Rhodium-catalyzed Enantioselective Hydrogenation of β -phthalimide

Acrylates to synthesis of β^2 -Amino Acids

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Instruments and Materials

All solvents were dried and degassed by standard methods and stored under nitrogen. All the commercially available catalysts and ligands were brought from Strem Chemicals and without further purification. ManniPhos were synthesized according to the procedures reported previously.¹ All reactions were carried out under an atmosphere of nitrogen using the standard Schlenk techniques or in a nitrogen-filled glovebox, unless otherwise noted.

NMR spectra were recorded on BRUKER DRX 400 spectrometers. Chemical shifts are reported in parts per million (ppm) down field from TMS with the solvent resonance as the internal standard. Coupling constants (*J*) are reported in Hz and refer to apparent peak multiplications. High resolution mass spectra (HRMS) were recorded on Applied Biosystems Mariner System 5303. GC analysis was performed on an Agilent HP-4890 GC instrument with FID as detector. Enantiomeric excess (ee) were determined by HPLC analysis on an Agilent HP-1120. Melting points were determined using a Mettler FP5 melting apparatus in open capillaries and were uncorrected. Optical rotations were measured on a JASCO, P-1020 high sensitive polarimeter.

General Procedure for the Preparation of Acrylates (2a-2b)

Scheme 1. The general method for preparation of the acrylates (**2a-2b**)

Ethyl 2-(hydroxy-methyl) acrylate (**10a**)²

To a stirred suspension of *para*-formaldehyde (33.0 g, 1.1mol) in water (100 ml) was added 1N H_3PO_4 (4 ml). The mixture was heated to 90 °C for 1.5h. After the

solution was cooled to room temperature, THF (100 ml), ethyl acrylate (109 ml, 1.0 mol), and DABCO (11.3g, 0.1 mol) were added, and the reaction mixture was stirred at room temperature for 36 h. To the reaction mixture sodium chloride (35 g) and ether (100 ml) were added. The organic layers were separated and then the product was extracted from the aqueous layers with ether, the combined organic layers were washed with brine and dried over magnesium sulfate, the solvents were evaporated under reduced pressure and the residue was distilled under vacuum, giving 104 g of **10a** with 80% yield.

Ethyl 2-(acetoxymethyl)acrylate (11a**)³**

A stirred mixture of ethyl 2-(hydroxyl-methyl)acrylate **10a** (10 g, 77 mmol) and pyridine (6.7g, 85 mmol) in CH₂Cl₂ (75 ml) was cooled to 0 °C, then acetyl chloride (7.9 g, 100 mmol) was added dropwise. The cold bath was removed after 5 min. The mixture was stirred at room temperature for 24 h, hydrolyzed and extracted with ether (100 ml). The ethereal solution was washed with water, aqueous saturated solution of NH₄Cl, brine and dried over MgSO₄. The solvent was evaporated giving **11a** as colorless oil (11.8 g, 89% yield).

Ethyl 2-(phthalimidomethyl)acrylate(2a**)⁴**

To the suspension of potassium phthalimide (2.35 g, 12.7 mmol) in dry DMF (50 ml) was added the solution of ethyl 2-(acetoxymethyl)acrylate **11a** (2.2g, 12.7 mmol) in dry DMF (10 ml). The reaction was run at room temperature and monitored by TLC. After the reaction was complete, the reaction mixture was poured into water and extracted with ether and concentrated in vacuum leaving a white solid, which was recrystallized with ethyl acetate/ hexane (1/4) giving the desired compound **2a** in 70.3% yield. Mp: 87-88 °C; ¹H NMR (400 MHz, CDCl₃): δ 1.29 (t, *J* = 7.2 Hz, 3H), 4.22 (q, *J* = 3.2 Hz, 2H), 4.57 (s, 2H), 5.57 (s, 1H), 6.33 (s, 1H), 7.74 (dd, *J* = 5.4, 2.8 Hz, 2H), 7.87 (dd, *J* = 5.4, 3.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 14.8, 39.0, 61.7, 124.1, 126.5, 132.6, 134.8, 135.3, 165.9, 168.8; HRMS (APCI) calcd for C₁₄H₁₄NO₄[M+1]: 260.0917, found: 260.0903.

Methyl 2-(phthalimidomethyl)acrylate (**2b**)

In a manner similar to that described for **2a**, the compound **2b** was prepared as a white solid. Mp: 99-100 °C; ¹H NMR (400 MHz, CDCl₃): δ 3.80 (s, 3H), 4.57 (s, 2H), 5.59 (s, 1H), 6.33 (s, 1H), 7.74 (dd, *J* = 5.4, 2.8 Hz, 2H), 7.87 (dd, *J* = 5.4, 3.2 Hz, 2H); ¹³C NMR (100 MHz): δ 38.9, 52.8, 124.2, 126.7, 132.6, 134.8, 135.0, 166.4, 168.3; HRMS (APCI) calcd for C₁₃H₁₂NO₄[M+1]: 246.0761, found: 246.0755.

General Procedure for the Preparation of Acrylates (**2c-2j**)

Scheme 2. The general method for preparation of the acrylates (**2c-2j**)

(*E*)-Methyl 2-(phthalimidomethyl)-3-phenyl-acrylate (**2c**)

Methyl 3-hydroxy-3-phenyl-acrylate (**12c**)⁵

Methyl acrylate (15.0 g, 0.174 mol) and benzaldehyde (15.0 g, 0.141 mol) were stirred in the presence of DABCO (15.9 g, 0.141 mol) for 24 h at room temperature. The reaction mixture was diluted with ether and washed successively with HCl, NaHCO₃ and H₂O. The organic layer was dried over Na₂SO₄, and then removing the excess methyl acrylate and solvent. The crude product was purified by flash chromatography to give the desired product Methyl 3-hydroxy-3-phenyl-acrylate **12c** (23.1 g) in 85.1% yield.

(*Z*)-Methyl 2-(bromomethyl)-3-phenyl-acrylate (**13c**)⁶

To the 3-hydroxy-2-methylene-3-phenylpropanoic acid methyl ester (3.84 g, 0.02 mol) was added aq.HBr (48%, 20 g) and concentrated H₂SO₄ (98%, 1 ml). After the

resulting mixture was stirred at room temperature overnight □ the reaction mixture was washed with brine and extracted with ether and concentrated in vacuum, flash chromatography gave the desired product (Z)-methyl 2-(bromomethyl)-3-phenyl-acrylate **13c** (4.6 g) in 90% yield. ¹H NMR (400 MHz, CDCl₃): δ 3.89 (s, 3H), 4.40 (s, 2H), 7.33-7.49 (m, 3H), 7.57-7.58 (d, *J* = 7.6 Hz, 2H), 7.84 (s, 1H).

(E)-Methyl 2-(phthalimidomethyl)-3-phenyl-acrylate (2c)⁴

To the suspension of potassium phthalimide (1.85 g, 10.0 mmol) in dry DMF (10 ml) was added the solution of (Z)-2-(bromomethyl)-3-phenyl-methyl acrylate (2.55g, 10.0 mmol) in dry DMF (10 ml). The reaction was run at room temperature and monitored by TLC. After the reaction was complete, the reaction mixture was poured into water and extracted with ether and concentrated in vacuum leaving a white solid, which was recrystallized with ethyl acetate/ hexane (1/4) to giving the desired compound **2c** (2.5 g) in 77.8% yield. Mp: 112-113 °C; ¹H NMR (400 MHz, CDCl₃): δ 3.76 (s, 3H), 4.76 (s, 2H), 7.29-7.30 (m, 1H), 7.35-7.39 (m, 2H), 7.47 (d, *J* = 7.2 Hz, 2H), 7.66 (dd, *J* = 5.4, 2.8 Hz, 2H), 7.77 (dd, *J* = 5.4, 3.2 Hz, 2H), 7.96 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 36.4, 52.8, 123.8, 127.1, 129.1, 129.3, 129.6, 132.6, 134.5, 135.3, 143.9, 167.6, 168.5; HRMS (APCI) calcd for C₁₉H₁₆NO₄[M+1]: 322.1074, found: 322.1057.

In a manner similar to that described for **2c**, the compounds **2d-2j** were prepared in 50-60% yield from three steps.

(E)-Methyl 2-(phthalimidomethyl)-3-(4-chlorophenyl)-acrylate (2d)

Mp: 133-134 °C; ¹H NMR (400 MHz, CDCl₃): δ 3.76 (s, 3H), 4.72 (s, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.68 (dd, *J* = 5.4, 2.8 Hz, 2H), 7.78 (dd, *J* = 5.4, 3.2 Hz, 2H), 7.88 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 36.3, 52.9, 123.9, 127.7, 129.5, 131.0, 132.6, 133.7, 134.6, 135.4, 142.6, 167.4, 168.5; HRMS (APCI) calcd for C₁₉H₁₅NO₄Cl[M+1]: 356.0684, found: 356.0696.

(E)-Methyl 2-(phthalimidomethyl)-3-(4-fluorophenyl)-acrylate (2e)

Mp: 142-143 °C ^1H NMR (400 MHz, CDCl_3): δ 3.76 (s, 3H), 4.73 (s, 2H), 7.04 (t, $J=8.8$ Hz, 2H), 7.48 (dd, $J=8.4$, 5.6 Hz, 2H), 7.68 (dd, $J=5.6$, 3.2 Hz, 2H), 7.79 (dd, $J=5.4$, 3.2 Hz, 2H), 7.90 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 36.3, 52.9, 116.2, 116.4, 123.9, 127.1, 131.3, 131.7, 131.8, 132.6, 134.6, 142.8, 162.2, 164.7, 167.5, 168.5; HRMS (APCI) calcd for $\text{C}_{19}\text{H}_{15}\text{NO}_4\text{F}[\text{M}+1]$: 340.0980, found: 340.0960.

(E)-Methyl 2-(phthalimidomethyl)-3-(4-trifluoromethylphenyl)-acrylate (2f)

Mp: 94-95 °C ^1H NMR (400 MHz, CDCl_3): δ 3.79 (s, 3H), 4.70 (s, 2H), 7.54-7.59 (m, 4H), 7.67 (dd, $J=5.2$, 3.2 Hz, 2H), 7.74 (m, 2H), 7.94 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 36.3, 53.1, 123.9, 124.3, 126.1, 129.1, 129.6, 132.5, 134.7, 135.0, 139.0, 141.9, 167.1, 168.4; HRMS (APCI) calcd for $\text{C}_{20}\text{H}_{15}\text{NO}_4\text{F}_3[\text{M}+1]$: 390.0948, found: 390.0956.

(E)-Methyl 2-(phthalimidomethyl)-3-(2-methoxyphenyl)-acrylate (2g)

Mp 131-132 °C; ^1H NMR (400 MHz, CDCl_3): δ 3.75 (s, 3H), 3.83 (s, 3H), 4.70 (s, 2H), 6.85 (d, $J=8.4$ Hz, 1H), 6.94 (m, 1H), 7.27 (m, 1H), 7.48 (d, $J=7.6$ Hz, 1H), 7.65 (dd, $J=5.4$, 3.0 Hz, 2H), 7.76 (dd, $J=5.2$, 3.2 Hz, 2H), 8.00 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 36.5, 52.6, 56.0, 111.2, 120.9, 123.6, 124.2, 127.2, 130.4, 130.8, 132.6, 134.3, 140.3, 157.8, 167.4, 168.3; HRMS (APCI) calcd for $\text{C}_{20}\text{H}_{18}\text{NO}_5[\text{M}+1]$: 352.1180, found: 352.1176.

(E)-Methyl 2-(phthalimidomethyl)-3-(4-methylphenyl)-acrylate (2h)

Mp: 90-91 °C; ^1H NMR (400 MHz, CDCl_3): δ 2.32 (s,

3H), 3.75 (s, 3H), 4.77 (s, 2H), 7.16 (d, $J = 8.0$ Hz, 2H), 7.37 (d, $J = 8.0$ Hz, 2H), 7.66 (dd, $J = 5.4, 3.0$ Hz, 2H), 7.77 (dd, $J = 5.4, 3.0$ Hz, 2H), 7.92 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 21.9, 36.4, 52.7, 123.8, 126.2, 129.8, 129.9, 132.4, 132.7, 134.4, 139.6, 144.0, 167.8, 168.5; HRMS (APCI) calcd for $\text{C}_{20}\text{H}_{18}\text{NO}_4[\text{M}+1]$: 336.1230, found: 336.1207.

(*E*)-Methyl 2-(phthalimidomethyl)-3-(2-thienyl)-acrylate (2i)

Mp: 144-145 °C; ^1H NMR (400 MHz, CDCl_3): δ 3.76 (s, 3H), 4.92 (s, 2H), 7.11 (t, $J = 4.0$ Hz, 1H), 7.41 (d, $J = 2.8$ Hz, 1H), 7.53 (d, $J = 4.8$ Hz, 1H), 7.68 (dd, $J = 5.0, 3.0$ Hz, 2H), 7.81 (s, 2H), 8.04 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 36.7, 52.8, 122.5, 123.8, 128.1, 131.0, 132.7, 134.3, 134.5, 136.1, 137.8, 167.9, 168.4; HRMS (APCI) calcd for $\text{C}_{17}\text{H}_{14}\text{NO}_4\text{S}[\text{M}+1]$: 328.0638, found: 328.0624.

(*E*)-Methyl 2-(phthalimidomethyl)-4-methyl-pent-2-enoate (2j)

Mp: 105-106 °C; ^1H NMR (400 MHz, CDCl_3): δ 1.09 (d, $J = 6.8$ Hz, 6H), 3.03 (m, 1H), 3.71 (s, 3H), 4.57 (s, 2H), 6.79 (d, $J = 6.8$ Hz, 1H), 7.69 (dd, $J = 5.4, 3.0$ Hz, 2H), 7.82 (dd, $J = 5.4, 3.0$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 22.6, 28.8, 34.8, 52.5, 123.8, 124.2, 132.7, 134.5, 155.0, 167.8, 168.4; HRMS (APCI) calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_4[\text{M}+1]$: 288.1230, found: 288.1213.

General procedure for asymmetric hydrogenation

In a nitrogen-filled glovebox, to a solution of $[\text{Rh}(\text{COD})_2]\text{BF}_4$ (2.0 mg, 0.005 mmol) in anhydrous and degassed CH_2Cl_2 (1 mL) was added ligand **9g** (0.011 mmol). After stirring the mixture for 30 min, a substrate (0.5 mmol) dissolved in CH_2Cl_2 (1 mL) was added. The reaction mixture was transferred to a Parr stainless autoclave. The autoclave was purged three times with hydrogen and the pressure was set to the desired pressure, the hydrogenation was performed at room temperature for 12 h. After carefully

releasing the hydrogen, the solvent was removed. Conversion was directly determined by GC or ^1H NMR spectroscopy. The enantiomeric excess was determined by HPLC after purification on silica gel. The absolute configuration of the product was determined by measurement of its optical rotation and comparison to the literature value.

Ethyl 2-(phthalimidomethyl)-propanoate (3a)

White solid, Mp: 63-64 °C; ^1H NMR (400 MHz, CDCl_3): δ 1.16-1.22 (m,

6H), 2.95 (m, 1H), 3.74 (dd, $J = 13.6, 6.8$ Hz, 1H), 3.95 (dd, $J = 13.6, 7.6$ Hz, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 7.72 (dd, $J = 5.2, 2.8$ Hz, 2H), 7.85 (dd, $J = 5.2, 3.2$

Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.7, 15.3, 39.1, 41.2, 61.5, 124.0, 132.6, 134.7, 168.8, 174.6; HRMS (APCI) calcd for $\text{C}_{14}\text{H}_{16}\text{NO}_4$ [$\text{M}+1$]: 262.1074, found: 262.1058; $[\alpha]_{\text{D}}^{25} = -19.6$ (c 0.17, CH_2Cl_2) for 99.1% ee; HPLC (UV 254 nm, Chiralcel OD-H (0.46 cm x 25 cm), Ethanol/Hexane = 2/98, 0.7 mL/min), $t_1 = 15.2$ min, $t_2 = 16.4$ min.

Methyl 2-(phthalimidomethyl)-propanoate (3b)

White solid, Mp: 89-90 °C; ^1H NMR (400 MHz, CDCl_3):

δ 1.21 (d, $J = 7.2$ Hz, 3H), 2.97-2.99 (m, 1H), 3.67 (s, 3H), 3.76 (dd, $J = 14.0, 6.8$ Hz, 1H), 3.95 (dd, $J = 13.6, 7.6$ Hz, 1H), 7.72 (dd, $J = 5.4, 3.0$ Hz, 2H), 7.85 (dd, $J = 5.4, 3.0$ Hz,

2H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.3, 39.1, 41.2, 52.6, 124.0, 132.6, 134.7, 168.8, 175.0; HRMS (APCI) calcd for $\text{C}_{13}\text{H}_{14}\text{NO}_4$ [$\text{M}+1$]: 248.0917, found: 248.0929; $[\alpha]_{\text{D}}^{25} = -19.7$ (c 0.97, CHCl_3) for 98.3% ee, (*R*); lit.⁷ $[\alpha]_{\text{D}}^{25} = -17.2$ (c 0.95, CHCl_3) for 84% ee, (*R*); HPLC (UV 254 nm, Chiralcel OD-H (0.46 cm x 25 cm), Ethanol/Hexane = 8/92, 0.5 mL/min), $t_1 = 15.6$ min, $t_2 = 17.7$ min.

Methyl 2-(phthalimidomethyl)-3-phenyl-propanoate (3c)

White solid, Mp: 89-90 °C; ^1H NMR (400 MHz, CDCl_3): δ 2.83 (dd, $J = 14.0, 6.4$ Hz, 1H), 3.05 (dd, $J = 13.2, 7.6$ Hz, 1H), 3.28 (m, 1H), 3.58 (s, 3H), 3.84 (dd, $J = 14.0, 6.0$ Hz, 1H), 3.98 (dd, $J = 13.8, 8.2$ Hz, 1H), 7.13-7.25 (m, 5H), 7.69-7.72 (m, 2H), 7.80 (dd, $J = 5.2, 3.2$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 36.6, 40.2, 46.4, 52.7, 124.0, 127.2, 129.1, 129.4, 132.5, 134.7, 138.7, 168.7, 173.9; HRMS (APCI) calcd for $\text{C}_{19}\text{H}_{18}\text{NO}_4$ [$\text{M}+1$]: 324.1230, found: 324.1205. $[\alpha]_{\text{D}}^{25} = +5.5$ (c 0.8, CH_2Cl_2) for 92% ee; HPLC (UV 254 nm, Chiralcel OD-H (0.46 cm x 50 cm), i-PrOH/Hexane = 1/99, 1.0 mL/min), $t_1 = 104.7$ min, $t_2 = 109.9$ min.

Methyl 2-(phthalimidomethyl)-3-(4-chlorophenyl)-propanoate (3d)

^1H NMR (400 MHz, CDCl_3): δ 2.79 (m, 1H), 3.01 (m, 1H), 3.22-3.25 (m, 1H), 3.59 (s, 3H), 3.84-3.96 (m, 2H), 7.11-7.17 (m, 4H), 7.70 (m, 2H), 7.81 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 35.8, 40.1, 46.3, 52.7, 124.0, 129.2, 130.7, 132.5, 133.0, 134.8, 137.2, 168.7, 176.6; HRMS (APCI) calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_4\text{Cl}$ [$\text{M}+1$]: 358.0841, found: 358.0829. $[\alpha]_{\text{D}}^{25} = +10.6$ (c 0.42, CH_2Cl_2) for 86.4% ee; HPLC (UV 254 nm, Chiralcel OD-H (0.46 cm x 50 cm), i-PrOH/Hexane = 15/85, 1.0 mL/min), $t_1 = 36.5$ min, $t_2 = 43.0$ min.

Methyl 2-(phthalimidomethyl)-3-(4-fluorophenyl)-propanoate (3e)

White solid, Mp: 76-77 °C; ^1H NMR (400 MHz, CDCl_3): δ 2.80 (dd, $J = 14.2, 6.2$ Hz, 1H), 3.00 (dd, $J = 13.8, 8.6$ Hz, 1H), 3.20-3.24 (m, 1H), 3.59 (s, 3H), 3.84 (dd, $J = 13.6, 6.0$ Hz, 1H), 3.97 (dd, $J = 14.0, 8.0$ Hz, 1H), 6.89-6.94 (m, 2H), 7.14-7.17 (m, 2H), 7.71 (dd, $J = 8.4, 3.6$ Hz, 2H), 7.81 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 35.7, 40.1, 46.5, 52.7, 115.8, 116.0, 124.0, 130.8, 130.9, 132.5, 134.3, 134.7, 161.0, 163.5, 168.6, 173.7; HRMS (APCI) calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_4\text{F}$ [$\text{M}+1$]: 342.1136, found: 342.1133. $[\alpha]_{\text{D}}^{25} = +4.8$ (c 0.41, CH_2Cl_2) for

95.9% ee; HPLC (UV 254 nm, Chiralcel OD-H (0.46 cm x 50 cm), i-PrOH/Hexane = 15/85, 1.0 mL/min), t_1 = 33.9 min, t_2 = 38.7 min.

Methyl 2-(phthalimidomethyl)-3-(4-trifluoromethylphenyl)-propanoate (3f)

White solid, Mp: 70-71 °C; ^1H NMR (400 MHz, CDCl_3):

δ 2.88 (dd, J = 14.0, 6.8 Hz, 1H), 3.12 (dd, J = 14.0, 8.4 Hz, 1H), 3.30-3.33 (m, 1H), 3.61 (s, 3H), 3.89 (dd, J = 14.0, 6.4 Hz, 1H), 3.99 (dd, J = 13.6, 7.6 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.70 (dd, J = 5.2, 3.2 Hz, 2H), 7.80 (dd, J = 5.0, 2.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3):

δ 36.8, 40.7, 46.5, 53.4, 124.5, 124.8, 126.5, 129.9, 130.2, 132.9, 135.3, 135.5, 143.4, 169.2, 174.0; HRMS (APCI) calcd for $\text{C}_{20}\text{H}_{17}\text{NO}_4\text{F}_3$ [$\text{M}+1$]: 392.1104, found: 392.1087. 94.6% ee; HPLC (UV 254 nm, Chiralcel OD-H (0.46 cm x 50 cm), i-PrOH/Hexane = 5/95, 1.0 mL/min), t_1 = 27.3 min, t_2 = 31.7 min.

Methyl 2-(phthalimidomethyl)-3-(2-methoxyphenyl)-propanoate (3g)

White solid, Mp: 123-124 °C; ^1H NMR (400 MHz, CDCl_3):

δ 2.93-2.97 (m, 2H), 3.37 (m, 1H), 3.58 (s, 3H), 3.76 (s, 3H), 3.81 (dd, J = 13.4, 5.8 Hz, 1H), 3.97 (dd, J = 13.6, 8.0 Hz, 1H), 6.78-6.84 (m, 2H), 7.12 (t, J = 8.2 Hz, 2H), 7.69 (dd, J = 5.4, 3.0 Hz, 2H), 7.81 (dd, J = 5.4, 3.0 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3):

δ 31.6, 40.3, 44.6, 52.5, 55.8, 110.8, 121.0, 123.9, 127.2, 128.6, 131.3, 132.7, 134.6, 158.1, 168.7, 174.4; HRMS (APCI) calcd for $\text{C}_{20}\text{H}_{20}\text{NO}_5$ [$\text{M}+1$]: 354.1336, found: 354.1314. $[\alpha]_{\text{D}}^{25}$ = +17.7 (c 0.70, CH_2Cl_2) for 85.4% ee; HPLC (UV 254 nm, Chiralcel OD-H (0.46 cm x 50 cm), i-PrOH/Hexane = 10/90, 1.0 mL/min), t_1 = 32.0 min, t_2 = 42.8 min.

Methyl 2-(phthalimidomethyl)-3-(4-methylphenyl)-propanoate (3h)

White solid, Mp: 85-86 °C; ^1H NMR (400 MHz,

CDCl₃): δ 2.23 (s, 3H), 2.78 (dd, J = 14.0, 6.8 Hz, 1H), 3.01 (dd, J = 14.2, 8.2 Hz, 1H), 3.24-3.26 (m, 1H), 3.59 (s, 3H), 3.83 (dd, J = 13.6, 6.0 Hz, 1H), 3.96 (dd, J = 13.4, 7.8 Hz, 1H), 7.01-7.08 (m, 4H), 7.68 (dd, J = 5.4, 3.0 Hz, 2H), 7.79 (dd, J = 5.2, 3.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 21.6, 36.2, 40.2, 46.3, 52.6, 123.9, 129.2, 129.8, 132.6, 134.6, 135.5, 136.7, 168.7, 174.0; HRMS (APCI) calcd for C₂₀H₂₀NO₄[M+1]: 338.1387, found: 338.1381. [α]_D²⁵ = +5.8 (c 0.22, CH₂Cl₂) for 76% ee; HPLC (UV 254 nm, Chiralcel OD-H (0.46 cm x 50 cm), i-PrOH/Hexane = 3/97, 0.5 mL/min), t_1 = 70.8 min, t_2 = 75.7 min.

Methyl 2-(phthalimidomethyl)-3-(2-thienyl)-propanoate (3i)

White solid, Mp: 112-113 °C; ¹H NMR (400 MHz, CDCl₃): δ 3.09-3.12 (m, 1H), 3.23-3.29 (m, 2H), 3.64 (s, 3H), 3.90- 3.93 (m, 1H), 3.99 (dd, J = 14.0, 7.2 Hz, 1H), 6.87 (d, J = 3.2 Hz, 2H), 7.11 (d, J = 2.8 Hz, 2H), 7.71 (m, 2H), 7.83 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 30.5, 39.8, 47.0, 52.8, 124.0, 124.7, 126.5, 127.5, 132.5, 134.7, 140.8, 168.6, 173.4; HRMS (APCI) calcd for C₁₇H₁₆NO₄S [M+1]: 330.0795, found: 330.0772; [α]_D²⁵ = +2.3 (c 0.50, CH₂Cl₂) for 55.4% ee; HPLC (UV 254 nm, Chiralcel OD-H (0.46 cm x 50 cm), i-PrOH/Hexane = 1/99, 1.0 mL/min), t_1 = 116.8 min, t_2 = 131.2 min.

Methyl 2-(phthalimidomethyl)-4-methyl-pentanoate (3j)

¹H NMR (400 MHz, CDCl₃): δ 0.89-0.93 (m, 6H), 1.32-1.33 (m, 1H), 1.67-1.70 (m, 2H), 2.93 (m, 1H), 3.64 (s, 3H), 3.74 (dd, J = 14.0, 5.2 Hz, 1H), 3.91 (dd, J = 14.0, 8.8 Hz, 1H), 7.71 (dd, J = 5.4, 3.0 Hz, 2H), 7.84 (dd, J = 5.2, 3.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 22.7, 23.1, 23.7, 39.5, 40.8, 41.5, 43.6, 52.7, 124.1, 132.7, 134.8, 168.7, 175.0. HRMS (APCI) calcd for C₁₆H₂₀NO₄ [M+1]: 290.1367, found: 290.1386; [α]_D²⁵ = -6.0 (c 0.38, CH₂Cl₂) for 49.5% ee; HPLC (UV 254 nm, Chiralcel OD-H (0.46 cm x 50 cm), i-PrOH/Hexane = 5/95, 0.4 mL/min), t_1 = 35.6 min, t_2 = 37.8 min.

General Procedure for Hydrolysis of 3a and 3c to form (*R*)- α -Methyl- β -alanine and (*R*)- α -Benzyl- β -aminopropionic acid.⁷

A mixture of Methyl 2-(phthalimidomethyl)-3-phenyl-propanoate (**3c**) (1mmol, 261 mg), 6 M HCl (15 mL) was heated under reflux for 24 h. The solution was cooled and the precipitated phthalic acid was filtered off. The filtrate was evaporated to dryness and the result solid was dissolved in hot 2-propanol and the NH₄Cl salt removed by filtration. Removal of the 2-propanol gave the amino acid hydrochloride which was dissolved in water and passed with an ion exchange column (IR-4B Amberlite resin). Removal of the water gave the free amino acid (**(*R*)- α -Methyl- β -alanine**) 88.6 mg in 86% yield. ¹H NMR (400 MHz, D₂O): δ 1.18 (d, J = 7.2Hz, 3H), 2.59-2.64 (m, 1H), 3.05 (dd, J = 12.9, 5.3 Hz, 1H), 3.11 (dd, J = 12.9, 8.4 Hz, 1H). $[\alpha]_D^{25}$ = -14.6 (c 1, 1M HCl) (lit.⁸ $[\alpha]_D^{26}$ = -12.6 (c 1, 1M HCl) for 84% ee of *R*-enantiomer). The (**(*R*)- α -Benzyl- β -aminopropionic acid**) was obtained by hydrolysis of **3c** with the same procedure to that described above. ¹H NMR (400 MHz, D₂O): δ 2.88 (m, 2H), 3.04 (m, 3H), 7.36 (m, 5H). $[\alpha]_D^{25}$ = +10.8 (c 1, 1M HCl) (lit.⁹ $[\alpha]_D^{29}$ = +11.3 (c 1, 1M HCl) for *R*-enantiomer).

References

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¹H NMR LIU-1 IN CDCl₃

1.33
1.31
1.29

4.59
4.27
4.26
4.24
4.22

5.57

6.33

7.89
7.88
7.88
7.87
7.76
7.75
7.75
7.74

ppm

2.7752

1.7517

1.9726

1.0000

0.9963

1.5075

1.7006

Integral

ppm

¹³C NMR LIU-1 IN CDCl₃

¹³C NMR LIU-8 IN CDCl₃

¹H NMR LIU-2 IN CDCL₃

¹³C NMR L1U-2 IN CDCl₃

¹H NMR LIU-2 IN CDCl₃

¹³C NMR 410-2 IN CDCl₃

¹H NMR LIU-3 IN CDCL₃

¹³C NMR LIU-3 IN CDCL₃

¹H NMR LIU-21 IN CDCl₃

¹³C NMR LIU-21 IN CDCl₃

¹H NMR LIU-6 IN CDCL₃

¹³C NMR LIU-6 IN CDCL₃

¹H NMR LIU-7 IN CDCL₃

¹³C NMR LIU-7 IN CDCl₃

¹H NMR LIU-3 IN CDCL₃

8.036
7.805
7.699
7.691
7.686
7.679
7.539
7.527
7.421
7.414
7.127
7.116
7.106

4.921

3.757
3.750

3.6512

2.6136

1.0000
2.0531
2.3170
0.9520
1.1356
1.0709

[Integrat]

ppm

¹³C NMR LIU-3 IN CDCL₃

¹H NMR LIU-25 IN CDCL₃ 2004/06/25

25
13C NMR LIU-25 IN CDCL3 2004/06/25

¹H NMR LIU-10 IN CDCl₃

¹³C NMR (LXC-101n CDCl₃)

15.331
14.681

41.204
39.129

61.514

77.389
77.706
78.023

124.002

132.618
134.706

168.825
174.579

3a

ppm

26
¹H NMR LIU-25 IN CDCL₃ 2004/06/25

¹³C NMR LIU-26 IN CDCL₃ 2004/06/25

¹H NMR (400 MHz, CDCl₃)

0.08
0.00

4.03
4.01
4.00
3.98
3.89
3.87
3.85
3.84
3.58
3.28
3.10
3.08
3.07
3.05
2.88
2.86
2.84
2.83

7.82
7.81
7.80
7.72
7.71
7.70
7.69
7.25
7.23
7.21
7.20
7.18
7.15
7.13

ppm

1.1294
1.1317
3.0523
1.0000
1.1275
1.1346

1.7341
1.9451
4.7761

Integral

ppm

¹³C NMR LIU-19 IN CDCL₃

52.662
46.401
40.205
36.565

78.019
77.702
77.384

138.676
134.658
132.541
129.363
129.113
127.151
123.960

173.899
168.672

ppm

¹H NMR LIU-20 IN CDCl₃

0.08
0.00

0.88
0.86

1.26

2.79
2.81
2.83
2.84
3.01
3.03
3.04
3.06
3.22
3.23
3.25
3.59
3.84
3.86
3.88
3.89
3.96
3.98
4.00
4.02

7.11
7.13
7.17
7.19
7.70
7.71
7.72
7.72
7.81
7.81
7.82
7.83

ppm

Integral

1.7298
1.9489

1.7783
1.9312

1.1095
1.1035
3.0036

1.0000
1.1130
1.1199

3.0259

1.4209

ppm

¹³C NMR LIU-20 IN CDCl₃

¹H NMR LIU-22 IN CDCL₃

0.07
0.01
0.00

1.25

1.62

2.80

2.82

2.84

2.85

3.00

3.03

3.04

3.06

3.20

3.22

3.24

3.59

3.60

3.84

3.85

3.87

3.89

3.97

3.99

4.00

4.02

6.89

6.92

6.94

7.14

7.15

7.17

7.27

7.71

7.71

7.73

7.74

7.81

7.82

7.84

ppm

1.1043
1.1343
3.0617
1.0000
1.1323
1.1414

1.6773
1.9872
1.9461
1.8199

Integral

ppm

13C NMR LIU-22 IN CDCL3 2004/06/25

¹H NMR LIU-27 IN CDCL₃ 2004/07/13

¹³C NMR LIU-27 IN CDCl₃ 2004/07/13

Current Data Parameters
 F2 - Acquisition Parameters
 Date_ 20060526
 Time 13:56
 INSTRUM drx400
 PROCNO 1
 F2 - Acquisition Parameters
 Date_ 20060526
 Time 13:56
 INSTRUM drx400
 PROCNO 1

===== CHANNEL f1 =====
 NUC1 1H
 P1 8.20 usec
 PL1 0.00 dB
 SF01 400.1332521 MHz

F2 - Processing parameters
 S1 32768
 SF 400.1300160 MHz
 K0H 6M
 SSB 0
 LB -0.50 Hz
 GB 0.1
 PC 1.40

10 NMR plot parameters
 C1 20.00 cm
 C2 8.00 cm
 C3 10.000 000
 F1 4001.30 Hz
 F2 -1.000 000
 F3 -400.13 Hz
 K0H 0.550000 ppm/cm
 AZCM 220.07150 Hz/cm

1H NMR D-1 IN CDCL3 06.05.26

13C NMR (DMSO-d6) 130.108, 127.1, 126.004, 125.004, 124.004, 123.004, 122.004, 121.004, 120.004, 119.004, 118.004, 117.004, 116.004, 115.004, 114.004, 113.004, 112.004, 111.004, 110.004, 109.004, 108.004, 107.004, 106.004, 105.004, 104.004, 103.004, 102.004, 101.004, 100.004, 99.004, 98.004, 97.004, 96.004, 95.004, 94.004, 93.004, 92.004, 91.004, 90.004, 89.004, 88.004, 87.004, 86.004, 85.004, 84.004, 83.004, 82.004, 81.004, 80.004, 79.004, 78.004, 77.004, 76.004, 75.004, 74.004, 73.004, 72.004, 71.004, 70.004, 69.004, 68.004, 67.004, 66.004, 65.004, 64.004, 63.004, 62.004, 61.004, 60.004, 59.004, 58.004, 57.004, 56.004, 55.004, 54.004, 53.004, 52.004, 51.004, 50.004, 49.004, 48.004, 47.004, 46.004, 45.004, 44.004, 43.004, 42.004, 41.004, 40.004, 39.004, 38.004, 37.004, 36.004, 35.004, 34.004, 33.004, 32.004, 31.004, 30.004, 29.004, 28.004, 27.004, 26.004, 25.004, 24.004, 23.004, 22.004, 21.004, 20.004, 19.004, 18.004, 17.004, 16.004, 15.004, 14.004, 13.004, 12.004, 11.004, 10.004, 9.004, 8.004, 7.004, 6.004, 5.004, 4.004, 3.004, 2.004, 1.004, 0.004

Current Data Parameters
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PROCNO: 1
F2 - Acquisition Parameters
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Time : 14:02
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PROBHD : 5 mm QNP1H
PULPROG : zgpg30
TD : 65536
SOLVENT : DMSO
COC13 : 101.32
NS : 1024
DS : 4
SWH : 23148.148 Hz
FIDRES : 0.35313 Hz
AQ : 3.4156276 sec
RG : 8192
DM : 21.580 usec
DE : 6.00 usec
TE : 298.2 K
D1 : 1.00000000 sec
D11 : 0.03000000 sec
NOREST : 0.00000000 sec
NORM : 0.01500000 sec
===== CHANNEL f1 =====
NUC1 : 13C
P1 : 8.20 usec
PL1 : 1.50 dB
SFO1 : 100.6254015 MHz
===== CHANNEL f2 =====
CPDPRG2 : waltz16
NUC2 : 1H
PCPD2 : 80.00 usec
PL2 : 5.00 dB
PL12 : 23.00 dB
SFO2 : 400.1320037 MHz
F2 - Processing parameters
SI : 32768
SF : 100.6120030 MHz
WDW : EM
SSB : 0
B : 4.00 Hz
ZC : 0
GC : 1.40
ID NMR slit parameters
S : 20.00 cm
D : 5.00 cm
F : 20.00 cm
I : 20.00 cm
R : 20.00 cm
Z : 10.00 cm
Z2 : 10.00 cm
Z3 : 10.00 cm
Z4 : 10.00 cm
Z5 : 10.00 cm
Z6 : 10.00 cm
Z7 : 10.00 cm
Z8 : 10.00 cm
Z9 : 10.00 cm
Z10 : 10.00 cm
Z11 : 10.00 cm
Z12 : 10.00 cm
Z13 : 10.00 cm
Z14 : 10.00 cm
Z15 : 10.00 cm
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Z87 : 10.00 cm
Z88 : 10.00 cm
Z89 : 10.00 cm
Z90 : 10.00 cm
Z91 : 10.00 cm
Z92 : 10.00 cm
Z93 : 10.00 cm
Z94 : 10.00 cm
Z95 : 10.00 cm
Z96 : 10.00 cm
Z97 : 10.00 cm
Z98 : 10.00 cm
Z99 : 10.00 cm
Z100 : 10.00 cm

¹H NMR LTU-17 IN CDCL₃

¹³C NMR LIU-17 IN CDCL₃

¹H NMR LIU-16 IN CDCl₃

¹³C NMR LIU-16 IN CDCl₃

14.787
23.345
30.006
30.341
30.573
32.570
39.852
46.992
52.818

77.434
77.751
78.069

124.011
124.755
126.552
127.490
132.527
134.734
140.858

168.654
173.456

ppm

¹³C NMR LIU-28 IN CDCl₃ 2004/07/13