

Sulfinimine Mediated Asymmetric Synthesis of 1,3-Disubstituted Tetrahydroisoquinolines: A Stereoselective Synthesis of *cis*- and *trans*-6,8-Dimethoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline

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Supporting Information

General Procedure. Column chromatography was performed on silica gel, Merck grade 60 (230-400 mesh). Analytical and preparative thin-layer chromatography was performed on precoated silica gel plates (250 and 1000 microns) purchased from Analtech Inc. TLC plates were visualized with UV or in an iodine chamber. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. IR spectra were recorded using NaCl plates or KBr discs on a Mattson 4020 FTIR. ¹H NMR and ¹³C NMR spectra were recorded on a General Electric Omega 500, operating at 500 and 125 MHz, respectively and the spectra were referenced to solvent residues as internal standards. HPLC separations were carried out on a Hewlett Packard HP 1100-series chromatograph equipped with a diode array detector. HRMS were performed in the Department of Chemistry, Drexel University, Philadelphia, PA using a Fissions ZAB HF double-focusing mass spectrometer. Elemental analyses were performed in the Department of Chemistry, University of Pennsylvania, Philadelphia, PA.

THF and diethyl ether were freshly distilled under argon from a purple solution of sodium and benzophenone. Diglyme was dried using sodium metal and chloroform was dried using calcium hydride. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. *N,N*-Diethyl-2,4-dimethoxy-6-methylbenzamide (**5**)¹ and (*S*)-(+)-*N*-(*S*)-(+)-*N*-(acetylidene)-*p*-toluenesulfinamide (**6**)² were prepared as previously described.

(*S,S*,*R*)-(+)-*N*-[1-Methyl-2-(2-*N,N*-diethylbenzamido)ethyl]-*p*-toluenesulfinamide (7**).** LDA (6.4 mL, 9.6 mmol, 3 equiv) and THF (20 mL) was added to an oven-dried 100-mL round-bottomed flask equipped with a magnetic stirrer, a rubber septa and argon inlet. The solution was cooled to -78 °C and **5** (1.6 g, 6.4 mmol, 2 equiv) in THF (10 mL) cooled to -78 °C was added dropwise via cannula over 15 min. The reaction mixture turned orange and upon further addition of **5** became red. After stirring for 30 min, (*S*)-(+)-**6** (0.6 g, 3.4 mmol, 1.0 equiv) in THF (15 mL) was added dropwise over 20 min. The solution remained red and was stirred for 2 h before quenching with sat. NH₄Cl (3 mL). After warming to rt, the reaction mixture was diluted with H₂O (30 mL) and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (20 mL), dried (MgSO₄), and concentrated. Flash chromatography (20-50% EtOAc/ hexane) afforded 0.974 g (68%) of a yellow oil ; [α]_D²⁰ 11.0 (*c* 1.60, CHCl₃); IR (neat) 3434, 3204, 1605, 1089, 1064 cm⁻¹; ¹H NMR (CDCl₃) δ 0.95 (m, 3 H), 1.08 (d, *J* = 6.5, 1.3H), 1.14 (d, *J* = 6.5,

1.4H), 1.25 (m, 3 H), 1.35 (d, $J = 6.5$, .3 H), 2.38 (m, 3 H), 2.5 (dd, $J = 15.5$, 9.2, .5H), 2.6 (dd, $J = 10.5$, 9.2, .5 H), 2.73 (dd, $J = 10.5$, 9.2, .5 H), 2.87 (dd, $J = 10.5$, 9.2, .5 H), 3.2 (m, 2 H), 3.44 (m, 2H), 3.56 (m, 2 H), 3.74 (m, 6 H), 4.44 (d, $J = 7.7$, 0.5 H), 5.42 (d, $J = 7.7$, 0.5 H), 6.34 (m, 0.5 H), 6.37 (m, 0.5 H), 6.39 (m, 0.5 H), 6.44 (m, 0.5 H), 7.15 (m, 1 H), 7.25 (d, $J = 7.2$, 1 H), 7.38 (d, $J = 7.2$, 1 H), 7.51 (d, $J = 7.2$, 1 H); ^{13}C NMR (CDCl_3) δ 14.4, 14.5, 14.8, 21.7, 21.9, 22.7, 24.7, 39.5, 39.6, 40.4, 42.9, 43.5, 43.6, 51.0, 51.1, 51.4, 51.5, 56.0, 56.1, 97.4, 97.5, 106.9, 107.7, 126.5, 126.6, 127.0, 129.7, 129.8, 130.0; HRMS (FAB) calcd for $\text{C}_{23}\text{H}_{32}\text{N}_2\text{O}_4\text{S} + \text{Na}$ 455.1998, found 455.1968.

***N,N*-Diethyl-2-hydroxymethyl-4,6-dimethoxybenzamide.** Further elution (60% EtOAc/ hexane) afforded 0.25 g (15) of a yellow oil; IR (neat) 3391, 1605, 1049 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.03 (t, $J = 7.3$, 3 H), 1.25 (t, $J = 7.3$, 3 H), 3.05-3.22 (m, 2 H), 3.48-3.61 (m, 3 H), 3.78 (s, 3 H), 3.83 (s, 3 H), 4.30 (bd, $J = 12.1$, 2 H), 4.55 (d, $J = 12.1$, 2 H), 6.39 (d, $J = 2.2$, 1H), 6.57 (d, $J = 2.2$, 1 H); ^{13}C NMR (CDCl_3) δ 13.4, 14.5, 39.8, 43.7, 56.1, 56.2, 64.7, 98.5, 106.1, 141.6, 157.1, 161.9, 165.8, 167.6, 169.2. Anal calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_4$: C, 62.90; H, 7.92; N, 5.24. Found C, 63.29; H, 7.79; N, 4.80.

***(R)*-(-)-*N,N*-Diethyl-2-(2-aminopropyl)-4,6-dimethoxybenzamide (8).** In a 50-mL round-bottomed flask equipped a magnetic stir bar was placed (*S,S,R*)-(+)-**(7)** (1.0 g, 2.3 mmol, 1.0 equiv), MeOH (20 mL), and TFA (0.9 mL, 11.7 mmol, 5.0 equiv). After stirring the reaction mixture for 8 h, it was concentrated to give a yellow oil that was dissolved in DCM (2 mL) and passed through a short silica gel pad eluting sequentially with hexane (50 mL), 50% EtOAc/ hexane (50 mL), and MeOH (60 mL). The MeOH fraction containing the amine salt was concentrated, dissolved in DCM (10 mL), and stirred with 20 % NaOH (10 mL) for 30 min. The aqueous phase was washed with EtOAc (3 x 10 mL), and the combined organic phases were washed with brine (20 mL), dried (MgSO_4), and concentrated to afford 0.591 g (87 %) of a thick yellow oil; $[\alpha]_{\text{D}}^{20}$ -25.7 (c 1.56, CHCl_3); IR (neat) 3423, 1620, 1203, 1154, 1097 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.00 (dt, $J = 7.2$, 1.5, 3 H), 1.09 (d, $J = 6.3$, 1.5 H), 1.13 (d, $J = 6.3$, 1.5 H), 1.23 (dt, $J = 7.2$, 1.5, 3 H), 1.98 (bs, 2 H), 2.3 (dd, $J = 10.7$, 8.5, .5 H), 2.4 (dd, $J = 10.7$, 8.5, .5 H), 2.55 (dd, $J = 8.6$, 5.6, .5 H), 2.68 (dd, $J = 8.6$, 5.6, .5 H), 3.0-3.2 (m, 3H), 3.3 (m, 1H), 3.4 (m, 1H), 3.76 (s, 3H), 3.81 (s, 3H), 6.35 (m, 1.5 H), 6.42 (s, 5 H); ^{13}C NMR (CDCl_3) δ 12.6, 13.7, 23.6, 23.7, 38.5, 38.6, 42.6, 42.7, 43.7, 47.1, 48.0, 55.3, 96.4, 96.5, 105.8, 106.5, 119.4, 119.7, 138.6, 138.2, 156.6, 156.8, 156.6, 156.8, 160.4, 160.6, 168.1, 168.2. HRMS calcd for $\text{C}_{16}\text{H}_{26}\text{N}_2\text{O}_3$ (M+H), 295.19; found 295.2014.

***(3R)*-(-)-6,8-Dimethoxy-3-methyl-3,4-dihydro-1(2*H*)-isoquinolone (9).** To an oven-dried 50-mL round-bottomed flask equipped with a magnetic stirrer, rubber septa, and Ar inlet was placed (*R*)-(-)-**(8)** (0.309 g, 1.05 mmol, 1.0 equiv) in THF (10 mL). The solution was cooled to -78°C and *t*-BuLi (2.0 mL, 3.4 mmol, 3.2 equiv) was added dropwise to give a yellow solution that became red. After stirring for 30 min, the reaction mixture was quenched with sat. NH_4Cl (2 mL) and warmed to rt. The solution was diluted with H_2O (20 mL) and the aqueous phase was extracted with EtOAc (3 X 10 mL). The combined organic phases were washed with brine (10 mL), dried (MgSO_4) and concentrated. Purification by flash chromatography (6:2:2, EtOAc:MeOH:hexane) afforded 0.186 g (80 %) of a white solid mp $127-8^\circ\text{C}$; $[\alpha]_{\text{D}}^{20}$ -

87.3 (c 1.05, CHCl₃); IR (neat) 3274, 1653, 1090; ¹H NMR (CDCl₃) δ 1.27 (d, *J* = 6.6, 3 H), 2.74 (dd, *J* = 15, 11, 2 H), 2.81 (dd, *J* = 15.0, 3.7), 3.85 (s, 3 H), 3.91 (s, 3H), 5.6 (bs, 1H), 6.3 (d, *J* = 2.2, 1 H), 6.4 (d, *J* = 2.2, 1 H); ¹³C NMR (CDCl₃) δ 21.5, 39.1, 47.0, 56.0, 56.8, 98.3, 104.9, 111.1, 143.6, 162.6, 163.7, 165.6; HRMS calcd for C₁₂H₁₅NO₃ (M+H), 211.11; found 211.1121.

The enantiomeric excess was determined to be 92% by HPLC analysis using a Chiralcel OD column; gradient: 20% IPA/ hexane to 30% IPA/ hexane at 10 min.; 1 mL/min, 280 nm; (*R*)-isoquinoline *t_R* = 15.0 min, (*S*)-isoquinoline *t_R* = 14.0 min).

(3*R*)-6,8-Dimethoxy-1-chloro-3-methyl-3,4-dihydro-1(2*H*)-isoquinoline (10). Attempted preparation of imine **11**. To a two-necked 25-mL round-bottomed flask equipped with a magnetic stirrer, rubber septa, reflux condenser, and Ar inlet was placed (3*R*)-(-)-**9** (0.070 g, 0.317 mmol, 1.0 equiv), dry benzene (3 mL), and POCl₃ (0.2 mL, 2.16 mmol, 6.8 equiv). The reaction mixture was refluxed for 1.5 h, concentrated in vacuo at ca. 60 °C and the residue was washed with benzene (2 mL) to azeotropically remove traces of POCl₃. The residue was cooled to -30 °C and a solution of 5 % TEA in ether (2 mL) was added dropwise. After stirring the crude reaction mixture for 10 min it was filtered through an alumina column and eluted with ether to afford 0.038 g (50%) of the imidoyl chloride as a yellow oil; ¹H NMR (CDCl₃) δ 1.39 (d, *J* = 7.0, 3 H), 2.45-2.58 (m, 2H), 2.68 (dd, *J* = 15.2, 3.9, 2 H), 3.52-3.61 (m, 2 H), 3.84 (s, 3H), 3.88 (s, 3 H), 6.33 (d, *J* = 2.5, 1 H), 6.37 (d, *J* = 2.5, 1 H).

The crude imidoyl chloride **10** was placed in an oven-dried 10 mL round-bottomed flask equipped with a magnetic stirrer under argon and THF (3.5 mL) was added at 0 °C. A catalytic amount of [1,3-bis-(diphenylphosphinopropane)Ni(II)chloride (ca. 3 mg) was added to the solution which then turned blue. The solution was stirred for 20 min at 0 °C and methylmagnesium bromide (60 μL, 0.18 mmol, 1.1 equiv) was added dropwise at which time the solution became brownish yellow. The reaction mixture was stirred for 3.5 h, quenched with sat. NH₄Cl (2 mL), diluted with H₂O (8 mL), and the aqueous phase was washed with EtOAc (3 x 5 mL). The combined organic phases were washed with brine, dried (MgSO₄), and concentrated to afford a complex mixture of products by TLC.

(3*S*)-(+)-1-methyl-3-phenyl-3,4-dihydroisoquinoline (13). In a 10-mL round bottomed flask equipped with a magnetic stirring bar, reflux condenser and argon inlet was placed (*S*)-(-)-3-phenylisoquinolone (**12**)¹ (0.087 g, 0.39 mmol), dry benzene (3.5 mL) and POCl₃ (0.20 mL). The reaction mixture was refluxed for 1.5 h, concentrated under reduced pressure at 60 °C and a 5% solution of TEA in ether (2 mL) was added at -30 °C. After stirring for 10 min, the solution was filtered through an alumina column and eluted with ether to give 0.070 g (74%) of the crude imidoyl chloride as an oil; ¹H NMR (CDCl₃) δ 7.85 (dd, *J* = 8 Hz, 1.5 Hz, 1H), 7.48-7.29 (m, 7H), 7.22 (d, *J* = 7Hz), 1H), 4.84 (dd, *J* = 13 Hz, 6.5 Hz, 1 H), 3.0 (m, 2H); ¹³C NMR δ 155.25, 142.42, 137.63, 132.37, 128.52, 127.93, 127.59, 127.28, 126.96, 126.77, 63.26, 34.56. Further elution with EtOAc and methanol (3:1) gave 0.021 g (24%) of **12**.

In a 25 mL two-neck round-bottomed flask equipped with a stirring bar and rubber septa under argon was placed the crude chloride (0.036 g, 0.149 mmol) in ether (3 mL) and ca 0.001 g (1.2%) of [1,3-bis(diphenylphosphinopropane)Ni(II)chloride. Methylmagnesium bromide (60 μ L, 0.18 mmol 1.2 equiv) was added dropwise and the reaction mixture turned reddish immediately and yellowish on stirring. After stirring for 25 min methylmagnesium bromide (15 μ L, 0.45 mmol, 0.3 equiv) was added and the reaction mixture stirred for 5 min. Wet ether (20 mL) was added, dried (MgSO_4), and concentrated to give a solid that was purified by silica gel flash column chromatography (hexane:EtOAc 10:1) to give 0.027 g (81%) of a white solid, mp 88 $^{\circ}\text{C}$; $[\alpha]_D^{20}$ -131.7 (c 0.34, CHCl_3); [lit.³ $[\alpha]_D^{20}$ 126 (c 2.05, ethanol) for the enantiomer]; IR (KBr) 1613, 1567, 1420, 1289, 1135 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.50 (s, 3 H), 2.85 (dd, J = 15, 15 Hz, 1 H), 2.95 (dd, J = 15, 5.5 Hz, 1 H), 4.55 (m, 1 H), 7.21-7.60 (m, 9 H); ^{13}C NMR (CDCl_3) δ 23.44, 34.69, 60.96, 104.98, 125.38, 126.84, 127.07, 127.13, 127.46, 128.46, 130.75, 136.90, 144.50, 164.38. Anal calcd for $\text{C}_{16}\text{H}_{15}\text{N}$: C, 86.84; H, 6.83; N, 6.33. Found: C 86.58; H, 6.62; N, 5.62.

2-Bromo-1,5-dimethoxytoluene (14). In a 250-mL two-necked round bottomed flask equipped with stirring bar and rubber septa under an argon atmosphere, 3,5-dimethoxytoluene (1.2 g, 7.88 mmol) was dissolved in dry CHCl_3 (60 mL). *N*-Bromosuccinamide (1.19 g, 8.04 mmol) was added and the reaction mixture was refluxed for 4 h. The organic portion was washed with CHCl_3 (60 mL), washed with H_2O (20 mL), dried (MgSO_4) and concentrated. Purification by silica gel column chromatography (hexane/EtOAc 50:1) gave 1.23 g (82%) of a white solid, mp 55 $^{\circ}\text{C}$ [lit.⁴ 57 $^{\circ}\text{C}$]; ^1H NMR (CDCl_3) δ 2.39 (s, 3 H), 3.82 (s, 3 H), 3.95 (s, 3 H), 6.22 (s, 1 H), 6.31 (s, 3 H).

2,4-Dimethoxy-6-methylbenzonitrile (15). In a 250-mL two-necked round-bottomed flask equipped with stirring bar and rubber septa under an argon atmosphere, was placed **14** (1.2 g, 5.17 mmol) in dry DMF (40 mL). CuCN (0.694 g, 7.75 mmol) was added and the solution was stirred at 120 $^{\circ}\text{C}$ for 16 h. The reaction mixture was cooled, H_2O (30 mL) was added, and the organic phase was washed with CHCl_3 (60 mL), H_2O (20 mL), brine (20 mL), and dried (MgSO_4). Concentration and purification by silica gel column chromatography (hexane/EtOAc 5:1) gave 0.911 g (89%) of a white solid, mp 68 $^{\circ}\text{C}$; IR (KBr) 2214, 1620, 1565 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.46 (s, 3 H), 3.84 (s, 3 H), 3.88 (s, 3 H), 6.29 (s, 1 H), 6.38 (s, 1 H); ^{13}C NMR (CDCl_3) δ 20.70, 55.51, 55.88, 95.64, 106.99, 116.16, 145.10, 163.03, 163.83. Anal calcd for $\text{C}_{10}\text{H}_{11}\text{NO}_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.98; H, 6.28; N, 7.60.

(*S,S,R*)(+)-*N*-[1-Methyl-2-(4,6-dimethoxybenzonitrile)-ethyl]-*p*-toluenesulfinamide (16). In a 100-mL two-necked round bottomed flask equipped with stirring bar and rubber septa under an argon atmosphere was placed LDA (5.98 mL, 1.5 M in THF, 8.98 mmol) in dry diglyme (40 mL) and cooled to -78 $^{\circ}\text{C}$. To the reaction mixture was added dropwise **15** (0.8 g, 4.49 mmol) in diglyme (3 mL). After stirring for 0.5 h, (*S*)-(+)-**6** (0.89 g, 4.93 mmol) in diglyme (2 mL) was added dropwise and the solution was stirred for 0.5 h. At this time the reaction mixture was quenched

with saturated NH_4Cl (10 mL), washed with diethyl ether (60 mL), dried (MgSO_4), and concentrated. Purification by silica gel column chromatography (hexane/ EtOAc 5:1) gave 1.0 g (68%) of a white solid mp $110\text{ }^\circ\text{C}$; de $>97\%$; $[\alpha]_D^{20} +41.6$ (c 1.3, CHCl_3); IR (KBr) 3250, 2945, 2216, 1598, 1465 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.33 (d, $J = 6.6\text{ Hz}$, 3 H), 2.44 (s, 3 H), 3.10 (m, 2 H), 3.86 (m, 1 H), 3.89 (s, 3 H), 3.94 (s, 3 H), 6.54 (d, $J = 2.1\text{ Hz}$, 1 H), 6.40 (d, $J = 2.1\text{ Hz}$, 1 H), 7.29 (d, $J = 7.5\text{ Hz}$, 2 H), 7.52 (d, $J = 7.5\text{ Hz}$, 2 H); ^{13}C NMR (CDCl_3) δ 21.31, 22.68, 43.37, 52.58, 55.71, 56.03, 96.69, 107.43, 116.27, 125.54, 130.42, 141.29, 142.12, 145.77, 163.14, 163.96. Anal calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_3\text{S}$: C 63.66; H, 6.19; N, 7.82. Found: C, 63.26; H, 6.30; N, 7.54.

(3R)-(+)-6,8-Dimethoxy-1,3-dimethyl-3,4-dihydroisoquinoline (11). In a 50-mL of two-necked round bottomed flask equipped with a stirring bar and rubber septa under an argon atmosphere was placed (*S,S,R*)-(+)-**16** (0.5 g, 1.39 mmol) in ether (40 mL) at $-20\text{ }^\circ\text{C}$. MeLi (3.96 mL, 1.4 M in diethyl ether, 5.57 mmol) was added dropwise and after 0.5 h, 2 N HCl (5 mL) was added. After stirring for 15 min the aqueous phase was brought to pH 8-9 by addition of 10% NaOH (20 mL) and washed with ether (3 x 20 mL). The organic phase was dried (MgSO_4), concentrated and purified by silica gel chromatography (hexane/EtOAc 5:2) to give 0.193 g (65%) of a gum. The gum was converted to its hydrochloride salt at $0\text{ }^\circ\text{C}$ using concentrated HCl (2 mL) in methanol (10 mL). The solid was separated and crystallized from *n*-hexane/DCM; mp $189\text{ }^\circ\text{C}$ (lit.⁵ $190\text{--}191\text{ }^\circ\text{C}$, for the HCl salt); $[\alpha]_D^{20} +139$ (c 0.6, CH_3OH), [lit.⁵ -141 (c 0.9, CH_3OH) for the enantiomer of the free base]; IR (neat): $3366, 2870, 1606, 1459\text{ cm}^{-1}$; ^1H NMR (CDCl_3) δ 1.34 (d, $J = 6.9\text{ Hz}$, 3 H), 2.31 (dd, $J = 15.3, 15.3\text{ Hz}$, 1 H), 2.40 (s, 3 H), 2.57 (dd, $J = 15.6, 4.6\text{ Hz}$, 1 H), 3.28 (m, 1 H), 3.80 (s, 6 H), 6.28, 6.32 (2d, $J = 2.1\text{ Hz}$, 2H); ^{13}C NMR (CDCl_3) δ 21.81, 27.44, 35.14, 51.22, 55.26, 97.07, 104.11, 113.03, 142.28, 158.92, 161.78, 163.07. HRMS calcd for $\text{C}_{13}\text{H}_{17}\text{N}$ (M+H), 220.1337; found 220.1330.

(1R,3R)-(-)-6,8-Dimethoxy-1,3-dimethyl-1,2,3,4-tetrahydro-isoquinoline (4). In a 25-mL of two-necked round bottomed flask equipped with a stirring bar and rubber septa under an argon atmosphere was placed LAH (0.097 g, 2.55 mmol) in THF (25 mL) at $-78\text{ }^\circ\text{C}$. Isoquinoline (3R)-(+)-**11** (0.080 g, 0.365 mmol) in THF (2 mL) was added followed by the dropwise addition of trimethyl aluminum (1.27 mL, 2 M in hexanes, 2.55 mmol). The reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 0.5 h, at $-45\text{ }^\circ\text{C}$ for 1 h at $-25\text{ }^\circ\text{C}$ for 1 h and at $0\text{ }^\circ\text{C}$ for 1 h. At this time the reaction mixture was cooled to $-45\text{ }^\circ\text{C}$, quenched with saturated NaF (2 mL) and stirred for 15 min. The solution was filtered and concentrated to give 0.093 g (93%) of a gum. The product was converted to its HCl salt using concentrated HCl (2 mL) and methanol (10 mL). Evaporation gave a solid that was crystallized from *n*-hexane/DCM mp $>260\text{ }^\circ\text{C}$; $[\alpha]_D^{20} -7.4$ (c 0.9, CH_3OH), [lit.⁵ -7.58 (c 0.6 CH_3OH) for the HCl salt]. Spectral properties were in agreement with literature values.⁵

(1*S*,3*R*)-(-)-6,8-Dimethoxy-1,3-dimethyl-1,2,3,4-tetrahydroiso-quinoline 17.

In a 25-mL of two-necked round bottomed flask equipped with a stirring bar and rubber septa under an argon atmosphere was placed (0.08 g, 0.365 mmol) of (3*R*)-(+)-**11** in dry methanol (15 mL) and NaBH₄ (0.015 g, 0.401 mmol) at 0 °C. The reaction mixture was stirred for 15 h, Al₂O₃ (0.5 g) was added, and concentrated. Purification by silica gel column chromatography (Et₃N, EtOAc) gave 0.072 g (91%) of a gum that was converted to its HBr salt using 48% HBr (2 mL). Methanol (10 mL) was added and the solution concentrated to give a solid that was crystallized EtOH; mp >260 °C; [α]²⁰_D -130 (*c* 1, CH₃OH) [lit.⁶ +132 (*c* 1.01, CH₃OH) for the HBr salt of the enantiomer]. Spectral properties were in agreement with literature values.⁶ The ¹⁹F NMR of the Mosher amide of (-)-**17** confirmed that the ee was >95%.

References

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