Friedel−Crafts cyclization and deoxygenation at the C-1 position;[12] and (10) Heck reaction of optically active phthalimidovinylglycinol with aryl halides followed by olefin hydrogenation and TfOH-catalyzed cyclization.[13]

As regards (*S*)-2-amino-5-methoxytetralin **1**, hitherto successful approaches to it were reported only three-fold: (1) lipase-catalyzed enantioselective acetylation of (±)-**1**;[6] (2) *ω*-aminotransferase-catalyzed amination of 5-methoxy-2-tetralone;[8] and (3) resolution of (±)-2-(*N*-benzylamino)-5-methoxytetralin via diastereomeric salt formation with (*S*)-mandelic acid followed by catalytic hydrogenolysis.[4a] Indeed, the resolution process should compete favorably with those chemoenzymatic processes if it could be effected with (±)-**1** itself rather than its *N*-benzyl derivative, since, being a primary amine, the off-enantiomer of the former would be much easier to racemize for recycling.[3a] However, to the best of our knowledge, successful reports on direct resolution of (±)-2-aminotetralins were few,[2a,4] and that of (±)-**1** was no exception, which was fortified by the literature precedent describing unsuccessful attempts to obtain crystalline diastereomeric salts from (±)-**1** while it was lacking in detailed experimental discussion.[4a]

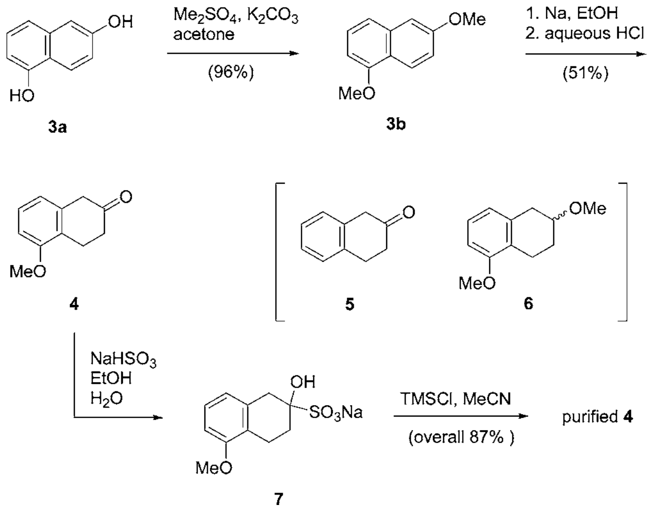
Hence, we ventured to re-examine the resolution of (±)-**1** into (*S*)-**1** via diastereomeric salt formation, anticipating that the overall throughput of the resolution process [net atom efficiency with (±)-**1**] should exceed 50% once the off-enantiomer (*R*)-**1** could be recycled via racemization.[3]

Results and Discussion

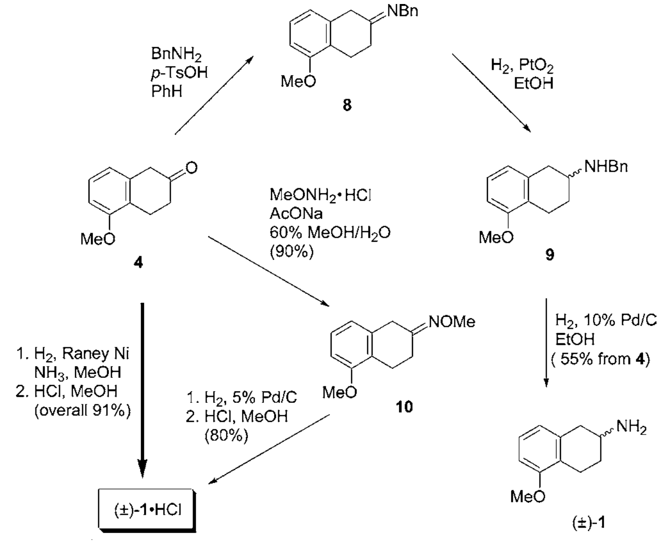
Preparation of 5-Methoxytetralone (4) via Birch's Reduction. Our synthetic venture commenced with preparation of 5-methoxy-2-tetralone **4** (Scheme 1):[14,15] Bis *O*-methylation (Me_2SO_4, K_2CO_3, acetone)[16] of 1,6-dihydroxynaphthalene **3a** gave dimethyl ether **3b** in 96% yield, which was subjected to Birch's reduction under the conditions described by Conforth et al. (Na, EtOH; concd HCl).[14] The protocol being a widely accepted standard one notwithstanding, the resulting **4** turned out to be less pure than expected, as GC−MS and GC analyses showed the presence of two contaminants: a 2-desmethoxy byproduct, tetralone **5** [*m*/*z* 146 (M^+), 0.16%], and an overreduced byproduct, (±)-1,6-dimethoxytetraline **6** [*m*/*z* 192 (M^+), 6.7%].

Possessing no carbonyl functionality, tetraline **6** would survive the ensuing reductive amination unchanged when tetralone **5** would suffer the amination. In addition, being furnished with no functionality to be engaged in salt formation, **6** should less adversely affect isolation of the aminated product (±)-**1** than **5**, or more precisely, the aminated product thereof. Hence, we decided to focus on removing **5** as much as possible and defining its tolerable level.

Scheme 1. **Preparation of 5-methoxy-2-tetralone 4**



Scheme 2. **Preparation of (±)-2-amino-5-methoxytetralin hydrochloride 1·HCl**



When the crude Birch reduction product was subjected to fractional distillation in vacuo, fractions boiling at 120−122 °C/0.2 mmHg were collected which contained **4**, **5**, and **6** in 85.50%, 0.16%, and 6.70% yield, respectively, with the net yield of **4** being estimated at 51% by GLC analysis. While tetralone **5** in question could not be removed completely, preliminary experimentation (use test) suggested that the distilled **4** was suitable to be employed in the ensuing transformations including reductive amination (Scheme 2) and diastereomeric salt formation (Scheme 3). Thus, hereinafter, discussion will be elaborated on the synthetic endeavors that have been made with the distilled 5-methoxy-2-tetralone **4**.

In the meantime, strict purification of the distilled **4** was further attempted but to no avail: its treatment with $NaHSO_3$ in aqueous EtOH gave bisulfite adduct **7** as solid precipitates (Scheme 1). When using Kjell's nonaqueous protocol (TM-

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(12) (a) Melillo, D. G.; Larsen, R. D.; Mathre, D. J.; Shukis, W. F.; Wood, A. W.; Colleluori, J. R. *J. Org. Chem.* **1987**, *52*, 5143. (b) Nordlander, J. E.; Payne, M. R.; Njoroge, F. G.; Vishwanath, V. M.; Han, G. R.; Laikos, G. D.; Balk, M. A. *J. Org. Chem.* **1985**, *50*, 3619.(c) Baxter, A. D.; Murray, P. J.; Taylor, R. J. K. *Tetrahedron Lett.* **1992**, *33*, 2331. (d) Amari, G.; Delcanale, M.; Razzetti, R.; Monici Preti, P. A.; Rondelli I. (Chiesi Farmaceutici S.p.A.) WO 01/85668, 2001.

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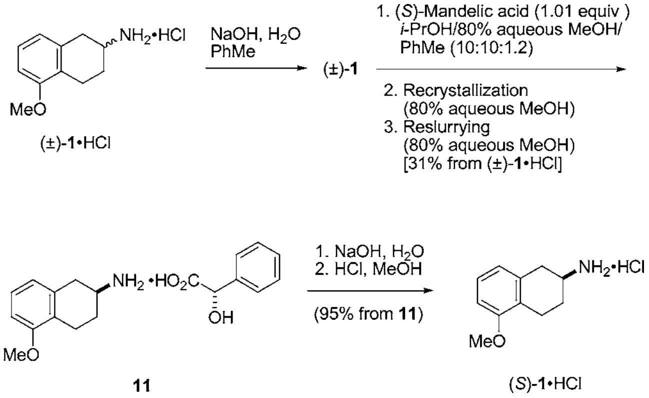
(14) Conforth, J. W.; Robinson, R. *J. Chem. Soc.* **1949**, 1855.

(15) For the preparation of (±)-2-amino-5-methoxytetralin **1** from 5-methoxytetralone, see: Ye, Q.; Grunewald, G. L. *J. Med. Chem.* **1989**, *32*, 478.

(16) Abell, A. D.; Phillips, A. J.; Budhia, S.; McNulty, A. N.; Neubauer, B. L. *Aust. J. Chem.* **1998**, *51*, 389.

Scheme 3. **Chiral separation of (±)-1·HCl into (*S*)-1·HCl using diastereomeric salt 11 between (*S*)-1 and (*S*)-mandelic acid**



SCl, MeCN),[17] **4** could be regenerated from **7** in an overall yield of 87% from the distilled **4** in a more reliable manner than under the common aqueous conditions (aqueous Na_2CO_3).[18] However, the bisulfite formation proved to be only marginally effective for the strict purification, since GLC analysis showed that the 5-methoxy-2-tetralone **4** thus processed was composed of **4**, **5**, and **6** in 97.50%, 0.13%, and 2.50% yield, respectively, compared with the composition prior to the bisulfite formation [**4**/**5**/**6** (85.50:0.16:6.70)].

Preparation of (±)-2-Amino-5-methoxytetralin Hydrochloride (1)·HCl. To transform the carbonyl group of 5-methoxy-2-tetralone **4** into a primary amine function, three different methods were examined as summarized in Scheme 2: (1) reductive amination of **4** with $BnNH_2$ followed by catalytic hydrogenolysis of the *N*-Bn group in **9**;[19] (2) preparation of oxime *O*-methyl ether **10** followed by catalytic reduction;[20] and (3) reductive amination of **4** with aqueous NH_3.[21] After they were evaluated for the practicality, the third alternative, being classical but most concise and productive, proved to be the amination method of choice, as discussed below.

Hydrogenation of *N*-Benzyl Imine (8) Followed by Hydrogenolytic Removal of the *N*-Benzyl Group. *N*-Benzyl imine **8** was prepared from **4** under the usual conditions ($BnNH_2$, a catalytic amount of *p*-TsOH·H_2O, PhH; azeotropic removal of H_2O). When **8** was subjected to catalytic hydrogenation (PtO_2, H_2 at 3.9 bar, EtOH), *N*-benzylamine **9**[19] was obtained with the *N*-Bn group surviving the reductive conditions intact. After **9** was purified as a crystalline hydrochloride salt, catalytic hydrogenolysis (10% Pd/C, H_2 at 5.9 bar, EtOH) of the freed **9** afforded (±)-2-amino-5-methoxy-tetralin **1** of 99% purity (GLC) in 55% overall yield from the distilled **4**.

Catalytic Reduction of Oxime *O*-Methyl Ether (10). Now that the moderate overall yield and operational complexity had detracted from the practicality of the $BnNH_2$-mediated amination method, catalytic reduction of oxime *O*-methyl ether **10** was attempted: When **4** was treated with $MeONH_2$·HCl and AcONa in MeOH, **10** was formed quantitatively.[20a] Hydrogenation [5% Pd/C (wet); H_2 at 2.0 bar (initial pressure); 10% solution of HCl in MeOH; ambient temperature] proceeded uneventfully with **10** on a 1 g scale to afford (±)-**1** in 80% overall yield from the distilled **4**. However, when the reduction was run on a 10 g scale under more condensed conditions, the yield of (±)-**1** dropped abruptly, which should be ascribed to **10** suffering from hydrolysis by the water contained in the Pd catalyst used. Indeed, the hydrolysis back to **4** could be suppressed if a dry Pd catalyst were used; however, industrial use of dry Pd/C should be prohibited in case the solvent being used would ignite in contact with it. Hence, we decided to discontinue further investigation into preparing (±)-**1** en route from oxime *O*-methyl ether **10**.

Reductive Amination of 4 with Aqueous NH_3. Considering the labile nature of 2-tetralones under basic conditions,[18] we had not dared to attempt the reductive amination using excess NH_3 in protic media at the outset. However, since none of the stepwise amination methods explored so far turned out viable, we eventually chose to resort to the amination methodology using aqueous NH_3 as a nitrogen source, which is classical but less popular nowadays due to its relatively harsh conditions compared with those applied to the $NaBH_3CN$- or $NaBH(OAc)_3$-mediated reactions. [22,23]

When **4** was treated with aqueous NH_3 in MeOH in the presence of catalytic Raney Ni under an atmosphere of H_2 (2.9−3.9 bar), reductive amination proceeded smoothly at temperatures between 70 and 80 °C, despite its suspected vulnerability to basic conditions,[18] to afford (±)-2-amino-5-methoxytetralin **1**, which, on treatment with methanolic HCl, was converted into the hydrogen chloride salt (±)-**1**·HCl of favorable crystallinity. Finally, its purity could be increased up to 99.5% (GLC) or 99.2% (HPLC) through a single crystallization from AcOEt in 91% overall yield from the distilled **4**.

Resolution of (±)-1 into (*S*)-1 via Diastereomeric Salt Formation. Having established a scalable method to access (±)-**1**·HCl, we explored five commercially available chiral acids for the ability to resolve (±)-**1** in arbitrarily selected solvents, as summarized in Table 1.[24] Among those tested, (*S*)-mandelic acid (MA, entry 4) was identified as the

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(18) Soffer, M. D.; Bellis, M. P.; Gellerson, H. E.; Stewart, R. A. *Organic Syntheses*; John Wiley & Sons: New York, 1963; Collect. Vol. IV, pp 903−906.

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(20) (a) DeMarinis, R. M.; Shah, D. H.; Hall, R. F.; Hieble, J. P.; Pendleton, R. G. *J. Med. Chem.* **1982**, *25*, 136. (b) Ames, D. E.; Evans, D.; Grey, T. F.; Islip, P. J.; Richards, K. E. *J. Chem. Soc.* **1965**, 2636.

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(24) For a comprehensive treatise on resolution, see: (a) Jacques, J.; Collet, A.; Wilden, S. H. *Enantiomers, Racemates and Resolutions*; Krieger Publishing Co.: Malabar, 1991; Chapter 5, pp251−358. (b) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; Chapter 7, pp 297−464.

Table 1. **Resolution of (±)-1 via diastereomeric salt formation**

entry	resolving agent (equiv)	crystallization solvent	yield[a] (%)	optical purity of (*S*)-**1**[b] (% ee)
1	(*R*,*R*)-DBTA[c] (0.5)	75% (v/v) aqueous MeOH	41[d]	39
2	(*R*,*R*)-DTTA[e] (0.5)	80% (v/v) aqueous MeOH	46[f]	62
3	(*S*,*S*)-TA[g] (1.0)	87% (v/v) aqueous MeOH	14	73
4	(*S*)-MA[h] (1.0)	80% (v/v) aqueous MeOH	42	81
5	(*S*)-CSA[i] (1.0)	2-propanol	48	8.0

[a] Yield of each diastereomeric salt after crystallization. [b] Determined by HPLC (Method 3, Experimental Section). [c] (*R*,*R*)-DBTA: dibenzoyl L-(2*R*,3*R*)-tartaric acid. [d] The salt consisted of (*S*)-**1** and (*R*,*R*)-DBTA in a 2:1 ratio. [e] (*R*,*R*)-DTTA: ditoluoyl L-(2*R*,3*R*)-tartaric acid [f] The salt consisted of (*S*)-**1** and (*R*,*R*)-DTTA in a 2:1 ratio. [g] (*S*,*S*)-TA: D-(2*S*,3*S*)-tartaric acid. [h] (*S*)-MA: L-(*S*)-mandelic acid. [i] (*S*)-CSA: (1*S*)-10-camphorsulfonic acid.

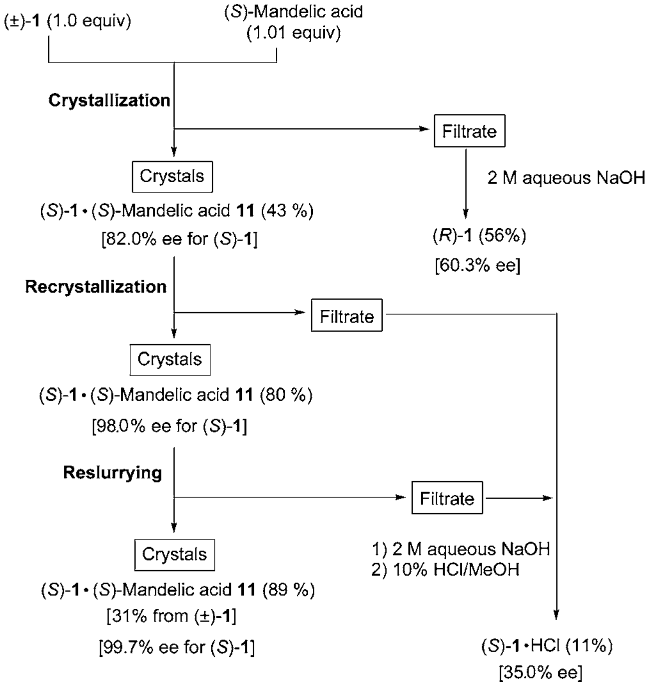
resolving agent of choice on the basis of the preliminary results listed in the table, whereas it was reported in the preceding literature[4a] that (*S*)-MA had formed a crystalline diastereomeric salt only with (±)-2-*N*-benzylamino-5-methoxytetralin **9**.

Experimental parameters affecting both crystallization and recrystallization profiles, such as stoichiometry, solvent, temperature, and aging (crystal digestion), were examined to enhance the resolution efficiency. After experimentation, the optimum conditions were eventually defined as follows: (±)-**1**·HCl was treated with an aqueous solution of NaOH to liberate free (±)-**1**, which was then combined with (*S*)-MA (1.01 equiv) in a (10:10:1.2 v/v/v) mixture of *i*-PrOH, 80% (v/v) aqueous solution of MeOH, and PhMe (Scheme 3). The freed (±)-**1** having been extracted into PhMe, the same solvent was included in the mixed solvent system on purpose such that each volume of two other solvents could be adjusted on the basis of the amount of PhMe that might still contaminate (±)-**1** after concentration in vacuo. The precipitated solids, which were collected in 43% yield and shown to contain (*S*)-**1** of 82.0% ee by chiral HPLC, were then recrystallized from 80% (v/v) aqueous solution of MeOH to give the solids containing (*S*)-**1** of 98.0% ee (chiral HPLC) in 80% yield. Finally, the solids thus recrystallized were reslurried in 80% (v/v) aqueous solution of MeOH to provide the diastereomeric salt **11** with the (*S*)-**1** contained in it being enriched in 99.7% ee (chiral HPLC) in 31% overall yield from (±)-**1**·HCl, as summarized in Scheme 4.

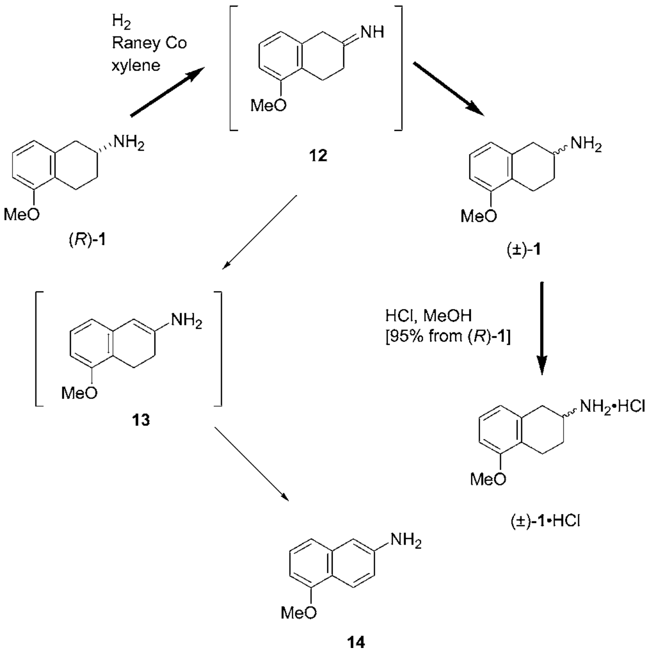
The diastereomeric salt **11** of such high stereochemical integrity was treated with an aqueous solution of NaOH to liberate free (*S*)-**1**, which was eventually converted into the hydrochloride salt (*S*)-**1**·HCl of 99.7% ee (chiral HPLC) in 95% yield; the resulting (*S*)-**1**·HCl proved to be a monohydrate when the water content was determined by Karl Fisher's water titration.

Racemization of the Off-Enantiomer (*R*)-1. Having worked out the resolution of (±)-**1** into (*S*)-**1**, we devoted our effort to recycling the off-enantiomer (*R*)-**1** to improve the throughput of the overall resolution process. The antipodal amine (*R*)-**1** being equipped with no functionality that could help to make the primary amine group stereochemically vulnerable, we chose to racemize (*R*)-**1** through an oxidation−reduction mechanism comprising (1) dehydrogenation of (*R*)-**1** to imine **12** and (2) scrambled hydrogenation of **12** to (±)-amine **1** (Scheme 5).[3b] When a dilute xylene solution of (*R*)-**1**, which had been retrieved from the mother liquors collected at each filtration step (Scheme 4), was treated with an excessive amount of Raney Co at 120

Scheme 4. **Formation and purification of diastereomeric salt 11**



Scheme 5. **Racemization of the off-enantiomer (*R*)-1 over Raney Co**



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(25) For more complicated procedures to racemize off-enantiomers of 2-aminotetralins via *N*-chlorination, see: Yamaura, M. (Nippon Kasei Chemical Co., Ltd.) *Jpn. Kokai Tokkyo Koho* 275,131, 2002.

°C under a hydrogen atmosphere, racemization took place as expected.

To enhance the productivity of (±)-**1** against the catalyst usage, the amount of the Raney Co catalyst should be reduced and the concentration of (*R*)-**1** increased, each as much as possible. Under such stringent conditions, higher temperatures of 150 °C had to be applied to drive the racemization to completion, which caused a byproduct of intense UV absorption to be produced. Thus, the reaction was carefully analyzed by GC-MS to elucidate the structure of the byproduct and thereby to gain insight into the mechanism of its generation. As a result, the byproduct in question was identified as 2-amino-5-methoxynaphthalene **14** on the basis of *m*/*z* 173 (M^+); and a plausible mechanism for its formation can be formulated as follows (Scheme 5): Raney Co catalyzed dehydrogenation gave imine **12**, a putative intermediate leading to the racemization. When heated to high temperatures around 150 °C, **12** tended more to participate in olefin-tautomerization leading to enamine **13** with increase in the thermodynamic stability due to the olefin-conjugation with the benzene ring. Finally, further dehydration of **13** took place on the catalyst surface to afford aminonaphthalene **14** with extra gain in the thermodynamic stability through aromatization.

Being driven thermodynamically, the side reaction (**12** → **13** → **14**) would be suppressed if the racemization could be effected at lower temperatures. Hence, commercially available samples of Raney Co were evaluated for the ability to catalyze the racemization at a practical concentration [not less than 10% (w/v)] and at the lowest possible temperatures where formation of **14** could be confined to a negligible level. Among the Raney Co catalysts assessed, the one available from Kansai Catalyst, Co., Ltd. (Japan) was found to best fulfill such requirements: when a 10% (w/v) xylene solution of (*R*)-**1** (35% ee) was heated at 130 °C under an atmosphere of hydrogen (2.0−2.7 bar) in the presence of the Raney Co catalyst [Kansai Catalyst, Co.; 10% (w/w) based on (*R*)-**1**], the racemization went to completion in 14 h where the aromatization to **14** could be suppressed to not more than 0.15% (GLC). The crude free amine (±)-**1** thus obtained was finally treated with methanolic hydrogen chloride to precipitate its hydrochloride salt (±)-**1**·HCl in 95% overall yield from the (*R*)-**1** of 35% ee.

Conclusion

In conclusion, a scalable synthesis of (*S*)-**1**·HCl has been developed successfully through resolution via diasteromeric salt formation. Comments worth making on this process development work are as follows: (1) Despite its susceptibility to basic conditions, 5-methoxy-2-tetralone **4** underwent smooth reductive amination with excess aqueous NH_3 over Raney Ni to give (±)-2-amino-5-methoxytetralin **1**, the overall yield of (±)-**1**·HCl from **4** being 91%. (2) Resolution of (±)-**1** was first achieved via diastereomeric salt formation with (*S*)-mandelic acid (1.01 equiv) to give (*S*)-**1**·HCl of 99.7% ee in 29% overall yield from (±)-**1**·HCl. (3) The off-enantiomer (*R*)-**1** arising from the resolution was racemized by heating its xylene solution (10% w/v) over Raney Co (Kansai Cataltyst, Co., Ltd.) at 130 °C under hydrogen (2.0−2.7 bar) to afford (±)-**1**·HCl in 95% yield with aromatization to 2-amino-5-methoxynaphthalene **14** being suppressed in 0.15%.

Experimental Section

Mp's and bp's are uncorrected. Mp's were measured on an Electrothermal 1A8104 melting point apparatus. ^1H NMR spectra were recorded at 400 MHz on a Varian UNITY-400 spectrometer for solutions in $CDCl_3$, CD_3OD, or DMSO-d_6 with tetramethylsilane as an internal standard. FT-IR spectra were recorded on a Nicolet AVATAR 360 spectrometer. GLC analyses were performed on a Shimazu GC-17A gas chromatograph. GC−MS analyses were performed on Hewlett-Packard 5890 series II (GC) and HP5971A (MS) chromatographs. High-resolution mass spectra were recorded on a JEOL JMS-DX-303 spectrometer. Elemental analyses were performed on a Yanagimoto CH or CHN MT-5 analyzer. Optical rotations were measured on a Horiba SEPA-200 polarimeter. Water content was measured on a Kyoto Electronics Karl Fisher moisture titrator MKC-210.

Analytical Methods. A. GC−MS. Method to detect and identify **5**, **6**, 2-aminotetralin, and **14**: column, HP Ultra1 (cross-linked methyl silicon gum; 25 m × 0.2 mm*ϕ*); carrier gas, He; column head pressure, 5.0 psi (0.3 bar); column temperature, 50−250 °C (10 °C/min) and 250 °C (10 min); injection temperature, 250 °C; detection temperature, 280 °C; detection, EI (70 eV); t_R 13.1 min for **5** [*m*/*z* 146 (M^+)], 13.5 min for 2-aminotetralin [*m*/*z* 147 (M^+); generated from **5**], 16.4 min for **6** [*m*/*z* 192 (M^+)], 16.5 min for **4** [*m*/*z* 176 (M^+)], 16.7 min for (±)-**1** [*m*/*z* 177 (M^+)], 19.7min for **14** [*m*/*z* 173 (M^+)].

B. GLC. (1) Method 1 to assess chemical purity of **3b** and to quantify **6** contained in **4**: column, J&W DB-WAX (30 m × 0.25 mm*ϕ*); carrier gas, He, 0.6 mL/min; injection temperature, 250 °C; column temperature, 230 °C; detection temperature, 250 °C; split ratio, 1:100; detection, FID; t_R 8.3 min for **6**, 12.4 min for **4**, 14.8 min for **3b**. (2) Method 2 to quantify **5** contained in **4**: column, Shimazu Hicap CBP1 M-25 (25 m × 0.2 mm*ϕ*); carrier gas, He, 1.5 mL/min; injection temperature, 270 °C; column temperature, 40−250 °C (10 °C/min) and 250 °C (5 min); detection temperature, 290 °C; split ratio, 1:100; detection, FID; t_R 13.1 min for **5**, 16.5 min for **4** (unresolved from **6**), 18.0 min for **3b**. (3) Method 3 to quantify (±)-, (*S*)-, and (*R*)-**1**, **5**, **10**, and **14**: the same conditions described for Method 2; t_R 13.1 min for **5**, 13.4 min for 2-aminotetralin, 16.7 min for (±)-, (*S*)-, and (*R*)-**1**, 18.1 min for **10**, 19.1 min for **14**.

C. HPLC. (1) Method 1 to assess chemical purity of (±)-**1**·HCl: column, COSMOSIL 5C18 (250 mm × 4.6 mm*ϕ*); elution, *i*-PrOH/10 mM solution of sodium octanesulfonate in 0.1% H_3PO_4 aqueous solution (40:60), 0.5 mL/min; column temperature, ambient; detection, UV at 254 nm; t_R 6.3 min for (*S*)-mandelic acid, 7.3 min for (±)-**1**, (*S*)-**1**, and (*R*)-**1** (unresolved from **14**), 13.1 min for **4**. Method 2 to quantify **14** contained in (±)-**1**·HCl: column, COSMOSIL 5C18 (250 mm × 4.6 mm*ϕ*); elution, MeCN/H_2O/AcOH/sodium dodecyl sulfate (450:550:0.2:1.2), 1.0 mL/min; column temperature, ambient; detection, UV at 254 nm; t_R 8.7 min for **14**·HCl, 9.5 min for (±)-, (*R*)-, and (*S*)-**1**·HCl.

(3) Method 3 to determine optical purity of (*S*)-**1**, (±)-**1**·HCl, and (*R*)-**1**: column, DAICEL CROWNPACK CR (+) (150 mm × 4.0 mmϕ); elution, MeOH/0.1 M aqueous solution of $HClO_4$ (15:85), 1.3 mL/min; column temperature, 45 °C; detection, UV at 220 nm; t_R 54 min for (*R*)-**1**, 70 min for (*S*)-**1**.

1,6-Dimethoxynaphthalene (3b). Under an atmosphere of Ar was added Me_2SO_4 (53.2 g, 422 mmol) dropwise to a stirred heterogeneous mixture of 1,6-dihydroxynaphthalene **3a** (available from Aldrich; 19.2 g, 120 mmol), K_2CO_3 (60.1 g, 440 mmol), and anhyd acetone (200 mL) over 15 min at ambient temperature. The mixture was stirred and heated at reflux for 2.5 h. The mixture was allowed to cool to ambient temperature, and insoluble materials were filtered off. The filtrate was concentrated in vacuo to give a brown syrup (36.0 g), which solidified spontaneously on standing at ambient temperature. *n*-Hexane (100 mL) was added, and the mixture was heated at reflux until complete dissolution. The solution was allowed to cool to ambient temperature to induce crystallization. The mixture was ice-cooled, and precipitated solids were collected by filtration to give a first crop of **3b** (16.0 g). A second crop of **3b** (5.7 g) was obtained from the mother liquor according to the aforementioned procedures; a total yield of **3b**, 21.7 g (96.1%);[16] GLC (Method 2) t_R 18.0 min for **3b** (99.7%); ^1H NMR δ ($CDCl_3$) 8.15 (d, $J = 8.8$ Hz, 1H), 7.38−7.30 (m, 2H), 7.14−7.10 (m, 1H), 7.11 (s, 1H), 6.68 (d, $J = 7.2$ Hz, 1H), 3.97 (s, 3H), 3.91 (s, 3H).

5-Methoxy-2-tetralone (4). Under an atmosphere of N_2 was added Na (138.2 g, 6.00 mol) in portions to a stirred solution of **3b** (132 g, 0.70 mol) in EtOH (1700 mL) at temperatures between 40 and 60 °C over 14 h. After the addition was complete, the reaction mixture was heated to 85 °C. The stirring was continued at the same temperature for 30 min, when Na was dissolved completely. An additional amount of Na (22.2 g, 0.97 mol) was added in portions at ambient temperature. The mixture was stirred and heated at 85 °C for 2 h. The mixture was allowed to cool to ambient temperature, and H_2O (500 mL) was added carefully with ice-cooling. To the mixture was added a concd aqueous HCl solution (1200 mL) dropwise over 2 h, during which the inner temperature was maintained at 55 °C with spontaneous heat evolution. H_2O (1500 mL) was added to dissolve the precipitated inorganic solids, and the mixture was extracted with isopropyl ether (IPE; 700 mL × 1, 500 mL × 1, 300 mL × 2). The combined IPE extracts were washed with H_2O (100 mL × 5), dried ($MgSO_4$), and treated with activated charcoal. The solution was concentrated in vacuo to give crude **4** as a deep red oil (120.1 g); GC−MS t_R 13.1 min for **5** [*m*/*z* 146 (M^+)], 16.4 min for **6** [*m*/*z* 192 (M^+)], 16.5 min for **4** [*m*/*z* 176 (M^+)]. Fractional distillation in vacuo gave purified **4** (72.9 g, 50.5%; contaminated by **5** in not more than 0.2% as assessed by GLC: vide infra); bp 120−122 °C/0.2 mmHg (lit.:[14] bp 120 °C/0.5 mmHg); GLC (Method 1) t_R 8.3 min for **6** (6.7%), 12.4min for **4** (85.5%), 14.8 min for **3b** (4.8%); GLC (Method 2) t_R 13.1 min for **5** (0.16%), 16.5 min for **4** (91.6%; unresolved from **6**), 18.0 min for **3b** (4.9%). This distilled material was employed in the next reductive amination step without further purification.

Purification of 4 via Bisulfite Adduct (7). To a stirred solution of $NaHSO_3$ (30.0 g) in H_2O (53.0 mL) and EtOH (16.0 mL) was added **4** [GLC (Method 1), 85.5%; 20.3 g] at ambient temperature. The mixture was stirred at ambient temperature for 2 h, and the precipitated solids were collected by filtration and washed with EtOH (50 mL × 2). Air-drying at an oven temperature of 50 °C overnight gave **7** as white powders (35.7 g); mp 270 °C (dec); IR ν_{max} (KBr) 3522, 3407, 3286, 2937, 2839, 1666, 1591, 1473, 1442, 1253, 1200, 1061, 972, 897, 760, 708 cm^{-1}; ^1H NMR δ (DMSO-d_6) 7.04 (t, $J = 8.0$ Hz, 1H), 6.69 (d, $J = 8.0$ Hz, 1H), 6.63 (d, $J = 7.6$ Hz, 1H), 4.92 (s, 1H), 3.80 (s, 3H), 3.16 (d, $J = 16$ Hz, 1H), 2.78 (d, $J = 16$ Hz, 1H), 2.70 (dd, $J = 5.6$ Hz, 16 Hz, 1H), 2.58−2.42 (m, 1H), 2.12−2.02 (m, 1H), 1.90−1.78 (m, 1H). A portion of **7** (1.0 g) was suspended in MeCN (5.0 mL). To the stirred mixture was added TMSCl (1.4 mL, *d* 0.856, 11.0 mmol) dropwise under an atmosphere of N_2. The mixture was stirred at ambient temperature for 2 h, and AcOEt (30 mL) was added. The mixture was washed with H_2O (20 mL × 2), dried ($MgSO_4$), and concentrated in vacuo to give **4** as a slightly yellow oil (0.52 g, 87% overall yield from the distilled **4**); GLC (Method 1) t_R 8.3 min for **6** (2.5%), 12.4 min for **4** (97.5%); GLC (Method 2) t_R 13.1 min for **5** (0.13%), 16.5 min for **4** (99.5%; unresolved from **6**); IR ν_{max} (film) 3413, 2943, 2837, 1716, 1589, 1467, 1528, 1090, 964, 781 cm^{-1}; ^1H NMR δ ($CDCl_3$) 7.18 (t, $J = 8.0$ Hz, 1H), 6.78 (d, $J = 8.4$ Hz, 1H), 6.73 (d, $J = 7.2$ Hz, 1H), 3.85 (s, 3H), 3.57 (s, 2H), 3.09 (t, $J = 6.8$ Hz, 2H), 2.52 (t, $J = 6.4$ Hz, 2H).

(±)-2-Amino-5-methoxytetralin (1). Catalytic Reduction of *N*-Benzyl Imine (8) Followed by Hydrogelolytic *N*-Debenzylation. Under an atmosphere of N_2, a solution of **4** [GLC (Method 1), 85.5%; 2.0 g, net 9.7 mmol], $BnNH_2$ (1.82 g, 17.0 mmol), and *p*-TsOH·H_2O (32.2 mg, 0.17 mmol) in PhH (30 mL) was stirred and heated at reflux for 3 h with azeotropic removal of generated water. The volatiles (PhH and excess $BnNH_2$) were evaporated off in vacuo, and the residue was dissolved in EtOH (50 mL). To the solution was added PtO_2 (23.3 mg), and the mixture was stirred under an atmosphere of H_2 at an initial pressure of 3.9 bar at ambient temperature. The mixture was stirred at ambient temperature for 3 h. The catalyst was filtered off and washed with EtOH (5 mL). The combined filtrate and washing were concentrated in vacuo to give crude **9** (2.09 g), which was dissolved in a mixture of EtOH (20 mL) and a 10% (w/v) EtOH solution of HCl (10 mL; HCl, a concd aqueous solution). The solution was decolorized with activated charcoal. The charcoal was filtered off and washed with MeOH (5 mL). The combined filtrate and washing were concentrated in vacuo. The solid residue was recrystallized from MeOH (10 mL) and IPE (10 mL). The precipitated solids were collected by filtration to give the hydrochloride salt of **9** (9.39 g) as white powders.[4a,19] A 2 M aqueous solution of NaOH (75 mL) was added, and the mixture was extracted with IPE (75 mL × 1). The IPE solution was dried (Na_2SO_4) and concentrated in vacuo to give **9** (2.09 g) as a brown oil;[19] ^1H NMR δ ($CDCl_3$) 7.40−7.20 (m, 5H), 7.00−7.05 (m, 1H), 6.77 (d, $J = 7.6$ Hz, 1H), 6.65 (d, $J = 7.2$ Hz, 1H), 3.90 (s, 2H), 3.81 (s, 3H), 3.10−2.90 (m, 3H), 2.70−2.50 (m, 2H), 2.08−2.02 (m, 1H), 1.70−1.50 (m, 2H). A portion of **9** (1.46 g) was dissolved in EtOH (50 mL). To the solution was added 10% Pd/C (E type, N.E. Chemcat Corporation; water content, 48.2%; 1.95 g). The mixture was stirred under an atmosphere of H_2 (initial pressure, 5.9 bar) with heating at 45 °C. The mixture was stirred at the same temperature for 3 h, and it was allowed to cool to ambient temperature. The catalyst was filtered off and washed with EtOH (5 mL). The combined filtrate and washing were concentrated in vacuo to give (±)-**1** as a brown oil (0.77 g, 55%);[4a,15] GC−MS t_R 13.5 min for 2-aminotetralin [*m/z* 147 (M^+); generated from **5**], 16.7 min for (±)-**1** [*m/z* 177 (M^+)]; GLC (Method 3) t_R 16.7 min for (±)-**1** (99.0%). ^{1}H NMR δ ($CDCl_3$) 7.09 (t, J = 8.0 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 6.64 (d, J = 8.4 Hz, 1H), 3.80 (s, 3H), 3.10−3.05 (m, 1H), 3.00−2.84 (m, 2H), 2.68−2.50 (m, 2H), 2.10−1.98 (m, 1H), 1.62−1.50 (m, 1H), 1.40 (br.s, 2H).

(±)-2-Amino-5-methoxytetralin Hydrochloride (1)·HCl. Catalytic Reduction of Oxime *O*-Methyl Ether (10). To a solution of $MeONH_2$·HCl (0.92 g, 10.8 mmol) in 60% (v/v) aqueous solution of MeOH (15 mL) was added NaOAc (0.92 g, 10.9 mmol); on addition, the mixture became neutral. A solution of **4** [GLC (Method 1), 85.5%; 1.30 g, net 6.30 mmol] in 60% (v/v) aqueous solution of MeOH (15 mL) was added dropwise at ambient temperature. The mixture was stirred at ambient temperature for 2 h. AcOEt (150 mL) was added, and the layers were separated. The organic layer was washed with H_2O (50 mL × 2), dried (Na_2SO_4), and concentrated in vacuo to give **10** as a brown oil (1.45 g, quantitative);[20a] GLC (Method 3) t_R 18.1 min for **10** (89.5%); IR ν_{max} (film) 2939, 2897, 2835, 1724, 1639, 1589, 1470, 1261, 1088, 1053, 968, 887, 771, 725 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 7.14 (t, J = 8.0 Hz, 1H), 6.80−6.62 (m, 2H), 3.89, 3.84, 3.83, and 3.75 (each s, total 6H), 3.49 and 3.28 (each s, total 2H), 2.89−2.84 (m, 2H), 2.62 and 2.51 (each t, J = 6.8 Hz; J = 6.8 Hz, J = 6.8 Hz; total 2H). The crude **10** thus obtained was dissolved in a mixture of MeOH (40 mL) and 10% (w/v) solution of HCl in MeOH (11 mL). To the solution was added 5% Pd/C (K type, N.E. Chemcat Corporation; water content, 55.6%; 650 mg), and the mixture was stirred under an atmosphere of H_2 (initial pressure, 2.0 bar) at ambient temperature. The stirring was continued for 2.5 h. The catalyst was filtered off and washed with MeOH (5 mL). The combined filtrate and washing were concentrated in vacuo. To the residue was added AcOEt (40 mL), and the mixture was stirred and heated to reflux. The heterogeneous mixture was stirred and heated at reflux for 30 min, and it was allowed to cool to ambient temperature. The precipitated solids were collected by filtration, washed with AcOEt (5 mL), and air-dried at an oven temperature of 50 °C overnight to give a first crop of (±)-**1**·HCl as white powders [0.88 g, 65.2% overall yield from **4**; GLC (Method 3), >99%]. A second crop of (±)-**1**·HCl (0.20 g, 14.8% overall yield from **4**) was obtained as off-white powders from the mother liquor in the same manner as described above; a total yield of (±)-**1**·HCl, 1.08 g (80% overall yield from **4**); mp 260−264 °C (lit.: mp 258−260 °C;[19] mp 265−268 °C[20a]); GLC [Method 3; injected was 10 μL of the AcOEt solution of (±)-**1** that was prepared as follows: a solution of (±)-**1**·HCl (about 10 mg) in H_2O (0.5 mL) was basified to pH > 10 with a 2 M aqueous solution of NaOH (several drops) and extracted with AcOEt (0.2 mL)] t_R 16.7 min for (±)-**1** (99.0%); IR ν_{max} (KBr) 3446, 2921, 1587, 1531, 1469, 1259, 1238, 1078, 767, 694 cm^{-1}; ^{1}H NMR δ (CD_3OD) 7.12 (t, J = 8.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 3.80 (s, 3H), 3.58−3.42 (m, 1H), 3.18−3.08 (m, 1H), 3.01−2.90 (m, 1H), 2.88−2.76 (m, 1H), 2.72−2.60 (m, 1H), 2.30−2.16 (m, 1H), 1.88−1.70 (m, 1H).

Reductive Amination of 4 with Ammonia. A 230 mL bomb (autoclave) was charged with **4** [GLC (Method 1), 85.5%; 9.87 g, net 47.8 mmol], a concd aqueous solution of NH_3 (20.4 g, 336 mmol), and MeOH (27 mL). The mixture was stirred until it became homogeneous. Raney Ni (NDHT-90, Kawaken Fine Chemicals Co., Ltd., 0.60 g) was added, and the mixture was stirred under an atmosphere of H_2 (initial pressure, 3.9 bar) and heated to 70 °C over 15 min. The stirring was continued at 70 °C for 4 h and at 80 °C for 3.5 h, during which H_2 was replenished to restore the pressure to 3.9 bar every time when it dropped to 2.9 bar. When the sum of the pressure difference amounted to 9.4 bar, the absorption of H_2 ceased and **4** was consumed completely as confirmed by HPLC (Method 1). The catalyst was filtered off and washed with MeOH (10 mL). The combined filtrate and washing were concentrated in vacuo. To the residue was added a 10% (w/v) solution of HCl in MeOH (20 g), and the mixture was concentrated in vacuo. To the solid residue (15.1 g) was added AcOEt (30 mL), and the suspension was stirred and heated at reflux for 15 min. The mixture was allowed to cool to ambient temperature. The precipitated solids were collected by filtration, washed with AcOEt (10 mL × 1), and air-dried with heating at an oven temperature of 50 °C overnight to give (±)-**1**·HCl [9.48 g, net 91.0% yield; GLC (Method 3), 99.5%; HPLC (Method 1), 99.2%; water content determined by K. Fisher's method, 1.7% (monohydrate)]; mp 260−264 °C (lit.: mp 258−260 °C;[19] mp 265−268 °C[20a]); GLC [Method 3; injected was 10 μL of the AcOEt solution of (±)-**1** that was prepared as follows: a solution of (±)-**1**·HCl (about 10 mg) in H_2O (0.5 mL) was basified to pH > 10 with a 2 M aqueous solution of NaOH (several drops) and extracted with AcOEt (0.2 mL)] t_R 16.7 min for (±)-**1** (99.5%); GC−MS t_R 16.7min for (±)-**1** [*m/z* 177 (M^+)]; HPLC (Method 1) t_R 7.3 min for (±)-**1**·HCl (99.2%); IR ν_{max} (KBr) 3446, 2921, 1587, 1531, 1469, 1259, 1238, 1078, 767, 694 cm^{-1}; ^{1}H NMR δ (CD_3OD) 7.12 (t, J = 8.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 3.80 (s, 3H), 3.58−3.42 (m, 1H), 3.18−3.08 (m, 1H), 3.01−2.90 (m, 1H), 2.88−2.76 (m, 1H), 2.72−2.60 (m, 1H), 2.30−2.16 (m, 1H), 1.88−1.70 (m, 1H).

(*S*)-2-Amino-5-methoxytetralin Hydrochloride (1)·HCl. Liberation of Free (±)-Base (1). To a stirred and ice-cooled 1 M aqueous solution of NaOH (80 mL) were added (±)-**1**·HCl [water content, 1.7% (monohydrate); GLC (Method 3), 99.5%; HPLC (Method 1), 99.2%; 12.2 g, net 56.1 mmol] and PhMe (70 mL). The mixture was well mixed, and the layers were separated. The aqueous layer was extracted with

PhMe (70 mL). The combined PhMe layer and extract were washed with H_2O (50 mL × 1), dried (Na_2SO_4), and decolorized with activated charcoal (Darco G-60; 0.3 g). The solution was concentrated in vacuo to give (±)-**1** (10.0 g, quantitative) as a colorless oil. This was employed in the next step without further purification.

Diastereomeric Salt Formation with (*S*)-Mandelic Acid. To a stirred homogeneous mixture of (*S*)-mandelic acid (8.58 g, 56.4 mmol), *i*-PrOH (50 mL), and an 80% (v/v) aqueous solution of MeOH (30 mL) was added dropwise a homogeneous mixture of (±)-**1** (10.0 g, 56.1 mmol), PhMe (5.8 mL), and 80% (v/v) aqueous solution of MeOH (20 mL). When the addition was one-third completed, solids started to precipitate. After the addition was complete, the mixture was stirred and heated at reflux for 30 min. The resulting homogeneous mixture was allowed to cool to temperatures between 23 and 27 °C over 3 h, and it was maintained at the same temperature range for 3 h. The precipitated solids were collected by filtration, washed with *i*-PrOH (20 mL), and air-dried at 50 °C overnight to give **11** (7.94 g, 43%), which was shown to contain (*S*)-**1** of 82.0% ee by HPLC [Method 3; injected was 10 μL of the solution of (*S*)-**1** in the mobile phase that was prepared as follows: A suspension of **11** (about 10 mg) in H_2O (0.5 mL) was basified to pH > 10 with a 2 M aqueous solution of NaOH (several drops). The mixture was extracted with AcOEt (0.2 mL). A portion (20 μL) of the AcOEt extract was concentrated in vacuo to give a residue, which was dissolved in the mobile phase (2 mL)] t_R 54 min for (*R*)-**1** (9.0%), 70 min for (*S*)-**1** (91.0%).

Recrystallization of Diastereomeric Salt (11). To the salt **11** (obtained by the method described in the preceding paragraph; 7.94 g, 24.1 mmol) was added 80% (v/v) aqueous solution of MeOH (39.7 mL). The suspension was stirred and heated at reflux for 30 min until it became homogeneous. The resulting solution was allowed to cool to 5 °C over 3 h, and it was kept at the same temperature for 1 h. The precipitated solids were collected by filtration, washed with *i*-PrOH (10 mL), and air-dried at 50 °C overnight to give **11** (6.37 g, 80.2%) containing (*S*)-**1** of 98.0% ee as determined by HPLC (Method 3; for the preparation of an analytical sample, see the preceding paragraph).

Reslurrying the Recrystallized Salt (11). To the recrystallized salt **11** (obtained by the method described in the preceding paragraph; 6.37 g, 19.7 mmol) was added 80% (v/v) aqueous solution of MeOH (31.9 mL). The suspension was stirred and heated at reflux for 30 min, during which it remained heterogeneous. The mixture was allowed to cool to 5 °C over 3 h, and it was kept at the same temperature for 1 h. The precipitated solids were collected by filtration, washed with *i*-PrOH (10 mL), and air-dried at 50 °C overnight to give further purified **11** [5.65 g, 88.7% yield; 30.6% overall yield from (±)-**1**], which was shown to contain (*S*)-**1** of 99.7% ee by HPLC (Method 3; for the preparation of an analytical sample, see the paragraph on diastereomeric salt formation with (*S*)-mandelic acid); mp 200−201 °C; $[\alpha]^{20}_D$ −0.60 (*c* 1.00, MeOH); IR ν_{max} (KBr) 3250, 2933, 2088, 1564, 1470, 1377, 1330, 1250, 1192, 1092, 1059, 770, 735, 679, 514, 478 cm^{-1}; ^1H NMR δ (DMSO-d_6) 7.36 (d, $J = 7.6$ Hz, 2H), 7.25−7.16 (m, 2H), 7.14−7.04 (m, 2H), 6.75 (d, $J = 7.6$ Hz, 1H), 6.65 (d, $J = 7.6$ Hz, 1H), 4.66 (s, 1H), 3.78 (s, 3H), 3.36−3.32 (m, 1H), 3.00−2.90 (m, 1H), 2.82−2.64 (m, 2H), 2.54−2.40 (m, 1H), 2.10−1.98 (m, 1H), 1.70−1.54 (m, 1H). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.21; H, 7.07; N, 4.20. Found: C, 69.28; H, 7.04; N, 4.25.

Preparation of the Hydrochloride Salt of (*S*)-1 [(*S*)-1·HCl]. To a stirred and ice-cooled 1 M aqueous solution of NaOH (51 mL) was added the salt **11** (obtained by the method described in the preceding paragraph; 5.65 g, 17.2 mmol) followed by xylene (50 mL). The mixture was well mixed, and the layers were separated. The aqueous layer was extracted with xylene (50 mL). The combined xylene layer and extract were washed with H_2O (20 mL × 3), dried (Na_2SO_4), and decolorized with activated charcoal (Darco G-60; 0.1 g). The solution was concentrated in vacuo until the volume was reduced to 60 mL. To the residue were added MeOH (15 mL) and 10% solution (w/v) of HCl in MeOH (6.5 mL, 18.1 mmol). The resulting solution was heated at 60 °C at a reduced pressure (200−140 mmHg) to distill off MeOH, during which solids started to precipitate. The mixture was allowed to cool to ambient temperature, and the precipitated solids were collected by filtration. The solids were washed with AcOEt (20 mL) and air-dried at an oven temperature of 50 °C for 4 h to provide (*S*)-**1**·HCl as white powders [3.80 g, 95.2%; water content determined by K. Fisher's method, 7.9% (monohydrate)]; GLC [Method 3; injected was 1 μL of the AcOEt solution of (*S*)-**1** that was prepared as follows: a solution of (*S*)-**1**·HCl (about 10 mg) in H_2O (0.5 mL) was basified to pH > 10 with a 2 M aqueous solution of NaOH (several drops) and extracted with AcOEt (0.2 mL)] t_R 16.7 min for (*S*)-**1** (99.9%); HPLC [Method 1; injected was 10 μL of a solution of (*S*)-**1**·HCl (about 1 mg) in the mobile phase (2 mL)] t_R 7.3 min for (*S*)-**1**·HCl (100%); HPLC [Method 2; injected was 10 μL of a solution of (*S*)-**1**·HCl (about 1 mg) in the mobile phase (2 mL)] t_R 9.5 min for (*S*)-**1**·HCl (100%); HPLC [Method 3; injected was 10 μL of a solution of (*S*)-**1**·HCl (about 1 mg) in the mobile phase (2 mL)] t_R 54 min for (*R*)-**1** (0.15%), 70 min for (*S*)-**1** (99.85%); mp 262−265 °C [lit.:[4a] mp 260 °C (dec)]; $[\alpha]^{20}_D$ −68.0 (*c* 2.00, MeOH) {lit.:[4a] $[\alpha]^{20}_D$ −61 (*c* 2, MeOH)}; IR ν_{max} (KBr) 3446, 2921, 1587, 1531, 1469, 1259, 1238, 1078, 767, 694 cm^{-1}; ^1H NMR δ (CD_3OD) 7.12 (t, $J = 8.0$ Hz, 1H), 6.77 (d, $J = 8.0$ Hz, 1H), 6.71 (d, $J = 8.0$ Hz, 1H), 3.80 (s, 3H), 3.58−3.42 (m, 1H), 3.18−3.08 (m, 1H), 3.01−2.90 (m, 1H), 2.88−2.76 (m, 1H), 2.72−2.60 (m, 1H), 2.30−2.16 (m, 1H), 1.88−1.70 (m, 1H). Anal. Calcd for $C_{11}H_{16}ClNO \cdot H_2O$: C, 57.21; H, 7.67; N, 6.05; Cl, 15.35. Found: C, 57.01; H, 7.83; N, 6.04, Cl, 15.30.

Racemization of the Off-Enantiomer (*R*)-(1). Recovery of (*R*)-1. H_2O (50 mL) was added to the combined filtrate and washing that had been collected in the course of the crystallization of **11** according to the description in the paragraph on diastereomeric salt formation with (*S*)-mandelic acid. The mixture was concentrated in vacuo to remove MeOH and *i*-PrOH. To the heterogeneous residue in which the diastereomeric salt had partly precipitated was added a 2 M aqueous solution of NaOH (48 mL). The mixture was well mixed and extracted with PhMe (50 mL × 2). The combined PhMe extracts were washed with H_2O (20 mL × 3) and concentrated in vacuo to give (*R*)-**1** (5.53 g, 96.5%) as a brown oil, the optical purity of which was determined to be 60.3% ee by HPLC (Method 2); GLC (Method 3) t_R 16.7 min for (*R*)-**1** (99.3%).

Recovery of (*S*)-1 of Low Optical Purity. All the filtrates and washings were combined which had been collected in both recrystallization and reslurrying steps according to the description in the respective paragraphs on recrystallization of diastereomeric salt **11** and reslurrying the recrystallized salt **11**. To the solution was added H_2O (20 mL). MeOH and *i*-PrOH were all evaporated off in vacuo to give a heterogeneous residue in which the diastereomeric salt partly precipitated. To the residue was added a 2 M aqueous solution of NaOH (10 mL). The mixture was well mixed and extracted with xylene (20 mL × 2). The combined xylene extracts were washed with H_2O (10 mL × 3) and concentrated in vacuo until the volume in the pot reached 29 mL. To the residue were added MeOH (5 mL) and a 10% (w/v) solution of HCl in MeOH (2.6 g). The resulting solution was heated at a reduced pressure (200−140 mmHg) to distill off MeOH, during which solids started to precipitate. The mixture was allowed to cool to ambient temperature. The precipitated solids were collected by filtration, washed with xylene (10 mL), and air-dried at an oven temperature of 50 °C for 4 h to give (*S*)-**1**·HCl (1.26 g, 84.5%), the optical purity of which was determined to be 35.0% ee by HPLC (Method 3).

Raney Co-catalyzed Racemization of (*R*)-1. To a solution of (*R*)-**1** (obtained according to the procedures described in the paragraph on recovery of (*R*)-**1**; 60.3% ee; 5.53 g, 31.2 mmol) in xylene (50 mL) was added Raney Co (Kansai Catalyst, Co., Ltd.; 0.55 g). The mixture was stirred under an atmosphere of H_2 at a pressure between 2.0 and 2.7 bar with heating at 130 °C for 14 h. The mixture was allowed to cool to ambient temperature; an aliquot of the mixture was taken and analyzed by HPLC (Method 3) and GLC (Method 3) to confirm that the optical purity of (*R*)-**1** decreased to not more than 0.4% ee and that **14** was formed in less than 0.15%. The catalyst was filtered off and washed with MeOH (10 mL). To the combined filtrate and washing was added a 10% (w/v) solution of HCl in MeOH (11.2 g, 32.8 mmol). The resulting solution was heated at 60 °C at a reduced pressure (200 → 140 → 50 mmHg) to distill off MeOH, during which solids started to precipitate. The heterogeneous residue was allowed to cool to ambient temperature. The precipitated solids were collected by filtration, washed with xylene (10 mL), and air-dried at an oven temperature of 50 °C overnight to give a first crop of (±)-**1**·HCl (5.36 g, 80.5%); GLC (Method 3) t_R 16.7 min for (±)-**1** (99.7%), 19.1 min for **14** (0.02%). The combined filtrate and washing were concentrated in vacuo to give a solid residue. PhMe (15 mL) was added, and the mixture was stirred and heated at reflux for 30 min, during which the mixture remained heterogeneous. The mixture was allowed to cool to ambient temperature. The precipitated solids were collected by filtration, washed with PhMe (5 mL), and air-dried with heating at 50 °C overnight to give a second crop of (±)-**1**·HCl (0.97 g, 14.7%); GLC (Method 3) t_R 16.7 min for (±)-**1** (98.2%), 19.1 min for **14** (1.08%); a total yield of the racemized (±)-**1**·HCl, 6.44 g, 95.2% yield; total contamination by **14**, <0.2%.

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