The Practical Synthesis of (2*S*)-7-Methoxy-1,2,3,4-tetrahydro-2-naphthylamine *via* Optical Resolution of 2-(3-Methoxybenzyl)succinic Acid

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We describe the practical synthetic route for (2*S*)-7-methoxy-1,2,3,4-tetrahydro-2-naphthylamine [(2*S*)-2-amino-7-methoxytetraline; (*S*)-AMT]. (2*R*)-2-(3-Methoxybenzyl)succinic acid [(*R*)-1] was obtained by the optical resolution of 2-(3-methoxybenzyl)succinic acid (1) as the salt of (1*R*,2*S*)-2-(benzylamino)cyclohexylmethanol (7), and (*R*)-1 was converted to the optically active (2*S*)-7-methoxy-1,2,3,4-tetrahydro-2-naphthoic acid [(*S*)-2] by the intramolecular Friedel-Crafts reaction followed by catalytic hydrogenation. (*S*)-AMT was obtained from the acid (*S*)-2 by Hofmann rearrangement without racemization.

Key words optical resolution; (2*S*)-2-amino-7-methoxytetraline; (2*R*)-2-(3-methoxybenzyl)succinic acid; β-adrenoceptor

Recently, some new β2- and β2/β3-adrenoceptor agonists have been developed. In this field, currently, we are developing a new uterine relaxant KUR-1246[1] and a new ureteral relaxant KUL-1248,[2] while Sanofi-Synthelabo is studying SR58611A[3] as a bronchodilator, as shown in Fig. 1. The optically pure compounds are required in large quantities for further evaluation. (2*S*)-7-Methoxy-1,2,3,4-tetrahydro-2-naphthylamine [(*S*)-AMT] is a very important intermediate for the synthesis of these compounds. In this paper, we describe an efficient and practical method for the synthesis of (*S*)-AMT.

Some synthetic methods for (*S*)-AMT have been reported. One of them is the optical resolution of racemic AMT as the salt of (*R*)-mandelic acid.[3] This is not efficient method because it is difficult to racemize the (*R*)-rich AMT recovered from the mother liquor. (*S*)-AMT can be directly produced from 7-methoxy-2-tetralone using the specialized transaminase enzyme,[4] but this enzyme is not easily obtainable. (*S*)-AMT also can be produced from commercially available L-aspartic acid and anisole,[3] but it is necessary to use highly toxic reagents, PCl_5 and $SnCl_4$.

We thought that the optically active 2-(3-methoxybenzyl)-succinic acid (**1**) or 7-methoxy-1,2,3,4-tetrahydronaphthoic acid (**2**)[5] was derived to (*S*)-AMT. Several groups have reported the synthetic methods for the optically active benzylsuccinic acid derivatives. Evans's chiral enolate methodology[6] needs the low temperature condition, and the asymmetric hydrogenation of benzylidenesuccinic acid derivatives with a chiral diphosphine complex of rhodium or ruthenium obtained unsatisfactory results.[7] We tried optical resolution of the acids **1** or **2**, because the racemates could be easily prepared under the usual reaction conditions in large quantity, and it was expected to racemize the other configuration of the acid components recovered from the mother liquors.

The acid **5** was prepared by the Stobbe condensation[8] of 3-methoxybenzaldehyde (**3**) and diethyl succinate (**4**), followed by hydrolysis in 81% yield. After hydrogenation of **5** with 10% Pd–C, the acid **1** was obtained in 82%. The reaction of **1** with Ac_2O followed by the intramolecular Friedel–Crafts reaction in the presence of $AlCl_3$ produced the ketone **6** in 86% yield. The ketone **6** was reductively deoxygenated with 10% Pd–C and H_2SO_4 in AcOH to give the acid **2** in 88% yield.

The acid **1** or **2** and an optically active amine were dissolved in hot solvent and allowed to stand at room temperature. The precipitate was collected and recrystallized from the same solvent. The optically active amine, the solvent, the yield, the optical purity of the acids, and the resolution efficiency (RE) are shown in Tables 1 and 2. The optical purity of the acids **1** and **2** were determined by HPLC using a chiral column, after the transformation of the acids to the corresponding methyl esters by treatment with trimethylsilyldiazomethane (TMS–CHN_2).

The optical resolution of the acid **1** using (1*R*,2*S*)-2-(benzylamino)cyclohexylmethanol (**7**) gave the corresponding salt in 37% yield with good optical purity of 90.1% ee. The salt of **1** and (1*S*)-1-phenyl-2-(4-tolyl)ethylamine (**8**) was obtained in 10% yield with the excellent optical purity of

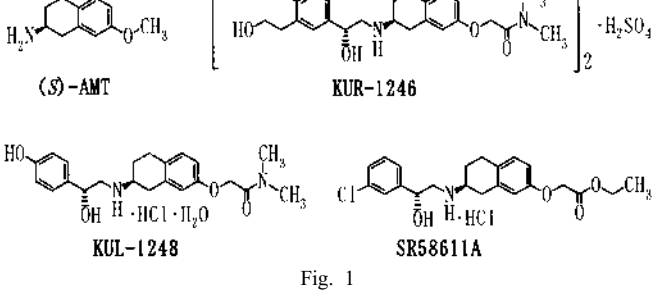

Fig. 1

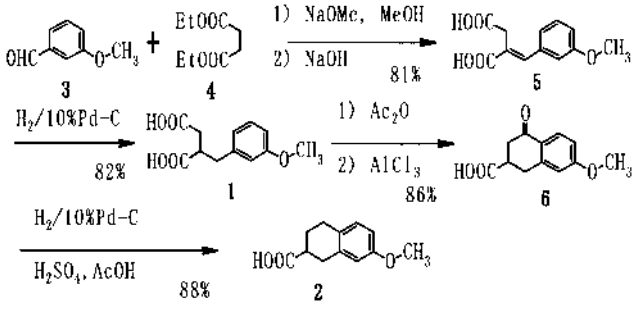

Chart 1

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Table 1. Optical Resolution of the Acid **1** Using Chiral Amines

Chiral amine	Solvent	Yield (%)	ee (%)[a]	RE[b]
(1*R*,2*S*)-2-(Benzylamino)cyclohexylmethanol (**7**)	EtOH	37	90.1 (*R*)	33
(1*R*,2*S*)-Norephedrine	EtOH	19	65.1 (*R*)	12
(1*S*)-1-Phenylethylamine (2eq)	iso-PrOH	58	16.7 (*R*)	10
(1*S*)-1-Phenyl-2-(4-tolyl)ethylamine (**8**)	EtOH	10	99.0 (*S*)	10
Quinine	EtOH	31	57.0 (*S*)	18

a) The ee and configuration of the acid **1** are shown. *b*) yield×ee÷100.

Table 2. Optical Resolution of the Acid **2** Using Chiral Amines

Chiral amine	Solvent	Yield (%)	ee (%)[a]	RE[b]
(1*S*,2*R*)-2-Amino-1,2-diphenylethanol	H_2O–EtOH[c]	46	11.4 (*S*)	5
(1*S*)-2-Amino-1-propanol	H_2O–EtOH[c]	16	46.0 (*S*)	7
(1*R*,2*S*)-2-(Benzylamino)cyclohexylmethanol (**7**)	EtOH	17	93.4 (*S*)	16
(1*S*)-1-(1-Naphthyl)ethylamine	H_2O–EtOH[c]	17	84.5 (*S*)	14
(1*R*)-1-Phenylethylamine	EtOH	9	36.0 (*S*)	3

a) The ee and configuration of the acid **2** are shown. *b*) yield×ee÷100. *c*) 10% (v/v) aqueous EtOH.

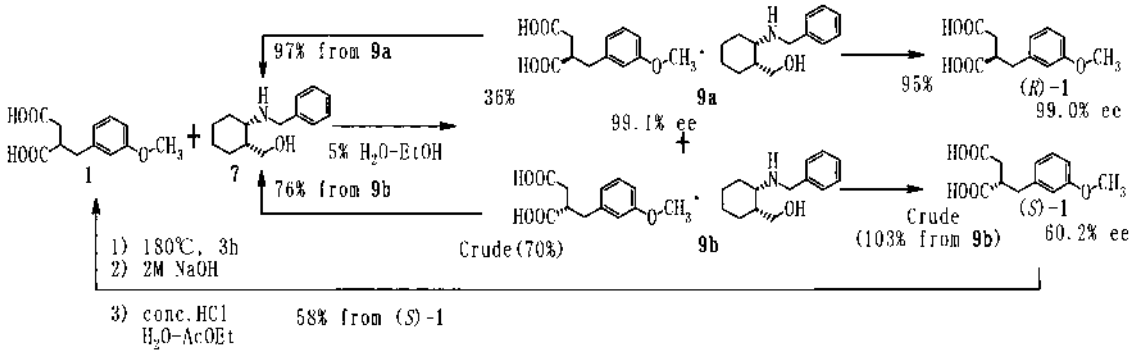

Chart 2

99.0% ee, however, the unsuitable (*S*)-configuration of **1** was obtained by using commercially available **8**. The optically active 1-phenylethylamine performed the optical resolution of benzylsuccinic acid well in our previous report,[9] but gave the unsatisfactory result in the one of **1**. On the other hand, the acid **2** was resolved by the amine **7** and (1*S*)-1-(1-naphthyl)ethylamine as the corresponding salt in 17% yield with 93.4% ee and 17% yield with 84.5% ee, respectively. We calculated the RE value from the yield and the optical purity, and decided to use the combination of **1** and **7** in the optical resolution because of the best RE value of 33.

After the optimization of the optical resolution using **1** and **7**, the salt **9a** was given in 36% yield with 99.1% ee from 5% aqueous EtOH. The salt **9a** was treated with hydrochloric acid to give the free acid (*R*)-**1** in 95% yield with 99.0% ee (Chart 2). And the optically active amine **7** was recovered from the salt **9a** in 97% yield. Furthermore, (*S*)-**1** (60.2% ee) recovered from the mother liquor was racemized by heating for 3 h at 180 °C, followed by hydrolysis to give racemic **1**. We tried to determine the configuration of (*R*)-**1** using the X-ray analysis of the salt **9** but could not obtain a good crystal for the X-ray analysis. Therefore, we prepared the salt of the acid (*R*)-**1** and (1*R*,2*S*)-norephedrine. This salt provided a good crystal for the X-ray analysis. It was determined that the acid (*R*)-**1** had the (*R*)-configuration, as shown in Fig. 2.

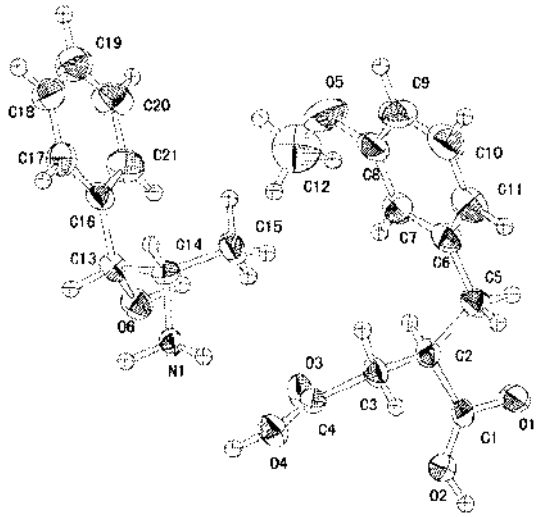

Fig. 2. ORTEP of the Salt of Acid **1** and (1*R*,2*S*)-Norephedrine

The acid (*R*)-**1** gave (*R*)-**6** in 84% with 98.5% ee and (*S*)-**2** in 86% with 97.8% ee using the same method as the racemate **1**. The amide **10** was produced *via* the corresponding acyl chloride in 96% yield with 98.6% ee, and then the Hofmann rearrangement[10] of **10** with Br_2 and *tert*-BuONa in *tert*-BuOH gave the *tert*-butoxycarbonyl (Boc) compound **11** in 87% yield with 98.0% ee. The Boc compound **11** was

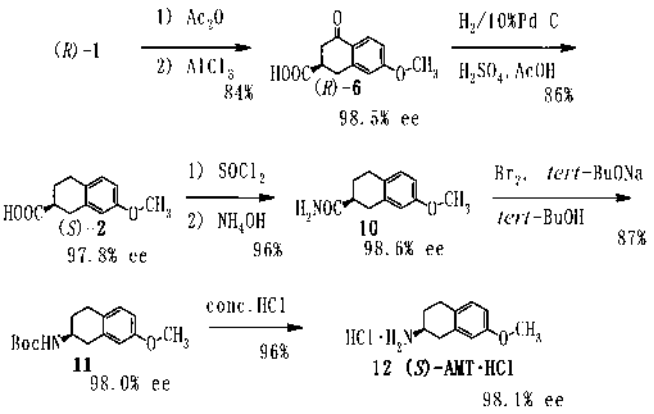

Chart 3

treated with concentrated hydrochloric acid (conc. HCl) to give (*S*)-AMT·HCl (**12**) in 96% yield with 98.1% ee (Chart 3).

In conclusion, we established the efficient and practical route for the synthesis of (*S*)-AMT·HCl (**10**). We found that the optically active acid (*R*)-**1** was obtained *via* the optical resolution of the racemic acid **1** as the salt of the optically active amine **7**, and (*S*)-AMT was derived by the Hofmann rearrangement of the amide **10**.

Experimental

All melting points were determined using a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet 510 FT-IR or AVATAR 320 FT-IR spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AMX-400 (400 MHz) or DRX-500 (500 MHz) spectrometer using tetramethylsilane as the internal standard. Mass spectra were measured using a JEOL JMS-SX102A mass spectrometer. Optical rotations were measured with a JASCO DIP-370 polarimeter.

The ee values of the prepared compounds were determined by HPLC using a chiral column (Chiralcel OD, 4.6 mm i.d.×250 mm, Daicel Chemical Industries Co., Ltd.) under the conditions of the flow rate of 1.0 ml/min, the detection of 220 nm (UV) and the indicated mobile phase.

2-(3-Methoxybezylidene)succinic Acid (5) Na (19.5 g, 0.85 g atom) was added carefully to MeOH (500 ml) cooled in an ice-bath. After Na was dissolved, diethyl succinate (**4**) (166 ml, 1.0 mol) and MeOH (50 ml) were added to the solution at room temperature. A solution of 3-methoxybenzaldehyde (**3**) (68.1 g, 0.5 mol) in MeOH (150 ml) was added dropwise to the solution over 1.5 h under reflux, and then the solution was refluxed for 5 h. 5 M NaOH (430 ml, 2.15 mol) was added to the solution and refluxed overnight. The MeOH in the mixture was evaporated under reduced pressure, and the resulting solution was diluted with water (200 ml), washed with ether (600 ml), then acidified with conc. HCl. The precipitate was collected by filtration, washed with water (3×100 ml), and dried to give **5** (95.3 g, 81%) as a pale yellow solid. An analytical sample was prepared by recrystallization from AcOEt to give a white solid. mp 158—160 °C. IR (KBr): 2939, 1720, 1678, 1578, 1430 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.39 (2H, s), 3.77 (3H, s), 6.95—6.98 (3H, m), 7.36 (1H, t, J=8.1 Hz), 7.72 (1H, s), 12.54 (2H, br s). ^{13}C-NMR (DMSO-d_6) δ: 33.87, 55.43, 114.63, 114.95, 121.56, 127.87, 130.12, 136.61, 140.25, 159.64, 168.76, 172.49. HR-MS (FAB) *m/z*: Calcd for $C_{12}H_{12}O_5$ M$^+$: 236.0685. Found: 236.0651. *Anal*. Calcd for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 60.72; H, 5.20.

2-(3-Methoxybenzyl)succinic Acid (1) A mixture of **5** (93.0 g, 0.39 mol) in EtOH (1 l) was hydrogenated over 10% Pd–C (50% wet, 9.0 g) for 7 h at room temperature under atmospheric pressure. The Pd–C was filtered off and the filtrate was concentrated under reduced pressure. The resulting residue was recrystallized from AcOEt–hexane to give **1** (77.0 g, 82%) as a white solid. mp 133—135 °C. IR (KBr): 2964, 1701, 1599, 1434 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.25 (1H, dd, J=4.3, 16.9 Hz), 2.42 (1H, dd, J =9.1, 16.9 Hz), 2.68—2.74 (1H, m), 2.86—2.92 (2H, m), 3.73 (3H, s), 6.74—6.79 (3H, m), 7.20 (1H, t, J=8.0 Hz), 12.22 (2H, s). ^{13}C-NMR (DMSO-d_6) δ: 35.19, 37.28, 42.72, 55.25, 112.09, 115.02, 121.54, 129.67, 140.66, 159.57, 173.27, 175.51. HR-MS (FAB) *m/z*: Calcd for $C_{12}H_{14}O_5$ M$^+$: 238.0841. Found: 238.0827. *Anal*. Calcd for $C_{12}H_{14}O_5\cdot 0.2H_2O$: C, 59.60; H, 6.00. Found: C, 59.61; H, 5.91.

7-Methoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid (6) A mixture of **1** (14.47 g, 60.7 mmol) and Ac_2O (6.3 ml, 66.8 mmol) in AcOEt (25 ml) was refluxed for 1 h. The solution was concentrated under reduced pressure, and AcOH was removed as the azeotrope using toluene (2×50 ml). The solution of the residue oil in chlorobenzene (25 ml) was added dropwise to a suspension of $AlCl_3$ (16.19 g, 121.4 mmol) in chlorobenzene (30 ml) cooled in an ice-bath over 0.5 h. The mixture was stirred for 2 h at room temperature. Ice in water (100 ml) was added to the mixture cooled in an ice-bath, and then the precipitate was collected by filtration to give **6** (11.48 g, 86%) as a white solid. An analytical sample was prepared by recrystallization from a mixture of THF, CH_3CN, and EtOH to give a white solid. mp 210—213 °C. IR (KBr): 2985, 1721, 1645, 1597 cm^{-1}. ^{1}H-NMR (MeOH-d_4) δ: 2.77—2.82 (2H, m), 3.14—3.32 (3H, m), 3.86 (3H, s), 6.83—6.90 (2H, m), 7.91 (1H, d, J=8.3 Hz). ^{13}C-NMR (MeOH-d_4) δ: 33.71, 41.70, 41.84, 56.49, 114.28, 115.17, 126.97, 130.78, 146.85, 166.29, 177.12, 198.04. HR-MS (FAB) *m/z*: Calcd for $C_{12}H_{13}O_4$ (M+H)$^+$: 221.0814. Found: 221.0807. *Anal*. Calcd for $C_{12}H_{12}O_4\cdot 0.2H_2O$: C, 64.39; H, 5.58. Found: C, 64.37; H, 5.53.

7-Methoxy-1,2,3,4-tetrahydro-2-naphthoic Acid (2) A mixture of **6** (10.50 g, 47.7 mmol) and H_2SO_4 (0.13 ml) in AcOH (200 ml) was hydrogenated over 10% Pd–C (1.00 g) for 12 h at 80 °C under atmospheric pressure. The Pd–C was filtered off, and the filtrate was concentrated under reduced pressure. Water (100 ml) was added to the resulting residue, and then the precipitate was collected by filtration to give **2** (8.62 g, 88%) as a white solid. An analytical sample was prepared by recrystallization from EtOH to give a white solid. mp 126—127 °C (lit.[5a] mp 127—127.5 °C). IR (KBr): 3194, 1728, 1610, 1508 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.65—1.74 (1H, m), 2.02—2.09 (1H, m), 2.58—2.92 (5H, m), 3.69 (3H, s), 6.66—6.68 (2H, m), 6.96 (1H, d, J=9.1 Hz), 12.25 (1H, s). ^{13}C-NMR (DMSO-d_6) δ: 26.09, 27.35, 31.71, 39.33, 55.28, 112.43, 113.80, 127.89, 129.79, 136.42, 157.57, 176.59. HR-MS (FAB) *m/z*: Calcd for $C_{12}H_{14}O_3$ M$^+$: 206.0943. Found: 206.0917. *Anal*. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.61; H, 6.84.

Optical Resolution of 1 or 2 The acid (1 or 2) (1.00 g) and an optically active amine (1.0 or 2.0 eq) were dissolved in hot solvent and allowed to stand at room temperature. The precipitate was collected and then recrystallized. The optically active amine, the used solvent, the yield of the salt, the ee of the acid, and the RE are shown in Tables 1 and 2. The ee was determined using the methyl ester derived by the following method. Each salt was dissolved in CH_2Cl_2 (1 ml) and 1 M HCl (1 ml). The organic layer (0.8 ml) was separated, dried over $MgSO_4$, and added to MeOH (0.4 ml). TMS–CHN_2 (10% solution in hexane; 0.03 ml) was then added to the mixture. The solution was shaken for 30 min and concentrated to give the methyl ester derivative. The ee of the dimethyl ester of **1** was determined by HPLC (mobile phase, hexane–iso-PrOH, 4 : 1). The ee of the methyl ester of **2** was determined by HPLC (mobile phase, hexane–iso-PrOH, 99 : 1).

(1*R*,2*S*)-2-(Benzylamino)cyclohexylmethanol (2*R*)-2-(3-Methoxybenzyl)succinate (9a) (1*R*,2*S*)-2-(Benzylamino)cyclohexylmethanol (**7**) (21.93 g, 0.10 mol) and **1** (23.82 g, 0.10 mol) were dissolved in 5% (v/v) aqueous EtOH (250 ml) at 50 °C, and then the mixture was cooled to room temperature. The precipitate was collected by filtration to give a white solid (20.57 g, 45%) with 81.4% ee of the acid **1**. The solid was recrystallized from 5% (v/v) aqueous EtOH (250 ml) to give **9a** (16.23 g, 36%) as a white solid with 99.1% ee of the acid **1**. The ee of the acid **1** was determined by the above-mentioned method. mp 143—145 °C. IR (KBr): 3131, 2939, 1749, 1616, 1580, 1418 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15—1.42 (4H, m), 1.48—1.82 (4H, m), 2.30—2.37 (1H, m), 2.42 (1H, dd, J=8.8, 16.1 Hz), 2.49 (1H, dd, J=3.0, 16.1 Hz), 2.67 (1H, dd, J=9.3, 13.9 Hz), 2.83—2.90 (1H, m), 3.10—3.17 (2H, m), 3.53 (1H, dd, J=3.2, 11.4 Hz), 3.77 (3H, s), 4.02 (1H, t, J=11.1 Hz), 4.09 (1H, dd, J=12.1, 25.6 Hz), 6.74 (1H, dd, J= 2.4, 7.9 Hz), 6.77 (1H, s), 7.18 (1H, t, J=7.8 Hz) 7.31—7.38 (5H, m), 7.6—9.0 (3H, br). ^{13}C-NMR ($CDCl_3$) δ: 21.22, 24.53, 24.64, 27.81, 36.72, 37.48, 38.09, 44.94, 49.50, 55.51, 59.76, 62.47, 112.07, 115.34, 121.95, 129.48, 129.59, 129.77, 129.96, 132.08, 141.37, 160.02, 177.63, 179.93. $[\alpha]_D^{25}$ +10.6° (c=1.0, MeOH). *Anal*. Calcd for $C_{26}H_{35}NO_6$: C, 68.25; H, 7.71; N, 3.06. Found: C, 68.16; H, 7.81; N, 3.20.

(2*R*)-2-(3-Methoxybenzyl)succinic Acid [(*R*)-1] A mixture of **9a** (16.10 g, 35 mmol), 2 M NaOH (39 ml, 78 mmol), water (40 ml), and toluene (80 ml) was stirred for 1 h at room temperature. The separated organic layer was extracted with water (20 ml), the combined aqueous layer was acidified with conc. HCl (7.0 ml), and extracted with AcOEt (3×50 ml). The combined AcOEt layer was washed with brine (10 ml), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was recrystal-

lized from AcOEt–hexane to give (*R*)-**1** (7.96 g, 95%) as a white solid. The ee of (*R*)-**1** was determined to be 99.0% ee using the dimethyl ester derived with TMS–CHN_2 (10% solution in hexane) in CH_2Cl_2–MeOH by HPLC (mobile phase, hexane–iso-PrOH, 4 : 1). mp 89—89.5 °C. IR (KBr): 3023, 2964, 1710, 1700, 1610, 1586, 1435 cm^{-1}. $[\alpha]_D^{27}$ −13.0° (*c*=1.0, MeOH). HR-MS (FAB) *m/z*: Calcd for $C_{12}H_{14}O_5$ M^+: 238.0841. Found: 238.0832. *Anal*. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.48; H, 5.97.

Recovery of the Chiral Amine 7 The separated toluene solution in the synthesis of the acid (*R*)-**1** was concentrated under reduced pressure, and the residue was crystallized from EtOH–water to give **7** (6.78 g, 88%) as a white solid. $[\alpha]_D^{26}$ +25.0° (*c*=1.0, MeOH). [Commercially available **7**: $[\alpha]_D^{26}$ +25.0° (*c*=1.0, MeOH)]

Racemization of Recovered (S)-1 The (*S*)-**1** (16.13 g, 60.2% ee) recovered from the mother liquor of the optical resolution was stirred for 3 h at 180 °C. 2 M NaOH (50 ml) was added to the oil and stirred for 1 h at 80 °C. The solution was acidified with conc. HCl (7.0 ml) and extracted with AcOEt (50 ml and 30 ml). The combined AcOEt layer was washed with brine (10 ml), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was suspended in hot AcOEt–hexane. After cooling, the solid was collected by filtration to give **1** (9.27 g, 58%, 1.0% ee) as a white solid. $[\alpha]_D^{26}$ +0.4° (*c*=1.0, MeOH).

Crystal Structure of (1*R*,2*S*)-2-Amino-1-phenylpropan-1-ol (2*R*)-2-(3-Methoxybenzyl)succinate (1*R*,2*S*)-2-Amino-1-phenylpropan-1-ol [(1*R*,2*S*)-norephedrine] (76 mg, 0.50 mmol) and (*R*)-**1** (120 mg, 0.50 mmol) were dissolved in EtOH (1.0 ml) at 50 °C, then cooled to room temperature. The precipitate was collected by filtration to give the title compound as a white solid (76 mg, 39%). A colorless crystal was obtained by recrystallization from EtOH. Crystal data: Monoclinic, $P2_1$ (No.4), Z=4; a=5.514 b=33.161 c=11.267 Å; $\alpha=\gamma=90.0$, $\beta=100.459°$. Intensity data were collected under the cryo stream at 213 K with graphite monochromated Mo–Kα radiation (λ=0.71069 Å) on a Rigaku RASA-7R diffarctometer, 2θ(max)=55.0°. The decay of the crystal was monitored by three standard reflections, but no decay was observed. Of 2713 measured reflections, 1883 had $I>3\sigma$, and 2354 were unique and were used for the structure analysis. The structure was solved by a direct method (SIR-92) and refined through a full-matrix least squares method to R=0.051 and Rw=0.054 using the TEXSAN-TEXRAY Structure Analysis Package (Ver. 1.9), Molecular Structure Corporation. Hydrogen atoms were incorporated at fixed positions with C–H= 0.95 Å. mp 139 °C. IR (KBr): 3088, 1586, 1258 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.91 (3H, d, *J*=6.6 Hz), 2.10—2.21 (2H, m), 2.52—2.60 (1H, m), 2.99 (2H, dd, *J*=4.7, 13.5 Hz), 3.30—3.40 (1H, m), 3.72 (3H, s), 4.78 (1H, d, *J*= 3.0 Hz), 6.72—6.75 (3H, m), 7.15—7.18 (1H, m), 7.27—7.40 (5H, m). ^{13}C-NMR (DMSO-d_6) δ: 12.54, 37.50, 37.81, 44.52, 51.97, 55.19, 72.29, 111.71, 114.99, 121.63, 126.38, 127.66, 128.49, 129.48, 141.72, 142.19, 159.49, 174.77, 177.25. $[\alpha]_D^{26}$ −8.4° (*c*=1.0, MeOH). *Anal*. Calcd for $C_{21}H_{27}NO_6$: C, 64.77; H, 6.99; N, 3.60. Found: C, 64.75; H, 7.12; N, 3.76.

(2*R*)-7-Methoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid [(*R*)-6] The cyclization of (*R*)-**1** (2.85 g, 12.0 mmol) was carried out as described for the synthesis of **6** to give (*R*)-**6** (2.23 g, 84%) as a white solid. The ee of (*R*)-**6** was determined to be 98.5% ee by HPLC (mobile phase, hexane–EtOH–TFA, 960 : 40 : 1). An analytical sample was prepared by recrystallization from EtOH to give a white solid. mp 189—189.5 °C. IR (KBr): 3019, 1722, 1644, 1596 cm^{-1}. $[\alpha]_D^{27}$ −14.6° (*c*=1.0, MeOH). HR-MS (FAB) *m/z*: Calcd for $C_{12}H_{13}O_4$ $(M+H)^+$: 221.0814. Found: 221.0820. *Anal*. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 64.95; H, 5.56.

(2*S*)-7-Methoxy-1,2,3,4-tetrahydro-2-naphthoic Acid [(*R*)-2] The reductive deoxygenation of (*R*)-**6** (2.64 g, 12.0 mmol) was carried out as described in the synthesis of **2** to give (*R*)-**2** (2.13 g, 86%) as a white solid. The ee of (*R*)-**2** was determined to be 97.8% ee using the methyl ester derived with TMS–CHN_2 (10% solution in hexane) in CH_2Cl_2–MeOH by HPLC (mobile phase, hexane–iso-PrOH, 99 : 1). An analytical sample was prepared by recrystallization from EtOH to give a white solid. mp 135—137 °C. IR (KBr): 3191, 1730, 1610, 1506 cm^{-1}. $[\alpha]_D^{27}$ −44.6° (*c*=1.0, MeOH). HR-MS (FAB) *m/z*: Calcd for $C_{12}H_{15}O_3$ $(M+H)^+$: 207.1021. Found: 207.1042. *Anal*. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.94; H, 6.89.

(2*S*)-7-Methoxy-1,2,3,4-tetrahydro-2-naphthoamide (10) A mixture of (*R*)-**2** (1.031 g, 5.0 mmol) and $SOCl_2$ (1.45 ml, 20.0 mmol) in toluene (5 ml) was stirred for 2 h at 80 °C. The solution was concentrated, then the solution of the resulting residue in toluene (2 ml) was added to 28% ammonium solution (5 ml) cooled in an ice-bath. The precipitate was collected by filtration to give **10** (0.984 g, 96%) as a white solid. The ee of **10** was determined to be 98.6% ee by HPLC (mobile phase, hexane–iso-PrOH, 4 : 1). An analytical sample was prepared by recrystallization from EtOH to give a white solid. mp 159—160 °C. IR (KBr): 3355, 3190, 1660, 1624, 1503 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.81—1.91 (1H, m), 2.09—2.16 (1H, m), 2.53—2.61 (1H, m), 2.76—3.02 (4H, m) 3.77 (3H, s), 5.63 (1H, br s), 5.85 (1H, br s), 6.63 (1H, d, *J*=2.4 Hz), 6.70 (1H, dd, *J*=2.4, 8.3 Hz), 6.99 (1H, d, *J*=8.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 27.25, 28.13, 32.93, 41.67, 55.66, 112.76, 114.04, 128.15, 130.12, 136.34, 158.10, 178.29. $[\alpha]_D^{25}$ −60.8° (*c*=1.0, MeOH). HR-MS (FAB) *m/z*: Calcd for $C_{12}H_{15}NO_2$ M^+: 205.1103. Found: 205.1059. *Anal*. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.88; H, 7.41; N, 6.83.

(2*S*)-2-*tert*-Butoxycabonylamino-7-methoxy-1,2,3,4-tetrahydronaphthalene (11) *tert*-BuOH (6 ml) was added to a solution of *tert*-BuONa (1.27 g, 13.2 mmol) in THF (8 ml) at room temperature and then the white solid was immediately precipitated. Compound **10** (0.821 g, 4.0 mmol) was added to the mixture cooled in an ice-bath and, after 10 min, Br_2 (0.24 ml, 4.5 mmol) was added. The mixture was warmed in a water-bath (55 °C) for 20 min and concentrated under reduced pressure. Water (10 ml) was added to the resulting residue and extracted with AcOEt (3×20 ml). The combined organic layer was washed with Na_2SO_3 solution (5 ml) and brine (5 ml), dried over $MgSO_4$, and concentrated under reduced pressure to give **11** (0.961 g, 87%) as a solid. The ee of **11** was determined to be 98.0% ee by HPLC (mobile phase, hexane–iso-PrOH, 99 : 1). An analytical sample was prepared by purification using silica gel chromatography (Fuji Silysia Co., Ltd.; BW-350; eluent, AcOEt–hexane, 1 : 5) to give a white solid. mp 102—104 °C. IR (KBr): 3364, 2984, 2927, 1686, 1526 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 1.68—1.77 (1H, m), 2.00—2.07 (1H, m), 2.60 (1H, dd, *J*=8.1, 16.3 Hz), 2.80 (2H, t, *J*=6.1 Hz), 3.08 (1H, dd, *J*=4.8, 16.3 Hz), 3.76 (3H, s), 3.90—4.02 (1H, br), 4.52—4.64 (1H, br), 6.59 (1H, d, *J*=2.7 Hz), 6.70 (1H, dd, *J*=2.7, 8.4 Hz), 6.99 (1H, d, *J*=8.4 Hz). ^{13}C-NMR ($CDCl_3$) δ: 26.67, 28.83, 29.60, 36.74, 46.57, 55.64, 79.62, 112.91, 114.32, 128.02, 130.06, 135.79, 155.74, 158.12. $[\alpha]_D^{27}$ −65.0° (*c*=1.0, MeOH). HR-MS (FAB) *m/z*: Calcd for $C_{16}H_{23}NO_3$ M^+: 277.1678. Found: 277.1675. *Anal*. Calcd for $C_{16}H_{23}NO_3 \cdot 0.3H_2O$: C, 67.96; H, 8.41; N, 4.95. Found: C, 68.02; H, 8.36; N, 5.08.

(2*S*)-7-Methoxy-1,2,3,4-tetrahydro-2-naphthylamine Hydrochloride (12) A mixture of **11** (0.856 g, 3.1 mmol) and conc. HCl (0.8 ml, 9.6 mmol) in EtOH (5 ml) was stirred for 1 h at 60 °C. The mixture was concentrated under reduced pressure and the resulting residue was suspended in EtOH–hexane. The solid was collected by filtration to give **12** (0.631 g, 96%). The ee of **12** was determined to be 98.1% ee using the acetamido derived with Ac_2O in ether–1 M NaOH by HPLC (mobile phase, hexane–iso-PrOH, 9 : 1). An analytical sample was prepared by recrystallization from iso-PrOH to give a white solid. mp 207—209 °C (lit.[3] 203—205 °C). IR (KBr): 2850, 2008, 1611, 1503 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.70—1.79 (1H, m), 2.09—2.16 (1H, m), 2.72—2.85 (3H, m), 3.06 (1H, dd, *J*=4.8, 16.2 Hz), 3.35—3.43 (1H, m), 3.71 (3H, s), 6.68 (1H, d, *J*=2.5 Hz), 6.72 (1H, dd, *J*=2.5, 8.3 Hz), 7.01 (1H, d, *J*=8.3 Hz), 8.37 (3H, s). ^{13}C-NMR (DMSO-d_6) δ: 26.39, 27.36, 33.55, 46.98, 55.39, 113.13, 113.74, 127.10, 129.85, 134.29, 157.81. $[\alpha]_D^{26}$ −67.6° (*c*=1.0, MeOH) [lit.[3] $[\alpha]_D^{20}$ −66.1° (*c*=0.5, MeOH)]. *Anal*. Calcd for $C_{11}H_{16}NOCl \cdot 0.2H_2O$: C, 60.80; H, 7.61; N, 6.45. Found: C, 60.75; H, 7.50; N, 6.45.

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