CONTENTS

(A) General Procedure for Asymmetric Hydrogenation

Solid *trans*-$RuCl_2$[(*R*)-xylbinap][(*R*)-daipen] [(*R*,*R*)-**1a**] (6.1 mg, 0.0050 mmol)[1] was placed in a 100-mL glass autoclave equipped with a Teflon-coated magnetic stirring bar, a pressure gauge, and a gas inlet tube attached to a hydrogen source.[2] Air present in the autoclave was replaced by argon.[3] 2-Propanol (10 mL),[4] 2-dimethylaminoacetophenone (**2c**) (1.63 g, 10.0 mmol),[5] and a 1.0 M *t*-C_4H_9OK solution in *tert*-butyl alcohol (0.10 mL, 0.10 mmol)[6] which had been degassed by bubbling argon were added to the autoclave under a stream of argon. The mixture was degassed by five vacuum–filling with argon cycles. Air present in the gas inlet tube was removed by flushing with a stream of hydrogen.[7] Hydrogen was initially introduced into the autoclave at a pressure of 5 atm, before being reduced to 2 atm by carefully releasing the stop valve. After this procedure was repeated seven times, the vessel was pressurized to 8 atm. The reaction mixture was vigorously stirred at 25 °C for 12 h. After the hydrogen gas was carefully vented, the solvent was removed under reduced pressure. Subsequently, the residue was purified by bulb-to-bulb distillation to give (*R*)-2-dimethylamino-1-phenylethanol [(*R*)-**3c**] (1.49 g, 90% yield), $[\alpha]^{27}_D$ –64.0° (*c* 0.64, C_2H_5OH) (HCl salt), lit.[8] $[\alpha]^{25}_D$ +67.9° (*c* 1.01, C_2H_5OH), (*R*), 95% ee. ^1H

NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 6, NCH_3), 2.37 (dd, 1, J = 3.6 and 12.4 Hz, CH(OH)C*H*H), 2.48 (dd, 1, J = 10.8 and 12.4 Hz, CH(OH)CH*H*), 3.95 (br s, 1, OH), 4.69 (dd, 1, J = 3.6 and 10.8 Hz, C*H*OH), 7.2–7.4 (m, 5, aromatics). The enantiomeric excess determined by chiral HPLC analysis of its benzoate was 93%. HPLC (column, CHIRALCEL OD (4.6 mm i.d. x 250 mm, Daicel Chemical Industries); eluent, 2:98 2-propanol–hexane; temp, 40 °C; flow rate, 0.3 mL/min; detection, 254-nm light; retention time (t_R) of *R* isomer, 18.2 min (96.7%); t_R of *S* isomer, 16.0 min (3.3%).

Notes

(1) For preparation procedure, see: Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529–13530.

(2) For details, see: Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1993**, *71*, 1–13; Takaya, H.; Ohta, T.; Inoue, S.; Tokunaga, M.; Kitamura, M.; Noyori, R. *Org. Synth.* **1994**, *72*, 74–85.

(3) Argon gas (99.998%) was further purified by passing through a BASF catalyst R3-11 column at 80 °C.

(4) Guaranteed-reagent grade 2-propanol was freshly distilled over CaH_2 before use.

(5) The substrate was washed with a 0.1 M KOH solution prior to use. Otherwise catalytic activity is substantially lowered.

(6) Purchased from Aldrich Chemical Co.

(7) Hydrogen of 99.99% purity was used.

(8) See: Supporting Information of Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629–631.

(B) Reaction Conditions and Analytical Data of α-Amino Alcohol Products

Hydrogenation of dimethylaminoacetone (2a). Conditions: (*R*,*R*)-**1a** (1.5 mg, 0.00125 mmol), **2a** (253 mg, 2.5 mmol), 1.0 M *t*-C_4H_9OK solution in *tert*-butyl alcohol

(20 μL, 0.02 mmol), 2-propanol (2.5 mL), 8 atm H_2, 25 °C, 4 h. Addition of a 1.0 M HCl solution in ether (3.0 mL, 3.0 mmol) to the resulting solution followed by removal of solvent gave crude (*S*)-1-dimethylamino-2-propanol [(*S*)-**3a**] hydrochloride. The yield of 99% was determined by ^{1}H-NMR analysis using methyl propionate (δ = 3.59, 3H, CH_3O) as an internal standard. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.10 (d, 3, *J* = 6.0 Hz, C*H*$_3$CHOH), 2.75 (d, 3, *J* = 4.8 Hz, N(C*H*$_3$)CH$_3$), 2.79 (d, 3, *J* = 4.8 Hz, N(CH$_3$)C*H*$_3$), 2.90–2.97 (m, 1, C*H*HN), 3.02–3.08 (m, 1, CH*H*N), 4.03–4.11 (m, 1, C*H*OH), 9.95 (br s, 1, HCl). Obtained (*S*)-**3a** hydrochloride was dissolved in CH_2Cl_2 (10 mL), and then distilled water (0.2 mL) and NaOH (120 mg, 3 mmol) were added to neutralize the product. After stirring for 2 h, the solvent was removed under reduced pressure carefully because of the low bp of **3a** (121–127 °C, Aldrich catalogue). Bulb-to-bulb distillation of the resulting mixture gave **3a** contaminated with water. This was diluted with CH_2Cl_2 (3 mL) and dried with Na_2SO_4. Filtration and careful concentration gave (*S*)-**3a** (205 mg, 79% yield). $[\alpha]^{27}_D$ +21.1° (*c* 1.01, CH_3OH), lit. $[\alpha]_D$ –23.7° (*c* 1.11, CH_3OH), *R* isomer, Chan, M. M.-L.; Robinson, J. B. *J. Med. Chem.* **1974**, *17*, 1057–1060. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, 3, *J* = 6.4 Hz, C*H*$_3$CHOH), 2.14 (dd, 1, *J* = 3.2 and 12.2 Hz, C*H*HN), 2.22–2.27 (m, 1, CH*H*N), 2.27 (s, 6, N(CH$_3$)$_2$), 3.45 (br s, 1, OH), 3.77–3.80 (m, 1, C*H*OH). The enantiomeric excess determined by ^{1}H-NMR analysis using europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] [Eu(hfc)$_3$] as a chiral shift reagent was 92%: conditions [**3a** (22 mg, 0.21 mmol), Eu(hfc)$_3$ (200 mg, 0.17 mmol)]; C-2 methine proton signal of (*R*)-**3a**, δ 6.20 (3.8%); signal of (*S*)-**3a**, δ 6.57 (96.2%).

Hydrogenation of [(methyl)(phenyl)amino]acetone (2b). Conditions: (*R*,*R*)-**1a** (1.5 mg, 0.00125 mmol), **2b** (408 mg, 2.5 mmol), 1.0 M *t*-C_4H_9OK solution in *tert*-butyl alcohol (25 μL, 0.025 mmol), 2-propanol (2.5 mL), 8 atm H_2, 25 °C, 13 h. (*S*)-1-[(Methyl)(phenyl)amino]-2-propanol [(*S*)-**3b**] (384 mg, 93% yield, 81% ee). HPLC (column, CHIRALCEL OD; eluent, 10:90 2-propanol–hexane; temp, 30 °C; flow rate, 0.5 mL/min; detection, 254-nm light; t_R of (*R*)-**3b**, 22.2 min (9.3%); t_R of *S* isomer, 14.7 min (90.7%). $[\alpha]^{23}_D$ +19.0° (*c* 0.55, CH_3OH). The absolute configuration was

determined by comparison of the sign of rotation with that of a reference sample [(*S*)-**3b**] which was prepared by reaction of (*S*)-propylene oxide and *N*-methylaniline (Posner, G. H.; Rogers, D. Z. *J. Am. Chem. Soc.* **1977**, *99*, 8208–8218), $[\alpha]^{23}_D$ +26.3° (*c* 0.54, CH_3OH), >99% ee. **Hydrogenation of 2-dimethylaminoacetophenone (2c).** See Part A. **Hydrogenation of 2-[(acetyl)(methyl)amino]acetophenone (4a).** Conditions: (*R*,*R*)-**1a** (1.2 mg, 0.0010 mmol), **4a** (383 mg, 2.0 mmol), 1.0 M *t*-C_4H_9OK solution in *tert*-butyl alcohol (20 μL, 0.020 mmol), 2-propanol (4 mL), 8 atm H_2, 25 °C, 4 h. (*R*)-2-[(Acetyl)(methyl)amino]-1-phenylethanol [(*R*)-**5a**] (337 mg, 87% yield, 99% ee). $[\alpha]^{20}_D$ –100.9° (*c* 0.70, $CHCl_3$). The absolute configuration and enantiomeric excess were determined by chiral HPLC analysis after conversion to (*R*)-2-[(benzoyl)(methyl)amino]-1-phenylethanol [(*R*)-**5c**], whose absolute configuration was determined as below: reaction conditions (hydrolysis, 0.4 M KOH in 10:1 C_2H_5OH–H_2O at 80 °C, 15 h; benzoylation, 1.05 equiv of C_6H_5COCl and 4.6 equiv of $N(C_2H_5)_3$ in CH_2Cl_2 at 25 °C, 2 h), HPLC (column, CHIRALCEL OD; eluent, 10:90 2-propanol–hexane; temp, 40 °C; flow rate, 0.3 mL/min; detection, 254-nm light; t_R of (*R*)-**5c**, 42.2 min (99.7%); t_R of *S* isomer, 48.0 min (0.3%). $[\alpha]^{21}_D$ –95.3° (*c* 1.05, $CHCl_3$). **Hydrogenation of 2-(benzoylamino)acetophenone (4b).** Conditions: (*R*,*R*)-**1a** (2.0 mg, 0.0020 mmol), **4b** (479 mg, 2.0 mmol), 1.0 M *t*-C_4H_9OK solution in *tert*-butyl alcohol (20 μL, 0.020 mmol), 2-propanol (4 mL), 8 atm H_2, 25 °C, 20 h. 2-(Benzoylamino)-1-phenylethanol [(*R*)-**5b**] (442 mg, 92% yield, 95% ee). $[\alpha]^{21}_D$ –64.2° (*c* 0.45, $CHCl_3$). HPLC (column, CHIRALCEL OD-H (4.6 mm i.d. x 150 mm); eluent, 10:90 2-propanol–hexane; temp, 40 °C; flow rate, 0.3 mL/min; detection, 254-nm light; t_R of (*R*)-**5b**, 21.6 min (97.6%); t_R of *S* isomer, 24.0 min (2.4%). The absolute configuration was determined by the sign of rotation after deacylation (2.0 M KOH in 10:1 C_2H_5OH–H_2O at 80 °C, 24 h). $[\alpha]^{15}_D$ –42.9° (*c* 0.48, C_2H_5OH), lit. $[\alpha]^{20}_D$ –42.2° (*c* 1 C_2H_5OH), (*R*), 95% ee, Brussee, J.; Dofferhoff, F.; Kruse, C. G.; Van Der Gen, A. *Tetrahedron* **1990**, *46*, 1653–1658. **Hydrogenation of 2-[(benzoyl)(methyl)amino]acetophenone (4c).** Conditions: (*R*,*R*)-**1a** (1.5 mg, 0.00125 mmol), **4c** (633 mg, 2.5 mmol), 1.0 M *t*-C_4H_9OK solution in *tert*-butyl alcohol (25 μL,

0.025 mmol), 2-propanol (2.5 mL), 8 atm H_2, 25 °C, 12 h). (*R*)-2-[(Benzoyl)(methyl)amino]-1-phenylethanol [(*R*)-**5c**] (613 mg, 96% yield, 99.8% ee). $[\alpha]^{17}_D$ –96.5° (*c* 1.06, $CHCl_3$). HPLC (column, CHIRALCEL OD; eluent, 10:90 2-propanol–hexane; temp, 40 °C; flow rate, 0.3 mL/min; detection, 254-nm light; t_R of (*R*)-**5c**, 42.2 min (99.9%); t_R of *S* isomer, 48.0 min (0.1%). The absolute configuration was determined by the sign of rotation after removal of the benzoyl group (0.4 M KOH in 10:1 C_2H_5OH–H_2O at 80 °C, 8 h). $[\alpha]^{23}_D$ –39.7° (*c* 0.70, C_2H_5OH), lit. $[\alpha]^{20}_D$ –40.7° (*c* 1.3, C_2H_5OH), (*R*), Ito, Y.; Amino, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1983**, *105*, 1586–1590. **Hydrogenation of 2-[(methoxycarbonyl)(methyl)amino]acetophenone (4d).** Conditions: (*R*,*R*)-**1a** (1.2 mg, 0.0010 mmol), **4d** (415 mg, 2.0 mmol), 1.0 M *t*-C_4H_9OK solution in *tert*-butyl alcohol (20 μL, 0.020 mmol), 2-propanol (3.2 mL), methanol (0.8 mL), 8 atm H_2, 25 °C, 14 h). (*R*)-3-Methyl-4-phenyl-1,3-oxazolidine-2-one [(*R*)-**6**] (348 mg, 98% yield, 99% ee). $[\alpha]^{21}_D$ –39.4° (*c* 0.53, $CHCl_3$). The absolute configuration and enantiomeric excess were determined by chiral HPLC analysis after conversion to (*R*)-**5c**: reaction conditions (hydrolysis, 0.4 M KOH in 10:1 C_2H_5OH–H_2O at 80 °C, 10 h; benzoylation, 1.05 equiv of C_6H_5COCl and 4.6 equiv of $N(C_2H_5)_3$ in CH_2Cl_2 at 25 °C, 2 h), HPLC (column, CHIRALCEL OD; eluent, 10:90 2-propanol–hexane; temp, 40 °C; flow rate, 0.3 mL/min; detection, 254-nm light; t_R of (*R*)-**5c**, 42.2 min (99.4%); t_R of *S* isomer, 48.0 min (0.6%). **Hydrogenation of 2-[(*tert*-butoxycarbonyl)(methyl)amino]acetophenone (4e).** Conditions: (*R*,*R*)-**1a** (1.5 mg, 0.0010 mmol), **4f** (499 mg, 2.0 mmol), 1.0 M *t*-C_4H_9OK solution in *tert*-butyl alcohol (20 μL, 0.020 mmol), 2-propanol (4 mL), 8 atm H_2, 25 °C, 7 h. (*R*)-2-[(*tert*-Butoxycarbonyl)(methyl)amino]-1-phenylethanol [(*R*)-**5e**] (474 mg, 94% yield, 99.4% ee). $[\alpha]^{20}_D$ –55.1° (*c* 0.62,$CHCl_3$). The absolute configuration and enantiomeric excess were determined by chiral HPLC analysis after conversion to (*R*)-**5c**: reaction conditions (deprotection, 0.4 M KOH in 10:1 C_2H_5OH–H_2O at 80 °C, 15 h; benzoylation, 1.1 equiv of C_6H_5COCl and 3 equiv of $N(C_2H_5)_3$ in CH_2Cl_2 at 25 °C, 30 min), HPLC (column, CHIRALCEL OD; eluent, 10:90 2-propanol–hexane; temp, 40

°C; flow rate, 0.3 mL/min; detection, 254-nm light; t_R of (*R*)-**5d**, 42.2 min (99.7%); t_R of *S* isomer, 48.0 min (0.3%). The *tert*-butoxycarbonyl group was also removed by treatment with 1.0 M HCl in ether at 25 °C for 22 h. Neutralization of the product gave (*R*)-2-(methylamino)-1-phenylethanol in 95% yield. $[\alpha]^{22}_D$ –42.5° (*c* 0.52, C_2H_5OH).

Hydrogenation of 2-(*tert*-Butoxycarbonylamino)cyclohexanone (7). Conditions: (*R,S*)-**1b** (3.0 mg, 0.0020 mmol), **7** (160 mg, 0.75 mmol), 0.5 M KOH solution in 2-propanol (1.0 mL, 0.50 mmol), 2-propanol (2.5 mL), 8 atm H_2, 25 °C, 5 h. A 99:1 mixture of (1*S*,2*R*)-2-(*tert*-butoxycarbonylamino)cyclohexan-1-ol [(*S,R*)-**8**] in 82% ee and the trans isomer (153 mg, 95% yield). $[\alpha]^{18}_D$ +22.5° (*c* 0.49, CH_2Cl_2). The diastereomeric ratio and enantiomeric excess of (*S,R*)-**8** were determined by chiral GC analysis. GC (column, Chirasil-DEX CB, df = 0.25 μm, 0.32 mm i.d. x 25 m, CHROMPAC; carrier gas, helium (50 kPa); column temp, 150 °C; injection temp, 200 °C); t_R of (*R,S*)-**8**, 30.5 min (8.9%); t_R of *S,R* isomer, 29.2 min (88.7%); t_R of trans isomers, 28.1 min (1.4%); t_R of **7**, 14.8 min (1.0%). The absolute configuration of (*S,R*)-**8** was determined by the sign of rotation after conversion to (1*S*,2*R*)-2-(benzyloxycarbonylamino)cyclohexan-1-ol: reaction conditions (removal of the *tert*-butoxycarbonylamino group, 1.0 M HCl in ether at 25 °C for 21 h; benzyloxycarbonylation, 1.2 equiv of benzyl chloroformate and 3 equiv of $NaHCO_3$ in 1:1 H_2O–CH_2Cl_2 at 25 °C for 3 h). $[\alpha]^{22}_D$ +27.1° (*c* 0.35, 95% C_2H_5OH), lit. $[\alpha]^{20}_D$ +19.8° (*c* 1.5, 95% C_2H_5OH), (1*S*,2*R*), 63% ee, Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2813–2817. The absolute configuration and enantiomeric excess of the trans product were not determined. **Hydrogenation of 2-[(benzoyl){2-(3,4-dimethoxyphenyl)ethyl}amino]-4'-benzyloxyacetophenone (9).** Conditions: (*R,R*)-**1a** (1.5 mg, 0.00125 mmol), **9** (1.27 g, 2.5 mmol), 1.0 M *t*-C_4H_9OK solution in *tert*-butyl alcohol (50 μL, 0.050 mmol), 2-propanol (2.5 mL), 8 atm H_2, 25 °C, 24 h. (*R*)-2-[(Benzoyl){2-(3,4-dimethoxyphenyl)ethyl}amino]-1-(4-benzyloxyphenyl)ethanol [(*R*)-**10**] (1.28 g, 100% yield, 97% ee). $[\alpha]^{15}_D$ –23.3° (*c* 0.66, $CHCl_3$). HPLC (column, CHIRALPAK AD (4.6 mm i.d. x 250 mm, Daicel Chemical Industries); eluent, 25:75 2-propanol–hexane; temp, 40 °C; flow rate, 1.0 mL/min;

detection, 254-nm light; t_R of (*R*)-**10**, 11.7 min (98.6%); t_R of *S* isomer, 14.8 min (1.4%). The absolute configuration was determined by the sign of rotation after conversion to (*R*)-denopamine hydrochloride [(*R*)-**11**] as described in Part C.

(C) Synthesis of (*R*)-Denopamine Hydrochloride

(*R*)-Denopamine [(*R*)-**11**] hydrochloride was synthesized according to the literature.[1] Potassium hydroxide (85% purity, 660 mg, 10.0 mmol) and (*R*)-**10** (1.28 g, 2.5 mmol) were dissolved in ethanol (25 mL) and water (2.5 mL), and the mixture was heated under reflux for 8 h. Water was added to the mixture and the product was extracted with ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was diluted with ether (30 mL). To this solution, a 1.0 M HCl solution in ether (3.0 mL, 3.0 mmol) was dropwise added. Removal of the solvent under reduced pressure gave (*R*)-1-(4-benzyloxyphenyl)-2-[2-(3,4-dimethoxyphenyl)ethylamino]ethanol hydrochloride (1.10 g, 99% yield). Recrystallization from ethanol to afford an optically pure compound (927 mg, 84% recovery). $[\alpha]^{25}_D$ –30.5° (*c* 0.96, CH_3OH), lit.[1] $[\alpha]_D$ –30.1° (*c* 1, CH_3OH), (*R*). The enantiomeric excess was determined by chiral HPLC analysis of the neutralized compound: column, CHIRALPAK AD; eluent, 20:80 2-propanol–hexane; temp, 40 °C; flow rate, 0.5 mL/min; t_R of *R* compound, 19.2 min (100%); t_R of *S* isomer, 21.2 min (0%). The amino alcohol hydrochloride (444 mg, 1.0 mmol), 5% Pd on charcoal (307 mg, 0.14 mmol), 2-propanol (25 mL), and distilled water (5 mL) were placed in a 50-mL round-bottomed flask and degassed. The mixture was stirred under hydrogen atmosphere at 25 °C for 3 h. Solid components were removed by celite filtration, and the resulting solution was concentrated under reduced pressure to give (*R*)-1-(4-hydroxyphenyl)-2-[2-(3,4-dimethoxyphenyl)ethylamino]ethanol [(*R*)-denopamine, (*R*)-**11**] hydrochloride (337 mg, 95% yield). Recrystallization of this compound from ethanol gave pure (*R*)-**11** hydrochloride (272 mg, 77% yield). $[\alpha]^{27}_D$ –38.5° (*c* 0.30, CH_3OH), lit.[2] $[\alpha]^{27}_D$ –38.0° (*c* 0.70, CH_3OH), (*R*). ^1H NMR (400 MHz, DMSO-d_6) δ 2.55–2.76 (m, 6, $CH_2NCH_2CH_2$), 3.71 (s, 3, OCH_3), 3.73 (s, 3, OCH_3), 4.49 (dd, 1, *J* =

5.2 and 7.4 Hz, C*H*OH), 6.67–6.70 (m, 3, aromatics), 6.79–6.84 (m, 2, aromatics), 7.10 (d, 2, J = 8.8 Hz, meta protons of C_6H_4OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 35.55, 50.93, 55.38, 55.53, 57.59, 71.25, 111.90, 112.56, 114.67, 120.38, 126.99, 132.89, 134.85, 147.04, 148.61, 156.23.

References

(1) Kawaguchi, T.; Saito, K.; Matsuki, K.; Iwakuma, T.; Takeda, M. *Chem. Pharm. Bull.* **1993**, *41*, 639–642.

(2) Ikezaki, M.; Umino, N.; Gaino, M.; Aoe, K.; Iwakuma, T.; Oh-ishi, T. *Yakugaku Zasshi* **1986**, *106*, 80–89.

(D) Asymmetric Hydrogenation of 3-Dimethylaminopropiophenone[1]

Solid (*R*,*R*)-**1a** (7.3 mg, 0.0060 mmol) was placed in a 500-mL glass autoclave equipped with a Teflon-coated magnetic stirring bar, a pressure gauge, and a gas inlet tube attached to a hydrogen source. Air present in the autoclave was replaced by argon. 2-Propanol (30 mL) and a 1.0 M *t*-C_4H_9OK solution in *tert*-butyl alcohol (60 μL, 0.06 mmol) which had been degassed by bubbling argon were added to the autoclave under a stream of argon. The mixture was degassed by five vacuum–filling with argon cycles, and then was heated at 60 °C for 30 min under argon atmosphere.[2] After cooling to room temperature, 2-propanol (30 mL) and 3-dimethylaminopropiophenone (**12**) (10.6 g, 60.0 mmol) which had been degassed by bubbling argon were added under a stream of argon. The mixture was degassed by five vacuum–filling with argon cycles. Air present in the gas inlet tube was removed by flushing with a stream of hydrogen. Hydrogen was initially introduced into the autoclave at a pressure of 5 atm, before being reduced to 2 atm by carefully releasing the stop valve. After this procedure was repeated seven times, the vessel was pressurized to 8 atm. The reaction mixture was vigorously stirred at 25 °C for 5 h. After the hydrogen gas was carefully vented, the solvent was removed under reduced pressure to give crude (*R*)-1-phenyl-3-dimethylaminopropan-1-ol [(*R*)-**13**]. The yield determined by ^1H-NMR analysis using methyl propionate (δ = 3.67, 3H, CH_3O) as an internal standard was 96%. The residue

was purified by bulb-to-bulb distillation to give 98% pure (*R*)-**13** (9.84 g, 93% yield, 97.5% ee) contaminated with about 2% of 1-phenylpropan-1-ol. $[\alpha]^{26}_D$ +32.0° (*c* 1.70, CH_3OH), lit.[3] $[\alpha]_D$ +27.6° (*c* 1.61, CH_3OH), (*R*). ^1H NMR (400 MHz, $CDCl_3$) δ 1.76–1.88 (m, 2, CH(OH)CH_2), 2.30 (s, 6, N(CH_3)$_2$), 2.47 (ddd, 1, *J* = 4.0, 5.4, and 12.7 Hz, C*H*HN), 2.66 (ddd, 1, *J* = 4.0, 8.8, and 12.7 Hz, CH*H*N), 4.94 (dd, 1, *J* = 4.0 and 8.0 Hz, C*H*OH), 6.86 (br s, 1, OH), 7.22–7.42 (m, 5, aromatics). HPLC (column, CHIRALCEL OD (4.6 mm i.d. x 250 mm, Daicel Chemical Industries); eluent, 10:90 2-propanol–hexane; temp, 30 °C; flow rate, 0.5 mL/min; detection, 254-nm light; t_R of (*R*)-**13**, 12.5 min (98.75%); t_R of *S* isomer, 16.2 min (1.25%).

Notes

(1) See Notes of Part A.

(2) This pretreatment diminished the induction period and also minimized β-elimination of **12**.

(3) Andrisano, R.; Angeloni, A. S.; Marzocchi, S. *Tetrahedron* **1973**, *29*, 913–916.

(E) Synthesis of (*R*)-Fluoxetine Hydrochloride

To a DMF solution (23 mL) of (*R*)-**13** (2.0 g, 11.2 mmol) was portionwise added NaH (402 mg, 16.7 mmol) at 0 °C, and the mixture was heated at 90 °C for 30 min. After addition of 4-chlorobenzotrifluoride (4.03 g, 22.3 mmol) at room temperature, the mixture was heated at 100 °C for 1 h. At room temperature, another portion of NaH (402 mg, 16.7 mmol) was added, and this mixture was again heated at 100 °C for 1 h. After cooling to room temperature, saturated $NaHCO_3$ aqueous solution was added to the mixture and this was extracted with ethyl acetate. The combined organic layers were washed with brine, dried with $NaSO_4$, and filtered. The solution was concentrated under reduced pressure to give (*R*)-3-dimethylamino-1-phenyl-1-(4-trifluoromethylphenoxy)propane (3.62 g, 98% purity, 100% yield). To a 1,2-dichloroethane solution (18.6 mL) of the *R* ether (3.0 g, 9.28 mmol) was dropwise added α-chloroethyl chloroformate (1.39 g, 9.28 mmol)[1] at 0 °C. The mixture was

stirred at 0°C for 20 min and at 50 °C for 1 h. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was diluted with methanol (20 mL) and heated at 50 °C for 1 h. The resulting solution was concentrated under reduced pressure. Addition of a 1:1 mixture of ethyl acetate and hexane to the residue resulted in white powder of (*R*)-fluoxetine [(*R*)-**14**] hydrochloride (3.07 g, 98% purity, 96% yield). The crude product (500 mg) was recrystallized from a 1:1 mixture of ethyl acetate and hexane to give pure (*R*)-**14** hydrochloride (436 mg, 87% recovery). $[\alpha]^{27}_D$ −14.8° (*c* 1.00, $CHCl_3$), lit. $[\alpha]^{23}_D$ −13.8° (*c* 1, $CHCl_3$), (*R*), >99.8% ee.[2] ^1H NMR (400 MHz, $CDCl_3$) δ 2.43–2.55 (m, 2, CH_2CH_2N), 2.62 (s, 3, $NHCH_3$), 3.10–3.16 (m, 2, CH_2CH_2N), 5.48 (dd, 1, *J* = 4.4 and 8.4 Hz, CHO), 6.90 (d, 2, *J* = 8.8 Hz, protons at C-2 position of 4-$CF_3C_6H_4$), 7.24–7.36 (m, 5, C_6H_5), 7.41 (d, 2, *J* = 8.8 Hz, protons at C-3 position of 4-$CF_3C_6H_4$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.92, 34.49, 46.04, 76.94, 115.78, 123.21 (J_{CF} = 32.8 Hz), 124.16 (J_{CF} = 269.9 Hz), 126.67, 126.73 (J_{CF} = 3.6 Hz), 128.34, 128. 97, 139. 07, 159. 66.

References

(1) Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081–2082. See also: Ratz, A. M.; Weigel, L. O. *Tetrahedron Lett.* **1999**, *40*, 2239–2242.

(2) Corey, E. J.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5207–5210.

(F) Asymmetric Hydrogenation of 1-(4-Fluorophenyl)-4-[(5-fluoro-2-pyrimidinyl)-1-piperazinyl]butanone: Synthesis of BMS 181100

The ketonic substrate was prepared according to the literature.[1] Conditions of asymmetric hydrogenation: (*S,S*)-**1a** (1.5 mg, 0.00125 mmol), 1-(4-fluorophenyl)-4-[(5-fluoro-2-pyrimidinyl)-1-piperazinyl]butanone (**15**) (866 mg, 2.50 mmol), 1.0 M *t*-C_4H_9OK solution in *tert*-butyl alcohol (50 μL, 0.050 mmol), 2-propanol (5 mL), 8 atm H_2, 25 °C, 12 h. The resulting solution was concentrated under reduced pressure, and the residue was purified by filtration through silica gel (5 g) eluted with ethyl acetate, giving (*R*)-1-(4-fluorophenyl)-4-[(5-fluoro-2-pyrimidinyl)-1-piperazinyl]butan-1-ol

[BMS 181100, (*R*)-**16**] (843 mg, 97% yield, 99.4% ee) as a white solid. $[\alpha]^{25}_D$ +14.6° (*c* 1.05, CH_3OH), lit. $[\alpha]^{25}_D$ +14.3° (*c* 0.53, CH_3OH), (*R*), >99.9% ee.[2] ^1H NMR (400 MHz, $CDCl_3$) δ 1.65–1.98 (m, 4, $CH(OH)CH_2CH_2$), 2.44–2.65 (m, 6, $(CH_2)_2CH_2N$ and C-2 and C-6 protons of piperazinyl), 3.83 (m, 4, C-3 and C-5 protons of piperazinyl), 4.66 (dd, 1, *J* = 2.4 and 7.6 Hz, C*H*OH), 6.98–7.02 (m, 2, meta protons of C_6H_4F), 7.32–7.35 (m, 2, ortho protons of C_6H_4F), 8.19 (s, 2, protons of pyrimidinyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.56, 39.52, 43.81, 52.73, 58.74, 72.95, 114.82 (J_{CF} = 21.1 Hz), 127.12 (J_{CF} = 7.7 Hz), 141.26 (J_{CF} = 2.8 Hz), 145.04 (J_{CF} = 21.5 Hz), 151.61 (J_{CF} = 248.1 Hz), 158.7, 161.69 (J_{CF} = 244.0 Hz). HPLC (column, CHIRALPAK AD; eluent, 5:95 2-propanol–hexane; temp, 40 °C; flow rate, 0.5 mL/min; detection, 254-nm light; t_R of (*R*)-**16**, 29.4 min (99.7%); t_R of *S* isomer, 27.4 min (0.3%).

References

(1) Synthesis of 1-(4-fluorophenyl)-4-[(2-pyrimidinyl)-1-piperazinyl]butanone: Ramachandran, P. V.; Gong, B.; Brown, H. C. *Chirality* **1995**, *7*, 103–110. Preparation of 2-chloro-5-fluoropyrimidine: Dunaiskis, A.; Staigers, T.; Keltonic, T.; Chappie, T.; Meltz, C.; Dugger, R.; Sanner, M. A. *Org. Prep. Proced. Int.* **1995**, *27*, 600–602.

(2) Yevich, J. P.; New, J. S.; Lobeck, W. G.; Dextraze, P.; Bernstein, E.; Taylor, D. P.; Yocca, F. D.; Eison, M. S.; Temple, D. L., Jr. *J. Med. Chem.* **1992**, *35*, 4516–4525.