ASYMMETRIC SYNTHESIS OF (+)-L-733, 060 AND (+)-CP-99, 994 BASED ON A NEW CHIRAL 3-PIPERIDINOL SYNTHON

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Optical rotations were recorded on a Perkin-Elmer 341 automatic polarimeter. ^1H -NMR and ^{13}C -NMR spectra were recorded on Varian unity +500 spectrometer. Unless otherwise noted, ^1H -NMR spectra were registered in CDCl_3 , and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si . IR spectra were recorded on a Nicolet Avatar 360 FT-IR spectrophotometer. Mass spectra were recorded by Bruker Dalton Esquire 3000 plus and Finnigan Mat-LCQ (ESI direct injection). HRFABMS spectra were recorded on a Bruker APEX-FTMS apparatus. Elemental analyses were performed using a Vario RL analyzer. Melting points were determined on a Yanaco MP-500 melting point apparatus and are uncorrected.

The L-glutamic acid used in this study was commercially available. Tetrahydrofuran was distilled prior to use from sodium benzophenone ketyl. Methylene chloride was distilled from phosphorus pentoxide. Dimethylformamide was distilled from calcium hydride. Silica gel (zhifu, 300-400 mesh) from Yantai silica gel factory (China) was used for column chromatography, eluting (unless otherwise stated) with ethyl acetate/petroleum ether (PE) (60-90 °C) mixture.

(S)-N-(4-Methoxybenzyl)-tetrahydro-5-oxo-2-furancarboxamide (7)

A mixture of **6** (6.263 g, 48.2 mmol), prepared from L-glutamic acid according to known procedure,¹ and thionyl chloride (10.6 mL, 150.0 mmol) was refluxed for 5 h and then stirred at room temperature overnight. The excess thionyl chloride was removed in vacuo and the residue was dissolved in dry CH_2Cl_2 (40 mL). At 0 °C and under nitrogen atmosphere, triethylamine (10 mL, 71.9 mmol) and 4-methoxybenzylamine (6.3 mL, 48.0 mmol) in CH_2Cl_2 (8 mL) were added successively. After being stirred at rt for 3 h, water (20 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated at reduced pressure to give **7** (8.380 g, 70%) as a colorless needle crystal. Mp: 92-93 °C (EtOAc). $[\alpha]_{\text{D}}^{20}$ -4.89° (*c* 0.9, CHCl_3). IR (film) ν_{max} : 3349, 3326, 2925, 1777, 1667, 1646, 1540, 1513, 1249, 1188, 1050 cm^{-1} . ^1H -NMR (500 MHz, CDCl_3) δ 7.10 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.60 (brs, 1H), 4.89 (dd, *J* = 7.7, 7.7 Hz, 1H), 4.44 (dd, *J* = 14.4, 5.8 Hz, 1H), 4.36 (dd, *J* = 14.4, 5.8 Hz, 1H), 3.78 (s, 3H), 2.67 (m, 1H), 2.57 (dd, *J* = 8.0, 8.0 Hz, 2H), 2.38 (m, 1H). ^{13}C -NMR (125 MHz, CDCl_3) δ : 175.73, 168.98, 159.07, 129.31, 129.19 (2C), 114.04 (2C), 77.37, 55.21, 42.65, 27.51, 25.74. MS (APCI): 122 ($\text{M}^+ - 127$, 100), 250 ($\text{M}^+ + 1$, 30). HRESIMS calcd for $[\text{C}_{13}\text{H}_{15}\text{NO}_4 + \text{H}]^+$: 250.1074; found 250.1079. Anal. Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_4$: C, 62.65;

H, 6.02; N, 5.62. Found: C, 62.64; H, 6.08; N, 5.41.

(S)-3-Hydroxy-1-(4-methoxybenzyl)-2,6-piperidinedione (8)

(S)-8

To a mixture of **7** (4.205 g, 16.89 mmol) and potassium *tert*-butoxide (794 mg, 7.09 mmol) was added dry THF (50 mL) at -78°C and under nitrogen atmosphere. After being stirred for 1 h at -78 – -40°C , the reaction was quenched with saturated NH_4Cl . The THF was removed in vacuo and the residue was extracted with EtOAc (3×30 mL). The EtOAc extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4 , and concentrated to give compound **8** (3.800 g, yield 90%) as a white crystal. Mp: 98 – 99°C (EtOAc). $[\alpha]_{\text{D}}^{20} -70.00^{\circ}$ (c 1.2, CHCl_3). IR (film) ν_{max} : 3465, 2960, 1730, 1677, 1514, 1338, 1305, 1249, 1177, 1112, 997 cm^{-1} . ^1H -NMR (500 MHz, CDCl_3) δ : 7.32 (d, $J = 8.6$ Hz, 2H), 6.80 (d, $J = 8.6$ Hz, 2H), 4.90 (s, 2H), 4.22 (ddd, $J = 12.9, 5.4, 1.4$ Hz, 1H), 3.78 (s, 3H), 3.55 (dd, $J = 2.6, 1.4$ Hz, 1H), 2.88 (ddd, $J = 18.1, 4.8, 2.6$ Hz, 1H), 2.66 (ddd, $J = 18.1, 12.9, 5.4$ Hz, 1H), 2.34 (dddd, $J = 12.9, 5.4, 5.4, 2.6$ Hz, 1H), 1.88 (dddd, $J = 12.9, 12.9, 12.9, 4.8$ Hz, 1H). ^{13}C -NMR (125 MHz, CDCl_3) δ : 175.13, 171.05, 159.09, 130.47 (2C), 128.74, 113.77 (2C), 68.35, 55.20, 43.04, 30.87, 25.20. MS (EI) 249 (M^+ , 100), 231 ($\text{M}^+ - \text{H}_2\text{O}$, 1), 203 (28), 176 (22). HRESIMS Calcd for $[\text{C}_{13}\text{H}_{15}\text{NO}_4 + \text{Na}]^+$: 272.0893; Found: 272.0897. Anal. Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_4$: C, 62.65; H, 6.02; N, 5.62; Found: C, 62.58; H, 5.98; N, 5.41.

(S)-3-[(*tert*-Butyldiphenylsilyl)oxy]-1-(4-methoxybenzyl)-2,6-piperidinedione (9)

(S)-9

To a mixture of **8** (4.100 g, 16.47 mmol), imidazole (2.239 g, 32.93 mmol) and a catalytic amount of DMAP in anhydrous CH_2Cl_2 (40 mL), at 0°C and under nitrogen atmosphere, was added slowly a solution of *tert*-butyldiphenylchlorosilane (4.7 mL, 18.10 mmol) in CH_2Cl_2 (5 mL). After being stirred at room temperature overnight, water (20 mL) was added. Aqueous phase was separated, washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. After flash chromatographic purification (eluent: EtOAc/PE = 1: 8), **9** (7.538 g, yield 94%) were obtained as a colorless oil. $[\alpha]_{\text{D}}^{20} -36.71^{\circ}$ (c 1, CHCl_3). IR (film) ν_{max} : 2958, 2932, 2857, 1685, 1513, 1306, 1249, 1160, 1111, 703 cm^{-1} . ^1H -NMR (500 MHz, CDCl_3) δ : 7.68–6.80 (m, 14H), 4.87 (d, $J = 13.8$ Hz, 1H), 4.84 (d, $J = 13.8$ Hz, 1H), 4.29 (dd, $J = 8.2, 4.2$ Hz, 1H), 3.79 (s, 3H), 2.88 (ddd, $J = 17.9, 6.2, 6.2$ Hz, 1H), 2.46 (ddd, $J = 17.9, 8.2, 5.6$ Hz, 1H), 1.96–1.83 (m, 2H), 1.09 (s, 9H). ^{13}C -NMR (125 MHz, CDCl_3) δ : 171.70, 171.64, 158.90,

135.99 (2C), 135.77 (2C), 133.27, 132.39, 130.31 (2C), 130.08 (2C), 129.38, 127.83 (2C), 127.71 (2C), 113.70 (2C), 69.89, 55.24, 42.47, 29.35, 26.82, 26.16, 19.38. MS (ESI) 488 ($M^+ + 1$, 100). Anal. Calcd for $C_{29}H_{33}NO_4Si$: C, 71.46; H, 6.78; N, 2.87. Found: C, 71.57; H, 6.68; N, 2.59.

(5*S*, 6*RS*)-5-[(*tert*-Butyldiphenylsilyl)oxy]-6-hydroxy-1-(4-methoxybenzyl)-2-piperidinone (10)

(5*S*, 6*RS*)-10

To a cooled solution of **9** (4.300 g, 8.83 mmol) in MeOH/ CH_2Cl_2 (4:1, 25 mL), was added $NaBH_4$ (1.006 g, 26.47 mmol). After being stirred for 30 min, the reaction was quenched by successive addition of saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography (eluent: EtOAc/PE = 1:2) to give 2.832 g of *cis*-**10** and 0.622 g of *trans*-**10** (combined yield 80%). Major *cis*-diastereoisomer: White crystal. Mp: 165-166 °C (EtOAc/PE = 1:1). $[\alpha]_D^{20}$ -54.28° (*c* 1.3, $CHCl_3$). IR (film) ν_{max} : 3342, 2931, 2857, 1662, 1513, 1471, 1427, 1247, 1112, 703, 507 cm^{-1} . 1H -NMR (500 MHz, $CDCl_3$) δ : 7.62-6.80 (m, 14H), 5.05 (d, *J* = 14.7 Hz, 1H), 4.60 (d, *J* = 2.2 Hz, 1H), 4.12 (d, *J* = 14.7 Hz, 1H), 3.90 (ddd, *J* = 9.9, 3.5, 2.2 Hz, 1H), 3.80 (s, 3H), 3.00 (s, 1H), 2.55 (ddd, *J* = 17.8, 5.3, 5.3 Hz, 1H), 2.20 (ddd, *J* = 17.8, 9.8, 6.6 Hz, 1H), 2.07 (m, 1H), 1.60 (m, 1H), 1.10 (s, 9H). ^{13}C -NMR (125 MHz, $CDCl_3$) δ : 169.30, 158.85, 135.63 (2C), 135.48 (2C), 132.79, 132.60, 130.22, 129.60 (2C), 129.58 (2C), 127.98 (2C), 127.93 (2C), 113.90 (2C), 79.86, 69.16, 55.27, 46.63, 29.06, 26.93, 23.83, 19.16. Minor *trans*-diastereoisomer: White crystal. Mp: 174.5-175.5 °C (EtOAc/PE = 1:1). $[\alpha]_D^{20}$ +31.71° (*c* 0.9, $CHCl_3$). 1H -NMR (500 MHz, $CDCl_3$) δ : 7.56-6.76 (m, 14H), 5.04 (d, *J* = 14.7 Hz, 1H), 4.54 (d, *J* = 3.1 Hz, 1H), 4.15 (d, *J* = 14.7 Hz, 1H), 3.92 (brs, 1H), 3.78 (s, 3H), 2.82 (m, 1H), 2.65 (dd, *J* = 17.7, 5.9 Hz, 1H), 2.38 (dd, *J* = 17.7, 6.0 Hz, 1H), 2.06 (m, 1H), 1.62 (brs, 1H), 0.98 (s, 9H). ^{13}C -NMR (125 MHz, $CDCl_3$) δ : 170.45, 158.92, 135.70 (2C), 135.64 (2C), 133.32, 133.07, 129.99, 129.79 (2C), 129.70, 129.25, 127.78 (2C), 127.66 (2C), 114.02 (2C), 81.69, 68.51, 55.26, 46.34, 27.19, 26.83, 22.78, 19.16. MS (ESI): 490 ($M^+ + 1$, 100). Anal. Calcd for $C_{29}H_{35}NO_4Si$: C, 71.17; H, 7.16; N, 2.86. Found: C, 71.42; H, 7.08; N, 2.57.

(5*S*, 6*S*)-5-Hydroxy-1-(4-methoxybenzyl)-6-phenyl-2-piperidinone (13)

(5*S*, 6*S*)-13

To an ice-bath cooled solution of **10** (1.000 g, 2.04 mmol) in dry CH_2Cl_2 (20 mL) was added

slowly and under nitrogen atmosphere, $\text{BF}_3 \cdot \text{OEt}_2$ (2.5 mL, 20.25 mmol). After being stirred for 72 h at room temperature, saturated aqueous NaHCO_3 (1 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were stirred for 24 h at room temperature. Water (10 mL) was added and the solution was basified with an aqueous NaOH solution to reach pH 8. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL) and the combined organic layers were washed with brine (5 mL), dried with anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography (eluent: $\text{EtOAc/PE} = 2:1$) to give **13** (0.515 g, yield 81%) as a white crystal. Mp: 172.5-173.5 °C (EtOAc/PE). $[\alpha]_{\text{D}}^{26} -63.39^\circ$ (c 0.6, CHCl_3). IR (film) ν_{max} : 3308, 2945, 1615, 1509, 1417, 1243, 1171, 710 cm^{-1} . $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 7.42-6.82 (m, 9H), 5.51 (d, $J=14.6$ Hz, 1H), 4.48 (d, $J=5.2$ Hz, 1H), 4.04 (ddd, $J=13.7, 8.3, 5.2$ Hz, 1H), 3.80 (s, 3H), 3.29 (d, $J=14.6$ Hz, 1H), 2.78 (ddd, $J=18.3, 5.2, 5.2$ Hz, 1H), 2.61 (ddd, $J=18.3, 8.8, 8.8$ Hz, 1H), 1.81 (m, 2H), 1.39 (d, $J=7.8$ Hz, 1H, D_2O exchangeable). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ : 169.72, 159.08, 135.32, 129.73 (2C), 128.89 (2C), 128.84 (2C), 128.63 (2C), 114.01 (2C), 67.24, 63.33, 55.28, 47.32, 29.49, 25.50. MS (ESI) 312 (M^++1 , 100), 334 (M^++23 , 66). Anal. Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_3$: C, 73.31; H, 6.75; N, 4.50. Found: C, 73.63; H, 6.44; N, 4.38.

(2*S*, 3*S*)-3-Hydroxy-1-(4-methoxybenzyl)-2-phenylpiperidine (14)

(2*S*, 3*S*)-14

To an ice-bath cooled suspension of lithium aluminum hydride (281 mg, 7.39 mmol) in dry THF (6 mL), was added, under nitrogen atmosphere, a solution of **13** (460 mg, 1.48 mmol) in dry THF (4 mL). The resulting mixture was stirred for 3 h at room temperature. The mixture was re-cooled with an ice-bath, then wet ether (5 mL), a 10% solution of sodium hydroxide (0.4 mL) and H_2O (0.1 mL) were added successively. The mixture was allowed to reach rt, stirred for 30 min, and filtered through celite. After being concentrated at reduced pressure, the residue was purified by flash chromatography on silica gel (eluent: $\text{EtOAc/PE} = 1:4$) to afford **14** (355 mg, 81%) as a pale yellow oil, which was crystallized from acetone. Pale yellow crystal. Mp: 106-107 °C. $[\alpha]_{\text{D}}^{26} +21.14^\circ$ (c 1.1, CHCl_3). IR (film) ν_{max} : 3423, 2936, 2854, 1511, 1453, 1246, 1177, 1117, 1033, 827, 703 cm^{-1} . $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 7.46-6.83 (m, 9H), 3.83 (d, $J = 13.6$ Hz, 1H), 3.80 (s, 3H), 3.76 (brs, 1H), 3.36 (brs, 1H), 3.04 (brd, $J = 9.5$ Hz, 1H), 2.95 (d, $J = 13.6$ Hz, 1H), 2.84-2.42 (brs, 1H), 2.09-1.93 (m, 3H), 1.61 (m, 1H), 1.51 (m, 1H). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ : 158.75, 140.50, 130.10 (2C), 128.65 (2C), 128.38 (2C), 127.57 (2C), 113.61 (2C), 72.12, 69.93, 58.64, 55.26, 53.09, 31.45, 19.68. MS (ESI) 298 (M^++1 , 100), 320 (M^++23 , 15). Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_2$: C, 76.77; H, 7.74; N, 4.71. Found: C, 76.53; H, 7.65; N, 4.84.

(2*S*, 3*S*)-1-(*tert*-Butoxycarbonyl)-3-hydroxy-2-phenylpiperidine (15)

(2S,3S)-15

To a mixture of **14** (136 mg, 0.46 mmol) and Pd(OH)₂/C (110 mg, 20% Pd) were added ethanol (5 mL) and di-*tert*-butyldicarbonate (0.32 mL, 1.39 mmol). After being stirred at rt under an atmosphere of H₂ for 72 h, the mixture was filtered over celite and concentrated. The residue was purified by flash chromatography on silica gel (eluent: CH₂Cl₂/CH₃COCH₃ = 20:1) to provide **15** (112 mg, 88%) as a colorless oil. $[\alpha]_D^{15} +53.77^\circ$ (*c* 1.0, CHCl₃). IR (neat) $\nu_{\max}$: 3445, 2974, 2938, 2869, 1692, 1675, 1453, 1414, 1366, 1295, 1252, 1171, 1147, 1081, 964, 701 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃) δ : 7.48-7.24 (m, 5H), 5.33 (d, *J* = 5.5 Hz, 1H), 4.08 (ddd, *J* = 14.4, 5.5, 4.9 Hz, 1H), 4.00 (dd, *J* = 13.5, 5.1 Hz, 1H), 3.03 (ddd, *J* = 13.5, 12.0, 3.7 Hz, 1H), 1.88-1.75 (m, 3H), 1.73-1.63 (m, 1H), 1.38 (s, 9H). ¹³C-NMR (125 MHz, CDCl₃) δ : 155.43, 138.46, 128.40 (2C), 128.38 (2C), 127.19, 79.92, 70.07, 59.23, 39.46, 28.32, 27.69, 23.11. MS (ESI) 278 (M⁺+1, 25), 300 (M⁺+23, 100). HRESIMS calcd for [C₁₆H₂₃NO₃+H]⁺: 278.1751; Found: 278.1745.

(2S,3S)-1-(tert-Butoxycarbonyl)-2-phenyl-3-[(3,5-bis(trifluoromethyl)benzyl)oxy]piperidine (16)

(2S,3S)-16

To an ice-bath cooled mixture of sodium hydride (60% dispersion in mineral oil, 15 mg, 0.63 mmol) and dry DMF (0.4 mL), was added slowly, under nitrogen atmosphere, a solution of **15** (60 mg, 0.22 mmol) in dry DMF (0.6 mL). After being stirred for 30 min at room temperature, a solution of 3,5-bis(trifluoromethyl)benzyl bromide (60 μ L, 0.33 mmol) in dry DMF (0.2 mL) was added and the resulting mixture was stirred for 48 h at room temperature. The reaction was quenched with water (10 mL) and extracted with Et₂O (5 $\times$ 3 mL). The combined organic layers were washed with brine (3 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on silica gel (eluent: Et₂O/PE=1:8) to provide **16** (68 mg, 75%) as a colorless oil. $[\alpha]_D^{28} +36.90^\circ$ (*c* 1.0, CHCl₃). IR (neat) $\nu_{\max}$: 2981, 2942, 2871, 1692, 1412, 1366, 1279, 1175, 1136, 1095, 885, 704, 683 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃) δ : 7.78-7.22 (m, 8H), 5.70 (brs, 1H), 4.75 (d, *J* = 12.5 Hz, 1H), 4.71 (d, *J* = 12.5 Hz, 1H), 3.95 (m, 1H), 3.88 (m, 1H), 2.77 (ddd, *J* = 13.4, 12.9, 3.5 Hz, 1H), 2.04-1.96 (m, 2H), 1.78-1.76 (m, 2H), 1.46 (s, 9H). ¹³C-NMR (125 MHz, CDCl₃) δ : 155.31, 141.04, 138.03, 131.50 (q, *J* = 33.4 Hz), 128.35 (2C), 128.32 (2C), 127.19 (2C), 127.09 (2C), 123.25 (q, *J* = 272.6 Hz), 121.45 (2C), 80.15, 78.71, 69.17, 55.48, 39.26, 28.41, 25.86, 24.19. MS (ESI) 504 (M⁺+1, 50), 526 (M⁺+23, 100).

(2*S*, 3*S*)-2-Phenyl-3-[(3,5-bis(trifluoromethyl)benzyl)oxy]piperidine (1) **(2*S*, 3*S*)-1**

To an ice-bath cooled solution of **16** (50 mg, 0.10 mmol) in dry CH₂Cl₂ (1 mL), and under nitrogen atmosphere, was added trifluoroacetic acid (80 μ L, 1.04 mmol). The solution was stirred for 24 h at room temperature. Excess trifluoroacetic acid was removed under reduced pressure and water (2 mL) was added. The reaction mixture was basified with dilute NaOH and extracted with CH₂Cl₂ (3 $\times$ 2 mL). The CH₂Cl₂ extracts were washed with brine (1 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: CH₂Cl₂/MeOH/NH₃·H₂O = 100: 3: 1) to give **1** (37 mg, 93%) as a colorless oil. Treatment of **1** with hydrochloride gave (+)-(2*S*, 3*S*)-2-phenyl-3-[(3,5-bis(trifluoromethyl)benzyl)oxy]piperidine hydrochloride salt. Mp: 213–215 °C. $[\alpha]_D^{28} +84.49^\circ$ (*c* 0.8, MeOH) {lit.² Mp: 215–216 °C. $[\alpha]_D^{23} +87.3^\circ$ (*c* 1, MeOH)}. IR (neat, free base) $\nu_{\max}$: 3323, 2935, 2857, 1460, 1374, 1353, 1279, 1174, 1133, 890, 703, 682 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, free base) δ : 7.76–7.30 (m, 8H), 4.58 (d, *J* = 12.5 Hz, 1H), 4.19 (d, *J* = 12.5 Hz, 1H), 3.90 (brs, 1H), 3.74 (brs, 1H), 3.35 (ddd, *J*=12.5, 2.0, 2.0 Hz, 1H), 2.86 (ddd, *J*=12.5, 12.5, 2.8 Hz, 1H), 2.28 (brd, *J* = 13.7 Hz, 1H), 1.96–1.85 (m, 1H), 1.80–1.70 (m, 1H), 1.60–1.55 (m, 1H). ¹³C-NMR (125 MHz, CDCl₃, free base) δ : 141.75, 141.21, 131.30 (q, *J*=32.3 Hz), 128.19 (2C), 127.48 (2C), 127.21 (2C), 126.80 (2C), 123.35 (q, *J*=271.5 Hz), 121.23 (m, 2C), 77.29, 70.08, 64.26, 47.08, 28.45, 20.48. MS (ESI) 404 (*M*⁺+1, 100). HRESIMS calcd for [C₂₀H₁₉NOF₆+H]⁺: 404.1444; Found: 404.1454.

(*S*)-1-(*tert*-Butoxycarbonyl)-2-phenyl-3-piperidinone oxime (18) **(*S*)-18**

Dimethyl sulfoxide (0.45 mL, 6.35 mmol) was added dropwise to a cooled (-78 °C) solution of oxalyl chloride (0.27 mL, 3.08 mmol) in CH₂Cl₂ (7 mL). The mixture was stirred at -78 °C for 5 min, and then a solution of **15** (570 mg, 2.06 mmol) in CH₂Cl₂ (3 mL) was added dropwise. The mixture was stirred at -78 °C for 1 h. After adding *i*-Pr₂NEt (1.10 mL, 6.33 mmol), the mixture was allowed to warm slowly to -20 °C. Hydroxy amine hydrochloride (720 mg, 10.36 mmol) and anhydrous potassium carbonate (1.420 g, 10.29 mmol) were added and the mixture was stirred at -20 °C for 5 h, then allowing warm up. Water (10 mL) was added and aqueous layer was separated and extracted with CH₂Cl₂ (3 $\times$ 8 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc: PE =1:3) to yield **18** (430 mg, 72%) as an inseparable isomer mixture, which was used

in the next step without further purification.

S7

(2*S*, 3*S*)-1-(*tert*-Butoxycarbonyl)-3-amino-2-phenylpiperidine (20)

(2*S*, 3*S*)-20

To an ice-bath cooled solution of **18** (520 mg, 1.79 mmol) in dry THF (10 mL), was added slowly and under nitrogen atmosphere, acetic anhydride (0.51 mL, 5.40 mmol). After being stirred at room temperature overnight, the solvent was removed under reduced pressure. To the crude product was basified with a saturated Na₂CO₃ to reach a pH of 7. The resulting mixture was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **19** as a colorless oil, which was used immediately and without further purification in the next step.

Borane-methyl sulfide complex (0.51 mL, 5.38 mmol) was added dropwise to a solution of the crude **19** in THF (12 mL). The mixture was stirred at 55 °C for 24 h, then methanol (3 mL) was added and the mixture was stirred at 55 °C for another 24 h. Water (10 mL) was added and phases were separated. The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on silica gel (eluent: EtOAc: PE: NH₃: H₂O: MeOH = 100: 100: 1: 5) to yield **20** (220 mg, 55%) as a colorless oil. $[\alpha]_D^{23} +26.0^\circ$ (*c* 1.0, CHCl₃). IR (neat) $\nu_{\max}$: 3367, 2931, 2866, 1690, 1453, 1411, 1399, 1365, 1300, 1271, 1252, 1149, 702 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃) δ : 7.42-7.22 (m, 5H), 5.19 (d, *J*=5.9 Hz, 1H), 4.00 (brd, *J*=11.2 Hz, 1H), 3.16 (m, 2H), 1.85 (m, 1H), 1.76 (m, 1H), 1.68 (m, 2H), 1.38 (s, 9H). ¹³C-NMR (125 MHz, CDCl₃) δ : 155.36, 139.10, 129.38 (2C), 128.17 (2C), 127.24, 79.72, 60.47, 51.02, 39.75, 29.17, 28.34, 24.28. HRESIMS calcd for [C₁₆H₂₄N₂O₂+H]⁺: 277.1911; Found: 277.1906.

Adduct of (2*S*,3*S*)-1-(*tert*-butoxycarbonyl)-3-(2-methoxybenzylamino)-2-phenylpiperidine and 2-methoxybenzyl alcohol (22)

To a solution of 2-methoxybenzylaldehyde (385 mg, 2.83 mmol) in THF (6 mL) was added a solution of **20** (260 mg, 0.94 mmol) in THF (4 mL). After being stirred at room temperature overnight, the solvent was removed under reduced pressure. Sodium borohydride (215 mg, 5.66 mmol) was added to a solution of the residue in methanol (6 mL). After being stirred for 3 h, saturated aqueous NaHCO₃ (2 mL) and H₂O (5 mL) were added successively. The mixture was extracted with CH₂Cl₂ (3 × 10 mL) and the organic phases were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on silica gel (eluent: EtOAc: PE = 1: 8) to yield **22** (294 mg, 80%) as a

colorless oil. $[\alpha]_D^{23} +25.7$ (c 0.9, CHCl_3).

S8

IR (film) ν_{max} : 2929, 2853, 1690, 1462, 1412, 1365, 1243, 1149, 753 cm^{-1} . $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 7.60-6.86 (m, 13H), 5.56 (brs, 1H), 4.64 (brs, 1H), 3.97 (d, $J=13.2$ Hz, 1H), 3.92 (m, 1H), 3.87 (d, $J=13.2$ Hz, 1H), 3.86 (s, 3H), 3.58 (s, 3H), 3.33 (m, 1H), 2.92 (dd, $J=13.0, 12.8$ Hz, 1H), 2.12 (brs, 1H), 2.05 (brs, 1H), 1.82 (brd, $J=13.0$ Hz, 1H), 1.60 (m, 1H), 1.40 (s, 9H). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ : 157.53, 157.41, 154.74, 137.00, 131.17, 129.80 (2C), 129.67, 129.12, 128.90, 128.66 (2C), 127.88 (2C), 120.75 (2C), 120.64 (2C), 110.20 (2C), 80.24, 61.99, 56.96, 55.26, 55.11, 45.99, 38.93, 28.37, 24.93, 24.10.

(2S, 3S)- 3-(2-Methoxybenzylamino)-2-phenylpiperidine (2)

(2S, 3S)-2

To an ice-bath cooled solution of **22** (150 mg, 0.28 mmol) in methanol (2 mL), was added a solution of hydrogen chloride in methanol (1 mL). After being stirred at room temperature overnight, the mixture was basified with a saturated sodium bicarbonate solution to reach pH 7. The mixture was extracted with CH_2Cl_2 (3×5 mL) and the organic layers were washed with brine (3 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography on silica gel (eluent: EtOAc: PE: NH_3 : H_2O : MeOH = 100: 100: 1: 5) to yield **2** (80 mg, 96%). $[\alpha]_D^{16} +75.1^\circ$ (dihydrochloride, c 0.6, MeOH). IR (neat, free base) ν_{max} : 3329, 2928, 2854, 1492, 1462, 1242, 1031, 752, 701 cm^{-1} . $^1\text{H-NMR}$ (500 MHz, CDCl_3 , free base) δ : 7.36-6.72 (m, 9H), 3.88 (brs, 1H), 3.68 (d, $J=13.9$ Hz, 1H), 3.44 (s, 3H), 3.40 (d, $J=13.9$ Hz, 1H), 3.27 (ddd, $J=12.3, 2.1, 2.1$ Hz, 1H), 2.80 (dd, $J=12.5, 3.5$ Hz, 1H), 2.77 (dd, $J=12.5, 3.5$ Hz, 1H), 2.13 (brd, $J=13.5$ Hz, 1H), 2.20-1.85 (m, 1H), 1.60 (ddd, $J=13.0, 3.5, 3.5$ Hz, 1H), 1.40 (brd, $J=13.0$ Hz, 1H). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ : 157.59, 142.10, 129.67, 128.22 (2C), 127.93 (2C), 126.66, 126.31 (2C), 119.99, 109.79, 63.86, 54.75, 54.63, 47.66, 46.75, 28.01, 20.17. HRESIMS calcd for $[\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}+\text{H}]^+$: 297.1961; Found: 297.1961.