Highly Diastereoselective Heterogeneously-Catalyzed Hydrogenation of Enamines for the Synthesis of Chiral β -Amino Acid Derivatives

(Supporting Information)

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Suppl 1. *Z/E* Isomeric Ratios and UV and ^1H -NMR Data.

Entry	Enamine	% <i>E</i> isomer ^a	<i>Z/E</i> λ_{max} (nm) ^b	<i>Z/E</i> δ NH (ppm) ^a
1	2a	18%	287/ 275	9.50/ 6.20
2	2b	25%	292/ 276	9.64/ 6.30
3	2c	19%	290/ 276	9.60/ 6.20
4	2f	7%	297/ 281	10.50/ 5.67
5	2g	2%	298/--	9.50/--
6	2h	2%	299/--	9.48/--
7	2i	2%	302/--	9.50/--
8	2k	1%	305/--	10.21/ 5.12

^a Thermodynamic ratio after RT age for 12 days in THF- d_8 .

^b HPLC diode array in acetonitrile/ aqueous $\text{Na}_2\text{B}_4\text{O}_7$.

Suppl 2. X-ray Structure of Phenyl PGA-Aminoester **3g**.(HCl salt).

Suppl 3. Hydrogenation of **2a** with D₂ and PtO₂ in THF-*d*₈

Experimental: The acid-washed catalyst (25 mg) was placed under deuterium gas (90 psig) in THF-*d*₈ (0.75 mL). After 3 h, the solution was brought into a glove box and the black, finely dispersed catalyst was isolated by filtration and then dried under reduced pressure for 5 h. This pre-reduced catalyst (4.6 mg) was transferred to a THF-*d*₈ solution (0.75 mL) containing **2a** and the resulting heterogeneous slurry placed under deuterium gas (90 psig) for 5 h. The solution was vented, filtered and the filtrate concentrated under reduced pressure. The resulting light yellow oil was dissolved in benzene-*d*₆ and a single pulse ¹H-NMR spectrum was acquired. Integration showed 90.4% deuterium incorporation into the α and β positions of **3a**.

Suppl 4. Model for the diastereofacial selective binding and hydrogenation on the platinum catalyst.

EXPERIMENTALS

General: (*S*)-PGA was purchased from DSM and Omegachem, Inc. PtO₂ (lot#323760) was purchased from Englehard. Pressure reaction vessels used for the hydrogenation were purchased from Andrews Glass Company. The THF and MeOH (OmniSolv grade) used for the hydrogenations were obtained from EMD Chemicals and used without further purification.

Z-PGA-Enamines:

1) Methyl (2Z)-3-[(1*S*)-2-amino-2-oxo-1-phenylethyl]amino}but-2-enoate (1a**).** Methyl acetoacetate (2.0 g, 17.2 mmol) and (*S*)-PGA (2.58 g, 17.2 mmol) were dissolved in MeOH 200 mL) at 40 °C and acetic acid (0.5 mL, 8.6 mmol) was added. Solids formed after 1 h at 40 °C. The mixture was cooled to 4 °C and filtered. The solids were rinsed with cold MeOH and dried to afford the enamine (3.3 g, 77% yield). $[\alpha]_D^{25} = -92$ (c 0.44, DCM). mp = 159 °C. ¹H-NMR (DMSO-d₆, 400 MHz): δ 9.46 (d, *J* = 8 Hz, 1H), 7.70 (br, 1H), 7.37 (m, 4H), 7.28 (m, 2H), 5.19 (d, *J* = 8 Hz, 1H), 4.44 (s, 1H), 3.52 (s, 3H), 1.73 (s, 3H). NOE enhancement: 4.5% C-4 methyl group upon irradiation of the olefinic hydrogen. ¹³C-NMR (DMSO-d₆, 100 MHz): δ 171.2, 169.5, 160.1, 139.8, 128.7, 127.8, 126.4, 83.1, 59.0, 49.6, 19.4. Anal. Calcd for C₁₃H₁₆N₂O₃: C, 62.89; H, 6.50; N, 11.28; O, 19.33. Found: C, 62.60; H, 6.56; N, 11.21; O, 19.32.

2) Methyl (2Z)-3-[(1*S*)-2-amino-2-oxo-1-phenylethyl]amino}-4-methylpent-2-enoate (2b**).** Methyl isobutyryl acetate (7.59 g, 50.0

mmol) and (*S*)-PGA (7.51 g, 50.0 mmol) were mixed in IPA (40 mL) at 40 °C and acetic acid (1.43 mL, 25 mmol) was added. A slurry formed quickly. The mixture was stirred overnight at 40 °C, cooled to 3 °C then was filtered. The solids were rinsed with IPA and dried to afford the enamine as a white solid (11.6 g, 84% yield). $[\alpha]_D^{25} = -57$ (c 0.58, DCM). mp = 170 °C. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 9.55 (d, *J* = 8 Hz, 1H), 7.76 (s, 1H), 7.40 (m, 4H), 7.30 (m, 2H), 5.29 (d, *J* = 8 Hz, 1H), 4.48 (s, 1H), 3.54 (s, 3H), 2.44 (m, 1H), 1.08 (d, *J* = 7 Hz, 3H), 0.78 (d, *J* = 7 Hz, 3H). nOe enhancement: 2.5% and 3.5% for the *i*-Pr methyl groups upon irradiation of the olefinic hydrogen. ¹³C-NMR (DMSO-*d*₆, 100 MHz): δ 171.5, 170.5, 170.2, 140.6, 129.0, 128.1, 126.6, 79.2, 58.5, 49.9, 29.2, 22.4, 21.1. Anal. Calcd for C₁₅H₂₀N₂O₃: C, 65.20; H, 7.30; N, 10.14; O, 17.37. Found: C, 62.82; H, 7.22; N, 9.71; O, 17.25.

3) Methyl (2*Z*)-3-[[*(1S)*-2-amino-2-oxo-1-phenylethyl]amino]-4-phenylbut-2-enoate (2c).

Methyl 3-oxo-4-phenylbutanoate (1.76 g, 9.16 mmol) and (*S*)-PGA (1.38 g, 9.16 mmol) were mixed in IPA (18 mL) and acetic acid (0.26 mL, 4.6 mmol) and stirred 18 h over a 50 °C bath. The resulting slurry was cooled and filtered. The solids were rinsed with cold MeOH and dried to afford the enamine (2.20 g, 74% yield). $[\alpha]_D^{25} = -63$ (c 0.40, DCM). mp = 169 °C. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 9.46 (d, *J* = 8 Hz, 1H), 7.71 (s, 1H), 7.34 (d, 4H), 7.26 (m, 4H), 7.20 (m, 1H), 7.08 (d, 2H), 5.10 (d, *J* = 8 Hz, 1H), 4.30 (s, 1H), 3.50 (s, 3H), 3.32 (q, 2H). nOe enhancement: 3.5% allylic hydrogens upon irradiation of the olefinic hydrogen. ¹³C-NMR (DMSO-*d*₆, 100 MHz): δ 170.8, 169.4, 161.7, 139.9, 136.3, 128.7, 128.6, 128.6, 127.8, 126.7, 126.3, 84.6, 58.6, 49.7, 37.9. Anal. Calcd for C₁₉H₂₀N₂O₃: C, 70.35; H, 6.21; N, 8.64; O, 14.80. Found: C, 70.31; H, 6.30; N, 8.98; O, 14.49.

4) (2*S*)-2-[[*(1Z)*-1-benzyl-3-oxo-3-piperidin-1-ylprop-1-en-1-yl]amino]-2-phenylacetamide (2f).

4-Oxo-1-phenyl-4-piperidin-1-ylbutan-2-one (13.8 g, 56.0 mmol) and (*S*)-PGA (8.42 g, 56.0 mmol) were stirred in MeOH (70 mL) with acetic acid (1.6 mL, 28 mmol) 3 days at 40 °C. The mixture was concentrated and the residue was purified by flash chromatography (80-100% EtOAc/ hexane) and then was crystallized (EtOAc/ hexane) to afford the enamine (7.4 g, 35%). $[\alpha]_D^{25} = -86$ (c 0.44, MeOH). mp = 155 °C. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 10.23 (d, *J* = 9 Hz, 1H), 7.60 (br, 1H), 7.29 (m, 9H), 7.19 (m, 1H), 7.10 (br, 1H), 4.99 (d, *J* = 9 Hz, 1H), 4.81 (s, 1H), 3.32-3.35 (m, 6H), 2.49 (m, 2H), 1.41 (m, 4H). nOe enhancement: 4% allylic hydrogens upon irradiation of the olefinic hydrogen. ¹³C-NMR (DMSO-*d*₆, 100 MHz): δ 171.3, 168.3, 158.2, 140.3, 137.3, 128.4, 128.3, 127.5, 126.5, 126.4, 85.1, 58.9, 38.6, 25.8, 24.3. Anal. Calcd for C₂₃H₂₇N₃O₂: C, 73.18; H, 7.21; N, 11.13; O, 8.48. Found: C, 73.19; H, 7.33; N, 11.12; O, 8.54.

5) (2*Z*)-3-[[*(1S)*-2-amino-2-oxo-1-phenylethyl]amino]-4-

phenylbut-2-enamide (2e). 3-Oxo-4-phenylbutanamide (1.85 g, 10.4 mmol) and (*S*)-PGA (1.56 g, 10.4 mmol) were stirred in MeOH (18 mL) with acetic acid (0.30 mL, 5.2 mmol) 4 days at 40 °C. The mixture was diluted with MTBE, washed with sat'd sodium bicarbonate, dried (MgSO₄)

and concentrated. The residue was purified by flash chromatography (50-100% EtOAc/hexane) and then crystallized (EtOAc/ hexane) to afford the enamine (0.63 g, 20%). $[\alpha]_D^{25} = +9$ (c 0.18, DCM). mp = 188 °C. $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ 9.89 (d, $J = 8.8$ Hz, 1H), 7.61 (s, 1H), 7.33 (m, 4H), 7.28 (d, $J = 7$ Hz, 3 H), 7.21 (m, 1H), 7.15 (d, 7 Hz, 2H), 7.10 (s, 1H), 6.6 (br, 1H), 6.1 (br, 1H), 5.01 (d, $J = 8.8$ Hz, 1H), 4.37 (s, 1H), 3.27 (q, 2H). nOe enhancement: 4.7% allylic hydrogens upon irradiation of the olefinic hydrogen. $^{13}\text{C-NMR}$ (DMSO- d_6 , 100 MHz): δ 171.7, 171.4, 157.2, 140.5, 137.2, 128.5, 128.4, 127.4, 126.4, 126.4, 89.4, 58.9, 38.1. Anal. Calcd for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.51; H, 6.10; N, 13.48.

6) Methyl 2-[[[(1S)-2-amino-2-oxo-1-phenylethyl]amino]cyclohex-1-ene-1-carboxylate (2d).

Methyl cyclohexane-2-carboxylate (8.22 g, 50.0 mmol) and (*S*)-PGA (150.751 g, 50.0 mmol) were dissolved in MeOH (40 mL) at 40 °C and acetic acid (1.43 mL, 25 mmol) was added. Solids formed in a few minutes. The mixture was stirred 1 h at 40 °C then was cooled to 3 °C and was filtered. The solids were rinsed with MeOH (10 mL) and dried in a vacuum oven to afford the enamine as a white solid (12.5 g, 87% yield). $[\alpha]_D^{25} = -177$ (c 0.48, MeOH). mp = 201 °C. $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ 9.73 (d, $J = 7.9$ Hz, 1H), 7.67 (s, 1H), 7.27 (m, 4H), 7.27 (m, 1H), 7.21 (s, 1H), 5.18 (d, $J = 7.9$ Hz, 1H), 3.58 (s, 3H), 2.29 (m, 1H), 2.16 (m, 2H), 1.90 (m, 1H), 1.49 (m, 1H), 1.40 (m, 3H). $^{13}\text{C-NMR}$ (DMSO- d_6 , 100 MHz): δ 171.4, 169.6, 157.3, 140.2, 128.5, 127.5, 126.3, 90.0, 58.5, 50.1, 26.1, 23.5, 22.1, 21.6. Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_3$: C, 66.65; H, 6.99; N, 9.72; O, 16.65. Found: C, 66.30; H, 7.00; N, 9.64; O, 16.66.

7) Methyl (2Z)-3-[[[(1S)-2-amino-2-oxo-1-phenylethyl]amino]-3-phenylacrylate (2g).

Methyl 3-oxo-3-phenylpropanoate (20.2 g, 114 mmol) and (*S*)-PGA (17.0 g, 114 mmol) were added to MeOH (60 mL) with acetic acid (3.25 mL, 57 mmol) and stirred 4 days over a 40 °C bath. The mixture was concentrated and the residue was purified by flash chromatography (40-60% EtOAc/ hexane) to afford an oil, which was crystallized in 20% EtOAc/ hexane (250 mL) to afford after drying 19.7 g enamine (56% yield). $[\alpha]_D^{25} = -68$ (c 0.49, DCM). mp = 142 °C. $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ 9.46 (d, $J = 9$ Hz, 1H), 7.65 (s, 1H), 7.39 (m, 1H), 7.33 (m, 2H), 7.24 (m, 4H), 7.11 (m, 4H), 4.92 (d, $J = 9$ Hz, 1H), 4.51 (s, 1H), 3.61 (s, 3H). nOe enhancement: 2.3% ortho phenyl hydrogens on main chain upon irradiation of the olefinic hydrogen. $^{13}\text{C-NMR}$ (DMSO- d_6 , 100 MHz): δ 171.0, 169.0, 162.5, 140.0, 135.5, 129.2, 128.2, 128.2, 127.3, 127.2, 126.1, 86.4, 59.9, 49.8. Anal. Calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_4$: C, 67.05; H, 5.92; N, 8.23; O, 18.80. Found: C, 69.46; H, 5.99; N, 8.94; O, 16.66.

8) (2S)-2-[[[(1Z)-3-oxo-1-phenyl-3-piperidin-1-ylprop-1-en-1-yl]amino]-2-phenylacetamide (2k).

3-Oxo-1-phenyl-3-piperidin-1-ylpropan-1-one (10.1 g, 43.7 mmol) and (*S*)-PGA (6.6 g, 44 mmol) in IPA (40 mL) and acetic acid (1.9 mL, 33 mmol) were stirred 4 days at 40 °C. The mixture was concentrated and purified by flash chromatography and crystallization (EtOAc/ hexane) to afford the enamine (6.9 g, 43%). $[\alpha]_D^{25} = +86$ (c 0.26, DCM). mp = 126 °C. $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ 10.17 (d, J

= 9 Hz, 1H), 7.56 (s, 1H), 7.07-7.37 (m, 11H), 4.84 (s, 1H), 4.80 (d, J = 9 Hz, 1H), 3.41 (br, 4H), 1.56 (br, 2H), 1.33 (br, 4H). nOe enhancement: 3% ortho phenyl hydrogens on main chain upon irradiation of the olefinic hydrogen. ^{13}C -NMR (DMSO- d_6 , 100 MHz): δ 171.5, 167.7, 160.0, 140.5, 137.0, 128.8, 128.2, 128.1, 127.5, 127.2, 126.4, 87.4, 60.4, 25.8, 24.3. HRMS (M+1) for $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_2$ calcd 364.2025 expt 364.2017

9) (2Z)-3-[[[(1S)-2-amino-2-oxo-1-phenylethyl]amino]-3-phenylacrylamide (2j).

3-Oxo-3-phenylpropanamide (6.53 g, 40.0 mmol) and (S)-PGA (6.01 g, 40.0 mmol) in IPA (35 mL) and acetic acid (1.2 mL, 20 mmol) were stirred 4 days at 40 °C. The mixture was concentrated and the residue was dissolved in EtOAc (150 mL). The undissolved solids (PGA salt) were filtered off and the filtrate was concentrated. Purification by flash chromatography (0-10% MeOH/ EtOAc) followed by crystallization afforded the enamine (5.47 g, 46% yield) as a white solid. $[\alpha]_D^{25}$ = +18 (c 0.33, DCM). mp = 111-130 °C. ^1H -NMR (DMSO- d_6 , 400 MHz): δ 9.74 (d, J = 10 Hz, 1H), 7.58 (s, 1H), 7.33 (m, 3H), 7.22 (m, 3H), 7.16 (m, 2H), 7.08 (m, 3H), 6.9 (br, 1H), 6.3 (br, 1H), 4.79 (d, J = 10 Hz, 1H), 4.60 (s, 1H). nOe enhancement: 1.9% ortho phenyl hydrogens on main chain upon irradiation of the olefinic hydrogen. ^{13}C -NMR (DMSO- d_6 , 100 MHz): δ 172.0, 171.5, 159.2, 140.9, 137.1, 129.2, 128.6, 128.5, 127.8, 127.6, 126.8, 92.8, 60.8. HRMS (M+1) for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_2$ calcd 296.1399 expt 296.1403

10) Methyl (2Z)-3-[[[(1S)-2-amino-2-oxo-1-phenylethyl]amino]-3-(4-methoxyphenyl)acrylate (2h)

Methyl 3-(4-methoxyphenyl)-3-oxopropanoate (10.41 g, 50.0 mmol) and (S)-PGA (7.51 g, 50.0 mmol) in IPA (40 mL) and acetic acid (1.43 mL, 25 mmol) were stirred 5 days at 40 °C. The mixture was concentrated and EtOAc (50 mL) was added. The undissolved solids (PGA salt) were filtered off and the filtrate was concentrated. The residue was purified by flash chromatography (30-100% EtOAc/ hexane) to afford the enamine (7.21 g) as an amorphous solid, which was heated and stirred in MTBE (150 mL) to afford a slurry. The solids were filtered and dried to afford the enamine (5.96 g, 35%). $[\alpha]_D^{25}$ = -31 (c 0.56, DCM). mp = 93 °C (broad). ^1H -NMR (DMSO- d_6 , 400 MHz): δ 9.41 (d, J = 8.9 Hz, 1H), 7.64 (s, 1H), 7.26 (m, 3H), 7.16 (m, 3H), 7.05 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 4.95 (d, J = 8.9 Hz, 1H), 4.50 (s, 1H), 3.75 (s, 3H), 3.60 (s, 3H). nOe enhancement: 2.5% meta hydrogens to CH_3O - upon irradiation of the olefinic hydrogen. ^{13}C -NMR (DMSO- d_6 , 100 MHz): δ 171.2, 169.1, 162.6, 160.0, 140.1, 128.8, 128.3, 127.9, 127.4, 126.2, 113.7, 86.3, 60.1, 55.2, 49.9. Anal. Calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 66.74; H, 5.85; N, 7.89.

11) Methyl (2Z)-3-[[[(1S)-2-amino-2-oxo-1-phenylethyl]amino]-3-[4-(trifluoromethyl)phenyl]acrylate (2i).

Methyl 3-oxo-3-[4-(trifluoromethyl)phenyl]propanoate (5.18 g, 20.0 mmol) and (S)-PGA (3.00 g, 20.0 mmol) in IPA (25 mL) and acetic acid (1.2 mL, 20 mmol) were stirred 2 days at 40 °C. The mixture was cooled to RT, n-heptane (10 mL) was added to precipitate the unreacted PGA and filtered. The filtrate was concentrated and the residue was purified

by flash chromatography (50-70% EtOAc/ hexane) to afford the enamine as an amorphous solid (6.2 g, 82%) which contained a small amount of the E-enamine isomer. The solids were crystallized from MTBE to afford the pure Z-enamine (4.18 g, 55%) as a white solid. $[\alpha]_D^{25} = -79$ (c 0.57, DCM). mp = 91 °C (broad). $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ 9.43 (d, $J = 8.6$ Hz, 1 H), 7.70 (d, $J = 8$ Hz, 2 H), 7.60 (s, 1H), 7.30 (d, $J = 8$ Hz, 2H), 7.24 (~t, 4 H), 7.10 (d, $J = 6.5$ Hz, 2 H), 4.86 (d, $J = 8.6$ Hz, 1H), 4.57 (s, 1H), 3.62 (s, 3H). nOe enhancement: 2.1% meta hydrogens to CF_3 upon irradiation of the olefinic hydrogen. $^{13}\text{C-NMR}$ (DMSO- d_6 , 100 MHz): δ 170.8, 168.9, 160.9, 139.8, 139.6, 128.4, 128.3, 127.6, 126.2, 125.2, 87.3, 59.9, 50.1. Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_3$: C, 60.32; H, 4.53; N, 7.40; F, 15.06. Found: C, 60.23; H, 4.36; N, 7.37; F, 14.96.

Hydrogenated PGA-Amines:

General Procedure: A pressure reaction vessel is charged with the PGA-enamine, PtO_2 and THF and the resulting slurry is cooled to 0 °C. The vessel is pressure purged with nitrogen (3 x 40 psig) and hydrogen (2 x 40 psig) and then pressurized with hydrogen (90 psig). The reaction mixture is agitated for 30 minutes and then allowed to warm to room temperature over 15 min. After stirring for the prescribed amount of time (see Tables 1 and 3 in paper), the vessel is carefully vented to atmospheric pressure and the resulting slurry is filtered through Solka floc. The filter cake is rinsed with THF (3x) and the filtrates are combined and concentration. The residue was purified by flash chromatograph (EtOAc/ hexane) and was crystallized (EtOAc/ hexane) when possible. *CAUTION: The reduced platinum catalyst is pyrophoric, should be kept wet with solvent, and exposure to air should be minimized.*

1) Methyl (3*R*)-3-([(1*S*)-2-amino-2-oxo-1-

phenylethyl]amino}butanoate (3a). Flash chromatography (90% EtOAc/ hexane) afforded the ester (0.17 g, 66% yield). $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ 7.57 (bs, 1H), 7.45 (m, 2H), 7.39 (m, 2H), 7.33 (m, 1H), 7.20 (bs, 1H), 4.31 (bd, $J = 4$ Hz, 1H), 3.67 (s, 3H), 2.99 (m, 1H), 2.59 (dd, $J = 15, 7$ Hz, 2H), 2.38 (dd, $J = 15, 7$ Hz, 2H), 1.11 (d, $J = 6$ Hz, 3H). $^{13}\text{C-NMR}$ (DMSO- d_6 , 100 MHz): δ 174.1, 172.2, 140.6, 128.1, 127.3, 127.2, 63.0, 51.2 47.9 41.3, 19.8. HRMS ($M+1$) for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_3$ calcd 251.1396 expt 251.1396

2) Methyl (3*S*)-3-([(1*S*)-2-amino-2-oxo-1-phenylethyl]amino)-4-

methylpentanoate (3b). Flash chromatography (70-85% EtOAc/ hexane) afforded pure amine (0.27 g, 82% yield). $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ 7.42 (bs, 1H), 7.37 (m, 2H), 7.31 (m, 2H), 7.24 (m, 1H), 7.12 (bs, 1H), 4.20 (d, $J = 6$ Hz, 1H), 3.59 (s, 3H), 2.68 (m, 1H), 2.33 (m, 2H), 1.77 (m, 1H), 0.83 (d, $J = 7$ Hz, 3H), 0.76 (d, $J = 7$ Hz, 3H). $^{13}\text{C-NMR}$ (DMSO- d_6 , 100 MHz): δ 174.1, 172.8, 140.7, 128.0, 127.4, 127.1, 63.2, 57.4, 51.3, 29.7, 18.3, 17.4. HRMS ($M+1$) for $\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}_3$ calcd 279.1709 found 279.1705

3) Methyl (3*R*)-3-([(1*S*)-2-amino-2-oxo-1-phenylethyl]amino)-4-phenylbutanoate (3c). Flash chromatography (80-100% EtOAc/

hexane) afforded the amine as a resin (0.25 g, 88% yield). This was crystallized from EtOAc/ hexane. ¹H-NMR (DMSO-d₆, 400 MHz): δ 7.45 (s, 1H), 7.24 (m, 8H), 7.11 (m, 3H), 4.31 (d, *J* = 6.5 Hz, 1H), 3.55 (s, 3H), 2.97 (m, 1H), 2.80 (dd, *J* = 6.0, 13.3 Hz, 1H), 2.58 (dd, *J* = 7.0, 13.3 Hz, 1H), 2.37-2.46 (m, 2H), 2.29 (dd, *J* = 5.8, 15.2 Hz, 1H). ¹³C-NMR (DMSO-d₆, 100 MHz): δ 173.8, 172.1, 140.2, 138.7, 129.2, 128.2, 128.0, 127.2, 127.2, 126.1, 62.8, 54.0, 51.4, 38.5. HRMS (M+1) for C₁₉H₂₂N₂O₃ calcd 327.1709 expt. 327.1701

4) (2S)-2-[[[(1R)-1-benzyl-3-oxo-3-piperidin-1-ylpropyl]amino]-2-phenylacetamide (3f). Flash chromatography (5% MeOH/ EtOAc) afforded the amine as an oil which was crystallized from 1:1 EtOAc/ hexane to afford the product as a white solid (1.02 g, 88% yield). ¹H-NMR (DMSO-d₆, 400 MHz): δ 7.65 (s, 1H), 7.1-7.3 (m, 11H), 4.33 (d, *J* = 4.6 Hz, 1H), 3.39 (m, 2H), 3.20 (m, 2H), 2.98 (m, 1H), 2.81 (dd, *J* = 5.7, 13.2 Hz, 1H), 2.59 (dd, *J* = 6.9, 13.2 Hz, 1H), 2.3-2.5 (m, 2H), 2.22 (dd, *J* = 5.5, 15.2 Hz, 1H), 1.52 (m, 2H), 1.36 (m, 4H). ¹³C-NMR (DMSO-d₆, 100 MHz): δ 174.1, 169.1, 140.5, 139.2, 129.3, 128.2, 128.0, 127.3, 127.1, 126.0, 62.9, 54.2, 45.9, 41.8, 37.0, 26.0, 25.2, 23.9. HRMS (M+1) for C₂₃H₂₉N₃O₂ calcd 380.2346 found 380.2338

5) (3R)-3-[[[(1S)-2-amino-2-oxo-1-phenylethyl]amino]-4-phenylbutanamide (3e). Stirring the residue in 1:1 EtOAc/ hexane followed by filtration and drying afforded the amine as a white solid (0.20 g, 98% yield). ¹H-NMR (DMSO-d₆, 400 MHz): δ 7.64 (s, 1H), 7.46 (s, 1H), 7.25 (m, 8H), 7.11 (m, 3H), 6.83 (s, 1H), 4.36 (s, 1H), 2.97 (br, 1H), 2.80 (dd, *J* = 5.5, 13.2 Hz, 1H), 2.57 (dd, *J* = 7.0, 13.2 Hz, 1H), 2.28 (br, 1H), 2.10 (m, 2H). ¹³C-NMR (DMSO-d₆, 100 MHz): δ 174.1, 173.2, 140.5, 139.0, 129.3, 128.2, 128.0, 127.3, 127.2, 126.0, 62.8, 53.9, 39.4. HRMS (M+1) for C₁₈H₂₁N₃O₂ calcd 312.1712 found 312.1717

6) Methyl (1S,2R)-2-[[[(1S)-2-amino-2-oxo-1-phenylethyl]amino]cyclohexanecarboxylate (3d).

Flash chromatography (75% EtOAc/ hexane) afforded the pure amine (1.79 g, 94% yield). ¹H-NMR (DMSO-d₆, 400 MHz): δ 7.42 (bs, 1H), 7.36 (m, 2H), 7.31 (m, 2H), 7.25 (m, 1H), 4.18 (d, 1H), 3.62 (s, 3H), 2.89 (bm, 1H), 2.63 (m, 1H), 2.28 (t, *J* = 6 Hz, 1H), 1.78 (q, *J* = 10 Hz, 1H), 1.70 (m, 1H), 1.50 (bm, 4H), 1.25 (bm, 2H). ¹³C-NMR (DMSO-d₆, 100 MHz): δ 174.1, 174.0, 140.9, 128.1, 127.2, 62.9, 59.7, 52.8, 51.1, 45.4, 28.5, 23.8, 23.4, 20.7, 14.1. HRMS (M+1) for C₁₆H₂₂N₂O₃ calcd 291.1709 expt 291.1707

7) Methyl (3S)-3-[[[(1S)-2-amino-2-oxo-1-phenylethyl]amino]-3-phenylpropanoate (3g). Flash chromatography (75% EtOAc/ hexane) afforded the pure amine as a resin. ¹H-NMR (DMSO-d₆, 400 MHz): δ 7.59 (d, *J* = 2.4 Hz, 1H), 7.2-7.3 (m, 11H), 3.98 (q, *J* = 7.7 Hz, 1H), 3.72 (d, *J* = 5.3 Hz, 1H), 3.56 (s, 3H), 3.14 (m, 1H), 2.86 (dd, *J* = 8.1, 15.4 Hz, 1H), 2.58 (dd, *J* = 6.4, 15.4 Hz, 1H). ¹³C-NMR (DMSO-d₆, 100

MHz): δ 173.9, 171.6, 142.4, 140.1, 128.5, 128.2, 127.4, 127.4, 127.3, 127.2, 63.5, 57.6, 51.4, 42.3. HRMS (M+1) for $C_{18}H_{20}N_2O_3$ calcd 313.1552 expt. 313.1556

8) (2S)-2-[(3-oxo-1-phenyl-3-piperidin-1-ylpropyl)amino]-2-

phenylacetamide (3k). Flash chromatography (EtOAc/ hexane) afforded the amine as a white solid foam (0.41 g, 92% yield). 1H -NMR (DMSO- d_6 , 400 MHz): δ 7.99 (s, 1H), 7.36-7.19 (m, 11H), 4.03 (m, 1H), 3.70 (d, J = 5 Hz, 1H), 3.46 (m, 1H), 3.35 (m, 1H), 3.30 (m, 3H), 3.01 (bt, 1H), 2.81 (dd, J = 8.6, 15 Hz, 1H), 2.52 (dd, 4.9, 15 Hz, 1H), 1.52 (m, 2H), 1.39 (4 H). ^{13}C -NMR (DMSO- d_6 , 100 MHz): δ 174.1, 168.6, 143.2, 140.5, 128.3, 128.1, 127.2, 127.2, 127.0, 63.6, 57.8, 46.0, 42.0, 40.7, 25.8, 25.2, 24.0. HRMS (M+1) for $C_{22}H_{27}N_3O_2$ calcd 366.2181 expt. 366.2179

9) 3-[(1S)-2-amino-2-oxo-1-phenylethylamino]-3-

phenylpropanamide (3j). Suspension of the residue in EtOAc/ hexane and filtration afforded the product as a white solid (0.25 g, 80% yield).

1H -NMR (DMSO- d_6 , 400 MHz): δ 7.74 (s, 1H), 7.42 (s, 1H), 7.32 (m, 4H), 7.24 (m, 6H), 7.16 (s, 1H), 6.83 (s, 1H), 3.97 (bq, 1H), 3.74 (d, J = 5 Hz, 1H), 3.05 (bt, 1H), 2.52 (dd, J = 9.1, 15 Hz, 1H), 2.30 (dd, J = 5.1, 15 Hz, 1H). ^{13}C -NMR (DMSO- d_6 , 100 MHz): δ 174.0, 172.5, 143.2, 140.4, 128.3, 128.1, 127.2, 127.1, 127.1, 63.3, 57.5, 43.7. HRMS (M+1) for $C_{17}H_{19}N_3O_2$ calcd 298.1555 expt. 298.1561

10) methyl 3-[(1S)-2-amino-2-oxo-1-phenylethylamino]-3-(4-methoxyphenyl)propanoate (3h). Crystallization from EtOAc/ hexane afforded the amine as a white solid (0.40 g, 46% yield).

1H -NMR (DMSO- d_6 , 400 MHz): δ 7.55 (s, 1H), 7.23 (m, 8H), 6.89 (d, J = 8.6 Hz, 2H), 3.92 (br-q, 1H), 3.74 (s, 3H), 3.72 (1H), 3.55 (s, 3H), 3.06 (br-t, 1H), 2.84 (dd, J = 8, 15 Hz, 1H), 2.54 (dd, J = 6.5, 15 Hz, 1H). ^{13}C -NMR (DMSO- d_6 , 100 MHz): δ 173.8, 171.5, 158.4, 140.1, 134.1, 128.2, 128.1, 127.2, 127.1, 113.7, 63.3, 56.8, 55.0, 51.2, 42.4. HRMS (M+1) for $C_{19}H_{22}N_2O_4$ calcd 343.1663 expt. 343.1663

11) Methyl 3-[(1S)-2-amino-2-oxo-1-phenylethylamino]-3-[4-(trifluoromethyl)phenyl]propanoate (3i). Flash chromatography (80% EtOAc/ hexane) afforded the amine as a resin.

1H -NMR (CD $_3$ OD, 400 MHz): δ 7.66 (d, J = 8 Hz, 2H), 7.54 (d, J = 8 Hz, 2H), 7.27 (m, 5H), 4.25 (m, 1H), 3.88 (s, 1H), 3.68 (s, 3H), 2.89 (dd, J = 9.0, 16.0 Hz, 1H), 2.70 (dd, J = 5.6, 16.0 Hz, 1H). ^{13}C -NMR (CD $_3$ OD, 100 MHz): δ 178.0, 173.6, 148.0, 140.7, 129.8, 129.3, 129.2, 128.7, 126.8, 126.8, 65.6, 59.1, 52.4, 43.0. HRMS (M+1) for $C_{19}H_{19}F_3N_2O_3$ calcd 381.1426 expt. 381.1433

Deprotected Amines:

General Procedure: A pressure reaction vessel is charged with PGA-amine, acetic acid (2.5 molar equiv), water, THF, and 30% Pd(OH) $_2$ (20 wt% based on PGA-amine) and

warmed to 50 °C. The vessel is pressure purged with nitrogen (3 x 40 psig) and pressurized with hydrogen (40 psig) and the reaction solution is stirred for 12 hours. After cooling to room temperature, the vessel is vented and the solution is filtered through Solka floc. The filter cake is then washed with THF. *CAUTION: The reduced palladium catalyst is pyrophoric, should be kept wet with solvent, and exposure to air should be minimized.* The filtrates are combined and the solvent is removed under reduced pressure to yield a mixture of the desired β -amino acid derivative as the acetate salt and 2-phenylacetamide byproduct. The assay yield of the amine salt was determined by $^1\text{H-NMR}$ using added dichloromethane as an internal reference. The stereochemical assignment was made by measuring the optical rotation of the crude product as its HCl salt and comparing its sign with what is reported in the literature or of an authentic reference sample. The HCl salt was prepared by addition of HCl/ ether and evaporation to dryness.

1) Methyl (3R)-3-aminobutanoate acetate

Assay yield was 99%. $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 3.73 (s, 3H), 3.65 (m, 1H), 2.70 (m, 2H), 1.95 (s, 3H), 1.34 (d, J = 6.6 Hz, 3H). $^{13}\text{C-NMR}$ (CD_3OD , 100 MHz): δ 178.4, 172.5, 52.8, 45.6, 39.1, 23.0, 18.9. HRMS ($M+1$) for $\text{C}_5\text{H}_{11}\text{NO}_2$ calcd 118.0868 expt. 118.0864. Observed (HCl salt): $[\alpha]_{\text{D}}^{27}$ = negative (water) (Thus, stereochemistry is *R* as shown). Literature for (*R*)-enantiomer (HCl salt): $[\alpha]_{\text{D}}^{28}$ = -37.0 (c 0.73, water). *J. Org. Chem.* **1992**, 57, 2396.

2) Methyl (3S)-3-amino-4-methylpentanoate acetate

Assay yield was 85%. $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 3.74 (s, 3H), 3.38 (m, 1H), 2.76 (dd, J = 4.0, 17.3 Hz, 1H), 2.59 (dd, J = 8.7, 17.3 Hz, 1H), 1.96 (m, 1H), 1.93 (s, 3H), 1.01 (~t, 6H). $^{13}\text{C-NMR}$ (CD_3OD , 100 MHz): δ 179.3, 173.4, 55.2, 53.1, 35.5, 32.3, 23.7, 19.0, 18.5. HRMS ($M+1$) for $\text{C}_7\text{H}_{15}\text{NO}_2$ calcd 146.1181 expt. 146.1178. Observed (HCl salt): $[\alpha]_{\text{D}}^{25}$ = negative (MeOH) (Thus, stereochemistry is *S* as drawn). Literature for the (*R*)-enantiomer (HCl salt): $[\alpha]_{\text{D}}^{25}$ = +28.2 (c 0.48, MeOH). *Tetrahedron* **1995**, 51, 12337.

3) Methyl (3R)-3-amino-4-phenylbutanoate acetate

Assay yield was 72%. $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.3 (m, 5H), 3.71 (m, 1H), 3.69 (s, 3H), 2.64 (dd, J = 4.8, 17.0 Hz, 1H), 2.54 (dd, J = 7.8, 17.0 Hz, 1H), 1.94 (s, 3H). $^{13}\text{C-NMR}$ (CD_3OD , 100 MHz): δ 172.9, 137.5, 130.6, 130.2, 128.6, 52.7, 51.0, 40.9, 37.9, 23.1. HRMS ($M+1$) for $\text{C}_{11}\text{H}_{15}\text{NO}_2$ calcd 194.1181 expt. 194.1184. Observed (HCl salt): $[\alpha]_{\text{D}}^{25}$ = negative (MeOH) (Thus, stereochemistry is *R* as drawn). Literature for the (*R*)-enantiomer (HCl salt): $[\alpha]_{\text{D}}$ = -9.2 (c 1.5, MeOH). *Biosci. Biotech. Biochem.*, **1996**, 60, 916.

4) [(1R)-1-benzyl-3-oxo-3-piperidin-1-ylpropyl]amine acetate

Assay yield was 92%. $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.3 (m, 5H), 3.78 (m, 1H), 3.52 (m, 2H), 3.32 (m, 2H), 3.08 (dd, J = 6.3, 13.7 Hz, 1H), 2.96 (dd, J = 8.5, 13.7 Hz, 1H), 2.64 (m, 2H), 1.96

(s, 3H), 1.63 (m, 2H), 1.51 (m, 4H). ^{13}C -NMR (CD_3OD , 100 MHz): δ 177.9, 169.8, 137.3, 130.6, 130.2, 128.6, 51.5, 49.2, 47.6, 44.0, 39.6, 34.6, 27.4, 26.7, 25.4, 22.8. HRMS ($\text{M}+1$) for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}$ calcd 247.1810 expt. 247.1802. Observed (HCl salt): $[\alpha]_{\text{D}}^{20}$ = negative (MeOH) (Thus, stereochemistry is *R* as shown). Authentic sample of (*S*)-enantiomer (HCl salt), prepared from Boc-L- β -homophenylalanine via EDC coupling with piperidine, followed by HCl deprotection: $[\alpha]_{\text{D}}^{20}$ = +37 (c 1.4, MeOH).

5) (3*R*)-3-amino-4-phenylbutanamide acetate

Assay yield was 93%. ^1H -NMR (CD_3OD , 400 MHz): δ 7.3 (m, 5H), 3.75 (m, 1H), 3.07 (dd, J = 6.1, 13.7 Hz, 1H), 2.90 (dd, J = 8.6, 13.7 Hz, 1H), 2.55 (m, 2H), 1.96 (s, 3H). ^{13}C -NMR (CD_3OD , 100 MHz): δ 178.4, 175.2, 136.9, 130.6, 130.2, 128.6, 51.4, 39.7, 36.4, 23.0. HRMS ($\text{M}+1$) for $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}$ calcd 179.1184 expt. 179.1176. Observed (HCl salt): $[\alpha]_{\text{D}}^{20}$ = negative (MeOH) (Thus, stereochemistry is *R* as shown). Authentic sample of (*S*)-enantiomer (HCl salt), prepared from Boc-L- β -homophenylalanine via EDC coupling with ammonia, followed by HCl deprotection: $[\alpha]_{\text{D}}^{20}$ = +11 (c 1.0, MeOH).

6) Methyl (1*S*,2*R*)-2-aminocyclohexanecarboxylate acetate

Assay yield was 60%. ^1H -NMR (CD_3OD , 400 MHz): δ 3.73 (s, 3H), 3.40 (m, 1H), 2.96 (~q, 1H), 2.05 (m, 1H), 1.89 (~s, 3H), 1.82 (m, 2H), 1.69 (m, 2H), 1.3-1.6 (m, 3H). ^{13}C -NMR (CD_3OD , 100 MHz): δ 179.2, 174.8, 52.7, 51.1, 43.8, 28.9, 27.3, 23.8, 23.6, 23.5; HRMS ($\text{M}+1$) for $\text{C}_8\text{H}_{15}\text{NO}_2$ calcd 158.1181 expt. 158.1180. Observed (HCl salt): $[\alpha]_{\text{D}}^{25}$ = positive (MeOH) (Thus, stereochemistry is 1*S*,2*R* as drawn). Literature for (1*R*,2*S*)-enantiomer (HCl salt): $[\alpha]_{\text{D}}$ = -0.9 (c 0.51, MeOH). *Tetrahedron Asymmetry* **2000**, 11, 1593.

7) Methyl 3-amino-3-phenylpropanoate + methyl 3-phenylpropanoate. Debenzylation was attempted on only one aryl PGA-enamine (**3g**). This PGA-amine (50 mg) was dissolved in toluene (2 mL), acetic acid (25 μL) and 7.5% $\text{Pd}(\text{OH})_2/\text{C}$ (40 mg) were added, and the mixture was stirred overnight at 50 $^\circ\text{C}$ under 40 psig of H_2 . The reaction mixture contained a trace of unconverted **3g**, 2-phenylacetamide byproduct, and a mixture of the two products, the β -aminoester and over-reduced phenylpropanoate in 1:1.3 ratio.

Note: Thus, under hydrogenolysis conditions, the removal of the PGA group appears to be problematic with 3-arylpropanoates due to the presence of competing benzylic sites for hydrogenolysis. The degree of over-reduction should be less severe with electron-deficient 3-arylpropanoates such as **3i** and heterocyclic compounds such as 3-pyridyl propanoates that can be protonated.