

Asymmetric Synthesis of Functionalized *trans*-2,6-Disubstituted Piperidines using *N*-Sulfinyl δ -Amino β -Ketoesters. Synthesis of (-)-Lasubine (I).

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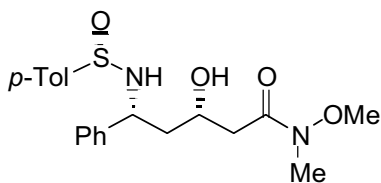
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Supporting Information

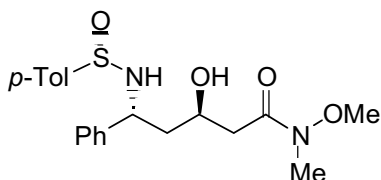
General Procedures. Column chromatography was performed on silica gel, Merck grade 60 (230-400 mesh). TLC plates were visualized with UV, in an iodine chamber, or with phosphomolybdic acid, unless noted otherwise. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 polarimeter and IR spectra were recorded, using NaCl plates or as KBr disks, on a Mattson 4020 FTIR. ¹H NMR and ¹³C NMR spectra were recorded on a GE Omega 500, operating at 500 and 125 MHz, respectively. 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.

Dichloromethane was distilled over calcium hydride under an inert atmosphere. THF and ether were freshly distilled under argon from a purple solution of sodium and benzophenone ketyl. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. (*S_S,3*S*,5*R**)-(+)-Methyl 3-hydroxy-5-(*p*-toluenesulfinylamino)-5-phenyl-pentanoate (*syn*-**2a**),¹ (*S_S,3*R*,5*R**)-(+)-methyl 3-hydroxy-5-(*p*-toluenesulfinylamino)-5-phenyl pentanoate (*anti*-**2b**),¹ and (*R_S,3*R*,5*S**)-(-)-methoxy-*N*-methyl-3-hydroxy-5-(3,4-dimethoxyphenyl)-5-*N*-(*p*-toluenesulfinyl)pentanamide (**9**)² were prepared as described earlier.

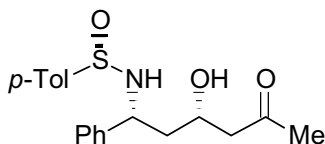


(*S_S,3*S*,5*R**)-(+)-3-Hydroxy-5-phenyl-5-*N*-(*p*-toluenesulfinyl)aminopentanoic acid *N*-methoxy *N*-methyl amide (**3a**). In a 250-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon inlet was placed *N,O*-dimethylhydroxylamine hydrochloride (4.9 g, 49.8 mmol, 9.0 equiv) in THF (80 mL). The solution was cooled to -78 °C, and *n*-BuLi (39.8 mL, 99.5 mmol, 18.0 equiv, 2.5 M in hexanes) was added dropwise. The reaction mixture was stirred for 15 min after removing the dry ice/acetone bath, cooled to -78 °C and (+)-**2a** (2.0 g, 5.53 mmol) in THF (30 mL) was added dropwise. The reaction mixture was stirred for 3 h, and quenched at -78 °C with sat. NH₄Cl (30 mL). The reaction mixture was washed with EtOAc (2 x 25 mL), the organic phases were dried (MgSO₄), and concentrated. Purification by flash chromatography (5% MeOH/15% DCM/EtOAc) gave 2.1 g (98%) of an oil; [α]_D²⁰ 72.1 (*c* 2.4, CHCl₃); IR (neat) cm⁻¹ 3413, 3228, 1645, 1452; ¹H NMR (CDCl₃) δ 7.56 (d, 2 H, *J* = 8.07 Hz), 7.4 (d, 2 H, *J* = 7.33 Hz), 7.38 (m, 2 H), 7.3 (m, 3 H), 5.6 (s, 1 H), 4.8 (m, 1 H), 4.3 (broad s, 1 H), 4.2 (m, 1 H), 3.6 (s, 3 H), 3.2

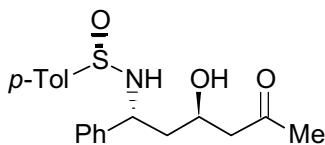
(s, 3 H), 2.5 (m, 1 H), 2.4 (s, 3 H), 2.2 (m, 1 H), 2.0 (m, 1 H), 1.8 (m, 1 H); ^{13}C NMR (CDCl_3) δ 173.4, 143.2, 142.6, 141.5, 130.0, 129.1, 128.2, 127.4, 125.7, 68.0, 61.6, 58.2, 45.0, 40.0, 32.2, 21.8. HRMS calcd for $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_4\text{S}$ ($\text{M}+\text{Na}$) 413.1512. Found 413.1511.



($S,S,3R,5R$)-(+)-3-Hydroxy-5-phenyl-5-*N*-(*p*-toluenesulfinyl)aminopentanoic acid *N*-methoxy *N*-methyl amide (3b). Purified by preparative TLC (5% MeOH/15% CH_2Cl_2 /EtOAc) gave 90% of an oil; $[\alpha]_D^{20}$ 26.5 (*c* 0.17, CHCl_3); IR (neat) cm^{-1} 3623, 2925, 1652; ^1H NMR (CDCl_3) δ 7.6 (d, 2 H, $J = 8.0$ Hz), 7.3–7.4 (m, 7 H), 5.32 (d, 1 H, $J = 5.5$ Hz), 4.85 (m, 1 H), 4.12 (m, 2 H), 3.7 (s, 3 H), 3.18 (s, 3 H), 2.6 (m, 2 H), 2.41 (s, 3 H), 2.0 (m, 3 H); ^{13}C NMR (CDCl_3) δ 173.0, 143.0, 142.4, 141.2, 130.5, 129.4, 128.9, 128.4, 126.4, 66.1, 61.9, 56.8, 44.3, 38.7, 30.5, 22.0. HRMS calcd for $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_4\text{S}$ ($\text{M}+\text{Na}$) 413.1511. Found 413.1514.



($S,S,1R,3S$)-(+)-1-Phenyl-1-(*N*-*p*-toluenesulfinyl)amino-3-hydroxy-5-oxo-hexane (4a). In a 100-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed (+)-**3a** (0.8 g, 2.05 mmol) in ether (50 mL). The solution was cooled to -78°C and MeMgBr (6.8 mL, 20.5 mmol, 10.0 equiv) was added dropwise. The reaction mixture was stirred for 8 h, warming from -78°C to rt, and quenched with sat. NH_4Cl (10 mL). The solution was extracted with EtOAc (2 x 10 mL), the combined organic phases were dried (MgSO_4), and concentrated. Purification by flash chromatography (50% EtOAc/DCM) gave 0.66 g (94%) of an oil; $[\alpha]_D^{20}$ 56.0 (*c* 2.31, CHCl_3); IR (neat) cm^{-1} 3367, 3243, 1706, 1421, 1050; ^1H NMR (CDCl_3) δ 7.5 (d, 2 H, $J = 8.07$ Hz), 7.4 (d, 2 H, $J = 8.4$ Hz), 7.3 (m, 3 H), 7.2 (d, 2 H, $J = 8.07$ Hz), 5.4 (d, 1 H, $J = 2.57$ Hz), 4.75 (m, 1 H), 4.2 (m, 1 H), 3.87 (d, 1 H, $J = 2.93$ Hz), 2.5 (m, 2 H), 2.4 (s, 3 H), 2.1 (s, 3 H), 1.95 (m, 1 H), 1.75 (m, 1 H); ^{13}C NMR (CDCl_3) δ 209.4, 143.0, 142.6, 141.7, 129.9, 129.1, 128.2, 127.8, 125.8, 125.7, 67.5, 58.2, 50.8, 44.8, 31.1, 21.8. HRMS calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_3\text{S}$ ($\text{M}+\text{Na}$) 368.1296. Found 368.1293.

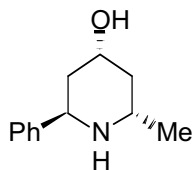


($S,S,1R,3R$)-(+)-1-Phenyl-1-(*N*-*p*-toluenesulfinyl)amino-3-hydroxy-5-oxo-hexane (4b). Purification by preparative TLC (50% EtOAc/DCM) gave 88% of an oil; $[\alpha]_D^{20}$ 27.0 (*c* 0.2, CHCl_3); IR (neat) cm^{-1} 3589, 2921, 1702, 1551; ^1H NMR (CDCl_3) δ 7.6 (d, 2 H, $J = 8.1$ Hz), 7.4–7.3 (m, 7 H), 5.1 (d, 1 H, $J = 6.0$ Hz), 4.8 (m, 1 H), 4.2 (m, 1 H), 3.5 (d, 1 H, $J = 3.0$ Hz), 2.7 (dd, 1 H, $J = 9.0$ Hz, $J = 17.5$ Hz), 2.5 (dd, 1 H, $J = 3.0$ Hz, $J = 17.5$ Hz), 2.4 (s, 3 H), 2.1 (s, 3 H), 1.9 (m, 2 H); ^{13}C NMR (CDCl_3) δ 172.8, 142.0, 137.1, 130.9, 130.2, 129.9, 129.2, 128.4, 128.0, 127.4, 126.0, 65.3, 56.5, 50.2, 44.8, 31.2, 21.8. HRMS calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_3\text{S}$ ($\text{M}+\text{Na}$) 368.1296. Found 368.1309.

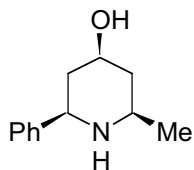
General procedure for the preparation of *cis*- and *trans*-2,6-disubstituted piperidines. In a 10-mL, round-bottomed flask, equipped with a magnetic stirring bar,

and argon balloon was placed (+)-**4a** (0.05 g, 0.145 mmol) in THF (3 mL). The solution was cooled to 0 °C and 10 drops of 2 N HCl was added dropwise. The mixture was stirred for 15 min and quenched with 28% NH₄OH (0.5 mL). The reaction mixture was diluted with CH₂Cl₂ (10 mL), the organic phase was separated, dried (MgSO₄), and concentrated. The residue was dissolved in ether (8 mL) and added via syringe to the hydride reagent at -78 °C. The solution was kept at this temperature for 30 min, at -45 °C for 1 h, at -20 °C for 1 h, and at 0 °C for 8 h. The solution was quenched by addition of sat. Na₂SO₄ (5 mL) and filtered through Celite. The filtrate was extracted with CH₂Cl₂ (2 x 10 mL), dried over MgSO₄, and concentrated.

(2R,4R,6R)-(+)-2-Methyl-6-phenylpiperidin-4-ol (6). Purification by preparative TLC (9:1 EtOAc:MeOH) gave 68% of a solid, mp 112-114 °C [lit.³ mp 114 °C for (2S,4S,6S)]; [α]_D²⁰ 37.5 (c 0.2, CHCl₃) [lit.³ [α]_D²⁰ -33.8 (c 0.86, CHCl₃) for (2S,4S,6S)]; ¹H NMR (CDCl₃) δ 7.4 (m, 2 H), 7.3 (m, 2 H), 7.2 (m, 2 H), 4.28 (m, 1 H), 4.14 (dd, 1 H, *J* = 2.44 Hz, *J* = 11.72 Hz), 3.28 (m, 1 H), 1.85 (m, 1 H), 1.75 (m, 3 H), 1.5 (m, 2 H), 1.1 (d, 3 H, *J* = 6.34 Hz); ¹³C NMR (CDCl₃) δ 143.9, 128.9, 127.6, 127.3, 66.4, 56.3, 47.2, 41.4, 41.1, 22.9. HRMS calcd for C₁₂H₁₇NO (M+H) 192.1388. Found 192.1392.



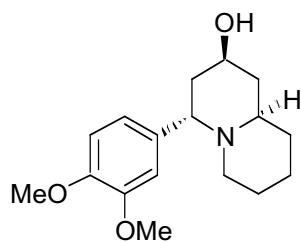
(2S,4R,6R)-(-)-2-Methyl-6-phenylpiperidin-4-ol (7). In a 25-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed DIBAL-H (0.29 mL, 0.29 mmol, 2.0 equiv, 1.0 M solution in hexanes) in anhydrous ether (3 mL) at -15 °C. *n*-Butyllithium (0.12 mL, 0.29 mmol, 2.0 equiv, 2.5 M solution in hexanes) was added dropwise and the solution was stirred at this temperature for 1 h to form the “ate” complex. In a separate 10-mL, round-bottomed flask, equipped with a magnetic stirring bar and argon balloon, was placed (+)-**4a** (0.05 g, 0.145 mmol) in THF (3 mL). The solution was cooled to 0 °C and 10 drops of 2 N HCl was added dropwise, the reaction mixture was stirred for 15 min and quenched with 28% NH₄OH (0.5 mL). The solution was diluted with CH₂Cl₂ (10 mL), the organic phase was dried (MgSO₄), and concentrated. The residue was dissolved in ether (8 mL) and was added dropwise, via syringe, to the -78 °C solution of the “ate” complex. The reaction was stirred at -78 °C for 1 h, at -45 °C for 1 h, at -20 °C for 1 h, and at 0 °C for 8 h. At this time the reaction mixture was quenched with sat. Na₂SO₄ (1 mL), filtered through Celite, dried (MgSO₄), concentrated. Purification by preparative TLC (10% MeOH/EtOAc) gave 0.016 g (60%) of a solid; mp 125-126 °C; [α]_D²⁰ -24.8 (c 0.5, CHCl₃); IR (KBr) cm⁻¹ 3297, 1459, 1305, 1112; ¹H NMR (CDCl₃) δ 7.4 (m, 2 H), 7.3 (m, 2 H), 7.2 (m, 2 H), 4.41 (t, 1 H, *J* = 4.2 Hz), 3.9 (m, 1 H), 2.95 (m, 1 H), 2.5 (m, 1 H), 1.96 (m, 1 H), 1.8 (m, 2 H), 1.2 (d, 3 H, *J* = 6.23 Hz); ¹³C NMR (CDCl₃) δ 143.1, 128.9, 127.0, 126.9, 66.1, 53.8, 45.8, 43.5, 38.9, 22.8. HRMS calcd for C₁₂H₁₇NO (M+H) 192.1388. Found 192.1384.



(2R,4S,6R)-(+)-2-Methyl-6-phenylpiperidin-4-ol (8). Purification by preparative TLC (10% MeOH/EtOAc), gave 70% of a solid; mp 120 °C; [α]_D²⁰ 29.0 (c 0.5, CHCl₃), [α]_D²⁰ 5.0 (c 0.4, MeOH), [lit.⁴ [α]_D²⁰ -5.9 (c 0.8, MeOH) for (2S,4R,6S)]; ¹H NMR (CDCl₃) δ 7.3

(m, 5 H), 3.8 (m, 1 H), 3.7 (dd, 1 H, $J = 2.44$ Hz, $J = 11.72$ Hz), 2.9 (m, 1 H), 2.1 (m, 1 H), 1.8 (broad s, 2 H), 1.45 (q, 1 H, $J = 11.72$ Hz, $J = 22.95$ Hz), 1.15 (m, 4 H); ^{13}C NMR (CDCl_3) δ 144.4, 128.9, 127.7, 127.2, 70.2, 60.1, 51.1, 43.8, 22.9. Spectral properties were in agreement with literature values.⁴

(*R_S*,3*R*,5*S*)-(-)-1-(3,4-Dimethoxyphenyl)-1-(*N*-*p*-toluenesulfinyl)amino-3-hydroxy-5-oxo-9-chlorononane (10). In a 25-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon was placed magnesium (0.243 g, 10.0 mmol) in ether (10 mL). A few drops of 1-bromo-4-chlorobutane (1.68 g, 9.8 mmol) was added to the solution and the reaction was initiated by warming with a heat gun. After initiation the solution was cooled to 0 °C and the remainder of the halide was added dropwise over 15 min maintaining the temperature at 0-5 °C. When the reaction was complete the solution was stirred for 1 h at rt. In a separate 100-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed (-)-**9** (0.45 g, 1.0 mmol) in THF (8 mL). The solution was cooled to -78 °C and the preformed Grignard reagent was added via cannula. The solution was stirred for 8 h, warming from -78 °C to rt, and quenched with sat. NH_4Cl (10 mL). At this time the reaction mixture was extracted with EtOAc (2 x 15 mL), the organic phases were dried (MgSO_4), and concentrated. Purification by flash chromatography (50% EtOAc/hexanes) gave 0.25 g (53%) of a oil; $[\alpha]_{\text{D}}^{20}$ -20.5 (c 0.95, CHCl_3); IR (neat) cm^{-1} 3261, 1706, 1512; ^1H NMR (CDCl_3) δ 7.55 (d, 2 H, $J = 9.0$ Hz), 7.27 (d, 2 H, $J = 9.0$ Hz), 6.98 (m, 2 H), 6.86 (d, 1 H, $J = 7.0$ Hz), 5.31 (br s, 1 H), 4.7 (m, 1 H), 4.19 (m, 1 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 3.7 (m, 1 H), 3.5 (t, 2 H, $J = 6.0$ Hz), 2.35-2.55 (m, 7 H), 1.65-2.0 (m, 6 H); ^{13}C NMR (CDCl_3) δ 211.1, 148.8, 142.7, 135.5, 130.0, 125.7, 125.5, 120.2, 119.3, 111.5, 110.4, 65.1, 56.4, 55.8, 48.9, 45.0, 44.4, 43.0, 32.2, 21.8, 21.1. HRMS calcd for $\text{C}_{24}\text{H}_{32}\text{ClNO}_5\text{S}$ ($\text{M}+\text{Na}$) 504.1587. Found 504.1575.



(-)- Lasubine I (12). In a 25-mL, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed (-)-**10** (0.1 g, 0.21 mmol) in THF (3 mL). To this solution was added 6-8 drops of 2 N HCl at 0 °C, and after stirring for 15 min, the reaction mixture was quenched with 28% NH_4OH (0.5 mL). The solution was extracted with CH_2Cl_2 (3 x 5 mL), the organic phase was washed with brine (5 mL), dried (MgSO_4), and concentrated. In a separate 25-mL, one-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed DIBAL-H (0.46 mL, 0.46 mmol, 2.2 equiv, 1.0 M solution in hexanes) in anhydrous ether (3 mL) at -15 °C. *n*-Butyllithium (0.18 mL, 0.46 mmol, 2.2 equiv, 2.5 M solution in hexanes) was added dropwise and the solution was stirred at -15 °C for 1 h to form the “ate” complex. The preformed imine was added at -78 °C via a syringe to the ate complex under an argon atmosphere. The reaction mixture was stirred at -78 °C for 4 h, -45 °C for 4 h, -20 °C for 4 h, and 10 °C for 8 h. At this time

the reaction mixture was quenched with sat. Na₂SO₄ (0.5 mL), filtered through Celite, dried (MgSO₄), and concentrated. Purification by preparative TLC (9:1 EtOAc:MeOH) gave 0.036 g (60%) of an oil; [α]_D²⁰ -7.9 (c 0.2, CHCl₃); [lit.⁵ [α]_D²⁰ -8.0 (c 0.2, CHCl₃)]; Spectral properties were in agreement with literature values.⁵

References

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