Supplementary Material (ESI) for Chemical Communications

Enantioselective synthesis of β-amino esters and its application to the synthesis of the enantiomers of the antidepressant Venlafaxine

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Supporting Information

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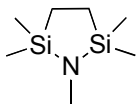
All diazo compounds were synthesized from the corresponding methyl arylacetates by a procedure reported before.[1]



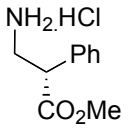
1,2,2,5,5-pentamethyl-1-aza-2,5-disilacyclopentane[2] (**4**) To a solution of methyl amine (2M in THF, 22.3 mL, 44.6 mmol) and triethylamine (13 mL, 93.3 mmol) in DCM (30 mL) at 0 ^{o}C, a solution of 1,2-bis(chlorodimethylsilyl)ethane (10 g, 44.6 mmol) in DCM (20 mL) was added slowly, then the reaction was stirred at room temperature for 2.5 h. Petroleum ether (30 mL) was then added. The inorganic salt was filtered and the filtrate was concentrated. Another portion of petroleum ether (30 mL) was added and the salt was filtered off again. The crude product was purified by distillation at reduced pressure to give 4.77 g product (61%). ^{1}H NMR (500 MHz, acetone-d6) δ 2.47 (s, 3H), 0.70 (s, 4 H), 0.01 (s, 12H).[2] This compound was freshly distilled prior to use in the carbenoid reactions.

Representative procedure of the synthesis of β-amino esters 5a-h:

Method A: 1,2,2,5,5-pentamethyl-1-aza-2,5-disilacyclopentane **4*** (346.8 mg, 2 mmol) and Rh_2(*S*-DOSP)$_4$ (18.8 mg, 1 mol%) were dissolved into degassed 2,2-dimethylbutane (5 mL) and toluene (1 mL). Then methyl aryldiazoacetate **7** (1 mmol) in 2,2-dimethylbutane (10 mL) was added over 2 h via syringe pump at -40 ^{o}C and stirred for 10 min. A second portion of Rh_2(*S*-DOSP)$_4$ (18.8 mg, 1 mol%) was then added. The reaction was warmed slowly to room temperature. The solvent was removed under reduced pressure, then the residue was dissolved into dry ether (4 mL) and HCl solution in ether (1M, 4 mL) was added slowly. The resulted mixture was stirred for 0.5 h, then

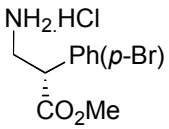
aq. HCl solution (1M, 2 mL) was added. The organic layer was separated and washed with HCl solution (2 x 2 mL). The combined aqueous layers were washed with ether (2 x 2 mL), then basified to pH > 8 with $NaHCO_3$/NaOH followed by the extraction with EtOAc. The combined EtOAc extracts were washed with brine and dried on Na_2SO_4. The solvent was removed and the oil was dissolved into dry ether (3 mL) and treated with HCl/ether (1M, 1 mL) to give the hydrochloride salt of the product as a precipitate.

Method B: 1,2,2,5,5-pentamethyl-1-aza-2,5-disilacyclopentane **4** (173.4 mg, 1 mmol) and Rh_2(*S*-DOSP)$_4$ (37.6 mg, 1 mol%) were dissolved into degassed 2,2-dimethylbutane (5 mL) and toluene (1 mL). Then methyl aryldiazoacetate **7** (2 mmol) in 2,2-dimethylbutane (20 mL) was added over 5 h via syringe pump at 0 ^oC and stirred for another 10 min. A second portion of Rh_2(*S*-DOSP)$_4$ (37.6 mg, 1 mol%) was then added. The reaction was warmed slowly to room temperature. The solvent was removed under reduced pressure, then the residue was dissolved into dry ether (4 mL) and HCl solution in ether (1 M, 4 mL) was added slowly. The resulted mixture was stirred for 0.5 h, then aq. HCl solution (1 M, 2 mL) was added. The organic layer was separated and washed with HCl solution (2 x 2 mL). The combined aqueous layers were washed with ether (2 x 2 mL), then basified to pH > 8 with $NaHCO_3$/NaOH followed by the extraction with EtOAc. The combined organic layers were washed with brine and dried on Na_2SO_4. The solvent was removed and the oil was dissolved into dry ether (3 mL) and treated with HCl/ether (1M, 1 mL) to give the hydrochloride salt of the product as a precipitate.



Methyl 3-amino-2*S*-phenylpropionate hydrochloride (**5a**.HCl) white solid, yield 53%. Mp = 157-160°C; $[\alpha]^{25}_D$ = -106.7° (*c* = 0.36, 95% EtOH); IR (film): 3028, 2952, 1731, 1234, 1006, 705 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 7.47-7.42 (m, 3H), 7.35 (d, *J* = 7.6 Hz, 2H), 4.13 (t, *J* = 7.6 Hz, 1H), 3.72 (s, 3H), 3.65 (dd, *J* = 13.1, 7.3 Hz, 1H), 3.40 (dd, *J* = 13.1, 7.6 Hz, 1H); ^{13}C NMR (75 MHz, D_2O, DSS, DEPT) δ 165.0, 125.8, 121.3(CH), 120.7(CH), 120.0(CH), 44.9(CH_3), 40.2(CH), 32.6(CH_2); HRMS (EI) calcd.for $C_{10}H_{14}O_2N$ (M^+): 180.1019. Found 180.1016.

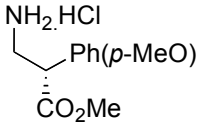
To determine the enantiomeric excess of the above compound, it was converted to its benzyl trifluoroacetamide. A small sample of the salt was dissolved into DCM with PhCHO (1 eq), then $NaHB(OAc)_3$ (3 eq) was added and the reaction was stirred for 8 h. After work-up, the crude product was treated with TFAA in DCM followed by flash chromatography (petroleum ether/ether) to give the amide. ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.23 (m, 8H), 7.10 (d, *J* = 7.0 Hz, 2H), 4.60 (d, *J* = 16.4 Hz, 1H), 4.24-4.21 (m, 1H), 4.08 (d, *J* = 16.4 Hz, 1H), 3.83 (dd, *J* = 13.7, 8.0 Hz, 1H), 3.68 (s, 3H), 3.51 (dd, *J* = 13.8, 7.3 Hz, 1H); ee 97% by HPLC (AD-RH, 1.0 mL/min, 5% isopropanol in hexanes, t_R= 4.4 (major) and 6.4 (minor) min, UV 254nm).



Methyl 3-amino-2*S*-(4-bromophenyl)propionate hydrochloride (**5b.**HCl) white solid, yield 53%. Mp = 182-184°C; $[\alpha]^{25}_D$ = -78.3° (*c* = 0.35, 95% EtOH); IR (film): 2950, 1726,

1223, 823 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 7.60 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 4.12 (t, *J* = 7.3 Hz, 1H), 3.72 (s, 3H), 3.65 (dd, *J* = 13.1, 7.6 Hz, 1H), 3.40 (dd, *J* = 13.2, 7.3 Hz, 1H); ^{13}C NMR (75 MHz, D_2O, DSS) δ 174.8, 135.4, 134.5, 132.1, 124.4, 55.3, 50.0, 42.8; HRMS (ESI) calcd.for $C_{10}H_{13}O_2NBr$ (M^+): 258.0124. Found 258.0123.

To determine the enantiomeric excess of the above compound, it was converted to its benzyl trifluoroacetamide. A small sample of the amine salt was dissolved into DCM with PhCHO (1 eq), then $NaHB(OAc)_3$ (3 eq) was added and the reaction was stirred for 8 h. After work-up, the crude product was treated with TFAA in DCM followed by flash chromatography (petroleum ether/ether) to give the amide. ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.2 Hz, 2H), 7.40-7.34 (m, 3H), 7.18-7.13 (m, 4H), 4.58 (d, *J* = 6.5 Hz, 1H), 4.21 (d, *J* = 6.2 Hz, 1H), 4.17 (t, *J* = 7.6 Hz, 1H), 3.77 (dd, *J* = 13.8, 7.9 Hz, 1H), 3.66 (s, 3H), 3.49 (dd, *J* = 13.7, 7.0 Hz, 1H); ee 94% by HPLC (AD-RH, 1.0 mL/min, 5% isopropanol in hexanes, t_R= 4.9 (major) and 8.2 (minor) min, UV 254nm).

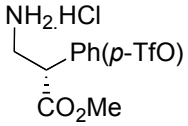


Methyl 3-amino-2*S*-(4-methoxyphenyl)propionate hydrochloride (**5c**.HCl) light yellow solid, yield 62%. Mp = 181-183°C; $[\alpha]^{25}_D$ = -79.6° (*c* = 1.10, 95% EtOH); IR (film): 3014, 2931, 1732, 1514, 1253 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 7.10 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.89 (t, *J* = 7.3 Hz, 1H), 3.63 (s, 3H), 3.52 (s, 3H), 3.43 (dd, *J* = 13.1, 7.6 Hz, 1H), 3.19 (dd, *J* = 13.1, 7.6 Hz, 1H); ^{13}C NMR (75 MHz, D_2O, DSS, DEPT) δ 176.2(C), 161.8(C), 132.3(CH), 129.1(C), 117.6(CH), 58.1(CH_3),

55.8(CH_3), 50.4(CH), 43.6(CH_2); HRMS (ESI) calcd.for $C_{11}H_{16}O_3N$ (M^+): 210.1125. Found 210.1123.

To determine the enantiomeric excess of the above compound, it was converted to its benzyl trifluoroacetamide. A small sample of the amine salt was dissolved into DCM with PhCHO (1 eq), then $NaHB(OAc)_3$ (3 eq) was added and the reaction was stirred for 8 h. After work-up, the crude product was treated with TFAA in DCM followed by flash chromatography (petroleum ether/ether) to give the amide. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.30 (m, 3H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 7.0 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.60 (d, *J* = 16.2 Hz, 1H), 4.17 (t, *J* = 7.6 Hz, 1H), 4.09 (d, *J* = 16.2 Hz, 1H), 3.82-3.79 (m,1H), 3.80 (s, 3H), 3.67 (s, 3H), 3.47 (dd, *J* = 13.4, 7.3 Hz, 1H). ee 93% by HPLC (AD-RH, 1.0 mL/min, 5% isopropanol in hexanes, t_R= 6.7 (major) and 8.7 (minor) min, UV 254nm).

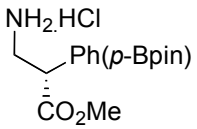
Methyl 3-amino-2*R*-(4-methoxyphenyl)propionate hydrochloride $[\alpha]^{25}_D$ = 82.3° (*c* = 1.41, 95% EtOH);



Methyl 3-amino-2*S*-(4-trifluoromethanesulfonyloxyphenyl)propionate hydrochloride (**5d**.HCl) white solid, yield 63%. Mp = 163-165°C; $[\alpha]^{25}_D$ = -59.4° (*c* = 0.33, 95% EtOH); IR (film): 2875, 1737, 1210, 1134 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 7.41 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 4.23 (dd, *J* = 8.8, 5.8 Hz, 1H), 3.65 (dd, *J* = 13.1, 8.8 Hz, 1H), 3.60 (s, 3H), 3.30 (dd, *J* = 13.1, 5.8 Hz, 1H); ^{13}C NMR (75 MHz,

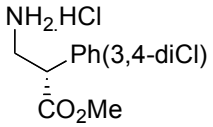
D_2O, DSS) δ 175.6, 152.4, 138.4, 133.5, 125.3, 121.6(CF_3), 56.3, 51.0, 44.1; HRMS (ESI) calcd.for $C_{11}H_{13}O_5NF_3S$ (M^+): 328.0461. Found 328.0465.

To determine the enantiomeric excess of the above compound, it was converted to its benzyl trifluoroacetamide. A small sample of the amine salt was dissolved into DCM with PhCHO (1 eq), then $NaHB(OAc)_3$ (3 eq) was added and the reaction was stirred for 8 h. After work-up, the crude product was treated with TFAA in DCM followed by flash chromatography (petroleum ether/ether) to give the amide. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.24 (m, 7H), 7.13 (d, *J* = 6.7 Hz, 2H), 4.59 (d, *J* = 16.2 Hz, 1H), 4.33 (d, *J* = 16.2 Hz, 1H), 4.25 (dd, *J* = 8.5, 6.4 Hz, 1H), 3.76 (dd, *J* = 13.8, 8.5 Hz, 1H), 3.71 (s, 3H), 3.55 (dd, *J* = 13.7, 6.4 Hz, 1H); ee 85% by HPLC (AD-RH, 1.0 mL/min, 5% isopropanol in hexanes, t_R= 5.5 (major) and 6.8 (minor) min, UV 254nm).



Methyl 3-amino-2*S*-(4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl)propionate hydrochloride (**5e**.HCl) white solid, yield 55%. Mp = 192°C (dec.); $[\alpha]^{25}_D$ = -50.3° (*c* = 0.37, 95% EtOH); IR (film): 2981, 1735, 1361, 1215, 1143, 1090, 859, 833, 659 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 7.79 (d, *J* = 7.9 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 4.16 (t, *J* = 7.3 Hz, 1H), 3.72 (s, 3H), 3.67 (dd, *J* = 13.2, 7.6 Hz, 1H), 3.39 (dd, *J* = 13.2, 7.3 Hz, 1H), 1.19 (s, 12H); ^{13}C NMR (75 MHz, D_2O, DSS) δ 175.8, 139.3, 137.4, 130.5, 78.3, 55.9, 51.2, 43.5, 26.5; HRMS (EI) calcd.for $C_{16}H_{24}O_4N^{10}B$ (M^+-H): 304.1829. Found 304.1825.

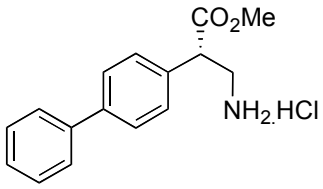
To determine the enantiomeric excess of the above compound, it was converted to its benzyl trifluoroacetamide. A small sample of the amine salt was dissolved into DCM with PhCHO (1 eq), then $NaHB(OAc)_3$ (3 eq) was added and the reaction was stirred for 8 h. After work-up, the crude product was treated with TFAA in DCM followed by flash chromatography (petroleum ether/ether) to give the amide. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.3 Hz, 2H), 7.36 – 7.24 (m, 5H), 7.08 (d, *J* = 7.3 Hz, 2H), 4.60 (d, *J* = 16.3 Hz, 1 H), 4.24 (t, *J* = 7.7 Hz, 1 H), 3.98 (d, *J* = 16.3 Hz, 1 H), 3.88 (dd, *J* = 13.4, 6.2 Hz, 1 H), 3.66 (s, 3 H), 3.48 (dd, *J* = 13.4, 7.7 Hz, 1 H), 1.34 (s, 12H); ee 71% by HPLC (AD-RH, 1.0 mL/min, 5% isopropanol in hexanes, t_R= 4.6 (major) and 8.9 (minor) min, UV 254nm).



Methyl 3-amino-2*S*-(3,4-dichlorophenyl)propionate hydrochloride (**5f**.HCl) white solid, yield 30%. Mp = 125-128°C; $[\alpha]^{25}_D$ = -81.6° (*c* = 0.38, 95% EtOH); IR (film): 2954, 2876, 1719, 1253, 1229, 1030, 872, 833 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 7.51 (d, *J* = 2.0 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.24 (dd, *J* = 8.2, 2.0 Hz, 1H), 4.15 (t, *J* = 7.3 Hz, 1H), 3.72 (s, 3H), 3.67 (dd, *J* = 13.3, 8.2 Hz, 1H), 3.39 (dd, *J* = 13.3, 7.0 Hz, 1H); ^{13}C NMR (75 MHz, D_2O, DSS) δ 174.7, 136.8, 134.9, 134.6, 133.6, 132.5, 130.4, 55.7, 50.0, 43.0; HRMS (EI) calcd.for $C_{10}H_{11}O_2NCl_2$ (M^+-H): 247.0161. Found 247.0164.

To determine the enantiomeric excess of the above compound, it was converted to its benzyl trifluoroacetamide. A small sample of the amine salt was dissolved into DCM with PhCHO (1 eq), then $NaHB(OAc)_3$ (3 eq) was added and the reaction was stirred for

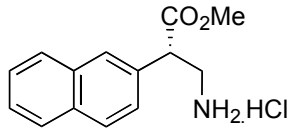
8 h. After work-up, the crude product was treated with TFAA in DCM followed by flash chromatography (petroleum ether/ether) to give the amide. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.2 Hz, 1H), 7.40 – 7.34 (m, 4H), 7.14 (d, *J* = 7.0 Hz, 2H), 7.08 (dd, *J* = 8.2, 2.1 Hz, 1H), 4.61 (d, *J* = 16.2 Hz, 1 H), 4.34 (d, *J* = 16.2 Hz, 1 H), 4.18 (dd, *J* = 8.4, 6.5 Hz, 1 H), 3.88 (dd, *J* = 13.6, 8.4 Hz, 1 H), 3.66 (s, 3 H), 3.48 (dd, *J* = 13.6, 6.5 Hz, 1 H), 1.34 (s, 12H); ee 65% by HPLC (AD-RH, 1.0 mL/min, 5% isopropanol in hexanes, t_R= 8.1 (major) and 9.2 (minor) min, UV 254nm).



Methyl 3-amino-2*S*-(4-biphenyl)propionate hydrochloride (**5g**.HCl) light yellow solid, yield 54%. Mp = 215-219°C; $[\alpha]^{25}_D$ = -84.6° (*c* = 0.35, 95% EtOH); IR (film): 2954, 2875, 1726, 1488, 1264, 1248, 1012, 836, 757 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 7.67 (d, *J* = 7.9 Hz, 2H), 7.63 (d, *J* = 7.6 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.40 -7.34 (m, 3H), 4.19 (t, *J* = 7.5 Hz, 1H), 3.73 (s, 3H), 3.68 (dd, *J* = 13.1, 8.3 Hz), 3.38 (dd, *J* = 13.1, 6.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO, DSS) δ 171.4, 139.9, 139.5, 134.6, 129.0, 128.6, 127.6, 127.3, 126.6, 52.4, 47.9, 40.6; HRMS (ESI) calcd.for $C_{16}H_{18}O_2N$ (M^+): 256.1332. Found 256.1330.

To determine the enantiomeric excess of the above compound, it was converted to its benzyl trifluoroacetamide. A small sample of the amine salt was dissolved into DCM with PhCHO (1 eq), then $NaHB(OAc)_3$ (3 eq) was added and the reaction was stirred for 8 h. After work-up, the crude product was treated with TFAA in DCM followed by flash chromatography (petroleum ether/ether) to give the amide. ^{1}H NMR (500 MHz, $CDCl_3$) δ

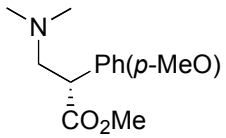
7.58 (d, *J* = 7.9 Hz, 4H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.37 – 7.32 (m, 6H), 7.12 (d, *J* =7.0 Hz, 2H), 7.36 – 7.24 (m, 5H), 7.08 (d, *J* = 7.3 Hz, 2H), 4.64 (d, *J* = 16.5 Hz, 1 H), 4.28 (t, *J* = 7.3 Hz, 1 H), 4.20 (d, *J* = 16.5 Hz, 1 H), 3.86 (dd, *J* = 13.7, 8.0 Hz, 1 H), 3.71 (s, 3 H), 3.56 (dd, *J* = 13.7, 7.0 Hz, 1 H); ee 95% by HPLC (AD-RH, 1.0 mL/min, 5% isopropanol in hexanes, t_R= 6.4 (major) and 8.2 (minor) min, UV 254nm).



Methyl 3-amino-2*S*-(2-naphthyl)propionate hydrochloride (**5h**.HCl) light yellow soild, yield 75%. Mp = 152-156°C; $[\alpha]^{25}_D$ = -101.6° (*c* = 0.49, 95% EtOH); IR (film) 2954, 1732, 1248, 1216, 1168, 1003, 822, 748 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 7.77 - 7.71 (m, 4H), 7.43 - 7.38 (m, 2H), 7.30 (d, *J* = 8.5 Hz, 1H), 4.23 (t, *J* = 7.6 Hz, 1H), 3.66 (dd, *J* = 13.1, 7.7 Hz, 1H), 3.61 (s, 3H), 3.39 (dd, *J* = 13.1, 7.3 Hz, 1H); ^{13}C NMR (75 MHz, D_2O, DSS) δ 175.9, 135.8, 135.5, 134.3, 132.1, 130.5, 130.4, 129.64, 129.60, 128.0, 55.8, 51.4, 43.6; HRMS (EI) calcd.for $C_{14}H_{15}O_2N$ (M^+-H): 229.1097. Found: 229.1099.

To determine the enantiomeric excess of the above compound, it was converted to its benzyl trifluoroacetamide. A small sample of the amine salt was dissolved into DCM with PhCHO (1 eq), then $NaHB(OAc)_3$ (3 eq) was added and the reaction was stirred for 8 h. After work-up, the crude product was treated with TFAA in DCM followed by flash chromatography (petroleum ether/ether) to give the amide. ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 - 7.83 (m, 3 H), 7.73 (s, 1 H), 7.56 - 7.52 (m, 2 H), 7.42 - 7.32 (m, 4 H), 7.16 - 7.11 (m, 2 H), 4.62 (d, *J* = 16.0 Hz, 1 H), 4.44 (t, *J* = 7.5 Hz, 1 H), 4.10 (d, *J* = 16.0 Hz, 1 H), 3.97 (dd, *J* = 6.1, 13.7 Hz, 1 H), 3.72 (s, 3 H), 3.64 (dd, *J* = 13.8, 7.5 Hz, 1 H); ee 80% by

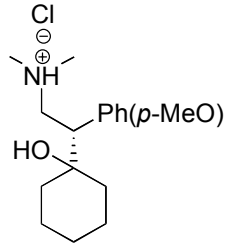
HPLC (AD-RH, 1.0 mL/min, 5% isopropanol in hexanes, t_R= 4.4 (major) and 5.8 (minor) min, UV 254nm).



Methyl 3-N,N-dimethylamino-2*S*-(4-methoxyphenyl)propionate (*S*-**8**) **5c**.HCl (491 mg, 2 mmol) was dissolved into DCM (25 mL) with formaldehyde (37%, 486 mg, 6 mmol) at room temperature followed by a spatula of $MgSO_4$ to remove the water, then sodium triacetoxyborohydride (1.846 g, 8 mmol) was added. The solution was stirred overnight, then quenched with sat. $NaHCO_3$ solution. The solution was acidified with HCl (1M, 10 mL) and the organic layer was extracted with HCl (1M, 3 x 10 mL). The combined aqueous layers were extracted with ether (3 x 10 mL). Then sat. $NaHCO_3$ sloution was used to neutralize the solution to PH > 8. Then the solution was extracted with EtOAc (4x10 mL). The combined organic layers were washed with brine and dried on $MgSO_4$. The product was pure enough for further use without additionalpurification, 393 mg (82%). Mp = 41-43°C; $[\alpha]^{25}_D$ = -34.7° ($CHCl_3$, *c* = 1.69); IR (film): 2950, 2821, 2770, 1735, 1512, 1247, 1034 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 3.78-3.73 (m, 1H), 3.76 (s, 3H), 3.65 (s, 3H), 3.09 (dd, *J* = 12.2, 10.1Hz, 1H), 2.41 (dd, *J* = 12.2, 5.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 173.8(C), 158.9(C), 129.4(C), 128.9(CH), 114.0(CH), 62.9(CH_2), 55.2(CH_3), 51.9(CH_3), 49.3(CH), 45.6(CH_3); HRMS (MH^+, ESI) calcd.for $C_{13}H_{20}O_3N$: 238.1438. Found 238.1437.

Methyl 3-N,N-dimethylamino-2*R*-(4-methoxyphenyl)propionate (*R*-8) yield 78%.

$[\alpha]^{25}_{D} = 35.6°$ (*c* = 1.1, $CHCl_3$).



(+)-Venlafaxine (*S*-6).HCl salt Magnesium turnings (960 mg, 40mmol) was added to ether (50 mL), then 1,5-dibromopentane (3.45 g, 15 mmol) was added and the mixture was heated to reflux for 2h until most of the Magnesium was consumed, then to ether (120 mL) the solution of methyl 3-N,N-dimethylamino-2*S*-(2-bromo-4-methoxyphenyl)-propionate (200 mg, 0.84 mmol) in ether (10 mL) and the Grignard reagent (separated from the ether layer) were added simultaneously over 0.5 h at 0 ^{o}C, and stirred at room temperature overnight. Then hydrochloric acid solution (1M, 15 mL) was added to quench the reaction. The organic layer was separated and extracted with hydrochloric acid solution (1M, 2 x 15 mL). The combined aqueous layers were then extracted with ether (2 x 15 mL). Then sat. $NaHCO_3$ solution was used to neutralize the aqueous solution to pH > 8. The solution was again extracted with EtOAc (4 x 50 mL), and the combined organic layers were washed with brine and dried on $MgSO_4$. The solvent was removed and the residue was treated with HCl in ether (1M, 5 mL). The salt was washed with ether to give the title compound as the HCl salt (194 mg, slightly impure). The crude product (100 mg) was further purified by recrystallization from ethyl acetate to give 69 mg pure product as white crystals, 49% overall yield . Mp = 223-225 ^{o}C (lit.[3] mp = 224-226^{o}C); $[\alpha]^{25}_{D} = -4.3°$ (*c* = 1.07, EtOH), lit $[\alpha]^{25}_{D} = -4.7°$ (*c* = 0.945, EtOH)[4]; IR (film): 2935, 2857, 2832, 1513, 1248, 1180, 1037 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.79 (br,

1H), 7.13 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.04 (dd, *J* = 12.5, 3.3 Hz, 1H), 3.81 (s, 3H), 3.39 (t, *J* = 4.9 Hz, 1H), 3.15-3.10 (m, 1H), 2.82 (d, *J* = 4.9 Hz, 3H), 2.59 (d, *J* = 4.9 Hz, 3H), 1.73-0.89 (m, 10H); ^{13}C NMR (DEPT, 75 MHz, $CDCl_3$) δ 158.8 (C), 131.2 (C), 130.1 (CH), 114.0 (CH), 73.5 (C), 60.3 (CH_2), 55.2 (CH_3), 52.4 (CH), 45.0 (CH_3), 42.6 (CH_3), 36.6 (CH_2), 31.4 (CH_2), 25.3 (CH_2), 21.5 (CH_2), 21.1 (CH_2); HRMS (EI, free amine) calcd.for $C_{17}H_{27}O_2N$ (M^+): 277.2036. Found 277.2036; ee > 99% by HPLC (AD-H, 0.4 mL/min, 3% isopropanol in hexanes, 0.1% TEA, t_R= 16.2 (major), UV 274nm).

(-)-Venlafaxine (*R*-6).HCl salt 41% yield after recrystallization, $[\alpha]^{25}_D$ = 3.4° (*c* = 0.99, EtOH).

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