Asymmetric Syntheses of 1-Alkyltetrahydro-β-carbolines and a 9-Thio Analogue

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Tetrahydro-β-carbolines, (*S*)-tetrahydroharman (8a) and (*S*)-1-phenyltetrahydro-β-carboline (8b), were asymmetrically synthesized starting from (*R*)-phenylglycinol and 1-benzyl-3-(2-bromoethyl)indole (1). Asymmetric synthesis of the 9-thio analogue (15) of 8a was also achieved.

Keywords tetrahydro-β-carboline; (*S*)-tetrahydroharman; (*S*)-aryltetrahydro-β-carboline; tetrahydrobenzo[4,5]thieno[2,3-*c*]pyridine; phenylglycinol; asymmetric synthesis

Tetrahydro-β-carboline alkaloids are widely distributed among plants, and have interesting biological activities. The development of a convenient method for the asymmetric synthesis of 1-alkyltetrahydro-β-carbolines (IV) (Chart 1) is very important in connection with the asymmetric synthesis of tetrahydro-β-carboline alkaloids. Several reports on their highly stereoselective synthesis have recently appeared.[1)]

We have previously succeeded in the synthesis of enantiomerically pure 1-alkyltetrahydroisoquinolines (III) *via* the stereoselective alkylation of chiral oxazolo[2,3-*a*]tetrahydroisoquinolines (II) with Grignard reagents (Chart 1).[2)] This methodology seemed to be applicable to the asymmetric synthesis of IV. We therefore selected (*S*)-tetrahydroharman (**8a**) and (*S*)-1-phenyltetrahydro-β-carboline (**8b**) (Chart 2), simple indole alkaloids, as typical examples of IV and investigated their asymmetric syntheses. From the viewpoint of medicinal chemistry, thio analogues of tetrahydro-β-carboline alkaloids with biological activity are interesting target structures. Consequently, asymmetric synthesis of the 9-thio analogue (**15**) of tetrahydroharman (**8a**) was also attempted. This paper describes convenient asymmetric syntheses of **8a**, **8b** and **15**.

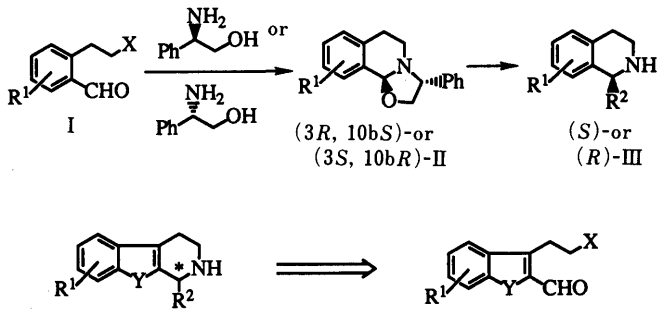

Chart 1

Based on the previous findings, asymmetric synthesis of **8a** was achieved as shown in Chart 2. The formyl intermediate (**2**) was easily prepared by the Vilsmeier–Haack reaction of **1** in 50% yield. Treatment of **2** with (*R*)-phenylglycinol at room temperature followed by azeotropic distillation with benzene gave the crude iminium salt (**3**), which was then cyclized to the chiral **4** with 85% de by treatment with Et_3N at −5 °C. The crude **4** accompanied with its diastereomer, on recrystallization from EtOH, afforded diastereomerically pure **4**, mp 117—118 °C, $[\alpha]_D^{25}$ −73° (c=0.4, $CHCl_3$), in 62% yield. The diastereomeric purity of **4** was confirmed by 500 MHz nuclear magnetic

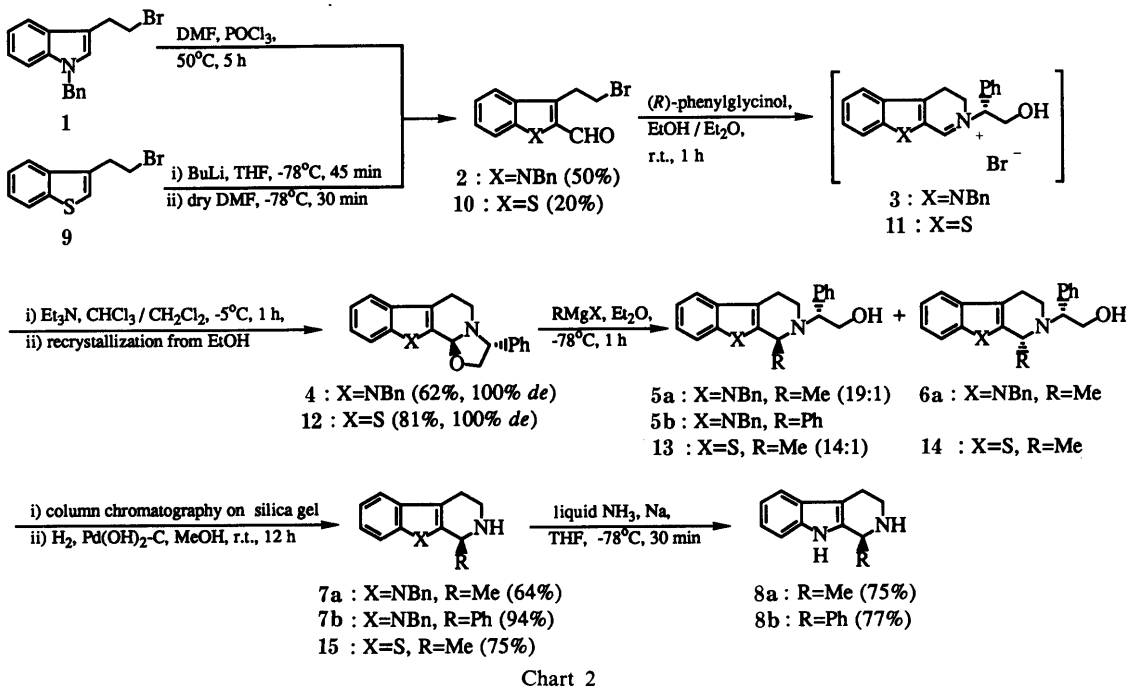

Chart 2

resonance (NMR) spectroscopy. The diastereomerically pure intermediate **4** was then asymmetrically methylated by reaction with MeMgI in Et_2O at −78 °C. The reaction gave a 19:1 (90% de) mixture of (*S*)- and (*R*)-1-methylated derivatives **5a** and **6a**. The major diastereomer **5a** was separated from **6a** by column chromatography on silica gel. Hydrogenolysis of **5a** on $Pd(OH)_2$–carbon gave **7a**. The benzyl group of the indole ring in **7a** was removed by treatment with sodium in liquid ammonia, affording enantiomerically pure **8a**.[3] The configuration of **8a** was determined to be *S* by comparison of its optical rotation, $[\alpha]_D^{25}$ −51.1° (*c*=0.5, EtOH), with the literature value, $[\alpha]_D^{25}$ −52° (*c*=2.0, EtOH).[3]

This methodology was applied to the asymmetric synthesis of (*S*)-1-aryltetrahydro-β-carboline (**8b**). Phenylmagnesium bromide in Et_2O was used to phenylate **4** at −78 °C. The thin layer chromatographic (TLC) and high performance liquid chromatographic (HPLC) analyses of the resulting compound (**5b**) showed that only one diastereomer was produced. The structure of **5b** was identified based on the great similarity of the NMR spectral pattern not to that of **6a** but to that of **5a**. Compound **5b** was also converted to enantiomerically pure **8b**, mp 195—196 °C, $[\alpha]_D^{21}$ −4.0° (*c*=0.5, $CHCl_3$).

The thio-analogue **15** was also synthesized by applying a synthetic approach similar to that used for **8a** (Chart 2). The synthesis of the key formyl intermediate **10** was first attempted through the Vilsmeier–Haack formylation of **9**. However, the reaction did not occur, and the starting material was recovered. Meanwhile, lithiation of **9** with BuLi followed by treatment of dimethylformamide (DMF) gave the desired **10** in 20% yield. Compound **10** was then converted to the diastereomerically pure **12**, mp 137—139 °C, $[\alpha]_D^{24}$ −112° (*c*=0.2, $CHCl_3$) in 81% yield by reaction with (*R*)-phenylglycinol followed by treatment with Et_3N. The reaction of **12** with MeMgI at −78 °C gave a 14:1 (87% de) diastereomeric mixture of 1-methylated derivatives (**13** and **14**). The major diastereomer, separated by column chromatography, could be assigned as the (*S*)-1-methyl derivative (**13**) based on the close similarities of the TLC, HPLC, and NMR spectral characteristics to those of the corresponding (*S*)-1-methylcarboline derivative (**5**). Hydrogenolysis of **13** on $Pd(OH)_2$–carbon gave enantiomerically pure **15**, $[\alpha]_D^{23}$ −37° (*c*=0.1, $CHCl_3$) in 75% yield.

The synthetic strategies shown in Chart 2 should provide general and useful methods for asymmetric syntheses of 1-alkyltetrahydro-β-carbolines and their 9-thio analogues.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were recorded on a JASCO A-102 spectrometer. Mass spectra (MS) were recorded on a Shimadzu LKB 9000 spectrometer and fast atom bombardment mass spectra (FAB-MS) were recorded on a VG-70SE spectrometer. ^{1}H-NMR spectra were run on a Hitachi R-24 (60 MHz) spectrometer or on a Varian VXR-500 (500 MHz) spectrometer. Optical rotations were measured on a JASCO DIP-4 spectrometer. Analytic HPLC was performed with a Shimadzu SPD-6A instrument on a chiral phase column, Chiralcel OD (Daisel) or a silica gel column, Chemcosorb 5Si-U (Chemco). Preparative HPLC was performed with a Waters 510 instrument on a silica gel column, μ-Porasil (RCM Model, Waters). Merck silica gel 60 (230—400 mesh) and Wako activated alumina (300 mesh) were employed for column chromatography. Extracts were dried over anhydrous $MgSO_4$.

1-Benzyl-3-(2-bromoethyl)indole (1) PBr_3 (12.5 ml, 340 mmol) was added dropwise to a solution of 1-benzyl-3-(2-hydroxyethyl)indole (30 g, 120 mmol) in Et_2O (300 ml) at 0 °C. The reaction mixture was stirred at room temperature for 3 h, quenched with 10% $NaHCO_3$ solution, and extracted with Et_2O. The Et_2O layer was washed with saturated NaCl solution and dried. The residue was purified by column chromatography on silica gel (hexane:AcOEt=10:1) to give 32 g (84%) of **1** as a viscous oil. *Anal.* Calcd for $C_{17}H_{16}BrN$: C, 64.98; H, 5.13; N, 4.46. Found: C, 65.12; H, 5.23; N, 4.62. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.05—3.80 (4H, m), 5.19 (2H, s), 6.95 (1H, s), 6.82—7.40 (3H, m), 7.40—7.70 (1H, m). EI-MS *m/z*: 315 (M^++2), 313 (M^+).

1-Benzyl-3-(2-bromoethyl)-2-formylindole (2) Compound **1** (30 g, 96 mmol) dissolved in dry DMF (200 ml) was added under cooling with ice-water to a mixture of dry DMF (60 ml, 77 mmol) and $POCl_3$ (36 ml). The reaction mixture was then stirred for 5 h at 50 °C and quenched with 10% $NaHCO_3$ solution. The reaction mixture was extracted with Et_2O and, the Et_2O layer was washed with saturated NaCl solution and dried. Evaporation of the solvent gave an oily mass which was purified by column chromatography on silica gel (hexane:AcOEt=5:1) followed by recrystallization from Et_2O to give 16 g (49%) of **2**, mp 95—97 °C. *Anal.* Calcd for $C_{18}H_{16}BrNO$: C, 63.23; H, 4.71; N, 4.09. Found: C, 63.17; H, 4.72; N, 4.12. IR (Nujol): 1655 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.30—3.93 (4H, m), 5.76 (2H, s), 6.81—7.50 (8H, m), 7.72 (1H, dd, *J*=7 and 2 Hz), 10.02 (1H, s).

(3*R*,11b*S*)-11-Benzyl-3-phenyl-2,3,5,6-tetrahydro-11b*H*-oxazolo-[3′,2′:1,2]pyrido[3,4-*b*]indole (4) A mixture of (*R*)-phenylglycinol (4 g, 29 mmol) and **2** (10 g, 29 mmol) was stirred in a mixture of dry tetrahydrofuran (THF) (20 ml) and dry Et_2O (200 ml) at room temperature for 0.5 h. The solvent was then evaporated off under reduced pressure. Azeotropic distillation was done with dry benzene (3×100 ml) at 80 °C under reduced pressure to give crude **3** as a solid.

Et_3N (8.14 ml, 58 mmol) was added dropwise at 0 °C to a solution of the crude **3** in dry $CHCl_3$ (100 ml). The mixture was then stirred at 0 °C for 2 h, washed with H_2O, and concentrated. Crystallization of the residue from EtOH gave 2.5 g of optically pure **4** (62%), mp 117—118 °C. The diastereoisomeric purity was confirmed by examination of the 500 MHz NMR spectrum. *Anal.* Calcd for $C_{26}H_{24}N_2O$; C, 82.07; H, 6.36; N, 7.36. Found: C, 82.27; H, 6.61; N, 7.55. ^{1}H-NMR (60 MHz, acetone-d_6) δ: 2.73—3.00 (2H, m), 3.04—3.30 (2H, m), 3.78 (1H, t, *J*=2 Hz), 4.28—4.43 (2H, m), 5.49 (2H, s), 5.72 (1H, s), 6.98—7.78 (14H, m). FAB-MS (positive ion mode) *m/z*: 381 [(M+1)$^+$]. $[\alpha]_D^{25}$ −73.0° (*c*=0.4, $CHCl_3$).

(1*S*,1′*R*)-9-Benzyl-2-(2-hydroxy-1-phenylethyl)-1-methyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indole (5a) A solution of **4** (1.5 g, 4.0 mmol) in dry Et_2O (100 ml) was added dropwise at −78 °C to a solution of MeMgI (15.8 mmol) in dry Et_2O (50 ml). The mixture was stirred at −78 °C for 3 h, then the reaction was quenched with NH_4Cl, and the mixture was extracted with Et_2O. The Et_2O layer was washed with H_2O, dried, and concentrated to give a 19:1 (90% de) mixture of **5a** and (1*R*,1′*R*)-9-benzyl-2-(2-hydroxy-1-phenylethyl)-1-methyl-1,2,3,4-tetrahydropyrido[3,4-*b*]-indole (**6a**). The mixture was separated by preparative HPLC to give 1.02 g (72%) of **5a** and 120 mg (8%) of **6a**, each as an amorphous powder.

5a: *Anal.* Calcd for $C_{27}H_{28}N_2O$: C, 81.78; H, 7.12; N, 7.06. Found: C, 82.01; H, 7.35; N, 7.14. IR (neat): 3450 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.25 (3H, d, *J*=6 Hz), 2.43—3.55 (5H, m), 3.62—4.02 (3H, m), 4.94 (2H, s), 6.60—6.95 (1H, m), 6.95—7.32 (7H, m), 7.15 (5H, s), 7.35—7.70 (1H, m). FAB-MS (positive ion mode) *m/z*: 397 [(M+1)$^+$]. $[\alpha]_D^{25}$ −52° (*c*=0.7, $CHCl_3$).

6a: *Anal.* Calcd for $C_{27}H_{28}N_2O$: C, 81.78; H, 7.12; N, 7.07. Found: C, 81.95; H, 7.28; N, 7.30. IR (neat): 3410 cm^{-1}. ^{1}N-NMR (60 MHz, $CDCl_3$) δ: 1.29 (3H, d, *J*=7 Hz), 2.12 (1H, s), 2.35—2.75 (2H, m), 2.75—3.24 (2H, m), 3.34—3.72 (3H, m), 4.10 (1H, q, *J*=7 Hz), 5.16 (2H, dd, *J*=4, 3 Hz), 6.74—7.49 (9H, m), 7.19 (5H, s). FAB-MS (positive ion mode) *m/z*: 397 [(M+1)$^+$]. $[\alpha]_D^{25}$ −103.5° (*c*=0.2, $CHCl_3$).

Similarly, (1*S*,1′*R*)-9-benzyl-2-(2-hydroxy-1-phenylethyl)-1-phenyl-1,2,-3,4-tetrahydropyrido[3,4-*b*]indole (**5b**) was prepared from **4** and phenylmagnesium bromide. The crude product was purified by flash chromatography on alumina (AcOEt:hexane=1:4) to give **5b** in 77% yield (100% de), mp 155—156 °C (from EtOH). The diastereoisomeric purity was confirmed by TLC and HPLC analyses. *Anal.* Calcd for $C_{32}H_{30}N_2O$: C, 83.81; H, 6.59; N, 6.11. Found: C, 83.72; H, 6.71; N, 6.31. IR (Nujol): 3590 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.76 (1H, br s), 2.52—3.42 (4H, m), 3.75—4.06 (3H, m), 4.43 (1H, d, *J*=16 Hz), 4.68 (1H, s), 4.94 (1H, d, *J*=16 Hz), 6.52—6.83 (2H, m), 7.14 (10H, s with shoulder), 7.44—7.75 (2H, m). FAB-MS (positive ion mode) *m/z*: 459 [(M+1)$^+$]. $[\alpha]_D^{26}$ +31.3° (*c*=1.0, $CHCl_3$).

(*S*)-(+)-9-Benzyl-1-methyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indole (7a) A solution of **5** (0.47 g, 1.2 mmol, 100% de) in absolute MeOH (20 ml)

was hydrogenated with $Pd(OH)_2$–carbon (120 mg). After the completion of H_2 absorption, the catalyst was filtered off and the filtrate was evaporated. The residue was made basic with 10% $KHCO_3$ solution and extracted with $CHCl_3$. The $CHCl_3$ layer was dried and evaporated. The resulting crude mass was purified by column chromatography on silica gel ($CHCl_3$: MeOH = 9 : 1) to give 210 mg (64%) of **7a** as a viscous oil. *Anal.* Calcd for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.76; H, 7.51; N, 10.28. IR (neat): 3330 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.28 (3H, d, J = 6 Hz), 1.70 (1H, br s), 2.51—3.40 (4H, m), 3.95 (1H, q, J = 6 Hz), 5.03 (2H, s), 6.70—7.50 (9H, m). FAB-MS (positive ion mode) m/z: 277 $[(M+1)^+]$. $[\alpha]_D^{25}$ +18.1° (c = 0.14, $CHCl_3$).

Similarly, (*S*)-(+)-9-benzyl-1-phenyl-1,2,3,4-tetrahydropyrido[3,4-*b*]-indole (**7b**) was prepared in 77% yield, mp 98—100 °C (from a mixture of hexane and Et_2O). *Anal.* Calcd for $C_{24}H_{22}N_2$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.42; H, 6.83; N, 8.45. IR (neat): 3310 cm^{-1}. ^{1}H-NMR (60 MHz, CCl_4) δ: 1.55 (1H, br s), 2.50—3.09 (4H, m), 4.48 (1H, d, J = 16 Hz), 4.84 (1H, s), 5.03 (1H, d, J = 16 Hz), 6.50—6.87 (2H, m), 7.05 (5H, s), 7.12 (5H, s). FAB-MS (positive ion mode) m/z: 339 $[(M+1)^+]$. $[\alpha]_D^{25}$ +65.7° (c = 0.7, EtOH).

(*S*)-(−)-Tetrahydroharman (8a) Sodium (0.167 g, 7.25 mmol) was added to liquid NH_3 (21 ml) at −78 °C. A solution of **7** (0.2 g, 0.725 mmol) in dry THF (5 ml) was then added to the solution dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 30 min. The NH_3 and THF were evaporated off and the residue was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, dried, and evaporated to give 60 mg (75%) of **8a** as crystals. The optical purity was confirmed by chiral HPLC analysis (hexane and iso-PrOH (10 : 1) eluant; flow rate = 1 ml/min; wavelength = 254 nm; retention time = 35 min). The spectral properties were in good agreement with the literature values. mp 175—177 °C (lit.[3] mp 177—180 °C). $[\alpha]_D^{22}$ −51.1° (c = 0.5, EtOH) [lit.[3] $[\alpha]_D^{25}$ −52° (c = 2.0, EtOH)]. IR (Nujol): 3320, 3480 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.37 (3H, d, J = 6 Hz), 2.36 (1H, br s), 2.50—3.45 (4H, m), 4.10 (1H, q, J = 6 Hz), 6.90—7.30 (3H, m), 7.30—7.60 (1H, m), 8.18 (1H, br s).

Similarly, (*S*)-(+)-1-phenyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indole (**8b**) was prepared in 78% yield, mp 195—196 °C (from EtOH). *Anal.* Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 82.49; H, 6.71; N, 11.45. IR (neat): 3450, 3260 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.74 (1H, br s), 2.61—3.02 (2H, m), 3.02—3.44 (2H, m), 5.04 (1H, s), 6.87—7.64 (4H, m), 7.28 (5H, s), 7.64—7.89 (1H, br s). FAB-MS (positive ion mode) m/z: 249 $[(M+1)^+]$. $[\alpha]_D^{21}$ +40° (c = 0.5, $CHCl_3$).

2-Formyl-3-(2-bromoethyl)benzo[*b*]thiophene (10) BuLi (1.37 M in hexane, 18.1 ml, 24.8 mmol) was added dropwise to a solution of 3-(2-bromoethyl)benzo[*b*]thiophene (**9**) (4.6 g, 19.1 mmol) in dry THF (120 ml) under Ar at −78 °C. The reaction mixture was stirred at −78 °C for 45 min, then dry DMF (2.9 ml, 38.2 mmol) was added dropwise. After being stirred for a further 30 min, the reaction mixture was quenched with H_2O and extracted with Et_2O. The Et_2O layer was washed with H_2O and dried. The solvent was evaporated off and the residue was column-chromatographed on silica gel (hexane : AcOEt = 8 : 1) to give **10** (1 g, 20%), mp 101—103 °C (from a mixture of hexane and Et_2O). *Anal.* Calcd for $C_{11}H_9BrOS$: C, 49.08; H, 3.37. Found: C, 49.28; H, 3.57. IR (Nujol): 1660 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.71 (4H, s with shoulder), 7.31—7.60 (2H,m), 7.81—8.09 (2H, m), 10.30 (1H, s). FAB-MS (positive ion mode) m/z: 271 $[(M+1)^+ +2]$, 269 $[(M+1)^+]$.

(3*R*,11b*S*)-3-Phenyl-2,3,5,6-tetrahydro-11b*H*-benzo[4,5]thieno[2,3-*c*]-oxazolo[3,2-*a*]pyridine (12) A solution of **10** (1 g, 3.7 mmol), (*R*)-phenylglycinol (0.6 g, 4.4 mmol), and a catalytic amount of *p*-toluenesulfonic acid in a mixture of dry Et_2O (20 ml) and absolute EtOH (7 ml) was stirred for 12 h at room temperature. The solvent was evaporated off under reduced pressure. Azeotropic distillation was done with dry benzene (50 ml × 3) and finally with CCl_4 (50 ml) to give **11** as a solid, which was used in the following reaction without further purification.

The crude **11** was dissolved in a mixture of dry CH_2Cl_2 (60 ml) and dry $CHCl_3$ (30 ml), then Et_3N (0.44 g, 4.3 mmol) was added dropwise at −78 °C. The mixture was washed with H_2O, and concentrated. Crystallization of the residue from MeOH gave optically pure **12** (0.9 g, 81%). The diastereoisomeric purity was confirmed by examination of the 500 MHz NMR spectrum, mp 137—139 °C (from MeOH). *Anal.* Calcd for $C_{19}H_{17}NOS$: C, 74.23; H, 5.57; N, 4.56. Found: C, 74.46; H, 5.76; N, 4.72. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.53—3.00 (2H, m), 3.02—3.45 (2H, m), 3.82 (1H, t, J = 4 Hz), 4.13 (1H, dd, J = 12, 4 Hz), 4.40 (1H, dd, J = 12, 4 Hz), 5.82 (1H, s), 7.34 (5H, s), 7.05—8.00 (4H, m). FAB-MS (positive ion mode) m/z: 3.08 $[(M+1)^+]$. $[\alpha]_D^{24}$ −112° (c = 0.2, $CHCl_3$).

(1*S*,1′*R*)-2-(2-Hydroxy-1-phenylethyl)-1-methyl-1,2,3,4-tetrahydrobenzo[4,5]thieno[2,3-*c*]pyridine (13) The reaction of **12** (0.64 g, 2.0 mmol) with MeMgI (8 mmol) was carried out as described for the reaction of **4** with MeMgI. The reaction was quenched with NH_4Cl solution and the mixture was extracted with Et_2O. The Et_2O layer was extracted with 10% HCl. The aqueous layer was made basic with $KHCO_3$ and extracted with Et_2O. The Et_2O layer was washed with H_2O, dried, and concentrated to give a 14 : 1 (87% de) mixture of **13** and (1*R*,1′*R*)-2-(2-hydroxy-1-phenylethyl)-1-methyl-1,2,3,4-tetrahydrobenzo[4,5]thieno[2,3-*c*]pyridine (**14**) in 95% yield. The mixture was separated by open column chromatography on silica gel (hexane : AcOEt = 3 : 1) to give optically pure **13** as a hygroscopic solid (0.53 g, 1.6 mmol) in 80% yield. IR (neat): 3450 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.42 (3H, d, J = 7 Hz), 2.10 (1H, s), 2.45—3.54 (4H, m), 3.85 (3H, s), 4.05 (1H, q, J = 7 Hz), 7.30 (5H, s), 7.05—7.87 (4H, m). FAB-MS (positive ion mode) m/z: 324 $[(M+1)^+]$. $[\alpha]_D^{23}$ −73° (c = 0.1, $CHCl_3$).

(*S*)-1-Methyl-1,2,3,4-tetrahydrobenzo[4,5]thieno[2,3-*c*]pyridine (15) A solution of **10** (0.42 g, 1.3 mmol) in absolute MeOH (20 ml) was hydrogenated on $Pd(OH)_2$–carbon (195 mg). After the completion of H_2 absorption, the catalyst was filtered off and the filtrate was evaporated. The crude residue was purified by column chromatography on silica gel ($CHCl_3$: MeOH = 9 : 1) followed by molecular distillation (oil bath temp. 125—130 °C (0.09 mmHg)) to give **15** (0.2 g, 0.98 mmol) in 75% yield as an oil. The chiral HPLC analysis (hexane and iso-PrOH (10 : 1) eluant; flow rate = 1.0 ml/min; wavelength = 254 nm; retention time = 8 min) of the free base showed its enantiomeric purity to be 100% ee. IR (neat): 3300 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.42 (3H, d, J = 7 Hz), 1.70 (1H, s), 2.46—2.90 (2H, m), 2.95—3.55 (2H, m), 4.15 (1H, q, J = 7 Hz), 7.15—7.90 (4H, m). FAB-MS (positive ion mode) m/z: 204 $[(M+1)^+]$. $[\alpha]_D^{23}$ −37° (c = 0.1, $CHCl_3$). Hydrochloride salt of **15**: mp 240—242 °C (from a mixture of Et_2O and MeOH). *Anal.* Calcd for $C_{12}H_{13}NS \cdot HCl$: C, 60.11; H, 5.89; N, 5.84. Found: C, 60.39; H, 5.79; N, 6.09.

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References and Notes

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