Practical Synthesis of Enantiomerically Pure β^2 -Amino Acids via Proline-Catalyzed Diastereoselective Aminomethylation of Aldehydes

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Supporting Information

General Procedures. Analytical thin-layer chromatography (TLC) was carried out on Whatman TLC plates precoated with silica gel 60 (250 μ m thickness). Visualization was performed using a UV lamp or potassium permanganate stain. Column chromatography was performed on EM Science silica gel (230-400 mesh) or Biotage flash column chromatography system.

Instrumentation. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Bruker AC-300 (300 MHz) spectrometers. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^1H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), or quartet (q). All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker AC-300 (75 MHz) spectrometer. Mass spectra (MS) were obtained using an electrospray ionization (ESI) mass spectrometer. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Perkin-Elmer 241 digital polarimeter and are reported as follows: $[\alpha]_D^{25}$ (c in g per 100 mL solvent).

Monitoring the Mannich reaction by ^1H NMR: A small aliquot (e.g., 50 μ L via a micropipettor) of the reaction mixture from the reaction flask at $-25\text{ }^\circ\text{C}$ was immediately injected to a NMR tube with 650 μ L CDCl_3 pre-cooled at $-25\text{ }^\circ\text{C}$. The reaction solution and NMR solvent was mixed at $-25\text{ }^\circ\text{C}$, and then warmed to ambient temperature for ^1H NMR analysis. It is important to prepare the NMR solution at low temperature in order to measure the accurate conversion and diastereoselectivity of the Mannich reaction. NMR parameter: RG (gain) = 1; NS = 32 (or more scans). Examples of the ^1H NMR spectra are shown below:

Mannich reaction for extended reaction time (excess aldehyde starting material was used):

Retro-Michael reaction of the Mannich products:

Table 2. Synthesis of Boc-β²-Amino Acids with Hydrophobic Side Chains:

3 simple operations
> 40% overall yield

entry ^a	R	dc ^b	7 ^c	isolated yield % (major diastereomer)	9
a	Pr	86:14	62	92	85
b	ⁿ Hex	89:11	51	92	89
c	Bn	88:12	62	99	92
d	ⁱ Pr	90:10	49	95	91
e	CH ₂ ⁱ Pr	83:17	51	96	90
f		84:16	52	91	95

^a 2.0 eq (entry a-d) or 1.5 eq (entry e-f) aldehyde was used; yield (sum of two diastereomers) of the Mannich reaction was > 90% as determined by ¹H NMR of the crude reaction mixture before reduction; the reduction is quantitative. ^b Determined by ¹H NMR of the crude reaction mixture before reduction. ^c Isolated via recrystallization or column chromatography.

Characterizations of **7a**, **8a**, and **9a** were reported in our original publication.¹

(S)-b-ⁿHexyl-g-(S)-N-benzyl-a-methylbenzylamino alcohol (7b): Colorless oil. TLC R_f = 0.28 (EtOAc/Hexanes, v/v, 1:5). ¹H NMR (300 MHz, CDCl₃) δ 7.23-7.37 (m, 10H), 5.01 (br, 1H), 4.03 (q, J = 6.6 Hz, 1H), 3.92 & 3.96 (s, 1H), 3.58 (m, 1H), 3.33 & 3.38 (s, 1H), 2.95-3.01 (m, 1H), 2.53-2.54 (m, 1H), 2.39-2.47 (m, 1H), 1.86-1.4 (m, 1H), 1.35 (d, J = 6.6 Hz, 3H), 1.22-1.28 (m, 8H), 0.94-0.98 (m, 2H), 0.87 (t, J = 6.6 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 142.8, 140.0, 129.5, 128.7, 128.42, 128.38, 127.5, 127.3, 68.5, 56.5, 55.2, 54.9, 36.8, 31.9, 30.3, 29.8, 27.5, 22.8, 14.3, 9.6. TOF-MS-ESI: [M+H]⁺ calculated 354.3, found 354.6. Optical rotation: [α]_D²⁵ = + 9.4° (c = 0.50, MeOH).

(S)-b-ⁿHexyl-g-Boc-amino alcohol (8b): Colorless oil (may solidify upon staying at rt). TLC R_f = 0.07 (EtOAc/Hexanes, v/v, 1:5). ¹H NMR (300 MHz, CDCl₃) δ 4.77 (br, 1H), 3.55-3.58 (m, 1H), 3.28-3.41 (m, 3H), 3.03-3.12 (m, 1H), 1.53-1.58 (m, 1H), 1.45 (s, 9H), 1.18-1.32 (m, br, 10H), 0.88 (t, J = 6.9 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 157.9, 80.1, 62.8, 41.8, 41.1, 32.0, 29.7, 28.9, 28.6, 27.3, 22.9, 14.3. TOF-MS-ESI: [M+H]⁺ calculated 260.2, found 260.5; [M+Na]⁺ calculated 282.2, found 282.5; [2M+Na]⁺ calculated 541.4, found 542.0. Optical rotation: [α]_D²⁵ = + 5.0° (c = 0.50, MeOH).

(S)-a-ⁿHexyl-β²-Boc-amino acid (9b): Colorless viscous oil. TLC R_f = 0.32 (MeOH/CH₂Cl₂, v/v, 1:10). ¹H NMR (300 MHz, CDCl₃) δ 10.91 (br, 1H), 5.05 & 6.57 (br, 1H), 3.16-3.49 (m, 2H), 2.61 (br, 1H), 1.28-1.68 (m, 18H), 0.88 (t, J = 6.9 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 180.9 & 179.4, 158.1 & 156.2, 81.2 & 79.8, 46.2 & 45.9, 42.9 & 41.6, 31.7, 29.9, 29.3, 28.5, 27.1, 22.8, 14.2. TOF-MS-ESI:

¹ Ch, Y.; Gellman, S. H. *J. Am. Chem. Soc.* 2006, 128, 6804.

[M-H]⁻ calculated 272.2, found 272.6; [2M-H]⁻ calculated 545.4, found 546.2. Optical rotation: $[\alpha]_D^{25} = +6.0^\circ$ ($c = 0.50$, MeOH).

(S)-b-Benzyl-g-(S)-N-benzyl-a-methylbenzylamino alcohol (7c): White solid; mp = 96-97 °C; TLC R_f = 0.22 (EtOAc/Hexanes, v/v, 1:5). ¹H NMR (300 MHz, CDCl₃) δ 7.07-7.37 (m, 15H), 4.48-4.49 (br, 1H), 3.98 (q, J = 6.6 Hz, 1H), 3.81 & 3.86 (s, 1H), 3.57 (br, 1H), 3.32 & 3.36 (s, 1H), 3.03-3.10 (m, 1H), 2.46-2.54 (m, 2H), 2.31-2.34 (m, 2H), 2.17-2.23 (m, 1H), 1.90 (d, J = 6.6 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 142.9, 140.3, 140.0, 129.5, 129.1, 128.7, 128.6, 128.4, 18.45, 128.35, 127.5, 127.3, 126.2, 67.3, 56.8, 55.2, 53.8, 39.0, 36.7, 10.2. TOF-MS-ESI: [M+H]⁺ calculated 360.2, found 360.6. Optical rotation: $[\alpha]_D^{25} = +31.4^\circ$ ($c = 0.50$, MeOH). X-ray quality crystals were obtained via slow evaporation of a hexanes solution; and the x-ray diffraction structure is shown below:

(S)-b-Benzyl-g-Boc-amino alcohol (8c): Pale yellow solid; mp = 70-71 °C; TLC R_f = 0.03 (EtOAc/Hexanes, v/v, 1:5). ¹H NMR (300 MHz, CDCl₃) δ 7.31-7.15 (m, 5H), 4.76 (m, 1H), 3.61-3.56 (m, 1H), 3.48-3.39 (m, 2H), 3.29-3.20 (m, 1H), 3.15-3.05 (m, 1H), 2.68-2.61 (m, 1H), 2.54-2.47 (m, 1H), 1.92-1.87 (m, 1H), 1.45 (s, 9H). ¹³C NMR (75 MHz, CDCl₃): δ 157.9, 140.1, 129.18, 129.15, 128.7, 126.4, 80.2, 62.2, 43.8, 40.5, 35.6, 28.6. TOF-MS-ESI: [M+H]⁺ calculated 266.2, found 266.5; [M+Na]⁺ calculated 288.2, found 288.5; [2M+Na]⁺ calculated 553.4, found 553.9. Optical rotation: $[\alpha]_D^{25} = +12.6^\circ$ ($c = 1.0$, MeOH).

(S)-Boc-β²-Homophenylalanine-OH (9c): White solid; mp = 82-83 °C; TLC R_f = 0.33 (MeOH/CH₂Cl₂, v/v, 1:10). ¹H NMR (300 MHz, CDCl₃) δ 10.93 (br, 1H), 7.31-7.20 (m, 5H), 6.72 & 5.02 (br, 1H), 3.44-2.58 (m, 5H), 1.42-1.37 (m, 9H). ¹³C NMR (75 MHz, CDCl₃): δ 179.4 & 179.3, 158.1 & 156.1, 138.4, 129.0, 128.8, 126.8, 81.4 & 79.9, 47.7 & 47.4, 42.3 & 41.5, 36.0 & 35.9, 28.5 & 28.4. TOF-MS-ESI: [M-H]⁻ calculated 278.3, found 278.5; [2M-H]⁻ calculated 557.6, found 558.0. Optical rotation: $[\alpha]_D^{25} = -45.0^\circ$ ($c = 1.0$, CH₂Cl₂).

(S)-b-Isopropyl-g-(S)-N-benzyl-a-methylbenzylamino alcohol (7d): Colorless oil; TLC R_f = 0.19 (EtOAc/Hexanes, v/v, 1:5). ^1H NMR (300 MHz, CDCl_3) δ 7.37-7.23 (m, 10H), 5.07-5.04 (br, 1H), 4.05 (q, J = 6.6 Hz, 1H), 3.95 & 3.91 (s, 1H), 3.62-3.56 (br, 1H), 3.37 & 3.33 (s, 1H), 3.10-3.04 (m, 1H), 2.62-2.59 (m, 2H), 1.78-1.73 (m, 1H), 1.49-1.42 (m, 1H), 1.37 (d, J = 6.6 Hz, 3H), 0.84 & 0.78 (diastereotopic, d, J = 6.9 Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 142.7, 138.9, 129.5, 128.7, 128.4, 127.5, 127.4, 66.5, 56.5, 56.1, 52.5, 42.2, 28.8, 20.5, 20.0, 9.5. TOF-MS-ESI: $[\text{M}+\text{H}]^+$ calculated 312.2, found 312.5. Optical rotation: $[\alpha]_D^{25} = +19.2^\circ$ (c = 0.50, MeOH).

(S)-b-Isopropyl-g-Boc-amino alcohol (8d): Pale yellow solid; mp = 68-69 $^\circ\text{C}$; TLC R_f = 0.05 (EtOAc/Hexanes, v/v, 1:5). ^1H NMR (300 MHz, CDCl_3) δ 4.80 (br, 1H), 3.69-3.66 (m, 1H), 3.55-3.51 (m, 1H), 3.38-3.35 (m, 1H), 3.28-3.17 (m, 2H), 1.66-1.61 (m, 1H), 1.32-1.30 (m, 1H), 0.95 & 0.94 (diastereotopic, d, J = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ 157.9, 79.9, 61.9, 47.9, 39.7, 28.6, 27.3, 20.8, 20.7. TOF-MS-ESI: $[\text{M}+\text{H}]^+$ calculated 218.2, found 218.4; $[\text{M}+\text{Na}]^+$ calculated 240.2, found 240.4; $[2\text{M}+\text{Na}]^+$ calculated 457.4, found 457.8. Optical rotation: $[\alpha]_D^{25} = +11.4^\circ$ (c = 0.50, MeOH).

(S)-Boc- β^2 -Homovaline-OH (9d): White solid; mp = 70-71 $^\circ\text{C}$; TLC R_f = 0.28 (MeOH/ CH_2Cl_2 , v/v, 1:10). ^1H NMR (300 MHz, CDCl_3) δ 6.90 & 5.05 (br, 1H), 3.53-3.38 (m, 1H), 3.29-3.10 (m, 1H), 2.50-2.41 (m, 1H), 2.05-1.89 (m, 1H), 1.49-1.45 (m, 9H), 1.02-0.96 (m, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ 180.6 & 179.3, 158.1 & 156.2, 81.2 & 79.8, 45.9 & 45.6, 42.9 & 41.6, 31.9, 28.6, 20.4, 14.1. TOF-MS-ESI: $[\text{M}-\text{H}]^-$ calculated 230.2, found 230.5; $[2\text{M}-\text{H}]^-$ calculated 461.3, found 462.0. Optical rotation: $[\alpha]_D^{25} = +35.4^\circ$ (c = 0.50, MeOH).

(S)-b-2-Methylpropyl-g-(S)-N-benzyl-a-methylbenzylamino alcohol (7e): Colorless oil; TLC R_f = 0.22 (EtOAc/Hexanes, v/v, 1:5). ^1H NMR (300 MHz, CDCl_3) δ 7.34-7.26 (m, 10H), 5.12 (br, 1H), 4.03 (q, J = 6.9 Hz, 1H), 3.98 & 3.93 (s, 1H), 3.54 (br, 1H), 3.39 & 3.35 (s, 1H), 2.98-2.92 (m, 1H), 2.56-2.52 (m, 1H), 2.46-2.38 (m, 1H), 2.08-1.93 (br, 1H), 1.58-1.54 (m, 1H), 1.35 (d, J = 6.9 Hz, 3H), 0.90-0.78 (m, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ 142.8, 138.9, 129.5, 128.7, 128.4, 128.3, 127.5, 127.3, 68.8, 56.5, 55.3, 55.1, 39.5, 34.5, 25.6, 23.1, 22.9, 9.5. TOF-MS-ESI: $[\text{M}+\text{H}]^+$ calculated 326.2, found 326.6. Optical rotation: $[\alpha]_D^{25} = +13.8^\circ$ (c = 0.50, MeOH). X-ray quality crystals were obtained via vapor diffusion of Et_2O to a MeOH-EtOAc solution of **7e** HCl salt;² and the x-ray diffraction structure is shown below:

² See “ General procedures for isolating the major diastereomers via recrystallization “ in the main text

(S)- b-2-Methylpropyl-g-Boc-amino alcohol (8e): White solid; mp = 54-55 °C; TLC R_f = 0.07 (EtOAc/Hexanes, v/v, 1:5). ^1H NMR (300 MHz, CDCl_3) δ 4.81 (br, 1H), 3.60-3.53 (m, 1H), 3.48-3.44 (m, 1H), 3.37-3.31 (m, 1H), 3.09-3.02 (m, 1H), 1.72-1.58 (m, 2H), 1.45 (s, 9H), 1.19-0.98 (m, 2H), 0.89 (d, J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ 157.9, 80.0, 62.9, 41.2, 39.3, 28.6, 25.4, 23.0, 22.9. TOF-MS-ESI: $[\text{M}+\text{Na}]^+$ calculated 254.2, found 254.4; $[\text{2M}+\text{Na}]^+$ calculated 485.4, found 485.9. Optical rotation: $[\alpha]_D^{25} = +5.6^\circ$ (c = 0.50, MeOH).

(S)-Boc- β^2 -Homoleucine-OH (9e): White solid; mp = 56-57 °C; TLC R_f = 0.28 (MeOH/ CH_2Cl_2 , v/v, 1:10). ^1H NMR (300 MHz, CDCl_3) δ 10.26 (br, 1H), 6.68 & 5.04 (br, 1H), 3.44-2.98 (m, 2H), 2.73-2.61 (m, 1H), 1.75-1.65 (m, 1H), 1.54-1.44 (m, 11H), 0.94-0.91 (m, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ 181.0 & 179.6, 158.1 & 156.1, 81.3 & 79.8, 44.3 & 44.0, 43.3 & 42.0, 39.1 & 38.8, 29.9, 20.5, 26.0, 22.60 & 22.56. TOF-MS-ESI: $[\text{M}-\text{H}]^-$ calculated 244.2, found 244.5; $[\text{2M}-\text{H}]^-$ calculated 489.4, found 490.1. Optical rotation: $[\alpha]_D^{25} = +12.4^\circ$ (c = 0.50, MeOH).

(S)-b-Cyclohexylmethyl -g-(S)-N-benzyl-a-methylbenzylamino alcohol (7f): Colorless oil (may solidify upon staying at rt). TLC R_f = 0.28 (EtOAc/Hexanes, v/v, 1:5). ^1H NMR (300 MHz, CDCl_3) δ 7.34-7.25 (m, 10H), 5.15 (d, J = 7.8 Hz), 4.03 (q, J = 7.5 Hz, 1H), 3.97 & 3.92 (s, 1H), 3.57-3.54 (m, 1H), 3.39 & 3.35 (s, 1H), 2.98-2.91 (m, 1H), 2.55-2.51 (m, 1H), 2.45-2.37 (m, 1H), 2.02 (br, 1H), 1.70-1.61 (m, 4H), 1.36 (d, J = 7.5 Hz, 3H), 1.22-1.13 (m, 4H), 0.84-0.78 (m, 4H). ^{13}C NMR (75 MHz, CDCl_3): δ 142.8, 138.9, 129.5, 128.7, 128.42, 128.39, 127.5, 127.3, 68.9, 56.6, 55.3, 38.0, 35.3, 33.9, 33.8, 33.6, 26.8, 26.53, 26.47, 9.7. TOF-MS-ESI: $[\text{M}+\text{H}]^+$ calculated 366.3, found 366.7. Optical rotation: $[\alpha]_D^{25} = +17.2^\circ$ (c = 0.50, MeOH). X-ray quality crystals were obtained via vapor diffusion of Et_2O to a MeOH-EtOAc solution of **7f**-HCl salt;² and the x-ray diffraction structure is shown below:

(S)- b-Cyclohexylmethyl-g-Boc-amino alcohol (8f): White solid; mp = 69-71 °C; TLC R_f = 0.08 (EtOAc/Hexanes, v/v, 1:5). ^1H NMR (300 MHz, CDCl_3) δ 4.86 (br, 1H), 3.56-3.29 (m, 4H), 3.08-3.01 (m, 1H), 1.80-1.67 (m, 6H), 1.45 (s, 9H), 1.28-1.03 (m, 6H), 0.91-0.84 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 157.8, 79.9, 63.0, 41.3, 38.4, 36.6, 34.9, 33.8, 28.6, 26.8, 26.49, 26.47. TOF-MS-ESI: $[\text{M}+\text{H}]^+$ calculated 272.2, found 272.5; $[\text{M}+\text{Na}]^+$ calculated 294.2, found 294.5, $[\text{2M}+\text{Na}]^+$ calculated 565.4, found 566.0. Optical rotation: $[\alpha]_D^{25} = +23.0^\circ$ ($c = 0.50$, CH_2Cl_2).

(S)-a-Cyclohexylmethyl- β^2 -Boc-amino acid 9f: White solid; mp = 98-99 °C; TLC R_f = 0.35 (MeOH/ CH_2Cl_2 , v/v, 1:10). ^1H NMR (300 MHz, CDCl_3) δ 6.71 & 5.00 (br, 1H), 3.43-2.95 (m, 2H), 2.73 (br, 1H), 1.79-1.57 (m, 6H), 1.48-1.44 (m, 9H), 1.35-1.18 (m, 6H), 0.94-0.86 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 180.8 & 179.6, 81.3 & 79.8, 43.5 & 43.2, 42.1, 37.6 & 37.5, 35.3, 33.4 & 33.1, 28.6, 26.7, 26.32 & 26.29. TOF-MS-ESI: $[\text{M}-\text{H}]^-$ calculated 284.2, found 284.6; $[\text{2M}-\text{H}]^-$ calculated 569.4, found 570.2. Optical rotation: $[\alpha]_D^{25} = -27.1^\circ$ ($c = 1.0$, CH_2Cl_2).³

³ Optical rotation of this compound in MeOH is weak ($[\alpha]_D^{25} = \sim +1.0^\circ$ ($c = 5.0$, MeOH)), and such a small reading is not reliable.

Scheme 3. Synthesis of Fmoc- β^2 -amino acids with protected functionalized side chains.

β^2 -Homoglutamic Acid (**13a**):

The aldehyde precursor used for the synthesis of Fmoc- β^2 -Glu(*t*-Bu)⁴ was prepared by modification of a previously reported method.⁵ Briefly, glutaric anhydride was allowed to react with *t*-butanol to yield mono *t*-butyl glutarate **S1**.⁵ The carboxylic acid was converted to the corresponding Weinreb amide (**S2**) and subsequently reduced with DIBAL-H to yield aldehyde **10a**. Aldehyde **10a** was subjected to the diastereoselective Mannich reaction conditions to afford *N,N*-disubstituted amino alcohol **11a**. Hydrogenolysis followed by Fmoc-protection and oxidation yielded Fmoc- β^2 -Glu(*t*-Bu) **13a**, which suitable for use in solid phase peptide synthesis.

Carboxylic acid S1: Prepared as previously described in the literature.⁵ Glutaric anhydride (10.0 g, 87.6 mmol) was weighed into a dry flask and purged with N₂. Dry toluene (50 mL) was added followed by *N*-hydroxysuccinimide (3.0 g, 26.1 mmol), 4-dimethylaminopyridine (1.07 g, 8.8 mmol), anhydrous *tert*-butanol (24.3 mL, 262.3 mmol), and triethylamine (3.6 mL, 25.8 mmol). The flask was fitted with a reflux condenser, heated to 115°C, and allowed to stir for 16 h under N₂. The solution was cooled to room temperature, diluted with 300 mL EtOAc, and washed with 5% aqueous NaHSO₄ (3×) followed by brine. The organic layer was dried over MgSO₄, filtered and concentrated. The crude material was purified by chromatography eluting with 1:1 hexanes/EtOAc to yield 4.48 g (27% yield) of the product as a colorless oil. TLC R_f = 0.34 (EtOAc/hexanes, v/v, 1:1). ¹HNMR (300MHz, CDCl₃): δ 10.83 (br s, 1H), 2.42 (t, *J* = 7.4 Hz, 2H), 2.31 (t, *J* = 2.31 Hz, 2H), 1.92 (m, 2H), 1.45 (s, 9H). ¹³CNMR (75 MHz, CDCl₃): δ 179.2, 172.3, 80.5, 34.4, 33.0, 28.0, 20.0. ESI-TOF-MS: [M-H]⁻ calculated 187.1, found 187.4.

Weinreb amide S2: Prepared by a modification of a literature method.⁵ The starting carboxylic acid **S1** (4.4 g, 23.4 mmol) was dissolved in CH₂Cl₂ (100 mL). *N,O*-dimethylhydroxylamine·HCl (2.51 g, 25.7 mmol), 1-hydroxybenzotriazole hydrate (3.93 g, 25.7 mmol), diisopropylethylamine (9.0 mL, 51.7 mmol), and EDC·HCl (4.93 g, 25.7 mmol) were added sequentially to the reaction mixture. The solution was allowed to stir at room temperature for 2 h and then concentrated under vacuum to remove most of the CH₂Cl₂. The crude material was diluted with EtOAc

⁴ Lelais, G.; Campo, M. A.; Kopp, S.; Seebach, D. *Helv. Chim. Acta* **2004**, 87, 1545-1560.

⁵ Bitan, G.; Muller, D.; Kasher, R.; Gluhov, E. V.; Gilon, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1501-1510.

(300 mL), and washed successively with 5% aqueous NaHSO₄ (3×), 5% aqueous NaHCO₃ (3×), and brine. The organic layer was dried over MgSO₄, filtered and concentrated to afford 5.14 g (95% yield) of the product as a pale yellow oil which was used without further purification. TLC R_f = 0.44 (EtOAc/hexanes, v/v, 1:2). ¹H NMR (300 MHz, CDCl₃) δ 3.68 (s, 3H), 3.18 (s, 3H), 2.48 (t, *J* = 7.4 Hz, 2H), 2.30 (t, *J* = 7.4 Hz, 2H), 1.92 (m, 2H), 1.45 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 174.0, 172.7, 80.2, 77.5, 61.3, 35.0, 32.3, 31.0, 28.2, 20.2. ESI-TOF-MS: [M+H]⁺ calculated 232.2, found 232.4.

Aldehyde 10a: Weinreb amide **S2** (5.0 g, 21.6 mmol) was dissolved in dry THF (100 mL) and the solution was cooled to 0 °C under N₂. Diisobutylaluminum hydride (43 mL of a 1.0 M solution in CH₂Cl₂, 43 mmol) was added over 5 min.

The reaction mixture was allowed to stir at 0 °C for 30 min and then quenched by slow addition of EtOAc (50 mL). The solution was poured into water (200 mL) and extracted with EtOAc (2 × 400 mL). The combined organic layers were washed successively with satd. NaHCO₃ (100 mL) and brine (100 mL), dried over MgSO₄, filtered and concentrated. The crude material was purified by chromatography eluting with 3:1 hexanes/EtOAc to yield 2.2 g (59% yield) of the product as a colorless oil. TLC R_f = 0.76 (EtOAc/hexanes, v/v, 1:2). ¹H NMR (300 MHz, CDCl₃) δ 9.78 (t, *J* = 1.4 Hz, 1H), 2.51 (td, *J* = 7.3 Hz, 1.4 Hz, 2H), 2.28 (t, *J* = 7.3 Hz, 2H), 1.92 (m, 2H), 1.45 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 201.2, 171.9, 80.0, 42.7, 34.1, 27.8, 17.3. ESI-TOF-MS: [M+Na]⁺ calculated 195.1, found 195.1.

(S)-b-Carboxyethyl-tert-butyl ester-g-(S)-N-benzyl-a-methylbenzyl amino alcohol (11a): L-Proline (40 mg, 0.35 mmol) was suspended in DMF (2 mL) and allowed to stir at room temperature overnight. The mixture was then cooled to -25 °C in a temperature-regulated cooling bath. Aldehyde **10a** (300 mg, 1.74 mmol) in DMF (0.5 mL) was added followed by *N,O*-acetal **3** (296 mg, 1.16 mmol) in DMF (0.5 mL). The reaction mixture was allowed to stir at -25 °C for 2 h, ¹H NMR

analysis indicated complete conversion of the limiting reagent,⁶ and then warmed to 0 °C.⁷ NaBH₄ (174 mg, 4.6 mmol) was added followed by MeOH (1 mL). The reaction mixture was allowed to stir at 0 °C for 20 min. and then transferred slowly into a solution of saturated aqueous. NH₄Cl (10 mL). The resulting milky suspension was extracted with Et₂O (3 × 30 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered and concentrated. The crude material was purified by chromatography eluting with 4:1 hexanes / EtOAc to yield 207 mg (45% yield) of the desired product (the major diastereomer) as a colorless oil. TLC R_f = 0.58 (EtOAc/hexanes, v/v, 1:2). ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.20 (m, 10H), 4.52 (br s, 1H), 4.01 (q, *J* = 6.9 Hz, 1H), 3.86 (d, *J* = 13.2 Hz, 1H), 3.55 (m, 1H), 3.38 (d, *J* = 13.2 Hz, 1H), 3.04 (dd, *J* = 10.8 Hz, 8.0 Hz, 1H), 2.55 (m, 1H), 2.44 (dd, *J* = 12.8, 10.8 Hz, 1H), 2.18 (t, *J* = 7.7 Hz, 2H), 1.88 (m, 1H), 1.42 (s, 9H), 1.35 (d, *J* = 6.9 Hz, 3H), 1.40-1.30 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 172.1, 142.4, 138.7, 129.1, 128.4, 128.1, 128.0, 127.2, 127.0, 80.2, 66.9, 56.2, 54.8, 53.7, 36.3, 33.1, 28.0, 25.0, 9.5. ESI-TOF-HRMS: [M+H]⁺ calculated 398.2695, found 398.2693. Optical rotation: [α]_D²⁵ = + 38.0° (*c* = 0.5, CHCl₃).

⁶ The reaction time varied (as in other Mannich reactions discussed in this paper), partially because of the limited solubility of proline catalyst. It is important to monitor the reaction by ¹H NMR for optimal results when aldehyde starting material is not in excess.

⁷ Addition of NaBH₄ (and MeOH) at -25 °C, and then replacement of the -25 °C bath with an ice bath was used in the synthesis shown in Table 2 and for β²-homolysine. Although no studies were performed to compare the difference of these two procedures, addition of NaBH₄ at -25 °C before the switch to an ice bath is recommended.

(S)-b-Carboxyethyl-tert-butyl ester-g-Fmoc-amino alcohol (12a): Benzyl protected amino alcohol **11a** (282 mg, 0.71 mmol) was dissolved in MeOH (10 mL) under N₂. Ammonium formate (448 mg, 7.10 mmol) was added followed by Pd/C (282 mg of 10 wt. % on activated carbon, wet). The reaction mixture was refluxed overnight. The mixture was cooled to room temperature and filtered over celite with thorough MeOH washes of the filter agent to recover all product. The filtrate was concentrated to a residue to which CH₂Cl₂ (7 mL) was added followed by diisopropylethylamine (123 μ L, 0.71 mmol) and Fmoc *N*-hydroxysuccinimide ester (239 mg, 0.71 mmol). The reaction mixture was allowed to stir at room temperature for 1 h. The solution was diluted with EtOAc (70 mL) and washed successively with 5% aqueous NaHSO₄, 5% aqueous NaHCO₃, and brine. The organic layer was dried over MgSO₄, filtered and concentrated. The crude material was purified by chromatography eluting with 2:1 to 1:1 hexanes / EtOAc to yield 240 mg (80% yield) of the product as a colorless oil. TLC R_f = 0.43 (EtOAc/hexanes, v/v, 1:1). ¹HNMR (300 MHz, CDCl₃) δ 7.74 (d, *J* = 7.6 Hz, 2H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.29 (td, *J* = 7.6 Hz, 1.3 Hz, 2H), 5.37 (t, *J* = 7.2 Hz, 1H), 4.41 (d, *J* = 6.9 Hz, 2H), 4.19 (t, *J* = 6.9 Hz, 1H), 3.6-3.0 (m, 5H), 2.28 (m, 2H), 1.55 (m, 3H), 1.44 (s, 9H). ¹³CNMR (75 MHz, CDCl₃) δ 173.3, 157.6, 143.80, 143.78, 141.3, 127.6, 127.0, 124.9, 119.9, 80.6, 77.2, 66.7, 62.1, 47.2, 41.03, 40.99, 32.9, 28.0, 23.1. ESI-TOF-HRMS: [M+Na]⁺ calculated 448.2100, found 448.2101. Optical rotation: [α]_D^{rt} = + 8.8° (*c* = 0.5, CH₂Cl₂).

(S)-Fmoc-b²-homoglutamic acid tert-butyl ester (13a): Fmoc-amino alcohol **12a** (185 mg, 0.44 mmol) was dissolved in acetone (4 mL) and cooled to 0 °C. Jones reagent (1.75 mL of a 0.5 M H₂Cr₂O₇ solution in H₂O, 0.88 mmol) was added dropwise. The reaction mixture was warmed to room temperature and allowed to stir for 2 h. *i*-PrOH (1 mL) was added, and the reaction mixture was allowed to stir for an additional 15 min. to quench the remaining Jones reagent. The reaction mixture was partitioned between H₂O (50 mL) and EtOAc (150 mL). The organic layer was separated, dried over MgSO₄, filtered and concentrated. The crude material was purified by chromatography eluting with 60:40:1 hexanes / EtOAc / AcOH to yield 129 mg (68% yield) of the product as a colorless oil. The product could be obtained as a solid by dissolving the oil in minimal EtOAc followed by dilution with heptane, overnight refrigeration, and filtration to collect the product as a white solid. mp = 118-120°C. TLC R_f = 0.47 (MeOH/CH₂Cl₂, v/v, 1:9). ¹HNMR (300 MHz, DMSO-d₆) δ 12.32 (br s, 1H), 7.86 (d, *J* = 7.3 Hz, 2H), 7.67 (d, *J* = 7.4 Hz, 2H), 7.50-7.35 (m, 3H), 7.31 (t, *J* = 7.4 Hz, 2H), 4.35-4.15 (m, 3H), 3.21 (m, 1H), 3.06 (m, 1H), 2.45 (m, 1H), 2.21 (m, 2H), 1.66 (m, 2H), 1.36 (s, 9H); ¹³CNMR (75 MHz, DMSO-d₆) δ 175.6, 172.3, 156.8, 144.6, 141.4, 128.3, 127.7, 125.9, 120.8, 80.3, 66.1, 47.4, 45.0, 42.6, 33.1, 28.4, 25.0; ESI-TOF HRMS (*m/z*) [M-H]⁻ obsd. = 438.1904 (calc. = 438.1917). Optical rotation: [α]_D^{rt} = +1.0° (*c* = 1.0, CHCl₃).

β²-Homotyrosine (13b)

The aldehyde precursor **10b** used for the synthesis of β²-homotyrosine (**13b**) was prepared from *p*-cresol as outlined below.

1-tert-Butoxy-4-methylbenzene (S3): A solution of *p*-cresol (20 g, 185 mmol) in anhydrous CH₂Cl₂ (370 mL) was cooled to -15 °C. Catalytic conc. H₂SO₄ (1 mL) was

added to the stirred solution. Isobutene gas was bubbled through the reaction mixture for 15 min. The reaction mixture was stirred under N₂ at –15 °C for an additional 20 min. Saturated aqueous NaHCO₃ was added to the reaction flask until reaction mixture was neutralized. [Caution: The reaction must be kept cold until the acid is completely quenched. Warmer temperatures result in extensive Friedel-Crafts alkylation side products. Under these conditions, the major side product is Friedel-Crafts alkylation *ortho* to the hydroxyl group.] The layers were separated, and the organic layer was collected and washed with 1 M aqueous NaOH. The combined aqueous layers were further extracted with CH₂Cl₂, and all the organic layers were combined, dried over MgSO₄, filtered and concentrated to give a crude product, from which the product was isolated via chromatography (19:1 Hexanes:EtOAc) as a clear oil (13.3 g, 44% yield); TLC R_f = 0.64 (Hexanes/EtOAc, v/v, 7:3). ¹H NMR (300 MHz, CDCl₃): 7.05 (m, 2H), 6.88 (m, 2H), 2.31 (s, 3H), 1.32 (s, 9H). ¹³C NMR (75 MHz, CDCl₃): 153.1, 132.9, 129.5, 124.3, 78.2, 29.0, 20.9. TOF-MS-ESI: [M+Na]⁺ calculated 187.23, found 187.3

3-(4-*tert*-Butoxyphenyl)-propan-1-ol (S4):⁸ A solution of 1-*tert*-Butoxy-4-methylbenzene (S3) (8.81g, 53.7 mmol) in anhydrous THF (165 mL) was cooled to –15 °C under N₂. KO^tBu (80.6 mL, 1 M in THF, 80.6 mmol) and *n*-BuLi (32.2 mL, 2.5 M in hexane, 80.6 mmol) were added; upon addition the reaction mixture turned a deep red color. After 1 h, (2-Bromoethoxy)-*tert*-butyl-dimethylsilane (17.3 mL, 80.6 mmol) was added by a syringe to the cold solution. The red color began to dissipate, and the reaction mixture was gradually warmed to room temperature and was stirred overnight under N₂. The reaction mixture was poured into a separation funnel containing 400 mL H₂O. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 200 mL). The extraction was monitored by TLC. The combined organic layers were dried over MgSO₄, filtered and concentrated to give an oil. The crude oil was filtered through a silica gel plug with excess EtOAc. The filtrates were collected and concentrated to give a yellow oil. The yellow oil was dissolved in anhydrous THF (85 mL). TBAF (85 mL, 1M in THF, 80.6 mmol) was added, and the reaction mixture was stirred at room temperature under N₂. After complete conversion of the silyl ether, the reaction was diluted with H₂O (200 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated to give an oil. The crude oil was purified by chromatography (7:3 Hex: EtOAc) to yield 6.60 g product (59% yield) as a clear oil; TLC R_f = 0.25 (Hex/EtOAc, v/v, 7:3). ¹H NMR (300 MHz, CDCl₃): 7.08 (m, 2H), 6.91 (m, 2H), 3.68 (m, 2H), 2.67 (m, 2H), 1.88 (m, 2H), 1.33 (s, 9H). ¹³C NMR (75 MHz, CDCl₃): 153.6, 136.8, 128.9, 124.4, 78.3, 62.5, 34.5, 31.6, 29.0. TOF-MS-ESI: [M+H]⁺ calculated 209.30, found 209.1; [M+Na]⁺ calculated 231.1, found 231.1; [2M+Na]⁺ calculated 439.6, found 439.3

S4

3-(4-*tert*-Butoxyphenyl)propionaldehyde (10b): To a solution of 3-(4-*tert*-butoxyphenyl)-propan-1-ol S4 (2.39 g, 11.5 mmol) in anhydrous CH₂Cl₂ (115 mL) under N₂ was added PCC (3.73 g, 17.3 mmol). The reaction flask was fitted with a reflux condenser, and the reaction mixture was stirred under N₂ for 90 min. Anhydrous Et₂O (120 mL) was added to the reaction mixture, and a brown solid precipitated out. The resulting slurry was filtered through a pad of silica gel to remove the solid. The brown gum left in the reaction flask was washed with Et₂O (3 x 50 mL). The combined filtrate was concentrated to give a yellow oil (1.54 g, 65% crude yield) that was carried on to the next step without further purification. TLC R_f = 0.50 (Hex/EtOAc, v/v, 7:3). ¹H NMR (300 MHz, CDCl₃): 9.82 (t, J=1.5

10b

⁸ Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Org. Chem.* **2003**, 68, 4281.

Hz, 1H), 7.08 (m, 2H), 6.91 (m, 2H), 2.92 (t, J=7.5 Hz, 2H), 2.77 (t, J=7.5Hz, 2H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3): 201.9, 154.0, 135.3, 128.8, 124.5, 45.6, 29.0, 27.7. TOF-MS-ESI: $[\text{2M}+\text{Na}]^+$ calculated 435.55 found 435.6.

(S)-b-4-tert-Butoxyphenyl-g-(S)-N-benzyl-a-methylbenzylamino alcohol

(11b): A suspension of L-proline (357 mg, 3.1 mmol) in HPLC grade DMF (50 mL) was stirred at room temperature under N_2 for 12 h. The mixture was cooled to $-25\text{ }^\circ\text{C}$ under N_2 and aldehyde **10b** (2.49 g, 12.1 mmol) was added. *N,O*-acetal **3** (2.37 g, 9.3 mmol) was then added to the cooled solution, and the reaction mixture was stirred at $-25\text{ }^\circ\text{C}$ under N_2 . The reaction was monitored by NMR for conversion of the starting aldehyde. If the reaction proceeds too long, elimination of the dibenzylamine to give the α,β -unsaturated aldehyde (retro-Michael reaction of the Mannich product) occurs. When the reaction was complete, the reaction mixture was warmed to $0\text{ }^\circ\text{C}$, and NaBH_4 (1.06 g, 27.9 mmol) and MeOH (10 mL) were added.⁷ The reaction mixture was stirred for 2 h at $0\text{ }^\circ\text{C}$. The mixture was poured slowly into saturated aqueous NH_4Cl (25 mL), and the resulting milky mixture was extracted with Et_2O (3 x 50 mL; the extraction was monitored by TLC). The organic layers were combined, dried and concentrated to give a crude mixture, from which the major diastereomer was isolated via chromatography eluting with 10:1 Hexanes:EtOAc. After column chromatography, the pure major diastereomer contained a small amount of the chiral dibenzylamine that is a byproduct from the retro-Michael reaction of the Mannich product. This amine streaks through the column, and it can be eliminated with repeated chromatography, but this causes the yield to suffer. This small impurity does not affect the next step of the synthesis. Isolated yield = 43% (desired diastereomer). TLC R_f = 0.48 (Hex/EtOAc, v/v, 7:3). ^1H NMR (300 MHz, CDCl_3): 7.36-7.26 (m, 10H), 6.96 (m, 2H), 6.89 (m, 2H), 4.00 (q, J=6.9 Hz, 1H), 3.84 (d, J=13 Hz, 1H), 3.56 (m, 1H), 3.32 (d, J=13 Hz, 1H), 3.05 (dd, J=10.5, 8 Hz, 1H), 2.43 (m, 2H), 2.28 (d, J=7.4 Hz, 2H), 2.16 (m, 1H), 1.32 (s, 9H), 1.29 (d, J=6.7 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): 153.7, 142.9, 139.1, 135.2, 129.5, 128.7, 128.5, 128.4, 127.6, 127.4, 127.2, 127.1, 127.0, 124.4, 78.4, 67.3, 66.1, 56.8, 55.2, 53.9, 39.2, 36.0, 29.1, 15.5, 10.2. TOF-MS-ESI: $[\text{M}+\text{H}]^+$ calculated 432.6, found 432.3. $[\alpha]_D^{25} = +16.5^\circ$ (c = 9.2, MeOH)

(S)-b-4-tert-Butoxyphenyl-g-Fmoc-amino alcohol (12b): Benzyl amino alcohol (**11b**) (1.5 g, 3.48 mmol) was dissolved in MeOH (35 mL). Ammonium formate (4.52 g, 69.6 mmol), HOAc (199 μL , 3.48 mmol) and Pearlman's catalyst (0.75 g, 50% by mass) were added (gas began to evolve from the reaction mixture upon addition of Pearlman's catalyst). The reaction mixture was heated to reflux under N_2 and stirred at reflux for 12 h.

Debenzylation was monitored by NMR because completely debenzylated material and mono-debenzylated material could not be resolved by TLC. The reaction mixture was filtered through celite to remove the solid catalyst after complete debenzylation. The filtrate was concentrated and was carried on to the next step without further purification. ^1H NMR (300 MHz, CD_3OD): 7.15 (m, 2H), 6.94 (m, 2H), 3.17 (dd, J=10.6, 3.9 Hz, 1H), 3.52 (dd, J=10.8, 7.4 Hz, 1H), 2.99 (m, 2H), 2.60 (m, 2H), 2.15 (m, 1H), 1.31 (s, 9H). ^{13}C NMR (75 MHz, CD_3OD): 154.0, 134.1, 129.4, 124.2, 78.3, 63.3, 42.4, 40.6, 34.2, 28.0. TOF-MS-ESI: $[\text{M}+\text{H}]^+$ calculated 238.4, found 238.1; $[\text{2M}+\text{H}]^+$ calculated 475.7, found 475.3.

The amino alcohol crude product dissolved in anhydrous CH_2Cl_2 (30 mL) was cooled to $0\text{ }^\circ\text{C}$. Fmoc-OSu (1.17 g, 3.48 mmol) and DIEA (6.1 mL, 34.8 mmol) were added to the solution. The mixture was stirred at $0\text{ }^\circ\text{C}$ for 2 h (TLC indicated complete reaction). The reaction mixture was transferred to a separation funnel and washed with water. The organic layer was collected, dried over MgSO_4 , filtered

and concentrated. The product was isolated via chromatography (EtOAc/Hexanes, 7:3) as a white solid. The product co-elutes with and cannot be easily purified from Fmoc-OH. The mixture was taken into the next step, and the Fmoc-OH was easily separable from the final amino acid. Estimated yield of the two step transformation is about 45%. TLC R_f = 0.29 (Hex/EtOAc, v/v, 1:1). ^1H NMR (300 MHz, CDCl_3): 7.77 (m, 2H), 7.58 (m, 2H), 7.43-7.29 (m, 4H), 7.04 (m, 2H), 6.91 (m, 2H), 4.94 (t, J = 5.9 Hz, 1H), 4.47 (d, J = 6.1 Hz, 2H), 4.21 (t, J = 6.5 Hz, 1H), 3.54 (m, 1H), 3.41-3.3.13 (m, 3H), 3.05 (t, J = 6.5 Hz, 2.58 (m, 1H), 2.47 (m, 1H), 1.61 (m, 1H), 1.32 (s, 9H) ^{13}C NMR (75 MHz, CDCl_3): 158.0, 157.0, 144.1, 141.6, 134.8, 129.5, 127.9, 127.3, 125.2, 125.1, 124.5, 120.2, 78.5, 67.1, 67.0, 62.3, 47.5, 47.3, 43.6, 41.4, 34.9, 29.1. TOF-MS-ESI: $[\text{M}+\text{Na}]^+$ calculated 482.6, found 482.2; $[2\text{M}+\text{Na}]^+$ calculated 942.1, found 941.4.

(S)-Fmoc- β^2 -Homotyrosine (13b): A solution of **12b** (170 mg, crude product from above containing Fmoc-OH) in acetone (3.7 mL) was cooled to 0 °C. Jones's reagent (1.11 mL of 0.5 M $\text{H}_2\text{Cr}_2\text{O}_7$, 0.56 mmol) was added, and the reaction mixture was stirred for ~12 h, during which time it warmed to room temperature. Excess $i\text{PrOH}$ (4 mL) was added, and the reaction mixture was stirred until it turned green. The solution was diluted with H_2O (3 mL), and the acetone and $i\text{PrOH}$ were removed via rotary evaporation. The remaining aqueous mixture was extracted with Et_2O (3 x 4 mL, the extraction was monitored by TLC), and the combined organic layers were dried over MgSO_4 , filtered and concentrated. The crude product was purified on a Biotage Flash Chromatography system with a gradient of 12%-100% EtOAc in Hexanes. The product (73 mg, 62% yield) was obtained as a clear, foamy solid after concentrating the flash chromatography fractions, re-dissolving in CHCl_3 , concentrating, and drying under vacuum. TLC R_f = 0.24 (EtOAc/Hex, v/v, 1:1), mp 48-57°C. ^1H NMR (300 MHz, CDCl_3): 7.74 (m, 2H), 7.56-7.35 (m, 4H), 7.29-7.26 (m, 2H), 7.07-7.03 (m, 2H), 7.00-6.84 (m, 2H), 5.22 (br, 1H), 4.37 (m, 2H), 4.17 (m, 1H), 3.38-2.74 (br, 5H), 1.31-1.24 (m, 9H). ^{13}C NMR (75 MHz, CDCl_3): 158.1, 156.8, 154.2, 152.9, 144.0, 143.7, 141.4, 133.1, 129.5, 127.9, 127.2, 125.3, 124.5, 120.2, 78.6, 77.4, 67.1, 47.3, 42.4, 41.8, 35.2, 29.0. TOF-MS-ESI: $[\text{M}-\text{H}]^-$ calculated 472.6, found 472.2; $[2\text{M}-\text{H}]^-$ calculated 946.11, found 945.3. $[\alpha]_D^{25}$ = -2.32 (c =9.26, CH_2Cl_2)

β^2 -Homolysine (13c):

The aldehyde precursor **10c** used for the synthesis of β^2 -Homolysine (**13c**) was prepared from 6-aminohexanol as outlined below:

6-(di-Boc)-amino hexanol (S5): 6-amino-hexanol (1.10 g, 9.4 mmol) was dissolved in 115 mL of THF and cooled to -10 °C. $n\text{-BuLi}$ (12.5 mL, 2.5 M hexane solution) was then added dropwise producing a white precipitate.

The reaction mixture was left to stir for 5 min followed by addition of Boc_2O (7.0 g, 32.0 mmol). After 45 min, the reaction was quenched with saturated aqueous NH_4Cl , and the mixture was extracted with EtOAc. The combined organic fractions were washed with saturated aqueous NaHCO_3 and then brine, dried over MgSO_4 , filtered, and concentrated to give a yellow oil. The yellow oil was dissolved in 180 mL of MeOH, followed by addition of 90 mL of 1 N NaOH, and left to stir for 15.5 h. The reaction mixture was diluted with water, and extracted with EtOAc. The combined organic fractions were washed with brine, dried over MgSO_4 , filtered, and concentrated.

Chromatography (EtOAc/Hexanes; 1:3) afforded **S5** as a yellow oil. TLC R_f = 0.23

(EtOAc/Hexanes, v/v, 1:3). ^1H NMR (300 MHz, CDCl_3): d 3.64 (t, J = 6.4 Hz, 2H), 3.56 (t, J = 7.3 Hz, 2H) 1.60-1.55 (m, 4H), 1.50 (s, 18H), 1.44-1.26 (m, 5H). ^{13}C NMR (75 MHz, CDCl_3): d 153.0, 82.2, 62.9, 46.5, 32.8, 29.1, 28.3, 26.7, 25.6. TOF-MS-ESI: $[\text{M}+\text{Na}]^+$ calculated 340.3, found 340.5.

6-(di-Boc)-amino-hexanal (10c): Compound **S5** (0.75 g, 2.4 mmol) was dissolved in 30 mL of CH_2Cl_2 followed by addition of PCC (0.77g, 3.6 mmol). The reaction mixture was left to stir for 14.5 h and purified over a silica plug, eluting with 1:3 EtOAc/Hexanes, to yield a clear oil, (0.66 g, 88% yield).

TLC R_f = 0.30 (EtOAc/Hexanes, v/v, 1:4). ^1H NMR (300 MHz, CDCl_3): d 9.76, (t, J = 1.7 Hz, 1H), 3.56, (t, J = 7.4 Hz, 2H), 2.44, (td, J = 7.3, 1.7 Hz, 2H), 1.69-1.54 (m, 5H) 1.50 (s, 18 H), 1.38-1.28 (m, 2H) ^{13}C NMR (75 MHz, CDCl_3): d 202.6, 152.9, 82.3, 46.3, 43.9, 28.9, 28.3, 26.5, 22.0. TOF-MS-ESI: $[\text{M}+\text{Na}]^+$ calculated 338.3, found 338.5.

(S)-b-(1-(Di-Boc)-4-butyl-g-(S)-N-benzyl-a-methylbenzylamino alcohol (11c):

L-proline (0.18 g 0.7045 mmol) was suspended in 26 mL of DMF and stirred over night followed by cooling to -30°C . Aldehyde **10c** (3.67 g, 11.6 mmol) dissolved in 3 mL of DMF was added to the reaction mixture via a syringe, followed by drop-wise addition of N,O-acetal **3** (2.0 g, 7.8 mmol). The reaction mixture was left to stir for 4.5 h at -25°C , and NMR analysis of a small aliquot of solution indicated completion of the reaction. NaBH_4 (0.59 g, 15.6 mmol) was added to the reaction mixture with 4 mL of MeOH, and the reaction mixture was left to stir at 0°C for 20 min. The reaction mixture was then slowly poured to an aqueous solution of saturated NH_4Cl followed by extraction with Et_2O . The organic fractions were combined, washed with brine, dried over MgSO_4 , filtered and concentrated to give an oil, from which the major diastereomer was isolated by column chromatography, eluting with 1:4 EtOAc:hexanes, to yield a clear oil, (2.4 g, 54% yield). TLC R_f = 0.26 (EtOAc/Hexanes, v/v, 1:4). ^1H NMR (300 MHz, CDCl_3) d 7.36-7.22 (m, 10H), 4.82 (br s, 1H), 4.02(q, J = 6.9 Hz, 1H) 3.91, (d, J = 13 Hz, 1H), 3.58-3.50 (m, 3H), 3.36 (d, J = 13 Hz, 1H) 3.00 (m, J = 8.7 Hz, 1H) 2.55 (m, J = 12 Hz, 1H), 2.43 (m, J = 12 Hz, 1H), 1.94-1.84 (m, 1H), 1.56-1.46, (m, 2H), 1.49 (s, 18H) 1.35, (d, J = 6.8, Hz, 2H) 1.30-1.20 (m, 2H) 1.05-0.98, (m, 2H). ^{13}C NMR (75 MHz, CDCl_3): d 153.0, 142.7, 138.9, 129.4, 128.7, 128.39, 128.3, 127.5, 127.3, 82.3, 68.1, 56.4, 55.1, 54.6, 46.3, 36.9, 29.9, 29.5, 28.3, 24.7, 9.5 TOF-MS-ESI: $[\text{M}+\text{H}]^+$ calculated 541.7, found 541.8. Optical rotation: $[\alpha]_D^{25} = +5.6^\circ$ (c = 7.1, MeOH).

(S)-b-(1-(di-Boc)-amino-4-butyl -g- Fmoc-amino alcohol (12c):

Compound **11c** (0.32 g, 0.53 mmol) was dissolved in 20 mL of MeOH followed by addition of ammonium formate (0.34 g, 5.3 mmol) and 0.32 g of wet 10% Pd/C. The reaction mixture was heated to reflux and stirred under nitrogen for 7 h. The reaction mixture was cooled to room temperature and filtered through celite with an excess of MeOH. Evaporation of solvent yielded a clear oil. The oil was dissolved in 10 mL of CH_2Cl_2 , DIEA (300 μL , 1.72 mmol) and Fmoc-OSu (0.20 g, 0.59 mmol) were added and the reaction mixture was left to stir for 10 h. The reaction mixture was diluted with EtOAc and washed with saturated NaHSO_4 , saturated NaHCO_3 , brine, dried over MgSO_4 , filtered and concentrated. Evaporation of solvent produced an oil, which was purified via column chromatography, eluting with 1:1 EtOAc:hexanes, to yield a clear oil (0.24 g, 81% yield), 81%. TLC R_f = 0.11 (EtOAc/Hexanes, v/v, 1:1). ^1H NMR (300 MHz, CDCl_3) d 7.74 (d, J = 7.5 Hz, 2H), 7.59 (d, J = 7.4 Hz, 2H), 7.38 (t, 7.4 Hz 2H), 7.27 (t, 7.4 Hz 2H), 5.58 (t, J = 6.4 Hz, 1H), 4.396, (d, 7.2 Hz, 2H) 4.19 (t, J = 6.8 Hz, 1H), 3.61-3.35 (m,

6H) 3.16-3.08(m, 1H) 1.61-1.56 (m, 3H) 1.50 (s, 18H) 1.35-1.22 (m, 4H). ^{13}C NMR (75 MHz, CDCl_3): d 158.10, 153.26, 144.10, 141.56, 127.91, 127.26, 125.24, 120.19, 82.45, 67.05, 62.83, 47.54, 45.85, 41.57, 41.11, 29.27, 28.33, 27.96, 24.10. TOF-MS-ESI: $[\text{M}+\text{Na}]^+$ calculated 591.7, found 591.8. Optical rotation: $[\alpha]_D^{25} = +7.2^\circ$ ($c = 8.1$, CH_2Cl_2).

(S)- β^2 -Homolysine(diBoc)-OH (13c): **12c** (0.23 g, 0.41 mmol) was dissolved in 9 mL of acetone and cooled to 0 °C followed by drop-wise addition of a 1.3 mL Jones reagent (0.5 M $\text{H}_2\text{Cr}_2\text{O}_7$ solution in water). The reaction mixture was left to stir for 4 h while gradually warming to room temperature followed by quenching with an excess of isopropanol. After stirring for an additional 3 h the reaction mixture was diluted with water and a small amount of ether, and then carefully acidified to pH 2 with 10% aqueous NaHSO_4 . The aqueous layer was extracted with ether and the combined organic fractions were washed with brine and dried (MgSO_4). Evaporation of solvent produced an oil that was purified by column chromatography eluting with 1:2 EtOAc:hexanes and 1% AcOH to produce a white foam upon evaporation of solvent (0.18 g, 77% yield). TLC $R_f = 0.24$ (EtOAc/Hexanes, v/v, 1:2). ^1H NMR (300 MHz, CDCl_3) d 8.99 (br s, 1H), 7.74 (d, $J = 7.0$ Hz, 2H), 7.57 (d, $J = 7.3$ Hz, 2H), 7.38 (t, $J = 7.0$ Hz, 2H), 7.29 (t, $J = 7.3$ Hz, 2H), rotamers 6.57, 6.26, 5.42 (t, $J = 6.0$ Hz) rotamers 4.52, 4.35 (m, 2H), 4.22 (m, 1H), 3.56 (m, 2H) rotamers 3.47-3.05 (m, 2H), rotamers 2.66, 2.33, (m, 1H) 1.70-1.36, (m, 5H) 1.49 (s, 18H), 1.28-1.20 (m, 1H) ^{13}C NMR (75 MHz, CDCl_3): d rotamers 179.5 and 178.5, rotamers 157.8 and 156.8, rotamers 144.1 and 143.8, 141.4, 127.8, 127.2, rotamers 125.2 and 124.9, 120.1, 82.4, rotamers 67.3 and 67.0, rotamers 50.7 and 47.3, rotamers 46.2 and 45.7, rotamers 42.8 and 42.1, rotamers 29.8 and 29.3 rotamers 29.7 and 29.1, rotamers 28.2 and 24.3. TOF-MS-ESI: $[\text{M}+\text{Na}]^+$ calculated 582.7, found 582.0. Optical rotation: $[\alpha]_D^{25} = +2.3^\circ$ ($c = 11.3$, CH_2Cl_2).

(*S*)-N,O-acetal (**3**): ^1H NMR of the crude reaction mixture before work-up:

(*S*)-N,O-acetal (**3**) (^1H NMR):

0.007

^1H NMR in CDCl_3

(*S*)-N,O-acetal (**3**) (^{13}C NMR):

^{13}C NMR in CDCl_3

^1H NMR and ^{13}C NMR for compounds shown in Table 2

7b (^1H NMR):

7b (^{13}C NMR):

8b (^1H NMR):

8b (^{13}C NMR):

9b (^1H NMR):

9b (^{13}C NMR):

180.897
179.572

158.082
156.291

81.222
79.682
77.650
77.230
76.798

46.157
45.870
42.922
41.621

31.749
29.875
29.347
28.548
27.170
22.752
14.211

^{13}C NMR in CDCl_3 (exist as rotamers)

7c (^{13}C NMR):

^{13}C NMR in CDCl_3

8c (^1H NMR):

^1H NMR in CDCl_3
sample contains tiny amount of solvent EtOAc

8c (^{13}C NMR):

9c (^1H NMR):

9c (^{13}C NMR):

7d (¹H NMR):

7d (^{13}C NMR):

8d (^1H NMR):

8d (^{13}C NMR):

9d (^1H NMR):

9d (^{13}C NMR):

7e (¹H NMR):

7e (¹³C NMR):

142.763
138.907
129.468
128.740
128.412
128.358
127.544
127.320

77.631
77.207
76.783
68.789

56.526
55.262
55.137

39.490
34.395

25.635
23.111
22.915

9.483

¹³C NMR in CDCl₃

8e (^1H NMR):

8e (^{13}C NMR):

9e (^1H NMR):

9e (^{13}C NMR):

180.960
179.607

158.123
156.146

81.303
79.766
77.645
77.214
76.797

44.281
44.005
43.276
41.953
39.114
38.828
29.874
28.540
25.989
22.606
22.559

**^{13}C NMR in CDCl_3
(as rotamers)**

7f (^1H NMR):

7f (^{13}C NMR):

8f (^1H NMR):

^1H NMR in CDCl_3

8f (^{13}C NMR):

9f (^1H NMR):

^1H NMR in CDCl_3

9f (^{13}C NMR):

^1H NMR and ^{13}C NMR for compounds in the synthesis of β^2 -Homoglutamic Acid:

^1H NMR and ^{13}C NMR for compounds in the synthesis of β^2 -Homotyrosine:

^{13}C NMR in CDCl_3

^1H NMR in CDCl_3

^1H NMR and ^{13}C NMR for compounds in the synthesis of β^2 -homolysine:

---END of Supporting Information---