

Supporting Information

A Catalyst that Plays Multiple Roles: Asymmetric Synthesis of β -Substituted Aspartic Acid Derivatives through a Four-Stage, One-Pot Procedure

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General. Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions. All reagents used are commercially available from Aldrich, Fluka, and Acros Chemicals. All solvents were dried and distilled by standard procedures. All acid chlorides were distilled by standard procedures. Polymer supported catalyst **2b** was made according to literature precedence.¹ The ¹H and ¹³C NMR spectra were acquired on a Varian Unity Plus 400 MHz instrument in CDCl₃. The ¹H (400 MHz) and ¹³C (101 MHz) chemical shifts are given in parts per million () with respect to internal TMS standard or residual solvent peaks. HPLC analysis was performed with a Waters Millipore Model 510 head unit a Regis Technologies (*R,R*) Whelk-01 Chiral, a Waters Millipore Lambda-Max Model 481L spectrophotometer and a Hewlett Packard integrator. Solution phase IR data were recorded on a Bruker IFS-55 FTIR spectrometer.

General procedure for β -substituted aspartic acids **9a-h.**² A 25 mL round-bottom flask equipped with a stir bar was loaded under nitrogen with α -chloroamine **5** (63 mg, 0.26 mmol), proton sponge **10** (83 mg, 0.39 mmol), and the benzoylquinine catalyst **2a** (6 mg, 0.013 mmol). Toluene (1 mL) was added to the mixture and stirred for 1 h. The solution was diluted with toluene (7 mL) and cooled to -78 °C in a dry ice/acetone bath. Phenylacetyl chloride **1a** (20 mg, 0.13 mmol) in toluene (1 mL) was added to the reaction dropwise. The reaction was allowed to slowly warm to room temperature overnight. Excess methanol (6 mL)³ was added and the solution was refluxed.⁴ The reaction was monitored by TLC and stopped when all of the α -lactam had reacted (~ 4 h). The solvent was removed in vacuo and the residue was taken up in chloroform (10 mL) and washed with 1 M HCl (3 x 10 mL). The organic layer was dried with MgSO₄ and filtered through Celite. The filtrate was concentrated and the residue was submitted to flash column chromatography to yield **9a** in 62% yield (22 mg) and 95% ee.

***N*-Benzoylchloroglycine ethyl ester (**5**).** Benzamide (3.54 g, 29.2 mmol) was mixed with ethyl glyoxylate⁵ (3.0 g, 29.2 mmol) in EtOAc and refluxed for 12 h. The reaction was worked up by removal of the solvent and any excess glyoxylate *in vacuo* and the residue recrystallized from EtOAc/hexanes. To a suspension of *N*-benzoylhydroxyglycine ethyl ester (2.8 g, 20 mmol) in CH₂Cl₂ (10 mL) at ambient temperature was added oxalyl chloride (4.5 g, 44 mmol). The mixture was stirred 12 h followed by removal of the excess oxalyl chloride and solvent by reduced pressure rotary evaporation. The resulting solid was dried under high vacuum to afford quantitatively 11.1 g of the desired *N*-benzoylchloroglycine ethyl ester **5**. mp = 67-69 °C; ¹H NMR (CDCl₃): 7.85 (d, 1H), 7.57 (m, 1H), 7.49 (m, 3H), 7.19 (d, 1H), 6.49 (d, 1H), 4.35 (m, 2H), 1.36 (t, 3H) ppm; ¹³C NMR (CDCl₃) 166.5, 166.0, 132.7, 132.2, 128.7, 128.4, 127.4, 63.2, 60.5 ppm; IR (CHCl₃): 1744, 1685, 1508, 1484, 1338; Anal Calcd for C₁₁H₁₂NO₃Cl: C, 54.8; H, 5.02; N, 5.81; Cl, 14.5. Found C, 54.9; H, 5.00; N, 5.79, Cl, 14.5.

¹ Hafez, A. M.; Taggi, A. E.; Wack, H.; Drury, W. J., III; Lectka, T. *Org. Lett.* **2000**, *2*, 3963-3965.

² Ketene **3e** from 4-methoxyphenoxyacetyl chloride was formed at 0 °C in 6 mL of toluene and the imine solution was added to it at -78 °C.

³ For the synthesis of **9f-h**, methanol was substituted with 0.26 mmol of the corresponding amine (**8b-d**), which was added directly to the reaction mixture at room temperature and stirred until the reaction was complete by TLC.

⁴ The methanolysis of the α -lactam proceeds faster if the toluene is removed and the crude mixture is refluxed in methanol.

⁵ Tschaen, D. H.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058-5064.

(3R,4R)-2-Benzoylamino-3-phenyl-succinic acid 1-ethyl ester 4-methyl ester (9a). White crystalline solid recrystallized from Et₂O/hexanes: mp = 149-150°C; [α]_D = +26.5° (c = 0.01, CHCl₃); ¹H NMR (CDCl₃) 7.84-7.79 (m, 2H), 7.58-7.41 (m, 4H), 6.95 (brd, 1H), 6.83 (dd, 4H), 5.48 (dd, 1H), 5.19 (d, 1H), 4.10 (qt, 2H), 3.75 (s, 3H), 1.22 (t, 3H) ppm; ¹³C NMR (CDCl₃) 174.1, 171.5, 168.1, 135.4, 132.8, 131.8, 130.3, 130.0, 129.8, 129.5, 128.3, 67.0, 56.1, 53.9, 53.2, 15.1 ppm; IR (CHCl₃) 1222, 1377, 1463, 1508, 1674, 1741, 2157 cm⁻¹; HPLC (5% *i*PrOH/1.0% HOAc/hexanes, 1.0 mL/min) (*R,R*) = 64.2, (*R,S*) = 59.3, (*S,R*) = 69.1, (*S,S*) = 72.8 min. Anal Calcd for C₂₀H₂₁NO₅: C, 67.5; H, 5.96; N, 3.94. Found C, 67.5; H, 5.97; N, 3.96.

(3R,4R)-2-Benzoylamino-3-phenoxy-succinic acid 1-ethyl ester 4-methyl ester (9b). White crystalline solid recrystallized from Et₂O/hexanes: mp = 131-132°C; [α]_D = +18.6° (c = 0.01, CHCl₃); ¹H NMR (CDCl₃) 7.83 (d, 2H), 7.53 (m, 1H), 7.46 (m, 2H), 7.29 (m, 2H), 7.03 (t, 1H), 6.98 (d, 1H), 6.90 (2, 2H), 5.53 (dd, 1H), 5.32 (d, 1H), 4.23 (q, 2H), 3.79 (s, 3H), 1.21 (t, 3H) ppm; ¹³C NMR (CDCl₃) 168.8, 168.6, 167.8, 157.4, 133.9, 132.2, 129.9, 128.9, 127.5, 122.9, 115.8, 77.6, 62.6, 54.0, 53.2, 14.3 ppm; IR (CHCl₃) 1212, 1418, 1471, 1518, 2388 cm⁻¹; HPLC (5% *i*PrOH/1.0% HOAc/hexanes, 1.0 mL/min) (*R,R*) = 50.5, (*R,S*) = 42.9, (*S,R*) = 53.0, (*S,S*) = 61.8 min. Anal Calcd for C₂₀H₂₁NO₆: C, 64.7; H, 5.70; N, 3.77. Found C, 64.6; H, 5.69; N, 3.77.

(3R,4R)-2-Benzoylamino-3-(4-methoxy-phenyl)-succinic acid 1-ethyl ester 4-methyl ester (9c). White crystalline solid recrystallized from Et₂O/hexanes: mp = 137-138°C; [α]_D = +17.4° (c = 0.01, CHCl₃); ¹H NMR (CDCl₃) 8.07 (d, 1H), 7.71 (d, 2H), 7.43-7.29 (m, 4H), 7.14 (d, 2H), 6.77 (d, 1H), 5.25 (dd, 1H) 4.44 (d, 1H), 4.17 (q, 2H), 3.72 (s, 3H), 3.71 (s, 3H), 1.21 (t, 3H) ppm; ¹³C NMR (CDCl₃) 173.2, 170.5, 159.3, 133.9, 133.7, 131.7, 130.2, 129.6, 128.5, 127.1, 126.3, 114.2, 61.9, 55.2, 55.0, 52.5, 14.0 ppm; IR (CHCl₃) 1261, 1437, 1513, 1674, 1734, 2380 cm⁻¹; HPLC (5% *i*PrOH/1.0% HOAc/hexanes, 1.0 mL/min) (*R,R*) = 35.5, (*R,S*) = 32.2, (*S,R*) = 44.6, (*S,S*) = 48.9 min. Anal Calcd for C₂₁H₂₃NO₆: C, 65.4; H, 6.01; N, 3.63. Found C, 65.4; H, 6.00; N, 3.60.

***Cis*-(3R,4R)-2-Benzoylamino-3-(4-chloro-phenyl)-succinic acid 1-ethyl ester 4-methyl ester (9d).** White crystalline solid recrystallized from Et₂O/hexanes: mp = 154-155°C; [α]_D = +23.6° (c = 0.01, CHCl₃); ¹H NMR (CDCl₃) 7.72 (d, 2H), 7.59-7.40 (m, 5H), 7.36 (d, 2H), 6.64 (d, 1H), 5.31 (dd, 1H), 4.41 (d, 1H), 4.21 (q, 2H), 3.75 (s, 3H), 1.25 (t, 3H) ppm; ¹³C NMR (CDCl₃) 172.8, 170.4, 167.4, 150.3, 133.1, 132.1, 130.1, 129.2, 129.1, 128.9, 127.5, 62.6, 54.9, 52.6, 51.8, 14.3 ppm; IR (CHCl₃) 1216, 1422, 1474, 1513, 2395 cm⁻¹; HPLC (5% *i*PrOH/1.0% HOAc/hexanes, 1.0 mL/min) (*R,R*) = 29.1, (*R,S*) = 41.3, (*S,R*) = 49.1, (*S,S*) = 61.8 min. Anal Calcd for C₂₀H₂₀NO₅Cl: C, 61.6; H, 5.17; N, 3.59; Cl, 9.09. Found C, 61.4; H, 5.19; N, 3.58; Cl, 9.11.

***Cis*-(3R,4R)-2-Benzoylamino-3-(4-methoxy-phenoxy)-succinic acid 1-ethyl ester 4-methyl ester (9e).** White crystalline solid recrystallized from Et₂O/hexanes: mp = 140-141°C; [α]_D = +16.5° (c = 0.01, CHCl₃); ¹H NMR (CDCl₃) 7.83 (d, 2H), 7.54-7.44 (m, 3H), 6.97 (d, 1H), 6.89-6.70 (m, 4H), 5.51 (dd, 1H), 5.21 (d, 1H), 4.24 (q, 2H), 3.77 (s, 3H), 3.76 (s, 3H), 1.23 (t, 3H) ppm; ¹³C NMR (CDCl₃) 169.0, 168.7, 167.8, 155.5, 151.5, 133.9, 135.2, 128.9, 127.5, 117.6, 114.9, 62.6, 55.9, 54.8, 53.1, 14.4 ppm; IR (CHCl₃) 1261, 1380, 1501, 1670, 1757, 2253 cm⁻¹; HPLC (5% *i*PrOH/1.0% HOAc/hexanes, 1.0 mL/min) (*R,R*) = 29.4, (*R,S*) = 26.8, (*S,R*) = 32.7, (*S,S*) = 35.0 min. Anal Calcd for C₂₁H₂₃NO₇: C, 62.8; H, 5.78; N, 3.49. Found C, 62.8; H, 5.80; N, 3.46.

***Cis*-(3R,4R)-2-Benzoylamino-*N*-benzyl-3-phenyl-succinamic acid ethyl ester (9f).** White crystalline solid recrystallized from Et₂O/hexanes: mp = 197-198 °C; [α]_D = +17.8° (c = 0.01, CHCl₃); ¹H NMR (CDCl₃) 7.78 (d, 1H), 7.74 (d, 2H), 7.49-7.41 (m, 4H), 7.34-7.28 (m, 6H), 7.20 (t, 2H), 5.88 (brt, 1H), 5.21 (dd, 1H), 4.56-4.35 (m, 3H), 4.21 (qt, 2H), 1.23 (t, 3H) ppm; ¹³C NMR (CDCl₃) 174.1, 172.0, 170.9, 138.3, 135.6, 134.0, 131.5, 128.9, 128.7, 128.5, 128.1, 127.6, 127.5, 127.1, 78.3, 61.9, 55.3, 52.8, 43.7, 14.1 ppm; IR (CHCl₃) 1378, 1473, 1667, 1792, 1821, 2245 cm⁻¹; HPLC (10% *i*PrOH/1.0% HOAc/hexanes, 1.0 mL/min) (*R,R*) = 20.9, (*R,S*) = 14.7, (*S,R*) = 28.9, (*S,S*) = 30.4 min. Anal Calcd for C₂₆H₂₆N₂O₄: C, 72.5; H, 6.09; N, 6.51. Found C, 72.6; H, 6.08; N, 6.51.

***Cis*-(3R,4R)-2-Benzoylamino-*N*-glycine-3-phenyl-succinamic acid ethyl ester (9g).** White crystalline solid recrystallized from Et₂O/hexanes: mp = 152-153°C; [α]_D = +23.2° (c = 0.01, CHCl₃); ¹H NMR (CDCl₃) 7.83 (d, 1H), 7.72 (d, 2H), 7.46 (t, 1H), 7.37 (t, 2H), 7.33-7.23 (m, 5H), 6.31 (brt, 1H), 5.19 (dd, 1H), 4.52 (d, 1H), 4.19 (qt, 2H), 3.98 (t, 2H), 3.70 (s, 3H), 1.22 (t, 3H) ppm; ¹³C NMR (CDCl₃) 173.5, 171.8, 170.8, 168.4, 136.4, 135.0, 132.7, 129.9, 129.8, 129.6, 129.3, 128.2, 62.9, 56.3, 53.7, 53.5, 42.4, 15.1 ppm; IR (CHCl₃) 1216, 1419, 1484, 1513, 1660, 1725, 1748, 2390 cm⁻¹; HPLC (10% *i*PrOH/0.5% HOAc/hexanes, 1.0 mL/min) (*R,R*) = 8.64, (*R,S*) = 6.36, (*S,R*) = 7.09, (*S,S*) = 9.63 min. Anal Calcd for C₂₂H₂₄N₂O₆: C, 72.5; H, 6.09; N, 6.51. Found C, 72.4; H, 6.08; N, 6.53.

***Cis*-(3R,4R)-2-Benzoylamino-*N*-serine-3-phenoxy-succinamic acid ethyl ester (9h).** White crystalline solid recrystallized from Et₂O/hexanes: mp = 150-151°C; [α]_D = +21.5° (c = 0.01, CHCl₃); ¹H NMR (CDCl₃) 7.84 (d, 2H),

7.53 (t, 1H), 7.45 (t, 2H), 7.29 (t, 2H), 7.20 (d, 2H), 7.04 (t, 1H), 6.70 (d, 2H), 5.58 (dd, 1H), 5.21 (d, 1H), 4.73 (quint, 1H), 4.19 (qt, 2H), 3.97-3.80 (m, 2H) 3.64 (s, 3H), 2.94 (brt, 1H), 1.17 (t, 3H) ppm; ^{13}C NMR (CDCl_3) 170.3, 168.7, 167.8, 167.6, 156.9, 133.2, 132.1, 129.8, 128.6, 127.4, 123.0, 115.9, 78.4, 62.4, 62.2, 55.0, 54.2, 52.7, 14.0 ppm; IR (CHCl_3) 1261, 1381, 1485, 1670, 1757, 2253 cm^{-1} ; HPLC (10% *i*PrOH /0.5% HOAc/hexanes, 1.0 mL/min) (*R,R*) = 12.3, (*R,S*) = 10.7, (*S,R*) = 15.4, (*S,S*) = 17.7 min. Anal Calcd for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_8$: C, 60.3; H, 5.72; N, 6.11. Found C, 60.3; H, 5.72; N, 6.13.

(*R,R*)-2-amino-3-hydroxyapartic acid (11). The protected hydroxyapartic acid derivative **9e** was converted to **11** using known procedures. All data were consistent with published reports.⁶

⁶ (a) Riordan, J. M.; McLean, T. L.; Stammer, C. H. *J. Org. Chem.* **1975**, *40*, 3219-3221. (b) Cardillo, G.; Gentilucci, L.; Tolomelli, A.; Tomasini, C. *Synlett*, **1999**, 1727-1729.