Asymmetric Synthesis of *syn*-(2*R*,3*S*)- and *anti*-(2*S*,3*S*)-Ethyl Diamino-3-phenylpropanoates from *N*-(Benzylidene)-*p*-toluenesulfinamide and Glycine Enolates

Franklin A. Davis* and Jianghe Deng
Department of Chemistry, Temple University, Philadelphia, PA 19122
fdavis@temple.edu

General Procedures. Column chromatography was performed on silica gel, Merck grade 60 (230-400 mesh). TLC plates were visualized with UV, in an iodine chamber, or with phosphomolybdic acid, unless otherwise noted. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. Ethyl (dibenzylamino)acetate (**1**)[1] and (*S*)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide (**2**)[2] were prepared according to literature procedures.

(S_S,2*R*,3*S*)-(+)-Ethyl-2-(*N*,*N*-dibenzylamino)-3-*N*-(*p*-toluenesulfinyl)amino-3-phenylpropanoate (3). In a 50-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed ethyl (dibenzylamino)acetate (**1**) (0.810 g, 2.86 mmol), THF (20 mL), and LDA (1.91 mL, 1.5 M in cyclohexane from Aldrich) was added dropwise at -78ºC. The yellow-orange solution was stirred at this temperature for 60 min and (+)-**2** (0.139 g, 0.57 mmol) in THF (5 mL, cooled to -78ºC) was added dropwise via a double-ended needle. The reaction mixture was stirred for 30 minutes, quenched by addition of sat. aq. NH_4Cl (8 mL), and slowly warmed to rt. The aqueous phase was extracted with EtOAc (3 X 10 mL) and the combined organic phases were washed with brine, dried (Na_2SO_4), and then concentrated. Chromatography (10% EtOAc/hexane) afforded 0.206 g (68%) of an oil; $[\alpha]^{20}_D$ = +86.0 (*c* 0.5, $CHCl_3$); IR (neat): 3229, 3030, 1734, 1093 cm^{-1}; ^{1}H NMR ($CHCl_3$) δ 1.05 (t, *J* = 9.0 Hz, 3H), 2.40 (s, 3H), 3.22 (d, *J* = 16.5 Hz, 2H), 3.37 (d, *J* = 14.0 Hz, 1H), 3.96 (m, 4H), 4.85 (d, *J* = 14.0 Hz, 1H), 5.38 (s, 1H), 7.18 (m, 15H), 7.26 (d, *J* = 10.0 Hz, 2 H), 7.44 (d, *J* = 10.0 Hz, 2 H); ^{13}C NMR δ 14.6, 21.8, 54.3, 54.5, 60.7, 66.4, 125.4, 127.6, 128.5, 128.6, 128.68, 128.69, 129.5, 129.7, 129.9, 138.1, 138.3, 141.4, 143.5, 168.7. HRMS calcd. for $C_{32}H_{34}N_2O_3SNa$ (M + Na): 549.2188. Found: 549.2181.

(2*R*,3*S*)-(-)-Ethyl-2,3-diamino-3-phenylpropanoate (4). In a 10-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed ethanol (5 mL) and (+)-**3** (0.112 g, 0.21 mmol), and TFA (0.082 ml, 1.06 mmol) was added at 0ºC. The reaction mixture was stirred for 2 h at rt and concentrated. The solution was passed through a short pad of silica gel and the silica gel was eluted 20% EtOAc/hexane (100 mL) to remove the sulfinyl by-product, with MeOH (30 mL), and the filtrate concentrated. The residue was dissolved in DCM (10 mL) and sat. aq $NaHCO_3$ solution was used to adjust the pH to ~7. The organic phase was separated, dried (Na_2SO_4), and concentrated in a 25-mL, two-necked, round-bottomed flask. To the flask, equipped with a magnetic stirring bar and rubber septum, was added EtOH (5 mL), cat. $Pd(OH)_2$, and the solution was placed under a balloon atmosphere of H_2. The reaction mixture was stirred for 12 h at rt, the solution filter through Celite, and concentrated. Chromatography (100:10:1 DCM/MeOH/NH_4OH) afforded 0.027g (61%) of an oil; $[\alpha]^{20}_D$ = -25.3 (*c* 1.1, $CHCl_3$); IR (neat): 3316, 3243, 1712, 1107 cm^{-1}; ^{1}H NMR

($CHCl_3$) δ 1.42 (t, J = 7.0 Hz, 3H), 1.81 (bs, 4H), 3.62 (d, J = 5.5 Hz, 1H), 4.08 (m, 2H), 4.24 (d, J = 5.5 Hz, 1H), 7.25 (m, 1H), 7.32 (m, 4H); ^{13}C NMR δ 14.3, 58.7, 61.1, 61.2, 127.1, 127.7, 128.7, 142.6, 174.2. HRMS calcd. for $C_{11}H_{17}N_2O_2$(M + H): 209.1290. Found: 209.1291.

(S_S,2*S*,3*S*)-(-)-Ethyl-2-*N*-(diphenylmethyleneamino)-3-*N*-(*p*-toluenesulfinyl)-amino-3-phenylpropanoate (6). In a 50-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed *N*-(diphenylmethylene)glycine ethyl ester (**5**) (0.398 g, 1.46 mmol), in THF (16 mL). The solution was cooled to -78ºC and LDA (0.97 mL, 1.5 M in cyclohexane from Aldrich) was added dropwise. The yellow-orange solution was stirred for 60 min at this temperature and (+)-**2** (0.222 g, 0.91 mmol) in THF (5 mL) at -78ºC was added dropwise via a double-end needle. The reaction mixture was stirred for 20 min, quenched by addition of sat. aq. NH_4Cl (5 mL), and slowly warmed to rt. The aqueous phase was separated, and extracted with EtOAc (3 X 8 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. Chromatography (15% EtOAc/hexane) afforded 0.41 g (89%) of an oil; $[\alpha]^{20}_D$ = -63.0 (*c* 1.1, $CHCl_3$); IR (neat): 3276, 3058, 1733, 1093 cm^{-1}; ^{1}H NMR ($CHCl_3$) δ 1.13 (t, J = 7.0 Hz, 3H), 2.37 (s, 3H), 4.06 (m, 2H), 4.39 (d, J = 7.0 Hz, 1H), 5.00 (t, J = 6.0 Hz 1H), 5.33 (d, J = 7.0 Hz, 1H), 6.88 (d, J = 6.5 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 7.25-7.42 (m, 11H), 7.60 (m, 4H); ^{13}C NMR δ 14.4, 21.8, 60.9, 61.7, 70.6, 125.9, 128.2, 128.4, 128.6, 128.8, 129.0, 129.2, 129.3, 129.9, 131.0, 136.2, 138.9, 139.6, 141.7, 142.8, 170.5, 172.8 (one carbon missing due to the overlap in the aromatic region). HRMS calcd. for $C_{31}H_{30}N_2O_3SNa$ (M + Na): 533.1874. Found: 533.1881.

(2*S*,3*S*)-(+)-Ethyl-2,3-diamino-3-phenylpropanoate (7). In a 50-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed EtOH (5 mL), (-)-**6** (0.080 g, 0.15 mmol), and TFA (0.120 mL, 1.5 mmol). The reaction mixture was stirred for 12 h at rt and concentrated. The residue was dissolved in DCM (10 mL), and sat. aq $NaHCO_3$ solution was used to adjust the pH to ~7. The organic phase was separated, dried (Na_2SO_4), and concentrated. Chromatography (100:10:1 DCM/MeOH/NH_4OH) afforded 0.025 g (80%) of an oil; $[\alpha]^{20}_D$ = +22.7 (*c* 0.65, $CHCl_3$); IR (neat): 3374, 3300, 2925, 1734, 1206 cm^{-1}; ^{1}H NMR ($CHCl_3$) δ 1.23 (t, J = 7.0 Hz, 3H), 3.69 (d, J = 5.5 Hz, 1H), 4.14 (q, J = 7.0 Hz, 2H), 4.26 (d, J = 5.5 Hz, 1H), 7.29 (m, 5H); ^{13}C NMR δ 14.8, 59.2, 61.2, 61.6, 127.7, 128.4, 129.1,142.0, 174.5.

(4*R*,5*S*)-(-)-Ethyl-2-oxo-5-phenylimidazolidine-4-carboxylate (9). In a 10-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed DCM (5 mL), (-)-**4** (0.026 g, 0.12 mmol), and 1,1-carbonyldiimidazole (**8**) (0.024 g, 0.15 mmol). The reaction mixture was refluxed for 4 h, cooled to rt, washed with 5% HCl solution, H_2O (2 mL), dried (Na_2SO_4), and concentrated. Chromatography (90% EtOAc/hexane) afforded 0.020 g (67%) of a white solid mp 129-130 ºC; $[\alpha]^{20}_D$ = -99.5 (*c* 0.63, MeOH); IR (neat): 3157, 2915, 1754, 1124 cm^{-1}; ^{1}H NMR (CD_3OD) δ 1.34 (t, J = 7.0 Hz, 3H), 4.10 (d, J = 5.1 Hz, 1H), 4.28 (m, 2H), 4.90 (d, J = 5.1 Hz, 1H), 5.40 (m, 5H); ^{13}C NMR δ 13.3, 59.4, 61.7, 62.8, 125.9, 128.2, 128.8, 142.0, 161.8, 171.6. HRMS calcd. for $C_{12}H_{15}N_2O_3$ (M + H): 235.1083. Found: 235.1087.

(4*S*,5*S*)-(+)-Ethyl-2-oxo-5-phenylimidazolidine-4-carboxylate (10). The general procedure of the preparation of (-)-**9** was followed. Chromatography (90%

EtOAc/hexane) afforded 0.010 g (63%) of a white solid mp 136.5-137.5 ºC; $[\alpha]^{20}_{D}$ = +82.9 (*c* 0.24, MeOH); IR (neat): 3143, 2928, 1745, 1103 cm^{-1}; ^{1}H NMR (CD_3OD) δ 0.82 (t, *J* = 7.0 Hz, 3H), 3.57 (m, 1H), 3.77 (m, 1H), 4.67 (d, *J* = 9.6 Hz, 1 H), 5.23 (d, *J* = 9.6 Hz, 1 H), 7.38 (m, 5H); ^{13}C NMR δ 170.6, 165.2, 138.2, 128.7, 128.5, 127.7, 61.2, 60.7, 59.3, 13.1.

(4*R*,5*S*)-(-)-4-(Hydroxymethyl)-5-phenylimidazolidin-2-one (11). In a 10-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed THF (2 mL), H_2O (1 mL), and (-)-**9** (0.018mg, 0.077 mmol). To the solution was added $NaBH_4$ (0.029 g, 0.77 mmol) and the reaction mixture was stirred for 4 h. At this time the solution was diluted with EtOAc (8 mL), washed with brine (4 mL), dried (Na_2SO_4), and concentrated. Chromatography (5% MeOH/DCM) afforded 0.011g (74%) of an oil; $[\alpha]^{20}_{D}$ = -28.9 (*c* 0.43, CH_3OH) [lit.[3] $[\alpha]^{20}_{D}$ = -30.8 (*c* 0.92, CH_3OH)]; ^{1}H NMR (CD_3OD) δ 3.67 (m, 3H), 4.68 (d, *J* = 4.8 Hz, 1H), 7.40 (m, 5H); ^{13}C NMR δ 58.4, 63.0, 63.4, 125.8, 127.6, 128.5, 142.5, 164.2. Spectral properties were consistent with literature values.[3]

(4*S*,5*S*)-(+)-4-(Hydroxymethyl)-5-phenylimidazolidin-2-one (12). Chromatography (5% MeOH/DCM) afforded 0.005 g (76%) of an oil; $[\alpha]^{20}_{D}$ = +100.9 (*c* 0.12, CH_3OH) [lit.[3] $[\alpha]^{20}_{D}$ = -99.9 (*c* 0.73, CH_3OH) of the enantiomer of **12**]. ^{1}H NMR (CD_3OD) δ 3.11 (m, 2H), 4.15 (m, 1H), 5.06 (d, *J* = 9.0 Hz, 1H), 7.40 (m, 5H); ^{13}C NMR δ 58.0, 58.1, 62.2, 126.7, 127.8, 128.1, 137.7, 165.1 Spectral properties were consistent with literature values.[3]

References

1) Scolasstico, C.; Conca, E.; Prati, L. *Synthesis* **1985**, 850.
2) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang. T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403.
3) Rossi, F. M.; Powers, E. T.; Yoon, R.; Rosenberg, L.; Meinwald, J. *Tetrahedron* **1996**, *52*, 10279.