterated solvent (CDCl_3 as $\delta = 7.26$ ppm, DMSO as $\delta = 2.50$ ppm). ^1H NMR data are reported as follows; chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broadened, m = multiplet), coupling constant, and assignment. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker ARX-400 (100 MHz) or a Varian Gemini-2000 (75 MHz) spectrometer. The samples were dissolved in CDCl_3 and DMSO, and chemical shifts are reported in ppm relative to the solvent (CDCl_3 as $\delta = 77.0$ ppm, DMSO as $\delta = 39.5$ ppm). Fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded on a Bruker ARX-400 (376 MHz) spectrometer. Elemental analyses were performed at the Analytical

Laboratory of the Graduate School of Bioagricultural Sciences, Nagoya University. High resolution mass spectra (HRMS) were recorded on a JEOL JMS-700 are reported in *m/z*. Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel coated glass plate 60 F₂₅₄ (Merck, #1.05715). Silica gel 60 (particle size 63-200 μm , 70-230 mesh ASTM, Merck Ltd.) was used for open-column chromatography. Silica gel 60 (spherical, particle size 40-50 μm , Kanto Chemical Co., Inc.) and silica gel 60 N (spherical, neutral, particle size 40-50 μm , Kanto Chemical Co., Inc.) were used for flash column chromatography. Unless otherwise noted, non-aqueous reactions were carried out in oven-dried (120 $^{\circ}\text{C}$) or flame-dried glassware under nitrogen or argon. Dry THF and CH_2Cl_2 were purchased from Kanto Chemical Co., Inc. All other commercially available reagents were used as received.

Experimental Procedures and Characterization Data

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Aldehyde 5: In a 300 mL flask equipped with a dropping funnel, 95% H₂SO₄ (80 mL) and 69% HNO₃ (11.0 mL, 169 mmol) were placed, and it was cooled to 0 °C. *p*-Fluorobenzaldehyde **4** (17.2 mL, 161 mmol) was added dropwise over 10 min. The reaction mixture was allowed to warm to room temperature. After being stirred for 1 h, the reaction mixture was poured into ice (200 g). The resultant solution was extracted with CH₂Cl₂ (200 mL x2). The organic layer was washed with H₂O and brine, and the dried over Na₂SO₄. The solution was concentrated to dryness *in vacuo*. The residue was purified by recrystallization (from Et₂O-hexane) to give **5** (18.3 g, 67%) as a yellow powder.

IR (KBr) $\nu_{\max}$ 3067, 2859, 1705, 1615, 1542, 1351 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.51 (1H, dd, *J* = 10.0, 8.5 Hz), 8.21 (1H, ddd, *J* = 8.5, 4, 2 Hz), 8.59 (1H, dd, *J* = 7, 2 Hz), 10.05 (1H, s); ¹³C NMR (100 MHz, CDCl₃) δ 119.7 (d, *J*_{C-F} = 22 Hz), 127.8x 2, 133.0, 135.6 (d, *J*_{C-F} = 10 Hz), 158.7 (d, *J*_{C-F} = 274 Hz), 188.2; ¹⁹F NMR (376 MHz, CDCl₃) δ -107.9; HRMS (EI) for C₇H₄FN₂O₃ [*M*⁺], calcd 169.0175, found: 169.0157.

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Alcohol 6: In a flask equipped with a dropping funnel, aldehyde **5** (5.0 g, 31.0 mmol) was dissolved in MeOH (30 mL), and it was cooled to 0 °C. To this solution was added a solution of NaBH₄ (1.76 g, 47.0 mmol) in H₂O (7.5 mL) dropwise over 20 min. After being stirred at room temperature for 1 h, the reaction mixture was concentrated *in vacuo*. The aqueous layer was neutralized with 1*N* aqueous HCl and extracted with Et₂O (150 mL x2). The organic layer was washed with brine (100 mL x2), and then dried over Na₂SO₄. The solution was concentrated to dryness *in vacuo*. The residue was

used for the next reaction without further purification.

The residue was dissolved in EtOH (50 mL), and 10% Pd/C (100 mg) was added. The reaction vessel was charged with H₂ gas. After being stirred vigorously at room temperature for 16 h, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated to dryness *in vacuo*. The residue was used for the next reaction without further purification.

The residue was dissolved in a mixture of AcOH (50 mL), TFA (5 mL) and H₂O (5 mL), and it was cooled to 3 °C. To this solution was added NaNO₂ (3.2 g, 46.0 mmol) and the solution was stirred for 10 min. To the solution was added NaN₃ (3.0 g, 46.0 mmol) at the same temperature. After being stirred for additional 10 min, the reaction mixture was poured into an ice-cooled saturated aqueous NaHCO₃ (200 mL). The resultant solution was extracted with AcOEt (300 mL x1). The organic layer was washed with saturated aqueous NaHCO₃ (50 mL x3) and brine, and then dried over Na₂SO₄. The solution was concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, AcOEt/hexane 1:5) to give **6** (3.53 g, 68% in 3 steps) as a dark red oil.

IR (KBr) ν_{max} 3323, 2127, 1607, 1514, 1424, 1317, 1228 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.79 (1H, br s), 4.65 (2H, s), 7.04-7.12 (3H, m); ¹³C NMR (100 MHz, CDCl₃) δ 64.1, 116.6 (d, $J_{\text{C-F}}$ = 19 Hz), 119.4, 124.0 (d, $J_{\text{C-F}}$ = 7 Hz), 127.9 (d, $J_{\text{C-F}}$ = 11 Hz), 137.9 (d, $J_{\text{C-F}}$ = 3 Hz), 154.1 (d, $J_{\text{C-F}}$ = 249 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -128.2; HRMS (EI) for C₇H₆FN₃O [M⁺], calcd 167.0495, found: 167.0490.

7a

Bromide 7a: Alcohol **6** (5.96 g, 35.7 mmol) was dissolved in CH₂Cl₂ (120 mL), and it was cooled to 0 °C. To this solution was added CBr₄ (21.7 g, 65.4 mmol) and PPh₃ (13.6 g, 52.3 mmol) at the same temperature. After being stirred at room temperature for 20 min, the reaction mixture was concentrated *in vacuo* to remove three-quarters of the solvent. The resulting mixture was passed through a column packed with flash silica gel (eluted with CH₂Cl₂), and then concentrated to dryness *in vacuo*. The residue was

purified by flash column chromatography (silica gel, Et₂O/hexane 1:65) to give **7a** (4.95 g, 60%) as a yellow oil.

IR (KBr) ν_{max} 2125, 1607, 1514, 1420, 1319 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.41 (2H, s), 7.02-7.14 (3H, m); ¹³C NMR (100 MHz, CDCl₃) δ 31.7, 117.0 (d, $J_{\text{C-F}}$ = 19 Hz), 121.7, 126.4 (d, $J_{\text{C-F}}$ = 8 Hz), 128.3 (d, $J_{\text{C-F}}$ = 12 Hz), 134.9 (d, $J_{\text{C-F}}$ = 4 Hz), 154.7 (d, $J_{\text{C-F}}$ = 251 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -126.2; HRMS (EI) for C₇H₅BrFN₃ [M⁺], calcd 228.9651, found: 228.9630.

7f

Iodide 7f: Bromide **7a** (4.9 g, 21.0 mmol) was dissolved in acetone (160 mL), and it was cooled to 0 °C under nitrogen. To this solution was added NaHCO₃ (9.0 g, 107 mmol) and NaI (19.2 g, 128 mmol) at the same temperature. After being stirred at room temperature for 3 h, the reaction mixture was poured into an ice-cooled water. The resultant solution was extracted with AcOEt (400 mL x1). The organic layer was washed with brine (400 mL x2), and then dried over Na₂SO₄. The solution was concentrated to dryness *in vacuo*. The residue was purified by column chromatography (neutral silica gel, Et₂O/hexane 1:19) to give **7f** (5.64 g, 96%) as a yellow oil.

IR (KBr) ν_{max} 2121, 1605, 1513, 1420, 1319 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.38 (2H, s), 7.01 (1H, dd, J = 10.5, 8.5 Hz), 7.05-7.12 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ 3.2, 117.0 (d, $J_{\text{C-F}}$ = 19 Hz), 121.3, 126.1 (d, $J_{\text{C-F}}$ = 7 Hz), 128.2 (d, $J_{\text{C-F}}$ = 12 Hz), 136.5 (d, $J_{\text{C-F}}$ = 4 Hz), 154.2 (d, $J_{\text{C-F}}$ = 251 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -126.8; HRMS (EI) for C₇H₅FIN₃ [M⁺], calcd 276.9512, found: 276.9501.

Compound 8a: Bislactim ether **2** (400 mg, 2.17 mmol) was dissolved in dry THF (5.8 mL), and it was cooled to $-78\text{ }^{\circ}\text{C}$ under nitrogen. To this solution was added *n*-BuLi (1.6 M solution in hexane; 1.35 mL, 2.17 mmol) dropwise over 5 min. After the solution was stirred at the same temperature for 30 min, $\text{BF}_3\cdot\text{OEt}_2$ (410 μL , 3.20 mmol) was added. The resultant slurry solution was stirred for 30 min, and a solution of 3-azido-4-fluoro benzyl iodide **7f** (450 mg, 1.73 mmol) in THF (3.6 mL) was added dropwise at $-78\text{ }^{\circ}\text{C}$ over 30 min. After being stirred for additional 1 h, the reaction mixture was quenched with a mixture of saturated aqueous NH_4Cl (7.2 mL) and aqueous ammonia (28%, 0.8 mL). The resultant solution was extracted with Et_2O (30 mL x1). The organic layer was washed with water and brine, and then dried over anhydrous Na_2SO_4 . The solution was concentrated to dryness *in vacuo*. The residue was purified by column chromatography (neutral silica gel, Et_2O /hexane 1:4) to give **8a** (472 mg, 82%) as a yellow oil.

$[\alpha]_{\text{D}}^{29} +36$ (*c* 0.87, CHCl_3); IR (KBr) ν_{max} 2945, 2124, 1697, 1514, 1239 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.64 (3H, d, $J = 7\text{ Hz}$), 0.97 (3H, d, $J = 7\text{ Hz}$), 2.17 (1H, m), 3.04 (2H, br d, $J = 5\text{ Hz}$), 3.48 (1H, t, $J = 4.0\text{ Hz}$), 3.67 (3H, s), 3.71 (3H, s), 4.27 (1H, br q, $J = 5\text{ Hz}$), 6.82 (1H, m), 6.87 (1H, dd, $J = 8.0, 2.0\text{ Hz}$), 6.98 (1H, dd, $J = 10.5, 8.5\text{ Hz}$); ^{13}C NMR (100 MHz, CDCl_3) δ 16.5, 19.0, 31.5, 39.1, 52.2, 52.4, 56.3, 60.5, 116.0 (d, $J_{\text{C-F}} = 19\text{ Hz}$), 122.2, 126.9 (d, $J_{\text{C-F}} = 11\text{ Hz}$), 127.2 (d, $J_{\text{C-F}} = 6\text{ Hz}$), 134.6, 153.5, (d, $J_{\text{C-F}} = 248\text{ Hz}$), 162.0, 164.1; ^{19}F NMR (376 MHz, CDCl_3) δ -130.1; HRMS (EI) for $\text{C}_{16}\text{H}_{20}\text{FN}_5\text{O}_2$ [M^+], calcd 333.1601, found: 333.1591.

9

Methyl ester 9: Compound **8a** (300 mg, 0.90 mmol) was dissolved in THF (3.6 mL), and it was cooled to 0 °C. To this solution was added 2*N* aqueous HCl (3.0 mL). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was cooled to 0 °C and adjusted to pH 9 with 1*N* aqueous ammonia (6.0 mL). The solution was concentrated to dryness *in vacuo*. The aqueous layer was extracted with CH₂Cl₂ (20 mL x3). The organic layer was washed with brine, and then dried over Na₂SO₄. The solution was concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, MeOH/CH₂Cl₂ 1:19) to give **9** (172 mg, 81%) as a yellow amorphous.

$[\alpha]_D^{27} +14.8$ (*c* 1.60, CHCl₃); IR (KBr) $\nu_{\max}$ 2953, 2124, 1736, 1605, 1514 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.65 (2H, br s), 2.83 (1H, dd, *J* = 14, 7.5 Hz), 3.03 (1H, dd, *J* = 14, 5 Hz), 3.72 (1H, m), 3.74 (3H, s), 6.88-6.95 (2H, m), 7.02 (1H, m); ¹³C NMR (75 MHz, CDCl₃) δ 40.2, 52.2, 55.7, 116.7 (d, *J*_{C-F} = 19 Hz), 121.8, 126.6 (d, *J*_{C-F} = 7 Hz), 127.9 (d, *J*_{C-F} = 11 Hz), 134.5 (d, *J*_{C-F} = 3 Hz), 154.1 (d, *J*_{C-F} = 249 Hz), 175.4; ¹⁹F NMR (376 MHz, CDCl₃) δ -129.2; HRMS (EI) for C₁₀H₁₁FN₄O₂ [M⁺], calcd 238.0866, found: 238.0868.

1

Phenylalanine 1: Methyl ester **9** (127 mg, 0.53 mmol) was dissolved in dioxane (1.8 mL). To this solution was added a solution of LiOH (45 mg) in H₂O (3.6 mL) at room temperature. After being stirred for 5 min, the reaction mixture was neutralized to pH 7

with 1*N* aqueous HCl.

To the solution was added NaHCO₃ (225 mg, 2.66 mmol) followed by a solution of *N*-(9-fluorenylmethoxycarbonyloxy)succinimide (215 mg, 0.64 mmol) in dioxane (4.8 mL) at room temperature. After being stirred at the same temperature for 40 min, the reaction mixture was adjusted to pH 1 with 1*N* aqueous HCl. The resultant solution was extracted with AcOEt (20 mL x2). The organic layer was washed with brine, and then dried over Na₂SO₄. The solution was concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, AcOH/MeOH/CH₂Cl₂ 0.5:10:90) to give **1** (220 mg, 92% in 2 steps) as a white solid.

[α]_D²⁶ +37 (c 0.80, CHCl₃); IR (KBr) $\nu_{\max}$ 3295, 2363, 2124, 1697, 1589, 1514 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.90 (1H, dd, *J* = 14, 11 Hz), 3.14 (1H, dd, *J* = 14, 4 Hz), 3.38 (1H, br s), 4.16-4.29 (4H, m), 7.14 (1H, m), 7.20-7.37 (4H, m), 7.44 (2H, t, *J* = 7.5 Hz), 7.66 (2H, d, *J* = 7.5 Hz), 7.75 (1H, d, *J* = 8.6 Hz), 7.91 (2H, d, *J* = 7.5 Hz); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 35.4, 46.5, 55.1, 65.6, 116.3 (d, *J*_{C-F} = 18.4 Hz), 120.0, 121.9, 125.1, 126.4 (d, *J*_{C-F} = 11 Hz), 126.9, 127.6, 135.5, 140.6, 143.6, 143.7, 152.5 (d, *J*_{C-F} = 243.9 Hz), 155.9, 173.0; ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -125.7; Anal. Calcd. for C₂₄H₁₉FN₄O₄: C, 64.57; H, 4.29; N, 12.55. Found: C, 64.64; H, 4.30; N, 12.47.