SUPPORTING INFORMATION

Primary Amino Acid Derivatives: Compounds with Anticonvulsant and Neuropathic Pain Protection Activities

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1. General Methods and Procedures

General Methods. Melting points were determined in open capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on an ATI Mattson Genesis FT-IR spectrometer. Absorption values are expressed in wavenumbers (cm^{-1}). Optical rotations were obtained on a Jasco P-1030 polarimeter at the sodium D line (589 nm) using a 1 dm path length cell. NMR spectra were recorded at 300 or 400 MHz (^{1}H) and 75 or 100 MHz (^{13}C) using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are reported in parts per million (ppm) from TMS. Low-resolution mass spectra (LRMS) were recorded with a BioToF-II-Bruker Daltonics spectrometer by Drs. M. Crowe and S. Habibi at the University of North Carolina Department of Chemistry. The high-resolution mass spectra (HRMS) were recorded on a Bruker Apex-Q 12 Telsa FTICR spectrometer by Drs. M. Crowe and S. Habibi. Microanalyses were performed by Atlantic Microlab, Inc. (Norcross, GA). Reactions were monitored by analytical thin-layer chromatography (TLC) plates (Aldrich, catalog no. Z12272-6, or Dynamic Adsorbents Inc., catalog no. 84111) and analyzed with 254 nm light. The reaction mixtures were purified by medium pressure liquid chromatography (MPLC, CombiFlash *Rf*) with self-packed columns (silica gel from Dynamic Adsorbents Inc., catalog no. 02826-25) or by flash column chromatography using silica gel (Dynamic Adsorbents Inc., catalog no. 02826-25). All chemicals and solvents were reagent grade and used directly from commercial sources without further purification. THF was distilled from blue sodium benzophenone ketyl. Yields reported are for purified products and were not optimized. All compounds were checked by TLC, ^{1}H and ^{13}C NMR, MS, and elemental analyses. The analytical results are within ±0.40% of the theoretical value. The TLC, NMR, and analytical data confirmed the purity of the products was ≥95%.

General Procedure for the Preparation of *N*-Benzyloxycarbonyl Amino Acids and *N*-Benzyloxycarbonyl Amino Methyl Esters (Method A). $NaHCO_3$ (2.5–3.3 equiv) was added to an aqueous solution of amino acid (0.4–0.5 M) and the solution was cooled to 0 °C in an ice bath under an inert atmosphere (Ar or N_2) before benzylchloroformate (1.1–1.5 equiv) was added dropwise. The reaction proceeded for 45 min at 0 °C and then allowed to warm to room temperature (24 h). Amino acid derivatives: The aqueous layer was washed with EtOAc (3x), acidified to pH ~1 with aqueous concentrated HCl, and extracted with EtOAc (3x). The second set of organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo. The crude product was used for the next step without further purification or purified by recrystallization from hot EtOAc/hexanes. Amino methyl ester derivatives: The aqueous layer was extracted with CH_2Cl_2 (3x), dried (Na_2SO_4), concentrated in vacuo, and purified by column chromatography (SiO_2).

General Procedure for the Preparation of *N*-Benzylamide Amino Acid Derivatives Using the Mixed Anhydride Coupling (MAC) Method (Method B). An anhydrous THF solution of carboxylic acid (0.5–2.0 M) was cooled to -78 °C in a dry ice/acetone bath under an inert atmosphere (Ar or N_2), and 4-methylmorpholine (NMM) (1.3–1.5 equiv) was added. After the mixture was stirred (2–10 min), isobutyl chloroformate (IBCF) (1.1–1.5 equiv) was added leading to the precipitation of a white solid. The reaction was allowed to proceed for an additional 15–25 min, and then benzylamine (1.05–1.36 equiv) was added at -78 °C. The reaction mixture was allowed to stir at room temperature (1.5 h), and then the insoluble salts were filtered. The organic layer was concentrated in vacuo, and the product was purified by column chromatography (SiO_2).

General Procedure for the Conversion of Cbz-Protected PAADs to PAADs Using Pd-Catalyzed Hydrogenation (Method C). A MeOH solution of Cbz-protected PAAD (0.05–0.1 M) was hydrogenated (1 atm) in the presence of 10% Pd-C at room temperature (3 h–7 d). The mixture was filtered through a bed of Celite®, the filtrate was evaporated in vacuo, and the product was purified by column chromatography (SiO_2).

General Procedure for the Preparation of Alkoxy-Substituted Cbz-PAADs Using Silver (I) Oxide-Mediated Alkylation (Method D). To a CH_3CN solution of Cbz-protected PAAD (0.01–0.1 M) were successively added Ag_2O (5 equiv) and the alkyl iodide (10 equiv) at room temperature. The reaction mixture was stirred (room temperature–50 °C, 5–7 d) and then the insoluble salts were filtered and the filtrate evaporated in vacuo. The product was purified by column chromatography (SiO_2) followed by recrystallization.

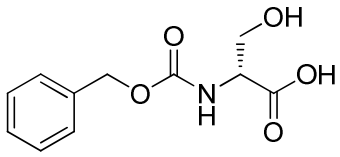
General Procedure for the Conversion of *t*Boc-Protected PAADs to PAADs Using TFA Deprotection (Method E). TFA (15 equiv) was added to an anhydrous CH_2Cl_2 solution of the *t*Boc-protected PAAD (0.3 M) at room temperature. The solution was stirred (1 h) and then the solvent was evaporated in vacuo. The crude product was diluted with CH_2Cl_2 and extracted with aqueous 1 M HCl (3x). The combined aqueous layers were washed with CH_2Cl_2 (2x), basified (pH 10–12) with aqueous 4 M NaOH, and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine (2x), dried (Na_2SO_4), evaporated in vacuo, and purified by column chromatography (SiO_2).

General Procedure for the Preparation of *N*-(Benzyloxycarbonyl)-3-*N*-Aminopropanoic Methyl Ester Derivatives Using the Michael Addition of Amines to Dehydroalanine Derivatives (Method F). An anhydrous CH_2Cl_2 solution of serine methyl ester (0.2 M) was cooled to 0 °C under an inert atmosphere (Ar or N_2), and triethylamine (Et_3N) (1.2 equiv) was added. After the mixture was stirred (10 min), methanesulfonyl chloride (MsCl) (1.2 equiv) was added. The reaction was allowed to proceed for an additional 1 h, and then Et_3N (1.2 equiv) was added at 0 °C. The reaction was allowed to stir at room temperature (3 h), and then the solvent was evaporated in vacuo to give the crude Cbz-dehydroalanine-methyl ester. An anhydrous primary, secondary, or tertiary amine solution in THF (5–20 equiv) and MeOH (1:1) was added directly to the crude material and stirred overnight. The organic layer was concentrated in vacuo to give the crude product, which was diluted with CH_2Cl_2, successively washed with saturated aqueous Na_2CO_3 (3x) and brine (2x), dried (Na_2SO_4), concentrated in vacuo, and purified by column chromatography (SiO_2).

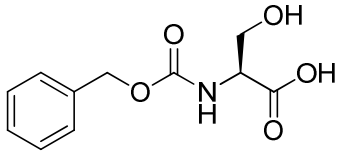
General Procedure for the Preparation of *N*-Benzylamide Amino Acid Derivatives Using the LiOH Hydrolysis/DMTMM Amide Coupling Method (Method G). Methyl ester (0.1 M) was dissolved in THF and H_2O (1:2) and LiOH (1 equiv) was added. The reaction was stirred at room temperature (1.5 h) and then benzylamine hydrochloride (1.2 equiv) and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) (1.2 equiv) were added and the solution stirred overnight (18 h). The organic layer was evaporated in vacuo, and CH_2Cl_2 was added to the remaining aqueous layer. The binary mixture was basified (pH 9–10) with aqueous 1 M NaOH, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2

(3x). The organic layers were combined, washed with brine (3x), dried (Na_2SO_4), and purified by column chromatography.

2. Preparation of (*R*)-, (*S*)-, and (*R,S*)-*N*-Benzyl 2-Amino-3-hydroxypropionamide ((*R*)-, (*S*)-, and (*R,S*)-7)

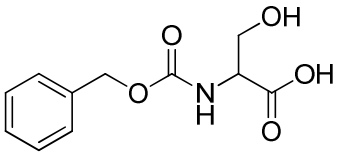


(*R*)-*N*-(Benzyloxycarbonyl)-2-amino-3-hydroxypropionic Acid ((*R*)-30).[1] Utilizing Method A with D-serine (5.00 g, 47.6 mmol), $NaHCO_3$ (10.0 g, 118.9 mmol), H_2O (100 mL) and benzyl chloroformate (10.0 mL, 71.4 mmol) gave the crude product after workup that was further purified by recrystallization from hot EtOAc/hexanes to give the desired product (7.38 g, 65%) as a white solid: mp 115–116 °C (lit.[1] mp 117–119 °C); $[\alpha]^{25}_D$ –5.12° (*c* 6.0, acetic acid) (lit.[2] (*S*): $[\alpha]^{12}_D$ +5.8° (*c* 6, acetic acid)); R_f 0.43 (1:3 MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.67 (d, J = 4.2 Hz, C**H**$_2$OH), 4.03–4.09 (m, C**H**), 4.83–4.96 (br s, N**H**), 5.04 (s, C**H**$_2$Ph), 7.32–7.38 (m, Ph**H**); ^{13}C NMR (75 MHz, DMSO-d_6) δ 56.7 (**C**H), 61.4 (**C**H$_2$OH), 65.5 (**C**H$_2$Ph), 127.7, 127.8, 128.4, 137.0 (**C**$_6$H$_5$), 156.1 (O**C**(O)NH), 172.2 (**C**(O)OH).

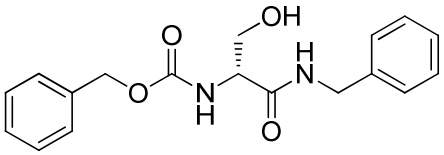


(*S*)-*N*-(Benzyloxycarbonyl)-2-amino-3-hydroxypropionic Acid ((*S*)-30).[2] The previous procedure was repeated using L-serine (5.00 g, 47.6 mmol), $NaHCO_3$ (10.0 g, 118.9 mmol), H_2O (100 mL), and benzyl chloroformate (10.0 mL, 71.4 mmol) to give the desired product (7.94 g,

70%) as a white solid: mp 116–117 °C (lit.[2] mp 117–119 °C); $[\alpha]^{25}_{D}$ +5.51° (*c* 6.0, acetic acid) (lit.[2] $[\alpha]^{12}_{D}$ +5.8° (*c* 6, acetic acid)); R_f 0.41 (1:3 MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.66 (d, J = 4.5 Hz, C**H**$_2$OH), 4.02–4.09 (m, C**H**), 4.83–4.94 (br s, N**H**), 5.04 (s, C**H**$_2$Ph), 7.29–7.38 (m, Ph**H**); ^{13}C NMR (75 MHz, DMSO-d_6) δ 56.6 (**C**H), 61.3 (**C**H$_2$OH), 65.4 (**C**H$_2$Ph), 127.7, 127.8, 128.3, 137.0 (**C**$_6$H$_5$), 156.0 (O**C**(O)NH), 172.1 (**C**(O)OH).

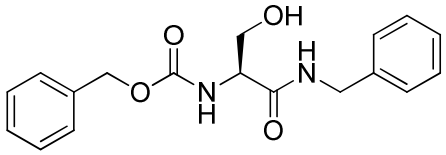


(*R,S*)-*N*-(Benzyloxycarbonyl)-2-amino-3-hydroxypropionic Acid ((*R,S*)-30).[3] The previous procedure was repeated using DL-serine (20.00 g, 0.19 mol), $NaHCO_3$ (40.00 g, 0.48 mol), H_2O (400 mL), and benzyl chloroformate (40.0 mL, 0.29 mol) to give the desired product (38.04 g, 84%) as a white solid: mp 124–125 °C (lit.[3] mp 120–122 °C); R_f 0.39 (1:3 MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.66 (d, J = 4.8 Hz, C**H**$_2$OH), 4.03–4.09 (m, C**H**), 4.72–4.97 (br s, N**H**), 5.04 (s, C**H**$_2$Ph), 7.28–7.40 (m, Ph**H**); ^{13}C NMR (75 MHz, DMSO-d_6) δ 56.6 (**C**H), 61.3 (**C**H$_2$OH), 65.4 (**C**H$_2$Ph), 127.7, 127.8, 128.3, 137.0 (**C**$_6$H$_5$), 156.0 (O**C**(O)NH), 172.1 (**C**(O)OH).

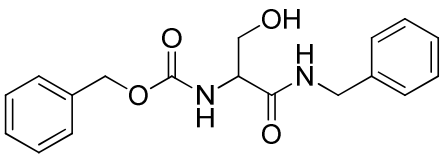


(*R*)-*N*-Benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-hydroxypropionamide ((*R*)-31).[4] Utilizing Method B with (*R*)-**30** (5.00 g, 20.9 mmol), NMM (2.98 mL, 27.2 mmol), IBCF (2.98 mL, 23.0 mmol), and benzylamine (2.40 mL, 21.9 mmol) gave the crude product that was purified by flash

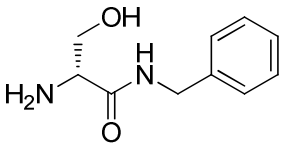
column chromatography (SiO_2; 1:20 MeOH/$CHCl_3$) to give the desired product (5.16 g, 75%) as a white solid: mp 146–147 °C (lit.[4] mp 147–149 °C); $[\alpha]^{25}_D$ +5.1° (*c* 2.1, MeOH) (lit.[4] $[\alpha]^{23}_D$ +4.6° (*c* 2.0, MeOH); R_f 0.44 (1:20 MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.50–3.67 (m, C**H**$_2$OH), 4.06–4.13 (m, C**H**), 4.30 (d, J = 6.3 Hz, NHC**H**$_2$), 4.90 (t, J = 5.7 Hz, O**H**), 5.04 (s, C**H**$_2$OC(O)), 7.20–7.38 (m, Ph**H** and OC(O)N**H**), 8.42 (t, J = 6.0 Hz, C(O)N**H**); ^{13}C NMR (75 MHz, DMSO-d_6) δ 42.0 (**C**H$_2$NH), 57.4 (**C**H), 61.8 (**C**H$_2$OH), 65.5 (O**C**H$_2$Ph), 126.6, 127.0, 127.7, 127.8, 128.2, 128.3, 137.0, 139.3 (2 **C**$_6$H$_5$), 155.9 (**C**(O)O), 170.2 (**C**(O)NH).



(*S*)-*N*-Benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-hydroxypropionamide ((*S*)-31).[5] The previous procedure was repeated using (*S*)**-30** (5.00 g, 20.9 mmol), NMM (2.98 mL, 27.2 mmol), IBCF (2.98 mL, 23.0 mmol), and benzylamine (2.40 mL, 21.9 mmol) to give the desired product (4.84 g, 71%) as a white solid: mp 148–149 °C (lit.[5] mp 148–149.5 °C); $[\alpha]^{25}_D$ –5.8° (*c* 2.1, MeOH) (lit.[5] $[\alpha]^{23}_D$ –5.4° (*c* 1.04, MeOH)); R_f 0.45 (1:20 MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.54–3.68 (m, C**H**$_2$OH), 4.06–4.13 (m, C**H**), 4.30 (d, J = 6.0 Hz, NHC**H**$_2$), 4.90 (t, J = 5.4 Hz, O**H**), 5.04 (s, C**H**$_2$OC(O)), 7.20–7.38 (m, Ph**H** and OC(O)N**H**), 8.42 (t, J = 6.3 Hz, C(O)N**H**); ^{13}C NMR (75 MHz, DMSO-d_6) δ 42.0 (**C**H$_2$NH), 57.3 (**C**H), 61.8 (**C**H$_2$OH), 65.5 (O**C**H$_2$Ph), 126.6, 127.0, 127.7, 127.8, 128.2, 128.3, 137.0, 139.3 (2 **C**$_6$H$_5$), 155.9 (**C**(O)O), 170.1 (**C**(O)NH).

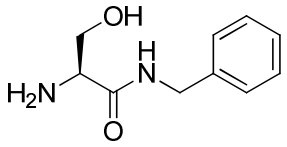


(*R,S*)-*N*-Benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-hydroxypropionamide ((*R,S*)-31).[6] The previous procedure was repeated using (*R,S*)-**30** (10.00 g, 41.8 mmol), NMM (5.97 mL, 54.4 mmol), IBCF (5.96 mL, 46.0 mmol), and benzylamine (4.79 mL, 43.9 mmol) to give the desired product (12.25 g, 89%) as a white solid: mp 140–141 °C (lit.[6] mp 142 °C); R_f 0.33 (1:20 MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.54–3.67 (m, C**H**$_2$OH), 4.06–4.13 (m, C**H**), 4.30 (d, J = 6.0 Hz, NHC**H**$_2$), 4.90 (t, J = 5.7 Hz, O**H**), 5.02 (s, C**H**$_2$OC(O)), 7.20–7.38 (m, Ph**H** and OC(O)N**H**), 8.42 (t, J = 6.0 Hz, C(O)N**H**); ^{13}C NMR (75 MHz, DMSO-d_6) δ 42.0 (**C**H$_2$NH), 57.3 (**C**H), 61.8 (**C**H$_2$OH), 65.5 (O**C**H$_2$Ph), 126.6, 127.0, 127.7, 128.2, 128.3, 137.0, 139.3 (2 **C**$_6$H$_5$), 155.9 (**C**(O)O), 170.1 (**C**(O)NH), one aromatic peak was not detected and is believed to overlap with nearby signals.

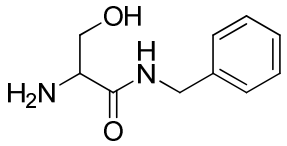


(*R*)-*N*-Benzyl 2-Amino-3-hydroxypropionamide ((*R*)-7).[4] Utilizing Method C with (*R*)-**31** (1.82 g, 5.53 mmol), 10% Pd-C (180 mg), and MeOH (200 mL) (8 h) gave the crude product that was purified by MPLC to give the desired product (0.56 g, 53%) as a white solid: mp 95–96 °C (lit.[4] mp 88–90 °C); $[\alpha]^{25}_D$ –0.48° (*c* 1.5, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.84 (br s, N**H**$_2$), 3.25 (dd, J = 4.8, 4.8 Hz, C**H**), 3.42–3.56 (m, C**H**$_2$OH), 4.29 (d, J = 6.0 Hz, C**H**$_2$NH), 4.72–4.86 (br s, O**H**), 7.20–7.33 (m, Ph**H**), 8.35 (t, J = 6.0 Hz, N**H**); ^{13}C NMR (75 MHz, DMSO-d_6) δ 41.8 (NH**C**H$_2$), 57.0 (**C**H), 64.4 (**C**H$_2$OH), 126.6, 127.1, 128.2, 139.6 (**C**$_6$H$_5$),

173.4 (**C**(O)NH); HRMS (ESI) 217.0953 [M + Na^+] (calcd for $C_{10}H_{14}N_2O_2Na^+$ 217.0953); Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found C, 61.94; H, 7.27; N, 14.31.



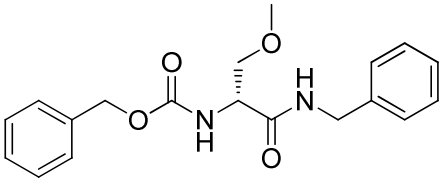
(*S*)-*N*-Benzyl 2-Amino-3-hydroxypropionamide ((*S*)-7). The previous procedure was repeated using (*S*)-**31** (1.46 g, 4.44 mmol), 10% Pd-C (140 mg), and MeOH (200 mL) (8 h) to give the desired product (0.54 g, 63%) as a white solid: mp 91–92 °C; $[\alpha]^{25}_D$ +4.88° (*c* 1.5, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.27 (dd, *J* = 5.1, 5.1 Hz, C**H**), 3.42–3.57 (m, C**H**$_2$OH), 4.30 (d, *J* = 6.2 Hz, C**H**$_2$NH), 7.19–7.34 (m, Ph**H**), 8.37 (t, *J* = 6.2 Hz, N**H**); ^{13}C NMR (75 MHz, DMSO-d_6) δ 41.8 (NH**C**H$_2$), 57.0 (**C**H), 64.3 (**C**H$_2$OH), 126.6, 127.1, 128.2, 139.6 (**C**$_6$H$_5$), 173.2 (**C**(O)NH); HRMS (ESI) 217.0953 [M + Na^+] (calcd for $C_{10}H_{14}N_2O_2Na^+$ 217.0953); Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found C, 61.91; H, 7.31; N, 14.21.



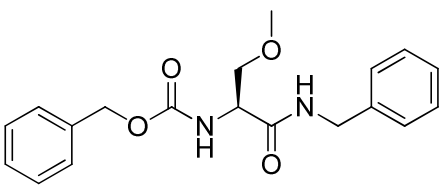
(*R,S*)-*N*-Benzyl 2-Amino-3-hydroxypropionamide ((*R,S*)-7). The previous procedure was repeated using (*R,S*)-**31** (1.33 g, 4.07 mmol), 10% Pd-C (130 mg), and MeOH (200 mL) (8 h) to give the desired product (0.52 g, 66%) as a white solid: mp 90–91 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.14 (br s, N**H**$_2$), 3.27 (dd, *J* = 4.5, 4.8 Hz, C**H**), 3.42–3.57 (m, C**H**$_2$OH), 4.30 (d, *J* = 6.5 Hz, C**H**$_2$NH), 4.62–4.88 (br s, O**H**), 7.19–7.34 (m, Ph**H**), 8.37 (t, *J* = 6.5 Hz, N**H**); ^{13}C NMR (75 MHz, DMSO-d_6) δ 41.8 (NH**C**H$_2$), 57.0 (**C**H), 64.2 (**C**H$_2$OH), 126.6, 127.1, 128.2, 139.5 (**C**$_6$H$_5$), 173.2 (**C**(O)NH); HRMS (ESI) 217.0953 [M + Na^+] (calcd for $C_{10}H_{14}N_2O_2Na^+$

217.0953); Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found C, 61.69; H, 7.33; N, 14.41.

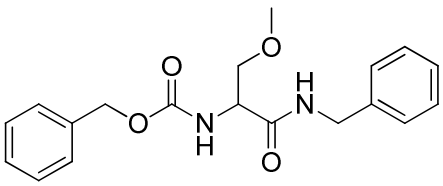
3. Preparation of (*R*)-, (*S*)-, and (*R,S*)-*N*-Benzyl 2-Amino-3-methoxypropionamide ((*R*)-, (*S*)-, and (*R,S*)-8)



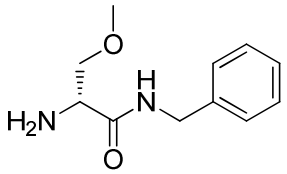
(*R*)-*N*-Benzyl 2-*N*-(Benzylcarboxycarbonyl)amino-3-methoxypropionamide ((*R*)-35).[4] Utilizing Method D with (*R*)-**31** (4.00 g, 12.2 mmol), Ag_2O (14.12 g, 60.9 mmol), MeI (7.59 mL, 121.9 mmol), and CH_3CN (400 mL) at room temperature (5 d) gave the crude product that was purified by flash column chromatography (SiO_2, 1:10 MeOH/CH_2Cl_2) followed by recrystallization from hot EtOAc to give the desired product (2.86 g, 69%) as a white crystalline solid: mp 129–130 °C (lit.[4] mp 128–130 °C); $[\alpha]^{25}_D$ +2.8° (*c* 1.0, MeOH) (lit.[4] $[\alpha]^{23}_D$ +2.8° (*c* 1.1, MeOH)); R_f 0.39 (1:1 EtOAc/hexanes); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.25 (s, OC**H**$_3$), 3.46–3.55 (m, C**H**$_2$OCH$_3$), 4.24–4.30 (m, C**H**, NHC**H**$_2$Ph), 5.04 (s, OC**H**$_2$Ph), 7.22–7.38 (m, 2 Ph**H**), 7.47 (d, J = 8.1 Hz, N**H**C(O)O), 8.53 (t, J = 5.7 Hz, N**H**C(O)); ^{13}C NMR (75 MHz, DMSO-d_6) δ 41.7 (NH**C**H$_2$), 54.3 (**C**H), 57.7 (O**C**H$_3$), 65.1 (O**C**H$_2$Ph), 71.6 (**C**H$_2$OCH$_3$), 126.3, 126.6, 127.3, 127.4, 127.8, 127.9, 136.6, 138.8 (2 **C**$_6$H$_5$), 155.6 (O**C**(O)), 169.3 (**C**(O)NH).



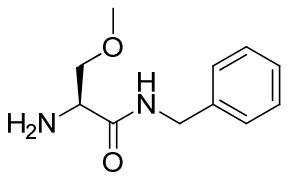
(*S*)-*N*-Benzyl 2-*N*-(Benzylcarboxycarbonyl)amino-3-methoxypropionamide ((*S*)-35).[5] The previous procedure was repeated using (*S*)-**31** (4.00 g, 12.2 mmol), Ag_2O (14.12 g, 60.9 mmol), MeI (7.59 mL, 121.9 mmol), and CH_3CN (400 mL) to give the desired product (3.13 g, 75%) as a white crystalline solid: mp 131–132 °C (lit.[5] mp 130–132 °C); $[\alpha]^{25}_D$ –2.9° (*c* 1.1, MeOH) (lit.[5] $[\alpha]^{24}_D$ –3.3° (*c* 1.1, MeOH)); R_f 0.36 (1:1 EtOAc/hexanes); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.25 (s, OC**H**$_3$), 3.47–3.57 (m, C**H**$_2$OCH$_3$), 4.25–4.30 (m, C**H**, NHC**H**$_2$Ph), 5.04 (s, OC**H**$_2$Ph), 7.20–7.37 (m, 2 Ph**H**), 7.48 (d, *J* = 8.1 Hz, N**H**C(O)O), 8.53 (t, *J* = 5.4 Hz, N**H**C(O)); ^{13}C NMR (75 MHz, DMSO-d_6) δ 41.7 (NH**C**H$_2$), 54.3 (**C**H), 57.8 (O**C**H$_3$), 65.1 (O**C**H$_2$Ph), 71.6 (**C**H$_2$OCH$_3$), 126.3, 126.6, 127.3, 127.4, 127.8, 127.9, 136.6, 138.9 (2 **C**$_6$H$_5$), 155.6 (O**C**(O)), 169.3 (**C**(O)NH).



(*R,S*)-*N*-Benzyl 2-*N*-(Benzylcarboxycarbonyl)amino-3-methoxypropionamide ((*R,S*)-35).[7] The previous procedure was repeated using (*R,S*)-**31** (4.00 g, 12.2 mmol), Ag_2O (14.12 g, 60.9 mmol), MeI (7.59 mL, 121.9 mmol), and CH_3CN (400 mL) to give the desired product (2.53 g, 61%) as a white crystalline solid: mp 126–127 °C (lit.[7] mp 140–141 °C); R_f 0.39 (1:1 EtOAc/hexanes); IR (nujol mull) 3220, 2910, 1692, 1639, 1542, 1459, 1376, 1310, 1265, 1125, 1051, 967, 752, 698 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.25 (s, OC**H**$_3$), 3.50–3.52 (m, C**H**$_2$OCH$_3$), 4.22–4.34 (m, C**H**, NHC**H**$_2$Ph), 5.04 (s, OC**H**$_2$Ph), 7.23–7.36 (m, 2 Ph**H**), 7.48 (d, *J* = 8.1 Hz, N**H**C(O)O), 8.53 (t, *J* = 5.4 Hz, N**H**C(O)); ^{13}C NMR (75 MHz, DMSO-d_6) δ 41.7 (NH**C**H$_2$), 54.3 (**C**H), 57.7 (O**C**H$_3$), 65.1 (O**C**H$_2$Ph), 71.6 (**C**H$_2$OCH$_3$), 126.3, 126.6, 127.3, 127.4, 127.8, 127.9, 136.7, 138.9 (2 **C**$_6$H$_5$), 155.6 (O**C**(O)), 169.3 (**C**(O)NH).

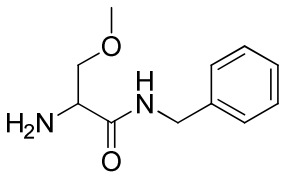


(*R*)-*N*-Benzyl 2-Amino-3-methoxypropionamide ((*R*)-8).[4] Utilizing Method C with (*R*)-**35** (2.00 g, 5.85 mmol), 10% Pd-C (0.2 g), and MeOH (100 mL) (5 h) gave the crude product that was purified by flash column chromatography (SiO_2; 1:10 MeOH/$CHCl_3$). The resulting oil was dissolved in CH_2Cl_2 (20 mL) and was extracted with aqueous 0.1 N HCl (3 x 20 mL). The aqueous layers were combined and washed with CH_2Cl_2 (2 x 60 mL). The aqueous layer was basified to pH 10–12 with aqueous 0.1 N NaOH, and then extracted with CH_2Cl_2 (3 x 100 mL). The CH_2Cl_2 layers were combined, dried ($MgSO_4$), and concentrated in vacuo to give the desired product (0.89 g, 73%) as a waxy solid: mp 39–40 °C; $[\alpha]^{25}_D$ –1.5° (*c* 1.6, MeOH) (lit.[4] $[\alpha]^{23}_D$ – 2.0° (*c* 1.5, MeOH)); R_f 0.26 (1:20 MeOH/$CHCl_3$); IR (nujol mull) 3366, 3302, 3140, 2904 (br), 1955, 1886, 1815, 1667, 1457, 1373, 1152, 966, 726 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.82 (s, N**H**$_2$), 3.25 (s, OC**H**$_3$), 3.35–3.44 (m, C**H**C**H**$_2$), 4.23–4.36 (m, C**H**$_2$Ph), 7.20–7.34 (m, Ph**H**), 8.36–8.44 (br t, N**H**); ^{13}C NMR (75 MHz, DMSO-d_6) δ 41.5 (**C**H_2PH), 54.3 (**C**H), 57.8 (**C**H_3), 74.8 (CH**C**H_2), 126.3, 126.7, 127.8, 139.1 (**C**$_6H_5$), 172.6 (**C**(O)); Anal. Calcd for $C_{11}H_{16}N_2O_2$·0.18H_2O: C, 62.49; H, 7.80; N, 13.25. Found C, 62.13; H, 7.82; N, 13.10.



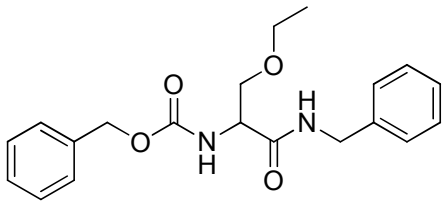
(*S*)-*N*-Benzyl 2-Amino-3-methoxypropionamide ((*S*)-8).[5] The previous procedure was repeated using (*S*)-**35** (2.00 g, 5.85 mmol), 10% Pd-C (0.2 g), and MeOH (100 mL) to give the

desired product (1.12 g, 92%) as a waxy solid: mp 39–40 °C; $[\alpha]^{25}_{D}$ +1.7° (*c* 1.5, MeOH) (lit.[5] $[\alpha]^{23}_{D}$ +1.8° (*c* 0.8, MeOH)); R_f 0.39 (1:20 MeOH/$CHCl_3$); IR (nujol mull) 3474, 3365, 3125 (br), 1949, 1885, 1817, 1662, 1520, 1457, 1369, 1240, 1189, 1106, 970, 727 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.84 (s, N**H**$_2$), 3.25 (s, OC**H**$_3$), 3.35–3.44 (m, C**H**C**H**$_2$), 4.23–4.36 (m, C**H**$_2$Ph), 7.20–7.34 (m, Ph**H**), 8.36–8.45 (br t, N**H**); ^{13}C NMR (75 MHz, DMSO-d_6) δ 41.5 (**C**H_2PH), 54.3 (**C**H), 57.8 (**C**H_3), 74.8 (CH**C**H_2), 126.3, 126.7, 127.8, 139.1 (**C**$_6H_5$), 172.6 (**C**(O)); Anal. Calcd for $C_{11}H_{16}N_2O_2$•0.15H_2O: C, 62.56; H, 7.79; N, 13.28. Found C, 62.25; H, 7.91; N, 13.16.

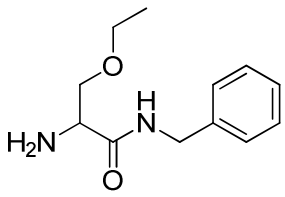


(*R,S*)-*N*-Benzyl 2-Amino-3-methoxypropionamide ((*R,S*)-8).[7] The previous procedure was repeated using (*R,S*)-**35** (2.00 g, 5.85 mmol), 10% Pd-C (0.2 g), and MeOH (100 mL) to give the desired product (0.42 g, 32%) as a pale yellow oil: R_f 0.37 (1:20 MeOH/$CHCl_3$); IR (neat) 3227, 3177, 3063, 2900 (br), 1959, 1884, 1814, 1540, 1456, 1361, 1253, 1187, 1110, 927, 739, 701 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.82 (br s, N**H**$_2$), 3.25 (s, OC**H**$_3$), 3.37–3.44 (m, C**H**C**H**$_2$), 4.23–4.36 (m, C**H**$_2$Ph), 7.19–7.34 (m, Ph**H**), 8.36–8.44 (br t, N**H**); ^{13}C NMR (75 MHz, DMSO-d_6) δ 41.5 (**C**H_2PH), 54.3 (**C**H), 57.8 (**C**H_3), 74.8 (CH**C**H_2), 126.3, 126.7, 127.8, 139.1 (**C**$_6H_5$), 172.6 (**C**(O)); Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found C, 63.18; H, 7.66; N, 13.41.

4. Preparation of (*R,S*)-*N*-Benzyl 2-Amino-3-ethoxypropionamide ((*R,S*)-9)



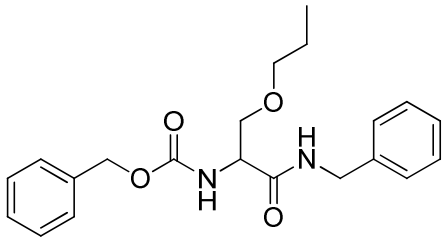
(*R,S*)-*N*-Benzyl 2-*N*-(Benzylcarboxycarbonyl)amino-3-ethoxypropionamide ((*R,S*)-36). Utilizing Method D with (*R,S*)-**31** (1.88 g, 5.73 mmol), Ag_2O (6.64 g, 8.59 mmol), EtI (6.94 mL, 85.9 mmol), and CH_3CN (400 mL) (40–50 °C, 7 d) gave the crude product that was further purified by flash column chromatography (SiO_2, 1:10 MeOH/CH_2Cl_2) followed by recrystallization from hot toluene to give the desired product (1.04 g, 51%) as a white crystalline solid: mp 100–101 °C; R_f 0.48 (1:1 EtOAc/hexanes); IR (nujol mull) 3297, 2941 (br), 2729, 2680, 1688, 1645, 1538, 1457, 1374, 1242, 727 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.08 (t, J = 6.9 Hz, C**H**$_3$), 3.44 (q, J = 6.9 Hz, OC**H**$_2$CH$_3$), 3.50–3.60 (m, CHC**H**$_2$), 4.22–4.37 (m, C**H**, C**H**$_2$Ph), 5.04 (s, OC**H**$_2$Ph), 7.22–7.46 (m, 2 Ph**H**), 8.53 (t, J = 5.7 Hz, N**H**C(O)); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.6 (OCH$_2$**C**H$_3$), 41.6 (NH**C**H$_2$), 54.5 (**C**H), 65.1 (O**C**H$_2$CH$_3$ or O**C**H$_2$Ph), 65.3 (O**C**H$_2$Ph or O**C**H$_2$CH$_3$), 70.0 (**C**H$_2$OCH$_2$CH$_3$), 126.3, 126.6, 127.3, 127.4, 127.8, 127.9, 136.6, 138.9 (2 **C**$_6$H$_5$), 155.5 (**C**(O)O), 169.4 (**C**(O)NH); HRMS (ESI) 357.1814 [M + H^+] (calcd for $C_{20}H_{24}N_2O_4H^+$ 357.1814); Anal. Calcd for $C_{20}H_{24}N_2O_4$; C, 67.40; H, 6.79; N, 7.86. Found C, 67.12; H, 6.67; N, 7.89.



(*R,S*)-*N*-Benzyl 2-Amino-3-ethoxypropionamide ((*R,S*)-9). Utilizing Method C with (*R,S*)-**36** (1.00 g, 2.81 mmol), 10% Pd-C (0.1 g), and MeOH (30 mL) (18 h) gave the crude product that

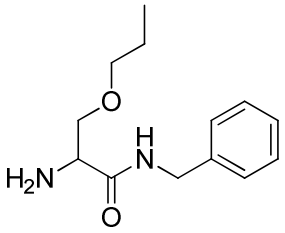
was purified by flash column chromatography (SiO_2; 1:10 MeOH/CH_2Cl_2). The resulting oil was dissolved in CH_2Cl_2 (10 mL) and was extracted with aqueous 0.1 N HCl (3 x 10 mL). The aqueous layers were combined and washed with CH_2Cl_2 (2 x 30 mL). The aqueous layer was basified to pH 10–12 with aqueous 0.1 N NaOH, and then extracted with CH_2Cl_2 (3 x 60 mL). The CH_2Cl_2 layers were combined, dried ($MgSO_4$), and concentrated in vacuo to give the desired product (0.42 g, 68%) as a pale yellow oil: R_f 0.33 (1:1 EtOAc/hexanes); IR (neat) 3319, 3177, 3062, 2865, 1957, 1883, 1812, 1662, 1535, 1455, 1361, 1254, 1107, 1022, 870, 738 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.10 (t, J = 7.2 Hz, C**H**$_3$), 1.82 (s, N**H**$_2$), 3.29–3.49 (m, C**H**C**H**$_2$OC**H**$_2$CH$_3$), 4.22–4.37 (m, C**H**$_2$Ph), 7.20–7.33 (m, Ph**H**), 8.36–8.45 (br t, N**H**C(O)); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.7 (OCH$_2$**C**H$_3$), 41.5 (NH**C**H$_2$), 54.5 (**C**H), 65.3 (O**C**H$_2$CH$_3$), 72.7 (**C**H$_2$OCH$_2$CH$_3$), 126.3, 126.7, 127.8, 139.2 (**C**$_6$H$_5$), 172.8 (**C**(O)NH); HRMS (ESI) 223.1450 [M + H$^+$] (calcd for $C_{12}H_{18}N_2O_2H^+$ 223.1447); Anal. Calcd for $C_{12}H_{18}N_2O_2$•0.06CH_2Cl_2; C, 63.63; H, 8.02; N, 12.30. Found C, 63.67; H, 8.21; N, 12.32.

5. Preparation of (*R,S*)-*N*-Benzyl 2-Amino-3-propoxypropionamide ((*R,S*)-10)



(*R,S*)-*N*-Benzyl 2-*N*-(Benzylcarboxycarbonyl)amino-3-propoxypropionamide ((*R,S*)-37). Utilizing Method D with (*R,S*)-**31** (3.29 g, 10.0 mmol), Ag_2O (11.59 g, 50.1 mmol), propyl iodide (14.7 mL, 150.4 mmol), and CH_3CN (100 mL) (40–50 °C, 7 d) gave the crude product that was further purified by flash column chromatography (SiO_2, 1:10 MeOH/CH_2Cl_2) followed

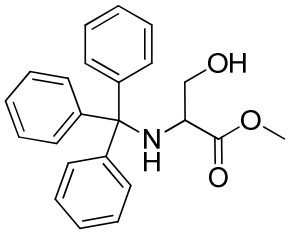
by recrystallization from hot EtOAc/hexanes gave the desired product (1.71 g, 46%) as a pale orange crystalline solid: mp 101–102 °C; R_f 0.58 (1:20 MeOH/CH_2Cl_2); IR (nujol mull) 3279, 2927 (br), 2728, 1682, 1644, 1544, 1459, 1377, 1237, 696 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.83 (t, J = 6.9 Hz, C**H**$_3$), 1.42–1.53 (m, C**H**$_2$CH$_3$), 3.33 (1/2 AB_q, J = 6.0 Hz, OC**H**H'CH_2CH_3), 3.35 (1/2 AB_q, J = 6.0 Hz, OCH**H'**CH_2CH_3), 3.50–3.60 (m, CHC**H**$_2$), 4.23–4.36 (m, C**H**, C**H**$_2$Ph), 5.01 (1/2 AB_q, J = 12.6 Hz, OC**H**H'Ph), 5.07 (1/2 AB_q, J = 12.6 Hz, OCH**H**'Ph), 7.23–7.37 (m, 2 C_6**H**$_5$), 7.43 (d, J = 8.1 Hz, N**H**C(O)), 8.52 (t, J = 6.3 Hz, N**H**CH_2Ph); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.0 (**C**H$_3$), 21.9 (**C**H$_2$CH$_3$), 41.7 (NH**C**H$_2$Ph), 54.5 (**C**H), 65.1 (O**C**H$_2$Ph), 69.8 (**C**H$_2$OCH$_2$ or CH$_2$O**C**H$_2$CH$_2$), 71.5 (**C**H$_2$OCH$_2$ or CH$_2$O**C**H$_2$CH$_2$), 126.3, 126.6, 127.3, 127.4, 127.8, 127.9, 136.6, 138.9 (2 **C**$_6$H$_5$), 155.6 (**C**(O)O), 169.4 (**C**(O)NH); HRMS (ESI) 393.1790 [M + Na^+] (calcd for $C_{21}H_{26}N_2O_4Na^+$ 393.1790); Anal. Calcd for $C_{21}H_{26}N_2O_4$; C, 68.09; H, 7.07; N, 7.56. Found C, 68.20; H, 7.19; N, 7.64.



(*R,S*)-*N*-Benzyl 2-Amino-3-propoxypropionamide ((*R,S*)-10). Utilizing Method C with (*R,S*)-**37** (1.42 g, 3.85 mmol), 10% Pd-C (0.15 g), and MeOH (50 mL) (6 h) gave the crude product that was purified by flash column chromatography (SiO_2; 1:100 MeOH/CH_2Cl_2). The resulting oil was dissolved in CH_2Cl_2 (10 mL) and extracted with aqueous 0.1 N HCl (3 x 10 mL). The aqueous layers were combined and washed with CH_2Cl_2 (2 x 30 mL). The aqueous layer was basified to pH 10–12 with aqueous 0.1 N NaOH, and then extracted with CH_2Cl_2 (3 x 60 mL). The second set of CH_2Cl_2 layers were combined, dried ($NaSO_4$), and concentrated in vacuo to

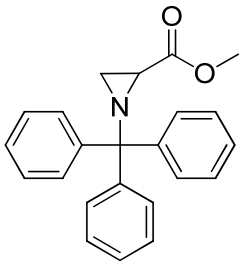
give the desired product (0.66 g, 72%) as a pale orange oil: R_f 0.52 (1:100 MeOH/CH_2Cl_2); IR (neat) 3338, 3123, 2935, 2868, 1661, 1528, 1457, 1362, 1256, 1108, 699 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.85 (t, J = 7.8 Hz, C**H**$_3$), 1.44–1.56 (m, C**H**$_2$CH$_3$), 1.82 (br s, N**H**$_2$), 3.31–3.46 (m, C**H**C**H**$_2$OC**H**$_2$CH$_2$), 4.23–4.37 (m, C**H**$_2$Ph), 7.19–7.32 (m, C$_6$**H**$_5$), 8.36–8.45 (br t, N**H**C(O)); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.1 (**C**H$_3$), 22.0 (**C**H$_2$CH$_3$), 41.5 (NH**C**H$_2$), 54.4 (**C**H), 71.6 (**C**H$_2$OCH$_2$ or CH$_2$O**C**H$_2$CH$_2$), 72.8 (**C**H$_2$OCH$_2$ or CH$_2$O**C**H$_2$CH$_2$), 126.2, 126.6, 127.7, 139.2 (**C**$_6$H$_5$), 172.7 (**C**(O)NH); Anal. Calcd for $C_{13}H_{20}N_2O_2$; C, 66.07; H, 8.53; N, 11.85. Found C, 65.80; H, 8.29; N, 11.58.

6. Preparation of (*R,S*)-*N*-Benzyl 2-Amino-3-allyloxypropionamide ((*R,S*)-11)



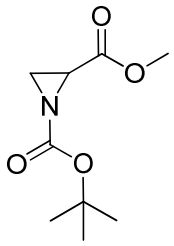
(*R,S*)-Methyl 3-Hydroxy-2-(*N*-tritylamino)propionate ((*R,S*)-39).[8] To a solution of DL-serine methyl ester hydrochloride (20.00 g, 0.13 mol) and Et_3N (35.82 mL, 0.26 mol) in CH_2Cl_2 (80 mL) at 0 °C, was added in one portion a solution of TrCl (36.53 g, 0.13 mol) in CH_2Cl_2 (80 mL). The mixture was allowed to stir at 0 °C (18 h) under N_2 and then successively washed with aqueous 10% citric acid (120 mL) and saturated aqueous brine (120 mL). The organic layer was dried (Na_2SO_4) and evaporated in vacuo to give the crude product (44.58 g, 96%) as a pale yellow crystalline solid. The product was used in the next step without further purification: R_f 0.72 (1:10 EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 2.38–2.54 (br s, 1 H), 2.89–3.02 (br s, 1 H), 3.26 (s, OC**H**$_3$), 3.50–3.59 (m, C**H**, C**H**H'OH), 3.69–3.73 (m, CH**H'**OH), 7.15–7.29 (m,

9 Ph**H**), 7.44–7.50 (6 Ph**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.1 (O**C**H_3), 58.0 (**C**H), 65.1 (**C**H_2OH), 126.8, 128.1, 128.9, 145.8 (3 $\mathbf{C_6}H_5$), 174.1 (**C**(O)).

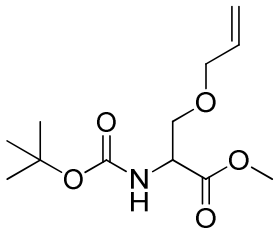


(*R,S*)-Methyl *N*-Tritylaziridine-2-carboxylate ((*R,S*)-40).[9] Crude (*R,S*)-**39** (44.00 g, 0.12 mol) was dissolved in CH_2Cl_2 (250 mL) and cooled to 0 °C under N_2. Methanesulfonyl chloride (10.37 mL, 0.13 mol) was added to the cooled solution, followed by the dropwise addition of Et_3N (25.47 mL, 0.18 mol). The resulting solution was allowed to stir at 0 °C (30 min) and then successively washed with aqueous 10% citric acid (250 mL) and saturated aqueous brine (250 mL), dried (Na_2SO_4), and evaporated in vacuo to give the crude mesylate. The crude mesylate was dissolved in DME (250 mL) and Et_3N (33.97 mL, 0.24 mol) was added. The mixture was stirred at 80 °C (72 h) and then concentrated to dryness in vacuo. The crude product was dissolved in EtOAc (250 mL), successively washed with aqueous 10% citric acid (250 mL) and saturated aqueous brine (250 mL), dried (Na_2SO_4), evaporated in vacuo, and purified by recrystallization from hot EtOH to give the desired product (26.43 g, 63%) as an off white solid: mp 131–132 °C (lit.[9] mp 133 °C); R_f 0.16 (1:10 EtOAc/hexanes); IR (nujol mull) 2927, 2859, 1719, 1596, 1454, 1375, 1291, 1216, 1077, 1027, 923, 869, 754, 707, 637 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (dd, J = 1.6, 6.2 Hz, NC**H**H'CH), 1.89 (dd, J = 2.7, 6.2 Hz, CHH'C**H**N), 2.26 (dd, J = 1.6, 2.7 Hz, NCH**H'**CH), 3.75 (s, OC$\mathbf{H_3}$), 7.18–7.30 (9 Ph**H**), 7.48–7.52 (6 Ph**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8 (N**C**H_2CH), 31.9 (CH_2**C**HN), 52.3 (O**C**H_3), 74.6 (N**C**Ph_3),

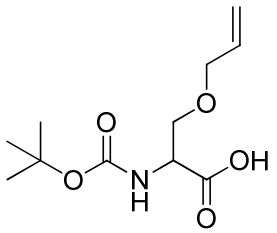
127.1, 127.9, 129.5, 143.8 (3 $\mathbf{C_6}H_5$), 172.1 (**C**(O)); HRMS (ESI) 344.1663 [M + H^+] (calcd for $C_{23}H_{21}NO_2H^+$ 344.1651).



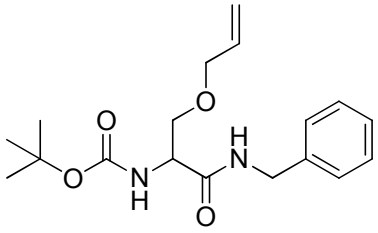
(*R,S*)-Methyl *N*-(*t*-Butoxycarbonyl)aziridine-2-carboxylate ((*R,S*)-41).[10] (*R,S*)-**40** (16.48 g, 48.02 mmol) was dissolved in CH_2Cl_2 (240 mL) and MeOH (1.53 mL, 48.02 mmol) was added and the solution was cooled to 0 °C in an ice bath under N_2 before TFA (7.13 mL, 96.05 mmol) was added dropwise. Et_3N (33.47 mL, 0.24 mol) was added dropwise at 0 °C and the reaction stirred at 0 °C (10 min) before Boc_2O (11.53 g, 52.83 mmol) in CH_2Cl_2 (60 mL) was added dropwise. The reaction was allowed to warm to room temperature (18 h) and then successively washed with aqueous 10% citric acid (3 x 300 mL), H_2O (3 x 300 mL), and saturated aqueous brine (2 x 300 mL), dried (Na_2SO_4), evaporated in vacuo, and purified by flash column chromatography (SiO_2; 1:100–1:10 MeOH/CH_2Cl_2) to give the desired product (6.79 g, 70%) as a pale yellow oil and as a 1:1 mixture of isomers A and B: R_f 0.47 (1:10 EtOAc/hexanes); IR (neat) 3483, 3427, 2980, 1737, 1630, 1449, 1378, 1328, 1156, 1029, 965, 853, 801, 751, 686, 597, 530 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45, 1.46 (2 s, (C(C$\mathbf{H_3}$)$_\mathbf{3}$), 2.52–2.58 (m, NHC$\mathbf{H_2}$CH), 3.03–3.06 (m, NHCH_2C**H**), 3.78, 3.79 (2 s, OC$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.6 (C(**C**H_3)$_3$), 31.0 (N**C**H_2CH), 34.6 (CH_2**C**HN), 52.3 (O**C**H_3), 81.9 (**C**(CH_3)$_3$), 159.3 (N**C**(O)O), 168.6 (**C**(O)OCH_3); HRMS (ESI) 224.0909 [M + Na^+] (calcd for $C_9H_{15}NO_4Na^+$ 224.0899).



(*R,S*)-Methyl 2-*N'*-(*t*-Butoxycarbonyl)amino-3-allyloxypropionate ((*R,S*)-44). (*R,S*)-**41** (6.22 g, 30.93 mmol) was dissolved in anhydrous CH_2Cl_2 (30 mL) and cooled to 0 °C in an ice bath. Then, allyl alcohol (6.31 mL, 92.79 mmol) followed by BF_3•Et_2O (3.82 mL, 30.93 mmol) was successively added. The reaction was continued at 0 °C (45 min) and then saturated aqueous $NaHCO_3$ (30 mL) was added and stirred (30 min). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). Both sets of organic layers were combined, dried (Na_2SO_4), evaporated in vacuo, and purified by flash column chromatography (SiO_2; 1:10–1:1 EtOAc/hexanes followed by 1:10 MeOH/CH_2Cl_2) to give the desired product (1.52 g, 19%) as a pale yellow oil: R_f 0.55 (1:10 EtOAc/hexanes); IR (neat) 3379, 3301, 2930, 1716, 1507, 1453, 1362, 1167, 929, 866, 781, 658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, C(C**H**$_3$)$_3$), 3.65 (dd, J = 3.6, 9.2 Hz, C**H**H'OCH_2), 3.76 (s, OC**H**$_3$), 3.85 (dd, J = 3.2, 9.2 Hz, CH**H'**OCH_2), 3.93–4.03 (m, CH_2OC**H**$_2$), 4.42–4.44 (m, C**H**), 5.17–5.27 (m, OCH_2CHCH_2), 5.42 (d, J = 9.2 Hz, N**H**), 5.79–5.95 (m, OCH_2CHCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4 (C(**C**H_3)$_3$), 52.5 (O**C**H_3), 54.1 (**C**H), 70.0 (**C**H_2OCH_2), 72.3 (CH_2O**C**H_2), 80.0 (**C**$(CH_3)_3$), 117.4 (OCH_2CHCH_2), 134.2 (OCH_2CHCH_2), 155.6 (**C**(O)N), 171.3 (**C**(O)OCH_3).

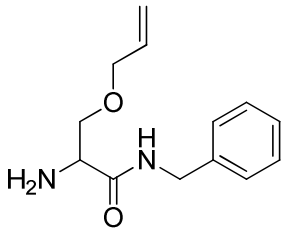


(*R,S*)-Methyl 2-*N'*-(*t*-Butoxycarbonyl)amino-3-allyloxypropionic Acid ((*R,S*)-46). (*R,S*)-**44** (1.13 g, 4.36 mmol) was dissolved in anhydrous THF (44 mL) and a solution of LiOH (0.6 M, 7.27 mL, 4.36 mmol) was added at room temperature (18 h) and then the solvent was evaporated in vacuo. The crude product was diluted with H_2O (25 mL), acidified to pH 3 with aqueous 1 M $KHSO_4$, and extracted with EtOAc (6 x 25 mL). The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to give the crude product (1.07 g, 99%) as a pale yellow oil. The product was used for the next step without further purification: R_f 0.44 (1:20 MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3OD) δ 1.45 (s, C(C**H$_3$)$_3$**), 3.68 (dd, J = 3.4, 9.8 Hz, C**H**H'OCH_2), 3.79 (dd, J = 5.0, 9.8 Hz, CH**H'**OCH_2), 3.95–4.04 (m, CH_2OC**H$_2$**), 4.30 (t, J = 4.0 Hz, C**H**), 5.14–5.30 (m, OCH_2CHC**H$_2$**), 5.83–5.93 (m, OCH_2C**H**CH_2); ^{13}C NMR (100 MHz, CD_3OD) δ 27.3 (C(**C**$H_3)_3$), 53.8 (**C**H), 69.4 (**C**H_2OCH_2), 71.7 (CH_2O**C**H_2), 79.3 (**C**$(CH_3)_3$), 116.0 (OCH_2CH**C**H_2), 134.3 (OCH_2**C**HCH_2), 156.4 (**C**(O)N), 172.4 (**C**(O)OH).



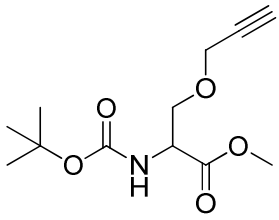
(*R,S*)-*N*-Benzyl 2-*N'*-(*t*-Butoxycarbonyl)amino-3-allyloxypropionamide ((*R,S*)-48). Utilizing Method B with (*R,S*)-**46** (1.05 g, 4.28 mmol), NMM (0.62 mL, 5.57 mmol), IBCF (0.61 mL, 4.71 mmol), and benzylamine (0.49 mL, 4.50 mmol) gave the crude product that was purified by flash column chromatography (SiO_2; 1:10–1:1 EtOAc/hexanes followed by 1:10 MeOH/CH_2Cl_2) to give the desired product (1.25 g, 87%) as a pale yellow solid: R_f 0.19 (1:10 EtOAc/hexanes); mp 70–71 °C; IR (neat) 3305, 3037, 2968, 1707, 1532, 1365, 1250, 1167, 1041, 948, 869, 744, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, C(C**H$_3$)$_3$**), 3.56 (dd, J = 6.4, 9.4 Hz, C**H**H'OCH_2),

3.87 (dd, J = 4.0, 9.4 Hz, CH**H'**OCH_2), 3.95–4.04 (m, $CH_2OC\mathbf{H_2}$), 4.26–4.34 (m, C**H**), 4.47 (d, J = 5.6 Hz, $NHC\mathbf{H_2}Ph$), 5.15–5.25 (m, $OCH_2CHC\mathbf{H_2}$), 5.37–5.52 (br d, C(O)N**H**), 5.78–5.88 (m, $OCH_2C\mathbf{H}CH_2$), 6.81–6.87 (br t, N**H**CH_2Ph), 7.23–7.33 ($C_6\mathbf{H_5}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4 ($C(\mathbf{C}H_3)_3$), 43.6 ($NH\mathbf{C}H_2Ph$), 54.3 (**C**H), 69.9 ($\mathbf{C}H_2OCH_2$), 72.4 ($CH_2O\mathbf{C}H_2$), 80.4 ($\mathbf{C}(CH_3)_3$), 117.7 ($OCH_2CH\mathbf{C}H_2$), 127.5, 127.6, 128.8 (3 Ar**C**), 134.1 ($OCH_2\mathbf{C}HCH_2$), 138.1 (1 Ar**C**), 155.6 (O**C**(O)N), 171.3 (C**C**(O)N).

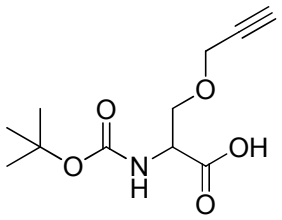


(*R,S*)-*N*-Benzyl 2-Amino-3-allyloxypropionamide ((*R,S*)-11). Utilizing Method E with (*R,S*)-**48** (1.17 g, 3.50 mmol), TFA (3.90 mL, 52.52 mol), and CH_2Cl_2 (12 mL) gave the crude product after workup that was further purified by flash column chromatography (SiO_2; 1:100–1:10 MeOH/CH_2Cl_2) to give the desired product (285 mg, 35%) as a pale yellow oil: R_f 0.44 (1:20 MeOH/CH_2Cl_2); IR (neat) 3446, 3299, 2920, 2863, 1658, 1530, 1454, 1355, 1256, 1090, 1001, 930, 737, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61–1.73 (br s, N$\mathbf{H_2}$), 3.62 (t, J = 5.6 Hz, C**H**), 3.66–3.74 (m, $C\mathbf{H_2}OCH_2$), 4.00 (app. t, J = 1.2 Hz, $CH_2OC\mathbf{H}H'$), 4.02 (app. t, J = 1.6 Hz, $CH_2OCH\mathbf{H'}$), 4.41–4.51 (m, $NHC\mathbf{H_2}Ph$), 5.17–5.29 (m, $OCH_2CHC\mathbf{H_2}$), 5.84–5.93 (m, $OCH_2C\mathbf{H}CH_2$), 7.24–7.35 ($C_6\mathbf{H_5}$), 7.73–7.81 (br t, N**H**CH_2Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.3 ($NH\mathbf{C}H_2Ph$), 55.2 (**C**H), 72.3 ($\mathbf{C}H_2OCH_2$), 72.4 ($CH_2O\mathbf{C}H_2$), 117.5 ($OCH_2CH\mathbf{C}H_2$), 127.5, 127.8, 128.8 (3 Ar**C**), 134.5 ($OCH_2\mathbf{C}HCH_2$), 138.6 (1 Ar**C**), 172.8 (**C**(O)N); HRMS (ESI) 235.1452 [M + H$^+$] (calcd for $C_{13}H_{18}N_2O_2H^+$ 235.1447); Anal. Calcd for $C_{13}H_{18}N_2O_2 \bullet 0.20H_2O$: C, 65.61; H, 7.80; N, 11.77. Found: C, 65.21; H, 7.92; N, 11.60.

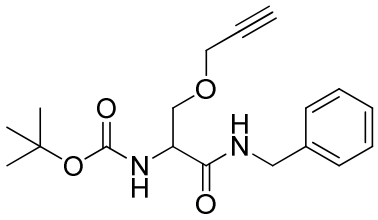
7. Preparation of (*R,S*)-*N*-Benzyl 2-Amino-3-(prop-2-ynyloxy)propionamide ((*R,S*)-12)



(*R,S*)-Methyl 2-*N*-(*t*-Butoxycarbonyl)amino-3-(prop-2-ynyloxy)propionate ((*R,S*)-45). (*R,S*)-**41** (6.85 g, 34.06 mmol) was dissolved in anhydrous CH_2Cl_2 (48 mL) and cooled to 0 °C in an ice bath. Then, propargyl alcohol (6.03 mL, 102.18 mmol) followed by BF_3•Et_2O (4.20 mL, 34.06 mmol) was successively added. The reaction was continued at 0 °C (15 min) and then saturated aqueous $NaHCO_3$ (48 mL) was added and stirred (30 min). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). Both sets of organic layers were combined, dried (Na_2SO_4), evaporated in vacuo, and purified by flash column chromatography (SiO_2; 1:100 MeOH/CH_2Cl_2) to give the desired product (1.06 g, 12%) as a pale yellow oil: R_f 0.35 (1:10 EtOAc/hexanes); IR (neat) 3396, 3265, 2976, 2880, 2118, 1713, 1507, 1451, 1358, 1213, 1169, 1108, 1065, 925, 869, 778, 663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, C(C**H**$_3$)$_3$), 2.45 (t, J = 2.4 Hz, CH_2CC**H**), 3.77 (dd, J = 3.6, 9.2 Hz, C**H**H'OCH_2), 3.78 (s, OC**H**$_3$), 3.96 (dd, J = 2.8, 9.2 Hz, CH**H'**OCH_2), 4.15 (d, J = 2.4 Hz, CH_2OC**H**$_2$), 4.43–4.44 (m, C**H**), 5.38 (d, J = 8.4 Hz, N**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5 (C(**C**H_3)$_3$), 52.7 (O**C**H_3), 54.0 (**C**H), 58.7 (**C**H_2CCH), 69.9 (**C**H_2OCH_2), 75.2 (CH_2C**C**H), 79.0 (CH_2**C**CH), 80.2 (**C**$(CH_3)_3$), 155.6 (**C**(O)N), 171.1 (**C**(O)OCH_3); HRMS (ESI) 280.1167 [M + Na^+] (calcd for $C_{12}H_{19}NO_5Na^+$ 280.1161).

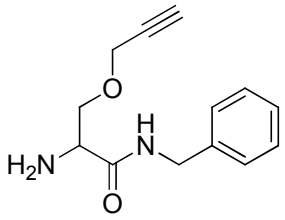


(*R,S*)-2-*N*-(*t*-Butoxycarbonyl)amino-3-(prop-2-ynyloxy)propionic Acid ((*R,S*)-47). (*R,S*)-**45** (959 mg, 37.30 mmol) was dissolved in anhydrous THF (37 mL) and a solution of LiOH (0.6 M, 6.22 mL, 37.30 mmol) was added at room temperature (18 h) and then the solvent was evaporated in vacuo. The crude product was diluted with H_2O (25 mL), acidified to pH 3 with aqueous 1 M $KHSO_4$, and extracted with EtOAc (6 x 25 mL), dried (Na_2SO_4), and evaporated in vacuo to give the crude product (916 mg, 99%) as a pale yellow, waxy solid. The product was used for the next step without further purification: R_f 0.46 (1:20 MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, CD_3OD) δ 1.45 (s, C(C**H**$_3$)$_3$), 2.87 (t, J = 2.3 Hz, CH_2CC**H**), 3.76 (dd, J = 3.9, 9.6 Hz, C**H**H'OCH_2), 3.89 (dd, J = 4.6, 9.6 Hz, CH**H'**OCH_2), 4.17 (d, J = 2.3 Hz, CH_2OC**H**$_2$), 4.32 (t, J = 4.2 Hz, C**H**); ^{13}C NMR (75 MHz, CD_3OD) δ 28.8 (C(**C**H_3)$_3$), 55.2 (**C**H), 59.3 (**C**H_2CCH), 70.6 (**C**H_2OCH_2), 76.4 (CH_2C**C**H), 80.2 (CH_2**C**CH), 80.9 (**C**$(CH_3)_3$), 158.1 (**C**(O)N), 173.7 (**C**(O)OCH_3).



(*R,S*)-*N*-Benzyl 2-*N'*-(*t*-Butoxycarbonyl)amino-3-(prop-2-ynyloxy)propionamide ((*R,S*)-49). Utilizing Method B with (*R,S*)-**47** (894 mg, 3.68 mmol), NMM (0.53 mL, 4.78 mmol), IBCF (0.52 mL, 4.05 mmol), and benzylamine (0.42 mL, 3.86 mmol) gave the crude product that was purified by flash column chromatography (SiO_2; 1:10–1:1 EtOAc/hexanes) to give the desired

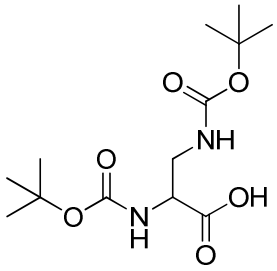
product (1.10 g, 90%) as a pale yellow solid: mp 100–101 °C; R_f 0.77 (1:1 EtOAc/hexanes); IR (nujol mull) 3332, 3263, 2878, 2114, 1710, 1660, 1539, 1457, 1369, 1300, 1249, 1166, 1092, 1020, 943, 871, 663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, C(C**H$_3$**)$_3$), 2.45 (t, J = 2.4 Hz, CH_2CCH), 3.70 (dd, J = 6.2, 9.2 Hz, C**H**H'OCH_2), 3.97 (dd, J = 3.8, 9.2 Hz, CH**H'**OCH_2), 4.11–4.23 (m, CH_2OCH_2), 4.25–4.39 (m, C**H**), 4.49 (d, J = 5.2 Hz, NHC**H$_2$**Ph), 5.31–5.42 (br d, C(O)N**H**), 6.66–6.72 (br t, N**H**CH_2Ph), 7.25–7.34 (m, C_6**H$_5$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5 (C(**C**$H_3)_3$), 43.7 (NH**C**H_2Ph), 54.3 (**C**H), 58.8 (**C**H_2CCH), 69.7 (**C**H_2OCH_2), 75.4 (CH_2C**C**H), 79.1 (CH_2**C**CH), 80.6 (**C**$(CH_3)_3$), 127.7, 127.8, 128.9, 138.1 (**C$_6$**H_5), 155.2 (O**C**(O)N), 170.2 (C**C**(O)N); HRMS (ESI) 355.1645 [M + Na^+] (calcd for $C_{18}H_{24}N_2O_4Na^+$ 355.1634); Anal. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 65.26; H, 7.44; N, 8.42.



(*R,S*)-*N*-Benzyl 2-Amino-3-(prop-2-ynyloxy)propionamide ((*R,S*)-12). Utilizing Method E with (*R,S*)-**49** (973 mg, 2.93 mmol), TFA (3.26 mL, 43.94 mol), and CH_2Cl_2 (10 mL) gave the crude product after workup that was further purified by flash column chromatography (SiO_2; 1:100–1:10 MeOH/CH_2Cl_2) to give the desired product (512 mg, 75%) as a pale yellow oil: R_f 0.29 (1:100 MeOH/CH_2Cl_2); IR (neat) 3344, 3295, 3142, 3066, 2909, 2114, 1659, 1527, 1454, 1357, 1258, 1095, 1023, 916, 737, 697 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.64–1.72 (br s, N**H$_2$**), 2.45 (t, J = 2.4 Hz, CH_2CC**H**), 3.62 (dd, J = 4.0, 6.2 Hz, C**H**), 3.76 (dd, J = 6.2, 9.2 Hz, C**H**H'OCH_2), 3.84 (dd, J = 4.0, 9.2 Hz, CH**H'**OCH_2), 4.13–4.24 (m, CH_2OCH_2), 4.41–4.51 (m,

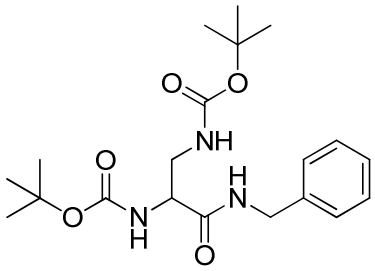
NHC**H**$_2$Ph), 7.24–7.35 (m, C_6**H**$_5$), 7.73–7.81 (br t, N**H**CH_2Ph); ^{13}C NMR (400 MHz, $CDCl_3$) δ 43.4 (NH**C**H_2Ph), 55.1 (**C**H), 58.7 (**C**H_2CCH), 72.3 (**C**H_2OCH_2), 75.1 (CH_2**C**CH), 79.4 (CH_2**C**CH), 127.6, 127.8, 128.8, 138.5 (**C**$_6$$H_5$), 172.5 (C**C**(O)N); HRMS (ESI) 233.1294 [M + H^+] (calcd for $C_{13}H_{16}N_2O_2H^+$ 233.1290); Anal. Calcd for $C_{13}H_{16}N_2O_2$•0.09CH_2Cl_2: C, 65.59; H, 6.80; N, 11.69. Found: C, 65.54; H, 6.97; N, 11.68.

8. Preparation of (*R,S*)-*N*-Benzyl 2,3-Diaminopropionamide ((*R,S*)-13)

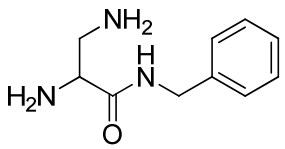


(*R,S*)-*N,N*'-2,3-Bis(*t*-butoxycarbonyl)aminopropionic Acid ((*R,S*)-63).[11] 2,3-Diaminopropionic acid hydrochloride (5.00 g, 35.57 mmol) and $NaHCO_3$ (29.88 g, 0.36 mol) were dissolved in H_2O (150 mL) and dioxane (150 mL). Boc_2O (31.05 g, 142.3 mmol) was added and the reaction was stirred at room temperature (18 h). The mixture was diluted with H_2O (100 mL), washed with CH_2Cl_2 (2 x 150 mL), acidified to pH 2 with aqueous concentrated HCl, and extracted with CH_2Cl_2 (3 x 200 mL). The organic layers were combined, washed with H_2O (3 x 200 mL), dried (Na_2SO_4), and evaporated in vacuo. The residue was recrystallized from hot toluene to give the desired product (6.72 g, 62%) as a white solid: mp 126–127 °C (lit.[11] mp 118–124 °C); IR (nujol mull) 3311, 2920 (br), 1741, 1689, 1530, 1469, 1372, 1284, 1161, 1107, 1044, 868, 773, 719, 671 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.41 (s, C(C**H**$_3$)$_3$), 1.42 (s, (C(C**H**$_3$)$_3$)**'**), 3.24 (t, J = 5.9 Hz, C**H**$_2$NH), 3.96–4.03 (m, C**H**), 6.80 (t, J = 5.9 Hz, $(CH_3)_3COC(O)N$**H**), 6.88–6.91 (d, J = 8.1 Hz, $(CH_3)_3COC(O)N$**H'**); ^{13}C NMR (75 MHz,

DMSO-d_6) δ 27.8 (2 **C**$(CH_3)_3$), 40.8 (**C**H_2NH), 53.4 (**C**H), 77.6, 77.8 (2 **C**$(CH_3)_3$), 155.0, 155.3 (2 **C**(O)O**C**$(CH_3)_3$), 171.9 (**C**(O)OH).

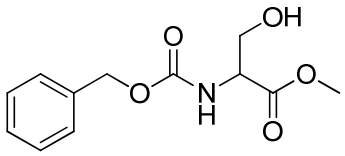


(*R,S*)-*N*-Benzyl *N',N''*-2,3-Bis(*t*-butoxycarbonyl)aminopropionamide ((*R,S*)-64). Utilizing Method B with (*R,S*)-**63** (1.77 g, 5.82 mmol), NMM (0.83 mL, 7.57 mmol), IBCF (0.75 mL, 6.40 mmol), and benzylamine (0.64 mL, 6.11 mmol) gave the crude product that was recrystallized twice from hot EtOAc to give the desired product (1.54 g, 67%) as a white solid: mp 141–142 °C; R_f 0.52 (1:20 MeOH/CH_2Cl_2); IR (nujol mull) 3319, 2919, 2860, 1687, 1531, 1456, 1371, 1304, 1247, 1169, 1044, 952, 873, 746, 698, 639 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, C(C**H$_3$**)$_3$), 1.43 (s, C(C**H$_3$**)$_3$**'**), 3.45–3.60 (m, C**H$_2$**NH), 4.18–4.29 (m, C**H**), 4.39 (dd, J = 5.0, 15.4 Hz, NHC**H**H'Ph), 4.51 (dd, J = 5.6, 15.4 Hz, NHCH**H'**Ph), 5.11–5.24 (br t, $(CH_3)_3$COC(O)N**H**), 5.89 (d, J = 6.0 Hz, $(CH_3)_3$COC(O)N**H'**), 6.96–7.05 (br t, N**H**CH_2Ph), 7.24–7.35 (C_6**H$_5$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 28.4 (2 **C**$(CH_3)_3$), 42.5 (NH**C**H_2Ph), 43.5 (**C**H_2NH), 56.0 (**C**H), 80.0, 80.4 (2 **C**$(CH_3)_3$), 127.5, 127.6, 128.8, 138.1 (**C$_6$**H_5), 156.4, 157.3 (2 **C**(O)O**C**$(CH_3)_3$), 170.8 (**C**(O)NHCH_2Ph); HRMS (ESI) 416.2151 [M + Na^+] (calcd for $C_{20}H_{31}N_3O_5Na^+$ 416.2162); Anal. Calcd for $C_{20}H_{31}N_3O_5$: C, 61.05; H, 7.94; N, 10.68. Found: C, 61.16; H, 7.98; N, 10.49.



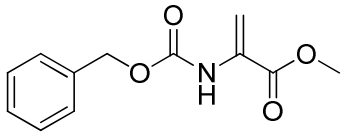
(*R,S*)-*N*-Benzyl 2,3-Diaminopropionamide ((*R,S*)-13). Utilizing Method E with (*R,S*)-**64** (1.71 g, 4.35 mmol), TFA (4.86 mL, 65.23 mmol), and CH_2Cl_2 (15 mL) gave the crude product after workup that was further purified by recrystallization from hot EtOAc/hexanes to give the desired product (427 mg, 51%) as a white solid: mp 119–120 °C; R_f 0.17 (1:10 MeOH/CH_2Cl_2); IR (nujol mull) 3316, 2924, 2858, 1645, 1523, 1459, 1376, 731 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 2.70–2.95 (m, C**H**$_2$NH$_2$), 3.35–3.42 (m, C**H**), 4.40 (s, NHC**H**$_2$Ph), 7.21–7.35 (m, C$_6$**H**$_5$); ^{13}C NMR (75 MHz, CD_3OD) δ 44.2 (NH**C**H$_2$Ph), 46.7 (**C**H$_2$NH$_2$), 57.5 (**C**H), 128.5, 128.8, 129.8, 140.0 (**C**$_6$H$_5$), 175.9 (**C**(O)NH); HRMS (ESI) 216.1107 [M + Na^+] (calcd for $C_{10}H_{15}N_3ONa^+$ 216.1113); Anal. Calcd for $C_{10}H_{15}N_3O•H_2O$: C, 61.91; H, 7.84; N, 21.66. Found: C, 61.54; H, 7.90; N, 21.38.

9. Preparation of (*R,S*)-*N*-Benzyl 2-Amino-3-(*N',N'*-dimethyl)aminopropionamide ((*R,S*)-15)

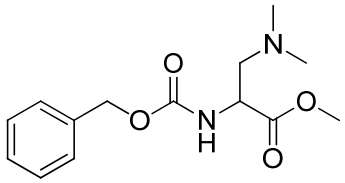


(*R,S*)-*N*-(Benzyloxycarbonyl)-serine Methyl Ester ((*R,S*)-50).[12] Utilizing Method A with DL-serine methyl ester hydrochloride (10.0 g, 64.3 mmol), $NaHCO_3$ (17.8 g, 212.1 mmol), and H_2O (130 mL) gave the crude product after workup that was further purified by flash column chromatography (SiO_2; 1:100 MeOH/CH_2Cl_2) to give the desired product (12.17 g, 75%) as a pale yellow oil: R_f 0.29 (1:100 MeOH/CH_2Cl_2); IR (neat) 3413, 3362, 3033, 2954, 2893, 1708,

1522, 1219, 1065, 912, 746, 700 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.59–3.69 (m, C**H**$_2$OH, C**H**$_3$), 4.14–4.20 (m, C**H**), 4.98 (t, J = 6.0 Hz, O**H**), 5.05 (s, OC**H**$_2$Ph), 7.29–7.38 (m, C$_6$**H**$_5$), 7.55 (d, J = 7.8 Hz, N**H**); ^{13}C NMR (75 MHz, DMSO-d_6) δ 51.5 (**C**H$_3$), 56.3 (**C**H), 60.9 (**C**H$_2$OH), 65.3 (O**C**H$_2$Ph), 127.4, 127.5, 128.0, 136.6 (**C**$_6$H$_5$), 155.7 (N**C**(O)O), 170.9 (CH**C**(O)); HRMS (ESI) 276.0844 [M + Na^+] (calcd for $C_{12}H_{15}NO_5Na^+$ 276.0848).

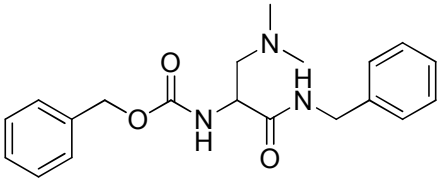


***N*-(Benzyloxycarbonyl)amino-dehydroalanine Methyl Ester (51).**[13] (*R,S*)-**50** (1.00 g, 3.95 mmol) was dissolved in anhydrous THF (20 mL) and cooled to 0 °C before the dropwise addition of Et_3N (0.66 mL, 4.74 mmol). After 10 min, MsCl (0.37 mL, 4.74 mmol) was added dropwise at 0 °C, which led to the formation of a precipitate. After 1 h at 0 °C, Et_3N (0.66 mL, 4.74 mmol) was added and the reaction was warmed to room temperature (3 h). The precipitate was filtered, washed with anhydrous THF, and the filtrate was evaporated in vacuo to give a crude oil (0.58 g, 62%) that was used without further purification: R_f 0.54 (1:10 EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 3.30–3.75 (br s, N**H**), 3.83 (s, OC**H**$_3$), 5.16 (s, OC**H**$_2$Ph), 5.79 (s, C**H**H'), 6.25 (s, CH**H'**), 7.26–7.39 (m, C$_6$**H**$_5$).



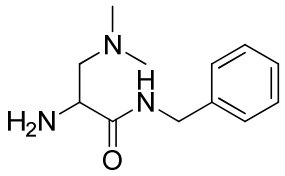
(*R,S*)-2-*N*-(Benzyloxycarbonyl)amino-3-(*N',N'*-dimethyl)aminopropionic Methyl Ester ((*R,S*)-58). Utilizing Method F with (*R,S*)-**50** (6.11 g, 24.14 mmol), Et_3N (4.0 mL, 28.97 mmol),

MsCl (2.2 mL, 28.97 mmol), dimethylamine (in 2 M THF, 100 mL, 193.1 mmol), and MeOH (100 mL) gave the crude product after workup that was further purified by flash column chromatography (SiO_2, 1:100–1:10 MeOH/CH_2Cl_2) to give the desired product (4.51 g, 67%) as an orange oil: R_f 0.47 (1:20 MeOH/CH_2Cl_2); IR (neat) 3494, 3248, 3145, 1718, 1524, 1458, 1213, 1056, 908, 850, 745, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, N(C**H**$_3$)$_2$), 2.57–2.69 (m, C**H**$_2$N(CH$_3$)$_2$), 3.73 (s, OC**H**$_3$), 4.30–4.36 (m, C**H**), 5.10 (s, OC**H**$_2$Ph), 5.89 (d, J = 6.3 Hz, N**H**), 7.27–7.36 (m, C$_6$**H**$_5$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.6 (N(**C**H$_3$)$_2$), 52.4 (**C**H$_3$ or **C**H), 52.8 (**C**H$_3$ or **C**H), 59.9 (**C**H$_2$N(CH$_3$)$_2$), 67.0 (O**C**H$_2$Ph), 128.2, 128.5, 136.4 (**C**$_6$H$_5$), 156.2 (N**C**(O)O), 172.4 (CH**C**(O)), one aromatic peak was not detected and is believed to overlap with nearby signals; HRMS (ESI) 303.1322 [M + Na^+] (calcd for $C_{14}H_{20}N_2O_4Na^+$ 303.1321); Anal. Calcd for $C_{14}H_{20}N_2O_2$; C, 59.99; H, 7.19; N, 9.99. Found C, 60.17; H, 7.29; N, 9.85.



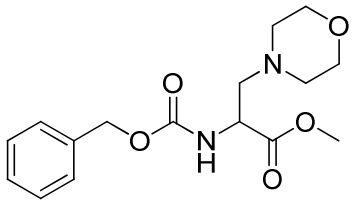
(*R,S*)-*N*-Benzyl 2-*N'*-(Benzyloxycarbonyl)amino-3-(*N'',N''*-dimethyl)aminopropionamide ((*R,S*)-60). Utilizing Method G with (*R,S*)-**58** (3.88 g, 13.85 mmol), LiOH (0.33 g, 13.85 mmol), benzylamine hydrochloride (2.39 g, 16.62 mmol), DMTMM (4.60 g, 16.62 mmol), and THF/H_2O (140 mL/70 mL) gave the crude product after workup that was further purified by flash column chromatography (SiO_2, 1:3 CH_2Cl_2/EtOAc followed by 1:10 MeOH/CH_2Cl_2) to give the desired product (1.67 g, 34%) as an orange solid: mp 82–83 °C; R_f 0.44 (1:20 MeOH/CH_2Cl_2); IR (nujol mull) 3403, 3149, 2856 (br), 1706, 1655, 1550, 1457, 1375, 1255, 1058, 904, 850, 732, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, N(C**H**$_3$)$_2$), 2.43 (dd, J = 8.7, 12.4 Hz, C**H**H'N(CH$_3$)$_2$), 2.60 (dd, J = 6.2, 12.4 Hz, C**H**H'N(CH$_3$)$_2$), 4.09–4.19 (m, C**H**),

4.38 (dd, J = 5.3, 14.9 Hz, NHC**H**H'Ph), 4.53 (dd, J = 6.2, 14.9 Hz, NHCH**H'**Ph), 5.08 (1/2 AB_q, J = 12.2 Hz, OC**H**H'Ph), 5.13 (1/2 AB_q, J = 12.2 Hz, OCH**H'**Ph), 5.86–6.01 (br d, N**H**C(O)), 7.23–7.36 (m, 2 C_6**H**$_5$), 8.36–8.55 (br t, N**H**CH_2Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.5 (NH**C**H_2Ph), 45.2 (N(**C**$H_3)_2$), 51.2 (**C**H), 61.2 (**C**H_2N$(CH_3)_2$), 67.1 (O**C**H_2Ph), 127.5, 127.6, 128.2, 128.3, 128.7, 128.8, 136.4, 138.5 (**C**$_6$H$_5$), 156.4 (N**C**(O)O), 171.1 (CH**C**(O)); HRMS (ESI) 378.1798 [M + Na^+] (calcd for $C_{20}H_{25}N_3O_3Na^+$ 378.1794); Anal. Calcd for $C_{20}H_{25}N_3O_3$; C, 67.58; H, 7.09; N, 11.82. Found C, 67.58; H, 7.15; N, 12.02.

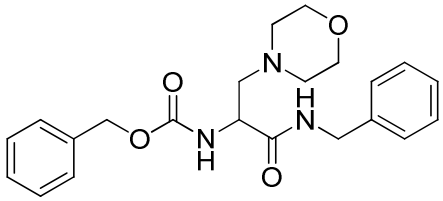


(*R,S*)-*N*-Benzyl 2-Amino-3-(*N',N'*-dimethyl)aminopropionamide ((*R,S*)-15). Utilizing Method C with (*R,S*)-**60** (1.08 g, 3.03 mmol), 10% Pd-C (0.1 g), and MeOH (30 mL) gave a crude oil that was purified by flash column chromatography (SiO_2; 1:100–1:20 MeOH/CH_2Cl_2) to give the desired product (0.40 g, 60%) as a pale orange oil: R_f 0.26 (1:10 MeOH/CH_2Cl_2); IR (neat) 3447, 3116, 3006, 2848, 2731, 1661, 1526, 1458, 1362, 1259, 1113, 1037, 935, 870, 739, 701, 602 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (s, N**H**$_2$), 2.26 (s, N(C**H**$_3)_2$), 2.42 (dd, J = 8.8, 12.3 Hz, C**H**H'N$(CH_3)_2$), 2.60 (dd, J = 6.0, 12.3 Hz, CH**H'**N$(CH_3)_2$), 3.50 (dd, J = 6.0, 8.8 Hz, C**H**), 4.38–4.52 (m, NHC**H**$_2$Ph), 7.24–7.36 (m, C$_6$**H**$_5$), 8.20–8.34 (br t, N**H**CH_2Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.2 (NH**C**H_2Ph), 45.4 (N(**C**$H_3)_2$), 52.5 (**C**H), 63.0 (**C**H_2N$(CH_3)_2$), 127.5, 127.8, 128.8, 138.8 (**C**$_6$H$_5$), 174.4 (CH**C**(O)); HRMS (ESI) 244.1434 [M + Na^+] (calcd for $C_{12}H_{19}N_3ONa^+$ 244.1426); Anal. Calcd for $C_{12}H_{19}N_3O_2$•0.33H_2O; C, 63.41; H, 8.72; N, 18.49. Found C, 63.38; H, 8.52; N, 18.21.

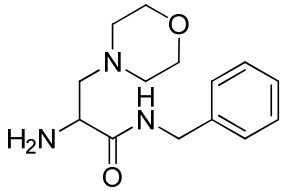
10. Preparation of (*R,S*)-*N*-Benzyl 2-Amino-3-morpholinopropionamide ((*R,S*)-16)



(*R,S*)-2-*N*-(Benzyloxycarbonyl)amino-3-morpholinopropionic Methyl Ester ((*R,S*)-59). Utilizing Method F with (*R,S*)-**50** (7.00 g, 27.66 mmol), Et_3N (4.6 mL, 33.19 mmol), MsCl (2.6 mL, 33.19 mmol), and morpholine (24.2 mL, 276.6 mmol) gave the crude product after workup that was further purified by flash column chromatography (SiO_2, 1:100–1:20 MeOH/CH_2Cl_2) to give the desired product (6.58 g, 74%) as a white solid: mp 69–70 °C; R_f 0.53 (1:10 MeOH/CH_2Cl_2); IR (nujol mull) 3284, 2904 (br), 1749, 1679, 1528, 1457, 1373, 1302, 1269, 1207, 1159, 1109, 1054, 1007, 904, 862, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.37–2.50 (m, N(C**H**$_2$CH$_2$)$_2$O), 2.65–2.76 (m, C**H**$_2$N(CH$_2$CH$_2$)$_2$O), 3.64 (t, J = 4.5 Hz, N(CH$_2$C**H**$_2$)$_2$O), 3.75 (s, OC**H**$_3$), 4.35–4.41 (m, C**H**), 5.09 (1/2 AB_q, J = 12.2 Hz, OC**H**H'Ph), 5.14 (1/2 AB_q, J = 12.2 Hz, OCH**H'**Ph), 5.67–5.69 (d, J = 6.6 Hz, N**H**), 7.31–7.40 (m, C_6**H**$_5$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.2 (O**C**H$_3$), 52.5 (**C**H), 53.8 (N(**C**H$_2$CH$_2$)O), 59.2 (**C**H$_2$N(CH$_2$CH$_2$)O), 67.0 (N(CH$_2$**C**H$_2$)O), 67.2 (O**C**H$_2$Ph), 128.4, 128.7, 136.4 (**C**$_6$H$_5$), 156.1 (N**C**(O)O), 172.4 (CH**C**(O)), one aromatic peak was not detected and is believed to overlap with nearby signals; HRMS (ESI) 345.1431 [M + Na^+] (calcd for $C_{16}H_{22}N_2O_5Na^+$ 345.1427); Anal. Calcd for $C_{16}H_{22}N_2O_5$; C, 59.61; H, 6.88; N, 8.69. Found C, 59.53; H, 6.79; N, 8.59.

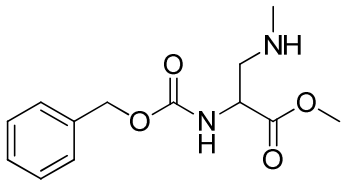


(*R,S*)-*N*-Benzyl 2-*N'*-(Benzyloxycarbonyl)amino-3-morpholinopropionamide ((*R,S*)-61). Utilizing Method G with (*R,S*)-**59** (5.00 g, 15.52 mmol), LiOH (0.37 g, 15.52 mmol), benzylamine hydrochloride (2.67 g, 18.62 mmol), DMTMM (5.15 g, 18.62 mmol), and THF/H_2O (150 mL/75 mL) gave the crude product after workup that was further purified by column chromatography (SiO_2, 1:100–1:10 MeOH/CH_2Cl_2) followed by recrystallization from hot EtOAc/hexanes to give the desired product (3.49 g, 57%) as a white solid: mp 103–104 °C; R_f 0.50 (1:20 MeOH/CH_2Cl_2); IR (nujol mull) 3418, 3290, 3140, 2912 (br), 1658, 1554, 1457, 1376, 1260, 1113, 1037, 869, 732, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.26–2.82 (m, C**H**$_2$N(C**H**$_2$CH$_2$)$_2$O), 3.41–3.56 (m, N(CH$_2$C**H**$_2$)$_2$O), 4.10–4.21 (m, C**H**), 4.33 (dd, J = 4.8, 14.6 Hz, NC**H**H'Ph), 4.54 (dd, J = 6.3, 14.6 Hz, NCH**H'**Ph), 5.08 (1/2 AB_q, J = 12.3 Hz, OC**H**H'Ph), 5.13 (1/2 AB_q, J = 12.3 Hz, OCH**H'**Ph), 5.87–5.94 (br d, N**H**C(O)), 7.25–7.39 (m, C_6**H**$_5$) 8.10–8.23 (m, N**H**CH$_2$Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.9 (NH**C**H$_2$Ph), 50.6 (**C**H), 53.5 (N(**C**H$_2$CH$_2$)O), 60.3 (**C**H$_2$N(CH$_2$CH$_2$)O), 67.0 (N(CH$_2$**C**H$_2$)O), 67.2 (O**C**H$_2$Ph), 127.9, 128.0, 128.3, 128.4, 128.7, 129.0, 136.4, 138.2 (2 **C**$_6$H$_5$), 156.3 (N**C**(O)O), 170.7 (CH**C**(O)); HRMS (ESI) 420.1884 [M + Na^+] (calcd for $C_{22}H_{27}N_3O_4Na^+$ 420.1899); Anal. Calcd for $C_{22}H_{27}N_3O_4$; C, 66.48; H, 6.85; N, 10.57. Found C, 66.52; H, 6.82; N, 10.64.



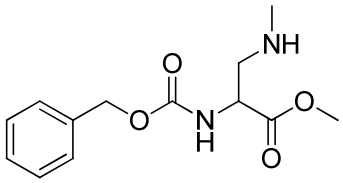
(*R,S*)-*N*-Benzyl 2-Amino-3-morpholinopropionamide ((*R,S*)-16). Utilizing Method C with (*R,S*)-**61** (2.50 g, 6.29 mmol), 10% Pd-C (0.25 g), and MeOH (60 mL) gave the crude product that was further purified by flash column chromatography (SiO_2; 1:100 MeOH/CH_2Cl_2) to give the desired compound (0.94 g, 57%) as a white solid: mp 84–85 °C; R_f 0.24 (1:20 MeOH/CH_2Cl_2); IR (nujol mull) 3401, 3237, 3168, 3096, 2920 (br), 1650, 1598, 1458, 1375, 1115, 946, 876, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.83 (s, N**H$_2$**), 2.37–2.55 (m, C**H**H'N(C**H$_2$**CH$_2$)$_2$O), 2.67 (dd, J = 5.7, 12.3 Hz, CH**H'**N(CH$_2$CH$_2$)$_2$O), 3.53–3.69 (m, C**H**, N(CH$_2$C**H$_2$**)$_2$O), 4.43 (d, J = 5.7 Hz, NHC**H$_2$**Ph), 7.24–7.36 (m, C$_6$**H$_5$**), 8.06–8.18 (br t, N**H**CH$_2$Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.2 (NH**C**H$_2$Ph), 51.6 (**C**H), 53.5 (N(**C**H$_2$CH$_2$)O), 61.9 (**C**H$_2$N(CH$_2$CH$_2$)O), 67.0 (N(CH$_2$**C**H$_2$)O), 127.5, 127.8, 128.8, 138.5 (**C$_6$**H$_5$), 174.1 (CH**C**(O)); HRMS (ESI) 286.1533 [M + Na^+] (calcd for $C_{14}H_{21}N_3O_2Na^+$ 286.1532); Anal. Calcd for $C_{14}H_{21}N_3O_2$; C, 63.85; H, 8.04; N, 15.96. Found C, 63.71; H, 7.99; N, 15.77.

11. Attempted Synthesis of (*R,S*)-2-*N*-(Benzyloxycarbonyl)amino-3-(*N'*-methylamino)propionic Methyl Ester ((*R,S*)-53)

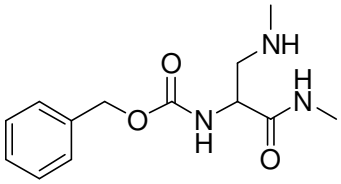


Attempted Synthesis of (*R,S*)-2-*N*-(Benzyloxycarbonyl)amino-3-(*N'*-methylamino)propionic Methyl Ester ((*R,S*)-53).[14, 15] Utilizing Method F with (*R,S*)-**50** (4.67 g, 18.45 mmol), Et_3N (3.1 mL, 22.14 mmol), MsCl (1.7 mL, 22.14 mmol), methylamine (in 2 M THF, 92.3 mL, 184.51 mmol), and MeOH (92.3 mL) gave the crude product after workup that was further purified by flash column chromatography (SiO_2; 1:20 MeOH/CH_2Cl_2) to give the desired product (1.38 g,

28%) as an orange oil and (*R,S*)-*N*-methyl-2-*N*'-(benzyloxycarbonyl)amino-3-(*N''*-methylamino)propionamide (2.06 g, 42%) as an orange solid.



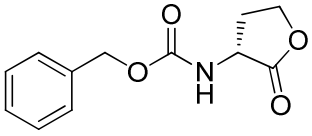
(*R,S*)-2-*N*-(Benzyloxycarbonyl)amino-3-(*N'*-methylamino)propionic Methyl Ester ((*R,S*)-53): R_f 0.26 (1:20 MeOH/CH_2Cl_2); IR (neat) 3326, 3032, 2952, 2853, 2800, 2360, 1960, 1716, 1530, 1451, 1218, 1054, 912, 746, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16–1.26 (br s, N**H**CH_3), 2.40 (s, NHC**H$_3$**), 2.89–3.02 (m, C**H**$_2$NHCH_3), 3.75 (s, OC**H$_3$**), 4.42–4.48 (m, C**H**), 5.12 (s, OC**H**$_2$Ph), 5.81 (d, J = 7.5 Hz, N**H**C(O)O), 7.27–7.37 (m, C_6**H$_5$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.4 (NH**C**H_3), 52.7 (O**C**H_3 or **C**H_2NHCH_3), 52.8 (O**C**H_3 or **C**H_2NHCH_3), 53.9 (**C**H), 67.2 (O**C**H_2Ph), 128.2, 128.3, 128.7, 136.4 (**C$_6$**H_5), 156.3 (N**C**(O)O), 172.3 (CH**C**(O)); HRMS (ESI) 267.1352 [M + H^+] (calcd for $C_{13}H_{18}N_2O_4H^+$ 267.1345); Anal. Calcd for $C_{13}H_{18}N_2O_4$; C, 58.63; H, 6.81; N, 10.52. Found C, 58.36; H, 6.82; N, 10.67.



(*R,S*)-*N*-Methyl 2-*N*'-(Benzyloxycarbonyl)amino-3-(*N''*-methylamino)propionamide: mp 122–123 °C; R_f 0.32 (1:10 MeOH/CH_2Cl_2); IR (nujol mull) 3319, 3217, 3170, 3041 (br), 1719, 1660, 1593, 1547, 1457, 1377, 1250, 1153, 1052, 850, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.72 (s, N**H**CH_3), 2.42 (s, NHC**H$_3$**), 2.64 (dd, J = 8.0, 11.7 Hz, C**H**H'NHCH_3), 2.80 (d, J = 4.8

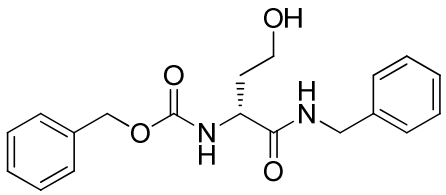
Hz, C(O)NHC**H**$_3$), 3.11 (dd, J = 3.6, 11.7 Hz, CH**H'**NHCH$_3$), 4.08–4.14 (m, C**H**), 5.11 (s, OC**H**$_2$Ph), 6.11 (d, J = 5.7 Hz, N**H**C(O)), 7.28–7.36 (m, C$_6$**H**$_5$) 7.49–7.60 (br s, OC(O)N**H**CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 26.3 (C(O)NH**C**H$_3$), 36.3 (NH**C**H$_3$), 53.2 (**C**H, CH**C**H$_2$), 67.2 (O**C**H$_2$Ph), 128.2, 128.4, 128.7, 136.4 (**C**$_6$H$_5$), 156.6 (N**C**(O)O), 171.8 (CH**C**(O)); HRMS (ESI) 288.1327 [M + Na$^+$] (calcd for $C_{13}H_{19}N_3O_3Na^+$ 288.1324); Anal. Calcd for $C_{13}H_{19}N_3O_3$; C, 58.85; H, 7.22; N, 15.84. Found C, 58.82; H, 7.22; N, 15.66.

12. Preparation of (*R*)-*N*-Benzyl 2-Amino-4-hydroxybutanamide ((*R*)-17)

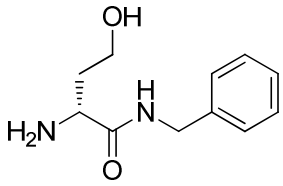


(*R*)-2-(Benzyloxycarbonyl)amino-γ-lactone ((*R*)-69).[16] D-Homoserine (5.00 g, 42.00 mmol) was dissolved in aqueous 1 M Na_2CO_3 (50 mL) and cooled to 0 °C in an ice bath under N_2. Benzyl chloroformate (6.48 mL, 46.20 mmol) was added dropwise and the reaction was maintained at 0 °C (30 min) before warming to room temperature (18 h). The solution was acidified to pH 2 with aqueous concentrated HCl and extracted with EtOAc (3 x 75 mL). The combined organic layers were dried (Na_2SO_4), evaporated in vacuo, and purified by recrystallization from hot EtOAc/hexanes to give the desired product (7.32 g, 74%) as a white solid: mp 130–131 °C (lit.[16] mp 118–120 °C); R_f 0.67 (1:20 MeOH/CH_2Cl_2); IR (nujol mull) 3428, 3062, 2856, 1777, 1694, 1550, 1458, 1380, 1295, 1176, 1076, 1011, 946, 844, 739, 694, 629 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.14–2.29 (m, CHC**H**H'), 2.74–2.82 (m, CHCH**H'**), 4.21–4.29 (m, **C**H), 4.34–4.48 (m, CHCH$_2$C**H$_2$**O), 5.13 (s, OC**H$_2$**Ph), 5.34–5.42 (br d, N**H**), 7.32–7.38 (m, C$_6$**H$_5$**); ^{13}C NMR (75 MHz, CDCl$_3$) δ 30.2 (CH**C**H$_2$CH$_2$O), 50.6 (**C**HCH$_2$CH$_2$O), 65.9 (CHCH$_2$**C**H$_2$O), 67.4 (O**C**H$_2$Ph), 128.3, 128.5, 128.7, 136.0 (**C**$_6$H$_5$), 156.3 (N**C**(O)O), 175.3

(**C**(O)O); HRMS (ESI) 258.0753 [M + Na^+] (calcd for $C_{12}H_{13}NO_4Na^+$ 258.0742); Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.59. Found: C, 61.26; H, 5.65; N, 6.00.

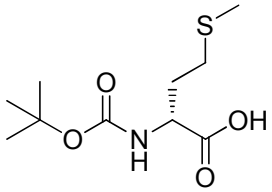


(*R*)-*N*-Benzyl 2-*N'*-(Benzyloxycarbonyl)amino-4-hydroxybutanamide ((*R*)-70). A mixture of (*R*)-**69** (4.20 mg, 17.87 mmol) and benzylamine (3.90 mL, 35.73 mmol) was stirred in anhydrous pyridine (70 mL) at 80 °C (18 h). The mixture was allowed to cool to room temperature and was diluted with CH_2Cl_2 (50 mL). The organic layer was successively washed with aqueous 1 M HCl (3 x 50 mL), H_2O (3 x 50 mL), and brine (2 x 50 mL), dried (Na_2SO_4), and evaporated in vacuo. The crude product was purified by recrystallization from hot EtOAc to give the desired product (3.57 g, 58%) as a white solid: mp 126–127 °C; R_f 0.56 (1:20 MeOH/CH_2Cl_2); IR (nujol mull) 3087, 2916 (br), 1694, 1656, 1552, 1457, 1343, 1255, 1159, 1085, 1019, 727 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.65–1.89 (m, CHC**H$_2$**), 3.40–3.46 (m, C**H$_2$**OH), 4.10–4.17 (m, C**H**), 4.21–4.35 (m, NHC**H$_2$**), 4.59 (t, O**H**), 5.03 (s, OC**H$_2$**Ph), 7.23–7.37 (m, 2 C_6**H$_5$**), 7.46 (d, J = 8.1 Hz, OC(O)N**H**), 8.46 (t, J = 6.0 Hz N**H**CH_2Ph); ^{13}C NMR (75 MHz, DMSO-d_6) δ 34.9 (CH**C**H_2), 42.0 (NH**C**H_2), 52.3 (**C**H_2OH), 57.5 (**C**H), 65.4 (O**C**H_2Ph), 126.6, 127.0, 127.7, 127.7, 128.2, 128.3, 137.0, 139.5 (2 **C$_6$**H_5), 155.9 (O**C**(O)), 172.1 (C**C**(O)); HRMS (ESI) 365.1462 [M + Na^+] (calcd for $C_{19}H_{22}N_2O_4Na^+$ 365.1477).



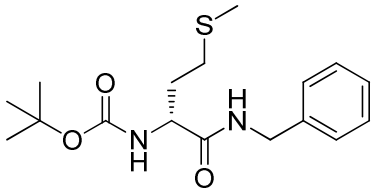
(*R*)-*N*-Benzyl 2-Amino-4-hydroxybutanamide ((*R*)-17). Utilizing Method C with (*R*)-**70** (1.50 g, 4.38 mmol), 10% Pd-C (0.15 g), and MeOH (45 mL) gave the crude product that was further purified by flash column chromatography (SiO_2; 1:100–1:10 MeOH/CH_2Cl_2) to give the desired product (0.53 g, 57%) as a white solid: mp 88–89 °C; R_f 0.40 (1:10 MeOH/CH_2Cl_2); $[\alpha]^{25}_D$ +4.8° (*c* 1.1, CH_2Cl_2); IR (nujol mull) 3265, 2965 (br), 1649, 1540, 1457, 1365, 1251, 1142, 1080, 1024, 952, 801, 724, 602, 549 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.79–1.90 (m, C**H**H'CH_2OH), 1.93–2.19 (m, CH**H'**CH_2OH, N$\mathbf{H_2}$), 3.61 (t, *J* = 6.6 Hz, C**H**), 3.76–3.88 ($CH_2C\mathbf{H_2}$OH), 4.46 (d, *J* = 6.3 Hz, NHC$\mathbf{H_2}$Ph), 7.25–7.38 (m, $C_6\mathbf{H_5}$), 7.56–7.64 (br t, N**H**CH_2Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.6 (**C**H_2CH_2OH), 43.0 (NH**C**H_2Ph), 54.1 (**C**H), 60.6 (CH_2**C**H_2OH), 127.3, 127.5, 128.5, 137.9 ($\mathbf{C_6}H_5$), 175.0 (**C**(O)N); HRMS (ESI) 209.1288 [M + H^+] (calcd for $C_{11}H_{16}N_2O_2H^+$ 209.1290); Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.31; H, 7.86; N, 13.31.

13. Preparation of (*R*)-*N*-Benzyl 2-Amino-4-(methylthio)butanamide ((*R*)-19)



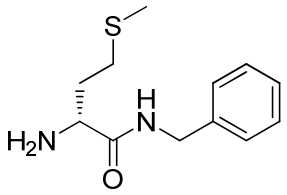
(*R*)-2-*N*-(*t*-Butoxycarbonyl)amino-4-(methylthio)butanoic Acid ((*R*)-66).[17] D-Methionine (5.00 g, 33.55 mmol) was dissolved in dioxane (20 mL) and aqueous 1.25 M NaOH (25 mL) and

then cooled to 0 °C in an ice bath under N_2. Boc_2O (7.69 g, 35.22 mmol) in dioxane (5 mL) was added dropwise and the reaction was allowed to warm to room temperature (18 h) before the organic layer was evaporated in vacuo. The remaining aqueous layer was diluted with aqueous 1 M $KHSO_4$ (50 mL) and extracted with EtOAc (3 x 75 mL). The organic layers were combined and washed with brine (2 x 200 mL), dried (Na_2SO_4), and evaporated in vacuo to give the crude product (8.19 g, 98%) as a pale yellow oil. The product was used for the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, C(C**H**$_3$)$_3$), 1.95–2.06 (m, C**H**H'CH_2SCH_3), 2.11 (s, SC**H**$_3$), 2.12–2.26 (m, CH**H'**CH_2SCH_3), 2.58 (t, J = 8.0 Hz, C**H**$_2$$SCH_3$), 4.18–4.64 (m, C**H**), 5.24–5.27 (d, J = 8.0 Hz, N**H**C(O)).



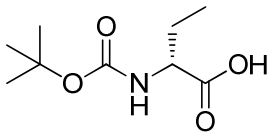
(*R*)-*N*-Benzyl 2-*N'*-(*t*-Butoxycarbonyl)amino-4-(methylthio)butanamide ((*R*)-67). Utilizing Method B with (*R*)-**66** (7.10 g, 28.50 mmol), NMM (4.07 mL, 37.05 mmol), IBCF (4.04 mL, 31.35 mmol), and benzylamine (3.27 mL, 29.92 mmol) gave the crude product that was purified by recrystallization (2x) from hot EtOAc/hexanes to give the desired compound (4.21 g, 44%) as a white solid: mp 104–105 °C; R_f 0.59 (1:20 MeOH/CH_2Cl_2); IR (nujol mull) 3369, 3305, 2924, 1655, 1527, 1456, 13.73, 1328, 1293, 1247, 1170, 1055, 856, 739, 692 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, C(C**H**$_3$)$_3$), 1.87–1.99 (m, C**H**H'CH_2SCH_3), 2.06 (s, SC**H**$_3$), 2.07–2.16 (m, CH**H'**CH_2SCH_3), 2.50–2.60 (m, C**H**$_2$$SCH_3$), 4.29–4.48 (m, C**H**, NHC**H**$_2$Ph), 5.40–5.42 (d, J = 7.5 Hz, N**H**C(O)), 6.88–6.96 (br t, N**H**CH_2Ph), 7.23–7.34 (C_6**H**$_5$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.0 (S**C**H_3), 28.0 (C(**C**H_3)$_3$), 30.0 (**C**H_2SCH_3), 31.4 (**C**$H_2CH_2SCH_3$), 43.1 (NH**C**H_2Ph), 53.2

(**C**H), 79.8 (**C**$(CH_3)_3$), 127.1, 127.3, 128.4, 137.7 (m, **C$_6$**H_5), 155.4 (N**C**(O)O), 171.3 (N**C**(O)C); HRMS (ESI) 339.1751 [M + H^+] (calcd for $C_{17}H_{26}N_2O_3SH^+$ 339.1742); Anal. Calcd for $C_{17}H_{26}N_2O_3S$: C, 60.33; H, 7.74; N, 8.28; S, 9.47. Found: C, 60.18; H, 7.80; N, 8.25; S, 9.18.

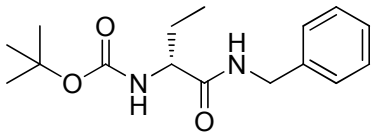


(*R*)-*N*-Benzyl 2-Amino-4-(methylthio)butanamide ((*R*)-19). Utilizing Method E with (*R*)-**67** (1.64 g, 4.85 mmol), TFA (5.40 mL, 72.74 mol), and CH_2Cl_2 (15 mL) gave the crude product that was further purified by flash column chromatography (SiO_2; 1:100–1:10 MeOH/CH_2Cl_2) to give the desired product (0.87 g, 76%) as a pale yellow oil: R_f 0.58 (1:20 MeOH/CH_2Cl_2); IR (neat) 3315, 3032, 2918, 1655, 1524, 1441, 1356, 1249, 1082, 1027, 956, 737, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, N**H$_2$**), 1.73–1.87 (m, C**H**H'CH_2SCH_3), 2.10 (s, SC**H$_3$**), 2.16–2.27 (m, CH**H'**CH_2SCH_3), 2.62 (t, J = 7.4 Hz, C**H$_2$**SCH_3), 3.55 (dd, J = 4.4, 8.3 Hz, C**H**), 4.45 (d, J = 6.0 Hz, NHC**H$_2$**Ph), 7.25–7.36 (m, C_6**H$_5$**), 7.57–7.64 (br t, N**H**CH_2Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.5 (S**C**H_3), 30.9 (**C**H_2SCH_3), 34.3 (**C**$H_2CH_2SCH_3$), 43.4 (NH**C**H_2Ph), 54.5 (**C**H), 127.6, 127.9, 128.9, 138.6 (**C$_6$**H_5), 174.6 (N**C**(O)); HRMS (ESI) 239.1224 [M + H^+] (calcd for $C_{12}H_{18}N_2OSH^+$ 239.1218); Anal. Calcd for $C_{12}H_{18}N_2OS$: C, 60.47; H, 7.61; N, 11.75; S, 13.45. Found: C, 60.17; H, 7.62; N, 11.52; S, 13.69.

14. Preparation of (*R*)-*N*-Benzyl 2-Aminobutanamide ((*R*)-21)

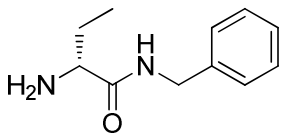


(*R*)-2-*N*-(*t*-Butoxycarbonyl)aminobutanoic Acid ((*R*)-77).[18] D-2-Aminobutanoic acid (3.50 g, 33.94 mmol) and Na_2CO_3 (8.99 g, 84.85 mmol) was dissolved in a mixture of H_2O/acetone (70 mL/70 mL). Boc_2O (8.15 g, 37.34 mmol) was added in one portion at room temperature and the mixture stirred overnight (18 h). The organic layer was evaporated in vacuo and the remaining aqueous layer was washed with Et_2O (50 mL), acidified to pH ~2 with aqueous 1 M $KHSO_4$, and extracted with EtOAc (3 x 50 mL). The second set of organic layers was combined, dried (Na_2SO_4), and evaporated in vacuo to give the crude product (6.83 g, 99%) as a colorless oil and as a 2:1 mixture of conformers A (major) and B (minor). The product was used for the next step without further purification: R_f 0.55 (1:20 MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J = 7.6 Hz, $CH_2C\mathbf{H_3}$), 1.45 (s, $C(C\mathbf{H_3})_3$), 1.68–1.79 (m, $C\mathbf{H}H'CH_3$), 1.86–1.95 (m, $CH\mathbf{H'}CH_3$), 4.04–4.13 (m, $C\mathbf{H_B}$), 4.24–4.35 (m, $C\mathbf{H_A}$), 5.11 (d, J = 7.6 Hz, $N\mathbf{H_A}$), 6.41 (d, J = 7.6 Hz, $N\mathbf{H_B}$), 9.20–9.65 (br s, O**H**); ^{13}C NMR (400 MHz, $CDCl_3$) δ 9.8 ($(CH_2\mathbf{C}H_3)_\mathbf{A}$), 9.9 ($(CH_2\mathbf{C}H_3)_\mathbf{B}$), 25.8 ($\mathbf{C}H_2CH_3$), 28.5 ($C(\mathbf{C}H_3)_3$), 54.6 ($(\mathbf{C}H)_\mathbf{A}$), 56.0 ($(\mathbf{C}H)_\mathbf{B}$), 80.3 ($(\mathbf{C}(CH_3)_3)_\mathbf{A}$), 81.8 ($(\mathbf{C}(CH_3)_3)_\mathbf{B}$), 155.8 ($(O\mathbf{C}(O)N)_\mathbf{A}$), 157.1 ($(O\mathbf{C}(O)N)_A$), 177.2 ($(\mathbf{C}(O)OH)_\mathbf{A}$), 177.5 ($(\mathbf{C}(O)OH)_\mathbf{B}$).



(*R*)-*N*-Benzyl 2-*N'*-(*t*-Butoxycarbonyl)aminobutanamide ((*R*)-83). Utilizing Method B with (*R*)-**77** (6.16 g, 30.33 mmol), NMM (4.33 mL, 39.43 mmol), IBCF (4.30 mL, 33.36 mmol), and benzylamine (3.48 mL, 31.84 mmol) gave the crude product that was recrystallized from hot

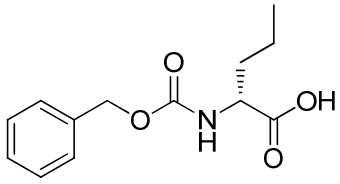
EtOAc/hexanes to give the desired product (5.94 g, 67%) as a white solid: mp 70–71 °C; R_f 0.33 (1:10 EtOAc/hexanes); $[\alpha]^{25}_D$ +18.6° (*c* 1.0, CH_2Cl_2); IR (nujol mull) 3317, 2869 (br), 1688, 1648, 1525, 1457, 1376, 1245, 1166, 1058, 1012, 908, 865, 757, 656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.6 Hz, $CH_2C\mathbf{H_3}$), 1.39 (s, $C(C\mathbf{H_3})_3$), 1.58–1.69 (m, C**H**H'CH_3), 1.80–1.91 (m, CH**H'**CH_3), 4.04–4.16 (m, C**H**), 4.36 (dd, *J* = 6.0, 14.8 Hz, NHC**H**H'Ph), 4.45 (dd, *J* = 6.0, 14.8 Hz, NHCH**H'**Ph), 5.26 (d, *J* = 8.4 Hz, N**H**), 6.82–6.89 (br t, N**H**CH_2Ph), 7.22–7.31 (m, 2 $C_6\mathbf{H_5}$); ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.2 ($CH_2\mathbf{C}H_3$), 26.0 ($\mathbf{C}H_2CH_3$), 28.4 ($C(\mathbf{C}H_3)_3$), 43.5 (NH$\mathbf{C}H_2$Ph), 56.0 (**C**H), 80.0 ($\mathbf{C}(CH_3)_3$), 127.5, 127.7, 128.8, 138.3 ($\mathbf{C_6}H_5$), 156.0 (O**C**(O)N), 172.3 (**C**(O)NH); HRMS (ESI) 315.1694 [M + Na^+] (calcd for $C_{16}H_{24}N_2O_3Na^+$ 315.1685); Anal. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 66.00; H, 8.33; N, 9.56.



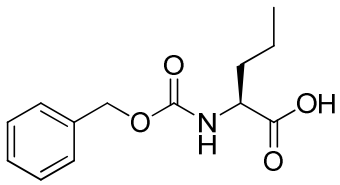
(*R*)-*N*-Benzyl 2-Aminobutanamide ((*R*)-21). Utilizing Method E with (*R*)-**83** (4.87 g, 16.67 mmol), TFA (18.57 mL, 0.25 mol), and CH_2Cl_2 (55 mL) gave the crude product after workup that was further purified by flash column chromatography (SiO_2; 1:100–1:10 MeOH/CH_2Cl_2) to give the desired compound (1.86 g, 58%) as a pale yellow oil: R_f 0.53 (1:20 MeOH/CH_2Cl_2); IR 2966, 1659, 1529, 1456, 1357, 1292, 1082, 1025, 928, 736, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.2 Hz, $CH_2C\mathbf{H_3}$), 1.38–1.46 (br s, $N\mathbf{H_2}$), 1.51–1.66 (m, C**H**H'CH_3), 1.83–1.97 (m, CH**H'**CH_3), 3.35 (dd, *J* = 4.5, 7.8 Hz, C**H**), 4.44 (d, *J* = 5.7 Hz, NHC$\mathbf{H_2}$Ph), 7.26–7.35 (m, $C_6\mathbf{H_5}$), 7.61–7.73 (br t, N**H**CH_2Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.2 ($CH_2\mathbf{C}H_3$), 28.2 ($\mathbf{C}H_2CH_3$), 43.2 (NH$\mathbf{C}H_2$Ph), 56.5 (**C**H), 127.5, 127.8, 128.8, 138.7 ($\mathbf{C_6}H_5$), 175.0 (**C**(O)N);

HRMS (ESI) 193.1348 [M + H^+] (calcd for $C_{11}H_{16}N_2OH^+$ 193.1341); Anal. Calcd for $C_{11}H_{16}N_2O$•0.06CH_2Cl_2: C, 67.22; H, 8.22; N, 14.17. Found: C, 67.23; H, 8.31; N, 14.36.

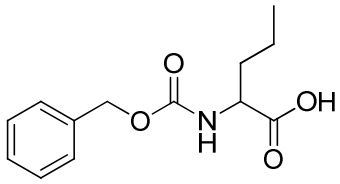
15. Preparation of (*R*)-, (*S*)-, and (*R,S*)-*N*-Benzyl 2-Aminopentanamide ((*R*)-, (*S*)-, and (*R,S*)-22)



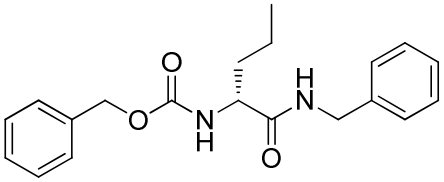
(*R*)-2-*N*-(Benzyloxycarbonyl)aminopentanoic Acid ((*R*)-91).[19] Utilizing Method A with D-norvaline (5.00 g, 42.7 mmol), $NaHCO_3$ (8.97 g, 106.8 mmol), benzyl chloroformate (9.00 mL, 64.1 mmol) and H_2O (100 mL) gave the desired product (9.15 g, 85%) as a white solid after workup and the compound was used for the next step without further purification: mp 88–89 °C (lit.[19] mp 84–85 °C); $[\alpha]^{25}_D$ +4.2° (*c* 2.0, acetone) (lit.[20] (*S*): $[\alpha]^{12}_D$ –4.2° (*c* 2, acetone)); R_f 0.61 (1:1 EtOAc/hexanes); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.86 (t, J = 7.8 Hz, $CH_2C\mathbf{H}_3$), 1.24–1.41 (m, $C\mathbf{H}_2CH_3$), 1.51–1.67 (m, $CHC\mathbf{H}_2$), 3.91–3.99 (m, C**H**), 5.03 (s, $OC\mathbf{H}_2Ph$), 7.27–7.41 (m, $C_6\mathbf{H}_5$), 7.58 (d, J = 8.1 Hz, N**H**); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.1 ($\mathbf{C}H_3$), 18.4 ($\mathbf{C}H_2CH_3$), 32.5 ($CH\mathbf{C}H_2$), 53.2 (**C**H), 65.0 ($O\mathbf{C}H_2Ph$), 127.4, 127.5, 128.0, 136.7 ($\mathbf{C_6}H_5$), 155.9 (N**C**(O)O), 173.7 (CH**C**(O)).



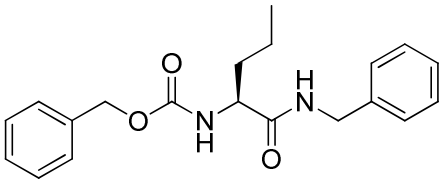
(*S*)-2-*N*-(Benzyloxycarbonyl)aminopentanoic Acid ((*S*)-91).[20] The previous procedure was repeated using L-norvaline (5.00 g, 42.7 mmol), $NaHCO_3$ (8.97 g, 106.8 mmol), and benzyl chloroformate (9.00 mL, 64.1 mmol), and H_2O (100 mL) to give the desired product (7.78 g, 73%) as a white solid: mp 85–86 °C (lit.[20] mp 86 °C); $[\alpha]^{25}_D$ –4.3° (*c* 2.1, acetone) (lit.[20] $[\alpha]^{12}_D$ –4.2° (*c* 2, acetone)); R_f 0.43 (1:10 MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.86 (t, J = 7.5 Hz, $CH_2C\mathbf{H}_3$), 1.25–1.41 (m, $C\mathbf{H}_2CH_3$), 1.50–1.71 (m, $CHC\mathbf{H}_2$), 3.90–3.98 (m, C**H**), 5.03 (s, $OC\mathbf{H}_2Ph$), 7.29–7.37 (m, Ph**H**), 7.58 (d, J = 8.1 Hz, N**H**); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.4 ($\mathbf{C}H_3$), 18.7 ($\mathbf{C}H_2CH_3$), 32.8 ($CH\mathbf{C}H_2$), 53.5 (**C**H), 65.3 ($O\mathbf{C}H_2Ph$), 127.7, 127.8, 128.3, 137.0 ($\mathbf{C}_6H_5$), 156.2 (N**C**(O)O), 174.0 (CH**C**(O)).



(*R,S*)-2-*N*-(Benzyloxycarbonyl)aminopentanoic Acid ((*R,S*)-91). The previous procedure was repeated using DL-norvaline (5.00 g, 42.7 mmol), $NaHCO_3$ (8.97 g, 106.8 mmol), benzyl chloroformate (9.00 mL, 64.1 mmol), and H_2O (100 mL) to give the desired product (8.55 g, 80%) as a white solid: mp 90–91 °C; R_f 0.57 (1:1 EtOAc/hexanes); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.86 (t, J = 7.2 Hz, $CH_2C\mathbf{H}_3$), 1.26–1.42 (m, $C\mathbf{H}_2CH_3$), 1.51–1.69 (m, $CHC\mathbf{H}_2$), 3.91–3.99 (m, C**H**), 5.04 (s, $OC\mathbf{H}_2Ph$), 7.27–7.39 (m, $C_6\mathbf{H_5}$), 7.58 (d, J = 8.1 Hz, N**H**); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.1 ($\mathbf{C}H_3$), 18.4 ($\mathbf{C}H_2CH_3$), 32.5 ($CH\mathbf{C}H_2$), 53.2 (**C**H), 65.0 ($O\mathbf{C}H_2Ph$), 127.4, 127.5, 128.0, 136.7 ($\mathbf{C_6}H_5$), 155.8 (N**C**(O)O), 173.7 (CH**C**(O)).

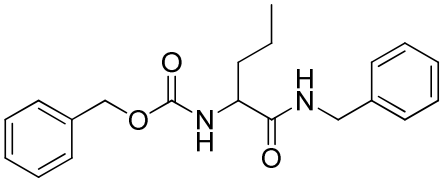


(*R*)-*N*-Benzyl 2-*N*-(Benzyloxycarbonyl)aminopentanamide ((*R*)-93). Utilizing Method B with (*R*)-**91** (5.00 g, 19.9 mmol), NMM (2.85 mL, 25.9 mmol), IBCF (2.82 mL, 21.9 mmol), and benzylamine (2.28 mL, 20.9 mmol) gave the crude product that was purified by flash column chromatography (SiO_2; 1:10 MeOH/CH_2Cl_2) followed by recrystallization from hot toluene to give the desired compound (3.49 g, 52%) as a white solid: mp 139–141 °C; $[\alpha]^{25}_D$ +11.5° (*c* 1.1, MeOH); R_f 0.27 (1:100 MeOH/CH_2Cl_2); IR (nujol mull) 3290, 2934 (br), 2358, 1692, 1643, 1540, 1458, 1375, 1258, 1058, 737, 694 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.85 (t, J = 7.5 Hz, $CH_2C\mathbf{H}_3$), 1.20–1.37 (m, $C\mathbf{H}_2CH_3$), 1.46–1.67 (m, $C\mathbf{H_2}CH_2CH_3$), 3.98–4.06 (m, C**H**), 4.28 (d, J = 5.9 Hz, $C\mathbf{H}_2Ph$), 5.03 (s, $OC\mathbf{H}_2Ph$), 7.23–7.37 (m, 2 $C_6\mathbf{H_5}$), 7.43 (d, J = 8.1 Hz, N**H**C(O)), 8.43 (t, J = 5.9 Hz, $N\mathbf{H}CH_2Ph$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.2 ($\mathbf{C}H_3$), 18.3 ($\mathbf{C}H_2CH_3$), 33.6 ($CH\mathbf{C}H_2$), 41.6 ($\mathbf{C}H_2Ph$), 54.1 (**C**H), 65.0 ($O\mathbf{C}H_2Ph$), 126.3, 126.7, 127.3, 127.4, 127.8, 127.9, 136.7, 139.0 (2 $\mathbf{C_6}H_5$), 155.6 (N**C**(O)O), 171.7 (CH**C**(O)); HRMS (ESI) 363.1686 [M + Na^+] (calcd for $C_{20}H_{24}N_2O_3Na^+$ 363.1685); Anal. Calcd for $C_{20}H_{24}N_2O_3 \bullet 0.12H_2O$; C, 70.11; H, 7.13; N, 8.18. Found C, 69.75; H, 7.20; N, 8.35.



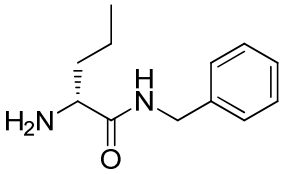
(*S*)-*N*-Benzyl 2-*N*-(Benzyloxycarbonyl)aminopentanamide ((*S*)-93). The previous procedure was repeated using (*S*)-**91** (5.00 g, 19.9 mmol), NMM (2.85 mL, 25.9 mmol), IBCF (2.82 mL, 21.9 mmol), and benzylamine (2.28 mL, 20.9 mmol) to give the crude product that was further

purified by flash column chromatography (SiO_2; 1:10 MeOH/$CHCl_3$) to give the desired compound (4.02 g, 60%) as a white solid: mp 134–135 °C; $[\alpha]^{25}_D$ –13.2° (*c* 1.1, MeOH); R_f 0.28 (1:100 MeOH/CH_2Cl_2); IR (nujol mull) 3285, 2938 (br), 1693, 1644, 1542, 1458, 1377, 1260, 1112, 1059, 739, 695 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.85 (t, J = 7.5 Hz, CH_2CH_3), 1.20–1.38 (m, CH_2CH_3), 1.46–1.65 (m, $CH_2CH_2CH_3$), 3.98–4.06 (m, C**H**), 4.28 (d, J = 6.0 Hz, CH_2Ph), 5.03 (s, OCH_2Ph), 7.20–7.44 (m, 2 Ph**H**, N**H**C(O)), 8.42 (t, J = 6.0 Hz, N**H**CH_2Ph); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.2 (CH_3), 18.3 (CH_2CH_3), 33.6 ($CHCH_2$), 41.6 (CH_2Ph), 54.1 (**C**H), 65.0 (OCH_2Ph), 126.7, 126.9, 127.3, 127.4, 127.8, 127.9, 136.7, 139.0 (2 C_6H_5), 155.6 (N**C**(O)O), 171.7 (CH**C**(O)); HRMS (ESI) 363.1687 [M + Na^+] (calcd for $C_{20}H_{24}N_2O_3Na^+$ 363.1685); Anal. Calcd for $C_{20}H_{24}N_2O_3$; C, 70.56; H, 7.11; N, 8.23. Found C, 70.28; H, 7.19; N, 8.31.



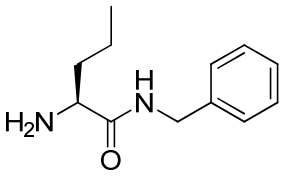
(*R,S*)-*N*-Benzyl 2-*N*-(Benzyloxycarbonyl)aminopentanamide ((*R,S*)-93).[21] The previous procedure was repeated using (*R,S*)-**91** (5.00 g, 19.9 mmol), NMM (2.85 mL, 25.9 mmol), IBCF (2.82 mL, 21.9 mmol), and benzylamine (2.28 mL, 20.9 mmol) to give the crude product that was further purified by flash column chromatography (SiO_2; 1:10 MeOH/CH_2Cl_2) followed by recrystallization from hot toluene to give the desired compound (4.72 g, 70%) as a white solid: mp 136–137 °C (lit.[21] mp 138–139 °C); R_f 0.27 (1:100 MeOH/CH_2Cl_2); IR (nujol mull) 3290, 2930 (br), 1689, 1641, 1538, 1459, 1375, 1257, 1057, 753, 702 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.85 (t, J = 6.9 Hz, CH_2CH_3), 1.17–1.40 (m, CH_2CH_3), 1.47–1.68 (m, $CH_2CH_2CH_3$), 3.99–4.06 (m, C**H**), 4.28 (d, J = 5.9 Hz, CH_2Ph), 5.03 (s, OCH_2Ph), 7.23–7.37

(m, 2 $C_6\mathbf{H_5}$), 7.43 (d, J = 8.4 Hz, N**H**C(O)), 8.43 (t, J = 5.9 Hz, N**H**CH_2Ph); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.2 (**C**H_3), 18.3 (**C**H_2CH_3), 33.6 (CH**C**H_2), 41.6 (**C**H_2Ph), 54.1 (**C**H), 65.0 (O**C**H_2Ph), 126.3, 126.7, 127.3, 127.4, 127.8, 127.9, 136.7, 139.1 (2 $\mathbf{C_6}H_5$), 155.6 (N**C**(O)O), 171.7 (CH**C**(O)); HRMS (ESI) 363.1685 [M + Na^+] (calcd for $C_{20}H_{24}N_2O_3Na^+$ 363.1685); Anal. Calcd for $C_{20}H_{24}N_2O_3$; C, 70.56; H, 7.11; N, 8.23. Found C, 70.36; H, 7.17; N, 8.19.

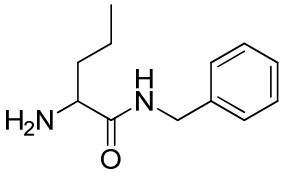


(*R*)-*N*-Benzyl 2-Aminopentanamide ((*R*)-22). Utilizing Method C with (*R*)-**93** (2.00 g, 5.88 mmol), 10% Pd-C (0.2 g), and MeOH (60 mL) gave the crude product further purified by flash column chromatography (SiO_2; 1:100 MeOH/CH_2Cl_2). The resulting oil was dissolved in CH_2Cl_2 (10 mL) and was extracted with aqueous 1 M HCl (3 x 10 mL). The aqueous layers were combined and extracted with CH_2Cl_2 (2 x 30 mL). The aqueous layer was basified to pH 10–12 with aqueous 1 M NaOH, and then extracted with CH_2Cl_2 (3 x 60 mL). The CH_2Cl_2 layers were combined, dried ($NaSO_4$), and concentrated in vacuo to give the desired product (0.95 g, 79%) as a pale yellow oil: $[\alpha]^{25}_D$ –9.4° (*c* 1.0, MeOH); R_f 0.64 (1:10 MeOH/CH_2Cl_2); IR (neat) 3307, 3033, 2956, 2870, 1658, 1525, 1456, 1358, 1250, 700 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.86 (t, J = 7.4 Hz, $CH_2C\mathbf{H}_3$), 1.19–1.42 (m, $C\mathbf{H}_2CH_3$, C**H**H'CH_2CH_3), 1.47–1.61 (m, CH**H**'CH_2CH_3), 1.78 (br s, N$\mathbf{H}_2$), 3.15–3.20 (app. t, C**H**), 4.28 (d, J = 5.7 Hz, C$\mathbf{H}_2$Ph), 7.20–7.34 (m, $C_6\mathbf{H_5}$), 8.34 (t, J = 5.7 Hz, N**H**CH_2Ph); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J = 7.2 Hz, $CH_2C\mathbf{H}_3$), 1.32–1.58 (m, C$\mathbf{H_2}CH_3$, C**H**H'CH_2CH_3, N$\mathbf{H}_2$), 1.81–1.93 (m, CH**H'**CH_2CH_3), 3.41 (dd, J = 4.1, 8.0 Hz, C**H**), 4.45 (d, J = 6.0 Hz, C$\mathbf{H}_2$Ph), 7.24–7.37 (m, $C_6\mathbf{H_5}$), 7.60–7.72 (br s, N**H**CH_2Ph); ^{1}H NMR (300 MHz, CD_3OD) δ 0.92 (t, J = 7.2 Hz, $CH_2C\mathbf{H}_3$), 1.28–1.42 (m,

C**H**$_2$CH$_3$), 1.44–1.56 (m, C**H**H'CH$_2$CH$_3$), 1.58–1.71 (m, CH**H**'CH$_2$CH$_3$), 3.28–3.33 (m, C**H**), 4.35 (1/2 AB$_q$, J = 15.0 Hz, C**H**H'Ph), 4.41 (1/2 AB$_q$, J = 15.0 Hz, CH**H**'Ph), 4.86 (s, N**H**$_2$), 7.20–7.34 (m, C$_6$**H**$_5$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.5 (**C**H$_3$), 18.2 (**C**H$_2$CH$_3$), 37.1 (CH**C**H$_2$), 41.5 (**C**H$_2$Ph), 54.2 (**C**H), 126.3, 126.8, 127.8, 139.3 (**C**$_6$H$_5$), 175.0 (CH**C**(O)); HRMS (ESI) 229.1317 [M + Na$^+$] (calcd for C$_{12}$H$_{18}$N$_2$ONa$^+$ 229.1317); Anal. Calcd for C$_{12}$H$_{18}$N$_2$O; C, 69.87; H, 8.80; N, 13.58. Found C, 69.98; H, 8.73; N, 13.37.

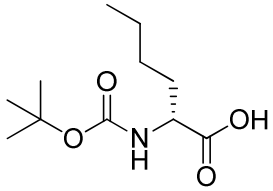


(*S*)-*N*-Benzyl 2-Aminopentanamide ((*S*)-22). The previous procedure was repeated using (*S*)-**93** (3.00 g, 8.82 mmol), 10% Pd-C (0.3 g), and MeOH (100 mL) to give the desired product (1.76 g, 97%) as a pale yellow oil: $[\alpha]^{25}_D$ +9.4° (*c* 1.5, MeOH); R_f 0.65 (1:10 MeOH/CH$_2$Cl$_2$); IR (neat) 3351, 3265, 3032, 2928, 2873, 1655, 1534, 1456, 1358, 1250, 701 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.86 (t, J = 6.6 Hz, CH$_2$C**H**$_3$), 1.22–1.42 (m, C**H**$_2$CH$_3$, C**H**H'CH$_2$CH$_3$), 1.48–1.61 (m, CH**H**'CH$_2$CH$_3$), 1.78 (br s, N**H**$_2$), 3.17 (t, J = 6.9 Hz, C**H**), 4.28 (d, J = 6.0 Hz, C**H**$_2$Ph), 7.20–7.34 (m, Ph**H**), 8.34 (t, J = 4.8 Hz, N**H**CH$_2$Ph); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.5 (**C**H$_3$), 18.2 (**C**H$_2$CH$_3$), 37.1 (CH**C**H$_2$), 41.5 (**C**H$_2$Ph), 54.2 (**C**H), 126.3, 126.8, 127.8, 139.3 (**C**$_6$H$_5$), 175.0 (CH**C**(O)); LRMS (ESI) 207.12 [M + H$^+$] (calcd for C$_{12}$H$_{18}$N$_2$OH$^+$ 207.12); Anal. Calcd for C$_{12}$H$_{18}$N$_2$O•0.32H$_2$O; C, 67.99; H, 8.86; N, 13.22. Found C, 67.93; H, 8.76; N, 13.21.



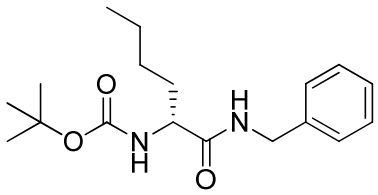
(*R,S*)-*N*-Benzyl 2-Aminopentanamide ((*R,S*)-22).[21] The previous procedure was repeated using (*R,S*)-**93** (2.00 g, 11.76 mmol), 10% Pd-C (0.2 g), and MeOH (60 mL) to give the desired product (0.88 g, 72%) as a pale yellow oil: R_f 0.65 (1:10 MeOH/CH_2Cl_2); IR (neat) 3292, 3064, 2957, 1655, 1528, 1457, 1358, 1250, 700 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.86 (t, J = 6.6 Hz, CH_2CH_3), 1.24–1.42 (m, CH_2CH_3, $CHH'CH_2CH_3$), 1.48–1.61 (m, $CHH'CH_2CH_3$), 1.74 (br s, NH_2), 3.15–3.18 (app. t, CH), 4.28 (d, J = 5.9 Hz, CH_2Ph), 7.20–7.34 (m, C_6H_5), 8.36 (t, J = 5.9 Hz, $NHCH_2Ph$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J = 7.2 Hz, CH_2CH_3), 1.32–1.58 (m, CH_2CH_3, $CHH'CH_2CH_3$, NH_2), 1.81–1.93 (m, $CHH'CH_2CH_3$), 3.41 (dd, J = 4.2, 8.1 Hz, CH), 4.45 (d, J = 6.0 Hz, CH_2Ph), 7.24–7.37 (m, C_6H_5), 7.58–7.70 (br s, $NHCH_2Ph$); ^1H NMR (300 MHz, CD_3OD) δ 0.92 (t, J = 7.2 Hz, CH_2CH_3), 1.28–1.43 (m, CH_2CH_3), 1.44–1.56 (m, $CHH'CH_2CH_3$), 1.58–1.71 (m, $CHH'CH_2CH_3$), 3.28–3.32 (m, CH), 4.35 (1/2 AB_q, J = 14.9 Hz, CHH'Ph), 4.41 (1/2 AB_q, J = 14.9 Hz, CHH'Ph), 4.88 (s, NH_2), 7.21–7.34 (m, C_6H_5); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.5 (CH_3), 18.2 (CH_2CH_3), 37.1 ($CHCH_2$), 41.5 (CH_2Ph), 54.2 (CH), 126.3, 126.8, 127.9, 139.3 (C_6H_5), 175.1 (CHC(O)); HRMS (ESI) 229.1320 [M + Na^+] (calcd for $C_{12}H_{18}N_2ONa^+$ 229.1317); Anal. Calcd for $C_{12}H_{18}N_2O$•0.18H_2O; C, 68.81; H, 8.83; N, 13.37. Found C, 68.48; H, 8.81; N, 13.27.

16. Preparation of (*R*)-*N*-Benzyl 2-Amino-2-pentanamide ((*R*)-23)



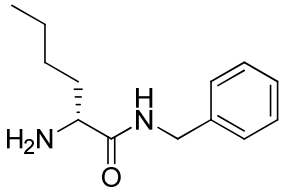
(*R*)-2-*N*-(*t*-Butoxycarbonyl)amino-2-pentanoic Acid ((*R*)-78). D-Norleucine (2.00 g, 15.2 mmol) was added to H_2O/acetone (25 mL/25 mL) followed by the addition of Boc_2O (3.85 mL,

16.8 mmol) and Na_2CO_3 (1.78 g, 16.8 mmol). The reaction was stirred at room temperature (22 h) and then Et_2O (30 mL) was added. The layers were separated and the aqueous layer was acidified to pH ~2 with an aqueous 1 M solution of $KHSO_4$. The aqueous layer was washed with Et_2O (3 x 40 mL) and the organic layers were combined, dried (Na_2SO_4), and evaporated in vacuo. The crude mixture was purified by flash column silica gel chromatography (1:10 MeOH/CH_2Cl_2) to give the desired product (3.53 g, 100%) as a clear oil as a 1:1 mixture of conformers: R_f 0.54 (1:10 MeOH/CH_2Cl_2); IR (nujol mull) 3050, 1714, 1515, 1402, 1247, 1167 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88–0.93 (br t, C**H**$_3$), 1.22–1.83 (m, C(C**H**$_3$)$_3$, C**H**$_2$C**H**$_2$C**H**$_2$), 4.08–4.20 (br s, N**H**, conformer a or b), 4.29–4.31 (br dd, C**H**NH, conformer a or b), 5.12 (d, J = 8.1 Hz, C**H**NH, conformer a or b), 6.23–6.40 (br s, N**H**, conformer a or b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.5, 27.5, 28.5, 32.3, 53.6 (**C**H$_2$**C**H$_2$**C**H$_2$**C**H$_3$, NH**C**H, C(**C**H$_3$)$_3$,), 80.2 (**C**(CH$_3$)$_3$), 155.8 (NH**C**(O)O), 177.4 (**C**(O)OH); HRMS (ESI) 254.1370 [M+Na^+] (calcd for $C_{11}H_{21}NO_4Na^+$ 254.1368).



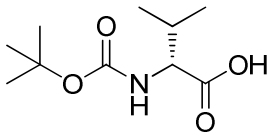
(*R*)-*N*-Benzyl 2-*N*-(*t*-Butoxycarbonyl)amino-2-pentanamide ((*R*)-84). Utilizing Method B with (*R*)-**78** (3.19 g, 13.8 mmol), NMM (1.67 mL, 15.2 mmol), IBCF (1.97 mL, 15.2 mmol), and benzylamine (1.66 mL, 15.2 mmol) gave the crude product that purified by flash column chromatography (SiO_2; 2:5 EtOAc/hexanes) to give the desired product (3.33 g, 75%) as a white solid: mp 69–70 °C; R_f 0.57 (2:5 EtOAc/hexanes); IR (nujol mull) 3484, 3327, 3132, 2927, 2857, 1686, 1527, 1457, 1373, 1317, 1245, 1170, 1067, 1010, 863, 744, 661, 473 cm^{-1}; ^1H NMR (300

MHz, $CDCl_3$) δ 0.86–0.91 (br t, C**H$_3$**), 1.26–1.86 (m, C(C**H$_3$**)$_3$, C**H$_2$**C**H$_2$**C**H$_2$**CH$_3$), 4.09–4.20 (br m, N**H**), 4.33–4.84 (m, NHC**H$_2$**) 5.12 (d, J = 8.1 Hz, NHC**H**), 6.71–6.84 (br s, N**H**), 7.21–7.32 (m, C$_6$**H$_5$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 27.9, 28.4, 32.5, 43.5, 54.8 (**C**H$_2$**C**H$_2$**C**H$_2$**C**H$_3$, NH**C**H, NH**C**H$_2$, C(**C**H$_3$)$_3$,), 80.1 (**C**(CH$_3$)$_3$), 127.5, 127.7, 128.8, 138.3 (**C$_6$**H$_5$), 155.9 (NH**C**(O)), 172.5 (NH**C**(O)O); HRMS (ESI) 453.1152 [M+Cs$^+$] (calcd for $C_{18}H_{28}N_2O_3Cs^+$ 453.1154); Anal. Calcd for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.81; N, 8.74. Found C, 67.65; H, 8.93; N, 8.74.

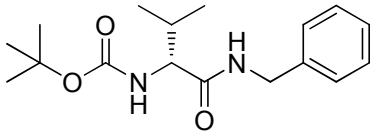


(*R*)-*N*-Benzyl 2-Amino-2-pentanamide ((*R*)-23). Utilizing Method E with (*R*)-**84** (3.33 g, 9.78 mmol), TFA (10.9 mL, 0.15 mol), and CH_2Cl_2 (33 mL) gave the crude product after workup that was further purified by flash column chromatography (SiO_2; 1:10 MeOH/CH_2Cl_2) to give the desired product (1.83 g, 80%) as a colorless oil: $[\alpha]^{25}_D$ –3.5° (*c* 2.6, EtOH); R_f 0.55 (1:10 MeOH/CH_2Cl_2); IR (nujol mull) 3494, 3119, 2993, 1653, 1528, 1456, 1247, 735, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87–0.92 (br t, C**H$_3$**), 1.31–1.60 (m, C**H**H'C**H$_2$**C**H$_2$**CH$_3$, N**H$_2$**), 1.80–1.95 (br m, CH**H'**CH$_2$CH$_2$CH$_3$), 3.31–3.43 (m, NHC**H**), 4.42 (d, J = 6.0 Hz, NHC**H$_2$**), 7.25–7.32 (m, C$_6$**H$_5$**), 7.59–7.78 (br s, N**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 28.1, 34.9, 43.1, 55.3 (**C**H$_2$**C**H$_2$**C**H$_2$**C**H$_3$, NH**C**H, NH**C**H$_2$), 127.4, 127.8, 128.7, 138.7 (**C$_6$**H$_5$), 172.5 (NH**C**(O)); HRMS (ESI) 221.1655 [M+H$^+$] (calcd for $C_{13}H_{21}N_2O^+$ 221.1654); Anal. Calcd for $C_{13}H_{20}N_2O$•0.15H_2O: C, 69.32; H, 9.02; N, 12.44. Found C, 69.35; H, 9.16; N, 12.37.

Preparation of (*R*)- and (*S*)-*N*-Benzyl 2-Amino-3-methylbutanamide ((*R*)- and (*S*)-24)

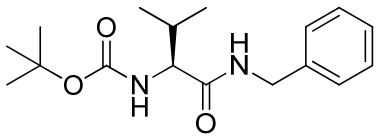


(*R*)-2-*N*-(*t*-Butoxycarbonyl)amino-3-methylbutanoic Acid ((*R*)-79).[22] D-Valine (5.00 g, 42.71 mmol) was dissolved in aqueous 2 M NaOH (43 mL) and cooled to 0 °C in an ice water bath. Boc_2O (11.18 g, 51.25 mmol) was slowly added and the reaction was allowed to warm to room temperature (18 h). The mixture was acidified to pH 2 using aqueous concentrated HCl and then extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to give the crude product (8.50 g, 92%) as a pale yellow oil. The product was used for the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83–1.02 (m, CH(C**H**$_3$)$_2$), 1.45 (s, C(C**H**$_3$)$_3$), 2.15–2.28 (m, C**H**(CH$_3$)$_2$), 4.27 (dd, J = 4.7, 9.1 Hz, C**H**CH(CH$_3$)$_2$), 5.06 (d, J = 9.1 Hz, N**H**).

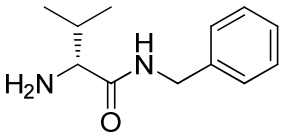


(*R*)-*N*-Benzyl 2-*N*'-(*t*-Butoxycarbonyl)amino-3-methylbutanamide ((*R*)-85).[23] Utilizing Method B with (*R*)-**79** (8.50 g, 39.14 mmol), NMM (5.60 mL, 50.89 mmol), IBCF (5.55 mL, 43.06 mmol), and benzylamine (4.50 mL, 41.10 mmol) gave the crude product that was recrystallized from hot EtOAc to give the desired compound (6.64 g, 55%) as a white solid: mp 122–123 °C (lit.[23] mp 112–115 °C); R_f 0.67 (1:20 MeOH/CH_2Cl_2); IR (nujol mull) 3297, 2900 (br), 1690, 1645, 1530, 1458, 1378, 1299, 1247, 1166, 1020, 930, 875, 744, 693, 585, 508 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, J = 6.9 Hz, CH(C**H**$_3$)CH$_3$), 0.95 (d, J = 6.6

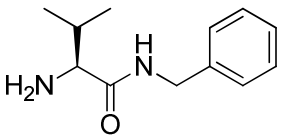
$CH(CH_3)C\mathbf{H_3}$), 1.40 (s, $C(C\mathbf{H_3})_3$), 2.18–2.26 (m, $C\mathbf{H}(CH_3)_2$), 3.94–4.00 (br t, $C\mathbf{H}CH(CH_3)_2$), 4.36 (dd, J = 6.0, 14.7 Hz, NHC**H**H'Ph), 4.46 (dd, J = 6.0, 14.7 Hz, NHCH**H'**Ph), 5.25 (d, J = 9.3 Hz, N**H**C(O)), 6.71–6.79 (br t, $N\mathbf{H}CH_2Ph$), 7.21–7.33 ($C_6\mathbf{H_5}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5 ($CH(\mathbf{C}H_3)(CH_3)$'), 19.9 ($CH(CH_3)(\mathbf{C}H_3)$'), 28.9 ($C(\mathbf{C}H_3)_3$), 31.4 ($\mathbf{C}H(CH_3)(CH_3)$'), 43.9 ($NH\mathbf{C}H_2Ph$), 60.7 (**C**H), 80.4 ($\mathbf{C}(CH_3)_3$), 128.0, 128.2, 129.2, 138.7 ($\mathbf{C_6}H_5$), 156.6 (N**C**(O)O), 172.3 (C**C**(O)N).



(*S*)-*N*-Benzyl 2-*N'*-(*tert*-Butoxycarbonyl)amino-3-methylbutanamide ((*S*)-85).[24] The previous procedure was repeated using commercially available (*S*)-**79** (4.00 g, 18.42 mmol), NMM (2.63 mL, 23.95 mmol), IBCF (2.61 mL, 20.26 mmol), and benzylamine (2.11 mL, 19.34 mmol) to give the crude product that was recrystallized from hot EtOAc to give the desired compound (2.89 g, 51%) as a white solid: mp 122–123 °C; R_f 0.24 (1:10 EtOAc/hexanes); IR (nujol mull) 3116, 2910 (br), 1689, 1646, 1527, 1458, 1375, 1301, 1249, 1163, 1018, 725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, J = 7.2 Hz, $CH(C\mathbf{H_3})CH_3$), 0.97 (d, J = 7.2 Hz, $CH(CH_3)C\mathbf{H_3}$), 1.42 (s, $(C\mathbf{H_3})_3$), 2.12–2.23 (m, $C\mathbf{H}(CH_3)_2$), 3.92 (dd, J = 6.2, 8.6 Hz, C**H**), 4.39–4.50 (m, $NHC\mathbf{H_2}$), 5.06–5.14 (br d, C(O)N**H**), 6.36–6.44 (br t, $N\mathbf{H}CH_2Ph$), 7.25–7.34 ($C_6\mathbf{H_5}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9 ($CH(\mathbf{C}H_3)(CH_3)$'), 19.4 ($CH(CH_3)(\mathbf{C}H_3)$'), 28.3 ($(\mathbf{C}H_3)_3$), 30.7 ($\mathbf{C}H(CH_3)_2$), 43.5 ($NH\mathbf{C}H_2$), 60.2 (**C**H), 80.0 ($\mathbf{C}(CH_3)_3$), 127.5, 127.7, 128.7, 138.0 ($\mathbf{C_6}H_5$), 156.0 (O**C**(O)), 171.6 (C**C**(O)).



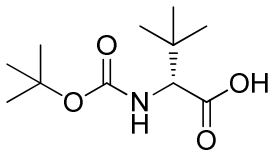
(*R*)-*N*-Benzyl 2-Amino-3-methylbutanamide ((*R*)-24). Utilizing Method E with (*R*)-**85** (4.00 g, 13.06 mmol), TFA (14.56 mL, 0.20 mol), and CH_2Cl_2 (45 mL) gave the crude product after workup that was further purified by flash column chromatography (SiO_2; 1:100–1:10 MeOH/CH_2Cl_2) to give the desired compound (2.25 g, 83%) as a pale yellow oil: R_f 0.70 (1:20 MeOH/CH_2Cl_2); IR (neat) 3316, 3064, 2961, 1952, 1881, 1812, 1655, 1525, 1459, 1364, 1240, 1081, 1028, 882, 700, 608, 488 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, J = 6.8 Hz, $CH(C\mathbf{H_3})CH_3$), 0.97 (d, J = 6.8 Hz, $CH(CH_3)C\mathbf{H_3}$), 1.31 (s, $N\mathbf{H_2}$), 2.24–2.35 (m, $C\mathbf{H}(CH_3)_2$), 3.23 (d, J = 3.9 Hz, $C\mathbf{H}CH(CH_3)_2$), 4.35–4.49 (m, $NHC\mathbf{H_2}Ph$), 7.21–7.33 (m, $C_6\mathbf{H_5}$), 7.72–7.81 (br t, $N\mathbf{H}CH_2Ph$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1 ($CH(\mathbf{C}H_3)CH_3$), 19.7 ($CH(CH_3)\mathbf{C}H_3$), 30.1 ($\mathbf{C}H(CH_3)_2$), 43.0 ($NH\mathbf{C}H_2Ph$), 60.2 ($\mathbf{C}H$), 127.2, 127.7, 128.6, 138.7 ($\mathbf{C_6}H_5$), 174.4 ($N\mathbf{C}(O)$); HRMS (ESI) 207.1501 [M + H^+] (calcd for $C_{12}H_{18}N_2OH^+$ 207.1497); Anal. Calcd for $C_{12}H_{18}N_2O$•0.04CH_2Cl_2: C, 68.93; H, 8.69; N, 13.35. Found: C, 68.97; H, 8.82; N, 13.37.



(*S*)-*N*-Benzyl 2-Amino-3-methylbutanamide ((*S*)-24).[24] The previous procedure was repeated using (*S*)-**85** (2.57 g, 8.39 mmol), TFA (9.35 mL, 0.13 mol), and CH_2Cl_2 (28 mL) to give the crude product after workup that was further purified by flash column chromatography (SiO_2; 1:20 EtOAc/hexanes followed by 1:10 MeOH/CH_2Cl_2) to give the desired compound (1.65 g, 96%) as a white solid: mp 52–53 °C; $[\alpha]^{28.5}_D$ –27.1° (*c* 0.6, CH_2Cl_2) (lit.[24] $[\alpha]^{20}_D$ –27.2° (*c* 0.5, CH_2Cl_2)); R_f 0.47 (1:20 MeOH/CH_2Cl_2); IR (nujol mull) 3012, 2904 (br), 1645, 1550, 1458,

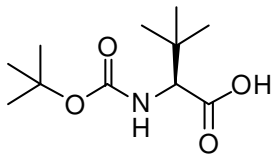
1375, 1165, 1078, 1028, 965, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, J = 6.8 Hz, CH(C**H$_3$**)CH$_3$), 0.99 (d, J = 6.8 Hz, CH(CH$_3$)C**H$_3$**), 1.43 (s, N**H$_2$**), 2.28–2.40 (m, C**H**(CH$_3$)$_2$), 3.27 (d, J = 4.0 Hz, C**H**), 4.42 (dd, J = 6.2, 14.8 Hz, NHC**H**H'), 4.48 (dd, J = 6.0, 14.8 Hz, NHCH**H'**), 7.24–7.34 (C$_6$**H$_5$**), 7.62–7.70 (br t, N**H**CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1 (CH(**C**H$_3$)CH$_3$), 19.8 (CH(CH$_3$)**C**H$_3$), 30.9 (**C**H(CH$_3$)$_2$), 43.1 (NH**C**H$_2$), 60.2 (**C**H), 127.3, 127.7, 128.6, 138.6 (m, **C$_6$**H$_5$), 174.3 (**C**(O)); HRMS (ESI) 207.1502 [M + H^+] (calcd for $C_{12}H_{18}N_2OH^+$ 207.1497); Anal. Calcd for $C_{12}H_{18}N_2O$•0.30H_2O: C, 68.09; H, 8.86; N, 13.23. Found: C, 67.71; H, 8.89; N, 13.19.

17. Preparation of (*R*)- and (*S*)-*N*-Benzyl 2-*N'*-Amino-3,3-dimethylbutanamide ((*R*)- and (*S*)-25)

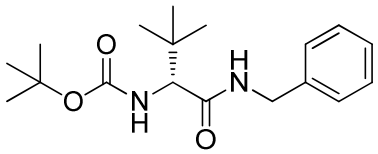


(*R*)-2-*N*-(*t*-Butoxycarbonyl)amino-3,3-dimethylbutanoic Acid ((*R*)-80). Boc_2O (9.16 g, 41.96 mmol) was added to an H_2O/acetone (75/75 mL) solution of D-*tert*-leucine (5.00 g, 38.14 mmol) and Na_2CO_3 (10.11 g, 95.35 mmol). The reaction was stirred at room temperature (18 h) and then Et_2O was added. The layers were separated and the aqueous layer was acidified to pH ~2 with an aqueous 1 M solution of $KHSO_4$. The acid aqueous layer was extracted with EtOAc (3 x 100 mL) and then the EtOAc layers were combined, dried (Na_2SO_4), and evaporated in vacuo to give the crude product (8.12 g, 92%) as a pale yellow solid and as a 2:1 mixture of conformers A (major) and B (minor). The product was used for the next step without further purification: ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (s, CC(C**H$_3$**)$_3$), 1.45 (s, OC(C**H$_3$**)$_3$), 3.85–3.92 (br d, C**H$_B$**), 4.13 (d, J = 8.0 Hz, C**H$_A$**), 5.12 (d, J = 8.0 Hz, N**H$_A$**), 6.16–6.22 (br d, N**H$_B$**), 10.02–10.45 (br s, O**H**).

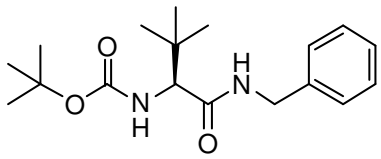
^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5 (CHC(**C**H_3)$_3$), 28.3 (OC(**C**H_3)$_3$), 34.0 (CH**C$_B$**(CH$_3$)$_3$), 34.5 (CH**C$_A$**(CH$_3$)$_3$), 61.6 (**C**H$_A$), 63.6 (**C**H$_B$), 80.0 (O**C$_A$**(CH$_3$)$_3$), 81.6 (O**C$_B$**(CH$_3$)$_3$), 155.6 (O**C$_A$**(O)), 156.6 (O**C$_B$**(O)), 176.8 (C**C**(O)).



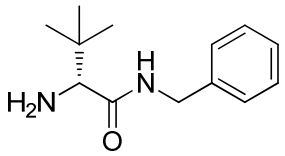
(*S*)-2-*N*-(*t*-Butoxycarbonyl)amino-3,3-dimethylbutanoic Acid ((*S*)-80).[25] Boc_2O (8.24 g, 37.76 mmol) was added to a H_2O/*t*-butyl alcohol (45 mL/45 mL) solution of L-*tert*-leucine (4.50 g, 34.33 mmol) and NaOH (1.51 g, 37.76 mmol). The reaction was stirred at room temperature (18 h) and then the organic layer was evaporated in vacuo. The aqueous layer was acidified to pH ~2 with an aqueous 1 M $KHSO_4$. The aqueous layer was extracted with EtOAc (3 x 50 mL) and the organic layers were combined, dried (Na_2SO_4), and evaporated in vacuo to give the crude product (7.55 g, 95%) as a white solid and as a 2:1 mixture of conformers A (major) and B (minor): mp 105–106 °C (lit.[25] mp 122 °C); $[\alpha]^{25}_D$ –2.8° (*c* 1.1, CH_2Cl_2); R_f 0.77 (1:20 MeOH/CH_2Cl_2); IR (nujol mull) 2910 (br), 1660, 1531, 1458, 1373, 1223, 1161, 1061, 1011, 900, 850, 724 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, CC(C**H$_3$**)$_3$), 1.45 (s, OC(C**H$_3$**)$_3$), 3.88 (d, *J* = 7.4 Hz, C**H$_B$**), 4.14 (d, *J* = 9.5 Hz, C**H$_A$**), 5.16 (d, *J* = 9.5 Hz, N**H$_A$**), 6.38 (d, *J* = 7.4 Hz, N**H$_B$**), 10.91–11.16 (br s, CO_2**H**). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7 (CHC(**C**H_3)$_3$), 28.5 (OC(**C**H_3)$_3$), 34.7 (CH**C**(CH$_3$)$_3$), 61.8 (**C$_A$**HC(CH$_3$)$_3$), 63.8 (**C$_B$**HC(CH$_3$)$_3$), 80.2 (O**C$_A$**(CH$_3$)$_3$), 81.8 (O**C$_B$**(CH$_3$)$_3$), 155.9 (O**C$_A$**(O)NH), 157.7 (O**C$_B$**(O)NH), 176.9 (**C**(O)OH).



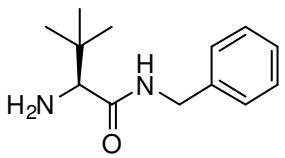
(*R*)-*N*-Benzyl 2-*N'*-(*t*-Butoxycarbonyl)amino-3,3-dimethylbutanamide ((*R*)-86). Utilizing Method B with (*R*)-**80** (3.50 g, 15.14 mmol), NMM (2.16 mL, 19.68 mmol), IBCF (2.15 mL, 16.66 mmol), and benzylamine (1.74 mL, 15.90 mmol) in anhydrous THF (150 mL) gave the crude product (3.97 g, 82%) as a pale solid. The product was used immediately for the next step without further purification.



(*S*)-*N*-Benzyl 2-*N'*-(*tert*-Butoxycarbonyl)amino-3,3-dimethylbutanamide ((*S*)-86).[24] The previous procedure was repeated using (*S*)-**80** (4.53 g, 19.60 mmol), NMM (2.80 mL, 25.48 mmol), IBCF (2.78 mL, 21.56 mmol), and benzylamine (2.25 mL, 20.57 mmol) in anhydrous THF (200 mL) to give the crude product that was purified by flash column chromatography (SiO_2; 1:10–1:1 EtOAc/hexanes) to give the desired product (4.58 g, 73%) as a white solid: mp 150–151 °C; $[\alpha]^{25}_{D}$ +3.1° (*c* 1.0, CH_2Cl_2); R_f 0.36 (1:10 EtOAc/hexanes); IR (nujol mull) 2911 (br), 1714, 1644, 1543, 1459, 1374, 1228, 1170, 1066, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (s, CHC(C**H**$_3$)$_3$), 1.39 (s, OC(C**H**$_3$)$_3$), 3.91 (d, *J* = 9.5 Hz, C**H**), 4.35 (dd, *J* = 5.4, 15.0 Hz, NHC**H**H'Ph), 4.48 (dd, *J* = 5.9, 15.0 Hz, NHCH**H'**Ph), 5.35 (d, *J* = 9.5 Hz, OC(O)N**H**), 6.44–6.51 (br m, CC(O)N**H**), 7.20–7.33 (m, C$_6$**H**$_5$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6 (CC(**C**H$_3$)$_3$), 28.3 (OC(**C**H$_3$)$_3$), 34.5 (C**C**(CH$_3$)$_3$), 43.4 (NH**C**H$_2$Ph), 62.3 (**C**H), 79.6 (O**C**(CH$_3$)$_3$), 127.3, 127.7, 128.6, 138.1 (**C**$_6$H$_5$), 156.0 (O**C**(O)N), 171.1 (**C**(O)N).



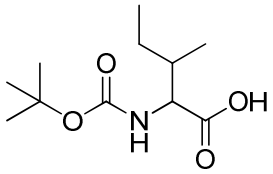
(*R*)-*N*-Benzyl 2-*N'*-Amino-3,3-dimethylbutanamide ((*R*)-25).[26] Utilizing Method E with (*R*)-**86** (3.80 g, 11.87 mmol), TFA (13.22 mL, 0.18 mol), and CH_2Cl_2 (40 mL) gave the crude product after workup that was further purified by flash column chromatography (SiO_2; 1:20 EtOAc/hexanes followed by 1:10 MeOH/CH_2Cl_2) to give the desired compound (2.17 g, 83%) as a pale yellow solid: mp 65–66 °C (lit.[26] mp 53–54 °C); $[\alpha]^{28.5}_D$ +21.8° (*c* 0.5, CH_2Cl_2); R_f 0.48 (1:20 MeOH/CH_2Cl_2); IR (nujol mull) 3291, 2957, 1643, 1555, 1452, 1361, 1259, 1188, 1018, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, (C**H**$_3$)$_3$), 1.45 (s, N**H**$_2$), 3.12 (s, C**H**), 4.42 (dd, *J* = 4.0, 12.8 Hz, NHC**H**H'), 4.46 (dd, *J* = 4.0, 12.8 Hz, NHCH**H'**), 7.05–7.13 (br m, N**H**), 7.24–7.34 (m, C$_6$**H**$_5$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8 ((**C**H$_3$)$_3$), 34.2 (**C**(CH$_3$)$_3$), 43.1 (N**C**H$_2$), 64.4 (**C**H), 127.4, 127.9, 128.6, 138.6 (**C**$_6$H$_5$), 173.5 (**C**(O)); HRMS (+ESI) 221.1654 [M+H$^+$] (calcd. for $C_{13}H_{20}N_2OH^+$ 221.1653). Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.25; N, 12.72. Found: C, 70.83; H, 9.20; N, 12.75.



(*S*)-*N*-Benzyl 2-Amino-3,3-dimethylbutanamide ((*S*)-25).[24, 27] The previous procedure was repeated using (*S*)-**86** (2.50 g, 7.81 mmol), TFA (8.70 mL, 0.12 mol), and CH_2Cl_2 (26 mL) to give the crude product after workup that was further purified by flash column chromatography (SiO_2; 1:100–1:10 MeOH/CH_2Cl_2) to give the desired compound (1.58 g, 92%) as a white solid:

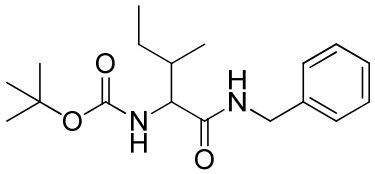
mp 65–66 °C (lit.[27] mp 53–54 °C); $[\alpha]^{25}_{D}$ –15.2° (*c* 0.51, CH_2Cl_2) (lit.[24] $[\alpha]^{20}_{D}$ –17.5° (*c* 0.56, CH_2Cl_2); R_f 0.19 (100% EtOAc); IR (nujol mull) 2912 (br), 1649, 1555, 1459, 1372, 1260, 1192, 1023, 941, 839, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (s, C(C**H**$_3$)$_3$), 1.47 (s, N**H**$_2$), 3.14 (s, C**H**), 4.44 (d, *J* = 5.7 Hz, NHC**H**$_2$Ph), 7.04–7.12 (br t, C(O)N**H**), 7.24–7.36 (m, C_6**H**$_5$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.0 (C(**C**H_3)$_3$), 34.4 (**C**$(CH_3)_3$), 43.4 (NH**C**H_2Ph), 64.7 (**C**H), 127.6, 128.1, 128.9, 138.8 (**C**$_6$$H_5$), 173.6 (**C**(O)N); HRMS (ESI) 221.1652 [M + H^+] (calcd for $C_{13}H_{20}N_2OH^+$ 221.1654); Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.90; H, 9.10; N, 12.54.

18. Preparation of (*R,S*)-*N*-Benzyl 2-Amino-3-methylpentanamide ((*R,S*)-26)

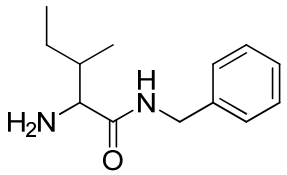


(*R,S*)-2-*N*-(*t*-Butoxycarbonyl)amino-3-methylpentanoic Acid ((*R,S*)-81).[28] A solution of DL-isoleucine (5.00 g, 38.14 mmol) in a mixture of dioxane (75 mL) and aqueous 1 M NaOH (37.5 mL) was cooled to 0 °C in an ice water bath. Boc_2O (9.16 g, 41.97 mmol) was added slowly and the reaction was allowed to warm to room temperature (18 h), and then the solvent was evaporated in vacuo. The resulting crude oil was dissolved in EtOAc (50 mL), the aqueous layer was acidified to pH 2 with aqueous 1 M $KHSO_4$ and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to give the crude product with minor impurities (9.10 g) as a pale yellow oil and as a 1:1 mixture of conformers A and B. The product was used for the next step without further purification: ^1H NMR (300 MHz, $CDCl_3$)

δ 0.82–0.98 (m, 2 C**H**$_3$), 1.18–1.32 (m, C**H**$_2$), 1.45 (s, C(C**H**$_3$)$_3$), 1.82–2.03 (m, C**H**), 4.33 (dd, J = 4.4, 8.7 Hz, NHC**H**$_A$), 4.43 (dd, J = 3.5, 9.5 Hz, NHC**H**$_B$), 5.02 (d, J = 9.5 Hz, N**H**$_B$), 5.08 (d, J = 8.7 Hz, N**H**$_A$), 10.52–11.35 (br s, O**H**).

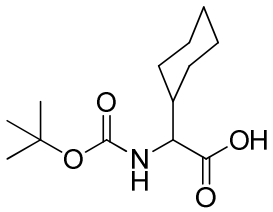


(*R,S*)-*N*-Benzyl 2-*N*'-(*t*-Butoxycarbonyl)amino-3-methylpentanamide ((*R,S*)-87). Utilizing Method B with (*R,S*)-**81** (9.10 g, 39.37 mmol), NMM (5.63 mL, 51.18 mmol), IBCF (5.59 mL, 43.31 mmol), and benzylamine (4.52 mL, 41.34 mmol) gave the crude product that was purified by recrystallization from hot EtOAc/hexanes to give the desired compound (7.16 g, 57%) as a white solid and as a 1:1 mixture of conformers A and B: mp 104–105 °C; R_f 0.59 (1:20 MeOH/CH_2Cl_2); IR (nujol mull) 3393, 3282, 2912, 1658, 1554, 1458, 1375, 1308, 1253, 1168, 1041, 723 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84–0.96 (m, 2 C**H**$_3$), 1.01–1.26 (m, C**H**$_2$), 1.40, 1.41 (2 s, OC(C**H**$_3$)$_3$), 1.74–2.04 (m, CHC**H**), 3.98 (dd, J = 6.7, 8.7 Hz, NHC**H**$_A$ or NHC**H**$_B$), 4.15 (dd, J = 3.5, 9.5 Hz, NHC**H**$_B$ or NHC**H**$_A$), 4.36–4.51 (m, NHC**H**$_2$Ph), 4.96–5.18 (m, $(CH_3)_3COC(O)N$**H**), 6.54–6.62 (br t, N**H**CH_2Ph), 7.17–7.35 (m, C_6**H**$_5$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.8, 12.1 (CH_2**C**H_3), 14.9, 16.1 (CH**C**H_3), 19.6, 22.3 (**C**H_2CH_3), 26.8, 28.8 (C(**C**H_3)$_3$), 37.9, 38.0 (CH**C**H), 43.8, 43.9 (NH**C**H_2Ph), 58.9, 59.8 (C**H**), 80.2, 80.3 (**C**$(CH_3)_3$), 127.9, 128.2, 129.0, 129.1, 138.7, 138.8 ((**C**$_6$H$_5$)$_A$, (**C**$_6$H$_5$)$_B$), 156.3, 156.6 (N**C**(O)O), 172.4, 172.6 (C**C**(O)N), two aromatic peaks were not detected and are believed to overlap with nearby signals; HRMS (ESI) 321.2187 [M + H$^+$] (calcd for $C_{18}H_{28}N_2O_3H^+$ 321.2178); Anal. Calcd for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.81; N, 8.74. Found C, 67.22; H, 9.00; N, 8.65.

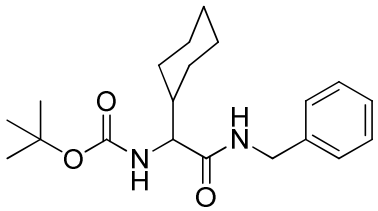


(*R,S*)-*N*-Benzyl 2-Amino-3-methylpentanamide ((*R,S*)-26). Utilizing Method E with (*R,S*)-**87** (4.00 g, 12.49 mmol), TFA (13.92 mL, 0.19 mol), and CH_2Cl_2 (40 mL) gave the crude product after workup that was further purified by flash column chromatography (SiO_2; 1:100–1:10 MeOH/CH_2Cl_2) to give the desired compound (2.24 g, 81%) as a pale yellow oil and as a 1:1 mixture of diastereomers: R_f 0.73 (1:20 MeOH/CH_2Cl_2); IR (neat) 3308, 3068, 2962, 2926, 2876, 1656, 1521, 1457, 1365, 1247, 1081, 1026, 934, 852, 737, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.77–0.96 (m, 2 C**H$_3$**), 1.00–1.46 (m, (C**H$_2$**CH_3), N**H$_2$**), 1.92–2.17 (m, CHC**H**), 3.26 (d, J = 3.6 Hz, (C**H**)$_A$ or (C**H**)$_B$), 3.36 (d, J = 3.6 Hz, (C**H**)$_A$ or (C**H**)$_B$), 4.36–4.49 (m, NHC**H$_2$**Ph), 7.21–7.33 (m, C_6**H$_5$**), 7.74–7.82, 7.83–7.91 (2 br t, N**H**CH_2Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9 (CH_2**C**H_3), 13.1, 16.2 (CH**C**H_3), 23.7, 26.7 (**C**H_2CH_3), 37.1, 38.0 (CH**C**H), 42.9, 43.0 (NH**C**H_2Ph), 57.9, 59.9 (C**H**), 127.2, 127.6, 127.7, 128.5, 138.7, 138.7 ((**C$_6$**H_5)$_A$, (**C$_6$**H_5)$_B$), 174.4, 174.7 (C**C**(O)N), two aromatic peaks were not detected and are believed to overlap with nearby signals; HRMS (ESI) 221.1663 [M + H^+] (calcd for $C_{13}H_{20}N_2OH^+$ 221.1654); Anal. Calcd for $C_{13}H_{20}N_2O$•0.03CH_2Cl_2: C, 70.20; H, 9.07; N, 12.57. Found: C, 70.19; H, 9.21; N, 12.54.

19. Preparation of (*R*)-2-Amino-*N*-benzyl-2-cyclohexylacetamide ((*R*)-27)

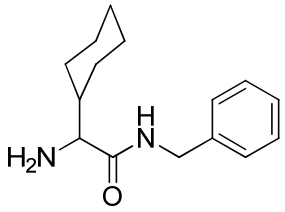


(*R*)-2-(tert-Butoxycarbonylamino)-2-cyclohexylacetic Acid ((*R*)-82). Boc_2O (3.05 g, 14.0 mmol) was added to an H_2O/acetone (25/25 mL) solution of 2-amino-2-cyclohexylacetic acid (2.00 g, 12.7 mmol) and Na_2CO_3 (2.02 g, 19.0 mmol). The reaction was stirred at room temperature (16 h) and then Et_2O was added. The layers were separated and the aqueous layer was acidified to pH ~1 with an aqueous 1 M solution of $KHSO_4$. The acid aqueous layer was washed with Et_2O (3 x 100 mL) and then the organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo to give the desired product (2.90 g, 89%) as a white gummy solid and a 4:1 mixture of conformers A (major) and B (minor): mp 68–75 °C; IR (nujol mull) 2898, 1721, 1675, 1525, 1456, 1373, 1241, 1167, 1068, 919, 793, 729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07–1.30 (m, 2 C$\mathbf{H_2}$), 1.45 (s, (C$\mathbf{H_3}$)$_3$), 1.59–1.89 (m, 3 C$\mathbf{H_2}$), 3.99–4.09 (br s, C$\mathbf{H_B}$), 4.24 (dd, *J* = 4.8, 8.7 Hz, C$\mathbf{H_A}$), 5.04 (d, J = 8.7 Hz, N$\mathbf{H_A}$), 6.01–6.10 (br t, N$\mathbf{H_B}$), 7.60–7.15 (br s, CO_2**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 26.0, 26.0, 27.9, 28.3, 29.5, 31.1, 40.7 ((**C**H_3)$_3$, **C$_6$**H_{11}), 58.2 (NH**C**HC(O)), 80.0 (**C**$(CH_3)_3$), 155.8 (N**C**(O)), 177.0 (**C**(O)).



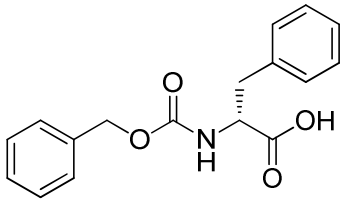
(*R*)-*N*-Benzyl-2-(tert-butoxycarbonylamino)-2-cyclohexylacetamide ((*R*)-88). Utilizing Method B with (*R*)-**82** (500 mg, 2.0 mmol), NMM (0.26 mL, 2.3 mmol), IBCF (0.31 mL, 2.3 mmol), and benzylamine (0.26 mL, 2.3 mmol) gave the desired product (600 mg, 86%) as a white solid: mp 138–139 °C; R_f 0.21 (1:9 EtOAc/hexanes); IR (nujol mull) 3335, 2907, 2859, 1659, 1528, 1457, 1374, 1300, 1247, 1171, 1021, 872, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95–1.25 (m, 2 C$\mathbf{H_2}$), 1.42 (s, (C$\mathbf{H_3}$)$_3$), 1.59–1.83 (m, 3 C$\mathbf{H_2}$), 3.89 (dd, *J* = 6.6, 8.7 Hz, C**H**),

4.46 (d, J = 6.3 Hz, NC**H$_2$**), 4.99–5.05 (br d, N**H**), 6.17–6.25 (br m, N**H**), 7.24–7.33 (m, C$_6$**H$_5$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 26.1, 28.3, 29.8, 40.2, 43.4 ((**C**H$_3$)$_3$, **C**H$_2$N, **C$_6$**H$_{11}$), 59.8 (NH**C**HC(O)), 79.9 (**C**(CH$_3$)$_3$), 127.5, 127.7, 128.7, 138.0 (Ar**C**), 155.9 (N**C**(O)), 171.5 (**C**O); HRMS (ESI) 479.1307 [M + Cs$^+$] (calcd for $C_{20}H_{30}N_2O_3Cs^+$ 479.1311).

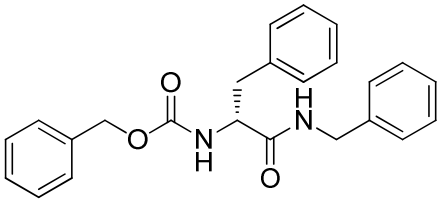


(*R*)-2-Amino-*N*-benzyl-2-cyclohexylacetamide ((*R*)-27). Utilizing Method E with (*R*)-**88** (1.10 g, 3.2 mmol), TFA (2.40 mL, 31.8 mmol), and CH_2Cl_2 (50 mL) gave the crude product after workup that was purified by flash column chromatography (SiO_2; 0:5:95–5:90:5 MeOH/EtOAc/Et_3N) to give the desired product (530 mg, 68%) as a yellow solid: mp 94–96 °C; $[\alpha]^{27}_D$ +24.0° (*c* 0.5, $CHCl_3$); R_f 0.55 (95:5 EtOAc/Et_3N); IR (nujol mull) 3273, 3153, 2898, 2855, 1641, 1551, 1455, 1376, 1233, 1081, 1022, 886, 795, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92–1.34 (m, 1 C$_6$**H$_{11}$**), 1.45–1.71 (m, 5 C$_6$**H$_{11}$**), 1.85–1.94 (m, 5 C$_6$**H$_{11}$**), 3.20 (d, J = 3.9 Hz, C**H**), 4.39 (d, J = 5.7 Hz, NC**H$_2$**), 7.17–7.30 (m, C$_6$**H$_5$**), 7.49–7.62 (br m, N**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1, 26.2, 26.3, 26.6, 30.3, 41.0, 43.1 (**C**H, 6 **C**H$_2$), 60.0 (NH**C**HC(O)), 127.3, 127.7, 128.6, 138.6 (4 Ar**C**), 174.2 (**C**(O)); HRMS (ESI) 247.1810 [M + H$^+$] (calcd $C_{15}H_{22}N_2OH^+$ 247.1810). Anal. Calcd for $C_{15}H_{22}N_2O$•0.08H_2O: C, 72.73; H, 9.01; N, 11.31. Found: C, 72.43; H, 8.89; N, 11.34.

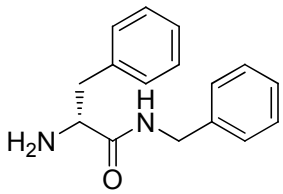
20. Preparation of (*R*)-*N*-Benzyl 2-Amino-3-phenylpropionamide ((*R*)-28)



(*R*)-2-*N*-(Benzyloxycarbonyl)amino-3-phenylpropionic Acid ((*R*)-92).[29, 30] Benzyl chloroformate (5.09 mL, 36.35 mmol) and aqueous 4 M NaOH (12 mL) were added simultaneously over a 30 min period to a vigorously stirred solution of D-phenylalanine (5.00 g, 30.29 mmol) dissolved in aqueous 4 M NaOH (10 mL)/aqueous 1 M $NaHCO_3$ (30 mL) at 0 °C. The mixture was then warmed to room temperature and stirred overnight (18 h). The reaction was washed with Et_2O (2 x 100 mL) and then the aqueous mixture was added to a stirred mixture of aqueous 4 M HCl (66 mL) and EtOAc (100 mL). The aqueous layer was separated and then extracted with EtOAc (3 x 100 mL). All of the organic layers were combined, successively washed with H_2O (3 x 100 mL) and brine (2 x 100 mL), dried (Na_2SO_4), and then evaporated in vacuo to give the desired product (6.74 g, 74%) as an off-white solid and as a 2:1 mixture of conformers A (major) and B (minor): mp 88–89 °C (lit.[29] mp 85–88 °C); $[\alpha]^{25}_D$ +4.3° (*c* 1.0, MeOH) (lit.[29] $[\alpha]^{25}_D$ +4.1° (*c* 1.0, MeOH)); R_f 0.52 (1:20 MeOH/CH_2Cl_2); IR (nujol mull) 3461, 3319, 2919, 1695, 1531, 1457, 1260, 1053, 904, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.87–2.95 (m, (CHC$\mathbf{H_2}$Ph)$_B$), 3.07 (dd, *J* = 6.6, 14.1 Hz, (CHC**H**H'Ph)$_A$), 3.19 (dd, *J* = 5.6, 14.1 Hz, (CHCH**H'**Ph)$_A$), 4.60–4.53 (m, C$\mathbf{H_B}$), 4.65–4.72 (m, C$\mathbf{H_A}$), 5.03 (d, *J* = 4.5 Hz, (OC$\mathbf{H_2}$Ph)$_B$), 5.07 (d, *J* = 3.3 Hz, (OC$\mathbf{H_2}$Ph)$_A$), 5.36 (d, *J* = 8.1 Hz, N$\mathbf{H_A}$), 6.45 (d, *J* = 8.1 Hz, N$\mathbf{H_B}$), 7.12–7.32 (m, 2 $C_6\mathbf{H_5}$), 10.32–10.58 (br s, O**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.8 (CH**C**H_2Ph), 54.8 (**C**H), 67.3 (O**C**H_2Ph), 127.3, 128.2, 128.4, 128.7, 128.7, 129.5, 135.7, 136.2 (2 $\mathbf{C_6}H_5$), 156.1 (O**C**(O)N), 176.2 (**C**(O)OH).



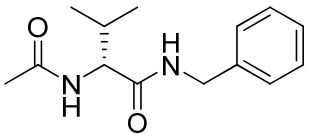
(*R*)-*N*-Benzyl 2-*N'*-(Benzyloxycarbonyl)amino-3-phenylpropionamide ((*R*)-94). Utilizing Method B with (*R*)-**92** (5.00 g, 16.71 mmol), NMM (2.39 mL, 21.73 mmol), IBCF (2.37 mL, 18.38 mmol), and benzylamine (1.92 mL, 17.55 mmol) gave the crude product that was recrystallized from hot EtOAc to give the desired compound (4.67 g, 72%) as an off-white solid: mp 154–155 °C; $[\alpha]^{25}_{D}$ +5.1° (*c* 1.1, CH_2Cl_2); R_f 0.85 (1:100 MeOH/CH_2Cl_2); IR (nujol mull) 3412, 3292, 2923, 2860, 1688, 1645, 1537, 1457, 1380, 1288, 1239, 1045, 743, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.99–3.15 (m, CHC**H**$_2$Ph), 4.24–4.44 (m, C**H**, NHC**H**$_2$Ph), 5.46 (d, *J* = 7.2 Hz, N**H**), 6.10–6.19 (br t, N**H**CH_2Ph), 7.03–7.36 (m, 3 C_6**H**$_5$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.0 (CH**C**H_2Ph), 43.7 (NH**C**H_2Ph), 56.7 (**C**H), 67.3 (O**C**H_2Ph), 127.2, 127.7, 127.9, 128.2, 128.4, 128.7, 128.8, 128.9, 129.5, 136.2, 136.6, 137.7 (3 **C**$_6$H$_5$), 156.2 (O**C**(O)N), 170.9 (C**C**(O)N); HRMS (ESI) 411.1697 [M + Na^+] (calcd for $C_{24}H_{24}N_2O_3Na^+$ 411.1685); Anal. Calcd for $C_{24}H_{24}N_2O_3$: C, 74.21; H, 6.23; N, 7.21. Found: C, 74.18; H, 6.28; N, 7.28.



(*R*)-*N*-Benzyl 2-Amino-3-phenylpropionamide ((*R*)-28). Utilizing Method C with (*R*)-**94** (3.50 g, 9.02 mmol), 10% Pd-C (0.35 g), and MeOH (90 mL) gave the crude product that was purified by flash column chromatography (SiO_2; 1:10 MeOH/CH_2Cl_2) to give the desired compound (2.22 g, 97%) as a pale yellow solid: mp 66–67 °C; $[\alpha]^{25}_{D}$ +63.3° (*c* 1.4, CH_2Cl_2); R_f 0.43 (1:20

MeOH/CH_2Cl_2); IR (nujol mull) 3293, 2924, 2859, 1641, 1539, 1457, 1373, 1261, 1105, 1031, 950, 845, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98–1.62 (br s, N**H$_2$**), 2.75 (dd, J = 9.0, 13.7 Hz, CHC**H**H'Ph), 3.29 (dd, J = 4.2, 13.7 Hz, CHCH**H'**Ph), 3.65 (dd, J = 4.2, 9.0 Hz, C**H**), 4.37–4.50 (m, NHC**H$_2$**Ph), 7.20–7.35 (m, 2 C_6**H$_5$**), 7.56–7.64 (br t, N**H**CH_2Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.2 (CH**C**H_2Ph), 43.3 (NH**C**H_2Ph), 56.6 (**C**H), 127.0, 127.5, 127.9, 128.8, 128.9, 129.5, 138.0, 138.5 (2 **C$_6$**H_5), 171.3 (C**C**(O)N); HRMS (ESI) 277.1321 [M + Na^+] (calcd for $C_{16}H_{18}N_2ONa^+$ 277.1317); Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.53; H, 7.16; N, 10.85.

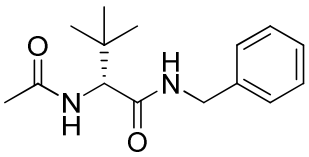
21. Preparation of (*R*)-*N*-Benzyl 2-Acetamido-3-methylbutanamide ((*R*)-105)



(*R*)-*N*-Benzyl 2-Acetamido-3-methylbutanamide ((*R*)-105). (*R*)-*N*-Benzyl 2-amino-3-methylbutanamide hydrochloride (0.79 g, 3.26 mmol) was dissolved in CH_2Cl_2 (60 mL) and then Et_3N (1.4 mL, 9.78 mmol) and acetyl chloride (0.28 mL, 3.91 mmol) were carefully added at 0 °C. The resulting solution was stirred at room temperature (2 h). Aqueous 10% citric acid (60 mL) was added, the layers separated, and the organic layer was washed with a saturated aqueous $NaHCO_3$ (60 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 60 mL). All of the organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was recrystallized with EtOAc to give the desired compound as a white solid: mp 223–224 °C; $[\alpha]^{26}_D$ +32.8° (*c* 0.5, $CHCl_3$); R_f 0.53 (100% EtOAc); IR (nujol mull) 3472, 3401, 3369, 3169, 3119, 2934, 2860, 1628, 1545, 1458, 1376, 1298, 1156, 727, 614, 542 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94–

0.97 (m, 6H), 1.98 (s, 3H), 2.04–2.11 (m, 1H), 4.25 (app t, J = 8.2 Hz, 1H), 4.37 (1/2 AB_q, J = 5.4, 14.8 Hz, 1H), 4.47 (1/2 AB_q, J = 5.8, 14.8 Hz, 1H), 6.18–6.21 (br d, 1H), 6.42–6.50 (br t, 1H), 7.24–7.34 (m, 5H), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-**105** gave only one signal for the acetyl methyl protons; ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 19.2 (2 $CH(\mathbf{C}H_3)_2$), 23.2 ($C(O)\mathbf{C}H_3$), 31.1 ($\mathbf{C}H(CH_3)_2$), 43.6 ($N\mathbf{C}H_2$), 58.7 (**C**HNH), 127.6, 127.7, 128.7, 137.7 ($\mathbf{C_6}H_4$), 170.2, 171.1 (2 **C**(O)); LRMS (ESI) 271.16 [M + Na^+] (calcd for $C_{14}H_{20}N_2O_2Na^+$ 271.14). Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.92; H, 8.24; N, 11.23.

22. Preparation of (*R*)-*N*-Benzyl 2-Acetamido-3,3-dimethylbutanamide ((*R*)-106)



(*R*)-*N*-Benzyl 2-Acetamido-3,3-dimethylbutanamide ((*R*)-106). (*R*)-*N*-Benzyl 2-amino-3,3-dimethylbutanamide hydrochloride (0.64 g, 2.5 mmol) was dissolved in CH_2Cl_2 (50 mL) and then Et_3N (1.0 mL, 7.50 mmol) and acetyl chloride (0.2 mL, 3.00 mmol) were carefully added at 0 °C, and the resulting solution was stirred at room temperature (2 h). Aqueous 10% citric acid (50 mL) was added, the layers separated, and the organic layer was washed with a saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). All the organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by chromatography (SiO_2; 30:70–70:30 EtOAc/hexanes) to give crude product that was recrystallized with EtOAc to give the desired product as a white solid: mp 199–200 °C; $[\alpha]^{25}_D$ – 6.1° (c 0.5, $CHCl_3$); R_f 0.19 (30:70 EtOAc/hexanes); IR (nujol mull) 3064, 2970, 2857, 1638,

1543, 1463, 1375, 1284, 1240, 1128, 1031, 901, 743, 600, 470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 9H), 1.86 (s, 3H), 4.29 (1/2 AB_q, J = 5.5, 14.8 Hz, 1H), 4.43 (1/2 AB_q, J = 5.8, 14.8 Hz, 1H), 4.45 (d, J = 9.4 Hz, 1H), 6.45 (d, J = 9.4 Hz, 1H), 7.18 (br t, J = 5.4 Hz, 1H), 7.23–7.32 (m, 5H), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-**106** gave only one signal for the acetyl methyl protons; ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1 (C(O)**C**H_3), 26.7 (C(**C**H_3)$_3$), 34.8 (**C**$(CH_3)_3$), 43.5 (N**C**H_2), 60.5 (**C**H), 127.4, 127.9, 128.6, 137.9 (**C**$_6$$H_4$), 170.1, 170.7 (2 **C**(O)); LRMS (ESI) 263.20 [M + H^+] (calcd for $C_{15}H_{22}N_2O_2H^+$ 263.18). Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.67; H, 8.55; N, 10.49.

23. Pharmacological Evaluation

Pharmacological evaluation conducted at UCB Pharma. All experiments were performed with the use of male NMRI mice (Charles River, France) weighing 25–30 g. All mice were kept on a 12/12 h light/dark cycle with lights on at 6 am and were housed at a temperature maintained at 20–24 ºC and at a humidity of 40–70%. The mice were kept in groups of 10 in Makrolon cages (Type III, 425 x 266 x 155 mm) containing a bedding layer of sawdust. The mice were allowed *ad libitum* access to standard dry pellet food and tap water before random assignment to experimental groups. Each experiment consisted of several groups of 10 mice, one group receiving the vehicle control and the other groups receiving different doses of compounds. All compounds were dissolved in 0.5% methylcellulose and injected ip (10 mL/kg volume) 30 min before testing. An effective dose protecting 50% of the mice (ED_{50}) against the convulsive endpoint and its associated 95% confidence interval, and a toxic dose impairing the rotorod performance of 50% of the mice (TD_{50}), were calculated using a non-linear fitting of the dose-response curve with GraphPad Prism 4 (GraphPad Software, San Diego, CA). In cases where the

dose-response could not be established, the minimal active dose (MAD) or maximal tolerated dose (MTD) was determined after statistical comparison (Fisher's exact test). This occurred when no further increase in protection was observed at a higher dose (plateau effect), a higher dose could not be tested because of CNS side effects, or there was loss of activity at higher doses.

In the 6 Hz test, partial-onset seizures were induced by a stimulator (ECT Unit 57800, Ugo Basile, Comerio, Italy) using a current intensity of 44 mA, delivered with 0.2 msec monopolar pulses at 6 Hz, for a duration of 3 sec through corneal electrodes as described by Kaminski and coworkers.[31] A drop of saline/Unicain 0.1% was placed on the eyes to ensure good conductivity and mild local anesthesia before electrical stimulation. After stimulation, each mouse was observed for 30 sec and the duration of immobility (stunned posture) was noted. Untreated mice reliably respond with seizures. After compound treatment, the mice were considered as protected against seizures if the duration of immobility was shorter than 7 sec.

The maximal electroshock seizures (MES) test identified compounds that prevent seizure spread and was induced by a stimulator (WITT Industrie Elektronik, Berlin, Germany) using a current of 50 mA, delivered with a pulse frequency of 50 Hz for 0.2 sec, through corneal electrodes as described by Klitgaard and coworkers.[32] Stimulation with this current caused tonic hindlimb extension in 100% of the vehicle-treated mice. The mice were considered as protected by the compound if they did not exhibit the tonic hindlimb extension following stimulation.

In the formalin test, mice were pretreated ip with compound or vehicle 30 min before intrapaw injection of formalin and then returned to their cage. Twenty min after pretreatment (10 min before the injection of formalin), the mice were individually placed in 6 mm thick Plexiglas cages (26 cm x 17 cm x 28 cm) and observed for drug induced side effects over a 10 min period.

Then, 25 µL of 1.5% formalin (1.5% aqueous solution of formaldehyde) was injected into the midplantar aspect of the right hindpaw (subplantar injection) and the mice were returned to the observation cage. The nociceptive response was defined as the duration of licking directed at the right hindpaw and was measured to the nearest sec for each consecutive 5 min time bin for 30 min after the injection of formalin.[33] A typical triphasic pattern of nociceptive response occurs.[34] An immediate (0–5 min) bout of intense flinching, licking, or biting behavior is followed by nociceptive silence (5–10 min), followed by a gradual increase in nociceptive licking that peaks at 15–20 min. The nociceptive response gradually decays to zero by 25–30 min after injection.[35] The bin 0–5 min after formalin injection constituted the early phase, where pain is due to direct excessive stimulation of primary afferent neurons. The sum of the remain four time bins (10–15 min, 15–20 min, 20–25 min, and 25–30 min) constituted the late phase, where pain is due to peripheral and central sensitization. The compound's efficacy in the late phase is viewed as predictive of efficacy in animal models of neuropathic pain. Therefore, the compound's primary outcome measure is the late-phase value at which 50% of mice display a paw lick duration ≤72 sec (ED_{50}), which corresponds to a 50% reduction of the nociceptive response relative to the mean of vehicle-treated mice. ED_{50} values, with 95% confidence limits where applicable, were calculated using JMP Version 5 for Windows (SAS Institute Inc.).

The adverse effects on motor coordination were assessed in a rotorod test (Treadmill for Mice, Ugo Basile, Italy) as described by Klitgaard and coworkers.[32] The device consisted of a rod with a diameter of 3 cm rotating at a constant speed of 6 rpm. Mice were pretrained and only mice that were able to remain on the rotorod for at least 60 sec in three consecutive trials were retained for testing. Within 24 h, the compound was administered and the number of mice unable to remain on the rod for at least 60 sec was recorded.

Pharmacological evaluation conducted at the NINDS ASP. Experiments were performed with the use of male albino Carworth Farms No. 1 mice (18–25 g) or male albino Sprague-Dawley rats (100-150 g). Housing, handling, and feeding were all in accordance with the recommendations in the "Guide for the Care and Use of Laboratory Animals."[36] All compounds were dissolved in 0.5% methylcellulose and administered ip (10 mL/kg volume) in mice and po (20 mL/kg) in rats. An effective dose protecting 50% of the mice and rats (ED_{50}) against the convulsive endpoint and its associated 95% confidence interval, as well as the toxic dose impairing the rotorod performance of 50% of the mice, or the positional sense/gait and stance performance of 50% of the rats (TD_{50}), were calculated by a computer program based on the methods described by Finney.[37]

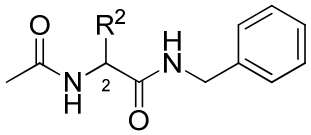
The MES test was induced by a stimulator using a current of 50 mA in mice, or 150 mA in rats, and delivered with a pulse frequency of 60 Hz for 0.2 sec through corneal electrodes.[38] A drop of 0.5% butacaine hemisulfate in 0.9% sodium chloride was placed on the eyes to ensure good conductivity and mild local anesthesia before electrical stimulation. Qualitative assessment of activity in mice was determined at 30 min and 4 h following doses of 30, 100, and 300 mg/kg of compound. Rats were tested at 0.25–4 h in 30 min intervals at a dose of 30 mg/kg. The mice or rats were considered as protected by the compound if they did not exhibit the tonic hindlimb extension following stimulation.

The subcutaneous Metrazol® (scMET) model primarily identifies compounds that raise the seizure threshold and was induced by subcutaneous injection of 0.5% solution of pentylenetetrazol in the posterior midline (85 mg/kg) in mice. This produces clonic seizures that last at least 5 sec in 97% (CD_{97}) of animals tested.[38] Mice were tested at 30 min and 4 h

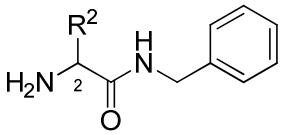
following doses of 30, 100, and 300 mg/kg of compound. The animals were considered protected when the compound abolished the effect of pentylenetetrazol on seizure threshold.

The adverse effects on motor coordination in mice were assessed in a rotorod test, similar to that conducted at UCB Pharma. Mice were positioned on a rod with a diameter of 1 in rotating at a constant speed of 6 rpm, and the ability of the mice to remain on the rod for at least 60 sec was recorded. Mice were tested at 30 min and 4 h following doses of 30, 100, and 300 mg/kg of compound. The adverse effects on motor coordination in rats were assessed in a positional sense test or gait and stance test. In the positional sense test, one hind leg was lowered over the edge of the table and the ability to transition back to a stable stance was recorded. In the gait and stance test, neurotoxicity was indicated by circular or zig-zag gait, ataxia, abnormal stance or posture, tremor, somnolence, stupor, or catalepsy.[38] Rats were tested at 0.25–4 h in 30 min intervals at a dose of 30 mg/kg.

Supporting Information Table S1. Comparison of the pharmacological activities of C(2)-hydrocarbon FAAs and their PAAD counterparts in rats (mg/kg)



FAA

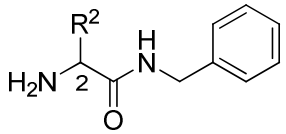


PAAD

			Rat (po)[a]				Rat (po)[a]	
R^2	**FAA Cpd No.**	**FAA Test Site**	**FAA MES,[b] ED_{50}**	**FAA Tox,[c] TD_{50}**	**PAAD Cpd No.**	**PAAD Test Site**	**PAAD MES,[b] ED_{50}**	**PAAD Tox,[c] TD_{50}**
CH_3	(*R,S*)-**100**[d]	NINDS	48 [1.0] (32–72)	>1000	(*R,S*)-**20**[e]	NINDS	14 [1.0] (7–22)	>500
$CH_2CH_2CH_3$	(*R,S*)-**103**[e]	NINDS	~30	>30	(*R,S*)-**22**	UCB	ND[f]	ND[f]
$CH(CH_3)_2$	(*R*)-**104**	NINDS	>30 [0.25–4.0]	>30 [0.25–4.0]	(*R*)-**24**	NINDS	11 [0.25] (9.1–13)	>500
$C(CH_3)_3$	(*R*)-**105**	NINDS	>30 [0.25–4.0]	>30 [0.25–4.0]	(*R*)-**25**	NINDS	11 [0.25] (8.7–15)	>500

[a] The compounds were administered orally to adult male albino Sprague Dawley rats. ED_{50} and TD_{50} values are in mg/kg. A dose-response curve was generated for all compounds that displayed sufficient activity and the dose-effect data for these compounds was obtained at the "time of peak effect" (indicated in hours in the brackets). Numbers in parentheses are 95% confidence intervals. [b] MES = maximal electroshock seizure test. [c] Tox = behavioral toxicity. [d] Béguin, C. *et al. Bioorg. Med Chem*. **2004**, *12*, 3079–3096. [e] LeTiran, A. *et al. J. Med. Chem*. **2002**, *45*, 4762–4773. [f] ND = not determined.

Supporting Information Table S2. Pharmacological activities of C(2)-*N*-benzylamide PAAD chiral sets in mice (mg/kg) at UCB and the NINDS ASP

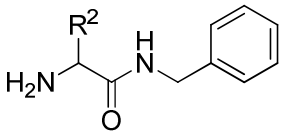


			Mice (ip)[a]					
Cmpd No.	**Test Site**	**R^2**	**MES[b], ED_{50}**	**6 Hz,[c] ED_{50}**	**Formalin, ED_{50}**	**Tox[d], TD_{50}**	**PI[e], MES**	**PI[e], Form**
(*R*)-**2**	UCB	LCM	3.3	10	15	19	5.8	1.3
(*R*)-**2**[f]	NINDS	LCM	4.5 [0.5] (3.7–5.5)	10	ND[g]	27 [0.25] (26-28)	6.0	
(*S*)-**2**[f]	NINDS	LCM	>100, <300	ND[g]	ND[g]	>300		
(*R*)-**7**	UCB	CH_2OH	ND[g]	>62	>62	>110		
(*S*)-**7**	UCB	CH_2OH	ND[g]	>62	>62	>110		
(*R,S*)-**7**	UCB	CH_2OH	ND[g]	>62	>62	>110		
(*R*)-**8**	UCB	CH_2OCH_3	34	>67	>67	>120	>3.5	
(*R*)-**8**	NINDS	CH_2OCH_3	48 [0.25] (40–61)	ND[g]	ND[g]	>30, <100 [0.25]		
(*R*)-**8**[h]	NINDS	CH_2OCH_3	>30, <100	ND[g]	ND[g]	>100, <300		
(*S*)-**8**	UCB	CH_2OCH_3	64	>70	120	63	1.0	0.5

(*R*)-**20**[i]	NINDS	CH_3	>10, <30	ND[g]	ND[g]	>100, <300		
(*S*)-**20**[i]	NINDS	CH_3	>300	ND[g]	ND[g]	>300		
(*R,S*)-**20**[i]	NINDS	CH_3	>100, <300	ND[g]	ND[g]	>300		
(*R*)-**22**	UCB	$CH_2CH_2CH_3$	21	66 (MAD)[j]	35	57	2.8	1.6
(*S*)-**22**	UCB	$CH_2CH_2CH_3$	>37	>210	100	ND[g]		
(*R,S*)-**22**	UCB	$CH_2CH_2CH_3$	39	120 (MAD)[j]	68[k] (17%)	ND[g]		
(*R*)-**24**	UCB	$CH(CH_3)_2$	16 (MAD)[j] 16[k] (100%)	74	20	47	2.9	2.4
(*R*)-**24**	NINDS	$CH(CH_3)_2$	15 [0.25] (13–18)	<100 [0.25–1.0]	15 [0.25]	70 [0.25] (63–80)	4.7	
(*S*)-**24**	NINDS	$CH(CH_3)_2$	>300 [0.5]	ND[g]	ND[g]	>300 [0.5]		
(*R*)-**25**	UCB	$C(CH_3)_3$	13	>71	>22	ND[g]		
(*R*)-**25**	NINDS	$C(CH_3)_3$	14 [0.25] (11–17)	~30 [0.25–0.5]	ND[g]	66 [0.25] (58–73)	4.7	
(*S*)-**25**	NINDS	$C(CH_3)_3$	42 [0.25] (37–46)	ND[g]	ND[g]	100 [0.25] (100–110)		

[a] The compounds were administered intraperitoneally to adult male NMRI mice under the auspices of UCB or administered intraperitoneally to adult male albino CF-1 mice under the auspices of the NINDS ASP. ED_{50} and TD_{50} values are in mg/kg and were determined 30 min after ip administration (UCB) or a dose-response curve was generated for all compounds that displayed sufficient activity and the dose-effect data for these compounds was obtained at the "time of peak effect" (indicated in hours in the brackets) (NINDS ASP). Numbers in parentheses are 95% confidence intervals. [b] MES = maximal electroshock seizure test. [c] 6 Hz test = psychomotor seizure model (44 mA, UCB; 32 mA, NINDS ASP). [d] Tox = neurological toxicity. TD_{50} value determined from the rotorod test. [e] PI = protective index (TD_{50}/ED_{50}). [f] Choi, D. *et al. J. Med. Chem.* **1996**, *39*, 1907–1916. [g] ND = not determined. [h] Andurkar, S.V. *et al. Tetrahedron: Asymmetry* **1998**, *9*, 3841–3854. [i] Béguin, C. *et al. Bioorg. Med. Chem*. **2004**, *12*, 3079–3096. [j] MAD = minimal active dose. [k] Single dose experiments where the mg/kg used is followed by the percentage protected in parenthesis.

Supporting Information Table S3. Comparison of the pharmacological activities of PAADs evaluated in mice (mg/kg) at UCB and the NINDS-ASP



		UCB[a]			NINDS-ASP[b]		
Cmpd No.	**R^2**	**MES,[c] ED_{50}**	**Tox,[d] TD_{50}**	**PI[e]**	**MES,[c] ED_{50}**	**Tox,[d] TD_{50}**	**PI[e]**
(*R*)-**2**	LCM	3.3	19	5.8	4.5 [0.5] (3.7–5.5)	27 [0.25] (26–28)	6.0
(*R*)-**8**	CH_2OCH_3	34	>117	>3.4	48 [0.25] (40–61)	>30, <100 [0.25]	
(*R*)-**21**	CH_2CH_3	16	46	2.9	18 [0.25] (10–25)	80 [0.25] (65–95)	4.4
(*R*)-**24**	$CH(CH_3)_2$	16 (MAD)[f]	47	2.9	15 [0.25] (13–18)	70 [0.25] (63–80)	4.8
(*R*)-**25**	$C(CH_3)_3$	13	ND[g]		14 [0.25] (11–17)	66 [0.25] (58–73)	4.7

[a] The compounds were administered intraperitoneally to adult male NMRI mice under the auspices of UCB. ED_{50} and TD_{50} values are in mg/kg and were determined 30 min after ip administration. [b] The compounds were administered intraperitoneally to adult male albino CF-1 mice under the auspices of the NINDS ASP. ED_{50} and TD_{50} values are in mg/kg. A dose-response curve was generated for all compounds that displayed sufficient activity and the dose-effect data for these compounds was obtained at the "time of peak effect" (indicated in hours in the brackets). Numbers in parentheses are 95% confidence intervals. [c] MES = maximal electroshock seizure test. [d] Tox = neurological toxicity. TD_{50} value determined from the rotorod test. [e] PI = protective index (TD_{50}/ED_{50}). [f] MAD = minimal active dose. [g] ND = not determined.

Supporting Information Table S4. Elemental analysis of prepared compounds.

No.	Formula	Calcd.				Found			
		C	H	N	S	C	H	N	S
(*R*)-**7**	$C_{10}H_{14}N_2O_2$	61.84	7.27	14.42		61.94	7.27	14.31	
(*S*)-**7**	$C_{10}H_{14}N_2O_2$	61.84	7.27	14.42		61.91	7.31	14.21	
(*R,S*)-**7**	$C_{10}H_{14}N_2O_2$	61.84	7.27	14.42		61.84	7.27	14.42	
(*R*)-**8**	$C_{11}H_{16}N_2O_2 \bullet 0.18H_2O$	62.49	7.80	13.25		62.13	7.82	13.10	
(*S*)-**8**	$C_{11}H_{16}N_2O_2 \bullet 0.15H_2O$	62.56	7.79	13.28		62.25	7.91	13.16	
(*R,S*)-**8**	$C_{11}H_{16}N_2O_2$	63.44	7.74	13.45		63.18	7.66	13.41	
(*R,S*)-**36**	$C_{20}H_{24}N_2O_4$	67.40	6.79	7.86		67.12	6.67	7.89	
(*R,S*)-**9**	$C_{12}H_{18}N_2O_2 \bullet 0.06CH_2Cl_2$	63.63	8.02	12.30		63.67	8.21	12.32	
(*R,S*)-**37**	$C_{21}H_{26}N_2O_4$	68.09	7.07	7.56		68.20	7.19	7.64	
(*R,S*)-**10**	$C_{13}H_{20}N_2O_2$	66.07	8.53	11.85		65.80	8.29	11.58	
(*R,S*)-**11**	$C_{13}H_{18}N_2O_2 \bullet 0.20H_2O$	65.61	7.80	11.77		65.21	7.92	11.60	
(*R,S*)-**49**	$C_{18}H_{24}N_2O_4$	65.04	7.28	8.43		65.26	7.44	8.42	
(*R,S*)-**12**	$C_{13}H_{16}N_2O_2 \bullet 0.09CH_2Cl_2$	65.59	6.80	11.69		65.54	6.97	11.68	
(*R,S*)-**58**	$C_{14}H_{20}N_2O_2$	59.99	7.19	9.99		60.17	7.29	9.85	
(*R,S*)-**60**	$C_{20}H_{25}N_3O_3$	67.58	7.09	11.82		67.58	7.15	12.02	
(*R,S*)-**15**	$C_{12}H_{19}N_3O_2 \bullet 0.33H_2O$	63.41	8.72	18.49		63.38	8.52	18.21	
(*R,S*)-**59**	$C_{16}H_{22}N_2O_5$	59.61	6.88	8.69		59.53	6.79	8.59	
(*R,S*)-**61**	$C_{22}H_{27}N_3O_4$	66.48	6.85	10.57		66.52	6.82	10.64	
(*R,S*)-**16**	$C_{14}H_{21}N_3O_2$	63.85	8.04	15.96		63.71	7.99	15.77	
(*R,S*)-**53**	$C_{13}H_{18}N_2O_4$	58.63	6.81	10.52		58.36	6.82	10.67	
(*R,S*)-**64**	$C_{20}H_{31}N_3O_5$	61.05	7.94	10.68		61.16	7.98	10.49	
(*R,S*)-**13**	$C_{10}H_{15}N_3O \bullet H_2O$	61.91	7.84	21.66		61.54	7.90	21.38	
(*R*)-**69**	$C_{12}H_{13}NO_4$	61.27	5.57	5.59		61.26	5.65	6.00	
(*R*)-**17**	$C_{11}H_{16}N_2O_2$	63.44	7.74	13.45		63.31	7.86	13.31	
(*R*)-**67**	$C_{17}H_{26}N_2O_3S$	60.33	7.74	8.28	9.47	60.18	7.80	8.25	9.18
(*R*)-**19**	$C_{12}H_{18}N_2OS$	60.47	7.61	11.75	13.45	60.17	7.62	11.52	13.69
(*R*)-**83**	$C_{16}H_{24}N_2O_3$	65.73	8.27	9.58		66.00	8.33	9.56	
(*R*)-**21**	$C_{11}H_{16}N_2O \bullet 0.06CH_2Cl_2$	67.22	8.22	14.17		67.23	8.31	14.36	
(*R*)-**93**	$C_{20}H_{24}N_2O_3 \bullet 0.12H_2O$	70.11	7.13	8.18		69.75	7.20	8.35	
(*S*)-**93**	$C_{20}H_{24}N_2O_3$	70.56	7.11	8.23		70.28	7.19	8.31	
(*R,S*)-**93**	$C_{20}H_{24}N_2O_3$	70.56	7.11	8.23		70.36	7.17	8.19	
(*R*)-**22**	$C_{12}H_{18}N_2O$	69.87	8.80	13.58		69.98	8.73	13.37	
(*S*)-**22**	$C_{12}H_{18}N_2O \bullet 0.32H_2O$	67.99	8.86	13.22		67.93	8.76	13.21	
(*R,S*)-**22**	$C_{12}H_{18}N_2O \bullet 0.18H_2O$	68.81	8.83	13.37		68.48	8.81	13.27	
(*R*)-**84**	$C_{18}H_{28}N_2O_3$	67.47	8.81	8.74		67.65	8.93	8.74	
(*R*)-**23**	$C_{13}H_{20}N_2O \bullet 0.15H_2O$	69.32	9.02	12.44		69.35	9.16	12.37	
(*R*)-**24**	$C_{12}H_{18}N_2O \bullet 0.04CH_2Cl_2$	68.93	8.69	13.35		68.97	8.82	13.37	
(*S*)-**24**	$C_{12}H_{18}N_2O \bullet 0.30H_2O$	68.09	8.86	13.23		67.71	8.89	13.19	
(*R*)-**25**	$C_{13}H_{20}N_2O$	70.87	9.25	12.72		70.83	9.20	12.75	
(*S*)-**25**	$C_{13}H_{20}N_2O$	70.87	9.15	12.72		70.90	9.10	12.54	
(*R,S*)-**87**	$C_{18}H_{28}N_2O_3$	67.47	8.81	8.74		67.22	9.00	8.65	
(*R,S*)-**26**	$C_{13}H_{20}N_2O \bullet 0.03CH_2Cl_2$	70.20	9.07	12.57		70.19	9.21	12.54	
(*R*)-**27**	$C_{15}H_{22}N_2O \bullet 0.08H_2O$	72.73	9.01	11.31		72.43	8.89	11.34	
(*R*)-**94**	$C_{24}H_{24}N_2O_3$	74.21	6.23	7.21		74.18	6.28	7.28	
(*R*)-**28**	$C_{16}H_{18}N_2O$	75.56	7.13	11.01		75.53	7.16	10.85	
(*R*)-**105**	$C_{14}H_{20}N_2O_2$	67.71	8.12	11.28		67.92	8.24	11.23	
(*R*)-**106**	$C_{15}H_{22}N_2O_2$	68.67	8.45	10.68		68.67	8.55	10.49	

Supporting Information Table S5. Mass spectra data of select compounds.

No.	Formula	Calcd.	Found
(*R*)-**7**	$C_{10}H_{14}N_2O_2Na^+$	217.0953	217.0953
(*S*)-**7**	$C_{10}H_{14}N_2O_2Na^+$	217.0953	217.0953
(*R,S*)-**7**	$C_{10}H_{14}N_2O_2Na^+$	217.0953	217.0953
(*R,S*)-**36**	$C_{20}H_{24}N_2O_4H^+$	357.1814	357.1814
(*R,S*)-**9**	$C_{12}H_{18}N_2O_2H^+$	223.1447	223.1450
(*R,S*)-**37**	$C_{21}H_{26}N_2O_4Na^+$	393.1790	393.1790
(*R,S*)-**40**	$C_{23}H_{21}NO_2H^+$	344.1651	344.1663
(*R,S*)-**41**	$C_9H_{15}NO_4Na^+$	224.0899	224.0909
(*R,S*)-**11**	$C_{13}H_{18}N_2O_2H^+$	235.1447	235.1452
(*R,S*)-**45**	$C_{12}H_{19}NO_5Na^+$	280.1161	280.1167
(*R,S*)-**49**	$C_{18}H_{24}N_2O_4Na^+$	355.1634	355.1645
(*R,S*)-**12**	$C_{13}H_{16}N_2O_2H^+$	233.1290	233.1294
(*R,S*)-**50**	$C_{12}H_{15}NO_5Na^+$	276.0848	276.0844
(*R,S*)-**58**	$C_{14}H_{20}N_2O_4Na^+$	303.1321	303.1322
(*R,S*)-**60**	$C_{20}H_{25}N_3O_3Na^+$	378.1794	378.1798
(*R,S*)-**15**	$C_{12}H_{19}N_3ONa^+$	244.1426	244.1434
(*R,S*)-**59**	$C_{16}H_{22}N_2O_5Na^+$	345.1427	345.1431
(*R,S*)-**61**	$C_{22}H_{27}N_3O_4Na^+$	420.1899	420.1884
(*R,S*)-**16**	$C_{14}H_{21}N_3O_2Na^+$	286.1532	286.1533
(*R,S*)-**53**	$C_{13}H_{18}N_2O_4H^+$	267.1345	267.1352
(*R,S*)-**64**	$C_{20}H_{31}N_3O_5Na^+$	416.2162	416.2151
(*R,S*)-**13**	$C_{10}H_{15}N_3ONa^+$	216.1113	216.1107
(*R*)-**69**	$C_{12}H_{13}NO_4Na^+$	258.0742	258.0753
(*R*)-**70**	$C_{19}H_{22}N_2O_4Na^+$	365.1477	365.1462
(*R*)-**17**	$C_{11}H_{16}N_2O_2H^+$	209.1290	209.1288
(*R*)-**67**	$C_{17}H_{26}N_2O_3SH^+$	339.1742	339.1751
(*R*)-**19**	$C_{12}H_{18}N_2OSH^+$	239.1218	239.1224
(*R*)-**83**	$C_{16}H_{24}N_2O_3Na^+$	315.1685	315.1694
(*R*)-**21**	$C_{11}H_{16}N_2OH^+$	193.1341	193.1348
(*R*)-**93**	$C_{20}H_{24}N_2O_3Na^+$	363.1685	363.1686
(*S*)-**93**	$C_{20}H_{24}N_2O_3Na^+$	363.1685	363.1687
(*R,S*)-**93**	$C_{20}H_{24}N_2O_3Na^+$	363.1685	363.1685
(*R*)-**22**	$C_{12}H_{18}N_2ONa^+$	229.1317	229.1317
(*S*)-**22**	$C_{12}H_{18}N_2OH^+$	207.12	207.12
(*R,S*)-**22**	$C_{12}H_{18}N_2ONa^+$	229.1317	229.1320
(*R,S*)-**78**	$C_{11}H_{21}NO_4Na^+$	254.1368	254.1370
(*R*)-**84**	$C_{18}H_{28}N_2O_3Cs^+$	453.1154	453.1152
(*R*)-**23**	$C_{13}H_{20}N_2OH^+$	221.1654	221.1655
(*R*)-**24**	$C_{12}H_{18}N_2OH^+$	207.1497	207.1501
(*S*)-**24**	$C_{12}H_{18}N_2OH^+$	207.1497	207.1502
(*R*)-**25**	$C_{13}H_{20}N_2OH^+$	221.1654	221.1653
(*S*)-**25**	$C_{13}H_{20}N_2OH^+$	221.1654	221.1652
(*R,S*)-**87**	$C_{18}H_{28}N_2O_3H^+$	321.2178	321.2187
(*R,S*)-**26**	$C_{13}H_{20}N_2OH^+$	221.1654	221.1663
(*R*)-**88**	$C_{20}H_{30}N_2O_3Cs^+$	479.1311	479.1307
(*R*)-**27**	$C_{15}H_{22}N_2OH^+$	247.1810	247.1810
(*R*)-**94**	$C_{24}H_{24}N_2O_3Na^+$	411.1685	411.1697
(*R*)-**28**	$C_{16}H_{18}N_2ONa^+$	277.1317	277.1321
(*R*)-**105**	$C_{14}H_{20}N_2O_2Na^+$	271.14	271.16
(*R*)-**106**	$C_{15}H_{22}N_2O_2H^+$	263.18	263.20

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