Total Synthesis of LFA-1 Antagonist BIRT-377 via Organocatalytic Asymmetric Construction of a Quaternary Stereocenter

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Supporting Information

General. Chemicals and solvents were either purchased *puriss p.A.* from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H₂SO₄ (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm), ¹H NMR and ¹³C NMR spectra were recorded on Bruker DRX-400, DRX-600 MHz. Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants *J* are given in Hz. The spectra were recorded in CDCl₃ as solvent at room temperature, TMS served as internal standard (δ = 0 ppm) for ¹H NMR, and CDCl₃ was used as internal standard (δ = 77.0 ppm) for ¹³C NMR. HPLC was carried out using a Hitachi organizer consisting of a D-2500 Chromato-Integrator, a L-4000 UV-Detector, and a L-6200A Intelligent Pump. Optical rotations were recorded on a Perkin Elemer 241 Polarimeter (λ =589 nm, 1 dm cell). High-resolution mass spectra were recorded on an IonSpec FTMS mass spectrometer with a DHB-matrix.

(*E*)-3-(4-bromophenyl)-2-methylacrylaldehyde (5): Method A. To a solution of dimethylammonium dimethyl carbamate (DIMCARB) (3 mL) and 4-bromobenzaldehyde (1.74 g, 9.4 mmol) in round-bottom flask was added propionaldehyde (1.36 mL, 18.6 mmol) and stirred at room temperature for 48 h. Then, DIMCARB was removed by distillation and the residue was diluted with 0.5 M H₂SO₄. The aqueous layer was extracted with CH₂Cl₂ and the combined organic phases were dried (Na₂SO₄), concentrated, and purified by flash column

chromatography (silica gel, hexanes/ethyl acetate = 95:5) to afford the desired product **5** (1.692 g, 80% yield). ¹H NMR (CDCl₃, 400 MHz): δ 2.05 (d, *J* = 0.9 Hz, 3H), 7.20 (s, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 9.58 (s, 1H).

Method B: To a cooled stirring solution of 4-bromobenzaldehyde (18.5 g, 0.1 mol) in MeOH (20 mL) 10% aqueous NaOH (4 mL) was added followed by slow addition of propionaldehyde (5.6 mL, 0.12 mol) over 3 h at room temperature. Then reaction mixture was stirred for an additional 2 h and cooled to 0 °C and quenched with 1 N HCl (15 mL). The precipitated solid was filtered and purified by flash column chromatography (silica gel, hexanes/ethyl acetate = 95:5) to afford the desired product **5** (17.55 g, 78% yield).

3-(4-bromophenyl)-2-methylpropan-1-ol (6): To a three neck round-bottom flask with LiAlH₄ (101.7 mmol, 1M ether solution) at 0 °C under N₂ was added aldehyde **5** (14.575 g, 64.78 mmol) in THF (300 mL) followed by AlCl₃ (34.98 mmol). The reaction temperature was increased to 65 °C and stirred for 11 h. The reaction was cooled to 0 °C and quenched with 2 N HCl (270 mL). Two layers are separated. The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic phases were dried (Na₂SO₄), concentrated, and purified by flash column chromatography (silica gel, hexanes/ethyl acetate = 70:30) to afford the desired product **6** (12.609 g, 85% yield). ¹H NMR (CDCl₃, 400 MHz): δ 0.90 (d, *J* = 8.0 Hz, 3H), 1.91 (m, 1H), 2.38 (dd, *J* = 12.0, 8.0 Hz, 1H), 2.74 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.50 (d, *J* = 4.0 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H).

3-(4-bromophenyl)-2-methylpropanal (4): To a three neck round-bottom flask with oxalyl chloride (5.475 mL, 60.34 mmol) in CH₂Cl₂ (125 mL) at -60 °C under N₂ was added DMSO (9.308 mL, 120.68 mmol) in CH₂Cl₂ (66 mL) followed by alcohol **6** (12.562 g, 54.85 mmol) in CH₂Cl₂ (55 mL) and stirred for 30 min. Et₃N (38.38 mL, 274.27 mmol) was added and the reaction mixture was stirred for 5 min and then allowed to warm to room temperature. The combined organic phases were washed with water and dried (Na₂SO₄), concentrated, and purified by flash column chromatography (silica gel, hexanes/ethyl acetate = 95:5) to afford the desired product **4** (11.828 g, 95% yield). ¹H NMR (CDCl₃, 400 MHz): δ 1.09 (d, *J* = 7.0 Hz, 3H), 2.55 (dd, *J* = 13.5, 8.2 Hz, 1H), 2.63 (m, 1H), 3.04 (dd, *J* = 13.5, 5.9 Hz, 1H), 7.04 (d, *J* =

8.2 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 9.70 (d, J = 1.5 Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 13.2, 35.9, 47.9, 120.3, 130.8, 131.6, 137.9, 203.9.

(*R*)-3-(4-bromophenyl)-2-(1,2-benzyloxycarbonylhydrazinyl)-2-methylpropanal (3): To a glass vial charged with (*S*)-5-(pyrrolidin-2-yl)-1H-tetrazole (104 mg, 0.75 mmol) was added CH_3CN (10 mL) followed by bis dibenzyl azodicarboxylate (1.59 g, 5 mmol), aldehyde **4** (1.703 g, 7.5 mmol) and the reaction was stirred at room temperature until completion as monitored by TLC (3 h). Then, a half saturated NH_4Cl solution and ethyl acetate were added with vigorous stirring, the layers were separated and the organic phase was washed with water. The combined organic phases were dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, hexanes/ethyl acetate = 70:30) to afford the desired product **3** (2.489 g, 95% yield). Recrystallization from hexanes/ethyl acetate (70:30) furnished the mother liquor with >99% ee (71% yield). $[\alpha]_D^{25} = 82.0$ (c = 1.0, CHCl_3); NMR spectrum exists as a mixture of rotamers at room temperature (CDCl_3 , 600 MHz, 50 °C): δ 1.15 (s, 3H), 2.83 (bs, 1H), 3.28 (bs, 1H), 5.04 – 5.21 (m, 4H), 6.76 (bs, 2H), 7.31 (m, 12H), 9.67 (bs, 1H); ^{13}C NMR (CDCl_3 , 150 MHz, 50 °C) δ 18.28, 37.41, 68.18, 70.27, 128.20, 128.47, 128.54, 128.58, 128.64, 131.78, 131.86, 135.32, 150.25, 155.58, 193.30; HRMS for $\text{C}_{26}\text{H}_{26}\text{BrN}_2\text{O}_5$ (MH^+): calcd 525.1027, obsd 525.1018; HPLC (Daicel Chirapak AS-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL/min, λ = 254 nm): t_R = 26.14 min (major), t_R = 33.36 min (minor).

(*R*)-3-(4-bromophenyl)-2-(1,2-benzyloxycarbonylhydrazinyl)-2-methylpropanoic acid (7): To a solution of amino aldehyde **3** (695 mg, 1.326 mmol) in *t*-BuOH- H_2O (5:1, 14 mL) at 4 °C NaClO_2 (5.30 mmol), NaH_2PO_4 (318 mg, 2.65 mmol) and 2-methyl-2-butene (5.3 mL of 2M THF solution, 10.61 mmol) was added and stirred for 12 h. After completion of the reaction as monitored by TLC the solvent was removed under vacuum. The crude material was extracted with ethyl acetate and washed with brine and water. The combined organic phases were dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, methanol/ethyl acetate = 5:95) to afford the corresponding acid **7** as a white solid (616 mg, 86% yield). $[\alpha]_D^{25} = 10.2$ (c = 0.5, MeOH); ^1H NMR (CD_3OD , 600 MHz, 50 °C): δ 1.71 (s, 3H), 3.37 (d, J = 13.2 Hz, 1H), 3.55 (bs, 1H), 5.40 – 5.48 (m, 5H), 7.29 (d, J = 7.8 Hz, 2H), 7.61 (m, 10H),

7.66 (d, $J = 7.8$ Hz, 2H); ^{13}C NMR (CD_3OD , 150 MHz, 50 °C) δ 21.35, 28.61, 69.17, 68.47, 69.42, 121.99, 129.10, 129.36, 129.56, 131.93, 132.39, 133.59, 134.12, 136.43, 137.32, 156.59, 175.78; HRMS for $\text{C}_{26}\text{H}_{25}\text{BrN}_2\text{O}_6\text{Na}$ (MNa^+): calcd 563.0788, obsd 563.0788.

(R)-Methyl 3-(4-bromophenyl)-2-(1,2-benzyloxycarbonylhydrazinyl)-2-methylpropanoate (8): To a solution of amino acid **7** (471 mg, 0.872 mmol) in toluene-MeOH (2:1, 20 mL) (trimethylsilyl)diazomethane (0.872 mL of 2 M solution in hexanes, 1.744 mmol) was added and stirred at room temperature for 10 min. Then the excess of trimethyl silyl diazomethane was quenched by drop wise addition of acetic acid. The solvent was removed under vacuum and the residue was purified by flash column chromatography (silica gel, hexanes/ethyl acetate = 70:30) to afford the desired product **8** (478 mg, 99% yield). $[\alpha]_D^{25} = 42.8$ ($c = 1$, CHCl_3); ^1H NMR (CDCl_3 , 600 MHz, 50 °C): δ 1.40 (s, 3H), 2.97 (bs, 1H), 3.26 (bs, 1H), 3.57 (s, 3H), 5.06 – 5.16 (m, 4H), 6.83 (bs, 1H), 7.29 (m, 14H); ^{13}C NMR (CDCl_3 , 150 MHz, 50 °C) δ 21.06, 41.21, 52.24, 67.94, 68.40, 107.95, 128.29, 128.12, 128.36, 128.54, 131.69, 131.95, 134.98, 135.65, 154.95, 156.19, 173.04; HRMS for $\text{C}_{27}\text{H}_{27}\text{BrN}_2\text{O}_6\text{Na}$ (MNa^+): calcd 577.0945, obsd 577.0941.

(R)-Methyl 3-(4-bromophenyl)-2-methyl-2-(1-benzyloxycarbonyl-2-(2,2,2-trifluoroacetyl)hydrazinyl)propanoate (9): A solution of amino acid ester **8** (453 mg, 0.817 mmol) in pyridine (2 mL) was heated at 40 °C for 18 h. Then the reaction was cooled to 0 °C and trifluoroacetic anhydride (0.596 mL, 4.29 mmol) was added and stirred at room temperature for 48 h. The volatiles were removed under vacuum and the residue was purified by flash column chromatography (silica gel, hexanes/ethyl acetate = 70:30) to afford the desired product **9** (417 mg, 99% yield). $[\alpha]_D^{25} = 14.3$ ($c = 1$, CHCl_3); ^1H NMR (CDCl_3 , 600 MHz, 50 °C): δ 1.43 (s, 3H), 3.12 (bs, 1H), 3.37 (bs, 1H), 3.64 (s, 3H), 5.13 (d, $J = 12.0$ Hz, 1H), 5.22 (d, $J = 12.0$ Hz, 1H), 6.94 (bs, 2H), 7.30 – 7.37 (m, 7H); ^{13}C NMR (CDCl_3 , 150 MHz, 50 °C) δ 21.24, 41.08, 52.66, 67.83, 69.08, 114.59, 116.51, 121.60, 128.33, 128.67, 128.71, 131.66, 132.20, 134.29, 135.09, 156.60, 156.85, 172.92; HRMS for $\text{C}_{21}\text{H}_{20}\text{BrF}_3\text{N}_2\text{O}_5\text{Na}$ (MNa^+): calcd 539.0408, obsd 539.0405.

(R)-Methyl 2-(benzyloxycarbonyl)-3-(4-bromophenyl)-2-methylpropanoate (2): To a solution of amino acid ester **9** (361 mg, 0.7 mmol) in MeOH (1.4 mL) 0.1 M solution of samarium iodide in THF (47.5 mL) was added under N₂ and stirred at room temperature for 30 min. The volatiles were removed under vacuum and the residue was purified by flash column chromatography (silica gel, hexanes/ethyl acetate = 70:30) to afford the desired product **2** (278 mg, 98% yield). $[\alpha]^{25}_{\text{D}} = -44.1$ ($c = 1$, CHCl₃); ¹H NMR (CDCl₃, 600 MHz, 50 °C): δ 1.61 (s, 3H), 3.13 (d, $J = 13.8$ Hz, 1H), 3.38 (d, $J = 13.8$ Hz, 1H), 3.72 (s, 3H), 5.07 (d, $J = 12.6$ Hz, 1H), 5.15 (d, $J = 12.6$ Hz, 1H), 5.38 (bs, 1H), 6.83 (d, $J = 7.8$ Hz, 2H), 7.28 (d, $J = 8.4$ Hz, 2H), 7.35 (m, 5H); ¹³C NMR (CDCl₃, 125 MHz, 50 °C) δ 23.80, 41.11, 52.59, 60.78, 66.53, 121.02, 128.20, 128.52, 131.36, 131.55, 135.25, 136.66, 154.62, 173.78; HRMS for C₁₉H₂₀BrNO₄Na (MNa⁺): calcd 428.0468, obsd 428.0470.

(R)-Methyl 2-amino-3-(4-bromophenyl)-2-methylpropanoate (10): To a solution of amino acid ester **2** (156 mg, 0.385 mmol) in AcOH (1.0 mL) 33% HBr in AcOH solution (0.7 mL) was added and stirred at room temperature for 24 h. The volatiles were removed under vacuum and the residue was diluted with ethyl acetate and water. The aqueous layer was neutralized with sat aq NaHCO₃ solution and extracted with CH₂Cl₂ (3 x 5 mL). The combined organic phases were dried (Na₂SO₄) and concentrated to afford the pure product **10** (103 mg, 99% yield). $[\alpha]^{25}_{\text{D}} = 17.4$ ($c = 1$, CHCl₃); ¹H NMR (CDCl₃, 400 MHz): δ 1.39 (s, 3H), 1.80 (bs, 2H), 2.77 (d, $J = 13.2$ Hz, 1H), 3.08 (d, $J = 13.2$ Hz, 1H), 3.70 (s, 3H), 7.03 (d, $J = 8.4$ Hz, 2H), 7.41 (d, $J = 8.4$ Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 26.43, 46.09, 52.22, 58.78, 121.06, 131.44, 131.64, 135.41, 177.08; HRMS for C₁₁H₁₅BrNO₂ (MH⁺): calcd 272.0281, obsd 272.0274.

(R)-5-(4-bromobenzyl)-3-(3,5-dichlorophenyl)-5-methylimidazolidine-2,4-dione (11): A solution of amine **10** (87 mg, 0.321 mmol) and 3,5-dichlorophenyl isocyanate (60 mg, 0.321 mmol) in dry DMSO (0.6 mL) was stirred at room temperature for 1 h. Then sodium carbonate (68 mg, 0.642 mmol) was added and stirred at 120 °C for 12 h. The reaction mixture was brought to room temperature and diluted with ethyl acetate and washed with water and aq NH₄Cl solution. The organic phase was dried (Na₂SO₄), concentrated, and purified by flash column chromatography (silica gel, hexanes/ethyl acetate = 70:30) to afford the desired product

11 (135 mg, 99% yield). $[\alpha]_D^{25} = 119.5$ ($c = 0.86$, CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz): δ 1.61 (s, 3H), 2.92 (d, $J = 13.6$ Hz, 1H), 3.14 (d, $J = 13.6$ Hz, 1H), 5.84 (bs, 1H), 7.01 (d, $J = 1.6$ Hz, 2H), 7.07 (d, $J = 8.4$ Hz, 2H), 7.34 (t, $J = 1.6$ Hz, 1H), 7.46 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 29.7, 43.7, 62.5, 122.1, 124.5, 128.5, 132.8, 131.7, 132.7, 135.2, 154.0, 174.0; HRMS for $\text{C}_{17}\text{H}_{12}\text{BrCl}_2\text{N}_2\text{O}_2$ ($\text{M}-\text{H}^+$): calcd 424.9465, obsd 424.9445.

(R)-5-(4-bromobenzyl)-3-(3,5-dichlorophenyl)-1,5-dimethylimidazolidine-2,4-dione (1): To a solution of hydantoin **11** (118 mg, 0.2769 mmol) in DMF (1 mL) at 4 °C lithium bi(trimethylsilyl)amide (0.321 mmol of 1M THF solution) followed by iodomethane (26 μL , 0.415 mmol) were added and stirred at room temperature for 3 h. The reaction mixture was diluted with water and extracted with ethyl acetate (3 x 5 mL). The combined organics were washed with aq NH_4Cl solution and dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, hexanes/ethyl acetate = 70:30) to afford the desired product **1** (115 mg, 94% yield). $[\alpha]_D^{25} = 131.6$ ($c = 1.0$, EtOH); HPLC (Daicel Chirapak AD, hexane/EtOH/ Et_2NH = 300:10:1, flow rate 1.0 mL/min, $\lambda = 254$ nm): $t_R = 15.62$ min, (+) **1** (BIRT-377); $t_R = 17.23$ min (-) **1**; ^1H NMR (CDCl_3 , 400 MHz): δ 1.63 (s, 3H), 2.97 (d, $J = 14.0$ Hz, 1H), 3.08 (s, 3H), 3.10 (d, $J = 15.2$ Hz, 1H), 6.84 (d, $J = 2.0$ Hz, 2H), 6.94 (d, $J = 8.4$ Hz, 2H), 7.29 (t, $J = 2.0$ Hz, 1H), 7.42 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 21.0, 25.3, 40.7, 65.6, 121.9, 124.5, 128.3, 131.1, 131.8, 132.8, 133.0, 135.0, 153.4, 173.3; HRMS for $\text{C}_{18}\text{H}_{16}\text{BrCl}_2\text{N}_2\text{O}_2$ (MH^+): calcd 440.9767, obsd 440.9759.