Supplementary Material

The Synthesis of α-Substituted β-Amino Acids Using Pseudoephedrine as a Chiral Auxiliary

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Experimental

General. Infrared spectra were recorded with a Nicolet Impact 400 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Unity 500 spectrometer at 500 and 125 MHz, respectively. Chemical shifts are reported in parts per million (ppm) relative to the residual solvent peak ($CHCl_3$, δ = 7.26, 77.0 ppm; CHD_2OD, δ = 3.30, 48.97 ppm; HOD, δ = 4.8 ppm for ^{1}H and ^{13}C, respectively). Melting points were taken on an Electrothermal 9100 system. Optical rotations were taken on a Jasco DIP-370 using a 3.5 mm I.D. X 100 mm sample cell. Reagents and solvents were obtained from Aldrich Chemical Company and were used without further purification. Boc-β-alanine was obtained from Advanced ChemTech and was used without further purification. Elemental analyses were performed by Desert Analytics Laboratory of Tucson, Arizona.

(1R,2R)-(+)-pseudoephedrine-β-alanine amide (2). Pivaloyl chloride (32.5 mL, 264 mmol) was added to a stirred, ice bath cooled solution of Boc-β-alanine (49.8 g, 264 mmol) and triethylamine (37.7 mL, 271 mmol) in dichloromethane (500 mL). The resulting mixture was stirred at 0 °C for 1 h. Additional triethylamine (47.0 mL, 338 mmol) was added to the reaction mixture followed by a solution of (1R,2R)-(+)-pseudoephedrine (43.5 g, 264 mmol) in dichloromethane (100 mL). The resulting mixture was allowed to warm to room temperature and was stirred for 14 h, then evaporated *in vacuo* giving a viscous residue. The residue was dissolved in 50% aqueous methanol (300 mL) and cooled to 0 °C followed by the addition of concentrated aqueous HCl (225 mL). The resulting solution was stirred for 4 h then dried in vacuo. The resulting residue was dissolved in water and the resulting solution was washed with 50% ethyl acetate/hexanes then basified with 50% aqueous NaOH (pH >12). The resulting basic aqueous mixture was extracted with dichloromethane (5x400 mL). The combined dichloromethane extracts were dried over Na_2SO_4 then filtered giving a turbid mixture. This mixture was further dried over K_2CO_3 (14 h) then filtered through a pad of celite. The solvent was removed *in vacuo* giving a colorless viscous oil. The crystallization of the residue from hot toluene gave the desired compound as a white solid (46.7 g, 75% yield) in two crops (33.3 g and 13.4 g, respectively). Mp = 90.5-91.5 °C. ^{1}H NMR (2:1 ratio of rotamers, * denotes peaks due to minor rotamer, ($CDCl_3$): δ = 0.969* (d, 1H, J = 6.5 Hz), 1.06 (d, 2H, J = 6.5 Hz), 2.38-2.56 (m, 2H), 2.60 (br-s, 2H), 2.80-2.86* (m, 0.7H), 2.87 (s, 2H), 2.94* (s, 1H), 2.99-3.30 (m, 1.3H), 4.06-4.14* (m, 0.3H), 4.52-4.63 (m, 1.7H, 7.26-7.38 (m, 5H). ^{13}C NMR (* denotes peaks due to minor rotamer, $CDCl_3$): δ = 14.38, 15.52*, 26.71, 36.02*, 36,82, 37.76, 38.05*, 56.33*, 58.22, 74.94*, 75.57, 126.6, 126.9*, 127.5*, 127.8, 128.2*, 128.4, 142.2*, 142.5, 173.4*, 173.5. IR (neat) ν = 3421, 2809, 1616, 1492 cm^{-1}. Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.85. Found: C, 65.86; H, 8.50; N, 11.75.

General procedure for the preparation of pseudoephedrine-β-alanine amide derivatives. Pseudoephedrine amide **2** (1 eq) was added flame dried LiCl (4 eq.) followed by THF (approximately 20 mL/g **2**). The resulting mixture was cooled to –5-0 °C by an ice/NaCl bath and lithium bis(trimethylsilyl)amide (3.2 eq.) was slowly added. After stirring for 1 h the alkyl halide (1.5 equivalents) was added, followed by stirring for 4 to 6 h until no starting material was observed by TLC. Water was then added to the reaction solution followed by acidification with 6 N HCl to pH ~ 3. The resulting mixture was then washed with 50% ethyl acetate/hexanes, and the aqueous phase cooled to 0°C, basified with 50% aqueous NaOH to pH > 12, and extracted with DCM (4x100 mL). The combined DCM extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* giving the desired

compound. Compounds **3a** and **3b** were used without further purification. Compound **3c** was crystallized from ether, while **3d** was crystallized from toluene.

(1R,2R)-Pseudoephedrine-N-[(2R)-2-methyl-3-aminopropionamide] (3a). Colorless oil (0.900g, 84% yield). ^{1}H NMR (~9:1 mixture of rotamers, * denotes peak due to minor rotamer, $CDCl_3$,): δ = 0.961-1.07 (m, 5.7H), 1.19* (d, 0.3H, *J* = 7.0 Hz), 2.41* (s, 0.2H), 2.68-2.97 (m, 9H), 4.53 (d, 0.9H, *J* = 9.0 Hz), 4.58* (d, 0.1H, *J* = 9.0 Hz), 4.75 (br-s, 1H), 7.26-7.37 (m, 5H). ^{13}C NMR (* denotes peaks due to minor rotamer, $CDCl_3$): δ = 14.30*, 14.90, 15.22, 15.37*, 39.07, 39.09*, 45.88, 45.94*, 57.99, 65.74, 74.75*, 75.35, 126.8, 126.9*, 127.6, 128.2, 128.5*, 142.2, 176.8. IR (neat): ν = 3377, 2978, 1616, 1492 cm^{-1}. Anal. Calcd for $C_{14}H_{22}N_2O_2$•0.3H_2O: C, 65.75; H, 8.91; N, 10.95. Found: C, 66.10; H, 8.85; N, 10.62.

(1R,2R)-Pseudoephedrine-N-[(2R)-2-ethyl-3-aminopropionamide] (3b). Colorless oil (1.40 g, 83% yield). ^{1}H NMR (~5:1 mixture of rotamers, * denotes peaks due to minor rotamer, $CDCl_3$): δ = 0.852* (t, 0.6H, *J* = 7.5 Hz), 0.880 (t, 2.4H, *J* = 7.5 Hz), 0.949* (d, 0.6H, *J* = 7.0 Hz), 0.98 (d, 2.4H, *J* = 7.0 Hz), 1.38-1.44 (m, 2H), 1.62-1.68 (m, 2H), 2.63 (br-s, 2H), 2.77-2.95 (m, 2H), 2.98 (s, 2.4H), 3.01* (s, 0.6H), 4.51 (d, 0.8H, *J* = 9.0 Hz), 4.55* (d, 0.2H, *J* = 9.0 Hz), 4.89 (br-s, 1H), 7.26-7.39 (m, 5H). ^{13}C NMR (* denotes peaks due to minor rotamer, $CDCl_3$): δ = 11.35, 11.82*, 14.54, 14.78*, 23.62, 23.69*, 29.37, 42.46, 42.75, 44.31*, 55.21, 74.97, 75.46*, 127.0*, 127.2, 127.9, 128.4, 141.4, 174.8. IR (neat): ν = 3345, 2963, 1618, 1454, 1310, 1110, 1050, 702 cm^{-1}. Anal. Calcd for $C_{15}H_{24}N_2O_2$: C, 68.15; H, 9.15; N, 10.60. Found: C, 67.93; H, 9.37; N, 10.51.

(1R,2R)-Pseudoephedrine-N-[(2R)-2-propyl-3-aminopropionamide] (3c). White solid (1.96 g, 83% yield). Mp = 82 °C. ^{1}H NMR (~7:1 mixture of rotamers, * denotes peaks due to minor rotamer, $CDCl_3$): δ = 0.891 (t, 3H *J* = 7.0 Hz), 0.947* (d, 0.4H, *J* = 7.0 Hz), 0.979 (d, 2.6H, *J* = 7.0 Hz), 1.24-1.36 (m, 4H), 1.59-1.64 (m, 2H), 2.56 (br-s, 2H), 2.87-2.95 (m, 2H), 2.98 (s, 2.6H), 3.20*, (s, 0.4H), 4.50 (d, 0.7H, *J* = 9.0 Hz), 4.59* (d, 0.3H, *J* = 9.0Hz), 4.92 (br-s, 1H), 7.27-7.39 (m, 5H). ^{13}C NMR (* denotes peaks due to minor isomer, CD_3OD): δ = 14.85, 16.25*, 21.74, 29.18*, 30.88, 33.60*, 34.18, 44.96*, 45.78, 45.96, 55.78, 59.66, 76.15, 128.2, 128.5*, 128.9, 129.0*, 129.4, 129.6*, 144.1, 178.0. IR (KBr): ν = 3343, 2958, 1617, 1453, 1049, 701 cm^{-1}. Anal. Calcd for $C_{16}H_{26}N_2O_2$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.88; H, 9.19; N, 10.10.

(1R,2R)-Pseudoephedrine-N-[(2R)-2-allyl-3-aminopropionamide] (3d). White solid (0.900g, 77% yield). Mp = 82.5-83 °C. ^{1}H NMR (~9:1 mixture of rotamers, * denotes peak due to minor rotamer, $CDCl_3$): δ = 0.979 (d, 2.7H, *J* = 6.5 Hz), 1.01* (d, 0.3H, *J* = 6.5 Hz), 2.11-2.38 (m, 2H), 2.52 (br-s, 2H), 2.87-3.01 (m, 6H), 2.971 (s, 3H), 4.51 (d, 0.9H, *J* = 9.0 Hz), 4.68* (d, 0.1H, *J* = 9.0 Hz), 4.88 (br-s, 1H), 4.99-5.01 (m, 1H), 5.04-5.09 (m, 1H), 5.69-5.75 (m, 1H), 7.263-7.394 (m, 5H). ^{13}C NMR (* denotes peaks due to minor rotamer, $CDCl_3$): δ = 14.68, 34.71, 44.80, 44.92, 75.82, 76.98, 116.8, 127.1, 127.8, 128.4, 135.6, 142.5, 176.5. IR (neat): ν = 3465, 2900, 1616, 1489 cm^{-1}. Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.45; H, 8.59; N, 10.13.

Typical procedure for the hydrolysis of pseudoephedrine amides. Water (~10 mL/ g **3**) was added to the pseudoephedrine amide **3**, and the resulting mixture was heated to reflux, stirred for 72 h. then cooled to room temperature and washed with dichloromethane (3x20 mL). The resulting aqueous solution was dried *in vacuo* giving a solid that was crystalized from methanol to provide the desired compound as a white solid.

(2R)-1-Amino-2-carboxypropane (4a). White solid (0.115g, 88% yield). Mp = 183-184 °C (dec) (lit. Mp = 185-186 °C)[4]. $[\alpha]^{26}_D$ = -12.6 (C = 1, 1 M HCl) (lit. $[\alpha]^{29}_D$ = -11.8 (C = 1, 1.1 M HCl)[4]). ^{1}H NMR (D_2O): δ = 1.18 (d, 3H, *J* = 7.5 Hz), 2.55-2.60 (m, 1H), 3.07 (dd, 1H, J_1 = 8.5 Hz, J_2 = 5.5 Hz), 3.10 (dd, 1H, J_1 = 13.0 Hz, J_2 = 8.5 Hz). ^{13}C NMR (D_2O): δ = 19.78, 43.90, 46.98, 186.2. IR (KBr): ν = 3429, 1735, 1653, 1537, 1462 cm^{-1}. Anal. Calcd for $C_4H_9NO_2$•0.25H_2O: C, 44.64; H, 8.90; N, 13.01. Found: C, 44.65; H, 8.75; N, 12.63.

(2R)-1-amino-2-carboxybutane (4b). White solid (0.399 g, 89% yield). Mp = 209 °C (dec). $[\alpha]^{26}_D$ = -2.9 (C = 1, 1 M HCl). ^{1}H NMR (20% CD_3OD/D2O): δ = 0.77 (t, 3H, *J* = 7.5 Hz), 1.42-1.49 (m, 2H), 2.26-2.30 (m, 1H), 2.88 (dd, 2H, J_1 = 8.5 Hz, J_2 = 5.0 Hz), 2.95 (dd, 2H, J_1 = 13.0 Hz, J_2 = 8.5 Hz). ^{13}C NMR (20% CD_3OD/D2O): δ = 11.73, 24.25, 41.89, 47.72, 181.8. IR (KBr): ν = 2965, 1630,

1508, 1412, 1341, 1086, 845 cm^{-1}. Anal. Calcd for $C_5H_{11}NO_2 \bullet 0.2H_2O$: C, 49.73; H, 9.52; N, 11.60. Found: C, 49.70; H, 9.39; N, 11.51.

(2R)-1-amino-2-carboxypentane (4c). White solid (0.265 g, 76% yield). Mp = 224-225 °C (dec). $[\alpha]^{27}_D$ = 3.5 (C = 1, 1 M HCl). ^{1}H NMR (20% CD_3OD/D2O): δ = 0.90 (t, 3H, *J* = 7.5 Hz), 1.29-1.36 (m, 2H), 1.47-1.60 (m, 2H), 2.50-2.53 (m, 1H), 3.04 (dd, 2H, J_1 = 8.0 Hz, J_2 = 5.0 Hz), 3.10 (dd, 2H, J_1 = 12.5 Hz, J_2 = 8.0 Hz). ^{13}C NMR (20% CD_3OD/D2O): δ = 14.42, 20.83, 33.25, 42.21, 46.24, 181.9. IR (KBr): ν = 2957, 1630, 1502, 1412, 1349, 1227, 1180, 841 cm^{-1}. Anal. Calcd for $C_6H_{13}NO_2 \bullet 0.15H_2O$: C, 53.83; H, 10.01; N, 10.46. Found: C, 53.83; H, 10.06; N, 10.38.

(2R)-1-amino-2-carboxypent-4-ene (4d). White solid (0.115g, 52% yield). Mp = 199.1-199-5°C (dec) $[\alpha]^{26}_D$ = -12.6 (C = 1, 1 M HCl). ^{1}H NMR (D_2O): δ = 2.26-3.39 (m, 2H), 2.52-2.62 (m, 1H), 3.03 (dd, 1H, J_1 = 13.0 Hz, J_2 = 5.0 Hz), 3.10 (dd, 1H, J_1 = 13.0 Hz, J_2 = 9.0 Hz), 5.08 (d, 1H, *J* = 11.0 Hz), 5.12 (d, 1H, *J* = 18.0 Hz), 5.73-5.80 (m, 1H). ^{13}C NMR (D_2O): δ = 38.96, 45.24, 49.34, 122.1, 139.2, 184.5. IR (KBr): ν = 3012, 2177, 1830, 1656, 1407 cm^{-1}. Anal. Calcd for $C_6H_{11}NO_2 \bullet 0.1H_2O$: C, 55.03; H, 8.62; N, 10.70. Found: C, 55.38; H, 8.44; N, 10.84.

Determination of chiral purity. Enantiomeric ratios were determined by capillary GCMS analysis of the isopropylester trifluoroacetamide derivatives **8a-d** of the amino acids. Samples were run on a Chirasil-Val (25 mx0.25 mm, film thickness 0.16 μm) column (Alltech, Deerfield, IL) installed in a Hewlett-Packard 5890 Gas Chromatograph with MS detection (70 eV EI) using a Kratos Profile HV-3 detector. Samples were injected at 1 μL of a 10 mg/mL ethyl acetate solution with a split ratio of 50:1. The oven temperature gradient was 80 ºC for 5min, 80-90 ºC at 2 ºC/min, 90-200 ºC at 5 ºC/min. Baseline resolution was observed in all cases except **4a**.

Preparation of derivatives for GC analysis. In a 2 dram vial was dissolved 1-5 mg of the amino acid in 0.2 N HCl (1 mL) which was then evaporated at 100 ºC under a stream of nitrogen. To this solid was added a solution prepared by pre-mixing isopropyl alcohol (3 mL) and acetyl chloride (250 μL). The vial was capped tightly and the solution heated at 100 ºC for 45 min. The solvent was then evaporated at 100 ºC under a stream of nitrogen and the residue treated with dichloromethane (3 mL) and trifluoroacetic anhydride (250 μL) in a tightly capped vial at 100ºC for 15 min. The solution was cooled and evaporated under a stream of nitrogen and the residue dissolved in ethyl acetate to a concentration of 10 μg/mL based on the amino acid weight.