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Epimerization-Crystallization Method in Optical Resolution of 2,2′-Dihydroxy-1,1′-binaphthyl, and Kinetic Study

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Optical resolution of 2,2′-dihydroxy-1,1′-binaphthyl (**1**) with (*R*,*R*)-1,2-cyclohexanediamine (**2**) in toluene yielded optically pure (*R*)-**1** in a yield of 160% based on the theoretical amount of the enantiomer contained in the racemate by selective crystallization of a less soluble complex, (*R*)-**1**·(*R*,*R*)-**2**, and epimerization of more soluble complex, (*S*)-**1**·(*R*,*R*)-**2**. Also optically pure (*S*)-**1** was obtained with the same enantiomer of the resolving agent, (*R*,*R*)-**2**, in a yield of 154%. (*R*,*R*)-1,2-Diphenyl-1,2-ethanediamine (**3**) was a suitable resolving agent for both **1** and 6,6′-dibromo-2,2′-dihydroxy-1,1′-binaphthyl. Kinetic study indicated that the reversible first-order rate constants for the epimerizations of (*S*)-**1**·(*R*,*R*)-**2** and (*S*)-**1**·(*R*,*R*)-**3** were larger than that for the racemization of (*S*)-**1**. The activation energy and frequency factor for the epimerization of (*S*)-**1**·(*R*,*R*)-**2** were 109 $\mathrm{kJ\,mol^{-1}\,K^{-1}}$ and $3\times10^{10}\ \mathrm{s^{-1}}$, respectively, and those for (*S*)-**1**·(*R*,*R*)-**3** were 96 $\mathrm{kJ\,mol^{-1}\,K^{-1}}$ and $1\times10^{8}\ \mathrm{s^{-1}}$, while those for the racemization of (*S*)-**1** were 85 $\mathrm{kJ\,mol^{-1}\,K^{-1}}$ and $9\times10^{5}\ \mathrm{s^{-1}}$, respectively.

Optically active 2,2′-dihydroxy-1,1′-binaphthyl (**1**) is well known to be a useful chiral compound for many asymmetric syntheses[1] and optical resolutions.[2] Thus a variety of investigations for optical resolution of **1** have been successfully conducted,[3] but epimerization of salt or complex comprised of undesirable enantiomer and resolving agent has not been reported and only one example has been reported for racemization of **1** to our knowledge.[4]

In this paper, the authors examine a resolution by isomerization-crystallization method, which consists of the following procedures, i.e., formation of diastereomeric complexes comprised of racemic **1** and optically active diamine, separation of the diastereomeric complexes, and epimerization of an undesirable complex. This paper reports also kinetic study of the epimerizations of complexes comprised of **1** and optically active diamines and racemization of **1** (Chart 1).

Results and Discussion

When a mixture of racemic 2,2′-dihydroxy-1,1′-binaphthyl (**1**) and (*R*,*R*)-1,2-diphenyl-1,2-ethanediamine (**3**) in benzene was heated to a homogeneous solution and allowed to cool to room temperature, colorless crystalline solid was obtained, which was purified by recrystallization once from benzene to yield colorless prisms. Analyses by ^{1}H NMR and IR spectra and elemental analysis showed that the colorless prisms were a complex comprised of (*R*)-**1** and (*R*,*R*)-**3**. Decomposition of the complex with dilute hydrochloric acid gave optically pure (*R*)-**1** in a yield of 45%.[5] (*R*,*R*)-1,2-cyclohexanediamine (**2**), which possess C_2 symmetry as same as **3** but is more easily available than **3**, was examined for use as the resolving agent for **1**. Racemic **1** was treated with (*R*,*R*)-**2** in benzene in the same manner as in the case of (*R*,*R*)-**3** to afford a complex comprized of (*R*)-**1**, (*R*,*R*)-**2** and benzene of crystallization as colorless prisms. Complexes including toluene or *m*-xylene as a solvent of crystallization were similarly obtained. Decompositions of the above complexes, comprized of (*R*)-**1**, (*R*,*R*)-**2**, and a solvent, with dilute hydrochloric acid gave optically pure (*R*)-**1** in yields of 80—86%. On the other hand, complexes including *o*- or *p*-xylene were obtained when the corresponding solvent was used. Optical purities of **1** recovered from the corresponding complex were, however, 50—60% ee even after recrystallization of the complex.

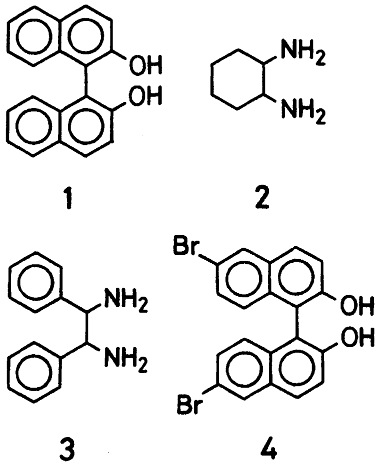

Chart 1.

A more soluble complex, (*S*)-**1**·(*R*,*R*)-**2**, was recovered from the filtrates separated from the less soluble complex, (*R*)-**1**·(*R*,*R*)-**2**, in the resolution of racemic **1** with (*R*,*R*)-**2**, and was decomposed with dilute hydrochloric acid to give (*S*)-**1** with a high optical purity of 96% ee. Although optically pure (*S*)-**1** was obtained by the resolution of racemic **1** using (*S*,*S*)-**2** as a resolving agent, the method is not economical since (*S*,*S*)-**2** is more expensive than (*R*,*R*)-**2**. Therefore, optical purification of (*S*)-**1**·(*R*,*R*)-**2** in the filtrate, which was separated from (*R*)-**1**·(*R*,*R*)-**2** in the resolution of racemic **1** with (*R*,*R*)-**2**, was examined by concentration of the filtrates and washing the precipitated crystalline residue with toluene. The optically purified (*S*)-**1**·(*R*,*R*)-**2** included no solvent of crystallization and gave optically pure (*S*)-**1** in a yield of 80% after treatment with dilute hydrochloric acid.

As described above, both optically pure (*R*)- and (*S*)-**1** were effectively obtained by resolution of racemic **1** using only one enentiomer of the diamine, (*R*,*R*)-**2**.

Naturally, resolutions of racemic **2** and **3** with optically active **1** succeeded in obtaining optically active **2** and **3** with optical purities of 90% ee and 98% ee, respectively, in a simillar manner as the resolution of racemic **1** with the optically active diamines. Moreover, it was found that optically active **2** was easily recovered by heating the optically active complex of **1** with **2** under reduced pressure although optically pure **1** completely was racemized.

The method was applied to a resolution of 6,6′-dibromo-2,2′-dihydroxy-1,1′-binaphthyl (**4**) with (*R*,*R*)-**3** to give optically pure (*R*)-**4** in a yield of 40%.

In order to develop a more economical resolution of **1**, epimerization of the complex formed in the resolution of racemic **1** with optically active **2** was examined.

When (*R*)-**1**·(*R*,*R*)-**2** was melted at 170 °C for 1 h, HPLC analysis showed that **1** included in the complex was completely racemized. Thus the epimerized diastereomeric complexes were recrystallized from toluene to separate (*R*)-**1**·(*R*,*R*)-**2** and (*S*)-**1**·(*R*,*R*)-**2**. Also (*S*)-**1**·(*R*,*R*)-**2** was epimerized by the same conditions and the epimerized diastereomeric complexes were separated to give (*R*)-**1**·(*R*,*R*)-**2** and (*S*)-**1**·(*R*,*R*)-**2**. Further, these epimerizations were also performed by refluxing the solutions of complexes in toluene for 15 h.

Using the epimerization-crystallization method with (*R*,*R*)-**2**, optically pure (*R*)-**1** was obtained in a yield of 160% by four successive epimerization-crystallization process. Optically pure (*S*)-**1** was obtained in 154% by four successive epimerization-crystallization process in a similar manner with the same enantiomer of resolving agent, (*R*,*R*)-**2**.

The kinetic studies of epimerization were performed by heating the solutions of (*S*)-**1**·(*R*,*R*)-**2** and (*S*)-**1**·(*R*,*R*)-**3** in a solvent such as benzene, toluene, and *m*-xylene at the boiling points. Racemization of (*S*)-**1** in the absence of (*R*,*R*)-**2** was also performed as a control experiment. These reactions obeyed the reversible first-order kinetics of $(k_1+k_2)t=\ln(100/OP)$, where k_1 and k_2 denote forward and reverse rate constants, respectively, and OP is optical purity of **1** at time t. As shown in Table 1, rate constants of the epimerization of (*S*)-**1**·(*R*,*R*)-**2** and (*S*)-**1**·(*R*,*R*)-**3** were larger than racemization of (*S*)-**1**. In the equation, k_1 was equal to k_2 because the optical purity of **1** at equilibrium was 0% ee. Activation energies and frequency factors were calculated using the data in Table by the equation expressed by $\ln k=\ln A-E_\mathrm{A}/RT$, where k is k_1 and k_2, A is a frequency factor, E_A is an activation energy of epimerization or racemization, R is the gas constant, and T is the absolute temperature. Activation energy and frequency factor for the epimerization of (*S*)-**1**·(*R*,*R*)-**2** were 109 kJ mol^{-1} K^{-1} and 3×10^{10} s^{-1}, respectively, and those for the epimerization of (*S*)-**1**·(*R*,*R*)-**3** were 96 kJ mol^{-1} K^{-1} and 1×10^{8} s^{-1}, respectively, while those for the racemization of (*S*)-**1** were 85 kJ mol^{-1} K^{-1} and 9×10^{5} s^{-1}. Although E_A calculated using the values of reaction temperature which were based on the boiling points of different solvents is not strictly correct, the k values obeyed the equation, $\ln k=\ln A-E_\mathrm{A}/RT$. Both the rate constants and the activation energies were in the order (*S*)-**1**·(*R*,*R*)-**2**>(*S*)-**1**·(*R*,*R*)-**3**>(*S*)-**1**. It was noteworthy that the values of E_A of the epimerizations were larger than that of racemization, notwithstanding the epimerization rates were much larger than racemization rate. Thus the acceleration of epimerization in comparison with the racemization was attributed to the frequency factor.

Table 1. Rate Constants for Epimerizations and Racemization

	T/K[a]	k_1+k_2/min^{-1}
(*S*)-**1**·(*R*,*R*)-**2**	354	1.84×10^{-4}
(*S*)-**1**·(*R*,*R*)-**2**	384	2.60×10^{-3}
(*S*)-**1**·(*R*,*R*)-**2**	417	4.22×10^{-2}
(*S*)-**1**·(*R*,*R*)-**3**	354	1.37×10^{-4}
(*S*)-**1**·(*R*,*R*)-**3**	384	1.48×10^{-3}
(*S*)-**1**·(*R*,*R*)-**3**	417	1.72×10^{-2}
(*S*)-**1**	354	2.52×10^{-5}
(*S*)-**1**	384	4.46×10^{-4}
(*S*)-**1**	417	1.78×10^{-3}

a) Reaction temperatures of the solutions; 354 K in benzene, 384 K in toluene, and 417 K in *m*-xylene.

Experimental

Materials. Racemic 2,2′-dihydroxy-1,1′-binaphthyl (**1**) was purchased from Tokyo Kasei Kogyo Co., Ltd. Optically pure (*S*)-**1** was obtained by the author's method.[6] Racemic 1,2-cyclohexanediamine (**2**) and (*R*,*R*)-**2** were purchased from Wako Pure Chemical Industries, Ltd. and the $[\alpha]_\mathrm{D}^{24}$ of (*R*,*R*)-**2** is −36.7° (*c* 4.14, H_2O). (*R*,*R*)-1,2-Diphenyl-1,2-ethanediamine (**3**) was prepared according to the reported method[7] and the $[\alpha]_\mathrm{D}^{24}$ is +103° (*c* 1.00, MeOH). All procedures of optical resolutions and epimerizations were carried out under a nitrogen atmosphere.

Analyses. Melting point was measured with a Yanaco MP-500D apparatus and is uncorrected. ^{1}H NMR spectrum was recorded on a JEOL JNM-PMX60 (60 MHz) spectrometer and is reported in ppm relative to tetramethylsilane used as an internal standard. IR spectrum was recorded with a JASCO A-202 spectrometer. Optical rotation was measured on a Union PM-101 polarimeter. Optical purity of resolved **1** was determined by HPLC analysis. The HPLC was performed with a Daicel CHIRALPAK OP (4.6 mm×250 mm) column with a mobil phase of MeOH at room temperature. The elution rate was 0.5 cm^3 min^{-1} and detection was carried out at ultraviolet (UV) 254 nm. Retention times of the (*R*)- and (*S*)-enantiomers were 15 and 21 min, respectively.

Resolution of 1 with (*R*,*R*)-3. To a solution of

3.00 g (14.1 mmol) of (*R*,*R*)-**3** in 16 cm^3 of benzene was added 4.05 g (14.1 mmol) of racemic **1**. After the mixture was heated to be a homogeneous solution, the solution was allowed to cool to room temperature. (*R*)-**1**·(*R*,*R*)-**3** was precipitated as colorless prisms and collected by filtration. Recrystallization from 16 cm^3 of benzene to give 2.05 g (4.11 mmol) of (*R*)-**1**·(*R*,*R*)-**3**. Mp 58—60 °C; $[\alpha]_D^{24}$ +7.19° (*c* 0.502, benzene); ^{1}H NMR ($CDCl_3$) δ=3.20 (s, 6H, $N\underline{H}_2$ and $O\underline{H}$), 3.78 (s, 2H, $C\underline{H}$–N), 6.8—8.1 (m, 12H), and 7.33 (s, 10H, $C_6\underline{H}_5$); IR (KBr disk) 3520, 3420, 3390, 3300, 3600—2000, 1615, 1590, and 1505 cm^{-1}.

Found: C, 81.61; H, 6.29; N, 5.32%. Calcd for $C_{34}H_{30}N_2O_2$: C, 81.90; H, 6.06; N, 5.62%.

To the prisms suspended in 3 cm^3 of ethanol, 26 cm^3 of 1 mol dm^{-3} of hydrochloric acid was added and stirred at room temperature for 30 min. Precipitated crystalline solid was collected by filtration, washed with water, and dried under reduced pressure (200 Pa) at 100 °C to give 0.899 g (3.14 mmol) of optically pure (*R*)-**1** in a yield of 45%.

Resolution of 1 with (*R*,*R*)-2 to Obtain (*R*)-1. To a solution of 10.0 g (87.6 mmol) of (*R*,*R*)-**2** in 750 cm^3 of benzene was added 25.1 g (87.7 mmol) of racemic **1**. After the mixture was heated to be a homogeneous solution, the solution was allowed to cool to room temperature. (*R*)-**1**·(*R*,*R*)-**2**·benzene was precipitated as colorless prisms and collected by filtration. Recrystallization from benzene to give 21.0 g (43.9 mmol) of (*R*)-**1**·(*R*,*R*)-**2**·benzene (1 : 1 : 1). Mp 153—157 °C (released benzene molecule at above 80 °C to whiten); $[\alpha]_D^{24}$ −16.1° (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=0.3—2.0 (m, 10H), 3.60 (s, 6H, $N\underline{H}_2$ and $O\underline{H}$), 7.1—8.3 (m, 12H), and 7.4 (s, 6H, $C_6\underline{H}_6$); IR (KBr disk) 3450, 3380, 3300, 3600—2000, 1620, 1600, and 1515 cm^{-1}.

Found: C, 80.12; H, 7.21; N, 5.88%. Calcd for $C_{32}H_{34}N_2O_2$: C, 80.30; H, 7.16; N, 5.85%.

The prisms were treated with dilute hydrochloric acid as described above to give 10.8 g (37.7 mmol) of optically pure (*R*)-**1** in a yield of 86%.

Complexes including the other solvent of crystallization were obtained in the same manner.

(*R*)-**1**·(*R*,*R*)-**2**·toluene (1 : 1 : 1): Mp 150—157 °C (released toluene molecule at above 110 °C to whiten); $[\alpha]_D^{24}$ −16.1° (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=0.3—2.0 (m, 10H), 2.30 (s, 3H, $PhC\underline{H}_3$), 3.68 (s, 6H, $N\underline{H}_2$ and $O\underline{H}$), and 7.0—8.0 (m, 17H).

(*R*)-**1**·(*R*,*R*)-**2**·*m*-xylene (1 : 1 : 1): Mp 150—155 °C (released *m*-xylene molecule at above 140 °C to whiten); $[\alpha]_D^{24}$ −16.1° (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=0.3—2.0 (m, 10H), 2.30 (s, 6H, $C\underline{H}_3$), 3.70 (s, 6H, $N\underline{H}_2$ and $O\underline{H}$), and 7.1—8.0 (m, 16H).

Resolution of 1 with (*R*,*R*)-2 to Obtain (*S*)-1. To a solution of 10.0 g (87.6 mmol) of (*R*,*R*)-**2** in 350 cm^3 of toluene was added 25.1 g (87.7 mmol) of racemic **1**. After the mixture was heated to be a homogeneous solution, the solution was allowed to cool to room temperature. The complex of (*R*)-**1**·(*R*,*R*)-**2**·toluene precipitated was collected by filtration. The filtrate was concentrated under reduced pressure (2.7×10^3 Pa) at 40 °C to give a pale yellow crystalline residue. Optical purities of **1** contained in the residue were 96% ee. Further, the residue was washed twice with 20 cm^3 of toluene to afford (*S*)-**1**·(*R*,*R*)-**2** as colorless prisms. Mp 129—131 °C; $[\alpha]_D^{24}$ +0.1° (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=0.3—2.0 (m, 10H), 3.60 (s, 6H, $N\underline{H}_2$ and $O\underline{H}$), and 7.0—8.1 (m, 12H); IR (KBr disk) 3450, 3380, 3300, 3600—2000, 1620, 1595, and 1510 cm^{-1}.

Found: C, 77.91; H, 7.11; N, 6.98%. Calcd for $C_{26}H_{28}N_2O_2$: C, 77.97; H, 7.05; N, 6.99%.

The prisms were treated with dilute hydrochloric acid as described above to give 10.5 g (36.7 mmol) of optically pure (*S*)-**1** in a yield of 84%.

Resolution of 1 with (*S*,*S*)-2 to Obtain (*S*)-1. (*S*)-**1**·(*S*,*S*)-**2**·toluene was obtained as colorless prisms from racemic **1** and (*S*,*S*)-**2** in the same manner as the resolution of **1** with (*R*,*R*)-**2**. Mp 150—157 °C; $[\alpha]_D^{24}$ +16.1° (*c* 1.00, $CHCl_3$).

The prisms were treated with dilute hydrochloric acid as described above to give optically pure (*S*)-**1**.

Resolution of 2 with (*R*)-1 to Obtain (*R*,*R*)-2. A 1.03 g (2.10 mmol) of (*R*)-**1**·(*R*,*R*)-**2**·toluene was obtained as colorless prisms from 1.40 g (4.89 mmol) of (*R*)-**1** and 0.558 g (4.89 mmol) of racemic **2** in the same manner as the resolution of **1** with (*R*,*R*)-**2**.

When the prisms were heated at 170 °C under reduced pressure (2.1×10^3 Pa) with a bulb-to-bulb distillation apparatus, 0.216 g (1.89 mmol) of (*R*,*R*)-**2** was distilled in a yield of 77%. $[\alpha]_D^{24}$ −43.7° (*c* 1.06, MeOH) (lit[8] $[\alpha]_D^{24}$ −44.1° (*c* 3, MeOH)).

Resolution of 3 with (*R*)-1 to Obtain (*R*,*R*)-3. A 18.0 g (36.1 mmol) of (*R*)-**1**·(*R*,*R*)-**3** was obtained as colorless prisms from 56.2 g (196 mmol) of (*R*)-**1** and 41.6 g (196 mmol) of racemic **3** in the same manner as the resolution of **1** with (*R*,*R*)-**3**.

To the prisms suspended in 23 cm^3 of methanol, 90 cm^3 of 1 mol dm^{-3} of hydrochloric acid was added and the mixture was stirred at room temperature for 30 min. Precipitated **1** was collected by filtration and washed with water. The filtrate was made alkaline by an addition of 15 cm^3 of 12 mol dm^{-3} of aqueous sodium hydroxide and extracted thrice with 50 cm^3 of toluene. The toluene layer was washed with 50 cm^3 of brine, dried with sodium hydroxide, and concentrated under reduced pressure (2.7×10^3 Pa) to give a crystalline residue. The residue was dried at 2.7×10^2 Pa to give 5.10 g (24.0 mmol) of (*R*,*R*)-**3** in a yield of 24%. $[\alpha]_D^{24}$ +105° (*c* 1.00, MeOH) (lit[7] $[\alpha]_D^{24}$ +106.9° (*c* 1.00, MeOH)).

Resolution of 4 with (*R*,*R*)-3 to Obtain (*R*)-4. A 0.868 g (1.32 mmol) of (*R*)-**4**·(*R*,*R*)-**3** was obtained as colorless prisms from 2.09 g (4.71 mmol) of racemic **4** and 96.4% ee of 1.00 g (4.71 mmol) of (*R*,*R*)-**3** in 20 cm^3 of ether in a similar manner as the resolution of **1** with (*R*,*R*)-**3**. Mp 100—102 °C; $[\alpha]_D^{24}$ −61.5° (*c* 0.501, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=2.80 (s, 6H, $N\underline{H}_2$ and $O\underline{H}$), 3.95 (s, 2H, $C\underline{H}$–N), and 6.90—8.16 (m, 20H); IR (KBr disk) 3425, 3350, 3270, 3100—2750, 1600, and 1570 cm^{-1}.

Found: C, 62.27; H, 4.92; N, 4.12%. Calcd for $C_{34}H_{28}Br_2N_2O_2$: C, 62.21; H, 4.30; N, 4.27%.

The prisms were treated with dilute hydrochloric acid as described above to give 0.417 g (0.938 mmol) of (*R*)-**4** in a yield of 40%. $[\alpha]_{578}^{24}$ −132° (*c* 0.502, CH_2Cl_2) (lit[9] $[\alpha]_{578}^{24}$ −129° (*c* 1.0, CH_2Cl_2)).

Epimerization of (*R*)-1·(*R*,*R*)-2. Method A: A 1.00 g (2.03 mmol) of (*R*)-**1**·(*R*,*R*)-**2**·toluene, obtained in the resolution of **1** with (*R*,*R*)-**2**, was heated to melt and stirred at 170 °C for 1 h. After the mixture was cooled to room temperature, the mixture was treated with dilute hydrochloric acid as described above and analyzed by HPLC to show complete racemization of **1**.

Method B: A suspension of 1.00 g (2.03 mmol) of (*R*)-**1**·(*R*,*R*)-**2**·toluene obtained in the resolution of **1** with (*R*,*R*)-**2**, in 10 cm^3 of toluene was heated to be a homogeneous solution and the solution was refluxed for 15 h. After the mixture was cooled to room temperature, the mixture was treated in the same manner as Method A to show complete racemization of **1**.

Epimerization of (*S*)-1·(*R*,*R*)-2. Epimerization of (*S*)-**1**·(*R*,*R*)-**2** was performed in the same manner as the case of that of (*R*)-**1**·(*R*,*R*)-**2**·toluene to result in complete racemization of **1**.

Resolution of 1 with (*R*,*R*)-2 to Obtain (*R*)-1 by Epimerization-Crystallization Method. To a solution of 40.0 g (350 mmol) of (*R*,*R*)-**2** in 1 dm^3 of toluene was added 100 g (349 mmol) of racemic **1**. After the mixture was heated to be a homogeneous solution, the solution was allowed to cool to room temperature. (*R*)-**1**·(*R*,*R*)-**2**·toluene was precipitated as colorless prisms and collected by filtration. The filtrate was concentrated under reduced pressure to give a pale yellow crystalline residue containing (*S*)-**1**·(*R*,*R*)-**2**. Epimerization of (*S*)-**1**·(*R*,*R*)-**2** was performed by the treatment of the residue using the Method A as described above. The diastereomeric complexes were separated by an addition of toluene and recrystallization of the mixture. This procedure of epimerization-separation was repeated four times. The prisms of (*R*)-**1**·(*R*,*R*)-**2**·toluene were combined and treated with dilute hydrochloric acid as described above to give 80.0 g (279 mmol) of optically pure (*R*)-**1** in a yield of 160%.

Resolution of 1 with (*R*,*R*)-2 to Obtain (*S*)-1 by Epimerization-Crystallization Method. To a solution of 40.0 g (350 mmol) of (*R*,*R*)-**2** in 1.4 dm^3 of toluene was added 100 g (349 mmol) of racemic **1**. After the mixture was heated to be a homogeneous solution, the solution was allowed to cool to room temperature. (*R*)-**1**·(*R*,*R*)-**2**·toluene was precipitated as colorless prisms and collected by filtration. The filtrate was concentrated under reduced pressure (2.7×10^3 Pa) at 40 °C to give a pale yellow crystalline residue. The residue was washed twice with 150 cm^3 of toluene to afford (*S*)-**1**·(*R*,*R*)-**2** as colorless prisms. On the other hand, (*R*)-**1**·(*R*,*R*)-**2**·toluene was epimerized by the Method A as described above and the diastereomeric complexes were separated by recrystallization from toluene. This procedure of epimerization-separation was repeated four times. The prisms of (*S*)-**1**·(*R*,*R*)-**2** were combined and treated with dilute hydrochloric acid as described above to give 76.9 g (269 mmol) of optically pure (*S*)-**1** in a yield of 154%.

Rate Constant for Epimerization and Racemization. After a mixture of 8.73 mmol of (*S*)-**1** and 8.73 mmol of (*R*,*R*)-**2** or (*R*,*R*)-**3** in 25 cm^3 of benzene, toluene, or *m*-xylene was rapidly heated to reflux, the solution was stirred at the boiling point. A 0.1 cm^3 aliquot of the solution was pipetted out at appropriate time intervals and was then poured rapidly into a mixture of 0.5 cm^3 of toluene and 0.5 cm^3 of 1 $mol\,dm^{-3}$ of hydrochloric acid. The optical purity of **1** was determined by HPLC analysis of the organic phase.

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