Asymmetric Synthesis of *syn*-α-Substituted β-Amino ketones using Sulfinimines and Prochiral Weinreb Amide Enolates.

Franklin A. Davis and Minsoo Song
Department of Chemistry, Temple University
Philadelphia, PA 19122
fdavis@temple.edu

General Information: All reagents were used as received unless otherwise noted. Tetrahydrofuran (THF), diethyl ether, dichloromethane, and toluene were purified by filtration on a GlassContour Seca solvent purification system. Unless otherwise mentioned, all reactions were carried under argon atmosphere. 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 on a Bruker 400 and a Varian 300 MHz NMR spectrometer. Sulfinimines were prepared by condensing the appropriate aldehyde with (*S*)-(+)-*tert*-butanesulfinamide (TB),[1] (*S*)-(+)-2,4,6-trimethylphenylsulfinamide (TMP),[2,3] and (*S*)-(+)-2,4,6-triisopropylphenylsulfinamide (TIPP).[3]

Typical procedure for the preparation of sulfinimines.[4] (*S*)-(+)-*N*-(propylidene)-2,4,6-trimethylbenzenesulfinamide (6a). In a 15 mL, flame-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, and rubber septum was placed (*S*)-(+)-2,4,6-trimethylphenylsulfinamide[2] (0.04 g, 0.219 mmol), propionaldehyde (0.024 mL, 0.329 mmol) in CH_2Cl_2 (6 mL). To the mixture was addedTi(OEt)$_4$ (0.224 mL, 1.095 mmol) at 0 °C, and the reaction mixture was stirred for 1 h under argon. At this time the reaction was quenched with water (5 mL), filtered through a Celite and washed the Celite with CH_2Cl_2 (100 mL). The combined organic layers were concentrated and flash chromatography (20% Et_2O/hexane) provided 0.046 g (94%) of a colorless oil; $[\alpha]^{20}_D$ +138.0 (*c* 1.7, $CHCl_3$); IR (KBr) 3144, 2972, 1086 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.24 (t, *J* = 4.7 Hz, 1H), 6.77 (s, 2H), 2.48 (dq, *J* = 4.8, 7.5 Hz, 2H), 2.39 (s, 6H), 2.20 (s, 3H), 1.11 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.2, 142.0, 138.6, 135.7, 131.2, 29.7, 21.4, 19.1, 10.1. HRMS calcd for $C_{12}H_{18}NOS$ (M+H) 224.33448. Found 224.1110.

(*S*)-(+)-*N*-(Benzylidene)-2,4,6-trimethylbenzenesulfinamide (6b). Chromatography (10% Et_2O/hexanes) gave 0.1 g (60%) of a colorless oil; $[\alpha]^{20}_D$ +103.2 (*c* 1.2, $CHCl_3$); IR (KBr) 3025, 2968, 2919, 1091 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.76 (s, 1H), 7.77 (m, 2H), 7.41 (m, 3H), 6.78 (s, 2H), 2.43 (s, 6H), 2.2 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 162.0, 142.0, 138.8, 135.8, 134.3, 132.8, 131.2, 129.9, 129.3, 21.4, 19.2. HRMS calcd for $C_{22}H_{18}NOS$ (M+H) 272.37728. Found 272.1108.

(*S*)-(+)-*N*-Propylidene-2,4,6-triisopropylbenzenesulfinami-de (7a). Flash chromatography (20% Et_2O/hexane) provided 0.052 g (85%) of a colorless oil; $[\alpha]^{20}_D$ +237.6 (*c* 1.0, $CHCl_3$); IR (KBr) 2963, 2870, 1083 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.27 (t, *J* = 4.8 Hz, 1H), 7.0 (s, 2H), 3.70 (pentet, *J* = 6.9 Hz, 2H), 2.82 (pentet, *J* = 6.9 Hz, 1H), 2.49 (dq, *J* = 4.8, 7.3 Hz, 2H), 1.09 – 1.23 (m, 21H); ^{13}C NMR ($CDCl_3$) δ 169.0, 153.0, 150.0,

135.0, 123.3(2C), 34.9, 30.0, 28.1, 24.7, 24.3, 24.1, 9.9. HRMS calcd for $C_{18}H_{30}NOS$ (M+H) 308.20481. Found 308.2046.

(*S*)-(+)-*N*-(Benzylidene)-2,4,6-triisopropylbenzenesulfinamide (7b). Flash chromatography (10% Et_2O/hexane) provided 0.179 g (77%) of a colorless oil; $[\alpha]^{20}_D$ +58.7 (*c* = 1.0, $CHCl_3$); IR (KBr) 2961, 2870, 1087 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.89 (s, 1H), 7.89 (m, 2H), 7.50 (m, 3H), 7.12 (s, 2H), 3.89 (pentet, *J* = 6.8 Hz, 2H), 2.92 (pentet, *J* = 6.9 Hz, 1H), 1.33 (d, *J* = 6.9 Hz, 3H), 1.28 (d, *J* = 6.7 Hz, 3H), 1.18 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 161.5, 153.0, 150.0, 134.9, 134.6, 132.5, 129.5, 129.1, 123.2, 34.6, 28.2, 24.6, 24.2, 24.0. HRMS calcd for $C_{22}H_{30}NOS$ (M+H) 356.204812. Found 356.2062.

Typical procedure for the preparation of *N*-sulfinyl α-alkyl β-amino Weinreb amides. (S_S,2*R*,3*R*)-(+)-*N*-methoxy-*N*-2-dimethyl-3-(*p*-toluenesulfinylamino)-3-phenylpropanamide (9). In a 15 mL, flame-dried, single-neck round-bottomed flask equipped with a magnetic stirring bar, and rubber septum was placed LiHMDS (0.34 mL, 0.338 mmol, 1.0 M solution in THF) under argon. A solution of *N*-methoxy-*N*-methylpropylamide (0.04 g, 0.338 mmol) in THF (0.7 mL) was added at -78 °C via cannula, and the solution was stirred for 2 h at this temperature. To the reaction mixture was added a solution of (*S*)-(+)-**4a** (0.041 g, 0.169 mmol) in THF (1.0 mL) and the reaction was monitored for completion by TLC (typically less than 30 min). At this time the reaction mixture was quenched with sat. aqueous NH_4Cl (1 mL) at -78 °C, warmed to rt, and extracted with EtOAc (2 x 10 mL). The combined organic phases were washed with brine (2 x 5 mL), dried ($MgSO_4$), and concentrated. Chromatography (50% EtOAc/hexanes) gave 0.077 g (99%) of a colorless oil as an inseparable mixture of diastereomers in a ratio of 87:13:1:<0.5 based on crude ^1H NMR. $[\alpha]^{20}_D$ + 91.9 (*c* 6.0, $CHCl_3$); ^1H NMR ($CDCl_3$) major compound δ 7.54 (m, 2H), 7.19 – 7.4 (m, 7H), 5.13 (d, *J* = 3.2 Hz, 1H), 4.74 (m, 1H), 3.53 (s, 3H), 3.2 (m, 1H), 3.02 (s, 3H), 2.34 (s, 3H), 1.04 (d, *J* = 7.2 Hz, 3H); minor compound δ 7.49 (m, 2H), 7.0-7.4 (m, 7H), 5.92 (bd, *J* = 6.8 Hz, 1H), 4.42 (t, *J* = 6.4 Hz, 1H), 3.0 (s, 3H), 2.97 (m, 1H), 2.24 (s, 3H), 1.12 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) major isomer δ 175.7, 143.2, 141.7, 140.2, 129.9, 128.8, 128.5, 125.6, 61.9, 59.1, 41.4, 32.4, 21.7, 12.2. Minor compound δ 142.2, 141.4, 129.7, 129.5, 127.6, 127.58, 126.0, 62.0, 58.7, 41.6, 21.6, 16.5. HRMS calcd for $C_{19}H_{25}N_2O_3S$ (M+H) 361.1586. Found 361.1584.

(S_S,2*R*,3*S*)-(+)-*N*-Methoxy-*N*,2-dimethyl-3-(*p*-toluenesulfinylamino)-3-pentanamide (10). Chromatography (50% Et_2O/hexanes) provided 0.056 g (78%) of product as a colorless oil as an inseparable mixture of diastereomers in a ratio of 83:10:4:3; $[\alpha]^{20}_D$ +126.8 (*c* 0.933, $CHCl_3$); IR (KBr) 3236, 2968, 1654 cm^{-1}; ^1H NMR ($CDCl_3$) major compound δ 7.52 (m, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 4.41 (d, *J* = 7.2 Hz, 1H), 3.60 (s, 3H), 3.35 (m, 1H), 3.06 (s, 3H), 2.33 (s, 3H), 1.75 (m, 1H), 1.58 (m, 2H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3Hz); ^{13}C NMR ($CDCl_3$). Major compound δ 176.8, 143.9, 142.1, 130.5, 126.5, 62.4, 60.0, 38.8, 33.1, 26.9, 22.3, 14.0, 11.8. HRMS calcd for $C_{15}H_{25}N_2O_3S$ (M+H) 313.15860. Found 313.1587.

(S_S,2*R*,3*R*)-(+)-*N*-methoxy-*N*,2-dimethyl-3-(2,4,6-trimethylphenylsulfinyl-

amino)-3-phenylpropanamide (11) Chromatography (50% Et_2O/hexanes) provided 0.064 g (99%) of a colorless oil as a separable mixture of diastereomers in a ratio of 96:4: $[\alpha]^{20}_D$ +80.2 (*c* 2.3, $CHCl_3$); IR (KBr) 3239, 2970, 1652 cm^{-1}; ^1H NMR ($CDCl_3$) major compound δ 7.29 (m, 5H), 6.79 (s, 2H), 5.81 (s, 1H), 4.80 (d, *J* = 2.8 Hz, 1H), 3.60 (s, 3H), 3.19 (m, 1H), 3.10 (s, 3H), 2.47 (s, 6H), 2.2 (s, 3H), 0.99 (d, 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) major compound δ 176.2, 141.0, 139.9, 138.7, 137.3, 131.1, 128.7, 128.5, 128.2, 62.0, 58.3, 40.9, 32.5, 21.4, 19.6, 11.1. HRMS calcd for $C_{21}H_{29}N_2O_3S$ (M+H) 389.18990. Found 389.1897.

(S_S,2*R*,3*S*)-(+)-*N*-methoxy-*N*,2-dimethyl-3-(2,4,6-trimethylphenylsulfinyl-amino)-3-pentanamide (12). Chromatography (50% EtOAc/hexanes) provided 0.048 g (72%) of a colorless oil as an inseparable mixture of diastereomers in a ratio of 80:17:3; $[\alpha]^{20}_D$ +80.2 (*c* 2.3, $CHCl_3$); IR (KBr) 3239, 2970, 1652 cm^{-1}; ^1H NMR ($CDCl_3$) major compound δ 6.76 (s 2H), 5.03 (d, *J* = 6.0 Hz, 1H), 3.66 (s, 3H), 3.37 (m, 1H), 3.2 (m, 1H), 3.11 (s, 3H), 2.49 (s, 6H), 2.19 (s, 3H), 1.78 (m, 1H), 1.54 (octet, *J* = 7.1 Hz, 1H), 1.05 (d, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); minor compound δ 4.3 (d, *J* = 8.0 Hz, 1H), 3.61 (s, 3H), 3.45 (m, 1H), 2.96 (m, 1H), 2.52 (s, 6H), 1.61 (m, 1H), 1.1 (d, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) major compound δ 176.4, 140.6, 139.2, 136.6, 131.0, 61.9, 59.2, 38.5, 32.4, 25.0, 21.3, 19.7, 12.5, 11.1 minor compound δ 139.8, 136.4, 131.1, 61.8, 60.8, 40.5, 27.3, 19.9 14.3, 10.8. HRMS calcd for $C_{17}H_{29}N_2O_3S$ (M+H) 341.1899. Found 341.190.

(S_S,2*R*,3*R*)-(+)-***N*-Methoxy-*N*-2-dimethyl-3-(2,4,6-triisopropylphenylsulfinyl-amino)-3-pentanamide (13).** Chromatography provided 0.066 g (68%) of an oil; $[\alpha]^{20}_D$ +45.0 (*c* 0.6, $CHCl_3$); IR (KBr) 3248, 2962, 1649, 1461 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.9 (s, 2H), 4.97 (d, *J* = 6.0 Hz, 1H), 3.83 (m, 2H). 3.30 (s, 3H); 3.31 (M, 1H), 3.23, 1H), 3.36 (s, 3H), 2.02 (quint, *J* = 6.9 Hz, 1H), 1.77 (m, 1H), 1.49 (m, 1H) 1.17 (d, *J* = 6.8 Hz, 6H), 1.09 (dd, *J* = 2.2 Hz, 112 H)m 1.01 (d, *J* = 7.2 Hz, 3H), 0.81 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 179.1, 152.1, 148.5, 140.0, 138.0, 128.7, 128.6, 128.2, 123.3, 62.0, 59.4, 41.2, 34.7, 32.4, 28.6, 24.9, 24.7, 24.1, 11.8. HRMS calcd for $C_{27}H_{41}N_2O_3S$ (M+H) 473.283790. Found 473.2821.

(S_S,2*R*,3*S*)-(+)-*N*-methoxy-*N*,2-dimethyl-3-(2,4,6-triisopropylphenylsulfinyl-amino)pentanamide (14). Chromatography (50% Et_2O/hexanes) provided 0.125 g (80%) of an oil; $[\alpha]^{20}_D$ +81.2 (*c* 0.97, $CHCl_3$); IR (KBr) 2962, 2870, 1653, 1457 cm^{-1}; ^1H NMR ($CDCl_3$) Major compound δ 6.91 (s, 2H), 4.97 (d, *J* = 6.0 Hz, 1H), 3.83 (m, 2H), 3.61 (s, 3H) 3.31 (m, 1H), 3.23 (m, 1H), 3.06 (s, 3H), 2.72 (pentet, *J* = 6.9 Hz, 1H), 1.77 (m, 1H), 1.49 (m, 1H), 1.17 (d, *J* = 6.8 Hz, 6H), 1.09 (dd, *J* = 2.2 6.6 Hz, 12 H), 1.01 (d, *J* = 7.2 Hz, 3H), 0.81 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.4, 151.7, 147.7, 138.9, 123.2, 61.9, 60.3, 39.1, 34.6, 32.4, 28.7, 24.7, 24.6 24.5, 24.1, 12.9, 11.3. HRMS calcd for $C_{27}H_{41}N_2O_3S$ (M+H) 425.28380. Found 425.2840.

(R_S,2*S*,3*S*)-(+)-*N*-methoxy-*N*,2-dimethyl-3-(2,4,6-triisopropylphenylsulfinyl-amio)pentanamide (14). Chromatography (50% Et_2O/hexanes) gave 0.031 g (20%) of a oil; $[\alpha]^{20}_D$ +56.2 (*c* 0.5, $CHCl_3$); IR (KBr) 2962, 2871, 1654, 1459 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.91 (s, 2H), 4.26 (d, *J* = 7.6 Hz, 1H), 3.89 (m, 2H), 3.52 (s, 3H), 3.43 (m, 1H), 3.02 (s,

3H), 2.87 (m, 1H), 2.71 (pentet, *J* = 6.9 Hz, 1H), 1.58 (m, 2H), 1.05 – 1.17 (m, 18H), 1.02 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.5, 151.8, 147.5, 139.6, 123.4, 61.8, 61.3, 40.1, 34.6, 28.7, 27.5, 24.9, 24.5, 24.1, 23.9, 14.4, 10.6. HRMS calcd for $C_{27}H_{41}N_2O_3S$ (M+H) 425.28380. Found 425.2840.

(2*R*,3*R*)-(-)-3-Amino-*N*-methoxy-*N*,2-dimethyl-3-phenylpropanamide (15a). In a 15 mL, flame-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, and rubber septum was placed compound (+)-**13** (0.057 g, 0.121 mmol) in anhydrous MeOH (6.0 mL) and the solution was cooled to 0 °C. To the solution was added HCl (0.480 mL, 0.480 mmol, 1.0 M solution in Et_2O) via syringe and the resulting mixture was stirred for 30 min. At this time the reaction mixture was brought to pH 9 using 1.0 N aqueous NaOH and concentrated. Chromatography (5% MeOH/CH_2Cl_2 with < 1% Et_3N) provided 0.026 g (97%) of a colorless oil; $[\alpha]^{20}_D$ -28.2 (*c* 1.0, $CHCl_3$); IR (KBr) 3445, 2963, 1655, 1458, 1124 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.13 – 7.32 (m, 5H), 4.19 (d, *J* = 6.4 Hz, 1H), 3.42 (s, 3H), 3.1 (m, 1H), 2.89 (s, 3H), 1.76 (s, 2H), 1.13 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.8, 144.7, 128.6, 127.5, 127.2, 61.7, 57.5, 43.3, 32.4, 13.0. HRMS calcd for $C_{12}H_{19}N_2O_2$ (M+H) 223.14466. Found 223.1446.

(2*R*,3*S*)-(-)-3-Amino-*N*-methoxy-*N*,2-dimethylpentanamide (15b). Chromatography (10% MeOH/CH_2Cl_2, < 1% Et_3N) provided 0.041 g (99%) of product as a white solid, mp 160-161 °C; $[\alpha]^{20}_D$ -17.85 (*c* 1.025, $CHCl_3$); IR (KBr) 3378, 2965, 1658, 1463 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.33 (bs, 2H), 3.73 (s, 3H), 3.21 (s, 3H), 3.22 (m, 2H), 1.78 (m, 2H), 1.30 (d, *J* = 6.9 Hz, 3H), 1.07 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 140.4, 115.0, 54.0, 47.1, 31.9, 24.7, 20.5, 4.2, 3.4. HRMS calcd for $C_8H_{19}N_2O_2$ (M+H) 175.14466. Found 175.1448.

(2*R*,3*R*)-(+)-*N*-Methoxy-*N*,2-dimethyl-3-(*p*-toluenesulfonamido)-3-phenylpropanamide (16a). In a 5 mL, flame-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, and rubber septum was placed (-)-**15a** (0.026 g, 0.117 mmol) in CH_2Cl_2 (1.5 mL) and the solution was cooled to 0 °C. To the solution was added Et_3N (0.032 mL, 0.234 mmol), a catalytic amount of DMAP, and the mixture was stirred for 15 min at which time *p*-toluenesulfonyl chloride (0.034 g, 0.178 mmol) was added. After stirring for 2 h at 0 °C, the reaction mixture was quenched with water (6.5 mL) and diluted with CH_2Cl_2 (5 mL). The aqueous phase was extracted with CH_2Cl_2 (5 mL x 2), and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. Chromatography (50% Et_2O/hexanes to Et_2O) gave 0.030 g (68%) of a white solid, mp 170-171 °C; $[\alpha]^{20}_D$ +73.4 (*c* 0.5, $CHCl_3$); IR (KBr) 3248, 2979, 1327, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.49 (m, 2H), 7.05 (m, 5H), 5.57 (bd, *J* = 4.4 Hz, 1H), 4.4 (t, *J* = 6.8 Hz, 1H), 3.41 (s, 3H), 3.17 (t, *J* = 6.4 Hz, 1H), 2.83 (s, 3H), 2.28 (s, 3H), 1.07 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.8, 143.3, 139.9, 137.4, 129.6, 128.5, 127.8, 127.7, 127.4, 61.8, 59.7, 41.7, 32.3, 21.2, 13.5. HRMS calcd for $C_{19}H_{25}N_2O_4S$ (M+H) 377.1535. Found 377.1534.

(2*R*,3*S*)-(+)-*N*-methoxy-*N*,2-dimethyl-3-(4-methylphenylsulfonamido-pentanamide (16b). Chromatography (50% Et_2O/hexane) gave 0.057 g (76%) of a white solid, mp 118 °C; $[\alpha]^{20}_D$ +0.75 (*c* 0.933, $CHCl_3$); IR (KBr) 3247, 2971, 2937, 1658, 1159

cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69 (m, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 4.85 (bd, *J* = 6.8 Hz, 1H), 3.55 (s, 3H), 3.26 (m, 1H), 3.06 (m, 1H), 3.0 (s, 3H), 2.34 (s, 3H), 1.48 (m, 2H), 0.99 (d, *J* = 7.2 Hz, 3H), 0.63 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 175.6, 134.4, 129.4, 120.8, 118.6, 52.8, 48.9, 37.3, 29.8, 23.4, 16.8, 12.8, 4.6, 1.5. HRMS calcd for $C_{15}H_{24}N_2O_4S$ (M+H) 329.15351. Found 329.1537.

(2*R*,3*R*)-(+)-2-Methyl-3-(4-methylphenylsulfonamido)-3-phenylpropanoic acid (17). In a 5 mL, flame-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, reflux condenser, and rubber septum was placed (+)-**16a** (0.009 g, 0.024 mmol) and aqueous KOH (1 mL) in EtOH (1.0 mL). The reaction mixture was refluxed for 48 h at 80 °C, the solution cooled to rt, acidified to pH <2 using conc. HCl, and diluted with CH_2Cl_2 (10 mL). The solution was vigorously stirred for 30 min at which time the aqueous phase was extracted with CH_2Cl_2 (2 X 10 mL), and the combined organic phases were dried ($MgSO_4$), and concentrated. Chromatography (35% EtOAc/hexanes to MeOH) provided 0.008 g (99%) of a white solid, mp 145 °C; $[\alpha]^{20}_D$ +46.5 (c 0.23, EtOAc); ^1H NMR (CD_3OD) δ 7.45 (m, 2H), 7.09 (m, 2H), 4.47 (d, *J* = 9.6 Hz, 1H), 2.71 (m,1H), 2.32 (s, 3H), 1.24 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (CD_3OD) δ 180.7, 144.3, 142.0, 140.3, 130.5, 129.2, 129.1, 128.4, 128.3, 62.4, 21.7, 16.2 HRMS calcd for $C_{17}H_{20}NO_4S$ (M+H) 334.1113. Found 334.1113.

(2*R*,3*S*)-(-)-2-Methyl-*N*-(*p*-tolutenesulfsulfonyl)-3-aminopentanal (18b). In a 5 mL, flame-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar and rubber septum was placed (+)-**16b** (0.019 g, 0.058 mmol) in THF (1.0 mL). The solution was cooled to -78 ºC and DIBAL-H (0.290 mL, 0.29 mmol, 1.0 M solution in CH_2Cl_2) was added via syringe. After stirring for 10 min, the reaction mixture was quenched with Rochell salt at -78 °C, and warmed up to rt. The reaction mixture was diluted with EtOAc (5 mL) and stirred vigorously until two layers were obtained. The organic phases were separated, dried ($MgSO_4$), and concentrated. Flash chromatography (50% Et_2O/hexanes) gave 0.011 g (71%) of a white solid, mp 84-85 °C; $[\alpha]^{20}_D$ -47.2 (*c* 1.0, $CHCl_3$); IR (KBr) 3282, 2972, 1718, 1162 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.48 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 7.6 Hz, 2H), 4.66 (d, *J* = 9.2 Hz, 1H), 3.45 (m, 1H), 2.44 (m, 1H), 2.36 (s, 3H), 1.38 (m, 2H), 1.01 (d, *J* = 7.2 Hz, 3H), 0.68 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 203.9, 143.9, 138.3, 130.0, 127.4, 56.3, 49.7, 25.7, 21.9, 10.9, 9.8. HRMS calcd for $C_{13}H_{20}NO_3S$ (M+H) 270.11639. Found 270.1163.

(2*R*,3*S*)-(-)-2-Methyl-*N*-(*p*-toluenesulfonyl)-3-aminopentanol (19). In a 5 mL, flame-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, and rubber septum was placed (-)-**18** (0.010 g, 0.037 mmol) in CH_2Cl_2 (2.0 mL). The solution was cooled to 78 °C and $LiEt_3BH$ (0.19 mL, 0.186 mmol, 1.0 M solution in THF) was added. After stirring for 1.5 h at this temperature, the reaction mixture was quenched with sat. aqueous NH_4Cl (1.0 mL) at -78 °C, and warmed up to rt. The solution was extracted with EtOAc (2 x 10 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography (50% EtOAc/hexanes) provided 0.010 g (99%) of a colorless oil, $[\alpha]^{20}_D$ -33.2 (*c* 0.37, $CHCl_3$). [lit.[4] $[\alpha]^{20}_D$ -35.0 (*c* 0.6, $CHCl_3$)]. NMR data and the physical data were identical with the reported data.[4]

(2*S*,3*S*)-(-)-*N*-Methoxy-*N*,2-dimethyl-3-(4-methylphenylsulfonamido)-pentanamide (20). In a 10 mL, flame-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, and rubber septum was placed *anti*-(+)-**14** (0.070 g, 0.165 mmol) in MeOH (8.0 mL). The solution was cooled to 0 °C, HCl (0.66 mL, 1.0 M solution in Et_2O) was added via syringe and the reaction mixture was stirred for 30 min. At this time the solution was brought to pH 9 using 1.0 N aqueous NaOH and concentrated. The triisopropylphenylsulfinyl by-products were removed by a short pad of silica gel chromatography (5% MeOH/CH_2Cl_2 with < 1% Et_3N), and the crude amine was concentrated and placed in a 5 mL, flame-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar and rubber septum. To the flask was added CH_2Cl_2 (2.0 mL), Et_3N (0.045 mL, 0.33 mmol), and catalytic amount of DMAP and the solution was cooled to 0 °C. The mixture was stirred for 15 min and *p*-toluenesulfonyl chloride (0.047 g, 0.248 mmol) was added. After stirring for 2 h at 0 °C, the reaction mixture was quenched with water (0.5 mL) and diluted with CH_2Cl_2 (5 mL). The aqueous phase was extracted with CH_2Cl_2 (5 mL x 2), and the combined organic phases were washed with brine (3 mL), dried ($MgSO_4$), and concentrated. Chromatography (50% Et_2O/hexanes to Et_2O) gave 0.036 g (67%) of a white solid mp 115-6 ºC, $[\alpha]^{20}_D$ -1.5 (*c* 1.2, $CHCl_3$); IR (KBr) 3245, 2967, 2963, 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 4.85 (d, *J* = 8.0 Hz, 1H), 3.55 (s, 3H), 3.24 (pentet, *J* = 6.6 Hz, 1H), 2.98 (s, 3H), 2.34 (s 3H), 1.48 (m, 2H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.63 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 175.6, 143.4, 138.4, 129.8, 127.6, 61.8, 57.9, 38.9, 32.4, 25.7, 21.8 13.6, 10.5. HRMS calcd for $C_{15}H_{24}N_2O_4S$ (M+H) 329.15351. Found 329.1537.

(2*S*,3*S*)-(+)-2-Methyl-3-(4-methylphenylsulfonamido)pentanoic acid (21). Chromatography (35% EtOAc/hexanes to CH_2Cl_2) gave 0.029 g (95%) of a colorless oil; $[\alpha]^{20}_D$ +51.7 (*c* 0.35, $CHCl_3$); IR (KBr) 3278, 2973, 2937, 1733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 5.06 (d, *J* = 10.0 Hz, 1H), 3.25 (heptet, *J* = 4.67 Hz, 1H), 2.53 (m, 1H), 2.35 (s 3H), 1.46 (m, 1H), 1.30 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.71 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 179.0, 143.7, 138.6, 130.0, 127.4, 58.0, 43.4, 24.7, 21.9 13.5, 10.9. HRMS calcd for $C_{13}H_{20}NO_4S$ (M+H) 286.1113. Found 286.1114.

(3*S*,4*S*)-(-)-4-Ethyl-3-methyl-1-tosylazetidin-2-one (22). In a 5 mL, flame-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, and rubber septum was placed (-)-**21** (0.008 g, 0.028 mmol), DCC (0.007 g, 0.034 mmol), and 4-pyrrolidinopyridine (0.001 g, 0.007 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred for 18 h at rt, filtered through Celite washing with CH_2Cl_2 (10 mL). The filtrate was washed with water (3 mL), 5% aqueous AcOH (2 mL), and H_2O (2 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Chromatography (10% Et_2O/hexanes) gave 0.005 g (67%) of a white solid mp 85 ºC; $[\alpha]^{20}_D$ -37.3 (*c* 0.33, $CHCl_3$); IR (KBr) 3291, 2974, 2935, 1777 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.81 (m, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 3.93 (ddd, *J* = 4.4, 6.4, 9.9 Hz, 1H), 3.25 (dq, *J* = 7.6, 6.4 Hz 1H), 2.38 (s, 3H), 2.02 (m, 1H), 1.55 (m, 1H), 1.15 (d, *J* = 7.6 Hz, 3H), 0.88 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 168.3, 145.4, 136.7, 130.3, 127.7, 60.6, 47.7 22.5, 22.0, 10.8, 8.6. HRMS calcd for $C_{13}H_{18}NO_3S$ (M+H) 268.10074. Found 268.1005. Upon irradiation

of the C-3 proton H at δ 3.25, a positive NOE was observed on the C-4 methyl at δ 0.89 (4.5%).

(S_S,3*S*,4*R*)-(+)-*N*-(2,4,6-Triisopropylbenzenesulfinyl)-3-amino-4-methyl nonan-5-one (23a). In a 5 mL, flame-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, and rubber septum was placed Weinreb amide **14** (0.017 g, 0.04 mmol) in THF (0.6 mL). To the solution was added *n*-butylmagnesium chloride (0.11 mL, 0.212 mmol, 2.0 M solution in THF) at 0 °C via syringe and the resulting mixture was stirred for 8 h at rt. The reaction mixture was quenched by addition of sat. aqueous NH_4Cl (1 mL) at 0 °C and extracted with Et_2O (2 x 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Chromatography (20% Et_2O/hexanes) provided 0.014 g (83%) of a colorless oil; $[\alpha]^{20}_D$ +98.6 (*c* 0.7, $CHCl_3$); IR (KBr) 3584, 2961, 2871, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.99 (s, 2H), 4.87 (d, *J* = 7.6 Hz, 1H), 3.87 (bs, 2H), 3.33 (m, 1H), 3.02 (m, 1H), 2.8 (quint, *J* = 6.9 Hz, 1H), 2.43 (m, 2H), 1.65 (m, 1H), 1.48 (m, 4H), 1.26 (m, 1H), 1.24 (d, *J* = 7.2 Hz, 6H), 1.17 (d, *J* = 6.8 Hz, 12H), 1.09 (d, *J* = 7.2 Hz, 3H), 0.87 (t, *J* = 7.8 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 206.6, 144.1, 139.9, 131.0, 115.5, 53.2, 42.2, 34.1, 26.9, 21.0, 18.2, 16.9, 16.8, 16.7, 16.3, 14.9, 6.5, 5.2, 3.7. HRMS calcd for $C_{25}H_{44}NO_2S$ (M+H) 422.309277. Found 422.3086.

(S_S, 2*R*, 3*S*)-(+)-*N*-(2,4,6-Triisopropylbenzenesulfinyl)-3-amino-2-methyl-1-phenylpentan-1-one (23b). Chromatography (20% Et_2O/hexanes) provided 0.012 g (72%) of a colorless oil; $[\alpha]^{20}_D$ +99.6 (*c* 0.25, $CHCl_3$); IR (KBr) 3266, 2963, 2871, 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.91 (m, 2H), 7.52 (m, 1H), 7.42 (m, 2H), 7.0 (s, 2H), 7.2 (d, *J* = 6.8 Hz, 1H), 3.96 (m, 1H), 3.84 (m, 2H), 3.52 (m, 1H), 2.79 (quintet, *J* = 7.0 Hz, 1H), 1.8 (m, 1H), 1.63 (m, 1H), 1.12 – 1.19 (m, 21H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 204, 151.9, 147.7, 138.9, 137.1, 133.6, 129.1, 128.9, 123.3, 60.7, 44.5, 34.6, 28.7, 24.9, 24.6, 24.5, 24.1, 14.0, 11.5. HRMS calcd for $C_{27}H_{40}NO_2S$ (M+H) 442.277977. Found 442.280.

(S_S,2*R*,3*S*)-(+)-2-Ethyl-*N*-methoxy-3-(*p*-toluenesulfinylamino)-3-hexanamide (25). In a 25 mL, flame-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, rubber septum was placed LiHMDS (0.96 mL, 0.958 mmol, 1.0 M solution in THF) under argon, the solution was cooled to -78 °C, and *N*-methoxy-*N*-methylbutyramide **24** (0.126 g, 0.958 mmol) in THF (1.5 mL) was added at -78 °C via cannula. After stirring for 2 h at this temperature, a solution of (*S*)-(+)-*N*-(butylidene) *p*-toluenesulfinamide (**1**)[5] (0.100 g, 0.479 mmol) in THF (3.5 mL) was added. On consumption of starting material as judged by TLC (typically less than 30 min.), the reaction mixture was quenched with sat. aqueous NH_4Cl (2 mL) at -78 °C, warmed up to rt, and extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with brine (2 x 10 mL), dried ($MgSO_4$), and concentrated. Chromatography (35% EtOAc/hexanes) provided 0.124 g (75%) of a colorless oil as a mixture of diastereomers in a ratio of 71:12:10:7 that required two chromatographies (35% EtOAc/hexanes) to give 0.061 g (36%) of a colorless oil. This material slowly epimerizes on standing due to trace amount of acid in $CDCl_3$ and was immediately taken on to the next step; $[\alpha]^{20}_D$ + 121.1 (*c* 0.9, $CHCl_3$); IR (KBr) 3465, 3242, 2962, 1652 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.61 (m, 2H),

7.31 (m, 2H), 4.49 (bd, J = 6.0 Hz, 1H), 3.71 (s, 3H), 3.54 (m, 1H), 3.18 (s, 3H), 3.09 (m, 1H), 2.43 (s, 3H), 1.36 – 1.82 (m, 6H), 0.99 (t, J = 7.1 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 175.4, 143.4, 141.5, 129.9, 125.8, 61.7, 57.1, 47.0, 35.5, 32.4, 21.6, 21.4, 19.9, 14.2, 12.5. HRMS calcd for $C_{17}H_{29}N_2O_3S$ (M+H) 341.1899. Found 341.1898.

(S_S,4*S*,5*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-6-amino-5-ethylnonan-4-one (3). In a 5 mL, flame-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, rubber septum was placed crude (+)-**25** (0.018 g, 0.05 mmol) in THF (1.0 mL) and the solution was cooled to 0 ºC. Propylmagnesium chloride (0.13 mL, 0.266 mmol, 2.0 M solution in Et_2O) at 0 °C was added to the reaction mixture via syringe and the solution was stirred for 16 h at rt. The reaction mixture was quenched by sat. aqueous NH_4Cl (1 mL) at 0 °C and extracted with EtOAc (2 x 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Chromatography (35% Et_2O/hexanes) provided 0.015 g (93%) of product as a colorless oil; $[\alpha]^{20}_D$ +70.75 (*c* 0.8, $CHCl_3$) [lit.[5] $[\alpha]^{20}_D$ +63.7 (*c* 0.67, $CHCl_3$)]. ^{1}H and ^{13}C NMR spectra were identical to literature values.[5]

References

(1) Weix, D. J.; Ellman, J. A. *Org. Synth.* **2005**, *82*, 157.
(2) Ramachandar, T.; Wu, Y.; Zhang, J.; Davis, F. A. *Org. Synth.* **2006**, *83*, 131.
(3) (a) Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Su, X.; Wilkinson, H. S.; Lu, Z.-H.; Magiera, D.; Senanayake, C. H. *Tetrahedron* **2005**, *61*, 6386. (b)) Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Pflum, D. A.; Senanayake, C. H. *Tetrahedron Lett.* **2003**, *44*, 4195.
(4) Davis, F. A.; Reddy, G. V.; Liang, C.-H. *Tetrahedron Lett.* **1997**, *38*, 5139.
(5) Davis, F. A.; Yang, B. *J. Am. Chem. Soc.* **2005**, *127*, 8398.