

J | A | C | S

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

J. Am. Chem. Soc., 1997, 119(4), 656-673, DOI:[10.1021/ja9624073](https://doi.org/10.1021/ja9624073)

Terms & Conditions

Electronic Supporting Information files are available without a subscription to ACS Web Editions. The American Chemical Society holds a copyright ownership interest in any copyrightable Supporting Information. Files available from the ACS website may be downloaded for personal use only. Users are not otherwise permitted to reproduce, republish, redistribute, or sell any Supporting Information from the ACS website, either in whole or in part, in either machine-readable form or any other form without permission from the American Chemical Society. For permission to reproduce, republish and redistribute this material, requesters must process their own requests via the RightsLink permission system. Information about how to use the RightsLink permission system can be found at <http://pubs.acs.org/page/copyright/permissions.html>



ACS Publications

MOST TRUSTED. MOST CITED. MOST READ.

Copyright © 1997 American Chemical Society

Supporting Information

(S,S)-Pseudoephedrine N,N-Diallylglycinamide (6): A solution of *n*-butyllithium in hexanes (2.71 M, 809 μ L, 2.19 mmol, 1.95 equiv) was added to a slurry of anhydrous lithium chloride (286 mg, 6.75 mmol, 6.00 equiv) and diisopropylamine (315 μ L, 2.25 mmol, 2.00 equiv) in tetrahydrofuran (5 mL) at -78 $^{\circ}$ C. After 15 min, a solution of (S,S)-(+)-**1** (250 mg, 1.12 mmol, 1 equiv) in tetrahydrofuran (3 mL with a 2-mL wash) was added via cannula to the lithium diisopropylamide slurry over a 1-min period. After stirring for 20 min at -78 $^{\circ}$ C, allyl iodide (113 μ L, 1.24 mmol, 1.1 equiv) was added to the dark yellow suspension. After stirring for 20 min at -78 $^{\circ}$ C, the reaction was terminated by the addition of aqueous hydrochloric acid solution (1 M, 20 mL). The resulting biphasic mixture was warmed to 23 $^{\circ}$ C, ethyl acetate (40 mL) was added and the layers were separated. The organic layer was extracted with two additional 20-mL portions of 1 M aqueous hydrochloric acid solution. The aqueous layers were combined, and the resulting solution was cooled in an ice-bath and carefully basified to pH 14 by the addition of 50% aqueous sodium hydroxide solution. The basic aqueous solution was then extracted with four 40-mL portions of dichloromethane. The combined organic extracts were dried over anhydrous potassium carbonate, filtered and concentrated in vacuo. The oily residue was purified by chromatography on silica gel eluting with a gradient of methanol, triethylamine and dichloromethane (4:4:92 \rightarrow 10:10:80) to afford 101 mg (30%) of **6**, 37 mg (13%) of C-alkylated product (**7c**) and 79 mg (32%) of recovered **1**. IR (neat) 3381, 3076, 2987, 1622, 1454, 1406, 1110, 1051, 921, 762, 702; 1 H NMR (CDCl₃, 2:1

ratio of rotamers, * denotes minor rotamer resonances) δ 7.26-7.40 (m, 5H), 5.76-6.03 (m, 2H), 5.28 (d, 4H, $J=12.0$), 5.13-5.20* (m, 4H), 4.61* (d, 1H, $J=8.0$), 4.51 (d, 1H, $J=9.5$), 4.19* (m, 1H), 4.01 (m, 1H), 3.68 (d, 1H, $J=12.9$), 3.40 (dd, 2H, $J=6.9, 2.6$), 3.22* (s, 4H), 3.06-3.13 (m, 3H), 2.95 (s, 3H), 2.86* (s, 3H), 1.11* (d, 3H, $J=5.7$), 0.95 (d, 3H, $J=6.8$) ^{13}C NMR (CDCl_3) 170.4, 142.4, 135.0*, 132.7, 128.5, 128.3*, 128.2, 127.5*, 126.7, 126.2*, 120.3, 118.2*, 76.1*, 74.7, 59.3, 57.0*, 56.7, 56.5, 56.0*, 26.8, 16.3, 14.2*. HRMS Calcd. for $\text{C}_{18}\text{H}_{27}\text{N}_2\text{O}_2$ (M+H) 303.2072; Found 302.2056

(S,S)-Pseudoephedrine D-alaninimide (7a): Prepared by the alkylation of (S,S)-(+)-1 (224 mg, 1.01 mmol, 1 equiv) with iodomethane (78 μL , 1.26 mmol, 1.25 equiv) following the procedure outlined for **7b** (alkylation time: 1 h). The product was isolated as the corresponding diacetate, which was prepared using the following procedure. Acetic anhydride (0.500 mL, 5.30 mmol, 5.25 equiv) and 4-dimethylaminopyridine (10 mg) were added to a solution of the crude alkylation reaction product in pyridine (2.5 mL) at 23 °C. After stirring for 1 h at 23 °C, the reaction was diluted with water (5 mL) and 1 M aqueous hydrochloric acid solution (25 mL). The resulting solution was extracted with ethyl acetate (2 x 40 mL) and the combined organic layers were extracted with saturated aqueous sodium bicarbonate solution (2 x 30 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The oily residue was purified by chromatography on silica gel eluting with a gradient of hexanes, methanol and ethyl acetate (20:0:80 \rightarrow 0:0:100 \rightarrow 0:5:95) to afford 240 mg (75%) of the diacetate of **7a** as an oil. The diastereomeric excess of the

product was determined to be 82% by capillary GC analysis, as described in the general procedures (210 °C, major R_t = 7.08 min, minor R_t = 6.33 min). IR (neat) 3294, 2982, 1736, 1637, 1373, 1236, 1026, 702; ^1H NMR (CDCl_3 , 1:1 ratio of rotamers) δ 7.27-7.39 (m, 5H), 6.93 (d, 0.5H, $J=7.8$), 6.81 (d, 0.5H, $J=7.5$), 5.75 (d, 0.5H, $J=9.9$), 5.72 (d, 0.5H, $J=9.7$), 5.02 (m, 1H), 4.86 (m, 0.5H), 4.44 (m, 0.5H), 2.93 (s, 1.5H), 2.84 (s, 1.5H), 1.96 (s, 6H), 1.43 (d, 1.5H, $J=6.8$), 1.28 (d, 1.5H, $J=6.8$), 0.98 (d, 1.5H, $J=6.7$), 0.93 (d, 1.5H, $J=7.0$). HRMS Calcd. for $\text{C}_{17}\text{H}_{25}\text{N}_2\text{O}_4$ (M+H) 321.1814; Found 321.1805.

(S,S)-Pseudoephedrine D-lucinamide (7d): Prepared by the alkylation of (S,S)-(+)-1 (1.003 g, 4.51 mmol, 1 equiv) with isobutyl iodide (1.623 mL, 5.41 mmol, 5.00 equiv) following the procedure outlined for **7b** with the exception that the reaction was warmed to 23 °C after the addition of isobutyl iodide and held at that temperature for 24 h. The product was purified by chromatography on silica gel eluting with a gradient of methanol, triethylamine and dichloromethane (2.5:2.5:95→5:5:90) to afford 830 mg (66%) of **7d** as a solid. The solid product was dissolved in hot (80 °C) toluene (10 mL) and the resulting solution was cooled to -20 °C. The crystals that formed were collected by filtration and were dried in vacuo to afford 541 mg (43%) of analytically pure **7d**. The diastereomeric excess of the product was determined by capillary GC analysis as described in the general procedures (200 °C, major R_t = 11.8 min, minor R_t = 9.2 min). The chromatographed product was shown to be 95% de (the de of the crude product could not be determined because the acetylated minor diastereomer and the acetylated starting material co-eluted) and the recrystallized product was

shown to be $\geq 99\%$ de. Mp 86-88 °C; TLC $R_f = 0.63$ (5% MeOH, 5% NEt_3 , 90% CH_2Cl_2); IR (neat) 3353, 2956, 2868, 1627, 1454, 1382, 1115, 1051, 1020, 760, 702; ^1H NMR (5:1 rotamer ratio, * denotes minor rotamer peaks, CDCl_3) δ 7.16-7.33 (m, 5H), 4.55 (m, 2H), 3.99* (m, 1H), 3.71* (dd, 1H, $J=3.5, 9.8$), 3.57 (dd, 1H, $J=4.2, 9.2$), 2.92* (s, 3H), 2.82 (s, 3H), 1.73 (m, 1H), 1.38* (m, 2H), 1.19 (m, 2H) 1.03 (d, 3H, $J=6.9$), 0.92-0.99* (m, 9H), 0.88 (2d, 6H, $J=6.5$); ^{13}C NMR (CDCl_3) δ 177.4, 176.4*, 142.2, 141.9*, 128.4*, 128.1, 128.0*, 127.4, 126.8*, 126.4, 75.5, 74.8*, 57.5, 49.8, 44.0, 31.4, 26.9*, 24.4, 23.6*, 23.3, 21.5*, 21.4, 15.5*, 14.2. Anal. Calcd. for $\text{C}_{16}\text{H}_{26}\text{N}_2\text{O}_2$ C, 69.03; H, 9.41; N, 10.06. Found C, 69.27; H, 9.57; N, 9.83.

(S,S)-Pseudoephedrine D-cyclopropylmethylglycinamide (7e): Prepared by the alkylation of (S,S)-(+)-**1** (350 mg, 1.57 mmol, 1 equiv) with iodomethylcyclopropane (0.43 g, 2.36 mmol, 1.5 equiv) following the procedure outlined for **7b**. The product was purified by chromatography on silica gel eluting with 5% concentrated ammonium hydroxide solution, 10% methanol, 85% ethyl acetate to afford 303 mg (70%) of **7e**. An earlier fraction afforded 41 mg (9%) of a mixture comprised predominantly of the homoallylic isomer along with a small amount of **7e**. The desired product was purified further by mixed solvent recrystallization with a minimum volume of ethyl acetate and isopropyl ether in two crops to afford 241 mg (56%) of **7e** which was pure by elemental analysis but was contaminated with 1% of the homoallylic isomer (by GC analysis). The diastereomeric excess of the product was determined by capillary GC analysis as described in the general procedures (200 °C,

major R_t = 9.2 min, minor R_t = 7.9 min, acetylated homoallylic isomer R_t = 7.3 min). The crude product was shown to be 98% de and the recrystallized product was shown to be $\geq 99\%$ de. Mp 82-84 °C ; TLC R_f = 0.45 (5% NH_4OH , 10% MeOH, 85% EtOAc); IR (neat) 3350, 2990, 1623, 1490, 1452, 1376, 1116, 1050, 1020, 760, 702 cm^{-1} ; ^1H NMR (5:1 rotamer ratio, * denotes minor rotamer peaks, CDCl_3) δ 7.4 - 7.2 (m, 5 H), 4.61 (d, J = 8.0 Hz, 1 H), 4.50 (br app quint, J ~ 7 Hz), 4.1* (br, 1 H), 3.8* (dd, 1 H), 3.73 (t_{app} , J = 6.5 Hz, 1 H), 2.94* (s, 3 H), 2.89 (s, 3 H), 1.4 - 1.2 (m, 2 H), 1.08 (d, J = 6.8 Hz, 3 H), 1.00* (d, J = 6.7 Hz, 3 H), 0.7 - 0.6 (m, 1 H), 0.5 - 0.4 (m, 2 H), 0.1 - 0.0 (m, 2 H) ; ^{13}C NMR (CDCl_3) δ 177.3, 176.1,* 142.4, 142.0,* 128.7,* 128.4, 127.7, 127.0,* 126.7, 75.8, 75.1,* 57.8, 57.6,* 52.6,* 52.3, 40.6, 40.2,* 31.6, 27.1,* 15.7,* 14.5, 7.9,* 7.7, 5.0,* 4.8, 4.3, 3.9* ; MS (EI) 277, 221, 193, 169, 148, 136 ; HRMS (EI) for $\text{C}_{16}\text{H}_{25}\text{N}_2\text{O}_2$ (M+H), calcd 277.1916, found 277.1904. Anal. Calcd. for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.61; H, 8.65; N, 10.24

(S,S)-Pseudoephedrine D-2-methoxyphenylalaninamide (7g): Prepared by the alkylation of (S,S)-(+)-1 (280 mg, 1.26 mmol, 1 equiv) with 2-methoxybenzylbromide (380 mg, 1.89 mmol, 1.5 equiv) following the procedure outlined for **7b**. The product was purified by chromatography on silica gel eluting with 5% of concentrated ammonium hydroxide solution, 10% methanol, 85% ethyl acetate to afford **7g** (357 mg, 83%) as an oil. The diastereomeric excess of the product was determined by capillary GC analysis, as described in the general procedures (235 °C, major R_t = 9.4 min, minor R_t = 8.0 min). The product was found to be 91% de. TLC R_f = 0.55 (5%

NH₄OH, 10% MeOH, 85% EtOAc); IR (neat) 3362, 2977, 1633, 1494, 1455, 1244, 1051, 1027, 756, 703 cm⁻¹ ; ¹H NMR (4:1 rotamer ratio, * denotes minor rotamer peaks, CDCl₃) δ 7.5 - 7.3 (m, 6 H), 7.15 (dd, *J* = 7.3, 1.6 Hz, 1 H), 7.0 - 6.8 (m, 2 H), 4.65 (d, *J* = 7.8 Hz, 1 H), 4.46 (br m, 1 H), 4.2* (dd, 1 H), 4.05 (dd, *J* = 8.8 Hz, 5.1 H), 3.85 (s, 3 H), 3.80* (s, 3 H), 3.6* (dd, 1 H), 3.0* (s, 3 H), 2.85 (obscure, 1 H), 2.84 (s, 3H), 2.7 (dd, 1 H), 2.57 (dd, *J* = 8.8, 13.1 Hz, 1 H), 1.06 (d, *J* = 6.9 Hz, 3 H) ; ¹³C NMR (CDCl₃) δ 176.7, 157.2, 142.1, 131.9, 131.4, 128.3, 128.1, 127.9, 127.4, 127.0, 126.4, 125.8, 120.3, 109.9, 75.6, 74.9,* 57.8, 57.4,* 54.9, 51.0, 37.9,* 37.6, 31.1, 26,* 15.2,* 14.1 ; MS (EI) 343, 285, 235, 221, 203, 150 ; HRMS (EI) for C₂₀H₂₇N₂O₃, calcd 343.2022: found, 343.2020.

2-Chloro-3-methoxymethoxy-6-methylpyridine: 2-Chloro-3-hydroxy-6-methylpyridine¹ (4.50 g, 31.3 mmol, 1 equiv) was added in small portions over a 15-min period to a slurry of sodium hydride (60% dispersion in mineral oil, 1.57 g, 39.2 mmol, 1.25 equiv) in tetrahydrofuran (30 mL) at 0 °C. After the addition was complete, chloromethyl methyl ether (3.63 mL, 37.6 mmol, 1.20 equiv) was added dropwise to the resulting suspension. After stirring for 2 h at 0 °C, excess sodium hydride was quenched by the slow, careful addition of water (50 mL). Ethyl acetate (75 mL) was added and the layers were separated. The aqueous layer was extracted with a second portion of ethyl acetate (50 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 20% ethyl acetate in hexanes to

afford 5.68 g (97%) of the title compound as a liquid. IR (neat) 2959, 2972, 2850, 2829, 1567, 1455, 1271, 1156, 1098, 1071, 974, 824, 678; ^1H NMR (CDCl_3) δ 7.41 (d, 1H, $J=8.2$), 7.04 (d, 1H, $J=8.2$), 5.25 (s, 2H), 3.54 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (CDCl_3) δ 151.1, 146.9, 140.0, 124.3, 122.4, 95.0, 56.2, 22.9. Anal. Calcd. for $\text{C}_8\text{H}_{10}\text{ClNO}_2$ C, 51.21; H, 5.37; N, 7.47. Found C, 50.71; H, 5.24; N, 4.44.

6-Bromomethyl-2-chloro-3-methoxymethyloxypyridine: A mixture of 2-chloro-3-methoxymethyloxy-6-methylpyridine (1.00 g, 5.35 mmol, 1 equiv) and *N*-bromosuccinimide (1.90 g, 10.7 mmol, 2.00 equiv) in carbon tetrachloride (15 mL) was heated to reflux. Immediately upon reaching reflux, a catalytic amount of 2,2'-azobis(isobutyronitrile) (ca. 10 mg) was added to the refluxing suspension. Reflux was maintained for 45 min, at which time the mixture was allowed to cool to 23 °C. The crude reaction mixture was partitioned between ether (50 mL) and water (30 mL). The organic layer was washed with a mixture of saturated aqueous sodium bicarbonate solution (30 mL) and saturated aqueous sodium thiosulfate solution (10 mL), and then with water (20 mL). The aqueous layers were extracted with a second portion of ether (40 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with a gradient of dichloromethane in hexanes (25→50%) to afford 853 mg (60%) of the title compound as an oil which solidified upon standing. IR (neat) 2960, 1564, 1455, 1379, 1268, 1235, 1207, 1157, 1096, 1072, 969, 832; ^1H NMR (CDCl_3) δ 7.48 (d, 1H, $J=8.3$), 7.33 (d, 1H, $J=8.3$), 5.28 (s, 2H),

4.49 (s, 2H), 3.52 (s, 3H); ^{13}C NMR (CDCl_3) δ 149.1, 148.9, 140.5, 124.0, 123.1, 95.0, 56.6, 32.4. Anal. Calcd. for $\text{C}_8\text{H}_9\text{BrClNO}_2$ C, 36.05; H, 3.40; N, 5.26. Found C, 36.20; H, 3.44; N, 5.17.

2-Chloro-3-methoxymethoxy-6-iodomethylpyridine: Solid anhydrous sodium iodide (2.63 g, 17.5 mmol, 3.00 equiv) was added to a solution of 6-bromomethyl-2-chloro-3-methoxymethoxypyridine (1.56 g, 5.84 mmol, 1 equiv) in acetone (25 mL), and the resulting solution was deoxygenated. After stirring for 2 h at 23 °C, ether (100 mL), saturated aqueous sodium bicarbonate solution (50 mL) and saturated aqueous sodium thiosulfate solution (5 mL) were added to the reaction mixture and the layers were separated. The aqueous layer was extracted with ether (50 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (25 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The resulting yellow solid residue was recrystallized from a minimum volume of hot hexanes. After the recrystallization mixture had cooled, and the product had crystallized, the recrystallization flask was cooled at 0 °C for 1 h, and the product was collected by filtration to afford 1.48 g (81%) of the title compound as a stable solid. The solid product was found to be stable to storage at 23 °C for >1 week. Mp 79-80 °C; IR (neat) 2955, 1560, 1456, 1376, 1260, 1157, 1069, 968, 956, 921, 833; ^1H NMR (CDCl_3) δ 7.43 (d, 1H, $J=8.3$), 7.30 (d, 1H, $J=8.3$), 5.27 (s, 2H), 4.46 (s, 2H), 3.52 (s, 3H); ^{13}C NMR (CDCl_3) δ 150.6, 148.3, 140.3, 124.0, 122.5, 95.0, 56.5, 4.6. Anal. Calcd. for $\text{C}_8\text{H}_9\text{ClINO}_2$ C, 30.65; H, 2.89; N, 4.47. Found C, 30.78; H, 2.71; N, 4.43.

(S,S)-PseudoephedrineGlycylglycinamide(8): Trimethylacetyl chloride (139 μ L, 1.12 mmol, 1.00 equiv) was added slowly to a solution of *N*-Boc-glycine (197 mg, 1.12 mmol, 1.00 equiv) and triethylamine (172 μ L, 1.24 mmol, 1.10 equiv) in dichloromethane (5 mL) at 0 °C to produce a colorless suspension. After stirring at 0 °C for 20 min, a second portion of triethylamine (172 μ L, 1.24 mmol, 1.10 equiv) was added, followed by the addition of solid (S,S)-(+)-1 (250 mg, 1.12 mmol, 1 equiv). After stirring for 30 min at 0 °C, the reaction mixture was diluted with water (25 mL), followed by the addition of 1 M aqueous hydrochloric acid solution (25 mL) and ethyl acetate (50 mL). The layers were separated, and the aqueous layer was extracted with a second portion of ethyl acetate (20 mL). The combined organic layers were washed with saturated aqueous potassium carbonate solution (25 mL), and were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with a gradient of methanol in ethyl acetate (0→2%) to provide pseudoephedrine *N*-Boc-glycylglycinamide (344 mg, 81%) as an oil.

Trifluoroacetic acid (3 mL) was added to a solution of pseudoephedrine *N*-Boc-glycylglycinamide (161 mg, 0.424 mmol) in anisole (1 mL) at 23 °C. After stirring at 23 °C for 2.5 h, the reaction solution was diluted with water (10 mL), 1 M aqueous hydrochloric acid solution (10 mL), and ethyl acetate (40 mL). The layers were separated and the organic layer was washed with two additional 15-mL portions of 1 M aqueous hydrochloric acid solution. The aqueous layers were combined and the

resulting solution was cooled in an ice bath and was basified to pH 14 by the slow, cautious addition of 50% sodium hydroxide solution. The basified aqueous solution was extracted with four 40-mL portions of dichloromethane and the combined organic layers were dried over potassium carbonate, filtered and concentrated in vacuo to provide an oil which solidified rapidly. The solid was recrystallized by dissolving in hot toluene (4 mL, 75 °C) and allowing the resulting solution to cool slowly to 23 °C. Upon cooling, a mixture of crystals and oil was observed to form on the bottom of the recrystallization flask. The mixture was warmed slowly until the oil had dissolved, and the mixture was again allowed to cool slowly. After standing for 4 h at 23 °C, the crystals that had formed were collected by filtration and were dried in vacuo to afford 72 mg (61%) of **8**. IR (neat) 3368, 2982, 1633, 1535, 1490, 1454, 1413, 1311, 1112, 1048, 762, 704; ¹H NMR (CDCl₃, 1:1 mixture of rotamers, * denotes minor rotamer) δ 8.00 (s(br), 1H), 7.28-7.37 (m, 5H), 4.55-4.62 (m, 1.5H), 4.35 (d(br), 0.5H, *J*=17.4), 4.05-4.16 (m, 1.5H), 3.90 (m, 0.5H), 3.39 (s, 2H), 2.98 (s, 1.5H), 2.88 (s, 1.5H), 1.2-2.0 (s(br), 3H), 1.07 (obscure d, 1.5H), 0.97 (d, 1.5H, *J*=6.7); ¹³C NMR (1:1 ratio of rotamers) δ 173.1, 169.2, 169.0, 141.7, 141.3, 128.4, 128.2, 127.9, 127.7, 126.7, 126.6, 75.0, 74.7, 57.5, 56.3, 44.6, 44.5, 41.2, 40.9, 29.5, 26.8, 15.1, 14.0. Anal. Calcd. for C₁₄H₂₁N₃O₃ C, 60.20; H, 7.58; N, 15.04. Found C, 60.24; H, 7.67; N, 14.93.

(*R,R*)-Pseudoephedrine *N*-methyl-*L*-2-aminobutyramide (12b**):** A solution of *n*-butyllithium in hexanes (2.69 M, 4.64 mL, 12.5 mmol, 2.95 equiv) was added slowly to a solution of diisopropylamine (480 μL, 12.7 mmol, 3.00 equiv) in tetrahydrofuran (10

mL) at 0 °C. The resulting solution was stirred for 10 min at 0 °C, then was cannulated slowly, over a 5-min period, into a slurry of anhydrous (*R,R*)-(-)-**2** (1.00 g, 4.23 mmol, 1 equiv), *N*-methylethanolamine (340 μL, 4.23 mmol, 1.00 equiv) and lithium chloride (1.08 g, 25.4 mmol, 6.00 equiv) in tetrahydrofuran (15 mL) at 0 °C. After stirring at 0 °C for 20 min, iodoethane (423 μL, 5.29 mmol, 1.25 equiv) was added to the pale yellow suspension. After stirring at 0 °C for 4 h, water (40 mL) and dichloromethane (50 mL) were added to the homogenous solution. The organic layer was separated and the aqueous layer was extracted with three 30-mL portions of dichloromethane. The organic layers were combined and the resulting solution was dried over anhydrous potassium carbonate, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 4% methanol, 4% triethylamine, and 92% dichloromethane to afford 857 mg (77%) of **12b** as an oil which slowly solidified upon standing. No convenient procedure for recrystallization of the solid was found. The diastereomeric excess of the product was determined by capillary GC analysis as described in the general procedures (210 °C, major R_t = 6.9 min, minor R_t = 7.6 min). Both the crude and purified products were found to be 95% de. IR (neat) 3316, 2968, 1621, 1480, 1454, 1405, 1115, 1075, 1052, 762, 730, 703; ^1H NMR (5:1 ratio of rotamers, * denotes minor rotamer resonances) δ 7.24-7.38 (m, 5H), 4.59-4.67 (m, 1H), 4.47 (m, 1H), 4.36 (s (br), 1H), 4.12* (m, 1H), 3.35* (dd, 1H, $J=7.5, 5.7$), 3.26 (t_{app} , $J=6.4$), 2.99* (s, 3H), 2.87 (s, 3H), 2.32* (s, 3H), 2.26 (s, 3H), 1.83* (m, 1H), 1.76 (s(br), 1H), 1.65* (m, 1H), 1.46 (m, 2H), 1.18 (d, 1H, $J=7.0$), 1.04* (t, 3H, $J=7.5$), 0.98* (d, 3H, $J=6.7$), 0.89 (t, 3H, $J=7.5$); ^{13}C NMR (CDCl_3 5:1 ratio of rotamers, * denotes minor diastereomer resonances) δ 175.7, 174.8*, 142.2, 128.4*,

128.1, 127.9*, 127.4, 126.7*, 126.3, 75.3, 74.7, 61.5*, 60.8, 57.5*, 57.4, 34.5*, 34.1, 31.6, 26.6*, 26.0*, 25.9, 15.5*, 14.3, 10.4*, 9.8. HRMS Calcd. for C₁₅H₂₅N₂O₂ (M+H) 264.1838. Found 264.1836.

(S,S)-Pseudoephedrine N-Boc-D-phenylalaninamide (13f): A solution of *n*-butyllithium in hexanes (1.67 M, 1.88 mL, 3.14 mmol, 3.10 equiv) was added slowly to a suspension of anhydrous lithium chloride (258 mg, 6.09 mmol, 6.00 equiv) and diisopropylamine (455 μ L, 3.25 mmol, 3.20 equiv) in tetrahydrofuran (3.5 mL) at -78 °C. The resulting slurry was warmed to 0 °C, and after stirring for 10 min at 0 °C, the slurry was cooled to -78 °C. A solution of (S,S)-(+)-**3** (327 mg, 1.01 mmol, 1 equiv) in tetrahydrofuran (2 mL + 1 mL wash) was added via cannula to the reaction suspension. After stirring at -78 °C for 5 min, the reaction mixture was warmed to 0 °C and was maintained at that temperature for 1 h, at which time it was cooled to -45 °C. Benzyl bromide (181 μ L, 1.52 mmol, 1.50 equiv) was added to the resulting pale yellow suspension. After stirring for 5 h at -45 °C, the solution was warmed to -20 °C. After stirring for 2 h at -20 °C, the reaction was terminated by the addition of 0.5 M aqueous potassium bisulfate solution (20 mL). The biphasic mixture was extracted with ethyl acetate (2 x 50 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The product was purified by chromatography on silica gel eluting with a gradient of ethyl acetate in hexanes (20 \rightarrow 50%) to afford 321 mg (79%) of **13f** as a foam. The diastereomeric excess of the product was determined by capillary GC analysis, as outlined above, to be 87% (see **7f** for retention times). IR(neat) 3422, 2978, 1701, 1629, 1491, 1458, 1365, 1249, 1169, 1049, 737, 701; ¹H NMR (3:1 rotamer ratio, * denotes minor

rotamer peaks, CDCl₃) δ 7.18-7.35 (m, 10H), 5.57 (d, 1H, *J*=8.1), 5.36* (d, 1H, *J*=9.3), 4.96* (m, 1H), 4.46-4.79 (m, 3H), 4.25* (m, 1H), 3.87 (s(br), 1H), 3.21* (dd, 1H, *J*=13.8, 5.5), 2.86-3.01 (m, 2H), 2.94* (s, 3H), 2.58 (s, 3H), 1.42 (s, 9H), 1.33* (s, 9H), 0.98* (d, 3H, *J*=6.6), 0.76 (d, 3H, *J*=6.8); ¹³C NMR (CDCl₃) δ 173.0, 172.2*, 155.7, 155.6*, 143.7, 143.6*, 141.4, 141.2*, 141.1, 141.0*, 136.9*, 136.0, 129.5*, 129.3, 128.6*, 128.3, 128.2, 127.8*, 127.5, 127.4*, 126.9, 126.8*, 126.7, 125.0, 119.8, 75.4, 75.1*, 66.9, 66.7*, 58.1*, 56.3, 52.6, 51.8*, 46.9, 39.4, 38.4*, 30.3, 27.1*, 15.5*, 14.0. Anal. Calcd. for C₂₄H₃₂NO₄ C, 69.88; H, 7.82; N, 6.79. Found C, 70.00; H, 7.52; N, 6.72.

***N*-Boc-*D*-Allylglycine(15c):** Prepared by the hydrolysis of **7c** (537 mg, 2.05 mmol, 1 equiv) following the procedure outlined for **15f** (hydrolysis time: 70 min). The product, **15c**, was obtained as an oil (399 mg, 91%) which was pure by spectroscopic and elemental analysis. The enantiomeric excess of the product was determined by chiral HPLC analysis as described above (pH 1.5 HClO₄ mobile phase, 0.4 mL/min, 200 nm, major R_t = 4.8 min, minor R_t = 5.8 min). The product was shown to be ≥99% ee. IR (neat) 3324, 3081, 2980, 2932, 1715, 1513, 1395, 1369, 1251, 1163, 1053, 1025, 922; ¹H NMR (2:1 rotamer ratio, * denotes minor rotamer peaks, CDCl₃) δ 8.86 (s(br), 1H), 6.37* (d, 1H, *J*=5.2), 5.73 (m, 1H), 5.14-5.19 (m, 3H), 4.40 (m, 1H), 4.19* (m, 1H), 2.57 (m, 2H), 1.44 (s, 9H); ¹³C NMR 176.0, 156.7*, 155.4, 132.1, 119.1, 81.7*, 80.1, 54.2*, 52.7, 36.3, 28.1. Anal. Calcd. for C₁₀H₁₇NO₄ C, 55.80; H, 7.96; N, 6.51. Found C, 55.71; H, 8.14; N, 6.56.

N-Boc-D-Leucine (15d): Prepared by the hydrolysis of **7d** (222 mg, 0.797 mmol, 1 equiv) following the procedure outlined for **15b** (hydrolysis time: 90 min). The product, **15d**, was obtained as a waxy solid (178 mg, 97%) which was pure by spectroscopic and elemental analysis. The enantiomeric excess of the product was determined by chiral HPLC analysis as described above (pH 1.5 HClO₄ mobile phase, 0.8 mL/min, 200 nm, major R_t = 5.2 min, minor R_t = 10.6 min). The product was shown to be ≥99% ee. IR(neat) 3326, 2960, 1723, 1515, 1393, 1369, 1251, 1166, 1050, 1026; ¹H NMR (2:1 rotamer ratio, * denotes minor rotamer peaks, CDCl₃) δ 8.33 (s(br), 1H), 6.29* (d, 1H, J=6.2), 5.04 (d, 1H, J=8.4), 4.32 (m, 1H), 4.14* (m, 1H), 1.51-1.78 (m, 3H), 1.45 (s, 9H), 0.96 (d, 6H, J=6.3); ¹³C NMR (CDCl₃) δ 178.0, 177.7*, 156.7*, 155.7, 81.6*, 80.1, 53.1*, 52.0, 41.4, 28.3, 24.7, 24.6*, 22.8, 21.7. Anal. Calcd. for C₁₁H₂₁NO₄, 57.12; H, 9.15; N, 6.05; Found C, 57.33; H, 9.15; N, 5.87.

N-Boc-D-Cyclopropylmethylglycine(15e): Prepared by the hydrolysis of **7e** (133 mg, 0.52 mmol, 1 equiv) following the procedure outlined for **15b** (hydrolysis time: 3 h) with the following exceptions: the hydrolysis was carried out in 4:1 methanol / water (5 mL); 1 mL of saturated aqueous sodium bicarbonate solution was added in lieu of a stoichiometric amount of sodium bicarbonate; dioxane was omitted; di-*tert*-butyl dicarbonate was added as a concentrated solution in tetrahydrofuran (0.5 mL); acidification of the final product was achieved with aqueous hydrochloric acid solution (1 M, see note in **15b** procedure). The product, **15e**, was obtained as an oil (103 mg,

93%) which was pure by elemental analysis but contained ca. 1% of the 2-amino-5-hexenoic acid (homoallylic) derivative. The enantiomeric excess of the product was determined by chiral HPLC analysis as described above (pH 1.5 HClO₄ mobile phase, 0.4 mL/min, 200 nm, major R_t = 7.0 min, minor R_t = 9.5 min). The product was shown to be ≥98% ee. IR (neat) 3324, 2979, 1716, 1508, 1394, 1368, 1247, 1164, 1052, 1023 cm⁻¹; ¹H NMR (2:1 rotamer ratio, * denotes minor rotamer peaks, CDCl₃) δ 6.51* (br d, *J* ~ 6 Hz, 1 H), 5.29 (d, *J* = 5.9 Hz, 1 H), 4.39 (br q, *J* ~ 6.5 Hz, 1 H), 4.18* (br, 1 H), 1.70 (br t, 2 H), 1.44 (s, 9 H), 0.75 (br, 1 H), 0.48 (br d, *J* ~ 7 Hz), 0.12 (br s, 2 H); ¹³C NMR (CDCl₃) δ 177.3, 177.1, * 156.9, * 155.6, 81.6, * 80.1, 55.3, * 53.9, 37.3, * 37.1, 28.4, * 28.3, 22.8, 7.3, * 7.0, 4.6, * 4.3; MS (EI) 230, 184, 174, 155, 128; HRMS (EI) for C₁₁H₂₀NO₄ (M+H), calcd 230.1392, found 230.1399. Anal. Calcd. for C₁₁H₁₉NO₄: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.62; H, 8.78; N, 6.11.

N-Boc-D-2-Methoxyphenylalanine(15g): Prepared by the hydrolysis of **7g** (500 mg, 1.46 mmol, 1 equiv) following the procedure outlined for **15b** (hydrolysis time: 4 h) with the following exceptions: the hydrolysis was carried out in 1:1 methanol / water (6 mL); 3 mL of saturated aqueous sodium bicarbonate solution was added in lieu of a stoichiometric amount of sodium bicarbonate; acidification of the final product was achieved with 1 M aqueous hydrochloric acid solution (see note in **15b** procedure). The product was purified by crystallization from ethyl acetate / hexanes (1:5, 18 mL) to afford 370 mg (86%) of analytically pure **15g**. The enantiomeric excess of the product was determined by chiral HPLC analysis as described above (pH 2.0 HClO₄, 5%

MeOH mobile phase, 0.7 mL/min, 200 nm, major $R_t = 17.3$ min, minor $R_t = 24.6$ min). The crude product was shown to be 94% ee, the isolated product was 96% ee. Mp 150 - 152 °C ; IR (neat) 3350, 2977, 1715, 1496, 1395, 1368, 1246, 1164, 1051, 1028, 754 cm^{-1} ; ^1H NMR (4:1 rotamer ratio, * denotes minor rotamer peaks, CDCl_3) δ 7.25 (dt, $J = 8.1, 1.7$ Hz, 1 H), 7.15 (d, $J = 7.3$ Hz, 1 H), 6.95 (q_{app}, $J \sim 7.3$ Hz, 2 H), 5.6* (br, 1 H), 5.35 (br d, $J = 10.6$ Hz, 1 H), 4.46 (br q, $J = 6.1$ Hz, 1 H), 3.83 (s, 3 H), 3.2 - 3.1 (m, 2 H), 1.39 (s, 9 H), 1.34* (s, 9 H) ; ^{13}C NMR (CDCl_3) δ 177.4, 157.7, 155.8, 131.4, 128.6, 124.6, 120.8, 110.5, 80.1, 55.2, 54.3, * 33.9, * 32.5, 28.3, 28.1* ; MS (EI) 295, 239, 178, 150, 121 ; HRMS (EI) for $\text{C}_{15}\text{H}_{21}\text{NO}_5$, calcd 295.1420: found 295.1419. Anal. Calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.76; H, 7.29; N, 4.53.

***N*-Fmoc-D-2-Aminobutyric acid (16b)**: Prepared by the hydrolysis of **7b** (405 mg, 1.62 mmol, 1 equiv) following the procedure described for **16c** (hydrolysis time: 90 min) with the exception that *N*-(9-fluorenylmethylcarbonyloxy)-succinimide (600 mg, 1.78 mmol, 1.1 equiv) was used in the acylation step in place of 9-fluorenylmethyl chloroformate. The product was purified by recrystallization in two crops from ethyl acetate-hexanes (1:2, 9 mL first crop, 3 mL second crop) to afford 525 mg (99%) of analytically pure **16b**. The enantiomeric excess of the product was determined by chiral HPLC analysis as described above (pH 1.5 HClO_4 mobile phase, 0.4 mL/min, 200 nm, major $R_t = 4.1$ min, minor $R_t = 5.2$ min). The product was shown to be $\geq 99\%$ ee. Mp 155-158 °C; IR (neat) 3306, 3067, 2973, 1714, 1531, 1451, 1239, 1106, 1091, 1048, 910, 759, 738; ^1H NMR (3:1 rotamer ratio, * denotes minor rotamer peaks, CDCl_3) δ 11.11 (s(br), 1H), 7.79 (d, 2H, $J=7.4$), 7.62 (m, 2H), 7.42 (t, 2H, $J=7.4$), 7.33 (t,

2H, $J=7.3$), 6.52* (d, 1H, $J=6.4$), 5.44 (d, 1H, $J=8.0$), 4.38-4.54 (m, 3H), 4.25 (t, 1H, $J=6.9$), 4.09* (m, 1H), 1.98 (m, 1H), 1.77 (m, 1H), 1.00 (t, 3H, $J=7.3$), 0.92* (t, 1H, $J=6.8$); ^{13}C NMR (CDCl_3) δ 177.2, 156.1, 143.8, 143.6, 141.3, 127.7, 127.0, 125.0, 124.7*, 120.0, 67.6*, 67.1, 54.9, 47.1, 25.5, 9.5. Anal. Calcd. for $\text{C}_{19}\text{H}_{19}\text{NO}_4$ C, 70.14; H, 5.89; N, 4.30. Found C, 70.01; H, 5.87; N, 4.28.

***N*-Fmoc-D-Leucine (16d):** Prepared by the hydrolysis of **7d** (255 mg, 0.916 mmol, 1 equiv) following the procedure described for **16c** (hydrolysis time: 90 min). The product was purified by recrystallization from ethyl acetate-hexanes (6 mL, 1:2) to afford 261 mg (81%) of analytically pure **16d**. The enantiomeric excess of the product was determined by chiral HPLC analysis as described above (pH 1.5 HClO_4 mobile phase, 0.8 mL/min, 200 nm, major $R_t = 5.2$ min, minor $R_t = 10.6$ min). The product was shown to be $\geq 99\%$ ee. Mp 151-152 °C; IR(neat) 3400, 3338, 2958, 1714, 1525, 1450, 1336, 1265, 1048, 759, 739; ^1H NMR (3:1 rotamer ratio, * denotes minor rotamer peaks, CDCl_3) δ 10.81 (s(br), 1H), 7.72 (d, 2H, $J=7.3$), 7.56 (m, 2H), 7.36 (t, 2H, $J=7.3$), 7.27 (t, 2H, $J=7.2$), 6.36* (d, 1H, $J=8.0$), 5.33 (d, 1H, $J=8.7$), 4.41 (m, 3H), 4.19 (t, 1H, $J=6.9$), 4.10* (m, 1H), 1.52-1.70 (m, 3H), 0.93 (d, 6H, $J=5.2$), 0.82-0.90* (m, 6H); ^{13}C NMR (CDCl_3) δ 177.8, 177.5*, 157.0*, 156.2, 143.7, 143.5, 143.3*, 141.2, 127.6, 127.0, 125.0, 124.7*, 119.9, 67.7*, 67.0, 52.8*, 52.3, 47.0, 46.9*, 41.2, 40.8*, 24.6, 22.8, 22.6*, 21.6, 21.5*. Anal. Calcd. for $\text{C}_{21}\text{H}_{23}\text{NO}_4$ C, 71.37; H, 6.56; N, 3.96; Found C, 71.52; H, 6.70; N, 4.03.

enantiomeric excess of the product was determined by chiral HPLC analysis as described above (pH 2.0 HClO₄ mobile phase, 0.8 mL/min, 200 nm, major R_t = 9.5 min, minor R_t = 12.7 min). The product was shown to be ≥99% ee. Mp 182-184 °C; IR(neat) 3418, 1694, 1538, 1450, 1261, 1045, 739, 702; ¹H NMR (7:1 rotamer ratio, * denotes minor rotamer peaks, CDCl₃) δ 7.77 (d, 2H, J=7.4), 7.54 (m, 2H), 7.40 (t, 2H, J=7.3), 7.26-7.33 (m, 5H), 7.15 (m, 2H), 5.65* (s(br), 1H), 5.20 (d, 1H, J=7.8), 4.71 (m, 1H), 4.33-4.49 (m, 2H), 4.20 (t, 1H, J=6.8), 3.17 (m, 1H), 2.94* (m, 2H); ¹³C NMR (CD₃OD) δ 173.8, 157.1, 143.8, 141.1, 137.3, 128.9, 128.6, 127.4, 126.8, 126.4, 125.0, 124.9, 119.6, 66.6, 55.6, 46.9, 37.2. Anal. Calcd. for C₂₄H₂₁NO₄ C, 74.40; H, 5.46; N, 3.62. Found C, 74.35; H, 5.39; N, 3.67.

***N*-Fmoc-D-2-Methoxyphenylalanine(16g):** Prepared by the hydrolysis of **7g** (750 mg, 2.19 mmol, 1 equiv) following the procedure described for **16c** (hydrolysis time 5 h) with the following exceptions: the hydrolysis was conducted in water-methanol (7 mL, 2.5:1); saturated aqueous sodium bicarbonate solution (5 mL) was used in lieu of a stoichiometric amount of solid sodium bicarbonate; *N*-(9-fluorenylmethylcarbonyloxy)-succinimide (820 mg, 2.40 mmol, 1.1 equiv) was used in the acylation step in place of 9-fluorenylmethyl chloroformate. The product was purified by recrystallization from ethyl acetate and hexanes (25 mL, 1:4) to afford 742 mg (81%) of analytically pure **16g**. The enantiomeric excess of the product was determined by chiral HPLC analysis as described above (pH 2.0 HClO₄, 5% MeOH mobile phase, 0.7 mL/min, 200 nm, major R_t = 17.3 min, minor R_t = 24.6 min). The crude product was shown to

be 94% ee, the isolated product was 98% ee. Mp 164-166 °C ; IR (neat) 3350, 2950, 1715, 1495, 1450, 1246, 1051, 757, 739 cm⁻¹ ; ¹H NMR (300 MHz, CDCl₃) δ 7.75 (d, *J* = 7.5 Hz, 2 H), 7.52 (t, *J* = 7.6 Hz, 2 H), 7.39 (t, *J* = 7.3 Hz, 2 H), 7.3 - 7.2 (m, 3 H), 7.15 (d, *J* = 7.4 Hz, 1 H), 6.90 (q_{app}, *J* ~ 7 Hz, 2 H), 5.70 (d, *J* = 7.2 Hz, 1 H), 4.57 (q, *J* = 6.1 Hz, 1 H), 4.34 (d, *J* = 6.8 Hz, 2 H), 4.18 (t, *J* = 6.8 Hz, 1 H), 3.80 (s, 3 H), 3.2 (m, 2 H) ; ¹³C NMR (CDCl₃) δ 177.0, 157.6, 156.1, 143.9, 143.8, 141.4, 131.4, 128.9, 127.8, 127.1, 125.2, 124.4, 121.0, 120.0, 110.6, 67.1, 55.3, 54.8, 47.1, 32.4 ; MS (EI) 417, 371, 196, 178, 165, 121; HRMS (EI) for C₂₅H₂₃NO₅, calcd 417.1576, found 417.1586. Anal. Calcd. for C₂₅H₂₃NO₅: C, 71.93; H, 5.55; N, 3.36. Found: C, 71.70; H, 5.58; N, 3.13.

***N*-Boc-D-Pipecolic acid (17):** Prepared by the hydrolysis of **11** (267 mg, 0.966 mmol, 1 equiv) following the procedure outlined for **15c** (hydrolysis time: 3 h). After an initial 2-h reaction period at 0 °C in the presence of di-*tert*-butyl dicarbonate (253 mg, 1.16 mmol, 1.2 equiv) and 2 h at 23 °C, additional di-*tert*-butyl dicarbonate (253 mg, 1.16 mmol, 1.2 equiv) was added. After stirring at 23 °C for 6 h, a third portion of di-*tert*-butyl dicarbonate (253 mg, 1.16 mmol, 1.2 equiv) was added. After stirring for 12 h at 23 °C, work-up and isolation were carried out as outlined for **15c**. The product was purified by recrystallization from ether : hexanes (first crop: ca 2:1, 9 mL; second crop: ca 2:1, 3 mL) to afford 171 mg (77%) of analytically pure **17**. The enantiomeric excess of the product was determined by chiral HPLC analysis as described above (Chiralpak WH column (25 cm x 10 mm), 0.05 M CuSO₄, 5 mL/min, 250 nm, major R_t

= 9.3 min, minor R_t = 13.5 min). The product was shown to be 96% ee. IR (neat) 3455, 3122, 2934, 1694, 1394, 1368, 1280, 1253, 1161, 1044, 932, 872; ^1H NMR (1:1 rotamer ratio, CDCl_3) δ 10.89 (s(br), 1H), 4.93 (s(br), 0.5H), 4.78 (s(br), 0.5H), 3.96 (m, 1H), 2.95 (m, 1H), 2.23 (m, 1H), 1.69 (m, 3H), 1.47 (s, 9H), 1.24-1.47 (m, 2H); ^{13}C NMR (CDCl_3) δ 177.9, 156.1, 80.3, 54.6, 53.5, 42.0, 41.0, 28.3, 26.5, 24.7, 24.5, 20.7. Anal. Calcd. for $\text{C}_{11}\text{H}_{19}\text{NO}_4$ C, 57.63; H, 8.35; N, 6.11. Found C, 57.49; H, 8.38; N, 5.86.

***N*-Boc-*N*-Methyl-D-2-aminobutyric acid (18 b):** Prepared by the hydrolysis of **12b** (420 mg, 1.59 mmol, 1.00 equiv) following the procedure outlined for **15b** (hydrolysis time: 10 h). The product, **18b**, was isolated as an analytically pure solid (308 mg, 89%). The enantiomeric excess of the product was determined by chiral HPLC analysis as described above (Chiralpak WH column (25 cm x 10 mm), 1.0 nm CuSO_4 , 5 mL/min, 255 nm, major R_t = 21.7 min, minor R_t = 13.0 min). The product was shown to be 98% ee. Mp. 117-120 °C; IR (neat) 3100, 2977, 1694, 1455, 1393, 1154; ^1H NMR (CDCl_3 , 1:1 mixture of rotamers) δ 10.98 (s(br), 1H), 4.70 (dd, 0.5H, $J=8.8, 4.9$), 4.36 (dd, 0.5H, $J=10.6, 4.8$), 2.86 (s, 1.5H), 2.80 (s, 1.5H), 2.01 (m, 1H), 1.75 (m, 1H), 1.48 (s, 4.5H), 1.45 (s, 4.5H), 0.95 (m, 3H); ^{13}C NMR (CDCl_3) δ 177.1, 177.0, 156.7, 155.8, 80.6, 60.6, 59.1, 30.9, 30.4, 28.2, 22.2, 21.7, 10.8, 10.6. Anal. Calcd. for $\text{C}_{10}\text{H}_{19}\text{NO}_4$ C, 55.28; H, 8.81; N, 6.45. Found C, 55.47; H, 9.24; N, 6.53.

N-Boc-N-Methyl-D-phenylalanine (18f): Prepared by the hydrolysis of **12f** monohydrate (150 mg, 0.435 mmol, 1.00 equiv) following the procedure outlined for **15b** (hydrolysis time: 18 h) with the exception that the reaction was carried out in 2:1 water-methanol (2.7 mL). The product, **18f**, was isolated as an oil (104 mg, 85%). The enantiomeric excess of the product was determined by chiral HPLC analysis as described above (Chiralpak WH column (25 cm x 10 mm), 1.0 nm CuSO₄, 5 mL/min, 255 nm, major R_t = 32.0 min, minor R_t = 12.4 min). The product was shown to be 95% ee. IR (neat) 2977, 1698, 1480, 1455, 1393, 1368, 1329, 1254, 1157, 961, 861, 752, 700; ¹H NMR (CDCl₃, 1:1 rotamer ratio) δ 9.75 (s, 1H), 7.17-7.32 (m, 5H), 4.91 (dd, 0.5H, J=11.0, 5.0), 4.63 (dd, 0.5H, J=10.9, 4.2), 3.33 (m, 1H), 3.05 (m, 1H), 2.76 (s, 1.5H), 2.70 (s, 1.5H), 1.38 (s, 4.5H), 1.33 (s, 4.5H); ¹³C NMR (CDCl₃) δ 176.2, 156.2, 155.0, 137.4, 137.1, 128.9, 128.8, 128.5, 128.4, 126.7, 126.6, 80.7, 80.5, 61.4, 60.1, 35.2, 34.6, 32.5, 28.2, 28.1. Anal. Calcd. for C₁₅H₂₁NO₄ C, 64.50; H, 7.58; N, 5.01. Found C, 64.17; H, 7.59; N, 4.77.

D-2-Aminobutyric acid (19b): Prepared by the hydrolysis of **7b** (1.51 g, 6.03 mmol, 1 equiv) following the procedure outlined for **19c** (hydrolysis time: 10 h) to afford 548 mg (88%) of **19b**. The enantiomeric excess of the product was determined by chiral HPLC analysis as described above (pH 1.5 HClO₄ mobile phase, 0.4 mL/min, 200 nm, major R_t = 4.1 min, minor R_t = 5.2 min). The product was shown to be ≥99% ee. [α]_D²⁰ = -7.71° (c=4.23, H₂O), lit.² -7.86° (c=4, H₂O); ¹H NMR (D₂O) δ 3.58 (t, 1H, J=5.7), 1.76 (m, 2H), 0.84 (t, 3H, J=7.5). Anal. Calcd. for C₄H₉NO₂ C, 46.58; H, 8.81; N, 13.58. Found C, 46.62; H, 9.17; N, 13.45.

D-Leucine (19d): Prepared by the hydrolysis of **7d** (580 mg, 2.08 mmol, 1 equiv) following the procedure outlined for **19c** (hydrolysis time: 12 h) to afford 238 mg (87%) of **19d**. The enantiomeric excess of the product was determined by chiral HPLC analysis as described above (pH 1.5 HClO₄ mobile phase, 0.8 mL/min, 200 nm, major R_t = 5.2 min, minor R_t = 10.6 min). The product was shown to be ≥99% ee. $[\alpha]_D^{20} = +10.7^\circ$ (c=2.01, H₂O), lit.² +11.1° (c=1, H₂O); ¹H NMR (D₂O) δ 3.59 (t, 1H, J=5.4), 1.57 (m, 3H), 0.82 (m, 6H). Anal. Calcd. for C₆H₁₃NO₂ C, 54.94; H, 9.99; N, 10.68. Found C, 54.60; H, 9.84; N, 10.93.

D-Cyclopropylmethylglycine(19e): Prepared by the hydrolysis of **7e** (595 mg, 2.15 mmol, 1 equiv) following the procedure outlined for **19c** (hydrolysis time: 12 h) to afford 219 mg (79%) of **19e** which was pure by elemental analysis but was contaminated with ca. 1% of but contained ca. 1% of 2-amino-5-hexenoic acid. The enantiomeric excess of the product was determined by chiral HPLC analysis as described above (pH 1.5 HClO₄ mobile phase, 0.4 mL/min, 200 nm, major R_t = 7.0 min, minor R_t = 9.5 min). The crude hydrolyzate was shown to be ≥97% ee and the isolated product was shown to be ≥98% ee. $[\alpha]_D^{20} = +7.5^\circ$ (c=0.1, H₂O), lit.³ -12.4° (L-enantiomer, c=0.13, H₂O); ¹H NMR (D₂O) δ 3.76 (t, 1 H, J = 6.0 Hz), 1.75 (t, 2 H, J = 7.0 Hz), 0.7 (m, 1 H), 0.50 (d_{app}, 2 H, J = 7.0 Hz), 0.12 (s_{app}, 2 H). Anal. Calcd. for C₆H₁₁NO₂: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.73; H, 8.74; N, 10.84.

D-Phenylalanine 19f: Prepared by the hydrolysis of **7f** (520 mg, 1.66 mmol, 1 equiv) following the procedure outlined for **19c** (hydrolysis time: 18 h) to afford 212 mg (77%) of **19f**. The enantiomeric excess of the product was determined by chiral HPLC analysis as described above (pH 2.0 HClO₄ mobile phase, 0.8 mL/min, 200 nm, major R_t = 9.5 min, minor R_t = 12.7 min). The crude hydrolyzate was shown to be 98% ee and the isolated product was shown to be ≥99% ee. $[\alpha]_{\text{D}}^{20} = +36.5^{\circ}$ (c=1.02, H₂O), lit.² +34.5° (c=1, H₂O); ¹H NMR (D₂O) δ 7.18-7.33 (m, 5H), 3.86 (dd, 1H, J=7.9, 5.2), 3.16 (dd, 1H, J=14.5, 5.2), 2.99 (dd, 1H, J=14.5, 8.0). Anal. Calcd. for C₉H₁₁NO₂ C, 65.44; H, 6.71; N, 8.48. Found C, 65.23; H, 6.65; N, 8.32.

(S,S)-Pseudoephedrine N-Boc-D-2-aminobutyramide (13b): 2-(*tert*-Butoxycarbonyloxyimino)-2-phenylacetonitrile (153 mg, 0.623 mmol, 1.5 equiv) was added to a solution of **7b** (104 mg, 0.415 mmol, 1 equiv) and triethylamine (29 μL, 0.21 mmol, 0.50 equiv) in a solution of dioxane (1 mL) and water (1 mL) at 23 °C. After stirring the resulting solution at 23 °C for 2 h, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with a gradient of ethyl acetate in hexanes (30→50%) to afford 143 mg (98%) of **13b** as an oil. The product was identical with the material produced by the alkylation of **3** (see procedure above).

(S,S)-Pseudoephedrine N-Boc-D-phenylalaninamide (13f): Prepared by the acylation of **7f** (73 mg, 0.234 mmol, 1 equiv) following the procedure described above for **13b**. Purification of the crude acylation residue by chromatography on silica gel eluting with a gradient of ethyl acetate in hexanes (35→50%) afforded **13f** (85 mg, 88%) as an oil. The product was identical with the material produced by alkylation of **3** (see procedure above).

N-Boc-D-2-Aminobutyric acid (15b): Prepared by the hydrolysis of **13b** (98 mg, 0.280 mmol, 1 equiv), as described above for **15c** (hydrolysis time: 5 h), to afford 54 mg (95%) of **15b** as an oil which was identical to the product prepared by the hydrolysis of **7b**. The product was shown to be 96% ee by chiral HPLC analysis (see **15b** above).

N-Boc-D-Phenylalanine (15f): Prepared by the hydrolysis of **13f** (85 mg, 0.206 mmol, 1 equiv), as described above for **15c** (hydrolysis time: 2.5 h), with the exception that the reaction was conducted with tetrabutylammonium hydroxide (40%, 675 μ L, 1.03 mmol, 5.00 equiv) in 4 mL of water and 2 mL of *tert*-butanol, to afford 53 mg (97%) of **15f** as an oil, which was identical to the product prepared by the hydrolysis of **7f**. The product was shown to be 94% ee by chiral HPLC analysis (see **15f** above).

(S,S)-Pseudoephedrine N-Fmoc-D-phenylalaninamide (21f): 9-Fluorenylmethyl chloroformate (99 mg, 0.384 mmol, 1.20 equiv) was added to a biphasic mixture of **7f** (100 mg, 0.320 mmol, 1 equiv) in dioxane (1 mL) and saturated aqueous sodium bicarbonate solution (1 mL). After stirring vigorously for 2 h at 23 °C, water (10 mL) was added and the resulting mixture was extracted with ethyl acetate (2 x 25 mL). The

combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with a gradient of ethyl acetate in hexanes (40→50%) to afford 165 mg (96%) of **21f** as a viscous oil. IR(neat) 3411, 3295, 3029, 2980, 1713, 1632, 1494, 1451, 1248, 1047, 910, 759, 737, 701; ¹H NMR (3:1 rotamer ratio, * denotes minor rotamer peaks, CDCl₃) δ 7.74 (d, 2H, *J*=7.2), 7.73* (d, 2H, *J*=6.6), 7.58 (t, 2H, *J*=7.7), 7.50* (t, 2H, *J*=6.8), 7.19-7.41 (m, 14H), 5.86 (d, 1H, *J*=8.2), 5.72* (d, 1H, *J*=9.0), 5.03* (m, 1H), 4.84 (m, 1H), 4.07-4.67 (m, 5H), 3.26* (dd, 1H, *J*=13.7, 5.3), 2.89-3.01 (m, 1H), 2.95* (s, 3H), 2.59 (s, 3H), 0.96* (d, 1H, *J*=6.6), 0.78 (d, 3H, *J*=6.9); ¹³C NMR (CDCl₃) δ 173.5, 172.4*, 155.4, 154.8, 141.4, 141.3*, 137.1*, 136.2, 129.5*, 129.3, 128.6*, 128.5*, 128.3, 128.2, 127.7, 126.9*, 126.7, 126.4*, 79.8, 79.2*, 75.4, 75.1*, 58.0*, 56.4, 52.2, 51.1*, 39.3, 38.7*, 30.5, 28.2, 27.2*, 15.4*, 13.9. HRMS Calcd. for C₃₄H₃₅N₂O₄ (M+H) 534.2519. Found 535.2506.

IR Data for Selected Compounds

1 IR (neat, cm⁻¹) 3361, 2981, 1633, 1486, 1454, 1312, 1126, 1049, 926, 760, 703;

2 IR (neat) 3330, 2980, 2884, 2802, 1634, 1453, 1406, 1310, 1110, 1051, 761, 703;

3 IR (neat) 3417, 2978, 2935, 1714, 1644, 1251, 1169, 1051, 763, 703;

7b IR (neat) 3359, 2966, 1634, 1454, 1108, 1051, 762, 703;

7c IR (neat) 3256, 3072, 2978, 1632, 1491, 1453, 1109, 1051, 918, 762, 703;

7f IR (neat) 3357, 3027, 2980, 1625, 1492, 1453, 1050, 1050, 761, 701;

7h IR (neat) 3363, 2952, 2895, 1633, 1454, 1416, 1247, 1112, 1052, 861, 842, 760, 702;

7j IR (neat) 3357, 2964, 1630, 1560, 1456, 1374, 1268, 1156, 1071, 975, 703;

11 IR (neat) 3304, 2933, 1629, 1490, 1452, 1403, 1112, 1052, 899, 761, 732, 702;

12f IR (neat) 3308, 3027, 2975, 1618, 1491, 1452, 1406, 1115, 1028, 701;

13b IR (neat) 3413, 2975, 2934, 1704, 1632, 1494, 1454, 1367, 1249, 1170, 1050, 764, 736, 702;

13c IR (neat) 3141, 3332, 2978, 2934, 1704, 1633, 1494, 1454, 1367, 1251, 1170, 1049, 1022, 918, 763, 702;

15b IR (neat) 3326, 2977, 1714, 1514, 1395, 1369, 1252, 1164;

15f IR (neat) 2979, 1714, 1504, 1455, 1394, 1368, 1252, 1165, 1053, 700;

16c IR (neat) 3408, 3320, 3067, 2952, 1714, 1520, 1450, 1338, 1226, 1052, 925, 759, 740;

21b IR (neat) 3406, 3320, 3063, 2970, 1714, 1632, 1451, 1411, 1264, 1084, 1049, 760, 740, 702;

1. Weis, C. D. *J. Heterocycl. Chem.* **1976**, *13*, 145.

2. "Dictionary of Organic Compounds" 6th ed., Chapman and Hall, London, 1996.

3. Ohta, T.; Nakajima, S.; Sato, Z.; Aoki, T.; Hatanaka, S.; Nozoe, S. *Chem. Lett.* **1986**, 511.